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Table of Contents

(#2074-2079) Vasculitis II: Population Studies

ARHP Concurrent Abstract Session
(#2080-2085) ARHP IV: Clinical Practice, Patient Care and Health Services

TUESDAY, NOVEMBER 15, 2016

8:30 AM - 4:00 PM
ACR/ARHP Poster Session C
(#2086-2981)

11:00 AM - 12:30 PM
ACR Plenary Session III: Discovery 2016
(#2982-2987)

2:30 - 4:00 PM
ACR Concurrent Abstract Sessions
(#2988-2992) 2016 Rheumatology Research Foundation Edmond L. Dubois, MD Memorial Lectureship: Systemic Lupus Erythematosus – Clinical
(#2993-2998) Biology and Pathology of Bone and Joint
(#2999-3004) Orthopedics, Low Back Pain and Rehabilitation
(#3005-3010) Pediatric Rheumatology – Clinical and Therapeutic Aspects II: Juvenile Arthritis
(#3011-3016) Rheumatoid Arthritis – Clinical Aspects IV: Managing Patients in Remission
(#3017-3022) Rheumatoid Arthritis – Human Etiology and Pathogenesis I
(#3023-3028) Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy III: Small Molecules and Early Intervention
(#3029-3034) Sjögren's Syndrome I: Clinical Insights
(#3035-3040) Spondylarthropathies Psoriatic Arthritis – Pathogenesis, Etiology I
(#3041-3046) Vasculitis III: Pathogenic Mechanisms

ARHP Concurrent Abstract Session
(#3047-3052) ARHP V: Epidemiology and Public Health

4:30 - 6:00 PM
ACR/ARHP Combined Abstract Session
(#3053-3058) ACR/ARHP Combined Abstract Session: Rehabilitation

ACR Concurrent Abstract Sessions
(#3059-3064) Education
(#3065-3070) Epidemiology and Public Health II: Obesity, Cancer and Mortality
(#3071-3076) Metabolic and Crystal Arthropathies I: Mechanisms of Disease
(#3077-3082) Miscellaneous Rheumatic and Inflammatory Diseases II
(#3083-3088) Rheumatoid Arthritis – Clinical Aspects V: Challenges in the Assessment and Management of Established RA
(#3089-3094) Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy IV: Biomarkers
(#3095-3100) Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment IV: Psoriatic Arthritis – Clinical
(#3101-3106) Systemic Lupus Erythematosus – Clinical Aspects and Treatment IV: Biomarkers
(#3107-3112) T Cell Biology and Targets in Autoimmune Disease - Oral Session

WEDNESDAY, NOVEMBER 16, 2016

9:00 AM - 10:30 AM
ACR/ARHP Combined Abstract Session
(#3113-3118) ACR/ARHP Combined Abstract Session: Pediatric Rheumatology

ACR Concurrent Abstract Sessions
(#3119-3124) Genetics, Genomics and Proteomics II
(#3125-3130) Metabolic and Crystal Arthropathies II: Clinical Practice
(#3131-3136) Osteoarthritis – Clinical Aspect II: Treatment and Imaging
(#3137-3142) Quality Measures and Quality of Care II
(#3143-3148) Rheumatoid Arthritis – Animal Models II
(#3149-3154) Rheumatoid Arthritis – Clinical Aspects VI: Management of Early Rheumatoid Arthritis
(#3155-3160) Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment V: Imaging of Spondyloarthritis
(#3161-3166) Spondylarthropathies Psoriatic Arthritis – Pathogenesis, Etiology II
(#3167-3172) Systemic Lupus Erythematosus – Clinical Aspects and Treatment V: Damage and Morbidity
(#3173-3178) Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics II
(#3179-3184) Vasculitis IV: Diagnosis and Assessment of Disease Activity

11:00 AM - 12:30 PM
ACR Concurrent Abstract Sessions
(#3185-3190) Epidemiology and Public Health III: Psoriatic Arthritis and More
(#3191-3196) Health Services Research II
(#3197-3202) Imaging of Rheumatic Diseases III: Crystal Arthritis, Osteoarthritis, Connective Tissue Disease and Vasculitis
(#3203-3208) Pediatric Rheumatology – Clinical and Therapeutic Aspects III: Autoinflammatory Diseases and Juvenile Dermatomyositis
(#3209-3214) Rheumatoid Arthritis – Clinical Aspects VII: The Impact of Treating to Target
(#3215-3220) Rheumatoid Arthritis – Human Etiology and Pathogenesis II
(#3221-3226) Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy V: New Biologics and Remission Induction
(#3227-3232) Sjögren's Syndrome II: Basic Insights
(#3233-3238) Systemic Lupus Erythematosus – Clinical Aspects and Treatment VI: Quality of Life
(#3239-3244) Systemic Lupus Erythematosus – Human Etiology and Pathogenesis II
(#3245-3250) Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics III

ARHP Concurrent Abstract Session
(#3251-3256) ARHP VI: Rehabilitation Sciences

ACR LATE-BREAKING ABSTRACT SESSIONS

TUESDAY, NOVEMBER 15, 2016

8:30 AM - 4:00 PM
ACR/ARHP Poster Session C
(#7L-19L) ACR Late-breaking Abstract Poster Presentations*

4:30 - 6:00 PM
ACR Concurrent Abstract Session
(#1L-6L) ACR Late-breaking Abstract Oral Presentations*

*Please Note: ACR Late-breaking Abstracts are listed below in numeric order instead of presentation order.

Abstract Number: 1

Factors Predicting Likelihood of Remaining Positive for Rheumatoid Arthritis-Related Autoantibodies Following Autoantibody Screening

Jill M. Norris[1], Elizabeth A. Bemis[1], M. Kristen Demoruelle[2], Michael Weisman[3], Jane H. Buckner[4], Peter K. Gregersen[5], Ted R Mikuls[6], James R. O'Dell[6], Richard M. Keating[7], Kevin D. Deane[8] and V. Michael Holers[8], [1]Epidemiology, Colorado School of Public Health, Aurora, CO, [2]Rheumatology, University of Colorado School of Medicine, Aurora, CO, [3]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [4]Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]Feinstein Insititute for Medical Research, Manhasset, NY, [6]Rheumatology, University of Nebraska Medical Center, Omaha, NE, [7]Division of Rheumatology, Scripps Health, La Jolla, CA, [8]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Epidemiology and Public Health - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: RA-related autoantibodies are typically elevated prior to the onset of RA. Screening for autoantibody (aAb) positive individuals is a means to assemble a cohort at very high risk for future RA for epidemiologic and intervention studies. However, little is known about the stability of RA-related aAbs over time in individuals without RA who screen positive in a non-clinical setting.

Methods: Studies of the Etiology of RA (SERA) prospectively follows subjects who are RA-free but are at increased risk for future RA because they are a first-degree relative (FDR) of an RA proband (n=1774), or are from a cohort enriched for HLA-DR4 alleles (n=631). We tested serum aAbs to CCP (CCP2 and/or CCP3.1), RF, and RF IgG, IgA and IgM isotypes. Positivity was based on cut-offs as defined by manufacturer's recommendations (CCP and RF isotypes) or ACR recommendations (RF). Overall, 23% (551/2405) tested positive for at least one aAb during screening. To evaluate outcomes of aAb+ subjects identified via screening, the cohort was limited to those who had at least one follow-up visit after their 1staAb+ visit (n= 315). For prediction analyses, we explored high titer aAb, as defined by 2-times (2x) and 3-times (3x) the cutoff.

Results: Over a mean follow-up of 5.1 years, 146 (46.3%) remained aAb+ at all visits (Persistent), 61 (19.4%) were aAb+ again on at least one follow-up visit, but fluctuated between aAb negative and aAb+ during follow-up (Intermittently Positive), and 108 (34.3%) were seronegative on all follow-up visits (Reverter) (Table 1). To address the question as to what predicts a person will test aAb+ again in those who were screened-positive, we combined the Persistent and Intermittently Positive groups to form a group that was aAb+ on two or more occasions (n=207). To examine the likelihood of testing aAb+ again after a screened-positive test, we conducted bivariate logistic regression models with every variable listed in Table 1 as a potential predictor. Table 2 lists the variables significantly associated with testing positive again. Age, sex, race/ethnicity, FDR status, shared epitope status, ever smoking, high CRP, and joint signs were not associated with testing aAb+ after the initial screened aAb+ test.

Conclusion: In this cohort of at-risk individuals who screen aAb+, the presence of any aAb at > 2x cutoff at screening predicts who will test positive again, while a 3x cutoff does not improve prediction. Demographic and environmental exposures were not associated aAb+ persistence, perhaps due to their primary influence at other stages of disease, including the initial development of RA-related aAbs.

Table 1. Characteristics of Individuals in SERA who Tested Positive for an RA-related Autoantibody During Screening stratified by Autoantibody Status on Follow-up

	Persistent N = 146	Intermittently Positive N = 61	Reverter N = 108
Age at first positive visit (Mean±SD)	47.6±16.5	46.4±17.0	45.2±14.6
Number of visits (including screening) (Mean±SD)	3.4±1.7	4.7±1.5	2.9±1.3
Length of Follow-up in years (Mean±SD)	3.9 ±2.6	5.8±2.5	4.0±2.7
Sex (%female)	111 (76.0)	50 (82.0)	78 (72.2)
Race/Ethnicity (%Non-Hispanic White)	116 (79.5)	53 (86.9)	78 (72.2)
First Degree Relative of an RA Proband (%)	119 (81.5)	55 (90.2)	87 (80.6)
Shared Epitope positive (%)	70 (48.0)	39 (63.9)	64 (59.3)
Ever smoker (%)	51 (34.9)	23 (37.7)	42 (38.9)
CRP+ at first positive visit (%)	47 (32.2)	19 (31.2)	30 (27.8)
CCP+ at first positive visit† (%)	54 (37.0)	12 (19.7)	17 (15.7)
CCP+ > 2x cutoff at first positive visit† (%)	40 (27.4)	4 (6.6)	6 (5.6)
CCP+ >3x cutoff at first positive visit† (%)	32 (21.9)	2 (3.3)	6 (5.6)
RF+ at first positive visit (%)	53 (36.3)	18 (29.5)	27 (25.0)
RF+ > 2x cutoff at first positive visit (%)	25 (17.1)	4 (6.6)	4 (3.7)
RF+ > 3x cutoff at first positive visit (%)	14 (9.6)	2 (3.3)	3 (2.8)
RF isotype+ at first positive visit‡ (%)	98 (67.1)	43 (70.5)	73 (67.6)
RF isotype+ > 2x cutoff at first positive visit‡ (%)	51 (34.9)	13 (21.3)	11 (10.2)
RF isoty pe+ > 3x cutoff at first positive visit‡ (%)	41 (28.1)	6 (9.8)	5 (4.6)
≥1 Swollen joint at first positive visit* (%)	13/121 (10.7)	8/51 (15.7)	10/90 (11.1)
≥1 Tender or swollen joint at first positive visit* (%)	34/121 (28.1)	11/51 (21.6)	26/90 (28.9)

†Either CCP2 or CCP3.1 ‡ IgM, IgG, or IgA *joints included are: wrist, MCP, PIP, MTP and elbow; 57 individuals excluded due to missing exam data.

Table 2. Factors associated with the likelihood of testing autoantibody positive after the first positive (screening) test

aAb status at first positive (screening) visit	OR (95% CI)*	p-value	Percentage who test aAb positive again
Any aAb+ (definition of cohort)	-	-	65.7%
Any aAb+ > 2x cutoff	**5.50 (3.15-9.61)**	**<0.01**	85.2%
Any aAb+ > 3x cutoff	**4.49 (2.40-8.41)**	**<0.01**	85.6%
CCP+ †	**2.51 (1.38-4.54)**	**<0.01**	79.5%
CCP+ > 2x cutoff †	**4.59 (1.89-11.15)**	**<0.01**	88.0%
CCP+ > 3x cutoff †	**3.34 (1.36-8.23)**	**<0.01**	85.0%
RF+	1.57 (0.93-2.64)	0.09	72.4%
RF+ > 2x cutoff	**4.23 (1.45-12.38)**	**<0.01**	87.9%
RF+ > 3x cutoff	4.23 (1.45-12.38)	0.08	84.2%
RF+ isotype ‡	1.02 (0.62-1.69)	0.92	65.9%
RF+ isotype >2x cutoff ‡	**3.95 (1.98-7.87)**	**<0.01**	85.3%
RF+ isotype >3x cutoff ‡	**6.05 (2.33-15.72)**	**<0.01**	90.4%

*OR represents the increased odds of testing positive again given their particular aAB+ status (and titer) at the first positive visit. †Either CCP2 or CCP3.1 ‡IgM, IgG, or IgA

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None; **P. K. Gregersen**, None; **T. R. Mikuls**, None; **J. R. O'Dell**, Lilly, 5,Bristol-Myers Squibb, 5,GlaxoSmithKline, 5,Coherus, 5,Medac, 5; **R. M. Keating**, None; **K. D. Deane**, Inova Diagnostics, Inc., 9; **V. M. Holers**, Patents, 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/factors-predicting-likelihood-of-remaining-positive-for-rheumatoid-arthritis-related-autoantibodies-following-autoantibody-screening

Abstract Number: 2

Rheumatoid Arthritis (RA)-Related Autoimmunity and Lumbar Bone Mineral Density in a Multi-Ethnic Community-Dwelling Population

Jan M. Hughes-Austin[1], Joachim H. Ix[2], Michael H. Criqui[3], Ronit Katz[4], Matthew Budoff[5], Jon T. Giles[6], Kiang Liu[7] and Darcy S. Majka[8], [1]Orthopaedic Surgery, University of California, San Diego, La Jolla, CA, [2]University of California, San Diego, La Jolla, CA, [3]Family Medicine and Public Health, University of California, San Diego, La Jolla, CA, [4]University of Washington, Seattle, WA, [5]Cardiology, Harbor-UCLA Medical Center, Torrance, CA, [6]Rheumatology, Columbia University Medical Center, NY, NY, [7]Department of Preventive Medicine, Northwestern University, Chicago, IL, [8]Rheumatology, Northwestern University Feinberg School of Medicine, Chicago, IL

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016
Session Title: Epidemiology and Public Health - Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Previous studies suggest that antibodies to citrullinated protein antigens (ACPA) contribute to decreased hand bone mineral density (BMD) in RA-free individuals. No evidence exists with regard to associations of ACPA or rheumatoid factor (RF) with general osteoporosis or more clinically relevant lumbar spine BMD; a common site for compression fractures, immobility, and pain. Therefore, we sought to determine whether RA-related autoantibodies were associated with lumbar BMD in a community based population sample in order to help delineate whether previous findings of decreased hand BMD in those with RA-related autoantibodies may also indicate systemic bone changes.

Methods: In the Multi-Ethnic Study of Atherosclerosis (MESA), a multi-ethnic, multi-center, prospective study of community-dwelling individuals designed to study characteristics of subclinical and clinical cardiovascular disease, we evaluated 1924 participants with measures of RA-related autoantibodies: RF IgA and IgM isotypes and anti-cyclic citrullinated peptide (anti-CCP) antibodies, as well as volumetric BMD (vBMD) from the third lumbar vertebra (L3) by computed tomography. RA-related autoantibodies were analyzed as dichotomous variables (positive vs negative) based on pre-specified cut-offs, and vBMD was analyzed as a continuous variable. We investigated associations between RA-related autoantibody positivity and vBMD using ANCOVA, stratified by sex *a priori*, and adjusting for age, race, weight, diabetes, self-reported arthritis, current smoking, c-reactive protein, education, estimated glomerular filtration rate, albumin/creatinine ratio, physical activity (mets/week), hypertension, alcohol use, thiazide and loop diuretics (and hormone replacement therapy in women).

Results: Among 1924 MESA participants (956 women), the mean age was 62 years, and 40% were Caucasian, 13% were Chinese, 20% were African American, and 26% were Hispanic. Mean L3 vBMD was 111 mg/cc in women and 121 mg/cc in men. Twenty percent were positive for RF, and 1% of men and 2% of women were positive for anti-CCP (Table 1). In women, there was no association of vBMD with RF positivity or anti-CCP positivity in either minimally or fully adjusted models. Results were similar in men. Sensitivity analysis stratified by self-reported arthritis showed similar results.

Conclusion: In a multi-ethnic community-based population sample, RA-related autoantibody positivity was not significantly associated with lumbar BMD. As this finding was in contrast to previous findings in hand BMD, further research is needed to determine whether bone changes are local (e.g., RA-specific joints) or systemic.

Table 1. Proportion of MESA participants positive for RA-related autoantibodies and their association with bone mineral density

	Women (n=956)			Men (n=968)		
	n (%) positive	BMD B(SD)	p-value	n (%) positive	BMD B(SD)	p-value
Rheumatoid Factor (IgA or IgM)	189 (20)			193 (20)		
Adjusted for age and race		1.82 (2.6)	0.4881		4.52 (2.6)	0.086
Fully adjusted*		0.09 (3.1)	0.9774		3.97 (2.8)	0.1532
Anti-CCP	15 (2)			13 (1)		
Adjusted for age and race		13.84 (8.3)	0.0953		-2.33 (9.1)	0.798
Fully adjusted*		12.46 (9.8)	0.2035		-6.81 (9.4)	0.4673
Either RF or Anti-CCP	195 (20)			199 (21)		
Adjusted for age and race		2.83 (2.6)	0.2774		3.98 (2.6)	0.1261
Fully adjusted*		1.19 (3.1)	0.7028		3.20 (2.7)	0.2444

*Fully adjusted for age, race, weight, diabetes, self-reported arthritis, current smoking, CRP, education, eGFR, ACR, physical activity mets/week, HTN, current alcohol use, and use of thiazide and loop diuretics (and hormone replacement therapy in women) [Results are interpreted as the difference in BMD mg/cc in the RA-related autoantibody positive participants compared to the RA-related autoantibody negative participants.]

Disclosure: J. M. Hughes-Austin, None; **J. H. Ix**, None; **M. H. Criqui**, None; **R. Katz**, None; **M. Budoff**, None; **J. T. Giles**, None; **K. Liu**, None; **D. S. Majka**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/rheumatoid-arthritis-ra-related-autoimmunity-and-lumbar-bone-mineral-density-in-a-multi-ethnic-community-dwelling-population

Abstract Number: 3

The Presence of Rheumatoid Factor Is Associated with Lower Bone Mass in Korean Health Screening Male Subjects without Clinically Apparent Arthritis

Jiwon Hwang[1], Joong Kyong Ahn[2], **Yeonghee Eun**[3], Hyemin Jeong[3], Eun-Jung Park[4], Hyungjin Kim[3], Jaejoon Lee[3], Eun-Mi Koh[3] and Hoon-Suk Cha[5], [1]Department of Medicine, National Police Hospital, Seoul, Korea, The Republic of, [2]Department of Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [4]Department of Medicine, Division of Rheumatology, Department of Medicine, Jeju National University Hospital, Jeju University School of Medicine, Jeju, South Korea, [5]Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea

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Background/Purpose: Close relationship between the immune and skeletal systems has been recognized through the bone loss in rheumatoid arthritis (RA). Rheumatoid factor (RF) is present in approximately 70-80% of RA patients, which is an autoantibody directed against the Fc component of IgG and associated with osteoporosis and reduced bone mineral density (BMD) in RA. RF is also found nonspecifically in chronic inflammatory condition such as sarcoidosis, hepatitis B or C, and tuberculosis. However, the influence of RF to bone loss is scarcely known in subjects without any specific medical problem. This cross-sectional study aimed to investigate the association between the presence of RF and BMD in Korean healthy male subjects without any history of joint disease.

Methods: Of the 84,344 males who had undergone a comprehensive health checkup program in 2012, 1,390 healthy subjects were recruited, whose BMD and RF results were available. Subjects with history of diabetes, kidney disease, thyroid disease, and malignancy, and taking medicine regarding these diseases, osteoporosis, and arthritis were excluded based on self-reported questionnaire. The RF titer $\geq$ 20 IU/ml was considered positive. BMD was categorized into 3 groups based on T-score; normal (T-score $\geq$ -1.0), osteopenia (-1.0 > T-score > -2.5) and osteoporosis (T-score $\leq$ -2.5). The association between the presence of RF and BMD was assessed by multiple linear regression analysis.

Results: Of 1,390 males, the mean age was 52.8 ± 10.9 years (range, 22 – 83) and RF was positive in 64 subjects (4.6%). Demographics including smoking history, alcohol consumption, the frequency of vigorous exercise and body mass index (BMI), and laboratory data were not different between RF-positive and –negative subjects except hepatitis B surface antigen, which was more frequently seen in RF-positive subjects (15.6% vs. 4.3%, p = 0.001). Low bone mass (osteopenia and osteoporosis) of lumbar spine was more prevalent in subjects aged 50 or more compared with those younger than 50 years (28.0% vs. 10.7%, p < 0.001) while no differences of femur neck and total hip. RF-positive subjects had significantly lower BMD compared to RF-negative subjects in lumbar spine (1.10 ± 0.18 g/cm2vs. 1.17 ± 0.16 g/cm2, p = 0.002) but neither in femur neck nor total hip. In subjects with higher titer RF ($\geq$ 40 IU/ml), the mean BMD of lumbar spine was significantly decreased than those with lower titer RF (one-way ANOVA, F(3, 1190) = 3.527, p = 0.015). After adjusting for multiple confounders such as age, BMI, glomerular filtration rate, serum concentration of calcium, phosphorus, and uric acid, and lifestyle factors (drinking, smoking, and physical exercise), RF positivity was negatively associated with BMD at lumbar spine (B = -0.055 and SE = 0.027, p = 0.039).

Conclusion: Our results provide epidemiological evidence that the presence of RF could have an unfavorable impact on bone density in apparently healthy male subjects. Additional studies to elucidate the osteoimmunological mechanism of RF are warranted.

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Abstract Number: 4

Rheumatoid Arthritis (RA)-Related Joint Symptoms and Thoracic Bone Mineral Density in an RA-Free Community Dwelling Population

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Background/Purpose: Osteoporosis, defined by Tscore < -2.5, is one of the main consequences of RA and it appears early in the disease. It is twice as prevalent in RA as it is in the general population; and low bone mineral density (BMD) in RA is associated with increased risk of hip and vertebral fractures. It is not known exactly whether this degeneration begins in pre-clinical RA and whether joint symptoms provide clinicians insight into these degenerative changes, especially in the spine. Therefore, we investigated associations between RA-specific joint symptoms and thoracic BMD in a community-based cohort free of RA.

Methods: We evaluated associations between presence of RA-specific joint symptoms and thoracic BMD (tBMD) using computed tomography (CT) in 31 individuals from the Studies of the Etiology of RA who were RA-free based on the 1987 ACR and 2010 ACR/EULAR criteria for RA. A physician confirmed joint swelling; participants self-reported stiffness and pain in the wrist, elbow, or any metacarpophalangeal, proximal interphalangeal, or metatarsophalangeal joints. Thoracic BMD on CT was measured using OsiriX 7.5 (Pixmeo, Geneva, Switzerland), and calculated using average BMD of T7-T9 vertebrae. Sex-specific Tscores were calculated as follows: $T_{(female)} = (BMD_{(individual\ mean)} - 222)/36$; $T_{(male)} = (BMD_{(individual\ mean)} - 215)/33$; where < -2.5 is considered osteoporosis and < -1.0 is considered osteopenia. Associations between joint symptoms and tBMD were evaluated using ANCOVA and adjusted for age, race, body mass index (BMI), pack-years smoking, high sensitivity c-reactive protein (CRP), number of autoantibodies (Anti-CCP, RF-IgG, RF-IgM, RF-IgA), and the source of their recruitment into SERA (as a first degree relative or health fair participant).

Results: Among 31 SERA participants, average(SD) age was 54(13), BMI was 27(5), CRP was 3(4), Tscore was -1(2), 45% were women, 94% were non-Hispanic White, and everyone had an average of 1(1) autoantibody. Joint swelling was associated with lower Tscores, although the association was marginally significant (p=0.08). Neither joint stiffness nor pain was associated with Tscores (Table).

Conclusion: In a cohort of RA-free individuals, neither joint swelling, stiffness, nor pain was significantly associated with tBMD Tscores. These preliminary data were limited by small sample size. Joint swelling was marginally associated with tBMD, thus future research with larger sample size is required to determine whether joint swelling may be linked to bone density.

Table. Associations between joint symptoms and thoracic BMD presented as a Tscore

		Tscore	
	n (%) positive	**B (SD)**	**p-value**
Joint Swelling	2 (6)		
Age, race, cohort adjusted		-1.49 (0.8)	0.0837
Fully adjusted*		-1.70 (0.9)	0.0823
Joint Stiffness	5 (16)		
Age, race, cohort adjusted		-0.27 (0.6)	0.6541
Fully adjusted*		-0.37 (0.7)	0.5793
Joint Swelling+Stiffness	7 (23)		
Age, race, cohort adjusted		-0.79 (0.5)	0.1429
Fully adjusted*		-0.98 (0.6)	0.1087
Joint Pain	7 (23)		
Age, race, coh ort adjusted		-0.38 (0.5)	0.4826
Fully adjusted*		-0.62 (0.6)	0.3115

*Fully adjusted for age, race, BMI, pack-years smoking, CRP, number of autoantibodies, cohort (FDR vs Health Fair)

Disclosure: J. M. Hughes-Austin, None; **J. H. Ix**, None; **S. R. Ward**, None; **M. K. Demoruelle**, None; **V. M. Holers**, Patents, 9; **J. M. Norris**, None; **K. D. Deane**, Inova Diagnostics, Inc., 9.

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Abstract Number: 5

Rheumatoid Arthritis and Periodontitis: Association and Characteristics of Chronic Periodontitis

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Background/Purpose: Recent clinical-epidemiological data suggest that periodontitis (P) shows higher prevalence in rheumatoid arthritis (RA) patients. However, due to the scarcity of epidemiological studies, the strength of association is limited, with odds ratios (OR) ranging from 1.82-8.05. The prevalence of P in the adult Spanish population[1] varies from 16 -30%,with a lower prevalence of severe P (5-11%). Nevertheless, the prevalence of P in Spanish RA patients is unknown. Our purpose is: 1.To determine the prevalence of P and its association in RA patients in our reference area.2.To describe the characteristics of P in RA patients.

Methods: Observational, descriptive, cross-sectional, case-control study of RA patients > 18 years old (ACR/EULAR 2010) in a hospital Rheumatology Department, and a control group with non-inflammatory joint disease, who had at least 4 teeth, had not received dental prophylaxis or antibiotics 6 months before the study. Socio-demographic and anthropometric variables included were body mass index, smoking status, Graffar scale, stress level, annual dental prophylaxis, and co-morbidities such as osteoporosis (OP), diabetes mellitus (DM), dyslipidemia (DS), arterial hypertension, ischemic cardiovascular disease (ICD). Periodontal Variables: plaque index (PI), bleeding on probing (BoP), probing pocket depth (PPD), recession (REC), clinical attachment level (CAL). The dental team: 2 periodontists, 2 general dentists and 1 dental hygienist with inter-observer variability<30%. Full mouth CAL, PPD and periapical x-rays were taken. CAL was classified according to the European Workshop in 2005 (Tonetti),into level 0 (absence), TL1 (mild), TL2 (severe).Statistical analysis with Stata 13.1 using Student´s t test , Kruskal Wallis and Chi-square test.

Results: 344 patients were included: 187 RA (147 F/40 M) and 157 controls (101F/56M). The two groups were similar in age 54.9 (17.9), BMI 27.8 (4.6), stress level, DM and ICD and different in gender (>nº of males in controls), socioeconomic status (lower level in RA patients), > nº of current and former smokers in the RA group (19.25%vs 8.92%/ 24.6%vs 11.46%),OP (23.45% RA vs 7.8%), DS (hypertriglyceridemia) 11.23% RA vs 4.46% in controls. 182/187 RA patients had P (97. 33%) vs 104/157 (66.24%) with P in controls. Regarding severity P: TL1 in 52.41% RA vs 54.14%;TL2 in 44.92% RA patients vs 12.1% in controls (p<0.001), OR 18.55 (CI 95% 7.18-47.87),which was maintained after adjusting for confounders: OR 16.25 + 9.29 (95% CI 5.23 – 49.86). Moreover, RA patients had poor periodontal status with a dramatic increase in all periodontal parameters: PI, PPD, nº and percentage of PPD ≥5mm and BoP (p<0.001) compared with the control group.

Conclusion: 1.Our study showed a strong association between RA and periodontitis with an adjusted OR 16.25. 2. The prevalence of severe periodontitis was significantly greater in RA patients than controls or the general population. 3. There were no differences in the prevalence of mild periodontitis between groups. 4. With respect to severity, RA patients showed more severe periodontitis than controls. **References:** 1Bravo-Pérez M C-PE. Encuesta de salud oral en España

2005.RCOE.11(4):409-56.

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Abstract Number: 6

Lower Omega-3 Fatty Acid Biomarkers Are Associated with Inflammatory Arthritis in a Population Positive for Anti-Citrullinated Protein Antibodies

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Background/Purpose: Antibodies to citrullinated protein antigens (ACPA) can be elevated prior to onset of inflammatory arthritis (IA) and RA. However, understanding of factors related to development of ACPA, or transition from ACPA+ to clinically-apparent IA is limited. Omega-3 fatty acids (n-3 FA) have immunomodulating properties. In subjects at-risk for developing RA, we found higher levels of n-3 FA percentage in red blood cells (n-3 FA % in RBCs) were associated with a lower prevalence of positivity for ACPAs and rheumatoid factor (RF), suggesting n-3 FAs may be protective against development of autoantibodies. However, the relationship between n-3 FAs and IA in ACPA+ subjects remains unknown.

Methods: At Colorado-based health fairs from 2008-2014, subjects without a previous diagnosis of RA were tested for serum ACPA using the commercial assay anti-cyclic citrullinated peptide 3 (Inova), and were recruited for follow-up research study visits. At their baseline study visit, they underwent symptom assessment and joint examination; the presence of IA and RA by 2010 criteria was established. Blood was also drawn to measure n-3 FA % in RBCs, a biomarker that reflects the average n-3 FA levels over the preceding ~2 months. The relationship between IA and RBC n-3 FA% was assessed using logistic regression.

Results: Fifty-two ACPA+ individuals without a prior diagnosis of RA were identified at health-fairs and agreed to participate in a follow-up baseline study visit; 41 were without IA, and 11 had IA that was previously undiagnosed (none were on disease modifying therapy). Subjects with IA at baseline were more likely to be smokers and report taking n-3 FA supplements, and test positive for RF and C-reactive protein (Table 1). Increasing total n-3 FA and DPA levels in RBCs (an n-3 FA generally synthesized through physiologic processes and not dietary) were associated with significantly lower odds of IA at baseline, adjusting for > 10 pack years and n-3 FA supplement use (both of which met confounding criteria) (Table 2).

Table 1: Demographic and descriptive characteristics of participants positive for inflammatory arthritis compared to those who were not positive for inflammatory arthritis at the baseline study visit.

Variable	IA at Baseline: Yes (n = 11)	IA at Baseline: No (n = 41)	p-value
Age (mean ± SD)	56.5 ± 10.0	55.6 ± 10.3	0.80
Female n (%)	9 (81.8)	22 (53.7)	0.17
Non-Hispanic White n (%)	8 (72.7)	33 (80.5)	0.65
Education > High School n (%)	9 (81.8)	36 (87.8)	0.63
BMI (mean ± SD)	28.3 ± 6.4	26.9 ± 4.8	0.43
Ever Smoke Yes n (%)	9 (81.8)	18 (45.0)	0.04
Current Smoker Yes n (%)	3 (27.3)	2 (5.0)	0.06
Pack Years > 10 n (%)	5 (45.5)	8 (19.5)	0.12
Omega-3 Fatty Acid Supplement Use n (%)	9 (81.8)	19 (46.3)	0.04
Shared Epitope Positive n (%)	7 (63.6)	18 (43.9)	0.24
RF Nephelometry Positive n (%)	6 (54.5)	5 (12.2)	<0.01
C-Reactive Protein Positive n (%)	6 (54.5)	9 (22.0)	0.06

Table 2: Inverse association between omega-3 fatty % in red blood cells and baseline **presence of inflammatory arthritis**.

n-3 FA % in RBC	Odd Ratio	95% CI	p-value
Alpha-linolenic acid (ALA;18:3n-3)	2.35	0.85 – 6.51	0.10
Eicosapentaenoic acid (EPA; 20:5 n-3)	0.28	0.06 – 1.24	0.09
Docosapentaenoic acid (DPA; 22:5n-3)	0.14	0.04 – 0.54	<0.01
Docosahexaenoic acid (DHA; 22:6n-3)	0.51	0.22 – 1.22	0.13
EPA+DHA	0.45	0.15 – 1.02	0.09
Total n-3 FA (summed ALA, EPA, DPA, DHA)	0.30	0.10 – 0.92	0.04

Models adjusted for sex, pack years ≥ 10, and n-3 fatty acid supplement use. IA at baseline IA n = 11; No IA at baseline n = 41. Odds ratio is for a one standard deviation increase in n-3 FA% in RBC.

Conclusion: We found that lower levels of n-3 FAs in individuals were associated with IA in this unique population of ACPA+ individuals. These extend our prior work by suggesting that in addition to having a potentially protective effect against autoimmunity, n-3 FAs may also be important in the transition to IA once an individual is ACPA+. Our findings support the potential beneficial role of n-3 FAs in the preclinical state in RA, not only in decreasing the risk of developing ACPA and RF but also potentially decreasing the transition from an ACPA+ state to IA, findings which warrant further investigation.

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Abstract Number: 7

Long-Term Dietary Changes after Rheumatoid Arthritis Diagnosis in Swedish Women: Data from a Population Based Cohort

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Background/Purpose:

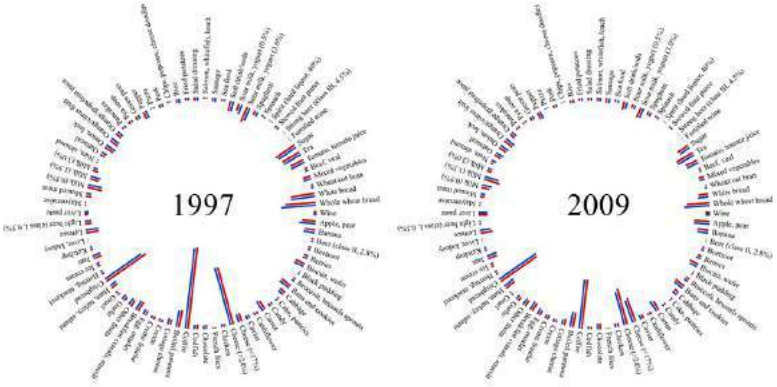
The interest of dietary factors in rheumatoid arthritis (RA) has increased among researchers and RA patients over the last decade. Although several interventions as well as epidemiological studies of dietary aspects have shown benefits for RA disease course, there is still a lack of specific dietary recommendations for RA. We hypothesized that women who have been diagnosed with RA change their diet in order to improve their disease status. The aim of this study was to investigate the long-term changes in diet after RA diagnosis in Swedish women.

Methods:

This study included primarily 22,007 women from the Swedish Mammography Cohort (SMC). These women were asked to complete two food frequency questionnaires (FFQ), in 1997 and 2009. In 2003, the SMC was linked to the Swedish Rheumatology Quality register (SRQ) and the Outpatient Register in order to track incident RA cases and provide clinical data. During the period from 1997 to 2009, 380 women were diagnosed with RA. Women who did not complete the FFQ in 1997 and/or 2009 were excluded (n=249). Dietary changes after RA diagnosis were analyzed based on the frequency intake of 82 food items in 1997 and 2009, with two approaches; linear mixed models (191 RA cases versus 21,567 non-RA cases) and hierarchical cluster analysis (191 RA cases versus 573 matched controls (non-RA cases)).

Results:

The majority of the 82 food items did not significantly differ in intake between RA and non-RA cases in 1997 and 2009. RA cases had significantly decreased intake of three and four food items in 1997 and 2009, respectively. (Figure)



Intake (times/week) in 1997	Non-RA	RA	p value
Wheat/oat bran	0.70	0.49	0.008
Blackpudding	0.35	0.28	0.027
Apple, pear	4.41	3.64	0.003

Intake (times/week) in 2009	Non-RA	RA	p value
Low-fat milk	2.52	1.96	0.045
Oatmeal	2.17	1.82	0.049
Fried potatoes	0.70	0.56	0.002
Beer, up to 3.5% alcohol	0.21	0.14	0.049

Results from mixed models showed that the dietary intake changed significantly from 1997 to 2009 for 44 (53.7%) food items in RA cases and 82 (100%) food items in non-RA cases. Both RA and non-RA cases increased/decreased their intake of all the food items in the same manner. Dietary changes between RA and non-RA cases were not significant for 79 (96.3%) food items, the very few significant differences were intake of whole wheat bread, rice and wheat/oat bran. Non-RA cases increased their intake of these three food items more than the RA cases. (Table)

Food item	Times per week 1997→2009 (mean ± SD) RA (n=191)	Non-RA (21,567)	p value
Whole wheat bread	6.80 ± 0.45	7.75 ± 0.04	0.037
Rice	0.81 ± 0.06	0.94 ± 0.01	0.034
Wheat/Oat bran	0.38 ± 0.11	0.62 ± 0.01	0.028

The hierarchical cluster analysis did not identify any meaningful clusters based on the total intake of all food items which did not allow comparison of dietary pattern changes over time between RA cases and controls.

Conclusion:

This study showed that women who had been diagnosed with RA had similar changes in dietary patterns over time as the general population, and did not change their diet due to their disease. Based on earlier evidence on the advantages of improved nutritious diet in RA, specific dietary recommendations for patients with RA are needed.

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Abstract Number: 8

What Factors Relate to Patients Contributing Longitudinal Data Using Smartphone Technology? Findings from RA Patients Participating in Arthritispower Registry

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Background/Purpose: Data capture of patient reported outcomes (PROs) is gradually shifting from data collection on paper in medical office to use of computer or mobile based technologies between doctor visits. Concerns have been raised that patients may have limited interest in contributing data over time, or that they may only record new data when there has been a change in their clinical status. We evaluated the patterns and factors associated with longitudinal PRO data capture among participants in the PCORI-funded Patient Powered Research Network for adult rheumatologic conditions, ArthritisPower.

Methods: Patients in the registry were asked to voluntarily complete PROs including the RAPID3 and 4 PROMIS instruments (pain interference, physical function, fatigue, and sleep disturbance) plus disease-specific information via a mobile application (App) on their smartphone or computer. We evaluated the average time assessment it took patients to

record each of the instruments and the total number of unique days that patients recorded PROs. Given the newness of the registry (launched late 2015), longitudinal data was defined as contributing at least 2 sets of PROs on unique calendar days. We tested the hypothesis that patients would contribute longitudinal data only when at least one of their scores exceeded a minimally important difference (MID) of any of the 5 PROs examined (generally 2-3 units for PROMIS instruments; 3.6 units for RAPID3). Demographic factors associated with multiple PRO reports were identified using logistic regression among patients who had been enrolled in the registry for at least 3 months.

Results: At the time of analysis, ArthritisPower had recruited 2,103 patients, most (approximately 68%) had RA, and 20% provided their Twitter handle. Average (SD) age was 50 (12); 87% were women. The mean assessment time for each of the PROMIS instruments ranged from a low of 16 seconds (sleep disturbance) to a high of 105 seconds (RAPID3). The average score for pain interference was 64.3 (SD: 6.3), physical function 37.5 (6.5), sleep disturbance 59.3 (8.4), fatigue 64.2 (8.4), and RAPID3 15.7 (5.3). Of 1,946 patients who registered the Smartphone App more than 3 months prior to analysis, 20.6% never contributed any PRO information, 53.3% answered once, and 26.1% answered at least twice. Among patients with longitudinal data (>=2 assessments), the mean change score of PROs between pairwise PRO assessments was <1 point for all instruments (Table). Only 23.1% of patients contributing longitudinal data had a change greater than the MID in any of the 5 PRO measures. Patients with RA (OR: 1.54, 95% CI: 1.14-2.06), biologic use (2.12, 1.43-3.15), and those with Twitter accounts (1.40, 1.08-1.82) were more likely to contribute longitudinal PRO data in the absence of regular reminders.

Conclusion: Multiple factors were associated with patient willingness to contribute longitudinal PRO data. Importantly, some patients were willing to contribute longitudinal PRO data even without a change in their health state exceeding any MID and without physicians' requests. Additional efforts are needed to engage patients to contribute PRO data over time, and to maximize patient engagement.

Tables: Mean change between 1st and 2nd visit among patients with longitudinal data

	Mean Change from 1st to 2nd Visit	**Absolute mean change from 1st to 2nd Visit**	**% of patients exceeding change > MID**
PROMIS Physical function	-0.4 (3.8)	2.7 (2.7)	34.2%
PROMIS Pain Interference	-0.4 (5.4)	3.9 (3.6)	52.3%
PROMIS Sleep Disturbance	0.2 (6.1)	4.6 (4.0)	56.0%
PROMIS fatigue	-0.03 (6.6)	4.8 (4.4)	55.6%
RAPID3	0.2 (3.8)	2.8 (2.6)	29.8%
MID: Minimally important difference (3 points for PROMIS instruments and 3.6 for RAPID3)			

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Abstract Number: 9

Effects of Alcohol Consumption on the Severity of Inflammation in Hand and Foot Joints Detected with MR Imaging

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Background/Purpose: Moderate alcohol consumption is associated with a lower risk on RA development. (1,2) It is also associated with less severe systemic inflammation. Based on these data, we hypothesized that alcohol consumption is also associated with the severity of local inflammation in hand and foot joints at presentation of RA. Second, as symptom-free individuals also have a low degree of MRI-detected inflammation in MCP, wrist, and MTP joints (3), and because alcohol consumption is shown associated with C-reactive protein (CRP) levels in a J-shaped curve in the general population (4), we also supposed that alcohol consumption is associated with the severity of inflammation in small joints in symptom-free volunteers. The present large-scale MRI study was undertaken to evaluate these hypotheses.

Methods: MRI was performed at disease presentation in 171 RA-patients, included in the Leiden Early Arthritis Clinic (EAC) cohort and in 193 asymptomatic volunteers from the general population. Alcohol consumption was analysed as continuous measure and also categorized in four groups; non-drinkers, participants that consume 1-7 drinks/week, 8-14 drinks/week and >14 drinks/week and analysing a dose effect. A unilateral contrast-enhanced 1.5T MRI of MCP, wrist and MTP-joints was performed. Each MRI was scored by two readers on synovitis, bone marrow edema and tenosynovitis; the sum of these yielded the MRI inflammation score. Association of alcohol consumption with CRP was also evaluated. Kruskal Wallis test was used.

Results: Although a J-shaped curve was seen in the association between alcohol consumption and CRP level in RA-patients, with the lowest levels in patients consuming 1-7 drinks a week (p=0.037), alcohol consumption was not associated with the severity of MRI-detected inflammation of hand and foot joints at presentation with RA (p=0.55). Also within asymptomatic volunteers alcohol consumption was not associated with the severity of local inflammation in hand and foot joints (p=0.33).

Conclusion: Despite the facts that other have shown that moderate alcohol consumption is protective to RA development and associated with less systemic inflammation in the general population, and that our data confirms a J-shaped association of alcohol consumption with CRP-levels in RA, there is no association between alcohol consumption and the severity of inflammation in hand and foot joints. The pathophysiological mechanism of the protective effect of alcohol is not well understood but the present data suggest that local inflammation is not involved. References: 1. Jin Z, Xiang C, Cai Q, Wei X, He J. Alcohol consumption as a preventive factor for developing rheumatoid arthritis: a dose-response meta-analysis of prospective studies. *Ann Rheum Dis*2014;73:1962–1967. 2. Scott IC, Tan R, Stahl D, Steer S, Lewis CM, Cope AP. The protective effect of alcohol on developing rheumatoid arthritis: a systematic review and meta-analysis. *Rheumatology*2013;52:856–867. 3. Mangnus L, Steenbergen H w. van, Reijnierse M, Helm-van Mil A h. m. van der. MR-detected features of inflammation and erosions occur in symptom-free persons from the general population. *Arthritis Rheumatol*2016:n/a-n/a. 4. Imhof A, Froehlich M, Brenner H, Boeing H, Pepys MB, Koenig W. Effect of alcohol consumption on systemic markers of inflammation. *The Lancet* 2001;357:763–767.

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Abstract Number: 10

The Utility of Screening for Infectious Diseases in Recipients of Anti-TNF-α Therapy

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The Utility of Screening for Infectious Diseases in Recipients of Anti-TNF-α Therapy _ Choi, Kristal, Mertz, Lester, Heigh, Russell, Yiannias, James, Blair, Janis

Background/Purpose: Tumor necrosis factor-α inhibitors (TNF-I) are commonly used today to treat a wide variety of immune-mediated disorders. These medications are linked with an increased risk of mycobacterial, viral, and fungal infections, and some society guidelines recommend screening for tuberculosis (TB), hepatitis B (HBV) and C (HCV), human immunodeficiency virus (HIV), and active life-threatening fungal infections. The aim of our study was to determine the number of patients with infectious diseases identified on screening; and to describe what evaluation, treatment, and follow-up transpired for these individuals.

Methods: We electronically searched for all patients receiving TNF-I from 9/4/2010 to 4/22/2015. The records for patients screening positive for HBV, HCV, TB, and HIV were then reviewed in detail.

Results: 2218 individuals received TNF-I during the study period. 656 patients had at least one of the following laboratory tests checked: hepatitis B surface antibody (HBsAb), hepatitis B surface antigen (HBsAg), and hepatitis B core antibodies (HBc total Ab). Of these, 37 (5.6%) were positive for HBsAb only, 1 (0.1%) was positive for HBsAg only, 3 (0.5%) were positive for HBc total Ab only, and 5 (0.8%) were positive for both HBsAb and HBc total Ab. One patient had a known history of chronic HBV prior to the initiation of a TNF-I, and one patient was tested due to the development of symptoms only. Thus, there were 7 (1.0%) new diagnoses of HBV diagnosed by screening. All 7 cases were maintained or eventually started on their TNF-I. One case received treatment with lamivudine when started on a TNF-I. 662 patients were tested for HCV via antibody test, and 2 (0.3%) were found to be positive on pre-screening. Follow-up RNA testing was negative in one case and positive in the other. The latter patient was referred to Hepatology, and the initiation of the TNF-I was delayed due to the new diagnosis. 557 were tested for TB via the QuantiFERON-TB Gold In-Tube assay, and 13 (2.3%) were positive. After excluding patients who had a known history of latent TB and those who were tested due to the development of symptoms only, there were a total of 7 (1.3%) new diagnoses of TB found on screening. Five (71.4%) cases were diagnosed with latent TB, and were appropriately treated. TNF-I was initiated in 4/5 cases after > 1 month of treatment with isoniazid. Two positive assays found on pre-screening were thought to be false positives, and TNF-I was initiated with no TB treatment. Two patients were screened for HIV with an antigen and antibody combination assay, and both were negative.

Conclusion: Few new cases, and no active cases, of HBV, HCV, TB, and HIV are identified in recipients of TNF-I therapy during routine screening.

	HBV	HCV	TB	HIV
Total number screened	656	662	557	2
Total new cases diagnosed on screening (%)	7 (1.0%)	2 (0.3%)	7 (1.3%)	0 (0%)
Pre-screening	4	2	5	0
Annual screening	3	0	2	0
TNF-I delayed or held	0	1	4	0
Treatment initiated for infection	1	0	5	0
Sub-specialty referral	6	1	7	0

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Abstract Number: 11

Drug Prescribing Trends in Adults with Rheumatoid Arthritis: A Population-Based Comparative Study from 2005-2014

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Background/Purpose: To examine drug prescribing trends for patients with rheumatoid arthritis (RA) over recent years and compare them to matched non-RA subjects.

Methods: Retrospective prescription data were examined from 2005-2014 in a population-based cohort of patients with RA and comparable non-RA subjects. Index date was 1/1/2005 for both cohorts. Drugs for or related to the treatment of RA were excluded. Comparisons between cohorts of percentages of patients with at least 1 prescription in a specific drug category/class were performed using Poisson regression models adjusted for age and sex.

Results: A total of 497 patients with RA (71% female) and 527 non-RA comparator subjects (70% female) were included in the study. Median age at index for RA and non-RA subjects was 61 years (range 25-95) and 63 years (range 26-95), respectively. Among the patients with RA, the median duration of RA at index was 7.5 years (range 0 to 24.8). Median time from index to last follow-up for both cohorts was 9.9 years. Comorbidities prior to index were similar among both cohorts with notable exceptions of peptic ulcer disease (13% non-RA vs 19% RA; p=0.006) and peripheral vascular disease (12% non-RA vs 19% RA; p=0.006). Former and/or current smoking was more common among patients with RA (55%) compared to non-RA (46%; p=0.018). The overall observed percentage of subjects who were prescribed at least 1 drug over the ten-year period was somewhat higher among the RA compared to non-RA subjects (relative risk [RR]: 1.04; 95% confidence interval [CI]: 0.99, 1.08). Over the study period, both cohorts demonstrated significant increases in the percentages of patients with at least 1 prescription (7% increase over 10 years in RA, p<0.001; 11% increase in non-RA, p<0.001). Drugs that were more common among RA than non-RA subjects included antimicrobials (50% RA vs 41% non-RA in 2014; RR: 1.24), calcium metabolism modifiers (10% RA vs 6% non-RA in 2014; RR: 1.78), thyroid hormone replacement therapy (23% RA vs 19% non-RA in 2014; RR:1.21), antidepressants (34% RA vs 27% non-RA in 2014; RR: 1.12), antiasthma/inhaled glucocorticoids (RR: 1.21), proton pump inhibitors (28% RA vs 18% non-RA in 2014; RR: 1.45), anti-ulcer (RR: 1.58), contraceptives (5% RA vs 2% non-RA in 2014; RR: 1.69), anti-hypertensives (55% RA vs 49% non-RA in 2014; RR: 1.11) and some others. Prescription drugs that were less common in RA than non-RA were statins (29% RA vs 35% non-RA in 2014; RR: 0.83) and other antilipemic drugs (RR: 0.56). Use of pregabalin/gabapentin (RR: 1:18; 95%CI: 0.98-1.44) and ophthalmic (RR: 1.10; 95%CI: 0.97-1.24) drugs was not statistically different between those with RA and non-RA subjects.

Conclusion: There was a marked overall increase in prescriptions drugs for both RA and non-RA cohorts over the study period with some prescribing patterns differing between the cohorts. RA patients, at higher risk for cardiovascular events, were consistently prescribed less statins and non-statin antilipemic and were regularly prescribed more proton pump inhibitors than non-RA comparators. The clinical implications of these differences in prescribing patterns require further evaluation.

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Abstract Number: 12

Benefit of Early Therapy with Methotrexate and Prednisone in Patients with Early Rheumatoid Arthritis and Undifferentiated Early Arthritis (CONAART)

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Background/Purpose: To analyze clinical remission in patients with early RA and undifferentiated arthritis (UA) during the first 2 years of treatment using methotrexate (MTX) and prednisone.

Methods: Database included patients diagnosed with early RA, less than 2 years of evolution. Patients were divided into 3 groups according to when the treatment was started 0-3 months, >3-6 months or >6 months of onset of symptoms. Descriptive statistics were applied to each of the variables Student’s t-test and the chi-squared test were applied and Fisher’s exact test was used where necessary. Univariate analysis was performed using Mann Whitney test and Multivariate logistic regression models were used to measure the association with remission defined by DAS 28, SAI, CDAI, and ACR/EULAR scores. A value of $p \leq 0.05$ was considered significant.

Results: Of 2078 included patients, 442 were available for the intent-to-treat analysis (ITT). 83% were women with mean age 52.74 years (SD 14.05) and a median duration of symptoms of 6.5 months (IQR 3.0–12.0) by the time they entered into the study. Of the total, 303 (68.6%) had RA (ACR 1987) and 139 (31.4%) UA. ESR 35.15 mm/h (IQR15-48.75), CRP 16.77 mg/dl,(IQR 0.5 to 11.51), positive RF in 275 (62.2%) patients. The clinical characteristics at baseline were: HAQ 1.17 (IQR 0.5-1.75), DAS 28 5.14 (SD 1.32), CDAI 25.98 (IQR 15-35), IAS 28.68 (IQR 18.42-38.57), hands SENS 8.34 (IQR 2-13), feet SENS 2.64 (IQR 0-4). During the study, 415 (93.9%) received MTX (average dose 15mg/week) and prednisone (average dose 7.97 mg/day) in 410 (99.8%) patients. MTX and prednisone were initiated with a mean at 8.83 (IQR 3-13) months and 7.55 (IQR 2-12) months, respectively, from the onset of symptoms. The patients who reached remission at some point in 2 years follow-up measured by DAS 28 were in 305 (69%), by IAS in 288 (65.2%), by CDAI in 255 (57.7%) and by ACR/EULAR score in 224 (50.7%) patients. Table 1 and 2 show higher remission percentages in a group of patients were treated with combination therapy with MTX and prednisone, especially in those who the onset of symptoms was before 6 months of evolution of the disease. In multivariate analysis, patients treated with MTX achieved remission at some point the follow up with DAS28 (OR 3.88, 95%CI 1.66-9.06, p=0.002), IAS (OR 2.98, 95%CI 1.50-5.88, p=0.002), CDAI (OR 3.00, 95%CI 1.57-5.72, p=0.001), ACR/EULAR score (OR 2.80, 95%CI 1.49-5.25, p=0.001) and lower HAQ at baseline in those who had less 3 months from the onset of symptoms. Table 1: Remission percentages in patients who received combined treatment with MTX and prednisone. Univariate analysis.

Remission	MTX/Prednisone (NO) n (%)	MTX/Prednisone (YES) n (%)	P
DAS 28 < 2.6	93 (60.0%)	212 (73.9%)	**0.004**
SAI < 5.5	87 (56.1%)	201 /70.0%)	**0.005**
CDAI < 2.8	81 (52.3%)	174 (60.6%)	0.11
ACR/EULAR	65 (41.9%)	159 (55.4%)	**0.007**

Table 2. Remission by the different scores depending on the time of treatment start from the onset of symptoms. Univariate analysis.

Remission	MTX/Prednisone 0-3 months n (%)	MTX/Prednisone >3-6 months n (%)	MTX/Prednisone > 6 months n (%)	P
DAS 28 < 2.6	87 (73.7%)	70 (76.8%)	128 (63.7%)	**0.04**
SAI < 5.5	87 (73.7)	67 (70.5%)	121 (60.2%)	**0.03**
CDAI < 2.8	82 (68.9%)	60 (63.2%)	100 (49.8)	**0.02**
ACR/EULAR	74 (62.2%)	56 (58.9%)	85 (42.3%)	**0.01**

Conclusion: Early treatment with MTX and prednisone is associated with greater opportunities to reach remission.

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Abstract Number: 13

Genetic Variants of the Vasoactive Intestinal Peptide (VIP) Gen in Association with Rheumatoid Arthritis Treatment Requirements

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Background/Purpose: Biomarkers to recognize patients with a more intensive therapy necessity in rheumatoid arthritis are essential and scarce. VIP has shown immunoregulatory properties both *in vivo* and *ex vivo* in human and murine cells. We recently reported that low VIP serum levels are associated to a worse clinical course in patients with early arthritis. We aim to validate the association of genetic variants of VIP to its serum levels in a new cohort of early arthritis patients and to associate those variants with treatment requirements.

Methods: Princesa Early Arthritis Register Longitudinal (PEARL) study includes patients with early arthritis (EA). Demographic, clinical, laboratory, therapeutic, radiological data and biological samples are systematically collected

along follow-up (baseline, 6, 12, 24 and 60 months). We carried out the study in two phases with two different sets of patients from the PEARL register after a preliminary screening, as follows: *Screening* VIP serum levels were measured by Enzyme-Immunolinked-Assay (EIA, Martinez et al. 2014) in a set of EA patients. From that set, 11 patients with high and 9 patients with low VIP serum levels were selected for sequencing of VIP gen. Amplification and sequencing was performed using BigDyeDirect sequencing kit (Applied Biosystems) and were analyzed by capillary electrophoresis on a 3500xL genetic Analyzer (Applied Biosystems). 16 single nucleotide polymorphisms (SNPs) were selected due to its differential distribution in patients with extreme VIP levels. *Discovery and Validation Phases* Genetic variants selected by sequencing were genotyped in 93 EA patients for the discovery phase of the study and 131 EA patients for the validation phase, using pre-designed SNP Genotyping Assays (Applied Biosystems). In both sets of patients VIP serum levels were measured by EIA. We used the backward-stepwise selection to fit several multivariate models by generalized estimating equations for repeated measures after previous bivariate analysis to determine the adjusting variables. Statistical analysis was performed using Stata 12 for Windows (StataCorp PL, College Station, TX, USA).

Results: We found that patients with CC genotype of the SNP rs688136 had higher serum VIP levels either in the discovery and validation populations, as well as in the meta-analysis of both sets (p=0.033, p=0.007 and p=0.004, respectively). This effect was impaired by the presence of minor alleles of rs35643203 and/or rs12201140, which had a clear trend towards the association with low serum VIP levels (p=0.118 and p=0.049 respectively). We also observed a significant correlation between the combination of the different alleles of those SNPs and the treatment intensity. Patients with CC genotype of rs688136 and no minor alleles of the two other polymorphisms required less treatment than those who had the CC genotype but at least one of the minor alleles (p=0.022).

Conclusion: In two populations of patients of the PEARL study a combination of genetic variants of VIP associated with VIP serum levels are also associated with the requirements of treatment of those patients.

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Abstract Number: 14

Failure Predictors to Anti-Tumor Necrosis Antagonists in Patients with Chronic Arthritis: Results of a National Registry Biobadasar

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Background/Purpose: to analyze failure predictors to anti-tumor necrosis (TNF) therapy in patients who have switched these drugs during chronic arthritis treatment.

Methods: BIOBADASAR is a national registry from Argentina. Patients with Autoimmune Rheumatic Diseases are included with appropriate diagnostic criteria and different forms of chronic arthritis who are treatment with biological drugs (bDMARDs). A control population matched for diagnosis and demographic features, free of bDMARDs therapy is included. Using this registry, we have analyzed patient switching of TNF antagonists. The log-rank test was used to compare survival curves, and Cox regression models were used to assess independent factors associated with discontinuing medication.

Results: From August 2010 to January 2016, 3397 patients were registered with: RA 2745 (78.6%), PsA 395 (11.3%), JIA 150 (4.3%), AS 107 (3.07%); mean age: 57.1±14.8 yrs; 78.4% female. 1853/3397(54,5%) patients received a total of 2079 treatment cycles: Etanercept (ETA) was used in 1155 (55.6%), adalimumab (ADA) in 601 (28.9%), infliximab (INF) in 156 (7.5%), certolizumab in 118 (5.7%) and golimumab in 49 (2.4%). More than one anti TNF was used in 1520/1853 (82%) patients. The median survival time of TNF antagonists was 36 (range, 1-243) months. TNF antagonists were discontinued in 890 (42.8%) cycles. The reasons for discontinuation were inefficacy in 350 (39.3%), adverse events in 274 (30.8%), lack of drug provision by medical insurance in 173 (19.4%), lost to follow-up in 57 (6.4%), pregnancy in 15 (1.7%), unknown reasons in 13 (1.59%) and disease remission in 8 (0.9%) patients. ETA was discontinued in 502/1155 (45.4%), mostly 117 (23%) due to lack of insurance payment ((p=0.001), INF was discontinued in 54 (51.9%) due to persistently active disease (p=0.005). Survival of the first TNF antagonist after one year of treatment was slightly higher for certolizumab (0.85 (95% CI 0.77-0.91) and ETA (0.82, 95%CI 0.80-0.84)) compared to golimumab (95%CI 0.80, 0.65-0.89), ADA (0.79, 95%CI 0.76- 0.82) and INF (0.77, 95% CI 0.69-0.84). Among patients with concomitant use of MTX, 65.7% (585) were discontinued vs not in 830 (69.8%) (p=0.045); corticosteroids were discontinued in 50.8% vs not in 34.9% ($p \leq 0.00001$). In a logistic regression model, predictors of discontinuation were: female (OR 1.59, 95% CI 1.26–2.00), ≥60 years old (OR 1.28, 95% CI 1.06–1.53), smoker (OR 1.51, 95% CI 1.11–2.05), use of corticosteroids (OR 1.97, 95% CI 1.62–2.38), INF (OR 8.73, 95% CI 5.17–14.7), ETA (OR 3.48, 95% CI 2.30–5.27) and ADA (OR 3.38, 95% CI 2.20–5.19). Concomitant use of MTX had a protective effect (OR 0.67, 95% CI 0.55–0.82).

Conclusion: We found higher rates of discontinuation of TNF antagonists in patients who used INF and ETA, including a higher frequency of discontinuation due to inefficacy in INF and lack of coverage by insurance in ETA. Specific analysis of failure predictors identified being a female, ≥60 years old, a smoker, and use of corticosteroids, INF, ETA and ADA as the main failure predictors of discontinuation of TNF antagonists in patients with chronic arthritis. On the other hand, the concomitant use of MTX had a protective effect.

Abstract Number: 15

Adverse Events and Persistency of Biologics in Rheumatoid Arthritis Patients with Interstitial Lung Disease

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Background/Purpose: Interstitial lung disease (ILD) is one of the most important extra-articular manifestations of rheumatoid arthritis (RA). The prevalence of RA associated ILD (RA-ILD) is reported as 1-58% depending on the study population and the definition of ILD, and RA-ILD is known to be associated with increased respiratory infection and higher mortality in RA patients. Recently, use of biologics is increasing; however, the safety and persistency of biologics in RA-ILD patients are not established. We aimed to compare the incidence of adverse events (AEs) and persistency of biologics in RA patients with or without ILD.

Methods: A total of 981 RA patients with chest radiograph or chest computed tomography (CT) data at enrollment were extracted from BIOlogics Pharmacoepidemiologic StudY (BIOPSY) cohort, a nationwide multicenter prospective inception cohort for biologic users of RA patients in Korea. We classified them into two groups: 1) RA-ILD group as patients with ILD, and 2) RA-non ILD group as patients without ILD detected by chest radiograph or CT. We compared the incidence of AEs including respiratory infection and mortality during use of biologics between two groups, and then tested the differences of drug discontinuation rates due to AEs, infection, and respiratory infection between RA-ILD and RA-non ILD groups using Kaplan-Meier survival analysis and log-rank test. In addition, crude and multivariable Cox proportional hazard model were used to identify the impact of ILD on AEs in RA patients with biologics.

Results: The 42 patients (4.3%) revealed to have RA-ILD by chest radiograph or chest CT, and the rest of 939 patients were included in RA-non ILD group. Patients in RA-ILD group were older (62.6 ± 9.6 vs. 51.8 ± 13.2 years, $p<0.01$), and male patients were more in RA-ILD group (31.0% vs. 13.3%, $p<0.01$). During mean follow-up of 20 months with 1,611 person years (PY), the incidence of AEs was higher in RA-ILD group compared with RA-non ILD group (IRR 1.55, CI 1.11-2.17). In addition, the incidence of infection and respiratory infection were higher in RA-ILD group (IRR 2.38, CI 1.32-4.30 for infection, IRR 3.00, CI 1.50-5.99 for respiratory infection, respectively). The biologics discontinuation rate due to AEs was comparable in two groups ($p=0.13$), whereas the biologics discontinuation rate due to infection ($p=0.03$) and respiratory infection ($p<0.01$) were significantly higher in RA-ILD group. After adjusting for variables, age (HR 1.27, CI 1.15-1.41) and having ILD (HR 10.77, CI 2.26-51.41) were risk factors for mortality in RA patients with biologics.

Conclusion: The incidence of adverse events, especially respiratory infections were higher in RA-ILD patients with biologics compared with RA-non ILD patients. In addition, the biologics discontinuation rate due to infection, especially respiratory infection was significantly higher in RA-ILD patients. Concerning the mortality, ILD increased the mortality in RA patients with biologics.

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Abstract Number: 16

Differences Between Patient and Physician Global Assessment on Rheumatoid Arthritis Disease Activity Status in High and Lower Income Countries Contribute to Inequity

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Background/Purpose: Rheumatoid arthritis (RA) patients score their global disease activity (ptGD) on average higher than physicians (phGD). This difference can vary between countries with high and lower gross national income (GNI). Also, patients with RA in lower GNI countries have less access to biologic disease modifying anti rheumatic drugs (bDMARDs) and synthetic (cs)DMARDs. With targeted treatment aiming at low disease activity (LDA) or remission, this could influence treatment. The aim was to compare differences between ptGD and phGD in high and lower GNI countries and to assess if potential differences are associated with disease activity measures.

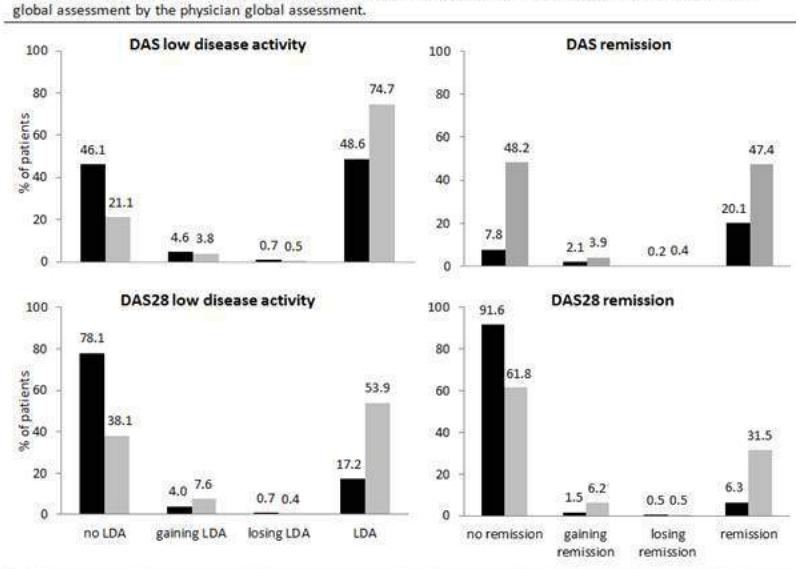
Methods: RA patients included in the METEOR database were selected from countries ≥30 patients with >1 visit, available phGD and disease activity score (DAS) or DAS28. Countries were divided in high and lower GNI (World Bank definition, high income GNI per capita ≥$12746). ptGD and phGD were measured on a 100 mm visual analogue scale (100 worst score). A difference ≥20 mm between ptGD and phGD (GDdif=ptGD–phGD) was considered clinically relevant. Susequently, ptGD was artificially substituted by phGD in the DAS and DAS28, in order to assess the potential influence of the discrepancies in globals on the number of patients in LDA or remission.

Results: From high GNI countries 6928 patients were included, from lower GNI countries 5136 patients. DAS was available in 10420 patients (6179 from high GNI countries), DAS28 in 11173 patients (6839 from high GNI countries). Patients from lower GNI countries had higher disease activity [mean (SD) DAS28 4.6 (1.8) vs 3.4 (1.8); DAS 2.5 (0.9) vs 1.8 (0.9)], longer disease duration at diagnosis [55 (69) vs 27 (59) weeks] and less often reached LDA [DAS28 49% vs 75%; DAS 20% vs 48%] or remission [DAS28 7% vs 32%; DAS 20% vs 48%] than patients from high GNI countries. Compared to high GNI countries, in lower GNI countries, more patients had a GDdif ≥20mm with ptGD>phGD (44% vs 30%) and fewer patients had a GDdif <20mm (47% vs 67%). Also, more patients had a GDdif ≥20mm with ptGD<phGD (9% vs 3% in lower vs high GNI countries). Replacing ptGD by phGD resulted in a mean (SD) change in DAS and DAS28 of 0.09 (0.1) and 0.4 (0.6) in high GNI countries and 0.9 (0.1) and 0.4 (0.7) in lower GNI countries. For both DAS and DAS28, the percentage of patients changing disease activity status is low in all countries, with most patients gaining LDA or remission (fig 1).

Conclusion: Compared to high GNI countries, patients from lower GNI countries had higher disease activity and less often reached LDA or remission. Clinically relevant differences between ptGD and phGD were found in more than 1/2 of the patients in lower GNI countries and in 1/3 of the patients in high GNI countries, with potentially more impact on disease

activity assessments in lower GNI countries than in high GNI countries. These results give further support to observations that access to 'good RA care' is worse in lower than higher GNI countries (inequity).

Figure 1: Percentage of patients changing DAS and DAS28 disease activity status after replacement of the patient global assessment by the physician global assessment.



Black bars represent lower gross national income countries: Brazil, India, Mexico and South-Africa. Grey bars represent high gross national income countries: Czech Republic, Spain, France, United Kingdom, Greece, Ireland, Italy, Netherlands, Portugal, Qatar and United States. Outer bars describe patients not changing disease activity status. The inner two bars describe patients changing disease activity status. LDA = low disease activity.

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Abstract Number: 17

The Importance of Achieving Clinical Response to Treatment and Changes in Physical Ability and Quality of Life on Worker Productivity Outcomes in Rheumatoid Arthritis: Results from the British Society for Rheumatology Biologics Register

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Background/Purpose: It is well known that patients with RA experience health-related job loss, more days absent from work (i.e., absenteeism), and to a greater extent, a decrease of at-work productivity (i.e., presenteeism). However, little is known about the effect of biologic treatments on absenteeism and presenteeism. The aim of this study was to investigate whether achieving clinical response to treatment, and changes in physical ability and quality of life (QoL) during the first six months predict absenteeism and presenteeism at one year in patients commencing treatment with biologic therapy for RA.

Methods: Patients recruited to the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) commencing biologics for RA and in full or part-time paid employment at inclusion were included in this study. DAS28, HAQ, and QoL (EQ-5D) were measured at baseline, six months, and 1 year. Patients were categorised into good/moderate vs. poor responders according to the EULAR response criteria at 6 months. Changes from baseline in physical ability and QoL at 6 months were calculated. Absenteeism in the last month, and presenteeism (*0=no interference – 10=complete interference)*, were measured at all three time points using the RA specific Work Productivity Survey (WPS-RA). Due to excessive zero values in the WPS-RA, zero inflated negative binomial regression (ZINB) was used to assess whether treatment response, HAQ and EQ-5D changes at six months predicted absenteeism and presenteeism at one year.

Results: Since most patients were still in employment at 1 year (work disabled n=4), data on 263 patients with baseline and 1 year WPS-RA were used. The mean age was 51 years (SD 8.6), median disease duration was 6 years (IQR 3-13); 78% were female. At baseline, median [IQR] scores were: DAS28 5.8 (5.3-6.4), HAQ 1.3 (0.6-1.6) and EQ-5D 0.6 (0.5-0.7). At baseline, 21% reported ≥1 days absent from work, and the median presenteeism score was 3.0 (IQR 0-5). Presenteeism scores significantly improved over 1 year (median 1.0 [IQR 0-4], Kruskal-Wallis Test: $H(2) = 18.70$, $p<0.001$), as did absenteeism (17% reported ≥1 days absent) although a Chi-square test demonstrated this to be non-significant. Compared to non-responders, EULAR good/moderate responders were 2.8x more likely to be classified in the zero group for presenteeism at 1 year, (OR 2.89, [95% CI 0.99, 8.50], *p=.0.05*), and although non-significant there was a trend towards increases in HAQ at 6 months resulting in lower probability of being in the zero group presenteeism at 1 year ($p<0.07$) (table 1). Changes in EQ-5D scores at 6 months did not appear to predict presenteeism or absenteeism at one year.

Conclusion: The results suggest that if a moderate/good response to biologic therapy is observed at six months, a reduction in presenteeism over the following six months can be expected. The results of this analysis are promising, particularly with regard to presenteeism which remains to be a major economic issue. Table 1. Six month predictors of presenteeism and absenteeism at one year follow up.

	N	Value	Presenteeism ZINB†	Absenteeism ZINB†
EULAR response - good/moderate, n (%)	215	175 (81)	1.07 (0.77 – 1.49) ¶ 2.89 (0.99 – 8.50)* §§	0.4 (0.04 – 1.68) ¶ 0.87 (0.63– 1.22) §
Change in HAQ score at six months, mean (SD)	205	-0.35 (0.52)	1.11 (0.75 – 1.65) ¶ 0.50 (0.23 – 1.07) §	1.34 (0.42 – 4.27) ¶ 0.39 (0.97– 1.57) §
Change in EQ-5D score at six months, mean (SD)≠	240	0.13 (0.28)	0.16 (0.03 – 0.09) ¶ 0.39 (0.12 – 0.45) §	0.18 (0.03 – 1.34) ¶ 0.36 (0.01– 0.22) §

ZINB: Zero inflated negative binomial regression model

†Adjusted for age, gender, and disease duration.

*$p<0.05$.

¶ Relative change in count part of ZINB model, assuming non-zero score

§ Odds ratio for being in zero scoring group of ZINB model.

≠ A unit increase of 0.06 (a minimal clinically important difference in EQ-5D scores)

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Abstract Number: 18

The Impact of Disease-Related and Contextual Factors on Work Outcomes in Chronic Inflammatory Arthritis Patients Treated with Biologics: A Systematic Review

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Background/Purpose: Biological therapy has been shown to have a positive effect on work outcomes, such as work participation and/or work disability in patients with chronic inflammatory rheumatic diseases. However, work outcomes are often dependent on contextual factors. Our objective is to specifically identify both the disease-related and contextual factors that impact work outcomes in patients with chronic inflammatory arthritis treated with biologics.

Methods: A systematic literature search was conducted using the Medline, Embase, two Cochrane, and CINAHL databases as well as hand searches from conference archives and clinicaltrials.gov to identify publications relating to chronic inflammatory rheumatic diseases (specifically rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic erythematous lupus (SLE), Sjogren's syndrome, or systemic sclerosis (Ssc)) in double-blind, randomized-controlled biological therapy trials with work outcomes as a primary or secondary outcome. Only studies that describe a relationship between either a disease-related or contextual (CoFas) factor and work outcome were included. A critical appraisal of the included studies was performed to determine methodological flaws in the study design and to assess for possible bias.

Results: Of the 1649 abstracts retrieved, 13 studies met inclusion criteria. The RCT's included 3 chronic inflammatory diseases (AS= 3, PsA =2, RA = 8). The follow-up period was between 12 weeks to 2 years. Biologics used include etanercept (4 studies), infliximab (3 studies), adalimumab (3 studies), and single studies with golimumab, abatacept, and certolizumab pegol. Despite study heterogeneity, there was an overall positive effect of biological therapy on work outcomes. Disease-related factors which correlated with work outcomes included patient-reported outcomes such as the health assessment questionnaire (HAQ) in 7 studies, fatigue in 3 studies, and pain in 2 studies, as well as specific disease activity and remission markers. Only 6 studies examined contextual factors. Specifically, personal factors such as female gender (4 studies) and older age (4 studies) had a negative impact on work outcomes. Environmental factors that correlated with better work outcomes include non-manual type of jobs, higher baseline number of hours worked, and lower baseline number of sick days.

Conclusion: Our results show that the positive effect of biological therapy on work outcomes is likely a result of interplay between better disease control as well as favorable patient and work environment contextual factors. Further trials identifying these variables will be important for the evaluation and prediction of work outcomes in RCT's with biological therapy for patients with chronic inflammatory diseases.

Disclosure: J. Shu, None; **P. Lambiris**, None; **C. Bombardier**, None.

Abstract Number: 19

Tumour Necrosis Factor Inhibition Is Associated with Weight Gain in Patients with Inflammatory Arthritis

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Background/Purpose: Targeted blockade of tumour necrosis factor (TNF) has been a major therapeutic advance in the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS). TNF (or "cachectin", as it was initially called) may be responsible for the weight loss observed in patients with active RA via its inhibitory effect on the enzyme lipoprotein lipase which regulates fat metabolism. "Rheumatoid cachexia" may be an important contributor to morbidity and mortality in RA. Low body weight in RA patients was associated with increased disability and radiological progression of joint damage. Other factors are also important in RA-related weight loss, for example lack of physical activity due to joint pain and restriction of movement, or anorexia from a combination of ill-health and medications. The effect of corticosteroids (CS) on body weight is an important confounder. TNF inhibition has been associated with variable effects on body weight in patients with inflammatory arthritis. We sought to determine if TNF inhibition (TNFi) resulted in weight gain in patients with inflammatory arthritis.

Methods: In this retrospective cohort study, the following data were obtained for all patients initiated on a biologic disease modifying anti-rheumatic drug (bDMARD) through the Mid-North Coast Arthritis Clinic (MNCAC) for inflammatory arthritis up to Jan 25, 2012: age, sex, type of inflammatory arthritis, initial bDMARD, body weight at 3 initial consecutive time-points, CRP, ESR, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) or Disease Activity Score-28 joints (DAS28) as appropriate, and oral corticosteroid dose (mg/d). Change in body weight over 3 time-points following commencement of the initial bDMARD was calculated. Regression modeling (mixed linear models) was undertaken to ascertain the effect of parameters (age, sex, disease activity, bDMARD, daily dose of oral corticosteroid) on body weight.

Results: N=301 patients were initiated on a bDMARD. N=98 were excluded for the following reasons (insufficient time on treatment for 3 weighs, n=55; incomplete data, n=32; intentional weight loss, n=9; refused weighing, n=1; failure to commence therapy, n=1). The remaining 203 patients were included and had commenced the following bDMARDS: 184 TNFi, 8 tocilizumab, 8 abatacept, 3 rituximab. Patients initiated on a TNFi gained weight at the rate of 0.03 (95 CI: 0.013-0.035, $p<0.001$) kg per week, independent of corticosteroid dose and disease activity. There was no change in weight in those initiated on a non-TNFi bDMARD (n=19).

Conclusion: TNF inhibition resulted in minor weight gain. This side effect is often forgotten. It is possible that weight loss may be predictive of clinical response to TNFi. This needs to be investigated in a larger prospective study

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Abstract Number: 20

Diabetes and Other Comorbidities in Rheumatoid Arthritis Patients Starting a Biologic DMARD: A Multi-Database Cohort Study

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Background/Purpose: Patients with rheumatoid arthritis (RA) are known to have an increased comorbidity burden. Presence of diabetes or other comorbidities such as cardiovascular disease (CVD) may affect the treatment decisions for RA. Limited information is available regarding biologic initiation patterns in RA patients with various comorbid conditions. We aimed to compare the frequency of diabetes and other comorbidities in RA patients starting different classes of biologic DMARDs.

Methods: Using longitudinal claims data from Medicaid (2000-2010), Medicare (2008-2013) and a commercial health plan (MarketScan 2006-2015), we conducted a cohort study that included RA patients who initiated a biologic DMARD. We included 3 categories of biologic DMARDs: 1) TNF inhibitors (TNFi), 2) abatacept and 3) other biologics including rituximab, tocilizumab and tofacitinib. Patients were required to be naive to all biologic DMARDs for at least 365 days prior to the date of the 1st biologic drug dispensing (i.e., index date). We assessed the prevalence of diabetes and other comorbidities in the 365-day period prior to the index date in each data source.

Results: There were a total of 148,584 biologic DMARD initiators: 25,878 in Medicaid, 40,663 in Medicare and 81,831 in MarketScan. Mean age (SD) in years was 46.8 (12.0) in Medicaid, 73.1 (6.3) in Medicare and 53.7 (13.0) in MarketScan. Over 75% were female. Across all three databases, 115,903 (78%) started a TNFi, 13,547 (9%) abatacept and 18,922 (13%) other biologics. Diabetes was common, affecting 22.8% in Medicaid, 35.3% in Medicare and 17.7% in MarketScan. Hypertension (36.1-78.6%), hyperlipidemia (21.3-67.7%), coronary heart disease (8.3-30.0%), heart failure (2.7-14.7%) and other cardiovascular comorbidities were common in all three databases. Compared to abatacept or other biologic initiators, TNFi initiators were younger and had a lower proportion of CV comorbidities including coronary heart disease, heart failure, stroke, and atrial fibrillation and malignancy at baseline. Differences in diabetes prevalence across treatment groups were less pronounced (**Table**).

Conclusion: Diabetes and CV comorbidities were common in RA patients starting a biologic DMARD across all three databases. Cardiovascular comorbidity profile was different in TNFi initiators compared to initiators of abatacept or other biologics. Our findings highlight the need for future research accounting for these differences appropriately in comparative effectiveness and safety studies of biologic DMARDs in multimorbid RA patients to inform treatment decisions.

Table. Baseline characteristics of different biologic starters

		TNFi	Abatacept	Other biologics
N				
	Medicaid	24,647	498	733
	Medicare	25,792	6,107	8,764
	MarketScan	65,464	6,942	9,425
Age, years				
	Medicaid	46.8±11.9	48.7±12.0*	48.1±12.6*
	Medicare	72.6±6.1	73.8±6.3*	74.2±6.6*
	MarketScan	52.8±12.9	56.9±13.0*	57.9±13.1*
Diabetes				
	Medicaid	22.6%	24.1%	30.0%*
	Medicare	35.5%	34.8%	35.3%
	MarketScan	16.9%	19.8%*	21.7%*
Coronary heart disease				
	Medicaid	8.8%	11.2%	12.8%*
	Medicare	28.2%	31.6%*	34.2%*
	MarketScan	7.3%	12.3%*	12.6%*
Heart failure				
	Medicaid	4.2%	6.0%*	10.8%*
	Medicare	12.7%	17.4%*	18.8%*
	MarketScan	2.0%	5.2%*	6.2%*
Stroke				
	Medicaid	2.2%	3.8%*	4.1%*
	Medicare	6.7%	7.2%	7.9%*
	MarketScan	1.7%	2.7%*	3.3%*
Atrial fibrillation				
	Medicaid	1.1%	2.2%*	2.7%*
	Medicare	10.3%	14.1%*	15.4%*
	MarketScan	2.2%	4.4%*	5.4%*
Hypertension				
	Medicaid	35.6%	41.2%*	50.0%*
	Medicare	78.2%	80.3%*	78.9%
	MarketScan	36.5%	44.2%*	48.0%*
Hyperlipidemia				
	Medicaid	21.1%	23.7%	26.1%*
	Medicare	67.3%	69.3%*	68.0%
	MarketScan	29.9%	34.3%*	36.4%*
Malignancy				
	Medicaid	3.5%	3.6%	26.9%*
	Medicare	14.6%	16.9%*	48.3%*
	MarketScan	5.6%	9.2%*	24.4%*

*p<0.05 compared to TNFi

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Abstract Number: 21

Outcomes of Rheumatoid Arthritis Patients with Hip Fracture

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Background/Purpose: Rheumatoid arthritis (RA) is a well-known risk factor for osteoporosis and hip fracture. Recent studies suggest RA patients fracture at a younger age and suffer higher rates of morbidity and mortality[1]. The purpose of this study is to characterize RA patients with hip fracture in an integrated healthcare system in the US.

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[1] Lin YC et al. Rheumatoid arthritis patients with hip fracture: a nationwide study. *Osteoporos Int*. 2015; 26:811-817

Methods: This retrospective cohort study, conducted in Kaiser Permanente Northern California, examined data from 13,550 women ≥ age 65 years with an incident hip fracture during 2000-2010. Demographic characteristics, comorbidity index (Charlson, CCI), prior fracture history and recent bisphosphonate (BP) therapy (2 prescriptions £1 year prior to hip fracture) were determined using health plan databases. RA was defined by a problem-list diagnosis and ≥3 visit diagnoses of RA. Rehospitalization (£30 days of discharge) and mortality outcome (£1 year) were assessed post-fracture. Standard descriptive statistics were used to examine differences in age, race/ethnicity, CCI, recent BP use, and prior fractures among women with and without RA experiencing hip fracture. Multivariable logistic regression analyses were used to examine the association of RA and mortality, rehospitalization, and recent BP use.

Results: Among 13,550 women who had a hip fracture, 339 (2.5%) had RA. Women with RA were slightly younger compared to women without RA (mean age 79.4±6.9 vs 82.5±7.4), and were twice as likely to be under age 75 (29.5 vs 15.1%, p<0.01). A larger proportion of RA patients were of non-white race/ethnicity (23.3 vs 16.3%), had greater comorbidity (CCI≥3, 37.5 vs 21.5 %), and were more likely to have had a prior fracture (44.8 vs 37.3%; all p<0.01). Fracture type (femoral neck vs trochanteric fracture) was similar between the two groups. Overall mortality rates at 1, 3, 6, and 12 months did not differ significantly for women with vs without RA (5.0 vs 6.4%, 10.6 vs 12.8%, 14.8 vs 17.0%, and 19.8 vs 22.9%, respectively), and RA status was not associated with greater mortality outcome even after adjusting for differences in age, race/ethnicity, prior fracture, recent BP use and CCI (adjusted odds ratio, OR 0.9, 95% CI 0.7-1.2). Readmission rate within 30 days was also similar for women with and without RA (12.7 vs 12.0%, p=0.69), with no increased risk for women with RA (adjusted OR 1.0, CI 0.7-1.4). However, women with RA had 3-fold greater odds of having received bisphosphonate therapy within the year prior to hip fracture (adjusted OR 3.0, CI 2.3-3.8).

Conclusion: Women with RA were younger and had greater comorbidity at the time of hip fracture. However, RA status did not appear to be independently associated with increased morbidity and mortality post hip fracture. The higher proportion of RA women with a prior fracture and evidence of recent BP therapy is consistent with their higher underlying fracture risk. Future studies should focus on prevention strategies to decrease risk of hip fracture in RA patients.

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Abstract Number: 22

Incidence and Factors Associated with the Development of Non Alcoholic Fatty Liver Disease(NAFLD) Among Patients with Rheumatoid Arthritis

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Background/Purpose: NAFLD is a leading cause of chronic liver disorders, unrelated to significant alcohol use. RA and NAFLD have shared risk factors such as age, gender, race/ethnicity, metabolic syndrome, obesity, diabetes, and dyslipidemia[1]. Little is known about the incidence of NAFLD in patients with RA. This study determined the incidence rate, time to event, and factors associated with the development of NAFLD in this population.

Methods: Longitudinal data from the Corrona RA registry (2001-2014) of adults without NAFLD (n=17,481) were used in this retrospective analysis. The Fibrosis-4 index[2], a validated noninvasive tool, was used to determine the presence of NAFLD (score ³1.3) at baseline**.** Kaplan Meier and adjusted Cox proportional hazard analysis were used to determine the incidence rate, time to event, and the predictors associated with NAFLD. Factors identified *apriori* and significant variables from the unadjusted analysis were included in the multivariate analysis (see Table 2).

Results: At baseline, the mean age of the cohort was 54 years (SD 12.4); 88 % were Caucasian; 79% female; with an average RA disease duration of 8 years. The most prevalent comorbidities were hypertension (37%), dyslipidemia (22%), and metabolic syndrome (19%). About 72% had a BMI ≥25, 70% were currently using MTX, and 40% reported using alcohol. The cumulative overall incidence was 31%; mean time to NAFLD was 7 years, 1.4% with advanced disease (see Table 1). In the multivariate analysis (see Table 2), independent predictors for increased risk for NAFLD were age (middle and elderly), hypertension, CVD, dyslipidemia, metabolic syndrome, exercise, use of MTX, and non-MTX antirheumatic drugs. Factors associated with reduced risk of NAFLD were gender (female), BMI ≥25, all RA disease duration categories, having insurance and being divorced/separated.

Conclusion: During the study period of 13 years, a third of patients with RA in this study developed mild/moderate NAFLD in a fairly short period of time. RA patients with dyslipidemia, metabolic syndrome, hypertension and cardiovascular disease were at higher risk for developing NAFLD. The ubiquitous prevalence of NAFLD is an emerging public health challenge, highlights the need for early diagnosis and management of NAFLD.

Table1: Overall NAFLD Incidence Rates and Time to Event
(N=40,300, n= 17481)

Variable	Incidence Cases n (%)	Incidence Cases/ 1000PY [95% CI]	Time to Event (years) [95% CI]
Overall NAFLD[1]	5328 (30.5%)	95.03 [92.60, 97.45]	7.18 [7.09,7.29]
Mild/Moderate NAFLD[2]	5079 (29.1%)	90.59 [88.21, 92.96]	7.35 [7,24,7.47]
Advanced NAFLD[3]	249 (1.4%)	4.44 [3.89, 4.99]	12.84 [12.78,12.90]

1-FIB-4 score ³ 1. 3; 2= FIB-4 score ³ 1. 3 but < 2.67; ³ 2.67= Advanced disease

Table 2: Adjusted Analyses -Significant Predictors for the development of NAFLD

Baseline Factors	Hazard Ratio	95.0% CI	*p Value*
Age* Referent Younger (18-<40)			
Middle Age (40 -<60)	5.16	4.16, 6.40	**< .001**
Elderly (>=60)	13.94	11.22, 17.31	**< .001**
Gender (Female)	0. 81	0.76,0.86	**< .001**
Marital Status: Referent Single / Widowed			
Divorced or Separated	0.87	0.79, 0.97	**0.010**
Insurance (yes) **	0.89	0.83, 0.95	**0.001**
Exercise (Yes)	1.09	1.02, 1.15	**0.009**
Hypertension **	1.11	1.04, 1.19	**0.003**
Cardiovascular Disease**	1.19	1.08, 1.31	**0.001**
Dyslipidemia *	1.31	1.20, 1.42	**0.001**
Obese (BMI >=25) *	0.84	0.79, 0.90	**< .001**
Metabolic Syndrome*	1.21	1.09, 1.35	**0.001**
Disease Duration** Referent Early RA			
2 to 5 years	0.87	0.80, 0.94	**0.001**
5 to 10 years	0.87	0.80, 0.95	**0.001**
>10 years	0.88	0.82, 0.95	**0.001**
MTX use *	1.08	0.01, 1.16	**0.021**
cDMARD Use**	1.08	1.01, 1.15	**0.027**

BMI = Body Mass Index; CDAI = Clinical Disease Activity Index; MTX= Methotrexates; cDMARD = Conventional disease modifying antirheumatic drugs (excluding MTX). * - Identified apriori; ** met significance (*p* =value or +/_10% difference)

Reference [1] Ahmed, M.(2006). Rheumatoid arthritis induced-fatty liver theory: One reason for global increase in prevalence of diabetes. *Medical Hypotheses*,*66*(4),862-863. [2] Shah, A.,et.al.,(2009). Use of the Fib-4 Index for non-invasive evaluation of fibrosis in nonalcoholic fatty liver disease. *Clinical Gastroenterology And Hepatology*. *7*(10),1104.

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Abstract Number: 23

Incidence of Non Alcoholic Fatty Liver Disease By Key Risk Factors Among Patients with Rheumatoid Arthritis

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Background/Purpose: The prevalence and characteristics of patients with nonalcoholic fatty liver disease **(**NAFLD) have not been well characterized in the RA population. The purpose of this analysis was to report the incidence rates and time to event by key risk factors among patients with RA.

Methods: Longitudinal data (2001- 2014) on a cohort of adult RA patients without NAFLD at the index baseline visit from the Corrona Registry were used in this retrospective analysis. Fibrosis-4 index[1] was used to determine the presence of NAFLD. Kaplan-Meier survival analysis was conducted to determine rate and time to event (NAFLD). Breslow (Generalized Wilcoxon) test was used to determine if there were significant differences in the survival distribution for the categorical variables.

Results: This incident NAFLD cohort consisted of 17,481 RA patients. As shown in table 1, higher NAFLD incidence rates were seen among the elderly (53.2), women (70.9), and Caucasians (85) per 1,000 patient years. At baseline, those in Clinical Disease Activity Index remission had the lowest incidence rate whereas the highest rates were seen among those in low disease activity (15.4 vs. 29.3 cases per 1,000 person-years). Those with metabolic syndrome (vs. without) and MTX users (vs. nonusers) had higher incidence rates of 115.3 vs. 45.4 and 69.1 vs. 25.9 cases per 1,000 person-years, respectively. Nonusers (vs. users) of steroids and biologics also had higher incidence rates (62.7 vs.30.2 and 55.5 vs. 39.4 cases per 1,000 person-years respectively) as was for nonsmokers and nonusers of alcohol. There was significant difference in the time to event (NAFLD) for the elderly (4.5 years vs. younger 11.6 years), men (6.4 years vs. 7.3 years for women), and African Americans (6.7 years vs. 8.1 years for Caucasians). Similar differences were also seen for patients with (vs. without) metabolic syndrome, diabetes, dyslipidemia, cardiovascular disease, and hypertension, as well as users of methotrexate, steroids, non users of biologics, smokers, and nonusers of alcohol.

Conclusion: In this cohort of RA patients**,** incidence of NAFLD varied by demographic factors (higher for Caucasians and women) as well as clinical factors with the highest among those with metabolic syndrome followed by nonusers of alcohol. However, among RA medications, only current use of methotrexate was associated with higher NAFLD rates. Onset of NAFLD appears to be sooner for those with the presence of chronic risk factors such as metabolic syndrome, diabetes, dyslipidemia, CVD, and hypertension. Further understanding for the appropriate management of RA patients at risk for NAFLD is warranted.

Table 1: NAFLD Incidence Rate by Key Risk Factors and Time to Event among RA Patients (N= 40,300, n=17481)

Variable		n (%)	Incidence Rate /1000 PY [95% CI]	Time to Event (years) [95% CI]	Time $\chi 2$ *p*-value*
Age	Younger (18-<40)	2133 (12.2%)	1.64 [1.31,1.98]	11.62 [11.36, 11.88]	1994.8
	Middle Aged (40 <60)	9360 (53.5%)	40.15 [38.52, 41.77]	8.15 [8.09, 8.31]	< .001
	Elderly (>=60)	988 (34.3%)	53.24 [51.38, 55.10]	4.56 [4.44, 4.61]	
Gender	Male	3707 (21.2%)	24.10 [22.83, 25.37]	6.42 [6.21, 6.64]	57.69
	Female	13774(78.8%)	70.93 [68.81, 73.06]	7.39 [7.27, 7.52]	< .001
Race	Caucasians	1546 (88.5%)	85.41 [83.10, 87.73]	7.18 [7.09, 7.29]	12.55
	African American	1116 (6.4%)	5.64 [5.02, 6.26]	6.76 [6.20, 7.25]	< .006
	Asian	286 (1.6%)	1.21 [0.92, 1.50]	7.53 [6.78, 8.29]	
	Other	614 (3.5%)	2.76 [2.33, 3.20]	7.71 [7.20, 8.30]	
Metabolic Syndrome	Yes	2229 (18.3%)	115.36 [112.72, 118.00]	5.19 [4.95, 5.43]	305.30
	No	14174 (81.7%)	45.48 [43.76, 47.21]	7.28 [7.36, 7.59]	< .001
Diabetes	Yes	1208 (6.9%)	7.88 [7.15, 8.62]	6.11 [5.77, 6.46]	27.78
	No	16273 (93.1)	87.14 [84.81, 89.48]	7.25 [7.14, 7.37]	< .001
Dyslipidemia	Yes	3824 (21.9%)	24.58 [23.30, 25.86]	5.04 [4.87, 5.22]	351.56
	No	13657 (78.1%)	70.45 [68.33, 72.57]	7.59 [7.47, 7.71]	< .001
Alcohol use	Yes	7027 (40.2%)	35.62 [34.08, 37.15]	7.51 [7.33, 7.69]	59.98
	No	10453 (59.8%)	89.80 [87.44, 92.17]	6.92 [5.59, 6.49]	< .001
CVD	Yes	1129 (6.5%)	9.24 [8.45, 10.03]	4.60[4.29, 4.90]	183.64
	No	16352(93.5%)	85.79 [83.47, 88.11]	7. 36 [7.24, 7.7.47]	< .001

Hypertension	Yes	6518 (37.3)	39.40 [37.79, 41.01]	5.99 [5.82, 6.16]	313.26
	No	10963 (62.7%)	55.63 [53.73, 57.53]	7.75 [7.61, 7.88]	< .001
Smoking Status	Yes	7208 (41.4%)	38.72 [37.12, 40.32]	6.91 [6.73, 7,10]	22.73
	No	10193 (58.6%)	55.95 [54.05, 57.85]	7.37 [7.23, 7.51]	< .001
MTX Current Use	Yes	12274 (70.2%)	69.13 [67.03, 71.23]	7.08 [6.96, 7.21]	13.62
	No	5207 (29.8%)	25.90 [24.58, 27.21]	7.44 [7.24, 7.64]	< .001
Steroids	Yes	5199 (29.7%)	30.25 (28.83, 31.67)	7.01 [6.82, 7.20]	20.15
	No	12282 (70.3%)	62.74 [58.66, 66.82]	7.24 [7.12, 7.38]	< .001
Biologics	Yes	7688 (44.0%)	39.47 [37.86, 41.08]	7.35 [7.18, 7.52]	27.49
	No	9793 (56.0)	55.56 [53.66, 57.45]	7.05 [6.90, 7.19]	< .001

* *p*-value across categories; PY= Patient Years; CI- Confidence Interval; CV = CramerÕs V; CVD = Cardiovascular disease; MTX= Methorexate; cDMARD= Conventional Disease-modifying antirheumatic drugs

Reference [1]Shah, A., et.al., (2009). Use of the Fib-4 Index for non-invasive evaluation of fibrosis in nonalcoholic fatty liver disease. *Clinical Gastroenterology And Hepatology. 7*(10),1104.

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Abstract Number: 24

Modifiable Rheumatoid Arthritis Factors and Impact on Cardiovascular Risk

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Background/Purpose: Cardiovascular disease (CVD) is a major source of morbidity and mortality in RA, but current management goals follow general population recommendations without tailoring based on RA characteristics. The published and internally validated Expanded Risk Score for CVD in RA (ERS-RA) may provide useful information for CVD management. The ERS-RA identified 3 modifiable RA factors at baseline which were predictive of future CV risk: prednisone use, functional status as defined by the health assessment questionnaire disability index (HAQ-DI), and the clinical disease activity index (CDAI). We examined whether changes after baseline in these modifiable RA factors correlate with changes in CVD risk.

Methods: Using data from a large RA registry of 15,711 subjects recruited from rheumatology practices in North America, we categorized 10-year risk of CVD using the ERS-RA. We then used Cox proportional hazards regression to determine if adding information on RA factors during follow-up, had effects on relative risk of CV events (MI, stroke, CV death). Changes in the three modifiable factors were categorized as follows: prednisone use was noted as unchanged, increased if daily dose was increased by at least 25%, or decreased if lowered by at least 25%; HAQ-DI score were categorized as unchanged, increased if higher by at least 0.5 units, or reduced if lowered by at least 0.5; and CDAI was categorized as unchanged, increased if higher by at least 25%, or decreased if lower by 25%. Cox proportional hazards models were fit using updated information on the three RA factors using information updated every six months. Hazard ratios were estimated worsened or improved values, compared with no change from baseline.

Results: Median follow-up in this cohort was 34 months with 53,861 person-years of follow-up. During this period, 342 CV events were confirmed for an overall incidence rate of 6.35 per 1,000 person-years (95% CI 5.71 -7.06). The **Table** illustrates the considerable changes in RA factors after baseline, with more than half of subjects demonstrating changes in CDAI, 30% in prednisone use, and 26% in HAQ-DI. Multivariable hazard ratios demonstrate a 30% reduction in CV risk for subjects with reduction in HAQ-DI (95% CI 0.46 – 1.06) and a 56% increase in risk for subjects with increased prednisone dosage (95% CI 1.12 – 2.16).

Conclusion: Cardiovascular risk appears to be modifiable for patients with RA. These preliminary analyses suggest that improvements in HAQ-DI score and reduced prednisone dose may be associated with reduced CV risk overtime. If confirmed, this information may provide useful evidence for constructing CV risk management recommendations specific to RA.

Table. Change in RA modifiable CV risk factors from baseline.

Rheumatoid arthritis factor	Number of subjects (%)
CDAI	
Stable	6,725 (42.8)
Improved	5,954 (37.9)
Worsened	3,032 (19.3)
mHAQ-DI	
Stable	11,702 (74.5)
Improved	2,003 (12.8)
Worsened	2,006 (12.8)
Prednisone use	
Stable	11,042 (70.3)
Less	2,692 (17.1)
More	1,977 (12.6)

CDAI, clinical disease activity index; mHAQ-DI, modified Health Assessment Questionnaire

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Abstract Number: 25

Have Outcomes of Patients with Inflammatory Arthritis Improved in the New Millennium? a Comparison of the 10 Year Outcome in Cohorts Recruited in 1990-4 and 2000-4

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Background/Purpose: New treatments have improved the short term outlook for patients with inflammatory polyarthritis (IP) over the past 20 years. However there is limited evidence on whether long term outcomes have changed. This study compared the 10 year outcomes (mortality, disease activity, disability) in 2 cohorts of patients recruited in 1990-4 and 2000-4.

Methods: Adults, aged ≥16 with ≥2 swollen joints for ≥4 weeks, were recruited to the Norfolk Arthritis Register (NOAR). Patients recruited from 1990-94 and 2000-04 made up cohorts 1 (C1) and 2 (C2) respectively. Patients were excluded if baseline assessment was ≥2 years after symptom onset. Baseline assessments included demographics, smoking status, 51 swollen / tender joint counts (SJC51 / TJC51), HAQ and self-report comorbidities. RF, ACPA and CRP were measured from stored blood samples. Patients were reassessed at 1-3, 5, 7 and 10 years. CRP was only measured at 5 and 10 years when blood samples were taken. Mortality data were provided by the Office for National Statistics. Censoring occurred after 10 years of follow up. The association between cohort and mortality was assessed using a Cox proportional hazard model. The associations between cohort and longitudinal disease activity (SJC51 / TJC51) / disability were assessed using random effects models. First age at symptom onset and gender were included as covariates. Then additional variables (baseline RF, ACPA, smoking status; time varying DMARD use, HAQ, SJC51, TJC51, CRP, comorbidities) were included.

Results: Of 1653 included patients (C1 = 1022, C2 = 631), 962 (58.2%) patients met the 2010 RA criteria (C1 = 614 (60.1%), C2 = 348 (55.1%)). At baseline, patients in C2 were older, had lower SJC51 / TJC51 but had worse HAQ (see table). 948 patients (57.3%) completed 10 years of follow up (C1 = 607 (59.4%), C2 = 341 (54.0%)) whilst 306 (18.5%) patients died (C1 = 187 (18.3%), C2 = 119 (18.8%)). In an age and gender adjusted model, C2 was associated with a reduced risk of death compared to C1 (HR 0.77, 95% CI 0.61, 0.97). Adjusting further for possible confounders did not explain the reduced risk (HR 0.69, 95% CI 0.51, 0.94). C2 had lower longitudinal SJC51 compared to C1 in age and gender adjusted (SJC51: β -1.79, 95% CI -2.22, -1.36) and further adjusted models (SJC51: β -1.56 95% CI -1.94, -1.19). TJC51 was also lower in C2 and approached significance (age and gender adjusted: β -0.18, 95% CI -1.01, 0.65; further adjusted: β -0.65, 95% CI -1.31, 0.01). Physical disability was higher in C2 compared to C1 (β 0.09, 95% CI 0.03, 0.16), adjusting for age and gender. In the further adjusted model disability did not differ between cohorts (β -0.03, 95% CI -0.09, 0.03).

Conclusion: Over 10 years mortality risk and disease activity were improved in C2, although disability was not. C2 patients may have increased expectations of the efficacy of therapy or increased availability of devices may explain the similar HAQ scores.

Table – Baseline characteristics of all patients and stratified by cohort

	Total cohort		1990-94		2000-04		
	N	Median (IQR)	N	Median (IQR)	N	Median (IQR)	p
Age at onset (years)	1653	55 (43 – 68)	1022	54 (41 – 67)	631	58 (47 – 70)	<0.0001 ~
Gender (N (%) female)	1070 (64.7)		662 (64.8)		408 (64.7)		0.980 ^
Symptom duration (months)	1653	5.7 (3.0 – 10.1)	1022	5.1 (2.7 – 9.4)	631	6.6 (3.9 – 11.3)	<0.0001 ~
Swollen joint counts:							
28	1653	4 (1 – 9)	1022	5 (1 – 11)	631	2 (0 – 6)	<0.0001 ~
51	1653	5 (2 – 11)	1022	6 (2 – 13)	631	3 (1 – 8)	<0.0001 ~
Tender joints counts:							
28	1653	4 (1 - 10)	1022	5 (2 – 12)	631	2 (0 – 8)	<0.0001 ~
51	1653	6 (2 – 15)	1022	7 (3 – 16)	631	4 (1 – 12)	<0.0001 ~
CRP (mg/l)	1338	7 (2 – 19)	817	5 (0 – 16)	521	9.5 (3 – 22)	<0.0001 ~
DAS28	1338	3.77 (2.81 – 4.81)	817	3.95 (2.88 – 5.02)	521	3.60 (2.65 – 4.53)	<0.0001 ~
HAQ	1626	0.75 (0.25 – 1.50)	1010	0.75 (0.25 – 1.38)	616	0.88 (0.38 – 1.63)	0.0017 ~
Smoking Status:	1590		1021		569		0.737
Never, N(%)	504 (31.7)		323 (31.6)		181 (31.8)		
Ex-smoker, N(%)	669 (42.1)		424 (41.5)		245 (43.1)		
Current smoker, N(%)	417 (26.2)		274 (26.8)		143 (25.1)		
Current sDMARDs use, N(%)	431 (26.1)		153 (15.0)		278 (44.1)		<0.001 ^
Met 2010 RA criteria, N(%)	961 (58.1)		614 (60.1)		347 (55.0)		0.042 ^

** p values resulting from comparison of baseline score across the two cohorts, ~ = Mann-Whitney U test, ^ = χ^2*
DAS28 = Disease activity score (28), HAQ = Health assessment questionnaire, IQR = Interquartile range, l = Litres, mg = Milligrams, N = Number of patients with available data, RA = Rheumatoid arthritis, sDMARD = Synthetic Disease Modifying Anti-Rheumatic Drugs

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Abstract Number: 26

Rheumatoid Factor Positivity Increases All-Cause and Cancer Mortality Risk in Korean Healthy Examinees: A Kangbuk Samsung Health Study

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Background/Purpose: Several studies have reported increased overall mortality in association with rheumatoid factor (RF) in RA. However, the clinical significance including health outcomes of RF in general populations are incompletely known. Thus, the aim of this study was to determine the association of RF with mortality due to all-causes, cardiovascular disease (CVD), and cancer-cause in Koreans without RA participating in a health-screening program. Furthermore, we analyzed whether the titers of RF had implication for the mortality outcome in healthy screening subjects.

Methods: A cohort study was performed in 295,837 participants free of osteoarthritis or rheumatoid arthritis (RA), and who had undergone health screening between 2002 and 2012 and been followed-up to determine the risk of all-cause, CVD, and cancer-specific mortality with respect to the presence or titer of RF. To determine whether the participants were deceased, we used National Death Index death certificates.

Results: The prevalence of RF positivity (≥ 20 IU/mL) was 4.4%. During 1,447,403 person-years of follow-up, 1,402 participants died. Comparing subjects with RF-negativity with those positive for RF in a sex-adjusted model, the HRs for

all-cause and cancer mortality were 1.66 (95% CI = 1.39–1.98) and 1.84 (95% CI = 1.44–2.35), respectively. After adjusting for confounding factors, RF positivity was still significantly associated with the risk for all-cause or cancer mortality (HR=1.50, 95% CI = 1.19–1.90; HR=1.56, 95% CI = 1.12–2.16, respectively). However, the HR for cardiovascular mortality was not higher in subjects with RF-positivity than in those with RF-negativity (HR=0.98, 95% CI=0.45–2.11). The HRs for all-cause, CVD, and cancer mortality were estimated in terms of RF levels. After adjusting for confounding factors, all-cause and cancer mortality risk was significantly greater in subjects with an RF titer greater than 100 IU/mL than in those with RF-negativity (HR=2.68, 95% CI=1.72–4.19; HR=2.89, 95% CI=1.58–5.28, respectively). On the other hand, RF titer did not show significant association with an increased risk of CVD mortality.

Conclusion: In healthy South Korean examinees without RA, RF was associated with a greater risk of all-cause and cancer mortality, suggesting that it predicts greater mortality, even among the apparently healthy population. This result would shed new light on the clinical significance of RF on mortality in the general populations.

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Abstract Number: 27

A Rheumatologist's Assessment of Therapy Responses (Rxresp) and Rheumatoid Factor Status (neg/pos) in 1995 Predicted Mortality through 2015 in a Community-Based Cohort of Incident Rheumatoid Arthritis Cases and Matched Control Subjects

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Background/Purpose: Greater disease severity, older age, positive serum rheumatoid factor (RF), and long-standing glucocorticoid usage contribute to increased mortality of rheumatoid arthritis (RA) patients. This study aimed to analyze all-cause mortality through 2015 as related to 1974 baseline cohort entry demographic factors, 1995 clinical assessment of therapy response (Rxresp) of incident RA, and RF status pre- and post-onset of RA vs non-RA matched cohort control (CN) subjects.

Methods: All incident RA cases identified in 1995 from the 1974 community-based cohort (n=21,061 adults) satisfied 1987 revised ACR criteria. Cases (n=54) were matched (1 RA: 4CN) with 216 cohort CN subjects on age, gender, and race (Caucasian). All subjects (N=270) were regularly followed for survival. Two investigators independently determined causes of death (CODs) from the completed death certificate codes without knowledge of RA vs CN status. Baseline (1974) serum isotype-specific IgM and IgA RF assays were performed (TheraTest Laboratories, Chicago, IL) with coefficients of variation (CVs ±SE) of 16.0 (±2.1) and 20.2 (± 1.6), respectively. In 1995, RF status was also extracted from RA patients' clinical records. Therapy response (Rxresp) categories (1= good, 2=fair, 3=limited) were assessed by the sole community rheumatologist. Cox regression models estimated hazard ratios (HRs) for all-cause mortality through 2015, including covariates of 1974 demographic and baseline serological variables, 1995 Rxresp, and RF categories by 1974 and 1995 results (0=both negative, 1=only 1995 positive, 2=both 1974 and 1995 positive).

Results: The 38 (70.4%) deaths in 54 RA exceeded (p=0.003) the 102 (47.2%) in 216 matched CN (Table). The difference (p=0.012) persisted in Cox models (Exp β 1.66, 95% CIs 1.12-2.47), including covariates of cohort entry age deciles (p<0.001, Exp β 2.70, 95% CIs 2.19-3.33), years of completed education (p=0.010, Exp β 0.91, 95% CIs 0.85-

0.98), and degree of cigarette smoking (p=0.048, Exp β 1.13, 95% CIs 1.00-1.28). In Cox models, 19 good Rxresp RA had similar (p=0.978) mortality to their 76 matched CN (Table). Mortality was strongly (p=0.001) increased in 35 fair/limited Rxresp RA vs 140 CN (Exp β 2.11, 95% CIs 1.33-3.33) (Table). The 35 fair/limited Rxresp RA had significantly (p=0.012) greater mortality (29, 82.9%) than the 19 good Rxresp RA (9, 47.4%) (Table). In 15 RF-negative RA cases in 1974 and 1995, the 8 good Rxresp had similar mortality (63%) to the 7 fair/limited Rxresp cases (57%) (p=1.00). In the 39 RF-positive cases, fair/limited Rxresp was a strong (p=0.002) predictor of mortality (Table, footnote). Mortality of RA cases was also predicted (p=0.015) by a scale of 1974 and 1995 RF status, particularly for 1974 and 1995 RF-positive cases (p=0.004, Exp β 6.25, 95% CI 1.80-21.7) (Figure). Fair/limited vs good Rxresp independently predicted (p=0.013) RA mortality in Cox model, including the RF scale (0,1,2) and demographic covariates (Fig).

Conclusion: Assessment in 1995 of fair/limited vs good Rxresp in RA patients predicted (p=0.012) greater mortality through 2015, particularly in RF-positive cases (p=0.002). Mortality was significantly (p=0.004) greater in 9 consistently RF-positive RA vs 15 consistently RF-negative cases. Interaction of Rxresp categories and RF status on RA mortality outcome deserves further research.

Mortality Outcome of Rheumatoid Arthritis (RA) Patients through 2015 by their Rheumatologist's assessment of having Good vs Fair or Limited Responses to Therapy in 1995 and by Negative vs Positive Serum Rheumatoid Factor in 1974 and 1995

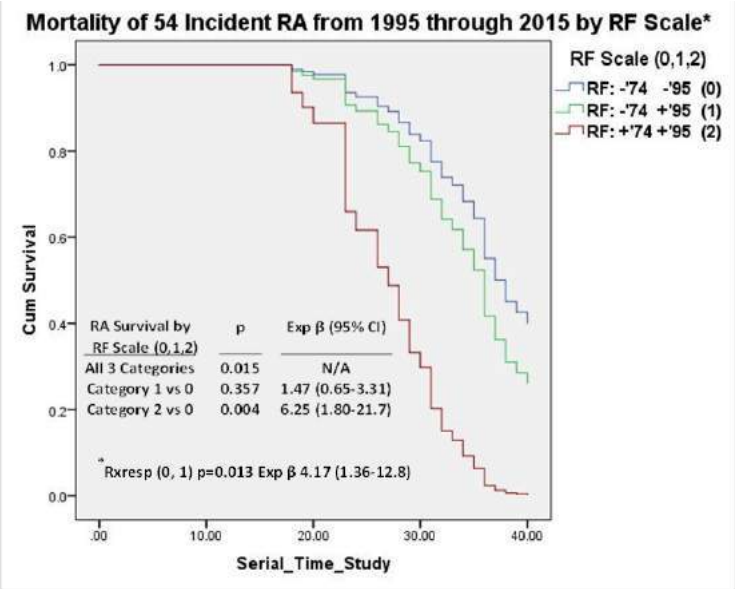
RA Mortality Outcomes by RF Status in 1974 & 1995 vs Total Mortality in CN	Rheumatologist's Assessment of Therapy Responses in 1995: Good* (N=19)	Fair/Limited† (N=35)	Total‡ (N=54)	Good vs Fair/Limited Responses (p values)
RF Negative in 1974 & 1995:	(n=8)	(n=7)	(n=15)	
Alive	3	3	6	
Dead	5	4	9	
% Dead	63%	57%	61%	1.00
RF Positive in 1995 only$:	(n=6)	(n=24)	(n=30)	
Alive	4	3	7	
Dead	2	21	23	
% Dead	33%	88%	77%	0.016
RF Positive in 1974 &1995$:	(n=5)	(n=4)	(n=9)	
Alive	3	0	3	
Dead	2	4	6	
% Dead	40%	100%	67%	0.167
Total RA:	(N=19)	(N=35)	(N=54)	
Alive	10	6	16	
Dead	9	29	38	
% Dead	47.4%	82.9%	70.4%	0.012
Total CN:	(N=76)	(N=140)	(N=216)	
Alive	45	69	114	
Dead	31	71	102	
% Dead	40.8%	50.7%	47.2%	0.199
RA vs CN Dead: (p values)	0.978	0.001	0.012	
[Exp β (±SE)]	1.01 (0.44-2.35)	2.11 (1.33-3.33)	1.66 (1.12-2.47)	

* In good therapy repsonses, deaths in RF neg vs any pos (p=0.370)

† In fair or limited therapy responses, deaths in RF neg vs any pos (p=0.079)

‡ In total subjects, deaths in 38 (70.4%) of 54 RA exceeded (p=0.003) 102 (47.2%) of 216 matched CN subje

$ In 39 combined RF positive RA, deaths through 2015 were greater (p=0.002) in 25 (89%) of 28 fair/limited Rxresp than in 4 (36%) of 11 good Rxresp in 1995



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Abstract Number: 28

Baseline Serum Inflammatory Biomarkers at Cohort Entry in 1974 Predicted Cardiovascular Disease (CVD) Mortality from 1995 through 2015 in a Prospective, Community-Based Study of Incident Rheumatoid Arthritis (RA) Patients and Matched Non-RA (CN) Subjects

Alfonse T. Masi[1], Azeem A. Rehman[2], Laura Jorgenson[3] and Jean C. Aldag[3], [1]University of Illinois, College of Medicine at Peoria, Peoria, IL, [2]Neurosurgery, University of West Virginia Medical School, Morgantown, WV, [3]Medicine, University of Illinois College of Medicine at Peoria, Peoria, IL

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Baseline Serum Inflammatory Biomarkers at Cohort Entry in 1974 Predicted Cardiovascular Disease (CVD) Mortality from 1995 through 2015 in a Prospective, Community-Based Study of Incident Rheumatoid Arthritis (RA) Patients and Matched non-RA (CN) Subjects Author Block: Alfonse T. Masi[1], Azeem A. Rehman[2], Laura C. Jorgenson[1], Jean C. Aldag[1], [1]University of Illinois College of Medicine at Peoria, Peoria, IL. [2]University of West Virginia, Morgantown, WV.

Background/Purpose: Inflammatory pathways have been incriminated in total and cardiovascular disease (CVD) mortality of rheumatoid arthritis (RA) patients (Arthritis Rheum. 2005 Mar;52(3):722-32). Current studies have analyzed serum inflammatory biomarkers in RA patients as related to total and CVD mortality outcomes. No reports are available on serum inflammatory biomarkers before clinical onset of RA as related to total or CVD mortality outcomes. The aim of this study is to investigate baseline pre-clinical inflammatory biomarkers as related to all-cause and CVD mortality of incident RA cases and matched non-RA comparison (CN) subjects in a long-term prospective cohort.

Methods: All incident RA cases were identified who had onsets between 1977 and 1995 from a 1974 community cohort (n=21,061 adults) and satisfied 1987 revised ACR criteria. Cases (n=54) were matched (1 RA: 4CN) with 216 cohort CN subjects on age, gender, and race (Caucasian). All subjects (N=270) were regularly followed for survival through 2015. Two investigators independently determined causes of death (CODs) from the completed death certificate codes without knowledge of RA vs CN status. Baseline (1974) serum immunologic factors were anonymously assayed at national referral laboratories. Assay values were log-transformed and standardized by z-scores in females and males. Multiple imputation (MI) was utilized to enter a minority of randomly missing biomarker z-scores. Individual biomarker z-scores were also analyzed as ranks (1= lowest, 5= highest) within the 54 separate matched sets of 1 RA and 4 CN. Logistic regression was used to identify ranked variables which predicted mortality outcome through 2015, in total deaths and by CVD, respiratory, malignancy, and all other CODs. The dichotomized (neg=0, pos=1) z-scores of predictive ranked factors were entered as covariates in Cox regression models in addition to 1974 baseline demographic and CN_RA status. Pairs of independent dichotomous (neg/pos) selected z-scores were combined (0=both negative, 1=either positive, 2=both positive) to enhance mortality prediction.

Results: In all subjects, total mortality was predicted by ranks of C-reactive protein (CRP) ($p=0.033$, Exp β 1.17, 95% CIs 1.03-1.33). The CVD deaths were predicted by ranks of soluble tumor necrosis factor receptor 1 (sTNF-R1) ($p=0.001$ Exp β 1.41, 95% CIs 1.14-1.75) in Cox regression models, including baseline demographic covariates. The dichotomous (neg/pos) z-scores of the preceding predictive biomarkers were paired (CRP_sTNF-R1) into a 3-scale score, which significantly predicted total mortality ($p=0.002$, Exp β 1.42, 95% CIs 1.13-1.78). That paired predictive biomarker (CRP_sTNF-R1) was an even stronger predictor of CVD mortality ($p<0.001$, Exp β 2.06, 95% CIs 1.39-3.07) (Figure 1). Its Exp β was slightly greater for RA [2.97 (0.97-9.09)] than CN [1.98 (1.27-3.10)], but was significant ($p=0.003$) only in the larger sample of CN subjects. Excluding the preceding 50 CVD deaths, the paired biomarker did not predict ($p=0.130$) total mortality in 220 remaining subjects (Figure 2). In the 220 non-CVD subjects, mortality differed slightly ($p=0.045$) between those who had neither vs both dichotomous z-scores positive. As found in our previous analyses, RA vs CN status did not predict ($p=0.357$) 50 CVD deaths [Expβ=1.37 (0.70-2.70)] (Figure 1), but did significantly ($p=0.003$) predict all other-cause mortality combined in the remaining 220 subjects [Expβ=2.10 (1.29-3.41)] (Figure 2). The paired biomarker was not a significant predictor of the separate non-CVD CODs.

Conclusion: Ranks (1-5) of serum CRP and sTNF-R1 z-scores significantly predicted either total or CVD mortality in 270 subjects. A 3-scale pairing of the preceding dichotomous z-scores (CRP_sTNF-R1) significantly ($p<0.001$) predicted CVD mortality, but not ($p=0.130$) non-CVD mortality in the remaining 220 subjects. The relation of pre- and post-clinical onset serum inflammatory biomarkers to total, CVD, and other cause-specific mortality deserves further study in RA and CN subjects.

Figure 1:

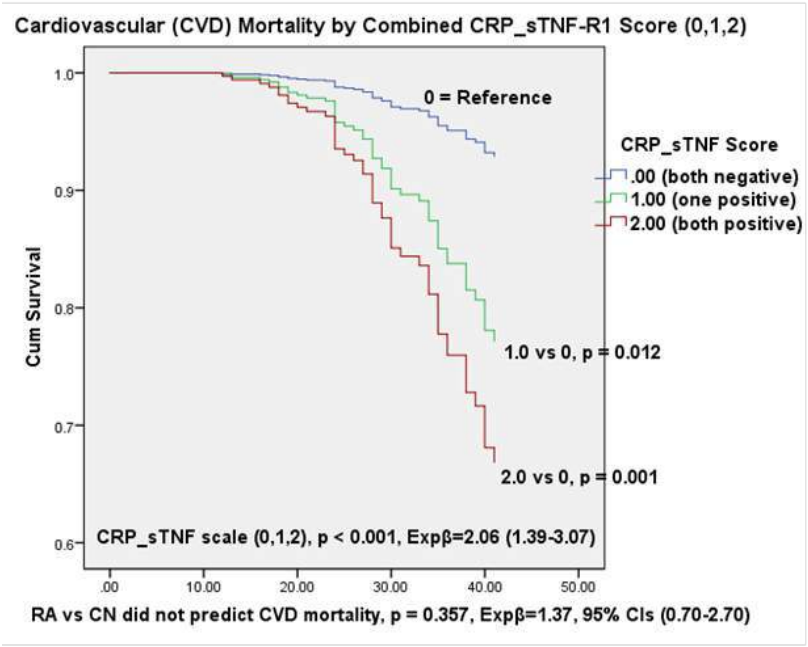
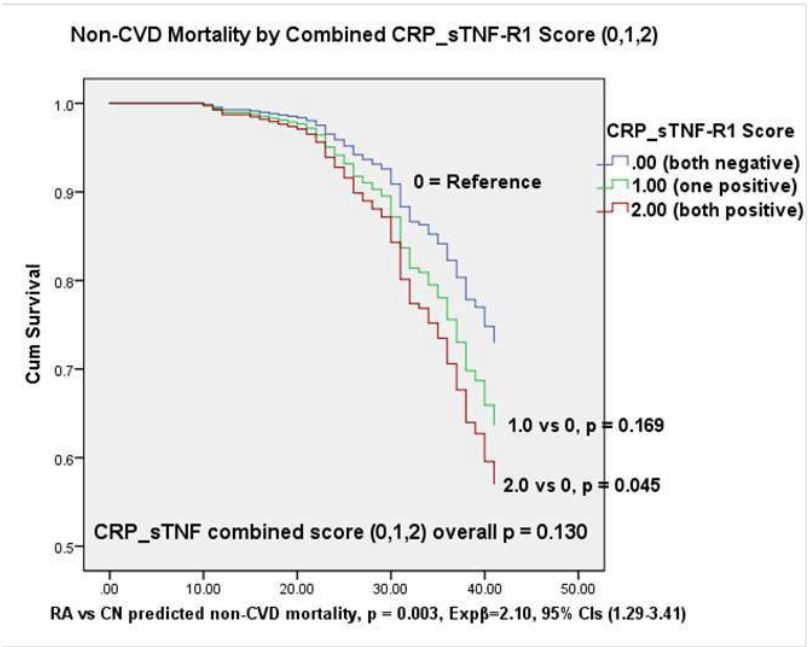


Figure 2:



Disclosure: A. T. Masi, None; **A. A. Rehman**, None; **L. Jorgenson**, None; **J. C. Aldag**, None.

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Abstract Number: 29

Risk of Vascular Mortality in Seniors with New-Onset Rheumatoid Arthritis

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Background/Purpose: RA patients are known to be at increased risk of vascular morbidity and mortality, although conflicting reports exist for incident RA patients. Our aim was to evaluate the risk of cardiovascular and cerebrovascular disease (CVD) mortality in seniors with incident RA in Ontario, Canada.

Methods: We undertook a population-based cohort study of incident RA patients aged 66 years or older (ensuring comprehensive drug coverage) from 2000 to 2013. We identified four non-RA general population comparators for each RA patient, matched on age, sex and region of residence. All patients were followed until death (primary cause due to CVD ascertained from vital statistics, with censorship for deaths due to competing cause), out-migration, or end of study period (Dec 2013). Crude and adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using multivariable Cox models, controlling for time-varying drugs (statins, antihypertensives, NSAIDs, COX-II inhibitors), baseline comorbidities, healthcare use, and socioeconomic status.

Results: 28,322 RA patients and 113,288 comparators were followed for 142,534 and 502,823 person years, respectively. During a median follow-up of 4 years, 1,947 (6.9%) RA patients and 6,340 (5.6%) comparators died due to CVD, corresponding to CVD mortality rates of 13.7 (95% CI 13.1-14.3) and 12.6 (95% CI 12.3-12.9) per 1000 patient-years, respectively. Risk of vascular mortality was not greatly increased in incident RA relative to age/sex/area-matched comparators (unadjusted HR, 1.02; 95% CI 0.96-1.09; adjusted HR, 0.98; 95% CI 0.91-1.05). Risk for CVD mortality was lower in patients using statins (HR, 0.60; 95% CI 0.56-0.64), COX-II inhibitors (HR, 0.68; 95% CI 0.59-0.78) and NSAIDs (HR, 0.74; 95% CI 0.62-0.90), and in those with a prior joint replacement (HR, 0.80; 95% CI 0.72-0.90); and greater with pre-existing comorbidities (coronary artery disease, hypertension, COPD/asthma, renal failure, cerebrovascular disease, acute myocardial infarction, diabetes), use of antihypertensive agents (HR, 1.17; 95% CI 1.09-1.25), and being in a lower socioeconomic status (HR, 1.32; 95% CI 1.20-1.46)

Conclusion: In these analyses, seniors with incident RA were not shown to have an increased risk of vascular mortality, although longer follow-up is warranted. Use of statins, COX-II inhibitors, and NSAIDs was associated with a decreased risk for vascular mortality, although residual confounding cannot be ruled out.

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Abstract Number: 30

Impact of Interstitial Lung Disease on Mortality of Patients with

Rheumatoid Arthritis

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Background/Purpose: Interstitial lung disease (ILD) is one of the most important extra-articular manifestations in patients with rheumatoid arthritis (RA). The prevalence of ILD in patients with RA has been shown to vary widely between 1% and 58% depending on the study population and the definition of ILD. Some studies have supported ethnicity-related differences in the prevalence of ILD and ILD in RA; however, these results have not yet been conclusive. In addition, ILD is known to be associated with higher mortality; however, the effect of ILD on mortality among Asian RA patients is not enough. In this study, we aimed to determine the prevalence of ILD in Korean patients with RA and assess the effect of ILD on their mortality.

Methods: A total of 3,555 patients with RA with chest X-ray or chest computed tomography (CT) data at enrollment were extracted from the KORean Observational study Network for Arthritis (KORONA) cohort, a nationwide prospective cohort for patients with RA in Korea. Patients were classified into two groups: 1) ILD group as patients with ILD by chest X-rays or chest CT scans, and 2) non-ILD group as patients without ILD by these modalities. After comparing demographic and clinical characteristics at enrollment between the groups, log rank test was used to test the differences in survival between the ILD group and the non-ILD groups. With adjusting age, sex, smoking history, medications, RA severity, and comorbidities, cox proportional hazard model was made to identify the impact of ILD on RA mortality.

Results: Sixty-four patients (1.8%) were identified with ILD. The ILD group patients were older at diagnosis (54.9 ± 11.6 years in ILD group vs. 45.5 ± 12.9 years in non-ILD group, $p<0.01$) and at enrollment (63.2 ± 9.2 years vs. 53.6 ± 12.1 years, $p<0.01$) than non-ILD group patients, and male (29.7% vs. 15.5%, $p<0.01$) patients were more common in the ILD group. In regard to medication, methotrexate was used less (57.8% vs. 82.1%, $p<0.01$), and oral glucocorticoid was used more (89.1% vs. 76.3%, $p=0.03$) in the ILD group compared with the non-ILD group. During mean follow-up of 24 months, 6 patients (9.4%) in the ILD group and 25 patients (0.7%) in the non-ILD group died; survival rates were significantly worse in the ILD group ($p<0.01$) by log-rank test. On adjusted analysis, ILD was significantly associated with an increased mortality risk (HR 9.41, CI 3.63-24.39, $p<0.01$); the risk of mortality in patients with ILD was even higher than in patients with cardiovascular disease (HR 4.85, CI 2.03-11.64, $p<0.01$) or malignancy (HR 3.40, CI 1.19-9.68, $p=0.02$).

Conclusion: The prevalence of ILD was 1.8% in Korean patients with RA. ILD was a major risk factor for increased mortality in p atients with RA.

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Abstract Number: 31

Patients with Either Rheumatoid Arthritis (RA) or Axial Spondyloarthritis (axSpA) Self-Reported Flares in 24% of Assessments: An Observational Study of 86 Patients Assessed Weekly over 3 Months (ie, 1,100 assessments)

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Background/Purpose: The evolution of RA and axSpA is characterized by alternated periods of flares and remission. This fluctuating disease activity can be self-assessed by a single question [1]. The objective was to assess the frequency of flares when assessed weekly and the link between flares and well-validated patient reported outcomes (PROs).

Methods: In this prospective longitudinal multicenter observational study aiming to explore physical activity and its relation with disease activity. Patients had definite axSpA (ASAS criteria) or RA (ACR/EULAR criteria). Patients were asked to complete every week during 3 months different PROs including pain and patient global assessment (PGA) and flare status. Flares were recorded using the question (« has your disease flared up during the last 7 days ? ») [1], with a categorical response: no flare, flare lasting 1 to 3 days or flare lasting more than 3 days. Flare frequency was calculated by the number of reported flares divided by the number of completed questionnaires over the 3 months. The frequency of flares in RA and axSpA patients was compared by Mann-Whitney test. Pain and PGA were compared across assessments according to flare status using ANOVA on repeated measures (linear mixed-effects model).

Results: 86 patients (45 RA and 41 axSpA patients) were included in this analysis: 37 (43.0%) were males, with a mean age of 46.3 (±11.7) and a mean disease duration of 10.8 (±7.9) years, 48 (55.8%) were receiving a biologic. RA and axSpA patients had respectively a mean DAS 28 of 2.2 (±1.0) and a mean BASDAI of 3.5 (±2.1). Patients reported flares on average in 23.9% (±23.1) of the weekly questionnaires, with a mean frequency of '1 to 3 days flares' and '>3 days flares' respectively of 17.2% (±17.0) and 6.7% (±14.1). Flare frequency and duration of flares were higher in RA than axSpA, in particular for short flares, though this difference did not reach statistical significance (Table 1). Pain and PGA were higher when patients self-reported flares and in particular longer flares rather than "bad days" (Table 2). Table 1: Mean frequency of flares per patient according to their duration in RA and axSpA patients

	All patients (n=83)	RA (n=45)	axSpA (n=41)	p
Frequency of all flares, mean (SD)	23.9 (±23.1)	27.0 (±24.5)	20.5 (±21.3)	0.20
Frequency of 1-3 days flares, mean (SD)	17.2 (±17.0)	20.4 (±19.5)	13.8 (±13.1)	0.16
Frequency of >3 days flares, mean (SD)	6.7 (±14.1)	6.6 (±10.9)	6.8 (±17.1)	0.31

Table 2: PROs according to flare status

	No flare (n=836 questionnaires)	1-3 days flares (n=191 questionnaires)	>3 days flares (n=73 questionnaires)	P
Pain 0-10, mean (SD)	2.2 (±1.8)	4.4 (±1.7)	6.5 (±2.0)	<0.0001
PGA 0-10, mean (SD)	2.3 (±1.9)	4.4 (±1.8)	6.4 (±2.3)	<0.0001

Conclusion: self-reported flares were frequent in RA and axSpA, in this population of long-standing disease with good inflammation control. Long flares (>3 days) were less frequent. Self-reported flares were substantiated by higher PROs. More work is needed on long-term effects of flares. 1. VP Byberk et al, RMD Open, 2016; 2(1):e000225.

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Abstract Number: 32

Comparison of Effects of Leukocyte-RICH and Leukocyte-Poor Platelet-RICH Plasma on PAIN and Functionality in Patients with Lateral Epicondylitis

Havva Talay Calis[1], Melek Yerlikaya[2], Serap Sütbeyaz[3], Hatice Sayan[2], Nurdan Özkan[2], Ali Koç[4] and Çiğdem Karakükçü[5], [1]Departmentbof Physical Medicine and Rehabilitation, Kayseri Education and Research Hospital, Kayseri, Turkey, [2]Department of Physical Medicine and Rehabilitation, Kayseri Education and Research Hospital, Kayseri, Turkey, [3]Department of Physical Medicine and Rehabilitation, Kayseri Edıcation and Research Hospital, Kayseri, Turkey, [4]Department of Radiology, Kayseri Education and Tesearch Hospital, Kayseri, Turkey, [5]Department of Biochemistry, Kayseri Education and Research Hospital, Kayseri, Turkey

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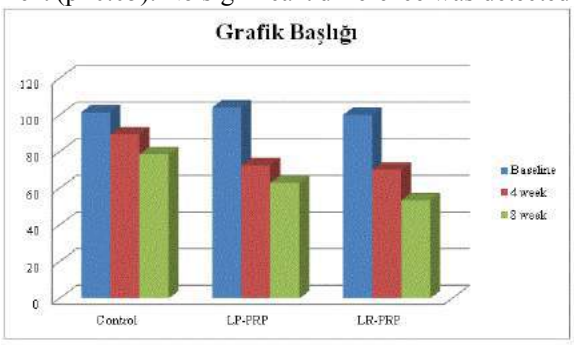
Comparison of effects of leukocyte-rich and leukocyte-poor platelet-rich plasma on pain and functionality in patients with lateral epicondylitis Melek Yerlikaya[1], Havva Talay Çalýþ[1], Serap Tomruk Sütbeyaz [1], Hatice Sayan[1], Nurdan Ýbiþ[1], Ali Koç[2], Çiðdem Karakükçü[3] [1]Kayseri Training and Research Hospital, Department of Physical Medicine and Rehabilitation, Turkey, [2]Department of Radiology, Kayseri Training and Research Hospital, Kayseri, Turkey, [3]Department of Biochemistry, Kayseri Training and Research Hospital, Kayseri, Turkey

Background/Purpose : We think that leukocyte concentration in PRP can affect local inflammatory response. In this study, we aimed to compare effects of leukocyte-rich and leukocyte-poor PRP on pain, functionality and post-injection local inflammatory reactions and adverse effects in patients with lateral epicondylitis.

Methods : Overall, 90 patients with lateral epicondylitis-related pain (VAS score≥5) over >3 months were included to the study and randomly assigned into 3 groups. Normal saline (1.5 cc) was injected to the group 1 while a single dose of LP-PRP (1.5 cc) and LR-PRP (1.5 cc) were injected to groups 2 and 3, respectively. Same exercise program was prescribed to all three groups. The patients were assessed with VAS, Patient-Rated Tennis Elbow Evaluation (PRTEE), grip and pinch strength, extensor tendon thickness and cortical derangement at baseline and on weeks 4 and 8 after therapy. All patients were questioned regarding paracetamol use and adverse effects after therapy.

Results: The mean age was 47.63±9.05 years in the control group while 45.03±8.57 years in LP-PRP and 46.49±8.73 years in LR-PRP group. The groups were comparable regarding age. No significant differences were detected between groups regarding, VAS, PRTEE, , grip and pinch strength measurements, extensor tendon thickness and cortical derangement (p>0.05). No significant difference was detected in paracetamol use and post-injection reactions among groups.



\s **Figure 1:** Patient-based PRTTE scores in groups

Conclusion: In our study, PRP was found to have no superiority to control groups in patients with lateral epicondylitis. Leukocyte concentration in PRP was also found to have no association to improvement in pain and function or adverse effects.

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Abstract Number: 33

Prevalence of Growth Hormone Deficiency in Fibromyalgia Patients

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Background/Purpose: Low levels of Insulin-dependent growth factor 1 (IGF-1) have been described in Fibromyalgia (FM) patients, suggesting that they have adult growth hormone (GH) deficiency. The prevalence of low IGF-1 and low GH has not yet been described. This study describes these prevalences.

Methods: Seventy-eight female FM patients were studied over a four year period in a solo private rheumatology practice. All fulfill 1990 and 2010 ACR FM criteria. Mean age was 45 years (range 20-68). Serum IGF-1 levels were measured and IV GH stimulation testing performed using either arginine or glucagon as the secretagogue.

Results: Mean IGF-1 was 133 ng/ml as compared to the expected level of 235 ng/ml. Of the 78 patients, 70 had low-for-age IGF-1. Of the 48 that took the IV GH stimulation test, 44 failed necessitating the use of subcutaneous GH preparations . The prevalence of GH deficiency in FM was at least 56%.

Conclusion: GH deficiency is more common than believed in FM. More FM patients should be so tested.

Disclosure: T. Romano, None;

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Abstract Number: 34

Differential Analgesic Pharmacological Effects on Brain Connectivity in Fibromyalgia (FM)

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Background/Purpose: Brain imaging techniques including functional magnetic resonance imaging (fMRI) may be useful in probing the mechanisms of action of centrally acting analgesics. Previously we have used brain resting state functional connectivity (fcMRI) outcomes to predict clinical pain response in fibromyalgia (FM) for the two efficacious compounds pregabalin (PG), preclinically shown to reduce presynaptic cell calcium thereby reducing the concentration of glutmate, an excitatory neurotransmitter, into the synapse, and milnacipran (MLN), preclinically shown to inhibit the reuptake of serotonin and norepinephrine, improving descending modulation. Here we extend our analyses to determine if these compounds have a differential effect on brain connectivity patterns in human patients with fibromyalgia.

Methods: 28 female FM patients were included in this study. 13 completed a double-blind placebo-controlled crossover study with PG, and 15 completed a similar study with MLN. All patients underwent a 6 minute fcMRI scan pre- and post-treatment for both the drug and placebo (PBO). Patients reported clinical pain pre- and post-treatment using a 0-10 rating scale. fcMRI data were analyzed with *a priori* regions of interest approach using the Conn toolbox running in SPM8 and Matlab. Regions previously identified as independently predictive for PG and MLN were cross-utilized in both data sets. Changes in fcMRI were analyzed in SPM8 with paired t-tests (within treatment) and a flexible factorial interaction (PG vs MLN) that included seed-to-whole brain correlation maps. Finally, PG and MLN were directly contrasted with a two-sample t-test.

Results were significant on the cluster level with a false discovery rate p value < 0.05 derived from an uncorrected voxel level p value < 0.001. Significant results were correlated with changes in clinical pain in SPSS v22 Results: PG significantly decreased fcMRI between the anterior and posterior insula seeds to the dorsolateral prefrontal cortex (DLPFC, $p = 0.003$ and $p = 0.05$). Decreases in PG anterior insula – DLPFC fcMRI were associated with reduced clinical pain ($rho = 0.830$, $p < 0.001$). MLN significantly increased fcMRI between the subgenual anterior cingulate (sgACC) seed and the inferior parietal lobule (IPL, $p = 0.040$). Increased sgACC – IPL fcMRI was associated with reduced clinical pain ($rho = -0.515$, $p = 0.049$). When directly compared MLN significantly increased and PG significantly decreased fcMRI between the right DLPFC seed and the precuneus ($p = 0.007$). PG DLPFC – precuneus fcMRI, decreases were associated with reductions in clinical pain ($rho = 0.808$, $p = 0.001$). No PG seeds produced significant fcMRI relationships in the MLN data and no MLN seeds displayed significant fcMRI relationships in PG data.

Conclusion: These data demonstrate differential effects of PG and MLN on resting brain activity, thus providing further evidence that these compounds may have different mechanisms of action. PG was found to act more so on pro-nociceptive brain regions, whereas MLN acted more so on an anti-nociceptive brain region. These results suggest that a combination of

both PG and MLN in the same patient may be more effective due to the medications working on separate yet complementary brain processes.

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WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-etiology-of-fibromyalgia-may-be-related-to-increased-muscle-tension-rather-than-central-sensitization

Abstract Number: 36

Dysautonomia and Osteoporosis in 2300 Ehlers-Danlos Hypermobile Patients, As Defined By the Brighton Criteria

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Dysautonomia and Osteoporosis in 2300 EDS type III patients, as defined by the Brighton criteria

Background/Purpose: To highlight the high frequency of Dysautonomia (Dys) and Osteoporosis in Ehlers-Danlos type III (EDS-III), complications that are very frequent and usually undiagnosed. Identify the percentage of EDS-III that are not hypermobile (negative Beighton Score (BSc) with positive Brighton Criteria (BC)). Stress the need to make the diagnosis using the Brighton Criteria and not relaying only on the Beighton Score .

Methods: We have studied 2300 EDS-III patients. The BSc and the BC were applied to all patients. Age: range 16 - 87, average 44.43. Females 78.7%. Patients were grouped in < 30 y/o (A), and over 30 y/o (B). Dysautonomia was clinically evaluated in 2283 patients. Densitometries were done in 1060 patients (OMS criteria). Patients younger than age 16 were excluded since the BC has been validated only for ages 16 and over.

Results: 2300/2868 patients had EDS-III (80.2%). BSc negative: 51.0%. Dys total group: positive: M 30.14%, F 56.16%; Group A: M 60.8%, F 84.04%; Group B: M 21.6%, F 60.1%. BMD total group: normal 31.6%, Osteopenia 47.9%, Osteoporosis 20.5%; **Osteopenia**: Group A: M 45.7%, F 50.4%, Group B: M 53.5%, F 48.0%; **Osteoporosis**: Group A: M 8.6%, F 9.8%, Group B: M 20.0%, F 22.9%.

Positive Dysautonomia (1164) in 2283 EDS-III patients evaluated

Positive	**Total Positive Group n = 1164**		**Group A (< 30 y/o) n = 382**		**Group B (≥ 30 y/o) n = 782**	
Males	148	30.4 %	65	**60.8 %**	83	21.6 %
Females	1016	56.2 %	317	**84.0 %**	699	60.1 %
	1164		382		782	

Bone Mineral Density studied in 1060 EDS-III patients

	Total Group	Group A (< 30 y/o) n = 89		Group B (≥ 30 y/o) n = 741	
	%	Males	Females	Males	Females
Normal BMD	31.6	45.7	50.1	26.5	29.1
Osteopenia	47.9	45.7	40.1	53.5	48.0
Osteoporosis	20.5	**8.6**	**9.8**	20.0	22.9

Conclusion: • EDS-III is extremely frequent in our Clinic (80.2%), referral Center. • Significant percentage of EDS-III patients are not hypermobile (BSc negative in 51.0%). In some studies, many EDS-III patients are excluded when only applying the BSc rather than the BC, this is our reason for preferring to use the term Ehlers-Danlos type III, instead of Ehlers-Danlos Hypermobile. • Dysautonomia is very prevalent in young EDS-III females (84%). Low BMD is frequent, even at young ages, including Osteoporosis, 8.6% in males and 9.8% in females.

Disclosure: J. F. Bravo, None;

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Abstract Number: 37

Association Between Fibromyalgia and Bone Mineral Density: A Systematic Review and Meta-Analysis

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Background/Purpose:

Previous studies have shown that fibromyalgia syndrome (FMS) is associated with low level of physical activity and exercise, which may lead to an increased risk of osteoporosis. However, studies of bone mineral density (BMD) in fibromyalgia have shown conflicting results. Thus, we conducted a systematic review and meta-analysis to better characterize the association between FMS and BMD.

Methods:

A comprehensive search of the databases of the MEDLINE and EMBASE was performed from inception through May 2016. The inclusion criterion was the observational studies' assessment of the association between fibromyalgia and bone mineral density in adult subjects. Fibromyalgia was diagnosed in accordance with the American College of Rheumatology (ACR) criteria for the diagnosis of fibromyalgia syndrome. BMD was measured at the lumbar spine and femoral neck by dual-energy X-ray absorptiometry (DEXA). Pooled mean difference (MD) of BMD at each site and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method. The between-study heterogeneity of effect-size was quantified using the Q statistic and I^2.

Results:

Data were extracted from 4 observational studies involving 680 subjects. At lumbar spine (L2-L4), BMD is significantly decreased in patients with FMS compared with controls with pooled MD of -0.02 (95% CI -0.03 to -0.01, P-value=0.003, I^2=0%) (Figure 1). At femoral neck, BMD is not significantly decreased in patients with FMS compared

with controls with pooled MD of -0.01 (95% CI -0.02 to 0.01, P-value=0.23, I^2=0%) (Figure 2).

Conclusion:

In this meta-analysis, we observe that bone mineral density at lumbar spine is decreased in FMS compared with normal individuals. Patients with FMS should be assessed for risk of osteoporosis. Figure 1: BMD at Lumbar spine

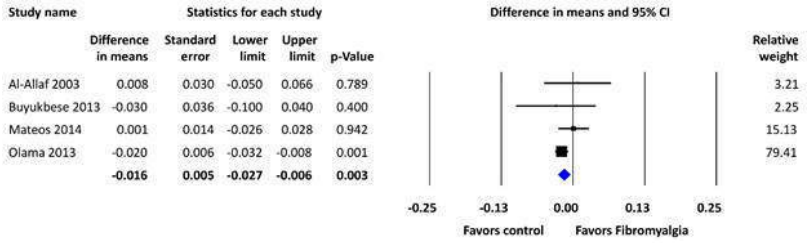
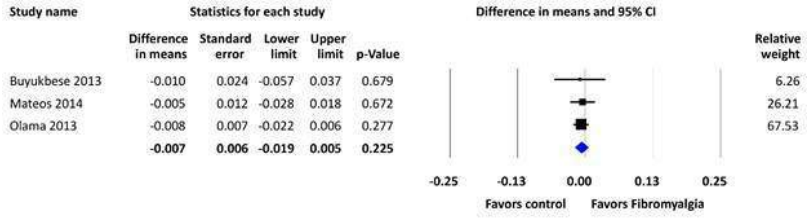


Figure 2: BMD at Femoral Neck



Disclosure: S. Upala, None; **A. Sanguankeo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/association-between-fibromyalgia-and-bone-mineral-density-a-systematic-review-and-meta-analysis

Abstract Number: 38

How Does Thiol/Disulphide Homeostasis Change in Fibromyalgia Patients?

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Our aim was to investigate the thiol/disulphide homeostasis, which has an important role in many cellular activities such as antioxidant protection, detoxification, cell growth and apoptosis in fibromyalgia patients.

Methods: The study population was formed of a total of 93 participants; 46 females of which were diagnosed with fibromyalgia and 47 (1 male, 46 females) healthy volunteers. Fibromyalgia patients were diagnosed using criteria American College of Rheumatology (ACR). In both groups, native thiol-disulphide exchanges were examined using the

automated measurement method newly developed by Erel and Neselioglu.

Results: When we determine at the thiol/disulphide homeostasis parameters in both groups, we can see the mean native thiol (p=0.000), total thiol (p=0.004), native thiol/total thiol (p=0.000) levels and white blood cell (p=0.040) were lower in the fibromyalgia group than the control group. The mean disulphide level (p=0.008), the disulphide/native thiol ratio (p=0.000), the disulphide/ total thiol (p=0.000) levels and glucose (p=0.041) were higher in the fibromyalgia group when compared to the control group. A negative correlation was determined between age, marital status, waist circumference, fibromyalgia impact questionnaire (FIQ) and native thiol, total thiol levels. Low thiol levels and high disulphide levels in the fibromyalgia patients were found to be independent of gender, age and body mass index.

Conclusion: In this study we have shown that thiol/disulphide homeostasis may be used as a novel oxidative stress marker in fibromyalgia patients. Further studies are needed to confirm the pathophysiologic role of thiol/ disulphide homeostasis in fibromyalgia.

Disclosure: B. Ekinci, None; **C. Bicer**, None; **P. Baran**, None; **S. Haliloglu**, None; **H. Uzkeser**, None; **A. Carlioglu**, None.

Abstract Number: 39

Effects of Pregabalin (Lyrica®) on Cerebrospinal Fluid Substance P in Human Subjects with Fibromyalgia Syndrome

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Background/Purpose: Fibromyalgia Syndrome [FMS] is a common chronic pain disorder. Pregabalin (PGB) is one of three medications approved by the FDA for treatment of FMS. Substance P (SP), a neuropeptide known to facilitate pain transmission, is elevated in the cerebrospinal fluid (CSF) of FMS. The mechanism of PGB benefit in FMS is uncertain, but it is known to inhibit SP production by neurons *in vitro*. Our objective was to measure PGB's effect, if any, on CSF SP in FMS.

Methods: This study was investigator-initiated, -designed, -conducted, and –analyzed. It was randomized (2:1, PGB:PBO), double-blinded, placebo (PBO)-controlled, and involved only FMS females, 18-65 years of age. Funding was provided by a research grant from Pfizer Inc., which also provided the study medications (150mg PGB capsules, identical-appearing PBO). It was not an efficacy or safety clinical trial, since the primary outcome variable was biological (mean change in CSF SP level with PGB therapy). The 1990 ACR Research Classification Criteria were required for entry. At Screening (Visit #1), informed consent was obtained, patients were examined for diagnosis, validated self-report measures were completed, a blood sample was obtained, participants began to taper-off potentially-interfering medications, and were off for 5+ half-lives. At Baseline (Visit #2), the self-report measures were repeated, CSF was collected for storage at -70°C, and patients were randomized to PGB or PBO, at bedtime. The dosage was increased over a period of 2 weeks to therapeutic (300-450 mg/24 hrs). After 6 full weeks of therapeutic dosage (Visit #4), the Patient Global Impression of Change (PGIC) was assessed, and a second CSF was stored. Numbered CSF samples were analyzed in-blind for SP and biogenic amines. Treatment groups were contrasted on the mean, using analysis of variance, and on categorical outcomes with Fisher’s Exact Test. All statistical testing was two-sided with a significance at 5%.

Results: The study was originally powered for 90 randomized subjects, but, a budget cut limited the sample size, leaving the study inadequately powered. Eighty four patients signed informed consent; 38 screen failed; 46 were randomized (PGB n=31, PBO n=15), five randomized patients later withdrew consent (PGB n=3, PBO n=2). A total of 41 completed the study (PGB n=28, PBO 13), each with 2 stored CSF samples. At Baseline, treatment groups did not differ in any respect (demographic, clinical, laboratory). At Visit #4, the PGIC distribution varied significantly (p=0.02) with treatment [PGB 60.7% (17/28) cf. PBO 30.7% (4/13) reporting being Much- to Very Much-Improved] while CSF SP had increased numerically in both groups (CSF SP, fmol/ml, PGB +15.8±56.7, PBO +10.8±60.2, p=0.94). Correlations between clinical outcomes and spinal fluid measures were noted. A statistical model was developed. The observed adverse events had been anticipated, and were generally mild. One post-spinal headache was considered serious, as it required blood patch treatment.

Conclusion: The study design produced comparable treatment groups. PGB affected clinically relevant improvement in more than half of the PGB-treated patients but the CSF SP concentration trended to rise.

Disclosure: I. J. Russell, Pfizer Inc., 2; **J. E. Michalek**, Pfizer Inc, 2; **S. Trevino-Mendez**, Pfizer Inc, 2.

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Abstract Number: 40

Lateral Epicondylitis Treatment: Comparison of Bandage, Laser Therapy and Extra-Corporeal Shock Wave Therapy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lateral epicondylitis is one of the most common conditions affecting elbow and characterized by a lesion of the common extensor tendon with or without inflammation. Main aim of treatments is pain relief and restoration of muscle condition. There is a wide spectrum of treatments used for management of lateral epicondylitis such as analgesic medications, exercise, orthoses and physical therapy. Extra-corporeal shock wave therapy is recommended as an alternative treatment for lateral epicondylitis. Although there are wide varieties of treatment choice, there is no consensus on its management. The aim of this study was to compare the efficacy of bandage, laser and extra-corporeal shock wave therapy in the treatments of lateral epicondylitis.

Methods: In this prospective, randomized controlled trial; 60 patients (44 women, 16 men, and mean age 46, 1±10 years) with lateral epicondylitis were enrolled. Patients were allocated into 3 treatment groups. Group 1 received only bandage, group 2 received bandage and laser, group 3 received bandage and extra-corporeal shock wave therapy. Outcome measures were visual analogue scale, disabilities of the arm, shoulder, and hand questionnaire, Nottingham health profile, pain-free grip strength, Duruoz hand index and Patient rated tennis elbow evaluation. All patients evaluated initially, at fourth week and after twelve week.

Results: All groups including splinting had statistically significant improvements compared to pre-treatment, posttreatment. The improvements were observed in more parameters in laser group than the other groups.

Conclusion: To our knowledge, this is the first study that comparing extra-corporeal shock wave therapy and laser therapy in laterals epicondylitis. In this study we found that splinting, combination of splinting and laser or extra-corporeal shock wave therapy has positive effects on pain, function and quality of life in the management of lateral epicondylitis. However, the laser therapy seems to more effective than the others.

Disclosure: F. Icyer, None; **H. Uzkeser**, None; **S. Karatay**, None.

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Abstract Number: 41

Human Papilloma Virus Vaccination, Fibromyalgia and Dysautonomia

Manuel Martínez-Lavín[1], Paola-Kinara Reyes-Loyola[2] and Laura-Aline Martinez-Martinez[3], [1]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico, [2]Rheumatology, National Institute of Cardiology, Mexico, Mexico, [3]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, TX, Mexico

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Session Time: 9:00AM-11:00AM

Background/Purpose: In a questionnaire-based case series, we described the clinical features of 45 patients who had the onset of a chronic illness soon after HPV vaccination. Fifty three percent of them fulfilled the 2010 ACR fibromyalgia diagnostic criteria (Clin Rheumatol 2015;34:1981). The objective of the present report is to correlate fibromyalgia severity with dysautonomia severity in an enlarged cohort of patients who developed a chronic ailment soon after HPV vaccination.

Methods: We e-mailed the 2010 ACR fibromyalgia diagnostic criteria questionnaire and a validated dysautonomia questionnaire (COMPASS-31) to individuals who had the onset of a chronic illness after HPV vaccination. Those subjects who had a disease onset within the following three months after HPV immunization are included in this report. We correlate the total COMPASS-31 score with the following 2010 ACR fibromyalgia diagnostic criteria domains: Polysymptomatic Distress Scale, Widespread Pain Index values, and Symptoms Severity Scale.

Results: Fifty five eligible patients filled out both questionnaires. Thirty five (63 %) of them fulfilled the 2010 ACR fibromyalgia diagnostic criteria. At vaccination time, those patients who fulfilled the 2010 ACR fibromyalgia diagnostic criteria were older than those who did not (17 +/- 8 year old vs. 14 +/- 5 year old. $P = 0$ 0.038). Twenty three percent of all post HPV vaccine fibromyalgia girls had their disease onset within 24 hours after vaccination. In the fibromyalgia group COMPASS-31 score was 52-4 +/- 17-8, reflecting widespread dysautonomia symptoms. Likewise fibromyalgia domain scores were high, implying the presence of severe fibromyalgia (table). COMPASS-31 score correlated with the three 2010 fibromyalgia diagnostic criteria domains: With Polysymptomatic Distress Scale ($rho=0.642$, $p<0.0001$), with Widespread Pain Index ($rho=0.550$, $p=0.001$) and with Symptoms Severity Scale ($rho=0.633$, $p<0.0001$). After a mean period of 4.5 years after vaccination, none of the immunized girls with fibromyalgia was able to work or attend school on a regular basis.

Conclusion: This questionnaire-based case series sub-analysis suggests that in young girls, disabling fibromyalgia may follow HPV vaccination. Correlations between Compass-31 scores and the 2010 fibromyalgia diagnostic criteria questionnaire suggest that in this group of HPV vaccinated girls, fibromyalgia and dysautonomia may share clinical and pathogenetic features. Table

Post HPV vaccination fibromyalgia patients (n = 35)	
Age (years)	20 ± 8
Female	100 %
Age at first HPV dose	17 ± 8
Illness onset within 24 hr. after vaccination, n (%)	8 (22.9%)
Illness onset between 24 hours to 3 months, n (%)	27 (77.1%)
ACR 2010 FM Polysymptomatic Distress Scale	36 ± 13
ACR 2010 FM Widespread Pain Index	10 ± 5
ACR 2010 FM Symptoms Severity Scale	26 ± 9
COMPASS-31 scale value	52.4 ± 17.8

Disclosure: M. Martínez-Lavín, None; **P. K. Reyes-Loyola**, None; **L. A. Martinez-Martinez**, None.

Abstract Number: 42

Small Fibre Neuropathy Biopsies (SFN) in Primary Fibromyalgia Revealed Predominant Association with Metabolic Syndrome (in addition to other known treatable causes of SFN) but No Clear Distinction Related to Biopsy Results

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Background/Purpose: To assess patients with primary fibromyalgia (pFM) for small fibre neuropathy (SFN) and to correlate biopsy results between groups and with known causes of SFN

Methods: A total of 21 patients with pFM (M:F=19:2) had 3mm skin punch biopsies from 2 leg sites-proximal and distal (20cm below right iliac crest and 10cm above right lateral malleolus) following appropriate consent. PGP-5 has been used as a pan axonal marker. Clinical assessments obtained on pain, sleep disturbance, effect of the disease on well being past week and past month , FM pain and FM fatigue (all on a VAS 0-10; 10=worse positive). Fabro fatigue scale (0-90), Rotterdam emotional scale (30-120) ability to perform activities (8-32; 8 best ability). Each patient from the pFM group was examined for conditions known to be associated with SFN [1]: namely: Thyroid disease (hypo and hyper), metabolic syndrome, insulin resistance, diabetes, Family history (Fx) of diabetes, impaired Glucose tolerance, sarcoid, coeliac disease, B12 deficiency, chemotherapy drugs, para-neoplastic syndrome, antiviral drugs, Human Immunodeficiency Virus (HIV), Neurotoxins, palindromic rheumatism, Fx of psoriasis, hepatitis, Systemic Lupus Erythematosus, Sjogren's, amyloidosis, restless syndrome, Guillain Barre, demyelinating polyneuropathy, complex regional pain syndrome and alcoholism. Demographic, ethnic, clinical, laboratory and disease associated comparisons between SFN(+) and SFN(-) biopsy groups took place.

Results: Age (mean) of the group was of 44.48 years (y) sd (+10.9) range (20-73). Age of symptoms onset was of 32.7 y (+ 10.9)(range 12-50) while mean age of diagnosis was 40.5 y (+ 8.9)(range 21-55). Data on tender point evaluation showed that all 21 patients were fulfilling 2011 criteria for FM while 18 of 21 patients were fulfilling the 1999 criteria having >11 tender points. Biopsy results showed 14 patients of 21 (66.6%) of pFM patients to be positive for SFN while 7 patients (33.3%) were negative. Looking at SFN associations, a total of 19 of 21 patients with pFM(90.4%) had an

associated cause from those listed related to SFN. More specifically 7 patients had metabolic syndrome (including diabetes and Fx of diabetes), 5 patients had hypothyroidism, 4 had B12 deficiency and 3 patients had family history of psoriasis. No predominant distribution according to biopsy results was found. Similarly no difference between the demographic, ethnic, clinical or laboratory characteristics between SFN (+) and SFN(-) found.

Conclusion: Metabolic syndrome along with other known causes of SFN is related to pFM. Reference: [1]. Hovaguimian A, Gibbons C. Diagnosis and treatment of pain in small fibre neuropathy. Curr Pain Headache Rep. 2011;15(3)193-200.

Disclosure: E. Roussou, None; **J. Chan**, None; **I. Bodi**, None; **A. Radunivics**, None.

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Abstract Number: 43

Comorbid Development of Fibromyalgia and Posttraumatic Stress Disorder after Exposure to a Combat Environment

Katrina Lawrence-Wolff[1], Jay B. Higgs[2], Douglas Williamson[3], Stacey Young-McCaughan[4], Jim Mintz[4], Bernard Hildebrand[1], Antoinette Brundige[4], Kevin Kelly[5], Adam Borah[5], Brett Litz[6], Elizabeth Hembree[7], Alan Peterson[4] and STRONG STAR Consortium, [1]Rheumatology, San Antonio Military Medical Center, San Antonio, TX, [2]Rheumatology, San Antonio Military Medical Center, Fort Sam Houston, TX, [3]Duke Univeresity, Durham, NC, [4]The University of Texas Health Science Center at San Antonio, San Antonio, TX, [5]Carl R. Darnall Army Medical Center, Fort Hood, TX, [6]VA Boston Healthcare System, Boston, MA, [7]University of Pennsylvania, Philadelphia, PA

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Background/Purpose: Traumatic experiences are postulated mediators of the development of Fibromyalgia Syndrome (FMS). The STRONG STAR Consortium study of PTSD provides a unique opportunity to study FMS in a large population of service members (SM) exposed to combat stress. We have previously reported a baseline 3% prevalence of fibromyalgia among active duty service members prior to deployment (Hildebrand et al, 2014). This cohort has now been re-assessed following deployment to a combat environment.

Methods: Active duty US SM were recruited as part of a STRONG STAR Consortium study to evaluate genetic and environmental predictors of combat-related PTSD. Participants completed surveys immediately prior to overseas deployment to a combat environment and again upon return. The research classification of fibromyalgia was ascertained using the modified 2010 ACR survey criteria. Demographics, military service, and PTSD were assessed using standardized and psychometrically validated assessments.

Results: Questionnaires were completed both prior to and following deployment by 1761 SM from the original cohort of 4119. The pre-deployment (pre-D) prevalence of FMS was 2% vs post-deployment (post-D) 8% ($p<.00001$, odds ratio 8.2, 95% CL=4.8-14.0). The prevalence of PTSD was 20% pre-D and 23% post-D ($p<.0415$, OR=1.2, 95% CL=1.0-1.45). Stratification of groups by their fibromyalgia and PTSD classification revealed several trends: Among those without FMS pre-D, 13% of SM with pre-D PTSD developed FMS post-D (i.e., developed FMS during deployment) while only 6% without PTSD pre-D developed FMS post-D ($p<.0001$, OR=2.4, 95% CL=1.64-3.59). Among those without FMS pre-D, 23% with post-D PTSD developed FM, while only 3% of those without post-D PTSD met criteria for FMS ($p<0001$, OR=11.0, 95% CL=7.3-16.6). Conversely, 71% who met criteria for FMS pre-D also met criteria for pre-D PTSD while only 19% without FMS met criteria for PTSD ($p<.00001$, OR=10.2, 95% CL=5.0-20.9). Post-D, this ratio was similar in that 68% who met criteria for FMS also met criteria for PTSD while only 19% who did not meet criteria for FMS met criteria for PTSD ($p<.00001$, OR=9.4, 95% CL=6.5-13.6). For those SM gaining a new PTSD diagnosis post-D, the rate

of new FMS was also significantly higher (22%) than for those who did not acquire new PTSD post-D (2.3%, p<.00001, OR=11.8, 95% CL=7.2-19.3).

Conclusion: This is the first longitudinal study to assess the prevalence of FMS before and after a military deployment to a combat environment. Exposure to an environment in support of combat operations is strongly associated with an increased prevalence of FMS. Additionally, FMS and PTSD appear to be highly comorbid. Future research should consider the influence of other mental health diagnoses, repeated deployments, head injuries, genetic variations, and particular job exposures on the risk for FMS.

Disclosure: K. Lawrence-Wolff, None; **J. B. Higgs**, None; **D. Williamson**, None; **S. Young-McCaughan**, None; **J. Mintz**, None; **B. Hildebrand**, None; **A. Brundige**, None; **K. Kelly**, None; **A. Borah**, None; **B. Litz**, None; **E. Hembree**, None; **A. Peterson**, None.

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Abstract Number: 44

Ambroxol for Fibromyalgia. One-Group Pretest-Posttest Open Label Clinical Observation

Laura-Aline Martinez-Martinez[1], Luis-Fernando Perez[2], Gumaro Acosta[2], Lizbeth Becerril[3], Pedro Rodriguez-Henriquez[4], Omar-Eloy Muñoz-Monroy[5], Luis H. Silveira[6], Angelica Vargas Guerrero[7] and Manuel Martínez-Lavín[7], [1]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, TX, Mexico, [2]National Institute of Cardiology, Mexico, Mexico, [3]Hospital Juarez, Mexico, Mexico, [4]Rheumatology, Instituto Nacional de Cardiología Ignacio Chávez, Mexico City, Mexico, [5]Hospital Militar, Mexico City, Mexico, [6]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City DF, Mexico, [7]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico

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Background/Purpose: A consistent line of investigation proposes that fibromyalgia is a sympathetically maintained neuropathic pain syndrome. Moreover it has been suggested that dorsal root ganglia and peripheral sensory neuron sodium channels may play a major role in fibromyalgia pain transmission (BMC Musculoskelet Disord. 2012;13:23). Ambroxol (2-amino-3,5-dibromo-N-[trans-4-hydroxycyclohexyl]benzylamine) is a secretolytic agent used in the treatment of various airway disorders since the late 1970s. More recently it was determined that this compound also has potent anti-neuropathic pain properties. In vitro studies have shown that ambroxol is stronger than lidocaine in sensory neuron sodium channel blockade (Neurosci Lett, 2006;395:179). Furthermore; this medication is effective in the neuropathic pain animal model (Pharmacol Biochem Behav. 2010;97:249). Ambroxol has good safety profile. In many countries this compound is freely dispensed as over-the-counter medication. Our objective was to evaluate the add-on effect of ambroxol in the treatment of fibromyalgia.

Methods: In this one-group pretest-posttest open label pilot clinical observation we recruited 26 patients with fibromyalgia that fulfilled the 2010 ACR diagnostic criteria. The institutional ethics and research committees approved the protocol. Ambroxol was added to the stable pharmacological therapy. Ambroxol was prescribed at the usual clinical dosage of 30 mg PO 3 times a day x 1 month. At the beginning and at the end of the study all participants filled out the following questionnaires: the Revised Fibromyalgia Impact Questionnaire (FIQ-R), the Hospital Anxiety and Depression Scale (HADS), the 2010 ACR diagnostic criteria including the following domains: Widespread Pain Index (WPI), Symptoms Severity Scale (SSS) and Polysymptomatic Distress Scale (PDS).

Results: Patients mean age was 45±10 years. All of them female. At the end of the study; FIQ-R decreased from a baseline

value of 62±15.6 to 51.1±18.9 (p = 0.023). VAS for pain decreased from 76.4±14.4 to 56.2±30.4 (p = 0.010). WPI diminished from 14.6±3.0 to 10.4±5.2 (p = 0.001), SSS from 9±4 to 7±2 (p=0.014), PDS from 24±5 to 17±7 (p<0.001). HADS anxiety and depression scores had not significant changes. Side effects were minor and did not required drug withdrawal.

Conclusion: In this pilot study the use of ambroxol was associated to decreased fibromyalgia pain and improved fibromyalgia symptoms. The open nature of our study does not allow extracting the placebo effect from the positive results. The drug was well tolerated. Ambroxol newly recognized pharmacological properties could theoretically interfere with fibromyalgia pain pathways. Dose finding controlled studies are warranted.

Disclosure: L. A. Martinez-Martinez, None; **L. F. Perez**, None; **G. Acosta**, None; **L. Becerril**, None; **P. Rodriguez-Henriquez**, None; **O. E. Muñoz-Monroy**, None; **L. H. Silveira**, None; **A. Vargas Guerrero**, None; **M. Martínez-Lavín**, None.

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Abstract Number: 45

Small Fiber Neuropathy in Rheumatology Clinics

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Session Time: 9:00AM-11:00AM

Background/Purpose: , Small Fiber Neuropathy (SFN) is a condition prevalent in patients with rheumatic diseases, particularly Fibromyalgia. The presence of neuropathic pain with normal nerve conduction studies raises the possibility of a neuropathy confined purely to the small unmyelinated nerve fibers: a small fiber neuropathy. Our clinical observations suggest small fiber neuropathy is an under-recognized but common manifestation of fibromyalgia that has important diagnostic significance. Testing for SFN assists providers in formulating specific diagnosis of symptoms in patients evaluated by rheumatologists. These small fiber neuropathies can be diagnosed through a 3-mm punch biopsy and may offer insight into the pathogenesis of some cases of fibromyalgia. Objective:, The purpose of this study is to discuss SFN, the importance of its association with rheumatologic conditions, diagnosis and treatment.

Methods: ,This was retrospective open label study carried out at two centers. 19 patients diagnosed with fibromyalgia according to American College of Rheumatology criteria underwent epidermal nerve fiber density to determine if the patient has SFN. A 3-mm punch biopsy samples were obtained from the right leg; 10 cm proximal to the lateral malleolus and 10 cm distal to the greater trochanter of the lateral upper thigh. Both specimens are placed in anatomically designated sample tubes. Biopsy samples were shipped to the Corinthian Reference Lab in Benbrook, Texas (with the exception of one sample sent to Therapath Neuropathology Laboratory in New York) where nerve fibers are manually counted and patient's biopsy specimen are interpreted. Nerve fiber density is determined through pathological review.

Results: 19 patients were in the study, 16 females (84.2%) and 3 males (15.8%) underwent skin biopsies, every patient had been diagnosed with and being treated for fibromyalgia and complaining of neuropathy with normal nerve conduction test , 6 patients have Sjogren's Syndrome (31.6%), 2 patients have Hashimoto's thyroiditis (10.5%), 1 patient has sarcoidosis (5.3%), 6 patients have low vitamin D (31.6 %), 5 patients have low vitamin B12 (26.3%), 3 patients have Rheumatoid Arthritis (15.8%) and 3 have lupus (15.8%). Upper and lower normal values were provided specifically for each patient to which each patients nerve fiber density was compared to. 11 patients (57.9%) presented with significantly decreased upper and lower nerve fiber density. Only 1 patient (5.3%) had normal lower nerve fiber density values and 5

patients (26.3%) had a normal upper nerve fiber density value. Two patients (10.5%) had both normal upper and lower nerve fiber density.

Conclusion: Results obtained coincide with our clinical observations that SFN serves as a component in patients with rheumatologic conditions, specifically fibromyalgia. 17 out of 19 patients with fibromyalgia and neuropathic pain were found to have a small fiber neuropathy based on reduced epidermal nerve fiber density on a standard 3-mm punch biopsy. Impaired small fiber function in patients with fibromyalgia, pointing towards a neuropathic nature of pain in fibromyalgia. These results suggest testing of possible underlying conditions including connective tissue disease, glucose metabolism, vitamin D deficiency, B12 deficiency, sarcoidosis, and others is warranted. Further large prospective study is needed including treating underlying conditions and or other modalities including use of immune globulin.

Disclosure: S. Metyas, None; **R. Messiah**, None; **T. Gettas**, None; **C. Chen**, None; **D. Arkfeld**, None.

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Abstract Number: 46

Novel Composite Responder Endpoints for Fibromyalgia Therapy Assessment

R Michael Gendreau[1], Lesley Arnold[2], Daniel J. Clauw[3], Judith Gendreau[4], Bruce Daugherty[4] and Seth Lederman[4], [1]Gendreau Consulting LLC, Poway, CA, [2]University of Cincinnati, Cincinnati, OH, [3]Chronic Pain & Fatigue Research Center, University of Michigan, Ann Arbor, MI, [4]Tonix Pharmaceuticals, New York, NY

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Background/Purpose: Novel composite responder definitions for fibromyalgia (FM) clinical trials have been proposed by the Outcome Measures in Rheumatology (OMERACT) FM subcommittee. These definitions which include key symptom and functional domains relevant to FM patients, were validated using outcome data from 12 previous registration trials of 4 other medications (Arnold L et al, Arth Rheum 64:885, 2012.) TNX-102 SL* is a proprietary sublingual formulation of cyclobenzaprine hydrochloride (2.8 mg) being studied for conditions with sleep disruption, including fibromyalgia and post-traumatic stress disorder (PTSD). "BESTFIT" was a 12-week Phase 2, randomized, double-blind, placebo-controlled trial conducted at 17 US sites, designed to evaluate this medication as a potential treatment for FM. A total of 205 participants were randomized (TNX=103; placebo=102).

Methods: The two recommended OMERACT responder definitions were evaluated: the FM30 Short, which defines a responder as ≥30% reduction in pain, ≥10% improvement in physical function plus a ≥30% improvement in either sleep or fatigue, and the FM30 Long, which defines a responder as ≥30% reduction in pain, ≥10% improvement in physical function plus ≥30% improvement in any two of the following measures: sleep, fatigue, depression, anxiety or cognition. Individual patient level analyses determine if each participant in the study met the response criteria.

Results: The table below compares a standard pain responder analysis (≥30% improvement in pain based on daily diary data), which was the secondary efficacy endpoint in the "BESTFIT" study, to the alternative composite responder

Responder Definition/ Result (pain based on diary)	Physical Function Measure	Additional Symptom Measures	Result (TNX-102 SL vs. placebo; p-value)
30% Pain Responder	None	None	34.0% vs. 20.6%; p=0.033
FM30 Short Ver 1	SF-36 physical function	1[a]	23.3% vs. 11.8%; p=0.038
FM30 Short Ver 2	SF-36 PCS score	1[a]	25.2% vs. 11.8%; p=0.015
FM30 Long Ver 1	SF-36 physical function	2[b]	21.4% vs. 9.8%; p=0.031
FM30 Long Ver 2	SF-36 PCS score	2[b]	23.3% vs. 9.8%; p=0.011

PCS: Physical Component Summary

[a]1: either FIQR sleep or FIQR energy;
[b]2: any 2 out of FIQR sleep, FIQR energy, FIQR depression or FIQR anxiety.

definitions proposed by OMERACT.

Additional improvements in other domains were noted as well. Systemic adverse events reported were similar to placebo. The most common local adverse event was transient tongue or mouth numbness occurring in 44% of the TNX-102 SL patients and in 2% of placebo patients.

Conclusion: Routine bedtime usage of TNX-102 SL improved multiple symptoms of FM. Comparison of response rates determined by either 30% reductions in pain alone, or by the proposed composite definitions, were all statistically significant. Although the apparent response rate for the composite definitions is necessarily less than that seen with the pain response only analysis, the actual statistical separation between treatment groups is enhanced. This analysis using the composite responder criteria developed by OMERACT suggests that the improvements in FM symptoms in this study of TNX-102 SL may not be limited to an analgesic response, since these composite criteria also require improvements in other somatic and functional symptoms.

* TNX-102 SL is an Investigational New Drug and has not been approved for any indication.

Disclosure: R. M. Gendreau, Tonix Pharmaceuticals, 5; **L. Arnold**, Pfizer, Inc, 9,Zynerba, 9,Astellas, 9,Lilly, 2,Allergen, 2,Daiichi Sankyo, 9,Tonix, 2; **D. J. Clauw**, Pfizer, Lilly, Tonix, Zynerba, Apptinix, Cerephex, IMC, 5,Paizer, Lilly, Cerephex, Tonix, 2; **J. Gendreau**, Tonix Pharmaceuticals, 3; **B. Daugherty**, Tonix Pharmaceuticals, 3; **S. Lederman**, Tonix Pharmaceuticals, 3.

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Abstract Number: 47

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn

Abstract Number: 48

Fibromyalgia Impact Is a Potential Mediator for the Associations of Self-Efficacy and Pain Catastrophizing with Physical Functioning in Persons with Fibromyalgia

Sun Yu[1], Lori Lyn Price[2], Jeffrey B. Driban[1], William F. Harvey[1] and Chenchen Wang[1], [1]Rheumatology, Tufts Medical Center, Boston, MA, [2]Biostatistics Research Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA

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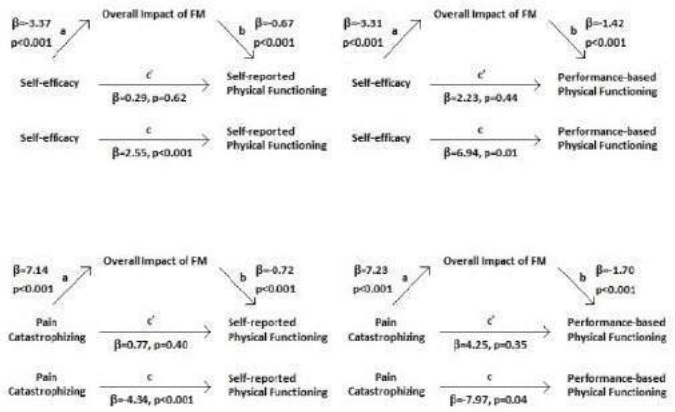
Background/Purpose: Fibromyalgia (FM) is a chronic multidimensional disorder that causes physical and psychological impairment, incurring significant healthcare costs. Self-efficacy and pain catastrophizing have been shown consistently to predict disability in chronic pain populations. However, the extent and the mechanism of their impact on physical functioning in people with FM are yet unclear. The purpose of this study is to examine if self-efficacy and pain catastrophizing are associated with both self-reported and performance-based physical functioning in individuals with FM. We also explore the potential of the overall impact of FM as a mediator.

Methods: We analyzed the baseline data from a randomized controlled trial comparing the effects of Tai Chi and aerobic exercise in individuals meeting both the 1990 and 2010 ACR Criteria for FM. Participants completed the 8-Item Arthritis Self-Efficacy Scale modified for FM (ASES-8, range 0-10), Catastrophizing subscale of the Coping Strategies Questionnaire (CSQ-CAT, range 0-42), 36-Item Short-Form Health Survey Physical Functioning scale (PF-10, range 0-100), and the Revised Fibromyalgia Impact Questionnaire (FIQR, range 0-100), with higher scores indicating higher levels of the respective constructs measured, as well as the 6-Minute Walk Test (6MWT, measured in meters). Pearson correlation and multivariate linear regression analyses were used to test for associations. We also performed mediation analyses (Baron and Kenney with Sobel test and bootstrapping) using the FIQR as a mediator.

Results: We included 224 participants (mean age: 51.8 years [SD=12.0]; mean BMI: 30.7 kg/m^2 [SD=6.7]; 92.9% women; 61.2% white; 22.3% black). ASES-8 and CSQ-CAT were significantly associated with PF-10 (r= 0.25 and -0.30 respectively, both p<0.001) and with 6MWT (r=0.17 and -0.14 respectively, p=0.01 and 0.04 respectively). When adjusted for age, gender, obesity, and education, only the association between CSQ-CAT and 6MWT became insignificant (p=0.06). In addition, mediation analyses revealed that the FIQR attenuated the associations of ASES-8 and CSQ-CAT with PF-10 and 6MWT (see Figure).

Conclusion: Our study shows that, while FM patients' belief in the ability to manage FM-related symptoms and the tendency to catastrophize pain may shape the perception of his or her physical capacity and also influence the level of physical performance, they may not independently predict physical functioning in individuals with FM. The results of the mediation study show that the overall impact of FM, often viewed as a dependent variable, attenuates the associations between the cognitive constructs and physical functioning, suggesting its potential as a mediator. Future longitudinal studies designed to verify the directionality of the relationships are warranted.

Figure. Mediation Analyses*



*Results of the mediation study using the method suggested by Baron and Kenney with Sobel testing and bootstrapping. Path a: independent variable to mediator; Path b: mediator to dependent variable after controlling for independent variable; Path c': indirect path through mediator; and Path c: direct path; Total: c + c'. *Data used were cross-sectional and the directionality is not yet verified.*

Disclosure: S. Yu, National Institutes of Health, 2; **L. L. Price**, None; **J. B. Driban**, None; **W. F. Harvey**, None; **C. Wang**, National Institutes of Health, 2.

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Abstract Number: 49

Efficacy of Mirogabalin on Patient-Reported Pain and Sleep Interference in Patients with Diabetic Neuropathic Pain: Secondary Outcomes of a Phase 2 Proof-of-Concept Study

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Background/Purpose: Mirogabalin is a novel, preferentially selective a2d-1 ligand intended for treatment of pain associated with fibromyalgia and neuropathic pain. Mirogabalin efficacy and safety was evaluated in a randomized, double-blind, placebo-controlled and active comparator (pregabalin)-controlled, adaptive proof-of-concept phase 2 study in patients with diabetic peripheral neuropathic pain (DPNP) (*Diabetes Care* 2014;37:3253–61). Mirogabalin administered once or twice daily (5-30 mg/d) showed early and sustained reductions in average daily pain score (ADPS) relative to placebo ($P<0.05$ for 15, 20, and 30 mg/d) after 5 wk of treatment. Pain reduction with pregabalin 300 mg/d was not significantly different from placebo at end of 5 wks' treatment. The most common adverse events (AEs) with mirogabalin were dizziness (9.4%), somnolence (6.1%), and headache (6.1%). Here we report key secondary outcomes of mirogabalin on patient-reported pain and sleep interference.

Methods: Adults (≥18 years) with type 1 or 2 diabetes, HbA_{1c} ≤10% at screening, and DPNP for ≥6 months were eligible. Subjects (N=452) were randomly assigned (2:1:1:1:1:1:1 ratio) to receive placebo, dose-ranging mirogabalin (5, 10, 15, 20, or 30 mg/d), or pregabalin (300 mg/d) for 5 wk. Secondary efficacy end points included modified brief pain inventory (BPI) score, and average daily sleep interference score (ADSIS).

Results: At wk 5, statistically significant reduction in ADSIS was observed in the mirogabalin 15, 20, and 30 mg/d groups, compared with the placebo group (**Fig 1**). Baseline and mean changes from baseline in ADSIS and ADPS values at wk 5 (**Fig 2**) were strongly correlated. Four of the 6 BPI subscales showed significant differences in change from baseline to end point in at least 2 of the mirogabalin groups (15 and 30 mg/d), compared with placebo ($P<0.05$). Overall, a low incidence of treatment-related AEs was reported for mirogabalin.

Conclusion: These results support the efficacy of mirogabalin for improving patient-reported pain and sleep interference in patients with DPNP. Results support a direct impact on pain at the 3 highest tested doses of mirogabalin in this DPNP population. Current data did not support an indirect effect of mirogabalin on pain via an improvement of sleep, in contrast to what has been reported for pregabalin. This may be owing to duration of the current study and variability of results observed at tested doses of pregabalin across the larger and longer duration DPNP pregabalin studies. Investigation is underway in large phase 3 studies to clarify the relationship in pain reduction and sleep improvement. **Figure 1. Mean change in ADSIS from baseline to end of treatment.**

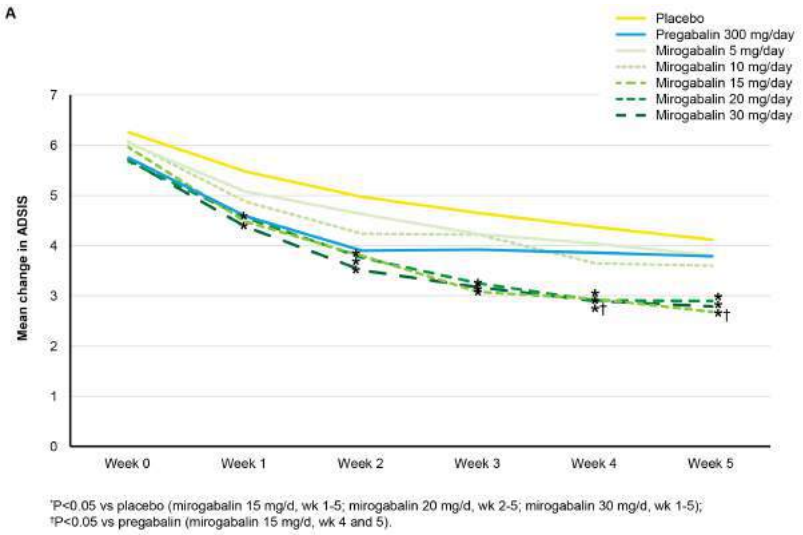
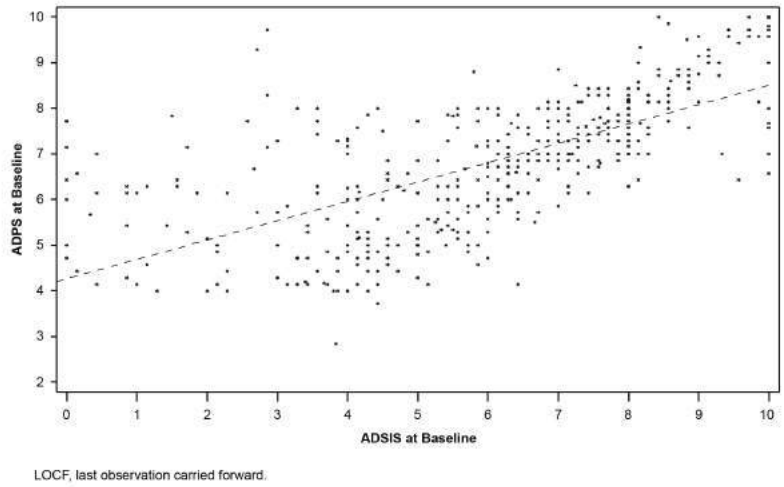


Figure 2. Correlation plot of weekly ADPS change from baseline and ADSIS change from baseline at wk 5 (LOCF).



Disclosure: D. Merante, D Sankyo Pharma Development Ltd., 3; **J. Rosenstock**, Daiichi Sankyo, 2,Daiichi Sankyo, 5; **U. Sharma**, None; **K. Feins**, Daiichi Sanyo Pharma Development, 3; **C. Hsu**, mirogabalin, 3; **A. Vinik**, MedScape, 9,Pfizer,Merck, Hydra, Neurometrix, ISIS Pharm, Astellas, Alnylam, Mitsubishi Tanabe, 5,ADA, NIH, Impeto, Daiichi Sankyo, 2.

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Abstract Number: 50

Tai Chi Significantly Modulates Resting State Functional Connectivity of the Cognitive Control Network in Fibromyalgia

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Session Time: 9:00AM-11:00AM

Background/Purpose: Fibromyalgia (FM) is a common and complex musculoskeletal pain syndrome with unsatisfactory treatment options. Studies suggest that Tai Chi mind-body exercise may be a promising treatment for Fibromyalgia. However, the underlying mechanism of Tai Chi remains unclear. Previous studies suggest that Tai Chi may modulate individuals' cognitive function which interacts reciprocally with pain. Thus, in this pilot brain imaging study, we first compared the resting-state functional connectivity (rsFC) of the cognitive control network (CCN) of FM patients to that of the matched healthy controls, and further examined how Tai Chi practice can modulate the CCN rsFC in relation to clinical outcomes.

Methods: We conducted a 3-month, non-randomized comparison trial of Tai Chi for participants with FM (ACR 1990 and 2010 criteria) vs. healthy controls. The 60-minute group sessions occurred twice-weekly. Each subject participated in two identical fMRI scanning sessions at baseline (Scan 1) and 3 months (Scan 2) after the end of Tai Chi intervention. Using a 3T Siemens MRI system, 8-minute resting state fMRI data were collected. Healthy matched controls were scanned only once. We also administered the Revised Fibromyalgia Impact Questionnaire (FIQR) before and after each fMRI scan. Seed-based rsFC was analyzed with CONN (https://www.nitrc.org/projects/conn/). Bilateral dorsolateral prefrontal cortex (DLPFC) was applied as the seed to explore the rsFC of cognitive control network. A threshold of voxelwise $p< 0.005$ and $p< 0.05$ Family-Wise Error (FEW) correction was applied for rsFC analysis.

Results: Twenty-one participants with FM and 20 age, gender, and BMI-matched healthy controls completed the study. One individual with FM and 1 healthy control were excluded from the rsFC analysis due to excessive head movement during scan. After Tai Chi interventions, there was a significant decrease in the total FIQR score (mean ± SD, pre: 45.7 ± 18.3, post: 36.4 ± 21, $p < 0.001$) and the three FIQR domains: Function (pre: 12.2 ± 6.1, post: 8.5 ± 6.4, $p< 0.001$), Overall Impact (pre: 8.9 ± 6.2, post: 7.0±5.7 $p<0.05$), and Symptom (pre: 25.4 ± 8.3, post: 20.9 ± 11.7, $p< 0.02$). Analysis of CCN rsFC showed that compared to matched healthy controls, FM patients were found to have significantly greater rsFC between DLPFC and bilateral rostral anterior cingulate cortex (rACC) / medial prefrontal cortex (MPFC), and the left precentral gyrus. In addition, we found 1) significant increase in the DLPFC rsFC at left rACC / MPFC after Tai Chi practice, and 2) a significant positive association ($p = 0.026$) between the baseline cluster Fisher z values at rACC/MPFC and corresponding cognitive performance, measured by the FIQR Overall Impact subscores after controlling for age at baseline.

Conclusion: Our results suggest that Tai Chi practice can significantly increase rsFC between the CCN and rACC / MPFC over 12 weeks in patients with FM. Our study further implies that Tai Chi may achieve clinical improvement by strengthening the cognitive control / adaption / coping process in individuals with FM. Elucidation of the mechanism will open a new window for FM management.

Disclosure: J. Kong, None; **K. Jorgenson**, None; **Z. wang**, None; **E. Wolcott**, None; **W. F. Harvey**, None; **C. Wang**, None.

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Abstract Number: 51

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-14

Abstract Number: 52

Pregabalin Dose-Response for Sleep Quality and Pain Response in Fibromyalgia: A Post-Hoc Analysis of Three Randomized Trials

Andrew Clair[1], Ed Whalen[1], Neal Thomas[1] and **Lynne Pauer**[2], [1]Pfizer, New York, NY, [2]Pfizer, Groton, CT

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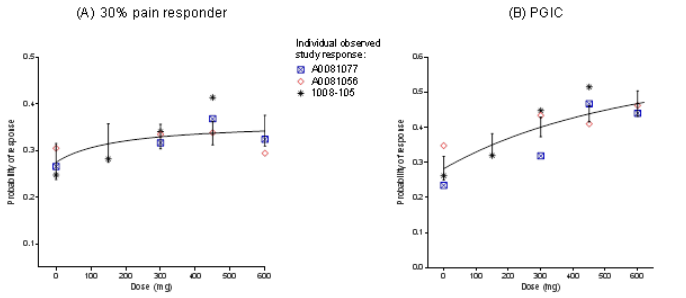
Background/Purpose: Pregabalin is often administered for treatment of fibromyalgia (FM) at daily doses lower than approved by the US Food and Drug Administration (starting dose 150 mg; recommended dose 300–450 mg). The objective of this post-hoc analysis was to characterize pregabalin efficacy across a range of doses and set expectations regarding the incidence of adverse events (AEs) through the course of FM treatment.

Methods: A hyperbolic E_{max} dose-response model using patient data pooled from 3 FM placebo-controlled trials examined the dose-response of pregabalin for pain (≥30% pain response), patient global impression of change (PGIC) and sleep quality. All patients had a diagnosis of FM based on the 1990 ACR criteria. After starting treatment, new incidences of AEs by study week were used to assess safety. Trials are identified by Pfizer study number (ClinicalTrials.gov identifier): 1008-105, A0081056 (NCT00645398), A0081077 (NCT00230776).

Results: The likelihood of FM patients achieving ≥30% pain response incrementally increased from 27.5% (90% CI, 23.8–31.5%) with placebo to 31.5% (27.5–35.8%) at 150 mg/d, 33.0% (30.4–35.7%) at 300 mg/d, 33.7% (31.3–36.3%) at 450 mg/d and 34.2% (31.0–37.6%) at 600 mg/d. The likelihood of improvements in PGIC increased in a dose-dependent manner with higher pregabalin doses (Fig. 1). Incremental improvements in sleep quality also occurred with increasing doses (Fig. 2). It was not possible to estimate the value of E_{max} and ED_{50} parameters for sleep quality over the current dose range and therefore the upper plateau of the dose-response curve was not attained for this endpoint. The resulting curve appears linear, a finding not expected over a broader dose range or using data from different trials. Dizziness and somnolence were commonly reported AEs. New incidences of dizziness and somnolence were highest after 1 week of treatment and were considerably fewer subsequently, decreasing week by week for the same dose (Fig. 3).

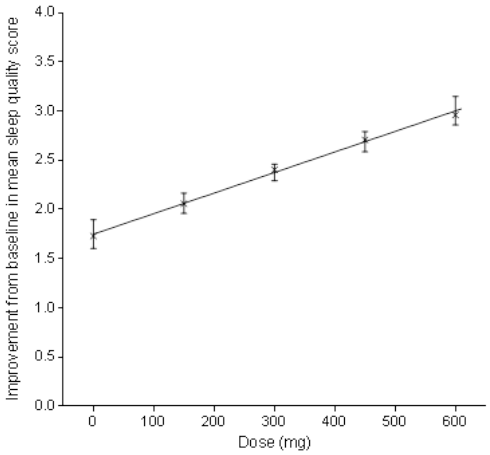
Conclusion: These data demonstrate the dose-response of pregabalin for pain, PGIC, and sleep, and highlight the incremental benefit of achieving the maximum recommended doses of 300–450 mg/d for treatment of FM. Common AEs are generally seen within 1 week of starting treatment, with few subsequent new reports for the same dose. This study was sponsored by Pfizer.

Fig. 1 Dose response analysis of effects of pregabalin on (A) pain relief and (B) PGIC at study endpoint



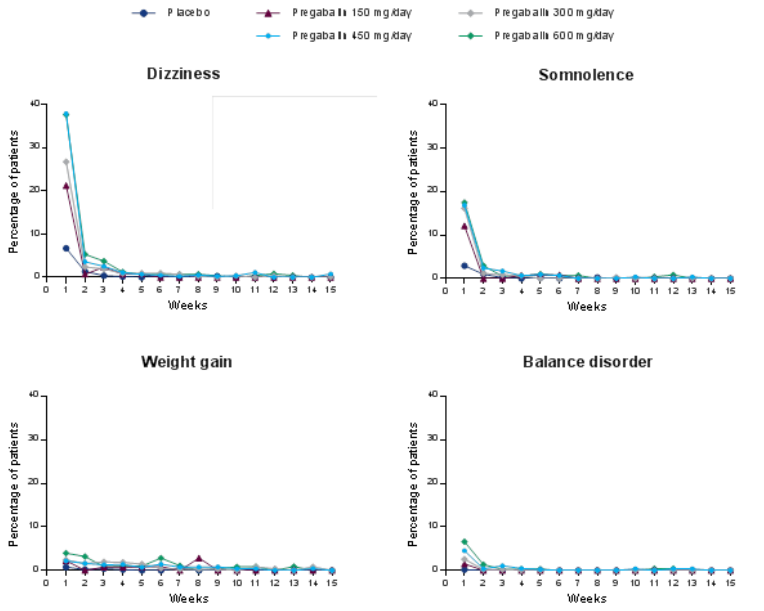
The data points are the individual observed study response, the curve is the hyperbolic E_{max} model and the bars are ± 90% confidence intervals for the true response proportion.

Fig. 2 Dose response analysis of effects of pregabalin on sleep quality at Week 8



Data shown are the combined mean observed study response ± 90% confidence intervals for studies A0081077, A0081056 and 1008-105 at Week 8.
Sleep quality scores range from 0 = 'best possible sleep' to 10 = 'worst possible sleep'.

Fig. 3 Incidence of most common adverse events in FM patients, by study week



Treatment-emergent adverse events (all-causality) reported in ≥5% of pregabalin-treated patients and, twice the rate of the placebo group, and with adverse event related discontinuation ≥1%.

Disclosure: A. Clair, Pfizer, 1,Pfizer, 3; **E. Whalen**, Pfizer Inc, 1,Pfizer Inc, 3; **N. Thomas**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Pauer**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 53

Efficacy of Cannabis Flos in Patients with Fibromyalgia: A Monocentric

Observational Study

Maria Chiara Gerardi[1], Alberto Batticciotto[2], Rossella Talotta[1], Maria Chiara Ditto[1], Fabiola Atzeni[2] and Piercarlo Sarzi-Puttini[1], [1]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milan, Italy, [2]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milano, Italy

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Efficacy of Cannabis flos in patients with fibromyalgia: a monocentric observational study

Background/Purpose: Fibromyalgia (FM) is a syndrome characterized by chronic widespread pain, fatigue, sleep and affective disturbances. Treatment is based on the symptomatic relief of symptoms but only modest results are achieved. There are few evidences on the effectiveness of cannabinoids in the improvement of FM symptoms. A cannabinoid (Cannabis flos 19%), containing tetrahydrocannabinolic acid 19% and cannabidiolic acid <1% used as orally decoction, is available in Italy for treating chronic pain. The aim of the this study was to evaluate the efficacy of Cannabis flos 19% on pain, fatigue, sleep disturbances, anxiety and depression in FM patients.

Methods: Fifteen patients affected by FM according to the ACR 2010 criteria and treated with Cannabis flos 19% (30 mg twice a day for the first month, 60 mg twice a day for the second month), have been evaluated at baseline and after 2 months of treatment with the following questionnaires: the Fibromyalgia Impact Questionnaire revised (FIQR), the Fibromyalgia Activity Score (FAS), the Functional Assessment of Chronic Illness Therapy (FACIT), the Pittsburgh Sleep Quality Index (PSQI), the Zung Self-Rating Anxiety Scale (ZS-RA) and the Zung Self-Rating Depression Scale (ZS-RD).

Results: Table 1 shows the demographic and clinical characteristics of the patients involved in study. 11/15 patients completed the 2-months follow up. After 2 months of treatment a statistical significant improvement in the terms of medians values of VAS pain (8.2±1 *vs* 6.2±2.4, p= 0,0273), FAS (7.8±1.7 *vs* 6.2±2.1, p= 0,0494), FACIT (13.5±7.4 *vs* 22.9±10.5, p= 0,0042), ZR-SA (66.2±14 *vs* 57.6±13.3, p= 0,0172) and ZS-RD (58±10.3 *vs* 48.7±11.5, p= 0,0491) has been found; while the median FIQ-R scores (74.4±17.2 *vs* 60.3±24.3, p= 0,0615) and sleep disturbances scores (PSQI, 11±2.8 *vs* 10.5±3.8, p= 0,5435) didn't change. Two patients (13%) stopped the treatment for inefficacy. Furthermore, although adverse events range from mild to moderate two patient stopped the treatment: one for the apparence of confusion and sweating and one for the mood deflection.

Conclusion: This study showed that Cannabis flos 19% is effective in improving pain, fatigue, anxiety and depression in FM patients. Further studies are suggested in order to confirm this preliminary data on efficacy and safety of this therapy for treating FM patients. **Table 1. Demographic and clinical characteristics of FM patients**

	FM patients (n=15)
Age, median (IQR)	53(50-54)
Female/Male	13/2
BMI, median (IQR)	26.6 (22-29)
No smokers, n(%)	4(27)
Ever smokers, n(%)	3(20)
Smokers, n(%)	8(53)
Disease duration (*months*), median (IQR)	180 (120-240)
Treatment, n (%)	
Pregabalin	2 (13)
Duloxetine	7 (47)
Amitriptyline	1 (7)
Tramadol	4(27)
Tapentadol	2 (13)
Others SNRIs	2(13)
Others opioids	3(20
Benzodiazepine	4(27)

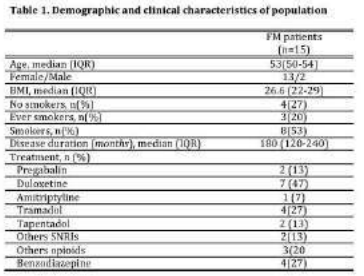
Table 1. Demographic and clinical characteristics of population

	FM patients (n=15)
Age, median (IQR)	53(50-54)
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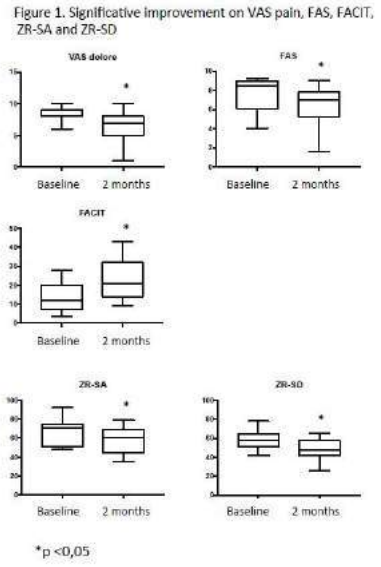

Disclosure: M. C. Gerardi, None; **A. Batticciotto**, None; **R. Talotta**, None; **M. C. Ditto**, None; **F. Atzeni**, None; **P. Sarzi-Puttini**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-of-cannabis-flos-in-patients-with-fibromyalgia-a-monocentric-observational-study

Abstract Number: 54

Patients with Fibromyalgia in General Have Higher Self-Report Questionnaire Scores Than Patients with Rheumatoid Arthritis: Implications for Clinical Trials and Clinical Research

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Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes - Poster I: Basic Science Focus

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with rheumatoid arthritis (RA) who are included in clinical trials generally are selected for measures indicating high disease activity, such as more than 6 swollen and/or tender joints and/or erythrocyte sedimentation rate (ESR) greater than 28. These inclusion criteria enhance the possibility of documenting responses to therapy. Patient questionnaire scores are correlated significantly with joint counts and to a lesser (but nonetheless significant) extent with ESR and other laboratory acute phase reactants. However, observations in clinical care suggest that scores on a multidimensional health assessment questionnaire (MDHAQ) generally are higher in patients who have distress, such as fibromyalgia or depression etc., than in patients with RA, unless the RA patients also have secondary distress. We therefore analyzed formally scores on an MDHAQ in patients with FM vs RA seen in routine care.

Methods: All patients with all diagnoses seen at one academic rheumatology center complete a multidimensional health assessment questionnaire (MDHAQ) at all visits in the waiting area, before seeing the rheumatologist in routine care. The MDHAQ includes 0-10 scores for physical function (FN), 0-10 pain (PN) visual analog scale (VAS), 0-10 patient global estimate (PATGL) VAS, compiled into a 0-30 RAPID3, as well as a 0-10 fatigue VAS, 0-48 RADAI self-report joint count, 0-60 symptom checklist, and demographic data. Mean levels of measures were compared in patients with RA or FM, analyzed using t tests.

Results: Patients with FM had higher scores for all MDHAQ scales studied, including FN, pain, PATGL, fatigue, RADAI, and symptom checklist (Table) ($p<0.001$). For example, RAPID3 scores were 11.4 for RA vs 17.8 for FM ($p<0.001$) (Table).

Conclusion: Evidence that patients who have FM have higher MDHAQ scores may initially appear to compromise the possible value of self-report questionnaire data in RA. However, the data may be informative in clinical research and clincial care in at least 2 ways: 1. It may be desirable to exclude patients from clinical trials who might have self-report scores that are extremely high, e.g., pain VAS >8/10, symptom checklist >24/60 of 60, as these patients are unlikely to respond to therapy, whether they have primary or secondary FM while meeting criteria for another rheumatic disease. 2. In routine care, high MDHAQ self-report scores may provide clues to identify patients who have primary or secondary FM, which is seen in 15-30% of patients with RA, SLE, or other rheumatic diagnoses. High self-report scores in FM may prove informative in rheumatology toward better interpretation of clinical researchand improved patient care.

Mean levels of MDHAQ measures in RA and FM

	RA	FM
Function (0-10)	2.6	3.6
Pain (0-10)	4.8	7.4
Patient Global Estimate (0-10)	4.3	6.9
RAPID3 (0-30)	11.4	17.8
RADAI self-report joint count (0-48)	10.6	
Fatigue (0-10)	3.9	6.9
Symptom Checklist (0-60)	7.6	17.5
$p < 0.001$ for all		

Disclosure: T. Pincus, Health Report Services Inc., 4; **I. Castrejón**, None; **J. Block**, None; **N. Cook**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/patients-with-fibromyalgia-in-general-have-higher-self-report-questionnaire-scores-than-patients-with-rheumatoid-arthritis-implications-for-clinical-trials-and-clinical-research

Abstract Number: 55

Identification of Endogenous Autoantigens Bound to Anti-Citrullinated Peptide Antibodies in Rheumatoid Arthritis: A Key Role for Citrulline

Residues in Histone 4

Xiaobo Meng[1], Peyman Ezzati[1], Irene Smolik[2], Carol Hitchon[3] and Hani El-Gabalawy[4], [1]UNIVERSITY OF MANITOBA, WINNIPEG, MB, Canada, [2]Arthritis Center, University of Manitoba, Winnipeg, MB, Canada, [3]University of Manitoba, Winnipeg, MB, Canada, [4]University of Manitoba Arthritis Center, Winnipeg, MB, Canada
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Background/Purpose: Anti-Citrullinated Peptides Antibodies (ACPA) aid in rheumatoid arthritis (RA) diagnosis. The nature of autoantigens specifically bound to ACPA immune complex *in vivo*remains unclear. We therefore sought to identify citrullinated proteins bound to ACPA immune complexes in RA synovial fluids (SFs) and to delineate their immunodominant epitopes.

Methods: ACPA were isolated from RA and non-RA SFs by immunoaffinity using immobilized cyclic citrullinated peptides-3 (CCP3). The composition of the antigen-antibody immune complexes was determined using mass spectrometry. Synthetic peptides containing citrulline residues derived from the target protein were used in ELISA assays to determine the immune reactions of sera from RA patients, controls, and a cohort of first degree relatives of RA patients.

Results: Histone family members were the most frequent autoantigens bound to anti-CCP3 antibodies in RA SFs. H4, H3, H2B, and H2A were identified in 90%, 68%, 53%, and 42% tested samples respectively. A histone 4 peptide containing citrulline at position R39 (Cit39) was a specific ACPA autoantigen to all anti-CCP3+ RA SFs (n=34). Another citrulline at R40 (Cit40) proved to be minor antigenic. Anti-H4 Cit39-40 antibodies were found in sera from 93% (158/170) of anti-CCP3+ RA patients, 77% (20/26) anti-CCP3+ individuals without arthritis, and 2.5% (2/80) controls.

Conclusion: Histones are prominent endogenous autoantigens binding to anti-CCP3 antibodies from RA patients. Anti-citrullinated histone 4 accounts an important part of all ACPA detected by anti-CCP3 standard.

Disclosure: X. Meng, None; **P. Ezzati**, None; **I. Smolik**, None; **C. Hitchon**, None; **H. El-Gabalawy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identification-of-endogenous-autoantigens-bound-to-anti-citrullinated-peptide-antibodies-in-rheumatoid-arthritis-a-key-role-for-citrulline-residues-in-histone-4

Abstract Number: 56

A Systems Biology Approach to Investigating Beneficial Effects of Endurance Exercise in Myositis Patients

Jessica Boehler[1,2], Marshall Hogarth[3], Matthew Barberio[3], Svetlana Ghimbovschi[2], Kristy Brown[1,2], Li Alemo Munters[4], Ingela Loell[4], Yi-Wen Chen[2,5], Helene Alexanderson[6], Ingrid E. Lundberg[7] and Kanneboyina Nagaraju[5,8], [1]Department of Integrative Systems Biology, The George Washington University, Washington, DC, [2]Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC, [3]Research Center for Genetic Medicine, Children's National Medical Center, Washington, DC, [4]Karolinska University Hospital, Rheumatology Unit, Department of Medicine, Solna, Karolinska Institutet, Karolinska University Hospital, Sweden, Stockholm, Sweden, [5]Department of Integrative Systems Biology, The George Washington University, Washington, DC, [6]Department of NVS, Division of Physical Therapy, Karolinska Institutet, Huddinge, Sweden, [7]Department of Medicine, Rheumatology Unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [8]Research Center for Genetic Medicine, Children’s National Medical Center, Washington, DC
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Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are skeletal muscle disorders characterized by proximal muscle weakness and inflammation. Recent studies have suggested that endurance exercise improves disease activity in PM and DM by suppressing inflammation and promoting muscle growth through activation of an aerobic muscle phenotype. The molecular mechanisms underlying disease improvement are not fully understood. We hypothesized that endurance exercise induces alterations in skeletal muscle microRNAs that control genes and proteins relevant to disease pathogenesis.

Methods: Patients, diagnosed as PM or DM according to the Bohan and Peter classification, were randomized into a 12-week endurance exercise group that consisted of cycling for 1 hour/3 times a week or a non-exercised control group. Muscle biopsies from the vastus lateralis were collected before and after the 12-week training program. MicroRNA expression profiling was determined using the Affymetrix platform, mRNA using the Illumina platform and proteomics using SuperSILAC mass spectrometry. Post intervention values were normalized to pre-intervention values and a t-test for unequal variance comparing exercised vs. control patients was used to determine significant changes ($p<0.05$). Ingenuity Pathway Analysis (IPA) MicroRNA Target Filter was used to identify gene targets. Gene expression profiling and proteomics were used to verify microRNA targets that were altered by exercise in the patients' skeletal muscle. IPA Core Analysis was used to determine the function of significantly changed transcripts and proteins.

Results: Endurance exercise differentially altered 188 microRNAs. Approximately one fourth of these microRNAs are predicted to target over 12,000 genes. We have found that endurance exercise alters microRNAs that affect various processes involved in the pathogenesis of myositis. MicroRNA-target transcripts altered after endurance exercise control genes that affect vasculature, inflammatory cells and skeletal muscle cells. We also found that anti-inflammatory, anti-fibrotic, and muscle regenerative and metabolic processes are affected favorably. MicroRNA-targeted proteomic analysis of these samples further confirmed that these pathways are altered at the protein level.

Conclusion: To our knowledge, this is the first systems biology study investigating microRNA, and its regulation on mRNA and protein, before and after exercise in myositis patients. Identified microRNAs can serve as biomarkers to assess disease progression, as well as monitor responses to therapy.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-systems-biology-approach-to-investigating-beneficial-effects-of-endurance-exercise-in-myositis-patients

Abstract Number: 57

Genetic Polymorphism of IL-1RN Encoding the IL-1 Receptor Antagonist Predicts Radiographic Severity of Symptomatic Knee OA

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Background/Purpose: Growing numbers of studies show increased expression in Osteoarthritis (OA) of inflammatory cytokines, such as IL-1β and TNFα, in joint tissues and peripheral blood mononuclear (PBM) cells. The IL1 receptor antagonist (IL1RN) gene cluster region has been associated with susceptibility to knee OA, thereby further implicating inflammation in OA pathogenesis. In these studies, we examined the association of IL-1RN haplotype with the radiographic severity of symptomatic knee OA (SKOA).

Methods: Genomic DNA from SKOA patients from three cohorts (NYU I, NYU-II and OAI – clinical characteristics are described in Table 1) in this prospective analysis were used to genotype three single nucleotide polymorphisms (SNPs) [rs419598, rs315952 & rs9005) based on our prior publications. Genotyping was accomplished by PCR using validated SNP primers and probes (Applied Biosystems) along with detection using allelic discrimination computation. Genotypes were scored blinded to all patients' data. Statistical analyses for associations of genotype with OA radiographic severity used Chi square and Fisher's exact test, with linear regression, adjusting for age, gender and BMI. Non-fasting Heparin plasma IL-1Ra levels were determined using R&D system ELISA kit.

Results: Carriage of two copies of a haplotype consisting of IL1RN rs419598, IL1RN rs315952 and IL1RN rs9005 (TTG-2), had a population frequency of 18%, and was associated with a significantly increased risk of more severe radiographic SKOA (KL1-2 vs. KL3/4; OR > 3.07; 95% CI 1.67 -5.68; p=0.000), compared to SKOA patients with zero copies of TTG (TTG-0) in all three cohorts (Table 1). Furthermore, narrower baseline radiographic medial joint space width (mJSW) was similarly associated with TTG-2 haplotype (Table 2). TTG-2 patients exhibited decreased JSW compared to TTG-0 patients of comparable age (50-80 years), consistent with earlier onset of disease. Biologically, TTG-2 patients in two of the cohorts had reduced plasma concentrations of the "protective" IL1RN gene product, IL-1Ra, (297 to 338 pg/ml; p=0.14) relative to TTG-0 OA patients.

Conclusion: IL-1RN haplotype TTG (rs9005, rs419598 and rs315952) predicted high risk for greater severity of radiographic knee OA. Carriers of two copies of the TTG SNP also exhibited lower plasma IL-1Ra concentrations. These data are consistent with the hypothesis that a relative deficiency of IL-Ra typified by TTG-2 patients results in enhanced IL-1β action in joint tissues and more severe OA. These genetic markers may also be useful as tools for enriching OA clinical trials for disease progressors.

Table 1: Baseline Clinical Characteristics and Association of IL-1RN Haplotype (TTG) With Radiographic Severity In Symptomatic Knee OA Patients

Mean (SD)								OA Severity (KL1/2 vs. KL3/4)	
IL-1RN Haplotype (TTG)	**Cohorts (N=612)**	**Gender % Female**	**Age**	**BMI**	**VAS pain**	**NRS pain**	**mJSW (mm)**	**Odds ratio (95% CI)**	**p value**
rs41958, rs315952, rs9005	**NYU-I (146)**	61.64	62.46 (10.11)	26.62 (3.58)	41.70 (28.30)	N/A	3.26 (1.75)	5.38 (1.25 – 23.28)	0.024
	NYU-II (226)	63.72	60.42 (10.68)	26.20 (3.45)	N/A	N/A	3.18 (1.31)	4.19 (1.35 – 13.01)	0.016
	OAI (240)	62.08	61.96 (8.90)	30.35 (5.09)	N/A	6.36 (1.60)	3.48 (1.7)	2.26 (0.90 – 5.70)	0.107
	All three cohorts combined							3.07 (1.67 – 5.68)	0.0003

Table 2: Association of IL-1RN Haplotype (TTG) With Baseline Radiographic Medial Joint Space Width (mJSW) In Symptomatic Knee OA Patients

		TTG (0 copies)	TTG (2 copies)	
IL-1RN Haplotype (TTG)	**Cohorts**	**Mean JSW (SD) in mm**	**Mean JSW (SD) in mm**	**p value**
rs41958, rs315952, rs9005	NYU-I	3.62 (1.681)	2.51 (1.66)	0.013
	NYU-II	3.31 (1.25)	2.68 (1.75)	0.074
	OAI	3.82 (1.43)	3.18 (1.24)	0.094
	All three cohorts combined	3.52 (1.43)	2.92 (1.82)	0.005

Disclosure: M. Attur, Interleukin Genetics, Inc., 7; **S. Ma**, None; **J. Samuels**, None; **S. Krasnokutsky Samuels**, None; **H. Zhou**, None; **J. Bencardino**, None; **M. C. Hochberg**, None; **B. Mitchell**, None; **V. B. Kraus**, None; **J. M. Jordan**, None; **S. B. Abramson**, Interleukin Genetics, Inc., 7.

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Abstract Number: 58

Detecting Novel Candidate Risk Genes in Rheumatoid Arthritis with Gene-Based Association Testing

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Background/Purpose: Rheumatoid arthritis (RA) is driven by immune-system dysfunction with contribution from genetic risk factors. Emerging data from genomewide association studies (GWAS) of single nucleotide polymorphisms (SNPs) has revealed 100 risk SNPs in RA outside the HLA region. Beyond GWAS, novel approaches for interpretation of big data are needed to unravel the complex genetics of RA. Our aim is to identify novel risk genes to improve the power of GWAS. We performed a gene-based association analysis using extended Simes procedure (GATES) in RA.

Methods: Our dataset consisted of 14,361 RA cases and 43,923 controls from GWAS meta-analysis in Europeans, from publicly available summary statistics[1]. All RA cases fulfilled the 1987 ACR criteria or were diagnosed by a rheumatologist. A powerful Knowledge-based mining system for Genome-wide Genetic studies (KGG) was used to run GATES for gene-based association testing with 8,694,488 SNPs (excluding extended MHC, chromosome 6, 25-33 Mb)[2]. Genes were defined as ± 5kb. Genomic control was calculated by median of Chi-square statistic. We accounted for linkage disequilibrium (LD) between SNPs from 1000 Genomes Project for Europeans. Bonferroni correction was used for multiple testing. LocusZoom was used for visual interpretation of risk loci and genes.

Results: Our genome analysis build used ~8.7 million SNPs assigned to 25,539 genes; 51% of SNPs were located inside genes. GATES revealed a total of 115 genes significantly associated with RA compared with controls ($p<1.96E-6$, Bonferroni corrected). The majority of GATES top gene hits were located on chromosomes 6, 1, 2 and 19 (22.6%, 20%,

7.8% and 7.8% respectively). From these 115 genes, we identified 43 RA risk loci: 23 risk loci contained a single top risk gene, while 20 risk loci contained two or more risk genes by GATES. Compared to the meta-GWAS results by Okada et al.[1], our GATES top genes were replicated for 26 loci; however 17 risk loci had a different top gene by GATES. Our analysis revealed 1 potentially new RA risk locus, located on chromosome 11 (start position 118528941 bp) containing TREH-PHLDB1-MIR6716. Additionally, GATES identified 6 new top gene hits for each of the following 6 risk loci: RPP14 (for DNASE1L3-ABHD6-PXK), PXT1 (for ETV1), MIR5708 (for TPD52), DDX6 (for CXCR5), SUOX (for CDK2), and PCAT29 (for LOC145837). 3 of these loci (ETV1, TPD52 & CDK2) are novel RA risk loci identified by Okada et al.[1] and require further analysis to determine top risk genes in the region given our GATES results.

Conclusion: Gene-based association analysis with GATES of big data from meta-analysis of GWAS confirmed prior risk loci and identified potential novel candidate gene hits in RA. Our results will be used subsequently to identify gene-gene interactions and perform genomewide pathway analysis to improve our understanding of the complex genetics in RA.
References: 1. Okada Y, Wu D, Trynka G, Raj T, Terao C, et al. Genetics of rheumatoid arthritis contributes to biology and drug discovery. Nature. 2014 Feb 20;506(7488):376-81. 2. Li MX, Gui HS, Kwan JS, Sham PC. GATES: a rapid and powerful gene-based association test using extended Simes procedure. Am J Hum Genet. 2011 Mar 11;88(3):283-93.

Disclosure: A. Lenert, None; **D. Fardo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/detecting-novel-candidate-risk-genes-in-rheumatoid-arthritis-with-gene-based-association-testing

Abstract Number: 59

Novel Agents for Blocking the Interaction of Immune Complexes with the Activatory FcγRIIIa Receptor

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Background/Purpose: Protein-protein interactions are essential for the control of cellular functions and critical for regulation of the immune system. One example is the binding of Fc regions of Immunoglobulin G to their receptors (Fcγ Receptors). High structural homology between FcγRIIIa and FcγRIIIb has led to the lack of specific agents against this important therapeutic target. We aimed to develop a novel drug development pipeline using artificial binding proteins called Adhirons both for the identification of novel therapeutics and to guide drug discovery through the identification of novel hot spots/ druggable surfaces on the receptor.

Methods: We transiently transfected vectors encoding FcγRIIIa and FcγRIIa ectodomains into HEK293T cells and the resulting secreted proteins were purified. We additionally cloned sequences encoding full-length FcγRIIIa, FcγRIIIb and FcγRIIa into expression vectors and created stably transfected HEK293 cells expressing each receptor. The FcγRIIIa ectodomain was used as a target for screening an Adhiron library using ‘phage display. High affinity binders were used in Surface Plasmon Resonance (SPR), cellular assays (IgG binding assays and immune complex-induced TNF release and phagocytosis in THP-1-derived macrophage cells) and X-ray crystallography.

Results: Here we report the identification of FcγRIIIa-specific Adhirons. SPR experiments confirmed a pool of Adhirons that bound FcγRIIIa, but not FcγRIIa. Selective blockade of IgG binding to FcγRIIIa, but not FcγRIIa or FcγRIIIb, was detected for 3 Adhirons using flow cytometry assays in HEK293 cells that ectopically expressed individual FcγRs. We also demonstrated blockade of immune-complex induced effector functions downstream of FcγRIIIa signalling in THP-1-derived macrophage cells. Co-crystal structures revealed one Adhiron bound directly to the Fc binding site whereas two others acted as allosteric inhibitors. The structural basis for the specificity of the competitive inhibitor has been defined.

Conclusion: The results suggest that Adhirons can be developed to inhibit protein-protein interactions that were previously considered to be "undruggable". Adhirons that inhibit the activatory FcγRIIIa (expressed on macrophages) but not the highly homologous FcγRIIIb (expressed on neutrophils), have been identified. This level of specificity has not been achieved using more conventional monoclonal antibody-based technology. Furthermore, the allosteric binders highlight a novel FcγRIIIa 'hot spot', which could be used in *in silico*-based Medicinal Chemistry design tools.

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Abstract Number: 60

A Single Nucleotide Polymorphism of IL6-Receptor Is Associated with Response to Tocilizumab in Rheumatoid Arthritis: Results from Toci and ROC Studies

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Background/Purpose: Biological agents (boDMARDs) have modified the therapeutic management of patients with rheumatoid arthritis (RA). However, boDMARDs can induce sustained remission in only 30% of RA patients. Identify predictive markers of response to boDMARDs would be a real progress in clinical practice. Wang et al. previously explored response to tocilizumab (TCZ) by genome-wide association in 1,683 RA patients. They found out eight loci not recognized to be linked with the interleukin (IL)-6 pathway. More recently, Enevold et al. have shown a haplotype of 3 single-nucleotide polymorphisms (SNPs) on *IL6R*gene associated with clinical response to TCZ (AAC haplotype for rs12083537, rs2228145, and rs4329505, respectively) in a retrospective cohort of 79 RA Caucasian patients. Our study aimed to test the association of these 3 SNPs with TCZ response in two populations of French RA patients.

Methods: *Patients:* Two independent RA cohort were used for this study: 1) TOCI, a multicentric retrospective French

study including 160 RA patients treated with TCZ, 2) ROC, a multicentric prospective French randomized controlled trial comparing the efficacy of a second TNF blocker to another boDMARD (abatacept, TCZ or rituximab) in RA patients who failed to a first TNF blocker. Among the 292 patients included in ROC, 62 patients received TCZ after randomization in the non-TNF blocker arm. Patients were evaluated at 0 and 3 months after initiation of TCZ. Efficacy of TCZ was assessed using the European League Against Rheumatism (EULAR) response criteria. *Genotyping:*3 SNPs on IL6R were genotyped using KasPar method on both samples (LGC-genomics, UK). *Statistics:*the proportion of patients with EULAR response (moderate or good) was compared across the genotypes of the 3 SNPs on TOCI and ROC studies. A meta-analysis was performed, by allele analysis, to confirm the association on the 2 samples with Mantel-Haenszel method.

Results: Fourty height patients in the TOCI group (78.7 %) and 125 patients in the ROC group (79.6 %) reached good or moderate EULAR responses. The SNP rs2228145 did not respect the Hardy Weinberg equilibrium. The GG genotype of rs12083537 was significantly associated with a lower response rate in both cohort [TOCI: 89.2% of responders for AA genotype vs 65.2 % for AG or GG genotype (p=0.044), ROC patients: 87.2% of responders for AA genotype vs 72.2 % for AG or GG genotype, p=0.018]. Combining these two studies, we confirmed the lower response rate with G allele carriage (OR (95% CI) = 0.35 (0.16-0.61), p=0.001). No association was found with the SNP rs4329505 (alone or in a haplotype with rs12083537).

Conclusion: In this study, the rs12083537 of IL6R was associated with response to TCZ in two different independent RA cohorts. Although insufficient to be used in the daily practice, these results strengthen literature data in the search of predictive markers to the response to TCZ.

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Abstract Number: 61

Killer Immunoglobulin-like Receptors Are Associated with Ankylosing Spondylitis

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Background/Purpose: Killer immunoglobulin-like receptors (KIRs) are expressed predominantly on the surface of natural killer (NK) cells and some T-cells and are important in regulating the inflammatory phenotype of these cell types. The 17 known KIR genes are arranged in variable content haplotypes that differ substantially in composition across the human population. Specific HLA subtypes act as KIR ligands, and the repertoire of HLA and KIR alleles carried has been shown to alter risk for autoimmune or infectious diseases by shifting activation thresholds of cytotoxic NK cells. We aimed to interrogate patterns in, and statistical interactions between, *KIR* genes and *HLA* alleles in a large population of individuals with ankylosing spondylitis (AS), in which *HLA-B*27* in particular exerts a substantial genetic contribution to disease.

Methods: Gene dosages across *KIR* loci were imputed from Immunochip genotype data for 10464 AS cases and 15239

control *HLA*-typed individuals using the statistical package KIR*IMP. Differences in *KIR* gene content and haplotype composition were assessed, with additional consideration of *HLA* type used to investigate gene-gene interactions and co-occurrence patterns in cases and controls.

Results: We identified a statistical interaction between the HLA-Bw4 recognising *KIR* genes *KIR3DL1* and *KIR3DS1* and *HLA-B*27* (a Bw4 type allele). Presence of the NK cell activating receptor *KIR3DS1* increased risk of AS in *HLA-B*27* positive individuals, but was protective in *HLA-B*27* negative individuals *(P interaction = 0.007)*. In contrast, inhibitory receptor *KIR3DL1* exhibited the opposite pattern of association, with presence of the gene being protective in *HLA-B27* positive individuals but risk predisposing in *HLA-B*27* negative individuals *(P interaction = 0.002)*. We observed a suggestive disease association with KIR locus variant rs775859 *($P=2x10^{-5}$)* and a significant interaction between the variant used to tag the presence of the *KIR2DL5* gene and *HLA-B*27 ($P=3x10^{-4}$)*, with carriage of both *KIR2DL5* and *HLA-B27* increasing disease risk. Intriguingly, a significantly lower frequency of *KIR2DL5* was also seen in *HLA-B*27* positive controls relative to *HLA-B27-ve* controls *(P=0.001, OR=0.81)*, indicative of evolutionary pressure against this co-occurrence. In *HLA-B*27* negative individuals there was a strong interaction between the *KIR2DL3* gene and *HLA-C*12* (*P interaction* = $7.1x10^{-5}$).

Conclusion: Interactions between HLA-B*27 and specific KIR receptors may contribute to AS by altering the inflammatory activity of NK cells.

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Abstract Number: 62

Increased Frequency of Anti-Drug Antibodies in Patients Carrying Compatible IgG1 Allotypes and Treated with Anti-TNF Antibodies

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Background/Purpose: One of the causes of insufficient response to biological drugs is the production of anti-drug antibodies (ADA) (1). These antibodies can decrease the effectiveness of treatment by altering bioavailability or by neutralizing the drug. In addition, they may contribute to hypersensitivity reactions. Some ADA are directed against IgG allotypes, which are protein polymorphisms able to induce an immune response in incompatible subjects. Infliximab (INX) and adalimumab (ADM) have the G1m17,1 allotypes, while about 50% of the Europeans are homozygous for the incompatible G1m3,n allotypes. Therefore, the allotypes could contribute to ADA and, in this way, explain the recently described loss of efficiency of INX in allotype-incompatible RA patients (2). This motivated our analysis of the usefulness of IgG1 allotypes as biomarker of the development of ADA against INX and ADM.

Methods: The presence of ADA was determined in 252 consecutive patients with inflammatory arthritis in the Hospital La Paz (116 with rheumatoid arthritis (RA), 74 with ankylosing spondylitis (AS), 26 with psoriatic arthritis, 17 with non-radiographic spondylitis, 11 with spondylitis and inflammatory bowel disease, 3 with uveitis and 5 with other arthropathies). Patients were assessed during INX treatment (151), or with ADM (82), or sequentially during treatment with INX and ADM (19). ADA were determined by two-site bridging ELISA as described (1). Allotypes of IgG1 were determined by genotyping 2 SNPs, rs1071803 (for allotype G1m17 / G1m3) and rs11621259 (for allotype G1m1 / null)

with the SNaPshot Multiplex kit (Applied Biosystems) as reported (2).

Results: Patients with compatible allotypes (carriers of G1m17,1) showed a larger frequency of ADA (33% *vs.* 20%, p = 0.02) and a trend toward higher titers of these antibodies (18.0 x10^3 *vs.* 8.3 x10^3 AU, ns) than patients with incompatible allotypes (homozygous for G1m3,n). This association was clearer in patients treated with INX (41% *vs.* 25%, p = 0.03) than in those treated with ADM (18% *vs.* 12%, ns). ADA were more frequent in patients treated with INX than in those treated with ADM, as already known. Multivariate analysis showed that the frequency of ADA was increased in patients with RA compared to other diseases (OR = 7.6, p <0.0001), and decreased in older patients (OR = 0.65 per 10 years, p < 0.001). Other factors, such as sex, having AS against other diseases, and treatment with methotrexate or corticosteroids, were not associated with ADA.

Conclusion: Patients with compatible allotypes showed more frequently ADA than patients with incompatible allotypes, showing for the first time this association in patients treated with INX and reinforcing the previously reported association for ADM (3). These results suggest a genetic factor in linkage with the allotype, but different from it, that will predispose to ADA. References: 1. Pascual-Salcedo D, et al. Rheumatology (Oxford). 2011;50:1445. 2. Montes A, et al. Arthritis Res Ther. 2015;17:63. 3. Bartelds GM, et al. Arthritis Res Ther. 2010;12:R221 Funding was provided by the Instituto de Salud Carlos III (Spain) through grants PI14/01651 and RD12/009/008, which are partially financed by the European Regional Development Fund of the EU.

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Abstract Number: 63

Identification of Immune Gene Modules in Good Responders to Adalimumab in Rheumatoid Arthritis

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Background/Purpose: Despite the revolutionary impact of TNF inhibitor (TNFi) therapy in rheumatoid arthritis (RA), up to 40% of patients fail to respond adequately. Whilst non-responder (NR) patients can be switched to alternative therapies at 3 months, many experience a delay in switching as some will subsequently respond to treatment by 6 months, which may be detrimental to patient outcomes. Ideally, blood-based biomarkers would be available to objectively predict and monitor response to TNFi but current measures, such as CRP levels, do not correlate very well with objective measures of synovitis. The aim of my work therefore, was to identify an expression signature to predict or monitor treatment response to adalimumab in a large sample cohort of patients about to start treatment.

Methods: 50 extreme EULAR good-responders (GR) and 20 extreme NR to adalimumab were selected from the Biologics in RA Genetics and Genomics Study Syndicate (BRAGGSS) cohort. Total RNA was extracted from whole blood using the MagMAX™ RNA isolation kit before (baseline) and following 3 months of therapy. RNA was amplified and converted into biotinylated sense-strand DNA using the Affymetrix WT PLUS kit and hybridized onto Affymetrix GeneChip® human transcriptome arrays. Quality control and differential expression analysis (both individual transcripts and splice variants) were assessed using the Affymetrix expression and transcriptome analysis console™ and appropriate Bioconductor packages. Weighted gene co-expression network analysis (WGCNA) was performed to identify co-regulated genes correlated with response. WGCNA alleviates the multiple testing issue inherent in microarray data analysis and could hold greater power for detecting clinically applicable biomarkers.

Results: In GR, there were 11 gene co-expression modules, which significantly changed over 3 months of treatment. The most significant module (p= 1e-05) was highly enriched for genes involved in macrophage function, specifically osteoclast differentiation, chemokine signaling and leukocyte transendothelial migration. Transcript significance for treatment time-point and module membership were highly correlated, suggesting genes which change over time are the most important genes within the module. The module was also highly correlated with individual DAS components: tender joint count, swollen joint count, patient global health and CRP. This immune based signature of response is consistent with findings at the individual transcript and splice-level, which showed significant changes in HLA, T-cell signalling and MMP genes implicated in RA pathogenesis. Specifically, upregulation of immune genes at 3 months could reflect migration of immune cells from the inflamed joint into the peripheral blood in a positive response to therapy. No significant changes were observed over time in NR.

Conclusion: Identification of an immune blood-based signature of response early in the treatment time-course could aid timely therapeutic switching in NR. It could also offer a superior measure of ultrasound-determined synovitis than CRP alone. Subsequent work will include replication in an independent cohort and integration of genotype and serum microRNA data.

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Abstract Number: 64

Enrichment of Immune Pathways in Genes Under Geographically Restricted Adaptation in the Gullah African American Population of South Carolina

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Background/Purpose: The reasons for the ethnic disparities in rheumatologic and autoimmune diseases (ADs) are largely unknown. We posit that population-specific selection influencing the allele frequencies at some loci contribute to ethnic

disparities. Relative to other African-Americans (AA), the Gullah population of coastal South Carolina and Georgia has lower European admixture and higher ancestral homogeneity from the Sierra Leone (SL) area in West Africa. The shorter genetic distance between the Gullah and SL suggests that population genetic signals, such as regions under recent selection, may be more easily detected in the Gullah than in other AA populations. We sought to leverage the relative closeness between the Gullah and SL to identify autoimmune risk alleles with evidence of population differentiation that may result from geographically restricted, subtle selective pressure.

Methods: We computed the fixation index (F_{ST}) between populations, a measure of population differentiation that measures the degree of genetic differentiation at a locus. Using genome-wide genotype data on 277 healthy Gullah, 400 SL, and 203 YRI from the HapMap3 Project, we computed the Weir and Cockerham's (1984) F_{ST} (in VCFTOOLS) and the Hudson estimator for F_{ST} (in EIGENSOFT) between Gullah and SL, and Gullah and YRI. A total of 582,100 autosomal SNPs met standard GWAS quality control. We prioritized variants in the top 0.01% of highest F_{ST} between populations, then selected gene regions where at least another variant was in the top 0.1% of highest F_{ST}. For these genes, trait associations were compiled from the *NHGRI-EBI GWAS Catalog*, and *Ingenuity Pathway Analysis*was used to identify significant pathways and biological functions among the top genes.

Results: Although the low F_{ST} estimates between the Gullah and their ancestors supports their genetic proximity (F_{ST}=0.003), the loci in the top 0.01% of highest F_{ST} were different between Gullah and SL, and between Gullah and YRI. While the loci with highest F_{ST} between Gullah and SL were enriched for genes involved in *Cellular Function and Maintenance* (P=6.1E-04), the top genes between Gullah and YRI were enriched for *Cancer*functions (P=4.1E-04). Although only a small fraction of the genes have been reported as associated with an AD, the most significant pathways were immune-related, for both the genes showing population differentiation between Gullah and SL (antigen presentation, P=4.9E-04; allograft rejection signaling, P=8.3E-04), and between Gullah and YRI (CCR3 signaling in eosinophils, P=4.8E-04; role of NFAT in regulation of the immune response, P=1.5E-03).

Conclusion: We identified several regions that show evidence of selection in the Gullah, including the *HLA* and *CD36*, which are known to be under selection that happened pre-admixture. The paucity of genes associated with ADs might be due to the lack of genetic association studies in AA. The enrichment of immune pathways suggests that autoimmune risk alleles might be present in the Gullah, as well as other AA. Given the increased prevalence of several ADs in AA, identification of regions under selection in the Gullah can further the understanding of the natural history and disease risks in AA and help explain the ethnic disparity.

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Abstract Number: 65

Genetic Heterogeneity in the Risk of Lupus Nephritis According to Ancestry

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Genetic heterogeneity in the risk of lupus nephritis according to ancestry

Background/Purpose: Lupus nephritis (LN) is a severe consequence of systemic lupus erythematosus (SLE) that affects minority populations in higher proportions. The causes behind these ethnic differences are not fully elucidated. We aimed to identify genetic variants that contribute differentially to the risk of LN across different ancestral groups.

Methods: 1244 SLE patients from five different racial/ethnic groups were studied. Genome-wide single nucleotide polymorphism (SNP) genotyping was performed with the Axiom LAT1 array (World Array 4, Affymetrix), which is composed of 817,810 SNP markers across the genome and was specifically designed to provide maximal coverage for diverse ethnic populations, including West Africans, Europeans and Native Americans. Genetic ancestry was determined by principal component analysis (PCA). The first 3 PCs (pc1, pc2, pc3) separated Europeans (n=535), Hispanics (n=252), African Americans (n=232) and Asians (n=223). A further PCA was performed to separate northern (n=295) vs southern Europeans (n=242). We utilized a candidate gene approach for genetic variants that have been identified in previous genetic studies of SLE risk, chronic kidney disease and/or LN. Allele frequencies for risk alleles were calculated for each ancestry group. Case-control associations between candidate SNPs and LN were performed within each ancestry group, adjusting for disease duration and principal components. We also utilized meta-analysis to test for heterogeneity and examine associations across the 5 ethnic groups.

Results: Overall, 606 participants (48.7%) had LN as defined by the ACR renal criterion. The prevalence of LN varied across the ethnic groups, ranging from 38% to 60.7%. Sixty out of 67 candidate gene SNPs varied significantly in frequency across the 5 ancestry groups ($p < 7$ E-4) in patients without LN. Association tests for risk of LN within each ancestry group revealed differences in the magnitude and significance (Table 1). Moreover, most SNPs were associated with LN for only 1 or 2 ancestry groups. The most significantly associated SNPs included recently identified risk variants for chronic kidney disease GWAS such as *NFATC1*, suggesting pleiotropy/poligenicity. Tests of heterogeneity (Breslow-day test, I2 square statistic) revealed significant heterogeneity according to ancestry for 6 candidate SNPs, indicating differential contribution of genetic risk variants to risk of LN according to ancestry.

Conclusion: These results demonstrate significant variation in the frequency of risk alleles as well as differential association with the risk of LN according to ancestry. These findings further support the hypothesis that genetic factors contribute importantly to observed ancestry differences in severe outcomes of SLE.

Table 1. Top Associations between previously described risk variants with lupus nephritis by ancestry

			NORTH EUROPEANS		SOUTH EUROPEANS		HISPANICS		ASIANS		AFRICAN AMERICANS		Breslow-day	I^2 statistic
SNP	*GENE*	MA	OR	P	OR	P	OR	P	OR	P	OR	P	test	
rs17696736	*TRAFD1*	G	**1.766**	**0.001492**	1.394	0.09134	1.215	0.357	0.4841	0.6127	0.553	0.1179	**0.03355**	**59.81**
rs3184504**	*SH2B3*	C	**0.6294**	**0.01078**	0.71	0.08683	1.114	0.6078	2.17	0.5829	0.7424	0.4058	0.1549	0
rs9888739	*ITGAM*	T	**1.631**	**0.0263**	1.049	0.8327	1.058	0.8213	0.5304	0.3077	1.017	0.9286	0.1619	37.12
rs1143679	*ITGAM*	A	**1.533**	**0.05112**	1.338	0.2298	1.318	0.33	0.3663	0.1449	1.071	0.8119	0.1847	29.52
rs6459680	*RNF32*	G	**1.483**	**0.05347**	1.217	0.3168	1.164	0.5052	0.6767	0.06457	1.001	0.9979	**0.04395**	**58.97**
rs7805747	*PRKAG2*	A	1.23	0.2758	**0.5714**	**0.01126**	1.013	0.9573	0.529	0.7617	1.138	0.5363	0.0746	52.54
rs1635852	*JAZF1*	C	0.823	0.2903	**0.6473**	**0.02656**	**0.5723**	**0.00558**	1.376	0.2306	0.9756	0.9139	0.09563	49.05
rs849142	*JAZF1*	C	0.8219	0.2888	**0.6564**	**0.03211**	**0.5976**	**0.00958**	2.719	0.1472	1.241	0.3968	0.1708	37.04
rs4917014	*IKZF1*	G	1.049	0.7997	**1.583**	**0.0339**	**0.6543**	**0.02726**	1.219	0.4131	1.013	0.9729	0.6216	0
rs12460876	*SLC7A9*	C	0.8131	0.2398	**0.6629**	**0.04514**	1.024	0.9022	0.9142	0.6766	0.7125	0.105	0.2438	26.5
rs9271366*		G	1.071	0.7626	**1.747**	**0.04684**	1.153	0.59	1.501	0.05909	1.081	0.7411	0.6971	0
rs1801274	*FCGR2A*	A	1.232	0.2438	0.921	0.6657	**0.6788**	**0.03566**	0.7755	0.2556	1.069	0.7554	0.1995	33.16
rs8091180**	*NFATC1*	G	0.7677	0.1696	0.8158	0.3274	**0.6756**	**0.04499**	0.8724	0.5955	**2.274**	**0.003209**	0.3796	3.73
rs2248932	*BLK*	A	1.261	0.1987	0.9768	0.9099	**1.514**	**0.05066**	0.8191	0.4298	0.9116	0.6672	**0.04072**	**59.65**
rs1990760	*IFIH1*	C	0.8715	0.4647	0.8813	0.5282	1.204	0.3044	**1.784**	**0.0235**	0.8485	0.5333	0.2307	28.03
rs12537284*		A	0.9124	0.676	0.707	0.1811	1.462	0.06859	**0.0597**	**0.02502**	0.9169	0.8452	**0.02858**	56.89
rs1049564	*PNP*	A	0.7388	0.2121	0.9097	0.6812	0.8091	0.3659	1.014	0.9561	**0.4932**	**0.002276**	0.3211	14.33
rs7062536	*PRPS2*	A	0.8166	0.5196	1.142	0.7055	0.6915	0.08871	0.7218	0.187	**1.628**	**0.02544**	**0.04236**	**59.29**
rs7197475	*PRR14*	T	0.9185	0.6221	0.7987	0.2745	1.01	0.9617	1.195	0.5355	**0.5936**	**0.03076**	0.241	26.78
rs10774021**	*SLC6A13*	C	1.15	0.436	0.9895	0.9574	1.285	0.2032	1.04	0.8747	**0.6661**	**0.03821**	0.09153	49.83
rs6920220	*TNFAIP3*	A	0.6972	0.08441	0.9823	0.9384	1.553	0.17	1.93	0.618	**2.024**	**0.04602**	**0.02965**	**62.21**
rs11574914	*CCL22*	A	1.111	0.5604	0.7181	0.1323	1.05	0.8066	0.7507	0.3986	**0.475**	**0.05026**	0.08373	**50.86**

*genetic variants described in SLE Lupus nephritis GWAS ** genetic variants described in chronic renal disease GWAS

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Abstract Number: 66

Very Rare X Chromosome Abnormalities in SLE and SjöGren's May Localize X Gene Dose Effect

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Background/Purpose: Sjögren's syndrome and systemic lupus erythematosus (SLE) are chronic, autoimmune diseases that are related by clinical and serological manifestations as well as genetic risks. Both diseases are much more commonly found in women compared to men at a ratio of about 10 to 1. We have previously shown that relatively common X chromosome aneuploidies, 47XXY (Klinefelter's syndrome, 1 in 500 live male births) and 47XXX (1 in 1000 live female births), are enriched among men and women, respectively, with Sjögren's or SLE. We undertook this study to describe rare X chromosome aneuploidies among large cohorts of patients with these diseases.

Methods: We examined large cohorts of Sjögren's syndrome or SLE patients with intensity plots of X chromosome single nucleotide polymorphism (SNP) alleles. In addition, we also carried out karyotype of peripheral blood mononuclear cells from Sjögren's syndrome and SLE subjects.

Results: Among 2,426 women with SLE we found three patients with a triple mosaic consisting of 45X/46XX/47XXX, a statistically significant increase compared to controls and the known birth rate by binomial confidence intervals. Among 2138 women with Sjögren's syndrome, one patient had 45X/46XX/47XXX with a triplication of the distal p arm of the X chromosome in the 47XXX cells. Neither the triple mosaic nor a partial triplication were found among controls. In fact, the triple mosaic occurs in approximately 1 in 25,000 to 50,000 live female births, while a partial triplication such as the one found is even rarer. In another cohort of Sjögren's patients, we found a mother-daughter pair in which the mother had an inversion of the proximal region of Xq and the daughter had a Xp isochrome with partial triplication of distal Xp.

Conclusion: Very rare X chromosome abnormalities are present among patients with either Sjögren's or SLE. These rare variants may be informative as to location of a gene or genes on the X chromosome that mediate a gene dose effect as well as critical cell types in which a gene dose effect is operative.

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Abstract Number: 67

Polymorphisms of ERAP1, IL23R and TRAILR1 Are Associated with MRI-Sacroiliitis in Early Axial Spondyloarthritis: Data from the French DESIR Cohort

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Polymorphisms of *ERAP1, IL23R* and *TRAILR1* are associated With MRI-Sacroiliitis in Early Axial Spondyloarthritis: Data from the French DESIR Cohort

Background/Purpose: Spondyloarthritis (SpA) is a highly heritable disease, often affecting the sacroiliac joints. Single nucleotide polymorphisms on *ERAP1*, *IL23R* and *TRAIL-R1*(or Tumor Necrosis Factor-related Apoptosis-inducing Ligand Receptor 1) are associated with SpA susceptibility and structural changes on sacroiliac joints on radiographs. The aim of this study was to test the association between these polymorphisms and the presence of sacroiliitis on magnetic resonance imagery (MRI), in a French early SpA cohort (DESIR: Devenir des Spondyloarthrites Récentes).

Methods: All patients included in the DESIR cohort fulfilling the Assessment of SpondyloArthritis international Society (ASAS) diagnosis criteria for axial SpA, AMOR or European Spondyloarthropathy Study Group (ESSG) criteria, were included in this study. All MRI were scored by two experienced readers, according to Spondyloarthritis Research Consortium of Canada (SPARCC) score and ASAS definition. *Genotyping:* Three SNPs on *IL23R (rs1004819, rs10889677, rs2201841)*, 4 SNPs on *ERAP1 (*rs17482078, rs10050860, rs27434, rs2287987*)*, 1 SNP on *TRAILR1* (rs20575) were genotyped using KasPar method (LGC-genomics, UK). The haplotype of the 3 SNPs on *IL23R* and the 4 SNPs on *ERAP1*were built with Plink software. *Statistics:* Univariate analyses using a Chi square test and a Wilcoxon tests were performed to assess whether a haplotype of *ERAP1, IL23R* and a genotype of the SNP on *TRAILR1*were associated with MRI sacroiliitis or SPARCC score respectively.

Results: Among the 708 patients included in the DESIR cohort, 645 fulfilled at least one of the criteria set for SpA. Among them, 403 (62,6%) patients were *HLA-B27* positive. 214 patients (34.2%) had a MRI sacroiliitis and 161 (25%) patients had SPARCC MRI sacroiliitis score higher than 4. The haplotype TAG of *IL23R* was associated with MRI sacroiliitis with SPARCC criteria (SPARCC median=0.75 [0-8] in TAG patients versus 0[0-2] in non-TAG patients, p=0.0021), while rs20575 on *TRAILR1* was associated with MRI sacroiliitis using SPARCC criteria (SPARCC median=1[0-6.5] in G allele carriers versus 0[0-2] in G allele non-carriers, p=0.0046). These associations were stronger in *HLA-B27* positive patients (SPARCC median in TAG carriers of *IL23R* = 1[0-10.5] versus 0[0-4] in TAG non-carriers, p=0.0058; in G allele of *TRAILR1* carriers: 1.5[0-10.5], versus 0[0-4] in G allele non-carriers, p=0.0044). The haplotype CCAT of ERAP1 was associated with MRI sacroiliitis with ASAS criteria (47.1% of patients with sacroiliitis in CCAT carriers, versus 30.4% in non-carriers, p=0.046). Stratification on the presence of *HLA-B27* enhanced this association (60% of patients with sacroiliitis in CCAT carriers, versus 31.6% in non-carriers in *HLA-B27*positive patients, p = 0.0035).

Conclusion: In the DESIR cohort, *ERAP1, TRAILR1* and *IL23R* polymorphisms were associated with the presence of MRI sacroiliitis in SpA, particularly in *HLA-B27*patients. *This work received an institutional support by the French Society of rheumatology.*

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Abstract Number: 68

Epigenetic and Expression Analysis of Ankylosing Spondylitis Association Loci Point to Key Cell Types Driving Disease

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Background/Purpose: Susceptibility to ankylosing spondylitis (AS) is primarily genetic; thus far 113 susceptibility variants for AS have been identified. However, most of the AS associated SNPs do not directly affect protein-coding genes. Studies of disease- and trait-associated SNPs suggest they may act by affecting gene regulatory regions in specific cell types or tissues. Therefore, identifying the AS relevant cell types is crucial for further mechanistic studies.

Methods: We applied several bioinformatics methods to utilize epigenetic, gene and protein expression information to identify the primary relevant cell types through which genetic variants associated with AS operate. In total, there are 113

AS associated loci; 39 of them show genome-wide significance in AS-only analyses, whereas the remainder are genome-wide significant in analyses leveraging pleiotrophy with other related diseases (Crohn's disease (CD), psoriasis, primary sclerosing cholangitis (PSC) and ulcerative colitis (UC))[1].

Results: AS-associated SNPs are disproportionately found in regions bearing epigenetic marks indicating transcriptional activity found in immune cell types including monocytes, CD4+ and CD8+ T cells, NK cells, regulatory T cells, and B cells. Gene expression studies showed enrichment of AS associated loci in genes specifically expressed in monocytes and NK cells while protein expression study shows protein products of AS associated loci were significantly enriched in CD8+ T cells. Epigenetic analyses also showed evidence that AS-associated signals operate in gut cell types including in mucosa from the small intestine, sigmoid colon and rectum. These findings particularly relate to pleiotropic loci also associated with IBD, psoriasis, and PSC.

Conclusion: These findings highlight the role of key immune cell types in the mechanism by which genetic associations with AS drive the disease, as well as providing further evidence for the involvement of the gut in the pathogenesis of AS.

[1]Ellinghaus D. at al, Nature Genetics 2016

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Abstract Number: 69

IL-32 Promoter SNP rs4786370 Predisposed to Modified Lipoprotein Profiles in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with a chronic inflammatory disease such as rheumatoid arthritis (RA) are at higher risk of developing cardiovascular diseases (CVD). Interleukin (IL)-32 has previously been shown to be involved in the pathogenesis of RA and might also be linked to the development of atherosclerosis. However the exact mechanism linking IL-32 to CVD still needs to be elucidated.

Methods: Whole blood was obtained from individuals from the NBS cohort and RA patients from 2 independent cohorts to study the influence of a functional genetic variant IL-32 on lipid profiles and CVD risk. DNA was isolated and genotyped for the single nucleotide polymorphism (SNP) rs4786370 in *IL-32* using a taqman genotyping assay. Lipid profiles were measured and matched to the specific IL-32 genotypes.

Results: The allelic distribution of the IL-32 promoter SNP was similar in all three groups. Interestingly, significantly

higher levels of high density lipoprotein cholesterol (HDLc) were observed in individuals from the NBS cohort and RA patients from the Nijmegen cohort homozygous for the C allele (p=0.0141 and p=0.0314 respectively). This finding was independent of the presence of plaques or previous CVD events in these groups. In contrast, the CC-genotype was associated with elevated low density lipoprotein cholesterol (LDLc) and total cholesterol (TC) in individuals at higher risk for CVD (plaque positive) (p=0.0396; p=0.0363 respectively). Within RA patients with a previous CVD event, the LDLc and TC levels were lower compared to RA patients without a previous CVD event, independent of the genotype (p<0.0001).

Conclusion: The rs4786370 promoter polymorphism of IL-32 is equally expressed in all three cohorts. However, this genetic variant has a specific functional effect on the lipid profile of individuals from the NBS cohort and RA patients, resulting in increased HDLc levels. Future studies should focus on the mechanism behind the increase in HDLc in individuals with the IL-32 promoter SNP and its possible protective role against CVD.

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Abstract Number: 70

Identifying Distal Interactions Between RUNX1 and JIA Associated Single Nucleotide Polymorphisms By Chromosome Conformation Capture

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Background/Purpose: 17 genetic loci have now been identified to confer susceptibility to JIA; several of these loci harbour genes involved in the *IL2* pathway suggesting that this may be an important signalling cascade involved in JIA. It is hypothesised that the regions containing variants increasing the risk of disease may act as regulatory elements that modulate gene expression. Indeed capture Hi-C data, which identifies physical DNA interactions, has shown that a JIA susceptibility single nucleotide polymorphism (SNP), rs9979383, located in a gene enhancer region, makes strong contact with the promoter of RUNX1, a crucial transcription factor involved in the regulation of IL-2. Characterising the extent of these interaction and understanding the underlying mechanism is likely to provide important information as to how this variant increases risk of JIA. The aim of this study was to design a bioinformatics pipeline to prioritise the most likely functional candidate SNPs and to design and perform functional experiments to define the mechanisms by which these JIA associated variants contribute to disease pathogenesis.

Methods: In order to prioritise the most likely functional candidate SNPs for follow up a bioinformatics pipeline was designed, curating bioinformatics tools and data to create a step-wise assessment of each SNP. In-house generated Capture

Hi-C data for the *IL2* pathway regions were assessed for interactions between associated SNPs and nearby genes. Fragments near JIA associated SNPs showed looping at several points around the haematopoiesis master regulator gene; *RUNX1*, a key gene in the *IL2*pathway. Chromosome Conformation Capture (3C) experiments were implemented to validate interactions in the selected regions. To test for a genotype specific effect nine B-lymphocyte cell lines, three of each genotype, were selected for this experiment.

Results: The highest prioritised SNP in the *RUNX1*gene region was identified as rs9799383 based on transcription factors, Hi-C data and histone marks. Interactions in TT genotype cell lines occurs significantly more frequently in one tested interaction. Interestingly, a 1.7 fold increase in frequency is observed in the same interaction when data from all cell lines are grouped together, as well as a separate interaction showing a 2.7 fold increase in interaction frequency.

Conclusion: The bioinformatics approach to investigating potential functional variants proved to be highly informative and aided the design of 3C experiments. Cell lines grouped by genotype show mostly insignificant difference compared to controls, however one genotype specific interaction is observed in TT cell lines. This observed interaction appears to interact with the RUNX1 promoter region. The observed long range interactions are indicative of a distal regulatory effect that may influence gene expression of *RUNX1*. These findings inform further experiments and have suggested several potential transcription factors which may be driving JIA susceptibility in the *RUNX1* region.

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Abstract Number: 71

A Rare Coding Allele in IFIH1 is Protective for Psoriatic Arthritis

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Background/Purpose: Psoriatic Arthritis (PsA) is an inflammatory arthritis associated with psoriasis estimated to present in approximately 14% of psoriasis patients in the UK. As a complex disease, PsA is influenced by both genetic and environmental factors. Genome-wide association studies (GWAS) have reported risk alleles for both PsA and psoriasis that are common, with a frequency > 5% in the population. However, association with rare coding alleles has not yet been reported for PsA alone.

Methods: In this study, we attempt to identify rare coding variants (MAF < 5%) associated with PsA. We genotyped 41,267 variants in 1,980 PsA cases and 5,913 controls of Caucasian decent using the Infinium HumanExome-12 BeadChip (v1-0) (Illumina) and the Infinium HumanCoreExome-24 BeadChip (v1-0) (Illumina). We applied single-point analysis

using the Fisher's exact test in PLINK with all variants passing QC. We performed multiple-variant analysis with rare variants alone using the SKAT package in R. We then applied conditional analysis using PLINK to investigate independent effects. We also analysed an independent cohort of 2,234 PsA cases and 5,708 healthy controls of European descent, where we performed single-point analysis using Firth logistic regression. A meta-analysis of the discovery and independent summary statistics was performed using PLINK.

Results: Upon performing single-point analysis, we found the strongest association at the rs35667974 SNP (P=2.39x10^{-6}, OR=0.47), mapping to the *IFIH1* gene and encoding an Ile923Val missense mutation. We replicated this association within an independent North American dataset (P=2.5x10^{-5}, OR=0.49), which was highly significant in meta-analysis with the discovery dataset (P=4.67x10^{-10}). *IFIH1* was also found to have a strong association when performing multiple-variant analysis (SKAT, P=6.77x10^{-6}). The association of the rare coding allele was independent of the common PsA variant at the same locus (rs984971) when performing conditional logistic regression (P_{cond}=4.0x10^{-6}) and conditional haplotype analysis (P=2.95x10^{-7}).

Conclusion: For the first time, we report a rare coding allele at *IFIH1* to be protective for PsA. This association has been previously reported for psoriasis and type 1 diabetes, highlighting the relevance of this allele in immune-related diseases. The association that we identified in PsA provides strong evidence to suggest that *IFIH1* is a causal gene. This finding could provide further insight into the mechanism of disease for PsA. The functional role of *IFIH1* might be investigated in PsA using this coding change.

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Abstract Number: 72

Longitudinal Expression of CXCL10 in Psoriasis Patients That Develop Psoriatic Arthritis

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Longitudinal Expression of CXCL10 in Psoriasis Patients that Develop Psoriatic Arthritis Patients Fatima Abji[1], Remy Pollock[1] Kun Liang[2], Vinod Chandran[1,3], Dafna D. Gladman[1,3] [1]University of Toronto, Toronto Western Hospital, [2]Department of Statistics and Actuarial Science, University of Waterloo, [3]Division of Rheumatology, Faculty of Medicine, University of Toronto

Background/Purpose: Psoriatic arthritis (PsA), an inflammatory musculoskeletal disease, develops in approximately 30% of patients with psoriasis. We previously found that C-X-C motif chemokine 10 (CXCL10) was elevated in psoriasis patients that developed PsA compared to those that did not develop PsA over the same psoriasis duration, thus suggesting CXCL10 is a predictive biomarker of PsA. In this study, we monitored the expression of CXCL10 over time in psoriasis patients that develop PsA.

Methods: Psoriasis patients were followed prospectively beginning in 2006, and were assessed yearly by a rheumatologist for the presence of PsA. Psoriasis patients who developed PsA were termed 'converters', and serum samples were taken at baseline and follow-up visits. The expression of CXCL10 and CRP were measured using Milliplex MAP human magnetic bead panels (EMD Millipore), according to the manufacturer's instructions. Data were acquired using the Luminex 200 system and analyzed with the Bio-Plex Manager software (Bio-Rad Laboratories). Statistical differences in protein levels prior to PsA conversion were compared by the Wilcoxon signed rank test and post-conversion by the Friedman test with a Dunn's Multiple Comparisons post-test ($p<0.05$ was accepted as significant).

Results: CXCL10 and CRP were measured in 19 psoriasis patients at baseline and at five follow-up time points. CXCL10 levels decreased over time (Figure 1), with a significant reduction at follow-up visit 3 (median 269.4 pg/ml, interquartile range [IQR] 198.6-399.6), visit 4 (median 225.3 pg/ml, IQR 155.1-387.9) and visit 5 (median 226.5 pg/ml, IQR 193.2-450.8) compared to post-conversion visit 2 levels (median 562.16 pg/ml, IQR 338.5-601.8, $p<0.001$). No significant differences in CRP levels were observed.

Conclusion: We observed a reduction in serum CXCL10 expression in psoriasis patients after they developed PsA which was maintained over time. These results support our previous findings of elevated CXCL10 in synovial fluid compared to serum from PsA patients, reflecting the localized production of CXCL10 over time. This study contributes to our understanding of the role of CXCL10 in the pathogenesis of PsA.

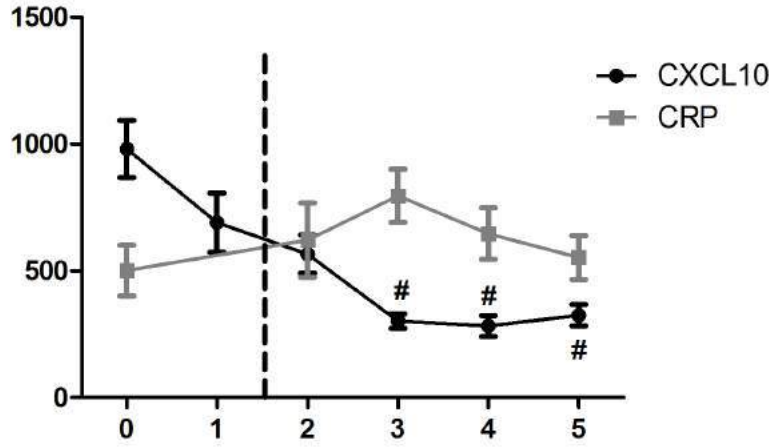

Figure 1: Line graph of CXCL10 and CRP expression in serum from 19 psoriasis converters measured at baseline (0) and follow-up visits (1-5). Dashed line indicates conversion to PsA. A significant difference compared to the post-conversion visit (2) is indicated by # ($p<0.001$). CRP concentration is expressed per 100 ng/ml.

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Abstract Number: 73

Dysregulation of Hypomethylated Age-Related CpG Sites Characterize T-Cells and Monocytes from Treatment Naive Rheumatoid Arthritis Subjects

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Background/Purpose: In the general population, an increase in chronological age is associated with differential DNA methylation of particular CpGs in a highly conserved fashion. Since age is a key risk factor for many rheumatic diseases, we tested whether DNA methylation (DNAm) patterns exhibited during normal aging occur prematurely in subjects with systemic autoimmune rheumatic diseases (SARD).

Methods: Peripheral blood $CD4^+$T-cells and $CD14^+$monocytes were sorted from incident treatment naïve rheumatoid arthritis (RA, n=13) and systemic sclerosis (SSc, n=17) subjects, as well as systemic lupus erythematosus subjects (SLE, n=12 - not all of whom were treatment naïve), and healthy controls (HC, n=8). Illumina HumanMethylation450 BeadChip and Illumina TruSeq stranded RNA-seq were used to perform genome-wide methylome and transcriptome analysis. First, we compared chronological and predicted age across SARDs using the Horvath calculator, a publicly available 'epigenetic-aging-signature' based on DNAm levels at 353 CpG sites (*Genome Biology* 2013). Second, using principal component of explained variance (PCEV), we examined whether the 353 CpGs were associated with chronological age in treatment-naïve RA and SSc, separately. Finally, we verified the findings from the PCEV analysis by examining the methylation levels in RA and SSc at sites that have been reported to correlate between chronological age and methylation levels (Lin and Wagner, *PLOS Genetics*2015).

Results: Across SARDs, the estimated age predicted using the Horvath calculator was younger than chronological age in both T-cells (average age acceleration -6.04 years, p=1.4E-12) and monocytes (average age acceleration -1.2 years, p=0.023). We found similar results in SSc [T-cells average age acceleration -7.91 years (p=7.36E-09), and monocytes average age acceleration -2.51 years (p=0.015)], and in RA T cells (average age acceleration -6.49 years, p=6.59E-0.4). We were unable to establish differences in predicted and chronological age in RA monocytes and SLE T cells and monocytes. PCEV analysis showed that the 353 CpGs in the Horvath model correlated with age in SSc (p value 0.002), but not in RA (p 0.268). We verified the findings of the PCEV analysis by examining methylation levels at CpGs reported to be correlated with aging (97 hyper- and 402 hypomethylated). Again, the CpG sites correlated with age as expected in SSc. However, while the correlations with hypermethylated CpGs were as expected in RA, this was not the case with hypomethylated CpGs, where evidence of more methylation than expected in both T cells and monocytes was found.

Conclusion: The models that predict aging-associated epigenetic drift in the general population did not predict premature aging in our SARDs patients. Moreover, age-associated DNAm patterns at hypomethylated CpG sites seem to be coherently modified in RA. This provides additional evidence supporting dysregulated aging in RA and novel mechanistic clues.

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Abstract Number: 74

Arthritis-Associated DNA Hypermethylation Provokes Increased Antibody Expression in Mouse Model of Rheumatoid Arthritis

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Background/Purpose: Although a number of epigenetic alterations have been revealed in rheumatoid arthritis (RA), it remained an open question whether these epimutations play role in RA etiology or are consequences of the pathogenesis. We investigated how arthritis-specific DNA methylation events could contribute to the dysregulation of a gene regulatory network leading to increased autoantibody production, and development of polyarthritis in a mouse model of RA.

Methods: In B cells isolated from arthritic mice, DNA methylation profile changes were explored by methylated CpG island recovery assay (MIRA-chip). Disease-associated gene expression patterns were also investigated using microarray platforms and quantitative *reverse transcription PCR (*RT-qPCR). DNA methyltransferase inhibitor, 5`-Azacitidine (Aza) was employed to reactivate hypermethylated genes in cell cultures and animal studies. Gene expression changes were monitored using RT–qPCR and Western blotting. Mice with proteoglycan-induced arthritis (PGIA) were treated with Aza and its effects were followed in B cells by flow cytometry, histochemistry, RT-qPCR and ELISA. ShRNA expressing plasmid constructs were constructed and introduced into cell cultures for targeted silencing of gene of interest.

Results: A group of promoters with arthritis-specific DNA methylation profile was identified by MIRA-chip. The promoter region of AhR transcription factor encoding gene was differentially methylated in B cells isolated from arthritic mice, which de novo hypermethylation resulted in downregulated expression of AhR. Selective inhibition of DNA methylation restored AhR expression, which was associated by reduced expression of post-recombinant IgG1 in B cells and low level of IgG1 in sera of Aza treated animals. AhR directly regulates genes are implicated in germinal center formation within secondary lymph nodes. Aza treatment provided significant protection against disease onset, and abolished inflammatory reactions in synovial joints of arthritic mice.

Conclusion: AhR is a master regulator of IgG maturation and its epigenetic inactivation by DNA methylation significantly contributes to RA pathogenesis. Targeted reactivation of AhR employing DNA methylation may have therapeutic potential for treatment of polyarthritis.

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Abstract Number: 75

Genetic Analysis of Urate Transporters ABCG2, SLC17A3, SLC22A11 and SLC17A1 in Primary Hyperuricemia and Gout

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Background/Purpose: The urate transporters are one of the genetic determinants of serum uric acid concentrations. In the present study, we describe the analysis of sequencing variants in the *ABCG2*, *SLC17A3*, *SLC22A11* and *SLC17A1* genes, physiologically important urate transporters whose dysfunction can play a role in pathogenesis of hyperuricemia, in a cohort with primary hyperuricemia and gout.

Methods: The cohort consisted of 150 individuals: 32/118 primary hyperuricemics/gout. The definition of hyperuricemia was as follows: >420/360 µmol/l at two repeated measurements at intervals of at least 4 weeks in men/women. Gouty arthritis was diagnosed according to the 1977 preliminary criteria of the American College of Rheumatology for acute arthritis of gout. Patients suffering from secondary gout were excluded. In total, 7050 PCR amplicons were sequenced directly: 10 for *SLC17A3*, 10 for *SLC17A1*, 10 for *SLC22A11*, 17 for *ABCG2*.

Results: In the *SLC17A3* gene were found 7 intronic/3 exon variants (2 non-synonymous *rs1165165*, rs*56027330*), in *SLC17A1* 7 intronic/1 non-synonymous exon variant (*rs1165196*) and in *SLC22A11* 3 intronic/4 exon variants (2 non-synonymous *rs201209258*, *rs75933978*). Allele frequencies for all exon and intron variants found in *SLC17A1, SLC17A3* and *SLC22A11* genes were not statistically significant compare to general Caucasian population. In the *ABCG2* gene, 16 intronic variants were detected. In the case of c.689+1G>A, related to an individual with severe gouty phenotype, two abnormal splicing variants were identified: a) r.[532_689del]; b) r.[532_689del], r.[944_949del]. Identified deletions lead to frameshift and premature stop codon introduction[1]. From the 9 exon variants detected, there were 7 non-synonymous: p.V12M (*rs2231137*), p.Q141K (*rs2231142*), p.R147W (*rs372192400*), p.T153M (*rs753759474*), p.F373C (*rs752626614*), p.T434M (*rs769734146*) and p.D620N (*rs34783571*). Heterozygous p.V12M variant was detected in 7 individuals. Heterozygous variant p.R147W, p.T153M, p.F373C, p.T434M and p.D620N was detected once, variant p.D620N was detected twice also in heterozygous state. All these five allelic variants were *in silico* predicted using Polyphen, Sift and Provean program as a probably damaging and were not detected in control cohort of 150 normouricemia subjects. The p.Q141K, previously functionally characterized variant with a strong effect on uric acid secretion impairment, was in cohort of hyperuricemic/gout patients presented with significantly higher minor allele frequency (MAF)=0.19 (42 heterozygotes/5 homozygotes), than in population of European origin (MAF=0.09) and world-wide population (MAF=0.12).

Conclusion: Our results show that genetic factor *ABCG2* should be considered as one of the common risks for hyperuricemia/gout. In clinical practice, *ABCG2* dysfunction can be estimated easily by genotyping and these findings will help to recognize a trait of hyperuricemia at a very early stage**.** References*:* 1. Stiburkova B et al. Novel dysfunctional variant in ABCG2 as a cause of severe tophaceous gout: biochemical, molecular genetics and functional analysis. Rheumatology (Oxford). 2016 Jan;55(1):191-4. Acknowledgements*:* Czech Republic Ministry of Health AZV 15-26693A.

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Abstract Number: 76

Chromatin Interactions Reveal Novel Gene Targets for Drug Repositioning in Rheumatic Diseases

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Background/Purpose: The treatment of rheumatic diseases can be both expensive and ineffective with up to 1/3 of patient's failing to respond to current treatments. There is therefore a need to identify new effective treatments and to target the best treatment to individual patients. Although genetic studies have been successful in identifying common variation associated with disease susceptibility, a large proportion of these lie outside traditional protein-coding regions. Many show enhancer activity but it is often unclear which gene(s) they regulate and how they contribute to disease. Chromatin folding brings linearly distant areas of the genome, such as promoters and enhancers, into close proximity, driving gene expression. Capture Hi-C (CHi-C) is a new method which interrogates these interactions in a high-throughput, high-resolution manner, linking implicated enhancers to causal genes. Utilising our existing CHi-C data on 3 rheumatic diseases, RA, JIA and PsA, targeting all known genetic associations, we explored the potential of this interaction data to identify potentially causal genes that are targets for existing drugs, which could be repositioned for use in these diseases.

Methods: Chromatin interaction data for T- and B-cells in the 3 diseases was re-called using CHiCAGO v2 using a score cut-off of ≥ 5. Interactions between disease regions and gene promoters were identified using BEDTOOLS v2.21.0 and intersected with known drug targets from DrugBank v4.5.0. Existing treatments for each disease were identified by the presence of the relevant name in the 'indication' field.

Results: Overall 850 genes were identified as interacting with a rheumatic disease associated region. Of these, 61 are existing drug targets (303 drugs) (Table 1) and 9 are existing therapies used in the treatment of disease, primarily RA.

Table 1 Summary of drug targets identified by CHi-C

Disease	Number of genes identified by CHi-C	Number of genes which are existing drug targets	Number of drugs Identified	Number of drugs withdrawn	Number of drugs currently used	Number of drugs for potential repositioning
RA	510	41	106	4	9	93
JIA	324	16	74	0	1	73
PSA	196	13	147	0	0	147
All	850	61	303	4	9	290

Conclusion: Our study identifies genes which are implicated in disease, are the target of existing drugs and offer the potential for drug repositioning. Of the potential drugs identified for RA, 14 are used in the treatment of various cancers particularly leukemias and 11 are used in the treatment of diabetes and multiple sclerosis. Interestingly, 17 potential drugs identified for PsA are used in the treatment of schizophrenia and 11 in the treatment of hypertension. This data shows a novel insight into how functional annotation of genetic associations in rheumatic diseases can provide gene targets for re-positioned therapies.

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Abstract Number: 77

Integrated Analysis of Microrna and mRNA Expression Profiles Related to Cardiovascular Disease in Monocytes from Systemic Lupus Erythematosus and Primary Antiphospholipid Syndrome Patients

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Background/Purpose: The interplay between miRNAs and their mRNA targets might constitute an important mechanism in the regulation of the proatherothrombotic status of SLE and APS patients. Aim: To investigate the contribution of deregulated miRNAs to the altered gene profile associated to cardiovascular disease (CVD) in SLE and APS.

Methods: Thirty-three SLE patients, 23 APS patients, and 27 healthy donors were included in the study. Gene Expression Microarray (44K, Agilent, one colour) and nCounter microRNA Expression Arrays (NanoString Technologies) were performed, respectively, to analyze mRNA and miRNA expression profiles on isolated monocytes. Target genes of the differentially expressed miRNAs and interaction networks were identified by using the Ingenuity Pathway Analysis Software (IPA). The resulting identified interactions were validated by RT-PCR on the whole cohorts of SLE and APS patients. The predicted miRNA-mRNA interactions were also tested by functional analyses using microRNA over expression experiments in monocytes purified from SLE and APS patients.

Results: Comparative analysis of the mRNA profiles showed significantly different expressions of 1222 genes in SLE and 519 genes in APS monocytes in relation to healthy monocytes. Functional analysis by using IPA showed that about 30% of altered genes were involved in inflammation and cardiovascular disease (CVD). Comparative analysis of the microRNA profiles showed significantly different expressions of 37 miRNAs in SLE and 22 miRNAs in APS monocytes. Functional IPA analysis showed that microRNAs altered were mainly related to connective tissue disorders, inflammatory response and reproductive system disease in both autoimmune conditions. In SLE, a total of 63 genes were inversely correlated, and predicted as CVD-related target genes of 23 differentially expressed microRNAs. In APS, a total of 56 genes were inversely correlated, and predicted as CVD-related target genes of 19 differentially expressed miRNAs. Interaction networks of those genes and some microRNAs differentially expressed in SLE and APS monocytes were also identified and showed to be specific of each autoimmune disease. Among them, the overexpression of STAT3, PPARg and CMKLR1 associated to inhibition of miR-130a and miR-149 were verified in SLE patients. In APS patients the overexpression of IL-1A, LDLR, TGF-b, VCAM, VEGF-A and STAT-1 were associated with inhibition of miR-199, miR-30 and miR-145. The expression of these genes and miRNAs correlated with specific parameters related to inflammation, oxidative stress and thrombosis in each autoimmune disease. Moreover, association of these genes and miRNAs with the occurrence and type of thrombotic events, obstetric complications and presence of pathologic CMIT were demonstrated. Transfection studies further confirmed the relationship between these identified target genes and specific miRNAs in both autoimmune disorders.

Conclusion: We have identified novel and specific microRNA-mRNA regulatory networks related to CVD in SLE and APS patients, thus delineating novel genetic controls of the diverse biological processes and factors related to the cardiovascular pathology present in these autoimmune conditions. Supported by FIS (PI01333/2015) and CTS-7940.
Disclosure of Interest: None declared

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Abstract Number: 78

Whole Blood Gene Modules Show Differences Between Active Lupus Nephritis and Quiescent Disease As Well As Absence of Plasmablast Signature in This Adult Population

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Background/Purpose: SLE is a complex disease with heterogeneous manifestations. It seems unlikely that all patients labeled as SLE have homogenous molecular pathology. An approach to evaluating the complexity is gene expression, wherein all the transcribed genes are assessed at once. Here we looked at the use of the Chaussabel 2008 modules developed on Affymetrix arrays in a heterogeneous adult SLE patient. The goal was to evaluate performance in separating disease activity from quiescent disease within lupus.

Methods: This study was conducted with SLE patients from the Hopkins Lupus Cohort following informed consent. Adult patients were eligible if they were aged 18 to 75 years old and met the definition of SLE as defined by the revised American College of Rheumatology classification criteria. Clinical and laboratory values were recorded at every visit. High disease activity was defined as presence of nephritis and significant proteinuria. Low disease activity was defined as PGA = 0 and the absence of steroids or immunosuppression (other than hydroxychloroquine). Typical SLE was a random mix of SLE disease activity including nephritis. Healthy controls were recruited and had no evidence of autoimmune disease. RNA collected from whole blood and analyzed as previously described [1]. Comparison with the pediatric SLE cohort used publically available data on the NIH GEObus (GSE11909).

Results: Patient characteristics are shown in the below Table 1.

	High Activity N=13	Low Activity N=25	Healthy N= 51	Typical SLE N=95
Average Age (sd)	43.9(12)	44(14)	39(11)	46(12)
Ethnicity (%)				
African American	23	44	27	38
White	62	52	73	58
Average SLEDAI	7	0	NA	2.7
Mycophenolate (N)	6	0	NA	21
Azathioprine (N)	2	0	NA	12
Average Prednisone (mg)	8.5	0	NA	3

Table 1. The 13 patients universally have lupus nephritis at the clinical visit, eight of who were already on therapy. There are a higher proportion of African Americans in the Low Activity group. Table 2 shows the results of the modular analysis. We were not able to demonstrate the significant plasmablast signature seen in the pediatric population. We were able to show a higher neutrophil signature with the lupus nephritis group.

Module Name	Module Number	Pediatric SLE Untreated vs. HC		Adult SLE High vs No Activity		Adult SLE SLE vs HC	
		UP	DOWN	UP	DOWN	UP	DOWN
plasma cells	1.1	45	0	8	0	4	14
erythrocytes	1.2	5	5	5	9	20	7
B-Cells	1.3	1	4	3	36	1	30
none	1.4	5	4	5	18	8	19
myeloid	1.5	13	6	9	15	32	4
none	1.6	5	5	1	11	0	45
ribosomal	1.7	0	78	5	64	11	40
none	1.8	3	5	2	27	6	21
cytotoxic	2.1	2	21	1	40	2	29
neutrophils	2.2	33	0	55	0	29	4
erythrocytes	2.3	26	3	9	3	9	8
ribosomal	2.4	0	77	0	74	5	36
none	2.5	1	27	3	3	6	5
myeloid	2.6	23	2	10	3	28	8
none	2.7	1	31	0	4	1	7
T-cells	2.8	0	42	0	56	1	32
none	2.9	3	12	8	1	3	40
none	2.1	4	8	8	11	18	8
none	2.11	2	6	2	8	4	22
Interferon	3.1	91	0	97	0	97	0
inflammation	3.2	13	2	16	4	20	14
inflammation	3.3	9	6	8	7	17	8
none	3.4	6	14	2	16	2	25
none	3.5	14	18	5	5	14	5
none	3.6	6	5	2	15	2	19
none	3.7	4	9	1	23	17	9
none	3.8	1	13	1	45	4	42
none	3.9	2	11	1	29	3	23

Table 2. Comparison of modules between patient groups.

Conclusion: The Chaussabel modules showed notable differences between active lupus nephritis and quiescent disease. The interferon module, as defined in the 2008 modules, did not markedly differ between the groups analyzed. The neutrophil module was notably increased in the lupus nephritis population. **References:** 1. Zollars, E. *et al*. BAFF (B cell activating factor) transcript level in peripheral blood of patients with SLE is associated with same-day disease activity as well as global activity over the next year. *Lupus Sci. Med.* **2,** (2015)

Disclosure: E. Zollars, None; **G. Hardiman**, None; **B. Wolf**, None; **S. Courtney**, None; **N. Allaire**, Biogen Idec, 3; **A. Ranger**, Biogen Idec, 1; **M. Petri**, None.

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Abstract Number: 79

A NOVEL Missense Mvk mutation in a Family with Familial Mediterranean Fever-like Disease

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Monogenic autoinflammatory diseases are mainly disorders of innate immunity and characterized by unprovoked inflammatory attacks. We studied a consanguineous family with two affected children, with an initial diagnosis of Familial Mediterranean Fever (FMF). While recurrent febrile attacks with serositis, high acute response and parental origin were consistent with FMF, disease onset before age one year, delay in growth, no mutation in MEFV and poor response to colchicine were not typical features of this disease.

Methods: SNP genotype data for all family members were used for multipoint linkage analysis. Targeted sequencing was performed for *MVK* residing in one of the linked regions and seven other autoinflammation related genes, *IL1RN, LPIN2*, *MEFV, NLRP12, NLRP3, TNFRSF1A* and *PSTPIP1*. After the identification of the causative mutation, serum IgD and urinary mevalonic acid levels were measured.

Results: Linkage analysis detected seven candidate regions. The largest candidate region, at 12q24.11-q24.31 (LOD=1.92), contained 191 genes. Novel homozygous c.481T>C (p.Cys161Arg) mutation in *MVK*, the gene responsible for Hyper IgD Syndrome (HIDS) was identified. At the protein level, cysteine at position 161 is totally conserved in mammals. Urinary mevalonic acid was not detected for either patient, and serum IgD level was slightly elevated for only one patient.

Conclusion: We identified a novel homozygous *MVK* mutation in patients with a FMF-like disease but without a typical HIDS phenotype. We hypothesize that this novel mutation underlies the atypical clinical presentation. Phenotypic variability of HIDS is well known, and our findings further expand the *MVK* mutation phenotype.

Disclosure: I. Karacan, None; **S. Ugurlu**, None; **A. Tolun**, None; **E. Tahir Turanli**, None; **H. Ozdogan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-novel-missense-mvk-mutation-in-a-family-with-familial-mediterranean-fever-like-disease

Abstract Number: 80

Impact of a Patient Support Program on Abandonment of Adalimumab Treatment Initiation in Patients with Rheumatoid Arthritis, Ankylosing Spondylitis, and Psoriatic Arthritis

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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: Treatment abandonment (failure to start therapy after prescription) is common among patients (pts) prescribed specialty pharmaceuticals. AbbVie offers a pt support program (PSP) for adalimumab (ADA)-treated pts, which includes assistance with medication costs, nurse support, injection training, pen disposal and medication reminders.[1] PSP may reduce abandonment in RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA). We investigated associations between PSP and rate of ADA treatment abandonment in US pts with RA, AS and PsA.

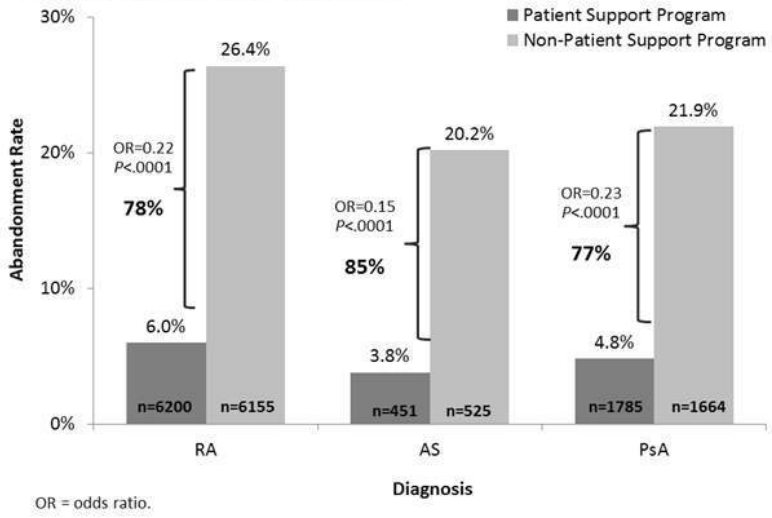
Methods: A longitudinal study was conducted using pt-level data from AbbVie's PSP database linked with Source Healthcare Analytics US claims data. Pts aged ≥18 years with a RA, AS or PsA diagnosis, ≥1 pharmacy claim (paid or reversed) for ADA and no ADA claim before 2012 were included; the index date was the first ADA claim from 1/2012–1/2015. Pts required medical coverage ≥3 months pre-index date and pharmacy coverage ≥3 months pre-/post-index date. Abandonment was defined as reversal of first ADA claim (eg, pt did not take possession of medication) with no paid claim during 3 months of follow-up. Abandonment rate was compared between pts who enrolled in any component of the PSP (PSP cohort) vs those who did not (non-PSP cohort) within 30 days of treatment initiation using 2-sample z-test of proportions. The likelihood of abandonment was assessed using logistic regression, controlling for baseline characteristics.

Results: A total of 16780 pts (RA: 6200 PSP, 6155 non-PSP; AS: 451 PSP, 525 non-PSP; PsA: 1785 PSP, 1664 non-PSP) were included. At baseline in RA and PsA, PSP pts were younger (50.5 vs 52.0 yr; $P<.0001$ and 48.5 vs 49.3 yr; $P=.042$, respectively) and less likely to be male (20.4% vs 22.5%; $P=.005$ and 41.2% vs 47.8%; $P=.0001$, respectively) than non-PSP pts. No significant difference was observed regarding age in AS, but PSP pts were less likely to be male vs

non-PSP pts (50.1% vs 57.7%; *P*=.018). The PSP cohort had lower expected per-patient out of pocket contribution for ADA across diseases (RA [$222 vs $312; *P*<.0001], AS [$136 vs $240; *P*<.0001] and PsA [$179 vs $261; *P*<.0001]) and greater frequency of specialty pharmacy use for first ADA fill (RA: 55.7% vs 47.3%; *P*<.0001, AS: 65.4% vs 49.5%; *P*<.0001, PsA: 58.8% vs 54.8%; *P*=.0173). After controlling for baseline characteristics among PSP vs non-PSP pts, abandonment risk was 78% lower in RA (6.0% vs 26.4%; odds ratio [OR]=0.22; *P*<.0001), 85% lower in AS (3.8% vs 20.2%; OR=0.15; *P*<.0001) and 77% lower in PsA (4.8% vs 21.9%; OR=0.23; *P*<.0001) (**Figure**).

Conclusion: Enrollment in AbbVie's free-to-patient PSP was associated with 77–85% reduced abandonment of ADA treatment among US pts with RA, AS and PsA. **References:** 1. https://www.humira.com/humira-complete

Figure. Significantly Lower Risk of Treatment Abandonment Among RA, AS and PsA Patients Enrolled in Patient Support Program



Disclosure: P. Mease, AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, 2,AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, 5,AbbVie, Amgen, BMS, Celgene, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, 8; **M. Mittal**, AbbVie, 3,AbbVie, 1; **M. Skup**, AbbVie, 3,AbbVie, 1; **M. Davis**, Medicus Economics, which received payment from AbbVie to participate in this research, 3; **A. Ganguli**, AbbVie, 3,AbbVie, 1; **S. Johnson**, Medicus Economics, which received payment from AbbVie to participate in this research, 3; **M. Schiff**, AbbVie, Amgen, BMS, Eli Lilly, JNJ, Novartis, Roche, UCB, 5,AbbVie, 8.

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Abstract Number: 81

Understanding the Importance of a Patient's Role in the Management of RA: Physician- and Patient-Based Survey

Ara Dikranian[1], James Galloway[2], Joern Kekow[3], Cristiano A.F Zerbini[4], Maria de la Vega[5], Gavin Lee[6], Anna Maniccia[7], Eustratios Bananis[8], Dario Ponce de Leon[9] and Allan Gibofsky[10], [1]San Diego Arthritis Medical Clinic, San Diego, CA, [2]King's College, and King´s College Hospital, London, United Kingdom, [3]University of Magdeburg, Clinic of Rheumatology, Magdeburg, Germany, [4]Centro Paulista de Investigação Clinica, São Paulo, Brazil, [5]CEIM Investigaciones Médicas, Buenos Aires, Argentina, [6]Hong Kong Sanatorium & Hospital, Hong Kong SAR, China, [7]Pfizer Inc, New York, NY, [8]Pfizer Inc, Collegeville, PA, [9]Pfizer Inc, Lima, Peru, [10]Rheumatology, Weill Cornell Medicine, and Hospital for Special Surgery, New York, NY

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Background/Purpose: RA is a chronic, debilitating condition for which there is no cure. To identify and better understand the perspectives of both healthcare providers (HCPs) and patients (pts) regarding RA treatment and management, the RA NarRAtive global advisory panel developed an HCP- and pt-based survey.

Methods: The RA NarRAtive initiative comprises a global advisory panel of 39 RA experts. An HCP-based and a pt-based survey, designed by the working group, were fielded online between Aug 2015 and Oct 2015, and between Sept 2014 and Jan 2016, respectively. Responses are presented from pts treated by a rheumatologist, and HCPs who were rheumatologists in all countries (orthopedists also included in Japan). All respondents are from the same 15 countries.

Results: 3,987 pts responded, of whom 1,667 were managed by a rheumatologist: mean age 51.5 years (yrs), 64% female, median time since diagnosis 7 yrs; respondents represented a wide spectrum of disease activity: moderate to severe (33%; 556) and severe (10%; 159). In total, 1,666 HCPs responded to the survey, 51% were mostly in office- or clinic-based practice and 22% were in mostly hospital- or lab-based practice; mean number of pts with RA that HCPs saw per month was 92.0; HCPs reported that disease activity was moderate to severe in 32.5% of their pts and severe in 17.4%. In the HCP survey, 90% of respondents were satisfied with their communications with pts; however, 68% acknowledged, 'I wish my pts and I talked more about goals and treatment.' In the pt survey, 53% of pts acknowledged that dialogue with the HCP would optimize the management of their RA. However, 61% of respondents felt uncomfortable raising concerns or fears to their HCP. 93% of HCP respondents discussed quality of life (QoL) issues with their pts including impact of RA on ability to work, participation in activities, and lifestyle goals. 86% discussed treatment-related issues including adherence to therapy, medication preferences, and whether pts seek treatment from other HCPs. The most common topics that patients reported worrying about and that HCPs believed their patients worry about are similar; although a greater proportion of HCPs believed their pts worry about treatment side effects/failure. HCPs and pts had similar views on what they would most like to change about currently available RA medications, ie severity and number of side effects, cost, and efficacy. RA remission was ranked higher in the HCP survey than in the pt survey as a treatment goal; while pts frequently referred to symptom reduction. Overall, 88% of HCPs agreed that pts who are involved in making treatment decisions tend to be more satisfied with their treatment experience; 74% felt that pts who are not involved are less likely to adhere to treatment. Setting treatment goals with pts and agreement on the treatment plan are considered important by 78% and 79% of HCPs, respectively, as well as being able to have an open dialogue (86%).

Conclusion: Differences between treatment goals set by pts and HCPs were reported, thus highlighting the importance of an open pt-HCP dialogue in the successful management of RA. These findings could help improve adherence and pt satisfaction with their disease management.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/understanding-the-importance-of-a-patients-role-in-the-management-of-ra-physician-and-patient-based-survey

Abstract Number: 82

Patients with Rheumatoid Arthritis in Germany: Are They Ready for Ehealth Via Mobile Medical Applications?

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Background/Purpose: Mobile medical Applications (mApps) with diary functions and integrated patient-reported outcome instruments allow patients (pts) with rheumatoid arthritis (RA) to self-monitor their disease apart from out-pts visits and thus might strengthen self-management. In a project evaluating the usability of a mApp with diary function we studied pts' given information technology (IT) prerequisites, especially their hitherto use of Internet and apps on mobile devices.

Methods: Inclusion criteria were RA diagnosis, age of consent and German speaking. 268 consecutive RA out-pts were screened, 157 (58.6%) owned an App-compatible device, and 60 pts (38.2%) agreed to complete paper-based questionnaires assessing experiences and knowledge regarding IT aspects, App/internet use, and sociodemographic and clinical trial data. Ethic approval and pts' signed informed consents were obtained. The identifier at clinicaltrials.gov is NCT02565225.

Results: Pts were predominantly female (78.3%), mean±SD age was 50.1±13.1 years (yrs), mean disease duration 10.5±9.1 yrs. 50% had a high education level. 93.3% reported substantial experience with a smartphone, 70.0% with a tablet. 80% wanted to use the project-App on their smartphone, 20% on their tablet. Pts were familiar with their devices for 3.0±2.4 yrs. Internet use via the device was reported for private (91.7%) and official business issues (30.0%). 43.3% confirmed Internet use via the device during business hours. It was accessed via the contract of their device by 66.7% (3G 37.5%; 4G 27.5%), via WIFI at home (81.7%) or in public areas (35.0%) for 2.3±2.9 hours/day. 90.0% already used Apps, these reported use of health (24.1%), diet (9.3%), games (37.0%), communication/social media networks (59.3%), news (59.3%), weather information (79.6%), music (33.3%), sport (20.4%) and productivity (24.1%) Apps. Most (94.4%) stated use of free-of-charge Apps, 44.4% of Apps with costs. Although being informed that the project mApp was not build to send data via the Internet 18.3% believed that data entered in the mApp will be stored in a cloud, 35.0% had no idea how the data is stored. 51.7% think they know the way an App works. Perceived data security on their App-compatible device was rated 3.0±1.4 (1(= high)–6(= low) Likert scale). 63.3% rated new media technology as predominantly beneficial for patient-physician interaction.

Conclusion: More than half of the pts owned App-compatible devices. Pts apply them for mobile Internet and App use even in business hours. Technical requirements for patient-physician communication via mobile devices are fulfilled in these pts, although IT literacy seems still to be narrowed in some pts. However, eHealth concepts via a mApp for monitoring disease apart from the physician visits seem feasible. Our project will deliver further important data of the mApp - a powerful tool at our fingertips.

Disclosure: J. G. Richter, None; **C. Kampling**, None; **G. Chehab**, None; **H. Acar**, None; **A. Becker**, None; **M. Schneider**, None.

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Abstract Number: 83

A Qualitative Study Exploring Participants' Perception of the Making It Work Program, an Online Program to Help People with Inflammatory Arthritis Maintain Employment

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Background/Purpose: Health services addressing employment needs for people with arthritis are lacking. To address this need, we developed the Making it Work (MiW) program, an on-line self-management program aimed at helping people with inflammatory arthritis (IA) deal with employment issues. As part of a randomized controlled trial evaluating program effectiveness, this study aimed to explore participants' experience and obtain insight on the perceived benefits and drawbacks of participating in the MiW program.

Methods: All MiW participants who attended the final group meeting between January 2015 and April 2016 were included in this study. Semi-structured debrief group discussions were conducted by the group facilitator at the end of the last online group meeting, which was recorded and transcribed. Using content analysis, transcripts were coded and concepts grouped into meaningful clusters to identify emerging themes. All participants had IA; were currently employed; aged 18-59 years; concerned about their ability to work; and had access to a computer.

Results: The sample included 62 participants [87% female; mean (SD) age: 46(9.9) years; disease duration: 9(9.1) years; with RA (51%), AS (13%), PsA (18%), or SLE (18%); working full time (69%); 19% self-employed]. Several participants highlighted the problem solving and goal setting technique, as well as strategies to manage fatigue and stress, as "really helpful" tools for managing their arthritis both at and outside of work. People newly diagnosed with IA or interested in making changes to their work now or further "down the road" described the modules as most "informative". Some expressed interest in revisiting the material in the future. However, not all module content was relevant for everyone, as job situation (e.g. self-employed) or disease characteristics (e.g. those without fatigue) meant some content (e.g. disclosure or job accommodations, or dealing with fatigue) was not applicable to some workers. Perceived benefits/drawbacks of participation clustered around four themes: 1) Heightened awareness of how their arthritis affected their work; of their rights; and of resources available to them. 2) Empowerment vs. Frustration. Although most participants felt empowered by their increased awareness, a few became increasingly frustrated because they were unable to make changes to their work situation. 3) Improved self-efficacy. Many described feeling more confident about dealing with the challenges at work due to their arthritis, as a result of strategies and skills learnt. 4) Validation, resulting from groups meetings. Participants described that recognizing that their symptoms and struggles at work were shared by others with IA provided emotional relief from self-blame and self-doubt; being able to identify with and connect to other group members was comforting; receiving confirmation for strategies they had been using prior to MiW encouraged them to "keep at it".

Conclusion: This study provides insight into what participants found helpful about the MiW program. These findings are informative to health professionals assisting clients in dealing with employment issues and researchers designing arthritis programs dealing with employment.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-qualitative-study-exploring-participants-perception-of-the-making-it-work-program-an-online-program-to-help-people-with-inflammatory-arthritis-maintain-employment

Abstract Number: 84

Treatment Outcomes and Predictors of Patient Support Program Use Among Patients with Rheumatoid Arthritis: Results from a Post-Marketing

Observational Study (PMOS)

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Session Time: 9:00AM-11:00AM

Background/Purpose: Patient (pt) support programs (PSPs) are offered to Rheumatoid arthritis (RA) pts to help manage treatment of this chronic disease. Little information is available regarding the impact of these PSPs on disease management and factors affecting their use. The purpose of this study was to assess characteristics and predictors that influence pt participation in the PSP among adalimumab (ADA)-treated RA pts.

Methods: In this multinational, ex-US study, RA pts with an insufficient response to ≥1 disease-modifying antirheumatic drug (DMARD) newly initiating ADA (1 prior biologic DMARD was allowed) were enrolled. Pts were offered a panel of "Core elements" (starter pack, call center/hotline, nursing services, educational material, and injection guide; offered in all participating countries) and "Other elements" (e.g, refill reminders, email, newsletters, support groups, home delivery, and financial assistance; vary by country) of PSP. PSP participation was captured via a PSP utilization questionnaire at each study visit. Pts were classified based on PSP participation: ever (PSP users) vs never (PSP non-users) which served as a dependent variable in a multivariate logistic regression model examining the following parameters: baseline (BL) age, sex, race, RA disease duration, prior use of biologic DMARD, Health Assessment Questionnaire Disability Index (HAQ-DI), Patient Activation Measure-13 (PAM-13), BL Simplified Disease Activity Index (SDAI), and BL 28-joint DAS based on CRP (DAS28(CRP)).

Results: Of the 1,025 pts included in the Intent-to-treat population, 48.7% were PSP users. The BL demographics and clinical characteristics are enlisted (Table). After adjusting for BL demographics and clinical characteristics, the odds ratio of using a PSP was significantly lower in pts who previously used a biologic DMARD. Several factors, including female sex, and higher HAQ-DI, and DAS28(CRP) at BL, had statistically non-significant lower likelihood of PSP utilization (**Figure**). Study discontinuation rates were significantly (P<0.001) lower among PSP users vs PSP non-users (25.5% vs 41.6%).

Conclusion: In pts with moderate to severe RA newly initiating ADA, PSP users were found to have differences in baseline demographics and clinical characteristics. After accounting for these baseline differences, being naïve to prior biologic DMARD treatment was significantly associated with PSP participation. Pt participation in the PSP was associated with better retention in the study, underscoring a potential link between PSP participation and treatment adherence that should be further explored in prospective studies.

Figure: Predictors of PSP use among RA patients. Odds ratios are adjusted for each other

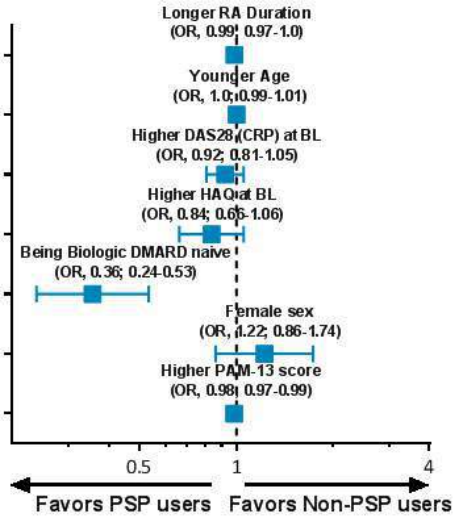

Table: Baseline Demographics and Clinical characteristics

	All Patients (N=1025)	PSP-users (N=499)	PSP-non-users (N=526)
Female, n (%)	790 (77.1)	380 (76.2)	410 (77.9)
White, n (%)* **	903 (88.1)	419 (84.0)	484 (92.0)
RA Duration (years)	7.8 (8.4)	8.2 (8.8)	7.5 (8.05)
Prior biologic DMARDs, n (%)* **	182 (17.8)	56 (11.2)	126 (24.0)
Age (Years)	54.3 (13.3)	54.4 (13.2)	54.2 (13.4)
DAS28 (CRP)**	5.3 (1.17)	5.4 (1.18)	5.2(1.14)
SDAI**	35.6 (15.19)	37.3(16.34)	34.0 (13.89)
CDAI	33.3 (13.80)	34.4 (14.41)	32.3 (13.16)
CRP (mg/L)* **	21.6 (47.8)	28.1 (63.6)	15.5 (24.4)
HAQ-DI*	1.50 (0.72)	1.55 (0.73)	1.44 (0.71)
PAM-13 score	59.9 (14.96)	60.9 (15.27)	58.9 (14.60)

***, **, *: *P*-value < 0.001, 0.01, and 0.05, respectively comparing PSP users vs PSP non-users

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Abstract Number: 85

Evaluation of Patient Satisfaction with the on-Tracc Program; Benefits of a Joint Approach

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SESSION INFORMATION

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Background/Purpose: The University of Alberta Division of Rheumatology has launched a new multidisciplinary clinic, the On-TRACC Program (**O**n **T**reating **R**heumatoid **A**rthritis – Providing **A**ccess to **C**are), which provides aggressive treat to target (T2T) disease modification and co-morbidity management in a shared-care model of rheumatologists and advanced care practitioners (ACP). Primary Objective: To evaluate patient satisfaction in patients enrolled in the On-TRACC program compared to those treated in general rheumatology clinics through a patient satisfaction survey.

Methods: We performed an observational cross-sectional survey study using a modified version of the Leeds Satisfaction Questionnaire (LSQ), a validated and reliable tool developed for inflammatory arthritis (IA) outpatient clinics, to compare satisfaction between the two patient groups: On-TRAAC and the traditional model of care (TMC). The six groups included in the questionnaire's subscales, and thus assessed with this survey included: (1) provision of information, (2) empathy with the patient, (3) attitude towards the patient, (4) access to and continuity with the caregiver, (5) technical competence and (6) overall satisfaction. A sub-group analysis of patient satisfaction between the first and second visit in the On-TRACC group was also performed. Markers of disease activity including DAS 28-CRP, HAQ (Health Assessment Questionnaire) and CRP were assessed over time in the On-TRACC group.

Results: A total of 75 patients completed the survey (27 patients in the On-TRAAC group and 48 in the TMC). The average age of the participants was 53 years and included 24 males and 51 females. The overall satisfaction score was 4.36 in the TMC group and 4.48 in the On-TRAAC group (higher values represents higher satisfaction). Ten patients in the On-TRAAC group performed the survey at least twice and showed an overall trend towards improved satisfaction on subsequent visits with an initial overall satisfaction score of 4.48 and follow up score of 4.55. No statistically significant differences were noted between groups, or within the On-TRACC group. Within the On-TRACC group, markers of disease activity including DAS 28 CRP, HAQ and CRP all showed improvement between baseline and follow-up visits.

Conclusion: While patients in both treatment groups were very satisfied with their care, patients in the On-TRACC group were at least as satisfied with their care as those in the TMC, and there was a trend towards improved satisfaction with the multi-disciplinary care model. This has important implications as it lends support to the use of this alternate model of care in the provision of services to those with IA, which has potential benefits from both a clinical and health economics perspective. Larger patient numbers with longer follow-up are needed to provide meaningful comparisons between these different models of care. Table 1. Baseline characteristics and overall satisfaction

Characteristic	On Tracc Group (n=27)	TMC (n=48)
Mean age (Range) ± SD	50.6 years (22-85) ± 16.63	54.4 years (18-87) ± 16.39
Gender	6 Male (22%) 21 Female (78%)	18 Male (37.5%) 30 Female (62.5)
Duration of Inflammatory Arthritis	< 1 year = 8 (30%) 1-5 years = 6 (22%) > 5 years = 13 (48%)	< 1 year = 6 (12.5%) 1-5 years = 22 (46%) > 5 years = 20 (41.5%)
Ethnic Origin	22 Caucasian (81%) 2 Asian (7.5%) 2 First nations (7.5%) 1 Mixed ethnicity (4%)	Unknown
Smoking Status	2 Current smokers (7%) 8 Ex-smokers (30%) 17 Never smokers (63%)	Unknown
Baseline CRP	5 patients < 1 (19%) 20 patients > 1 (74%)	Unknown
Baseline DAS 28 CRP	10 patients < 2.6 (37%) 15 patients > 2.6 (56%)	Unknown
Overall Satisfaction	4.48	4.36

Disclosure: J. Roberts, None; **S. O. Keeling**, None; **S. J. Katz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluation-of-patient-satisfaction-with-the-on-tracc-program-benefits-of-a-joint-approach

Abstract Number: 86

Optimizing the Efficiency of Patient Data Capture Using Smartphone Technology: Evaluation of the Correlation Between Promis Instruments for PRO Data Capture

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Background/Purpose: Patient-reported outcomes (PROs) are key to enabling the comprehensive assessment of patient-centered benefits in comparative effectiveness research (CER). However, the relationships between different PROMIS instruments and condition-specific disease activity measures in diseases such as rheumatoid arthritis (RA) have not been well studied. The objectives of this analysis were to evaluate the longitudinal relationship between different PROMIS instruments and the RAPID3, a measure of self-reported patient disease activity.

Methods: Four PROMIS instruments: pain interference, physical function, sleep disturbance, and fatigue as well as the RAPID3 were administered to participants in the PCORI-funded ArthritisPower patient registry. After descriptive analytics, we estimated multiple correlations between PROMIS instruments and the RAPID3. For each PRO instrument and with each assessment used as the unit of measure, we used model of fit, also called R-squared (the proportion of variance of outcomes that can be explained by the predictors), calculated from mixed models to understand how longitudinal PROs were related to each other. Using pain as an example, we evaluated the R-squared for each model with additional PROs and demographic factors including enrollment age, sex, race, twitter account, region and visit times.

Results: A total of 1,546 unique participants who answered the survey one or more times was included in the analysis, with mean (SD) age of 49 (12) years. The mean score for pain interference was 63.7 (SD: 7.0), physical function 37.5 (7.1), sleep disturbance 58.4 (8.7), fatigue 63.8 (8.8), and RAPID3 15.5 (5.7). Most PROMIS instruments were low to moderately (around 0.2) correlated with each other and the RAPID3. Using pain interference as an example, R-squared measures revealed a high total variance explained (R^2=49%) between pain interference and physical function (Table); those involving pain, physical function, fatigue, sleep disturbance and RAPID3 also revealed a higher variance contribution with these additional PROs (66%). Additional adjustment for demographic factors added little variance explanation (1.4%).

Conclusion: PROMIS pain interference, physical function, sleep disturbance, fatigue instruments and RAPID3 are low to moderately correlated to each other. Age, gender, race and other demographic factors play little role in explaining variance in PROs. These results suggest potential efficiencies in using some measures to predict or impute the values for other measures and to optimize the frequency of patient data collection using at-home technologies including Smartphone Apps.

Table: Total variance explained by predictors (R-Squared) using PROMIS pain interference as the dependent variable		
Models with PROMIS pain interference as the dependent variable	**Pain variance that was not able to explained by predictors**	**Total pain variance that could be explained by predictors (R-Squared)**
Baseline model: no predictors	42.6	N/A
Model with predictors: PROMIS physical function	22.6	46.9%
Model with predictors: PROMIS physical function, sleep	20.7	51.6%
Model with predictors: PROMIS physical function, sleep, fatigue	18.7	56.1%
Model with predictors: PROMIS physical function, sleep, fatigue, RAPID3	15.3	64.1%
Model with predictors: PROMIS physical function, sleep, fatigue, RAPID3 and others (age, gender, race, region, etc.)	15.1	64.7%
Model with only demographic predictors: age, gender, race, region, etc.	42.3	0.7%

Disclosure: H. Yun, Amgen, 2; **J. Beaumont**, None; **S. Yang**, None; **J. Willig**, None; **W. B. Nowell**, None; **S. D. Ginsberg**, None; **K. V. Clayton**, None; **S. Hazel**, None; **C. Wiedmeyer**, None; **J. Curtis**, None.

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Abstract Number: 87

Familiarity Vital for Telemedicine Uptake Among Parents of Pediatric Rheumatology Patients

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Background/Purpose: The United States pediatric rheumatology (PR) workforce is committed to a mission of providing children access to PR care. With a limited number and distribution of pediatric rheumatologists, telemedicine has been proposed as one way to meet this mission. Because low familiarity with telemedicine is a known barrier to successful implementation, the purpose of this study was to assess familiarity with telemedicine and how this influenced opinions about this modality among parents/guardians of PR patients in the Upper Midwest.

Methods: For six weeks in 2015, English-speaking guardians of patients being evaluated at the University of Minnesota

Pediatric Rheumatology Clinic were eligible to participate in a needs-assessment survey. Responses were analyzed using descriptive statistics.

Results: Of 221 participants eligible for the survey, 159 (72%) responded. The majority were guardians of adolescent Caucasian patients and had private insurance. The most common diagnosis was juvenile idiopathic arthritis, and 28% (45/159) traveled more than three hours to the clinic. Only 8% (13/158) of respondents reported that they or a family member or friend had ever used telemedicine, and the majority of respondents (75%, 115/154) felt that they did not know enough about telemedicine to determine if such visits are better, equal, or worse to in-person visits. Fifteen percent (23/154) felt that telemedicine visits are worse than in-person visits, and 10% (16/154) felt that telemedicine visits are either equal or better. Those familiar with telemedicine were more likely to report a preference for telemedicine over in-person visits (27% vs 3%; p=0.0087). They were also more likely to report telemedicine visits as equal to or better than in-person visits (42% vs 8%; p=0.0033), and 60% (3/5) of these respondents preferred telemedicine visits themselves. Still, an overwhelming majority of respondents (95%, 144/152) reported a preference for in-person visits over the option of telemedicine, and this preference persisted even when travel to the clinic was reported as inconvenient (inconvenient 92%, convenient 97%; p=0.2881). Neither views on telemedicine visits compared to in-person visits nor preference for in-person visits significantly differed by patient demographics, insurance type, length of time the child was a patient in the clinic, travel time, or frequency of internet use.

Conclusion: Most respondents prefer in-person visits over the option of telemedicine; however, familiarity with this modality was low, and most did not feel that they knew enough to assess the quality of telemedicine visits. Familiarity with telemedicine positively influenced both a preference for telemedicine and the assessment of the quality of telemedicine. Sample bias existed because only those who came to the PR clinic were surveyed. Efforts to increase familiarity with telemedicine may foster increased acceptability and are therefore vitally important when implementing a telemedicine program.

Disclosure: D. R. Bullock, None; **R. K. Vehe**, None; **L. Zhang**, None; **C. K. Correll**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/familiarity-vital-for-telemedicine-uptake-among-parents-of-pediatric-rheumatology-patients

Abstract Number: 88

Patient-Clinician Co-Participation in Design of an App for RA Management Via Telehealth Yields an App with High Usability and Acceptance

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Background/Purpose: Traditional management of rheumatoid arthritis (RA) is by rheumatologist review 3 to 6 monthly. This is not sustainable in many healthcare systems as demand exceeds rheumatologist capacity, with these demands projected to increase. Mobile software (an application or app) could enable patients to provide remote monitoring of health status via patient reported outcomes (PROs), patient-performed joint counts and electronic messages to health care professionals (HCP). This worked aimed to 1. Assess opinions of people with RA and HCP regarding design and functionality of an app and acceptability and usefulness of an app assisted telehealth approach for RA 2. Develop an app and 3. Assess usability of the app.

Methods: Semi-structured interviews were undertaken with people with RA (ACR 2010 criteria) and HCP, recruited

from a hospital rheumatology service. Interviews explored technology use, app functionality, barriers and facilitators to app use and potential impacts of app implementation on service provision and experience. Thematic analysis was performed and recruitment concluded when saturation achieved. An app (RAConnect) was developed in iOS and android with design and function informed by interview data. People with RA used RAConnect on their mobile devices for one month then usability was assessed (System usability scale) and free text feedback collected.

Results: Nine people with RA (27-79yrs, 7 females, 1-26yrs of RA, low-moderate disease activity) and 11 HCP were interviewed. Four themes were identified 1. Variable app readiness. 2. Reduced barriers with high app usability and text message communication. 3. Pros and cons of PROs, with some ambivalence 4. Resource allocation and engagement - PRO reporting via an App is acceptable to guide HCP in allocation of limited resource while also increasing patient engagement. Usability testing with 16 people with RA confirmed RAConnect had high usability (SUS 80/100, 90th centile). Both the app and a telehealth approach had high acceptability. "*I think a wraparound thing like RAConnect would allow better spacing between appointments and for me it would make them less stressful*."48Male "*I think that it has the potential to be very useful in managing my RA. It is easy to use and may mean less visits to the rheumatologist*." 49Male. "*It'll be a great tool for both the Doctors, their clinical staff and their patients."* 70Female.

Conclusion: A patient-held app for RA monitoring and communication with rheumatology care provider will be acceptable and desirable for many patients. Further research is required to develop multi-media material to train people with RA to perform joint counts and to validate patient-performed joint counts. During implementation assessment of the patient experience of using this telehealth system, disease outcomes, costs and impact on workflow of HCP will be required.

Disclosure: R. Grainger, None; **T. Langlotz**, None; **H. Townsley**, None; **W. Taylor**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/patient-clinician-co-participation-in-design-of-an-app-for-ra-management-via-telehealth-yields-an-app-with-high-usability-and-acceptance

Abstract Number: 89

2015 ACR/ARHP Workforce Study (WFS): Adult Rheumatology Specialists in the United States: Effect of Gender and Generation

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Background/Purpose: Workforce surveys are essential to plan for training, recruitment, practice management, funding, and access to care. Gender and generational differences may have significant effects on the future rheumatology workforce. The 2015 WFS provides a description of the current workforce and projected supply and demand models for 2015-2030.

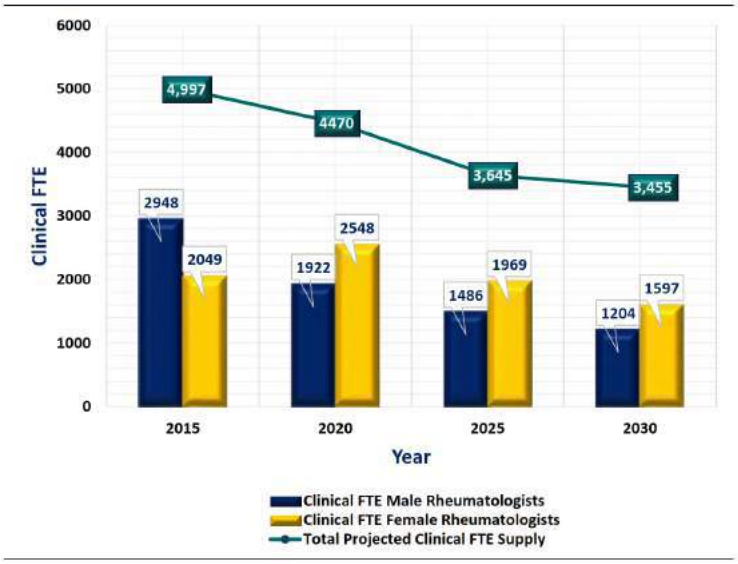
Methods: Web-based surveys were distributed to U.S. rheumatology professionals and Fellow-in Training (FITs). Supply (current providers, new graduates, retirement/workload trends, practice settings) and demand (healthcare utilization, practice trends, disease prevalence, population demographics, per capita income) factors were calculated.

Results were compared with the 2005 rheumatology workforce study.

Results: The response rate was 38.5% from adults (1297/3366) and 93.4% from FITs (464/497). The supply/demand model predicts a 31% decline in clinical FTE supply from 4,997 to 3,455 by 2030, and a 138% increase in demand from

6,155 to 8,184 by 2030, generating an excess demand for 4,729 adult rheumatologists. Gender/generational effects were subsequently estimated. The current adult workforce is 59% men and 41% women. In 2015, annual patient visits were 3,133 for men and 2,249 for women rheumatologists, compared with 2005 a decline of 14% for men and 19% for women overall and 17% for men and 35% for women rheumatologists under age 40. By 2030, women are projected to comprise 59% of the workforce. Millennials (born 1982-2004) comprise 6% of the current workforce and 50-75% of the 2030 workforce. Since 2005, there has been a reported 5% decrease per week in patient load for millennials which had a synergist effect when added to gender-generational modeling. 18% of current fellows reported planning part-time employment, 90% of whom were women. The declining clinical FTE relates to rising women/male ratio, millennials, and part-time workers.

Conclusion: The rheumatology workforce will be primarily millennial women by 2030, with the shift from a majority of men to women projected to occur between 2018 and 2020. Since women comprise the majority of part-time workers, and conduct fewer patient annual visits, this has significant implications for rheumatology supply. The millennial generation brings a higher percentage of women into the rheumatology workforce and greater emphasis on work-life balance for both sexes resulting in a predicted reduction in patient visits, clinical FTEs per rheumatologist and overall working hours. Whether millennials will continue working fewer hours throughout their careers is unknown. Women, the majority of our future workforce, are more likely to work part-time. Millennials, both men and women, see a lower patient volume at a time when demand for rheumatology FTEs will increase. The next decades bring challenges for rheumatology requiring innovative approaches to provide access to care for patients.



Disclosure: C. Deal, None; **M. B. Bolster**, None; **J. S. Hausmann**, None; **D. Battafarano**, None; **S. Monrad**, None; **M. Ditmyer**, None.

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Abstract Number: 90

Impacts of Anti-TNF Treatment on Improvement in Work Place and Household Productivity in Patients with Psoriatic Arthritis

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Background/Purpose: Psoriatic arthritis (PsA) is a unique inflammatory arthritis that affects the skin, nails, and the joints. Most of the patients consider PsA to have a significant effect on their quality of life, which significantly impairs work productivity and daily activities. The aim of this study was to determine the long-term effects of anti-TNF agents on work productivity measures in patients with PsA.

Methods: Male or female patients with confirmed diagnosis of PsA and initiated an anti-TNF treatment were enrolled and followed-up for 9 months in this multi center, prospective, observational post marketing study. Patients evaluated workplace and household productivity by completing Work Productivity and Activity Impairment (WPAI) questionnaire and assessed global assessment of disease activity, pain, and fatigue using a visual analogue scale (VAS) at baseline and every 3 months until 9th month visit. Disease Activity Score 28 (DAS-28) was evaluated by the physicians at each visit according to the American College of Rheumatology Response Criteria for rheumatoid arthritis. Patients enrolled between January 2014 and April 2016 were included in this initial statistical analysis.

Results: A total of 120 patients were included in this study and 55.0% of the patients were female. Mean (±SD) age was 41.5 (±11.1) years and mean time since diagnosis of PsA was 6.7 (±6.5) years. Mean duration of anti-TNF treatment was 8.9 (±2.2) months. Significant improvements were observed in the number of swollen and tender joints, as well as score of enthesitis and dactylitis at the end of the study comparing to baseline ($p<0.001$). At each visit an improvement in DAS-28 scores was observed when compared to the previous visit ($p<0.001$). Throughout the study, all patient reported VAS scores (global assessment of disease activity, nocturnal back pain and fatigue, total back pain, global assessment of pain and fatigue) reduced significantly ($p<0.001$). Mean number of missing working days was significantly reduced (5.3 vs. 1.3 days; $p<0.001$), however the numerical increase in mean number of working hours was not statistically significant when compared to baseline (39.5 vs. 45.6 hours; $p=0.126$). Patients experienced an improvement in work productivity on the basis of missed hours during the last 7 days due to health problems ($p<0.001$). Patient reported WPAI scores revealed that during anti-TNF treatment, health related problems that effect productivity were significantly reduced ($p<0.001$).

Conclusion: Patients with PsA experienced a significant improvement in their clinical evaluations and work productivity during long-term anti-TNF treatment.

Table 1. Mean results at each visit and statistical significance

	N	Mean	p
Mean number of missing working days (per month)			
Baseline	106	5.3	
3rd month visit	87	2.9	**<0.001**
6th month visit	81	1.7	
9th month visit	73	1.3	
Mean number of working days (per week)			
Baseline	106	6.1	
3rd month visit	87	6.0	0.194
6th month visit	83	6.0	
9th month visit	75	5.5	
Mean DAS 28 Score			
Baseline	118	5.36	
3rd month visit	100	3.51	**<0.001**
6th month visit	93	3.07	
9th month visit	89	2.69	
Mean VAS scores			
Global assessment of disease activity by patients			
Baseline	120	6.63	
3rd month visit	102	3.90	**<0.001**
6th month visit	92	3.05	
9th month visit	86	2.97	
Global assessment of disease activity by physicians			
Baseline	120	6.35	
3rd month visit	102	3.46	**<0.001**
6th month visit	92	2.64	
9th month visit	87	2.32	
Global assessment of nocturnal back pain and fatigue			
Baseline	120	5.50	
3rd month visit	102	3.08	**<0.001**
6th month visit	92	2.59	
9th month visit	87	2.13	
Global assessment of total back pain			
Baseline	120	5.20	
3rd month visit	102	3.29	**<0.001**
6th month visit	92	2.51	
9th month visit	87	2.29	
Global assessment of pain and fatigue			
Baseline	120	6.28	
3rd month visit	102	4.30	**<0.001**
6th month visit	92	2.91	
9th month visit	87	2.76	

Disclosure: O. Karadag, Pfizer Inc, 2,Abbvie, 2,Abbvie, 5,BMS, 5,MSD, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5,Sanofi-Aventis Pharmaceutical, 5; **E. Dalkilic**, Abbvie, 8,MSD, 8,Roche Pharmaceuticals, 8,UCB, 8,Pfizer Inc, 8; **A. M. Onat**, BMS, 8,MSD, 8,Pfizer Inc, 8,UCB, 8,Roche Pharmaceuticals, 8; **O. Kucuksahin**, UCB, 8,Pfizer Inc, 8,Abbvie, 8,MSD, 8,Roche Pharmaceuticals, 8; **T. Kasifoglu**, Abbvie, 8,BMS, 8,Roche Pharmaceuticals, 8,MSD, 8,Actelion Pharmaceuticals US, 8; **B. Kisacik**, MSD, 8,BMS, 8,Pfizer Inc, 8,Abbvie, 8; **O. N. Pamuk**, UCB, 8,Abbvie, 8,Roche, 8,BMS, 8,MSD, 8; **N. Yilmaz**, None; **S. S. Koca**, None; **V. Yazisiz**, Pfizer Inc, 8,MSD, 8; **P. Talu Ocakci**, None; **M. Sayarlioglu**, Pfizer Inc, 8,Abbvie, 8,MSD, 8,BMS, 8,UCB, 8,Celtrion, 8; **E. Terzioglu**, Abbvie, 5,Pfizer Inc, 5,MSD, 5,UCB, 5,BMS, 5,Abdi İbrahim İlaç, 5; **S. Erten**, Pfizer Inc, 8,Novartis Pharmaceutical Corporation, 8; **M. F. Oksuz**, None; **U. Kalyoncu**, None.

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Abstract Number: 91

A Systematic Review of Smartphone Applications for Measuring and

Recording Rheumatoid Arthritis Disease Activity

Rebecca Grainger[1,2], Hermaleigh Townsley[3], Bonnie White[4], Tobias Langlotz[5] and William Taylor[1,6], [1]University of Otago Wellington, Wellington, New Zealand, [2]Wellington Regional Rheumatology Unit, Hutt Valley District Health Board, Lower Hutt, New Zealand, [3]Department of Medicine, University of Otago Wellington, Wellington, New Zealand, [4]Department of Medicine, University of Otago Wellington, Wellington South, New Zealand, [5]Department of Information Science, University of Otago, Dunedin, New Zealand, [6]Wellington Regional Rheumatology Unit, Hutt Valley District Health Board, Wellington, New Zealand

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Background/Purpose: It is recommended that management of rheumatoid arthritis (RA) requires regular quantitative assessment of RA activity. Treat to target management could be facilitated by use of smartphone applications ("apps") for input, storage, and transmission of validated RA disease activity measures. These data could be used by rheumatologists in clinical practice or by people with RA. However, potential users of apps must have confidence in app quality. This review assesses the functionality and quality of apps for RA disease activity monitoring by: 1) systematically identifying apps for monitoring of RA; 2) summarizing and comparing features to RA disease activity monitoring guidelines; and 3) rating app quality according to the recently developed Mobile App Rating Scale (MARS)[1].

Methods: A systematic search of the Google Play and iTunes stores was conducted to identify smartphone apps designed for measurement of RA disease activity by people with RA and rheumatologists. Apps were excluded if: 1) content was for information, education, or reference only; 2) for use by clinicians only: 3) only included treatment algorithms; or 4) were not in English. Android and iOS Apps were downloaded to smartphones and features/functionality described then apps rated by two independent reviewers using the MARS. App features were compared with EULAR and ACR recommendations for monitoring of RA disease activity.

Results: The search identified 721 apps in the Google Play store and 216 in iTunes store, of which 19 unique apps met criteria for inclusion (16 Google play, 11 iTunes store, 8 both). Fourteen apps included at least one validated instrument for measurement of RA disease activity. Eleven apps allowed users to enter a joint count (homunculus n=4, number of joints n=7). Eight of these apps used the standard 28 swollen and tender joint count and functioned as composite disease activity (CDA) calculators, with no capacity to store data. Eight apps included at least one ACR/EULAR recommended RA CDA measure but only one provided the formula for calculation. Ten apps included data recording, storage, and retrieval. Only one app, Arthritis Power, included both a RA CDA measure and tracked data but this app did not include the standard 28 joint count. The median MARS score for apps was 3.41 (maximum 5). Of the five apps which scored >4/5 on the MARS rating, only one included a CDA score endorsed by ACR/EULAR but this app did not have a data tracking function.

Conclusion: No current apps for RA have functionality for entry of validated disease activity instruments, composite disease activity measures including 28 joint counts, and allow tracking of these data. Current apps are configured as calculators for rheumatologists or tracking tools for people with RA. The latter do not uniformly collect data using validated instruments. Apps which were higher quality according to the MARS collected only patient reported outcomes. Collaboration between rheumatologists, people with RA, app developers and health systems is required to develop appropriate, high quality apps for use by rheumatologists and people with RA in co-management of RA. 1. Stoyanov et al. JMIR Mhealth Uhealth. 2015;3(1):e27–9.

Disclosure: R. Grainger, None; **H. Townsley**, None; **B. White**, None; **T. Langlotz**, None; **W. Taylor**, None.

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Abstract Number: 92

Is Patient Support Program (PSP) Participation Associated with Longer Persistence and Greater Adherence Among New Users of Adalimumab?

Einav Srulovici[1,2], Vishvas Garg[3], Adi Ghilai[2], Becca Feldman[2], Moshe Hoshen[2], Ran Balicer[2], Martha Skup[4] and Maya Leventer-Roberts[2], [1]School of Nursing, University of Haifa, Haifa, Israel, [2]Clalit Research Institute, Clalit Health Services, Tel Aviv, Israel, [3]AbbVie Inc, North Chicago, IL, [4]AbbVie Inc., North Chicago, IL

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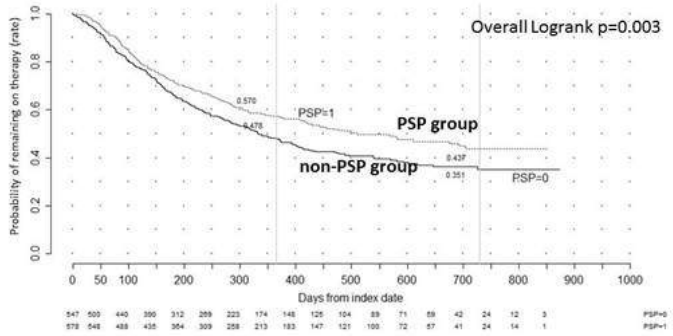
Background/Purpose: In Israel, patients treated with adalimumab (ADA) can enroll in a patient support program (PSP) provided by AbbVie, which includes a home visit by a registered nurse, telephone calls, and outreach by mail. Clalit Health Services (CHS), a payer/provider system with over four million members, maintains a complete electronic medical record database, which can be used to track the effect of PSP on outcomes. The objective of this study was to examine whether PSP participation is associated with a longer persistence and/or a greater adherence to ADA.

Methods: This is a retrospective cohort study of new ADA users, comparing PSP enrollees (PSP group) vs. those that did not enroll (non-PSP group) using patient-level data from the CHS database. The index date was defined as the date of the patients' first purchase of ADA occurring between 01/08/2012 and 31/12/2014. Demographic and clinical characteristics were compared between groups at baseline. Persistence was assessed using survival analyses of time until discontinuation, defined as the date of the last purchase or prescription preceding a 90-day gap without a purchase. Adherence (medication possession ratio) among patients persistent on ADA was compared between PSP and non-PSP groups using the *Mann-Whitney U test* during the 0-6 months, 0-12 months, and 12-24 months following the index. Subgroup analyses were conducted by clinical indications (rheumatoid disease (RD), inflammatory bowel disease (IBD), and dermatologic disease).

Results: There were 755 patients in the PSP group and 765 in the non-PSP group who met the inclusion criterion. Baseline characteristics were similar between cohorts. Among those with at least 6 months of follow-up post-index date, the PSP group had significantly longer mean persistence as compared to non-PSP group (319 vs. 298 days, respectively; p=0.003). Subgroup analyses yielded similar findings for the clinical indications of RD (p=0.015) and IBD (p=0.031). Further, at 12 and 24 months, the PSP group was more likely to be persistent on medication as compared to the non-PSP group: 57.0% vs. 47.8% (p=0.002) and 43.7% vs. 35.1% (p=0.003), respectively (**Figure**). The mean adherence rates among those with varying lengths of persistence were all greater than 80%. The 6-month adherence rate among those with at least 6 months persistence was significantly greater for the PSP group compared to the non-PSP group (p=0.024). Subgroup analyses yielded similar finding in the clinical indication of RD (p=0.046)**.**

Figure. Survival Analysis of Time to Discontinuation in the PSP vs. Non-PSP groups



Conclusion: A patient support program provided by Abbvie was associated with a longer persistence among new users of ADA. It was also associated with a higher adherence rate within the first 6 months.

Disclosure: E. Srulovici, None; **V. Garg**, AbbVie Inc, 1; **A. Ghilai**, None; **B. Feldman**, None; **M. Hoshen**, None; **R. Balicer**, None; **M. Skup**, AbbVie, 3,AbbVie, 1; **M. Leventer-Roberts**, None.

Abstract Number: 93

2015 ACR/ARHP Workforce Study in the United States: Adult Rheumatologist Supply and Demand Projections for 2015-2030

Daniel Battafarano[1], Seetha Monrad[2], John Fitzgerald[3], Marcy Bolster[4], Chad Deal[5,6], Anne R. Bass[7], Rodolfo Molina[8], Alan R. Erickson[9], Benjamin J Smith[10], Karla B. Jones[11], Jonathan S. Hausmann[12], Val Gokenbach[13], Kamilah Lewis[14] and Marcia Ditmyer[15], [1]Medicine, San Antonio Military Medical Center, San Antonio, TX, [2]Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [3]Medicine, UCLA, Los Angeles, CT, [4]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [5]Orthopedic and Rheumatology Institute, Cleveland Clinic Foundation, Cleaveland, OH, [6]Dept of Rheum & Imm Dis /A 50, Cleveland Clinic Foundation, Cleveland, OH, [7]Rheumatology, Hospital for Special Surgery, New York, NY, [8]Arthritis Associates PA, San Antonio, TX, [9]Omaha VA Medical Center and University of Nebraska Medical Center, Omaha, NE, [10]Rheumatology, McIntosh Clinic, P.C., Thomasville, GA, [11]Rheumatology, Nationwide Children's, Columbus, OH, [12]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA, [13]Academy for Academic Leadership, Detroit, MI, [14]American College of Rheumatology, Atlanta, GA, [15]Academy for Academic Research, Las Vegas, NV
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Background/Purpose: The 2015 ACR Workforce study updated the current and projected adult rheumatology workforce for the next 15 years.

Methods: The 2015 ACR/ARHP Workforce Study was completed using several primary and secondary data sources, including, ACR member database, state licensure registries, 2005 ACR workforce study, professional organizations, and other medical literature. These data were supplemented with a web-based survey about work settings, practice patterns, retirement planning, and demographics. Utilizing an integrated workforce modeling methodology, supply and demand projections were computed for adult rheumatologists from 2015-2030. The factors affecting supply included the current adult rheumatology workforce, demographic changes, the number completing fellowships, retirement trends, patient workload and practice settings. Multivariate regression modeling was used to determine significant factors affecting demand. These included healthcare utilization, provider practice trends, disease prevalence, population demographics, per capita income and access to care trends. Clinical FTE was defined as 1.0 FTE for private practice and 0.5 FTE for academic practice. It was assumed that 80% of the adult rheumatology workforce was in private practice vs. 20% in academic practice.

Results: The 2015 ACR current adult workforce is estimated to be 5,595 providers (4,497 Clinical FTE). A comparison of the actual vs. clinical FTE projections from 2015 through 2030 are presented in Figure 1. The estimated excess demand for 2015 is 1,118 (6,115 demand-4,997 supply) which equates to an excess demand of approximately 36%. By 2030, the Clinical FTE is projected to be 3,455, a 31% decrease from 2015. A projected demand of 8,184 translates into an excess demand of 4,729 (138% increase) from 2015. Projected trends are similar to those from the 2005 workforce study (Figure 2). These trends are likely due to increase in aging population/retirements, coupled with the decrease in clinical FTE relative to increases in number of females, part-time workers, and millennials.

Conclusion: The rheumatology workforce projections reflect a significant shift in the mix of the future workforce by 2030. Over the next 15 years, baby boomer retirements, a millennial predominance, and a female gender shift, will parallel an increased demand in adult rheumatology care. Regional and innovative strategies will be necessary to manage access to care and reduce barriers to care for rheumatology patients.

Figure 1. Comparison Total Numbers vs. Clinical FTE for Adult Rheumatologists

Figure 2. Comparison of Projected Supply and Demand of Adult Rheumatology Workforce

Disclosure: D. Battafarano, None; **S. Monrad**, None; **J. Fitzgerald**, None; **M. Bolster**, Johnson and Johnson, 1,Eli Lilly and Company, 2,RRF Amgen Fellowship Award, 9; **C. Deal**, None; **A. R. Bass**, None; **R. Molina**, None; **A. R. Erickson**, Amgen, 2; **B. J. Smith**, American Board of Internal Medicine, 9; **K. B. Jones**, None; **J. S. Hausmann**, None; **V. Gokenbach**, None; **K. Lewis**, None; **M. Ditmyer**, None.

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Abstract Number: 94

Performance of the Patient Reported Outcomes Measurement Information System (PROMIS) Measure for Physical Function in Early RA

Till Uhlig, Inge C Olsen, Anna-Birgitte Aga, Siri Lillegraven, Tore K Kvien and Espen A. Haavardsholm, Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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Background/Purpose: The Patient Reported Outcomes Measurement Information System (PROMIS) initiative has developed and calibrated item banks for the assessment of physical function and other domains chronic diseases. Our objective was to assess the construct validity of PROMIS 20 items for physical function (PROMIS PF-20) in patients with early rheumatoid arthritis (RA).

Methods: RA patients who fulfilled the ACR/EULAR 2010 classification criteria, with <2 years from first patient reported swollen joint and who were DMARD naïve with indication for DMARD treatment were included in the tight control treat-to-target ARCTIC trial. The 230 patients were at baseline assessed with PROMIS PF-20 which had been translated to Norwegian according to recommended procedures. Other assessments were disease activity score based on 44 joints (DAS), patient global assessment of disease activity, investigator global assessment, pain and fatigue on 100 mm visual analogue scales, and health related quality of life (SF-36) with physical (SF-36 PCS) and mental (SF-36 MCS) component summaries. Patients were grouped according to DAS as low (<2.4), moderate (>2.4 and <3.7), and high (>3.7) disease activity. Pearson's correlation coefficient is used to assess correlations, and Analysis of Variance (ANOVA) to assess difference between DAS groups.

Results: The mean (SD) age for the 230 patients in ARCTIC was 51.4 (13.7) years, disease duration 7.1 (5.4) months, DAS 3.5 (2.0), 61.0% were females and 82.2% anti-CCP positive. Correlations between PROMIS PF-20 and many other outcomes were mainly moderate to high (patient global -0.68, pain -0.66, SF-physical functioning scale 0.83, and SF-36 PCS 0.82), but associations were lower for investigator global -0.44, fatigue -0.38, and SF-36 MCS 0.23 (all p<0.001). The table shows how higher DAS levels discriminate PROMIS PF-20 and other outcomes. **Table**: Scores according to disease activity groups (Means and SD)

	Low DAS N=43	Moderate DAS N=102	High DAS N=85	P-value (ANOVA)
PROMIS PF-20	46.0 (9.1)	40.4 (7.4)	34.0 (6.7)	<0.001
Patient global (VAS)	30.8 (21.1)	45.2 (21.2)	64.8 (20.4)	<0.001
Pain (VAS)	30.4 (21.9)	44.7 (21.2)	60.4 (21.6)	<0.001
Fatigue (VAS)	30.7 (28.1)	38.9 (26.4)	47.2 (30.2)	0.006
SF36 PCS (0-100)	43.5 (9.6)	37.7 (8.0)	31.0 (8.1)	<0.001
SF36 MCS (0-100)	49.7 (10.6)	49.9 (10.1)	47.9 (11.0)	0.39
Investigator global (VAS)	20.6 (11.7)	34.2 (14.2)	58.3 (16.5)	<0.001

Conclusion: Evaluation of physical function applying the PROMIS PF-20 was feasible, and our results support construct validity of the instrument.

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Abstract Number: 95

An Analysis of Malpractice Litigation in Rheumatology

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Background/Purpose: Medicine is an increasingly more litigious environment, and the probability of a practitioner facing a medical malpractice claim is high. Given the tumultuous liability insurance climate, and a shift in the public attention towards curbing the practice of defensive medicine, an understanding of medical malpractice claims is prudent. To the authors' best knowledge, no studies have provided an analysis of malpractice litigation in the subspecialty of rheumatology. This study delineates the medico-legal factors that compel plaintiffs to file medical malpractice claims related to the management of rheumatic diseases.

Methods: The online legal database, WestLaw, was searched to delineate all medical malpractice cases related to rheumatology across a 31-year period from 1985-2015. All state and federal jury verdicts and settlements relevant to the search criteria were considered.

Results: A total of 30 rheumatic disease malpractice cases were evaluated in this 31-year period. Ten cases were excluded from the analysis due to duplicity or lack of relevance to rheumatology. The average age of the patient was 51.9 years, and 45 percent were female. The cases were distributed across 10 states. The jury found in favor of the plaintiff in 20 percent of cases with a mean payout of $2,776,364, and in favor of the defendant in 60 percent of the cases. A failure to diagnose and/or a failure to treat in a timely manner were the two most commonly alleged causes of malpractice. Settlements were reached in 15 percent of the cases with most payouts undisclosed. Rheumatologists accounted for 33.3 percent of all named defendants.

Conclusion: In the case of rheumatic disease, a majority of the verdicts were in favor of the defendant, and settlements were reached in the minority of cases. When the verdict favored the plaintiff, mean payouts were substantial at over $2 million. Rheumatologists accounted for a small percentage of all co-defendants.

Disclosure: A. Prabhu, None; **R. Gupta**, None; **R. Thomas**, None; **C. V. Oddis**, None.

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Abstract Number: 96

Transforming Healthcare in Rheumatology: From Inpatient to Outpatient Care without Reductions in Healthcare Quality

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Background/Purpose: The implementation of a major program to improve the quality of care in inflammatory arthritides (rheumatoid arthritis-RA, spondyloarthritis- SpA and psoriatic arthritis- PsA) included the increased use of biologics and shifting clinically appropriate cases from inpatient to outpatient care, in response to patient preferences. These changes led to a significant improvement in patient outcomes, reductions in the number of inpatient days of care, and increases in the use of outpatient care. This is the first study to examine the reimbursement and patient outcome implications of this quality improvement program, which is similar to other programs being implemented across Norway and internationally. The aim of this study is to examine quantitatively the changes in reimbursements and patient outcomes associated with this programmatic change in inflammatory arthritides.

Methods: This prospective observational study was performed at the Department of Rheumatology, Hospital for Rheumatic Diseases in Haugesund, Norway. Before May 2016 the Department of Rheumatology required 22 inpatient beds. After 1 May 2015 the quality improvement program was implemented, including a major switch from inpatient to outpatient healthcare, and the number of beds required was reduced to 6. The Diagnosis related group (DRG) system was used to measure the clinical production of the department for the period from May 1 to December 31, 2015 and compare it

to the same period in 2014. One DRG point is reimbursed at 21 000 Norwegian Krones (US$2520). The mean Modified Health Assessment Questionnaire (MHAQ) for patients with RA and PsA and mean BASFI (Bath Ankylosing Spondylitis Functional Index) for SpA were used as outcome measures indicating the quality of care provided.

Results: From May 1 to December 31 2014, 981 admissions were recorded, while during the same period in 2015 the number was reduced to 534. The production of the inpatient unit from May 1 to December 31, 2014 was 871 DRG points while during the same period in 2015 production was reduced to 623 DRG points. The number of outpatient clinic consultations increased from 4 397 in during the same period of 2014 to 5 588 in during the comparable period in 2015 and the number of DRG points increased from 539 to 654, respectively. The mean MHAQ (RA and PsA) and mean BASFI (SpA) at the end of December 2015 were 0.47 and 3, respectively, while in December 2014 the comparable measures were 0.47 and 3, respectively (p=1 and p=0.9). In total 2 800 000 NOK (335 000 USD) was saved during the study period compared to 2014.

Conclusion: Switching from inpatient to outpatient care for patients with inflammatory arthritides leads to lower costs and reduced number of medical errors without any reductions in quality of health care provided. These encouraging results should be further confirmed in larger studies.

Disclosure: A. P. Diamantopoulos, None; **T. T. Brown**, None.

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Abstract Number: 97

Effects of DMARD Tapering on Treatment Costs and Work Productivity in Rheumatoid Arthritis Patients- an Analysis from the Prospective Randomized Controlled Retro- Study

Melanie Hagen[1], Camille P Figueiredo[2], Jayme Fogagnolo Cobra[3], Judith Haschka[4], Michaela Reiser[5], Matthias Englbrecht[6], Axel J. Hueber[7], Bernhard Manger[6], Arnd Kleyer[8], Stephanie Finzel[9], Hans-Peter Tony[10], Stefan Kleinert[11], Joerg Wendler[12], Florian Schuch[12], Monika Ronneberger[12], Martin Feuchtenberger[13], Martin Fleck[14], Karin Manger[15], Wolfgang Ochs[16], Matthias Schmitt-Haendle[17], H.-M. Lorenz[18], HG Nüßlein[19], R Alten[20], Joerg C. Henes[21], Klaus Krüger[22], Georg Schett[7] and Juergen Rech[7], [1]Internal Medicine 3 – Rheumatology and Immunology, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany, [2]Rheumatology Division, Faculdade de Medicina da USP, São Paulo, Brazil, [3]Instituto de Reumatologia de Sao Paolo, Sao Paolo, Brazil, [4]Medical Department II, St. Vincent Hospital, the VINFORCE Study Group, Academic Teaching Hospital of Medical University of Vienna, Vienna, Austria, Vienna, Austria, [5]Department of Internal Medicine 3, University of Erlangen-Nuremberg, Erlangen, Germany, [6]Department of Internal Medicine 3, Rheumatology & Clinical Immunology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [7]Department of Internal Medicine 3 – Rheumatology and Immunology, Universitätsklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [8]Department of Internal Medicine 3, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [9]Rheumatology and Clinical Immunology, University Medical Center Freiburg, Freiburg, Freiburg, Germany, [10]Rheumatology/Immunology, Medical Clinic II, University Clinic Wuerzburg, Würzburg, Germany, [11]Rheumatologische Schwerpunktpraxis Erlangen, Erlangen, Germany, [12]Schwerpunktpraxis Rheumatologie, Erlangen, Germany, [13]Rheumatologie/Klinische Immunologie, Kreiskliniken Altötting-Burghausen, Burghausen, Germany, [14]Department of Internal Medicine I, University of Regensburg, 93042 Regensburg, Germany, [15]Rheumatology Practice Bamberg, Bamberg, Germany, [16]Internistisch-rheumatologische Praxisgemeinschaft Bayreuth, Bayreuth, Germany, [17]Rheumatology Practice, Bayreuth, Germany, Bayreuth, Germany, [18]Im Neuenheimer Feld 41, UNI-Klinikum Heidelberg, Medizinische Klinik,, Heidelberg, Germany, [19]University of Erlangen, Nürnberg, Germany, [20]Rheumazentrum Ruhrgebiet, Herne, Germany, [21]Department of Internal Medicine II, Division of Rheumatology, University Hospital Tuebingen, Tuebingen, Germany, [22]Praxiszentrum St. Bonifatius, München, Germany

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Effects of DMARD Tapering on Treatment Costs and Work Productivity in Rheumatoid Arthritis Patients- an Analysis from the Prospective Randomized Controlled RETRO- Study

Background/Purpose:

Achieving remission is the most important treatment goal in patients with rheumatoid arthritis (RA). With the development and wider use of highly effective disease modifying anti-rheumatic drugs (DMARD) about half of RA patients reach a state of disease remission, raising the question about tapering or stopping anti-rheumatic treatment. The aim of this study was to assess the effect of a controlled DMARD tapering regimen on treatment costs and work productivity in RA patients in remission.

Methods:

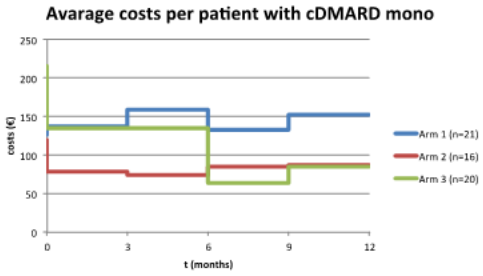
101 RA patients in sustained remission (DAS28 <2.6 for more than 6 months), enrolled in the multicenter randomized controlled RETRO Study, were analyzed (1). Patients either continued DMARDs (arm1), tapered dose by 50% (arm 2) or entire stopped DMARDs after tapering (arm 3) for one year. Assessment of DMARD costs and work productivity was done every three months in all 101 patients including those remaining in remission and those relapsing a re-starting their original DMARD regimen.

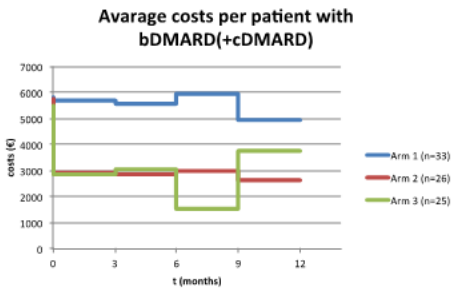
Results:

RA patients treated with conventional DMARDs, baseline quarterly treatment costs of 154€ remained stable in arm 1 (156€), while decreasing to 81€ in arm 2 and 75€ in arm 3. In patients treated with biologic DMARDs quarterly treatment costs were 5,708€ at baseline. They remained stable in arm1 (5,533€) and decreased to 3,036€ in arm 2 and 2,668€ in arm 3. Overall DMARD costs were reduced by 327,292€ within one year, while outcome was very good with patients either remaining in remission or immediately regaining remission when exposed to original DMARD regimen after relapse.

Conclusion:

Controlled tapering of DMARD treatment leads to effective reduction of treatment costs in RA patients in sustained remission.





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Abstract Number: 98

Daily Symptom Reports in a Smartphone-Based Study 'Cloudy with a Chance of Pain': Patterns of Attrition over the First Six Months

Katie Druce[1], Sabine N van der Veer[2], Mohammed A Chowdhury[1], John McBeth[3], Jamie C Sergeant[1], Rikesh Patel[3] and **William G Dixon**[4], [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Health e-Research Centre, University of Manchester, Manchester, United Kingdom, [3]Manchester Academic Health Science Centre, Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, Great Britain

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Background/Purpose: The increasing uptake of smartphones and health apps provides opportunities for epidemiological studies to collect regular information from large numbers of people. This offers temporally-rich self-reported data as well as access to novel data such as geolocation. However, the extent to which participants will join and remain engaged with such studies over time is not clear. It is also unclear whether certain subgroups will remain more engaged than others, introducing possible selection bias. *Cloudy with a Chance of Pain* is a UK smartphone-based study investigating the link between the weather and pain in people with chronic pain. This study aimed to examine patterns of engagement and factors associated with it over the first six months.

Methods: Eligible participants in this study were recruited between 01/20/2016 and 02/29/2016. Follow-up data were available until 06/14/2016. After completing baseline characteristics, participants received daily prompts to complete a motif of 10 symptoms including pain, fatigue, and mood. Participants were categorised as 'active' if they reported data within the last 28 days of follow-up (05/17/2016-06/14/2016); we determined their rates of data completion prior to this period. Participants without data in the last 28 days were considered 'inactive'. The proportion of motifs completed was defined as the number of days with complete motifs divided by the number of possible complete motifs since recruitment. We examined differences between active and inactive participants, and between active users with high (≥80% motifs completed) and low (<80% motifs completed) engagement.

Results: We included 7124 participants reporting at least one symptom; 1459 (20%) were considered 'active'. Active participants were older (median (IQR): 54(45-62) vs 48 (40-58), p<0.001) and more likely to be female (83.4% vs 79.2%, p<0.001) compared to those inactive. Of the self-reported conditions, only headache and non-specific arthritis differed between active and inactive participants. Active participants completed 67% of possible motifs during the study period, compared to inactive participants who completed 8.7%. Of active users, 49% had high engagement throughout follow-up. Those with low engagement completed 43.2% of possible entries; only age was found to significantly differ between these groups (Table). Of the inactive participants, 1038 completed only one motif.

Conclusion: Following high initial recruitment, 20% of participants remained active after more than four months of data collection, half of whom provided data on more than 80% of eligible days. Engagement rates were higher in older participants. Although selection bias due to attrition needs to be considered when analysing results, these results suggest that our method is a viable and sustainable alternative to more traditional data collection.

	All participants (n=7124)		Of active users (n=1459):	
	Active (n=1459)	Inactive (n=5665)	High engagement (≥80% total motifs) (n=711)	Low engagement (<80% total motifs) (n=748)
Age , median (IQR)	54 (45-62)	48 (40-58)**	56 (46-63)	53 (44-61)**
Sex, n (%)	1154 (83.4)	4157 (79.2)**	559 (83.3)	595 (83.6)
Proportion of participants with condition, n (%)				
Rheumatoid Arthritis, n (%)	291 (21.0)	992 (18.9)	145 (21.6)	146 (20.5)
Spondyloarthopathy, n (%)	131 (9.5)	468 (8.9)	65 (9.7)	66 (9.3)
Crystal Arthritis, n (%)	46 (3.3)	197 (3.7)	24 (3.6)	22 (3.1)
Non Specified Arthritis, n (%)	604 (43.7)	2063 (39.3)**	284 (42.3)	320 (44.9)
Fibromyalgia, n (%)	306 (22.1)	1263 (24.1)	140 (20.9)	166 (23.3)
Chronic Headache, n (%)	81 (5.9)	394 (7.5)**	36 (5.4)	45 (6.3)
Neuropathic Pain, n (%)	173 (12.5)	680 (13.0)	81 (12.1)	92 (12.9)
Completeness of data				
Median days in study (IQR)	141 (137-144)	141 (137-141)	141 (138-145)	141 (136-143)
Total no possible entries in group	160743	623416	78828	81915
Total no complete motifs in group	107726	54080	72327	35399
Proportion of possible motifs completed	67.0	8.7	91.7	43.2

Disclosure: K. Druce, None; **S. N. van der Veer**, None; **M. A. Chowdhury**, None; **J. McBeth**, None; **J. C. Sergeant**, None; **R. Patel**, None; **W. G. Dixon**, None.

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Abstract Number: 99

Academic and Non-Academic Rheumatology: Practice Trends and Common Barriers to Practice from the 2015 ACR/ARHP Workforce Study Survey

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Background/Purpose: Ten years have elapsed since the last ACR workforce study (WFS), and it is anticipated that rheumatologists will face many challenges to train and sustain a workforce of rheumatology specialists that will meet future needs. Analyzing the current workplace and identifying barriers to practice may help identify strategies and solutions.

Methods: As part of the WFS, a web-based survey was administered to the ACR membership, targeting clinically active practitioners. Survey responses were analyzed to compare demographics, practice patterns, retirement planning, and barriers to practice between rheumatologists working in academic work settings vs. those in non-academic work settings. Qualitative data was gathered regarding barriers to practice and assessed to identify common themes.

Results: There were a total of 1996 completed survey responses (31.5% response rate: 1996/6342) 1,578 of which provided information about practice setting and were included in the analysis; not every respondent answered every question. 54.5% (n=868) of respondents self-reported their primary work setting as non-academic (including solo practice, single- and multi-specialty, and government) vs. 45.5% (n=726) who reported working in academic settings. Demographics are listed in Table 1. Non-academics reported working slightly fewer hours per week than academics, but spent 50% more time seeing patients, and saw more than twice as many patients each week. Weak correlations were found in average reported work hours per week and patient workload ($r=0.227$; $p<0.01$) between academics and non-academics. 40% (n=348) of non-academic practitioners anticipate retiring in the next 10 years, compared with 29% (n=212) in academic settings. Almost 60% (n=391) of non-academic practitioners plan to reduce their patient load in the next ten years by up to 50%, compared to 40% (n=262) of academicians.

Table 2 lists the top 10 barriers to practice reported by respondents. Insurance issues and electronic health records (EHR) were the top two (2) barriers to practice reported by both those working in non-academic and academic settings. Two common areas of dissatisfaction were reimbursement rates (n=476; 29.8%) and requirements for EHR (n=457; 28.6%).

Conclusion: Despite a number of differences between current practitioners in academic vs non academics, rheumatologists identify common and pervasive barriers to practice regardless of practice setting. Advocacy efforts focusing on reimbursement levels and EHR implementation/use should be a high priority to help support the existing and future workforce.

Table 1. Demographic Breakdown comparing Academic Settings vs. Non-Academic Settings [#]

Variable	Academics		Non-Academics		
Gender	**N**	**%**	**N**	**%**	
Male	271	49.2	414	57.0	
Female	274	49.7	304	41.9	
Age Group	**N**	**%**	**N**	**%**	
<35	53	9.5	50	6.9	
36-45	152	27.6	171	23.6	
46-55	108	19.6	162	22.3	
>56	238	43.2	343	47.2	
Specialty	**N**	**%**	**N**	**%**	
Adult	395	34.5	691	60.3	
Pediatric	212	91.8	8	3.4	
Full-time vs. Part-time	**N**	**%**	**N**	**%**	
Full-time	566	43.4	711	54.5	
Part-time	60	29.3	136	15.9	
Retirement Plans	**N**	**%**	**N**	**%**	
Next 5 years	101	13.9	170	19.6	
Next 10 years	111	15.3	178	20.5	
Reduction patient Load	**N**	**%**	**N**	**%**	
Yes	237	43.5	389	53.7	
50% or less	175	24.5	304	35.0	
Patient Load	**Mean**	**SEM**	**Mean**	**SEM**	**t-value**
	N=564		**N=763**		
Total average	32	0.2	68	0.2	16.1**
New Patient	7	0.2	10	0.3	7.4*
Follow-up	25	0.6	58	0.8	15.7**
Average Hours	**Mean**	**SEM**	**Mean**	**SEM**	**t-value**
	N=458		**N=706**		
Average Total Hours Worked Weekly	56.1	0.6	51.2	0.7	5.01**
Clinical setting	20.7	0.6	32.2	0.5	13.9**
Clinical hospital setting	4.5	0.2	3.1	0.2	4.3*
Patient Follow-up	4.6	0.2	4.2	0.1	1.7
Patient Records	6.5	0.3	7.4	0.3	2.5*
Reviewing Labs	3.4	0.2	3.9	0.3	2.8*
Other relating to work setting	16.4	0.6	0.4	0.2	12.8**

*p<0.01; **p<0.001

[#]Not every respondent answered every question

Table 2. Reported Barriers to Practice[1]

1.	Insurance issues (e.g., poor reimbursement, preauthorization, low contract rates, paperwork, etc.)
2.	Electronic Health Record implementation
3.	Lack of staff
4.	Incentives not aligned properly
5.	PQRS too bothersome
6.	Poor administrative support
7.	Lack of loan repayment options
8.	High cost medications for patients
9.	Difficult recruiting
10.	Lack of time with patients

[1]Ranked in order of importance, with 1 receiving the greatest number of responses

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Abstract Number: 100

Patient Support Program for Adalimumab-Treated Patients in Brazil: Impact on Patients' Adherence and Persistence

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Background/Purpose: The Brazilian public healthcare system covers treatment with adalimumab for rheumatoid arthritis, Crohn's disease, ankylosing spondylitis and psoriatic arthritis, in line with local guidelines. Patients treated with adalimumab in Brazil can opt-in to a Patient Support Program (PSP) offered by AbbVie, which includes elements such as nurse and telephone support. The impact of this program on patient outcomes in the Brazilian setting has not been studied previously. The objective of the study is to evaluate the relationship of PSP enrollment and treatment utilization outcomes (adherence and persistence) among patients who initiate adalimumab.

Methods: Longitudinal data on the utilization of AbbVieÕs PSP were linked with the Brazilian Health System claims database called DATASUS, which includes data on patients that initiated treatment with adalimumab between 2013 and 2015. Patients using adalimumab in DATASUS not matched with AbbVie PSP database were categorized as non-users (non-PSP). Adherence was calculated using proportion of days covered (PDC), defined as the number of months of treatment with adalimumab divided by the number of months of patient follow-up. Patients were considered adherent if they had a PDC ³ 80%[1]. Persistence was calculated as the interval between treatment initiation and treatment discontinuation (defined as a gap of 90 days since the last obtainment of adalimumab). Adherence and persistence were compared between the PSP and non-PSP cohorts using *t* tests.

Results were segmented for patients with at least 6, 12 and 24 months follow-up. **Results:** 21,690 patients were included in the analysis: 3,313 in the PSP cohort and 18,377 in the non-PSP cohort. Patient characteristics were similar between groups: 63% were female, with an average age of 47 years (± 14.6). The percentages of patients with a PDC ³ 80% in the PSP vs non-PSP cohorts were: 89.4% vs 79.6% ($p<0.05$) in 6 months, 84.3% vs 68.6% ($p<0.05$) in 12 months and 77.6% vs 59.8% ($p<0.05$) in 24 months. The average treatment persistence in the PSP vs non-PSP groups were: 5.87 vs 5.73 months ($p<0.05$), 11.65 vs 11.05 months ($p<0.05$) and 22.37 vs 20.30 months ($p<0.05$) in the 6, 12 and 24 month time periods, respectively. Subgroup analyses by clinical indication showed consistent findings, in favor of the PSP, as displayed in Table 1.

Table 1: Differences in proportion of days covered (PDC) between patient support program (PSP) users and non-users segmented by disease, according to ICD-10 codes

Proportion of patients with PDC≥80%	PSP user	PSP non-user	Difference	p-value
Rheumatoid arthritis (M05.0, M05.1, M05.2, M05.3, M05.8, M06.8 and M08.0)				
6 months	88.5%	76.8%	11.7%	<0.05
12 months	81.2%	65.5%	15.7%	<0.05
24 months	77.5%	57.5%	20.0%	<0.05
Ankylosing spondylitis (M45 and M46.8)				
6 months	88.8%	82.0%	6.8%	<0.05
12 months	85.5%	71.0%	14.5%	<0.05
24 months	78.7%	62.5%	16.2%	<0.05
Crohn's disease (K50.0, K50.1 and K50.8)				
6 months	89.6%	82.6%	7.0%	<0.05
12 months	86.2%	71.9%	14.3%	<0.05
24 months	72.2%	60.6%	11.6%	<0.05
Psoriatic arthritis (M07.0 and M07.3)				
6 months	91.9%	81.9%	10.0%	<0.05
12 months	88.0%	72.1%	15.9%	<0.05
24 months	82.5%	63.6%	18.9%	<0.05

Conclusion: Across the indications studied, adalimumab users participating in the AbbVieÕs free-to-patient PSP demonstrated improved adherence and persistence to treatment compared to patients not participating in the PSP.

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Abstract Number: 101

Rheumatology Care Utilization and Geographic Distance from Rheumatology Sites within the United States Veteran Affairs Health Care System

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Background/Purpose: Within the Veteran Affairs (VA) health care system, there are often large geographic distances between patients and rheumatology providers. The purpose of this study was to determine if Veterans with inflammatory arthritis (IA) living far from VA rheumatology sites utilize rheumatology providers and therapies less frequently than patients located close to rheumatology sites.

Methods: Veterans with IA were included if they had ≥2 international classification of diseases-9 (ICD9) codes for rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis, prior to the beginning of the study period (January 1, 2014 to December 31, 2014). Geocoding was used to calculate the geographic distance between the coordinates of Veteran's home and the nearest VA site with rheumatology services. Exposure to medications was determined by medication dispensation. Primary and secondary stop codes were used to identify rheumatology encounters, defined as face-to-face visits with a rheumatology provider. Data sources included the national Corporate Data Warehouse and the Managerial Cost and Accounting Pharmacy dispensing data.

Results: The study included 75,804 Veterans, with 61.2%, 28.4%, and 10.4% living <40 miles, 40-99 miles and ≥100 miles from the nearest rheumatology site, respectively. The mean age ranged from 66.4 - 66.6, and 89 - 91% were male (Table 1). Rheumatology encounter(s) occurred for 43.7%, 33.7%, and 24.3% of Veteran living <40 miles, 40-99 miles and ≥100 miles from a rheumatology site, respectively (Figure 1). Higher percentages of Veterans living within 40 miles of a VA rheumatology site were exposed to non-biologic DMARD(s), biologic DMARD(s), and corticosteroid(s), compared to Veterans living 40-99 miles or >100 miles from a VA rheumatology site (Figure 2).

Conclusion: Rheumatology encounters occurred for fewer Veterans with IA living farther from VA rheumatology sites than Veterans living closer to VA rheumatology sites. Exposure to biologic DMARDs, non-biologic DMARDs, and corticosteroids was also associated with closer geographic proximity to VA rheumatology sites.

Table 1. Demographics, rheumatology encounters, and exposure to therapies

	<40 miles		**40-99 miles**		**≥100 miles**	
	n = 46,395		**n = 21,536**		**n = 7,873**	
	No. (%) or ±SD	**95% CI**	**No. (%) or ±SD**	**95% CI**	**No. (%) or ±SD**	**95% CI**
Age, mean	66.4 ± 12.6		66.6 ± 11.7		66.4 ± 11.8	
Male	41,270 (89.0)		19,601(91.0)		7,183 (91.2)	
White Race	35,121 (75.7)		17,057 (79.2)		6,329 (80.4)	
Black Race	6,463 (13.9)		2,064 (9.6)		466 (5.9)	
Other Race†	1,123 (2.4)		372 (1.7)		267 (3.4)	
Unknown Race ‡	3,688 (7.9)		2,043 (9.5)		811 (10.3)	
# Veterans with ≥1 rheumatology encounter	20,742 (44.7)	44.3-45.2	7,365 (34.2)	33.6-34.8	1,953 (24.8)	23.9-25.8
# Veterans exposed to non-biologic DMARD(s)§	16,744 (36.1)	35.7-36.5	7,479 (34.7)	34.1-35.4	2,693 (34.2)	33.2-35.3
# Veterans exposed to biologic DMARD(s)§§	10,413 (22.4)	22.1-22.8	4,337 (20.1)	19.6-20.7	1,516 (19.3)	18.4-20.1
# Veterans exposed to corticosteroid(s)§§§	15,658 (33.7)	33.3-34.2	6,640 (30.8)	30.2-31.5	2,372 (30.1)	29.1-31.2

† Other Race includes American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Asian

‡ Unknown race includes declined to answer, unknown by patient, and missing data

§Non-biologic DMARDS included apremilast, auranofin, azathioprine, chloroquine, cyclophosphamide, cyclosporine, hydroxychloroquine, gold sodium thiomalate, leflunomide, methotrexate, minocycline, penicillamine, sulfasalazine, and tofacitinib

§§Biologic DMARDS included § Non-biologic DMARDS included adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, secukinumab, tocilizumab, and ustekinumab

§§§Corticosteroids included betamethasone, cortisone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, triamcinolone

Figure 1. Rheumatology encounter(s) and distance from closest VA rheumatology site

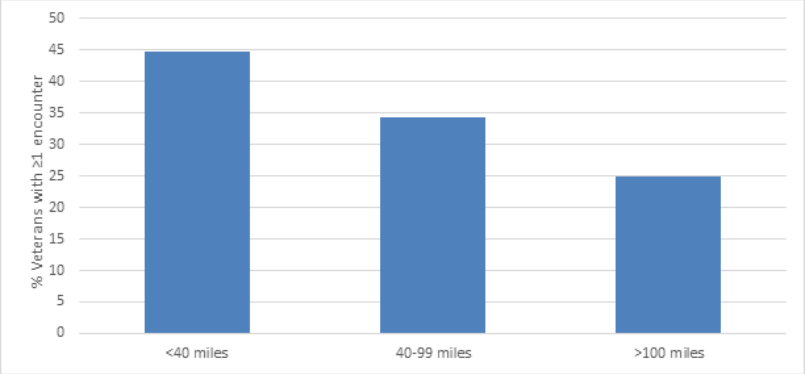
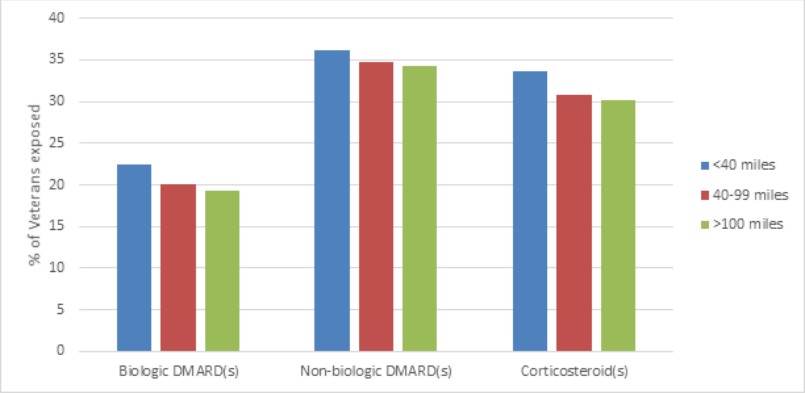


Figure 2. Exposure to therapy and distance from closest VA rheumatology site



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Abstract Number: 102

The 2015 American College of Rheumatology (ACR) Workforce Study: A Snapshot of Academic Division Directors

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Background/Purpose: The ACR has engaged in workforce studies as a mechanism to address ongoing and future needs of college members. In order to address needs over the next decade, the ACR developed and completed a workforce survey in 2015. The data included specific descriptive information about division directors (DD) who are critical to future training and research in rheumatology.

Methods: The ACR appointed a committee to develop a workforce survey in association with The Academy for Academic Leadership (AAL). The survey was completed on line by rheumatology professionals, fellows in training and patients with rheumatologic diseases. Secondary data included an environmental scan and comprehensive literature review. This abstract contains descriptive data obtained for rheumatology professionals who self-identified as division directors.

Results: There were 166 Division Directors who responded to the survey (61.5% (n=102) male, 37.3% (n=62) female and 1.2% (n=2) chose not to answer). The majority were adult rheumatologists (59.1%, n=94), 35.8% (n=57) were pediatric rheumatologists, 8 (5.1%) self-identified as Adult-Ped. A majority of respondents were between the ages of 46-65 (n=110; 69.1%), non-Hispanic (n=131; 82.9%), practicing over 20 years (n=84, 53.8%). The average number of years in their position was 10.3, with 27 (18%) reporting they have been in their position for more than 20 years with a preferred length as Director of 9 years. Over 40% (n=83) plan to retire in the next 10 years with 50% (n=78) planning on reducing their patient workload by up to 50% in the next ten years. Division Directors reported plans to recruit a total of 167 new faculty overall to 88 centers. Most clinical faculty recruits were for time in clinical practice and teaching with <25% effort in clinical research. Recruitment for translational or bench research and administrative positions were

unusual. Table 1 details retention and recruitment reported issues.

Conclusion: The DD survey reveals that the DD population is somewhat homogenous population who has served in their positions for lengthy periods. Most new recruitments are for clinical junior faculty. Recruitment and retention challenges involve inability to match salary, educational debt, no tenure, loss or lack of research funding and career advancement. There is a suggestion that improvement in divisional support and mentoring may promote retention in the academic workforce.

Table 1. Reported Retention and Recruitment Reasons

Most Common Reported Reasons	Retention - N(%)	Recruitment - N(%)
Educational debt	26 (10.0)	38 (14.0)
Inability to match salary	111 (42.5)	124 (45.8)
Tenure	9 (3.5)	7 (2.6)
Loss or lack of grant funding	48 (18.4)	80 (29.5)
Career Advancement	67 (25.7)	22 (8.1)

Table 2. **Most Common Reasons Reported for Leaving Academics**

- Lack of strong divisional and institutional support
- Difficulty obtaining funding for research and /or other activities
- Lack of autonomy of my practice schedule
- Desire for higher pay
- Desire for shorter work hours
- Inadequate mentoring
- Preference for community/clinical care
- Retired

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Abstract Number: 103

People with Rheumatoid Arthritis Recruited from an Online Patient Community May Differ from Clinical Populations in Symptoms and Impacts

Anna Kristina Gutierrez[1], Susan J. Bartlett[1,2], Michelle Jones[3], W. Benjamin Nowell[4], Seth D. Ginsberg[4], Vivian P. Bykerk[5], Jeffrey R. Curtis[6] and Clifton Bingham III[7], [1]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Department of Medicine, Division of ClinEpi, Rheumatology, Respirology, McGill University, Montreal, QC, Canada, [3]Johns Hopkins University School of Medicine, Baltimore, MD, [4]Global Healthy Living Foundation, CreakyJoints, Upper Nyack, NY, [5]Divison of Rheumatology, Hospital for Special Surgery, New York, NY, [6]Division Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [7]Johns Hopkins University, Baltimore, MD

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Background/Purpose: Patients are increasingly recruited from online communities to provide insight regarding their lived experiences and preferences for treatment and services. We compared physical, social, and emotional health patient reported outcomes in people with rheumatoid arthritis (RA) recruited from an online patient community with those seen in an arthritis clinic in one academic medical center.

Methods: Participants were recruited from 2 sources: a single academic rheumatology clinic, and www.creakyjoints.org, an online arthritis patient community. Clinic participants were selected through convenience sampling of patients. Online participants were invited via email and screened for probable RA using a modified version of the connective tissue screening questionnaire (CSQ) that added a DMARD checklist and questions concerning personal and family history of psoriasis to improve specificity for RA. Patients provided sociodemographic and disease information and completed PROMIS fixed item Short Forms (SF): Physical Function 4a/20a (PF), Pain Interference 4a/8a (PI), Fatigue 4a/7a/8a, Ability to Participate in Social Roles and Activities 4a/8a (PSRA), Depression 4a/8a, Anxiety 4a, and Sleep Disturbance 4a. PROMIS scores are reported as T-Scores with a population mean of 50 and SD of 10, with higher scores indicating more of the trait measured. Groups were compared using t-tests.

Results: Compared to clinic patients (n=52), online participants (n=200) had more education (69% vs 92% >High School), shorter disease duration (mean[SD]: 15[11] vs 10[10] yrs) and were more likely to be disabled due to RA (15% vs 32%) (all $p<0.05$), but did not differ by age, sex, or minority status. Most clinic participants were relatively well-controlled with 64.6% in LDA or remission; mean CDAI was 7 (SD 7). Scores comparing different length PROMIS SF for the same trait (e.g. fatigue) were similar. Compared with the US population, both groups had worse PF and greater PI and fatigue. Compared with clinic patients, online participants reported significantly greater impairments in PF (42[12]) vs 34[6]), PI (56[10] vs 65[7]), fatigue (55[14] vs 66[8]), PSRA (49[11] vs 39[7]), depression (50[11] vs 58[10]), anxiety (50[11] vs 58[9]) and sleep disturbance (51[10] vs 58[8])(all p's < .001).

Conclusion: These results suggest that patients recruited through online arthritis communities may differ in some demographic features from those seen in an academic clinic. On average, online participants reported significantly worse physical, social, and emotional health. A limitation of the study is the absence of information regarding disease activity, treatment, and comorbidities. Better understanding these differences will be important to improve generalizability of PRO results from online communities. Funding PCORI IP2-PI0000737 and SC14-1402-10818. **Table I. Comparison of selected RA symptoms and impacts between clinic and online patients.**

PROMIS short form	Clinic Mean (SD) N=52	Online Mean (SD) N=200	p value
Physical Function			
4a	43.9 (10.2)	36.3 (5.4)	<.001
20a	41.9 (11.5)	34.0 (6.4)	<.001
Pain Interference			
4a	56.3 (9.8)	64.9 (6.6)	<.001
8a	56.2 (10.0)	65.0 (7.0)	<.001
Fatigue			
4a	54.1 (13.4)	65.3 (8.1)	<.001
7a	54.6 (11.2)	65.6 (8.1)	<.001
8a	54.8 (13.5)	66.0 (7.8)	<.001
Ability to Participate in Social Roles and Activities			
4a	48.9 (10.5)	39.3 (6.3)	<.001
8a	48.8 (11.1)	38.6 (6.7)	<.001
Depression			
4a	51.1 (10.7)	58.0 (9.5)	<.001
8a	50.1 (11.4)	57.7 (9.6)	<.001
Anxiety			
4a	50.3 (10.5)	57.9 (9.1)	<.001
Sleep Disturbance			
4a	51.4 (9.8)	58.4 (7.8)	<.001

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Abstract Number: 104

Incremental Direct Expenditures Due to Osteoarthritis: A Nationally Representative Study Using Medical Expenditure Panel Survey Data

Jyothi Menon, Purdue University, West Lafayette, IN
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Background/Purpose: Osteoarthritis is characterized by symptoms related to abnormalities in joints, subchondral bones and periarticular structures. In the United States, it was estimated that twenty-seven million adults suffered from osteoarthritis in 2005. The objectives of this study were to determine incremental health care resource utilization and incremental health care expenditures, associated with Osteoarthritis.

Methods: An observational database analysis was conducted using information from the Medical Expenditure Panel Survey (MEPS). Individuals 18 years of age or older and employed during 2011 were eligible for inclusion in the sample for analyses. Individuals were identified with Osteoarthritis diagnosis based on ICD-9-CM diagnosis codes. Out of a sample of 26,992 individuals, 1,354 were diagnosed with osteoarthritis. Using sampling weights provided, individuals with osteoarthritis were compared to individuals without osteoarthritis on health care resource utilization and expenditures.

Results: Compared to individuals with osteoarthritis, significantly lower mean unadjusted hospitalizations (0.24 v 0.09, $p<0.001$), mean unadjusted outpatient room visits (12.93 v 4.89, $p<0.001$) and mean unadjusted emergency room visits (0.33 v 0.22, $p<0.001$) were observed among those without osteoarthritis. Compared to individuals with osteoarthritis, significantly lower mean unadjusted inpatient expenditures ($3,563 v $1,1,91 $p<0.001$), mean unadjusted outpatient expenditures ($3,242 v $1,223, $p<0.001$), mean unadjusted emergency room expenditures ($295 v $ 187, $p<0.001$), and mean unadjusted medication expenditures ($2,336 v $962, $p<0.001$) and mean unadjusted total expenditure ($9651 v $3,415, $p<0.001$) were observed among those without osteoarthritis. Incremental health care resource utilization examined included annual hospitalization, annual hospital days, annual emergency room visits, annual outpatient visits. Incremental health expenditures examined included annual inpatient expenditures, annual outpatient expenditures, annual emergency room expenditures, annual miscellaneous expenditures, annual medication expenditures and annual total expenditures. Incremental resource utilization and incremental resource expenditures were estimated using regression models, adjusting for other covariates including age, gender, sex, region, marital status, insurance coverage, comorbidities, anxiety, asthma, hypertension and hyperlipidemia. Multivariate regression models revealed incremental mean annual resource use associated with osteoarthritis of 70 additional hospitalizations per 100 osteoarthritic patients annually, and 363 additional visits per 100 osteoarthritic patients annually. Mean annual incremental total expenditures associated with osteoarthritis were $2,046. Mean annual incremental expenditures were largest for inpatient expenditures at $826, followed by mean annual incremental outpatient expenditures of $659, and mean annual incremental medication expenditures of $325.

Conclusion: Osteoarthritis was associated with considerable incremental health care resource utilization and expenditures.

Disclosure: J. Menon, None;

Abstract Number: 105

Regional Primary Care Rheumatology Networks for Patients with Rheumatic and Musculoskeletal Diseases: Need for a National Approach

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Background/Purpose: Regional primary care rheumatology networks of health professionals (HPs) are instituted to improve the quality of care for patients with rheumatic and musculoskeletal diseases (RMDs). The aim was to describe their characteristics, the success and failure factors, and the satisfaction of patients treated by network members in the Netherlands.

Methods: Data on the organizational structure and processes, education, patient load, perceived success / failure factors, and organizational / educational needs were collected by interviewing 19 existing network coordinators, and an online surveys among all members A maximum of 4 patients per member were asked to complete an online survey comprising the Consumer Quality Index (CQ) subscales Information, Attitude of HPs, and Cooperation and Self-management (range 1-4), and a Numeric Rating Scale on therapy satisfaction (range 1-10).

Results: 17 networks set membership criteria, 5 had a formal organizational structure, 7 imposed a membership fee, 17 collaborated with a hospital rheumatology department, 15 included only physical therapists, 18 organized network meetings for professionals and 11 for patients. There were 479 network members (median 18 per network, range 7-106). All coordinators expressed the need for central support regarding network organization and activities. Of 256 responders 54 (21%) did not completed the survey because they had not seen patients with RMDs in the past year. 214 network members (50%) completed the survey, 82 (38%) followed accredited postgraduate education on RMDs, whereas 159 (74%) expressed a need for standardization of postgraduate education and organizational support. The most frequently mentioned success factors were: patient satisfaction, presence of diagnostic and treatment protocols and the organization of meetings, whereas failure factors mentioned were: low patient load, poor visibility, suboptimal communication with rheumatologists and patients, and a lack of affordable and (continuing) postgraduate education. The 149 patients who returned the survey were highly satisfied: CQ Information 3.8 (SD 0.3); Attitude of health professionals 3.9 (SD 0.3); and Cooperation and Self-management 3.5 (SD 0.5), satisfaction mean score was 8.7 (SD 0.8).

Conclusion: Structure and process of regional primary care networks focusing on the management of patients with RMDs shows considerable variation. Although added value with respect to patient satisfaction is plausible, there is a need for support of regional networks on the national level, standardization of postgraduate education, improvement of communication with rheumatologists and patients and their visibility. **This study was financially supported by the Dutch Arthritis Association.**

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Abstract Number: 106

Patient Satisfaction Survey of a Newly Set up Physiotherapist Lead Axial

Spondyloarthritis Clinic

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Background/Purpose:

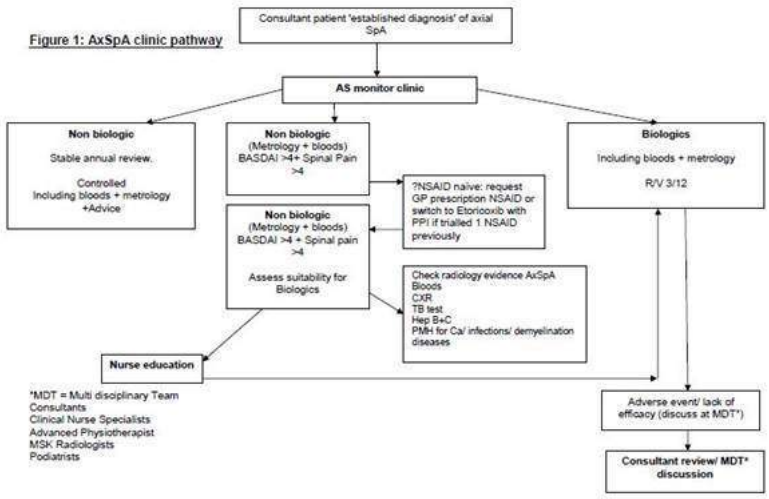
Present guidelines (National Institute for Health and Care Excellence- NICE technology appraisal guidance TA143 2008 and TA233 2011; National Ankylosing Spondylitis Society 2010) on axial spondyloarthritis (AxSpA) support the management and monitoring of patients based on a pharmacological and physical measurement approach. In the UK, these patients often require multiple appointments with a variety of health professionals including Consultants, nurses and physiotherapists all reviewing different aspects of their condition.

Methods: To streamline these appointments, reduce the number of visits individuals need to make and release capacity in the consultant clinics, in 2014 we trialled a 'one-stop shop' approach with an experienced Advanced Rheumatology Physiotherapist leading the clinic with medical escalation and governance arrangements in place (see Figure 1). As this was a significant change in delivery of care we assessed the satisfaction of a sample of consecutive patients attending the clinic throughout a twelve month period. Patients were informed of the change in the service organisation prior to their attendance of the clinic. A validated Patient Reported Experience Measure questionnaire (PREM) (Bosworth A et al. 2015), as developed by Commissioning for Quality in Rheumatoid Arthritis (CQRA), a British multidisciplinary group of stakeholders, was used. The questionnaire comprises of 8 domains that have been evidenced as being most important to patients' experiences of National Health Service (NHS) services.

Results: 64 patients completed the questionnaire (mean age 51.6 ± SD11.7; M 58/64, 87.5%). Most of the patients (46/64, 71.9%) had a disease duration of more 10 years, with approximately 50% on biologics. Percentage of patients who answered 'strongly agreed' or 'agreed' for the overall satisfaction of the service was 100% (73.4% and 26.6% respectively). The specific domains results are shown in the table.

Domain	Number of Questions	Patient satisfaction (strongly agree or agree) (%)	Range (%)
Needs and preferences	5	99.1	95.3 - 100
Co-ordination of care	4	96.7	89.5 - 100
Information about care	4	93.3	85.1 - 96.9
Daily living	2	87.0	80.4 - 92.2
Emotional aspects	2	89.6	87.3 - 91.9
Family and friends	1	86.9	-
Access to care	1	100	-
Overall evaluation	-	100	-

Conclusion: Our study suggested that overall patients were satisfied that their care was delivered by an Advanced Physiotherapist. This could present significant improvements in cost and quality of care delivered to this patient group. Although all areas scored highly for satisfaction, some domains identified areas for potential improvement within the service. These will be reviewed after further evaluation with a wider sample population. .



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Abstract Number: 107

Improvement of Quality and Cost-Effectiveness of Rheumatology Care By Creating Long-Term Alliances with Pharmaceutical Companies

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Background/Purpose: Biological therapies have importantly contributed to controlling disease activity in patients with inflammatory rheumatic diseases. As the high costs of biologics are a threat to affordability and accessibility of these drugs for patients, attempts are made to decrease both the price and the quantity of the biological use. Examples of these attempts are start-/stopcriteria, dose reduction strategies and reduction of medication waste. Since recently, both intravenous- (infliximab) and subcutaneous (etanercept) biosimilars are available in Europe. Furthermore, pharmaceutical companies are altering their marketing strategies from a technology push/aggressive marketing targeted on individual doctors, to a new form of long term partnerships between hospitals as organizations and pharmaceutical companies. These partnerships should not only result in more attractive drug prices, but also to co-creation of innovations to improve decreased drug use, accessibility, affordability and the quality of healthcare. On top of that, long term partnerships prevent yearly time consuming price negotiations between hospitals and pharmaceutical companies. *Aim:* To create value-based long term partnerships between our hospital and pharmaceutical companies in order to improve both the quality and the cost-effectiveness of rheumatologic patient care.

Methods: First, an independent working group of rheumatologists and pharmacists employed at our hospital prepared a

list of interchangeable biologics for new patients with rheumatoid arthritis, psoriatic arthritis and spondyloarthritis. Then, nine pharmaceutical companies were invited to offer a proposition for partnership with our hospital. This proposition had to include a combination of a multi year attractive price proposition and a proposal for projects for optimization of biological drug use and/or improvement of rheumatology care. Separate meetings with the CEO, head of pharmacy and the medical managers of the rheumatology department of our hospital and representatives of the pharmaceutical companies were scheduled in order to discuss the propositions and find the common goals in the partnerships. All proposals were put in a model, in order to calculate long-term benefits/costs.

Results: 1936 patients in the Sint Maartenskliniek use biologics for their rheumatic disease. 21 rheumatologists of the Sint Maartenskliniek declared all tumor necrosis factor alpha inhibiting drugs (TNF-i), tocilizumab (RA only) and abatacept (RA only) interchangeable with respect to new patients with above mentioned diagnoses and declared the reference products of TNF-i infliximab (Remicade ®) and etanercept (Enbrel ®) interchangeable with their biosimilar counterparts for both new and current users. After separate sessions with individual pharmaceutical companies, three companies were selected and finally two were granted a first or second position of preference for a period of four years with a six month adjustment window of the price according to developments in the market. The model was used to calculate costs and benefits of each proposal. As a result of this process, a 25% reduction of the price of biologics was obtained (compared to last years price), as well as an increase in mutual investments in care projects such as e-health, medication adherence and care pathways.

Conclusion: Creating long-term alliances between hospitals and pharmaceutical companies is an effective strategy to achieve substantial reduction of medication costs (price and quantity) and improvement of quality of care.

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Abstract Number: 108

Does Receiving Physical Therapy for Knee Osteoarthritis Impact Downstream Healthcare Utilization?

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Background/Purpose: The clinical effectiveness of supervised exercise therapy for individuals with knee osteoarthritis (KOA) is well known. However, it is unclear whether participation in a supervised therapy program impacts downstream utilization of health services. The purpose of this study is to determine the impact of four different supervised physical therapy (PT) programs on KOA-related health service utilization over a 2-year period.

Methods: This is a secondary analysis of data from a 2-year multisite randomized clinical trial of 300 individuals with KOA per ACR criteria. Participants were randomized to one of four PT strategies: (1) 12 visits of exercise therapy alone; (2) 9 visits of exercise therapy + 3 booster sessions spaced across 12 months; (3) 12 visits of exercise + manual therapy; (4) 9 visits of exercise + manual therapy + 3 booster sessions. Participants were queried at baseline, 1 year, and 2 years

regarding 12-month utilization of health services commonly accessed by those with KOA (**Table 1)**. Chi-square analyses compared health service utilization at baseline vs. 1 year and baseline vs. 2 years for the full cohort and for subgroups who did/did not receive manual therapy and booster sessions. Logistic regression was used to determine if treatment group allocation predicted health service utilization after adjusting for age, race, and baseline physical function.

Results: Across the full cohort, statistically significant reductions in utilization of many health services were observed following participation in the study (**Table 1**). Use of non-opioid and opioid pain medications for the knee reduced substantially over the two-year period. Reductions in knee joint injections and visits to physicians (especially primary care physicians) also significantly dropped over the study period. Logistic regression analyses revealed that treatment group allocation was generally not a significant predictor of health service utilization. Individuals who received booster sessions were less likely to have knee imaging at one year (adjusted OR 0.51; 95% CI 0.29-0.92). Those who received manual therapy were less likely to have had recent imaging at baseline (adjusted OR 0.59, 95% CI 0.37-0.94) and less likely to have visited a rheumatologist at 1 year (adjusted OR 0.50, 95% CI 0.26-0.95) and 2 years (adjusted OR 0.49, 95% CI 0.27-0.88). All other regression models comparing booster to non-booster groups and manual therapy to non-manual therapy groups did not achieve statistical significance.

Conclusion: Downstream utilization of many common health services reduced over two years for individuals with KOA participating in a randomized clinical trial of structured PT. The study did not include a control group so the reduction in utilization may not be a direct effect of participating in the PT intervention. Treatment group allocation was not a significant predictor of health service utilization.

Table 1. Utilization of Health Services Over Time: Overall Cohort

	Baseline (n = 300) **% (n)**	**1 year (n = 271)** **% (n)**	**2 years (n = 267)** **% (n)**
Knee Injection	33.0% (99)	24.0% (65)*	28.5% (76)*
Knee Arthroscopy	2.3% (7)	1.5% (4)	0.0% (0)
Knee Imaging	56.3% (169)	24.4% (66)	30.7% (82)
Non-Opioid Oral Pain Medication	82.3% (247)	69.0% (187)*	61.4% (164)*
Opioid Pain Medication	10.0% (30)	9.6% (26)*	5.6% (15)*
Primary Care Physician Visits	50.3% (151)	22.9% (62)*	27.3% (73)*
Orthopaedic Surgery Visits	35.0% (105)	24.0% (65)*	33.3% (89)
Rheumatology Visits	10.0% (30)	7.4% (20)*	11.2% (30)*
Rehabilitation Services	13.3% (40)	10.7% (29)	15.0% (40)
Massage Therapy	6.7% (20)	6.6% (18)*	5.6% (15)*
Durable Medical Equipment	17.3% (52)	12.9% (35)	17.6% (47)*

**indicates statistically significant difference from baseline utilization (p<.05)*

Disclosure: A. Bove, None; **C. Bise**, None; **K. Smith**, None; **J. Fritz**, None; **J. Childs**, None; **G. P. Brennan**, None; **J. H. Abbott**, None; **G. K. Fitzgerald**, None.

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Abstract Number: 109

Inter-Professional Satisfaction and Perceptions of Collaborative Practice of an Innovative Model of Care for the Early Detection of Axial Spondyloarthritis

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Network, Toronto, ON, Canada, [6]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [7]Medicine, Rheumatology, University of Toronto, Toronto, ON, Canada, [8]University of Toronto, Toronto, ON, Canada, [9]Rheumatology, Toronto Western Hospital, University of Toronto, Spondylitis Clinic, Toronto, ON, Canada
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Background/Purpose: Emerging models of care in rheumatology are integrating interdisciplinary approaches at different stages of the patient's care pathway. Such models of have recently been implemented in the early identification of axial spondyloarthritis (SpA). The Toronto Western Hospital SpA Screening Clinic links with community-based primary care physicians (PCPs), physiotherapists (PTs), chiropractors (DCs) and nurse practitioners (NPs) to facilitate the early detection of axial SpA and uses advanced practice physiotherapists and specialist rheumatologists located at an academic tertiary care hospital to confirm diagnosis and initiate early treatment for axial SpA. Collaborative inter-professional practice is an essential component for successful implementation of novel models of care for chronic diseases that require ongoing assessment and management from many health care professionals. The objective of this study was to examine the inter-professional satisfaction and perceptions of collaborative practice of an innovative model of care for the early detection of axial SpA in Toronto, Canada.

Methods: A cross-sectional survey was conducted of referring health care providers (HCPs) to the Toronto Western Hospital SpA Screening Clinic and included PCPs, PTs, DCs and NPs. HCPs were sent an electronic questionnaire with questions related to general satisfaction of the SpA Screening Clinic and HCP's perceptions and experience with the inter-professional collaborative process of the SpA Screening Clinic. An adapted version of the Modified Index of Interdisciplinary Collaboration was used to assess inter-professional collaboration. The survey was administered using Survey Monkey®. Data analyses consisted of descriptive statistics and were conducted using Microsoft Excel 2010.

Results: Thirty-two out of 59 (54%) referring HCPs participated in the survey. The majority of respondents were PCPs (65.6%), followed by PTs or DCs (21.9%). The majority of referring HCPs to the SpA Screening Clinic reported positive indicators of satisfaction and included: receiving communication about their referred patients in a timely manner (53.1%); being informed regarding their referred patients' management plan (51.6%) and future re-referral rate for another patient with suspected axial SpA (83.9%). Overall perceptions of inter-collaborative practice were high with respect to referring HCPs relationship with the SpA Screening Clinic: interdependence subscale mean score=2.04 (SD 0.41); newly created professional activities subscale mean score=2.19 (SD 0.2); flexibility subscale mean score=2.47 (SD 0.18) and collective ownership subscale mean score=2.25 (SD 0.21), with 1 representing the highest possible perception of collaboration and 5 being the lowest possible perception.

Conclusion: These results suggest overall inter-professional satisfaction and high levels of perceived inter-professional collaboration with an innovative model of care aimed at the early detection of axial SpA. The results of this study may inform future research on the impact of inter-professional collaboration on outcomes for patients attending the Toronto Western Hospital SpA Screening Clinic.

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Abstract Number: 110

Patient Decisions Related to Hip and Knee Arthroplasty and the Factors Influencing Them

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Background/Purpose: Patient-engaged research can improve the safety and satisfaction outcomes of hip and knee arthroplasty (joint replacement surgery). Patients are able to identify the decisions that are most important to them when undergoing hip and knee arthroplasty and the factors they view as important in making those decisions.

Methods: Forty-nine participants were recruited from ArthritisPower Patient-Powered Research Network and CreakyJoints patient community to participate in structured one-hour discussions held via webinar during January to April 2016 to understand patient experience with joint replacement. Patients described decisions that were most important to them and the factors they used to make those decisions. Discussions were transcribed and coded to identify themes; patient decisions and factors were identified and categorized; and co-occurrence of decisions with factors was tabulated. Demographic and procedure-related characteristics were captured.

Results: Seven decisions emerged that were influenced by at least ten factors (Table). The most important decisions involved whether to have surgery, selection of surgery date, surgeon, facility, implant device, and ancillary health care professionals (HCPs) and services. Factors included current situation, expectations of having or not having surgery, professional and word-of-mouth familiarity with surgeon/HCP, procedure, services and device, and perceived value. Patients' current situation and health status and their expectations of surgery were most commonly used to make decisions about whether and when to have surgery. Patients' trust of and communication with doctors was the most commonly used factor when deciding on arthroplasty surgeon.

Conclusion: Arthroplasty patients are concerned about a variety of decisions. Patient-centered research should maximally address questions of importance to patients and this study is a first step in identifying and prioritizing topics that matter most to patients and the information that patients currently use to make joint replacement decisions. **Table: Arthroplasty Decisions Important to Patients and the Most Common Factors Influencing Them**

Decisions Important to Patients	Most Common Factors Influencing Decisions
Surgery: Whether to have partial or total hip/knee joint replacement surgery (arthroplasty)	Current life situation and health status (44%), Expectations of having surgery (11%), Expectations of NOT having surgery (11%), Information provided to patient by doctor or other HCP (11%), Alternatives to surgery that have been tried or are known about (11%)
Timing: When to have surgery	Current life situation and health status (38%), Expectations of having surgery (19%), Alternatives to surgery that have been tried or are known about (19%), Expectations of NOT having surgery (8%)
Surgeon: Which surgeon will perform surgery	Trust and communication with surgeon (45%), Perceived value of surgeon's expertise (19%), Expectations of having surgery (16%), Information accessed by patient autonomously (10%)
Facility: Where surgery will be performed (e.g., geographic location, specific hospital or medical center)	Information provided to patient by doctor or other HCP (28%), Trust and communication with HCP (18%), Firsthand familiarity with facility (18%), Expectations of having surgery (18%), Information accessed by patient autonomously (9%), Perceived value of facility expertise (9%)
Device: Which implant device will be installed during surgery	Expectations of having surgery (39%), Information provided to patient by doctor or other HCP (18%), Perceived value of device (16%), Trust and communication with HCP (11%)
Other HCPs: Who/which other health care professionals (HCPs) besides the surgeon will be involved in care during and after surgery (e.g., anesthesiologist, physical therapist)	Expectations of having surgery (30%), Trust and communication with HCP (20%), Current life situation and health status (20%), Perceived value of other HCPs (20%), Firsthand familiarity with other HCPs (10%)
Other Services: What other services will be necessary before, during or after surgery (e.g., mental health)	Expectations of having surgery (71%), Trust and communication with HCP (14%), Current life situation and health status (14%)

Disclosure: W. B. Nowell, None; **S. Venkatachalam**, None; **E. Harden**, None; **T. Concannon**, None.

Abstract Number: 111

Influences of Osteoarthritis Pain, Comorbid Insomnia, and Depression on Health Care Use in Older Adults with Osteoarthritis

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Background/Purpose: Osteoarthritis (OA), the most common type of arthritis, is prevalent and costly. Pain is the principal reason patients with OA seek treatment. Older adults with OA often report co-existing insomnia and depression. OA pain, insomnia, and depression greatly increase health care use (HCU) in this population. The purpose of this study is to examine the independent and combined effects of OA pain, insomnia and depression on HCU.

Methods: 8,057 participants aged 60+ with an electronic medical record OA diagnosis were mailed a screening survey which asked about their pain, sleep disturbance, and depressive symptoms. Pain was assessed by the Graded Chronic Pain Scale (GCPS); Grades 2-4 were positive for chronic pain. Insomnia severity was measured by the Insomnia Severity Index (ISI); a score of 7 or greater indicates at least mild insomnia. Depression was measured by the Patient Health Questionnaire depression scale (PHQ-8), with a score greater than 9 representing current depression. All participants were members of Group Health Cooperative (GHC), a Seattle-based health maintenance organization. HCU variables were extracted from participant medical records and included total number of office visits, length of stay (LOS) (days), and outpatient costs related to OA, insomnia and depression. Patient demographics (age, sex, race, ethnicity, education, employment and martial status), days of enrollment in GHC a year before screening date, and Charlson Comorbidity Index scores were also recorded. Negative binominal model and generalized linear model were used for the data analysis.

Results: 3,056 participants completed the survey and gave permission to access their medical records. Average age was 72 years; participants were largely Caucasian (87.4%), female (66.3%), married (59.3%) and highly educated (86.4% community college or higher). Participants had a positive level of pain (46.6%), at least mild insomnia (55.1%), and current depression (17.3%). For independent effects on HCU controlling for patient characteristics, OA pain, insomnia, and depression were associated with office visits ($p < 0.001$). In addition, OA pain ($p < 0.001$), insomnia ($p = 0.020$), and depression ($p < 0.001$) were associated with outpatient costs, but none were associated with LOS. For joint effects of those symptoms controlling for patient characteristics, pain was significantly related to office visits and outpatient costs ($p < 0.001$) but not LOS. Insomnia given pain level contributed to office visits ($p < 0.01$) but not for outpatient costs. Depression given pain level contributed to both office visits and outpatient costs ($p < 0.01$). No significant interactions were found between pain and insomnia, or pain and depression.

Conclusion: OA pain and depression were associated with office visits and outpatient costs in this population after adjusting for covariates. However, insomnia was only associated with office visits prior to adjustment. OA pain, insomnia, and depression were not associated with LOS in this population. Joint contributions of pain, insomnia and depression to HCU were additive.

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Abstract Number: 112

Leveraging a Learning Network to Implement and Standardize Self-Management Support into Care Delivery: Experience of Pediatric Rheumatology Care and Outcomes Improvement Network

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Background/Purpose: Disease outcomes can depend, to a large extent, on one's ability to manage their condition effectively. For children with JIA this means managing oral, injectable, or intravenous medications, managing multiple appointments, regular blood work, imaging studies, and performing home exercise programs. These activities must be integrated into daily life with consideration for developmental, intellectual, and psychosocial well-being of the child and family. Provision of Self-Management Support (SMS) is one of 6 essential elements of care identified in The Chronic Care Model. Practice teams must develop systematic processes designed to address self-management and foster patient's confidence and self-management skills. However, providers are not routinely trained in providing SMS. The purpose of this study was to develop systematic processes by which practice teams within Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) develop skills, tools, and mechanisms to effectively implement SMS.

Methods: Three key components utilized to prepare for successful implementation of SMS by teams included: 1) provider and health care team training in Behavior Change Counseling (BCC), 2) tool development for self-management assessment, barrier assessment, and an action plan worksheet, 3) use of quality improvement (QI) methods to identify successful implementation processes, and to support their application within PR-COIN practice teams. A co-production model, including researchers, health providers and parents was used for tool development and process integration.

Results: Nine centers participated in two 4 hour training sessions on BCC and elements of SMS delivered via interactive webinar technology. A self-management assessment tool (assessing visit goals, self-efficacy, health distress, and adherence), barriers assessment, intervention tools, and action plan were tested across 9 centers and refined. Data tracking of performance for tool implementation and barriers to treatment were collected. 84% or participants completed BCC training. Aggregate data for tool integration into clinic flow was 85%. Of multiple barriers assessed, concern for long term side effects was highest for all medication modalities. Specific barriers to adherence of medications were forgetting to take medication and pain associated with injections. Monthly webinars were conducted to debrief on progress, learnings and share best-practices on SMS implementation. Feedback from teams and parents indicated SMS tools used in clinical encounters were helpful to address barriers/concerns of patients, to decrease provider assumptions and increase patient activation.

Conclusion: This project implemented a novel approach to SMS training with interactive webinar instruction showing feasibility of this technology to facilitate future spread of SMS skills training to other centers. The co-production model with caregivers collaborating with teams facilitated the tool development and relevance to target audience. Specific QI methods building on skills learned from participation in PR-COIN allowed more efficient uptake of SMS into clinic practice.

Abstract Number: 113

Online Consultation for Chinese Patients with Rheumatic Diseases Based on Smart System of Disease Management (SSDM) Mobile Tools: A Study of Medical Economics

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Background/Purpose: China does not have primary medical care and referral system. Patients can choose any hospital or any doctor they like to seek medical care. As a result, most patients with rheumatic diseases rushed to a few large cities. Survey shows more than 40% of the rheumatic disease patients are unnecessary to go to hospital and they only need advices from specialist. Smart System of Disease Management (SSDM) is a series of applications for chronic diseases management, which develop the interaction between doctors and patients. The study shows that, after training, the RA patients can master the SSDM and perform self-management, including DAS28 and HAQ evaluations, as well as medication and lab test data entries. The purpose of this study is to evaluate the feasibility and benefit of the medical economics of online consultation based on SSDM by rheumatologist.

Methods: The rheumatologists and nurses implemented the education and training programs on using SSDM and assisted the patients in downloading SSDM APP. The SSDM includes doctors' application and patients' application. The patient application includes self-assessment (DAS28, HAQ), medication management, adverse events management and laboratory records. After data entry, patients can synchronize data to the authorized doctor. On the basis of understanding of the disease activities, medication and laboratory test results, the rheumatologists can accept consultation request from the patients and supply them with advices in forms of text and or telephone call.

Results: Between February 14, 2015 and June 12, 2016, 30 rheumatologists supplied 132 patients with 136 times free and 55 paid consultations. In which there were 176 times text Q&A and 15 telephone consultations. Paid consultation included 43 times text Q&A and 12 telephone consultations. The consulting fee ranged from RMB 50 to 500 yuan (USD:RMB =1:6.6) each in average of 275.45 ± 90.20 yuan, which rate match the registration fee in hospital. The total fee for consultations was 15,150 yuan. 75.8% patients receiving online consultation lived in different cities with the rheumatologists. If patients seek medical in hospital, in addition to the registration fees and medical expenses, the mean cost of transportation, accommodation, meals and lost wages was 1081.68 ± 523.28 (200 to 1,800) yuan. The total of cost for all patients would have been 248,250 yuan, which is 15.38 times higher than online consultation. SSDM can save up to 93.90% cost for patients. Survey shows all patients were satisfied and 64.86% of them were "very satisfied" with the consultation services.

Conclusion: Using SSDM system to obtain online consultation, Chinese patients with rheumatic disease can enjoy reduced cost with high satisfaction. In the era lack of primary care system in China, SSDM may serve a complimentary platform to control medical care cost, as well as relieve the tensions between health care professionals and patients.

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Abstract Number: 114

The Effect of Triage Assessments on Identifying Inflammatory Arthritis and Reducing Rheumatology Wait Times in Ontario

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Background/Purpose: Excessive delays to rheumatologists have been documented and triage assessments of suspected IA referrals from primary care may be a key strategy to expedite access to rheumatologists. We evaluated the positive and negative predictive values (PPV and NPV) of triage assessments by extended role practitioners (ERP) for identifying patients with IA. We also estimated the time from primary care referral to rheumatology consultation, comparing those patients who were expedited by an ERP (suspected IA) versus those who were not.

Methods: Patients with possible IA were identified from rheumatologists' wait lists through a paper triage process. Patients were included if they were adults and newly referred by a general practitioner or nurse practitioner within the previous month. An ERP established a weekly triage clinic in each participating rheumatologist's office and assessed each patient using a standardized tool to identify patients for an expedited rheumatologist consult. Non-expedited patients went back on the waiting list to receive the next available routine appointment. Patients were then followed for three months post referral with dates of rheumatologist consultations and clinical diagnoses identified by chart review. We determined the proportion of patients correctly triaged by ERPs for expedited access. The median (interquartile range) time from primary care referral to the first rheumatologist consultation was determined, comparing patients who were prioritized for an expedited assessment versus those who were not, and compared to the provincial average (median: 66 days)*.

Results: Six rheumatologists agreed to participate in the study. Of 317 patients identified from the rheumatologists' wait lists as having possible IA, 177(56%) met inclusion criteria and received an ERP triage assessment (female: 67%; mean age (SD): 53 (14)). Of these, 75/177 patients (42%) were prioritized by the therapist for an expedited appointment with the rheumatologist. For expedited patients, 71/75(95%) were seen by the rheumatologist within 3 months of referral and the median (IQR) time from referral to rheumatologist consultation was 37 (24.3-54.8) days. Upon consultation, the rheumatologist suspected IA or connective tissue disease (CTD) in 58/71(PPV=0.817). Among those not prioritized**, 68/101 patients (67%) were seen by the rheumatologist within three months of referral and the median (IQR) time from referral to rheumatologist visit was 100 (68.3-131.5) days. Of those, 13/68 received a differential diagnosis of IA/CTD (NPV=0.809).

Conclusion: Triage by an ACPAC trained ERP resulted in a high number of patients with suspected IA/CTD being correctly prioritized for a rheumatology consultation. For prioritized patients, the wait time was less than the provincial

median. These results suggest that an ERP working in a triage role can improve access to rheumatology care for patients with suspected IA. *Widdifield et al. "Patterns of care among first-time referrals to rheumatologists: Characteristics and timeliness of consultations and treatment in Ontario, Canada" Arthritis Care & Research 2016; Apr 25. doi:10.1002/acr.22910. **1 patient missing

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Disclosure: C. Bombardier, None; **S. Brooks**, None; **M. Bell**, None; **A. Cesta**, None; **T. Kendzerskaya**, None; **R. Sweezie**, None; **J. Widdifield**, None; **L. Fullerton**, None; **V. Ahluwalia**, None; **A. Karasik**, None.

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Abstract Number: 115

Early Inflammatory Arthritis Presentation, Management and Outcomes in Canadian Aboriginal Patients

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Background/Purpose: Differences in access to care that influence the timing and quality of treatment interventions may create outcome inequities for Aboriginal patients with inflammatory arthritis. Our study compares Aboriginal and Caucasian patients in disease presentation, treatment strategy, and outcomes over five years.

Methods: Participants were enrolled in a prospective multi-center early arthritis cohort, and treated with routine care. Inclusion criteria for the present study were < 1 year symptom duration, self-identified as Aboriginal or Caucasian, and completion of >1 follow-up visit. Baseline demographics, clinical characteristics, and therapy escalation for moderate (DAS28 >3.2) or high (DAS28 >5.1) disease activity states (defined as any of increased dose of methotrexate, addition of a DMARD, and/or addition or switching biologic) were compared using standard descriptive statistics. The frequency of remission and use of DMARD, biologic and steroid therapy were compared between groups. Mixed-model repeated measures and Poisson regression analysis were used to determine rates of change for disease activity measures over five years, with adjustment for baseline demographics and disease activity measures.

Results: The study sample included a total of 2173 patients (Aboriginal n=100; Caucasian n=2073), 70% female with mean(sd) age of 54(15) years, symptom duration of 179(91) days, and baseline DAS28 4.87(1.48). Differences in current smoking status, body mass index, education, and household income disfavoured Aboriginal patients (Table 1, all $p<0.01$). Aboriginal patients were more frequently seropositive and less likely to have erosions at baseline, but did not differ in symptom duration, number of comorbid conditions, nor baseline HAQ and DAS28 scores. Therapy was escalated at ~50% and 60% of visits where patients were in moderate and high disease activity states respectively, with no differences between groups in the frequency or type of strategy used (i.e. use of oral steroids, combination DMARD therapies or biologics). DAS28 remission was less frequent in Aboriginal patients at all visits up to 36 months (3 months 16% vs 30%; 12-months 16% vs 50%; 36-months 40% vs 59%, p values <0.01). This was driven by higher values for all DAS28

components. In particular, swollen joint counts in Aboriginal patients improved at a significantly slower rate (slope difference between groups p=0.029), and patient global scores did not improve significantly (p=0.115) in Aboriginal patients.

Conclusion: We observed differences in disease phenotype in Aboriginal patients, and worse disease outcomes despite having a treatment escalation strategy similar to the Caucasian population. This may reflect disparities in socioeconomic status and differences in environmental exposures associated with worse disease outcomes.

Table 1. Baseline Demographics Differing Between Aboriginal and Caucasian Participants in the Cohort*		
	Aboriginal (n=100)	Caucasian (n=2073)
Mean Body Mass Index	29.7 (6.1)	27.9 (6.0)
Current smoker frequency	32 (32%)	377 (18%)
Education (²High School)	68 (68%)	882 (42%)
Household income (²$50,000/annum)	51 (51%)	708 (34%)
RF positive	60 (71%)	1061 (57%)
Anti-CCP positive	42 (66%)	770 (52%)
Presence of Erosions	12 (12%)	423 (21%)
***Reported as mean(SD) or n(%) as appropriate**		

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Abstract Number: 116

Racial Differences in Self-Reported Pain and Disability: A Longitudinal Study of Knee Osteoarthritis

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SESSION INFORMATION

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Background/Purpose: Pain and disability from knee osteoarthritis (KOA) has been reported to be greater among African-Americans (AAs) than Whites (WHs), though progression in KOA-related symptoms by race has not been described. Our objective is to compare self-reported pain and disability between AAs and WHs, with or at high-risk of KOA, over 9 years of follow-up.

Methods: The Osteoarthritis Initiative is a longitudinal cohort study of participants with or at risk of KOA, with up to 9

years of annual self-reported pain and disability assessments including WOMAC pain, pain severity in the past 30 days using a numerical rating scale (NRS), and WOMAC disability. Mixed models for repeated measures were used to estimate race group means and change in group means during follow-up, adjusted for age, sex, education, marital status, body mass index, and depression. Generalized linear mixed models for multinomial logistic regression were used to estimate the relative odds of reporting clinical improvement and worsening, based on established clinically important differences [CID], for AAs compared to WHs. The referent outcome was no CID, and 2 knees per participant were accounted for with random intercepts.

Results: A total of 3790 WH and 874 AA subjects were included, with baseline mean WOMAC pain subscale scores of 1.9 (SD 2.8) and 4.4 (SD 4.4), respectively. During the first year follow-up, there was a significantly greater decline in mean WOMAC pain among AAs compared to WHs (-0.64 [95% CI: -0.78 to -0.50] vs. -0.15 [95% CI: -0.21 to -0.08]; $p<0.0001$), while mean pain levels remained stable between the 1 year and 9 year follow-up visits. Pain severity and WOMAC disability had similar patterns, with a significantly greater decline among AAs from baseline to first year follow-up, followed by relatively stable group means. However, AAs had significantly increased odds of reporting clinically important worsening and improvement in pain and disability among nearly all consecutive annual clinic visits, and across all three outcome measures, compared to WHs (Table 1).

Conclusion: Race-specific group means suggest that AAs report a precipitous drop in KOA-related symptoms between first administration at baseline and second administration 1 year later, followed by stable average pain and disability. Closer examination revealed that AAs were more likely than WHs to report CID, both worsening and improvement, in KOA pain and disability, revealing substantial within-person variance among AAs. Whether the increased variability in responses from AAs reflects fluctuations in actual pain and disability experienced or lack of cross-cultural instrument validity is unknown. Self-reported measures of symptoms are accepted as primary endpoints in randomized controlled trials (RCTs). RCTs that rely on changes in these measures to demonstrate drug efficacy may suffer from obscured treatment effects among AAs.

Table 1. Race and Self-Reported Clinically Important Differences in Pain and Disability Over Consecutive Annual Visits

		Whites		African Americans			
		Worsening	Improvement	Worsening		Improvement	
	Year	n (%)	n (%)	n (%)	OR_W (95% CI)	n (%)	OR_I (95% CI)
WOMAC Pain Subscore † [0-20]	0-1	631 (8.8)	1286 (17.9)	215 (14.0)	2.15 (1.79, 2.59)	488 (31.8)	2.42 (2.11, 2.79)
	1-2	650 (9.5)	996 (14.6)	238 (17.7)	2.35 (1.96, 2.81)	302 (22.5)	1.96 (1.66, 2.31)
	2-3	595 (8.8)	1030 (15.3)	206 (16.1)	2.27 (1.88, 2.76)	303 (23.6)	1.94 (1.65, 2.30)
	3-4	617 (9.2)	992 (14.7)	214 (16.9)	2.36 (1.95, 2.85)	297 (23.5)	2.05 (1.73, 2.44)
	4-5	740 (11.7)	926 (14.6)	198 (15.8)	1.65 (1.36, 1.99)	296 (23.7)	1.99 (1.67, 2.37)
	5-6	607 (9.8)	1058 (17.1)	229 (18.9)	2.43 (2.01, 2.94)	291 (24.0)	1.79 (1.51, 2.11)
	6-7	702 (11.5)	853 (14.0)	211 (17.5)	1.90 (1.57, 2.31)	280 (23.2)	2.08 (1.75, 2.49)
	7-8	579 (9.7)	1053 (17.7)	194 (16.6)	2.14 (1.75, 2.62)	304 (26.0)	1.87 (1.57, 2.22)
	8-9	618 (11.2)	837 (15.1)	195 (18.1)	2.00 (1.63, 2.45)	246 (22.8)	1.88 (1.56, 2.26)
Pain Severity in Past 30 Days ‡ [0-10]	0-1	1377 (19.3)	1592 (22.3)	273 (18.1)	1.13 (0.95, 1.34)	508 (33.6)	1.85 (1.60, 2.15)
	1-2	1390 (20.5)	1295 (19.1)	282 (21.2)	1.10 (0.93, 1.31)	293 (22.1)	1.23 (1.04, 1.46)
	2-3	1325 (19.8)	1203 (18.0)	290 (22.8)	1.28 (1.08, 1.51)	265 (20.9)	1.28 (1.08, 1.53)
	3-4	1312 (19.6)	1249 (18.7)	296 (23.7)	1.37 (1.15, 1.63)	273 (21.8)	1.33 (1.11, 1.58)
	4-5	1268 (20.1)	1201 (19.0)	302 (24.2)	1.36 (1.15, 1.61)	268 (21.5)	1.27 (1.07, 1.52)
	5-6	1247 (20.2)	1198 (19.4)	265 (21.8)	1.18 (0.99, 1.41)	274 (22.6)	1.27 (1.07, 1.51)
	6-7	1163 (19.1)	1151 (18.9)	292 (24.1)	1.42 (1.19, 1.69)	245 (20.2)	1.20 (1.00, 1.43)
	7-8	1126 (18.9)	1131 (19.0)	260 (22.2)	1.38 (1.15, 1.65)	292 (24.9)	1.54 (1.30, 1.84)
	8-9	1067 (19.3)	997 (18.0)	268 (24.8)	1.55 (1.29, 1.86)	251 (23.2)	1.55 (1.28, 1.87)
WOMAC Disability Subscore § [0-68]	0-1	1081 (15.1)	742 (10.4)	408 (26.9)	2.44 (2.07, 2.87)	268 (17.7)	2.27 (1.90, 2.73)
	1-2	714 (10.6)	790 (11.7)	254 (19.2)	2.32 (1.92, 2.81)	259 (19.5)	2.12 (1.77, 2.56)
	2-3	715 (10.8)	781 (11.8)	265 (21.0)	2.58 (2.12, 3.13)	251 (19.9)	2.23 (1.85, 2.70)
	3-4	779 (11.7)	752 (11.3)	259 (20.9)	2.34 (1.93, 2.83)	244 (19.7)	2.28 (1.88, 2.77)
	4-5	670 (10.7)	980 (15.6)	260 (21.2)	2.51 (2.06, 3.05)	234 (19.1)	1.53 (1.26, 1.86)
	5-6	822 (13.5)	770 (12.6)	221 (18.6)	1.75 (1.44, 2.13)	275 (23.2)	2.35 (1.93, 2.85)
	6-7	610 (10.1)	1013 (16.8)	252 (21.6)	2.64 (2.16, 3.23)	219 (18.8)	1.38 (1.13, 1.68)
	7-8	947 (16.2)	641 (11.0)	210 (18.6)	1.41 (1.15, 1.73)	247 (21.9)	2.46 (2.01, 3.01)
	8-9	618 (11.4)	814 (15.1)	200 (19.1)	2.11 (1.70, 2.61)	235 (22.5)	1.89 (1.55, 2.32)

Note: n refers to number of knees; Odds Ratio for Worsening (ORW); Odds Ratio for Improvement (ORI); 95% Confidence Interval (CI); Western Ontario and McMaster Universities Arthritis Index (WOMAC)
†WOMAC Pain Subscore CID criteria: ≥1.5 decrease for improvement, ≥2.2 increase for worsening (Angst et al, 2001)
‡Pain Severity in Past 30 Days CID criteria: ≥1.7 decrease for improvement; ≥1.7 increase for worsening (Farrar et al, 2001)
§WOMAC Disability Subscore CID criteria: ≥6.0 decrease for improvement; ≥6.0 increase for worsening (Tubach et al, 2005)

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Abstract Number: 117

The Relationship Between Socioeconomic Factors and Dmards Use in Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder affecting millions of Americans with societal costs estimated in the billions. With the expansion in the number of biologic drugs available, the cost of care has continued to increase. Socioeconomic factors have been shown to affect the likelihood of immunosuppressive therapy prescribed in RA. The purpose of this study was to examine the association between medication prescribed and socioeconomic factors including gender, race, and median household income.

Methods: This was a retrospective, single center, hospital-affiliated outpatient cohort study. A systematic review of the electronic medical record yielded over 4000 patient's records. These records were reviewed and of these, 116 patients who met the ACR/EULAR (2010) classification criteria for RA were randomly selected. General demographic information including age, gender and zip code, as well as serological testing was obtained through chart review. Supplemental socioeconomic information for each zip code in Southwest Virginia was obtained from the United States Government Census website. The data was analyzed by Kruskal-Wallis Test, Mann-Whitney U Test using SAS9.3.

Results: Table 1 outlines the frequency of medication prescribed in the cohort. Among the 116 patients, there was no relationship between socioeconomic factors and medication prescribed. There was no statistical relationship between gender and medication prescribed including NSAIDs (p=0.153), corticosteroids (p=0.172), DMARDs (p=0.26) and biological drugs (p=0.350).There was no statistical relationship between race and medications including NSAIDs (p=0.890), corticosteroids (p=0.221), DMARDs (p=0.475) and biological drugs (p=0.673). There was no statistical relationship between median household income and medication prescribed including NSAIDs (p=0.071), corticosteroids (p=0.296), DMARDs (p=0.228) and biological drugs (p=0.046)

Table 1
Medications Used in the Cohort

	Frequency	Percentage
None	31	27%
Biologics Monotherpay	2	2%
DMARDs	49	42%
Biologics+DMARDs	32	28%
DMARDs+Small Moleculars	2	2%
Total	116	100%

Table 2
Medications by Race

	Non-caucasian	Caucasian	p-value
Biologics	35.0%	30.2%	0.673
DMARDs	65.0%	72.9%	0.475
NSAIDs	60.0%	58.3%	0.890
corticosteroids	50.0%	64.6%	0.221

Conclusion: There was no relationship between socioeconomic factors and the medications prescribed in our RA cohort. This may be the result of standardization of RA treatment, and the adoption of "treat to target" ethos in RA. The limitations of this study include the small sample size and its restriction to a single center.

Disclosure: A. Bankole, None;

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Rates and Determinants of Persistent Patient-Physician Discordance in Global Assessment of Disease Activity in Latinos with Rheumatoid Arthritis in the United States

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Background/Purpose: Patients and physicians often differ in their assessments of Rheumatoid arthritis (RA) activity [PGA and EGA respectively]. Such differences may jeopardize attainment of remission. We evaluated proportions of patients with persistently discordant and concordant evaluations (PGA-EGA) over time, and determinants thereof.

Methods: We evaluated 271 Latinos with established RA at baseline (T1) and 12 months later (T2). Tender (TJC) and swollen (SJC) joint counts, pain [visual analogue scale (VAS)], fatigue (VAS), disability [Health Assessment Questionnaire-HAQ-DI], and depression assessments [Patient Health Questionnaire-9 (PHQ9)] were collected. PGA and EGA were captured on 0-10cm VAS; persistent discordance was defined as (PGA-EGA)>=3cm at both time points. Persistently concordant (pC) subjects had -3<PGA-EGA<3, persistently positive discordant (pPD) had (PGA-EGA) >=3, while persistently negative discordant (pND) ones had (PGA-EGA) <=-3. Mutlinomial forward stepwise logistic regression analysis identified independent predictors of individual group membership compared to the pC group (referent).

Results: We observed pC in 94 (34.7%) subjects, pPD in 51 (18.8%), and pND in 4 (1.5%), [figure 1a]. Another 60 (22.2%) changed from baseline concordant to discordant [50 (18.5%) PD, and 10 (3.7%) ND], 43 (15.8%) from baseline PD to either C [41 (15.1%)] or ND [2 (0.7%)], and an additional 19 (7%) patients shifted from baseline ND to either C [15 (5.5%)], or PD [4 (1.5%)]. The magnitude of (PGA-EGA) difference in the four largest groups is shown in figure 1b. Patients in the pPD group were more likely to have higher T1 disability, pain, and depression scores, lower baseline TJC and SJC, and less likely to have improvement in pain compared to those in the pC (all p=<0.007, table 1).

Conclusion: Persistently positively discordant PGA-EGA assessments are common in Latinos with RA (18.8%), potentially jeopardizing remission attainment. Determinants of this state do not include markers of disease activity but rather, higher baseline functional disability, depression scores, pain, and lack of improvement in pain.

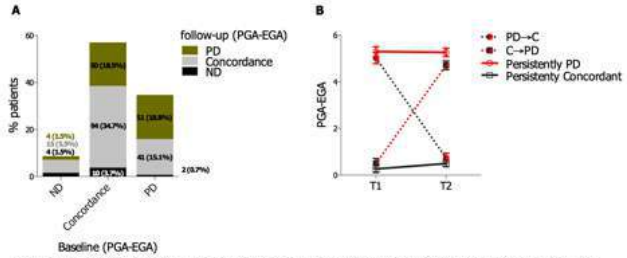

Figure 1: A. Persistence of PGA-EGA discordance over time. **B.** Magnitude of discordance between patients and physicians on respective evaluations of disease activity over time.

Table 1: Independent predictors of unique group membership compared to the persistently Concordant (pC) group as referent

State	parameters	B	Std Error	p	OR	95% CI
Persistent Positive Discordance (pPD)	Intercept	-6.276	0.946	0.000		
	HAQ-DI-T1	1.521	0.450	0.001	4.576	1.894-11.056
	PHQ9-T1	0.154	0.057	0.007	1.166	1.043-1.303
	TJC-T1	-0.526	0.131	0.000	0.591	0.457-0.765
	TJC-change	0.287	0.107	0.007	1.332	1.081-1.642
	SJC-change	0.659	0.204	0.001	1.933	1.297-2.880
	Pain-change	-1.013	0.180	0.000	0.363	0.255-0.517
	SJC-T1	-0.983	0.228	0.000	0.374	0.239-0.585
	Pain-T1	1.310	0.208	0.000	3.706	2.467-5.566
Concordant to Positive Discordant (C¨PD)	Intercept	-2.686	.524	0.000		
	HAQ-DI-T1	0.544	0.396	0.170	1.723	0.793-3.744
	PHQ9-T1	0.146	0.056	0.009	1.158	1.038-1.291
	TJC-T1	-0.475	0.132	0.000	0.622	0.480-0.806
	TJC-change	0.431	0.128	0.001	1.538	1.198-1.975
	SJC-change	0.714	0.184	0.000	2.043	1.425-2.927
	Pain-change	-1.034	0.164	0.000	0.355	0.257-0.491
	SJC-T1	-0.607	0.189	0.001	0.545	0.377-0.789
	Pain-T1	0.670	0.164	0.000	1.955	1.418-2.696
Positive Discordant to Concordant (PD¨C)	Intercept	-2.981	0.567	0.000		
	HAQ-DI-T1	1.199	0.418	0.004	3.318	1.463-7.522
	PHQ9-T1	0.087	0.056	0.117	1.091	0.978-1.217
	TJC-T1	-0.193	0.135	0.154	0.825	0.633-1.075
	TJC-change	-0.085	0.079	0.283	0.919	0.787-1.072
	SJC-change	-0.111	0.109	0.311	0.895	0.722-1.109
	Pain-change	-0.205	0.163	0.207	0.815	0.592-1.120
	SJC-T1	-0.687	0.206	0.001	0.503	0.336-0.753
	Pain-T1	0.462	0.174	0.008	1.588	1.129-2.234

Disclosure: G. A. Karpouzas, None; **E. Hernandez**, None; **C. Cost**, None; **S. Ormseth**, None.

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Impact of Socioeconomic Status on Disease Outcomes in Japanese Patients with Rheumatoid Arthritis Under the Japanese National Insurance System

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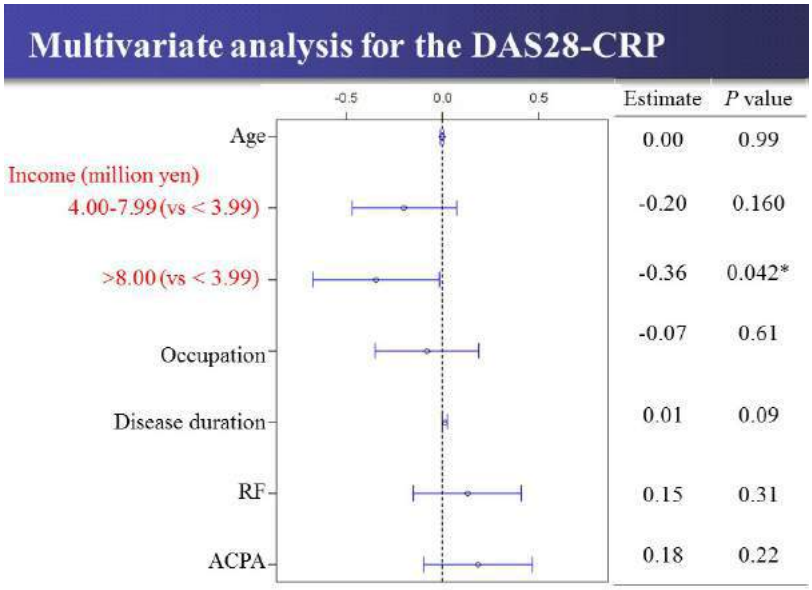
Background/Purpose: Several studies showed lower socioeconomic status (SES) was associated with higher disease activity and lower quality of life (QOL) in patients with rheumatoid arthritis (RA). However, health insurance system may influence the association between SES and disease outcomes. Because Japan has the unique national insurance system, all Japanese citizens are required to be enrolled in the national insurance system. In addition, most patients pay 30 % of medical cost whereas patients aged 70 and older, patients with low income and patients with disabilities pay 0 to 20 % of cost depending on age, income and severity of disabilities. The impact of SES on RA disease outcomes in the Japanese health system is still unknown because it has never been examined in a Japanese cohort. It is also important for policymakers in other countries to refer to Japanese findings when they make or improve their health insurance system. We evaluated the effect of SES among Japanese patients with RA on disease activity, activities of daily living (ADL) and QOL in the Japanese national health insurance system.

Methods: A questionnaire survey was conducted among 339 patients with RA in Kobe University Hospital. Clinical characteristics included age, sex, disease duration, Steinbrocker stage and class classification, rheumatoid factor, anti-citrullinated protein antibody, use of corticosteroid, methotrexate, and biologic. Disease activity was assessed according to the DAS28-CRP, ADL according to the Japanese version of the Health Assessment Questionnaire (HAQ), and QOL according to the Japanese version of the EQ-5D. SES included income, education level and occupation. Univariate and multivariate analyses were conducted to examine the association of SES with DAS28-CRP, HAQ and EQ-5D. Because proportion of biologic use and self-pay were assumed as the intermediate variables between SES and disease outcomes, we evaluated whether they were associated with SES to investigate the possible mechanism through which SES affected disease outcomes.

Results: Univariate analyses showed patients with lower income had significantly higher DAS28-CRP ($P = 0.03$) and HAQ score ($P = 0.001$). Although education level was not associated with DAS28-CRP, HAQ or EQ-5D, patients with occupation had lower HAQ score than patients without ($P < 0.001$). Multivariate analyses adjusted for the confounders revealed the similar results (Figure). Although patients with lower income had lower proportion of self-pay ($P < 0.001$), lower income was associated with lower proportion of biologic use.

Conclusion: SES may influence disease activity and ADL among patients with RA in Japan. Although Japanese health insurance system successfully decreased self-pay among patients with lower income, it did not have enough effectiveness to increase the proportion of biologic use among such patients. More efforts are needed to solve equity issue.



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Reproductive Tract Infections (RTI) in Indian (Asian) Women of Child Bearing Age Suffering from RA:I Don't Ask Them, They Don't Tell Me

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Background/Purpose: Several factors including disease process and drug therapy allegedly predispose to infections in RA. Socioeconomic constraints on our setting impose unique impediments. RTI are rampant in younger women (WHO, 1999). Similar data in RA is woefully lacking.

Methods: A convenience sample of 400 consenting patients (ACR 1988 classified, age group 15-49 years, median disease duration 3 years, 80% RF/CCP seropositive) under supervised standard rheumatology care in a popular community center (CRD) were selected. On physician global assessment, patients were classified 10% asymptomatic, 56% mild, 34% moderate-severe [88% methotrexate, 33% chloroquin, 46% prednisolone (< 7.5 mg daily)]. 32 patients recalled past urinary tract infections and 6 had concurrent diabetes. Patients were interviewed comprehensively using a-priori validated relevant questionnaires. Gynecological examination was supervised by a senior gynecologist (RR).Vaginal smears (wet mount) were quickly examined (gold standard) by microbiologist (AV) to diagnose RTI as per WHO recommendations for community based management of RTI in developing countries; classified into bacterial vaginosis (includes gonococci/chlamydia),candida and trichomonas infections. No further culture/characterization studies were carried out. Standard methods used for statistical analysis (SPSS). Sample size of 384 subjects was calculated based on ~40% prevalence of RTI (Government of India Family Health Survey 1998-99).

Results: Prior to this study, none of the patients had ever volunteered or been questioned on RTI in our setting. Currently, relevant symptoms and clinical signs were recorded by 42% and 45% patients respectively. 39.3% cohort were diagnosed RTI; 32% bacterial vaginosis, 6.5% candidiasis, 0.8% trichomoniasis. 26% of RTI were asymptomatic; 9% lacked signs. A combination of vaginal itching and discharge and low back pain was 100% sensitive and 83.7% specific for diagnosis of RTI. None tested seropositive for syphilis. Some relevant features pertaining to QOL and functional ability were – HAQ (Indian version) disability classify- 84% mild, 16% moderate-severe; SF-36 data-61% moderate severe body pain and ~8% with major limitation on bathing/dressing. Several independent significant ($p<0.05$) risk factors for RTI(on univariate analysis/ logistic regression) were identified -notably * Age< 30 years, *small house, public toilet, *use of indigenous sanitary pads during menses,*difficulty/inability for certain physical activities (bathing, toilet use, lifting/carrying groceries, arising from floor), nervousness, * DMARD use (not an individual drug or steroid except chloroquine). Those marked with asterisk remained significant in a multivariable analysis; adjusted odds ratio for DMARD use 3.96 (95% confidence interval 1.9, 7.9).

Conclusion: This cross sectional community based clinical study unraveled a large burden of RTI in women suffering from RA. Surprisingly, the prevalence was similar to national statistics. However, regular screening algorithms for RTI are urgently required to prevent neglect and improve overall standard care in rheumatology practice.

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Abstract Number: 121

Systemic Lupus Erythematosus (SLE) Is a Salient Cause of Premature Mortality in the United States: A Sex-Based Exploration

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Background/Purpose: The epidemiology of SLE has a complex gendered aspect, characterized by marked differences between the sexes in terms of the incidence, prevalence, and clinical manifestations. Males are reportedly less likely to be afflicted with SLE and women of childbearing age are disproportionately impacted. Females with SLE have more frequent exacerbations in general, but male patients appear to have significantly greater multi-systemic damage accrual and disease severity. Monitoring the fatal outcomes of SLE and frequency of common patterns of causes of death may offer insight into emerging health issues affecting contemporary SLE patients and can suggest the direction of future epidemiological investigations, particularly through a sex-based lens. This study provides a nuanced understanding of causes of deaths, related co-morbidities, and mortality differentials between males and females with SLE.

Methods: A cross-sectional study was performed on ~2.7 million death records from 2014 using the National Center for Health Statistics Multiple Cause of Death (MCOD) database, a population-based electronic medical recording of all death certificates issued in the United States. ICD-10 codes were isolated from the MCOD files and classified according to the Clinical Classifications Software (CCS), a well-developed categorization scheme that collapses ICD-10 codes into 260 clinically relevant categories. We compared sex-stratified demographic characteristics and the most frequently cited conditions in decedents with and without SLE. Relative risks quantified the risk of dying with the most frequently cited conditions among decedents aged ≤50 years comparing those with and without SLE to estimate the burden of premature deaths in this population.

Results: In 2014, there were 2,036 decedents with SLE in the United States. Females and Blacks comprised 86.2% and

30.7% of all SLE-related deaths, respectively. Female decedents with SLE died, on average, 22 years earlier (median age at death was 59 years) than those without SLE. Male decedents with SLE died 12 years earlier (median age at death was 61 years) than non-SLE males. Top causes of death in females and males with SLE were heart disease, diabetes, and hypertension. Among decedents aged ≤50 years, males with SLE had higher co-occurrence of coagulation and hemorrhagic disorders and chronic renal failure compared with those without SLE (RR: 16.69, 95% CI: 10.50-27.44; and RR: 5.76, 95% CI: 2.76-12.00, respectively). These co-morbid conditions were also important contributory causes of premature mortality among women, but to a lesser degree (RR: 4.98, 95% CI: 3.69-6.70; and RR: 8.55, 95% CI: 6.89-10.61, respectively).

Conclusion : Our findings identify important clinically relevant comorbidities that need to be considered more carefully in the course of patients' clinical management and the natural history of SLE disease.

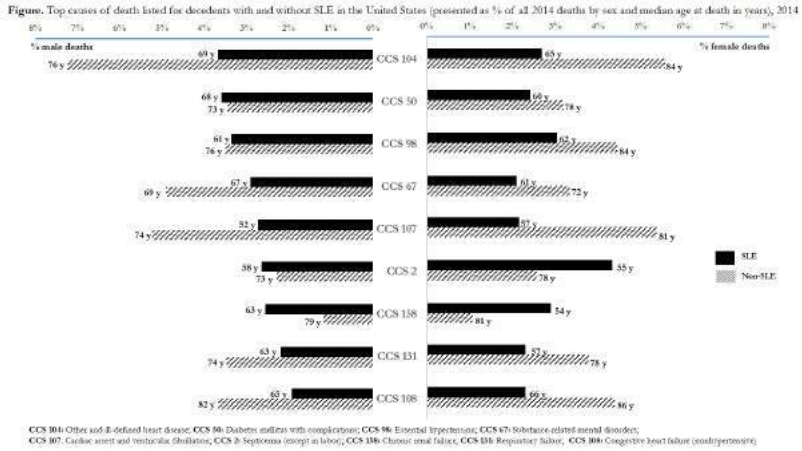

Figure. Top causes of death listed for decedents with and without SLE in the United States (presented as % of all 2014 deaths by sex and median age at death in years), 2014

CCS 104: Other and ill-defined heart disease; CCS 50: Diabetes mellitus with complications; CCS 98: Essential hypertension; CCS 67: Substance-related mental disorders; CCS 107: Cardiac arrest and ventricular fibrillation; CCS 2: Septicemia (except in labor); CCS 158: Chronic renal failure; CCS 131: Respiratory failure; CCS 108: Congestive heart failure (nonhypertensive)

Disclosure: T. Falasinnu, None; **J. F. Simard**, None.

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Abstract Number: 122

A Small Number of Patients with SLE Account for Most of the Direct and Indirect Hospitalization Costs

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that can affect multiple organ systems and is associated with high morbidity. Studies have shown that there is a substantial health care costs associated with hospitalization of SLE patients. Among chronic, complex disease, often a small percentage of patients account for the majority of health care spending. **Objective:** To identify if there is a high risk, high cost group of SLE patients among all hospital admissions for SLE over a 2 year period.

Methods: We conducted a financial analysis of all admissions for systemic lupus erythematosus at the Strong Memorial Hospital between the July 1st of 2013 and June 30thof 2015. The total number of admissions for diagnosis code 710.0 was calculated based on primary or secondary diagnosis for the 2 fiscal years. The diagnosis of SLE was confirmed based on the presence of at least 4 criteria or had to be made by a rheumatologist. The age at time of admission and age when diagnosis of SLE was first made, gender, race, reason for admission and the zip code of the primary residence were recorded. Additionally, we noted the number of readmissions within a year and readmission within a 30-day period. We then determined the total cost of admissions, readmission and recorded the length of stay for all admissions and readmissions.

Results: The total number of confirmed cases of SLE admissions for the 2 years was 387 that comprised 202 patients. Of these 175 (45%) were due to readmissions (within a year) and 113 (29%) were readmissions within a 30 day period. The total cost of all admissions was $10,353,617 for the 2 years while the cost of readmissions was $1,772,675.00 per year. The cost of all readmissions within the 30-day period was $1,182,375 for the 2 year period. The length of stay for all SLE admissions was 1,564 days per year. Approximately, 44% of admitted patients were of American origin with 60% residing within the city of Rochester.Further analysis showed that 28 (16%) of the patients accounted for about 40% of the total cost of all admissions ($3,900,156), 45% of the length of stay, 49% of all admissions and 76% of all 30-day readmissions. These high risk patients were more likely to be younger, have earlier onset of SLE, more likely to be African American and more likely to be from within the city limits. The average cost of hospitalization for the high risk patients was $150,000 compared to $51,808 for other SLE patients. See Table

Conclusion: Hospitalizations of patients with SLE is a major cause for health care costs and readmission rates for SLE are high. A small group of high risk, high cost patient's account for majority of the hospitalization costs and length of stay among all SLE patient hospitalizations. A high-riskcare management plan could substantially reduce costs and improve quality of care for these patients.

	High risk SLE patient	**SLE patient**
Average cost/patient/YEAR	$ 150,000.06	$ 51,808.41
Average LOS/patient	48.3 days	15.6 days
Mean age (at admission)	38.2 years	45.5 years
Mean age (at initial diagnosis)	20 years	30.2 years
AA: C: A: H	61%: 29%: 7%: 3%	44%: 49%: 2%: 4%
Females: Males	82%:18%	91%:9%
Rochester zip code	75%	60%

AA: African American; C: Caucasian; A: Asian; H: Hispanic; LOS-length of stay

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-small-number-of-patients-with-sle-account-for-most-of-the-direct-and-indirect-hospitalization-costs

Abstract Number: 123

A Panel of Urinary Biomarkers to Assess Renal Involvement in Latin American Patients with Systemic Lupus Erythematosus

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Background/Purpose: Some previous studies in Caucasian, Asian, and African-american patients have shown promising results for several urinary biomarkers in patients with lupus nephritis (LN). However, information regarding urinary biomarkers in Mestizo and Afro-Latin American patients is very limited. We investigated whether levels of urinary of monocyte chemoattractant protein 1 (MCP-1), neutrophil gelatinase-associated lipocalin (NGAL), ceruloplasmin (CP), transferrin (TP) and TWEAK are good biomarkers to differentiate patients with LN among Latin American SLE patients.

Methods: SLE patients meeting the revised ACR classification criteria for SLE were recruited from a referral University Hospital. Urinary levels of MCP-1, NGAL, CP, TF and TWEAK were measured using a commercial ELISA kits, R&D system, Minneapolis, USA for MCP-1, NGAL and TWEAK and Assaypro, Missouri, USA for CP and TF. Serum Anti C1q antibodies were measured by ELISA (Inova, San Diego, USA). SLE activity was measured with SLEDAI. Pearson or Spearman's rank correlations were used to examine associations between continuous variables. Additionally, ROC curves were done.

Results: 100 SLE patients were recruited (87% female) with median age of 33.4 ± 12.4 years and median disease duration of 7.6 ± 7.3 years. Mestizo (75%) and Afro-Latin American (22%) were majority. Mean SLEDAI score was 8.8 ± 9.0 and mean SLICC was 0.3 ± 0.6. Afro-Latin American had significantly higher prevalence of LN and serositis, and higher SLEDAI scores than Mestizo patients. All urinary biomarkers and anti C1q antibodies were significantly higher in patients with LN than in patients without LN. Additionally, NGAL, CP, TF and TWEAK were significantly higher in patients with active LN than in inactive LN (Table). NGAL levels were significantly higher in Afro-latin American patients (56 ± 56 vs 35 ± 46 pg/ml, $p=0.04$). No significant differences were found in urinary biomarkers levels among proliferative and non-proliferative forms of LN. We found significant positive correlation between all urinary markers and SLEDAI (r score ranging from 0.31-0.51, $p<0.05$ for all). A ROC curve for urinary biomarkers for LN in all SLE patients showed a good level of sensitivity and specificity for all, especially for CP (AUC 0.87), TF (AUC 0.84) and TWEAK (AUC 0.78).

Conclusion: In our cohort, Afro-Latin American were more severely affected with higher disease activity and more LN. We found several urinary biomarkers with good discriminative power to differentiate LN in Latin American SLE patients. Those markers were moderate correlated with disease activitiy. NGAL, CP, TF and TWEAK were significantly higher in patients with active LN.

Table. Urinary levels of several biomarkers and serum anti C1q antibodies according renal involvement and LN activity.

	Total SLE patients n=100	Group A LN n=66	Group B No LN n=44	p value A vs B	Group C Active LN* n=36	Group D Non-active LN N=21	p value C vs D
MCP-1 (mean ± SD), pg/ml	1678.6 ± 3722.3	2293.1 ± 4473.0	472.4 ± 596.5	**0.015**	1114.5 ± 1887.9	696.3 ± 1032.4	0.542
NGAL (mean ± SD), pg/ml	39.9 ± 48.9	54.4 ± 56.1	16.0 ± 16.6	**<0.001**	67.2 ± 60.8	20.8 ± 34.2	**0.014**
CP (mean ± SD), ng/ml	2618.1 ± 1392.0	3169.9 ± 1214.6	1778.4 ± 1296.2	**<0.001**	3640.3 ± 650.7	2428.3 ± 1423.1	**0.005**
TF (mean ± SD), ng/ml	1383.4 ± 562.3	1595.7 ± 397.8	978.8 ± 588.6	**<0.001**	1756.1 ± 102.0	1345.9 ± 583.1	**0.001**
TWEAK (mean ± SD) pg/ml	1552.6 ± 1666.7	1913.5 ± 1806.0	780.1 ± 1001.6	**<0.001**	2520.3 ± 1824	869.0 ± 1340.0	**<0.001**
Anti C1q (mean ± SD), IU	65.2 ± 75.5	77.9 ± 81.0	37.9 ± 57.5	**0.02**	92.2 ± 77.0	53.2 ± 79.7	0.129
* Active LN defined as current 24 hrs proteinuria levels > 500 mg/dl.	24 urine hours determination was not available	at the moment of urine biomarker	determination in 9 patients				

Disclosure: J. A. Gómez-Puerta, None; **B. L. Ortiz Reyes**, None; **T. Urrego**, None; **A. L. Vanegas**, None; **C. H. Muñoz**, None; **M. Restrepo**, None; **W. Rojas-Zuleta**, None; **S. Arteaga**, None; **L. A. Gonzalez**, None; **G. Vásquez**, None.

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Abstract Number: 124

Socioeconomic-Demographic, Disease Activity, Treatment and Immunologic Variables Affect B Cell Subtypes in Systemic Lupus Erythematosus

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Background/Purpose: B cell subset proportions within the B cell pool, also known as B cell signatures (BCS), reflect not only systemic lupus erythematosus (SLE) disease activity status, but also therapy effects. In this study, we evaluated

whether socioeconomic-demographic, disease activity, immunologic, and treatment factors, may influence BCS in SLE patients.

Methods: Peripheral blood mononuclear cells were isolated from 37 patients who fulfilled the ACR Classification criteria for SLE, and from 14 healthy individuals. Socioeconomic-demographic (age, ethnicity, primary language, highest level of education, health insurance), disease activity (duration, SLEDAI score), and immunologic variables (parity, anti-dsDNA), as well as type of treatment received (standard of care therapy (SCT) vs Belimumab), were collected. B cell subsets (nonmemory =T1, T2, Follicular Mature (FM); memory =IgM, IgM/IgD, IgD, switched) were identified via flow cytometry. Student T-Test, one-way ANOVA, Dunnett's and Tukey's post-hoc tests were used for statistical analyses.

Results: Ethnicity, race, age, level of education, and primary language do not alter B cell subsets in SLE patients. SLE patients with either HMO-private or federal health insurance have less T1 subsets as compared to those with HMO-public insurance ($p = 0.0004$). SLE patients with either HMO-private or federal insurance have more FM subsets as compared to SLE patients with HMO-public insurance ($p = 0.0041$). Both T2 ($p = 0.0030$) and IgD ($p = 0.0389$) subsets from SLE patients with SLEDAI score 1-5 were lower as compared to healthy controls. Patients with SLE duration of disease from 0-5 or 6-10 years have lower T2 subsets as compared to healthy controls ($p = 0.0020$). Patients with SLE duration from 0-5 years have higher FM subsets as compared to healthy controls ($p = 0.036$). SLE patients have lower proportions of T2 subsets, irrespective of the presence or absence of anti-dsDNA, as compared to healthy controls ($p = 0.0052$). The presence of anti-dsDNA is associated with lower IgD subsets as compared to healthy controls ($p = 0.0204$). SLE patients with children have lower T1 ($p = 0.0326$) and higher FM ($p = 0.0448$) subsets as compared to those with none. SLE patients treated with SCT have lower T1 subsets as compared to those treated with both SCT and Belimumab ($p = 0.0303$). SLE patients treated with either SCT or Belimumab have lower T2 cells as compared to healthy controls ($p = 0.0102$). SLE patients treated with SCT have lower switched B cells as compared to those treated with both SCT and Belimumab ($p = 0.0064$). SLE patients treated with both SCT and Belimumab have higher switched B cells as compared to healthy controls ($p = 0.0064$).

Conclusion: To our knowledge, this is the first study showing that socioeconomic-demographic, disease activity, and immunologic variables are associated with unique B cell profiles in SLE patients.

Disclosure: A. Bravo, None; **M. T. Ngo**, None; **M. De Vera**, None; **K. M. D. Torralba**, GlaxoSmithKline, 9,ACR, USSONAR, 9; **A. Benitez**, None.

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Abstract Number: 125

Increased Hypertension and Renal Disease in African Americans Compared to Caucasians with Systemic Lupus Erythematosus

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Background/Purpose: African Americans have higher rates of SLE and SLE nephritis compared to Caucasians. These epidemiologic associations come mainly from cohort studies that collect standardized information on SLE-related conditions but may not take advantage of the longitudinal data on comorbidities in the electronic health record (EHR). We assessed differences in comorbidities in African Americans vs. Caucasians with SLE using an EHR-based phenome-wide association study (PheWAS). Similar to genome-wide association studies, a PheWAS compares two groups using ICD-9 codes in place of single nucleotide polymorphisms.

Methods: We used our validated algorithm of ≥ 4 counts of the SLE ICD-9 code (710.0) and ANA positive ≥ 1:160 while excluding dermatomyositis and systemic sclerosis ICD-9 codes to identify SLE cases in a de-identified EHR called the Synthetic Derivative (SD). The SD contains over 2.5 million subjects with clinical data collected longitudinally over several decades. Our algorithm has an internally validated positive predictive value of 94% and a sensitivity of 86%. PheWAS was performed in African Americans vs. Caucasians adjusting for age and sex in logistic regression models and correcting for multiple testing using Bonferroni. PheWAS excludes subjects that have a one time count for an ICD-9 code to minimize the effect of coding errors.

Results: We identified 270 African Americans and 715 Caucasians with SLE. African Americans and Caucasians were predominantly female (89% vs. 90%, $p = 0.83$) with African Americans having a significantly younger current mean age (44 ± 17 vs. 53 ± 17, $p < 0.001$) and age at first SLE ICD-9 code (35 ± 16 vs. 43 ± 17, $p < 0.001$) with similar mean years of follow-up in the EHR (9 ± 5 vs. 10 ± 5, $p = 0.10$). Adjusting for sex and current age, compared to Caucasians, African Americans had 48 ICD-9 based phenotypes that met the Bonferroni threshold for significance ($p < 1.30 \times 10^{-4}$) including mostly renal and cardiac codes. The most significant codes were hypertension odds ratio (OR) = 4.25 (95% CI 3.05 – 5.92), $p = 1.43 \times 10^{-17}$, renal dialysis OR = 10.90 (95% CI 6.11 – 19.48), $p = 6.83 \times 10^{-16}$, and hypertensive heart and/or renal disease OR = 6.41 (95% CI 4.04 – 10.16), $p = 2.77 \times 10^{-15}$ (Table 1). Compared to Caucasians, African Americans were more likely to have codes related to SLE ACR criteria including pleurisy/pleural effusion, nephritis, pericarditis, pancytopenia, and joint effusions (all $p < 0.05$).

Conclusion: Using a large EHR, we found that African Americans had more codes related to ACR SLE criteria including renal disease as well as hypertension. While in the general population African Americans are twice as likely to have hypertension compared to Caucasians, our data show an even more pronounced effect in African Americans vs. Caucasians with SLE. Additional studies are needed to determine the mechanisms for this racial disparity.

Table 1.

ICD-9 Codes	Code Present	Code Absent	Adjusted Odds Ratio for current age and sex (95% CI)	p value
Hypertension (401)	423	494	**African American:** 4.25 (3.05 – 5.92) **Caucasian**: 1.00 (ref)	$p = 1.43 \times 10^{-17}$
Essential hypertension (401.1)	408	494	4.24 (3.03 – 5.94)	$p = 4.00 \times 10^{-17}$
Renal dialysis (585.31)	73	600	10.90 (6.11 -19.48)	$p = 6.83 \times 10^{-16}$
Hypertensive heart and/or renal disease (401.2)	119	494	6.41 (4.04 -10.16)	$p = 2.77 \times 10^{-15}$
Other anemias (285)	266	557	3.86 (2.75 – 5.41)	$p = 4.43 \times 10^{-15}$
End stage renal disease (585.32)	76	600	8.57 (4.97 – 14.79)	$p = 1.12 \times 10^{-14}$
Hypertensive chronic kidney disease (401.22)	103	494	6.63 (4.08 – 10.77)	$p = 2.27 \times 10^{-14}$
Acute renal failure (585.1)	149	600	4.43 (2.98 – 6.60)	$p = 2.19 \times 10^{-13}$
Pleurisy/pleural effusion (507)	127	700	4.39 (2.92 – 6.62)	$p = 1.30 \times 10^{-12}$

Disclosure: A. Barnado, None; **R. Carroll**, None; **C. Casey**, None; **J. C. Denny**, None; **L. J. Crofford**, None.

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Abstract Number: 126

Anti-Neutrophil Cytoplasmic Antibodies (ANCA) in African-American Patients: Disease Associations and Clinical Outcomes in an Urban Cohort

Philip McCarthy[1], Jenna Hudy[2], Marie Melville[2], Danielle Robson[1], John McKinnon[2], Sandeep Soman[2] and Kathleen Maksimowicz-McKinnon[3], [1]Michigan State University College of Osteopathic Medicine, East Lansing, MI, [2]Henry Ford Hospital, Detroit, MI, [3]Rheumatology, Henry Ford Hospital, Detroit, MI

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Background/Purpose: Antineutrophil cytoplasmic antibody-associated vasculitis (AAV) has been most extensively described and studied in non-African-American populations. The significance of and associations with ANCA in African-Americans, especially outside of AAV, has not been well characterized.

Methods: Retrospective chart review of patients self-identified as African-American with positive ANCA testing was performed. Records were reviewed in detail to classify patients as definite AAV using the revised Chapel Hill 2012 AAV criteria, probable AAV (in patients in whom biopsy evidence was absent but with a preponderance of clinical and serologic evidence to support the diagnosis), possible AAV (no biopsy evidence, compatible clinical/serologic picture, but less compelling evidence), and unlikely AAV. The presence of other autoimmune disorders, infectious disorders, and medications known to be associated with ANCA positivity were also documented.

Results: 77 African-American patients with ANCA were identified, of which 49 (63.6%) were female with a mean age of 57 at symptom onset. Of these patients, 21 had established AAV (27.3%), 3 had probable AAV (3.9%), 14 had possible AAV (18.2%) and 10 (13%) were deemed unlikely to have AAV. Eleven patients (14.3%) had drug-induced vasculitis, either from hydralazine or cocaine use. Sixteen patients (20.8%) had other autoimmune diseases, and of these, half were determined to have active vasculitis. Only 2 patients (2.6%) had vasculitis secondary to chronic viral infection (hepatitis). Patients most often were P-ANCA positive (51.9%), and often had other positive autoimmune serologies including antinuclear antibodies (42.9%) and rheumatoid factor (18.2%). Remarkably, 30 patients (38.9%) developed end-stage renal disease (ESRD). Considering other common comorbidities in this population potentially related to renal failure, diabetes mellitus (DM) was present in 20.7% of patients (mean duration=2 years, mean glycated hemoglobin=6.2) and hypertension (HTN) in 76.6% (mean duration 8 years, mean number of medications=1). Fourteen patients (18.1%) died, with a mean time to death of only 10 months from the time of their underlying diagnosis associated with ANCA.

Conclusion: ANCA are often detected in conditions other than AAV in African-American patients, and are frequently associated with other etiologies of vasculitis. Over one-third of African-American patients with ANCA developed ESRD, which given the data regarding HTN and DM in this population, seems unlikely to be wholly attributable to these comorbidities alone. Further study to explore the potential pathogenic role of ANCA in African-American patients, especially in regard to renal disease, is warranted.

Disclosure: P. McCarthy, None; **J. Hudy**, None; **M. Melville**, None; **D. Robson**, None; **J. McKinnon**, None; **S. Soman**, None; **K. Maksimowicz-McKinnon**, None.

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Abstract Number: 127

Disease Characteristics and Outcomes in African-American Patients with Antineutrophil Cytoplasmic Antibody-Associated Vasculitis: a High Risk Group for Poor Outcomes

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Background/Purpose: Antineutrophil antibody-associated vasculitis (AAV) has been most extensively described and studied in non-African American populations. Little is known about the characteristics and outcomes of AAV in African American patients.

Methods: Retrospective chart review of patients self-identified as African-American with positive antineutrophil cytoplasmic antibody testing was performed. Records were reviewed in detail to establish disease classification of patients using the revised Chapel Hill 2012 AAV criteria.

Results: 21 patients with definite AAV were identified (10 GPA, 8 MPA, 3 with isolated renal AAV). Fourteen (66.7%) were female, with a mean age at symptom onset of 59 years. 4 patients (19%) were C-ANCA/PR-3 positive, all of whom had GPA. 100% of isolated renal AAV and 75% of MPA patients were P-ANCA/MPO positive. Nine patients (42.8%) were antinuclear antibody positive, and 5 patients (23.8%) had a positive rheumatoid factor. At the time of diagnosis for the 18 GPA and MPA patients, recurrent sinusitis was found in 12 patients (66.7%), but otalgia or otitis was less common, noted in only 4 patients (22.2%) Sixteen patients (88.9%) had pulmonary infiltrates, ten patients (55.6%) had diffuse alveolar hemorrhage, and 8 patients (44.4%) required mechanical ventilation at presentation. 11 patients (52.3%) of the entire cohort required hemodialysis at presentation, and 12 patients (57.1%) ultimately developed end stage renal disease (ESRD). Fourteen patients had concomitant hypertension, with a mean number of antihypertensive medications of 1.7. Seven patients had diabetes mellitus, with a mean glycated hemoglobin of 7.5 and mean duration of disease of 7.7 years. 9 patients (42.8%) developed at least one relapse, with a mean time to relapse of 20.5 months following diagnosis. Eight patients (38%) died, with a mean time to death from diagnosis of 32 months.

Conclusion: African-American patients with AAV frequently present with pulmonary and renal manifestations, which are often severe at onset, requiring supportive care. More than half of this cohort went on to develop ESRD, and over one-third died on average within 3 years following their diagnosis, demonstrating that AAV may have an aggressive course in these patients. There are many possible factors that could influence these outcomes, including other comorbid conditions, delay in diagnosis, genetics, environmental factors, and limited access to care. Further study is needed to better understand factors that influence AAV severity and course in this population in order to improve long-term outcomes and survival.

Disclosure: P. McCarthy, None; **D. Robson**, None; **J. Hudy**, None; **M. Melville**, None; **J. McKinnon**, None; **S. Soman**, None; **K. Maksimowicz-McKinnon**, None.

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Abstract Number: 128

Call to Action: Cardiovascular Comorbidities in Medicare Rheumatology Beneficiaries

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SESSION INFORMATION
Session Date: Sunday, November 13, 2016
Session Title: Healthcare Disparities in Rheumatology - Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Cardiovascular (CV) manifestations of Rheumatological inflammatory diseases have become increasingly recognized, and, in some patients, might even constitute the initial presentation of a Rheumatological disorder. The objective of this study was to examine the CV co-morbidities in Medicare beneficiaries using 2013 aggregated Part B Medicare data.

Methods: Aggregated tables by physician national identifier as well as State and HCPCS codes have been made available with beneficiary demographic and health characteristics. The 2013 data is based on all Medicare part B non-institutional claims. Since claims data is used for payment, it is felt that the documentation of disease processes is reliable. For each chronic condition outlined in table, the prevalence was averaged across all providers. Population numbers were calculated by multiplying unique beneficiary counts by percent prevalence. National disease prevalence percentages and numbers were obtained from the Medicare chronic conditions warehouse. Complete cases of data where then extracted to examine state trends. Beneficiary numbers with the respective disease were calculated, aggregated and plotted by state.

Results: Mean beneficiary age was 70 years with the majority of females, white, and aged between 65 to 74 (Table 1). The prevalence of hypertension (65%) and hyperlipidemias (53%) were highest CV comorbidities and were higher compared to the national figures. (Table 1). Moreover, all comorbidities were higher in the rheumatology beneficiary population compared to the national population. Ischemic heart disease prevalence was 32% compared to 19% in the national population. Of note, the prevalence of diabetes was slightly lower (29%) than the ischemic heart disease in both populations. State trends revealed that the highest prevalence of cardiovascular comorbidities was in Florida, even though California has the largest beneficiary population (Figure 1). The pattern of prevalence of hypertension and hyperlipidemia were closely related over all the states.

Conclusion: The past decade has brought many new insights regarding excessive burden of CV co-morbidities associated with Rheumatological inflammatory diseases. This study has highlighted strong evidence of high CV co-morbidities prevalence among Medicare beneficiaries placing this group under high CV risk category based on the recent national guidelines. Taken together, these findings underscore the complexity of the Rheumatological inflammatory diseases and highlight the key role of further epidemiological research in understanding these intriguing conditions. In addition, priority should be given to pay attention to control of factors affecting CV co-morbidities in this high-risk population.

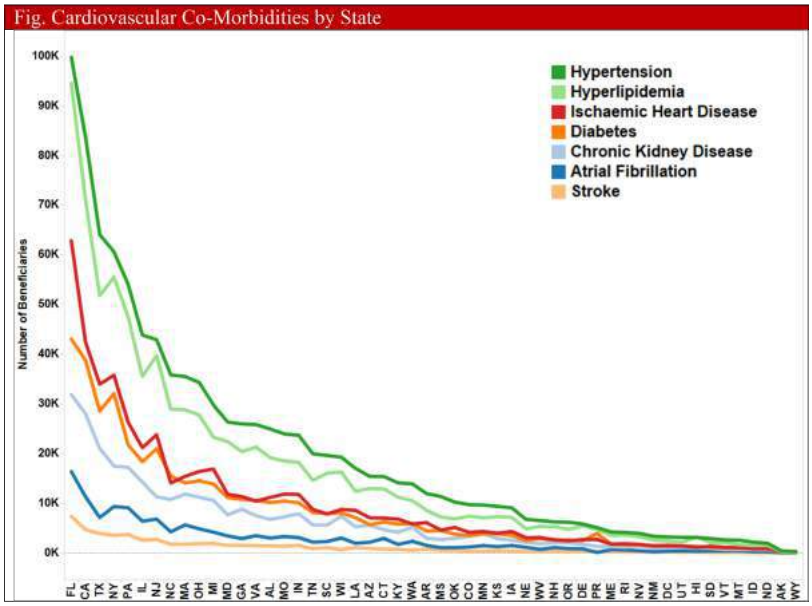
Table 1: Key Demographic Factors

Demographic Factors	Number (Percentage)
Number of Female Beneficiaries	1,151,417 (75%)
Number of Male Beneficiaries	385,537 (25%)
Number of Non-Hispanic White Beneficiaries	1,184,949 (77%)
Number of Black or African American Beneficiaries	109,147 (7%)
Number of Hispanic Beneficiaries	75,352 (5%)
Number Other Race	26,352 (2%)
Average Age of Beneficiaries	70
Number of Beneficiaries Age 65 to 74	648,220 (42%)
Number of Beneficiaries Age 75 to 84	427,337 (28%)
Number of Beneficiaries Age Greater 84	150,172 (10%)
Number of Beneficiaries Age Less 65	287,963 (19%)

Table 2: Prevalence of Cardiovascular Co-morbidities

Chronic Condition	National Prevalence (n=55,277,442)	Rheumatology Beneficiary Prevalence (n=1,543,431)
Hypertension	20,426,302 (37.0%)	1,015,681 (65.3%)
Hyperlipidemia	16,347,454 (29.6%)	843,412 (53.0%)
Ischemic Heart Disease	10,547,270 (19.1%)	503,626 (32.4%)
Diabetes	10,441,385 (18.9%)	439,879 (29.2%)
Chronic Kidney Disease	6,050,057 (10.9%)	319,692 (22.2%)
Heart Failure	5,355,637 (9.7%)	249,987 (17.3%)
Atrial Fibrillation	2,863,545 (5.2%)	141,915 (9.7%)
Stroke / Transient Ischemic Attack	1,378,435 (2.5%)	57,944 (4.7%)

Rheumatology prevalence is calculated by averaging the percent prevalence of the chronic condition per provider.
Source:
1. https://www.ccwdata.org/web/guest/medicare-tables-reports accessed 5-3-2016
2. 2013 PUF Aggregate Table



Disclosure: G. S. Kaeley, None; **S. Dodani**, None.

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Abstract Number: 129

Ultrasound Is More Reliable Than Inflammatory Parameters (ESR and CRP) to Evaluate Disease Activity in Rheumatoid Arthritis Patients on Tocilizumab Therapy

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases - Poster I: Ultrasound and Emerging Technologies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The goal of therapy of rheumatoid arthritis(RA) is to achieve a remission or at least low disease activity. Tocilizumab completely interrupt the effect of IL-6 and showed a full inhibition of CRP production[1]. So we are interested in whether it will influence the outcome measure to predict RAactivity in daily practice.This study aimed to investigate whether RA patients on tocilizumab therapy had the same efficacy on ultrasound and inflammatory parameters as compared with adalimumab treatment.

Methods: We compared RA patients on tocilizumab and adalimumab therapy and evaluated inflammatory parameters and ultrasound score. Gray scale synovial hypertrophy (SH) and power Doppler (PD) ultrasound were performed on bilateral dorsal radio-carpal joints of in patient. The sum of the score was calculated.Independent t test was used to compare inflammatory mediators and ultrasound scores between tocilizumab and adalimumab.

Results: A total of 48 patients with RA (24 tocilizumab and 24 adalimumab) were enrolled. The age, gender, rheumatoid factors and ACCP were no difference between these two groups. The mean ultrasound was 2.33±1.40 (Tocilizumab) and 2.08±1.53 (Adalimumab), p=0. 570. The ESR , CRP and DAS 28 were lower at Tocilizumab group. (Table 1)

Conclusion: From this study, in patients on tocilizumab therapy, the laboratory parameter and clinical evaluation was lower than adalimab depite the same ultrasound score beteen the two group. So we cannot measure disease activity based only on clinical evaluation. We suggest using PD ultrasound evaluation in all the patients on tocilizumab therapy to actually reflect the true nature of disease entity in these patients.

Table 1.Comparison between tocilizumab and adalimumab group based on laboratory and ultrasound score

	Tocilizumab(n=24)	Adalimumab(n=24)	P value
ESR (mm/hr)	20.75±25.19	47.38±26.22	0.001
CRP (mg/L)	0.97±0.89	11.71±12.43	0.001
DAS28	5.33±0.63	5.90±0.69	0.003
Ultrasound scores	2.33±1.40	2.08±1.53	0.558

Disclosure: Y. C. Chen Sr., None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ultrasound-is-more-reliable-than-inflammatory-parameters-esr-and-crp-to-evaluate-disease-activity-in-rheumatoid-arthritis-patients-on-tocilizumab-therapy

Abstract Number: 130

Anti-CCP Status Determines the Power Doppler Oscillation Pattern in Rheumatoid Arthritis – a Prospective Study

Ottar Gadeholt[1], Tobias Wech[2], Sebastian Schuh[1], Eva Christina Scharbatke[1], Eva Niederle[1], Hans-Peter Tony[3] and Marc Schmalzing[4], [1]Rheumatology/Immunology, Medical Clinic II, University Clinic Wuerzburg, Wuerzburg, Germany, [2]Experimental Rradiology, University Clinic Wuerzburg, Wuerzburg, Germany, [3]Rheumatology/Immunology, Medical Clinic II, University Clinic Wuerzburg, Würzburg, Germany, [4]Rheumatology/Clinical Immunology, Medical Clinic II, University Clinic Wuerzburg, Würzburg, Germany

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Title: Anti-CCP Status Determines the Power Doppler Oscillation Pattern in Rheumatoid Arthritis – a Prospective Study Abstract:

Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease leading to joint destruction. Serologically, it can be differentiated according to rheumatoid factor (RF), anti-cyclic-citrullinated-peptide antibodies (anti-CCP) or both. This differentiation is prognostically and therapeutically relevant. No method has been described to separate the two forms phenotypically. We hypothesize that a differentiation is possible by evaluating oscillation patterns in power Doppler sonography (PDS).

Methods: In a prospective study, 20 patients with anti-CCP-positive RA and 20 patients with anti-CCP-negative RA with active wrist synovitis were examined. A PDS scan was performed, and perfusion maxima (Pmax) and minima (Pmin) as well as the difference (ΔP) were determined by a blinded study member. The difference was standardized (sΔP) by dividing by Pmax, and the anti-CCP-positive and -negative patients as well as the RF-positive and -negative were compared to each other.

Results: In the ultrasonographic evaluation we found a highly significant difference in sΔP between anti-CCP positive and

anti-CCP negative patients (Median 19.01% vs. 42.92%, p<0.0001) (Fig.1). sΔP is independent of disease activity. ΔP did not differ between the groups. Also, in anti-CCP-positive patients there was a completely linear correlation between Pmax and Pmin, this was far less marked in anti-CCP-negative patients (Fig.2). The difference between RF positive and RF negative patients was significant, but less pronounced than for anti-CCP.

Conclusion: Anti-CCP-positive and anti-CCP-negative RA display different PDS oscillation patterns. This constitutes a non-serological parameter to differentiate between the two forms. The difference in PDS oscillation patterns suggests that the underlying pathological process differs between the forms.

Fig.1: Comparison of sΔP between CCPp and CCPn patients

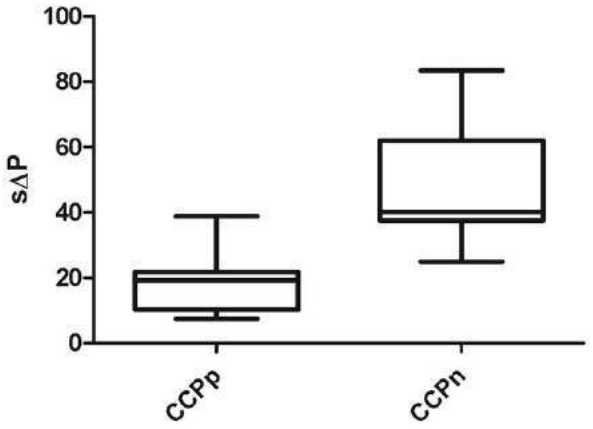
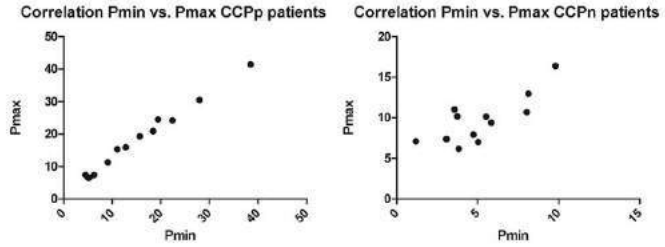


Fig. 2: Correlation between Pmin and Pmax for CCPp and CCPn subgroups
(Note different scale of the X- and Y-axis)



Disclosure: O. Gadeholt, None; **T. Wech**, None; **S. Schuh**, None; **E. C. Scharbatke**, None; **E. Niederle**, None; **H. P. Tony**, Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 5,Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 8; **M. Schmalzing**, None.

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Abstract Number: 131

Analysis of Correlation and Causes for Discrepancy Between Quantitative and Semi Quantitative Doppler Scores in Synovitis in Rheumatoid Arthritis

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Background/Purpose: Doppler ultrasound plays an increasing role for monitoring disease activity in rheumatoid arthritis (RA). This study aimed to evaluate the association between two semi-quantitative color Doppler ultrasound scoring systems (SQS) currently in use, and the novel quantitative scoring (QS) of color Doppler pixel count.

Methods: Adult patients with RA and inadequate clinical response to anti-rheumatic therapy were examined with musculoskeletal ultrasound (MSUS) upon entering a prospective study with add-on therapy. Dorsal MSUS of the wrists, metacarpophalangeal joint (MCP) 2-5 and metatarsophalangeal joint (MTP) 2-5 in both sides were performed. All MSUS images with sign of synovitis were collected and the QS was measured. Five assessors blinded to the QS evaluated all the images independently from each other, according to either SQS method. Association between QS and SQS was studied using correlations and multilevel models taking into account the clustering of ratings at the rater, patient and joint levels.

Results: Analysis of the 1190 ratings collected revealed a strong correlation (ρ=0.89, $p<0.0001$) and significant associations ($p<0.0001$, for all multilevel models) between QS and SQS. Correlations between QS and SQS according to Szkudlarek et al. (ρ=0.87, $p<0.0001$) or Hammer et al. (ρ=0.91, $p<0.0001$) were similar. A total of 239 (20.1%) images were given a SQS grade that did not match that expected based on initial QS, using predefined cutoffs. Main explanations for discrepancies were different perceived region of interest (ROI) (40.7%) and Doppler pixel count near cutoffs between SQS grades (32.3%).

Conclusion: We showed that both SQS methods correlated well with QS to assess synovial activity in RA. This suggests that any of these methods can be used to assess synovial activity in RA, but also that SQS methods are intrinsically limited when the Doppler pixel count is close to the cutoffs between the SQS grades. Another main reason for discrepancy was different perceived ROI that might underline the need for further consensus on how to define the ROI at the joint level. Analysis discrepancies between these methods may help guide further revision of criteria used to assess disease activity with MSUS in RA.

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Abstract Number: 132

Ultrasound Performed Among RA Patients in Real Life Setting Can Predict Loss of Remission, Especially When Done Early after Reaching Remission

Pascal Zufferey[1], Giorgio Tamborrini[2], Burkhard Moeller[3], Adrian Ciurea[4], Laure Brulhart[5], Sandra Blumhardt[6], Martin Toniolo[7] and Hans Ruedi Ziswiler[8], [1]Department of Rheumatology, University Hospital Lausanne, Lausanne, Switzerland, [2]Bethesda spital, Basel, Switzerland, [3]Rheumatology & Clin Immunology, Inselspital Bern, Bern, Switzerland, [4]Center of Experimental Rheumatology, University Hospital Zurich, Zurich Schlieren, Switzerland, [5]médecine, hôpital neuchateulois, La chaux de fond, Switzerland, [6]rheumatology, USZ, zurich, Switzerland, [7]Department of Rheumatology, University Hospital of Zurich, Zurich, Switzerland, [8]Osteorheuma, Bern, Switzerland
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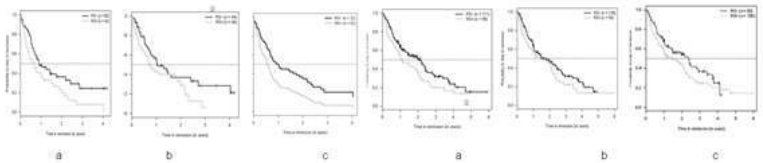
Background/Purpose: Previous publications have suggested that patients in clinical remission with residual ultrasound (US) synovitis flare more often and do not stay in remission as long as those without residual US synovitis. Those studies based essentially on Doppler mode have been performed in single centers by a few highly skilled operators. Recent studies performed among real life cohort have however shown that the predictive value of US could be not be as clear as previously suggested. The objective of this study was to investigate the predictive value of US residual synovitis on loss of remission in a real life settings and in particular how the time point when ultrasound was performed influence remission survival

Methods: This is retrospective longitudinal cohort study nested into the Swiss RA registry (SCQM) registry. It included all RA patients with at least one US score done in clinical remission (DAS<2.6) and at least two clinical evaluations implemented in the registry between 2009 and 2016. US significant residual synovitis was based on the Swiss SONAR score, which adopted the single joint definition of pathologies according to OMERACT for 22 joints using both a B mode and a Doppler mode. Flare was defined as DAS >2.6 or change in medication. Duration of remission was calculated either since the first visit before US with a DAS <2.6 or the last visit with a DAS>2.6. An early US subset group was defined when US performed within 6 months after start of remission. Left and right imputation analysis were applied to better estimated the real duration of remission before and after US was performed. Several cofactors for loss of remission were also analyzed.

Results: 264 RA patients were included. 328 eligible remission phases were available. 103/261 remissions were considered as early US (<6 months) according to the predefined mode of calculation. 198 loss of remission was objectivized in the overall cohort and 84 in early US subgroup. Time in remission before US whatever score used was the only independent covariate factor in both the overall cohort and the early US subgroup. The table summarized the hazard ratio for loss of remission adjusted for time in remission and other covariate using left (L) and right imputation (R) according to: B mode (>2 grade 2 synovitis), Doppler mode and combined score in the total cohort and in the early USsubset . Median times to loss of remission using B mode were 2.1 (95% CI: 1.4, 2.4) for US- and 1.1 year (95% CI: 0.9, 2) for US+ (log-rank p-value = 0.024) in the early subset group (right imputation).

	HR	Lower 95	Upper 95
Overall cohort: L/R	L/R	L/R	L/R
B mode n=328	1.2/1.3.	0.95/0.97	1.7/1.7
Doppler n=297	1.1/1.2	0.83/0.89	1.5/1.6
Combined score , n=281	1.3/1.4	0.95/*1.01*	1.9/2
Early US: L/R			
B mode, n=103/261	*2/1.5*	*1.2/1.08*	*3.2/2.1*
Doppler, n= 88/261	1.3/1.2	0.70/0.87	2.4/1.8
Combined score, n=84/221	1.7/1.4	0.88/0.96	3.3/2

Figure below summarize Kaplan -Meyer plot of time to loss of remission in the early US subset group according to a: B mode, b: Doppler mode, c: combined scores (left / right imputation).



Conclusion: Our study confirmed that ultrasound has a modest independent predictive value for loss of remission when applied in a real life cohort. In this condition, US done early in remission using B mode seems to have the best predictive

value.

Disclosure: P. Zufferey, None; **G. Tamborrini**, None; **B. Moeller**, None; **A. Ciurea**, None; **L. Brulhart**, None; **S. Blumhardt**, None; **M. Toniolo**, None; **H. R. Ziswiler**, None.

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Abstract Number: 133

Agreement Between DAS28-ESR, DAS28-CRP, SDAI, CDAI (Simplified/Clinical Disease Activity Index), ACR/EULAR Remission Criteria and Ultrasound Scoring (Naredo-12) in Patients with Rheumatoid Arthritis in Routine Care

Marion Cugnet[1], Mélanie Trabelsi[2], Paul Ornetti[1], Philippe Gaudin[3], Stéphanie Rouanet[4] and **Athan Baillet**[2], [1]Rheumatology, Dijon University Hospital, France, Dijon, France, [2]Rheumatology, Grenoble University Hospital, France, Echirolles, France, [3]Grenoble University Hospital, France, Grenoble, France, [4]StatEthic, Levallois-Perret, France, Levallois Perret, France

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Session Time: 9:00AM-11:00AM

Background/Purpose: Clinical remission is now a realistic goal in managing rheumatoid arthritis (RA) with treat to target strategy assessed according to different composite scores (DAS28, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), ACR-EULAR 2011 for remission). There are, however, no validated ultrasound remission criteria because of continuing uncertainty on the signification of persistent synovial hypertrophy in B-mode or Power Doppler (PD) mode in RA patients in clinical remission. Objective: evaluate correlations between the validated 12 joints-Naredo ultrasound score (B-mode (0-3), PD (0-3), combined B+PD (0-6) or PDUS (0-3, max between B-mode or PD)) and the DAS28-ESR, DAS28-CRP, CDAI, SDAI and ACR-EULAR criteria for remission in routine care.

Methods: French multicenter cross-sectional study in 11 rheumatology departments. The inter and intra-observer reproducibility for the ultrasound scoring was good to excellent. Inclusion criteria were as follows: RA meeting ACR-EULAR criteria, <15 years of progression, DAS-28-ESR<2.6 for at least 3 months, with a stable treatment including corticoids if necessary (equivalent prednisone<0.1 mg/kg) for 6 months. A standardized US examination was performed by an experience ultrasonographist blinded to clinical data. Spearman's correlation coefficients were determined between the Naredo12 B-mode (min-max,0-36), PD mode (0-36), combined mode (0-72) and PDUS (0-36) scores and the different clinical remission scores. The impact of disease duration or duration of the clinical remission on ultrasound scores was also assessed (Kruskall-Wallis's test).

Results: 225 patients were included consecutively (58.6±12.4 years, 68.4% women, RA duration 6±3.7ans, 71.3% ACPA+, duration of remission 20.8±19.4 months, 92% on methotrexate, 52.4% on biotherapy, 9.8% on corticoids, DAS28-ESR=1.7, 75% in ACR-EULAR remission). 68.9% of patients had a PD Naredo score of 0, 82.7% ≤ 1, 90.7%≤2. Table 1 presents correlations between ultrasound scores and clinical scores. These correlations were weak to moderate, depending on the set of criteria. No association was found between ultrasounds scores and duration of the remission or of the disease.

Conclusion: The Naredo score in PD mode showed the best construct validity whatever the clinical score chosen, even though the correlations remained relatively weak, in part because of differences between the joints analyzed (12 US joints including ankles vs. 28 clinical joints without ankles). The CDAI and SDAI, which are more stringent for clinical remission appeared to correlate better than the DAS28-ESR score which is the most widely used in everyday practice. Other real–life studies are necessary to evaluate the potential added value of this combined US-clinical assessment of RA

remission in routine care.

	DAS28-VS	DAS28-CRP	CDAI	SDAI
Naredo 12 combined (0-72)	0.113 (-0.01; 0.24)	0.281 (0.15; 0.40)	0.251 (0.12; 0.38)	0.273 (0.15; 0.39)
Naredo in B-mode (0-36)	0.086 (-0.04; 0.21)	0.253 (0.12; 0.37)	0.202 (0.07; 0.32)	0.228 (0.10; 0.35)
Naredo in D-mode (0-36)	0.192 (0.06; 0.01)	0.229 (0.09; 0.35)	0.323 (0.20; 0.43)	0.315 (0.19; 0.43)
Naredo in PDUS (0-36)	0.089 (-0.04; 0.22)	0.257 (0.13; 0.38)	0.214 (0.09; 0.34)	0.238 (0.11; 0.36)

Disclosure: M. Cugnet, None; **M. Trabelsi**, None; **P. Ornetti**, None; **P. Gaudin**, None; **S. Rouanet**, None; **A. Baillet**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/agreement-between-das28-esr-das28-crp-sdai-cdai-simplifiedclinical-disease-activity-index-acreular-remission-criteria-and-ultrasound-scoring-naredo-12-in-patients-with-rheumatoid-arthritis-i

Abstract Number: 134

Synovitis Assessed By the German 7-Joint Ultrasound Score (US7S) Is Associated with the Reversible Activity-Related Component of Physical Disability in Patients with Rheumatoid Arthritis

Jakub Zavada[1], Petra Hanova[1], Jana Hurnakova[1], Lenka Szczukova[2], Michal Uher[2], Šárka Forejtová[1], Martin Klein[1], Heřman F Mann[1], Marta Olejarova[1], Olga Sleglova[1], Olga Ruzickova[1] and Karel Pavelka[1], [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Brno, Czech Republic

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Session Time: 9:00AM-11:00AM

Background/Purpose: Restoring normal functioning is a major therapeutic aim. Differences in the sources of functional limitations should be considered in the interpretation of functional measures. We investigated the longitudinal relationship between HAQ and 7-joint ultrasound score (US7S[1]) in a prospective cohort of patients with RA.

Methods: A cohort of 185 RA pts (46 incident/139 prevalent, mean±SD age 55±14 years, 47% RF+, 63% ACPA+, baseline DAS28-CRP 3.7±1.5, HAQ 0.78±0.73, disease duration incident vs. prevalent pts. 0.9±0.7 vs. 8.1± 8.3 resp.) was followed up for 29±9 months. Assessments at baseline and then annually comprised DAS28-CRP, HAQ and US7S[1]. US7S includes 7 joints of the clinically dominant hand and foot and consists of 5 sub-scores for synovitis (syn) and tenosynovitis (ten) assessed by grey-scale (GS) and Power-Doppler (PD), and an erosions score (ES). A linear mixed model was used to assess the longitudinal relationship between US7 sub-scores and HAQ. We used current and time-lag models to explore the association between HAQ and predictors measured at the same time or at the previous visit 12 month ago, resp.

Results: Current model: In univariate analyses (table 1) HAQ was positively associated with GSsyn, PDsyn, PDten and GSten US7 sub-scores with resp. β coefficients significantly higher in incident than in prevalent patients. In a multivariate

analysis (table 2) the US7 sub-scores were individually no longer significant predictors of HAQ, although the R^2 of the model was improved by addition of US7 items from 37.4 to 48.7 ($p<0.001$ for improvement of R^2). Time-lag model: In multivariate analyses (table 3) after adjustment for previous DAS28 and/or previous HAQ, both previous PDsynUS and GSsynUS were significantly and inversely associated with the current HAQ (table 3).

Conclusion: US7S subscores for synovitis were associated with the reversible activity-related component of HAQ, and may help to identify patients with higher chance for functional improvement. **References:** [1]Backhaus M. et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009 Sep 15;61(9):1194-201 **Acknowledgements:** This work was supported by the project (Ministry of Health, Czech Republic) for consensual development of research organization 023728.

Table 1 Current model. Univariate analyses and interaction with incident(i) /prevalent(p) RA. Predicted variable – current HAQ, univariate predictors current DAS28-CRP, GS and PD synovitis and tenosynovitis.

Predictor	RA	β (95% CI)	p-value*	p-value**	% variability explained - R^2
DAS28-CRP	all	0.193 (0.165; 0.221)	**<0.001**		42.9
	i	0.235 (0.177; 0.292)	**<0.001**	0.097	
	p	0.179 (0.147; 0.211)	**<0.001**		
GSsynUS	all	0.019 (0.012; 0.027)	**<0.001**		4.5
	i	0.037 (0.022; 0.052)	**<0.001**	**0.011**	
	p	0.014 (0.006; 0.023)	**0.001**		
PDsynUS	all	0.027 (0.017; 0.036)	**<0.001**		5.2
	i	0.041 (0.024; 0.058)	**<0.001**	**0.039**	
	p	0.020 (0.008; 0.031)	**0.001**		
GStenUS	all	0.062 (0.021; 0.102)	**0.003**		2.6
	i	0.135 (0.054; 0.217)	**0.001**	**0.042**	
	p	0.038 (-0.008; 0.084)	0.109		
PDtenUS	all	0.057 (0.028; 0.086)	**<0.001**		3.2
	i	0.111 (0.051; 0.170)	**< 0.001**	**0.044**	
	p	0.041 (0.009; 0.073)	**0.013**		
ES	all	0.016 (-0.011; 0.043)	0.253		1.1
	i	-0.021 (-0.100; 0.057)	0.597	0.321	
	p	0.021 (-0.008; 0.051)	0.152		

** p-value of significance of given β. ** p-value of significance of difference between incident and prevalent RA.*

Table 2 Current model. Multivariate analyses; predicted variable – HAQ, comparison of models based on demographic, clinical and immunological parameters with or without US7 subscales.

	Model without US-7		**Model with US-7**	
Predictor	**β (95% CI)**	**p-value**	**β (95% CI)**	**p-value**
Female	0.210 (0.054; 0.367)	**0.008**	0.215 (0.060; 0.371)	**0.007**
Age (years)	0.147 (0.100; 0.195)	**< 0.001**	0.145 (0.097; 0.193)	**< 0.001**
BMI	0.016 (0.002; 0.030)	**0.029**	0.015 (0.001; 0.029)	**0.035**
RF+ or ACPA+	0.046 (-0.089; 0.181)	0.501	0.037 (-0.098; 0.173)	0.589
Prevalent vs. incident RA	-0.018 (-0.170; 0.134)	0.821	0.019 (-0.154; 0.192)	0.829
DAS28-CRP	0.190 (0.163; 0.218)	**< 0.001**	0.204 (0.170; 0.238)	**< 0.001**
GSsynUS	-		0.005 (-0.019; 0.029)	0.670
PDsynUS	-		0.003 (-0.023; 0.029)	0.827
GStenUS	-		-0.040 (-0.162; 0.082)	0.519
PDtenUS	-		0.018 (-0.073; 0.110)	0.694
Erosions score	-		-0.038 (-0.111; 0.035)	0.306
R2 (% variability explained)	37.4		48.7	
Improved R2	-		11.3	**< 0.001***

** p-value of significance for improvement of prediction*

Table 3 Time-lag model. Multivariate analyses using either previous HAQ or DAS28 or both, and previous PDsynUS or GSsynUS (previous = measured 12 months ago) to predict current HAQ.				
Analysis No	**Predictor**	**β (95% CI)**	**p-value**	**% variability explained by the model (R2)**
1	Previous HAQ	0.773 (0.709; 0.837)	**< 0.001**	65.3
	Previous PDsynUS	-0.016 (-0.026; -0.005)	**0.003**	
2	Previous PDsynUS	-0.025 (-0.039; -0.011)	**0.001**	33.7
	Previous DAS28	0.164 (0.116; 0.212)	**< 0.001**	
3	Previous HAQ	0.711 (0.628; 0.794)	**< 0.001**	65.9
	Previous PDsynUS	-0.022 (-0.033; -0.010)	**< 0.001**	
	Previous DAS28	0.053 (0.008; 0.098)	**0.022**	
4	Previous HAQ	0.764 (0.700; 0.828)	**< 0.001**	64.8
	Previous GSsynUS	-0.009 (-0.017; -0.001)	**0.032**	
5	Previous GSsynUS	-0.012 (-0.023; -0.001)	**0.028**	33.6
	Previous DAS28	0.146 (0.098; 0.194)	**< 0.001**	
6	Previous HAQ	0.713 (0.629; 0.797)	**< 0.001**	65.2
	Previous GSUS_syn	-0.012 (-0.021; -0.003)	**0.006**	
	Previous DAS28	0.042 (-0.004; 0.088)	0.071	

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Abstract Number: 135

The 8-Joint Ultrasound Score Is a Useful Marker for Monitoring Therapeutic Response in Rheumatoid Arthritis

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Background/Purpose: Musculoskeletal ultrasonography (US) is one of the standard tools for the diagnosis and monitoring of rheumatoid arthritis (RA). Although we and other groups have proposed several sets of US assessment procedures in arbitrary combinations of selected joints, there is still no consensus in defining the joints to evaluate. Here, we investigated whether US assessment in the selected 8 joints which we have advocated as a routine assessment for detecting RA synovitis is also useful for monitoring response to treatment for RA.

Methods: Power Doppler (PD) US was performed in 24 joints, including all PIP, MCP, bilateral wrist and knee joints, as comprehensive evaluation in 15 RA patients treated with certolizumab pegol (CZP). Before and after treatment with CZP, PD signals and gray-scale (GS) images were scored semiquantitatively from 0 to 3 in each joint. Total PD score-24 and total PD score-8 were calculated by summing up PD scores of the 24 joints and the selected 8 joints (bilateral second and third MCP, wrist, and knee joints), respectively. Total GS score-24 and total GS score-8 were also calculated by summing up GS scores of the 24 joints and the selected 8 joints, respectively.

Results: Change amount of total PD score-8 by treatment with CZP exhibited strong correlations with the changes of disease activity indices, SDAI ($r_S = 0.92$, $p < 0.01$) and DAS28-CRP ($r_S = 0.89$, $p < 0.01$). Change amount of total PD score-24 also correlated strongly with the changes of SDAI ($r_S = 0.91$, $p < 0.01$) and DAS28-CRP ($r_S = 0.86$, $p < 0.01$), and the correlation coefficients were comparable with those for total PD score-8. Although the change of total PD score-8 correlated well with the changes of some components of disease activity indices, including swollen joint count ($r_S = 0.81$, $p < 0.01$), tender joint count ($r_S = 0.91$, $p < 0.01$), CRP ($r_S = 0.82$, $p < 0.01$) and ESR ($r_S = 0.63$, $p < 0.01$), there were no significant correlations between the changes of total PD score-8 and the changes of patient's global assessment ($r_S = 0.39$, $p > 0.05$) and evaluator's global assessment ($r_S = 0.22$, $p > 0.05$). The change of total PD score-24 correlated more weakly with the changes of swollen joint count ($r_S = 0.74$, $p < 0.01$) and tender joint count ($r_S = 0.86$, $p < 0.01$) as compared to total PD score-8. The correlation coefficients between the change of total PD score-24 and the changes of CRP ($r_S = 0.85$, $p < 0.01$) and ESR ($r_S = 0.62$, $p < 0.01$) were comparable with those for total PD score-8. There were no significant correlations between the changes of total PD score-24 and the changes of patient's global assessment ($r_S = 0.42$, $p > 0.05$) and evaluator's global assessment ($r_S = 0.27$, $p > 0.05$). The changes of total GS score-8 and total GS score-24 correlated to the changes of SDAI with the same level of correlation coefficients ($r_S = 0.69$, $p < 0.01$, and $r_S = 0.70$, $p < 0.01$).

Conclusion: This study indicates that the change of the 8-joint US scores by treatment correlated with the changes of disease activity indices as strongly as the change of the comprehensive 24-joint scores. Thus the 8-joint assessment can be a useful method for monitoring response to treatment in RA patients.

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Abstract Number: 136

The 7-Joints Musculoskeletal Ultrasound Score (US7 score) Predicts Therapeutic Change in Patients with Early Rheumatoid Arthritis

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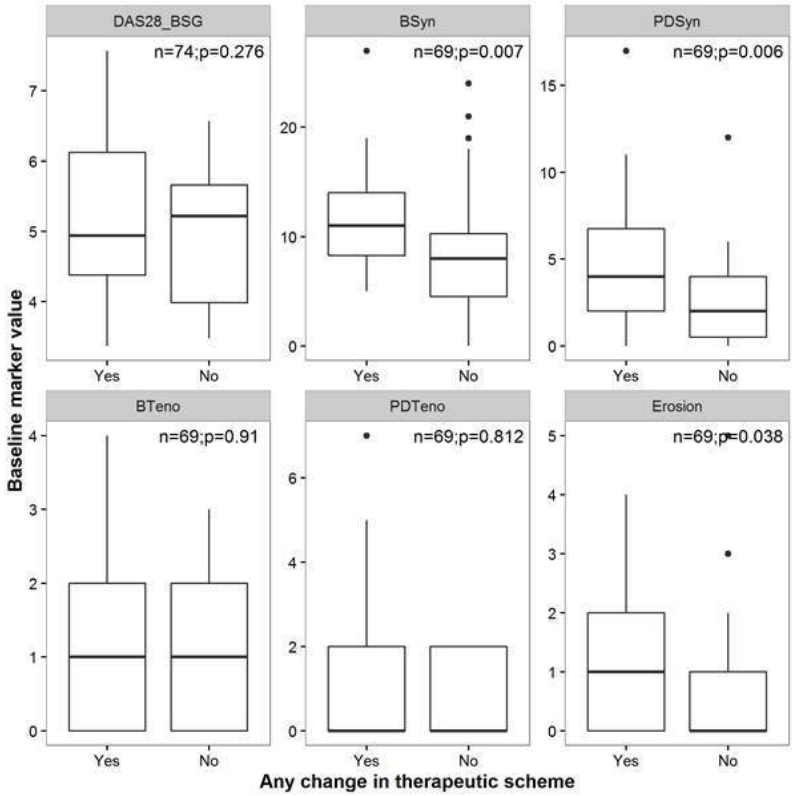
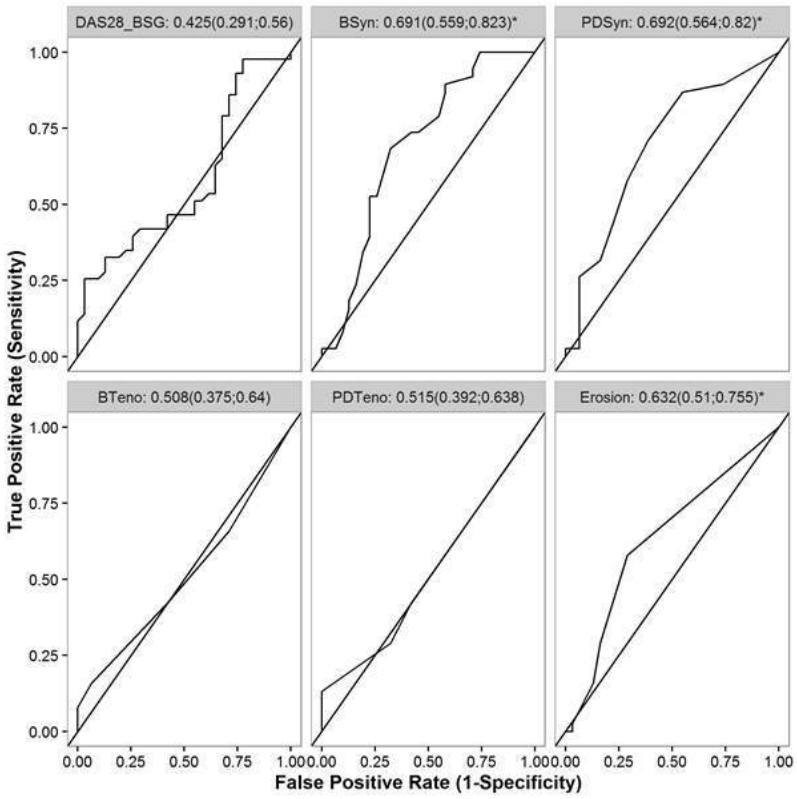
Background/Purpose: Treatment decisions in patients with Rheumatoid Arthritis (RA) after the "Treat to Target (T2T)" -principle is widely recommended, as this management strategy leads to a better outcome (1). Recently, the additional use of musculoskeletal ultrasound (US) within the T2T-strategy was recommended (2). However, superior value in terms of outcome of US- compared to the use of (only) clinical scores-guided strategy has not been demonstrated (3). To assess potential clinical and imaging markers which may have the capacity to predict changes of therapy.

Methods: In this ongoing observational study ('Arthromark'), patients with early RA (disease duration $\leq$2 years) are included before therapy initiation/change and amongst others parameters are assessed by the clinical score DAS28(ESR) and by all items of the 7-joint US score (US7 score; (4)) at baseline (before therapy initiation/change), and after 1.5, 3, 6, and 12 months. At each visit, treatment decision of the antirheumatic therapy is performed according to the T2T-principle. Treatment change contains any modification of the antirheumatic therapies during the 12 months follow-up, i.e. doses escalation, combination of conventional DMARD therapies, and additional/change to biologic therapies. The following two patient groups were considered in the analysis: **1)** patients that underwent any change in the antirheumatic therapy, and **2)** patients that underwent none of the changes mentioned above. This analysis aimed to investigate the association between this change and the clinical (DAS28) and the ultrasound (US7) parameters at baseline. The differences between these two patient groups regarding baseline DAS28(ESR) as well as the ultrasound scores were examined applying statistical tests (Mann-Whitney-U test for continuous variables, χ^2test for categorical variables). The significance level was 0.05, which was not adjusted for multiple testing. Furthermore, ROC analysis was performed to investigate the ability of these baseline variables in discriminating the two patient groups.

Results: 74 patients were included in the analysis (average age 52.37 years; 75.68% female). On average, time since first diagnosis was about half a year (max. 2.03 years). At baseline, DAS28(ESR) was 5.14 (min. 3.37, max. 7.57) on average. No statistically significant difference was shown between the two groups regarding baseline DAS28(ESR), however in terms of the baseline US7 synovitis B-mode score, the US7 synovitis Power Doppler score, and the US7 erosion score (**Figure 1**). These results agree with the results of the ROC analyses (**Figure 2**), where the AUC of the baseline US7 synovitis B-mode score, the US7 synovitis Power Doppler score, and the US7 erosion score were significantly different from 0.5, indicating that these variables can discriminate patients with and without therapeutic change well enough. According to the ROC analyses, DAS28(ESR) and the US7 tenosynovitis scores (B-mode and Power Doppler) show relatively poorer discriminating performance.

Conclusion: These analyses give a quantitative insight into the association between DAS28(ESR) and US7 score measurements at baseline and any therapeutic change during the course of the study. The results suggest that the synovitis ultrasound scores (in B-mode and Power Doppler) and the erosion score, in contrast to DAS28(ESR), might be able to predict the therapeutic change during the treatment course of patients.





References: [1] Smolen J, et al. Ann Rheum Dis 2016;75:3–15. [2] Horton S, et al. Rheumatology 2016 Published Online First [3] Dale J, et al. Ann Rheum Dis. Mar 29 2016. [4] Backhaus M, et al. Arthritis Rheum 2009; 61;1194-1201

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Abstract Number: 137

Imaging Remission By Musculoskeletal Ultrasound Leads to a Better Functional Outcome – Results of the US Impera Study – US 7-Score Implementation Study in Early Rheumatoid Arthritis

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Background/Purpose: Novel treat-to-target strategies present new challenges to treatment monitoring in rheumatoid arthritis (RA). To compare functional outcomes in early RA patients monitored by standard of care alone (clinical cohort) or with an additional musculoskeletal ultrasound examination (US cohort) following a treat-to-target strategy in a nationwide investigator-initiated study in Germany.

Methods: Functional, clinical and laboratory parameters monitored over 18 months in both cohorts were: Health Assessment Questionnaire (HAQ), Disease Activity Score 28 (DAS28), Visual Analogue Scale (VAS), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Ultrasound remission criteria used in the US cohort were: gray-scale ultrasound (GSUS) <2 at joint level and power Doppler ultrasound (PDUS) = 0. We additionally compared HAQ, DAS28, VAS, ESR and CRP in US cohort subgroups with and without ultrasound remission.

Results: In all 313 patients (US cohort: n=166, clinical cohort: n=147), laboratory activity, DAS28, VAS and HAQ decreased to low-disease activity levels within 18 months after the beginning or change of antirheumatic therapy, with no significant differences between groups. However, US cohort members with ultrasound remission (n=79) had significantly lower HAQ (0.401 vs. 0.741, p=0.002), DAS28 (2.2 vs. 3.4, p<0.001) and VAS disease activity scores (16.6 mm vs. 33.9 mm, p<0.001) than those without ultrasound remission (n=87).

Conclusion: Treat-to-target strategies reduced disease activity and improved functional outcomes (HAQ) in our early RA patients, irrespective of the monitoring regimen. However, patients with ultrasound remission had significantly better disease activity scores and functional outcomes. Accordingly, ultrasound should be strongly considered as an additional monitoring tool in clinical practice.

		HAQ	DAS28	ESR (mm/h)	CRP (mg/l)	Patient's VAS (mm)
Baseline						
Total population (n=313)	Clinical cohort (n=147)	1.020	5.1	33.1	23.0	56.9
	US-cohort in total (n=166)	1.050	5.2	29.3	17.2	57.3
		p=0.600	p=0.596	p=0.194	p=0.073	p=0.998
Subgroup analysis of US-cohort (n=166)	Non-remission group (n=87)	1.120	5.3	32.2	20.6	57.1
	Remission group (n=79)	0.971	5.1	26.2	13.7	57.4
		p=0.208	p=0.316	p=0.182	p=0.272	p=0.945
Month 18						
Total population (n=313)	Clinical cohort (n=147)	0.555	2.8	18.1	6.4	26.7
	US-cohort in total (n=166)	0.579	2.8	16.6	6.4	25.6
		p=0.758	p=0.800	p=0.174	p=0.585	p=0.397
Subgroup analysis of US-cohort (n=166)	Non-remission group (n=87)	0.741	3.4	18.4	7.8	33.9
	Remission group (n=79)	0.401	2.2	14.6	4.6	16.6
		p=0.002*	p<0.001*	p=0.406	p=0.089	p<0.001*

*p<0.05 for significant difference

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Abstract Number: 138

Measuring Agreement in the Ultrasonographic Evaluation of Disease Activity in Rheumatoid Arthritis Patients. a Latin-American Multicenter Exercise Assessing the Influence of Sonographer Experience and Expertise

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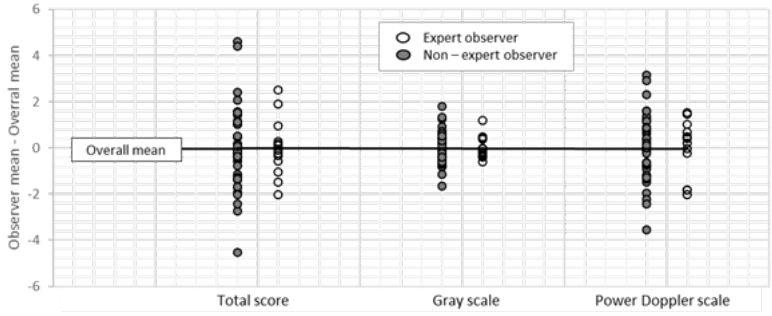
Background/Purpose: Ultrasonography (US) is an important tool in rheumatology practice. However, it highly depends on sonographer's experience. The **objective** of our study was to evaluate intra and inter-reader reliability of ultrasound assessment in rheumatoid arthritis (RA) using a Score named REUMA (Rapid Evaluation by US to Monitor Arthritis) among observers across Latin American using a web tool.

Methods: We conducted a cross-sectional study. Fifty-one Latin American ultrasonographers with different experience took part in a web- based US reading exercise evaluating static images from 20 RA patients. The 4 – joints US scores was calculated for each patient including bilateral radiocarpal, midcarpal and second metacarpophalangeal joints. Power Doppler (PD) and gray scale (GS) were graded from 0 to 3. US scores comes as the result of the addition of PD and GS score, with a total score ranged from 0 – 36, being 36 the highest disease activity. Five patients were evaluated twice in order to address intra – rater reliability. The inter and intra-rater reliability was assessed using a two-way random, absolute, individual and average-measures intra-class correlation coefficient (ICC), with reliability being poor for ICC <0.40, fair for 0.40 to 0.59, good for 0.60 to 0.74, and excellent for values between 0.75 and 1.0. Furthermore, we stratified sonographers according to US experience (defining High experience as: at least 5 years of experience and 80 US assessments/month), evaluating differences in intra – reader reliability, inter-reader reliability, and variation of observers means between patients. Statistical significance was assessed at a type I error rate of 0.05.

Results: A total of 1020 US image assessments were performed. Mean 4-joints US score was 17 ± 8 (Doppler subscale 10 ± 4; Synovitis subscale 7 ± 4). The ICC was in the excellent range for intra [(individual ICC = 0.945 (IC95% 0.905 – 0.965); average ICC = 0.972 (IC95% 0.950 – 0.982)] and inter- reader reliability [(individual ICC = 0.867 (IC95% 0.786 – 0.934); average ICC = 0.997 (IC95% 0.995 – 0.999)]. When comparing high with low experience sonographers, there

was no significant differences in intra-class correlation coefficient. However, there was a greater variation between the means among low experience readers, ranging from 13 to 22, in comparison with 14 to 18 in higher experience sonographers (**Figure 1**), which could introduce a bias to inter – reader reliability estimates.

Conclusion: Ultrasonography represents an excellent complementary tool to evaluate disease activity in patients with rheumatoid arthritis. However, its reliability is related to sonographer expertise and experience. Low – experience readers exhibit a higher variation on disease activity estimates. It is necessary to develope US training programs in order to improve reliability. **Figure 1.** Agreement with the mean between multiple observers in total score, gray and power doppler subscale.



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Reliability of Ultrasound in Detecting Cartilage Change in Patients with Rheumatoid Arthritis: A Study By Omeract Ultrasound Task Force

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Background/Purpose: The assessment of cartilage and bone damage in rheumatoid arthritis (RA) has traditionally relied on radiographical analyses in which joint space loss served as a surrogate marker of cartilage loss. Discernment of the relative contributions of damage to cartilage and other soft tissue structures within the joint space narrowing score however is not possible. Recently musculoskeletal ultrasonography (MSUS) was shown to be a reliable and reproducible tool for the assessment of cartilage in RA in the small joints of the hand. We aimed to produce MSUS consensus-based definitions of cartilage change in RA and assess its intraobserver and interobserver reliability.

Methods: We conducted a Delphi study on US defined cartilage change and a proposed semiquantitative (SQ) US scoring system for cartilage change in RA. A written Delphi questionnaire was developed based on a systematic literature review and expert international consensus and was distributed via consecutive written questionnaires by email to a group 35 rheumatologists from 17 countries with experience in musculoskeletal US. Taskforce members performed US B mode examination of the metacarpal cartilage in metacarpophalangeal joints 2-5 in RA patients and the images were collected in an electronic database. A reference image atlas of cartilage changes was developed for scoring 123 anonymized images including 25 duplicate images. These were sent to the participants who independently scored the images. Intraobserver reliability was assessed by CohenÕs kappa and interobserver reliability by FleissÕ kappa.

Results: Group agreement (76-100%) was reached for 6 statements concerning: i) MSUS definition and assessment of normal hyaline cartilage, ii) elementary cartilage lesions in MSUS and iii) grading of elementary cartilage lesions inpatients with RA in a two-round Delphi consensus process. A three-grade SQ (0-2) scoring system (grade 0, normal cartilage; grade 1, minimal change: blurring of outer and/or subchondral margin, focal thinning or incomplete loss of homogeneity of echostructure; grade 2, severe: diffuse thinning or complete loss of homogeneity of echostructure) was agreed for scoring cartilage damage in RA (Figure 1). Both intra- and inter-observer reliability were good (κ value of 0.87 and 0.64 respectively).

Conclusion: This study demonstrates that US is a reliable tool for evaluating cartilage in RA and strongly supports the use of a new reliable semiquantitative MSUS scoring system for cartilage change.

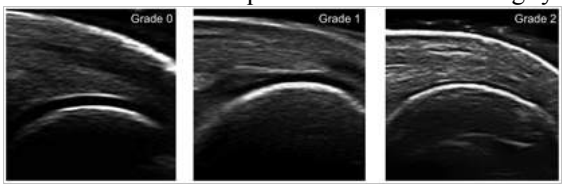

Figure 1. Three-grade semiquantitative scoring system (0-2) for scoring cartilage damage in RA.

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Duftner, None; **M. Gutierrez**, None; **H. B. Hammer**, None; **C. Hernandez-Diaz**, None; **A. Iagnocco**, None; **K. Ikeda**, None; **D. Kane**, None; **H. I. Keen**, None; **S. Kelly**, None; **E. Kővári**, None; **E. De Miguel**, None; **I. Möller**, None; **U. M. Døhn**, None; **E. Naredo**, None; **J. C. Nieto**, None; **C. Pineda**, None; **A. Rodriguez**, None; **W. A. Schmidt**, None; **M. Szkudlarek**, None; **R. G. Thiele**, Amgen, 8,AbbVie, 8,BioClinica, 5; **L. Terslev**, None; **R. J. Wakefield**, None; **D. Windschall**, Roche Pharmaceuticals, 2,Novartis Pharmaceutical Corporation, 2; **M. A. D'Agostino**, None; **P. Balint**, None.

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Abstract Number: 140

Relationship Between the Prevalence of Subclinical Tenosynovitis and Therapy in Patients with RA in Clinical Remission: Results from Italian Society of Rheumatology Study Group

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Background/Purpose: This study is a sub-analysis of the data from the patient cohort of STARTER (The Sonographic Tenosynovitis Assessment in RheumaToid arthritis patiEnts in Remission) study group conducted by the Musculoskeletal Ultrasound Study Group of the Italian Society for Rheumatology (SIR). In this study we have proved the association between prevalence of ultrasound tenosynovitis in patients with RA in remission and increased risk of flare in one year. The aim of this ancillary study was to evaluate if the patients in combo therapy with DMARDs and Biologic present lower ultrasound joint and/or tendon involvement in compare to patients treated with only DMARDs or Biologic in monotherapy.

Methods : STARTER is a multicentre cohort study promoted by the Musculoskeletal Ultrasound Study Group of SIR that includes 25 Italian rheumatology units. 427 consecutive patients with a diagnosis of RA according to the American College of Rheumatology (ACR) criteria 1987 or ACR/EULAR (European League Against Rheumatism) 2010 criteria and in clinical remission were recruited between October 2013 and June 2014; at baseline (T0), 6 (T1) and 12 (T2) months each patient was undergoing clinical evaluation (performed by rheumatologists blinded to the ultrasound data) and ultrasound by using a semi-quantitative score 0-3 gray scale (GS) and power doppler (PD) for the evaluation of the flexor and extensor tendons of the fingers and wrists. For each patient it was calculated a final score of GS-tenosynovitis, PD-tenosynovitis. The ultrasound remission was defined as a score = 0. Were included in the study 427 patients, divided into 3 subgroups according to background therapy at baseline: patients with biologic in monotherapy (BIO), patients with DMARD in monotherapy (DMARDs), patients in combo therapy (DMARDs + BIO).

Results : 257 patients completed the observation period. 49 pts in BIO group (19.7%, F34 / M15), 152 pts in the DMARDs group (59.14% -F105 / M47), 56 pts in BIO + DMARDs group (21.79% -F47 / M9). The demographic and clinical characteristics at baseline are presented in Table 1 and 2. At baseline, 56.03% (144/257) of patients showed tenosynovitis, the 48.98% (24/49) BIO, the 57.89% (88/152) DMARDs, the 57.14% (32/56) DMARDs + BIO. The tenosynovitis involvement at baseline, at 6 and 12 months showed into three different subgroups analyzed, has no

statistically significant changes (Fig. A). In the BIO group, there was a patient who had a flare few days prior to follow up visit at T12.

Conclusion : As shown in STARTER study, the prevalence of subclinical tenosynovitis is relevant in the subpopulation of patients with RA in clinical remission. The analysis into subgroups, based on the therapy performed, although it did not show any significant differences, demonstrated a trend to a lower prevalence of inflammatory manifestations of the tendons of the hands and wrists in favor of patients with combo therapy (DMARDs + BIO) than patients with only DMARDs o Biological in monotherapy. These results could indicate a higher probability to getting better outcomes in patients treated by combo therapy.

GROUP (257)	AGE (m±SD)	BMI (m±SD)	Durata Malattia (M-IQR)	Durata Remissione (M-IQR)	Steroids (Y/N)	NSAID (N/Y)	RF (-/+)	Anti-CCP (-/+)
BIO (49)	54.63±13.4	24.59±3.6	12.27 (9.1-17.9)	16 (10-30)	27/22	21/28	18/31	23/26
DMARDs (152)	57.59±13.6	24.67±4.3	4.92 (2.29-9.35)	12 (6-24)	78/74	75/77	77/75	71/80
DMARDs+BIO (56)	55.36±11.8	24.70±4.1	8.06 (5.7-14.7)	14 (9.5-24)	35/21	26/30	23/33	20/03/16

GROUP (257)	Flare Questionnaire (M-IQR)	HAQ (M-IQR)	DAS28 (m±SD)	CDAI (m±SD)	SDAI (m±SD)
BIO (49)	5 (0-20)	0.250 (0-0.625)	1.97±0.7	3.04±3.3	4.03±6.7
DMARDs (152)	2 (0-10)	0 (0-0.250)	2.07±0.7	2.07±2.1	2.24±2.1
DMARDs+BIO (56)	1 (0-7.5)	0.062 (0-0.250)	1.86±0.7	1.60±1.8	1.94±1.9
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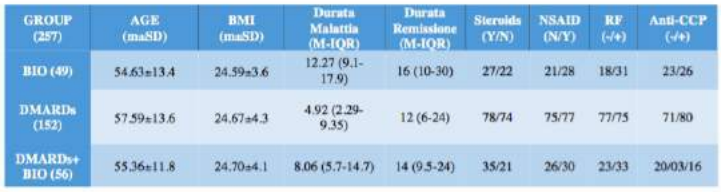
Tab.1 Demographic and therapeutic characteristics at baseline into 3 subgroups **Tab.2** Clinimetric characteristics at baseline into 3 subgroups

Tenosynovitis



GROUP (257)	AGE (maSD)	BMI (maSD)	Durata Malattia (M-IQR)	Durata Remissione (M-IQR)	Steroids (Y/N)	NSAID (N/Y)	RF (-/+)	Anti-CCP (-/+)
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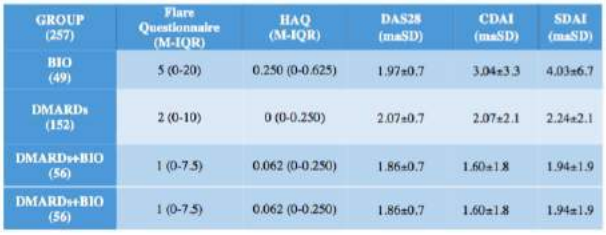

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Tab.2 Clinimetric characteristics at baseline into 3 subgroups

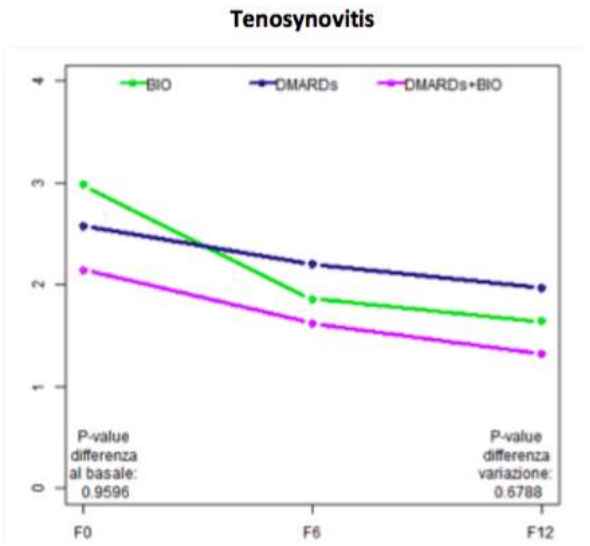

Fig.A

Fig.A

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The Usefulness of SMI Technology on Ultrasound for the Evaluation of Active Synovitis in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases - Poster I: Ultrasound and Emerging Technologies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Many imaging modalities, including ultrasound (US) have been used in evaluating rheumatoid arthritis (RA). Previous literatures revealed that US using power doppler imaging (PDI) may be correlated with the degree of synovitis and represent the disease activity in clinical course. The superb microvascular imaging (SMI) is a new software introduced by Toshiba, which can show a vascularity more sensitively excluding artifacts. Therefore, this prospective study was aimed to evaluate the clinical usefulness of the SMI technology for detection of active synovitis in patients with with RA, compared to power doppler imaging (PDI).

Methods: This prospective observational study includes 39 patients with RA (29 females; range of age, 18-83 years; mean age, 52.9 ± 18.1 years), from June, 2015 to May, 2016. All the included patients underwent ultrasound about both wrists and hands (radiocarpal or ulnaocarpal, metacarpophalangeal, and proximal interphalangeal joints; total 22 joints). All the

ultrasound examinations were performed at volar side of wrists and hands, using both PDI and SMI using Aplio TM 500 Ultrasound (Toshiba Medical Systems Corporation), and their results were scored for each joint from grade 0 to grade 3 according to the vascularity (grade 0, no vascularity; grade 1, single vessel; grade 2, vascular flow less than 50% in field of view; grade 3, equal to 50% or more). The sum of grades for 22 joints was compared between PDI (PDI-sum) and SMI (SMI-sum). We also evaluated the correlation between the sum of grades values and inflammatory laboratory parameters including the erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and disease activity score 28 (DAS28).

Results: The mean values of ESR, CRP and DAS28 were 31.0 ± 18.1 mm/hr, 8.17 ± 8.47 mg/L and 3.72 ± 1.08, respectively. The number of clinical remission (DAS28 score below 2.6) was 7 (17.9%). The positive rates of rheumatoid factor and anti-cyclic citrullinated antibody were 82.1% and 76.9%, respectively. The sum of grades 22 joints was significantly higher in SMI-sum compared to PDI-sum (14.33 ± 8.76 vs. 7.56 ± 5.71, $p < 0.001$). The SMI-sum score was highly correlated with the PDI-sum score ($\gamma = 0.789$, $p < 0.001$). The SMI-sum score and PDI-sum score were correlated with CRP value ($\gamma = 0.365$, $p = 0.026$; $\gamma = 0.473$, $p = 0.002$, respectively). All of the patients with clinical remission showed active synovitis at more than one joint in both SMI and PDI.

Conclusion: SMI can show more sensitive vascularity than PDI in RA patients. We can detect active synovitis in the RA patients with clinical remission through SMI. SMI could be a useful technology for evaluation of active synovitis in RA patients, especially for detection of clinically subtle, but active synovitis in the RA patients with remission.

Disclosure: G. Y. Lee, None; **S. Kim**, None; **S. T. Choi**, None; **J. S. Song**, None.

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Abstract Number: 142

Quality Assessment of Ultrasound Guided Synovial Biopsies Performed in Clinical Practice

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SESSION INFORMATION
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Background/Purpose: Synovial tissue is the principal target and end organ involved in the pathogenesis of multiple articular disease processes. Histological and bacteriological analyses of synovial tissue (ST) are useful in clinical practice for the diagnosis of undifferentiated arthritis. Ultrasound (US) allows an evaluation of the synovial thickness and inflammation. It also helps to perform real-time synovial biopsy and detect nearby structures such as tendons, nerves and vessels. The aim of this study was to assess quantity and quality of synovial tissue obtained by ultrasound guided synovial biopsies, in clinical practice.

Methods: We retrospectively analyzed all synovial biopsies performed between January 2007 and December 2014 in the Rheumatology Department of Nantes University Hospital. Synovial biopsies were performed under real-time US guidance (Philips HD11 XE) using a core biopsy needle with a 14 or 16G caliber semi-automatic Tru-cut needle. This technique allows to collect multiple synovial samples during a single procedure. Hematoxylin and eosin stained slides were analyzed by one operator (AN), blindly from clinical data. Size, area, presence/absence of synovial tissue, presence/absence of lining layer, other types of tissues were assessed and compared to pathologist's analysis (gold standard).

Results: 75 biopsy procedures were analyzed (73 patients). 125 samples were available for analysis corresponding to a median number of samples taken per patient of 1 (IQR 1-3). Mean length and width of the biopsy samples were 6.34 millimeters (mm) (+/- 3.60) and 1.70 mm (+/- 0.77) respectively. The mean total area of the samples was 8.77 mm^2. Biopsies showed synovial tissue at the histological examination in 102 samples (80.1%). The average area of synovial

tissue in these samples was 6.36 mm2 corresponding to 72.5% of the total area of biopsied tissue. The other types of tissue present on these biopsies were connective tissue in 101 cases (80.8%), adipose tissue in 42 cases (33.6%), tendon in 14 cases (11.2%) and fibrin in 24 cases (19.2%). The 23 sample retrieving no synovial tissue were composed of fibrin in 15 cases (12%), conjunctive and adipose tissue in 17 cases (13.6%), tendon in 3 cases (3.15%), cartilage in 3 cases (3.15%) and muscle in one case (0.8%). Synovial lining layer was found in 92.6% of the successful biopsies. Interobserver reliability for presence/absence of synovial tissue between AN and the pathologist was high with a kappa coefficient of 0.90 (95%CI = 0.763 to 1).

Conclusion: Our study is the first to assess quality and quantity of synovial tissue obtained by ultrasound guided biopsy, in the clinical setting. In 80% of the biopsy procedures, quantity and quality of the synovial tissue were high enough to allow a proper histological examination. Given the fact that conjunctive and adipose tissues as well as fibrin were frequently seen on histological examination, retrieving a minimal number of 3 samples per patient appears to be required for appropriate pathology assessment in the clinical setting.

Disclosure: A. Najm, None; **M. F. Heymann**, None; **G. Bart**, None; **Y. Maugars**, None; **B. Le Goff**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/quality-assessment-of-ultrasound-guided-synovial-biopsies-performed-in-clinical-practice

Abstract Number: 143

Assessment of Patient Satisfaction, Functionality and Quality of Life after Ultrasound Guided Knee Intervention: A Prospective Study Tejas Sheth, MD. Beverly Johnson, MD, MS. Department of Rheumatology, Albert Einstein College of Medicine, Bronx, NY

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First publication: September 28, 2016

SESSION INFORMATION

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Background/Purpose: Patient satisfaction about health care experience has emerged, as a surrogate of quality of care. The Patient Protection and Affordable Care Act has allowed patient satisfaction data to help determine Medicare reimbursement. The use of US guidance for the injection and aspiration of joints has improved accuracy.[1] The aim of this study was to determine if differences exist in the level of patient satisfaction, functionality and quality of life in adult patients receiving US guided (USG) versus landmark guided (LMG) knee procedures.

Methods: This prospective, randomized study enrolled 40 patients undergoing knee procedures to USG or LMG groups. Visual analogue scale (VAS) for pain, Knee injury and Osteoarthritis Outcome Score (KOOS) and patient satisfaction score on 5 point Likert scale were measured pre-procedure, immediate (<30 mins) and late (2-4 weeks) post-procedure. Mann-Whitney U test and ANOVA were used to compare continuous variables and chi-square test was used for categorical variables.

Results: 37 patients were included in the final analysis after exclusion of 3 dropouts (18 in LMG arm, 19 in USG arm). There were no significant differences between patients getting LMG or USG procedures with respect to age, sex, race, ethnicity, pre-procedural VAS pain and pre-procedural KOOS scores (Table 1). Patients in both groups had significant decrease in pain immediately and later post-procedure. Those in the USG group had significantly better improvement in pain and satisfaction at both the end points. Patients getting USG procedures reported significantly better KOOS scores (Pain, Symptoms, Activities of daily living, Sports-recreation & Quality of life) at 2-4 weeks (Figure 1, 2).

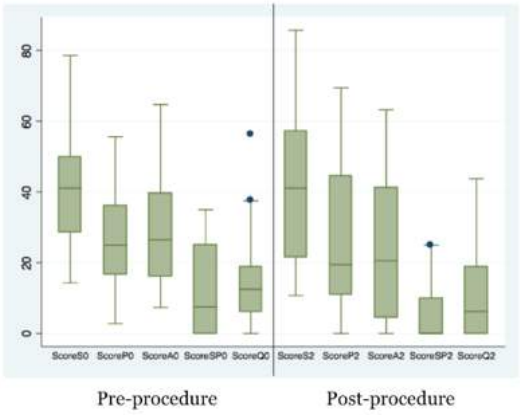
Conclusion: USG knee procedures were associated with higher patient satisfaction, both immediately after the procedure and after 2-4 weeks. USG knee procedures resulted in greater improvement in symptoms, pain and quality of life scales after 2-4 weeks as compared to LMG knee procedures. In a time when patient satisfaction is increasingly important for

insurance reimbursement, our study supports not only better quantitative outcomes with pain and function, but also greater patient satisfaction with USG knee procedures. Reference: 1. Cunnington J et al. Arthritis and rheumatism. Jul 2010;62(7):1862-1869.

Table 1: Comparison of demographic variables and outcome measures between LMG and USG groups.

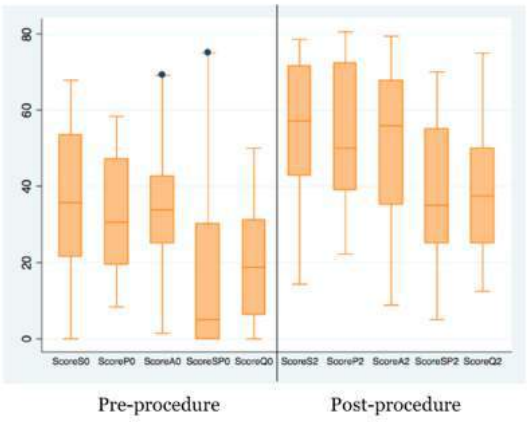
	LMG (n=18)	USG (n=19)	P value
Age (Mean ± SD)	58.27 ± 9.64	60.89 ± 10.4	0.54
Sex (F, %)	12 (66.7)	14 (73.7)	0.64
Race (n, %)			0.25
Caucasian	2 (11.1)	0	
Black	6 (33.3)	5 (26.3)	
Other	10 (55.6)	14 (73.7)	
Ethnicity (n, %)			0.12
Hispanic	5 (27.8)	10 (52.6)	
Non-Hispanic	13 (72.2)	9 (47.4)	
Pathology (n, %)			0.85
OA	10 (55.6)	11 (57.9)	
RA	6 (33.3)	5 (26.3)	
Crystal Disease	2 (11.1)	3 (15.8)	
VAS pre-procedure (Mean ± SD)	9.05 ± 1.2	8.84 ± 1.7	0.90
VAS immediate post-procedure (Mean ± SD)	4.05 ± 2.5	1.63 ± 1.6	0.001
VAS delayed post-procedure (Mean ± SD)	6.38 ± 3.8	2.68 ± 2.0	0.004
Satisfaction immediate post-procedure (Mean ± SD)	4.11 ± 1.0	4.89 ± 0.3	0.002
Satisfaction delayed post-procedure (Mean ± SD)	3.38 ± 1.6	4.52 ± 0.9	0.028
KOOS Score pre-procedure			
S Score (Mean ± SD)	40.47 ± 16.9	37.96 ± 18.3	0.228
P Score (Mean ± SD)	25.61 ± 13.9	33.91 ± 14.8	0.109
A Score (Mean ± SD)	29.41 ± 17.4	35.75 ± 17.8	0.229
SP Score (Mean ± SD)	11.38 ± 12.9	18.15 ± 21.6	0.482
Q Score (Mean ± SD)	16.31 ± 14.0	20.72 ± 14.1	0.265
KOOS Score post-procedure			
S Score (Mean ± SD)	42.85 ± 22.6	56.20 ± 17.2	0.050
P Score (Mean ± SD)	27.31 ± 21.8	52.48 ± 18.4	<0.001
A Score (Mean ± SD)	24.83 ± 21.5	52.94 ± 19.3	<0.001
SP Score (Mean ± SD)	12.50 ± 13.5	38.68 ± 17.9	<0.001
Q Score (Mean ± SD)	14.93 ± 13.0	39.80 ± 17.3	<0.001
Change in KOOS Score			
Change S Score (Mean ± SD)	2.38 ± 21.4	18.23 ± 14.6	0.012
Change P Score (Mean ± SD)	1.70 ± 27.5	18.57 ± 12.8	0.021
Change A Score (Mean ± SD)	0.33 ± 24.6	17.18 ± 16.9	0.020
Change SP Score (Mean ± SD)	3.33 ± 15.8	20.53 ± 16.4	0.002
Change Q Score (Mean ± SD)	1.04 ± 21.2	19.08 ± 10.9	0.002

Figure 1: Box plot of comparison of KOOS Scores pre and post-procedure for LMG procedures.



ScoreS=Symptoms score, ScoreP=Pain score, ScoreA=Activities score, ScoreSP=Sports and recreational activity score, ScoreQ=Quality of life score. 0 = Pre-procedure, 2 = 2-4 weeks post-procedure

Figure 2: Box plot of comparison of KOOS Scores pre and post-procedure for USG procedures.



ScoreS=Symptoms score, ScoreP=Pain score, ScoreA=Activities score, ScoreSP=Sports and recreational activity score, ScoreQ=Quality of life score. 0 = Pre-procedure, 2 = 2-4 weeks post-procedure

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Abstract Number: 144

Safety, Tolerability and Feasibility of Minimally Invasive Ultrasound-Guided Synovial Biopsyof Wrist and Metacarpophalangeal Joints – an Ultrasound Follow-up Study

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Background/Purpose: The development of ultrasound-guided synovial biopsy will enable synovial tissue collection from small joints and will facilitate molecular studies, thus improving the understanding of mechanisms of inflammatory arthropathies as small joints are frequently involved in these diseases. Objective: To assess the safety, tolerability and feasibility to perform synovial biopsies from wrist and metacarpophalangeal (MCP) joints, using a minimally invasive

ultrasound (US)-guided technique in patients suffering from rheumatoid arthritis (RA), spondylarthropathies (SA) or undifferentiated arthritis (UA).

Methods: Two target joints (TJ) were biopsied: wrist and MCP. Patients with at least one clinically swollen joint at these levels, suffering from RA, SA, or UA underwent a US examination. The TJ chosen for the biopsy was the joint with the most important inflammatory changes on gray-scale (GS) US. GS synovitis and power-Doppler (PD) activity were assessed by OMERACT scores, on the day of the biopsy, as well as 2 weeks (w), 6w and 6 months (m) after the biopsy. In addition, tendon tears, hematoma, paratenonitis and tenosynovitis were searched on US examinations. Patient-reported outcomes (PRO) were assessed as previously described[1]. A standard questionnaire (pain, swelling and stiffness of the TJ using a visual analogue scale from 0 to 10) was given to all patients on the day of the biopsy as well as 1w, 2w, and 6w after the biopsy. Tolerability and the patient-reported willingness to repeat the procedure was assessed using the five-point Likert scale

Results: 56 patients suffering from RA (36), SA (9) and UA (11) underwent US-guided biopsy of the wrists (28) and MCP (28) joints (Figure). A non-significant increase in pain 24 h after the procedure was reported by all except one patient. No difference in PRO of the biopsied joints was reported 2w and 6w after the biopsy, as compared to assessment before the biopsy. No infection or haemorrhage was observed after the biopsy. No differences in PRO after the biopsy were observed between patients suffering from RA, SA or UA. We registered three adverse events specifically linked to the procedure: persistent thumb hypoesthesia (1 patient), hypotension (vagal reaction) during the procedure (2 patients). At 6w and 6m follow-up, no other safety concerns were reported. At the TJ, US scores tended to decrease 2w after the procedure. Treatment response at the TJ was similar to the response of non-biopsied joints matched for the baseline US parameters.

Conclusion: With the exception of study of Kelly *et al,* data on safety, tolerability, feasibility and PRO using minimally invasive US-guided biopsy are lacking. In this work, we confirm that US-guided biopsy of wrist and MCP joints is feasible, safe and well tolerated by patients. Furthermore, no differences in PRO between RA, SA and UA were observed. As for any other innovative tool, this technique should be compared with other available techniques of synovial biopsy.

[1]Kelly S. et al. Ultrasound-guided synovial biopsy: a safe, well-tolerated and reliable technique for obtaining high-quality synovial tissue from both large and small joints in early arthritis patients. Ann Rheum Dis. 2015;74:611-6117. We acknowledge Pr C. Pitzalis and S. Kelly for giving us the opportunity to learn and further disseminate minimally invasive ultrasound-guided technique, and for fruitful discussions.

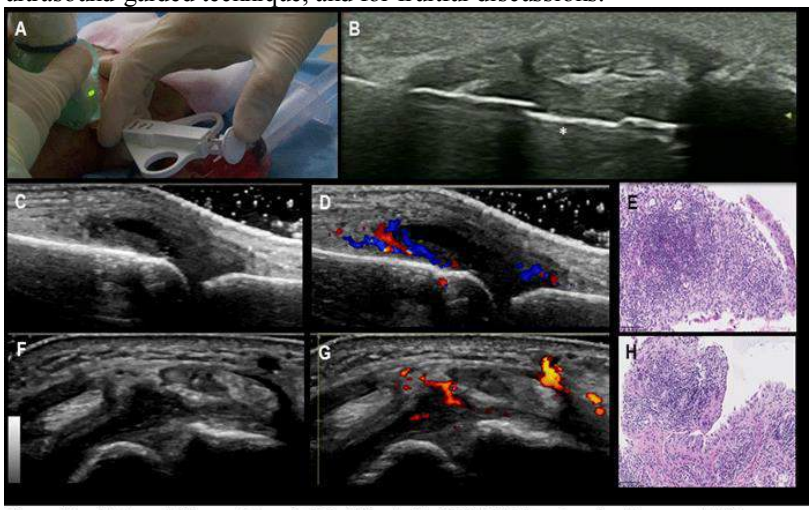

Figure. US-guided synovial biopsy of the wrist (A, B, F-H) and of the MCP (C-E) joints. Synovium biopsy needle (A) as seen with US (B) at the wrist level. A guillotine-type needle with an open throw (*) is used to cut the tissue. Prior to biopsy, MCP (C, D) synovitis is depicted by GS-US (C) and by color Doppler-US (D). Wrist synovitis (F, G) is depicted by GS-US and by PD-US (G). Histological images (E and H) of the corresponding GS-US (C and F) and Doppler US (D and G) images showing blood vessel proliferation and strong inflammatory infiltrates in the synovial sublining.

Disclosure: L. Meric de Bellefon, None; **P. Durez**, None; **C. Galant**, None; **A. Nzeusseu Toukap**, None; **A. Avramovska**, None; **B. R. Lauwerys**, None; **F. A. Houssiau**, None; **M. S. Stoenoiu**, None.

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Abstract Number: 145

Reduction in Musculoskeletal Ultrasound (MSK-US) Payments in 2014: Effects & Consequences

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Background/Purpose: Rapid rise in the use of diagnostic and interventional MSK-US within the Medicare population between 2011 and 2013 has been documented amongst non-radiology MSK providers.[1] Due to rapid escalation of cost and utilization, Medicare recently identified interventional MSK-US CPT 76942 as a potentially incorrectly estimated code leading to the reported payment reductions.[2] The key objective of this study was to determine the four-year trend of utilization of diagnostic and interventional MSK-US using the recently available 2014 Medicare Part B data. The secondary objective was to assess the impact of CPT 76942 code revaluation by Medicare.

Methods: A retrospective secondary analysis of Medicare Physician Supplier Payment Summary (PSPS) files from 2011 – 2014 was used to describe the services and total payments on utilization of MSK-US. PSPS data is aggregated on multiple factors with certain exclusions, including absence of technical costs such as those billed by Radiology. Therefore, service count data more accurately reflects utilization across specialties. CPT 76881, 76882 and 76942 were coded as diagnostic MSK-US and interventional MSK-US respectively. Non-duplicative billing claims of these codes were summed for each years and provider specialty. MSK provider specialties were also grouped into six groups. Descriptive analysis was conducted using R-Studio (Version 0.98.1102) and Tableau (Version 9.3).

Results: Interventional MSK-US services continued to grow in most specialties except for Radiology where they continued to decline every year (Table 1). Orthopedics continued to rank the highest for interventional MSK-US services, whereas Rheumatologists' services remained fairly stable with a minor reduction from 2013 to 2014. Strikingly, there was a 60-65% cut in payments in 2014 (Figure 1). There continued to be a greater utilization of interventional than diagnostic MSK-US among all MSK providers except Podiatry (Table 1 and 2).

Conclusion: A marked dissociation of interventional MSK-US services from diagnostic services continued to be seen in most MSK specialties. The radical cut in payments is notable not only due to its magnitude but also that it pre-dated bundled billing of common joint injections with MSK-US. The next logical step for future research will be to assess and correlate the reduction in the observed payment with the reduction of interventional MSK-US. 1. Kaeley GS, Kraemer D, Smotherman C, Dodani S. Musculoskeletal Ultrasound (MSK-US): Innovation or Overutilization? Arthritis Rheumatol. 2015;67.

2. 2014-Medicare-Physician-Fee-Schedule-Final-Rule. 2014

Table 1. Stratified Services and Payments for Interventional MSK-US:2011-2014

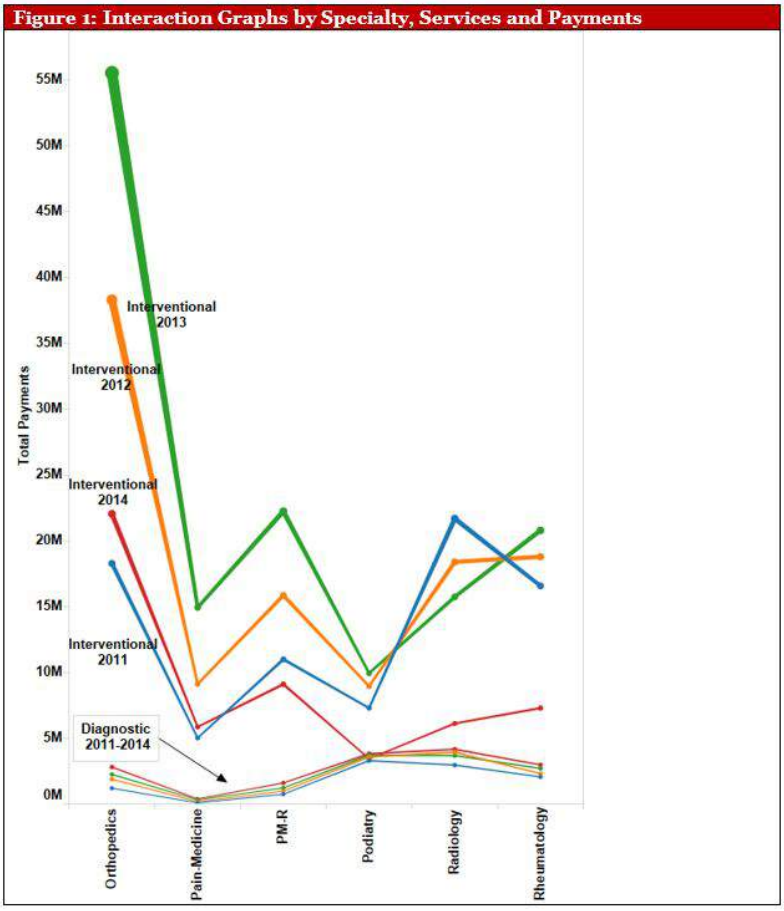
INTERVENTIONAL MSK-US		SERVICES			PAYMENTS		
Specialty	Year	Total Services	Annual Change	Cumulative Change	Total Payments	Annual Change	Cumulative Change
Orthopedics	2011	110,194			$18,265,453		
	2012	228,527	107%	107%	$38,291,935	110%	110%
	2013	336,541	47%	205%	$55,519,275	45%	204%
	2014	380,686	13%	245%	$22,033,349	-60%	21%
Pain-Medicine	2011	33,399			$5,018,728		
	2012	59,247	77%	77%	$9,116,122	82%	82%
	2013	97,988	65%	193%	$14,923,597	64%	197%
	2014	107,631	10%	222%	$5,854,970	-61%	17%
PM-R	2011	67,400			$10,989,414		
	2012	98,488	46%	46%	$15,845,584	44%	44%
	2013	138,697	41%	106%	$22,228,861	40%	102%
	2014	160,231	16%	138%	$9,098,877	-59%	-17%
Podiatry	2011	46,368			$7,292,693		
	2012	55,801	20%	20%	$8,946,745	23%	23%
	2013	61,593	10%	33%	$9,936,656	11%	36%
	2014	60,051	-3%	30%	$3,435,393	-65%	-53%
Radiology	2011	527,241			$21,674,832		
	2012	410,000	-22%	-22%	$18,387,040	-15%	-15%
	2013	297,147	-28%	-44%	$15,732,318	-14%	-27%
	2014	192,854	-35%	-63%	$6,119,598	-61%	-72%
Rheumatology	2011	102,421			$16,564,800		
	2012	113,144	10%	10%	$18,777,939	13%	13%
	2013	125,579	11%	23%	$20,782,347	11%	25%
	2014	124,897	-1%	22%	$7,287,389	-65%	-56%

PM-R – Physical Medicine and Rehabilitation (includes Sports Medicine), Pain Management includes Interventional Pain Management, Orthopedics includes Hand Surgery, Radiology includes Interventional Radiology.

Table 2. Stratified Services and Payments for Diagnostic MSK-US:2011-2014

DIAGNOSTIC MSK-US		SERVICES			PAYMENTS		
Specialty	Year	Total Services	Annual Change	Cumulative Change	Total Payments	Annual Change	Cumulative Change
Orthopedics	2011	17,844			$1,201,095		
	2012	26,688	50%	50%	$1,884,973	57%	57%
	2013	33,895	27%	90%	$2,248,942	19%	87%
	2014	44,976	33%	152%	$2,810,486	25%	134%
Pain-Medicine	2011	1,370			$94,576		
	2012	2,719	98%	98%	$181,131	92%	92%
	2013	5,137	89%	275%	$313,524	73%	232%
	2014	5,865	14%	328%	$386,462	23%	309%
PM-R	2011	10,058			$745,724		
	2012	13,806	37%	37%	$978,527	31%	31%
	2013	18,191	32%	81%	$1,221,637	25%	64%
	2014	24,890	37%	147%	$1,601,918	31%	115%
Podiatry	2011	65,383			$3,298,051		
	2012	63,065	-4%	-4%	$3,572,297	8%	8%
	2013	66,055	5%	1%	$3,703,380	4%	12%
	2014	70,396	7%	8%	$3,821,300	3%	16%
Radiology	2011	115,163			$2,960,385		
	2012	135,343	18%	18%	$3,942,002	33%	33%
	2013	140,807	4%	22%	$3,684,137	-7%	24%
	2014	153,080	9%	33%	$4,156,669	13%	40%
Rheumatology	2011	27,170			$2,062,204		
	2012	29,506	9%	9%	$2,310,484	12%	12%
	2013	36,021	22%	33%	$2,706,841	17%	31%
	2014	42,121	17%	55%	$2,975,370	10%	44%

PM-R – Physical Medicine and Rehabilitation (includes Sports Medicine), Pain Management includes Interventional Pain Management, Orthopedics includes Hand Surgery, Radiology includes Interventional Radiology.



Disclosure: G. S. Kaeley, None; **S. Dodani**, None.

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Abstract Number: 146

Ultrasound Features of the Posterior Tibialis Tendon and Peroneus Brevis Tendon Entheses: A Comparison Study Between Healthy Adults and Inflammatory Arthritis

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Background/Purpose: Ultrasound imaging is highlighting the prominent role of tendinitis in systemic rheumatic disease. Because of challenging anatomy, limited literature exists on the sonographic appearance of the posterior tibialis (PTT) and the peroneus brevis (PBT) tendon entheses. Our objectives were to determine the anatomic features and best imaging techniques of normal PTT and PBT using musculoskeletal ultrasound and to compare these findings to subjects with inflammatory arthritis.

Methods: Per IRB approval, subjects over the age of 18 without previous foot/ankle fracture or surgery were enrolled as: healthy controls (HC), rheumatoid arthritis (RA), and spondyloarthropathy (SpA). Bilateral PTT and PBT entheses were imaged longitudinally to compare two angles of insonation: 1) perpendicular to the skin surface and 2) 45˚ cephalad. A MyLab 70 Biosound Esaote Ultrasound machine with 6-18 MHz linear transducer was used with standardized presets. Three sonographers, blinded to demographics, diagnosis and each other, scored the images on multiple semi-quantitative scales, including tendon visibility/irregularity, pre-insertional and insertional tendon diameter, Doppler signal, presence of erosions, and tenosynovial effusion. Statistical analysis was conducted by the chi squared test, Tukey multiple comparisons post hoc test, and a mixed-effects, ordered logistic regression analysis.

Results: Eighty-eight subjects were enrolled: HC (n=37), RA (n=21), and SpA (n=20). Complete enthesis visualization was achieved more frequently in the perpendicular than in the cephalad view for the PBT (76.3% versus 58.7%), but more frequently in the cephalad view for the PTT (58.0% versus 19.6%). The PTT partially inserted and traversed the navicular en route to the metatarsals in 87.3% of subjects. Table 1 demonstrates the findings at the PBT and PTT entheses. Insertional tendon diameters were not significantly different. RA and SpA subjects had higher rates of PTT fiber disruption, tenosynovial effusion, and Doppler signal than HC. No significant differences existed at the PBT enthesis. Controlling for patient demographics, intra-observer variability, and idiosyncrasy of the grading system, RA and SpA subjects were 5.1 times (log-odds ratio 1.63, $p<0.001$) and 3.6 times (log-odds ratio 1.27, $p<0.001$) as likely as a HC to have a pathological sonographic result.

Conclusion: This study is the first to describe PBT and PTT imaging techniques that are both feasible and useful for rheumatologists. Perpendicular transducer aim is optimal for imaging the PBT, while cephalad transducer orientation was more effective for evaluation of the PTT. Unlike distal PBT imaging, PTT imaging distinguished HC from disease state, with both RA and SpA patients showing features of PTT enthesopathy much more commonly. This study confirms PTT enthesopathy as a sonographic manifestation of inflammatory arthritis.

	Healthy Control (n=37)	Rheumatoid Arthritis (n=21)	P value	Spondyloarthropathy (n=20)	P value
PBT enthesis diameter, mm (SD)	1.72 (0.43)	1.72 (0.29)	NS	1.72 (0.30)	NS
PTT pre-insertional diameter, mm (SD)	4.55 (0.53)	4.98 (0.98)	0.035	4.74 (0.98)	NS
PTT enthesis diameter, mm (SD)	1.93 (0.49)	2.10 (0.68)	NS	2.02 (0.77)	NS
PBT fiber disruption, %	0	0	NS	3.3%	NS
PTT fiber disruption, %	1%	21.3%	<0.001	22.7%	<0.001
PBT Doppler signal, %	0	6.1%	<0.01	1.7%	NS
PTT Doppler signal, %	0	15.6%	<0.001	5.8%	<0.01
PBT tenosynovial effusion, %	4.5%	5.6%	NS	2.5%	NS
PTT teno synovial effusion, %	7.2%	22.9%	<0.001	12.5%	<0.001

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Abstract Number: 147

Ultrasonographic Evaluation of Subclinical Enthesitis in Patients with Psoriasis

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Background/Purpose: Psoriasis is a diseases with diverse skeletal manifestations of which enthesistis is the primary lesion. However, enthesitis may often develop without any symptoms or signs. The primary objective of this study is to evaluate presence of subclinical enthesitis with ultrasonography in patients with psoriasis without any clinical findings of arthritis and/or enthisitis. Secondary objective is to compare ultrasonographic findings with clinical severity of psoriasis and enthesitis.

Methods: 30 patients with psoriasis without clinical findings of arthritis or enthesitis and 30 healthy volunteers as a control group were involved in the study. In the patient group PASI (Psoriasis Area and Severity Index), NAPSI (Nail Psoriasis Severity Index), MASES (Maastricht Ankylosing Spondylitis Entheses Score) and SPARCC (Spondyloarthritis Research Consortium of Canada); in the control group MASES and *SPARCC* scores were calculated. An investigator blind to clinical scores performed ultrasonographic examination on SPARCC scoring sites: bilateral achilles tendon, calcaneal insertion of the plantar fascia, patellar tendon insertion at the base of patella, quadriceps tendon insertion of the upper edge of the patella, trochanter major, supraspinatus tendon insertion at great tuberosity of humerus, medial epicondyle and lateral epicondyle. Acute, chronic and total enthesitis scores were calculated as described in literatures (1,2).

Results: In the patient group the total enthesitis score was significantly higher than the control group.(4.70±3.54SD in the patient group vs 2.90±2.36SD in the control group, p=0.04) There were no significant differences in the acute enthesitis score and chronic enthesitis scores between the groups.(acute enthesitis score the 0.83±1.08SD in the patient group vs 0.37±0.71 in the control group, p= 0.05; chronic enthesitis score 3.87±3.20SD in the patient group vs 2.53±2.09SD in the control group, p=0.14) There was no significant relationship between NAPSI, PASI, MASES, SPARCC scores and the ultrasonographic enthesitis scores in the patient group. In the patient group, there was a low level of statistically significant correlation between MASES and SPARCC scores.(r=0.38 p=0.03) There was no correlation between any of the other clinical scores.

Conclusion: Entheseal changes are common in clinically asymptomatic patients with psoriasis. Ultrasound may be useful in early detection of enthesitis. Reference:

1. Kaeley GS. Review of the use of ultrasound for the diagnosis and monitoring of enthesitis in psoriatic arthritis. *Curr Rheumatol Rep*. 2011;13(4):338-345.
2. Hamdi W, Chelli-Bouaziz M, Ahmed MS, et al. Correlations among clinical, radiographic, and sonographic scores for enthesitis in ankylosing spondylitis. *Joint Bone Spine*. 2011;78(3):270-274.

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Which Are the Ultrasound Lesions Underlying Dactylitis?

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Background/Purpose: Dactylitis (DACT) is defined as diffuse swelling of the digit and is included in the ASAS criteria for spondyloarthritis. It is a hallmark feature of psoriatic arthritis (PsA), occurring in 16-24% of cases. One of the main problems with the definition of dactylitis is the existence of a chronic non-tender form. The lack of tenderness suggests inactive disease, but subclinical inflammation may exist. Objective. To assess ultrasound (US) pathological lesions in dactylitic digits of patients suffering from PsA.

Methods: Consecutive PsA patients suffering from at least one DACT in feet or hand were included. The presence of DACT was diagnosed at clinical examination. At US examination, the entire DACT digit was scanned both on dorsal and palmar/plantar sides. The following ultrasound pathological lesions were scored: soft tissue thickness and edema, synovitis of MCP, PIP and DIP joints, inflammatory involvement of both flexor (tenosynovitis) and extensor (paratenonitis) tendons, nail bed vascularity, synovio-entheseal complex at DIP level, enthesitis of flexor tendon, intra-articular and extra-articular bone proliferation. Gray-scale (GS) and power-Doppler (PD) synovitis and tenosynovitis were assessed according to OMERACT scores (0-3). Nail bed vascularisation was scored 0 to 3. The other US lesions were scored 0 (absent) or 1 (present), both in GS and PD. The standard (HAQ) questionnaire, tender and swollen joint count, tenderness of DACT, global disease activity scored by physician and by patient were assessed in all patients.

Results: Twenty-eight DACT from 17 consecutive patients (8 men and 9 women) suffering from PsA were examined by US. Mean age was 43.3±11.2 years. Nine patients presented with hand DACT and 8 patients with foot DACT. Ten patients had single DACT. Seven patients presented with multiple DACT: 3 simultaneous DACT in 4 patients and 2 simultaneous DACT in 3 patients. Seven patients were on non-biologic DMARD, 2 patients were on combined therapy with biologics, one patient was on biologic monotherapy and 7 patients were DMARD naïve. Soft tissue thickness was present in all DACT. Synovitis of at least one joint was present in all DACT (28/28). The MCP synovitis was present in 75% (21/28) of DACT, PIP synovitis in 60% (17/28) of DACT, and DIP synovitis in 43% (12/28) of DACT. Inflammatory involvement of tendons was observed in 75% (21/28) of DACT: more flexor than extensor tendons were involved. Enthesitis was present in 68% (19/28) of DACT. Nail bed hypervascularisation (PD grade 3) was present in 14% (4/28) of DACT. Bone proliferation was present in 46% of DACT (13/28). A significant association between tenderness and the presence of PD and/or edema in the soft tissue was observed ($p<0.01$). The frequency of synovitis, tenosynovitis and enthesitis did not differ significantly between tender and non-tender DACT.

Conclusion: We show that US pathological lesions in DACT are more heterogeneous than previously reported. In particular, DACT is characterized by simultaneous involvement of joints, tendons and soft tissue. A significant amount of joint, tendon and entheseal inflammation persists in non-tender DACT. Tenderness tends to be associated with the presence of edema and/or PD inside the soft tissue, but larger samples are required to confirm these results. The impact of current treatments on inflammation might differ according to joint, tendon or entheseal level involved in DACT.

Disclosure: A. Nzeusseu Toukap, None; **A. Durnez**, None; **P. Navarro Guerra**, None; **M. Stoenoiu**, None.

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Abstract Number: 149

Comparation of Ultrasonic Imaging of Enthesopathy in the Lower Extremity in Patients with Psoriatic Arthritis, Psoriasis and Other Inflammatory

Arthritis

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Background/Purpose: To investigate the characteristics and differences of the ultrasonic imaging of enthesopathy in the lower extremity in patients with psoriatic arthritis(PsA), psoriasis(Ps) and other inflammatory arthritis, to explore the risk factors of Ps developing into PsA in the long term course, and to investigate the clinical practical value of the musculoskeletal ultrasound (MSUS) as a diagnostic modality in PsA.

Methods: Sex- and age-matched patients with 44 Ps, 44 PsA and 44 healthy controls (HCs) as well as 22 ankylosing spondylitis (AS), 22 rheumatoid arthritis (RA) and 11 osteoarthritis(OA) visting to the dermatological and rheumatic outpatient and ward department of the Chinese PLA general hospital were consecutively enrolled. MSUS of the lower limbs¡¯ entheses were performed, and then a comparation of ultrasonic imaging of enthesopathy between the 6 groups was made.

Results: 304(69.1%) of 440 enthesal sites were abnormal in Ps, compared with 345(78.4%) and 107(24.3%) abnormalities respectively in PsA and HCs (*P*=0.002, 0.000). The presence of erosion and power doppler (PD) signal in Achilles tendon were significantly higher in PsA than in Ps (9 vs 1, 12 vs 1, *P*=0.011, 0.002). Logistic regression results showed that a longer course of Ps may be a risk factor of developing into PsA (regression coefficient was 0.10, OR=1.10, *P*£¼0.001). The Glasgow Ultrasound Enthesitis Scoring System(GUESS) score was higher in PsA than in AS, RA and OA (*P*£¼0.001). The area under the ROC curve revealed that the GUESS accuracy in diagnosing PsA was 88.4 % with sensitivity and specificity of 86.4 and 79.8 %, respectively, at a cutoff value of 4.5.

Conclusion: The frequency of enthesopathy in the lower limbs was significantly higher in Ps and PsA who were absence of extremity musculoskeletal symptoms than HCs when detected by MSUS. Erosion and PD signal in Achilles tendon and a longer course of Ps may be the predictive factors of PsA. MSUS might help to identify entheseal changes in PsA.

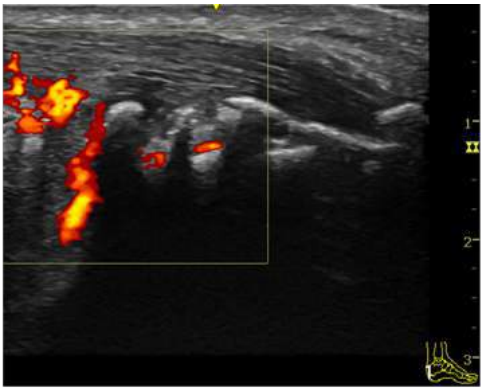

Figure 1 male, 45 years old, diagnosed as PsA for 8 years, representative US findings indicative of enthesopathy on longitudinal scan in left Achilles tendon are: enthesophyte, bone erosion, bursitis and PD signal in acute phase.

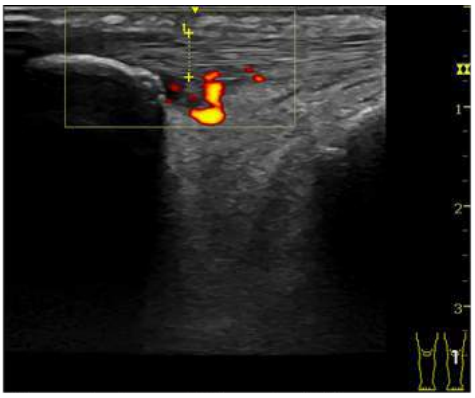

Figure 2 male, 43 years old, diagnosed as PsA for 6 years, representative US findings indicative of enthesopathy on longitudinal scan in left proximal patellar ligament are: entheseal thickness, bone erosion, bursitis and PD signal in acute phase.

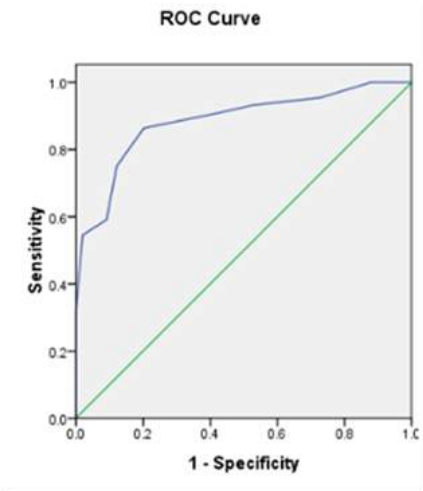

Figure 4 The GUESS accuracy in diagnosing PsA was 88.4 % with sensitivity and specificity of 86.4 and 79.8 %, respectively, at a cutoff value of 4.5.

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Abstract Number: 150

Ultrasonography and Magnetic Resonance Imaging Changes in Polymyalgia Rheumatica Patients Treated By Tocilizumab

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Background/Purpose: Clinical and biological exams are the basis for polymyalgia rheumatic (PMR) monitoring. New imaging techniques such as ultrasound (US) and magnetic resonance imaging (MRI) were recently developed to assess diagnosis and activity of PMR (1). However, concordances between MRI and US, and their sensitivity to change, have never been evaluated. Our objectives were to assess 1- imaging changes of both MRI and US (bursitis and intra articular effusion modifications) in patients treated by tocilizumab and which technique is more able to detect improvements according to the site and 2- the concordance between US and MRI at the first visit.

Methods: 20 glucocorticoid-free patients fulfilling Chuang's PMR criteria, with recent and active disease, were included in a prospective open-label study [ClinicalTrials.gov: NCT01713842] (2). They received three tocilizumab infusions at weeks 0, 4 and 8, without glucocorticoids, followed by oral prednisone from weeks 12 to 24. 18 patients were examined with both US (B and power Doppler mode) and MRI (T1 and T2-STIR weighted sequences) at baseline, week 2 and week 12. A semi-quantitative analysis was performed, scoring from 0 to 3 the disease activity (0= no lesion, 1= mild, 2 = moderate, 3= marked). Imaging were read by one blind reader for MRI and two trained readers for US. Wilcoxon signed-rank test and weighted Kappa coefficient were used for statistical analysis.

Results: 28 shoulders and 30 hips were analysed. No concordance between US and MRI observations was significantly noted at baseline. Activity significantly changed between week 0 and week 12 for hips and shoulders bursitis with MRI (p = 0,005) and US (p=0,029). Considering effusion, imaging lesions of all the joints significantly changed in US (p =0,001) but not in MRI (p=0,231). Bursitis improvement was detected more easily by MRI for the hips (73 %) and by US for the shoulders (57 %). Shoulders and hips effusions significantly regressed in US (improvement 25 to 47%). There was a low proportion of worsening, whether for bursitis (5% with MRI and 17,5% with US) or effusion (10 % with MRI and 3,5% with US).

Conclusion:

US and MRI allow to evaluate the evolution of joints involvement in PMR patients treated by tocilizumab. The two imaging techniques should be used differently, considering shoulders or hips for MRI.

1 Dasgupta B et al. Rheumatology 2010;49:186–90. 2-Devauchelle-Pensec V et al Ann Rheum Dis. 2016 Feb29.doi:10.1136. .

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Abstract Number: 151

Distinct Phenotypes in Palindromic Rheumatism: Ultrasound and MRI during Palindromic Flares

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Background/Purpose: Palindromic rheumatism (PR) is defined as a recurrent, self-abortive arthritis and/or para-arthritis, which progresses to RA in up to 50% patients (pts), particularly those that are anti-CCP+(1). The anatomical basis for the palindromic flare is unclear and may provide insights into the initial phases of RA. We aimed to describe the ultrasound (US) and MRI phenotype of palindromic flare, focussing on intra- and peri-articular inflammation, as compared to early RA.

Methods: Pts were recruited from a prospective PR cohort. Palindromic flares were defined as the presence of ≥2 of pain, swelling, erythema in or around ≥ 1 joint, that later returned to normal. Comprehensive blinded US assessment (wrists, MCPs, PIPs, elbows, knees, MTPs, bilateral ECU and 2nd - 5th finger flexor tendons) was performed during flares. Tenosynovitis (TSV), peri-tendinous oedema (PTO), peri-articular soft tissue inflammation and subcutaneous (s/c) oedema were reported at each joint region. MRI was performed on the most symptomatic region during flare. MRIs were RAMRIS scored and descriptively scored by a blinded experienced reader for TSV, PTO, peri-articular soft tissue inflammation and s/c oedema. The same information was collected in the early RA pts.

Results: Twenty one flares were captured in 15 PR pts and imaged by US (21) and MRI (9) between May 2015 and April 2016 and compared with US and MRI of 16 early RA pts. The mean age of PR pts was 47 years, 10/15 (67%) were anti-CCP+ and 5/15 (33%) anti-CCP-. 13/15 (87%) were DMARD naive. All 15 pts had US (1pt had 3 flares captured, 4 pts had 2, and the remainder had 1) and 8 pts had MRI (4 anti-CCP+, 4 anti-CCP-, 1 had 2 flares captured). On US 10/15 pts (67%) had peri-articular inflammation and/or s/c oedema, in 6 pts this was without synovitis or TSV. Grey scale synovitis was present in 9/15 pts (60%), TSV and/or PTO were present in 5/15 (33%) pts. Power Doppler (PD) synovitis was present in only 3/15 (20%) pts. No erosions were found. On MRI, synovitis was present in 7/8 pts (88%), bone marrow oedema (BME) in 1 (11%) and no erosions were found. US (table 1) and MRI (table 2) lesions are shown for all palindromic flares and early RA pts.

Conclusion: PR has a distinct phenotype with peri-articular soft tissue inflammation and s/c oedema common in PR flares and occurring independently of synovitis and TSV. Synovitis and TSV appear more prevalent on MRI in anti-CCP+ rather than anti-CCP- PR pts in whom s/c oedema seems a prominent finding. The low prevalence of PD synovitis, BME and erosions further distinguishes PR flares from the imaging phenotype in RA. (1)Russell et al. J Rheum 2006

	Palindromic Rheumatism		**Early RA**
	anti-CCP+ (n=15)	**anti-CCP- (n=6)**	**(n=16)**
Synovitis	7 (56%)	4 (67%)	7 (44%)
Tenosynovitis	3 (25%)	2 (33%)	Not available
Peri-tendinous oedema	2 (13%)	0 (0%)	Not available
Peri-articular inflammation	8 (62%)	3 (50%)	Not available
Subcutaneous oedema	7 (47%)	4 (67%)	Not available
Erosions	0 (0%)	0 (0%)	Not available

Table 1.

	Palindromic Rheumatism		Early RA
	anti-CCP+ (n=4)	anti-CCP- (n=5)	(n=16)
Synovitis	4 (100%)	3 (60%)	10 (62%)
Tenosynovitis	3 (75%)	3 (60%)	6 (38%)
Peri-tendinous oedema	3 (75%)	3 (60%)	0 (0%)
Peri-articular inflammation	3 (75%)	3 (60%)	0 (0%)
Subcutaneous oedema	1 (25%)	3 (60%)	0 (0%)
Bone marrow edema	0 (0%)	1 (20%)	3 (19%)
Erosions	0 (0%)	0 (0%)	9 (56%)

Table 2.

Disclosure: K. Mankia, None; **M. A. D'Agostino**, None; **L. Horton**, None; **J. L. Nam**, None; **J. E. Freeston**, None; **A. J. Grainger**, None; **P. Emery**, None.

Abstract Number: 152

Median Nerve Stiffness Measured By Elastosonography in Patients with Rheumatoid Arthritis Is Higher Than Controls

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Session Time: 9:00AM-11:00AM

Background/Purpose: Carpal tunnel syndrome (CTS) is the most frequent neuropathy of all entrapment neuropathies, believed to be present in 3.8% of the general populatio. Idiopathic CTS is the most common diagnosis in patients with CTS. However, there are a lot of conditions that generate secondary CTS, it is considered that rheumatoid arthritis (RA) is one of the disease generate secondary CTS. The pathophysiology of CTS of RA might be a little bit different from idiopathic CTS. RA is a disease that has the characteristics to generate inflammatory synovial proliferation of the joint and tenosynovitis. Although inflammation of the wrist joint and synovial tissue of the flexor tendons can cause increased pressure in the carpal tunnel, there is a possibility that even RA patients without symptoms of CTS also have subclinical median nerve damage because of the synovial proliferation and inflammation. This aim of this study was to compare the elasticity of the median nerve between patients with RA without symptom of CTS and controls by quantitative elastosonography.

Methods: This study was performed with institutional review board approval and written informed consent from all participants. Four hundred two hands in 201 patients with RA and 222 hands in controls were included. All participants were examined both wrists. Patients were excluded in this study if they had conditions associated with an increased

incidence of CTS (diabetes mellitus, acute trauma, pregnancy, hypothyroidism, hyperthyroidism or connective tissue disease except for RA), history of wrist or hand fracture, surgery, history of other systemic neurologic disorders and radiculopathy. Patients with bifid median nerve, or any mass lesion identified on US examination of the wrist were also excluded from this study. US was performed by using a 5- to18-MHz linear array transducer (HI VISION Ascendus; Hitachi-Aloka Medical,Tokyo, Japan). We attached an acoustic coupler (EZU-TECPL1; Hitachi-Aloka Medical) with a standardized elasticity to the transducer as a reference medium. The inlet of the carpal tunnel at the scaphoidpisiform level and the proximal portion of the carpal tunnel inlet were scanned in a transverse plane. The cross-sectional area (CSA) and the elasticity of the median nerve, which was measured as the acoustic coupler /median nerve strain ratio, were evaluated. The measurements were repeated two times, and the average strain ratio was used for analysis.

Results: Three hundred forty-two hands in 177 patients with RA (139 female, mean age was 63.8 years old) and 158 hands in 81 controls (68 female, mean age was 71.5 years old) were analyzed. The CSA of the median nerve at the level of inlet of the carpal tunnel and proximal portion of the carpal tunnel inlet were not significantly differenced in both groups. Strain ratio in the patients with RA were significantly higher than those in the controls (2.66 vs 2.20; p=0.003 in right hand, 2.59 vs 2.13; p=0.002 in left hand) at the inlet of the carpal tunnel level. However, strain ratio at the proximal portion of the carpal tunnel inlet level was not significantly differenced in both groups.

Conclusion: The median nerve stiffness measured by elastosonography in patients with RA without symptom of CTS is higher than controls. This results suggest that inflammation of flexor tendon and wrist joint may generate fibrotic change for median nerve.

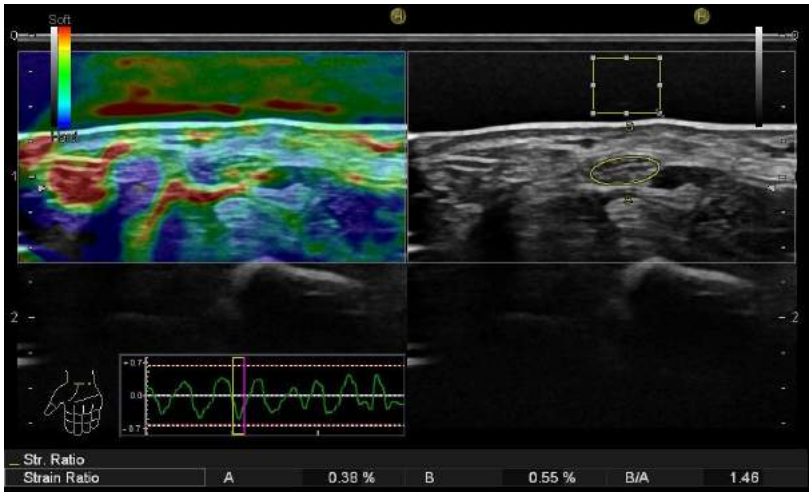

Figure: The images of acoustic coupler /median nerve strain ratio.

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Abstract Number: 153

Synovial Immunophenotype and Ultrasonography: A Contemporaneous Study of Different Compartments of the Knee Joint

Aurélie Najm[1,2], Carl Orr[3], Benoît Le Goff MD PhD[1], Ursula Fearon[4] and Douglas J. Veale[5], [1]Rheumatology, Nantes University Hospital, Nantes, France, [2]Rheumatology, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland, [3]Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin 4, Ireland, [4]Trinity College Dublin, Department of Molecular Rheumatology, Trinity College Dublin, Dublin, Ireland, [5]Consultant Rheumatologist, Centre for Arthritis and Rheumatic Disease, St. Vincent's University Hospital and University College Dublin, Dublin 4, Ireland

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Background/Purpose: Histological analysis of synovial tissue, despite being a reliable and accurate assessment for synovitis, is not routinely performed. Ultrasonography (US) is a fast, available and low cost imaging tool and has been validated for detecting synovitis. Ultrasonographic and macroscopic findings at arthroscopy have been shown to correlate well. However, a few studies have assessed the correlation of ultrasonographic and immunophenotypic features of synovial tissue, with contradictory results and mostly on long lasting rheumatoid arthritis patients. The aims of this study were (a) to assess the correlation between ultrasonographic and histological scores for inflammation and vascularity in knee joint synovitis; and (b) to evaluate the strength of the correlation for both inflammation and vascularity scores in the 3 major compartments of the knee using US, arthroscopic and histological evaluation.

Methods: Patients of an early arthritis cohort were prospectively included in the study. One operator (AN) performed a knee ultrasonography (B mode and Power Doppler mode) of the three major compartments (medial, lateral and superior) prior the arthroscopy. B mode synovitis grade and Power Doppler activity were scored semi-quantitatively. A different operator (CO/DV) then performed a knee arthroscopy and scored macroscopic aspects with a 100-mm numeric scale (NS) blinded to the US findings. Biopsies were obtained from each compartment, stained with standard H&E, CD68 and Factor VIII, and then analyzed by another operator (UF) blinded to both the US and arthroscopic findings and scored for lining layer hyperplasia, inflammation and vascularity. Statistical analysis was made with non parametric Spearman correlation test.

Results: 26 patients were included. 17 had rheumatoid arthritis (RA) (ACR/EULAR 2010 criteria). 3 patients had psoriatic arthritis (PsA) (CASPAR criteria), 4 had osteoarthritis (OA), 1 had gout and 1 had undifferentiated arthritis. 17 patients (65.4%) were untreated at inclusion. Strong correlations were observed between: US synovitis grade and histological inflammation score (r=0.60; p=0.002), US Power Doppler grade and histological score for vascularity (r=0.69; p<0.001); US measured synovial thickness and lining layer hyperplasia (r=0.61; p=0.002); US synovitis grade and CD 68 score (r=0.49; p=0.02). The findings were homogeneous within the joint as high positive correlations were observed for both histological lining layer hyperplasia and inflammation between lateral and medial compartments (r=0,95; p<0,0001 and r=0.68; p=0.014 respectively), lateral and superior compartments (r=0.78; p=0.001 and r=0.51; p=0.048, respectively) and medial and superior compartments (r=0.69; p=0.004 and r=0.69; p=0.004, respectively).

Conclusion: B mode and Power Doppler US findings strongly correlate with histological inflammation and vascularity scores in actively inflamed knee joints. Ultrasound is therefore an accurate tool for knee joint synovitis assessment of the four most common rheumatic disease diagnoses - RA, PsA, OA and gout.

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Abstract Number: 154

Radiographic Knee Osteoarthritis in Patients Complaining of Knee Pain: Ultrasound Features

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Background/Purpose: to date diagnosis of knee osteoarthritis (OA) is based on clinical examination and radiological features. Our objetive was to evaluate the diagnostic test properties of ultrasound (US) for the detection of radiographic knee OA.

Methods: consecutive patients complaining of knee pain were included. Exclusion criteria were: younger than 18 years old, history of knee surgery or trauma, severe knee deformities and corticosteroid injection within the last 2 months. US examinations were performed by an experienced rheumatologist, blinded to clinical and radiological data, using a MyLab 70 machine (Esaote) provided with a multi-frequency linear transducer (4-13 MHz). Standardized scanning method was adopted in order to evaluate the following US abnormal findings: osteophytes (protrusions at the joint margin seen in two planes and visualized as either proximal or distal to the joint) and degenerative femoral hyaline cartilage involvement (presence of at least two of the following: loss of sharpness of the cartilage margins, loss of homogeneity of the cartilage layer and cartilage thinning focal or extend to the entire cartilaginous layer). Weight-bearing anteroposterior (AP) and lateral knee radiographs were read by an experienced rheumatologist, blinded to the clinical and US data, who determine the presence or absence of radiological degenerative changes and classified the severity of knee OA using Kellgren-Lawrence (KL) grading scale.

Results: 281 patients (mean age 64 ± 17 years, 173 (61,6%) female) were included for a total of 322 knees evaluated (41complained of bilateral knee pain). Both the presence of osteophytes and/or femoral hyaline cartilage involvement detected by US were more frequent in those knees with radiographic changes indicative of OA regardless severity acording KL grading scale (Table 1). Table 2 shows the diagnostic test properties of the US abnormal findings for the detection of knee OA using radiological data as reference method.

Conclusion: US demonstrate an excellent sensitivity with an adequate specificity for the detection of radiographic knee OA. US femoral hyaline cartilage involvement and/or US osteophytes showed the best sensitivity while isolated US osteophytes showed the best specificity. US could be used in patients with knee pain when OA is suspected. **Table 1.** Frequency of the US abnormal findings according radiographic features of knee OA.

	Presence of radiological degenerative changes, n: 188				**Abscence of radiological degenerative changes, n: 144**
	KL 1, n: 36	**KL 2, n: 20**	**KL 3, n: 118**	**KL 4, n: 14**	
US femoral hyaline cartilage involvement, % (CI 95%)	77 (64-92)	70 (49-90)	97 (93-99)	100	24 (17-31)
US osteophytes, % (CI 95%)	62 (44-73)	90 (76-100)	85 (79-92)	100	14 (8-20)
US femoral hyaline cartilage involvement and/or US osteophytes, % (CI 95%)	92 (82-100)	100	95 (91-99)	100	24 (16-31)
US: ultrasound; OA: osteoarthiritis; KL: Kellgren-Lawrence					

Table 2. Diagnostic test properties of the US abnormal findings for the detection of knee OA using radiological data as reference method.

	Sensitivity, % (CI 95%)	Specificity, % (CI 95%)	PPV, % (CI 95%)	NPV, % (CI 95%)
US femoral hyaline cartilage involvement	90 (86-95)	75 (68-83)	84 (79-89)	85 (78-91)
US osteophytes	82 (77-88)	86 (80-92)	89 (84-94)	78 (71-84)
US femoral hyaline cartilage involvement and/or US osteophytes	95 (92-98)	76 (69-83)	85 (80-90)	92 (87-97)
US: ultrasound; PPV: positive predictive value; NPV: negative predictive value; CI: confidence interval				

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Abstract Number: 155

Evaluation of Ultrasonography As Modality for Identification of Calcium Crystal Deposits in Patients of Primary Osteoarthritis of Knee Joint

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Background/Purpose: Calcium deposition diseases, the disordered calcification of cartilage and/or periarticular soft tissue, are associated with aging, degenerative joint disease, and genetic and metabolic disorders. These conditions are often diagnosed by plain radiography; however, definitive diagnosis requires synovial fluid analysis. Recently Ultrasonography has emerged as a very useful tool for assessment of musculoskeletal disorders. This study was planned to assess the performance of Ultrasonography to detect calcium crystal deposits, as compared to Radiography and Crystal examination, in primary osteoarthritis patients.

Methods: Twenty consecutive primary osteoarthritis patients, who fulfilled ACR criteria for knee osteoarthritis, were enrolled from the rheumatology out patient department of a tertiary care centre. Radiological and sonographic assessment was performed to assess the extent and severity of joint involvement. Presence of crystals in synovial fluid were evaluated by polarized microscope. For the purpose of reproducibility and objectivity in USG findings, the evidence of calcium deposits was taken as presence of chondrocalcinosis of femoral condylar cartilage or meniscal deposits of calcium.

Results: Eight patients were males 12 were females. Average age of patients was 62.6 years. Average duration of illness was 5.5 years. Total 40 knee joints were assessed. Evidence of calcium deposit was seen in radiographs of 11 knee joints (only condrocalcinosis in 5, only meniscus calcification in 4 and both in 2), while USG detected calcification in 35 knee joints (only condrocalcinosis in 2, only meniscal calcification in 12 and both in 21) [p=<0.0005]. The synovial fluid examination revealed Calcium crystals in 16 patients (CPPD in 14 and BCP in 2 patients). The difference between USG analysis and Synovial fluid analysis was not statistically significant.

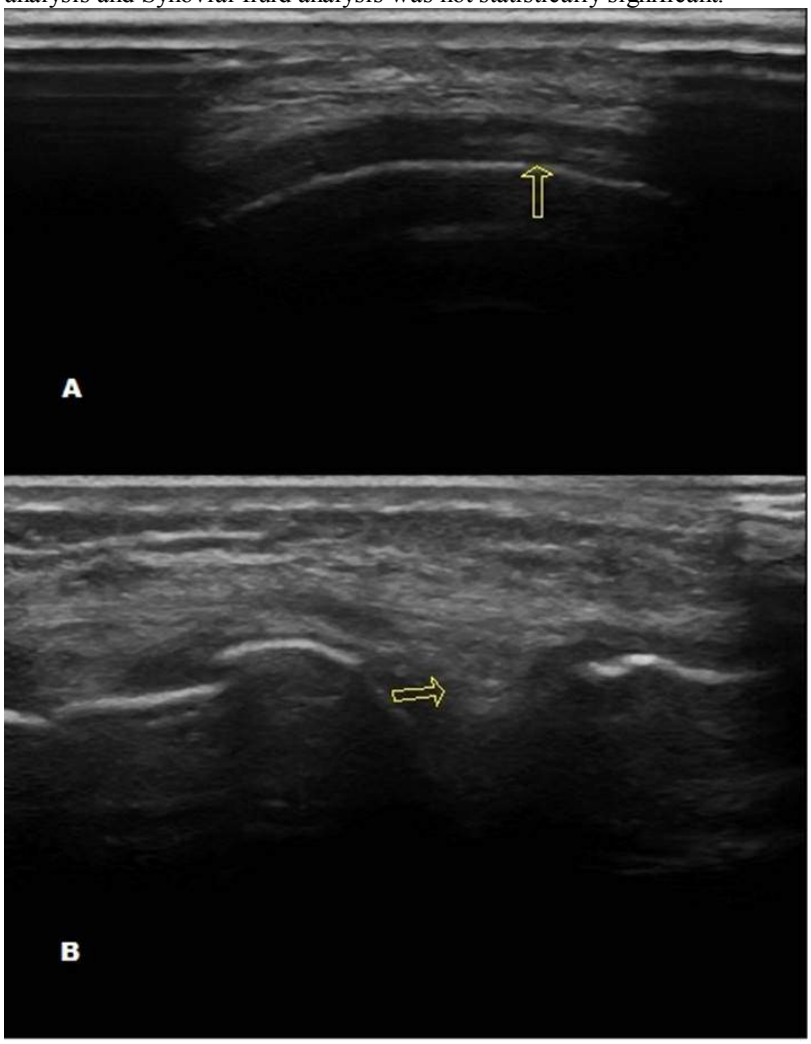

Figure 1. USG images showing A. Chondrocalcinosis in femoral condyle and B. Calcium deposits in Medial meniscus.

Conclusion: Ultrasonography has high sensitivity and specificity for detection of calcium crystal deposits. It is a better modality than plain or digital radiographs, and it appears more sensitive than Synovial fluid crystal examination. However larger studies are needed to be carried out to establish its accurate efficacy.

Disclosure: S. K. Das, None; **D. Srivastava**, None; **U. Dhakad**, None; **M. Singh**, None; **R. Srivastava**, None; **A. Wakhlu**, None.

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Abstract Number: 156

Detection of Finger Joint Osteophytes and Bone Erosions By Ultrasound; A Comparison to Computed Tomography and Histology

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Graz, Austria, [2]Department of Rheumatology and Clinical Immunology, Medical Faculty, University Medical Center, University of Freiburg, Freiburg, Germany, [3]Department of Anatomy, Medical University of Graz, Graz, Austria, [4]Core Facility Alternative Biomodels & Preclinical Imaging, Medical University of Graz, Graz, Austria, [5]5Institute of Pathology, Medical University of Graz, Graz, Austria
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Background/Purpose: Ultrasound (US) is an emerging technique for the examination of osteoarthritis of the hands (HOA).Bone erosions and osteophytes are hallmarks of advanced HOA. We studied the reliability of US findings in proximal interphalangeal (PIP) and distal interphalangeal (DIP) joints compared to micro computed tomography (µCT) and histology in fingers of dissecting room cadavers.

Methods: We obtained 30 fingers with and without signs of nodal HOA from 15 cadavers donated to the Institute of Anatomy. Written informed consent had prior been given in the lifetime of the individuals. We analyzed PIP and DIP joints using an Esaote MyLabTwice US machine with a 6-18Mhz probe and a Siemens INVEON µCT. The occurrence of erosions and osteophytes was scored for 16 defined regions of each joint (ulnar, radial, dorsal, palmar, dorso-ulnar, palmo-ulnar, dorso-radial, palmo-radial aspect of the joint region of the proximal and distal articulating bone). Thereafter, finger joints were fixed in 4% formalin and embedded in acrylic resin. Serial sections of the joints were stained with haematoxilin/eosin, safranin O, and Pappenheim's solution. Erosions and osteophytes in the different joint regions were assessed. Differences between groups were analyzed using Wilcoxon signed-rank test. Correlations were analyzed with Spearman-Rho test.

Results: In the PIP joints US detected more erosions than µCT (28 vs. 19, p=0.028). The findings of both methods correlated well (r=0.51, p=0.004). The number of erosions in histology correlated significantly with the findings of the µCT (r=0.61, p=0.047) but not with US. US and µCT detected a similar frequency of osteophytes (225 vs. 248, p=0.028) in the PIP joints. Both methods correlated well with each other(r=0.47, p=0.009). Only US correlated with histology (r=0.76, p=0.006). In the DIP joints US, µCT and histology did not yield correlating results. US and µCT detected a similar number of osteophytes in the DIP joints (333 vs. 245, p=0.13) and the findings of both methods correlated significantly (r=0.46, p=0.013). The number of osteophytes on histologic examination did not correlate with osteophytes in US or µCT (r=0.14, p=0.63 and r=0.43, p=0.13, respectively).

Conclusion: US is comparable to µCT in the identification of osteophytes in PIP and DIP joints. Erosions identified by US should be interpreted with caution. Both US and µCT overestimate the frequency of erosions and osteophytes compared to histologic examination.

Abstract Number: 157

Synovitis of Sternoclavicular and Peripheral Joints Can be Detected By Ultrasound in Patients with SAPHO Syndrome

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Background/Purpose: Synovitis-acne-pustulosis-hyperostosis-osteitis (SAPHO) syndrome is characterized by multiple osteoarticular inflammation and dermatologic disorders such as palmoplantar pustulosis. Although the single available study evaluated enthesitis by ultrasound (US), we have been unable to find any study that evaluated abnormalities detected by US of the sternoclavicular joint (SCJ) and peripheral joint (PJ) in patients with SAPHO syndrome. The objective of the present study was to determine the prevalence of US abnormalities of the SCJ and PJ in patients with SAPHO syndrome.

Methods: Thirteen patients with SAPHO syndrome who fulfilled diagnostic criteria proposed by Kahn for SAPHO syndrome 2003 and 13 healthy individuals age- and sex-matched were enrolled. Synovitis, defined by synovial hypertrophy with power Doppler (PD) signals, of the SCJ and the PJ including wrist, MCP, PIP and the other symptomatic joints were evaluated by US.

Results: All of the patients had anterior chest wall symptoms, and spinal and peripheral symptoms were seen in 69.2% and 46.2% of the patients, respectively. Synovitis with PD signals was detected in 16 (61.5%) of the 26 SCJ and 11 (84.6%) of the SAPHO syndrome patients, and none of the controls. Synovitis with PD signals in any PJ was detected in 4 (30.7%) of the SAPHO syndrome patients. Tenosynovitis or tendinitis of the hands was seen in two (15.4%) patients.

Conclusion: Our study has demonstrated that US can detect the abnormalities of the SCJ and PJ in SAPHO syndrome with high sensitivity. US may be a useful method for the early diagnosis of SAPHO syndrome. ADDIN EN.REFLIST

Disclosure: M. Umeda, None; **S. Kawashiri**, None; **A. Nishino**, None; **H. Nakamura**, None; **A. Kawakami**, None.

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Abstract Number: 158

Musculoskeletal Ultrasound Is a Sensitive Imaging Tool for the Assessment of Dynamic Changes of Bone Erosions in Inflammatory Arthritis: A Comparative Analysis with High-Resolution Peripheral Quantitatve Computed Tomography

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Background/Purpose: Correct detection of bone erosions is crucial both for diagnosis and for monitoring of treatment response in patients with inflammatory joint diseases. Musculoskeletal ultrasound (MSUS) is known to have a higher sensitivity than conventional radiography regarding detection of bone erosions (1). Therefore, MSUS is increasingly used as an imaging outcome parameter. Standardization and validation of MSUS is a current task of the OMERACT ultrasound working group. **Aim:** Our study aimed to investigate the sensitivity and specificity of MSUS in the detection of erosions over time compared to HR-pQCT as a gold standard.

Methods: This is a follow-up study on our 2012 cross-sectional comparative analysis on MSUS and HR-pQCT (2). Four of 6 healthy individuals, 6/6 psoriatic arthritis patients and of 9/14 rheumatoid arthritis patients were available for follow-up and received an MSUS and an HR-pQCT scan of the clinically dominant hand. Again, bone erosions at the radial, palmar, and dorsal site of metacarpophalangeal (MCP) joint two, as well as the palmar and dorsal regions MCP joints 3 and 4 were assessed for prevalence and severity. Data were then compared to those taken in 2012. Prevalence and severity of bone erosions as determined by US and by micro-CT were recorded and compared. MSUS was graded as described earlier (2).

Results: After eliminating those datasets without follow-up from the baseline cohort sensitivity of MSUS as compared to HR-pQCT for correct detection of erosions was 95% and specifiity was 74%. For this analysis, grade 1 lesions were included. At follow-up sensitivity was 85% and specifiity 79%. At follow-up, 36 MSUS-lesions were no longer detectable in MSUS; 21/36 were false-positive lesions at baseline. Only one false-positive lesions was detected at both time points. One new lesion was detected by MSUS and confirmed by HR-pQCT. Overall grading in MSUS indicating severity of one erosions regressed; these findings were confirmed by HR-pQCT (p=0.04).

Conclusion: This is the first study assessing change of bone erosions over time using MSUS and HR-pQCT. MSUS was confirmed a sensitive imaging tool able to detect dynamic changes of erosions; it could be used for monitoring of treatment response in inflammatory joint diseases. Knowledge of predilection sites of erosions and physiological cortical breaks might help to correctly differentiate bone erosions from vessel channels and further increases the diagnostic value of MSUS. **References:** 1. Wakefield RJ, Gibbon WW, Conaghan PG, O'Connor P, McGonagle D, Pease C, et al. The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography. Arthritis Rheum. 2000 Dec;43(12):2762-70. 2. Finzel S, Ohrndorf S, Englbrecht M, Stach C, Messerschmidt J, Schett G, et al. A detailed comparative study of high-resolution ultrasound and micro-computed tomography for detection of arthritic bone erosions. Arthritis Rheum. May;63(5):1231-6.

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Abstract Number: 159

Assessing Agreement Among Measures of Inflammation Detected on Magnetic Resonance Imaging, Ultrasound and Clinical Findings in the Feet of Patients with Early Rheumatoid Arthritis

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Background/Purpose: In metatarsalphalangeal (MTP) joints 2-5 of patients with early rheumatoid arthritis (RA), we

aimed to assess the agreement between i) Magnetic Resonance Imaging (MRI) and ultrasound (US) findings of inflammation, and ii) clinical swelling and each of MRI and US findings of inflammation.

Methods: Participants with early RA (ACR criteria) were recruited. Clinical exam was followed by an MRI scan (1.0 Tesla peripheral MRI) and US scan of MTPs 2-5 of the most symptomatic foot. MRI scans were scored by a blinded radiologist using OMERACT RAMRIS criteria for bone marrow edema (BME) (0-3) and synovitis (0-3). Using OMERACT criteria, US images were assessed for synovial thickening (0-3), synovial flow (power Doppler (PD)) (0-3), and erosions (present/absent) in each MTP joint by a rheumatologist, who also assessed swelling (presence/absence) in each MTP. To compare inflammation on MRI versus US, kappa statistics were determined for: MRI synovitis and US synovial thickening, MRI synovitis and US PD, MRI BME and US synovial thickening, and MRI BME and US PD. Agreements between clinical swelling and each MRI and US feature of inflammation (0 = absent, ≥1 on MRI or US = present) were assessed using kappa statistics. The proportions of imaging-detected inflammation also detected clinically were determined.

Results: The study included 33 women, 6 men; mean age 51.6 years (standard deviation=10.2). Table 1 presents weighted kappa statistics for agreement between MRI and US findings of inflammation. Like agreement between synovitis on MRI and US PD, agreement between MRI detected BME and US PD was fair to good. Table 2 presents agreement between clinical swelling and inflammation on MRI and US. Neither US synovial thickness nor MRI synovitis agreed with clinical swelling. There was fair agreement (kappas 0.2322-0.3664) between clinical swelling and each of US PD and MRI BME, but this was stronger in some joints than others. Table 1: Agreement in Inflammation detected by MRI and Ultrasound

	Joint	kappa	95% CI
MRI synovitis vs. US synovial thickening	MTP2	0.0415	-0.0804, 0.1634
	MTP3	0.0683	-0.0545, 0.1910
	MTP4	0.2541*	0.0135, 0.4947
	MTP5	0.2905*	-0.0971, 0.6781
MRI synovitis vs. US power Doppler	MTP2	0.2838*	0.0112, 0.5565
	MTP3	0.4700*	0.2417, 0.6984
	MTP4	0.3358*	0.0367, 0.6349
	MTP5	0.2506*	-0.0942, 0.5954
MRI BME vs. US synovial thickening	MTP2	0.0376	-0.0820, 0.1572
	MTP3	0.0285	-0.0733, 0.1303
	MTP4	0.2400*	0.0045, 0.4755
	MTP5	0.1784*	-0.1199, 0.4766
MRI BME vs. US power Doppler	MTP2	0.2680*	-0.0130, 0.5490
	MTP3	0.2729*	0.0191, 0.5266
	MTP4	0.3294*	0.0286, 0.6302
	MTP5	0.2290*	-0.0987, 0.5567

*denotes kappa is significant ($p<0.05$) Table 2: Agreement in Swelling on Clinical Exam compared to Ultrasound and MRI findings of Inflammation

	Joint	Kappa	95% CI	Prevalence Index	Bias Index	% of imaging detected inflammation also detected clinically
Clinical swelling vs. US synovial thickening	MTP2	0.0612	-0.0852, 0.2077	0.2250	0.5250	37.1
	MTP3	0.0428	-0.1341, 0.2197	-0.1220	0.4878	21.4
	MTP4	0.0267	-0.1409, 0.1943	-0.5610	0.3415	6.3
	MTP5	0.1323	-0.1874, 0.4520	- 0.7561	0.1463	12.5
Clinical swelling vs. US power Doppler	MTP2	0.1659	-0.1093, 0.4411	-0.5366	-0.2195	60.0
	MTP3	0.3664*	-0.0022, 0.7351	-0.6829	-0.0732	60.0
	MTP4	0.2870*	-0.2124, 0.7864	-0.8537	0.0488	25.0
	MTP5	0.2322*	-0.2113, 0.6757	-0.8293	0.0732	20.0
Clinical Swelling vs. MRI Synovitis	MTP2	-0.0680	-0.3544, 0.2184	-0.1000	0.2000	31.8
	MTP3	0.1000	-0.1467, 0.3467	-0.3000	0.3000	25.0
	MTP4	0.0625	-0.1601, 0.2851	-0.6500	0.2500	8.3
	MTP5	-0.0843	-0.1799, 0.0113	-0.7750	0.1250	0
Clinical Swelling vs. MRI BME	MTP2	0.2799*	-0.0272, 0.5869	-0.2368	0.0789	50.0
	MTP3	0.2714*	-0.0012, 0.5440	-0.3421	0.2368	35.3
	MTP4	0.0579	-0.1639, 0.2796	-0.6316	0.2632	8.3
	MTP5	0.1857	-0.2098, 0.5812	-0.7895	0.1053	16.7

*denotes kappa is significant ($p<0.05$) There was fair agreement between ultrasound PD and MRI features of BME and synovitis; and ultrasound synovitis and MRI synovitis and BME, but only for MTP4 and 5. There was similar fair agreement between clinical swelling and imaging features of inflammation (BME and PD), but poor for clinical swelling and imaging measures of swelling.

Conclusion: These findings confirm agreements in the imaging parameters of inflammation and suggest that imaging by US and MRI are better than clinical assessment in determining synovial inflammation.

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Abstract Number: 160

Ultrasound Assessment of Rheumatoid Arthritis Patients. External Validation and Inter-Rater Reliability of a 4-Joint Ultrasonographic Scoring System

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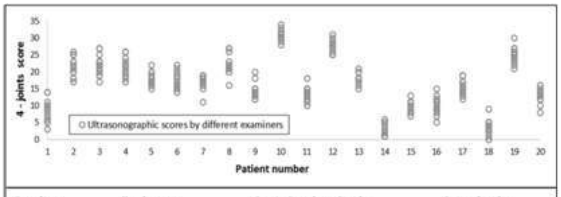
Background/Purpose: Although Ultrasound (US) has demonstrated to be a sensitive and specific tool, its feasibility in daily clinical practice is still under debate. We have developed and validated a fast 4-joints ultrasonographic (US) score to assess disease activity in RA patients. This score named REUMA (***R**apid **E**valuation by **U**S to **M**onitor **A**rthritis*) showed an excellent correlation with 28-joint US assessment and good responsiveness. In order to generalize the utilization of this new and simple US score, we evaluated the performance of this score using an external sample of RA patients and assessed the intra and inter-reader reliability. **Material and**

Methods: We conducted a multicenter cross-sectional study, including ambulatory patients with RA diagnosed according to ACR/EULAR 2010 criteria. Clinical data, demographic and disease characteristics were recorded. The 4-joints US score was calculated for each patient including bilateral radio and intracarpal joint and second metacarpophalangeal. Power Doppler (PD) and gray scale (GS) were graded from 0 to 3, according to OMERACT standards. Total 4-joints US score comes as the result of the addition of PD and GS scores, with a total score ranged from 0–36, being 36 the highest disease activity. Inter and intra-rater reliability were assessed in a web-based exercise using static images from 20 patients, evaluated by 15 ultrasonographers from different centers. Statistical analysis included evaluation of psychometric properties of the 4-joints score including construct validity and internal consistency (Cronbach's α coefficients). The inter and intra-rater reliability were assessed using a two-way random, absolute, average-measures intra-class correlation coefficient (ICC)

Results: 210 RA patients from 9 Rheumatology Centers were included. Mean age was 53 ± 10 years, 89% were female, and disease duration was 8 ± 6 years. Baseline DAS28 score was 3.97 ± 1.47. Mean 4-joints US score was 9 ± 7 (Doppler subscale 3 ± 4; Synovitis subscale 6 ± 4). The score showed an acceptable confiability (Cronbach's α = 0.89) and good correlation with DAS28 (rho spearman= 0.81, $p<0.01$). Floor and ceiling effect were 8% and 0%, respectively. The ICC was excellent for intra [ICC = 0.981 (IC95% 0.955 – 0.999)] and inter-reader reliability [(ICC = 0.994 (IC95% 0.988 – 0.997). Figure 1 shows distribution of US scores and descriptive statistics on the 20 measurements for each of the 15 readers. There is low variation between the means of the readers, with no obvious outliers, and consistent variation within readers (p = 0.84).

Conclusion: The 4-joint US score represents a fast and reliable instrument, with a high degree of absolute agreement between observers from multiple centers. These characteristics make this score an excellent candidate to assess RA patients in daily rheumatology practice. Figure 1. Distribution of 4-joints US scores among 20 patients for each of the

fifteen examiners.



Examiner	Total score			Power Doppler subscale			Gray subscale		
	Mean ± SD	Min	Max	Mean ± SD	Min	Max	Mean ± SD	Min	Max
1	14±7	1	28	8±4	0	14	7±4	1	14
2	16±7	4	30	10±3	4	16	6±4	0	14
3	16±8	0	30	10±5	0	16	6±4	0	16
4	15±8	0	31	8±4	0	16	7±5	0	20
5	18±7	3	31	11±4	2	16	7±6	0	23
6	16±8	1	29	9±4	1	16	7±5	0	23
7	16±7	2	30	10±4	2	17	7±6	0	26
8	19±9	1	34	11±5	1	17	9±7	0	32
9	18±8	3	30	11±4	2	17	8±7	1	33
10	18±7	5	32	11±3	5	17	9±8	0	36
11	18±9	1	33	10±5	1	16	9±8	0	38
12	15±7	2	30	10±4	1	16	7±8	0	39
13	16±7	3	30	10±4	2	16	8±9	0	42
14	16±8	1	30	10±4	1	16	8±9	0	43
15	17±8	1	30	11±4	1	18	9±13	0	61
Overall	16±8	0	34	10±4	0	18	7±7	0	61

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Abstract Number: 161

Are Ultrasound Definitions in Gout Reliable?: Preliminary Results from a Latin American Reliability Exercise

Tomas Cazenave[1], Anthony M. Reginato[2], Marwin Gutierrez[3], Christian A. Waimann[4,5], Santiago Ruta[6], Lucio Ventura[7], Cristina Hernandez-Diaz[8], Marcelo Audisio[9], Ana Bertoli[10], Clarisa Sandobal[11], Carla Solano[12], Félix Fernández Castillo[13], Rodolfo Arape[14], Maritza Quintero[15], Oscar Sedano[16] and Carlos Pineda[17], [1]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rhode Island Hospital, The Warren Alpert School of Medicine at Brown University, Providence, RI, [3]Instituto Nacional de Rehabilitación, Mexico, Mexico, [4]Escuela Superior de Ciencias de la Salud, UNICEN., Olavarria,, Argentina, [5]Rheumatology, Hospital Dr. Hector Cura, Olavarria, Argentina, [6]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [7]Instituto Nacional de Rehabilitación, Ciudad de México, Mexico, [8]Instituto Nacional de Rehabilitación, Mexico City, Mexico, [9]Servicio de Reumatología del Hospital Nacional de Clínicas, Córdoba, Argentina, [10]Instituto Reumatológico Strusberg, Córdoba, Argentina, [11]Hospital José María Cullen, Santa Fe, Argentina, [12]Hospital Nacional Rosales, Salvador, El Salvador, [13]Clínica Razetti, Barquisimeto, Venezuela (Bolivarian Republic of), [14]Centro Clínico La Isabelica, Carabobo, Venezuela, [15]Instituto Autónomo Hospital Universitario de Los Andes, Universidad de Los Andes, Mérida, Venezuela, [16]Escuela de ecografia musculoesqueletica y articular ECOSERMEDIC, Lima, Peru, [17]Instituto Nacional de Rehabilitation, Mexico, Mexico
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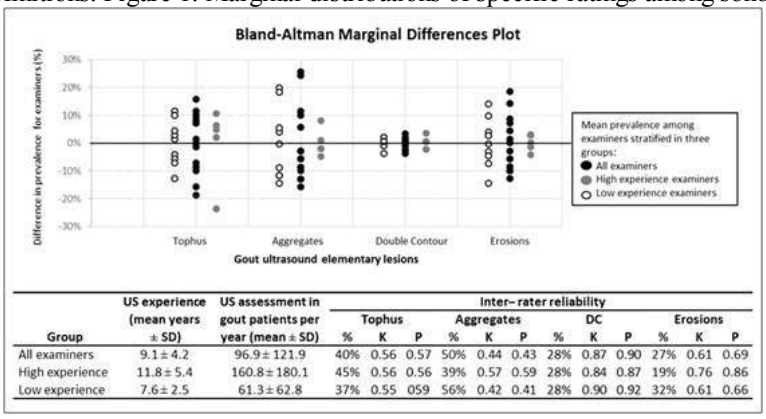
Background/Purpose: Although there is a consistent body of evidence supporting the use of Ultrasound (US) in Gout, several definitions for US lesions have been proposed. Recently, the OMERACT US Group has proposed a set of 4 definitions, including double contour (DC), aggregates, tophus and erosions. Objective: to evaluate intra and inter-reader

reliability of the US definitions of elementary lesions in gout developed by the OMERACT US Gout Task Force.

Methods: A reliability exercise based on the reading of US images was conducted during the 2016 PANLAR Congress by the PANLAR US Study Group. Fourteen rheumatologists from 6 Latin American countries with different experience in US participated. US images of both normal and gouty elementary lesions were collected by 2 sonographers highly experienced in gout. The image set consisted in 70 static images and 10 videos that were displayed for 20 seconds. Participants were asked to determine the presence of any of the 4 elementary lesions in each image. Nine images was displayed twice to estimate intra-reader reliability. Statistical analysis: Intra and Inter-reader reliability was calculated by the Cohen's kappa coefficient, considering Landis and Koch criteria (<0.2 poor, 0.21–0.4 fair, 0.41–0.6 moderate, 0.61–0.8 good, and 0.81–1 excellent). Furthermore, we stratified sonographers according to their US experience (defining High experience: >5 years of US experience and >50 US gout assessments/year).

Results: A total of 980 image assessment were performed. Aggregates was the more frequent lesions (50%), followed by Tophus (40%), DC (28%) and Erosions (27%). The mean intra-reader values were good to excellent in all lesions: DC= 0.90, aggregates = 0.86, erosions = 0.79 and tophus = 0.76. Mean Kappa inter-reader coefficients showed variability depending on the type of lesion, being moderate for aggregates (K= 0.44) and tophus (K=0.56), good for erosions (K=0.61), and excellent for DC (K=0.87). Kappa estimates and marginal distributions of specific ratings are showed in Figure 1 and Table 2. When comparing high with low experience sonographers, those with high experience showed better intra and inter-reader reliability and lower marginal heterogeneity.

Conclusion: The reliability of the new OMERACT US definitions of elementary lesions in gout varied depending on the type of lesion and evaluator experience. Ultrasonography training programs are necessary to improve the reliability of these new gout US definitions. Figure 1. Marginal distributions of specific ratings among sonographers and relation with personal experience.



Group	US experience (mean years ± SD)	US assessment in gout patients per year (mean ± SD)	Inter- rater reliability											
			Tophus			Aggregates			DC			Erosions		
			%	K	P	%	K	P	%	K	P	%	K	P
All examiners	9.1 ± 4.2	96.9 ± 121.9	40%	0.56	0.57	50%	0.44	0.43	28%	0.87	0.90	27%	0.61	0.69
High experience	11.8 ± 5.4	160.8 ± 180.1	45%	0.56	0.56	39%	0.57	0.59	28%	0.84	0.87	19%	0.76	0.86
Low experience	7.6 ± 2.5	61.3 ± 62.8	37%	0.55	059	56%	0.42	0.41	28%	0.90	0.92	32%	0.61	0.66

Table 2. Intra-rater reliability.

Light's kappa intra-rater reliability	**Tophus**	**Aggregates**	**DC**	**Erosion**
All examiners Kappa	0.76	0.86	0.90	0.80
Lowest kappa	0.53	0.10	0.50	0.50
Highest kappa	1.00	1.00	1.00	1.00
Light's Kappa in high experience	0.91	1,00	1.00	0.95
Light's Kappa in low experience	0.70	0.68	0.78	0.84

Disclosure: T. Cazenave, None; **A. M. Reginato**, None; **M. Gutierrez**, None; **C. A. Waimann**, None; **S. Ruta**, None; **L. Ventura**, None; **C. Hernandez-Diaz**, None; **M. Audisio**, None; **A. Bertoli**, None; **C. Sandobal**, None; **C. Solano**, None; **F. Fernández Castillo**, None; **R. Arape**, None; **M. Quintero**, None; **O. Sedano**, None; **C. Pineda**, None.

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Abstract Number: 162

Automated Segmentation of Cartilage Provides Comparable Accuracy and Better Responsiveness Than Manual Segmentation: Data from the

Osteoarthritis Initiative

Gwenael Guillard[1], Graham R. Vincent[1], Philip G. Conaghan[2], Alan Brett[3] and Michael A Bowes[1], [1]Imorphics Ltd, Manchester, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]Imorphics Ltd, MANCHESTER, United Kingdom

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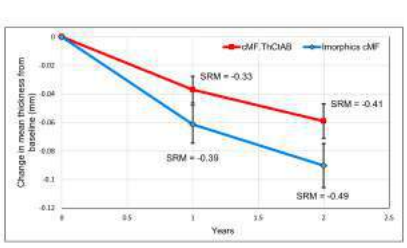
Automated Segmentation of Cartilage Provides Comparable Accuracy and Better Responsiveness Than Manual Segmentation: Data from the Osteoarthritis Initiative *Guillard G., *Vincent G.R., *Brett, A., **Conaghan, P.G., *Bowes M.A. * Imorphics, Manchester, UK: ** University of Leeds, Leeds, UK

Background/Purpose: A fully automated cartilage segmentation method based on active appearance modelling (AAM), has demonstrated superior performance for a number of tissues including knee and prostate (using MRI), and abdominal, head and neck organs (using CT). Automated segmentation of tissues with minimal change is often insensitive, due to smoothing approximations of such change. In this study we compared the responsiveness of cartilage thickness in the central medial femur region (cMF) using either automatic segmentation or careful manual segmentation, using 565 knees from the Osteoarthritis Initiative over a 2-year period, together with the agreement between the 2 methods.

Methods: 565 knees with OA were analysed at 0,1, and 2 years within the OAI, and results are available on the OAI website (https://oai.epi-ucsf.org/datarelease/ImageAssessments.asp). We compared change from baseline using a pairwise student t-test 0f mean thickness of the manual cMF.ThCtAb region, and a comparable region within an AAM of the femur (Figure 1). Responsiveness was assessed using the standardised response mean (SRM). Agreement between the methods was assessed using a Bland Altman plot (Figure 2). Each image is automatically segmented using AAMs of bone and cartilage through multi-start optimisation. Initially, this fits low-density low-resolution models but ends in a robust matching of detailed high resolution models. Finally, the voxels contained in the cartilage region are assigned with a non–linear regression function, trained with a probably approximately correct (PAC) learning method.

Results: Change in manual cMF at 1 year was 0.037mm, confidence limit (0.028,0.046), $p<10^{-4}$, SRM -0.33; at 2 years was 0.059 (0.047,0.081), $p<10^{-4}$, SRM -0.41. Change in automated cMF at 1 years was 0.061(0.048,0.074), $p<10^{-4}$, SRM -0.39; at 2 years was 0.090 (0.075,0.105), $p<10^{-4}$, SRM -0.49. The methods agreed well, with a systematic bias of -0.034mm, with a 95% confidence limit of 0.37mm, comparable to manual test-retest agreement (unpublished data)

Conclusion: Automated cartilage segmentation using AAMs provides comparable cartilage thickness measures to careful manual segmentation, and improved responsiveness. Manual cartilage segmentation is labour intensive and limits the pursuit of OA clinical trials. Automation now provides an equally accurate alternative, allowing for the segmentation of large datasets such as the OAI.



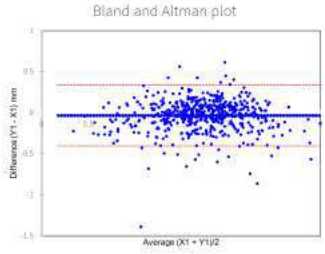


Figure 1: Change in cartilage thickness in cMF region for automated and manual segmentation (left).
Figure 2: Agreement between automated and manual methods (right)

Disclosure: G. Guillard, Imorphics Ltd, 3; **G. R. Vincent**, Imorphics Ltd, 3; **P. G. Conaghan**, AbbVie, Flexion, Eli Lilly, Novartis, Pfizer Inc, Roche, 5,AbbVie, Novartis, Roche, 8; **A. Brett**, Imorphics Ltd, 3; **M. A. Bowes**, Imorphics Ltd, 3.

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Abstract Number: 163

Fluorescence Optical Imaging Reveals Distinct Patterns of Hand Joint Inflammation in Seropositive and Seronegative Early Rheumatoid Arthritis

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Background/Purpose: Detection of abnormal Rheumatoid Arthritis (RA) related autoantibodies, Rheumatoid Factor (RF) and Anti- Citrullinated Peptide Antibody (ACPA), along with musculoskeletal ultrasound (MSUS) plays a critical role in early RA (eRA) diagnosis. Fluorescence optical imaging (FOI) is an emerging modality that detects subclinical hand joint inflammation[1], and may therefore prove valuable in early RA assessment. Here, we analyzed the FOI results of eRA patients to determine whether patterns of hand joint inflammation were able to distinguish seropositive from seronegative eRA.

Methods: Inflammation on FOI is defined by altered microcirculation (capillary leakage/perfusion), which is seen as abnormal optical signal intensities during visual inspection of a 360-second series of hand and wrist joint images (34 joints per patient). Unsupervised ascending hierarchical clustering was used to identify clusters of patients with different patterns of joint involvement in FOI. The robustness of clustering was verified using k-means, and agreements between the 2 methods were assessed using Cohen's kappa. Baseline clinical and biological characteristics of patients were compared between the clusters using non-parametric tests.

Results: Out of 1326 joints of 39 eRA patients (26 females; 9 with erosive RA; 54% RF+; and 69% ACPA+), 400 (30%) were considered positively inflamed by FOI. The mean (±SD) number of active joints detected by FOI was 10.3 ± 7.2 (Table). Unsupervised hierarchical clustering of joint involvement according to FOI distinguished 2 separate clusters of patients: Cluster1 (n=29) & Cluster2 (n=10). The proportion of seropositive patients was significantly higher in cluster 1 versus cluster 2 (26/29 versus 3/10, $p<0.01$) (Figure). The distribution of inflammation throughout the joints, except for right MCP2, PIPs 5, left MCP1 & DIPs in cluster 2 displayed distinguishable patterns ($p<0.05$) compared to cluster 1, which showed joint inflammation to be largely concentrated around wrists, right MCP2, bilateral MCP3, and to a lesser degree around PIPs 2-4 & left MCP2. The DIPs showed no significant differences between clusters.

Conclusion: Unsupervised hierarchical clustering revealed two distinct inflammatory patterns of joint involvement that may be distinguished in early RA, using fluorescence optical imaging. The proportions of seropositive patients were significantly different between these patterns, suggesting that FOI identifies patterns of joint involvement that are different for seropositive and seronegative RA. References: 1. Kisten Y, Györi N, af Klint E, et al. 2015 Detection of clinically manifest and silent synovitis in the hands and wrists by fluorescence optical imaging. RMD Open 2015;1: e000106. doi:10.1136/ rmdopen-2015-000106 (http://rmdopen.bmj.com/content/1/1/e000106.full.pdf+html)

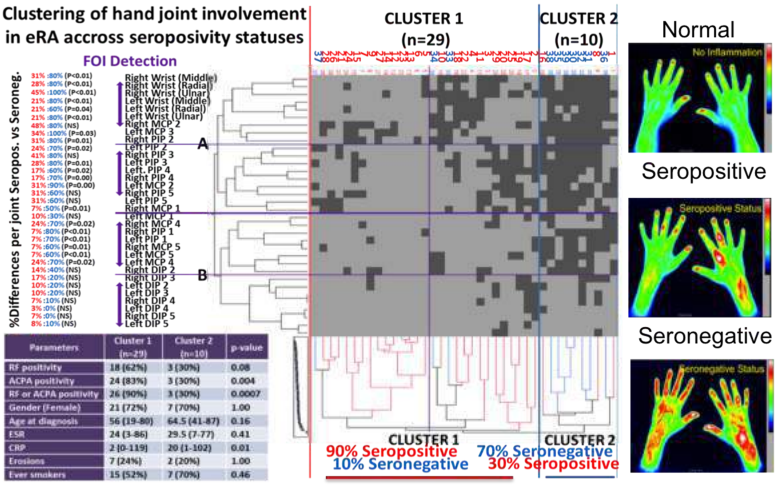

TABLE 1: Patient characteristics, laboratory results and imaging diagnostics according to RF and ACPA status

Baseline Characteristics		All Patients Mean (±SD) (N=39)	RF(+) & ACPA(+) (n=19)	RF(+) & ACPA (-) (n=2)	RF(-) & ACPA(+) (n=8)	RF(-) & ACPA(-) (n=10)
Gender	Female: N (%)	28 (72%)	16 (84%)	1 (50%)	3 (38%)	8 (80%)
Age	years (yrs)	56 (±17.4) yrs	54 (±17.2) yrs	64 (±4.2) yrs	44 (±16.1) yrs	68 (±12.6) yrs
Symptom or disease duration	months	18.2 (±21.7)	14.6 (±22.8)	40.5 (±27.6)	32.9 (±22.9)	8.8 (±6.3)
Anti-Citrullinated Peptide Proteins (ACPA) Status:	Positive: N (%) or Mean	27 (69%) or 527.7	431.4 (±630.7)	0 (0%)	513.5 (±675.8)	0 (0%)
	Negative (<25): N (%)	12 (31%) or <25	0 (0%)	<25 (±00.0)	0 (0%)	<25 (±00.0)
Rheumatoid Factor (RF) Status:	Positive: N (%) or Mean	21 (54%) or 376.9	406.7 (±630.4)	93.5 (±79.9)	0 (0%)	0 (0%)
	Negative (<20): N (%)	18 (46%) or <20.0	0 (0%)	0 (0%)	<20.0 (±00.0)	<20.0 (±00.0)
ESR levels	mm/hr	30.2 (±23.3)	34.9 (±22.8)	7.0 (±5.6)	24.0 (±16.4)	30.8 (±22.3)
CRP Levels	mg/L	22.9 (±33.6)	22.4 (±34.6)	1.5 (±5.8)	2.7 (±3.2)	31.1 (±37.5)
Smoking Status	Previous and current	22 (56%)	10 (53%)	1 (50%)	5 (63%)	6 (60%)
X-Rays	Bone erosions N (%)	9 (23%)	5 (26%)	0 (0%)	3 (38%)	1 (10%)
Clinical Assessment	Hand &/or wrist inflammation	29 (69%)	13 (68%)	1 (50%)	6 (75%)	9 (90%)
	Swollen hand joint count	7.8 (±8.1)	5.3 (±6.2)	1.5 (±2.1)	3.6 (±3.4)	17.0 (±7.7)
Musculoskeletal Ultrasound	Hand &/or wrist inflammation	37 (95%)	17 (89%)	2 (100%)	8 (100%)	10 (100%)
	MSUS synovitis joint count	9.7 (±7.7)	8.3 (±7.6)	3.5 (±0.7)	7.8 (±5.9)	15.4 (±7.6)
Fluorescence Optical Imaging	Hand &/or wrist inflammation	37 (95%)	18 (95%)	2 (100%)	7 (88%)	10 (100%)
	FOI synovitis joint count	10.3 (±7.2)	9.1 (±6.3)	6.5 (±3.5)	6.1 (±4.2)	16.6 (±7.4)
Digital/Disease Activity (DACT) Scores	Hand &/or wrist inflammation	37 (95%)	17 (90%)	2 (100%)	8 (100%)	10 (100%)
	DACT Mean Scores	4.1 (±2.1)	3.3 (±1.8)	3.0 (±0.1)	4.6 (±2.4)	5.5 (±1.9)

ABBREVIATIONS: SD – Standard Deviation, ACPA - anti-citrullinated peptide protein, RF – Rheumatoid Factor, ESR – Erythrocyte Sedimentation Rate, CRP – C-Reactive Protein, RA- Rheumatoid Arthritis

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Abstract Number: 164

99mtc-Hdp Digital Blood Flow Scintigraphy for Assessment of Raynaud Phenomenon Associated with Hand-Arm Vibration Syndrome

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Background/Purpose: This study aimed to analyze the 99mTc-HDP scintigraphic features in hand-arm vibration syndrome (HAVS) and to compare with primary Raynaud's phenomenon (RP) and secondary RP associated with connective tissue disease (CTD).

Methods: 99mTc-HDP digital blood flow and pool scintigraphy were performed in 59 patients with primary RP, 73 patients with HAVS-related RP and 38 patients with CTD-related RP, and clinical features were collected by a retrospective review of medical records. We calculated 6 ratios by using the time-activity curve and static blood pool images; the chilled to ambient hand and wrist ratios of the first peak height, the initial slope, and blood pool uptake. We analyzed 4 morphologic characteristics: an initial spike curve, a slow progress pattern, paradoxically increased uptake pattern in the time-activity curve and the inhomogeneous radioactivity uptake in the blood pool image.

Results: All 73 patients with HAVS-related RP were mine workers. The onset duration of RP after exposure to vibration was 21.8±7.3 years with 6.3±7.0 years of vibration exposure time. The chilled to ambient hand ratios of the first peak height and the initial slope were significantly lower in patients with HAVS-related occupational RP, compared to patients with primary RP. The presence of paradoxically increased uptake pattern of hand was significantly lower in HAVS compared to primary RP.

Conclusion: There were significant differences of both quantitative and morphologic characteristics of 99mTc-HDP scintigraphy between primary RP and HAVS. The results suggest that each disease might have quite different pathophysiology and thus different criteria should be applied to evaluation of each RP. Determination of separate cut off values for 99mTc-HDP scintigraphy is necessary to establish the accurate diagnosis of HAVS.

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Abstract Number: 165

The Apparent Diffusion Coefficient As a Quantitative Imaging Biomarker of Therapeutic Response in Enthesitis-Related Arthritis

Timothy Bray[1], Kanimozhi Vendhan[1], Nicola Ambrose[2], David Atkinson[1], Shonit Punwani[1], Corinne Fisher[2], Debajit Sen[2], Yiannis Ioannou[2] and Margaret Hall-Craggs[1], [1]Centre for Medical Imaging, UCL, London, United Kingdom, [2]Arthritis Research UK Centre for Adolescent Rheumatology, University College London, London, United Kingdom
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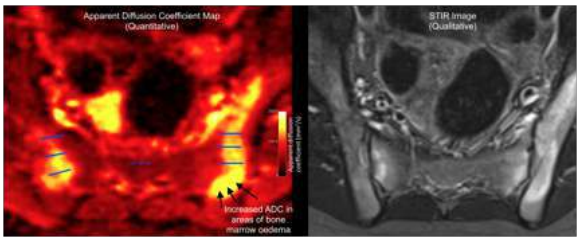
Background/Purpose **:** Early treatment in enthesitis-related arthritis (ERA) may have a disease-modifying effect with consequently improved outcomes. However, disease activity may be difficult to assess, leading to a lack of confidence that inflammation is adequately controlled. Clinical evaluation is helpful in assessing disease activity of peripheral joints in ERA, but is less accurate for assessing sacroiliitis. Magnetic resonance imaging (MRI) is sensitive for detecting sacroiliitis, but current imaging methods are qualitative and rely on visual assessment by a radiologist. Quantitative imaging biomarkers (QIBs) rely on pixel values in the image itself, and may therefore be used to assess inflammation in a more objective, reproducible fashion. This study aims to evaluate diffusion-weighted imaging (DWI) as QIB of therapeutic response in adolescents with enthesitis-related arthropathy (ERA).

Methods **:** 22 adolescents with ERA underwent routine MRI and DWI before and after tumour necrosis factor inhibitor (TNFi) therapy [Figure 1]. Each patientÕs images were visually scored by two radiologists using a modification of the Spondyloarthritis Research Consortium of Canada (SPARCC) system (1). Sacroiliac joint apparent diffusion coefficient (ADC) and normalized ADC (nADC) were measured for each patient using a previously described technique (2). Therapeutic clinical response was defined as an improvement in physician global assessment of more than 30% and radiological response defined as at least a 2.5-point drop in SPARCC score.

Results: For both radiological and clinical definitions of response, reductions in ADC and nADC after treatment were greater in responders than in non-responders (for radiological response: ADC: p<0.01; nADC: p=0.055; for clinical response: ADC: p=0.33; nADC: p=0.089). ADC and nADC could predict radiological response with a high level of sensitivity and specificity (the area under the receiver operating characteristic curves were ADC: 0.97, nADC: 0.82).

Conclusion **:** DWI measurements reflect response to TNFi treatment in ERA patients with sacroiliitis. DWI is more objective than visual scoring, and has the potential to be automated. ADC/nADC could be used as biomarkers of sacroiliitis in the clinic and in clinical trials. **References** 1. Maksymowych WP et al. Arthritis Care Res. 2005;53:703Ð9. 2. Vendhan K et al. Br J Radiol. 2015;18:20150775. **Figures**

Figure 1 Ð Quantitative DWI (left) and conventional STIR imaging (right) in an ERA patient with sacroiliitis. Intensities in the ADC map represent the ADC for each pixel (see colour bar) but pixels in the STIR images have arbitrary values. SIJ ADC is measured using three linear regions of interest (ROIs, solid blue lines) placed on each sacroiliac joint; this is repeated for four consecutive slices. A further ÔreferenceÕ ROI is placed on sacral bone to normalize SIJ ADC for individual patients (dotted blue line).



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Abstract Number: 166

Prevalence of Radiographic Thymic Alteration and Its Clinical Association in Systemic Autoimmune Diseases

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Background/Purpose: While thymic alteration such as hyperplasia, cyst and neoplasia has been precisely studied particularly in myasthenia gravis [1], only a few small-scale studies have been reported in a part of systemic autoimmune diseases [2-4]. We conducted a large-scale cross-sectional analysis on prevalence of radiographic thymic alteration and its clinical association in various systemic autoimmune diseases.

Methods: Consecutive and unbiased 500 patients who had visited at our service and had been evaluated by chest CT scan between January 2013 and December 2015 were enrolled. Thymus size and the radiographic pattern on high-resolution CT

image were quantitatively interpreted. We defined hyperplasia as more than 13mm thickness and graded the patterns by four-point scale (grade 0-3) according to previous study [5,6]. Their association to clinical information was statistically analyzed.

Results: Thymoma and thymic cyst were found in 3 (0.6%) and 1 (0.2%), respectively. After above cases and less than 30 year-old patients were excluded, 488 were served for following analysis. 78% were women and mean age was 63.0 ± 13.9 years old. These included 168 patients with rheumatoid arthritis (RA), 63 with systemic sclerosis (SSc), and 37 with primary Sjögren's syndrome (pSS). Thymic hyperplasia was found in 90 (18%) overall. These included 41 (24%) with RA, 6 (10%) with SSc, and 7 (19%) with pSS. Remarkably, patients with granulated pattern (grade 1 and over) was more frequent (42%) as compared to undiagnosed controls. These included 78 (46%) patients for RA, 32 (51%) patients for SSc, and 17 (46%) for pSS. Regarding clinical association, when RA patients is classified by hyperplasia and granulated pattern, proportion of serum anti-cyclic citrullinated peptide antibody (ACPA)-positivity were significantly higher in alteration group compared to normal group (93% vs. 70% and 89% vs. 63%; *P*=0.004 and 0.0005, odds ratio=6.1 and 5.0). In addition, titer of ACPA was also positively correlated to both hyperplasia and granulated pattern (*P*=0.048 and 0.009).

Conclusion: Thymic alteration was found in quite a few patients with various systemic autoimmune diseases. In RA patients, radiographic thymic alteration, especially granulated pattern significantly correlates to ACPA status and may reflect activation of germinal centers in the thymic medulla. References： [1] Clinic Rev Allerg Immunol 2016 Jun 6. [Epub ahead of print], [2] Semin Arthritis Rheum. 1998; 28:73-79, [3] Joint Bone Spine. 2013; 80:48-51, [4] Rheumatology(Oxford). 2014; 53:732-736, [5] Radiology. 2013; 268(1):245-253, [6] Eur Radiol. 2016; 26(1):15-24

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Abstract Number: 167

Bone Mineral Density Loss in Clinically Suspect Arthralgia Is Associated with Subclinical Inflammation and Progression to Clinical Arthritis

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Background/Purpose: Peripheral bone mineral density (BMD) can be decreased in early rheumatoid arthritis but it is unknown if BMD loss emerges already before arthritis is clinically apparent. We aimed to study if BMD loss occurs in patients with clinically suspect arthralgia (CSA), if it is associated with progression to clinical arthritis and if it is associated with MRI-detected subclinical inflammation.

Methods: Patients with CSA had arthralgia for <1 year and were suspect to progress to RA according to their rheumatologists. At baseline a 1.5T MRI was performed of unilateral MCP, wrist and MTP-joints and scored on synovitis, bone marrow edema and tenosynovitis;. summing these features yielded the MRI-inflammation score. Digital X-ray radiogrammetry (DXR) was used to measure BMD on two sequential conventional hand radiographs (mean interval between radiographs 4.4 months). The change in BMD was studied; BMD loss was defined as decrease of ≥2.5 mg/cm^2/month. Patients were followed on arthritis development for median 18.4 months.

Results: In CSA-patients (n=108) change in BMD was negatively associated with age (β=-0.03, p=0.007). Within CSA-patients BMD loss was associated with arthritis development (adjusted for age HR=6.1, 95%CI=1.7;21.4) and was most frequently measured in the months before clinical arthritis development. The MRI-inflammation scores were associated with the change in BMD (adjusted for age β=-0.05, p=0.047). The MRI-inflammation score and BMD loss were both independently associated with arthritis development (HR=1.1 95%CI=1.1;1.2 and HR=4.6 95%CI=1.2;17.2 respectively).

Conclusion: In CSA-patients BMD loss is associated with MRI-detectable subclinical inflammation and with progression to clinical arthritis.

Disclosure: L. Mangnus, None; **H. W. van Steenbergen**, None; **M. Reijnierse**, None; **J. Kälvesten**, Employee of Sectra AB, 3; **A. H. M. van der Helm-van Mil**, None.

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Abstract Number: 168

Prevalence of Diastolic Dysfunction and Structural Heart Disease in Axial Spondyloarthritis: A Prospective Case Control Study Using Echocardiography

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Background/Purpose: The aim of our study was to describe the prevalence of diastolic dysfunction (DD) and structural heart disease (SHD) among a cohort of Axial Spondyloarthritis (AxSpA) patients matched with a healthy control population. Aortic dilation, aortic insufficiency (AI) and DD have been reported in Ankylosing Spondylitis (AS), although their true prevalence remains uncertain. New pharmacologic therapies for AxSpA may have further impacted the prevalence of heart disease in this population. Studies to date have been small and lacked control populations, resulting in controversial recommendations for routine echocardiographic screening in AxSpA patients.

Methods: Prospective transthoracic echocardiograms were performed on 125 AxSpA patients and 56 age-matched healthy controls. Leading edge aortic root (AoR) measurements were made and normalized for body surface area. Measurements were also taken at the aortic annulus, sino-tubular junction and ascending aorta. DD was graded in accordance with the American Society of Echocardiography guidelines. Chi square tests and Wilcoxan rank sum analyses were used in the univariate analysis. A subgroup analysis was also performed in a matched group of 90 AS patients meeting the modified New York criteria and 45 healthy controls.

Results: Participants were 68% male with a mean age of 42.8±12 years. Mean AxSpA disease duration was 18.2 ± 12 years. The modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) for the overall population was 7.1±14.5 units and 9.9±16.5 units for the AS population. Mean AoR diameter was 3.29±0.36 cm for cases and 3.24±0.32 cm for controls. There was no difference in linear aortic measurements, the presence of AI or DD between the two groups. The subgroup analysis of AS patients alone did not show any differences in these outcomes when compared to controls.

Conclusion: While there are differences among individual measurements used in the assessment of diastolic function, there is no clinically relevant difference in the prevalence of DD between cases and controls. Furthermore, there is no significant increase in AoR size or in the presence of AI in AxSpA patients when compared with healthy controls. These

findings are the first basis of evidence to support the current recommendations against routine echocardiographic screening in asymptomatic AxSpA patients. Future subgroup analyses should focus on the impact of pharmacologic therapies on SHD and DD in this population.

Table 1: Baseline Characteristics of the Study Population

Population Characteristics	AxSp Patients n=125	AS Patients n=90
Baseline disease activity (ASDAS - CRP)	2.97 ± 1.25	3.09 ±1.35
Disease activity at time of echo (ASDAS - CRP)	2.0 ± 0.89	1.99 ± 0.94
Baseline CRP (mg/L) Reference range <6.3 mg/L	16.2 ± 22.7	13.6 ± 14.8
CRP at time of echo (mg/L) Reference range <6.3 mg/L	5.5 ± 6.5	6.12 ± 6.84
Treatment with NSAIDs	57.2%	46%
Treatment with TNFi	52%	56%

ASDAS - Ankylosing Spondylitis Disease Activity Score, CRP - C-Reactive Protein, NSAID - Non-steroidal Anti-inflammatory Drug, TNF-i - Tumor Necrosis Factor Inhibitor

Table 2: Echocardiographic Variables in the Study Population

Variables	AxSp Patients n=125	Controls n=56	95% CI	p-value	AS Patients n=90	Controls n=45	95% CI	p-value
Mean E wave velocity cm/s	77	69.4	71.8, 76.9	0.01	76.5	69.6	71.1, 77.2	0.03
Mean A wave velocity cm/s	58.4	48	52.8, 57.4	0.00	59.9	46.4	52.5, 58.0	0.00
Mean deceleration time ms	195.3	212.9	194.6, 207.2	0.02	193.9	212.9	193.1, 207.7	0.03
Mean lateral e' velocity cm/s	12.7	14.3	12.7, 13.8	0.02	12.6	14.5	12.6, 13.9	0.08
Mean septal e' velocity cm/s	9.6	9.5	9.2, 10	0.77	9.5	9.6	9.0, 9.96	0.83
Diastolic dysfunction (grade 1 and above)	22%	23%	–	0.9	27%	22%	–	0.58
AoR diameter > 1.96 Z score above predicted mean	3%	2%	-0.3, -0.05	0.97	2%	2%	-0.37, -0.4	1.00
Aortic Insufficiency (trace and above)	45%	54%	–	0.27	49%	53%	–	0.88

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Abstract Number: 169

Ultrasound and Magnetic Resonance Imaging Fusion of Images and B-Flow Evaluation of Tenosynovitis – a Pilot Study on New Imaging Techniques in Rheumatoid Arthritis Patients

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Background/Purpose: Image fusion is an advanced imaging technology, which enables fusion of ultrasound (US) and magnetic resonance imaging (MRI). This fusion gives for each US probe position an exact projection of the corresponding anatomical area on a previously obtained MR image, during a live US assessment. This study is the first to address image fusion of US and MRI tenosynovitis. The aim of this study was to assess and compare US and MRI visualisation of tenosynovitis using image fusion technique.

Methods: Fifteen rheumatoid arthritis patients with US verified tenosynovitis in the wrist or hand had an MRI performed of the affected wrist or hand. A subsequent image fusion was performed, i.e. the MR images and a live US assessment of one tendon sheath were fused. In order to compare the two imaging modalities quantitatively, the area of the tendon and tendon sheath in the transverse axis was measured on US and MRI for each image fusion. Due to partial volume artefacts (voxel containing two different tissues and therefore possessing a signal average of tendon and tendon sheath) on MRI two measures were performed; area 1) the circumference of the black tendon, i.e. excluding voxels containing two types of tissue 2) the circumference of the grey line that surrounds the black tendon, i.e. including voxels containing two types of tissue. Tenosynovitis was assessed using the proposed OMERACT semi-quantitative scoring system for US and MRI. US scoring was therefore based on both grey scale and Doppler, whereas MRI scoring was based only on post-contrast tenosynovial enhancement, measured as distance from the tendon to end of the enhanced tendon sheath.

Results: The median circumference area of the tendons and tendon sheaths on US and MRI 1 and 2 were respectively 0.16 (25;75 pctl: 0.10;0.25), 0.9 (0.06-0.18) and 0.13 of (0.10;0.25) for the tendons and 0.18 (0.13-0.26), 0.27 (0.20-0.45) and 0.23 (0.16-0.40) for the tendon sheaths. Statistically significant differences were found for all measured areas between US and MRI, except for the US tendon area and the MRI tendon area 2 (Wilcoxon's test; p=0.47). Overall agreement between US and MRI tenosynovitis scoring systems was good (see table 1).

Conclusion: In conclusion, we found that US and MRI have good agreement for quantitative assessment of tendons and scoring of tenosynovitis, when comparing the two modalities using image fusion, if the partial volume artefacts on MRI are taken into account.

Table 1 Tenosynovitis scores on tendon level (0-3) for CD, GS and MRI area 1 and 2. Delta scores for MRI area 1 and 2 with CD or GS as reference. Further, percentage of exact agreement and percentage of close agreement is used for comparing the agreement between the scores.

Patient no	Tendon sheath	CD	MRI_1	MRI_2	ΔCD;MRI_1	ΔCD;MRI_2	GS	ΔGS;MRI_1	ΔGS;MRI_2
1	Extensor carpi ulnaris	3	3	3	0	0	3	0	0
2	Flexor pollicis longus	2	1	2	1	0	2	1	0
3	Flexor carpi radialis	2	3	3	-1	-1	2	-1	-1
4	Flexor tendon of the 4th digit	3	3	3	0	0	2	-1	-1
5	Flexor tendons of the 5th digit	3	3	3	0	0	2	-1	-1
6	Flexor tendon of the 2nd digit	2	2	1	0	1	2	0	1
7	Extensor carpi ulnaris	3	3	3	0	0	3	0	0
8	Extensor carpi ulnaris	0	1	1	-1	-1	1	0	0
9	Extensor carpis radialis brevis/longus	2	3	2	-1	0	1	-2	-1
10	Extensor pollicis longus	2	1	1	1	1	2	1	1
11	Extensor digitorum communis/indicis proprius	2	3	3	-1	-1	3	0	0
12	Flexor tendon of the 3rd digit	0	2	1	-2	-1	1	-1	0
13	Extensor digiti minimi	1	2	1	-1	1	1	-1	0
14	Flexor carpi radialis	2	2	2	0	0	2	0	0
15	Extensor carpi ulnaris	3	2	2	1	1	1	1	1
	The percentage of exact agreement (PEA)				40	47		40	53
	The percentage of close agreement (PCA)				93	100		93	100

Note: no number; GS grey scale; CD colour Doppler; MRI magnetic resonance imaging; MRI_1, area measured from the circumference of the black tendon; MRI_2, area measured from the circumference of the grey line that surrounds the black tendon; PEA, expresses the percentage of the patients receiving the same score; PCA, is the percentage of the patients where the score differ no more than 1.0.

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Abstract Number: 170

Low Baseline Temperature and Low Basal Flow Can be Related to the Paradoxical Raynaud's Phenomenon in Hand Perfusion Scintigraphy

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SESSION INFORMATION

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Background/Purpose: Raynaud's phenomenon (RP) is a clinical disorder that is characterized by paroxysmal vasospasm of small blood vessel after cold exposure or vibration. Radiopharmaceutical perfusion scintigraphy is a noninvasive and quantitative method for evaluation of RP. Interestingly, the increased perfusion or blood pool activity after cold exposure in one-hand chilling protocol has been reported, they are called paradoxical RP. However, little is known about the paradoxical reaction. In this study, we compared radiopharmaceutical perfusion imaging and thermography in patients with RP for the understanding of paradoxical RP.

Methods: Sixty male patients with secondary RP caused by hand arm vibration syndrome were included in this study. Radiopharmaceutical perfusion scintigraphy and thermography were performed for all patients. Blood flow by radiopharmaceutical perfusion scintigraphy in each hand was measured with one hand chilling protocol. According to the chilled finger to ambient finger ratio (CAR), we divided 60 enrolled patients into low and high ratio groups in each hand.

The finger to palm ratio in the ambient hand (FPRa) and the finger to palm ratio in the chilled hand (FPRc) were analyzed, and the correlations between blood flow ratios by radiopharmaceutical perfusion scintigraphy and temperature by thermography was evaluated.

Results: Among total 60 patients, the numbers of patients with paradoxical RP, that is classified as high ratio group, were 13 (21.7%) and 12 (20.0%) in left and right hand, respectively, and 6 patients showed paradoxical RP in both hands. FPRa showed positive correlations with baseline temperature (Left, $\gamma = 0.276$, $p = 0.033$; Right, $\gamma = 0.424$, $p = 0.001$, respectively), and CAR showed negative correlations with baseline temperature (Left, $\gamma = -0.291$, $p = 0.024$; Right, $\gamma = -0.273$, $p = 0.035$, respectively). In the high-ratio group, the FPRc values after cold exposure were significantly higher than those of ambient state (Left, 65.8 ± 23.2 vs. 49.2 ± 20.7, $p < 0.001$; Right, 61.5 ± 16.4 vs. 49.9 ± 9.6, $p = 0.013$, respectively); while in the low-ratio group, the FPRc values were significantly lower than those of ambient state (Left, 49.9 ± 19.6 vs. 57.0 ± 22.6, $p < 0.001$; Right, 51.5 ± 24.1 vs. 61.3 ± 21.9, $p < 0.001$, respectively). In the high-ratio group, baseline temperatures of the left digit were significantly lower than those in the low-ratio group (Left, 25.2 ± 2.9°C vs. 23.1 ± 3.1°C, $p = 0.037$; Right, 25.2 ± 2.9°C vs. 22.7 ± 3.1°C, $p = 0.018$, respectively) and baseline temperatures of the right digit tended to be lower than those in the low-ratio group (Left, 25.1 ± 2.9°C vs. 23.5 ± 3.1°C, $p = 0.093$; Right, 25.1 ± 2.8 vs. 23.3 ± 3.5°C, $p = 0.100$, respectively).

Conclusion: Paradoxical RP was detected in 20.0 ~ 21.7% of hand perfusion scintigraphy. Low basal blood flow and low baseline temperature of the digit can be related with paradoxical RP in hand perfusion scintigraphy.

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Abstract Number: 171

From 3D Printed Bones to Arthritis Patients – Arthro-Haptic Experience Supporting Disease Awareness

Arnd Kleyer[1], Laura Beyer[2], Christoph Simon[2], Fabian Stemmler[3], Juergen Rech[3], Matthias Englbrecht[4], Bernhard Manger[4], Gerhard Krönke[5], Georg Schett[3] and Axel J. Hueber[3], [1]Department of Internal Medicine 3, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [2]Rheumatology, University of Erlangen-Nuremberg, Erlangen, Germany, [3]Department of Internal Medicine 3 – Rheumatology and Immunology, Universitätsklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [4]Department of Internal Medicine 3, Rheumatology & Clinical Immunology, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [5]Universitätsklinikum Erlangen, Erlangen, Austria

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Background/Purpose: RA and PsA result in joint destruction and functional disability if left untreated. Although therapies for patients with RA and PsA are effective and well-tolerated, recent evidence highlighted poor adherence to these anti-rheumatic treatment. Various factors hamper the adherence of patients with (false) medical beliefs and lack of knowledge being the major obstacles. We therefore aim to develop tools that help patients to understand and experience the impact of joint disease. In this study, we used high resolution peripheral quantitative computed imaging (HR-pQCT) to develop a virtual 3D reconstruction of finger joints. We then investigated (i) the feasibility to generate exact 3D models of arthritic and healthy joints, and tested (ii) whether these prototypes are accepted by patients and helped them to better understand and experience their medical condition.

Methods: HR-pQCT (Scanco) measurements were performed in healthy individuals and patients with erosive and non-erosive inflammatory joint disease. Then, a 3D printable file was generated and printed (objet30). Ten healthy participants (HC), 15 RA patients and 15 PsA patients, who were demonstrated printed healthy and arthritic joints, underwent a

detailed, standardized interview to investigate if the “arthro-haptic” experience helped to improve their understanding of the disease. Ethical approval was obtained; all patients and HC consented for the study.

Results: Utilizing HR-pQCT images of MCP heads, high quality and exact 3D models were created. For better visualization and haptic experience, bones were enlarged 3:1. The prototypes achieved a resolution as low as 24 µm. Erosions in different sizes as well as the trabecular network were visualized in detail, demonstrating a structural reduction in arthritic vs healthy bone. The erosions were mainly found at a region close beneath the cartilage area either radial/ulnar or dorsal. No erosions were identified at the palmar location. Artificial truncation separated the MCP head in 2 parts; the print showed a dorsal porous structured cortical defect with irregularly shaped borders, which normally could not be detected in plain X rays. In addition, a cystic structure which was also detected by MRI showed contrast enhancement and contained a new erosion at a two year follow up. After 3D demonstration (healthy vs. erosive joint, visually and haptically) HC and arthritis patients were asked for their emotional opinion. 26/39 (66%) were deeply affected, often quoting “shock”. 13/15 (86%) of the RA and 11/15 (73%) of the PsA patients stated, that they would rethink their attitude regarding medication adherence after being confronted with the 3D models. More importantly, 21/24 (87,5%) of RA and PsA patients expressed that they would have wished to see such 3D prints during their first disease specific conversations. 16/27 (59%) would appreciate seeing their own joint.

Conclusion: Using arthro-haptic 3D joints may help patients to better understand the impact of inflammatory arthritides on bone integrity and long-term damage. Additional studies need to prove that the better understanding will improve adherence of patients.

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Abstract Number: 172

S100A8/A9 Produced during Experimental Osteoarthritis Induces a Systemic Decrease in BM Monocytes and Increases Ly6C High Monocytes Locally in the Joint

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Background/Purpose: In response to pro-inflammatory cytokines released locally during osteoarthritis (OA), such as the alarmins S100A8/A9, monocytes can be recruited from the bone marrow (BM) to the site of injury. Monocyte chemoattractant protein-1 (MCP-1) drives monocyte migration via binding with C-C chemokine receptor type 2 (CCR2). In mice, two functionally distinct monocyte populations are described: pro-inflammatory Ly6C-high monocytes ($CCR2^{high}$) and patrolling Ly6C-low monocytes ($CCR2^{low}$). The objectives of our study are to investigate the systemic effects of locally induced OA on BM monocyte populations and their recruitment to the OA joint in collagenase induced OA (CiOA), and the involvement of S100A8/A9 herein.

Methods: CiOA was induced by unilateral-articular collagenase-injection in C57BL/6 mice. At day 7, 21 and 42, mice were sacrificed together with age-matched saline-injected control mice (n=6/group), and expression of several pro-inflammatory cytokines, and MCP-1 and CCR2 were measured in the synovium and serum. During CiOA and control conditions, the absolute amount of cells in the BM of the contralateral femur was measured. Cells from BM, blood and synovial tissue were isolated and analyzed by FACS. Monocyte subsets were identified as

(B220/CD90/CD49b/NK1.1/Ly6G)^{low}CD11b^{high}(F4/80/MHCII/CD11c)^{low} and further distinguished by their Ly6C expression. In addition, we investigated the role of S100A8/A9 on monocyte populations during early CiOA using S100A9$^{-/-}$ mice.

Results: Synovial expression of the pro-inflammatory cytokines IL-1β, IL-6, TNF-α, S100A8 and S100A9 were increased at day 7, but only expression of S100A8 and S100A9 remained high until day 21. Local induction of CiOA resulted in systemic effects within the BM as shown by the significant decrease in total cell numbers at day 7 and 21 (both 14%), which decrease is suggested to be Ly6C high monocytes since the absolute amount of these cells decreases. Concurrently, relative number of Ly6C high monocytes and macrophages were significantly increased (764% and 251%, respectively) locally in the synovium at CiOA day 7, corresponding with the increased synovial mRNA expression of MCP-1 (151-fold) and CCR2 (41-fold). Since S100A8/A9 is sustainably expressed during CiOA and intra articular injection of S100A8 leads to significant induction of MCP-1 (8-fold) in the synovium, we next investigated the role of S100A8/A9 during early CiOA in more detail using S100A9$^{-/-}$ mice. S100A9$^{-/-}$ mice show less synovial activation, less cell influx and less cartilage degradation compared to wild type (WT) mice. Interestingly, there was no decrease in cell numbers or Ly6C high monocytes in the BM of S100A9$^{-/-}$ mice. Moreover, in contrast to WT mice, the patrolling Ly6C low monocytes were significantly increased (205%) in S100A9$^{-/-}$ mice, whereas the pro-inflammatory Ly6C high monocytes were not affected.

Conclusion: Local induction of OA induces systemic release of BM-derived Ly6C high monocytes, which are found subsequently increased locally in the synovium, a process that may be regulated by the sustained release of S100A8/A9 from the synovium via MCP-1.

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Abstract Number: 173

S100A8/A9, a Potent Serum and Molecular Imaging Biomarker for Synovial Inflammation and Joint Destruction in Seronegative Experimental Arthritis

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Background/Purpose: Seronegative joint diseases, including psoriatic arthritis and juvenile idiopathic arthritis, are characterized by the lack of autoantibodies, which are relevant biomarkers for predicting disease activity in rheumatoid arthritis. Promising alternative biomarkers are the Damage Associated Molecular Patterns (DAMPs), S100A8, S100A9 and the heterodimer S100A8/A9. These proteins are specifically expressed and released by infiltrating phagocytes and may therefore serve as relevant biomarkers for joint inflammation and destruction in seronegative arthritis. In this study we determined the biomarker potential of serum S100A8/A9 and in vivo imaging of synovial S100A8 to asses joint inflammation and damage in the IL-1 receptor antagonist deficient (IL-1Ra$^{-/-}$) mice, a mouse model for seronegative arthritis in which serum autoantibodies are not correlated to disease activity.

Methods: Serum levels of S100A8/A9 and various cytokines were monitored during arthritis development in IL-1Ra$^{-/-}$ mice using ELISA and Luminex and were correlated to macroscopic and microscopic parameters for joint inflammation and damage. Local S100A9 expression and matrix metalloproteinase (MMP) mediated cartilage damage in the ankle joints were investigated by immunohistochemistry. In addition local S100A8 and activated MMPs were monitored in vivo by optical imaging using anti-S100A8-Cy7 and AF-489-Cy7, a specific tracer for activated MMPs.

Results: Starting at week 8, serum levels of S100A8/A9 were significantly increased (1640 ± 1008 ng/ml at week 16) in IL-1Ra$^{-/-}$ mice compared to WT BALB/c control mice (429 ± 191 ng/ml, $P = 0.005$) and strongly correlated to joint swelling ($r = 0.766$, $P < 0.0001$), while serum levels of IL-1β, IL-6, TNF-α, IL-17, IL-4 or IFN-α did not. In addition, high serum S100A8/A9 levels at week 10 were predictive for increased joint swelling at week 16 ($r = 0.576$, $P = 0.0002$). Next to macroscopic swelling, increased serum S100A8/A9 also correlated to microscopic cell influx ($r = 0.794$, $P < 0.0001$) and was reflected by local expression of S100A9 within the synovium, indicating the activated synovial lining as the source of increased serum S100A8/A9. Local expression of S100-DAMPs could also be monitored non-invasively by in vivo optical imaging using anti-S100A8-Cy7. Next to a biomarker for inflammation, S100-DAMPs may also be used for assessing joint damage. Indeed, arthritic IL-1Ra$^{-/-}$ mice showed increased cartilage damage ($r = 0.687$, $P < 0.0001$) which coincided with MMP-mediated neoepitope (VDIPEN) expression and in vivo imaging of activated MMPs.

Conclusion: These findings underline the potential of S100-DAMPs as a systemic and local biomarker in seronegative arthritis, not only for assessing inflammation but also joint damage.

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Abstract Number: 174

Protein Modified with Citrulline and/or Malondialdehyde-Acetaldehyde Bind to Different Scavenger Receptors

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Background/Purpose: Antibodies to citrullinated proteins are highly specific and potentially pathogenic in rheumatoid arthritis (RA). Proteins modified with malondialdehyde-acetaldehyde (MAA) are present in RA synovium where they co-localize with citrullinated proteins. Moreover, MAA-modified proteins are bound and internalized by scavenger receptors (SRs) present on immune cells. However, the mechanism(s) by which citrullinated proteins are recognized by cells of the immune system to initiate antibody and T cell responses remains unknown. Thus, we examined proteins modified with MAA and/or citrulline to determine the impact of these modifications on SR binding.

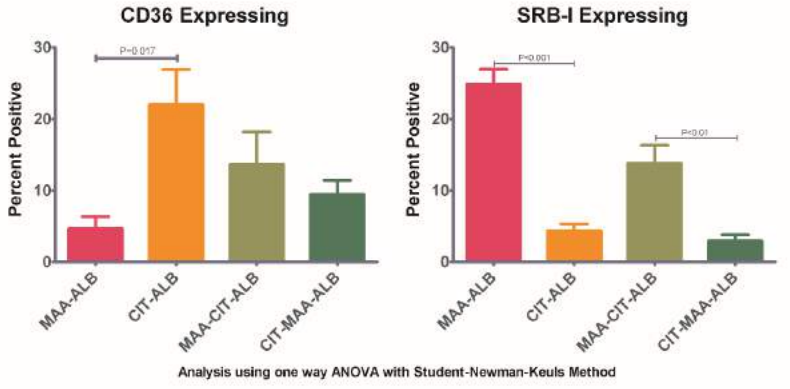
Methods: Binding studies were performed using Chinese Hamster Ovary (CHO) cells transfected with individual SRs: type A (SR-A), type B-1 (SRB-I), CD36, TLR-2, and TLR-4. Cells were incubated on ice for 90 minutes with 25 µg/ml of human serum albumin (ALB) modified with: MAA (MAA-ALB), citrulline (CIT-ALB), MAA then citrulline (MAA-CIT-ALB), or citrulline then MAA (CIT-MAA-ALB). Cells were washed to remove unbound proteins, incubated with a polyclonal goat anti-human albumin antibody, and detected using a Cy5-conjugated rabbit anti-goat IgG antibody. Cells

were fixed in paraformaldehyde and subjected to Flow cytometry at 650 nm wavelength. Analysis was performed using FlowJo V10. Data is expressed as percent positive compared to isotype control with non-specific ALB binding subtracted as background.

Results: CHO cells expressing CD36 preferentially bound CIT-ALB (P=0.017), but not MAA-ALB (Figure 1). In contrast, SRB-I preferentially bound MAA-ALB (P<0.001), but not CIT-ALB. Interestingly, the MAA-CIT-ALB modification showed slightly less binding than CIT-ALB to CD36 and MAA-Alb to SRB-I, but resulted in binding to both receptors equally, suggesting the double modification results in less specific binding. Additionally, MAA-CIT-ALB binding was increased compared to CIT-MAA-ALB binding on SRB-I (P<0.01) expressing cells. CHO control cells had background binding levels of ~5% for all antigens. Preliminary data using SR-A, TLR-2, and TLR-4 expressing CHO cells demonstrate similar unique binding patterns with these two modifications on albumin (Data not shown).

Conclusion: CHO cells expressing a single SR demonstrated differential binding of MAA-modified and/or citrullinated albumin that was unique to each receptor. Interestingly, co-modifications resulted in a decrease in the binding of ALB as compared to CIT-ALB (to CD36) or MAA-ALB (to SRB-1). However, there was an increase in the binding to both receptors suggesting that co-modification with MAA and CIT may increase the number of different receptors to which they bind. Further studies are underway to evaluate other SR binding of other proteins including histone, vimentin, and fibrinogen modified with MAA and/or CIT.

Figure 1



Disclosure: T. P. Pospisil, None; **M. J. Duryee**, None; **K. C. Easterling**, None; **L. W. Klassen**, None; **J. R. O'Dell**, Eli Lilly and Company, Medac, Coherus, BMS, GSK, 5; **D. R. Anderson**, None; **T. R. Mikuls**, None; **G. M. Thiele**, None.

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Abstract Number: 175

Suppressor of Cytokine Function One (SOCS1) Is Elevated in Non-Classical Monocytes and Correlates with Disease Activity in Systemic Lupus Erythematosus Patients

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, systemic autoimmune disease resulting from dysregulated innate and adaptive immune components that result in an inflammatory response. Cytokines produced by inflammatory monocytes are increased in SLE patients and signal through the JAK-STAT pathway. SOCS proteins (suppressor of cytokines signaling), specifically SOCS1 and SOCS3 are upregulated by Jak-STAT signallin and then function to limit JAK-STAT signalling. Thus SOCS proteins assure that the JAK-STAT signals are transient and contain the innate and adaptive immune responses. The expression of SOCS proteins in SLE patients has not been assessed. Reports of SOCS1 and SOCS3 mRNA expression in SLE patients are conflicting and have been obtained from whole peripheral blood (PB), thus the cells with dysregulated SOCS expression could not be determined. Our objective was to assess SOCS1 and SOCS3 protein expression in circulating monocytes subsets from SLE patients, and to determine the relationship between SOCS1 and SOCS3 expression and disease activity.

Methods: PB samples were collected from SLE patients and healthy controls through an IRB-approved protocol. American College of Rheumatology or Systemic Lupus International Collaborating Clinics classification criteria for SLE was used to establish diagnosis. Disease activity was determined by using the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K 30 Days). PB mononuclear cells (PBMCs) were isolated by red blood cell lysis. PBMCs were stained for flow cytometry to identify classical, intermediate, and non-classical monocytes based on CD14 and CD 16 expression. Intracellular staining was used to evaluate SOCS1 and SOCS3 protein expression in monocyte subsets. Median fluorescence intensities (MFI) for SOCS1 and SOCS3 from SLE patients were compared to healthy patients by one-tailed Mann-Whitney U-test $p<0.05$. Spearman's rho correlation was used to test the relationship between SOCS1/3 expression and disease activity, complement proteins (C3 and C4).

Results: Expression of SOCS1 and SOCS3 in monocytes subsets obtained from healthy (n=11) and SLE (n=11) patients were compared. No difference in the monicyre distribution among the subsets was observed between SLE patients and healthy controls. In SLE patients non-classical monocytes showed significantly elevated SOCS1 protein levels (p=0.03) and SOCS1 levelst were positively correlated with disease activity (r=0.56, p=0.04) and negatively correlated with serum C3 (r=-0.56, p=0.04) and C4 (r=-0.79, p=0.003) levels. SOCS3 was also significantly elevated in non-classical monocytes from SLE patients (p=0.01) and negatively correlated with C4 (r=-0.80, p=0.01). The expression of SOCS1 and SOCS3 in classical and intermediate monocytes did not differ between SLE and healthy controls.

Conclusion: In SLE patients SOCS1 is elevated in non-classical monocytes as compared to healtht controls and the levels of SOCS1 in SLE patients correlate with clinical indicators of more active disease. Further studies are needed to determine the role of SOCS1 and SOCS3 in the pathogenesis of SLE and as potential disease activity indicators. _

Disclosure: T. Khawar, None; **J. Cooke**, None; **N. Daoud**, None; **V. Sandhu**, None; **W. Davis**, None; **W. Peters**, None; **K. M. D. Torralba**, GlaxoSmithKline, 9,ACR, USSONAR, 9; **M. T. Ngo**, None; **S. Lezcano**, None; **K. J. Payne**, None; **A. J. Weldon**, None.

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Abstract Number: 176

Endoplasmic Reticulum Stress Induces Lupus Kidney Disease By Facilitating Antigen Cross-Presentation Via the Increase of Endosomal Sec61

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Background/Purpose: Repeated immunization with exogenous antigen such as ovalbumin (OVA) induces SLE in mice otherwise not prone to spontaneous autoimmune diseases, in which autoantibody-inducing CD4 (*ai* CD4) T cell that had undergone *de novo* T cell receptor (TCR) revision was generated. The *ai* CD4 T cells induced varieties of autoantibody including anti-dsDNA antibody and matured CD8 T cells into effector cytotoxic T lymphocyte (CTL) *via* antigen cross-presentation in dendritic cell (DC), after which they caused tissue injuries (Tsumiyama K et al. PLoS ONE 4(12): e8382, 2009; J Immunol. 191: 91, 2013). We here studied the molecular mechanism of antigen cross-presentation to show that accumulation of cross-presentable antigen in the cytoplasm *via*Sec61, translocation channel of protein involved in ER-associated degradation (ERAD), finally induces lupus tissue injury in an experimental model based on our 'self-organized criticality theory' explaining the cause of SLE.

Methods: Bone marrow-derived DC (BMDC) was generated from BALB/c mice. BALB/c mice were repeatedly immunized with ovalbumin (OVA) to induce SLE, and splenic DC (spDC) was isolated from these mice. DCs were cultured with fluorescent-labeled OVA, an inhibitor of Sec61 Exotoxin A and/or an inducer of ER stress Tunicamycin. Immunofluorescent staining, immunoprecipitation and immunoblotting were performed to detect early endosome antigen 1 (EEA1), calnexin, Sec61, OVA and unfolded protein response (UPR)-related molecules. OVA/MHC class I complex was detected under flow cytometry.

Results: Engulfed OVA was co-localized with endosomal marker EEA1, which was then separated from EEA1 in DCs. OVA never co-localized with ER marker calnexin, whereas OVA was co-localized and co-precipitated with translocon Sec61. OVA in the cytoplasm of BMDC became undetectable when co-cultured with the inhibitor of Sec61 Exotoxin A, and thus, antigen was exported directly from endosome to cytoplasm *via* Sec61. When the amount of OVA accumulated in the cytoplasm was decreased dose-dependently by inhibiting Sec61 using Exotoxin A, the amount of OVA/MHC class I complex expressed on BMDC was significantly decreased. Instead, the amount of endosomal Sec61 and cytoplasmic OVA was both increased upon co-culture with an inducer of ER stress Tumicamycin in BMDC. Similarly, in the mice with lupus kidney disease generated upon repeated immunization with OVA, both endosomal Sec61 and cytoplasmic OVA were up-regulated in their spDC. Further, expression of UPR-related molecules including Bip, IRE1, XBP1 and PERK, and phosphorylated eIF2α was significantly up-regulated, which indicated that ER stress increases endosomal Sec61 thereby increasing the amount of antigen accumulated in the cytoplasm. The cytoplasmic antigen which is cross-presentable finally augments lupus tissue injury.

Conclusion: We found in the first that antigen was transported from endosome to cytoplasm *via* Sec61 for antigen cross-presentation. Second, antigen cross-presentation was promoted in proportion to the amount of antigen accumulated in cytoplasm of DC. Third, ER stress increased endosomal Sec61 thereby contributing to the induction of lupus tissue injury by facilitating antigen cross-presentation.

Disclosure: K. Tsumiyama, None; **S. Shiozawa**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/endoplasmic-reticulum-stress-induces-lupus-kidney-disease-by-facilitating-antigen-cross-presentation-via-the-increase-of-endosomal-sec61

Abstract Number: 177

Treatment with Dexamethasone and Monophosphoryl Lipid a Removes Disease-Associated Transcriptional Signatures in Monocyte-Derived Dendritic Cells from Rheumatoid Arthritis Patients and Confers the Ability to Modulate CD4+ T Cell Responses

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First publication: September 28, 2016

SESSION INFORMATION

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Background/Purpose: Tolerogenic dendritic cells (TolDCs) are promising tools for therapy of autoimmune diseases such as rheumatoid arthritis (RA). Here we characterise TolDCs from RA patients modulated with dexamethasone and monophosphoryl lipid A (MPLA) concerning gene expression, phenotype, cytokine profile, migratory properties and T cell-stimulatory capacity to explore their suitability for autologous cellular therapy.

Methods: TolDCs were generated from monocytes of 9 RA patients, meeting 2010 ACR/EULAR criteria, and 10 healthy controls, using dexamethasone for tolerization and MPLA for activation (MPLA-tDCs). The phenotype of MPLA-tDCs and their migratory behaviour towards lymphoid chemokines were analysed by flow cytometry and transwell assays. Cytokine secretion of MPLA-tDCs and their ability to activate autologous antigen-specific T cells was determined by flow cytometry and ELISA. Genome-wide transcriptional analysis was performed and differential expression was defined by a false discovery rate of ≤ 0.05.

Results: MPLA-tDCs derived from RA patients, exhibited characteristics of semi-mature DCs (Fig 1), such as: reduced expression of costimulatory and coactivation molecules and the capacity to migrate in response to ligands of lymph node homing chemokine receptors CCR7 and CXCR4. These cells displayed an anti-inflammatory cytokine profile inducing hyporesponsiveness and IL-10 secretion of autologous CD4+ T cells specific to synovial antigens. Global transcriptome analysis demonstrated that treatment with dexamethasone and MPLA overcame RA-associated effects on gene expression profiles of monocyte-derived DCs (Fig 2).

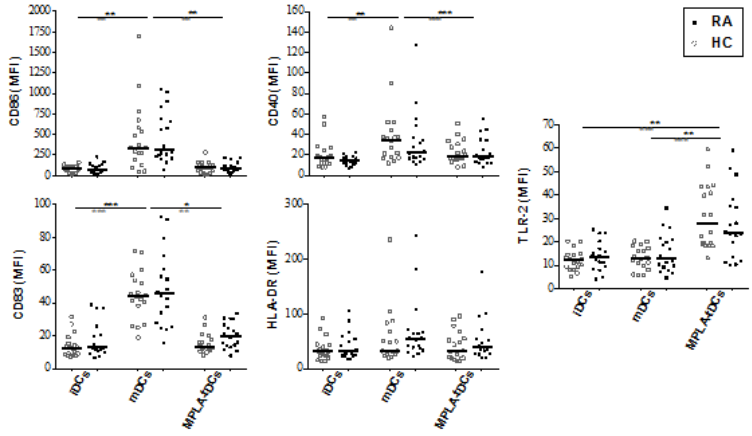

Figure 1. MPLA-tDCs from rheumatoid arthritis patients and healthy controls display low expression of maturation

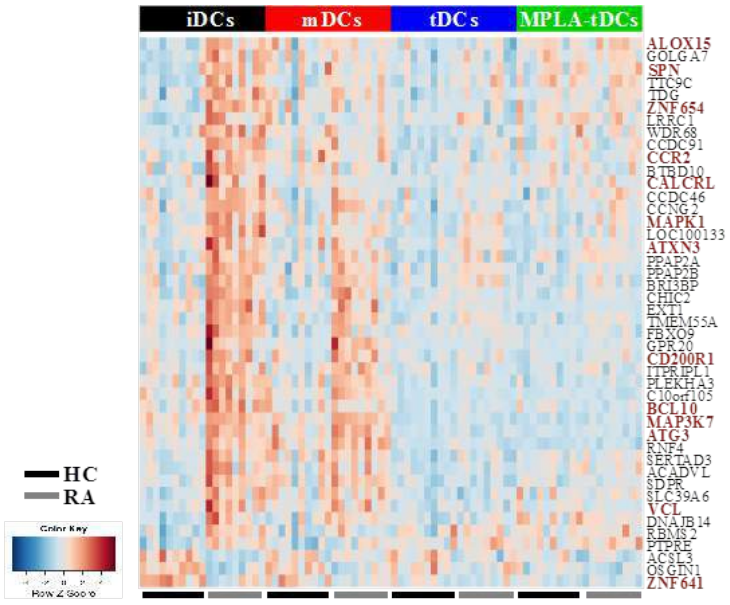

Figure 2. Conditioning with dexamethasone and MPLA induces similar transcriptional profiles on moDCs from RA patients and healthy controls, and reverses disease-associated effects on gene expression in MPLA-tDCs derived from monocytes of rheumatoid arthritis patients

markers and high TLR2.

Conclusion: Monocyte-derived DCs of RA patients have the potential to develop stable tolerogenic features when modulated with dexamethasone and MPLA, irrespective of disease status. The ability of MPLA-tDCs to impair T cell responses to synovial antigens validates their potential for the treatment of RA. Funding: Fondecyt-Chile 1100102 and 1140553, and Millennium Institute on Immunology and Immunotherapy P09-016-F.

Disclosure: P. García-González, None; **O. Neira**, None; **K. Schinnerling**, None; **A. Sepúlveda-Gutiérrez**, None; **J. Maggy**, None; **L. Hoyos**, None; **R. Morales**, None; **G. Ubilla-Olguín**, None; **A. Mehdi**, None; **H. Nel**, None; **L. Soto**, None; **B. Pesce**, None; **M. C. Molina**, None; **M. Cuchacovich**, None; **M. Larrondo**, None; **D. Catalán**, None; **C. M. Hilkens**, None; **R. Thomas**, None; **R. Verdugo**, None; **J. C. Aguillón**, None.

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Abstract Number: 178

Alpha-Enolase Promotes Pro-Inflammatory Phenotype of Monocytes-Derived Macrophages

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatism. RA is multifactorial involving genetic, environmental, endocrine, psychological and immunological factors. In 2002, our research team has discovered alpha-enolase (ENO1) as an autoantigen in RA and has recently demonstrated its effect on monocytes, inducing inflammation mediated through CD14-dependent TLR4 signaling pathway. Monocytes can differentiate into

dendritic cells, osteoclasts or macrophages. Macrophages are involved in RA pathophysiology and can be polarized in different phenotypic profiles, pro-inflammatory (M1 macrophages) or immuno-regulatory (M2 macrophages). The main objective of this study was to determine the effect of ENO1 on monocytes differentiation into macrophages and on their polarization.

Methods: Monocytes of healthy donors were cultured with M-CSF (Macrophage-Colony Stimulating) or GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor) for 5 days for their differentiation into macrophages and for 3 supplemental days with IFN-g and/or LPS or IL-4 and/or IL-10 for M1 or M2 polarization respectively. Monocytes and monocytes-derived macrophages were also cultured with ENO1, or control BSA, to investigate its effect on monocytes differentiation and macrophages polarization. Microscopy, flow cytometry and ELISA were performed to determine the macrophages polarization profile (M1 or M2) induced by ENO1.

Results: Firstly, we showed that ENO1 did not induce monocytes differentiation into macrophages in contrast to M-CSF and GM-CSF. However, in macrophages differentiated with M-CSF or GM-CSF, ENO1 induces M1 polarization in terms of morphology, surface markers and cytokines production. ENO1 can also initiate repolarization in M1 of macrophages previously polarized in M2. Finally, we showed that ENO1 induced a cytokine inflammatory response higher in macrophages differentiated with GM-CSF compared to M-CSF.

Conclusion: These results showed for the first time the potential role of native ENO1 in the inflammatory process of RA through its interaction with macrophages, promoting their polarization into pro-inflammatory M1 profile. Our project, aimed to understand the role ENO1 in RA pathophysiology, opens interesting research perspectives on cell types derived from monocytes.

Disclosure: P. Rottenberg, None; **M. Fréret**, None; **S. Calbo**, None; **O. Vittecoq**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/alpha-enolase-promotes-pro-inflammatory-phenotype-of-monocytes-derived-macrophages

Abstract Number: 179

CD11b+Gr1dimcells, Which Are Induced By GM-CSF Produced By Th17 and Group3 Innate Lymphoid Cell, May Facilitate the Progression of Pneumonitis in SKG Mice

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Background/Purpose: Rheumatoid lung disease is a prognostic factors of rheumatoid arthritis in human. The pathogenesis and the mechanism of rheumatoid lung disease is unclear. Zymosan A (ZyA)-treated SKG mice develop not only arthritis but also pneumonitis. To clarify the mechanism of rheumatoid lung disease in human, we analyzed the pneumonitis in SKG mice, which is similar to rheumatoid lung disease in human.

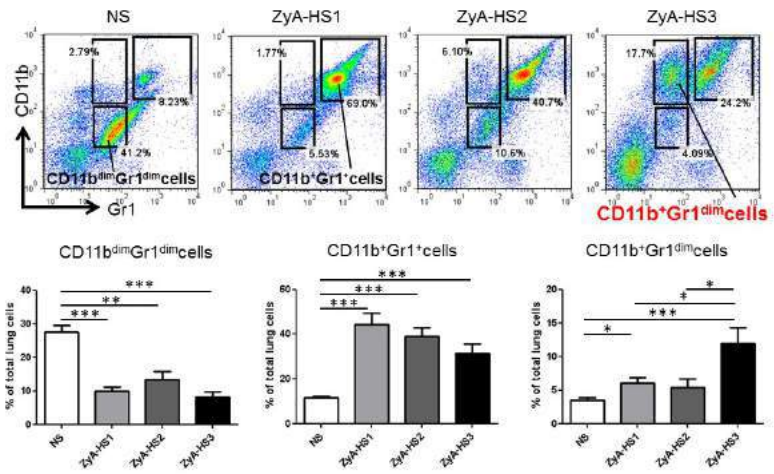
Methods: SKG mice were induced pneumonitis by ZyA injection. The severity of pneumonitis three months after ZyA injection was evaluated by the area of diffusely affected lesion in HE stain, as follows: histological score (HS) 0: affected area <10%, HS1: 10-29%, HS2: 30-59%, HS3: ≥60%. Lung-infiltrating cells (T cells, myeloid cells, innate lymphoid cells (ILCs)) were evaluated by flow cytometry. In vitro, lung-infiltrating cells were cultured with GM-CSF (and IL-4) for 5 days and evaluated by flow cytometry. CSFE-labeled naïve T cells were cultured with isolated $CD11b^{+}Gr1^{dim}$cells from lung, and stimulated with anti-CD3 and anti-CD28 monoclonal antibodies. After three days, Cell proliferation was

examined by measuring CFSE fluorescence with flow cytometry.

Results: Histological analysis revealed that ZyA-treated mice developed various severity of pneumonitis; HS1: 30%, HS2: 50%, HS3: 20%. Unique cells with large and bright nucleus emerged only in the specimen of HS3. Flow cytometric analysis revealed that $CD11b^{+}Gr1^{+}$cells, $CD11b^{+}Gr1^{dim}$cells, Th17 cells, regulatory T cells (Treg), and ILC3s were increased, and the proportion of these cells varied depending on the HS: $CD11b^{+}Gr1^{+}$cells decreased as the progression of HS, while $CD11b^{+}$ $Gr1^{dim}$cells emerged only in the lung of HS3 (Figure1). Most of $CD11b^{+}$ $Gr1^{dim}$cells expressed CD11c, and the cells facilitated the naïve T cell proliferation in vitro. GM-CSF (and IL-4) induced the differentiation of $CD11b^{+}Gr1^{dim}$cells from total lung cells. The GM-CSF mRNA was significantly increased in the lung of ZyA-treated SKG mice compared to that of normal saline (NS)-treated SKG mice. Intracellular cytokine staining revealed that GM-CSF-producing Th17 and ILC3s were significantly increased in the lung of ZyA-treated SKG mice.

Conclusion: $CD11b^{+}Gr1^{dim}$cells, which are induced by GM-CSF produced by Th17 and ILC3s, may facilitate the progression of pneumonitis in SKG mice.

Figure1 : $CD11b^{+}Gr1^{dim}$cells emerged in the lung of HS3.



Disclosure: S. Sendo, None; **J. Saegusa**, None; **T. Okano**, None; **S. Takahashi**, None; **A. Morinobu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cd11bgr1dimcells-which-are-induced-by-gm-csf-produced-by-th17-and-group3-innate-lymphoid-cell-may-facilitate-the-progression-of-pneumonitis-in-skg-mice

Abstract Number: 180

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-2

Abstract Number: 181

Functional and Quantitative Changes of CCR6+ type3 Innate Lymphoid Cells in Murine Collagen-Induced Arthritis

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Background/Purpose: Innate lymphoid cells (ILCs) are a group of lymphocytes that lack antigen-specific receptors and have important roles in mediating immune responses and in regulating tissue homeostasis. ILCs are classified into three subsets, ILCs 1, 2, and 3, based on their patterns of cytokine production and transcription factors (TFs) expression. ILC3s are dependent on Retinoic-acid-receptor-relates orphan receptorγt (RORγt) and produce cytokines such as IL-17, IL-22, and Tumor necrosis factor -α (TNF-α), which play critical roles in inflammatory arthritis. ILC3s are further subdivided into several populations based on the expression of surface markers. LTi cells, which express chemokine receptor 6 (CCR6), are important for development and maintenance of lymph nodes and secondary lymphoid tissues. Another subgroup is natural cytotoxicity receptor (NCR) $^{+}$ ILC3s, which are essential for the epithelial barrier and host protection in the intestine. In rheumatic diseases, the increase of the number of NCR^{+} ILC3s was reported in patients with psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS). It has also been shown that CCR6^{+}ILC3s have increased in synovium fluid (SF) of patients with PsA. In this study, we tried to evaluate the ILCs 1,2, and 3 both in quantity and quality in various tissues isolated from collagen induced arthritis (CIA) model mice in order to clarify the role of ILCs in the development of rheumatoid arthritis (RA).

Methods: We isolated lymphocytes from bone marrow (BM), spleen, peripheral blood (PB), local lymph nodes (LNs) and joints in normal and CIA model mice. ILC1s, ILC2s, CCR6^{+}ILC3s and NCR^{+}ILC3s were determined by flow cytometry using surface markers, NK1.1 (ILC1), IL-33R (ILC2), CCR6 and NKp46 (ILC3). Gene expression of the TFs and cytokines were measured by quantitative real-time PCR (qPCR) to confirm that ILC subsets are precisely classified by these surface markers. Finally, we compared the absolute cell number, ratio, gene expressions of TFs and cytokines of each ILC sunset in normal and in CIA model mice.

Results: CCR6^{+}ILC3s showed high gene expression of RORγt, IL-17, IL-22 and TNF-α as reported previously. In CIA model mouse, in addition to the increase of ratio of CCR6^{+}ILC3s in PB and joints, the levels of gene expression of TFs and cytokines were significantly elevated. Almost all of NKp46^{+}ILC3s expressed NK1.1, which is a marker for ILC1s. NKp46^{+}ILC3s showed lower gene expression of RORγt, IL-17 and IL22 than CCR6^{+}ILC3, while they showed high gene expression of T-bet and Interferon-γ(IFN-γ), suggesting that NKp46^{+} ILC3s in our purification method may include a fraction of ILC1s. Another marker which can further subdivide NKp46^{+}ILC3 population is required.

Conclusion: CCR6^{+}ILC3 produce IL-17, IL-22 and TNF-α, which are essential cytokines for the development of CIA. CCR6^{+}ILC3s may play roles in pathogenesis of RA through its production of cytokines.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/functional-and-quantitative-changes-of-ccr6-type3-innate-lymphoid-cells-in-murine-collagen-induced-arthritis

Abstract Number: 182

Histone Methylation in γδ T Cells As a Biomarker of Behcet's Disease Activity

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Background/Purpose: Behcet's disease (BD) is a chronic recurrent, multisystem inflammatory disorder. The phenotypic characteristics include oral aphtha, genital ulcers, uveitis and skin lesions. No specific laboratory tests have been known in BD. Reported in BD have been an increased number of γδ T cells in the peripheral blood and hyperactivity of neutrophils. Although a line of evidence has suggested genetic contributions to the disease, etiopathogenesis of BD is still unclear and non-genetic factors, like environment, infection or epigenetics, may play pivotal roles in the pathogenesis. Epigenetic mechanisms including posttranslational histone modifications are known to regulate gene expression without altering the genomic sequence. The association of specific histone modifications with gene expression is very well defined, such as H3K27me3, which may be characteristics of repressed genes, or H3K4me3, which may present in many active genes. Histone modifications in major rheumatic diseases, such as rheumatoid arthritis, have been investigated, while studies on histone modifications in BD are limited. From the functional point of view, it is important to analyze differences of histone modifications in each functional subclass of the entire peripheral blood nucleated cells. To examine the histone modifications of peripheral white blood cells (WBCs) in BD, we have established a novel method analyzing histone methylation in each subset defined by the surface markers using fluorescence-activated cell sorting (FACS).

Methods: WBCs were obtained from patients with active and inactive BD and healthy controls (HC). Six immune cell types were stained with antibodies against surface markers and classified as below : CD4+ T cells, CD8+ T cells, γδ T cells, CD16+CD66b+ neutrophils, CD4+CD25+Foxp3+ Tregs, and CD19+ B cells. All samples were analyzed with a FACSCanto II cytometer. As a quantitative measure of H3K4me3 and H3K27me3, mean fluorescence intensity (MFI) was used and normalized using isotype controls.

Results: H3K27me3 MFI levels of BD in CD4+T cells, CD8+T cells and γδT cells were significantly decreased, compared with HC. H3K27me3 MFI levels of BD in neutrophils were significantly increased. In contrast, H3K4me3 MFI levels of BD in CD4+T cells, CD8+T cells, γδ T cells and Tregs were significantly decreased, compared with those of HC. H3K4me3/H3K27me3 MFI ratio of BD was significantly lower in neutrophils and Tregs, and higher in γδ T cells of BD than that of HC. H3K27me3 MFI of active BD were significantly decreased in γδ T cells as compared to inactive BD. H3K4me3/H3K27me3 MFI ratio of active BD was significantly higher in γδ T cells than in inactive BD.In addition, the similar result was also observed between active and inactive phasesin the same patients. Preliminary observations suggest IL-17 secretion on γδ T cells in BD.

Conclusion: Differences in histone modifications could be detected by FACS in peripheral WBCs in BD patients. Aberrant histone methylation in γδ T cells may be associated with the pathogenesis of BD. It is suggested that histone methylation could be a new candidate-biomarker for BD and that γδ T cells might be a possible therapeutic target in BD.

Disclosure: Y. Aizaki, None; **Y. Araki**, None; **K. Sato**, None; **K. Yokota**, None; **T. Mimura**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/histone-methylation-in-%ce%b3%ce%b4-t-cells-as-a-biomarker-of-behcets-disease-activity

Abstract Number: 183

Protective Role of Mucosal-Associated Invariant T (MAIT) Cells in an Imiquimod-Induced Psoriasis Model

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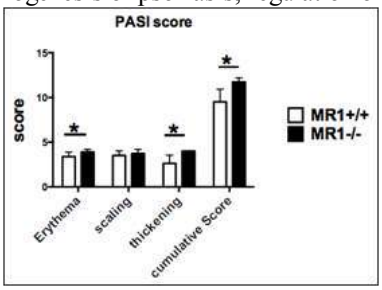
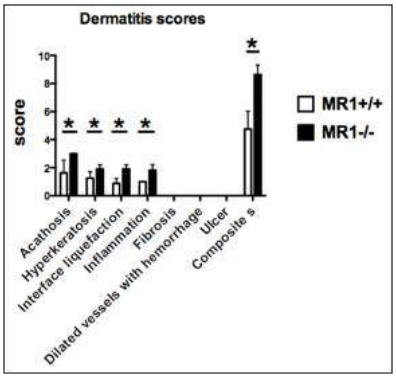
Background/Purpose: Psoriasis is a chronic inflammatory disease of the skin and is often accompanied by arthritis. The underlying pathogenesis of psoriasis is still unclear, but T-helper 1 (Th1) and Th17 cells are thought to play important roles. Mucosal-associated invariant T (MAIT) cells are innate lymphocytes that are restricted by MHC-related molecule-1 (MR1), express a semi-invariant TCRa chain: Va7.2-Ja33 in humans and Va19-Ja33 in mice. Previously, we have shown that MAIT cells inhibited the progression of autoimmune encephalomyelitis (EAE), and the inhibition of EAE was accompanied by reduced autoreactive Th1 and Th17 responses. Therefore, we sought to investigate whether MAIT cells have a suppressive role in an animal model of psoriasis by using $MR1^{-/-}$ mice lacking MAIT cells.

Methods: A murine imiquimod (IMQ)-induced model of psoriasis (J Immunol. 2009; 182: 5836-45) was induced in $MR1^{-/-}$ and $MR1^{+/+}$C57BL/6J mice at 8 to 10 weeks of age. Mice were topically treated with 62.5mg of 5% IMQ cream (Mochida Pharmaceutical) on the shaved back for 5 consecutive days. Mice were injected with 500ml of phosphate-buffered saline on day 1 and 3. The severity of skin inflammation was monitored every day, and scored by usning linical Psoriasis Area and Severity Index (PASI) score. Erythema, scaling, and thickening of the back skin were scored on the scale from 0 to 4. (J Immunol. 2009; 182: 5836-45). Skin samples were stained with haematoxylin-eosin, and the severity were graded on a scale of 1 to 3 for acanthosis; 1 to 2 for hyperkeratosis, interface liquefaction, inflammation, dermal cellularity, presence of dilated vessels with hemorrhage; 0 to 1 for ulcer or erosion. Differences between groups were assesed using the Mann-Whitney U test, and the significance level was set at $p < 0.05$.

Results: Both $MR1^{-/-}$ and $MR1^{+/+}$C57BL/6J mice equally developed erythema. $MR1^{-/-}$C57BL/6J mice displayed significantly severe scales and thickness of the back skin than $MR1^{+/+}$ mice. The histopathological analysis revealed there was a significant worsening of dermatitis and the higher dermatitis score in $MR1^{-/-}$ mice compared to control $MR1^{+/+}$C57BL/6J mice.

Conclusion: The present study indicated that MAIT cells play a suppressive role for the development of psoriasis. In humans, MAIT cells have recently been found in normal and psoriatic skin. Although further verification for mechanisms of the function of MAIT cells for pathogenesis of psoriasis, regulation of MAIT cell functions may become a novel therapeutic strategy for psoriasis.





Disclosure: G. Murayama, None; **A. Chiba**, None; **H. Toda**, None; **K. Yamaji**, None; **N. Tamura**, None; **S. Miyake**, ASUBIO PHARMA CO., LTD, 2,TAIHO PHARMACEUTICAL CO., LTD., 5.

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Abstract Number: 184

Upregulation and Activation of the IFI16-Sting-IRF3-IFN Pathway in Sjogren's Salivary Glands

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SESSION INFORMATION

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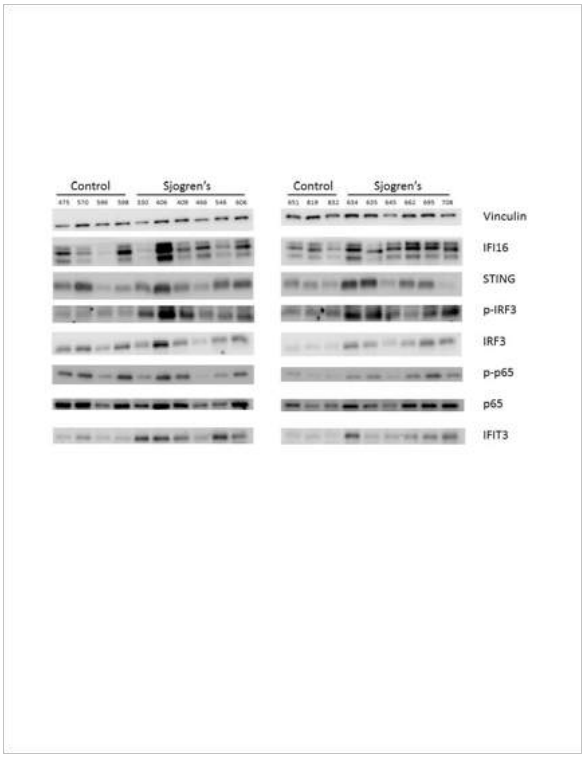
Background/Purpose: Type I IFN expression is known to be upregulated in the salivary glands of patients with SjogrenÕs syndrome, but the upstream stimuli responsible for this IFN signature are not known. IFI16 is a cytoplasmic DNA sensor that stimulates the production of type I IFN in response to cytoplasmic DNA via the STING-IRF3/NFkB pathway. IFI16 expression is also induced by IFN I, and therefore establishes a mutually reinforcing feedback loop. IFI16 is the target of autoantibodies in SjogrenÕs syndrome and is known to be expressed in the salivary gland. We sought to determine whether the elements of this DNA sensing pathway downstream of IFI16 were upregulated in the labial salivary glands of patients with SjogrenÕs syndrome.

Methods: Protein lysates were generated from minor salivary glands obtained from patients with SjogrenÕs syndrome (n=12) and sicca controls (n=7). All patients with SjogrenÕs syndrome met the ACR criteria for SjogrenÕs syndrome; none of the controls met these criteria. Protein lysates were subjected to SDS-PAGE electophoresis followed by Western blotting for the following proteins: IFI16, STING, IRF3, phospho-IRF3, p65, phospho-p65, IFIT3 (as a marker of type I IFN signaling), and vinculin (as loading control). Western blot results were subjected to densitometry analysis and statistical analysis was performed using GraphPad Prism 7.00 (Mann-Whitney analysis for nonparametric variables).

Results: IFI16, STING, IRF3, and p-IRF3 were found to be upregulated in SjogrenÕs patients as compared to controls. The ratio of phosphorylated IRF3/total IRF3 was also increased in SjogrenÕs patients, implying enhanced activation of this signaling pathway. IFIT3, which is a marker of type I IFN expression, was also upregulated in patients. While NF-kB has been proposed to signal downstream of IFI16 in in vitro studies, we did not find p65 to be significantly upregulated nor phosphorylated in SjogrenÕs patients as opposed to controls.

Conclusion: These data indicate that the STING-IRF3-IFN DNA sensing pathway which functions downstream of IFI16 is upregulated and activated in the target tissues of SjogrenÕs patients. These data imply that DNA sensing in the minor salivary gland may be a stimulus for IFN I production in this tissue. Figure 1: Western Blot Analysis of Salivary Gland Protein Lysates



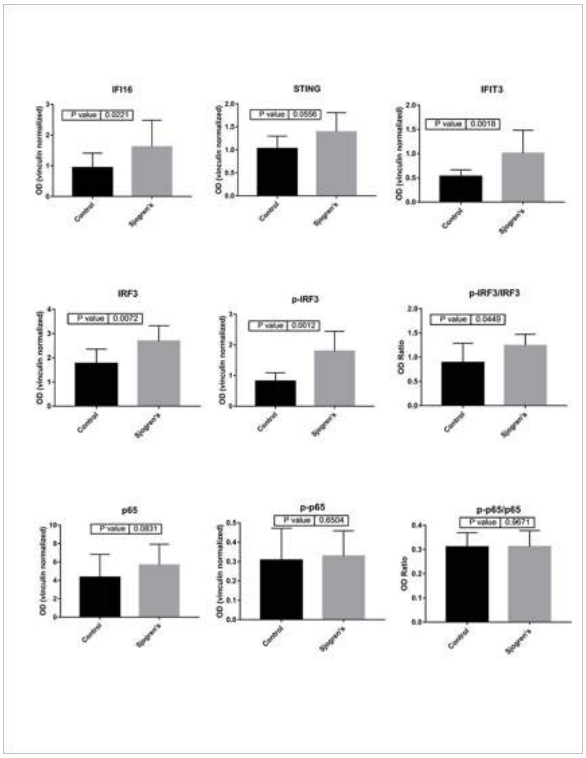


Figure 2: Quantification of Western Blot Data

Disclosure: B. Antiochos, None; **L. Casciola-Rosen**, None; **A. Rosen**, None.

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Abstract Number: 185

The Interferon Gene Signature Is Increased in Early DMARD Naive Rheumatoid Arthritis and Predicts a Poorer Response to Initial Therapy

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Background/Purpose: Type 1 interferons, such as interferon-α, are of increasing interest in autoimmunity due to their pleiotropic effects on the immune system. Approximately 20-30% of established rheumatoid arthritis (RA) patients have a positive interferon gene signature (IGS) suggesting active type 1 interferon signalling, While this can predict a poor response to biological therapies, such as rituximab, it has not been shown to correlate with disease activity. Since some treatments, such as steroids, can modify the IGS we wished to examine the prevalence and prognostic value of the IGS in early drug naïve RA.

Methods: 50 DMARD and glucocorticoid naïve early RA patients fulling ACR/EULAR (2010) criteria for RA, 23 established RA patients, 23 SLE patients and 23 healthy controls had whole blood RNA isolated (Tempus, ThermoFisher) and expression of 5 interferon signature genes quantified (MxA, IFI6, OAS1, ISG15, IFI44L) by RT-PCR (Taqman, ThermoFisher) using the Roche Universal probe library. The mean expression of these genes was termed the IGS score and defined as positive if was ≥ 2 standard deviations above that seen in the healthy population. EULAR responses were recorded after 3-6 months on standard DMARD therapy and some early RA patients also had their IGS repeated 1 and 3 months following diagnosis. Statistical analysis included ordinal and nominal logistic regression, multiple regression analysis, Wilcoxon signed rank, Mann-Whitney U and Chi^2 tests (GraphPad Prism v 5.0, San Diego USA and JMP Statistical Visualization Software v 11, SAS Inc, NC). Significance was defined when $p<0.05$.

Results: Twice as many early RA patients as established RA patients exhibited an IGS (42% vs 21%). There was significantly upregulated expression of interferon signature genes in early RA compared with established RA and were at similar levels to those reached in SLE. We observed a significant fall in early RA IGS expression between baseline and 3 months. The baseline IGS score significantly associated with DAS-28 at baseline and 6 months. This association was mainly driven by the CRP and SJC components. The IGS also predicted poorer EULAR response to initial therapies and increased glucocorticoid requirements at both 3 and 6 months (p all <0.05). See table 1 for summary of prognostic findings.

Clinical outcomes at 6 months after diagnosis	**Association with baseline IGS score**	**P value**
DAS-28	positive	0.002
Probability of achieving a "Good" EULAR response	inverse	0.044
Number of additional glucocorticoids administrations	positive	<0.0001

Table 1: Baseline IGS score significantly predicts a poorer response to initial therapy in a range of clinical outcome measures.

Conclusion: We demonstrate an increased IGS in early RA. This mirrors other autoimmune conditions, such as primary sjogrens syndrome and type 1 diabetes where early exposure to type 1 interferons is key in disease pathogenesis. For the first time in RA we show that the IGS correlates with disease activity and in fact has prognostic value in early disease. This could inform management and therapeutic stratification, particularly with regard to therapies that target type 1 interferons and related pathways.

Disclosure: F. A. H. Cooles, None; **A. E. Anderson**, None; **D. W. Lendrem**, None; **J. Norris**, None; **A. G. Pratt**, None; **C. M. U. Hilkens**, None; **J. D. Isaacs**, None.

Abstract Number: 186

Impact of TLR Stimulation on Cytokine Production in Macrophage Subsets: TLR2 Stimulation Impairs Anti-Inflammatory Activity of M2 Macrophages

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Background/Purpose: Toll-like receptors (TLRs) have been shown to contribute to the inflammatory response in rheumatoid arthritis (RA). A number of TLRs have been found to be upregulated in synovial tissue (TLR2, TLR3, TLR4), synovial monocytes (TLR4) as well as macrophages (TLR2, TLR4) in RA versus osteoarthritis (OA). Based on phenotypic and functional differences macrophages can be divided into different subsets. At present there is limited knowledge on the functional role of macrophage subsets in rheumatoid arthritis. Here we investigated the impact of TLR2, TLR3 and TLR4 signaling on monocytes (M0) and monocyte derived M1 and M2 macrophages. We compared inflammatory and anti-inflammatory cytokine release, cell surface marker and TLR gene expression as well as viability of M0, M1 and M2 macrophages.

Methods: Monocytes were isolated from buffy coats of 4-6 healthy donors by CD14 microbead separation and differentiated into M1 and M2 by culturing them in the presence of 50ng/ml GM-CSF and M-CSF, respectively, for 6 to 8 days. For M0, CD14+ cells were kept in standard medium for 3 days. Subsequently, cells were stimulated for 24 hours with Pam3, LPS or PolyIC. Cytokine release was measured by ELISA, gene expression by qRT-PCR and viability by WST-1 assay. Cells were stained with fluorescently labeled antibodies for CD markers and analyzed by FACS.

Results: We demonstrate that stimulation of M2 macrophages with the TLR2-ligand Pam3 but not with the TLR4-ligand LPS leads to a decrease in the IL-10/IL-6 and IL-10/IL-8 ratio. TLR2 and TLR3 basal gene expression levels were similar between the cell types, whereas TLR4 expression was 3.7 fold higher in M2 than M0 or M1. TLR4 was strongly downregulated by LPS and Pam3 in M1 and M2, but not in M0. In contrast, TLR2 was upregulated by Pam3 and LPS. CD14 and CD163 expression was not affected by TLR ligands. CD86 levels were increased in M1 by all TLR ligands tested and in M0 by Pam3 but decreased in M2 by LPS and Pam3. CD80 was increased by Pam3 and LPS in M1 and by LPS in M2. Stimulation with TLR2 ligands was found to significantly increase M2 viability.

Conclusion: We demonstrate that stimulation of in vitro differentiated M2 macrophages with TLR2 ligands leads to increased proinflammatory cytokine production, suggesting that the antiinflammatory activity of M2 macrophages is reduced in an inflammatory milieu with abundant TLR2 ligands as can be found in RA. In line with these observations, Pam3 upregulated TLR2 mRNA expression in M2 macrophages in an autocrine fashion and increased M2 viability, thereby enhancing TLR2-induced proinflammatory effects.

Disclosure: L. Quero, None; **A. Gehringer**, None; **D. Kyburz**, None.

Abstract Number: 187

Commensal Microbiota Tune Systemic Toll-like Receptor-Mediated Inflammatory Responses

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Background/Purpose: Although commensal microbiota are thought to contribute to the development of autoimmunity, the cellular and molecular mechanisms connecting changes in gut microbiota to the development of autoreactive adaptive immune responses remain elusive. Preclinical models of autoimmunity demonstrate reduced disease severity and defective adaptive immune responses in autoimmune-prone mice treated with antibiotics or housed in germ-free conditions. As many autoimmune diseases show evidence of chronic Toll-like receptor (TLR) activation, we posited that defects in TLR-driven innate immune responses may explain the defective adaptive immune responses and reduced disease severity seen in antibiotic-treated mice.

Methods: We tested our hypothesis by using two murine models of TLR-driven systemic inflammation in mice treated with or without broad-spectrum antibiotics. Analysis of systemic inflammation was performed 10-14 days after a single dose of pristane (TLR7-driven inflammation) or after 5 doses of CpG (TLR9-driven inflammation) in mice treated with or without antibiotics. Systemic inflammation was determined by analysis of diffuse alveolar hemorrhage, cytopenias, hypercytokinemia, hepatosplenomegaly, and inflammation-induced myelopoiesis, which develop in these models of TLR-driven inflammation. TLR9 responsive cells isolated from mice treated with 0-5 doses of CpG were analyzed for production of IL-12 following *ex vivo* stimulation with CpG.

Results: Mice treated with broad-spectrum antibiotics were protected from developing systemic immunopathology following TLR-driven inflammation *in vivo*, as evidenced by lack of diffuse alveolar hemorrhage, cytopenias, hypercytokinemia, and hepatosplenomegaly following injection of pristane or repeated doses of CpG. This was not from baseline defects in innate immune cell numbers or TLR responsiveness, as numbers of TLR responsive cells and TLR-driven cytokine production following a single dose of CpG were preserved in antibiotic-treated mice. However, antibiotics abolished the inflammation-induced myelopoiesis and expansion of peripheral TLR responsive monocytes that accompanies both pristane- and CpG- induced immunopathology.

Conclusion: We demonstrate that antibiotic-treated mice have normal baseline responses to TLR-driven inflammatory signals, but fail to develop end-organ damage or sustained systemic inflammation to chronic TLR triggers *in vivo*. Disease protection in antibiotic-treated mice correlated with defective inflammation-induced myelopoiesis and inhibition of peripheral monocyte expansion that drive ongoing TLR immune responses in these models of sustained systemic inflammation. Our data implicate a novel mechanism for how commensal organisms contribute to the development of autoimmunity by tuning systemic innate immune responses in the setting of chronic TLR stimulation.

Disclosure: L. K. Weaver, None; **C. Biswas**, None; **E. M. Behrens**, None.

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Abstract Number: 188

Responsiveness to X-Linked Toll-like Receptors Differs Between Mice with XY and XX Sex Chromosome Complement, Regardless of the Gonadal Sex

Brandon Pham, Isela Valera and Ram R. Singh, UCLA, Los Angeles, CA
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Background/Purpose: Males and females differ in mounting immune response to pathogens. Females appear immune privileged, mounting stronger immune response to pathogens and vaccination. While this limits females' susceptibility to infection compared to males, it increases their likelihood, in some cases, by 10-15-fold to develop autoimmune disease. Mechanisms underlying the sex dimorphism in immune/autoimmune responses are not well understood. Since many immune response genes are encoded on sex chromosomes, we posit that a differential expression and/or function of these X/Y-linked genes underlie the differences in immune/autoimmune responses. Here, we investigate the responses of immune cells to two X-linked genes, toll-like receptor 7 and 8 (*Tlr7* and *Tlr8*).

Methods: To dissect the role of sex chromosomes in the absence of confounding hormonal influences, we used the four-core genotype (FCG) mouse model where findings in the XX females (XXF) can be compared with XY females [XYF, XY^{-Sry}]; and XX males [XXM, XX.Sry^{Tg}] can be compared with XY males [XYM, XY^{-Sry}.Sry^{Tg}]. Spleen cells from XYF and XXF mice were stimulated with TLR agonists IMI, R848, Poly I:C, and CpG and then analyzed for cellular proliferation by flow cytometry. Poly I:C and CpG, which stimulate TLR3 and TLR9, respectively, showed similar proliferation patterns to control in both XXF and XYF. IMI and R848, which target TLRs located on the X chromosome (TLR7 and TLR7/8, respectively), were also used to stimulate cells. XYF spleen cells showed increased cellular proliferation in response to stimulation by high concentrations of IMI and R848.

Results: First, we found that as compared to XXF mice, XYF mice had splenomegaly, with increased total cells per spleen ($p < 0.05$, $n = 6$). The proportion of individual immune cells also varied between XXF and XYF mice, with higher proportions of granulocytes and lower proportions of T and B cells in XYF mice as compared to XXF mice, although the absolute numbers of all cell types were higher in XYF vs. XXF spleens. Second, XYF and XYM spleen cells proliferated more vigorously to TLR7 ligand imiquimod and TLR7/8 ligand R848 than XXF and XXM, respectively, whereas the proliferative responsiveness to TLR3 and TLR9 ligands, Poly I:C and CpG, respectively, were not different between XX and XY mice, regardless of the gender. XYF and XXF spleen cells responded similarly to anti-CD3/CD28 stimulation.

Conclusion: These results suggest that the sex chromosome genotype might have consequences for the composition of immune cells and the responsiveness to innate receptors, which in turn could significantly alter immune/autoimmune responses. Ongoing studies will investigate mechanisms underlying these sex-related differences. Acknowledgement: B.P. is an undergraduate Barry Goldwater Scholar, I.V. is a recipient of an NIH/NHLBI K01 grant, and R.R.S. is supported by NIH R01 AR56465, AI80778, and R21 HD82812.

Disclosure: B. Pham, None; **I. Valera**, None; **R. R. Singh**, None.

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Abstract Number: 189

Nutraceutical Therapy with Polyphenol-Rich Pomegranate Fruit Extract (POMx) Inhibits Systemic NFκB-Mediated Inflammation in a Murine Model of Endotoxemia

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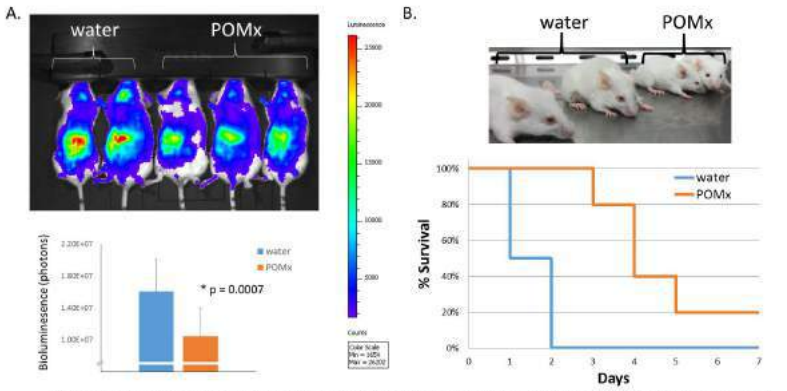
Background/Purpose: The pomegranate fruit is cultivated worldwide for dietary consumption, but has been used therapeutically in Eastern medicine from times dating back to ancient Egypt due to its potent anti-inflammatory properties. Recent studies have attributed this well-documented immunomodulatory influence to anthocyanin and hydrolysable tannins, which are polyphenolic compounds contained in the edible part of the fruit. A commercially- standardized nutraceutical preparation of a polyphenol-rich pomegranate extract (POMx) has previously been created and shown to suppress disease activity in a murine model of rheumatoid arthritis and inhibit NFkB activity in human cell lines. In the present study, our objective was to establish an animal model to longitudinally measure systemic effects of POMx on NFkB-mediated inflammation *in vivo*.

Methods: Endotoxemia was induced in BALB/C-Tg(NFkB-RE-luc)-Xen mice, which have a firefly luciferase cDNA reporter gene under the regulation of 3 kB responsive binding sites, by injection of lipopolysaccharide (LPS). NFkB-mediated inflammation was determined following a sub-lethal dose of LPS (2 mg/kg) by measuring whole-body bioluminescent signals using the Xenogen *in vivo* imaging system (IVIS 200). The emitted photons were quantified for each mouse at baseline, 2 hr, 4 hr, and 24 hr. Lethal endotoxemia was induced by LPS injection (25 mg/kg) for survival curve analysis. Prior to any LPS injection, mice were pre-treated for one week with water or POMx (34mg/kg/day) and continued daily treatment was provided in survival experiments.

Results: Relative to NFkB-RE-luc mice given water, POMx inhibited NFκB-induced luciferase activity after sub-lethal endotoxemia induction with LPS injection. Systemic inflammatory responses measured by IVIS photon quantification of NF-kB activation were significantly suppressed with POMx treatment. Lethal endotoxemia led to 50% survival of control mice receiving water after 24 hr, but POMx treatment resulted in 100% survival. Subsequently, while all controls did not survive past 48 hr, daily dosing of POMx resulted in 20% total survival after 7 days.

Conclusion: This novel application of the NF-kB-regulated luciferase mouse model establishes a system that may facilitate the future therapeutic development of POMx as an anti-inflammatory nutraceutical extract by enabling the longitudinal analysis of systemic NFkB-mediated inflammatory responses and will permit further elucidation of the mechanism of NFkB inhibition *in vivo*.



A) Bioluminescent imaging following sub-lethal LPS stimulation at 2 hr (top) and photon intensity quantitation after 4 hr (bottom). B) Representative photograph of surviving mice at 24 hr (top) and Kaplan-Meier survival curve (bottom) with lethal dose of LPS.

Disclosure: N. A. Young, None; **M. Mobeen**, None; **T. M. Haqqi**, None; **W. N. Jarjour**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/nutraceutical-therapy-with-polyphenol-rich-pomegranate-fruit-extract-pomx-inhibits-systemic-nf%ce%bab-mediated-inflammation-in-a-murine-model-of-endotoxemia

Abstract Number: 190

Pharmacokinetics, Pharmacodynamics, and Tolerability of Verinurad, a Selective Uric Acid Reabsorption Inhibitor, in Healthy Adult Male Subjects

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Session Time: 9:00AM-11:00AM

Background/Purpose: Verinurad (RDEA3170) is a selective uric acid reabsorption inhibitor in clinical development for the treatment of gout and asymptomatic hyperuricemia. The aim of this study was to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of verinurad following single and multiple doses in healthy adult males.

Methods: This was a Phase 1, randomized, double-blind, placebo-controlled, single- and multiple-ascending dose study. Panels of 8 male subjects (6 active, 2 placebo) received a single oral dose of verinurad or placebo in either a fasted (2 mg, 5 mg, 20 mg, 40 mg) or fed (5 mg, 20 mg) state and panels of 12 male subjects (9 active, 3 placebo) received ascending doses of once-daily verinurad (1 mg, 5 mg, and 10 mg) or placebo in a fasted state for up to 10 days. Verinurad was administered as an oral solution for 1 and 2 mg doses and in tablet form for doses >2 mg. Serial plasma/serum and urine samples were assayed for verinurad and uric acid at predetermined time points. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).

Results: A total of 81 adult males aged 18–54 years enrolled and completed the study. Following single oral doses of verinurad, absorption was rapid and exposure (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) increased in a dose-proportional manner up to the maximum dose tested; C_{max} was achieved at 0.5–0.75 hours post-dose in the fasted state, and was slightly delayed to 1.25 hours post-dose in the fed state. Food appeared to decrease AUC by about 23% and C_{max} by about 50%. Following multiple daily doses, there was modest accumulation of verinurad. Urinary excretion of verinurad accounted for approximately 2% of the administered dose, suggesting that renal excretion is a minor elimination pathway for unchanged verinurad. Reductions in serum uric acid (sUA) correlated with dose. Under fasted conditions, single-dose administration of verinurad 2, 5, 20, or 40 mg reduced sUA levels by 16%, 24%, 48%, and 62%, respectively. Following multiple once-daily dosing for 10 days, verinurad reduced sUA levels by 22%, 44%, and 61% for the 1, 5, and 10 mg doses, respectively. A persistent pharmacologic effect (>15% fractional excretion of uric acid relative to baseline) was evident for at least 24 hours after dosing for verinurad doses of 2 mg or above. Verinurad was well tolerated at all doses. No serious AEs, severe AEs, discontinuations due to AEs or clinically significant laboratory or ECG abnormalities were reported.

Conclusion: Single and multiple doses of verinurad were well tolerated, absorption was rapid and exposure was dose-proportional. Verinurad increased urinary uric acid elimination and resulted in sustained reductions in sUA. These data support further clinical evaluation of once-daily verinurad as a treatment for gout.

Disclosure: M. Gillen, AstraZeneca, 3; **Z. Shen**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3.

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Abstract Number: 191

Pharmacokinetics, Pharmacodynamics, and Tolerability of Concomitant Multiple Dose Administration of Verinurad (RDEA3170) and Febuxostat in Healthy Adult Male Subjects

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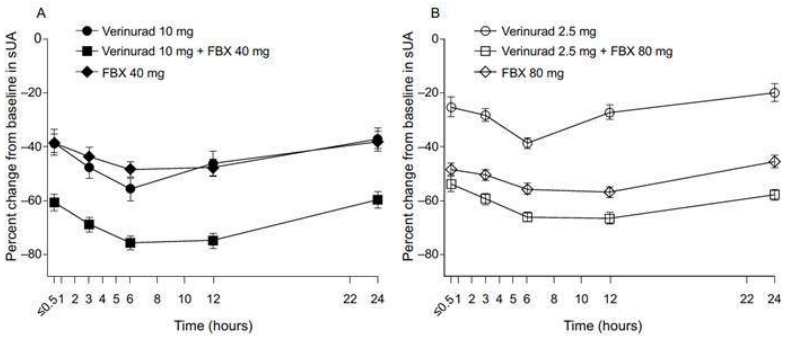
Background/Purpose: Verinurad (RDEA3170) is a novel selective uric acid reabsorption inhibitor in clinical development for the treatment of gout and asymptomatic hyperuricemia. This Phase 1, single-blind, multiple dose, drug-drug interaction (DDI) study evaluated the pharmacokinetics (PK), pharmacodynamics, and tolerability of verinurad in combination with febuxostat (FBX) in healthy male volunteers.

Methods: Subjects were randomized to receive once-daily doses of FBX or verinurad or placebo alone for 7 days, FBX + verinurad or FBX + placebo on days 8−14, and the alternative single agent (FBX or verinurad or placebo) on days 15−21. Subjects received either the combination of verinurad 10 mg + FBX 40 mg or verinurad 2.5 mg + FBX 80 mg. Serial plasma/serum and urine samples were drawn at predetermined time points on Days 7, 14 and 21, and assayed for verinurad, FBX, and uric acid. Baseline samples were drawn on Day −1. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).

Results: Of 23 randomized subjects, 20 completed the study. FBX 40 mg had no apparent effect on the plasma C_{max} and AUC for verinurad 10 mg, whereas FBX 80 mg increased the plasma C_{max} and AUC for verinurad 2.5 mg by 25% and 33%, respectively. Verinurad had no effect on FBX PK. Renal clearance of verinurad was unchanged by FBX. The mean maximal reduction in serum uric acid (sUA) was 76% with verinurad 10 mg + FBX 40 mg compared with verinurad 10 mg (56%) or FBX 40 mg (49%) alone (Figure 1A) and was 67% with verinurad 2.5 mg + FBX 80 mg compared with verinurad 2.5 mg (38%) or FBX 80 mg (57%) alone (Figure 1B). Consistent with the mechanism of action (MOA) of verinurad, 24-hr fractional excretion of uric acid (FEUA) increased (2.5 mg: 7.6%; 10 mg: 12.8%) vs baseline (6.5% and 6.0%, respectively). Renal clearance of uric acid (CL_{UR}) increased similarly (2.5 mg: 9.0 mL/min; 10 mg: 12.3 mL/min) vs baseline (8.3 and 7.3 mL/min, respectively). The increases were maintained for 24 hours with verinurad 10 mg + FBX 40 mg (FEUA: 11.8%; CL_{UR}: 13.6 mL/min). Consistent with its MOA, FBX 40 mg and 80 mg decreased the amount of uric acid excreted in urine (246 and 221 mg, respectively, vs baseline: 695 and 818 mg), FEUA (4.8 and 4.2%, respectively, vs baseline: 6.3 and 6.5%), and CL_{UR} (4.9 and 5.0 mL/min, respectively, vs baseline: 7.7 and 8.7 mL/min). No serious AEs, discontinuations due to AEs, or clinically significant laboratory or ECG abnormalities were noted during the study.

Conclusion: No DDI was found with the verinurad 10 mg + FBX 40 mg combination and only a modest one with verinurad 2.5 mg + FBX 80 mg. Both combinations were safe and well tolerated and resulted in greater reduction of sUA than either verinurad or FBX alone. These results support the continued development of this novel approach for the treatment of gout and hyperuricemia.

Figure 1. Mean (SE) percent change from baseline in sUA at steady state following multiple doses



Disclosure: J. VanderLugt, None; **M. Gillen**, AstraZeneca, 3; **X. Yang**, AstraZeneca, 3; **J. Hall**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacokinetics-pharmacodynamics-and-tolerability-of-concomitant-multiple-dose-administration-of-verinurad-rdea3170-and-febuxostat-in-healthy-adult-male-subjects

Abstract Number: 192

Pharmacodynamic and Pharmacokinetic Study of Verinurad in Adult Male

Subjects with Mild, Moderate, and Severe Renal Impairment: A Phase 1, Open-Label Study

William B Smith[1], Jesse Hall[2], Jolene Berg[3], Michal Kazimir[4], Amy Yamamoto[2], Caroline Lee[2], Susan Walker[2] and Thomas C. Marbury[5], [1]Volunteer Research Group, Knoxville, TN, [2]Ardea Biosciences, Inc., San Diego, CA, [3]DaVita Clinical Research, Minneapolis, MN, [4]DaVita Clinical Research, Lakewood, CO, [5]Orlando Clinical Research Center, Orlando, FL

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

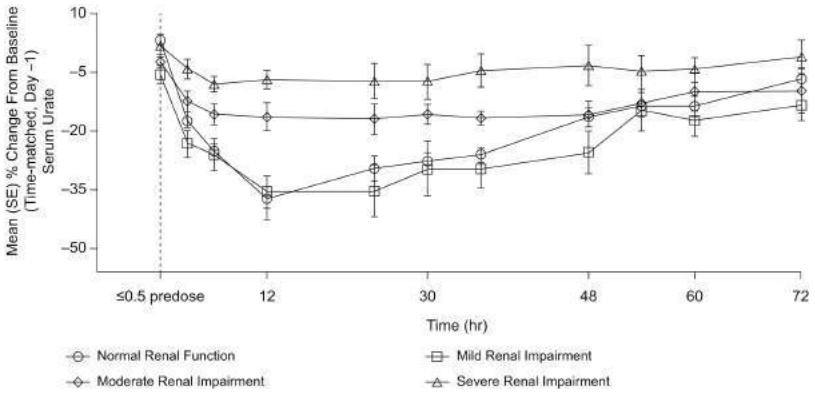
Background/Purpose: Verinurad (RDEA3170) is a high-affinity, selective URAT1 inhibitor in development for the treatment of gout and asymptomatic hyperuricemia. This Phase 1, single-dose, open-label study investigated the pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in adult subjects with mild, moderate, or severe renal impairment and matched controls with normal renal function (NCT02219516).

Methods: Adult males aged 18-85 years were enrolled with a screening serum uric acid (sUA) 4.5-10 mg/dL and creatinine clearance calculated by Cockcroft-Gault formula of 60 to <90 mL/min (mild renal impairment), 30 to <60 mL/min (moderate impairment), 15 to <30 mL/min (severe impairment), or ≥90 mL/min (matched controls). Oral verinurad 15 mg was administered once under fasted conditions. Serial blood and urine samples were taken 30 min before and up to 72 hours postdose. Safety assessments included laboratory, ECG, and vital sign parameters as well as adverse event (AEs) reporting.

Results: PD data were based on 7-8 subjects per group. Verinurad decreased sUA in all groups, with greatest changes in the normal function and mild renal impairment groups (Figure). Mean (SD) maximal % change in sUA from baseline (Emax) was -38.3(14.8)%, -36.9(13.6)%, -20.5(6.64)%, and -12.6(6.94)%, respectively, in the normal function and mild, moderate, and severe renal impairment groups. Increase in the amount of excretion of uric acid due to verinurad treatment decreased in subjects with moderate and severe renal impairment. Plasma Cmax and AUC of verinurad increased with decreasing renal function. Verinurad at the 15 mg dose was well tolerated, with no serious AEs, no subject withdrawals due to AEs, and no Renal Events Adjudication Committee (REAC)-adjudicated renal events during treatment. One patient in each renal impairment group had treatment-emergent AEs considered possibly related to verinurad, which were categorized as gastrointestinal in nature. There were no clinically meaningful changes noted in laboratory values or vital signs.

Conclusion: The sUA lowering effect of verinurad was observed across the spectrum of renal function. Consistent with the verinurad renal-dependent mechanism of action, decreasing sUA lowering was demonstrated with increasing renal impairment. Verinurad safety and tolerability were similar across all stages of renal impairment.

Figure. Mean % change from baseline in sUA (mg/dL) following single-dose verinurad 15 mg in subjects with mild, moderate, and severe renal impairment and matched controls



Disclosure: W. B. Smith, New Orleans Center for Clinical Research, 3; **J. Hall**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **J. Berg**, DaVita Clinical Research, 3; **M. Kazimir**, DaVita Clinical Research, 3; **A. Yamamoto**,

Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **C. Lee**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S. Walker**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **T. C. Marbury**, Orlando Clinical Research Center, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacodynamic-and-pharmacokinetic-study-of-verinurad-in-adult-male-subjects-with-mild-moderate-and-severe-renal-impairment-a-phase-1-open-label-study

Abstract Number: 193

Pharmacokinetics, Pharmacodynamics, and Tolerability of Verinurad, a Selective Uric Acid Reabsorption Inhibitor, in Healthy Japanese Male Subjects

Michael Gillen[1], Jeffrey N. Miner[2] and Shakti Valdez[3], [1]AstraZeneca, Gaithersburg, MD, [2]Discovery Biology, Ardea Biosciences, Inc., San Diego, CA, [3]Ardea Biosciences, Inc., San Diego, CA

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Chronic gout is a significant clinical problem in Asia, including Japan, where many patients remain suboptimally treated with currently available therapies. Verinurad (RDEA3170) is a selective uric acid reabsorption inhibitor in clinical development for the treatment of gout and asymptomatic hyperuricemia. The aim of this study was to evaluate the pharmacokinetics, pharmacodynamics, and tolerability of verinurad in healthy Japanese and non-Asian adult male subjects.

Methods: This was a Phase 1, randomized, single-blind, placebo-controlled study (NCT01872832). Panels of 8 Japanese male subjects were randomized in a 3:1 ratio to receive a modified-release formulation of oral verinurad (2.5 mg, 5 mg, 10 mg, 15 mg) or placebo administered as a single dose in a fasted state and as multiple once-daily doses in a fed state for 7 days. A panel of 8 non-Asian male subjects received single and multiple doses of oral verinurad (10 mg) or placebo. Serial plasma/serum and urine samples were assayed for verinurad and uric acid at predetermined time points. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).

Results: Of 48 randomized subjects, 46 (Japanese: 39, non-Asian: 7) completed the study. Treatment groups were generally well balanced; however, mean body weight and body mass index were approximately 14% and 7% lower, respectively, in Japanese than non-Asian subjects. Following single- or multiple-oral doses of verinurad in Japanese subjects, exposure (maximum plasma concentration [C_{max}] and area under the plasma concentration-time curve [AUC]) increased in a near dose-proportional manner under fasted or fed conditions. The time to C_{max} (T_{max}) was approximately 1.25–2.0 hours post-dose under fasted conditions. A moderate-fat meal delayed T_{max} up to 5 hours post-dose and increased plasma verinurad exposures up to 109%. Following once-daily multiple doses, there was modest accumulation of verinurad. C_{max} and AUC were approximately 38% and 23% higher, respectively, in Japanese versus non-Asian subjects, largely due to the difference in body weight. Mean reductions in serum uric acid following once-daily multiple dosing of verinurad 10 mg were 62% and 58% at maximum reduction and 46% and 44% at 24 hours post-dose in Japanese and non-Asian subjects, respectively. Verinurad was well tolerated at all doses. One Japanese subject discontinued verinurad due to an AE of urticaria that resolved after 11 days. No serious AEs, Grade 3 or 4 AEs, or clinically significant laboratory or ECG abnormalities were noted.

Conclusion: Verinurad significantly lowered serum uric acid and was well tolerated in both healthy Japanese and non-Asian males, despite small differences in plasma pharmacokinetics. These data support further evaluation of once-daily verinurad as a treatment for hyperuricemia with or without gout in the Japanese population.

Disclosure: M. Gillen, AstraZeneca, 3; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S.**

Valdez, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacokinetics-pharmacodynamics-and-tolerability-of-verinurad-a-selective-uric-acid-reabsorption-inhibitor-in-healthy-japanese-male-subjects

Abstract Number: 194

Pharmacokinetics, Pharmacodynamics, and Tolerability of Concomitant Multiple Dose Administration of Verinurad (RDEA3170) and Allopurinol in Adult Male Subjects with Gout

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

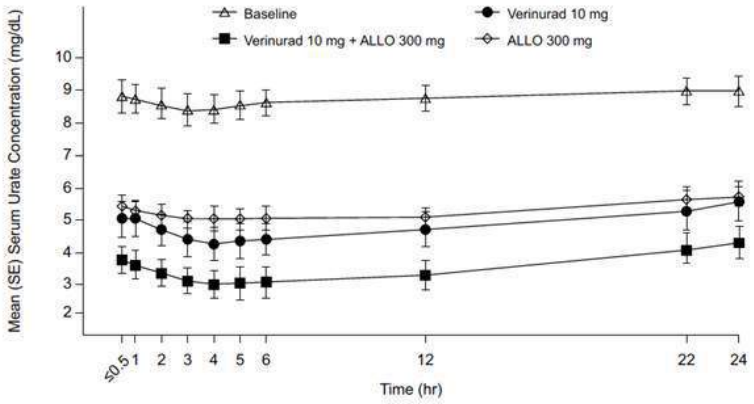
Background/Purpose: Verinurad (RDEA3170) is a novel selective uric acid reabsorption inhibitor in clinical development for the treatment of hyperuricemia and gout. This Phase 1, single-blind, multiple dose, drug-drug interaction study evaluated the pharmacokinetics (PK), pharmacodynamics, and tolerability of verinurad in combination with allopurinol (ALLO) in adult male subjects with gout.

Methods: Adult males with gout, aged 18-75 years, with serum uric acid (sUA) ≥8 and ≤10 mg/dL were randomized to receive once-daily oral doses of ALLO 300 mg or verinurad 10 mg alone for 7 days, ALLO 300 mg + verinurad 10 mg on Days 8−14, and the alternative single agent (verinurad 10 mg or ALLO 300 mg) on Days 15−21. Colchicine 0.6 mg was taken once daily from day −14. Serial plasma/serum and urine samples were drawn at predetermined time points on Days 7, 14 and 21 and assayed for verinurad, ALLO, oxypurinol (OXY), colchicine, and uric acid. Baseline samples were drawn on Day –1. Safety was assessed by adverse event (AE) reports, laboratory tests, vital signs, and electrocardiograms (ECGs).

Results: Subjects (N=12) were mostly white (58.3%) with mean (SD) age of 51 (10) years. Following multiple doses, ALLO had no effect on C_{max} and AUC of verinurad. ALLO C_{max} was increased 33% but AUC was unaltered by verinurad. The C_{max} and AUC for OXY, the active metabolite of ALLO, were reduced 32% and 38%, respectively, by verinurad. Colchicine plasma exposures were unaltered by verinurad. ALLO had no effect on urinary excretion of verinurad, whereas urinary excretion of OXY was increased 19% by verinurad. The mean maximal decrease in sUA was 65% with verinurad + ALLO compared with verinurad (51%) or ALLO (43%) alone (Figure). Consistent with the mechanism of action (MOA) of verinurad, 24-h fractional excretion of uric acid (FEUA) and clearance of uric acid (CL_{UR}) were increased in the absence (9.2% and 11.5 mL/min, respectively) or presence of ALLO (7.9% and 11.8 mL/min) vs baseline (4.5% and 5.7 mL/min) or ALLO alone (3.7% and 5.0 mL/min). Consistent with its MOA, ALLO decreased the amount of uric acid excreted in 24-h urine (363 mg) compared with baseline (683 mg), verinurad alone (739 mg) or verinurad + ALLO (522 mg) but had no effect on FEUA or CL_{UR}. No serious AEs, discontinuations due to AEs, or clinically significant laboratory or ECG abnormalities were noted.

Conclusion: Although a modest drug–drug interaction was found between verinurad and ALLO, the combination was safe and well tolerated at the studied doses and resulted in greater reduction of sUA than either alone. These results support the evaluation of verinurad + ALLO as an alternative once-daily treatment option for hyperuricemia and gout.

Figure. Serum urate concentration-time profiles for verinurad 10 mg, ALLO 300 mg, and verinurad 10 mg + ALLO 300 mg



Disclosure: J. Hall, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Gillen**, AstraZeneca, 3; **X. Yang**, AstraZeneca, 3; **S. Liu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S. Walker**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **V. Clauson**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Kankam**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacokinetics-pharmacodynamics-and-tolerability-of-concomitant-multiple-dose-administration-of-verinurad-rdea3170-and-allopurinol-in-adult-male-subjects-with-gout

Abstract Number: 195

Pharmacodynamics, Pharmacokinetics, and Safety of Verinurad in Combination with Febuxostat Versus Febuxostat Alone and Verinurad Alone in Japanese Adults with Gout or Asymptomatic Hyperuricemia: A Phase 2a, Open-Label Study

Masanari Shiramoto[1], Masatoshi Sugeno[2], Sha Liu[3], Zangong Shen[3] and Jesse Hall[3], [1]SOUSEIKAI PS Clinic, Fukuoka, Japan, [2]AstraZeneca K.K., Osaka, Japan, [3]Ardea Biosciences, Inc., San Diego, CA

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

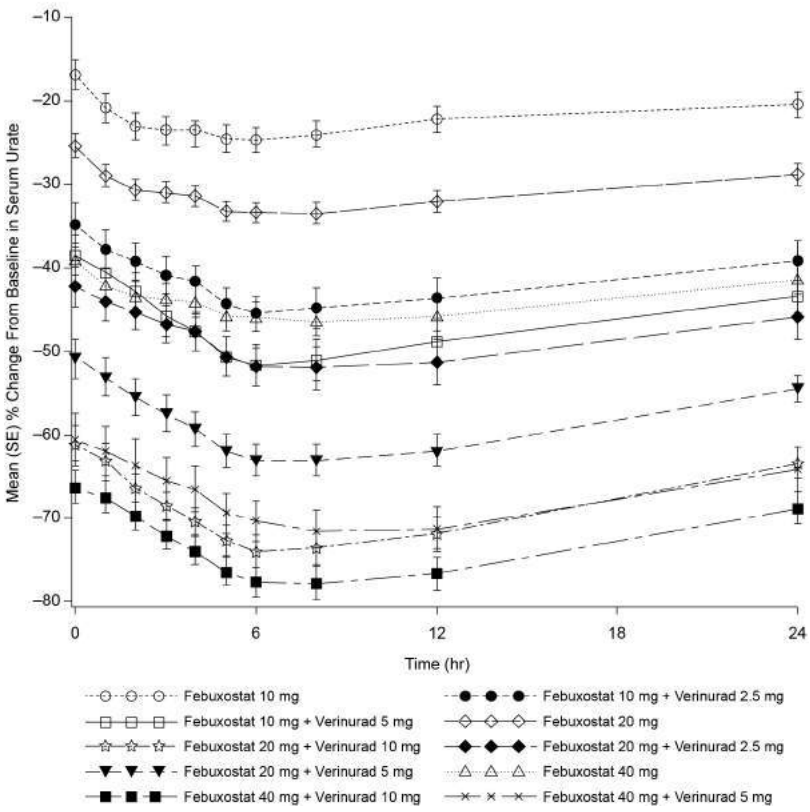
Background/Purpose: Verinurad (RDEA3170) is a high-affinity URAT1 inhibitor in development for the treatment of gout and asymptomatic hyperuricemia. This Phase 2a, randomized, open-label, single-site study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with febuxostat versus febuxostat alone and verinurad alone in Japanese male adults with gout or asymptomatic hyperuricemia (NCT02317861).

Methods: Japanese male patients aged ≥20 and ≤70 years with gout or asymptomatic hyperuricemia and serum uric acid (sUA) ≥8 mg/dL were randomized to 1 of 6 cohorts to receive febuxostat (10 mg, 20 mg, and 40 mg) alone; febuxostat in combination with verinurad (dose range 2.5 mg to 10 mg); verinurad (2.5 mg to 15 mg) alone; or benzbromarone (50 mg) alone (4 treatment periods per cohort, each treatment period 7 days). The study drugs were administered once daily in the morning after breakfast. Serial blood and urine samples were measured at preset intervals on Days -1, 1, 2, 7, 8, 14, 15, 21, 22, 28 and 29 for PD and PK endpoints. Safety assessments included adverse events (AEs) and laboratory, electrocardiogram, and vital sign parameters.

Results: Seventy-two patients with gout (n=37) or hyperuricemia (n=35) were randomized in this study. Addition of verinurad (2.5 mg to 10 mg) to febuxostat (10 mg, 20 mg, or 40 mg) decreased sUA in dose-dependent manner (Figure). Verinurad coadministered with febuxostat increased the amount of uric acid recovered in urine (Aeur), compared with baseline and the same dose of febuxostat administered alone, yet comparable with benzbromarone. Plasma Cmax and AUC exposures of verinurad and febuxostat exhibited dose proportional increases within the investigated dose range. No clear PK drug-drug interaction of verinurad and febuxostat with each other was observed. Verinurad at doses from 2.5 mg to 15 mg was well tolerated, with no serious AEs or withdrawals due to AEs. One treatment-emergent AE (diarrhea) was considered possibly related to both verinurad and febuxostat. Laboratory values and vital signs indicated no clinically meaningful changes.

Conclusion: Verinurad coadministered with febuxostat dose-dependently decreased sUA while maintaining Aeur comparable to benzbromarone. All dose combinations of verinurad and febuxostat in this study were generally well tolerated.

Figure. Mean % change from baseline in sUA (mg/dL) following multiple oral doses of febuxostat alone and in combination with verinurad (PD analysis set) .



Disclosure: M. Shiramoto, SOUSEIKAI PS Clinic, 3; **M. Sugeno**, AstraZeneca K.K., 3; **S. Liu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **Z. Shen**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **J. Hall**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pharmacodynamics-pharmacokinetics-and-safety-of-verinurad-in-combination-with-febuxostat-versus-febuxostat-alone-and-verinurad-alone-in-japanese-adults-with-gout-or-asymptomatic-hyperuricemia-a-pha

Abstract Number: 196

Pharmacodynamic Effects and Safety of Verinurad in Combination with Allopurinol Versus Allopurinol Alone in Adults with Gout: A Phase 2a, Open-Label Study

Roy Fleischmann[1], Peter Winkle[2], Jesse Hall[3], Xiaohong Yan[3], Jeffrey N. Miner[3,4], Liz Hicks[3], Shakti Valdez[3] and

Martha Hernandez-Illas[5], [1]Medicine, University of Texas Southwestern Medical Center, Dallas, TX, [2]Anaheim Clinical Trials, Anaheim, CT, [3]Ardea Biosciences, Inc., San Diego, CA, [4]Discovery Biology, Ardea Biosciences, Inc., San Diego, CA, [5]QPS MRA (Miami Clinical Research), Miami, FL
First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016
Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

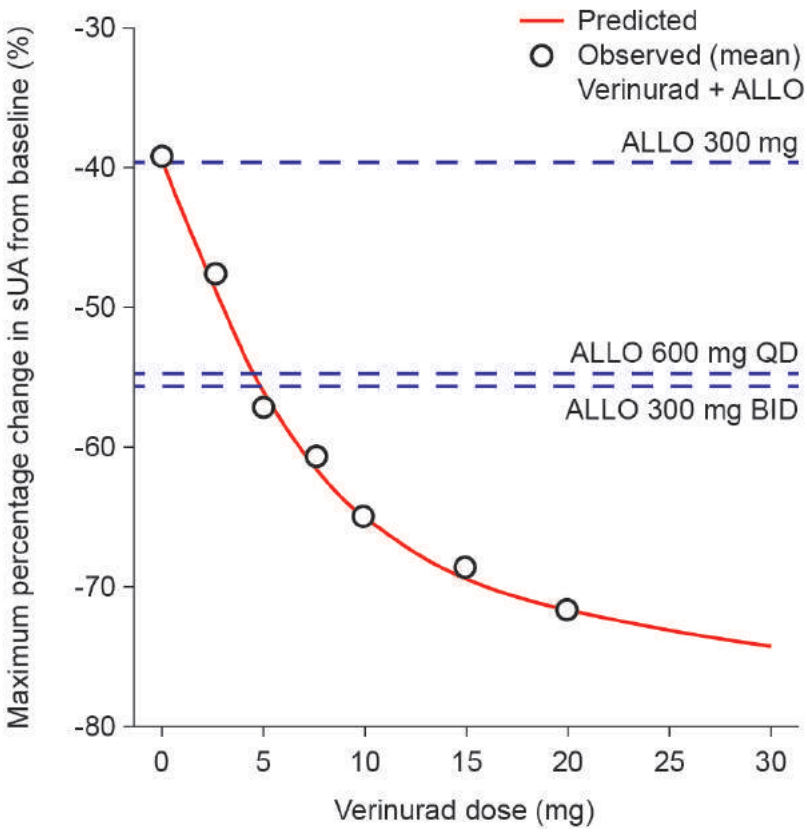
Background/Purpose: Verinurad (RDEA3170) is a high-affinity, selective URAT1 inhibitor in development for treatment of gout and asymptomatic hyperuricemia. This Phase 2a, randomized, open-label, multicenter study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with allopurinol versus allopurinol alone in adults with gout (NCT02498652).

Methods: Patients aged 18-75 years with gout and serum uric acid (sUA) ≥8 mg/dL were randomized to 1 of 2 cohorts to receive allopurinol (300 mg) combined with verinurad (dose range 2.5 mg to 20 mg) and allopurinol 300 mg or 600 mg alone (each treatment period 7 days). Medications were administered once daily ~30 min after breakfast (for allopurinol 300 mg b.i.d. group, the second allopurinol dose was in the evening). Colchicine 0.6 mg for gout flare prophylaxis was initiated at approximately Day -14 (start of urate-lowering therapy [ULT] washout) or Day -7 if not on ULT. Serial blood and urine samples were measured on Days -1, 1, 7, 14, 21, 28, and 35 for PD and PK endpoints. Safety assessments included adverse events (AEs) and laboratory, ECG, and vital sign parameters.

Results: Forty-one patients were randomized (n=20–21 per cohort). Serum PD data pooled across cohorts demonstrated maximal % decrease in sUA from baseline (Emax) at 6-10 h after verinurad and allopurinol combination treatment. Addition of verinurad (2.5 mg to 20 mg) to allopurinol decreased sUA in dose-dependent manner (Figure). Greater sUA reductions were observed for dose combinations of verinurad ≥5 mg with allopurinol 300 mg versus allopurinol 600 mg alone, while allopurinol 600 mg once daily was equivalent to allopurinol 300 b.i.d. Emax was 46.9%, 58.9%, 59.9%, 67.1%, 68.4%, and 74.3% for verinurad at doses of 2.5, 5, 7.5, 10, 15, and 20 mg combined with allopurinol 300 mg, versus 39.7%, 53.8%, and 54.4% with allopurinol 300 mg, allopurinol 600 mg, and allopurinol 300 mg b.i.d. alone. No drug-drug interaction on verinurad and allopurinol plasma PK parameters was observed. Verinurad decreased oxypurinol Cmax by 19.0-32.4% and AUC0-24 by 20.9-39.2%; reductions in oxypurinol Cmax and AUC0-24 were dose dependent, with no further decreases above 15 mg verinurad dose. Verinurad at doses from 2.5 mg to 20 mg was well tolerated, with no serious AEs, withdrawals due to AEs, or renal-related events during combination treatment. Laboratory values and vital signs indicated no clinically meaningful changes. There were no cases of serum creatinine elevation ≥1.5x baseline.

Conclusion: Verinurad coadministered with allopurinol dose-dependently decreased sUA. All dose combinations of verinurad and allopurinol were generally well tolerated with no serious AEs or renal-related events during combination

Figure. Maximum sUA percentage change



treatment.

Disclosure: R. Fleischmann, Ardea Biosciences, Inc., a member of the AstraZeneca Group., 2; **P. Winkle**, None; **J. Hall**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **X. Yan**, AstraZeneca, 3; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **L. Hicks**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S. Valdez**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Hernandez-Illas**, None.

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Abstract Number: 197

Pharmacodynamic Effects and Safety of Verinurad in Combination with Febuxostat Versus Febuxostat Alone in Adults with Gout: A Phase 2a, Open-Label Study

Roy Fleischmann[1], Peter Winkle[2], Jesse Hall[3], Shakti Valdez[3], Sha Liu[3], Xiaohong Yan[3], Liz Hicks[3] and Martha Hernandez-Illas[4], [1]Medicine, University of Texas Southwestern Medical Center, Dallas, TX, [2]Anaheim Clinical Trials, Anaheim, CT, [3]Ardea Biosciences, Inc., San Diego, CA, [4]QPS MRA (Miami Clinical Research), Miami, FL

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Verinurad (RDEA3170) is a high-affinity, selective URAT1 inhibitor in development for treatment of gout and asymptomatic hyperuricemia. This Phase 2a, randomized, open-label, multicenter study investigated the multiple-dose pharmacodynamics (PD), pharmacokinetics (PK), and safety of oral verinurad in combination with febuxostat versus febuxostat alone in adults with gout (NCT02246673).

Methods: Patients aged 18-75 years with gout and serum uric acid (sUA) ≥8 mg/dL were randomized to 1 of 5 cohorts to receive febuxostat (40 mg and 80 mg) alone and in combination with verinurad (dose range 2.5 mg to 20 mg; 4 treatment periods per cohort, each treatment period 7 days). Medications were administered once daily ~30 min after breakfast. Colchicine 0.6 mg for gout flare prophylaxis was initiated at approximately Day -14 (start of urate-lowering therapy [ULT] washout) or Day -7 if not on ULT. Serial blood and urine samples were measured at preset intervals on Days -1, 1, 7, 14, 21, and 28 for PD and PK endpoints. Safety assessments included adverse events (AEs) and laboratory, ECG, and vital sign parameters.

Results: Sixty-four patients were randomized (n=12–14 per cohort). Serum PD data pooled across cohorts demonstrated maximal % decrease in sUA from baseline (Emax) at 8-12 h after dosing. Addition of verinurad to febuxostat decreased sUA in dose-dependent manner (Figure 1). Greater sUA reductions were observed for dose combinations of verinurad ≥5 mg with febuxostat 40 mg versus febuxostat 80 mg alone. The rate of urinary uric acid excretion was reduced by febuxostat alone, but comparable to baseline levels with verinurad combined with febuxostat (Figure 2). Verinurad plasma exposures increased with verinurad dose and were comparable for febuxostat 40 mg and 80 mg doses. No drug-drug interaction on verinurad and febuxostat plasma PK parameters was observed. Verinurad at doses from 2.5 mg to 20 mg was well tolerated, with no serious AEs, withdrawals due to AEs, or renal-related events. The most frequent treatment-emergent AE possibly related to study medication was pain in extremity, in 2 patients receiving verinurad. Laboratory values and vital signs showed no clinically meaningful changes. There were no cases of serum creatinine elevation ≥1.5x baseline.

Conclusion: Verinurad coadministered with febuxostat dose-dependently decreased sUA while maintaining urine uric acid levels comparable to baseline. All dose combinations of verinurad and febuxostat in this study were generally well tolerated with no serious AEs or renal-related events during combination treatment.

Figure 1. Maximum sUA percentage change

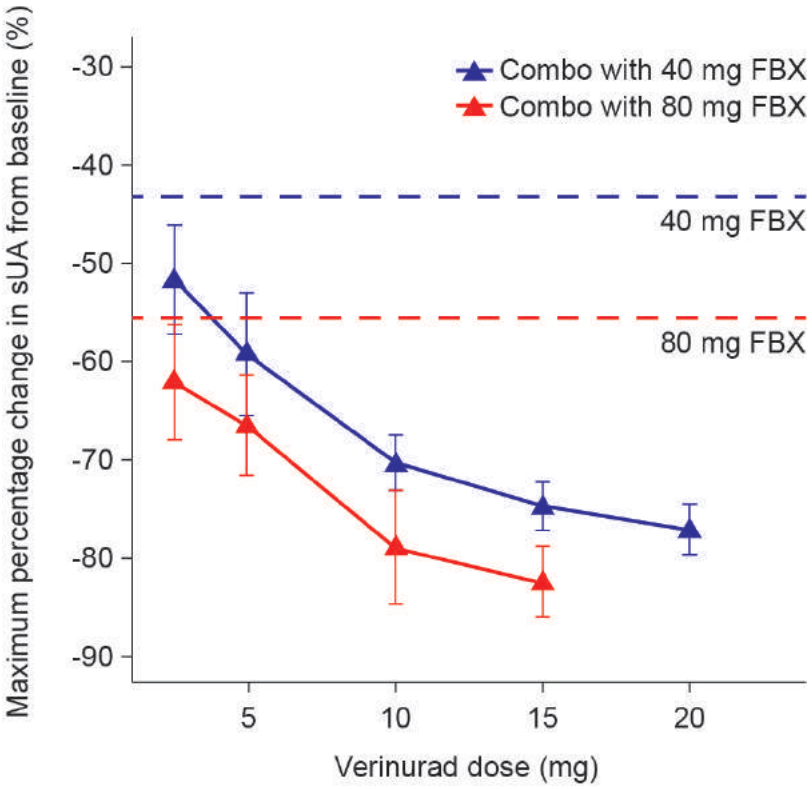
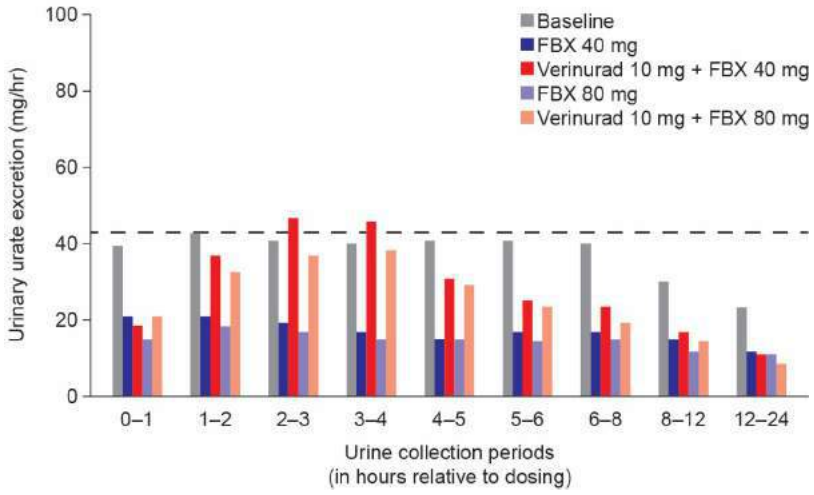


Figure 2. Urinary urate excretion



Disclosure: **R. Fleischmann**, Ardea Biosciences, Inc., a member of the AstraZeneca Group., 2; **P. Winkle**, None; **J. Hall**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S. Valdez**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **S. Liu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **X. Yan**, AstraZeneca, 3; **L. Hicks**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Hernandez-Illas**, None.

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Abstract Number: 198

A Phase 2 Study to Evaluate the Efficacy and Safety of Febuxostat Extended- Versus Immediate-Release Formulations in Patients with Gout and Moderate Renal Impairment

Lhanoo Gunawardhana[1], Michael A. Becker[2], Andrew Whelton[3], Barbara Hunt[1], Majin Castillo[1], Xinxin Dong[1] and Kenneth Saag[4], [1]Takeda Pharmaceuticals International, Deerfield, IL, [2]Medicine, University of Chicago, Chicago, IL, [3]Johns Hopkins University, Hunt Valley, MD, [4]University of Alabama at Birmingham, Birmingham, AL

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

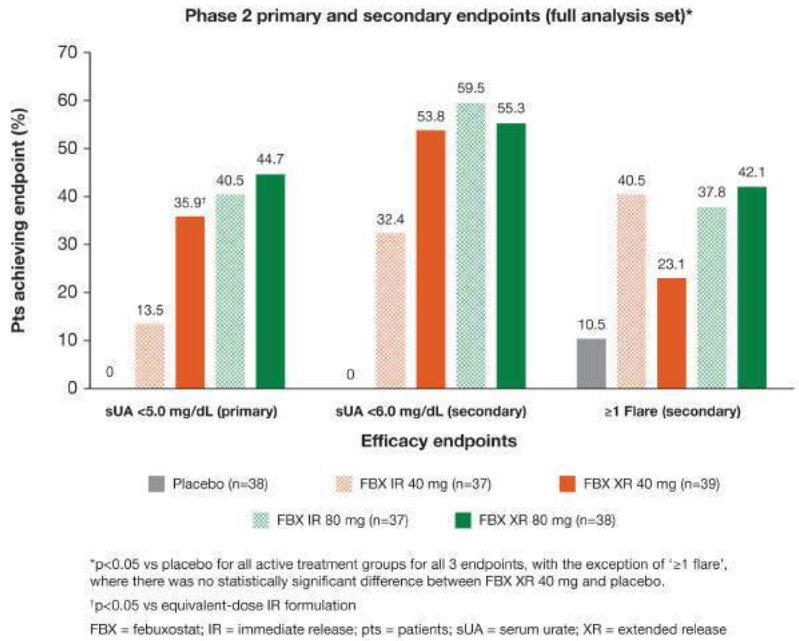
Session Time: 9:00AM-11:00AM

Background/Purpose: Data generated by Phase 1 and 2 studies suggest that the extended-release (XR) formulation of febuxostat (FBX) may provide equal or better reduction in serum urate level (sUA) in patients (pts) with gout, with reduced exposure (C_{max} and AUC), compared with an immediate-release (IR) formulation. This Phase 2 study was conducted to evaluate the efficacy and safety of FBX XR compared with FBX IR in pts with gout and moderate renal impairment.

Methods: In a Phase 2, multicenter, randomized, placebo-controlled, double-blind study, pts with gout (sUA ≥8.0 mg/dL, moderate renal impairment [estimated glomerular filtration rate ≥30 mL/min and <60 mL/min], and ≥1 gout flare within the previous 12 months) received placebo or FBX XR 40 mg, XR 80 mg, IR 40 mg, or IR 80 mg once daily for 3 months. The primary endpoint was the proportion of pts with sUA <5.0 mg/dL at Month 3. Secondary endpoints were proportions of pts with at least 1 flare requiring treatment during the 3-month treatment period and of pts with sUA <6.0 mg/dL at Month 3.

Results: A total of 189 pts received treatment with placebo (n=38) or FBX XR 40 mg (n=39), XR 80 mg (n=38), IR 40 mg

(n=37), or IR 80 mg (n=37). A higher proportion of pts receiving FBX XR 40 mg achieved sUA <5.0 mg/dL versus (vs) IR 40 mg at Month 3 (35.9% vs 13.5%, respectively; p=0.034). All FBX groups showed a higher proportion of pts with at least 1 flare during treatment compared with placebo-treated pts, but a smaller proportion of pts in the FBX XR 40-mg group experienced flares compared with IR 40 mg (23.1% vs 40.5%, respectively). Additionally, a numerically higher proportion of pts achieved sUA <6 mg/dL with FBX XR 40 mg compared with IR 40 mg (53.8% vs 32.4%, respectively). FBX XR 80 mg did not differentiate from IR 80 mg for the primary or secondary endpoints. Primary and secondary endpoint results are shown (**Figure**). Treatment-emergent and treatment-related adverse events were infrequent and generally did not differ among treatment groups.



Conclusion: Significantly more pts receiving FBX XR 40 mg achieved the primary endpoint of sUA reduction to <5.0 mg/dL at the Month 3 visit compared with FBX IR 40 mg. There was a trend toward lower flare rates in the FBX XR 40 mg vs the IR 40 mg group. Overall, incidence rates of treatment-emergent and treatment-related adverse events were low.

Disclosure: L. Gunawardhana, Takeda Pharmaceuticals, 3,Takeda Pharmaceuticals, 1; **M. A. Becker**, Takeda, Ardea/AstraZeneca, Ironwood, Horizon, 2,Takeda, Ardea/AstraZeneca, Ironwood, Horizon, CymaBay, Pfizer, SelectaBio, 5; **A. Whelton**, Takeda, 8; **B. Hunt**, Takeda, 3; **M. Castillo**, Takeda, 3; **X. Dong**, Takeda Pharmaceuticals, 3; **K. Saag**, Takeda, Horizon, Ardea/AstraZeneca, 2,Takeda, Horizon, Ardea/AstraZeneca, 5.

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Abstract Number: 199

A Phase 3 Study to Evaluate the Efficacy and Safety of Febuxostat Extended- Versus Immediate-Release Formulations in Patients with Gout

Kenneth Saag[1], Michael A. Becker[2], Andrew Whelton[3], Barbara Hunt[4], Majin Castillo[4], Krisztina Kisfalvi[4] and Lhanoo Gunawardhana[4], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Medicine, University of Chicago, Chicago, IL, [3]Johns Hopkins University, Hunt Valley, MD, [4]Takeda Pharmaceuticals International, Deerfield, IL

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

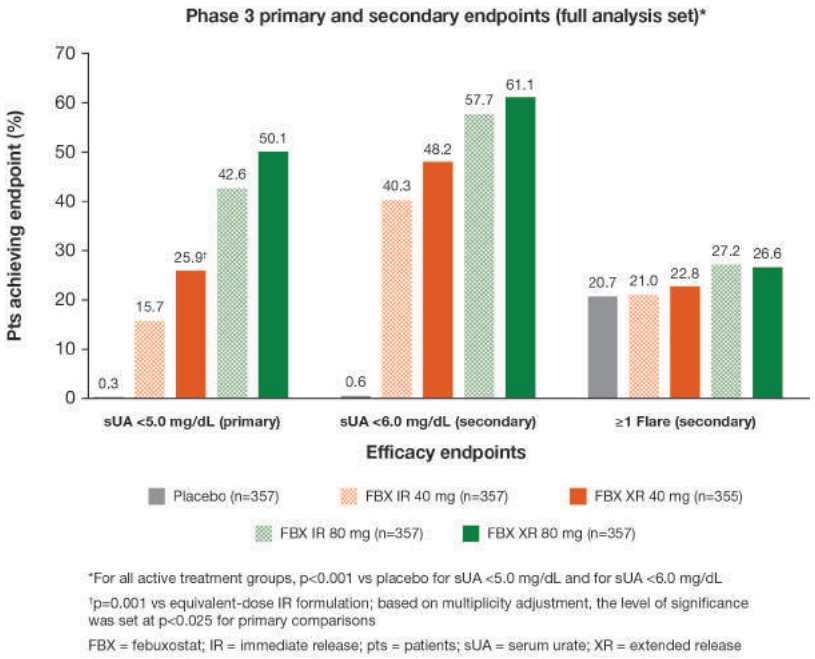
Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Data generated by Phase 1 and 2 studies suggest that the extended-release (XR) formulation of febuxostat (FBX) may provide equal or better reduction in serum urate level (sUA) in patients (pts) with gout, with reduced exposure (C_{max} and AUC), compared with the immediate-release (IR) formulation. This Phase 3 study was conducted to evaluate the efficacy and safety of FBX XR compared with FBX IR in gout pts with normal or impaired renal function.

Methods: In a Phase 3, multicenter, randomized, placebo-controlled, double-blind study, pts with gout (sUA ≥8.0 mg/dL, estimated glomerular filtration rate ≥15 mL/min, and ≥1 gout flare within the previous 12 months) received placebo or FBX XR 40 mg, XR 80 mg, IR 40 mg, or IR 80 mg once daily for 3 months. The primary endpoint was the proportion of pts with sUA <5.0 mg/dL at Month 3. Secondary endpoints were proportions of pts with at least 1 flare requiring treatment during the 3-month treatment period and of pts with sUA <6.0 mg/dL at Month 3.

Results: A total of 1783 pts received treatment with placebo (n=357) or FBX XR 40 mg (n=355), XR 80 mg (n=357), IR 40 mg (n=357), or IR 80 mg (n=357). A higher proportion of pts receiving FBX XR 40 mg achieved sUA <5.0 mg/dL versus (vs) IR 40 mg at Month 3 (25.9% vs 15.7%, respectively; p=0.001). Although the difference was not statistically significant, more FBX XR 80-mg treated pts achieved the primary endpoint compared with IR 80 mg (50.1% vs 42.6%, respectively). Neither FBX XR treatment group differentiated from its respective IR treatment group for the secondary endpoint of proportion of pts with at least 1 flare requiring treatment during the 3-month treatment period. A numerically higher proportion of pts achieved sUA <6.0 mg/dL with FBX XR 40 mg compared with IR 40 mg (48.2% vs 40.3%, respectively), and the observed difference between FBX XR 80 mg vs IR 80 mg for this endpoint was small (61.1% vs 57.7%, respectively). Primary and secondary endpoint results are shown (**Figure**). Treatment-emergent and treatment-related adverse events were infrequent and generally did not differ among treatment groups.



*For all active treatment groups, p<0.001 vs placebo for sUA <5.0 mg/dL and for sUA <6.0 mg/dL
†p=0.001 vs equivalent-dose IR formulation; based on multiplicity adjustment, the level of significance was set at p<0.025 for primary comparisons
FBX = febuxostat; IR = immediate release; pts = patients; sUA = serum urate; XR = extended release

Conclusion: Significantly more pts receiving FBX XR 40 mg achieved the primary endpoint of sUA reduction to <5.0 mg/dL at the Month 3 visit compared with FBX IR 40 mg. Overall, the incidence rates of treatment-emergent and treatment-related adverse events were low. Both FBX formulations were efficacious in lowering sUA and were generally well tolerated.

Disclosure: K. Saag, Takeda, Horizon, Ardea/AstraZeneca, 2,Takeda, Horizon, Ardea/AstraZeneca, 5; **M. A. Becker**, Takeda, Ardea/AstraZeneca, Ironwood, Horizon, 2,Takeda, Ardea/AstraZeneca, Ironwood, Horizon, CymaBay, Pfizer, SelectaBio, 5; **A. Whelton**, Takeda, 8; **B. Hunt**, Takeda, 3; **M. Castillo**, Takeda, 3; **K. Kisfalvi**, Takeda, 3; **L. Gunawardhana**, Takeda Pharmaceuticals, 3,Takeda Pharmaceuticals, 1.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-phase-3-study-to-evaluate-the-efficacy-and-safety-of-febuxostat-extended-versus-immediate-release-formulations-in-patients-with-gout

Abstract Number: 200

The Safety and Efficacy of Benzbromarone in Gout in Aotearoa New Zealand

Lisa K. Stamp[1], Janine Haslett[1], Christopher Frampton[1], Doug White[2], David Gardner[3], Simon Stebbings[4], Guy Taylor[5], Rebecca Grainger[6], Rajesh Kumar[7], Sunil Kumar[8], Tracey Kain[9], David Porter[10], Michael Corkill[11], Angela Cathro[12], Scott Metcalfe[12], John Wyeth[12] and Nicola Dalbeth[13], [1]University of Otago, Christchurch, New Zealand, [2]Waikato Hospital, Hamilton, New Zealand, [3]Hawkes Bay DHB, Napier, New Zealand, [4]Department of Medicine, Dunedin School of Medicine, University of Otago, Dunedin, New Zealand, [5]Whanganui Hospital, Whanganui, New Zealand, [6]Wellington Regional Rheumatology Unit, Hutt Valley District Health Board, Lower Hutt, New Zealand, [7]Taranaki Hospital, New Plymouth, New Zealand, [8]Middlemore Hospital, Auckland, New Zealand, [9]Tauranga Hospital, Tauranga Hospital, Tauranga, New Zealand, [10]Porter Rheumatology Ltd, The Collingwood Centre, Nelson, New Zealand, [11]North Shore Hospital, Auckland, New Zealand, [12]Pharmaceutical Management Agency, Wellington, New Zealand, [13]Department of Medicine, University of Auckland, Auckland, New Zealand

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

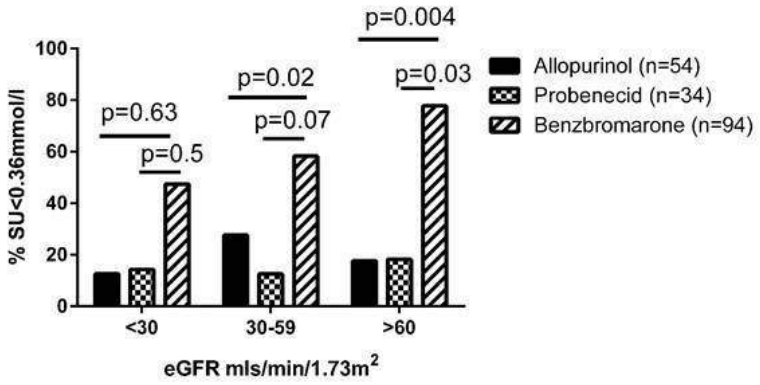
Background/Purpose: Benzbromarone is a potent uricosuric, but is not widely available due to concerns about hepatotoxicity. In Aotearoa New Zealand benzbromarone has been available since April 2013, subject to funding restrictions, for patients with inadequate urate-lowering response or intolerance to allopurinol and probenecid. The aim of this study was to assess the safety and efficacy of benzbromarone in a real-life setting.

Methods: All patients who received funding for benzbromarone from 1/4/2013 to 30/9/2014 were identified. Prescribers were sent a questionnaire for each individual. Information on demographics, efficacy of previous urate-lowering drugs and reasons for discontinuation were collected. Specific information about the dose, effect on serum urate, adverse effects and liver function tests after commencing benzbromarone was recorded.

Results: Completed questionnaires were returned for 123/164 (75%) patients. 85 (69.1%) were male, 70 (56.9%) were New Zealand European and 46 (37.4%) were Māori or Pacific Island. The mean (SD) duration of gout was 15 (9.4) years and tophi were present in 70 (56.9%). Mean (SD) SU prior to any ULT was 0.61 (0.11) mmol/l (range 0.36-0.94 mmol/l; n=106). Mean (SD) serum urate prior to benzbromarone was 0.57 (0.12) mmol/l and estimated glomerular filtration rate (eGFR) 50.3 (22.8) ml/min/1.73m^2. The median dose of benzbromarone was 100mg/day (25-200mg/day). Six months after commencing benzbromarone, mean (SD) serum urate was 0.35 (0.12) mmol/l. Renal impairment was common, with 22/112 (19.6%) patients having eGFR <30mls/min/1.72m^2, 55/112 (49.1%) eGFR >30-59 mls/min/1.72m^2 and 35/112 (31.3%) eGFR >60mls/min/1.72m^2. With each drug there was no statistically significant difference in the number of patients who achieved SU<0.36mmol/l based on eGFR. However, at each eGFR numerically more people on benzbromarone achieved SU<0.36 mmol/l, compared with the other two allopurinol and probenecid (Figure 1).

Benzbromarone related adverse events included rash (n=4), diarrhoea (n=9), nausea (n=6), and urate stones (n=3). Liver function tests abnormalities were uncommon and tended to be mild. There were 14 patient deaths; none were considered related to benzbromarone. Allopurinol had been prescribed prior to benzbromarone in 117/123 patients; median maximum allopurinol dose was 200mg/day (range 25-600mg/day), and 19% patients received allopurinol >300mg/day.

Conclusion: Benzbromarone provides useful urate-lowering efficacy and does not appear unsafe in patients with gout. It remains effective even in those with renal impairment. Urate-lowering therapy prescribing requires further optimisation.



Disclosure: **L. K. Stamp**, Pharmaceutical Management Agency of new Zealand, 6; **J. Haslett**, None; **C. Frampton**, None; **D. White**, None; **D. Gardner**, None; **S. Stebbings**, None; **G. Taylor**, None; **R. Grainger**, None; **R. Kumar**, None; **S. Kumar**, None; **T. Kain**, None; **D. Porter**, None; **M. Corkill**, Pharmaceutical Management Agency, 5; **A. Cathro**, Pharmaceutical Management Agency, 3; **S. Metcalfe**, Pharmaceutical Management Agency (PHARMAC) NZ, 3; **J. Wyeth**, Pharmaceutical Management Agency (PHARMAC) NZ, 3; **N. Dalbeth**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-safety-and-efficacy-of-benzbromarone-in-gout-in-aotearoa-new-zealand

Abstract Number: 201

Allopurinol Reduces the Risk of Myocardial Infarction (MI) in the Elderly: A Study of Medicare Claims

Jasvinder A. Singh[1] and Shaohua Yu[2], [1]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL

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SESSION INFORMATION

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Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

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Session Time: 9:00AM-11:00AM

Background/Purpose: To assess whether allopurinol use reduces the risk of myocardial infarction (MI) in the elderly.

Methods: We used the 2006-2012 5% random sample of Medicare beneficiaries to study the association of new allopurinol initiation and the risk of incident MI, in a cohort study. Multivariable-adjusted Cox regression models adjusted for age, gender, race and Charlson index, in addition to various cardio-protective medications (beta-blockers, ACE inhibitors, diuretics, statins). We calculated hazards ratio (HR) with 95% confidence intervals (CI). Sensitivity analyses adjusted for coronary artery disease (CAD) risk factors including hypertension, hyperlipidemia, diabetes, and smoking.

Results: 1,544 of the 29,298 episodes of incident allopurinol use were associated with incident MI (5.3% episodes). Allopurinol use was associated with reduced hazards of MI, with HR of 0.85 (95% CI, 0.77 to 0.95). Compared to no allopurinol use, longer allopurinol use durations were associated with lower HR of MI: 1-180 days, 0.98 (95% CI, 0.84 to 1.14); 181 days to 2 years, 0.83 (95% CI, 0.72 to 0.95); and >2 years, 0.70 (95% CI, 0.56 to 0.88). Other factors associated with higher hazard of MI were: age 75-<85 and ≥85, male gender, higher Charlson index score and the use of ACE-inhibitor. Adjustment for CAD risk factors confirmed these findings.

Conclusion: Incident allopurinol use was associated with a reduction in the risk of incident MI. Longer allopurinol use durations reduced the risk of incident MI incrementally. Future studies need to assess underlying mechanisms of this association and to assess risk-benefit ratio of allopurinol use for MI prevention.

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **S. Yu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/allopurinol-reduces-the-risk-of-myocardial-infarction-mi-in-the-elderly-a-study-of-medicare-claims

Abstract Number: 202

Allopurinol Use and the Risk of Ventricular Tachycardia in the US Elderly: A Study of Medicare Claims Data

Jasvinder A. Singh[1] and John Cleveland[2], [1]Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Rheumatology, University of Alabama at Birmingham (UAB), Birmingham, AL

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess whether allopurinol use reduces the risk of ventricular tachycardia in the elderly.

Methods: We used the 2006-2012 5% random sample of Medicare beneficiary cohort to study the association of new allopurinol initiation and the risk of incident ventricular tachycardia. Multivariable-adjusted Cox regression models adjusted for age, gender, race, and Charlson index, in addition to various cardio-protective medications (beta-blockers, ACE inhibitors, diuretics, statins). We calculated hazards ratio (HR) with 95% confidence intervals (CI).

Results: 2,665 of the 40,004 episodes of incident allopurinol use were associated with incident ventricular tachycardia (6.7% episodes). Allopurinol use was associated with reduced hazards of ventricular tachycardia, with unadjusted HR of 0.84 (95% CI, 0.77 to 0.91); multivariable-adjusted HR 0.81 (95% CI, 0.74 to 0.87) (Table 1). Compared to no allopurinol use, longer allopurinol use durations were associated with lower HR of ventricular tachycardia: 181-365 days, 0.77 (95% CI, 0.67 to 0.89); 1 to 2 years, 0.85 (95% CI, 0.73 to 0.98); and >2 years, 0.75 (95% CI, 0.62 to 0.90). Other factors associated with higher hazard of ventricular tachycardia were: age 75-<85 and ≥85, male gender, higher Charlson index score, and the use of beta blockers. Allopurinol dose was also significant in univariate analysis but not in the multivariate analysis (Table 2).

Conclusion: Incident allopurinol use was associated with a reduction in the risk of incident ventricular tachycardia; allopurinol dose was not. Longer allopurinol use durations reduced the risk of incident ventricular tachycardia incrementally. Future studies need to assess underlying mechanisms of this association and to assess risk-benefit ratio of allopurinol use for ventricular tachycardia prevention. Table 1: Univariate and multivariate adjusted hazard ratios for ventricular tachycardia based on allopurinol use.

	Unadjusted HR (95% CI) [p-value]	Multivariable-adjusted HR (95% CI) [p-value]
Allopurinol use-ref, no		
Yes	0.84 (0.77, 0.91) [p<0.0001]	0.81 (0.74, 0.87) [p<0.0001]

Table 2: Univariate and multivariate adjusted hazard ratios for ventricular tachycardia based on allopurinol dose and duration.

	Unadjusted HR (95% CI) [p-value]	Multivariable-adjusted HR (95% CI) [p-value]
Allopurinol dose use1		
<200 mg/day	ref	ref
200-299 mg/day	0.85 (0.74, 0.98) [p=0.02]	0.90 (0.78, 1.03) [p=0.12]
>300 mg/day	0.79 (0.71, 0.88) [p<0.0001]	0.93 (0.83, 1.04) [p=0.21]
Allopurinol use duration		
0 days	ref	ref
1-180 days	0.91 (0.81, 1.03) [p=0.13]	0.92 (0.81, 1.05) [p=0.23]
181 days -2 years	0.81 (0.72, 0.90) [p=0.0001]	0.80 (0.71, 0.90) [p=0.0002]
>2 years	0.75 (0.62, 0.90) [p=0.0021]	0.76, (0.63, 0.93) [p=0.0067]

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **J. Cleveland**, None.

Abstract Number: 203

Allopurinol Dose Escalation and Mortality Among Patients with Gout: A National Propensity-Matched Cohort Study

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Allopurinol Dose Escalation and Mortality among Patients with Gout: A National Propensity-Matched Cohort Study

Background/Purpose: Numerous epidemiologic studies show that hyperuricemia and gout are associated with increased mortality while treatment with allopurinol is associated with reduced mortality. Studies examining surrogate markers of cardiovascular risk indicate that allopurinol may have a beneficial dose effect. Our objective was to determine whether allopurinol dose escalation is associated with decreased all-cause and cause-specific mortality relative to non-escalation.**Methods:** In this 10-year observational, new user, active-comparator study of U.S. Veterans with gout and ≥ 40 years of age, we used propensity score matching with Cox proportional hazards and competing risks regression to compare all-cause and cause-specific mortality between allopurinol dose-escalators and non-escalators. National VA data was linked to the National Death Index to determine dose escalation and mortality outcomes.**Results:** After matching, all characteristics were well balanced between groups. Among 6,009 dose escalators and 6,009 matched non-escalators, there were 2,133 deaths during observation corresponding to a mortality rate of 46.8 per 1,000 person-years. There were

no differences between groups in all-cause mortality (HR 0.97; 95% CI 0.89 to 1.05, Figure 1), cardiovascular mortality (HR 0.99; 95% CI 0.87 to 1.12), or cancer mortality (HR 0.93; 95% CI 0.75 to 1.14). Dose escalation even among dose escalators was limited with only 10% of dose escalators receiving daily allopurinol doses above 300 mg (Table 1). Consistent with incomplete dose escalation, only 31% achieved serum urate (SU) < 6.0 mg/dL after 2-years (Table 2). Sensitivity analyses limited to those achieving SU goal and their matches showed an 8% reduction in cardiovascular mortality for dose escalators relative to non-escalators although this did not reach statistical significance (HR 0.92; 95% CI 0.75 to 1.14). **Conclusion:** Although no association was found between allopurinol dose escalation and reduced mortality, the findings were likely limited by suboptimal dose escalation observed in practice even among dose escalators. Other study designs should be considered for further investigation of the potentially beneficial effect of allopurinol on mortality. Table 1 Baseline and Follow-up Allopurinol Dosing by Group

	Baseline		Follow-up	
	Dose Escalators	Non-Escalators	Dose Escalators	Non-Escalators†
Allopurinol Dose*	(n = 6,009)	(n = 6,009)	(n = 6,009)	(n = 6,009)
≤ 100	75%	76%	1%	78%
> 100 & < 300	20%	19%	38%	18%
300	5%	5%	51%	5%
> 300	<1%	<1%	10%	<1%

Totals may add to more than 100% due to rounding. * Dose represents the average daily dose with allopurinol equivalents used for febuxostat in follow-up calculations. † A small proportion of non-escalators (3.5%) had their dose decreased during the 2-year follow-up.

Table 2 Follow-up Serum Urate (SU) by Group

	Dose Escalators	Non-Escalators
	(n = 6,009)	(n = 6,009)
SU Tested	91%	77%
At SU Goal < 6.0 mg/dL*	31%	12%
Follow-up SU, mean mg/dL	6.9 ± 1.9	7.6 ± 1.7

Values are percentages and mean ± SD. Only the last value on record for follow-up was used if there were multiple. * Calculation includes those missing SU tests. Among only those with follow-up testing 34% of dos e escalators and 16% of non-escalators were at SU goal.

Disclosure: B. W. Coburn, None; **K. Michaud**, None; **D. A. Berman**, None; **T. R. Mikuls**, None.

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Abstract Number: 204

The Safety and Efficacy of Allopurinol Dose Escalation in People with Gout, a Randomised Controlled Trial

Lisa K. Stamp[1], Peter T. Chapman[2], Murray Barclay[3], Anne Horne[4], Christopher Frampton[1], Paul Tan[5], Jill Drake[6] and Nicola Dalbeth[5], [1]University of Otago, Christchurch, New Zealand, [2]Christchurch Hospital, Christchurch, New Zealand, [3]Medicine, University of Otago, Christchurch, New Zealand, [4]Department of Medicine, University of Auckland, Auckland, New Zealand, [5]University of Auckland, Auckland, New Zealand, [6]Rheumatology, Immunology and Allergy, Christchurch Hospital, Christchurch, New Zealand

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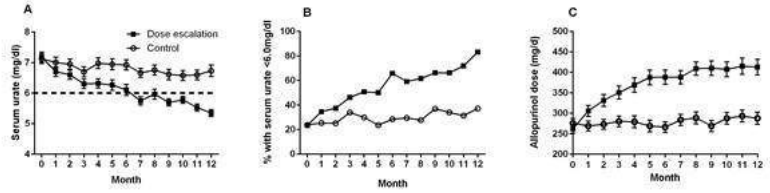
Background/Purpose: Allopurinol is the most widely used urate lowering therapy. Many patients on allopurinol fail to achieve target serum urate (SU), in part due to concerns about the relationship between allopurinol dose and adverse events (AEs). The aim of this randomised controlled trial was to determine the efficacy and safety of allopurinol dose escalation using a treat to target SU approach.

Methods: An open randomised controlled trial comparing creatinine clearance (CrCL)-based allopurinol dose and allopurinol dose escalation was undertaken. Patients with gout, defined by 1977 ARA criteria, receiving at least CrCL-based allopurinol dose for ≥1 month and SU ≥6mg/dL were recruited. Severe chronic kidney disease was not an exclusion. Patients were randomised to continue current dose (control) or dose escalation (DE) for 12 months. In the DE group, allopurinol was increased monthly by 50mg-100mg/d until SU was <6mg/dL. The primary endpoint was reduction in SU and AEs coded according to Common Terminology Criteria for Adverse Events.

Results: One hundred and eighty-three participants (93 control and 90 DE) were recruited. At baseline, mean CrCL was 60 (SD 27) ml/min, urate was 7.2 (SD 1.6) mg/dL and allopurinol dose 269mg/d (range 100-600mg/d). In intention to treat analysis, mean ± SEM SU was 6.7 ± 0.2mg/dL in control participants compared to 5.7 ± 0.2mg/dL DE ($p<0.001$) at 12 months (Figure). SU <6mg/dL at month 12 was achieved in 32% control participants and 69% DE participants ($p<0.001$). During the 12-month period, 58.9% of the control group and 54.3% of the DE group experienced a gout flare ($p=0.58$). There were 43 serious adverse events in 25 controls and 35 events in 22 DE participants. Only one was considered probably related to allopurinol (increased INR in a DE patient on warfarin). Five control participants and 5 DE participants died; no deaths were considered allopurinol related. There were no cases of allopurinol hypersensitivity syndrome. Eleven control participants developed rash; one was thought to be probably allopurinol related leading to allopurinol discontinuation. Eight DE participants' developed rash; 2 were considered possibly related but settled despite continuing allopurinol and 1 was probably related and allopurinol was discontinued. Mild elevations in liver function tests were common in both groups and a few moderate increases in GGT were noted. One DE patient stopped allopurinol due to abnormal LFTs. There was no significant difference in renal function changes between randomised groups.

Conclusion: Higher than CrCL-based doses of allopurinol can effectively lower SU in the majority of patients. Allopurinol dose escalation is well tolerated.

Figure: (A) Mean serum urate, (B) percentage at target serum urate, and (C) mean allopurinol dose.



Disclosure: L. K. Stamp, None; **P. T. Chapman**, None; **M. Barclay**, None; **A. Horne**, None; **C. Frampton**, None; **P. Tan**, None; **J. Drake**, None; **N. Dalbeth**, None.

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Abstract Number: 205

Serum Uric Acid Lowering Treatment Appears Unnecessary during Hemodialysis

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Session Type: ACR Poster Session A

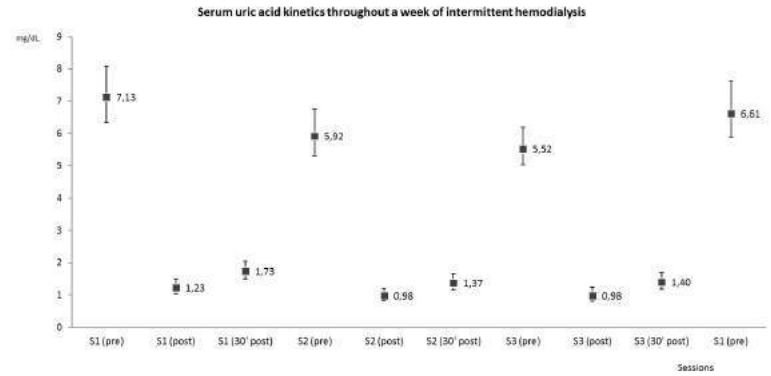
Session Time: 9:00AM-11:00AM

Background/Purpose: Gout patients often suffer from renal disease, some ultimately developing end-stage renal disease (ESRD) and requiring hemodialysis (HD) replacement therapy. Though some reports suggested that tophi disappear after HD, urate-lowering agents are frequently continued, often based on persistent high SUA levels before HD. Also, the impact of SUA levels in the survival of patients on hemodialysis (HD) is under discussion. The aim of the study was to assess the SUA reduction achieved under HD and analyze the kinetics of SUA in a week of intermittent HD.

Methods: SUA levels were determined before and after HD sessions in consecutives 96 patients with end-stage renal disease (ESRD), and compared through paired samples Student's t test. Variables related to HD were analyzed whether associated with SUA reductions ≥80% using Student's t test or ANOVA. Also, a kinetics study on selected 10 patients with hyperuricemia (SUA before HD> 6.8 mg/dL) throughout intermittent HD sessions in a week period was performed; differences in SUA levels were analyzed by repeated measures ANOVA.

Results: Patients were mean aged 66.5 years (SD±13.8), being 62 males (64.6%). Mean time on HD replacement was 7.1 years (±7.2). Before starting HD, 43.0% had hyperuricemia and 21.6% reported gout. Sixteen (16.4%) continued on urate-lowering agents after HD. Mean SUA levels before and after HD session was 5.2mg/dL (± 1.0) and 1.0mg/dL (±0.4), respectively. Mean SUA reduction following HD was 80.2% (95%CI 78.4-82.0); 51 patients (56.7%) showed SUA reduction ≥80%. HD-related variables Kt/v<1.3 (p=0.006) and blood efflux<400mL/min (p=0.004) significantly associated with achieving SUA reduction ≥80%. **Figure** shows the SUA kinetics study: SUA significantly reduced all over the period and persisted below hyperuricemia threshold (p=0.015).

Conclusion: Under HD replacement therapy SUA levels effectively reduced and persisted below saturation point, suggesting that urate-lowering therapy appears unnecessary for patients with gout and ESRD.



Disclosure: R. Soriano, None; **M. Andrés**, None; **E. Oliveira**, None; **C. Trigo**, None; **E. Pascual**, None; **M. D. Arenas**, None.

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Abstract Number: 206

Renal Safety of Lesinurad: A Pooled Analysis of Phase III and Extension Studies

Robert Terkeltaub[1], Raymond Malamet[2], Kathleen Bos[2], Jingyi Li[2], David Goldfarb[3], Michael Pillinger[4], Diana Jalal[5],

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Background/Purpose: Lesinurad is a selective uric acid reabsorption inhibitor approved in the United States and European Union at 200 mg daily dose in combination with a xanthine oxidase inhibitor (XOI) for treatment of hyperuricemia associated with gout in patients unable to achieve target serum uric acid on XOI (allopurinol or febuxostat) alone. Approval of lesinurad was based on three pivotal, placebo-controlled, 12-month phase III (core) studies evaluating lesinurad 200 mg (LESU200) and 400 mg (LESU400) in combination with XOI. Patients completing core studies were eligible to enter extension studies, continuing LESU+XOI at the same dose or randomized from placebo to LESU200 or LESU400 plus XOI.

Methods: Renal-related and kidney stone safety data were pooled from core studies to compare LESU200+XOI and LESU400+XOI with XOI alone and from core studies + extension studies to evaluate the impact on renal safety of extended LESU+XOI treatment. Renal-related treatment-emergent adverse events (TEAEs) were a customized list of 36 preferred terms selected from the Medical Dictionary for Regulatory Activities (MedRA) Renal and Urinary Disorders System Organ Class (SOC), the Investigations SOC and the Acute Renal Failure MedRA Standardized MedRA Query (SMQ). Descriptive statistics are provided for patients receiving ≥1 dose of study medication. To adjust for varying treatment duration, TEAEs are expressed as exposure-adjusted incidence rates (EAIRs; subjects with events per 100 person-years).

Results: In the core studies, EAIRs for any renal-related TEAE, serious renal-related TEAEs, and renal-related TEAEs leading to discontinuation were similar with XOI alone and LESU200+XOI and lower than with LESU400 +XOI (Table 1). Similar results were found for kidney stone and serious kidney stone TEAEs. The most common renal-related TEAE was increased serum creatinine (sCr). EAIRs for sCr elevations ≥1.5x baseline were higher with LESU+XOI than XOI alone (Table 1). Overall, 75% and 84% of sCr elevations in the XOI alone and LESU+XOI groups, respectively, were resolved at last study assessment; 75% and 66% resolved without interruption of medication. Exposure to extended LESU+XOI treatment in core+extension studies did not show an increase from core studies in EAIRs for any renal-related or kidney stone adverse event category (Table 2).

Conclusion: Lesinurad at the approved dose of 200 mg once-daily combined with XOI demonstrated comparable rate of adverse events to XOI alone. There was no clinically relevant increase in these adverse events with the extension of treatment beyond 1 year.

Table 1. A Pooled Analysis of Exposure-Adjusted Renal-Related and Kidney Stone Adverse Event Incidence Rates in Three Pivotal, Similarly Designed, Placebo-Controlled 12-Month Phase III (Core) Studies Evaluating Lesinurad 200 mg and 400 mg in Combination with Xanthine Oxidase Inhibitors

	XOI alone (N=516) (PY=408.5)	LESU200+XOI (N=511) (PY=396.3)	LESU400+XOI (N=510) (PY=390.5)
Renal-Related Adverse Event Category [n (rate)]			
Any TEAE	23 (5.6)	29 (7.3)	60 (15.4)
Serious TEAE	2 (0.5)	0	5 (1.3)
Any TEAE leading to randomized study medication discontinuation	5 (1.2)	6 (1.5)	17 (4.4)
sCr elevations ≥1.5 x baseline	12 (2.9)	29 (7.3)	73 (18.7)
Kidney Stone Adverse Event Category [n (rate)]			
Kidney stone TEAEs	9 (2.2)	3 (0.8)	13 (3.3)
Serious kidney stone TEAEs	1 (0.2)	0	3 (0.8)

LESU, lesinurad; XOI, xanthine oxidase inhibitor; sCr, serum creatinine; PY, patient years. Exposure-adjusted incidence rates are expressed as subjects with events per 100 person-years.

Table 2. A Pooled Analysis of Exposure-Adjusted Renal-Related and Kidney Stone Adverse Event Incidence Rates in Core+Extension Studies

	Patients Receiving Lesinurad Since Core Studies*		All Patients in Core+Extension Studies†	
	LESU200+XOI (N=511) (PY=752.7)	LESU400+XOI (N=510) (PY=746.3)	LESU200+XOI (N=666) (PY=926.5)	LESU400+XOI (N=666) (PY=917.9)
Renal-Related Adverse Event Category [n (rate)]				
Any TEAE	63 (8.4)	105 (14.1)	80 (8.6)	134 (14.6)
Serious TEAE	4 (0.5)	8 (1.1)	4 (0.4)	13 (1.4)
Any TEAE leading to randomized study medication discontinuation	15 (2.0)	27 (3.6)	17 (1.8)	32 (3.5)
sCr elevations ≥1.5 x baseline	58 (7.7)	120 (16.1)	75 (8.1)	156 (17.0)
Kidney Stone Adverse Event Category [n (rate)]				
Kidney stone TEAEs	7 (0.9)	17 (2.3)	10 (1.1)	18 (2.0)
Serious kidney stone TEAEs	0	5 (0.7)	1 (0.1)	5 (0.5)

LESU, lesinurad; XOI, xanthine oxidase inhibitor; sCr, serum creatinine; PY, patient years. Exposure-adjusted incidence rates are expressed as subjects with events per 100 person-years.

*Patients receiving LESU200+XOI or LESU400+XOI since core studies

†Patients receiving LESU200+XOI or LESU400+XOI since core studies plus patients on XOI alone during core studies randomized to LESU200+XOI or LESU400+XOI for extension studies

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Disclosure: R. Terkeltaub, Aequus BioPharma, 5,Ardea/Astra-Zeneca, 5,Revive, 5,SOBI, 5,Selecta, 5,Relburn, 5,ProThera, 5,Horizon, 5; **R. Malamet**, AstraZeneca, 3; **K. Bos**, AstraZeneca, 3; **J. Li**, AstraZeneca, 3; **D. Goldfarb**, AstraZeneca, Revive, Cymabay, Retrophin, 9; **M. Pillinger**, None; **D. Jalal**, None; **J. Hu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **K. Saag**, Ardea/AstraZeneca, Horizon, Takeda, 5.

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Abstract Number: 207

Integrated Safety of Lesinurad, a Novel Uric Acid Reabsorption Inhibitor for the Treatment of Gout

Michael A. Becker[1], Robert T. Keenan[2], Puja Khanna[3], Raymond Malamet[4], Kathleen Bos[4], Jingyi Li[4], Jia Hu[5] and William White[6], [1]University of Chicago, Chicago, IL, [2]Rheumatology, Duke University, Durham, NC, [3]Rheumatology, University of Michigan, Ann Arbor, MI, [4]AstraZeneca Pharmaceuticals, Wilmington, DE, [5]Ardea Biosciences, Inc., San Diego, CA, [6]University of Connecticut School of Medicine, Farmington, CT

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Background/Purpose: Lesinurad is a selective uric acid reabsorption inhibitor recently approved at 200 mg daily in combination with a xanthine oxidase inhibitor (XOI) for treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid on XOI (allopurinol or febuxostat) alone. We integrated safety data for lesinurad (LESU) based on: (1) 3 large, pivotal, placebo-controlled, 12-month phase III (core) trials evaluating LESU 200 mg and LESU 400 mg in combination with an XOI; and (2) 2 extension studies, in which LESU-treated patients continued to receive LESU + XOI at the same dose and initially placebo-treated patients were randomized to receive LESU 200 mg or LESU 400 mg in addition to the XOI provided in the preceding core trial.

Methods: Safety data were pooled from the 3 core studies and 12-month extension studies using descriptive statistics for

patients receiving ≥1 dose of study medication. To adjust for varying treatment durations, treatment-emergent adverse events (TEAEs) are expressed as exposure-adjusted incidence rates (subjects with events per 100 person-years [PY]).

Results: In the core studies, adverse event rates were comparable for XOI alone and LESU 200 mg + XOI groups for any TEAEs, serious TEAEs, and TEAEs leading to discontinuation (Table 1). Adverse event rates were higher with LESU 400 mg + XOI. Major adverse cardiovascular event (MACE) rates, which included cardiovascular death, myocardial infarction, or stroke, in the core studies were 0.71 (95% CI 0.15, 2.08), 0.96 (0.26, 2.47), and 1.94 (0.84, 3.82) per 100 PY for XOI alone, LESU 200 mg + XOI, and LESU 400 mg + XOI, respectively. Renal-related TEAE rates in the core studies were 5.6, 7.3, and 15.4 per 100 PY, respectively. Longer exposure in the core + extension studies did not result in increases in any TEAEs, serious TEAEs, or TEAEs leading to discontinuation (Table 2). MACE rates were low in the core + extension studies, at 1.05 (95% CI 0.50, 1.93) and 1.48 (0.81, 2.48) per 100 PY in the LESU 200 mg + XOI and LESU 400 mg + XOI groups, respectively. Renal events in the core + extension studies were lower in the LESU 200 mg + XOI than LESU 400 mg + XOI group at 8.6 and 14.6 per 100 PY, respectively.

Conclusion: Lesinurad at the approved dose of 200 mg once-daily combined with XOI demonstrated a consistent, acceptable safety profile. There were no new safety concerns in the extension studies.

Table 1. Pooled Analysis of Exposure-Adjusted Adverse Event Incidence Rates in 3 Pivotal Placebo-Controlled 12-Month Phase III Studies Evaluating Lesinurad 200 mg and 400 mg in Combination with Xanthine Oxidase Inhibitors

Adverse Event Category [n (rate)]	XOI alone (N=516) (PY=408.5)	LESU 200 mg + XOI (N=511) (PY=396.3)	LESU 400 mg + XOI (N=510) (PY=390.5)
Any TEAE	363 (88.9)	386 (97.4)	407 (104.2)
Any TEAE with RCTC toxicity Grade 3 or 4	48 (11.8)	52 (13.1)	67 (17.2)
Any TEAE possibly related to randomized study medication	80 (19.6)	98 (24.7)	118 (30.2)
Any TEAE possibly related to XOI	52 (12.7)	49 (12.4)	66 (16.9)
Any TEAE possibly related to prophylaxis	52 (12.7)	56 (14.1)	61 (15.6)
Any serious TEAE	29 (7.1)	24 (6.1)	44 (11.3)
Any fatal TEAE	0 (0)	2 (0.5)	3 (0.8)
Any TEAE leading to randomized study medication discontinuation	28 (6.9)	32 (8.1)	48 (12.3)

LESU: lesinurad; PY, patient years; RCTC, Rheumatology Common Toxicity Criteria; TEAE: treatment-emergent adverse event; XOI, xanthine oxidase inhibitor. Exposure-adjusted incidence rates are expressed as subjects with events per 100 person-years.

Table 2. Pooled Analysis of Exposure-Adjusted Adverse Event Incidence Rates in 3 Pivotal Placebo-Controlled 12-Month Phase III Studies + 2 Extension Studies Evaluating Lesinurad 200 mg and 400 mg in Combination with Xanthine Oxidase Inhibitors

Adverse Event Category [n (rate)]	LESU 200 mg + XOI (N=666) (PY=926.5)	LESU 400 mg + XOI (N=666) (PY=917.9)
Any TEAE	531 (57.3)	552 (60.1)
Any TEAE with RCTC toxicity Grade 3 or 4	93 (10.0)	115 (12.5)
Any TEAE possibly related to randomized study medication	158 (17.1)	187 (20.4)
Any TEAE possibly related to XOI	77 (8.3)	101 (11.0)
Any TEAE possibly related to prophylaxis	76 (8.2)	81 (8.8)
Any serious TEAE	63 (6.8)	84 (9.2)
Any fatal TEAE	7 (0.8)	7 (0.8)
Any TEAE leading to randomized study medication discontinuation	68 (7.3)	86 (9.4)

LESU: lesinurad; PY, patient years; RCTC, Rheumatology Common Toxicity Criteria; TEAE: treatment-emergent adverse event; XOI, xanthine oxidase inhibitor. Exposure-adjusted incidence rates are expressed as subjects with events per 100 person-years.

Disclosure: M. A. Becker, Takeda, 2,Savient, 2,Ardea/AstraZeneca, 2,Takeda, 5,Savient, 5,Horizon, 5,Ardea/AstraZeneca, 5,CymaBay, 5,Pfizer Inc, 5; **R. T. Keenan**, AstraZeneca, 5,Crealta Pharmaceuticals, 5,Takeda, 5; **P. Khanna**, AstraZeneca, 2; **R. Malamet**, AstraZeneca, 3; **K. Bos**, AstraZeneca, 3; **J. Li**, AstraZeneca, 3; **J. Hu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **W. White**, AstraZeneca, 5.

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Abstract Number: 208

Examination of Serum Uric Acid (sUA) Lowering and Safety with Extended Lesinurad + Allopurinol Treatment in Subjects with Gout

Kenneth Saag[1], Michael A. Becker[2], Chris Storgard[3], Maple Fung[3], Jia Hu[3] and Thomas Bardin[4], [1]University of Alabama at Birmingham, Birmingham, AL, [2]University of Chicago, Chicago, IL, [3]Ardea Biosciences, Inc., San Diego, CA, [4]Hôpital Lariboisière, Paris, France

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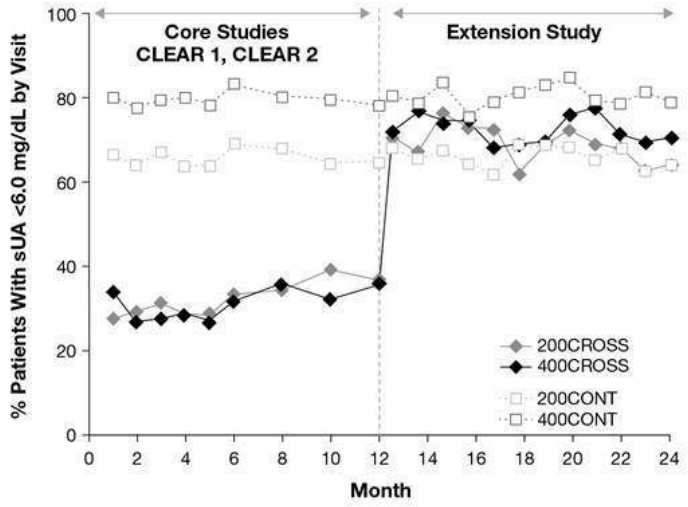
Background/Purpose: Two replicate, randomized, core Phase III trials (CLEAR 1 & 2) reported significantly more subjects treated with lesinurad 200 mg (LESU200) or 400 mg (LESU400), combined with allopurinol (ALLO), achieved target sUA <6.0 mg/dL at 6 and 12 months than with ALLO alone (P<0.0001).[1,2] The safety profile of LESU200+ALLO was comparable to ALLO alone, except for higher incidences of predominantly reversible serum creatinine (sCr) elevations. **Objectives:** Assess long-term safety and efficacy of LESU+ALLO therapy in subjects enrolled in the CLEAR 1 and 2 extension study (NCT01808131).

Methods: Efficacy was assessed for those completing the core study and either continuing core LESU+ALLO treatment (200CONT, 400CONT) or crossing over into extension studies from core ALLO alone to ALLO+LESU200 (200CROSS) or LESU400 (400CROSS). Core LESU200+ALLO or LESU400+ALLO subjects and 200CONT and 400CONT extension groups are reported for safety. Efficacy endpoints included proportion of subjects with target sUA <6.0 mg/dL and mean sUA levels. Treatment-emergent adverse events (TEAEs) were calculated as exposure-adjusted incidence rates (EAIRs; subjects with events per 100 person-years).

Results: For efficacy, 200CONT (n=239) and 400CONT (n=232) groups receiving treatment for up to 24 months, and 200CROSS (n=121) and 400CROSS (n=122) groups, receiving treatment for up to 12 months, were analyzed. Proportion of subjects with sUA <6.0 mg/dL during core and extension are shown (Figure). Mean (SD) sUA (mg/dL) for 200CONT, 200CROSS, 400CONT and 400CROSS groups, respectively, were 6.96 (1.14), 6.92 (1.33), 6.80 (1.20) and 6.99 (1.14) at baseline of core studies, and 5.71 (1.80), 6.68 (1.57), 5.06 (1.94) and 6.68 (1.38) at end of 12-month core studies. After 12 months in the extension study when all patients received LESU, mean (SD) sUA (mg/dL) was 5.75 (1.77), 5.78 (1.92), 5.01 (1.95) and 5.25 (1.77), respectively. For safety, a pooled analysis on a total of 405 (LESU200) and 401 (LESU400) subjects receiving lesinurad in combination with ALLO from the core studies was conducted. During the core and extension study period, EAIRs of TEAEs and serious TEAEs at any time were 54.2 and 5.8 for LESU200 and 57.2 and 8.3 for LESU400. EAIRs of renal-related TEAEs and serious renal-related TEAEs were 7.4 and 0.5 for LESU200 and 14.2 and 0.8 for LESU400. EAIRs of kidney stone TEAEs were 0.5 and 2.0 for LESU200 and LESU400, respectively. EAIRs of sCr elevations ≥1.5x baseline was 7.8 and 17.0 for LESU200 and LESU400, respectively. The majority of elevations (91.7% and 87.8%, respectively) were resolved by analysis cut-off.

Conclusion: Subjects treated with LESU+ALLO therapy through 2 years continued to be at sUA target; those crossing from ALLO monotherapy had increased proportions reach target. Safety during continued treatment in the extension studies was consistent with the profile observed in the core studies.

Figure. Proportion of patients with sUA <6.0 mg/dL during core and extension studies



ITT Population, Observed Cases, Patients who Enrolled in Extension.

Disclosure: K. Saag, Takeda, Horizon, Ardea/AstraZeneca, 2,Takeda, Horizon, Ardea/AstraZeneca, 5; **M. A. Becker**, Takeda, Ardea/AstraZeneca, Ironwood, Horizon, 2,Takeda, Ardea/AstraZeneca, Ironwood, Horizon, CymaBay, Pfizer, SelectaBio, 5; **C. Storgard**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Fung**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **J. Hu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **T. Bardin**, Ipsen, 2,Menarini, 2,AstraZeneca, 5,Ipsen, 5,Menarini, 5,Novartis Pharmaceutical Corporation, 5,Savient, 5,Sobi, 5,Takeda, 5,Cymabay, 5.

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Abstract Number: 209

Clinical Response of Tophus and Flares to Extended Use of Lesinurad in

Combination with a Xanthine Oxidase Inhibitor in Patients with Gout

Thomas Bardin[1], Nicola Dalbeth[2], Robert Terkeltaub[3], Chris Storgard[4], Maple Fung[4], Jia Hu[4] and Fernando Perez-Ruiz[5], [1]Hôpital Lariboisière, Paris, France, [2]University of Auckland, Auckland, New Zealand, [3]Medicine-Rheumatology, VA Medical Ctr/University of California San Diego, San Diego, CA, [4]Ardea Biosciences, Inc., San Diego, CA, [5]Hospital de Cruces and Biocruces Health Research Institute, Vizcaya, Spain

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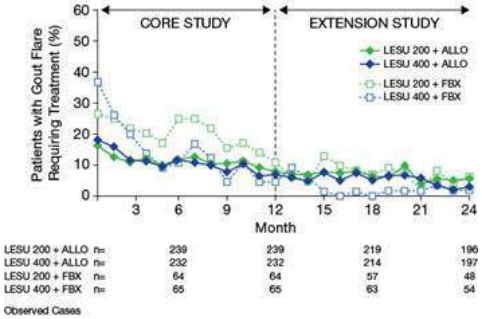
Background/Purpose: Three randomized, double-blind, Phase III trials reported that greater proportions of patients treated with lesinurad 200 mg (LESU200) or 400 mg (LESU400), combined with the xanthine oxidase inhibitor (XOI) allopurinol (ALLO; CLEAR 1 and 2) or febuxostat (FBX; CRYSTAL), achieved serum uric acid (sUA) targets at 6 months versus xanthine oxidase inhibitor (XOI) alone. This analysis evaluated the impact of long-term treatment with lesinurad + XOI on tophus and flares for at least 1 year and up to 2 years.

Methods: Patients completing 12 months in the core CLEAR and CRYSTAL studies could enroll in respective uncontrolled extension studies (NCT01808131; NCT01808144). Patients randomized to LESU200 + XOI or LESU400 + XOI in the core studies who continued on combination therapy in the extension studies were analyzed. Efficacy endpoints included: (1) proportion of patients with complete resolution (CR) of ≥1 target tophus (ie, measurable tophus on hands/wrists and/or feet/ankles 5–20 mm in longest diameter), (2) percent reductions in the total area of all target tophi, and (3) proportion of patients experiencing a gout flare requiring treatment (GFRT).

Results: A total of 239 (LESU200+ALLO) and 232 (LESU400+ALLO) patients continued in the CLEAR extension (n=32 and 33, respectively, with target tophi at baseline); 64 (LESU200+FBX) and 65 (LESU400+FBX) patients continued in the CRYSTAL extension. Proportion of patients with CR of ≥1 target tophus increased from end of core study (1 year) to 2 years: from 25.0% to 43.8% in LESU200+ALLO and 30.3% to 36.4% in LESU400+ALLO, and from 26.6% to 53.1% in LESU200+FBX and 35.4% to 58.5% in LESU400+FBX (LOCF). Percent reduction in the total area of all target tophi versus baseline changed from end of core study to 2 years: from 11.6% to 41.8% in LESU200+ALLO and 42.7% to 49.3% in LESU400+ALLO, and from 54.8% to 68.3% in LESU200+FBX and 58.6% to 72.4% in LESU400+FBX (LOCF). Proportion of patients with a GFRT per month decreased during continued combination treatment in both extension studies (Figure). The proportion of patients with a GFRT during Months 1, 12, and 24 were, respectively, 16.3%, 7.9%, and 5.6% in LESU200+ALLO; 18.1%, 6.9%, and 3.0% in LESU400+ALLO; 26.6%, 10.9%, and 6.3% in LESU200+FBX; and 36.9%, 4.6%, and 1.9% in LESU400+FBX. Extended treatment with LESU + XOI did not result in increased exposure-adjusted incidence rates of adverse events (AEs), AEs leading to discontinuation of lesinurad, serious AEs, or clinical laboratory abnormalities.

Conclusion: The CLEAR and CRYSTAL extension studies showed that patients treated with lesinurad + XOI for up to 2 years exhibited continued increases in the rate of complete resolution of tophi and reduction in tophus area, as well as decreased rates of gout flares.

Figure. Patients With Gout Flares Requiring Treatment (GFRT) During Core Study and Extended Treatment With Lesinurad + XOI



Disclosure: T. Bardin, Ipsen, 2,Menarini, 2,AstraZeneca, 5,Ipsen, 5,Menarini, 5,Novartis Pharmaceutical Corporation,

5,Savient, 5,Sobi, 5,Takeda, 5,Cymabay, 5; **N. Dalbeth**, AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,AstraZeneca, 8,Teijin, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Crealta, 9,Cymabay, 9; **R. Terkeltaub**, Ardea Biosciences, Inc., 5,AstraZeneca, 5,Takeda, 5,Relburn, 5,REVIVE, 5; **C. Storgard**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Fung**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **J. Hu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **F. Perez-Ruiz**, AstraZeneca, 5,Menarini, 5,Pfizer Inc, 5.

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Abstract Number: 210

Skin Events with Febuxostat in Gout Patients and Previous Skin Reactions to Allopurinol. a Retrospective Review

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Background/Purpose: Allopurinol is the most used urate-lowering agent for patients with gout, but around 10% of patients show intolerance to this drug, often at skin, which can be severe. Febuxostat (FBX) has been proposed for allopurinol-intolerant patients due to its different structure. However, data regarding safety in those with previous skin reactions to allopurinol is still limited (*Chohan.2011;38:1957. Bardin. 2016;83:314*) as these patients were excluded from pivotal trials. The aim was to assess the cutaneous safety of FBX when used in patients with previous skin reactions to allopurinol.

Methods: Retrospective review of patients with crystal-proven gout treated with FBX in our Unit until December 2015. Those with previous skin reaction to allopurinol were selected. We registered epidemiological (age, gender), clinical (skin events), laboratory variables (serum uric acid, glomerular filtration rate), and HLA-B*5801 status. The primary study variable was the rate of patients also presenting skin reactions with FBX. A descriptive analysis with estimation of the 95% confidence interval (95%CI) is presented.

Results: Out 102 gout patients treated with FBX in our Unit, we identified 24 patients with prior allopurinol-related skin events. The median age was 68.5 years (p25-p75 53.7-71.0), being 18 males (75%). Most used starting dose of FBX was 80mg/d (n=16), others were 5mg/d (n=1), 40mg/d (n=4) or 120mg/d (n=3). Median glomerular filtration rate at that time was 77.2 mL/min (62.7-68.6). We identified five patients (20.8%; 95%CI 3-38%) who also developed skin reactions with FBX (see table): in four cases a nonspecific rash, but one suffered from a Stevens-Johnson syndrome. They were HLA-B*5801 negative, and none of these patients presented skin reactions to benzbromarone.

Conclusion: In our series, one out five patients with previous skin reaction to allopurinol also developed after FBX. Larger studies are needed to confirm these results, but this finding strengths caution when using FBX in this subgroup of patients.

Characteristics of five patients developing skin reactions with both allopurinol and febuxostat

Gender	Age	Allopurinol start		Febuxostat start		Rash with febuxostat	Outcome with benzbromarone	HLA-B*5801 status
		Dosage (mg/d)	GFR (mL/min)	Dosage (mg/d)	GFR (mL/min)			
Female	70	50	78	120	77.2	Nonspecific	No rash	N/A
Male	69	N/A	90	40	90.5	Stevens-Johnsons	No rash	Negative
Female	68	100	52	80	80.3	Nonspecific	No rash	Negative
Male	45	50	90	80	90.9	Nonspecific	No rash	Negative
Female	41	300	40	5	40.9	Nonspecific	No rash	Negative

Disclosure: N. Quilis, None; **M. Andrés**, Menarini, 5; **C. Muñoz**, None; **P. Vela**, None; **E. Pascual**, Menarini, 5.

Abstract Number: 211

Safety and Efficacy of Febuxostat in Advanced CKD Patients with Hyperuricemia

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Background/Purpose: Dosing adjustments and increased risk of serious side effects of uric acid lowering agents in patients with reduced renal function lead to undercorrection of hyperuricemia in patients with advanced chronic kidney disease(CKD) and gout. Febuxostat is highly effective and well-tolerated to treat hyperuricemia in CKD patients. Although several evidences demonstrated the usefulness of febuxostat in hyperuricemic CKD patients, clinical studies aimed at the CKD patients with inappropriately controlled hyperuricemia by allopurinol have been relatively lacking. The study objective is to evaluate the safety and efficacy of febuxostat in patients, who had CKD with severe renal impairment and did not meet with the target uric acid levels using allopurinol.

Methods: Data were collected from 168 patients who had CKD with more than stage 3b and changed from allopurinol to febuxostat due to uncontrolled hyperuricemia between 2005 and 2014 at Yonsei University Medical Center. Uric acid and creatinine were analyzed at baseline and during the first 6 and 12 months after conversion of febuxostat. Estimated glomerular filtration rate was calculated using the formula of MDRD equation. The patients were defined as a well-controlled state when the uric acid values of the study subjects reached within 6.0 mg/dL.

Results: The mean age was 60.7±14.6 years, and 129 patients (76.8%) were male. The number of patients was 25 (14.9%) in CKD stage 3b, 75 (44.6%) in stage 4, 8 (4.8%) in stage 5, 38 (22.8%) in patients treated with maintenance dialysis, 22 (13.1%) in patients underwent kidney transplantation. The mean estimated GFR (eGFR) and uric acid levels at baseline was 23.1±17.3 ml/min/1.73m^2 and 8.3±2.4 mg/dL, respectively. Most of the patients was treated with 40 or 80mg of febuxostat during the study period. The mean uric acid levels at 6- and 12-month after febuxostat treatment were significantly reduced compared to uric acid levels at baseline (5.2±2.1 mg/dL at 6-month and 4.9±2.2 mg/dL at 12-month, $p<0.001$, respectively). More than 70% of study subjects reached to the target of uric acid levels less than 6mg/dL at 6- and 12-months after treatment of febuxostat [122 (72.6%) patients at 6-month and 133 (79.2%) patients]. The creatinine levels at baseline and 6-month were comparable (3.42±2.03 vs. 3.38±2.16 mg/dL at baseline and 6-month, $p=0.61$), meanwhile, the creatinine levels were significantly increased after 12-month compared to those at baseline (3.69±2.46 mg/dL, $p<0.01$). Abnormality of liver function test was observed in only one patient during the follow up period. None of the patients did not discontinue drug due to adverse events.

Conclusion: Present study demonstrated that substantial hyperuricemic CKD patients treated with febuxostat were achieved the target of uric acid levels without adverse events. Febuxostat is an effective and safe uric acid lowering drug in allopurinol-intolerant patients with advanced CKD.

Disclosure: Y. J. Oh, None; **S. M. Jung**, None; **S. W. Lee**, None; **Y. B. Park**, None; **J. J. Song**, None.

Abstract Number: 212

Pegloticase Provides Clinical Benefit in Patients with Chronic Refractory Gout Who Did Not Meet the Clinical Trial Biochemical Definition of Response

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Background/Purpose: Pegloticase is a recombinant uricase conjugated to polyethylene glycol approved for the treatment of chronic refractory gout refractory. The pivotal clinical trials for pegloticase defined responders as patients with plasma uric acid (UA) <6.0 mg/dL for ³80% of the time during extensive monitoring from both the week 9 infusion to just before the week 13 infusion and from the week 21 infusion to week 25 (final visit). Nonresponders did not meet this stringent criterion, but had a substantial decrease in UA after the first pegloticase dose followed by a return to a UA level >6mg/dL after ~6 weeks of therapy.[1] Whether these subjects received persistent clinical benefit from the transient reduction in UA is not known and is the subject of this analysis.

Methods: This analysis used results from two randomized controlled trials (RCTs)[1] to assess the clinical efficacy in responders and nonresponders to treatment (8 mg of pegloticase delivered every 2 weeks [q2w]). Serum UA was measured before each infusion and assessment of gout flares, tophus reduction, Patient Global Assessment (PGA), tender and swollen joints (TJC and SJC), pain measured with a 100 mm visual analog scale (VAS) and a variety of Patient Reported Outcomes were determined for four groups: responders, all nonresponders including those who exited the study and were not available for the UA assessments at 3 and 6 months, per-protocol (PP) nonresponders who received all planned pegloticase infusions in the 6-month RCTs, and patients who received placebo.

Results: The analysis included 36 responders, 49 nonresponders, 24 PP nonresponders, and 43 patients who received placebo. Responders exhibited mean reductions in serum UA to <0.5 mg/dL at 3 and 6 months. Both nonresponders and PP nonresponders had a transient decrease in UA that returned to a mean >6mg/dL by 7 weeks. Results for both responders and nonresponders indicated significant reduction in tophi and improvements from baseline in PGA, TJC, SJC, pain, and ASHI (**Table**). Improvements were greatest for responders, but were also significant for both groups of nonresponders. No significant improvements were observed in the patients who received placebo.

Conclusion: These results indicate that chronic refractory gout patients not achieving a protocol-defined biochemical response still have significant clinical benefits with pegloticase treatment. This suggests that the substantial, but transient, reduction in UA achieved in patients categorized as nonresponders in the RCTs can result in sustained clinical benefit. These benefits are not merely a result of being enrolled in a clinical trial or receiving hydrocortisone as prophylaxis for infusion reactions (IR) since they were not observed in patients who received placebo and a similar IR prevention protocol.

Tophus Resolution at 6 months				Complete		Partial	
Responder (n=36)				52.0%		16%	
Nonresponder (n=49)				25.0 %		25%	
Per Protocol (PP) Nonresponder (35)				26.9%		26.9%	
Placebo (n=43)				10.0%		20%	
Time	Mean	SD	P-value*	Time	Mean	SD	P-value*
Flares				Patient Global Assessment (PGA)			
Responder (n=36)				Responder (n=36)			
Baseline	2.1	1.9	-	Baseline	49.9 (n=35)	28.1	-
6 months	1.0	1.4	P=0.009	6 months	12.3 (n=36)	14.2	p<0.0001
Nonresponder (n=49)				Nonresponder (n=49)			
Baseline	1.3	1.5	-	Baseline	46.0 (n=49)	28.5	-
6 months	0.6	1.0	P=0.0002	6 months	22.7 (n=25)	24.2	P=0.0009
PP Nonresponder (n=24)				PP Nonresponder (n=24)			
Baseline	1.3	1.6	-	Baseline	52.1 (n=24)	27.0	-
6 months	0.8	1.1	P=0.63	6 months	20.2 (n=23)	21.2	P=0.0002
Placebo (n=43)				Placebo (n=43)			
Baseline	1.7	2.7	-	Baseline	52.6 (n=43)	28.9	-
6 months	1.3	1.5	P=0.63	6 months	43.8 (n=38)	32.1	P=0.2
Tender Joint Count (TJC)				Swollen Joint Count (SJC)			
Responder (n=36)				Responder (n=36)			
Baseline	11.7	13.3	-	Baseline	10.5	11.7	-
6 months	2.7	6.4	p<0.0001	6 months	2.1	3.8	p<0.0001
Nonresponder (n=49)				Nonresponder (n=49)			
Baseline	11.6 (n=49)	12.8	-	Baseline	7.7	10.6	-
6 months	6.4 (n=25)	10.3	P=0.02	6 months	3.8 (n=25)	6.0	P=0.02
PP Nonresponder (n=24)				PP Nonresponder (n=24)			
Baseline	13.5 (n=24)	13.8	-	Baseline	7.8 (n=24)	8.1	-
6 months	5.8 (n=23)	9.5(n=23)	P=0.02	6 months	3.3 (n=23)	5.3	P=0.008
Placebo (n=43)				Placebo (n=43)			
Baseline	14.1 (n=43)	14.8	-	Baseline	13.2	13.7	-
6 months	13.1 (n=38)	15.9 (n=38)	P=0.5	6 months	10.1 (n=38)	12.8	P=0.2
SF-36 Bodily Pain				VAS Pain			
Responder (n=36)				Responder (n=36)			
Baseline	41.2	26.6	-	Baseline	44.0	26.7	-
6 months	65.6	25.0	P=0.0004	6 months	24.1	24.3	P=0.003
Nonresponder (n=49)				Nonresponder (n=49)			

Baseline	40.4	24.3	-	Baseline	44.4	28.7	-
6 months	56.8 (n=25)	25.1	P=0.003	6 months	34.6.7 (n=25)	27.7	P=0.2
PP Nonresponder (n=24)				PP Nonresponder (n=24)			
Baseline	33.8 (n=23)	21.2	-	Baseline	50.25 (n=23)	30.9	-
6 months	57.4	21.4	P=0.0003	6 months	34.5	27.2	P=0.08
Placebo (n=43)				Placebo (n=43)			
Baseline	35.3	23.0	-	Baseline	53.9	28.1	-
6 months	35.8	21.7	P=0.7	6 months	57.2	27.6	P=0.5
SF-36 ASHI				HAQ-DI Functionality Index Scale			
Responder (n=36)				Responder (n=36)			
Baseline	55.4	29.1	-	Baseline	1	0.8	-
6 months	78.8	28.3	P=0.002	6 months	0.8	0.8	P=0.20
Nonresponder (n=49)				Nonresponder (n=49)			
Baseline	53.6	28.3	-	Baseline	1.2	0.9	-
6 months	69.7	29.1	P=0.02	6 months	0.9	0.8	P=0.20
PP Nonresponder (n=24)				PP Nonresponder (n=24)			
Baseline	49.5	26.3	-	Baseline	1.3	0.9	-
6 months	70.3	24.6	P=0.004	6 months	0.9	0.7	P=0.06
Placebo (n=43)				Placebo (n=43)			
Baseline	45.8	27.3	-	Baseline	1.2	1.0	-
6 months	46.6	29.0	P=1.0	6 months	1.3	0.9	P=0.7
* vs baseline							

References

1. Lipsky PE, et al. Arthritis Ther Res. 2014;16:R60.

Disclosure: B. F. Mandell, Horizon Pharma, 2,Horizon Pharma, Astra Zeneca, 5; **M. Weisman**, Horizon Pharma, 5; **A. Yeo**, Horizon Pharma, 5; **P. E. Lipsky**, AMPEL BioSulutions, 4.

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Abstract Number: 213

Prophylaxis for Infusion Reactions to Pegloticase: An Analyis of Two Different Corticosteroid Pre-Infusion Regimens in US Community Rheumatology Practices

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Background/Purpose: Corticosteroids are commonly utilized, along with other agents in clinical practice for pre-infusion prophylaxis prior to the administration of therapeutic biologic proteins. Two steroids, methylprednisolone and hydrocortisone, are commonly used. Because of the differing characteristics of these two agents, a chart review evaluating outcomes was performed.

Methods: Nineteen sites completed a retrospective chart review of pegloticase treated gout patients who completed at least three (3) infusions since 1/1/2012. Pegloticase is typically administered at 8 mg every 2 weeks, the FDA approved dose. Data collected included demographics, gout history, contraindications to both infusion reaction prophylaxis and gout flare prophylaxis medications, pre and post treatment serum uric acid (sUA) level, and prior gout treatment. This analysis includes data from 92 patients. Data were analyzed using multiple logistic regression, with number of infusions as a response variable and age, sUA prior to the last infusion, type of infusion prophylaxis corticosteroid (hydrocortisone or methylprednisolone) as treatment outcome predictor variables.

Results: Patient characteristics are similar to the typical pegloticase treated population.

Table 1 – Patient Characteristics

Age (years)	Mean	61.5
	Range	38 – 77
Sex (n, %)	Male	74 (82%)
	Female	18 (18%)
Race (n, %)	Caucasian	73 (79%)
	Black:	11 (12%)
	Asian	6 (7%)
	Other/NA	1 (1%)
Disease Duration (years)	Mean	13.5
	Range	4 – 30
Number of Infusions (n)	Median per Patient	7
	Total	670
Corticosteroid:		
Hydrocortisone	Number of patients (n)	31
	Mean Dose	198 mg
	Modal Dose	200 mg
	Range	150 – 200 mg
Methylprednisolone	Number of patients (n)	61
	Mean Dose	77 mg
	Modal Dose	50 mg
	Range	40 – 120 mg

Use of methylprednisolone as compared to hydrocortisone as pre-infusion prophylaxis was a significant ($p<.001$) predictor of pegloticase therapy duration (number of infusions). Furthermore, the mean number of infusions when methylprednisolone was used (8.48) was significantly higher than when hydrocortisone was used (4.93) ($p<.001$). As previously published, serum uric acid (sUA) drawn immediately prior to infusion was also a significant predictor of continued therapy and remains a key determinant for sustained pegloticase infusions. There was no significant difference between sUA levels prior to initiation of pegloticase therapy for these two groups.

Table 2 – Pre-Infusion Prophylaxis

Corticosteroid		Overall	Infusion Reaction and/or Discontinuation	
			No	Yes
Hydrocortisone	n	31	18	13
	Infusions (mean)	4.935	5.889	3.615
	Infusions (range)	3 – 16	3 – 16	3 – 5
Methylprednisolone	n	61	56	5
	Infusions (mean)	8.475	8.786	5.0
	Infusions (range)	3 – 13	4 – 13	3 – 7

Conclusion: Data from this retrospective chart review indicates that methylprednisolone pre-infusion therapy may allow for longer pegloticase therapy duration as compared with hydrocortisone. However, this modality imposes a significantly higher glucocorticoid load that may suppress symptoms of an infusion reaction rather than inhibit pegloticase drug antibody

formation. The long term use of methylprednisolone prophylaxis may result in glucocorticoid related adverse effects. Methylprednisolone use as compared to hydrocortisone for infusion prophylaxis needs further study to determine efficacy and long-term safety.

Disclosure: A. Majjhoo, Horizon Pharma, Inc., 5,Horizon Pharma, Inc., 8; **K. Okposo**, Horizon Pharma, Inc, 3; **M. Zdanis**, Horizon Pharma, Inc., 5,Amgen, Inc., 5.

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Abstract Number: 214

Anakinra Compared to Prednisone on the Treatment of Acute CPPD Crystal Arthritis, a Randomized, Controlled, Double-Blind Study

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Background/Purpose: Calcium pyrophosphate crystal-induced arthritis (CPPD) is an acute crystal arthritis, frequently involving the wrist or the knee. Monosodium urate in gout or CPPD in pseudogout have been shown to trigger the release of IL-1β, a strong pro-inflammatory cytokine, through a complex intracellular molecular cascade. IL-1 blockade showed efficacy in treating acute gouty arthritis in phase 3 controlled studies, and there are published retrospectives series and case reports showing a good clinical response in CPPD arthritis in blocking IL-1 with anakinra, an IL-1 receptor antagonist. This randomized controlled trial was designed to evaluate the efficacy and safety of anakinra versus prednisone to treat acute CPPD arthritis.

Methods: Single center, randomized, double blinded controlled study. ISRCTN registration number: ISRCTN46471047. Patients presenting, between 2012 and 2015, with an acute CPPD arthritis (< 5 days duration), were randomly assigned in a 1:1 ratio to a treatment of anakinra 100 mg s.c. + placebo matching prednisone or prednisone 30 mg + placebo matching anakinra s.c. for 3 days. Acute CPPD arthritis was defined as presence of clinical symptoms and CPPD crystals in joint fluid aspiration at screening or in the medical history. Primary outcome was the pain evaluation at 72 hours post dose on a 0-100 mm VAS scale. Secondary outcomes were assessments by the patient and physician of pain intensity and global response over a 28 days period.

Results: Fifteen patients were randomized, 8 assigned to anakinra and 7 assigned to prednisone treatment. Baseline characteristics of both groups were comparable. Three patients (2 in the anakinra group and 1 in the prednisone group) presented a flare 2 weeks after the intervention and were excluded from the study, treated with medication not allowed by the protocol (including open label treatment with anakinra for 1 patient). The study was stopped after 3 years due to a persistent low inclusion rate, reaching only 30% of the 50 expected randomized patients, mainly linked to the short requested delay of symptoms duration for inclusion. Pain reduction at 72 hours on a VAS scale compared with baseline was statistically significant in the anakinra group (-39 mm, p=0.02) but not statistically significant in the prednisone group (-23 mm, p=0.07). There was no statistically significant difference between both groups concerning the primary outcome. All other outcome measures were in favour of the anakinra group, but without being statistically significant due to an underpowered study. No serious adverse events were observed in both groups.

Conclusion: Both anakinra and prednisone seem to be effective in the treatment of acute CPPD-induced arthritis and we observed a trend in favour of anakinra, but non statistically significant, due to an underpowered study. More prospective randomized controlled trials are needed with more patients, probably with a multicentric design.

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Abstract Number: 215

Anakinra Is Effective and Well Tolerated in Medically Complex Patients Including Transplant Recipients with Gout

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Background/Purpose: Anakinra is a biologic response modifier that competitively antagonizes the biologic effects of interleukin-1β. Conventional treatments for the inflammatory response to acute gout are often contraindicated or can exacerbate comorbidities in medically complicated hospitalized patients. We report on the efficacy and safety of Anakinra for treatment of acute gouty arthritis in a medically complex in-patient cohort. Anakinra is not FDA approved for treatment of gout.

Methods: Retrospective chart review of all adult in-patients who received Anakinra in a 1017 bed hospital system from 2011 through 2015 in Rochester, New York. Only those patient treated for episodes of acute gouty arthritis were included. Data collected: demographics, medical comorbidities, prior treatments for gout, duration of hospitalization, concurrent infections, Anakinra dosing, response to treatment, adverse events.

Results: Of 28 adult in-patients receiving Anakinra over 5 years, 18 patients were treated for gout. The average age was 67.7 years. The average length of stay was 21.3 days. The average Charlson Comorbidity index[1] was 7.6. A representative patient with a Charlson Comorbidity index of 7 was scored as follows; age of 78 years old (3 points), CHF (1 point), prior MI (1 point), CKD 3 (2 points). Twelve of 18 cases were crystal proven at time of presentation. Average CRP during peak of symptoms was 163mg/dl. Average calculated GFR was 49ml/min. There were 3 transplant recipients (2 liver, 1 kidney) and 2 patients had implanted portable left ventricular assist devices. Seven patients were also receiving antibiotics at the time Anakinra was administered (Klebsiella pneumonia, 2 Enterococcal uti, C. difficile colitis, toe ulcer, 2 unknown). Thirteen of 18 patients had failed to respond to systemic corticosteroids and one to intraarticular treatment prior to receiving Anakinra. All patients responded to 1 or more doses of Anakinra. (Four of 18 responded to a single dose, 14 of 18 patients required 2 or 3 total doses). There was one adverse event for which Anakinra was a possible cause (worsening encephalopathy in decompensated liver failure patient).

Conclusion: Anakinra is an effective treatment for acute gouty arthritis in medically complex patients including those refractory to corticosteroids. Anakinra appears to be a safe treatment option for patients with extensive comorbid illnesses where conventional gout treatments may exacerbate comorbid diseases. The short half-life of anakinra is of additional utility for immunocompromised patients, such as solid organ transplant recipients, and patients with active infections. 1. Charlson, M et al. J Clin Epidemiol, 1994 Nov;47(11):1245-51. Validation of a combined comorbidity index.

Disclosure: C. Palma, None; **T. Topping**, None; **D. Tabechian**, None.

Abstract Number: 216

Colchicine Prescribing As a Parameter for QA/QI Process in Gout Care

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Background/Purpose: Because of the large increase in the price of colchicine with the FDA granted market exclusivity the Pharmacy at the Mpls VA HCS asked the Rheumatology Clinic to conduct a QA/QI review related to colchicine prescriptions refillable for up to one year. We intended to evaluate whether the prescribing of colchicine was appropriate related to the certainty of a gout diagnosis or other disorders treated with colchicine. We also evaluated the safety of prescribed colchicine dosing related to renal impairment, control of hyperuricemia in those on chronic colchicine therapy, the presence of co-morbid conditions and potential multiple drug interactions,

Methods: The pharmacy database provided a list of all patients with active, refillable prescriptions for colchicine at the Minneapolis VA HCS. We developed a structured chart review document to gather data from the electronic medical record of those with colchicine prescriptions. Diagnosis of gout was designated as 1) definite gout with urate crystals identified in synovial fluid, tophi, x-ray changes of osseous tophi) 2) probable gout (clinical picture and 6/12 ACR criteria for acute gout), 3) Other diagnoses treated with colchicine included pseudogout, pulmonary fibrosis, pericarditis . 4) Indeterminate reason in the EMR for colchicine yet patient receiving colchicine with/without urate lowering treatment (often in patients co-managed with outside provider 5) No evidence for dx of gout by reported clinical exam, lab tests or x-ray yet taking colchicine. Diagnostic designations 1), 2), 3) were considered appropriate prescribing of colchicine and those with 4) and 5) not appropriate prescribing of colchicine. Laboratory test results, medical history data, x-ray findings, co-morbidities were collected to evaluate the appropriateness of prescribed dosing of colchicine.

Results: 420 patients had prescriptions recorded in the pharmacy database in Nov 2011. The average age was 68.9 yrs (13% <60y; 39% 60-69y; 21% 70-79yr; 25% 80-89y, 3% >90yr) Only 9% of subjects did not have any co-morbidities; 222 had 1 or 2 (53%) and 161 had 3 or 4 (46%). The most common co-morbidities were diabetes, hypertension, chronic kidney disease, and heart failure. 32 patients actually did not have active prescriptions for colchicine and 32 had died before the chart review. Colchicine was designated appropriate in three groups: 1) 128 with definite gout (30%), 87 with probable gout (21%) and 20 with pseudogout and other diagnoses (4.7%). In 134 gout diagnosis was indeterminate (32%) and colchicine prescription was not designated as appropriate. Colchicine dosing was appropriate relative to renal function in 91% of patients. Interestingly concomitant urate lowering therapy was prescribed in only 239 (56.8%) with 170 (40.4%) at target uric acid of <7 and 69 (16.4%) with uric acid >7. Of concern is the lack of urate lowering therapy in 129 (30.7%) of those on chronic colchicine.

Conclusion: Assessment of colchicine prescribing revealed areas of deficient quality of care related to chronic administration of colchicine in nearly one third of patients without a definite or probable diagnosis of gout. These patients may be exposed unnecessarily to risk of adverse drug effects and may be subject to additional costs. There is concern for chronic colchicine treatment to suppress gouty arthritis without treatment of associated hyperuricemia because permanent joint damage may occur. Chart review of the electronic medical record to obtain clinical data presents challenges due to incomplete data recording. There was minimal evidence of ongoing monitoring for potential colchicine side effects. Because of these concerns about quality of gout care, we have set up a Gout management clinic to properly evaluate diagnostic data and to monitor responses and side effects to improve the quality of gout care. Thus far 79 patients came to Gout Clinic, 45 no showed, 64 died before appointment, and 165 declined the appointment. We will continue monitoring the quality of gout care in this new clinic.

Abstract Number: 217

The Effect of Regular Treatment on Disability in a Cohort of Patients with Gout.

Janitzia Vazquez-Mellado[1,2], Carlos O Lopez Lopez[3], Citlallyc Gomez-Ruiz[4], Everardo Alvarez-Hernandez[4], Ingris Pelaez-Ballestas[4], Ruben Burgos-Vargas[2,5] and Aaron Vazquez-Mellado[4], [1]Facultad de Medicina, UNAM, Professor, Mexico city, Mexico, [2]Rheumatology, Hospital General de México, Mexico City, Mexico, [3]Rehabilitation, Hospital General de Mexico, Mexico city, Mexico, [4]Rheumatology, Hospital General de Mexico, Mexico city, Mexico, [5]Universidad Nacional Autonoma de Mexico, Mexico, Mexico

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Background/Purpose: The severity of gout is often associated with poor patient compliance and sub-optimal medical treatment. Our objective was to determine the prevalence, characteristics, and factors associated with disability at baseline visit and the effect of regular treatment in patients with gout.

Methods: We analyzed baseline, 6, 12 and 18-months follow-up data of patients with gout from GRESGO, a cohort of 445 consecutive patients with gout seen for the first time at the Rheumatology Department and treated according to published guidelines (urate lowering therapy, acute attacks prophylaxis, NSAID and glucocorticoids) including treatment for associated diseases. Variables included demographic, clinical, and biochemical data; HAQ and EuroQoL questionnaires as well as VAS for pain and health. According to the use of daily life aids, specifically wheel chairs or gait aids (walking frames, canes or crutches) at baseline visit, we made two subgroups: one in need of such aids (GD) and another without them (GNoD). This protocol was approved by the local IRB and patients signed and informed consent for their participation. Statistical analysis included t test, X2, and logistic regression.

Results: Most patients (97%) were males; the mean ages at onset and at baseline were 34.4 (12.7) years and 47.5 (12.7) years; disease duration was 13.1 (10.7) years; 68% had tophi. There were 89 patients (20%) in GD group: 26% required 2 or more gait aids, 48% canes, 10% wheel chairs and 15% other walking frames; and 356 (80%) in GNoD group. GD had lower educational and socioeconomic levels and more severe disease (table 1); although there were no differences in age 47.9 (12.3) VS 47.4 (12.9) and disease duration 14.8 (9.9) VS 12.7 (10.9), p=NS, the frequency of renal and heart diseases was higher in GDAt the six-month follow-up, the effect of proper treatment had improved the clinical condition of 57% of patients in GD; 18 still required daily life aids; and 25% were lost to follow-up. At the 18-months evaluation 36 (40%) patients still had adequate functioning.

	GD %	GNoD %	p	Exp(B)	p
Low socioeconomic level	54	40	0.016	1.60	0.063
>3 Flares/last year	62	43	0.001	0.548	0.022
Previous glucocorticoid usage	67	53	0.017	1.36	0.25
Hypertension	47	35	0.048	1.30	0.30
Lithiasis	21	12	0.048	1.46	0.25
Chronic renal failure*	24	14	0.036	1.71	0.08
Heart failure	3.4	0.8	0.023	4.67	0.07
Hospitalization/gout reasons	33	14	0.001	1.46	0.13
Died during follow-up (n/%)	3/3.4	6/1.7	NS		

As expected, patients in GD had also significantly more or higher frequency of tender, swollen, limited joints, tophi, HAQ, EUROQoL, lost laboral days/6 months and VAS for pain and health. Nine (2%) patients died during follow-up: 3 (3.37%)

from GD and 6 (1.68%) from GNoD.

Conclusion: Disability occurred in 20% of gout patients attending a Rheumatology Department for the first time. These patients were low-socioeconomic level young men with very severe and active disease (> flares/hospitalizations, > tophi) and also associated renal and heart disease. And probably higher mortality.Proper treatment improves functioning in up two 40% of patients with disability in the baseline visit.

Disclosure: J. Vazquez-Mellado, None; **C. O. Lopez Lopez**, None; **C. Gomez-Ruiz**, None; **E. Alvarez-Hernandez**, None; **I. Pelaez-Ballestas**, None; **R. Burgos-Vargas**, None; **A. Vazquez-Mellado**, None.

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Abstract Number: 218

Accuracy of Humasens-Plus Point-of-Care Uric Acid Meter Using Capillary Blood Obtained By Fingertip Puncture

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Background/Purpose: A key factor in the success of gout management is the long-term lowering of serum uric acid (sUA) levels below predetermined targets (5 or 6 mg/dL). Monitoring of uricemia in gout patients is therefore important, especially during drug titration, and is presently done in the laboratory on serum samples obtained after venous puncture. An accurate sUA meter that would allow rapid testing by the health care professionals and self-measurement of uric acid by the gouty patient should improve patient monitoring and management of gout. This study aimed to assess the reliability of immediate uricemia measurement in capillary blood samples obtained from fingertip puncture using the HumaSens-plus point-of-care meter compared with that of a standard laboratory assay.

Methods: Finger-prick blood sUA levels were measured from 238 consenting diabetic patients using the commercially available HumaSens-plus sUA meter (European Conformity marked and approved for EU market use only). Each patient also had a venous sample taken and prepared as Li-Heparin plasma for analysis in the biochemistry laboratory using a uricase automated colorimetric assay. Since the sUA meter has a dynamic range of 3–20 mg/dL, a subject's capillary reading was excluded from statistical analysis when the meter read LO or HI, indicating that the subject's sUA value was lower than or higher than the calibrated range. Statistical analysis included calculation of the Pearson's correlation coefficient (PCC) between the 2 measured values and Bland-Altman graphic representations of means and differences between the 2 measurement results. A total of 206 paired measurements were calculated to be necessary for calculation of a PCC of 80% with a precision of 0.10 and an alpha risk of 0.05%.

Results: Eighteen capillary samples were marked LO by the meter: 15 were confirmed by standard biochemistry to be below 3 mg/dL, and 3 were above (3.2, 3.4, and 7.1 mg/dL). Two capillary samples were read HI and were measured at 5.1 and 3.6 mg/dL by biochemistry. In the remaining 218 samples, PCC was 0.92, and Bland-Altman curve showed acceptable agreement all over the tested values, with the following limits of agreement: [-1.1 mg/dL; 1.39 mg/dL]. On average, plasma measurements were 1.03-fold higher than capillary measurements. Accuracy was 92.7% at the 20% margin. Predictive value was 77.1% for a capillary measurement found to be above the target (6 mg/dL) by biochemistry measurement. For capillary measurement found to be below the target by biochemistry measurement, predictive value was 92.7%.

Conclusion: HumaSens meters were easy to use, and these preliminary results showed that the meters give results that are

reasonably comparable to those of the laboratory assay; as a result, they may be useful in the clinic and in epidemiologic studies. Further studies are underway to better understand discrepancies between the two techniques by looking at drug intakes and other biochemical and hematologic parameters measured in these patients, as well as by comparing results of both techniques to liquid chromatography-mass spectrometry reference measurements.

Disclosure: S. Fabre, None; **J. M. Launay**, None; **J. F. Gautier**, None; **A. Platt**, AstraZeneca, 3; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **G. Hughes**, AstraZeneca, 3; **P. Richette**, Algorithm, Astellas, AstraZeneca, Ipsen, Menarini, Novartis, Savient, Takeda, 8,Ipsen, Menarini, 2,AstraZeneca, Biomex, Ipsen, Menarini, Novartis, Savient, Sobi, 5; **T. Bardin**, None.

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Abstract Number: 219

Presence of Monosodium Urate Crystals By Dual-Energy Computed Tomography in Gout Patients Treated with Allopurinol

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Background/Purpose: Chronic hyperuricemia predisposes to deposition of monosodium urate (MSU) crystals in musculoskeletal and other tissues, causing chronic inflammation, acute gout flares, joint damage, and disfiguring tophi. Dual-energy computed tomography (DECT) is a useful imaging tool to detect and quantify MSU crystal deposits. This study assessed the evidence of MSU crystal deposition using DECT scanning among gout patients treated with allopurinol and the potential determinants associated with the observed deposits.

Methods: This multicenter DECT study recruited gout patients from the USA and New Zealand who were taking allopurinol at ≥300 mg daily for at least 3 months. MSU crystal deposition was measured using DECT in hands/wrists, knees, and feet/ankles bilaterally. The presence of MSU crystals as well as the total volume of crystals were assessed according to gout characteristics and serum uric acid (sUA) levels.

Results: Patients (N=147) were predominately male (91.8%), with mean (SD) age 58.7 (10.9) years and gout duration 15.3 (11.1) years. Mean sUA prior to scanning (within 1 month) was 6.0 (1.6) mg/dL, with approximately 46% of patients above the sUA target of 6.0 mg/dL. The median allopurinol dose was 300 mg (range, 300-700 mg) daily. 67.8% of patients had MSU crystal deposits with a total median crystal volume of 0.06 cm^3 (range, 0 to 19.53 cm^3). Those with sUA ≥6.0 mg/dL and palpable tophi showed the highest prevalence of urate deposits (88%), and those with sUA <6.0 mg/dL and no palpable tophi showed the lowest prevalence (47%). Those who reported a gout flare within the prior 3 months (versus none), were prescribed allopurinol doses >300 mg (versus 300 mg), and had palpable tophi (versus none) were more likely to have deposition.

Conclusion: Despite a stable dose of allopurinol for more than 3 months, and even with sUA at the target level, a substantial proportion of gout patients continue to have evidence of MSU crystal deposition by DECT scan. Patients with palpable tophi, sUA levels ≥6.0 mg/dL, and gout flares within the prior 3 months appear to have a higher frequency of MSU crystal deposition. These patients may need continuation and/or intensification of their urate-lowering therapy

Table. Subjects with urate deposition on their DECT scan according to palpable tophus status and sUA level.			
	sUA ≥6.0 mg/dL	sUA <6.0 mg/dL	Total
Palpable tophi			
Presence of urate deposits	15/17 (88.2%)	19/26 (73.1%)	34/43 (79.1%)
Median volume (range) for positive scans*	0.39 (0.01-19.53) cm^3	0.28 (0.05-2.57) cm^3	0.32 (0.01-19.53) cm^3
No palpable tophi			
Presence of urate deposits	39/49 (79.6%)	23/49 (46.9%)	62/98 (63.3%)
Median volume (range) for positive scans*	0.11 (0.01-1.23) cm^3	0.14 (0.01-0.89) cm^3	0.13 (0.01-1.23) cm^3
Total			
Presence of urate deposits	54/66 (81.8%)	42/75 (56.0%)	96/141 (68.1%)
Median volume (range) for positive scans*	0.13 (0.01-19.53) cm^3	0.22 (0.01-2.57) cm^3	0.16 (0.01-19.53) cm^3
*Positive scans include scans with presence (>0 cm^3) of urate deposits (numerators). Denominators are the number of subjects with non-missing DECT scan results.			

regimen.

Disclosure: N. Dalbeth, Cymabay, 9,AstraZeneca, 2,Fonterra, 2,Novartis Pharmaceutical Corporation, 2,AstraZeneca, 8,Teijin, 8,AstraZeneca, 9,Fonterra, 9,Pfizer Inc, 9,Takeda, 9,Crealta, 9,Cymabay, 9; **S. Nicolaou**, University has an MRA with Siemens Healthcare, 9; **S. Baumgartner**, Ardea Biosciences, a member of the AstraZeneca Group, 3; **J. Hu**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **M. Fung**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **H. K. Choi**, None.

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Abstract Number: 220

Urate Lowering Therapy Regresses Ultrasound Abnormalities in Gout

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Background/Purpose: Detection of double contour sign (DCS) and hyperechoic aggregates (HAG) is a reliable method in detecting urate crystal deposition by ultrasound (US) which has been studied extensively. Worldwide attempts have been made to assess response by measuring Tophi size, but USG has not shown good correlation with other modalities in assessing Tophi size. Our study was aimed at progression / resolution of presence of DCS and HAGs after urate lowering therapy.

Methods: 14 patients of proven gout were followed up for progression / resolution of US findings after one year of urate lowering therapy. US evaluation was done at the beginning of urate lowering therapy and repeat US was done at one year. The ultrasound scans were obtained applying guidelines issued by The Working Group for Musculoskeletal Ultrasound in the EULAR Standing Committee on International Clinical Studies including Therapeutic Trials. DCS was looked for at three articular cartilage sites (first metatarsal, tibiotalar and femoral condyle) whereas HAGs were looked for at three joint sites (radiocarpal, first metatarsal and femoral condyle) and two tendon sites (patellar and triceps). Ultrasound was

done using multifrequency linear array transducer (8–13 MHz) of Logiq E; GE Medical Systems Ultrasound, on B mode gray scale (GS).

Results: In 14 patients, 84 sites were examined for double contour sign (DCS) and 140 sites for hyperechoic aggregates (HAG). In the initial evaluation, DCS was present in 34 out of 84 sites which got reduced to 27 in the follow up (20.5% reduction). HAG were present in 23 out of 140 sites in the initial study which got reduced to 11 out of 140 in the follow up (52 % reduction). Overall there was a 33.3% reduction of US abnormalities over one year follow up after urate lowering therapy. The mean serum uric acid level was 9.44 mg/dl (range- 2.6-13.7mg/dl) before initiation of urate lowering therapy and was 6.7 mg/dl (range 3.9-10.3) at one year follow up. Among the fourteen patients, compliance to drugs and dietary modifications were good for eleven patients and three were non-compliant. The mean serum uric acid levels in the good compliance group was 9.09 mg/dl at the initiation of therapy and mean levels got reduced to 6.0mg/dl after one year of follow up. The resolution of US abnormalities was seen in the compliant group while there was no resolution of US abnormalities in the non-compliant group.

Conclusion: Urate lowering therapy results in marked resolution of DCS and HAGs in gout. Compliance to urate lowering therapy and diet in resolution of US abnormalities is important. Qualitative assessment of presence and absence of DCS and HAGs can be used a guide to successful therapy.

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Abstract Number: 221

Ultrasound in Gout: The Clinical Application

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Background/Purpose: The utility of ultrasound (US) in aiding the diagnosis of gout has been well established. The latest 2015 gout classification criteria have included the US as one of the criteria. However, in a daily hectic outpatients and inpatients practice, with limited resources, the selection of joints for US examination is crucial. Therefore, we aimed to determine the prevalence of positive US findings in joints of the lower limb among gout patients.

Methods: Data was collected prospectively from 15th January 2016 to 31st May 2016. Patients who fulfilled 2015 ACR/ EULAR gout classification criteria were recruited. US examination of the bilateral first metatarsophalangeal (MTP1), midfoot, ankle and knee joints were performed by an experienced rheumatologist. Typical US lesions in gout such as double contour signs (DCS), tophi, and bone erosions were identified according to the international consensus of OMERACT. The frequencies of the positive US findings were analyzed using a descriptive analysis.

Results: There was a total of 78 patients were recruited, the majority (n=76) were male. The mean age of the patient was 52.3 ¡Ó 16.1 years. A total of 624 joints were examined. The frequency of DCS on ankles, MTP1, knees and midfoot were 98.7%, 96.8%, 95.5%, and 17.9% respectively. The majority of tophi were detected via the US on MTP1 (90.4%), while

9.6% of the midfoot, 11.5% of the ankle, and 16.0% of the knee joints had tophi depositions. Of 156 MTP1 joints examined, 68 (43.6%) had erosions.

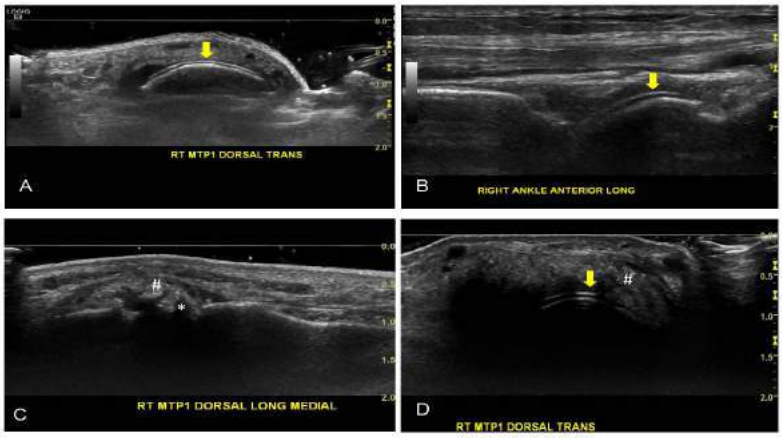
Conclusion: MTP1 consistently demonstrated a high frequency of positive US findings (DCS, tophi and bone erosions). The US of the midfoot showed infrequent gout lesions, especially DCS. In daily practice to detect gout, US examinations of the MTP1 are preferred while the US of the midfoot could be omitted. US examination of the ankle and knee joints could be considered in particular looking for DCS. Bone erosions may not be detected by the US if coexistence of tophi depositions on large joint such as knees and ankles.

Table 1. The distribution of double contour signs, tophi, and bone erosions according to joints.

n (%)	MTP1	Midfoot	Ankles			Knees
			Anterior	Medial	Lateral	
DCS	151 (96.8)	28 (17.9)	149 (95.5)	154 (98.7)	145 (92.9)	149 (95.5)
Tophi	141 (90.4)	15 (9.6)	6 (3.8)	6 (3.8)	18 (11.5)	25 (16.0)
Bone erosions	68 (43.6)	19 (12.2)	-	-	-	-

Abbreviations: DCS, double contour signs; MTP1, first metatarsophalangeal joint.

Figure 1. Typical ultrasound findings on gout patients.



Arrow showed double contour sign. # showed tophi. * showed erosions. Abbreviations: RT, right; MTP1, first metatarsophalangeal joint; TRANS, transverse view.

Disclosure: C. T. Lin, None; **C. H. Lim**, None; **Y. H. Chen**, None; **D. Y. Chen**, None.

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Role of Synovial Biopsy in Diagnosis of Crystal Arthropathies

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Title: Role of Synovial Biopsy in Diagnosis of Crystal Arthropathies

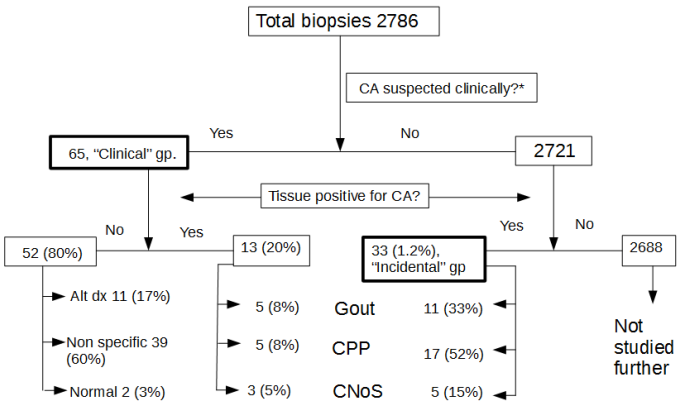
Background/Purpose: Diagnosis of crystal arthropathies (CAs) can be challenging. Advances in arthroscopy and ultrasound guided procedures have enhanced the ease and availability of synovial biopsy as a diagnostic test for rheumatologists, leading us to examine the role of synovial biopsy in CAs.

Methods: We performed word searches on synovial biopsies in the pathology database of a tertiary referral medical center between 1988 and 2015 and identified two groups. (1) A "clinical" group where CA was clinically suspected and listed as a primary or secondary indication for biopsy (with biopsy subsequently either positive or negative for CA); this would be typical of biopsy requests for CA originating from a rheumatology setting. (2) An "incidental" group, where a CA was identified on biopsies submitted from diagnostic and therapeutic procedures without a preoperative suspicion of CA. We reviewed electronic medical records of these cases to extract clinical details.

Results: Of 2786 synovial biopsies reported during the study period, 98 cases were selected for further study (Fig. 1). The mean age was 55 +/-16 years and 45% were female. Biopsy reports in the two groups are summarized in Fig. 1. On restricting analysis of the "clinical" group to only biopsies with CA as the primary clinical suspicion (n=31), the proportion of CA positive biopsies rose to 16% for gout, 13% for CPPD, 10% for unspecified crystal, with 39% overall positive for any crystal, while 22% had an alternate diagnosis and 39% were non-diagnostic. Absolute alcohol was the fixative used for 81% of the specimens in the "clinical" group. Seven of the 33 "incidental" positive biopsies were mass lesions suspected to be neoplastic, but diagnosed by biopsy as gout (n=4) or CPP (n=3). Clinical characteristics of patients from either group with a biopsy diagnosis of gout and CPP respectively were compared with the "clinical" patients negative for CA. (Table 1) Synovial fluid findings could not be analyzed due to a paucity of data.

Conclusion: Synovial biopsy is useful in the diagnosis of CAs, (a) yielding a diagnosis that can influence management in 61% of cases, (b) detecting a CA in 39%, and (c) identifying a specific CA in 29%, when CA is the primary indication for biopsy. Biopsy-positive gout is associated with the presence of bone cysts, while biopsy-positive CPP is associated with older age, monoarticular disease, chondrocalcinosis and bone cysts. An unexpected diagnosis of CA or crystal deposition occurs in 1% of synovial biopsies from procedures with no prior suspicion of a CA, including occasional mass lesions clinically mimicking a neoplasm.

Fig. 1: Analysis of Biopsy Findings



Abbreviations: Alt dx, Alternative diagnosis; CA, Crystal arthropathy; CPP, Calcium Pyrophosphate; CNoS, Crystal not specified; gp, group.

* including primary and secondary preoperative clinical suspicion of CA

Table 1: Comparison of clinical features-gout versus crystal-negative, and CPP versus crystal-negative

Variable	Tissue Diagnosis				
	Crystal negative, n=52	Gout, n=16		CPP, n=22	
	Mean (SD) or Freq (%)	Mean (SD) or Freq (%)	p (95% CI)	Mean (SD) or Freq (%)	p (95% CI)
Age	49.9 (17.5)	56.6 (10.9)	0.08 (-0.8-14)	65.4 (11.4)	0.00003 (8.6-22.3)*
Single vs Multiple joints affected	21 (39.7%)	3 (33.3%)	0.7 (0.3-10.7)	14 (77.8%)	0.03 (0.05-0.9)*
ESR	36.8 (33.5)	32.1 (43.4)	0.6 (-35-14)	52.2 (47.7)	0.5 (-20-56)
CRP	4.3 (6.9)	2.2 (3.2)	0.92 (-5.4-1.3)	1.82 (3)	1 (-6.3-1.3)
Chondrocalcinosis	7 (13.2%)	2 (12.5%)	1 (0.2-11.7)	10 (45.5%)	0.005 (0.05-0.7)*
Osteophytes	20 (37.7%)	8 (50%)	0.4 (0.2-2.2)	11 (50%)	0.4 (0.2-1.9)
Bone sclerosis	5 (10.4%)	1 (6.3%)	1 (0.2-78.7)	6 (27.3%)	0.07 (0.06-1.3)
Erosions	19 (35.8%)	9 (56.3%)	0.16 (0.2-1.6)	9 (40.9%)	0.79 (0.3-2.6)
Bone cysts	1 (1.9%)	4 (25%)	0.009 (0.001-0.7)*	4 (18.2%)	0.02 (0.002-0.98)*

CI, confidence interval; CPP, calcium pyrophosphate; CRP, C-reactive protein; ESR, Erythrocyte Sedimentation Rate; Freq, Frequency; SD, Standard Deviation
* $p < 0.05$.

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Abstract Number: 223

Clinical Predictors of Acute Gout Flares within Hospitalized Patients at a Tertiary Care Center in New York

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Background/Purpose: Gout is the most prevalent inflammatory arthritis worldwide. Within the healthcare setting, gout flares contribute to substantial morbidity and complicated hospital stays. Identifying risk factors and preventing flares are mainstays of therapy. This case-case-control study aims at exploring the risk factors for developing an acute gout flare with special emphasis on inpatient stressors and gout attacks in the hospital setting.

Methods: This is a case-case-control study of all consecutive gout flares from January 2010 to January 2015. The first group of cases comprised patients who developed a gout exacerbation after 48 hours of admission to the hospital. The second group consisted of patients whose gout flare manifested within 48 hours of hospital admission. The control group included chronic gout patients that were hospitalized during the same time frame as cases but did not experience an acute gout attack during their stay. Two multivariable models were constructed, one including predictors of flare-up within hospitalized patients (>48 hrs), and the other including predictors for flare-up upon hospital admission (<48 hrs).

Results: A total of 530 patients were included in this study (184 gout cases >48 hrs of admission, 159 gout cases <48 hrs of admission, and 187 chronic gout controls). There were no significant differences in gender distribution, age means, length of stay, or Charlson comorbidity scores across all study groups. In the first multivariable model (gout attack>48 hrs of admission vs chronic gout controls), recent gastrointestinal bleeding (OR 3.0; CI 1.1-8.2), placement of a urinary catheter (OR 4.1; 95% CI 1.9-8.6), and antibiotic use >3 days (OR 3.2; 95% CI 1.4-7.5) constituted independent predictors of gout exacerbation within hospitalized patients. Subgroup antibiotic analysis revealed that inpatient gout exacerbations were associated with recent use of cephalosporins (p<0.001), quinolones (p=0.01), metronidazole (p=0.03),

and vancomycin (p=0.001). In the second multivariable model, controls were more likely to have the following factors compared to cases: COPD (OR 1.89; 95% CI 1.1-3.3), rheumatoid arthritis (OR 4.2; 95% CI 1.2-15.3), recent infection (OR 2.2 95% CI 1.2-15.3), and a bedrest activity (OR 4.6 95% CI 1.7-12.6) order. In both models, Allopurinol (p<0.001) and Colchicine (p=0.003) use were significantly associated with chronic gout controls compared to cases.

Conclusion: Urinary catheter placement, antibiotic use, and gastrointestinal bleeding within 30 days seem to be unique predictors for gout flares within hospitalized patients. Prior use of cephalosporins (within 30 days) constituted an especially robust risk factor for an acute inpatient gout flare compared to controls. The design of this study permits for a more reliable assessment of inpatient risk factors compared to the classic case-control design.

Disclosure: L. El Khoury, None; **M. Yasmin**, None; **N. Zeineddine**, None; **J. Saabiye**, None; **S. Riaz**, None; **S. Arnaout**, None; **T. El Imad**, None; **S. El-Sayegh**, None; **R. Obeid**, None.

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Abstract Number: 224

Patient Perception of Gout Flares As a Measure of Outcome: Results from an International Study

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Patient Perception of Gout Flares as a Measure of Outcome:

Results from an International Study

Background/Purpose: Attacks (flares) are one of the primary manifestations of gout. It is not known how infrequently gout flares need to occur for patients to consider their disease to be in remission, in a state of low activity (LDA), or in an acceptable state (PASS). In addition, it is not clear what time horizon should be used to determine these disease activity states. The aim of this study is to estimate the patient-perceived frequency of gout flares associated with disease activity states along with a clear time-horizon for these estimates

Methods: We enrolled 374 individuals with gout from 15 international sites in a cross-sectional study. We inquired about flare frequencies in the past 6 and 12 months and actual and hypothetical perception of disease states: remission ("gout is gone"), LDA ("gout control is satisfactory") or acceptable state ("gout requires no more treatment") with relation to flares. Data from one half of the group (discovery group) was used to estimate the best discriminatory cutpoints to distinguish remission vs. non-remission, LDA vs. no-LDA, and PASS vs. no-PASS using logistic regression. We then applied these

estimates to the second half of the group (validation group) to calculate sensitivity and specificity of these thresholds. Results at 6 and 12-month recollection intervals were compared. **Results**: The mean age of participants was 52.7 years (SD 13.9), 90.2% were men, and 33.2% had tophi. Participants reported experiencing a median of 2 (IQR 0-4) and 3 (IQR 1-8) flares in the 6- and 12-month preceding period, respectively. From the flare perspective, 24.5% of and 22.6% of participants reported that their gout was in remission. Flare frequency thresholds for disease states were lower with asking the participants about hypothetical (imagined) scenarios than when with their past recollection of disease states within the validation cohort (Table). Recollection of one flare or less in the prior 6 and 12 month periods provided the best predictive cutpoints between a between being or no being in remission, LAD, or PASS (Table). Responses at 6 and 12 months had comparable performance.

Conclusion: Recollection of one flare or less in the previous 6-month period provides the best discrimination for patient-reported gout flare remission state, although the diagnostic performance of this threshold is limited. A 12-month recall period does not outperform a 6-month recall period for assessing gout flare disease states.

Table. Diagnostic performance of cutpoints for different gout flare disease states.

	Scenarios based on recollection of past flares				Hypothetical scenarios			
Disease state	Past 6 months		Past 12 months		Past 6 months		Past 12 months	
Remission vs non-remission	1 or less	SN:79% SP:60%	1 or less	SN: 69% SP:62%	No flares	SN:67% SP:20%	No flares	SN: 53% SP: 22%
LDA vs non-LDA	1 or less	SN:65.0% SP:77.1%	1 or less	SN:50.4% SP:82.4%	No flares	SN:49.8% SP:30.2%	No flares	SN:44.4% SP:40.1%
PASS vs non-PASS	1 or less	SN:71.3% SP:79.7%	No flares	SN:33.7% SP:97.3%	1 or less	SN:60.6% SP:31.0%	1 or less	SN:51.7% SP:31.6%

LDA: low-disease activity, PASS: patient acceptable state, SN: sensitivity, SP: specificity

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Abstract Number: 225

Patterns of Joint Involvement in Gout Flares

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Background/Purpose: Gout flares are the most common manifestations of gout. Awareness of possible disease

presentations beyond the traditionally recognized podagra is essential for accurate and early diagnosis. Gout flares sparing the first metatarsophalangeal (MTP1) joint may be prone to misdiagnosis as physicians may not consider other patterns of joint involvement in a gout flare. We therefore examined gout flare joint patterns in two large gout cohorts.

Methods: We used data from the Boston Online Gout Study (BOGS), a longitudinal internet-based case-crossover study recruited from the community in the US, and the Study for Updated Gout Classification Criteria (SUGAR), a single time-point international cohort of patients presenting to Rheumatology clinics, to identify patterns of joint involvement and their frequency in gout flares through latent class analysis. In BOGS, we analyzed the joints affected in the first recurrent gout flare reported during the study, while in SUGAR, we analyzed the joints affected at study enrollment. Latent class models with different numbers of classes (patterns) were evaluated, with the optimal number determined by statistical parameters, mean posterior probability of class membership, and clinical judgment.

Results: BOGS included 724 participants, 78% men, mean age 54 years, with mean gout duration of 8 years. SUGAR included 509 subjects with crystal-proven gout, 86% men, mean age 60 years and mean gout duration of 6 years. The optimal model for both studies included four patterns of predominant joint involvement, with mean posterior probability of class membership being ≥79%, indicating a good fit of the group trajectories model. In BOGS, the most common pattern was involvement of lower limb joints (including MTP1), with a prevalence of 49.8%, followed by MTP1 monoarthritis (32.5%), upper limb joint involvement (14.5%), and polyarticular flare (3.1%). Similar patterns were identified in SUGAR, with MTP1 monoarthritis (39.4%) and knee/ankle involvement (37.1%) being the most common, followed by upper limb joint pattern (14.8%) and polyarticular flare (8.6%). (Table) Of note, 43.7% and 64.2% of subjects in BOGS and SUGAR, respectively, had a gout flare in joint(s) other than the MTP1. Upper limb and polyarticular flares appeared to be associated with longer disease duration.

Table. Characteristics of gout flare joint patterns in both cohorts.

Boston Online Gout Study (N=724)	**MTP1 monoarthritis**	**Lower limb[1]**	**Upper Limb[2]**	**Polyarticular**
Prevalence (%)	32.5	49.8	14.5	3.1
N	238	368	97	21
Age, mean ± SD	54.3 ± 12.0	54.7 ± 13.0	55.1 ± 12.1	49.3 ± 10.7
Male, N (%)	187 (78.6)	294 (79.9)	76 (78.4)	11 (52.4)
Gout duration (years), mean ± SD	6.8 ± 9.0	8.1 ± 8.8	10.8 ± 11.4	9.6 ± 9.7
Study for Updated Gout Classification Criteria (N=509)	**MTP1 monoarthritis**	**Knee/ankle**	**Upper limb[2]**	**Polyarticular**
Prevalence (%)	39.4	37.1	14.9	8.6
N	177	217	72	43
Age, mean ± SD	62.4 ± 15.3	57.9 ± 14.7	64.3 ± 13.4	60.6 ± 12.8
Male, N (%)	144 (81.4)	195 (89.9)	62 (86.1)	39 (90.7)
Gout duration (years), mean ± SD	6.5 ± 7.8	8.9 ± 8.4	10.2 ± 9.6	12.0 ± 9.6

1: knee, ankle, heel, instep, first metatarsophalangeal joint, other metatarsophalangeal joint; 2: hand, wrist, elbow. MTP: metatarsophalangeal joint; SD: standard deviation.

Conclusion: We identified similar patterns of joint involvement in two large cohorts of gout patients from both the community and Rheumatology practices. While MTP1 monoarthritis was common, other lower extremity joint patterns were also common. These findings are important to increase awareness of different gout flare presentations among health care providers to improve gout flare diagnosis, including a not uncommon pattern of upper limb involvement. Importantly, lack of MTP1 involvement does not rule out the possibility of a gout flare, especially among patients with longer disease duration.

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Abstract Number: 226

Comparing the Burden of Illness of Patients with Tophaceous and Non-Tophaceous Gout in France, Germany, Italy, Spain, UK, and USA

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Background/Purpose: Gout is the most common form of inflammatory arthritis, with an increasing prevalence worldwide. ACR management guidelines recommend a target serum uric acid (sUA) <6 mg/dL, or <5 mg/dL in patients with tophaceous disease. Patients with significant crystal burden (tophaceous gout) are considered to have higher humanistic and economic burden of illness. These analyses describe patient and treatment characteristics and resource utilization in gout patients with and without tophi.

Methods: Data were assessed from physician surveys and in-depth patient chart audits in France, Germany, Italy, Spain, UK, and USA. Flares, organ/joint damage and tophi were extracted from clinical charts. Type/dose gout treatment, time on current therapy, physician type, and patient sociodemographic factors were identified. Demographic characteristics and comorbidities, sUA levels, and use of colchicine for acute flares during the 12-month study period were compared using chi-square or Fisher's exact tests.

Results: Of the 2505 patients identified, 612 (24. 43%) had physician-confirmed tophaceous gout and 1893 (75.57%) had non-tophaceous gout. Patients with tophi were older (61.6 vs 57.4 years), had gout for a slightly longer period (2.8 vs 2.4 years), reported more flares (3.2 vs 1.7 per year) over the last 12 months, and were more likely to have higher sUA (12-month mean 7.80 vs 7.34 mg/dL) (all $p<0.001$). Levels of comorbidities were significantly higher in patients with tophi including cardiovascular disease, chronic obstructive pulmonary disease, congestive heart failure, diabetes, depression, hypertension, osteoarthritis, and Stage III and Stage IV/V chronic kidney disease (all $p<0.001$). Patients with tophi were more likely to be treated with urate-lowering therapy (87.9% vs 72.4%; $p<0.001$). Of the urate-lowering therapies, patients with tophi were less likely to use allopurinol (52.5% vs 59.0%; $p=0.003$) and more likely to use febuxostat (28.9% vs 11.0%; $p<0.001$). Patients with tophi were more likely to use colchicine (40.7% vs 29.2%; $p<0.001$) and steroids (43.8% vs 18.7%; $p<0.001$), and less likely to use NSAIDs (35.6% vs 42.9%; $p=0.001$) for acute flares. Fewer patients with tophi achieved sUA targets of ≤6 mg/dL and no flares (15.7% vs 27.0%; $p<0.001$) or ≤5 mg/dL and no flares (5.9% vs 12.4%; $p<0.001$) versus patients without tophi. Patients with tophi made more gout-related office visits (5.18 vs 4.42; $p=0.155$) and more made ≥1 gout-related emergency visit (26.8% vs 7.9%; $p<0.001$), hospitalization (12.7% vs 2.2%; $p<0.001$), or had gout-related surgery (4.4% vs 0.1%; $p<0.001$) over 12 months.

Conclusion: Less than 30% of gout patients achieve treatment targets and patients with tophi are less likely to achieve these goals than patients without tophi. Patients with tophi have significantly greater burden of disease and greater frequency of comorbidities than patients without tophi. Preventing development of tophi or resolving crystal burden by treating to guideline targets is an important but rarely achieved goal for patients with and without tophi.

Disclosure: P. Khanna, AstraZeneca, 2; **E. Tafesse**, AstraZeneca, 3; **S. Baumgartner**, Ardea Biosciences, a member of the AstraZeneca Group, 3; **A. Walker**, AstraZeneca, 3; **R. Morlock**, Ardea Biosciences, 5.

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Abstract Number: 227

Inadequately Treated Chronic Gout As the Main Reason for Primary Gout Admission in an Urban Adult Population: Results of a Retrospective Cohort Study

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Background/Purpose: Inadequately treated patients with chronic gout are at risk for an acute attack and many often require hospitalization. An acute attack of gout increases health care costs by an average of $6000 per day. This study was conducted with two main objectives :(1) to assess whether inadequately treated gout or non-compliance with urate lowering therapy (ULT) was responsible for primary gout admission and (2) to determine whether admissions complicated by acute gout resulted in increased in-patient length of stay and how it impacts health care cost.

Methods: Data was collected for adult patients admitted between January 2010 and December 2014 at The Brooklyn Hospital Center with either a primary or secondary discharge diagnosis of Acute Gout using ICD 9 codes. Patient data included demographics, diagnoses, length of stay, gout medications. Patients were placed into two groups: Group A included persons whose primary admitting diagnosis was acute gout and Group B consisted of patients who had gout coded as an active secondary diagnosis. Group B subjects were compared with a matched cohort of 121 subjects with gout whose admission was not complicated by acute gout during the current hospitalization period of January 2010 to December 2014.

Results: 182 subjects were studied, 97(53.3%) were in group A and 85(46.7%) were in group B. 67.0% of the subjects were male with mean age of 64.80, SD +/-12.87 years. 86.3% of the subjects were African Americans. Primary admission diagnosis for Group B subjects were stroke 1.7%, Chest pain 6.0%, acute CHF 8.8%, GI Bleed 3.3%, and other diagnoses 26.9%. Only 37% of Group A subjects were on prior ULT, excluding 8 newly diagnosed cases of gout, with RR: 0.49 (95% CI, 0.37, 0.61). The mean length of stay for Group A subjects was 5.2 days and for Group B it was 8.6 days. The mean length of stay for the matched cohorts was 4.4 days. All data were adjusted for age, gender and race. Centers of Medicare & Medicaid Services, (CMS) reimbursement of primary admission diagnosis for Group B ranged from $8630 to $7900. An additional diagnosis of acute gout did not change the Diagnosis Related Groups (DRGs) resulting in no additional CMS reimbursement. CMS reimbursed $8448 per a primary acute gout admission, a sum of $819,456 for the 5years period.

Conclusion: Inadequately treated chronic gout was the main reason for primary gout admission at the Brooklyn Hospital Center between January 2010 to December 2014.The length of stay for patients whose primary admission was complicated by acute gout was nearly doubled when compared with patients admitted with a similar primary diagnosis. Increase length of stay did not result in a corresponding increase in CMS reimbursement. This study identified the magnitude and the cost associated with primary gout admissions and emphasized the need for initiation of ULT and adequate control of uric-acid levels as per the ACR 2012 guidelines, by primary care physicians in the outpatient setting in conjunction with a rheumatologist.

Disclosure: M. Sealey, None; **I. Barry**, None; **T. Sam**, None; **O. Awe**, None; **S. Green**, None.

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Abstract Number: 228

Sick Leave and Disability Pension in Working-Age Gout Patients before and after Diagnosis – a Population Based Case-Control Study

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Metabolic and Crystal Arthropathies - Poster I: Clinical Practice

Session Type: ACR Poster Session A

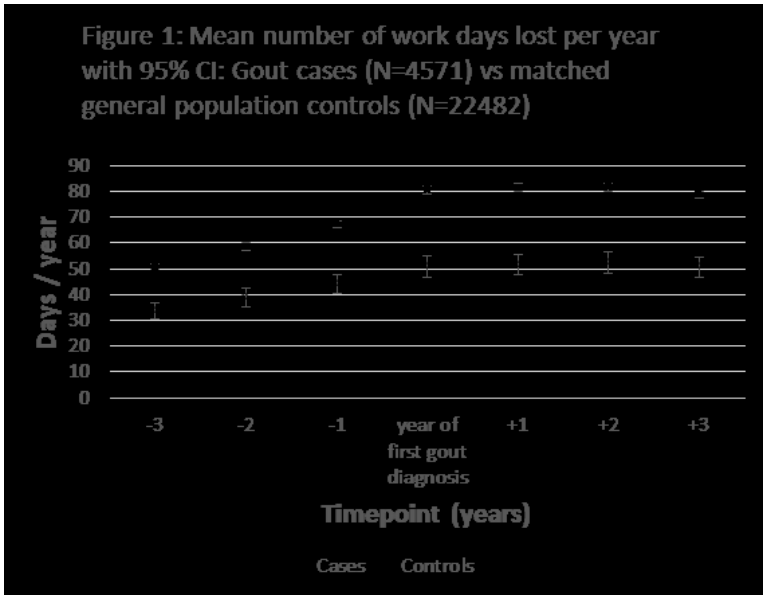
Session Time: 9:00AM-11:00AM

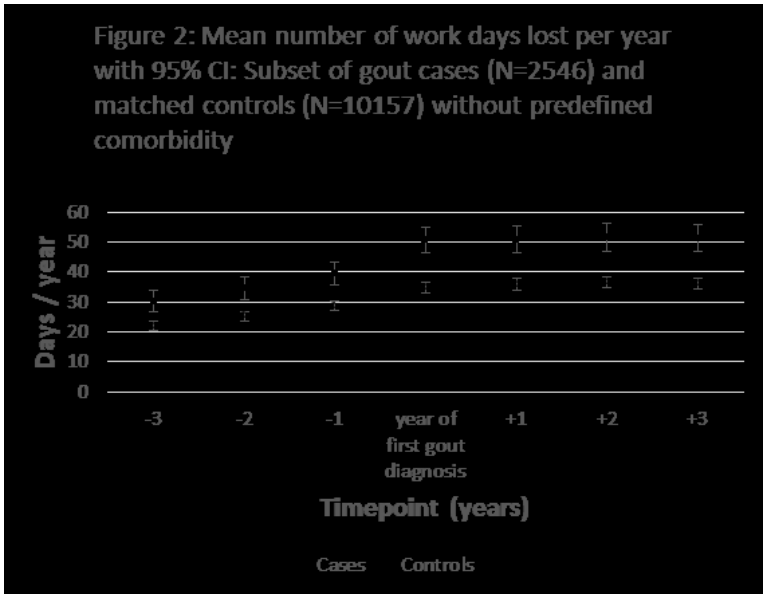
Background/Purpose: Gout is the most common form of inflammatory arthritis with a prevalence of 1.5% in our area in the age group 50-59 years. Gout has a substantial association with several comorbidities. Studies on the impact of gout on indirect costs on a population level are however scarce. The aim of the present study was therefore to describe the yearly difference in absenteeism due to sick leave (SL) and disability pension (DP) in patients with gout and matched population based controls.

Methods: Gout cases were defined in the population based health care database (VEGA) of the Western Swedish Health Care Region (WSHCR) by having a first diagnosis of gout in the years 2003-2009 by ICD-10 codes (M10 and M14.0) in VEGA. Cases were included if their age at the time of the first diagnosis of gout was ≤62 years, to allow for a follow-up period of 3 years before reaching the retirement age of 65 years. Five controls for each case, matched for age, sex and place of residence were chosen from the census register by Statistics Sweden. Data on predefined comorbidities registered previous to the index year was collected from VEGA by ICD-10 codes for cases and controls. Yearly net days of SL and DP for cases and controls were retrieved from Statistics Sweden for a period of 3 years before and after the index year. The difference between cases and controls in yearly net days lost from work due to SL and DP were calculated in the whole population, with a subanalysis of those without predefined comorbidities. Mean values with 95% CI for SL and DP days for the gout cases and controls were calculated by ANOVA, accounting for the matched design and applying non-parametric bootstrapping to calculate confidence intervals.

Results: 4571 gout cases were matched to 22482 population controls. The median age at diagnosis of gout was 53 years and 77% of the study group was male. The total number of work days lost was significantly higher for gout cases compared to the general population at the time of gout diagnosis as well as in the years preceding and following the gout diagnosis. Gout patients were absent from work on average 71 days per year while controls were absent on average 46 days per year (figure 1). In a subgroup analysis of 2546 cases and 10157 matched controls without predefined comorbidities this difference remained but was less pronounced (44 vs 31 days) (figure 2).

Conclusion: Work days lost due to SL and DP were substantially higher in patients with gout compared to controls in a population based setting. Comorbidities explained only slightly more than half of this increase suggesting that socioeconomic or other factors closely related to gout are of importance.





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Abstract Number: 229

Relationship Between Patient and Disease Factors and Severity of Gout in a Real-World Population

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Background/Purpose : Gout is the most prominent clinical manifestation of hyperuricemia, and is the most common cause of inflammatory arthritis. The symptoms of gout (eg, intense joint pain, redness, heat, and swelling) can have a have a significant impact on patients' ability to function, with subsequent decreases in quality of life and increases in healthcare-related costs. Clinicians routinely consider gout severity when making treatment decisions, but the clinical features they use to define severity have not been well characterized. Therefore, we examined patient- and disease-related attributes of clinician-assessed gout severity.

Methods: Data were assessed from a survey of US physicians and in-depth patient chart audits. Gout severity was measured using physician global assessment. Additionally, serum uric acid (sUA) levels, flares, organ/joint damage, tophi, sociodemographic factors, and physician type (eg, primary care, rheumatologist) were identified. Descriptive and multivariate (stepwise logistic regression) statistics described differences among patients with severe vs moderate and mild gout.

Results: A total of 1159 patient charts were abstracted (185 with severe gout, 681 with moderate gout, and 293 with mild gout; 81% male; 38% ≥61 years of age; 71% white). Patients with severe gout had gout for a longer period than those with

moderate or mild disease (66 mo vs 43 mo vs 38 mo; P <0.01). Tophi were reported in almost 74% of patients with severe gout, 19% with moderate gout, but only 3% of patients with mild gout (P <0.01). Patients with severe gout reported an average of ~3 flares per year vs ~2 flares per year for those with moderate gout, and only ~1 flare per year for those with mild gout (P <0.01). There were no differences in most recent sUA levels (7.2 mg/dL severe vs 6.8 mg/dL mild and moderate; P =0.08) or the proportions of patients who reached sUA goal (39% vs 42% vs 40%; P =0.42) by gout severity. The percentage of patients using urate-lowering therapy (ULT) differed by disease severity: 91% with severe, 80% with moderate, and 49% with mild (P <0.01). A model predicting gout severity found that having tophi or a greater number of flares per year, being female or of low social economic status, and having chronic heart failure, diabetes, or osteoarthritis were significant predictors of severe disease.

Conclusion: In this analysis, physician-assessed gout severity was more dependent on gout-specific attributes (tophi and flares), gender, socioeconomic status, and comorbidities than sUA (which was not a good indicator of gout severity). The lack of difference in sUA levels by gout severity may, in part, be a result of more patients with severe gout reporting use of ULT. These results should help physicians identify patients with factors aside from high sUA, who may be at risk of more severe gout, and who may require more careful monitoring and intensive management.

Disclosure: M. Pillinger, None; **S. Krasnokutsky Samuels**, None; **R. Malamet**, AstraZeneca, 1,AstraZeneca, 3; **B. Schechter**, AstraZeneca, 1,AstraZeneca, 3; **D. C. Taylor**, Ironwood Pharmaceuticals, 1,Ironwood Pharmaceuticals, 3; **R. Morlock**, Consulting fees, 5.

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Abstract Number: 230

A Survey of Knowledge of Optimal Gout Management in an Academic Primary Care Setting

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Background/Purpose: We reviewed previous treatment approaches for gout in patients referred to a university rheumatology practice for gout management. All patients met the 2015 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) gout classification criteria. We observed a paucity of concomitant prophylactic treatments that included non-steroidal anti-inflammatories (NSAID's) and colchicine. We also observed that treat to target of serum uric acid levels was lacking. This prompted a survey of primary care physicians and medical residents to evaluate the educational gaps that might be a focus of further medical education.

Methods: A standard questionnaire was developed using input from senior rheumatologists. A core set of principles for the treatment and prevention of gouty arthritis based on the ACR/EULAR recommendations was utilized. All primary care physicians and medical residents from an academic university medical center were invited to participate in an anonymous electronic survey. Participants were requested to avoid researching or reading about management of gouty arthritis prior to survey completion. The survey was sent from the office of the Internal Medicine program director to help in improving response rates.

Results: One hundred and one out of two hundred and eight invitees, (or 48.6 percent,) completed the survey. Ninety-two percent of respondents were resident physicians and 8 percent of respondents were primary care attending physicians. Seventy-two percent of respondents felt comfortable or very comfortable in managing gout. Twenty-six percent indicated that they were very uncomfortable in gout management. Two percent of respondents indicated they would refer to a specialist for all gout management. When asked to identify a treatment target of serum uric acid only 30 percent were able to do so correctly. Fifty-six percent of respondents reported using colchicine in under one-half of the cases. Thirty-four

percent of the respondents had never prescribed concomitant colchicine.

Conclusion: In our academic setting there was a lack of knowledge of the 2015 ACR/EULAR gout classification criteria and the 2012 ACR approach to management. For the most part this was in resident physicians. Too few attending physicians answered the questionnaire to be able to make any conclusions regarding their understanding of treatment for gout. Our data suggests a divergence of current clinic practices in gout treatment by residents from the recommended management guidelines. We suggest that this indicates better dissemination of knowledge to physicians in training is needed.

Disclosure: S. Wade, None; **M. Abeles**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-survey-of-knowledge-of-optimal-gout-management-in-an-academic-primary-care-setting

Abstract Number: 231

Impact of an Educational Program for the Management of Gout Directed to Primary Care Physicians

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Background/Purpose: Gout is the most frequent inflammatory arthritis in males, and therefore a common cause for consultation in both primary care and specialist settings. Despite its frequency, the diagnosis and treatment for this condition are far from desirable. There is evidence of gout management improvement through educational programs targeted at primary care physicians. Objective: To measure the impact in diagnostic and therapeutic attitudes towards patients with gout, in primary care physicians, before and after performing an educational intervention based on a clinical case.

Methods: Through a training program aimed at general physicians with interest in musculo-skeletal diseases, an initiative of the Sociedad Española de Reumatología [Spanish Rheumatology Society] and the Sociedad Española de Médicos de Atención Primaria [Spanish Society for Primary Care Physicians], sessions were held in 6 Spanish locations. In the sessions, a general physician presented a clinical case about a patient with hyperuricaemia, intermittent arthritis, condrocalcinosis in knee joints and several associated comorbidities. In first place, 5 questions with multiple-choice answers were formulated, regarding the diagnosis and treatment deemed appropriate. Later, the case was evaluated and discussed by a rheumatologist, and the same questions were repeated. Answers were recorded by electronic means.

Results: A total of 195 physicians, divided in 6 locations, attended the sessions. Statistically significant results for each evaluated area are summarized below: Diagnosis: initially 21.8% of the attendants deemed arthrocentesis necessary for the diagnosis, but complementary investigations appeared to be more important (67.3%). Afterwards, a significant increase in the need for arthrocentesis was observed (46.7%). Comorbidities: 52.6% of the attendants decided to prescribe a non-steroidal anti-inflammatory drug (NSAID) to the fictional patient, with chronic kidney disease. After the discussion, the broad majority of assistants opted for alternatives such as steroids (41.23%) and only 4.74% still preferred NSAIDs. Initial complexity for diagnosis: a small percentage (12.7%) considered that a solid diagnosis was not possible without a sample of synovial fluid. This percentage rose up to 55.5% after the intervention. Prophylaxis: Colchicine-based prophylaxis was prescribed initially by 57.4% of physicians, and after the session, by most of them (71.6%). Urate lowering drugs: A change was observed in the use of urate lowering medications, from an initial 64.7%, up to 85.1% after the discussion. There was a reduction in the number of referrals to specialists, but it was not statistically significant.

Conclusion: Through educational initiatives for primary care physicians it is possible to optimize the perception of diagnosis and treatment in patients with gout.

Disclosure: S. Chinchilla, None; **I. Urionagüena**, None; **F. Perez-Ruiz**, Fundación Española de Reumatología, 2,Asociación de Reumatólogos del Hospital de Cruces, 2,Menarini, 8,AstraZeneca, 8,AstraZeneca, 5,Menarini, 5.

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Abstract Number: 232

Impact of Gout Flare Prophylaxis and Urate-Lowering Therapy on Endothelial Function, Smooth Muscle Responsiveness and Markers of Inflammation: Results of a Prospective Observational Pilot Study

Talia Igel[1,2], Aaron Garza Romero[2], Virginia Pike[3], Stuart Katz[4], Binita Shah[5], Irina Dektiarev[4], Svetlana Krasnokutsky Samuels[6] and Michael H. Pillinger[7], [1]Monash University School of Medicine, Melbourne, Australia, [2]Medicine/Rheumatology, NYU School of Medicine, New York, NY, [3]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY, [4]Medicine/Cardiology, NYU School of Medicine, New York, NY, [5]NYU School of Medicine, Division of Cardiology, New York, NY, [6]Svetlana Krasnokutsky, NYU Hospital for Joint Diseases, New York, NY, [7]NYU School of Medicine, New York, NY

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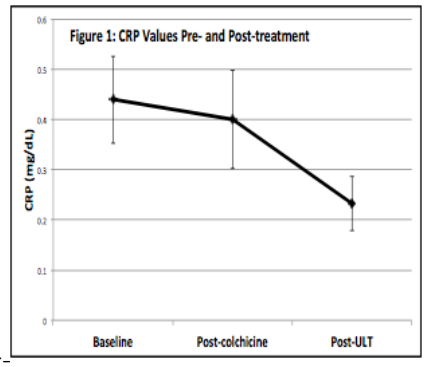
Background/Purpose: To date, most studies of gout and cardiovascular disease have been cross-sectional or retrospective, and have addressed the outcome of acute coronary syndromes. Less is known regarding the impact of gout on basic vascular health, including arterial endothelial function. We asked whether initiating gout treatment with colchicine and urate-lowering therapy (ULT) reduces inflammation (CRP), and improves endothelial function as measured by brachial artery flow-mediated dilation (FMD).

Methods: Gout patients initiating treatment with their physicians were enrolled. Physicians agreed to follow a care strategy that sequenced colchicine and ULT (allopurinol or febuxostat) initiation. Demographics and cardiovascular risk factors were recorded, and CRP and FMD were measured at baseline, after 6 weeks of colchicine (0.6 mgs daily), and again 4 weeks after ULT had been titrated to clinical target (<6.0 mg/dL; <5.0 mg/dL for patients with tophi) in the presence of continuing colchicine.

Results: 34 untreated male gout patients (mean age 57.9 years) were enrolled. To date, 32 have completed post-colchicine, and 22 have completed post-ULT assessments. CRP decline was observed from baseline to post-colchicine and further to post-ULT (total change from baseline, 0.207 mg/dL) (Figure). Overall we observed no net FMD improvement post-colchicine, but patients who experienced CRP reduction post-colchicine had higher rates of FMD improvement than CRP non-responders (58.8% versus 25.0% FMD response). We stratified the overall cohort based on smoking status, and observed greater rates of post-colchicine improvement in both FMD and CRP in the non-smoker, compared with the smoker group. FMD improvement occurred in 60.0% of non-smokers versus 38.1% of smokers; CRP improved in 75% of non-smokers versus 52.4% of smokers. Non-smokers with CRP improvement were also more likely than non-smoker CRP non-responders to demonstrate FMD improvement (66.7% versus 50% response rate). Baseline to post-ULT trends in CRP improvement were also more pronounced in the non-smoker group, with 75% of non-smokers versus 56% of smokers experiencing a CRP decrease. Analysis of FMD outcomes in patients post-ULT is ongoing.

Conclusion: This prospective observational pilot study suggests that treatment with colchicine and ULT is associated with an overall reduction in CRP. Among patients whose CRP declined, FMD also tended to improve, suggesting a common beneficial effect. Smoking appears to hinder improvement in inflammation and vascular function in response to colchicine and ULT. Data from the third and final (ULT) stage of the study are still being collected with analyses ongoing. Larger and longer studies may be warranted to confirm the anti-inflammatory and pro-vascular benefits of colchicine and ULT in

patients undergoing gout treatment initiation._



Disclosure: T. Igel, None; **A. Garza Romero**, None; **V. Pike**, None; **S. Katz**, None; **B. Shah**, Takeda, 2; **I. Dektiarev**, None; **S. Krasnokutsky Samuels**, Crealta/Horizon, 5; **M. H. Pillinger**, Takeda, 2,AstraZeneca, 5,Crealta/Horizon, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-gout-flare-prophylaxis-and-urate-lowering-therapy-on-endothelial-function-smooth-muscle-responsiveness-and-markers-of-inflammation-results-of-a-prospective-observational-pilot-study

Abstract Number: 233

New Cardiovascular Risk Factors Screening in Patients with Gout

Juan Carlos Ordoñez[1], Mariano Andres[1], Francisca Sivera[2], Loreto Carmona[3], Paloma Vela[4,5], Eliseo Pascual[4,5] and Jose Antonio Bernal[4], [1]RHEUMATOLOGY, HOSPITAL GENERAL UNIVERSITARIO DE ALICANTE, Alicante, Spain, [2]RHEUMATOLOGY, HOSPITAL GENERAL UNIVERSITARIO DE ELDA, Elda, Spain, [3]Instituto de Salud Musculo Esqueletica, Madrid, Spain, [4]RHEUMATOLOGY, HOSPITAL GENERAL UNIVERSITARIO ALICANTE, Alicante, Spain, [5]Medicina, Universidad Miguel Hernandez, Elche, Spain

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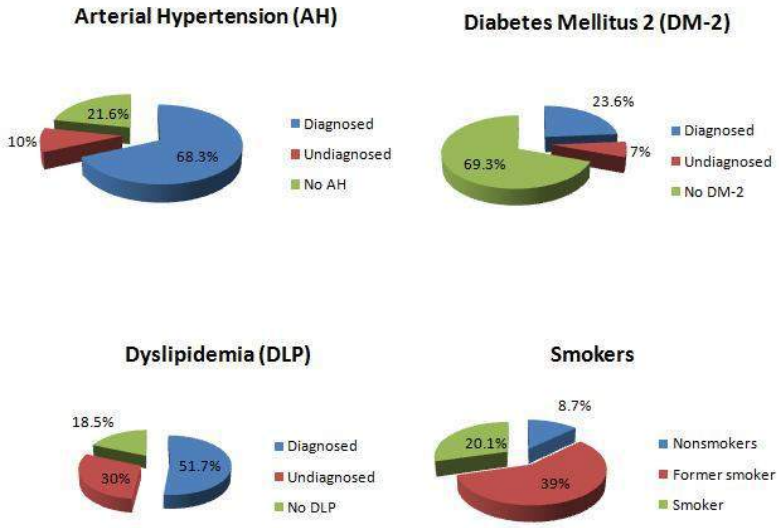
Background/Purpose: Gout is a disease triggered by the crystallization of uric acid in the joints secondary to persistent hyperuricemia, that leads to chronic inflammation. Patients with gout frequently have comorbidities including cardiovascular (CV) disease, kidney failure, diabetes mellitus etc. In fact, some these can increase the levels of uric acid and contribute to develop gout, and also deteriorate the CV profile of these patients. The aim of the present study was to assess the prevalence of unknown cardiovascular risk factors (CVRF) in patients with gout.

Methods : Cross-sectional analysis of a inception cohort of gout patients recruited by consecutive sampling in our rheumatology unit. Gout was diagnosed by visualization of monosodium urate crystals in synovial fluid or tophus sample. A structured CV assessment included CVRF, measurement of blood pressure, anthropometry and lab tests. Arterial Hypertension (AH) was defined by previous diagnosis, blood pressure ≥140/90mmHg and/or use of antihypertensive agents. Type 2 Diabetes Mellitus (DM-2) was defined by previous diagnosis, fasting blood glucose ≥126 mg/dL, glycosylated haemoglobin ≥6.5%; presence of microangiopathic complications was also registered. Dyslipidemia (DLP) was defined by previous diagnosis, use of hypolipidemic agents, or total cholesterol >200 mg/dL and/or triglycerides > 150 mg/dL. A descriptive analysis of the results is presented.

Results : The study involved 199 patients. The mean age was 63.4 (SD+/- 13.2) years, with 171 (85.9%) men. At inclusion the prevalence of CVRF was: AH in 136 patients (68.3%), DLP in 13 (51.8%), and DM-2 in 47 (23.6%). Seventy-six (38.6%) were found obese, smoking background was present in 40 (20.1%), use of diuretics (loop and/or thiazide) in 87 (43.7%), and chronic renal failure in 57 (28.6%). After structured assessment, the following undiagnosed CVRF were found: DLP in 59 patients (29.6%), AH in 20 (10.1%) and DM-2 in 14 (7%) [Figure]. New CVRF were found in 94 (46.7%) patients, among them 52 (26.1 %) had one CVRF, 13 (6.5%) had 2 CVRF, and even 3 CVRF were

identified in 2 cases (1.0%).

Conclusion : Half of our patients showed at least one unknown CVRF, mostly DLP followed by hypertension and DM-2. This finding highlights the need for active screening for new CVRF in patients diagnosed with gout, due to the potential impact on the proper CV management.



Disclosure: J. C. Ordoñez, None; **M. Andres**, None; **F. Sivera**, None; **L. Carmona**, None; **P. Vela**, None; **E. Pascual**, None; **J. A. Bernal**, None.

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Abstract Number: 234

Coexistent Gout and Rheumatoid Arthritis: Comparison of Comorbidity, Autoantibodies, Disease Measures, and All-Cause Mortality

Bryant R. England[1,2], Tina D. Mahajan[3], Namrata Singh[4], Brian W Coburn[3], Grant W. Cannon[5], Gail S. Kerr[6], Andreas Reimold[7], Angelo L. Gaffo[8] and Ted R Mikuls[9], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]VA Nebraska-Western Iowa, Omaha, NE, [3]Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [4]Internal Medicine, University of Iowa Hospitals and Clinics and Iowa City VA, Iowa City, IA, [5]Internal Medicine, Veterans Affairs Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [6]Washington DC VAMC, Georgetown University Hospital, Howard University Hospital, Washington, DC, [7]Dallas VA Medical Center and University of Texas Southwestern Medical Center, Dallas, TX, [8]Birmingham VA & University of Alabama at Birmingham, Birmingham, AL, [9]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Coexistent RA and gout were previously believed to be exceedingly rare due to several hypothesized mechanisms encompassing inhibition of crystal formation, deposition, and activation. While now well recognized to coexist, the influence of gout on RA disease measures, medication selection, and long-term outcomes remains unknown. We aimed to assess the associations of comorbid gout with RA measures, treatments, and outcomes.

Methods: Participants in a longitudinal observational cohort of US veterans with RA fulfilling the 1987 ACR criteria were screened for gout within national administrative data for 12 months prior to enrollment using the Healthcare Cost and Utilization Project Clinical Classification Software and within the registry database for urate lowering medications or colchicine. Gout was confirmed by the presence of a physician diagnosis of gout in electronic medical records. Patient characteristics, RA measures, and medications were obtained from the registry, and vital status was determined using linkage with the National Death Index. We compared baseline characteristics using chi-square and independent t-tests. We studied the associations of gout with RA disease characteristics and medication use using multivariable logistic and linear regression models and all-cause mortality with multivariable Cox proportional hazards regression models.

Results: In 2,068 participants (91% male), we identified 107 with coexistent gout (5.2%). At enrollment, RA & gout was associated with older age, higher body mass index, comorbidity, swollen joint count, functional disability, and less frequent shared epitope alleles and NSAID use (Table 1). There were non-significant trends toward less seropositivity and lower autoantibody titers in RA & gout. Odds of ever receiving prednisone, DMARDs, and biologics did not differ between RA and RA & gout (all $p>0.54$). The odds of ever achieving DAS28 (OR 0.72, 95% CI 0.48-1.07, $p=0.11$) or CDAI (OR 0.67, 95% CI 0.41-1.11, $p=0.12$) remission were less common in RA & gout vs. RA alone, although these associations were not statistically significant. Gout was not associated with all-cause mortality (multivariable HR 1.14, 95% CI 0.72-1.80, $p=0.57$) among RA patients.

Conclusion: To our knowledge, this is among the largest studies of coexistent RA and gout described to date. The male predominance, older age, and high comorbidity of participants in the cohort make it an ideal setting for the study of coexistent RA and gout. Gout is associated with demographic and genetic parameters, higher comorbidity burden, and RA measures including higher swollen joint counts and functional disability. These findings highlight the need for identification and treatment of comorbid gout and further study to better understand the mechanisms underpinning these differences and the potential impact that gout therapies might have on RA outcomes.

Table 1. Comparison of patient characteristics at enrollment between RA and coexistent RA and Gout.			
	RA	RA & Gout	P
Demographics			
Age at enrollment, years	63.8 (10.9)	67.7 (10.3)	<0.001
Smoking status Current Former Never	27.1 52.9 20.0	17.0 59.4 23.6	0.06
Body mass index, kg/m^2	28.3 (5.7)	29.8 (5.7)	0.01
RDCI score* (0-9)	2.3 (1.7)	2.9 (1.6)	<0.001
RA Characteristics			
Disease duration, years	11.8 (11.4)	9.9 (12.0)	0.10
RF positivity, %	80.2	74.3	0.17
Anti-CCP positivity, %	78.0	71.7	0.15
RF titer, IU/ml	341 (713)	285 (614)	0.43
Anti-CCP titer, U/ml	247 (404)	199 (363)	0.24
Shared epitope allele, %	72.6	57.3	0.003
hsCRP, mg/dL	1.2 (2.0)	1.3 (2.0)	0.85
Swollen joint count (0-28)	5.4 (6.0)	0.02	
Tender joint count (0-28)	5.3 (6.8)	6.3 (7.4)	0.12
Patient global (0-100mm)	40.7 (25.5)	43.0 (23.4)	0.39
Provider global (0-100mm)	34.4 (22.9)	35.4 (22.9)	0.71
Pain (0-10)	4.6 (2.8)	4.8 (2.8)	0.42
MD-HAQ (0-3)	0.9 (0.6)	1.1 (0.5)	0.004
Medications			
Prednisone, %	41.8	51.5	0.06
NSAIDs, %	35.4	20.6	0.002
Methotrexate, %	54.5	60.6	0.30
Biologic, %	28.1	23.4	0.32
Values mean (SD) unless otherwise noted. *Rheumatic Disease Comorbidity Index			

Disclosure: B. R. England, None; **T. D. Mahajan**, None; **N. Singh**, None; **B. W. Coburn**, None; **G. W. Cannon**, Amgen, 2; **G. S. Kerr**, UCB, Janssen, 9; **A. Reimold**, None; **A. L. Gaffo**, None; **T. R. Mikuls**, Pfizer Inc, 5,Roche Pharmaceuticals, 2.

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Abstract Number: 235

Concurrence of Rheumatoid Arthritis and Calcium Pyrophosphate Deposition Disease: Description of a Cohort

Viktoriya Sabchyshyn[1] and Ann K. Rosenthal[2,3], [1]Medicine, Medical College of Wisconsin, Milwaukee, WI, [2]Medicine, Clement J. Zablocki VA Medical Center, Milwaukee, WI, [3]Medicine, Medical College of Wisconsin, Milwaukee, WI
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Background/Purpose: Calcium pyrophosphate deposition disease (CPDD) is an often un-recognized form of acute and chronic arthritis preferentially affecting the elderly. Some controversy exists about a possible association of rheumatoid arthritis (RA) with CPDD. While early studies suggested that RA and CPDD rarely overlapped, more recent data suggest that CPDD may be more common in patients with RA than in the general population. Possible explanations for this association include diagnostic confusion, higher imaging rates in patients with existing arthritis, or increased deposition of CPP crystals in the damaged RA cartilage. The purpose of our study was to describe a cohort of well-characterized patients with both CPPD and RA, and to generate possible hypothesis about the nature of the relationships between these diseases.

Methods: After approval from the local IRB, a cohort of patients with both RA and CPDD was collected from a university based rheumatology clinic. Patients were identified by participating providers and were included if they satisfied ACR criteria for RA and had CPDD noted radiographically or by synovial fluid crystal identification. A total of 21 such patients seen in the year 2015-2016 were selected for further analysis. Their records were reviewed and analyzed for age, sex, age of RA onset with the diagnosis based on ACR criteria, age of CPDD onset (using either crystal identification or chondrocalcinosis), pattern of joint involvement , joint surgeries, and laboratory values, including rheumatoid factor (RF), cyclic citrullinated peptide antibody (CCP), iron studies, PTH , and calcium levels.

Results: This cohort with both RA and CPDD had a mean age of 75 years, with a mean age of RA onset of 53 years. Two thirds were women and most were seropositive. Medications included typical DMARDs and biologics for 18/21 patients. One was on no medications, and two were on low dose prednisone. The mean age of CPDD onset was 69.9 years, with the mean RA disease duration prior to the onset of CPDD of 13.4 years. One patient had a simultaneous diagnosis of both RA and CPDD. The majority of the patients were diagnosed with CPDD based on the presence of chondrocalcinosis (15/21) and the most commonly involved joint was the knee. Other involved joints were typical of the joint pattern seen with CPDD. Three patients underwent joint replacement of the joints involved with CPDD. No patient had significant abnormalities of PTH levels or elevated iron levels. Calcium supplements were used in about 50% of patients.

Conclusion: The results of our study support existing data that CPDD tends to co-occur with RA after years of disease. The typical demographics of CPDD and its pattern of joint involvement are preserved in patients with RA who develop CPDD, and thus association is not likely to be due to diagnostic confusion. Further studies to understand the connection between these diseases are warranted. Table 1. Patient characteristics

Patient characteristics	
Mean age (years) at study onset	75 (range 57-92)
Women: Men	14:7
Mean age at RA diagnosis (years)	53 (range 20-85)
Mean age at CPDD diagnosis (years)	69.9 (range 47-86)
Mean RA duration prior to CPDD onset (years)	13.4 (range 0-36)
RF +/total available values	12/14
CCP+/total available values	8/8
Calcium supplementation	11
Joints involved in CPDD:	Knees: 14 Wrists: 6 Shoulder:1 Hips: 1

Disclosure: V. Sabchyshyn, None; **A. K. Rosenthal**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/concurrence-of-rheumatoid-arthritis-and-calcium-pyrophosphate-deposition-disease-description-of-a-cohort

Abstract Number: 236

Intrathoracic Manifestations of IgG4-Related Disease: Findings in a Cohort Study from North America

Sian Yik Lim[1], Micheal McInnis[2], Zachary Wallace[3], Vikram Deshpande[4,5], Sharma Amita[6] and John H. Stone[7], [1]Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Department of Radiology, Cardiothoracic Imaging, University of Toronto, Toronto, ON, Canada, [3]Division of Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [4]Pathology, Massachusetts General Hospital, Boston, MA, [5]Department of Pathology, Massachusetts General Hospital, Boston, MA, [6]Massachusetts General Hospital, Boston, MA, [7]Rheumatology Unit, Massachusetts General Hospital, Boston, MA

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SESSION INFORMATION

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The intrathoracic manifestations of IgG4-related disease (IgG4-RD) have been described in only a limited number of patients. No prior studies have provided detailed descriptions of the clinical, radiological, and pathology features of IgG4-related lung disease (IgG4-RLD) in patients from North America.

Methods: We reviewed a cohort of IgG4-RD patients to identify those with intrathoracic disease manifestations. The medical records of 143 subjects with clinicopathologic diagnoses of IgG4-RD were screened to determine which had undergone computed tomography (CT), positron emission tomography (PET), or magnetic resonance (MR) imaging of the thorax. All thoracic imaging studies were reviewed by two thoracic radiologists to document intrathoracic manifestations of IgG4-RD. Data pertaining to patient clinical characteristics, radiologic features, and pathology were collected and analyzed.

Results: Sixty-three subjects had undergone CT, PET, or MRI studies of the chest. Of these, 36 had intrathoracic manifestations consistent with IgG4-RD. Twenty-seven (75%) of these subjects had involvement of the lung, pleura, or both. Intrathoracic manifestations typically occurred in the setting of systemic IgG4-RD, but 75% of the patients with intrathoracic disease had no respiratory symptoms at the time of imaging. Mediastinal/hilar lymphadenopathy, detected in 25 patients (69%), was the most common intrathoracic imaging manifestation. Airway disease consisting of bronchial wall thickening was also commonly noted (50%, 18 patients). Pulmonary nodules were identified in 12 patients (33%). Interlobular septal thickening (28%, 10 patients) and subpleural reticulation (11%, 4 patients) were also observed. Airspace disease consisting of consolidation was also noted in six patients (17%) and ground glass opacity in ten patients (28%). Other intrathoracic manifestations included pleural disease (25%, 9 patients), pericardial disease (8%, 3 patients), vascular involvement (aortitis, pulmonary arteritis, coronary arteritis) (14%, 5 patients), and paravertebral masses (22%, 8 patients). Follow-up with regard to treatment response of intrathoracic findings (defined as improved/stable clinical or radiological findings) to prednisone was available in 12 patients. On prednisone, 8 of 12 patients (66.7%) demonstrated overall improvement or stability of their disease. Follow-up to rituximab treatment was available in 11 cases. On rituximab, ten out of 11 patients (90.1%) demonstrated improvement or stable disease.

Conclusion: In conclusion, the heterogeneity of intrathoracic IgG4-RD manifestations pose significant challenges in diagnosis. The radiologic findings in the lung, in particular, are more diverse than any other organ commonly affected by this disease. Many patients with IgG4-RLD are relatively asymptomatic despite substantial burdens of disease within the lung. The intrathoracic manifestations of IgG4-RD responded well to glucocorticoids and B cell depletion. Because effective treatment is available for IgG4-RD, detection and treatment of disease this asymptomatic stage may lead to better patient outcomes.

Disclosure: S. Y. Lim, None; **M. McInnis**, None; **Z. Wallace**, None; **V. Deshpande**, None; **S. Amita**, None; **J. H. Stone**, Genentech and Biogen IDEC Inc., 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/intrathoracic-manifestations-of-igg4-related-disease-findings-in-a-cohort-study-from-north-america

Abstract Number: 237

Characterization of Peripheral Lymphocyte Phenotype in Patients with IgG4-Related Disease

Satoshi Kubo[1], Shingo Nakayamada[2], Maiko Yoshikawa[1], Yusuke Miyazaki[1], Jidong Zhao[1], Ippei Miyagawa[3], Shigeru Iwata[4], Shintaro Hirata[1], Kazuhisa Nakano[3], Kazuyoshi Saito[3] and Yoshiya Tanaka[5], [1]The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [2]First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [3]University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [4]First Department of Internal Medicine, School of Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan, [5]University of Occupational and Environmental Health, Kitakyushu, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose:

IgG4 related disease (IgG4-RD) is a systemic disease that is characterized by the infiltration of IgG4secreting plasma cells and effector T cells into various organs. However, the characteristics and pathological role of immune cell subsets remain unclear. The aim of this study was to investigate the characteristic phenotype of immune cell subsets in IgG4-RD.

Methods:

Peripheral blood mononuclear cells were obtained from 16 patients with IgG4-RD, 4 with primary Sjogren syndrome (pSS) and 23 healthy donors (HD). The phenotype of circulating B cells, T cells were defined based on comprehensive flow cytometric analysis for human immune system termed 'the Human Immunology Project' by NIH/FOCIS. $CD4^+Bcl\text{-}6^+$ T follicular helper (Tfh) cells were detected by immunohistochemistry in salivary glands obtained by the biopsy.

Results:

Baseline characteristics of patients with IgG4-RD were (means); age 60 years old, symptom duration 19 months, serum IgG 2735 mg/dl, IgG4 694 mg/dl, CRP 0.7 mg/dl. The proportions of $CD3^+CD4^+CD45RA^-CCR7^-$ effector memory T cells, $CD3^+CD4^+CD45RA^+CCR7^-$ effector T helper cells increased, whereas naive T cells decreased in IgG4-RD, compared to HD and pSS. There was no difference in the proportion of well known helper T cell subsets (Th1, Th17, and Treg) between IgG4-RD, pSS and HD. On the other hand, the proportions of $CD4^+CXCR5^+ICOS^+$ Tfh and $CD19^+CD20^-CD27^+CD38^+$ plasmablasts were significant higher in IgG4-RD, compared to pSS and HD. Moreover, the proportion of Tfh in peripheral blood tended to be higher in patients whose Tfh more densely accumulated in the salivary gland. Among multiple immune cell subsets, the proportion of Tfh and that of plasmablasts were positively correlated, revealing statistical clustering. Of note, the percentage of plasmablasts was correlated with serum IgG levels. Furthermore, the proportion of plasmablasts and that of Tfh were higher in patients with extra glandular manifestations, compared to patients without them. After treatment with glucocorticoids, the proportion of plasmablasts and that of Tfh decreased with the improvement of clinical manifestations.

Conclusion: These results revealed that the higher proportion of Tfh cells and plasmablasts is characteristically observed in IgG4-RD. The frequency of Tfh was correlated with that of plasmablasts, and the Tfh/plasmablast axis contributed to

organ manifestation of IgG4-RD. Our findings would clarify the pathogenesis of IgG4-RD through the interaction between Tfh cells and plasmablasts and suggest a potential as the therapeutic target of this disease.

Disclosure: S. Kubo, Bristol-Myers Squibb, 5; **S. Nakayamada**, None; **M. Yoshikawa**, None; **Y. Miyazaki**, None; **J. Zhao**, None; **I. Miyagawa**, None; **S. Iwata**, None; **S. Hirata**, None; **K. Nakano**, None; **K. Saito**, None; **Y. Tanaka**, Bristol-Myers Squibb, MSD, Chugai, Mitsubishi-Tanabe, Astellas, AbbVie, Daiichi-Sankyo, 2,UCB Pharma, Mitsubishi-Tanabe, Abbott, AbbVie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Eli Lilly, Quintiles, MSD, Asahi Kasei, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characterization-of-peripheral-lymphocyte-phenotype-in-patients-with-igg4-related-disease

Abstract Number: 238

Identifying Immunoglobulin G4-Related Disease in Archived Pathological Specimens

Priya Prakash[1], Faisal Saeed[2], Slavica Bobic[3], Kirk Sperber[1], Julia Yegudin-Ash[1], Humayun Islam[2] and Amy Wasserman[4], [1]Medicine-Rheumatology, New York Medical College / Westchester Medical Center, Valhalla, NY, [2]Pathology, New York Medical College / Westchester Medical Center, VALHALLA, NY, [3]Medicine-Rheumatology, New York Medical College / Westchester Medical Center, valhalla, NY, [4]Medicine - Rheumatology, New York Medical College / Westchester Medical Center, VALHALLA, NY

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Immunoglobulin G4-related disease (IgG4-RD) is a recently defined entity characterized by a diffuse or mass forming inflammatory reaction rich in IgG4-positive plasma cells. Due to the fact that IgG4-RD was only fully described in the past decade, the epidemiology and prevalence of this disease is still not understood. It is likely that many pathology specimens prior to this time period were not recognized as IgG4-RD.The purpose of this study is to identify IgG4-RD in a by retrieving archived pathological slides originally diagnosed as idiopathic sclerosing masses, fibrosis or chronic inflammation in our tertiary care center.

Methods: This is a retrospective review of archived pathological slides at Westchester Medical Center from the years 2005-2015.We initially retrieved 105 cases using various search criteria from the Pathology database. Of these, 23 cases were included in this study, which fulfilled our final inclusion criteria of biopsy-proven idiopathic sclerosing masses, fibrosis and/or chronic inflammation. Immunohistochemical stains were performed on these specimens including IgG4. In this study we defined IgG4–RD as immunohistochemistry (IHC) > 10 IgG4+ plasma cells/ HPF and IgG4+/IgG ratio>40%, as well as the presence of characteristic histopathology architecture (dense lymphoplasmacytic infiltrate, storiform fibrosis and obliterative phlebitis) [1,2]. Other epidemiological data obtained were age, gender, organ involved and original tissue pathology diagnosis.

Results: Thirty-four percent of the biopsies (n=8/23) were reclassified as IgG4-RD. The most common original histological diagnosis for the eight reclassified specimens was chronic sialadenitis (Table Image) with submandibular gland most frequently involved, followed by parotid gland and retroperitoneal mass. The reclassified specimens were more common in females (5/8) and those above ages 60 (5/8).

Conclusion: This is the only known reported retrospective review study of archived pathological slides for IgG4-RD. The results highlight the ability to reconsider diagnosis, if needed, by performing appropriate immunohistochemical analysis on archived specimens to identify IgG4-RD. Chronic sialadenitis was the most common mimicker of IgG4-RD. **Reference :** 1. Deshpande V, et al. Consensus statement on the pathology of the IgG4-related disease. Modern Pathol. 2012; 25:1181–92 2. Khosroshahi A, et al. International Consensus Guidance Statement on the Management and Treatment of IgG4-Related Disease. Arthritis & Rheumatology, 2015; 67: 1688–1699.

Disclosure: P. Prakash, None; **F. Saeed**, None; **S. Bobic**, None; **K. Sperber**, None; **J. Yegudin-Ash**, None; **H. Islam**, None; **A. Wasserman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identifying-immunoglobulin-g4-related-disease-in-archived-pathological-specimens

Abstract Number: 239

Malignancies in Korean Patients with Immunoglobulin G4-Related Disease

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Several studies have implicated the increased risk of malignancy in patients with immunoglobulin G4-related disease (IgG4-RD). Hence, we first evaluated the risk and the type of malignancy in Korean patients with IgG4-RD.

Methods: Clinical and laboratory results of patients with IgG4-RD according to the comprehensive diagnostic criteria for IgG4-RD were retrospectively collected using Clinical Data Repository in Severance Hospital, Seoul, South Korea, between January 2006 and November 2015. One hundred and eighteen patients were included, and 35 were classified as having definite, 70 as possible and 13 as probable IgG4-RD. We compared baseline clinical and laboratory variables between patients with definite and those with possible/probable IgG4-RD. Also we calculated the standardized incidence ratios (SIRs) for malignancies using the data from the Korea Central Cancer Registry.

Results: The median age was 60.0 years old, and 91 patients (77.1%) were male. Malignancies were found in 12 of 118 patients (10.1%), and lymphoma (4, (25.0%)) was the most frequent malignancy related to IgG4-RD. Comparison of patients with definite and possible/probable IgG4-RD revealed that definite IgG4-RD patients had higher serum IgG level and frequent multiple organ involvement. Analysis of SIRs elucidated that overall incidence of malignancy was increased in patients with IgG4-RD compared to the general population (SIR 23.08 [95% CI 11.92, 40.31]), and the overall risk of SIRs was highest in Non-Hodgkin lymphoma (SIR 400.00 [95% CI 109.00, 1024.00]).

Conclusion: Our data showed that the increased risk of malignancy, especially lymphomas, was observed in Korean patients with IgG4-RD compared to general population.

Disclosure: S. S. Ahn, None; **J. J. Song**, None; **Y. B. Park**, None; **S. W. Lee**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/malignancies-in-korean-patients-with-immunoglobulin-g4-related-disease

Abstract Number: 240

The Relationship Between Serum Cholinesterase, Number of Organ

Involvement and Fibrotic Markers in Japanese Patients with IgG4-Related Disease

Satoshi Inotani[1], Yoshinori Taniguchi[2], Mitsuhiro Kawano[3], Natsuki Maeda[4], Hirofumi Nishikawa[5], Mio Matsuura[5], Kosuke Inoue[6], Taro Horino[5], Shimpei Fujimoto[5] and Yoshio Terada[6], [1]Rheumatic Disease Center, Kurashiki Medical Center, Kurashiki, Japan, [2]Endocrinology, Metabolism,Nephrology and Rheumatology, Kochi University, Kochi, Japan, [3]Division of Rheumatology, Kanazawa University Graduate School of Medicine, Kanazawa, Japan, [4]Endocrinology,Metabolism,Nephrology and Rheumatology, Kochi Medical School, Nankoku, Japan, [5]Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi Medical School, Nankoku, Japan, [6]Kochi University, Nankoku, Japan
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SESSION INFORMATION
Session Date: Sunday, November 13, 2016
Session Title: Miscellaneous Rheumatic and Inflammatory Diseases - Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate the relationship between serum cholinesterase (ChE) level, number of organ involvement, serum fibrotic markers and imaginational outcome in Japanese patients with IgG4-related disease (IgG4-RD).

Methods: The clinical symptoms, laboratory, pathological and FDG-PET/CT findings of Japanese patients with IgG4-RD (n=20) were assessed. Several laboratory data of IgG4-RD with multiple organs' involvements (IM) (n=10), IgG4-RD with limited organ's involvement (IL) (n=10), ANCA-associated vasculitis (AAV) (n=10) and Sjogren syndrome (SjS) (n=10) were comparatively examined. Furthermore, we studied the relationship between the numbers of organ involvement (NOI), several fibrotic markers (ELF score and serum Dkk-1) and imaginational outcome in IgG4-RD group.

Results: Serum ChE levels were significantly lower in IM group than IL, AAV and SjS groups. In total IgG4-RD cases, ChE levels inversely correlated with NOI and fibrotic score, and fibrotic score positively correlated with NOI. Finally, Dkk-1, one of Wnt inhibitors, levels in IM were significantly lower than IL and healthy subjects ($p<0.05$). Moreover, low level of Dkk-1 before and after treatment tended to predict the progression of organ atrophy.

Conclusion: The ELF score and serum Dkk-1 level might be clinically useful indicators of active fibrosis and the extent of IgG4-RD. Notably, continuous lower levels of Dkk-1 were related to organ atrophy and serum ChE levels could predict these phenomena.

Disclosure: S. Inotani, None; **Y. Taniguchi**, None; **M. Kawano**, None; **N. Maeda**, None; **H. Nishikawa**, None; **M. Matsuura**, None; **K. Inoue**, None; **T. Horino**, None; **S. Fujimoto**, None; **Y. Terada**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-relationship-between-serum-cholinesterase-number-of-organ-involvement-and-fibrotic-markers-in-japanese-patients-with-igg4-related-disease-2

Abstract Number: 241

Analysis of 84 Patients with IgG4-Related Disease and Malignancy

Kazunori Yamada[1,2], Ichiro Mizushima[2], Hideki Nomura[3] and Mitsuhiro Kawano[2], [1]Department of Advanced Research in Community Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan, [2]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan, [3]Department of General Medicine, Kanazawa University Hospital, Kanazawa, Japan
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Background/Purpose: IgG4-related disease (IgG4-RD) is a systemic inflammatory disease characterized by an elevated serum level of IgG4, infiltration of IgG4-positive cells in affected organs and fibrosis, and is becoming widely recognized. Recently, some reports have described the relationship between IgG4-RD and malignancy. However, patient background factors such as affected organs and ethnicity in these reports were different. Furthermore, only a few reports analyzed IgG4-RD patients with malignancy who were treated by rheumatologists. This prompted us to analyze the clinical features of IgG4-RD patients with malignancy.

Methods: Between November 2004 and September 2015, we retrospectively evaluated 84 patients with IgG4-RD in our hospital. We analyzed the prevalence of malignancy, relationship between the appearance of malignancy and diagnosis of IgG4-RD, type of cancer, and related factors. We compared mean age, gender, laboratory data, affected organs and therapy between the malignancy and non-malignancy groups. We also analyzed the standardized incidence ratio (SIR) of newly recognized malignancy after the diagnosis of IgG4-RD.

Results: There were 53 and 31 male and female patients, respectively with a mean age of 64.9 (range 41-81) years. Average observation period was 4.6 years. Mean serum levels of IgG and IgG4 were 2324±1040 mg/dL, 704±644 mg/dL. The mean number of affected organs was 2.8. The affected organs were as follows: salivary glands (53.6%), lacrimal glands (48.8%), lung (36.9%), retroperitoneum/ periaorta (29.8%), kidney (23.8%) and pancreas (21.4%). Twenty-one malignancies developed in 18 of 84 patients (21.4%), before the diagnosis of IgG4-RD in 11 malignancies in 11 patients (mean 4.3 years earlier, range 0.6-14 years), and after 10 malignancies in 9 patients (mean 1.7 years later, range 0-9 years). Colon cancer, prostate cancer and malignant lymphoma (ML) were seen in three patients each, and gastric, lung and renal cancers and in two patients each. ML developed after the onset of IgG4-RD in all patients. Only two patients developed malignancy in the same organ as affected by IgG4-RD. No significant differences were seen in mean age, gender, laboratory data, affected organs and the prevalence of corticosteroid therapy or the mean dose of prednisolone. We analyzed SIR of newly recognized malignancy after the diagnosis of IgG4-RD in 83 patients who were observed for more than one year. We found that SIR within one year of diagnosis of IgG4-RD was 4.62 and that of the total period of observation was 1.92.

Conclusion: The present study clarified the incidence, timing, type of malignancy in patients with IgG4-RD treated by rheumatologists. Malignancies developed at a high frequency. However, no specific characteristics were identified, making periodic screening for malignancy of particular importance.

Disclosure: K. Yamada, None; **I. Mizushima**, None; **H. Nomura**, None; **M. Kawano**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/analysis-of-84-patients-with-igg4-related-disease-and-malignancy

Abstract Number: 242

Clinical and Laboratory Features of IgG4-Related Retroperitoneal Fibrosis/Periarteritis in Japan: Retrospective Multicenter Study of 99 Cases

Ichiro Mizushima[1], Satomi Kasashima[2], Motohisa Yamamoto[3], Takako Saeki[4], Kazunori Yamada[5], Dai Inoue[6], Fuminori Kasashima[7], Yasushi Matsumoto[7], Eisuke Amiya[8], Kenji Notohara[9], Yasuharu Sato[10], Yoh Zen[11], Shigeyuki Kawa[12], Mitsuhiro Kawano[1] and Nobukazu Ishizaka[13], [1]Division of Rheumatology, Kanazawa University Hospital, Kanazawa, Japan, [2]Department of Clinical Laboratory and Pathology, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Japan, [3]First Department of Internal Medicine, Sapporo Medical University School of Medicine, Sapporo, Japan, [4]Department of Internal Medicine, Nagaoka Red Cross Hospital, Nagaoka, Japan, [5]Department of Advanced Research in Community Medicine, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Japan, [6]Department of Radiology, Kanazawa University Graduate School of Medical Science, Kanazawa, Japan, [7]Department of Cardiovascular Surgery, National Hospital Organization, Kanazawa Medical Center, Kanazawa, Japan, [8]Department of Cardiovascular Medicine, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [9]Department of Pathology, Kurashiki Central Hospital, Kurashiki, Japan, [10]Department of Pathology, Okayama University Graduate School of Medicine, Okayama, Japan, [11]Department of Diagnostic Pathology, Kobe University Graduate School of Medicine, Kobe,

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Session Time: 9:00AM-11:00AM

<span">

Background/Purpose: IgG4-related disease (IgG4-RD) is a recently recognized systemic inflammatory disorder that can affect many organs. It frequently causes retroperitoneal/periarterial lesions, which are referred to as IgG4-related retroperitoneal fibrosis/periarteritis (RF/P). However, clinical and laboratory features of this disease have not been well clarified. This study aimed to clarify the clinical and laboratory features of IgG4-related RF/P. <span">

Methods: We retrospectively evaluated clinical features including subjective symptoms, laboratory data, and imaging findings at diagnosis in 99 patients (pts) diagnosed with IgG4-related RF/P by experienced physicians. The diagnosis of this disease was made principally on the basis of the presence of consistent retroperitoneal/periarterial radiological findings, the fulfillment of the comprehensive diagnostic criteria or each set of organ-specific diagnostic criteria, and exclusion of other diseases. <span">

Results: Eighty-four pts were men, and 15 were women (average age 67.4 years). At diagnosis, 42.4% of pts presented subjective symptoms including pain (23.2%), fever (8.1%), and edema (4.1%). Allergic predisposition was found in 37.4% of pts. Hydronephrosis was detected in 21.2%. Current or past smoking was present in 65.4%.<span">IgG4-related other organ involvement was detected in 69.7%, and the average number of involved other organs was 1.9 (range: 0-8). Serologically, the average serum IgG4 level was 851 mg/dL (range: 59-3610), and 91.8% of pts had serum IgG4 > 135 mg/dL. Hypocomplementemia was observed in 24.4%. An elevated serum C-reactive protein (CRP) level (> 1 mg/dL) was found in 23.6%. The affected aorta/artery comprised mainly 8 thoracic aortas, 67 abdominal aortas, 50 iliac arteries, 8 mesenteric arteries, and 9 coronary arteries. Luminal dilatation of the affected lesions at diagnosis was observed in 26.3% of pts. On the other hand, 24.3% had retroperitoneal, periureteral, or renal pelvic lesions.<span"> Compared with pts without biopsy of the retroperitoneal/periarterial lesions, pts with it showed significantly lower serum IgG4 levels (643 vs 953 mg/dL, *P*=0.011) and IgG4/IgG ratio (23.9 vs 31.1 %, *P*=0.022), higher serum IgE (1,533 vs 543 IU/mL, *P*=0.020) and CRP levels (1.65 vs 0.56 mg/dL, *P*=0.025), lower incidence of other organ involvement (30.3 vs 86.4 %, *P*<0.001) and allergy (21.2 vs 45.5 %, *P*=0.027), and higher incidence of luminal dilatation (42.4 vs 18.2 %, *P*=0.015), pain (36.4 vs 16.7 %, *P*=0.043), and current smoking (58.8 vs 26.6 %, *P*=0.020). Multivariate logistic regression analysis indicated that the presence of other organ involvement [Odds ratio (OR); 0.011, *P*<0.001], serum CRP elevation (OR; 3.81, *P*=0.002), and the presence of iliac artery lesion (OR; 0.049, *P*=0.008) had an independent influence on the performance of biopsies of the retroperitoneal/periarterial lesions.

Conclusion: The present study clarified the clinical and laboratory features of IgG4-related RF/P, and suggested the possibility that biopsy of the retroperitoneal/periarterial lesions was avoidable in pts with other organ involvement.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-and-laboratory-features-of-igg4-related-retroperitoneal-fibrosisperiarteritis-in-japan-retrospective-multicenter-study-of-99-cases

Abstract Number: 243

Eosinophilic Angiocentric Fibrosis : A Mimic of Vasculitis in IgG4 Related Disease Spectrum

Raphaël Lecomte[1], Antoine Néel[2], Olivier Malard[3], Jérôme Martin[4], Michael Hénoux[3], Elisabeth Cassagnau[5] and Mohamed Hamidou[6,7], [1]Internal Medicine Department, CHU Nantes, Nantes, France, [2]Department of Internal Medicine,

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Miscellaneous Rheumatic and Inflammatory Diseases - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Eosinophilic angiocentric fibrosis (EAF) is a rare localized fibro-inflammatory lesion involving usually upper respiratory tract and the orbit. It could mimic ENT manifestations of systemic vasculitis particularly GPA. The diagnosis is based on characteristic histologic findings with a mixed inflammatory infiltrate with eosinophils and fibrosis around small caliber arteries with « onion-skin » pattern. Some autors suggest that EAF is a part of the spectrum of IgG4-related systemic disease.

Methods: We report 3 cases of histology-proven EAF. Demographic, clinical, biological, radiologic and histological features are examined. The 3 patients had a 18-fluorodeoxyglucose positron emission tomography (FDG PET) and evaluation of circulating total plasmablast count (CD19low, CD38+, CD20-, CD27+).

Results: table Two females and one male patients were aged from 29 to 50 years. The disease involved the nasal cavity in two cases and the subglottic area in the third case. The demographic, biological and clinical features (table) were consistent with reports of EAF published previously. All cases demonstrated a dense fibrotic stroma with a perivascular onion skin type pattern and an inflammatory infiltrate with eosinophils, lymphocytes and plasma cells. No vasculitis, granuloma formation or necrosis were identified in any of these cases. All patients had a radiological evaluation with a computed tomography (CT) and a FDG-PET. CT evaluations showed expanding soft tissue masses into the maxillary sinus and anterior nasal cavity in 2 cases and soft tissue thickening in the sub-glotting region of the larynx in one case. There was bone destruction in one case. The FDG-PET showed an enhanced FDG uptake of the EAF lesion. No other abnormal hypermetabolic foci were detect on this exam. The serum IgG4 concentration was normal in the 3 cases (from 23 to 50 mg/dL). The circulating plasmablast count was increased in 2 cases (6728/mL et 2958/mL) and normal in the third patient (508/mL). Two patients received glucosteroids associated in one with colchicin without efficiency. Patients with sinonasal lesion underwent partial surgical excision with relapse in the 2 cases. Patient with the subglottic stenosis was improved by endoscopic dilatation.

Conclusion: EAF is an unrecognized entity mimicking a necrotizing vasculitis limited to upper respiratory tract. FDG PET confirms that EAF is a limited pathology without extra-ENT involvment. The anatomopathology examination by an experienced pathologist is the cornerstone of the diagnosis. Despite some differences, EAF share many characteritics with IgG4 related disease like clinical presentation, similar histologic pattern and increase of plasmablast count.

	Patient 1	Patient 2	Patient 3
Sex/Age (years)	F/34	M/50	F/29
Manifestation	Broad nasal ridge	Saddle nose deformity	Erosive rhinitis/suglottic rhinitis
Blood cell count	Normal	Normal	Normal
Eosinophils (mL)	240	180	120
CRP (mg/L)	<5	3.2	<5
Polyclonal hyperglobulinemia (g/L)	Yes/14.6	Yes/15.0	Yes/19.3
ANCA	Negative	Negative	Negative
Antinuclear antibodies	Negative	>1/2560 without specificity	1/640 without specificity
C3/C4 (g/L)	0.79/0.17	1.13/0.23	1.22/0.19
Serum IgG4 (mg/dL)	23	31	50
Plasmablast count (/mL)	672	508	2956
FDG PET uptake	Limited	Limited	Limited

Disclosure: R. Lecomte, None; **A. Néel**, None; **O. Malard**, None; **J. Martin**, None; **M. Hénoux**, None; **E. Cassagnau**, None; **M. Hamidou**, None.

Abstract Number: 244

Leflunomide and Glucocorticoids Combination Therapy for the Induction and Maintenance of Remission in Patients with IgG4-Related Disease

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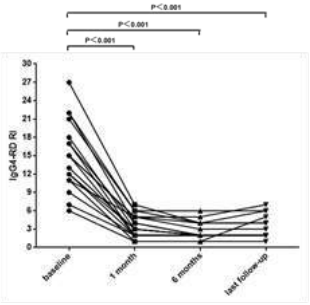
Background/Purpose: Good response could be observed after applying glucocorticoids (GCs) in patients with IgG4-related disease (IgG4-RD), however, the risk of disease relapse was reported relatively high during or after GCs tapering. Recurrent relapses may lead to more damages precipitated in involved organs and high cumulative dose of GCs correlating to severe adverse effects. Hence, it¡¯s important to find an effective immunosuppressive agent (IM) to maintain remission in IgG4-RD. However, to date, studies about IMs in IgG4-RD are all exploratory and the existing evidences are far from enough to identify which IM is more effective. This study was conducted to identify the efficacy and safety of leflunomide (LEF) combined with GCs in treating IgG4-RD.

Methods: Data of patients diagnosed as IgG4-RD between November 2012 and November 2015 were summarized retrospectively. Only patients treated by LEF plus GCs and had been followed up with more than 3 visits and 6 months were enrolled. During all subsequent visits, clinical symptoms, laboratory and imaging findings, changes in treatment, LEF-related adverse events and disease activity reflected by IgG4-RD Responder Index (IgG4-RD RI) were obtained. All available medical records were reviewed combined with additional information through telephone follow-up. Clinical outcomes were assessed by IgG4-RD RI as well as laboratory and imaging examinations.

Results: Eighteen patients including 14 untreated patients and 4 retreated patients with relapsing disease were enrolled. The mean (S.D.) onset age was 54.0 (9.6) years with a male to female ratio of 2.6:1. The mean (S.D.) follow-up period was 11.1 (6.9) months. All patients had active disease with mean (S.D.) IgG4-RD RI of 15.0 (5.6) at baseline and obtained disease response at 1 month. At the last follow-up, the mean (S.D.) IgG4-RD RI was declined to 3.1(1.7) and was 2.5(1.2) in patients without relapse. The mean (S.D.) serum level of IgG4 was declined from 1451.2(1956.8) mg/dl to 254.5(321.1) mg/dl. GCs were all tapered to maintenance dose at 6 months and the mean (S.D.) dose was 7.3 mg/d at the last follow-up. 66.7% (12/18) and 61.1% (11/18) patients were in remission at 6 months and the last follow-up, respectively. 16.7% (3/18) patients relapsed in the clinical course. Adverse effects (AEs) were observed in 1 patient with elevated hepatic enzymes and 1 patient with rashes. These AEs resolved immediately after withdrawn of LEF.

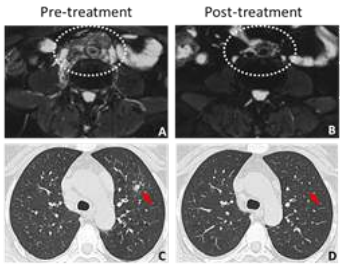
Conclusion: LEF and GCs combination therapy is effective in treating IgG4-RD with a few reversible adverse effects, and LEF is a promising steroid-sparing agent for IgG4-RD.

Figure 1 IgG4-RD RI during the follow-up period



IgG4-RD Responder Index (IgG4-RD RI) decreased at 1 month, 6 months and the last follow-up compared with baseline.

Figure 2 Imaging findings of two patients with IgG4-RD



(A and B) MRI T_2-weighted(T_2W) images of retroperitoneum in a 53-year-old man (Patient 10). A decrease in dimension of retroperitoneal fibrosis (white circle) was observed after treatment for 6 months. **(C and D)** Thin-section pulmonary CT scans of a 48-year-old woman (Patient 17). The round shaped lesion (red arrow) disappeared after treatment for 6 months.

Disclosure: Y. Wang, None; **D. Gao**, None; **G. Luo**, None; **K. Li**, None; **Z. Zhao**, None; **J. Zhu**, None.

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Abstract Number: 245

Efficacy of Cyclophosphamide Therapy in Idiopathic Retroperitoneal Fibrosis in a Retrospective Monocentric Analysis

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Background/Purpose: Ormond's disease (idiopathic retroperitoneal fibrosis ,IRF) is a rare disease. Main clinical symptom is compression of the ureters leading to renal failure. A majority of patients is believed to have IgG4-related disease causing the symptoms. Until today no therapy is approved for the treatment of IRF. In our center cyclophosphamide bolus therapy over 6 months is used in treating these patients. Only few data is available on treatment approaches for IRF and even less differentiating between IgG4RD and non-IgG4-RD IRF

Methods: Patient data of the last 15 years from our center were evaluated concerning, clinical, serological and radiological response to cyclophosphamide therapy. Patients were differentiated according to the diagnosis of IgG4RD in available biopsies.

Results: In a total of 20 patients 7 patients could be diagnosed with having IgG4RD according to the biopsy, 4 were negative and 1 biopsy remained unclear. For 8 patients no biopsy was available. IgG4 negative patients had a significant higher volume of the retroperitoneal mass than positive and unclear patients at the time of diagnosis. The volume of the

retroperitoneal mass was significantly reduced under therapy only in the group of IgG4RD positive and unclear patients (P=0.003 and 0.0039). Renal function (creatinine) was impaired in all three groups initially and no significant improvement could be observed in any of the groups under therapy. Unfortunately, IgG4 serum levels were only available for very few patients therefore follow up was impossible.

Conclusion: In about 50% of the patients a significant reduction of the retroperitoneal mass in IRF could be observed under treatment with cyclophopshamide bolus therapy, without improvement of renal function in this time frame. IgG4RD negative patients might profit less from the therapy with cyclophosphamide. Prospective studies in larger cohorts and with a longer follow-up are need to get a more accurate idea about the efficacy in IRF.

Disclosure: B. F. Hoyer, None; **C. Kumpert**, None; **M. Makowski**, None; **B. Rudolph**, None; **U. Schneider**, None; **G. R. Burmester**, AbbVie, Bristol-Myers Squibb, MedImmune, Merck, Pfizer, Roche, and UCB, 2,AbbVie, Bristol-Myers Squibb, MedImmune, Merck, Pfizer, Roche, and UCB, 5,AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Roche, and UCB, 8; **F. Hiepe**, None.

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Abstract Number: 246

Efficacy of Colchicine and IL-1 Inhibitors in Amyloidosis Associated with Familial Mediterranean Fever: A Retrospective Analysis

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Background/Purpose: Familial Mediterranean fever (FMF), the most common form of hereditary autoinflammatory diseases, is associated with increased risk for secondary (AA) amyloidosis. We herein aimed to investigate the features of FMF patients with amyloidosis with respect to their responses to current therapies.

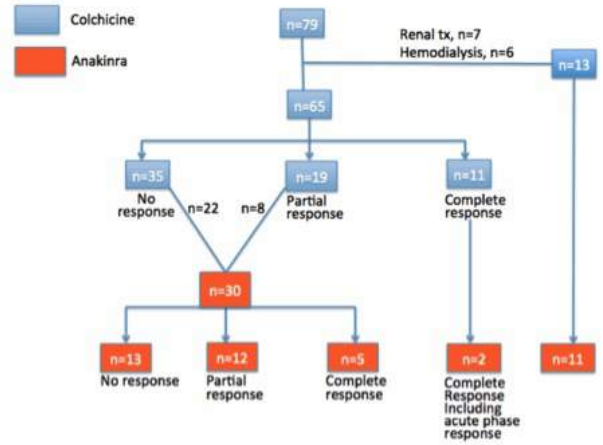
Methods: We enrolled FMF patients with amyloidosis who were regularly followed-up for at least 6 months between 1978 and 2015 into the study. Starting times for colchicine, anakinra or canakinumab and treatment responses were recorded using a standard form. Proteinuria (spot urine protein/creatinine ratio) and C-reactive protein (CRP) levels were measured in every three months during follow-up. Partial response was defined as ³ 50% decrease in baseline proteinuria accompanied by a normal serum creatinine level, whereas complete response was defined as <0.3 gr/d baseline proteinuria and stable serum creatinine. Chi-square test was used to test associations between treatment response and CRP concentrations.

Results: We identified 79 FMF patients with confirmed AA-type amyloidosis, and all were on colchicine treatment. Their demographic features are shown in Table 1. Mean time to diagnosis after the first symptom was 10 years. Patients were evaluated for partial and complete response after mean follow-up period of 66±85 months. Response to full-dose colchicine was observed in 30/65 patients [partial response in 19 (29%), complete response in 11 (17%)]; and 54% was non-responder to colchicine. Anakinra was added to treatment in 22 patients with inadequate response to colchicine, which resulted in partial response in 12, and complete response in 2. Eight patients with partial response to colchicine also received anakinra for better control of attacks and/or elevated acute phase response, and a complete response was achieved in 3 patients. In 3 patients, anakinra was switched to canakinumab because of local injection site reaction (1

patient) and persistence of proteinuria (2 patients). Among those, two patients had partial response, and another underwent hemodialysis due to progressive kidney failure. No significant association was observed between normalized CRP levels and response to treatment with respect to proteinuria and creatinine levels (colchicine; p=0.67, anakinra or canakinumab;p=0.82). No serious infection requiring hospitalization was detected in association with IL-1 blockade.

Table 1. Demographic features of FMF patients with amyloidosis.

Male/Female	40/39
Age of onset (mean±SD)	16±12(2-68)
Age of diagnosis (mean±SD)	27±13(7-70)
Family history of FMF	47%
Time to diagnosis(mo)	121±136(2-576)
Family history of amyloidosis (%)	18%
Arthritis at presentation (%)	60%
MEFV variations (n=46)	M694V,68% V726A,10% M680I,15% Others,7%
IL-1 inhibitors n(%)	43(54%)
Patients on hemodialysis	7(9%)
Renal Transplantation n(%)	17(21%)
High CRP levels in attack-free periods n(%)	31(39%)



Conclusion: Amyloidosis still remains as an important complication of FMF, but patients with amyloidosis comprise a heterogeneous group including those ineffective treated with or refractory to colchicine. Therefore, it is possible to observe a satisfactory response to full-dose colchicine in an important proportion of patients. On the other hand, IL-1 inhibitors, both anakinra and canakinumab, seem to be an effective and safe option for those patients with an inadequate response to full-dose colchicine or with an intolerance to effective doses of colchicine. Efficacy of strict control of inflammatory response by IL-1 blockade on amyloidosis-associated clinical findings such as proteinuria and renal failure needs to be explored in longer series.

Disclosure: B. Toz, None; **S. Tecer**, None; **E. Oğuz**, None; **M. Erdugan**, None; **B. Artim-Esen**, None; **S. Kamali**, None; **M. Inanc**, None; **L. Ocal**, None; **B. Erer**, None; **A. Gul**, None.

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Abstract Number: 247

ANTI-Interleukin 1 Therapy in FMF Amyloidosis: A Single Center Experience

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Background/Purpose: Recently there is increasing number of reports pointing out the efficacy of anti-interleukin 1(anti-IL1)therapy to control AA amyloidosis secondary to autoinflammatory diseases. Here we report our experience in IL-1 blockade in patients with AA amyloidosis secondary to FMF.

Methods: Twenty three FMF patients withhistologically proven secondary AA amyloidosistreated with anti-IL1 agents (canacinumab and anakinra). Creatinine, creatine clearance, 24-hour urine protein, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)parameters were measured before and throughout the treatment period in order to evaluate the response. One patient on anakinra for less than a month, therefore the renal functions were not evaluated for her. Patients were closely monitored and adverse events were also reported.

Results: Twenty three (12 female, 11male) patients with AA amyloidosis secondary to FMF who were also on colchicine (mean dose: 1.86±0.58mg/day) were started on anti-IL1 agents (11 on canakinumab, 16 on anakinra).Four patients using Canakinumab were previously on Anakinra. The mean age was 42.5±10.82 years, while the mean duration of FMF was 24.3±8.2 years. The mean follow-up period on anti-IL1 was 14.9±11.5 months (14.5±13.5months on anakinra; 15.45±9.43 months on canakinumab). Fifteen patients are still on anti-IL-1 therapy (9 on anakinra, 6 on canakinumab). Renal functions remained stable after therapy for 9 out of 15 patients (24-hour urine protein from 5754,6±7787.6mg/dlto 4205.286±5717.645 mg/dl, creatinine clearance from 63.41±25.36 to 71.08±31.66 and creatinine from 1.44±0.46 to 1.62±0.69), while CRP (from 21.34±26.40 mg/L to 18.94±32.74 mg/L) and ESR (from 67.44±34.12 mm/h to 34.5±29.16 mm/h) decreased.Renal functions and acute phase reactants improved with therapy in 6 patients (24-hour urine protein from 5153.33±6432.11 mg/dlto1051.733±4571.181 mg/dl;creatinine clearance from 100,76±54.03 to 81.68±40.23 and creatinine from 1.16±0.61 to 1.11±0.60), CRPfrom 22.31±24.66 mg/Lto 2.82±10.65 mg/L; ESR from 64.16±29.73 mm/hto 13.00±14.52 mm/h).Among patients remained stable during anti-IL-1 therapy, 2 were on hemodialysis. In one patient with renal transplantation, amyloidosis was evident in the transplanted kidney and anakinra was introduced and she remained stable.Global patient assessment score of the whole group decreased significantly (from 7.04±3.07 to 1.6±1.94) with IL-1 blockade. Among patients on anakinra, in 5 patients therapy was terminated due to increased proteinuria in 3 and allergic reaction in 2. One patient recieving anakinra with end-stage renal insufficiency died in another center. Treatment was stopped in 5 patients on canakinumab because of increased proteinuria in 3,lichen planus in 1. One patient was lost to follow up despite improvement who was admitted back to the clinic 7 months later with lung adenocarcinoma. A switch from anakinra to canakinumab was made in 4 patients due to allegic reaction in 1 and non-response in 3.

Conclusion: Anti-IL1 therapy can improve or stabilize renal functions in patients with AA amyloidosis secondary to FMF.The efficacy and safety of anti-IL1 therapy in this group of patients in the long-term needs further research.

Disclosure: S. Ugurlu, None; **B. Ergezen**, None; **H. Ozdogan**, None.

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Abstract Number: 248

Disease Severity and High Attack Frequency Under Colchicine Treatment Is Associated with Increased Carotid Intima Media Thickness in FMF

Murat Karabacak[1], Ali Ugur Unal[2], Gulsen Ozen[3], Zeynep Erturk[4], Yasemin Yalcinkaya[3], Zeynep Komesli[1], Nevsun Inanc[3], Pamir Atagunduz[3] and Haner Direskeneli[5], [1]Marmara University Faculty of Medicine, Istanbul, Turkey, [2]Marmara University, School of Medicine, Rheumatology, Istanbul, Turkey, [3]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [5]Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey

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Background/Purpose: Cardiovascular (CV) risk assessment is infrequently performed in Familial Mediterranean Fever (FMF), an autoinflammatory disorder with only acute attacks of inflammation. As a surrogate marker of atherosclerosis, carotid intima media thickness (cIMT) is shown to be increased in FMF in previous studies, but the association of cIMT with traditional cardiovascular risk scores is not explored. In this study we aimed to investigate cIMT in FMF and show its relationship to traditional cardiovascular risk scores, disease severity and attack frequency.

Methods: In this cross sectional study, consecutive FMF patients (n=60, M/F: 30/30, mean age= 36.5±9.7 years) were compared to healthy controls (n=60, M/F: 29/31, mean age= 36.8±8.7 years). 10-year CV risk was assesed by 2013 American College of Cardiology/American Heart Association (ACC/AHA) CV risk estimator. FMF severity score-2 (F-SS-2) score was implemented to FMF patients to determine disease severity. Genetic mutations of FMF patients were also recorded.

Results: M694V was positive in 63% of FMF patients, either homozygote, heterozygote or compound heterozygote. 48% of FMF patients had mild, 22% had intermediate and 30% had severe disease according to F-SS-2. Groups were similar in demographic, clinical and biochemical parameters, except for sedimentation rate which was 10±4 mm in control group and 18±11 mm in the FMF group ($p< 0.001$). ACC/ AHA risk scores were similar in both groups: 2.5±2.9) in FMF patients vs. 2.4±2.1 in controls ($p= 0.93$). However, median cIMT was significantly higher in the FMF group compared to controls (FMF: 0.59 mm (IQR= 0.17) vs Controls: 0.52 mm (IQR= 0.13), $p= 0.002$). Patients with severe disease had a higher mean cIMT of 0.62±0.09 mm than those with non-severe disease (0.57±0.09 mm ($p= 0.045$). In multiple regression analysis for all participants, only age and CRP positivity are significantly associated with CIMT ($p< 0.001$ and $p= 0.001$ respectively). In the FMF group, attack frequency while on colchicine treatment (rho= 0.40, $p= 0.002$) correlated with CIMT, whereas attack frequency before starting colchicine was not associated ($r= 0.08$, $p= 0.53$).

Conclusion: cIMT was significantly increased in FMF, but traditional cardiovascular risk scores failed to reflect this change. Attack frequency, which may reflect unsuppressed inflammation, may contribute to the increased cIMT. Therefore, our data suggests that FMF patients, especially those with high attack frequency and severe disease, should be monitored more closely for ischemic CV disease. Further studies are also required to clarify whether better disease control leads to improved cIMT levels.

Disclosure: M. Karabacak, None; **A. U. Unal**, None; **G. Ozen**, None; **Z. Erturk**, None; **Y. Yalcinkaya**, None; **Z. Komesli**, None; **N. Inanc**, None; **P. Atagunduz**, None; **H. Direskeneli**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/disease-severity-and-high-attack-frequency-under-colchicine-treatment-is-associated-with-increased-carotid-intima-media-thickness-in-fmf

Abstract Number: 249

MiR-204-3p Associates with an Increased Level of IL-6 in Familial Mediterranean Fever By Targeting the PIK3 Signaling Pathway

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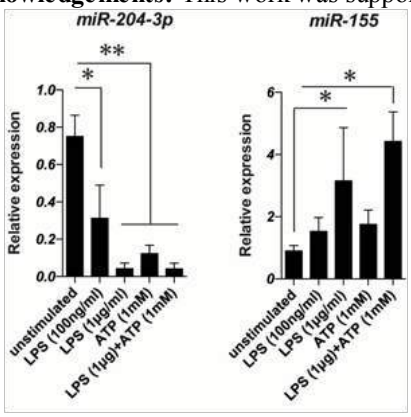
Background/Purpose: Familial Mediterranean fever (FMF) is caused by a number of mutations of the MEFV gene, coding for a protein named pyrin that acts as a major regulatory component of the inflammasome. Accumulating evidence has shown the association of microRNAs (miRNAs) with the development of inflammatory disorders (1). However, little is known about the precise role of miRNAs in FMF. **Objective:** The aim of this study was to identify a serum miRNAs profile and potential biomarkers in FMF and clarify their gene targets for understanding the pathogenesis of autoinflammatory diseases.

Methods: We performed miRNA microarray (Toray 3D-gene miRNA oligo chips) to screen miRNAs in the serum from FMF in attack and in remission. We subsequently examined the effect of candidate miRNAs on cytokine production by using THP-1 cells. Macrophages derived from THP-1 cells were transfected with miRNA mimics or miRNA inhibitor and stimulated with LPS+ATP for 24 hours. We collected the supernatants for the quantification of inflammatory cytokine production. To identify the target genes, we overexpressed its miRNA and performed Agilent expression microarray (SurePrint G3 Human GE 8x60K).

Results: We found that miR-204-3p was greatly decreased in the serum from FMF patients in attack. In vitro study, the expression of miR-204-3p was suppressed by ATP+LPS stimulation in macrophages derived from THP-1 cells. Inhibition of miR-204-3p significantly induced the production of IL-6 whereas overexpression of miR-204-3p inhibited its production. Bioinformatic analysis showed that miR-204-3p is predicted to target genes implicated in Toll like receptor pathway through regulation of PIK3 signaling.

Conclusion: These data suggest that serum miR-204-3p has a potential as a useful biomarker among patients with FMF and that miR-204-3p plays a critical role as a suppressor to regulate the production of IL-6 by targeting PIK3 signaling pathway. **References:**

1. Singh RP, Massachi I, Manickavel S, et al. The role of miRNA in inflammation and autoimmunity. Autoimmun Rev. 2013 Oct;12(12):1160-5. **Acknowledgements:** This work was supported by the Japan Agency for Medical Research and Development (No. 15657398).



Disclosure: T. Koga, None; **K. Migita**, None; **A. Yachie**, None; **Y. Ueki**, None; **K. Agematsu**, None; **J. Masumoto**, None; **K. I. Yoshiura**, None; **K. Eguchi**, UCB Pharma, 5; **A. Kawakami**, None.

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Abstract Number: 250

Application of the 2016 European Leage Against Rheumatism (EULAR)

/American College of Rheumatology (ACR)/Paediatric Rheumatology International Trials Organisation (PRINTO) Classification Criteria of Macrophage Activation Syndrome in Patients with Adult Onset Still's Disease

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SESSION INFORMATION

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Session Title: Miscellaneous Rheumatic and Inflammatory Diseases - Poster I

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Background/Purpose: Macrophage activation syndrome (MAS) is acute systemic inflammation arising in the context of various autoimmune and autoinflammatory conditions, which is often life-threatening. In 2016, EULAR/ACR/PRINTO Collaborative Initiative group developed new criteria for the classification of MAS in patients with systemic onset juvenile idiopathic arthritis (JIA) (1). Adult onset Still's disease (AOSD) is considered to be an adult counterpart of systemic onset JIA. Therefore, we evaluated the clinical significance of 2016 EULAR/ACR/PRINTO classification criteria for MAS in patients with AOSD.

Methods: We retrospectively reviewed the Severance Hospital's electronic medical records of patients hospitalized with fever and AOSD. From 2005 to 2015, 64 patients were identified. According to the 2016 classification criteria for MAS, patients were defined as having MAS when they had fever, ferritin level of over 684, and fulfilled more than 2 of the following 4 criteria: platelet count ≤181,000, AST > 48 units/L, triglycerides > 156 mg/dL, fibrinogen ≤ 360 mg/dL. Clinical and laboratory data of patients with and without MAS were compared using the two-tailed Student's t-test or the chi-square test. Delta ferritin level was calculated by dividing the maximum level of ferritin level during the admission by i) the initial ferritin level on the date of MAS diagnosis for patients with MAS or ii) on the date of admission in patients without MAS. Univariate and multivariate analysis were used to evaluate factors associated with in-hospital mortality.

Results: Among 64 patients with AOSD, 36 patients (56.2%) were classified as MAS. There were 12 deaths (33.3%) in patients with MAS while there was no death (0.0%) in patients without MAS ($p<0.001$). Comparison of baseline characteristics between patients with and without MAS showed differences in gender, platelet, ESR, AST, ALT, total protein, lactate dehydrogenase (LDH), fibrinogen, triglyceride and ferritin levels (Table 1). In patients with MAS, total protein ($p=0.044$) and delta ferritin≥50% ($p=0.007$) was significantly associated with in-hospital mortality. Multivariate analysis with variables with p-values < 0.05 in univariate analysis revealed that delta ferritin≥50% was associated with in-hospital mortality (OR 8.097, 95% confidence interval, 1.422-46.097, $p=0.018$) (Table 2).

Conclusion: These findings suggest that MAS is a frequent complication in patients with AOSD and is associated with in-hospital mortality. Furthermore, in patients with MAS, delta ferritin levels of over 50% were also associated with in-hospital mortality. Although early recognition is important for the proper management of MAS, there has been no single specific test to detect MAS. We demonstrated that the new 2016 classification criteria, composed of 5 simple laboratory tests, are significantly associated with poor outcome in febrile AOSD. Therefore, patients with AOSD should be monitored carefully for development of MAS based on 2016 EULAR/ACR/PRINTO classification criteria.

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Abstract Number: 251

Persistent Pruritic Skin Lesions with Dyskeratotic Cells in Upper Layer of Epidermis Are Specific and Associated with High Levels of Serum IL-18 in Adult-Onset Still's Disease

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Background/Purpose: Adult-onset Still's disease (AOSD) is an acute and systemic inflammatory disorder that is characterized by high spiking fever, evanescent rash, arthralgia/arthritis and hyperferritinemia. However, recent reports showed that not only typical evanescent salmon-colored rash but also atypical skin lesions, persistent pruritic papules and plaques, could be associated with AOSD. The atypical skin lesions are histologically characterized to have the dyskeratotic cells in upper layer of epidermis.

Methods: We retrospectively assessed clinical and histological findings of skin lesions including persistent pruritic skin lesions in Japanese patients with AOSD (n=7). Moreover, we compared serological and histological finding of AOSD with that of dermatomyositis (DM) (n=6), drug eruptions (DE) (n=6), and Graft versus Host disease (GVHD) (n=6).

Results: AOSD with persistent pruritic skin lesions (n=5) histologically showed dyskeratotic cells only in upper layer of epidermis and horny layer without intraepidermal infiltrations of inflammatory cells. These dyskeratotic cells were positive by TUNEL and ssDNA stainings, suggesting apoptotic cells. AOSD with evanescent rash (n=2) histologically showed no dyskeratosis. On the other side, the pathological findings of DM (n=6), DE (n=6) and GVHD (n=6) had dyskeratotic cells in all layers of epidermis with inflammatory cells infiltrations. Notably, all of AOSD with atypical skin lesions (n=5) had very high levels of serum IL-18 (74,300~307,000 pg/ml).

Conclusion: AOSD with persistent pruritic skin lesions is characterized and specific by prominent epidermal apoptosis, especially involving the upper layers. Therefore, it could play a pivotal role to recognize the atypical skin lesions of AOSD for correct early diagnosis. Finally, the high levels of serum IL-18 might be related with epidermal apoptosis of keratinocyte in AOSD.

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Abstract Number: 252

Cytokine Profiles of Korean Patients with Adult Onset Still's Disease Treated with Biologic Agents

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Background/Purpose: Adult onset Still's disease (AOSD) is a rare inflammatory disorder of unknown etiology. Several studies have reported that pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-18, tumor necrosis factor (TNF)-α, and interferon (INF)-γ, are involved in the pathogenesis of AOSD. Refractory AOSD patients have been treated successfully with anti-cytokine biologics. Herein, we analyzed cytokines to investigate predictors for therapeutic response of biologic drugs in refractory AOSD.

Methods: Twenty two AOSD patients who treated with anti-TNFα agents or anti-IL-6 receptor agent were recruited from a university hospital for rheumatic diseases in Korea. The dosages of anti-TNFα (infliximab in 18 patients, etanercept in 4, and adalimumab in 3) and tocilizumab in 12 were same as those of rheumatoid arthritis. Serum cytokines (TNFα, IL-1β, IL-6, IL-8, IL-17α, and INF-γ) and IL-2 receptor α were analyzed by multiplex flowcytometry. A good response to biologic agents was defined as decreased modified Pouchot score more than 2 score compared to initial treatment of biologic agents. A no response to biologic agents was defined as no decrease of modified Pouchot score. We used the Mann-Whitney test for continuous variable.

Results: Seven (36.8%) patients showed good response to anti-TNFα inhibitors and 3 (13.6%) patients showed partial response. Nine (47.4%) patients did not respond to anti-TNFα inhibitors. Three (25%) patients showed good response to tocilizumab (TCZ), 4 (33.3%) showed partial response, and 5 (41.7%) showed no response. At starting time point of anti-TNFα inhibitors, levels of TNFα, IL-1β, IL-6, and IFNγ in no responders was higher compared to those with good response, but without statistically significant differences (Table 1). At starting time point of TCZ, conversely, the levels of TNFα and IL-6 in no responders was lower compared to responders including good and partial response (Table 2). We didn't raise the dosage of infliximab in no responders, nine patients, in whom TCZ was used as second biologic therapy. Of those, five (55.6%) patients showed improvement in clinical and laboratory findings.

Conclusion: This study showed that AOSD patients who were refractory to biologic agents might have distinct cytokine profiles. Therefore, dosage and sort of biologic agents in AOSD patients might be individualized according to pre-treatment cytokine profiles.

Table 1. Cytokine levels of AOSD patients before anti-TNFα therapy.

	Total (n = 19)	Good response (n = 7)	No response (n = 9)	p
TNFα (pg/mL)	11.19 (20.06)	6.34 (9.71)	14.96 (25.43)	0.632
IL-1β (pg/mL)	6.23 (13.25)	2.32 (2.70)	9.65 (17.79)	0.600
IL-2Rα (pg/mL)	676.47 (593.44)	971.12 (790.92)	447.30 (236.86)	0.101
IL-6 (pg/mL)	54.52 (126.31)	45.34 (77.11)	61.66 (159.13)	0.427
IL-8 (pg/mL)	41.96 (73.61)	69.19 (100.55)	20.77 (37.73)	0.396
IL-17α (pg/mL)	0.77 (1.01)	0.50 (0.32)	0.97 (1.32)	0.745
IL-18 (pg/mL)	42,339.33 (60,876.27)	65,983.73 (79,663.30)	21,650 (30,396.91)	0.165
INFγ	48.27 (117.13)	11.99 (8.87)	76.49 (153.67)	0.708

Values are the mean (SD) unless otherwise indicated. Of 19 AOSD patients, three was partial response. Mann-Whitney test

Table 2. Cytokine levels of AOSD patients before anti-IL-6 receptor therapy.				
	Total (n = 12)	**Response (n = 7)**	**No response (n = 5)**	**p**
TNFα (pg/mL)	12.70 (25.63)	13.80 (33.51)	**11.17 (10.83)**	0.048
IL-1β (pg/mL)	9.29 (19.92)	10.40 (25.00)	7.35 (8.10)	0.927
IL-2Rα (pg/mL)	559.34 (329.61)	611.73 (398.97)	485.99 (220.16)	0.755
IL-6 (pg/mL)	31.15 (32.71)	39.38 (32.61)	**19.63 (32.61)**	0.268
IL-8 (pg/mL)	22.90 (31.92)	23.90 (40.28)	21.51 (19.07)	0.343
IL-17α (pg/mL)	1.29 (1.00)	1.01 (0.53)	1.68 (1.42)	0.639
IL-18 (pg/mL)	39,062.61 (43,665.18)	49,258.95 (45,788.29)	23,768.10 (41,301.81)	0.171
INFγ	54.55 (94.18)	56.73 (115.54)	51.49 (65.94)	0.639
Values are the mean (SD) unless otherwise indicated. Mann-Whitney test				

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Abstract Number: 253

Corticosteroid-Free Tocilizumab Monotherapy for Adult Onset Still's Disease: Results in Six Month

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Background/Purpose:

To assess the efficacy and safety of tocilizumab (TCZ) monotherapy for the induction therapy of adult onset Still's disease (AOSD) in a prospective, single-arm, single-center, cohort, pilot study.

Methods: Eight AOSD patients (male 2, female 6) who had agreed with our prospective trial since April 2010 till May 2015 were enrolled. Patients received 8 mg/kg of intravenous TCZ fortnightly for the first two months (five courses), then monthly for the next 5 months and after that TCZ was discontinued and patients were followed up for another 6 month with careful monitoring of clinical symptoms and signs related to AOSD relapses. In this report, we evaluated the efficacy and safety at the sixth month. Efficacy was evaluated by serum markers (WBC, CRP and serum ferritin), clinical symptoms and ratio of patients who required additional therapy, and safety was evaluated by adverse events for six months.

Results: The mean age was 45.2. Fever, arthralgia, rash and sore throat were observed in 100%(n=8/8), 100%(n=8/8), 87.5%(n=7/8) and 75.0%(n=6/8) respectively. LOCF analysis revealed that WBC, CRP and serum ferritin level decreased significantly from 14075 ± 4732/μl to 7042 ± 2939/μl, from 12.2 ± 7.4 mg/dl to 0.32 ± 0.62mg/dl and from 9176 ± 8077ng/ml to 3380 ± 5615ng/ml in 6 month respectively (each, $P<0.01$). The improvement rate of fever, arthralgia and eruption were 100%(n=8/8), 75.0%(n=6/8) and 71.4%(n=5/7). Only 2 patients required additional therapy (prednisolone).The reason of cessation consisted of lack of efficacy (25%, n=2) and adverse event (12.5%, n=1). An adverse event was UTI. There were no other significant adverse events.

Conclusion: TCZ monotherapy may be an alternative treatment strategy for AOSD.

Disclosure: T. Kondo, None; **Y. Okada**, None; **A. Shibata**, None; **K. Chino**, None; **A. Okuyama**, None; **H. Takei**, None; **K. Amano**, Chugai, 2.

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Abstract Number: 254

NLRP12 Autoinflammatory Disease: A Chinese Case Series and Literature Review

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic autoinflammatory diseases (SAIDs) are a genetically heterogeneous group of rheumatic diseases that are driven by abnormal activation of the innate immune system. As one of the SAIDs, the nucleotide-binding oligomerization domain like receptor protein (*NLRP*)12 autoinflammatory disease (NLRP12-AD) is an autosomal dominant disorder associated with the mutations in the *NLRP12* gene. SAIDs have been hardly reported in the Chinese population, and NLRP12-AD has been reported only in Caucasians. We report the first case series of NLRP12-AD in the Chinese population coupled with literature review.

Methods: Three Han Chinese adult patients with clinical phenotype suggestive of NLRP12-AD carrying *NLRP12* variants were treated by the authors in 2015. Their phenotype and genotype were carefully documented and studied. A PubMed search for SAIDs was conducted between January, 1990 and January, 2016, and we focused on NLRP12-AD.

Results: All three adult patients (2 men and 1 woman) developed periodic disease in adulthood. They presented with recurrent fever (n=3), polyarthralgia (n=3), myalgia (n=3), urticaria (n=2), lymphadenopathy (n=2) and erythema nodosa (n=1). All patients carry the *NLRP12* mutation F402L. Based upon our analysis of the clinical data on a total of 26 patients with NLRP12-AD in the literature, both familial and sporadic cases were equally reported, and late-onset cases accounted for 28%. NLRP12-AD patients typically present with periodic fever, urticaria-like rash, arthralgia/arthritis, myalgia, lymphadenopathy and splenomegaly. Genotyping identifies the *NLRP12* gene mutations, notably F402L (55%). Relative to the literature reports, our patients had the similar phenotypic and genotypic features. Patients with NLRP12-AD usually respond to glucocorticoid therapy.

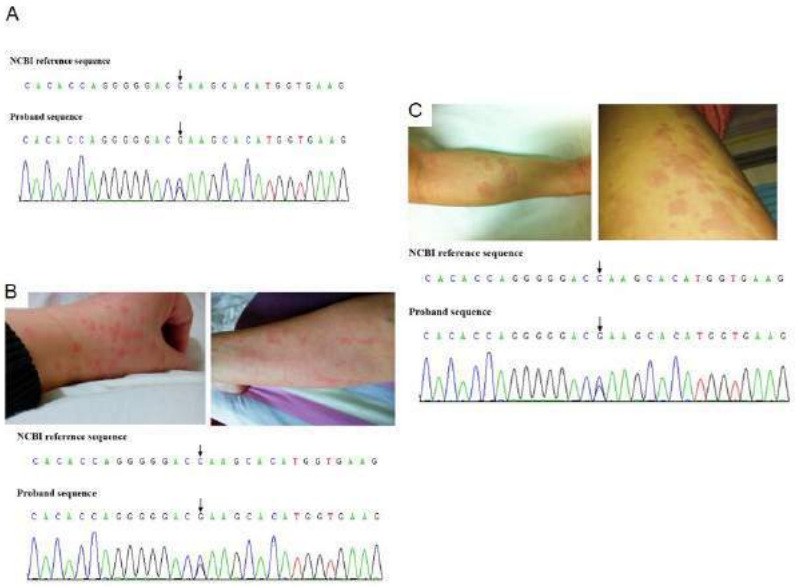
Conclusion: As one of the SAIDs, NLRP12-AD has been sparsely reported in the Caucasian population. Our report is the first to confirm its presence in the Chinese population. An awareness and screening of the *NLRP12* gene mutations in patients with unexplained periodic fever syndrome may reduce misdiagnosis and improper treatment.

References:

J¨¦ru I, et al. Mutations in NALP12 cause hereditary periodic fever syndromes. Proc Natl Acad Sci U S A 2008; 105(5):1614-9. Borghini S, et al. Clinical presentation and pathogenesis of cold-induced autoinflammatory disease in a family with recurrence of an NLRP12 mutation. Arthritis Rheum 2011; 63(3):830-9.

A table to summarize the clinical manifestations of 29 patients with NLRP12-AD A table to distinguish FCAS, NLRP12-

AD, and cold-induced urticaria **Fig. 1. A**: *NLRP12* mutation analysis and phenotype. *Patient 1*. Arrows indicate the position of the mutation; **B**: *Patient 2*. Urticarial rash on the limbs. Arrows indicate the position of the mutation; **C**: *Patient 3*. Urticarial rash on the arms and legs. Arrows indicate the position of the mutation.



Disclosure: M. Shen, None; **L. Tang**, None; **X. Shi**, None; **X. Zeng**, None; **Q. Yao**, None.

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Abstract Number: 255

Safety and Efficacy of Long-Term Canakinumab Therapy in Patients with CAPS: Final Results from Beta-Confident Registry

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Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) is a rare auto-inflammatory disease encompassing a spectrum of 3 phenotypes: familial cold auto-inflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID).[1] The estimated frequency of CAPS ranges from 1 to 3 per million.[2,3] The β-Confident Registry (NCT01213641) is a multicenter, long-term, prospective, observational study with an enrollment period of 5 years (yrs) to monitor the long-term safety and efficacy of canakinumab (CAN) for CAPS. Here we report the overall final results. The primary objective of the Registry was to monitor the safety of CAN, focusing on serious adverse events (SAEs) including serious infections, vertigo, malignancies, and hypersensitivity

reactions.

Methods: : Cumulative safety data were reported as incidence rate per 100 patient-yrs (IR/100 pyrs) from the enrollment of the first patient (November 2009) until end of study (December 2015). After enrollment patients were followed up for at least 1 yr. The Registry protocol did not mandate any visits or procedures; however, all observed and reported AEs and SAEs or AEs potentially related to CAN were recorded. Efficacy was measured using physician's global assessment (PGA).

Results: Overall, 288 patients (FCAS, n=42; MWS, n=170; NOMID, n=34; others, n=42) were enrolled at 39 sites across 13 countries, with a mean patient exposure duration of 3.6 yrs. Of these, 22 (8.0%) discontinued CAN: 5 due to AEs, 10 due to poor efficacy and patient preference, and 7 due to other reasons. The IR/100 pyrs for overall AEs was 100.0. Among the phenotypes of CAPS, patients with FCAS had the lowest IR/100 pyrs (78.1) than patients with MWS (113.4), and NOMID (119.0). The most common AEs were infections and infestations (IR/100 pyrs, 39.1). Overall, 161 SAEs were reported by 86 patients (IR/100 pyrs, 16.3), most commonly, infections (IR/100 pyrs, 5.0). One death (metastatic rectal adenocarcinoma in a 76-yr-old MWS patient) was reported. Of 23 patients who received pneumococcal vaccination (PPV), 15 (65.0%) reported local post-PPV injection site reactions, of which 5 were considered serious. Based on PGA, 31.0% of patients had no disease activity, whereas most (59.0%) of the others experienced mild/moderate disease activity at Month 54. Similarly, disease activity was absent or mild/moderate in patients with *NLRP3* mutation-negative CAPS (n=13) treated with CAN.

Conclusion: The β-confident Registry is the largest CAPS cohort documented in a registry. This Registry showed that the safety profile of canakinumab was consistent with previous findings and efficacy was sustained for more than 5 years. Canakinumab therapy was also effective in patients with *NLRP3* mutation-negative CAPS. References:

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3. Tilson H, et al. *Orphanet J Rare Dis*. 2013;10;8:139.

Disclosure: H. M. Hoffman, Burroughs-Wellcome, 2,Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 8,Sobi, 5; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, SOBI, and Baxalta, 5; **P. N. Hawkins**, None; **T. van der Poll**, None; **U. A. Walker**, Novartis Pharmaceutical Corporation, 5; **A. Speziale**, Novartis Pharmaceutical Corporation, 3; **Y. Joubert**, Novartis Pharmaceutical Corporation, 3; **H. H. Tilson**, Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 256

Muckle-Wells Syndrome in Chinese Adult Patients

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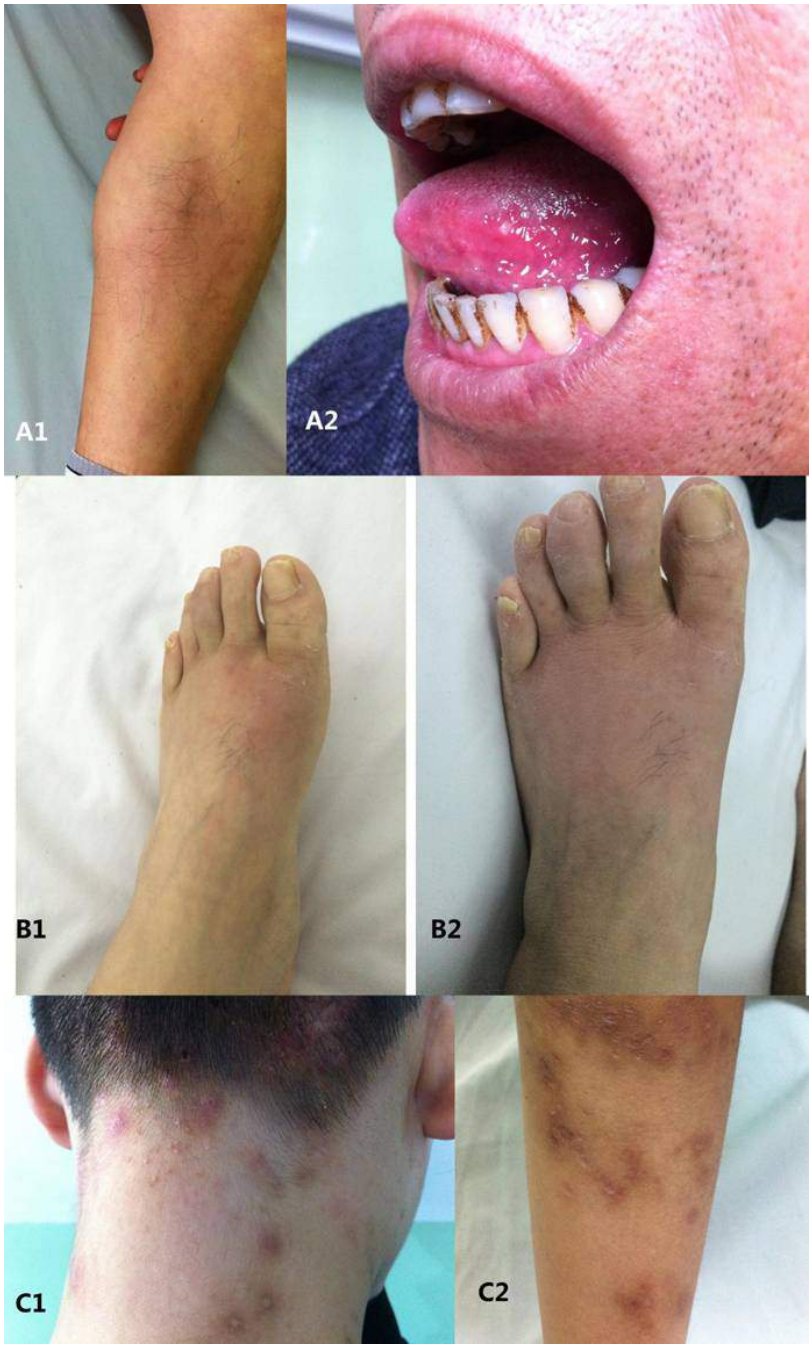
Background/Purpose: Muckle-Wells syndrome (MWS) is a rare autoinflammatory disease, which is categorized as one of the three cryopyrin-associated periodic syndromes (CAPS). MWS is characterized by recurrent episodes of fever, rash and joint pain, and may lead to renal amyloidosis and severe neurological involvements such as hydrocephalus and progressive hearing loss. Here we describe the first cohort of MWS patients in Chinese population, with emphasis on clinical features and gene variations.

Methods: Four Han Chinese patients were diagnosed as MWS from the year 2013 to 2016 at our adult clinic for autoinflammatory diseases. All the diagnoses were confirmed by mutations in the NLRP3 gene. All relevant clinical and genetic data were collected retrospectively and followed up prospectively.

Results: All the four patients were male. The median age at disease onset was 4.5 (ranging from 2 to 46) years and the mean disease duration before diagnosis was 14.25¡À12.63 (ranging from 1 to 29) years. One patient had adult onset disease at the age of 46, and the remaining patients experienced delayed diagnosis into adulthood because of physicians' unfamiliarity with this syndrome in China. All patients denied positive family history. All patients had intermittent febrile episodes with moderate to high temperature. One patient's attacks could be triggered by cold exposure. The mean duration of fever attacks was 3.81¡À2.51 (ranging from 0.25 to 6) days and the interval between attacks ranged from several weeks to several months. Skin rashes were present in all patients, which could be erythematous macular or papular, urticarial, erythema nodosa-like and Sweet disease-like. Two out of 4 suffered from frequent oral ulcers, 2/4 conjunctivitis, 2/4 myalgia, 2/4 headache, 2/4 arthralgia, 1/4 prominent polyarthritis, 1/4 pharingitis, 1/4 abdominal pain, 1/4 severe sensorineural hearing loss, 1/4 epilepsy, 1/4 chronic meningitis with communicating hydrocephalus. All patients had moderately elevated peripheral leukocyte count and systemic inflammatory markers during attacks, which return to normal during intervals. Each patient carried a novel heterozygous mutation in NLRP3 gene, including Q705K, V72M, D31V, T350M, respectively. Three patients had good response to the combination of moderate to high dose of prednisone and conventional DMARDs. Due to economic constraints and unavailability of anti-interleukin 1 therapies in China, only one patient received an anti-TNF¦Áagent. None showed evidence of renal amyloidosis.

Conclusion: Our observational study suggests for the first time that MWS could be identified among adult Chinese patients with intermittent fever of unknown cause, but with unique features compared with previously reported patient cohorts. Our patients are exclusively male without positive family history, with fewer presentations of urticarial rash and hearing loss, and responded better to conventional oral treatments. Considering the lack of amyloidosis, whether our patients had better outcome remains to be seen. The more accurate characterization of Chinese patients suffering from MWS and CAPS needs further studies. Figure 1. A1& A2: erythematous macular and oral ulcer of one patient. B1& B2: resolution of transient arthritis in 1st TMP within one day. C1& C2: new maculopapular rash in the neck and pigmentation after rash disappearance in the forearm.



Disclosure: D. Wu, None; **M. Shen**, None; **X. Zeng**, None.

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Abstract Number: 257

CNS Manifestations of Patients with Muckle-Wells Syndrome

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: CAPS is a rare autoinflammatory disease associated with mutations in the NLRP3 gene that result in overactivation of the inflammasome, increased secretion of IL-1beta and IL-18, and systemic inflammation. Muckle-Wells syndrome (MWS) is a rare autosomal dominant disease which causes sensorineural deafness, recurrent hives, and joint pain. CNS manifestations are one of the prominent clinical features in children with CINCA/NOMID, but they have been described only rarely in patients with FCAS and MWS.

Methods: Here we present the imagination findings of CNS involvement in a family whose 11 members have MWS. Clinical data was collected during the course of ongoing patient care.

Results: We evaluated the clinical features of 11 patients who were referred to our center. The median age of the patients was 25 years (range: 9–65years). The ratio of females /males was 1.2 (6/5). All patients had arthritis with exacerbation on exposure to cold and ocular involvement, mostly in the form of conjunctivitis and far less commonly uveitis, irideal synechiae, band keratopathy, cataract, and impaired vision. The median age of onset of arthritis was 7 years (2-30y), the median age of onset of ocular involvement was 8 years (2-45 y). Hearing loss in 73.6% of patients was detected, with a 15 years (12-63 y) as the median age of onset. All patients except one had urticarial rash. The median age of onset of urticarial rash was 8 years (7-30 y). Three patients had recurrent headache attacks. Neurological examination was normal in all and cranial MR was obtained in 8 out of 11 patients. While 4 out of 8 patients had normal MR findings; the enlargement of the ventricles and gliotic focus in the subcortical white matter associated with a deepening of the cerebral sulci in 2 patients; enlarged ventricles and cerebellomedullary cisterns in 2 patients were detected. There was no mutation detected in the study of MEFV (all exons), TNFRSF1A (exons 2-to-7), MVK (all exons), NLRP3 (all exons), NOD2 (exons 4, 8 and 9) and PSTPIP1 (exons 10 and 11) genes. Anakinra was started in 6 patients and two patients were treated with canakunimab . Following anti-IL1 treatment, attacks of arthritis and urticaria are getting fully under control, advances in keratopathy and hearing loss could be partially controlled.

Conclusion: CAPS are usually inherited disorders caused by an autosomal dominant mutation. Neurological manifestations may be one of the major clinical features and were mostly reported in cases with CINCA/NOMID. Currently, there is no fixed demarcation between FCAS and MWS or MWS and CINCA/NOMID. Distinguishing between these cryopyrinopathies may be difficult because they have symptoms in common. During attacks, patients develop severe headaches and will have findings of ‘aseptic’ meningitis in the cerebrospinal fluid (CSF), with predominately neutrophils and eosinophils cellular infiltrate. Our three cases had recurrent headache and two of them had enlarged ventricles and cerebellomedullary cisterns in cranial MR. Although neurological findings was reported rarely in cases with MWS, cranial MR should be requested in patients with MWS who has headache.

Disclosure: S. S. KILIC, None; **S. cekic**, None; **J. Aróstegui**, None.

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Abstract Number: 258

Unmet Psychosocial Needs in Patients with CAPS

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Background/Purpose: Cryopyrin-associated periodic syndrome (CAPS) is a rare autoinflammatory disease. Generalized manifestations like recurrent fever and fatigue and organ disease like reduced vision, hearing loss, bone deformities and aseptic meningitis impair the patients' well-being. While most physical complaints are well defined and managed by effective IL-1 inhibition, areas of psychosocial needs are much less explored and often unsatisfied even in treated patients. The purpose of this study was to identify unmet needs in the psychosocial support of children and adults with CAPS.

Methods: A qualitative study of children and adults diagnosed with CAPS cared for at the autoinflammation reference center Tuebingen was performed. Patients and their families were invited to participate in structured focus group interviews grouped according to age and involvement with the disease: children <14 years, adolescents and young adults 14-21 years, adults >21 years; parents; other family members. Open questions were asked to the group. The group discussion was recorded, transcribed to text and analysed for mentioning of certain topics. Frequency of naming and relevance indicated by discussion participants was calculated and graded.

Results: The five focus groups comprised of 42 individuals including 25 CAPS patients; 10 females, 15 males, including five children, eight adolescents/young adults and 12 adults. In addition unaffected individuals included 14 parents and three other family members. Key domains of unmet needs identified included information about the disease, understanding of patients' needs, intervention in social network and exchange of experiences. The area of need identified in all focus groups and named most often was school. Specifically lack of appreciation by teachers (13) and fellow students (21) was named. In adolescents and adults groups other frequently named areas were employment agency, health insurance organizations and general practitioners.

Conclusion: Major unmet needs of children and adults with CAPS were identified as various displays of ignorance by the patients' environment. The need for psychosocial support exists particularly in school.

Disclosure: J. B. Kuemmerle-Deschner, Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5,Novartis Pharmaceutical Corporation, 7; **G. Erbis**, Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 5; **T. Sergiichuk**, None; **S. Hansmann**, None; **I. Haug**, None; **S. Benseler**, None.

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Abstract Number: 259

Rituximab in Refractory Cardiac Sarcoidosis – Single Center Experience

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Background/Purpose: Cardiac sarcoidosis is a life threatening condition for which there is limited data to guide optimal steroid-sparing agents. B-cells have been reported to be involved in the pathogenesis of sarcoidosis and individual instances of successful rituximab use have been described.

Methods: We identified all patients at a single center with cardiac sarcoidosis (defined by endomyocardial biopsy or biopsy of different organ confirming sarcoidosis plus consistent cardiac imaging) treated with rituximab with at least 1 follow-up.

Results: Mean ± standard deviation age at diagnosis for the 3 men and 2 women identified was 50.9 ± 8.8 years. Median follow-up at our center for sarcoidosis was 2.7 years (range 1.3-7.1). One patient had isolated cardiac sarcoidosis. The remaining 4 had extracardiac involvement: thoracic lymphadenopathy (3, 60%), pulmonary (1, 20%), renal (1, 20%), parotid gland (1, 20%), and neurologic (1, 20%). Endomyocardial biopsies were positive in 2 of 3 patients. All had abnormal findings on PET and/or MRI. Four had cardiac involvement at the time of sarcoid diagnosis. Cardiac

manifestations included both arrhythmia (high grade AV block, ventricular tachycardia) and heart failure. All 5 had an implantable cardioverter defibrillator (ICD) over their follow-up. All 5 received corticosteroids and had failed or were intolerant to at least 1 additional immunosuppressant before rituximab. Mycophenolate mofetil was the most common (4, 80%). Methotrexate was used in 2 (40%), azathioprine 1 (20%), infliximab 1 (20%), and leflunomide 1 (20%). Rituximab 1000 mg IV x 2 doses, 2 weeks apart, was given to 4 patients. One received only 1 dose due to insurance limitations. Three patients received 1000 mg IV x 2 doses after at least 6 month intervals, for a total of 2, 3 and 4 rounds, for each patient, respectively. The median follow-up following first rituximab was 0.8 (range 0.2-1.9) years. All received prednisone with doses successfully reduced over follow-up. Two also received methotrexate with rituximab, with one having to discontinue due to renal dysfunction. All had serial cardiac PETs. In all, there was qualitative improvement in inflammation as assessed by a decrease in FDG uptake. In one patient, all FDG uptake was eliminated in two serial cardiac PETs following the first and second round of rituximab. Due to insurance issues, the third round of rituximab was delayed to 10 months and with recurrence of FDG uptake that stabilized on subsequent cardiac PET. Three had improvement of ejection fraction as measured by cardiac PET following first rituximab infusion: 26% to 54%, 33% to 47%, and 32% to 40%. One had stability and 1 had worsening from 45% to 28% but the latter was performed in the setting of ectopic beats and echocardiogram performed at similar time points demonstrated stability. No individuals died during follow-up. One individual is currently listed as class IB for heart and kidney transplant. No side effects from rituximab were noted.

Conclusion: Rituximab for treatment refractory/steroid-intolerant cardiac sarcoidosis appears to be effective and well-tolerated. Further work is needed to determine its ideal position in a regimen to treat cardiac sarcoidosis.

Disclosure: M. Krause, None; **L. T. Cooper Jr.**, None; **P. Chareonthaitawee**, None; **S. Amin**, None.

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Abstract Number: 260

Risk of Cardiovascular Disease Among Patients with Sarcoidosis: A Population-Based Retrospective Cohort Study

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Session Time: 9:00AM-11:00AM

Risk of Cardiovascular Disease Among Patients With Sarcoidosis: A Population-Based Retrospective Cohort Study

Background/Purpose: Several epidemiologic studies have demonstrated an increased incidence of atherosclerotic cardiovascular disease (CVD) among patients with chronic inflammatory disorders such as rheumatoid arthritis and systemic lupus erythematosus. However, data on sarcoidosis, another relatively common immune-mediated chronic inflammatory disorder, are still limited.

Methods: 345 patients (50% female; 90% Caucasian, 5% African-American; mean age 45.6 years) with incident sarcoidosis in 1976-2013 in a geographically well-defined population were identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology, compatible clinical presentation, and exclusion of other granulomatous diseases. 345 sex and age-matched comparators (50% female; 95% Caucasian, 1% African-American; mean age 45.4 years) were also identified from the same underlying population. Medical records of both cases and comparators were individually reviewed for CVD including coronary artery disease (CAD), congestive heart failure (CHF), atrial fibrillation (AF), cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA). The prevalence of all and individual CVD prior to index date was compared between the 2 groups using Fisher's exact test. The cumulative incidence of all and individual CVD adjusted for the competing risk of death was estimated. Cox proportional hazards models with adjustment

for age, sex, calendar year, current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity were used to compare the rate of development of CVD, individually and in combination, between cases and comparators.

Results: The prevalence of overall and individual CVD prior to index date was not significantly different between 2 groups (p-value = 0.21 for overall CVD). Adjusting for age, sex and calendar year, the risk of incident CVD after index date was significantly elevated among patients with sarcoidosis with adjusted hazard ratio (HR) of 1.57 (95% CI, 1.15 – 2.16). Further adjustment for current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity yielded adjusted HR of 1.66 (95% CI, 1.09 – 2.55). Sensitivity analysis including only CVD that occurred at least 6 months after index date to reduce the likelihood of detection bias was also performed. The adjusted HR for overall CVD slightly decreased to 1.50 and remained statistically significant (95% CI, 1.06 – 2.06). Significantly increased risk was also observed in some individual CVD as shown in table 1.

Conclusion: Patients with sarcoidosis have a higher risk of CVD. How this risk should be addressed in clinical practice requires further investigation.

Subtype of cardiovascular disease	Number of events after index date for case/comparator	HR (95% CI) for all events after index date, adjusting for age, sex and calendar year	Number of events that occurred after at least 6 months index date for case/comparator	HR (95% CI) for events that occurred at least 6 months after index date, adjusting for age, sex and calendar year
CAD	54/38	1.55 (1.02 – 2.35)	53/38	1.52 (1.00 – 2.31)
CHF	45/24	2.06 (1.25 – 3.38)	43/24	1.97 (1.19 – 3.24)
AF	33/18	1.93 (1.08 – 3.43)	31/18	1.80 (1.01 – 3.24)
CVA	32/14	2.51 (1.34 – 4.71)	31/14	2.45 (1.30 – 4.60)
TIA	6/4	1.68 (0.47 – 5.96)	5/4	1.44 (0.38 – 5.37)
PAD	13/9	1.55 (0.66 – 3.63)	13/9	1.55 (0.66 – 3.63)
AAA	4/4	1.13 (0.28 – 4.53)	3/4	0.86 (0.19 – 3.85)

Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-of-cardiovascular-disease-among-patients-with-sarcoidosis-a-population-based-retrospective-cohort-study

Abstract Number: 261

Sarcoidosis Is Associated with Increased Risk of Venous Thromboembolism: A Population-Based Study

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Sarcoidosis is Associated With Increased Risk of Venous Thromboembolism: A Population-Based Study

Background/Purpose: Chronic inflammation has been increasingly recognized as a risk factor of venous thromboembolism (VTE). Several epidemiologic studies have demonstrated an increased incidence of VTE among patients with chronic inflammatory disorders such as rheumatoid arthritis, inflammatory myositis and vasculitis. However, data on sarcoidosis, another relatively common immune-mediated chronic inflammatory disorder, are still limited.

Methods: 345 patients (50% female; 90% Caucasian, 5% African-American; mean age 45.6 years) with incident sarcoidosis in 1976-2013 in a geographically well-defined population were identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology, compatible clinical presentation, and exclusion of other granulomatous diseases. 345 sex and age-matched comparators (50% female; 95% Caucasian, 1% African-American; mean age 45.4 years) were also identified from the same underlying population. Medical records of both cases and comparators were individually reviewed for both subtypes of VTE including deep venous thrombosis (DVT) and pulmonary embolism (PE). The prevalence of VTE, DVT and PE prior to index date was compared between the 2 groups using Fisher's exact test. The cumulative incidence of VTE adjusted for the competing risk of death was estimated. Cox proportional hazards models with adjustment for age, sex, calendar year, current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity were used to compare the rate of development of VTE between the 2 groups.

Results: The mean length of follow-up was 15.1 years and 16.8 years for cases and comparators, respectively. The prevalence of VTE prior to index date was not significantly different between cases and comparators (1.4% and 1.4%, p-value = 1.0). After index date, 27 VTE events were observed among cases and 10 VTE events were observed among comparators. After adjusting for age, sex and calendar year, the risk of incident VTE after index date was significantly elevated among patients with sarcoidosis with adjusted hazard ratio (HR) of 3.04 (95% CI, 1.47 – 6.29). Increased risk was observed in both DVT (HR 3.14; 95% CI 1.32 – 7.48) and PE (HR 4.29; 95% CI 1.21 – 15.23). Further adjustment for current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity yielded adjusted HR of 3.04 (95% CI 1.25 – 7.39) for VTE, adjusted HR of 3.00 (95% CI 1.05 – 8.58) for DVT and adjusted HR of 4.24 (95% CI 1.11 – 16.18) for PE. Sensitivity analysis including only VTE that occurred at least 6 months after index date to reduce the likelihood of detection bias was also performed. The adjusted HR for VTE slightly decreased to 2.73 and remained statistically significant (95% 1.30 – 5.72). The adjusted HR for DVT and PE decreased to 3.00 (95% CI; 1.25 – 7.20) and 3.58 (95% CI; 0.98 – 13.03), respectively.

Conclusion: Patients with sarcoidosis have a higher risk of VTE. It is possible that this risk is related to the systemic inflammatory nature of the disease, however further investigations are required to address this increased risk in clinical practice.

Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/sarcoidosis-is-associated-with-increased-risk-of-venous-thromboembolism-a-population-based-study

Abstract Number: 262

Seasonal Variation in Incidence of Sarcoidosis: A Population-Based Study 1976-2013

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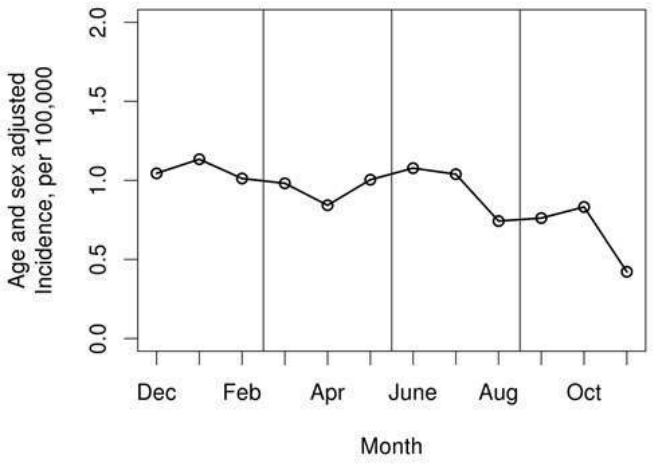
Seasonal Variation in Incidence of Sarcoidosis: A Population-Based Study 1976-2013

Background/Purpose: Sarcoidosis is a multi-systemic disorder of unknown etiology. Studies of seasonal and regional patterns of incidence of sarcoidosis may provide more understanding of potential environmental triggers of this disease. However, previous studies on the seasonality of sarcoidosis have yielded conflicting results.

Methods: A cohort of adult patients with incident sarcoidosis in 1976-2013 in a geographically well-defined population was identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology and radiologic features of intrathoracic sarcoidosis, compatible clinical presentation and exclusion of other granulomatous diseases. The only exception to the requirement of histopathological confirmation was stage I pulmonary sarcoidosis that required only radiographic evidence of symmetric bilateral hilar adenopathy. Age and sex adjusted incidence rates were calculated using population estimates for adults based on decennial census counts as the denominators. Seasonal variation was compared using Poisson regression models.

Results: The cohort included 345 cases of incident sarcoidosis (mean age 35.4 years, 50% female, 90% Caucasian and 5% African-American). Patients in this cohort were less likely to have incident sarcoidosis in the autumn season with an age and sex adjusted rate of 2.0/100,000 (95% CI 1.5-2.5) compared with winter (3.2/100,000; 95% CI 2.6-3.8), spring (2.8/100,000; 95% CI 2.2-3.4) and summer (2.9/100,000; 95% CI 2.2-3.5; p=0.011; figure 1). Subgroup analysis per decade (1976-1985, 1986-1995, 1996-2005 and 2006-2013) consistently showed lower incidence of sarcoidosis in autumn (rate ratios for autumn compared to spring were 0.53, 0.70, 0.64 and 0.85, respectively), although statistical power was insufficient to demonstrate statistical significance at p <.05.

Conclusion: There is seasonal variation in the incidence of sarcoidosis, with lower rates consistently seen in autumn in the past more than three decades. The results may have implications for the understanding of the etiology of sarcoidosis.



Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

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Abstract Number: 263

How Does Sarcoidosis Present in Spain? Characteristics at Diagnosis of 979 Patients from the Sarcogeas-SEMI Registry

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Fernández[24], Alberto Gato Diez[25], Neera Toledo Samaniego[26], Miriam Akasbi[27], Angel Robles[28], Inmaculada Ojeda[29], Maria José Vives[30], María Penadés Vidal[31], César Morcillo[32], Moisés De Vicente[33], **Soledad Retamozo**[2,34], Lucio Pallarés[11], Manuel Ramos-Casals[35], Roberto Pérez-Alvarez[4] and SARCOGEAS Registry, GEAS-SEMI, [1]Autoimmune Diseases Unit, Department of Medicine, Hospital CIMA- Sanitas, Barcelona., Bacelona, Spain, [2]Laboratory of Systemic Autoimmune Diseases "Josep Font", CELLEX, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Systemic Autoimmune Diseases, ICMID, Hospital Clinic, Barcelona, Barcelona, Spain, [3]Primary Care Research Group, IDIBAPS, Centre d'Assistència Primària ABS Les Corts, CAPSE, Barcelona, Barcelona, Spain, [4]Department of Internal Medicine, Hospital Alvaro Cunqueiro, Vigo, Vigo, Spain, [5]Department of Internal Medicine, Hospital Ramón y Cajal, Madrid, Spain, Madrid, Spain, [6]Department of Internal Medicine, Hospital Universitario Central de Asturias, Oviedo, Oviedo, Spain, [7]Department of Internal Medicine, Hospital Universitari Joan XXIII, Tarragona, Tarragona, Spain, [8]Department of Internal Medicine, Hospital Clínico, Zaragoza, Zaragoza, Spain, [9]Department of Internal Medicine, Hospital Virgen de la Salud, Toledo, Toledo, Spain, [10]Department of Internal Medicine, Hospital Universitario Miguel Servet, Zaragoza, Zaragoza, Spain, [11]Department of Internal Medicine, Hospital Son Espases. Palma de Mallorca, Palma de Mallorca, Spain, [12]Department of Internal Medicine, Hospital Virgen del Rocio, Sevilla, Sevilla, Spain, [13]Department of Internal Medicine, Hospital Parc Taulí, Sabadell, Sadabell, Spain, [14]Department of Internal Medicine, Hospital de Cabueñes, Gijón, Gijón, Spain, [15]Department of Internal Medicine, Althaia, Xarxa Assistencial de Manresa, Manresa, Spain, [16]Department of Internal Medicine, Hospital Clínico San Cecilio, Granada, Granada, Spain, [17]Department of Internal Medicine, Hospital de Santa Coloma de Gramanet, Barcelona, Barcelona, Spain, [18]Department of Internal Medicine, Hospital General San Jorge, Huesca, Huesca, Spain, [19]Department of Internal Medicine, Hospital de Santa Caterina, Girona, Girona, Spain, [20]Department of Internal Medicine, Hospital Virgen Macarena, Sevilla, Sevilla, Spain, [21]Department of Internal Medicine, Hospital Infanta Sofía, San Sebastián, San Sebastian, Spain, [22]Department of Internal Medicine, Hospital de Poniente El Ejido, Almería, Almería, Spain, [23]Department of Internal Medicine, Hospital Universitario Puerta del Mar, Cádiz, Cadiz, Spain, [24]Department of Internal Medicine, Hospital da Barbanza, A Coruña, A Coruña, Spain, [25]Department of Internal Medicine, Complejo Hospitalario Albacete, Albacete, Albacete, Spain, [26]Department of Internal Medicine, Hospital Gregorio Marañón, Madrid, Madrid, Spain, [27]Department of Internal Medicine, Hospital Infanta Leonor, Madrid, Madrid, Spain, [28]Department of Internal Medicine, Hospital La Paz, Madrid, Madrid, Spain, [29]Department of Internal Medicine, Hospital Valle del Guadiato, Córdoba, Cordoba, Spain, [30]Department of Internal Medicine, Parc Sanitari San Joan de Déu, San Boi de Llobregat, Barcelona, Spain, [31]Department of Internal Medicine, Hospital De Manises, Valencia, Valencia, Spain, [32]Department of Medicine, Hospital CIMA-Sanitas, Barcelona, Barcelona, Spain, [33]Department of Internal Medicine, Hospital Nuestra Señora del Prado, Talavera, Talavera, Spain, [34]Rheumatology Unit, Hospital Privado Centro Médico de Córdoba, Argentina, Córdoba, Argentina, [35]Laboratory of Systemic Autoimmune Diseases "Josep Font", CELLEX, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Department of Systemic Autoimmune Diseases, ICMID, Hospital Clinic, Barcelona, Spain, Barcelona, Spain
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Background/Purpose: To characterize the main epidemiological, clinical and radiological features at presentation of sarcoidosis in a large multicenter cohort from Southern Europe.

Methods: In January 2016, the Autoimmune Diseases Study Group (GEAS-SEMI) created a national registry (SARCOGEAS) of patients with sarcoidosis. Sarcoidosis was diagnosed in agreement with the criteria proposed by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis. Organ involvement was retrospectively determined in each patient at the time of diagnosis using the 2014 WASOG organ assessment instrument. Ethnicity was defined according to the FDA classification. Two outcomes (association with neoplasia and death) were assessed at the end of follow-up.

Results: The cohort consisted of 979 patients (85% biopsy-proven), including 562 (57%) women and 417 (43%) men, with a mean age at diagnosis of 47.02 ± 15.44 years. One hundred twenty-three (13%) patients were born outside Spain. With respect to the FDA ethnic classification, 858 (88%) patients were classified as White, 83 (8%) as Hispanic, 21 (2%)

as Black/African American and 17 (2%) as Asian. Thoracic involvement was present at diagnosis in 910 (93%) patients. With respect to diagnostic tests, data on the radiographic stage at diagnosis was available in all but 15 patients, with stage II (38%) and stage I (30%) being the most frequently-reported patterns. According to the WASOG classification, the most frequently reported extrathoracic involvements at diagnosis were cutaneous in 334 (34%) patients, extrathoracic lymph nodes in 179 (18%), liver involvement in 120 (12%) and ocular involvement in 109 (11%). Potentially life-threatening WASOG involvements were reported in frequencies less than 10%, including neurological involvement in 67 (7%) patients, kidney involvement in 46 (5%) or cardiac involvement in 18 (2%). Therapeutic approaches included the use of oral glucocorticosteroids in 552 (56%) patients, immunosuppressive agents in 76 (8%, mainly methotrexate in 35 patients, azathioprine and 21 and mycophenolate in 7) and biological agents in 13 (1%, including infliximab in 9 cases, adalimumab in 4, rituximab in 2, etanercept in 1 and bevacizumab in 1). After a mean follow-up of 87.9 months, neoplasia was reported in 112 (11%) patients and death in 91 (9%).

Conclusion: This is one of the largest series of sarcoidosis reported out of the US, predominantly composed by White patients in nearly 90% of cases. Clinical presentation is dominated by adenopathies (both thoracic and extrathoracic) and cutaneous features (erythema nodosum), with lower frequencies in the main extrathoracic involvements than that reported in US and Japanese series.

Disclosure: P. Brito-Zerón, None; **B. Kostov**, None; **M. Pérez de Lis**, None; **G. Fraile**, None; **R. Gómez De La Torre**, None; **M. Roca Herrera**, None; **B. De Escalante Yangüela**, None; **A. Alguacil**, None; **M. P. Perez Conesa**, None; **F. J. Rascón**, None; **J. S. Garcia Morillo**, None; **C. Feijoo Massó**, None; **E. Fonseca Aizpuru**, None; **M. Bonet**, None; **N. Faro Minguez**, None; **G. De La Red Bellvis**, None; **E. Calvo Begueria**, None; **A. Gómez Lozano**, None; **E. Peral Gutiérrez De Ceballos**, None; **J. F. Gómez Cerezo**, None; **G. Cruz Caparrós**, None; **P. Perez Guerrero**, None; **S. Rodríguez Fernández**, None; **A. Gato Diez**, None; **N. Toledo Samaniego**, None; **M. Akasbi**, None; **A. Robles**, None; **I. Ojeda**, None; **M. J. Vives**, None; **M. Penadés Vidal**, None; **C. Morcillo**, None; **M. De Vicente**, None; **S. Retamozo**, None; **L. Pallarés**, None; **M. Ramos-Casals**, None; **R. Pérez-Alvarez**, None.

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Abstract Number: 264

Ethnicity-Related Differences in the Clinical Presentation of Sarcoidosis in Spain (SARCOGEAS-SEMI Registry)

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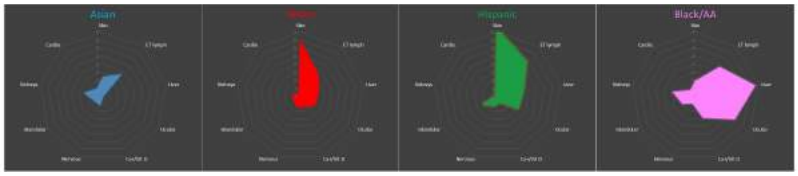
Background/Purpose: To evaluate the influence of ethnicity on the clinical presentation of sarcoidosis in a large multicenter cohort from Southern Europe.

Methods: In January 2016, the Autoimmune Diseases Study Group (GEAS-SEMI) created a national registry (SARCOGEAS) of patients with sarcoidosis. Sarcoidosis was diagnosed in agreement with the criteria proposed by the American Thoracic Society/European Respiratory Society/World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) 1999 statement on sarcoidosis. Organ involvement was retrospectively determined in each patient at the time of diagnosis using the 2014 WASOG organ assessment instrument. Ethnicity was classified according to the FDA classification. Two outcomes (association with neoplasia and death) were assessed at the end of follow-up.

Results: The cohort consisted of 979 patients (85% biopsy-proven), including 562 (57%) women and 417 (43%) men, with a mean age at diagnosis of 47.02 ± 15.44 years. With respect to the FDA ethnic classification, 858 (88%) patients were classified as White, 83 (8%) as Hispanic, 21 (2%) as Black/African American and 17 (2%) as Asian. Epidemiologically, the lowest frequency of women was reported in Blacks/African Americans (24% vs. 58%W, 59%A and 60%H, p=0.018) Radiologically, the highest frequency of radiological stages involving the lung parenchyma was found in Hispanics (79% vs. 71%BAA, 67%W and 56%A, p=0.041). With respect to extrathoracic WASOG involvements, the highest frequencies of cutaneous involvement were found in Hispanics and Whites (41% and 35% vs. 12%A and 9%BAA, p=0.011), ocular involvement in Blacks/African Americans (29%% vs. 14%H, 11%W and 0%A, p=0.021), liver involvement in Blacks/African Americans (38% vs. 16%H, 12%W and 0%A, p=0.021), and kidney involvement in Blacks/African Americans and Asians (14% vs. 11% vs 5%W and 1%H, p=0.037) (Figure 1). After a mean follow-up of 87.9 months, neoplasia was reported in 112 (11%) patients and 91 (9%) patients died. Sarcoidosis was more frequently related to neoplasia in Whites (13% vs. 6%H, 0%BAA and 0%A, p=0.042), who also had the highest mortality rate (10% vs. 5%BAA, 1%H and 0%A, p=0.015).

Conclusion: In a predominantly White Southern European population of patients diagnosed with sarcoidosis, ethnicity played a significant role in the presentation and prognosis of the disease even after taking into account the lower frequencies of ethnicities associated with poor outcomes (Black/African Americans and Hispanics). Consideration of ethnic disparities in the clinical presentation of sarcoidosis may be essential in reaching an early diagnosis, the search for histopathological confirmation and the prompt introduction of specific therapy in Mediterranean patients with sarcoidosis.



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Characterization of Eye Sarcoidosis with or without Systemic Involvement: Application of Iwos Criteria in an Uveitis Unit

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Background/Purpose: Sarcoidosis(Sa) eye involvement is the most common extrapulmonary manifestation and the initial presentation in 5-20% of cases. The definitive diagnosis is histopathological. The sensitivity(S) of the conjunctival biopsy is low,so Ocular Sa(OSa) diagnostic criteria(C.) were proposed:IWOS(First International Workshop on Ocular Sarcoidosis),with high S and specificity(1/0.95), but they have been poorly validated. Our purpose was to apply the IWOS C., to analyze their consistency with the clinical diagnosis of OSa and to asses differential features between patients with OSa and those with systemic involvement

Methods: Cross-sectional study. Clinical records from patients with presumed Sa who had been followed for 10 years in a multidisciplinar Uveitis Unit (Ophthalmology/Rheumatology) were reviewed. Clinical variables and complementary tests results were analyzed. IWOS C. were applied if OSa was suspected. Chi-square test and Kappa coefficient were used

Results: 71 patients included: 47 OSa,13 with ocular-systemic involvement (OS-Sa) and 11 with systemic involvement (SSa). Women/Men 57%/43%, mean follow-up time 9.42 years (±8.55), with no intergroup differences. Significant differences between patients with OSa vs. OS-Sa/SSa were observed: mean age at diagnosis (40.23 ±18.18 vs. 57.54 ±17.65/48.27 ±17 years,p=0.01); mean ESR(16.74 ±12.73 vs. 26.38± 15/19.4 ±31.55 mm/h, p=0.01); mean CRP(3.58 ±4.29 vs. 8.12 ±8.11/10.24 ±14.37 mg/L, p=0.03); CT abnormalities (16.6% vs. 90%/92%, p=0.001); positive biopsy(0% vs. 8/100%, p=0.002); general, joint, respiratory and skin symptoms (OSa 6-12% vs SSa 15-50%,p=0.002). ACE was

increased in 74.6%, with a mean value of 71.98 ±33.59 U/L, no intergroup differences. Altered lacrimal scintigraphy was more often found in the OSa subset (26.7%) vs. OS-Sa/SSa (23.1%/0%), without statistical significance. Comparing OSa vs. OS-Sa patients, ocular involvement was as follows: anterior segment involvement 48% vs 61.5%, intermediate segment 21.3% vs. 15.4%, posterior segment 8.5% vs 0%, panuveitis 21.2% vs. 23.1%, p=0.001. If OSa,bilateral involvement was present in 60% of patients, unilateral involvement was more frecuent in OS-Sa (76%), p=0.06.There were no significant differences regarding uveitis's presentation,course and number of crisis and specific intraocular findings. Applying IWOS Criteria and comparing OSa vs OS-Sa we can classify: Definite OSa 0% vs. 69.2%, Presumed OSa 23.4% vs. 7.7%, Probable OSa 14.9% vs. 15.4% and Possible OSa 2.1% vs. 0%; not fulfilling criteria:59.6% vs. 7.7%(p=0.001). The kappa coefficient between suspicion of OSa/OS-Sa and not fulfilling/fulfilling criteria was 0.30 (p=0.003)

Conclusion: We could classify as Presumed vs. Probable Ocular Sarcoidosis in 25% vs. 15% of patients with suspicion but who hadn't undergone a biopsy. We excluded the diagnosis in 60%. There wasn't a good consistency between the suspected diagnosis/IWOS Criteria fulfillment. Ocular Sarcoidosis patients were younger and had lower ESR/CRP levels. Involvement of the anterior ocular segment was the most frequent one, bilateral in Ocular Sarcoidosis and unilateral in Ocular-Systemic Sa

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Abstract Number: 266

Diffuse Idiopathic Skeletal Hyperostosis and Obesity- Is There a Causal Relationship?

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Background/Purpose: Diffuse Idiopathic Skeletal Hyperostosis (DISH) is an incompletely understood condition characterized by new bone formation affecting the spine. Despite reported links between DISH and obesity, the nature of the relationship is unknown. To investigate further, we constructed an obesity genetic risk score (GRS) for BMI and assessed association with DISH.

Methods: A convenience sample of 3,117 patients from the COPDGene Study was used to investigate the association between BMI GRS and DISH. Two readers visually scored spine imaging for DISH based on Resnick criteria. BMI served as the obesity phenotype. Genotyping was performed using the Illumina Omni-Express Chip. A 97 SNP BMI GRS based on validated GWAS loci was calculated. Univariate analyses assessing association of age, sex, race, diabetes status (self-report or taking anti-diabetic medication), BMI GRS with DISH were performed. In addition, a logistic regression model adjusted for age, sex, race, and diabetes, was used to evaluate the association of BMI GRS with DISH. The association of the BMI GRS with BMI served as a positive control. The COPDGene study, initiated 2007-2011, enrolled 10,129 smokers to define subtypes and genetic associations of smoking related lung disease. HRCT of the chest, DNA, demographic and anthropometric data and medical history were obtained.

Results: We analyzed 437 DISH cases and 2,680 controls among men and women in the COPDGene study with available

HRCTs of the chest. See Table 1 for odds ratios (OR) for the univariate and multivariate models. On univariate analysis, DISH correlated with male sex, increasing BMI and increasing age. The correlation between BMI and BMI GRS was significant (p<0.0001). The OR between DISH and BMI GRS was 1.02 (95% CI 1.00-1.04, p=0.019), but when separated by race subgroups, the p-value was not significant in either African Americans or non-Hispanic whites. In the overall multivariate model, there was no significant association between DISH and BMI GRS with OR 1.004 (95% CI 0.99-1.02, p=0.68). **Table 1. Association between DISH and clinical features and BMI GRS**

Variable	Odds Ratio	Adjusted* Odds Ratio	Confidence Interval	P-value
Age (years)	1.06	1.07	1.06-1.08	<0.0001
Gender (male)	2.96	3.50	2.72-4.50	<0.0001
Race (non-Hispanic White)	1.52	0.94	0.71-1.24	0.64
BMI (kg/m^2)	1.09	1.12	1.10-1.14	<0.0001
DM (reported history and medications)	2.64	1.49	1.13-1.97	0.005
BMI GRS	1.02	1.00	0.99-1.02	0.68

***Adjusted for age, gender, race, DM history**

Conclusion: Our results suggest obesity does not share a direct genetic association with DISH. However, it is associated with DISH, which may be due to effects of a shared mechanism such as inflammation. In addition, direct and indirect effects of elevated leptin levels and decreased adiponectin levels, present in obese patients, may play a role to alter bone formation. The role of smoking remains to be elucidated. More studies are needed to further explore the mechanism driving the relationship between obesity and DISH.

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Abstract Number: 267

Diffuse Idiopathic Skeletal Hyperostosis: Can We Identify Different Clinicoradiological Patterns?

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Background/Purpose: Diffuse Idiopathic Skeletal Hyperostosis (DISH) was described based on vertebral radiological signs (Resnick). Subsequently, Utsinger presented other criteria that add extraspinal involvement that allowed DISH diagnosis even without vertebral signs. Mader et al have tried to develop a new set of criteria without a final consensus about the inclusion of multiple peripheral enthesopathies. **Objective:** Identify clinicoradiological patterns of DIH patients based on the spinal and / or extraspinal involvement and study their distinctive features.

Methods: We conducted a cross-sectional study of patients who fulfilled DISH Resnick's and / or Utsinger's criteria. Demographic, clinical, radiographic and comorbidity data were collected. Exclusion criteria: a) History of spondyloarthropathy, b) HLAB27 +, c) Personal or first degree of psoriasis or Inflammatory Bowel Disease. Variables: clinical, comorbidity and radiological variables were collected. X-rays of spine and joints (pelvis, elbows, knees, feet, hands and shoulders) were reviewed. We defined three clinical-radiological patterns: a) Peripheral: meets Utsinger's but

not Resnick's criteria with > 3 enthesopathies. b) Axial: Resnick and Utsinger's criteria but < 3 enthesopathies. c) Mixed: Resnick and Utsinger's criteria but > 3 enthesopathies. Statistical analysis: We performed a univariate analysis by frequency (categorical) and main statistical and a bivariate descriptive analysis using ANOVA and Fisher's exact test with a confidence level of 95%.

Results: we included 97 patients, 57, 7% were male. The average age at diagnosis was 65.6 y (47-85) but the age of onset of symptoms was 58.2 y (36-80). The delay in diagnosis was 6.36 years (0-25). All patients met Utsinger criteria but 25.8% did not meet Resnick's definition. The symptoms that led to the diagnosis were: 43.7% pain and/or limitation of thoracic-lumbar spine, 16.7% pain and/or limitation cervical spine, 24% a peripheral enthesopathy, 5.2% hip pain and 10.4% was a radiological finding. We identified: a) Axial pattern (30.9%); b) Peripheral pattern (29.4%); and Mixed pattern (30.9%). Although the value of retrospective data is limited, the clinical history of enthesopathy was collected in a 46.2%. 30 patients were not eligible for statistical analysis because of lack of sufficient data. The predominance of female sex (p=0,004) and a younger age of onset (p=0,027) in peripheral pattern were statistically significative. We also found differences in presenting symptoms between those three phenotypes (p=0,014).

Conclusion: We propose three patterns in DISH based on clinical symptoms and characteristic radiological signs. We found statistical differences especially in gender, age at onset and the presenting symptoms. We need prospective studies to elucidate if they correspond to different stages or if they are different phenotypes of the disease.

Disclosure: T. Clavaguera, None; **R. Valls**, None; **M. C. Rodriguez-Jimeno**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diffuse-idiopathic-skeletal-hyperostosis-can-we-identify-different-clinicoradiological-patterns

Abstract Number: 268

Effect of Abatacept Treatment on T Cells in Muscle Tissue and Peripheral Blood in Polymyositis and Dermatomyositis Patients

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Background/Purpose: Abatacept (CTLA4-Ig), a blocking agent for T cell co-stimulation, has been proven beneficial in several autoimmune diseases. The aim of the study was to measure local and systemic immune cell effects of abatacept in the context of polymyositis and dermatomyositis by comparing baseline with 6-month follow-up samples after abatacept treatment.

Methods: 14 patients were included in this substudy of a 6 months' treatment delayed-start design trial. Abatacept was given as intravenous infusions 10mg/kg monthly, in total 7 times. Muscle biopsies and blood samples were taken at inclusion and 6 months of active therapy. Frozen biopsies from the two time points (n=6 patients) were sectioned and

immunohistochemically stained for T cell, macrophage, and B cell markers. Conventional quantification and image analysis were used to calculate the expression of different markers in muscle tissue sections. Frozen PBMCs (n=13 patients) from baseline and 6 months treatment were analyzed with a 29-antibody panel by mass cytometry (CyTOF) focusing on T cell features. Citrus and t-test were used to analyze the CyTOF results.

Results: Following 6 months treatment, the expression ratio of $FOXP3^+/CD4^+$ in muscle sections increased significantly (P=0.03). For peripheral blood CyTOF data, 8 significant different clusters were identified by citrus analysis, which distinguished baseline from follow-up. The proportion of regulatory T cells ($CD3e^+CD4^+CD25^+FOXP3^+$) increased significantly (P=0.04) at follow-up. More specifically, the proportion of effector/memory like Tregs, $CD3e^+CD4^+CD25^+FOXP3^+CCR6^+CD5^+$ cells, increased significantly (P=0.01) while the other Treg subsets did not significantly change.

Conclusion: Our data from peripheral blood suggest that compared to other T cell subsets, regulatory T cells in IIM are relatively resistant to abatacept therapy. Amongst Tregs, the naïve subset were most sensitive. Similarly we observed an increase of Tregs also in affected muscle tissue which could allow more efficient muscle fiber regeneration/healing, implicating that abatacept may be a beneficial drug for myositis.

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Abstract Number: 269

The Immunoproteasomes Are Essential for Maintaining Myokine Production and MHC Class I Expression in Idiopathic Inflammatory Myopathies

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Background/Purpose: Idiopathic inflammatory myopathies (IIMs) are muscle diseases, characterized by inflammatory infiltration and increased expression of MHC class I molecules on myofibers. Immunoproteasome, as a proteolytic complex that shapes the repertoire of antigenic peptides, has been previously demonstrated to be over-expressed in IIMs at mRNA level. In this study, we aim to investigate the functional role of immunoproteasome in the pathogenesis of IIMs.

Methods: Skeletal muscle biopsy specimens from 45 individuals with well diagnosed (ENMC criteria) inclusion body myositis (IBM, n=12), immune-mediate necrotizing myopathy (IMNM, n=12) and dermatomyositis (DM, n=12), in addition to non-IIMs (nIIMs, n=3) and healthy controls (HC, n=6) were included in this study. Immunoproteasome expressions within the muscle fibers and cellular infiltrates were examined by dual immunofluorescence (IF) and immunoblot. Proteasomal activity was measured in the patient muscle biopsies. Primary human myoblasts were used to determine the most effective cytokine in the induction of immunoproteasome expression. Additionally, the role of immunoproteasome during the *in vitro* inflammatory conditions was investigated in myoblasts by using shRNA based gene silencing and

specific chemical inhibitors. The effect of both approaches in MHC-I expression and myokine production was measured by FACS and real time PCR, respectively.

Results: Immunoblots showed significant increase in the expression of relevant players of the immunoproteasome, β1i or β5i in IBM (n=9) and DM (n=9) muscle biopsies compared to HC (n=6). However, the expression in IMNM (n=9) was moderate. In addition, the chymotrypsin-like activity of proteasome reflected the expression of β1i and β5i in the muscle biopsies. Dual IF revealed that both myofibers and muscle infiltrating cells including CD8+ T-cells and CD68+ macrophages in IIMs (n=6 for IBM, IMNM and DM) expressed β1i or β5i. In fact, the expression of β1i and β5i co-localized with the MHC class I expressing myofibers. In contrast, the muscle fibers of HC (n=4) and nIIMs (n=3) were negative for both β1i and β5i. Our *in vitro* study in the cultures of human primary myoblasts showed that pro-inflammatory cytokines, TNF-α, IFN-α, IFN-β and IFN-γ are able to upregulate β1i and β5i expression. Selective inhibition or depletion of β5i amplified the TNF-α or IFN-γ mediated expression of myokines in myoblasts. Furthermore, we found that specific inhibitors of β1i or β5i reduced the cell surface expressions of MHC class I in myoblasts induced by IFN-γ.

Conclusion: We demonstrated that the immunoproteasome expression and activity are increased in skeletal muscle and could involve in pathologic MHC class I expression in IIMs. Therefore, the suppression of the immunoproteasome expression could be an approach to reduce antigen presentation by skeletal muscles and consequently the cytotoxic effect of T-cells. However, functional analyses revealed that immunoproteasome is also important to maintain the myokines that mediate attraction of immune cells in muscles fibers. Thus, the imbalance between two functions may have an impact on the disease phenotype or severity in IIMs.

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Abstract Number: 270

Retinoic Acid-Inducible Gene-I Increased in Peripheral CD3+T Lymphocytes of Patients with Dermatomyositis

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Background/Purpose: The dysregulation of innate immunity contribute to pathogeneses of dermtomyositis (DM). Previous study indicated that high expression of retinoic acid-inducible gene-I (RIG-I) in skeletal muscle tissue participated the mechanism of muscle damage. The aim of the study was to determine gene and protein expression of RIG-I in peripheral CD3+T lymphocytes of DM patient and to evaluate the correlation between the RIG-I in T lymphocyte and clinical characteristics.

Methods: The study population included 26 treatment-naive DM patients from Department of Rheumatology at China-Japan Friendship Hospital between July 2015 and February 2016 who fulfilled the criteria of definitive DM proposed by Bohan and Peter. All patients did not have indication of clinical symptom, laboratory and auxiliary examinations of virus infection. 14 age-and sex-matched healthy controls were enrolled. The gene and protein expression of RIG-I in peripheral T lymphocytes were determined by RT-PCR and Western blot. Clinical characteristics such as rash, muscle strength, interstitial lung disease (ILD), esophageal involvement and laboratory examination were recorded. Muscle strength and severity of rash were measured by using the Manual Muscle Test (MMT8) and the modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI). 8 patients were followed up after 6 months therapy with glucocorticoid

accompanies with immunosuppressor or not. T-test were used to compare the differences between groups and Spearman's rank was applied to investigate the correlation between the RIG-I expression level and clinical characteristics.

Results: Patients were composed of 9 males and 17 females whose average disease duration was 7.69± 6.39 months. 17 patients and 5 patients were complicated with ILD and esophageal involvement respectively. The average MMT8 score and CDASI were 72.15±6.72 and 19.96 ±10.96 respectively. DM patients had significantly higher level of RIG-I both in gene (0.091 ± 0.051 vs 0.052 ± 0.024; p=0.011) and protein (0.30 ± 0.18 vs 0.18 ± 0.08; p=0.005) expression in T lymphocytes than did healthy control subjects. The levels of protein expression were significantly decreased after therapy with 6 months follow-up (0.32 ± 0.16 vs 0.23 ± 0.17; p=0.017). The gene expression level of RIG-I correlated positively with CDASI score (r=0.455, p=0.02) and negatively with T lymphocyte count (r=-0.466, p=0.016). However, RIG-I level showed no correlation with serum Creatine Kinase (CK) level (p=0.356) and MMT8 score (p=0.284). Patients with ILD had higher gene expression level of RIG-I than that without lung disease involvement (0.107 ± 0.493 vs 0.501 ± 0.029; p=0.006). There was no significant difference between patients with esophageal involvement or not (0.084 ± .0.042 vs 0.093 ± 0.054; p=0.747).

Conclusion: The RIG-I expression level increased significantly in peripheral CD3+T lymphocytes of DM patient and descended after treatment. The increased RIG-I level in T lymphocytes were displaying significant association with rash severity and peripheral lymphopenia. Patients with ILD were more likely to have high level of RIG-I in peripheral T lymphocyte.

Disclosure: L. Zhang, None; **Q. Xia**, None; **W. Li**, None; **Q. Peng**, None; **G. Wang**, None.

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Abstract Number: 271

Impaired Satellite Cell Activation and Myofiber Transition during Skeletal Muscle Regeneration in Patients with Polymyositis and Dermatomyositis

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Background/Purpose: Satellite cells are myogenic stem cells that are essential for myofiber repair, growth and homeostasis in postnatal life. A decline in satellite cell performance has been previously linked with age-associated loss of muscle mass and function; and may also underlie skeletal muscle dysfunction in patients with polymyositis (PM) and dermatomyositis (DM). Successful regeneration of skeletal muscle relies not only on satellite cells, but also on a fine balance between pro- and anti-inflammatory factors. We **hypothesize** that in disease processes such as PM/ DM where chronic inflammation ensues, dysregulated inflammatory responses could lead to inhibition of effective muscle repair and remodeling by inhibiting satellite cell activation and myofiber maturation, and promoting scar tissue formation.

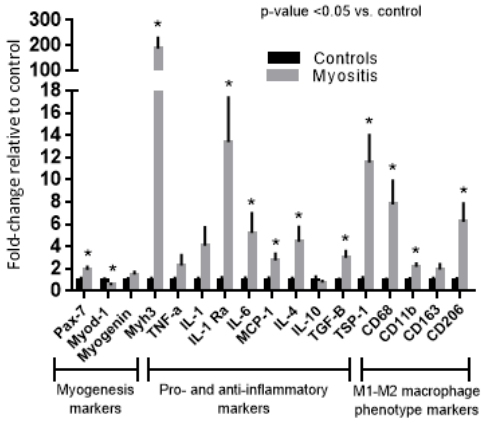
Methods: Skeletal muscle biopsy samples were obtained from 12 treatment refractory DM/PM patients; and 12 generally healthy volunteers who served as age, sex and BMI matched controls. Control biopsy samples were obtained from a skeletal muscle biorepository maintained by the University of Kentucky. Markers of myogenesis, M1/M2 macrophage phenotypes, and pro- and anti-inflammatory markers were assessed by RT-PCR. The data are represented as fold-change compared to controls. Mean values were compared between controls and PM/DM using two sample t-tests. Spearman rank

correlations were used to examine the relationships of markers of myogenesis and immunity with selected disease activity/ damage measures among PM/DM subjects.

Results: In **Figure1**, gene expression of Pax7, a marker of quiescent satellite cells, and embryonic myosin heavy chain (MyH3), a marker of regenerative myofiber formation, are significantly upregulated, while gene expression of MyoD1 and myogenin, markers of activated satellite cells, are either significantly downregulated or not significantly different between PM/DM and controls. Gene expression of pro- (IL6, MCP1) and anti-inflammatory (IL1 Ra, IL4, TGFB and TSP1) markers, as well as both M1 (CD68/11b) and M2 (CD68/206) macrophage markers are significantly upregulated in PM/DM versus controls. Among the markers of myogenesis, only myogenin significantly correlated with MMT-8 muscle testing (r=-0.68, p=0.022), MDAAT muscle disease activity VAS (r=0.82., p=0.002) and serum CK level (r=0.87, p<0.001).

Conclusion: These findings suggest that in PM/DM, the pool of quiescent satellite cells is maintained; regenerative myofiber formation occurs to a certain extent; while activation and terminal differentiation of satellite cells is inhibited. It is interesting to note that gene expression of MyH3 did not correlate significantly with muscle strength. Further studies are needed to determine if embryonic-to-adult myosin heavy chain switch occurs normally in patients with PM/DM, and its effect on functional restoration of myofibers.

Figure 1



Disclosure: B. Hanaoka, None; **P. R. Nagareddy**, None; **M. Campbell**, None; **L. J. Crofford**, None; **C. A. Peterson**, None; **L. G. Rider**, None; **F. W. Miller**, None.

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Abstract Number: 272

Interferon Chemokine Score and Other Cytokine Measures Predict Changes in Disease Activity in Patients with Juvenile and Adult Dermatomyositis

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Background/Purpose: Serum cytokines play an important role in the pathogenesis of myositis by initiating and perpetuating various cellular and humoral autoimmune processes. The aim of this study was to measure interferon (IFN)-inducible chemokines (IFNCK), Th1, Th2, Th17, innate, and regulatory cytokines in patients with adult dermatomyositis (DM) and juvenile dermatomyositis (JDM) at multiple visits to identify biomarkers predictive of changes in disease activity.

Methods: Multiplexed immunoassays (Meso Scale Discovery) enabled simultaneous measurement of IFN-regulated chemokines and other pro- and anti-inflammatory cytokines specific to differentiation of specific T cell and innate pathways. Cytokine scores were computed for IFNCK (IP-10, MCP-1), Th1 (IFNγ, TNFα, and IL2), Th2 (IL4, IL10, IL12, and 1L 13), Th17 (IL6, IL17, IL1β), innate (MIP-1α, MIP-1β, IL8), and regulatory (IL10, TNFα) factors. Spearman correlation was used to examine whether cytokines at a previous visit predict change at the next visit, adjusting for disease activity at the previous visit.

Results: The study included 30 patients (13 DM and 17 JDM) with at least 2 visits (68 visits total). Mean age (SD) at inclusion was 53.3 (18.6) years in DM and 9.9 (5.6) years in JDM, 70% female, 87% Caucasian. Most patients were included at their time of diagnosis. The mean (SD) physician global, muscle and extra-muscular disease activity VAS scores at inclusion were 45 (24), 40(30) and 35(20) cm, respectively. The IFNCK score predicted change in physician global (r=0.30; p=0.012), muscle (r=0.29; p=0.016) and extra-muscular (r=0.24; p=0.05) disease activity. The Th17 score also predicted change in physician global (r=0.28; p=0.020), muscle (r=0.25; p=0.041) in DM and JDM, but extra-muscular only in DM (r=0.41; p=0.029). IL6 levels also predicted change in physician global (r=0.31; p=0.011), muscle (r=0.33; p=0.006) and extra-muscular (r=0.33; p=0.007) disease activity, but these associations were predominately among DM.

Conclusion: IFNCK and other cytokine scores may be useful biomarkers to predict changes in disease activity among myositis patients. Differing associations for JDM and DM may indicate biological differences between diseases that warrant specific biomarkers for each to best predict changes in disease activity.

Disclosure: C. S. Crowson, None; **J. M. Olazagasti Lourido**, None; **M. S. Hein**, None; **R. S. Pendegraft**, None; **M. A. Strausbauch**, None; **T. B. Niewold**, None; **F. C. Ernste**, None; **T. L. Wampler Muskardin**, None; **E. J. Peterson**, None; **E. C. Gillespie**, None; **A. M. Reed**, None.

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Abstract Number: 273

Juvenile Dermatomyositis Patient-Derived Induced Pluripotent Stem Cells Do Not Retain Disease Expression Signatures

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Background/Purpose: Monozygotic twins discordant for JDM are rare, composing only 1% of our entire registry of 525 JM patients. These individuals represent a unique opportunity identify persistent gene expression differences in JDM children by allowing for a control with an identical genome, as well as environmental control with respect to early development

Methods: We recruited a pair of monozygotic, white, male twins discordant for Juvenile Dermatomyositis (JDM), age 9.5 years, and a race, sex matched 7.2 year old control for this IRB approved study. The JDM^{+} twin (MSA=probably MJ positive) held his medications (oral prednisone 7 mg, Sub Q MTX 12.5 mg) on the morning of the blood draw. We isolated PBMCs within two hours of blood draw and expanded erythroblasts in culture for 9-12 days. We induced pluripotentcy by transduction with Sendai virus carrying *Oct3/4*, *Sox2*, *Klf4*, and *cMyc*. After documenting normal karyotypic analysis, we profiled the transcriptomes of 3 separate clones from each of the three individuals to detect persistent JDM gene expression differences.

Results: In the comparison of the JDM iPSC clones to the unrelated control, three algorithms only agreed on 11 differentially expressed (DE) genes out of 54 total. This included increased expression of *HLA-DQB1* (FC 7.6-7.8) and *SRD5A3* (FC 2.1), but decreases in expression for *MTRNR2L8* (FC -5.6) and *ZNF718* (FC -2.6) in the JDM-derived cells. 2 of 3 algorithms agreed that the JDM-derived clones also had increased expression of *HLA-DRB1* (FC 4.8). However, virtually the same genes were DE in the unaffected twin compared to the control. Comparing the JDM affected twin and the unaffected twin clones revealed one gene (*ZDBF2*) of only nominal significance for decreased expression in the JDM clones (adj. p-value 0.10, FC -1.6). Clustering of the top 50 genes from the JDM - control comparison along with *ZDBF2* demonstrated that the twins cluster with each other, rather than the unaffected twin clustering with the unrelated control.

Conclusion: 1) iPSC generation reprograms any baseline JDM disease signatures from the original PBMCs. 2) There are inter-individual genetic differences that affect baseline gene expression, as evidenced by the shared expression patterns between discordant twins. **Speculation**: Genetic factors increase risk for developing JDM, but the initiation of the disease process requires a trigger. It remains to be seen if JDM iPSCs manifest persistent epigenetic changes that prime them for an inflammatory response when presented with a suitable antigenic stimulus.

Disclosure: E. D. O. Roberson, None; **L. Cao**, None; **D. J. Morales-Heil**, None; **D. Xu**, None; **Y. Galat**, None; **V. Galat**, None; **S. Tarvin**, None; **C. C. Huang**, None; **L. M. Pachman**, None.

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Abstract Number: 274

Splicing Factor Proline/Glutamine-Rich Is a Novel Autoantigen of Dermatomyositis and Associated with Anti-Melanoma Differentiation-Associated Gene 5 Antibody.

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Background/Purpose:

Anti- melanoma differentiation-associated gene 5 (MDA5) antibody positive dermatomyositis (DM) and clinically amyopathic DM (CADM) often develop rapidly progressive interstitial lung disesase (RP-ILD), but the pathogenesis is still unclear. We noticed that the sera from many anti-MDA5 antibody positive patients immunoprecipitated the common 110kDa polypeptide. Thus we intended to identify the autoantigen and investigated the clinical significance.

Methods:

Autoantibodies were screened in 340 patients with various connective tissue diseases (CTDs) and 15 healthy controls (HCs) by immunoprecipitation with [^{35}S]methionine-labeled HeLa cells. Immunoabsorbent column chromatography was used to purify the reactive autoantigen and the polypeptide was analyzed by peptide mass fingerprinting.

Results: Anti-110 kDa antibody was detected in 25 DM/CADM patients but not in patients with other CTDs or HCs. All patients with anti-110 kDa antibody were also positive for anti-MDA5 antibody, and had interstitial lung disease. The corresponding polypeptide was identified as splicing factor proline/glutamine-rich protein (SPFQ). Anti-SFPQ antibody was detected at diagnosis and newly appeared in some patients during the disease course. The onsets of DM/CADM had seasonal patterns and showed two peaks according to the temporal appearance of anti-SFPQ antibody. 67% (8/12) of disease onset of patients who had anti-SFPQ antibody at diagnosis were between August and October, whereas 69% (9/13) of those who had newly appearing anti-SFPQ antibody during the disease course were between January and March.

Conclusion:

We identified the anti-110 kDa antibody as DM/CADM specific autoantibody that recognizes SFPQ in patients who also have anti-MDA5 antibody. The onset of DM/CADM with anti-MDA5 antibody had seasonality according to the appearance time of the antibody to SFPQ, which has a role in innate immune responses. These findings may provide new insights into the pathogenesis of DM/CADM with anti-MDA5 antibody.

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Abstract Number: 275

In Vitro Activation of Type I Interferon Pathway Reproduces the Characteristics Damages Observed in Dermatomyositis Patients

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Background/Purpose: The type I interferons (IFN-I) including IFN-a, and IFN-b are key cytokines involved in innate immune response to viral infection. Almost all cells can produce IFN-I, express IFN-I receptor (IFNAR) and induce the transcription of IFN stimulated genes (ISGs), which have anti-proliferative and immunomodulatory activities. Idiopathic inflammatory myopathies (IIMs) are acquired auto-immune diseases. Among the IIMs, Dermatomyositis (DM) is characterized by skin lesions, muscle specific pathologic features combining inflammatory infiltration with HLA-ABC over-expression and vasculopathy. It is known that DM patients express up-regulated ISGs in muscle fibers, endothelial cells (EC), skin tissues and peripheral blood. However, the effect of the IFN-I on myoblasts (MB), myotubes (MT) and EC has not been well determined. Therefore, the aim of this study is to determine if MB, MT and EC present functional changes when exposed to IFN-I.

Methods:

The effect of the activation of IFN-I pathway on the differentiation of MB, and EC and on MT was analyzed *in vitro*. Thus, those cells were cultured with recombinant IFN-I, IFN-a, IFN-β and Poly (I:C) (PIC), an agonist of TLR3 receptor.

Results:

The results on MB showed that PIC, IFN-a and IFN-β abolished myotube formation and decreased myogenin (MyoG) expression. In differentiated MT, all stimuli induced ISGs (MxA and OAS1). Moreover, IFN-a, IFN-β and PIC dramatically reduced myotube surface. Next, IFN-a and IFN-b neutralization and IFNAR blocking experiments confirmed the specificity of the results. Neutralization and blocking experiments in differentiating MB treated with IFN-I, IFN-a and PIC, reverted the myotube formation and myogenin expression. Along the same lines, the surface area in differentiated MT area was restored. In addition, qPCR results showed the upregulation of genes involved in muscle atrophy such as Murf1 and Atrogin with a decrease of MyoG expression. The overexpression of Murf1 and atrogin was confirmed at the protein level *in vivo,* in muscle biopsies from DM patients. The presence of both proteins was detected in perifasicular areas, where atrophic fibers cluster. All stimuli induced HLA-ABC and TLR3 expression in differentiated MT and the presence of IFN-I in the supernatants in MB and MT. The activation of IFN-I pathway in EC, led to a decrease in cell proliferation and ISG up-regulation (MxA, RIG-I, ISG15 and TLR3). Tube formation assay with EC in the IFN-I-activated EC showed a disruption of the vascular network formation, indicating that IFN-I impairs angiogenesis *in vitro*.

Conclusion: In conclusion, *in vitro* treatment with IFN-I or IFN-I pathway activation recapitulates the characteristic pathological features (muscular and vascular damage) defining DM. This emphasizes the key role of the IFN-I pathway in the pathophysiology of DM, results that potentially may lead to new avenues for therapeutic approaches.

Disclosure: L. Ladislau, None; **X. Suárez-Calvet**, None; **C. Benjamin**, None; **S. Toquet**, None; **B. Terrier**, None; **F. Rozenberg**, None; **V. Mouly**, None; **G. Butler Browne**, None; **W. Stenzel**, None; **O. Benveniste**, None; **Y. Allenbach**, None.

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Abstract Number: 276

Histological Study on the Expression of Transcriptional Intermediary Factor 1 (TIF1) in the Patients with Idiopathic Inflammatory Myopathies

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Background/Purpose: Myositis-specific antibodies in patients with inflammatory myopathies are known to be associated with various clinical manifestations, classifications and diagnosis. Among them, recently found anti-transcriptional intermediary factor 1 (TIF1) α, β, or γ antibodies has been reported to be associated with dermatomyositis (DM) accompanied by cancer. Although previous studies have evaluated the association of the antibodies in serum and clinical subtypes, the information about the target antigen is insufficient. The purpose of this study was to confirm the overexpression of TIF1s in the muscle and skin tissues of patients with inflammatory myopathies.

Methods: From February 2004 to November 2014, skin and muscle biopsies were performed on 45 patients diagnosed with dermatomyositis and polymyositis. We stained skin and muscle tissue by immunohistochemistry using anti-TIF1α, β, or γ and compared with the results of healthy control. We analyzed the association between the clinical manifestations and protein expression in each tissue.

Results: When compared with the control group, any antigens showed no significant overexpression in the muscle. However, TIF1α showed higher positive rate in the skin of DM (12/15 [80%]) than in the skin of healthy control (0/7 [0%]) (p=0.001). TIF1γ expression was higher in the muscle of patients with DM while there was no expression in the muscle of healthy controls (DM, 8/19 [80%] vs. healthy control 0/7 [0%], p=0.039). In the tissues of inflammatory myopathies, TIF1α and TIF1γ demonstrated higher positive rates in the skin than in the muscle (TIF1α, muscle, 4/35 [11%] vs. skin, 12/15 [80%], p<0.001; TIF1γ, muscle, 10/35 [29%] vs. skin, 13/15 [87%], p<0.001). When analyzing DM patients only, the result was similar (TIF1α, muscle, 1/19 [5%] vs. skin, 12/15 [80%], p<0.001; TIF1γ, muscle, 8/19 [42%] vs. skin, 13/15 [87%], p=0.013). TIF1β showed strong positivity in all tissues of myositis or healthy control. Analyzing the association with TIF1s expression and cancer, there was no significant difference in the positive rate of TIF1α or γ in the muscle or skin between the myositis patient with or without cancer.

Conclusion: TIF1α was expressed more in the skin of DM patients than that in that of control group and TIF1γ in the muscle of DM patients than in that of control. The expression of TIF1α in the skin and TIF1γ in the muscle of cancer associated DM was not higher than those of DM without cancer. Thus the expression levels of TIF1α in the skin and TIF1γ in the muscle may be associated with myositis rather than with cancer.

Disclosure: Y. Kim, None; **J. Kim**, None; **S. W. Kang**, None; **S. C. Shim**, None; **I. S. Yoo**, None; **S. J. Yoo**, None; **S. H. Chang**, None.

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Abstract Number: 277

Abnormal Composition of Circulating T and B Cells in Patients with Polymyositis and Dermatomyositis Is More Biased in Those with Interstitial Lung Diseases

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Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are systemic inflammatory myopathies. They sometimes accompany interstitial lung disease (ILD), which can lead often to fatal outcome. For PM and DM treatment, high dose corticosteroid and cytotoxic drugs are used as first line therapies. Additionally, the effectiveness of T- and B-cell targeted therapies for refractory PM/DM has been reported. Although the clinical evidence indicates the T- and B-cell involvement in the pathogenesis of PM/DM, the lymphocyte subsets that contribute to the pathogenesis remain unclear. Analyzing peripheral blood mononuclear cell (PBMC) subsets will provide important insights into the understanding of the immune status and the pathogenesis in PM/DM. The aim of this study was to elucidate the lymphocyte subset biases of peripheral blood from the patients with PM/DM.

Methods: PBMCs from 17 (4 PM and 13 DM) patients including 8 patients with ILDs and from 18 healthy donors (HDs) were examined for lymphocyte subsets with flow cytometry according to the standardized immunophenotyping (Nat Rev Immunol 2012;12:191-200). Lymphocyte subsets were compared among patients with ILDs, those without ILDs, and HDs. In 6 DM patients, the lymphocyte subsets before and after the successful treatment were compared.

Results: The PM/DM patients had larger subsets of naïve CD4 T and naïve B cells, and smaller subsets of naïve CD8 T, central memory CD8 T (CD8 T_{CM}), effector memory CD4 T (CD4 T_{EM}), Th1, and memory B cells than HDs. These biased subsets were compared among the patients with ILDs, those without ILDs, and HDs. The patients with ILDs had larger biases in all of these subsets, except for Th1 cell subset, than HDs. Similar trends were also observed in PM/DM patients without ILDs although the differences were not statistically significant. Among the biased subsets in the patients, the naïve B cell subset decreased and the memory B cell subset increased after treatment.

Conclusion: The biases in naïve and memory T- and B- cell subsets suggest abnormal homeostatic regulation or migration of the smaller subsets from the peripheral blood into the inflamed tissues in PM/DM. Normalization of the biases in B-cell subsets after treatment implies B-cell involvement in the pathogenesis. The biases in T- and B-cell subsets in the patients with ILDs may represent intensive autoimmunity.

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Abstract Number: 278

Expression of Anti-Microbial Peptide LL-37 Correlates to the Activation of Type I Interferon Pathway in Patients with Idiopathic Inflammatory Myopathies

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Background/Purpose: Polymyositis (PM) and dermatomyositis (DM) are systemic autoimmune diseases whose pathogenesis remain unclear. The type I interferon system has recently been suggested to have a role in subgroups of myositis patients, however the triggering factor have not yet been clarified. The anti-microbial peptide, LL-37, carriers numerous immunomodulatory properties in addition to its anti-microbial activity and is implicated in the pathogenesis of several autoimmune diseases through activation of the type I interferon pathway. The aim of this study was to explore a potential role of LL-37 in the pathogenesis of PM and DM.

Methods: Muscle biopsies taken from 6 PM, 6 DM and 5 healthy controls(HC) and skin biopsies taken from both affected (5 DM) and non-affected(3 of DM) areas and 6 HC were immunohistochemically stained for LL-37(monoclonal and polyclonal), CD66b(neutrophil), MxA(type I interferon induced protein) and BDCA-2(pDC). Double immunofluorescence stainings for LL-37 and CD66b was performed. The expression of LL-37 in muscle was confirmed with western blot.

Results: The expression of LL-37 was significantly increased in muscle tissue and symptomatic skin in patients with PM/DM compared to that in HC. LL-37 was mainly expressed by neutrophils as confirmed with double staining. The expression of monoclonal LL-37 positively correlated to CD66b expression in both muscle and skin tissues in PM/DM patients($R=0.9$ and 0.74 respectively, $P<0.01$). BDCA-2 positive pDCs was significantly increased in muscle tissue in patients when compared to HC. MxA was expressed in the same areas as LL-37, CD66b and BDCA-2, and positively correlated with CD66b expression in muscle tissue in all patients($R=0.59$, $P<0.05$). Moreover, the muscular expression of LL-37 and CD66b correlated with increased serum creatine kinase levels($R=0.62$ and 0.71 respectively, $P<0.05$). Monoclonal LL-37 expression in muscle tissue in patients with short disease duration correlated negatively to FI-2 score ($P<0.05$, $R=0.77$).

Conclusion: The data indicated that neutrophil-derived LL-37 may induce type I interferon production in affected muscle and skin tissues in patients with PM and DM and be involved in the pathogenesis of these conditions.

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Abstract Number: 279

Increased Heat Shock Protein 90 in Muscle Tissue and Plasma in Idiopathic Inflammatory Myopathies Correlates with Disease Activity and Skeletal Muscle Involvement

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Background/Purpose: Heat shock proteins (Hsps) are chaperones playing important roles in skeletal muscle physiology, adaptation to exercise or stress, and activation of inflammatory cells. The aim of our study was to assess Hsp90 expression in muscle biopsies and plasma of patients with idiopathic inflammatory myopathies (IIM) and to characterize its association with IIM-related features.

Methods: Total of 277 patients with IIM (198 females, 79 males; mean age 54.8; disease duration 4.1 years; dermatomyositis (DM, 104)/polymyositis (PM, 104)/cancer associated myositis (CAM, 42)/ necrotizing myopathy (IMNM, 27)) and 100 age-/sex-matched healthy individuals were included in plasma analysis and 50 muscle biopsy samples were stained for Hsp90 (PM-10, DM-10, IMNM-10, myodystrophy-10, myasthenia gravis-10). Patients with PM/DM fulfilled Bohan and Peter criteria and CAM was defined as cancer within 3 years of IIM diagnosis. Plasma Hsp90 was measured by ELISA (eBioscience, Vienna, Austria). Clinical disease circumstances were evaluated by Myositis Disease Activity Assessment (MYOACT), Myositis Intention to Treat Index (MITAX), Myositis Damage Index (MDI), physician and patient global activity using VAS and manual muscle testing (MMT8). CK, LD, ALT, *AST*and CRP were analyzed by routine techniques and IIM-specific autoantibodies by in-line blot and immunoprecipitation. Data are presented as median.

Results: In muscle biopsies Hsp90 expression was higher in IIM than in myodystrophy (myasthenia gravis used as another control was negative). Increased Hsp90 was detected in perifascicular degenerating and regenerating fibers, inflammatory cells (DM, PM), and necrotic and regenerating fibers (IMNM). Plasma Hsp90 levels were increased in IIM patients compared to healthy controls (20.2 vs. 9.2 ng/ml, $p < 0.0001$), and in individual subgroups of IIM vs. healthy controls (PM: 19.4, DM: 22.4, CAM: 19.1, IMNM: 19.6 ng/ml, $p < 0.0001$ for all). Hsp90 levels in all patients positively correlated with LD and AST ($r=0.551$, $p < 0.0001$; $r=0.372$, $p < 0.0001$, respectively), and there was a trend towards correlation with CK ($r=0.111$, $p=0.068$). Increased Hsp90 was associated with decreased MMT8 values ($r=-0.136$, $p=0.029$), in particular in proximal muscles. Hsp90 positively correlated with patient and doctor disease activity ($r=0.222$, $p=0.0004$; $r=0.217$, $p=0.0005$, respectively), pulmonary and muscle disease activity ($r=0.201$, $p=0.001$; $r=0.146$, $p=0.018$, respectively), MITAX and MYOACT ($r=0.175$, $p=0.005$; $r=0.159$, $p=0.012$, respectively), and with MDI extent/severity ($r=0.215$, $p=0.003$; $r=0.120$, $p=0.041$, respectively). Higher Hsp90 was found in patients with interstitial lung disease, cardiac involvement and dysphagia (25.4 vs. 18.9, $p=0.004$; 27.5 vs. 19.3, $p=0.004$; 25.0 vs. 18.2, $p=0.018$, respectively).

Conclusion: We demonstrate increased Hsp90 expression in IIM muscle biopsy samples, specifically in inflammatory cells, degenerating, regenerating and/or necrotic fibers. Increased Hsp90 plasma levels in IIM patients are associated with disease activity and damage, and with the involvement of proximal skeletal muscles, heart and lungs. Acknowledgement: Supported by AZV-16-33542A.

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Abstract Number: 280

Increased Expression of TIF-1 Gamma in Duodenal Adenocarcinoma from a Patient with p155/140 Dermatomyositis: A Causal Relationship?

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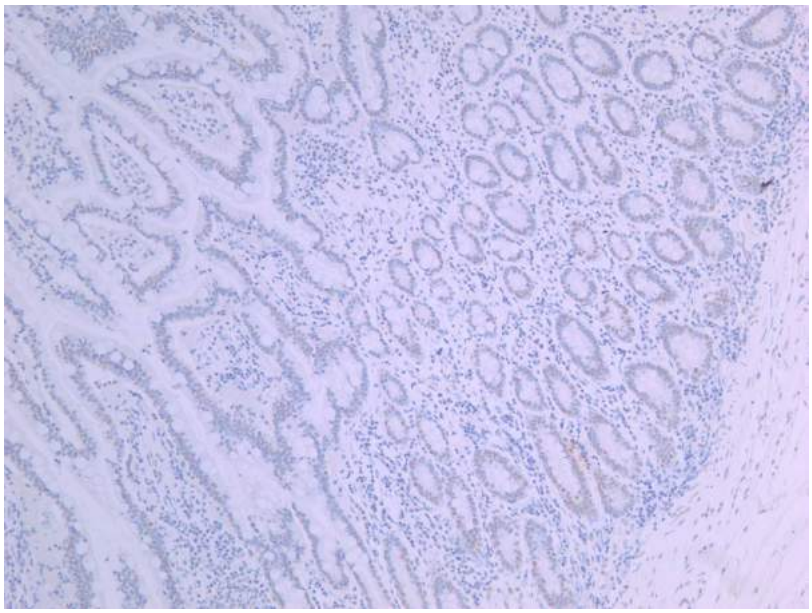
Increased expression of TIF-1 gamma in duodenal adenocarcinoma from a patient with p155/140 dermatomyositis: a causal relationship?

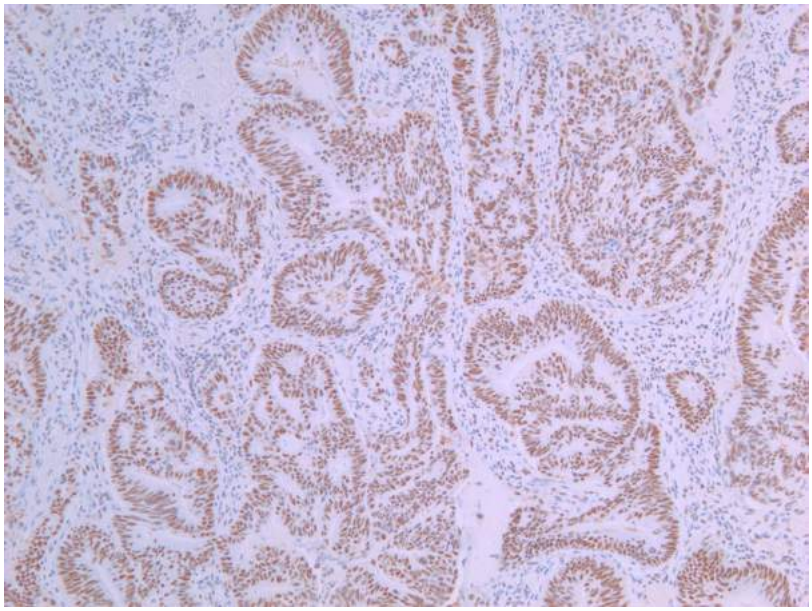
Background/Purpose: Dermatomyositis is associated with an underlying malignancy in about 24% of cases. Anti-p155/140 antibodies have a strong predictive value for malignancy in adult dermatomyositis patients. The proposed target of the p155/140 antibodies are the TIF-1 family proteins, in particular TIF-1γ. Overexpression of TIF-1γ has been associated with the onset and progression of human hepatocellular carcinoma as well as with poor prognosis and worse survival in breast cancer, which suggests that it may play a role in carcinogenesis and represent a novel prognostic marker. We postulated that TIF-1γ was overexpressed in the duodenal adenocarcinoma of a patient with p155/140 dermatomyositis.

Methods: The patient's intestinal mass was processed following standard protocols for clinical examination and staging of intestinal cancer. After the primary diagnosis was made, formalin/PFA-fixed paraffin-embedded tissue blocks representative of the adenocarcinoma, adjacent normal small intestinal mucosa, as well as small intestinal adenocarcinoma tissue from a patient without dermatomyositis were selected for immunohistochemical staining with an anti-TIF-1γ mouse monoclonal primary antibody (Abcam Inc. Catalog nr. ab57172).

Results: The non-neoplastic small intestinal mucosa (figure 1) adjacent to the tumor showed an expected pattern of staining, with faint nuclear positivity in the regenerating cells of the crypts. The tumor cells (figure 2), however, showed strong diffuse nuclear staining, consistent with high levels of TIF-1γ. The small intestine adenocarcinoma from a patient without dermatomyositis also showed strong diffuse nuclear positivity.

Conclusion: We present the first evidence to our knowledge of TIF-1 overexpression in a solid tissue malignancy from a patient with anti-TIF-1γ (anti-p155/140) dermatomyositis. TIF-1γ was markedly overexpressed in the adenocarcinoma tissue from both the patient with p155/140 dermatomyositis and the patient without dermatomyositis, but showed only faint nuclear expression in the healthy intestinal tissue. The most intriguing question remains why TIF-1γ overexpression in malignant cells does not lead to an autoimmune response in each case and whether genetic alterations in the TRIM33 locus may render TIF-1γ immunogenic in a specific subset of patients.





Disclosure: M. DiStasio, None; **G. Stojan**, None.

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Abstract Number: 281

Characterization of Anti-3-Hydroxy-3-Methylglutaryl Coenzyme a Reductase Autoantibodies in Juvenile Idiopathic Inflammatory Myopathies

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Background/Purpose: Autoantibodies (Abs) to 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase (HMGCR) identified in adult myositis patients with immune-mediated necrotizing myopathies (IMNM) have been associated with severe weakness, HLA DRB1*11, and statin use. The prevalence and features of juvenile idiopathic inflammatory myopathies (JIIM) patients with this myositis autoantibody (MSA) have not previously been described. Our purpose was to evaluate the prevalence, clinical features and outcomes of JIIM with anti-HMGCR Abs.

Methods: We examined the prevalence of HMGCR Abs in the Childhood Myositis Heterogeneity Study, a nationwide registry of JIIM patients. We also examined demographics and clinical features, outcomes, responses to therapy and associated HLA alleles for this MSA, and whether this MSA can be distinguished from other MSAs in children with myositis.

Results: Of the 441 JIIM patients tested, anti-HMGCR Abs were detected in the serum of 5 patients (1.1%) by ELISA and confirmed by immunoprecipitation. Among these 5 patients, 3 had juvenile dermatomyositis (JDM) and 2 had juvenile polymyositis (JPM). Median age at diagnosis was 8.1 years, 60% were female, 3 were Caucasian, 1 each was Black and Hispanic. HLA typing revealed the DRB1*0701-DQA1*0201 haplotype in 4 patients, and DRB1*0701 allele alone in the 5th (OR =$1.4X10^7$, P≤0.001 vs. healthy controls). None of the patients had a documented statin exposure. All patients had severe disease and were hospitalized at onset, and 2 used a wheelchair. Proximal and distal weakness, falling episodes, muscle atrophy, joint contractures and arthralgias were uniformly present in JIIM patients with anti-HMGCR Abs, and most of these were increased in frequency compared to other MSAs, including anti-synthetase (ARS), p155/140, MJ, and MSA-negative (p = 0.038 – 0.005), but not different from those with anti-SRP Abs. The median highest serum CK in patients with HMGCR Abs was 17,000 U/L [IQ range 441– 17,112 U/L]. Two patients' muscle biopsies showed prominent myonecrosis, myophagocytosis, degeneration, fiber size variation, and mild mononuclear cell infiltration. In 2/3 JDM patients, rashes were frequently mild and improved quickly. Other frequent features were fatigue (5/5), weight loss (4/5), dysphagia, regurgitation, dyspnea (3/5 each), while interstitial lung disease, cardiac involvement and Raynaud's were absent or infrequent, differing from anti-SRP and ARS Abs. The median number of drug received was 8.0 [IQ range 4.0-9.0] in patients with HMGCR Abs, with a median of 9 treatment trials and 2.6 drug therapies per trial over 22 months. All patients received oral prednisone and MTX; 4 IV methylprednisolone, 3 IVIG, 2 cyclophosphamide, and 2 biologics. Patients had partial responses to many of these, and none entered remission. Four patients had a chronic and 1 had polycyclic disease course. On final evaluation, 3 had continued weakness, 2 had elevated serum CK.

Conclusion: Anti-HMGCR Ab is an uncommon MSA in patients with JIIM, and as in adults, is associated with severe weakness, a necrotizing myopathy, and treatment-refractory disease. Interestingly, unlike adults, statin use has not been identified and a different HLA allele, HLA DRB1*0701, is associated in JIIM cases.

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Abstract Number: 282

From 'immune Mediated Necrotizing Myopathy' to 'antibody-Mediated Necrotizing Myositis: Towards the Pathogenic Role of Anti-SRP and Anti-Hmgcr Antibodies'

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Background/Purpose: Immune mediated necrotizing myopathy (IMNM) has been recently added as a new entity among dermatomyositis, polymyositis and sporadic inclusion body myositis. IMNM is defined by predominant muscle fiber necrosis and no or few inflammatory infiltrates. Two auto-antibodies are held to be specifically associated with IMNM: the anti-signal recognition particle antibody (SRP) and anti-3-Hydroxy-3-Methylglutaryl-CoA Reductase antibody (HMGCR). Those antibodies target ubiquitous cytoplasmic proteins. The clinical phenotype of SRP and HMGCR patients is characterized by severe proximal weakness of skeletal muscles, whereas extra-muscular manifestations are mild or absent. However, it is unknown to which extent pathological features are similar and muscular immune mechanisms especially those involved in the necrosis are largely unknown. It is crucial to gain insight in pathophysiology of the disease regarding its severity and refractory course.

Methods: Thus, we aim to precisely describe the morphology of skeletal muscle alterations of both conditions in a series of SRP and HMGCR patients, and analyze molecular immune mechanisms at the muscular level. Muscle biopsies from SRP (n=25) and HMGCR (n=19) patients were analyzed and compared to myositis patients (Jo-1, n=21 and dermatomyositis, n=7).

Results: SRP patients have the most important muscle deficit compare to HMGCR, Jo1 and dermatomyositis patients. Along that line, CK levels in SRP patients were the highest whereas the DM group had the lowest values. SRP patients showed the highest proportion of necrotic fibers and strikingly this proportion was similar in HMGCR and Jo1 patients. However, necrosis occurred in perifascicular regions only in Jo-1 patients, whereas it was randomly distributed in SRP and HMGCR patients. Creatine kinase levels correlated with proportion of necrotic fibers. Regeneration of fibers also correlated with necrosis and occurred much more frequently. Inflammation was regularly observed. Macrophages were the most abundant but T cells densities were in a quarter of cases in the same range as myositis controls. In addition, presence of T cells densities in SRP and HMGCR patients correlated with the proportion of necrotic fibers. qPCR and immunohistochemistry analysis showed the presence of classically activated macrophages in a Th-1 immune environment. These M1 macrophages were involved in myophagocytosis. In addition, humoral immunity with activation of the classical pathway of the complement cascade was observed. This was accompanied by a sarcolemmal immunoglobulins depositions and alternatively activated macrophages. Finally, positive membrane staining for SRP and HMGCR proteins were detected both *in vitro* (primary muscle cells culture) and *in vivo*(muscle biopsies for IMNM patients) on some muscle fibers.

Conclusion: SRP and HMGCR myopathies can no longer be considered as non-inflammatory myopathies since the inflammation is correlated with muscle necrosis, which involves humoral immunity including myositis-specific autoantibodies.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/from-immune-mediated-necrotizing-myopathy-to-antibody-mediated-necrotizing-myositis-towards-the-pathogenic-role-of-anti-srp-and-anti-hmgcr-antibodies

Abstract Number: 283

Extracellular Histidyl-tRNA Synthetase in Myositis

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Background/Purpose: Histidyl-transfer RNA synthetase (HisRS, Jo-1) is a major autoantigen in myositis with lung involvement[1-4]. Simultaneous presence of anti-Jo-1 and anti-Ro52 antibodies has been demonstrated in patients with myositis[5-7]. We investigated the presence of HisRS in the extracellular compartments plasma, sera and bronchoalveolar lavage fluid (BALF). In addition, the occurrence of anti-Jo-1 antibody isotypes as well as anti-nuclear antibodies (ANA) was evaluated in BALF and sera from patients with myositis.

Methods: HisRS was measured in sera, plasma and BALF from patients with myositis (in both anti-Jo-1 positive and anti-Jo-1 negative patients), sarcoidosis, rheumatoid arthritis (RA) and healthy controls (HC) by dot-blot, western-blot, immunoprecipitation and mass spectrometry. The presence in BALF and sera of anti-Jo-1 isotypes and ANA was analysed by ELISA and addressable laser bead immunoassay.

Results: HisRS was detected in sera, plasma and BALF of patients with myositis, sarcoidosis and RA, and in HC. Systemic HisRS levels were significantly elevated in anti-Jo-1 positive myositis (14 out of 20 sera) compared to anti-Jo-1 negative myositis (10/18), sarcoidosis (0/8) and RA (3/15) patients, and HC (5/23). In BALF, significant levels of HisRS were detected in 6/8 HC and 5/8 sarcoidosis, compared to 4/8 myositis (2 anti-Jo-1 positive and 2 anti-Jo-1 negative). Our results suggest the presence of a factor in BALF with high binding capacity for HisRS and HisRS complexed with anti-HisRS-N-terminal antibody. C1q-immune complexes (IC) binding HisRS were not the binding factor. However, anti-Jo-1 antibodies as well as anti-Ro52 IgG were identified in myositis BALF (5/8 patients were positive for anti-Jo1 IgG, 3/8 for anti-Jo1 IgA, 3/8 for anti-Jo1 IgM and 4/8 for anti-Ro52 IgG). Furthermore, a positive correlation between the presence of anti-Jo-1 IgG and anti-Ro52 IgG in myositis BALF was identified (r^2=0.881; p=0.007).

Conclusion: HisRS was detected both in blood and BALF. The identification of extracellular HisRS, anti-Jo-1 isotypes and anti-Ro52 IgG in myositis BALF may provide additional clues for the development of autoimmunity in the lungs.
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Abstract Number: 284

Gene-Environmental Interaction of HLA-DRB1*03:01 and Smoking for the Development of Anti-Jo-1 Autoantibodies in Idiopathic Inflammatory Myopathies: A UK Study

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Background/Purpose: The idiopathic inflammatory myopathies (IIM) are a heterogeneous group of rare autoimmune diseases characterised by muscle weakness and extramuscular manifestations. The most common autoantibody in IIM is anti-Jo-1, present in ~20% of patients and associated with anti-synthetase syndrome; a distinct clinical entity characterised by the presence of myositis, interstitial lung disease, Raynaud's and mechanics' hands. The development of anti-Jo-1 antibodies is also associated with the presence of HLA-DRB1*03:01. Smoking is a risk factor for ACPA+ rheumatoid arthritis in patients possessing the shared epitope. A previous study has suggested an interaction between smoking and DRB1*03 for the development of anti-Jo-1 antibodies in IIM. We sought to replicate this in a large single-country cohort using high resolution HLA imputation data.

Methods: Eight hundred and seventy two UK patients of Caucasian descent were recruited through the UK Myositis Network (UKMYONET) and Juvenile Dermatomyositis Research Group (JDRG) comprising predominantly of adult and juvenile dermatomyositis and polymyositis patients. Juvenile cases were included as a group of patients not exposed to smoking. Smoking was defined as 'having ever smoked at least one cigarette a day for as long as a year' at the time of recruitment. Antibody testing was conducted using immunoprecipitation. DRB1*03:01 was imputed from SNP genotyping information using SNP2HLA. Five hundred and ninety one patients had complete data for smoking, DRB1*03:01 and anti-Jo-1 status.

Results: A strong effect was seen with DRB1*03:01 and the development of anti-Jo-1 antibodies (see table 1). In DRB1*03:01 negative cases, an association was found between smoking and the development of anti-Jo-1 antibodies (p=0.04). In DRB1*03:01 positive cases, an association between smoking and the development of anti-Jo-1 antibodies almost reached statistical significance (p=0.052). No departure from a multiplicative effect between smoking and DRB1*03:01 was observed using anti-Jo-1 as the outcome measure, suggesting that there is no interaction between smoking and DRB1*03:01 status. When repeating the analysis in adult cases only, the effect of smoking did not reach statistical significance for the development of anti-Jo-1 antibodies.

Conclusion: Smoking may be associated with an increased risk of developing anti-Jo-1 antibodies, independent of DRB1*03:01 status. The exposure to smoking in adulthood may contribute to the increased frequency of anti-Jo-1 antibodies in adult compared to juvenile IIM cases.

Table 1 Anti-Jo-1 frequency by smoking and HLA-DRB1*03:01 status using DRB1*03:01 negative non-smokers as the reference group. Includes 591 adult and juvenile patients.

Smoking status	DRB1*03:01 status	Jo-1 +ve, n (%)	Jo-1 –ve, n (%)	OR, 95% CI	P value
Negative	Negative	6 (3)	211 (97)	1.0	
Positive	Negative	7 (8)	76 (92)	3.24, 1.06-9.94	0.04
Negative	Positive	40 (20)	156 (80)	9.02, 3.73-21.80	P<0.0001
Positive	Positive	30 (32)	65 (68)	16.23, 6.22-49.28	P<0.0001

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Abstract Number: 285

Antibodies to Small Ubiquitin-like Modifier Activating Enzyme: Frequency and Characteristics of Antibody-Positive Patients in an Unselected Cohort

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Background/Purpose: Antibodies to small ubiquitin-like modifier activating enzyme (SAE) are associated with diagnosis of dermatomyositis (DM). The aims of this study were to establish the frequency, demographic and clinical characteristics of SAE antibody-positive patients in a referral setting, and to evaluate the performance of a line immunoblot assay (LIA) for detection of SAE antibodies.

Methods: Consecutive samples (n=3,921) received at ARUP Laboratories for myositis antibodies testing were screened by protein immunoprecipitation (IP) of S^{32}-labeled K562 cells. Antinuclear antibodies (ANA) were detected by indirect immunofluorescent antibody (IFA) test. Of these, 13 samples with distinct bands corresponding to approximately 40 and 90 kDa were identified as suspicious of SAE and tested for SAE antibodies by LIA. As controls, 170 disease controls and 44 self-proclaimed healthy controls were also evaluated by LIA. Clinical and laboratory data for all SAE antibody-positive patients were sought to confirm diagnosis.

Results: Twelve out of 13 patient samples with 40 and 90 kDa bands observed in the IP assay were positive in the LIA. SAE antibodies were identified in 2 of the disease control samples, one signal recognition particle (SRP) antibody-positive sample with additional bands at 40 and 90 kDa and one transcriptional intermediary factor 1-γ (TIF1γ) antibody-positive sample with no apparent bands corresponding to 40 and 90 kDa bands (false positive rate = 0.5%). SAE antibodies were not identified in any of the self-proclaimed healthy controls. Overall very good qualitative agreement was observed between the two methods for SAE antibody marker (Cohen's *kappa* = 0.92, 95% CI 0.81-1.00). The positive, negative, and total percent agreements were 92.3% (95% CI 64.0-99.8%), 99.5% (95% CI 97.4-100%), and 99.5% (95% CI 97.5-100%), respectively. SAE antibodies were detected by IP and LIA in 12/3,921 sera (0.3%). Patients positive for SAE in both methods all had a confirmed diagnosis of DM, with characteristic cutaneous manifestations and varying degrees of muscle involvement. Presence of SAE antibodies was mainly associated with homogeneous and/or speckled antinuclear antibody patterns by IFA.

Conclusion: Identification of SAE antibodies is important not only for diagnosis, but also for prognosis and disease management in patients with DM since some of the other DM-associated autoantibodies have been associated with malignancy or rapidly progressive interstitial lung disease. Testing for SAE antibodies is currently only performed by a small number of labs, primarily on a research basis. LIA confirmed the presence of SAE antibodies in patients with 40 and 90 kDa bands observed in the IP assay. Combined use of both methods improves reliability for the diagnosis of DM in patients undergoing evaluation for inflammatory myopathies.

Disclosure: A. Tebo, None; **T. Jaskowski**, None; **L. Peterson**, None.

Abstract Number: 286

Clinical Significance and Prognostic Value of Neutrophil to Lymphocyte Ratio in Patients with Dermatomyositis

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Background/Purpose: Recent studies have suggested that neutrophil to lymphocyte ratio (NLR) could be an emerging predictive marker of disease activity or mortality in patients with chronic inflammatory diseases, cardiovascular diseases or malignancies. This study was aimed to evaluate the clinical significance and prognostic value of NLR in patients with dermatomyositis.

Methods: We retrospectively reviewed 176 patients with newly diagnosed dermatomyositis who satisfied Peter and Bohan criteria between August 2003 and January 2016. Clinical characteristics and laboratory findings were compared between survivor group and non-survivor group. Using the receiver operating characteristics curves, the cut-off value of NLR for predicting survival was calculated. Univariate and multivariate analyses using Cox proportional hazard model were performed to identify associated factors with survival.

Results: During follow-up (range 0.22-119.4 months), 24 patients (13.6%) died. Non-survivor group had older age (p = 0.011), more interstitial lung disease (ILD, p = 0.015), higher NLR (p = 0.011), lower albumin (p < 0.001), and higher creatinine level (p = 0.005) than survivor group. NLR showed significant positive correlation with C-reactive protein (CRP, r = 0.386, p <0.001), creatine kinase (CK, r = 0.161, p = 0.036), and lactate dehydrogenase (LDH, r = 0.3253, p = 0.001), and negative correlation with albumin (r = -0.298, p <0.001). The optimal cut-off value of NLR for overall survival was 3.8 with the area under the curve of 0.717. According to the cut-off value of 3.8, we classified 87 patients (49.4 %) into the low NLR group and 83 patients (47.2 %) into the high NLR group. The higher NLR group was associated with fever (p = 0.001), the higher muscle enzymes (CK, p = 0.025; LDH, p = 0.001), higher CRP (p < 0.001), lower albumin (p < 0.001), high-dose glucocorticoid therapy (p = 0.031), acute interstitial pneumonia (p = 0.024) and death (p < 0.001). Kaplan-Meier analysis and log-rank test demonstrated a significant difference in survival curves according to NLR of 3.8 (p < 0.001). Cox hazard regression analysis showed that NLR >=3.8, low albumin, the presence of ILD and old age were independent predictors for death (Table 1).

Conclusion: Our results demonstrated that higher level of the NLR was associated with worse overall survival and the NLR may play a role as an independent prognostic marker in patients with dermatomyositis.

- Table 1. Multivariate Cox hazard regression analysis of risk factors for death in patients with dermatomyositis

Variable	Death		
	HR	95% CI	p-value
Age	1.087	1.038-1.137	<0.001
NLR >= 3.8	4.905	1.413-17.025	0.012
Interstitial lung disease	3.421	1.313-8.917	0.012
Albumin	0.498	0.270-0.921	0.026

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-significance-and-prognostic-value-of-neutrophil-to-lymphocyte-ratio-in-patients-with-dermatomyositis

Abstract Number: 287

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-relation-of-patellofemoral-joint-alignment-and-trochlear-morphology-to-superolateral-hoffas-fat-pad-edema-the-multicenter-osteoarthritis-study

Abstract Number: 288

Glucose Homeostasis Influences the Risk of Incident Knee Osteoarthritis

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Background/Purpose: Knee osteoarthritis (KOA), particularly accelerated KOA, is associated with older age and being overweight. Greater age and weight are associated with impaired glucose homeostasis and elevated inflammation. There is a lot of interest in the role of glucose homeostasis and inflammation in KOA but it is unclear if they are associated with incident accelerated KOA. We aimed to determine if serum measures of impaired glucose homeostasis (glucose concentrations or glycated serum protein, GSP) or inflammation (high-sensitivity C-reactive protein, CRP) are related to incident KOA or incident accelerated KOA.

Methods: We conducted a case-control study using data from baseline and the first 4 annual visits of the Osteoarthritis Initiative. All participants had no radiographic KOA at baseline (Kellgren-Lawrence [KL] < 2). We classified 3 groups: 1) accelerated KOA: ≥ 1 knee progressed to advance-stage KOA (KL Grade 3 or 4) within 48 months, 2) typical onset of KOA: ≥ 1 knee increased in radiographic scoring within 48 months (excluding those with accelerated KOA), and 3) No KOA: no change in KL grade by 48-months. We did 1:1:1 matching based on sex. Weight-bearing, fixed flexion posterior-anterior knee radiographs were obtained at all visits. A laboratory blinded to group assignment conducted high-sensitivity singleplex assay for CRP (Aviscera Bioscience), colormetric/endpoint assay (GSP, MyBiosource), and glucose concentrations with deproteinized samples. Samples were tested in duplicate. Due to nonlinear relationships, we used 3 piece-wise multinomial logistic regression models to determine if baseline CRP, GSP, or glucose were associated with typical onset of KOA or incident accelerated KOA compared with no KOA. We adjusted for age, body mass index, and sex.

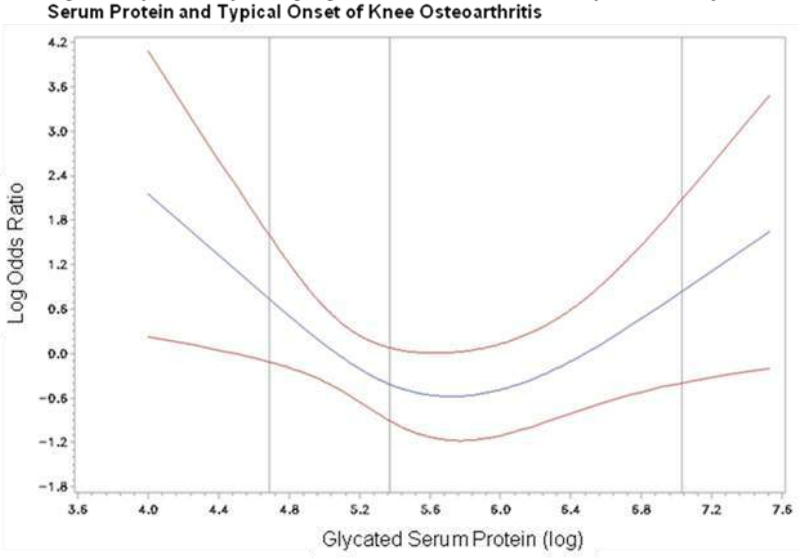
Results: We analyzed 54 adults/group and described their characteristics in Table 1. Baseline CRP, GSP, and glucose were not significantly associated with incident accelerated KOA (Table 2). However, lower and higher GSP concentrations were associated with a typical onset of KOA compared with adults with concentrations (log) closer to 5.4 (Table 2, Fig. 1).

Conclusion: Glucose homeostasis may predict individuals at risk of typical onset of KOA but not accelerated KOA. This is further evidence that accelerated KOA may be a distinct disorder from KOA.

Table 1. No Significant Baseline Differences Among Those with Accelerated Knee Osteoarthritis (AKOA), Typical Onset of Knee Osteoarthritis (KOA), and no KOA			
Baseline variable	**No KOA (n = 54)**	**KOA (n = 54)**	**AKOA (n = 54)**
Females (n, %)	24 (63%)	24 (63%)	24 (63%)
Presence of Diabetes (n, %)	1 (2%)	0 (0%)	4 (8%)
Age (years)	59 (8)	57 (8)	62 (9)
Body Mass Index (kg/m^2)	27.3 (4.9)	27.9 (4.6)	28.9 (4.7)
Fasting Time (hrs)	12 (2)	12 (3)	12 (2)
C-reactive Protein (mg/L)	3.53 (1.09)	3.16 (1.15)	3.70 (1.05)
Glycated Serum Protein (ln)	5.47 (0.58)	5.51 (0.83)	5.48 (0.77)
Glucose (mg/dL)	111.25 (24.34)	106.38 (24.90)	107.27 (32.16)
Frequencies were analyzed with Chi-Square test and group means with paired-sample t-tests.			

Table 2. Baseline Glycated Serum Protein Concentrations are Associated with a Typical Onset of Knee Osteoarthritis (KOA)			
Predictor	**No KOA**	**KOA (n=54) Adjusted OR**	**Accelerated KOA (n=54) Adjusted OR**
C-Reactive Protein < 3.4 mg/L	**REFERENCE**	0.70 (0.37,1.34)	1.27 (0.58,2.79)
C-Reactive Protein > 3.4 mg/L	**REFERENCE**	0.69 (0.33,1.45)	0.91 (0.46,1.79)
Glycate Serum Protein (log) < 5.4	**REFERENCE**	**0.14 (0.03,0.74)**	0.20 (0.04,1.09)
Glycate Serum Protein (log) > 5.4	**REFERENCE**	**2.40 (1.02,5.63)**	1.78 (0.73,4.30)
Glucose <115 mg/dL	**REFERENCE**	0.99 (0.97,1.02)	0.98 (0.96,1.00)
Glucose >115 mg/dL	**REFERENCE**	0.99 (0.95,1.03)	1.02 (0.98,1.05)
All analyses are based on piece-wise regression models with cutpoints defined by graphing splines. All analyses are adjusted for age, body mass index, and sex (matching variable). There were no interactions with body mass index.			

Figure 1. Spline Analysis Highlights the Nonlinear Relationship between Glycated Serum Protein and Typical Onset of Knee Osteoarthritis



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Abstract Number: 289

Metabolic and Inflammatory Links to Development of Rotator Cuff Tear in Hand Osteoarthritis

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Background/Purpose: Rotator cuff tear (RCT) and hand osteroarthritis (HOA) are commonly accompanied because they share a similar pathogenesis. However, there was no previous study investigating the relationship between RCT and HOA. The aim of this study was to estimate the prevalence and associated factors of developing RCT in patients with HOA.

Methods: In this study, we enrolled 1150 individuals who lived in Gyeongnam province in Korea from June 2013 to December 2015. Physical examinations were performed by rheumatologists and orthopedists. Plain radiography of hands and magnetic resonance imaging (MRI) of shoulders were performed in all participants. Serum levels of high sensitive C reactive protein (hsCRP) and high density lipoprotein (HDL) were checked. RCT was diagnosed by clinical examination and MRI findings. Diagnosis of HOA was made by the 1990 American College of Rheumatology classification criteria. Severity of radiographic HOA was assessed by sum of Kellgren–Lawrence (KL) grades of total involved joints on plain radiographs.

Results: The prevalence of RCT was higher in patients with HOA group (192/307, 62.5%) than those without HOA (410/827, 49.5%, $p < 0.001$). Among 307 with HOA, patients with RCT were older (62.69 ± 7.04 vs. 59.11 ± 7.69, $p < 0.001$) and showed higher hsCRP (1.51 ± 3.78 vs. 0.67 ± 0.70, $p = 0.004$) and lower HDL levels (55.66 ± 15.46 vs. 60.48 ± 12.45, $p = 0.003$) compared to those without RCT. There were no significant differences in gender, smoking, comorbidities, work period, body mass index, a number of affected joints, HOA severity, and prevalence of erosive HOA between both groups. Multiple logistic regression analysis showed significant associations of age (odds ratio [OR] 1.06; 95% confidence interval [CI] 1.02 - 1.10), serum levels of hsCRP (OR 1.37, CI 1.04 - 1.80), and HDL (OR 2.13, CI 1.14 3.98) with RCT in HOA patients.

Conclusion: The prevalence of RCT is high and age and serum levels of hsCRP and HDL have predictive roles in the development of RCT in HOA patients.

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Abstract Number: 290

Viscosupplemenation Efficacy in Knee Oa Is Similar in Single-Injection Vs. Multi-Week Formulations and Across OA Severity and BMI Subgroups, but Better in Younger Patients

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Background/Purpose: Hyaluronic acid (HA) viscosupplementation is widely used in patients with knee osteoarthritis (KOA), but variable reported outcomes have impacted its incorporation into treatment algorithms. The current study examined clinical predictors of response to HA injections.

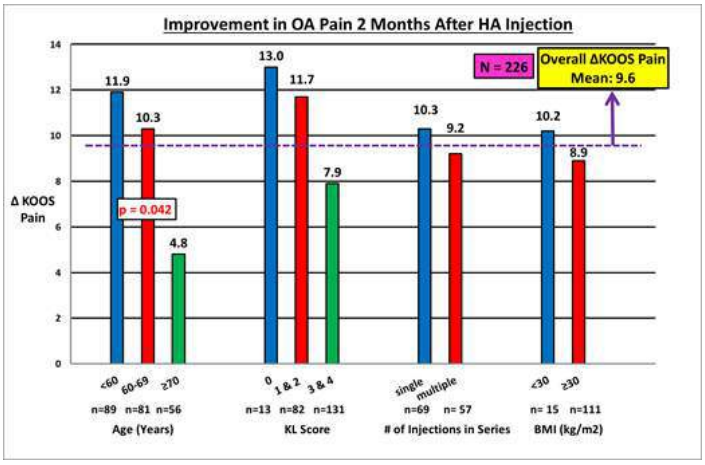
Methods: Patients receiving HA injections during routine visits were enrolled if they had KOA pain for ≥1 month and VAS pain ≥30. Baseline assessments included BMI, the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire, and standing knee xrays scored for Kellgren-Lawrence grade. The use of single vs multi-week HA products, anatomic injection approach, and use of ultrasound guidance were additional variables. Patients completed the KOOS at 2 months post-treatment to evaluate improvement from baseline.

Results: We screened 384 and enrolled 287 patients (65.5% female, age 62 years ±11, 28-88; BMI 31.0 kg/m^2±6.7, 18-54) with a baseline mean KOOS pain score (0 to 100) of 51.5 ±17.4, We obtained 2 month follow-up from 226 patients, with a mean KOOS pain improvement of 9.6 (Fig. 1) and similar results with other KOOS subscores. After 2 months, younger patients reported significantly better ΔKOOS pain improvement. Those <60 benefitted more than the 60-69 age group, with the mildest response from those 70 and older (11.9±16.7 vs 10.3±17.8 vs 4.8±14.4, p=0.042). A similar trend followed for the % of patients who showed any improvement in these subgroups (73.0%, 65.4%, 60.7%).

Patients with less severe radiographic disease trended towards more improvement, with KL0 vs KL1/2 vs KL3/4 ΔKOOS pain scores of 13.0±17.4, 11.7±17.7 and 7.9±16.0, p=0.205 and response rates of 76.9%, 71.9%, and 66.4%.

Those receiving a single-dose injection had similar ΔKOOS pain results than the traditionally-used multi-week versions (10.3±15.0 vs 9.2±17.5, p=0.674). This single-dose group displayed a higher % of any improvement (76.8% vs 63.1%). Obese (BMI>30) and non-obese patients responded similarly with ΔKOOS pain averages of 10.2 and 8.9 and response rates of 68.7% and 65.8%. Further breakdown into smaller BMI subgroups was similarly unrevealing, as was a linear regression of BMI vs ΔKOOS Pain (R=0.178, p= 0.674). In addition, we found no significant difference in outcome from various anatomic needle approaches (medial, lateral, flexed knee) or from the use of ultrasound guidance.

Conclusion: Younger KOA patients responded better 2 months following a course of HA viscosupplementation, and there was a trend towards more improvement in patients with less severe radiographic disease. Obesity, anatomic approach and ultrasound guidance did not appear to impact response. Single-injection formulations provided as much improvement as multi-injection products by KOOS scores – with less time and expense. These results could tailor future algorithms for more appropriate and cost-effective use of HA in KOA management.



Disclosure: T. Mukherjee, None; **F. Bomfim**, None; **E. Wilder**, None; **L. Browne**, None; **S. Aharon**, None; **K. Toth**, None; **E. Strauss**, None; **J. Samuels**, None.

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Abstract Number: 291

Relation of Foot Pronation during Walking to Risk of Worsening Lateral Patellofemoral and Medial Tibiofemoral Cartilage Damage

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Background/Purpose: Foot pronation can lead to lateral patellofemoral (PF) maltracking with reduced tibiofemoral (TF) varum, inciting speculation that the highly pronated foot reported in knees with osteoarthritis (OA) could increase risk of worsening lateral PF joint damage, while reducing risk of worsening medial TF damage. Yet, longitudinal data is lacking and dynamic foot pronation measured during the early, mid, and terminal phases of walking may differ from measures in static standing. Our purpose was to explore the relation of foot pronation measured during each phase of walking to the 2-year risk of worsening lateral PF and medial TF cartilage damage. Pronation effects on PF tracking and knee varus moment tend to be maximal during the early stance phase.

Methods: The Multicenter Osteoarthritis Study (MOST) includes adults aged 50-79 years with or at risk of knee OA. At the 60 month exam, high-resolution plantar pressure profiles were acquired during 5 trials of self-paced walking. From

these, we measured foot pronation during the early, mid, and terminal stance phases using the Pronation-Supination Index (PSI), as described by Motooka, et al. (same-day retest ICC 0.46 to 0.94), where lower values indicate greater pronation. From 1.0 T MRIs, readers scored (0-6) one knee per subject for cartilage damage in each sub-region of the lateral PF (2 sub-regions) and medial TF (5 sub-regions) compartments using WORMS (weighted kappa > 0.63). Among sub-regions with submaximal scores at 60 months, worsening damage was any increase in WORMS score at 84 months. Separate logistic regression models estimated the relative odds of worsening lateral PF and medial TF cartilage damage within quintiles of increasing foot pronation compared to feet with the least pronation. Adjustments were made for age, sex, and BMI. GEE accounted for non-independent knee sub-regions.

Results: 1067 and 1104 subjects (mean age 66.8 ± 7.6 years, BMI 29.6 ± 4.8 kg/m2, 60.7% female) contributed to the analysis of worsening lateral PF and medial TF cartilage damage, respectively. Compared to feet with the least pronation, odds of worsening lateral PF damage were 2.35 (95% CI: 1.38, 4.01) times greater in limbs with the greatest foot pronation during early stance ($p < 0.002$). A non-significant trend suggested a possible relation between greater early phase foot pronation and reduced odds of medial TF worsening. There was no association between foot pronation during other phases of walking and risk of worsening knee damage (Table).

Conclusion: In adults with or at-risk of knee OA, feet with the greatest foot pronation during the early stance phase of walking are at increased risk of worsening knee cartilage damage in the lateral PF compartment. These findings could inform efforts to refine preventative footwear interventions for compartment-specific knee OA.

Table. Relative odds (OR) of worsening lateral patellofemoral and medial tibiofemoral cartilage damage in quintiles of increasing foot pronation (PSI) during the early, mid, and terminal stance phases walking.

	PSI (high)	Increasing Pronation →			PSI (low)
Lateral Patellofemoral Worsening Cartilage					
Early Stance Phase					
PSI range	68.2, 57.6	57.6, 55.1	55.0, 53.1	53.1, 50.8	50.7, 36.8
# knees (sub-regions)	209 (397)	215 (413)	212 (405)	214 (417)	217 (415)
% worsening	5.8%	9.2%	9.1%	5.3%	12.0%
Adj OR	1.00	1.66	1.64	0.92	2.35*
(95% CI)	(Reference)	(0.97, 2.86)	(0.94, 2.87)	(0.49, 1.73)	(1.38, 4.01)
Mid Stance Phase					
PSI range	69.5, 57.6	57.6, 54.4	54.4, 52.0	52.0, 48.8	48.8, 34.6
# knees (sub-regions)	210 (402)	215 (412)	214 (410)	214 (414)	214 (409)
% worsening	7.0%	8.0%	9.5%	8.5%	8.6%
Adj OR	1.00	1.17	1.41	1.25	1.26
(95% CI)	(Reference)	(0.68, 2.01)	(0.84, 2.36)	(0.73, 2.17)	(0.63, 2.39)
Terminal Stance Phase					
PSI range	58.9, 39.3	39.3, 33.3	33.2, 27.8	27.8, 21.9	21.9, 6.4
# knees (sub-regions)	216 (412)	216 (420)	213 (415)	210 (394)	212 (406)
% worsening	7.8%	9.0%	9.2%	5.8%	9.6%
Adj OR	1.00	1.19	1.18	0.74	1.23
(95% CI)	(Reference)	(0.71, 1.98)	(0.71, 1.95)	(0.41, 1.32)	(0.72, 2.10)
Medial Tibiofemoral Worsening Cartilage					
Early Stance Phase					
PSI range	68.2, 57.6	57.6, 55.1	55.0, 53.1	53.1, 50.8	50.7, 36.8
# knees (sub-regions)	221 (1082)	221 (1079)	220 (1081)	221 (1088)	221 (1092)
% worsening	9.0%	8.9%	7.0%	6.7%	7.8%
Adj OR	1.00	0.97	0.74	0.72	0.84
(95% CI)	(Reference)	(0.63, 1.50)	(0.49, 1.13)	(0.46, 1.13)	(0.55, 1.29)
Mid Stance Phase					
PSI range	69.5, 57.6	57.6, 54.4	54.4, 52.0	52.0, 48.8	48.8, 34.6
# knees (sub-regions)	219 (1077)	223 (1093)	221 (1082)	220 (1085)	221 (1085)
% worsening	7.8%	7.3%	8.8%	6.3%	9.2%
Adj OR	1.00	0.88	1.08	0.76	1.12
(95% CI)	(Reference)	(0.57, 1.37)	(0.70, 1.67)	(0.48, 1.20)	(0.73, 1.72)
Terminal Stance Phase					
PSI range	58.9, 39.3	39.3, 33.3	33.2, 27.8	27.8, 21.9	21.9, 6.4
# knees (sub-regions)	221 (1081)	221 (1079)	221 (1093)	220 (1079)	221 (1090)
% worsening	9.0%	6.3%	6.9%	7.5%	9.7%
Adj OR	1.00	0.69	0.75	0.81	1.04
(95% CI)	(Reference)	(0.44, 1.09)	(0.48, 1.16)	(0.53, 1.23)	(0.68, 1.59)

Odds ratios (OR) adjusted for age, sex, BMI.

* Statistically significant ($p = 0.0017$)

Disclosure: K. D. Gross, None; **H. J. Hillstrom**, None; **C. Brown**, None; **R. Jones**, None; **J. Stefanik**, None; **M. C. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **D. T. Felson**, zimmer knee creations, 5.

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Abstract Number: 292

Knee Osteoarthritis and the Risk of Fall Injuries Among Older Adults: The Health ABC Study

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Background/Purpose: Falls are the leading cause of injury-related morbidity and mortality in older adults. To our knowledge no studies have examined the association between knee OA and fall injuries.

Methods: Using data from the Health ABC Knee Osteoarthritis Substudy, a community-based study of white and black adults ages 70-79 (42% black; 48% men) at baseline (1997-1998), we tested the associations (at the person-level) between knee pain without radiographic OA (ROA), knee ROA without pain, and knee symptomatic ROA (sROA) and incident fall injuries among 962 adults mean (SD) age 74.7 (2.9) years. We also examined whether these associations differed by sex, obesity status, and fall injury type (fracture vs. non-fracture). Knee ROA was defined as having a Kellgren-Lawrence grade of ≥2 in at least one knee. Knee sROA was defined as having both ROA and pain symptoms (during the last 30 days) in the same knee. Fall injuries were defined using a validated diagnoses code algorithm from linked Medicare claims (99.2% linkage) as any unique event with a fall code (E880-888) and/or non-vertebral fractures (800-804, 807-829). Cox regression modeling was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Covariates associated with the exposure or outcome at $p<0.1$ were included in multivariate adjusted models.

Results: The mean (SD) follow-up time was 7.50 (3.02) years. The prevalence of sROA, pain without ROA, ROA without pain, and no ROA or pain was 34.4%, 40.0%, 4.8%, and 20.8%, respectively. Of the 962 participants, 274 (28.5%) had an incident fall injury. Compared with those without ROA or pain, individuals with pain without ROA (HR= 1.28; 95% CI: 0.89, 1.85), ROA without pain (HR= 1.18; 95% CI: 0.59, 2.39), and sROA (HR=1.24; 95% CI: 0.83, 1.85) did not have a significantly increased risk of fall injuries (Table). Among men only, and compared with men without ROA or pain, those with pain without ROA (HR= 2.13; 95% CI: 1.01, 4.50, p-value=0.048) and sROA (HR=2.28; 95% CI: 1.00, 5.18, p-value=0.049) had a significantly higher risk of fall injuries (Table). The association between knee OA and fall injuries did not differ by obesity status or fall injury type.

Conclusion: Both knee sROA and knee pain without ROA were independently associated with a borderline increased risk of incident fall injuries in men only. **Table.** Adjusted risk of fall injuries associated with knee pain without ROA, knee ROA with pain, and knee sROA

	Knee pain without ROA[a] HR (95% CI)	Knee ROA without pain[a] HR (95% CI)	Knee sROA[a] HR (95% CI)
Overall			
MV model (n=938)[b]	1.28 (0.89, 1.85)	1.18 (0.59, 2.39)	1.24 (0.83, 1.85)
Men			
MV model (n=371)[b]	2.13 (1.01, 4.50)*	1.79 (0.48, 6.73)	2.28 (1.00, 5.18)*
Women			
MV model (n=567)[b]	1.09 (0.71, 1.67)	0.98 (0.42, 2.27)	1.03 (0.64, 1.65)

Abbreviations: ROA, radiographic osteoarthritis; sROA, Symptomatic ROA; HR, hazard ratio; CI, confidence intervals; MV, multivariate model [a]The reference group comprises participants without ROA or pain in a knee [b]Adjusted for age, race, sex, site, BMI, smoking, physical activity, health status, hypertension, myocardial infarction, prior falls, poor vision, NSAISD use, steroid use, calcium use, vitamin D use, and antidepressants *$p<0.05$

Disclosure: K. E. Barbour, None; **R. M. Boudreau**, None; **N. Sagawa**, None; **J. A. Cauley**, None; **M. C. Nevitt**, None; **T. Fujii**, None; **K. Patel**, None; **E. S. Strotmeyer**, None.

Abstract Number: 293

A Systematic Review and Network Meta-Analysis of Long-Term Trials of Pharmacological Treatments in Knee Osteoarthritis

Dario Gregori[1], Giampaolo Giacovelli[2], Clara Minto[1], Beatrice Barbetta[2], Francesca Gualtieri[2], Danila Azzolina[1], Paola Vaghi[2] and **Lucio C. Rovati**[2,3], [1]Unit of Biostatistics, Epidemiology and Public Health, Department of Cardiac, Thoracic and Vascular Sciences, University of Padova, Padova, Italy, [2]Clinical Research Department, Rottapharm Biotech, Monza, Italy, [3]University of Milano Bicocca, Milano, Italy

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Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA) is a chronic and progressive degenerative disease. While management of OA should be directed to long-term control of symptoms and joint structure changes, existing pharmacological agents are mostly studied for their effects on symptoms for short-term periods. This is the first systematic review and meta-analysis investigating the effects of available medications over long-term treatment courses on symptoms and structure in knee OA.

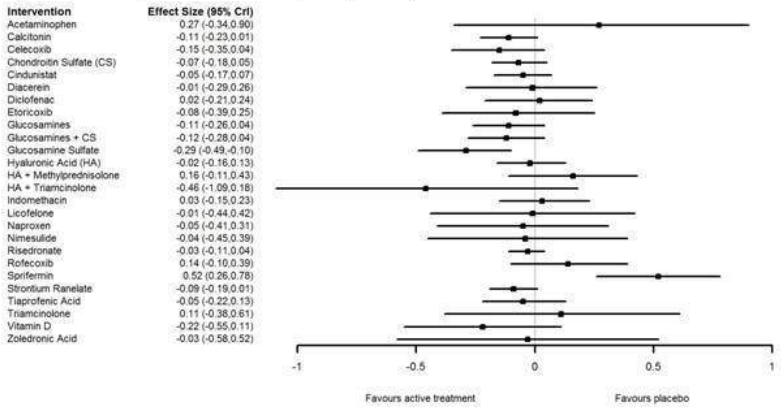
Methods: The Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Scopus and Web of Science were searched for randomized controlled trials (RCTs) of pharmacological interventions in knee OA published until February 29, 2016. Reference lists of retrieved articles were also screened for additional trials. Only RCTs with treatment/follow-up of at least one year were eligible. The primary outcome was knee OA pain change from baseline to the endpoint (≥ 12 months) on a validated scale. Secondary outcomes were changes in physical function and joint structure expressed as radiologic medial tibiofemoral joint space narrowing (JSN). We performed a random-effects network meta-analysis within a Bayesian framework. Imputation methods for mean changes and variability measures were adopted to include papers with incomplete data. Quality of evidence was rated based on the GRADE approach.

Results: Out of 5992 articles for RCTs of drug therapy in knee OA, 38 RCTs involving 18833 patients met the long-term

eligibility criteria and included virtually all available pharmacological intervention categories: 27 interventions including placebo for pain (Figure), 13 for physical function and 17 for JSN, with trial duration ranging between 1 and 3 years. There was no evidence of efficacy for most interventions vs placebo, with the exception of prescription glucosamine sulfate that was significant on pain (Figure) and physical function, with a Glass' Delta Effect Size (ES) of -0.29 [95% credibility interval: -0.49; -0.10] and -0.32 [-0.52, -0.12], respectively, and high quality of evidence rated by GRADE. Glucosamine sulfate, chondroitin sulfate and strontium ranelate were the only interventions able to significantly reduce radiologic JSN (ES 0.42 [0.20; 0.64], 0.20 [0.08; 0.31] and 0.20 [0.06; 0.35], respectively).

Conclusion: This network meta-analysis shows no evidence of efficacy in the long-term management (at least one year) of knee OA for available medications including NSAIDs, corticosteroids, acetaminophen, putative disease-modifiers, most bone acting agents or Slow Acting Drugs in OA. The only exception is prescription glucosamine sulfate, that is consistently effective on symptoms and joint structure changes, while chondroitin sulfate and strontium ranelate are effective only on structure. Additional long-term RCTs of available and new medications are needed in OA.

Figure. Estimates of long-term treatment effects on pain compared with placebo



Disclosure: D. Gregori, Rottapharm Biotech, 5; **G. Giacovelli**, Rottapharm Biotech, 3; **C. Minto**, Rottapharm Biotech, 5; **B. Barbetta**, Rottapharm Biotech, 3; **F. Gualtieri**, Rottapharm Biotech, 3; **D. Azzolina**, Rottapharm Biotech, 5; **P. Vaghi**, Rottapharm Biotech, 3; **L. C. Rovati**, Rottapharm Biotech, 3.

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Abstract Number: 294

Serum Urate Levels Predict Joint Space Narrowing in Non-Gout Patients with Medial Knee Osteoarthritis

Charles Oshinsky[1], Mukundan Attur[2], Sisi Ma[3], Hua Zhou[3], Fangfei Zheng[1], Meng Chen[4], Jyoti Patel[2], Jonathan Samuels[5], Virginia Pike[6], Ravinder Regatte[7], Jenny Bencardino[8], Leon Rybak[9], Steven B. Abramson[10], Michael H. Pillinger[11] and Svetlana Krasnokutsky Samuels[12], [1]Medicine/Rheumatology, NYU School of Medicine, NEW YORK, NY, [2]Rheumatology Research, NYU - Hospital for Joint Diseases, New York, NY, [3]Bioinformatics, New York University, New York, NY, [4]NYU School of Medicine, NEW YORK, NY, [5]Division of Rheumatology, Department of Medicine, NYU Langone Medical Center, New York, NY, [6]Medicine/Rheumatology, NYU School of Medicine/NYU Hospital for Joint Diseases, New York, NY, [7]NYU Department of Radiology, NEW YORK, NY, [8]Radiology, NYU Langone Medical Center, New York, NY, [9]Department of Radiology, NYU Langone Medical Center, New York, NY, [10]Dept of Rheumatology/Medicine, Hosp for Joint Diseases/NYU, New York, NY, [11]NYU School of Medicine, New York, NY, [12]NYU School of Medicine, Division of Rheumatology, New York, NY

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Background/Purpose: Osteoarthritis (OA) etiopathogenesis includes an inflammatory component. Published reports indicate that synovial fluid urate levels, even in patients without gout, associate with OA prevalence/severity. Whether serum urate (sUA), the precursor for gout and a biomarker for cardiovascular and kidney disease, may serve as a biomarker to convey or predict OA risk is not known. We investigated whether sUA levels associate with knee OA radiographic severity and contrast MRI-measured quantitative synovial volume (SV), and whether sUA levels predict radiographic progression, in a gout-free knee OA cohort.

Methods: We assessed sUA in 88 gout-free subjects who completed a 24-month prospective, natural history knee OA study. Subjects had symptomatic medial knee OA, met ACR knee OA criteria and had BMI <33 at study entry. sUA was measured (enzyme-colorimetry) in serum frozen and banked at baseline. At baseline and 24 months, patients underwent standardized weight-bearing fixed-flexion posteroanterior knee radiographs (SynaFlexer™). Twenty-seven subjects additionally had a dynamic gadolinium-enhanced 3.0T knee MRI that was read for quantitative synovial volume (SV). A musculoskeletal radiologist, blinded to subject data, determined joint space width (JSW) and Kellgren-Lawrence (KL) grades at each time point. Joint space narrowing (JSN) was determined as JSW change from baseline to 24 months. Pearson's correlations, student's t-tests, one-way ANOVA with post hoc Tukey-Kramer tests, ROC and AUC curves were used in statistical analyses, as appropriate.

Results: sUA correlated with JSN in both univariate ($r=0.40$, $p\leq0.01$) and multivariate analyses (adjusting for age, gender and BMI, $r=0.28$, $p=0.010$). There was a significant difference in mean JSN after dichotomization of sUA at 6.8mg/dL, the solubility point for serum urate, even after adjustment for age, gender and BMI (JSN [±SEM] of 0.90mm±0.20mm for sUA≥6.8; JSN [±SEM] of 0.31mm±0.09mm for sUA<6.8, $p<0.01$). Baseline sUA distinguished progressors (JSN>0.2mm), and fast progressors (JSN>0.5mm), from non-progressors (JSN≤0.0mm) in multivariate analyses (area under the receiver operating characteristic curve [AUC] 0.626, $p=0.027$; AUC 0.620, $p=0.045$, respectively). sUA also correlated with SV ($r=0.44$, $p=0.0040$), a possible marker of JSN, though this correlation did not persist after controlling for age, gender and BMI ($r=0.13$, $p=0.562$).

Conclusion: In non-gout patients with knee OA, sUA levels predict JSN and may serve as a biomarker for OA progression.

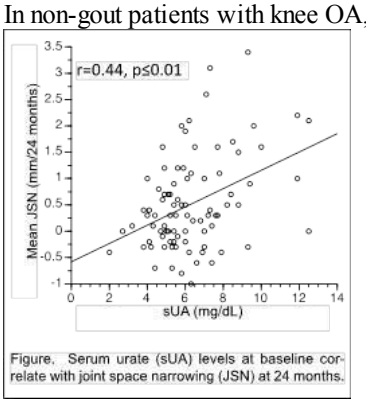

Figure. Serum urate (sUA) levels at baseline correlate with joint space narrowing (JSN) at 24 months.

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Abstract Number: 295

Efficacy and Safety of Fasinumab for Osteoarthritic Pain in Patients with Moderate to Severe Osteoarthritis of the Knees or Hips

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Background/Purpose: Osteoarthritis (OA) is an important cause of chronic pain in older adults. Fasinumab is a fully-human, high-affinity monoclonal antibody directed against the nerve growth factor (NGF). By selectively blocking NGF, fasinumab has the potential to effectively modulate NGF associated pain without causing some of the well-known adverse side effects of commonly used analgesic medications such as opioids and NSAIDS. We assessed the efficacy and safety of fasinumab on pain due to OA in patients with intolerance or inadequate pain relief from analgesics.

Methods: Adult patients were required to have a diagnosis of OA of the knee or hip based on American College of Rheumatology classification criteria. Eligible patients had an inadequate response or were intolerant to standard-of-care pain medications. Patients were required to have a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale score of ≥4 and a Kellgren-Lawrence X-ray grading of ≥2 in at least one hip or knee joint. Patients were excluded if they had evidence of joint instability on screening imaging or if they had significant concomitant medical conditions that could interfere with the efficacy or safety assessments. Eligible patients were randomized to receive placebo or 1 mg, 3 mg, 6 mg, or 9 mg of fasinumab subcutaneously every 4 weeks through Week 12. Primary efficacy was measured as a change from baseline to week 16 for the WOMAC pain subscale. WOMAC physical function and Patient Global Assessment (PGA) were measured as secondary endpoints. The primary efficacy variables were analyzed using a mixed-effect model repeated measure approach.

Results: Four hundred and nineteen subjects received at least one dose of study medication. At week 16, LS mean changes from baseline in the WOMAC pain subscale in patients were -2.25 for placebo, -3.35 (1 mg), -3.33 (3 mg), -3.03 (6 mg), and -3.65 (9 mg) for the fasinumab groups; all fasinumab groups showed significant improvement vs placebo ($p \leq 0.05$). Improvements were also observed for WOMAC physical function and PGA. Fasinumab was generally well tolerated. As expected for the class of NGF antibodies, certain neuromuscular events, including arthralgia, paraesthesia, hypoaesthesia, and peripheral edema, occurred more commonly in fasinumab treated patients. During the study period, there were the following number of subchondral insufficiency fracture cases: 1, 0, 2, 0, and 4 in the placebo, 1 mg, 3 mg, 6 mg and 9 mg groups, respectively. There was 1 case of rapidly progressive osteoarthritis in each of the 3 mg, 6 mg, and 9 mg fasinumab groups.

Conclusion: <span",'serif'; mso-fareast-language:="mso-fareast-language:" mso-ansi-language:="mso-ansi-language:" mso-fareast-theme-font:="mso-fareast-theme-font:" font-size:="font-size:" ar-sa;"="AR-SA;"" mincho';="Mincho';" mso-fareast-'ms="mso-fareast-'MS" 12pt;="12pt;" minor-fareast;="minor-fareast;" en-us;="EN-US;" mso-bidi-language:="mso-bidi-language:">These 16-week results suggest that fasinumab provided significant clinical benefit in relieving osteoarthritic pain compared with placebo in patients with moderate to severe OA who have inadequate pain relief or are intolerant to other analgesics. Fasinumab was generally well tolerated in the majority of patients in this study. Clinicaltrials.gov NCT02447276

Disclosure: J. Maloney, Regeneron, 1,Regeneron, 3; **A. Kivitz**, None; **T. J. Schnitzer**, Regeneron, 8; **P. Dakin**, Regeneron, 1,Regeneron, 3; **C. Stehman-Breen**, Regeneron, 1,Regeneron, 3; **G. Geba**, Regeneron, 1,Regeneron, 3.

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Abstract Number: 296

Knee Osteoarthritis As Risk for Hip Osteoarthritis

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Knee osteoarthritis as risk factor for hip osteoarthritis

Background/Purpose: While the hip and knee are linked biomechanically, the risk of hip osteoarthritis (OA) in persons with knee OA has not been well studied. Knee OA is associated with weak hip girdle muscles which may predispose to hip OA. Furthermore, persons with painful knee OA may alter their gait and abnormally load other lower extremity joints. We examined the risk of hip OA in those with knee OA in the Multicenter Osteoarthritis Study (MOST).

Methods: MOST is a NIH funded cohort study of risk factors for knee OA. To evaluate hip OA, we used long limb films which included hip imaging obtained at baseline and 60 months follow-up. Radiographic hip OA was defined using the modified Croft definition, and we defined incident radiographic hip OA as development of OA at 60 months. To evaluate knee OA, PA and lateral weight bearing films were obtained at baseline. A knee had radiographic OA if that knee had either tibio-femoral or patello-femoral OA (Kellgren and Lawrence score >=2). Symptomatic knee OA was defined as knee with radiographic OA and knee pain on most days in a month. For the 1st analysis, the exposure groups were knees with or without (either unilateral or bilateral) radiographic knee OA at baseline. For the 2nd analysis, the exposure groups were knees with or without symptomatic knee OA at baseline. The outcomes for both analyses were incident radiographic hip OA. For both analyses, we compared the risk of incident radiographic hip OA in hips with or without (radiographic or symptomatic) knee OA. The analyses were adjusted for hip OA risk factors including age, sex, BMI, knee injury/surgery. We carried out subanalyses among those with unilateral prevalent radiographic and symptomatic knee OA to compare the risk of incident ipsilateral vs contralateral hip OA at 60 months.

Results: In the 1st analysis, the risk of incident radiographic hip OA with any radiographic knee OA was not significantly greater than risk of incident radiographic hip OA without any radiographic knee OA (see table 1). For the 2nd analysis, there was an increased risk of incident radiographic hip OA with any symptomatic knee OA (see table 1), and this increased risk was limited to the subset of subjects with unilateral symptomatic knee OA (adjusted OR 1.99, $p = 0.01$). Among those with prevalent radiographic or symptomatic knee OA, we found no predilection for ipsilateral vs. contralateral incident hip OA (see table 2).

Conclusion: Pre-existing radiographic knee OA did not increase risk for incident radiographic hip OA, but symptomatic knee OA may increase risk for incident radiographic hip OA.

Table 1

1st Analysis: Incident Radiographic Hip OA in subjects with **radiographic** knee OA

	n/n (%)	Crude Risk Ratio	Crude p value	Adjusted Risk Ratio*	Adjusted p value
Subjects without knee OA	30/907 (3.31%)	1.00 (reference)	(ref)	1.00 (reference)	(ref)
Subjects with **any** knee OA	44/889 (4.95%)	1.50 (0.94, 2.38)	0.09	1.55 (0.94, 2.55)	0.08
Subjects with **unilateral** knee OA	20/439 (4.56%)	1.38 (0.78, 2.43)	0.27	1.36 (0.75, 2.45)	0.31
Subjects with **bilateral** knee OA	24/450 (5.33%)	1.61 (0.94, 2.76)	0.08	1.71 (0.93, 3.13)	0.08

2nd Analysis: Incident Radiographic Hip OA in subjects with **symptomatic** knee OA

	n/n (%)	Crude Risk Ratio	Crude p value	Adjusted Risk Ratio*	Adjusted p value
Subjects without knee OA	52/1374 (3.78%)	1.00 (reference)	(ref)	1.00 (reference)	(ref)
Subjects with **any** knee OA	22/380 (5.79%)	1.59 (0.96, 2.62)	0.07	1.67 (0.99, 2.80)	0.05
Subjects with **unilateral** knee OA	21/301 (6.98%)	1.91 (1.15, 3.18)	0.01	1.99 (1.17, 3.36)	0.01
Subjects with **bilateral** knee OA	1/79 (1.27%)	0.35 (0.05, 2.51)	0.29	0.38 (0.05, 2.83)	0.35

n/n = hips with outcome/subjects total
* Adjusted for age, sex, BMI, knee injury/surgery

Table 2

Incident radiographic hip OA in subjects with unilateral **radiographic** knee OA

	Hip, *n/n* (%)	Crude RR (95% CI)	p value	Adjusted RR* (95% CI)	p value
Ipsilateral Side	10/428 (2.34%)	(Ref)		(Ref)	
Contralateral Side	13/432 (3.01%)	1.29 (0.57, 2.94)	0.54	1.29 (0.57, 2.95)	0.54

Incident radiographic hip OA in subjects with unilateral **symptomatic** knee OA

	Hip, *n/n* (%)	Crude RR (95% CI)	p value	Adjusted RR* (95% CI)	p value
Ipsilateral Side	11/295 (3.73%)	(Ref)		(Ref)	
Contralateral Side	11/295 (3.73%)	1.00 (0.43, 2.31)	1.0	1.00 (0.43, 2.30)	1.00

n/n = hips with outcome/subjects total
* Adjusted for knee injury/surgery

Disclosure: **C. Kim**, None; **S. Sheehy**, None; **C. Lewis**, None; **M. M. Clancy**, None; **M. C. Nevitt**, None; **J. Torner**, None; **C. E. Lewis**, None; **A. Guermazi**, MerckSerono, TissueGene, OrthoTrophix, AstraZeneca, Genzyme, 5,Boston Imaging Core Lab, LLC, 1; **D. T. Felson**, zimmer knee creations, 5.

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Genetic and Environmental Correlation of Osteoarthritis at the Hands, Knees, and Spine

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Background/Purpose: Osteoarthritis (OA) may affect multiple joint sites, including the hands, knees, and spine. Studies have suggested high heritability for hand OA, but OA in the major diarthrodial joint affected in the back, the facet joint, is unknown. Also, the heritability of OA has been found to be joint specific especially for hand and knee OA, but it is unknown whether facet joint OA shares heritability or even occurrence with OA elsewhere. Our goals were to determine whether there are shared genetic and environmental components to OA across distinct joint sites; we determined the heritabilities, genetic correlations, and environmental correlations between hand, knee, and facet joint OA.

Methods: Analyses were based on the Framingham Study, a community-based study in the US in which subjects were studied irrespective of OA status. We created a summary index score for hand OA by summing bilateral Kellgren-Lawrence (KL) scores at the 2^{nd}-5^{th} distal interphalangeal, 2^{nd}-5^{th} proximal interphalangeal, 1^{st}-5^{th}metacarpophalangeal, thumb interphalangeal, and 1st carpometacarpal joints from posteroanterior hand radiographs. We assessed knee OA by summing KL scores from bilateral anteroposterior knee radiographs. We obtained measures of facet joint OA from thoracic CT imaging and summed Pathria and Weishaupt semi-quantitative scores at bilateral facet joints from T4 to L4 to obtain a summary index score. There were 1,259 individuals from the second generation cohort that underwent both hand and knee OA assessments. A total of 1,191 individuals from the second and third generation cohorts underwent facet joint OA assessments, of which 500 also had knee and hand OA assessments. We used a variance components method based on familial pedigrees to estimate heritability of hand, knee, and facet joint OA and bivariate models to estimate genetic and environmental correlations between OA at each joint site. All models were adjusted for age and sex.

Results: Mean age was 69±8 years and mean BMI was 29±5 kg/m^2. About 54% were women. Mean summary index score for hand, knee, and facet joint OA was 7±12 (range=0 to 69), 1±2 (range=0 to 8), and 28±13 (range=3 to 66), respectively. There were 266 families, ranging in size from 1 to 30 individuals. Estimated heritabilities for hand, knee, and facet joint OA were 62±9%, 13±9%, and 62±8%, respectively. Phenotypic correlation was significant between hand OA and knee OA (ρ_P(SE)=0.20 (0.03), p<0.01), but not between hand OA and facet joint OA (ρ_P(SE)=0.05), p=0.52). Neither genetic correlation (ρ_G(SE)=0.27 (0.24), p-0.28) nor environmental correlation (ρ_E(SE)=0.22 (0.11), p=0.07) was significant between hand and knee OA. For knee OA and facet joint OA, phenotypic correlation was significant (ρ_P(SE)=0.09 (0.04), p=0.04), but neither genetic (ρ_G(SE)=-0.12 (2.27), p=0.94), nor environmental correlation (ρ_E(SE)=0.19 (0.20), p=0.29), was significant.

Conclusion: Heritability was high (>60%) for OA at the hands and facet joints, and low (<15%) for OA at the knees. While knee OA commonly occurs with hand and facet joint OA, we found little evidence of genetic or environmental correlation across joint sites, suggesting that the genetic and environmental influences on OA are site-specific.

Disclosure: M. S. Yau, None; **Y. Zhou**, None; **D. P. Kiel**, None; **E. J. Samelson**, None; **D. T. Felson**, None.

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Abstract Number: 298

Disease Progression in Osteoarthritis Is Driven By Multiple Disease Parameters Leading to Comparable Levels of Joint Destruction

Anne C. Bay-Jensen[1], Asger Bihlet[2], Inger Byrjalsen[2], Jeppe Andersen[3], Christian S. Thudium[4], Bente J. Riis[2], Claus Christiansen[2], Hans Guehring[5], Martin Michaelis[5], Christoph Ladel[5] and Morten Asser Karsdal[6], [1]Rheumatology, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [2]Nordic Bioscience, Clinical Development, Herlev, Denmark,

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Background/Purpose: There is a need for successful drug development in osteoarthritis (OA) as there are currently no disease modifying drugs approved for OA. This may be due to: patient heterogeneity resulting from different disease drivers, clinical studies are complicated by unintended inclusion of patients with little or no disease activity (DA)/progression, lack of surrogate markers for DA in OA. The aim was to investigate clinical characteristics of an RA-like phenotype in OA in 2 OA phase III studies.

Methods: Biochemical DA was assessed in serum from RA and OA patients by the acute reactant CRP and its proteolytic product CRPM[1]. Association between CRPM and DA scores was investigated by spearman's rho in the placebo group of the LITHE study (n=193, a phase III RA RCT[2]). OA patients were divided into 4 groups: patients with no inflammation [CRPM<9nM], local inflammation [CRPM>9nM/hsCRP<3g/L], acute inflammation [CRPM<9nM/hsCRP>3g/L], and active disease [CRPM>9nM/hsCRP>3g/L] (table). Biomarkers of soft tissue degradation (C1M, C3M), cartilage degradation (C2M, UCTX-II), bone balance (CTX/OC) and macrophage activity (VICM) were measured in the placebo groups of 2 phase III OA clinical trials (SMC1 and SMC2) including patients with radiographic knee OA[3]. Kellgren-Lawrence grade (KLG), joint space width (JSW) and WOMAC were recorded at baseline and 2 years

Results: *Association between DA and CRPM in RA.* There was a significant correlation between DA and CRPM: HAQ (0.24. p=0.0007), VAS pain (0.16, p=0.023) and DAS28 (0.29, p<0.0001). CRP accounted for about 30% of the biological variation in CRPM, indicating CRP and CRPM reflect different biological processes, and provide independent information. *Identification of OA phenotypes.* The mean CRPM level was significantly high in RA than OA patients (17.1 vs. 8.5, p<0.0001); however, 31-40% of OA patients had CRPM>9nM, thus overlapping with 75% of the RA. *Tissue degradation in OA.* In SMC1, C1M and VICM were significantly increased in patients with high DA (p<0.0001). C2M was higher (p=0.006) in patients with local inflammation. C3M was higher in patients with local inflammation, but without acute inflammation (table). The results was replicated in SMC2. *OA phenotypes and progression.* There were no difference in 2-year progression of KLG, JSW, WOMAC amongst the 4 groups.

Conclusion: This study provides a major finding: Clinical outcome measures were not different between the groups. Consequently, these data indicate that each different phenotype progress at a comparable rate; however, the underlying pathogenesis is likely to be different, thus should be targeted differently.[1]Siebuhr OAC,22,44,2014.[2]Bay-Jensen, SAR,43,470,2014.[3]Karsdal OAC, 23, 532,2015.

	NoinflammationLow CRPM (<3mg/L), Low CRP (<9nM)		local inflammation High CRPM, Low CRP		acute inflammation Low CRPM, High CRP		high disease activity (DA) High CRPM, High CRP		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	ANOVA
C1M	17.7	4.0	19.9	5.1	22.6	5.6	30.6	11.2	<0.000001
C3M	5.6	2.2	7.1	2.6	6.3	1.8	8.2	2.6	<0.000001
VICM	10.0	7.8	10.0	7.9	10.3	8.5	14.2	13.4	0.006
C2M	0.24	0.13	0.27	0.13	0.23	0.13	0.24	0.10	0.006
UCTXII	256	164	289	185	285	191	233	148	ns
CTX/NMID	10.7	4.1	10.2	3.6	11.0	3.8	10.1	3.1	ns

Disclosure: A. C. Bay-Jensen, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2; **A. Bihlet**, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience A/S, 3; **J. Andersen**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3; **C. S. Thudium**, Nordic Bioscience A/S, 3; **B. J. Riis**, Nordic Bioscience A/S, 1; **C. Christiansen**, Nordic Bioscience A/S, 1; **H. Guehring**, Merck KGaA, 3; **M. Michaelis**, Merck KGaA, 3; **C. Ladel**, Merck KGaA, 3; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3.

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Abstract Number: 299

Minimally Important Differences for Four Patient-Reported Outcomes Measurement Information System (PROMIS) Short Forms: Physical Function, Pain Interference, Depression, and Anxiety Among Adults with Knee Osteoarthritis

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Background/Purpose: Patient-Reported Outcomes Measurement Information System (PROMIS) provides reliable, valid measures of health status to resolve many challenges with comparability and interpretability in OA. Minimally important differences (MID) allow for meaningful interpretation of patient-reported outcomes, however, MIDs of PROMIS scores are unknown for OA. Our purpose was to establish a range of MIDs for 4 PROMIS Short Forms: Physical Function, Pain Interference, Depression, and Anxiety for knee OA following the guidelines of the PROMIS Instrument Validation Standards.

Methods: We performed a longitudinal analysis using the pooled, similar treatment effects that resulted from a randomized trial comparing Tai Chi with physical therapy in adults with symptomatic knee OA (ACR criteria). Participants completed surveys before and after 12-week intervention (**Table**). We used legacy anchors as a reference to estimate the MIDs. We paired a set of legacy anchors with each PROMIS instrument based on similarity of their target constructs or clinical relevance (**Table**). We further defined important change in each anchor measure based on previously published MID (range = MID to 2 times MID). Among participants with important change for each anchor we calculated the absolute mean change in corresponding PROMIS T-scores to determine an individual MID estimate. We then used distribution-based methods to evaluate the quality of each MID, and only selected MIDs that met 3 *a priori* criteria: 1) Spearman correlations between the anchor and PROMIS change scores ≥0.3; 2) subset sample sizes ≥10; and 3) the absolute values of the effect sizes (Cohen's *d*) between 0.2–0.8. The lowest and highest selected-MID estimates created the lower and upper bound of an initial MID range for each PROMIS instrument. When the lower bound estimate was smaller than the standard error of measurement (SEM, i.e. smallest change score exceeding measurement error), the lower bound would be set to the SEM.

Results: We had 165 participants (mean age 61 years, 70% female, 53% white, 92% KL Grade ≥ 2). Of 14 estimated MIDs, 8 met all criteria. Four MIDs did not meet criterion #3 (described above); 2 MIDs did not meet criterion #1; and 1 MID did not meet criterion #2 (**Table**). The SEMs for PROMIS Depression, Anxiety, Physical Function, and Pain Interference were 2.3, 2.3, 1.9, and 1.8, respectively. The final MID ranges were: PROMIS Depression = 2.8 to 3.0; PROMIS Anxiety = 2.3 to 3.4; PROMIS Physical Function = 1.9 to 2.2; and PROMIS Pain Interference = 2.4 to 3.1. These correspond to 20-33% of the normalized standard deviation units per scale.

Conclusion: We established the first estimates of MID for PROMIS Physical Function, Pain Interference, Depression, and Anxiety Short Forms among those with symptomatic knee OA. This information will be an important standard of reference to better apply or interpret PROMIS instruments in future studies. < td width="126" valign="top">

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Table. Quality Criteria for Minimally Important Difference Estimates			
PROMIS Depression			
MID Legacy Anchor	**Spearman correlation**	**Sub-sample Size**	**MID Effect Size**
Patient global*		X	X
SF-36 Mental Health	**X**	**X**	**X**
Beck Depression	X	X	
Perceived Stress	**X**	**X**	**X**
PROMIS Anxiety			
MID Legacy Anchor	**Spearman correlation**	**Sub-sample Size**	**MID Effect Size**
Patient global*		X	
SF-36 Mental Health	**X**	**X**	**X**
Beck Depression	X	X	
Perceived Stress	**X**	**X**	**X**
PROMIS Physical Function			
MID Legacy Anchor	**Spearman correlation**	**Sub-sample Size**	**MID Effect Size**
Patient global*	**X**	**X**	**X**
SF-36 Physical Function	**X**	**X**	
WOMAC Function	X		
PROMIS Pain Interference			
MID Legacy Anchor	**Spearman correlation**	**Sub-sample Size**	**MID Effect Size**
Patient global*		X	X
SF-36 Bodily Pain	**X**	**X**	**X**
WOMAC Pain	**X**	**X**	**X**
*Because the Patient Global is a single-item scale, subsets of participants were selected who had a larger amount of score change on the Patient Global anchor than its previously published anchor MID, but no more than (1 + legacy MID).			

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Abstract Number: 300

Mindfulness Predicts Treatment Response from Non-Pharmacological Therapy in Knee Osteoarthritis

Augustine Lee[1], Lori Lyn Price[2], Xingyi Han[3], Mei Chung[4], William F. Harvey[1], Jeffrey Driban[5], Timothy E. McAlindon[6] and Chenchen Wang[1], [1]Rheumatology, Tufts Medical Center, Boston, MA, [2]Clinical Care Research, Tufts Medical Center, Boston, MA, [3]Public Health and Community Medicine, Tufts University, Boston, MA, [4]Department of Public Health and Community Medicine, Tufts University School of Medicine, Boston, MA, [5]Tufts Medical Center,

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Background/Purpose: Mindfulness is the ability to maintain a heightened awareness of one's moment-to-moment experiences without judging or reacting. Recent evidence suggests that mindfulness may improve outcomes in chronic pain, but no study has examined whether mindfulness is a predictor of treatment response in OA. Our objective was to evaluate whether OA participants with higher baseline mindfulness are more likely to achieve OMERACT-OARSI treatment response after exercise intervention.

Methods: We performed a longitudinal analysis of pooled participants from a randomized trial comparing Tai Chi mind-body exercise to standard physical therapy regimen with similar treatment effect among adults with symptomatic knee OA (ACR criteria). A participant subset completed the WOMAC, Patient Global Assessment, and Five Facet Mindfulness Questionnaire (FFMQ) before and after 12-week intervention. Those among this subset were stratified into tertiles based on their total mindfulness score. Treatment response was defined based on OMERACT-OARSI criteria: 1) ≥ 50% improvement in pain or function and change of ≥ 20 points on a scale of 0 to 100 in WOMAC pain or function, or 2) ≥ 2 of the following criteria: improvement of ≥20% and change > 10 points in WOMAC pain, improvement of ≥ 20% and change > 10 points in WOMAC function, or improvement of ≥20% in Patient Global and change > 10 points. We calculated risk ratios for each paired tertile comparison, and analysis of variance or chi-square tests to check for characteristic differences among the tertiles at baseline.

Results: We measured 76 of 86 baseline participants (mean age 60 years, 74% female, 48% white, 87% KL Grade ≥2, and 85% college-educated), for their follow-up visit. **Table 1** summarizes the baseline characteristics of participants by tertile. The only difference in baseline characteristics was that higher mindfulness had higher BMI ($p = 0.01$). **Table 2** summarizes the distribution of treatment response. Those with higher mindfulness were 1.4-fold more likely to meet responder criteria than those with either medium (95% CI: 1.1, 1.8; $p = 0.01$) or lower mindfulness (95% CI: 1.1, 1.8; $p = 0.01$). No difference was found between medium and lower mindfulness (1.0; 95% CI: 0.7, 1.4; $p = 0.98$).

Conclusion: Knee OA participants with higher mindfulness are 40% more likely to respond to exercise intervention. Higher mindfulness may be a novel predictor of non-pharmacological treatment response among people with symptomatic knee OA. This finding may help optimize the design of exercise interventional trials in OA.

Table 1. Demographic and Clinical Characteristics of Participants by Mindfulness Levels					
Variable		**Lower Mindfulness**	**Medium Mindfulness**	**Higher Mindfulness**	***p*-value**
Age, years		63.1 (10.5)	57.4 (9.5)	60.5 (10.8)	0.11
BMI		29.9 (6.3)	33.0 (6.3)	35.3 (7.4)	**0.01**
Sex, N	**Female**	19	20	25	0.18
	Male	10	8	4	
Pain duration, years; Mean (SD)		11.2 (16.0)	8.2 (8.4)	11.5 (15.1)	0.61
Kellgren Lawrence Grade, N	**0**	0	1	1	0.35
	1	2	4	0	
	2	10	9	12	
	3	14	11	9	
	4	2	3	6	
Race, N	**White**	11	14	16	0.37
	Black	11	8	11	
	Other	7	6	2	
Education, N	**High school**	7	3	3	0.33
	College	9	11	12	
	College Grad	5	9	4	
	Graduate School	8	5	10	
Intervention, N	**Tai Chi**	17	13	16	0.64
	Physical Therapy	12	15	13	
Total Mindfulness [min: max:] FFMQ Score Range, 39-195		124 (8.4) [98; 134]	141 (3.6) [135; 148]	161 (9.5) [149; 181]	
WOMAC Pain* Score Range, 0-500mm		289.0 (111)	253.7 (93.1)	253.8 (95.7)	0.31
WOMAC Function* Score Range, 0-1700mm		946.4 (387.2)	930.8 (335.1)	921.1 (360.6)	0.96
Patient Global Assessment* Score Range, 0-10cm		5.2 (2.2)	5.1 (2.0)	5.2 (2.2)	0.98
All values are mean (SD), unless otherwise stated. FFMQ = Five Facet Mindfulness Questionnaire, higher scores = higher mindfulness; SD= Standard Deviation. *Higher scores = more pain, worse function, or more global disease.					

Table 2. Distribution of Treatment Response by Mindfulness Levels*			
Mindfulness Tertile	**No Treatment Response**	**Treatment Response†**	**Row Total**
Lower, N (%) [Score Min: 98; Max: 134]	7 (30.4%)	16 (69.6%)	23
Medium, N (%) [Score Min: 135; Max: 148]	8 (30.8%)	18 (69.2%)	26
Higher, N (%) [Score Min: 149; Max: 181]	**1 (3.7%)**	**26 (96.3%)**	**27**
Column Total	16	60	76
*Mindfulness measured as total Five Facet Mindfulness Questionnaire score; Score Range, 39-195. †Treatment response as defined by the OMERACT-OARSI Responder Criteria for OA.			

Disclosure: A. Lee, National Institutes of Health, 2; **L. L. Price**, None; **X. Han**, None; **M. Chung**, None; **W. F. Harvey**, None; **J. Driban**, None; **T. E. McAlindon**, None; **C. Wang**, National Institutes of Health, 2.

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Abstract Number: 301

Predictive Factors for Response to Ultrasound-Guided Intra-Articular Glucocorticoids in Knee Osteoarthritis

Samy Slimani[1], Amel Aissoug[2], Souhila Aouidane[3], Hocine Bounecer[1], Hachemi Makhloufi[1] and Aïcha Ladjouz Rezig[4], [1]Department of Medicine, University of Batna, Batna, Algeria, [2]Private practice office of rheumatology, Batna, Algeria, [3]Public Health, University Hospital of Batna, Batna, Algeria, [4]Department of Medicine, University of Algiers 1, Algiers, Algeria

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Session Type: ACR Poster Session A

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Background/Purpose: To investigate predictive factors for good outcome of ultrasound intra-articular glucocorticoids in knee osteoarthritis (OA).

Methods: We conducted a prospective monocenter cohort study including 116 patients with knee OA, after failure to standard treatments, with pain > 4 (numerical rating scale NRS 0-10). Patients received an ultrasound-guided injection of 40 mg triamcinolone acetonide in their most painful knee. We exhaustively collected demographic and clinical data at inclusion, as well as lab, radiographs and ultrasound parameters of the included knees. WOMAC score was calculated at inclusion and after 4 weeks. Responders were defined as patients with at least 40% improvement of their WOMAC score. Univariate analysis was performed in order to select possible predictive factors, and stepwise multiple logistic regression analyses were conducted to identify predictors of response.

Results: Among the 116 patients, 101 were females. Median age was 64 years (40-85) and mean duration of the disease was 14.1 ± 14,8 years. Mean BMI was 29.9 ± 3.8 Kg/m^2. Mean NRS of pain was 8.4 ± 1.2 and mean WOMAC was 73.3 ± 11,8 at inclusion. 70.0% of the knees were grade 3 or 4 of Kellgren-Lawrence. 98% of knees expressed ultrasound synovial effusion and/or hypertrophy at inclusion. After 4 weeks, 61.2% of patients were responders. Regression analysis showed that patients with a BMI < 30 Kg/m^2(OR=0.38, 95%CI 0.16-0.89) and an ESR < 20 mm (OR=0.27, 95%CI 0.08-0.90) were more likely to respond to ultrasound-guided glucocorticoids injection. Having both predictive factors of good response increases the response rate to 73.5%, whereas having no predictive factor decreases the response rate to 25.0%.

Conclusion: Our study is the largest study evaluating predictive factors of response for intra-articular glucocorticoids injections in knee OA. Also, it is the first study of predictive factors for ultrasound-guided injections. Patients with high BMIs and high ESR seem less likely to respond to intra-articular injections.

Disclosure: S. Slimani, None; **A. Aissoug**, None; **S. Aouidane**, None; **H. Bounecer**, None; **H. Makhloufi**, None; **A. Ladjouz Rezig**, None.

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Abstract Number: 302

Long-Lasting Local Knee Structural Pathology Is Associated with Persistent

Multi-Site Pain

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Background/Purpose: Knee pain is the most common manifestation of knee osteoarthritis (OA) and typically accompanied by pain at other sites. Knee structural pathology in MRI, such as bone marrow lesions (BMLs), effusion and cartilage defects, appear to be strongly associated with knee OA-pain through abnormal excitability in peripheral and central pathways. However, whether persistent multi-site pain (MSP) is maintained by long-lasting peripheral structural pathology remains unknown. This study, therefore, aimed to determine whether long-lasting knee structural pathology--BMLs, effusion and cartilage defects is associated with persistent MSP and explore the underlying mechanisms.

Methods: Data from the prospective Tasmanian Older Adult Cohort study was utilized. Knee pain and pain at other sites (neck, back, hands, shoulders, hips and feet) was measured by a questionnaire at baseline and 2.6 years later. T1-weighted or T2-weighted fat saturated MRI of the right knee was performed to assess the BMLs, effusion and cartilage defects at baseline and 2.6 years. Knee radiographic OA was assessed by X-ray at baseline. Long-lasting structural lesion was defined as the presence of a lesion at both baseline and follow-up. Persistent MSP was defined as the presence of knee pain plus other site pain at both baseline and follow-up. Logistic regression modelling was used with adjustment for potential confounders.

Results: In 394 participants (mean age 63 years, mean BMI of 27.3 kg/m^2 and 51% women), 25% of participants with knee pain had pain present in at least one other site at baseline and 2.6 years. The presence of BMLs, effusion and cartilage defects at both baseline and follow-up were: 38%, 26% and 30% of the participants, respectively. Persistent knee pain plus other site pain was respectively associated with long-lasting BMLs (OR 1.94, 95% CI 1.13 to 3.33), effusion-synovitis (OR 2.24, 95% CI 1.24 to 4.03), and cartilage defects (OR 2.33, 95% CI 1.31 to 4.13) in multivariable analyses. However, there was no significant association of the presence of knee structural pathology only at either baseline or follow-up with persistent knee pain plus other site pain (all P>0.05).

Conclusion: Longer duration of the presence of BMLs, effusion and cartilage defects is associated with persistent knee pain plus other site pain, suggesting that nociceptive input induced by knee structural lesions may be a key factor in the maintenance of persistent multi-site pain in which sensitization may be implicated. The importance of this to clinicians and researchers is that the timing of treatment of knee structural pathology may normalize the increased sensitivity (sensitization).

Disclosure: F. Pan, None; **J. Tian**, None; **D. Aitken**, None; **F. M. Cicuttini**, None; **C. Ding**, None; **G. Jones**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-lasting-local-knee-structural-pathology-is-associated-with-persistent-multi-site-pain

Abstract Number: 303

Knee Physical Exam Findings and Self-Reported Symptoms Are Associated with MRI-Detected Effusion-Synovitis Among Participants with or at Risk for Knee Osteoarthritis: Data from the Osteoarthritis Initiative (OAI)

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Background/Purpose: Inflammation has been implicated in the pathogenesis of KOA, but the relevance of physical exam findings and patient-reported symptoms of inflammation is unknown. Our objectives were to examine the association between physical exam findings, including bulge sign and patellar tap, as well as participant-reported symptoms, with MRI-detected effusion-synovitis (ES) in two samples: knees that developed radiographic OA (ROA) and knees that went on to knee replacement (KR).

Methods: The Osteoarthritis Initiative (OAI) is a longitudinal cohort study of participants with or at risk for ROA. Two samples with available MRI readings were utilized: 355 knees that developed incident ROA within 4 years of follow-up (323 participants) and 225 knees that underwent KR within 5 years of follow-up (195 participants). The bulge sign and patellar tap were conducted by trained examiners at baseline, 2 years, and 4 years. Questionnaires assessing participant-reported knee swelling and knee pain when straightening fully, in the last 7 days, were administered at the same visits. MRI was performed with 3-T systems (Trio; Siemens, Erlangen, Germany). Non-contrast effusion-synovitis (ES) was scored using the MRI Osteoarthritis Knee Score (MOAKS). Logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) to assess the association between physical exam findings and participant-reported symptoms with MRI-detected ES, with generalized estimating equations to account for two knees in an individual and multiple time points.

Results: The 323 participants in the ROA group were predominantly female (66%), overweight and obese (42%, 39% respectively), white (81%), with mean age 60 years. The 195 participants in the KR group were also largely female (58%), overweight and obese (37%, 47% respectively), white (86%), with mean age 65 years. Among knees that developed ROA, those with bulge sign or patellar tap had significantly higher odds of ES, compared to those without these findings (OR=3.67 [95%CI: 2.43, 5.54]). In addition, among knees that went on to KR, a modest association was found with presence of these findings (OR=1.91 [95%CI: 1.28, 2.85]). Knees with participant-reported swelling in the last 7 days, and pain when straightening fully had significantly higher odds of ES, with evidence of dose-response based on the frequency of swelling, and severity of pain, in both ROA knees, and KR knees (Figure 1).

Conclusion: A bulge sign and patellar tap on physical exam were associated with MRI-detected ES, as well as participant-reported knee swelling and knee pain when straightening fully in participants who developed ROA as well as those who progressed to KR. The magnitude of association was greater for frequent and severe self-reported symptoms, compared to physical exam findings, and among early OA knees compared to end-stage OA knees when ES was more prevalent.

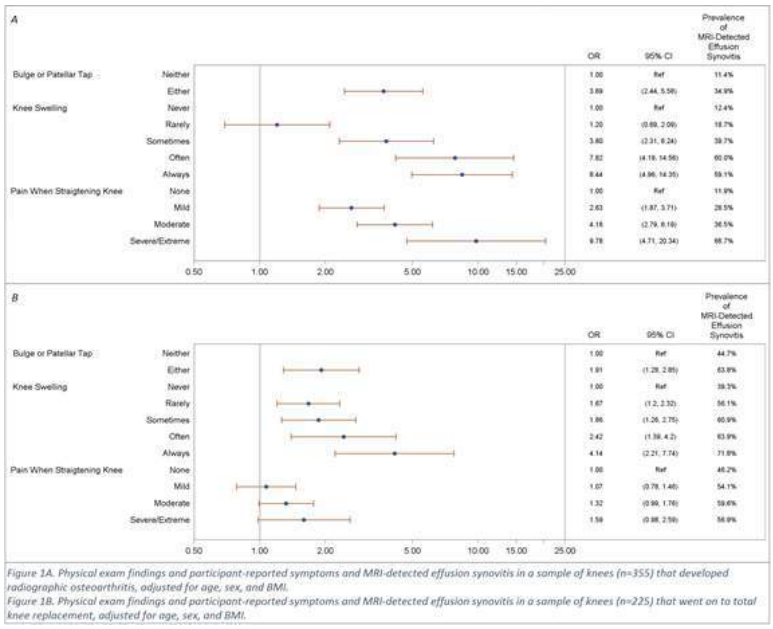

Figure 1A. Physical exam findings and participant-reported symptoms and MRI-detected effusion synovitis in a sample of knees (n=355) that developed radiographic osteoarthritis, adjusted for age, sex, and BMI.
Figure 1B. Physical exam findings and participant-reported symptoms and MRI-detected effusion synovitis in a sample of knees (n=225) that went on to total knee replacement, adjusted for age, sex, and BMI.

Disclosure: A. Berlinberg, None; **J. Westra**, None; **E. L. Ashbeck**, None; **J. Trost**, None; **F. Roemer**, Research of Boston Core Imaging Lab, 3; **A. Guermazi**, MerckSerono, TissueGene, OrthoTrophix, AstraZeneca, Genzyme, 5,Boston Imaging Core Lab, LLC, 1; **C. K. Kwoh**, Abbvie, 2,EMD Serono, 2.

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Abstract Number: 304

Gait Abnormalities Due to Hip Osteoarthritis Are Different in Men and Women

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Background/Purpose: Gait mechanics are different in healthy men and women.[1] It is unknown whether or not the gait changes associated with hip osteoarthritis (OA), also differ in men and women. The goal of this study was to investigate sex differences in hip OA-related gait mechanics, using a previously described[2] cohort of subjects with and without hip OA. The hypotheses tested were (1) gait kinematics and kinetics are different in asymptomatic men and women, but not in men and women with hip OA and (2) the extent of hip OA gait abnormalities are different in men and women.

Methods: An IRB-approved data repository was used to identify 150 subjects with symptomatic, radiographically-verified hip OA (age 62 ± 10, 86 F/64M, BMI 28±5) and 159 asymptomatic subjects (age 56 ± 9, 104 F/55 M, BMI 27 ± 5). All subjects had undergone gait analysis using standard published methods. The gait variables used for this study were the dynamic hip range of motion in the sagittal plane, and peak external moments about the hip in the sagittal, frontal, and transverse planes. Variables were averaged from trials collected at subjects' self-selected normal walking speeds. Analysis of variance was used to compare gait variables for men and women, with and without hip OA.

Results: H1 – The peak hip adduction moment was higher but the peak external rotation moment was lower in healthy

woman compared to healthy men (p = 0.037, p = 0.026). These differences were not seen in the hip OA group (Fig. 1.) H2 – All gait variables were lower in people with hip OA compared to healthy subjects. However, the magnitude of the OA vs healthy group difference in the peak adduction moment was 43% larger for women than men. The OA vs. healthy group difference in the peak external rotation moment was 55% larger for men than women (p < 0.001). There were no other sex-specific differences (p = 0.395-0.948).

Conclusion: Both hypotheses were supported. Sex differences in gait kinetics were seen in the healthy subjects, and were similar to those previously reported. [3,4] These differences were not preserved in subjects with hip OA. Moreover, compared to men, women with OA had greater deficits (vs. asymptomatic women) in the peak hip adduction moment, which is balanced by the hip abductors. Men, had greater deficits in the peak hip external rotation moment, which is balanced by muscles that internally rotate the hip during midstance. The hip abductors participate in this function during this phase of gait. Thus, these findings demonstrate that hip OA may result in different gait adaptations in men vs. women, particularly with respect to the role of the hip abductors. A better understanding of sex-specific gait adaptations could lead to new rehabilitation-based approaches to address the utilization and outcomes disparities in OA and THA. **References:** [1]Ko et al., J Biomech, 44:1974-9, 2011. [2]Foucher et al., J Biomech, 44:373-8, 2011. [3]Moisio et al., J Biomech, 36:599-603, 2003. [4]Boyer et al., J Biomech, 41:3360-5, 2008.

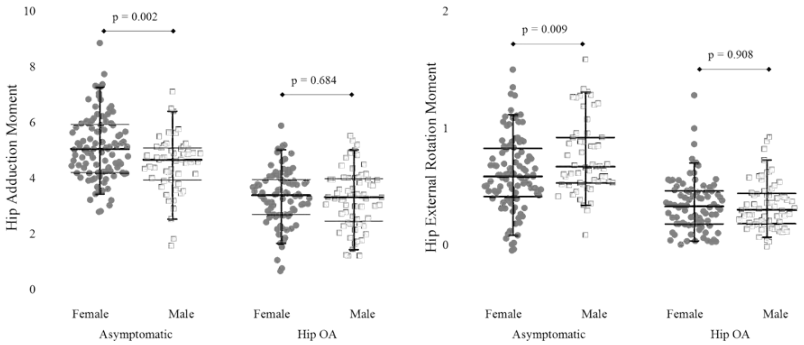

Figure 1. Peak hip adduction and external rotation moments (%BWxHt) for women and men with and without symptomatic hip OA. Gait variables were significantly decreased compared to their respective control group in both men and women (p<0.001), but the sex differences seen in the asymptomatic group were absent in the OA group.

Disclosure: K. C. Foucher, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gait-abnormalities-due-to-hip-osteoarthritis-are-different-in-men-and-women

Abstract Number: 305

Using a Large Prospective Cohort of Patients to Examine Differences in Performance and Self-Reported Outcomes Following Total Knee Replacement

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Background/Purpose: Previous studies show differences between self-report measures and performance/functional measures following total knee arthroplasty (TKA). We investigated the hypothesis that this trend would hold true in a large prospective cohort of patients (no exclusion criteria) undergoing primary unilateral TKA.

Methods: De-identified data from 345 patients (age 63.8 y/o, 44% male, BMI of 32.37), undergoing primary unilateral TKA, were included in this study. Data were drawn from a clinical registry of all patients seeking rehabilitation services at ATI Physical Therapy, (Greenville, SC) from January 2014-January 2016. The performance measure used was the Timed Up and Go (TUG). The self-report measure used was the disability subscale of the Western Ontario and McMaster Universities Arthritis Index (WOMAC). All measures were collected at baseline (pre-TKA), early post-TKA (<20 days after TKA) and later post-TKA (30 to 45 days after TKA). One-way repeated measure ANOVA's were then performed on each outcome (TUG and WOMAC separately) to test for the effect of time. Post-hoc contrasts compared the change in outcomes from baseline scores. Secondarily, Pearson product moment correlations were calculated by using change scores from baseline ([initial-final/initial]*100) to evaluate the relationship across time points between TUG and WOMAC disability subscale.

Results: TKA resulted in a significant worsening of mean TUG times from baseline to early post-TKA (3.16 sec; $p<0.001$), while WOMAC disability subscale scores demonstrated functional improvement (-5.22; $p<0.005$). At the later post-TKA time point, mean TUG times significantly improved from baseline (-2.56 sec; $p<0.001$) and WOMAC disability subscale scores had a large significant improvement (-20.52; $p<0.001$). Pearson product moment correlations revealed that change in the WOMAC total disability subscale was not significantly correlated ($p>0.05$) with change in TUG times from baseline to the early or later post-TKA time points.

Conclusion: At early post-TKA, patients reported improved scores from baseline on the WOMAC while poorer times were observed on the TUG. Similarly, for later post-TKA, the lack of correlation between changes in WOMAC and TUG measures from baseline, further suggests that patient-reported and performance outcomes may be measuring different constructs. Therefore, they should both be used for assessment as they provide different, but complementary information. Using only patient-reported outcomes is likely to disguise critical deficits impairing patient function. This is particularly true during the early post-TKA period when patients perception of their physical function (self-report) contrasts with more objective assessments (performance testing). Failure to identify underlying functional deficits, not captured using self-report measures, may result in inappropriate discharge planning and long term functional decline.

Disclosure: B. Loyd, None; **W. Hafner**, None; **A. Kittelson**, None; **D. Waugh**, None; **J. DelGiorno**, None; **J. Stevens-Lapsley**, None.

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Abstract Number: 306

MRI-Detected Cartilage Damage, Meniscal Damage, and Meniscal Extrusion Prior to Incident Radiographic Osteoarthritis and the Subsequent Trajectory of Joint Space Loss

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Background/Purpose: Loss of joint space width (JSW) on x-ray is the recommended standard to define osteoarthritis progression. However, both cartilage and meniscal damage contribute to JSW loss, yet neither are seen on radiographs. The extent to which JSW loss on x-ray reflects cartilage damage vs. meniscal damage/extrusion is unknown. Our objective was to evaluate the impact of medial cartilage and meniscal damage/extrusion 1 year prior to incident radiographic osteoarthritis (ROA) on the subsequent trajectory of medial JSW.

Methods: Knees (n=327) from the OAI that developed incident ROA (IROA) through 48 months of follow-up were identified based on Kellgren-Lawrence grade (KLG) ≥2. MRI Osteoarthritis Knee Score (MOAKS) was used to assess cartilage damage (≥1.1 vs. <1.1) and meniscal damage/extrusion (i.e., tears and maceration [≥2 vs. <2] or extrusion [≥3mm vs. <3mm]) in the year prior to incident ROA. Annual fixed JSW (fJSW) (x=0.250 mm) on x-ray was assessed over three years of follow-up. The sample included n=1,289 fJSW measures in 327 knees from 301 participants between 2 years prior to IROA and up to 2 years after IROA detection. Trajectories of mean medial fJSW and change in medial fJSW, with 95% confidence intervals (CI), were estimated using mixed models with participant and knee treated as random effects.

Results: As seen in Figure 1, knees with medial cartilage damage one year prior to IROA (compared to knees without damage) had a significantly lower mean medial fJSW in the three years following, with a difference in mean fJSW of 0.393mm [95%CI: 0.182, 0.604; p<0.0003] one year later, 0.454mm [95%CI: 0.233, 0.676; p<0.0001] two years later, and 0.754mm [95%CI: 0.508, 1.000; p<0.0001] three years later. Similarly, knees with medial meniscal damage one year prior to IROA (compared to those without damage) had significantly lower mean medial fJSW in the 3 years following, with a difference in mean fJSW of 0.238 [95%CI: 0.002, 0.474; p<0.0483] one year later, 0.288 [95%CI: 0.041, 0.534; p<0.0223] 2 years later, and 0.448 [95%CI: 0.180, 0.716; p<0.0011] 3 years later. Although those with meniscal extrusion had less fJSW one year prior to IROA, there was no significant difference in trajectory of fJSW loss for knees with meniscal extrusion vs. those without. There was no significant difference in the trajectory of fJSW loss among those with cartilage and meniscal damage/ extrusion vs. those with only cartilage damage.

Conclusion: Knees with medial tibiofemoral cartilage damage in the year prior to IROA, with or without meniscal damage/extrusion, had significant loss of mean medial fJSW over the following 3 years. Meniscal extrusion was associated with differences in concurrently measured fJSW, but not the future trajectory of fJSW. While loss of fJSW reflects both cartilage and meniscal damage, the magnitude of the differences suggests cartilage damage is the predominant factor in the future loss of fJSW.

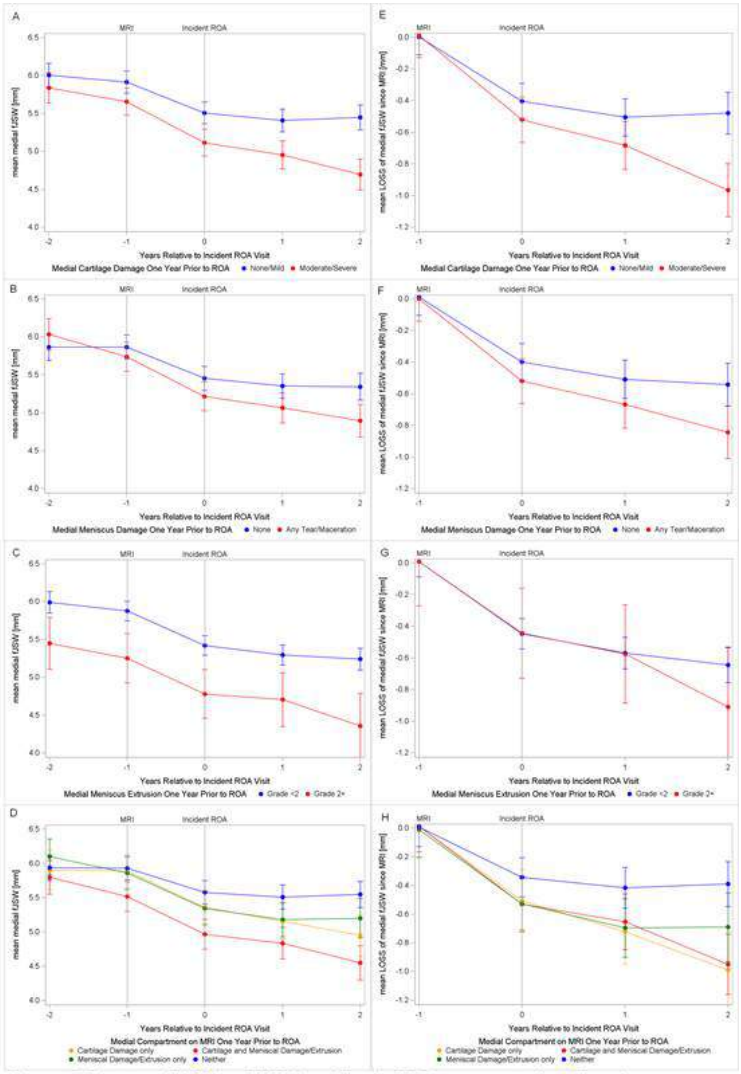

Figure 1. Trajectory of fJSW and fJSW loss following MRI assessment of cartilage damage, meniscal damage, and meniscal extrusion

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Disclosure: C. K. Kwoh, Abbvie, 2,EMD Serono, 2; **F. Roemer**, Research of Boston Core Imaging Lab, 3; **E. L. Ashbeck**, None; **C. Ratzlaff**, None; **J. Duryea**, None; **A. Guermazi**, MerckSerono, TissueGene, OrthoTrophix, AstraZeneca, Genzyme, 5,Boston Imaging Core Lab, LLC, 1.

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Abstract Number: 307

Visualizing Different Patterns of Cartilage Change: A Two-Year Study of Data from the Osteoarthritis Initiative

Amanda R. Canavatchel[1], Grace H. Lo[2], Michael P. LaValley[3], Ming Zhang[1], Jeffrey B. Driban[4], Lori Lyn Price[5], Eric Miller[6], Charles Eaton[7] and Timothy E. McAlindon[8], [1]Tufts Medical Center, Boston, MA, [2]Immunology, Allergy, Rheumatology, Baylor College of Medicine, Houston, TX, [3]Biostatistics, Boston University School of Public Health, Boston, MA, [4]Rheumatology, Tufts Medical Center, Boston, MA, [5]Biostatistics Research Center, Institute for Clinical Research and Health Policy Studies, Tufts Medical Center, Boston, MA, [6]Department of Electrical and Computer Engineering, Tufts University, Medford, MA, [7]Brown University, Providence, RI, [8]Division of Rheumatology, Tufts Medical Center, Boston, MA

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Background/Purpose: Traditionally, regions of the knee that are assessed in clinical trials are selected based on anatomy or responsiveness to change. However, it is unclear whether there are regions of the articular cartilage that are changing together over time. The purpose of the study was to visualize and explore which regions of cartilage change together longitudinally.

Methods: To determine the locations of greatest longitudinal cartilage change, we measured a convenience sample of 100 knees with baseline and 24-month MRIs from the Osteoarthritis Initiative. Sample included knees that were primarily Kellgren-Lawrence grades 2 or 3, with few progressing over 24 months. One reader (MZ) (intraclass correlation coefficient [ICC] 3,1 model > 0.86 at baseline) used customized software to measure the Cartilage Damage Index (CDI) in the medial and lateral compartments of the femur, tibia, and patellar cartilage on paired baseline and 24-month double echo steady state MRIs. For the whole knee CDI, cartilage thickness is measured in 12 informative locations for the medial and lateral patella, and in 9 locations for the medial and lateral femur and tibia (total of 60 CDI sites per knee). Using changes in CDI measures at each location over 24 months, we performed a factor analysis to identify sites that changed together. Factors with an eigenvalue > 1 were retained.

Results: The factor analysis produced 20 factors (Figure 1) accounting for 74% of the variance in CDI changes. To visualize the findings of the factor analysis, we created a figure that identifies the CDI points with factor loadings greater than or equal to 0.4 based on their anatomic location within the knee (medial and lateral patella, femur, and tibia). The factors are listed from greatest to smallest eigenvalues, or those explaining the largest percent of variability to those explaining the smallest percent of variability. Notably, the first 3 factors, that account for 23% of the total variation, only involved CDI locations in the patella. Surprisingly, very few of the factors (4) represent a combination of the articular surfaces that anatomically are adjacent to one another. Many of the factors (13) only involve one articular surface.

Conclusion: Factor analysis **on this sample** suggests that much of the variation in CDI change measures comes from regions on the patella. The patellofemoral joint is often overlooked in OA research, but our results suggest more research on this region of the knee is needed. Also, we found that it is uncommon for articular cartilage to change in conjunction with the adjacent articular surface (e.g. medial tibia cartilage does not necessarily change when the medial femur cartilage changes). These findings suggest that new strategies that evaluate change in cartilage may improve our understanding of OA progression.

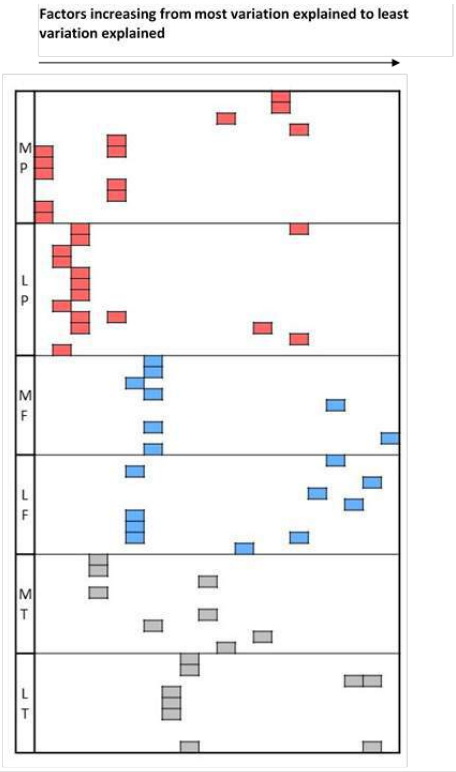

Figure 1. Sites with patterns of change stratified by knee cartilage location. Sites with color represent factor loadings with an absolute value of > .4. Sites are ordered from most anterior to most posterior regions within the cartilage. Abbreviations used: MP, medial patella; LP, lateral patella; MF, medial femur; LF, lateral femur; MT, medial tibia; LT, lateral tibia.

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Abstract Number: 308

Crepitus As a Risk Factor for Symptomatic Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Background/Purpose: Incident symptomatic OA is a common outcome of interest in epidemiologic studies of risk factors for OA. We postulate that evaluating this outcome in those who do have radiographic OA (ROA) at baseline but do not have frequent knee symptoms will be more informative than the other at-risk groups. Crepitus is the complaint of hearing

grating, cracking or popping sounds in and/or around a joint. This is a common symptom in the clinical setting and is possibly predictive of incident knee OA. Our purpose was to evaluate whether the association between crepitus and incident knee symptomatic osteoarthritis (SOA) is better detected in a group with ROA but without frequent knee symptoms than other at-risk groups.

Methods: This was a person-based longitudinal study using data from the Osteoarthritis Initiative (OAI). We evaluated the right knee only and specifically focused on people at baseline without SOA. Crepitus was assessed using the Knee injury and Osteoarthritis Outcome Score (KOOS) questionnaire at baseline. PA semi-flexed knee radiographs and frequent knee pain ("During the past 12 months, have you had pain, aching, or stiffness in or around your right knee on most days for at least one month? By most days, we mean more than half the days of a month" were assessed at baseline and 48-month visits.) were assessed at baseline and 48-month visits. ROA was defined as Kellgren and Lawrence (KL) grade ≥ 2. We performed logistic regression with crepitus as the predictor and incident SOA by the 48 month visit as the outcome. Subgroup analyses were performed by three groupings: (1) +ROA, -Sx: those with ROA, but no frequent symptoms at baseline, (2) –ROA, +Sx: with frequent symptoms but no ROA at baseline, and (3) -ROA, -Sx without ROA or frequent symptoms at baseline.

Results: 2936 people each contributed one observation with a mean age of 61.1 (9.3) years and mean BMI of 28.2 (4.7) kg/m². 42% were male. Incident SOA was least common in knees that never had crepitus and most common in those who always had crepitus (p for trend <0.0001) (Table 1). More than 75% of incident SOA cases originated from the +ROA, -Sx subgroup, despite it constituting about a third of the total number of observations.

Conclusion: Subjective knee crepitus strongly predicts incident SOA over 4 years. Crepitus evaluated as a subjective assessment, therefore offers utility for identification of at-risk individuals, predictive modeling, and future research. Selecting those with ROA but without frequent knee symptoms, may optimally power studies to evaluate incident SOA.

TABLES

Table 1. Overall association of crepitus with incident tibiofemoral SOA.

		Incident SOA	Unadjusted Odds Ratio for Incident SOA	Adjusted Odds Ratio for Incident SOA*
All those without SOA at baseline	n = 2936 people	Total cases = 349		
Crepitus Frequency	Never	178/1851 (9.6%)	Ref	Ref
	Rarely	49/332 (14.8%)	1.6 (1.2 – 2.3)	1.6 (1.1 – 2.3)
	Sometimes	66/463 (14.3%)	1.6 (1.1 – 2.1)	1.7 (1.2 – 2.3)
	Often	36/199 (18.1%)	2.1 (1.4 – 3.1)	2.2 (1.5 – 3.3)
	Always	20/91 (22.0%)	2.6 (1.6 – 4.4)	3.2 (1.9 – 5.5)
			p for trend < 0.0001	*p for trend < 0.0001*

***adjusted for age, sex, and BMI.**

Table 2. Subgroup associations of crepitus with incident tibiofemoral SOA.				
		Incident SOA	Unadjusted Odds Ratio for Incident SOA	Adjusted Odds Ratio for Incident SOA*
People with ROA but without symptoms at baseline. (+ROA, -Sx)	n = 926 people	Total cases = 265		
	Never	142/565 (25.1%)	Ref	Ref
	Rarely	35/111 (31.5%)	1.4 (0.9 – 2.1)	1.3 (0.9 – 2.1)
	Sometimes	44/145 (30.3%)	1.3 (0.9 – 1.9)	1.2 (0.8 – 1.9)
	Often	29/68 (42.6%)	2.2 (1.3 – 3.7)	2.1 (1.2 – 3.5)
	Always	15/37 (40.5%)	2.0 (1.0 – 4.0)	2.0 (1.0 – 3.9)
			p for trend < 0.0001	*p for trend = 0.03*
People without ROA but with symptoms at baseline. (-ROA, +Sx)	n = 529 people	Total Cases = 41		
	Never	12/246 (4.9%)	Ref	Ref
	Rarely	5/53 (9.4%)	2.0 (0.7 – 6.0)	2.0 (0.7 – 6.2)
	Sometimes	13/133 (9.8%)	2.1 (0.9 – 4.8)	2.2 (0.9 – 5.0)
	Often	6/60 (10.0%)	2.2 (0.8 – 6.0)	2.2 (0.8 – 6.4)
	Always	5/37 (13.5%)	3.0 (1.0 – 9.2)	3.5 (1.1 – 11.3)
			p for trend < 0.0001	*p for trend < 0.0001*
People without ROA and symptoms at baseline (-ROA, -Sx)	n = 1467 people	Total Cases = 43		
	Never	24/1032 (2.3%)	Ref	Ref
	Rarely	9/165 (5.5%)	2.4 (1.1 – 5.3)	2.4 (1.1 – 5.4)
	Sometimes	9/183 (4.9%)	2.1 (1.0 – 4.8)	2.2 (1.0 – 5.0)
	Often	1/70 (1.4%)	0.5 (0.1 – 3.7)	0.5 (0.1 – 3.8)
	Always	0/17 (0.0%)	**	**
			p for trend=0.3	*p for trend =0.3*
*adjusted for age, sex, and BMI. **In this set of analyses, because the "Always" group had 0 events, we collapsed the "Often and Always" groups into the same group.				

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Abstract Number: 309

Periarticular Tibial Knee Bone Mineral Density Is Associated with Knee Symptoms

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Periarticular Tibial Knee Bone Mineral Density is Associated with Knee Symptoms Lo GH, Driban JB, LaValley M, Strayhorn M, Price LL, Eaton CB, McAlindon TE

Background/Purpose: Relative local knee periarticular bone mineral density (paBMD) as measured by dual x-ray absorptiometry (DXA) has been associated with features of radiographic knee osteoarthritis (OA). We postulated that this measure is associated with knee pain and measures of quality of life. To address this question, we evaluated the association of paBMD with pain and quality of life.

Methods: We performed a cross-sectional study of a subgroup of the incidence subcohort of the Osteoarthritis Initiative (OAI) who had knee DXA scans from the 72-month visit. We evaluated the right knee using identical GE Lunar Prodigy scanners, generating knee medial:lateral paBMD ratios focused on the tibial plateau. Frequency of knee pain was assessed using the 72-month visit question, "In the past 12 months, have you had pain, aching or stiffness in or around your knee on most days for at least one month?" The Knee injury and Osteoarthritis Outcome Score quality of life (QOL) assessments were also evaluated as outcomes – each item was dichotomized with a high score considered a symptomatic outcome. We performed logistic regression with a predictor of medial:lateral paBMD groups based on biologic cut points (1) low paBMD Ratio group with scores < 1.02, (2) neutral group (referent) with scores ≥ 1.02 and < 1.17, (3) high group with scores ≥ 1.17 and < 1.24 and (4) very high group with scores ≥ 1.24. Analyses were adjusted for age, sex, and BMI.

Results: 985 participants, 51% female, were included with a mean age of 65.4 (8.4) years and BMI of 28.1 (4.9) kg/m^2. The very high paBMD Ratio group had more pain compared to the neutral group (Table 1).

Table 1. Medial:Lateral paBMD Ratio Groups as predictors for frequent knee pain.			
Medial:Lateral paBMD Ratio groups	Prevalence of Frequent Knee Pain	Unadjusted OR	Adjusted OR*
Low (<1.02)	41/193 (21%)	1.0 (0.7 – 1.6)	1.0 (0.7 – 1.6)
Neutral (≥1.02, <1,17)	107/517 (21%)	Referent	Referent
High (≥1.17, <1,24)	32/142 (23%)	1.1 (0.7 – 1.7)	1.1 (0.7 – 1.7)
Very High (≥1.24)	33/106 (31%)	***1.7 (1.1 – 2.8)***	***1.7 (1.1 – 2.8)***
	Prevalence of QoL Q1 How Often Aware of Knee Problems		
Low (<1.02)	96/193 (50%)	***1.4 (1.0 – 1.9)***	***1.5 (1.4 – 2.1)***
Neutral (≥1.02, <1,17)	217/515 (42%)	Referent	Referent
High (≥1.17, <1,24)	72/140 (51%)	***1.5 (1.0 – 2.1)***	***1.4 (1.0 – 2.1)***
Very High (≥1.24)	57/106 (54%)	***1.6 (1.1 – 2.4)***	***1.7 (1.1 – 2.6)***
	Prevalence of QoL Q2 How Often Modified Lifestyle		
Low (<1.02)	32/194 (17%)	1.0 (0.6 – 1.5)	1.0 (0.6 – 1.6)
Neutral (≥1.02, <1,17)	88/516 (17%)	Referent	Referent
High (≥1.17, <1,24)	41/141 (29%)	***2.0 (1.3 – 3.1)***	***2.0 (1.3 – 3.1)***
Very High (≥1.24)	23/106 (22%)	1.4 (0.8 – 2.2)	1.3 (0.8 – 2.3)
	Prevalence of QoL Q3 How Often Troubled by Lack of Confidence in Knee		
Low (<1.02)	26/194 (13%)	1.3 (0.8 – 2.1)	1.4 (0.8 – 2.3)
Neutral (≥1.02, <1,17)	55/515 (11%)	Referent	Referent
High (≥1.17, <1,24)	23/141 (16%)	1.6 (1.0 – 2.8)	1.5 (0.9 – 2.6)
Very High (≥1.24)	17/106 (16%)	1.6 (0.9 – 2.9)	1.4 (0.8 – 2.6)
	Prevalence of QoL Q4 How Much Difficulty Have with Knee?		
Low (<1.02)	31/194 (16%)	1.3 (0.8 – 2.1)	1.4 (0.9 – 3.0)
Neutral (≥1.02, <1,17)	65/515 (13%)	Referent	Referent
High (≥1.17, <1,24)	28/141 (20%)	***1.7 (1.1 – 2.8)***	***1.7 (1.0 – 2.8)***
Very High (≥1.24)	22/106 (21%)	***1.8 (1.1 – 3.1)***	***1.7 (1.0 – 3.0)***
*Adjusted for Age, sex, and bmi.			

Conclusion: Relative local paBMD is associated with contemporaneous knee pain and some quality of life assessments. These findings may suggest that changes within the local bone have a clinically relevant influence on knee pain. Modification of the medial:lateral paBMD Ratio may improve knee pain and assist in identifying new targets of therapy.

Disclosure: G. H. Lo, NIH, 2; **J. B. Driban**, None; **M. P. LaValley**, NIH, 2; **M. T. Strayhorn**, None; **L. L. Price**, NIH, 2; **C. Eaton**, NIH, 2; **T. E. McAlindon**, NIH, 2.

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Abstract Number: 310

A Novel One Stage Technique Applicable during Arthroscopy for the Mobilization of Synovial Mesenchymal Stromal Cells Towards Joint Regeneration

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Background/Purpose: , The discovery of MSCs in the synovium and synovial fluid (SF) provided a potential mechanism for repairing cartilage “from the top down”. Indeed, we have shown in a canine model that MSCs injection into synovial fluid in canine OA is associated with MSC adhesion to damaged cartilage which may potentially contribute to subsequent joint repair (Baboolal T et al ARD 2015). Moreover, it is possible that SF-MSCs may be lost under joint irrigation at arthroscopic procedures. The purpose of this work was threefold; first to test the hypothesis that SF-MSCs can be replaced, and also their numbers further increased by synovial agitation, second that these cells were capable of rapid adhesion to clots and third that the clot composition improve MSC migration.

Methods: , Initially, ex-vivo mechanical agitation of both excised porcine and human synovium was tested using a panel of cytology brushes and custom made prototypes. Based on the prototype devices a “synovial brush” for human in vivo intra-operative MSC release in patients undergoing arthroscopy was developed and compared to a conventional cytology brush. Colony-forming unit-fibroblast (CFU-F) assay was performed to quantify released MSCs. Adhesion to clots was studied by comparing Platelet Rich Plasma (PRP), Whole Blood (WB) and Fibrin Glue (FG) to evaluate the effect of this adjunctive therapies on MSC function. Migration studies were performed using passage 2-4 synovial MSCs in trans-well migration assay. MSC migration, over a five hour period, was compared between PRP and pooled human Platelet Lysate (hPL). The functional integrity of brushed MSCs was confirmed using trilineage assays for bone, fat and cartilage differentiation.

Results: Ex-vivo mechanical agitating of the synovium with the cytology brush compared to irrigation alone increased MSC number 2.7-fold (n=10, p=0.002). Based on in vitro studies, we selected a custom designed synovial brush for in vivo studies in patients and compared to the cytology brush, the custom designed brush resulted in a median 65-fold increase in the number of CFU-Fs (n=8, p=0.0148). Trilineage differentiation of released synovial MSCs was at least comparable to donor match synovial fluid MSCs. We also noted that existing standard arthroscopic procedures with irrigation during arthroscopy effectively removed the majority of CFU-Fs from the joint cavity. Released synovial MSCs adhered to clots within 30 minutes with no difference seen between clot compositions. These MSCs demonstrated a trend for a better migration towards hPL compared to PRP.

Conclusion: Conventional arthroscopy procedures wash away SF-MSCs. Using a novel brushing technique and a custom designed synovial brush, synovial MSCs can be mechanically released in vivo, and these cells were capable of rapid migration and adhesion and had excellent preservation of chondrogenesis. Collectively these findings show that endogenous minimally manipulated MSCs can be readily increased, and provide a one-stage procedure combining synovial brushing with arthroscopy towards a low cost simple procedure in developing endogenous MSCs for joint repair in OA. This knowledge may aid in the development of a Rheumatological medical arthroscopy strategy.

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Abstract Number: 311

Comparative Effectiveness of Ayurveda and Conventional Care in Knee Osteoarthritis – a Randomized Controlled Trial

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Background/Purpose: Ayurveda is used to treat knee osteoarthritis (OA) despite limited evidence. We aimed to evaluate the effectiveness of complex multimodality Ayurvedic treatment in comparison to conventional care in OA knee patients.

Methods: Patients with OA of the knee according to ACR criteria were included in a multicenter randomized, controlled trial and treated in 2 hospital outpatient clinics and 2 private outpatient clinics with a total of 5 physicians and 20 therapists participating. Patients received either Ayurvedic treatment (n=77) or conventional care (n=74) with 15 treatments over 12 weeks. Primary outcome was the change on the Western Ontario and McMaster University Osteoarthritis (WOMAC) Index after 12 weeks. Secondary outcomes included the WOMAC subscales, a pain disability index, numeric rating scales for pain and sleep quality, a pain experience scale, a quality-of-life index, a profile of mood index, rescue medication use, and safety issues.

Results: A total of 151 patients (Ayurveda n=77, conventional care n=74) were included. Changes of the WOMAC Index from baseline to 12 weeks were more pronounced in the Ayurveda group (mean difference 61.1 [95% CI 52.4;69.6]) than in the conventional group (32.0 [95% CI 21.4;42.6]) resulting in a significant difference between groups ($p<0.001$) and a clinically relevant effect size (Cohen's d 0.68 [95% CI 0.35;1.00]). Similar tendencies were observed for all secondary outcomes at week 12. Effects were sustainable at follow-ups after 6 and 12 month.

Conclusion: The results suggest that a complex Ayurvedic treatment might be clinically superior to a complex non-surgical conventional intervention in the treatment of OA of the knee.

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Association Between Grip Strength and Hand and Knee Radiographic Osteoarthritis in Older Adults: Data from the Dong-Gu Study

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Background/Purpose: Although some studies have shown a negative relationship between grip strength and hand osteoarthritis (OA), little is known about how grip strength is related to specific radiographic features of hand OA, such as osteophytes, joint space narrowing, and erosion. In addition, no reported study has examined whether grip strength, as a measure of muscle activity, is related to knee OA, which may also show a one-way effect of reduced muscle strength on OA. In this large, population-based cohort study, we took advantage of the availability of subjects without hand pain to evaluate the effect of grip strength on OA using a novel, semi-quantitative grading system. We also examined whether grip strength was related to detailed radiographic features of OA.

Methods: Data from 2,251 subjects enrolled in the Dong-gu study, who had no hand joint pain, were analyzed to investigate the relationship between grip strength and OA. Hand grip strength was measured using a hand-held dynamometer, and radiographs of the hand and knee were scored according to a semi-quantitative grading system. Multiple linear regressions were used to explore associations between grip strength and radiographic features of OA.

Results: Grip strength in men and women was negatively related to hand (both $p < 0.001$) and knee (men, $p < 0.001$; women, $p = 0.010$) OA after adjusting for confounders. Hand (men, $p < 0.001$; women, $p = 0.001$) and knee (both $p < 0.001$) joint space narrowing showed the strongest associations with low grip strength, regardless of sex. Moreover, the severity of hand osteophytes in women ($p = 0.001$), knee osteophytes in men ($p = 0.006$), hand malalignment (men, $p = 0.008$; women, $p = 0.041$), and subchondral cysts (men, $p < 0.001$; women, $p = 0.007$) was correlated with low grip strength in both sexes.

Conclusion: Among subjects without hand joint pain, low grip strength was associated significantly with hand and knee radiographic OA, regardless of sex. Among all types of OA radiographic damage, low grip strength showed the strongest association with joint space narrowing.

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Abstract Number: 313

The Relation of Serum Urate to Radiographic Knee and Hand Osteoarthritis

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Background/Purpose: Increasing evidence suggests a role for uric acid as a danger signal for the innate immune system,

which could contribute to OA development and/or progression. If serum urate (SUA) is a true risk factor for OA, urate-lowering drugs could help prevent incident or progressive OA. However, SUA and knee OA are both associated with obesity; thus any association may be confounded by body mass index (BMI). Hand OA, in contrast, may be less affected by BMI, and may provide a better reflection of the systemic metabolic effects of urate. We therefore evaluated the relation of SUA to radiographic knee and hand OA (ROA) in a large community cohort unselected for OA, accounting for BMI.

Methods: We performed a cross-sectional study among subjects of the Framingham Original Cohort 50 years and older. SUA was assessed at exams 20 and 21 (1986-1992) and ROA at exam 22 (1990-1994). ROA of each tibiofemoral joint and of each hand joint was defined as KL ≥2. We categorized SUA as: <5mg/dL, 5-<6mg/dL, 6-<7mg/dL, 7-<9mg/dL, and ≥9mg/dL. We evaluated the sex-specific relation of SUA to the prevalence of ROA using logistic regression, adjusted for age and BMI, with generalized estimating equations to account for the correlations of joints within individuals. We repeated these analyses with SUA as a continuous variable, and categorized as quintiles.

Results: There were 329 men and 575 women with SUA and radiographic data available, among whom 89 and 156 had knee OA, and 252 and 500 had hand OA, respectively. Men with SUA >9 mg/dL had 3.3 times significantly higher prevalence of knee ROA compared with those with SUA <5 mg/dL, though the number of individuals in this category was small (table). The other SUA levels were not associated with knee or hand ROA in men or women (table), nor was there a significant test for linear trend. When SUA was assessed as a continuous variable, the prevalence of knee ROA among men and women was 1.1 times higher (95% CI 0.88-1.25 and 0.93-1.31 for men and women, respectively) for each mg/dL increment of SUA, and for hand ROA it was 1.0 (95% CI 0.94-1.10 and 0.95-1.10, respectively) (table). There was also no relation of SUA quintiles with knee or hand ROA (data not shown).

Conclusion: There was no dose-response relationship between SUA and ROA of the knee or hand. While men in the highest SUA level (>9 mg/dL) had significantly higher prevalence of knee ROA, given the small numbers and lack of replication in women or in hand ROA, this could be a chance finding. On the other hand, this sample had very few individuals with very high SUA levels; thus, we cannot rule out a possible threshold effect. Repeating this study in a sample with greater numbers of individuals with higher levels of SUA is warranted. Nonetheless, it is possible that systemic urate is not wholly biologically relevant for the risk of OA, and rather urate in the joint micro-environment must be evaluated to gain insights into the role urate may play on OA pathogenesis.

Table: Relation of serum urate to prevalent radiographic tibiofemoral and hand osteoarthritis.

	N of joints with ROA (%)	Crude OR (95% CI)	Adjusted[1] OR (95% CI)	P-Value
KNEE ROA				
Serum urate analyzed as categories				
Men				
<5 mg/dL	34/165 (20.6)	1.0 (ref)	1.0 (ref)	
5-<6 mg/dL	38/136 (27.9)	1.50 (0.78,2.86)	1.73 (0.88,3.41)	0.1
6-<7 mg/dL	21/128 (16.4)	0.76 (0.37,1.57)	0.88 (0.42,1.83)	0.7
7-<9 mg/dL	23/120 (19.2)	0.92 (0.46,1.82)	0.98 (0.48,2.00)	0.9
≥9 mg/dL	7/16 (43.8)	3.01 (1.16,7.81)	3.31 (1.28,8.55)	0.01
Women				
<5 mg/dL	112/542 (20.7)	1.0 (ref)	1.0 (ref)	
5-<6 mg/dL	59/208 (28.4)	1.52 (0.96,2.41)	1.31 (0.80,2.14)	0.3
6-<7 mg/dL	39/118 (33.1)	1.90 (1.09,3.29)	1.57 (0.87,2.84)	0.1
7-<9 mg/dL	29/92 (31.5)	1.79 (0.96,3.34)	1.38 (0.67,2.85)	0.4
≥9 mg/dL	4/12 (33.3)	1.92 (0.34,10.70)	1.62 (0.20,13.07)	0.6
Serum urate analyzed continuously				
Men	105/497 (21.1)	1.06 (0.90,1.25)	1.05 (0.88,1.25)	0.6
Women	207/796 (26.0)	1.18 (1.03,1.37)	1.10 (0.93,1.31)	0.2
HAND[2] ROA				
Serum urate analyzed as categories				
Men				
<5 mg/dL	392/1709 (22.9)	1.0 (ref)	1.0 (ref)	
5-<6 mg/dL	546/2455 (22.2)	0.96 (0.68,1.36)	0.95 (0.66,1.36)	0.8
6-<7 mg/dL	446/2088 (21.4)	0.91 (0.65,1.28)	0.88 (0.62,1.25)	0.5
7-<9 mg/dL	518/2014 (25.7)	1.16 (0.83,1.63)	1.07 (0.76,1.52)	0.7
≥9 mg/dL	54/249 (21.7)	0.93 (0.48,1.81)	0.86 (0.43,1.70)	0.7
Women				
<5 mg/dL	1940/6123 (31.7)	1.0 (ref)	1.0 (ref)	
5-<6 mg/dL	1386/4069 (34.1)	1.11 (0.88,1.40)	1.14 (0.90,1.44)	0.3
6-<7 mg/dL	697/2039 (34.2)	1.12 (0.84,1.49)	1.09 (0.81,1.47)	0.6
7-<9 mg/dl	619/1673 (37.0)	1.27 (0.94,1.70)	1.13 (0.81,1.56)	0.5
≥9 mg/dL	89/240 (37.1)	1.27 (0.53,3.06)	1.07 (0.39,2.94)	0.9
Serum urate analyzed continuously				
Men	1956/8515 (23.0)	1.04 (0.96,1.12)	1.02 (0.94,1.10)	0.7
Women	4731/14144 (33.4)	1.05 (0.98,1.12)	1.02 (0.95,1.10)	0.6

[1]Adjusted for age and body mass index; [2]Fifteen joints for each hand: first interphalangeal, four distal interphalangeal, four proximal interphalangeal, five metacarpophalangeal, and trapeziometacarpal joints. SUA: serum urate; ROA: radiographic osteoarthritis; OR: odds ratio; CI: confidence interval.

Disclosure: A. B. Vargas-Santos, None; **N. Lu**, None; **J. Niu**, None; **D. T. Felson**, None; **T. Neogi**, None.

Abstract Number: 314

The Clinical Efficacy and Safety of the Gumiganhwal-Tang in Knee Osteoarthritis: A Phase II Randomized Double Blind Placebo Controlled Study

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Background/Purpose: Gumiganghwal-tang (GMGHT) is a traditional herbal medicine consisted of nine different herbs. GMGHT inhibit the production and mRNA expression of inflammatory cytokine production TNF IL B on LPS-stimulated peritoneal macrophages in a dose-dependent manner. It is empirically used for the treatment of inflammatory disease including common cold and various pain, but there are few reports on clinical trials to clarify its efficacy and safety. The current study aimed to investigate the clinical efficacy and safety of GMGHT in patients with knee OA.

Methods: This was a 6-week, multicenter, phase 2, double-blind, randomized, and placebo controlled study of GMGHT vs placebo. Eligible patients who fulfilled American College of Rheumatology criteria were randomized to receive either GMGHT or placebo. Clinical assessments included measurement of knee pain and function with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), patient global assessment (PGA), and knee pain scores every 2 weeks.

Results: A total of 128 patients enrolled (female n=117, 91.4%; mean age 58.7 ¡¾ 8.1 years) was enrolled. At baseline, pain VAS was 67.2¡¾1.4, 71.3¡¾1.6 (treatment and placebo group, respectively, p=0.84) and total WOMAC score was 55.2¡¾1.6, 55.6¡¾1.5 (p=0.84). At 6-week, pain VAS was 43.0¡¾2.5, 61.6¡¾2.5 (treatment and placebo group, respectively, p<0.01) and total WOMAC score was 34.1¡¾2.4, 46.9¡¾1.8 (p<0.01, Figure 1). None of patients discontinued because of treatment emergent adverse events. Expected adverse event including dyspepsia, liver function abnormality, and low extremity edema was comparable between both groups (Table1).

Conclusion: Treatment of GMGHT resulted in significant improvement in pain, function and global assessment, and it was generally safe and well-tolerated in patients with OA.

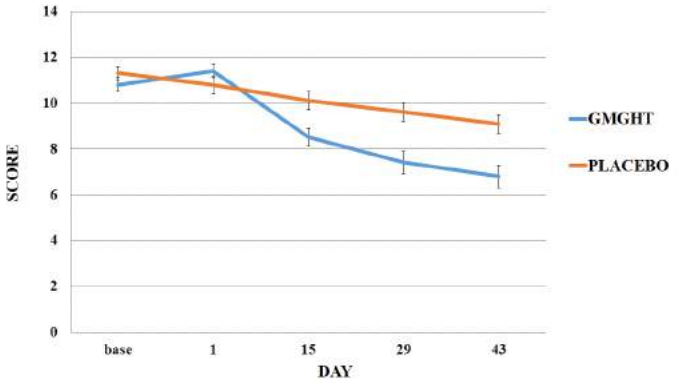
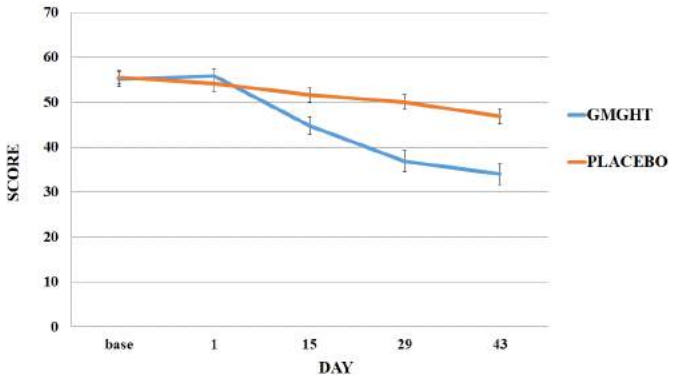


Figure 1. Outcome measures in patients with knee OA who were treated with GMGHT; change from baseline to week 6 in patient¡¯s pain VAS (A) and the total WOMAC score (B)

(A)



(B) **Table 1**. Summary of adverse events

	GMGHT (n=63)	Placebo (n=67)	p-value
Patient with any of adverse events, n (%)	14(22.2)	16(23.9)	0.83
Patient who discontinued due to with serious adverse events, n (%)	1(1.6)	1(1.5)	1.00
Gastrointestinal			
Dysgeusia, n (%)	3(4.8)	4(6.0)	1.00
Dyspesia, n (%)	2(3.2)	4(6.0)	0.68
Constipation, n (%)	0	1(1.5)	-
Flatulance, n (%)	2(3.2)	3(4.5)	1.00
Lower extremity edema, n (%)	1(1.6)	1(1.5)	1.00
Laboratory abnormalitie			
Transient LFT elevaion, n (%)	2(3.2)	1(1.5)	0.61
Transient Creatinine elevation, n (%)	2(3.2)	1(1.5)	0.61

Disclosure: S. H. Chang, None; **M. I. Kang**, None; **S. S. Nah**, None.

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Abstract Number: 315

Hip Inflammation MRI Scoring System (HIMRISS) to Predict Response to Hyaluronic Acid (HAnox-M-XL) Injection in Hip Osteoarthritis

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Background/Purpose: To assess predictors of response, according to hip MRI inflammatory scoring system (HIMRISS), in a sample of patients with hip osteoarthritis (OA) treated by hyaluronic acid (HA) injection (HAnox-M-XL).

Methods: 60 patients with hip OA were included. Clinical outcomes were assessed at baseline and three months after HAnox-M-XL injection by WOMAC50 scoring. On hip MRI performed just before HA injection, bone marrow lesion (BML) and synovitis were assessed by HIMRISS by four readers. The inter-reader reliability of HIMRISS, and associations between MRI features and clinical data were assessed. Logistic regression (univariate and multivariate) was used to explore associations between MRI features and response to HA injection, according to WOMAC50 response at three months.

Results: Inter-reader intra-class correlation coefficients for HIMRISS varied from 0.64 [0.52-0.74] for acetabular bone marrow lesion (BML), to 0.86 [0.81-0.89] for HIMRISS total. 45.5% of patients met WOMAC50 response. At baseline,

WOMAC-function correlated significantly to HIMRISS synovitis-effusion (r=0.27, p=0.03). In univariate analysis, BML femoral according to binary assessment (p=0.025), HIMRISS BML femoral (p=0.0038), HIMRISS BML acetabular (p=0.042) and HIMRISS total (p=0.0092) were associated negatively with WOMAC50 response. In multivariate analysis, adjusted for age and BMI, HIMRISS femoral BML (p=0.02) and HIMRISS total (p=0.016) were negatively associated with response. At a HIMRISS threshold of <15, 82% of patients were responders, with specificity SP=0.97, sensitivity SN=0.39, and positive and negative predictive values of 0.91 and 0.64 respectively.

Conclusion: HIMRISS is reliable for total scores and sub-domains (acetabular and femoral BML, and synovitis-effusion). It permits identification of responders to HAnox-M-XL injection in hip OA patients.

Disclosure: N. Deseyne, None; **D. Loeuille**, None; **T. Conrozier**, None; **U. Weber**, None; **J. Jaremko**, None; **H. Lellouche**, None; **B. Maillet**, None; **J. Paschke**, None; **J. Epstein**, None; **W. P. Maksymowych**, None.

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Abstract Number: 316

Postural Stability Is Associated with Lower Pain, Lower Stiffness, and Higher Muscle Power Among Adults with Symptomatic Knee Osteoarthritis

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Background/Purpose: Postural stability is an indicator of static standing balance and a critical component of physical function and fall prevention among those with knee OA. Examining associations between postural stability and physical or functional health outcomes can inform the better monitoring of disease progression and design of ideal treatments. There is limited research on the association between postural stability and outcomes of physical health and functional status in knee OA. The purpose of this study was to investigate the relationships between postural stability and pain, stiffness, physical function, walking ability, and muscle strength and power in a large population of adults with symptomatic knee OA.

Methods: We performed a cross-sectional analysis of baseline data collected as part of a randomized trial comparing Tai Chi with physical therapy. Participants who met the ACR criteria for symptomatic knee OA completed the WOMAC and a battery of physical performance tests (Berg Balance, 6 Minute Walk, 20 Meter Walk, muscle strength and power) at baseline (**Table**). Postural stability was quantified using a standardized balance force plate to measure center of pressure (COP) excursions in Anterior–Posterior (A-P) and Medial-Lateral Direction (M-L), with eyes open and closed. Greater excursion amplitude indicates greater postural instability.

Results: There were 173 participants (mean age: 60 years, BMI: 33, 69% female, 55% white, and 93% Kellgren/Lawrence Grade ≥ 2). Greater COP excursion amplitude, with eyes open or closed and in the A-P or M-L direction, was associated with higher pain (r=0.15-0.16, P<=0.05) and stiffness (r=0.24-0.25, P<=0.002). Greater COP excursion amplitude in the M-L direction (eyes open or closed) or A-P direction (eyes open) was also significantly associated with lower peak power at low (r=-0.15- -0.17, P<=0.05) or high resistance (r=-0.16- -0.19, P<=0.04). COP excursion variables were not significantly associated with BMI, WOMAC function, dynamic balance (Berg balance), muscle strength, or the walk tests (**Table**).

Conclusion: Participants with symptomatic knee OA who had greater postural stability tended to have less pain, less stiffness, and more muscle power. Our findings indicate that therapeutic interventions that positively modulate postural stability may reduce pain and stiffness among those with knee OA. In addition, static postural stability may be an

informative performance metric to assist researchers and clinicians to better monitor symptoms, design novel treatment, or prevent future falls.

Table. Correlation Coefficients between Postural Stability and Health Outcomes

	Center of Pressure (COP) Excursion Amplitude (meters)*			
Outcome Variables	**Medial-Lateral, r (*p*-value)**		**Anterior-Posterior, r (*p*-value)**	
	Eyes Open†	**Eyes Closed†**	**Eyes Open†**	**Eyes Closed†**
WOMAC Pain† (Total Range: 0-500)	**0.15 (0.05)**	**0.15 (0.05)**	**0.16 (0.04)**	**0.16 (0.03)**
WOMAC Physical Function† (Total Range: 0-1700)	0.11 (0.16)	0.08 (0.29)	0.11 (0.16)	0.09 (0.22)
WOMAC Stiffness† (Total Range: 0-200)	**0.24 (0.001)**	**0.25 (0.001)**	**0.24 (0.001)**	**0.24 (0.002)**
Muscle Power‡ (40% of 1RM), Watts	**-0.17 (0.03)**	**-0.15 (0.05)**	-0.13 (0.08)	-0.12 (0.12)
Muscle Power‡ (70% of 1RM), watts	**-0.19 (0.01)**	**-0.16 (0.04)**	**-0.16 (0.04)**	-0.13 (0.08)
6-Minute Walk, Meters	-0.10 (0.21)	-0.08 (0.33)	-0.09 (0.22)	-0.12 (0.13)
20-Meter Walk†, Seconds	0.01 (0.90)	-0.02 (0.83)	0.01 (0.85)	0.03 (0.69)
Muscle Strength¶, Newtons	-0.1 (0.18)	-0.08 (0.33)	-0.08 (0.33)	-0.05 (0.40)
BMI†, kg/m^2	0.07 (0.34)	0.1 (0.21)	0.12 (0.13)	0.12 (0.11)
Berg Balance Score† (Total Range: 0-56)	-0.03 (0.72)	-0.03 (0.68)	-0.02 (0.81)	-0.03 (0.68)

Associations were evaluated using Pearson's correlation coefficients. P ≤ 0.05 was considered significant. 1RM = one-repetition maximum.

*Measured using a standardized balance force plate to measure COP excursions. †Higher scores indicated worse health outcomes. ‡Peak leg press muscle power is the product of dynamic muscular force and muscle contraction velocity, and was measured using 5-repetition bilateral leg press performed as fast as possible with resistance set to 40% (low) and 70% (high) of the 1RM. ¶Muscle strength is the maximal force-generating capacity of skeletal muscle, and measured as the maximum load that could be moved throughout the full range of motion while the subject maintained proper form.

Disclosure: W. Liu, None; **A. C. Lee**, National Institutes of Health, 2; **W. F. Harvey**, None; **L. L. Price**, None; **J. B. Driban**, None; **C. Wang**, National Institutes of Health, 2.

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Abstract Number: 317

Leg Muscle Imbalance Is Associated with Radiographic Grade or Pain in Knee Osteoarthritis

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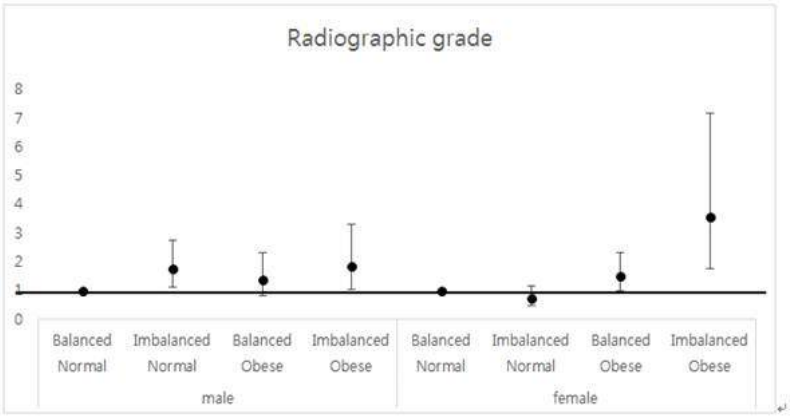
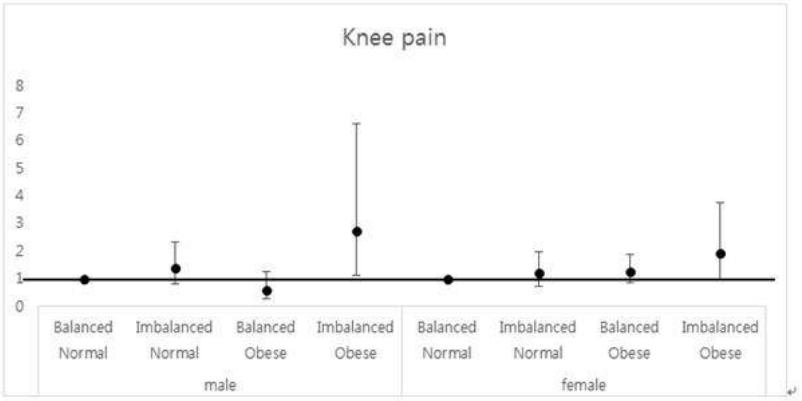
Background/Purpose: Osteoarthritis**(**OA) has been recognized as a progressive disease resulting from stress in synovial joint tissues including periarticular muscles. In knee OA, quadriceps muscle mass and strength were shown to be associated with knee OA symptoms, prevalence and progression. As one of the measures to evaluate periarticular muscles in knee OA, muscle mass imbalance or difference in both leg muscles has not been investigated. Therefore, we examined if leg muscle imbalance is related to higher prevalence of knee OA and its radiographic grade as well as symptoms.

Methods: We conducted a cross-sectional study using data from the Fifth Korean National Health and Nutrition Examination Survey (KNHANES V). Males or females aged 60 years or older who underwent both knee radiographs and DXA scans were included. Patient characteristics, bilateral knee x-rays with KL grade readings, body composition by DXA scans were obtained as part of KNHANES V. Muscle imbalance index was defined as |(left leg muscle mass)/(both legs muscle mass) x 100 -50|. Statistical analyses were performed to examine the relationships between muscle imbalance index and radiographic grade and knee symptoms.

Results: Total 2,548 patients (1,126 of men and 1,422 of women) were included in the analysis. The characteristics of males and females were significantly different. Males were younger, had smaller BMI but bigger muscle mass and lesser fat mass in both legs, exercised more than female patients. Muscle imbalance index was averaged at 0.94¡¾0.03 in males and 1.04¡¾0.03 in females. The index was significantly greater in women (p=0.01). The imbalance index was positively associated with the KL grade as well as knee pain especially in males. The most imbalanced group had 2.3 times worse radiographic grade and 2.8 times more likely to have knee pain than the least imbalanced group in males. In males with radiographic knee OA (KL grade >=2), those with the highest quantile of muscle imbalance were 3 times more likely to have knee pain compared with those in the lowest quantile. When subjects were divided into 4 different groups by obesity (BMI>=25kg/m^2) and the muscle imbalance index (4^{th} quantile vs. the rest) – balanced normal, balanced obese, imbalanced normal, and imbalanced obese, those with imbalanced obese were 1.8 times or 3.6 times worse radiographic grade of knee osteoarthritis in males or females, respectively (Figure). In males, having leg muscle imbalance irrespective of their weight status related to significantly worse radiographic grade of knee OA compared with normal males.

Conclusion: Leg muscle imbalance was associated with radiographic knee OA grade as well as prevalent knee pain. In males, muscle imbalance was significantly related to worse radiographic knee grade or knee pain, whereas obesity alone was not related to neither of them.





Disclosure: J. Y. Lee, None; **K. Han**, None; **Y. G. Park**, None; **S. H. Park**, None.

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Abstract Number: 318

Observer Variability of Joint Space with Measurements Is Subject Related in Medial Knee Osteoarthritis

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Background/Purpose: Assessment of structural progression of knee osteoarthritis (OA) requires quantitative evaluation of the radiographic joint space width (JSW). Significant reduction in the rate of narrowing of JSW represents a crucial readout in the evaluation of potential disease modifying agents for OA. However, as the knee is geometrically complex, quantitative JSW readings can only be performed on radiographs obtained using special techniques, and even in such cases, the variability in measurements (both intra-observer and inter-observer) is often large. Thus, to confidently demonstrate significance, longitudinal OA studies often require very large group sizes to achieve satisfactory power. Reducing observer variability at baseline could be a useful strategy to permit smaller or shorter structural OA studies. It has long been clear that observer variability is observer-related. However, we observed that the geometry of individual knee joints often predisposes to exagerrated measurement variability. Here we tested the hypothesis thatthere is

a study subject–related component to observer variability of JSW mesurements, and that this can be assessed at baseline to minimize the risk of observed variability in longitudinal studies.

Methods: With IRB approval and after obtaining informed consent, 20 subjects with symptomatic medial compartment knee OA (Kellgren-Lawrence grade 2-3, pain on ambulation >30 mm on a 100 mm visual analog scale) were evaluated at baseline and longitudinally as part of a larger trial. Subjects underwent semi-flexed fluoroscopic-guided PA knee radiography (Schuss view) at baseline and at 12 months. Medial compartment JSWs were quantified using Image J software (US NIH, Bethesta, MD, http://rsb.info.nih.gov/ij/) twice by the same observer, and these measurements were repeated after 8 years. The difference in the measured medial JSWs between the measurements made at baseline and those repeated after 8 years of the baseline x-ray for each subject was calculated (baseline observer variability for the individual subject). Similarly, the difference between two measurements of 12-month xrays were calculated for each subject (follow-up observer variability). Pearson's correlation test was used for analysis.

Results: Baseline observer variabilities ranged from -1.55 to 0.88, with a mean ±SD of -0.05 ± 0.44. Similarly, the variability of the 12 month measurements ranged from -1,13 to 1.35, with a mean ±SD of 0.13 ± 0.44. The discrepancy at baseline was related to the measured discrepancy of the subjects at 12 months, (Pearson's r=0.51, p=0.02), and these measurements were consistent when re-assessed 8 years later (intraclass correlation coefficient 0.97 (95 % CI 0.93-0.99)).

Conclusion: These data suggest that some knees are subject to greater measurement variability than other knees, and that these differences remains constant over time. It may be possible to identify knees that are highly prone to measurement error at baseline, and to thereby reduce groups sizes in OA trials by excluding such knees. . Selecting patients with radiographs resulting in better observer variabilty at baseline might allow performing disease modifying OA studies with smaller number of patients or shorter duration.

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Abstract Number: 319

Incident Participation Restriction in Adults with Knee Osteoarthritis: Do Positive and Negative Affect Matter? the Multicenter Osteoarthritis Study

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Background/Purpose: Participation restrictions, common among people with knee osteoarthritis (OA), may be due to psychological factors. Many people with OA experience chronic pain, which can alter levels of positive and negative affect. Positive affect consists of emotional vitality and optimism, whereas negative affect is defined by unpleasant engagement or distress. Positive and negative affect may impact participation restriction over time; however, little is known of their long-term effects. We investigated the risk of incident participation restriction over 84 months with positive

and negative affect among adults with or at risk of knee OA.

Methods: Data are from the Multicenter Osteoarthritis Study (MOST). Participants with participation restriction at baseline or who underwent total knee replacement during the 84 months were excluded. Participation restriction was measured using the Instrumental Role Limitation subscale of the Late Life Disability Index at 0, 30, 60, and 84 months. The Center for Epidemiological Studies Depression Scale was used to measure positive and negative affect at baseline. Scale values were dichotomized at the median to create high and low positive and negative affect groups. The risks of incident participation restriction over 84 months due to low positive affect, high negative affect, and combinations of low and high positive and negative affect were calculated in binomial regression analyses, adjusting for demographic factors, disease factors, and function. We tested the interaction between low positive and high negative affect.

Results: Of the 1810 participants at baseline, 470 (26%) (m=62.1 years, 56% female) had incident participation restriction over 84 months. In adjusted analyses, participants with low positive affect had 20% greater risk of incident participation restriction, and participants with high negative affect had 50% greater risk (Table 1). In the combination analysis, participants with both low positive affect and high negative affect had the highest adjusted risk of incident participation restriction [RR=1.8] compared to other combinations of positive and negative affect, but the interaction between positive and negative affect was not significant.

Conclusion: People with or at risk of knee OA with low positive and high negative affect are at increased risk of participation restrictions over time and efforts aimed at preventing participation restriction in this population should consider these psychological profiles.

Table 1. Risk ratios (RR) of incident participation restriction over 7 years (N=1810)

	Subjects n (%)	Crude RR [95%CI]	Multivariable Adjusted RR [95%CI]†
Positive Affect			
Low	754 (41.7)	1.5* [1.3, 1.8]	1.2* [1.0, 1.4]
High	1056 (58.3)	(ref)	(ref)
Negative Affect			
High	632 (34.9)	1.8* [1.5, 2.1]	1.5* [1.3, 1.7]
Low	1178 (65.1)	(ref)	(ref)
Combination			
Low PA/High NA	413 (22.8)	2.1* [1.7, 2.5]	1.8* [1.4, 2.1]
Low PA/Low NA	342 (18.9)	1.3* [1.0, 1.7]	1.2 [0.9, 1.5]
High PA/High NA	220 (12.1)	1.7* [1.3, 2.1]	1.4* [1.1, 1.8]
High PA/Low NA	836 (46.2)	(ref)	(ref)

*$p<.05$
†*All models adjusted for: sex, age, education, race, marital status, site, comorbidity, BMI, knee OA, 20-meter walk time, widespread pain, knee pain, knee stiffness; positive and negative affect were also adjusted for in models for analyses 1 and 2, respectively*

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Abstract Number: 320

The Value of Adjusting for Physical Activity When Measuring Osteoarthritis-Related Pain

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Background/Purpose: Measures of chronic pain typically do not account for individuals' physical activity (PA) levels. Although PA is essential for managing conditions like osteoarthritis (OA), some people may reduce activity to manage their pain. Recent research showed that a PA-adjusted pain measure was more strongly associated with radiographic OA severity than an unadjusted pain measure. We extend this area of research by examining whether PA-adjusted pain is also more closely associated with key function and quality of life outcomes.

Methods: In a subset of 140 Veterans (M age=61.8 years, 87.1% male) enrolled in a clinical trial of group vs. individual physical therapy, we used the Western Ontario and McMaster Universities Osteoarthritis (WOMAC) Pain Scale and calculated four composite **WO**MAC pain and **P**hysical **A**ctivity (WOPA) scores using accelerometer-derived data. Specifically, WOMAC pain scores were adjusted for: 1) step counts, 2) time in sedentary activity, 3) time in moderate-intensity activity, and 4) energy expenditure (kilocalories). All data were from baseline assessments. We examined associations of WOMAC pain score and each of the four WOPA scores with six OA-related outcomes: 6-minute walk test, 8-foot walk test, chair stand test, self-reported satisfaction with physical function, fatigue (brief fatigue inventory), and anxiety / depressive symptoms (single item). Analyses were partial correlations, controlling for age, gender and body mass index.

Results: Significant ($p<0.05$) associations were found between WOMAC / WOPA scores and OA-related outcomes in the majority (22/30) of models (Table 1). In all cases greater pain was associated with poorer outcomes. For the four OA-related outcomes that measure aspects of physical function (six-minute walk, chair stands, 8-foot walk, satisfaction with function), the step-count adjusted and energy expenditure adjusted WOMAC pain scores had stronger associations (partial r's=0.24-0.45) than the unadjusted WOMAC pain scores (partial r's=0.15-0.25). For fatigue, unadjusted WOMAC pain and energy expenditure adjusted WOMAC pain scores had similar associations (partial r's=0.27 and 0.28), and for anxiety and depressive symptoms, the unadjusted WOMAC pain score had the strongest association (partial r=0.31).

Conclusion: Results suggest PA-adjusted pain measures may add increased value in predicting some OA-related outcomes and should be explored further, particularly in longitudinal studies. Step-count adjusted pain (which was associated with radiographic OA severity in previous research) and energy expenditure adjusted pain may be particularly useful in predicting functional outcomes.

Table 1. Partial Spearman Correlations (r) of Pain / Physical Activity Measures with OA-Related Outcomes

	WOMAC Pain r (p-value)	WOMAC-Step Count r (p-value)	WOMAC-Sedentary / Light Activity r (p-value)	WOMAC-≥ Moderate Intensity Activity r (p-value)	WOMAC-Energy Expenditure r (p-value)
6-Minute Walk	-0.19 (0.04)	**-0.32 (<0.01)**	-0.15 (0.09)	-0.17 (0.06)	-0.31 (<0.01)
Chair Stands	0.15 (0.11)	**0.36 (<0.01)**	0.08 (0.36)	0.17 (0.07)	0.35 (<0.01)
8 Foot Walk	0.25 (<0.01)	0.42 (<0.01)	0.20 (0.03)	0.36 (<0.01)	**0.45 (<0.01)**
Satisfaction with Function	-0.22 (0.02)	**-0.26 (<0.01)**	-0.20 (0.03)	-0.17 (0.06)	-0.24 (<0.01)
Brief Fatigue Inventory	0.27 (<0.01)	0.19 (0.03)	0.25 (<0.01)	0.04 (0.64)	**0.28 (<0.01)**
Anxiety & Depression	**0.31 (<0.01)**	0.20 (0.03)	0.28 (<0.01)	-0.02 (0.83)	0.14 (0.13)

Strongest association for each outcome variable in **bold**.

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Abstract Number: 321

Results of a Phase 3 Clinical Trial to Evaluate the Efficacy and Safety of Romosozumab in Men with Osteoporosis

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Background/Purpose: Treatment with romosozumab (Romo) has been shown to rapidly increase BMD in postmenopausal women with low BMD through a dual effect on bone, increasing bone formation and decreasing bone resorption (McClung *NEJM* 2014), and is being investigated for anti-fracture efficacy in postmenopausal women with osteoporosis. Here we report the results of the primary analysis of a phase 3 placeBo-contRolled study evaluatIng the efficacy anD safety of Romo in treatinG mEn with osteoporosis (BRIDGE; NCT02186171).

Methods: This randomized, double-blind, multicenter study enrolled ambulatory men age 55–90 with a lumbar spine (LS), total hip (TH), or femoral neck (FN) T score ≤ –1.5 and a history of fracture after age 45, or a T score ≤ –2.5. Men were randomized 2:1 to receive Romo 210 mg or placebo (Pbo) SC once monthly for 12 months. All subjects received daily calcium and vitamin D. The primary endpoint was the percentage change from baseline in LS BMD by dual x-ray absorptiometry (DXA) at month 12. Secondary and exploratory endpoints included the percentage change from baseline in BMD by DXA at months 6 (LS, TH, and FN) and 12 (TH and FN), and the percentage change from baseline in the serum bone turnover markers P1NP and CTX, respectively. Safety endpoints included incidence of adverse events (AEs).

Results: A total of 245 men were enrolled (163 Romo, 82 Pbo). Subjects had a baseline mean (SD) age of 72 (7.3) years, baseline mean LS, TH, and FN T-scores of –2.3, –1.9, and –2.3, respectively, and 54% had a historical fracture. In the Romo group, statistically significant gains in BMD from baseline were observed at all sites evaluated at months 6 and 12 (month 12: LS [12.1%] [Figure], TH [2.5%], and FN [2.2%]) (all $P < 0.05$ vs Pbo). Romo treatment also resulted in a rapid and transient increase in the bone formation marker P1NP that peaked at month 1 (median increase from baseline 86%) and gradually returned toward baseline. The bone resorption marker CTX decreased after the first dose of Romo, with the greatest decrease observed at month 1 (median decrease from baseline 31%), and remained below baseline through month 12. The overall subject incidence rates of AEs and serious AEs were balanced between treatment groups. Injection site reactions were reported in 5.5% and 3.7% of subjects in the Romo and Pbo groups, respectively; most reactions were reported as mild in severity. The subject incidence of positively adjudicated cardiovascular serious AEs was 4.9% (8/163) in the Romo group and 2.5% (2/81) in the Pbo group. The subject incidence of positively adjudicated cardiovascular death was 0.6% (1/163) in the Romo group and 1.2% (1/81) in the Pbo group.

Conclusion: In men with osteoporosis, treatment with Romo for 12 months demonstrated a dual effect by increasing bone formation and decreasing bone resorption resulting in significant gains in BMD at the spine and the hip compared with Pbo, and was generally well tolerated.

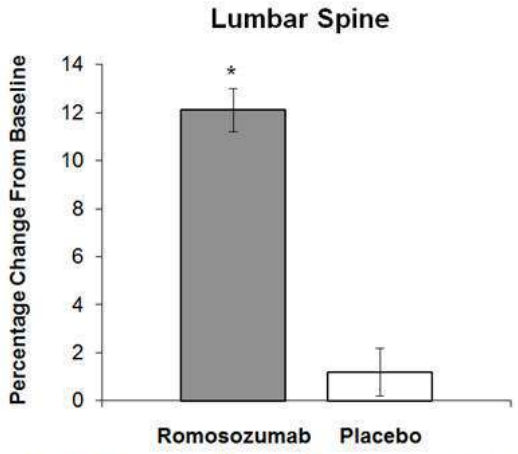

Figure. Percentage change from baseline in bone mineral density at month 12 in men receiving romosozumab 210 mg or placebo subcutaneous once monthly. Data are least-squares means and 95% confidence intervals. *$P < 0.0001$ vs placebo.

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The Activating Patients at Risk for Osteoporosis Study: A Randomized Trial within the Global Longitudinal Study of Osteoporosis in Women Cohort

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Background/Purpose: To improve the rate of osteoporosis medication use in women with a prior fracture we developed and implemented a tailored, educational, direct-to-patient video intervention to provide information about reducing fracture risk with osteoporosis medications.

Methods: We conducted a controlled, randomized clinical trial of our novel intervention among US women in the Global Longitudinal Study of Osteoporosis in Women cohort with self-reported fracture history who were not currently using osteoporosis therapy. The primary outcome at 6 months follow-up was self-report of osteoporosis medication use. Secondary outcomes included self-reported use of calcium and vitamin D supplementation and bone density testing. Missing data were treated with multiple imputation and the outcomes (proportions) were compared by chi square test using intent-to-treat analysis.

Results: We randomized 2684 women to receive the intervention materials or usual care. Study participants were 92.6% Caucasian, with a mean (SD) age 74.9 (8.0) years, had some college education (76.7%), in good health (84.6%), and a self-reported lower than average risk for osteoporosis (40.0%). In the 12 months prior to randomization, 1390 women reported talking with their doctor regarding osteoporosis, 7.4% reported a fracture, vitamin D or calcium supplementation were reported as 83.5% and 68.6%, respectively. We observed no differences in sociodemographic characteristics and no significant differences in the primary (11.7% vs 11.4%) and secondary (calcium, 31.8% vs 32.6%; vitamin D, 41.3% vs 41.9%; bone density, 61.8% vs 57.1%) end points between the intervention and usual care groups. Exploratory post-hoc analyses demonstrated that women in the intervention arm had more favorable views towards osteoporosis medications compared with the usual care arm and a lower proportion were in the unaware and uninvolved stages of behavior change regarding osteoporosis medications (64.1.% vs. 68.8%, raw p =0.028). We found that barriers to treatment were higher in the intervention, as compared to usual care arm at 6 months: concerns regarding osteonecrosis of the jaw (28.9% vs 24.6%, raw p=0.031) and difficulty in taking/remembering to take osteoporosis medications (22.0% vs 18.1%, raw p=0.03).

Conclusion: This randomized study testing a novel, personalized educational intervention, did not increase the use of osteoporosis therapy at 6 months. The intervention appeared to have influenced participants' readiness for behavior change.

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Abstract Number: 323

Effect of 10 Years of Denosumab Treatment on Bone Histology and Histomorphometry in the Freedom Extension Study

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Background/Purpose: Denosumab (DMAb) has been associated with low incidence of spine and non-spine, including hip, fractures through 10 years of treatment (Bone *ASBMR* 2015). Questions about bone safety arose in response to the FREEDOM transiliac crest biopsy findings: low numbers of tetracycline labels were observed with low dynamic parameters of remodeling (Reid *JBMR* 2010). In the FREEDOM Extension, bone biopsies were performed in subjects with 5 years of DMAb treatment and findings were similar to those in subjects with 2 or 3 years of DMAb treatment in FREEDOM (Brown *JBMR* 2014). We now report bone biopsy findings in subjects with 10 years of DMAb treatment.

Methods: A subset of subjects with 10 years of DMAb exposure (3 years FREEDOM + 7 years Extension) participated in a transiliac bone biopsy substudy. Subjects underwent a tetracycline/demeclocycline labeling procedure prior to their bone biopsy visit (6 months after their last DMAb dose); samples were prepared and analyzed according to standard procedures by the Mayo Clinic as previously described (Reid *JBMR* 2010). Continuous and categorical variables were summarized using descriptive statistics.

Results: There were 22 biopsies evaluable for qualitative histology in subjects with 10 years of DMAb exposure; all specimens showed normally mineralized lamellar bone. There was no evidence of pathologic findings, including osteomalacia, woven bone, or marrow fibrosis. There were 21 biopsies evaluable for histomorphometry; these showed that the antiresorptive effects of DMAb were maintained over time. In addition, indicators associated with bone formation and structure (including osteoid surface, osteoid width, and eroded surface) were generally similar to those at years 2/3 and 5 (Table). As part of the analysis of dynamic parameters, the presence of tetracycline labels was reviewed in all biopsies. The percentage of samples with any tetracycline label in trabecular bone has steadily increased over time from 34% in year 2/3, to 43% in year 5, and 77% in year 10; the percentage of samples with any label in cortical bone has remained steady from 57%, to 64%, and 55%, respectively. Double tetracycline labeling of trabecular or cortical bone was found in 7 (32%) subjects at year 10.

Conclusion: Bone histology showed normal bone microarchitecture, and histomorphometry was consistent with DMAb mechanism of action. There was no evidence of progression in the degree of low remodeling with long-term exposure to DMAb. **Table 1:** Bone histomorphometry in FREEDOM and its extension

	FREEDOM		**Extension**		
	Year 2/3		**Year 5**		**Year 10**
	Placebo	**Denosumab**	**Cross-over**	**Long-term**	**Long-term**
	N = 45	**N = 47**	**N = 13**	**N = 25**	**N = 22**
Denosumab exposure (years)	0	2–3	2	5	10
Parameter	Median (Q1, Q3)				
Eroded surface/ bone surface (%)	1.0 (0.6, 1.9)	0.2 (0.0, 0.7)	0.2 (0.0, 0.4)	0.1 (0.0, 0.3)	0.3 (0.0, 0.9)
Osteoid surface (%)	6.8 (3.6, 10.1)	0.4 (0.2, 1.2)	0.5 (0.2, 0.7)	0.1 (0.0, 0.8)	0.1 (0.0, 0.2)
Osteoid width (μm)	8.7 (6.4, 11.0)	5.4 (4.4, 7.4)	5.6 (3.3, 6.6)	3.3 (0.0, 7.4)	4.2 (0.0, 7.4)
Mineral apposition rate (μm/d)	0.8 (0.7, 0.8)	0.3 (0.3, 0.5)	0.6 (0.5, 0.7)	0.4 (0.3, 1.1)	0.3 (0.3, 0.3)
Bone formation rate, volume based (%/yr)	14.6 (8.6, 21.8)	0.4 (0.2, 0.8)	1.2 (0.7, 1.3)	2.2 (0.2, 4.7)	0.3 (0.2, 2.8)
Activation frequency ($year^{-1}$)	0.200 (0.120, 0.330)	0.002 (0.001, 0.004)	0.017 (0.011, 0.020)	0.031 (0.001, 0.071)	0.001 (0.001, 0.012)

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Abstract Number: 324

A Placebo Controlled Trial of Vertebral Fill Technique Vertebroplasty for Acute Painful Osteoporotic Fracture (VAPOUR Trial)

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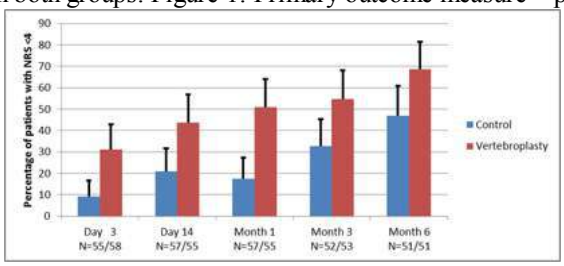
Background/Purpose: Evaluation of efficacy and safety of percutaneous vertebral fill technique vertebroplasty in subjects with acute vertebral fracture (symptom duration less than six weeks) .

Methods: Randomized, parallel group, placebo controlled trial. The proceduralists utilized a vertebral fill cement technique, achieving cement distribution from the superior to the inferior end plate. Primary outcome measure patient rated pain intensity less than 4 (Numerical Rating Scale) measured at two weeks. Secondary outcome measures recorded at time points 3 days, 14 days, 28 days, 3 months and 6 months were functional disability (The Roland-Morris Low Back Pain and Disability Questionnaire (RDQ), The Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO. Effectiveness analyses by intention-to-treat principle. Proportions compared using a two-sided chi-squared or exact (conditional binomial) test. Changes in quality of life measures (pain/ functional disability scores) analysed using *t*-tests enabling comparisons with published studies. All comparisons were two-sided with a significance level of 5% considered as being statistically significant.

Results: 120 subjects were enrolled (59 control arm, 61 vertebroplasty arm). Female 73%, Male 27%. Mean age 80 years (SD 7.2) The proportion of patients achieving an NRS <4 at 14 days was 43.6% in the vertebroplasty group and 21% in the control group (p=0.011). Mean decrease in change in NRS pain score from baseline greater in the vertebroplasty group at all time points (p<0.05). Mean reduction in RDQ from baseline favoured vertebroplasty from day 14 to month 6. (p<0.05). There was minimal difference Mean QUALEFFO l between groups. Four serious adverse events occurred; 2 in the placebo group and 2 in the vertebroplasty group.

Conclusion: Percutaneous Vetebroplasty performed during the first six weeks post fracture utilizing a vertebral fill technique, is more effective than placebo in reducing pain, and improving function in patients with vertebral fracture. Serious adverse events were the same in both groups. Figure 1: Primary outcome measure – percentage (%) of patients with NRS < 4) all time points p<0.05)



Disclosure: **P. Bird**, None; **W. Clark**, None; **T. Diamond**, None; **G. Schlaphoff**, None; **P. Smerdely**, None; **P. Gonski**, None; **P. McNeil**, None.

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Abstract Number: 325

Ebselen Is a Potential Anti-Osteoporosis Agent By Suppressing RANK Ligand-Induced Osteoclast Differentiation in Vitro and Lipopolysaccharide-Induced Inflammatory Bone Destruction In Vivo

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Background/Purpose: Ebselen is a non-toxic seleno-organic drug with anti-inflammatory and antioxidant properties that is currently being examined in clinical trials to prevent and treat various diseases, including atherosclerosis, stroke, and cancer/We investigated the effects of ebselen on RANKL-induced differentiation of osteoclasts and their functions and the underlying molecular mechanisms. Furthermore, we determined the effects of ebselen on LPS-induced bone erosion in vivo.

Methods: We cultured BMMs for 4 days in the condition of M-CSF and RANKL pretreated with ebselen. The cells were then stained with TRAP solution, rhodamine-conjugated phalloidin for F-actin ring labeling and DAPI solution to detect apoptotic body formation. The change of F-actin ring on mature osteoclasts induced by ebselen was quantified by calculating the ratio of actin ring positive (AR+) osteoclasts versus actin ring negative (AR-) osteoclasts. to detect the formation of apoptotic osteoclasts, we performed TUNEL (TdT-mediated dUTP-biotin nick endlabeling) assay. Primary calvaria osteoblasts and BMCs were co-cultured and were re-seeded in hydroxyapatite-coated plates or dentin slices with or without ebselen. ICR mice were divided into 4 experimental groups comprising 5 mice each: phosphate-buffered saline-treated (control) group, ebselen only-treated group, LPS only-treated group, and LPS and ebselen-treated group. Ebselenor PBS was administered orally every 8 days, and LPS was injected intraperitoneally on days 1 and 4. μ-CT data containing 3D images and bone parameters and histological data were acquired

Results: Ebselen suppressed the formation of TRAP-positive multinucleated cells in an osteoblast/osteoclast co-culture by regulating the ratio of RANKL/osteoprotegerin secreted by osteoblasts. In addition, ebselen treatment in the early stage of osteoclast differentiation inhibited RANKL-dependent osteoclastogenesis by decreasing the phosphorylation of IκB, PI3K, and Akt in early signaling pathways and by subsequently inducing c-Fos and nuclear factor of activated T-cells c1. Further, ebselen induced apoptosis of osteoclasts in the late stage of osteoclast differentiation. In addition, ebselen treatment suppressed filamentous actin ring formation and bone resorption activity of mature osteoclasts. Reflecting these in vitro effects, administration of ebselen recovered bone loss and its μ-CT parameters in lipopolysaccharidemediated mouse model. Histological analysis confirmed that ebselen prevented trabecular bone matrix degradation and osteoclast formation in the bone tissues. Finally, it was proved that the anti-osteoclastogenic action of ebselen is achieved through targeting N-methyl-D-aspartate receptor.

Conclusion: These results indicate that ebselen is a potentially safe drug for treating metabolic bone diseases such as

osteoporosis.

Disclosure: C. Lee, None; **J. M. Baek**, None; **J. Y. Kim**, None; **W. S. Lee**, None; **W. H. Yoo**, None; **M. S. Lee**, None.

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Abstract Number: 326

Cortical Bone Changes in Pre- and Postmenopausal Healthy Women Measured with HR-pQCT

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Background/Purpose: Increased fracture rates are well-recognized in adults with trabecular and cortical bone deficits, but cortical evaluation has been poorly studied. The aim of this study is to analyze the cortical bone parameters using high-resolution peripheral quantitative computed tomography (HR-pQCT, Scanco Medical AG, Switzerland) parameters in a cohort of 450 healthy women and compare these cortical parameters in pre- and postmenopausal.

Methods: The distal radius (DR) and distal tibia (DT) of 228 premenopausal women and 222 postmenopausal women were scanned using HR-pQCT. The entire volume of interest (VOI) was automatically separated into cortical and trabecular regions using a threshold-based algorithm and the following cortical parameters were obtained: cortical volumetric bone mineral density (Ct.vBMD), cortical thickness (Ct.Th). Moreover, cortical porosity (Ct.Po) was calculated as the percentage of void space in the cortex. Stiffness was analysed with a software specific finite element analysis (Scanco Medical AG, Switzerland). Significance was accepted at $p < 0.05$.

Results: At distal radius, the density (Ct.vBMD) and thickness (Ct.Th) showed an important decrease of these parameters up to 10 years after menopause, and remained stable after this period. Differently, Ct.Po showed a continue alterations (increase) linearly with age. Regarding distal tibia site, the deterioration of the Ct.vBMD, Ct.Th and Ct.Po were observed linearly with aging. The Pearson correlation demonstrated that density and thickness cortical parameters at DR and DT showed a moderate significant correlation (Ct.vBMD: DR: r= 0.521, DT: r=0.316; Ct.Th: DR: r= 0.619, DT: r= 0.392, $p<0.01$) and a weak correlation with cortical porosity (Ct.Po- DR: r= -0.162, DT: r= -0.273 ($p<0.01$) with stiffness parameter.

Conclusion: Our results showed that cortical parameters of the distal radius have a different behavior during aging comparing to distal tibia site. Moreover, cortical density/thickness showed better correlation with strength parameter, suggesting that density/thickness parameter are better for predicting cortical bone quality comparing to cortical porosity.

Disclosure: J. C. Alvarenga, None; **R. M. R. Pereira**, None.

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Abstract Number: 327

Drug Retention Rate of Oral Bisphosphonate in Patients with Rheumatoid

Arthritis

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Background/Purpose: As rheumatoid arthritis (RA) is a well-established risk factor for osteoporosis and compression fracture, non-adherence to bisphosphonate (BP) therapy in patients with RA can adversely affect clinical outcome. Our study aimed to investigate the drug retention rate of oral BP and analyze the associated factor for this rate in RA patients under routine care.

Methods: In this retrospective longitudinal study, 410 RA patients in whom the first oral BP such as ibandronate (150 mg/month), risedronate (35 mg/week) and alendronate (70 mg/week) initiated from April 2003 to September 2015 at a university-affiliated rheumatology center in South Korea were included. Seropositve RA was defined as having for a positive test result for presence of either rheumatoid factor or anti–cyclic citrullinated peptide antibody. The drug retention rate was calculated using the Kaplan-Meier method and the predictors of this rate were identified by Cox-regression analyses.

Results: The mean age was 65.9 ¡¾ 11.3 years and 399 (96.6%) and 332 (81%) patients were female and seropositive RA, respectively. During the study period, 283 (69%) patient discontinued oral BP. The cause of BP discontinuation was as follows: treatment failure, 35.7%; adverse events, 6.4%; patients¡¯ decision, 43.1%; drug holidays, 2.8%; cost, 12%. The 2-year drug continuation rate was 65.8, 40 and 42.1% and the median retention was 39.2, 13.1 and 18.8 months for ibandronate, risedronate and alendronate, respectively. The drug retention rate significantly differed among the 3 oral BP (p<0.001, Fig. 1). In multivariable Cox regression models, risedronate demonstrated a worse retention rate than ibandronate (HR=2.34, 95% CI=1.79-3.06, p<0.001, Table 1). Additionally, seropositve RA patients showed a better BP retention rate than those without this feature (HR=0.59, 95% CI=0.42-0.84, p=0.004).

Conclusion: Persistence of BP treatments was suboptimal in RA patients under routine care. Monthly ibandronate showed better retention rate than weekly risedronate, suggesting that a longer dosing interval may improve the adherence of BP treatment in RA patients.

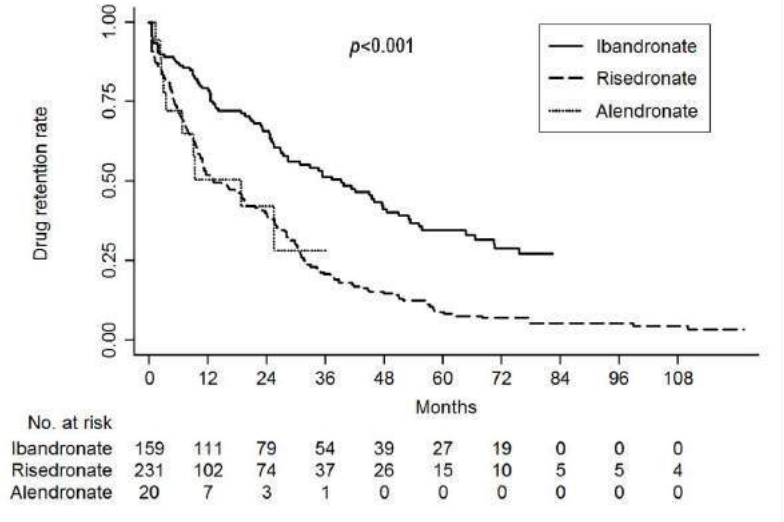

Figure 1. Kaplan-Meier survival curve of oral bisphosphonate in patients with rheumatoid arthritis Table 1. Cox-proportional hazard regression analyses with backward model selection for tacrolimus discontinuation according to causes.

Variables	Univariable			Multivariable	
	HR (95% CI)	*p*		[a]HR (95% CI)	*p*
Age, years	0.99 (0.98-1.01)	0.58		-	-
Male	1.34 (0.67-2.61)	0.39		-	-
Glucocorticoids use	1.06 (0.72-1.55)	0.755			
Previous compression fracture	1.43 (0.97-2.1)	0.07		-	-
Seropositive RA	0.66 (0.48-0.92)	0.014		0.59 (0.42-0.84)	0.004
Disease duration > 24 months	0.68 (0.53-0.87)	0.002		-	-
BP	1.08 (0.41-2.87)	0.87			
Ibandronate	ref.				
Risedronate	2.23 (1.72-2.88)	<0.001		2.34 (1.79-3.06)	<0.001
Alendronate	2.22 (0.14-4.3)	0.018		1.66 (0.76-3.62)	0.205

[a] Estimated using multivariable Cox regression model with backward selection including age, gender, previous compression fracture, seropositive RA, disease duration and the type of BP

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Abstract Number: 328

A Study of Serum Electrolyte Levels after Denosumab Administration

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Background/Purpose: Denosumab is an antiresorptive drug used for the treatement of postmenopausal osteoporosis. One of the major and critical adverse events of denosumab injection is hypocalcemia, which is most often observed in the one-week period following administration. Examination of albumin-adjusted calcium (Ca) level after one week is recommended to exclude the presence of hypocalcemia. Although hypophosphatemia has been reported to be an adverse event with a frequency of more than 1% in patients subcutaneously administered 120mg of denosumab for tumor treatment, there have been no reported data regarding its frequency in patients administered 60mg for osteoporosis. The purpose of the present study was to evaluate the occurrence of denosumab adverse events, focusing on serum electrolyte levels soon after administration, as well as to confirm its efficacy.

Methods: Forty-three women between the ages of 55 and 91 years with postmenopausal osteoporosis were enrolled and treated with a 60mg subcutaneous injection of denosumab and an oral calcium tablet combined with native vitamin D and magnesium (Mg).Serum Ca and phosphorus (P) were measured at baseline and at 1,2,3,and 4 weeks after administration. Serum Mg, bone formation marker intact serum procollagen type 1 N-terminal propeptide (P1NP), and bone resorption marker tartrate-resistant acid phosphatase-5b (TRACP-5b) were also evaluated at baseline and 4 weeks after

administration. Laboratory investigations after a second injection were performed in 33 patients in the same manner. Bone mineral density (BMD) was measured at baseline and 6 months after administration.

Results: Both serum Ca and P electrolyte levels significantly decreased soon after administration. Hypocalcemia was detected in 3 patients: 2 patients 1 week after administration, and 1 patient 2 weeks after. Hypophosphatemia was observed in 10 patients: 8 patients 1 week after administration and 2 patients after 2 weeks. Hypocalcemia was observed 1 week after the second administration in 1 of the 33 patients. Hypophosphatemia was detected in 1 patient 1 week after. Serum Mg levels were within normal limits on all examinations. There were no patients who discontinued the treatment due to adverse events in the present study. All serum electrolyte levels recovered within 4 weeks of each administration. At 4 weeks, P1NP level was decreased by 24.0% and TRACP-5b was decreased by 66.9 %. At 6 months, BMD of the lumbar spine was increased by 2.5%, the femur by 1.5%, and the distal radius by 0.6%.

Conclusion: Adverse events were not observed clinically throughout the duration of the study period. However,hypocalcemia and hypophosphatemia were observed within 1 or 2 weeks after the first and/or second administration of denosumab. Therefore, measuring serum electrolyte levels of Ca and P within in 1 or 2 weeks is strongly recommended for the detection of hypocalcemia and hypophosphatemia. Furthermore, denosumab administration resulted in a low bone remodeling ratio reflected by decreases in both P1NP and TRACP-5b levels, and increase in BMD, which may reduce fracture risk.

Disclosure: K. NAKASEKO, None; **T. SUDO**, None; **T. ASANO**, None.

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Abstract Number: 329

Explore the Possible Mechanisms of 1,25(OH)2D3 on the Formation of Osteoclasts in Rheumatoid Arthritis

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Background/Purpose: In our previous study, several conclusions are reached like: (1) IL-22 can promote inflammation and osteoclast formation in the process of RA;(2) 1,25(OH)2D3 decreases serum IL-22 level in RA patients, and acts as a dose-dependent inhibition of expression of RANKL;(3) 1,25(OH)2D3 may inhibits the expression of RANKL by blocking IL-22-mediated JAK-2 /STAT-3and p38MAPK/ NF-κB transduction pathways.In this study, we will compare the formation of osteoclasts in different treatment groups to explore whether the 1,25(OH) 2D3 can inhibit the formation of osteoclasts by affecting the IL-22-mediated JAK-2 / STAT-3 and p38MAPK/ NF-κB signal transduction pathways.

Methods: 1. In this trial all the osteoclast precursors PBMCs came from the peripheral blood of healthy volunteers, the consentrations of RANKL, M-CSF, 1,25(OH)2D3 respectively: 30ng/mL、25ng/mL、1nM. All the samples were devided into the following groups: GroupA: PBMC+M-CSF；GroupB: PBMC+M-CSF+RANKL；GroupC: PBMC+M-CSF+RANKL+1,25(OH)2D3. Detected the levels of the osteoclasts' marker TRAP, cathepsin K, matrix metalloproteinase (MMP)-9 mRNA by RT-PCR to assess the effect of the agents. 2.Isolate FLS from RA synovial tissue of patients and culture them to generation 4~8, add IL-22 to stimulate the secretion of RANKL. Isolate PBMC from the peripheral blood of healthy volunteers, add the M-CSF pretreatment after 24h when the cells adherent, co-culture the two kind cells. At the same time, add RANKL, M-CSF, IL-22, 1,25(OH)2D3 and different signal transduction protein inhibitors according to the experimental groups.The consent rations of RANKL and M-CSF are the same to part1, the consentration of IL-22 is

10ng/ml. We devided all the samples into the following 5 groups: Group a: PBMC+RA-FLS+M-CSF; Group b: PBMC+RA-FLS+M-CSF+RANKL; Group c: PBMC+RA-FLS+M-CSF+IL-22+1,25(OH)2D3; Group d: PBMC+RA-FLS+M-CSF+1,25(OH)2D3+IL-22+AG490; Group f: PBMC+RAFLS+M-CSF+1,25(OH)2D3+ IL-22+SB203580.

Results: 1.In the part1 the number of osteoclasts (multiple nuclear TRAP positive cells)in groupA, B, C respectively 7±>0.816, 30±2.944, 5±2.16. There was statistically significant difference between groups(P<0.05). 2.The mRNA of the three makers to osteoclast is higher in group B compared with the other two groups (P<0.05). But the difference between group A and C has no statistically significance(P>0.05). 3.In the part 2 the number of osteoclasts in the Groups a,b,c,d,f respectively 7.5±1.732, 38.5±3.416, 0.5±0.477, 21.75±3.775, 9±2.944. The number in the Group b is higher than in Group a, The difference was statistically significant(P<0.05); the difference between Groups c,d,f and Group b also has statistically significant(P<0.05); the difference between Groups d,f and Group c also has statistically significant (P<0.05). 4.The expression of the target genes in the Groups a,c,d and the Group f are lower than the Group b. There has no statistically significant difference between Group a and c, d and f (P>0.05). The differences between other groups are statistically significant(P<0.05).

Conclusion: 1,25(OH)2D3 can inhibit the formation of osteoclasts by blocking the IL-22-mediated JAK-2/STAT-3 signaling pathway.

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Abstract Number: 330

Safety of Denosumab in Postmenopausal Osteoporosis and in Cancer and Bone Metastase Treatment: A Systematic Review and Meta-Analysis

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Background/Purpose: Denosumab is a RANK ligand antibody and the first biologic agent used for the treatment of post-menopausal osteoporosis (OP) and prevention of bone metastases complications. The aim of this meta-analysis was to assess the safety of Denosumab.

Methods: Data sources included MEDLINE, EMBASE, Cochrane Library, and recent abstracts from ACR and EULAR congresses were searched until March 2016. Randomized controlled trials comparing the safety of Denosumab to placebo or bisphosphonates (BP) in postmenopausal OP and in cancer (either cancer with bone metastases or with hormone therapy) were selected. Data were extracted by one investigator, confirmed by another, and pooled in meta-analysis using Review Manager software (Cochrane collaboration).

Results: 6136 articles were of potential interest, and 19 met the inclusion criteria. 7 articles (3859 patients) compared the safety of Denosumab to BP in post-menopausal OP. There was no significant difference when comparing Denosumab with bisphosphonates in any adverse events (AAE) (RR=0.98, 95% CI=0.95-1.01) serious adverse event (SAE) (RR=1.04, 95% CI=0.81-1.33) and all infections (AI) (RR=1.11, 95% CI=0.98-1.25). Regarding Denosumab versus placebo in post-menopausal OP, 7 studies (8724 patients) were included and there was no significant difference in AAE (RR=0.98, 95% CI=0.94-1.01), SAE (RR=1.03, 95% CI=0.96-1.11), AI (RR=1.11, 95% CI=0.98-1.25), however cellulitis was more frequently found with Denosumab (RR=8.03, 95% CI=1.44-4.00). No cases of osteonecrosis of the jaw (ONJ) has been reported. 5 articles were pooled to compare Denosumab with BP in patients with bone metastases and no significant difference was found in AAE (RR=0.99, 95% CI=0.98-1.00), SAE (RR=0.99, 95% CI=0.95-1.03), AI (RR=1.01, 95% CI=0.89-1.13) and ONJ (RR=1.40, 95% CI=0.92-2.13). 4 articles were selected concerning patients treated with placebo or Denosumab in breast and prostate cancer without bone metastases. Although no significant difference was found in AAE (RR 1.01, 95 % CI=0.99-1.03), use of Denosumab was associated with a significantly increased risk of hypocalcemia (RR 5.20, 95 % CI=1.34-20.13) and of cholecystitis (RR 3.43, 95 % CI= 1.01-11.69).

Conclusion: In post-menopausal OP, Denosumab had a relatively good safety profile although significantly more cellulitis occurred when compared with placebo. For patient with cancer, Denosumab was associated with more hypocalcemia and cholecystitis than placebo; that could be explained by a relative immunosuppression and a higher dose of Denosumab used in these patients. Patients with bone metastases treated with Denosumab tended to have a higher risk of ONJ although not significant.

Disclosure: M. Aubailly, None; **B. Combe**, None; **C. Gaujoux-Viala**, None; **C. Lukas**, None; **J. Morel**, None; **H. Che**, None.

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Abstract Number: 331

Biologic Disease-Modifying Anti-Rheumatic Drug Use and the Risk of Non-Vertebral Osteoporotic Fractures in Japanese Patients with Rheumatoid Arthritis: Results from the IORRA Cohort Study

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Previous U.S. and Canadian studies [1-3] have suggested that no significant associations exist between use of biologic disease-modifying anti-rheumatic drugs (DMARDs) and risk of non-vertebral fractures in patients with rheumatoid arthritis (RA), although previous small studies reported that biologic DMARDs preserve bone mineral density. Our objective was to determine the association between biologic DMARD use and the risk of non-vertebral osteoporotic fractures in Japanese patients with RA.

Methods:

The Institute of Rheumatology Rheumatoid Arthritis (IORRA) study, which began in 2000, was a prospective cohort study of Japanese patients with RA conducted at the Institute of Rheumatology, Tokyo Women's Medical University (Tokyo, Japan). More than 116 publications have described various characteristics including fracture rate [4], fracture site, and

risk factors for fractures [5] in Japanese patients with RA using this cohort. A nested case-control study was conducted using the IORRA cohort. RA subjects were followed from cohort entry until the earliest non-vertebral osteoporotic fracture at elbow, forearm, hip, humerus, pelvis, shoulder, and wrist. Controls were matched to cases (4:1 ratio) by age, sex, and date of cohort entry. Biologic DMARD exposure was defined as being on treatment for ≥ 180 days pre-fracture (index). Conditional logistic regression was used to assess the association between biologic DMARD use and the risk of non-vertebral osteoporotic fractures.

Results:

Over the study period, 565 cases were identified (2,822 controls). The most common fracture sites were hip (25.3%), wrist (21.1%), and shoulder (15.2%). In total, 230 subjects (51 cases and 179 controls) were exposed to biologic DMARDs. The median duration of exposure was 2.5 (interquartile range [IQR], 1.0-4.0) and 2.5 (IQR, 1.0-4.5) years in cases and controls, respectively. We were unable to demonstrate an association between biologic DMARD use and fracture risk (hazard ratio [HR] 1.11; 95% confidence interval [CI], 0.75-1.65) (Table). Baseline Japanese health assessment questionnaire disability index (JHAQ-DI), daily prednisone (PSL) dose, and bisphosphonate use were significantly ($P < 0.001$) associated with fracture risk.

Conclusion: Despite the positive impact of biologic DMARDs on bone remodeling observed in small studies, we were unable to demonstrate a reduction in the risk of non-vertebral osteoporotic fractures in Japanese patients with RA as reported in U.S. and Canadian patients with RA.

Table. Hazard ratios (95% confidence interval) of non-vertebral osteoporotic fractures in Japanese patients with RA: Multivariate analyses.

Factor	HR (95% CI)	*P*
RA disease duration	1.00 (0.99-1.01)	0.49
Body mass index	1.02 (0.99-1.05)	0.17
JHAQ-DI	1.59 (1.39-1.81)	< 0.001
NSAIDs use	1.06 (0.86-1.31)	0.56
Daily PSL dose, mg/day	1.06 (1.03-1.10)	< 0.001
Bisphosphonate use	1.51 (1.21-1.88)	< 0.001
Active vitamin D3 use	1.20 (0.92-1.58)	0.18
Proton pomp inhibitor use	0.76 (0.57-1.01)	0.059
Biologic DMARD use	1.11 (0.75-1.65)	0.59

References 1) Kawai VK, et al. Arthritis Care Res (Hoboken). 2013;65:1085-94; 2) Kim SY, et al. J Bone Miner Res. 2012;27:789-96; 3) Roussy JP, et al. Osteoporos Int. 2013;24:2483-92; 4) Ochi K, et al. Osteoporos Int. 2015;26:961-8; 5) Furuya T, et al. Osteoporos Int. 2013;24:1257-65.

Disclosure: T. Furuya, None; **E. Inoue**, None; **M. Nakayama**, None; **E. Tanaka**, Abbvie, Eisai Pharmaceutical, Chugai Pharmaceutical, Bristol Myers Squibb, Astellas Pharmaceutical, Pfizer, Takeda Pharmaceutical, Daiichi Sankyo Pharmaceutical, Mitsubishi Tanabe Pharmaceutical, Nippon Kayaku, and Santen Pharmaceutical., 5; **K. Ikari**, AbbVie, Inc., Asahi Kasei Pharma Corp., Astellas Pharma Inc., Bristol-Myers Squibb Co., Chugai Pharmaceutical Co., Eisai Co., Ltd. Hisamitsu Pharmaceutical Co. Inc., Janssen Pharmaceutical K.K., Kaken Pharmaceutical Co. Ltd., Mitsubishi Tanabe Pharma Co.,, 2; **A. Nakajima**, None; **A. Taniguchi**, None; **H. Yamanaka**, Abbott, AbbVie, Asahikasei, Astellas, AstraZeneca, Bristol-Myers Squib, Chugai, Daiichi Sankyo, Eisai, GlaxoSmithKline, Janssen, Mitsubishi Tanabe, MSD, Nippon Kayaku, Pfizer, Santen, Taishotoyama, Takeda, and Teijin; has received consulting fees from Abb, 2,Abbott, AbbVie, Astellas, Bristol-Myers Squib, Chugai, Eisai, Mitsubishi Tanabe, Pfizer, Takeda, and Teijin, 8.

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Abstract Number: 332

A Comparison of Electronic and Manual Fracture Risk Assessment Tools in Screening US Veterans at Risk for Osteoporosis

Tyler Williams[1], Phillip Lawrence[2], Jacob Crook[3], Richard Nelson[3], Joanne Lafleur[4] and Grant W. Cannon[5], [1]Salt Lake

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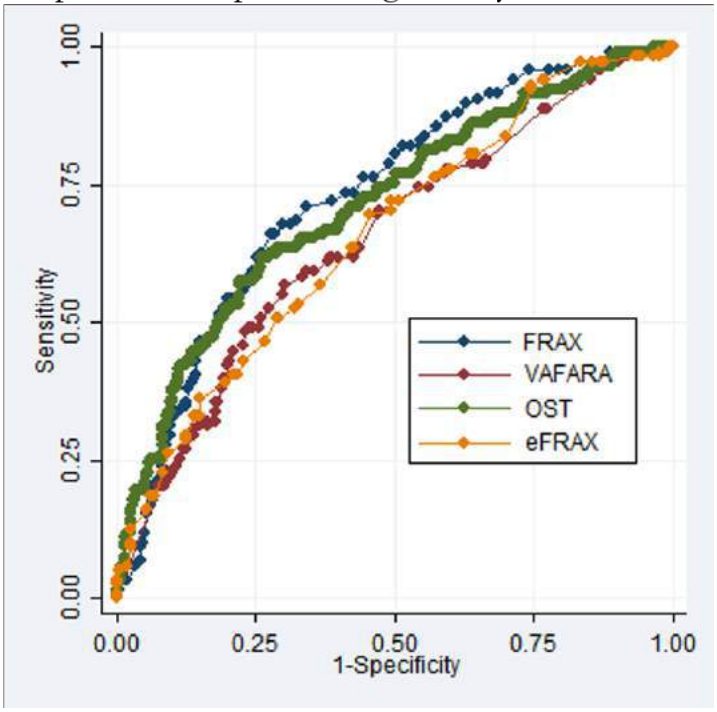
Background/Purpose: Osteoporosis-related fractures contribute to increased morbidity and mortality in those affected and substantial economic burden to society. Effective screening for osteoporosis with fracture risk assessment tools (FRATs) is crucial to allow for needed preventive therapies. Electronic medical records (EMRs) present an important opportunity to identify patients at high risk for osteoporosis-related fractures. We compared the performance of four FRATs in identifying patients with osteoporosis by bone mineral density (BMD) T-score: The Veterans Affairs Fracture Absolute Risk Assessment Tool (VA-FARA), The World Health Organization's Fracture Risk Assessment Tool (FRAX) based on patient-reported risk factors, the electronic FRAX (e-FRAX) which obtains inputs from the EMR, and the Osteoporosis Self-Assessment Screening Tool (OST). VA-FARA, FRAX, and e-FRAX are designed to identify fracture risk, which correlates with osteoporosis. OST is designed to identify osteoporosis.

Methods: We performed a cross-sectional analysis of all patients enrolled in the VA Salt Lake City Bone Health Team (BHT) from February 1, 2012 through February 1, 2013 who had a DXA. Patients were eligible for BHT intervention if they were males age 70+ or females age 65+. BMD scores were obtained by chart abstraction for each patient. Osteoporosis risk factors were obtained from a screening questionnaire which patients completed prior to DXA scan for calculation of FRAX. For VA-FARA and eFRAX risk factors were derived from the EMR. Clinical risk scores were then calculated and compared against the gold standard of DXA-based osteoporosis. Receiver operator characteristic (ROC) curves were plotted for each test and areas under the curve (AUC) were compared.

Results: A cohort of 473 patients met eligibility criteria (mean age 80.3 years, 98% male). Of these, 118 patients (25%) had osteoporosis as defined by DXA score < -2.5. There was no statistically significant difference between FRATs in identifying DXA-based osteoporosis. ROC curves are shown in figure 1. ROC statistics are shown in Table 1.

Conclusion: Our study suggests that FRATs perform similarly in identifying osteoporosis defined by BMD T-score among elderly Veterans. Electronic osteoporosis screening methods have a significant ease-of-use advantage by passively collecting risk factor data from the EMR. If these tools perform similarly for fracture outcomes as well, they could replace manual FRAX and thus improve efficiency in identifying individuals who should be sent for DXA scan to screen for osteoporosis.

Figure 1: ROC curves for FRAX, VAFARA, and OST to predict osteoporosis diagnosis by DXA score.



		95% CI	
	ROC statistic	LL	UL
FRAX w/o DXA	0.73	0.68	0.78
VAFARA	0.65	0.60	0.71
OST	0.71	0.66	0.77
eFRAX	0.66	0.60	0.72

Disclosure: T. Williams, None; **P. Lawrence**, None; **J. Crook**, None; **R. Nelson**, None; **J. Lafleur**, None; **G. W. Cannon**, Amgen, 2.

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Abstract Number: 333

An Assessment of Bone Health and Fracture Risk in a Bariatric Surgery Population at an Urban Medical Center

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Background/Purpose: Bariatric surgery is the most effective treatment for severe obesity.[1,2] Increased bone resorption has been demonstrated after bariatric surgery.[3] However, there have been limited and conflicting reports as to the prevalence of osteoporosis and occurrence of fractures after surgery.[3,4] Existing clinical practice guidelines for the perioperative nutritional, metabolic and nonsurgical support of the bariatric surgery patient recommend checking pre- and post-operative vitamin D and post-operative PTH among other tests. Furthermore, bone density measurements is recommended at 2 years post-surgery. [5] This study aimed to describe the incidence of significant bone loss and fractures in the post-bariatric surgery population in an urban medical center. In addition, it also aimed to assess whether our physicians were following current practice guidelines for the monitoring of bone health in bariatric patients.

Methods: This retrospective observational study included chart review (SD, LM, AI) from electronic medical records. Patients who had undergone bariatric surgery at MetroHealth Medical Center since January 1, 1999 to December 31, 2015 were identified by ICD-9 code gastric bypass 43664 and 43665, sleeve gastrectomy 43775 and gastric banding 43770, and were included in the study. Data were collected using Research Electronic Data Capture (REDCap). The following data were reviewed: demographics; date and type of bariatric procedure; pre- and post-surgery vitamin D, parathyroid hormone (PTH), C-terminal telopeptide (CTX), N-terminal telopeptide (NTX) and bone alkaline phosphatase; bone density survey [Dual-energy X-ray absorptiometry (DXA)] dates & results; and fractures if any, including type (fragility or traumatic) and location. Descriptive analyses were performed and included measures of central tendency (mean and median) and variability (standard deviation, minimum and maximum). Wilcoxon signed rank test was used to assess statistical significance between certain distributions such as race and body mass index (BMI) or vitamin D levels.

Results: Five hundred twenty-three patients were included in the study. There were 437 females and 86 males, with a mean age of 45.39; 48.76% were identified as White and 39.77% were identified as African-American (Table 1). The most common surgical procedure was gastric bypass 80.31%, followed by sleeve gastrectomy 16.63%, and gastric banding 3.06%. Average days of patient follow-up after bariatric surgery were 1162 days. Pre-surgical mean BMI was 48.98 kg/m^2, with African-Americans having a significantly greater BMI than Whites and Hispanics ($p = 0.0009$). Post-surgical weight loss median percent difference was 22.60% loss 6 months after surgery, 29.96% 12 months after surgery, and 26.12% at 3 or more years after surgery. Vitamin D was checked in 83.4% of patients before surgery, but was only checked in 41.87% of patients within 1 year after surgery. Vitamin D levels were within normal range (30.0 - 100.0 ng/mL) up to 1 year after surgery for patients who have had their levels checked. There was no significant difference in post-surgical vitamin D levels among races ($p = 0.1770$). PTH was checked in only 6.70% of patients 6 months after surgery, and in only 5.16% at 1 year post-surgery. CTX, NTX and bone alkaline phosphatase were rarely measured. Only 19 patients (3.63%) had DXA prior to surgery. Eleven patients (2.10%) had DXA within 2 years after surgery, and 16 patients (3.06%) had DXA more than 2 years after surgery. Four of the 19 patients who had DXA pre-surgery had repeat scans post-surgery (1 within 2 years, and 3 after 2 years), all showed significant bone mineral density (BMD) decrease (Table 2). Only 10 fractures were observed in the study; 3 were fragility and 7 were traumatic. Mean time to fracture for those who had a fragility fracture was 4.93 years. The location of the 3 fragility fractures were the wrist (n=1) and fibula (n=2). All of the 3 patients underwent gastric bypass procedure.

Conclusion: There is considerable discrepancy between current physician practice at our urban medical center and recommended clinical practice guidelines for bone health monitoring in the bariatric population. Vitamin D, PTH and DXA were infrequently checked in our bariatric surgery patients. In the few patients who had pre- and post-operative bone density measurements, significant bone loss was observed. Despite this large survey of bariatric patients, there is a low incidence of fractures post-bariatric surgery over a follow up time of 3 years. **Demographics (n=523)** Age (Mean): 45.39 N Observed Percent Sex Female Male 437 86 83.56 16.44 Race White Black Hispanic Unavailable/ Declined 255 208 31 29 48.76 39.77 5.93 5.54 Table 1. Patient demographics **Location N observed BMD Change** Hip Within 2 years After 2 years 0 1 0.217 Lumbar spine Within 2 years After 2 years 0 1 0.100 Radius Within 2 years After 2 years 1 1 0.058 0.142 Table 2: Bone mineral density changes by location. Least significant change with GE Lunar: spine 0.018g/cm^2, and femur and forearm 0.036g/cm^2; all changes were significant. References [1]Chang S_H, Stoll CRT, Song J, et al. The effectiveness and risks of bariatric surgery: an updated systematic review and meta-analysis, 2003-2012. JAMA Surg. 2014; 149(3):275-87. [2] Sjostrom L, Peltonen M, Jacobson P, et al. Bariatric surgery, long-term

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Disclosure: S. Diomampo, None; **L. Muhieddine**, None; **A. Igoe**, None; **C. Thomas**, None; **S. Hassan**, None.

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Abstract Number: 334

Predictors of Fragility Fractures in Patients with Rheumatoid Arthritis Not on Steroids: An Observational Study

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Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased fracture risk, however, this is confounded by a coexisting use of steroids. This study aims to quantify the association between fragility fracture risk and traditional risk factors, including bone mineral density (BMD), in an RA population that have never used steroids; further, we aim to differentiate the associations that trabecular (lumbar spine) and cortical bone (femoral neck) have with fracture risk.

Methods: Data was collated from all patients referred for a DXA scan at a North West of England hospital between 2004 and 2015. Patient's baseline characteristics and BMD were recorded and body mass index (BMI) measured. Only patients with RA were included and those who had previous used steroids were excluded. The population was divided by previous fragility fracture status. Baseline variables were compared using the Student T-test (continuous variables) and chi-squared test (categorical variables). Patients details recorded at time of scan included age, sex, BMI, and the presence of risk factors including smoking, alcohol, and family history of osteoporosis. The predictors of fracture were modelled using traditional risk factors including lumbar spine and femoral neck BMD. This was quantified using logistic regression analysis, adjusted for age, gender and BMI.

Results: 669 patients, 85% female and of median age 65 years (IQR 57.9, 71.9) were included in the analysis. 189 (28%) of patients had previously sustained a fragility fracture. Traditional risk factors were not associated with previous fragility fracture sustainment, as shown in table 1. However, the number of risk factors incrementally increased risk of fracture (OR 7.21, 95% CI 5.22, 9.94). Higher BMD of both the lumbar spine and femoral neck was associated with reduced fragility fracture sustainment, as shown in table 2.

Table 1: Risk of Fracture in Patients with Traditional Risk Factors	
Traditional Risk Factors	**Risk of Fracture** **OR, 95% upper and lower CI**
Smoker	1.21 (0.86, 1.71)
Alcohol	1.72 (0.83,3.58)
Sex	1.36 (0.82, 2.24)
Family History	1.59 (0.97, 2.59)
Secondary Osteoporosis	1.18 (0.73, 1.91)
BMI	0.97 (0.94, 1.00)
Age At Scan	1.02 (1.00, 1.04)
Cumulative Number of Risk Factors	7.21 (5.22, 9.94)

Table 2: BMD in the Non-Fracture vs. Fracture Cohorts		
	BMD in the Non-fracture vs Fracture Cohorts, Adjusted for Age, Gender and BMI **(OR, 95% upper and lower CI)**	**BMD in the Non-fracture vs Fracture Cohorts, Not Adjusted for Age, Gender and BMI** **(OR, 95% upper and lower CI)**
L1-L4 BMD	1.16 (1.06, 1.47)	1.14 (1.05, 1.36)
Left Femoral Neck BMD	1.08 (1.02, 1.36)	1.07 (1.02, 1.26)
Right Femoral Neck BMD	1.04 (1.01, 1.19)	1.04 (1.01, 1.18)

Conclusion: This study of a large population of RA patients without steroid exposure revealed that low lumbar spine and femoral neck BMD was associated with fragility fracture sustainment, whereas individual traditional risk factors, were not associated with fragility fracture sustainment; rather, only the number of traditional risk factors was associated. Therefore, it may be that BMD is the only important predictor of future fragility fracture risk in RA patients without steroid exposure. Because lumbar spine BMD is not included within the FRAX tool, we would advocate its use when estimating risk.

Disclosure: S. Dyball, None; **M. Bukhari**, Merck, Roche, Mennarini, Amgen, Pfizer, Eli-Lilly, Sanofi-Aventis , Abbvie, 8.

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Abstract Number: 335

High Risk of Osteoporosis and Long Term Joint Damage in Adults with a History of Juvenile Idiopathic Arthritis

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Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is a heterogeneous group of chronic inflammatory arthritides. JIA is the most common cause of musculoskeletal disability in children, and greater than 1/3 of children with JIA have persistent disease into adulthood. JIA is associated with decreased bone mineral density, growth abnormalities and erosive joint damage. We aimed to determine the prevalence of clinical osteoporosis and related outcome measures in adults with a history of JIA at Penn State Hershey Medical Center.

Methods: We performed a retrospective analysis of 67 adult patients with a history of JIA, age of onset ≤ 16 years, treated at Penn State Hershey from January 1st 2013-June 1st, 2015. After medical record extraction with review by two physicians, covariates focusing on JIA and osteoporosis risk factors were recorded in a REDCap database. Clinical osteoporosis was defined as a clinical diagnosis of osteoporosis by the physician and/or fragility fracture. Standard descriptive statistics were used to calculate means, standard deviations and frequencies. Covariates were compared between subjects with and without clinical osteoporosis using nonparametric tests. Statistical significance was determined by P values of <= 0.05.

Results: Patients had a mean age of 26 years, disease duration of 19 (+/- 9.5) years and were 85% female with 67.2% having polyarticular disease. Twelve percent (8/67) had clinical osteoporosis. Clinical osteoporosis was associated with longstanding disease features including disease duration and current age ($p=0.05$), increased disability scores on the health assessment questionnaire ($p=0.035$), history of orthopedic and joint replacement surgery ($p < 0.0001$ for both), increased frequency of current glucocorticoid use ($p=0.0052$), erosive joint disease ($p=0.01$) and there was a trend for association with ETOH use ($p=0.07$). More clinical osteoporosis subjects were using calcium and vitamin D ($p=0.0052$), had DEXA scans ordered ($p < 0.0001$) and vitamin D levels within the past year. No significant difference was observed for JIA classification subtype, gender, BMI, tobacco use, current or history of methotrexate or Tumor Necrosis Factor α-inhibitor use.

Conclusion: Adult patients with a history of JIA have a high prevalence of clinical osteoporosis, which is associated with both long standing JIA and glucocorticoid use. Adult Rheumatology providers should have increased awareness of poor osteoporotic outcomes in this unique patient population. Table: **Univariate Analysis of Osteoporotic vs Non-Osteoporotic subjects with a History of JIA**

Item	Overall Mean±SD (N)/%(Ratio)	Osteoporosis Mean±SD (N)/%(Ratio)	No osteoporosis Mean±SD (N)/%(Ratio)	p-value
Demographics and JIA Disease Features				
Age	26.09 ± 8.177 (67)	38.76 ± 26.49 (8)	22.75 ±7.34 (59)	0.0454*
Age at diagnosis	7.03 ± 4.90 (66)	5.47 ± 3.62 (8)	5.68 ± 8.53 (58)	0.9922
Disease Duration	18.99 ± 9.48 (66)	31.10 ± 27.08 (8)	18.28 ± 10.90 (58)	0.0483*
BMI	28.88 ± 9.11 (67)	23.09 ± 5.44 (8)	27.49 ± 10.57 (59)	0.1593
Gender (% Female)	85% (57/67)	75% (6/8)	86.4% (51/59)	0.3413
Current tobacco use	7.6% (5/66)	12.50% (1/8)	6.90% (4/58)	0.4873
Current ETOH use	43.3% (26/60)	75.00% (6/8)	38.46% (20/52)	0.0669
HAQ	0.3966 ± 0.55 (58/67)	0.6875 ± 1.0625 (8)	0.0625 ± 0.6250 (50)	0.0351*
RF positive (%)	24.4% (10/41)	40.00% (2/5)	22.22% (8/36)	0.5801
Current Glucocorticoid Use	11.9% (8/67)	50.0% (4/8)	6.8% (4/59)	0.0052*
Bone Outcomes				
Osteopenia on X rays	50.9% (27/53)	100.00% (7/7)	43.48% (20/46)	0.0100*
Erosions on X rays	50.9% (27/53)	100.00% (7/7)	43.48% (20/46)	0.0100*
Erosions and Osteopenia X-rays	34.0% (18/53)	100.00% (7/7)	23.91% (11/46)	0.0002*
Any Orthopedic Surgery	32.8% (22/67)	100.00% (8/8)	23.73% (14/59)	<0.0001*
Joint Replacement Surgery	13.4% (9/67)	75.00% (6/8)	5.08% (3/59)	<0.0001*
Fractures (excluding fragility)	20.9% (14/67)	50.00% (4/8)	16.95% (10/59)	0.0528

Disclosure: H. Dodanwala, None; **D. Feger**, None; **N. Longson**, None; **N. J. Olsen**, None; **B. E. Ostrov**, None; **R. R. June**, Pfizer Inc, 2.

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Abstract Number: 336

The Risk of Subsequent Osteoporotic Fractures Is Decreased in Patients Experiencing Fracture While on Denosumab

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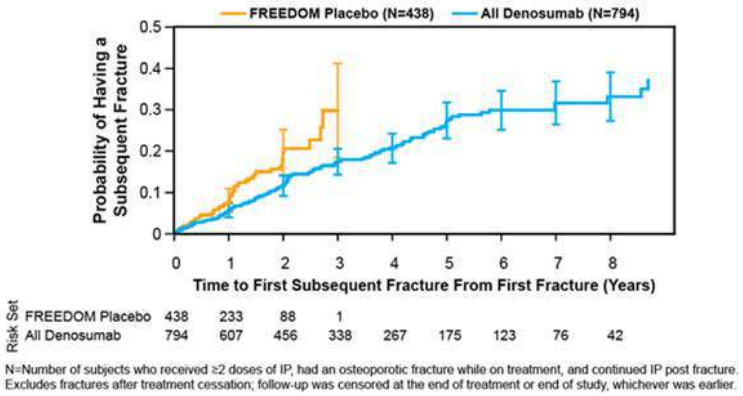
Background/Purpose: Osteoporosis is a common, progressive condition leading to increased bone fragility and susceptibility to fracture. Although osteoporosis therapy decreases fracture risk, fractures while on any current treatment can occur and do not necessarily represent treatment failure. It is therefore of interest to assess whether patients who fracture on denosumab (FREEDOM and FREEDOM Extension) experience a lower risk of subsequent fracture continuing on therapy than those on placebo who have fractured.

Methods: During FREEDOM, postmenopausal women with osteoporosis were randomized to placebo or denosumab for 3 years. During the 7-year Extension, all participants were allocated to receive denosumab. In this analysis, we report subsequent osteoporotic fractures (new vertebral or nonvertebral) in subjects who received ≥2 doses of denosumab during FREEDOM or the Extension, had an osteoporotic fracture while on treatment, and continued treatment post-fracture, compared with subsequent fractures in FREEDOM placebo subjects. These subsequent fractures were analyzed as recurrent events using the stratified Cox model with the robust variance estimation adjusting for prior fracture.

Results: During FREEDOM, 438 placebo and 272 denosumab subjects had an osteoporotic fracture (mean age at first on-study fracture: 74.1 and 74.5 years, respectively). Of these, there were 54 (12.3%) and 24 (8.8%) subjects who had ≥1 subsequent fractures in the placebo and denosumab groups, respectively. Adjusted subject incidence per 100 patient-years was lower for denosumab (6.7) vs placebo (10.1). Combining all subjects on denosumab from FREEDOM and the Extension for up to 10 years, 794 (13.7%) subjects had an osteoporotic fracture while on denosumab (mean age at first on-study fracture: 76.5 years). Of these, one or more subsequent fractures occurred in 144 (18.1%) subjects, with an adjusted subject incidence of 5.8 per 100 patient-years, similar to FREEDOM denosumab (6.7 per 100 patient-years). Among subjects with ≥1 subsequent fracture, 90% had only 1, and spine fracture was most frequent. The risk of having subsequent on-study osteoporotic fractures was lower in all denosumab subjects compared with placebo subjects (HR 0.60 [95% CI: 0.43–0.81]; p=0.0012; Figure).

Conclusion: The risk of a second fracture with continued denosumab treatment remains lower than placebo, thus suggesting that a fracture sustained while on denosumab is not necessarily indicative of a treatment failure, and continuation of treatment should be considered.

Figure: Time to First Subsequent Osteoporotic Fracture Among Placebo and All Denosumab Subjects Who Had an Osteoporotic Fracture in FREEDOM and the FREEDOM Extension



N=Number of subjects who received ≥2 doses of IP, had an osteoporotic fracture while on treatment, and continued IP post fracture.
Excludes fractures after treatment cessation; follow-up was censored at the end of treatment or end of study, whichever was earlier.

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5,Amgen, 8.

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Abstract Number: 337

Denosumab Treatment for 10 Years in Postmenopausal Women with Osteoporosis Was Associated with Substantially Lower Fracture Incidence Relative to Their Baseline FRAX-Predicted Probability

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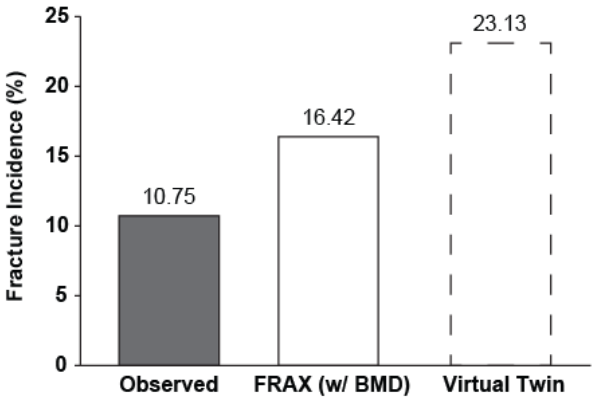
Background/Purpose: Denosumab is approved for treating postmenopausal women with osteoporosis at high risk for fracture. The placebo-controlled FREEDOM trial and its active-treatment Extension investigated the efficacy and safety of denosumab for up to 10 years. The lack of a long-term control group in the Extension, however, limits the ability to evaluate long-term efficacy. We used two approaches to put denosumab's 10-year anti-fracture efficacy into perspective. First, we compared the 10 year observed cumulative incidence of major osteoporotic (MOP; hip, clinical spine, forearm, or humerus) and hip fracture in subjects who completed the Extension with the 10-year fracture probability predicted at baseline by FRAX (a computer-based algorithm assessing fracture probability from clinical risk factors).[1] The 10-year MOP fracture rate was also compared with that estimated for a hypothetical cohort of 10 year placebo controls (virtual twins).

Methods: Subjects in this analysis received 10 years of denosumab (3 years FREEDOM; 7 years Extension; 60 mg Q6M), completed the 10-year visit, and missed ≤1 dose in FREEDOM and ≤1 dose in the Extension (n=1,278). Kaplan-Meier estimates of cumulative 10-year incidence of MOP and hip fracture were determined. Ten-year probability of fracture predicted by FRAX (calculated with femoral neck BMD) at FREEDOM baseline was also estimated. Rate of MOP fracture in a hypothetical cohort of 10-year placebo controls (virtual twins) was estimated using a previously described simulation method and baseline characteristics identical to the 10-year denosumab completer group.[2,3]

Results: The observed cumulative 10-year fracture incidence (95% CI) was lower than the 10 year mean (SD) fracture probability predicted by FRAX for both MOP (10.75% [9.05%–12.46%] vs 16.42% [9.06%]; Figure) and hip (1.17% [0.58%–1.76%] vs 6.14% [6.52%]) fractures. The observed cumulative 10-year MOP fracture incidence was also significantly lower than the estimated virtual twins fracture rate (10.75% [9.05%–12.46%] vs 23.13% [17.76%–28.87%]; RR=0.49 [0.36–0.64]).

Conclusion: Fracture incidence with 10 years of denosumab treatment in postmenopausal women with osteoporosis was lower than the 10-year probability predicted by FRAX for both MOP and hip fractures. It was also lower than the fracture rate estimated in a hypothetical cohort of 10-year placebo controls for MOP fracture. These data support the long-term efficacy of denosumab in reducing MOP and hip fractures. **References:** [1]https://www.shef.ac.uk/FRAX/index.aspx; [2]Vittinghoff *Stat Med* 2010; [3]Papapoulos *Osteoporos Int* 2015

Figure. Ten-year Observed, FRAX-predicted, and Virtual Twin-estimated MOP Fracture Incidence



Disclosure: E. Siris, Amgen, Merck, Radius, 5; **N. Pannacciulli**, Amgen Inc., 1,Amgen Inc., 3; **P. Miller**, Alexion, Amgen, Boehringer Ingelheim, Immunodiagnostics, Eli Lilly & Company, Merck, Merck Serrano, National Bone Health Alliance, Novartis, Radius Pharma, Roche Diagnostics, Regeneron, Daiichi Sankyo, Inc., Ultragenyx, 2,Amgen, AgNovos, Lilly, Merck, Radius Pharma, Roche, Ultragenyx, 9,Allergan Pharmaceuticals, Grunenthal Group, 9; **E. Lewiecki**, Amgen, Merck, Lilly, 2,Amgen, Merck, Lilly, Shire, Alexion, 5,Shire, 8; **R. Chapurlat**, Amgen, Merck, Chugai, 2,Amgen, Lilly, BMS, Abbvie, Pfizer, Chugai, 5; **E. Jódar-Gimeno**, Amgen, MSD, 2,Amgen, Lilly, MSD, 5,Amgen, Lilly, 8; **N. Daizadeh**, Amgen Inc., 1,Amgen Inc., 3; **R. Wagman**, Amgen, 1,Amgen, 3; **J. Kanis**, None.

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Abstract Number: 338

Abaloparatide-SC Significantly Reduces Vertebral and Nonvertebral Fractures and Increases Bone Mineral Density (BMD) Regardless of Age, BMD T-Score, or Prior Fracture at Baseline

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Background/Purpose: Abaloparatide is a novel 34 amino acid peptide created to be a potent and selective activator of the PTH 1 receptor signaling pathway and is under investigation for use in the treatment of postmenopausal women with osteoporosis.

Methods: ACTIVE (Abaloparatide Comparator Trial In Vertebral Endpoints) was a trial of 2463 postmenopausal women

with osteoporosis (aged 49-86 years; mean=69 years old) who were randomized to double-blinded abaloparatide-SC 80 µg or placebo, or open-label teriparatide 20 µg SC for 18 months. Prespecified subgroup analyses were performed to evaluate if fracture risk reduction was consistent across different levels of baseline risk. Risk factor subgroups were defined categorically by BMD T-score of the lumbar spine, total hip and femoral neck (≤-2.5 vs >-2.5 and ≤-3.0 vs >-3.0), fracture history (yes vs no), prevalent vertebral fracture (yes vs no) and age (<65 vs 65 to <75 vs ≥75 years old) at baseline.

Results: Abaloparatide-SC increased BMD from baseline at the lumbar spine 9.2%, total hip 3.4% and femoral neck 2.9% (all p<0.0001 vs placebo). Abaloparatide-SC reduced morphometric vertebral fractures 86% (p<0.0001), nonvertebral fractures 43% (p=0.049) and major osteoporotic fractures 70% (p=0.0004) compared to placebo and reduced major osteoporotic fractures compared to teriparatide by 55% (p=0.031). Results of forest plots show consistent fracture reduction in the abaloparatide arm for new morphometric vertebral or nonvertebral fractures without any interactions caused by baseline risk factors. In addition, there were no meaningful interactions among any of the baseline risk factors and magnitude of BMD accrual by abaloparatide-SC.

Conclusion: These data suggest that abaloparatide-SC may have potential to provide protection against fractures consistently across a wide variety of ages and baseline risks, including those with and without prior fractures, and will likely be useful for a broad group of postmenopausal women with osteoporosis.

Disclosure: F. Cosman, Radius Health, Inc., 5,Amgen, 5,Amgen, 2,Merck Human Health, 9,Tarsa, 9,Sermonix, 9; **G. Hattersley**, Radius Health, Inc., 1,Radius Health, Inc., 3; **P. Miller**, Radius Health, Inc, 5,Radius Health, Inc, 9,AgNovos, 9,Amgen, 9,Eli Lilly and Company, 9,Merck Human Health, 9,Roche Pharmaceuticals, 9,Alexion Pharmaceuticals, Inc., 2,Amgen, 2,Boehringer Ingelheim, 2,Immunodiagnostics, 2,Eli Lilly and Company, 2,Merck Serrano, 2,NBHA, 2,Novartis Pharmaceutical Corporation, 2,Novo Nordisk, 2,Roche Diagnostics, 2,Takeda, 2; **M. Y. Hu**, Radius Health, Inc., 1,Radius Health, Inc., 3; **L. A. T. Russo**, None; **B. Riis**, Nordic Biosciences, 1,Radius Health, Inc, 1; **G. Williams**, Radius Health, Inc., 1,Radius Health, Inc., 3; **L. Fitzpatrick**, Radius Health, Inc., 1,Radius Health, Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/abaloparatide-sc-significantly-reduces-vertebral-and-nonvertebral-fractures-and-increases-bone-mineral-density-bmd-regardless-of-age-bmd-t-score-or-prior-fracture-at-baseline

Abstract Number: 339

Assessment of High-Resolution Peripheral Quantitative Computed Tomography Parameters and Markers of Bone Metabolism in Community-Dwelling Elderly with and without Vertebral Fractures – the Sao Paulo Ageing & Health Study

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Background/Purpose: Bone mineral density(BMD) by dual X-ray absorptiometry(DXA) is currently standard clinical tool for predicting osteoporotic fracture. However, DXA doesn't allow studying abnormalities that predict different fracture risks independent of areal BMD, such as trabecular and cortical bone compartments and bone microarchitecture. High-resolution peripheral quantitative computed tomography(HR-pQCT) is non-invasive method to assess cortical and trabecular microarchitecture and bone mechanical competence in clinical studies on postmenopausal women with low

bone mass. However, there are no studies on HR-pQCT in general elderly population. Thus, we sought to verify the association between fragility fractures and bone microarchitecture and strength using HR-pQCT and markers of bone turnover in older adults.

Methods: 276 older adults were assessed by questionnaire. Lateral scans of spine obtained from Vertebral Fracture Assessment (VFA) by DXA were done to assess vertebral fractures (semiquantitative method). HR-pQCT was performed at the distal radius and tibia and following parameters were analyzed: volumetric bone mineral density(vBMD) - total(Tt), trabecular(Tb) and cortical(Ct), structural parameters - trabecular number(Tb.N), trabecular thickness(Tb.Th.), trabecular separation(Tb.Sp), cortical thickness(Ct.Th) and strength variables - Stiffness(S), Estimated ultimate failure load(Fult) and Apparent modulus(Epp). Serum levels of aminoterminal propeptide of procollagen type I(PINP) and C-terminal telopeptide of type I collagen (CTX) were evaluated.

Results: The mean age was 79.4± 4.1 years. According to DXA, osteopenia and osteoporosis were observed in 44.2% and 38.9%, respectively. At least one vertebral fracture was observed in 56.2% of subjects. At distal tibia, individuals with vertebral fractures had lower vBMD(Tt.vBMD, $p=0.001$; Tb.vBMD, $p<0.001$), lower Tb.N, $p<0.001$, higher Tb.Sp, $p<0.001$ and lower strength parameters(S, $p=0.002$; F.ult, $p=0.002$; E.app, $p=0.034$). At distal radius, subjects with vertebral fractures had lower volumetric density(Tt.BMD,$p<0.001$; Tb.BMD,$p<0.001$; Ct.BMD,$p=0.021$), lower structural parameters(Tb.N,$p<0.001$; Tb.Th, $p=0.030$; Ct.Th,$p=0.013$), higher Tb.Sp,$p<0.001$; and lower bone strength(S, F.ult, E.app). Bone turnover markers were significantly different between fracture and non fracture groups: CTX (0.25 ± 0.16 vs. 0.30 ± 0.18 ng/mL, $p=0.004$) and P1NP(38.2 ± 29.2 vs. 40.6 ± 19.5 ng/mL, $p=0.035$). After adjusting for potential confounding variables, logistic regression model revealed that Tb.vBMD at distal tibia (OR 0.98, 95%CI 0.98–0.99, $p<0.001$)) and CTX (OR 0.821, 95%CI 0.697–0.966, $p=0.017$) were independently associated with vertebral fractures

Conclusion: HR-pQCT detected marked differences on bone microstructure between older adults with vertebral fractures and those without fractures independent of areal BMD by DXA. Lower trabecular volumetric BMD was independently associated with vertebral fracture in community-dwelling elderly. Moreover, lower CTX was also linked to vertebral fracture and could indicate low bone turnover as risk factor for fractures in advanced-aged population.

Disclosure: G. H. F. Torres, None; **L. F S Guzman**, None; **J. C. Alvarenga**, None; **L. H. J. Neto**, None; **V. F. Caparbo**, None; **D. S. Domiciano**, None; **R. M. Oliveira**, None; **N. H. M. Lopes**, None; **R. M. R. Pereira**, None.

Abstract Number: 340

Hydroxychloroquine: A Potential Treatment for Osteoporosis By Osteoclast Inhibition!

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Background/Purpose:

We recently showed that patients with primary Sjögren Syndrome (pSS) have significantly higher bone mineral density (BMD) in the lumbar spine and femoral neck compared with healthy controls. The majority of those patients (69%) were using hydroxychloroquine (HCQ), which may have favourable effects on BMD. The aims of this study are to evaluate the effect of HCQ on osteoclast function and to identify a potential mechanism of action.

Methods:

Osteoclasts were cultured from PBMC-sorted monocytes for 14 days. All cultures were treated with different HCQ doses (0, 1 and 5 µg/ml). At multiple time-points, staining with an acidification marker (acridine orange) was performed as measure for intracellular pH. The ratio of FITC (neutral pH) vs. TRITC (acidic pH) fluorescence intensities were analyzed. Additionally, a fluorescent cholesterol uptake assay was performed and fluorescence intensities were analyzed as measure for cholesterol uptake.

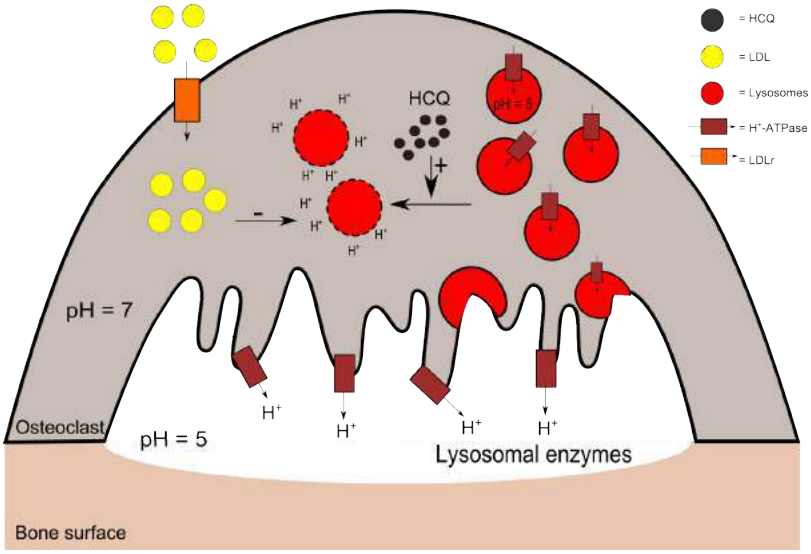
Results :

The difference in surface resorption by osteoclasts was significant between HCQ dose 1 and 5 µg/ml vs. control (4.3 ± 1.0% for HCQ dose 1 µg/ml and 1.6 ± 0.8% for HCQ dose 5 µg/ml vs. 16.2 ± 3.2% for the controls, P = 0.037 and P = 0.011 respectively). We also found that the FITC:TRITC ratio of the HCQ 5 µg/ml group was significantly reduced (lower intracellular pH) at day 12 and day 14 following continuous HCQ treatment compared to the controls (day 12: 1.06 ± 0.05 for the control vs. 0.87 ± 0.03 for HCQ 5 µg/ml, P = 0.034 and day 14: 0.92 ± 0.03 for the controls vs. 0.59 ± 0.03 for HCQ 5 µg/ml, P = 0.037). Furthermore, cholesterol uptake was significantly increased in HCQ 5 µg/ml compared to control (day 7: 31673 ± 1922 RU for HCQ 5 µg/ml vs. 14583 ± 3217 RU for the control, P = 0.0015 and day 11: 18297 ± 229.7 RU for HCQ 5 µg/ml vs. 4902 ± 259.6 RU for the controls, P = 0.0003). In addition, the LDL receptor gene expression was significantly increased in the HCQ 5 µg/ml cells compared to the controls (P = 0.03).

Conclusion :

In agreement with our clinical data, we demonstrate that HCQ suppresses bone resorption *in vitro*. We hypothesize that women (with pSS) benefit from HCQ since their BMD decreases dramatically in the first few years following menopause due to enhanced osteoclast activity.

We also showed that HCQ decreases the intracellular pH in mature osteoclasts and stimulates cholesterol uptake. We postulate that HCQ induces osteoclastic lysosomal membrane permeabilization (LMP) leading to apoptosis and associated decreased resorption. However, the osteoclast tries to decrease LMP by increasing cholesterol uptake and LDL expression **(Figure)**.



Disclosure: T. Both, None; **P. L. V. Daele**, None; **B. Van der Eerden**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hydroxychloroquine-a-potential-treatment-for-osteoporosis-by-osteoclast-inhibition

Abstract Number: 341

Evaluation of 25-Hydroxyvitamin D Levels in Rheumatologic Diseases

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Background/Purpose: Previous evidence indicates an association between vitamin D deficiency and autoimmune diseases. The aim of this study was to evaluate serum 25 hydroxyvitamin D (25OHD) and bone mineral density (BMD) in patients with rheumatologic diseases (RD) in Argentinean patients. In addition, 25OHD levels were analyzed in function of disease activity.

Methods: This retrospective study evaluated 106 patients with RD (64 with rheumatoid arthritis (RA), 12 spondyloarthropathies (SA), 13 systemic lupus erythematosus (SLE) and 17 other collagenopathies (OC) [vasculitis, scleroderma, indiferenciateted disease connective tissue, superposition syndrome of connective tissue disease]) and was compared with a control group (CG, n=102) matched by age (CG= 55.82±1.48 years; RD= 55.28±1.30, sex and body mass index. All the patients were from Rosario (32º52´18´´S) and Buenos Aires (34º36´14´´S) cities. Exclusion criteria: supplemented with vitamin D, pregnancy, intestinal malabsorption, chronic liver or kidney disease or cancer. Date are expressed as mean±SEM. Differences between groups were analyzed using the Mann–Whitney or Kruskal–Wallis test. Correlations were performed with Spearman's correlation test. The difference was considered significant if $p<0.05$.

Results: No differences between groups were observed in serum calcium, phosphatemia, urinary calcium, parathormone and urinary deoxipiridinoline. Significant differences were found in alkaline phosphatase (CG= 102.90±5.40 UI/l; RD= 167.2±8.59) and 25OHD (CG= 25.64±1.06 ng/ml; RD= 19.17±0.66). 25OHD significantly correlated with erythrocyte sedimentation rate (ERS) [r= -0.26] and reactive C-protein (RCP) [r = -0.27] as acute phase reactants. RD patients had significant lower 25OHD levels (RA= 19.89±0.81; SA=15.64±1.76; SLE= 19.81±2.49; and OC= 18.44±1.48) than CG (25.64±1.06 ng/ml). No correlation between 25OHD levels and DAS-28 and HAQ-DI scores were found. However, lower values of 25OHD were found at higher scores: HAQ-20 ≤2= 22.41±1.45 ng/ml, HAQ-20 >2= 18.80±0.95, p=0.047; DAS28 ≤3.2= 21.43±1.62 ng/ml, DAS28 >3.2= 19.78±0.95l, p=0.157. Activity scores in others RD couldn´t be analyzed because small number of patients. No significant differences were found in lumbar spine BMD between premenopausal or postmenopausal (postM) patients, but femoral neck BMD was significantly lower in postM RD patients (0.775±0.026 g/cm^2; T-score −1.94±0.20) than in postM CG patients (0.802±0.020; T-score −1.24±0.16).

Conclusion: In both groups 25OHD levels were under 30 ng/ml. However, 25OHD levels were lower in RD patients (deficiency) than CG (insufficiency). Lower values of 25OHD were found at higher ERS and RCP in all RD and at higher activity disease scores in RA.

Disclosure: M. L. Brance, None; **L. R. Brun**, None; **M. S. Larroude**, None; **M. P. Sacnun**, None; **C. Aeschlimann**, None; **G. Berbotto**, None; **I. Chavero**, None; **M. Palatnik**, None; **A. Sánchez**, None.

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Abstract Number: 342

Presence of Vertebral Fractures and Disc Disease in Post Menopausal Females with Height Loss As a Possible Screening Method for Osteoporosis

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Background/Purpose: The presence of non-traumatic vertebral fracture can identify a patient who has clinical osteoporosis. However, approximately 75% of vertebral fractures are asymptomatic and as many as 45% of vertebral fractures in North America go unrecognized. As a result, a significant number of cases of osteoporosis are missed and left untreated, leaving patients vulnerable to future fractures and morbidity and contributing to the economic burden of osteoporosis related fractures in the United States. We investigated whether women with 2 or more inches of height loss have a high incidence of fractures, whether the degree of height loss correlates with presence of fractures, and how these findings correlate with bone density, in order to test whether height loss could be a potential screening tool for osteoporosis. Additionally, we assessed how many of these patients with 2 or more inches of height loss had been treated for osteoporosis in the past.

Methods: From among all postmenopausal female patients seen at our academic Osteoporosis Center, we prospectively enrolled a cohort of 100 subjects self-reporting two or more inches of height loss from maximum height. Enrollment occurred over a two-year period. Patients with a history of spinal surgery or significant scoliosis (>10% spinal curvature) were excluded. At intake, all patients had radiographs of the lumbar and thoracic spine (AP and lateral). A vertebral fracture was defined as >20% vertebral height loss based on the guidelines from the Vertebral Fracture Initiative by the International Osteoporosis Foundation. Intervertebral disc disease was classified based on the Genant modification of the Sharp method.

Results: Of 100 patients with height loss, 76 had a fracture of the thoracic or lumbar spine, or both. 58 women had fractures of their thoracic spine and 50 of their lumbar spine. Among the 76 women with a diagnosis of fracture, 21 (28%) had never been treated for osteoporosis. Among the 24 patients without fractures, the average T-Score was -2.0 of the spine. Among all the patients, 96 had intervertebral disc disease (94 had thoracic and 75 had lumbar disc disease). When evaluating the degree of height loss in all of the patients, there was no significant difference between the patients who had sustained a fracture and those who had not.

Conclusion: In this study, 2 or more inches of height loss was explained by vertebral fracture and presence of disc disease, or both, with the majority of subjects demonstrating fractures pathognomonic for osteoporosis. Individuals with 2 or more inches of height loss and no fractures had T scores mainly in the osteopenic-osteoporotic range. Our data therefore suggest that any patient with 2 or more inches of height loss should be evaluated for both vertebral fractures and osteoporosis. Significantly, 28% of women with radiographic findings of compression fracture had not previously been treated for osteoporosis, underlining the need for better screening and treatment.

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Abstract Number: 343

Correlation Between Metacarpal Cortical Bone Mineral Density Measured By Dual X-Ray Densitometry and Radiogrammetry on Early Arthritis Patients

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Background/Purpose: Low bone mass at metacarpal (MC) diaphysis measured by radiogrammetry (DXR) has been described as a poor prognostic factor in rheumatoid arthritis (RA). However, this technique is not available in our environment. Our group has previously described the measurement of bone mineral density (BMD) at metacarpophalangeal joints (MCP) by dual X-ray absorptiometry (DXA). This measurement showed an acceptable correlation with the DXR at MC bones. However, DXR at MC bones mainly assesses cortical bone, whereas DXA at MCP mainly analyzes trabecular bone. Therefore, we have developed a procedure to evaluate MC's (2nd to 4th) bone mass of the nondominant hand through DXA. The aim of our study was to evaluate the correlation between BMD at 2nd to 4th MC of the nondominant hand measured by DXA with data obtained by DXR in patients with early arthritis (EA).

Methods: We studied 171 patients belonging to the Princesa Early Arthritis Reginster Longitudinal (PEARL) Study (84% women, 55.4 years at symptoms onset; 56.7% fulfilled RA 2010 criteria; 52% RF+ and 43.5% ACPA+). Demographic, clinical and laboratory data were collected per protocol. Hand X-rays were performed at baseline and after one year of follow-up, as well as nondominant hand BMD assessment by DXA (Hologic © QDR4500, Elite). The standard Hologic© software allows to design regions of interest (ROI) tailored to the researcher needs. In order to develop ROIs in DXA similar to that in DXR, the ROI generator was placed on every MC mid third of the diaphysis (aprox 17x17 mm). The ROI was rotated to be aligned to the MC longitudinal axis, avoiding overlap between adjacent ROIs. The BMD by DXA was the average of 3 successive measurements. The BMD by DXR was measured with standardized software by Sectra (Linköping, Sweden) on hand digital X-ray (GE © DX Definium 8000). Statistical analysis was performed using Stata 12 for Windows, including linear correlations according to the Spearman test between the BMD values of MC by DXA and DXR and BMD by DXA at global hand and MCP joints. In addition, a multivariate analysis was performed to determine which variables accounted for the differences between MC bone mass measured by DXR and DXA.

Results: 248 BMD measurements (154 at baseline and 94 at second visit) of the 3 regions described whose values are shown in Table 1.

	MC-DXR	MC DXA	Total Hand DXA	MCP DXA
BMD (g/cm2; mean ± SD)	0.529±0.074	0.427±0.060	0.327±0.041	0.265±0.040
Difference with MC-DXR	-	0.104±0.074*	0.206±0.060*	0.268±0.053*
Correlation with MC-DXR	-	0.865*	0.824*	0.717*

As shown in table 1, MC bone mass measured by DXA shows the lowest absolute difference and the best correlation with MC bone mass by DXR. Female gender (beta coefficient = 0.013; p = 0.039), patients older than 65 years (beta coefficient = 0.014; p = 0.019) and patients with higher body mass index (beta coefficient = 0.002 by kg/m2; p = 0.019) were significantly associated with lower differences between the values of MC by DXA and DXR.

Conclusion: There is an excellent correlation between BMD evaluated by DXA and by DXR at cortical level of the MC bones. Our findings open the possibility of exploring the value of MC-BMD assessment through DXA as a prognostic marker in patients with EA. Acknowledgement: FIS PI12/01578, FIS PI14/00442, Fondo Europeo de Desarrollo Regional (FEDER) and PFIZER Spain.

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Abstract Number: 344

Is Rheumatoid Arthritis a Risk Factor for Fractures: A Systematic Review of Observational Studies

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Background/Purpose: Rheumatoid Arthritis (RA) is a known risk factor for osteoporosis. There are many factors that contribute to this increased risk, including the use of glucocorticoids, systemic inflammation due to the disease process and relative physical inactivity. Only a few studies have assessed the risk of fractures in RA. The objective of this systematic review was to assess the risk of fractures in adults with RA compared with controls from the general population.

Methods: Two authors screened citations from the following electronic databases: MEDLINE (1946 to July 2015), EMBASE (1947 to July 2015), Cochrane Database of Systematic Reviews (2005 to July 2015) and CINAHL (1981 to July 2015). Included citations had to be written in English, only include patients greater than or equal to 18 years of age and compare fracture incidence/prevalence between RA patients and a control group. Case control, cohort and cross-sectional studies were included. Abstracts and conference proceedings were not searched. The primary outcome was fracture incidence and/or prevalence. Two authors abstracted data using a standardized data abstraction form. The quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS).

Results: The searches resulted in 3451 citations, and after applying the inclusion criteria, we selected seventeen observational studies comparing fracture incidence and/or prevalence between RA and controls. Overall, the results demonstrated that the risk of fracture was elevated in RA compared to controls in 14 of the 17 studies. Thirteen studies were adjusted for glucocorticoid use and there was an increased risk of fracture with glucocorticoid use in 4/13 of these studies. Seven studies analyzed RA severity or functional impairment as a risk factor for fracture and the risk of fracture was elevated in 2/7 of these studies. Fracture ascertainment was performed by searching medical records in seven studies, analyzing spine radiographs in six studies, self-reported history in two studies and by multiple methods in two studies. Eight studies evaluated fractures at multiple sites, whereas nine studies evaluated fractures only at a single site (spine in 6 and hip in 3). Only two studies reported specific data on fragility fractures, whereas in the remaining studies, the fracture mechanisms were not defined. Assessment using the NOS revealed that the studies were of high quality. Scoring by NOS criteria revealed that 14/17 studies scored 4/4 on selection, all studies scored 2/2 on comparison and 13/17 studies scored 3/3 on outcome/exposure. Limitations of the studies included the following: studies enrolled a diverse range of patient and control group populations, and generally included all types of fractures determined by various methods and involving multiple sites. Some studies only included women while others included both genders. The studies took place in different countries. These differences between the studies made it difficult to directly compare them. Due to the marked study heterogeneity, a meta-analysis was not performed.

Conclusion: The risk of fracture in RA is elevated when compared to the general population.

Disclosure: A. Gupta, None; **S. Pipe**, None; **T. Towheed**, None; **T. Anastassiades**, None.

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Abstract Number: 345

The Relationship Between Anti-Cyclic Citrullinated Peptide (anti-CCP) Levels and Bone Mineral Density (BMD) or Fragility Fracture in Patients with Rheumatoid Arthritis (RA)

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Background/Purpose: To explore the relationship of anti-CCP levels with BMD or fragility fracture in patients with RA

Methods: This is a prospective cross sectional study. Consecutive RA patients who visited Rheumatology clinic at Chang Gung Memorial Hospital in Kaohsiung between 01-Sep- 2014 and 31-May-2016 were enrolled in this study. Those patients who fulfilled the classification criteria of RA (ACR 2010) and inclusion criteria were registered as participants. During the period, we checked anti-CCP, ESR, CRP, DAS28 for each participant at enrollment and collected demographics, evidence of prevalent fragility fracture (history or radiography), personal life style and behaviors, risk factors of fragility fracture in FRAX tool, and medication history. We also measured BMD when anti-CCP checked. The descriptive summary is presented in the form of mean ± standard deviation. Continuous variables were evaluated by one-way ANOVA or Kruskal-Wallis test. Chi-square test or Fisher's exact test were used for the qualitative variables. A level of statistical significance of $p < 0.05$ was used for all statistical tests performed.

Results: A total of 521 participants were enrolled during the period. Demographics are presented in Table 1. The participants were categorized into 4 groups according to quartiles of anti-CCP levels(QI -IV). There were 130, 127, 132, and 132 participants in group I to IV, respectively. There was no obvious difference between ages, gender, body mass index, disease duration (Table 1), prevalence of fragility fracture (Table 2) between groups. However, the levels of RF ($p<0.0001$), ESR ($p<0.0001$), CRP ($P= 0.009$), and DAS28 ($p<0.0001$) was significant different between the groups. The BMD (g/cm^2) of lumbar spine (total), from QI to IV, of each group was 0.902±0.177, 0.836± 0.155, 0.859±0.167, and 0.866±0.190 ($p=0.0244$), respectively. While, the BMD (g/cm^2) of femoral neck was 0.661±0.129, 0.599±0.107, 0.623±0.126, 0.620±0.121, respectively ($p=0.0011$) (Table 2).

Conclusion: The levels of anti-CCP in RA patients are related to levels of RF and disease activity, in terms of ESR, CRP, and DAS28. The BMD, either lumbar spine or femoral neck, is significantly different between anti-CCP levels, while, there is no obvious difference in prevalence of fragility fracture between the groups. Via this investigation, it suggests that increased risk of fragility fracture in RA patients may not be related to the disease activity or anti-CCP levels. Table 1 Demographics of participants

Groups	I	II	III	IV	p
Anti-CCP (u/mL) quartiles	~2	2 ~ 60	60 ~ 290	> 290	
n	130	127	132	132	
Anti-CCP (u/mL)	0.8±0.5	24.3±18.7	150.0±66.0	441.4±67.0	<0.0001
Sex (F, %)	114 (87.7)	111 (87.4)	112 (84.9)	110 (83.3)	0.704
Age (years)	56.5 ±11.0	59.1±11.2	58.5±10.8	59.68 ±10.9	0.1048
Disease duration (years)	9.3 ±5.3	9.3±4.9	8.9± (5.6	9.1±5.7	0.9251
BMI, kg/m^2	23.8±3.8	23.0 ±3.6	23.8±4.2	23.8±3.8	0.2786
Vit D (ng/mL)	22.7±7.4	22.4±7.1	23.5±9.1	22.8±7.8	0.7456
RF (IU/mL)	21.7±44.7	177.9±315.4	304.1 ±569.3	413.3±684.8	<0.0001
ESR (mm/h)	17.6 ±16.8)	24.8±21.0	24.1±20.2	31.6 ±26.4	<0.0001
DAS28 (ESR)	3.0 ±1.1	3.2±1.1	3.2 ±1.2	3.7 ±1.4	<0.0001
CRP (mg/L)	5.9±13.4	7.7 ±12.3	10.2± 20.5	14.2 ±31.2	0.009

Table 2 Bone mineral density and prevalence of fragility fracture of participants

Groups	I	II	III	IV	p
BMD (g/cm^2) spine (total)	0.902±0.177	0.836±0.155	0.859±0.167	0.866±0.190	0.0244
BMD (g/cm^2) femoral neck	0.661±0.129	0.599±0.107	0.623±0.126	0.620±0.121	0.0011
Hip fracture (n, %)	19(14.6)	28 (22.1)	23 (17.4)	26 (1 9.7)	0.4586
All fracture* (n, %)	27(21.1)	45(36.6)	38(30.9)	39(31.5)	0.0561

*Including history or evidence of any one fragility fracture at site of hip, spine, forearm, or pelvis

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Abstract Number: 346

Interest of Bone Texture Assessment By Trabecular Bone Score (TBS) in Kidney Transplants Recipients

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Background/Purpose: Osteoporosis in kidney transplant is complex and multifactorial. We studied the evolution of Trabecular Bone Score (TBS) and bone mineral density (BMD) in kidney transplant recipients as well as concurrent factors to their variations.

Methods: Transplant patients at Rouen University Hospital between August 2008 and January 2013 were selected. They must have received two bone densitometry exams measured by absportiometry dual-energy X-rays (DEXA). The TBS was calculated retrospectively.

Results: 66 patients were included. The change in the TBS was not significant between the two visits. The BMD increased significantly at three sites, lumbar spine + 3.3%, + 3.7% total hip, femoral neck + 2.2% ($p < 0.01$). The duration of corticosteroid therapy was negatively correlated with the TBS ($r = 0.41$) and BMD at the lumbar spine ($r = -0.52$) ($p < 0.0001$). Hyperparathyroidism or corticosteroid or chemotherapy induced diabetes was associated with poorest evolution of TBS (-0.046 95% CI [-0074, 0016] versus 0.031 95% CI [-0002, 0059], $p = 0.02$ and -0.048 95% CI [-0075, 0017] versus 0.038 95% CI [-0016, 0065], $p < 0.01$) while the results on BMD were not significant. Regarding bisphosphonates, there was a positive correlation with BMD at the total hip ($r = 0.33$, $p = 0.02$).

Conclusion: TBS provides additional information with BMD in the osteoporotic risk assessment in transplant recipients, particularly in relation to glucocorticoid therapy, hyperparathyroidism and diabetes.

Disclosure: M. Aubé, None; **A. Daragon**, None; **O. Vittecoq**, None; **D. Bertrand**, None; **M. Lemoine**, None; **J. F. Menard**, None; **C. Banse**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/interest-of-bone-texture-assessment-by-trabecular-bone-score-tbs-in-kidney-transplants-recipients

Abstract Number: 347

Clinical Analysis of Tumor-Induced Osteomalacia Misdiagnosed As Spondyloarthritis: A Report of 18 Cases

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Background/Purpose: To study and summarize the clinical features of tumor-induced osteomalacia(TIO) misdiagnosed as spondyloarthritis(SpA), aiming to explore the reasons of misdiagnosis and raise the correctness of TIO diagnosis.

Methods: A total of 18 TIO patients misdiagnosed as SpA from March 2002 to January 2016 in Department of Rheumatology of Chinese PLA General Hospital were enrolled. The clinical manifestations, laboratory examinations data, imaging features, Localization of tumors and histological characteristics were analyzed.

Results: 18 patients were included (11 males and 7 females) with a median age of 33 years (range 19-60). The mean disease duration was 3.8 years (range 0.17 to 20 years). All patients presented with persistent low back pain. The pain could not be relieved by rest or exercise, all patients had a history of taking nonsteroidal anti-inflammatory drugs and showed no obviously improvement. The inflammatory markers such as erythrocyte sedimentation rate and C-reactive

protein were usually normal. The level of serum calcium was normal or slightly lower, nevertheless, all patients had hypophosphatemia and increased level of alkaline phosphatase. Sacroiliac joint lesions were found in X-ray, CT or MRI, however the lesions in sacrum or ilium were predominant rather than in joints. Abnormal bone imaging in ribs, long bones and soft tissues in addition to joints could be detected by bone scintigraphy. And the technetium-99m octreotide scintigraphy (Figure 1a) was completed to detect the causative neoplasms, then targeted images with radiographs (Figure 1b), CT or MRI were used for further localization of the tumors. Successful localization of tumors was followed by surgical resection (13 of these 18 patients) and analysis by pathology studies. The pathology results indicated that the majority (46.2 %,6 of 13) were characterized as phosphaturic mesenchymal tumors (PMTs). After tumor resection, serum phosphorus levels normalized in all 13 surgical patients after a mean of 16 days (range 3-57 days), and Clinical symptoms were alleviated within 3 months (Figure 2).

Conclusion: TIO can be easily misdiagnosed as SpA because of the atypical clinical features and imaging changes of sacroiliac joint, however, the laboratory findings and response to the NSAIDs of the two conditions are different. Considering the complete surgical resection leading to normalization of parameters in laboratory tests and relief of symptoms of TIO patients, prompt diagnosis and surgical treatment is extremely essential. Comprehensive laboratory examinations and the technetium-99m octreotide scintigraphy can contribute to the timely diagnosis of TIO.

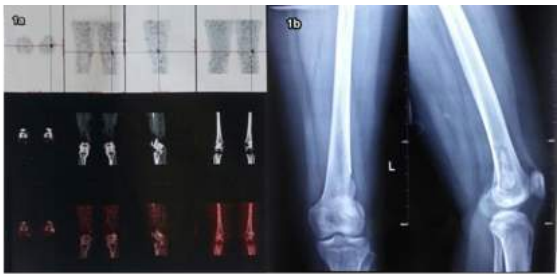

Figure 1a: 99mTc-octreotide scintigraphy: higher expression of SSTR on the left external tuberosity of femur. **Figure 1b**:X-ray: space occupying lesions in the left external tuberosity of femur.

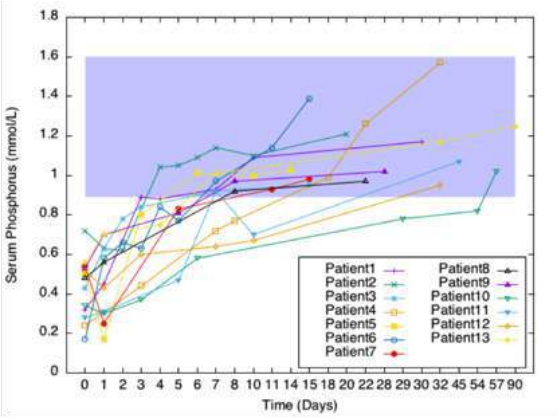

Figure 2 Changes in serum phosphorus concentrations before and after surgery in 13 tumor-induced osteomalacia misdiagnosed as spondyloarthritis patients. The shaded area represents the normal range for serum phosphorus concentration.

Disclosure: N. Sui, None; **J. Zhu**, None; **F. Sun**, None.

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Abstract Number: 348

Bisphosphonates-Related Atypical Femur Fractures: 8 Years' Experience in a Single Center

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Background/Purpose: Patients with rheumatoid arthritis (RA) are diagnosed with osteoporosis earlier than those without, and are therefore exposed to bisphosphonates for longer. However, the increasing use of bisphosphonates has raised concerns about atypical femur fracture. While patients with RA are at risk of atypical femur fracture, the impact of RA on the occurrence of atypical femur fracture is unclear. Here, we investigate the contribution of RA and other clinical factors on the development of bisphosphonates-related atypical femur fracture.

Methods: We conducted a retrospective case-control study in patients who have taken bisphosphonates for at least 1 year in Seoul St. Mary's Hospital, between 2008 and 2015. We identified patients with atypical femur fracture by reviewing surgical and radiographic records. Atypical femur fracture was classified based on the 2013 American Society for Bone and Mineral Research task force criteria. Three age- and sex- matched controls without the history of atypical femur fracture were randomly selected to each patient with an atypical femur fracture. Cox proportional hazards models were used to analyze the independent contribution of risk factors for bisphosphonates-related atypical femur fracture occurrence.

Results: In 35,104 patients who were prescribed BPs for at least a year during 8 year period, 43 female patients (mean age, 68 years) suffered atypical femur fracture (0.12%). Patients with atypical femur fracture exposed to bisphosphonates for 7.3 years. Patients with atypical femur fracture had exposed to bisphosphonates longer and continued bisphosphonates treatment without cessation. Twenty-eight percent of patients with atypical femur fracture were comorbid with RA. Glucocorticoids and disease modifying anti-rheumatic drugs were frequently used in patients with atypical femur fracture. Multivariate Cox regression analyses estimated that the hazards ratio of atypical femur fracture increased by 9.2 for long-term glucocorticoids use at least one year, 7.2 for prolonged bisphosphonates exposure without cessation and 1.3 for every kg/m^2 of the increased body mass index (BMI).

Conclusion *:* The incidence of bisphosphonates-related atypical femur fracture is very low. Although there is an association between atypical femur fracture and long-term bisphosphonates use, clinicians should remember that bisphosphonates significantly reduce the risk of osteoporotic fracture. We suggested that long-term bisphosphonates use without cessation, prolonged glucocorticoids use and higher BMI are risk factors for atypical femur fracture. These patients should be carefully followed up with X-rays or dual-energy bone densitometry during bisphosphonates treatment.

Disclosure: J. Koh, None; **S. H. Kim**, None; **H. Kim**, None; **M. K. Chung**, None; **J. H. Ju**, None; **S. H. Park**, None.

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Abstract Number: 349

Effects of Osteoporosis Treatments for Bone Loss and Pain-Related Behavior in the Hind Limb-Unloaded Mouse Model of Disuse Osteoporosis

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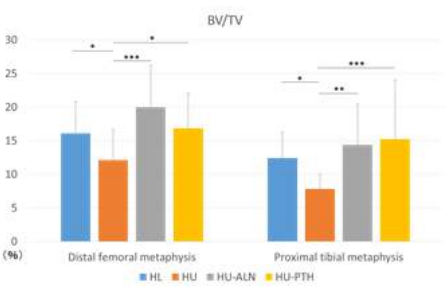
Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoporotic patients with no evidence of fractures sometimes experience vague lower back pain. However, there have been few reports regarding the correlation between osteoporosis and pain-related behavior. Our previous studies have indicated that hindlimb-unloading induced bone loss and mechanical hyperalgesia in hindlimb of mice. We investigated the effects of osteoporosis treatments on bone mass and pain-related behaviors in osteoporosis model mice with hindlimb unloading.

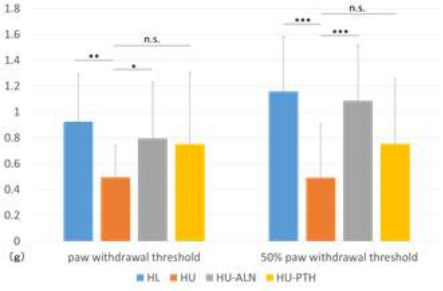
Methods: Male ddY mice (8 weeks old) were tail-suspended for 2 weeks and assigned to 4 groups; hindlimb-loaded mice treated with vehicle (control=HL), hindlimb-unloaded mice treated with vehicle (HU), hindlimb-unloaded mice treated with ALN (HU-ALN), hindlimb-unloaded mice treated with PTH (HU-PTH) (n=8/group). After 2 weeks tail-suspension, mice were reloaded and started treatment. For 2 weeks, mice were injected subcutaneously with 40μg/kg ALN twice a week, 40μg/kg PTH five times a week, or saline as vehicle. The bilateral distal femoral metaphyses and proximal tibial metaphyses were analyzed three-dimensionally by micro-computed tomography (μCT) 2 weeks after reloading and treatment. Mechanical sensitivity was also tested using von Frey filaments 2 week after reloading. The withdrawal threshold, the 50% withdrawal threshold and the frequency of the withdrawal response to the application of von Frey filaments to the plantar surface of the hind paws was examined. Measurement of pain-related behavior with von Frey filaments was interpreted as indicative of mechanical allodynia.

Results: μCT analysis of the distal femoral metaphysis and the proximal tibial metaphysis showed that significantly decreased bone volume/tissue volume (BV/TV) was significantly decreased in HU group compared with HL group. However, ALN treatment and PTH treatment increased BV/TV compared with saline in HU mice. (Fig.1) The paw withdrawal threshold and the 50% paw withdrawal threshold were significantly lower in HU group than in HL group, whereas it was significantly higher in HU-ALN group than in HU group. Similarly, it was tend to be higher in HU-PTH group than in HU group, but not significantly. (Fig.2) The paw withdrawal frequency stimulated by von Frey filaments with strength of 0.4-1.0 g was significantly higher in HU group than in HL group. Whereas it was significantly lower in HU-ALN group and HU-PTH group than in HU group with strength of 0.4-0.6g.

Conclusion: In this study, treatment of ALN or PTH recovered bone loss and mechanical hyperalgesia in disuse osteoporotic animal models by hindlimb-unloading. The results suggest that low bone volume itself is one of the causes of osteoporotic pain.



(Fig.1)



(Fig.2)

Disclosure: G. Miyamura, None; **H. Wakabayashi**, None; **T. Nakagawa**, None; **S. Kato**, None; **Y. Naito**, None; **A. Sudo**, None.

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Abstract Number: 350

Change in Bone Mineral Density with High-Dose Prednisone in Patients with

Rheumatoid Arthritis

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Background/Purpose: Recently, we showed that treatment with COBRA-light therapy including prednisone with initially 30 mg/day, was as effective as the original COBRA scheme, with initially 60 mg/day [1], in the treatment of rheumatoid arthritis (RA). Since high-dose glucocorticoids are associated with bone loss, we investigated the differences in bone mineral density (BMD) after one year of treatment in both arms. Therefore, this study aims to determine whether there is a significant difference in BMD between COBRA and COBRA-light, and to determine the difference in change in BMD between baseline and 52 weeks between these groups, at the lumbar spine (L1-L4), total hip, and femoral neck.

Methods: An open-label, randomised controlled, non-inferiority trial of patients with active, newly diagnosed RA following a treat-to-target protocol.

Results: BMD data were determined in 144 out of 164 included RA patients, all randomized to either COBRA (n=71) or COBRA-light (n=73) therapy. Both at baseline and after 52 weeks, no significant difference in BMD was found between COBRA and COBRA-light, at all sites. Changes between baseline and week 52 are shown in *Table 1*. No significant difference in change in BMD between COBRA and COBRA-light was found, at all sites. However, COBRA-light showed a significant decrease in BMD in the lumbar spine and total hip after 52 weeks, whereas the femoral neck and the COBRA group did not.

Conclusion: No difference in change in BMD between COBRA and COBRA-light was found. The overall bone loss was small, which suggests that the negative effects of (high-dose) prednisone on bone might be counteracted by the large reduction in disease activity as a result of combination therapy and tight control treatment. **References:** [1] Ter Wee MM, et al. Ann Rheum Dis 2015.

Table 1.
Changes in bone mineral density between baseline and week 52 during COBRA and COBRA-light therapy

	COBRA (n=71)			COBRA-light (n=73)		
	baseline	week 52	change	baseline	week 52	change
Lumbar spine	1.12 (0.17)	1.12 (0.17)	0.01%	1.10 (0.15)	1.09 (0.15)	-1.02%*
Total hip	0.95 (0.14)	0.95 (0.14)	0.05%	0.95 (0.12)	0.94 (0.13)	-1.16%*
Femoral neck	0.90 (0.16)	0.89 (0.17)	-0.59%	0.88 (0.12)	0.87 (0.11)	-0.98%

** Significant change between baseline and week 52 (p<0.05); Values are reported as mean (SD), unless otherwise specified.*

Disclosure: L. Rasch, None; **L. van Tuyl**, None; **M. Kremer**, None; **I. E. M. Bultink**, None; **M. Boers**, Mundipharma, 5,Pfizer, 5; **W. F. Lems**, Merck, Eli Lilly, Amgen, 5.

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Abstract Number: 351

Pre-Operative Magnetic Resonance Imaging Can Help in Predicting Two-Year Readmission in Acute Severe Osteoporotic Vertebral Fracture after Vertebroplasty

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Background/Purpose: The high rates of readmission among patients with osteoporotic vertebral fracture have reduced quality of life and increased mortality. This study aimed to determine predictors of readmission in such patients using magnetic resonance imaging (MRI).

Methods: This study reviewed records of osteoporosis patients with acute vertebral fractures proven by MRI between 2004 and 2007 for pre-operative MRI, subsequent readmission, and possible factors that increase readmission within two years. Clinical information like co-morbidities, previous hip fracture, and number of vertebral fractures were recorded. Primary outcome was readmission (within two years of discharge). Predictor variables were categorized and compared between readmissions and non-readmissions. Logistic regression was used for multivariate analysis.

Results: There were 106 patients with MRI-proven acute vertebral fractures who underwent vertebroplasty, including 33 with readmission within two years. There were no differences in age, BMI, sex, number of vertebral fracture, and underlying co-morbidities between readmissions and non-readmissions. However, the MRI signal intensity (SI) at the non-enhancement area parameter was different between the two groups (70.97±66.51 vs. 108.62±98.31; p=0.008). After adjusting for potential confounders, those with higher SI at the non-enhancement area had lower readmission risk (p=0.005; OR: 0.984, 95% CI: 0.973-0.995).

Conclusion: Pre-operative MRI may be predictive of readmission in patients with osteoporotic vertebral fracture. Recognizing the need to optimize primary and secondary prevention in these patients to improve quality of life is mandatory.

Table . Multivariable analysis of the odds ratios for readmission

Variables	Regression coefficient	S.E.	Wals	*p* value	OR (95% CI)
Age (years)	-0.054	0.032	2.812	0.094	0.947 (0.890-1.009)
Sex	0.602	0.629	0.914	0.339	1.825 (0.532-6.268)
Body mass index (kg/m2)	-0.056	0.042	1.778	0.182	0.945 (0.871-1.027)
Spine fracture (number)	-0.029	0.142	0.040	0.841	0.971 (0.736-4.284)
Previous hip fracture	0.692	0.644	1.152	0.283	1.997 (0.565-7.063)
Rheumatoid arthritis	-0.814	0.996	0.668	0.414	0.442 (0.063-3.121)
Diabetes mellitus	-0.781	0.445	3.081	0.079	0.457 (0.191-1.095)
Hypertension	-0.059	0.382	0.024	0.878	0.943 (0.446-1.994)
Heart disease	-0.382	1.135	0.113	0.736	0.682 (0.074-6.311)
Pulmonary disease	-0.263	1.045	0.063	0.802	0.769 (0.099-5.965)
Liver disease	-1.045	0.920	1.289	0.256	0.351 (0.058-2.136)
Glucorcorticoid use	0.498	0.630	.625	0.429	1.645 (0.479-5.653)
Enhancement SI	0.005	0.003	3.645	0.056	1.004 (1.000-1.010)
Non-enhancement SI	-0.016	0.006	7.929	0.005	0.984 (0.973-0.995)

Abbreviations: OR, odds ratio; SE, standard error; SI, signal intensity

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Disclosure: Y. C. Chen Sr., None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/pre-operative-magnetic-resonance-imaging-can-help-in-predicting-two-year-readmission-in-acute-severe-osteoporotic-vertebral-fracture-after-vertebroplasty

Abstract Number: 352

Can Lumbar Spine Bone Mineral Density Predict Readmission in Denosumab-Treated Chronic Kidney Disease Patients?

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Background/Purpose: This study investigated whether bone mineral density (BMD) affects readmission risk in patients with CKD who received denosumab therapy.

Methods: The study design was a retrospective case review of CKD patients. Baseline age, sex, and body mass index (BMI) were recorded for all patients included in the study. All comorbidities were recorded. All subjects underwent dual energy X-ray absorptiometry assay of the lumbar spine and right hip for BMD. The primary outcome was readmission. Predictive variables were categorized and compared between readmitted and non-readmitted patients. Logistic regression was used for multivariable analysis.

Results: A total 121 patients with CKD who received denosumab therapy were enrolled. Of these, 29 were readmitted within 2 years, and 92 had no readmission. The lumbar BMD differed between the readmission (-2.94±0.68) and non-readmission group (-2.09±1.48). The readmission group had a lower T score than the non-readmission group. When adjusted for potential confounding factors, a decreased lumbar BMD had a higher readmission risk. When the cut-off points determined by receiver operating characteristic (ROC) curve analysis were applied, the most precise point was set at a T score of -3(Table).

Conclusion: Osteoporosis in CKD patients is associated with a high risk of readmission; the best predictor after denosumab therapy was the lumbar spine T score. A lower T score (especially if less than -3) was associated with a higher probability of fracture readmission. It is essential to optimize primary and secondary prevention in these patients to improve their quality of life.

Table . Multivariable analysis of the odds ratios for readmission

Variables	Regression coefficient	S.E.	Wald	P- value	OR (95%CI)
Age (years)	-0.001	0.033	0.001	0.971	0.998 (0.936-1.065)
Gender	-0.317	0.739	0.183	0.668	0.728 (0.171-3.102)
Body mass index (kg/m2)	-0.037	0.073	0.259	0.611	0.963 (0.836-1.111)
Spine fracture (number)	0.12	0.188	0.404	0.525	1.127 (0.779-1.631)
BMD (lumbar)	-0.673	0.248	7.369	0.007	1.960 (1.206-3.189)
BMD (Total hip)	-0.336	0.548	0.377	0.539	0.714 (0.244-2.090)
BMD (Femoral neck)	-0.165	0.587	0.079	0.779	0.847 (0.269-2.677)
Neurological disease	0.763	0.69	1.222	0.269	2.143 (0.555-8.289)
Diabetes mellitus	0.367	0.623	0.348	0.556	1.443 (0.426-4.897)
Hypertension	0.151	0.639	0.056	0.813	1.163 (0.333-4.067)
Hyperlipidemia	0.857	1.049	0.667	0.414	2.355 (0.301-18.405)
Cardiovascular disease	0.117	0.691	0.029	0.865	1.124 (0.290-4.357)
Pulmonary disease	-0.116	0.861	0.018	0.893	0.890 (0.165-4.813)
Liver disease	-0.705	0.832	0.717	0.397	0.4941 (0.097-2.526)

OR, odds ratio; SE, standard error

Disclosure: Y. C. Chen Sr., None;

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Abstract Number: 353

Changes in Femoral Neck Bone Mineral Density Inverse Correlate with Egfr in Denosumab Treated Osteoporosis Patients? a Hospital-Based Analysis

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Background/Purpose: This study investigated the effect of different severities of CKD on bone mineral density (BMD) in patients treated with denosumab.

Methods: This study was a retrospective case review of CKD patients treated with denosumab. Baseline age, sex, and body mass index (BMI) were recorded for all patients. All comorbidities such as diabetes, hypertension, and liver and estimated glomerular filtration rate (eGFR) serum collagen type 1 cross-linked C-telopeptide (CTX) were also recorded. All subjects underwent dual energy X-ray absorptiometry assay of the forearm, lumbar spine, and total hip and femoral neck to determine the BMD. Changes in BMD between baseline and 1 year after denosumab administration were recorded. The correlation between the changes in BMD and eGFR was assessed.

Results: A total 108 patients with CKD who had received denosumab therapy were enrolled. The mean age was 71.04 ± 9.64 years, and 96 patients (88.9%) were women. Baseline eGFR correlated negatively with changes in the BMD of total hip (Rho = 28.7, P=0.01) and femoral neck (Rho = 40.6, P < 0.01) but not those in the spine and forearm. The lower the eGFR, the more was the improvement in BMD in the femoral neck after denosumab therapy. When changes in femoral neck BMD were assessed as outcome measures using linear regression, young patients (p = 0.001) and those with a low eGFR benefitted more from denosumab therapy (p = 0.029).

Conclusion: Denosumab therapy is effective in cases of low eGRF and young age. Aggressive medical attention is needed in these patients.

Table . Association of baseline eGFR and changes in femoral neck bone mineral density after adjusting variables

Variables	Regression coefficient	Standard error	P-value
Gender	0.025	0.023	0.278
Age (years)	-0.004	0.001	0.001
Body mass index (kg/m^2)	-0.002	0.002	0.34
Diabetes	-0.018	0.017	0.291
Hypertension	0.01	0.018	0.584
Hyperlipidemia	0.039	0.038	0.308
Liver disease	-0.004	0.021	0.837
Cardiovascular disease	0.015	0.018	0.402
Pulmonary disease	0.025	0.028	0.389
Neurological disease	0.028	0.024	0.25
Baseline CTX	-0.006	0.01	0.578
Baseline eGFR	-0.001	0	0.029

GFR: glomerular filtration rate

Disclosure: Y. C. Chen Sr., None;

mineral-density-inverse-correlate-with-egfr-in-denosumab-treated-osteoporosis-patients-a-hospital-based-analysis

Abstract Number: 354

A Longitudinal Cohort Study of Denosmab and Bisphosphonate for Prevention of Vertebral Fracture in Glucocorticoid-Induced Osteoporosis in Japanese

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Background/Purpose: In recent years, denosumab, a monoclonal antibody against RANKL, has been proven for effective treatment of primary osteoporosis. However, effects of denosmab for glucocorticoid-induced osteoporosis(GIOP) were not clearly resolved. We conducted a longitudinalcohort study to clarify effects of denosmab when compared with bisphosphonates on osteoporotic vertebral fractures in GIOP.

Methods: Patients with connective tissue diseases at Tokyo Medical Center was subjected for one year longitudinal cohort study. The number of subjects was 210 (female; 184, age; 65+/-14 (mean +/- SD), prednisolone dosage during 1yr; 6.2+/-5.1mg/day, disease duration; 11.7+/-11.3yr). Lumbar bone mineral densities (lBMD) were measured with Lunar 3030 (GE). Incident vertebral fractures were defined from XP with the semi-quantitated method (Genant, H. 1993). Prevalent vertebral fractures were seen in 97（46％） patiets. Bisphosphonates and denosmabwere used in 150 and 60 patients, respectively.

Results: 1) The value of lBMD (%YAM) at the base line was 81.7+/-14.7%. The rate of incident fractures during the follow-up period was 12.3%. 2) The group of denosmab showed higher values in age and prevalent fracture and lower value in lBMD than the group of Bisphosphonates ($p<0.05$). Increases in lBMD after 1 yr were not different in these two groups. Incident vertebral fractures were lower in the patients with denosmab (3.3%) than in those with bisphosphonates (16.0%), even though the denosmab group were at higher risk in age, prevalent fracture, and lBMD. 3) A logistic regression analysis revealed that statistically significant factors for incident fractures were lBMD (1% increase, OR; 0.95; 95%CI; 0.91-0.99, $p<0.01$), prednisolone dosages (1mg/day increase, 1.13, 1.03-1.25, $p<0.01$), prevalent fractures (3.61, 1.29-10.13, $p<0.01$), and denosmab treatment (vs bisphosphonates, 0.17, 0.03-0.54, $p<0.01$).

Conclusion: Our results suggested that denosmab might be effective for prevention of osteoporotic fractures in patients treated with glucocorticoids.

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Abstract Number: 355

Fracture Incidence Rates in Solid Organ Transplant Recipients: A Systematic Review and Meta-Analysis

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Background/Purpose: Transplants increase risk of bone loss and fractures and reduce quality of life. Information on fracture incidence is important when making clinical decisions about initiating anti-osteoporotic treatment and when assessing treatment success. No existing fracture assessment tool accounts for the additional risk transplant patients may experience over time. With this study, we aimed to estimate fracture incidence rates in transplant patients and present them in a uniform way, which could aid clinicians in making personalized patient care decisions.

Methods: We searched MEDLINE and PubMed from inception to May 2016 for all observational studies and randomized controlled trials (RCTs) involving solid organ transplant recipients and reporting on osteoporotic fractures. We included RCT data from groups which received no anti-osteoporotic treatment or were treated with calcium and vitamin D. Studies involving >50% bisphosphonate users were excluded. Two independent reviewers extracted data on hip, vertebral (morphometric /clinical), non-vertebral, and total fractures. We calculated fracture incidence rates per 1000 patient-years (PY) for each study and combined them using a random effects meta-analysis model.

Results: We included 42 studies (N=280,066, 99% were kidney transplant) (Table 1). Time since transplantation varied across studies (3 months-11.5 years; median 1 year). A majority of transplant recipients were started on pulse IV steroids, followed by high dose oral corticosteroids, which were tapered within 3-6 months. Most incident fractures were reported within one year post-transplant across all studies. Kidney transplant recipients experienced high risk of hip fracture (4 per 1000 PY) (Table 2). We also found a very high risk of vertebral (morphometric/clinical) fracture (81 per 1000 PY) in heart transplant recipients. Liver transplant recipients experienced high risks of vertebral and non-vertebral fractures (86 and 31 per 1000 PY, respectively).

Conclusion: This study found a high fracture risk in transplant recipients, especially within the first post-transplant year. Our results will support informed decision-making regarding anti-osteoporotic treatment and will aid policy makers in formulating standards of care. Current evidence is heterogeneous in terms of variables such as patient characteristics and follow-up. Researchers studying post-transplant care should aim for a homogeneous study design, which will enable precise estimation of fracture rates and treatment effects, as well as investigation of factors relating to variability in fracture risk among transplant recipients.

Table 1: Patient Characteristics							
Author, year	**N of patients, Female (%)**	**Mean age, years**	**Steroid regimen**	**Other Immunosuppressant use**	**Calcium and Vitamin D use**	**Bisphosphonate use (%)**	**Mean time from transplant, years**
Kidney							
Akaberi, 2008	238; 38.7	51	Steroids in 98%; median long-term prednisolone dose 5 mg	Cyclosporine in 82%, Tacrolimus in 14%	Calcium and Vitamin D supplementation in 73.8%	12.8	Median 3.5
Ball, 2002	59,944; 39.2	42% <40, 38% 40-54	ND	ND	ND	ND	ND
Durieux, 2002	59; 45.8	49.6	Prednisone 20 mg/day, tapered to 10 mg/day by 4-6 months after transplant; mean cumulative dose 37.7g	Azathioprine 92%, Cyclosporine 46%	ND (not excluded; mean dietary Calcium intake 906 mg)	0	8.5
Grotz, 1994	100; 46	44	ND	ND	0% for Vitamin D, 6% took Calcium (500 mg/day)	ND	5.25
Marcen, 2007	40; 40	41.8	Prednisone in 100%	Cyclosporine	ND	ND	10.8
Nair, 2014	69,740; 39	51	Steroids in 91%	Cyclosporine: 26% Tacrolimus: 64%, Mofetil Mycophenolate: 82%	ND	ND	2.2
Nikkel, 2009	68,814; 39.7	43.6	ND	ND	ND	ND	5
Nikkel, 2012	77,430; 39.7	49.0	Compared patients with (n=11,164) and without (n=66,266) early corticosteroid withdrawal	ND	ND	ND	4
Pichette, 1996	70; 34.3	46.1	Prednisone mean dose 0.19 mg/kg every other day or 0.11 mg/kg/day	Cyclosporine or Azathioprine	Vitamin D in 26% and Vitamin D and Calcium in 16%	ND	8.1
Vautour, 2004	86; 31	38.3	Steroids in 100%	Cyclosporine, Tacrolimus, or Azathioprine	ND	ND	Median 10.6
Coco, 2012 (RCT)	22; 28	48	All patients received prednisone 20 mg/day tapered to 5 mg/day by 90 days post-transplant	Tacrolimus (or Cyclosporine, <10% patients), Rapamycin, and Mofetil Mycophenolate	Calcium (as needed) and Calcitriol (0. 25 µg/day)	0 (Patients received an oral placebo)	Immediately post-transplant, 1 year follow-up
Cueto-Manzano, 2000 (RCT)	30; 47	48	All patients received prednisone 20 mg/day for 90 days tapered to 5-10 mg/day (mean dose 6.1 mg/day for Calcium and D patients and 4.6 mg/day for Control	Cyclosporine: 43% Azathioprine: 40% Cyclosporine and Azathioprine: 17%	Calcium (500 mg/day) and Calcitriol (0.25 µg/day) in 53% of patients	0	10.5

			patients)				
De Sevaux, 2002 (RCT)	111; 41	47	100 mg/day IV prednisone for first 3 days post-transplant, 0.35 mg/kg/day for the first month, then tapered to 0.10 mg/kg/day at 3 months (mean daily dose 7.2 mg)	Cyclosporine (or Azathioprine for select patients) and Mofetil Mycophenolate	Calcium (1000 mg/day) and Alfacalcidol (0.25 µg/day) in 41% of patients	0	Immediately post-transplant, 6 month follow-up
Smerud, 2012 (RCT)	63; 19	52.6	All patients received prednisolone. Mean cumulative dose over one year: 5,315 mg	Cyclosporine or Tacrolimus and Mofetil Mycophenolate	Calcium (500 mg twice a day) and Calcitriol (0.25 µg/day)	0 (Patients received an IV placebo)	0.051
Torregrosa, 2007 (RCT)	45; 51	55	All patients received prednisone: 5-7.5 mg/day	Cyclosporine or Tacrolimus with or w/o Mofetil Mycophenolate	Calcium (2500 mg/day) and Vitamin D (800 IU/day)	0	1.75
Torregrosa, 2010 (RCT)	49; 29	50.7	500 mg/day immediately post-transplant; then 1 mg/kg/day tapered to 10 mg/day over 1 month, then to 5 mg/day from 3 to 12 months	Tacrolimus with or w/o Mofetil Mycophenolate	Calcium (1500 mg/day) and Vitamin D (400 IU/day)	0	Immediately post-transplant, 1 year follow-up
Trabulus, 2009 (RCT)	21; 38	33.9	Mean cumulative dose of 13.6 g	Cyclosporine or Tacrolimus with Azathioprine or Mofetil Mycophenolate	Calcium (1000 mg/day) and Alfacalcidol (0.5 µg/day)	0	3.11
Liver							
Eastell, 1991	20; 100	ND	ND	ND	ND	ND	2
Giuchelaar, 2007	360; 61	49.54	All patients received prednisone; mean dose in fractured patients (4 months post-transplant)= 45.7mg/day	Tacrolimus or Cyclosporine with or w/o Azathioprine or Mofetil Mycophenolate	1.5g Cal/day with Vitamin D supplements	4.4	5.3
Krol, 2014	201; 29	53 (median)	IV MP 500mg given peri-operatively, then oral GC 20mg/day for 1 week, 10mg/day for 3 months, tapered to discontinue 3-6 months post-transplant. Maintenance= 2.5-10 mg/day.	Cyclosporine or Tacrolimus, with or w/o Mofetil Mycophenolate or Sirolimus	Calcium (500 mg/day) and Vitamin D (400 IU/day)	Patients taking bisphosphonate at baseline or initiating bisphosphonate during study (32%) were excluded	1
Leidig-Bruckner, 2001	130; 42	44.9	ND	Tacrolimus: 15% Cyclosporine and Azathioprine: 68%	Calcium and Vitamin D supplementation in 77%	0	3.3
Monegal 2001	45; 36	50.8	1 g of IV MP, tapered to 20 mg/day of prednisone after the first week, 15 mg after 2 months.	Cyclosporine and Azathioprine	Dietary Calcium intake of 1000 mg/day recommended, not enforced or supplemented	0	3
Ninkovic,	37; 46	51.3	10mg/kg IV MP, then	Cyclosporine	ND	ND	0.25

2002			oral GC 1mg/kg/day tapered to max 30 mg/day at 1 month and 5-10 mg/day at 3 months				
Premaor, 2011	531; 38.4	51.7	Pulse MP in 20.3%; Presdnisolone in 97.8%, with a median regimen duration of 3 months	Tacrolimus: 90.7% Azathioprine: 92.8% Sirolimus: 25.9% Mofetil Mycophenolate: 11.4%	Calcium and Vitamin D supplementation in 37.8%	27	5.12
Atamaz, 2006 (RCT)	49; 26.5	45	500 mg IV prednisone peri-operatively, then 100 mg/day tapered to 20 mg over 8 days, further tapered from 20 mg to 10 mg/day over 2 months, ultimately discontinued between 6-12 months	Cyclosporine or Tacrolimus	Calcium (1000 mg/day) and Calcitriol (0.25 µg/day)	0	Immediately post-transplant, 2 year follow-up
Bodingbauer, 2007 (RCT)	49; 24. 5	52	40 mg dexamethasone on the day of transplant, tapered to 4 mg/day by day 5, then substituted with 20 mg methylprednisolone per day, discontinued within 3 months	Cyclosporine: 63.6% Tacrolimus: 36.4%	Calcium (1000 mg/day) and Vitamin D (800 IU/day)	0	Immediately post-transplant, 2 year follow-up
Crawford, 2006 (RCT)	30; 23	49	500 mg IV MP on day 1, then 20 mg prednisone/day by day 12. Mean daily prednisone dose was 16.4 mg/day at 1 month, tapered to 9.5 mg/day by 3 months, and tapered to 3.8 mg/day by month 12	Cyclosporine or Tacrolimus and Azathioprine	Calcium (600 mg/day) and Vitamin D (1000 IU/day)	0 (Patients received an IV placebo)	Immediately post-transplant, 1 year follow-up
Guadalix, 2011 (RCT)	44; 14	54.6	500 mg IV MP peri-operatively, then 20 mg prednisone/day, tapered to withdrawal after 3 months	Tacrolimus (Cyclosporine or Mofetil Mycophenolate in select patients)	Calcium (1000 mg/day) and Vitamin D (800 IU/day)	0	Immediately post-transplant, 1 year follow-up
Kaemmerer, 2010 (RCT)	40; 30	50.9	500 mg IV MP peri-operatively, then tapered based on body weight. Mean cumulative dose after 12 months: 2,426 mg	Cyclosporine, Mofetil Mycophenolate, and Anti-thymocyte globulin	Calcium (1000 mg/day) and Vitamin D (800-1000 IU/day)	0	Immediately post-transplant, 2 year follow-up
Heart							
Dalle Carbonare, 2011	180; 13	53.2	Steroids 100%; mean dose 15.3 mg/day; in 40% mean cumulative dose ≥10 g	Cyclosporine and Azathioprine	No Calcium/Vitamin D supplementation. Mean daily Calcium intake	0	3.91

					=887.5 mg		
Glendenning, 1999	32; 15.6	50	87.5% receiving steroids; 5-15 mg/day	Cyclosporine and Azathioprine	2 patients were taking Calcium/Vitamin D or estrogen supplementation	ND	Median 2.58
Hariman, 2014	105; 16	55.5 (median, non-fracture); 61 (median, fracture)	68.6% receiving steroids	ND	Calcium and Vitamin D supplementation in 89%	40	1-5
Lee, 1994	31; 0	56	500 mg peri-operatively, 3 doses 125 mg every 8 hours, then tapered to 30 mg/day. Reduced to 5-10 mg/day by 6 months. Mean cumulative dose 6.8 g	Cyclosporine and Azathioprine	Calcium (1000 mg) and Vitamin D (250 IU) per day	ND	2.17
Leidig-Bruckner, 2001	105; 16	51.4	ND	Cyclosporine	Calcium and Vitamin D supplementation in 94%	0	3.7
Shane, 1993	40; 25	52	Mean 9.7 mg/day; mean cumulative dose 11.3 g	Cyclosporine	Cal (1000mg/day) and Vitamin D (50,000 IU/week) in 95%	ND	2.33
Shane, 1996	47; 28	ND	ND	ND	Calcium (1000mg/day and Vitamin D (400 IU/day)	ND	1
Fahrleitner-Pammer, 2009 (RCT)	17; 0	43.4	IV MP 1 g at the time of transplantation, then 750 mg on day 1 post-transplant, followed by oral prednisolone starting at 15 mg/day for 6 months, tapered until a lifetime maintenance dose of 5 mg/day was reached	Cyclosporine and Mofetil Mycophenolate	Calcium (500 mg/day) and Vitamin D (400 IU/day)	0 (Patients received an IV placebo)	Immediately post-transplant, 1 year follow-up
Lung							
Aris, 1996	45; 53	35	Prednisone started 0.5 mg/kg decreased to 15 mg every other day by 7months	Cyclosporine .	Calcium (1200 mg/day) and Ergocalciferol (800 IU/day)	ND	ND
Ferrari, 1996	14; 57	47	Prednisone 0.2 mg/kg/day for 1 week, 0.5 mg/kg/ per day for 3 months, then taper to 0.2 mg/kg/day	Cyclosporine and Azathioprine	Calcium (1000mg/day) and Vitamin D (1000 IU/day)	0	1
Hariman, 2014	210; 48	56 (median, non-	91% receiving steroids	ND	Calcium and Vitamin D supplementation	50	1-5

		fracture); 58 (median, fracture)			in 91%		
Spira, 2000	28; 43	53.5 (median)	IV MP 500 mg pre-transplant, followed by 0.5 mg/kg/day for the first 4 days. Day 4 post-transplant, prednisone 40 mg/day, tapered to 5 mg every 5 days until a dose of 20 mg during first 3 months	Cyclosporine and Azathioprine	Calcium and Vitamin D supplementation in 100%	0	1

ND= No data; RCT= Randomized Controlled Trial; IV= Intravenous administration; IU= International Units; MP= Methylprednisolone; GC= Glucocorticoid

Table 2: Incidence of Fractures in Transplant Patients per 1000 Patient-years (95%CI)

Median age, years	% Female, median	Hip Fracture	Vertebral Fracture	Non-Vertebral Fracture	Total Fracture
Heart Transplant (8 Observational Studies, 1 RCT*, 1001 Patients)					
53	16	3 (-28 to 33)	**81 (57 to 106)**	10 (-15 to 35)	**85 (57 to 114)**
Kidney Transplant (10 Observational Studies, 9 RCTs*, 276,851 Patients)					
46	40	**4 (1 to 7)**	**13 (8 to 18)**	**38 (28 to 47)**	**41 (37 to 45)**
Lung Transplant (4 Observational Studies, 327 Patients)					
47	50	4 (-167 to 175)	87 (-22 to 196)	68 (-43 to 179)	**126 (2 to 250)**
Liver Transplant (7 Observational Studies, 5 RCTs*, 1,887 Patients)					
51	33	10 (-22 to 41)	**86 (62 to 111)**	**31 (10 to 52)**	**107 (80 to 133)**

Statistically significant results are shown in bold. 95% CI= 95% Confidence Interval
*Randomized trial data was included only from study arms in which patients were receiving either no anti-osteoporotic treatment or were treated with Calcium and Vitamin D alone

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Osteoporotic Fracture As the Main Risk Factor in the Detection of Osteoporosis in Men Under 70 Years

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Background/Purpose: Osteoporosis (OP) in males under 70 years is less common than postmenopausal and senile, but generates significant social and health costs associated with morbidity and mortality from fractures. It´s common in patients with inflammatory rheumatic diseases and hepatic, bowel and endocrine pathologies, also in COPD patients and in those undergoing chronic corticosteroid therapy. Sometimes clinical risk factors of male OP go unnoticed, so the diagnosis is delayed and is done when one or more fractures by low energy mechanism have already produced, which is a late diagnosis. Bone Metabolism Unit at Basurto University Hospital receives from 2010 male patients with suspected OP. The objective of this study is to describe demographic and clinical characteristics of men ≤70 years evaluated in our OP consultation, with referral protocols according to risk factors.

Methods: A retrospective, descriptive study based on a review of database of these patients. We analyze origin of derivation, risk factors, presence of fractures at the moment of diagnosis, primary diagnoses and occurrence of refractures. All statistical analyses were performed using SAS for Windows statistical software, version 9.2.

Results: 199 patients, with a mean age of 57.74 years (18-70), from Primary Care (73), and general rheumatology (57), up to 65% of the total; 23 patients (11.5%) from traumatology; 15 from endocrinology (7.5%); 9 from gastroenterology (4.5%). 59.8% were smokers or former smokers, 25% had drinking habit. 20.1% had received prednisone doses ≥ 7.5 mg for more than 3 months. 12 patients had family history of fracture (6%), and 70 already had one or more fractures (35.1%): 57 one or more vertebral fractures, 5 hip fracture and 12 wrist fracture. 99 patients had OP with treatment indication by bone agent. 59.3% had secondary OP, main cause digestive disorders (malabsorption syndromes and inflammatory bowel disease) by 21%, 10% endocrine disorders and rheumatic inflammatory diseases also by 10%. Presence of fractures was associated with decreased DXA spine ($p = 0.027$) and hip ($p = 0.004$). A very weak correlation between higher FRAX fracture and number of risk factors was detected, on the other hand a moderate correlation was observed with the number of fractures (Spearman Rho = 0.472; $p < 0.001$). So does to the hip FRAX (Spearman Rho = 0.417; $p < 0.001$). Low levels of D vitamin showed association with decreased DXA in spine. Drinking habit showed statistically significant association ($p=0.032$) with a decrease in the T - score of hip. Among 70 patients with previous fractures, only 15 (21%) had received prior treatment with bone agent. 7 patients suffered refracture after starting treatment and during follow-up (74.2 months) (6-129).

Conclusion: For the correlation found with spine bone density, it seems important to keep enough D vitamin levels in this population. Almost 1/3 of our patients were referred for low energy mechanism fractures, which is an important failure in early diagnosis, and reveals an unmet need among different specialties of awareness on risk factors for male osteoporosis. Therapy with bone agent (oral biphosphonate mainly), seems useful in preventing new bone fractures in these patients.

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Osteoporosis and Breast Cancer: Outcomes at a Specialized Osteoporosis Clinic Following a Structured Assessment

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Background/Purpose: Women with breast cancer are at an increased risk for the development of bone loss and osteoporosis mainly due to adjuvant therapies, such as aromatase inhibitors (AI). AI therapy fully suppresses estrogen synthesis, further exacerbating the increased bone resorption and leading to an excess fracture risk. Thus, a close monitoring of bone mineral metabolism is recommended in these cases. The aim of the present study was to analyze bone health status and clinical characteristics of women with breast cancer referred by oncologist to a specialized clinic and their outcomes during follow-up.

Methods: Retrospective analysis of consecutive female patients with recent breast cancer (BC) and low bone mineral density (BMD) referred to the osteoporosis outpatient clinic for assessment, as agreed with oncologists. A descriptive analysis of epidemiological, clinical, laboratory, imaging, and dual energy x-ray absorptiometry (DEXA) data is presented, both at baseline and last visit. 95% confidence intervals (95%CI) were estimated for rate of fragility fractures (FF) at baseline and during follow-up.

Results: A total number of 122 female patients have been assessed up to May 2016; median aged 60.9 (SD±10.6) years old, 91.5% postmenopausal. BC was non-methastasic in 89 (70.3%), and 89 (70.3%) patients were on aromatase inhibitors (66 on letrozole). At baseline, 26 patients (21.0%, 95CI% 20.9-21.1) had previous FF, mostly vertebral (13) or non-vertebral (9), and two cases had suffered from multiple FF. BMDs were at osteoporotic range at the lumbar spine and osteopenic at both the femoral neck and hip. Median 25-hydroxyvitamin D levels were 23.9ng/mL (p25-75 18.1-45.1) at baseline. Regarding antiosteoporotic therapies, bisphosphonates were prescribed in 62 cases (66.6%), denosumab in 16 (17.2%), and raloxifene in one case (1.0%); the others were only on calcium plus vitamin D supplementation. A total of 102 patients were followed a median of 1.5 years (0.8-2.5), and 20 (16%) discontinued controls. During follow-up, new FF occurred in nine patients (9.0%, 95%CI 8.9-9.1), that were vertebral in 6, non-vertebral in 2, both in one case, while no hip FF were detected.

Conclusion: The outcomes of a structured assessment of female patients with BC and low BMD are reported here. Despite this, almost 10% of cases developed a new FF, highlighting the need for special attention to this singular, secondary form of osteoporosis.

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Abstract Number: 358

Increased Infection Risk with Concomitant Use of RANK Ligand-Inhibitor, Denosumab and TNF-Inhibitors or Other Biologics: Reality or Illusion? Long Term Experience at the University of Southern California

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Background/Purpose: Patients with autoimmune diseases are at increased risk of early onset osteoporosis due to multiple reasons including prolonged exposure to corticosteroids and the disease process itself in RA patients. Same patients are more likely to be on TNF inhibitors or other biologics, which causes them to be at an increased risk of infections. Denosumab, an anti-RANK ligand inhibitor used to treat osteoporosis, is associated with increased infection risk as Receptor activator of nuclear factor kappa-B ligand (RANKL) is also expressed on activated T and B lymphocytes(1). It is unknown if there is an added risk of infections when TNF inhibitors/biologic agents and denosumab are used concomitantly.

Methods: Data was collected and analyzed on 40 patients in the rheumatology clinic who had been on denosumab and TNF inhibitor/ other biologic for 5 years at the Keck Medical Center of USC.

Results: The mean age of the population was 70 ± 9.8 SD years, among which 98% were females. 75% had RA, 10% SLE, 2.5% SLE and Sjogren's, 2.5% SLE with Antiphospholipid Syndrome(APLS), 2.5% RA and SLE, 2.5 % Microscopic Polyangiitis, 2.5% Psoriatic arthritis, and 2.5% Neurologic Behcet's disease. We noted a 17.5% cumulative infection rate before denosumab over 2 years, which is 8.75 cases per 100 person-years. 9% hospitalization rate for infections was noted prior to denosumab. Importantly no infections developed within the first year of initiating denosumab. After 5 years of denosumab with TNF/other biologics, cumulative infection rate was 62.5 % and incidence rate was 12.5 cases per 100 person-years. In the FREEDOM Trial at 3 years, cumulative incidence rate of infections was 52.9%. In our study, 70% patients were on TNF inhibitors and 30% were on other biologics. At 5 years, Cumulative Infection rate was 71.4% among the TNF group and was 50% in the other biologics group. Urinary tract infection (UTI) accounted for the most common infection (17.5%). Other common infections: Pulmonary(15%), skin and soft tissue(12.5%), GI(5%), Tinea(5%)Herpes zoster(2.5%), HSVII(2.5%), sialadenitis(2.5%) . No opportunistic infections, and no reactivation of latent TB found in our patients.

Conclusion: No infections developed within the first year, suggesting a cumulative effect of increased infection risk, if any. We cannot attribute the overall infection rate solely to the combination of denosumab and biologics as patients who developed infections either had Diabetes Mellitus, urinary incontinence, recent surgery, underlying pulmonary disease. Whether prophylactic antibiotics are indicated in patients with recurrent infections PRIOR to denosumab is uncertain, but may be a consideration in certain patients. References: 1. Cummings SR, San Martin J, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med. 2009;361:756–765. doi: 10.1056/NEJMoa0809493

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The Association of Scheuermann's Disease with Osteoporotic Vertebral Fracture Risk

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Background/Purpose: Scheuermann's disease is one of the most frequent illnesses of the spine in teenagers. Its evolution over time is poorly understood. Spinal deformities, by impairing the biomechanics of spine, may be a new risk factor for osteoporotic vertebral fracture. Recently, prospective studies have demonstrated that disc space narrowing (DSN) and thoracic kyphosis could be new vertebral fracture risk factors and similar abnormalities are frequently observed in Scheuermann's disease. Our objective was to examine whether Scheuermann's disease is predictive of vertebral fracture in elderly men.

Methods: We assessed the Scheuermann's disease using the Berlin criteria (Armbrecht & al. Osteoporos Int, 2015, 26, 2509) among 766 spinal radiographs, made of men aged from 50 to 85 years old. Bone mineral density (BMD) was measured at baseline using a HOLOGIC 1500 QDR device. Data on incident vertebral fractures have been prospectively collected for 7,5 years and non-vertebral fractures for 10 years. We analyzed the relationship of Scheuermann's disease and each of its diagnostic criteria with BMD and with the risk of fracture.

Results: Scheuermann's disease prevalence was 25,2%. Scheuermann's disease was associated with lower BMD at the hip and higher BMD of lumbar spine and whole body after adjustment for age, weight, 17b-estradiol and 25-hydroxycholecalciferol. Vertebral fractures occurred in 27 men, peripheral fractures occurred in 60 men. Scheuermann's disease was not associated with an increased risk of vertebral fracture. However, vertebral endplate irregularity, one of its diagnostic criteria, was associated with an increased vertebral fracture risk after adjustment for the age, weight, lumbar spine BMD, prevalent vertebral fractures, prior falls, overall score of DSN due to osteoarthritis (Odds ratio= 2.69, 95% CI: 1.16; 6.26, $p<0.05$). In individuals with Scheuermann's disease, peripheral fracture risk was lower after adjustment for the age, weight, femoral neck BMD, prior fragility fracture (self-reported non-vertebral fractures and vertebral fractures), prior falls, overall score of DSN due to osteoarthritis, severe abdominal aortic calcification (Odds ratio= 0.47, 95% CI: 0.23; 0.99, $p<0.05$).

Conclusion: In this prospective cohort study in elderly men, Scheuermann's disease was not associated to an increased vertebral fracture risk, but with a decreased non vertebral fracture risk. Endplate irregularity, however, was substantially predictive of new vertebral fracture risk, which may be taken into account in the evaluation of the risk of fracture in elderly men.

Disclosure: M. Gaudé, None; **R. Chapurlat**, None; **P. Szulc**, None.

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Abstract Number: 360

Osteoporosis Prevalence in Lung Transplant Patients

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Background/Purpose: Osteoporosis prevalence in lung transplantation candidates is between 16-21%. In the last years, the survival rate after lung transplantation has definitely improved, due to the improvement of the surgical techniques, of the treatment in the intensive care unit and the development of better immunosuppressive therapy. In spite of this, it was observed that there is a rapid loss of bone mass in these patients in the first year post-transplantation, probably due to prolonged immobilization post-surgery, to high doses of glucocorticosteroids used to prevent acute rejection and to the immunosuppressive regimen. Prospective studies have been conducted which demonstrated changes in bone mass and a

major incidence of fractures in lung transplant patients. Our objectives were to determine the prevalence of osteopenia, osteoporosis and fractures in lung transplantation candidates and lung transplant patients in a reference center as well as to evaluate the change of bone mass pre and post transplantation.

Methods: We included 179 patients from the cohort of lung transplant patients of Vall d'Hebron University Hospital, whose femoral and lumbar bone mineral density determinations pre and post-transplant were available. Since it is a retrospective study and the moment of the post-transplant bone densitometry couldn't be standardized, the patients were stratified depending on the moment of the realization of the densitometry: less than 6 months, between 7 and 12 months and more than 12 months after the transplant.

Results: Out of the 179 patients, 110 were men and 69 were women, and their average age was 51±10.4 years. The prevalence of pre and post-transplant osteoporosis, osteopenia and symptomatic fractures is shown in table 1.

Table 1. Pre and post-transplant osteoporosis prevalence

Prevalence	Pretransplant(%)	Post-transplant(%)
Osteoporosis	38	38.5
Osteopenia	45.8	48.6
Normal	16.2	12.8
Fracturas	9.5	11.2

No significant differences were observed when comparing the percentage of men and women with osteoporosis and osteopenia before and after the transplant, in relation to the patients' sex or age. The change of bone mass post-transplant, expressed in gr/cm^2 was of 1.3% (±15.3) in the lumbar spine, -2.1 (±11.3) in the femoral neck and 2.1(±9) in the total femur. The patients' diagnostic change after lung transplant is shown in table 2.

Table 2. Change of bone density between pre and post-transplant

		Post-transplant		
		Normal	Osteopenia	Osteoporosis
Pre transplant	Normal	18 (62.1)	11 (37.9)	-
	Osteopenia	4 (4.9)	62 (75.6)	16 (19.5)
	Osteoporosis	1 (1.5)	14 (20.6)	53 (77.9)

More than 60% of the patients didn't have a diagnostic change after the transplant. Out of the 11 patients with normal pre transplant bone densitometry and post-transplant osteopenia, 9 had previously received osteoporosis treatment. Out of the patients with pre transplant osteopenia, 16 had osteoporosis afterwards, 8 of whom had not received previous treatment. 14 patients that had pre transplant osteoporosis improved to osteopenia post-transplant, out of which 12 had been previously treated.

Conclusion: In our series the prevalence of osteoporosis and osteopenia was of 38% and 45.8%, respectively. The prevalence of pre-transplant symptomatic fractures was of 9.5%. The prevalence of post-transplant osteoporosis and osteopenia was of 38.5% and 48.6%, respectively. The prevalence of post-transplant symptomatic fractures was of 11.2%. In our cohort, the majority of patients whose bone densitometry worsened from normal/osteopenia to osteoporosis had not received pre transplant prophylactic treatment. The post-transplant bone mass loss was between 1-2%, and the most affected regions were the total femur and the femoral neck.

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Abstract Number: 361

The Effect of Immunosuppressive and Antiresorptive Therapy on Bone Mineral Density in Lung Transplant Patients

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Background/Purpose: Osteoporosis is a very frequent complication in recipients of a lung transplant . The factors that intervene can be previous to the transplant, such as the individual risk, the underlying disease, the treatments received but also the ones related to the lung transplant, like the prolonged post-surgery immobilization. The rate of bone mass loss in the lumbar spine and the femoral neck in the first year is around 2-5% and fracture prevalence is between 18-37%. The objectives of this study were to evaluate the effect of antiresorptive, glucocorticosteroids and other immunosuppressive treatments on bone mineral density in lung transplant patients.

Methods: This is a retrospective study on a cohort of 179 patients who were submitted to lung transplant between 2004 and 2014 in the Vall d'Hebron University Hospital. A bone densitometry was practiced to all patients before and after the lung transplant. The comparison between the determinations was made by calculating the percentage of change in bone mass expressed in g/cm^2 at each of the explored region: the lumbar spine (L2-L4), the femoral neck and the total femur. For the analysis of the effect of immunosuppressant therapy on bone mineral mass, a subgroup of 136 patients was selected, who were receiving a standard treatment regimen: glucocorticosteroids, tacrolimus and mycophenolate. 3 groups were established, depending on the moment of the densitometry realization: in the first 6 months, between 6 and 12 months and more than 12 months after the lung transplant. The correlation between bone mineral loss in the regions of interest and the accumulated dose of each of the treatments was evaluated using logistic regression and multivariate analysis.

Results: Out of the 179 patients, 121 received treatment for osteoporosis after the lung transplant (89 were previously receiving it). Table 1 shows the number of treated patients as well as the received treatments. The average time (rank) between the start of the treatment and the realization of the bone densitometry post-transplant was of 24 months (5-120).

Table 1. Osteoporosis treatment after post-transplant

	Treated (n=121)	Not Treated (n=58)	p
Osteopenia	61 (50.4)	26 (44.8)	0.272
Osteoporosis	46 (38)	23 (29.7)	0.480
Normal	14 (11.6)	9 (15.5)	
Drug type			
Oral byphosphonate	64 (52.9)		
Intravenous byphosphonate	46 (38)		
Strontium ranelate	2 (1.7)		
Teriparatide	1 (1.7)		
Calcitonin	1 (0.8)		
Denosumab	3 (2.5)		

Among the 136 patients (58.8% men) who were selected for the study of the effect of immunosuppressants on bone mineral mass, 49 (36%) had been diagnosed of Chronic Obstructive Pulmonary Disease, 64 (47%) of Interstitial Lung Disease and 23 (17%) of other pulmonary diseases. The average percentage of variation of the bone mineral mass in all 136 patients was of +1.3% in lumbar spine, -3.4% in femoral neck and -2.3% in total femur. The percentage of variation of bone mineral mass pre and post-transplant in the treated patients was of 2.8% for the lumbar spine, -0.5% for the femoral neck and -1.3% for the total femur, in comparison to the group of untreated patients where the variation was of -2.5, -5.4% and -3.9, respectively. There was no significant difference in the average accumulated dose of glucocorticosteroids and immunosuppressants between patients whose post-transplant bone mineral mass improved or worsened, in none of the studied regions, nor in the global study or in either of the subgroups of studied diseases. In the multivariate analysis, feminine sex was the only variable which was associated to bone mineral loss in all the studied regions, except for the femoral neck.

Conclusion: The patients who received antiresorptive treatment pre transplant have a major increment of bone mineral mass at the lumbar spine and a lower post-transplant bone mineral mass loss than the not treated ones. No association was observed between glucocorticosteroid and other immunosuppressants and post-transplant bone mineral mass.

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antiresorptive-therapy-on-bone-mineral-density-in-lung-transplant-patients

Abstract Number: 362

Evaluation of Osteoporosis Risk Factors in Lung Transplant Patients

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Background/Purpose: Patients with a terminal lung disease have a great number of risk factors for the development of osteoporosis. Although much has been learned about the factors that contribute to bone mass loss, in our study we try to determine the risk factors in groups of similar diseases. The study´s objective is to determine if the known risk factors for low bone mass are more prevalent in each of the studied lung diseases and if these correlate with the presence of osteoporosis in lung transplantation candidates.

Methods: 179 patients were included, from the cohort of lung transplant patients of the Vall d'Hebron Univesity Hospital, whose pre transplant bone densitometry at lumbar spine and femoral neck were available. 3 groups of lung diseases were selected, due to the differences related to the grouping of risk factors and the glucocorticosteroid doses required before transplantation. The groups were: Chronic Obstructive Pulmonary Diseases (COPD), Interstitial Lung Diseases (ILD) and Other Diseases (Lymphangioleiomyomatosis, cystic fibrosis, primary and secondary pulmonary hypertension). The glucocorticosteroid dose was stratified as follows: high dose if it was more than 5mg/day for more than 3 months (or prednisone equivalent) or more than 3 times a year, and low dose if it didn't meet these conditions.

Results: 179 patients were included, with an average age of 51±10.4 years, without sex related differences. 69 were women (66% of them were at menopause at the moment of the transplantation). 12.3% (22 patients) of the patients had a low body mass index, 57% were smokers with an average of 24.7 packages/year, 5% consumed more than 40 grams of alcohol per day, 44% were sedentary, 8.4% had first degree relatives with an osteoporotic fracture, 15.6% had osteopenia and 86% had received glucocorticosteroids, 56.4% of them at high dose. The risk factors more prevalent in Chronic Obstructive Pulmonary Disease in comparison with the other groups as well as the prevalence of each of them are shown in Table 1.

Table 1. Risk factors for low bone mass and fractures for all the patients, in each of the lung disease

Risk factor	Total	COPD (n=65)	ILD (n=82)	Other (n=32)	COPD versus ILD		COPD versus Other	
					OR (CI)	p	OR (CI)	p
Menopausse	46 (66.6)	14 (77.8)	24 (82.7)	8 (36.4)	0.93 (0.71-1.2)	0.426	2.16 (1.2-3.89)	0.007
Calcium intake	41 (22.9)	19 (29.2)	17 (20.7)	5 (12.2)	1.23 (0.81-1.87)	0.235	1.44 (0.71-2.9)	0.213
Low body mass index	22 (12.3)	8 (12.3)	5 (6.1)	9 (28.1)	2.01 (0.69-5.88)	0.153	0.44 (0.19-1.03)	0.053
Smoking	102 (57)	58 (89.2)	38 (46.3)	6 (18.8)	1.92 (1.5-2.46)	0.000	4.75 (2.3-9.83)	0.000
packages/year	24.7(32.4)	51.1 (37)	12.1 (17)	3.4 (8)		0.000		0.000
Alcoholism	9 (5)	5 (7.7)	4 (4.9)	0	1.57 (0.44-5.64)	0.356	-	0.128
Sedentarism	79 (44.1)	37 (56.9)	34 (41.5)	8 (25)	1.37 (0.98-1.91)	0.045	2.27 (1.2-4.3)	0.003
Previous fracture	17 (9.5)	7 (10.8)	10 (12.2)	0	0.88 (0.36-2.19)	0.5	-	0.054
Fracture in a relative	15 (8.4)	5 (7.7)	5 (6.1)	5 (5.6)	1.26 (0.38-4.17)	0.475	2.03 (0.63-6.51)	0.195
Osteopenia producing disease	28 (15.6)	9 (13.8)	7 (8.5)	12 (37.5)	1.62 (0.64-4.12)	0.220	0.37 (0.17-0.78)	0.009
Oral glucocorticosteroids	154 (86)	62 (95.4)	75 (91.5)	17 (53.1)	1.04 (0.96-1.14)	0.270	1.79 (1.29-2.49)	0.000
High dosis	101 (56.4)	29 (46.8)	59 (78.7)	13 (76.5)	0.59 (0.44-0.80)	0.000	0.61 (0.42-0.89)	0.027
Vitamina D (ng/ml)	18.1 (12.3)	16.2 (11.3)	19.2 (11.3)	19.4 (15.7)		0.388		0.092
Parathormone (pg/ml)	66.7 (39.2)	73.2 (48)	59.8 (28)	71.1 (40.2)		0.060		0.521

The risk factors associated with osteoporosis in all the patients were a low body mass index, smoking and previous fracture. In the different groups of lung diseases, the risk factor associated with osteoporosis in the Chronic Obstructive Pulmonary Disease group as well as in the Interstitial Lung Disease group was the presence of a previous fracture, with an OR of 1.81 (1.44-2.28) and 3.31 (1.07-10.24), respectively. In the group of other diseases the risk factor associated to osteoporosis was the glucocorticosteroid treatment, with an OR of 1.95 (1.08-3.52), without differences related to the dose.

Conclusion: In our cohort, the risk factors for low bone mass, depending on the disease, were smoking and sedentarism in the Chronic Obstructive Pulmonary Disease group. In the same group there was a major prevalence of menopause and glucocorticosteroid treatment, in comparison to the other groups. But the prevalence of high glucocorticosteroid dose in this group was lower than in the others. The risk factors for osteoporosis in lung transplantation candidates were previous fractures, smoking and a low body mass index. In the Chronic Obstructive Pulmonary Disease and Interstitial Lung Disease groups the factor with greater association to osteoporosis was the presence of previous fractures and in the other diseases group glucocorticosteroid treatment.

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Abstract Number: 363

An Examination of Patient Knowledge and Education in Patients with Osteoporosis, Osteopenia and Normal Bone Mineral Density

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Background/Purpose: Osteoporosis represents a preventable and often treatable condition that is responsible for 1.5 million fractures annually in the United States. Proper patient knowledge represents a crucial aspect of disease management and has potential implications in treatment adherence and lifestyle modification. By examining how much patients know about their own diagnosis, their disease knowledge, and what resources they would like to use we aim to lay the groundwork for developing efficient patient education resources.

Methods: We surveyed 52 individuals and collected data on demographics, bone density test results, disease knowledge (using a validated survey), and educational sources both used and preferred. This was done to learn how much patients know about their condition on a fundamental level.

Results: 50% of participants diagnosed with osteoporosis correctly self-reported their condition, as did 21.1% diagnosed with osteopenia. Between the normal, osteopenia and osteoporosis groups there were no significant differences between their scores on the patient-knowledge questionnaire. The resources most used by patients were Handouts/Brochures and Internet/Personal Research, and patients reported a preference for learning directly from their Doctor/Nurse.

Knowledge Questionnaire (True/False)	**Percent Correct**
1) Osteoporosis means having a worse bone density than osteopenia. **T**	74.5%
2) Osteoporosis leads to an increased risk of bone fractures. **T**	98.1%
3) Osteoarthritis is another term for osteoporosis. **F**	75.0%
4) Osteoporosis causes joint pain. **F**	46.8%
5) Osteoporosis is more common in men. **F**	97.9%
6) If my mother has osteoporosis, then I am at a higher risk of getting it too. **T**	81.6%
7) Heavy drinking/alcohol use has been linked with osteoporosis/osteopenia. **T**	63.0%
8) Cigarette smoking can increase risk of osteoporosis. **T**	89.1%
9) Regular exercise especially walking is known to weaken bones and cause osteoporosis. **F**	96.0%
10) Decreased levels of sex hormones can increase the risk of getting osteoporosis. **T**	59.1%
11) Calcium is important for bone health. **T**	100%
12) Sardines and broccoli are good sources of calcium for people who cannot take dairy products. **T**	89.1%
13) A woman's risk of developing osteoporosis **decreases** after menopause.	93.6%
14) Taking prednisone regularly can **increase** risk of developing osteoporosis. **T**	81.8%
15) Taking Fosamax (alendronate) can **decrease** the risk of developing osteoporosis. **T**	66.7%

Conclusion: The majority of fractures occur in patients with osteopenia because they have not yet been treated or diagnosed. Our study confirms the lack of disease awareness in patients with osteopenia. We confirmed the invaluable role of medical personnel in teaching patients about bone density loss. It is through efficient learning that patients can be empowered to take charge of their health.

Disclosure: S. Beg, None; **A. Ziyar**, None.

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Abstract Number: 364

Serum Sclerostin Levels in Rheumatoid Arthritis (RA) and Its Correlation with Disease Activity and Bone Mineral Density

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Background/Purpose: Sclerostin, an osteocyte secreted protein encoded by SOST gene, is an important regulator of Wnt pathway. It prevents bone formation by blocking Wnt binding to its receptor. High levels of sclerostin have been reported in post-menopausal women with osteoporosis. Sclerostin can be induced during inflammation and may also inhibit repair of bone erosion in patients with rheumatoid arthritis (RA). There are few studies demonstrating the role of sclerostin on bone mass and disease activity in RA patients. This study aims to assess the serum sclerostin level in patients with RA and to correlate its level with disease activity and bone mineral density.

Methods: Forty-seven patients of RA fulfilling the ACR/EULAR (2010) criteria, attending the department of Rheumatology, King George Medical University, Lucknow, India were included in the study. Twenty-eight age- and sex-matched healthy controls were enrolled from the same geographic area. Apart from routine blood investigations; rheumatoid factor (RF), anti citrullinated protein antibody (ACPA), 25 hydroxy vitamin D, radiographs and bone mineral density (BMD) were also done. Disease activity was assessed by CDAI. Serum sclerostin levels of both cases and controls was assayed by using enzyme-linked immunosorbent assay (ELISA) assay [Elabscience, coefficient of variation (CV) < 10%] and compared with disease activity and bone mineral density.

Results: Mean age of RA patients was 32.7+6.8 yrs with mean duration of disease 4.2+2 yrs. Mean age of the control group was 28.7+6.3 yrs. Rheumatoid factor was positive in 29 out of 38 patients and anti citrullinated protein antibody was positive in 44 out of 47 patients. Mean sclerostin level among patients was 8422+3655 and that of control group was 6479+1510 (p value 0.002). Serum sclerostin level did not correlate significantly with ESR (r:-0.31, p:0.048), CRP (r:-0.11, p:0.65), CDAI (r:-0.11, p:0.45), BMD at lumbar spine(L1-4, r:.14, p:0.35) and femur (r:0.06, p: 0.67).

Conclusion: Serum sclerostin level did not correlate with disease activity and BMD in RA patients.

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Abstract Number: 365

Osteonecrosis of the Femoral Head Is Associated with Low Bone Mass.

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Background/Purpose: Osteonecrosis of the femoral head (ONFH) is characterized by epiphyseal necrosis that can lead to sub-chondral fracture, femoral head collapse and hip replacement. Osteoporosis (OP) and ONFH share common clinical and pathophysiological features such the occurrence of fracture, risks factors (GC and alcohol) and altered bone cells functions. This study was undertaken to study BMD in patients with pre-fractural (stage 1 and 2) and fractural stages (stage 3 and 4) of ONFH and to determine whether ONFH at a fractural stage was associated with an increased prevalence of OP

Methods: We included 243 patients with ONFH and 399 age and sex-matched healthy controls in this prospective controlled trial. Data was gathered including demography, risk factors, ARCO staging of ONFH and bone mineral density (BMD). Patients were stratified according to the staging (pre-fractural and fractural stages) of ONFH at diagnosis and BMD.

Results: BMD (defined by the T-score) was significantly lower in the ONFH group at both the femoral head (-0.96 ± 1.11) and the lumbar spine (-1.22 ± 1.47) compared to the control group (-0.55 ± 0.97 and -0.73 ± 1.31) ($p<0.01$). The ONFH group depicted a significantly higher proportion of osteopenia (50.39% vs 40.87%, $p =0.027$) and of OP (18.78% vs 7.33%, $p <0.001$) relative to the control group. Furthermore, we analyzed BMD of ONFH patients according to the stage of ONFH at diagnosis. We observed that stage 1-2 ONFH patients (53.86%) (but not stages 3-4) were at a higher risk of osteopenia than the control group (40.88%, $p =0.0203$) with an odds ratio of 1.27 (95% CI: [0.78; 2.06]). Moreover, stage 3 and 4 ONFH patients (25.31%) were at a higher risk of osteoporosis (with an odds ratio of 4.89 (95% CI: [2.77; 8.76]) than patients in the stage 1 and 2 group (7.24%, $p <0.001$) and compared to the control group (with an odds ratio of 4.89 7.33%, $p <0.001$).

Conclusion: Fractural stages ONFH were associated with a 5-fold risk of osteoporosis. Therefore, we advise that patients suffering of ONFH should be screened for low bone mass.

Disclosure: M. soyfoo, None; **V. Gangji**, None; **R. moreno**, None; **J. Rasschaert**, None; **J. P. Hauzeur**, Bone therapeutics, 5.

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Abstract Number: 366

Peripheral Osteoclastogensis Is Coming Back Along with Inflammation Twelve Months after Rituximab Therapy

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Background/Purpose: We investigated change of bone turnover markers in peripheral blood before, 6 and 12 months after rituximab therapy in seropositive RA patients.

Methods: Ten seropositive RA patients were enrolled. They had been refractory to antirheumatic drugs and anti TNF-¥á therapy, thus received rituximab, monoclonal anti-CD 20 antibody treatment. Rituximab 1000mg were infused on days 1 and 15. Peripheral blood mononuclear cells were collected before, 6 and 12 months after rituximab treatment. They were

cultured and number of osteoclasts was counted. In addition, CD 19 cells and complete blood count (CBC) along with ESR, CRP and RA disease activity such as DAS28 were assessed. Bone turnover markers including c-terminal telopeptide (CTX), osteocalcin, bone specific alkaline phosphatase (BSALP) were also measured using enzyme linked immunosorbent assay.

Results: The number of cultured osteoclasts from peripheral blood and serum level of CTX were lowered, six months after rituximab therapy (Table 1). BSALP which is bone formation marker also increased after the treatment. The acute phase reactants and RA disease activity, measured 6 months after rituximab therapy markedly responded to the treatment as CD 19 cells were depleted (Table 2). On the other hand, twelve months after rituximab therapy, the serum level of acute phase reactants began to rise and CD 19 cells increased in numbers. RA disease activity also got worse. Bone resorption pits by osteoclasts cultured from peripheral blood at 12 months after rituximab treatment significantly increased than bone resorption pits by osteoclasts from peripheral blood at 6 months after the treatment.

Conclusion: Peripheral osteoclastogenesis decreased when systemic inflammation is improved in RA patients 6 months after B cell depletion treatment. However, one year after rituximab treatment, systemic inflammation increased as peripheral B cell counts began to normalize. The area of bone resorption pit by cultured osteoclasts from peripheral blood increased as well. Therefore, we think peripheral osteoclastogenesis is coming back along with the inflammation, 12 months after rituximab treatment and rituximab therapy should be resumed within a year.

Table 1. Peripheral osteoclastogenesis and bone turnover markers

		At baseline	At 6 months	At 12 months
Ex vivo	**Number of osteoclasts (per well)**	**524 ± 301.1**	**299 ± 270.8***	**174 ± 131**
	Bone resorption pit by osteoclasts(%)	**22.9 ± 23.3**	**21.2 ± 16.7**	**39.3 ± 11.5****
In vivo	**CTX (ng/mL)**	**0.86 ± 0.45**	**0.5 ± 0.21***	**0.54 ± 0.19**
	Cathepsin K (pmol/L)	7.25 ± 1.94	7.2 ± 1.58	6.37 ± 1.17
	BSALP (U/L)	**7.42 ± 2.51**	**10.81 ± 5.2***	**8.58 ± 3.12**
	Osteocalcin (ng/mL)	28.11 ± 8.07	40.71 ± 18.19	30.6 ± 7.96

* denotes $p \leq 0.025$, at Baseline vs. at 6 months
**denotes $p < 0.05$, at 6 months vs. at 12 months

Table 2. CD 19 cells, systemic inflammation and RA disease activity

	At baseline	At 6 months	At 12 months
CD 19 cells (/㎕)	**660 ± 345.5**	**42 ± 103.5***	**298 ± 563†****
CBC (/㎕)	**7278 ± 2116.3**	**6550 ± 2149.2**	**6919 ± 1847.9**
ESR (mm/hr)	**56 ± 21.1**	**23 ± 13***	**31 ± 23.4†****
CRP (mg/dL)	**3.72 ± 2.72**	**0.82 ± 1.46***	**1.16 ± 1.11†**
DAS28-ESR	**7 ± 0.9**	**4.04 ± 0.86***	**5.55 ± 1.89****
DAS28-CRP	**6.39 ± 0.98**	**3.52 ± 0.69***	**5.04 ± 1.77****

* denotes $p \leq 0.025$, at Baseline vs. at 6 months
**denotes $p < 0.05$, at 6 months vs. at 12 months
† denotes $p = 0.008$, at Baseline vs. at 12 months

Disclosure: M. J. Lim, None; **W. Park**, None; **S. R. Kwon**, None; **K. H. Jung**, None.

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Microarray Analyses of Dorsal Root Ganglia for the Study of Pathways Contributing to Pain in Experimental Osteoarthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Destabilization of the medial meniscus (DMM) in the mouse knee results in slowly progressive joint damage, accompanied by pain-related behaviors. Secondary mechanical allodynia develops by week 4 after surgery, but is not maintained after sham surgery while it is maintained for 16 weeks after DMM. Eight weeks after DMM but not sham surgery, mice develop activity-induced pain. Development of chronic pain is characterized by molecular changes in the dorsal root ganglia (DRG), where the cell bodies of sensory neurons reside. Therefore, we sought to perform an unbiased discovery study on DRG cells at different time points after DMM in order to uncover pathways that may be involved in generating acute *vs.*persistent pain associated with experimental osteoarthritis (OA).

Methods: DMM or sham surgery was performed in the right knee of 10-week old male C57BL/6 mice. Age-matched naïve mice were also included. Four, 8, or 16 weeks after surgery, ipsilateral L3-L5 DRG (innervating the knee) were collected and pooled from each mouse, RNA was extracted, and an Affymetrix Mouse Transcriptome Array 1.0 was performed following manufacturer recommendations. A total of 3 mice (3 arrays) were used for each treatment per time point. Sham 8-week samples did not amplify well and were excluded from the study. Two types of analyses were performed, one looking for genes involved in post-surgical pain (called “early pain”), and one looking for genes involved in persistent pain (called “late pain”). “Early pain” compared naïve 4-week samples to data pooled from sham and DMM 4 week-samples. “Late pain” compared data pooled from naïve 8- and 16-week and sham 16-week samples to data pooled from DMM 8- and 16-week samples. Ingenuity pathway analysis software was used to identify pathways of interest among the differentially expressed genes ($p<0.01$).

Results: In the “early pain” analysis, 345 genes were differentially regulated, using a $p<0.01$ cut-off. The top 3 networks included genes related to 1) Cell morphology/Protein synthesis/Cellular function and maintenance; 2) Hematological system development and function/Hypersensitivity response/Inflammatory response; and 3) Cell cycle/Cell death, which were enriched in the pooled DMM/sham 4-week samples relative to the naïve 4-week controls. In the “late pain” sets, 227 genes were differentially regulated. The top networks included genes related to 1) Nervous system development/Cell-to-cell signaling; 2) Cell-mediated immune response/Cell function & maintenance; 3) Amino acid metabolism/Molecular transport; 4) Humoral immune response; and 5) Cell cycle, which were enriched in the pooled DMM 8- and 16-week samples relative to sham/naïve 8- and 16-week controls. In general, there was little overlap (10 genes) between the differentially expressed genes in the “early” *vs.*“late” pain set, supporting our choice for separating these sets as such.

Conclusion: This molecular study represents the first unbiased analysis in the DRG in a model of chronic OA-pain. Findings support behavioral data suggesting that distinct phases exist in the pain developing after DMM surgery. Future work will seek to validate these pathways with the aim to identify new analgesic targets for treating osteoarthritis pain.

Disclosure: R. E. Miller, None; **S. Ishihara**, None; **D. Syx**, None; **R. J. Miller**, None; **A. M. Valdes**, None; **A. M. Malfait**, None.

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Abstract Number: 368

A Systematic Review of Chronic Pain Assessments with Children and Young People: Exploring Administrative, Scoring and Classification Issues

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Background/Purpose: Pain is often the most troubling feature of musculoskeletal disease in children and young people (CYP). In paediatric pain research, recent attempts to standardise the assessment of chronic pain for CYP have been pivotal in establishing *which* measures should be used. However, guidance about *how* pain assessments should be administered is extremely limited. Furthermore, inconsistencies exist in pain scoring systems used to classify chronic pain as mild, moderate or severe in CYP. The aim of this review was to evaluate current evidence on pain assessment administration, scoring and pain classification in CYP with chronic pain.

Methods: Medline, EMBASE, CINAHL and PsycInfo were searched (inception to 18th January 2016) for studies in which uni-dimensional, self-report, pain assessments were used with CYP (aged 5-18 years) who suffered from a chronic pain condition (or illness conditions in which chronic pain was a feature). Two researchers reviewed full-text articles independently of each other for inclusion. Disagreements were identified and reviewed for inclusion by a third reviewer. Selected studies were critically appraised by the two independent reviewers. Quality criteria were adapted from existing recommendations for the selection, administration and interpretation of self-report scales with children. The maximum possible score was 8.

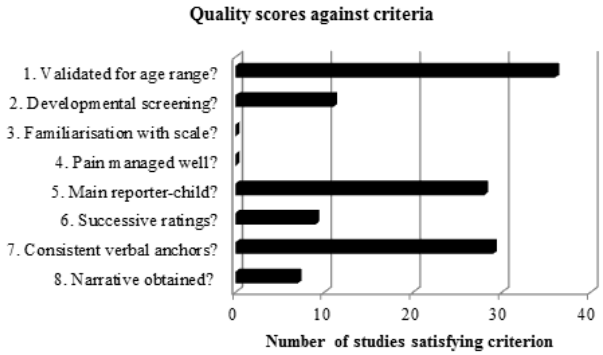
Table 1: Quality criteria used to evaluate the selection, administration and interpretation of pain scales in selected studies.

Quality of measure selection
1. Has the tool been validated for the age range with which it was used?
2. Were children screened for developmental delay or was a measure of competency conducted prior to pain assessment?
Quality of measure administration
3. Did the child have a chance to become familiar with the pain scale used e.g. by rating hypothetical scenarios?
4. Were children introduced to the scale at a time when they were not distracted by the level of pain they were experiencing?
5. Was the child the main reporter of pain at assessment?
6. Were successive pain ratings observed?
7. Were consistent verbal anchors used across patients?
Quality of measure interpretation
8. Was a narrative explanation of pain scores also obtained, at least at the first data collection point?

(adapted from von Baeyer 2006; 2014)

Results: Thirty-five studies were included from a sample of 628. Five papers reported the use of several scales. A total of 40 reports met the inclusion criteria for full review and used one or more of the following assessment types; Visual Analogue Scales, Numerical Rating Scales, Faces Pain Scales, Body Maps. None of the pain assessments undertaken met all quality criteria. The highest score achieved was 5 out of a maximum of 8, the lowest was 0 (median=3, IQR=3-4). Key administrative details were missing from the majority of reports with 22 failing to provide details of how the assessment was scored. Only two articles provided details of how pain scores were classified.

Table 2: Quality scores against criteria



Conclusion: Pain assessments were rarely administered in accordance with existing administrative guidance. The rationale for *how* pain measures were utilised with CYP with chronic pain was seldom provided and the reporting of pain assessments was poor. Details on the systems used to score and classify pain were missing in most published papers. Lack of standardisation remains a problem in chronic pain research. The finding of this review suggest that implementation of guidance for *how* to use, score and report pain assessment tools with CYP in chronic pain is necessary for both clinical practice and research.

Disclosure: R. Lee, None; **A. Rashid**, None; **D. Ghio**, None; **W. Thomson**, None; **L. Cordingley**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-systematic-review-of-chronic-pain-assessments-with-children-and-young-people-exploring-administrative-scoring-and-classification-issues

Abstract Number: 369

Opioid Prescriptions and Adverse Reactions in Children and Adolescents without Serious Diseases

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Background/Purpose: There is a well-described epidemic of deaths and hospitalizations related to opioid prescriptions in adults. However, little is known about opioid toxicity in children. We investigated the incidence of opioid toxicity and compared the safety of the most frequently prescribed opioid, codeine, to that of other opioids used by children and adolescents without serious diseases.

Methods: We studied a Tennessee Medicaid cohort of 424,382 children aged 2–17 years, who filled 1,133,089 opioid prescriptions for non-cancer pain. We excluded children with prior encounters indicating serious diseases (cancer, sickle cell anemia, congenital anomalies, hospitalization for a total of more than 30 days in the preceding year, or history of organ transplant), institutional residence, and history of drug abuse. The primary study endpoint was opioid toxicity, defined as an emergency department visit, hospitalization, or death attributed to opioid analgesic use. Medical records were reviewed to adjudicate the outcomes.

Results: The median length of opioid prescription was three days. Most prescriptions were for acute, self-limited conditions including dental procedures (31%), outpatient procedure/surgery (24%), trauma (18%), and minor infections (17%). There were 365 confirmed cases of opioid toxicity with a median follow-up time of opioid exposure of 17 days. At 17 days, the cumulative incidence of opioid toxicity was 33.2/100,000 prescriptions. Children taking any opioid at doses in the highest tertile had higher risk of toxicity than those in the lowest tertile (IRR=1.85, 95% CI=1.36-2.51). The use of tramadol [incident rate ratio (IRR)=3.03, 95% confidence interval (CI)=2.0-4.60] and oxycodone (IRR=1.87, 95% CI=1.19-2.95) was associated with increased risk of opioid toxicity compared to codeine. An analysis restricted to events leading to deaths, hospitalizations or escalation of care showed increased risk with meperidine (IRR=3.43, 95% CI 1.05-11.24) and tramadol (IRR=4.73, 95% CI 2.07-10.82).

Conclusion: We studied a cohort of children without serious underlying conditions who received opioid analgesics for mostly minor and self-limited outpatient disorders. The cumulative incidence of opioid toxicity was 33.2/100,000 prescriptions at 17 days of follow-up. The use of tramadol, oxycodone, and meperidine, and higher doses of opioids in general increased the risk of toxicity.

Disclosure: C. P. Chung, None; **S. T. Callahan**, None; **W. Cooper**, None; **W. Dupont**, None; **K. Murray**, None; **K. Hall**, None; **J. A. Dudley**, None; **C. M. Stein**, None; **W. Ray**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/opioid-prescriptions-and-adverse-reactions-in-children-and-adolescents-without-serious-diseases

Abstract Number: 370

Relationship Between Alcohol Consumption and Symptom Severity in Chronic Pain Patients

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Background/Purpose: As many as 25% of chronic pain patients use alcohol to manage pain.[1] Preliminary studies in fibromyalgia patients have shown that low to moderate alcohol consumption was associated with lower symptoms compared to no alcohol consumption.[2] We assessed a large cross-sectional chronic pain sample for associations between severity of symptoms and alcohol consumption.

Methods: 2585 patients (58% female) presenting to a university chronic pain clinic completed a survey battery and reported number of alcoholic drinks consumed per day. Patients were grouped by level of alcohol consumption (drinks per day): none, low (≤1), moderate (>1 and <3) and heavy (≥3). Associations between alcohol consumption and fibromyalgia symptom severity (SS) scale were assessed using analysis of covariance (ANCOVA). Univariate analysis was used to determine significant covariates, using chi-square (X^2) tests and one-way analysis of variance (ANOVA) for categorical and continuous variables, respectively. Bonferroni's post-hoc test was used to assess pairwise differences. Adjusted means ± standard deviation and pairwise differences (x) ± standard error are reported. Analysis performed using IBM SPSS 22.

Results: 1991 (70%) subjects did not consume alcohol; 594 subjects consumed alcohol and were grouped into low (n= 444), moderate (n= 120) and high (n= 30) levels. Univariate analysis revealed significant differences in gender (X^2= 41.4), fibromyalgia status (X^2= 29.8), smoking status (X^2= 26.4), opioid therapy (X^2= 47.7) and age (F= 3.4), all $p< .001$. After controlling for covariates, alcohol level had a significant effect on symptom severity (F= 5.8, $p< .001$). Adjusted mean SS scores were 6.8 ± 0.1, 6.5 ± 0.1, 5.9 ± 0.3 and 7.0 ± 0.4 for the no alcohol, low, moderate and high levels, respectively. Post hoc tests showed that the moderate alcohol consumers had significantly lower SS scores compared to

low alcohol consumers (x= 0.9 ± 0.3, p= .015) and non-drinkers (x= 1.3 ± 0.3, p< .001); no other significant pairwise differences were observed. These data represent a U-shaped curvilinear relationship (Figure 1).

Conclusion: The results suggest that consumption of moderate amounts of alcohol in chronic pain patients is associated with lower symptom severity compared to low or no alcohol consumption. These findings are similar to previous studies examining this relationship in fibromyalgia patients. These results should be further investigated for associations between alcohol consumption levels and other chronic pain symptoms.

1. Riley JL, King C. Self-report of alcohol use for pain in a multi-ethnic community sample. *J Pain*. 2009;10(9):944-952. doi:10.1016/j.jpain.2009.03.005. 2. Kim CH, Vincent A, Clauw DJ, et al. Association between alcohol consumption and symptom severity and quality of life in patients with fibromyalgia. *Arthritis Res Ther*. 2013;15(2):R42. doi:10.1186/ar4200.

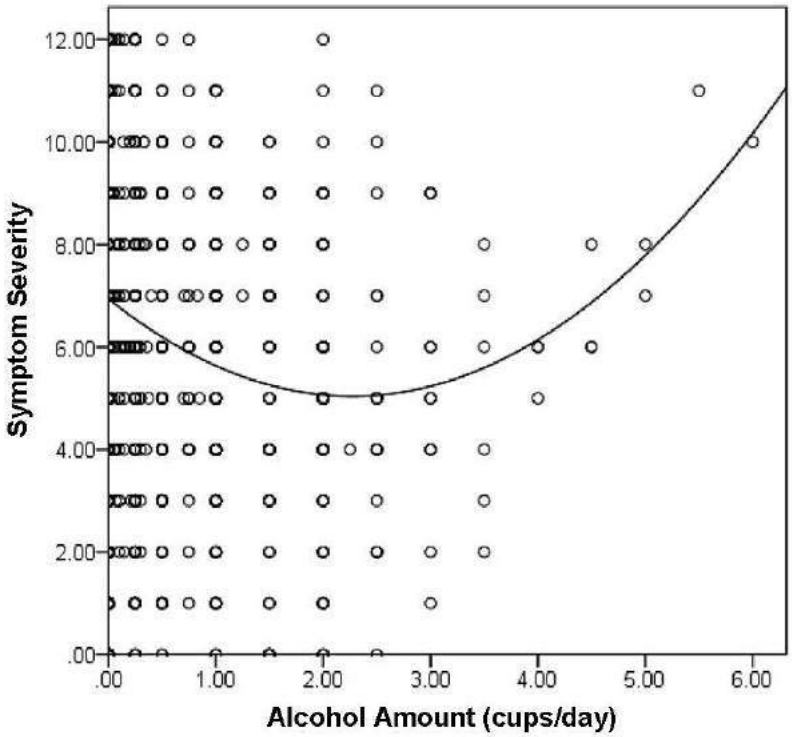

Figure 1. Relationship between alcohol amount and symptom severity depicting quadratic relationship.

Disclosure: J. R. Scott, None; **S. E. Harte**, None; **C. M. Brummett**, None; **R. E. Harris**, None; **A. L. Hassett**, None; **D. J. Clauw**, None.

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Abstract Number: 371

Chronic Pain in Children Seen at a Rheumatology Clinic: Healthcare Utilization Patterns

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Background/Purpose: Musculoskeletal (MSK) pain syndromes are common and the most prevalent type of chronic pain in the pediatric population. The chronic pain syndromes include central pain sensitization conditions such as Reflex Neurovascular Dystrophy, Reflex Sympathetic Dystrophy, Juvenile Fibromyalgia, Allodystrophy, and Complex Regional Pain Syndrome. The mean annual cost per child of care with chronic pain at tertiary pain centers was estimated at $11,787. To our knowledge, there is no robust data characterizing pediatric patients with chronic MSK pain syndromes prior to diagnosis at non-specialized pain centers. We describe the length to diagnosis, the healthcare utilization patterns, and economic burden of chronic MSK pain syndromes in pediatric populations. We hypothesized that the cost of MSK pain syndromes prior to diagnosis is similarly burdensome due to delayed diagnosis.

Methods: A retrospective chart review was conducted at a general pediatric rheumatology clinic at Nationwide Children's Hospital (NCH) in Columbus, OH. We included subjects with a diagnosis of primary chronic musculoskeletal (MSK) pain including Juvenile-Onset Fibromyalgia, RSD, and CRPS seen between 2010 and 2014. We excluded patients with primary rheumatologic disorders, with a chronic MSK pain syndrome diagnosed outside of the Nationwide Children's Hospital system or by a non-rheumatologic specialist. Of 118 with a primary diagnosis of chronic MSK pain 80 met inclusion criteria and were analyzed. We only evaluated visits within the NCH system. Data relating to MSK pain prior to diagnosis were collected from the NCH electronic medical records: date of symptom onset and diagnosis, number of emergency visits, number of hospital admissions, length of hospital admissions, number of outpatient visits, medications used, and imaging studies. Pain scores rated on a visual analogue scale (VAS) from 1-10 and functional disability using the Childhood Health Assessment Questionnaire (CHAQ) scores were recorded at the initial visit and at the time of diagnosis. The Medical Expenditure Panel Survey (MEPS) provided nationally representative data on health care service unit costs. Specifically we used the MEPS annual total expenses per visit mean estimates for office based visits, emergency room visits and inpatient admissions.

Results: The mean (±SD) age was 14.6 ±3.0 years. 89% were female and 86% were white. The average length of time from symptom onset to diagnosis was 18.2 ± 24.9 months. At diagnosis mean pain intensity was 6.45± 2.7 and mean CHAQ score were 0.74± 0.6. 29% went to the emergency room at least 1 time and 52% of those with 1 visit had diagnostic laboratory testing. 5% were admitted as inpatients. 81 % sought out one specialty consultation, 38% sought out two specialty consultations, and 35% sought out 3 or more specialty consultations. The most commonly visited specialist was rheumatology followed by orthopedics prior to a diagnosis. The mean cost estimate hospital, ED and office visits between 2009-2014 was $1910.66 ± 3807.6 (range: 213 -21216). 53% had xrays and 21% had MRI's while other imaging studies were not as frequently performed. 65% were prescribed Nsaids and 15% were prescribed Narcotics. There were no strong correlations between length of time diagnosis and costs.

Conclusion: Children with chronic MSK pain are undiagnosed for greater than 12 months and utilize multiple health services, undergo diagnostic testing and use several medications resulting in high costs even before diagnosis. Our estimate is likely an underestimate as our data only represented data from one site when many of children are being seen in multiple health care systems. Healthcare providers must be attuned to this diagnosis in patients with a long history of chronic MSK pain, high pain scores, and who are seen frequently by healthcare professionals.

Disclosure: F. Tian, None; **P. Guittar**, None; **S. M. Bout-Tabaku**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/chronic-pain-in-children-seen-at-a-rheumatology-clinic-healthcare-utilization-patterns

Abstract Number: 372

Effect of Chronicity on Pain Behaviors in Collagenase Induced Non-Inflammatory Monoarthritis in Mice

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Background/Purpose: Background/Purpose: Osteoarthritis pain remains a significant health problem due to a growing elderly population and the need for newer effective medical therapies. Osteoarthritis pain does not correlate well with radiographic severity, and loss of function in patients with osteoarthritis may result from pain, from altered biomechanics or from toxicity of analgesics. Previous studies of mice with osteoarthritis demonstrated evoked pain behaviors but no consistent change in gait or wheelrunning. Age may also alter pain behaviors in mice with arthritis. In order to better define the relationship between osteoarthritis, pain and function, we measured different types of pain behaviors in mice with osteoarthritis at a uniform age as a function of duration of arthritis and in response to different analgesic treatments.

Methods: Chronic non-inflammatory arthritis was produced by intra-articular (IA) injection of 10 µl collagenase (COL) (10IU) into the left knee of C57BL6 male mice 4 or 6 weeks prior to pain behavior testing using evoked pain score (EPS) and automated dynamic weight bearing (ADWB) device. EPS was a tally of fights and vocalizations/min with knee palpation at 15.6 psi. Percent weight and time on each limb was measured with ADWB apparatus (Bioseb, Vitrolles, France). IA vanilloids resiniferatoxin (RTX) or capsaicin (CAP) (10µl of 0.001%RTX or 0.01% CAP) were given 7 days prior to pain testing. IA botulinum toxin A (BTX) (10µl 0.02 IU) was injected 3 days before testing. Mice underwent pain behavior testing either 4 weeks or 6 weeks after COL injection. All mice were 12 weeks old at the time of testing.

Results: Arthritis pain behavior was low in naïve mice - EPS (0.57) and ADWB proportions for weight (40.9%) and time (97.4%) were normal. IA COL arthritis significantly increased EPS (4.0) after 4 weeks of arthritis and but had very little effect on ADWB for weight (39.7%) and time (98.0%). All IA therapies normalized EPS in arthritic mice. Forepaw compensatory weight bearing increased only from 9.3% in naïve mice to 10.9% in COL arthritic mice at 4 weeks (NS). However after 6 weeks of COL induced arthritis, the EPS was not significantly different from naive (0.8). ADWB measures for left hind-limb weight-bearing at 6 weeks dropped (to 37.6%) and time on the limb was reduced (to 95.2%). These differences were not statistically significant. However there was an increase in forepaw weight-bearing. After 6 weeks COL mice placed 15.8% weight on the forepaws (p=0.02). Both IA RTX and IA CAP normalized this compensatory forepaw weight-bearing in the 6 week arthritic mice.

Conclusion: IA COL monoarthritis increased evoked pain behaviors in mice after 4 weeks but had little effect on spontaneous pain measured by ADWB at this timepoint. After 6 weeks of chronic arthritis, EPS measures were no longer increased, but compensatory forepaw weight-bearing was increased significantly. This compensatory weight-bearing normalized after treatment with IA neurotoxin treatment. These results suggest that both neuroadaptive and behavioral adaptive mechanisms may be at play. Normalization of weight-bearing with analgesia suggests that alterations in weight-bearing are not just due to mechanical factors.

Disclosure: H. E. Krug, None; **C. W. Dorman**, None; **S. Frizelle**, None; **P. A. Valen**, None; **M. L. Mahowald**, None.

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Abstract Number: 373

Evidence for TMJ Pain As a Component of a Generalized Pain Phenotype

Jaren Trost[1], Jordan Westra[2], Erin L. Ashbeck[2], Adam Berlinberg[1] and C. Kent Kwoh[3], [1]Department of Medicine, University of Arizona, Tucson, AZ, [2]The University of Arizona Arthritis Center, Tucson, AZ, [3]1501 N. Campbell Avenue, Room 8303, The University of Arizona Arthritis Center, Tucson, AZ

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Background/Purpose: Chronic temporomandibular disorders develop with persistent pain in other areas of the body in some patients, suggesting a predisposition to a generalized pain phenotype. The objective of our study was to evaluate whether there is an association between temporomandibular joint (TMJ) pain, and pain in other joints, or a generalized pain phenotype.

Methods: The Osteoarthritis Initiative is a cohort study of participants with or at risk for knee osteoarthritis. TMJ pain was assessed via self-reported pain or aching across the face, cheek, or jaw, in the past 30 days at the 4-year visit. Logistic regression was used to estimate the association between recent TMJ pain and knee pain on most days of the month in the past 30 days, as well as hand pain and hip pain. Depression was ascertained using the Center for Epidemiologic Depression Scales (CES-D), and the number of reported body areas with pain was assessed using a homunculus (see figure legend for locations). Mean CES-D scores and number of body areas with pain were compared between participants reporting recent TMJ pain and those without using a two-sample t-test. All analyses were cross-sectional (n=3,852), and due to previously reported sex differences in TMJ pain, all analyses were conducted sex-stratified.

Results: Participants had a mean age of 61 years (SD 9.1), with 80% White and 17% African American. Recent TMJ pain was reported by 11% of females (n=2,225) and 5% of males (n=1,627). Females with TMJ pain had significantly higher odds of reporting knee pain (OR=1.40 [95%CI: 1.14, 1.72]), hand pain (OR=1.81 [95%CI: 1.39, 2.37]), and hip pain (OR=2.13 [95%CI: 1.62, 2.79]), compared to females without TMJ pain; and while the odds of knee, hand, and hip pain was higher among males with TMJ pain compared to males without TMJ pain, the associations were not significant (OR=1.23 [95%CI: 0.86, 1.77]; OR=1.37 [95%CI: 0.81, 2.32]; OR=1.26 [95%CI: 0.73, 2.17], respectively). Females reporting TMJ pain had higher levels of depression on average compared to those without TMJ pain (9.2 vs 7.0; difference of 2.2 [95%CI: 1.1, 3.4], p=0.0002) though we did not observe a significant difference among males (7.9 vs 6.2; difference of 1.7 [95%CI: -0.5, 3.8], p=0.13). Both females and males with TMJ pain had significantly higher mean counts of body pain areas compared to those without TMJ pain (4.2 vs 2.5; difference of 1.7 [95%CI: 1.3, 2.2], p< 0.0001, and 2.9 vs. 1.8; difference of 1.1 [95%CI: 0.4, 1.8], p=0.004, respectively; Figure 1)

Conclusion: Males and females reporting recent TMJ pain also reported pain in more body areas than those who did not have TMJ pain, suggesting a generalized pain phenotype. Females with TMJ pain were significantly more likely to have knee, hand, and hip pain. The management of patients with TMJ pain and pain in other joints may require a broader pain assessment and treatment strategies tailored to address a generalized pain phenotype.

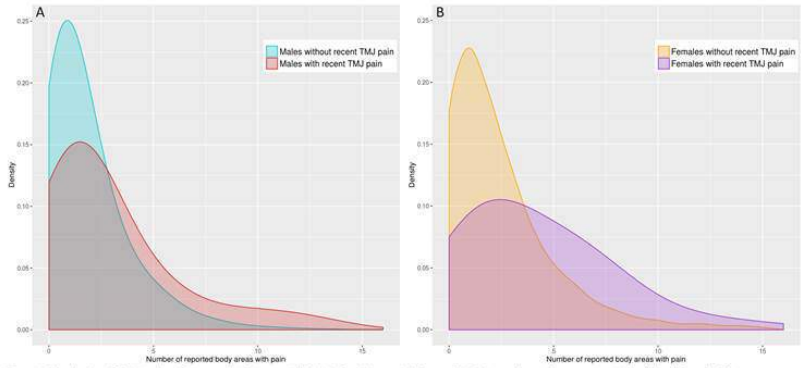

Figure 1. Distribution of the Number of Reported Body Areas with Pain in Participants with Recent TMJ Pain vs. those without, among Males (A) and Females (B).
The number of reported body areas with pain included: right and left shoulders, right and left elbows, right and left wrists, right and left hands, right and left ankles, right and left feet, neck, four locations on the back, and one area for other, for a total of 18 possible body areas.

Disclosure: J. Trost, None; **J. Westra**, None; **E. L. Ashbeck**, None; **A. Berlinberg**, None; **C. K. Kwoh**, Abbvie, 2,EMD Serono, 2.

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Abstract Number: 374

Anxiolytic Effects of the Novel α2δ Ligand Mirogabalin (DS-5565) in Sluka Model, an Experimental Animal Model of Fibromyalgia

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Anxiolytic Effects of the Novel Alpha-2-Delta Ligand Mirogabalin (DS-5565) in Sluka Model, an Experimental Animal Model of Fibromyalgia Yuki Domon[a], Naohisa Arakawa[a], Hiroyasu Murasawa[b], Hiroyuki Kobayashi[b], Kensuke Saeki[b], Yutaka Kitano[a] [a] Biological Research Laboratories, Daiichi Sankyo Co., Ltd., Tokyo, Japan [b] Hashima Laboratory, Nihon Bioresearch Inc., Gifu, Japan

Background/Purpose: Mirogabalin (DS-5565) is a novel ligand of the alpha-2-delta subunit of voltage-gated calcium channels. Mirogabalin possesses unique binding characteristics to alpha-2-delta subunits, and potent and long-lasting analgesic effects in fibromyalgia models and neuropathic pain models. Phase III clinical trials of mirogabalin in patients with fibromyalgia, diabetic peripheral neuropathic pain and postherpetic neuralgia are ongoing. Fibromyalgia is often associated with anxiety and depressive symptoms. In the present study, we investigated the anxiolytic effects of mirogabalin in intramuscular acidic saline injection model (Sluka model) in rats, an experimental animal model for fibromyalgia.

Methods: Male SD rats received two repeated intramuscular injections of acidic saline (pH 4.0) into the gastrocnemius muscle. After development of hyperalgesia, the animals received the test compound orally and the anxiolytic effects were determined in open field test and elevated plus maze test at 2 h after administration. Dose levels of mirogabalin were set at 3 and 10 mg/kg, and the normal and model control groups received vehicle (distilled water).

Results: Sluka model rats showed mechanical hyperalgesia demonstrated by decreased pain thresholds to von Frey filaments. In the open filed test, Sluka model rats significantly preferred the wall-area to the central-area compared with normal rats. In the elevated plus maze test, Sluka model rats exhibited significant decreases in the number of entries and time spent in the open-arm, and significant increases in time spent in the closed-arm. Taken together, Sluka model rats showed anxiety-related behaviors. A single oral administration of mirogabalin (3 and 10 mg/kg) significantly alleviated and normalized above anxiety-related behaviors in both tests.

Conclusion: Sluka model rats showed anxiety-related behaviors in open field test and elevated plus maze test. Mirogabalin alleviated the anxiety-related behaviors in Sluka model rats. Mirogabalin may provide effective anxiety relief for patients with fibromyalgia, as well as pain relief.

Figure 1 Effects of mirogabalin on anxiety-like behavior in open-field test in Sluka model rats.

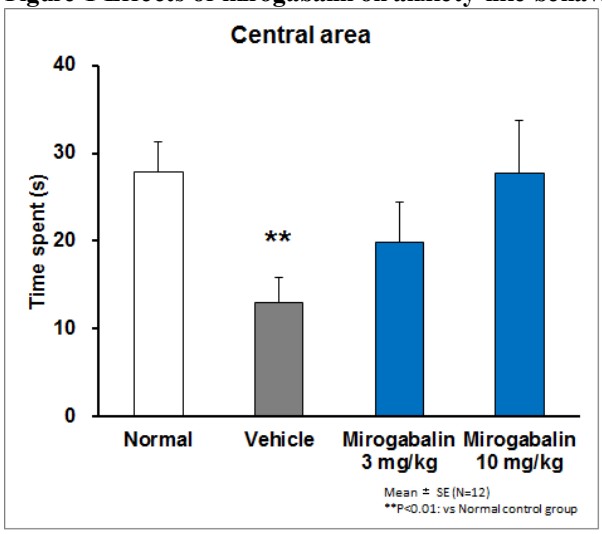
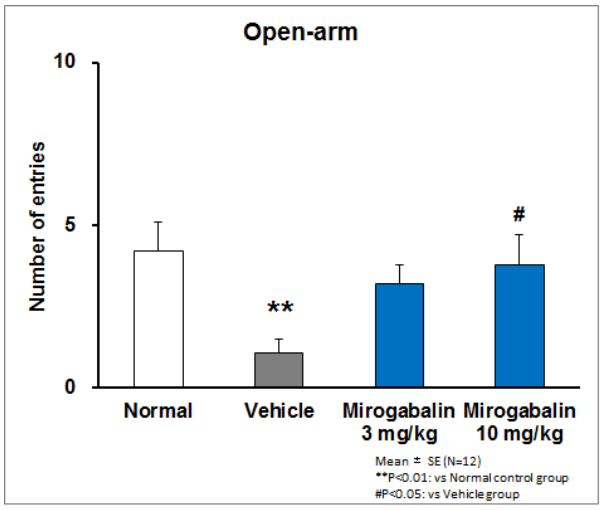
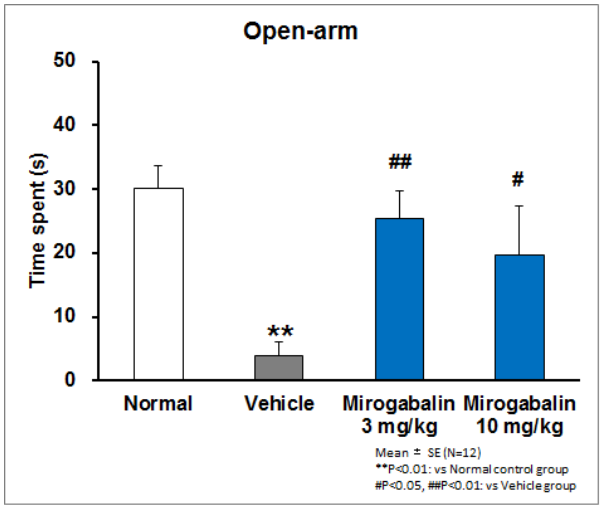


Figure 2 Effects of mirogabalin on anxiety-like behavior in elevated plus maze test in Sluka model rats.





Disclosure: Y. Domon, Daiichi Sankyo Co., Ltd., 3; **N. Arakawa**, Daiichi Sankyo Co., Ltd., 3; **H. Murasawa**, Daiichi Sankyo Co., Ltd., 5; **H. Kobayashi**, Daiichi Sankyo Co., Ltd, 5; **K. Saeki**, Daiichi Sankyo Co.,Ltd., 5; **Y. Kitano**, Daiichi Sankyo Co., Ltd., 3.

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Abstract Number: 375

Persistent Tactile Allodynia in Male Arthritic Mice Is Accompanied By Sprouting of Sensory and Sympathetic Nerve Fibers

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SESSION INFORMATION

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Session Title: Pain – Basic and Clinical Aspects - Poster
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Session Time: 9:00AM-11:00AM

Background/Purpose: Joint pain is the primary reason individuals with arthritis seek medical care. Unfortunately, arthritic pain is difficult to treat and current treatments are fraught with undesirable side effects. It is commonly thought that pain is evoked by inflammation and / or joint damage, leading to a peripheral and central sensitization. However, the severity of pain often does not correlate well with these factors. We hypothesize that, while inflammation leads to sensitization of joint terminals, over time, changes occurring within the joint itself may contribute to the ongoing pain state. Therefore, our goal was to characterize the time-course of changes occurring within cortical and trabecular bone of the femur, tibia, and ankle joint of arthritic mice using μCT analysis. Further, we examined the ankle joint for the presence of nerve sprouting of sensory and sympathetic nerve fibers as it has been shown that this sprouting may contribute to ongoing pain in other musculoskeletal diseases.

Methods: Using the K/BxN serum transfer model of arthritis, we have shown that male C75Bl/6 mice develop clinical signs of arthritis accompanied by a robust tactile allodynia. Importantly, male, but not female mice, show tactile allodynia persisting beyond the resolution of inflammation. For this reason, bones of arthritic male and female mice were analyzed on days 0, 10, and 28. We quantified arthritis-induced changes in the femur, tibia, talus, and calcaneus. For trabecular bone, we determined trabecular bone mineral density (tBMD), percent bone volume (BV/TV), trabecular thickness (Tb.Th), trabecular number (Tb.N), trabecular separation (Tb.Sp), the degree of anisotropy (DA); while for cortical bone, BMD (cBMD), cortical area (Ct.Ar), and cortical thickness (Ct.Th) were examined. Following μCT analyses, bones were decalcified, processed for immunohistochemistry as frozen sections and immunostained with anti-CGRP (peptidergic C-fibers), anti-NF200 (myelinated sensory fibers), anti-GAP43 (sprouted nerve fibers), anti-TH (sympathetic nerve fibers), and anti-CD68 (macrophages).

Results: In the distal femur and proximal tibia, arthritic mice showed decreased tBMD, BV/TV, Tb.N at day 28 as compared to age-matched naive mice. There were no major changes in the cortical bone of the femoral or tibial mid-diaphyses. In the talus, there were no significant changes in any trabecular bone parameters in female or male arthritic mice as compared to naïve. In the calcaneus, tBMD and BV/TV are significantly decreased in male and female arthritic animals as compared to naïve, with females showing greater bone loss at day 28. While there was no difference in Tb.Th or Tb.Sp, we found a significant decrease in Tb.N over time in arthritic females. In addition to these changes in bone parameters, a semi-quantitative analysis revealed greater density of CGRP+, TH+, NF200+, and GAP43+ innervation in ankles of male mice at day 28, relative to female animals.

Conclusion: Together, these results suggest that K/BxN serum transfer-induced arthritis results in sex-dependent changes in tactile allodynia, which are reflected in underlying differences in peripheral sensory innervation, but not bone loss.

Disclosure: S. Woller, None; **A. Martinez-Martinez**, None; **J. M. Jimenez-Andrade**, None; **T. Yaksh**, None; **M. Corr**, None.

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Abstract Number: 376

Initial Validation of the Patient Reported Outcomes Measurement Information System Pediatric Pain Intensity Scale in Juvenile Idiopathic Arthritis, Juvenile Fibromyalgia and Sickle Cell Disease

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Background/Purpose: The Patient Reported Outcomes Measurement Information System(PROMIS) is a publicly available assessment system offering multiple measures to assess physical, mental and social health. PROMIS measures are developed based on a rigorous mixed-methods approach, and modern measurement methods, including use of item response theory (IRT). Measures are developed for use across a spectrum of chronic conditions. The purpose of the project is development and calibation of instruments to measure aspects of pain in children as part of PROMIS. PROMIS Pediatric Pain Interference, Pain Behavior and Pain Quality measures were previously developed. The primary objective of this study is to evaluate the dimensionality and validity of the PROMIS Pediatric Pain Intensity Scale.

Methods: The initial pool of the pediatric PROMIS pain related items were developed based on literature reviews, clinician interviews, and qualitative research with patients with pain. In addition to the three item banks previously developed to assess various dimensions of pain in children, four items were identified as pain intensity items measuring worst pain, usual pain, average pain and current pain on a 5-point likert scale. We conducted confirmatory factor analysis (CFA) to assess dimensionality of these 4 items and looked correlations of the pain intensity scale with other pediatric PROMIS pain scales (pain interference and pain behavior), as well as a legacy pain intensity numeric rating scale.

Results: The sample populations included pediatric patients with juvenile idiopathic arthritis, fibromyalgia, and sickle cell disease, ages 8 to 18 recruited from outpatient hospital clinics in Ohio, Pennsylvania, and Georgia for a total sample size of N = 447. CFA shows good fit of the four items to a unidimensional model: comparative fix index (CFI)=1.00, Tucker-Lewis index (TLI)=1.00, and root mean square error of approximation (RMSEA)=0.013. The IRT slope parameters of the four items were 1.55, 2.06, 1.51, and 1.15. The category threshold parameters ranged from -2.92 to 2.97. Correlation with legacy pain intensity numeric rating scale is r = .94. Correlations with PROMIS pain interference short form is r = .75 and with PROMIS pain behavior short form is r = .74. “Usual” and “average” pain items provided similar information. Based on cognitive debriefing with study participants, the item worded with reference to “usual pain” was preferred over the“average pain” item. The measure perfomed well after exclusion of the “average pain” item, yielding a three item scale.

Conclusion: The pediatric PROMIS pain intensity scale provides a short, three-item unidimensional measure of pain and demonstrates convergent validity with other PROMIS pain measures. The pediatric PROMIS pain intensity scale provides a measure of self-reported pain intensity that can be used in pediatric clinical research or clinical practice settings.

Disclosure: E. Morgan, None; **C. Mara**, None; **B. Huang**, None; **A. Carle**, None; **K. Goldschneider**, None; **C. Dampier**, None; **S. Kashikar-Zuck**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/initial-validation-of-the-patient-reported-outcomes-measurement-information-system-pediatric-pain-intensity-scale-in-juvenile-idiopathic-arthritis-juvenile-fibromyalgia-and-sickle-cell-disease

Abstract Number: 377

Pain and Quality of Life Profiles in Colombian Patients with Rheumatoid Arthritis: A Mixed Cluster Analysis

Juan Manuel Cotte[1], Nicolás Molano-González[2], Deisy Hernández-Parra[3], Yenifer Delgado-Scarpetta[3], Adriana Rojas-Villarraga[2], Juan-Manuel Anaya[1] and Ricardo Pineda-Tamayo[3], [1]Center for Autoimmune Diseases Research (CREA). School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia., Bogotá, Colombia, [2]Center for Autoimmune Diseases Research (CREA). School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia., Bogotá D.C., Colombia, [3]Artmédica IPS, Medellin, Colombia, Medellin, Colombia
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

ABSTRACT

Background/Purpose: Among the symptoms of Rheumatoid Arthritis (RA), pain is often regarded as a critical factor related to quality of life (QoL) by patients, and the fact of having pain confers subjects with RA a 5 year mortality twice as high when compared with RA patients without pain (1,2). There are different causes of pain in RA patients, and the level of compromise in the QoL may vary among them too (3). The aim of this study is to identify different pain profiles in association to the QoL in Colombian RA patients.

Methods: This was a cross-sectional study involving 1395 patients with diagnosis of RA, all of whom had a registered EuroQoL, MDHAQ, CDAI and DAS-28 at the time of their involvement to a rheumatology specialized center, and a complete patient inclusion form which included data on disease characteristics, comorbid conditions and current treatment. A mixed-cluster analysis based on multivariate descriptive methods such as multiple factor analysis and k-means cluster analysis was done to summarize sets of related variables with strong associations and common clinical context. The variables used for the cluster analysis were the five dimensions of the EuroQoL, the Visual Analog Scale of the EuroQoL and the EuroQoL result (4).

Results: Four clusters were identified with varying degrees of pain and compromise on QoL (see figure 1). Due to the fact that cluster 2 was characterized by more severe pain and discomfort without severe compromise in the other dimensions, it was used as the reference group. When compared with the patients with the least compromise of their QoL as well as pain (cluster 4) this patients were identified to be older, whit a higher proportion of females, and they had a lower education level. Regarding treatment, this patients used significantly less methotrexate, and significantly more glucocorticoids and biologic therapy. When evaluating comorbid conditions, Cluster 2 had significantly more Fibromyalgia, Cardiovascular Disease and Diabetes, and they also had a higher CDAI and DAS-28. Finally, regarding disability, we identified that cluster 2, in spite of its association with severe pain, was the one with the second best disability profile according to the MDHAQ. All the results mentioned above were statistically significant.

Conclusion: In spite of the fact that the results of a study come from a single population, they underlie the importance of identifying different pain profiles in RA patients which may benefit from specific therapies. These findings also highlight the importance of personalized medicine, which may translate into better outcomes for our patients.

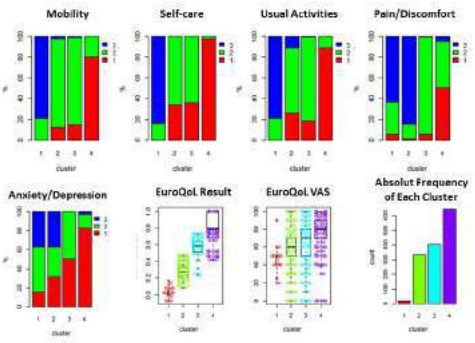

Figure 1. *Profile of each group with respect to the original variables used to build the groups.* Red bars represent the percentage of individuals in each cluster with no compromise for the given dimension, green the percentage of subjects with moderate compromise and blue the percentage of subjects with severe compromise.

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Disclosure: J. M. Cotte, None; **N. Molano-González**, None; **D. Hernández-Parra**, None; **Y. Delgado-Scarpetta**, None; **A. Rojas-Villarraga**, None; **J. M. Anaya**, None; **R. Pineda-Tamayo**, None.

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Abstract Number: 378

Effects of a Natural Product Containing Specialized Pro-Resolving Mediators in Subjects with OA, RA, or Other Chronic Inflammatory Conditions in a Multi-Clinic Case Series

Annalouise O'Connor[1], Sara Le Brun-Blashka[2], Kirti Salunkhe[2], Jyh-Lurn Chang[2] and John Troup[2], [1]R&D, Metagenics, Inc., Gig Harbor, WA, [2]Metagenics, Inc., Gig Harbor, WA

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Session Date: Sunday, November 13, 2016

Session Title: Pain – Clinical Aspects - ARHP Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The inflammatory response has an initiation phase and a resolution phase. Ideally, inflammation leads to complete resolution that enables tissue healing and a return to previous healthy condition. However, if it is left unresolved, the surrounding tissues can be damaged over time. Chronic unresolved inflammation has been linked to many chronic diseases, and clinically often manifests as pain in joint-related conditions. During the resolution phase, specialized pro-resolving mediators (SPMs) are produced from polyunsaturated fatty acids at the affected tissue site, orchestrating the resolution activities and expediting the return to homeostasis. Some individuals may not produce desirable levels of SPMs —due to lifestyle behaviors, dietary choices, age, or health status—and the inflammatory response is left unresolved. The objective of this study was to observe the effect of a natural product (LM-O3) containing standardized SPMs on select inflammatory biomarkers and on overall well-being assessed by multiple questionnaires in subjects with OA, RA, or other chronic inflammatory conditions.

Methods: The 8-week, IRB-approved, open-label case series was conducted at 6 clinical sites from where participants were recruited. Main inclusion criteria included individuals with (1) chronic pain lasting ≥ 3 months, (2) OA, RA or other joint-related conditions, or (3) fibromyalgia. LM-O3 contained fractionated lipid concentrate from natural sources standardized to 2 SPMs (18-hydroxyeicosapentaenoic acid and 17-hydroxydocosahexaenoic acid). After baseline assessment, all participants consumed 750 mg of LM-O3 as 6 softgels once daily taken with a lipid-containing meal. After Week 4, the dose of LM-O3 was titrated up to 1000 mg as 8 softgels once daily. Participants returned to the clinic at Weeks 4 and 8 for clinical evaluation (biochemical measurements, clinical symptomology and quality of life assessments relevant to clinical condition, compliance, and adverse events). Changes from baseline to Week 4 and Week 8 were analyzed separately using two-sided paired t-test.

Results: Thirty-four participants completed the study. Levels of hs-CRP were significantly reduced from 9.2±15.8 mg/L (mean±SD) at baseline to 5.2±9.5 mg/L at Week 4 (p=0.031) and to 6.3±10.6 mg/L at Week 8 (p=0.007). PGE_2 levels were also significantly reduced from 590.6±802.0 pg/mL at baseline to 350.6±334.3 pg/mL at Week 8 (p=0.039). Total scores on the Brief Pain Inventory, the American Chronic Pain Association Quality of Life Scale, and other subject-reported scales reflective of clinical diagnoses were significantly reduced at Week 4 and 8 compared with baseline. Results at the Week 4 and 8 assessments were comparable. No serious adverse events were reported. A subgroup analysis of 14 subjects diagnosed with OA or RA showed comparable results, including reduced pain and improved activities of daily living.

Conclusion: A SPM-containing natural product exerted beneficial effects on inflammatory biomarkers and reduced the severity of pain as well as the impact of pain on activities of daily function in subjects with health conditions associated with chronic unresolved inflammation.

Disclosure: A. O'Connor, Metagenics, 3; **S. Le Brun-Blashka**, Metagenics, 3; **K. Salunkhe**, Metagenics, 3; **J. L. Chang**, Metagenics, 3; **J. Troup**, Metagenics, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/effects-of-a-natural-product-containing-specialized-pro-resolving-mediators-in-subjects-with-oa-ra-or-other-chronic-inflammatory-conditions-in-a-multi-clinic-case-series

Abstract Number: 379

Pain Catastrophizing Decreases in RA Patients Starting, Adding or Switching a DMARD

Ezra Cohen[1], Alyssa Wohlfahrt[2], Robert R. Edwards[3], Clifton Bingham III[4], Marcy Bolster[5], Larry W. Moreland[6], Tuhina Neogi[7], Kristine Phillips[8] and Yvonne C. Lee[9], [1]Boston Children's Hospital, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [3]Anesthesiology, Brigham & Womens Hospital, Chestnut Hill, MA, [4]Divisions of Rheumatology and Allergy, Department of Medicine, Johns Hopkins University, Johns Hopkins University, Baltimore, MD, [5]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [6]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [7]Clinical Epidemiology, Boston University School of Medicine, Boston, MA, [8]Rheumatology, University of Michigan, Ann Arbor, MI, [9]Rheumatology Immunology & Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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Session Time: 9:00AM-11:00AM

Background/Purpose: In individuals with RA, catastrophizing is associated with poor pain outcomes. It is not known whether catastrophizing can be altered by treating RA with DMARDs, or if pain can predict changes in catastrophizing associated with DMARD treatment. The objective of this analysis was to identify changes in catastrophizing associated with DMARD therapy and to examine associations between baseline pain and subsequent catastrophizing levels. We also analyzed the opposite relationship to determine if baseline catastrophizing is associated with future pain.

Methods: We examined baseline (before DMARD initiation) and follow-up data (12-24 weeks after DMARD initiation) from the first 115 subjects in a prospective cohort of RA patients with active disease starting or switching DMARDs. Pain was measured by the Numeric Rating Scale (NRS) from 0-10, and pain catastrophizing was measured by the Pain Catastrophizing Scale from 0-52. We used paired t-tests to determine if pain catastrophizing changed over 12-weeks of DMARD treatment. Multivariable linear regression models were used to examine the association between: a) baseline pain catastrophizing as the independent variable and 12-week pain intensity as the outcome, and b) baseline pain intensity as the independent variable and 12-week pain catastrophizing as the outcome. These models controlled for age, gender, disease duration, swollen joint count and depression. In addition, baseline pain intensity was included as a covariate in the model examining the relationship between baseline catastrophizing and 12-week pain, and baseline catastrophizing was included in the model examining the relationship between baseline pain and 12-week catastrophizing.

Results: In this cohort of RA patients, median age was 54.9 years, and 78.1% were women. 38.8% started a non-biologic DMARD, and 61.2% started a biologic DMARD. Both pain and catastrophizing decreased after 12-weeks, from 5 to 3 on a 10-pt NRS (P <0.0001) and from 16 to 10 on the 52-point Pain Catastrophizing Scale (P <0.0001). High baseline pain was associated with greater catastrophizing at 12 weeks (β=0.92, p=0.04) (Figure). Baseline catastrophizing was not associated with pain at 12 weeks (β=0.02, p=0.36).

Conclusion: These findings demonstrate that after initiating a new DMARD, pain catastrophizing decreases in RA patients, suggesting that catastrophizing may have state-like properties, which can be altered by DMARD treatment. However,

despite DMARD treatment, individuals with high baseline pain had higher pain catastrophizing at 12-weeks, compared to those with low baseline pain. These findings suggest that aggressive initial treatment of pain may be useful in preventing future catastrophizing.

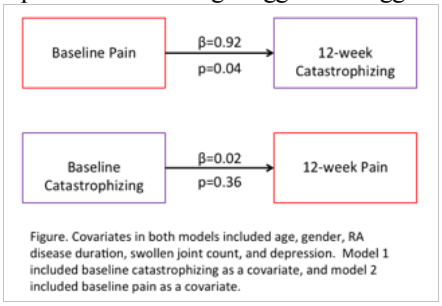

Figure. Covariates in both models included age, gender, RA disease duration, swollen joint count, and depression. Model 1 included baseline catastrophizing as a covariate, and model 2 included baseline pain as a covariate.

Disclosure: E. Cohen, None; **A. Wohlfahrt**, None; **R. R. Edwards**, None; **C. Bingham III**, None; **M. Bolster**, Johnson and Johnson, 1,Eli Lilly and Company, 2,RRF Amgen Fellowship Award, 9; **L. W. Moreland**, None; **T. Neogi**, None; **K. Phillips**, None; **Y. C. Lee**, None.

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Abstract Number: 380

Linear Discriminant Analysis of Cultured Fibroblast-like Synoviocytes Identifies 6 Candidate Genes Which Predict Extended Course in Juvenile Idiopathic Arthritis

AnneMarie Brescia[1], Megan Simonds[2], Suzanne McCahan[3], Tim Bunnell[3], Kathleen E. Sullivan[4] and Carlos D. Rosé[1], [1]Pediatric Rheumatology, Thomas Jefferson University/ AI duPont Hospital for Children, Wilmington, DE, [2]Nemours, Nemours Biomedical Research, Wilmington, DE, [3]Nemours Biomedical Research, Wilmington, DE, [4]Allergy Immunology, The Children's Hospital of Philadelphia, Philadelphia, PA

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster I: Juvenile Idiopathic Arthritis, Uveitis

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

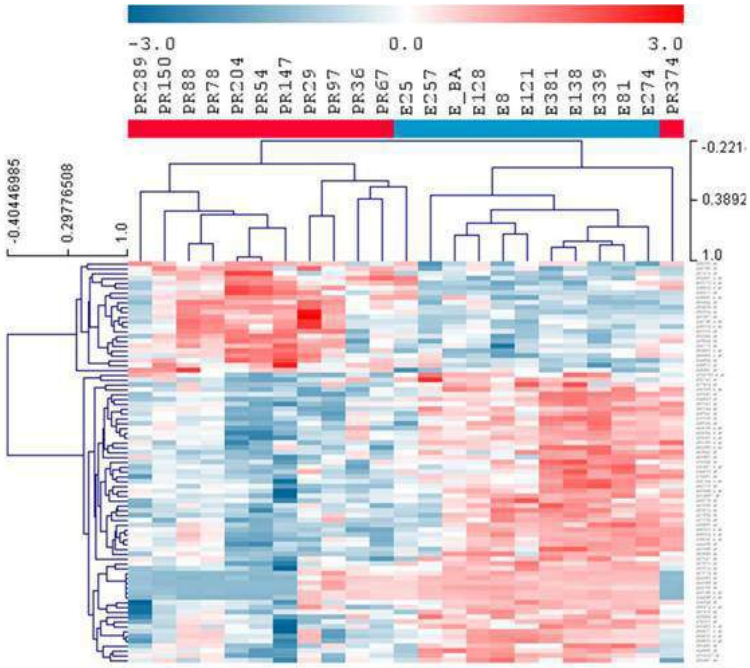
Background/Purpose: The goal of this project is the identification of informative synovial biomarkers to predict which children with oligoarticular juvenile idiopathic arthritis (JIA) will have a persistent course, with no more than 4 involved joints, vs those who will have an extended course, with a cumulative total of ≥5 affected joints after the first 6 months of disease.

Methods: As part of a separate ongoing IRB approved protocol, remnant synovial fluid was obtained from patients undergoing medically indicated arthrocenteses. All patients satisfied ACR classification criteria for JIA. Using our clinical database, JIA samples were separated into two groups: (1) oligoarticular JIA with persistent course (PR), (2) oligoarticular JIA with extended course (E). All samples were from steroid-naïve joints and most samples from E were obtained prior to extension. Primary cultures of fibroblast-like synoviocytes (FLS) were established for each subject. RNA from cultured passage 3-6 FLS were isolated, amplified and hybridized to Affymetrix Human GeneChips using the Affymetrix protocol. Expression values were determined with GC-RMA. Global gene expression of FLS from 12 PR and 11 E samples were obtained. Data was filtered for log2 expression >4 in all samples of either E or PR, then for absolute value of 1.5-fold change. Bioconductor package Linear Models for Microarray Analysis (LIMMA) revealed 83 probesets with statistically significant differential expression between E vs PR FLS (7% false discovery rate), shown in heatmap.

Results: Hierarchical clustering of the 83 probesets revealed samples from the different courses cluster together, with most of the PR to the left of the heatmap. Importantly, the all of the E were taken from the very first sample available,

which preceded extension in the majority of patients, highlighting that there are detectible differences in the gene expression of the FLS early in the course in the patients whose disease is destined to extend. Of these 83 probesets, 9 corresponded to genes with secreted proteins. We performed mathematical modeling with linear discriminant analysis (LDA) on these 9 genes to reveal 6 genes (KLHL13, MAMLD1, ANKRD44, CD14, HSPBAP1, and MBP) which could correctly predict group, E or PR, 100% of the time using leave-one-out cross validation. ELISA was used to confirm expression of these secreted proteins in synovial fluids.

Conclusion: We were able to demonstrate differential gene expression in FLS from JIA patients who remained PR vs those who were destined to extend, demonstrating detectible difference early in disease which may be useful for prediction. The differentially expressed genes, especially for secreted proteins, provide a starting point for development of biomarkers to distinguish between PR and E JIA using aspirated synovial fluid.



Disclosure: A. Brescia, None; **M. Simonds**, None; **S. McCahan**, None; **T. Bunnell**, None; **K. E. Sullivan**, None; **C. D. Rosé**, None.

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Calprotectin As a Multipotent Biomarker in Juvenile Idiopathic Arthritis

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Background/Purpose: Lack of specific diagnostic, prognostic or response to treatment markers in juvenile idiopathic arthritis (JIA) leads to study new potential markers, as serum calprotectin (S100A8/A9). This heterodimer, part of the S100 protein family, is directly released by activated leukocytes during inflammation, serves as an agonist of TLR4, activates endothelial cells and stimulates transendothelial migration of phagocytes at the site of inflammation. Increased serum calprotectin levels have been described in many inflammatory chronic diseases.To assess the use of serum calprotectin (sCal) as a marker of disease activity and its monitoring, as a classification and prognosis tool of response to treatment or risk of flares in patients with JIA.

Methods: Ninety-five patients with JIA from the CAP48 multicentric cohort were included in this study (mean age ± SEM: 14,3 ± 0,6 years; F/M sex ratio: 1,4/1; mean disease duration: 2,1 ± 0,6 and 5,0 ± 1,4 years for the newly-diagnosed and well-established JIA respectively), as well as 11 healthy controls (mean age ± SEM: 26,2 ± 0,2; F/M sex ratio: 1,7/1) obtained from the biobank of the Rheumatology department of the Erasme hospital. Enzyme-linked immunosorbent assay (ELISA) method was used to quantify sCal, with a commercial kit. This ELISA had first been adjusted in order to assess the quality of the detection method in sera matrix with spiking recoveries and to elaborate internal positive controls with sera of patients with active Crohn's disease.

Results: Patients with inactive JIA had a 4-fold increased level of sCal (6.555 ng/mL) compared to healthy controls (1.737 ng/mL), while patients with active JIA had themselves a 2-fold increased level of sCal (11.403 ng/mL) compared to patients with inactive disease. sCal was found to be slightly correlated to the Tender Joint Count and CHAQ (r/p = 0,2/0,04 and 0,3/0,006 respectively), moderately with the CRP (r/p = 0,2/0,05 and 0,5/0,04 for abnormal values) and strongly with the ESR (r/p = 0,8/0,0003. As for the CRP, sCal could differentiate forms with active oligoarthritis (persistent or extended oligoarthritis or enthesitis-related arthritis) (7.515 ng/mL) from polyarthritis (14.714 ng/mL) or systemic forms (26.976 ng/mL). However, sCal brought an added value compared to the CRP as a prognosis marker. Indeed, patients with active disease had higher serum levels if they were going to be future good-responders (pediACR> 30) at 6 months following the sample test, while patients with inactive disease had higher serum levels if they were going to flare up to 3 to 9 months following the sample test.

Conclusion: This study confirms potential uses of serum calprotectin as a prognosis marker of response to treatment and risk of flares. However, larger studies designed to evaluate sCal in JIA are needed. Attention should also be called in future studies to assess the possible role of sCal in the differential diagnosis of fevers of unknown origin in children.

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Tumor Necrosis Factor-α -308 a/G Gene Polymorphism in Children with Juvenile Idiopathic Arthritis: Relation to Disease Activity, Damage and Disability

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood and an important cause of disability. Its cause remains unknown, but likely includes complex interactions between genes and environmental exposures resulting in dysregulation of the immune system. TNF-α is a cytokine with an important role in inflammation and immune function. Several single nucleotide polymorphisms (SNPs) have been identified within the region of the TNF-α gene but only very small minority have proven functional consequences and were associated with JIA susceptibility. The aim of this work was to evaluate the clinical significance of serum levels of tumor necrosis factor alpha (TNFα) and -308 A/G promoter polymorphism in JIA patients and find any association to the subsets, clinical and laboratory features, disease activity and damage as well as functional disability.

Methods: Forty-eight JIA children and 30 controls were included in the present study. Juvenile arthritis disease activity score in 27 joints (JADAS-27) was calculated, juvenile arthritis damage index (JADI) assessed and Childhood Health Assessment Questionnaire (CHAQ) to measure the functional status. *Serum TNF-α* was assayed by ELISA and *gene (-308) promoter polymorphism* determined by polymerase chain reaction.

Results: The 48 JIA children (mean age: 11.5±2.8 years) were 13 systemic, 17 oligoarticular and 18 polyarticular onset. The serum TNF-α was significantly higher in patients (90.4±6.3 ng/ml) compared to control (3.5±2.6 ng/ml) ($p<0.0001$) with a tendency to be higher in the polyarticular subtype. All controls had TNF-α -308GG alleles. The frequency of GG genotype tended to be higher in systemic onset compared to oligoarticular and polyarticular subtypes. The serum TNF-α significantly correlated with JADAS-27 ($r=0.32, p=0.03$) and CHAQ ($r=0.37, p=0.01$) and negatively with the presence of GG alleles ($r=-0.48, p=0.001$). The GG alleles were significantly negatively associated with C-reactive protein ($r=-0.32, p=0.03$) with a tendency to negatively correlate with JADAS-27, CHAQ and JADI-extrarticular ($r=-0.28, p=0.06$; $r=-0.25, p=0.09$ and $r=-0.25, p=0.09$ respectively).

Conclusion: There is evidence of a possible influence of the −308 SNP promoter position on the production of TNF-*α*, the severity of JIA which may consequently influence the response to anti-TNF-*α* treatment.

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Potential Biomarkers of Disease Activity in Juvenile Idiopathic Arthritis – Data from the Portuguese Register, Reuma.Pt

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Background/Purpose: The classical inflammatory markers, C-reactive protein and erythrocyte sedimentation rate often do not adequately reflect JIA disease activity. Our objective was to assess the serum levels of DKK1, OPG, SOST, RANKL, greline, BAFF, leptine, APRIL, ACPA, CTD, RF IgA and IgM, INFy, IL1β, IL6, IL10, IL17 and TNF in patients with JIA, and detect their relation to disease activity.

Methods: Serum levels of selected cytokines were determined by ELISA in JIA patients registered in Reuma.pt. The Juvenile Arthritis Disease Activity score in 27 joints (JADAS27) and Childhood Health Assessment Questionnaire (CHAQ) were calculated. Multivariate linear regression was used for analyzing the relation between the potential serum biomarkers levels and JADAS27 and CHAQ, adjusting for gender, body mass index, age, disease duration and JIA categories.

Results: 281 patients, 66% female, mean age 17.3±10 years and mean disease duration 10.9±8.7 years. Ninety-eight were persistent oligoarticular (OligoP), 48 extended oligoarticular (OligoE), 45 polyarticular RF negative (poly RF-), 26 Poly RF+, 22 systemic, 28 enthesitis-related arthritis (ERA) and 14 psoriatic arthritis. The global analysis including all JIA patients revealed that APRIL, RF IgA and IL17 levels were correlated with JADAS27 (β=0.14, p=0.02; β=0.12, p=0.006; β=0.36, p=0.014; respectively) and IL6 was inversely correlated with JADAS27 (β=-0.06, p=0.03). Regarding CHAQ, we have found that APRIL, INFγ and TNF were correlated with CHAQ (β=0.01, p=0.001; β=0.003, p=0.02; β=0.003, p=0.04; respectively). In the separate analysis by JIA category, in OligoP, RF IgM, INFy, IL1β, and TNF were correlated with CHAQ (β=0.007, p=0.005; β=0.004, p=0.019; β=0.008, p=0.033; β=0.007, p=0.038; respectively), and, on the other hand, IL10 was inversely correlated with CHAQ (β=-0.007, p=0.023). In OligoE, RF IgA levels were correlated with JADAS27 and CHAQ (β=0.91, p=0.016; β=0.05, p=0.037). In patients with Poly RF+ the serum levels of OPG and ACPA were correlated with JADAS27 (β=0.06, p=0.024; β=0.03, p=0.05), and OPG was also correlated with CHAQ (β=0.004, p=0.032). In PolyRF- patients, DKK1 was correlated with JADAS27 (β=0.014, p=0.047), and serum levels of APRIL and RF IgM were associated with CHAQ (β=0.03, p<0.001; β=0.03, p<0.001). In systemic JIA, CTD lev els were correlated with JADAS27 (β=82.67, p=0.002), and DKK1 was inversely associated with JADAS27 (β=-0.009, p=0.035). In ERA category we have found leptin was correlated with JADAS27 and CHAQ (β=0.9, p=0.005; β=0.05,

p=0.029), and ACPA with CHAQ (β=0.005, p=0.031). Lastly, for psoriatic arthritis patients, APRIL and RF IgA levels were correlated with CHAQ (β=0.17, p=0.046; β=0.13, p=0.008), and DKK1 and SOST were inversely correlated with CHAQ (β=-0.0003, p=0.037; β=-0.001, p=0.030).

Conclusion: Our data underline the heterogeneity of different juvenile idiopathic arthritis categories. Interestingly, we have identified potential biomarkers of disease activity/functional status in JIA categories. Larger studies are needed in order to validate these results.

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WITHDRAWN

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Safety of Adalimumab in Pediatric Patients with Polyarticular Juvenile Idiopathic Arthritis, Enthesitis-Related Arthritis, Psoriasis, and Crohn's Disease

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Background/Purpose: Adalimumab (ADA) is a tumor necrosis factor (TNF) inhibitor used for treatment of chronic immune diseases. The safety of ADA treatment in pediatric patients (pts) is particularly important since prolonged treatment for these conditions is often required. The objective of this study is to evaluate the safety of ADA, alone or in combination with concomitant therapy, in pediatric pts with polyarticular juvenile idiopathic arthritis (pJIA), enthesitis-related arthritis (ERA), psoriasis (Ps), and Crohn's disease (CD).

Methods: Safety data from 6 clinical trials and their open-label extension studies were analyzed. Pts treated for pJIA (NCT00048542, NCT00775437, and NCT00690573) and ERA (NCT01166282 [interim week-52 data]) received ADA 24 mg/m^2 body surface area every other week (eow) or 20 mg eow (<30 kg) to 40 mg eow (≥30 kg). Pediatric pts treated for Ps (NCT01251614) received ADA 0.4 mg/kg (up to 20 mg) or 0.8 mg/kg (up to 40 mg) at week 0, then eow from week 1. Pediatric pts treated for CD (NCT00409682) received open-label ADA induction therapy (160 mg and 80 mg at weeks 0 and 2, respectively, if ≥40 kg; 80 mg and 40 mg if <40 kg), followed by double-blind maintenance dosing (high dose: 40

mg eow if ≥40 kg or 20 mg eow if <40 kg at week 4; low dose: 20 mg eow if ≥40 kg or 10 mg eow if <40 kg at week 4); weekly dosing was allowed for disease flare at week 12 or later; pts received high-dose eow or weekly ADA during an open-label extension (NCT00686374). Events (E) per 100 pt-years (PY) were calculated using adverse events (AEs) reported after the first ADA study dose through 70 days after the last study dose.

Results: The analysis included 577 pediatric pts, representing 1440.7 PY of ADA exposure **(Table)**. Over 90% of pts across indications reported treatment-emergent AEs. Common AEs were headache (13.6, 46.9, and 23.4 E/100 PY for pJIA and ERA, Ps, and CD, respectively), nasopharyngitis (12.4, 58.4, and 15.2 E/100 PY, respectively), and upper respiratory tract infection (30.2, 24.7, and 14.8 E/100 PY, respectively). The rates of serious AEs (E/100 PY) were 13.5 for pts with pJIA and ERA, 7.4 for pts with Ps, and 32.2 for pts with CD. One death was reported from an accidental fall (pt with Ps). There were no reports of malignancies, demyelinating disorders, pulmonary embolism, reactivation of hepatitis B, Stevens-Johnson syndrome, or erythema multiforme.

Conclusion: The safety profile of ADA in pediatric pts with pJIA, ERA, Ps, or CD was similar across indications, and no new safety signals specific to the pediatric population were identified. **Table. Treatment-Emergent Adverse Events Occurring in ≥1% of Patients in Pediatric Adalimumab Clinical Trials**

	pJIA and ERA N=274 Exposure, PYs=806.9		**Pediatric Ps N=111 Exposure, PYs=121.5**		**Pediatric CD N=192 Exposure, PYs=512.3**	
Treatment-Emergent Event	**N (%)**	**Events (Events/100 PY)**	**N (%)**	**Events (Events/100 PY)**	**N (%)**	**Events (Events/100 PY)**
Any AE	267 (97.4)	4239 (525.3)	100 (90.1)	630 (518.5)	189 (98.4)	2902 (566.5)
Serious AE	67 (24.5)	109 (13.5)	8 (7.2)	9 (7.4)	92 (47.9)	165 (32.2)
AE leading to discontinuation of ADA	24 (8.8)	31 (3.8)	3 (2.7)	3 (2.5)	61 (31.8)	77 (15.0)
Severe AE	45 (16.4)	67 (8.3)	17 (15.3)	24 (19.8)	67 (34.9)	114 (22.3)
Drug-related† AE	200 (73.0)	1536 (190.4)	48 (43.2)	176 (144.9)	115 (59.9)	621 (121.2)
Infection	224 (81.8)	1216 (150.7)	82 (73.9)	205 (168.7)	145 (75.5)	676 (132.0)
Serious infection	21 (7.7)	22 (2.7)	1 (0.9)	1 (0.8)	25 (13.0)	34 (6.6)
Opportunistic infection (excluding tuberculosis and oral candidiasis)	0	0	0	0	4 (2.1)	4 (0.8)
Oral candidiasis	2 (0.7)	2 (0.2)	0	0	4 (2.1)	7 (1.4)
Tuberculosis	3 (1.1)	3 (0.4)	2 (1.8)	2 (1.6)	1 (0.5)	1 (0.2)
Acti ve	1 (0.4)	1 (0.1)	0	0	0	0
Latent	2 (0.7)	2 (0.2)	2 (1.8)	2 (1.6)	1 (0.5)	1 (0.2)
Parasitic infection	3 (1.1)	5 (0.6)	0	0	1 (0.5)	1 (0.2)
Allergic reaction‡,§	41 (15.0)	62 (7.7)	7 (6.3)	9 (7.4)	19 (9.9)	25 (4.9)
Intestinal perforation	0	0	0	0	3 (1.6)	3 (0.6)
Intestinal stricture	—	—	—	—	6 (3.1)	6 (1.2)
Worsening/new onset of psoriasis‡	5 (1.8)	6 (0.7)	10 (9.0)	11 (9.1)	6 (3.1)	7 (1.4)
Hematologic disorders‖	10 (3.6)	16 (2.0)	2 (1.8)	3 (2.5)	27 (14.1)	36 (7.0)
Liver event¶	5 (1.8)	5 (0.6)	0	0	1 (0.5)	1 (0.2)
Injection site reaction‡	101 (36.9)	844 (104.6)	11 (9.9)	17 (14.0)	42 (21.9)	104 (20.3)

—, analyzed only in the CD population; ADA, adalimumab; AE, adverse event; CD, Crohn's disease; ERA, enthesitis-related arthritis; pJIA, polyarticular juvenile idiopathic arthritis; Ps, psoriasis; PYs, patient-years. *The ERA study includes interim week-52 data. †Investigator assessed as possibly or probably related to study drug. ‡None were serious. §Events included hypersensitivity (n=36), urticaria (n=27), asthma (n=16), eye pruritus (n=3), rash (n=3), bronchospasm (n=2), generalized pruritus (n=2), injection site urticaria (n=2), drug hypersensitivity (n=1), eyelid edema (n=1), generalized rash (n=1), and wheezing (n=1). One event of anaphylactic reaction was reported as an immune system disorder. ‖Events included anemia (n=24), leukopenia (n=17), neutropenia (n=10), lymphopenia (n=1), macrocytic anemia (n=1), microcytic anemia (n=1), and pancytopenia (n=1); 10 events were serious (leukopenia, n=2 and neutropenia, n=2 [JIA]; anemia, n=6 [CD]). ¶Events included liver disorder (n=3), hepatotoxicity (n=1), and hepatocellular injury (n=1) in the pJIA and ERA group, and 1 serious event of hepatitis in the CD group.

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Long-Term Efficacy and Safety of Adalimumab in Pediatric Patients with Enthesitis Related Arthritis

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster I: Juvenile Idiopathic Arthritis, Uveitis

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Enthesitis-related arthritis (ERA) is a JIA category primarily affecting entheses and peripheral joints but can involve the axial skeleton. Disease activity and structural change can adversely affect long-term physical function and quality of life of ERA patients (pts)**.** Adalimumab (ADA) has been previously demonstrated to be effective in children with polyarticular JIA and ERA. Objective of this study is to evaluate the persistence of efficacy and long-term safety of ADA compared to placebo (PBO) in children and adolescents with ERA.

Methods: This is a phase 3, multicenter, randomized, double-blind (DB) study in ERA pts aged ≥6-<18 years (yr) at baseline (BL). Methods have been previously described. Pts were randomized 2:1 to receive blinded ADA (24 mg/m^{2}BSA up to 40 mg every other week (wk) [eow]) or PBO for 12 wks followed by open-label (OL) ADA eow for up to an additional 192 wks. Primary endpoint was % change from BL in number of active joints with arthritis (AJC) at wk 12. Secondary variables assessed included enthesitis count (EC), tender (TJC) and swollen joint (SJC) counts, and American College of Rheumatology (ACR) Pediatric (Pedi) 30/50/70 responses. Kaplan Meier analysis was used to determine time to achieve SJC=0, TJC=0, and EC=0 from time of first ADA injection.

Results are summarized through 156 wks of treatment for efficacy and 204 wks for safety. Safety was assessed in terms of adverse events (AE). Results: 46 pts were randomized (ADA, n=31; PBO, n=15). No pts discontinued during DB period; 7 pts early escaped to OL ADA. 17 pts discontinued from OL period prior to wk 204 including 4 pts achieving remission. Percentage change from BL at wk 12 in AJC was greater in ADA group vs. PBO (-62.6±59.5 vs -11.6±100.5, *P*=0.039) with response maintained with continued ADA therapy through 156 wks (-88.3±27.7). During treatment with ADA 95.7%, 89.1%, and 89.1% of pts achieved SJC=0, TJC=0 and, EC=0, respectively. Median time from first dose of ADA to achieving SJC=0, TJC=0, and EC=0 was 41, 108, and 56 days, respectively. At wk 12 ACR Pedi70 was statistically significant in favor of ADA while EC, TJC, SJC, and ACR Pedi30/50 showed numerically greater, but not statistically significant improvement in favor of ADA with responses maintained through wk 156. During DB period AE incidence rates were similar [ADA/PBO (%)]: any AE (67.7/53.3), serious AE (3.2/0), and infectious AEs (29.0/20.0). Among pts who received at least 1 dose of ADA, any AE, serious AEs, infectious AEs, and serious infections were reported in 100%, 21.7%, 89.1%, and 8.7% respectively. Ten pts reported a total of 19 serious AEs through 204 wks of treatment. No deaths or malignancies were reported.

Conclusion: ADA reduced the signs and symptoms of ERA at wk 12 and efficacy was sustained through 156 wks. Safety profile observed through 204 wks of treatment in pediatric pts with ERA was consistent with that observed in children

aged ≥2 yrs treated for polyarticular JIA.

Weeks	% Change from BL in AJC[a], mean		Change from BL in EC[a], mean		Change from BL in SJC[a], mean		ACR Pedi 70 Responder[b], n (%)	
	PBO N=15	ADA N=31	PBO N=15	ADA N=31	PBO N=15	ADA N=31	PBO N=15	ADA N=31
12	-11.6	-62.6	-2.7	-4.4	-2.4	-3.5	3 (20.0)	17 (54.8)
	Any ADA (N=46)		Any ADA (N=46)		Any ADA (N=46)		Any ADA (N=46)	
24	-85.2		-6.8		-5.2		34 (73.9)	
52	-88.7		-6.6		-5.7		35 (76.1)	
108	-90.5		-6.3		-5.7		36 (78.3)	
156	-88.3		-6.0		-5.5		35 (76.1)	

[a]LOCF. [b]NRI.

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Abstract Number: 387

Rituximab Should be Considered in Rheumatoid Factor Negative Poly-Articular Juvenile Idiopathic Arthritis

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SESSION INFORMATION

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Background/Purpose: Selective peripheral B-cell depletion by rituximab (RTX) is a relatively recent advance in rheumatic diseases. RTX is an approved treatment in RA. Although very few studies have examined RTX in JIA, evidence in adults for its better effectiveness in seropositive compared to seronegative RA, may have led to reluctance for the use of RTX in RF negative poly-articular JIA. The aim of this study was to describe the use and outcomes among children with

JIA, including RF negative polyarticular subtype treated with RTX in the UK.

Methods: The UK Biologics for Children with Rheumatic Diseases (BCRD) study is a prospective register capturing information on JIA patients treated with biologic therapies. Demographic, disease information, disease activity before and after (median 5.5 months) rituximab (2 doses at 750mg per m^2, 2 weeks apart) and adverse events were analysed. Effectiveness of RTX was evaluated from the change in core set measures. The ACR pediatric (Pedi) criteria were applied for cases with complete information on disease activity.

Results: A total of 49 JIA patients treated with RTX were identified, 80% female, median (IQR) age at disease onset and start of RTX was 5 (3, 7) years and 15(6, 12) years respectively. RF (-) polyarticular was the commonest subtype (n=20) followed by RF (+) polyarthritis (n=12), oligoarticular extended (n=9), oligoarticular persistent (n=4), psoriatic (n=2) and 1 patient each with systemic-onset and enthesitis related arthritis. Most (n=46) had received treatment with at least 1 prior biologic before RTX, an anti-TNF being the most common (n=42), 16 received concomitant MTX. Most children started RTX following inadequate response to prior therapy (n=45). There were significant improvements in active and limited joint counts, physician assessment of disease activity and ESR; median functional ability (CHAQ score) did not improve (table1). The ACR Pedi criteria could be applied only in 20 children due to missing individual data items. ACR-Pedi30/50/70 were achieved in 65%, 56% and 20% overall, and in 73%, 56% and 43% of RF (-) polyarthritis. Most did not experience any adverse events related to RTX over the first 6 months of therapy, with 2 reported infusion reactions and 2 infections (1 serious).

Conclusion: In this small but varied JIA cohort, RTX therapy resulted in meaningful improvements in physician recorded outcomes in many children with JIA, including those with RF (-) arthritis with limited adverse effects, suggesting RTX may be an effective treatment option for children with subtypes other than RF(+) polyarthritis. Disability scores did not improve overall although this may reflect the severity of disease in this longstanding disease cohort.

Concomitant / previous therapies	**Value (n=49)**		
Concomitant DMARD therapy	19(38.9%)		
Methotrexate	16(32.7%)		
Hydroxychloroquine or Sulfasalazine	9(18.4%)		
Cyclophosphamide	1(2.0%)		
Previous use of other biologic drugs	46(93.8%)		
4 prior biologic drugs	1(2.0%)		
3 prior biologic drugs	7(14.3%)		
2 prior biologic drugs	14(28.6%)		
1 prior biologic drug	24(49.0%)		
Disease activity (n= number with value at baseline and follow-up)	**Pre-RTX (median , IQR)**	**Post-RTX median, IQR)**	**P value**
Active joint count (n=35)	4 (2,7)	1 (1,4)	0.0007
Limited joint count (n=34)	3(2,8)	1(0,3)	0.0005
ESR (mm/h) (n=32)	32 (24,47)	25(21,30)	0.005
Physician assessment of disease activity (10 cm) (n=20)	4.6(3.3, 6.1)	2(1.5, 3)	0.001
Parent/patient assessment of well-being (10cm) (n=19)	4.6 (2.5, 7.5)	3.5 (2.0,5.1)	0.2
CHAQ score (n=16)	1.1(0.5, 1.4)	1.1(0.2,1.4)	0.5

Table 1. Disease activity before and after RTX, and previous/concomitant therapies.

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Abstract Number: 388

Pharmacokinetics, Safety, and Tolerability of Tofacitinib in Pediatric Patients from Two to Less Than Eighteen Years of Age with Juvenile Idiopathic Arthritis

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor that is being investigated for juvenile idiopathic arthritis (JIA). Here, we report the pharmacokinetics (PK), safety, and taste acceptability of tofacitinib following multiple oral doses in patients (pts) 2–<18 years (yrs) old with active JIA.

Methods: Data were obtained from an open-label, non-randomized, multicenter, Phase I study (NCT01513902) where JIA pts were given 5 mg adult equivalent (based on body weight) of tofacitinib (tablet or solution) twice daily (BID) for 5 days (Table). There were 3 cohorts (COH) based on pt age, COH1: 12–<18 yrs, COH2: 6–<12 yrs, and COH3: 2–<6 yrs, with a target enrollment per group of ≥8 JIA pts for N=≥24 evaluable pts completing the study. Pts were enrolled in a step-wise approach beginning with the older age COH first. Subsequent younger age COH were enrolled following confirmation of safety and PK from the previous COH. PK parameters of tofacitinib were calculated using non-compartmental analysis of plasma concentration (conc)-time data. Taste acceptability of the solution formulation was listed and categorically summarized (frequency and %).

Results: 26 pts (COH1 [N=8], COH2 [N=9], and COH3 [N=9]) were included in this analysis. Pts' age ranged from 2–17 years; all were white except for one; there were 17 females and 9 males. Baseline disease characteristics were similar across all COH. All exposure metrics including geometric mean (GM) area under the conc-time curves (AUC_{tau}), maximum (C_{max}), minimum (C_{min}) and predose (C_{trough}) conc were lower in COH2 relative to those in COH1; however, due to higher doses in COH3 (modified after interim analysis of COH1 and 2), the mean AUC_{tau} in COH3 was comparable to COH1. GM apparent volume of distribution (V_z/F) decreased with age (COH1=104.9 L, COH2=71.0 L, COH3=51.4 L). Average terminal half-lives ($t_{½}$) were COH1=2.62 h, COH2=1.95 h, and COH3=1.77 h. GM tofacitinib CL/F were 53%, 39%, and 11% higher in COH1, COH2, and COH3 pts, respectively, vs adult RA pts (18.4 L/h) receiving tofacitinib 5 mg BID. GM CL/F and V/F parameters were similar between males and females. Tofacitinib, administered over 5 days as multiple dose tablets or solution formulation, was well tolerated and taste for the solution formulation was found acceptable in children with active JIA. No serious adverse events or new safety signals were identified.

Conclusion: PK results from this study established dosing regimens for pts aged ≥2 years to be used in the upcoming efficacy and safety studies of tofacitinib in JIA pts. Tofacitinib was well tolerated in this study in JIA pts. Overall, pts found the taste of the tofacitinib solution formulation to be acceptable.

Body weight (kg)	Tofacitinib dose BID (mg)	Volume (mL)
Dosing scheme for age 6 –<18 years		
5–11	1	1
12–18	1.5	1.5
19–24	2	2
25–31	2.5	2.5
32–39	3	3
≥40	5	5
Dosing scheme for age 2–<6 years		
5–6	1	1
7–9	1.5	1.5
10–12	2	2
13–15	2.5	2.5
16–19	3	3
20–22	3.5	3.5
23–26	4	4
27–29	4.5	4.5
≥30	5	5
BID, twice daily		

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Abstract Number: 389

Long-Term Effectiveness and Safety of Abatacept in Juvenile Idiopathic Arthritis: Interim Results from the Abatacept in JIA Registry

DJ Lovell[1], N Ruperto[2], N Tzaribachev[3], A Zeft[4], R Cimaz[5], V Stanevica[6], G Horneff[7], J Bohnsack[8], TA Griffin[9], R Carrasco[10], M Trachana[11], JA Dare[12], I Foeldvari[13], RK Vehe[14], TA Simon[15], N Baker[15], Hermine I. Brunner[16] and A Martini[2], [1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Istituto G. Gaslini Pediatria II Reumatologia, Genova, Italy, [3]University Medical Center Schleswig-Holstein, Bad Bramstedt, Germany, [4]Pediatric Rheumatology, Cleveland Clinic, Cleveland, OH, [5]Pediatrics, Ospedale Pediatrico Anna Meyer, Florence, Italy, [6]Riga Stradins University, Riga, Latvia, [7]Asklepios Klinik Zentrum für Allgemeine Paediatrie und Neonatologie, Sankt Augustin, Germany, [8]University of Utah School of Medicine, Salt Lake City, UT, [9]Levine Children's Hospital at Carolinas Medical Center, Charlotte, NC, [10]Pediatric Rheumatology, Specially For Children, Austin, TX, [11]Hippokration General Hospital, Thessaloniki, Greece, [12]University of Arkansas Medical Center, Little Rock, AR, [13]Hamburg Centre for Pediatric Rheumatology, Hamburg, Germany, [14]University of Minnesota, Minneapolis, MN, [15]Bristol-Myers Squibb, Princeton, NJ, [16]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: Abatacept is a widely approved and used biologic in children with juvenile idiopathic arthritis (JIA). The purpose of this study was to describe the longitudinal effectiveness and safety of abatacept in JIA patients.

Methods: Using a standardized protocol, clinical sites in the Pediatric Rheumatology Collaborative Study Group (PRCSG) and Paediatric Rheumatology International Trial Organization (PRINTO) enrolled patients with JIA currently on or starting abatacept in this longitudinal registry. Planned duration of follow-up is 10 years and data shown are those collected through 31 March, 2016 (up to 3 years of follow-up).

Results: *Overview.* Of 315 enrolled patients with JIA, 308 contributed data. The total mean person-years of observation were 231.9 years on abatacept. In this registry, 35 (11%) patients were new starters on abatacept (≤ 1 month of treatment), 207 (67%) had received abatacept for 1 month–1 year, 52 (18%) for 1–2 years and 14 (4%) >2 years. During follow-up, 224 (73%) patients continued abatacept. *Baseline.* Of the 308 patients with data, 246 (80%) were female, mean/median age at enrollment was 13.2/13.8 years, disease duration was 5.4/4.4 years, and the active joint count was 2.7/0. Baseline clinical, functional and health-related quality of life scores are shown in Table 1 based on results up to 3 years. A history of uveitis was recorded in 40 (13%) patients and 12 (4%) had active uveitis. JIA subtype was: systemic (2%), oligoarticular (21%), polyarticular RF– (53%), polyarticular RF+ (10%), psoriatic (4%), enthesitis-related (4%), undifferentiated (6%). Concomitant JIA medication was taken by 86% of patients (64% MTX, 49% NSAIDs, 17% systemic steroids, 5% leflunomide, 5% hydroxychloroquine, 1% cyclosporine, 1% sulfasalazine). *Follow-up safety.* A total of 30 AEs were reported (18 serious; all single occurrences) in 25 patients (0.8% of study population), resulting in an overall AE rate of 12.9 per 100 patient-years (95% CI 8.8, 18.2). There were 12 infections of special interest (5.0/100 patient-years, 95% CI 2.8, 8.8). Two patients discontinued abatacept due to a safety event (anaphylaxis). No new autoimmune diseases, deaths, malignances or tuberculosis cases were reported.

Conclusion: In this JIA cohort, abatacept demonstrated persistent effectiveness with low MD global disease activity, low number of active joints and over 30% of patients were in clinical inactive disease. Abatacept was well tolerated and no new safety signals were observed. 1. Wallace C, et al. *Arthritis Care Res* 2011;**63**:929–36. 2. Filocamo G, et al. *J Rheumatol* 2011;**38**:938–53.

Table 1. Follow-up effectiveness

Endpoints	Baseline (n=308)	3 months (n=247)	6 months (n=215)	12 months (n=121)	24 months (n=35)
Clinical					
MD Global	1.9/1.0	1.46/1.0	1.49/0.5	1.13/0.5	0.89/0.5
CID,[1] %	33	32	38	50	37
JAMAR Functional[2]	5.4/3.0	4.8/3.0	4.3/2.0	3.6/0.5	2.7/2.0
JAMAR HRQoL	6.9/6.0	6.0/5.0	5.6/4.0	4.9/3.0	5.1/4.0

Data are mean/median unless otherwise indicated CID=clinical inactive disease (Wallace criteria); JAMAR Functional=Juvenile Arthritis Multidimensional Assessment Report Functionality Scale Child (range 0–15); JAMAR HRQoL=Juvenile Arthritis Multidimensional Assessment Report Health-Related Quality of Life Scale Child (range 0–15); MD Global=MD Global Disease Activity (VAS 0–10); VAS=visual analog scale

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Abstract Number: 390

Use, Safety and Efficacy of Zrc 3197, a Biosimilar Candidate for Reference Adalimumab (Humira) from a Tertiary Pediatric Rheumatology Centre in India

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Background/Purpose: Reference Adalimumab is not available in our country but biosimilar ZRC 3197 is(1). This is lower priced and as healthcare is primarily self funded in India, it is now a practical option for many children with JIA and uveitis. This is the *first study* to analyse the use, safety and efficacy of ZRC 3197 in pediatric rheumatology patients.

Methods: Records of 29 children, who have been given ZRC3197 from Dec '14 till 15th June '16 were analysed to assess i.)Use, safety and efficacy in children with JIA ii.) Use, safety and efficacy in children with Uveitis. A predesigned proforma captured the demographic details, medications, 74 joint count and SUN classification for uveitis.

Results: 29 children (16 males) have received ZRC 3197 to date. **Indications:** JIA: (n=15) ERA 12, IBD and Psoriatic arthritis 1 each, PJIA 1.Median age at commencing ZRC 3197: 14.66yrs.(10.08-23.66) Uveitis (n=14); idiopathic:4, PJIA:4, OJIA:4,ERA:1,Behcets with uveitis:1.Median age at commencing ZRC 3197:8.66yrs.(5.16-20.16) All patients were on methotrexate/ and/or oral steroids/topical steroid eye drops. Median duration of therapy with ZRC3197:6 mths (0.5-17 mths) **Safety**: **Prebiologic screen:** Tuberculosis screening positive in 4: 2 drug anti tubercular therapy(ATT) for latent TB given to 3; 1 treated for TB disease. **Post biologic**: 1 child had multi dermatomal herpes zoster after 1 dose and drug was discontinued. **Efficacy**: a.)In 13 children with JIA, (2 patients's follow up <3 mo) ZRC3197 was effective in all domains noted at 3mo.and 6mo.of use(Table1) as determined by the Wilcoxon Signed Ranks test. Median duration to achieve inactive disease in 12 children was 3 weeks (2-32weeks), 3 were still active at last follow up, none flared till last follow up. **Table1: Efficacy of ZRC 3197 in children with JIA**

	Pre ZRC 3197	After 3 mo.	After 6 mo.
	n=15	n=13	n=9
Median Swollen joint count(range) (P Value)	2(0-4)	0(0-2) **(p=0.003)**	0(0-1) **(p=0.03)**
Median Tender joint count(range) P value	2(0-3)	0(0-1) **(p=0.004)**	0(0-1) **(p=0.024)**
Median Joints with limited range of movement(range) P value	1(0-3)	0(0-1) **(p=0.004)**	0(0-2) **(p=0.05)**
Median ESR(range) (p value)	58(6-120)	8(3-22) **(p=0.002)**	10(4-42) **(p=0.008)**
Median CRP(range) P value	20(3-99)	3(3-17) **(p=0.003)**	3(3-3) **(p=0.012)**
Median Patient/parent global VAS 0-100(range) P value	50(20-80)	0(0-20) **(p=0.001)**	0(0-10) **(p=0.01)**

b.)In children with uveitis, ZRC 3197 was effective(Table 2), median duration to achieve inactivity per SUN in 10 children was 4 weeks(2-24weeks). **Table 2: Efficacy of ZRC 3197 in Pediatric Uveitis**

	Pre ZRC3197	3m post ZRC3197	6m post ZRC3197
	n=14	n=10	n=8
Vision Improvement No improvement Deterioration		6 **(p=0.05)** 1 1*	5 **(p=0.02)** 1 3* *(due to cataract)
Flare Improvement No improvement Deterioration		8 **(p=0.02)** 1 1	5 **(p=0.038)** 3 0
Cells Improvement (no.)(p value) No improvement(No.) Deterioration(no.)		9**(p=0.003)** 1 0	7**(p=0.014)** 1 0
NCT Normal pressure High Pressure	10 4	9 **(p=0.083)** 1	7 **(p=0.046)** 0
Steroid drops Median (range) P value	5(0-16)	0 (0-4) **(p=0.007)**	0(0-0) **(p= 0.026)**

Conclusion: ZRC 3197 is a safe and rapidly effective agent for children with JIA and uveitis resistant to methotrexate. This is the first report of the use of ZRC3197 in children. References: 1. Jani RH,Gupta R,Bhatia G,Rathi G,Ashok Kumar P,Sharma R, et al.A prospective,randomized, double blind, multicentre, parallel-group,active controlled study to compare efficacy and safety of biosimilar adalimumab(Exemptia;ZRC-3197)and adalimumab (Humira) in patients with rheumatoid arthritis. International Journal of Rheumatic diseases.2015:doi:10.1111/1756-185x.12711

50(20-80)

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Abstract Number: 391

A Single Centre Experience from India on the Safety and Efficacy of Cipla Etanercept and Intas Etanercept and Its Comparison with Reference Etanercept(Enbrel) in Children with JIA

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SESSION INFORMATION

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Background/Purpose: Cost is a major impediment for use of biologic response modifiers (BRMs). Biosimilars/Intended copies, priced at almost half the reference molecule might be the answer. There is limited data on safety & efficacy of these in pediatric rheumatology. This study was thus undertaken to i.) Assess efficacy/safety of Cipla Etanercept(CE) &Intas Etanercept(IE) ii.)Compare efficacy of CE& IE with reference Etanercept & with each other

Methods: All children with JIA who were given CE & IE till 15.6.16 were included. CE/IE/Reference Etanercept was used in disease resistant to Methotrexate, NSAIDs & steroids. Age matched 39 children who received reference Etanercept were taken as control arm. Data was analysed by Wilcoxon Signed Ranks test at 0, 3 & 6 mths for: 74 joint count, joints with limited range of movt., ESR & CRP. Patients were also categorised as per Wallace criteria into active disease, inactive disease & clinical remission on & off medications.

Results: Total 69 children – 30 given CE & IE, 39 given reference Etanercept. Demographics –CE & IE given to 30(53% males).ERA: 60%,Polyarticular JIA:30% & others 10%. Median age of starting CE & IE: 8.41yrs. Reference Etanercept given to 39(61%males).ERA:66.6%, Polyarticular JIA:20% &13.4% others. Median age at starting :10.66 yrs Efficacy– Table 1 shows significant efficacy of CE & IE in all tested domains. Table 2 shows no difference in all tested domains of reference Etanercept when compared to CE &IE.Table 3 shows no significant difference in efficacy of CE vs IE.

Table 1: Efficacy Pre CE&IE and Post CE&IE

	Pre CE & IE	3months post CE&IE	6months post CE&IE
	n = 30	n=24	n=22
Swollen Joint Count Median (range) (p value)	2.5 (0-16)	0.00 (0-5) **p- 0.001**	0.00 (0-2) **p-0.001**
Limited Range of Movement Median (range) (p value)	0.01 (0-5)	0.00 (0-4) **p-0.006**	0.00 (0-5) **p-0.038**
ESR Median (range) (p value)	39 (5-120)	9 (2-59) **p-0.001**	6.50 (2-40) **p-0.001**
CRP Median (range) (p value)	12.05 (3-116)	3 (3-25) **p-0.001**	3 (3-3) **p-0.001**
Disease activity Inactive Active CRoM	0 100% 0	56% 44% 0	59.1% 31.8% 9.1%
Therapy: Methotrexate Steroids	93.3 % 73.3%	95.8% 16.6%	100% 4.54%

Table 2 : Comparison of efficacy between reference Etanercept and CE & IE

	Pre Reference Etanercept/CE&IE	3months post	6months post
Swollen Joint Count			
Reference Etanercept Median(range)	2 (0-16)	0.00(0-14)	0.00(0-2)
CE&IE Median (range)	2.5 (0-16)	0.00 (0-5)	0.00 (0-2)
(p value)	**0.474**	**0.92**	**0.594**
Limited Range of Movement Reference Etanercept Median(range)	1 (0-9)	0.00(0-8)	0.00(0-1)
CE&IE Median (range)	0.01 (0-5)	0.00 (0-4)	0.00 (0-5)
(p value)	**0.568**	**0.311**	**0.142**
ESR Reference Etanercept Median(range)	29.5 (2-125)	10(2-73)	10 (3-100)
CE&IE Median (range)	39 (5-120)	9 (2-59)	6.50 (2-40)
(p value)	**0.954**	**0.322**	**0.209**
Patients with inactive disease (%) Reference Etanercept		18/35 (51.4%)	19/32 (59.4%)
CE&IE		14/24 (56%)	13/22 (59.1%)
(p value)		**0.72**	**0.977**
Time to inactivity Reference Etanercept Median(range)	12.5weeks(1-28)		
CE&IE Median(range)	12weeks(4-36)		
P value	**0.793**		

Table 3 :Comparison of efficacy between CE and IE

	Pre Biosimilar	3months post biosimilar	6months post biosimilar
Swollen Joint Count			
CE			
Median (range)	4 (0-16)	0 (0-5)	0.00 (0-2)
IE			
Median(range)	1 (0-5)	0.00(0-2)	0.00(0-1)
(p value)	**0.25**	**0.84**	**0.84**
Limited Range of Movement			
CE			
Median (range)	0 (0-5)	0.00 (0-4)	0.00 (0-5)
IE			
Median(range)	1 (0-2)	0.00(0-1)	0.00(0-1)
(p value)	**1**	**0.80**	**0.39**
ESR			
CE			
Median (range)	30 (5-120)	9 (2-59)	8 (2-40)
IE			
Median(range)	45 (9-105)	5(2-28)	6 (2-20)
(p value)	**0.65**	**0.13**	**0.32**
CRP			
CE			
Median (range)	12.1 (3-116)	3 (3-25)	3 (3-3)
IE			
Median(range)	12 (3-35)	3 (3-24)	3 (3-3)
(p value)	**0.56**	**0.80**	**1**

Safety**:** CE/IE were safe with few side effects. Pre CE/ IE: HbsAg +ve:1; Screening for tuberculosis(TB) infection +ve in 5 Pre Reference Etanercept – Screening for TB +ve in 3 Post CE & IE: 12 weeks after starting IE, 1(3.33%) had cellulitis of the right foot. Reference Etanercept: 3 (Hemolytic anemia-1,Varicella-1,New onset uveitis-1).

Conclusion: CE & IE licensed for use in India are safe &effective in a cohort of 30 children with JIA. They are comparable to each other & the reference Etanercept with a similar efficacy& safety profile. This is the first comparative study of these two agents against reference Etanercept from a single centre & needs to be replicated in other centres with a longer follow up.

Disclosure: A. Shivpuri, None; **S. Mittal**, None; **M. Agarwal**, None; **S. Sawhney**, None.

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Abstract Number: 392

Safety and Clinical Response of Weekly Adalimumab in the Treatment of Juvenile Idiopathic Arthritis, Pediatric Chronic Uveitis and Other Childhood Rheumatic Diseases

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Every other week adalimumab is used to treat juvenile idiopathic arthritis (JIA) and other pediatric rheumatic diseases. It is common for pediatric rheumatologists to escalate to weekly dosing to achieve better disease control when needed. Weekly adalimumab has been demonstrated to be safe and effective in several autoimmune diseases in adults; however, to our knowledge, there have been no studies demonstrating the safety and effectiveness of weekly adalimumab in children with rheumatic diseases. We conducted a retrospective chart review of pediatric patients on weekly adalimumab to assess safety and clinical responsiveness.

Methods: Sixty-nine patients at the University of Minnesota or Gillette Children's Hospital were identified as treated with weekly adalimumab. Sixty (87%) were eligible for the chart review. Demographic and clinical data were collected. Basic descriptive analysis was performed to assess for adverse events and clinical response to weekly adalimumab.

Results: Sixty-three percent (38/60) of patients on weekly adalimumab were females, and the mean age at initiation of weekly dosing was ~14 years. Weekly adalimumab was used most commonly to treat uveitis and rheumatoid factor-negative polyarticular JIA. Most of the patients were also on a nonsteroidal anti-inflammatory drug (NSAID) and methotrexate (Table 1). Only three patients (5%) had an infection requiring hospitalization. One patient with sepsis was concurrently taking an NSAID, methotrexate, and cyclosporine for treatment of chronic uveitis with JIA. Two patients (3%) developed autoimmune disease (Table 2). Most children dislike the pain associated with adalimumab injections, and, thus, the common practice at our clinics is to stop weekly dosing by three months if it is not helpful in treating the disease. Therefore, for this chart review, if the patient continued the weekly dosing for at least three months we determined they had a positive clinical response. Ninety-percent (53/59) of patients were determined to have a positive clinical response. One patient was lost to follow-up prior to the three month point.

Conclusion: The use of weekly adalimumab in children in our centers was determined to be safe and effective. Ninety-percent of patients had a positive clinical response. Minor infections were common, but serious infections requiring hospitalization were uncommon. Two patients on weekly adalimumab developed autoimmune disease. Adalimumab-induced autoimmunity is a recognized issue, but further studies are needed to determine if weekly dosing increases this risk in children.

Table 1. Characteristics of patients on weekly adalimumab	
Characteristics	**N (%)**
Male	22 (36.7)
Age (in years) at diagnosis (mean ±SD)	7.7 (5.3)
Age (in years) at start of adalimumab (mean ±SD)	13.28 (4.9)
Age (in years) at start of weekly adalimumab (mean ±SD)	13.93 (4.78)
Positive clinical response to weekly adalimumab*	53 (90)
Diagnosis	
Oligoarticular JIA, persistent	10 (16.7)
Oligoarticular JIA, extended	0 (0)
RF-positive polyarticular JIA	2 (3.3)
RF-negative polyarticular JIA	15 (25.0)
Enthesitis-related JIA	9 (15.0)
Arthritis associated with IBD	1 (1.7)
Psoriatic arthritis	9 (15.0)
Systemic JIA	3 (5.0)
Uveitis	17 (28.3)
Other	9 (15.0)
Concurrent Medications	
NSAID	40 (66.7)
Methotrexate	50 (83.3)
Oral prednisone	28 (46.7)
Hydroxychloroquine	8 (13.3)
Leflunomide	7 (11.7)
Sulfasalazine	6 (10.0)
Mycophenolate	4 (6.7)
Cyclosporine	3 (5.0)
Azathioprine	2 (3.3)
Intravenous methylprednisolone	2 (3.3)
Rituximab	2 (3.3)
Abatacept	1 (1.7)
Intravenous immunoglobulin	1 (1.7)

*Positive clinical response defined as being on weekly dosing for at least three months
JIA=juvenile idiopathic arthritis, RF=rheumatoid factor, IBD=inflammatory bowel disease, NSAID=nonsteroidal anti-inflammatory drug

Table 2. Adverse events while patient was on weekly adalimumab	
Adverse event	**N (%)**
Infection not requiring antimicrobials	24 (40.0)
Infection requiring antimicrobials*	24 (40.0)
Sinusitis	11 (18.3)
Pharyngitis/tonsillitis	9 (15.0)
Ear infection	8 (13.3)
Respiratory infection/pneumonia	4 (6.7)
Cellulitis	1 (1.7)
Abscess	1 (1.7)
Shingles	1 (1.7)
Other	7 (11.7)
Infection requiring hospitalization	3 (5)
Viral pharyngitis and Behcet's flare	1 (1.7)
Sepsis	1 (1.7)
Acute appendicitis	1 (1.7)
Injection site reaction	4 (6.7)
Transaminitis†	2 (3.3)
Leukopenia‡	1 (1.7)
Anemia‡	3 (5)
Thrombocytopenia	0 (0)
Other autoimmune disease	2 (3.3)
Multiple sclerosis	1 (1.7)
Autoimmune hepatitis	1 (1.7)
Malignancy	0 (0)
Death	0 (0)

*Some patients had more than one type of infection,
†One case thought to be secondary to adalimumab,
‡Not thought to be secondary to adalimumab

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Abstract Number: 393

Association of Sex, Race and Ethnicity on Disease Outcomes in Juvenile Idiopathic Arthritis Patients

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Background/Purpose: JIA patients are predominantly non-Hispanic white and studies have shown that race and ethnicity may be associated with worse disease. This study assesses the associations of sex, race and ethnicity with disease outcomes in children with JIA in the Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) Registry. PR-COIN is a multicenter network that uses quality improvement methods to develop and evaluate specific JIA management strategies to improve outcomes in JIA.

Methods: A cross sectional analysis of children with JIA enrolled in the PR-COIN registry from 6/2010 and 7/2015 was done. Univariate statistics and tests of association were performed to compare patient characteristics associated with sex, race (White, African American (AA) and Asian) and ethnicity (Hispanic/Latino, non-Hispanic). One-way ANOVAs were used for all normally distributed continuous data, Wilcoxon Rank Sum for all non-normal continuous data, and Fischer's exact test for all categorical data.

Results: Race information was available for 2436/3192 children (90% white, 6% African American (AA) and 4% Asian). Ethnicity data was available for 2431 children (8% Hispanic/Latino. Characteristics of JIA patients by sex (F:M 2.5:1), race, and ethnicity are reported in tables 1-3. AA children were noted to have worse disease outcomes compared to other races ($p<0.0001$ for all observations). Asian children had the best overall disease outcome scores for all variables ($p<0.0001$). Hispanic children had a higher median JADAS score (3 vs 2.5 in non-Hispanics, $p<0.001$) and a lower median pain score (0.5 vs 1, $p<0.001$). Males, Asians and Hispanics started DMARDs and biologics significantly sooner than other groups ($p<0.0001$).

Conclusion: Race and ethnicity are associated with different disease outcomes in children with JIA. Similar to other studies, AA and Hispanic patients had worse outcomes with higher disease activity scores. However, patients overall tended to have good outcomes with minimal morning stiffness, and low GA, pain and disability scores. Understanding the etiology and clinical significance of outcome variations between sex, race and ethnicity may enable early identification of patients at risk for worse disease and help to improve the care of JIA patients.

Table 1: JIA Patient Characteristics

Outcome	Full Sample
Number	3192
JIA Subtype: n (%)	
Systemic Arthritis	182 (5.70)
Polyarticular, RF (+)	211 (6.61)
Polyarticular, RF (-)	901 (28.83)
Oligoarticular, persistent	840 (26.32)
Oligoarticular, extended	226 (7.08)
Psoriatic Arthritis	217 (6.80)
Enthesitis Related Arthritis	334 (10.46)
Undifferentiated Arthritis	73 (2.29)
Patient Characteristics: n (%)	
Male	779 (28.2)
Female	1983 (71.8)
Hispanic	246 (9.04)
Not Hispanic/Latino	2357 (86.59)
Not Documented	119 (4.37)
White	2327 (90.54)
Black	149 (5.80)
Asian	94 (3.66)
JIA Disease Outcome Measures: Median [IQR]	
CHAQ Score	0 [0-0.38]
Duration of Morning Stiffness	1 [1-2]
MD-GA	1 [0-2]
PGA	1 [0-3]
JADAS	2 [0-6]
Pain Score	1 [0-4]
Joint Count	0 [0-2]
Treatment: Mean (SD)	
Month to 1st Biologic	144.37 (130.36)
Month to DMARD	118.08 (121.86)

Note: IQR=interquartile range, Q1 and Q3; SD= Standard Deviation; MDGA=physician global assessment; CHAQ=Childhood Health Assessment Questionnaire; PGA=Patient GA. Duration of Morning Stiffness: 1: No Stiffness; 2: <15 min; 3: 15-30 min; 4: 30 min-1hr; 5: 1-2 hr; 6:2-4 hr; 7:4-8 hr; 8: >8 hr

Table 2. JIA Patient Characteristics by Race and Ethnicity

Race	White	African American	Asian	P Value*	Hispanic /Latino	Non-Hispanic	P Value*
Number (%)	2203 (90.44)	144 (5.91)	89 (3.65)		214 (8.31)	2217 (86.06)	
JIA Subtypes: n (%)							
Systemic Arthritis	117 (78.17)	19 (15.90)	7 (3.32)		16 (10.60)	130 (86.09)	
Polyarticular, RF (-)	697 (93.56)	28 (3.76)	20 (2.15)		88 (9.21)	828 (86.61)	
Polyarticular, RF (+)	148 (82.22)	21 (11.67)	11 (6.11)				
Oligoarticular, persistent	598 (88.59)	50 (7.40)	27 (4.0)				
Oligoarticular, extended	193 (94.15)	4 (1.95)	8 (3.90)		99 (10.83)	771 (84.35)	
Psoriatic Arthritis	174 (91.37)	10 (4.8)	5 (2.4)		11 (5.67)	172 (88.66)	
Enthesitis Related Arthritis	264 (91.32)	10 (3.84)	13 (2.56)		23 (7.59)	267 (88.12)	
Undifferentiated Arthritis	53 (95.63)	3 (3.75)	0 (0)		4 (6.9)	49 (84.48)	
JIA Disease Outcome Measures: Median [IQR]							
CHAQ Score (0-3)	0 [0-0.38]	0.25 [0-0.75]	0 [0-0.25]	<.0001	0 [0-0.50]	0 [0-0.50]	0.2041
Duration of Morning Stiffness†	1 [1-2]	1 [1-3]	1 [1-2]	<.0001	1 [1-2]	1 [1-2]	0.0004
MDGA (0-10)	1 [0-2]	1 [0-3]	1 [0-2]	<.0001	1 [0-2]	1 [0-2]	0.0122
PGA (0-10)	1 [0-3]	2 [0-5]	0 [0-2[	<.0001	1 [0-4]	1 [0-3]	<.0001
JADAS (0-64)	2 [0-6]	4 [1-8]	1.25 [0-5]	<.0001	3 [0.50-7]	2.5 [0-6]	<.0001
Pain Score (0-10)	1 [0-6]	3 [0-6]	0 [0-2]	<.0001	0.50 [0-4]	1 [0-4]	0.0001
Joint Count (0-64)	0 [0-2]	1 [0-3]	0 [0-1]	<.0001	0 [0-2]	0 [0-2]	0.0005
Treatment: Mean (SD)							
Months to 1st Biologic	134.00 (149.00)	108.97 (88.56)	99.89 (76.37)	<.0001	122.55 (102.61)	147.04 (132.87)	<.0001
Months to 1st DMARD	123.90 (121.49)	93.93 (111.42)	85.76 (82.23)	<.0001	99.72 (97.00)	120.74 (124.73)	<.0001

Note: The P-Value represents the significance level from either a Wilcoxon rank sum test or a One-Way ANOVA. All of the Disease Outcomes use the Wilcoxon Rank sum test because the data are not normally distributed; Treatments (Month to DMARD and Biologics) were normally distributed and are tested using a One-Way ANOVA. IQR=interquartile range, Q1 and Q3; SD= Standard Deviation; MDGA=physician global assessment; CHAQ=Childhood Health Assessment Questionnaire; PGA=Patient GA.

† Duration of Morning Stiffness: 1: No Stiffness; 2: <15 min; 3: 15-30 min; 4: 30 min-1 hr; 5: 1-2hr; 6:2-4 hr; 7:4-8 hr; 8: >8 hr

Table 3. JIA Patient Characteristics by Sex

Outcome	Male	Female	P Value*
Number	214 (8.31)	2217 (86.06)	
JIA Subtypes: n (%)			
Systemic Arthritis	70 (44.30)	88 (55.70)	
Polyarticular, RF (+)	30 (14.93)	171 (85.07)	
Polyarticular, RF (-)	184 (23.03)	615 (76.97)	
Oligoarticular, persistent	185 25.48)	541 (74.52)	
Oligoarticular, extended	34 (15.81)	181 (84.19)	
Psoriatic Arthritis	72 (36.00)	128 (64.00)	
Enthesitis Related Arthritis	152 (49.697)	154 (50.33)	
Undifferentiated Arthritis	26 (40.00)	39 (60.00)	
JIA Disease Outcome Measures: Median [IQR]			
CHAQ Score	0 [0-0.375]	0 [0-0.50]	<.0001
Duration of Morning Stiffness	1 [1-2]	1 [1-2]	0.9356
MD-GA	1 [0-2]	1 [0-2]	0.0031
PGA	1 [0-3]	1 [0-3]	<.0001
JADAS	2 [0-6]	2.5 [0-6]	<.0001
Pain Score	1 [0-4]	1 [0-4]	<.0001
Joint Count	0 [0-2]	0 [0-2]	0.0016
Treatment: Mean (SD)			
Months to 1st Biologic	115.215 (110.62)	155.78 (136.33)	<.0001
Months to 1st DMARD	100.42 (122.01)	124.73 (126.27)	<.0001

* The P-Value represents the significance level from either a Wilcoxon rank sum test or a One-Way ANOVA. All of the Disease Outcomes use the Wilcoxon Rank sum test because the data are not normally distributed; Treatments (Month to DMARD and Biologics) were normally distributed and are tested using a One-Way ANOVA. IQR= Interquartile Range; SD= Standard Deviation; CHAQ=Childhood Health Assessment Questionnaire; MDGA=Physician Global assessment; PGA=Patient Global Assessment. Duration of Morning Stiffness: 1: No Stiffness; 2: <15 min; 3: 15-30 min; 4: 30min-1 hr; 5: 1-2 hr; 6:2-4 hr; 7:4-8 hr; 8: >8 hr

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Abstract Number: 394

Effect of BMI on Symptoms and Outcomes in Juvenile Idiopathic Arthritis Patients

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Session Time: 9:00AM-11:00AM

Background/Purpose: Children with JIA are at risk for cardiovascular disease and obesity compounds this risk. There is limited data on the prevalence of elevated BMI in JIA patients (pts) and its effects on disease activity and physical function. This study aims to assess the prevalence of obesity and its effects on JIA pts in the Pediatric Rheumatology Care and Outcome Improvement Network (PR-COIN). We hypothesized that the pts with a high BMI would have worse outcomes.

Methods: We evaluated the de-identified data of JIA pts entered between 6/2010 and 7/2015. Data collected included demographics, height, weight, and pain, CHAQ, Juvenile Arthritis Disease Activity Score (JADAS), and pt and physician global assessment scores (PGA, MDGA). BMI measures body fat based on height and weight (kg/m^2). The average BMI is compared to typical values for other children of the same age and gender. Univariate statistics were used to describe the sample. To compare outcomes across subgroups and across time, a Wilcoxon Rank sum test and a Wilcoxon Sign Rank test was performed, respectively.

Results: 3317 pts were enrolled in the database across 13 sites in the US and Canada [Tables 1,2]. 125 pts were excluded due to missing data for a final sample of 3192 (17,451 visits). Mean age was 7.7 ± 4.9 years, and mean disease duration was 5.4 ± 4.4 years. Table 3 compares the outcome measures of overweight/obese (ov/ob) to normal/underweight JIA pts. All ov/ob except systemic and undifferentiated pts had higher pain scores ($p<0.0001$). Ov/ob oligo-, psoriatic, and ERA pts had higher CHAQ and MDGA scores ($p<0.05$). Ov/ob polyarthritis pts had worse disease activity, MDGA, CHAQ scores and more office visits ($p<0.0001$). Ov/ob systemic pts had the shortest disease duration prior to starting MTX ($p=0.001$) and more office visits ($p<0.0001$). Ov/ob undifferentiated pts had the shortest disease duration prior to the first course of steroids ($p<0.04$) and a longer disease duration prior to starting MTX ($p<0.003$) and biologics ($p<0.0001$) (data not shown). There was no difference in years to start steroid, MTX or biologic based on overweight status.

Conclusion: Results suggest that ov/ob pts have worse pain, disease, function and more office visits than underweight/normal weight JIA pts. Goals of treatment should not only include arthritis control, but dietary and exercise treatment and recommendations.

Table 1: Demographic Characteristics of Patients in the PR-COIN Registry

	Patients		Patient Visits	
Demographic Characteristic	N	%	N	%
Sample Size	3192		17451	
Sex				
Male	779	28.2	4019	25.37
Female	1983	71.8	11823	74.63
Ethnicity				
Hispanic	246	9.04	1142	7.26
Not Hispanic/Latino	2357	86.59	14069	89.47
Not Documented	119	4.37	513	3.26
Race				
White	2327	90.54	13863	91.85
Black	149	5.8	805	5.33
Asian	94	3.66	425	2.82
JIA Sub-type				
Systemic arthritis	182	5.70	1156	6.62
Polyarticular JIA, RF-	901	28.23	6035	34.58
Polyarticular JIA, RF+	211	6.61	1124	6.44
Oligoarticular JIA, persistent	840	26.32	3200	18.34
Oligoarticular JIA, extended	226	7.08	1711	9.80
Psoriatic arthritis	217	6.80	169	0.97
Enthesitis related arthritis	334	10.46	1185	6.79
Undifferentiated arthritis	73	2.29	1156	6.62
Obesity Status (1st visit)			Avg of all visits	
Underweight or Normal	2808	82.97	15047	82.97
Overweight	299	10.36	1879	10.36
Obese	189	6.67	1209	6.67
Obesity Status (last visit)				
Underweight or Normal	2695	81.79		
Overweight	365	11.08		
Obese	235	7.13		

Note: Obese refers to patients with a BMI of 30 or more; overweight refers to patients with a BMI of 25 or more; patients with a BMI below 25 fall into the underweight or normal category.

Table 2. JIA Patients and Health-Related Quality of Life Assessments*

JIA Subtype	**N/patient visits**	**BMI (5-55)**	**MDGA (0-10)**	**CHAQ (0-3)**	**PGA (0-10)**	**Pain Score (0-10)**	**AM Stiffness (1-4)**	**Active Joints (0-64)**
Systemic	182/1169	20.2 [16.9-24.6]	0 [0-2]	0 [0-0.38]	0 [0-3]	0.0 [0-3]	1 [1-2]	0 [0-1]
Polyarticular, RF (+)	211/1124	21.2 [18.2-25.7]	1 [0-2.5]	0 [0-0.62]	1.0 [0-4]	2.0 [0-4]	1 [1-2]	1 [0-3]
Polyarticular, RF (-)	901/6035	19.5 [16.5-23.14]	1 [0-2]	0 [0-0.5]	1.0 [0-4]	1.0 [0-4]	1 [1-2]	0 [0-2]
Oligoarticular, persistent	840/3200	17.9 [15.7-21.2]	0.5 [0-1.5]	0 [0-0.25]	0.50 [0-2]	0.0 [0-0.3]	1 [1-2]	0 [0-1]
Oligoarticular, extended	226/1711	19.1 [16.2-23.2]	0.5 [0-3]	0 [0-0.25]	0.50 [0-3]	0.5 [0-3]	1 [1-2]	0 [0-2]
Psoriatic arthritis	217/1169	20.9 [17.4-24.8]	1 [0-2]	0.13 [0-0.63]	1.5 [0-4]	2.0 [0-5]	1 [0-2]	0 [0-2]
Enthesitis related arthritis	334/1185	21.8 [19.0-25.3]	1 [0-3]	0.13 [0-4]	2.0 [0-5]	1.0 [0-4]	2 [1-4]	0 [0-2]
Undifferentiated arthritis	73/ 219	19.0 [16.8-23.1]	1 [0-2]	0.13 [0-.38]	1. 0 [0-3]	1.0 [0-4]	1 [1-2]	0 [0-1]

* Presented as median [interquartile range]; MDGA=physician global assessment; CHAQ=Childhood Health Assessment Questionnaire; PGA=Patient GA. † Duration of Morning Stiffness: 1: No Stiffness; 2: <15 min; 3: 15-30 min; 4: 30 min-1 hr; 5: 1-2 hr; 6:2-4 hr; 7:4- 8hr; 8: >8 hr

Table 3. Comparison of patient outcomes by overweight status for all JIA encounters.

Outcome	Not Overweight		Overweight/ Obese		Wilcoxon P-Value*
	N	Median	N	Median	
JADAS71	14,785	2	3,040	3	<0.0001
MDGA Score	13,254	0.5	2,743	1	<0.0001
CHAQ	12,523	0	2,625	0.125	<0.0001
PGA Score	11,664	1	2,277	1.5	<0.0001
Pain Score	13,993	3	2,947	5	<0.0001
Number of Visits	15,047	4	3,088	5	<0.0001

JADAS=Juvenile Arthritis Disease Activity Score; MDGA=physician global assessment; CHAQ=Childhood Health Assessment Questionnaire; PGA=Patient GA.

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The Influence of Early Achievement of "Clinically Inactive Disease" or "Minimal Disease Activity" on Long-Term Disability Outcomes in JIA

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Background/Purpose: Different definitions of clinically inactive disease (CID) for JIA have recently been shown to identify different groups of children. It is unclear whether long-term outcomes, such as low disability, differ between children who, early in disease, have no objective inflammatory signs (CID on Wallace's preliminary criteria) versus those who also have good global wellbeing (CID on clinical Juvenile Arthritis Disease Activity Score (cJADAS)). It is also unclear whether achieving CID is more beneficial to long-term outcomes than achieving minimal disease activity (MDA). This study assessed whether functional outcome within five years, measured by the Childhood Health Assessment Questionnaire (CHAQ), differs according to disease activity state at one year following presentation in children with JIA.

Methods: Children recruited to the Childhood Arthritis Prospective Study (CAPS), a multicentre UK inception cohort, prior to 1st January 2011 and with a physician's diagnosis of JIA (limited to oligoarticular, RF negative or positive

polyarticular subtypes) were selected. At one year following presentation, children were categorised into three disease states: i) CID using both Wallace's preliminary criteria and cJADAS, ii) CID using Wallace's preliminary criteria only and iii) No CID. In addition, children were assessed for MDA using the cJADAS. CHAQ scores were compared between each disease state group via univariate and multivariate zero-inflated negative binomial regressions with robust clustering at the patient level. Multivariate models adjusted for age and symptom duration at presentation, gender and ILAR subtype. Multiple imputation accounted for missing data.

Results: Of 832 children, 70% were female and the most common subtype was oligoarthritis (68%), followed by RF-negative (27%) and RF-positive polyarthritis (5%). At one year, 22% had achieved CID according to Wallace's preliminary criteria and cJADAS, 7% according to only Wallace's preliminary criteria and 56% to neither. Compared with those who had not achieved CID, children who had achieved CID on both tools at one year had 21% lower CHAQ scores (95% CI 10, 31%) and double the odds of zero disability (95% CI 1.5, 2.6) within the first five years. However, those who had achieved CID only on Wallace's preliminary criteria had similar CHAQ scores to the no CID group. There was no difference in functional ability between children who had achieved MDA or CID using JADAS at one year, with both achieving 27% lower CHAQ and having three times the odds of zero disability compared with children not in these states (Table 1).

Conclusion: Better long-term functional ability was only observed to increase when both objective measures of inflammation and subjective measures of the global picture of disease were taken into account. MDA may be an equally valid, but more feasible, treatment target to CID in patients with JIA.

Table 1. Associations between achievement of CID and MDA at one year and CHAQ scores within the first five years following initial presentation

Outcome definition at one year following presentation	IRR of higher CHAQ (95% CI)	P-value	IRR of CHAQ=0 (95% CI)	P-value
Combined states				
Not in CID on either tool	Reference	-	Reference	-
CID on Wallace's preliminary criteria only	1.1 (0.9, 1.3)	0.260	0.70 (0.43, 1.1)	0.139
CID on both Wallace's preliminary criteria and cJADAS10	0.79 (0.69, 0.90)	0.001	2.0 (1.5, 2.6)	<0.001
CID vs MDA				
MDA cJADAS10 (versus no MDA)	0.73 (0.65, 0.82)	<0.001	2.8 (2.2, 3.7)	<0.001
CID cJADAS10 (versus no CID)	0.73 (0.65, 0.82)	<0.001	2.7 (2.1, 3.5)	<0.001

IRR: Incidence rate ratio, CHAQ: Childhood Health Assessment Questionnaire, CID: Clinically inactive disease, MDA: Minimal disease activity, cJADAS10: Clinical Juvenile Arthritis Disease Activity Score weighted to 10 joints.

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Performance of Disease Activity Measures in Juvenile Spondyloarthritis in a Placebo Controlled Trial with Infliximab

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Session Time: 9:00AM-11:00AM

Background/Purpose: Several outcome measures in trials with juvenile-onset spondyloarthritis (Jo-SpA) have been borrowed from trials in juvenile idiopathic arthritis and from adult spondyloarthritis, but a proper psychometric analysis has never been conducted in patients with Jo-SpA. We aimed at assessing discriminatory aspects of several disease activity outcome measures and response criteria for Jo-SpA.

Methods: Data from a previously reported 12-week RCT comparing infliximab (IFX) and placebo (PBO) in patients <18 years with Jo-SpA and onset <16 years of age were analyzed. The primary endpoint of the trial was the number of active joints (both swollen and tender). Several other disease activity measures and response criteria were also tested (Table). Statistics to determine how well disease activity measures could discriminate between IFX and PBO included 'standardized mean difference' (SMD) and 'Guyatt's effect size. Both statistics are standardized measures to compare change from baseline per group. For categorical response criteria, the chi-square test (χ^2) was used. Higher numbers indicate better discriminatory capacity.

Results: Patients were randomised to IFX (n=12) and PBO (n=14). Of the continuous measures, the ASDAS showed the best and very good discrimination between IFX and PBO (SMD:1.98; Guyatt: 4.28) (Table). The physician's global, CRP, JADAS and JSpADA also discriminated well. The BASDAI (or its separate items), BASFI and spinal mobility measures performed worse. Of the response criteria ASAS40 and ACR Pedi 90 discriminated best between IFX and PBO (Table). ASDAS response criteria and ACR Pedi 30-70 also performed well. **Table: Discrimination between patients on infliximab and placebo at week 12**

0.005

CONTINUOUS OUTCOME MEASURES				
	Infliximab mean change (SD)	**PBO mean change (SD)**	**Guyatt's effect size**	**SMD**
ASDAS	2.4 (1.3)	0.5 (0.6)	4.28	1.98
Physician's global assessment, 0-10 mm VAS	5.2 (2.4)	1.6 (2.2)	2.34	1.56
JADAS27 (0-57)	12.7 (5.9)	4.3 (5.7)	2.22	1.46
JSpADA (0-8)	2.8 (1.2)	0.5 (1.4)	1.98	1.73
CRP (mg/L)	21.1 (8.4)	2.3 (10.9)	1.93	1.90
Total enthesitis (0-51)	8.5 (10.6)	1.6 (5.0)	1.71	0.85
Patient's global assessment, 0-10 mm VAS	4.3 (3.8)	0.8 (2.8)	1.55	1.08
BASDAI total (0-10)	3.3 (3.1)	0.9 (2.3)	1.41	0.90
Pain, 0-10mm VAS	3.3 (2.1)	-1.7 (3.2)	1.03	1.80
Active joint count (0-72)	4.4 (1.7)	2.6 (4.6)	0.96	0.51
	Infliximab mean change (SD)	**PBO mean change (SD)**	**Chi-square**	**p-value**
ACR Ped 90	8 (67%)	1 (7%)	10.12	0.001
ASAS40	6 (55%)	0 (0%)	10.05	0.002
ACR Ped 70	9 (75%)	2 (14%)	9.76	0.002
BASDAI50	8 (73%)	2 (14%)	8.77	0.003
ASDAS-MI	5 (63%)	0 (0%)	8.65	0.003
ACR Ped 50	11 (92%)	5 (36%)	8.55	0.003
ASDAS-CII	7 (88%)	2 (20%)	8.10	0.004
ASDAS-ID	7 (64%)	1 (8%)	7.74	
ACR Ped 30	11 (92%)	6 (43%)	6.80	0.009
JADAS27 MDA (≤2)	6 (50%)	1 (7%)	6.03	0.014
JADAS27 inactive disease/remission (≤1)	3 (25%)	0 (0%)	3.96	0.047
ASAS20	7 (64%)	4 (29%)	3.07	0.080

Conclusion: Of all continuous measures tested in adult axial SpA the ASDAS discriminates best between active treatment and PBO in patients with Jo-SpA. But the child specific JSpADA also performs well. Of all response criteria tested the child-specific ACR Pedi 30 to 90, as well as the adult ASAS40 and ASDAS response criteria work well. One of these measures should be used as primary endpoint in trials with Jo-SpA.

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Abstract Number: 397

Comorbidities Associated with Pediatric Psoriatic Arthritis

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Background/Purpose: In adults, psoriatic arthritis (PsA) is associated with an increased prevalence of obesity, hypertension, and diabetes. It is not yet known if pediatric patients with PsA also have a higher prevalence of these comorbidities. We evaluated the association of obesity, hypertension, and diabetes with PsA and psoriasis in children.

Methods: We conducted a cross-sectional study of children with PsA and psoriasis enrolled in The Health Improvement Network (THIN) database between 1994 and 2013. All psoriasis and PsA cases in the cohort had ≥ 1 READ code for psoriasis, or psoriasis and arthritis, respectively. The index date was defined as the first READ code entry for psoriasis or PsA. Controls were matched on age, sex, and practice at a 5:1 ratio. Prevalence of hypertension, diabetes, and obesity were calculated among patients in these groups. Hypertension and diabetes were identified using ≥ 1 READ code for these diagnoses. Age- and sex-specific z-scores for BMI (zBMI) were calculated. Differences in demographic and clinical characteristics were assessed using the t-test and Wilcoxon rank sum test, as appropriate.

Results: 6366, 1786, and 13351 children were identified as having juvenile arthritis (excluding PsA), PsA, and psoriasis, respectively. Among children with psoriasis, 280 (2.1%) had PsA. The mean age at PsA diagnosis was 7.7 (SD 4.5) years and psoriasis diagnosis was 9.8 (SD 4.0) years. 62.4% of the PsA, 56.7% of the psoriasis, and 56.5% of the controls were female. Table 1 summarizes characteristics of each patient population at the time of data collection. PsA patients were significantly more likely to have hypertension and diabetes than patients with psoriasis, but did not have a higher prevalence of hypertension and had a lower prevalence of diabetes compared to controls. zBMI was significantly higher in PsA compared to controls (1.1 vs 0.07, p-value 0.03) and psoriasis compared to controls (0.9 vs 0.07, p-value 0.01), but not significantly different between children with PsA and psoriasis (p-value 0.3).

Conclusion: PsA was found to be associated with an increased prevalence of hypertension and diabetes compared to patients with psoriasis, but not compared to healthy controls. Children with PsA and psoriasis also had a significantly higher mean zBMI compared to healthy controls.

Table 1: Comorbidities in Patients with Pediatric Psoriatic Arthritis and Psoriasis

	PsA (n=1,786), N(%)	Psoriasis (n=13,071), N(%)	Controls (n=64,339), N(%)	PsA vs. psoriasis p-value	PsA vs. Controls p-value
Hypertension	24 (1.3)	49 (0.4)	599 (0.9)	P<0.001	0.07
Hypertension w/out CKD	18 (1.0)	44 (0.3)	426 (0.7)	P<0.001	0.08
Diabetes	32 (1.8)	91 (0.7)	1,949 (3.0)	P<0.001	0.01
zBMI*, mean (SD)	1.1 (2.0)	0.9 (1.8)	0.7 (1.9)	0.3	0.03

Legend. The psoriasis group excludes patients with psoriatic arthritis. Psoriatic arthritis (PsA); chronic kidney disease (CKD); BMI z-score (zBMI).

* zBMI data only available for PsA for N=105; psoriasis for N=627; controls for N=11,174.

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Predictors of Clinical Remission with Etanercept in Pediatric Patients with Extended Oligoarticular, Enthesitis-Related Arthritis and Psoriatic Arthritis: Findings from the Clipper Study

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Background/Purpose: Etanercept (ETN) is approved in the EU for the treatment of children with juvenile idiopathic arthritis (JIA) categories of polyarticular, extended oligoarticular (eoJIA), enthesitis-related arthritis (ERA), and psoriatic arthritis (PsA), but little evidence is currently available regarding predictors of clinical remission. We evaluated

characteristics that may have predicted the achievement of clinical remission with ETN in the CLIPPER study.

Methods: In this ongoing, Phase 3b, open-label study, pediatric patients with eoJIA (2–17 y), ERA (12–17 y), or PsA (12–17 y) received ETN 0.8 mg/kg once weekly (maximum, 50 mg) for up to 96 weeks. Baseline demographic and disease characteristics that were significantly different ($p<0.05$) between children in remission or with active disease were analysed post hoc as categorical predictors (i.e., dichotomized continuous characteristics) in univariate logistic regression models; response and disease activity status after 12 weeks of ETN treatment were also considered as predictive factors. Clinical remission was defined with the JIA ACR Wallace 2011 remission criteria or Juvenile Arthritis Disease Activity Score 71-joint reduced count (JADAS71) clinical remission criteria (≤1) persisting for ≥24 weeks.

Results: Of the 127 patients enrolled in the trial, 42 (33%) and 54 (43%) achieved JIA ACR or JADAS71 clinical remission over 24 weeks, respectively. In univariate analyses, patients who had lower BMI and were shorter at baseline and those who were younger at the time of disease onset were significantly more likely to achieve JIA ACR and JADAS71 remission (table). Age >11 vs ≤11 years at baseline and C-reactive protein level >2.4 mg/L vs ≤2.4 were significant predictors of JIA ACR remission; HLA-B27+ vs HLA-B27– status and >11 vs ≤11 joints with limitation of motion at baseline were predictors of JADAS71 remission. Induction of JIA ACR and JADAS71 responses at 12 weeks was also predictive of sustained ACR and JADAS71 responses for 24 weeks.

Conclusion: Clinical remission after 12 weeks of etanercept treatment was the most important predictor of sustained clinical response over 24 weeks in pediatric patients with eoJIA, ERA, or PsA JIA subtypes. **Trial registration identifying number:** NCT00962741/NCT01421069

Table. Significant predictors of sustained clinical responses to ETN for 24 weeks.

	Sustained JIA ACR remission		Sustained JADAS71 remission	
Baseline characteristic	**n/N (%)**	**Odds Ratio (95% CI)**	**n/N (%)**	**Odds Ratio (95% CI)**
Age at onset, y		>7.6 vs ≤7.6 y		>7.6 vs ≤7.6 y
• ≤7.6	24/41 (59)	0.19 (0.08, 0.42)	23/41 (56)	0.44 (0.21, 0.94)
• >7.6	18/86 (21)		31/86 (36)	
12-week clinical outcome				
JIA ACR status		Remission vs		Remission vs
• Remission	11/15 (73)	active disease	12/15 (80)	active disease
• Active disease	31/108 (29)	6.83 (2.02, 23.09)	42/108 (39)	6.29 (1.67, 23.60)
JADAS71 status		Remission vs		Remission vs
• Remission	14/18 (78)	active disease	14/18 (78)	active disease
• Active disease	27/102 (27)	9.72 (2.94, 32.11)	39/102 (38)	5.65 (1.74, 18.41)

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Abstract Number: 399

Enthesitis in Juvenile Idiopathic Arthritis (JIA)

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Enthesitis in Juvenile Idiopathic Arthritis (JIA)

Background/Purpose: The characteristics of enthesitis, a feature in some children with juvenile idiopathic arthritis (JIA), t has not been well described in large prospective inception cohorts. We used data from a Canadian cohort to describe the characteristics of patients with enthesitis, the sites most commonly affected, and the temporal changes in the number of sites of enthesitis, relative to changes in active joint counts.

Methods: Children newly diagnosed with JIA at 16 Canadian centers from 2005 to 2010 were followed in the ReACCh-Out cohort for up to 5 years. For this analysis, all patients with >1 visit (n=1406) were included. The presence and location of enthesial tenderness on examination were recorded by pediatric rheumatologists in all children present at 0, 6, 12, 18, 24, 36, 48 and 60 months after enrolment. For this study, a child was said to have enthesitis if enthesial tenderness was present on >1 occasion and/or at >1 body site. The characteristics of patients with an without enthesitis were compared using univariate logistic regression on each characteristic. The number of tender enthesial sites was analyzed over time and compared to the number of active joint counts using linear mixed models for longitudinal data.

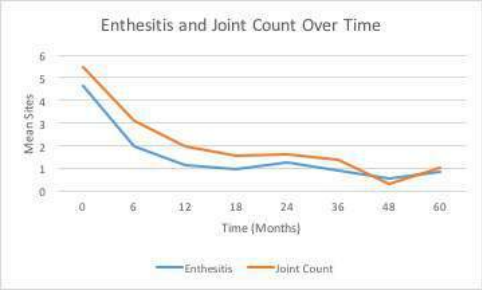
Results: A total of 219 patients (16% of the cohort) fulfilled our criteria for enthesitis; 8% fulfilled criteria at enrolment and 15% fulfilled criteria within 2 years. The most frequent sites of involvement were the calcaneal plantar insertion (39%), Achilles insertion (31%), and tibial tuberosity (30%). The characteristics of children with and without enthesitis are presented in Table 1. Children with enthesitis were older, more often male and 141 (64.4%) were categorized as enthesitis related arthritis; 57.1% had polyarticular involvement and 30% had sacroiliac involvement at some point during follow-up. The mean number of tender enthesial sites decreased dramatically over the follow-up period, roughly in parallel with the number of active joints (see Figure 1, p=0.16 for whole group). A mixed linear model analysis showed no significant difference in active joint counts over time in children with or without enthesitis (p=0.73).

Conclusion: The number of patients with enthesitis and their characteristics were generally as expected, except that over half the patients had polyarticular involvement. The number of tender enthesial sites and active joints decreased similarly over time in the enthesitis group, and the active joint counts decreased similarly over time in children with and without enthesitis. **Table 1: Characteristics of Patients With Versus Without Enthesitis**

Characteristic	Patients with Enthesitis	Patients without Enthesitis	OR (95% CI)
Number with Enthesitis	219 (15.6%)	1187 (84.4%)	-
Age of onset of JIA (Mean)	10.7 yrs (SD 3.2 yrs)	7.5 years (SD 4.6 yrs)	1.21 (1.16 Đ 1.26)
Male Sex	124 (56.6%)	365 (30.8%)	2.89 (2.15 Đ 3.88)
ANA Positive*	51 (23.3%)	563 (47.4%)	0.33 (0.24 Đ 0.47)
HLA-B27 Present**	70 (32.0%)	75 (6.3%)	4.58 (3.09 Đ 6.81)
JIA Subtype (Initial)	-	-	-
-ERA	141 (64.4%)	61 (5.1%)	**Reference**
-Oligoarticular	13 (5.9%)	546 (46%)	0.010 (0.006 Đ 0.02)
-Polyarticular RF Đve	17 (7.8%)	256 (21.6%)	0.029 (0.02 Đ 0.05)
-Polyarticular RF +ve	4 (1.8%)	53 (4.5%)	0.033 (0.01 Đ 0.09)
-Systemic	0 (0%)	86 (7.25%)	Cannot compute
-Psoriatic	5 (2.3%)	83 (7.0%)	0.026 (0.01 Đ 0.067)
-Unclassified	39 (17.8%)	102 (8.6%)	0.17 (0.1 Đ 0.27)
Uveitis (ever)	21 (9.6%)	198 (16.7%)	0.53 (0.33 Đ 0.85)
Sacroiliitis (ever)	66 (30.1%)	43 (3.6%)	11.5 (7.5 Đ 17.5)
Psoriasis (ever)	57 (26.0%)	273 (23.0%)	1.18 (0.85 Đ 1.64)
Polyarticular involvement (ever)	125 (57.1%)	487 (41.0%)	1.91 (1.43 Đ 2.56)

*ANA status unknown in 11.9% of the enthesitis group and 8.4% of the no enthesitis group **HLA-B27 status unknown in 26.5% of the enthesitis group and 56.0% of the no enthesitis group

Figure 1: Mean Number of Tender Enthesial Sites and Active Joints in Children with Enthesitis



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Foot Involvement in Enthesitis-Related Arthritis Subtype of Juvenile Idiopathic Arthritis: Clinical, Radiological and Functional Assessment

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Background/Purpose: Though foot involvement is common in juvenile idiopathic arthritis (JIA), it is often neglected by patients and physicians alike. The involvement could occur due to arthritis, enthesitis or tenosynovitis. Tarsitis is thought to be a harbinger for spondyloarthropathy. Thus this study was done to assess clinical and radiological involvement of feet as well as its impact on function in children with JIA-Enthesitis related arthritis (ERA).

Methods: We enrolled consecutive patients newly diagnosed with JIA ERA of age less then 18 years and disease duration less than 5 years seen during 2015. All patients underwent clinical examination of the feet and answered the Juvenile arthritis foot index (JAFI) questionnaire to assess functional impact. Radiological assessment included plain X-rays of the feet, US of the joints and entheses and MRI scan of one foot. HLAB27 was done by PCR.

Results: Fifty-five patients, with a median age of 14 years and duration of disease 1.9 years were included in the study. Eighty percent (37/46) were HLAB27 positive and 18 (32.7%) had radiographic sacroiliitis. Forty six (83.6%) patients had a history of foot pain while 36 had abnormal clinical exam: 15 had ankle, 8 had subtalar 24 had midfoot and 10 had forefoot joint involvement. Tendoachilles enthesitis was present in 21 whereas plantar fasciitis was seen in 7 patients. The median JAFI score was 4 (0-11) and the score correlated with history of foot pain ($r=0.66$; $p<0.01$) and foot swelling ($r=0.58$; $p<0.01$). On plain X-ray (N=40) 3 had midfoot joint space reduction and 3 had midfoot joint fusion. On US (N=55), 16 had ankle, 8 had subtalar and 19 patients had midfoot arthritis with the talonavicular (TN) joint being the most commonly involved. 27 had US active tendoachilles enthesitis and 11 had plantar fasciitis. On MRI (N=50) tarsitis was seen in 27 patients and TN was the most commonly involved joint. Bone marrow edema was seen in 33 patients with the calcaneum being the most commonly affected bone. Midfoot enthesitis was found in 14 patients and tenosynovitis in 17 patients. Clinical and US had 82% concordance at midfoot and 90% at tibiotalar joint. MRI had lower concordance rates (74% with clinical exam and 72% with ultrasound at midfoot) as it picked up additional findings in 12 patients.

Conclusion: Foot joints and entheses are involved in a substantial proportion of patients with JIA ERA patients and lead to functional disability. Early recognition and treatment may decrease damage.

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Abstract Number: 401

Humoral Immune Response after a Booster Dose with Tdap in Children and Adolescents with Juvenile Idiopathic Arthritis on Anti-TNF and in Healthy Controls

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Background/Purpose: Pertussis cases have increased worldwide and knowledge on immune response after adult Tdap vaccine is scarce. This study evaluated the humoral immune response profile after Tdap in children and adolescents with Juvenile Idiopathic Arthritis and in healthy controls.

Methods: After written informed consent, children and adolescents with Juvenile Idiopathic Arthritis (JIA) using anti-TNF and healthy controls (control) with three previous whole-cell DTP plus two booster vaccine doses received a Tdap dose. Blood samples were collected immediately before and 28 days after Tdap. Tetanus, diphtheria and pertussis antibodies were tested by ELISA. Antibodies>0.100 IU/mL were considered protective for tetanus and diphtheria. There isn't a consensus antibodies level considered protective for pertussis.

Results: JIA group (n=10) was represented for 7 (70%) female, with median age 13 (8-18), 4 (40%) with positive anti-nuclear antibodies (ANA), 1 (10%) with positive rheumatoid factor. Control group (n=9) was represented for 4 (44.4%) female, with median age 15.2 (9-15.6). JIA and control groups presented an increase in response to tetanus (p=0.0004, p=0.002) and diphtheria (p<0.0001, p=0.002) antibodies after Tdap booster dose on day 28 and were comparable in the proportion of immune subjects on day 0 (p=0.1226, p=0.3322) and on day 28 (p=0.3493, p=0.5). Everyone in both groups seroconverted to tetanus and diphtheria. In JIA group median antibodies level for pertussis were 10.796 IU/mL (2.4-197.09) and 83.8 IU/mL (8.4-196.69) on day 0 and day 28. In the control group median antibodies level for pertusis were 8.47 IU/mL (1.08-108.88) and 59.73 IU/mL (13.87-138.04) on day 0 and day 28.

Conclusion: In this preliminary study, children and adolescents with JIA using anti-TNF and healthy controls showed adequate humoral immune response to tetanus, diphtheria and pertussis after Tdap. Future research include increasing sample size correlating T follicular cells population with improved humoral immune response.

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Abstract Number: 402

The Risk of Hospitalized Infection Associated with Initiation of Abatacept Versus TNF Inhibitors in Juvenile Idiopathic Arthritis

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Background/Purpose: The comparative risk of infection with newer biologic agents, such as abatacept (ABA), in the treatment of juvenile idiopathic arthritis (JIA) has not been reported. We used claims data to compare rates of hospitalized infection among JIA patients initiating ABA or tumor necrosis factor inhibitors (TNFi).

Methods: We combined data from national U.S. Medicaid claims from 2000-2010 and MarketScan claims from 2010-2014. Patients with a physician diagnosis code for JIA before age 16 years and prior to new use of ABA or a TNFi were included. New use of ABA and of each of the 5 TNFi agents was defined by a 6 month baseline period of non-use prior to first observed use. Follow-up began on the day of the new prescription fill or infusion claim and was extended for 90 days beyond the days supplied for each subsequent fill. Study outcome was hospital discharge with any infection as the primary diagnosis. We calculated crude infection rates per 100 person-years and stratified results according to clinical factors during the baseline period: use of oral glucocorticoids (GC), use of a different biologic agent, and inpatient or outpatient infection. We also stratified by systemic JIA (SJIA) as defined by any diagnosis for macrophage activation syndrome or any use of relatively SJIA-specific medications (e.g., anakinra). Multivariable regression analyses were precluded by few observed outcomes.

Results: We identified 5,933 and 257 initiators of TNFi and ABA, respectively. The baseline patient characteristics are in Table 1, and the overall and stratified crude infection rates are in Table 2. ABA was strongly associated with SJIA and with use of a different biologic agent during baseline compared to TNFi. The overall crude infection rates were higher for ABA (4.14 [2.07-8.28]) compared to TNFi (1.50 [1.22-1.85]). SJIA was associated with much higher infection rates among ABA users, and, to a lesser extent, among TNFi users. All 8 ABA patients with infection outcomes had infections during the baseline period, but the overall proportions of patients with baseline infections were similar with ABA and TNFi.

Conclusion: Crude hospitalized infection rates following initiation of ABA were higher compared to TNFi. This may be partially explained by higher proportions of patients with SJIA and recent use of other biologics among ABA initiators compared to TNFi. Infection during baseline was a risk factor for subsequent infection and may importantly be the reason for initiation of ABA in some patients. Evaluation of the comparative safety of non-TNFi biologics in JIA is challenging due to small sample sizes and requires careful consideration of prescriber channeling.

Table 1.

Characteristic	TNFi	ABA
Number of patients	5933	257
Median age (25-75%)	13 (9-16)	14 (10-17)
Female (%)	4093 (69%)	204 (79%)
Median days of follow-up (25-75%)	245 (121-495)	186 (109-368)
SJIA (%)	455 (8%)	35 (14%)
Oral GC use during baseline (%)	2337 (39%)	143 (56%)
Biologic use during baseline (%)	1397 (24%)	152 (59%)
Infection during baseline (%)	2624 (44%)	126 (49%)

Table 2.

	Number of infections & Infection rate per 100 person-years [95% CI]	
Patients	TNFi	ABA
All	91 1.5 [1.2-1.9]	8 4.1 [2.1-8.3]
With SJIA	9 2.2 [1.2-4.3]	4 23.5 [8.8-62.5]
Without SJIA	82 1.5 [1.2-1.8]	4 2.3 [0.9-6.0]
With GC use during baseline	44 1.9 [1.4-2.5]	4 3.9 [1.5-10.4]
Without GC use during baseline	47 1.3 [1.0-1.7]	4 4.4 [1.7-11.8]
With biologic use during baseline	21 1.8 [1.2-2.8]	6 5.3 [2.4-11.9]
Without biologic use during baseline	70 1.4 [1.1-1.8]	2 2.5 [0.6-9.9]
With infection during baseline	60 2.3 [1.8-2.9]	8 8.2 [4.1-16.4]
Without infection during baseline	31 0.9 [0.6-1.3]	0 0.0 [0.0-3.9]

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High Rate of Serious Infection in Juvenile Idiopathic Arthritis Under Biologic Therapy in a Real Life Setting

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Background/Purpose: Most data about infections associated to biologic therapy in juvenile idiopathic arthritis (JIA) derive from registries designed to identify general adverse events that have not focused on risk factors for this condition. In addition, previous publications of biological therapies were performed in distinct settings regarding endemic area and infection surveillance protocol. Therefore, our objectives were to assess the rate of serious/opportunistic infections in JIA patients from a single tertiary center under biologic therapy using a standardized electronic protocol in order to identify possible risk factors associated to theses complications.

Methods: From August 2004 to March 2016, 107 consecutive JIA patients were longitudinally followed at the biologic therapy center of the Rheumatology Division of our tertiary university hospital using a standardized electronic database protocol including demographic data, clinical and laboratorial findings and treatment at baseline and at the moment of infection. Serious infections were defined as those requiring hospitalization or intravenous antibiotics and opportunistic infections included tuberculosis(TB), herpes zoster(HZ) and systemic mycosis. All subcutaneous and intravenous biologic agents are regularly administered in our center with previous infectious screening.

Results: The mean age at baseline was 14.6±5.7yrs, 71% were females and median disease duration prior to biologic therapy was 4.8yrs (0.1-21). A total of 398 patient-yrs (py) were included: 179py for etanercept (ETN), 92py for adalimumab (ADA), 22py for infliximab (IFX), 78py for abatacept (ABA) and 27py for tocilizumab (TCZ). The median time of biologic exposure was 3.0 years (0.15-11.5). We observed 35 serious/opportunistic infectious events in 27 (25%) patients:31 (88.6%) were serious infections and 7 (20%) opportunistic (1 TB, 5 HZ, 1 systemic candidiasis). The median time of total biologic exposure until infection was 18 months (1–91) and most common sites were: 34% skin/soft tissue, 23% urinary tract and 20% respiratory tract. No patient died due to infectious complications. Serious/opportunistic infections rates were 10.6/100py for ETN, 10.9/100py for ADA, 2.6/100py for ABA and 14.8/100py for TCZ. Comparison of 27 patients with and 80 without infection showed a higher frequency of systemic-onset JIA (44 vs. 20%,p=0.021), lower age at biologic therapy initiation (12 ± 6 vs. 16 ± 5yrs,p=0.005) and a history of previous serious infection (33 vs. 14%,p=0.042) in the former group. Further analysis of 35 patients with and 80 patients without infectious complications balanced for mean time of biologic exposure revealed a significantly higher frequency of lymphopenia (17 vs. 1%,p=0.003) during infection events. Disease activity parameters and concomitant treatment had no influence on infections rate (p>0.05).

Conclusion: This single center study demonstrated a high rate of serious infections in JIA patients under biologic therapy in a real life setting, except for ABA. Systemic-onset JIA, lower age at biologic therapy start, history of previous serious infections and lymphopenia were important risk factors for these complications.

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Abstract Number: 404

Disease Activity and Damage in Juvenile Idiopathic Arthritis: Comparison Between “Methotrexate” and “Biologic” Era

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Background/Purpose: The introduction of biologic agents at the beginning of the 2000s has represented a major advance in the management of juvenile idiopathic arthritis (JIA). These medications have been shown to be effective in a sizeable proportion of patients refractory or intolerant to methotrexate. However, in order to document the impact of the recent therapeutic progress on the prognosis of JIA there is the need to compare the long-term outcomes achieved with previous therapies with those obtained with the newer medications. We aimed to compare the level of disease activity and the amount of articular and extra-articular damage between patients treated in the "methotrexate" era and "biologic" eras.

Methods: Data for the "methotrexate" era were extracted from a previous study on disease outcome in 310 patients with disease onset before 2002 and disease duration of ≥5 years (Solari et al. A&R 2008;59:1571-9). Data for the "biologic" era were obtained with the present study by examining all consecutive patients with JIA who had disease onset between January 2002 and June 2011 and a disease duration of ≥5 years. Outcome assessments included joint counts, physician global assessment of overall disease activity on a visual analog scale, Juvenile Arthritis Disease Activity Score-10 (JADAS10), Juvenile *Arthritis* Multidimensional Assessment Report (*JAMAR*) completed by a parent, and acute phase reactants. The amount of articular and extra-articular damage was assessed through the Juvenile Arthritis Damage Index (JADI).

Results: Demographic and clinical features of patients seen in the two study periods were overall comparable. As compared to the older sample, patients treated more recently had received more frequently methotrexate (84.6 vs 64.5%) and biologic medications (60.4% vs 11.3%), and had undergone more commonly intra-articular corticosteroid injections (97.6% vs 79%). The comparison of disease activity and damage between the two cohorts is presented in the table. All items of JADI articular and extra-articular were decreased in the recent sample, with the exception of temporo-mandibular damage and leg-length discrepancy, whose frequency was comparable in the two datasets.
file:///C:/Users/23667/Desktop/Table.htm

Conclusion: Compared with patients treated in the "methotrexate" era, those treated in the "biologic" era have a higher frequency of inactive disease and less articular and extra-articular damage. These findings highlight the improvement in disease outlook achieved with the newer therapeutic modalities.

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Abstract Number: 405

Patterns of Medication Use in Children with Juvenile Idiopathic Arthritis: Results from the Childhood Arthritis & Rheumatology Research Alliance Registry

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Session Time: 9:00AM-11:00AM

Background/Purpose: The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry is a multicenter, prospective observational study collecting data from children with rheumatic diseases in order to characterize disease patterns, treatments, and outcomes. The current Registry began enrolling children with JIA in July 2015. This abstract describes patterns of medication use among children with JIA enrolled through March 31, 2016.

Methods: Children were enrolled into the CARRA Registry by participating centers in the US and Canada. Children with the following characteristics were eligible for enrollment: 1) new diagnosis of JIA within previous 6 months; 2) systemic JIA; 3) history of polyarthritis (≥ 5 joints involved during disease course); 4) newly starting or re-starting methotrexate or biologic. In the categorization of medication use, current and past medication use were combined, and non-biologic DMARDs included methotrexate, leflunomide, and sulfasalazine. Patients with incomplete data entry at the time of analysis were included, and missing data were not imputed.

Results: 1155 children were enrolled from 46 centers; 244 were newly diagnosed (29% of those with sufficient data to determine). Patient characteristics are summarized in the Table. Receipt of non-biologic DMARDs only (without receiving biologics) was observed in 18% of all children, and there was an increased proportion of newly diagnosed patients in this group (30%). Receipt of any biologic agent was present in 56% of all children, and this was less common among patients with persistent oligoarthritis (30%). Non-TNF inhibitor biologic use was common among systemic JIA (71%) and was very uncommon among ERA (2%) and psoriatic arthritis (0%), although smaller numbers of children with these JIA categories have been enrolled into the Registry to date. Any use of systemic glucocorticoids was present among 44% overall, and was increased among systemic JIA (81%) and RF+ polyarthritis (69%). Among newly diagnosed children, 38% were treated with biologics, 30% had received DMARD only, and 29% received systemic glucocorticoids.

Conclusion: By design, this large cohort of children with JIA from North America includes a high proportion of biologic users. Children with systemic JIA had the most frequent use of non-TNF inhibitor biologics and systemic glucocorticoids, consistent with treatment efficacy data. Longitudinal data generated from the long-term follow-up of Registry participants will provide important data on medication usage, as well as comparative safety and effectiveness.

	Frequency (%) or Median (25-75%)		
Characteristic	All Patients	Disease Duration > 6 Months	Disease Duration ≤ 6 Months
Number of patients	1155	609	244
Age at enrollment (years)	13.4 (8-16)	12.9 (8.7 – 16.2)	10.2 (5.1-14.2)
Female	866 (75)	457 (75)	177 (73)
White race	829 (81)	483 (82)	185 (82)
Private health insurance	762 (74)	452 (76)	178 (75)
Disease duration (years)	2.1 (0.4-5)	3.7 (1.7 – 6.7)	0.1 (0-0.3)
ILAR category:			
Oligoarthritis, persistent	125 (12)	47 (8)	70 (29)
Oligoarthritis, extended	76 (7)	52 (9)	6 (4)
Polyarthritis, RF-	436 (42)	282 (46)	64 (27)
Polyarthritis, RF+	93 (9)	65 (11)	16 (7)
Psoriatic arthritis	51 (5)	23 (4)	19 (8)
Enthesitis related arthritis	90 (9)	36 (6)	39 (16)
Systemic arthritis	149 (14)	96 (16)	25 (10)
Undifferentiated arthritis	11 (1)	8 (1)	2 (1)
ANA+	381 (33)	232 (38)	79 (32)
RF+	98 (8)	65 (11)	20 (8)
Anti-cyclic citrullinated peptide antibody	79 (7)	49 (8)	17 (7)
HLA-B27+	78 (7)	42 (7)	22 (9)
Polyarthritis course (≥ 5 joints involved during disease course)	772 (67)	498 (82)	121 (50)
Uveitis ever	91 (8)	62 (10)	1 (0.4)
Non-biologic use only	213 (18)	108 (18)	73 (30)
Any biologic use	650 (56)	426 (70)	93 (38)
Non-TNF inhibitor biologic use	180 (16)	120 (20)	18 (7)
Systemic glucocorticoid use	503 (44)	344 (56)	71 (29)

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Abstract Number: 406

Adults with Juvenile Idiopathic Arthritis Are Not Adults with Rheumatoid Arthritis

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Background/Purpose: Juvenile Idiopathic Arthritis (JIA) persisting into adulthood is associated with articular damage, increased disability and mortality. Approximately 100,000 polyarticular JIA patients will enter adult practices over the next 10-15 years and represent a distinct population for these providers. We initially searched the electronic medical record (EMR) for adult patients with JIA, but found that only physicians with pediatric training used the JIA diagnosis while the rheumatoid arthritis (RA) diagnosis was used by the adult rheumatologists. Considering differences in clinical features, we hypothesized that the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) RA criteria would have lower sensitivity than the 1987 RA criteria for classification of polyarticular JIA patients, compared to an adult-onset RA cohort.

Methods: Patients > 18 years of age with an established JIA diagnosis made ≤16 years who were seen by adult rheumatology between January 1st 2013-June 1st2015 were evaluated. EMR extraction with rheumatologist review was performed and disease features were recorded. A prospective observational cohort of RA was used for comparison. JIA was retrospectively classified using the International League of Associations for Rheumatology (ILAR) JIA classification criteria and RA was classified using the ACR/EULAR 2010 and the 1987 criteria. McNemar's test, chi-square, and Welch's t-test were used to test for group differences between polyarticular JIA and RA.

Results: 67 adult subjects had JIA, with 45 having polyarticular disease, were compared to 66 subjects with RA. Polyarticular JIA subjects had a mean age of 27 years, 89% were female, with mean disease duration of 20.6 years. 29% (9/31) were rheumatoid factor (RF) positive. While 71.1% (32/45) met the 1987 RA criteria, only 46.7% of polyarticular JIA subjects met the 2010 RA criteria ($p<0.0001$). RA subjects had a mean age of 56 years, were 78% female, with mean disease duration of 11.2 years. 74% (43/58) were RF positive. 81.8% (54/66) met the 1987 criteria whereas 87.9% met the 2010 RA criteria. Patients with RA were approximately 1.88 times (95% RR 1.36, 2.61) more likely to meet the 2010 ACR/EULAR RA criteria than those with polyarticular JIA.

Conclusion: Adults with polyarticular JIA have unique clinical characteristics from RA, highlighted by less than half meeting the 2010 ACR/EULAR RA classification criteria. Accurate classification is the first step to define optimal evaluation and treatment in this unique patient population. Rather than blurring the clinical picture, adult rheumatologists should have increased awareness of JIA disease subtype.

Demographics and Disease Characteristics: Polyarticular JIA vs. RA			
Variable	**Poly JIA** Mean ± SD or % (n)	**RA** Mean ± SD or %	**p-value**
Sample Size	45	66	
Current Age	27.37 ± 9.26	56.04 ± 13.60	<0.0001*
% Female	88.89% (40/45)	78.79% (52/66)	0.1654
Disease Duration	20.61 ± 10.60	11.19 ± 10.34	<0.0001*
HAQ	0.4281 ± 0.5800 (N = 40)	0.3179 ± 0.3985	
RF+	29.03% (9/31)	74.14% (43/58)	<0.0001*
CCP+	28.57% (2/7)	68.52% (37/54)	0.0870
ANA ≥ 1:40	58.06% (18/31)	38.46% (20/52)	0.0829
% Current MTX	24.44% (11/45)	37.88% (22/66)	0.2390
% Past MTX	68.89% (31/45)	43.94% (29/66)	0.0288*
% HTN	4.44% (2/45)	37.88% (25/66)	<0.0001*
% Meeting 1987	71.11% (32/45)	81.82% (54/66)	0.1849
% Meeting 2010	46.67% (21/45)	87.88% (58/66)	<0.0001*

Abstract Number: 407

Comparability of Proxy, Adolescent and Adult Measures of Functional Ability in Adolescents with JIA

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Background/Purpose: It is unclear which tool should measure functional ability in adolescents with JIA. The proxy-completed Childhood Health Assessment Questionnaire (P-CHAQ) is completed on the adolescent's behalf and an adolescent version (A-CHAQ) has not been validated. Since adolescence parallels transfer to adult care, the adult HAQ may be preferable to capture functional ability throughout transition. However, it is unclear how the HAQ compares with the two CHAQ tools. Agreement between the P-CHAQ, A-CHAQ and HAQ was assessed in adolescents with JIA during the three years following presentation to rheumatology.

Methods: Adolescents aged 11 to 17 years recruited before 1st January 2013 to the Childhood Arthritis Prospective Study (CAPS), a UK multicentre JIA inception cohort, were selected. Adolescents had complete data on proxy-completed P-CHAQ and adolescent-completed A-CHAQ and HAQ at presentation. These assessments were continued annually. At baseline, Wilcoxen signed-rank tests compared median scores, Spearman's correlations assessed pairwise correlations and percent agreement (defined as cores within 0.25 points) was assessed. Univariate and age and sex-adjusted associations between scores were assessed via zero-inflated negative binomial models. Multiple imputation accounted for missing data for longitudinal models, which had robust clustering at the patient level.

Results: Of 94 adolescents included, median age at diagnosis was 13 years (IQR 12 to 15) and 61% were female. Median disease duration at diagnosis was seven months (IQR 5 to 14) and the most common subtype was oligoarticular JIA (40%). Median baseline HAQ (0.5) was marginally lower than both CHAQ scores (both 0.6), although this difference was not clinically significant. In accordance, the highest agreement was between the two CHAQ tools (78%) and lowest between the HAQ and P-CHAQ (71%). Where discordant, the majority of HAQ scores fell below those from either CHAQ. Discordance between CHAQ scores was more evenly distributed (Table 1). Despite marginally different medians, the strongest correlation was between the HAQ and the A-CHAQ (0.91), with the lowest between the two CHAQ tools (0.83). After adjustment for age and sex, there was around 11% difference in scores at baseline and 8% over the course of three years (Table 2).

Conclusion: There was strong correlation, good concordance and similar associations between the P-CHAQ, A-CHAQ and HAQ in adolescents with JIA. The strong relationship between the HAQ and either CHAQ tool indicate the utility of HAQ in adolescents with JIA.

Table 1. Comparisons of the P-CHAQ, A-CHAQ and HAQ in adolescents with JIA at baseline

Score	Median score (IQR)	Comparison	Correlation	Percent agreement (%)	Percent discordant scores (%)	
					Higher	Lower
P-CHAQ	0.625 (0.125, 1.375)	**Vs. A-CHAQ**	0.84	77	10	12
A-CHAQ	0.625 (0.125, 1.250)	**Vs. HAQ**	0.93	76	20	4
HAQ	0.500 (0.000, 1.125)	**Vs. P-CHAQ**	0.85	71	9	20

P-CHAQ: Parent-assessed Childhood Health Assessment Questionnaire (CHAQ); A-CHAQ: Adolescent-assessed CHAQ; IQR: Interquartile range.

Table 2. Associations between P-CHAQ, A-CHAQ and HAQ at baseline and during the first three years of disease in univariate and multivariate regression models adjusting for age and sex

Comparison	Univariate IRR	95% CI	Multivariate IRR	95% CI
Baseline assessments				
P-CHAQ vs. HAQ	1.11	1.09, 1.13	1.12	1.10, 1.14
A-CHAQ vs. HAQ	1.11	1.09, 1.13	1.11	1.10, 1.13
P-CHAQ vs. A-CHAQ	1.11	1.09, 1.13	1.11	1.09, 1.13
Longitudinal assessments over the first three years following presentation				
P-CHAQ vs. HAQ	1.06	1.02, 1.10	1.09	1.06, 1.12
A-CHAQ vs. HAQ	1.05	1.02, 1.09	1.07	1.05, 1.11
P-CHAQ vs. A-CHAQ	1.07	1.04, 1.11	1.09	1.06, 1.11

P-CHAQ: Parent-assessed Childhood Health Assessment Questionnaire (CHAQ); A-CHAQ: Adolescent-assessed CHAQ; IRR: Incidence rate ratio; CI: Confidence interval

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Development and Initial Validation of the Parent and Child Versions of the Juvenile Arthritis Disease Activity Score

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Background/Purpose: Incorporation of parent-/child-reported outcomes in patient assessment is deemed increasingly important in the managment of children with juvenile idiopathic arthritis (JIA). Aim of the study is to develop and to validate parent-centered and child-centered versions of the Juvenile Arthritis Disease Activity Score (JADAS), named parJADAS and chiJADAS, respectively.

Methods: The parJADAS and chiJADAS include 4 measures: 1) parent/child assessment of disease activity; 2) assessment of pain intensity; 3) self/proxy assessment of joint disease; 4) assessment of morning stiffness (MS). Disease activity and pain are assessed on a 0-10 VAS. The active joint count is based on the count of any swollen or painful joint up to a maximum of 10 joints. MS duration is assessed on a Likert scale, ranging from no MS (0 points) to > 2 hours of MS (10 points). Validation was conducted on a dataset of 602 children with JIA who underwent 1749 visits at study unit. To account for repeated measurements in a single patient, construct validity was assessed by calculating between-subject and within-subject correlations of parJADAS and chiJADAS with cJADAS, JADAS10, physician global assessment of disease activity, number of active joints, parent/child rating of well-being and ESR. Discriminant ability was evaluated by comparing score levels between patients with active or inactive disease according to current criteria, and between patients who were satisfied or not satisfied with disease outcome. Sensitivity to change was tested using standardized response mean (SRM) in 2 subsequent visits performed no more than 6 months apart. Internal consistency was assessed with Cronbach‘s alpha coefficient and inter-rater reliability was assessed using the intraclass correlation coefficient (ICC).

Results: Between-subject correlations of parJADAS and chiJADAS were high (>0.70) with JADAS10, cJADAS10, parent/child rating of overall well-being, and moderate (0.40-0.70) with the other measurements. Moreover, in the same subject, changes over time of the parJADAS and chiJADAS corresponded to changes in disease activity, as indicated by high within-subject correlations with JADAS10, cJADAS10, physician global assessment of disease activity, parent/child rating of overall well-being, and active joint count. Both parJADAS and chiJADAS discriminated well between inactive and active disease and between satisfied and not satisfied patients ($p<0.001$). The responsiveness to clinical change of parJADAS was good (SRM = 0.84). The internal consistency was satisfactory, with Cronbach‘s alpha >0.80 for both PARJADAS and CHIJADAS. The inter-rater reliability between the parJADAS and the chiJADAS measured at the same visit was high, with ICC 0.92 (95% CI 0.90-0.93).

Conclusion: The parJADAS and chiJADAS were found to be valid and reliable for assessment of disease activity in JIA and may therefore be suitable for use in clinical practice, observational studies, and therapeutic trials. Both scores may potentially surrogate physician assessments when these are not available.

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Discordance Between Physician, Patient, and Parent Disease Assessment Scores in Juvenile Idiopathic Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Global assessment scores are increasing important in assessing disease activity by physicians and patients/parents (PGAmd, PGApatient/parent). The purpose of this study was to determine and characterize the discordance between these assessments JIA patients and to distinguish which patient and disease characteristics contribute to this discordance.

Methods: Patients in this study were part of the Pediatric Rheumatology-Care & Outcomes Improvement Network (PR-COIN) and data collected from the registry. Patient and disease characteristics were collected including PGAmd and PGApatient/parent scores (each on a 21-point visual analog scale from 0-10) from 202 established JIA patients at Stanford Children's Health, ages 2-18. PGA discordance was calculated as [PGApatient] – [PGAmd], could range from -10 to 10, and was classified as positive, negative, or none. No discordance was defined as agreement within 1 point. Negative discordance was defined as the patient's PGA being underrated by >1 point compared to the MDs, whereas positive discordance was the reverse. Discordance was "marked" if the difference was greater than three. Validated instruments were administered to specific age groups: 2-4, 5-7, 8-12, and 13-18. Descriptive statistics were calculated and logistic regression used to evaluate the association between the discordance category and the patient/disease characteristics for all positive and then all negative discordance, each with no discordance as the reference. We also compared MD and parent PGA scores (198 pairs), as well as patient-parent agreement (147 pairs).

Results: 138 (68.3%) patients were female with a mean (SD) age of 11.4y (4.5) and disease duration of 4.3y (3.8). Oligoarticular (31.7%), rheumatoid factor (RF) negative polyarticular (24.3%), and enthesitis-related arthritis (ERA) (17.8%) were the most common JIA subtypes. For physician-patient pairs, 82 (54%) had no discordance, 54 (36%) had positive/marked positive discordance, and 15 (10%) had negative/marked negative discordance. The results were similar for physician-parent discordance. When patient and parent responses were compared, there was greater concordance (69% agreement) than compared to MD-patient (54%) and MD-parent (65%). After age and sex adjustment, pain, morning stiffness, and elevated CHAQ scores were associated with increased odds of positive discordance. Patients with RF negative polyarticular and ERA had lower odds of negative discordance when compared to patients with oligoarticular disease in the MD-patient comparison and with increased odds of positive discordance in the MD-parent comparison.

Conclusion: It is important to understand what patients and parents perceive as important to their disease status and health outcomes. Discordance was seen in approximately 50% of MD-patient and MD-parent comparisons with the majority of the discordance being positive/marked positive (78% of MD-patient and MD-parent discordant pairs). Pain, the presence of morning stiffness, and higher CHAQ scores were found to be statistically significantly associated with positive discordance.

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Abstract Number: 410

Sleep and Its Relationship to Pain and Disease Activity in Turkish Children and Adolescent with Juvenile Idiopathic Arthritis

Ela Tarakci[1], Saime Nilay Baydogan[1], Kenan Barut[2], Amra Adrovic[2], Sezgin Sahin[2] and **Ozgur Kasapcopur**[3], [1]Istanbul University, Faculty of Health Science, Division of Physiotherapy and Rehabilitation, Istanbul, Turkey, [2]Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Istanbul, Turkey, [3]Department of Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Istanbul, Turkey

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile idiopathic arthritis is a broad term that describes a clinically heterogeneous group of arthritis of unknown cause, which begin before 16 years of age. Sleep problems are common among children with chronic illnesses such as JIA. However, little is known about the frequency and severity of sleep disturbance(s) and the factors that are associated with sleep problems in children with JIA. The aims of this study were to primarily investigate sleep quality and to secondarily examine possible associations of pain, disease activity, sleep disturbance in Turkish children and adolescent with JIA.

Methods: 96 patients with JIA (age range 8-18) participated in this study. Disease activity was assessed with The Juvenile Arthritis Disease Activity Score-27 (JADAS27). Pain severity was evaluated with a 100-mm Visual Analog scale (VAS). Sleep quality was evaluated with Pittsburgh Sleep Quality Index (PSQI). The PSQI is a self-rating questionnaire resulting in a global score between 0 and 21, which consists of seven subscores (sleep quality, sleep latency, Sleep efficiency, daytime dysfunction, sleep disturbance, use of sleeping medication, sleep duration). A global PSQI score above 5 indicates poor sleep.

Results: A total of 96 eligible patients with JIA (61 female, 35 male) were enrolled including 42 (43.8%) with polyarticular onset, 33 (34.8%) with oligoarticular subtype, 14 (14.6%) with systemic onset and 7 (7.3%) with other subtypes. The mean of age, duration of sleep and pain severity was 12.93±3.36, 8.43±1.59 and 23.80±24.82, respectively. 39.6% of participants were poor sleepers. Table 1 shows comparisons of the results of JADAS and VAS pain in patients with good/poor sleep quality groups. JADAS and VAS-pain were statistically significant worse in patients with poor sleep than in patients with good sleep ($p<0.05$). 96.1% of patients have reported that they have experience of sleep disturbance (65.6% of them; less than once a week, 30.2% of them; once or twice a week, 1% of them; three or more time week). Sleep quality was very good only for 29.2% of them. 84.4% of them have reported they sleep >7 hours. 66.7% of participants reported needed more than 15 minutes to fall asleep each night (sleep latency). Sleep efficiency was found as >85% for almost all patients.

Conclusion: The results of this study suggest that poor sleep are significant widespread in Turkish children and adolescent with JIA and poor sleep quality is associated with greater pain severity and disease activity among patients with JIA. Future research should investigate whether reducement in pain and disease activity can improve sleep quality in patients with JIA **Table 1.** Comparisons of the results of JADAS and VAS pain in patients with good/poor sleep quality groups

	Good Sleep n=58 (60.4%)	**Poor Sleep n=38 (39.6%)**		
	Mean (SD)	**Mean (SD)**	**t**	**p**
JADAS	4.65 (4.31)	6.96 (4.96)	-2.418	0.018
VAS-pain	16.81 (22.25)	34.47 (25.00)	-3.620	0.000

Abstract Number: 411

Evaluating Levels of Activity and Health-Related Quality of Life in a Cohort of Youth Athletes with Juvenile Idiopathic Arthritis

Tommy Gerschman[1], Jordan Raugust[2], Julia Brooks[3], Nicole Johnson[1], Nadia Luca[1], Rebeka Stevenson[1], Heinrike Schmeling[4], Paivi Miettunen[1] and Susanne Benseler[1], [1]Pediatrics, University of Calgary, Calgary, AB, Canada, [2]Department of Pediatrics, University of Calgary, Calgary, AB, Canada, [3]Pediatrics, Alberta Children's Hospital, Calgary, AB, Canada, [4]Paediatrics, University of Calgary, Calgary, AB, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: Children with JIA are increasingly being encouraged to be physically active and are participating in organized and competitive sports as youth athletes. These youth are at risk of experiencing pain and dysfunction related to their underlying rheumatic disease, as well as the sports-related injuries observed in the general population. Our objective was to describe the demographic characteristics as well as the physical activity level and health-related quality of life of a cohort of youth athletes who have a diagnosis of JIA.

Methods: The JIA Sport and Exercise Medicine Clinic at Alberta Children's Hospital is a multidisciplinary clinic run by a pediatric rheumatologist, physiatrist, and physiotherapist. All practitioners have a special interest and experience in pediatric sport and exercise medicine. The clinic includes children with a diagnosis of JIA followed in the hospital's Pediatric Rheumatology Clinic, who self-identify as athletes and are interested in attending a Sport and Exercise Medicine clinic. Prior to the clinic visit, each child is asked to complete a series of questionnaires which includes validated measures of level of physical activity (Hospital for Special Surgery Pediatric Functional Activity Brief Scale (HSS Pedi-FABS) (scores 2-30) and Physical Activity Questionnaire for Adolescents (PAQ-A) (scores 1-5)) and health-related quality of life (Pediatric Quality of Life Generic Core Scale (Version 4.0, Adolescent) (PedsQL GCS-A) and Pediatric Quality of Life (Version 3.0) Rheumatology Module (PedsQL-Rheum)).

Results: A total of 11 youth with JIA participated in the JIA Sport and Exercise Medicine Clinic between October 2014 – April 2015. Children had a median age of 14 years (range 10-17) and 64% were male. The median time since diagnosis was 4 years (range 1-14). The sub-types of JIA included oligoarticular, 7, enthesitis-related arthritis, 3, and polyarticular RF negative, 1. All children took at least one arthritis medication, including NSAIDs (8), non-biologic DMARDs (5), and biologic DMARD (1). Children were involved in a variety of primary sports including ice-hockey, soccer, baseball, football, running, gymnastics, ringette, and dance. The children indicated that they were active a median of 13 hours per week (range 3-22). The measures of physical activity revealed moderate to high mean scores (SD) on the PAQ-A, 2.84 (0.84), and HSS Pedi-FABS, 22.45 (6.27). Health-related quality of life was found to be low with mean scores (SD) on the PedsQL GCS-A of 81.03 (11.08), (Physical Health, 73.58 (18.77), and Psychosocial Health, 85.00 (9.37)). The mean scores (SD) on the PedsQL-Rheum were low to moderate for Pain and Hurt, 58.52 (24.25), Treatment, 76.62 (18.38), Worry 75.00 (23.86), and Communication, 71.97 (23.94). The score was high for Daily Activities, 95 (9.22).

Conclusion: Youth athletes with JIA are involved in a variety of sports. They are physically active for an above average number of hours per week but experience a significant degree of pain and have decreased scores of physical and psychosocial functioning. Additional support may need to be targeted to youth athletes with JIA to help them achieve their sports goals.

Disclosure: T. Gerschman, None; **J. Raugust**, None; **J. Brooks**, None; **N. Johnson**, None; **N. Luca**, None; **R. Stevenson**, None; **H. Schmeling**, None; **P. Miettunen**, None; **S. Benseler**, None.

Abstract Number: 412

Oral Glucocorticoids and Rates of Incident Diabetes Mellitus and Hypertension in Children with Juvenile Idiopathic Arthritis and Attention-Deficit/Hyperactivity Disorder

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Background/Purpose: Diabetes mellitus (DM) and hypertension (HTN) are well-known toxicities of glucocorticoids (GCs), but the risks of these complications are unclear in children with JIA. We studied rates of new-onset DM and HTN after oral GC exposure compared with non-users separately in children with JIA and children with attention-deficit/hyperactivity disorder (ADHD), a non-immune reference population.

Methods: Using Medicaid claims data (2000-2010), we identified children ages 1-18 diagnosed with JIA (based on diagnostic codes ± pharmacy claims) or ADHD (based on diagnostic codes). We studied oral GCs as time-varying exposures based on pharmacy claims after a ≥9-month GC-free baseline period. Incident DM was defined by new use of insulin or oral antidiabetic drugs; secondary type 2 DM definitions combined diagnoses and pharmacy claims. Incident HTN was defined by new use of antihypertensive drugs combined with diagnoses. We compared absolute rates of new DM and HTN in each cohort and used Cox regression to estimate hazard ratios (HRs) between GC-exposed and -unexposed children.

Results: Children with JIA contributed ~2,600 person-years (py) of GC-exposed time and ~38,000 py of unexposed time; children with ADHD had ~7,500 py exposed to GCs and ~1.6 million py unexposed. Compared with non-users, GC users were younger and more likely to be recently hospitalized before study entry. Within disease cohorts, exposed and unexposed groups were similar in terms of sex, race/ethnicity, and prior comorbidities. Compared with the unexposed, incremental rate differences of new DM drug use and type 2 diabetes were 10.4/1,000 py and 4.5/1,000 py in GC users with JIA, respectively, and 5.1/1,000 py and 1.7/1,000 py in GC users with ADHD, respectively (Table). The rate differences for new antihypertensive drug use were of similar magnitude: 15.4/1,000 py greater in GC users with JIA and 4.8/1,000 py greater in GC users with ADHD. After adjusting for age, sex, race/ethnicity, year of study entry, prior comorbidities and medications, and baseline healthcare utilization, GC exposure was associated with new DM drug use in children with JIA: current GC use, aHR 3.4 (95% CI 2.4, 4.8); any prior GC use, aHR 1.7 (95% CI 1.2, 2.4). The associations of GC use with type 2 DM in JIA, and with DM among children with ADHD, were similar (Table). The strength of association between GCs and HTN was even greater: current GC use, aHR 4.5 (95% CI 3.2, 6.2); any prior GC use, aHR 2.4 (95% CI 1.6, 3.6). Results for children with ADHD were also similar (Table).

Conclusion: In children with JIA, current oral glucocorticoid use is associated with a 3-fold increased rate of new treatment for diabetes mellitus and over 4-fold increased rate of new treatment for hypertension. These findings are similar among children with ADHD, but the absolute rates of these complications are higher in children with JIA. More work is

needed to clarify how GC dose and duration relate to these toxicities.

Table. Absolute and relative (hazard) rates of new diabetes mellitus and hypertension among GC-exposed and -unexposed children with JIA and ADHD

	Diabetes mellitus				Hypertension	
	New DM drug use[1]		New type 2 DM[2]		New HTN drug use[3]	
	JIA	ADHD	JIA	ADHD	JIA	ADHD
No. of outcomes/ person-years						
Never GC-unexposed[4]	163 / 38,323	3,423 / 1,579,778	78 / 38,538	1,230 / 1,583,059	140 / 37,864	2,129 / 1,577,660
Ever GC-exposed[4]	40 / 2,730	56 / 7,691	18 / 2,759	19 / 7,712	49 / 2,561	46 / 7,463
Incidence per 1,000 py (95% CI)						
Never GC-unexposed[4]	4.3 (3.7, 5.0)	2.2 (2.1, 2.2)	2.0 (1.6, 2.5)	0.8 (0.7, 0.8)	3.7 (3.1, 4.4)	1.4 (1.3, 1.4)
Ever GC-exposed[4]	14.7 (10.8, 20.0)	7.3 (5.6, 9.5)	6.5 (4.1, 10.4)	2.5 (1.6, 3.9)	19.1 (14.5, 25.3)	6.2 (4.6, 8.2)
Rate difference	10.4 (5.8,15.0)	5.1 (3.2, 7.0)	4.5 (1.5,7.5)	1.7 (0.6, 2.8)	15.4 (10.0, 20.8)	4.8 (3.0, 6.6)
Model 1[5]:						
No current GC exposure (ref)	1.0	1.0	1.0	1.0	1.0	1.0
Any current GC exposure,[4] aHR (95% CI)	3.4 (2.4, 4.8)	3.4 (2.6, 4.4)	3.2 (1.9, 5.4)	3.1 (2.0, 4.9)	4.5 (3.2, 6.2)	4.3 (3.2, 5.8)
Model 2[5]:						
Never GC exposure (ref)	1.0	1.0	1.0	1.0	1.0	1.0
Ever GC exposure,[4] aHR (95% CI)	1.7 (1.2, 2.4)	1.4 (1.3, 1.5)	1.9 (1.1, 3.2)	1.4 (1.2, 1.6)	2.4 (1.6, 3.6)	1.7 (1.6, 1.9)

ADHD, attention-deficit/hyperactivity disorder; aHR, adjusted hazard ratio; CI, confidence interval; DM, diabetes mellitus; GC, oral glucocorticoid; HTN, hypertension; py, person-years; ref, reference. [1]Insulin or oral antidiabetic drugs [2]Type 2 diabetes diagnosis based on combination of diagnosis claims and antidiabetic drug pharmacy claims [3]Because of their decreased specificity to hypertension diagnoses, beta-blockers and clonidine needed to be accompanied by ICD-9 code for hypertension within ± 4 months [4]Exposure status during the study period; exposure was reclassified in time-varying fashion; some subjects contributed time to both exposure cohorts [5] Models adjusted for age, sex, race/ethnicity, year of cohort entry, prior comorbidities (for DM: hypertension, obesity; for HTN:

diabetes, obesity), prior medications (for DM: antipsychotics, non-steroidal anti-inflammatories; for HTN: non-steroidal anti-inflammatories, stimulants), recent healthcare utilization (hospitalization, number of baseline medications, number of clinical encounters)

Disclosure: D. B. Horton, None; **F. Xie**, None; **L. Chen**, None; **M. Mannion**, None; **B. L. Strom**, AstraZeneca, 5,Bayer, 5,Boehringer Ingelheim, 5,GSK, 5,Eli Lilly and Company, 5,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,Takeda, 5,UCB, 5; **J. Curtis**, None; **T. Beukelman**, Novartis Pharmaceutical Corporation, 5,UCB, 5.

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Abstract Number: 413

Golimumab in Refractory Uveitis Associated to Juvenile Idiopathic Arthritis. Multicenter Study of 7 Cases and Literature Review

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Background/Purpose: According to a recent expert panel, in refractory juvenile idiopathic arthritis (JIA)-related uveitis, infliximab or adalimumab may be considered (Levy-Clarke et al. Ophthalmology 2014; 121:785-796). In some cases these biologic agents are not effective, or not tolerated. Golimumab (GLM) is a novel fully humanized anti-TNF-α monoclonal antibody. Our aim was to assess the efficacy of GLM in refractory uveitis associated with JIA.

Methods: Multicenter study of uveitis related to JiA and refractory to at least **a)** one standard synthetic immunosuppressive drug and, **b)** one anti-TNFα drug**.** The results were expressed as mean±SD or as median (25,75 interquartile range [IQR]) as appropriate. The Wilcoxon signed-rank test was used to compare continuous variables. Also a review of the literature regarding the effectiveness of GLM in uveitis related to JiA was performed.

Results: We assessed 7 (5 women/2 men) patients with 13 affected eyes; mean age 21.7±7.5 years. Uveitis was bilateral in 6. Cystoid macular edema (CME) was present in 3 patients (5 eyes). Besides corticosteroids and synthetic immunosuppressive drugs, patients had received a median of 2 biological agents (range 0-3): adalimumab (n=6), etanercept (n=1), infliximab (n=3), abatacept (n=2). GLM dosage regimen was 50 mg/sc every 4 weeks. GLM yielded an improvement in all ocular parameters. After 6 months of therapy the number of anterior chamber cells decreased from a median of 1 [0.25-1.5] to 0 [0-0.5] (p=0.02), vitritis from 0 [0-1] to 0 [0-0] (p=0.6); and optical coherence tomography (in 3 patients with CME) from 313.6±77.05 to 261.4±75.1 µm (p=0.03). Moreover, the best-corrected visual acuity increased from 0.5 to 0.62 (p=0.018). After a mean follow-up of 16.8±11.4 months, a complete remission of uveitis was achieved in

4 of 7 patients. The only observed adverse effects were local erythema at the injection site in 2 patients. A literature review of refractory JIA related uveitis treated with GLM is summarized in **Table.**

Conclusion: GLM appears to be a useful therapy in refractory JIA-related uveitis. **TABLE**

	Cordero-Coma M et al, 2014 (1)	**Miserocchi E et al, 2014 (2)**	**William M et al, 2012 (3)**	**Present series**
Number of cases, N	4	13	3	7
Sex (women/men)	3/1	10/3	2/1	5/2
Age (mean±SD, years)	25.5±5.80	25±5.37	17.33±8.73	21.71±7.48
Uveitis pattern (bilateral/unilateral)	3/1	13/0	2/1	6/1
Previous treatment	MTX, SSZ, AZA, ETN, IFX, ADA	MTX, ETN, IFX, ADA, RTX, ABA	MTX, AZA, IFX, DCZ, ADA, ETN, ABA	CFM, CyA, MTX, IFX, ETN, ADA
GLM regimen	50mg/sc every 4 weeks	50mg/sc every 4 weeks	50mg/sc every 3 weeks	50mg/sc every 4 weeks
Ocular remission after GLM, N	4	11	2	4
Adverse effects related to GLM	none	1 pulmonary infection 1 skin reaction	none	skin reaction
Months in treatment with GLM (mean±SD)	6 months	22.38±7.47 months	10±6.92 months	16.38±11.43 months
GLM withdrawal	no	no	one patient for inefficacy	one patient for inefficacy

*Abbreviations:*MTX: Methotrexate; SSZ: Sulfasalazine; AZA: Azathioprine; IFX:Infliximab; ETN: Etarnecept; ADA: Adalimumab; ABA: Abatacept; RTX: Rituximab; CyA :Cyclosporine; CFM: cyclophosphamide (1) Cordero-Coma M, et al. Mediators Inflamm. 2014; 2014: 717598 (2) Miserocchi E, et al. Ocul Immunol Inflamm. 2014; 22: 90-5 (3) William M, et al. J Ophthalmic Inflamm Infect. 2012; 2: 231-3

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Abstract Number: 414

Proposal for the Definition of Inactivity of Juvenile Idiopathic Arthritis Related Uveitis from the Multinational Interdisciplinary Working Group for Uveitis in Childhood Group (MIWGUC)

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile idiopathic arthritis (JIA) associated uveitis is the most common extraarticulare comorbidity of juvenile idiopathic arthritis. Nowdays it occurs in about 10-15% of JIA patients. As effective treatment options are emerging, is it extremely important to propose validated definition of inactivity, which is main aim of the treatment.

Methods: Multinational Interdisciplinary Working Group for Uveitis in Childhood Group (MIWGUC) had prospectively evaluated the validity of the proposed outcome measures(1). Based on these data, we proposed a definition of inacitivity using the nominal group technique in a consensus meeting in Barcelona, Spain, in November 2015.

Results: The following items were selected to define inacitivity. It is required, that in both eyes the following condition is reached: 1. Slit lamp total number of AC cells: 0 inflammatory cells *In aphakic patients ,some cells may be present, in the anterior vitreous 2. Absence of Optic disc edema *The presence of isolated optic disc edema may not be a sign of activity 3. Absence Macular edema *The presence of isolated macular edema may not be a sign of activity 4. Absence of Vitreous haze *The presence of isolated vitreous haze may not be a sign of activity 5. VAS score of activity physician 0-100: must be 0

Conclusion: We proposed items to define inactivity of JIA associated uveitis, which is a major goal of treatment. This proposal will be validated from the MIWGUC group in prospective study. References:

1. Heiligenhaus A, Foeldvari I, Edelsten C, Smith JR, Saurenmann RK, Bodaghi B, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis Care Res (Hoboken). 2012;64(9):1365-72.

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Abstract Number: 415

Proposal for a Damage Index for Juvenile Idiopathic Arthritis Related Uveitis from the Multinational Interdisciplinary Working Group for Uveitis in Childhood Group (MIWGUC)

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Background/Purpose: Juvenile idiopathic arthritis (JIA) associated Uveitis is the most common extraarticulare comorbidity of juvenile idiopathic arthritis. Nowdays it occurs about 10-15% of JIA patients. As innovative effective treatment options are emerging, it is extremely important for defining validated damage index in order to assess the effectivity of drugs to preventing damage, one of the main aims of the treatment.

Methods: Multinational Interdisciplinary Working Group for Uveitis in Childhood Group (MIWGUC) had prospectively evaluated the validity of the proposed outcome measures(1). Based on the data, we proposed a damage index using the nominal group technique in a consensus meeting in Barcelona, Spain, in November 2015.

Results: Following items were selected for assessing damage: Vision related permanent damage per eye /per patient - yes / no **Right eye Left eye** 1. flare 2. synechiae 3. cataract 4. maculopathy 5. Opticopathy 6. Decreased Visual acuity 7. Ocular hypertony – >21 mmHg 8. Ocular hypotony - <6 mmHg 9. Glaucomatous field loss and /or glaucomatous optic atrophy 10. Band-keratopathy 11. Epiretinal membrane formation 12. Visual deterioration – less then 0.3 in any eye 13. Uveitis related disability VAS 0-100 by ophthlamologist 14. Uveitis related disability VAS 0-100 by pediatric rheumatologist

Conclusion: We proposed items for assessing the damage index of JIA associated uveitis. The damage index should be a valid instrument for assessing the effectivity of a given drug in order to preventing damage. This proposal will be evaluated from the MIWGUC group in prospective study. References:

1. Heiligenhaus A, Foeldvari I, Edelsten C, Smith JR, Saurenmann RK, Bodaghi B, et al. Proposed outcome measures for prospective clinical trials in juvenile idiopathic arthritis-associated uveitis: a consensus effort from the multinational interdisciplinary working group for uveitis in childhood. Arthritis Care Res (Hoboken). 2012;64(9):1365-72.

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Abstract Number: 416

Uveitis Associated to Polyarticular Juvenile Idiopathic Arthritis

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Background/Purpose: Approximately 10-15% of patients (pts) with juvenile idiopathic arthritis (JIA) experience comorbid uveitis. The objective of this study is to explore events of uveitis and associated safety in pts with moderately/severely active polyarticular or polyarticular-course JIA (pJIA) who were prescribed and treated with adalimumab (ADA) and/or methotrexate (MTX) in routine clinical practice.

Methods: STRIVE is an ongoing, multicenter, non-interventional, observational registry of up to 10 years duration in pts with moderately/severely active pJIA who are treated with either ADA±MTX or MTX alone as part of routine clinical care. Pts could initiate ADA and/or MTX within 24 months prior to registry entry. Pts that completed ADA studies (DE038, M10-444) had option to roll-over into this registry. Ophthalmologists performed slit-lamp examination for uveitis at registry entry and specified visits in 3-6 month intervals through 5 yrs. Beyond 5 yrs, uveitis events were collected solely through adverse event (AE) reporting. Observational ocular AEs (e.g. cataract, glaucoma) were recorded from registry entry through yr 6.

Results: As of 1 June 2015, a total of 21/303 (6.9%) and 68/543 (12.5%) enrolled pts reported at least 1 case of JIA-associated uveitis at any visit in the MTX and ADA±MTX groups, respectively. In the JIA-associated uveitis population, 10 (47.6%) in MTX and 42 (61.8%) in ADA±MTX group presented with documented uveitis at registry entry. In the population without uveitis at registry entry, 11/293 (3.8%) and 26/501 (5.2%) pts in MTX and ADA±MTX arms, respectively had first documentation of uveitis post-enrollment. Most pts in the JIA-associated uveitis sub-population were female (73%), white (96%), with a mean age of 8.1 yrs; mean pJIA disease duration was 1.8 and 4.8 yrs for MTX and ADA±MTX groups at registry entry, respectively. Nine (42.9%) MTX and 48 ADA±MTX (72.7%) pts were positive for antinuclear antibodies at registry enrollment. For vast majority of pts,uveitis was localized to anterior layer. In ADA group, 45 (66.2%) pts with documented uveitis received concomitant MTX during the course of the registry. Through Month 42, majority of JIA-associated uveitis sub-population had either no new manifestation of uveitis or stabilized uveitis. A higher proportion of MTX vs ADA±MTX pts discontinued registry drug (15/21 [71.4%] vs. 21/68 [30.9%]), but continued to be monitored for safety follow-up. Of these, 2 (9.5%) and 1 (1.5%) in MTX and ADA±MTX group, respectively, discontinued the registry drug due to an AE, and 4 of the 15 pts in the MTX group discontinued MTX group and switched to ADA±MTX registry group. Two (0.4%) pts with glaucoma and 1 (0.2%) pt with cataract were reported in ADA±MTX group and none in MTX group; 2 of these patients had documented uveitis at registry enrollment.

Conclusion: Among pJIA pts with uveitis documented at registry entry, a higher percentage of pts were enrolled in ADA ±MTX group as per investigator judgment. No new safety signals for adalimumab were observed in JIA-associated uveitis sub-population treated per standard of care. Based on this interim analysis, JIA-associated uveitis appeared well-controlled during the course of this registry for pJIA pts with existing uveitis.

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Abstract Number: 417

Use of Tumor Necrosis Factor-α Inhibitors in Pediatric HLA-B27-

Associated Uveitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pediatric HLA-B27-associated uveitis is a common form of non-infectious uveitis (NIU) that can lead to ocular complications and vision loss. Methotrexate (MTX) is the usual first-line systemic treatment in NIU. Tumor necrosis factor-α inhibitors (TNFi) are primary therapy in other HLA-B27-associated diseases such as ankylosing spondylitis and inflammatory bowel disease. There is no standard treatment protocol for pediatric HLA-B27-associated uveitis. Given the success of TNFi in other HLA-B27-associated diseases, our aim is to describe MTX and TNFi use in pediatric HLA-B27-associated uveitis.

Methods: We reviewed medical records of 21 children with HLA-B27-associated uveitis. We compared demographics and clinical characteristics based on treatment with TNFi.

Results: There were 12 (57%) children with HLA-B27-associated uveitis alone (U), and 9 (43%) with JIA-associated uveitis (JIAU) that was all enthesitis related arthritis (Table 1). Most were non-Hispanic (86%) White (95%) males (52%), diagnosed at a median of 10.5 (8.1-11.8) years, with anterior (90%), unilateral (67%) disease and several complications. Of these, 14 (67%) did not require TNFi (8 topical steroids alone, 6 MTX alone,) and 7 (33%) required TNFi. There was a clinical trend of earlier treatment with TNFi in JIAU (0.5 vs. 2.6 years of MTX) despite similar uveitis duration before MTX start (0.2 vs. 0.3 years). Comparing by TNFi use, more females were treated with TNFi (60% vs. 9%, $p = 0.02$) (Table 2). There was no difference in race, age at uveitis diagnosis, uveitis type, laterality, or complications. Comparing by gender, more females 8/10 (80%) then males 5/11 (45%) also needed MTX. Although they had similar uveitis type (40% associated with ERA), complications (80%), and age at diagnosis (10.8 vs. 9.7 years), more females needed TNFi and MTX.

Conclusion: Usual treatment for pediatric NIU includes MTX and then TNFi if MTX fails, ocular complications arise/worsen or uveitis persists. Based on our results, it appears reasonable to treat pediatric HLA-B27-associated uveitis with MTX prior to TNFi. However, we demonstrate the increased use of TNFi in females despite a similar uveitis course. We were unable to determine clinical factors that explained this difference due to our sample size, but this requires further study. There may be an inherent gender difference in immune pathway response which may mitigate uveitis course and improve visual outcomes.

Table 1. Demographics and Clinical Characteristics of Children with HLA-B27-associated Uveitis

	All (N=21)	HLA-B27 associated uveitis alone (U) (N=12)	JIA-associated uveitis (JIAU) (N=9)	P-value**
Gender, female	10 (48%)	6 (50%)	4 (44%)	1.00
Hispanic	3 (14%)	1 (8%)	2 (22%)	0.55
Race*				
Caucasian	20 (95%)	11 (92%)	9 (100%)	1.00
African American	2 (10%)	2 (17%)	0	0.49
Age at Uveitis Diagnosis, years, median (25^{th} – 75^{th})	10.5 (8.1-11.8)	9.1 (5.9-10.9)	11.6 (10.1-14.1)	0.11
Duration of Uveitis To Date, years, median (25^{th} – 75^{th})	4.4 (2.0-5.9)	4.4 (2.8-5.9)	4.4 (1.6-5.9)	0.92
Bilateral Disease	7 (33%)	5 (42%)	2 (22%)	0.16
Location*				
Anterior	19 (90%)	10 (83%)	9 (100%)	0.49
Intermediate	5 (24%)	3 (25%)	2 (22%)	1.0
Other (Panuveitis)	2 (10%)	2 (17%)	0 (0%)	0.49
Complications*				
Any	17 (81%)	11 (92%)	6 (67%)	0.27
Synechiae	12 (57%)	9 (75%)	3 (33%)	0.09
Cataracts	6 (29%)	3 (25%)	3 (33%)	1.00
Cystoid Macular Edema	6 (29%)	3 (25%)	3 (33%)	1.00
Glaucoma/ Increased intraocular pressure	5 (24%)	4 (33%)	1 (11%)	0.34
Band Keratopathy	4 (19%)	2 (17%)	2 (22%)	1.00
Amblyopia	1 (5%)	0 (0%)	1 (11%)	0.43
Methotrexate Use, Ever	13 (62%)	6 (50%)	7 (78%)	0.37
Maximum dose >0.5 mg/kg/week	12 (92%)	6 (100%)	6 (86%)	0.52
Mode of administration, oral	7 (54%)	4 (67%)	3 (43%)	0.59
Duration of Uveitis Before MTX, years, median (25^{th} – 75^{th})	0.2 (0.0-0.6)	0.3 (0.2-0.6)	0.2 (0-1.7)	0.87
Duration of MTX Before TNFi use, years, median (25^{th} – 75^{th})	1.7 (0.4 – 3.6)	2.6 (1.0 – 5.6)	0.5 (0.0 – 1.9)	0.40
Adalimumab Use, Ever***	2 (29%)	2 (50%)	-	-
% on weekly	2 (100%)	2 (100%)	-	
Duration of Uveitis Before adalimumab, years, median (25^{th} – 75^{th})	3.0 (2.1-3.8)	3.0 (2.1-3.8)	-	
Infliximab Use, Ever***	5 (71%)	2 (50%)	3 (100%)	0.43
Duration of Uveitis Before infliximab, years, median (25^{th} – 75^{th})	1.9 (0.5-2.2)	4.0 (0.5-7.5)	1.9 (0.3-2.2)	0.80
Max Dose mg/kg, median (25^{th} – 75^{th})	8 (7 – 10)	7.3 (7 – 7.5)	10 (8 – 10)	0.20
Frequency every XX weeks, median (25^{th} – 75^{th})	4.0 (4.0-4.0)	4.0 (4.0-4.0)	4.0 (2.0-4.0)	1.0

*Not mutually exclusive ('select all that apply'): Race=one person identified as both races; Location= some patients have multiple locations of disease; Complications=some patients have multiple complications.

**Fisher's exact tests for categorical data or non-parametric Wilcoxon rank-sum tests between U and JIAU , alpha=0.05, two-sided p-value.

*** Out of 7 total who were taking a TNFi.

Table 2. Comparison of Children with HLA-B27-associated Uveitis Treated with a Tumor Necrosis Factor α Inhibitor (TNFi)

	All (N=21)	NO TNFi use (N=14)	TNF use (N=7)	P-value**
Gender, female	10 (48%)	4 (29%)	6 (86%)	0.02**
Hispanic	3 (14%)	2 (14%)	1 (14%)	1.00
Race*				
Caucasian	20 (95%)	14 (100%)	6 (86%)	0.33
African American	2 (10%)	1 (7%)	1 (14%)	1.00
Age at Uveitis Diagnosis, median	10.5 (8.1-11.8)	10.4 (6.5-11.8)	10.5 (8.1-13.5)	0.97
Duration of uveitis To Date, years, median (25^{th} – 75^{th})	4.4 (2.0-5.9)	4.4 (0.9-5.9)	4.4 (2.0-7.2)	0.58
Bilateral Disease	7 (33%)	3 (21%)	4 (57%)	0.26
Location*				
Anterior	19 (90%)	13 (93%)	6 (86%)	1.00
Intermediate	5 (24%)	2 (14%)	3 (43%)	0.28
Other (Panuveitis)	2 (10%)	14 (67%)	7 (33%)	1.00
Complications*				
Any	17 (81%)	11 (79%)	6 (86%)	1.00
Synechiae	12 (57%)	8 (57%)	4 (57%)	1.00
Cataracts	6 (29%)	4 (29%)	2 (29%)	1.00
Cystoid Macular Edema	6 (29%)	3 (21%)	3 (43%)	0.35
Glaucoma/ increased IOP	5 (24%)	3 (21%)	2 (29%)	1.00
Band Keratopathy	4 (19%)	3 (21%)	1 (14%)	1.00
Amblyopia	1 (5%)	1 (5%)	0 (0%)	1.00

*Not mutually exclusive ('select all that apply'): Race=one person identified as both races; Location= some patients have multiple locations of disease; Complications=some patients have multiple diseases. **Fisher's exact tests for categorical data or non-parametric Wilcoxon rank-sum tests between IU and JIA diseases, alpha=0.05, two-sided p-value.

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Discrepancy in Reported and Actual Rates of Counseling on Teratogenicity and the Need for Contraception When Initiating Mycophenolate in Women of Childbearing Age

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Background/Purpose: Many women of childbearing potential with autoimmune diseases require terotogenic medications, such as mycophenolate. On October 29, 2007 the FDA deemed mycophenolate a pregnancy class D medication given the risks of first trimester abortion and congenital malformations.[1] The encounter when mycophenolate is initiated is arguably the most important time to counsel patients on its risks and the need for effective contraception. We compared reported rates versus actual documentation of counseling in the electronic medical record (EMR).

Methods: We developed a 10 question, anonymous survey that was distributed to all rheumatology providers at our institution. The survey asked respondents at how often they provide and document adequate counseling when initiating mycophenolate in women of childbearing age. Subsequently, using our institution's De-identified Clinical Data Repository, we identified women aged 17-45 on mycophenolate who had been seen in one of our rheumatology clinics since October 29, 2007, and assessed actual documentation of counseling at initiation of mycophenolate.

Results: Fifteen faculty and fellows (83%) responded to the survey. On average, respondents reported providing and documenting adequate counseling when initiating mycophenolate in 74% and 64% of encounters, respectively. Of 219 charts reviewed, 65 patients met inclusion criteria; the patients included were predominately Caucasian (38%) with an average age of 35. In 5 encounters (8%) providers documented advising the patient that mycophenolate is a teratogen and in only 1 encounter did a provider discuss the specific risks (**Table I**). The need for contraception while taking mycophenolate and 6 weeks afterwards, as well as the type of contraception utilized were also scarcely documented (n=6, 9%; n=0, 0%; n=9, 14%, respectively). In 22 (34%) encounters providers documented discussion of other side effects or that information was provided. Barriers to effective counseling identified by the survey included lack of time (50%) and inadequate knowledge (33%).

Conclusion: Documentation of counseling on teratogenicity and the need for contraception at the initiation of mycophenolate was reported at much higher rates than was actually observed on chart review, despite higher documentation of other side effects. By educating providers and using the EMR to prompt them to provide counseling when prescribing mycophenolate, we may be able to increase documentation rates. Additionally, "dot phrases" with risks and contraception information could be imported into the provider note and patient instructions as a time saving strategy. **Table I.** Mean reported rates of counseling on the teratogenicity of mycophenolate and the need for contraception as compared to actual documentation of counseling

	Reportedly discussed	***Reportedly documented***	***Actually documented***
	(Reported % of initial encounters)	*(Reported % of initial encounters)*	*N=65 (%)*
Counseling point			
Mycophenolate use in pregnancy carries an increased risk of 1st trimester abortion	*49%*	*16%*	1 *(2%)*
Mycophenolate use in pregnancy carries an increased risk of congenital malformations	*83%*	*45%*	1 *(2%)*
The patient should use contraception during her entire treatment with mycophenolate	*84%*	*65%*	6 *(9%)*
The patient should continue contraception 6 weeks following cessation of mycophenolate	*37%*	*15%*	0 *(0%)*
The type(s) of contraception utilized (or to be utilized) by the patient	*55%*	*38%*	9 *(14%)*
The patient should alert her doctor when considering pregnancy	*87%*	*60%*	2 *(3%)*

References: 1. U.S. Food and Drug Administration. (2007, October 29) Cellcept (mycophenolate mofetil) October 2007.

Disclosure: J. Thomason, None; **A. Bays**, None.

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Abstract Number: 419

Performance of Framingham Risk Factor Score in Predicting Cardiovascular Events in Patients with Polymyalgia Rheumatica

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Background/Purpose: chronic inflammatory diseases are at a substantially increased risk of cardiovascular disease. Framingham risk score (FRS) underestimates cardiovascular risk in many inflammatory diseases. Our objective was to assess the predictive ability of Framingham score model for the 10-year risk of fatal and non-fatal CV diseases in patients with Polymyalgia Rheumatica (PMR).

Methods: we retrospectively reviewed electronic medical records of patients registered in our hospital after year 2000 with the diagnosis of PMR. Patients fulfilling ACR PMR 2012 criteria or with a clinical diagnose made by a rheumatologist were included. Patients with history of cardiovascular event before diagnosis, age greater of 80 years at diagnosis or with less than 10 years of follow up after diagnosis, were excluded. Framingham score was calculated at diagnosis, and based on the FRS, patients were classified into low, intermediate and high-risk categories. Cardiovascular (CV) events such as stroke, transient ischemic attack, coronary arterial disease and peripheral vasculopathy were identified during follow up. Discriminatory ability for CV risk prediction was estimated by the area under the receiver operating characteristic (ROC) curve. Global cardiovascular risk was calculated at 10 years after PMR diagnosis and compared with FRS estimated at diagnosis.

Results: A total of 97 patients were included. Patients characteristics are described in table. Among the 97 patients followed up for a total of 981.5 person-years, 18 CV events occurred with an incidence rate of 1.83 per 100 patient-years (95% CI: 1.1-2.9). There were no differences in clinical characteristics among patients with and without CV events (table). The area under the ROC curve for FRS was 0.61 (95% CI: 0.47- 0.74), indicating low discrimination between patients with and without a CV event. According to FRS 17 (17.5 %), 46 (47.4%) and 34 (35%) patients were classified into low, intermediate and high risk categories respectively. Across the three predicted CV risk groups the observed/predicted CV events (%) were:0.059/0.065; 0.2/0.13; and 0.24/0.26 for low, intermediate and high risk categories respectively. When observed vs predicted CV events in quintiles of CV risk were compared, the following values were obtained: 0.1 vs 0.072; 0.16 vs 0.12; 0.20 vs 0.16; 0.31 vs 0.34.

Conclusion: FRS showed low discrimination capacity between patients with and without a CV event. FRS primarily underestimated CV risk at low and intermediate risk levels, and mostly overestimated CV risk at higher risk levels. Table 1. Patients characteristics

Variables	Patients with CV events (n=18)	Patients without CV events (n= 79)	p value
Females, n (%)	65 (82)	16 (89)	0.495
Mean age at diagnosis (SD)	73.5 (5.5)	71.9 (6.1)	0.3034
Mean erythrocyte sedimentation rate (SD)	60.2 (34.5)	59.9 (26.4)	0.9823
Mean Total cholesterol mg/L (SD)	208.3 (44)	213.7 (39.9)	0.6129
Diabetes at baseline, n (%)	3 (16.7)	5 (6.33)	0.150
Hypertension at baseline, n (%)	14 (77.8)	50 (63.3)	0.242
Obesity (BMI (weight(kg)/Height(m)2)>30, n (%)	5 (27.8)	17 (21.5)	0.567
Median FRS (IQR)	17.8 (12.4-26.6)	14.4 (10.8-21.9)	0.5404
Mean time follow up (years), (SD)	11.6 (1.6)	11.7 (1.7)	0.7761
Smoking, n (%)			
Never	12 (67)	68 (86)	
Former	3 (16.7)	6 (7.6)	0.177
Current	3 (16.7)	5 (6.3)	

Disclosure: F. B. Mollerach, None; **S. Moyano**, None; **L. E. Pompermayer**, None; **J. M. Martinez Perez**, None; **M. Scolnik**, None; **J. Rosa**, None; **L. J. Catoggio**, None; **E. R. Soriano**, Abbvie, 2,Pfizer Inc, 3,UCB, 2,Janssen Pharmaceutica Product, L.P., 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Abbvie, 5,Pfizer Inc, 5,UCB, 5,Janssen Pharmaceutica Product, L.P., 5,Roche Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,Bristol-Myers Squibb, 5.

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Abstract Number: 420

Feasibility of a Rheumatology Staff Protocol for Tobacco Cessation Counselling and Quit Line Electronic Referral

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Background/Purpose: Smoking is a both a risk factor for developing rheumatoid arthritis (RA) and a predictor of severe, treatment-refractory disease in RA and other rheumatic conditions, yet, little is systematically done in rheumatology clinics to help patients quit smoking. We previously reported that only 10% of eligible RA visit notes documented tobacco counselling by rheumatologists; only one in 175 notes recommended quit line phone services. Quit line services are free in every state and recommended by US guidelines to improve quit rates four-fold, but are rarely leveraged in rheumatology clinics.

Methods: We designed a prospective study to examine the feasibility of a staff-led tobacco cessation intervention in three academic rheumatology clinics over six weeks in 2016, compared to 2012-2015. Medical assistants and nurses were educated on tobacco cessation and rehearsed evidence-based care in a one hour session. During clinic rooming, electronic health record (EHR) alerts prompted documentation of tobacco use, assessment of 30 day readiness to quit among users, and offers for electronic referral for quit line to phone the patient within one week. Process measures for assessing tobacco use and readiness to quit were compared (pre- post-) using standard EHR documentation fields. We compared quit line referral events to historic abstracted rates. Chi-square tests and logistic regression models were used to obtain odds ratios between the groups pre-intervention and during protocol implementation.

Results: Over the six week protocol pilot, 123 rheumatology visits with patients who smoke were compared to 4078 baseline visits with patients who smoke. Process measures showed that the protocol increased tobacco status documentation to 97% (OR 1.40, 95% CI 1.02-1.92) **Table 1**. Assessment of 30 day readiness to quit robustly increased from 3% before to 76% during the protocol intervention (OR 105, 65.7-167). Moreover, 32% (n=30) of those asked reported readiness to quit or cut back in the next 30 days. In total during the intervention, 12% (n=15 of 123 eligible visits) agreed to tobacco quit line electronic referral compared to 0.57% being offered referral (n=1 of 175) in our prior report ($p<0.001$).

Conclusion: The rheumatology staff protocol intervention for tobacco quit line electronic referral was feasible and tobacco cessation care improved by week six. A marked gain in assessing quit readiness, despite prior existence of this field in the EHR, shows that tools alone are ineffective and supports the need to study systematic implementation of such tools. A full six month pilot study is under way to assess protocol effectiveness including actual tobacco cessation rates. Given the importance of tobacco cessation for inflammatory disease activity and long term cardiovascular risk, methods should be studied to deliver tobacco cessation care or connect patients to proven quit resources.

Table 1. Tobacco use and quit readiness assessment and quit line referrals by visit before vs. during intervention

	Pre-Protocol n= 47,098 (n (%))	Protocol n= 1498 (n (%))	p	Protocol Unadjusted OR (95% CI)	Protocol Adjusted* OR (95% CI)
Tobacco Status Assessed	45,337 (96%)	1458 (97%)	0.031	1.41 (1.03, 1.94)	1.40 (1.02, 1.92)
Tobacco User (current)	4078 (9%)	123 (8%)	0.54		
Readiness to Quit Assessed	135 (3.3%)	94 (76%)	<.0001	94.7 (60.3, 148)	105 (65.7, 167)
Quit line referral	(<0.57% historic)	15 (12%)	<.0001		

*Adjusted for age, gender, race, utilization, and comorbidity.

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Educating Patients on the Cardiovascular Risks of Rheumatoid Arthritis: Usual Care Versus a Structured Approach

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Background/Purpose: Rheumatoid Arthritis (RA) carries a considerable increase of the risks for cardiovascular (CV) disease. It is unclear how well patients with RA understand such risks and what they do to minimize them. This study was designed to determine whether a structured approach (detailed explanation and a concise brochure) is more effective than a verbal explanation delivered to the patient when the diagnosis of RA is made.

Methods: Existing patients with an established diagnosis of RA followed at the Dallas Arthritis Center were administered a questionnaire. These patients had been given the traditional verbal explanation of CV risks. In the interventional phase of the study, newly diagnosed RA patients were given a simple brochure that illustrated CV risks associated with RA and suggested strategies to minimize them. The contents of the brochure were discussed with the patients in a structured fashion, *i.e.*, by rigorously following the scheme in the brochure and by answering patients' questions as each point was presented. In a follow-up visit after the diagnosis, the questionnaire was administered to patients who had received the structured explanation and the brochure. Responses of the two groups were compared using unadjusted odds ratios and the chi-square test.

Results: A total of 53 patients completed the questionnaire in the first phase and 33 completed the second phase. In group 1 (non-structured explanation with no brochure) 22 of the 53 patients (41.5%) indicated that they could recall having been given an explanation of the CV risks associated with RA and being encouraged to make appropriate life-style changes. However, 31 patients (58.5%) had no such recollection. In group 2 (structured explanation and brochure) 22 of 33 patients (66.7%) indicated that they could recall having been given an explanation of the CV risks associated with RA and being encouraged to make appropriate life-style changes, while 11 (33.3%) had no such recollection. This represents a highly significant change with respect to group 1, where only 41.5% recalled having received instructions (OR 2.82 95% CI 1.14 – 6.98; $p<0.05$). Patients' responses regarding lifestyle changes made are depicted in Table 1.

Conclusion: A brief structured explanation of CV risks associated with RA was more effective than a less formal unstructured explanation given as part of the initial or follow up encounters with regards to smoking behavior and switching to a healthier diet. Approximately half of the patients reported increasing their commitment to exercise, irrespective of how the suggestion was delivered and whether they recalled or not being given the advice. A high proportion of patients (4 out of 5) reported seeing their primary care provider (PCP), and structured or unstructured recommendations seemed to have little effect on this behavior.

Patients	Smokers (%)	Stopped Smoking (%)	Increased exercise (%)	Healthier diet (%)	See PCP (%)
Non-structured (n = 53)	**17** (*31.1*)	**8** (*47.1*)	**27** (*50.9*)	**29** (*54.7*)	**43** (*81.1*)
Recall instructions (n = 22)	**9** (*40.9*)	**4** (*44.4*)	**12** (*54.5*)	**13** (*59.1*)	**19** (*86.4*)
Do not recall (n = 31)	**8** (*25.8*)	**4** (*50.0*)	**15** (*48.4*)	**16** (*51.6*)	**24** (*77.4*)
Structured (n = 33)	**12** (*36.4*)	**9** (*75.0*)	**9** (*66.7*)	**26** (*78.8*)	**26** (*78.8*)
Recall instructions (n = 22)	**9** (*40.9*)	**8** (*88.9*)	**8** (*68.2*)	**19** (*86.4*)	**19** (*86.4*)
Do not recall (n = 11)	**3** (*27.3*)	**1** (*33.3*)	**1** (*63.6*)	**7** (*63.6*)	**7** (*63.6*)

Table 1 - Responses of the two groups stratified according to recollection.

Disclosure: M. Genta, None; **R. M. Genta**, None.

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Abstract Number: 422

Developing a Staff-Driven Electronic Smoking Cessation Referral Program in Rheumatology Clinics

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Background/Purpose: Patients with rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) have an increased risk of premature cardiovascular disease (CVD), making comorbid risk factors like smoking a prime intervention target for rheumatology patients who smoke. Primary care clinics have systems to promote cessation, but rheumatology clinics rarely address smoking adequately (Vreede 2015). Resources like free telephone quit lines exist that have already been shown to improve the odds of quitting, but patients must first be connected to them. The Ask-Advise-Connect model has been shown to increase the proportion of patients being referred to quit lines 13-fold (Vidrine 2013), but this model has not been studied thoroughly in specialty clinics. These tools show great promise for encouraging tobacco cessation, but they should be tailored for use in rheumatology in order to maximize their effectiveness. Our goal was to work with rheumatology clinic staff to 1) understand current tobacco cessation care practices and obstacles and 2) use that information to customize and implement a quit line referral intervention based on the Ask-Advise-Connect model.

Methods: We conducted participatory work system redesign with medical assistants (MAs) and nurses from three rheumatology clinics at a large, academic health system in 2015. Building on prior patient and provider interviews and staff focus groups, we held two hour-long focus groups using semi-structured interview questions to assess current processes, needs, and a proposed electronic health record (EHR)-based quit line referral process. The results were organized according to the Systems Engineering Initiative for Patient Safety (SEIPS) work system domains.

Results: 80% (9 MAs, 5 nurses) of the clinic staff participated in the focus groups. We found that smoking assessment was standard, but follow-up actions were rare. Barriers to assessing smoking and referring patients to cessation resources included discomfort discussing cessation with smokers and the absence of an easy referral process (Table 1). Using these findings, we developed a new staff-driven tobacco quit line referral process for MAs and nurses that leverages our EHR system. The process uses two decision-support EHR alerts with conversation prompts to assess use and 30-day readiness to quit (Ask), encourage cessation (Advise), and refer the patient to the state tobacco quit line using an electronic interface (Connect). We also created a rheumatology-specific educational brochure and an hour-long staff training program to support the workflow.

Conclusion: By working directly with our rheumatology MAs and nurses, we developed a new smoking assessment and referral protocol that addresses major obstacles to delivering consistent, effective care to rheumatology patients who smoke. We are testing the effectiveness of this intervention in a 6-month pilot.

Table 1. Results of Participatory Work System Redesign (n=14 MA and nurse participants)

Work System Components	Before Redesign	Protocol Redesign Components
People	Staff uncomfortable with tobacco conversations	1-hour education and rehearsal session with trained tobacco cessation experts
Organization	No tobacco care follow-up procedure	Standard protocol supported by clinic staff and leadership
Technology	No use of reminders to assess readiness to quit; no easy way to refer to quit line	EHR alert and order set with talking points for quit line referral; electronic interface to/from quit line
Environment	No physical cues for tobacco cessation conversations	Patient brochure on tobacco cessation tailored to rheumatology clinics discussing links with diseases
Tasks	Assessment of tobacco use only	**Ask** about tobacco use and 30-day readiness to quit, **Advise** quit line support, and **Connect** via e-referral to quit line who will call the patient within 48 hours
Staff Quotations	*"I never had the verbiage to continue… I never asked [about tobacco cessation] because I didn't know where to go from there."—Medical Assistant*	*"It doesn't seem like this [protocol] would be hard to do."—Medical Assistant*

Disclosure: D. Panyard, None; **E. Ramly**, None; **A. Gilmore-Bykovskyi**, None; **D. Lauver**, None; **R. Adsit**, None; **C. Maxcy**, None; **C. M. Bartels**, Pfizer, 2.

Abstract Number: 423

Cardiovascular Risk and Lipid Screening in Rheumatoid Arthritis Patients in a University Rheumatology Practice: Quality Improvement Project

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Background/Purpose: Meta-analyses of observational studies showed that RA patients' morbidity and mortality risks stemming from cardiovascular (CV) causes were, respectively, close to 50% and 60% higher than those of the general population. It has been proposed that high-grade inflammation affects multiple tissues and leads to endothelial dysfunction, dyslipidemia, more oxidative stress, increased levels of homocysteine, and insulin resistance. These effects accelerate atherogenesis and myocardial microvascular abnormalities. Research has shown that the tools used for risk assessment in the general population underestimate the true risk when they are applied to patients with proatherogenic diseases such as diabetes mellitus (DM) or chronic kidney disease (CKD). Evidence suggests that this is also the case with RA.

Methods: We reviewed the electronic medical records (EMR) of patients with the diagnosis of RA based on the ICD 9 codes, that were followed at the University of Virginia Rheumatology outpatient clinic in the 7/2014 – 5/2015 period. We reviewed age, gender, RF/CCP positivity, disease duration of more than 10 years, current smoking status, systolic blood pressure (SBP) and treatment, lipid panel (date, total cholesterol, HDL, LDL), cholesterol medications, DM status, aspirin use. We calculated the cardiovascular risk by multiplying the Framingham risk score by 1.5 as per EULAR recommendations.

Results: A total of 460 charts were reviewed. 78% of patients were female and 22% were male. 44.56% had lipid levels available in the EMR. Of the patients with documented lipid levels 49.75% had levels checked more than 2 years ago. Only 22.39% of the total patients reviewed had recent lipid levels documented in the EMR (less than 2 years old). Of the 359 female patients, 28.91% were on cholesterol medications although 60.84% had an LDL level greater than 100. 15.32% were smokers, 14.2% had a diagnosis of DM, while 29.24% had an SBP of more than 140. Of the 101 male patients, 56.41% were on cholesterol medications and 43.58% had an LDL level greater than 100. 22.77% were smokers, 19.8% had a diagnosis of DM, and 29.7% had an SBP of more than 140. Our data for female patients shows that the Framingham risk score is higher than the average population in all age groups except for the 55 - 64 years old age group and significantly higher in all age groups when multiplied by 1.5. Our data for male patients shows that the Framingham risk score is higher than the average population in all age groups except for the 60-69 years old age group and significantly higher in all age groups when multiplied by 1.5.

Conclusion: Studies have shown that RA patients have an increased cardiovascular risk, similar to DM and CKD population and twice as high as the general population. Our chart review shows that our RA patients have a number of CV risk factors and have an increased risk compared to the normal population based on calculated Framingham risk score as well as multiplication for RA. Additionally it appears that lipid screening and aggressive treatment for hypertension is underutilized in this population. We propose to send letters to the primary care practitioners to increase awareness of the CV risk assessment in RA.

Disclosure: D. Mosteanu, None; **X. Wang**, None; **D. Kimpel**, None; **J. Lewis**, None.

Abstract Number: 424

Adherence to American College of Rheumatology Immunization Recommendations for Rheumatoid Arthritis Patients in a Tertiary Care Health System and Opportunities to Close the Gap

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Background/Purpose: American College of Rheumatology (ACR) 2015 guidelines for the treatment of rheumatoid arthritis (RA) include recommendations for immunization against influenza, pneumococcus, hepatitis B (Hep B) and herpes zoster (HZV). The guidelines also recommend the indications and timing of administration of these killed vaccines (pneumococcal, influenza and Hep B), and live attenuated HZV vaccinations. The aim of our study is to measure adherence rates to these ACR immunization recommendations in rheumatoid arthritis patients in our tertiary health care system based rheumatology practice and to identify opportunities to close the gap, if any.

Methods: A retrospective review of the electronic health record (EHR) was performed to identify consecutive adult RA patients from January 1, 2016 to March 31, 2016 whose primary care physician (PCP) was within the affiliated health care system. Influenza vaccinations were captured only for the 2015-2016 flu season. In addition to the ACR recommendations for pneumococcal vaccinations, we determined the number of RA patients receiving the entire Advisory Committee on Immunization Practices (ACIP) recommended pneumococcal vaccination series. EHR review keywords included "vaccination," "immunization," "pneumococcal", "flu", "hepatitis", "zoster" and whether vaccinations were offered, or refused by the patient.

Results: A total of 85 adult RA patients were identified. The mean age was 61.5 yrs, 84.7% were female, 85.9% were Caucasian, and the mean duration of RA was 7.3 yrs. 82.4% were on a traditional DMARD, and 27.1% on a biologic DMARD. One patient was allergic to the influenza vaccination and was excluded. Of the remaining 84 patients who met the indications for influenza vaccination, 60.7% received the vaccination. 3.6% patients were offered the influenza vaccination but did not end up receiving it, and 10.7% refused vaccination. 52.9% of all RA patients received the pneumococcal vaccine. Of the three patients identified as being both at risk for Hep B (i.e. healthcare workers, intravenous drug abuse history and/or multiple sexual partners in last 6 months)and susceptible (anti-Hep B surface antibody negative), only one patient was subsequently vaccinated (33%). 29.2% of RA patients ≥ 50 years of age received the HZV vaccination. One HZV vaccine was deferred by the PCP secondary to prior initiation of immunosuppressant therapy. 16.7% received the entire ACIP recommended pneumococcal vaccination series.

Conclusion: At our tertiary health care system rheumatology clinic, rates of adherence to ACR recommendations for vaccinations are sub-optimal. Some limitations of our data include vaccinations potentially received outside the clinic setting (e.g. pharmacies and retail stores), individual clinic vaccine stocking schedules and supplies, and vaccinations recorded prior to the July, 2015 launch date of our EHR, leading to attrition of data. Analysis of care gaps and future steps include vaccination guideline education, EHR integration of reconciliation and new vaccination orders, and subsequently re-measure adoption and adherence.

Disclosure: M. Kimoto, None; **M. C. M. Wasko**, None; **T. S. Sharma**, None.

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Abstract Number: 425

Improving Pneumococcal Vaccination Rates for Immunosuppressed Patients in an Academic Rheumatology Clinic

Alison Bays[1], Renuka R. Nayak[2], Sara Murray[3], Darlene Young[4], Gabriela Schmajuk[5], Jinoos Yazdany[6] and Andrew Gross[7], [1]Rheumatology, University of Washington, Seattle, WA, [2]Rheumatology, UCSF, San Francisco, CA, [3]Medicine, UCSF, San Francisco, CA, [4]Medicine/Rheumatology, UCSF, San Francisco, CA, [5]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [6]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [7]Medicine/Rheumatology, University of California San Francisco, San Francisco, CA
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Background/Purpose: Patients with autoimmune conditions have higher rates of pneumococcal disease and they are often immunosuppressed. In 2014, the Advisory Committee on Immunization Practices issued new guidelines recommending vaccination with the 13-valent pneumococcal conjugate vaccine (PCV-13) for immunosuppressed patients. However, only 12% of patients on immunosuppression were vaccinated at our academic referral center. Our aim was to use the Institute for Healthcare ImprovementÕs Model for Improvement to increase the PCV-13 vaccination rate from 12% to 40%.

Methods: Plan-Do-Study-Act (PDSA) methodology was used over 3 cycles within a large rheumatology practice. Patients were eligible for vaccination if they were prescribed disease modifying antirheumatic drugs (DMARDs), biologic agents, or prednisone. Prior to the start of the intervention, vaccination rates were reviewed between 5/1/2014 and 3/1/2015. PDSA Cycles included: (1) Investigator-led educational session for providers regarding risks of pneumococcal disease and benefits of new vaccine (3/1/15 to 5/1/15); (2) Medical assistant (MA) training, utilization of the electronic medical record (EMR) by messaging patients if there was no documentation of their vaccination status prior to visit (5/1/15 to 7/1/15) (3) Creation of a paper form for MAs to complete and indicate patient eligibility followed by MAs writing electronic pended orders, if appropriate. (7/1/15-4/1/16) On a quarterly basis, vaccination rates were abstracted from the EMR (Apex and Clarity) and vaccination rates were tracked using p-charts.

Results: 9 rheumatology fellows, 11 faculty members, 1 nurse practitioner and 9 medical assistants participated in the quality improvement activity. Prior to the intervention, 12% patients had received a PCV-13 vaccination in clinic over a 10-month period. After the third PDSA cycle, over 52% of eligible patients received a PCV-13 vaccination (see Figure).

Conclusion: Targeted education for clinicians and medical assistants in conjunction with using EMR tools for patient reminders and MA-generated orders increased rates of pneumococcal vaccination from 12% to 52% in our large academic rheumatology practice. Ultimately, paper reminders for providers and pended orders by the MAs, in addition to previous interventions, resulted a sustained increase in vaccination rates over a 9-month period without further interventions. Future work will include surveying stakeholders and identifying remaining barriers to vaccination to further increase vaccination rates.

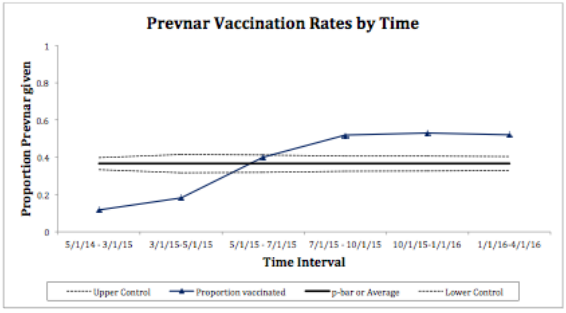

Figure 1. The dark blue triangles show the proportion of patients vaccinated with PCV13. The upper and lower control limits describe the variation of the denominator (different numbers of immunosuppressed patients were seen in each time period). The p-bar shows the average.

Disclosure: A. Bays, None; **R. R. Nayak**, None; **S. Murray**, None; **D. Young**, None; **G. Schmajuk**, None; **J. Yazdany**, None; **A. Gross**, None.

Abstract Number: 426

Herpes Zoster Vaccine: A Quality Improvement Study in Rheumatoid Arthritis Patients

Rochella A. Ostrowski and **Hina Chaudhry**, Rheumatology, Loyola University Medical Center, Maywood, IL
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Herpes Zoster Vaccine: A Quality Improvement Study in Rheumatoid Arthritis Patients Chaudhry, Hina S.; Ostrowski, Rochella A. Division of Allergy, Immunology, and Rheumatology, Loyola University Medical Center, Maywood, Illinois

Background/Purpose: The ACR recommends herpes zoster (HZ) vaccination prior to use of non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs) in RA patients and for those currently on non-biologic DMARD therapy. We evaluated the success rate of HZ vaccination or a documented discussion with eligible RA patients and whether it was affected by educational intervention.

Methods: In June 2015, a lecture on indications for HZ vaccine was given to the rheumatology practice at a single academic center; a pocket guide was provided. Records of RA patients over the age of 60 on medications including those in Table 1 were reviewed. Rates of HZ vaccination or a documented recommendation for the vaccine were compared between August 2014 and August 2015 (before and after the educational lecture). Patients excluded were those with HIV/AIDS, malignancy, tuberculosis therapy, pregnancy, prednisone > 20 mg/day (>/=2 weeks), biologic or contraindicated non-biologic DMARD, or documented fever at the visit. Clinical information was compared between the 2014 and 2015 groups. Fisher's exact test was used to compare the primary outcome in each year. Logistic regression was used to adjust for potential confounders. An anonymous survey was given to identify challenges to HZ vaccination

Results: 91 RA patients met inclusion criteria, 36 in 2014 and 62 in 2015, including 7 duplicate patients (Table 1). In 2014, 25% (9 patients) had a documented discussion or received the HZ vaccine; 22.2% received the vaccine while 33.3% already received it. In 2015, the rate of vaccination or documented discussion increased to 37% (23 patients). 8.7% received the vaccine (23% already received it). The difference in rates did not reach statistical significance. In multivariate analyses, the primary outcome not significantly affected by age, gender, race, year (surrogate for educational intervention), and clinic location. Only individual physician as a factor was significant (p=0.01).

Conclusion: Compliance rates were low for HZ vaccine in eligible RA patients despite educational intervention. Based on survey results, contraindication was the top reason for not giving the vaccine (Figure 1). However, 71.6% patients met criteria for vaccination. Ways to improve compliance include innovative use of electronic medical systems, creation of specialty prevention clinics, improved availability of the HZ vaccine, and increased education for practitioners. Additional studies are warranted to explore ways to improve HZ vaccination rates in eligible RA patients. **Disclosures**: H. Chaudhry, None; R. Ostrowski, None.

	2014 (n =36)	2015 (n=62)	
Mean Age (years)	69.6 (67.0 - 72.1)	69.9 (67.8 - 72.0)	
Gender (%)			
Male	22.2 (7.6, 36.5)	17.7 (8.0 - 27.5)	
Female	77.8 (63.5, 92.0)	82.3 (72.5 - 92.0)	
Race (%)			
Asian	2.8 (-2.9 – 8.4)	4.8 (-0.6 – 10.3)	
African American	16.7 (3.9 – 29.4)	9.7 (2.1 – 1.7)	
Caucasian*	80.6 (67.0 – 94.1)	85.5 (76.4 – 94.5)	
Medications (%)			
Sulfasalazine	8.3 (-1.1 – 17.8)	4.8 (-0.7 – 10.3)	
Methotrexate	55.6 (38.5 – 72.6)	62.9 (50.5 – 75.3)	
Leflunomide	13.9 (2.0 – 25.8)	19.4 (9.2 – 29.5)	
Azathioprine	2.8 (-0.3 – 8.4)	1.6 (-1.6 – 4.8)	
Hydroxychloroquine	52.8 (35.6 – 70.0)	37.1 (24.8 – 49.5)	
Prednisone ≤20mg	27.8 (12.4 – 43.1)	24.2 (13.2 – 35.2)	
Attending Rate (%) for Discussion of Zoster Vaccine with Patient	Attending 1: 0 Attending 2: 26.3 (5.2 – 4.7) Attending 3: 100 Attending 4: 33.3 (-9.5 – 7.6) Attending 5: 0% Attending 6: 0%	Attending 1: 10 (10.0 – 30.0) Attending 2: 52.9 (28.0 – 77.9) Attending 3: 0 Attending 4: 23.1 (-1.2 – 47.4) Attending 5: 75.0 (48.9 – 101.1) Attending 6: 50.0 (50.0 – 150.0)	Difference (Absolute) 10% increase 26.6% increase 100% decrease 10.2% decrease 75% increase 50% increase

Table 1. Characteristics of Rheumatoid Arthritis Patients Meeting Inclusion Criteria. Data is presented followed by 95% confidence intervals. Except for age, data are presented as percent values. *Includes Hispanic patients.

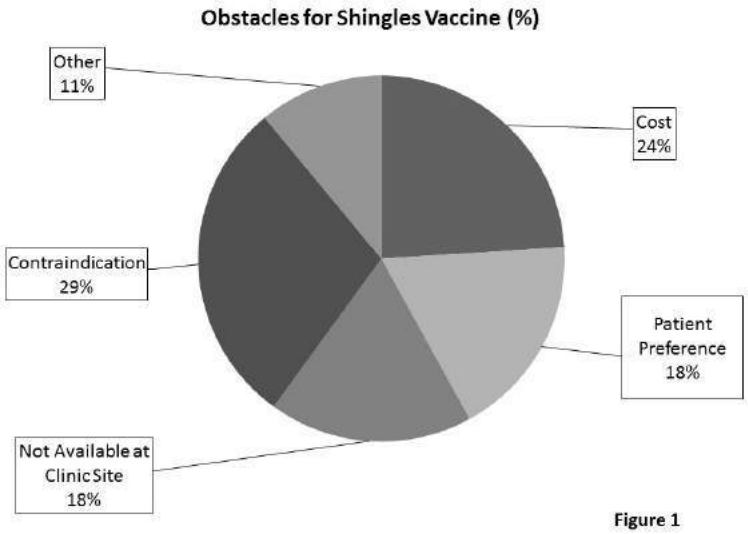

Figure 1

Disclosure: R. A. Ostrowski, None; **H. Chaudhry**, None.

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Abstract Number: 427

Identifying Barriers to Zoster Vaccination Rates Among RA Patients in an Academic Rheumatology Practice

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SESSION INFORMATION

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Background/Purpose: The risk of herpes zoster (HZ) infection in patients with rheumatic disease is 1.5 to 2 times that of the general population. The 2012 ACR Treatment Guidelines for rheumatoid arthritis (RA) added HZ vaccination as a

recommendation in accordance with CDC guidelines. Studies have shown HZ vaccination rates among RA patients ranging 1%–21%. We assessed HZ vaccination rates based on documentation in an academic practice with a focus on location of primary care provider (PCP).

Methods: A retrospective chart review of 639 RA patients (one-time ICD 9 code 714.0) seen by physician rheumatology providers from December 1, 2014 to June 30, 2015 was conducted. 50% of all eligible patients per provider were randomly selected for chart review. Patients with RA age ≥ 60 were included. Exclusion criteria were: 1. age < 60 2. biologic therapy 3. prednisone ≥ 20 mg/day for ≥ 14 days; MTX > 0.4 mg/kg/wk; azathioprine > 3 mg/kg/day 4. ongoing chemotherapy or radiation OR cancer remission < 3 mos 5. immunodeficiency 6. solid organ transplantation 7. HIV patients with CD 4 count < 200 8. pregnancy. An additional 61 patients were excluded for the following reasons: wrong diagnosis, seen outside the time frame, or not seen in rheumatology clinic. The primary outcome was vaccination status and difference in vaccination rates based on location of PCP. Chi-square was used to compare categorical variables.

Results: 193 patients met inclusion criteria. 89.2% were white and 77.3% female with a mean age of 70.15 yrs. (SD = 7.54, range: 60-98). 110 (56.7%) were Medicare beneficiaries and 44 (22.68%) were privately insured. Nearly all visits (97.9%) were follow-up visits. 73.2% had inactive disease. Of the 144 with internal PCPs, 30% were vaccinated vs. 8% of 49 with external PCPs. 12.4% of patients had a documented history of herpes zoster. 72% of patients were on MTX (4 pts on ≥ 20 mg) and 54.64% on prednisone (2 pts on > 10 mg). 27 (13%) of patients were vaccinated with 11 vaccinations given within the institution. Total vaccination percentage was 13.9% with 92.6% of the vaccinations appropriately given. Vaccination was addressed by the rheumatologist in 7.7% of patients.

Conclusion: Patients with internal vs. external PCPs were about 4 times more likely to be being vaccinated based on documentation. There was no difference in vaccination status based on insurance, disease duration, age of patients, or history of HZ. Similar to prior studies, rates of vaccination in eligible RA patients continue to be low even in large academic centers. Interventions to improve vaccination rates must be further explored with focus on collaboration between PCPs and rheumatologists.

Disclosure: A. Joglekar, None; **A. Blaske**, None; **N. Annapureddy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identifying-barriers-to-zoster-vaccination-rates-among-ra-patients-in-an-academic-rheumatology-practice

Abstract Number: 428

Random Forest Models Using Electronic Health Record Data Are Predictive of One-Year Outcomes in Lupus Nephritis Patients Taking Mycophenolate Mofetil Induction Therapy

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Background/Purpose: Lupus nephritis (LN) outcomes are affected not only by patient biology but also by patient, provider, and system factors. One way to improve outcomes in LN is to use a systems approach to stratify all patients in a population by their risk for LN treatment failure. We have demonstrated that traditional and novel biomarkers obtained at the time of renal biopsy can be used to create random forest machine learning models of one-year treatment outcomes. However, to predict system-level outcomes for care coordination, one must leverage available electronic health record (EHR) data to model outcomes. This project was designed to determine the effectiveness of using currently available EHR data to create random forest models predictive of one-year outcomes in LN.

Methods: 212 LN patients from one academic prospective cohort and two clinical trials of lupus nephritis were selected as follows. LN was defined by International Society for Nephrology/Renal Pathology Society (ISN/RPS) renal biopsy classification within two months of baseline data collection. All patients were started on mycophenolate mofetil as induction therapy. The following data were collected at the start of induction: age, sex, race, biopsy class (ISN/RPS), C3, C4, and DNA antibody levels, UPrCr, and estimated glomerular filtration rate (eGFR, Chronic Kidney Disease Epidemiology Collaboration formula). One-year complete response outcome was calculated from baseline and one year eGFR and UPrCR using the ACR renal response criteria modified for the LN and Rituximab trial. Random forest models were created in using the baseline EHR variables above to predict a one-year outcome of complete response versus partial response or treatment failure. A separate test set from 1/3 of the data was created for reporting the receiving operator characteristics area under the curve (ROC AUC).

Results: The model predicted the outcome in the test set with an ROC AUC of 0.74.

Conclusion: These results demonstrate that treatment response in patients on mycophenolate mofetil induction therapy can be predicted with a reasonable level of accuracy using data available in the EHR. This level of accuracy is sufficient to prioritize care coordination efforts to patients most at risk. The ideal implementation of this model would calculate the risk score in near real time in the EHR. Because the ISN/RPS classification is not typically reported in discreet fields, natural language processing would be necessary to extract these data. To have impact at a population level, the risk score must be visible in population level reports or dashboards so that high risk patients can be targeted for assistance to reduce patient, provider, and system barriers to good outcomes.

Disclosure: B. J. Wolf, None; **J. Oates**, None.

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Abstract Number: 429

Use of Electronic Medical Record to Identify Immunocompromised Patients in a Pediatric Rheumatology Clinic

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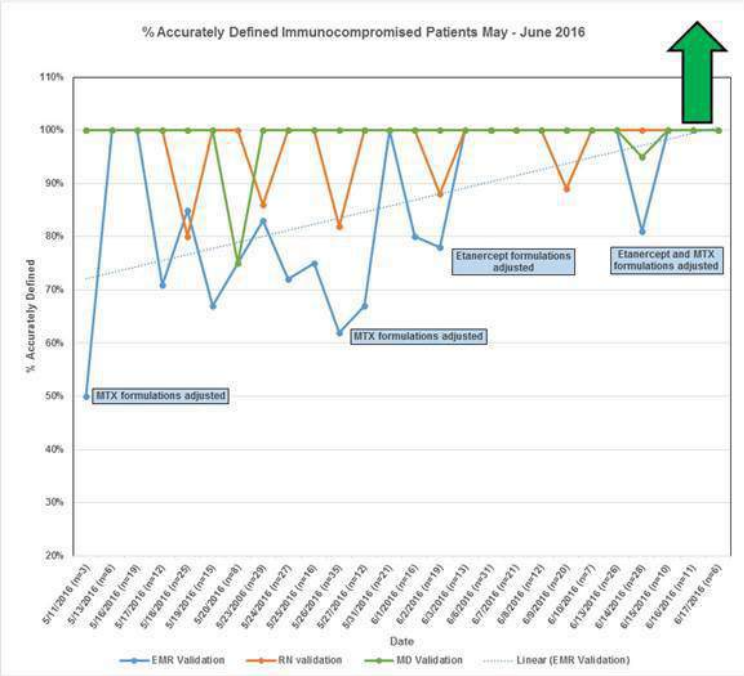
Background/Purpose: The increase in therapeutic options for our Pediatric Rheumatology patients has led to improved outcomes but has increased the number of immunocompromised (IC) patients. A reliable method of identifying IC patients is essential to their care. However, there is currently no automated method in our electronic medical record (EMR) that identifies a patient as IC. Relying on physician or staff identification of IC has the potential for human error and/or oversight, is time consuming and has not been standardized. The aim of our study was to formulate an IC operational definition to be used in an automated report via our EMR to accurately identify patients who should be classified as IC based on their current diagnoses and/or medications.

Methods: An operational definition of IC status was constructed and included 173 ICD-10 diagnostic codes and 617 immunosuppressant medications. These parameters were assembled in an EMR grouper-based report that was able to filter and flag IC patients scheduled in our clinic. Our EMR report's performance was tracked by comparing its identification accuracy to a pediatric rheumatologist and nurse evaluation. Daily reports for five consecutive weeks were

screened including a total of 448 patients scheduled. These comparisons were tracked and adjustments were made to operational definition based on EMR failures.

Results: In total, 214 patients were found to be IC during our data collection, based on multi-provider consensus. The physician and nurse continued to produce instances of human screening error, but our EMR performance steadily improved during our period of analysis. (Chart 1) The most common reason for our EMR failure to capture patients was formulation variations in our commonly utilized medications. Taking into account its cumulative improvement overtime, our EMR was able to capture 84% of the IC patients. The accuracy of the EMR is anticipated to reach 100% as we are able to obtain a complete list of all the names used for Methotrexate and Etanercept.

Conclusion: We have demonstrated that using EMR to identify IC patients is a unique and effective method that will provide level of reliability 3 (LOR#3). Automated identification of IC patients in Pediatric Rheumatology is efficient and will ultimately lead to better outcomes for our complex patient population. We believe that our EMR process of identifying IC patients is transferrable to other subspecialties and centers caring for similar at-risk patients. Once the operational definition for the EMR is perfected, we will use the EMR identification of IC to generate an automated report of Hepatitis B and Pneumococcal serologies, vaccination data, as well as Tuberculosis screening. In addition, we will be able to automatically notify other healthcare providers of IC status that will assist with potential harmful exposures such as live virus vaccines.



Disclosure: L. A. Favier, None; **E. A. Smitherman**, None; **A. Furnier**, None; **T. Ting**, None; **A. Watts**, None; **S. Kramer**, None; **M. Parwani**, None; **J. L. Huggins**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-electronic-medical-record-to-identify-immunocompromised-patients-in-a-pediatric-rheumatology-clinic

Abstract Number: 430

A Process to Obtain Hepatitis B Serology Screening on Immunocompromised Pediatric Rheumatology Patients

Emily Smitherman[1], Leslie A. Favier[1], Adam Furnier[2], Sandra Kramer[3], Barbara Speer[4], John Kues[4], Lara Danziger-Isakov[3], Rebecca Brady[5] and Jennifer L. Huggins[6], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]University of

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Background/Purpose: In the setting of today's heroin epidemic, hepatitis B infection remains a significant public health concern, especially for patients with immunocompromising conditions. With reports of up to 25% mortality associated with hepatitis B reactivation while on immunosuppressive therapy, these patients should be thoroughly screened with hepatitis B surface antibodies (anti-HBsAb) for evidence of immunity, in addition to hepatitis B core antibodies (anti-HBcAb) and hepatitis B surface antigen (HBsAg) for evidence of acute or chronic infection. Our aim was to develop a process to reliably complete hepatitis B screenings on patients receiving intravenously infused biologic medications within the rheumatology division at Cincinnati Children's Hospital Medical Center (CCHMC).

Methods: Providers within the rheumatology division recognized common barriers to obtaining hepatitis B serology. Eligible patients included all rheumatology patients receiving intravenous biologic therapy between January 2016 and June 2016. Interventions implemented during the study included education of clinic providers and nurses, pre-visit planning resulting in ordering of serology, and the development of physician "talking points" for patients.

Results: Prior to the intervention, only 4 patients had a complete set of hepatitis B serology obtained within the past year. Anti-HBsAb, anti-HBcAb, and HBsAg serologies were pre-ordered to be drawn at the time of infusion encounters, so there were very few misses (see Figures 1 and 2). The intervention began in January 2016 by targeting patients receiving infliximab, and expanded in April 2016 to include all rheumatology patients receiving infusions of abatacept, belimumab, golimumab, rituximab, and tocilizumab. By June 2016, a total of 109 patients had updated hepatitis B serology. We were able to identify that 71% of patients had negative or indeterminate results for anti-HBsAb and will require repeat vaccination. Much to our surprise, we identified 1 patient on infliximab with a positive anti-HBcAb, presumably from transplacental transmission. This patient is now being monitored by hepatology for re-activation of chronic hepatitis B infection.

Conclusion: We were able to successfully develop a method to update hepatitis B serology for at-risk rheumatology patients on biologic therapy. Next steps will be to develop a process to reliably provide vaccines for patients identified as seronegative; expand this process to screen all patients identified as immunocompromised within rheumatology; and then expand this process to other divisions at CCHMC.

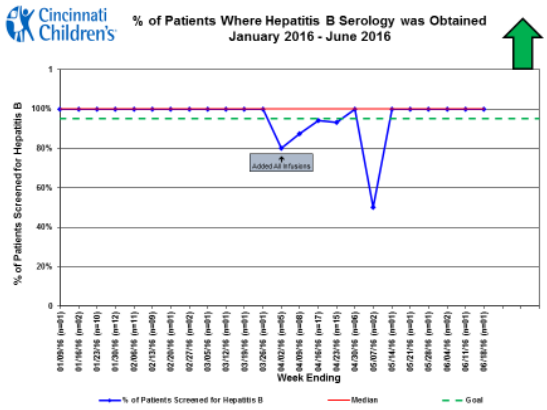

Figure 1. Run chart of percentage of patients with completed hepatitis B serology screen between January 2016 and June 2016

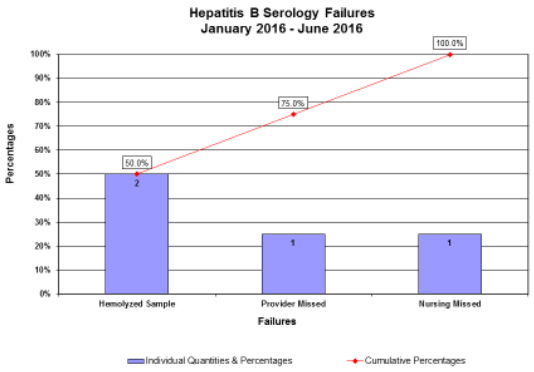

Figure 2. Pareto chart of hepatitis B serology failures between January and June 2016

Disclosure: E. Smitherman, None; **L. A. Favier**, None; **A. Furnier**, None; **S. Kramer**, None; **B. Speer**, None; **J. Kues**, None; **L. Danziger-Isakov**, None; **R. Brady**, Pfizer Inc, 2; **J. L. Huggins**, Pfizer Inc, 2.

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Abstract Number: 431

Wide Variations in Hepatitis B Screening Practices for Patients Receiving Rituximab

Gabriela Schmajuk[1], Chris Tonner[2], Laura Trupin[3], Jing Li[4] and Jinoos Yazdany[3], [1]San Francisco VA Medical Center, University of California, San Francisco, San Francisco, CA, [2]Rheumatology, University of California, San Francisco, San Francisco, CA, [3]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [4]University of California, San Francisco, San Francisco, CA

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Background/Purpose: Hepatitis B reactivation in the setting of rituximab use is a potentially fatal but preventable event. The rate of hepatitis B screening in patients receiving rituximab treatment is unknown. We used electronic health record (EHR) data to examine the proportion of patients who received adequate Hepatitis B screening prior to starting rituximab and also assessed patient and provider factors associated with inadequate screening.

Methods: Data derive from the EHR of a university health system, including diagnosis grouper codes, problem lists, medications, laboratory results, procedures codes, clinical encounter notes, and scanned documents. Data were extracted through back-end access to the EHR and supplemented via chart review by 2 physicians. We defined a cohort of patients who received rituximab between 6/1/2012 and 3/1/2016 (“index date”). We calculated the proportion of rituximab users who received inadequate screening for hepatitis B according to the Centers for Disease Control guidelines for detecting latent Hepatitis B infection (Hepatitis B surface antigen and Hepatitis B core antibody tests) prior to their first rituximab infusion during the study period. We used a relative risk regression model to identify independent predictors of inadequate testing. Variables included in the models were decided a priori and based on previously reported predictors of risk for Hepatitis B that may have influenced a provider’s decision to screen.

Results: 926 patients received rituximab during the study period. Mean age was 49 years; 50% were women; 51% were white. Most received rituximab for treatment of lymphoma (52%), kidney transplant rejection (10%), or multiple sclerosis (10%)– only 6% of orders were written by rheumatologists, for diagnoses such as vasculitis (4%) and rheumatoid arthritis (2%). Additional patient characteristics are shown in the Table. 565 (61%) patients had adequate screening for Hepatitis

B; 214 (23%) had no Hepatitis B test documented at all. Nephrologists treating renal transplant rejection were most likely to have adequate screening (90%). Multivariate regression showed that the strongest predictor of inadequate screening was department of the ordering provider (see Table).

Conclusion: We found wide variations in Hepatitis B screening practices among patients receiving rituximab, resulting in unnecessary risks to patient safety. Strategies including provider education, use of checklists, and clinical decision support within the EHR should be developed to improve rates of screening in this high-risk patient population.

Table. Patient characteristics and predictors of inadequate screening for Hepatitis B among patients receiving rituximab

Patient characteristics	Overall, out of 926 (N (%))	Overall with Inadequate Screening (%)	Adjusted Regression Model for Inadequate Screening† (RR (95% CI))
Sex			
Female	461 (50)	39	0.96(0.82, 1.12)
Male	465 (50)	39	1
Age (Mean (SD))	49.3 (19)	39	0.99(0.99, 1.00)
Race			
White	474 (51)	42*	1.21(0.89, 1.64)
African American	74 (8)	32	1.09(0.72, 1.63)
Asian	109 (12)	30	1
Hispanic	155 (17)	34	1.15(0.81, 1.64)
Other/multiple	114 (12)	44*	1.07(0.75, 1.52)
Charlson score			
0 to 1	162 (17)	60*	**1.73(1.27, 2.36)**
2 to 3	304 (33)	41*	**1.30(1.03, 1.64)**
4 to 7	212 (23)	32	1.12(0.86, 1.46)
8 + (ref)	248 (27)	29	1
Number of outpatient visits in 6 months prior to index date			
Less than 3	273 (29)	47*	**1.48(1.16, 1.89)**
4 to 7	233 (25)	49*	**1.54(1.21, 1.97)**
8 to 13	173 (19)	31	1.02(0.76, 1.36)
14 +	247 (27)	27	1
Rituximab ordering provider department			
Rheumatology	52 (6)	48*	**4.10(1.98, 8.49)**
Oncology	587 (63)	39*	**3.08(1.53, 6.21)**
Neurology	139 (15)	54*	**3.11(1.50, 6.45)**
Nephrology (Kidney Transplant)	84 (9)	10	1
Other	64 (7)	39*	**3.80(1.85, 7.81)**
Clinical Infusion Setting			
Outpatient	344 (37)	34*	**1.52(1.26, 1.82)**
Inpatient	582 (63)	48	1
Additional medications at index date			
Glucocorticoid - any dose (vs. none)	387 (42)	28*	**0.76(0.63, 0.92)**
Any additional immunosuppressant medications (vs. none)€	234 (25)	40	1.02(0.85, 1.22)
IVIG (vs. none)	20 (2)	10*	0.34(0.10, 1.21)
Year of index rituximab infusion			
2012	152 (16)	42*	**1.43(1.11, 1.83)**
2013	241 (26)	46*	**1.47(1.19, 1.80)**
2014	250 (27)	40*	**1.37(1.11, 1.70)**
2015	283 (31)	31	1

* Indicates that difference of proportion compared to other levels is statistically significant to $p < 0.05$ by chi square
† Relative risk regression model includes all variables listed in this table
€ Additional immunosuppressants include high dose steroids (prednisone equivalent > 10 mg/day), other disease modifying agents or chemotherapeutics

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Disclosure: G. Schmajuk, None; **C. Tonner**, None; **L. Trupin**, None; **J. Li**, None; **J. Yazdany**, None.

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Abstract Number: 432

Monitoring Hepatitis B Screening Compliance in Patients with Rheumatoid Arthritis (RA) Receiving Anti-TNF Therapy

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Background/Purpose: The risk of infection in patients with RA is higher than in comparable patients but still the vaccination rates in RA patients are low. The recent 2015 American College of Rheumatology guidelines for the treatment of rheumatoid arthritis **strongly recommended serologic testing and vaccination for hepatitis B** before and during anti-TNF therapy.

Methods: Patients who were getting anti-TNF therapy at the **VA Connecticut Healthcare System Newington campus** were identified from review of pharmacy records. 52 patients were identified after reviewing the charts of which **25 patients** met the **2010 American College of Rheumatology classification criteria for RA** and were included in this study. 27 patients taking anti-TNF therapy but who did not have RA were excluded (psoriatic arthritis, psoriasis, seronegative spondyloarthropathy etc). Hepatitis B serology was reviewed using the electronic medical record lab data base.

Results: 18 patients came to the VA for medication after being started on anti-TNF therapy by their private rheumatologists while remaining 7 were started at the VA. Only 2 (8%) patients had accurate hepatitis B serology, 7 (28%) had incomplete serology namely Hepatitis B Core ab was missing (4 were co-managed by private MD) and 16 (64%) patients had no Hepatitis B serology (14 were co-managed by private MD). The 23 identified patients lacking appropriate hepatitis B serology testing were contacted and the need for hepatitis B serology and vaccination was discussed. After further lab testing - 3 patients were found to be immune for hepatitis B, 2 patients had isolated anti-HBc status who on further testing had negative PCR for Hepatitis B viral load (i.e. resolved HBV infection) & 1 patient was lost to follow up. The remaining 19 patients underwent start of successful vaccination schedule for Hepatitis B.

Conclusion:

1. In our study sample we found **very poor and incomplete compliance (92%)** to hepatitis B screening in RA patients receiving anti-TNF therapy & majority of them (72%) were being co-managed by private rheumatologist.
2. We were able to **successfully vaccinate the RA patients** against Hepatitis B.
3. This study has also brought to our attention the need to **address the critical knowledge gap for the need to check Hepatitis B core ab levels**. Incomplete screening can lead to dangerous complications of reactivation of Hepatitis B**.** We found 2 patients with resolved HBV infection who needed close monitoring to prevent reactivation of Hepatitis B while on therapy.

Disclosure: V. Panthulu, None; **J. Waterman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/monitoring-hepatitis-b-screening-compliance-in-patients-with-rheumatoid-arthritis-ra-receiving-anti-tnf-therapy

Abstract Number: 433

The Prevalence of Latent Tuberculosis and Hepatitis B Found after Systematic Screening of Patients Starting with Biological Therapy in a Low-Endemic Area

Marin de Jong[1,2], Danielle Roosen[1], Andy Peters[1], Valerie Verstraeten[3], Marieke Pierik[1] and A. van Tubergen[4], [1]Department of Internal Medicine, division of Gastroenterology, Maastricht University Medical Centre, Maastricht, Netherlands, [2]NUTRIM – School for Nutrition and Translational Research in Metabolism, Maastricht University Medical Centre, Maastricht, Netherlands, [3]Department of Dermatology, Maastricht University Medical Centre, Maastricht, Netherlands, [4]Department of Internal Medicine, Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands

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Background/Purpose: Biologicals are a powerful treatment option for moderate to severe immune-mediated inflammatory diseases (IMID). Since biologicals modulate the immune system, the risk for reactivation of latent infections with a fulminant disease course, such as tuberculosis (TBC) or Hepatitis B (HBV), is increased. Guidelines therefore recommend screening for TBC and HBV before starting biological therapy. In 2012, at the Maastricht University Medical Centre+, we have introduced a central, multi-disciplinary and systematic screening of all IMID patients starting biological therapy. Prevalence data from systematic screening for latent TBC infection (LTBI) and HBV in patients prescribed biological therapy in a low-endemic area have not been reported thus far.

Methods: All IMID patients commencing biological treatment from May 2012 through July 2015, were included. Screening consisted of a detailed medical history on risk factors for LTBI (e.g. previous diagnosis of TBC, close contact with a TBC-infected person, previous living outside Europe, North-America and/or Australia) and HBV infection (occupation, history of intravenous drug abuse, sexual behaviour), a Quantiferon test (QFT), serology for HBV (HBs-Ag, anti HB-core) and a chest X-ray.

Results: In total, 547 of 549 patients (99.6%) starting biological therapy were screened. One patient (0.2%) tested positive for HBV without having reported any risk factor. Table 1 shows that 22 patients (4.0%) tested positive on QFT and were classified as LTBI patients. Of these, 14 did not report any risk factor, 18 had always lived in The Netherlands and 18 had never travelled outside of Europe, North America or Australia. Four patients had abnormalities on chest X-ray, 3 of them also tested positive on QFT and the other one turned out to have sarcoidosis, not LTBI. All LTBI patients were treated with isoniazid therapy. After a mean follow-up period of 19.8 ±8.8 months none of the patients had a reactivation of LTBI after the start of biological therapy.

	QFT Positive N=22	QFT negative N=525
Medical history, N (%) Risk factors No risk factors	8 (36.4) 14 (63.6)	37 (7.0) 488 (93.0)
Chest X-ray, N (%) Positive Negative	3 (13.6) 19 (86.4)	1 (0.2) 524 (99.8)

Table 1

Conclusion: The overall prevalence of LTBI and HBV in patients prescribed biological therapy in a low-endemic area is 4.0% and 0.2%, respectively. Systematic screening by means of QFT and HBV serology seems more reliable than history taking and chest X-rays alone. Since implementation of systematic screening of IMID patients, none of our patients showed reactivation of LTBI or HBV during biological therapy.

Disclosure: M. de Jong, None; **D. Roosen**, None; **A. Peters**, None; **V. Verstraeten**, None; **M. Pierik**, None; **A. van Tubergen**, None.

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Abstract Number: 434

Nurse Scheduled Telephone Visit: The Right Rheumatology Care for the Right Patient at the Right Time

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Background/Purpose: Rising healthcare costs have resulted in greater patient burden, higher health insurance costs, deductibles, and copayments. Access to care is delayed and problematic. Many of our patients have well controlled disease, yet scheduled follow up is based on patterns of behavior rather than disease control or patient needs. How we can deliver the right care for the right patient at the right time?

Methods: We proposed and developed a new visit type within our electronic health record (EHR) – a Nurse Scheduled Telephone Visit (NSTV). This was a scheduled encounter with the nurse via telephone. The nurse called the patient and collected data including disease activity measurement (RAPID3), events, problems, or symptoms that occurred since the last visit (probes) and assessed need for medication refills. The assessment was assigned one of two statuses – 1) RAPID3 with low disease activity AND all probes negative AND no refills needed, or 2) ANY of these items needed attention. The encounter was routed to the patient's rheumatologist. If status = 1, the encounter could be closed. If status = 2, further action was needed by the provider. Using PDSA (plan do study act) process improvement methodology, a pilot (cycle 1) was conducted. Patient travel cost and co-pay cost savings were calculated. The patients completed a survey after the NSTV. Based on the positive results in cycle 1, cycle 2 included presenting results to other rheumatologists seeking their insight to use this visit type across a broader array of patients and providers.

Results: **Cycle 1**: 6 of the 6 completed NSTVs had status = 1 and 1 requested a call back from his physician (status = 2) (Table 1). **Cycle 2**: 70 patients were enrolled over 2 months. Out of these, 14 completed visits thus far. 13 had status =1 and only 1 requested a call back from his physician (status = 2). Patients showed similar savings by avoiding co-pays and transportation costs in both cycles (Table 2). Our survey results showed 100% patient satisfaction. By extrapolating these results to our database of RA patients where 50% (1,200 patients) are in low disease activity or remission, using NSTV will reduce 1 visit per year and open up an additional 300 hours of clinic time.

Table 1: Nurse Scheduled Telephone Visit: Survey Results

	Patients who completed visit	Was this phone call more convenient to you?	Did this phone call save you time and money?	Do you prefer this phone call over an office visit?
Cycle 1	6	6	6	6
Cycle 2	14	14	14	14

Table 2: **Nurse Scheduled Telephone Visit: Cost and Convenience Analysis**

Cost saved	Co-pay	Transportation cost	Total cost saved	Time saved
Cycle 1	$14	$28	$42	1 hour and 34 min
Cycle 2	$24	$42	$65	2 hours and 45 min

Conclusion: As healthcare moves towards a value-based system, we propose the NSTV as a solution to improve patient experience, minimize cost burden to the patient, and increase access to care. It was well accepted by the patients and providers as an efficient resource in a busy clinic setting. It improved access in the clinic and reduced cost for the patient.

Disclosure: S. Butt, None; **E. Newman**, xG Health Solutions, 9; **N. Smith**, None.

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Abstract Number: 435

It Takes Two, an Interdisciplinary Approach to Increasing Hydroxychloroquine Screening Adherence

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Background/Purpose: Hydroxychloroquine (HCQ) is a widely used rheumatologic drug that carries a risk for irreversible retinal toxicity. The incidence of adverse effect increases to greater than 1% beyond the five year mark and screening is recommended annually beyond this time. This risk is mitigated through screening exams; 10-2 visual field testing (VF) and spectral domain optical coherence tomography (SD-OCT). In our practice setting, several visits to ophthalmology are needed to complete the screening. First the patient makes an appointment for consultation with the ophthalmologist, who then orders the testing to be done at a later date and finally the results are reviewed with the ophthalmologist.

Methods: To analyze the problem, the electronic medical record (EMR) was reviewed to identify the patients who have been on HCQ for five years or more. These patients were then cross-referenced with system procedure codes for the American Academy of Ophthalmology recommended monitoring options for HCQ related retinal toxicity in addition to the 10-2 visual field testing (VF) and (SD-OCT). Letters were sent to patients with brief education and a request to schedule an appointment. The investigators collaborated with the ophthalmology department to create a work flow for HCQ screening. Schedulers were educated about methods of screening and coached to schedule the required testing without an initial ophthalmology visit. This process streamlined the usual ophthalmology scheduling process, which involves seeing the ophthalmologist initially followed by a return visit(s) for the recommended screening and a return visit for test review.

Results: Of the 183 patients on HCQ longer than 5 years, 58.4% have not been screened. Chart review unearthed 183 patients on HCQ longer than five years. 148 of these patients did not have billing codes for screening tests in the EMR. Manual chart review revealed an additional 41 screened patients. Overall, the increase in monitoring for patients within the system was increased by 41.8%.

Conclusion: The pre-intervention process for HCQ monitoring was prohibitive for patients to receive timely monitoring. When patients called the ophthalmology scheduling department they were first scheduled with an ophthalmologist to establish the goal for the appointment. This initial visit is unnecessary if the only purpose of the visit is HCQ screening, as the guidelines are very specific. Further, the wait time to see an ophthalmologist is approximately three months or longer. There is additional wait time for an appointment for the visual field and SD-OCT testing post appointment. Tests meant to be performed annually could take four to six months to schedule and complete. Patients who identify themselves as requiring an ophthalmology appointment for the sole purpose of HCQ monitoring should be scheduled immediately for VF and SD-OCT without an initial visit with an ophthalmologist. The cumbersome appointment process was unknown to rheumatologists. It was only in working in an interdisciplinary fashion that the process was able to be more patient centered and timely.

Disclosure: C. Downey, None; **T. Govina**, None; **E. Newman**, xG Health Solutions, 9.

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Abstract Number: 436

Are Providers Recommending Appropriate Screening for Hydroxychloroquine-Induced Retinal Toxicity to Their Patients?

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Background/Purpose: Although well tolerated by most patients, hydroxychloroquine (HCQ) can cause irreversible retinal damage. The American Association of Ophthalmology (AAO) 2016 Guidelines recommend a baseline eye exam and then annual exam after 5 years of HCQ use in patients without risk factors for retinopathy. In this study, we evaluated whether patients who are receiving HCQ were counseled to receive screening for HCQ-induced retinal toxicity and whether screening procedures were congruent with AAO Guidelines.

Methods: We analyzed system-wide electronic health records (EHR) from a large, academic health center to identify 704 patients with a face-to-face encounter in which HCQ was prescribed between 1/1/2014- 3/14/2016. A random sample of 200 patients was chosen for further analysis. 19 patients were excluded because they were not taking HCQ or did not have >1 visit with a rheumatology or dermatology clinician based on chart review. Baseline characteristics of the patients were identified through queries of structured EHR fields. Physician chart review was used to determine if counseling on the need for retinopathy screening was documented and if patients had seen an ophthalmologist. Chi-square tests were used to determine if there was a significant difference in recommended retinopathy screening intervals based on clinical department. Among the subset of patients seen by an ophthalmologist within our system, we determined whether tests were performed according to AAO guidelines.

Results: Of the 181 patients included in the study, 82% were female, the mean age was 40±18.7 years, 43% were Caucasian, 23% were Asian, 17% Hispanic, 5% African American, and 12% other/multiple. The mean Charlson score was 2.1±2.6 and the majority (63%) had private insurance. 152 (84%) of the patients were counseled to undergo screening for HCQ-mediated retinopathy. Table 1 lists the screening intervals recommended by clinicians, which varied significantly by department. Interestingly, of the 69 incident HCQ users, only 2 were counseled to delay annual ophthalmologic exams until 5 years of HCQ use, the recommended interval for new, low-risk users per the AAO guidelines. 115 (64%) patients saw an ophthalmologist for retinopathy screening within the study period. Of the 48 patients who were seen by ophthalmologists in our system, 25 (51%) received the more sensitive screening tests now recommended in the AAO Guidelines.

Conclusion: In our study, a majority of patients were counseled by clinicians to receive screening for HCQ-mediated retinopathy. However, very few clinicians recommended the screening interval established by the AAO 2016 Guidelines for incident users, with most suggesting yearly screening regardless of duration of use. Additionally, many patients did not receive appropriate screening for HCQ-mediated retinopathy, despite the fact that it was recommended, highlighting an area for future quality improvement efforts.

Table 1- Screening Interval for HCQ-mediated Retinopathy Recommended by Prescribing Providers in Rheumatology and Dermatology Departments

	Rheumatologists (N=21)	Dermatologists (N=18)	
	N=135 patients	N=46 patients	
Screening interval recommended by physician			P<0.001
0 months - < 1 year	9 (7)	5 (11)	
Yearly	77 (57)	14 (30)	
Retinal toxicity screening recommended, no interval specified	22 (16)	25 (54)	
No documentation of need for retinal toxicity screening	27 (20)	2 (4)	

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Abstract Number: 437

Incidence of Gastrointestinal Events and Physician Compliance of Co-Prescribing Proton Pump Inhibitors in Chronic NSAID Users with Osteoarthritis, Rheumatoid Arthritis and Ankylosing Spondylitis

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Background/Purpose: The most common group of patients with chronic use of NSAIDs include those with rheumatic diseases such as osteoarthritis (OA), rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Serious GI complications such as bleeding, perforation and obstruction occur in about 1.5% of chronic NSAID users, while about 15% of patients report dyspepsia daily. Guidelines recommend co-therapy with PPIs or misoprostol and/or the use of COX-2 selective inhibitors in chronic NSAID users at high risk for GI events. Most such patients do not receive PPI co-therapy. We investigated the incidence of new GI events and physician compliance of co-prescribing PPIs to chronic NSAID users with RA, OA and AS at a large community hospital.

Methods: We conducted a retrospective cohort study using a simple random sample of 125 patients with OA, RA, AS who were started on NSAIDs between 1/1/2014- 12/31/2014 taken from ECW. Data was collected on 89 patients after excluding for age <30, duration of NSAID use <60 days, or no information on NSAID prescription. The study was divided as: 1) Inclusion period (1/1/2014– 12/31/2014) to identify NSAID prescription and PPI co-prescription. 2) Follow-up period (1/1/2015- 12/31/2015) to assess duration of NSAID/PPI use, and new GI events. 3) History period (1/12013 – 12/31/2013) to assess GI Risk Score (1 point each for Age>65 years, previous PPI use, GI symptoms, H.Pylori/EGD, aspirin, steroids, anticoagulation). Primary outcome measured was new GI event as dyspepsia, PUD, GERD or GI bleeding. We calculated relative risks of GI events by NSAID-PPI overlap time (none, some or complete), both unadjusted and adjusted for previous NSAID use, GI symptoms, cardiac disease, h.pylori/EGD, aspirin, steroids, and anticoagulant use.

Results: 13% of patients were on a PPI throughout NSAID use, 16% were on PPI for some time and 71% had no overlap of PPI. Only 17% were either co-prescribed or were already on a PPI at the time of NSAID prescription. There was a greater risk of GI event with greater raw number of days of NSAID use (Crude RR 1.002, p=0.007). After adjusting for covariates, those on PPI only some of the time were 4.67 times more likely to have a GI event as compared to those on complete overlap (p=0.003). Physicians were 5.31 times more likely to co-prescribe a PPI for patients with 1 or more GI risk factors. (Crude RR 5.31, p=0.007). Physicians co-prescribed PPIs 27% of the time in patients with high GI risk score as compared to 5% for patients with no GI risk factors (Crude p=0.002). Physicians were 5.31 times more likely to co-prescribe a PPI for patients with 1 or more GI risk factors. (Crude RR 5.31, p=0.007).

Conclusion: PPI co-therapy appears to have a protective effect on GI risk associated with chronic NSAID use in RA, OA and AS patients. Chronic NSAID users with higher GI risk factors are more likely to receive a PPI co-prescription, indicating that physicians consider patient's GI risk level when prescribing NSAIDs. However, 63% of patients who had GI risk factors did not receive a PPI co-prescription indicating incomplete adherence to clinical practice guidelines that recommend gastro-protection for at-risk chronic NSAID users. More awareness about PPI prophylaxis is needed among physicians prescribing NSAID for chronic use.

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Abstract Number: 438

Glucocorticoid Adverse Effects – the Patient Perspective

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Background/Purpose: Glucocorticoid (GC) use and adverse effects (AEs) are prevalent in rheumatic diseases, yet there is no standardized patient-reported outcome measure to assess benefit and risk. This study aims to determine the AEs related to GCs in two cohorts of GC users and determine the benefits and risks from the patient perspective. A secondary aim was to compare AEs amongst RA patients both exposed and unexposed to GCs.

Methods: Participants in cohort 1 attended an Australian tertiary rheumatology clinic with various rheumatic diseases and were taking an oral GC currently or within the past 12 months. Cohort 2 was from the Hospital for Special Surgery RA database (all met ACR/EULAR RA criteria) and included both GC users and non-users. The survey included a checklist of 19 known AEs and an open-ended question about presence of 'other GC side effects'. The median number of AEs experienced by each patient was compared between cohorts using poisson regression. All participants were asked to rate the three 'worst' AEs. Participants exposed to GCs were asked to indicate whether GC therapy helped 'a lot', 'a little', 'not sure' or 'not at all' and the ordinal trend between groups was compared using the Cochran Armitage exact test. GC-users were also asked whether the AEs they experienced were worse than the benefits of treatment (Yes/No/Not sure), and analyzed by chi-square.

Results: There were 55 participants from cohort 1 (71% female, median age 68, range 33-89yrs) and 124 from cohort 2 (83% female, median age 63, range 27-82). The disease range amongst cohort 1 was broad, with CTDs (14/55), RA (4/55), PMR (14/55) and GCA (5/55) most common. Amongst Cohort 2, 95 (77%) had ever used GCs (GC-users) and 29 (23%) were GC non-users. The median number of AEs was higher in cohort 1(7.7, 95% CI 7.0-8.5) compared to GC users in cohort 2, (5.3, 95% CI4.9-5.8), and both were higher than GC non-users (2.6, 95%CI 2.1-3.3). All patients in cohort 1 reported at least one GC AE compared to 86% of GC-users in Cohort 2 (p=0.002). The frequency of patient reported AEs and worst AEs are shown in Table 1. In both GC use cohorts, the majority (73%/62%) felt GCs helped their disease 'a lot', 11%/21% felt they helped 'a little', 9%/8% were 'not sure' and 2%/8% felt GCs did not help at all, with no difference between groups (ordinal p=1.0). Most participants in cohort 1(55%) and 2 (64%) reported that the benefits of treatment were greater than the AEs (p=0.67).

Conclusion: Apart from weight gain, AEs that are important from the patient perspective are poorly captured using current measures, and patients with different diagnoses may rate GC AEs and benefits differently. These hypothesis generating surveys reveal the need for further study and to develop a patient reported outcome measure for GC AEs and benefits so patients with rheumatic diseases can participate in informed treatment choices.

Table 1. Frequency of Patient Reported Adverse Events and Worst Adverse Events

Adverse Effect	Cohort N=55		Cohort 2- GC Users N=95		Cohort 2- GC Non-Users N=29	
	Number Reporting as AE	Number Reporting as worst AE	Number Reporting as AE	Number Reporting as worst AE	Number Reporting as AE	Number Reporting as worst AE
Thin skin or easy bruising	45 (82%)	9/45 (20%)	44 (46%)	7/44 (16%)	4 (14%)	0/4 (0%)
For women, vaginal thrush	26/39 (67%)	0/26 (0%)	8 /77 (10%)	1/8 (13%)	2/26 (8%)	1/2 (50%)
Weight gain	36 (65%)	9/36 (25%)	40 (42%)	13/40 (33%)	4 (14%)	0/4 (0%)
Sleep disturbance	30 (55%)	9/30 (30%)	49 (52%)	8/49 (16%)	9 (31%)	0/9 (0%)
Stomach upset or gastric reflux	30 (55%)	7/30 (23%)	38 (40%)	8/38 (21%)	9 (31%)	0/9 (0%)
Mood disturbance	28 (51%)	5/28 (18%)	24 (25%)	2/24 (8%)	5 (17%)	0/5 (0%)
Change in shape of face	27 (49%)	5/27 (19%)	20 (21%)	4/20 (20%)	0 (0%)	0/0
Increased appetite	27 (49%)	1/27 (4%)	32 (34%)	4/32 (13%)	3 (10%)	2/3 (67%)
Weakness of muscles	26 (47%)	2/26 (8%)	34 (36%)	8/34 (24%)	8 (28%)	3/8 (38%)
Depression	23 (42%)	0/23 (0%)	19 (20%)	5/19 (26%)	4 (14%)	0/4 (0%)
Swelling of feet or ankles	23 (42%)	2/23 (9%)	38 (40%)	2/38 (5%)	6 (21%)	4/6 (67%)
Thin bones or osteoporosis	21 (38%)	1/21 (5%)	29 (31%)	6/29 (21%)	3 (10%)	1/3 (33%)
High blood pressure	19 (35%)	4/19 (21%)	17 (18%)	1/17 (6%)	3 (10%)	1/3 (33%)
Change in body shape	19 (35%)	3/19 (16%)	27 (28%)	0/27 (0%)	1 (3%)	0/1 (0%)
Cataracts of eyes	17 (31%)	5/17 (29%)	17 (18%)	0/17 (0%)	7 (24%)	1/7 (14%)
Broken bones	12 (22%)	0/12 (0%)	15 (16%)	2/15 (13%)	0 (0%)	0/0
Thrush in the mouth	10 (18%)	0/10 (0%)	13 (14%)	0/13 (0%)	2 (7%)	2/2 (100%)
High blood sugars	9 (16%)	1/9 (11%)	18 (19%)	4/18 (22%)	1 (3%)	1/1 (100%)
Osteonecrosis of the hip	4 (7%)	0/4 (0%)	2 (2%)	0/2 (0%)	1 (3%)	1/1 (100%)

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Abstract Number: 439

Temple University Hospital Rheumatology Narcotic Contract

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Background/Purpose: The use of opioids in treating chronic pain can be difficult and is a common problem across multiple specialties, including rheumatology. Opioid contracts have become more common place in various outpatient practices to help standardize the way in which physicians prescribe narcotic medications and sets expectations and goals for both the provider and patient[1]. Currently, our office has no formal policy on prescribing controlled substances. This has led to lack of agreement between the expectations of health care providers and those of our patients resulting in frequent, unpredictable, and unsatisfactory number of phone calls and in-person interactions between patients and our staff related to narcotic prescriptions.

Methods: The objective of the study was to determine whether implementing a narcotic contract in the section of rheumatology will improve work flow by decreasing the number of narcotic-related EPIC phone messages. A rheumatology section meeting was held in July of 2015 regarding narcotic policy within TUH rheumatology practice and formal implementation of written narcotic contract was initiated in August 2015. Using questionnaires as a subjective measurement, we polled our staff of various positions (including physicians, nurses, medical assistant, and office personnel) on their perception of the number of narcotic prescription-related patient phone interactions both 6 months before and after initiation of the contract. Furthermore, using number of EPIC messages as our objective measurement of change, we compared the number of narcotic related phone encounters resulting in a narcotic prescription and the total number of narcotic prescriptions 6 months before and after the implementation of the contract. We also compared the total number of clinic encounters resulting in narcotic prescription 6 months before and after our intervention.

Results: Upon subjectively surveying our nurses and administrative assistants who handle the majority of incoming office

phone calls, 2/4 perceived the number of narcotic-related phone calls as increasing and 2/4 thought the number of phone calls were unchanged over the one year study period. On provider surveys, 4/11 providers had patients formally sign the written contract and 6/7 providers who did not have patients formally sign the contract, verbally referred to the new policy during office visits. Seventy three percent of providers agreed that the contract had positive effect on office work flow. The total number of EPIC messages and total number of office visits resulting in narcotic prescription decreased by 20% and 16% respectively, after implementation of the contract.

Conclusion: Although, subjective perception regarding number of narcotic phone calls encountered by office personnel did not decrease based on survey responses, there was an overall objective decrease in number of phone calls after implementation of the narcotic contract.

Disclosure: A. Zavitsanos, None; **K. Goh**, None; **S. Rathi**, None; **A. Livshits**, None; **I. Tan**, None.

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Abstract Number: 440

the Majority of Biologic Injectors Are Stored Under Suboptimal Conditions at Home

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Background/Purpose:

The introduction of biologics has significantly improved long-term outcome of immune-mediated inflammatory diseases. However, after discontinuation or switch of therapy, 26-49% of patients on subcutaneous biologics have unused injectors at home, leading to spillage of these costly drugs. When drug quality is ensured by proper storage within recommended temperature ranges (2˚C-8˚C), unused injectors could potentially be redistributed reducing spillage. The aim of this study was to assess the quality of home storage by evaluating the proportion of injectors stored within the recommended temperature range.

Methods:

All subcutaneous golimumab users at the Maastricht University Medical Centre+, irrespective of the indication, were asked to participate in this prospective study between April and October 2015. During 3 months, patients received golimumab in the original package provided in a sealed bag containing a validated temperature sensor connected to the internet. Patients were asked to store their medication as usual. Temperature was measured every 5 minutes. Deviations from the recommended range were defined as 1). > 30 minutes below 2˚C or above 8˚C and 2). any duration below 0˚C. After 3 months, patients filled out a questionnaire on their opinion about monitoring medication storage conditions at home and potential redistribution of unused injectors.

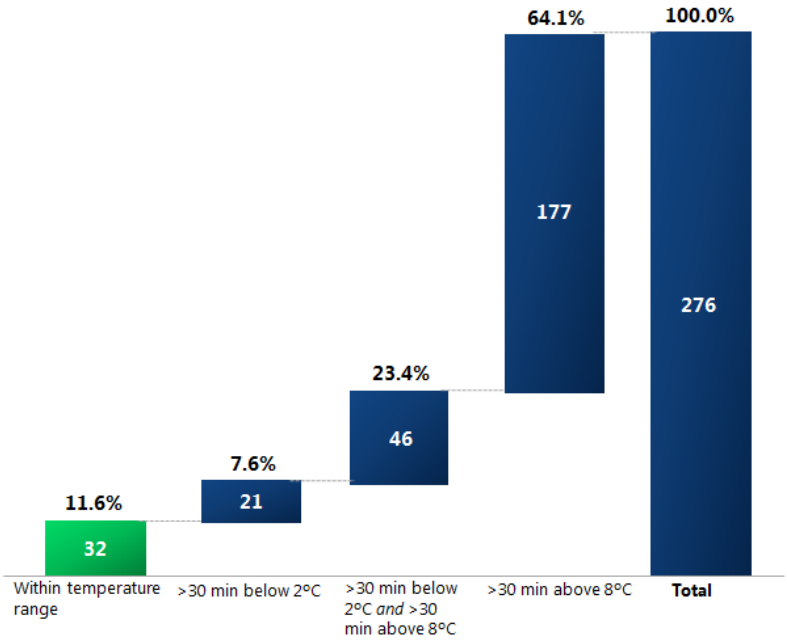
Results:

In total, 50 patients (46.3% male, mean age 52.3 ± 13.8 years) received 276 injectors with temperature sensors that generated 2,466,576 measurements. Figure 1 shows that 11.6% of the injectors were stored within the recommended temperature range. Of the remainder, 11.2% were stored more than 30 minutes below 0˚C and 19.6% were stored above

8°C for more than 48 hours. Of all patients, 95% would appreciate an alarm when the injector is not stored under the right conditions, and also 95% is willing to accept unused medication when product quality is ensured.

Conclusion:

Only a minority of injectors was stored within the recommended temperature range. This hinders not only redistribution of unused biologics, but is also alarming regarding the effectiveness of the drug in these patients. We are currently investigating how to improve biologics' home- and transport storage conditions and the criteria to be met for redistribution.



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Improving Care and Avoiding Errors. Can Our Patients Recall Their Medications and Create an Accurate Medication List?

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Background/Purpose: Medications errors are common and are an important cause of morbidity and mortality. We aimed to evaluate patient accuracy in recalling current medication use, doses and reasons for taking the medications in a general rheumatology outpatient clinic.

Methods: This is a descriptive study of 100 consecutive patients who attended clinic and voluntarily accepted to fill a

single questionnaire. The questionnaire consisted of name (s) of the medication (s) the patient was taking, dose, diagnosis associated with their medications, medical record number, sex and age. Once we had this information, the medical records were reviewed to look for discrepancies. Data collected was entered in Excel Files and was analyzed in STATA version 14. The information was verified and converted to groups of interest. Data whose overall category only had 5 cases were only presented as frequencies describing the patient's characteristics but were not fit for further analysis and thus they were eliminated from the bivariate and multivariate analysis. Association of variables was determined using a p-value < 0.05. To assess our objectives, frequency distributions were made to describe the characteristics of the patients. Then chi squares analysis were done for categorical variables in order to determine if they were associated to our variables of interest. For continuous variables such as age and number of prescriptions a t-test was performed. At last a logistic regression was done when we found characteristics that were significantly associated with our variable of interest. In the logistic regression we also assessed whether or not interaction among the variables existed in order to find the best explanation to the associations found between variables.

Results: We had 85 females and 15 males. Mean age was 47.13 ± 14 years. The average number of prescriptions per patient was six. Lack of knowledge regarding reason for taking medications was seen in 35 patients; fifty five did not recall the dose of medications prescribed. Discrepancies between the patient's and the electronic medical record medication list were identified in 71, with an average of two per patient; the majority of them were patient derived. The most common medications involved in errors were antidepressants/anxiolytics (19), vitamins (18), immunosuppressants (13), NSAIDS (12), antihypertensives (12) and anti-acids (9). The most common diagnosis in our clinics were fibromyalgia (33), osteoarthritis (16), RA (17), SLE (13) and others (26). The most common prescribed medications were antihypertensives (41), antidepressants (38), prednisone (25), hydroxychloroquine (25) and immunosuppressants (22). No significant associations were found between variables of interest.

Conclusion: Although most of our patients know the medical condition associated with a medication, the majority of them cannot precisely recall a medications list. This is a very important factor that can lead to medical errors. Patients should be educated regarding the importance of keeping an accurate medication list.

Disclosure: C. F. Gamarra-Hilburn, None; **S. Vila**, None.

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Abstract Number: 442

Comparison of Adherence and Dosing Interval of Subcutaneous Anti-TNF Biologics in Inflammatory Arthritis from a Canadian Administrative Database.

Peter Bhoi[1], Louis Bessette[2], Mary Bell[3], Cathy Tkaczyk[4], Francois Nantel[5] and Karina Maslova[1], [1]Janssen Inc., Toronto, ON, Canada, [2]Rheumatology, CHUL de Quebec, Quebec, QC, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [5]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada
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Background/Purpose: Subcutaneous (SC) anti-TNF agents such as Golimumab (GLM) Adalimumab (ADA), Etanercept (ETA) and Certolizumab pegol (CZP) have been used for many years for the treatment of inflammatory arthritis. It is known that across diseases, and especially with chronic diseases, adherence to therapy is an important modifiable factor that may compromises treatment outcomes. The aim of this analysis was to compare adherence and dosing interval of SC anti-TNF in the treatment of inflammatory arthritis.

Methods: We used the IMS Brogan database which combined both private (PDP) and public drug plans databases of the provinces of Ontario (OPDP) and Quebec (RAMQ). Target drugs included SC anti-TNF biologics for indication of

rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis combined. The Index period was from January 1, 2010 - June 30, 2012 and patients were followed for 24 months through June 30, 2014. Patient selection criteria were adult patients newly prescribed a target biologic drug with at least three prescriptions and retained on therapy at 24 months. Recommended dose regimens as per the Canadian product monographs were used to compare actual vs. expected drug utilization. The compliance rate (MPR) was calculated as the estimated days' supply in the defined period divided by the number of days in the defined period. Patients who scored >80% were considered adherent. For dose-interval analysis, the average days between units was estimated by taking the total days on therapy and dividing by the number of units the patient received. A unit is a syringe or vial; the total amount of drugs dispensed (in mg) were standardized at units as per the following: GLM: 50 mg; ADA: 40 mg; ETA: 50 mg; CZP: 200 mg. P-value obtained from Chi-square and Pair-wise comparison tests for statistical differences on the proportion of adherent patients; p-value < 0.05 is considered to be statistically significantly different.

Results: There were 4,035 new patients on target biologic drugs with at least three prescriptions and retained on therapy at 24 months. The number of patients for each biologic drug used was 683, 1400, 1765 and 187 for GLM, ADA, ETA and CZP, respectively. The data source was as follow: PDP national (N=2509), RAMQ (N=634) and OPDP (N=892). In 24 months-retained patients, there was a greater proportion of GLM-treated adherent patients (n=595/683, 87%, $p<0.0001$) compared to ADA- (n=1044/1400, 75%), ETA- (n=1285/1765, 73%) or CZP-treated patients (132/187, 71%). We also investigated the number of patients receiving biologic drug at a shorter dosing interval. That proportion was similar between groups and was 5%, 6%, 12% and 4% in GLM- (≤26 days), ADA- (≤12 days), ETA- (≤6 days) and CZP-treated patients (≤12 days), respectively.

Conclusion: In this real life Canadian administrative database, GLM has better adherence compared to other SC biologics. The reason for this difference and impact on long-term outcomes are currently under investigation.

Disclosure: P. Bhoi, Janssen Inc., 3; **L. Bessette**, None; **M. Bell**, None; **C. Tkaczyk**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3.

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Abstract Number: 443

Repetitive Requisition of Antinuclear Antibody Testing (ANA) in Outpatient Multispecialty Clinics in Patients with a Known Positive ANA

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Background/Purpose: ANA test is a commonly used initial screening for connective tissue diseases (CTD). The ultimate clinical utility of this highly sensitive test depends on the pretest diagnostic probability. It should not be a first line test for the investigation of musculoskeletal symptoms like fatigue or joint pains, unless accompanied by other clinical features to suggest autoimmune disease. It can be positive in multiple autoimmune and mixed connective tissue disorders. It can also be falsely positive in multiple other scenarios. ANA test rarely needs to be repeated. It is a diagnostic, not monitoring test. If an unexpected result is given, it is reasonable to repeat the test to confirm the finding. It is also useful to repeat if a person's illness has significantly changed. It, however, has no correlation to disease activity in SLE or other CTD. A trend of repeating ANA testing on patients with a history of positive ANA was noted in our outpatient multispecialty clinic. The purpose of this study is to review how frequently patients with known positive ANA testing undergo repeat ANA testing, the reason for it and the specialty and level of training of providers ordering it.

Methods: Retrospective chart review was performed on 598 patients who underwent ANA testing between April 1st, 2015 and March 31st, 2016. Data collected included: Age, gender, positive ANA test result, reason for ordering ANA, specialty and level of training of provider ordering ANA. Patients with a positive ANA were identified first followed by review of number of repeat ANA testing after first positive result. Data analyzed using percentage to determine frequency of events.

Results: Of the total of 598 patients undergoing ANA testing between April 1st 2015 and March 31st 2016, 196 (32.8%) patients had a positive result. All patients were older than 18 years, 140 (71.4%) were females and 56 (28.6%) were males. Repeat ANA was noted in 111 (56.6%) patients. Of those, 58 (52.2%) patients had repeat testing once, 23 (25.5%) twice, 11 (9.9%) three times, 8 (7.2) four times, 2 (1.8%) five times, and 9 (8.1%) six or more times. There were 2 patients who underwent repeat ANA test 33 and 56 times. A total of 194 (64.4%) of 301 providers ordering repeat ANA testing were identified. Rest were not available. Most were rheumatologists 76 (39.1%) and primary care physicians 67 (34.5%). Remaining included gastroenterology, pulmonary, dermatology, nephrology and emergency medicine. Majority of repeat tests wherein data was available (172 total) were ordered by attending physicians 162 (94.1%).

Conclusion: Further education and emphasis should be given on appropriate ANA testing criteria in order to decrease misuse and increase cost effectiveness.

Disclosure: L. Amorese-O'Connell, None; **P. Vaidya**, None; **D. Mahboob**, None; **C. Gn**, None; **S. Schwartz**, None.

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Abstract Number: 444

Improvement in Knee Arthrocentesis Via Constant Compression

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Background/Purpose: Arthrocentesis has emerged as a highly valuable diagnostic and therapeutic intervention for rheumatic diseases since first standardized by Hollander in the 1950's. Successful arthrocentesis of the knee, to decompress the effusive knee and provide objective material for laboratory analysis, is contingent upon obtaining sufficient synovial fluid. As a Quality Improvement process within the Division of Rheumatology, we introduced constant compression of the knee during arthrocentesis and determined whether quality measures including aspiration success and fluid volume were improved.

Methods: This Quality Improvement project was performed within the Rheumatology Division at the University of New Mexico Health Sciences Center and assessed quality improvement of intra-procedural constant compression during knee arthrocentesis in terms of overall success, outcome and quality among individual patients. All patients undergoing knee arthrocentesis for therapeutic/diagnostic reasons were sequentially included and classified prior to the procedure as to either non-effusive (dry) vs. effusive knees as per physical examination. The more effective conventional lateral knee arthrocentesis techniques alone were undertaken rather than the less effective medial approaches. Initially the patient underwent arthrocentesis with an elastomeric knee brace placed loosely around the knee with syringe exchange maneuvers performed as required to decompress large effusions if present. Upon termination of synovial fluid return using the conventional method, the elastomeric brace was securely tightened without disturbing either arthrocentesis needle or syringe and arthrocentesis was again attempted. Quality outcome measures included: 1) trace yield of synovial fluid with

initial arthrocentesis, 2) diagnostic yield of synovial fluid (defined as ≥0.25 ml) with and without compression, 3) total synovial yield in milliliters (ml) with and without compression. Pierson Chi squares two by two table analysis was performed on categorical data calculating both p values and confidence intervals. Measurement data was analyzed using the Student t-Test calculating both p values and confidence intervals as well.

Results: There were no complications encountered by the 113 patients in the cohort including, but not limited to infection, significant bruising or other hemorrhage. At least trace synovial fluid was obtained in 83.3%. However, diagnostic synovial fluid (at least 0.25 ml) was obtained in 31.9% without compression and 46.6% with compression (p=0.0001, z for 95% CI= 1.96, Pierson). Absolute volume of arthrocentesis fluid yield without compression was 3.7±6.6 ml versus 6.6±13.0 with compression (p=0.018, 95% CI -5.5881 <-2.9< -0.2119) corresponding to a mean 2.9±6.1 ml (80%) increase in synovial fluid yield. In the subset of 87 patients with a palpably dry knee at least trace synovial fluid was obtained in 79% of patients. Diagnostic synovial fluid (at least 0.25 ml) was obtained in 13.8% without compression and 42.5% with compression (p=0.0001, z for 95% CI= 1.96). In the palpably dry knee absolute volume of arthrocentesis fluid without compression was 0.3±0.9 ml versus 1.1±2.1 ml with compression (p=0.001, 95% CI -1.2801 <-0.8< -0.3199). This corresponds to a mean 0.8±1.6 ml (266%) increase in synovial fluid yield. In the subset of 26 patients with a palpably effusive knee, at least trace synovial fluid was obtained in 100% of patients. Diagnostic synovial fluid (at least 0.25 ml) was obtained in 96% without compression and 100% with compression (p=0.2, z for 95% CI= 1.96). In the palpably effusive knee absolute volume of arthrocentesis without compression was 15.4±14.1 ml versus 25.7±15.9 ml with compression (p=0.008, 95% CI --18.4686 <-10.3< -2.1314) corresponding to a mean 10.3±9.2 ml (67%) increase in synovial fluid yield.

Conclusion: The quality and success of knee arthrocentesis can be markedly improved through the application of constant compression using a circumferential knee brace. The overall success of diagnostic/therapeutic arthrocentesis can be significantly increased with markedly improved fluid yield compared to conventional arthrocentesis in both the clinically non-effusive and effusive knee. The increased synovial fluid return and arthrocentesis also provides additional value through confirmation of accurate intraarticular needle placement. As complete arthrocentesis has been demonstrated to improve subsequent intraarticular injection outcomes, constant compression with an elastomeric knee brace is a simple and economical quality improvement maneuver that can be incorporated into clinical musculoskeletal practice and injection clinics.

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Performance of Promis Measures in a Multi-Ethnic Population-Based Systemic Lupus Erythematosus (SLE) Cohort

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Background/Purpose: NIH's PROMIS (Patient-Reported Outcomes Measurement Information System) measures have the potential to improve and expand outcomes measurement in SLE, but have not been tested on a large scale in lupus.

Methods: Data were from the California Lupus Epidemiology Study (CLUES), a population-based, multi-ethnic SLE

cohort. All subjects' diagnoses were physician-confirmed. Subjects participated in a structured interview administered by a trained interviewer. Nine PROMIS short-forms (Table 1) were administered and scored to derive T-scores scaled to population means of 50 and SD of 10. Race and ethnicity were self-reported. Score distributions were examined. Deficits in function were defined as scores 1 SD "worse" than the population mean. Means (±SDs) were calculated for the total sample and by racial/ethnic group. Correlations with self-reported disease activity (Systemic Lupus Activity Questionnaire; SLAQ) and damage (Brief Index of Lupus Damage; BILD) were examined. We expected moderate to large correlations of current functioning with SLAQ, but small correlations with BILD. Differences in mean scores by race/ethnicity were tested by ANOVA and then in multivariable regression analyses controlling for age, sex, education, and poverty.

Results: To date, data from 197 individuals are available. The sample is 31% white, 22% Hispanic, 14% African American, and 33% Asian; 89% female; mean age 46 (±10) years; 13% with education ≤high school; 13% with poverty-level income; mean SLAQ score 8.2 (±7.3); and median BILD score 1 (IQR 0, 3). With the exception of Pain Intensity, mean scores were ±3 points of the population mean (Table 1). Correlations with disease activity (SLAQ) ranged from |0.47| — |0.73|. Correlations with disease damage (BILD) were lower, ranging from |0.1| — |0.3|, except for physical function (r=-0.38). Fewer than 5% of scores were at scale floors but relatively high proportions scored at the ceiling for 6 scales. Except for Pain Intensity, 17-30% had scores one SD worse than the population mean. In bivariate analyses, significant differences existed among racial/ethnic groups, but differences disappeared after adjusting for sociodemographic characteristics.

Conclusion: These 9 PROMIS short forms appear to function well in this multi-ethnic cohort of SLE patients. Few scores were at the scale floor, but relatively high portions were at the ceiling, suggesting potential weakness of the scales in measuring higher positive levels of function. Means were not substantially different than population means, but relatively large portions of the cohort exhibited deficits in physical and social functioning. Correlations with current disease activity were moderate to large, and correlations with disease damage were small, as expected. Differences in scores among racial/ethnic groups appear to be explained by differences in socioeconomic characteristics.

Table 1

	Mean ± SD T-score						Correlation with:				
Scale	Total (n=197)	White (n=60)	Hispanic (n=44)	Black (n=28)	Asian (n=65)	p-value *	SLAQ	BILD	% at "worst" score	% at "best" score	% with deficit †
PF	47.4 ± 9.6	49.8	46.1	41.9	49.9	.004	-0.69	-0.38	1.0	21.3	28.0
PIn	42.1 ± 9.8	42.7	44.1	46.7	37.5	<.0001	0.66	0.10	0.5	33.0	4.1
PIf	52.6 ± 9.5	52.5	54.4	56.0	49.1	.003	0.65	0.18	2.0	36.6	20.3
F	52.6 ± 11.3	53.1	52.9	54.2	48.9	.08	0.73	0.12	4.1	16.8	26.4
SD	51.5 ± 9.3	51.1	52.4	52.6	49.9	.44	0.47	0.10	2.0	5.1	16.8
SI	52.5 ± 10.4	52.2	52.1	54.1	51.0	.61	0.63	0.09	0.5	5.1	22.5
CA	47.7 ± 8.1	50.1	46.9	45.1	48.6	.04	-0.48	-0.20	1.5	13.2	20.6
SSR	51.4 ± 11.1	51.6	50.6	48.8	53.6	.25	-0.61	-0.17	3.4	25.6	30.4
PSR	49.7 ± 9.5	50.7	49.7	46.2	52.2	.05	-0.64	-0.28	2.1	23.6	19.2

Note: Only data from English-speaking participants is shown. PF = Physical Function PIn = Pain Intensity PIf = Pain Interference F = Fatigue SD = Sleep Disturbance SI = Sleep Impairment CA = Cognitive Ability SSR = Satisfaction with Social Roles PSF = Participation in Social Roles • p-value from comparison of racial/ethnic group means using ANOVA † Deficit defined as T-score 1 SD worse than population mean of 50. In a normal distribution, 16% of scores would be expected to fall in this range. Differences between racial/ethnic groups were not significant.

Disclosure: **P. P. Katz**, None; **J. Yazdany**, None; **L. Trupin**, None; **S. Rush**, None; **C. Lanata**, None; **C. G. Helmick**, None; **L. A. Criswell**, None; **M. Dall'Era**, None.

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Abstract Number: 446

A Multi-Group Confirmatory Factor Analyses of the Lupuspro Between Southern California and Filipino Samples of Patients with SLE

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Background/Purpose: Systemic lupus erythematosus (SLE) leads to a variety of health outcomes through complex disease paths. The LupusPro (LP) is a comprehensive self-report measure which assesses health and non-health related quality of life for patients with SLE. It is increasingly used in a variety of ethnicities and diverse populations, and continues to hold psychometric integrity. Research, however, is needed that examines the validity and factor structure of the LP in order to precisely understand its psychometric integrity as an outcome measure used cross-culturally. The major purpose of this research was to evaluate the performance of the LP in two divergent patient samples and to identify differences in model fit between the two samples that would illustrate the potential for adapting the LP measure in future research.

Methods: Two diverse samples including 236 patients with SLE were included one from an ethnically-diverse, urban region in Southern California, and the other from an ethnically-homogenous, rural region in Manila, Philippines. All patients met ACR classification criteria for SLE. Confirmatory factor analyses (CFA) were conducted in each sample separately and combined to provide evidence of the factorial integrity of the 12 subscales comprising the LP.

Results: Demographic analyses indicated significant differences in age, disease activity and duration, education, income, and medication use between groups. Results of the separate CFA's indicated moderate fit to the data for the hypothesized 12-factor model for both the Manila and California groups, respectively [χ^2 (794)=1283.32, p<.001, CFI=.793; χ^2 (794)=1398.44, p<.001, CFI=.858] (note: with large scales, χ^2 less than double the degrees of freedom indicated reasonable fit). The factor structures between the California and Manila groups were constrained to be equal between the two groups, and findings revealed that the factor structures of measured variables fit the two groups reasonably well (χ^2=2950.413, df =1697, p<.000; CFI=0.811) [14]. After removing seven constraints and eight correlations suggested by the Lagrange multiplier test, the model fit improved significantly [$\chi^2(15)$ = 147.165, p < .000].

Conclusion: This research provides for significant support for the subscale structure of the LP in two disparate cultural samples of SLE patients. Despite significant sociodemographic and clinical differences between the two samples, for the most part, the LP performed similarly in both samples. Table 1. Demographics and general characteristics < td width="12%"> (95.6)

	Multiethnic in SoCal	Filipinos in Manila	
			p
	(*n* = 136)	(*n* = 100)	
Female, *n* (%)	126(92.7)	94(94.0)	.683
Age (years), Mean ± SD	48.57± 13.87	34.75± 10.99	<.001***
Disease duration (years), Mean ± SD	16.90± 11.90	5.70± 5.18	<.001***
Education level, *n* (%)			.004**
Less than college	34(25.0)	44(44.0)	
Attended college	98(72.1)	56(56.0)	
Not specified	4(2.9)	0(0.0)	
Married/lives with partner, *n* (%)	76(55.9)	52(52.0)	.554
With gainful occupation, *n* (%)	71(52.2)	36(36.0)	.013*
Income level, *n* (%)			<.001***
Below poverty line	27(19.9)	41(41.0)	
Lower middle class	26(19.1)	38(38.0)	
Upper middle class	34(25.0)	15(15.0)	
Upper class	49(36.0)	6(6.0)	
Health insurance coverage, *n* (%)			<.001***
Insured	130	50(50.0)	
Uninsured	6(4.4)	45(45.0)	
Not specified	0(0.0)	5(5.0)	
Active SLE disease, *n* (%)*	11(8.1)	30(30.0)	<.001***
Medication use			
Prednisone, *n* (%)	59(43.4)	92(92.0)	<.001***
Immunosuppressants, *n* (%)	88(64.7)	88(88.0)	<.001***
Cytotoxics, *n* (%)	24(17.6)	22(22.0)	.404
Biologics, *n* (%)	62(45.6)	1(1.0)	<.001***

Note. Group comparisons made using χ^2 and *t* tests for categorical and continuous variables, respectively. Active disease as indicated by a Mex-SLEDAI score > 5. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 2. Means, standard deviations, and factor loadings of measured variables (LupusPRO) in the confirmatory factor analyses

LupusPRO Factors and Items	Southern California Mean (SD)	Factor loading	Manila Mean (SD)	Factor loading
I – Lupus Symptoms				
1. Hair loss	2.36 (1.43)	.49	2.86 (1.15)	.18
2. Skin rash	2.90 (1.45)	.58	2.94 (1.15)	.62
3. Lupus Flare	2.56 (1.18)	.72	2.93 (1.17)	.56
II – Cognition				
4. Memory	2.11 (1.27)	.80	2.86 (0.99)	.42
5. Concentration	2.24 (1.17)	.97	2.84 (0.96)	.84
III – Lupus Medications				
6. Med side effects	2.96 (1.22)	.84	2.91 (1.18)	.51
7. Number of meds	2.87 (1.26)	.70	2.59 (1.13)	.55
IV – Procreation				
8. Effect of meds on pregnancy	3.52 (1.11)	.86	2.96 (1.36)	.91
9. Unplanned pregnancy worry	3.87 (0.56)	.54	3.03 (1.30)	.48
V – Physical Health				
10. Meeting personal needs	3.39 (0.99)	.73	2.82 (1.41)	.61
11. In and out of bed	3.30 (0.98)	.79	2.94 (1.19)	.60
12. Meeting family responsibility	2.89 (1.09)	.77	2.65 (1.37)	.51
13. Taking care of dependents	2.99 (1.14)	.77	2.72 (1.37)	.56
14. Burden to others	2.94 (1.20)	.78	2.05 (1.12)	.12
VI – Pain Vitality				
15. Feel worn out	1.94 (1.22)	.81	3.06 (1.04)	.18
16. Pain and ache	1.96 (1.24)	.76	2.51 (1.02)	.37
17. Limited usual activities	2.66 (1.15)	.81	2.78 (1.09)	.66
18. Limited usual activities for long time	2.35 (1.28)	.94	2.66 (1.16)	.90
19. Limited in types of tasks and activities	2.24 (1.23)	.94	2.70 (1.14)	.84
VII – Emotional Health				
20. Worry for lupus impact on future	2.34 (1.34)	.77	2.34 (1.23)	.52
21. Loss of income worry	2.57 (1.48)	.72	2.20 (1.21)	.50
22. Anxious	2.51 (1.25)	.84	2.29 (1.05)	.60
23. Depressed	2.80 (1.19)	.75	2.44 (0.96)	.48
24. Lupus and more health problems	2.37 (1.27)	.81	2.18 (0.98)	.60
25. Concern for lupus symptom longevity	2.15 (1.33)	.84	2.09 (1.02)	.49
VIII – Body Image				
26. Dislike appearance	2.63 (1.29)	.91	2.73 (1.05)	.72
27. Thought less of self	3.00 (1.20)	.82	3.00 (1.00)	.32
28. Lack control over appearance	2.92 (1.20)	.89	2.94 (0.99)	.58
29. Self conscious of appearance	2.56 (1.35)	.92	2.58 (1.14)	.73
30. Embarrass of others' perceptions	2.88 (1.31)	.84	2.59 (1.07)	.73
IX – Desires-Goals				
31. Ability to plan events	2.59 (1.22)	.69	2.35 (1.14)	.47
32. Overall life satisfaction	2.43 (1.09)	.93	2.44 (1.21)	.60
33. Life enjoyment	2.50 (1.15)	.90	2.05 (1.30)	.88
34. Fulfill career goals	2.47 (1.46)	.58	2.22 (1.20)	.58
X – Social Support				
35. Support from friends	2.42 (1.37)	.82	2.15 (1.36)	.31
36. Support from family	2.67 (1.35)	.75	2.99 (1.06)	.46
XI – Coping				
37. Focus to improve my situation	2.79 (1.09)	.76	3.08 (0.94)	.53
38. Learn to live with lupus	3.18 (1.01)	.74	3.03 (1.00)	.42
39. Strength from spiritual/ religious beliefs	2.35 (1.58)	.32	3.06 (1.16)	.58
XII – Satisfaction with Care				
40. Dr. accessible for questions	3.61 (0.86)	.84	3.24 (0.96)	.71
41. Dr. understood impact of lupus on me	3.47 (0.92)	.89	3.43 (0.91)	.76
42. Dr. gave me lupus info	3.61 (0.86)	.86	3.39 (1.02)	.92

43. Dr. discussed side effects of lupus meds	3.50 (0.97)	.92	3.36 (0.99)	.84

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Abstract Number: 447

The Influence of Risk Presentation Format on Willingness to Start a Medication

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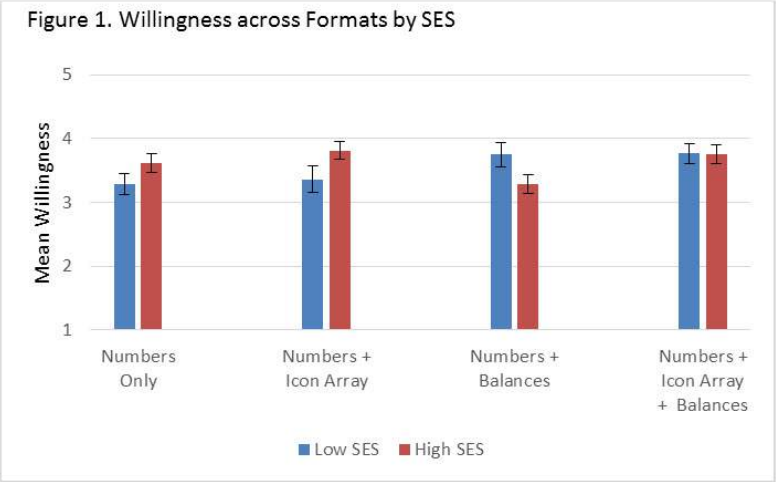
Background/Purpose: Patients with rheumatoid arthritis frequently refuse to escalate care because they overweight the probability of adverse events. Effectively communicating risk information to patients is difficult. Several approaches have been developed to facilitate comparative risks; however, recent data suggest that current approaches have a limited impact on risk perceptions and willingness to take medication. The objective of this study was to examine whether an icon array (IA), an illustration of the gist of how medications regulate the immune system (a series of balance beams), or both influence willingness to start a medication.

Methods: Patients with a rheumatic disease were mailed a survey in which they were asked to imagine that their symptoms had worsened and that their physician was recommending a new medication. We varied the probability of an adverse event (pneumonia requiring hospitalization): 2% or 0.2%, and the risk presentation format: numbers, numbers + IA, numbers + balance beams (BB), or numbers + both. Route of administration, benefit, and cost were held constant. Each subject responded to a single, randomly-assigned scenario. We controlled for socioeconomic status (SES), using a variable including both difficulty paying for medications as well as education, in a full-factorial model testing willingness to take the medication (measured on a 5-point scale).

Results: Of 1453 surveys, 465 patients completed the survey. Overall, the mean (SD) age was 59.0 (14.8); 79.7% were female; 83.2% White and 39.1% were classified as having low SES. There were no statistical differences in patient characteristics across the risk presentation formats. Willingness to start the medication was predicted by the interaction between the risk presentation format and SES ($F = 2.9$, $p = 0.03$). Willingness by SES status is described in the Figure 1. Among low SES subjects, addition of an IA did not affect willingness compared to the numbers-only format. In contrast, addition of BB (mean difference = 0.47, $p = 0.07$), or both IA and BB increased willingness (mean difference = 0.48, $p = 0.04$). Among high SES subjects, addition of an IA or BB or both did not influence willingness compared to the numbers only format. However, both formats including an IA increased willingness compared to the BB format among high SES subjects (mean difference IA vs BB= 0.53, $p =0.01$; mean difference IA vs IA + BB = 0.48, $p = 0.02$).

Conclusion: SES affects how subjects respond to risk presentation formats. IA marginally increases willingness in high SES subjects, while BB increases willingness in low SES subjects; when both IA and BB are present, SES differences disappear. BB, when not accompanied by an IA, may decrease willingness in high SES subjects. These results demonstrate the differential effects of risk presentation formats, and highlight the need to identify mechanisms underlying their effects



when implementing decision-support tools.

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Cross-Cultural and Construct Validity of the Animated Activity Questionnaire to Assess Activity Limitations in Patients with Hip and Knee Osteoarthritis in Different Languages

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Background/Purpose: The computerized Animated Activity Questionnaire (AAQ) assesses activity limitations in hip and knee osteoarthritis (HKOA), and consists of video animations from which patients can choose the animation that best

matches their own performance. Application of the AAQ in international studies requires good cross-cultural validity, i.e. minimal Differential Item Functioning (DIF) across countries. The aim of this study was to evaluate cross-cultural and construct validity of the AAQ in 7 languages.

Methods: Patients in 7 European countries completed the AAQ on a computer. Ordinal logistic regression analysis was used to evaluate DIF across languages (Dutch versus 6 other languages). DIF is defined as follows: if a patient in a country has the same level of activity limitation as a patient in the Netherlands (the reference country in which the AAQ is developed), he/she should score the same on each item of the AAQ. If there is a statistical significant difference between countries, there is DIF. Construct validity was assessed by testing correlations between the AAQ and a Patient Reported Outcome Measures (PROM) and performance-based tests. Analyses were adjusted for sex, age, weight, height, and affected joint. The influence of each individual item with DIF on the total score was calculated by means of comparing the correlation between AAQ score with and without the DIF item. A Spearman's correlation of 0.95 or less was interpreted as important influence of the DIF of that item on the total AAQ score.

Results: Data of 1239 patients were available. Compared to Dutch (n=279), none of the 17 items showed DIF in English (n=202), French (n=193), 1 item showed uniform DIF in Spanish (n=99) and Norwegian (n=62), and 2 items showed uniform DIF in Danish (n=201). For Italian (n=203) versus Dutch however, 6 items showed uniform DIF, and 1 item showed non-uniform DIF, indicating some problems with the cross-cultural validity between these countries. In all the languages, the occurrence of DIF did not influence the total score with correlations of 0.98-0.99 in comparing AAQ scores with and without DIF item(s). All the translated versions remain comparable with the original Dutch version. With regard to construct validity, the correlations with PROM (0.74) and performance-based tests (0.36-0.68) were partly as expected (> 0.60).

Conclusion: The AAQ, a new construct that can be placed on the continuum between PROMs and performance-based tests showed a good overall cross-cultural validity, and seems to have great potential for international use in research and daily clinical practice in many languages.

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Abstract Number: 449

the Animated Activity Questionnaire to Assess Activity Limitations in Patients with Hip and Knee Osteoarthritis: Reliability, Responsiveness, and Interpretation

Wilfred Peter[1], Henrica de Vet[2], Rudolf Poolman[3], Vanessa Scholtes[4], Dionne Timmermans[5], Nina Klein Essink[5] and Caroline Terwee[6], [1]Amsterdam Rehabilitation Research Centre, Reade, centre for rehabilitation and rheumatology, Amsterdam, Netherlands, [2]EMGO Institute, VU Medical Centre, Amsterdam, Netherlands, [3]Orthopedic department, Joint Reserach, OLVG, Amsterdam, Netherlands, [4]Department of Orthopedics, Joint Research, Onze Lieve Vrouwe Gasthuis, Amsterdam, Netherlands, [5]Orthopedics, Joint Research, OLVG, Amsterdam, Netherlands, [6]Dep of Epidemiology and Biostatistics, EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: A newly developed and (cross-cultural) validated measurement tool, the computerized Animated

Activity Questionnaire (AAQ) for assessing activity limitations in hip and knee osteoarthritis (HKOA) patients, consists of video animations from which patients can choose the animation that best matches their own performance. For application in daily clinical practice as well as in research, the aim of this study was to determine reliability, responsiveness, and interpretability of the AAQ.

Methods: First, 238 HKOA patients mixed from hospital and rehabilitation center completed the AAQ twice with 7 days in between. Test-retest reliability (intra-class correlation coefficient (ICC)) the Standard Error of Measurement (SEM), and the Smallest Detectable Change (SDC) were calculated. Second, 92 other patients with hip or knee OA were followed for 6 months in order to assess responsiveness. Patients received conservative physical therapy treatment or joint replacement surgery and were measured before intervention and 6 months later. We hypothesized that change scores on the AAQ (score range 0-100) correlated at least 0.6 with self-report (ADL subscore of the Hip disability and Knee Injury Osteoarthritis Outcome Score,), performance based tests (Timed Up and Go test, Stair Climbing Test, and 30 seconds Chair Stand Test), and a Global Rating of Change (GRC). To estimate the Minimal Important Change (MIC) of the AAQ an anchor-based MIC distribution method was used. The Receiver Operating Characteristic (ROC) method was used to find the optimal AAQ change score that best discriminates. The MIC was compared to the SDC in order to facilitate the interpretation of change scores.

Results: ICC for test-retest reliability was 0.93 (95%CI: 0.91-0.95). SEM and SDC were 4.9 and 13.5, respectively. After 6 months the change scores of the AAQ correlated 0.67 with self-reports, 0.47-0.55 with performance based tests, and 0.43 with GRC. The ROC curve showed an area under the curve of 0.71 with a sensitivity of 62% and a specificity of 79% for the optimal MIC of 9.12 for discrimination. The MIC was smaller than the SDC meaning that the change is important but cannot be distinguished from measurement error in individual patients.

Conclusion: The AAQ showed good internal consistency, test-retest reliability, and SDC resulting in an average mean score difference of the AAQ over 14% indicating a real improvement in activity limitations in a mix of surgical and conservative HKOA patients. The AAQ is considered responsive, despite the moderate correlations with performance-based tests and GRC, which seems to be caused by the slightly different, new construct the AAQ is measuring with regard to the domain activity limitations.

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Abstract Number: 450

Coming Full Circle with the Omeract RA Flare Questionnaire (RA-FQ): Further Evaluation of the Properties, Meaningfulness, and Utility through Rasch Analysis and Feedback from RA Patients

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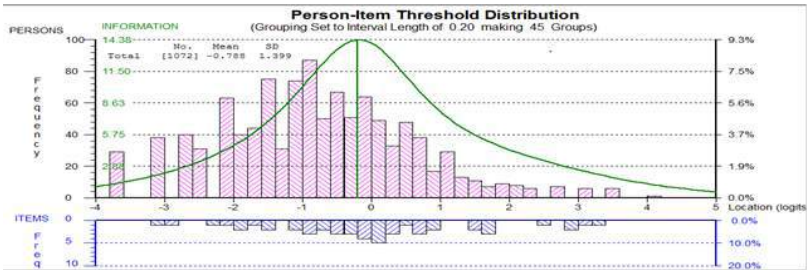
Background/Purpose: OMERACT Filter 2.0 encourages use of robust methods to develop new measures. Instrument results also should be highly relevant, easily scored and interpreted, and meaningful to stakeholders likely to use the instrument. We conducted Rasch analysis to further explore the psychometric properties OMERACT RA Flare Questionnaire (RA-FQ). We reviewed results with RA patients research partners (PRPs) to gain additional insight into the interpretability, meaningfulness, and utility of results.

Methods: People with RA in Canada (n=896), France (n=138), and the Netherlands (n=178) completed 5 items representing each of the OMERACT RA flare core domains. RUMM2030 was used to evaluate how the five items worked together, fit a unidimensional measurement continuum, and targeted the population of interest. We also evaluated reliability, response options, redundancy, local dependence, and response bias among groups (e.g., men vs. women, age categories, country/language). Ten PRPs first completed the questionnaire then reviewed individual and group findings to provide feedback.

Results: Rasch results supported use of the 5 items as a unidimensional measure of RA flare symptoms and impacts and the simply summation of items for a total score ranging from 0-50. Each item had ordered thresholds and acceptable fit. Reliability, was high (PSI =.91). Items and people covered a continuum ranging from -3.2 to +3.4 logits, and items were well-targeted to respondents. Overall model fit was excellent (χ^2 = 31.6, df=45; p=0.935). There was little evidence of differential item functioning by sex, age, or country/language. Items suggest flare symptoms and impacts increased together showing a consistent story of how individuals experience worsening RA disease activity. Among PRPs, scores ranged from 10 to 41. There was unanimous agreement from the patients that the story depicted and individual results obtained were easily understood, meaningful, and very reflective of their current state. Many patients noted that beyond clinical trials, the RA-FQ could also enhance communication between doctors and patients at routine visits. Several noted potential applicability in monitoring day-to-day status and with self management.

Conclusion: The Rasch results offer additional support for the robust psychometric properties of the RA-FQ. Feedback from RA PRPs increases confidence in the relevance, meaningfulness, and easy interpretation of RA-FQ results for clinicians, researchers, and patients.



Disclosure: S. J. Bartlett, None; **S. Barbic**, None; **V. P. Bykerk**, None; **B. Fautrel**, None; **F. Guillemin**, None; **A. den Broeder**, None; **R. Alten**, None; **R. Christensen**, None; **E. H. Choy**, None; **D. E. Furst**, None; **S. Hewlett**, None; **A. L. Leong**, None; **L. March**, None; **T. G. Woodworth**, None; **C. Bingham III**, None.

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Abstract Number: 451

Cross-Sectional and Longitudinal Construct Validity for the Improved Health Assessment Questionnaire Among Adults with Knee Osteoarthritis

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Background/Purpose: The improved Health Assessment Questionnaire (iHAQ) is a novel version of the HAQ (ACR-recommended metric of physical function for RA) based on Item Response Theory. However, there is limited evidence examining its performance in OA. Our purpose was to evaluate the cross-sectional and longitudinal construct validity of the iHAQ in knee OA.

Methods: In a randomized trial comparing Tai Chi with physical therapy among adults with symptomatic knee OA (ACR criteria), we pooled the similar treatment effect that was found and performed a cross-sectional and longitudinal analysis. Participants completed the iHAQ, Patient Global Assessment, Short Form-36, and WOMAC at baseline and after 12 weeks. We examined two iHAQ scoring methods: method A used all 20 items, method B used 16 (Range: 0-100; 100=more disability). Applying the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN) standard to assess cross-sectional construct validity, we tested 6 *a priori* hypotheses with the expected Spearman's correlations between iHAQ scores and legacy scores at 12 weeks. After a comparison of instruments, we formulated each hypothesis with the direction, strength, and rationale for expected correlation. Longitudinal construct validity was investigated similarly but used correlations in score changes from baseline to 12 weeks. Cross-sectional or longitudinal construct validity was based on number of confirmed hypotheses: High, 5-6 of 6 (>80%); Moderate, 3-4 of 6 (80-35%); or Poor, 0-2 of 6 (<35%).

Results: In 159 participants (71% female, 57% white, mean age 61 years), the 12-week median (Interquartile Range) iHAQ scores were respectively 12.5 (3.1, 25) and 9.4 (1.6, 23) for A and B methods. The change scores from baseline were -4.7 (-15.6, 3.1) for A; and -3.1 (-12.5, 3.1) for B. All associations were in the anticipated direction **(Table 1**). Affirming high cross-sectional construct validity, all 6 respective hypotheses (100%) were confirmed for both A and B methods (**Table 2)**. Indicating high longitudinal construct validity, 5 of 6 respective hypotheses (83%) were confirmed (**Table 3)**.

Conclusion: iHAQ is able to measure its intended construct and detect changes over time among those with knee OA, which supports its consideration as a novel, recommended outcome instrument in OA.

Table 1. Spearman's Correlations between iHAQ and Legacy Measures		
Legacy Measure	**iHAQ Method A†, rho**	**iHAQ Method B†, rho**
SF-Physical Function* (Score range: 0-100)	-0.6604	-0.6729
Change SF-Physical Function	-0.4757	-0.4868
SF-Mental Health (Score range: 0-100)	-0.3812	-0.3795
Change SF-Mental Health	-0.3042	-03278
WOMAC function (Score range: 0-1700)	0.5404	0.5487
Change WOMAC function	0.4972	0.5212
SF-Role Physical (Score range: 0-100mm)	-0.4629	-0.4830
Change SF-Role Physical	-0.3734	-0.3864
Patient Global (Score range: 0-10cm)	0.4946	0.5363
Change Patient Global	0.3055	0.3299
*Cross-sectional scores were taken at 12-week follow-up. †Change iHAQ scores were correlated with change legacy measures. Change scores reflected change from baseline to 12 weeks. Note: Consensus guidelines from COSMIN do not recommend reporting *p* values of correlation coefficients for the purposes of instrument validation.		

Table 2. Hypotheses for Cross-Sectional Construct Validity of the Improved HAQ

Hypotheses	Rationale	Correlation Result(s)		Confirmed?
1. There will be a strong* (≥ 0.5) negative correlation between iHAQ and Short Form (SF)-Physical Function after intervention	iHAQ and SF-Physical Function attempt to measure similar constructs	Expect‡≥ 0.50	Method A: -0.66 Method B: -0.67	Yes
2. The positive correlation between iHAQ with SF-Physical Function will be at least 0.1 higher than the correlation between iHAQ with SF-Mental Health	iHAQ and SF-Physical Function attempt to measure similar constructs, but iHAQ and SFMH attempt to measure unrelated constructs	Expect ≥ 0.10	Method A: 0.28 Method B: 0.29	Yes
3. There will be at least a mod-strong (≥ 0.4) positive correlation between iHAQ and WOMAC Function after intervention.	iHAQ and WOMAC Function attempt to measure similar constructs, but the WOMAC function is lower limb-specific	Expect≥ 0.40	Method A: 0.54 Method B: 0.55	Yes
4. There will be at least a moderate (≥ 0.3) positive correlation between iHAQ and WOMAC Pain after intervention.	iHAQ and WOMAC Pain attempt to measure loosely-related constructs	Expect≥ 0.30	Method A: 0.49 Method B: 0.51	Yes
5. There will be at least a moderate (≥ 0.3) negative correlation between iHAQ and SF-Role Physical after intervention.	iHAQ and SF-Role Physical attempt to measure loosely-related constructs	Expect≥ 0.30	Method A: -0.46 Method B: -0.48	Yes
6. There will be at least a weak-moderate (≥ 0.2) positive correlation between iHAQ and Patient Global Assessment after intervention.	iHAQ and Patient Global Assessment attempt to measure partially related constructs,	Expect≥ 0.20	Method A: 0.49 Method B: 0.54	Yes
Cross-Sectional Construct Validity Rating: High†		**Hypotheses Confirmed: 6 of 6; 100%**		

*Correlation strength: r ≥ 0.5, Strong; 0.5 > r ≥ 0.4, Moderate-Strong; 0.4 > r ≥ 0.3, Moderate; 0.3 > r ≥ 0.2, Weak-Moderate; 0.2 > r ≥ 0.1, Weak; and 0.1 > r, Negligible. †Overall construct validity was assigned based on percent of total hypotheses confirmed: High, (5-6 of 6 (≥75%); Moderate, 3-4 of 6 (50%≤ x <75%); or Poor, 0-2 of 6 (<50%). ‡For clarity, "Expect" values are expressed as absolute values.

Table 3. Hypotheses for Longitudinal Construct Validity of the Improved HAQ				
Hypotheses	**Rationale**	**Correlation Result(s)**		**Confirmed?**
1. There will be a strong* (≥ 0.5) negative correlation between change of iHAQ and change of Short Form (SF)-Physical Function	iHAQ and SF-Physical Function attempt to measure similar constructs	Expect‡ ≥ 0.50	Method A: -0.48 Method B: -0.49	No
2. The positive correlation of change on the iHAQ with that of the SF-Physical Function will be at least 0.1 higher than the correlation of change on the iHAQ with the SF-Mental Health	iHAQ and SF-Physical Function attempt to measure similar constructs, but iHAQ and SF-Mental Health attempt to measure unrelated constructs	Expect ≥ 0.10	Method A: 0.17 Method B: 0.16	Yes
3. There will be at least a moderate-strong (≥ 0.4) positive correlation between change of iHAQ and change of WOMAC Function	iHAQ and WOMAC-Function attempt to measure similar constructs, but the WOMAC function is lower limb-specific	Expect≥ 0.40	Method A: 0.497 Method B: 0.52	Yes
4. There will be at least a moderate (≥ 0.3) positive correlation between change of iHAQ and change of WOMAC Pain	iHAQ and WOMAC Pain attempt to measure loosely-related constructs	Expect≥ 0.30	Method A: 0.43 Method B: 0.44	Yes
5. There will be at least a moderate (≥ 0.3) negative correlation between change of iHAQ and of SF Role Physical	iHAQ and SF-Role Physical attempt to measure loosely-related constructs	Expect≥ 0.30	Method A: -0.37 Method B: -0.39	Yes
6. There will be at least a weak-moderate (≥ 0.2) positive correlation between change of iHAQ and change of Patient Global Assessment	iHAQ and Patient Global Assessment attempt to measure partially related constructs	Expect≥ 0.20	Method A: 0.31 Method B: 0.33	Yes
Longitudinal Construct Validity Rating: High†		**Hypotheses Confirmed: 6 of 6; 100%**		

*Correlation strength: r ≥ 0.5, Strong; 0.5 > r ≥ 0.4, Moderate-Strong; 0.4 > r ≥ 0.3, Moderate; 0.3 > r ≥ 0.2, Weak-Moderate; 0.2 > r ≥ 0.1, Weak; and 0.1 > r, Negligible. †Overall construct validity was assigned based on percent of total hypotheses confirmed: High, (5-6 of 6 (≥75%); Moderate, 3-4 of 6 (50 %≤ x <75%); or Poor, 0-2 of 6 (<50%). ‡For clarity, "Expect" values are expressed as absolute values.

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Abstract Number: 452

The Efficacy of Motivational Counselling and SMS-Reminders on Daily Sitting Time in Patients with Rheumatoid Arthritis: A Randomised Controlled Trial

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SESSION INFORMATION

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Session Title: Quality Measures and Quality of Care - ARHP Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with rheumatoid arthritis (RA) are more sedentary than the general population, which can have serious health consequences. Reducing sedentary behaviour (SB) and increasing light intensity physical activity is advocated as a potentially more achievable health promotion focus in patients with chronic diseases and mobility problems. Intervention studies have shown that behavioural approaches are effective in reducing SB in healthy populations. Whether this applies to patients with RA is yet to be determined. **Objective:** To test the efficacy of a 16-week individually tailored, behavioural intervention in reducing daily sitting time, pain and fatigue and improving health-related quality of life, self-efficacy, physical function and cardio-metabolic disease risk in patients with RA.

Methods: Parallel-group, observer-blinded randomized controlled trial (N=150). RA patients >18 years of age, self-reported daily sitting time > 5 hours and Health Assessment Questionnaire (HAQ) score < 2.5 were consecutively recruited from a rheumatology outpatient clinic. The intervention group (n=75) received three individual motivational counselling sessions with a health professional and text messages aiming at improving motivation for light intensity physical activity through reduction of SB. The control group (n=75) was encouraged to maintain usual lifestyle. Primary outcome was change from baseline in daily sitting time measured objectively by ActivPAL, analyzed using ANCOVA with a factor for group and adjustment for the outcome level at baseline. Primary analyses were based on the intention-to-treat population. Secondary outcomes included patient-reported outcomes and cardio-metabolic biomarkers (blood pressure, cholesterol levels, blood glucose, body weight and waist circumference).

Results: After 16 weeks, three participants were lost to follow-up. There was a mean decrease in daily sitting time of 1.61 hours (h)/day with the intervention and an increase of 0.59 h/day in the control group; between-group difference was -2.20 h/day (95%CI: -2.72 to -1.69; p<.0001) in favor of the intervention group. Most of the secondary outcomes were also

in favor of the intervention; VAS-pain: -22.36 (-29.27 to -15.44); VAS-fatigue: -26.80 (-34.32 to -19.30), physical function (HAQ): -0.42, (-0.54 to -0.30) and total cholesterol: -0.37 (-0.50 to -0.24) mmol/l.

Conclusion: An individually tailored, behavioral intervention effectively reduced daily sitting time by on average more than two hours in patients with RA and additionally improved patient-reported clinical outcomes and cholesterol levels. The results may be important for clinical practise and physical activity recommendations for patients with RA and can most likely be generalized to other populations with chronic disease and mobility limitations.

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Abstract Number: 453

Adaptation and Validation the Systemic Sclerosis Quality of Life Questionnaire into Spanish Using Rasch Analysis

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Background/Purpose: Systemic Sclerosis (SSc) represents a group of heterogeneous autoimmune disorders of connective tissue characterized by progressive fibrosis of the skin and internal organs [1]. The disease spectrum ranges from localized form, which causes physical disability to more systemic forms affecting internal organs and the vasculature, which may result in life threatening crises. The SSc Quality of Life Questionnaire (SScQoL) [2] is a 29-item, needs-based tool, which measures the disease impact on health and well being of patients with SSc. The aim of this study was to adapt the English SScQoL into Spanish and to determine measurement equivalence between the two versions of the tool.

Methods: This was a cross-sectional tool validation study involving cross-cultural adaptation and cross-cultural validation phases. In the first phase, we adapted the English SScQoL into Spanish using a 5-stage process involving: forward translation, synthesis of translations, backward translation, expert committee revision and pilot testing with 30 patients [3]. This process ensured conceptual equivalence between the English and the Spanish version of the SScQoL. For the cross-cultural validation phase, we recruited adult patients with SSc who were willing and able to complete the questionnaire unaided. We collected the data from both versions of SScQoL and analysed them by comparing with the Rasch model using fit statistics. Fit to the Rasch model implies construct validity, unidimensionality, reliability and statistical sufficiency. To discount local dependency, we grouped items into the following subscales: function, emotion, sleep, social and pain and repeated Rasch analysis at a subscale level. Finally, we pooled both the UK and the Spanish data in order to test measurement equivalence between the two cultures and to calibrate the SScQoL into a logit-based interval scale.

Results: The SScQoL translated well from English into Spanish providing a conceptually equivalent version of the tool. For the validation sample comprised 121 patients from the UK (male/female = 15/106) and 106 from Spain (male/female = 16/87). Their mean (SD) age was 57.1(12.1) and 58.0 (13.9) for the UK and Spain respectively. Table 1 presents item parameters, where non-significant Chi-Square probabilities indicate that most items did not deviate from the Rasch model although local dependency was evident (data not shown). Items were grouped into the afore-mentioned 5 subscales and re-

analysed, resulting in adequate fit to Rasch model. See table 2. There was no differential item functioning by culture, thus allowing for a common scale, which can be converted into logit-based transformed scores for use in parametric analyses when required.

Conclusion: The SScQoL was adapted successfully into Spanish and satisfied the strict requirements of the Rasch measurement model, thus establishing its cross-cultural validity. The SScQoL data obtained from Spain and the UK are therefore comparable. Further research is required to determine cross-cultural validity of the SScQoL in the American Spanish populations.

Table 1: Results of item analysis using Rasch models

	UK				**Spain**			
Items	Location	Fit Residuals	Chi-Square	P-Value	Location	Fit Residuals	Chi-Square	P-Value
1	1.54	-0.11	0.04	0.84	1.01	-1.01	3.09	0.08
2	1.12	0.98	1.35	0.24	0.36	0.66	1.83	0.18
3	-0.62	0.34	2.63	0.10	0.06	0.66	0.09	0.77
4	0.18	0.19	3.12	0.08	0.42	-0.06	1.38	0.24
5	-1.56	0.01	0.32	0.57	-2.23	-1.13	2.07	0.15
6	-1.57	-0.51	0.13	0.72	-0.29	-1.21	0.13	0.72
7	-0.88	0.32	0.24	0.62	-1.14	1.42	2.23	0.14
8	-0.19	0.22	0.20	0.65	-0.31	-0.24	0.76	0.38
9	-1.97	0.90	3.86	0.05	-0.03	0.24	1.45	0.23
10	0.07	-2.48	8.73	**0.00**	0.64	0.22	1.82	0.18
11	1.51	1.48	1.54	0.21	1.81	1.99	2.92	0.09
12	-3.13	-0.51	1.10	0.29	-3.37	-0.58	0.77	0.38
13	0.62	-0.41	0.01	0.92	0.15	0.17	0.64	0.42
14	-2.45	0.62	3.78	0.05	-1.91	-0.98	2.13	0.14
15	-0.03	-1.25	0.47	0.49	-0.06	-0.66	0.94	0.33
16	1.30	-1.09	0.00	0.97	1.75	-0.73	1.65	0.20
17	0.55	1.52	0.43	0.51	-0.31	-0.34	2.24	0.13
18	-1.60	-1.00	1.01	0.32	-0.95	-0.72	0.57	0.45
19	4.30	-0.25	0.38	0.54	2.49	-0.45	1.87	0.17
20	0.22	-0.70	1.01	0.31	0.16	-0.04	3.34	0.07
21	1.72	-1.38	2.41	0.12	2.58	-0.49	1.36	0.24
22	-1.59	-1.16	5.22	0.02	-1.44	-1.14	2.46	0.12
23	-0.85	-0.79	0.24	0.63	-0.85	0.54	0.18	0.67
24	0.42	1.37	1.93	0.17	2.39	0.11	1.44	0.23
25	2.44	-0.71	2.18	0.14	0.72	-0.13	1.40	0.24
26	-1.15	0.98	0.21	0.65	-1.14	0.39	1.77	0.18
27	1.79	-0.91	1.28	0.26	0.20	-0.24	0.45	0.50
28	-0.30	0.03	0.20	0.66	-0.11	-0.34	1.48	0.22
29	0.12	-2.43	4.92	0.03	-0.60	-0.72	0.01	0.91

Fit residual within +/-2.5 and non-significant p-value (>0.001 with Bonferroni correction) suggest fit to Rasch model.

Table 2: Summary fit statistics for the 5-subscale SScQoL

	Item Fit Residual		Person Fit Residual		Chi Square Interaction		Reliability	Strict unidimensionality test**
Analysis	**Mean**	**SD**	**Mean**	**SD**	**Value (DF)**	**p-value***	**PSI**	**Independent t-tests (95%CI)**
UK	0.02	1.54	-0.29	0.85	4.99 (5)	0.417	0.896	0.05 (0.01 to 0.09)
Spain	-0.27	1.35	-0.22	0.71	11.43 (5)	0.043	0.846	0.02 (-0.02 to 0.06)

SD, Standard deviation; DF, Degrees of freedom; *P-value = Chi-Square probability, where >0.05 (>0.01 for Bonferroni correction) suggest adequate fit to the model; PSI, Person separation index reliability; **Less than 5% significant independent t-tests suggest unidimensionality [4].

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Abstract Number: 454

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-3

Abstract Number: 455

Validity, Reliability and Sensitivity to Change of Four Different Patient-Reported Outcomes (PROs) to Measure the Domains Pain, Fatigue, Experienced Disease Activity and General Well-Being in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Quality Measures and Quality of Care - ARHP Poster

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: With Patient-Reported Outcomes (PROs), the patient's perspective can be assessed. Several forms can be used; Verbal Rating Scale (VRS), Numerical Rating Scale (NRS), Visual Analog Scale (VAS) and Likert-scale. Since contradictory findings exist with regard to advantages and disadvantages of these scales, the aim of this study was to assess the clinimetric properties (using OMERACT 2.0 filter) of these scales for the measurement of pain, fatigue, experienced disease activity (DA) and general well-being and to ask patients which scale they prefer most.

Methods: Patients (all fulfilling ACR criteria for RA) visiting the rheumatology outpatient clinic Bernhoven (Uden, the Netherlands) were included. They filled in a questionnaire directly after their visit, consisting of 21 items in 4 domains

using VRS, NRS, VAS and 5-point Likert scale. They were asked to fill in the same questionnaire 5 days after their visit and return it in a self-addressed envelope. DAS28(3) scores were calculated (absence of VAS global rating). Regarding truth, Pearson correlations with DAS28(3) were used for validity analysis. Regarding discrimination, Pearson correlations were used for reliability analysis and paired sample t-tests for sensitivity to change (patients in this group were treated with 120 mg methylprednisolone). Regarding feasibility, patients indicated which scale they preferred most.

Results: Two hundred fifty-seven patients (63% female) filled in the first questionnaire, of which 184 patients filled in questionnaire two. Mean DAS28(3) score was 3.16 (±1.15). Concerning truth, 211 stable patients were included for validity analysis. The highest correlation coefficient was found for NRS in the domain pain ($r = 0.41$, $p < 0.001$). On fatigue and DA VAS scored best, while Likert scored best on general well-being. With regard to discrimination, 153 patients were eligible for the reliability analysis, 31 patients for the sensitivity to change analysis. For fatigue NRS was most reliable ($r = 0.853$, $p < 0.001$). VAS was most reliable to measure pain and DA, while Likert scored best on general well-being. Regarding sensitivity to change, VAS pain was most sensitive ($t = 2.843$, $p < 0.005$), followed by Likert pain and NRS pain ($t = 2.340$ and $t = 2.151$ respectively, both $p < 0.05$). Patient indicated NRS as overall scale preference (first questionnaire 47.9%, second questionnaire 48.4%). Besides that, NRS was most preferred for every domain separately (45.1 to 50.0%) (Table1).

Conclusion: Mixed results exist with regard to the clinimetric properties of 4 scales to measure the 4 domains. The great majority of patients preferred NRS and NRS showed reasonable to good clinimetric properties for most domains. Therefore we might consider using NRS as the preferable scale for these PROs except may be for general well-being for which the Likert scale has some advantages.

OMERACT aspect	Domain	Scale	Values	
			r	p-value
Truth	Pain	1. NRS	0.41	<0.001
		2. VAS	0.40	<0.001
		3. VRS	0.37	<0.001
		4. Likert	0.34	<0.001
	Fatigue	1. VAS	0.16	<0.05
		2. Likert	0.14	0.05
		3. NRS	0.14	0.05
		4. VRS	0.11	0.10
	DA	1. VAS	0.35	<0.001
		2. NRS	0.32	<0.001
		3. Likert	0.31	<0.001
		4. VRS	0.28	<0.001
	General well-being	1. Likert	-0.29	<0.001
		2. VRS	-0.28	<0.001
		3. NRS	-0.25	<0.001
		4. VAS	-0.25	<0.001
Discrimination				
Reliability	Pain	1. VAS	0.850	<0.001
		2. NRS	0.83	<0.001
		3. VRS	0.77	<0.001
		4. Likert	0.76	<0.001
	Fatigue	1. NRS	0.853	<0.001
		2. VAS	0.83	<0.001
		3. VRS	0.77	<0.001
		4. Likert	0.76	<0.001
	DA	1. VAS	0.81	<0.001
		2. NRS	0.79	<0.001
		3. Likert	0.68	<0.001
		4. VRS	0.67	<0.001
	General well-being	1. Likert	0.57	<0.001
		2. VRS	0.53	<0.001
		3. NRS	0.50	<0.001
		4. VAS	0.49	<0.001
			t	
Sensitivity to change	Pain	VAS	2.84	<0.05
		Likert	2.34	<0.05
		NRS	2.15	<0.05
			%	
Feasibility				
Questionnaire 1		NRS	47.9	
Questionnaire 2		NRS	48.4	

Table1: Results of best scoring PROs according to OMERACT 2.0 filter

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Disclosure: L. Renskers, None; **P. L. C. M. van Riel**, None; **R. J. J. C. van Uden**, None.

Abstract Number: 456

Patient Engagement in Research: Understanding Patient Interest and Needs

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SESSION INFORMATION
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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: The goal of clinical and health-related research is to benefit the end-consumer—the patient. Since patients are the experts on their unique experiences living with their condition, they represent an important stakeholder to engage in the research process. Patient engagement in research is an expanding area, elevating patients from solely research subjects to active collaborators in research development, design and execution. Despite the recognized importance of patient engagement, little has been done to examine how to better prepare patients for inclusion. The objective of this study was to provide an informational session to patients on patient engagement in order to: 1) elicit feedback regarding what information and resources they need to feel confident in participating in research, and 2) gauge their level or interest in being involved in future research.

Methods: A learning session was conducted at the 2016 National Gathering Conference, which was hosted by Arthritis Introspective and the Arthritis Foundation and provided educational sessions to adults with rheumatic diseases and their loved ones. Individuals did not register in advance for the breakout session and all were eligible to participate. The session lasted 1.25 hours and presented: 1) the value of patient engagement in research, 2) different levels patients can be involved in the research process and 3) basic research concepts and examples, and was followed by a discussion. At its conclusion, participants were asked to complete a survey to provide feedback regarding the session, indicate their level of interest in engaging in research and identify beneficial information and resources to increase or improve their involvement.

Results: Twenty participants attended and completed the survey (n=20). Of them, 15% indicated that they had some prior research experience (eg. college research assistant, advanced research degree, research team involvement) while the remainder responded no prior experience. Forty percent responded they were unaware patients could be involved in research beyond being a research subject. Participants rated on a 5-point Likert scale (5=high) how well the session was able to accomplish certain goals: 1) improved understanding of research process (4), 2) improved understanding of how patients can be involved in research (4.2), 3) helped them feel empowered that their experiences matter (4.05) and 4) made them interested in getting involved in research at some level (4.1). After the session, 75% of participants indicated they wanted more research training. Participants expressed interest in trainings that are conducted in-person, online or via webinars. Concerns regarding involvement in research included knowledge and access to opportunities and confidence to collaborate with researchers and clinicians.

Conclusion: The results of this study suggest that patients benefit from a basic informational session on patient engagement. Future efforts should include the development and evaluation of additional trainings and resources to increase research understanding and elucidate the value of patient involvement. Improved access to opportunities for patients involvement should also be considered.

Abstract Number: 457

Novel Mechanism Mediated By the IL-23/Th17 Axis Contributing to Auto-Immune Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Animal Models - Poster I
Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Checkpoints and mechanisms regulating the onset of rheumatoid arthritis (RA) remain largely elusive. Apart from B cells and auto-antibodies, Th17 cells were shown to critically contribute to disease development. Mice lacking IL-23, a cytokine controlling the pathogenicity of Th17 cells, are completely protected against arthritis. Yet, the exact role of the IL-23/Th17 axis during this autoantibody-driven disease remain incompletely understood.

Methods: IL23A$^{-/-}$ mice and mice receiving an IL23 blocking antibody were analyzed during active and passive arthritis models including collagen-induced arthritis (CIA), the K/BxN arthritis model, collagen-antibody induced arthritis (CAIA) and K/BxN-serum transfer arthritis. Both clinical, histological and immunological parameters of arthritis were assessed. IgG glycosylation was analyzed using the MALDI-TOF technique. IgG activity was determined by measuring the cytokine release of immune-complex-stimulated myeloid cells. To study the crosstalk between B cells and Th17 cells, co-culture experiments were performed.

Results: Here we report, that the IL-23/Th17 axis did not directly contribute to auto-antibody induced inflammation within inflamed joints, but controlled the glycosylation profile and inflammatory activity of auto-antibodies during the prodromal phase of disease. Th17 cells were found to accumulate in germinal centers auf secondary lymphatic organs prior to onset of experimental arthritis, where they suppressed the expression of b-glactoside a2,6-sialyltransferase 1 (St6gal1) in differentiating plasmablasts. The consecutive change in the immunoglobulin G (IgG) glycosylation profile provoked a shift towards a pro-inflammatory autoantibody repertoire and triggered the inflammatory phase of arthritis. Plasmablasts of RA patients similarly displayed a decreased St6gal1 activity, while IgG from these individuals showed corresponding changes in its glycosylation profile as well as an increased inflammatory activity, suggesting that related pathways might contribute to onset and progression of autoantibody-mediated diseases in humans.

Conclusion: Our current findings identify a novel IL-23/Th17-dependent checkpoint that controls autoantibody activity, unmasks a preexisting breach in humoral tolerance, and initiates the transition from a stage of asymptomatic autoimmunity into inflammatory autoimmune disease.

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Abstract Number: 458

The TAM Receptors Axl and Mer Play a Protective Role in a Temporal and Spatial Manner in Inflammatory Arthritis

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Animal Models - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by an unrestrained inflammatory response in selective, anatomically distinct synovial joints. The innate immune system plays a crucial role in the pathogenesis of RA which is highlighted by the efficacy of biologicals directed against cytokines that are predominantly produced by macrophages. One family of tyrosine kinase receptors involved in an anti-inflammatory feedback mechanism are Tyro3, Axl and Mer (gene name *Mertk*; TAM). Of importance, Axl and Mer are mainly expressed on the antigen-presenting cells of the innate immune system. The plasma level of the TAM receptor ligand Growth arrest specific 6 (Gas6) is significantly reduced in RA patients suggesting this feedback mechanism is impaired in RA. We investigated the individual role of the TAM receptors Axl and Mer in an inflammatory model of arthritis that is driven by macrophages.

Methods: The KRN serum transfer model of arthritis was induced by two intraperitoneal injections of arthritic K/BxN serum in $Axl^{-/-}$, $Mertk^{-/-}$, $Axl^{-/-}Mertk^{-/-}$ and wild-type (WT) mice. Ankle joints were macroscopically scored for 7 days. At day 2 and 7, ankle joints were isolated for histology and immunohistochemistry. At day 7, knee joints were macroscopically scored and isolated for histology and immunohistochemistry.

Results: $Mertk^{-/-}$ mice had an increased macroscopic ankle score until day 4 whereas $Axl^{-/-}$ mice had an enhanced macroscopic score from day 4 until the end of the experiment at day 7. Histology of the ankle joints showed significantly more inflammation in $Mertk^{-/-}$ mice at day 2 and increased arthritis pathology in $Axl^{-/-}$ mice at day 7, reflecting the macroscopic ankle scores. Histological analysis of ankle joints of $Axl^{-/-}Mertk^{-/-}$ mice at day 7 showed enhanced inflammation and cartilage depletion compared to both $Axl^{-/-}$ and WT mice, indicating an additive effect of Axl and Mer deficiency. In contrast to the ankle joints at day 7, enhanced macroscopic score and arthritis pathology in the knee joints of $Mertk^{-/-}$ mice, compared to WT mice, was observed. No differences on arthritis pathology were detected in the knee joints of $Axl^{-/-}Mertk^{-/-}$ compared to $Mertk^{-/-}$ mice. To explain the discrepancy of Axl involvement between ankle and knee at day 7, we looked for Axl expression in synovium before the onset of arthritis. The cells in the lining layer of ankle synovium were strikingly Axl positive whereas the synovium of the knee joints was Axl negative.

Conclusion: These findings identify the TAM receptors Axl and Mer as important players in arthritis. The Mer receptor plays a protective role at the onset of arthritis whereas the Axl receptor takes over this role in established disease in ankle joints. In the knee joints, however, Mer but not Axl, plays a prominent protective role, likely due to the lack of Axl in naïve knee joints. These findings highlight differences in topographically distinct synovial joints in inflammatory arthritis.

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Abstract Number: 459

Resident Non-Classical Monocytes Are Critically Important for Tissue Destruction in Arthritis

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Background/Purpose: Bone destruction in rheumatoid arthritis is mediated by osteoclasts, which are derived from precursor cells of the myeloid lineage. Although there is much known about mature osteoclasts, the identity of osteoclast precursor populations during arthritis is poorly understood. Blood monocytes can be subdivided in classical inflammatory monocytes ($CD115^{+}Ly6C^{high}CCR2^{+}$) and non-classical resident monocytes ($CD115^{+}Ly6C^{-/low}CCR2^{-}$) and especially classical monocytes have been implicated in mediating tissue damage in autoimmunity.

Methods: HTNFtg mice were clinically scored once per week for grip strength and swelling. In addition, blood was collected every other week starting on week 4. Mice were sacrificed at week 10 - blood, spleen and bone marrow were collected for flow cytometry analysis. K/BxN Arthritis was induced in wild type mice, blood and spleen were collected 14 days after disease induction. HTNFtg/$CCR2^{-/-}$and hTNFtg mice were analyzed histologically. Different monocyte subsets were Facs-sorted and cultured in the presence of RANKL and MCSF to induce osteoclasts. RNA sequencing of RANKL stimulated osteoclast precursor cells was performed.

Results: Here we show that hTNFtg mice lacking CCR2, which lack circulating classical inflammatory monocytes, show enhanced local bone erosion and osteoclast generation in chronic TNF driven arthritis. When we correlated the number of the two monocyte subsets in blood with histological signs of joint destruction the number of inflammatory monocytes did not correlate at all with those parameters. In contrast, the number of non-classical monocytes in blood significantly correlated with the extent of tissue damage in both hTNFtg arthritis and also K/BxN serum transfer arthritis. Histological examination revealed that while all infiltrating monocytes express CD115, only a small fraction of these cells express Ly6C, suggesting that the synovial infiltrate predominantly consists of $Ly6C^{-/low}$ monocytes. Upon sorting resident and from blood, we demonstrate that resident $Ly6C^{-/low}$ monocytes are more potent to form osteoclasts *ex vivo* than classical $Ly6C^{high}$ monocytes. Genome-wide transcriptome profiling revealed increased expression of genes which are required for pre-osteoclast fusion in RANKL-stimulated resident $Ly6C^{-/low}$monocytes.

Conclusion: Non classical resident monocytes possess particular osteoclastogenic potential and their numbers in blood correlate with histological parameters of joint destruction in two different models of inflammatory arthritis. Therefore these cells may provide a biomarker for erosive inflammatory arthritis and even a possible target for therapeutically intervention.

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Abstract Number: 460

TAS5315, a Novel Bruton's Tyrosine Kinase Inhibitor, Demonstrates Anti-Inflammatory Effect in Autoimmune Disease Models

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Background/Purpose: Bruton's Tyrosine Kinase (BTK), a non-receptor tyrosine kinase is involved in intracellular signaling pathways downstream of several receptors, including the B cell receptor (BCR), Fcγ receptors (FcγR) and receptor activator of NF-κB (RANK). An aberrant activation of signaling pathway mediated by these receptors are reported to be associated with a progression of several autoimmune diseases such as rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Therefore, BTK inhibitor would be a potential therapeutic option for the treatment of RA and SLE. TAS5315 is a highly potent and selective BTK inhibitor and its inhibitory activity (IC_{50}) against anti-IgM-induced phosphorylation of BTK is 0.15 nmol/L. Here we describe the potential efficacy of TAS5315 in animal models of RA and SLE.

Methods: In vitro biochemical assay was performed using available kinase assay panels. In macrophages, the expression of inflammatory factors induced by IgG was measured with ELISA assay. To establish collagen-induced arthritis, male DBA/1 mice were injected on day-27 and-6 with an emulsion of complete Freund's adjuvant and bovine type II collagen. On day 0, mice were randomized into treatment groups. TAS5315 was administrated orally once daily for 15 consecutive days. Disease severity was evaluated by clinical score of paw swelling. In MRL/lpr lupus model, mice were randomized into treatment groups at 14 weeks. TAS5315 was administrated orally once daily from 14 to 20 weeks. At the end of treatment period, spleen and lymph nodes were extracted to measure their weights, and kidneys were extracted to analyze the histopathological changes. The serum levels of anti-dsDNA antibody and proteinuria were also measured at the end of treatment period.

Results: TAS5315 selectively inhibited the enzyme activity of BTK and had less off target inhibition against other kinases. In cell-based functional assay, TAS5315 significantly inhibited FcγR-mediated TNF-α production by macrophages in a dose dependent manner (IC_{50}= 47.2 nM). In established mouse CIA model,TAS5315 dose-dependently decreased the clinical score in arthritic mice compared with that in vehicle-treated mice. TAS5315-treated mice had a marked reduction in the levels of TNF-α, IL-1β and IL-6 in synovial fluid and MMP3 in plasma. In MRL/lpr lupus model, TAS5315-treated mice showed the improvement for several inflammatory responses, such as lymphadenopathy, splenomegaly and the incidence of glomerulonephritis. TAS5315-treated mice also showed lower serum levels of blood urea nitrogen (BUN) and anti-dsDNA antibodies than vehicle-treated mice.

Conclusion: Our study demonstrates that a novel BTK inhibitor, TAS5315, shows significant efficacy by inhibiting inflammation in both RA and SLE models. These data suggest that TAS5315 could be a promising therapeutic agent for human autoimmune disease including RA and SLE.

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Abstract Number: 461

Involvement of CD163-Positive Macrophages in the Pathogenesis of Arthritis Via Modulation of Inflammatory Cytokine and Chemokine Expression in the Synovium of a Murine Model

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Background/Purpose: Synovial-lining macrophages play a crucial role in the onset and maintenance of joint inflammation in arthritis. CD68 and CD163 are commonly used markers of synovial macrophages in the RA synovium. CD163 is a cell-surface glycoprotein of the group B cysteine-rich scavenger receptor family that binds to and internalizes hemoglobin-haptoglobin complexes, thereby releasing IL-10 and carbon oxide with strong anti-inflammatory effects. Serum-soluble CD163 levels are significantly elevated in long-standing RA patients. The restrictive expression of CD163 by monocytes-macrophages was confirmed in the affected joint tissues of RA patients; however, the pathogenic roles of CD163-positive macrophages in inflammatory arthritis remain unclear. We investigated the roles of CD163-positive macrophages in arthritis development in mice.

Methods: A collagen antibody-induced arthritis (CAIA) mouse model was established with a combination of monoclonal anti-type II collagen antibodies and lipopolysaccharide in C57BL/6 (B6)-background CD163 knockout (KO) mice. Arthritis was graded using a 0–16 clinical scale (0–4) per paw. Histological assessment of arthritis severity was performed on paraffin-embedded hematoxylin and eosin-stained sections, and synovial inflammation (inflammatory cell infiltration) and bone erosion were graded in a blinded fashion on an established 0–5 scale. Anti-Iba-1 and anti-NIMP-R14 antibodies were used for immunocytochemical staining to identify synovial tissue-resident macrophages and neutrophils, respectively. Anti-CD163 antibodies were used for histomorphometric quantitation of CD163-positive macrophages in the synovial tissue. Total RNA was isolated from the mouse ankle joints for gene expression analysis of pro-inflammatory cytokines IL-1β and IL-6 and the chemokine CXCL-1 before and 10 days after CAIA induction by quantitative RT-PCR.

Results: Immunohistochemistry revealed that CD163 antigens were restricted to Iba-1-positive synovial tissue-resident macrophages. The number of CD163-positive cells increased during arthritis. CD163 KO mice exhibited significant exacerbation of clinical scores during arthritis compared with control wild type (WT) B6 mice. Histomorphometric quantification of the arthritic changes in the joint tissues confirmed the clinical assessment, with significant increases in inflammation and bone erosion scores in CD163 KO mice. Recruitment of neutrophils was significantly increased in the synovial tissue of CD163 KO mice compared to that of WT mice. Correspondingly, mRNA expression of CXCL1 was significantly more up-regulated in the inflamed ankle joints obtained from CD163 KO mice than control mice. Additionally, CD163 KO mice showed significantly elevated IL-1b and IL-6 mRNA expression levels in the inflamed synovium.

Conclusion: CD163 deficiency exacerbates arthritis severity via up-regulation of synovial tissue IL-1b and IL-6. CD163-positive macrophage deficiency induced neutrophil recruitment via up-regulation of CXCL1 in the inflamed synovium. CD163-positive macrophages may play an inhibitory role in the pathogenesis of joint inflammation.

Disclosure: S. Kaieda, None; **H. Ida**, None; **T. Hoshino**, None.

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Abstract Number: 462

Selective Inhibition of MMP9 Using a Monoclonal Antibody As a Therapeutic Strategy for Rheumatoid Arthritis

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Background/Purpose: Matrix metalloproteinase-9 (MMP9), highly expressed by infiltrating inflammatory cells, pannus tissue, and multinucleated cells in the synovium and subchondral bone tissue, including osteoclasts, participates in joint destruction, drives inflammation via activation of cytokines and chemokines, and promotes tissue destruction by degrading the basement membrane of epithelia and vasculature. MMP9 knockout mice are protected from collagen-induced arthritis (CIA) disease progression. A potent, allosteric antibody that inhibits MMP9 is currently being investigated in clinical trials{Marshall et al 2015}. The ability of a functional murine analog of this antibody to reduce disease signs and symptoms in established, chronic mouse CIA model both as a single agent and in combination with anti-TNF, was investigated.

Methods: CIA was induced in male DBA/1J mice (n=15/group) and treatments were administered after disease establishment. Efficacy was assessed via metrics of joint injury including clinical score (erythema/ paw swelling, score 0-4) in addition to histopathological assessment of destructive joint remodeling (soft tissue changes: edema, necrosis, inflammatory cell infiltration, and fibroplasia, sum score 0-16; bone changes: cartilage damage, bone erosion, periosteal bone formation, synovitis, pannus formation, and joint destruction, sum score 0-24).

Results: All animals were included in the evaluation. In all endpoints assessed, treatment with each therapeutic agent, on its own or in combination, resulted in efficacy with respect to body weight change, clinical score, and histopathological measures. The combination group provided the best overall trend for therapeutic benefit, although statistical significance as compared to each single agent alone was not met in most parameters. Body weight recovery was superior in combination as compared to single agent therapies (52% vs. 12-34%, relative to sham; $p<0.05$ combination vs. single agents). Clinical score and histopathology measures in soft tissue and bone changes were most improved in the combination therapy group, although it did not achieve statistical significance as compared to each single agent (26% vs. 17-21%; 1.5 vs. 1.5-1.8; and 7 vs. 7-9, respectively). Importantly, combination therapy resulted in a significant number of limbs with zero or mild disease as compared to single agents (no disease sign: 256% vs. 172-223%; mild disease sign: 178% vs. 138-141%). Analysis of complete blood count at the end of study revealed no abnormalities in any treatment group.

Conclusion: Selective inhibition of MMP9 was effective in reducing disease severity in CIA models of RA. The combination of anti-MMP9 with anti-TNF was well tolerated and increased the number of limbs with no or mild disease compared to anti-TNF alone. Further studies are required to examine combination therapy of selective anti-MMP9 and anti-TNF therapies in a clinical setting.

Disclosure: S. Kim, Gilead Sciences, Inc., 3,Gilead Sciences, Inc., 1; **B. Carr**, Gilead Sciences, Inc., 1,Gilead Sciences, Inc., 3; **L. Tong**, Gilead Sciences, Inc., 1,Gilead Sciences, Inc., 3; **D. Jin**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **R. Wang**, Gilead Sciences, Inc., 1,Gilead Sciences, Inc., 3; **D. Marshall**, Gilead Sciences, Inc, 1; **D. Gossage**, Gilead Sciences, Inc., 1,Gilead Sciences, Inc., 3; **V. Smith**, Gilead Sciences, Inc., 1,Gilead Sciences, Inc., 3.

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Abstract Number: 463

Deficiency of Transmembrane Protein VISTA (V-domain Immunoglobulin Suppressor of T-cell Activation) Ameliorates Murine Collagen-II Antibody-Induced Arthritis

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Background/Purpose: The transmembrane protein VISTA, is a member of the B7/CD28 family of immune modulator proteins and can function as a negative immune checkpoint regulator through a currently undefined molecular mechanism(s). VISTA is expressed on myeloid cells and activated T-lymphocytes. Interestingly, qPCR analyses showed VISTA mRNA (human ortholog C10orf54) is expressed abundantly in human rheumatoid synovial tissue. The importance of VISTA expression on myeloid cells was investigated in the collagen-II antibody induced arthritis (CAIA) model.

Methods: Joint targeted inflammation was initiated in the CAIA model by passive-immunization of mice with anti-type-II collagen monoclonal antibodies (5-Clone Cocktail, Chondrex, Seattle) and intraperitoneal injection of LPS, 3 days afterwards. The CAIA model does not require lymphocytes for induction of transient, immune-complex driven joint inflammation (duration 14-15 days), but does require complement activation, neutrophils and monocytes. The arthritic response was evaluated for (1) DBA/1J mice treated with anti-VISTA antibody MH5A (Biolegend) versus hamster IgG as control, and also for (2) VISTA-deficient mice versus wild type, C57/B6 mice.

Results: A sustained attenuation of paw swelling compared to controls was observed from approximately 6-13 days after initiation, for mice treated with anti-VISTA monoclonal antibody MH5A, and for VISTA-deficient mice. Histologic analysis of all major joints involved (knees, ankles, paws) indicated overall reduced joint inflammation/damage in VISTA deficient mice compared to controls. Since C5a generation is crucial to CAIA development, levels of C5a in plasma of wild type and VISTA-deficient mice were determined by ELISA 5 days after passive immunization and found to be equivalent. However, FACS analyses of phagocytic cells isolated from bone marrow as well as in peripheral blood of both arthritic and non-arthritic VISTA-deficient mice consistently displayed reduced C5a receptor expression on neutrophils and on bone marrow derived macrophages. Consistent with these findings, acute C5a receptor responses (ERK, AKT phosphorylation) and chemotaxis to C5a were also diminished in macrophages cultured from VISTA deficient mice.

Conclusion: These findings implicate VISTA in arthritic pathology for the first time, possibly due to a role in recruitment of phagocytes to joints. Antibodies reactive with VISTA may be useful therapeutic agents for autoimmune arthritis where immune-complexes drive joint damage.

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Abstract Number: 464

an Anti-Fima Antibody Attenuates Porphyromonas Gingivalis-Associated Experimental Arthritis

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Background/Purpose: Evidence suggests that periodontal infection by *Porphyromonas gingivalis*(Pg) exacerbates rheumatoid arthritis (RA); however, the underlying mechanisms remain unknown. Here, we examined the pathogenic and therapeutic correlation between periodontitis and RA in a mouse model of arthritis.

Methods: Pg strain 2561 was obtained and cultured anaerobically. Collagen-induced arthritis (CIA) mice were infected with Pg or Pg pre-incubated with an anti-FimA antibody (aFimA Ab) specific for fimbriae which are a flexible appendage on the cell surface. Fimbriae plays a pathological role in adhering Pg to gingiva, so neutralizing Pg with aFimA decreases adherence of Pg in mouse cavity. aFimA Ab was cloned and produced by our manufacturing system. Immunohistochemical analysis, microcomputed tomography analysis, confocal microscopy, immunofluorescence analysis, electron microscopy, RT-PCR, and western blot assay were done for proarthritic effect of Pg and neurtralizing anti-arthritic effect of aFimA Ab.

Results: aFimA Ab inhibits Pg induced periodontitis in CIA mice. Pg infection altered the oral microbiota, increased alveolar bone loss, and caused synovitis and joint bone destruction. However, pre-incubation with aFimA Ab led to a significant reduction in the severity of both oral disease and arthritis. aFimA Ab treated Pg fails to trigger arthritis in CIA mice. aFimA Ab treated Pg suppresses cartilage erosion and bone destruction in the joint of CIA mice. Moreover, aFimA Ab attenuated bacteria attachment and aggregation on human gingival and rheumatoid synovial fibroblasts. We discovered bacteria utilized dendritic cells, macrophages, and neutrophils to migrate to the joints of CIA mice.

Conclusion: Pg-induced periodontitis plays a significant role in RA development. Inhibiting Pg adhesion using a FimA Ab prevented RA progression. Disrupting Pg fimbriae suppresses the migration of bacteria to the joints and ameliorates RA.

Disclosure: S. H. Jeong, None; **J. Lee**, None; **S. H. Kim**, None; **H. Kim**, None; **S. K. Kwok**, None; **S. H. Park**, None; **J. H. Ju**, None.

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Abstract Number: 465

Genetic and Metabolic Signatures of Purified Synovial Macrophage Subsets during an Acute Murine Model of Inflammatory Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) manifests in persistent synovial inflammation, cellular infiltration and pro-inflammatory cytokine production, and results in progressive joint destruction. Macrophages have been implicated in RA progression and persistence through production of degradative enzymes, cytokines, and chemokines. However, the mechanisms underlying these activities are not fully elucidated. We previously demonstrated that naïve mouse joints contain MHC II^+ and MHC II^- macrophages, the majority being MHC II^-tissue-resident macrophages that can limit initiation of an acute model of inflammatory arthritis. However, macrophages are plastic and can alternate their phenotype from an immunosuppressive to a proinflammatory phenotype depending on the microenvironment. Thus, we have optimized

a multi-parameter flow cytometry protocol to isolate synovial macrophage subsets to perform subset-specific transcriptomic and metabolic analysis.

Methods: K/BxN serum transfer-induced arthritis was initiated in 10-12 week old female C57BL/6 mice and clinical severity was assessed over a 21-day period. Flow cytometric analysis was employed to delineate macrophage subsets via expression of MHC II and CX3CR1 to obtain distinct macrophage populations. These populations were sorted throughout the course of arthritis and RNAseq was performed to obtain transcriptional profiles. In addition, flow cytometric analysis was employed to determine mitochondrial function of synovial macrophage subsets throughout the course of arthritis through the use of MitoSox Red, mBBr and JC-10 dyes.

Results: We observe that both the genetic and metabolic profiles of synovial macrophage subsets shift throughout the course of arthritis and contract back towards their steady-state phenotype during resolution of disease. PCA and clustering analysis of synovial macrophage subsets show that these populations display distinct genetic signatures and have identified gene clusters and cellular processes that dictate their function during arthritis intiation, progression and resolution. Further, synovial macrophages appear to shift towards a more metabolically active phenotype, with an increase in mitochondrial membrane potential, at the height of inflammation and contract back to normal as disease wanes.

Conclusion: We conclude that inflammation induces genetic and metabolic alterations in synovial macrophage subsets that coincide with initiation, progression and resolution phases of an acute model of inflammatory arthritis. These alterations indicate that specific macrophage subsets possess distinct genetic and metabolic profiles coinciding with designated functionality during the course of disease, thereby providing insight into potentially useful targets for therapy.

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Abstract Number: 466

Sexually Dimorphic Dysbiosis of Gut Microbiota in Tumor Necrosis Factor Transgenic Mice with Inflammatory-Erosive Arthritis

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Background/Purpose: Recent studies identify gut microbiota dysbiosis as a possible contributor to rheumatoid arthritis (RA) pathogenesis. RA patients have significantly different microbiomes than healthy controls. The K/BxN mouse model of arthritis does not develop disease in germ free conditions but adding commensal bacterial triggers arthritis in these mice. Sexual dimorphism may also contribute to differences in RA incidence, severity, and mortality. We recently described sex differences in the tumor necrosis factor transgenic (TNF-Tg) mouse model of RA wherein females have a decreased lifespan (166 vs 229 days). Here, we initiated a study to elucidate the microbiomes of male and female TNF-Tg mice.

Methods: Fecal samples were collected from 5.5 month male and female TNF-Tg mice that were housed separately (C57BL/6 background, n=10), an age when females have exacerbated disease. 16s DNA sequencing was performed to identify bacterial diversity. Beta-diversity and principal coordinate analysis (PCoA), i.e. a 3D representation of the specific differences between mice, were used to estimate bacterial diversity. Least discriminant analysis (LDA) was

applied to determine significantly enriched (LDA score>2) species between sexes.

Results: Females have significantly decreased beta-diversity ($p<0.05$), and PCoA demonstrated that females have a distinctly different microbiome based on a clear spatial separation (Fig. 1 A and B). LDA determined that females were significantly enriched in Bacteroidetes and males in Firmicutes (Fig. 2).

Conclusion: Dysbiotic microbiota, loss of bacterial diversity, and sex differences separately have been associated with several autoimmune and inflammatory diseases. Here we show for the first time that female TNF-Tg mice with advanced arthritis have significantly less microbial diversity than males. Furthermore, the female microbiome differs in part due to enrichment of the pathobiont Bacteroidetes whereas males display enrichment of Firmicutes. Others have reported that an altered ratio of Bacteroidetes/Firmicutes influences autoimmune and inflammatory disease progression. This initial study assessed sexually dimorphic microbiota in TNF-Tg mice, and analyses of wild-type littermates are underway. Since the published microbiomes of male and female C57BL/6 mice do not differ in beta-diversity or specific species enrichment, we hypothesize that the loss of diversity and enrichment in Bacteroidetes significantly contributes to the disease progression in female TNF-Tg mice.

Figure 1

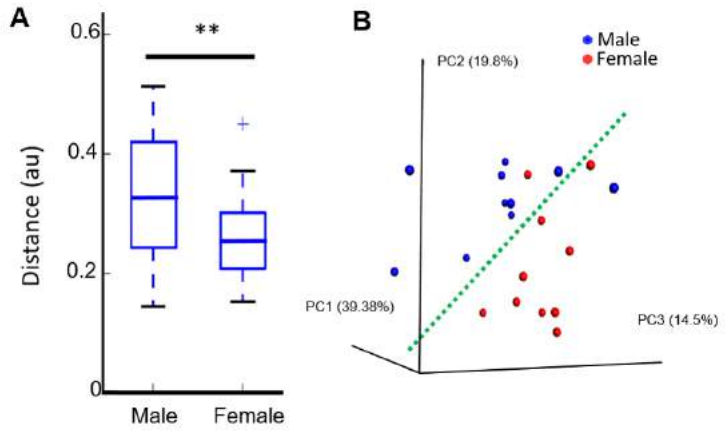
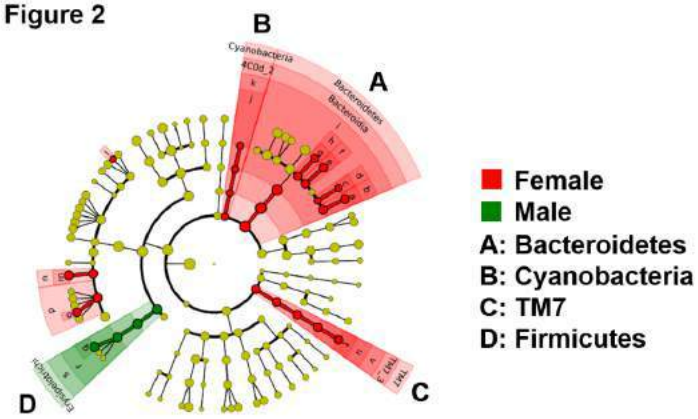


Figure 2



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Abstract Number: 467

Interleukin-21-Signaling in B Cells, but Not in T Cells, Is Indispensable for Development of Collagen-Induced Arthritis in Mice

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Background/Purpose: IL-21 is a T cell-derived cytokine whose receptor is expressed on variety of cells in immune system. IL-21was reported to be involved in the development of Th17 cells and follicular helper T cells, as well as in antibody production of B cells, all of which could be involved in the development of autoimmune diseases. Therefore, IL-21 might be involved in the pathogenesis of RA possibly via induction of pathogenic T cell responses and/or autoantibody production. However, these remains to be determined and might be analyzed in animal models of arthritis. The purpose of this study is to clarify the roles of IL-21 signaling in the pathogenesis of autoimmune arthritis

Methods: In order to declare the phathogenesis of IL-21 signaling for animal models of arthritis, we investigated the development of collagen-induced arthritis (CIA) in IL-21 receptor (IL-21R)-deficient mice. IL-21R-deificient or wild type (WT) C57BL/6 mice were immunized with chicken type II collagen (CII) emulsified in CFA on day 0 and were given boost injection with CII on day 21. Analyses of lymphcytes in regional lymph nodes by flow cytemeter and antigen(CII)-specific antibodys in serum were done. Lymphocytes of regional lymph nodes were restimurated by CII *in vitro* and then were analyzed by flow cytometer. Culture supernatants were also analyzed by ELISA. RAG-deficient mice which transfered T and B cells from WT or IL-21 R-deficient mice were induced CIA, because of comfirming which cells demand IL-21 signaling for developing arthritis *in vivo*.

Results: We found that IL-21R-deficient mice were resistant to the development of CIA. CII-specific antibody production was severely impaired in IL-21R-deficitent mice, which is consistent with the reduction of germinal center B cells. On the other hand, development of Th17 and Tfh cells was largely unaffected by the absence of IL-21 signaling. In addition, RAG-deficient mice were transferred WT CD4 T cells with WT or IL-21R-deficient B cells, and soon were induced CIA. We found that RAG-deficient mice transferred IL-21R-deficient B cells were resistant to the development of CIA, although which transferred WT B cells were susceptible.

Conclusion: Thus, IL-21 signaling is critically involved in the development of CIA mainly by inducing pathogenic autoantibody production of B cells.

Abstract Number: 468

Angiotensin II Exacerbates Bone Destruction in TNF-Transgenic Arthritis Mice

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Background/Purpose: Angiotensin II (Ang II) is known to function on various organs including kidneys, adrenal glands as well as the nervous and cardiovascular systems. In addition, recent studies have revealed that Ang II affects the skeletal system as well. The presence and up-regulation of receptors for Ang II and angiotensin converting enzyme, a key enzyme for the formation of Ang II, have been previously described in the synovial tissue in patients with rheumatoid arthritis (RA), suggesting the potential involvement of Ang II in the disease process. However, the details are not yet clear. The purpose of this study was to determine whether hypertensive stimulus Ang II further exacerbates TNF-induced bone destruction and systemic bone loss in a murine arthritis model.

Methods: To evaluate the role of Ang II in osteoclastogenesis, we conducted primary bone marrow-derived macrophages (BMMs) culture and co-culture with primary osteoblasts. In the BMMs culture, cells were treated with Ang II in the presence of RANKL. In the co-culture, cells were treated with Ang II in the presence of prostaglandin E2 and vitamin D. The formation of osteoclasts was examined by tartrate-resistant acid phosphatase (TRAP) staining. To investigate in vivo effect of Ang II, Ang II (1 μg/kg/min) was infused by osmotic pumps from 12 to 16 weeks of age in wild-type and TNF-transgenic (TNF-tg) mice. As controls, saline was infused by osmotic pumps in wild-type and TNF-tg mice. The swelling of the paws was graded as arthritis score once per week until 16 weeks of age. The bone property of talus and tibia was analyzed by micro-computed tomography (CT) to assess the extent of bone loss.

Results: In the BMMs culture, the number of TRAP-positive osteoclasts was not affected by Ang II stimulation, whereas, in the co-culture with osteoblasts, the number of osteoclasts was increased by Ang II treatment in a concentration-dependent manner. This result suggests that Ang II augments osteoclastogenesis through acting on osteoblastic cells not directly on BMMs. In vivo administration of Ang II significantly raised the systolic blood pressure in both wild-type and TNF-tg mice. Arthritis scores in TNF-tg mice were not altered by the Ang II infusion. Micro-CT analysis revealed that erosive bone destruction on the talus was significantly more severe in Ang II-infused TNF-tg mice compared to saline-infused TNF-tg mice. Bone volume per total volume in the trabecular bone of proximal tibia was significantly lower in TNF-tg mice than in wild-type mice, and further diminished by the Ang II infusion.

Conclusion: Ang II infusion exacerbated bone destruction and systemic bone loss without significant alteration in the severity of arthritis. These findings suggest that Ang II attributes to the bone destructive mechanisms mainly by increasing osteoclastogenesis with the minor effect on the inflammation in the murine arthritis model. Ang II could be a therapeutic target to protect the inflammatory bone destruction in patients with RA.

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Abstract Number: 469

Role of Microbiota in Development of Autoimmune Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease with an unknown cause. Observations of dysbiosis and mucosal inflammation in patients with RA has raised interest in studying microbial-mucosal interactions as a potential trigger of RA. Using the murine collagen-induced arthritis (CIA) model, we hypothesized that microbiota and mucosal inflammation are required for the development of autoimmune arthritis.

Methods: 4-6 DBA1j mice were treated with or without broad-spectrum antibiotics in the drinking water 7 days preceding and throughout the induction of CIA, by immunization of bovine type II collagen (CII) in Complete Freund's Adjuvant (CFA) on days 0 and 21. Fecal pellets and sera were collected every 7 days during the study for microbiome analysis and autoantibody development. Mice were euthanized on days 21 or 35 for tissue analyses for cytokines and autoantibodies by ELISA. Microbiome analyses were performed on fecal pellets by 16S sequencing of the bacterial rRNA.

Results: During the preclinical phase of CIA (without antibiotics), we find remarkable changes in the intestinal microbiome, specifically increased *Clostridia* and decreased *Lactobacillus* and *Bacteroides*. In parallel, intestinal permeability and cytokines IL-12 and IL-1β increased significantly (P value < 0.05). Furthermore, anti-CII autoantibodies were increased within the intestine, suggesting a developing mucosal immune response. In microbiota-depleted mice (antibiotic treated), CIA severity was reduced by 50% as assessed by clinical scores (P value < 0.01). Correspondingly, tissue cytokines and both serum and fecal anti-type II collagen antibody levels were reduced.

Conclusion: Taken together, these data suggest a model in which intestinal dysbiosis and mucosal immune responses drive the development of autoimmune arthritis. Future studies are aimed at elucidating the pathway by which microbiota and mucosal immune responses stimulate systemic autoantibody production that is necessary for the development of CIA.

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Abstract Number: 470

Crucial Involvement of Citrullinated Proteins and ACPA in the Development of Peptide-Glucose-6-Phosphate Isomerase Induced Arthritis

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Background/Purpose:

Various citrullinated proteins and anti-citrullinated protein antibodies (ACPA) are increased in patients with rheumatoid arthritis (RA). ACPA have high specificity for RA, and are the predictive factor of joint radiographic progression. It is considered that citrullinated proteins and ACPA may contribute to the development and progression of RA. However, the relevance in the course of arthritis development remains uncertain. In this study, we explored the pathogenic relevance of citrullinated proteins and ACPA in peptide glucose-6-phosphate isomerase (pGPI)-induced arthritis (pGIA) mice.

Methods: 1) The titers of anti-pGPI antibodies and ACPA in sera from pGIA mice were analyzed by ELISA.

2) Citrullinated protein expressions in joints, skins and lungs were examined by immunohistochemistry. The protein expressions in sera were examined by Western blot analysis.

3) Cl-amidine, the inhibitor of protein arginine deiminase (PAD), was injected intraperitoneally to pGIA mice. Clinical score, the titers of ACPA, citrullinated protein expressions, T cell response and the level of proinflammatory cytokines in sera were assessed.

Results: 1) The titers of anti-pGPI antibodies and ACPA in sera from pGIA mice were elevated from day14, and were significantly higher than those from control mice.

2) In immunohistochemistry, citrullinated proteins were detected in joints on day 14 and in skins on day 7 from pGIA mice, whereas not detected from control mice. In joints, citrullinated proteins were expressed in areas of synovial hyperplasia. In skins, these proteins were expressed in infiltrating inflammatory cells surrounding injected areas in subcutaneous tissues. In lungs, citrullinated proteins were not detected from pGIA or control mice. In sera, citrullinated protein was detected at approximately 120 kD on day 14 from pGIA mice, and significantly increased than control mice.

3) Cl-amidine treatment significantly decreased clinical and synovitis score. The titers of anti-pGPI antibodies and ACPA in sera were not significantly different, but tended to lower by Cl-amidine treatment. Citrullinated proteins in joints, skins and sera from treated mice were clearly decreased. The level of IL-6 in sera on day 14 was significantly decreased in Cl-amidine injected mice as compared with control mice, but pGPI-specific CD4+ T cell response was not changed.

Conclusion:

Citrullinated proteins and ACPA were increased in pGIA mice. Additionally, the inhibition of PAD decreased the expression of citrullinated proteins and the production of proinflammatory cytokines, resulting in the suppression of arthritis. These results suggested that PAD was involved in the pathogenesis and maintenance of autoimmune arthritis.

Disclosure: H. Kawaguchi, None; **I. Matsumoto**, None; **H. Ebe**, None; **N. Umeda**, None; **Y. Kondo**, None; **H. Tsuboi**, None; **T. Sumida**, None.

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Abstract Number: 471

Epstein-Barr Virus-Induced Expression of Receptor Activator Nuclear Factor-κb Ligand on B Cells Is Possibly Responsible for Erosive Arthritis in Epstein-Barr Virus-Infected Humanized Nonobese Diabetic/Shi-Scid/γcnull Mice

Mitsuhiro Iwata[1], Yosuke Nagasawa[1], Noboru Kitamura[1], Takamasa Nozaki[1], Eiko Ishizuka[1], Ken-Ichi Imadome[2], Shigeyoshi Fujiwara[3] and Masami Takei[1], [1]Division of Hematology and Rheumatology, Nihon University School of Medicine, Tokyo, Japan, [2]Division of Advanced Medicine for Virus Infections, National Research Institute for Child Health and Development, Tokyo, Japan, [3]Department of Allergy and Clinical Immunology, National Research Institute for Child Health and Development, Tokyo, Japan

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Background/Purpose: Humanized nonobese diabetic/Shi-scid/γc^{null} (NOG) mice, which are reconstituted with human hematoimmune system by transplantation with human $CD34^+$ hematopoietic stem cells (termed as humanization), have been shown to reproduce key aspects of human Epstain-Barr virus (EBV) infection. We previously demonstrated that EBV-infected humanized NOG (hu-NOG) mice developed erosive arthritis similar to that in Rheumatoid arthritis (RA). Furthermore we showed that human osteoclasts were present in the bone erosion sites and that human osteoclasts actually differentiated in vitro from osteoclast progenitors settled in the bone marrow of EBV-infected hu-NOG mice. However, the mechanisms for the development of human osteoclasts in the EBV-infected hu-NOG mice including cells supplying human receptor activator nuclear factor-κB ligand (RANKL), an essential molecule for osteoclast differentiation, have not been elucidated yet. In this study, we investigated the roles of EBV in RANKL expression responsible for osteoclastogenesis in EBV-infected hu-NOG mice.

Methods: Humanization of NOG mice and inoculation of hu-NOG mice with 5 to 20 × 10^2 TD_{50} (50% transforming dose) of EBV (B95-8) were performed as described in our previous study. After 8 to 10 weeks of the EBV inoculation, when erosive arthritis can be observed at a high rate, peripheral blood cells (PBCs) collected from the mice were stained with monoclonal antibodies (Abs) specific to human RANKL, CD19 and CD20 by multicolor immunofluorescence technique and analyzed by flow cytometry. To examine the effects of EBV on RANKL expression, not only EBV-free cord blood mononuclear cells (CBMCs) obtained after informed consent but also Ramos cells, an EBV-negative B-cell lymphoma cell line, were incubated with culture medium containing EBV (5 to 20 × 10^2 TD_{50}). Then, both cell types were stained with those Abs as mentioned above and analyzed by flow cytometry. Quantification of EBV DNA was performed by a real-time PCR assay.

Results: $RANKL^+$ cells were found in PBCs of the EBV-infected hu-NOG mice, most of which cells showed positivity for the B-cell markers, CD19 and CD20. In contrast, almost no $RANKL^+$ cells were detected in that of un-infected hu-NOG mice. Inoculation of CBMCs with the EBV in vitro induced RANKL on $CD19^+CD20^+$ B cells. The positivity for RANKL on B cells increased dramatically, reaching nearly 90% after 3 to 4 weeks of EBV inoculation. Real-time PCR assay showed a high level of EBV DNA (5 × 10^4 copies/μg of DNA) in these cells, indicating that the cells were actually infected with EBV. The experiments with Ramos cells showed that inoculation with the same dose of EBV as that with CBMCs markedly induced RANKL on the Ramos cells around 3 weeks after the EBV inoculation, whereas the cells without EBV inoculation remained negative for RANKL. EBV DNA was detected (1 × 10^4 copies/μg of DNA) in the EBV-inoculated Ramos cells.

Conclusion: Our present study demonstrates that EBV infection induces RANKL expression on B cells and that B cells, the primary target of EBV, are the predominant $RANKL^+$ population in the PBCs of EBV-infected hu-NOG mice, suggesting that EBV-induced $RANKL^+$ B cells play roles in osteoclastogenesis causing bone erosion in these mice.

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Abstract Number: 472

CCR6 Expression Regulates Arthritis in a T Cell Dependent Manner

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease, characterized by synovial infiltration of various inflammatory cells. Chemokines are involved in controlling the recruitment of different cell types into the synovial membrane. Increased production of MIP-3-a and accumulation of CCR6 expressing mononuclear cells can be found in joints of RA patients. CCR6 expression has also been reported on $CD4^+$ T cells, in particular regulatory as well as Th17 cells. Recent data suggest that $CD25^-Foxp3^+$ T cells upregulate CCR6 and promote arthritis. In this study, we investigated the role of CCR6 in the pathogenesis of arthritis using different arthritis models.

Methods: Clinical as well as histological signs of arthritis were investigated in the collagen-induced arthritis (CIA), K/BxN serum transfer arthritis and in the human tumor necrosis factor (hTNFtg) arthritis model, comparing *wt* and *CCR6-/-* mice. We analyzed the phenotype of lymph node cells by flow cytometry and cytokine concentrations in serum. Anti-collagen antibodies and cytokines were measured by enzyme-linked immunosorbent assay.

Results: Since CCR6 is an important component of the innate immune system we compared the development of arthritis in *CCR6-/-* mice in 2 different arthritis models known to be T cell independent, the K/BxN serum transfer arthritis and hTNFtg arthritis. In both models, we did not detect any significant differences in clinical signs of inflammation or histological severity of arthritis between wt and CCR6-/- mice. In additon, we could not detect differences in bone density between *wt* and *CCR6-/-* mice. To investigate the role of CCR6 as part of the adaptive immune system in the development of arthritis we induced CIA in *wt* and *CCR6-/-* mice. *CCR6-/-* mice were almost completely protected from CIA. Analyses of T cell subsets by flow cytometry revealed a significant reduction of $CD25^-Foxp3^+$ T cells.

Conclusion: These data suggest that CCR6 is not crucially involved in innate immunity driven arthritis, but is necessary for the development of autoimmune arthritis. Importantly, CCR6 is necessary for the generation of pathogenic $CD25^-Foxp3^+$ T cells in CIA, suggesting an important function of CCR6 on T cells in the development of autoimmune arthritis.

Disclosure: M. Bonelli, None; **A. Puchner**, None; **L. goeschl**, None; **S. Hayer**, None; **J. Smolen**, None; **C. Scheinecker**, None; **S. Blüml**, None.

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Abstract Number: 473

Migration, Colonization and Distribution of Bone Marrow Mesenchymal Stem Cells Transplanted in CIA Rats Were Traced By Green Fluorescent Protein

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Background/Purpose: To investigate the migration, colonization and distribution of bone marrow mesenchymal stem cells (BM-MSCs) traced by green fluorescent protein (GFP) in the immune organs and joints of CIA rats, and study the mechanism of MSCs in repairing damage.

Methods: 1.MSCs labeled with GFP was cultured, amplified and identified in vitro. 2.Injected with mixture of II type collagen and complete Freund's adjuvant into Wistar rats space at 14 days to establish the rat model of collagen induced arthritis (CIA): (1) It was randomly divided into five groups, including early intervention group (n=20), late intervention group (n=20), CIA early control group (n=12), late control group (n=12) and normal control group (n=12).(2) MSCs were injected from tail veins according to the number of 1×10^7/kg,and the control groups were given equal volume of normal saline. (3) Observe the changes of arthritis index, arthritis swelling degree,and appearance of imageology and pathology. 3.Observe the migration of transplanted stem cells by means of small animal in vivo imaging system. 4.The spleen, thymus, lymph nodes and joint tissues of the rats were made into pathological sections when transplanted at 3, 11, 30 and 42 days.The migration and distribution of the transplanted cells in the immune organs and the inflammatory joints were detected by immunohistochemistry.

Results: 1.(1)The arthritis index and degree of joint swelling in early and later intervention groups were decreased significantly than that of CIA control groups($P< 0.05$). (2)The early intervention group had lower arthritis index and the degree of joint swelling than the later intervention group ($P < 0.05$). 2.The small animal in vivo imaging system could not monitor the migration of MSCs transplanted into CIA rats in vivo , and the fluorescence interference of the animal itself was obvious. 3.The positive results of GFP was successfully detected by immunohistochemical method in the immune organs and joints of CIA rats, and sustainable for at least 42 days.

Conclusion: 1.MSCs transplanted through tail vein can migrate to the spleen, lymph nodes and thymus and joints,and can be long-term(42 days)colonization in these organizations. 2.GFP was not suitable for the detection of MSCs in the immune organs and joints of rats. 3.The intervention of MSCs for CIA rats was effective , and early intervention effect was better than advanced intervention.

Disclosure: J. Hou, None; **L. Zhang**, None; **G. Zhang**, None; **J. Gao**, None; **D. Ma**, None; **J. Fan**, None; **K. Xu**, None.

Abstract Number: 474

Impaired Cognition Is Linked to Brain Depletion in Brain-Derived Neurotrophic Factor Levels in a Rat Model of Rheumatoid Arthritis

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Background/Purpose: Cognitive dysfunction including depression-like symptoms is a frequent comorbidity of rheumatoid arthritis (RA)[1]. Mechanisms that have been linked to cognitive impairments in the general population such as endothelial dysfunction, systemic inflammation or functional limitations have particular relevance for RA. Brain-derived neurotrophic factor (BDNF) is abundantly expressed by endothelial cells and neurons in the brain, where it plays a crucial role in cognition. Surprisingly, the impact of RA on BDNF is poorly documented. Available studies reported higher circulating BDNF levels in RA patients than controls[2]. In order to gain further insights into the interplay between RA, cognitive dysfunction and BDNF, we explored brain and circulating BDNF levels in a rat model of RA.

Methods:

Adjuvant-induced arthritis (AIA) was used as a rat model of RA. Using Western blot analysis, BDNF expression were measured in two brain regions involved in cognition (frontal cortex and hippocampus) and in the microvasculature isolated from the whole cortex. BDNF levels were measured in serum and peripheral blood mononuclear cells (PBMC) and serum TNFα and IL-1β levels were measured in serum using ELISA and the Magpix® Luminex kit, respectively. Disease activity was assessed from the arthritis score, depression-like symptoms from the sugar preference test and physical limitations from mobility in activity chambers. All the parameters were evaluated on day 29-32 post-immunization (n=40) and in corresponding non-AIA control rats (n=28). Data were analyzed using non parametric tests. $P<0.05$ was considered statistically significant.

Results:

AIA resulted in physical limitations and depression-like symptoms. These alterations coincided with a significant decrease in BDNF levels in the frontal cortex (- 70%) and hippocampus (-50%) as well as in the cerebrovasculature (-40%). Conversely, BDNF levels in serum and in PBMC were higher in AIA than in controls (+30% and +75%, respectively). Serum but not brain BDNF levels were positively associated with the arthritis score and circulating TNF alpha levels. No association was observed with IL-1β.

Conclusion: The present results support the involvement of brain BDNF depletion in AIA-induced impaired cognition and identify TNFα as a potential actor in AIA-induced rise in circulating BDNF levels. From a clinical perspective, our data refute serum BDNF level as a reliable marker of brain BDNF levels or impaired cognition in RA. Given the evidence of low cerebrovascular BDNF levels in AIA interactions between cerebral endothelial dysfunction, cerebrovascular BDNF and cognition should be explored further. References:

1. Shin SY, Katz P, Wallhagen M, Julian L (2012) Cognitive impairment in persons with rheumatoid arthritis. Arthritis care & research 64:1144-1150. 2. Grimsholm O, Rantapaa-Dahlqvist S, Dalen T, Forsgren S (2008) BDNF in RA: downregulated in plasma following anti-TNF treatment but no correlation with inflammatory parameters. Clinical rheumatology 27:1289-1297.

Disclosure: M. Pedard, None; **P. Totoson**, None; **C. Prati**, None; **C. Demougeot**, None; **C. Marie**, None.

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Abstract Number: 475

N-3 Polyunsaturated Fatty Acids in Fat-1 Mice Attenuate Collagen Antibody-Induced Arthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: N-3 polyunsaturated fatty acids (PUFA) have anti-inflammatory effects and were considered useful for the treatment of rheumatoid arthritis (RA), however the mechanism is still unclear. Interleukin 17 (IL-17) is a pro-inflammatory cytokine produced by T helper 17 (Th17) cells which cause tissue inflammation and bone erosion. In contrast, regulatory T (Treg) cells down-regulate various immune responses by suppression of naïve T cells. The

imbalance between Th17 cells and Treg cell is important for the pathogenesis of RA. We investigated whether n-3 PUFAs attenuate collagen antibody-induced arthritis (CAIA) using fat-1 transgenic mice which contain the fat-1 gene from *Caenorhabditis elegans in which* n-6 PUFAs are converted into n-3 PUFAs in vivo.

Methods: To induce arthritis, the AthritoMab^{TM}CllmAb cocktail (4 mg/mouse, MD bioscience GmbH, Zurich, Switzerland) was injected intravenously. Three days after antibody administration, 100 μg LPS (*Escherichria coli* 055:B5; MD Biosciences) was injected intra-peritoneally. The severity of arthritis was assessed by clinical arthritis score and hind paw thickness. On day 9, the mice were sacrificed and joint tissues were harvested from each animal for end point histology. IL-6, IL-17 and IL-23 levels in whole blood were determined using Milliplex¢ç MAP kit (KomaBiotech, Korea). Flow cytometry analysis was conducted for Treg analysis.

Results: Clinical score was significantly attenuated in fat-1 mice compared to wild type on day 7 (1.6¡¾1.8, p=0.012) and day 9 (1.5¡¾1.6, p=0.003). Ankle thickness was also decreased significantly in fat-1 mice compared to WT (1.82¡¾0.11, p=0.008) (Fig 1). The pathologic finding showed that inflamed cell infiltration and bone destruction were reduced in fat-1 mice compared to WT ($p<0.05$) (Fig 2). The expression levels of IL-17 and related cytokines including IL-6 and IL-23 decreased in the spleen and ankle joint tissue of fat-1 mice. Furthermore, Treg cells were expanded in the spleen of fat-1 mice and Treg cell differentiation was higher in fat-1 mice than in wild type ($p<0.033$) (Fig 3).

Conclusion: These data suggest that n-3 PUFAs attenuate arthritis through increasing the number of Tregs and reducing IL-17 production. Therefore, dietary supplementation of n-3 PUFAs may be a promising therapeutic potential for the treatment of RA.

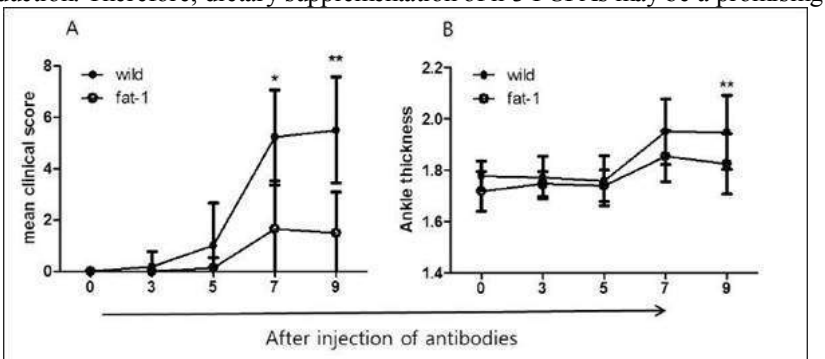

Figure 1. Clinical disease scores and ankle thickness in anti-collagen antibody induced WT and fat-1 mice. Arthritis was induced with 4mg collagen antibodies in WT and fat-1 mice. Clinical scores (A) and ankle thickness (B) were monitored every other day until day 9. Values are the mean±SD (n=5 mice/group). (*p<0.05, **p<0.01) WT: wild type

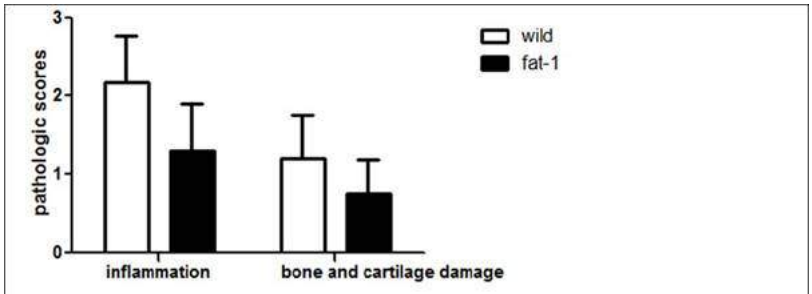

Figure 2. N-3 PUFAs inhibits ankle joint inflammation and bone and cartilage damage in CAIA mice. Ankle joints were collected on day 9, sectioned and stained with H&E in WT and fat-1 mice. This graph is a histopathological scores of the joint tissues. Pathologic scores were determined as described in the Materials and Methods. Values are the mean±SD (n=5 mice/group). (*p<0.05, **p<0.01)

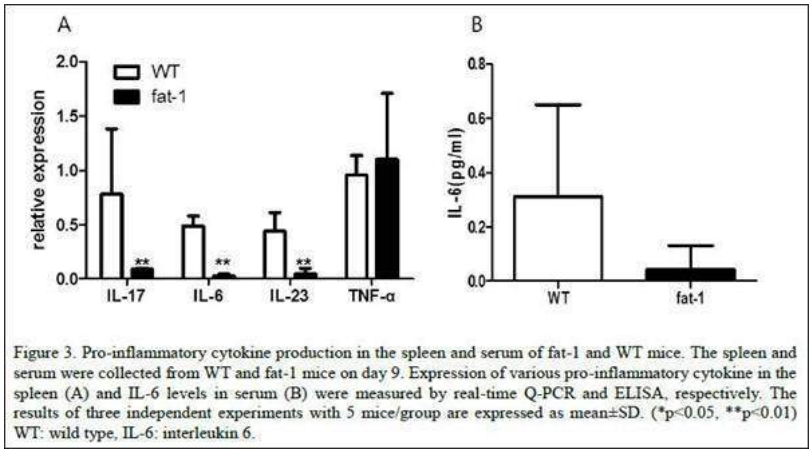

Figure 3. Pro-inflammatory cytokine production in the spleen and serum of fat-1 and WT mice. The spleen and serum were collected from WT and fat-1 mice on day 9. Expression of various pro-inflammatory cytokine in the spleen (A) and IL-6 levels in serum (B) were measured by real-time Q-PCR and ELISA, respectively. The results of three independent experiments with 5 mice/group are expressed as mean±SD. (*p<0.05, **p<0.01) WT: wild type, IL-6: interleukin 6.

Disclosure: S. C. Shim, None; **I. S. Yoo**, None; **C. K. Park**, None; **J. Y. Kim**, None; **Y. M. Kim**, None; **K. Lim**, None; **K. H. Kim**, None; **J. Kim**, None; **S. Y. Lee**, None.

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Abstract Number: 476

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-4

Abstract Number: 477

Conventional Non-Steroidal Anti-Inflammatory Drugs, but Not COX2 Selective Inhibitors, Are Beneficial on Vascular Function in Arthritis: A Study in Adjuvant Induced Arthritis

Frank Verhoeven[1], Clément Prati[2], Katy Maguin-Gaté[1], Perle Totoson[1], Daniel Wendling[3] and Céline Demougeot[1], [1]EA 4267 FDE, FHU INCREASE, Université de Bourgogne Franche-Comté, Besançon, France, [2]FDE EA4267, FHU INCREASE, Bourgogne Franche-Comté University, Besançon, France, [3]Service de Rhumatologie, CHU Jean Minjoz, Besancon, France

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) is associated with an increase in cardiovascular (CV) risk explained in part by an accelerated atherosclerosis as a consequence of endothelial dysfunction. Non-steroidal anti-inflammatory drugs (NSAID) are widely prescribed in RA patients in case of acute pain. Surprisingly, despite the commonly held belief that NSAID worsen CV risk, data concerning their impact on endothelial function in RA are lacking. The present study investigated the effect of naproxene (COX non-selective inhibitor), diclofenac (COX-1 preferential inhibitor) and celecoxib (COX-2 selective inhibitor) on vascular function in arthritic rats and identified the underlying mechanisms.

Methods: Adjuvant-induced arthritis (AIA) was induced in 6 weeks old male Lewis rats by injection of *Mycobacterium butyricum* in adjuvant at the basis of the tail. At the onset of arthritis, rats were daily treated (i.p) with naproxene (10

mg/kg/d), or diclofenac (5mg/kg twice a day), or celecoxib (3 mg/kg/d) or saline (Vehicle) for 21 days. Arthritis score and tarsus diameter were daily monitored. At the end of treatment, thoracic aortas were harvested to measure the relaxation to acetylcholine on pre-constricted aortic rings in the presence or not of inhibitor of nitric oxide (NO) synthase (L-NAME), arginase (nor-NOHA), EDHF (Apamin/Charybdotoxin), or a superoxide dismutase analog (Tempol). The relaxing effect of a NO donor (sodium nitroprussiate, SNP) was studied on endothelium-denuded aortic rings. Blood pressure and heart rate were also assessed.

Results: Compared to "Vehicle", AIA "Naproxene", AIA "Diclofenac" and "AIA Celecoxib" exhibited reduced ($p<0.05$) arthritic score and paw diameters. Diclofenac was responsible for an elevation of the blood pressure. Naproxene and diclofenac significantly ($p<0.05$) improved Ach-induced relaxation through distinct mechanisms. Naproxene increased NO synthase activity and EDHF production ($p<0.05$), decreased arginase activity ($p<0.05$) and decreased superoxide anions production ($p<0.05$). Diclofenac increased EDHF production ($p<0.05$), decreased arginase activity ($p<0.05$) and decreased superoxide anions production ($p<0.05$) but had no effect on NO synthase activity. By contrast, celecoxib did not modify Ach-induced relaxation but only increased NO synthase activity and EDHF production ($p<0.05$). The response of rings to the NO donor was unchanged after treatment whatever the treatment.

Conclusion: Our study demonstrates for the first time that naproxene and diclofenac are beneficial for endothelial function in case of arthritis, even though diclofenac enhanced blood pressure. Conversely, despite the same effect on the inflammatory symptoms, the COX-2 selective NSAID (celecoxib) did not improve endothelial function. From a clinical perspective, these results raise the question of the restriction of the use of COX-2 selective inhibitors in patients with inflammatory rheumatisms. In case of arthritis, the use of a non-selective COX inhibitor could be a preferential choice due to beneficial effects for the vascular function without changes in blood pressure.

Disclosure: F. Verhoeven, None; **C. Prati**, None; **K. Maguin-Gaté**, None; **P. Totoson**, None; **D. Wendling**, None; **C. Demougeot**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/conventional-non-steroidal-anti-inflammatory-drugs-but-not-cox2-selective-inhibitors-are-beneficial-on-vascular-function-in-arthritis-a-study-in-adjuvant-induced-arthritis

Abstract Number: 478

Evaluation of the Relationship Between Methotrexate Polyglutamation and Efficacy in the Collagen-Induced Arthritis Mouse Model

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

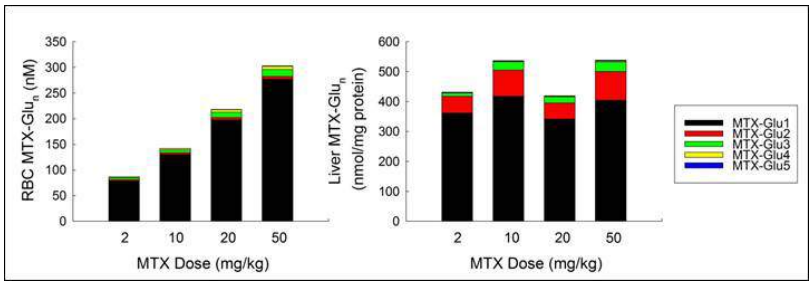
Background/Purpose: Polyglutamate metabolites of methotrexate (MTX) are believed to represent the pharmacologically active form of the drug and have been proposed as a biomarker to guide therapy in autoimmune arthritis. This work seeks to investigate the relationships between the formation of MTX polyglutamates and MTX efficacy in the collagen-induced arthritis (CIA) mouse model.

Methods: Arthritis was induced in male DBA/1 mice at 7-9 weeks of age by intradermal injection of chicken-collagen in complete Freund's adjuvant (Day 0) with a booster injection at Day 19 (n=25) and compared to healthy controls (n=5). Subcutaneous MTX injections of 0, 2, 10, 20, and 50 mg/kg were given weekly beginning at Day 14 for a total of 6 weeks. Animal weight and arthritis disease activity were routinely assessed by paw volume measurements and a 16-point clinical disease score. Mice were sacrificed at Day 54 and tissue samples were collected. Joint and liver tissues were submitted

for histopathologic scoring on a 16-point scale. Erythrocyte and liver samples were evaluated for MTX and its glutamate metabolites and plasma was analyzed for aspartate (AST) and alanine (ALT) aminotransferase activity.

Results: The disease induction protocol resulted in 100% incidence of arthritis by Day 30 and an average ± SEM clinical disease score of 13.8 ± 1.3, a 69 ± 4% increase in paw volume, and a 10 ± 2 joint histology score in the positive control group by the end of the study. MTX treatment resulted in a dose-dependent reduction in disease activity. Maximum response was observed with the 20 mg/kg dose resulting in a reduced clinical disease score of 4 ± 4 ($p<0.05$), a reduction in paw volume expansion to only 12 ± 7% ($p<0.001$), and a reduced joint histology score of 1 ± 1 ($p=0.02$). Changes in animal weight were proportionate to disease activity, not MTX dose, and no hepatic toxicity was observed by Roenigk histological scoring or by AST/ALT evaluation. Erythrocyte concentrations of MTX were proportional to dose and ranged from 87 ± 2 nM at the 2 mg/kg dose to 303 ± 33 nM at the 50 mg/kg dose. In contrast, MTX concentrations in the liver were independent of dose and averaged 483 ± 21 nmol/mg of tissue. In contrast to human studies, significant accumulation of MTX polyglutamates was not observed in erythrocytes or liver tissue. Without regard to dose, the non-polyglutamated parent form of MTX accounted for 91 ± 0.4 % and 80 ± 1.5 % of total MTX in erythrocytes and liver tissue, respectively.

Conclusion: Once weekly subcutaneous MTX was effective in reducing the severity of collagen-induced arthritis in mice despite negligible tissue accumulation of MTX polyglutamates, and resulted in no measurable hepatotoxicity.



Disclosure: R. Singh, None; **L. van Haandel**, None; **P. Kiptoo**, None; **M. L. Becker**, None; **T. Siahaan**, None; **R. Funk**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluation-of-the-relationship-between-methotrexate-polyglutamation-and-efficacy-in-the-collagen-induced-arthritis-mouse-model

Abstract Number: 479

Type II Collagen Secreted from Articular Chondrocytes Is Mainly Destroyed By Cathepsin S in RA Mice

Jinjun Zhao[1], Qin Huang[2], Hao Ren[1], Qingqing Ouyang[1] and Min Yang[1], [1]Nanfang Hospital，Southern Medical University, Guangzhou, China, [2]Department of Rheumatology, Nanfang Hospital，Southern Medical University, Guangzhou, China

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Session Title: Rheumatoid Arthritis – Animal Models - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Mast cells have long been recognized to increase strikingly in number in the synovial membrane of rheumatoid arthritis（RA），accounting for 5% of the surface synovial membrane cells. Type II collagen has the longest half-life in cartilage matrix. The main cells which might affect articular cartilage in RA are synovial fibroblasts, synovial macrophages and mast cells. The latter two could express cathepsin S. We aimed to find the cells which have the biggest influence on type II collagen secreted from articular chondrocytes and the possible mechanisms in RA mice.

Methods:

Four types of cells from collagen-induced arthritis model-established C57BL/6 mice were primary cultured，including synovial fibroblasts，peritoneal macrophages，bone marrow-derived mast cells and articular chondrocytes. The first three were co-cultured with articular chondrocytes separately. LHVS, a specific inhibitor of cathepsin S, and E64, a broad-spectrum inhibitor of cysteine protease, were added into the cocultures of macrophages and articular chondrocytes separately. Also, C48/80, an activator of mast cells, LHVS, and E64 were added into the cocultures of mast cells and articular chondrocytes separately. The culture supernatant fluid was collected. The concentration of cathepsin S and type II collagen were measured by ELISA. The expression of type II collagen mRNA in each group was detected with RTPCR.

Results:

Macrophages and mast cells expressed cathepsin S, while synovial fibroblasts did not express cathepsin S. Synovial fibroblasts had little effect on the expression of type II collagen from articular chondrocytes. When articular chondrocytes were co-cultured with macrophages，the expression of type II collagen decreased(8.79±2.79ng/ml),compared with the control group (17.75±7.84ng/ml). The secretion of type II collagen could return to normal by the inhibitors of cathepsin S, both LHVS(16.15±8.05 ng/ml) and E64 (12.55±6.64 ng/ml). When articular chondrocytes were co-cultured with mast cells, the type II collagen could be restrained by C48/80 (9.82±0.42ng/ml), compared with the control group(26.09±9.34ng/ml).Similarly，the secretion of type II collagen could return to normal by LHVS and E64（16.15±8.05 ng/ml，12.55±6.64 ng/ml，respectively）. There was no significant difference in the expression of type II collagen mRNA between different groups. It showed that the type II collagen was not suppressed at the transcription level, but was mainly destroyed by cathepsin S after secretion.

Conclusion:

Macrophages and mast cells are the major sources of cathepsin S, which might be the main factor that destroys type II collagen secreted from articular chondrocytes in RA mice.

Disclosure: J. Zhao, None; **Q. Huang**, None; **H. Ren**, None; **Q. Ouyang**, None; **M. Yang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/type-ii-collagen-secreted-from-articular-chondrocytes-is-mainly-destroyed-by-cathepsin-s-in-ra-mice

Abstract Number: 480

Local Cryotherapy Down-Regulates Local and Systemic IL-6/IL-17 Pathway with No Effect on TNF-α in Adjuvant-Induced Arthritis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Cryotherapy is widely and empirically used in an adjuvant and symptomatic setting in inflammatory rheumatic diseases, with a low level of evidence [1]. The aim of this work was to evaluate local and systemic anti-inflammatory effects of local cryotherapy (LC) in adjuvant-induced arthritis (AIA), comparing 2 techniques (ice and cold gas spray). We considered clinical (arthritis score and ankle diameter) and biological effects on IL-6, IL-17A, IL-1β, TNF-α local and systemic levels.

Methods: Arthritis was induced by a single Mycobacterium butyricum injection in male Lewis rat tails (day 0). At the onset of arthritis (day 11), rats were treated either by 30 minute-ice applications on hind paws (in cages lined with ice pops – n=10) or by 2 minute-cold gas pulverizations on both hind paws (n=9) twice a day for 14 consecutive days. Ten non-treated AIA rats were used as controls. At day 24 (the day after the last cold application), hind paws were grinded in order to measure cytokine gene expression levels by Q-RT-PCR. Plasmatic levels of the same cytokines were also measured in plasma by cytometry (Multiplex Magpix® ebioscience). IL-6 plasma levels were measured by ELISA (rat IL6 platinum ELISA, BMS625®, ebioscience).

Results: Ice application significantly reduced the mean arthritis score and ankle diameter from day 6 to day 14 ($p<0.001$) and globally throughout the 14 day treatment period (2-way ANOVA: $p<0.001$) compared to non-treated AIA controls. Cold gas first aggravated arthritis at days 11-12 ($p<0.01$) then improved clinical inflammation at days 21-24 ($p<0.001$). Skin temperature after LC didn't differ between treatment groups. Both techniques significantly reduced IL-6, IL-1β, IL-17A gene expression levels in hind paws at day 24 compared to non-treated AIA (by 60%, 87% and 50% respectively, $p<0.001$,$p<0.001$ and $p<0.05$). Cytokine gene expression levels correlated positively with hind paw arthritis score and ankle diameter. Conversely, LC had no effect on TNF-α gene expression in hind paws. LC also significantly reduced IL-17A plasmatic protein levels at day 24 (Ice : 47+/-3pg/ml versus 132+/-15pg/ml;n=9;p<00001 – cold gas : 89+/-12pg/ml versus 132+/-15pg/ml;$p<0.02$) and IL-17A plasmatic levels correlated positively with arthritis score, ankle diameter and negatively with weight gain. Ice also reduced IL-6 plasmatic levels (118+/-20pg/ml versus 197+/-60pg/ml;$p<0.05$) and IL-6 plasmatic levels correlated positively with ankle diameter. By contrast, LC had no effect on TNF-α nor IL-1β plasmatic levels.

Conclusion: These results demonstrate in vivo previously unknown therapeutic and anti-inflammatory effects of 14 day-LC in AIA. We observed both local (at the gene level in treated hind paws) and systemic (at the protein level in plasma) down-regulation of key cytokine pathways critically involved in the pathogenesis and severity of inflammatory rheumatic diseases. LC local and systemic anti-inflammatory effects were mainly IL-6 / IL-17A-driven and TNF-α-independent in this model. [1] Guillot X, et al. Cryotherapy in inflammatory rheumatic diseases: a systematic review. Expert Rev Clin Immunol. 2014;10(2):281-94.

Disclosure: X. Guillot, None; **H. Martin**, None; **K. Maguin-Gaté**, None; **S. Py**, None; **C. Demougeot**, None; **D. Wendling**, None; **N. Tordi**, None.

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Abstract Number: 481

Dual Effect of 3-Bromopyruvate on Both Th17 and Treg Cell Differentiation and Dendritic Cell Activation Ameliorates Autoimmune Arthritis in Mice

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Background/Purpose: Recent studies have shown that cellular metabolism plays an important role in regulating immune cell function. In the process of cell differentiation, both interleukin-17-producing helper T (Th17) cells and dendritic cells (DCs) show increase of glycolytic activity by upregulating glycolytic enzymes, such as hexokinase-2 (HK2). Blocking glycolysis by 2-deoxyglucose has recently been demonstrated to inhibits Th17 cell differentiation while promotes

regulatory T (Treg) cell generation, and then ameliorates experimental autoimmune encephalitis model. In addition, inhibition of glycolysis by 2-deoxyglucose has been reported to suppress activation of DCs. The aim of this study is to verify the effect of 3-bromopyruvate (BrPA), a specific inhibitor of HK2, on the differentiation and function of immune cells and on experimental arthritis in SKG mice.

Methods: Synovium from rheumatoid arthritis (RA) patients was stained by anti-HK2 antibody. Arthritis was induced in SKG mice by Zymosan A (ZyA) injection. BrPA (5mg/kg) was administered subcutaneously once daily. CD4+ T cells from spleens of unimmunized SKG mice were cultured with anti-CD3/anti-CD28, anti-IFN-γ, anti-IL-4, IL-6, TGF-β, IL-2, with and without BrPA for 5 days, and then analyzed by flow cytometry. Bone marrow (BM) cells from unimmunized SKG mice were cultured with GM-CSF and IL-4 (for 3 days), and with lipopolysaccharide (for 1 day) with and without BrPA, and then analyzed by flow cytometry.

Results: Immunohistochemistry revealed that HK2 expressing lymphocytes were increased in RA synovium. Treatment with BrPA significantly ameliorated arthritis of SKG mice (Figure). Histological scores of arthritis in BrPA-treated mice significantly were decreased compared to those of the control mice. Significant increase of Treg cells, decrease of Th17 cells, and decrease of CD40+CD86+CD11b+CD11c+ (activated) DCs were observed in the spleens from BrPA-treated SKG mice. *In vitro*, BrPA facilitated the differentiation of Treg cells, while it inhibited the development of Th17 cells. In addition, treatment of BM cells with BrPA reduced the proportion of activated DCs and inhibited the production of TNF-α, IL-6.

Conclusion: BrPA ameliorates autoimmune arthritis in SKG mice by facilitating the differentiation of Treg cells, and inhibiting the development of Th17 cells and activation of DCs.

Disclosure: T. Okano, None; **J. Saegusa**, None; **K. Nishimura**, None; **Y. Ueda**, None; **S. Sendo**, None; **S. Takahashi**, None; **K. Akashi**, None; **A. Onishi**, None; **A. Morinobu**, None.

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Abstract Number: 482

Comparison of Nonclinical Pharmacology, Pharmacodynamics and Efficacy Response of the Proposed Adalimumab Biosimilar GP2017 to Originator Adalimumab

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Background/Purpose: Biosimilars are created to be essentially the same as their reference marketed biopharmaceuticals which have lost exclusivity, and they aim to offer more affordable treatment. Development of the proposed adalimumab biosimilar GP2017 involved extensive characterization of the originator adalimumab followed by a step-wise target-directed and re-iterative technical development program involving state-of-the-art physicochemical and functional characterization methods. The nonclinical pharmacological characterization was designed to demonstrate similarity to the originator adalimumab at multiple stages. These included assessment of target molecular interactions, functional assays reflecting the mechanisms of action of adalimumab, pharmacokinetics (PK) and assessment of efficacy in an established human TNFα transgenic murine model of polyarthritis.

Methods: *In vitro* functional characterization of GP2017 to confirm similarity with the originator consisted of

comparative assays addressing binding to TNFα, complement component C1q, FcγR and FcRn and cell-based TNFα neutralization, antibody dependent cell mediated cytotoxicity (ADCC) and complement dependent cytotoxicity (CDC) potency assays. *In vivo*, GP2017 was evaluated in comparative rabbit PK studies and in the Tg197 human TNFα transgenic mouse model of polyarthritis. Shortly after the onset of disease, mice were treated twice weekly from 6 weeks until the age of 10 weeks, with either placebo, or 3 mg/kg GP2017 vs. originator adalimumab which is a most sensitive sub-therapeutic dose or saturating dose (30 mg/kg) of originator adalimumab. All the animals were sacrificed 3 days after the last treatment. Histological analysis of the joints and circulating TNFα and IL-6 levels were analyzed as pharmacodynamics (PD) endpoints. Swelling of ankles, hind limb distortion, impaired movement and body weight were also assessed.

Results: High degree of similarity was observed in target binding affinity and functional activity for TNFα, Fc-receptors and C1q binding for both GP2017 and the originator adalimumab. Also, bioassays for TNFα neutralization and for Fc dependent effector functions (ADCC and CDC) showed that GP2017 is similar to the originator adalimumab. Similar *in vivo* PK, efficacy and PD effects were shown for GP2017 and the originator adalimumab. In the murine model of polyarthritis, at 3 mg/kg dose level, a superimposable time-course profile could be demonstrated. GP2017 showed similar increase in body weight, same effect on in life arthritic symptoms and histopathological examination of the underlying lesions in the arthritic joints compared to the originator. Total TNFα and IL-6 levels were similar between the treatment groups at 3 mg/kg dose level. Consistent correlations were observed between total TNFα, IL-6, clinical and histopathology scores.

Conclusion: Similarity of GP2017 and the originator adalimumab was demonstrated based on *in vitro* pharmacology, *in vivo* PK, efficacy and safety in human TNFα transgenic murine models of polyarthritis at nonclinical level.

Disclosure: A. Dasilva, Sandoz Biopharmaceuticals, 3; **U. Kronthaler**, Sandoz Biopharmaceuticals, 3; **H. P. Hofmann**, Sandoz Biopharmaceuticals, 3; **V. Koppenburg**, Sandoz Biopharmaceuticals, 3; **M. Baron**, Sandoz Biopharmaceuticals, 3; **C. Fritsch**, Novartis Pharmaceutical Corporation, 3; **O. Hainzl**, Sandoz Biopharmaceuticals, 3; **A. Seidl**, Sandoz Biopharmaceuticals, 3.

Abstract Number: 483

Non-Steroidal Anti-Inflammatory Drugs Are More Beneficial Than Anti-Tnfα Drugs on the Radiographic Damage in Arthritis: A Study in Adjuvant Induced Arthritis

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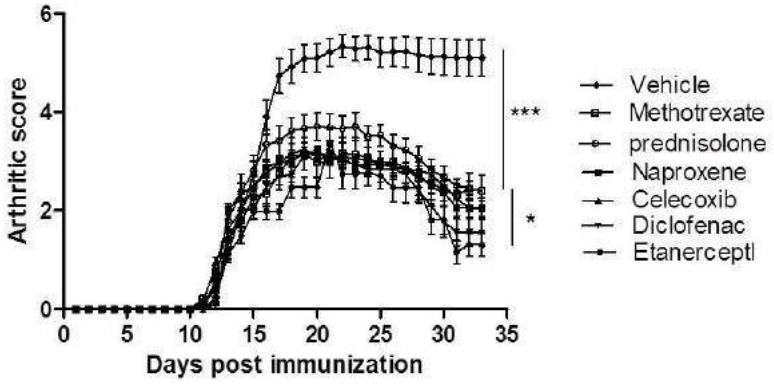
Background/Purpose: The management of the chronic inflammatory rheumatisms has dramatically evolved in the last decade with a concept of “treat to target”. The theory of a window of opportunity with more beneficial effects of an early intensive treatment is supported by several evidences. The positive impact of an early treatment with a TNFα blocker is expected but the place and the interest of non-steroidal anti-inflammatory treatments (NSAIDs) and glucocorticoids is not clear. The aim of this study was to evaluate the radiological outcomes after an early treatment during 21 days by Etanercept, or Naproxene, or Celecoxib, or Prednisone, or Diclofenac or Methotrexate in adjuvant induced arthritis in rats.

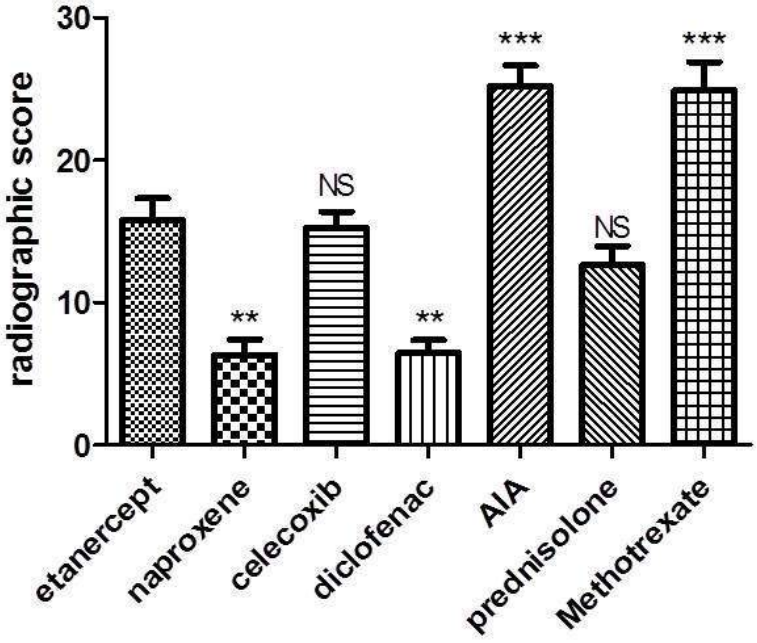
Methods: Adjuvant-induced arthritis (AIA) was induced in 6 weeks old male Lewis rats by injection of *Mycobacterium*

butyricum in adjuvant at the basis of the tail. At the onset of arthritis, rats were daily treated with Naproxene (10 mg/kg/d i.p), or Diclofenac (5mg/kg i.p twice a day), or Celecoxib (3 mg/kg/d i.p) or Prednisone (10 mg/kg/d i.p), or Etanercept (10 mg/kg/3 days, s.c.), or Methotrexate (1mg/kg/3 days, s.c.), or saline solution (Vehicle), for 21 days. Arthritic score was daily monitored. At the end of treatment, paws' radiological exam was performed with a BMA High Resolution Digital X Ray (40mV, 10mA). A score of 0 to 20 was determined for each paw using a grading scale modified from Ackerman *et al (1979)*.

Results: Compared to the Vehicle, all treatments significantly reduced($p<0.001$) arthritic score with a reduction of the arthritic score evaluated between 40% (for methotrexate) and 70% (for diclofenac). Compared to the vehicle, the radiographic score was improved by Naproxene, Diclofenac, Celecoxib, Glucocorticoids, Etanercept ($p<0.001$) but not by methotrexate. Compared to Etanercept, Naproxene and diclofenac showed less radiological structural changes ($p<0.01$).

Conclusion: Our study demonstrates for the first time that an early treatment with NSAIDs, excluding COX2 selective inhibitor, is more beneficial than Etanercept on the radiological damages in adjuvant induced arthritis. The close efficacy of all drugs on the arthritis score suggests that the beneficial impact of NSAID is not only driven by their impact on the systemic inflammation. NSAIDs should be used during the window of opportunity.





Disclosure: F. Verhoeven, None; **C. Prati**, None; **P. Totoson**, None; **R. Bordy**, None; **D. Wendling**, None; **C. Demougeot**, None.

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Abstract Number: 484

Targeting the BTK-JAK Axis in Preclinical Models of Rat Collagen-Induced Arthritis with GS-4059 in Combination with a JAK Inhibitor

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Background/Purpose: Bruton's Tyrosine Kinase (BTK) mediates signaling in hematopoietic cells important for the initiation and progression of rheumatoid arthritis (RA). GS-4059 is an oral, selective, irreversible BTK inhibitor being developed in RA. JAK inhibitors have demonstrated clinical efficacy in RA and exert their biological activity principally by blockade of proinflammatory cytokine signaling. Here we demonstrate that 1) the single agent activity of GS-4059 is efficacious in two different rat models of collagen-induced arthritis (CIA); 2) the combination of GS-4059 with a JAK inhibitor increases efficacy in a chronic CIA model; and 3) the activities of targeting BTK or JAK as single agents can be functionally differentiated.

Methods: The in vivo efficacy of GS-4059 and a JAK inhibitor were tested alone or in combination in rat CIA model. In the chronic model, dosing was initiated at the peak of disease and continued into the chronic phase; making the test more indicative of late treatment effects in the highly destructive macrophage-mediated phase, rather than in the acute, early, neutrophil mediated phase of this model. Efficacy evaluations were based on animal body weights, daily ankle caliper measurements, ankle diameter (expressed as area under the curve), terminal hind paw weights, and histopathologic evaluation of ankles and knees. Anti-type II collagen antibody levels in terminal serum were analyzed, and PK was collected to evaluate the relationship to efficacy. Joint tissue RNA and protein were analyzed for transcriptional and protein modulation.

Results: GS-4059 demonstrated dose-responsive efficacy in two rat CIA models. In the chronic model, administration of either GS-4059 or a JAK inhibitor showed efficacy on the clinical and histopathologic parameters. Combination therapy with GS-4059 and a JAK inhibitor showed significantly greater effects on paw weights, ankle swelling, and ankle histopathology scores than the single agents. Body weight loss was significantly inhibited in the combination therapy group, and weight was increased compared to the monotherapy arms, suggesting the combination treatment was more effective. Serum anti-type II collagen antibody (IgG) levels were significantly reduced in rats treated with the combination of GS-4059 and a JAK inhibitor. Knee ED-1 immunopositive osteoclast counts were significantly reduced in the animals treated with GS-4059 or the combination, but not in the single agent JAK inhibitor group, highlighting functionally distinct effects of BTK or JAK inhibition. PK analysis of GS-4059 and the JAK inhibitor showed serum exposure levels similar to those achieved in human studies.

Conclusion: GS-4059 is a novel BTK inhibitor that displayed in vivo therapeutic efficacy in the acute and chronic rat CIA models. Combining GS-4059 with a JAK inhibitor significantly improved clinical and histopathology scores, and reduced body weight loss in the rat CIA model, at exposures achieved in humans. These data suggest that simultaneously targeting BTK and JAK can provide an efficacious therapy for inflammatory diseases.

Disclosure: J. Di Paolo, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **C. Franci**, Gilead Sciences, 1; **T. Gentzler**, Gilead Sciences, 1; **B. Murray**, Gilead Sciences, 1; **L. Li**, Gilead, 3.

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Abstract Number: 485

Sexual Dimorphism of Popliteal Lymph Node Collapse As a Biomarker of Disease Progression in the Tumor Necrosis Factor Transgenic Mouse Model of Rheumatoid Arthritis

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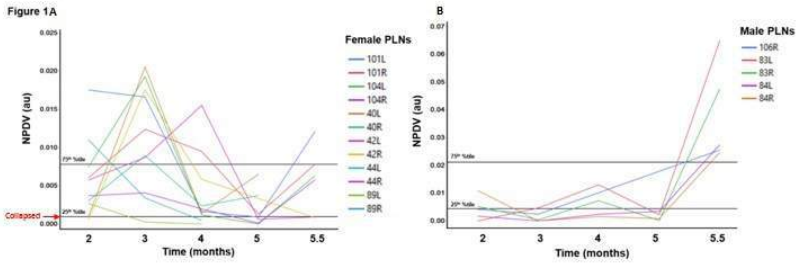
Background/Purpose: Although rheumatoid arthritis (RA) tends to occur earlier and with increased severity in females, the underling etiology of this sexual dimorphism is unknown. We have investigated the behavior of draining lymph nodes in murine models of inflammatory-erosive arthritis as a potential translational biomarker of arthritic initiation and flare. We have shown in tumor necrosis factor-transgenic (TNF-Tg) mice that ankle arthritis commences with enlargement of the popliteal lymph node (PLN) that continues to expand until the volume suddenly and stochastically collapses, coinciding with arthritic flare in the ipsilateral knee. To assess if this biomarker of disease onset and progression recapitulates the sexual dimorphism observed in clinical RA, we performed a longitudinal power Doppler ultrasound (PD-US) study of PLN in male and female TNF-Tg mice.

Methods: PD-US was performed on the PLN and knee of each leg in male (n=3 mice; 5 PLN/knees) and female (n=6 mice; 12 PLN/knees) TNF-Tg mice at 2, 3, 4, 5, and 5.5 months of age. PLNs were phenotyped as expanding if the normalized PD (NPDV) signal exceeded the 75th percentile, or collapsed if it dropped below the 25th percentile after an expanding classification, as previously described (1). Each PLN/knee was evaluated independently, and percentiles were computed for each sex separately. The frequencies of expanded or collapsed PLN over time were compared using Fisher's exact test; and knee NPDV comparisons used RM-ANOVA.

Results: There were more expanded nodes at 3 months in female TNF-Tg mice (Figure 1a) compared to males (Figure 1b) (6 vs 0, $p<0.01$), but at 5.5-months, male animals had significantly more expanding nodes (5 vs 0, $p<0.01$). The transition to collapsed nodes occurred in 5 females during the study period compared to 0 collapsed in males. Even more strikingly, all of the females with collapsed nodes before 4 months of age died before the final 5.5 month time point. There were no significant differences between sexes in knee NPDV at any time point, however both female and male displayed significantly increased NPDV at 5.5 vs. 5 months of age (0.19 ± 0.10, 0.24 ± 0.04 vs 0.04 ± 0.04, 0.11 ± 0.10, $p<0.05$).

Conclusion: This is the first demonstration that PLN collapse occurs earlier in female TNF-Tg mice. Interestingly, knee NPDV increases, indicative of inflammatory-erosive arthritis, occur at the same time in both sexes. Taken together, this data supports the hypothesis that the mechanisms of RA are sex dependent, confirming this animal model as representative of the sexual dimorphism seen in patients. Further work is needed to elucidate the mechanism for early PLN collapse and mortality of female TNF-Tg mice. 1. Bouta EM, Ju Y, Rahimi H, de Mesy-Bentley KL, Wood RW, Xing L, et al. Power Doppler Ultrasound Phenotyping of Expanding versus Collapsed Popliteal Lymph Nodes in Murine Inflammatory Arthritis. PLoS One. 2013;8(9):e73766.



Disclosure: E. Wu, None; **R. Bell**, None; **C. Rudmann**, None; **R. Wood**, None; **C. T. Ritchlin**, Amgen, Janssen Pharmaceutica Product, L.P., and UCB, 2,AbbVie, Amgen, Janssen Pharmaceutica Product, L.P., Regeneron, and UCB, 5; **H. Rahimi**, None; **E. Schwarz**, None.

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Abstract Number: 486

IRF5 Promotes Arthritis but Restricts Virus Replication and Spread during Chikungunya Virus Infection

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Background/Purpose: Chikungunya virus (CHIKV) is an arthritogenic alphavirus that invades the joints and causes chronic arthritis in up to 60% of infected individuals. Over the last two years, approximately 2 million people have been infected with CHIKV in the Western Hemisphere. The symptoms and immunological features of CHIKV arthritis mimic phenotypes observed in patients with untreated rheumatoid arthritis. Interferon regulatory factors (IRF) including IRF5 contribute to anti-viral immunity, but polymorphisms leading to over-expression of IRF5 increase the risk of developing rheumatologic disease. Thus, we reasoned that IRF5 expression may modulate the pathogenesis of CHIKV infection including the risk of developing severe CHIKV arthritis.

Methods: IRF5 knockout mice and wild-type control animals were infected with a highly pathogenic La Reunion strain of CHIKV and then monitored for virus replication, spread, and clinical features of disease including joint swelling, cytokine production, and leukocyte infiltration.

Results: We found that expression of IRF5 restricts CHIKV dissemination to distal joints, but at the expense of triggering more severe acute CHIKV arthritis. IRF5 expression was associated with enhanced cytokine production and leukocyte infiltration into the joints of infected animals.

Conclusion: IRF5 restricts CHIKV dissemination and promotes acute arthritis in mice. These findings suggest that over-expression of IRF5 in humans may limit the spread of arthritogenic alphaviruses to distal joints, but at the cost of promoting more severe clinical disease during the acute phase of infection.

Disclosure: J. Miner, None; **A. Smith**, None; **R. Shimak**, None; **M. Diamond**, None.

Abstract Number: 487

Limited Utility of Cytokine Profiles in Rheumatoid Arthritis Patients with Clinically Active Disease and Normal Inflammatory Indices

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Background/Purpose: Multiple biomarker disease activity (MBDA) cytokine panels identify RA subsets with continuing inflammation despite fulfilling clinical and acute phase reactants (APR) parameters of low disease activity or remission. However, the characteristics of MDBA in the RA subset of discordant disease, (clinically active, normal APR), are yet to be defined. Herein, we compared clinical characteristics and cytokine assays in RA concordant and discordant disease subsets.

Methods: RA patients enrolled in a longitudinal observational registry (VARA) were studied and clinical and disease status characteristics documented. Patients with high joint counts (TJC + SJC>3) and APR (ESR ≥ 28 + CRP ≥ 1.5) were categorized as Concordant (C1), those with TJC+SJC ≤3 and normal APR (ESR < 28 + CRP < 1.5) were C2, while those with TJC+SJC>3, but with ESR < 28 and CRP < 1.5 were categorized as Discordant (D). Discordant patients were further stratified into Low, Medium, High disease activity (DL, DM, DH), based on TJC+SJC of 4 or 5, 6-8, 9 or higher, respectively. Cytokines and chemokines (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17, GCSF, GM-CSF), IFN-γ, MCP-1, MIP-1β, TNF-α) were measured via bead-based multiplex assay and a cytokine score calculated (weighted average). Chi-square tests compared categorical measures by concordance status, t-, Wilcoxon rank sum and Kruskal-Wallis tests, ANOVA models, ordinary least squares regressions compared continuous measures.

Results: 1467, predominantly male, VARA patients had cytokine assays. Compared to C1 patients (n=434), D patients (n=174) were younger (62[11] vs 66[11] years), less frequently seropositive (RF [75% vs 91%], ACPA [72% vs 86%), with lower TJC (8.1 [7.1] vs. 10.0 [8.0] , SJC (6.1 [5.4] vs. 9.5 [6.9]) and DAS28-3v scores (3.8 [1.1] vs. 5.5 [1.1]. p<0.001). Cytokine scores at all levels of discordance were significantly lower than in C1 patients (p<0.001) (Table). DL, DM and DH subsets were not significantly different in cytokine scores, and were similar to C2 (n=356) patients. In multivariable analyses comparing C1 vs D patients, log CK Score was associated with RF status (p=0.037) and DAS28-3v scores (p=0.012). In the OLS model including C2 patients (mean log cytokine score = 1.99), there was significant association with RF (p=0.042), ACPA (p=0.031), but only a trend towards DAS28-3v scores (p=0.066).

Conclusion: In our RA discordant subset, cytokine scores were congruent with APR levels and disease status suggesting this particular MBDA at a single time point was not useful in delineating active disease. Prospective studies assessing disease outcomes in this RA subset may argue for less aggressive DMARD therapies.

Table: Associations of TJC+SJC >3 with cytokine assays/quartiles in RA patients with

Elevated and Normal Acute phase reactants

Group	Group Abbreviation	N	Cytokine Score Median (IQR)
TJC+SJC>3, ESR>28, CRP>1.5 (Concordant)	C1	174	11 (6-27)
TJC+ SJC >3 - <6, ESR<28, CRP<1.5 (Discordant, low activity)	DL	77	6 (4-11)
TJC+ SJC ≥6 - <9, ESR<28, CRP<1.5 (Discordant, moderate activity)	DM	91	6 (4-15)
TJC+ SJC ≥9, ESR<28, CRP<1.5 (Discordant, high activity)	DH	267	7 (4-20)

Disclosure: G. S. Kerr, UCB, Janssen, Crescendo, 9; **A. M. Alex**, None; **H. Sayles**, None; **T. R. Mikuls**, None.

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Abstract Number: 488

Exploring the Association Between Air Pollutant Exposure and Seropositivity in Rheumatoid Arthritis

Asha Mariam Alex[1,2], Gary A. Kunkel[3], Jorge Flautero Arcos[4], Richard Amdur[5] and Gail S. Kerr[6], [1]Rheumatology, Veterans Affairs Medical Center, Washington, DC, [2]Rheumatology, Georgetown University Hospital, Washington, DC, [3]Division of Rheumatology, George Wahlen VA Medical Center/University of Utah, Salt Lake City, UT, [4]Rheumatology, Howard University Hospital, Washington, DC, [5]Lead Biostatistician, Medical Faculty Associates Clinical Professor, Dept. of Surgery, George Washington University School of Medicine & Health Sciences, Washington, DC, [6]Washington DC VAMC, Georgetown University Hospital, Howard University Hospital, Washington, DC

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Background/Purpose: The etiology of rheumatoid arthritis (RA) is multi-factorial, with expression of HLA-DRB1 shared epitope (SE), smoking and socioeconomic status (SES) exerting influence. Prior studies have evaluated the associations of air pollutant (AP) exposure with RA incidence, but not RA seropositivity or titers. We evaluated the associations of AP exposure with RA autoantibody status independent of SES, SE expression and tobacco exposure.

Methods: Patients from 7 sites of the Veterans Affairs Rheumatoid Arthritis (VARA) registry were included in the analysis. Socio-demographic, HLADRB1 SE status, tobacco exposure and RA seropositivity parameters (rheumatoid factor [RF], anti-cyclic citrullinated peptide [ACPA]) were available. Mean exposure levels for AP (NO_2, SO_2, Particulate matter {$PM_{2.5}$, PM_{10}} and Ozone) were obtained from local air quality monitoring stations based on the patient's zip code for the year prior to VARA enrollment. Mean standardized scores of individual pollutants were used to calculate a global pollution score and patients were further grouped into pollution quartiles. For SES, the mean standardized score of a composite based on zip code was used, which included percent in labor force, percent unemployed, median household income, and percent below the poverty line, while years of education served as a surrogate. Generalized estimating equations (GEE), using the log of RF and ACPA titers with nested models based on VA location were used to determine independent associations of AP on RF and ACPA positivity and titers.

Results: There were 1078 Veterans (91.1% male, 80.4% Caucasian), with mean age of 69.4 +/- 10.4 years and disease

duration of 12.5 +/- 11.7 years. HLADRB1 SE was positive in 73%, while 80.6% and 75.1% were RF and ACPA positive, respectively. Univariate analyses of the individual AP scores revealed no association with either RF or ACPA positivity. In multivariate GEE models, former and current smoking ($p<0.0001$), HLA-DR SE positivity ($p <0.0001$), and lower education status ($p<0.0001$, $p=0.027$) were predictive of higher RF and ACPA titers, respectively. In the same model, while patients in quartile 2 and 4 of AP exposure had lower ACPA levels ($p= 0.03$, $p< 0.0002$), there were inconsistent associations of AP quartiles with RF (Table 1). Analyses of individual pollutants revealed higher $PM_{2.5}$ levels to be associated with higher RF and ACPA titers ($p=0.0005$, $p=0.0092$).

Conclusion: In a predominantly male RA population with long standing disease, while confirmation of the association of HLADRB1 SE and smoking with autoantibody seropositivity was found, there was an inverse relationship between higher levels of air pollutant exposure and ACPA. Only small particulate matter exposure ($PM_{2.5}$) was linked to higher RF and ACPA titers. The overall effect of air pollutants on RA autoantibody status appears to be a varied and complex relationship.

Table 1: Nested GEE multivariate model of association of global air pollution (quartiles) with RF and ACPA titers

	RF (Units/ml)				ACPA (Units/ml)			
Mean Pollution (quartile)	Adjusted mean	Lower 95% CI	Upper 95% CI	P value	Adjusted mean	Lower 95% CI	Upper 95% CI	p value
4	47.15	37.72	58.88	.68	39.03	32.37	47.00	.0002
3	49.72	44.26	55.85	.84	53.75	46.38	62.26	.28
2	39.49	32.63	47.74	.03	51.55	46.90	56.65	.03
1	48.88	40.85	58.45	Reference	62.48	51.44	75.83	Reference

Nested GEE multivariate model of linear relationship of PM2.5 exposure with RF and ACPA titers

	RF (Units/ml)				ACPA (Units/ml)			
Air Pollutant	Estimate	Lower 95% CI	Upper 95% CI	P value	Estimate	Lower 95% CI	Upper 95 % CI	P value
$PM_{2.5}$	0.088	0.038	0.137	0.0005	0.044	0.011	0.076	0.0092

Disclosure: A. M. Alex, None; **G. A. Kunkel**, None; **J. Flautero Arcos**, None; **R. Amdur**, None; **G. S. Kerr**, UCB, Janssen, 9.

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Abstract Number: 489

Early Detection of Inflammatory Arthritis: The Role of Musculoskeletal Symptoms, Infections and Rheumatoid Arthritis-Related Comorbidities in Primary Care

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Session Title: Rheumatoid Arthritis – Clinical Aspects - Poster I: Clinical Characteristics/Presentation/Prognosis

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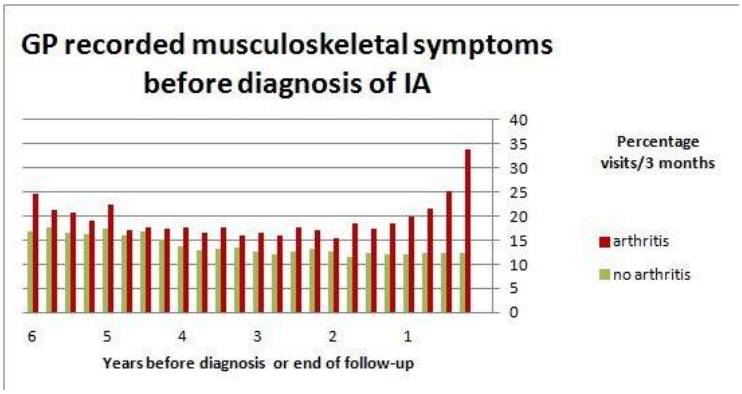
Session Time: 9:00AM-11:00AM

ACR ABSTRACT 2016 Early detection of inflammatory arthritis: the role of musculoskeletal symptoms, infections and rheumatoid arthritis-related comorbidities in primary care ***Background/Purpose:*** Rheumatoid arthritis is characterized by clinically apparent inflammatory arthritis (IA). A preclinical phase has been recognized in which symptoms arise and ambulatory care utilization increases. However, information on location and timing of symptoms before IA diagnosis is still largely lacking. The present study was undertaken to identify pathogenetic clues to the development of IA and to assist early identification of future IA patients with a focus on musculoskeletal symptoms, infections and chronic comorbidities.

Methods: We conducted a nested case-control study using data from electronic medical records of general practitioners, participating in NIVEL Primary Care Database, to evaluate timing and numbers of visits for 192 symptoms and diseases up to nine years before diagnosis of IA. To this end we used the International Classification of Primary Care (ICPC-1) coding system. 2772 patients who received a new diagnosis of IA between 2012 and 2014 were matched (ratio 1:2) with controls on age, gender, general practice and retrospective duration of follow-up. The frequency of primary care visits between the IA patients and controls were compared using logistic regression in different time periods before diagnosis.

Results: The consultation rate for musculoskeletal symptoms was increased in IA patients in the last 1.5 years before diagnosis with odds ratios (ORs) of 1.8 (confidence interval; CI: 1.6-2.1, p-value<0.05), 1.4 (CI 1.2-1.6, p<0,05) and 1.3 (CI 1.1-1.5, p<0.05), respectively, at 6, 12 and 18 months before diagnosis. For infections, the consultation rate was significantly higher 6 and 18 months prior to diagnosis (OR=1.2; both CI: 1.1-1.4, p-value<0.05). Finally, for IA-related disease and other chronic diseases a significant difference was observed only 3 months before diagnosis with ORs of 1.2 (CI 1.02-1.3, p<0.05) and 1.3 (CI 1.1-1.5, p<0.05) respectively. All ORs are corrected for age and gender. Important contributors to the above mentioned significance levels were presence of shoulder complaints (16.1% in the IA-patients versus 9.6% in the controls; chi2 73.9, p<0.001), hand/finger complaints syndrome (12.2% versus 5.6%; chi2 112.5, p<0.001), carpal tunnel syndrome (5% versus 2.5%; chi2 37.1, p<0.001) and foot/toe complaints (15.2% versus 9.2%; chi2 67.0, p<0.001).

Conclusion: We found significantly increased consultation rates in general practice for musculoskeletal symptoms and infectious diseases prior to the diagnosis of IA. This diverging trend started 4-6 years before diagnosis, but becomes statistically significant around 1.5 years preceding diagnosis. Possibly, these symptoms can be used to develop methods for earlier detection of IA in general practice.



Disclosure: M. van Beers-Tas, None; **M. Nielen**, None; **J. C. Korevaar**, None; **D. van Schaardenburg**, None.

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Abstract Number: 490

First Report of Symptoms Using the Symptoms in Persons at Risk of Rheumatoid Arthritis (SPARRA) Questionnaire

Marian van Beers-Tas[1], Lilian van Tuyl[2], Karim Raza[3], Rebecca J Stack[4], Axel Finckh[5], Delphine Courvoisier[6], Aase Hensvold[7], Anca I Catrina[7], Tanja A. Stamm[8], Erika Mosor[9] and Dirkjan van Schaardenburg[10], [1]Rheumatology, Amsterdam Rheumatology & Immunology Center, Reade, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [3]University of Birmingham, Rheumatology Research Group, Institute of Inflammation and Ageing, United Kingdom, Birmingham, United Kingdom, [4]Rheumatology, Sandwell and West Birmingham Hospitals NHS Trust, Birmingham, United Kingdom, [5]Rheumatology Division, University Hospital of Geneva, Geneva, Switzerland, [6]University hospital of Geneva, Geneva, Switzerland, [7]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [8]Internal Medicine III, Vienna Medical University, Vienna, Austria, [9]Section for Outcomes Research, CeMSIIS, Medical University of Vienna, Vienna, Austria, [10]Rheumatology, Amsterdam Rheumatology and immunology Center, location Academic Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands

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Background/Purpose: Persons at risk of rheumatoid arthritis (RA) may experience a variety of symptoms[1,2]. However, information on location, timing, severity and predictive value of these symptoms is largely lacking. The Symptoms in Persons At Risk of Rheumatoid Arthritis (SPARRA) questionnaire has been developed with support of EULAR to provide more insight into these symptoms. Aim of the study is to report the symptoms and symptom complexes using the SPARRA questionnaire in an international group of arthralgia patients at risk of developing RA.

Methods: The SPARRA questionnaire contains questions on presence, severity, impact and location of 13 symptoms derived from a qualitative study in seropositive arthralgia patients[1]. The items are: joint pain or swelling, joint stiffness, burning and tingling sensations, numbness, changes in skin colour, muscle cramps, weakness, fatigue, emotional distress, concentration difficulties and sleep problems. Answers are given on an ordinal scale. If present, number of days with a symptom per month (0, 1-5, 6-15, 16-30 days), severity (none, mild, moderate and severe) and influence (no, small, moderate or high impact) were recorded. Secondly, we recorded the location of joint pain. Finally, patients were asked to describe the pattern of symptom development over time. Patients were included in the Netherlands (N=68), United Kingdom (N=16), Sweden (N=15), Austria (N=11) and Switzerland (N=21). Validation of the questionnaire is ongoing.

Results: Of 131 arthralgia patients included, 85 were positive for anti-citrullinated protein antibodies (ACPA), 29 were positive for rheumatoid factor only, and 17 were seronegative with clinically suspect arthralgia. Most symptoms were present in a high percentage of patients, with pain as the most often experienced symptom and change of skin color rarely reported. When a symptom was present, it was usually experienced as moderate to severe, and with moderate impact by half of the patients (Table 1). The mean presence of symptoms was similar in the ACPA positive and negative groups, however, ACPA positive patients more often had severe symptoms (mean 61% versus 54%, NS) with higher impact (48% versus 41%, NS). Joint pain was most frequently located in the fingers. The most frequently reported pattern of symptoms was "coming and going, but always present" (32%).

Conclusion: The first results of the SPARRA questionnaire show multiple symptoms to be present in a high percentage of persons at risk for RA. These are often experienced as severe, with a high impact. References:

1. Stack, Rheumatology 2014

2. van Tuyl, Musculoskel Care 2015

Table 1: First results of the SPARRA questionnaire (N=131)			
Items	**Duration** At least 1 day in the past month	**Severity** If present, moderate to severe	**Influence** If present, moderate or high impact
Joint pain	79%	66%	54%
Joint swelling	35%	52%	50%
Joint stiffness	69%	68%	44%
Burning sensations	29%	63%	60%
Tingling sensations	39%	56%	39%
Numbness	27%	49%	44%
Change in skin colour	15%	40%	25%
Muscle cramps	41%	41%	21%
Weakness or loss of strength	62%	67%	54%
Fatigue	72%	76%	65%
Emotional distress	52%	54%	43%
Concentration difficulties	37%	56%	48%
Sleep problems	54%	70%	52%

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Abstract Number: 491

Anti-Citrullinated Peptide Antibodies Testing Rate over Time in Newly Diagnosed RA Patients – Data from Three Administrative Claims Databases (2007–2014)

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Background/Purpose: Current clinical guidelines recommend testing for anti-citrullinated protein antibodies (ACPA) at the time of RA diagnosis.[1] However, there is a lack of information about the frequency of ACPA testing at RA diagnosis or thereafter. The aim of this study was to describe the frequency of ACPA testing over time and to investigate the potential differences in demographics, co-morbidities and hospitalizations between patients (pts) who received ACPA tests versus those who did not.

Methods: Data from the three following US commercial healthcare claims databases (db) were analyzed: IMS PharMetrics Plus (db A), Optum Clinformatics Data Mart (db B) and Optum Clinformatics Data Mart Medicare (db C). Pts with two diagnosis codes for RA from January 1 2007 to December 31 2014, treatment with a DMARD, and continuous enrolment for at least 12 mths before and 6 mths after the index date were included. ACPA and RF testing claims identified by current procedural terminology codes were included in the analysis. ACPA testing rates were evaluated as number of pts with tests divided by total number of pts with and without tests. Multinomial logistic regression

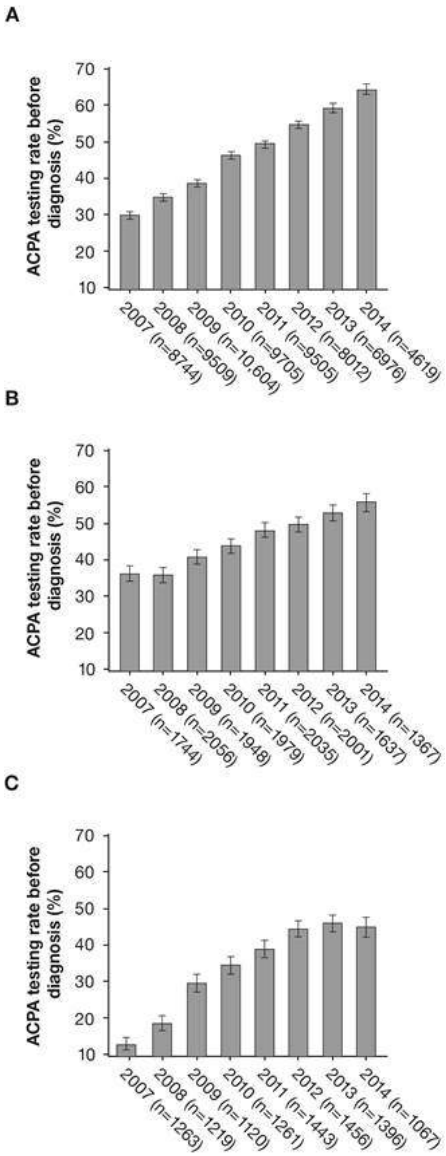
was used to evaluate baseline covariates associated with single ACPA test before the index date, single ACPA test after the index date and multiple ACPA tests.

Results: 67,674 newly diagnosed RA pts in db A (age 18–64 yrs), 14,767 in db B (age 18–64 yrs) and 10,225 in db C (age ≥65 yrs) met the study inclusion criteria. The overall ACPA testing rate (95% CI) was 70.6% (70.3, 70.9) in db A, 72.2% (71.5, 72.9) in db B and 63.5% (62.5, 64.4) in db C. The ACPA testing rates increased from 2007 to 2014 for all three db (Figure). The corresponding RF testing rates were 75.4% (75.1, 75.7), 85.1% (84.5, 85.6) and 77.8% (77.0, 78.6), respectively. Pts tested and not tested had similar characteristics, with a standardized difference of >0.10 in only a few co-morbidities. The odds ratio (OR) for pre-diagnosis testing for each year increase from 2007 to 2014 was 1.26 (95% CI: 1.25, 1.28) in db A, 1.19 (1.17, 1.22) in db B and 1.27 (1.23, 1.31) in db C. Women were more likely to have multiple tests in db A (OR: 1.15; 95% CI: 1.08, 1.21) and in db B (OR: 1.29; 95% CI: 1.14, 1.45), but not in db C (OR: 0.93; 95% CI: 0.80, 1.08). Pts who received ACPA tests, vs those who did not, had a lower rate of 1-yr hospitalization; the hazard ratio (95% CI) after adjustment for covariates was 0.76 (0.71, 0.80) in db A, 0.86 (0.75, 0.98) in db B and 0.76 (0.68, 0.85) in db C.

Conclusion: The ACPA testing rate, especially pre-diagnosis testing, increased significantly from 2007 to 2014. Women aged 18–64 yrs were more likely to have multiple tests. A slightly lower rate was seen in RA pts ≥65 yrs old.[2]

1. Aletaha D, et al. *Ann Rheum Dis* 2010;**69**:1580–8.

Figure 1. ACPA Pre-diagnosis Testing Rate 2007–2014 (A=PharMetrics; B=Optum; C=Optum Medicare)



Disclosure: E. Alemao, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **Z. Guo**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **L. Burns**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-citrullinated-peptide-antibodies-testing-rate-over-time-in-newly-diagnosed-ra-patients-data-from-three-administrative-claims-databases-2007-2014

Abstract Number: 492

Calprotectin Levels Correlate with Inflammation in Early Rheumatoid Arthritis before Disease-Modifying Antirheumatic Drug Treatment and after 12 Months of Treatment

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Calprotectin (MRP8/MRP14, S100A8/A9) is a major leukocyte protein previously shown to be associated with disease activity in patients with established rheumatoid arthritis (RA). Some studies indicate that it may be a more accurate measure of joint inflammation than erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Our objective was to compare the associations of calprotectin, ESR and CRP with clinical and ultrasound (US) measures of inflammation in patients with early RA, both before and after 12 months of aggressive disease-modifying antirheumatic drug (DMARD) treatment.

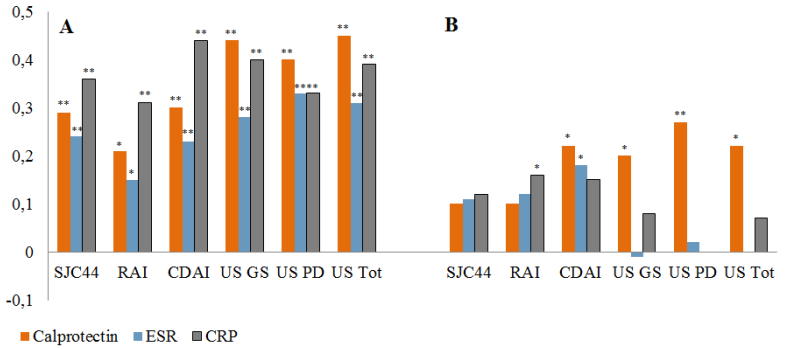
Methods: RA-patients (n=238) who fulfilled the 2010 ACR/EULAR classification criteria were recruited to the ARCTIC trial between 2010 and 2013. All patients had symptom duration from first swollen joint <2 years and were DMARD-naïve with indication for DMARD treatment. Calprotectin in EDTA-plasma was analyzed by ELISA in 212 patients at baseline and 163 patients at 12 months. US inflammation was evaluated using a standardized protocol with semi-quantitative scoring 0-3 for grey-scale (GS) and power Doppler (PD) in 32 joints (1). Clinical inflammation was assessed by 44 swollen joint count (SJC44), Ritchie Articular Index (RAI), ESR and CRP. Disease activity score (DAS) was calculated. Cross-sectional relationships were assessed by Spearman's correlations.

Results: A total of 212 patients were included: 61% female, 71% RF positive, 83% ACPA positive, mean (SD) age 50.8 (13.8) years, mean DAS 3.4 (1.2), median [25, 75 percentile] disease duration 5.9 [2.9, 10.6] months. At 12 months mean DAS was 1.2 (0.7); 75.5% were in remission according to DAS, 15.3% low, 8.7% moderate and 0.5% high DAS. The median baseline/12 month calprotectin was 1020 [562, 2153]/478[293, 794] µg/L, ESR 19 [11, 30]/9[5, 15] mm/h and CRP 7 [3, 17]/3[1, 5] mg/L. Calprotectin was significantly correlated with clinical and US markers of inflammation before treatment onset (table, figure A). After 12 months of treatment, calprotectin had a weaker, but statistically significant correlation with US scores, while no significant associations between ESR/CRP and US scores were found (figure B).

Table: Spearman's correlation coefficients; $^{*}p<0.05$, $^{**}p<0.001$

	Baseline n=212			**12 months n=163**		
	Calprotectin	ESR	CRP	Calprotectin	ESR	CRP
Calprotectin	NA	0.48**	0.64**	NA	0.43**	0.33**
ESR	0.48**	NA	0.62**	0.43**	NA	0.24*
CRP	0.64**	0.62**	NA	0.33**	0.24*	NA

Figure: Correlations between calprotectin/ESR/CRP and markers of inflammation at baseline (A) and after 12 months (B)



Spearman's correlation coefficients; *p<0.05, **p<0.001

Conclusion: Calprotectin was correlated with inflammation assessed by ultrasound before onset of DMARD treatment, and the association was also present after 12 months of DMARD treatment. This association was not found for ESR and CRP. The data support that calprotectin might be of interest when assessing disease activity in different stages of RA.

References: 1) Hammer HB et al Ann Rheum Dis 2011

Disclosure: M. K. Jonsson, None; **H. B. Hammer**, None; **H. H. Nordal**, None; **A. B. Aga**, None; **I. C. Olsen**, None; **K. A. Brokstad**, None; **T. K. Kvien**, Biogen, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, Novartis, Orion Pharma, Prizer, Sandoz, UCB, 5; **B. T. Fevang**, None; **S. Lillegraven**, None; **E. A. Haavardsholm**, AbbVie, 2,Pfizer Inc, 2,MSD, 2,UCB, 2,Roche Pharmaceuticals, 2.

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Abstract Number: 493

The 2010 ACR/EULAR Criteria Are Not Sufficiently Accurate in the Early Identification of Autoantibody-Negative Rheumatoid Arthritis

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Background/Purpose: The 2010-ACR/EULAR criteria were derived to classify RA earlier in time. Previous studies indeed observed that the 2010-criteria were fulfilled earlier than the 1987-criteria. This study determined whether the 2010-criteria perform equally in early detection of autoantibody-positive and autoantibody-negative RA.

Methods: From the total Leiden-EAC (n=3448) and ESPOIR (n=813) RA-patients who fulfilled the 1987-RA criteria at 1-year but not at presentation were selected (n=515 and n=53, respectively). These RA-patients were studied on the presence of ACPA and RF, and on fulfilling the 2010-criteria at baseline, as 2010-positivity indicated that these RA-patients were earlier identified.

Results: In the EAC, 67% of the selected RA-patients did already fulfil the 2010-criteria at baseline. In ESPOIR this was 57%, indeed demonstrating early classification with the 2010-criteria. Among the selected autoantibody-positive RA-patients of the EAC, 85% was identified at baseline already with the 2010-criteria. Within autoantibody-negative RA this was 45% ($p<0.001$). Similarly within autoantibody-positive RA-patients in ESPOIR 92% was 2010-positive at baseline, whereas this was only 25% within autoantibody-negative RA ($p<0.001$).

Conclusion: The 2010-criteria perform well in the early identification of autoantibody-positive RA, but autoantibody-negative RA-patients are still frequently missed with these criteria. This implies that other diagnostics are required for ACPA-negative patients.

Disclosure: D. M. Boeters, None; **C. Gaujoux-Viala**, None; **A. Constantin**, None; **A. H. M. van der Helm-van Mil**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-2010-acreular-criteria-are-not-sufficiently-accurate-in-the-early-identification-of-autoantibody-negative-rheumatoid-arthritis

Abstract Number: 494

Sensitivity and Specificity of 14-3-3η, Anti-CEP-1 and Anti-Sa Antibodies in

a Cohort of Seronegative and Suspected Rheumatoid Arthritis (RA) Patients from a Community Rheumatology Practice

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Background/Purpose: RA is the most common autoimmune inflammatory joint disease, affecting up to 1% of the world population. Detection of antibodies, specifically against IgM rheumatoid factor (IgM-RF) and anti-cyclic citrullinated peptide (anti-CCP) is widely used for the diagnosis of RA; both of these antibodies are included in the 2010 ACR/EULAR Rheumatoid Arthritis Classification Criteria. However, novel antibodies have been identified that can help further diagnose seronegative (IgM-RF and anti-CCP negative) RA patients. In addition to antibodies targeting cyclic citrullinated peptide (CCP), antibodies to citrullinated alpha-enolase peptide 1 (CEP-1) and citrullinated vimentin (Sa) have been found in RA synovium and serum. 14-3-3η is a protein also found in high levels in synovial fluid and serum of RA patients. The purpose of this study is to examine the sensitivity and specificity of 14-3-3η, anti-CEP-1 and anti-Sa antibodies in a cohort of seronegative RA and suspected RA patients.

Methods: The 3 assays were analyzed by enzyme-linked immunosorbent assay (ELISA) in serum from a community rheumatology practice in Los Angeles, CA (USA) using 176 samples of which, 130 were established RA patients and 46 suspected RA patients. Specificity was tested using 20 SLE, 16 psoriatic arthritis, 12 Sjogren's Syndrome and 20 Non-Rheumatic Disease Patient (NRDP) samples. Levels of 14-3-3η (Augurex Life Sciences Corp.), anti-CEP-1 and anti-Sa antibodies (Euroimmun) where measured using a laboratory developed test (LDT) at Rheumatology Diagnostics Laboratory, Inc. (RDL). Levels of anti-CCP IgG/IgA and IgM-RF were obtained on all serum samples.

Results: Out of 130 established RA patients, 50 (38%) were seronegative for both IgM-RF and anti-CCP antibodies. Of these 50 seronegative patients, 14-3-3η was positive in 5 patients (10%), while anti-CEP-1 and/or anti-Sa antibodies were positive in 5 additional patients (10%). Out of the 46 suspected RA patients, 38 (83%) were seronegative for both IgM-RF and anti-CCP antibodies. Of these 38 seronegative suspected RA patients, 14-3-3η was positive in 4 patients (11%), while no anti-CEP-1 or anti-Sa antibodies were positive.

Specificity of 14-3-3η, anti-CEP-1 and anti-Sa antibodies

		SLE Systemic Lupus Erythematosus	PSA Psoriatic Arthritis	SS Sjogren's Syndrome	NRDP Non-Rheumatic Disease Patient	Total
	n	20	16	12	20	68
14-3-3eta	Positive	0	1	2[b]	1	4
	Negative	20	15	10	19	64
	Specifcity	100%	94%	83%	95%	94%
Anti-CEP-1	Positive	0	0	1	1	2
	Negative	20	16	11	19	66
	Specifcity	100%	100%	92%	95%	97%
Anti-Sa	Positive	4[a]	0	0	0	4
	Negative	16	16	12	20	64
	Specifcity	80%	100%	100%	100%	94%
	Total Specificity	16/20 = 80%	15/16 = 94%	9/12 = 75%	18/20 = 90%	58/68 = 85%

a: ALL 4 SLE patients had predominantly inflammatory arthritis symptoms

b: 1 of 2 SS patients had active synovitis

Conclusion: In an established RA cohort negative for both IgM-RF and anti-CCP antibodies, further testing for 14-3-3η, anti-CEP-1 and anti-Sa antibodies identified an additional 20% of RA patients. In suspected RA patients (seronegative), 14-3-3η was positive in an additional 11%. The overall specificity of the 3 markers was 85%. In the autoimmune disease controls, most of the patients that tested positive for these antibodies had inflammatory arthritis/active synovitis, and therefore may have had an overlap syndrome.

Disclosure: D. Karayev, RDL, 3; **G. Shen**, RDL, 3; **Y. Lam**, RDL, 3; **A. Rimmer**, RDL, 3; **N. Lal**, RDL, 3; **E. Karayev**, RDL, 3; **K. Azarraga**, RDL, 3; **R. A. Blum**, RDL, 3; **A. L. Metzger**, RDL, 4; **R. I. Morris**, RDL, 4; **A. A. Horizon**, None.

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3%ce%b7-anti-cep-1-and-anti-sa-antibodies-in-a-cohort-of-seronegative-and-suspected-rheumatoid-arthritis-ra-patients-from-a-community-rheumatology-practice

Abstract Number: 495

The Relative Performance of 28-Joint Disease Activity Score Based on C-Reactive Protein with Three Versus Four Components in Patients with Rheumatoid Arthritis

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Background/Purpose: The commonly used version of the 28-joint disease activity score based on C-reactive protein (DAS28-CRP4) includes swollen and tender joint counts (S/TJC), CRP and the patient global assesment of disease activity (PGA), while the 3-component version (DAS28-CRP3) does not include PGA. We examined whether these two instruments can be used interchangeably, and if assessment of disease activity status and treatment response to a tumor necrosis factor inhibitor (TNFi), such as originator adalimumab (ADA) in patients (pts) with rheumatoid arthritis (RA), differs.

Methods: This *post hoc* analysis used data from five randomized controlled trials: PREMIER, OPTIMA and CONCERTO enrolled pts with early RA who were MTX- and TNFi-naïve; DE019 and MUSICA enrolled pts with established RA and an inadequate response to MTX. The correlation between the two versions was calculated by Pearson correlation coefficients. The change from baseline in DAS28-CRP3 and DAS28-CRP4, and the number of patients reaching low disease activity (LDA, DAS28-CRP $\leq$3.2) or DAS28-CRP <2.6, was assessed at Weeks 12 and 24/26. Data from pts with non-missing DAS28-CRP-3 and -4 is included, pooled across trials by randomized treatment into ADA+ MTX, or placebo (PBO)+MTX.

Results: The DAS28-CRP3 and -4 versions showed a strong correlation (0.98, p<0 .001) for pts receiving MTX or ADA+MTX across all 5 trials, at both Week 12 and 24/26. Overall, in both treatment groups, most pts who achieved DAS28-CRP3 <2.6 (or LDA), also achieved DAS28-CRP4 <2.6 (or LDA) at both Week 12 and 24/26 (Table 1). Both versions were comparably responsive, with similar changes from baseline for pts in either treatment group, similar treatment differences, and response rate differences between pts receiving ADA+MTX and pts on PBO+MTX at Weeks 12 (Table 2) and 24 (not shown).

Conclusion: While the patient perspective is important, when PGA is not available, the DAS28-CRP3 score is able to provide an assessment of disease activity which correlates highly with the DAS28-CRP4 version.

Table 1. Patients who achieved DAS28-CRP <2.6 or LDA by the 3-component or 4-component versions at Weeks 12 and 24				
	Week 12		Week 24	
	Patients with DAS3 <2.6	Patients with DAS3<2.6 but not DAS4 <2.6	Patients with DAS3 <2.6	Patients with DAS3<2.6 but not DAS4 <2.6
PBO + MTX	69	8/69 (11.6)	127	4/127 (3.1)
ADA 40 mg + MTX	193	14/193 (7.3)	248	10/248 (4.0)
	Patients with DAS3 LDA	Patients in DAS3 but not DAS4 LDA	Patients with DAS3 LDA	Patients in DAS3 but not DAS4 LDA
PBO + MTX	148	13/148 (8.8)	213	14/213 (6.6)
ADA 40 mg + MTX	346	19/346 (5.5)	424	16/424 (3.8)
Table 2. Change from Baseline measured by the 3-component (ΔDAS3) or 4-component (ΔDAS4) versions of the score at Week 12				
	ΔDAS3	treatment difference	ΔDAS4	treatment difference
PBO + MTX	-1.4	-0.7****	-1.6	-0.8****
ADA 40 mg + MTX	-2.1		-2.4	
LDA response rate measured by the 3-component (DAS3) or 4-component (DAS4) versions at Week 12				
	DAS3	response rate difference	DAS4	response rate difference
PBO + MTX	15.3	19.7****	16.4	19.8****
ADA 40 mg + MTX	34.9		36.3	
DAS28-CRP <2.6 response rate measured by the 3-component (DAS3) or 4-component (DAS4) versions at Week 12				
	DAS3	response rate difference	DAS4	response rate difference
PBO + MTX	7.1	12.4****	7.8	14.1****
ADA 40 mg + MTX	19.5		21.9	
**** p<0.001				

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Abstract Number: 496

Impact of Anti-Citrullinated Protein Antibody and/or Rheumatoid Factor on Rheumatoid Arthritis Manifestations and Outcomes

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SESSION INFORMATION

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Background/Purpose: RA Patients with anti-citrullinated protein antibody (ACPA) or rheumatoid factor (RF) are known to have worse clinical outcomes compared to seronegative patients. To determine if there were differences in clinical, laboratory features and outcomes of RA patients based on their ACPA and RF status (group I: ACPA+RF+, II: ACPA+RF -, III: ACPA -RF+, IV: ACPA-RF-). All patients fulfilled the 1987 ACR criteria for RA.

Methods: ACPA and RF titres were analysed by ELISA. Statistical analysis was conducted using STATA 13.0 (College Station, TX). We used Chi-square test or Fisher's exact test to compare categorical variables. We used ANOVA or Kruskal Wallis test for continuous variables, followed by posthoc Tukey's HSD test when appropriate. A two tailed significance level of 0.05 was chosen for all tests.

Results: The study population comprises 970 patients (group I 663, II 68, III 106, IV 133) with mean disease duration of 174.4 + 103.4 months. The gender distribution, educational level, smoking status, mean disease duration, age of onset, age at RA diagnosis, duration from onset to 1st DMARD and number of co-morbidities were similar among the 4 groups. At presentation, group I had significantly higher ESR (mean 59.9mm/hr vs 48.5-55.8mm/hr in the other 3 groups, $p = 0.005$). Group I patients were more likely to have deformed joints (65.3 % vs 42.1-65.2 % in other groups, $p<0.001$) despite higher usage of prednisolone (59.3 % vs 39.9-58.8 in other groups, $p <0.001$) and higher number of synthetic DMARDs (2.86 vs 2.31-2.74 in other groups, $p< 0.001$). Fewer patients in groups I & II (66.2% and 62.7% respectively) achieved remission (DAS 28 < 2.6) compared to those in groups III & IV (74.3 % and 78.2 % respectively, $p=0.02$). However, the HAQ and Short form 36 (SF 36) scores did not differ among the 4 groups.

Conclusion: ACPA+RF+ RA patients have higher baseline ESR and fewer achieve remission, despite higher use of synthetic DMARDs compared to ACPA-RF+ and ACPA-RF- patients. However, these differences did not affect their functional status or quality of life.

Abstract Number: 497

The Identification of an ACR Score with the Optimal Discriminatory Ability Between Treatments in Patients with Early and Established Rheumatoid Arthritis

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Background/Purpose: In patients (pts) with rheumatoid arthritis (RA), the American College of Rheumatology (ACR)20 score was developed to best discriminate effective from placebo (PBO) treatment, minimize PBO response rates, assess the efficacy of a drug vs PBO and clinical outcome over a period. Based on trials of pts with established RA and on use of csDMARDs, ACR20 was determined to be the best discriminator vs ACR 50/70[1]. However, it is unclear if ACR20 is also the best discriminator between treatments in studies conducted in the current era. The aim was to determine the cut-off value of the ACR score which can best discriminate between the efficacies of various treatments in RA pts in a clinical trial (CT). _

Methods: This *post hoc* analysis used data from the PREMIER[2] and OPTIMA[3] CTs in pts with early RA who were methotrexate (MTX) naïve and from the DE019[4] and ARMADA[5] CTs in pts with established RA who had failed prior DMARD(s). To identify the ACR score with best discrimination between treatments, the ACR response rate was calculated for each treatment arm at various time points for each cut-off from 0-100. The p-value was calculated for the difference between treatments at each cut-off to identify the cut-off for which the p-value was the smallest.

Results: In pts from PREMIER (early RA), the maximum difference and best p-value between the PBO+MTX (newly introduced MTX) vs originator adalimumab (ADA)+MTX arms was achieved at ACR60 (fig 1A) at Week (Wk) 26. Similarly, in OPTIMA (early RA), at Wk 26 the maximum difference and best p-value between the PBO+MTX vs ADA+MTX arms was achieved between ACR70-80 (fig 1B). In pts from DE019 (established RA), ACR35 had the best discriminatory ability and p-value, both at Wks 24 and 52, when comparing PBO+MTX [MTX-continued in MTX inadequate responders (MTX-IR)] vs ADA+MTX (fig 1C). Similarly, in established RA pts from ARMADA, for PBO+MTX vs ADA+MTX at Wk 24, smaller ACR cut-offs were more discriminatory and ACR 30 had the best p-value (fig 1D).

Conclusion: The ACR cut-off score with the best discriminatory ability differed in these 2 populations; In early RA higher ACR cutoffs were more discriminatory, while in established RA, lower ACR cutoffs were better. This may be due to the early RA CTs having active comparator arms with newly introduced MTX, while the established RA CTs control arms had PBO on background MTX in MTX-IR pts. Further analysis is needed to determine if an ACR response other than ACR20, should be used in CTs with a newly introduced active comparator. In addition, the optimal ACR cutoff may differ according to the population studied (early vs. established RA). **References**

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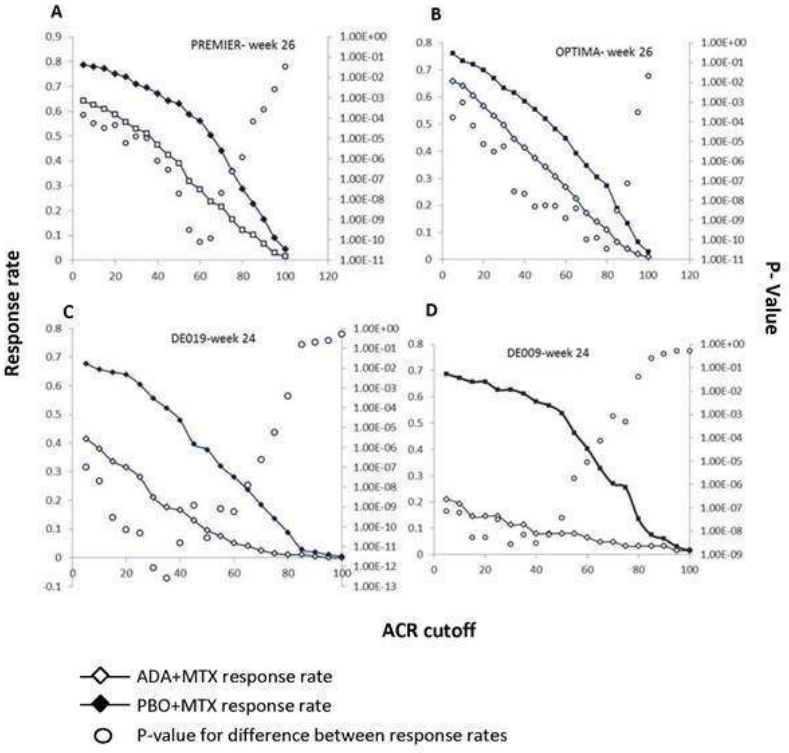

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Abstract Number: 498

Higher Serum Heavy Metals Concentrations Are Associated with Rheumatoid Arthritis : A Study of the Korean National Health and Nutrition Examination Survey (KNHANES)

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Background/Purpose: The heavy metal Cadmium (Cd) may contribute to the high risk of developing rheumatoid arthritis (RA) through the cigarette smoking and occupational exposure including air pollution. But, there was no definite report about association between heavy metals and RA.

Methods: We analyzed serum heavy metals (Cd, Hg and Pb) [N=53829, RA= 803 vs. control= 5410, from 2008 to 2013], serum Mn, urine As (AAS method), [N=20277, RA=330 vs. control=65, from 2008 to 2009] and serum Zn [N=8958, RA=133 vs. control=27, in 2010] in RA patients from the data of KNHANES. We analyzed the prevalence of RA and performed general linear model and logistic regression with complex sample design method adjusted by age, sex and smoking status to evaluate the association of the serum heavy metals or minerals levels and RA.

Results: The prevalence of RA was 1.59 % [95% CI; 1.33-1.89] from 2008 to 2013. Serum Cd levels were elevated in RA patients (RA vs. control; 1.44 ± 0.06 μg/L vs. 1.02 ± 0.02 μg/L, p=0.02), and serum Pb levels also increased in RA patients (2.33 ± 0.07 μg/dL vs. 2.12 ± 0.03 μg/dL, p=0.01). There were no differences of serum Hg level (4.22 ± 0.24 μg/L vs. 4.00 ± 0.01μg/L, p=0.49), serum Mn level (1.33 ± 0.04 μg/dL vs. 1.33 ± 0.07 μg/dL, p=0.27), serum Zn level (126.51 ± 4.71 μg/dL vs. 119.14 ± 12.65 μg/dL, p=0.48) and urine As level (AAS method; 192.70 ± 15.65 μg/L creat vs. 181.34 ± 42.22 μg/L creat, p=0.79) between RA patients and control.

The odds ratios [OR, 95% CI] of the RA prevalence according to increase 1 μg/L of serum Cd was 1.62 [1.28-2.05, p<0.001]. And the OR of RA prevalence according to increase 1 μg/dL of serum Pb levels is 1.37 [1.18-1.60, p<0.001].

Conclusion:

We showed increased risk of rheumatoid arthritis associated with the serum Cd and Pb levels in the KNHANES data of Korean populations.

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Abstract Number: 499

High Levels of Mir-451a Differentiate Patients at Risk of Developing RA from Healthy Controls

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Background/Purpose: Individuals with clinically suspect arthralgia (CSA) with positivity of antibodies to citrullinated protein antigens (ACPA) have articular symptoms without clinical signs of arthritis. CSA patients are considered at high risk for progression to RA. The altered expression of miRNAs contributes to the development and maintenance of autoimmune diseases. Moreover, miRNAs appear promising diagnostic and/or prognostic biomarkers. We aimed to investigate differentially expressed peripheral blood mononuclear cell (PBMC)-contained and cell-free circulating

miRNAs in CSA and healthy controls (HC).

Methods: The study included 19 CSA individuals and 23 HC. Clinical disease activity assessments (DAS28, SDAI) and disease activity assessed by patient on VAS were performed. By definition, all patients had swollen joint count 0. Ultrasound (US) of 28 small joints was performed in CSA to evaluate subclinical synovitis. Total RNA from plasma and PBMC was isolated using phenol-chloroform extraction or miRNeasy Mini Kit. A comprehensive analysis of miRNAs was performed using TaqMan® Low Density Array (TLDA) in 5 samples per group. The expression of miR-451a was further validated by single assays and normalized to RNU44 for PBMC or an average of 3 spike-in C. elegans controls for circulating miRNAs. dCt was used for relative quantification.

Results: All CSA patients were ACPA+ with CRP 9.1±19.6 mg/l. 9 CSA patients had no activity on US (grey scale≤1 and power doppler=0). Out of the 380 miRNAs analysed by TLDA, 194 miRNAs were detected in PBMC of CSA and 198 in HC while 125 circulating miRNAs were detected in plasma of CSA and 124 in HC. TLDA analysis revealed 2.43x higher levels of miR-451a in PBMC and 1.55x lower levels of circulating miR-451a in CSA compared to HC. Further validation confirmed 3.19x higher expression of miR-451a in PBMC in CSA compared to HC (p=0.001). These levels in CSA significantly correlated with DAS28(CRP) (r=0.575; p=0.010), SDAI (r=0.676; p=0.004) and VAS (r=0.484; p=0.036), but not with tender joint count (r=0.401; p=0.089), ESR (r=-0.042; p=0.869) or CRP (r=0.238; p=0.328). No difference in expression of circulating miR-451a or association with disease activity was demonstrated. Subclinical activity as per US findings had no effect on the levels of miR-451 in PBMC or plasma. There was no correlation between circulating and PBMC levels of miR-451a (r=0.265; p=0.124)

Conclusion: Although CSA cannot be considered a disease itself, and is rather a clinical suspicion of a disease, high levels of miR-451 in PBMC distinguish these at high risk individuals from HC. Moreover, miR-451 reflects the activity at this pre-clinical phase. Acknowledgement: MHCR 023728 and SVV 260263 projects.

Abstract Number: 500

Can Thiol/Disulphide Is a Novel Marker in Rheumatoid Arthritis?

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Background/Purpose: Rheumatoid arthritis is a chronic, systemic, autoimmune disease about 5% -%1 of world population affected. Highly reactive oxygen free radicals are believed to be involved in the pathogenesis of the disease. Our aim was to investigate the thiol/disulphide homeostasis, which has an important role in many cellular activities such as antioxidant protection, detoxification, cell growth and apoptosis in patients with rheumatoid arthritis.

Methods: Twenty female and five male patients diagnosed with RA according to American College of Rheumatology

1987 classification criteria and healthy, age, weight and height-matched 20 women and 5 men were evaluated. Disease activity was assessed using a variety of variables including erythrocyte sedimentation rate and C-reactive protein, tender joint count, swollen joint count, and Disease Activity Score-28.

Results: The mean ages of patients group (32.60±7.18) and control group (31.70±8.23) were similar (p=0.573). When we determine at the thiol/disulphide homeostasis parameters in both groups, we can see the mean native thiol (p=0.004), and native thiol/total thiol (p=0.000) levels is lower in the RA group than the control group. The mean disulphide level (p=0.000) was higher in the RA group than control group. The multiple regression analysis of thiol/disulphide balance and other risk factors was performed. Low thiol levels and high disulphide levels in patients with RA were found to be independent of gender, age and body mass index.

Conclusion: In this study we have shown that thiol/disulphide homeostasis may be used as a novel oxidative stress marker in patients with rheumatoid arthritis. Further studies are needed to confirm the pathophysiologic role of thiol/ disulphide homeostasis in rheumatoid arthritis

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Abstract Number: 501

Use of Rheumatologic Testing By Primary Care Physicians in Patients with Inflammatory Arthritis

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Background/Purpose: Anti-cyclic citrullinated peptide antibody (Anti-CCP) is a diagnostic tool that predicts the progression of undifferentiated polyarthritis and erosive disease in rheumatoid arthritis (RA). It is more sensitive (60%) and specific (98%) than rheumatoid factor (RF). Despite these advantages, we hypothesize that physicians underutilize anti-CCP and other diagnostic tests for RA, which results in delay of diagnosis of RA and delay of initiation of treatment with disease modifying anti-rheumatic drugs. We aimed to describe the primary care work-up of polyarthritis in patients who eventually received a diagnosis of RA.

Methods: We performed retrospective chart review in patients seen between 1/1/2010 and 6/15/2014 in two rheumatology clinics, one private practice and one in a community health center associated with an academic medical center.

Results: We identified 173 patients seen in one of two rheumatology clinics referred from 141 different primary care providers. The sample was 83% (n=143) female, and the mean±SD age was 55.5±18.6 years. The majority (75.7%) were treated at the private practice. Anti-CCP or RF was ordered by the referring provider (prior to presentation to the rheumatologist) in only 38.7% (95% CI 31.7%, 46.3%) of patients. The presence of anti-CCP or RF did not vary significantly by presenting site: 33.3% at the community health center vs. 40.5% at the private practice, p=0.47. Ordering of anti-CCP varied non-significantly by presenting site: 19.1% of patients at the community health center presented with anti-CCP compared to 32.1% of the patients seen at the private practice (p=0.12). Prior to presentation at the rheumatology clinics, ESR was ordered in 43.9% of patients and CRP was ordered in 33.0% of patients. Ordering of ESR and/or CRP varied by site: 28.6% of patients seen at the community health center presented with ESR or CRP, but 52.7% at the private practice (p=0.008) presented with ESR or CRP. Lyme titre was ordered in 0.0% of community health center patients vs. 9.6% of private practice patients, p=0.04. Radiological imaging performed by PCP was only documented for 38.2% (n=66) of patients, with x-ray being the most frequent (46/66 or 69.7%) and MRI a distant second (6/66 or 9.1%). Functional ability was documented in only 2.3% of referred patients (95% CI 0.9%, 6.1%). About half of all patients (68, 51.1%) had DMARDS initiated immediately on presentation to the rheumatologist. Interval to treatment ranged from 0 weeks to 144, but only 18.1% (n=24) waited longer than one month for treatment. Interval to treatment was not associated with CCP order by referring physician (50% waiting > 1 month if anti-CCP was ordered vs. 30.3% if anti-CCP was not, p=0.13).

Conclusion: Most primary care physicians failed to order diagnostic tests for RA prior to referring a patient with polyarthritis to a rheumatology clinic. In particular, primary care providers failed to order anti-CCP in 61% of referred patients who eventually received a diagnosis of RA. Failure to order anti-CCP did not appear to significantly delay initiation of treatment of RA. These findings suggest educational efforts should focus on emphasizing earlier diagnostic workup, especially anti-CCP, in patients suspected to have RA.

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Abstract Number: 502

Use, Usability and Feasibility of a Mapp for Patients with Rheumatoid Arthritis – First Results

Christina Kampling[1], Gamal Chehab[2], Hasan Acar[1], Arnd Becker[3], Matthias Schneider[4] and **Jutta G. Richter**[5], [1]Policlinic of Rheumatology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany, [2]Policlinic of Rheumatology, Heinrich-Heine-University, 40225 Duesseldorf, Germany, [3]Ortenau Klinikum Offenburg-Gengenbach, Gengenbach, Gengenbach, Germany, [4]Department of Rheumatology & Hiller Research Unit, Heinrich-Heine-University, Duesseldorf, Germany, [5]Policlinic of Rheumatology and Hiller Research Unit Rheumatology, Heinrich-Heine-University Duesseldorf, Duesseldorf, Germany

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Background/Purpose: Within the MiDEAR (Mobile medically supervised patient management in rheumatoid arthritis patients using DocuMed.rh and RheumaLive App) project patients (pts) with rheumatoid arthritis (RA) evaluate the usability of a mobile medical Application (mApp) with diary functions over nine months. The mApp includes two computerized patient-reported outcome questionnaires: the Hannover Functional Questionnaire (FFbH) and a modified RA disease activity index questionnaire (RADAI). In addition, it allows pts to document morning stiffness, pain (visual analogue scale), incapacity to work and medication. We studied pts' use of this kind of mApp outside of out-pts clinics, their satisfaction and the reported benefits in real-life settings.

Methods: Inclusion criteria were RA diagnosis, age of consent and German speaking. 268 consecutive RA out-pts (73.5% female) were screened, 157 (58.6%, 77.7% female) owned an App-able device. At baseline 60 out-pts consented to start the project. Pts downloaded the mApp on their own mobile device (either smartphone or TabletPC), documented their data voluntarily on not pre-specified intervals, and were followed on routine out-pts visits. During the out-pts visits pts evaluated the use, usability and feasibility of the mApp on paper-based questionnaires. Ethical approval and signed informed consents were obtained. The study is registered with the identifier NCT02565225 at clinicaltrials.gov.

Results: At baseline pts were predominantly female (78.3%), mean±SD age was 50.1±13.1 years (yrs), mean disease duration 10.5±9.1 yrs. 50% had a high education level. 90.0% already used Apps. 71.7% (n=43) remained in the project until the first follow-up. Reasons for discontinuation were fear of data theft (n=1), incompatible operating system (n=1), and other not App-related reasons (n=15). 97.7% (n=42) of the attending pts evaluated the mApp at first follow-up, n=39 had used the mApp at unspecific dates in between. Due to physical limitations (finger deformations) one patient reported problems to operate the mApp on a smartphone. Most pts (90.7%) rated mApp handling as easy. The average score of satisfaction with the mApp was 2.3±1.0 (Likert scale 1 (very satisfied) - 6 (very unsatisfied)) and the usefulness was 2.1±1.1 (Likert scale 1 (very useful) - 6 (not at all useful). Most pts (51.1%) stated that the mApp assisted them in an optimized self-monitoring of their disease. Better dealing with RA-related physical and medical needs due to App use was answered diversified with positive and negative responses.

Conclusion: At first follow-up the mApp use was feasible in the majority of the pts. mApp users were satisfied with the

mApp and assessed its utility as useful for self-monitoring their disease apart from out-pts visits. mApps - powerful tools at our fingertips - open great options for new management concepts. The ongoing project will deliver further data.

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Abstract Number: 503

Anti-CCP Titer and Prevalence Is Influenced By Age at Rheumatoid Arthritis Onset- Analysis Based on a Nationwide Database in Japan

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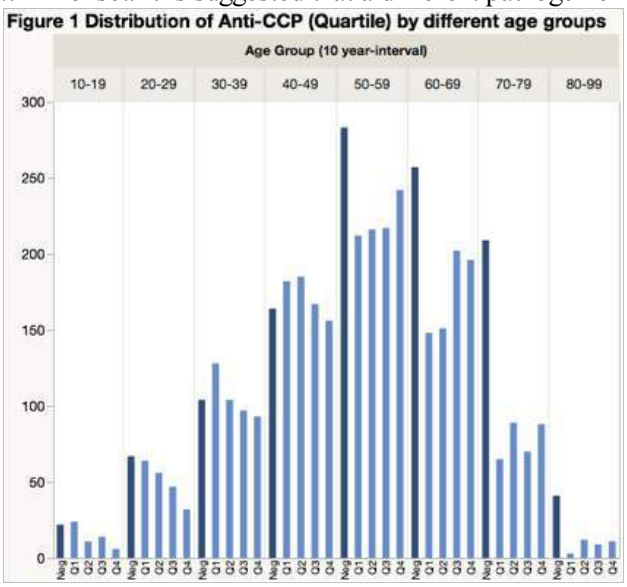
Session Time: 9:00AM-11:00AM

Background/Purpose: Previous studies demonstrated the lower prevalence of anti-CCP antibody and rheumatoid factor (RF) in elderly-onset rheumatoid arthritis (EORA). However, anti-CCP antibody titer in EORA has not been fully elucidated. In the present study, we aim to investigate RF and anti-CCP titers in patients with EORA and young-onset RA (YORA) based on a nationwide RA database, National Database of Rheumatic Diseases by iR-net in Japan (NinJa).

Methods: We analyzed 4,445 RA patients, whose anti-CCP titer data were available in NinJa 2014. The cutoff point used in the present study for defining EORA was 65 years of age. The Student unpaired t-test was used to compare the mean values, with p-values of <0.05 (after Bonferroni correction for multiple comparisons) considered to indicate statistical significance.

Results: Prevalence of RF and anti-CCP antibody in EORA (62.0% and 62.1%) was significantly lower than that in YORA (73.5% and 77.9%, respectively), as was consistent with previous studies. The average RF and anti-CCP titers increased, as the age at RA onset increased. There was thus a significant difference in RF levels between 20-29, 30-39 and 40-49 age groups (111, 118 and 103 IU/mL, respectively) and 70-79 age group (128 IU/mL). Anti-CCP titer was significantly higher in 60-69 age group (284 U/mL) than 20-29 age group (170 U/mL). Anti-CCP antibody levels were subsequently grouped into quartiles (Q1: 4.5-40, Q2: 40-124, Q3: 124-434, Q4: >434 U/mL). As shown in Figure 1, the proportion of anti-CCP negative RA patients was higher in the groups with age at disease onset above 50 years. Furthermore, there was a difference in the pattern of anti-CCP distribution, depending on the ages at RA onset. Thus, the higher titer quartiles (Q3 and Q4) were more frequently observed in RA patients with their age at disease onset above 50 years than in those below 50 years. There was a tendency of higher proportion of Q4 in RA patients with history of former and current smoking. However, since the prevalence of smoking is reported to be lower in the general population above 50 years of age in Japan than younger generations, extrinsic factors other than smoking could be involved in the higher-level production of anti-CCP antibodies in EORA.

Conclusion: We have demonstrated that lower positivity and higher titers of RF and anti-CCP antibodies were associated with increasing age at RA onset. It is suggested that a different pathogenic factors could contribute to anti-CCP production in elderly onset RA.



Disclosure: E. Kato, None; **T. Sawada**, None; **K. Tahara**, None; **H. Hayashi**, None; **M. Tago**, None; **H. Mori**, None; **S. Yoshizawa**, None; **J. Nishino**, None; **T. Matsui**, None; **S. Tohma**, None.

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Abstract Number: 504

Clinical Significance of Multiple Autoantibody Specificities in Rheumatoid Arthritis: The Role of Anti-Citrullinated Alpha-Enolase and Anti-Interferon Inducible Protein 16 Antibodies

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Background/Purpose: Anti-cyclic citrullinated peptide (anti-CCP) auto-antibodies (auto-Abs) represent the current gold standard for the diagnosis of rheumatoid arthritis (RA). However, growing evidence suggests that a variety of other citrullinated or not citrullinated self-proteins may act as autoantigens and lead to the production of auto-Abs. The identification of diagnostic and/or prognostic value of such novel auto-Abs is under intense investigation. We recently demonstrated that RA patients display higher prevalence of auto-Abs against the interferon-inducible protein 16 (anti-IFI16) but these auto-Abs do not have a good diagnostic value (1). Recent data showed that auto-Abs against citrullinated

alpha-enolase (anti-CEP1) are associated with erosive RA (2). The purpose of this study was to investigate the possible prognostic value of anti-CEP-1 and anti-IFI16 as well as the clinical implication of their association with anti-CCP in a cohort or RA patients.

Methods: Two-hundred and fifty-two RA patients were enrolled and serum samples were obtained. Auto-Abs were assessed as follows: anti-CCP EDIA 2nd generation ELISA kit (Eurodiagnostica); anti-CEP-1 IgG ELISA kit (Euroimmun). In a subgroup of 113 patients also anti-IFI16 auto-Abs were assessed with an in-house ELISA kit (1). Clinical and serological records of patients were collected and statistical analysis was performed with SPSS 21.0 software.

Results: One hundred and twenty patients (44%) displayed anti-CEP-1 and, among these, 97 patients (87%) also displayed anti-CCP. Logistic regression analysis revealed an association between both auto-Abs and RA-associated pulmonary disease (odds ratio-OR=2.9; 95%CI= 1.06-7.9; p=0.04). We also confirmed that anti-CEP-1 are associated with erosive RA, but, of interest, to a greater extent compared to anti-CCP (anti-CEP-1: OR=4.12; p=0.04; anti-CCP: OR=2.1; p=0.03). The analysis that included anti-IFI16 revealed that a small proportion of patients display all the three auto-Abs (9%), but the triple positivity was significantly associated with male gender (OR=3.5; p=0.02), the presence of rheumatoid nodules (OR=5,3; p=0.015) and pulmonary involvement (OR=2,6; p=0.007). Anti-IFI16 were associated to male gender independently of the presence of the other two auto-Abs.

Conclusion: Our study suggests that anti-CEP-1 auto-Abs may participate to the development of RA-associated pulmonary manifestation together with anti-CCP and that the assessment of multiple auto-Abs in daily practice may help clinician to stratify RA patients in order to identify those at higher risk to develop extra-articular manifestations. **References** 1-Alunno A et al. Arthritis Care Res 2016;68:440-5 2-Fisher BA et al. Ann Rheum Dis 2011;70:1095-1098

Disclosure: A. Alunno, None; **O. Bistoni**, None; **F. Pratesi**, None; **V. Caneparo**, None; **F. Topini**, None; **I. Puxeddu**, None; **M. De Andrea**, None; **S. Landolfo**, None; **P. Migliorini**, None; **R. Gerli**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-significance-of-multiple-autoantibody-specificities-in-rheumatoid-arthritis-the-role-of-anti-citrullinated-alpha-enolase-and-anti-interferon-inducible-protein-16-antibodies

Abstract Number: 505

The Longitudinal Stability of the RA Biomarkers RF and ACPA in Classifying RA Subtypes over Extended Follow up

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In recent years several studies suggest that first order stratification of RA should be based on the presence or absence of rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) in sera [1,2]. Both RF and ACPA can be detected in the sera of some patients years before the onset of arthritis [3,4]. It has been shown that in patients presenting with undifferentiated arthritis, both RF and ACPA are stable biomarkers, and rarely change over the course of the first year of disease [5]. The longitudinal course of these important and commonly used biomarkers in established RA over a prolonged period of time is less clear. The objective of our study was to determine the rates of seroconversion for RF and ACPA, in patients with RA over an extended period of follow up.

Methods: 155 subjects (111 Female, Age Range 31-90 years) with RA meeting ACR/EULAR classification criteria were included. All subjects had assessments of RF at diagnosis and at their most recent clinical follow up and 58 had assessments of ACPA at diagnosis and most recent follow up.

Results: Subjects were assessed for RF for a median of 4.49 years (IQR 1.92-8.40) following the sample taken at diagnosis. Seroconversion for RF was observed in 15/94 (16.0%) of patients. Where RF was detectable at diagnosis, it became undetectable in the sera of 10/61 (16.4%). Subjects were assessed for ACPA a median of 1.90 years (IQR 0.63-3.54) following the sample taken at diagnosis. Seroconversion was not observed in any of the 25 patients who were negative for ACPA at diagnosis. Where ACPA was detectable at diagnosis, it became undetectable in the sera of 1/35 (2.9%).

Conclusion: In addition to being more specific for RA, ACPA offers the advantage over RF of being more stable over time. Our data suggests little merit in repeat testing of ACPA over time, and suggests the index result can be used to appropriately sub-classify the RA phenotype. References: 1 Willemze A, Trouw LA, Toes RE, *et al.* The influence of ACPA status and characteristics on the course of RA. *Nat Rev Rheumatol* 2012;**8**:144–52. doi:10.1038/nrrheum.2011.204 2 Klareskog L, Catrina AI, Paget S. Rheumatoid arthritis. *Lancet* 2009;**373**:659–72. doi:10.1016/S0140-6736(09)60008-8 3 Nielen MMJ, van Schaardenburg D, Reesink HW, *et al.* Specific autoantibodies precede the symptoms of rheumatoid arthritis: A study of serial measurements in blood donors. *Arthritis Rheum* 2004;**50**:380–6. doi:10.1002/art.20018 4 Rantapaa-Dahlqvist S, de Jong BA, Berglin E, *et al.* Antibodies against cyclic citrullinated peptide and IgA rheumatoid factor predict the development of rheumatoid arthritis. *Arthritis Rheum* 2003;**48**:2741–9. doi:10.1002/art.11223 5 Mjaavatten MD, van der Heijde DM, Uhlig T, *et al.* Should Anti-citrullinated Protein Antibody and Rheumatoid Factor Status Be Reassessed During the First Year of Followup in Recent-Onset Arthritis? A Longitudinal Study. *J Rheumatol* 2011;**38**:2336–41. doi:10.3899/jrheum.110234

Disclosure: C. Orr, None; **F. Young**, None; **D. J. Veale**, None.

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Abstract Number: 506

The Relationship Between Elevations in CRP with Physical Function and Radiographic Progression over the Long-Term in Patients with Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: For patients (pts) with rheumatoid arthritis (RA), quantification of radiographic progression, through measures such as modified total Sharp score (mTSS), is not routinely captured in daily clinical practice. Surrogate markers of radiographic progression may facilitate identification of pts who require closer monitoring. The aim was to assess the relationship between elevations in C-reactive protein (CRP) values, over 10 years (yrs), with physical function

and radiographic progression.

Methods: This post hoc analysis used data from 2 trials: PREMIER,[1]a 2-yr randomized, controlled trial (RCT) in methotrexate (MTX)-naïve, early RA pts, receiving MTX, adalimumab (ADA) or ADA+MTX, and DE019,[2]a 1-yr RCT in RA pts with an inadequate response to MTX, receiving Placebo or ADA on background MTX. In both trials, pts completing the RCT could enter an open label extension (OLE) for a total treatment period of 10 yrs. CRP and the disability index of the health assessment questionnaire (HAQ-DI) were collected at regular visits throughout the RCTs and OLEs. Radiographic data were collected at baseline, 6 months, 1, 2, 3, 5, 6, 8 and 10 yrs. Spearman coefficients assessing correlations between CRP elevations (defined as CRP >upper limit of normal [ULN]) and HAQ-DI were calculated at all visits. The association of radiographic progression (ΔmTSS ≥0.5) with CRP elevations and time-averaged (TA)-CRP was assessed between x-ray reads by logistic regression and descriptive statistics.

Results: In both PREMIER and DE019, a significant, positive correlation was observed between CRP elevations and HAQ-DI at nearly all time points during the RCTs, and approximately half of the time points throughout the OLEs. Further, CRP elevations were associated with radiographic progression during the first half of PREMIER but these associations were not observed at any time point in DE019 **(Table 1)**. For pts who experienced ≥1 CRP elevation >ULN between x-ray reads, TA-CRP was significantly associated with radiographic progression only at yrs 5 and 6 in PREMIER. Radiographic progression was observed frequently among pts with elevations in CRP between x-ray reads; however, radiographic progression was still seen in 20-52% of pts without CRP elevations. Pts receiving MTX monotherapy in both RCTs experienced an increase in CRP elevations compared to those pts receiving ADA+MTX (91% vs 55% for MTX and ADA+MTX, respectively, at 2 yrs in PREMIER; 68% vs 33% for MTX and ADA+MTX, respectively, at 1 yr in DE019). Consistently, treatment was significantly associated with radiographic progression, as assessed by logistic regression.

Conclusion: CRP is an important marker of inflammation that can be used to identify pts at risk of radiographic progression, and this relationship appears dependent on pt disease characteristics. Structural evaluation remains important until further predictors are identified.

Table 1. Relationship between CRP elevations and radiographic progression (ΔmTSS ≥0.5) in patients from PREMIER and DE019 over 10 years

Visit	PREMIER Odds ratio (95% CI)	DE019 Odds ratio (95% CI)
Week 26/24	2.946 (1.001, 8.668)*	1.204 (0.549, 2.637)
Week 52	2.237 (1.260, 3.972)**	1.348 (0.632, 2.876)
Week 104	0.754 (0.358, 1.590)	1.528 (0.719, 3.246)
Week 156	2.099 (1.116, 3.949)*	1.864 (0.872, 3.986)
Week 264/260	2.077 (1.127, 3.828)*	1.547 (0.773, 3.097)
Week 312	1.295 (0.627, 2.676)	1.401 (0.668, 2.937)
Week 424/416	1.150 (0.632, 2.094)	1.672 (0.844, 3.312)
Week 520	0.861 (0.471, 1.574)	1.313 (0.666, 2.589)

**, *, p <0.01 and 0.05, respectively. CRP, C-reactive protein; mTSS, modified total Sharp score.

Ref:1.Breedveld et al. 2006. Arth Rheum;54:26; 2. Keystone et al. 2004. Arth Rheum;5:1400

Disclosure: A. Kavanaugh, AbbVie Inc., Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB., 2,AbbVie Inc., Amgen, Astra-Zeneca, BMS, Celgene, Centocor-Janssen, Pfizer, Roche, and UCB., 9; **B. Haraoui**, Abbott, Amgen, Bristol-Myers Squibb, Merck, Pfizer, Roche, and UCB., 5; **P. Sunkureddi**, Novartis, Bristol Myers Squibb, UCB, Pfizer, AbbVie and Takeda., 5,Novartis, Bristol Myers Squibb, UCB, Pfizer, AbbVie and Takeda., 8; **B. Wolfe**, AbbVie, 3,AbbVie, 1; **L. Wang**, AbbVie, 1,AbbVie, 3; **J. Suboticki**, AbbVie, 3,AbbVie, 1; **E. Keystone**, AbbVie, Amgen, AstraZeneca, BMS, Janssen, Pfizer, Roche, and UCB, 2,AbbVie, Amgen, AstraZeneca, BMS, Janssen, Pfizer, Roche, and UCB, 5,AbbVie, Amgen, AstraZeneca, BMS, Janssen, Pfizer, Roche, and UCB, 8.

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Abstract Number: 507

Comparison of Body Mass Index, Anti-Citrullinated Peptides Antibodies Status and Periodontal Condition in First Degree Relatives Individuals to Rheumatoid Arthritis

Sonia Unriza-Puin[1], **Wilson Bautista-Molano**[2,3], Gloria Lafaurie[4], Rafael R. Valle-Oñate[5], Phillipe Chalem[6], Lorena Chila[3], Juan Manuel Bello[7] and Consuelo Romero Sanchez[3,8], [1]Unit of Oral Basic Investigation, School of Dentistry, Universidad El Bosque, Bogota, Colombia, [2]Rheumatology Department School of Medicine HMC / UMNG, Bogotá, Colombia, [3]Unit of Oral Basic Investigation, School of Dentistry, Universidad El Bosque, Bogotá, Colombia, [4]Unit of Oral Basic Investigation-UIBO, School of Dentistry, Universidad El Bosque, Bogotá, Colombia, [5]Rheumatology, Rheumatology Department School of Medicine HMC / UMNG, Bogota, Colombia, [6]Fundación Instituto de Reumatología Fernando Chalem, Bogotá, Colombia, [7]Rheumatology Department School of Medicine HMC / UMNG, Bogota, Colombia, [8]Rheumatology, School of Medicine HMC / UMNG, Bogota, Colombia

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Background/Purpose: Association studies in rheumatoid arthritis (RA) have been focused in the pre-clinical phases of the disease in asymptomatic individuals with higher risk to develop RA such as first-degree relatives (FDR). Previous data has shown that obesity, the anti-citrullinated peptides antibodies (ACPA) status and the periodontal condition may modulate the severity and the clinical presentation of RA. The objective of this study were to investigate the body mass index (BMI), ACPA status, the frequency and severity of periodontal disease and the level of antibodies IgG-1, IGG-2 against *P. gingivalis* in healthy FDR individuals of RA-patients and compare these variables with a control group of healthy individuals from general population.

Methods: In total, 100 FDR individuals and 200 healthy controls paired by age and gender were included. Rheumatologic and periodontal assessment was performed as well as anti-*P gingivalis*antibodies and ACPA. The group-comparisons were analyzed using McNemar and Wilcoxon tests. A conditional logistic regression analyses was performed to establish associations between BMI, ACPA status and periodontitis in FDR individuals and control group.

Results: In the FDR-group, seventy percent were female with a mean age of 37.3±13 years. In the FDR-group 17% had obesity (BMI>30), compared to 7.5% in the control group. Additionally, there was association related to the presence of obesity in the FDR group (OR: 2.9, 95% CI 1.03-8.28). ACPA presence was found in 7% in FDR vs 2.5 % in control group (p=0.038), and was associated in the FDR group (OR: 2.4, 95% CI 0.7- 8.32). In the FDR-group 79% had periodontitis in comparison with control group 56% (p=0.001). Fifty percent of severe periodontitis was observed in FDR vs 9% in control group (p=0.009). A significant association was found in FDR individuals regarding the presence of periodontitis (OR: 3.95% CI 1.89–7.29). Results presented in Table 1. Regarding the presence of antibodies anti *P. gingivalis*(IgG1-IgG2) and smoking history, no differences between groups were found.

Conclusion: Obesity, ACPA expression and periodontitis (diagnosis and severity) can be considered as relevant risk factors associated to the development of RA in individuals FDR. The impact of interdisciplinary management, weight-loss interventions, recommendations on physical activity and screening of periodontal status in asymptomatic individuals at high-risk of developing RA such as FDR, should be further investigated. **Table 1.** Conditional logistic regression model for indicators related to the status of first-degree relatives of patients with RA (Obesity, ACPA, Periodontitis Diagnosis and adjusted Age)

	Unadjusted model		Adjusted model	
	OR	CI 95%	OR	CI 95%
Obesity (BMI≥30)	2.93	1.03 – 8.28	2.37	0.28 - 19.84
ACPA IgG-IgA (≥20 U)	2.45	0.72 – 8.32	11.82	0.07 - 1819.30
Periodontitis	3.70	1.88 – 7.29	7.63	1.07 - 54.30
Age	0.53	0.34 – 0.83	0.53	0.34 – 0.84

Periodontitis based on definition of CDC/AAP. Age = continuous Unadjusted model = includes ACPAs IgG/IgA, periodontitis, obesity and age Adjusted Model = includes ACPAs IgG-IgA, periodontitis, obesity, age and interaction of ACPAs IgG-IgA and Periodontitis with age and obesity

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Disclosure: S. Unriza-Puin, None; **W. Bautista-Molano**, None; **G. Lafaurie**, None; **R. R. Valle-Oñate**, None; **P. Chalem**, None; **L. Chila**, None; **J. M. Bello**, None; **C. Romero Sanchez**, None.

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Abstract Number: 508

Before Clinically Detectable Arthritis Develops, ACPA-Positive and ACPA-Negative Arthralgia Patients Have Different Symptoms

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Background/Purpose: Anti-citrullinated protein antibody (ACPA)-positive and ACPA-negative rheumatoid arthritis (RA) have different genetic risk factors and underlying biological mechanisms. Therefore, we hypothesized that patients' characteristics in the symptomatic phase before clinical arthritis has emerged are also different. We investigated this by studying the arthralgia phase of ACPA-positive and ACPA-negative patients.

Methods: Patients included in a clinically suspect arthralgia (CSA)-cohort were followed for 2 years or until arthritis development. At inclusion, information on initial symptoms and current symptoms was obtained, physical examination and MRI performed and blood samples taken.

Results were compared between ACPA-positive and ACPA-negative CSA-patients that later developed arthritis. Results: 60 patients (25-ACPA-positive, 35 ACPA-negative) included between April 2012 and March 2016 developed arthritis. 80% of ACPA-negative patients experienced morning stiffness as an initial symptom, compared to 52% of ACPA-positive patients (p=0.022). ACPA-positive patients more often had symptoms in both upper and lower extremities than ACPA-negative patients (40% versus 6%, p=0.001). ACPA-positive patients had a longer symptom duration at first presentation (median of 21.3 weeks versus 10.4 weeks, p=0.016) but converted to arthritis quicker (median 5.7 weeks versus 17.9 weeks after inclusion, p=0.015). A combination of variables clustered ACPA-positive and ACPA-negative patients in PLS-analysis.

Conclusion: In the phase preceding clinical arthritis, ACPA-negative and ACPA-positive arthralgia patients have

different characteristics. This contributes to the notion that ACPA-positive and ACPA-negative RA are different disease subsets.

Disclosure: L. E. Burgers, None; **H. W. van Steenbergen**, None; **L. Mangnus**, None; **T. W. Huizinga**, None; **A. H. van der Helm-van Mil**, None.

Abstract Number: 509

Association of Anti-Citrullinated Protein Antibody Positivity and Titer Levels to Low Hand BMD, and the Consequence of Low Hand BMD on DAS28 (CRP) Remission in Established RA: Findings from a US Observational Cohort

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Background/Purpose: Hand bone mineral density (BMD) loss is an independent predictor of radiographic joint progression,[1] and a potential indicator of vertebral and non-vertebral fracture risk.[2] The relationship between hand BMD loss and anti-cyclic citrullinated peptide-2 antibodies (anti-CCP2, a surrogate of anti-citrullinated protein antibodies [ACPA]) in patients (pts) with established RA is unclear. Therefore, we evaluated this association to assess joint progression and fracture risk in pts with established RA.

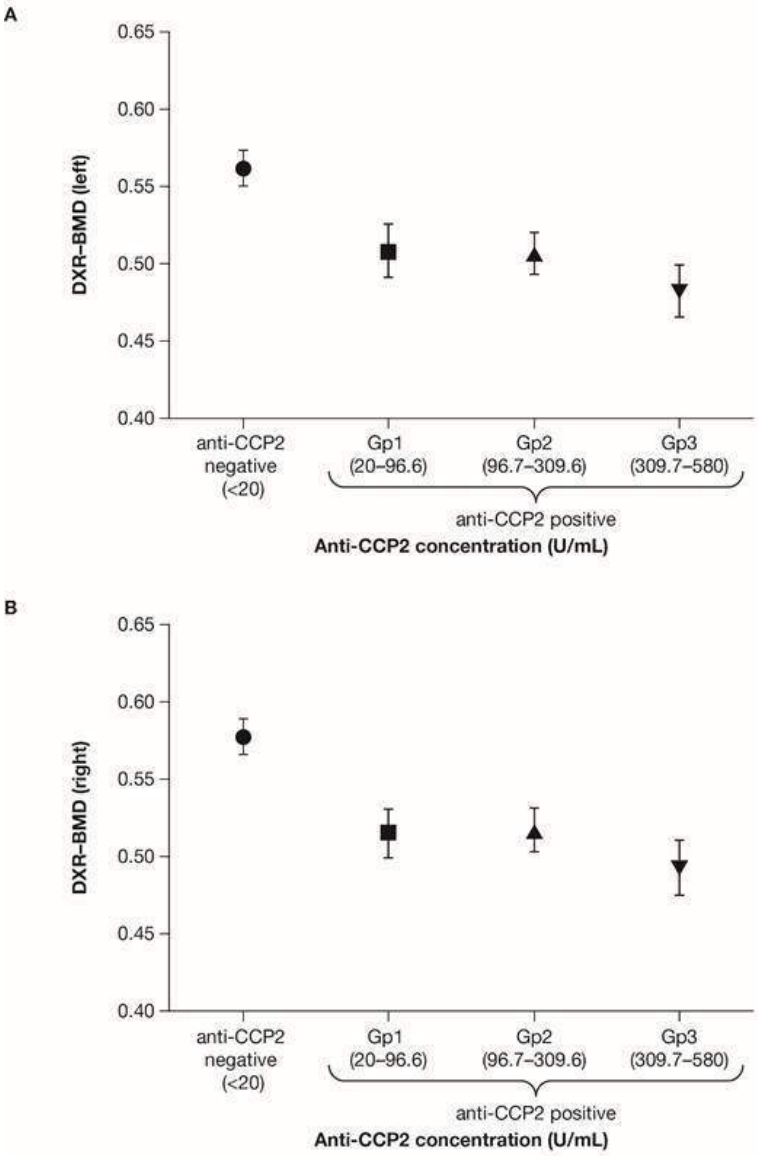
Methods: Pts enrolled in a single academic center, prospective, observational cohort registry of RA patients, established in 2003, were included. The registry comprises mostly pts with established RA; digitized hand radiographs were collected at baseline and every 2–3 yrs (± 3 mths) over 15 yrs from which hand BMD was measured using digital X-ray radiogrammetry (DXR–BMD; methodology: Sectra [Sweden]). The current cross-sectional analysis is based on available data of DXR-BMD and anti-CCP2 measured within 6 months. Anti-CCP2–IgG-positive (+) pts (≥20 U/mL) were distributed into equal groups (Gp1–3), representing increasing anti-CCP2 concentrations. Associations between DXR–BMD and anti-CCP2 status and titers (Gp1–3; categorical variable) were explored in univariate and multivariate regression analyses controlling for covariates (age, RA duration, BMI, smoking status and use of steroids, biologic DMARD, and osteoporosis medication). The association between DAS28 (CRP) remission (<2.6) and bone loss was analyzed in pts with DXR–BMD ≥0.5 and <0.5.

Results: A total of 149 pts (all women) were included (47 anti-CCP2 negative [–], 102 anti-CCP2+ [34 per group]). Age (mean: 60–63 yrs), BMI (mean: 26–29 kg/m^2), DAS28 (CRP; median 3.7–4.2) and biologic DMARD use (43–56%) did not differ by anti-CCP2 status (+/–) or titer group; mean disease duration was greater in the three anti-CCP2+ titer groups versus the anti-CCP2– group (p=0.0215). DXR–BMD was higher in the anti-CCP2– versus the anti-CCP2+ groups (anti-CCP2– vs Gp1–3: p<0.0001 for left and right hand). DXR–BMD decreased with increasing anti-CCP2 titer increase (Figure 1; linear trend p<0.001 for left and right hand). Patients with low DXR–BMD were less likely to be in DAS28 (CRP) remission (DXR–BMD ≥0.5, 36.5% vs DXR–BMD <0.5, 18.8%; p<0.05). Even after controlling for baseline confounding factors, the odds of being in remission were significantly lower for pts with DXR–BMD <0.5 versus ≥0.5

(odds ratio [95% CI], 0.355 [0.126, 0.998]; p=0.0496).

Conclusion: These data suggest that anti-CCP2+ pts with established RA, particularly those with high anti-CCP2 titers, have lower hand BMD and patients with lower hand BMD are less likely to be in remission. Such patients could be at increased risk of joint progression and fracture. 1. Hoff M, et al. *Ann Rheum Dis* 2009;**68**:324–9. 2. Haugeberg G, et al. *Ann Rheum Dis* 2004;**63**:1331–4.

Figure 1. Mean DXR-BMD by anti-CCP2 status and titer group



Number of patients in each titer group: anti-CCP2 negative, N=47; Gp1, N=34; Gp2, N=34; Gp3, N=34
Anti-CCP=anti-cyclic citrullinated peptide

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Abstract Number: 510

C-Reactive Protein and Disease Activity in Rheumatoid Arthritis: Impact of Obesity and Adiposity

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Background/Purpose: C-reactive protein (CRP) is used to assess disease activity in rheumatoid arthritis (RA), and previous work suggests that adiposity also impacts CRP levels. This study assessed associations between BMI and CRP, hypothesizing that increasing levels of obesity are associated with elevations of CRP independent of RA disease activity, paralleling what is seen in the general population.

Methods: Associations between BMI and CRP were assessed in two RA cohorts – 1) a cross-sectional Body Composition (BC) cohort (N = 451) pooled from 3 independent studies from US academic centers that included whole-body DXA measures of fat mass index, and 2) the longitudinal Veterans Affairs Rheumatoid Arthritis (VARA) registry (N = 1652). For comparison, associations were also evaluated in the general population using data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010 (N = 10,813). Linear and logistic regression analyses (defining high CRP as CRP > 1.0 mg/dL and using generalized estimating equations to incorporate repeated measures in VARA) were stratified by sex and adjusted for age, race, and smoking. Sequential models assessed the impact of adjustment for disease activity (swollen/tender joints, patient global score), and fat mass in BC only as this measure was not available for VARA.

Results: In all three cohorts (NHANES, VARA, BC), women in higher BMI categories had significantly higher CRP (all $p < 0.001$; BMI ≥ 35 vs 20-25 kg/m^2) (Figure). This association remained after adjusting for joint counts and patient global scores ($p < 0.001$ in BC; $p < 0.01$ in VARA) but was completely attenuated when adjusted for fat mass in BC. Women with BMI ≥ 35 kg/m^2 were also more likely to have an elevated CRP (Table 1). Again associations remained after adjusting for disease activity (BC: OR 4.05, $p = 0.02$; VARA: OR 2.82, $p = 0.01$), but were attenuated with adjustment for fat mass in the BC cohort (OR 0.99, $p = 1$). Among men, BMI ≥ 35 (vs BMI 20-25 kg/m^2) was not associated with higher CRP in VARA or BC (Figure). In VARA, but not in controls, men with low BMI <20 kg/m^2 had higher CRP and greater odds of an elevated CRP (all $p < 0.01$). In BC, fat mass index was associated with a greater odds of an elevated CRP in women (OR 1.69 per standard deviation, $p < 0.01$) but a lower odds in men (OR 0.60, $p < 0.01$).

Conclusion: Morbid obesity is associated with greater CRP in women with RA, similar to what is seen in the general population. This association is related to fat mass and not RA disease activity, necessitating caution when interpreting CRP among women with a high BMI. Causes of high CRP in low BMI men with RA require further study.

Table: Odds ratios for abnormal CRP > 1mg/dL in patients with rheumatoid arthritis in BC and VARA cohorts

	Women			
	BC Cohort		**VARA**	
	N = 263		**N = 149, obs = 1532**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
BMI <20 kg/m^2	0.57 (0.11, 3.09)	0.52	1.61 (0.58, 4.41)	0.36
20-25 kg/m^2	Reference	-	Reference	-
25-30 kg/m^2	0.85 (0.34, 2.09)	0.72	1.15 (0.59, 2.21)	0.68
30-35 kg/m^2	0.83 (0.30, 2.30)	0.73	1.54 (0.83, 2.88)	0.17
≥ 35 kg/m^2	4.47 (1.72,11.60)	< 0.01	2.72 (1.39, 5.32)	< 0.01
	Men			
	BC Cohort		**VARA**	
	N=188		**N = 1503, Obs = 15013**	
	OR (95% CI)	**p-value**		**p-value**
BMI <20 kg/m^2	1.03 (0.22, 4.75)	0.97	1.35 (1.11, 1.65)	< 0.01
20-25 kg/m^2	Reference	-	Reference	-
25-30 kg/m^2	0.44 (0.17, 1.16)	0.10	0.87 (0.76, 1.01)	0.06
30-35 kg/m^2	0.10 (0.02, 0.49)	< 0.01	0.93 (0.79, 1.11)	0.43
≥ 35 kg/m^2	0.37 (0.09, 1.49)	0.16	1.06 (0.84, 1.33)	0.61

Adjusted for age, race, smoking. BC also adjusted for study site. BMI: body mass index; BC: 3 pooled body composition studies of patients with rheumatoid arthritis; VARA: Veterans Affairs Rheumatoid Arthritis Registry

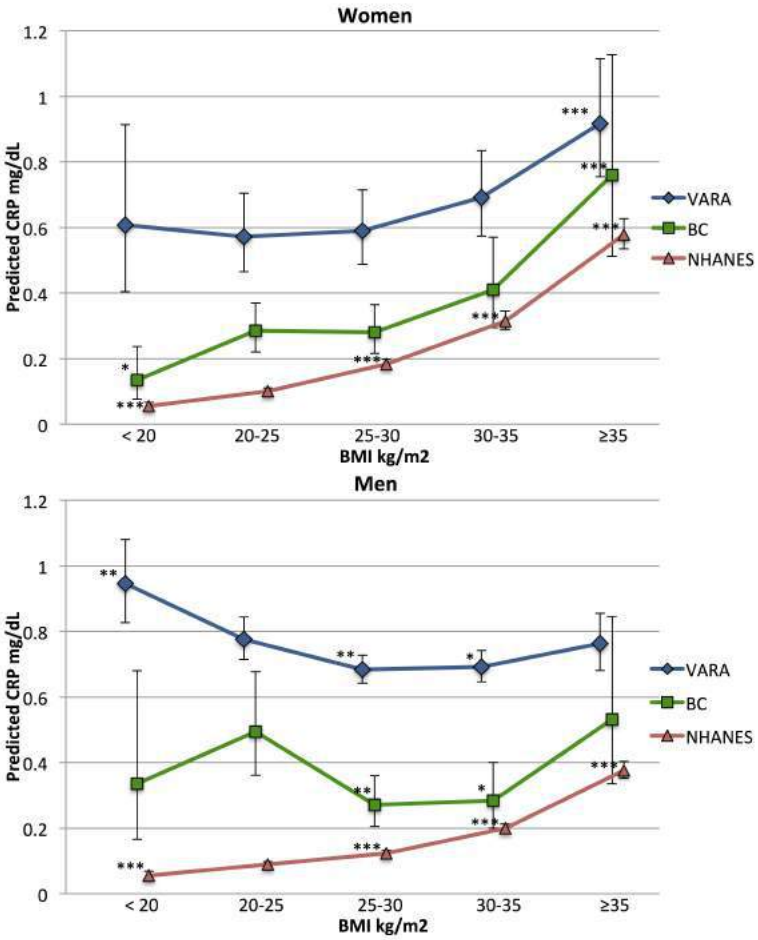

Figure: Predicted CRP in men and women by BMI category in patients with rheumatoid arthritis (VARA and BC) and the general population (NHANES): CRP predicted from linear regression models or GEE models (in VARA) of CRP at the means of age, race, smoking status, study site (in BC). BMI: body mass index; VARA: Veteran's Affairs Rheumatoid Arthritis Registry; BC: 3 pooled body composition studies of rheumatoid arthritis patients. NHANES: National Health and Nutrition Examination Survey 2007-2010. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs reference range BMI 20-25 kg/m2 category within each cohort.

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Abstract Number: 511

Complement C3 and C4 Levels and Its Correlation with Disease Activity in Rheumatoid Arthritis Patients

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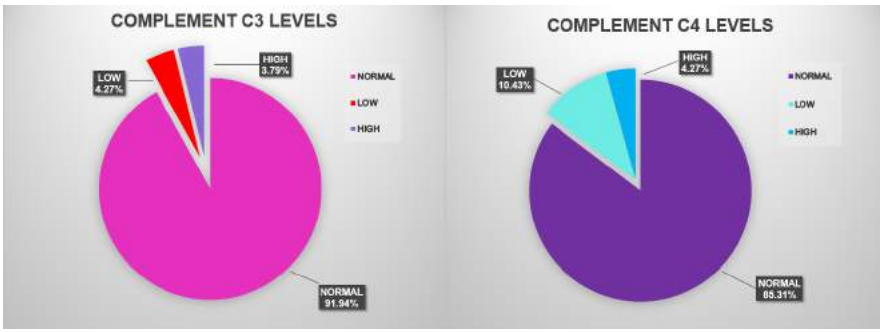
COMPLEMENT C3 AND C4 LEVELS AND ITS CORRELATION WITH DISEASE ACTIVITY IN RHEUMATOID ARTHRITIS PATIENTS

Background/Purpose: Cytokines play a major role in the pathogenesis of Rheumatoid arthritis. However, some studies have also noticed the presence of increased levels of activated products of the complement system, not only in synovial fluid, but also in plasma of these patients, implying that the activation of complement could be another crucial event in the RA inflammatory cascade. Makinde et al. observed that plasma levels of complement C3 and C4 were significantly increased in RA patients when compared to healthy subjects, and they seemed to be correlated with disease activity. The aim of our study was to determine plasma levels of complement C3 and C4 in RA patients and to assess their correlation with disease activity.

Methods: Multicenter, cross-sectional, observational study, that included consecutively RA patients according to 2010 ACR/EULAR criteria. Connective tissue disorders (including secondary Sjögren´s Syndrome) and other conditions that might modify complement levels were excluded. Demographic and RA characteristics, disease activity measures and serological analysis [complement C3 and C4, erythrosedimentation (ESR) and C reactive protein (CRP)] were collected.

Results: Two hundred and eleven patients (98% females) were included. Mean age 50 years (SD 14.7). Fifty-nine percent were under treatment with NSAIDs, 61% with Corticosteroids, 77% with DMARDs (most of them with Methotrexate) and 20.6% patients were on biologic therapy. Mean DAS28 score was 4.29 (SD 1.55). The median ESR and CRP were 46 mm/h (IQR 12-40) and 1.1 mg/dl (IQR 0.3-3.8), respectively. *Complement levels were mostly normal: C3 in 194 patients (92%) and C4 in 180 patients (85%). There was no correlation between DAS28 score and C3 (p*=0.79) or C4 (*p*=0.07) levels. Patients with increased levels of C4 showed a median PCR higher than patients with low C4 levels (1,95 mg/dl versus 0,40 mg/dl, *p*=0,039). This association was not observed with C3 levels. There was no correlation between complement and ESR. DMARs and/or biologic therapy didn´t modify C3 or C4 levels. However, we observed an association between the use of Corticosteroids and C4 levels (*p= 0,003*): patients on Corticosteroid therapy showed a higher proportion of low C4 levels than those without Corticosteroids (13% versus 6%).

Conclusion: Despite the literature findings, most of our RA patients had complement levels within normal ranges. Plasma levels of complement C3 and C4 did not correlate with disease activity. We emphasize the association between RCP and C4 as well as a higher proportion of low C4 levels in patients treated with corticosteroids.



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Abstract Number: 512

Anti-Cyclic Citrullinated Protein Antibody (ACPA) Positivity in General Population and Follow-up Results for ACPA Positive Persons

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Background/Purpose: To evaluate anti-cyclic citrullinated protein antibody positivity in the general population and to identify its prognosis.

Methods: Anti-cyclic citrullinated protein antibody (ACPA) were measured with immunochromatographic test in 3607 people who visited for routine annual medical check-up from November 2014 to March 2016. Four people with history of rheumatic diseases except for rheumatoid arthritis (RA) were excluded from analysis. For ACPA positive persons, consultation to rheumatology was recommended. They were examined ACPA with CLEIA method, anti-nuclear antibody test, and anti SS-A antibody test. Also rheumatologist performed detail physical examination. The classification criteria of 2010 ACR/EULAR were used for diagnosis of RA. Asymptomatic examinees with ACPA positive were recommended to visit every 6 months. Symptomatic examinees that did not fulfill classification criteria even if they have morning stiffness or joint pain were recommended to visit every 3 months. While follow-up period, an examinee that fulfills classification criteria was prescribed DMARDs in accordance with guidelines.

Results: ACPA positivity with immunochromatographic test was identified in 1.0% (n=37) of examinees. 51.4% were woman. There were no correlations between ACPA positivity and smoking, drinking, BMI, and history of cancer. Among ACPA positive examinees, 64%(n=24) consulted to rheumatology department. They were confirmed ACPA positivity with CLEIA method. 58.3% (n=14) were CLEIA method positive. 57.1% were woman. 4 examinees have already diagnosed as RA and 5 examinees have morning stiffness or joint pain, which did not fulfill classification criteria. Mean follow-up period of ACPA positive examinees with CLEIA and immunochromatographic method was 10.5 month. One of 5

symptomatic patients developed RA and she reached remission after 2 months after starting methotrexate.

Conclusion: Positivity of ACPA in general population was 1%. Regular follow-up of ACPA positive patients could lead prompt diagnosis and treatment.

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Abstract Number: 513

Low Serum 25-Hydroxyvitamin D Level Is Not Associated with Decreased Bone Mass or Bone Quality in Patients with Rheumatoid Arthritis

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Background/Purpose: Vitamin D deficiency in patients with rheumatoid arthritis (RA) is commonly observed. Previous studies have investigated the relationship between vitamin D deficiency and RA and increased risk of cardiovascular events and the role of immunomodulation. While RA is recognized as a risk factor for osteoporosis, there are few reports examining the relationship between vitamin D level and bone mass or metabolism markers in RA patients compared with healthy controls. To examine the relationship between serum 25-hydroxyvitamin D (25(OH)D) level, bone mineral density, and bone metabolic markers of RA patients compared with age-and sex-matched healthy volunteers (Vo group) using a cross-sectional method.

Methods: In 2010, we began a prospective cohort study called the TOMORROW Study (UMIN000003876) which compares data from RA patients with age- and sex-matched controls (Vo) recruited through mass media. Laboratory data were collected for all participants, including 25(OH)D level, insulin resistance, bone metabolic markers (urinary pentosidine, homocysteine, collagen type 1 cross-linked N-telopeptide (NTX), and osteocalcin), and anthropometric parameters. Bone mineral density of the lower extremities and body composition were determined using whole-body dual-energy X-ray absorptiometry (DXA). The parameters were compared with healthy controls, and multiple regression analysis was carried out in the RA population only. In RA patients, disease activity score 28 was measured by clinical assessment.

Results: There were 413 participants (208 RA patients, 205 Vo group; 349 females; mean age of 58 years) enrolled in the study. In RA patients (mean disease duration of 13 years), bone density was significantly lower ($p<0.01$; Student's *t*-test), and urinary NTX ($p<0.01$), pentosidine ($p<0.01$), and homocysteine ($p<0.05$) were higher compared with the Vo group. The serum 25(OH)D level was lower in RA patients compared with the Vo group ($p<0.01$) (Table). Multiple linear regression analysis in the RA population revealed no significant relationship between DXA and vitamin D level ($p=0.18$) or pentosidine ($p=0.61$).

Conclusion: No relationship was found between low vitamin D level and decreased bone mass or bone quality in RA patients.

Table: Differences between RA patients and healthy controls (Vo)

(Student's *t*-test)

variables	Vo (n=205)	RA (n=208)	P -value
HbA1c	5.1	5.2	0.37
HOMA-R	1.06	1.25↑	0.03
Serum 25(OH)D (ng/dL)	21.6	18.5↓	<0.001
DXA (g/cm^2)	1.03	0.97↓	<0.001
Urinary NTX (nM/mM・Cr)	44.3	59.0↑	<0.001
Osteocalcin (ng/mL)	7.3	7.2	0.81
Urinary pentosidine (pmol/mg Cr)	54.1	72.6↑	<0.001
Homocysteine (nmol/mL)	9.1	10.9↑	<0.001

Disclosure: K. Inui, None; **T. Koike**, None; **Y. Sugioka**, None; **T. Okano**, None; **K. Mamoto**, None; **M. Tada**, None; **H. Nakamura**, None.

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Abstract Number: 514

Gender Difference Is Apparent in the Risk of Forefoot Deformity in Patients with Rheumatoid Arthritis

Kentaro Inui[1], Tatsuya Koike[2], Tadashi Okano[1], Kenji Mamoto[3], Kazuki Orita[1], Yuko Sugioka[4], Masahiro Tada[5], Hiroaki Nakamura[3] and Orita incl, [1]Orthopaedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Center for Senile Degenerative Disorders, Osaka City University Medical School, Osaka, Japan, [3]Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [4]Center for Senile Degenerative Disorders (CSDD), Osaka City University Medical School, Osaka, Japan, [5]Orthopedic Surgery, Osaka City General Hospital, Osaka, Japan

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Background/Purpose: Forefoot involvement in patients with rheumatoid arthritis (RA) is common, and reported to be present in 50–90% of patients without any clear gender predisposition. However, patients with RA that undergo surgical treatment for their forefoot deformities are mostly female, which seems much higher rate than the prevalence of forefoot involvement by arthritis condition. In this study we evaluate the factors that contribute to forefoot deformity in RA, and investigate the significance of gender differences in forefoot deformity.

Methods: In this cross sectional study, 265 patients (530 feet) with RA (165 females) were enrolled. On AP and lateral standing radiographs of the foot, the angle formed by the first and second (M1/M2) and first and fifth metatarsal bones (M1/M5), the angle formed by the first metatarsal bone and the first proximal phalanx (HV), and the calcaneal pitch angle (CPA) were measured. Patient characteristics and laboratory tests were also analyzed for their potential association with forefoot deformity. As the indications for the surgical treatment of rheumatoid forefoot deformities are strongly influenced by the severity of the hallux valgus deformity, we therefore analyzed patient factors in relation to the measured HV angle.

Results: The HV angle was statistically greater in female RA patients than males. Patient age, sex, body mass index, disease duration, Steinbrocker staging, M1/M2 angle, M1/M5 angle, CPA, erythrocyte sedimentation rate, c-reactive protein, matrix metalloproteinase-3, and anti-citrullinated protein antibody measurements were correlated with the HV angle using a single regression analysis. Patient age, BMI, Steinbrocker stage, M1/M2 angle, M1/M5 angle, and the female gender were correlated independently with the HV angle.

Conclusion: The hallux valgus deformity observed in patients with RA was more severe in females, which was independent of other patient factors. This finding emphasizes that the female gender is a risk factor for the progression of the rheumatoid forefoot deformity.

	regression coefficient（β）	Standard Error	P value	Variance Inflation factor
Gender	**-3.175**	**1.295**	**<0.0001**	**1.12**
M1/M2	**1.538**	**0.171**	**<0.0001**	**1.48**
M1/M5	**0.458**	**0.118**	**0.0001**	**1.53**
stage	**2.942**	**0.437**	**<0.0001**	**1.56**

Disclosure: K. Inui, None; **T. Koike**, None; **T. Okano**, None; **K. Mamoto**, None; **K. Orita**, None; **Y. Sugioka**, None; **M. Tada**, None; **H. Nakamura**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/gender-difference-is-apparent-in-the-risk-of-forefoot-deformity-in-patients-with-rheumatoid-arthritis

Abstract Number: 515

The Association of Body Mass Index with the Severity of Magnetic Resonance Imaging-Detected Inflammation at Presentation; Opposite Effects in Early Rheumatoid Arthritis Compared to Other Arthritides and an Asymptomatic Population

L. Mangnus[1], W.P. Nieuwenhuis[2], H.W. van Steenbergen[2], T.W.J. Huizinga[3], M. Reijnierse[4] and A.H.M. van der Helm-van Mil[2], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [4]Radiology, Leiden University Medical Center, Leiden, Netherlands

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Rheumatoid Arthritis – Clinical Aspects - Poster I: Clinical Characteristics/Presentation/Prognosis

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: An increased body mass index (BMI) has been associated with slightly increased inflammatory

markers in the population. Within rheumatoid arthritis (RA) a high BMI has been associated with less radiographic progression; this phenomenon is unexplained. We explored the hypothesis that the association between BMI and inflammation detected with MRI is different in directionality in RA compared to patients with other arthritides and asymptomatic volunteers.

Methods: We studied 195 RA patients and 159 patients with other inflammatory arthritides at inclusion in the Leiden Early Arthritis Clinic cohort and 193 asymptomatic volunteers from the general population. All participants underwent a unilateral contrast-enhanced 1.5T MRI of MCP, wrist and MTP-joints. Each MRI was scored by two readers on synovitis, BME and tenosynovitis; the sum of these yielded the total MRI-inflammation score. Linear regression models were used.

Results: A higher BMI was associated with higher MRI-inflammation scores in arthritides other than RA (β=1.082, $p<0.001$) and asymptomatic volunteers (β=1.029, p=0.040), whereas it was associated with lower MRI-inflammation scores in RA (β=0.969, p=0.005). Evaluating the different types of inflammation separately showed that a higher BMI was associated with higher synovitis, BME and tenosynovitis-scores in arthritides other than RA (respectively β=1.084, $p<0.001$, β=1.021, p=0.24 and β=1.054, p=0.003), but with lower synovitis and BME scores in RA (respectively β=0.976, p=0.047 and β=0.954, p=0.002).

Conclusion: BMI is correlated with less severe MRI detected inflammation (synovitis and BME) in RA. This might explain the previous finding that BMI is correlated with less severe radiographic progression in RA.

Disclosure: L. Mangnus, None; **W. P. Nieuwenhuis**, None; **H. W. van Steenbergen**, None; **T. W. J. Huizinga**, None; **M. Reijnierse**, None; **A. H. M. van der Helm-van Mil**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-association-of-body-mass-index-with-the-severity-of-magnetic-resonance-imaging-detected-inflammation-at-presentation-opposite-effects-in-early-rheumatoid-arthritis-compared-to-other-arthrit

Abstract Number: 516

Development of RA Patient Preference Phenotypes

Liana Fraenkel[1,2], Carole Wiedmeyer[3], Gayathri Herath[2], George Michel[4] and Ben Nowell[3], [1]Medicine, Yale University School of Medicine, New Haven, CT, [2]Yale University School of Medicine, New Haven, CT, [3]CreakyJoints/Global Health Living Foundation, Upper Nyack, NY, [4]Yale University, New Haven, CT

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Session Time: 9:00AM-11:00AM

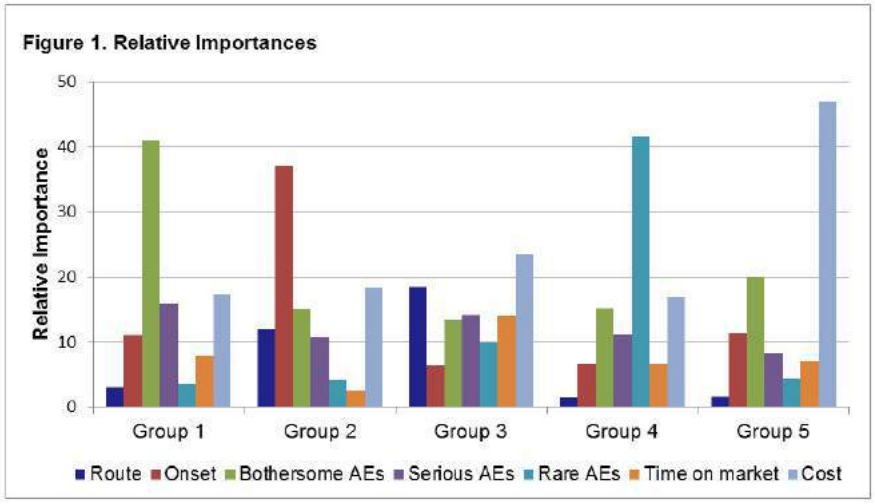
Background/Purpose: Many important treatment decisions for patients with RA are conditional on patient preferences and according to the Institute of Medicine mandate a shared decision making approach (SDM). Furthermore, SDM is being increasingly recognized as an important quality measure. One of the most common preference sensitive decisions in RA is how to escalate care when response to methotrexate monotherapy is inadequate. However, because of the number medications currently approved, asking patients to deliberate over the pros and cons related to each of these options in order to develop a preference, is extremely difficult. The objective of this study was to develop representative patient preference phenotypes to enable patient-physician dyads to effectively incorporate patient preferences at the point-of-care.

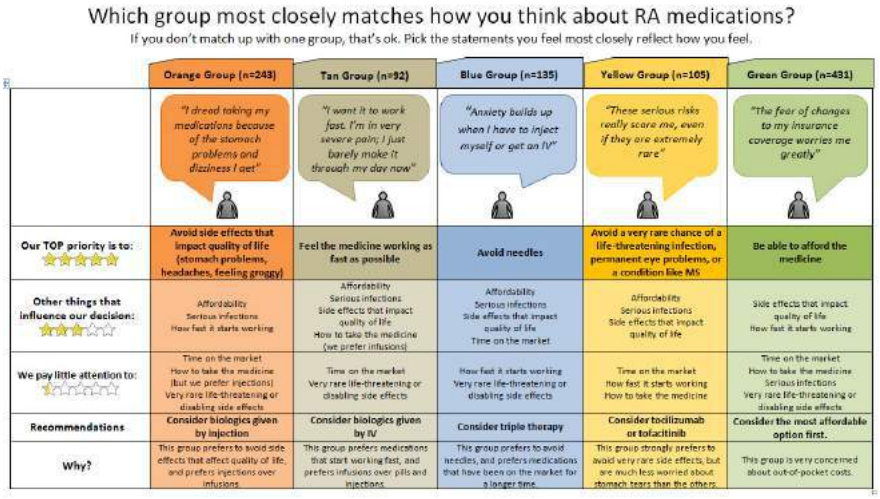
Methods: Persons with RA were invited to complete a Choice-Based Conjoint analysis survey including seven attributes (route of administration, time to onset of action, bothersome adverse events (AEs), serious AEs, extremely rare AEs, duration of time on the market and affordability) developed iteratively based on patient feedback. Each attribute was

described across three or four levels using plain language. Preference phenotypes were identified by applying latent class analysis to the conjoint data. Class solutions were replicated five times from random starting seeds. A five-group solution was chosen based on Akaike's information criterion. We calculated the percentage of importance assigned to each attribute and performed simulations to estimate preferences for triple therapy, SC and IV biologics, or tofacitinib.

Results: 1100 subjects completed the survey. Of these 49 were eliminated because they completed the survey in less than 10 minutes and an additional 45 people were excluded because they did not respond correctly to a dominant choice task. The mean age was 51.7 (11.2). The majority were female; (92%) and Caucasian (93%). Preferences (assuming low cost across options), and the reasons underlying each respondent's preference, clustered into five groups (Figure 1). There were no differences in the distribution of demographic or clinical characteristics across the five groups. Phenotypes were created based on the stated preference data (Figure 2).

Conclusion: RA patients' preferences vary and can be classified into distinct phenotypes. Ongoing research is evaluating whether enabling patients to identify with a preference phenotype facilitates SDM at the point-of-care.





Disclosure: L. Fraenkel, None; **C. Wiedmeyer**, None; **G. Herath**, None; **G. Michel**, None; **B. Nowell**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/development-of-ra-patient-preference-phenotypes

Abstract Number: 517

Association of Rheumatoid Arthritis Disease Activity and Clinical Profile

with Chronic Periodontitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Recent clinical data show a clear association between periodontitis (P) and RA. However, there is controversy over whether severity of P is associated with RA activity. Some studies have shown no association or even a negative association and only a study (Mikuls 2014) found a positive association between severity of P and RA activity. 1.To determine whether severity of P affects clinical expression and activity of RA. 2. To define characteristics of P in RA patients with high clinical activity.

Methods: Observational, cross-sectional, case-control study adult RA patients (ACR/EULAR 2010) in a hospital Rheumatology Department,with at least 4 teeth, no dental prophylaxis or antibiotic intake 6 months before. Socio-demographic/ anthropometric variables:smoking status, Graffar scale, annual dental prophylaxis and stress level. RA variables: DAS28 (ESR) DAS28 (CRP),SDAI, RF/ACPA titles, extra-articular manifestations and comorbidities such as osteoporosis (OP), diabetes mellitus (DM), dyslipidemia (DS); glucocorticoids (GC),synthetic and biological therapy (DMARDs/DMARDb). Periodontal variables: plaque index (PI), bleeding on probing (BoP), probing pocket depth (PPD), recession (REC), clinical attachment level (CAL). Dental team: 2 periodontists, 2 general dentists. Full mouth CAL PPD and periapical x-rays were taken. CAL was classified according to the European Workshop 2005 (Tonetti), into level 0 (absence), TL1 (mild), TL2 (severe).Statistical analysis (Stata 13.1) using Student´s t test , Kruskal Wallis and Chi-square test.

Results: We included 187 RA patients, F/M 78.6/21.4%,mean age 54.4 (SD 10.8) y, mean follow-up of 8.8 y, 18.72% had early RA. Positive RF/ACPA:74.9/67.8%. Mean clinical activity: DAS 28 (ESR) 3.81/ DAS 28 (CRP) 3.18/ SDAI 14.49, HAQ 0.76 (0.62). Disease activity: remission 20.86%, low activity 24.06%, moderate activity 45.45%, high activity 9.63%. Treatment: 47.06% received GC (mean daily prednisone 2.85 mg/dl); DMARDs monotherapy/combined 53%/11.76%, DMARDb 30%. Smoking status: current 19,25%/ former 24.6%; low socioeconomic status 36.36% (relative poverty 33.69%); annual dental prophylaxis 43%; dyslipidemia 53.47%, OP 55.86%. Regarding periodontal status,TL2 P in 69. 05% of patients with moderate/high activity vs 30.95% in patients with remission/low activity; 55.34% patients with TL1 P showed RA remission /low activity ($p<0.001$). A strong association was found between severe P and moderate/high RA activity, with an OR 57.65 + 37.40 (CI 95% 16.16- 205.62). Patients with moderate/high RA activity presented increased values of all periodontal parameters compared to low activity ($p<0.005$). We observed association between rheumatoid nodes, pleuritis and OP with severe P ($p =0.028$).

Conclusion: 1.High-activity RA is associated with severe P. 2. Patients with moderate/high activity RA have higher prevalence of both number and percentage of probing pocket depth ≥ 5mm. 3. Presence of rheumatoid nodes and osteoporosis are related to severe P. 4.These results suggest an independent relationship between severe P and RA with high clinical disease activity regardless of classical factors associated with P.

Abstract Number: 518

Contribution of Patient Global Assessment on Loss and Gain of Disease Remission in Patients with Established Rheumatoid Arthritis in Clinical Practice

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Patient global assessment (PGA) is part of the remission definitions in Rheumatoid arthritis (RA). We explored the proportion of patients who fail to achieve various remission definitions due to PGA ratings, and further assessed change in remission status attributed to PGA change at follow-up 12 months later.

Methods: We evaluated 271 patients with established RA in a single academic center. Remission definitions included DAS28 (disease activity score-28 joints)<2.6, CDAI (clinical disease activity index)=<2.8, SDAI (simplified disease activity index) =<3.3, and Boolean [tender joints=<1, swollen joints=<1, CRP (c-reactive protein) =<1, and PGA=<1]. Tentative remissions were computed for each scale by omitting the PGA component while retaining the same numeric threshold for definition. Subtracting observed remissions (R) from tentative ones yielded numbers of remissions lost (RL) due to PGA. Non-remissions (NR), observed remissions (R) and lost remissions (RL) at baseline and follow-up were cross-tabulated for each composite index. Differences in proportions of RL among various scales were compared with chi-squared tests, and PGA differences between R and RL for each scale were assessed with Mann-Whitney U tests.

Results: At baseline, tentative remissions were seen in 121 (44.6%), 105 (38.8%), 108 (39.9%), and 90 (33.2%) subjects respectively for DAS28, CDAI, SDAI and Boolean scales. RL comprised 17%, 52%, 57%, and 72% of the tentative ones for the respective scales (figure 1A). PGA was significantly lower for observed R vs. RL for all scales (figure 1B, p<0.0001). Baseline remission was maintained for the majority of patients at follow-up (table 1); of the remainder, roughly half were lost due to PGA change. Of patients with NR at baseline, 5-27% depending on scale remitted at follow-up, while 5-20% failed to do so because of PGA.

Conclusion: A significant proportion of patients with clinical measurements suggesting otherwise good disease control fail to be classified as or retain remission because of PGA ratings. Exploring and therapeutically addressing determinants of PGA will likely improve patient satisfaction and outcomes and lead to a more comprehensive disease remission.

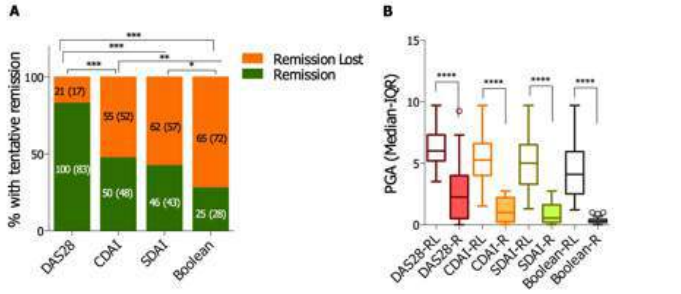

Figure 1: A. Proportion of tentative remissions lost due to PGA at baseline. **B.** PGA magnitude in patients achieving remission vs. those who loose remission due to PGA. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001

Table 1: Cross-tabulation of disease severity at baseline and follow-up

		Follow-up status, n (%)		
Baseline status	Scale	Remission (R)	Remission Lost (RL)	Non-Remission
Remission (R)	DAS28	71 (71)	11 (11)	18 (18)
	CDAI	33 (66)	9 (18)	8 (16)
	SDAI	32 (69.6)	7 (15.2)	7 (15.2)
	Boolean	15 (60)	5 (20)	5 (20)
Remission Lost (RL)	DAS28	8 (38)	2 (9.5)	11 (52.4)
	CDAI	8 (14.5)	23 (41.8)	24 (43.6)
	SDAI	10 (16.1)	27 (43.5)	25 (40.3)
	Boolean	8 (12.3)	36 (55.4)	21 (32.3)
Non-Remission (NR)	DAS28	41 (27.3)	8 (5.3)	101 (67.3)
	CDAI	21 (12.7)	26 (15.7)	119 (71.7)
	SDAI	18 (11)	31 (19)	114 (69.9)
	Boolean	9 (5)	37 (20.4)	135 (74.6)

Disclosure: G. A. Karpouzas, None; **E. Hernandez**, None; **C. Cost**, None; **S. Ormseth**, None.

Abstract Number: 519

Greater Fatigue at Baseline and Female Gender Predict Worse Disability in Early RA Despite Treatment to Target: A Comparison of Two Observational Cohort Studies from the United Kingdom

Sarah Twigg[1], Elizabeth M.A. Hensor[2], Jane E. Freeston[1], Ai Lyn Tan[1], Alan Tennant[3], Paul Emery[4], Ann Morgan[5] and YEAR consortium, IACON consortium , [1]NIHR Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [2]NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [3]Swiss Paraplegic Research,, Nottwil, Switzerland, [4]NIHR Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, University of Leeds, Leeds, United Kingdom, [5]NIHR-Leeds Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Although disability is part of the ‘core set’ of outcomes for RA research recommended by OMERACT (1), current therapeutic strategies focus on inflammation. The treat to target approach instigated in 2010 (2) saw a step-change in RA management, with frequent clinical review to achieve remission or low disease activity. The aim of this study was to compare disease activity (DAS28) and disability (measured by HAQ) in 2 early RA cohorts, both before and after the implementation of treat to target approaches.

Methods: Cases with recent onset RA recruited to Yorkshire Early Arthritis Register (YEAR) between 2002 and 2009 were treated with a ‘step-up’ approach, using synthetic DMARDs. Of 725 cases included, 585 met 1987 ACR RA classification criteria and a further 115 met 2010 criteria. A second cohort, IACON (INflammatory Arthritis CONtinuum),

recruited patients with early inflammatory arthritis between 2010 and 2014, treated according to 'treat to target' principles including biologic therapies. Data from 384 patients meeting 2010 ACR/EULAR classification were applied to the present study. Latent growth curve models of change in DAS28 and HAQ were compared between YEAR and IACON. Latent class growth analysis identified latent trajectories of change in HAQ-DI and logistic regression tested baseline predictors of HAQ trajectory, including age, gender, BMI, smoking status, CCP (RF considered separately) and fatigue. Presence of one or more common comorbidities was considered for the IACON group.

Results: Mean baseline DAS28 and HAQ were lower in IACON than YEAR (DAS28 4.01 vs. 4.70 and HAQ 1.13 vs. 1.27 in IACON and YEAR, respectively). A greater proportion of overall fall in DAS28 was achieved after 6 months in IACON (84%) than YEAR (68%). There were three latent trajectories of change in HAQ in YEAR and two in IACON (Figure 1). The 'high stable' group was not seen in IACON, possibly reflecting the more favourable change in DAS28 observed in this group. However, 66% of IACON cases followed a 'moderate reducing' HAQ trajectory, similar to the corresponding trajectory in YEAR. In both cohorts, female gender and higher baseline fatigue visual analogue score (VAS) predicted adverse HAQ trajectory. Odds ratios (OR) for moderate reducing compared to low reducing groups for females were 2.58 (95% confidence interval 1.69, 4.49) in YEAR and 5.81 (2.44, 14.29) in IACON. Corresponding OR per cm fatigue were 1.13 (1.07, 1.20) in YEAR and 1.16 (1.12-1.20) in IACON.

Conclusion: More favourable trajectories of change in DAS28 and HAQ were seen in the Treat to Target group, but females and those with greater fatigue were more likely to fit into an adverse HAQ trajectory, suggesting that such patients may benefit from interventions to improve function as well as reduce inflammation. **References**

1. Boers, M., *et al*. 1994. J Rheumatol Suppl, 41, 86.
2. Smolen JS, *et al*. Ann Rheum Dis 2010;69(4):631.

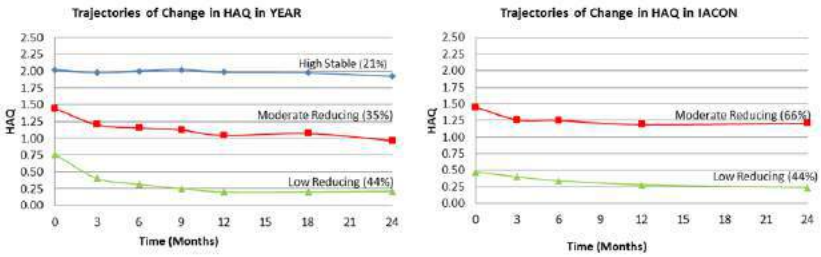

Figure 1. Trajectories of change in HAQ in YEAR and IACON cohorts
HAQ, Health Assessment Questionnaire; IACON, Inflammatory Arthritis disease CONtinuum; YEAR, Yorkshire Early Arthritis Register. Numbers in brackets represent percentage of cohort categorised into trajectory.

Disclosure: S. Twigg, None; **E. M. A. Hensor**, None; **J. E. Freeston**, None; **A. L. Tan**, None; **A. Tennant**, None; **P. Emery**, None; **A. Morgan**, None.

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Abstract Number: 520

The HAQ Reversible and Irreversible Components Measuring Function in Rheumatoid Arthritis

Mary Bell[1], Jacqueline Stewart[2], Boulos Haraoui[3], Edward Keystone[4], Philip Baer[5], Pauline Boulos[6], Dalton Sholter[7], Algis Jovaisas[8], Emmanouil Rampakakis[9], Julie Vaillancourt[10], Cathy Tkaczyk[11], Karina Maslova[12], Brendan Osborne[11], Allen J Lehman[12] and Francois Nantel[13], [1]University of Toronto, Toronto, ON, Canada, [2]Penticton Regional Hospital, Penticton, BC, Canada, [3]University of Montreal, Montreal, QC, Canada, [4]Mt. Sinai Hospital, University of

Toronto, Toronto, ON, Canada, [5]Independent Rheumatology Practice, Scarborough, ON, Canada, [6]Rheumatology, McMaster University, Hamilton, ON, Canada, [7]University of Alberta, Edmonton, AB, Canada, [8]Capital North Therapeutics & Research, Ottawa, ON, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]JSS Medical Research, Montreal, QC, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [12]Janssen Inc., Toronto, ON, Canada, [13]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada
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SESSION INFORMATION

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) functional impairment is composed of reversible and irreversible components. The aim of this analysis was to assess the reversible and irreversible components of RA physical function as measured by the Health Assessment Questionnaire (HAQ) in Canadian routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment with IFX or GLM for RA, ankylosing spondylitis, or psoriatic arthritis. Eligible participants for this analysis included RA patients treated with IFX enrolled since 2002 or with GLM enrolled since 2010, who had a HAQ >0 at baseline and at least one follow-up assessment with known HAQ score at remission or achievement of low disease activity (LDA). Remission was defined as SDAI ≤3.3, CDAI≤2.8, DAS28 <2.6, or achievement of the following four criteria: SJC ≤1, TJC ≤3, CRP level ≤0.8 mg/dL and MdGA ≤15mm. Low disease activity was defined as SDAI ≤11.0, CDAI ≤10.0 or DAS28 ≤3.2. HAQ scores at the time of RA remission or achievement of LDA represented the irreversible component of the disease functional limitation, namely the residual HAQ score, while the difference in HAQ scores from baseline to remission or LDA corresponded to the reversible component. In addition, the reversibility of HAQ score was determined as the relative improvement in baseline HAQ score at the time of remission or achievement of LDA and, the fraction of HAQ irreversibility was calculated as the residual HAQ score divided by the maximum possible HAQ score. Descriptive statistics were produced for HAQ reversible and irreversible parameters. The correlation of disease duration with the HAQ irreversible component was described with the Pearson's correlation coefficient. Multivariate linear regressions adjusted for age, gender, anti-TNF, baseline disease duration and HAQ score at baseline were performed to assess the impact of the type of coverage (private and public) on reversible and irreversible components of the disease. Level of statistical significance was set to 0.05.

Results: There were 753 patients included in this analysis (499 patients were on IFX and 254 on GLM) with a mean (SD) age of 56.4 (13.4) years, disease duration since diagnosis of 8.7 (9.3) years and HAQ score of 1.5 (0.7) at treatment initiation. The majority of patients were females (74.8%). At treatment initiation, 356 (47.8%) and 289 (38.8%) patients were on public and private drug coverage, respectively. The HAQ reversible and irreversible components in RA are presented in Table 1. Variation in the reversibility of HAQ score was observed among RA patients depending on the target outcome used for the calculation, with 44.8% reversibility reported based on DAS28 remission to 57.6% with SDAI remission and, from 33.1% based on CDAI-LDA to 36.4% with SDAI-LDA. Weak correlations between disease duration and HAQ irreversible component were observed for all the target outcomes with Pearson's coefficients varying from 0.105 based on derived definition of remission to 0.270 with CDAI remission and, from 0.119 based on SDAI-LDA to 0.202 with DAS28-LDA. Upon adjustment for age, gender, anti-TNF agent, baseline disease duration, and HAQ score at baseline, patients on private insurance were found to have significantly greater HAQ reversibility when assessed with SDAI remission (β= -27.39; P=0.029) and derived definition of remission (β= -17.94; P=0.036) than patients on public coverage. Coverage type was not found to have an impact the fraction of HAQ irreversibility and the irreversible component. **Table 1:**HAQ Reversible and Irreversible Components in Rheumatoid Arthritis.

Target Outcomes	N	Months from BL to Target, Mean (SD)	Change in HAQ score from BL to Target (Reversible component), mean (SD)	% Reversibility of BL HAQ score, mean (SD)	Residual HAQ score (Irreversible component), mean (SD)	Fraction of HAQ Irreversibility, mean (SD)
DAS28 remission	426	13.56 (13.24)	-0.67 (0.68)	-44.78 (45.59)	0.76 (0.67)	0.25 (0.22)
DAS28 low disease activity	573	10.73 (11.22)	-0.58 (0.67)	-34.97 (54.00)	0.86 (0.67)	0.29 (0.22)
CDAI remission	306	17.51 (14.00)	-0.84 (0.69)	-54.69 (53.03)	0.57 (0.56)	0.19 (0.19)
CDAI low disease activity	699	9.65 (9.27)	-0.55 (0.63)	-33.09 (52.32)	0.94 (0.70)	0.31 (0.23)
SDAI remission	266	17.14 (14.25)	-0.89 (0.70)	-57.56 (50.83)	0.57 (0.57)	0.19 (0.19)
SDAI low disease activity	594	10.90 (10.59)	-0.60 (0.65)	-36.39 (54.08)	0.89 (0.69)	0.30 (0.23)
Derived definition of remission	479	13.11 (12.25)	-0.60 (0.67)	-37.72 (53.41)	0.88 (0.71)	0.29 (0.24)

Conclusion: The results of this Canadian longitudinal observational study show variability in the proportions of reversibility and suggest that patients on private insurance at treatment initiation have a greater reversibility of RA functional impairment than patients on provincial coverage. However, the type of coverage did not have an impact on irreversible components of the disease.

Disclosure: M. Bell, Paid Consultant of Janssen Inc., Canada, 5; **J. Stewart**, Janssen Inc., 5; **B. Haraoui**, Janssen Inc., 5; **E. Keystone**, Abbott, AstraZeneca, Biotest, BMS, Crescendo, Hoffmann-LaRoche, Genentech, Janssen Inc, Eli Lilly and Company, Merck, Pfizer, UCB, 5; **P. Baer**, Janssen Inc., 5; **P. Boulos**, Janssen Inc., 5; **D. Sholter**, Janssen Inc., 5; **A. Jovaisas**, Janssen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **J. Vaillancourt**, JSS Research, 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3.

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Abstract Number: 521

Subcutaneous Adipose Tissue from Rheumatoid Arthritis Patients Is Characterized By an Abundance of Macrophages That Are Associated with Autoantibodies, Systemic Inflammation, and Immunomodulation

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Background/Purpose: Adipose tissue macrophages (ATMs) are a potent source of inflammatory cytokines with profound effects on adipose tissue function and systemic inflammation, yet their potential role in rheumatoid arthritis (RA) pathobiology is unstudied.

Methods: Periumbilical subcutaneous adipose tissue was obtained from 36 RA patients and 22 non-RA controls frequency matched on demographics and body mass index (BMI). Individuals with diabetes were excluded. Samples were stained for the macrophage marker CD68 and the average proportion of ATMs relative to total nucleated cells was compared between groups. Using real time polymerase chain reaction (RT-PCR), gene expression profiles for selected inflammatory cytokines, chemokines, and macrophage markers were assessed and their correlations with RA disease characteristics were explored.

Results: The RA and control groups were well matched [mean age=54 years, 75% female, mean BMI=28.1]. Median RA duration was 6.3 years and 77% were seropositive for rheumatoid factor (RF) or anti-CCP antibodies. A total of 78% were treated with non-biologic DMARDs, 44% with biologics, and 25% with prednisone. The proportion of ATMs was 76% higher in RA vs. non-RA samples (37.7 vs. 21.3%, respectively; $p<0.001$). ATMs aggregated into crown-like structures (CLSs) around adipocytes were more than 1.5-fold higher in the RA group compared with controls (0.58 vs. 0.23 CLSs/high-power field, respectively; $p=0.001$). ATMs were significantly more abundant in early RA and in those seropositive for anti-CCP (Fig1A&B). Users of methotrexate, leflunomide, and TNF inhibitors had a significantly lower proportion of ATMs compared with non-users (Fig1C&D). Average CLSs were significantly higher among those with RF (48% higher; $p=0.038$) or a serum CRP$\geq$10 mg/L (112% higher; $p=0.001$). Adipose expression of IL-6, MCP-1, MMP-9, osteopontin, C1q, and the macrophage markers CD64, CD68, and CD163 were all significantly associated with serum CRP, IL-6, DAS28 score, and duration of morning stiffness, all with Spearman correlation coefficients ranging between 0.3 and 0.7 and p-values<0.05. In a multivariable linear regression model predicting serum CRP; gender, biologic use, swollen joints, RF and/or anti-CCP seropositivity, BMI, and adipose MCP-1 expression level accounted for 63% of the explainable variability. Of this variability in CRP, adipose expression of MCP-1 independently accounted for 11% whereas swollen joints only accounted for 5%.

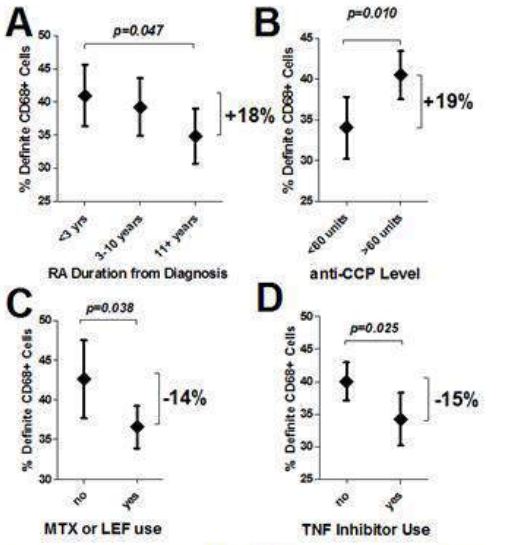

Figure. Associations of Rheumatoid Arthritis Characteristics with the Adjusted Average Proportions of Adipose Tissue Macrophages (i.e. % Definite CD68+ Cells). Adjusted means and 95% confidence intervals are depicted. All four graphs are derived from the same model including the covariates education level, rheumatoid arthritis duration, anti-cyclic citrullinated protein antibody seropositivity, methotrexate or leflunomide use, and TNF inhibitor use. RA=rheumatoid arthritis; CCP=cyclic citrullinated protein; MTX=methotrexate; LEF=leflunomide; TNF=tumor necrosis factor.

Conclusion: ATMs were more abundant in RA and associated with systemic inflammation and autoantibody status, suggesting possible contributions to the RA disease process. Lower levels of ATMs associated with specific RA treatments suggest that adipose tissue inflammation may be ameliorated by immunomodulation.

Disclosure: J. T. Giles, None; **A. W. Ferrante**, None; **R. Broderick**, None; **A. Zartoshti**, None; **J. Rose**, None; **H. Z. Zhang**, None; **R. Winchester**, None.

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Abstract Number: 522

Patient-Provider Discordance in Global Assessments of Disease Activity in Patients with Rheumatoid Arthritis: Persistence, Predictors and Impact

Divya N.V Challa[1], Zoran Kvrgic[1], Cynthia S. Crowson[2], Daniel Schaffer[1], Thomas G. Mason II[3], Scott T. Persellin[4], Clement Michet Jr.[1], Theresa L. Wampler Muskardin[1], Kerry Wright[1], Eric L. Matteson[1] and John M. Davis III[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology - Department of Medicine, Mayo Clinic Rochester, Rochester, MN, [4]Department of Rheumatology, Mayo Clinic Rochester, Rochester, MN, [5]Division of Rheumatology, Mayo Clinic, Rochester, MN

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Background/Purpose: Patient-provider discordance in global assessment (GA) of disease activity is a potential threat to patient-centered management of individuals with RA. The estimated prevalence of discordance is 33%. A crucial gap remains in the literature regarding the trends and predictors of discordance. Our aim was to determine the persistence over time, predictors and impact of discordance on treatment decisions.

Methods: A retrospective case-control study included 102 patients with discordance (defined as patient GA ≥25 mm higher than provider GA) and 102 patients without discordance matched on age, sex, RA disease duration and Clinical Disease Activity Index (CDAI <10 vs. ≥10). Data were collected for the baseline visit (date of diagnosis or earliest available visit); study visit and 11 additional clinical visits prior to the discordant visit. For the baseline visit, duration of symptoms, date of diagnosis, 1st DMARD/biologic used, and use of MTX in the 1st 6 months of diagnosis were recorded. Data for each clinical visit included the patient and provider GAs (0-100 mm), pain visual analog scales (0-100 mm), tender and swollen joint counts (0-28), HAQ, CDAI, radiographic erosions, ESR, CRP, and DMARD/biologic use or modification. Presence of comorbidities, including depression, anxiety, FM, or OA, and use of glucocorticoids, analgesics, antidepressants or anxiolytics, were also abstracted. Data were analyzed using linear and logistic regression models with smoothing splines for non-linear trends.

Results: The study included 204 patients with mean age of 60 years, mean RA duration of 7 years, mean CDAI score of 15.4. Analysis of the 3-year trends in the patient and provider GA demonstrated persistence and/or progression of discordance over time (see Figure). Cases had a greater percentage (mean 71% vs. 30%; p<0.001) and higher rate of discordant visits (1.6 vs. 0.6 per year; p<0.001) compared to controls. Baseline predictors of future discordance were (odds ratios [OR] are for a 10-unit change for each characteristic) age (OR=0.14, p=0.04), patient GA (OR=1.44, p<0.001), pain score (OR=1.28, p<0.001), and CDAI score (OR=1.70 per 12 unit increase, p=0.047). Depression (OR=2.00, p=0.04), ever use of antidepressants (OR=3.11, p=0.01) or FM pain medications (OR=2.90, p=0.04) also predicted future discordance. No differences were observed in the cumulative numbers of additions or modifications of the DMARD regimen or in treatment with conventional or biologic DMARDs between cases and controls (all p>0.05).

Conclusion: Patient-provider discordance tends to persist and/or progress over time and is associated with consistently higher pain. Early abrogation of inflammatory disease activity through treat-to-target strategies as well as early detection and treatment of comorbid depression and FM could lessen the development of patient-provider discordance.

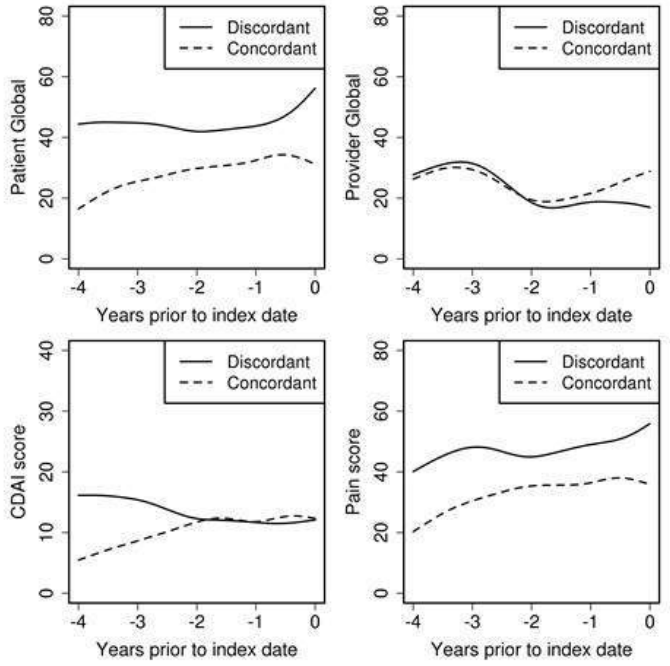

Figure: Comparison of trends in patient and provider global assessments, CDAI, and pain scores in cases with patient-provider discordance and concordant controls, preceding the index visit (time 0).

Disclosure: D. N. V. Challa, None; **Z. Kvrgic**, None; **C. S. Crowson**, None; **D. Schaffer**, None; **T. G. Mason II**, None; **S. T. Persellin**, None; **C. Michet Jr.**, None; **T. L. Wampler Muskardin**, None; **K. Wright**, None; **E. L. Matteson**, None; **J.**

M. Davis III, None.

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Abstract Number: 523

Mortality Profile of Patients with Rheumatoid Arthritis in France and Its Change in 10 Years

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Background/Purpose: Rheumatoid arthritis (RA) is associated with an excess of mortality. This risk depends on the disease activity, severity and associated comorbidities. Our objective was to study the mortality profile of RA patients in France using multiple-cause-of-death analysis.

Methods: Data were collected between 2000 and 2011 in the French Epidemiological Center for the Medical Causes of Death database, and death certificates issued upon the death of an adult for whom RA was an underlying cause of death (UCD) or an associated cause of death (ACD) were evaluated using multiple-cause-of-death analysis. Sex, age, sex ratio, standardized mortality rates, as well as frequency of the various causes of death were assessed. For the main causes of death, the observed number of deaths in relation to the expected number of deaths (O/E ratio) was calculated to measure the strength of association between RA listed as an ACD and the corresponding UCD.

Results: During the study period, 13,208 deaths related to RA were identified. RA was identified as the UCD in 4597 (35%) certificates. The number of certificates mentioning RA as the UCD decreased from 41% to 27% between 2000 and 2011. The mean±SD at death was 79 ± 9 years (51% with ≥80 years). The female: male ratio was 3.2 and remained stable during the follow-up period. This ratio was significantly higher in the population where RA was the UCD (4.1 vs. 2.8 p <0.001). The mean standardized mortality rate was 0.25 per 10^5 million people (range 0.21-0.28), and remained stable throughout the period. When RA was the UCD (n=4,597), the main ACDs were cardiovascular diseases (29%), infectious diseases (22%), and respiratory diseases (17%). When RA was an ACD (n=8,611), the most common UCDs were cardiovascular diseases (35% of certificates, including 877/3032 ischemic heart disease), neoplasms (14%), respiratory disease (9%) and infectious diseases (7%). The overall O/E ratio was >1 for infectious (3.58), respiratory (1.38) and cardiovascular diseases (1.25), but was <1 for neoplasms.

Conclusion: This is the first national study using a multiple-cause-of-death analysis to study the mortality profile in RA. Our results show that mortality related to cardiovascular, respiratory and infectious diseases is highly associated with RA. These data support the need to expand new strategies to prevent infectious and cardiovascular diseases in order to improve survival of RA patients.

Disclosure: J. Avouac, None; **F. Amrouche**, None; **C. Meune**, None; **G. Rey**, None; **A. Kahan**, None; **Y. Allanore**, None.

Abstract Number: 524

A Self-Determination Theory Based Intervention to Increase Levels of Cardiorespiratory Fitness, Self-Determined Motivation, Physical Activity and Improve Health Outcomes Among Patients Living with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) may cause joint damage leading to physical dysfunction and associates with increased cardiovascular (CV) risk. Regular physical activity (PA) can attenuate disease-related symptoms and improve function. Self-Determination Theory (SDT), a contemporary theory of motivation, has provided the foundation for PA promotion interventions among different patient groups but has not been applied to facilitating PA engagement in people living with RA. **Objectives:** To examine whether a 3-month SDT-based exercise intervention can lead to improvements in cardiorespiratory fitness (CRF, primary outcome), self-reported moderate PA, self-reported sitting time, functional disability and self-determined motivation towards PA participation in patients with RA.

Methods: Data were collected as part of the Physical Activity in Rheumatoid Arthritis (PARA) randomised controlled trial. The PARA study compared the effectiveness of two 3 month exercise programmes in N = 115 patients with RA (Mage = 54 ± 12.5 yrs). Patients in the experimental (N = 59) and control (N = 56) arm, both received the same gym-based exercise programme which was tailored for people with RA. However, the experimental arm also received one-on-one SDT informed consultations by a trained advisor that aimed to foster more self-determined motivation for PA. Assessments were carried out at baseline, 3, 6 and 12 month follow-up. Data analysed for the present work is from measures taken at baseline and at 3 months (immediately post intervention). CRF was assessed via an exercise tolerance test. Self-reported moderate PA, sitting time, functional disability and self-determined motivation for PA were measured using validated questionnaires. Repeated measures analyses of covariance (ANCOVAs) were conducted to examine main effect and group x time effects on targeted outcomes. Analyses were adjusted for age and exercise programme attendance.

Results: No significant group x time interactions were observed for cardiorespiratory fitness or functional disability. Significant interactions between groups were observed for: self-reported moderate PA (min/week) (F (1) = 4.31, p < .05), daily sitting time (min/day) (F (1) = 4.93, p < .05), and self-determined motivation for PA (F (1) = 5.72, p < .05). Specifically, favourable changes were seen in for these outcomes in the experimental, relative to the control arm (Table 1).

Conclusion: These findings suggest that a SDT-grounded PA intervention promotes adaptive motivational processes that may encourage increased engagement in moderate intensity PA in RA patients involved in a tailored exercise programme. However, more structured exercise interventions with additional support may be required to promote increases in PA engagement towards levels required to improve CRF in people living with RA. Table 1. Descriptive statistics

Variable		**Experimental arm** **M ± SD**		**Control Arm** **M ± SD**	
	Sample size post intervention (N = experimental, control)	Baseline (T1)	Post-intervention (3 months)	Baseline (T1)	Post-intervention (3 months)
Cardiorespiratory fitness (ml/kg·min)	N = 32,13	21.25 ± 4.83	22.21 ± 4.66	20.82 ± 4.37	21.26 ± 4.91
Functional disability *Health Assessment Questionnaire*	N = 31, 12	1.90 ± .56	1.81 ± .57	1.43 ± .53	1.49 ± .61
Moderate PA (min/week) *International Physical Activity Questionnaire*	N = 35, 12	561.49 ± 473.19	626.17 ± 637.43	968.50 ± 829.67	639.00 ± 544.00
Sitting time (min/day) *International Physical Activity Questionnaire*	N = 35, 12	284.28 ± 109.09	229.83 ± 102.42	204.58 ± 100.57	225.00 ± 85.33
Self-determined motivation for PA *Behavioural Regulation in Exercise Questionnaire*	N = 33, 128	.91 ± 2.08	6.73 ± 2.58	1.38 ± 1.93	5.06 ± 3.48

Disclosure: J. Duda, None; **S. Fenton**, None; **J. Veldhuijzen van Zanten**, None; **G. Metsios**, None; **P. Rouse**, None; **N. Ntoumanis**, None; **C. A. Yu**, None; **Y. Koutedakis**, None; **G. D. Kitas**, None.

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Abstract Number: 525

Predictors of Health Care Drop-out in an Inception Cohort of Patients with Early Onset Rheumatoid Arthritis

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Background/Purpose: The impact of inadequate therapy behavior in rheumatoid arthritis (RA) patient outcomes may be amplified by the fact that almost all individuals with poor drug compliance, eventually drop out of treatment and out of the health care system completely. In 2004, we established an early arthritis clinic (EAC) in a referral centre for rheumatic diseases. Once enrolled in the inception cohort, recent-onset RA patients underwent regular evaluations that included disease activity and compliance with treatment that was indicated according to a 'treat to target' (T2T) strategy. **Objectives** 1.- To describe the characteristics of patients who dropped out of health care (HDO) in an ongoing cohort of patients with recent onset RA at inclusion. 2.- To explore baseline and cumulative predictors for HDO, with emphasis on disease activity, treatment and persistence with therapy (P) as potential cumulative predictors.

Methods: Charts from patients attending the EAC from 2004 onwards were reviewed. Patients with HDO (*cases*) were defined when they did not return back to the clinic for at least one year. *Control s*were defined if compliant with all their scheduled visits and included patients lost to follow-up but who returned to the EAC within one year since their last visit. Persistence with therapy (P) was defined as length of time patients complied with treatment. A case-control nested within a cohort design was used to compare baseline and cumulative (up to HDO or equivalent follow-up) variables between cases and paired (according to age [±5 years], sex, autoantibodies and follow-up to HDO or equivalent) controls. Cox regression analysis was used to investigate predictors of HDO. Patients provided written informed consent.

Results: Data from 170 patients (89.4% female, [mean±SD] age: 38.2±12.6 years) with ≥1 year of follow-up were analyzed**;** up to December 2015, (median, range) follow-up was 86.6 months (43.2-123) during which 35 (20.6%) patients had HDO after 41.1 months (12.1-58.7) of follow-up. Baseline and cumulative variables related to disease activity, treatment and P entered regression models; cumulative n° of flares (OR: 2.45, 95%CI: 1.35-4.4, p=0.003), n° of DMARD/patient (OR: 2.89, 95%CI: 1.58 -5.27, p=0.001) and P<50% (OR: 3.06, 95%CI: 1.29-7.29, p=0.011) emerged as predictors of HDO. Five cases returned back to the EAC after (median, range) drop out time of 3.8 years (2.3-5.8); they exhibited higher disability and poorer function than 15 paired controls (1:3) and these negative outcomes were sustained up to their last follow-up.

Conclusion: Failure to control disease activity, intensive treatment and poor P predicted HDO in an inception cohort of RA patients. HDO impacted patient´s outcomes.

Disclosure: I. Contreras-Yáñez, None; **V. Pascual-Ramos**, None.

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Abstract Number: 526

Changes in the Functional Status of the Rheumatoid Arthritis (RA) Population over the Biologic Era

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Background/Purpose: In 1998, the first biologic disease modifying antirheumatic drug was approved in the United States for the treatment of RA. Since that time, biologics have become the standard of care for patients with moderate to severe RA. However, there is limited information on the general impact of biologics on the long term functional status of the RA population. This study examined baseline characteristics from patients enrolling in randomized clinical trials (RCT) from 1987 to 2012 to estimate changes in RA patient functional status following the introduction of biologics.

Methods: A systematic literature review was conducted in the Medline and Embase databases from 1987 to 2012 to identify RCTs enrolling RA patients that reported a baseline Health Assessment Questionnaire (HAQ) score. Weighted means for patient baseline characteristics reported in RCTs were used to construct multivariable linear regression models to examine predictors of change in RA patient functional status over time.

Results: A total of 51 RCTs were identified that met all study requirements; 36 RCTs allowed for weighted mean calculations and were included in the analyses. Correlation analyses and Regression models exploring the association between patient functional status and year of RCT publication were performed for five outcomes: HAQ, disease activity score (DAS-28), tender and swollen joint counts (TJC and SJC), and Sharp scores. Correlational analyses showed an inverse relationship between mean DAS-28 or SJC and year of publication over the study period. Other outcomes (HAQ and TJC) only presented a significant inverse relationship with year of publication for subset of the study period, 2005-2012. Linear regression models for DAS-28 and Sharp scores used all eligible data; models for HAQ, TJC, and SJC were developed using data from 2005-2012 (Table 1). Best fit linear regression models revealed year of publication to be a significant predictor of increased functional status scores over time for all outcomes; increased age was also a predictor of increased functional status in 4 of the 5 models.

Conclusion: Patient baseline characteristics in RCTs from 1987 to 2012 were used as a proxy to assess changes in the functional status of the RA population over time. The increase in the functional status of the RA population observed after the period that biologics became available suggests that biologics have been effective in managing disease and reducing disease severity within the RA population. Disclosure: B.S., and D.C. are employees of Amgen. B.B. and N.G. are employees of Health Analytics, LLC who was contracted by Amgen to conduct this study.

Table 1. Sample Characteristics and Significant Predictors

Sample Characteristics		Regression Model Results									
	Weighted Mean	HAQ N=31 R^2=.63		DAS-28 N=23 R^2=.63		TJC N=28 R^2=.57		SJC N=26 R^2=.69		Sharp N=10 R^2=.72	
		Estimate	p	Estimate	p	Estimate	p	Estimate	p	Estimate	p
Study Sample Size (n=36)	494	0.0002	**<0.01**	0.0004	0.08	0.0088	**<0.01**				
Age (years) (n=36)	52.5	-0.0241	**<0.05**	-0.072	**<0.05**	-0.8840	**<0.05**	-0.7791	**<0.001**		
RA Disease Duration (n=34)	8.2							-0.3206	0.08	4.0819	**<0.01**
Publication Year (n=36)	2008	-0.0560	**<.001**	-0.1125	**<0.01**	-1.4929	**<0.01**	-0.9559	**<0.001**	-1.5865	0.17
Female (n=35)	79.3%										
Prior DMARD Use (n=36)	66.6%			0.4382	**<0.05**						
HAQ (n=36)	1.5	N/A		N/A		N/A		N/A		N/A	
DAS-28 (n=23)	6.3	N/A		N/A		N/A		N/A		N/A	
TJC (n=33)	26.4	N/A		N/A		N/A		N/A		N/A	
SJC (n=33)	17.9	N/A		N/A		N/A		N/A		N/A	
Sharp Score (n=10)	36	N/A		N/A		N/A		N/A		N/A	

All data are derived from the 36 included articles; n indicates the number of articles included in the weighted mean or regression

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Disclosure: B. Brady, None; **N. Gerlanc**, None; **D. Collier**, Amgen, 1,Amgen, 3; **B. S. Stolshek**, Amgen, 1,Amgen, 3.

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The Summed Bilateral Elbow Extension Angle in Rheumatoid Arthritis Correlates with the DAS28-CRP(4) and May be an Independent Marker of Bad Prognosis

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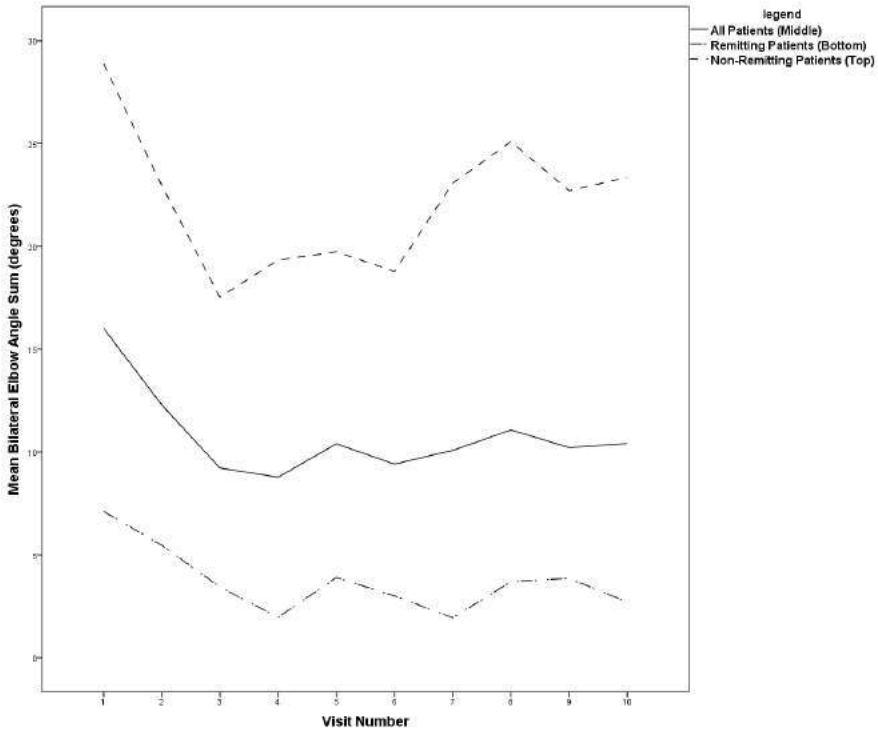
Background/Purpose: The elbow is an easily-examined joint and an important determinant of morbidity in rheumatoid arthritis (RA). In active RA the measured elbow extension angle, recorded as degrees of flexion, consists of the sum of a fixed (irreversible destruction) deficit and a functional deficit (potentially reversible by medical or physical therapy). In inactive RA, the angle approaches the fixed, irreversible baseline. One of us (Case) has been measuring the angle and obtaining the DAS28-CRP(4) as part of routine clinical care. We undertook a 3-year retrospective study (5/1/12 – 4/31/15) of RA patients in order to determine a relationship between disease activity and the elbow extension angle.

Methods: All RA patients seen during the first (recruitment) year of study were eligible if they had RA (ACR/EULAR criteria), had at least 4 visits, had at least 3 elbow and DAS determinations and at least one of each during the first and last 3 visits. A Grafco 12-1000 Orthopedic goniometer (GF Health Products, Atlanta GA) was used in all measurements. After determining the high (< 0.0001) correlation between right and left elbow extension angles, the sum (right plus left, in degrees of flexion, "ELB") was used for statistics. A baseline best ELB (i.e., lowest flexion contracture) was determined from the first 3 visits and a final from the last 3 visits up to and including visit 10 (after which patient numbers rapidly dropped off precluding statistics). 166 patients entered into the study. 23 were subsequently excluded. Correlation was assessed by Pearson, and group differences between remitters (defined as DAS < 2.6) and non-remitters (defined as DAS >= 2.6) were assessed by T-test. Statistics were calculated with IBM SPSS 22.

Results: The 143 patients had a mean age of 53.2 (SEM 13.2) years (122 females and 21 males). Patients were followed for a mean of 28.4 (SEM 6.6) months over a mean of 8.68 (SEM 2.41) visits. Because the best (i.e., lowest) mean ELB occurred between the 3rd and 4th visits, we conservatively chose the 4th visit in comparison with the 10th visit for statistical comparison (see Figure). Between visits 4 and 10 ELB increased from 19.3 (SEM 3.91) to 23.3 (SEM 5.91) (4.0 degrees) for non-remitters and from 1.96 (SEM 1.23) to 2.70 (SEM 2.38) (0.74 degrees) for remitters, a greater than 5-fold difference ($p<0.0001$). Correspondingly, the difference between the 4th and 10th visits for non-remitters was significant ($p<0.001$) but for remitters was not ($p=0.264$). The Figure shows all patients (___, middle line) and that remitters (_._., lower line) maintained ELB over the course of the study, while non-remitters (_ _ _, upper line) did not. Non-remitters also had a higher baseline ELB than remitters ($p<0.0001$).



Conclusion: The ELB closely correlates with disease activity. DAS non-remitters had a five-fold poorer ELB outcome than DAS remitters. Measurement of the ELB may be an important supplement to the rheumatologic exam in clinical and research settings.

Disclosure: J. P. Case, None; **C. Wang**, None; **H. Tucker**, None.

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Abstract Number: 528

Assessment of Metacarpal Head Bone Microarchitecture According to Presence or Not of Inflammation in Rheumatoid Arthritis Patients with Low Disease Activity

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Background/Purpose: Bone alteration at the metacarpeal head during rheumatoid arthritis (RA) disease remained under investigated. High-resolution peripheral quantitative computed tomography (HRpQCT) allows exploration of microarchitecture of metacarpeal heads during RA. Here, we explored microarchitecture parameters of metacarpeal heads

during in RA patients in low disease activity according to persistence or not of local inflammation assessed by US exam.

Methods: Thirty-three RA patients with erosion on second or third metacarpophalangeal joint were enrolled in this pilot study. All RA patients were treated with bDMARDs for at least 6 months and have low disease activity (DAS28<3.2) since at least 3 months. They were separated in two groups according to local inflammation assessed by US exam on the site of erosion. The group "inactive erosion" was defined by PowerDoppler US (PDUS) ≤ 1 at the metacarpeal joint with erosion, whereas the group "active erosion" was defined by PDUS≥2. Then, HRpQCT of second and third metacarpophalangeal joints was performed. Cortical and trabecular parameters were then assessed and compared in the two groups.

Results: The main characteristics of the RA population was summarized in the Table. Our RA population shared characteristic of RA patients treated with bDMARDs. Among the 33 RA patients, 21 RA patients were enrolled in the "inactive erosion" group, whereas 12 RA patients were enrolled in the "active erosion" group. No clinical or biological were different in the two groups. Bone volume assessed by BV/TV (%), cortical density (Dcort), and cortical thickness (CTh, µm) were similar in both groups. Trabecular parameters were more heterogeneous. Trabecular density (Dtrab) and trabecular number (TbN, mm^{-1}) were decreased in "active erosion" compared to "inactive erosion" (P<0.001 and <0.02, respectively), whereas trabecular separation (TbSp, µm) and distribution of trabecular separation (TbSpSD, µm) were increased in "active erosion" compared to "inactive erosion" (P=0.049 and 0.032, respectively). **Table. RA population characteristics according to local inflammation**

	Active erosion (n=12)	Inactive erosion(n=21)	P values
Female , %	69.2	76.2	NS
Age, years, median [range]	69 [47-78]	62 [42-77]	NS
MCP2/MCP3 assessed	11/1	18/3	NS
Date of diagnosis, years, median [range]	1996 [1976-2010]	2002 [1977-2012]	NS
DAS 28, median [range]	1.87 [0.84-2.85]	2.38 [0.97-3.2]	NS
ESR, mm/h, median [range]	6 [2-21]	8 [2-40]	NS
CRP, mg/L, median [range]	2 [0-6.6]	1.45 [0-12.5]	NS
RF +, %	70	70	NS
ACPA +, %	90	65	NS
Biologics %			
TNF blockers	50	71.4	
Tocilizumab	41.6	9.5	
Abatacept	8.3	19	
Biologics duration, *years* , median [range]	5 [2-11]	6 [2-11]	NS
Methotrexate %	58.3	80	NS

Conclusion: In RA patients in low disease activity treated by bDMARDs, persistence of local joint inflammation is associated with lower bone density at the metacarpal head. Inflammation involved mainly the trabecular compartment. Dtrab parameter was the strongly altered parameter and could be a candidate for prospective study assessing drug effect on periarticular bone damage.

Disclosure: S. Kong, None; **H. Locrelle**, None; **A. Amouzougan**, None; **D. Denarie**, None; **P. Collet**, None; **B. Pallot Prades**, None; **T. Thomas**, None; **H. Marotte**, None.

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Abstract Number: 529

The Relationship Between Promis and CDAI Scores, Disease Duration, Age and Gender in Patients with Rheumatoid Arthritis

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Background/Purpose: PROMIS (Patient-Reported Outcomes Measurement Information System) is a self-reported and parent-reported measure of global, physical, mental, and social health for the general population and those living with chronic conditions. Recent studies have demonstrated preliminary evidence of reliability and construct validity of PROMIS to assess Rheumatoid arthritis (RA) symptoms, impact, and feasibility of use in clinical care. The performance of PROMIS domains in subgroups and relationship to other disease activity scores in RA however has not been established. The aim of our study was to compare Clinical Disease Activity Index (CDAI) scores with PROMIS scores overall as well as stratify for disease duration, age and gender in RA patients.

Methods: This was a single center retrospective study. We analyzed the records of all RA patients seen over the last 6 months at the RA clinic in the University of Rochester. We compared the CDAI scores when available to the physical function (PF), pain interference (PI) and depression (Dep) PROMIS scores. We also calculated the effect of disease duration, age and gender on PROMIS PF, PI and Dep domains. Additionally, we compared the PROMIS scores of RA patients to a cohort of orthopedic patients with foot and ankle disease.

Results: We identified a total of 144 patients with RA with a median age of 59 and median disease duration of 10 years. There were 108 females and 36 males. CDAI scores were available for 45 patients. The mean CDAI score was 8.2 (median 2.5). PF decreased while PI and depression worsened with increase in CDAI scores (see Table 1). Scores for Dep (52.1), PF (40.0) and PI (61.6) were also worse for those with disease duration of less than 1 year since diagnosis of RA (median 52.1 and 61.6) compared with those with 1-5 years, 6-10 years and more than 11 years with RA (see Table 2). No significant difference was noted in PROMIS scores based on gender. Similarly, no difference was noted in PROMIS scores for the different age groups: those less 40 years, 40-50, 51-60 and those over 60 years. Surprisingly, no difference was noted in the PROMIS scores between the RA cohort when compared to all rheumatology patients (n=370) and a cohort of patients with foot and ankle disease (n=25,690).

Conclusion: Physical function, Pain Interference and depression PROMIS scores are associated with disease activity in RA patients as measured by CDAI. PROMIS scores are also affected by disease duration but not age or gender among RA patients. PROMIS is a valuable tool in the assessment of RA patients.

	Remission	Low disease Activity	Moderate disease activity	High disease activity
Physical Function	48.92	42.95	37.74	38.16
Pain	46.64	54.92	64.78	65.19
Mood	45.76	49.01	48.39	55.11

Table 1: relationship between CDAI and PROMIS scores

Disease Duration	Physical function	Pain	Mood
Less than 1 year	40.00	61.55	52.12
1-5 years	47.64	52.57	43.01
6-10 years	43.50	57.79	48.18
More than 11 years	41.77	55.98	48.80

Table 2: Effect of disease duration on PROMIS score in RA patients

Disclosure: A. Lieberman, None; **J. Baumhauer**, wright medical, Nextremity solutions, DJO, Cartiva, Ferring Pharma, 5; **C. Dasilva**, None; **A. P. Anandarajah**, None.

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Abstract Number: 530

Importance of Functional and Utility Evaluation on Disease Activity Level in Rheumatoid Arthritis: Interrelations and Predictive Value

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Background/Purpose: Rheumatoid Arthritis (RA) treatment targets remission or low disease activity, thus reducing the disease impact in patients' lives. Assessing different tools for effectiveness (disease activity, functional status and utility) could provide a more comprehensive approach in term of "achieve and maintain" the therapeutic goal. The aim of the present study is to evaluate interrelations of disease activity score – functional status – utility in a cohort of RA patients, treated with tumor necrosis factor alpha (TNF) antagonists and anti CD20 molecule.

Methods: Observational study in a cohort of RA patients in Romania, where data was gathered from the Romanian Registry of Rheumatic Diseases, which comprises all RA patients treated with biologics in the country. The three main variables under study were EQ5D (for utility), HAQ score (for functional status) and DAS28 and SDAI (for disease activity). The study cohort included only RA patients for whom were available all these data. The interrelations of the efficacy parameters were analyzed using correlation tests, T test, ANOVA, linear regression.

Results: The cohort included 777 RA patients, mean age 58.72 (±12.37) yrs, 84.4% women, mean RA duration 14.08 (±8.33) yrs, 77.1% retired, treated with etanercept (30.6%), adalimumab (22.7%), infliximab (original 6.3%, biosimilars 0.7%), rituximab (26.3%). 27.3% used steroids (20.2% with <7.5mg prednisone daily); mean current DAS28 score =3.66 (±1.52), mean ΔDAS28= 0.13 (±1.28), mean SDAI =14.27 (±13.79), mean HAQ score =1.14 (±0.64), mean EQ5D= 0.61±0.31. There was a strong negative association between DAS28 (and SDAI) and EQ5D: r = - 0.7 ($p<0.001$). HAQ score positively correlates with DAS28, same as with SDAI: r = 0.5 ($p<0.001$) whereas is a negative association between HAQ and EQ5D: r = - 0.6 ($p<0.001$). Disease activity dynamics (Δ DAS28 for the last 6 months) had a mild association with HAQ: r = 0.1 ($p<0.05$) and a negative one with EQ5D: r = -0.2 ($p<0.01$). Patient global assessment (PGA) on disease activity had a significant association both with HAQ (r=0.6, $p<0.001$) and EQ5D (r = - 0.6, $p<0.01$). Analyzing distribution of EQ5D and HAQ in DAS28 categories, there was a significant difference between categories ($p<0.001$); for EQ5D - DAS28: <2.6= 0.81(±.19), 2.6-3.2= 0.68(±.17), 3.2-5.1= 0.63(±.18), >5.1= 0.16(±.38); for HAQ - DAS28: <2.6= 0.73(±.57), 2.6-3.2= 0.98(±.5), 3.2-5.1= 1.25(±.52), >5.1= 1.76(±.56). There are significant predictive relations between DAS28, HAQ and EQ5D: linear regression model showed that DAS28 is strongly predicted by EQ5D (F = 798.7, t = - 28.2, B = - 3.48, $p<0.0001$), over than 50% of the variability of DAS28 being determined by the variability of EQ5D (adjusted R square = 0.51). HAQ score has a predictive value for DAS28 (F = 341.6, t = 18.4, B = 1.32, $p<0.0001$), roughly 30% of the variability of DAS28 being determined by the variability of HAQ (adjusted R square = 0.30). Disease

duration had not any influence on EQ5D, HAQ or DAS28.

Conclusion: Disease activity influences the patient well-being and functional status. Regression model showed that DAS28 could be predicted by the evaluation of EQ5D and HAQ level, regardless the disease duration.

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Abstract Number: 531

Disease Activity and Physical Fatigue As Related to Adherence and Health Literacy in Patients with Rheumatoid Arthritis

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Disease activity and physical fatigue as related to adherence and health literacy in patients with rheumatoid arthritis J. G. Kuipers[1], M. Koller[2], F. Zeman[2], K. Mueller[2], J. U. Rueffer[3], [1] Department of Rheumatology, Red Cross Hospital Bremen, Bremen, Germany [2] Center for Clinical Studies, University Hospital Regensburg, Regensburg, Germany [3] German Fatigue Society, Cologne, Germany

Background/Purpose:

Disease activity and fatigue are key endpoints to evaluate the outcome of treatment for rheumatoid arthritis (RA). Among factors that may contribute to good outcome are adherence (i.e., the extent to which patients' behaviors corresponds with agreed recommendations from their doctor) and health literacy (patients' understanding and use of health information).

Methods:

The survey included a representative, nationwide sample of German physicians specialized in rheumatology+ and patients with RA. The physician questionnaire included the disease activity score (DAS28) and medical prescriptions. The patient questionnaire included fatigue (EORTC QLQ-FA13) health education literacy (HELP), and patients' listings of their medications.

Adherence was operationalized in various ways: patient-reported (CQR5), behavioral (correspondence between physicians and patients listings of medications), physician-assessed (five-point rating scale ranging from 1=very adherent to 5=not at all adherent) and a combined measure of physician rating (1= very adherent, 0 = less adherent) and the match between physicians' prescriptions and patients' accounts of their medications (1 = perfect match, 0 = no perfect match), leading to three categories of adherence: high, medium and low. Linear regressions were calculated using DAS28 and Physical Fatigue as dependent variables and adherence, health literacy and the set of demographic and clinical variables as

predictor variables.

Results:

A total of 708 pairs of patient and physician questionnaires were analyzed. The mean age of the patients, of whom 73% were women, was 60 years (SD=12). At the time of assessment, 67% of the patients showed low disease activity (DAS28 < 3.2), 26% moderate disease activity (DAS28 3.2 to 5.1), and 4% high disease activity (DAS28 > 5.1).

	DAS			Physical Fatigue		
Predictor	**B (95%-CI)**	**p-value**	**R²**	**B (95%-CI)**	**p-value**	**R²**
CQR5	-.025 (-.164; .113)	.720	.000	.064 (-.035; .163)	.205	.002
Medication match doctor vs patient in %	-.003 (-.006; .001)	.120	.004	.001 (-.002; .003)	.668	.000
MTX, non-MTX-DMARDS, glucocorticoids and biologicals, all taken as prescribed	-.237 (-.456; -.019	**.033**	.007	-.063 (-.218; .092)	.426	.001
Adherence by doctor (ref. medium or less adherence)						
adherent	-.359 (-.668; -.051)	**.022**	.044	-.105 (-.330; .120)	.359	.012
very adherent	-.741 (-1.043; -.439)	**<.001**		-.265 (-.485; -.045)	**.018**	
Adherence composite score (ref. low adherence)						
medium adherence	-.266 (-.476; -.056)	**.013**	.034	-.082 (-.231; .068)	.284	.016
high adherence	-.579 (-.814; -.344)	**<.001**		-.277 (-.445; -.110)	**.001**	
HELP Capability of application of information	.428 (.300; .556)	**<.001**	.062	.350 (.260; .440)	**<.001**	.080
HELP Capability of understanding of medical information	.251 (.146; .357)	**<.001**	.033	.217 (.144; .290)	**<.001**	.049
HELP Communication capability	.249 (.122; .375)	**<.001**	.022	.328 (.243; .413)	**<.001**	.079

B, regression coefficient; 95%-CI, 95%- confidence interval, R², coefficient of determination

Multiple regression analyses show, that adherence by doctor (p = .000 and p = .034) as well as the adherence composite score (p = .000 and p = .001) are independent predictors as well as health literacy (p = .000) for DAS and Physical Fatigue when controlling for age, sex, smoking, drinking, sport.

Conclusion:

This study showed that DAS and Physical Fatigue were related to adherence and health literacy. This finding highlights the importance of patient education and counseling in order to increase both, medical understanding and adherence to therapy.

Disclosure: J. G. Kuipers, None; **M. Koller**, None; **F. Zeman**, None; **K. Mueller**, None; **U. Rueffer**, None.

Abstract Number: 532

The DAS28 Score May Misread Disease Activity in Rheumatoid Arthritis Patients

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Background/Purpose: The DAS28 is a measure of disease activity in rheumatoid arthritis (RA). DAS28 stands for 'disease activity score' and the number 28 refers to the 28 joints that are examined in this assessment [1, 2]. DAS28 is a composite outcome measure that assesses how many joints in the hands, wrists, elbows, shoulders, and knees are swollen (SJ) and/or tender (TJ), the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP) in the blood to measure the degree of inflammation, the patient's general health (GH) on a Visual Analogue Score (a simple scale) to assess how they are feeling on that day. These results are then fed into a complex mathematical formula to produce the overall disease activity score. A DAS28 of greater than 5.1 implies active disease. In the UK the NICE has approved the use of TNFα<span">inhibitors to treat patients with rheumatoid arthritis in accordance with the British Society for Rheumatology guidelines. Having a DAS28 score equal or greater than 5.1 on two occasions is one of the criteria required. Failure of anti-TNF treatment is defined as having a difference between baseline and 6 months post-treatment DAS28 score of < 0.6. Although DAS28 score is a validated tool for the identification of patients who are likely to benefit form anti-TNF treatment, it takes into account a number of subjective parameters which are likely to influence the overall result and reach the NICE threshold for the initiation of anti-TNF treatment [3]. The purpose of this study is to explore how an increase in the reported number of tender joints and/or GH would affect DAS28 score and to identify patients who although qualify for, might nor benefit from anti-TNF treatment.

Methods: We retrospectively investigated the GH, TJ, SJ, ESR, baseline DAS28 score and the DAS28 score 6 months after treatment of patients who qualified for anti-TNF treatment. The patients were divided in responders and non-responders to treatment. T-test was used to compare continuous variables between groups for parametric data and Mann-Whitney U test for non-parametric data. Pearson's correlation was used to investigate statistical dependence between variables. Multiple regression analysis was performed to assess the ability of a number of factors to predict the degree of reduction in DAS28 score after treatment.

Results: We reviewed the data of patients who received treatment with biologic factors for the last 2 years across East Kent Hospitals. One hundred and ten patients qualifying for and having received anti-TNF treatment for 6 months were included in the study. All baseline parameters where similar between the two groups. Eighty six patients had reduction in the DAS28 by 0.6 or more (responders) and 24 had reduction of less than 0.6 (non-responders). There was a statistically significant difference in the swollen-to-tender joints ratio between the responders and non responders (median difference = -0.55, 99.9%CI 0.46 - 0.64, $p<0.001$). Baseline GH and the number of tender joints were most strongly positively correlated with higher DAS28 score post treatment among all baseline factors (Pearson's $r = 0.87$ and 0.84 respectively, $p<0.001$). Multiple regression analysis revealed that a model containing the GH and the swollen-to-tender joints ratio was able to explain 70% of the variance in post-treatment DAS28 score reduction (F (2, 107)= 129, $p<0.001$). GH and the swollen-to-tender joints ratio each made a strong contribution to explaining the DAS28 score reduction (*beta*= 0.48 and 0.38 respectively, $p<0.001$ and $p<0.05$ respectively). Patients with high swollen-to-tender joints ratio and low GH were

more likely to have a bigger reduction in DAS28 score after treatment.

	Responding to treatment (n = 86)	Non-responding to treatment (n = 24)	p value
age (median)	55	45	p=NS
sex (% of males)	36%	17%	p=NS
number of tender joints (mean)	8.0	15.0	p<0.001
number of swollen joints (mean)	4.0	1.2	p<0.001
Swollen-to-tender joints ratio (mean)	0.7	0.1	p<0.001
GH (mean)	62.0	90.5	p<0.001
ESR (mean)	53.1	23.2	p<0.001
pre-treatment DAS score (mean)	5.7	5.7	p=NS
DAS score reduction post-treatment (mean)	1.9	0.2	p<0.001

Conclusion: We have identified a number of patients who fail anti-TNF treatment and in whom the DAS28 score is mainly the product of an increased score in the subjective components of it (GH and TJ). DAS28 score is the main criterion for the administration of anti-TNF treatment in the UK. We challenge the current practice of using DAS28 score per se for the identification of patients suitable for anti-TNF treatment and we recommend that more focus should be placed upon the individual components of it, especially on those which are objective and reproducible, and finally rely less on subjective criteria such as the GH and the number of tender joints, especially when a discrepancy between the number of swollen and tender joints exists (as in our population). A large study, in the UK population, involving thousands of patients is needed, to adjust the weights of the individual components and increase the reliability of the DAS28 score for the better identification of patients who will really benefit from anti-TNF treatment. This will save the NHS approximately £10,000 per patient and also avoid serious side effects associated with anti-TNF drugs, in this sub-group of patients who, based on our results, is unlikely to benefit from this class of medications. We suggest that the swollen-to-tender joints ratio merits further investigation as a possible predictor of treatment success or failure as other investigators have also suggested.

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What Proportion of Patients Fail to Achieve CDAI and SDAI Remission Based on Physician Global Assessment? an Analysis from the Prospective, Observational Registry

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Background/Purpose: Physician's Global Assessment of Disease Activity (MDGA) is a measure that is frequently incorporated in disease activity indices which reflects the physician's perception of disease activity in rheumatoid arthritis (RA). **Objectives:**The aim of this analysis was to assess the proportion of patients failing to achieve CDAI and SDAI remission based on MDGA in a real-world, routine clinical care setting in Canada. The aim of this analysis was to assess the proportion of patients failing to achieve CDAI and SDAI remission based on MDGA in a real-world, routine clinical care setting in Canada.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab (GLM). Eligible patients for this analysis included RA patients treated with IFX or GLM between 2005 and 2015. Modified versions of CDAI (mCDAI) and SDAI (mSDAI) were calculated by omitting MDGA from the formulas. Correlation of the standard and modified versions of each index was assessed with the Pearson's correlation coefficient. ROC curve analysis was used to identify new thresholds for the modified versions of low disease activity (LDA) and remission. Cross-tabulations with the Chi-square test were used to assess the agreement between the standard and modified definitions of remission and LDA.

Results: A total of 1206 patients were included in the analysis with a mean (SD) age of 56.1 (13.4) years and a disease duration of 8.4 (8.9) years. A strong positive correlation was observed between the standard and modified versions of CDAI ($r=0.99$; $P<0.001$) and SDAI ($r=0.99$; $P<0.001$). Based on ROC analysis the new thresholds for remission and LDA were: CDAI (remission=2.65, LDA=10.05) and SDAI (remission=3.31, LDA=10.73). The proportion of patients achieving remission by both indices was 17.8% and 19.5%, patients not achieving remission by both indices was 75.3% and 74.4%, and patients achieving remission by the new thresholds only was 6.9% and 6.1%, for CDAI and SDAI, respectively. Cross-tabulation of the standard and modified thresholds showed that an additional 8.4% and 7.6% of non-remission cases for CDAI and SDAI, respectively, would be classified as remission with the modified definitions. Similarly, an additional 17.6% and 15.1% of non-LDA cases for CDAI and SDAI, respectively, would be classified as LDA.

Conclusion: The results of this analysis showed that MDGA could account for up to 8% of non-remission cases and up to 18% of non-LDA cases as measured by CDAI and SDAI. Omission of MDGA from these disease activity indices could have a significant impact on patient management in preventing overtreatment with DMARDs and biologics and avoiding unnecessary switching of DMARDs and biologics.

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Abstract Number: 534

Discordance Between Physician-Stated Remission and 28-Joint Disease Activity Score (DAS28)-Defined Remission in Rheumatoid Arthritis Patients

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Background/Purpose: The goal in treatment of rheumatoid arthritis (RA) is to achieve a state of clinical remission. Updated treatment recommendations by EULAR/ACR task force highlight the importance of using validated composite measures of disease activity in routine clinical practice and emphasize the need for objective and measure-based treatment decision making. The DAS28 (ESR) is a standard tool used to assess RA disease activity endorsed by ACR and EULAR. This study examined the concordance of physician-stated remission and DAS28 remission.

Methods: Data were drawn from the 2014 Adelphi RA Disease Specific Programme in 5 European countries (France, Germany, Italy, Spain, UK). Rheumatologists provided details about the RA patients who visited them, including the use of composite clinical measures. Physician-stated remission was based on the question, "Is this patient currently in remission?" DAS28(3)-ESR remission was defined as a score <2.6. Multivariate logistic regression analyses were performed to investigate factors associated with discrepancies in rheumatologist-reported and DAS28 remission. Variables included in the multivariate model were selected based on clinical relevance and univariate analyses.

Results: This analysis included 307 physicians and 2,536 patients. Overall, 87.6% of rheumatologists practiced in a hospital (vs office only). For the 2,536 patients in this analysis, an objective measure of disease activity was performed for 1,386 (55.0%) of patients at the reference consultation, with notable regional variation. Out of 1,386 patients, 369 (26.6) had rheumatologist-reported remission and DAS28(3)-ESR defined remission; 575 (41.5%) had no remission from neither of the measurement; 41 (3.0%) patients' rheumatologist did not report remission but DAS28(3)-ESR remission was achieved; while 401 (28.9%) had rheumatologist-reported remission but not DAS28(3)-ESR defined remission. Multivariate analyses indicated that physician-reported anxiety and/or depression (odds ratio [OR] = 2.94), medium/high current pain assessment (OR = 3.10), and structural damage (OR = 2.00) were all significantly associated with physician over-reporting of remission compared with both physician and DAS28(3)-ESR agreement of remission (all $P \leq 0.001$). Agreement on a treat-to-target measure was significantly associated with lower likelihood of physician over-reporting of remission (OR = 0.46; $P = 0.001$).

Conclusion: Objective measures of RA disease activity are not universally used in clinical practice when reporting remission; when they are used, discordance exists between physician-reported remission and observed DAS28 remission. Multiple factors including disease severity, joint damage, anxiety/depression and physicians' agreement on treat-to-target were associated with likelihood of over-reporting of remission by physicians. Under-examination of patients and over-reporting of remission may result in sub-optimal treatment of patients with RA.

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Abstract Number: 535

Examination of Diurnal and Daily Variation of the Multi-Biomarker Disease Activity (MBDA) Score in RA to Establish the Minimally Important Difference

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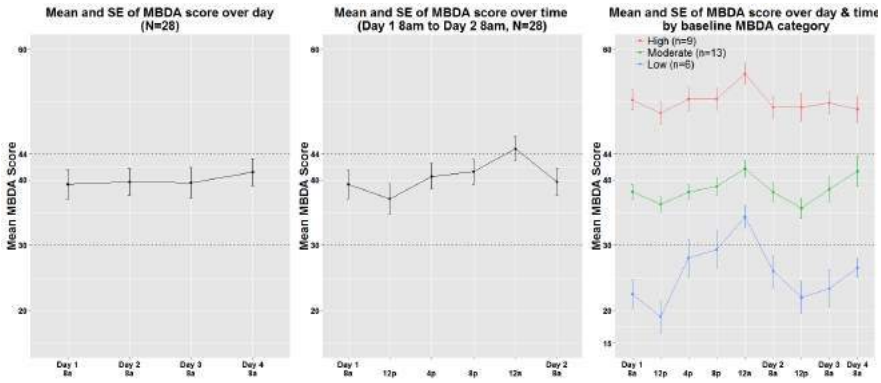
Background/Purpose: The biological variability in MBDA scores over a 24-hour period and day-to-day in patients with rheumatoid arthritis (RA) has not been well characterized. These data were obtained to determine a minimally important difference (MID) and establish a cut point for a meaningful change in MBDA scores over time.

Methods: 28 adults with clinically stable seropositive RA on stable medication (>8 weeks without changes), were recruited to a single US rheumatology research center. Serum samples were obtained 6 times over the first 24-hour period (8 AM, 12 PM, 4 PM, 8 PM, 12 AM and 8 AM) then at 12 PM in the next 24-hour period and at 8 AM the next two consecutive days, for a total of 9 time points. Diurnal variation was calculated using 6 time-points over the first 24 hours. Daily variation was determined using 4 time points taken at 8 AM on successive days. Combined diurnal and daily variation was calculated by using 9 time points over the four days. For each patient (n=28), changes in MBDA scores were calculated for all possible pairs of time points for: (a) Diurnal variation (15 possible pairs/patient, 420 total pairs), (b) Daily variation (6 possible pairs/patient, 168 total pairs) and (c) Diurnal and Daily variation (36 possible pairs/patient, 1008 total pairs). The mean change in MBDA score was determined for all pairs in each of the 3 analyses. The MID was calculated as twice the standard deviation (SD) using all available data.

Results: 28 patients were recruited for the following MBDA disease activity categories: 6 in low, 13 in moderate and 9 in high. Patient baseline characteristics were 64.3% women, mean age 61.9 years, mean MBDA score 39.3, and mean CDAI 19.9. With 96.4% patients on DMARDs, 8 patients were receiving biologics (1 rituximab; 7 anti-TNF, 6 in combination with MTX). No patients were on glucocorticoids. During the first day, the greatest and lowest mean MBDA scores were observed at 12 AM (midnight) and 12 PM (noon), respectively (Figure). The mean absolute change (SD) of MBDA score for diurnal variation was 4.3 (4.2). The largest variability in MBDA scores was observed for patients in the low MBDA category. The mean absolute change was 4.3 (4.4) for daily variation and 4.5 (4.5) in the combined daily and diurnal variation analysis. The MID was calculated as 9. Approximately 91% of the absolute changes determined for all pairs of MBDA score were ≤9.

Conclusion: Based upon short-term variability in the MBDA score among stable RA patients tested serially over time, the minimally important difference in the MBDA score was 9 units. Changes exceeding this threshold are unlikely to be due to diurnal and daily biological variation alone.



Disclosure: D. Chernoff, Crescendo Bioscience Inc., 1,Crescendo Bioscience Inc., 3; **R. J. Bolce**, Crescendo Bioscience Inc., 3; **C. C. Hwang**, Crescendo Bioscience Inc., 1,Crescendo Bioscience Inc., 3; **X. Wang**, Crescendo Bioscience Inc., 3; **A. Kivitz**, None; **J. R. Curtis**, Roche/Genentech, UCB, Janssel, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssel, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 536

Precision Medicine in Rheumatoid Arthritis: Systematic Literature Review and Meta-Analysis on the Diagnostic Accuracy of Anti-CCP Tests for the Diagnosis of Rheumatoid Arthritis

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Background/Purpose: Biological markers are objective molecular indicators possessing diagnostic, prognostic and predictive utility. The detection of antibodies to cyclic citrullinated peptides (Anti-CCP) may occur long before the onset of rheumatoid arthritis (RA) symptoms. A positive test is associated with severe erosive disease and can predict disease progression. Diagnostic accuracy is crucial for clinicians to initiate a more aggressive treatment plan early in the course of the disease. Objective of study: to compare diagnostic accuracy of anti-CCP tests from different manufacturers for RA diagnosis.

Methods: A rigorous systematic literature review identified studies from 2004-2015. Pooled estimates for sensitivity, specificity, positive likelihood ratio (LR+), negative LR (LR-) were calculated by random effects meta-regression. Covariates influence was analyzed in sub-analyses (RA-type and control type).

Results: Out of 3100 papers, 88 met the inclusion criteria reporting the diagnostic accuracy of CCP tests from 7 manufacturers, and including 22 studies from early RA patients (< 2 years), 9 studies from established RA patients (> 2 years), while 20 studies used serum samples from a mixed population of RA patients (combination of early and

established). Forty seven studies obtained control serum samples from diseased patients, 12 studies from healthy individuals, 28 studies from a mixed control populations and 5 studied defined the control group as non-RA. The included studies presented data from 34 countries worldwide. The Disease Activity Score in 28 joints (DAS28) was used to assess the severity of disease in rheumatoid arthritis (RA) patients in 17 studies (20.2%). Sensitivity ranged between 65.6-83.1%; specificity between 87.6-96.4%; LR+: 6.5-19; LR-: 0.2-0.4. Overall, the diagnostic performance of EuroImmune/Anti-CCP ELISA, ThermoFisher/EliA and Inova Diagnostics/Quanta Flash distinguished from the others by having high sensitivities, and the highest specificities and positive LRs. This result did not seem to be influenced by the investigated covariates. The single-gate analysis showed that the ThermoFisher/EliA CCP test sensitivity remained stable compared to the overall analysis; in particular, it had significantly better sensitivity than the both the Inova Diagnostics/Quanta Lite 3.0 test and the Euro-diagnostica/Immunoscan test. There was a non-significant trend in favor of the Roche/Elecsys test, however none of the comparator index tests were shown to have significantly better sensitivity than the ThermoFisher/EliA CCP test.

Conclusion: By maximizing LR+ and minimizing false negatives, accurate RA diagnosis is possible, allowing for timely appropriate treatment strategy. Results show: 1) EuroImmune/Anti-CCP ELISA, ThermoFisher/EliA and Inova Diagnostics/Quanta Flash generally have better diagnostic performance; 2) ThermoFisher/EliA and Roche/Elecsys appear as the best tests for diagnosing suspected RA.

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Abstract Number: 537

Differences and Associated Factors in General Disability and Hand Disability Between Patients with Rheumatoid Arthritis and Psoriatic Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) and psoriatic arthritis (PsA) are well-known disabling conditions, with high impact on patients functioning and quality of life. However, little is published about the differences in disability between RA and PsA patients. The aim of this study was to evaluate and compare general functional disability and specific hand disability in patients with RA and PsA.

Methods: A cross-sectional study was performed. Consecutive patients with RA and PsA attended in a hospital were selected and their medical records reviewed. Sociodemographic and clinical variables including disease duration and activity (DAS28), physical function (Health Assessment Questionnaire, HAQ), handgrip strength in both hands (using an isometric hand dynamometer), radiographic damage (modified Sharp/van der Heijde score (SHS)), and pharmacological treatments were collected following a standardized protocol. Descriptive and bivariate analyses were performed. Multivariate linear regression models completed were to assess disability associated factors.

Results are expressed as coefficient (coef) and 95% confidence interval (CI). Results: A total of 103 RA patients (82.5% were women, mean disease duration 16 years, mean HAQ 1.29, mean DAS28 3.61, mean SHS 45.81, mean grip strength of the right hand 11.22, mean grip strengh of the left hand 11.02, 60.8% on biologic therapy) and 94 patients with PsA (82.5% were women, mean disease duration 14 years, mean HAQ 0.57, mean DAS28 2.7, mean SHS 7.8, mean grip strength of the right hand 20.79, mean grip strength of the left hand 20.06, 51,1% on biologic therapy) were analyzed. Compared to PsA, RA patients were significantly more active, presented more damage and worse grip strength in both hands. Slightly differences were found between disease in the disease duration (p=0,020). In the multivariate regression analyses, poorer function (HAQ score) was associated with RA (compared with PsA) coef=0.24 (95% CI 0.04-0.45), female sex coef=0.37 (95% CI 0.16-0.57), DAS28 coef=0.23 (95% CI 0.16-0.31), and SHS, but not with disease duration. The same results were obtained when the handgrip strength (in each hand separately) were entered in the regression models.

Conclusion: In our study RA patients presented more general and hand disability compared to PsA patients. Other factors as female sex are also associated with poorer function.

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Abstract Number: 538

What Is the Relationship Between Early Metacarpophalangeal Erosions on MRI and Joint Pain in Rheumatoid Arthritis?

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Background/Purpose: Erosive damage to small joints is a hallmark feature of rheumatoid arthritis (RA). The degree to which early erosive damage contributes to joint pain in well-controlled disease is incompletely understood. The use of magnetic resonance imaging (MRI) combined with erosion segmentation software, such as Early Erosions in Rheumatoid Arthritis (EERA), provides opportunity for the study of small, early erosions. Our objective was to apply multiple linear regression modeling to determine how low levels of erosive damage contribute to joint pain in RA.

Methods: From a single rheumatology clinic, 125 patients satisfying early RA referral criteria were included. Clinical and laboratory disease measures were captured. MRI of both hands were acquired, and a single reader used EERA software to compute total erosive damage in the metacarpophalangeal (MCP) joints, in mm^3. A multiple linear regression model was constructed, with the dependent variable as patient-reported finger joint pain, rated none, mild, moderate, or severe. Predictor variables included age, sex, symptom duration > 1 year, disease-modifying antirheumatic drug (DMARD) or biologic use over preceding 3 months, disease activity score using erythrocyte sedimentation rate (DAS28 ESR), and MCP joint erosion volume. Sensitivity analyses were conducted, using daily or weekly history of illness-associated pain, rated on visual analog scale (VAS, 0 to 100), as alternative dependent variables.

Results: Patients were 76% female, 81% Caucasian, mean (SD) age 56 (13) years, symptom duration 4.3 (5.0) years, DAS28 ESR 4.5 (1.4), pain VAS 45 (31), with 55% using DMARD or biologic over the preceding 3 months. Mean MCP erosive damage was low at 37 (91) mm^3. The regression model ($R^2 = 0.225$, $p < 0.001$) showed no statistically significant relationship between finger pain and erosion volume ($B = 0.00008$, $p = 0.896$). Among other predictor variables, only DAS28 ESR ($B = 0.263$, $p < 0.001$) and 3 month history of DMARD or biologic use ($B = -0.314$, $p = 0.002$) were significantly associated with finger pain. Regression estimates were similar when right and left hands were analyzed independently. Using either of weekly or daily patient-reported illness-associated pain VAS as the dependent variable, again only DAS28 ESR and 3 month history of DMARD or biologic use were significant model predictors.

Conclusion: Low level of MCP joint erosive damage was not associated with increased finger pain or illness-associated pain in well-controlled RA. Lower acute disease activity and concurrent DMARD or biologic therapy were associated with decreased pain. Longitudinal models may help identify the threshold at which MCP joint damage becomes an important contributor to finger pain.

Summary of Parameter Estimates for Regression Models

Outcome Variable:	Finger Pain		Daily RA Pain (VAS)		Weekly RA Pain (VAS)	
Predictor	**Beta**	**Std. Error**	**Beta**	**Std. Error**	**Beta**	**Std. Error**
Constant	1.169	0.298	1.435	15.152	-11.256	14.851
Age (years)	-0.0024	0.0038	0.048	0.196	0.067	0.189
Male Sex	0.187	0.118	7.300	6.191	6.655	6.068
Symptom Duration > 1 year	-0.156	0.108	-5.045	5.483	-8.816	5.374
DMARD or Biologic Use in Previous 3mo.	-0.314*	0.102	-12.811*	5.258	-11.580*	5.154
DAS28	0.263*	0.036	10.804*	1.820	12.054*	1.784
MCP Joint Erosion Volume (mm^3)	-0.00008	0.01	-0.034	0.028	-0.024	0.028

RA, rheumatoid arthritis; VAS, visual analog scale; DMARD, disease-modifying antirheumatic drug; DAS28, disease activity score on 28 joints; MCP, metacarpophalangeal.
* $p < 0.05$

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Promis Short Forms Are Relevant to People Living with RA: Results of Cognitive Debriefing Interviews

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Background/Purpose: PROMIS® measures were developed to assess physical, mental, and social health across chronic diseases and include brief short forms (SFs; 4-8 items) to assess common symptoms and function. Because people with RA often live with high levels of debilitating symptoms, it is essential that the items query content that is relevant to people living with RA. Here, we report the results of cognitive debriefing of selected PROMIS SFs in people with RA.

Methods: Participants were patients with RA receiving treatment at one of 3 US academic rheumatology centers. One-on-one phone interviews were conducted using a "talk through" format after patients completed the following SFs: Physical Function v1.0 (PF 20a), Pain Interference v1.0 (PI; 8a), Fatigue v1.0 (FAT; 7a, 8a), Participation in Social Activities and Roles v2.0 (PSRA 8a). Perceived relevance of the items and responses were probed by a trained interviewer. Conversations were recorded and transcribed.

Results: The 32 participants were mostly female (72%) with a mean (SD) age of 54 (13) years and well-established disease (13 [10] yrs). Participants were racially (66% white, 19% black, 13% native American, 9% Asian, 13% multi-race) and geographically (34% mid-Atlantic; 41% East; 28% South; 28% rural) diverse. Ninety-seven percent had some college or higher education. On average, compared with the general US population, participants reported higher mean PI (57.9 [10.6]) FAT-7a (53.2 [9.9]), FAT-8a (55.3 [10.3]), and worse PF (42.2 [11.0]) and PSRA (46.7 [10.9]). Across domains, almost all items were rated as somewhat/very relevant (PF 87-100%; PI 87-100%; PSRA 84-100%) and question content and response options as somewhat/very easy to answer (PF 91%, PI 90%, PSRA 91%). Ratings were similar for fatigue except on one item ("How often were you too tired to take a bath or shower") where 25% of respondents rated it "not at all relevant." When asked how they select a response for pain and fatigue items, some (38% and 20%, respectively) thought of the intensity of symptoms, others (28% and 77%, respectively) thought of how the symptom impacted physical and role function, and the rest (34% and 33%, respectively) considered both intensity and function.

Conclusion: Almost all participants rated Physical Function, Pain Interference, Fatigue, and Participation in Social Roles and Activities SFs as relevant to their experience with RA and easy to answer. These results contribute new evidence of construct and content validation and the meaningfulness of scores in people with RA supporting use of these PROMIS SFs in research and clinical applications. Funding PCORI IP2-PI0000737 and SC14-1402-10818.

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The Importance of Outcome Measures in Rheumatoid Arthritis – Validity of the Routine Assessment of Patient Index Data 3 in a Real World Setting

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The Importance of Outcome Measures in Rheumatoid Arthritis - Validity of the RAPID3 (Routine Assessment of Patient Index Data 3) in a United States "Real World Setting"

Background/Purpose: Over the last five years the concept of "Treat to Target" has been accepted internationally and is gaining momentum in the United States (US). In a real world (RW) setting however, rheumatologists have been slow to consistently obtain and utilize objective outcome measures. It is currently estimated that approximately 50 percent of US rheumatologists are obtaining outcome measures and of those, approximately one third are using the outcome measures in treatment decisions. The RAPID3 is a pooled index of the 3 patient-reported American College of Rheumatology Core Data Set measures. It has been validated against the Disease Activity Score (DAS-28) and Clinical Disease Activity Index (CDAI). The goal, to compare high, moderate, low and remission categories of RAPID3 to DAS28, DAS28-CRP, CDAI and the Simplified Disease Activity Index (SDAI) in RA patients enrolled in the JointMan registry (JM). JM captures RA criteria, disease features, joint counts, outcome measures, serology, medication efficacy and safety.

Methods: Retrospective registry review of data from 22 US rheumatologists. All 5 outcomes were available in 4241 patients over 22876 visits from 2009 to 2016. Standard score ranges for measures were used. All five metrics were compared against each other using the Pearson's and Spearman's correlations.

Results: RAPID3 scores correlated significantly ($p < 0.0001$) with all other scores using both Pearson's and Spearman's correlation coefficients. Overall, 65.5% of patients who met DAS28/CDAI moderate/high activity criteria met similar RAPID3 severity criteria; 47.5% who met RAPID3 remission/low activity criteria met similar DAS28/CDAI criteria.

Category	Value(s)
Average Age, (SD)	64 (14.11)
Female, n (%)	3166 (74.65)
White, n (%)	3266 (77.01)
Fulfilled 1987 or 2010 Criteria for RA, n (%)	3058 (72.11)

General demographics for all patients

Pearson's Correlation Coefficient				
	Rapid3 Raw	CDAI	DAS28	DAS28-CRP
SDAI	0.5994	0.9769	0.8178	0.9091
DAS28-CRP	0.4434	0.9069	0.8907	
DAS28	0.4275	0.8112		
CDAI	0.6046			
Spearman's Correlation Coefficient				
	Rapid3 Raw	CDAI	DAS28	DAS28-CRP
SDAI	0.6979	0.9869	0.7843	0.8694
DAS28-CRP	0.4327	0.76	0.868	
DAS28	0.4043	0.7634		
CDAI	0.7039			

Correlation coefficients for all metrics

Disease Activity State	Rapid3		CDAI		Das28-CRP		DAS28-ESR		SDAI	
	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage	Count	Percentage
High	10797	47.23%	3688	16.13%	1191	5.21%	1139	4.98%	2920	12.77%
Moderate	6628	28.99%	7654	33.48%	5082	22.23%	7086	31.00%	7945	34.76%
Low	2940	12.86%	9228	40.37%	2200	9.62%	4061	17.76%	9490	41.51%
Remission	2495	10.91%	2290	10.02%	14387	62.94%	10574	46.26%	2505	10.96%

The distribution of disease activity states for each outcome metric.

Conclusion: In JM, the RAPID3 correlated with the CDAI and the SDAI strongly. RAPID3 correlated with the DAS28 and the DAS28-CRP at a moderate /low level. This data support continued use of the RAPID3 as an outcome measure and is the first publication validating the RAPID3 with the SDAI in a RW setting.

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Abstract Number: 541

Patient Goals in Rheumatoid Arthritis Care: A Literature Review

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Background/Purpose: While clinician goals when treating rheumatoid arthritis (RA) focus on achieving low disease activity or remission, RA patient goals remain largely unexplored. Patient-clinician goal concordance in other chronic diseases such as diabetes is associated with improved self-management. The aim of this literature review is to identify needs, goals, and expectations of RA patients in order to better guide systematic elicitation of patient goals in clinical encounters.

Methods: An academic librarian searched PubMed, Ovid MEDLINE, PsychINFO, and Cochrane database using a specialized algorithm that incorporated the subject terms: rheumatoid arthritis, goals, health priorities, attitude to health, needs, expectations, activities of daily living, quality of life, and treatment outcome. Search was limited to papers in English and adult patient populations. Titles and abstracts were retrieved and manually screened. The inclusion criteria for the papers were empirical investigations, quantitative or qualitative, involving assessments of the needs, goals, and expectations of adult patients with RA. Investigators then reviewed selected papers utilizing an inductive approach.

Results: Thirty-four articles were identified in the search, of which 21 were included in the final review. We identified 453 discrete patient goals (table) which were grouped into four major themes: 1) the bodily experience of RA, 2) achieving normalcy and wellness maintenance, 3) social connectedness and support, and 4) interpersonal and systemic

health care interactions.

***Conclusion*:** RA patients identify many goals not often explicitly considered by clinicians. The four major themes identified in this review will be used to inform a measure designed to capture RA patient goals which reflects that living with RA is a multidimensional experience. RA treatment goals must be collaboratively developed with clinicians and within the context of the patient's life. Future research should include the measurement of patient goals and the development of a tool designed to elicit patient goals for RA treatment and improve patient-clinician goal concordance.

Table - Domain-categorized RA patient goals (*n*=453)

The Bodily Experience of Rheumatoid Arthritis	**Achieving Normalcy and Wellness Maintenance**	**Social Connectedness and Support**	**Interpersonal and Systemic Health Care Interactions**
n=153	***n=127***	***n=30***	***n=143***
Maintain/improve function (30)	Empowerment/Self-efficacy (29)	Social support (12)	Patient-centered care (25)
General disease improvement (18)	Normalcy (24)	Social connection (9)	RA patient education improvement (25)
Energy improvement (17)	General wellbeing (19)	RA peer support (5)	Access to rheumatology care (17)
Pain improvement (17)	Cope with work (17)	Social acceptance/awareness of RA (4)	Sensitive delivery of medical care (17)
Stay mobile (16)	Freedom (15)		Access to support services (13)
Decrease medication side effects (9)	Cope with domestic pursuits (9)		Physician-patient communication (12)
Prevent progression (8)	Mood improvement (11)		Early RA care improvement (8)
Swelling improvement (7)	Reduce stress/anxiety (3)		Positive relationship with provider (8)
Reduction in medication (6)			Care coordination improvement (7)
Stiffness Improvement (6)			Trust in medical provider (5)
Improve treatment (5)			Access to primary care (2)
Improvement in physical appearance (4)			Cost effective treatment (2)
Sexual intimacy/fertility concerns (3)			Equity in RA treatment access (2)
Medication effectiveness (3)			
Fine motor skills improvement (2)			
General health maintenance (1)			
Remission (1)			

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Changes on Body Composition in Women with Long-Standing Established Rheumatoid Arthritis: Differences By Level of Disease Activity

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Background/Purpose: Studies on association between inflammatory activity and body composition changes in rheumatoid arthritis (RA) are controversial due to some limitations: use of low accuracy methods to evaluate body composition such as body mass index (BMI), or methods with high cost and operational complexity (CT and MRI); analysis not separated by sex; inclusion of women with different menopausal status and inclusion of non validated criteria to assess disease activity. Currently, the best method in clinical practice for body composition analysis is dual energy X-ray absorptiometry (DXA). However, no studies on RA activity and body composition by DXA included evaluation of visceral adipose tissue in patients with long standing RA. Thus, we sought to verify the association between body composition by DXA, including visceral fat, and inflammatory activity in women with long standing established RA.

Methods: 78 postmenopausal women with RA (ACR 2010) were assessed by questionnaire, laboratory tests and body composition by DXA (muscle mass, total body fat and visceral fat). Patients with conditions known to influence body composition were excluded. Disease activity was assessed by composite indices (DAS28, CDAI, SDAI) and C-reactive protein (CRP). The potential association between body composition and disease activity was analyzed by Pearson correlation, Fisher´s test, ANOVA and Tukey´s test ($P < 0.05$).

Results: The mean age and disease duration were 61.1 ± 7.7 and 18.1 ± 10.9 years, respectively. 70.5% of women had BMI ≥ 25kg/m^2. The mean values of DAS28 and CRP were 3.57 ± 1.36 and 9.1 ± 10.9 mg/L, respectively. There was a negative and statistically significant correlation between CRP and appendicular muscle mass index ($r = -0.234$, $P = 0.039$). After adjusting for disease duration, BMI, physical activity, current and cumulative dose of prednisone and comorbidities, we found that women with CRP>10 mg/L had lower appendicular muscle mass index than those with CRP 5-10mg/L and CRP<5mg/L (6.3 ± 0.8 kg/m^2, 7.2 ± 1.2 kg/m^2 and 6.8 ± 1.0 kg/m^2, respectively; $P = 0.013$). Regarding to body fat, women with moderate inflammatory activity (PCR 5-10mg/L) had more total fat than those with CRP>10mg/L and CRP<5mg/L (12.4 ± 3.5 kg/m^2, 9.9 ± 3.6 kg/m^2 and 10.5 ± 2.8 kg/m^2, respectively; $P = 0.014$). Similarly, women with PCR 5-10mg/L had more visceral fat than women with very high and lower PCR (812.5 ± 266.4cm^3, 604.3 ± 236.3cm^3 and 658.9 ± 255.6cm^3; $P = 0.009$).

Conclusion: PCR was the only activity parameter associated with body composition in women with long-standing RA. High inflammatory activity that persists after a long disease duration was associated with lower muscle mass and lower fat mass values (including visceral adipose tissue), suggestive of more exuberant rheumatoid cachexia. Moreover, moderate activity was associated with higher values of visceral fat, which is known to be associated with increased cardiovascular risk. These results point to the existence of different body composition profiles according to RA inflammatory status, suggesting the importance of individualized approaches to sarcopenia and adiposity according to each disease activity level in long-standing established RA.

Abstract Number: 543

Synovial Features of Rheumatoid Arthritis and Psoriatic Arthritis Differ in Patients in Clinical and Ultrasound Remission after Anti-TNF Therapy

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Background/Purpose: Persistent disease remission is the major goal of Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA) treatment. The combined use of clinical and ultrasound selection criteria to define remission status reduces the disease flare rate after treatment tapering or discontinuation in RA but not in PsA patients. The aim of the study was to define the synovial features of RA and PsA patients in clinical and ultrasound remission achieved through combination therapy with Methotrexate and TNF-blockers.

Methods: RA patients in stable remission (n=22) (DAS<1.6 for at least 6 months), RA patients in stable low disease activity (LDA) (n=8) (1.6<DAS<2.4 for at least 6 months) and PsA patients in stable remission (n=15) (DAS<1.6 and PASI=0 for at least 6 months) achieved by MTX+anti-TNF agents (Adalimumab 40mg or Etanercept 50mg) with Power Doppler (PDUS) negative Synovial Hypertrophy (SH) (confirmed twice 3 months apart) underwent synovial tissue biopsy. RA patients with high/moderate disease activity naïve to any DMARDs (n=50) were included as comparison group. Immunostaining for CD68, CD21, CD20, CD3, CD31 and Collagen was performed.

Results: PDUS negative RA patients in remission did not differ from PDUS negative RA patients in LDA and PDUS negative PsA patients in remission for age, sex, disease duration, treatment duration and mean dose of MTX or TNF-inhibitor regimen. PDUS negative RA patients in remission showed lower histological scores for synovial $CD68^+$ ($p=0.001$ for lining and sublining), $CD20^+$ ($p=0.01$ for lining and $p=0.03$ per sublining), $CD3^+$ ($p=0.01$ for lining and sublining), $CD31^+$ vessels ($p<0.001$) and collagen deposition ($p=0.03$ for lining and $p=0.01$ for sublining) compared to PDUS positive RA patients naïve to treatment with high/moderate disease activity. However, PDUS negative RA patients in LDA, showed lower histological scores only for sublining $CD68^+$ ($p=0.03$) and $CD20^+$ cells ($p=0.05$), lining $CD3^+$ cells ($p=0.04$), $CD31^+$ vessels ($p<0.001$) and sublining deposition of collagen ($p=0.05$) compared to PDUS positive RA patients naïve to treatment with high/moderate disease activity. In addition, there was no significant difference in terms of lining and sublining $CD68^+$, $CD20^+$, $CD3^+$, $CD31^+$ cells and collagen comparing PDUS negative RA patients in remission and in LDA respectively. On the contrary, PDUS negative PsA patients in remission did show higher histological scores for sublining $CD68^+$ ($p=0.04$) and $CD3^+$ cells ($p=0.04$) as well as $CD31^+$ vessels ($p=0.01$) than PDUS negative RA patients in remission.

Conclusion: PDUS negative RA patients in remission have comparable synovial histological features compared to PDUS negative RA patients in LDA. However, PsA patients in remission are characterized by higher degree of residual synovial inflammation compared to RA patients in remission despite PDUS negativity after TNF-inhibition success.

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Abstract Number: 544

Power Doppler Ultrasound Signal Associates with Abnormal HDL Function and Suppression of Paraoxonase 1 Activity in Patients with Rheumatoid Arthritis

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Background/Purpose: Musculoskeletal ultrasound (MSUS) can detect synovitis by Power doppler (PDUS) and can predict erosive progression on xrays in rheumatoid arthritis (RA) patients. Our previous work has reported an association of active RA with impairment in HDL function and suppression of paraoxonase-1 (PON1) activity, a novel risk factor for cardiovascular disease (CVD), which has been associated with carotid plaque in RA patients. In the current work we evaluated an association of PDUS signal with HDL function and PON1 activity in patients with RA.

Methods: Assessment of PDUS was performed on 24 RA patients naive to biologics in a pilot 12 month open-label study of subcutaneous abatacept. Seven joints were scanned by MSUS of the most affected side (wrist, MCP joint 2/3, PIP joint 2/3 and MTP joint 2/5) according to Backhaus et al. (*A&R* 2009;61:1194-201). PDUS was scored semiquantitatively according to published consensus definitions (*J Rheum.* 2005;32:2485-7). HDL's anti-oxidant function was measured by a cell free assay as described previously (*A&R* 2009; 60(10): 2870-9). PON1 activity was measured by a previously published assay with minor modifications (*A&R* 2012; 64(6):1828-37). Total and HDL cholesterol (HDL-C) levels were determined by standard methods.

Results: Patients with the highest baseline PDUS score (first tertile PDUS) had significantly worse HDL function as measured by a higher HDL inflammatory index (HII) compared to patients with lower baseline PDUS signals in the second and third PDUS tertiles (table). A higher PDUS score was significantly correlated with a higher HII (r= 0.50, p=0.01, n=24). In contrast, HDL-C and PON1 activity levels were lower in patients with high PDUS scores (table) and a significant inverse correlation was noted between PDUS score and PON1 activity (r=- 0.45, p=0.03, n= 24). Associations between other disease assessments (ESR, DAS28, or CDAI) and HDL function and PON1 activity were noted, but were of lesser magnitude than correlations with PDUS score (r values = -0.20- 0.30, all p values >0.15). Following treatment with abatacept for a minimum of 3 months, patients with the greatest decreases in PDUS showed modest associations for greater improvement in HDL function, PON1 activity, and HDL-C levels compared to patients with the lesser change in PDUS (table).

Conclusion: In a pilot study of 24 RA patients naïve to biologics, higher baseline PDUS scores identified patients with worse anti-oxidant function of HDL and lower PON1 activity. Improvement in PDUS score with abatacept treatment showed trends for improvement in HDL function, PON1 activity, and HDL-C levels. This data supports previous work suggesting a direct association of joint inflammation with abnormal HDL function, and suggests that further evaluation of PDUS as a non-invasive CV risk assessment tool in RA may be warranted.

	Tertile 1 PDUS-Baseline (n=8)	**Tertile 2 PDUS-Baseline (n=7)**	**Tertile 3 PDUS-Baseline (n=9)**
PDUS Score	12.4 ± 1.8	7.0 ± 1.0*	3.8 ± 1.1*
Age (years)	56 ± 12	39 ± 13*	53 ± 10
Gender (% female)	75	100	100
Ethnicity (% hispanic)	13	29	22
Race (% caucasian)	63	100	44
Methotrexate (% use)	63	57	22
Hydroxychloroquine (% use)	0	14	11
Prednisone (% use)	13	29	22
ESR (mm/hr)	56 ± 30	34 ± 17	39 ± 14
DAS28 (ESR, 4 variable)	6.7 ± 0.7	6.3 ± 0.8	5.9 ± 0.4*
CDAI	41 ± 6	39 ± 5	31 ± 4*
Total Cholesterol (mg/dL)	197 ± 63	208 ± 75	210 ± 51
HDL Cholesterol (mg/dL)	58 ± 16	69 ± 20	70 ± 28
HDL Inflammatory Index (HII)	4.47 ± 2.00	1.78 ± 0.56*	2.01 ±0.72*
PON1 Activity	82 ± 61	89 ± 54	170 ± 130
	Tertile 1 PDUS Δ (n=7)	**Tertile 2 PDUS Δ (n=9)**	**Tertile 3 PDUS Δ (n=8)**
Absolute Change in PDUS Score	-8.3± 2.4	-2.9 ± 1.1*	0.63 ± 1.9*
Absolute Change in HII	-1.36 ± 2.94	-0.22 ± 1.44	-0.53 ± 0.85
Absolute Change in PON1 Activity	8 ± 36	-33 ± 103	-45 ± 93
Absolute Change in HDL-C	25 ± 19	3 ± 44	7 ± 25

PDUS= power doppler ultrasound, ESR=erythrocyte sedimentation rate, DAS28=disease activity scale with 28 joint count, CDAI=clinical disease activity index, HDL= high density lipoprotein, PON1=paraoxonase 1. *P<0.05 compared to Tertile 1. Slight tertile size variability due to grouping of patients with the same PDUS baseline score/PDUS Δ score in the same tertile for unbiased comparisons.

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Abstract Number: 545

Utility of Power Doppler Ultrasound-Detected Synovitis for the Prediction of Short Term Flare in Rheumatoid Arthritis Patients in Clinical Remission

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ultrasound has been shown to detect subclinical synovitis in patients who are in clinical remission, in rheumatoid arthritis (RA). The value of power Doppler ultrasound (PDUS) to predict flares in patients with RA in remission has not been fully studied. To determine whether PDUS assessment of synovitis predicts short term flares in patients with RA in clinical remission.

Methods: Consecutive RA patients in clinical remission (DAS28 < 2.6) were included. US examinations were performed at baseline by the same rheumatologist, blinded to clinical data, using an Esaote MyLab 70 machine (6-18 MHz broad band multifrequency linear transducer). A total of 20 joints of both hands were assessed: wrists, first to fifth MCPs and second to fifth PIPs. PDUS signal was evaluated on a semi-quantitative scale from 0 to 3. PD synovitis was defined as the presence of intraarticular USPD signal ≥ 1, and was treated as a dichotomous variable. On the same day a complete clinical assessment was performed by another rheumatologist. Patients were followed-up and regularly assessed every two/three months. Flare was defined as the requirement of a change in disease modifying antirheumatic drugs (DMARDs) (increasing dose, adding or changing DMARDs or biologics therapy) by the treating rheumatologist (blinded to baseline PDUS findings); or an increase in DAS28 >1.2 or a DAS28 >3.2 on follow-up. Baseline variables and the presence of PDUS, were compared among patients with and without flares in univariate analysis. Multivariable analysis using a Cox proportional hazards model, with flare as the outcome variable, and PD signal, demographic characteristics, and baseline disease activity as independent variables were also calculated.

Results: 80 patients fulfilling DAS28 remission criteria were included. Baseline patients' characteristics are shown in the table. Among the 80 patients, 20 (25%) showed at least one joint with positive PDUS signal. Mean number of joints with PD signal was 1.75 (SD: 1.16, range 1-5). In 35 patients a treatment reduction was initiated by the treating rheumatologist, after inclusion in the study (blinded to baseline PDUS findings). Among the 80 patients on remission, 36 (45%) experienced a flare within follow up (median follow up (IQR): 15.4 (9.4-27.3) months). Flare occurred a median of 9.4 (IQR: 4.9-15.7) months after inclusion in the study (US date). In univariate analysis neither a positive PDUS signal, nor the reduction of treatment, nor the use of DMARDs in contrast with biologics, were associated with flares (table). In the multivariate Cox proportional hazards model, none of the variables were associated with an increased risk of flare.

Conclusion: Among RA patients in clinical remission synovial inflammation by PDUS was seen in 25%, but it was not associated with disease flare in the short term. None of the variables studied were associated with increased risk of flare.
Table. Patients' characteristics.

Feature	Patients with flares (n=36)	Patients without flares (n=44)	*p value*
Female, n (%)	28 (78)	33 (75)	0.771
Mean age (SD), years	60.7 (15.8)	58.1 (12.7)	
Mean disease duration (SD), years	6.2 (8.3)	8.2 (7.8)	0.3023
DMARDs alone, n (%)	25 (69.4)	29 (66)	0.737
Biologics DMARD combination, n (%)	7 (19.4)	13 (29)	0.2993
Biologics monotherapy, n (%)	4 (11)	2 (4.6)	0.2673
Erythrocyte sedimentation rate, median (IQR)	21.9 (14)	22.3 (13.4)	0.8900
Swollen joint count 28, mean (SD)	0.05 (0.2)	0.09 (0.3)	0.5562
Tender joint count 28, mean (SD)	0.11 (0.4)	0.11 (0.4)	09772
Mean DAS28 (SD)	2.07 (0.42)	2.06 (0.39)	0.9267
Patients with at least one joint having USPD signal ≥ 1, n (%)	12 (33)	8 (18)	0.119
Patients with treatment reduction, n (%)	17 (47)	18 (41)	0.571

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Abstract Number: 546

Boolean-Based Remission in Rheumatoid Arthritis Using Physician Versus Patient Global Assessment: Differences in Ultrasonographic Disease Activities, Sustainabilities, and Relapse Rates

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Patient global assessment (PtGA), despite not being exclusively related to disease activity, is included in Boolean-based remission (BR) criteria for RA. This study evaluated the US disease activities, sustainabilities, and relapse rates of RA patients in BR by using physician (Ph) GA (BR-PhGA) compared to those in BR by using PtGA (BR-PhGA).

Methods: Established RA patients in clinical remission (DAS28-ESR<2.6) for ≥6 months with a stable treatment regimen were included. Fulfillment of BR-PtGA and BR-PhGA criteria were assessed. A standard gray scale (GS) and power Doppler (PD) US examination of 28 joints (included in DAS28) for the presence of synovitis was performed at baseline

and 6th month (NI). GS and PD synovitis signals were semiquantitatively graded from 0 to 3. US disease activity was also categorized as US remission (PD-/GS-), inactive synovitis (PD-/GS+), and active synovitis (PD+/GS+). Clinical relapse (1. Loss of DAS28 remission; 2. Loss of BR) and US relapse (Loss of US remission due to 1. Any increase in PG/GS scores; 2. Only grade≥2 increase in PD/GS scores) rates (each of 4 definitions) were determined at 6th month.

Results: 96 out of 398 (24.1%) RA patients in DAS28 remission were enrolled (F/M=60/36, age 53±12, disease duration 11±5 yrs, bDMARDs 43%, RF/Anti-CCP positivity 83%). BR-PtGA was fulfilled in 37 (38.5%) and 31 (32.3%) patients and BR-PhGA was fulfilled in 61 (63.5%) and 66 (68.8%) patients at baseline and 6th month, respectively. Baseline US disease activities of patients in BR-PtGA and BR-PhGA were not significantly different (*Table 1*). PD and GS scores of patients in BR-PtGA were similar to those of not fulfilling BR-PtGA. However, patients in BR-PhGA had significantly lower PD and GS scores compared to non-remission counterparts, 0 (1-4) *vs* 4 (2-7), *P*=0.001; 3 (0-7) *vs* 6 (3-10), *P*=0.003, respectively. Loss of DAS28 remission rates were similar in both BR groups (16.2% *vs* 18%, *P*=0.82), whereas loss of corresponding BR was slightly lower in BR-PhGA patients (38% *vs* 21%, *P*=0.08). US relapse rates in BR-PtGA and BR-PhGA patients who were in US remission at baseline (loss of US remission: 3/10 *vs* 7/15, *P*=0.41; loss of US remission due to grade≥2 increase in PD/GS score: 1/16 *vs* 6/20, *P*=0.16), and changes in US disease activities over time were also comparable (*Table 2)*.

Conclusion: US verified disease activity of patients in BR-PhGA is similar to patients in BR-PtGA. BR-PhGA differentiates US inflammation better than the BR-PtGA with higher sustainability and similar US relapse rates. PtGA may be substituted with PhGA in BR, particularly in established RA patients.

Table 1. Baseline clinical characteristics and ultrasonographic disease activities of patients in BR- PtGA and BR-PhGA*			
	Boolean REM with PtGA (n=37)	**Boolean REM with PhGA (n=61)**	***P* value**
Age, mean±SD years	53.4±13.9	53.2±13.1	0.94
Female, %	62.2	62.3	0.99
Education level, mean±SD years	6.9±3.9	6.8±3.6	0.88
Disease duration, mean±SD years	10.4±5.0	10.4±5.2	0.98
RF/Anti-CCP positivity, %	83.8	82.0	0.82
Currently on biologic DMARDs, %	40.5	41.0	0.96
Currently on glucocorticoids, %	13.5	14.8	0.86
HAQ (0-3)	0.12 (0-0.69)	0.12 (0-0.50)	0.55
DAS28-ESR, mean±SD	2.08±0.44	2.10±0.43	0.81
PD synovitis sum score (0-84)	1 (0-4.5)	1 (0-4)	1.0
PD synovitis sum scores (without grade 1 signals)	0 (0-4)	0 (0-3)	0.99
GS synovitis sum score (0-84)	4 (0-7)	3 (0-7)	0.93
GS synovitis sum scores (without grade 1 signals)	2 (0-5.5)	2 (0-5.5)	0.82
US remission (PD-/GS-), %	27	24.6	0.79
PD-/GS- without grade 1 signals	43.2	44.3	0.92
Inactive synovitis (PD-/GS+), %	10.8	11.5	0.92
PD-/GS+, only with grade ≥2 GS signals	16.2	14.8	0.84
Active synovitis (PD+/GS+), %	62.2	63.9	0.86
PD+/GS+, only with grade ≥2 signals	40.5	41	0.96
US erosion, %	67.6	70.5	0.76
US tenosynovitis, %	21.6	21.3	0.97
**The values were presented as median (IQR) unless indicated otherwise.*			

Table 2. Change between baseline and 6th month of clinical and ultrasonographic findings of patients in BR-PtGA and BR-PhGA*		
	Boolean REM with PtGA (n=37)	**Boolean REM with PhGA (n=61)**
DDAS28	0.20 (0.40)	0.24 (0.59)
DHAQ	-0.1 (0.4)	-0.1 (0.4)
DPD synovitis sum score	-0.2 (2.1)	-0.3 (2.4)
DGS synovitis sum score	-0.5 (2.8)	-0.6 (3.1)
Change in PD scores, %	35.1	36.1
Decreased	37.8	32.8
Not changed	27.0	31.1
Increased		
Change in PD scores (without grade 1 changes), %	27.0	29.5
Decreased	54.1	49.2
Not changed	18.9	21.3
Increased		
Change in GS scores,%	48.6	49.2
Decreased	21.6	21.3
Not changed	29.7	29.5
Increased		
Change in GS scores (without grade 1 changes), %	27.0	29.5
Decreased	56.8	50.8
Not changed	16.2	19.7
Increased		
No. of patients who were not in US remission (PD-/GS-) at baseline	27	46
Achievement of US remission at 6th month, %	18.5	15.2
No. of patients who were not in US remission (PD-/GS- without g rade 1 signals) at baseline	21	35
Achievement of US remission at 6th month, %	19.0	31.4
**The values were presented as mean (SD) unless indicated otherwise. All P values>0.05*		

Disclosure: G. Ozen, None; **A. U. Unal**, None; **H. Direskeneli**, None; **N. Inanc**, None.

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Abstract Number: 547

Concordance Between Ultrasound Joint Synovitis and Clinical Joint Assessments By Patients or Physicians in Rheumatoid Arthritis

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Background/Purpose: Ultrasonography (US) has been prevalently used as a valid and objective modality for joint examination in patients with rheumatoid arthritis (RA). This study aimed to examine and compare the concordance between joint symptom, tenderness, or swelling and US synovitis.

Methods: Fifty patients with RA (84% female; median age, 69 years; disease duration, 2.4 years; disease activity score of 28 joints, 3.84) completed the self-evaluation of joint symptoms including pain and considerable stiffness in the (proximal) interphalangeal, metacarpophalangeal, wrist, elbow, shoulder, knee, and ankle joints. These joints were also subjected to physical examination by a physician to evaluate for the presence of tenderness and/or swelling, and to US examination for the presence of synovitis defined as gray-scale score ≥2 or power Doppler signal score ≥1.

Results: In a total of 1492 evaluated joints, symptoms, tenderness, and swelling were observed in 288 (19.3%), 182 (12.2%), and 220 (14.7%) joints, respectively, and US synovitis was observed in 317 (21.2%) joints. The overall concordance rate with US synovitis was the least for joint tenderness ($\kappa = 0.30$) when compared with joint symptoms ($\kappa = 0.39$) or swelling ($\kappa = 0.43$). Furthermore, US synovitis joint count of 28 joints showed a better correlation with swollen joint count ($r^2=0.53$, $p<0.0001$) and with symptomatic joint count ($r^2=0.54$, $p<0.0001$) than with tender joint count ($r^2=0.29$, $p<0.0001$).

Conclusion: Joint swelling and patient-reported joint symptoms showed better concordance with US synovitis than joint tenderness.

Disclosure: A. Hirata, None; **T. Ogura**, None; **S. Takenaka**, None; **H. Ito**, None; **Y. Fujisawa**, None; **K. Mizushina**, None; **M. Imamura**, None; **N. Hayashi**, None; **H. Kameda**, None.

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Abstract Number: 548

Body Mass Index Is Positively Correlated with Diverse Disease Activity Measures in Longstanding Rheumatoid Arthritis

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Background/Purpose: Obesity is a common problem with patients who have rheumatoid arthritis (RA). Adipose tissue has been shown to produce cytokines that are proinflammatory. The measurement of Body Mass Index (BMI) is a proxy for determining the amount of adipose tissue present in an individual. The impact of BMI on disease activity measures in RA have been contradictory, and, in fact, studies have shown that a high BMI is protective, as defined by x-ray changes for patients with early onset RA. The objective of this trial is to determine whether obesity and BMI are positively correlated with diverse disease activity measures (DAMs) in longstanding RA.

Methods: Patients at a community based rheumatology clinic undergo DAM assessments on a routine basis as part of the implementation of a treat to target (T2T) strategy. These assessments include the disease activity score in 28 joints (DAS28CRP), the power Doppler joint count (UPD), and the multibiomarker disease activity test (MBDA), as well as several other commonly assessed DAMs. The UPD includes scoring at six dorsal wrist and six dorsal MCP sites. The average duration of RA in patients at this clinic is > 10 years. Also, as currently mandated by the authorities, BMI and other vital signs are obtained on a regular basis. Correlations were determined by Pearson's coefficients, and categorical data was compared by T tests. Patients were categorized as underweight (BMI < 18), normal weight (BMI > =18 and <25), overweight (BMI >=25 and <30), and obese (BMI >= 30).

Results: Table 1 BMI and Comparisons with Diverse Disease Activity Measures

	N	BMI VS	Prob	Normal Wt Avg +/- SD	Overweight Avg +/- SD	Obese Avg +/- SD	Prob Nl vs Over	Prob Nl vs Obese	Prob Over vs Obese
Leptin	241	r=572	p<0.0001	11.8 +/- 19.7	19.2 +/- 18.4	30.4 +/- 23.9	p=0.01	p<0.0001	p<0.0001
DAS28CRP	260	r=537	p<0.0001	3.63 +/- 1.62	3.86 +/- 1.24	4.47 +/- 1.32	NS	p<0.0001	p<0.0001
DAS28ESR	236	r=285	p<0.005	4.11 +/- 1.38	4.10 +/- 1.45	4.47 +/- 1.32	NS	NS	p<0.0001
CRP	238	r=340	p<0.0001	4.6 +/- 13.8	7.2 +/- 15.1	6.0 +/- 8.9	NS	NS	NS
ESR	236	r=289	p<0.0001	18.3 +/- 13.7	19.0 +/- 20.4	21.9 +/- 19.4	NS	NS	p=0.02
MBDA	242	r=300	p<0.0001	37.7 +/- 13.6	40.6 +/- 16.2	41.3 +/- 12.7	NS	p=0.05	p<0.0001
HAQ	233	r=289	p<0.0001	1.9 +/- 1.6	1.8 +/- 1.4	2.7 +/- 1.8	NS	p=0.02	p=0.02
Pt Global	229	r=228	p<0.001	3.5 +/- 2.4	3.5 +/- 2.2	5.0 +/- 2.3	NS	NS	p<0.0001
TJC	271	r=222	p<0.001	7.1 +/- 6.8	7.6 +/- 9.7	11.4 +/- 7.5	NS	p=0.003	p<0.0001
CDAI	236	r=206	p<0.001	18.6 +/- 12.2	19.0 +/- 20.4	21.9 +/- 19.4	NS	p<0.001	p=.003
RAPIDIII	244	r=224	p<0.001	8.9 +/- 6.0	8.3+/- 5.1	11.4 +/- 7.5	NS	NS	p=0.02

There were only two patients in the underweight category, and that category was not included in this analysis.

Conclusion: BMI positively correlates with, and shows significant increases in weight categories for several important measures of disease activity in patients with longstanding RA. Though the DAS28CRP, MBDA, and UPD generally correlate significantly in this clinic (r= > 0.500), in this study, UPD was the only one of these measures that did not correlate with BMI (r = 0.090). One possible explanation is that power Doppler signals are very dependent on the distance of the probe from the site of the signal. The UPD method utilized includes assessments of the dorsal wrist at six out of twelve sites. Subcutaneous adipose tissue in overweight patients perhaps blunted the signals. Of interest, Leptin was significantly correlated with BMI and showed significant increases with weight categories. Leptin is produced by adipose tissue and is thought to be proinflammatory. Excess Leptin production might be contributory to the effects of BMI on RA disease activity. BMI is positively correlated with several important DAMs in patients with longstanding RA. Rheumatologists should significantly increase their efforts and resources to address and manage obesity in our RA patients.

Disclosure: C. Wiesenhutter, None;

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Abstract Number: 549

Work Status in Patients with Rheumatoid Arthritis Who Have Poor Prognostic Factors: Findings from a US Observational Cohort

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Background/Purpose: A number of studies have demonstrated the association between disease activity and work productivity in patients (pts) with RA. However, the relationship between work status and poor prognosis is unknown. This analysis characterized the proportion of pts with RA who had poor prognoses in an observational clinical cohort and evaluated poor prognostic factors and pts' work status.

Methods: Using the Corrona RA registry, we identified pts with RA who were biologic naïve at enrollment and had a follow-up visit at 12 months (± 3 months). Pts were characterized by RA prognosis based on factors from the 2008 ACR treatment recommendations,[1] including functional limitation (modified Health Assessment Questionnaire), extra-articular disease (Sjögren's syndrome, RA lung disease and/or nodules), seropositivity (RF and/or anti-cyclic citrullinated peptide antibodies) and erosions. Pts were categorized as having 0–1, 2 or 3+ poor prognostic indicators. Pts with missing information on any factor were excluded. Each of the three prognosis groups was compared at enrollment (including use of prior conventional synthetic DMARDs) according to use of TNF inhibitors vs non-TNF inhibitors. The relationship between poor prognosis category and work status was investigated at baseline and 12 months using a chi-squared test. A dichotomous variable was constructed, with working 'yes' defined as full- or part-time working, and working 'no' including pts who worked from home or were students, disabled or retired. Because a relationship between poor prognosis and work status might be driven by age differences (retirees are generally older), a frequency-matching approach was used

to match people across poor prognosis categories according to age group (18–44, 45–54, 55-64, 65–74, 75+ years).

Results: 3621 pts who enrolled in Corrona on/after January 2005 met the selection criteria: 1554 (42.9%), 1263 (34.9%) and 804 (22.2%) with a prognosis category of 0–1, 2 or 3+, respectively. Pts in the worst prognostic category were older (median age: 62 vs 58 years), had more established disease (median disease duration: 4 vs 1 years) and greater disease activity (median CDAI score: 14 vs 7) compared with those in the best prognosis category. After adjusting for age, there was a significant relationship between work and poor prognosis category; pts in the worst prognosis category were less likely to be in full- or part-time work at enrollment compared with those in the best prognosis category ($p<0.001$; Table). At the 12-month visit, the relationship between poor prognosis category and work status remained statistically significant ($p<0.001$; Table).

Conclusion: These data suggest that the proportion of pts with RA in full- or part-time employment was lower in those with poor prognostic factors. Further studies are needed to investigate whether treatment can prevent or reverse impairment of work status in pts with RA. 1. Saag K, et al. *Arthritis Rheum* 2008;**59**:762–84.

Table. Work status (full time/part time) at enrollment and at the 12-month visit by poor prognosis category after adjusting for age

	Poor prognosis indicators			
	0–1	**2**	**3+**	**p value***
Work status at enrollment				
Full time/part time, n (%)	398 (49.5)	351 (43.7)	297 (37.0)	<0.001
All others,† n	406 (50.5)	453 (56.3)	506 (63.0)	
Total, n	804	804	803	
Work status at 12-month visit				
Full time/part time, n (%)	383 (48.9)	314 (39.6)	277 (35.3)	<0.001
All others,† n	401 (51.1)	479 (60.4)	508 (64.7)	
Total, n	784	793	785	

*p value is calculated based on a chi-squared test of any relationship between work status and poor prognosis category; †worked from home or who were students, disabled or retired.

Disclosure: E. Alemao, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **L. Harrold**, Corrona, LLC, 1,Pfizer Inc, 2; **H. Litman**, Corrona, LLC, 3; **S. Connolly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Kelly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **W. Hua**, Corrona, LLC, 3; **L. Rosenblatt**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Rebello**, Corrona, LLC, 3; **J. Kremer**, Corrona, LLC, 1,AbbVie, Bristol-Myers Squibb, Genentech, Lilly, Novartis, Pfizer, 2,Corrona, LLC, 3,Genentech, 8.

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Abstract Number: 550

Despite Early Improvement and Limited Self-Reported Disability, Patients with Rheumatoid Arthritis Still Have Impaired Grip Strength 5 Years after Diagnosis

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Background/Purpose: In studies of rheumatoid arthritis (RA), disease activity and patient reported outcomes are often used as endpoints. However, these measures may not reflect the full impact of RA on function in all patients. The objective of this study were to: 1) investigate grip strength in early RA; 2) assess grip strength in patients with limited self-reported disability.

Methods: An inception cohort of patients with early RA (symptom duration ≤12 months), recruited in 1995-2005, was investigated. Grip force (Newton, N) was measured using the electronic instrument Grippit (AB Detektor, Gothenburg, Sweden). Average and peak grip force values of the dominant hand were evaluated and compared to the expected, based on age- and sex-specific reference values from the literature (Nilsen T et al. Scand J Occup Ther 2012; 19: 288-96). The paired t-test was used for these comparisons and for analysis of changes in grip force between visits. At each visit, expected values were subtracted from observed grip force values, and delta values were used for age-corrected analysis of changes over time. Limited self-reported disability was defined as a Health Assessment Questionnaire Disability Index (HAQ-DI) score of ≤ 0.5.

Results: A total of 225 patients with early RA (71 % women, mean age 60 years, 61 % RF positive, 57 % anti-CCP2 positive) were investigated. At baseline, the median HAQ-DI score was 0.75 (interquartile range 0.38-1.25). The mean baseline average grip force was 105 N [standard deviation (SD) 78], which was significantly lower than the corresponding expected values [266 N (SD 91) ($p<0.001$)]. Patients were managed according to usual care, with no pre-specified protocol for pharmacotherapy or rehabilitation. At 5 years, 44 % of the patients reported limited disability (HAQ-DI ≤ 0.5). The average grip force improved significantly from inclusion to the 12 month visit [age-corrected mean change: 34 N; 95 % confidence interval (CI) 26-43], and there was also some improvement between the 1-year and 5-year follow-up evaluations (age-corrected mean change 23 N; 95 % CI 14-32). At 5 years, the average grip force was still lower than expected overall (mean 139 N vs 244 N; $p<0.001$), and also among those with HAQ-DI ≤ 0.5 (mean 184 N vs 273 N; $p<0.001$). Similar patterns were observed for all comparisons of peak grip force values.

Conclusion: Grip strength improved in early RA, in particular during the first year, probably due to effects of pharmacologic anti-inflammatory treatment and rehabilitation. A substantial proportion of the patients had limited self-reported disability at 5 years after diagnosis. Among these, there was however still a significant reduction in grip strength. This suggests that further efforts to improve hand function are important in early RA.

Disclosure: M. Rydholm, None; **C. Book**, None; **I. Wikström**, None; **L. T. H. Jacobsson**, None; **C. Turesson**, None.

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Abstract Number: 551

Changes in Diverse Disease Activity Measures Are Highly Correlated Following the Initiation of Most Treatment Modalities in the Management of Longstanding Rheumatoid Arthritis

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Background/Purpose: Treating rheumatoid arthritis (RA) patients to target (T2T) has been shown to result in better outcomes in patients with relatively recent onset RA. The implementation of this method requires performing disease activity measures (DAMs) with the disease activity score in 28 joints (DAS28) being the most commonly used. The use of clinically based DAMs in patients with longstanding RA is problematic as structural damage, and other comorbidities can lead to elevated scores because of the impact on composite elements not related to inflammation i.e. patient global and tender joint count. Including additional DAMs, such as a power Doppler joint count (UPD) and multibiomarker disease activity (MBDA) could possibly lead to better assessment of this patient population. The purpose of this abstract is to determine the changes in these three diverse DAMs and the relationships of these changes following the initiation of specific treatment modalities in patient with longstanding RA.

Methods: Patients at a community based rheumatology clinic undergo DAM assessments on a routine basis as part of the implementation of a T2T strategy. These assessments include the DAS28CRP, a UPD, and the MBDA. The UPD includes scoring at six dorsal wrist and six dorsal MCP sites. Patients underwent assessments prior to change in therapy, and then generally about six months later. Patients who were on biologics and found to be under inadequate control, had their biologic discontinued and the new therapy added later, depending on the half-life of the discontinued medication. The average duration of RA in patients at this clinic is > 10 years. The average DAS28CRP 4.18 +/- 1.32, average MBDA 41.4 +/- 14, and the average UPD 7.8 +/- 4.3.

Results:

		Δ DAS28CRP			Δ MBDA			Δ UPD			DAS28CRP Vs MBDA	UPD Vs MBDA	DAS28CRP Vs UPD
	N	AVG	SD	Prob	AVG	SD	Prob	AVG	SD	Prob			
MTX/Leflunomide	10	-1.63	0.83	0.00002	-12.4	8.0	0.00025	-3.2	2.8	0.003	r = 0.510*	r = 0.325	r = 0.425
Anti-TNFs	16	-0.94	1.24	0.0029	-11.5	11.8	0.007	-3.0	3.8	0.003	r = 0.454*	r = 0.488*	r = 0.573*
Tocilizumab	12	-1.44	1.13	0.0004	+6.3	11.4	0.044	-4.5	3.3	0.001	r = -0.252	r =- 0.148	r = 0.277
Abatacept	10	-0.88	2.04	0.08	-2.5	10.8	0.24	-5	6.6	0.02	r =0.341	r =- 0.736*	r = 0.619*
Tofacitinib	11	-1.27	1.03	0.001	-11.3	13	0.035	-2.2	2.6	0.01	r =0.209	r =- 0.707*	r = 0.565*

*P value < 0.05

Conclusion: Changes in diverse DAMs have moderate to high correlations following the initiation of specific therapy with most treatment modalities utilized in the management of longstanding RA. Tocilizumab did not have a positive correlation between DAS and the MBDA, which has been previously reported, and is presumed to be secondary to its mode of action which leads to significant elevation of IL-6 in the serum. Tofacitinib, a Jak-1 inhibitor, did not have a significant correlation between DAS and the MBNA, which has also been reported recently for another Jak-1 inhibitor in development, but had significant correlation with UPD and the MBNA in this study. This data suggest the validity of adding more diverse DAMs, such as UPD, and MBDA to clinical measures, such as the DAS28CRP, as endpoints in the implementation of a T2T strategy in the management of longstanding RA.

Disclosure: C. Wiesenhutter, None;

measures-are-highly-correlated-following-the-initiation-of-most-treatment-modalities-in-the-management-of-longstanding-rheumatoid-arthritis

Abstract Number: 552

Disability in Early Rheumatoid Arthritis, Course and Predictors

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Background/Purpose: Patient reported outcome measures (PROMs), including the Health Assessment Questionnaire Disability Index (HAQ-DI), are valuable and reliable instruments for assessment of disease severity and disability in patient with early rheumatoid arthritis (RA), and have also been reported to have prognostic value. The aim of this study was to evaluate how disability varies over time in patients with early RA, and to identify early predictors of future disability in RA.

Methods: An inception cohort of patients with early RA (symptom duration ≤12 months), recruited in Malmö in 1995-2005, was followed in a structured program, including clinical evaluation and PROMs. Changes in HAQ-DI between different time points were assessed using the paired T-test. Potential predictors of moderate/severe disability (HAQ-DI >1.0) at 5 years were examined using logistic regression.

Results: A total of 233 patients (70 % women; mean age at diagnosis 60.5 years; 62 % RF positive; 57 % anti-CCP positive) were included. The median duration of symptoms at onset was 7 months. The median HAQ-DI score decreased from inclusion to 6 months (median 0.88 vs. 0.50; $p<0.001$), remained stable at 12 and 24 months, and then increased significantly again at 5 years (median 0.69; $p=0.002$ vs 24 months) and 10 years (median 0.75; $p=0.004$ vs 5 years). Baseline characteristics that predicted moderate to severe disability included high HAQ-DI scores [age-sex adjusted odds ratio (OR) 3.43 per unit; 95% confidence interval (CI) 1.88-6.27)] and high scores for pain and patient´s global assessment, but not laboratory markers of inflammation (Table). Patients with RF positive RA had a lower probability of a HAQ-DI >1 after five years (Table). Although RF negative patients were slightly older at diagnosis (mean 61.9 vs. 59.5 years) and had higher baseline HAQ scores (median 0.88 vs 0.75; $p=0.09$), there was a trend towards a negative association with 5-year moderate/severe disability also in analysis adjusted for age, sex and baseline HAQ-DI (OR 0.50; 95 % CI 0.23-1.07).

Conclusion: Disability decreased early in the disease course, and thereafter increased consistently from two years after diagnosis and onwards. The latter may be related to chronic joint damage and increasing age. Moderate to severe disability after 5 years was predicted by worse PROMs, but not by standard laboratory measures of disease activity. Patients with RF negative RA had worse disability, likely reflecting distinct factors influencing PROMs in this subgroup.

The relation between baseline characteristics in the early RA cohort and moderate/severe disability (HAQ-DI>1) at 5 years. Logistic regression analyses.

	Crude	Adjusted for age and sex
	Odds ratio (95% CI)	Odds ratio (95% CI)
Male sex	0.51 (0.23-1.15)	N/A
Age (per SD)	1.76 (1.18-2.64)	N/A
HAQ-DI (per SD)	2.31 (1.60-3.34)	2.01 (1.37-2.96)
Pain (VAS; per SD)	1.58 (1.12-2.23)	1.80 (1.22-2.64)
Patient´s global assessment (VAS; per SD)	1.50 (1.06-2.13)	1.51 (1.04-2.18)
Tender joints (per SD)	1.32 (0.94-1.85)	1.31 (0.90-1.90)
Swollen joints (per SD)	0.92 (0.66-1.29)	0.91 (0.62-1.34)
Rheumatoid factor positive	0.40 (0.20-0.79)	0.47 (0.23-0.95)
Anti-CCP positive	0.66 (0.32-1.35)	0.71 (0.33-1.48)
ESR (per SD)	1.13 (0.82-1.57)	1.02 (0.73-1.45)
CRP < 9 mg/l (below median)	1.00 (reference)	1.00 (reference)
CRP 9-27.5 mg/l (3rd quartile)	1.49 (0.67-3.28)	1.35 (0.59-3.10)
CRP > 27.5 mg/l (4th quartile)	1.30 (0.56-3.00)	1.09 (0.45-2.67)

CI=Confidence interval, N/A=Not applicable, SD=Standard deviation, VAS=Visual analogue scale

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Disclosure: T. Hansson, None; **C. Book**, None; **L. T. H. Jacobsson**, None; **C. Turesson**, None.

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Abstract Number: 553

Validation of Index of Activity Speed (Timed Up and Go test) for Outcome Measure of Patients with Long-Standing Rheumatoid Arthritis: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical Function

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Background/Purpose:

Total management including reconstructive joint surgery and rehabilitation should be needed for further improvements of physical function for long-standing RA patients. It is very important to set treatment goal for those management using index of activity speed [Timed Up and Go test (TUG)] and range of motion (ROM). The purpose of this study is to explore the characteristics of functional impairment and relationship TUG and physical function in RA patients who were needed joint surgery using multicenter prospective cohort.

Methods:

We started the prospective study in September, 2012 (Study registration: UMIN000012649). In this study, we used baseline (preoperation) data as follows; age, sex, disease duration, drug therapies, and disease activity, functional evaluations [TUG, HAQ-DI, DASH (upper limb function), joint ROM (hip, knee, ankle, shoulder, elbow, wrist)], and patient-reported outcome [EQ-5D (QOL) and BDI-II (depression)]. Correlation between TUG and other variables were determined. Association between TUG and no disability of daily activity in each 8 HAQ-DI categories and cut-off values for no disability were determined using ROC curve. TUG by disability in 8 HAQ-DI categories was compared by ANOVA with adjustment of age and sex. This study is supported by grant from the Japanese Ministry of Health, Labour and Welfare.

Results:

435 surgical patients were registered. Mean values for age, disease duration, and sex were 64.2 years, 17.1 years, and 89% female, respectively. Actually, even long-standing RA patients who were needed joint surgery had remission or low disease activity in this baseline data (median values for DAS28 (3.0) and CRP (0.2 mg/dl). 23.0% of the patients were treated with biologics. We confirmed the significant correlation ($r>0.3$) between TUG and Age, HAQ-DI, DASH, patient-reported outcome (EQ-5D) and range of motion (hip, knee, shoulder). We also found significant relationship between TUG and 5 of 8 categories in HAQ-DI.

The relevant association between TUG and category Walking, Arising, and Activity (AUC>0.7) was found based on ROC analyses. Cut-off value of TUG for HAQ remission (<0.5) was 8.6 seconds (sensitivity 64%, specificity 65%). Cut-off for no disability in category Arising, Walking, and Activity were 8.6s (sensitivity 74%, specificity 63%), 8.4s (sensitivity 76%, specificity 71%) and 8.2s (sensitivity 69%, specificity 66%), respectively. Age, sex-adjusted TUG for no disability in Arising, 9.2s (95%CI: 8.2-10.1), Waling, 8.6s (95%CI: 7.6-9.6), Activity, 8.6s (95%CI: 7.2-10.0).

Conclusion: TUG was significantly associated with other physical function measurements and patient-reported outcome. The cut-off values of TUG (~9 seconds) should be important for assessment of disability in patients with long-standing RA and could provide target of surgical procedure and rehabilitation program.

Disclosure: T. Kojima, None; **H. Ishikawa**, None; **S. Tanaka**, None; **N. Haga**, None; **K. Nishida**, None; **M. Yukioka**, None; **J. Hashimoto**, None; **H. Miyahara**, None; **Y. Niki**, None; **T. Kimura**, None; **H. Oda**, None; **S. Asai**, None; **K. Funahashi**, None; **M. Kojima**, None; **N. Ishiguro**, None.

Abstract Number: 554

Characteristics of Functional Impairment in Patients with Long-Standing Rheumatoid Arthritis Based on Range of Motion of Joints: Multicenter Prospective Cohort Study for Evaluation of Joint Surgery on Physical Function

Toshihisa Kojima[1], Hajime Ishikawa[2], Sakae Tanaka[3], Nobuhiko Haga[4], Keiichiro Nishida[5], Masao Yukioka[6], Jun Hashimoto[7], Hisaaki Miyahara[8], Yasuo Niki[9], Hiromi Oda[10], Shuji Asai[11], Koji Funahashi[1], Masayo Kojima[12] and Naoki Ishiguro[13], [1]Department of Orthopedic Surgery, Nagoya University Hospital, Nagoya, Japan, [2]Orthopedic Surgery, Niigata Rheumatic Center, Shibata, Japan, [3]Department of Orthopaedic Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [4]Rehabilitation Medicine, The University of Tokyo Hospital, Tokyo, Japan, [5]Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama city, Japan, [6]Orthopedic Surgery, Yukioka Hospital, Osaka, Japan, [7]Dept of Rheumatology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [8]Department of Rheumatology and Orthopaedic Surgery, Kyushu Medical Center, Fukuoka, Japan, [9]Orthopedic Surgery, Keio University School of Medicine, Tokyo, Japan, [10]Orthopedic Surgery, Faculty of Medicine, Saitama Medical Univeristy, Morohongo Moroyama, Japan, [11]Nagoya University Hospital, Nagoya, Japan, [12]Medical education, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [13]Department of Orthopedic Surgery, Nagoya University, Graduate School & Faculty of Medicine, Nagoya, Japan

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Background/Purpose:

Even now, in clinical practice, most of RA patients have long-standing disease and structural damage in their joints. Reconstructive joint surgery should be needed for further improvements of physical function for long-standing RA patients. It is very important to understand how much range of motion (ROM) should be needed to gain better physical function in each case.

The purpose of this study is to explore the characteristics of functional impairment in RA patients who were needed joint surgery based on ROM of joints using multicenter prospective cohort.

Methods:

We conducted this prospective study from 2012 to2015 (Study registration: UMIN000012649) supported by grant from the Japanese Ministry of Health, Labour and Welfare.

We collected data on age, sex, disease duration, drug therapies, disease activity, and physical functional including HAQ-DI. Joint range of motion including shoulder, elbow, wrist, hip knee ankle was also measured. ROM in each joint by disability in HAQ-DI categories was compared by ANOVA with adjustment of age and sex. Association between ROM of each joint and no disability of daily activity in each 8 HAQ-DI categories and cut-off values for no disability were determined using ROC curve. Independent impact of ROM each joint was also determined multivariate analysis.

Results:

460 patients who have data of ROM of any joints in registry were analyzed. Mean values for age, disease duration,

DAS28-CRP and sex were 64.5 years, 16.7 years, 3.14, and 86.8% female, respectively. Median values for CRP was 0.2 mg/dl. We could find significant association between ROM and disability in HAQ-DI category based on area under the ROC curve (AUC>0.7) as follows; shoulder in dressing, wrist in eating, hip, knee ankle in walking, shoulder in hygiene, shoulder in activity. The cut-off values of ROM of each joints for daily activity in each HAQ-DI category was shown in Table 1 using ROC curves (Table 1). Multivariate analysis adjusting disease activity, age, and sex, showed which joint had significant impact on disability of each category (Table 2).

Conclusion: ROMs of the joints were significantly associated with functional impairment. The information should be important for assessment of disability in patients with long-standing RA. The cut-off of ROM as shown in this study could be target of surgical procedure. It will be validated by further analysis of longitudinal data of this study.

Table 1: Cut-off value of ROM of each joint for disability in daily activity based on HAQ-DI category

		HAQ-DI category							
		Dressing	Arising	Eating	Waking	Hygiene	Reach	Grip	Activity
shoulder	abduction	132.8	142.8	131.3	141.0	141.0	133.5	131.3	138.8
elbow	flexion-extension	120.5	125.5	118.8	126.5	126.5	113.8	120.5	113.8
wrist	supination-pronation	150.3		150.8		153.3	156.0		150.3
wrist	flexion-extension	86.3	69.5	76.3		78.8	86.3	89.0	
knee	flexion-extension	133.8	133.8		133.8	131.3	123.8	123.8	133.8
hip	flexion-extension	126.3	131.3	131.3	126.3	126.3	113.8	131.3	126.3
ankle	flexion-extension	53.8	61.3	56.3	58.8	56.3	53.8	53.8	56.3

Cut-off values were determined using ROC curves when a significant association was found between ROM and disability in each category.

Table 2: Association between limited ROM and disability in daily activity based on HAQ-DI category: multivariate logistic regression analysis

		HAQ-DI category			
		Dressing	Arising	Eating	Waking
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
shoulder	abduction	5.14 (2.44 - 10.83) *	1.95 (1.13 - 3.37) *	3.92 (1.61 - 9.56) *	1.36 (0.75 - 2.48)
elbow	flexion-extension	2.33 (1.18 - 4.61) *	1.43 (0.82 - 2.50)	1.76 (0.82 - 3.79)	1.04 (0.58 - 1.86)
wrist	supination-pronati	1.23 (0.67 - 2.25)		0.99 (0.52 - 1.89)	
wrist	flexion-extension	1.86 (1.01 - 3.41) *	1.37 (0.80 - 2.34)	2.29 (1.25 - 4.18) *	
knee	flexion-extension	0.95 (0.52 - 1.74)	1.92 (1.11 - 3.34) *		2.92 (1.68 - 5.08) *
hip	flexion-extension	2.14 (1.15 - 3.97) *	1.69 (0.98 - 2.92)	1.40 (0.76 - 2.57)	3.50 (1.97 - 6.22) *
ankle	flexion-extension	1.46 (0.79 - 2.68)	1.20 (0.68 - 2.10)	1.55 (0.81 - 2.97)	1.63 (0.93 - 2.86)

		Hygiene	Reach	Grip	Activity
		OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
shoulder	abduction	3.21 (1.76 - 5.85) *	3.67 (1.27 - 10.61) *	1.91 (0.80 - 4.52)	5.14 (2.22 - 11.91) *
elbow	flexion-extension	1.87 (1.06 - 3.33) *	1.95 (0.79 - 4.81)	1.63 (0.74 - 3.59)	1.54 (0.71 - 3.35)
wrist	supination-pronati	1.07 (0.61 - 1.90)	0.84 (0.42 - 1.70)		1.24 (0.66 - 2.32)
wrist	flexion-extension	1.97 (1.11 - 3.50) *	2.43 (1.21 - 4.88) *	2.33 (1.22 - 4.43) *	
knee	flexion-extension	1.56 (0.89 - 2.73)	1.04 (0.47 - 2.30)	1.24 (0.56 - 2.71)	1.18 (0.64 - 2.32)
hip	flexion-extension	1.21 (0.68 - 2.17)	7.34 (1.58 - 34.04) *	2.28 (1.15 - 4.55) *	3.30 (1.67 - 6.51) *
ankle	flexion-extension	1.11 (0.63 - 1.98)	1.19 (0.55 - 2.58)	1.41 (0.67 - 2.95)	0.85 (0.45 - 1.62)

OR: Odds ratio, CI: Confidence interval
Cut-off values in Table 1 were used for dichotomization
Multivariate model was adjusted for age, sex, DAS28-CRP, and ROM of each joint
*p<0.05

Disclosure: T. Kojima, None; **H. Ishikawa**, None; **S. Tanaka**, None; **N. Haga**, None; **K. Nishida**, None; **M. Yukioka**, None; **J. Hashimoto**, None; **H. Miyahara**, None; **Y. Niki**, None; **H. Oda**, None; **S. Asai**, None; **K. Funahashi**, None; **M. Kojima**, None; **N. Ishiguro**, None.

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Abstract Number: 555

HAQ Score Is an Independent Predictor of Sustained Remission in Patients with Rheumatoid Arthritis

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Background/Purpose: We compared remission rates, according to different definitions of remission in rheumatoid arthritis (RA) and investigated the potential predictors of sustained remission at the 2-year follow-up.

Methods: We obtained data on 291 RA outpatients, seen from July 2009 to September 2012. Sociodemographic data and answers to questionnaires were collected in face-to-face interviews. Remission was defined according to the Disease Activity Score in 28 joints (DAS28)-ESR, DAS28-CRP, Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), and ACR/EULAR Boolean definition. Sustained remission was defined as when the patient continued in remission at two consecutive annual assessments. Predictors of sustained remission according to the DAS28-CRP were assessed by univariate and multivariate analyses.

Results: For the 291 RA patients, the remission rates of RA were 17.9% (DAS28-ESR), 54.3% (DAS28-CRP), 10.3% (SDAI), 10.0% (CDAI), and 5.8% (Boolean). On follow-up for 2 years, the sustained remission rates of RA were 46.5% (DAS28), 55.0% (DAS28-CRP), 37.5% (SDAI), 32.0% (CDAI), and 30.8% (Boolean). RA patients who achieve sustained remission according to the DAS28-CRP were younger, and had more education, higher monthly income, lower Health Assessment Questionnaire (HAQ) score, lower physician global assessment, lower patient global assessment, lower patient pain assessment, and higher EQ-5D. In multivariate analysis, only the HAQ score predicted sustained remission according to DAS28-CRP (OR=0.257, 95% CI 0.067–0.980, $p = 0.047$).

Conclusion: The remission rates of RA patients differed according to the definition of remission, and the highest sustained remission rate was classified by the DAS28-CRP. A lower HAQ score was an independent predictor of sustained remission over 2 years, according to the DAS28-CRP.

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Abstract Number: 556

Higher Multi Biomarker Disease Activity Scores Foreshadow Greater Longitudinal Improvement in RA Disease Activity

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Background/Purpose: Biomarkers in patients with rheumatoid arthritis (RA) have the attractive potential to help select patients that have a greater burden of disease activity and might have better treatment response when starting a new RA medication. This feature may be relevant both as inclusion criteria for a clinical trial or for clinical care.

Methods: We used Corrona, a large longitudinal registry of U.S. patients with rheumatoid arthritis that has been collected by more than 625 rheumatologists in 40 states. To be eligible for this analysis, patients had to be initiating one of 8 biologic DMARDs (adalimumab, etanercept, certolizumab pegol, golimumab, infliximab, abatacept, tocilizumab, rituximab) or tofacitinib and have a MBDA score processed no more than 6 months prior or 1 month after their initiation date. We evaluated CDAI at the corresponding 2 CORRONA visits: a baseline visit no more than 6 months prior to the initiation date ('baseline') and a follow-up CORRONA visit within 3-9 months subsequently. Patients also must have had baseline high disease activity as measured clinically using the CDAI (>22). Demographic and clinical variables at baseline were tested to determine their association with the MBDA score. General linear model analysis with change in CDAI between baseline and follow-up as the main outcome were evaluated according to MBDA category [low (<30), medium (30-44), and high (>44)], controlling for age, body mass index, and CDAI at baseline.

Results: There were 74 patients with baseline MBDA scores available that initiated a new medication that also had longitudinal follow-up data. Characteristics of these patients were median (IQR) age 61 (50,71) years, 76% women, 91% white; 14% with diabetes, 11% fibromyalgia, 11% current smokers, and 72% seropositive. Median (IQR) BMI was 30; CDAI 33 (36, 39); CRP 5.2 (2.3,15.2) mg/L; and MBDA score 45 (36-60). Patients with higher MBDA scores (>44) had greater crude mean change in CDAI (-15.5 units) compared to mean change in CDAI (-7.6 units) in those with low or medium MBDA scores. After adjusting for age, BMI, and baseline CDAI, patients in the high MBDA category had a mean 8 unit incrementally greater improvement in the CDAI ($p < 0.01$) compared to patients with baseline MBDA scores in the low to moderate range.

Conclusion: Among RA patients with high disease activity clinically who started a new medication for RA, MBDA scores in the high range (>44) were associated with significantly greater improvement in the CDAI over time compared to those starting with lower MBDA scores. The MBDA test may be useful to select patients who subsequently have a better response to treatment and thus provide utility even beyond clinical assessments of RA disease activity such as the CDAI.

Disclosure: J. Curtis, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **L. Harrold**, None; **J. Kremer**, None; **J. L. Palmer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/higher-multi-biomarker-disease-activity-scores-foreshadow-greater-longitudinal-improvement-in-ra-disease-activity

Abstract Number: 557

Differences in Clinical Outcomes in Different Socio-Economic and Racial Groups with Rheumatoid Arthritis: Data from National Inpatient Sample

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Session Time: 9:00AM-11:00AM

Background/Purpose: Studies have reported differences in healthcare utilization and outcome among different socioeconomic and ethnic groups. Complications like atherosclerotic cardiovascular diseases (ASCVD) have been documented to be higher among the African-American population and this disparity is more pronounced in the population with connective tissue disease. Similar disparities based on racial/ethnic background have been reported among treatment options for rheumatoid arthritis (RA). We tried to gain an insight into the differences in hospitalization outcomes among RA patients as per different socioeconomic and demographic variables utilizing a large US inpatient database.

Methods: We selected patients aged ≥18 years with and without RA to compare the differences in mortality, length of stay, cost of hospitalization and ASCVD incidence among different race, gender, type of insurance and income quartile range (Table 1). Patients with RA were selected based on ICD-9 codes (714.0, 714.1 and 714.2). Patients with concomitant diagnoses of SLE, polymyositis, dermatomyositis and systemic sclerosis were excluded. We used Nationwide Inpatient Database from 2009 to 2011. STATA version 13.0 (College Station, TX) for analysis to accommodate for the complex design of survey sample data (NIS). NIS is the largest publicly available all-payer inpatient care database in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of Healthcare Cost and Utilization Project.

Results: Mortality was most common among Caucasians (RA 2.4%, non-RA 2.37%, p=<0.0001), females (RA 2.67 %, non-RA 2.75%, p=<0.0001) and medicare patients (RA 2.7%, non-RA 3.32%, p=<0.0001). Mortality was lowest in the African American population among RApatients (1.97%, <0.0001) and in hispanics among the non-RA patients (1.58%, <0.0001). Length of stay was highest among the African-American (RA 5.53 days, non-RA 5.27 days, p=<0.0001), females (RA 5.19 days, non-RA 5.22 days, p=<0.0001) and the lowest income quartile (RA 5.27 days, non-RA 4.93 days, p=<0.0001). Patients with the highest income quartile, females and other races incurred the most charges during hospitalization. Incidence of ASCVD was highest among whites (RA 15.08%, non-RA 14.07%, p=<0.0001), females (RA 18.74%, non-RA 17.15%, p=<0.0001) and medicare patients (RA 16.9%, non-RA 19.9%, p=<0.0001).

Conclusion: Our findings indicate differences in clinical outcomes among different socio-economic groups in RA patients. Among patients with RA, we found higher rate of mortality and incidence of ASCVD among Caucasians. Similarly, females were found to have higher incidence of ASCVD, higher length of stay and hospital costs. Socio-economic and racial/ethnic influences may be important in interpreting differences in clinical outcomes relating to patients with RA.

	Mortality (%)		Mean LOS (days)		Mean Charge ($)		ASCVD incidence (%)	
	With RA	Without RA	With RA	Without RA	With RA	Without RA	With RA	Without RA
Caucasian	2.44	2.37	5.13	4.737745	13279.26	12109.85	15.08	14.07
African-American	1.97	1.95	5.53	5.27493	12818.3	11091.65	14.67	12.26
Hispanic	2.07	1.58	5.34	4.409065	14851.72	11232.64	11.85	8.58
Other	2.2	2.19	5.47	4.875703	14941.31	12592.53	13.49	11.53
p-value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Female	2.67	2.75	5.19	5.22	14250.11	13809.57	18.74	17.15
Male	2.17	1.81	5.14	4.44	12922.55	10496.22	13.41	10.32
p-value	**<0.0001**	**<0.0001**	0.1023	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Medicare	2.7	3.32	5.35	5.48	13202.82	13284.57	16.9	19.9
Medicaid	1.34	1.05	5.38	4.62	12626.63	9458.45	10.06	6.06
Private insurance	1.36	1.24	4.54	3.93	13948.86	11475.32	10	8.08
Self-pay	1.59	1.42	4.73	4.03	10913.64	9232.41	11.57	8.3
No charge	0.68	1.22	5.12	4.71	10560.43	9503.22	9.77	8.12
Other	2.39	2.33	4.59	4.31	13021.86	12081.95	12.63	8.43
p-value	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**<0.0001**
Income Quartile 1±	2.28	2.27	5.27	4.93	12123.11	10865.25	14.6	13.21
Quartile 2±	2.28	2.18	5.07	4.67	12942.07	11573.12	14.91	13.26
Quartile 3±	2.26	2.12	5.09	4.64	13735.14	12248.06	15.22	13.16
Quartile 4±	2.39	2.18	5.15	4.64	14696.85	13154.86	14.42	12.83
p-value	0.5656	**<0.0001**	**0.0001**	**<0.0001**	**<0.0001**	**<0.0001**	**0.0326**	0.1064

Table 1: Distribution of mortality, mean length of stay, mean hospital charge and ASCVD incidence by race, gender, type of insurance and income quartile range. ± For year 2011: Quartile 1 (1 - 38,999); Quartile 2 (39,000 - 47,999); Quartile 3 (48,000 - 63,999); Quartile 4 (64,000+)

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Abstract Number: 558

Clinical, Sonographic and Immunological Biomarkers of Ramris Progression in RA Patients in Clinical Remission: A Prospective Study with 12 Months of Follow-up

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Background/Purpose: To determine clinical, sonographic and immunological biomarkers predicting structural damage progression at 12 months of follow-up as measured by Magnetic Resonance Imaging (MRI) in a population of Rheumatoid Arthritis (RA) patients in clinical remission.

Methods: We included patients with RA in clinical remission defined as disease activity score of 28 joints (DAS28)-erythrocyte sedimentation rate (ESR) <2.6 for > 6 months. Serum cytokines and angiogenic mediators, Ultrasound scans of both hands and knees and MRI of dominant hand were performed at baseline and after 12 months.

Results: Forty-two patients completed the follow-up. 78% female, aged (median) 54 years; disease duration was 93 months; 85% ACPA positive; C-reactive protein (CRP) was 0.10 mg/dl; ESR 9 mm/h and DAS28-ESR: 2.00. Twelve (28%) patients were taking oral prednisone, 34 (81%) conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs), and 20 (47%) biological therapies. At baseline, 45% fulfilled criteria for ultrasound defined active synovitis (UdAS) (synovial hyperplasia>2+PD signal). Significant associations between baseline RAMRIS, body mass index (BMI), disease duration, prednisone treatment, lack of csDMARDs and the presence of UdAS (but not PD alone) with RAMRIS progression after 12 months were found. Serum levels of calprotectin were significantly correlated with bone edema progression.

Conclusion: We identified clinical and sonographic biomarkers of RAMRIS progression after 12 months of follow-up in patients with RA in clinical remission. The concept of ultrasound active synovitis, defined as the simultaneous occurrence of relevant synovial hyperplasia and PD is associated with RAMRIS progression after 12 months.

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Abstract Number: 559

Comparison of Multi-Dimensional Health Assessment Questionnaire (MD-HAQ)-Based and Patient-Reported Outcomes Measurement Information System (PROMIS) 29-Based Routine Assessment of Patient Index 3 (RAPID3) for Assessing Rheumatoid Arthritis Disease Activity

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Background/Purpose: Patient-reported outcomes measurement information system (PROMIS) 29 is recommended by the National Institute of Health (NIH) consensus panel as the preferred battery of measures to collect in musculoskeletal pain treatment studies. Physical function domain in the PROMIS29 short form has only 4 questions. We compared Routine Assessment of Patient Index 3 (RAPID3) scores based on multi-dimensional health assessment questionnaire (MD-HAQ)-based and patient-reported outcomes measurement information system (PROMIS) 29 to determine the degree of agreement.

Methods: For rheumatoid arthritis (RA) subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER), a cross-sectional analysis was performed for all RACER patients who completed MD-HAQ and PROMIS29 short form. Physical function based on PROMIS29 (PROMIS29-PF) was calculated using raw score of PROMIS29 physical function (PROMIS29-PF = ([20- PROMIS29-PF]/2). Association between physical function based on MD-HAQ and PROMIS29 was evaluated by Pearson¡¯s correlation coefficient. Bland-Altman 95% limits of agreement (LOA), kappa statistics, Lin¡¯s concordance coefficient were used to measure the agreement between RAPID3 score based on MD-HAQ and PROMIS29 (RAPID3-PROMIS).

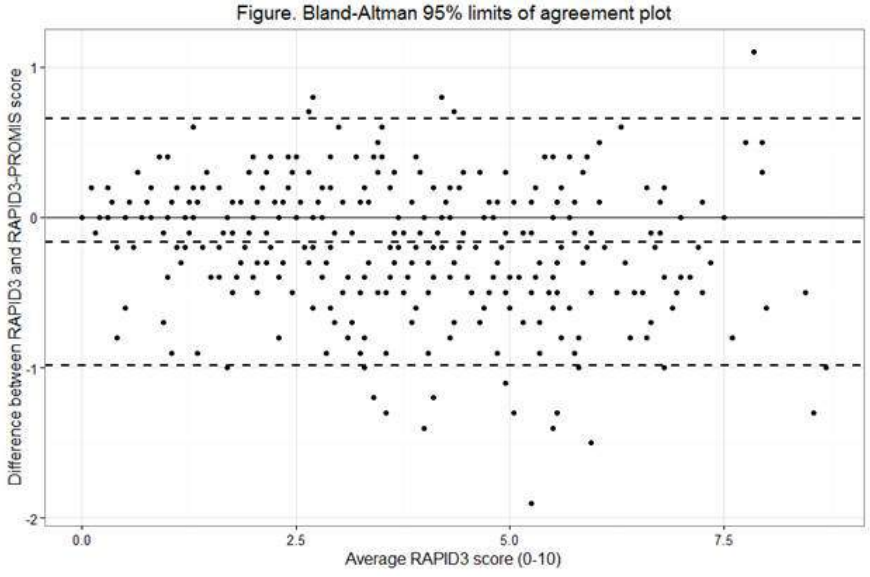
Results: For the 397 subjects analyzed, age was 64.2 +/- 13.8 (mean +/- SD) years with disease duration of 13.9 +/- 13.1 years. PROMIS-PF was strongly correlated with physical function based on MD-HAQ ($r = 0.83$, $p < 0.0001$). Overall agreement between disease severity categories of RAPID3 and RAPID3-PROMIS were substantial (percent agreement = 87.7, kappa = 0.83) (Table). RAPID3 scores (0-10) were slightly different (RAPID3 = 3.4, RAPID3-PROMIS = 3.6, $p < 0.01$). LOA for RAPID3 score were -0.98 and 0.65, with bias of -0.42 (Figure). Lin¡¯s coefficient of concordance showed substantial agreement (0.976).

Conclusion: There was very good agreement in RAPID3 scores based on MD-HAQ and PROMIS29 short form. Very low bias score and small values for LOA indicate that RAPID3 scores based on MD-HAQ and PROMIS29 are interchangeable.

Table. Disease activity categories by multi-dimensional health assessment questionnaire (MD-HAQ)-based and patient-reported outcomes measurement information system (PROMIS) 29-based Routine Assessment of Patient Index 3 (RAPID3)

		RAPID3-PROMIS		
RAPID3	Near remission	Low	Moderate	High
Near remission	**55**	6	0	0
Low	6	**37**	6	0
Moderate	0	9	**107**	15
High	0	0	6	**143**

Figure. Bland-Altman 95% limits of agreement plot



Disclosure: Y. G. Hwang, None; **J. Feng**, None; **H. Eng**, None; **J. Lyons**, None; **A. Fabio**, None; **L. W. Moreland**, None.

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Abstract Number: 560

There Is No Further Gain from Calculating Disease Activity Score in 28 Joints with High Sensitivity Assays of C-Reactive Protein Because of High Intraindividual Variability of CRP: A Cross Sectional Study and Theoretical Consideration

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Background/Purpose: The threshold for reporting of C-reactive protein (CRP) differs from laboratory to laboratory. Moreover, CRP values are affected by the intra individual biological variability.[1] With respect to disease activity score in 28 joints (DAS28) and Rheumatoid Arthritis (RA), precise threshold for reporting CRP is important due to the direct effects of CRP on calculating DAS28, patient classification and subsequent treatment decisions[2]

Methods: This study consists of two sections: a theoretical consideration discussing the performance of CRP in calculating DAS28 with regard to the biological variation and reporting limit for CRP and a cross sectional study of all RA patients from our department (n=876) applying our theoretical results. In the second section, we calculate DAS28 twice with actual CRP and CRP=9, the latter to elucidate the positive consequences of changing the lower reporting limit of CRP from <10mg/L to <3mg/L

Results: Theoretical considerations: lower reporting limit of <10mg/L leads to inaccurate patient classification in a great number of patients both because of biological variation, as well as the larger spectrum of numbers (0-9). In addition, reducing lower reporting limit for CRP to minimum<3mg/L results in optimizing patient classification (Figure 1). The logarithmic transformation of CRP in DAS28 formula has an important role Cross sectional study: 769 patients fulfilled the ACR criteria for RA were included, 107 excluded due to missing parameter used for DAS28 calculations. There was a statistically significant difference between patients´ DAS28 and new calculated DAS28 with CRP=9 ($p<0.001$). A total of 109 patients had a disease activity deviation (remission to low: 66, low to moderate: 39, moderate to high: 4)

Conclusion: Respecting DAS28 calculation, lower reporting limit for CRP<3 mg/L is acceptable and should be taken into consideration. A lower reporting limit for CRP<10 mg/l is too high. It is particularly relevant if treatment decisions are solely made on the basis of DAS28. Furthermore, we conclude that DAS28 in studies where the reporting limit of CRP is unknown are incomparable References:1.Macy EM, et al. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference intervals and epidemiological applications. Clin Chem. 1997;43:52-8 2.Asmussen R,

Antonsen S, Hansen IMJ. The influence of variation in C-reactive protein values on the DAS28 score. Ann Rheum Dis 2013;72:844

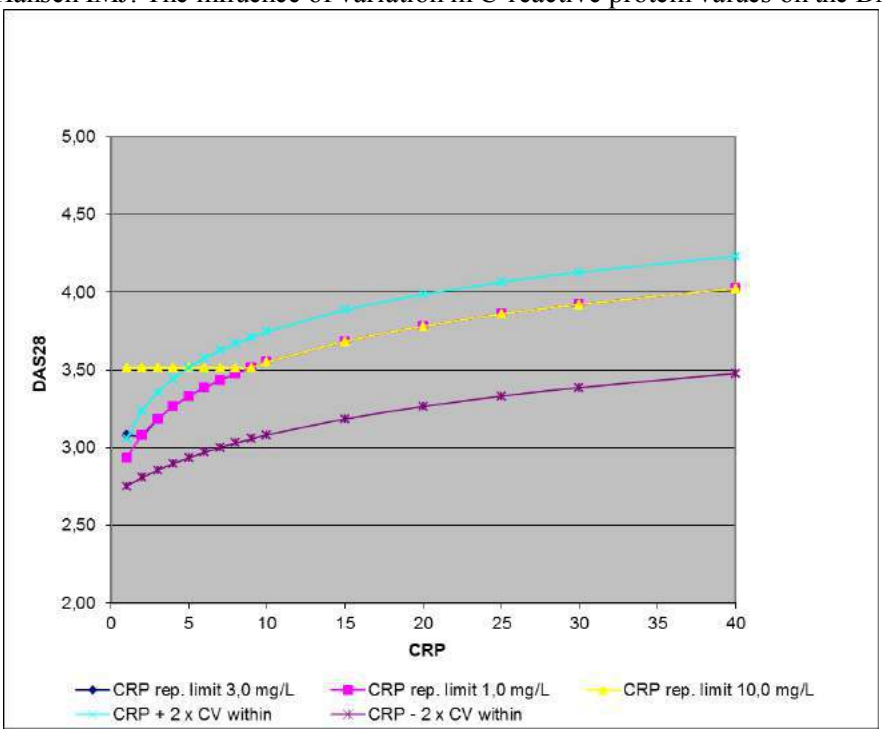

Figure 1: Dependency of Disease Activity Score in 28 joints to CRP (theoretical consideration). Tender joint: 3, Swollen joint: 1, patient global assessment: 34 and CRP ranges from 0 to 40. CRP: C-reactive protein. CV-Within: Intra-individual biologic variability

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Disclosure: I. M. J. Hansen, None; **R. Asmussen**, None; **S. Antonsen**, None; **A. Emamifar**, None.

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Abstract Number: 561

Sodium Intake Is Increased in Patients with Early Rheumatoid Arthritis and Is Associated with Radiographic Erosions

sarah marouen[1], Guilhem du Cailar[2], Rachel Audo[3], Cédric Lukas[4], Gaelle Vial[5], Anne Tournadre[6], Emmanuel Barrat[7], Jean Ribstein[2], Bernard Combe[8], Jacques Morel[9] and Claire I. Daien[10], [1]Rhumatology Department, Lapeyronie Hospital and Montpellier University, Montpellier, France, [2]Internal Medicine and Hypertension, Hopital Lapeyronie, Montpellier, France, [3]Rheumatology, Teaching Hospital of Lapeyronie, Montpellier, France, [4]Rheumatology, CHU Lapeyronie and EA2415, Montpellier University, University of Montpellier, France, [5]Rheumatology, Gabriel Montpied Hospital and Clermont Ferrand University, Clermont Ferrand, France, [6]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [7]Recherche et Développement, Laboratoire Lescuyer, AYTRE, France, [8]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [9]Rheumatology, Department of Rheumatology, Montpellier University Hospital, Montpellier, France, [10]Department of rheumatology, Lapeyronie Hospital and Montpellier University, Montpellier, France
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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease resulting from an interaction between genetic and environmental factors. Recently, sodium intake was suggested as a risk factor for autoimmune diseases by driving lymphocyte polarization toward a Th17 pathway. Our study aimed to assess sodium intake at RA diagnosis and in established RA and evaluate its impact on disease activity and severity.

Methods: The prospective cross-sectional study included 24 patients with RA at diagnosis (early RA) and 24 controls matched on age, gender and body mass index. Furthermore, 197 patients with established RA were included. Sodium intake was evaluated by 24-hr urinary sodium excretion, and the Food Frequency Questionnaire (FFQ) was used to evaluate potential diet confounding factors.

Results: Sodium intake was greater for patients with early RA (+650 mg/day of sodium, p=0.039) and established RA (p=0.046) than controls (figure 1) and was greater for patients with than without radiographic erosion at the time of diagnosis (p=0.028) (figure 2). It was lower for patients positive for rheumatoid factor and was not correlated with disease activity and severity for patients with established RA.

Conclusion: Patients with early and established RA show increased sodium consumption as compared to matched controls and that sodium consumption was associated with disease severity at diagnosis. Sodium may activate immune cells, which

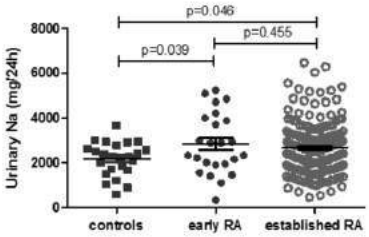

Figure 1. Sodium intake was increased in patients with early RA. Sodium intake was assessed by 24-hr urinary sodium excretion in patients with early RA, matched controls and patients with established RA. Horizontal bars are median and whiskers are SEM for the whole sample in compared by Student *t* test.

could worsen RA prognosis.

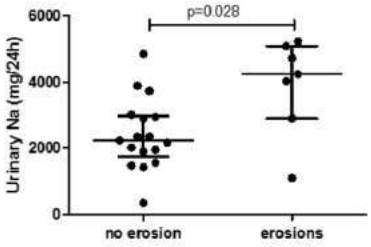

Figure 2. Sodium intake was increased in early RA patients with erosions. Horizontal bars are median and whiskers are IQR compared by Mann-Whitney test.

Disclosure: S. marouen, None; **G. du Cailar**, None; **R. Audo**, None; **C. Lukas**, None; **G. Vial**, None; **A. Tournadre**, None; **E. Barrat**, None; **J. Ribstein**, None; **B. Combe**, None; **J. Morel**, None; **C. I. Daien**, Pfizer Inc, 2.

Abstract Number: 562

Does Surgical Intervention to the Upper Extremity Make the Patients with Rheumatoid Arthritis Happy?

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Background/Purpose: Disease activity dramatically ameliorated with the use of bDMARD or a recently appeared tsDMARD and more than one-half of the patients with RA were in remission. However, some patients were still difficult to achieve remission due to comorbidities, aging and economic burden of drug cost. Therefore, still some patients needed to undergo surgical reconstruction for the structurally damaged joint due to RA. The purpose of this prospective cohort study was to clarify the effect of surgical intervention to the upper extremity from the aspect of QOL and mental health as well as physical function.

Methods: From December 2012 to September 2014, a primary surgery was scheduled in 150 patients (male:20, female:130) with RA. The mean age was 64 years old, and the mean duration of RA was 16 years. Steinbrocker's stage IV and class 2 were most frequent. The surgical site was 6 shoulders, 26 elbows, 73 wrists and 45 fingers or thumbs. There were 26 synovectomies, 39 arthroplasties without implant, 31 arthrodeses, and 54 joint replacements. EuroQol 5 dimension (EQ-5D), Beck Depression Inventory II (BDI-II), Japanese version of the Stanford Health Assessment Questionnaire (J-HAQ), and Disabilities of the Arm, Shoulder and Hand (DASH) were investigated just before the operation (baseline), and at 6 and 12 months after the operation.

Results: As a whole, EQ-5D improved from 0.708 at baseline to 0.747 ($p<0.001$) and 0.756 ($p<0.001$) at 6 and 12 months after the operation. Significant improvement in EQ-5D was noted in the elbow or the wrist surgeries, and all procedures other than synovectomy. BDI-II decreased from 13.8 at baseline to 12.3 ($p=0.004$) and 12.2 ($p=0.001$) at 6 and 12 months after the operation. At baseline, the patient was on the borderline of mild depression (between 14 and 19) and after the operation the patient was in minimal depression (between 0-13). Significant decrease in BDI-II was noted in the elbow or the wrist surgeries, and joint replacement. J-HAQ improved from 1.11 at baseline to 1.01 ($p=0.008$) and 0.95 ($p<0.001$) at 6 and 12 months after the operation. Significant improvement in J-HAQ was noted in the elbow or the wrist surgeries, and arthroplasty without implant and arthrodesis. DASH score decreased from 43.8 at baseline to 37.4 ($p<0.001$) and 36.3 ($p<0.001$) at 6 and 12 months after the operation. Significant decrease in DASH score was noted in the elbow or the wrist surgeries, and all surgical procedures.

Conclusion: The surgical intervention to the upper extremity in the patient with RA improved QOL and mental health as well as physical function. It made the disabled patient happy.

Disclosure: A. Abe, None; **H. Ishikawa**, None; **A. Murasawa**, None.

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Abstract Number: 563

Factors Associated with Cognitive Impairment in Korean Adults with Rheumatoid Arthritis

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Background/Purpose: For persons with chronic diseases such as rheumatoid arthritis (RA), intact cognitive function is crucial for performing main daily activities and adhering to self-management regimens. Persons with impaired cognitive function have decreased functional independence, reduced quality of life, and increased risk of mortality. Although several mechanisms may influence cognitive function in RA, it has not been well-studied in this population. This study explored the prevalence of cognitive impairment in persons with RA using a set of computerized neurocognitive tests and the factors that were significantly correlated with cognitive impairment.

Methods: Individuals with RA were recruited by their rheumatologists during follow-up visits at one university hospital in Korea. After getting signed consents, a trained research nurse assessed participants with a range of physical, psychosocial, and biological metrics. Cognitive function was assessed using a set of 6 computerized neurocognitive tests yielding 18 indices covering a range of cognitive domains. Subjects were classified as 'impaired' if they performed 1 *SD*below age-based population norms on each test. A total cognitive impairment score was calculated by summing the transformed scores, ranging from 0 (no impairment) to 18 (worst impairment). Pearson correlation coefficient analyses were conducted to identify the variables that might be significantly associated with cognitive impairment.

Results: Thirty three subjects with a mean (±*SD*) age of 64 (±11.8) years were included in the final analyses. 85% were female, 85% were married, and mean educational level was 9.6 (±4.9) years. Mean DAS-28 level was 2.6 (±1.5) and mean disease duration was 114 (±86.8) months. Mean HAQ score was 0.6 (±0.8), mean SPPB score was 7.4 (±2.5), and mean cardiovascular disease (CVD) risk factors were 2.9 (±1.5). 32.4% had depression and 70.6% had sleep problems. The proportion of persons who were classified as cognitively impaired on each test were 29% in Card Sorting Test (executive function), 56% in Trail Making Test (visuo-motor coordination), 74% in Visual Span Test (language memory), 79% in Verbal Learning Test (visuo-spatial memory), 24% in Visual Continuous Performance Test (continuous attention), and 65% in Word-Color Test (selective attention). Mean total cognitive impairment score was 10.7 (±4.1), and ranged from 2-17. 79% were classified as cognitively impaired on five or more test indices. Education (r=-493, $p<.05$), marital status (r=-.424, $p<.05$), income (r=-.661, $p<.05$), and CVD risk factors (r=.447, $p<.05$), SPPB score (r=-.485, $p<.05$) were significantly correlated with total cognitive impairment score.

Conclusion: A significant number of RA patients were cognitively impaired. Low educational levels, non-married status, low income, and increased CVD risk factors, and increased functional limitations may be potential risks of cognitive impairment in this population. These findings suggest that the burden of cognitive impairment in RA is significant, and future studies identifying specific etiological contributors to cognitive impairment are warranted.

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Abstract Number: 564

Serum Adiponectin and Body Composition in a Group of Patients with Rheumatoid Arthritis: Relationship Between Disease Parameters

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Background/Purpose: Patients with rheumatoid arthritis (RA) tend to have impaired distribution of adipose tissue and may have the risks of metabolic complications (1,2). The aim of this study was to determine the serum adiponectin levels and body composition in a group of patients with RA.

Methods: Fifty-five RA patients with a mean age of 53.5±9.7 years were recruited to this cross-sectional study. The demographic and clinical variables of the patients (age, sex, BMI, duration of disease) were determined. Disease activity parameters (DAS28-ESR, functional status assessed by HAQ and quality of life (QoL) assessed by RA-QoL questionnaires) were recorded. Serum adiponectin levels and body composition parameters (fat mass (FM) and fat-free mass (FFM)) were determined by ELISA and multi-frequency bioelectrical impedenace analysis respectively. Anthropometric measurements (weight, height, circumferences of waist (WC), mid-upper arm (MUAC), calf (CC) and neck (NC) and muscle strength assessments (hand-grip) were performed by a trained dietitian. The relationship between disease activity parameters, adiponectin levels and body composition variables were analyzed by Pearson and Spearman tests as needed.

Results: Forty-four female, 11 male RA patients with a mean disease duration of 127.0± 120.6 months were included to the study. Based on BMI, 23.6% of patients were overweight and 60% were obese. Obesity prevelance and mean fat mass (%) was significantly higher among female patients (p=0.000, for both). According to DAS28-ESR parameters 38.2% of patients were in remission state, 18.2% had low, 40% had moderate, 3.6% had severe disease activity. Disease activity parameters did not differ among female and male patients, while functional status determined by HAQ and quality of life assessed by RA-QoL scores of female patients were significantly higher than male patients (1.2±1.2 and 0.6±0.6, $p<0.05$; 12.7±8.3 and 6.0±4.5, $p<0.05$, respectively), indicating more disability in women. The mean serum adiponectin value was 16.08±6.95 µg/mL and did not differ significantly between sexes. Adiponectin was positively corelated with body fat (%) (r=0.427 p=0.001) and negatively corelated with fat-free mass (%) (r=-0.316, p;=0.021). Correlation between serum adiponectin and body fat was siginificant among female patients (r=0.409, p=0.006). No statistically significant correlations were found between serum adiponectin levels and anthropometric measurements. Body fat (%) was positively (r=0.609, p=0.047), fat-free mass (%) was negatively (r=-0.609, p=0.047) correlated with disease activity determined by DAS28-ESR.

Conclusion: Our data indicate that body composition is altered in RA patients and related with adinopectin and disease activity, which may increase the risk of cardiovascular disease, and emphasize an unmet need of dietitian consultation in the management of RA. References:

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2. Kang Y, Park HJ, Kang M. Adipokines inflammation, insülin resistance, and carotid atherosclerosis in patients with rheumatoid arthritis. Arthritis Res Ther 2013;15:r194.

Disclosure: P. BORMAN, None; **S. Vural**, None; **S. Kocaoglu**, None; **D. Dedebayraktar**, None; **S. Öteleş**, None; **P. Bilgiç**, None; **H. Sürer**, None.

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Abstract Number: 565

Factors Associated with Gastrointestinal Tolerance in Patients with Rheumatoid Arthritis and Methotrexate Daily Doses

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Background/Purpose: Methotrexate (MTX) is the cornerstone of rheumatoid arthritis (RA) treatment. We reported the liver safety with daily dose of MTX[1]. Weekly doses of MTX are frequently associated with gastrointestinal (GI) adverse events (45-60%)[2]. The aim of this study is to determine the frequency of methotrexate GI intolerance and its associated factors in patients with RA that receive daily doses of MTX.

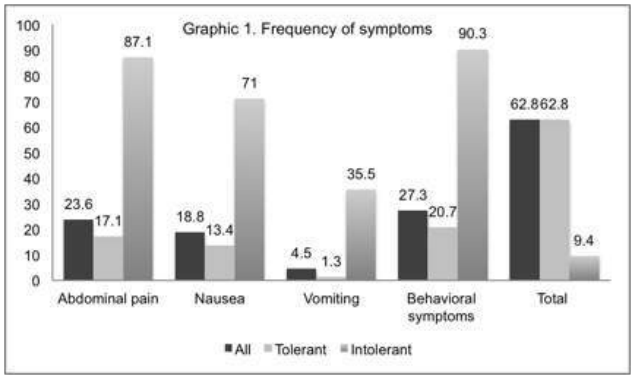
Methods: We applied the Spanish version of methotrexate intolerance severity score questionnaire (MISS) in patients with RA, which consists of four domains: abdominal pain, nausea, vomiting and behavioral symptoms. Each domain was ranked from 0-3 points being no complaint (0 points), mild (1 point), moderate (2 points), and severe (3 points)[3]. The MTX intolerance was determined with a score > 6, and was compared with other variables with Fisher or chi-squared tests; continuous variables were compared with parametric or non-parametric analysis as appropriated. A logistic regression model of MTX intolerance was performed with the relevant variables.

Results: We included 395 unselected patients with RA, 362 (91.6%) were women, mean age was 51.1 ± 12.4 SD years, mean of RA disease evolution 6.4 ± 7.5 SD years and the mean dose of MTX 13.3 ± 4.0 mg/week. The 47.9% (142) of patients had at least one GI adverse event and MTX intolerance was present in 9.4%. Tolerant subjects (52.5%) had at least one gastric symptom: abdominal pain 17.1%, nausea 13.4%, vomiting 1.3%, behavioral symptoms 20.7%. The bivariate analysis for association with MTX intolerance and other drugs showed no statistical significance.

Conclusion: The frequency of GI intolerance using MTX daily doses (9.4%) was similar to MTX weekly as previously reported (11%). Concomitant administration of other drugs was not associated with increasing gastrointestinal intolerance.

1. Braun J, et al. Arthritis Rheum. 2008 Jan;58(1):73–81
2. Martinez-Martinez MU, et al. Ann Rheum Dis 2012;71(Suppl3):199.
3. Bulatovic M, et al. Arthritis Rheum. 2011 Jul;63(7):2007–13

Table 1. Bivariate analysis				
	Total	Tolerant	Intolerant	P value
Methotrexate Mean (mg/week dose ±SD) Cumulative dose (gr ± SD)	13.3 ± 4.0 3.0 ± 3.2	13.6 ± 3.6 3.1 ± 3.3	12.9 ±4.7 2.6 ± 3.5	0.64 0.36
Sulfasalazine (%)	222 (56.2)	174 (58.2)	16 (51.6)	0.48
Chloroquine (%)	144 (36.5)	111 (37.1)	8 (25.8)	0.21
Prednisone (%) Mean dose (mg/day ± SD)	333(84.3) 4.3 ± 2.7	252 (84.3) 4.2 ± 2.7	28 (90.3) 4.3 ± 2.7	0.37 0.32
NSAID Diclofenac (%) Naproxen (%) Meloxicam (%)	75 (19) 183 (46.3) 82 (20.8)	53 (17.7) 145 (48.5) 69 (23.1)	8 (25.8) 14 (45.2) 6 (19.4)	0.26 0.72 0.63



Disclosure: A. N. Rangel-Botello, None; **M. U. Martinez-Martinez**, None; **C. Abud Mendoza**, None; **A. Bazua Gerez**, None; **Á. Cárdenas Hernández**, None; **L. Domínguez Salgado**, None; **J. Espinoza Martínez**, None; **H. García González**, None; **O. González Rivera**, None; **G. Hernández de la Cruz**, None; **G. Magaña Ávila**, None; **M. Martínez Rojas**, None; **M. Moctezuma Dávila**, None.

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Abstract Number: 566

Rheumatoid Arthritis Patients' Ability to Accurately Recall DMARD Information Immediately Following an Office Visit with Their Rheumatologist

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Background/Purpose: Patient misunderstandings about DMARDs may contribute to nonadherence. We present longitudinal observational data regarding whether patients can accurately recall medication information about a newly-prescribed DMARD immediately after a rheumatology office visit and whether this is associated with DMARD prescription filling behavior one week after the office visit.

Methods: We recruited a convenience sample of 38 adult English-speaking RA patients who were prescribed a new self-administered DMARD from one rheumatology clinic in a southeastern state. The office visit during which the new DMARD was prescribed was audiotape recorded. Immediately after this visit, patients completed a demographic survey and were asked to recall what their rheumatologist said about how to take the DMARD and its benefits, side effects, and risks. Office visits and patient interviews were transcribed verbatim. Two independent coders who were blinded to study hypotheses compared what the rheumatologist said during the office visit to what the patient recalled for 15 different medication topics (Table 1). Coders recorded whether the rheumatologist discussed this topic during the visit and whether the patient's recall of what the rheumatologist said was accurate (yes/no). Inter-reliability for the 15 topics was 0.89. We calculated descriptive statistics and examined bivariate associations to determine correlates of the patient inaccurately recalling (yes/no) any medication information (α=0.05).

Results: Participants were primarily women (87%) and white (71%). The mean age and disease duration were 49.1 (SD=13.4) and 9.4 years (SD=9.4), respectively. Only 12 (20%) patients were receiving a DMARD prescription for the first time. Nineteen patients (50%) inaccurately recalled information about at least one medication topic immediately after their office visit. Table 1 presents our study results. Patients with inaccurate recall had a longer disease duration ($t_{(36)}$=-3.4, p=0.02), lower health literacy (χ^2=7.1; p<0.01), and a lower household income (<$25,000 annually) ($\chi^2$=4.5; p=0.03). Patients with inaccurate recall were not less likely to get their prescription filled at 1-week follow-up (χ^2=2.6; p=0.11).

Conclusion: Half of patients inaccurately recalled medication information about a newly-prescribed DMARD immediately after their rheumatology office visit. A number of DMARD topics were not explicitly discussed during the office visit, but may have been discussed in previous visits. Patients with low health literacy, lower household income, and longer disease duration were more likely to inaccurately recall DMARD information.

Table 1: Characteristics of rheumatology office visits during which a new DMARD was prescribed

Topic	Rheumatologist **Did Not** Discuss Topic During Office Visit N (%)	Patient **Did Not** Accurately Recall Information About Topic N (%)	Examples of Inaccurate Recall
Long-term effectiveness of DMARD	30(79%)	0	-
How long patient should take DMARD (duration)	19(50%)	0	-
DMARD-other drug interactions	16(42%)	0	-
Contraindications	16(42%)	0	-
Costs of DMARD	12(32%)	0	-
Time until DMARD begins to take effect	11(29%)	2(5%)	Patient said it might take two weeks to see improvement when doctor said three months.
Timing to take DMARD	8(21%)	1(3%)	Patient said medication should be taken in afternoon when doctor said night.
Dosage	8(21%)	1(3%)	Patient says they are supposed to take 1 pill/day and doctor said 4 pills/day.
Severity of side effects	7(18%)	0	-
Mechanism of action	6(16%)	2(5%)	Patient said medication would stop cells from eating the bone in their body when doctor said it would reduce inflammation.
How to take DMARD	3(8%)	2(5%)	Patient said doctor didn't say how medication was supposed to be taken when doctor said it should be taken orally.
How often to take DMARD (frequency)	1(3%)	2(5%)	Patient said they should take pill daily when doctor said it should be taken one day per week.
Benefits of DMARD	1(3%)	10(26%)	Patient lists benefits of medication that were not discussed by doctor.
Side effect risk reduction strategies	1(3%)	5(13%)	Patient mentions having to engage in risk reduction strategies that were not recommended by doctor.
Side effects of DMARD	0	5(13%)	Patient lists kidney damage as side effect of medication when doctor did not mention kidney damage as side effect.

Disclosure: D. Carpenter, Arthritis Foundation, 2; **L. Geryk**, None; **C. Roberts**, None; **B. L. Jonas**, None; **S. J. Blalock**,

None.

Abstract Number: 567

Understanding Contextual Factors That Influence Decisions Related to Health and Work Among People with Recently Diagnosed Rheumatoid Arthritis

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Background/Purpose: In rheumatoid arthritis (RA), early diagnosis and treatment are essential to better outcomes. Many people defer seeking help or treatment for reasons that are currently not well accounted for, but often seem to be related to decisions concerning work. This study aims to understand the contextual factors that influence patients' decisions in the early stages of RA when dealing with concerns about their health and employment. Contextual factors are factors that mediate or moderate the effect of an intervention (e.g., a work disability prevention program) on outcomes (e.g., the patient's decision to continue working).

Methods: We conducted a secondary data analysis from 2 qualitative studies[1],[2]Participants were eligible if they were diagnosed with RA within the 12 months prior. The interview questions focused on how RA affected the daily lives of participants. In the first study we conducted 1 in-depth interview per participant, in the second study another set of participants were interviewed 3 times over a 1-year period. In the current analysis, transcripts were examined for participant experiences of the impacts of their health on employment, and the impacts of their employment on health. We used the constant comparison method, a theme-based, iterative, qualitative approach that foregrounds the experience of the participants. The analysis was done by one researcher, in consultation with researchers who previously worked with the dataset.

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[1] Townsend A et al. *BMJ Open* 2013; 3(e002164).

[2] Townsend A et al. *Chronic Illness* 2014; 10(4):259-72.

Results: A total of 48 interview transcripts from our two previous studies were examined. Most participants were women (91%) and roughly half (55%) were from rural or remote areas. We found that many participants continued to work despite pain and fatigue, and even if they had alternatives to working for their livelihood. In these instances people seemed to act counter to a "health first" logic. Physical limits and financial concerns were often the catalyst for work-related decisions, however, many participants deferred making a decision until one of these factors became so overwhelming that they were forced to act upon them. In situations where decisions had not been dominated by physical or financial necessity, factors that often influenced decision-making were related to a sense of attachment to work that included: love of occupation, sense of responsibility, the commitment to being a hard worker, and occupation defining identity. We broadly described

these factors as “work ethic.”

Conclusion: Our findings suggested that while physical limits and financial necessity were important contributors to patients’ decisions about work, these decisions might also be influenced by work ethic. Participants revealed the preference to stay at work despite difficulties with their health and challenges related to their work, suggesting that non-medical life-course factors could be as influential as physical or financial factors in one’s decision about employment. Further research is needed to understand the interplay of these contextual factors in the effectiveness of interventions on patient decision-making.

Disclosure: G. Macdonald, None; **C. Backman**, None; **A. F. Townsend**, None; **L. Li**, None.

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Abstract Number: 568

Triggering Receptor Expressed on Myeloid Cells (TREM) As a Novel Indicator of Disease Progression in ‘at-Risk’ Individuals

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Background/Purpose: Whilst the exact aetiology of rheumatoid arthritis (RA) remains unclear, current concepts suggest an environmental link with possible microbial triggers. Studying individuals at-risk of RA allows a unique opportunity to explore possible relationships. Furthermore, the identification of predictors of progression from at-risk to RA is of great clinical utility. Triggering receptor expressed on myeloid cells (TREM) modulates the innate immune response by either amplifying or dampening the toll like receptors (TLR) induced signalling[1]. Given the upstream nature of soluble-TREM (sTREM), and its close proximity to TLR in innate immune response to microbial triggers, we hypothesis that sTREM could be one of the first indicators of progression to RA.

Methods: sTREM was measured using Human TREM-1 Quantikine ELISA (R&D Systems, Minneapolis) in 32 at-risk individuals; 16 of whom progressed (ACPA+ Prog) and 16 whom did not (ACPA+ NProg), and 16 early RA (ERA) patients. The ACPA+ cohort had no evidence of ultrasound synovitis at baseline. Binary logistic regression models were conducted on at-risk patients. Model discrimination was assessed using classification plots and the area under the ROC curve. An optimum cut-off for the test variable, plus associated sensitivity and specificity achieved, were also determined. Further analyses were conducted on the same sample augmented with ERA patients, to assess the correlation between TREM, CRP and CCP titre values in this group; and on ERA patients only, to assess the correlation between TREM and DAS28 values in this group.

Results: Duration of follow-up was 0 to 133 months, mean duration of 36 months (SD 31.2). Mean time to RA diagnosis in those that progressed was 11.5 months (SD 14.3).

Variable	Group			
	ERA	ACPA+ Prog	ACPA+ NProg	All
Gender (n (%)) Female	9 (56.2%)	10 (62.5%)	11 (68.7%)	30 (62.5%)
Age (years) (mean (SD))	55.2 (14.8)	53.8 (13.6)	53.9 (10.3)	54.3 (12.7)
TREM IU (mean (SD))	539.3 (207.9)	711.0 (292.0)	405.0 (230.4)*	554.8 (271.9)
CRP ng/l (mean (SD))	40.3 (61.0)	4.77 (5.61)*	4.53 (6.59)**	18.6 (41.6)
CCP IU (mean (SD))	92.4 (127.1)	174.9 (108.8)	132.5 (135.1)	133.3 (126.1)
*n=15; **n=10				

A binary logistic regression model found that TREM was significantly associated with progression (p=0.009). The OR of 1.006 (95% CI 1.002 to 1.011) indicated that at best estimate, the odds of progression increased by 0.6% with each increase of 1 unit of TREM. The model classified 80.6% of cases correctly, with 12 out of 16 (75.0%) of ACPA+ P cases and 13 out of 15 (86.7%) of ACPA+ NP cases correctly classified. The area under the ROC curve was 0.825 (95% CI 0.674 to 0.976). Optimum combinations of sensitivity (81.3%) and specificity (80.0%) were obtained from a cut-off TREM value of 521.3 units. There were no substantive correlations between TREM, CRP values and CCP values.

Conclusion: In this first assessment high level of sTREM is significantly associated with disease progression in at-risk individuals. Furthermore, higher sTREM values are associated with greater odds of progression. It has potential to offer insights regarding disease pathogenesis and warrants further research. References: 1. Bouchon A et al, Nature 2001

Disclosure: L. Hunt, None; **S. Musaad**, None; **J. Stephenson**, None; **B. Burn**, None; **I. Matsuura**, None; **K. Mankia**, None; **J. L. Nam**, None; **P. Emery**, Pfizer,MSD,Abbvie,BMS,UCB,Roche,Novartis,Samsung, Sandoz, Eli Lillyand Company, 5.

Abstract Number: 569

WITHDRAWN

Abstract Number: 570

A Molecular Timeline for Preclinical RA Pathogenesis Defined By Dysregulated PTPN22, Hypercitrullination, and Aberrant Cytokine/Metabolic Profiles in PBMC of at-Risk Individuals

Hui-Hsin Chang[1], Nishant Dwivedi[2], Bo Sun[2], Deepak A. Rao[3], Jeffrey A. Sparks[3], Jennifer Kinslow[4], Yuko Okamoto[4], Kevin D. Deane[5], M. Kristen Demoruelle[6], Jill M. Norris[7], Elizabeth Karlson[2], V. Michael Holers[8] and **I-Cheng Ho**[1], [1]Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [3]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [4]University of Colorado School of Medicine, Aurora, CO, [5]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [6]Rheumatology, University of Colorado School

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Background/Purpose: One unique feature of RA is the presence of ACPA. PTPN22 is a phosphatase that also acts to suppress citrullination independently of its phosphatase activity by inhibiting the function of peptidyl arginine deiminases (PADs). A C-to-T single nucleotide polymorphism, converting an arginine (R620) of PTPN22 to a tryptophan (W620), renders PTPN22 unable to suppress PADs and is associated with higher risk of RA and hypercitrullination in PBMC. Th cells of RA patients are prone to differentiation into Th17 cells and display hypoglycolysis, hyperproliferation, and excessive reductive stress due to abnormal expression of PFKFB3, ATM, and G6PD. We postulate that these abnormal features and hypercitrullination predate the onset of clinical symptoms of RA and can be attributed to attenuated phosphatase and/or non-phosphatase activities of PTPN22.

Methods: PBMC were collected from healthy at-risk individuals (ARIs), including RA first-degree relatives and/or ACPA+ individuals, and healthy ACPA- control individuals. The PBMC were stimulated with anti-CD3. Intracellular staining, western blotting, and real time PCR were used to quantify the level of citrullinated proteins and the expression of various genes. The levels of cytokines and lactate in supernatant were measured with ELISA and a colorimetric assay. PBMC were also transfected with plasmid vectors expressing PTPN22 or PADs to examine the impact of these proteins on the phenotype of PBMC.

Results: Regardless of the ACPA status, a high level of citrullinated histone H3 (cit-H3) was detected in ARIs but not in the control populations. T cells were the major source of cit-H3 in ARI PBMC. Despite a normal level of G6PD, ARI PBMC expressed more IL-2 and IL-17, but less IL-4, ATM and PFKFB3, and were hypoglycolytic. These abnormal features and hypercitrullination correlated with impaired anti-CD3-mediated induction of PTPN22 and were rectified by exogenous PTPN22. A phosphatase-dead PTPN22 was still able to normalize the level of cit-H3, IL-4 and IL-17 but not IL-2, ATM, or PFKFB3. In contrast, W620-PTPN22 normalized the expression of IL-2, ATM, and PFKFB3, but not IL-4 or IL-17. Furthermore, forced expression of PAD2 or PAD4 in control PBMC induced hypercitrullination and reduced the expression of IL-4, whereas only PAD2 was able to enhance the expression of IL-17.

Conclusion: Our data depict a molecular timeline of preclinical RA (Figure 1): impaired induction of PTPN22 leading to attenuated phosphatase activity and PADs-mediated hypercitrullination. The attenuated phosphatase activity results in aberrant expression of IL-2, ATM, and PFKFB3, whereas PAD2- or PAD4-mediated hypercitrullination inhibits the expression of Th2 cytokine. However, only PAD2-mediated hypercitrullination can augment the expression of Th17 cytokines. All of these events take place with or without the development of ACPA and abnormal expression of G6PD.

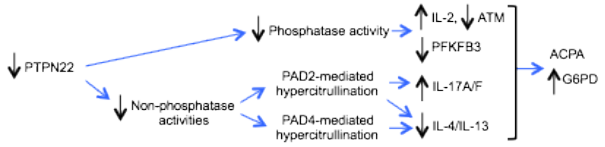

Figure 1: A series of molecular events triggered by impaired induction of PTPN22 in PBMC of ARIs

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Abstract Number: 571

High Titer Rheumatoid Arthritis Antibodies Distinguish Between PAD2 and PAD4 Citrullinated Fibrinogen

Nathalie Blachere[1,2], Salina Parveen[1], Mayu Frank[1], Brian D. Dill[1], Henrik Molina[1] and **Dana E. Orange**[1,3,4], [1]The Rockefeller University, New York, NY, [2]Howard Hughes Medical Institute, Chevy Chase, MD, [3]Rheumatology, Hospital for Special Surgery, New York, NY, [4]The New York Genome Center, New York, NY
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Background/Purpose: Most patients with rheumatoid arthritis (RA) harbor antibodies to citrullinated autoantigens, such as citrullinated fibrinogen. Two isoforms of peptidylarginine deiminase (PAD), PAD2 and PAD4, which catalyze citrullination with different substrate specificities, can be detected in rheumatoid arthritis (RA) synovium. This study was undertaken to determine whether RA patient antibodies preferentially bind PAD2 or PAD4 citrullinated fibrinogen.

Methods: RA patient and normal donor plasma was tested for binding to PAD2 or PAD4 citrullinated fibrinogen, native fibrinogen, or citrullinated fibrinogen peptides in various dilutions by ELISA and Western blot. Bands corresponding to masses demonstrating RA patient reactivity by Western blot were excised and analyzed by mass spectrometry.

Results: As expected, at low titers neither normal donors nor RA patients harbored antibodies to unreactive (native) plasma derived fibrinogen while RA patients harbored significantly elevated antibody to both PAD2 and PAD4 citrullinated fibrinogen. When plasma was further diluted to 1:250 and 1:1000, the OD of RA patient plasma binding of PAD4 citrullinated fibrinogen was significantly greater than PAD2 citrullinated fibrinogen ($p<0.01$). The ratio of ELISA OD of PAD4 citrullinated fibrinogen divided by PAD2 citrullinated fibrinogen was calculated for each patient. The mean ratios of PAD4/PAD2 citrullinated fibrinogen at the 1:250 and 1:1000 dilutions were 1.26 (95% confidence interval 1.18-1.35) and 1.39 (95% confidence interval 1.24-1.53) respectively, indicating preferential binding of PAD4 citrullinated fibrinogen. RA patient plasma also bound PAD4 citrullinated fibrinogen more than PAD2 citrullinated fibrinogen on Western blot at both 56kD and 76kD ($p<0.01$ for both bands). Increasing antibody titer associated with increasing avidity ($p<0.0001$) but there was no difference in avidity for PAD2 or PAD4 citrullinated fibrinogen at low or high titer. Mass spectrometry based analysis of bands corresponding to masses demonstrating RA patient reactivity on western blot identified a hotspot of citrullination of the beta chain of fibrinogen between arginine residues 44 and 74. This hotspot region was modified more heavily than any other site. Both enzymes hypercitrullinated fibrinogen, but PAD4 citrullinates arginines more intermittently, generating peptides with a mix of citrullinated and nonmodifed arginines.

Conclusion: At high titer, RA patient antibodies preferentially bind fibrinogen with a combination of both citrullinated and non-citrullinated arginines.

Disclosure: N. Blachere, None; **S. Parveen**, None; **M. Frank**, None; **B. D. Dill**, None; **H. Molina**, None; **D. E. Orange**, None.

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Abstract Number: 572

Anti-Periodontal Bacteria Antibody Titers Are Inversely Correlated with ACPA in RA-Free Individuals with Periodontal Disease Compared to Community Controls

Emma Weeding[1], Londyn Robinson[2], Jeremy Sokolove[3], Julie Marchesan[4], Steven Offenbacher[4], William H. Robinson[3], Ryan Demmer[5], Bryan Michalowicz[6] and Jerry A. Molitor[7], [1]Department of Internal Medicine, University of Michigan, Ann Arbor, MI, [2]University of Minnesota, Minneapolis, MN, [3]Stanford University School of Medicine, Stanford, CA, [4]Department of Periodontology, Dental School, University of North Carolina at Chapel Hill, Chapel Hill, NC, [5]Epidemiology, Columbia University Mailman School of Public Health, New York, NY, [6]Department of Developmental and Surgical Sciences, University of Minnesota, Minneapolis, MN, [7]Rheumatic/Autoimmune Diseases, University of Minnesota, Minneapolis, MN

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Session Title: Rheumatoid Arthritis – Human Etiology and Pathogenesis - Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) and periodontal disease (PD) are comorbid conditions that share multiple underlying risk factors and pathophysiological features. A dysbiotic periodontal microbiome might be an environmental trigger for RA, though the underlying mechanisms remain unclear. Several studies have focused on the ability of *Porphyromonas gingivalis* (*Pg*) to citrullinate human α-enolase, suggesting a direct relationship between periodontal bacteria and the development of serological autoimmunity, and possibly eventual autoimmune disease. We investigated the associations between 18 anti-citrullinated peptide antibodies (ACPAs) and antibodies to 18 species of periodontal bacteria in RA-free individuals with and without PD.

Methods: Adults with moderate to severe periodontal disease as defined by the 2000 American Academy of Periodontology definitions and no history of RA or RA symptoms were recruited for the PD group (n = 181). Periodontally healthy controls matched for age and sex were selected from the dental Atherosclerosis Risk in Communities (ARIC) cohort (n = 138). Serum anti-periodontal bacteria antibodies were measured using a rapid checkerboard immunoblotting technique. Analysis of ACPAs was performed using a multiplex assay platform. Linear regression models were used to examine the relationships between PD bacteria antibody titers and ACPA positivity while controlling for age, sex, and smoking status.

Results: Total number of ACPAs was equivalent between the PD and control groups, with 34% having at least one ACPA, and 7% having three or more ACPAs. For all but one PD bacterial species, antibody titers were significantly higher in the PD group compared to controls. Within the PD group, having a total of three or more ACPAs was generally associated with decreased anti-bacteria antibody titers including for *Pg*, *Tannerella forsythia*, and *Treponema denticola* (*Td*), though this reached statistical significance only with *Td* and marginally ($p = 0.09$). These trends were not seen with *Prevotella* species in the PD group, and were generally reduced or absent in the control group. Certain specific ACPAs were more strongly associated with decreased anti-bacterial antibody titers than others. Most notably, significantly decreased *Td* antibodies were associated with clusterin ACPA positivity ($p < 0.05$), and marginally with biglycan, fibrinogenA, and histone 2A ACPA positivity (all p-values < 0.10) in the PD group. Similar trends were seen with *Pg* across multiple ACPAs, and enolase across multiple bacterial species, but were generally weaker. There was no correlation between *Pg* antibody titers and enolase.

Conclusion: Relationships between ACPAs and PD bacteria antibody titers were predominantly inverse though largely not statistically significant in this small sample. The strongest relationships were found between distinct individual ACPAs and *Td* antibodies; results for *Pg* and enolase were relatively weak. Our results suggest an interplay between aberrant immune response to periodontal bacteria and serological autoimmunity, and have implications for future study of *P. gingivalis* and *T. denticola* as possible inciting factors of RA.

Disclosure: E. Weeding, None; **L. Robinson**, None; **J. Sokolove**, Abbvie, 3; **J. Marchesan**, None; **S. Offenbacher**, None; **W. H. Robinson**, None; **R. Demmer**, None; **B. Michalowicz**, None; **J. A. Molitor**, Pfizer Inc, 2.

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Abstract Number: 573

Synovial Fibroblast-Neutrophil Interactions Promote Pathogenic Adaptive Immunity in Rheumatoid Arthritis

Carmelo Carmona-Rivera[1], Erica Moore[2], Nithya Lingampalli[3], Hannes Uchtenhagen[4], Eddie James[5], Kevin L. Bicker[6], Heidi Wähämaa[7], Victoria Hoffmann[8], Anca I Catrina[7], Paul Thompson[9], Jane H. Buckner[5], William Robinson[10], David Fox[11] and Mariana Kaplan[2], [1]Systemic Autoimmunity Branch/ NIAMS, National Institutes of Health, Bethesda, MD, [2]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [3]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [4]Translational Research Program, Benaroya Research Institute at Virginia Mason, Seattle, WA, [5]Benaroya Research Institute at Virginia Mason, Seattle, WA, [6]Middle Tennessee State University, Murfreesboro, TN, [7]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [8]Division of Veterinary Resources, National Institutes of Health, Bethesda, MD, [9]University of Massachusetts, Worcester, MA, [10]Stanford University School of Medicine, Stanford, CA, [11]Department of Medicine [Division of Rheumatology], University of Michigan, Ann Arbor, MI

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Background/Purpose: Rheumatoid arthritis (RA) is characterized by development of humoral and cellular autoimmunity to citrullinated proteins and peptides. Autoimmunity to citrullinated antigens appears years before the onset of clinical symptoms of RA Neutrophil extracellular traps (NETs) are a source of citrullinated autoantigens and activate RA synovial fibroblasts (FLS), cells crucial in joint damage. We investigated the molecular mechanisms by which NETs promote proinflammatory phenotypes in FLS, and whether these interactions generate pathogenic anti-citrulline adaptive immune responses.

Methods: Shared epitope-positive RA FLS and control Osteoarthritis FLS were co-cultured with RA NETs and interactions visualized by confocal microscopy. Induction of inflammatory responses and MHC class II expression were assessed by qPCR. RA-FLS and Ag-specific RA T cells were co-cultured for 5 days and T cell activation was examined. HLADRB1*0401 transgenic mice were immunized with mouse FLS loaded with NETs or FLS alone. Antibodies to citrullinated proteins antigens (ACPAs) were quantified by ELISA, immunoblot and epitope mapping array. Cartilage integrity was assessed by safranin-O staining.

Results: NETs containing citrullinated peptides are internalized by FLS through a RAGE-TLR9 pathway promoting FLS inflammatory phenotype and their upregulation of MHC class II. Once internalized, arthritogenic citrullinated NET-peptides are loaded into FLS MHC class II and presented to Ag-specific T cells. HLADRB1*0401 transgenic mice immunized with mouse FLS loaded with NETs develop cartilage damage as well as ACPAs specific to citrullinated forms of relevant RA autoantigens implicated in disease pathogenesis.

Conclusion: These results suggest that NETs are a source of arthritogenic peptides in the synovium and implicate FLS as mediators in RA pathogenesis, through the internalization and presentation of citrullinated peptides to the adaptive immune system leading to pathogenic autoimmunity and cartilage damage.

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Abstract Number: 574

Anti-CCP3.1 and Anti-CCP3-IgA Antibodies Are Associated with Increasing Age in Subjects without Rheumatoid Arthritis

Heather Berens-Norman[1,2], Sonia Khatter[3], Wendy M. Kohrt[4], Catherine Jankowski[5], Michael Weisman[6], Michael Mahler[7], James R. O'Dell[8], Ted R Mikuls[8], Richard M. Keating[9], Jane H. Buckner[10], Peter K. Gregersen[11], Jill M. Norris[12], V. Michael Holers[13], Kevin D. Deane[13] and M. Kristen Demoruelle[13], [1]Division of Rheumatology, University of Colorado Denver, Aurora, CO, [2]Division of Rheumatology, University of Colorado School of Medicine, Denver, CO, [3]University of Colorado School of Medicine, Aurora, CO, [4]Geriatric Medicine Division, University of Colorado Denver, Aurora, CO, [5]University of Colorado College of Nursing, Aurora, CO, [6]Cedars-Sinai Medical Center, Los Angeles, CA, [7]Research and Development, Inova Diagnostics, San Diego, CA, [8]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [9]Division of Rheumatology, Scripps Health, La Jolla, CA, [10]Benaroya Research Institute at Virginia Mason, Seattle, WA, [11]The Feinstein Institute for Medical Research, Manhasset, NY, [12]Epidemiology, Colorado School of Public Health, Aurora, CO, [13]Rheumatology Division, University of Colorado Denver, Aurora, CO

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Background/Purpose: Serum anti-CCP antibodies are specific for RA in the setting of inflammatory arthritis (IA) and can be elevated for several years prior to the onset of IA during the preclinical period of autoimmunity in RA. Understanding the origins of anti-CCP is critical to understanding the etiology of RA. Prior studies demonstrate that positivity of autoantibodies (e.g. RF and ANA) increase with increasing age. Similar associations have not been reported for anti-CCP. We sought to further evaluate the association of age and anti-CCP3.1 that detects IgG and IgA reactivity in subjects without RA.

Methods: From the Studies of the Etiology of RA (SERA) cohort, we included 1037 RA-free first-degree relatives (FDRs) of probands with RA, and from the Myogenic and Osteogenic Responses to Exercise and Ibuprofen (MOXI) Study, we included the baseline sample of 187 subjects aged 59-75 years without RA. Serum was tested by ELISA for CCP2 (IgG, Axis-Shield) and CCP3.1 (IgG/IgA, Inova) with positivity based on manufacturerÕs recommendations. A random subset of 279 FDRs also had serum testing by ELISA on a CCP3 substrate using isotype-specific IgA (CCP-IgA) and IgG (CCP-IgG) secondary reagents (Inova, for research only) with positivity based on a cut-off level that was positive in <5% of 154 anonymous blood donors. Analyses included logistic regression and McNemarÕs test.

Results: FDRs were 81% female, 76% white, 40% ever smokers and 53% shared epitope (SE) positive. MOXI Subjects were 66% female, 82% white and 47% ever smokers. Overall in FDRs, anti-CCP3.1 positivity was more prevalent than CCP2 (8.2 v. 2.7%, p<0.01). There was an association between increasing age (per year) and anti-CCP3.1 positivity (OR=1.03 95% CI 1.02-1.05) that remained significant after adjusting for sex, race, smoking and SE. When stratified by age group, the higher prevalence of anti-CCP3.1 was significant after age 50 (Figure). In MOXI Subjects, anti-CCP3.1 positivity was also more prevalent than CCP2 (23.5 v. 1.6%, p<0.01). When considering specific isotypes, in FDRs ³50 years, anti-CCP-IgA positivity was more prevalent than CCP-IgG (17.3 v. 8.3%, p=0.04). Anti-CCP-IgA positivity was also associated with increasing age (per year) (OR=1.04 95% CI 1.02-1.07). There was no association of age and anti-CCP2 (p=0.78) or CCP-IgG (p=0.24).

Conclusion: This is the first study to demonstrate increasing anti-CCP3.1 positivity with increasing age in subjects without RA. This association appears to be driven by IgA reactivity, and may reflect an ongoing mucosal immune process. Additional studies are needed to determine potential pathogenicity or other phenotypic associations of anti-CCP-IgA in older adults, but these findings have important clinical and research implications. Age should be considered in the clinical interpretation of anti-CCP3.1 in subjects without IA, and identifying mechanisms of anti-CCP-IgA generation in older adults could provide insight into the etiology of RA.

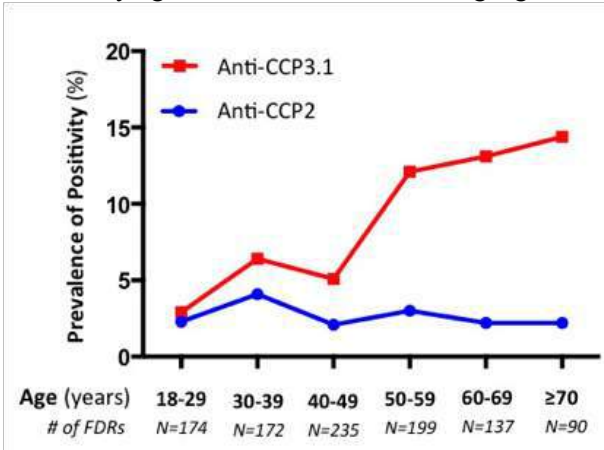

Figure. Anti-CCP2 and anti-CCP3.1 positivity in FDRs by age group. Prevalence of positivity for anti-CCP2 (blue) and anti-CCP3.1 (red) are depicted on the Y-axis by age group (X-axis). The number of FDRs studied per age group are listed under the associated age group. Results of McNemar's test comparing anti-CCP2 and CCP3.1 positivity in each age group are depicted as *<0.01.

Disclosure: H. Berens-Norman, None; **S. Khatter**, None; **W. M. Kohrt**, None; **C. Jankowski**, None; **M. Weisman**, None; **M. Mahler**, Inova Diagnostics, 3; **J. R. O'Dell**, None; **T. R. Mikuls**, None; **R. M. Keating**, None; **J. H. Buckner**, None; **P. K. Gregersen**, None; **J. M. Norris**, None; **V. M. Holers**, Patents, 9; **K. D. Deane**, Inova Diagnostics, Inc., 9; **M. K. Demoruelle**, Inova Diagnostics, Inc., 9.

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Abstract Number: 575

Differences in Histological Scores and Histoclinical Correlations in ACPA- Versus ACPA+ Rheumatoid Arthritis Patients

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Background/Purpose: Differences in the pathogenesis of ACPA- versus ACPA+ rheumatoid arthritis are still poorly understood. In this study, we compared patterns of synovial changes in both disorders, and how they correlate with clinical parameters of disease activity.

Methods: Semi-quantitative histological scores (0-3) on synovial hyperplasia, diffuse and perivascular lymphocytic infiltrates, vascular hypertrophy and fibrinoid necrosis were obtained retrospectively from 62 ACPA+ and 29 ACPA- synovial biopsies, obtained by needle-arthroscopy from the knee of rheumatoid arthritis patients. Clinical and biological indices of disease activity (DAS28-CRP, SDAI, CDAI and their individual components) were retrieved from the medical records at the time of biopsy (T0), and 6 months later. IL6 and IL6R immunostainings were performed on a subset of the samples. High-throughput transcriptomic data were available for 14 ACPA+ and 6 ACPA- patients.

Results: Synovial hyperplasia, vascular hypertrophy and fibrinoid necrosis scores were significantly higher in ACPA- compared to ACPA+ patients. Diffuse and perivascular lymphocytic infiltrates also scored higher in ACPA- patients, but the difference was not significant. Clinical and biological indices of disease activity were similar in both groups, as were IL6 and IL6R immunostaining quantifications. In ACPA+ patients, all (except vascular hypertrophy) histological scores correlated with clinical and/or biological scores of disease activity at T0. Fibrinoid necrosis in ACPA+ patients also correlated with disease activity 6 months later. By contrast, none of the histological scores displayed any correlation with disease activity measures in ACPA- patients. Transcriptomic analyses demonstrated a significant correlation between synovial hyperplasia and a T cell activation signature (e.g. IL6R, IL23R) in ACPA+ biopsies. This correlation was also present in ACPA- samples, but stronger correlations were found in this group with transcripts pointing at the activation of other T cell related pathways, such as IL10 and TGFβ2.

Conclusion: Synovial biopsies from ACPA- versus ACPA+ rheumatoid arthritis patients display different histological characteristics and histoclinical correlations. In particular, synovial biopsies from ACPA- patients have a higher cellularity, yet are associated with similar clinical disease activity. Preliminary transcriptomic data point at the presence of regulatory cells in ACPA- synovial tissue, as a potential explanation to this discrepancy.

Disclosure: F. Pirbuccus, None; **C. Galant**, None; **A. Nzeusseu Toukap**, None; **F. A. Houssiau**, None; **P. Durez**, None; **B. R. Lauwerys**, None.

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Abstract Number: 576

Anti-CCP3.1 and Anti-CCP3-IgA Are Elevated in RA-Free Subjects with Idiopathic Pulmonary Fibrosis

Scott Matson[1], Joshua J. Solomon[2], Jeffrey J. Swigris[2], Jonathan Chung[3], Michael Mahler[4], Kevin D. Deane[5] and M. Kristen Demoruelle[5], [1]Medicine, University of Colorado Denver, Aurora, CO, [2]Division of Pulmonary and Critical Care Medicine, National Jewish Health, Denver, CO, [3]Radiology, University of Chicago Medical Center, Chicago, IL, [4]Research and Development, Inova Diagnostics, San Diego, CA, [5]Rheumatology Division, University of Colorado Denver, Aurora, CO

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Background/Purpose: In RA-associated interstitial lung disease (RA-ILD), higher levels of anti-CCP antibodies have been associated with the presence and severity of ILD suggesting a potential role in the pathophysiology. Usual interstitial pneumonia (UIP) is the most common RA-ILD subtype and associated with a poor prognosis. Idiopathic pulmonary fibrosis (IPF) is a distinct form of ILD that is radiographically and pathologically similar to RA-UIP, but the role of anti-CCP in IPF has not been well studied. As such, we sought to compare anti-CCP in subjects with RA-UIP and IPF.

Methods: From the National Jewish Health serum biobank, we identified 36 patients with RA-UIP and 35 patients with IPF without RA (IPF-noRA). Diagnosis was confirmed by chart review. Serum was tested for the commercial assay CCP3.1 (IgG/IgA, Inova) and isotype-specific research assays using the CCP3 substrate for IgG and IgA (Inova). Anti-CCP3.1 positivity was based on manufacturer recommendations, and to evaluate specificity, we also tested 35 healthy Controls who were without RA or ILD based on self-report. For CCP-IgG and IgA assays, cut-off for positivity was set at a level that was positive in <5% in 154 random blood donors. Analyses included comparisons between groups (Chi-square/Fisher's) and within each group (McNemar's). Non-parametric testing compared change in diffusing capacity of the lung for carbon monoxide (DLCO) between anti-CCP(+) and (-) subjects.

Results: Subject characteristics are listed in the Table. Overall, anti-CCP3.1 was more prevalent in RA-UIP. However, anti-CCP3.1 positivity was significantly more prevalent in IPF-noRA than Controls (31 vs. 3%, $p<0.01$). Within IPF-noRA subjects, anti-CCP-IgA was more prevalent than CCP-IgG (31 vs. 6%, $p=0.02$), but within RA-UIP subjects, anti-CCP-IgA and IgG rates were similar (67 vs. 58%, $p=0.45$). In addition, 25/35 IPF-noRA and 20/36 RA-UIP subjects had pulmonary function tests at the time of serum collection and longitudinally within 2 years (median 1.1 years, range 0.3-2 years). In IPF-noRA subjects, anti-CCP3.1 and CCP-IgA positive subjects had a poorer prognosis [median decline in DLCO/year; for anti-CCP3.1 (+) vs. (-), 3.48 vs. 0.80, $p=0.04$; for anti-CCP-IgA (+) vs. (-), 2.78 vs. 0.69, $p=0.05$]. Similar associations were not seen in RA-UIP where the majority of subjects were anti-CCP (+).

Conclusion: We found that almost one third of IPF-noRA subjects are positive for the commercially available anti-CCP3.1, with isotype-specific testing demonstrating predominately anti-CCP-IgA, and positivity being associated with a more rapid progression of lung disease. Further study is needed to determine whether anti-CCP-IgA in these subjects represents a non-specific response to lung injury or a marker of a novel subset of IPF subjects that may be more responsive to immunosuppressive therapy. Longitudinal follow-up is needed to determine the risk of progression to classifiable RA in IPF-noRA subjects.

Table. Clinical Characteristics and Anti-CCP Positivity in RA-UIP and IPF						
	RA-UIP (N=36)	**IPF** (N=35)	**p-value***	**IPF** (N=35)	**Controls** (N=35)	**p-value****
Age, mean ± SD	64 ± 11	69 ± 8	0.02	69 ± 8	57 ± 7	<0.01
Female, %	50	23	0.02	23	63	<0.01
History of ever smoking, %	54	66	0.33	66	26	<0.01
≥10 pack years of smoking, %	38	50	0.31	50	14	<0.01
Anti-CCP3.1 positivity, %	69	31	<0.01	**31**	**3**	**<0.01**
Anti-CCP3-IgG positivity, %	67***	**6*** **	<0.01	6	-	
Anti-CCP3-IgA positivity, %	58***	**31*** **	<0.01	31	-	

*P-value compares RA-UIP and IPF subjects using t-test for age and Chi-square/Fisher's exact testing for other variables ** P-value compares IPF and healthy Control subjects using t-test for age and Chi-square/Fisher's exact testing for other variables ***Within IPF subjects using McNemar's test, anti-CCP3-IgA was significantly more prevalent than CCP3-IgG (31 vs. 6%, p=0.02). However within RA-UIP subjects, anti-CCP3-IgG and CCP3-IgA positivity were not significantly different (67 vs. 58%, p=0.45).
Abbreviations: CCP=cyclic citrullinated peptide; RA-UIP = rheumatoid arthritis-associated usual interstitial pneumonia; IPF=idiopathic pulmonary fibrosis

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Disclosure: S. Matson, None; **J. J. Solomon**, None; **J. J. Swigris**, None; **J. Chung**, None; **M. Mahler**, Inova Diagnostics, 3; **K. D. Deane**, Inova Diagnostics, Inc., 9; **M. K. Demoruelle**, Inova Diagnostics, Inc., 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anti-ccp3-1-and-anti-ccp3-iga-are-elevated-in-ra-free-subjects-with-idiopathic-pulmonary-fibrosis

Abstract Number: 577

TCZ Modulates the Production of Ccfdna Derived from RA Synovial Cells

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Session Type: ACR Poster Session A
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Background/Purpose: DNA is fragmented and released into blood circulation as a circulating cell-free DNA (ccfDNA) because of damage or death of cells. Although the lower concentration of ccfDNA is present in peripheral bloods from healthy individuals, significantly higher amount of those are detected in cancer patients or pregnant women (1). Thus, ccfDNA has recently been recognized as biomarkers of several medical conditions. In this study, we measured the amount of ccfDNA in peripheral bloods from RA patients and healthy controls, and in synovial fluid samples of knee joint from RA patients and osteoarthritis (OA) patients. Moreover, we investigated the mechanism of ccfDNA production and found that TCZ inhibited the production of ccfDNA derived from RA synovial cells.

Methods: The amount of ccfDNA was measured by qPCR in peripheral bloods from 29 patients with RA, and 21 healthy controls., and in synovial fluid of knee joint from 13 patients with RA, and 12 patients with OA. By using human synovial cells, culture-supernatants were collected in each steps of cellular-confluency; 40% to 120%. In addition, after stimulated with interleukin(IL)6/soluble IL6 receptor(sIL6R) or TNFα, synovial cells were further treated with and without tocilizumab(TCZ: 100μg/mL) or etanercept(ETN: 10μg/mL) to collect supernatants. When examining ccfDNA in supernatants by qPCR, we amplified both short and long DNA fragments using ALU115-bp primer and ALU247-bp primer to distinguish apoptotic fragments from non-apoptotic fragments, respectively. Viabilities of synovial cells were also examined by WST-8 assay.

Results: The amount of ccfDNA in RA patients was significantly increased as compared to healthy controls, and to OA patients. In supernatants, amounts of ccfDNA (ALU115 and ALU247) increased before 100% confluency cultured-state, and decreased after 100% confluency. Amounts of ccfDNA (ALU115 and ALU247) were significantly suppressed by TCZ treatment, while those with ETN were not changed. Notably, cellular viabilities showed no significant difference between non-treated and biological DMARDs-treated groups, and the ratio of ALU247 to ALU115 was significantly reduced by TCZ.

Conclusion: Results clearly showed that ccfDNA was a diagnostic biomarker for RA in both peripheral blood and joint fluid, and suggesting that ccfDNA in peripheral blood was derived from synovial tissue. Another source of ccfDNA was considered to be physiological cell division because the amount of ccfDNA was increased by cell proliferation and decreased in the growth inhibition by cell-to-cell contact. Thus it appeared that TCZ inhibit the physiological cell division and the ratio of ALU247 to ALU115 could represent the therapeutic response for TCZ, since ALU115 represents the total amount of ccfDNA and ALU247 specifically represents those released by cell division. **References:** (1) T B Hao, et al. 2014 Circulating cell-free DNA in serum as a biomarker for diagnosis and prognostic prediction of colorectal cancer. *British Journal of Cancer* 111(8):1482-9

Disclosure: N. Hashimoto, None; **K. Yoshida**, None; **T. Hashimoto**, None; **A. Nakai**, None; **K. Kaneshiro**, None; **K. Suzuki**, None; **Y. Kawasaki**, None; **N. Shibanuma**, None; **N. Nakagawa**, None; **Y. Sakai**, None; **A. Hashiramoto**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tcz-modulates-the-production-of-ccfdna-derived-from-ra-synovial-cells

Abstract Number: 578

Do Specific Anti-Citrullinated Antibodies Predict Different Phenotype of Rheumatoid Arthritis?

Mikael Brink[1], Monika Hansson[2], Linda Mathsson-Alm[3,4], Johan Rönnelid[5], Karl Skriner[6], Guy Serre[7], Lars Klareskog[2] and **Solbritt Rantapää-Dahlqvist**[1], [1]Rheumatology, Umeå University, Umeå, Sweden, [2]Rheumatology Unit, Department of Medicine, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [3]ThermoFisher Scientific, Uppsala, Sweden, Uppsala, Sweden, [4]Thermo Fisher Scientific, Uppsala, Sweden, [5]Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden, [6]Humboldt University of Berlin, Berlin, Germany, [7]Unité Différenciation Épidermique et Autoimmunité Rhumatoïde, Unité Mixte de Recherche, INSERM, Toulouse, France

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Background/Purpose: Antibodies against cyclic citrullinated peptides (anti-CCP) have been suggested to identify a more severe phenotype of rheumatoid arthritis. In this study we have analysed a number of antibodies against citrullinated peptides (ACPA) using a multiplex platform in an inception cohort of early RA in relation to disease inflammation and progressive severity.

Methods: Patients with early RA (≤12 months of symptoms) fulfilling the 1987 ARA criteria (n=1012, 681f/331m, mean age56.9±14.0 years) were sampled at the time of diagnosis and evaluated using disease activity score 28 (DAS28) (at baseline, 6, 12, 18 and 24 months) and with radiography using Larsen score (baseline and 24 months). Baseline plasma samples were analysed for presence of 17 different antibodies; ACPA (Fibrinogen α36-50 (Fibα36-50), Fibα573, Fibα591, Fibα621-635, Fibβ36-52, Fibβ60-74, Fibβ62-78 (72), Fibβ62-78 (74), filaggrin (Fil307-324), α-enolase peptide 5-21 (CEP-1), Vimentin (Vim) 2-17, Vim60-75)), or mutated proteins (Bla26, Pept1, Pept5, PeptZ1, PeptZ2) analysed using a custom-made microarray assay based on the ImmunoCAP ISAC system (Phadia AB, Sweden). Cut-off levels set at the 98th percentile of controls. Anti-CCP2 was analysed using ELISA (Euro Diagnostica, Sweden) and rheumatoid factor (RF) according to routine methods with cut-off at 95%.

Results:

The most frequent positive ACPA were; Fibβ60-74 (63%), Vim60-75 (56.6%), Fibβ36-52 (55.1%), Fil307-324 (54.9%), CEP-1 (53.7%) and Pept5 (52.0%) besides CCP2 (67.5%) and RF (74.3%). The median (IQR) number of ACPA positivity was 8 (11). Adding all ACPAs gave additional 13.1% of positivity in the anti-CCP2 negative group, yielding a total positivity of 77.5%. Positivity for CCP-1, Vim60-75, Fibα36-50, Pept5 and Vim2-17 was associated with area under curve (AUC) DAS28 during the 24 months compared with negativity ($p<0.05$). Increased ESR at baseline was associated with positivity vs. negativity for all antibodies except Fibβ62-78(72), Fibβ62-78 (74) and Pept1 ($p<0.05$). Positivity for Fil307-324, CEP-1, Fibα36-50, Fibα621-635, Fibβ36-52, Vim60-75, Vim2-17, PeptZ1 and Pept1 were significantly associated with radiological progression ($p<0.05$). CEP-1, Fibα621-635, Fibα36-50 and PeptZ2 remained significant in a logistic stepwise regression analysis adjusted for sex. Overall 69.1% were good-moderate EULAR responders, no significant relationships between antibodies and response to treatments were found except for positivity for Fibβ36-52 adjusted for all analysed antibodies, sex and being a smoker ($p=0.008$). Of the patients treated with biologics during the first 24 months (11.2%), positivity for antibodies against CCP2, Vim60 75, Fibα36-50, PeptZ1 and PeptZ2 were significantly more frequent vs. negativity.

Conclusion:

Disease activity and radiological progression are associated with different ACPA reactivities at the time of diagnose and during the 24 months follow up.

Disclosure: M. Brink, None; **M. Hansson**, None; **L. Mathsson-Alm**, None; **J. Rönnelid**, None; **K. Skriner**, None; **G. Serre**, None; **L. Klareskog**, None; **S. Rantapää-Dahlqvist**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/do-specific-anti-citrullinated-antibodies-predict-different-phenotype-of-rheumatoid-arthritis

Abstract Number: 579

MRI-Detected Osteitis Is Not Associated with the Presence or Level of ACPA Alone, but with the Combined Presence of ACPA and RF

Debbie M. Boeters[1], Wouter P. Nieuwenhuis[1], Marije K. Verheul[1], Elize C. Newsum[1], Monique Reijnierse[2], René E.M. Toes[1], Leendert A. Trouw[1] and Annette H.M. van der Helm-van Mil[1], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Radiology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose: Within rheumatoid arthritis (RA) bone marrow edema (BME, osteitis) and anti-citrullinated protein antibodies (ACPAs) are associated with radiographic progression. ACPA has been associated with BME, but it is unknown if this association is confined to ACPA and BME. We cross-sectionally studied the association of ACPA, rheumatoid factor (RF) and anti-carbamylated protein (anti-CarP) antibodies with BME and other types of MRI-detected inflammation (synovitis, tenosynovitis).

Methods: 589 DMARD-naïve early arthritis patients, included in the Leiden Early Arthritis Clinic, underwent contrast-enhanced 1.5T MRI of unilateral wrist, metacarpophalangeal and metatarsophalangeal-joints at baseline. BME, synovitis and tenosynovitis were scored by two readers. ACPA, RF and anti-CarP were determined at baseline.

Results: In univariable analyses ACPA-positive patients had higher BME-scores than ACPA-negative patients (median 4.5 vs. 2.0, $p<0.001$), but not more synovitis and tenosynovitis. Also RF (median 3.75 vs. 2.0, $p<0.001$) and anti-CarP antibodies (median 3.5 vs. 2.5, $p=0.012$) were associated with higher BME-scores. Because the autoantibodies were concomitantly present, analyses were stratified for the presence of different autoantibody combinations. ACPA+RF-anti-CarP- patients did not have higher BME-scores than ACPA-RF-anti-CarP- patients. However ACPA+RF+anti-CarP- and ACPA+RF+anti-CarP+ patients had higher BME-scores than ACPA-RF-anti-CarP- patients (median 5.0 and 4.5 vs. 2.0, $p<0.001$ and $p<0.001$). ACPA levels were not associated with BME-scores. Analyses within RA- and UA-patients revealed similar results.

Conclusion: The single presence of ACPA and ACPA-level were not statistically significant associated with BME-scores, but the combined presence of ACPA and RF did associate with more BME. This suggests an additive role of RF to ACPA in mediating osteitis.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mri-detected-osteitis-is-not-associated-with-the-presence-or-level-of-acpa-alone-but-with-the-combined-presence-of-acpa-and-rf

Abstract Number: 580

Preferential Distribution of M1 Monocytes in Anti-Cyclic Citrullinated Peptide Antibody Positive Patients with Rheumatoid Arthritis

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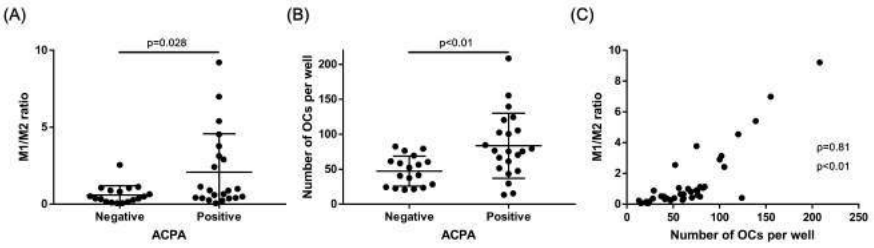
Background/Purpose: In rheumatoid arthritis (RA), bone erosions are caused mainly by osteoclasts. Osteoclasts are derived from monocytes and macrophages (MoMa). MoMa consists of different subtypes such as M1 and M2. Until now, little has been known regarding the relation of characteristic of RA with MoMa subtypes. We attempted to investigate relationship among MoMa subtypes (M1 or M2), ability of osteoclast differentiation, phagocytic ability of osteoclasts, and clinical characteristics in RA patients.

Methods: This study included 40 RA patients and 19 healthy donors. We collected baseline clinical variables including duration of disease, DAS28, positivity of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACPA), and treatments. Peripheral blood mononuclear cells (PBMC) were isolated from RA patients and healthy donors, then we investigated the number of M1/M2 cells by fluorescence-activated cell sorting. We defined M1 as CD14, CD68 and CCR2 positive cells and M2 as CD14, CX3CR1 and CD163 positive cells. We also obtained CD14 positive cells in PBMCs from RA patients and healthy donors using CD14 beads to investigate osteoclast differentiation *in vitro* with stimulation by macrophage colony stimulating factor (MCSF) and receptor activator of NF-*f*ÈB ligand (RANKL). Osteoclast differentiation was evidenced by tartrate-resistant acid phosphatase (TRAP) staining, then we counted number of osteoclasts. We also performed pit formation assay of osteoclasts to assess phagocytic ability of osteoclasts.

Results: Twenty seven patients (68%) had positive RF. Twenty two patients (55%) were ACPA positive. Median M1 rate in CD14 positive cells was 18.5% (6.7%-39.9%, IQR). Median M2 rate in CD14 positive cells was 33.3% (13.2%-65.9%, IQR). Median M1/M2 ratio was 0.59 (0.31-1.11, IQR). There were no differences between RA patients and healthy donors, and between RA patients with high disease activity and low disease activity regarding M1/M2 ratio or number of osteoclasts *in vitro*, respectively. ACPA positive patients had higher M1/M2 ratio *in vivo* (0.87 vs. 0.41, p=0.028) (Figure 1A) and more number of osteoclasts *in vitro* (Figure 1B) than ACPA negative patients (97 per well vs. 37 per well, p=0.003). Furthermore, there was positive correlation between M1/M2 ratio and the number of differentiated osteoclasts *in vitro* in RA patients (*f*Ï=0.81, p<0.01) (Figure 1C). Overall, number of osteoclasts *in vitro* correlated with area of pit formation. There was no relationship among treatments (including methotrexate, prednisolone and biologics), M1/M2 ratio and number of osteoclasts *in vitro*.

Conclusion: The presence of ACPA positively correlated with the circulating osteoclast precursors in RA patients which may attributed to M1 subtypes. Our present data may explain the preferential development of bone destruction in ACPA-positive RA patients.



Disclosure: S. Fukui, None; **N. Iwamoto**, None; **T. Shimizu**, None; **M. Umeda**, None; **A. Nishino**, None; **Y. Horai**, None; **T. Koga**, None; **S. Y. Kawashiri**, None; **K. Ichinose**, None; **Y. Hirai**, None; **M. Tamai**, None; **H. Nakamura**, None; **T. Origuchi**, None; **A. Kawakami**, None.

Abstract Number: 581

Cell-Mediated Neutrophil Lysis-a Mechanism Promoting Hypercitrullination in Rheumatoid Arthritis?

Tal Gazitt[1], Christian Lood[1], Xizhang Sun[2], David Feith[3], Jeffrey Ledbetter[2], Gordon Starkebaum[1], Thomas Loughran Jr.[4] and Keith B. Elkon[1], [1]Department of Medicine, Division of Rheumatology, University of Washington, Seattle, WA, [2]University of Washington, Seattle, WA, [3]Hematology and Oncology, University of Virginia, Charlottesville, VA, [4]Hematology Oncology, University of Virginia, Charlottesville, VA

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BACKGROUND/PURPOSE:

Protein citrullination, the post-translational conversion of arginine to citrulline, mediated by peptidylarginine deiminase (PAD) enzymes, is considered a likely mechanism for the stimulation of anti-citrullinated protein antibodies (ACPA) in patients with rheumatoid arthritis (RA). Hypercitrullination, the citrullination of multiple intracellular proteins, was recently demonstrated in synovial fluid (SF) cells from RA patients (Romero *et al.Sci Transl Med, 2013)*. This unique form of citrullination is proposed to occur via immune-mediated, pore-forming membranolytic pathways such as perforin-granzyme activation, but is not found in other physiological processes involving citrullination, such as NETosis. Indeed, recent findings demonstrate perforin and granzyme-producing $CD8^+$T effector cells in the synovium of pre-clinical RA patients as well as in the peripheral blood (PB) and SF of active RA patients, and persisting into disease remission.

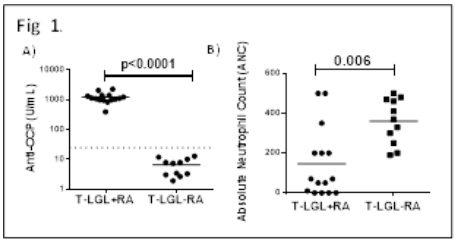
Insight into the existence of potential cytotoxic mechanisms occurring in RA comes from the co-occurrence of RA in up to 36% of cases of T-cell Large Granular Lymphocyte (T-LGL) Leukemia, a clonal condition characterized by severe neutropenia attributed to the killing of neutrophils or their precursors by cytotoxic $CD8^+$ T cells. Interestingly, $CD8^+$T cells with features of LGLs were found in the SF of RA patients without LGL leukemia, but not in the SF of psoriatic arthritis and ankylosing spondylitis patients. We thus decided to test LGL leukemia as a model for neutrophil-directed cytotoxicity contributing to hypercitrullination and disease propagation in inflamed joints of ACPA+ RA patients.

METHODS:

The sera of 11 T-LGL leukemia patients (T-LGL-RA) and 15 T-LGL leukemia patients with co-existing RA (T-LGL+RA) with absolute neutrophil count (ANC) < 500 were analyzed for ACPA positivity by ELISA. ACPA titers and ANC of each group of patients were compared using unpaired two-tailed T tests. Hypercitrullination in PB neutrophils was analyzed by immunoblotting electrophoresed neutrophil cell lysates using a broad-spectrum anti-citrulline antibody. Ionomycin was used as a positive control for hypercitrullination.

RESULTS:

All T-LGL+RA were ACPA positive, in stark contrast to the T-LGL patients without co-existing RA (Fig. 1A). Of interest, T-LGL+RA patients had decreased ANC (Fig. 1B) as compared to T-LGL-RA patients, supporting the hypothesis of neutrophil destruction in development of ACPA positivity. Importantly, hypercitrullination was observed in neutrophils isolated from both RA and T-LGL+RA patients.



CONCLUSION:

These results are consistent with the hypothesis that in T-LGL+RA, ACPA generation may result from neutrophil-directed lysis and hypercitrullination. Elucidating the cause of neutrophil-directed cytotoxicity may help to uncover a mechanism for hypercitrullination, ACPA formation and RA disease propagation.

Disclosure: T. Gazitt, None; **C. Lood**, None; **X. Sun**, None; **D. Feith**, None; **J. Ledbetter**, None; **G. Starkebaum**, None; **T. Loughran Jr.**, None; **K. B. Elkon**, Resolve Therapeutics, LLC, 4.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cell-mediated-neutrophil-lysis-a-mechanism-promoting-hypercitrullination-in-rheumatoid-arthritis

Abstract Number: 582

ACPA Induce Pathogenic Cytokines Expression in PBMC of ACPA+-RA Patients and Inhibition of Its Effect By Cit-ME a Synthetic Citrullinated Peptide

Smadar Gertel[1], Gidi Karmon[2], Eszter Szarka[3], , Esther Houri-Levi[4], Edna mozes[5], Yehuda Shoenfeld[4] and **Howard Amital**[6,7], [1]Sheba Medical Center, Zabludowicz Center for Autoimmune Diseases, affiliated to Sackler Faculty of Medicine, Tel-Aviv University, Ramat Gan, Israel, [2]Sheba Medical Center, Tel-Hashomer, Ramat-Gan, Israel, [3]Department of Immunology,, Eötvös Loránd University, Budapest,, Budapest, Hungary, [4]Zabludowicz Center For Autoimmune Diseases, Sheba Medical Center, Tel-Hashomer, Israel, Ramat-Gan, Israel, [5]Department of Immunology,, The Weizmann Institute of Science, Rehovot, Israel., Rehovot, Israel, [6]Department of Medicine B, Center for Autoimmune Diseases, Sheba Medical Center, Tel-hashomer, Israel, [7]Department of Internal Medicine 'D', Sackler Faculty of Medicine, Tel-Aviv University, Kfar-Saba, Israel

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ACPA induce pathogenic cytokines expression in PBMC of ACPA+-RA patients and inhibition of its effect by Cit-ME a synthetic citrullinated peptide.

Smadar Gertel[1], Gidi Karmon[1], Eszter Szarka[2], Esther Houri-Levi[3], Edna mozes[4], Yehuda Shoenfeld[1] and Howard Amital[1,3].

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Background/Purpose : Anti citrullinated protein autoantibodies (ACPA) are the major autoantibodies in rheumatoid arthritis (RA). ACPAs are directed against different citrullinated antigens, including filaggrin, fibrinogen, vimentin and collagen. Presence of ACPA is associated with joint damage and extra-articular manifestations, suggesting that ACPA are most likely arthritogenic autoantibodies in RA.

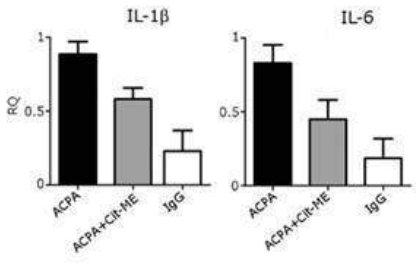
Methods: To verify the effect of ACPA on RA immune cells, PBMCs from ACPA$^+$-RA patients and healthy controls were co-cultured *in vitro* with ACPA. Binding of the latter to the cells were analyzed by flow cytometry and effect on cytokines mRNA expression by real-time PCR. The stimulating effects induced by ACPA were manipulated by addition of Cit-ME a novel multi-epitope citrullinated peptide.

Results: ACPA bound specifically to PBMCs from ACPA$^+$-RA patients via the Fab portion. ACPA induced an obvious pathogenic cytokine expression (4-13 fold increment) in immune cells derived from ACPA$^+$-RA patients. Moreover, ACPA up-regulated the IL-1b and IL-6 mRNA expression levels by 10 and 6, folds, respectively compared to control IgG.

Cit-ME, a genuine ligand for ACPA, inhibited the ACPA-induced up-regulation of Il-1b and Il-6 by 50% [Fig.].

Conclusion: ACPA binds to immune peripheral cells and enhances the synthesis of pathogenic cytokine expression. Together, these data suggests that ACPA is involved in the pathogenic effects in RA. Targeting ACPA in order to decrease its pathogenic capacity might provide a novel direction in the development of therapeutic strategies for RA.

Figure- ACPA induce IL-1b and IL-6 mRNA up-regulation. The Cit-ME, a multi-epitope citrullinated peptide, inhibited part of the ACPA cytokine up-regulation.



Disclosure: S. Gertel, None; **G. Karmon**, None; **E. Szarka**, None; **E. Houri-Levi**, None; **E. mozes**, None; **Y. Shoenfeld**, None; **H. Amital**, None.

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Abstract Number: 583

Associations of Serum Anti-Citrullinated Proteins and Cytokines with Radiographic Scores in African-American Rheumatoid Arthritis Patients

Dongmei Sun[1], William H Robinson[2], Xiangqin Cui[3], Vincent A. Laufer[4], Maria I. Danila[5], Richard J. Reynolds[6], Chander Raman[7], Stephanie Ledbetter[8], Alexander Szalai[9] and S. Louis Bridges Jr.[9], [1]Department of Medicine,

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Session Time: 9:00AM-11:00AM

Background/Purpose: Serum anti-citrullinated proteins (ACPA, including anti-CCP antibodies) and rheumatoid factor (RF) are critical diagnostic markers for RA, and are associated with more severe radiographic damage. The mechanisms of this association are unclear, but might involve serum cytokine levels, given our previous study reporting an association of IFN-γ receptor gene expression in peripheral blood mononuclear cells with radiographic damage in African-Americans with RA.

Methods: ACPA profiles (20 specificities) of 923 and cytokine profiles (17 cytokines) of 825 African-Americans with RA were generated from serum obtained at the time of enrollment into a large observational study. We stratified patents into four subgroups according to autoantibody positivity (CCP+/RF+, CCP+/RF-, CCP-/RF+, and CCP-/RF-). Associations of ACPA specificities and serum cytokine levels with radiographic severity were analyzed using a cross sectional approach, based on disease duration at the time of the enrollment: 0-12 months; 12-24 months; 24-48 months; 48-96 months; 96-120 months; and >120 months. The mean ± SE values of each subgroup of CCP and RF combination were analyzed and compared by student t-test. Correlations were analyzed using a zero-inflated binomial model (ZINB).

Results: After adjustment for disease duration at enrollment in the cohort, strong associations were found between radiographic scores and 11 of 20 ACPA specificities. Among patients with disease duration 0-48 months, radiographic scores were slightly higher for CCP+/RF+ compared to other subgroups. As expected, after 96 months of disease duration, the accrued radiographic damage was much higher in the double positive group compared to others subgroups. Almost all serum ACPA specificities were significantly higher at 0-48 months than at > 48 months disease duration. Among the CCP+/RF+ group, serum IL-1β, IL-6, and MCP-1 levels were higher as disease duration increased. Serum levels of IL-2, IL-5, IL-7, IL-12, IL-13 and IFN-γ were significantly higher in CCP+/RF+ compared to CCP-/RF- (p values <0.05). There was a strong association between total radiographic scores and log transformed serum IFN-γ levels (adjusted for age at disease onset, body mass index, and CCP status) (p = 0.0374, ZINB).

Conclusion: Our findings support the hypothesis that temporal changes in immunologic perturbations play a role in accumulated joint damage in RA. Specifically, the presence of ACPA specificities, the increasing elevation of IL-1β, IL-6, and MCP-1 over time, and elevated serum IL-2, IL-5, IL-7, IL-12, IL-13, and IFN-γ levels may contribute to the accrued joint damage in CCP+/RF+ patients. These findings may have important implications for stratifying African-Americans with RA according to risk of joint damage and may lead to different treatment strategies.

Abstract Number: 584

Glycoprotein VI: A Potential Target for ACPA-Mediated Platelet Activation?

John Stack[1], Anne Madigan[2], Laura Helbert[1], Niamh Redmond[1], Eimear Dunne[3], Dermot Kenny[3] and Geraldine M. McCarthy[2], [1]Rheumatology, Mater Misericordiae University Hospital, Dublin, Ireland, [2]Rheumatology, Mater Misericordiae University Hospital, Dublin 7, Ireland, [3]Molecular and Cellular Therapeutics, RCSI, Dublin 2, Ireland
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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
Session Title: Rheumatoid Arthritis – Human Etiology and Pathogenesis - Poster I
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Session Time: 9:00AM-11:00AM

Background/Purpose: Arterial thrombosis is a major cause of mortality in rheumatoid arthritis (RA),especially in anti-citrullinated protein antibody (ACPA)-positive patients Recent studies suggest that platelet activation is implicated in this pathway[1]. Platelet activation results in proteolytic cleavage and shedding of platelet specific glycoprotein VI (GPVI) detected in the plasma as soluble GPVI (sGPVI). Shedding of GPVI occurs in response to stimuli, including engagement with the low affinity immunoglobulin G (IgG) receptor (FcγRIIa) on platelets[2]. ACPA cause platelet activation *in vitro*, through the FcγRIIa receptor[1]. We hypothesized that ACPA in patients with RA would cause platelet activation via ligand binding with FcγRIIa causing increased shedding of sGPVI.

Methods: Following ethics approval and informed consent, blood samples were taken from patients with RA (n=111) and OA (n=16). Healthy control samples (n=48) were obtained from volunteers. Demographic and clinical data were collected for all participants. Blood samples were processed as double spun platelet poor plasma. sGPVI levels were measured using a standardized ELISA. Mann-Whitney U test and Kruskal – Wallis test was used to compare groups. SpearmanÕs Rank Correlation Coefficient was used to assess for associations between sGPVI levels and demographic and clinical markers. GraphPad Prism Version 6.05 was used for data analysis.

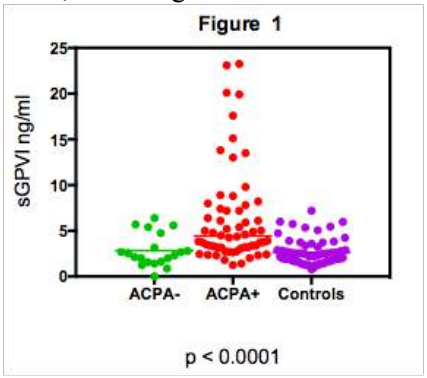
Results: Characteristics of ACPA positive RA vs ACPA negative RA are presented in Table 1. Patients with ACPA positive RA were significantly older, but no signficant correlation was observed between levels of sGPVI and age, CRP, fibrinogen, ESR, platetet count or DAS28 CRP. Patients with ACPA positive RA had significantly higher levels of sGPVI compared to ACPA negative RA and controls (Figure 1). Median (IQR) sGPVI levels were 4.3 ng/ml (3.80, 9.70) in ACPA positive RA , 2.4 ng/ml (31.5,4.3) in ACPA negative RA and 2.1ng/ml (1.6, 3.2) in controls ($p<0.0001$). ACPA titres correlated with sGPVI levels ($r=0.32$, $p=0.0026$).

Conclusion: Our results demonstrate that ACPA are associated with platelet activation as defined by increased levels of plasma sGPVI. These data could explain, in part, the aggravated cardiovascular risk in ACPA-positive patients . A monoclonal antibody targeting GPVI exists and has been shown to reduce myocardial infarct size in mice. The role of sGPVI as a marker of ACPA mediated platelet activation and therapeutic targeting of GPVI warrants further investigation.
1. Habets KL,*Arthritis Res Ther*. 2015;17:209 2. Newman PJ. *Blood*. 2010 Oct 28;116(17):3124-6.

Table 1 Characteristics of Patients with ACPA positive RA vs ACPA negative RA

	ACPA + RA	APCA - RA	*P* value
Total Number	65	21	
Female, n (%)	50 (76.9)	18 (85.7)	ns
Male, n (%)	15 (23)	3 (14)	ns
Age, yr (median [IQR])	62 [53-71]	52 [39-64]	0.01
CRP, mg/l (median [IQR])	8 [1-15.7]	6 [2-20.2]	ns
ESR, mm/hr (median [IQR])	19 [11-32]	15 [7-34]	ns
Fibrinogen g/l (mean +/- SEM)	3.37 +/- 1.12	3.06 +/- 0.68	ns
Platelet Count x 10^9(mean +/- SEM)	282+/- 98	285 +/- 80	ns
DAS28-CRP (Mean +/- SEM)	3.78 +/- 1.51	4.37 +/- 2.2	ns

ACPA ant-citrullinated protein antibodies, *RA* rheumatoid arthritis, *CRP* c- reactive protein, *ESR* erythrocyte sedimentation rate, *DAS28* Disease Activity Score in 28 joints, *IQR* interquartile range, *SEM* standard error of the mean, ns not significant, *sGPVI* soluble Glycoprotein VI



Disclosure: J. Stack, None; **A. Madigan**, None; **L. Helbert**, None; **N. Redmond**, None; **E. Dunne**, None; **D. Kenny**, None; **G. M. McCarthy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/glycoprotein-vi-a-potential-target-for-acpa-mediated-platelet-activation

Abstract Number: 585

Disease Associated Anti-Citrullinated Protein Memory B Cells in Rheumatoid Arthritis Persist in DAS Remission

Adam J. Pelzek[1], Caroline Grönwall[2], Lelise Getu[3], Pamela Rosenthal[4], Jeffrey D. Greenberg[5], Mandy J. McGeachy[6], Larry W. Moreland[7] and Gregg J. Silverman[8], [1]New York University School of Medicine, New York, NY, [2]Department of Medicine, Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, New York University School of Medicine, New York, NY, [4]Rheumatology, New York University School of Medicine, New York, NY, [5]New York University School of Medicine, Millburn, NJ, [6]Medicine, University of Pittsburgh, Pittsburgh, PA, [7]Rheumatology & Clinical Immunology, University of Pittsburgh, Pittsburgh, PA, [8]Department of Medicine, Division of Rheumatology, New York University School of Medicine, New York, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose: B cells are central drivers of seropositive RA, and B cells that express anti-citrullinated protein antibodies (ACPA) may arise from past and/or ongoing breaches in immune tolerance. While ACPA levels are only modestly affected by commonly prescribed therapeutic agents (e.g, Methotrexate, TNFi), it is unclear whether these treatments significantly affect autoimmune lymphocytes and whether these cells persist after treatment induced clinical remission. We therefore assessed the frequencies and epitope reactivity patterns of ACPA-producing switched-memory B cells, with comparisons to serum ACPA levels and disease activity scores.

Methods: In a cross-sectional study of seropositive RA patients that met 2010 ACR/EULAR criteria, blood samples were biobanked, and later cryopreserved PBMC were cultured +/- sCD40L/CpG2006/IL-21 for 6 days and then ELISpots performed. Synovial fluid mononuclear cells and FACS-sorted switched-memory B cells [CD19+/CD27+/IgD-] were cultured with CpG2006/IL-21 in the presence of a CD40L-expressing feeder cell line for 12 days. Sera, synovial fluid, and culture supernatants were analyzed by multiplex bead-based assay for ACPA-IgG reactivity for 8 citrullinated and native peptide/protein pairs, as well as reactivity with the diagnostic CCP3 peptide (Inova Diagnostics) and glutamine-containing CQP3, plus other control ligands. We then performed Spearman correlations.

Results: In select patients with active disease, we found a high frequency of synovial fluid cells that spontaneously secreted ACPA in culture, suggesting these ACPA producing B cells are especially common at the site of disease, and epitope specificities were similar to those in autologous synovial fluid. For cultures of PBMC from groups of patients receiving different treatment regimens (MTX or TNFi+/-MTX), ACPA-IgG secretion was also detected, although in vitro stimulation was generally required. In the circulation of these RA patients, switched memory B cells were the predominant source of ACPA-IgG. Notably, serum anti-CCP3-IgG levels significantly correlated with frequencies of ACPA-producing switched-memory B cells ($r = 0.57$, $p = 0.003$). For individual donors, the ACPA fine-specificity patterns in serum samples were similar to those in supernatants from cultured B cells. A majority (16/24) of RA patients had wells with detectable in vitro ACPA secretion. Yet frequencies of ACPA memory B-cells did not attain significant correlation with DAS28 scores ($r = 0.35$, $p = 0.09$). In fact, a subset of RA patients, which included patients treated with methotrexate and/or TNFi, had high frequencies of recirculating ACPA memory-B cells despite being in DAS remission.

Conclusion: We have documented that DAS score cannot be used as a predictor of reduced or absent ACPA memory B cell burden, as quiescent disease-associated anti-Cit memory B-cells commonly persist in peripheral circulation despite treatment to clinical remission. Our results help to explain why therapeutic cessation most often results in reactivation or flare. In the future, our platform may be useful for evaluating new agents and for informing treatment decisions in individual RA patients.

Disclosure: A. J. Pelzek, None; **C. Grönwall**, None; **L. Getu**, None; **P. Rosenthal**, None; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Janssen, Novartis and Pfizer, Eli Lilly, 5; **M. J. McGeachy**, None; **L. W. Moreland**, Genentech and Biogen IDEC Inc., 2,Pfizer Inc, 2,questcor, 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 5,Boehringer Ingelheim, 5,Acerta, 5,CVS/Caremark, 5,Smith Kline Beecham, 5; **G. J. Silverman**, Lilly, Genentech and BMS, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/disease-associated-anti-citrullinated-protein-memory-b-cells-in-rheumatoid-arthritis-persist-in-das-remission

Abstract Number: 586

Association Between ACPA Fine Specificity and High Resolution Computed

Tomography Lung Changes in Patients with Early Rheumatoid Arthritis

Vijay Joshua[1], Katerina Chatzidionysiou[1], Gudrun Reynisdottir[1], Aase Hensvold[1], Monika Hansson[1], Leonor Nogueira[2], Guy Serre[2], Johan Grunewald[3] and Anca I Catrina[1], [1]Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [2]Unité Différenciation Épidermique et Autoimmunité Rhumatoïde, Unité Mixte de Recherche, INSERM, Toulouse, France, [3]Division of Respiratory Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden

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Session Time: 9:00AM-11:00AM

Background/Purpose: Airways abnormalities that are consistent with inflammation are common in anti-CCP2 positive subjects without inflammatory arthritis. Anti-CCP2 antibodies are associated with high-resolution computed tomography (HRCT) parenchymal lung abnormalities in patients with early RA. This study aims to examine the association between ACPA fine specificities and HRCT lung changes in an early RA cohort.

Methods: Patients (n=106) with newly diagnosed RA according to the ACR 1987 criteria and na•ve to treatment with oral glucocorticoids or DMARDs were included. HRCT was performed in order to assess the presence parenchymal (nodules, ground-glass opacities, fibrosis, emphysema) and airway abnormalities (bronchiectasis, air trapping, air wall thickening). Bronchoscopy was performed on 22 patients to retrieve BAL. EliA system (Phadia) was used to detect RF IgA and IgM, anti-CCP2 IgA and IgG, and ISAC peptide microarray (Phadia) was used to detect antibodies against 10 citrullinated (Cit) peptidic antigens: CCP-1 (Filaggrin), CEP-1 (α-enolase), Vim 2-17, Vim 60-75 (Vimentin), Fib α 36-50, Fib α 573, Fib α 591, Fib α 621-635, Fib β 36-52, Fib β 60-74 (Fibrinogen). Logistic regression analysis was performed to examine associations between HRCT lung changes at the time of RA diagnosis and autoantibodies. Due to the potential risk for effect modification of smoking and its strong association with cit-Abs, we stratified the cohort according to current vs non-smokers.

Results: HRCT parenchymal and airway changes was present in 58 (54.7%) and 68 (64.2%) patients, respectively. The forced vital capacity (FVC) was significantly lower in the presence of airway abnormalities, while the ratio FEV_1/FVC was significantly lower in patients with parenchymal lung changes. Higher age, RF IgA, CCP2 IgG, ever smoking and pack-years above 24 were significant predictors of parenchymal lung changes. Some ACPA fine specificities, especially against Cit Fib and Vim peptides, were associated to parenchymal lung changes in ever smokers. The risk of having parenchymal changes increased parallel to the increase in number of ACPA specificities. Having more than 5 ACPA specificities at the time of diagnosis increased the risk of having parenchymal lung abnormalities in current smokers (OR=13.8, 95% CI=1.0-196.2, p=0.05) (Table 1). In the subgroup of patients that underwent bronchoscopy, antibodies against Cit Vim and Fib peptides were detected in the BAL mainly in current smoker (4/9, 45%) and to a lesser extent in non-smokers (3/13, 23%). Patients with Ab positivity in the BAL were also positive for same antibodies in paired serum samples.

Conclusion: The presence of RF IgA, anti-CCP2 IgG and antibodies to Cit Fib and Vim peptides were associated with parenchymal lung changes in early-untreated RA. The more ACPA fine specificities, the higher the risk of having

	All Patients (106)		Non-Smokers (75)		Current Smokers (31)	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Parenchymal changes						
Any RF	**2.4 (1.0-5.9)**	**0.05**	1.6 (0.6-4.6)	0.36	6.0 (1.0-37.4)	0.055
RF (IgM)	**2.4 (1.0-5.9)**	**0.05**	1.6 (0.6-4.6)	0.36	6.0 (1.0-37.4)	0.055
RF (IgA)	**3.4 (1.4-8.2)**	**0.01**	1.9 (0.7-5.4)	0.20	**12.9 (2.0-81.3)**	**0.01**
Any ACPA	**4 (1.6-10.4)**	**0.004**	2.6 (0.9-7.8)	0.09	**13.4 (1.7-108.5)**	**0.02**
ACPA (IgG)	**3.6 (1.4-9.1)**	**0.01**	2.6 (0.9-7.8)	0.09	**8.5 (1.2-59.3)**	**0.03**
ACPA (IgA)	1.7 (0.7-4.1)	0.26	1.2 (0.4-3.6)	0.78	2.0 (0.4-9.4)	0.40
CEP-1	1.3 (0.6-3.1)	0.51	0.8 (0.3-2.2)	0.66	4.3 (0.6-28.7)	0.14
CCP-1	1.9 (0.8-4.4)	0.13	1.9 (0.7-5.3)	0.22	2.2 (0.5-9.9)	0.32
Any cit vimentin	**2.5 (1.0-6.2)**	**0.04**	2.5 (0.8-7.2)	0.10	2.6 (0.5-14.0)	0.27
Any cit fibrinogen	**4.4 (1.6-11.9)**	**0.003**	**3.2 (1.0-9.9)**	**0.04**	**13.3 (1.2-153.4)**	**0.04**
No. of diff. ACPA specificities						
0 (Ref.)						
1-5	**3.4 (1.1-10.3)**	**0.03**	2.4 (0.7-8.8)	0.19	**12.9 (1-171.2)**	**0.05**
>5	**5.2 (1.6-17.0)**	**0.01**	3.5 (0.9-13.8)	0.07	**13.8 (1-196.2)**	**0.05**
Airway Changes						
Any RF	1.0 (0.4-2.5)	0.96	1.0 (0.3-2.7)	0.94	1.4 (0.2-8.1)	0.74
RF (IgM)	1.0 (0.4-2.5)	0.96	1.0 (0.3-2.7)	0.94	1.4 (0.2-8.1)	0.74
RF (IgA)	1.3 (0.6-2.9)	0.58	1.2 (0.5-3.3)	0.68	1.5 (0.3-7.3)	0.63
Any ACPA	1.6 (0.6-3.9)	0.31	1.4 (0.5-3.9)	0.56	3.0 (0.5-19.8)	0.25
ACPA (IgG)	1.5 (0.6-3.6)	0.40	1.4 (0.5-3.9)	0.56	2.2 (0.4-13.1)	0.40
ACPA (IgA)	1.8 (0.7-4.5)	0.22	2.2 (0.6-7.6)	0.22	1.9 (0.4-9.7)	0.45
CEP-1	2.0 (0.8-4.9)	0.13	2.2 (0.8-6.5)	0.14	2.2 (0.4-13.5)	0.39
CCP-1	1.2 (0.5-2.8)	0.67	1.0 (0.4-2.7)	0.97	1.7 (0.4-8.0)	0.51
Any cit vimentin	2.4 (0.9-6.0)	0.07	2.1 (0.7-6.2)	0.17	3.5 (0.6-22.0)	0.18
Any cit fibrinogen	1.2 (0.5-3.2)	0.65	1.2 (0.4-3.6)	0.74	1.5 (0.2-11.9)	0.72
No. of diff. ACPA specificities						
0 (Ref.)						
1-5	1.1 (0.4-3.3)	0.85	1.1 (0.3-3.8)	0.90	1 (0.1-9.6)	1.00
>5	2.2 (0.7-7.0)	0.18	2.4 (0.6-9.3)	0.22	2.3 (0.2-25.1)	0.49

parenchymal lung changes already at the time of RA diagnosis.

Disclosure: V. Joshua, None; **K. Chatzidionysiou**, None; **G. Reynisdottir**, None; **A. Hensvold**, None; **M. Hansson**, None; **L. Nogueira**, None; **G. Serre**, anti-CCP assays, 7; **J. Grunewald**, None; **A. I. Catrina**, None.

Abstract Number: 587

Synovial Immunophenotype and Anti-Citrullinated Protein Antibodies in Rheumatoid Arthritis Patients: Relationship to Treatment Response and Radiological Prognosis

Carl Orr[1], Aurélie Najm[2], Monika Biniecka[3], Francis Young[1], Ursula Fearon[4] and Douglas J. Veale[1], [1]Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin 4, Ireland, [2]Rheumatology, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland, [3]St. Vincent's University Hospital, Centre for Arthritis and Rheumatic Diseases, Dublin Academic Medical Centre, University College Dublin, Dublin, Ireland, [4]Trinity College Dublin, Department of Molecular Rheumatology, Trinity College Dublin, Dublin, Ireland

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SESSION INFORMATION

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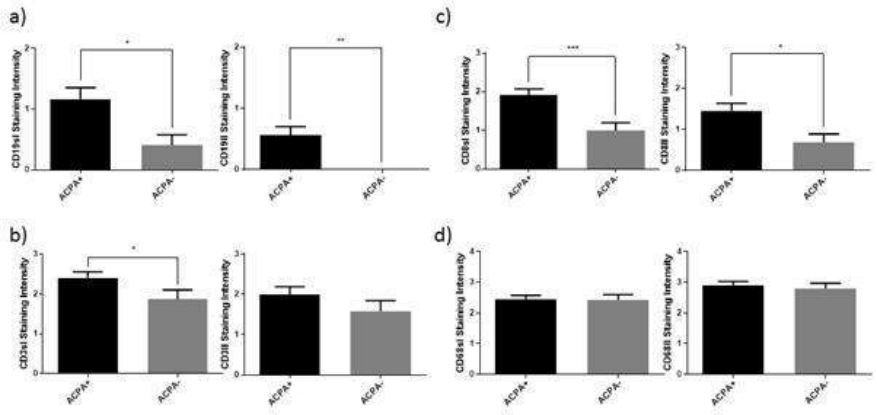
Session Time: 9:00AM-11:00AM

Background/Purpose: Circulating anti-citrullinated peptide antibodies (ACPA) have been proposed as an important clinical test for stratification of patients presenting with rheumatoid arthritis (RA). ACPA may be present in the serum of subjects several years before the onset of symptoms, and studies suggest that the presence of ACPA may predict more severe and erosive disease. However, studies to date investigating whether the two subgroups of RA (defined by the presence and absence of ACPA) have differing pathologies at the level of the synovial tissue, have yielded conflicting results.[1,2] The aims of our study were to examine synovial tissue immunophenotype according to ACPA status in patients with a clinical diagnosis of RA, and to determine the nature of the relationship between synovial infiltrate, response to treatment and erosions on plain film radiographs.

Methods: Consecutive patients with RA were prospectively recruited from rheumatology clinics and underwent clinical, serological and radiological assessment before and after treatment with non-biologic DMARD (nbDMARD) or TNF inhibitors (TNFi). Synovial tissue was obtained by arthroscopy from involved knee joints and immunohistologically stained for cell specific markers of B-cells (CD19), T-cells (CD3, CD4 and CD8), macrophages (CD68) and the blood vessel marker FVIII. Sections were scored using a validated semi-quantitative scoring method and analysis of synovial immuno-phenotype by ACPA status and EULAR response criteria to treatment was performed.

Results: 123 subjects (78 ACPA+) were included in the study. The synovium from ACPA+ RA was characterised by significantly higher CD19+ B-cells ($p<0.05$), CD3+ T cells ($p<0.05$) and CD8+ T cells ($p<0.05$), compared with ACPA- RA. CD19+ B-cells were also significantly higher in the synovium of ACPA+ patients naïve to treatment ($p=0.04$) (fig. 1). In addition, both CD19+ B-cell and CD4+ T-cell infiltrates were higher in patients who had evidence of erosive disease at follow-up ($p=0.0163$; $p=0.0024$, respectively). RA patients achieving a moderate-good EULAR response to nbDMARD or TNFi also had significantly higher infiltrates of CD3+ cells ($P<0.05$). Finally, CD68+ and CD8+ cells were significantly higher in TNFi responders vs non responders ($p<0.05$)

Conclusion: ACPA+ RA patients demonstrate significantly higher synovial B and T cell infiltrates and higher B cells were identified in treatment-naïve patients and associated with the erosions. 1 van Oosterhout M, *et al. Arthritis Rheum* 2008;**58**:53–60. 2 Gomez-Puerta JA, *et al.. Arthritis Res Ther* 2013;**15**:R182. Figure 1:



Semi-quantitative scoring of cellular expression in RA synovium of ACPA+ versus ACPA- patients, detailing scores for sublining and lining layers. ACPA+ n= 48-73, ACPA- n=22-42. anti-citrullinated peptide antibodies; sl, sublining; ll, lining layer. *, p≤0.05; **, p≤0.01; ***, p≤0.001. Data are expressed as mean ± SEM

Disclosure: C. Orr, None; **A. Najm**, None; **M. Biniecka**, None; **F. Young**, None; **U. Fearon**, None; **D. J. Veale**, None.

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Abstract Number: 588

Radiographic Progression Is Less Significant in Anti-Carbamylated Antibody-Positive Patients with Rheumatoid Arthritis (RA) Who Were Clinically Active and Under the Treatment with Biological Dmards

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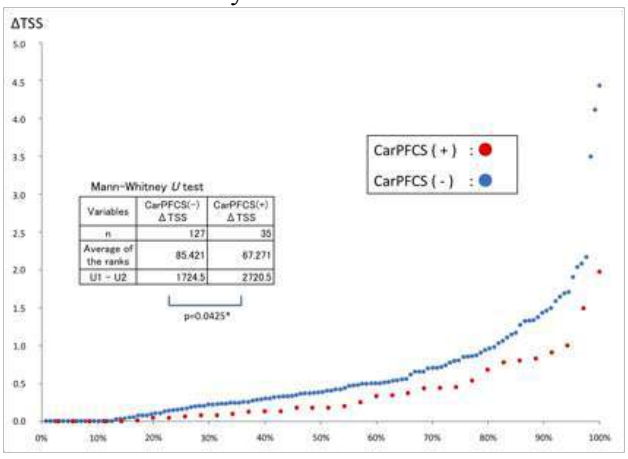
Background/Purpose: A newly discovered anti-carbamylated protein antibody (anti-CarP) is found prior to disease-onset, associates with the conversion towards arthralgia and with a more severe disease course in patients negative for ACPA. We here studied anti-CarP in162 rheumatoid patients who were clinically active and thus under treatment with biological DMARDs, and also in another group of 268 rheumatoid patients whose sera were measured on their first visit to our hospital.

Methods: Anti-CarP-Fetal Calf Serum (aCarPFCS) was measured by using ELISA in sera of 162 Japanese patients with RA who were clinically active (fulfilling either DAS-CRP > 4.0 or DAS-ESR > 4.2 and either CDAI > 22 or SDAI >26) and under treatment with biological DMARDs, and also in 268 patients with RA whose sera were measured for the first time of their visit to the hospital. The change in van der Heijde-modified total Sharp score per year DTSS was assessed using probability plots. Statistical tests were performed using Mann-Whitney U test.

Results: Cumulative probability plot of DTSS for aCarPFCS showed that radiographic progression was less significant in aCarPFCS-positive patients with RA (n=35) as compared with those negative for aCarPFCS (n=127) (Figure). The difference between the groups was p=0.0425 by using Mann-Whitney U test. The cumulative probability plot of DTSS for aCarPFCS in the sera of 268 rheumatoid patients whose sera could be measured on their first visit to the hospital was also similar, where radiographic progression was less significant in aCarPFCS-positive patients with RA (n=80) as compared with those negative for aCarPFCS (n=188). It was noted that radiographic progression seemed particularly less significant in those with relatively larger DTSS, i.e., relatively progressive patients with RA, suggesting that aCarP antibody may be raised in a similar fashion to anti-citrullinated protein antibody (ACPA) possibly cross-reactively but in fact acts rather inhibitory for disease.

Conclusion: Radiographic progression seems to be less significant in anti-carbamylated antibody positive patients with rheumatoid arthritis (RA) especially when they are basically progressive or when they were clinically active and under the treatment with biological DMARDs. The aCarPFCS and aCarPFib are measured by Drs. Verheul MK and Trouw LA,



Department of Rheumatology, Leiden University, Netherlands.

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Abstract Number: 589

Netosis-Derived Products Might Have Diagnostic Potential for Disease Activity, Atherosclerosis and Analysis of Therapeutic Effectiveness in Rheumatoid Arthritis Patients

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Background/Purpose: Neutrophil extracellular traps (NETs) have recently been implicated in vascular damage and atherothrombosis. Extruded DNA fibers containing multiple proinflammatory and thrombotic molecules induce the activation and recruitment of monocytes and dendritic cells to the vessel wall. Enhanced NETosis occurs in rheumatoid arthritis (RA), which has been shown related to the pathogenesis of this disorder. However, the relevance of this abnormality in the development of atherosclerosis, and the effects of new therapeutic approaches has not been elucidated yet. The aims of this study were: 1) To evaluate the association of netosis-derived products with the development of atherothrombosis in RA. 2) To study the role of biologic therapies in inhibiting NETosis.

Methods: One hundred RA patients and 30 healthy donors were included. Carotid intima media thickness (CIMT) was used as atherosclerosis marker. Inflammatory and prothrombotic molecules and oxidative stress markers were analyzed in plasma. Neutrophils were isolated and spontaneous and induced NETs formation was assessed through fluorescence microscopy. Oxidative stress status (JC1 and DCFH), myeloperoxidase (MPO), and neutrophil elastase (NE) protein expression were measured in neutrophils by flow cytometry. Cell-free DNA plasma levels were analyzed using specific ELISA-base kits. mRNA expression of peptidyl arginine deiminase 4 (PAD4) and various proatherothrombotic molecules were analyzed by RT-PCR.

Results: NETosis was found increased in RA patients, alongside MPO and NE protein expression in neutrophils. Cell free DNA plasma levels were further elevated, and strongly correlated with clinical parameters such as DAS28, CRP and ESR, and autoimmunity state (RF and anti-CCPs positivity). In addition, high levels of cell-free DNA were associated with elevated levels of IL-6, MCP-1, spSelectin and tPA in plasma, as well as with increased NTyr and decreased TAC and NO. At cellular level, cell free DNA plasma levels correlated with increased oxidative status in RA neutrophils (JC1 and DCFH) and mRNA expression of PADI4. Those patients having pathologic CIMT showed increased cell-free DNA plasma levels. Two new cohorts of 60 RA patients, treated either with Infliximab (n=40) or Tocilizumab (n=20) for six months were further evaluated. Both drugs promoted decreased generation of NETs, along with reduction of MPO, NE, PAD4, and the percentage of low density granulocytes, as well as of the proatherothrombotic profile of RA patients.

Conclusion: 1) Elements associated with the extrusion of NETs are significantly enhanced in RA patients. 2) NETosis-derived products, such as cell-free DNA, strongly correlated with clinical parameters, inflammatory and oxidative markers. Thus, NETosis-derived products demonstrated diagnostic potential for disease activity and atherosclerosis, as well as for analysis of therapeutic effectiveness in RA patients. Funded by CTS7940, PI15/01333, PI2013-0191,

CP15/00158.

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Abstract Number: 590

Microvesicles in the Lungs of Early Rheumatoid Arthritis

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Background/Purpose: Structural changes, increased tissue citrullination and signs of local inflammation are present in the pulmonary compartment of early seropositive RA and seropositive individuals at risk for developing RA. Cell-derived Microvesicles (MVs) are small particles (0.1-1.0 microns), formed by the outward blebbing of the plasma cell membrane, that can be released during and further contribute to inflammation. The MVs express surface markers similar to the cell of origin and have previously shown to induce tissue injury in the lung. We aimed to study the role of MVs in the lungs of early RA.

Methods: Bronchoalveolar lavage (BAL) fluid was obtained from 20 RA patients (8 females, 12 males, 16 sero-positive and 4 sero-negative, 9 smokers and 11 non-smoker, 59 median age). Additionally BAL samples from disease controls (10 patients with sarcoidosis with active lung inflammation) and healthy volunteers (n=3) were collected. Microvesicles derived from macrophage, endothelial cells, lymphocytes and T-cells were analysed by flow cytometry for phosphatidylserine, CD45, CD63E, CD68, CD154 and CD163 expression. Anti citrullinated protein antibodies (ACPA) were purified from the peripheral blood of RA patients by affinity chromatography, fluorescent labeled and used to identify expression of citrullinated proteins in MVs using flow cytometry.

Results: Elevated numbers of total MVs were observed in the BAL of RA (Mean±SD, 526.2±291.7, events/µL) compared with disease controls (402.3±107.5, $p>0.05$) and healthy volunteers (283.0±52.8, $p<0.05$). MVs derived from macrophage, endothelial cell and lymphocytes were significant increased in the BAL of RA patients (27.2± 13.4, events/ µL for macrophage derived MVs, 20.8±9.0 for endothelial derived MVs and 47.7±24.4 for lymphocytes derived MVs) as compared to both disease controls (16.1±6.0 for macrophage derived MVs, 12.3±3.6 for endothelial derived MVs and 25.1±11.9 for lymphocytes derived MVs) and healthy volunteers (5.9±1.9 for macrophage derived MVs, 10.1±2.9 for endothelial derived MVs and 8.1±5.0 for lymphocytes derived MVs), ($p<0.05$ for all comparisons). Citrulline containing MVs, detected by ACPA were significantly higher in RA compared to disease controls (6.6±2.7 vs 4.3±1.1, $p<0.05$) and healthy BAL (6.6±2.7 vs 3.3±1.4, $p<0.05$) whereas no such difference and significantly lower amount of MVs were detected using RA-derived IgGs others than ACPA as controls.

Conclusion: MVs and citrulline-containing MVs are present in the RA BAL in a higher proportion than in the BAL of either patient with inflammatory lung disease (sarcoidosis) and healthy controls, suggesting a role for MVs in RA-associated lung changes. Confirmation of current findings in larger samples and investigation of potential pathogenic effects of MVs are needed.

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Abstract Number: 591

Patient-Reported Outcomes for Etanercept Therapy in Adult Patients with Moderate to Severe Rheumatoid Arthritis Who Failed Adalimumab Treatment

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Background/Purpose: When a tumor necrosis factor inhibitor (TNFi) fails in a patient with moderate to severe rheumatoid arthritis (RA), new American College of Rheumatology (ACR) guidelines recommend a switch to either another TNFi or a non-TNFi biologic. The aim of this study was to evaluate disease activity and patient-reported outcomes (PROs) in RA patients who switched to etanercept after adalimumab failure.

Methods: Adults (age ≥ 18 years) with moderate to severe RA (disease activity score using 28-joint count and C-reactive protein ≥ 3.2) who failed to respond (1º failure) or lost a satisfactory response (2º failure) to adalimumab treatment, based on ACR20% improvement criteria (ACR20) or investigator judgment, were enrolled in an open-label, multicenter, single-arm study. After ≥ 2 weeks of washout for patients on adalimumab, etanercept 50 mg once weekly for 24 weeks was added to ongoing methotrexate treatment. Clinical Disease Activity Index (CDAI), Health Assessment Questionnaire (HAQ) disability index (DI), and pain visual analog scale (VAS) were evaluated at weeks 0, 4, 8, 12, 18, and 24. Other PROs including Medical Outcomes Short Form 36 (SF 36) and Work Productivity and Activity Impairment (WPAI) were assessed at weeks 0, 12, and 24. The primary efficacy endpoint (ACR20 at week 12) and safety data from this study were presented previously; this analysis focused on PROs at each visit.

Results: Of 85 patients studied (80% women; mean age 56.6 years), 84 were evaluable for efficacy. After being switched from adalimumab to etanercept, clinical outcomes and PROs improved from baseline at each study visit (Table). Improvement in mean HAQ DI (–0.31 points from baseline to week 24) exceeded the minimal clinically important difference of 0.22 points. Mean improvement in HAQ DI from baseline to week 24 by adalimumab failure and anti-adalimumab antibodies was –0.05 (1º failure, antibodies; n = 7), –0.65 (2º failure, antibodies; n = 17), –0.15 (1º failure, no antibodies; n = 22), and –0.37 (2º failure, no antibodies; n = 33). Improvements in other PROs (HAQ pain VAS, SF-36

physical function, and WPAI absenteeism/presenteeism) also were greatest for patients with 2º adalimumab failure and anti-adalimumab antibodies. Adverse events were consistent with the known safety profile of etanercept.

Table. Clinical Outcomes and PROs by Study Visit After Switching to Etanercept (N = 84)

Outcome	Baseline	Week 4	Week 8	Week 12	Week 18	Week 24
% with ACR20 response	–	19.0%	29.8%	35.7%	31.0%	34.5%
Mean CDAI	43.7	33.0	30.5	28.7	28.6	26.1
Mean HAQ DI	1.52	1.25	1.24	1.25	1.24	1.21
Mean HAQ pain VAS	63.2	50.3	42.8	44.0	45.8	40.6
Mean SF-36 physical function*	31.4	–	–	35.9	–	36.5
WPAI, % work missed†	15.3%	–	–	9.5%	–	5.5%
WPAI, % impairment working†	41.6%	–	–	29.2%	–	25.8%
WPAI, % activity impairment	57.9%	–	–	43.2%	–	40.0%

* For SF-36 physical function, increased scores indicate improved health; for all other PROs, decreased scores indicate improved health † Among employed patients (n = 41)

Conclusion: Clinical outcomes and PROs improved from baseline at every visit when RA patients switched to etanercept after adalimumab failure, particularly among those with anti-adalimumab antibodies and 2º loss of response to adalimumab. Limitations were small subgroup sample sizes, analysis of secondary endpoints, and lack of long-term outcomes after 24 weeks (6 months).

Disclosure: L. Bessette, Amgen, 2,Amgen, 5,Amgen, 8; **M. Khraishi**, Amgen, 2,Amgen, 5; **A. J. Kivitz**, Amgen, 2; **A. Kaliyaperumal**, Amgen, 3,Amgen, 1; **R. Grantab**, Amgen, 3,Amgen, 1; **M. Poulin-Costello**, Amgen, 3,Amgen, 1; **M. Isaila**, Amgen, 3,Amgen, 1; **D. Collier**, Amgen, 3,Amgen, 1.

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Abstract Number: 592

Impact of Adherence to Tumor Necrosis Factor Inhibitors on Radiographic Outcomes in US Veterans with Rheumatoid Arthritis

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Background/Purpose: Tumor necrosis factor inhibitors (TNFi) are effective therapy for rheumatoid arthritis (RA) and have been shown to reduce progression of joint structural damage as measured by the modified Sharp Score (mSS). This observational study evaluated the relationship between cumulative adherence to TNFi therapy and progression of structural joint damage during the first year of TNFi therapy in US Veterans.

Methods: US Veterans with RA who were ≥18 years of age and initiated TNFi use after at least six months of enrollment in the Veterans Affairs (VA) health care system were eligible for this study. Subjects were identified through a search of national VA administrative data and copies of digital radiographs retrieved. Subjects were required to have bilateral baseline hand x-rays during the interval of between six months prior and one month after TNFi initiation and a set of follow-up bilateral hand x-rays during the interval between 10 and 18 months after TNFi initiation. Subjects with non-TNFi biologic disease modifying anti-rheumatic drugs (DMARDs) use prior to TNFi initiation or between baseline and follow-up x-rays were excluded. Cumulative TNFi exposure was calculated from VA administrative data and compared to change in mSS interpreted by a single evaluator blinded to sequence of x-rays and drug exposure history. A longitudinal marginal structural model using inverse probability of treatment weights was used to compare the impact of cumulative adherence on mean change in mSS. Baseline disease characteristics (e.g., smoking history, age, seropositive status, co-morbidities, and concurrent medication) and time-varying covariates (erythrocyte sedimentation rate, C-reactive protein, and prednisone) were assessed for clinical and statistical importance and included in the adjusted model in addition to the crude analysis.

Results: There were 114 patients from 36 sites who met enrollment criteria and had baseline and follow-up x-rays acceptable for evaluation. The population's baseline demographic features were: mean±standard deviation age 59±11 years, 84% male, 68% positive for rheumatoid factor, and 58% positive for anti-cyclic citrullinated peptide antibody (aCCP). Baseline mSS was 20.5±14.2 (median 10, range 0-145). We observed decreases in the magnitude of mSS changes with increases in treatment adherence (i.e., cumulative TNFi exposure). In comparison to patients with no TNFi adherence, patients with the highest adherence had 20.2% and 33.3% less radiographic progression for the crude and adjusted model analysis, respectively.

	Mean change in mSS					
Cumulative months of adherence	Crude Model			Adjusted Model		
	Mean change	95% C.I.	Percent Difference*	Mean change	95% C.I.	Percent Difference
<1	0.86	(-0.96, 2.68)		1.11	(-0.70, 2.93)	
3	0.82	(-0.48, 2.11)	5.1%	1.02	(-0.29, 2.33)	8.3%
6	0.77	(-0.11, 1.66)	10.1%	0.93	(0.01, 1.85)	16.6%
9	0.73	(-0.05, 1.51)	15.2%	0.84	(0.00, 1.37)	25.0%
12	0.66	(-0.40, 1.78)	20.2%	0.74	(-0.38, 1.86)	33.3%

* Percent difference is the percent change seen by dividing the difference between the mean change for cumulative months of zero adherence and the mean change for other cumulative months of adherence by the mean change for cumulative months of zero adherences.

Conclusion: The progression of radiographic changes as measured by mSS was very small during the one year of observation. While there was a trend for less progression in patients with increased adherence to TNFi therapy, these differences were not statistically significant.

Disclosure: G. W. Cannon, Amgen, 2; **A. R. Erickson**, Amgen, 2; **C. C. Teng**, Amgen, 2; **T. Huynh**, Amgen, 2; **S. Austin**, Amgen, 2; **B. S. Stolshek**, Amgen, 1,Amgen, 3; **A. Mutebi**, Amgen, 1,Amgen, 3; **D. Collier**, Amgen, 3,Amgen, 1; **S. W. Wade**, Amgen, 5; **B. Sauer**, Amgen, 2.

Abstract Number: 593

Adalimumab (HUMIRA) Halts Radiographic Progression and Reduces Disease Activity in Patients with a Poor Initial Response to Methotrexate

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Background/Purpose: In patients (pts) with early rheumatoid arthritis (RA), conventional synthetic DMARDs (csDMARDs), preferably methotrexate (MTX), are recommended as first line therapy.[1,2] For pts who remain in moderate to high disease activity (HDA), despite csDMARDs, TNF inhibitors are a potential treatment option.[1] The purpose of this analysis was to evaluate clinical, functional, and radiographic outcomes following the addition of adalimumab (ADA) to a subgroup of MTX insufficient responders (IR) who experienced rapid radiographic progression (RRP) and/or remained in HDA.

Methods: OPTIMA[3] was a 78-week (wk) randomized, double-blind, double-period trial comparing safety and efficacy of ADA+MTX with placebo (PBO)+MTX in early RA pts. This post hoc analysis included pts who received PBO+MTX for 26 wks (Period 1) and did not achieve stable low disease activity [LDA, DAS28(CRP) <3.2] at wks 22 and 26. These MTX-IR pts received open-label (OL) ADA+MTX for a subsequent 52 wks (Period 2) and were categorized at wk 26 by 1) whether they experienced RRP [change from baseline (BL) in modified total Sharp score (mTSS) >1.5] and 2) disease activity [HDA = DAS28(CRP) ≥5.1 or moderate (MDA) = 3.2≤ DAS28(CRP) <5.1]. For each subgroup, BL values and changes from BL in DAS28(CRP), CDAI, SDAI, HAQ-DI, and mTSS were analyzed.

Results: At wk 26, 348 (75.7%) PBO+MTX pts did not achieve stable LDA and received OL ADA+MTX for up to 52 wks. Among these MTX-IR pts, 64 (18.5%) experienced RRP during Period 1; 111 (31.9%) and 202 (58.0%) were in HDA or MDA, respectively. Pts experiencing RRP had significantly higher mean BL DAS28(CRP), SDAI, and mTSS compared with non-RRP pts (**Table**). Following ADA addition, mean DAS28(CRP) and SDAI decreased in RRP pts to levels that were comparable with those observed in non-RRP pts; while mean mTSS did not progress further in both groups. MTX-IR pts who remained in HDA, versus those in MDA, had significantly higher mean BL disease activity scores and less clinical and functional improvements at wk 26, indicating that high BL activity may be a predictor of poor response to initial MTX therapy (**Table**). Importantly, regardless of wk 26 disease activity status, the addition of ADA resulted in a decrease in mean disease activity and HAQ-DI; among pts starting Period 2 in MDA, but not HDA, mean disease activity scores fell below the LDA threshold after 52 wks of OL ADA+MTX therapy.

Conclusion: The addition of ADA in early RA pts with a poor response to initial MTX therapy led to a reduction in disease activity and prevention of further radiographic progression. Nearly 20% of pts accumulated radiographic damage during the 26 wks of MTX exposure; the identification of unique characteristics within these pts may allow for a differential therapeutic approach to preserve structural integrity. **References:**

1. Singh JA, et al., *Arthritis Care Res*, 2016; 68(1):1-25.
2. Smolen JS, et al., *Ann Rheum Dis*, 2014; 73(3):492-509.
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Table. Change from baseline in outcome measures in MTX-IR pts based on rapid radiographic progression and disease activity status.

Outcome measure Mean (SD)[‖]		Rapid radiographic progression (BL to week 26)		P-value[a]	Disease activity status based on DAS28(CRP) at weeks 22 and 26[‡]		P-value[a]
		Yes (n = 64)	No (n = 284)		High (n = 111)	Moderate (n = 202)	
DAS28(CRP)	Baseline	6.5 (0.9)	6.1 (0.9)	**0.003**[b]	6.5 (0.8)	6.0 (0.9)	**<0.001**[b]
ΔDAS28(CRP)[†]	Week 26	-1.6 (1.3)	-1.6 (1.2)	0.153	-0.6 (0.9)	-1.9 (1.0)	**<0.001**
	Week 78	-3.3 (1.5)	-3.0 (1.5)	0.756	-2.8 (1.6)	-3.1 (1.4)	**<0.001**
CDAI	Baseline	44.2 (12.8)	41.7 (12.6)	0.156[b]	47.8 (11.7)	39.7 (12.1)	**<0.001**[b]
ΔCDAI[†]	Week 26	-17.6 (16.0)	-19.0 (14.4)	0.095	-8.9 (13.2)	-22.1 (12.5)	**<0.001**
	Week 78	-33.8 (14.9)	-30.8 (14.7)	0.462	-31.6 (16.2)	-30.8 (14.0)	**<0.001**
SDAI	Baseline	49.0 (14.6)	44.4 (13.4)	**0.017**[b]	51.8 (13.7)	42.2 (12.5)	**<0.001**[b]
ΔSDAI[†]	Week 26	-20.8 (17.1)	-20.4 (15.3)	0.180	-10.3 (14.6)	-23.6 (13.0)	**<0.001**
	Week 78	-37.3 (16.3)	-32.6 (15.7)	0.491	-33.9 (18.3)	-32.6 (14.5)	**<0.001**
HAQ-DI	Baseline	1.7 (0.6)	1.6 (0.6)	0.232[b]	1.7 (0.7)	1.6 (0.6)	0.521[b]
ΔHAQ-DI[†]	Week 26	-0.5 (0.6)	-0.6 (0.7)	0.079	-0.3 (0.6)	-0.6 (0.6)	**<0.001**
	Week 78	-1.0 (0.8)	-0.9 (0.7)	0.220	-0.8 (0.8)	-0.9 (0.7)	0.215
mTSS	Baseline	17.0 (19.7)	10.6 (18.1)	**0.013**[b]	10.5 (18.7)	12.4 (18.9)	0.387[b]
ΔmTSS[§]	Week 26	6.5 (7.7)	0.0 (1.0)	**<0.001**	1.6 (3.8)	0.8 (2.8)	**0.024**
	Week 78	6.8 (8.0)	0.1 (1.2)	**<0.001**	2.0 (4.6)	0.7 (2.6)	**0.002**

[‡]35 patients who were in LDA at week 26, but not week 22 were excluded from this analysis.
[†]Missing responses were imputed by last observation carried forward (LOCF).
[§]Missing responses were imputed using multiple imputation (MI) approach.
[‖]The changes shown at week 78 relate to changes from baseline; changes from week 26 to week 78 were not significantly different between the groups.
[a]P-value is based on ANCOVA model adjusting for baseline.
[b]P-value is based on one-way ANOVA.
Abbreviations: BL = Baseline, DAS28(CRP) = 28-joint disease activity score based on C-reactive protein, CDAI = clinical disease activity index, SDAI = simplified disease activity index, HAQ-DI = health assessment questionnaire disability index, mTSS = modified total Sharp score.

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Abstract Number: 594

Maintenance of Improvements in Patients' Physical Function, Workplace and Household Productivity, and Reduction in Caregiver Burden with 2 Years of Certolizumab Pegol Treatment in DMARD-Naive, Early RA Patients with Severe Progressive Disease

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SESSION INFORMATION

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Background/Purpose: Rheumatoid arthritis (RA) is associated with loss of physical function, work disability, and decreased quality of life. Early treatment with certolizumab pegol (CZP) in combination with optimized MTX improves physical function[1] and workplace and household productivity[2] in DMARD-naïve, early RA patients (pts) after 1 year. Here, we report the impact on physical function, and workplace and household productivity of 2 years of CZP+MTX therapy in early, active RA pts with severe progressive disease.

Methods: Pts treated with CZP (200 mg Q2W+MTX) or placebo (PBO+MTX) from C-EARLY Period 1 (NCT01519791),[1] who achieved sustained low disease activity (sLDA; DAS28[ESR] ≤3.2 at both Weeks [Wks] 40 and 52) entered Period 2 (NCT01521923),[3] a randomized, double-blind dose withdrawal study. At Wk 52, CZP-treated pts in sLDA were randomized 2:3:2 to CZP standard dose (200 mg Q2W+MTX), reduced dose-frequency (200 mg Q4W+MTX), or CZP stopped (PBO+MTX). The percentage of pts achieving normative physical function (HAQ-DI ≤0.5) at Wks 52 and 104; employment status, workplace and household productivity (Work Productivity Survey, WPS),[4] and need for assistance at baseline (BL), Wk 52, and Wk 104 are reported. Missing values were imputed using last observation carried forward (LOCF).

Results: 84, 126, 79 pts in the CZP standard, reduced dose-frequency, and CZP stopped groups, respectively, comprise the full analysis set. Pt characteristics and employment status at BL and Wk 52 were generally similar across all groups. The proportion of pts achieving normative physical function was generally maintained from Wk 52 to Wk 104 in CZP standard and reduced dose-frequency pts. Fewer pts who stopped CZP maintained normative physical function to Wk 104. Employed pts continuing CZP treatment (standard and reduced dose-frequency) maintained improvements achieved at Wk 52 in workplace and household productivity to Wk 104, with some worsening seen in CZP stopped pts. Similar trends were observed in household productivity. At Wk 104, more pts who stopped CZP experienced the need for regular assistance with usual activities than pts continuing CZP treatment (standard and reduced dose-frequency) (Table).

Conclusion: Pts who continued CZP treatment at the standard or reduced dose-frequency maintained the initial improvements over the second year in normative physical function, and workplace and household productivity, and also maintained the reduced need for regular assistance from a relative or friend. A deterioration was seen from Wks 52–104 in pts who stopped CZP after 1 year. **References:** 1. Emery P. Ann Rheum Dis 2016;doi:10.1136/annrheumdis-2015-209057; 2. Emery P. Ann Rheum Dis 2015;74(S2):712; 3. Emery P. Ann Rheum Dis 2016;75(S2):143; 4. Osterhaus J.

Table: C-EARLY: Improvements in normative physical function, workplace and household productivity, and reduction in need for assistance with daily activities over 2 years

		CZP stopped n=79	CZP reduced dose-frequency n=126	CZP standard dose n=84
Normative physical function, n (%)				
Normative physical function (HAQ-DI ≤0.5)	Wk 52	60 (75.9)	101 (80.2)	67 (80.7)
	Wk 104	45 (57.0)	89 (70.6)	60 (71.4)
Employment status [a], n (%)				
Employed	BL	49 (62.0)	78 (61.9)	49 (58.3)
	Wk 52	51 (64.6)	84 (66.7)	49 (59.0) [b]
	Wk 104	52 (65.8)	79 (62.7)	51 (60.7)
Productivity in the workplace (employed patients only) [a], mean (SD), median				
Absenteeism [c]	BL [d]	4.9 (8.4), 0.0	4.1 (8.2), 0.0	6.1 (9.4), 0.0
	Wk 52 [e]	0.2 (0.7), 0.0	0.1 (0.5), 0.0	0.1 (0.4), 0.0
	Wk 104 [f]	0.5 (1.5), 0.0	0.2 (0.9), 0.0	0.3 (0.9), 0.0
Presenteeism [g]	BL [d]	7.4 (9.8), 2.0	8.2 (10.3), 3.5	6.2 (7.0), 4.0)
	Wk 52 [e]	0.2 (0.9), 0.0	0.4 (1.2), 0.0	1.0 (4.5), 0.0
	Wk 104 [f]	1.5 (4.9), 0.0	0.6 (2.0), 0.0	0.8 (2.3), 0.0
Level of RA interference with work productivity [h]	BL [d]	5.3 (2.7), 6.0	5.4 (2.7), 5.0	6.2 (3.2), 7.0
	Wk 52 [e]	0.7 (1.3), 0.0	0.7 (0.9), 0.0	1.2 (2.1), 0.0
	Wk 104 [f]	2.3 (2.8), 1.0	0.9 (1.6), 0.0	1.2 (2.2), 0.0
Household productivity [a], mean (SD), median				
Household work days missed per month [i]	BL	7.3 (9.1), 3.0	7.8 (9.2), 4.0	9.8 (10.4), 5.0
	Wk 52	0.1 (0.5), 0.0	0.3 (1.1), 0.0	0.4 (1.3), 0.0 [b]
	Wk 104	1.4 (3.4), 0.0	0.7 (2.3), 0.0	0.8 (2.8), 0.0
Household work reduced productivity days [j]	BL	8.4 (9.3), 5.0	9.6 (9.9), 6.0	10.5 (10.2), 10.0
	Wk 52	0.4 (2.0), 0.0	0.6 (1.5), 0.0	0.5 (1.2), 0.0 [b]
	Wk 104	1.8 (4.5), 0.0	0.9 (3.0), 0.0	1.0 (3.4), 0.0
Level of RA interference with household productivity [h]	BL	5.4 (2.5), 5.0	5.9 (2.4), 6.0	5.9 (2.8), 6.0
	Wk 52	0.6 (1.2), 0.0	0.8 (1.3), 0.0	1.0 (1.8), 0.0 [b]
	Wk 104	2.0 (2.6), 1.0	1.0 (1.5), 0.0	1.1 (2.0), 0.0
Need of regular assistance with usual activities [k], n (%)				
From a relative or friend	BL	44 (55.7)	62 (49.6)	41 (48.8)
	Wk 52	1 (1.3)	8 (6.3)	2 (2.4) [b]
	Wk 104	6 (7.6)	6 (4.8)	2 (2.4)
From a paid caregiver	BL	3 (3.8)	3 (2.4)	3 (3.6)
	Wk 52	0	0	0 [b]
	Wk 104	0	1 (0.8)	0

Full analysis set, LOCF imputation. HAQ-DI: health assessment questionnaire-disability index. [a] Assessed through Work Productivity Survey; [b] n=83; [c] Absenteeism=work days missed in the previous month due to arthritis; [d] n=49 CZP stopped, n=78 CZP reduced dose-frequency, n=49 CZP standard dose; [e] n=51 CZP stopped, n=84 CZP reduced dose-frequency, n=49 CZP standard dose; [f] n=52 CZP stopped, n=79 CZP dose-reduced frequency, n=51 CZP standard dose; [g] Presenteeism=work days with productivity reduced by ≥50% in the previous month due to arthritis, does not include days counted in absenteeism; [h] 0–10 scale, 0=no interference and 10=complete interference; [i] Days missed of household work in the previous month due to arthritis; [j] Days with household productivity reduced by ≥50% in the previous month due to arthritis, does not include days counted in days missed; [k] Assessed through Case Report Form modules.

Arthritis Res Ther 2009;11:R73

Abstract Number: 595

Cinical Responses and Improvements in Patient-Reported Outcomes Are Associated with Increased Productivity in the Workplace and at Home in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol

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Background/Purpose: Rheumatoid arthritis (RA) is associated with work disability, loss of productivity and reduced quality of life. In established and early RA, compared with MTX alone, certolizumab pegol (CZP)+MTX significantly improves the signs and symptoms of RA,[1] inhibits radiographic progression and improves workplace/household productivity.[2,3] In early RA, the association between reaching clinical targets and patient (pt) treatment targets, in terms of workplace and household productivity, has not been assessed. We evaluated the association between CZP-mediated stringent clinical targets and improvements in workplace/household productivity.

Methods: C-EARLY (NCT01519791) was a double-blind, randomized controlled trial, which enrolled DMARD-naïve pts with active, moderate to severe, progressive, early RA (<1 yr from diagnosis).[2] Pts were randomized 3:1 to CZP+MTX or placebo (PBO)+MTX. MTX was titrated to 15–25 mg/wk by Wk 8; maximum tolerated dose (optimized dose) was maintained to Wk 52. Associations between clinical responses and workplace/household productivity outcomes were evaluated at Wk 52 in CZP pts. Clinical response criteria included sustained remission (sREM: DAS28[ESR] <2.6 at Wks 40 and 52), sustained low disease activity (sLDA: DAS28[ESR] ≤3.2 at Wks 40 and 52), radiographic non-progression (mTSS change ≤0.5), and normative physical function (HAQ-DI ≤0.5). Changes from baseline (BL) at Wk 52 in workplace/household productivity (Work Productivity Survey [WPS][4]) were compared in responders/non-responders, using a non-parametric bootstrap-t method. Missing data were imputed using LOCF for WPS outcomes and NRI for clinical responses.

Results: 879 pts were enrolled; 655 pts in the CZP+MTX group were included in the full analysis set. At BL, 52.3% pts were employed; similar burden at BL was seen between groups, except in absenteeism/presenteeism for pts in sREM/sLDA. Overall, pts achieving sREM/sLDA and normative function reported greater improvements in workplace/household productivity at Wk 52 vs non-responders (Table). An association was not seen between radiographic non-progression and workplace/household productivity (Table). Responders also reported greater improvements in family and social leisure activity participation (data not shown).

Conclusion: Achieving stringent clinical targets, such as sREM/sLDA and normative physical function, were associated with numerically greater improvements in workplace and household productivity after 1 yr in DMARD-naïve pts with early, moderate to severe, progressive RA treated with CZP. The ability to return to maximum levels of participation early in the disease course is an important goal for pts with RA. **References:** 1. Strand V. Arthritis Res Ther 2009;11:R170; 2. Emery P. Ann Rheum Dis 2016 doi:10.1136/annrheumdis-2015-209057; 3. Kavanaugh A. Arthritis Care Res

2009;61(11);1592–1600; 4. Osterhaus J. Arthritis Res Ther 2009;11:R73

Table: Change from baseline in workplace and household productivity at Week 52 of the C-EARLY study for CZP-treated patients by responder status for clinical and patient reported outcomes

		Workplace productivity (employed patients only), mean (SD)				Household productivity, mean (SD)			
		n	Absenteeism [a]	Presenteeism [b]	Level of arthritis interference on productivity [c]	n	Days missed [a]	Days with productivity reduced by ≥50% [b]	Level of arthritis interference on productivity [c]
sREM [d]	Responders, BL	125	4.2 (7.7)	6.7 (8.4)	5.3 (2.8)	189	8.5 (9.7)	9.2 (9.8)	5.7 (2.6)
	CFB	**125**	**-4.2 (7.7)***	**-6.2 (8.8)**	**-4.6 (2.7)****	**189**	**-8.3 (9.7)****	**-8.8 (9.6)****	**-5.1 (2.7)*****
	Non-responders, BL	226	3.4 (6.6)	5.5 (8.5)	5.3 (2.8)	466	8.6 (9.6)	9.2 (9.5)	6.0 (2.6)
	CFB	**226**	**-2.5 (6.4)**	**-4.3 (8.9)**	**-3.6 (3.0)**	**466**	**-6.1 (9.7)**	**-6.3 (10.4)**	**-3.7 (3.0)**
sLDA [e]	Responders, BL	179	4.2 (7.6)	7.1 (8.9)	5.4 (2.8)	287	8.2 (9.5)	9.5 (9.7)	5.8 (2.5)
	CFB	**179**	**-4.1 (7.5)****	**-6.5 (9.2)****	**-4.6 (2.7)*****	**287**	**-8.0 (9.5)****	**-9.0 (9.6)*****	**-4.9 (2.7)*****
	Non-responders, BL	172	3.1 (6.3)	4.7 (7.8)	5.2 (2.9)	368	8.9 (9.8)	8.9 (9.4)	6.1 (2.6)
	CFB	**172**	**-1.9 (5.9)**	**-3.3 (8.2)**	**-3.2 (3.1)**	**368**	**-5.8 (9.8)**	**-5.5 (10.5)**	**-3.4 (3.0)**
HAQ-DI ≤0.5	Responders, BL	197	3.8 (7.5)	6.2 (8.7)	5.1 (2.8)	315	8.0 (9.6)	9.3 (9.8)	5.7 (2.6)
	CFB	**197**	**-3.7 (7.4)**	**-5.8 (8.9)**	**-4.4 (2.8)****	**315**	**-7.7 (9.5)***	**-8.9 (10.0)*****	**-4.9 (2.8)*****
	Non-responders, BL	154	3.6 (6.5)	5.7 (8.1)	5.6 (2.8)	340	9.1 (9.7)	9.1 (9.3)	6.2 (2.5)
	CFB	**154**	**-2.3 (6.1)**	**-4.0 (8.8)**	**-3.4 (3.0)**	**340**	**-5.8 (9.9)**	**-5.3 (10.2)**	**-3.3 (2.9)**
mTSS ≤0.5 [f]	Non-progressor, BL	214	3.7 (7.0)	6.0 (7.9)	5.3 (2.9)	371	8.1 (9.1)	9.2 (9.5)	5.8 (2.5)
	CFB	**214**	**-3.4 (7.0)**	**-5.3 (8.3)**	**-4.2 (2.9)**	**371**	**-7.0 (9.1)**	**-7.8 (9.6)**	**-4.3 (2.8)**
	Progressor, BL	85	4.3 (7.7)	5.8 (9.1)	5.4 (2.6)	157	8.7 (10.3)	9.7 (10.5)	6.1 (2.6)
	CFB	**85**	**-3.7 (7.6)**	**-4.9 (9.2)**	**-4.3 (2.8)**	**157**	**-7.2 (10.6)**	**-8.0 (11.2)**	**-4.6 (3.0)**

Nominal p values for the difference in mean CFB between responders and non-responders: *p<0.05, **p<0.01 and ***p<0.001. [a] CFB in the number of days missed due to arthritis in the last month; [b] CFB in the number of days with productivity reduced by ≥50% due to arthritis in the last month; [c] CFB in the level of arthritis interference on productivity in the last month, as measured on a 0–10 point scale (0=no interference, 10=complete interference); [d] sREM, sustained remission (DAS28[ESR] <2.6 at both Wks 40 and 52); [e] sLDA, sustained low disease activity (DAS28[ESR] ≤3.2 at both Wks 40 and 52); [f] Radiographic set. BL, baseline; CFB, change from baseline; HAQ-DI, Health Assessment Questionnaire-Disability Index; mTSS, van der Heijde modified Total Sharp Score; sREM, sustained remission; sLDA, sustained low disease activity. Full analysis set unless otherwise stated.

Disclosure: V. P. Bykerk, AbbVie, Bristol-Myers Squibb, Pfizer, Genentech, Regeneron, UCB Pharma, 5; **P. Emery**, Pfizer, MSD, AbbVie, UCB, Roche, Brisol-Myers Squibb, Schering Plough, Novartis, Samsung, 5,Pfizer, MSD, AbbVie, UCB Pharma, Roche, Bristol-Myers Squibb, Schering Plough, Novartis, Samsung, 9; **M. Weinblatt**, Bristol Myers Squibb, Crescendo Bioscience, UCB Pharma, 2,Amgen, AbbVie, Bristol Myers Squibb, Crescendo Bioscience, UCB Pharma, Roche, 5; **G. R. Burmester**, AbbVie, MSD, Pfizer, Roche, UCB Pharma, 5; **D. E. Furst**, Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 2,Abbott, Actelion, Amgen, Bristol-Myers Squibb, BiogenIdec, Janssen, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 5,Abbott, Actelion, Amgen, Bristol-Myers Squibb, BiogenIdec, Janssen, Gilead, NIH, Roche/Genentech, 9,Abbott, Actelion, UCB Pharma, 9; **X. Mariette**, Pfizer, GlaxoSmithKline, and Roche, 2,Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma and Sanofi-Aventis, 5; **R. van Vollenhoven**, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma, 2,AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Pfizer, Roche, UCB Pharma, Vertex, 5; **O. Purcaru**, UCB Pharma, 3; **P. Ralston**, Hays Pharma, 3; **C. Bingham III**, UCB Pharma, 5.

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Abstract Number: 596

Association Between Plasma Certolizumab Pegol Concentration and Improvement in Disease Activity in Rheumatoid Arthritis and Crohn's

Disease

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Background/Purpose: Anti-TNFs neutralize the TNF-mediated component of inflammatory diseases such as rheumatoid arthritis (RA) and Crohn's disease (CD) to reduce disease activity. In this study, we aimed to identify the range of plasma certolizumab pegol (CZP) concentrations ([CZP]) associated with optimal improvement in disease activity for patients (pts) with RA and CD exposed to different dosing regimens.

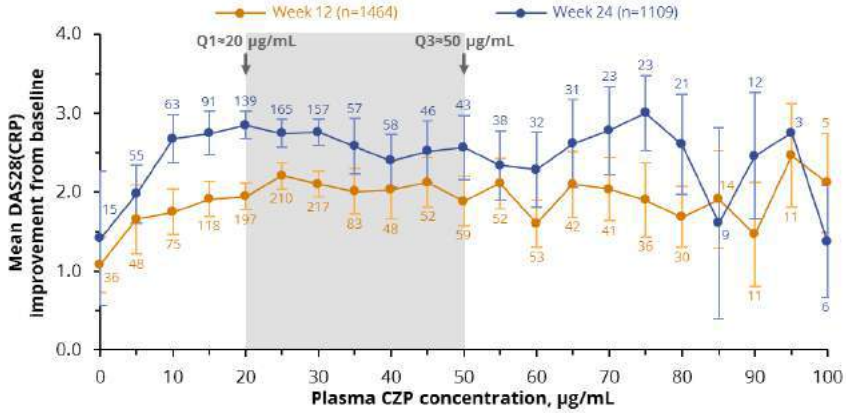
Methods: Efficacy endpoints by [CZP] were assessed using two methods: 1) correlation of measured [CZP] with disease activity (RA); 2) population PK/PD modeling (RA and CD). Observed RA data were from RAPID1 and RAPID2. Data for PK/PD modeling were pooled across multiple placebo-controlled CZP studies in RA and CD. RA pts were treated with a loading dose (CZP 400 mg at Weeks [Wks] 0, 2, 4) followed by a maintenance dose (RA: 200 mg or 400 mg Q2W). CD modeling was performed for the loading dose (CZP 400 mg at Wks 0, 2, 4) during induction phase, and maintenance dose (400 mg Q4W). [CZP] was measured using an ELISA validated in line with FDA/EMA regulatory requirements for bioanalytical methods. In RA, [CZP] was correlated with change from baseline in DAS28(CRP) (ΔDAS) and clinical disease activity index at Wks 12 and 24. In CD, [CZP] was correlated with Crohn's disease activity index (CDAI) remission (≤150 points), CRP response (≤5 mg/L), fecal calprotectin (FC) response (≤250 μg/g) and composite outcome (CDAI ≤150 and FC ≤250 μg/g) at Wks 6 and 26.

Results: In RAPID1/RAPID2 (n=1479 RA pts; data pooled for CZP 200 mg Q2W and 400 mg Q2W), the interquartile range (IQR) of measured [CZP] was 20–50 μg/mL, associated with ΔDAS ≥2.0 at Wk 12, and ΔDAS ≥2.4 at Wk 24 (Figure A). A similar [CZP] range was associated with improvement in clinical disease activity index (not shown). PK/PD modeling in RA (n=2621 pts) confirmed the [CZP] range observed for the CZP 200 mg Q2W and 400 mg Q2W regimens, with [CZP] ≥24 μg/mL associated with ΔDAS ≥2 at Wks 12 and 24. For the 400 mg Q4W regimen, similar ΔDAS improvements were predicted for [CZP] ≥15 μg/mL. In CD (n=2157 pts), receiver operating curve analysis showed a loading dose [CZP] of 36 μg/mL (Wk 6) and a maintenance [CZP] of 15 μg/mL (Wk 12) associated with response for the various outcomes analyzed (Figure B). In both RA and CD, predicted [CZP] thresholds associated with response were consistent with the IQRs of measured [CZP] (Figure C).

Conclusion: Based on these ELISA data, in pts with RA treated with the CZP 200 mg Q2W or 400 mg Q2W regimens, ΔDAS increased with [CZP] up to 20 μg/mL; the majority of pts had [CZP] ≥20 μg/mL, which was associated with a plateau effect in ΔDAS from Wk 12, averaging ~2.0 at Wk 12 and ~3.0 at Wk 24. PK/PD modeling predicted a lower [CZP] range for the 400 mg Q4W regimen, with similar efficacy. In pts with CD, the loading dose [CZP] range and association with efficacy were in line with RA results; maintenance [CZP] ranged 4–28 μg/mL.

Figure: Relationship between CZP concentration and improvement in disease activity in RA and CD patients

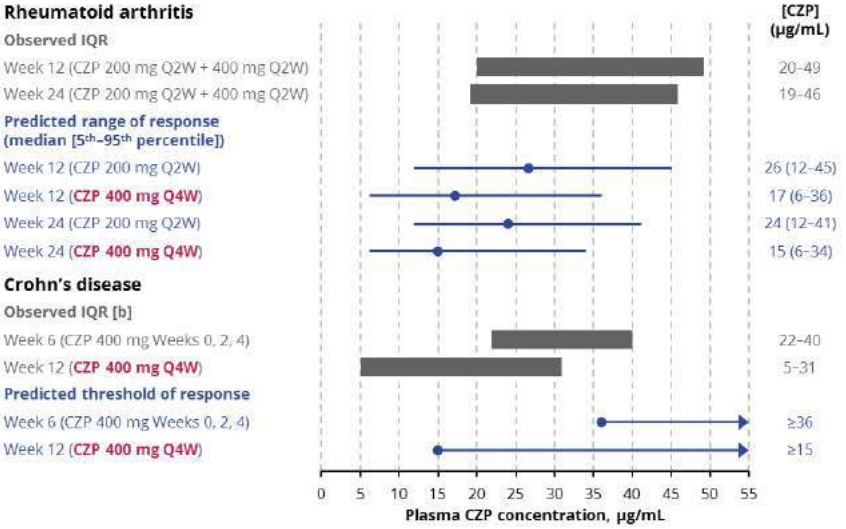
A) Observed concentration-effect curve of CZP in patients with RA (n=1479 patients from RAPID1 and RAPID2) [a]



B) Receiver operating curve analysis in CD of Week 6 and Week 12 plasma CZP concentration, and Week 6 and Week 26 outcomes (n=2157 patients)

Outcome	[CZP] Cut-off Week 6 (µg/mL)	Sensitivity (%)	Specificity (%)	[CZP] Cut-off Week 12 (µg/mL)	Sensitivity (%)	Specificity (%)
CDAI remission						
Week 6	31.8	57.2	55.7	-	-	-
CRP ≤5mg/L						
Week 6	31.9	65.1	69.4	-	-	-
FC ≤250 µg/g						
Week 6	32.7	73.9	60.3	-	-	-
Week 26	-	-	-	13.8	68.1	56.0
CDAI ≤150 and FC ≤250 µg/g						
Week 6	34.5	66.7	59.7	-	-	-
Week 26	36.1	67.1	65.0	14.8	73.2	57.3

C) Observed interquartile ranges of CZP concentration and predicted thresholds of clinical response according to the dosing regimens analyzed



Observed RA data were pooled from RAPID1/RAPID2 (RCTs: NCT00152386, NCT00160602; OLEs: NCT00175877, NCT00160641). Data for PK/PD modeling were pooled across multiple studies in RA (NCT00152386, NCT00160602, NCT00674362, NCT01451203, NCT01255761, NCT00791999, NCT00791921) and CD (C87005, NCT00152490, NCT00152425, NCT00329420, NCT00308581, NCT00552058). [a] Patients were grouped by [CZP] in 5 µg/mL increments (number of patients shown next to each data point); patients with [CZP] >100 µg/ml are not shown (26/1464 at Week 12 and 22/1109 at Week 24); error bars correspond to 95% confidence intervals; [b] Data from Vande Casteele, N. Inflamm Bowel Dis 2016;22:S42(P-103). CDAI: Crohn's disease activity index; FC: fecal calprotectin; IQR: interquartile range.

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Abstract Number: 597

Comparative Effectiveness of Different Anti-TNF Drugs As First Biological DMARD in RA: Results from the Nationwide Swedish Register 2010-2015

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Background/Purpose: Although evidence from randomized trials suggest similar efficacy and safety on a group level for the different anti-TNF drugs available for the treatment of RA, and many treatment guidelines rank them as interchangeable in terms of effect, there are few head-to-head comparisons and limited real world data on their comparative effectiveness in clinical practice. Our objective was therefore to perform a head-to-head comparison of the initial effectiveness of different TNF inhibitors among bionaïve patients with RA in a large population-representative sample

Methods: The Swedish Rheumatology Register (SRQ) covers about 95% of all biological treatment of RA, with data on clinical characteristics prospectively recorded at treatment initiation and at subsequent patient visits. We included all patients with RA registered in the SRQ as starting etanercept, infliximab (including originator product and its biosimilar), adalimumab, certolizumab pegol, or golimumab as their first ever biological DMARD (N=6149) between 1st Jan 2010 and 31st July 2015, with follow-up through March 31st2016. Effectiveness was defined as 1) remaining on therapy, 2) being in remission or low disease activity (DAS28<2.6), and 3) having achieved a EULAR response, all at the evaluation visit at 5 (3-8) months after start (defined as the visit closest to 151 days of all visits between 60 and 242 days; this method has previously been shown to capture 95% of patients with follow-up visits within one year of treatment initiation). Differences in crude proportions were tested across drugs using χ^2-tests. To take baseline differences in patient

characteristics into account, relative risks were estimated using generalized log-binomial regression adjusting for sex, age, concomitant use of DMARDs, Rheumatoid Factor, HAQ, and disease duration.

Results: : Across all anti-TNF drugs, about 90% remained on therapy until the evaluation visit, and most patients remaining on drug also had a positive response, with about 40% having DAS28 below 2.6, and almost half reaching a good EULAR response. As shown in the Table, only the crude proportion with DAS28 below 2.6 was statistically significantly different across treatments (p=0.011), but this difference was no longer significant after taking baseline characteristics, and proportions discontinuing drug, into account. Although some one-on-one comparisons approached borderline significance (e.g. lower proportion discontinuing therapy in adalimumab *vs.*etanercept, p=0.06), the number of pairwise tests lead to risk of false positives, and the global test showed no significant inter-drug difference.

Conclusion: These results suggest limited differences in effectiveness among available TNF inhibitors for the treatment of RA in current clinical practice, at least regarding the initial response among previously bionaïve patients

Status at evaluation visit at 5 months among all patients with RA initiating TNFi as first ever biologic DMARD 2010-2015 in Sweden

	Etanercept	*Infliximab*	*Adalimumab*	*Certolizumab pegol*	*Golimumab*	*P-value*
N	1826	1495	1087	979	762	
Observed percentage						
Discontinued	11.5	9.8	9.2	11.6	9.2	0.11
DAS28 < 2.6*	42.9	35.9	42.2	39.1	41.9	0.01
EULAR response*						
Good	47.3	42.0	46.8	46.0	46.0	0.23
Moderate	29.2	32.8	30.3	31.6	30.5	0.58
None	23.5	25.2	22.9	22.4	23.6	0.79
Adjusted relative risk†						
Discontinued	*Ref.*	0.89 (0.71-1.13)	0.77 (0.59-1.01)	1.01 (0.80-1.29)	0.83 (0.62-1.12)	0.25
DAS28 < 2.6‡	*Ref.*	0.92 (0.81-1.04)	1.03 (0.91-1.16)	0.95 (0.83-1.09)	0.99 (0.85-1.14)	0.54
EULAR response¶						
Good	*Ref.*	0.94 (0.83-1.06)	1.01 (0.88-1.15)	1.05 (0.92-1.20)	1.03 (0.89-1.20)	0.57
Good or Moderate	*Ref.*	0.99 (0.91-1.07)	1.02 (0.93-1.12)	1.06 (0.97-1.15)	1.05 (0.95-1.15)	0.59
None or discontinued	*Ref.*	1.07 (0.93-1.23)	0.93 (0.80-1.09)	1.08 (0.93-1.26)	0.95 (0.80-1.14)	0.32

Notes: P-values from $\chi 2$-tests for proportions, and type 3 Wald test in regression model, *) Proportion among those remaining on drug.

†) Adjusted for sex, age, RF, baseline disease duration, HAQ, and concomitant use of MTX, non-MTX DMARD, corticosteroids

‡) Comparing "remission" to "no-remission, or no longer on therapy"

¶) Comparing each response category to "any other response, or no longer on therapy"

.

Disclosure: T. Frisell, None; **M. Dehlin**, None; **D. Di Giuseppe**, None; **N. Feltelius**, None; **A. Kastbom**, BMS, Roche, UCB, 5; **C. Turesson**, Abbvie, BMS, Novartis, Pfizer, 5,Abbvie, Pfizer, Roche, 2; **J. Askling**, UCB, Roche, Merck, Pfizer, and Abbvie, 2.

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Abstract Number: 598

An Assessment of the Correlation Between Gender and Anticipated Drug Retention to TNF Inhibitors: A Meta-Regression Analysis

Cathy Lee Ching[1], Elie Donath[2] and Suresh Kumar[3], [1]Internal Medicine, University of Miami Miller School of Medicine/ JFK Med Ctr, Palm Beach Regional Campus GME Consortium, Atlantis, FL, [2]Internal Medicine, University of Miami Miller School of Medicine, JFK Med Ctr, Palm Beach Regional Campus GME Consortium, Atlantis, FL, [3]Rheumatology, Veterans Affairs Medical Center of West Palm Beach, West Palm Beach, FL

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Background/Purpose: It is generally believed that a wide variety of patient-specific factors, and in particular gender, are likely to influence the response and tolerability of DMARDs in patients with rheumatoid arthritis (RA).[1] In particular, several prospective studies have suggested that women may have lower remission rates than men as a result of having greater disease burden.[2]Despite this, very little is known about the true extent that many of these risk factors have on RA outcomes. The purpose of this analysis is to elucidate, via a meta-regression, the suspected relationship between female sex, drug retention rates and incidence of adverse events.

Methods: An extensive literature search for all RCT's involving treatment for RA with TNF inhibitors was performed and 18 studies were identified (including 2 studies assessing Certolizumab pegol, 6 that assessed Golimumab, 3 that assessed Infliximab and 7 that assessed Adalimumab). Meta-regression analysis, employing a random-effects model, was performed to evaluate whether gender may have influenced effect size among these four TNF-inhibitors. Outcomes evaluated included drug retention, drug discontinuation, adverse events, serious adverse events, serious infections and infusion reactions.

Results: The proportion of female participants in a given treatment arm was highly statistically significantly correlated with improved drug retention in that, for every 1% improvement in drug retention, a 1.03% increase in female participants (95% CI 0.65-1.41%, p=<0.0001) was observed. Similarly lower rates of drug discontinuation (and in particular - Lack/Loss of efficacy, Adverse events and Other- as a reason for drug discontinuation), serious adverse events, serious infections and infusion reactions were also associated with increasing proportions of female participants in the included studies. These models were adjusted for all relevant covariates of interest including age, study size and disease severity.

Conclusion: Female gender seems to be correlated with increased drug retention and decreased rates of study discontinuation for a variety of causes. This finding belies prior consensus on this topic and warrants further research this potential relationship in larger prospective cohort trials. **References:** 1.- Hider Samantha L, Buckley Caitriona, Silman Alan J, et al. Factors Influencing Response to Disease Modifying Antirheumatic Drugs in Patients with Rheumatoid Arthritis. J Rheumatol January 2005 32(1):11-16 2.- Forslind K, Hafström I, Ahlmén M, Svensson B. Sex: a major predictor of remission in early rheumatoid arthritis?. BARFOT Study Group. Ann Rheum Dis. 2007 Jan; 66(1): 46–52.

Disclosure: C. Lee Ching, None; **E. Donath**, None; **S. Kumar**, None.

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Abstract Number: 599

Real World United States-Based Clinical Experience with Prior Biologic Use Among First Time Golimumab Intravenous and Infliximab Treated

Rheumatoid Arthritis Patients

Sergio Schwartzman[1], Dennis Parenti[2], Shawn Black[2], Kehzen Tang[3], Yanli Wang[3] and Shelly Kafka[2], [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Janssen Scientific Affairs, LLC, Horsham, PA, [3]Janssen Research & Development, LLC, Spring House, PA

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Background/Purpose: AWARE (Comparative and Pragmatic Study of Golimumab IV Versus Infliximab in Rheumatoid Arthritis) is a Phase 4 comparator study designed to provide a real-world evidence (RWE) based assessment of intravenous golimumab (G-IV) and infliximab (IFX) in patients (pts) with rheumatoid arthritis (RA). Assessments include medical history, RA disease history, prior biologic RA therapies, clinical outcomes, infusion reactions, cost effectiveness, and safety. Here we report on prior biologic use patterns of an early cohort of AWARE pts.

Methods: This is a prospective, noninterventional, observational multicenter study being conducted in the United States, with 2-year study enrollment period and 3-year study duration. 1,200 adult RA pts will be enrolled to initiate treatment with either G-IV or IFX. All treatment decisions are made at the discretion of the treating rheumatologist; patient (pt) visits occur as per usual clinical practice. The primary objective is to compare the proportion of pts with an infusion reaction in RA pts treated with G-IV vs IFX. Secondary objectives include effectiveness assessments, cost effectiveness and patient reported outcomes (PROMIS-29, Pain Interference SF6b, Fatigue SF7a, SF36) and a novel Treatment Satisfaction Questionnaire for Medication–Intravenous, which assesses patient satisfaction with an infusion therapy.

Results: Mean (±SD) age of pts (n=114) was 59.7 (±12.02) years, with a mean body weight of 85.95 kg, 82.5% of pts were female. A total of 74 pts were administered G-IV and 40 pts were administered IFX. Overall, 69.0% of pts reported to have received at least 1 biologic prior to enrolling. Proportion of bionaive patients among G-IV users and IFX users were 23.3% and 45.0%, respectively. Concomitant methotrexate (MTX) use was reported in 54.1% of G-IV pts and 70.0% of IFX pts. Among all non-bionaïve pts, the most frequently used biologic was adalimumab (31.6%). A similar proportion of G-IV and IFX pts had prior adalimumab (32.4% and 30.0%, respectively), prior etanercept was reported in 29.7% of G-IV pts and 10.0% of IFX pts. Of the G-IV pts, 39.2% had prior exposure to IFX, and 15.0% of IFX pts had prior exposure to G-IV. Subcutaneous golimumab was used in 5.0% of IFX pts, and 2.7% of the G-IV pts. Abatacept was previously used in 18.9% of G-IV pts and 0% of IFX pts. 10.8% of G-IV pts had prior exposure to tocilizumab, 2.5% of IFX pts had prior exposure to that drug. Baseline CDAI scores were 33.67 (±14.8) in G-IV pts and 35.14 (±16.1) in IFX pts.

Conclusion: In this Phase 4 study, early evaluation of patient demographics confirms published data of current patients treated with biologic agents who have RA. Early analysis of previous biologic use in this RWE study exploring potential differences between G-IV and IFX, indicates that there may be differences in the extent of prior biologic experience of pts treated with either one of these drugs. Patients started on G-IV appeared to have had more extensive prior biologic experience and less concomitant MTX use compared to IFX pts. Greater MTX use by IFX pts may be related to the greater proportion of bionaïve pts in the IFX group. Such differences may have relevance in terms of ultimate efficacy, safety, and cost effectiveness in managing RA pts.

Abstract Number: 600

Disease Activity Trends after Dose Escalation of Infliximab (Remicade) – Results from United States Consortium of Rheumatology Researchers of North America Registry

Dennis Parenti[1], George W. Reed[2], Ying Shan[2], Kimberly Dandreo[2], Joel M. Kremer[3] and Raphael J. DeHoratius[4], [1]Janssen Scientific Affairs, LLC, Horsham, PA, [2]Corrona, LLC, Southborough, MA, [3]Albany Medical College, Albany, NY, [4]Janssen Scientific Affairs, LLC/Sidney Kimmel School of Medicine, Thomas Jefferson University, Horsham/Philadelphia, PA

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Background/Purpose: Dose escalation is a common strategy for patients (pts) on infliximab (IFX). This study examined the trend in disease activity across dose escalations to determine if dose escalation resulted in progressive lowering of disease activity.

Methods: Rheumatoid arthritis (RA) pts enrolled in the US Corrona registry initiating IFX on or after 1/1/2007 with an initial dose of 3mg/kg/Q8 weeks were identified. Eligible patients had at least 1 dose escalation and at least one follow-up visit after 1st dose escalation. Dose escalation was defined as an increase of >1mg/kg in dose and/or an increase in the frequency of dosing by ≥1 week. Trends in disease activity (CDAI) and functionality (HAQ) were summarized over time and scaled to number of dose escalations (CDAI at visits between escalations scaled to proportion of time between escalations). Locally weighted scatterplot smoothing (Lowess curve) were used to estimate trends over time.

Results: Eligible pts (N=185) had a mean 7.5 years duration of RA and 72.4% were female; mean CDAI (SD) was 19.6 (13.2) at time of initiation and 16.6 (12.0) at 1st dose escalation. Figure 1 shows the estimated mean CDAI over time for pts with 3 dose escalations and Figure 2 shows estimated CDAI for pts with 4 dose escalations. In pts with 3 dose escalations (n=30), there is a progressive decrease in mean CDAI from initiation until the 2nd dose escalation, and then the mean CDAI remains at a plateau. In pts with 4 dose escalations (n=12), the decrease in mean CDAI is less and the overall level of disease is higher; trends in HAQ are flat across 3 dose escalations (Figure 3).

Conclusion: Initial dose escalations (i.e. the first two) provide reduction in mean CDAI, while later dose escalations are related to maintaining disease activity levels. Pts with ≥3 dose escalations had higher levels of initial disease activity, smaller initial response, and little subsequent reduction in disease activity after the first two dose escalations. These results have potentially important clinical implications since these data suggest there may be diminishing clinical benefit in at least a subset of patients beyond the initial 2 dose escalations and that an assessment of the risk-benefit of further dose escalations should be considered.

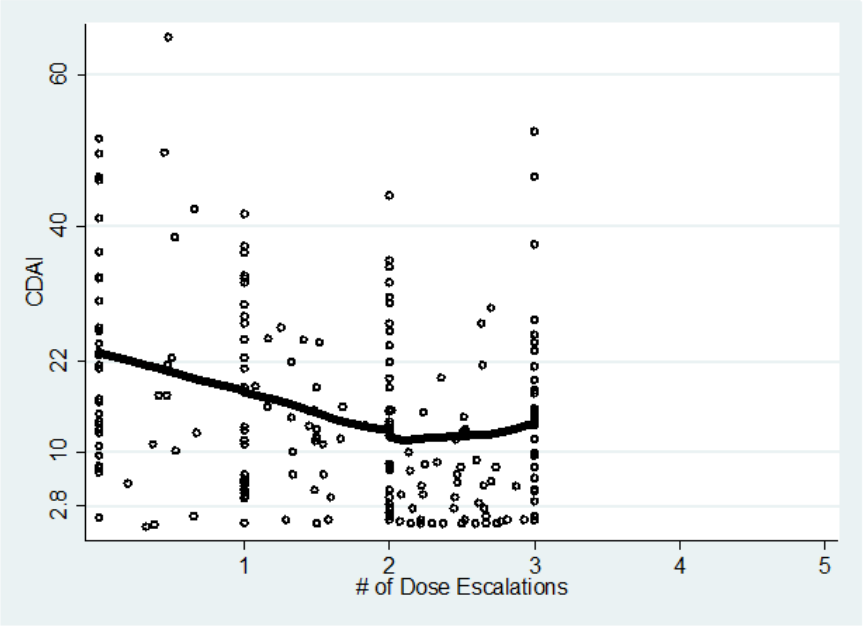

Figure 1. Lowess curve of CDAI in patients with 3 dose escalations

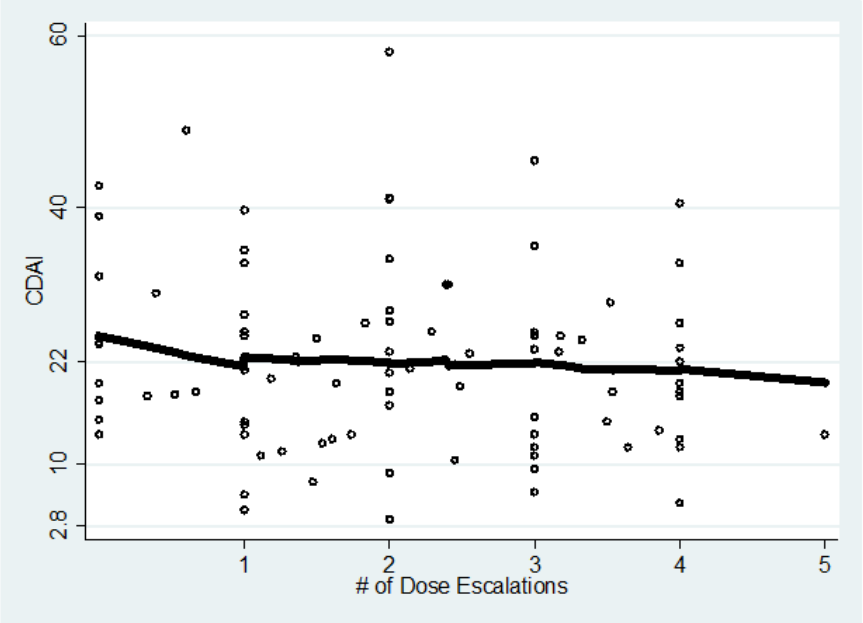

Figure 2. Lowess curve of CDAI in patients with at least 4 dose escalations

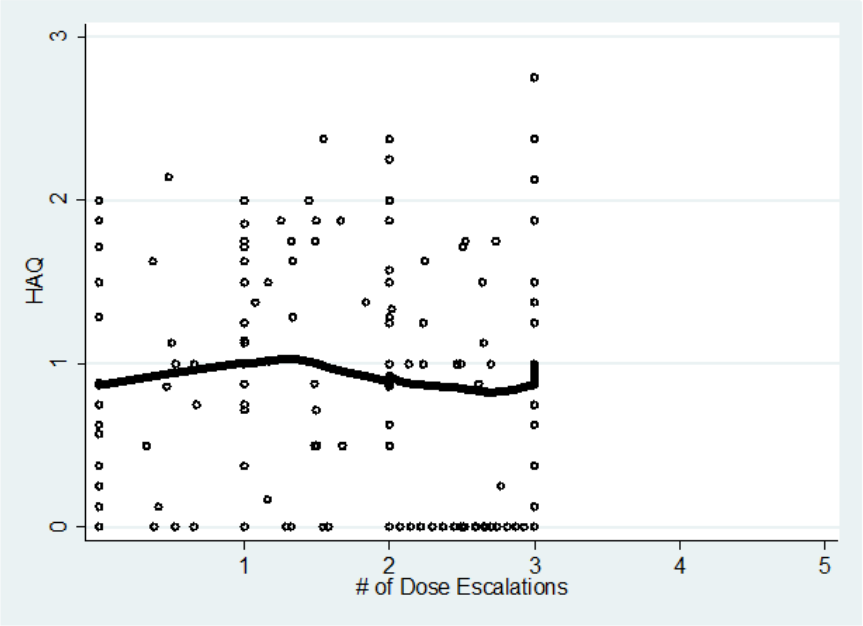

Figure 3. Lowess curve of HAQ in patients with 3 dose escalations

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Disclosure: D. Parenti, Janssen Scientific Affairs, LLC, 3; **G. W. Reed**, Corrona, LLC, 3; **Y. Shan**, Corrona, LLC, 3; **K. Dandreo**, Corrona, LLC, 3; **J. M. Kremer**, Janssen Scientific Affairs, LLC, 5; **R. J. DeHoratius**, Janssen Scientific Affairs, LLC, 3.

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Abstract Number: 601

Differing Contribution of Methotrexate Polyglutamation to Infliximab and Adalimumab Exposure As Compared to Etanercept

Thierry Dervieux[1], Joel M. Kremer[2], Tyler O'Malley[1], Alan J Kivitz[3], John Conklin[4] and Michael Weinblatt[5], [1]Research and Development, Exagen Diagnostics, Vista, CA, [2]Albany Medical College, Albany, NY, [3]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [4]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [5]Division of Rheumatology, Immunology and Allergy, Harvard Medical School, Brigham and Women's Hospital, Boston, MA

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Background/Purpose:

Methotrexate (MTX) is known to improve exposure and clinical outcome to anti-tumor necrosis factor (TNF) therapy. While the precise mechanism of action for the pharmacokinetic interaction is still elusive, immunosuppression and reduction in the likelihood of antidrug antibodies are likely significant contributors. This pilot study evaluated the impact

of MTX polyglutamation on anti-TNF exposure.

Methods:

The study was cross sectional by design, multicentered (three sites), and enrolled 230 consecutive adult rheumatoid arthritis subjects under MTX in combination with infliximab (61 subjects), adalimumab (83 subjects) or etanercept (86 subjects) for at least 12 weeks. At the time of a single visit, anti-coagulated blood was collected immediately before the infliximab infusion (trough) or randomly in relation to the last subcutaneous injection of adalimumab or etanercept. Steady state trough infliximabemia, random adalimumabemia or etanerceptemia were determined using a TNF reporter gene assay with chemiluminescent detection (expressed as µg/ml plasma). Red blood cells (RBC) MTX polyglutamates ($MTXPG_3$) were determined using liquid chromatography (expressed as nmol/L RBC). C-reactive protein (CRP) levels were determined using standard chemistry techniques (expressed as mg/L). Statistical analysis consisted of multivariate linear regression with anti-TNF exposure as dependent variable and RBC $MTXPG_3$ as independent predictor, adjusting estimates for TNF dosage, obesity status (BMI>30 Kg/m^2) and CRP levels. Estimates are reported as average±SEM.

Results:

All subjects enrolled in this study (59±1 years; 82% females) were under MTX therapy 8.8±0.4 years and prescribed anti-TNF therapy for 5.2±0.2 years. MTX dosage was 16±0.4 mg/week and RBC $MTXPG_3$ levels were 36±1 nmol/L. CRP levels were 8.7±0.6 mg/L with 35% obese subjects. Exposure to Infliximab (7.4±0.6 mg/Kg every 8 weeks), adalimumab (42±1 mg every other week) and etanercept (49±0.7 mg weekly) was 11.8±0.8 µg/ml, 6.2±0.9 µg/ml, and 3.2±0.2 µg/ml respectively. Higher anti-TNF dosage resulted in higher exposure to all biologics, while obesity status had a negative impact on infliximab and adalimumab exposure. Elevated CRP levels tended to be associated with lower exposure to all monoclonal antibodies. Heightened $MTXPG_3$ levels resulted in increased infliximabemia (partial R^2=0.09; p<0.01) and adalimumabemia (partial R^2=0.06; p=0.02) while polyglutamation had no impact on etanercept exposure.

Conclusion:

These data are consistent with the notion that MTX polyglutamation may impact exposure to infliximab and adalimumab that are immunogenic and prone to anti-idiotype antibody formation. Because etanercept is a fusion TNF receptor construct with little incidence of antidrug antibodies, the impact of MTX metabolism on its exposure is negligible.

Table: Multivariate analysis of anti-TNF exposure in relation to MTX polyglutamation after adjusting for dosage, obesity status, and CRP levels.

	Trough Infliximabemia µg/ml [n=61]	Random Adalimumabemia µg/ml [n=83]	Random Etanerceptemia µg/ml [n=86]
Total R^2	48.2%	33.5%	2.8%
Intercept	-1.25±1.59	4.50±2.54	1.33±1.57
Dose [mg per week]	0.11±0.01 (p<0.01)	0.44±0.10 (p<0.01)	0.06±0.03 (p=0.03)
$MTXPG_3$ [nmol/L]	0.08±0.03 (p=0.01)	0.07±0.03 (p=0.02)	-0.01±0.01 (p=0.26)
BMI>30 (Kg/m^2)	-3.70±1.30 (p<0.01)	-4.40±1.30 (p<0.01)	-0.04±0.48 (p=0.93)
CRP (mg/L)	-0.10±0.05 (p=0.04)	-0.44±1.33 (p<0.01)	-0.05±0.03 (p=0.10)

Disclosure: T. Dervieux, Exagen, 3; **J. M. Kremer**, None; **T. O'Malley**, exagen, 3; **A. J. Kivitz**, None; **J. Conklin**, Exagen, 3; **M. Weinblatt**, None.

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Abstract Number: 602

Efficacy and Safety of Switching Between Certolizumab Pegol and Adalimumab after Primary Anti-TNF Treatment Failure: 2-Year Results from a Randomized, Investigator-Blind, Superiority Head-to-Head Study

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SESSION INFORMATION

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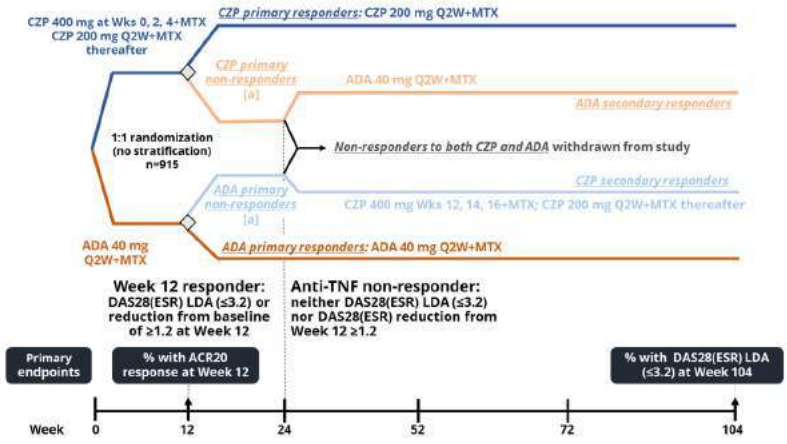
Background/Purpose: EULAR, ACR and treat-to-target guidelines recommend switching treatment in inadequate responders (IRs) to alternative therapy by Week (Wk) 12.[1-3] Although any biological (b)DMARD can be initiated in conventional synthetic (cs)DMARD IRs, many practitioners use a TNF inhibitor (TNFi) for primary biologic treatment. For TNFi IRs, an immediate switch to a second TNFi may be proposed despite there being no blinded, prospective clinical trials demonstrating the efficacy and safety of the immediate use of a second TNFi. EXXELERATE is the first randomized controlled trial (RCT) to address immediate switching to another TNFi, in a TNFi IR patient (pt) population.

Methods: EXXELERATE (NCT01500278) was a 104-wk randomized, investigator-blind, parallel-group, head-to-head superiority study comparing the early (Wk 12)- and later (Wk 104)-term efficacy and safety of certolizumab pegol (CZP)+MTX vs adalimumab (ADA)+MTX (Figure). Pts were randomized 1:1 to CZP+MTX or ADA+MTX. At Wk 12, pts were classified as responders (achieving either DAS28[ESR] ≤3.2 or a DAS28[ESR] reduction from baseline [BL] of ≥1.2), or non-responders (NRs). NRs originally randomized to CZP were switched to ADA, while NRs to ADA were switched to CZP (Figure). A pre-defined exploratory objective assessed early- and later-term efficacy of switching to a second TNFi using ACR20/50/70, low disease activity (LDA) and remission (REM). The safety of switching TNFi without a washout period was assessed by monitoring all TEAEs occurring after treatment switch and within 70 days of the final dose of initial study drug.

Results: At BL, 457 pts were randomized to CZP and 458 to ADA. Of the 122 pts who switched and continued after Wk 12, 65 CZP NRs were switched to ADA and 57 ADA NRs switched to CZP. Clinical improvement was observed in a considerable proportion of pts (Table); 33 pts (55.9%) switching to CZP and 40 pts (60.6%) switching to ADA responded 12 wks later (Wk 24) by achieving DAS28(ESR) ≤3.2 or a DAS28(ESR) reduction from Wk 12 of ≥1.2 and were classed as secondary responders. Further improvements in various measures of clinical efficacy were observed, though less so than the level achieved by primary responders (Table). A similar proportion of ADA to CZP and CZP to ADA pts reported TEAEs occurring after treatment switch and within 70 days of the final dose of initial study drug (n=24, 40.7%; n=30, 45.5%). There were no reported serious infectious events (SIEs).

Conclusion: EXXELERATE demonstrated that efficacy can be achieved using a second TNFi in a proven primary TNFi failure pt population. Furthermore, these results expand current RCT data by providing, in a controlled setting, clinical evidence for the safety of an immediate switch from one TNFi to another without a washout period, and demonstrating no increase in SIEs. **References:** 1. Smolen J. Ann Rheum Dis 2015;75(1):3–15; 2. Singh J. Arthritis Rheumatol 2016;68(1):1–26; 3. Smolen J. Ann Rheum Dis 2014;73(3):492–502

Figure: EXXELERATE study design



[a] Week 12 non-responders did not have DAS28(ESR) LDA or reduction from baseline ≥1.2 at Week 12.

Table: The percentage of patients achieving clinical responses at comparative time points during the EXXELERATE study

Study visit (weeks post-switch)	ADA primary non-responders switched to CZP (n=57)	CZP primary non-responders switched to ADA (n=65)	CZP secondary responders (n=33)	ADA secondary responders (n=40)	Comparative study visit	CZP primary responders (n=353)	ADA primary responders (n=361)
ACR20							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	43.9	40.0	72.7	60.0	Wk 12	86.1	85.9
Wk 36 (24 wks)	29.8	35.4	51.5	57.5	Wk 24	85.6	85.0
Wk 64 (52 wks)	33.3	38.5	57.6	62.5	Wk 52	77.9	79.5
Wk 104	19.3	32.3	33.3	52.5	Wk 104	64.9	66.8
ACR50							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	22.8	16.9	39.4	27.5	Wk 12	51.3	53.2
Wk 36 (24 wks)	19.3	20.0	33.3	32.5	Wk 24	63.5	62.6
Wk 64 (52 wks)	26.3	27.7	45.5	45.0	Wk 52	60.6	64.0
Wk 104	15.8	24.6	27.3	40.0	Wk 104	53.3	56.8
ACR70							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	10.5	7.7	18.2	12.5	Wk 12	28.0	26.9
Wk 36 (24 wks)	10.5	10.8	18.2	17.5	Wk 24	39.1	40.4
Wk 64 (52 wks)	12.3	13.8	21.2	22.5	Wk 52	43.6	43.5
Wk 104	10.5	15.4	18.2	25.0	Wk 104	36.7	41.3
DAS28(ESR) LDA [a]							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	21.1	18.5	36.4	30.0	Wk 12	38.5	36.8
Wk 36 (24 wks)	14.0	16.9	24.2	27.5	Wk 24	51.8	46.0
Wk 64 (52 wks)	22.8	12.3	39.4	20.0	Wk 52	53.5	48.5
Wk 104	10.5	20.0	18.2	32.5	Wk 104	45.6	42.4
DAS28(ESR) REM [b]							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	5.3	9.2	9.1	15.0	Wk 12	21.5	21.3
Wk 36 (24 wks)	7.0	12.3	12.1	20.0	Wk 24	32.9	29.4
Wk 64 (52 wks)	7.0	10.8	12.1	17.5	Wk 52	31.4	32.1
Wk 104	5.3	9.2	9.1	15.0	Wk 104	30.0	27.1
CDAI LDA [c]							
Wk 12 (0 wks)	3.5	1.5	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	33.3	26.2	54.5	35.0	Wk 12	53.3	52.4
Wk 36 (24 wks)	24.6	23.1	42.4	37.5	Wk 24	66.9	62.3
Wk 64 (52 wks)	28.1	27.7	48.5	45.0	Wk 52	65.7	65.7
Wk 104	21.1	24.6	36.4	40.0	Wk 104	56.1	56.2
CDAI REM [d]							
Wk 12 (0 wks)	0.0	0.0	0.0	0.0	Baseline	0.0	0.0
Wk 24 (12 wks)	3.5	4.6	6.1	7.5	Wk 12	13.6	13.9
Wk 36 (24 wks)	7.0	12.3	12.1	20.0	Wk 24	24.9	22.2
Wk 64 (52 wks)	7.0	9.2	12.1	15.0	Wk 52	28.6	26.3
Wk 104	5.3	12.3	9.1	20.0	Wk 104	29.1	26.3

All patients received at least one dose of study drug after Week 12. The study finished at Week 104. Response defined as patients achieving DAS28(ESR) ≤3.2 or a DAS28(ESR) reduction from BL of ≥1.2 at Week 12. CZP and ADA secondary responders responded at Week 24; [a] DAS28(ESR) ≤3.2; [b] DAS28(ESR) <2.6; [c] CDAI ≤10; [d] CDAI ≤2.8. Non-responder imputation was used to impute missing values. ADA, adalimumab; CZP, certolizumab pegol; LDA, low disease activity; REM, remission.

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GlaxoSmithKline, Pfizer, Roche, UCB Pharma, 2,AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Pfizer, Roche, UCB Pharma, Vertex, 5; **C. Cioffi**, UCB Pharma, 3; **C. Ecoffet**, UCB Pharma, 3; **L. Ionescu**, UCB Pharma, 3; **L. Gervitz**, UCB Pharma, 3; **L. Peterson**, UCB Pharma, 3; **J. Smolen**, UCB Pharma, 2,UCB Pharma, 5,UCB Pharma, 9.

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Abstract Number: 603

Additional Efficacy Results of SB4 (Etanercept Biosimilar) up to Week 100: Comparison Between Continuing SB4 and Switching from Reference Etanercept (Enbrel®) to SB4

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Background/Purpose: SB4 is approved by the European Medicines Agency as a biosimilar of the reference etanercept (ETN). Long term safety and efficacy of SB4 up to Week 100 have been reported previously.[1] Additional long term efficacy results will be reported.

Methods: In the phase III 52-week randomized, double-blind period of the study, patients with moderate to severe rheumatoid arthritis (RA) were treated with either 50 mg/week SB4 or ETN with background methotrexate (MTX). Patients in Czech Republic and Poland were enrolled into the following 48-week open-label, extension period of the study and received SB4. Efficacy in terms of ACR responses, disease activity score based on 28 joints (DAS28), simplified disease activity index (SDAI), clinical disease activity index (CDAI), and health assessment questionnaire-disability index (HAQ-DI) up to week 100 were compared. Radiographic progression was measured through modified Total Share Score.

Results: 245 patients from the randomized, double-blind study period enrolled into the extension study: 126 patients continued to receive SB4 (SB4/SB4) and 119 patients switched from ETN to SB4 (ETN/SB4). The ACR responses were comparable between SB4/SB4 and ETN/SB4 and they were also sustained in the extension period. The mean DAS28, SDAI, and CDAI were comparable between SB4/SB4 and ETN/SB4 during the extension period (Figure). At Week 100, similar proportion of patients achieved low disease activity based on DAS28, SDAI, or CDAI (49.2% vs. 54.8%; 33.3% vs. 38.3%; 30.9% vs. 40.0% in SB4/SB4 and ETN/SB4, respectively) and remission based on DAS28, SDAI, or CDAI (30.3% vs. 34.8%; 30.9% vs. 33.9%; 32.5% vs. 28.7% in SB4/SB4 and ETN/SB4, respectively). Patient-reported outcome measured by HAQ-DI was also comparable between SB4/SB4 and ETN/SB4 up to week 100. Radiographic progression was comparable and negligible between SB4/SB4 and ETN/SB4.

Conclusion: Long-term efficacy including DAS28, SDAI, CDAI, and HAQ-DI was comparable between SB4/SB4 and ETN/SB4 during the extension period. Efficacy was sustained after switching from ETN to SB4.

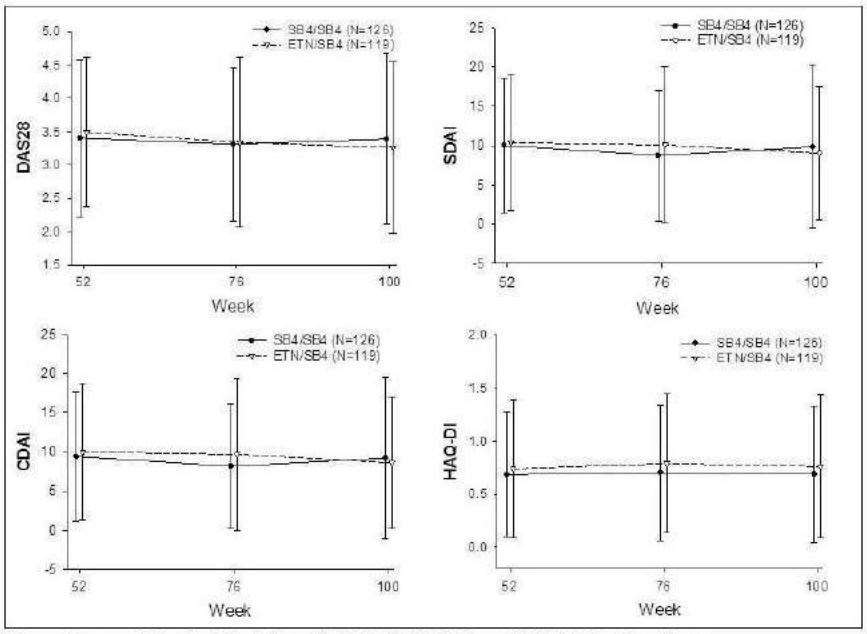

Figure. Mean and Standard Deviation of DAS28, SDAI, CDAI, and HAQ-DI after Transition

Reference

1. Emery P. et al. *Ann Rheum Dis* 2016;75(Suppl2): 236

Disclosure: P. Emery, Pfizer,MSD,Abbvie,BMS,UCB,Roche,Novartis,Samsung Bioepis, Sandoz, Eli Lillyand Company, 5; **J. Vencovský**, Biogen, Samsung Bioepis, 5; **A. Sylwestrzak**, Samsung Bioepis, 2; **P. Leszczyński**, Samsung Bioepis, Roche, MSD, Janssen, UCB, Novartis, GSK, BMS,, 2,Roche, MSD, UCB, Pfizer, Abbvie, 5; **W. Porawska**, Samsung Bioepis, 2; **B. Stasiuk**, Samsung Bioepis, 2; **J. Hilt**, Samsung Bioepis, 2; **Z. Mosterova**, Samsung Bioepis, 2; **S. Y. Cheong**, Samsung Bioepis, 3; **J. Ghil**, Samsung Bioepis, 3.

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Abstract Number: 604

Sustained Efficacy and Comparable Safety and Immunogenicity after Transition to SB5 (an Adalimumab Biosimilar) Vs. Continuation of SB5 or Reference Adalimumab (Humira®) in Patients with Rheumatoid Arthritis: Results of Phase III Study

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Background/Purpose: SB5 has been developed as a biosimilar of the reference adalimumab (ADL). The 24-week results of the phase III study have been reported.[1] Efficacy, safety, and immunogenicity results in the transition period (Week 24 to Week 52) will be presented.

Methods: Patients with RA were randomized in a 1:1 ratio to receive either 40 mg of SB5 or ADL every other week with background methotrexate. After 24 weeks of treatment, patients in the ADL group were re-randomized (1:1) to either be transitioned to SB5 (ADL/SB5) or continue on ADL (ADL/ADL) up to Week 50. Patients receiving SB5 continued to receive SB5 (SB5/SB5) but they followed the randomization procedure for blinding purposes. Efficacy, safety, and immunogenicity were assessed up to Week 52.

Results: After 24-weeks of treatment, 254 patients from SB5 continued to receive SB5 (SB5/SB5), 125 patients from ADL were transitioned to SB5 (ADL/SB5), and 129 patients from ADL continued to receive ADL (ADL/ADL). Baseline characteristics at baseline and disease activities at re-randomization were comparable across treatment groups. The ACR responses were sustained and comparable across treatment groups during the transition period in the full analysis set (Figure). At Week 52 the ACR20 response rates were 76.9% vs. 81.1% vs. 71.2% in SB5/SB5, ADL/SB5, and ADL/ADL in the per-protocol set. Other efficacy endpoints including radiographic change were also comparable across the treatment groups. The mean change from baseline in modified Total Sharp Score was 0.17 in SB5/SB5 vs. 0.25 in ADL/SB5 vs. 0.50 in ADL/ADL. The safety profile during the transition period was comparable across treatment groups. The proportion of patients with any treatment-emergent adverse events after transition was 32.3% in SB5/SB5, 37.6% in ADL/SB5, and 33.1% in ADL/ADL and two patients in ADL/ADL group only newly reported injection site reactions. The incidence of anti-drug antibody after transition was 15.7% vs. 16.8% vs. 18.3% in SB5/SB5, ADL/SB5, and ADL/ADL, respectively.

Conclusion: Efficacy, safety, and immunogenicity profiles were comparable between SB5/SB5, ADL/SB5, and ADL/ADL during the transition period (Week 24 to Week 52). There were no treatment emergent issues or clinically relevant

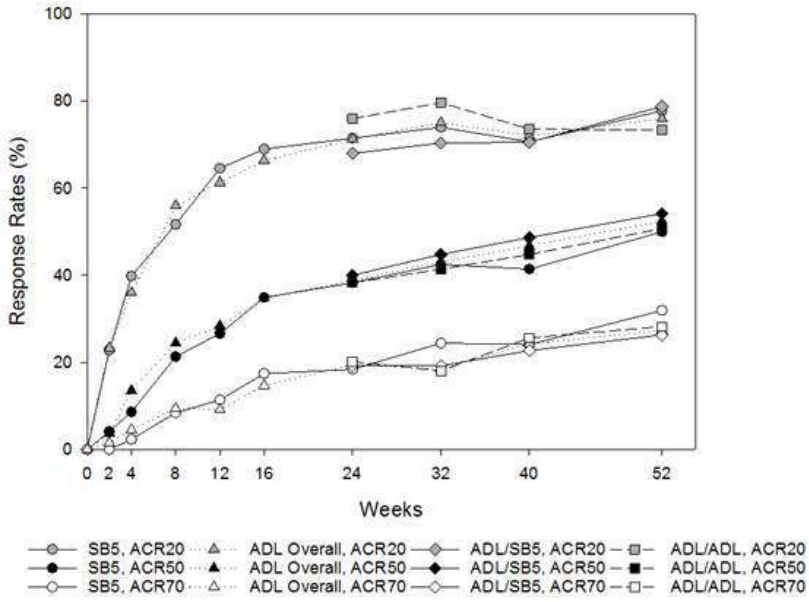

Figure. ACR Response Rates up to Week 52

immunogenicity precipitated by switching.

Reference 1. Weinblatt ME et al. *Arthritis Rheumatol.* 2015; 67 (suppl 10), 8L

Disclosure: M. Weinblatt, Amgen, BMS, Crescendo Bioscience, UCB, 2,Amgen, AbbVie, BMS, Eli-Lilly, Gilead, Merck, Pfizer Inc, Novartis, Roche, Samsung Bioepis, UCB, 5; **A. Baranauskaite**, Abbvie, Samsung Bioepis, 5; **J. Niebrzydowski**, Samsung Bioepis, 2; **E. Dokoupilova**, Samsung Bioepis, 2; **A. Zielinska**, Samsung Bioepis, 2; **K. Sitek-Ziolkowska**, Samsung Bioepis, 2; **J. Jaworski**, Samsung Bioepis, 2; **A. Racewicz**, Samsung Bioepis, 2; **M. Pileckyte**, Samsung Bioepis, 2; **K. Jedrychowicz-Rosiak**, Samsung Bioepis, 2; **V. Zhdan**, Samsung Bioepis, 2; **S. Y. Cheong**, Samsung Bioepis, 3; **J. Ghil**, Samsung Bioepis, 3.

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Abstract Number: 605

Assessment of Comparative Immunogenicity in Biosimilar Development: Immunogenicity and Pharmacokinetics Following a Single Dose of M923, a Proposed Biosimilar for Reference Adalimumab (HUMIRA®), Compared with US- and EU-Sourced Reference Adalimumab in Healthy Subjects

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Background/Purpose: M923 (BAX923), which is jointly being developed by Momenta and Baxalta, is a proposed biosimilar of reference adalimumab. Reference adalimumab is recognized to elicit antidrug antibodies (ADAs; seroconversion) in a significant proportion of patients, with a potential negative impact on efficacy. Host factors, including nature of the disease and background immunosuppressive therapy, are associated with the frequency of seroconversion. Normal healthy volunteers provide a relatively homogeneous and sensitive population in which to assess the relative immunogenicity of M923 and reference adalimumab with a focus on factors that are inherent to the products.

Methods: 324 healthy volunteers were randomized 1:1:1 to receive a single 40 mg dose of M923, US-sourced reference adalimumab, or EU-sourced reference adalimumab by subcutaneous injection then followed for 10 weeks, during which serum concentration of adalimumab and ADAs were recorded. Samples were screened for antibodies to M923, then confirmed for binding, sequentially, to EU reference adalimumab, US reference adalimumab, and M923. Samples positive on any confirmation assay were assessed for titer, neutralizing capacity (nADAs), and the presence of ADAs of IgE isotype. Bioequivalence of primary PK endpoints (C_{max}, AUC_{0-inf}, and AUC_{0-336}) was assessed in the primary analysis set (all evaluable subjects), and explored in subsets characterized by ADA and nADA status.

Results: The incidence, titer, time to emergence of ADAs, and proportion with nADAs were similar across groups (proportion of subjects with confirmed ADAs/nADAs positive titers: M923 = 78.0%/16.5%; US reference adalimumab = 80.6%/27.8%; EU reference adalimumab = 78.5%/20.6%). Presence of high titer nADAs was also associated with presence of IgE ADAs and with a reduction in exposure. PK bioequivalence, defined as 90% confidence intervals (CIs) for the geometric least squares mean ratios for all comparisons were within the confidence bounds of 80.00 to 125.00%, was achieved for all primary PK endpoints. Specifically, for the comparison of M923 with US reference adalimumab, the geometric LS mean ratios (90% CI) were C_{max} = 102.58 (97.31-108.14); AUC_{0-inf} = 104.20 (96.47-112.54); and AUC_{0-336} = 102.94 (97.88-108.27); similar results were observed for comparisons of M923 with EU reference adalimumab, and between US and EU reference adalimumab.

Conclusion: M923, demonstrated equivalent PK and comparable immunogenicity relative to both US- and EU-sourced reference adalimumab following administration of a single dose in normal healthy volunteers. Seroconversion and nADA formation were sufficiently frequent to support a robust comparison of immunogenicity and assessment of impact of ADA formation on PK.

Disclosure: J. Hillson, Momenta, 3,Momenta, 1; **T. Mant**, Quintiles Inc, 3; **T. Ganguly**, Momenta, 3; **W. Avery**, Momenta Pharmaceuticals, 3; **M. Rosano**, Momenta, 3; **C. Huntenburg**, Momenta, 3; **D. Palmer**, Shire, 3; **S. Darne**, Shire, 3; **B. Pavlova**, Shire, 3; **J. Doralt**, Shire, 3; **R. Reeve**, Quintiles, 3; **N. Goel**, Quintiles, 3; **D. Weilert**, Quintiles, 3; **P. Rhyne**, Q2 Solutions, 3; **J. Caminis**, Shire, 3; **J. Roach**, Momenta, 3.

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Abstract Number: 606

A Randomized, Double Blind, Single Dose Study to Assess the Pharmacokinetics, Safety, and Tolerability of ONS-3010 (Adalimumab, Oncobiologics, Inc.) Compared to Two Reference Products of Humira® (AbbVie) in Healthy Adult Subjects

Kenneth Bahrt[1], Joannes Reijers[2], Marlous Dillingh[2], Claudia Rehrig[1] and Jacobus Burggraaf[3], [1]Oncobiologics Inc, Cranbury, NJ, [2]Centre for Human Drug Research, Leiden, Netherlands, [3]Centre for Human Drug Research, Leiden,, Netherlands

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: ONS-3010 is being developed as a biosimilar candidate of Humira® (Adalimumab), a full-length recombinant human IgG1 monoclonal antibody specific for TNFα. This study evaluated the bioequivalence (BE) of single-dose pharmacokinetics (PK), safety and tolerability of ONS-3010 with specific assessment of immunogenicity compared to EU Humira® and US Humira®.

Methods: One hundred and ninety-eight (198) healthy male/female subjects (66 subjects per treatment group, gender balanced), were randomized to this double blind, single-dose study. The study duration was 14 weeks (screening: 4 weeks; PK/safety: 10 weeks). The subjects received a subcutaneous dose of 40 mg with either ONS 3010 or Humira® (EU or US product). PK and immunogenicity blood samples were collected at regular intervals. BE was assessed using general linear model procedures in SAS®, ANOVA on ln-transformed $AUC_{0-\infty}$, C_{max} (primary endpoints) and $AUC_{0\text{-last}}$. The ratio of geometric means with its 90% confidence intervals (CI), were calculated for $AUC_{0\text{-last}}$, $AUC_{0-\infty}$, and C_{max}. Equivalence bounds of 80.00-125.00% were used (ratio of geometric means [ONS-3010/Humira]: $AUC_{0-\infty}$, $AUC_{0\text{-last}}$, C_{max},). Adverse events (AEs) and serious AEs (SAEs) were monitored and recorded. Positive immunogenicity samples were investigated for specificity of binding.

Results: The PK profiles for EU Humira®, US Humira® and ONS-3010 were similar in shape (Figure 1). On the primary endpoints, $AUC_{0-\infty}$ and C_{max}, equivalence was demonstrated (i.e., ratio of geometric means ONS-3010/EU Humira® 1.03 [CI: 0.94 – 1.20] and 1.00 [0.92 – 1.08], ONS-3010/US Humira® 1.06 [0.94 – 1.20] and 1.06 [0.98 – 1.15], EU Humira®/US Humira® 1.04 [0.92 – 1.17] and 1.07 [0.99 – 1.15], for $AUC_{0-\infty}$ and C_{max} respectively). Equivalence was also demonstrated for the secondary PK endpoint, $AUC_{0\text{-last}}$. One SAE reported in the ONS-3010 treatment group led to hospitalization (bacterial abscess [Lymphadenitis colli]). AEs were evenly divided over treatments, usually mild in severity, and self-limiting (Table 1). Immunogenicity results showed similar profiles in the 3 treatment groups for anti-drug and neutralizing antibodies.

Figure 1 Concentration-Time Profiles

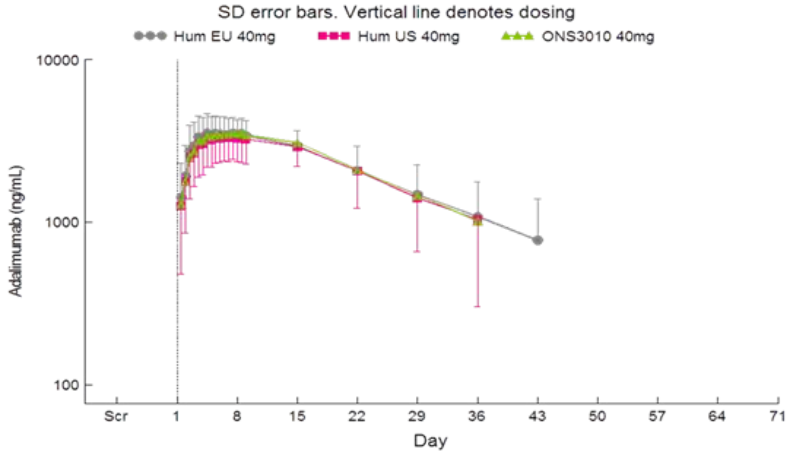

Table 1 Most Frequently Reported* Adverse Events

Preferred Term	ONS-3010 N (%)	Humira® EU N (%)	Humira® US N (%)
Burning sensation	12 (18.2)	29 (43.9)	31 (47.0)
Headache	29 (43.9)	20 (30.3)	27 (39.4)
Nasopharyngitis	12 (18.2)	19 (28.8)	12 (18.2)

*Regardless of relationship

Conclusion: The PK data for Humira® and ONS-3010 showed similar profiles over time. Equivalence was demonstrated on the primary ($AUC_{0-\infty}$ and C_{max}) and secondary (AUC_{0-last}) endpoints. There was no significant difference in immunogenicity or overall safety, except for a reduction in the burning sensation at the ONS-3010 injection site.

Disclosure: K. Bahrt, Oncobiologics, Inc, 3; **J. Reijers**, Oncobiologics, Inc, 2; **M. Dillingh**, Oncobiologics, Inc, 2; **C. Rehrig**, Oncobiologics, Inc, 3; **J. Burggraaf**, Oncobiologics, Inc, 2.

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Abstract Number: 607

The Clinical Response to Biologic and Non-Biologic Disease Modifying Antirheumatic Drugs (DMARDs) According to Gender in a French-Canadian Population with Rheumatoid Arthritis (RA)

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Background/Purpose: Several studies have reported that women with RA had higher level of pain, disease activity and functional impairment compared to men. In addition, women also seem to response less than men to biologic DMARDs (bDMARDs) and non-biologic DMARDs (nbDMARDs). Outcomes: Describe the disease activity and the clinical response to methotrexate (MTX) and bDMARDs in men and women with RA and evaluate the factors that could influence difference observed between genders.

Methods: Data on RA patients starting a treatment with MTX or a first bDMARD were extracted for the Rhumadata clinical database used in two rheumatologic centers. The baseline characteristics, the duration of the disease before the initiation of treatment, the concomitant treatments, the inflammatory markers (sedimentation rate, C-reactive protein) and the immunologic factor (rheumatoid factor, Anti-CCP) were extracted according to gender. A univariate analysis comparing the mean change between the men and women in the methotrexate and in the biologic groups was conducted for the « Health Assessment Questionnaire (HAQ)» and the « Clinical Disease Activity Index (CDAI) » at 6 and 12 months. A mutivariate analysis comparing those same parameters to adjust for the different baseline's characteristics is being conducted.

Results: 922 women (mean age: 53 (± 13); mean disease duration: 1.3 years (± 5.3)) and 316 men (mean age: 57 (± 12); mean disease duration: 1.5 years (± 5.4)) started MTX. 548 women (mean age: 54 (± 13); mean disease duration: 7.6 years (± 7.7)) and 159 men (mean age: 56 (± 12); mean disease duration: 6.6 years (± 7.4)) started a first bDMARD (TNFi: 84%). In the univariate analysis, the mean HAQ score at baseline, 6 and 12 months were higher in women than in men in the MTX group. However, both groups had a similar means change in HAQ score at 6 and 12 months. For the CDAI score, women and men in both groups had similar score at baseline, 6 and 12 months. Mean change in the CDAI score at 6 and 12 months was a slightly higher in men than women in both treatment groups, but the change was not statistically significant.

Conclusion: In this cohort of RA patients, women seem to have a more severe functional impairment throughout their illness, but do not seem to have a poorer response to nbDMARDs and bDMARDs compared to men. The analysis evaluating factors influencing disease activity changes over time in men and women is ongoing. Table

	Methotrexate			**First Biologic Agent**		
	Male	Female	P value	Male	Female	P value
N	316	922		159	548	
Mean HAQ Score						
Baseline	0.68 (0.54)	1.04 (0.66)	0,0005	1.12 (0.67)	1.33 (0.63)	0,0030
6 months	0.26 (0.38)	0.64 (0.66)	0,0001	0.56 (0.63)	0.86 (0.72)	0,0035
12 months	0.30 (0.44)	0.68 (0.62)	0,0024	0.55 (0.59)	0.84 (0.69)	0,0001
Mean change in HAQ Score						
6 months	-0.43 (0.50)	-0.37 (0.55)	0,5250	-0.48 (0.60)	-0.41 (0.59)	0,4590
12 months	-0.42 (0.49)	-0.40 (0.63)	0,8451	-0.56 (0.69)	-0.42 (0.56)	0,1683
Mean CDAI Score						
Baseline	19.95 (15.50)	20.64 (13.25)	0,8077	27.68 (14.12)	24.77 (12.03)	0,1210
6 months	5.20 (4.05)	8.09 (6.56)	0,0429	10.29 (10.42)	7.39 (6.14)	0,1689
12 months	4.80 (8.20)	6.40 (6.79)	0,4788	4.85 (4.66)	6.38 (5.88)	0,2336
Mean Change in CDAI Score						
6 months	-11.94 (15.00)	-11.40 (13.65)	0,8918	-21.10 (11.31)	-18.03 (11.91)	0,2273
12 months	-16.31 (18.37)	-12.11 (13.83)	0,3784	-25.64 (12.79)	-21.46 (11.50)	0,1257

Disclosure: S. Lagacé, None; **L. Bessette**, AbbVie, 2,Amgen, 2,BMS, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,UCB, 2,AbbVie, 5,Amgen, 5,BMS, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5,AbbVie, 8,Amgen, 8,BMS, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8,UCB, 8; **L. Coupal**, None; **D. Choquette**, None.

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Abstract Number: 608

Initial Intensive Therapy of Adalimumab and Methotrexate Is Associated with Long-Term Structural Remission and Low Disease Activity after

Adalimumab Discontinuation Is Maintained up to 3 Years in Japanese Patients: Hopeful-3 Study

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Background/Purpose: Although available data have suggested successful withdrawal of anti-TNF monoclonal antibodies after achieving low disease activity (LDA) or remission in patients with rheumatoid arthritis (RA), longer term follow-up data are needed to confirm these findings. The purpose of this study was to evaluate the feasibility of long-term adalimumab (ADA) discontinuation after achievement of LDA in Japanese patients with early RA.

Methods: In HOPEFUL-1, patients received initial therapy with either ADA 40 mg eow plus methotrexate (MTX weekly 6-8 mg) (intensive therapy) or MTX alone (MTX 6-8mg weekly, standard therapy) for 26 weeks, together followed by OL ADA+MTX for 26 weeks. In HOPEFUL-2, patients, who have continued ADA at the end of HOPEFUL-1, received OL ADA+MTX (ADA continuation) or OL MTX alone (ADA discontinuation) based on patient and physician decision for 52 weeks. HOPEFUL-3 was an observational study which included patients who had completed HOPEFUL-2 and continued for up to an additional 104 weeks. To assess efficacy, the primary endpoints were changes in 28-joint disease activity scores using C-reactive protein (DAS28-CRP) and the proportion of patients who achieved sustained LDA (DAS28–CRP <3.2) at week 208. Other endpoints, including modified total Sharp score (mTSS), were also evaluated. We compared the efficacy results between patients who received initial intensive therapy and standard therapy in HOPEFUL-1, and between patients who continued and discontinued ADA in HOPEFUL-2, using Fisher's exact test or the chi-square test for categorical variables, and the Wilcoxon rank sum test for continuous variables. To assess safety, all adverse events during HOPEFUL-3 were recorded. Fisher's exact test was used to compare the total number of adverse events between the ADA continuation and discontinuation groups.

Results:

Of 172 patients enrolled, 135 (ADA continuation, n=61; ADA discontinuation, n=74) with DAS28–CRP at both week 52 (start of HOPEFUL-2) and week 208 (end of HOPEFUL-3) were included in the effectiveness analysis. . Initial intensive therapy was associated with better outcome in terms of structural remission at week 208 compared with standard therapy (64% vs. 30%). At week 208, 59/74 (79.7%) and 58/61(95.1%) patients who discontinued and continued ADA, respectively, were in sustained LDA (p=0.01). The incidence of adverse events was significantly lower in the ADA discontinuation group than in the ADA continuation group (9.7% vs. 34.2%, p<0.001).

Conclusion: Approximately eighty percent of patients who discontinued ADA for 3 years after achieving LDA with ADA+MTX had sustained LDA with a lower incidence of adverse events than patients who continued ADA. Initial intensive therapy with ADA+ MTX demonstrated greater structural remission at 4 years compared to initial standard therapy with MTX alone despite 3 years of ADA discontinuation.

Yamanaka, AbbVie GK, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Otsuka, Pfizer, Takeda, UCB, 2,AbbVie GK, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Otsuka, Pfizer, Takeda, UCB, 5,AbbVie GK, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Otsuka, Pfizer, Takeda, UCB, 8; **N. Ishiguro**, Abbott Japan, Astellas, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Pfizer, Takeda, 2,AbbVie GK, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Otsuka, Pfizer, Takeda, UCB, 8; **N. Miyasaka**, AbbVie, Astellas, Banyu, Chugai, Daiichi Sankyo, Eisai, Janssen, Mitsubishi Tanabe, Takeda, Teijin, 2; **K. Kawana**, Abbvie, 1,Abbvie, 3; **N. Agata**, Abbvie, 1,Abbvie, 3; **T. Takeuchi**, AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Janssen, Mitsubishi Tanabe, Nippon Shinyaku, Pfizer, Sanofi, Santen, Takeda, Teijin, 2,AstraZeneca, Eli Lilly, Novartis, Mitsubishi Tanabe, Asahi Kasei Medical, 5,AbbVie, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Pfizer, Takeda, 8.

Abstract Number: 609

Economic Impact of Adalimumab Treatment in Japanese Patients with Rheumatoid Arthritis from the Anouveau Study (Clinicaltrial.gov: NCT01346488)

Yoshiya Tanaka[1], Kiyotaka Yamazaki[2], Ryo Nakajima[2], Shuichi Komatsu[3], Naoki Agata[4], Ataru Igarashi[5], Toshiro Tango[6] and Tsutomu Takeuchi[7], [1]University of Occupational and Environmental Health, Kitakyushu, Japan, [2]Post Marketing Study Group, Medical, AbbVie GK, Tokyo, Japan, [3]Scientific Project Manager Group, Medical, AbbVie GK, Tokyo, Japan, [4]Medical Communication, Medical, AbbVie GK, Tokyo, Japan, [5]Department of Drug Policy & Management, Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan, [6]Center for Medical Statistics, Tokyo, Japan, [7]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan
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Background/Purpose: Patients with Rheumatoid Arthritis (RA) experience loss of productivity such as missing their work and lowering their performance incurred by impaired physical functioning. Treatment with ADA resulted in significant sustained improvements in RA-related work productivity and activity impairment (AI) in Japanese patients with RA (DOI: 10.1136/annrheumdis-2016-eular.3068). The objective of this study is to assess economic impact of ADA on Japanese RA patients in the real-world setting.

Methods: In this 48-week, multicenter, prospective single-cohort study (ANOUVEAU study), 1,973 RA patients treated with ADA were asked to complete self-reported questionnaire on their work every 12 weeks. Of those, the data of 1,196 patients were available and were included in this analysis. The cohort was stratified into the following baseline employment status: Paid Worker (PW), employed for ≥ 35 hours/week n=649, Part Time Worker (PTW), employed for < 35 hours/week n=172 and Home maker (HM), non-employed n=375. Work-related outcomes including absenteeism (work time missed), presenteeism (impairment while working) and Overall Work Impairment (OWI) as well as AI were evaluated using the Work Productivity and Activity Impairment questionnaire for Rheumatoid Arthritis (WPAI-RA). The amount of productivity loss was estimated by multiplying absenteeism, presenteeism and OWI by the national average occupational wage rates for PW and PTW, and by multiplying AI by the estimated wage rate for domestic work for HM. Primary outcomes were 12-week change in productivity loss and cumulative reductions achieved with ADA treatment

during the study period.

Results: The amounts of productivity loss estimated from OWI at baseline and 12-week productivity loss at week 12, week 24, week 36, and week 48 were 5,106 USD, 3,322 USD ($p< 0.01$), 2,978 USD ($p< 0.01$), 2,901 USD ($p< 0.01$), and 2,828 USD ($p< 0.01$) for PW, and 3,791 USD, 2,899 USD ($p= 0.11$), 2,618 USD ($p= 0.02$), 2,424 USD ($p< 0.01$), and 2,278 USD ($p< 0.01$) for PTW, respectively (1 USD= 110 JPY, p-value for change from baseline, t-test). Moreover, the productivity loss estimated from AI at week 12, 24, 36 and 48 were 4,261 USD, 2,954 USD ($p< 0.01$), 2,618 USD ($p< 0.01$), 2,623 USD ($p< 0.01$) and 2,558 USD for HM, respectively ($p< 0.01$). The cumulative reductions in productivity loss for OWI, obtained from ADA treatment, at week 48 were 6,740 USD for PW and 3,148 USD for PTW. The reduction for AI at week 48 was 6,239 USD for HM.

Conclusion: In this study, the annual amounts of reduction in productivity loss of RA patients achieved from ADA treatment were estimated 6,740 USD for PW, 3,148 USD for PTW and 6,239 USD for HW. Given that the average annual income in Japan in 2014 was 37,727 USD, the results show that ADA has considerable economic impact on RA patients.

Disclosure: Y. Tanaka, Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, 2,Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline, 5,Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline, 8; **K. Yamazaki**, AbbVie GK, 3; **R. Nakajima**, AbbVie GK, 3; **S. Komatsu**, AbbVie GK, 3; **N. Agata**, AbbVie GK, 1,AbbVie GK, 3; **A. Igarashi**, Pfizer Japan Inc., CSL Behring Japan Inc., Gilead Science K.K., Fuji Film K.K., 2,Novartis Pharama K.K., AbbVie GK, Milliman Inc., Sony Inc., Eli Lilly Japan K.K., 5,Chugai Pharmaceutical Co. Ltd., CRECON Research and Consulting Inc., Terumo Corporation, Bristol-Myers Squibb K.K., Creativ Ceutical K.K., 8; **T. Tango**, AbbVie GK., Ajinomoto Pharma, Takeda Pharmaceutical Co. Ltd., Lion Corporation, 5; **T. Takeuchi**, AbbVie, Astellas, Bristol-Myers, Chugai, Daiichi Sankyo, Eisai, Janssen, Mitsubishi Tanabe, Nippon Shinyaku, Pfizer, Sanofi, Santen, Takeda, Teijin, 2,AstraZeneca, Eli Lilly, Novartis, Mitsubishi Tanabe, Asahi Kasei Medical, 5,AbbVie, Bristol-Myers Squibb, Chugai, Eisai, Janssen, Mitsubishi Tanabe, Pfizer, Takeda, 8.

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Abstract Number: 610

A Systematic Review and Meta-Analysis of Comparative Efficacy of Biologics in Treating Patients with Rheumatoid Arthritis: Assessment of Long-Term Radiographic Progression from Published Clinical Trials

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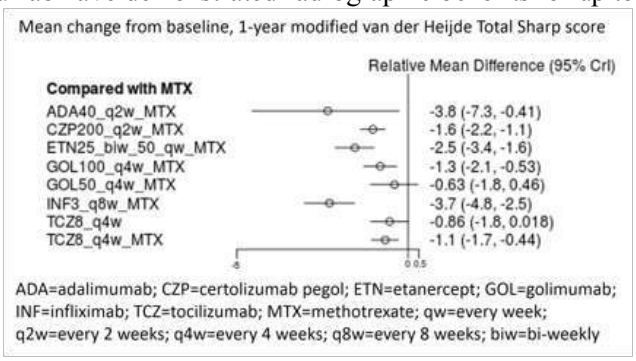
Background/Purpose: Previously, several studies have meta-analyzed clinical, functional or structural efficacy of biologics in treating rheumatoid arthritis (RA) patients. However, the comparative efficacy of biologics in inhibiting radiographic progression from a long-term perspective is still not fully understood. We compared 1-year radiographic efficacy of biologics using a Bayesian network meta-analysis (NMA), and reviewed radiographic data for up to 10 years

follow-up.

Methods: A systematic literature search of published peer-reviewed articles and scientific meeting abstracts identified randomized controlled trials investigating approved biologic therapies in combination with methotrexate (MTX) or tocilizumab alone in predominantly biologic-na•ve (< 20% biologic experienced) RA patients. Structural damage was analyzed as change from baseline using the modified van der Heijde Total Sharp Score (vdHS). One-year data were included in the NMA. Model parameters were estimated in a Bayesian framework using noninformative prior distributions. Longer term data (>1 year) was reviewed qualitatively in absence of sufficient data points for analysis. To assess the effect of biologic therapies in specific subpopulations, subgroup analyses were performed on: DMARD na•ve, DMARD inadequate responders, early RA, and established RA.

Results: Eleven clinical trials were identified and included in the NMA model. All biologics in combination with MTX showed decreased radiographic progression at 1 year compared to MTX alone, as defined by negative mean difference in vdHS change (Figure). Most interventions showed statistically significant effect, except for golimumab 50 mg every 4 weeks and tocilizumab 8mg/kg every 4 weeks.The largest statistically significant mean difference at 1 year was in adalimumab, where the increase in vdHS was 3.8 fewer units in patients administered adalimumab 40 mg every 2 weeks + MTX compared with those receiving MTX alone. Patients treated with infliximab 3 mg/kg every 8 weeks had the next highest relative effect at -3.7 versus MTX alone. Longer term radiographic data were found in 8 unique trials spanning 2 to 10 years of follow-up that demonstrate sustained slowing of radiographic progression for the following biologics (abatacept, certolizumab, etanercept, golimumab, infliximab and tocilizumab) in combination with MTX and adalimumab (+/-MTX). While the long term data did not contradict the efficacy of the 1-year outcomes, only 3 biologics (adalimumab, golimumab, tocilizumab) had 5 years of follow-up and only adalimumab had 10 years of follow-up. Subgroup results yielded consistent findings.

Conclusion: Biologics generally inhibit the progression of structural damage from a long-term perspective. Although some biologics like adalimumab have demonstrated radiographic benefits for up to 10 years, more research is needed to replicate this finding.



Disclosure: E. Murray, Doctor Evidence, AbbVie, 3; **Y. Butylkova**, Doctor Evidence, AbbVie, 3; **A. Ellis**, Doctor Evidence, AbbVie, 3; **M. Skup**, AbbVie, 3,AbbVie, 1; **J. Kalabic**, AbbVie Inc, 1,AbbVie Inc, 3; **V. Garg**, AbbVie Inc, 1,AbbVie Inc, 3.

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Abstract Number: 611

Analysis of a German Subpopulation with Active Rheumatoid Arthritis Treated with Golimumab As Add-on Therapy to Disease-Modifying Antirheumatic Drugs

Hendrik Schulze-Koops[1], Jürgen Wollenhaupt[2], Marita Winnemöller[3], **Ines Klaudius**[3] and Helena Löffler[3], [1]Division of Rheumatology, Division of Rheumatology and Clinical Immunology, Medizinische Klinik und Poliklinik IV, University of

Munich, Munich, Germany, [2]Schön Klinik Hamburg-Eilbek, Hamburg, Germany, [3]Medical Affairs, MSD Sharp & Dohme GmbH, Haar, Germany

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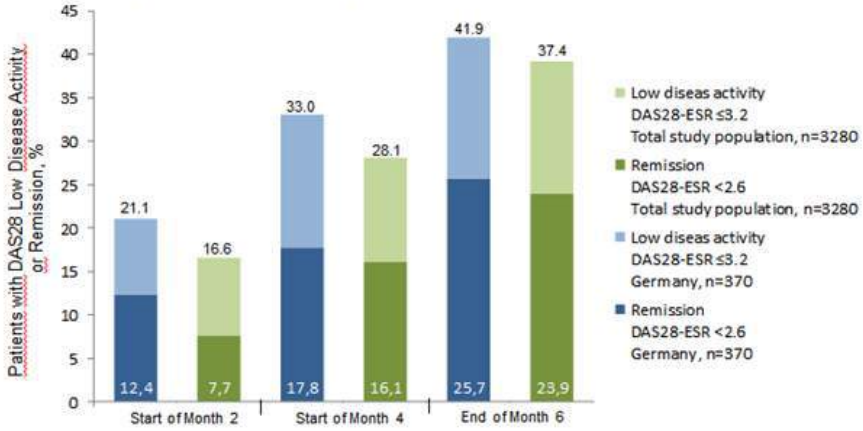
Session Time: 9:00AM-11:00AM

Background/Purpose: In previous clinical studies the human monoclonal TNFα-antibody golimumab (GLM) showed a good clinical response and a favorable benefit:risk profile in the treatment of moderate to severe active rheumatoid arthritis (RA). This was also shown in the clinical practice of the GO-MORE-study*. Until today it has not been examined whether the gathered GO-MORE study results can be referred to the clinical practice in Germany. The scope of the German subpopulation (GER) analysis was to investigate which are the treatment modalities of GLM in combination with predominately used methotrexate (MTX) and the different doses as well as other DMARD-combinations (e.g. leflunomide, LEF).

Methods: GO-MORE was a large open-label, multinational, prospective study in biologic-naïve patients (pts) with active RA*. The GER (n=370) was analysed in the context of the total study population (TSP, n=3.280; including GER) – purely descriptively as no formal comparison was performed. Good/moderate EULAR-(DAS28-ESR)-response depending on different DMARD-combinations and quality of life were evaluated. Enrolled pts (DAS28-ESR ≥3.2 despite DMARD-therapy) received 50mg GLM SC once monthly for 6 months.

Results: Within both groups females were more often affected than males (82.8% in TSP; 74.1% in GER). After 6 months of treatment 80.3% (297/370) of the pts of the GER achieved good/moderate EULAR-(DAS28-ESR)-response (TSP 82.1% (2.692/3.280)). 70.5% received GLM as add-on-therapy to MTX-treatment (81.2% TSP). The pts were preferably treated with GLM in combination with only MTX (207/368, 56.3%). At 6 months good/moderate EULAR-(DAS28-ESR)-response was achieved by 81.2% of the GLM+MTX treated pts (GLM+LEF (66/368, 17.9%): 81.8%; GLM+MTX+LEF (34/368, 9.2%): 73.5%) and furthermore 25.7% of the GER pts got into remission. GLM was well tolerated.

Figure: Percentage of patients achieving DAS28 remission/low disease activity (GER and TSP)



MTX 15mg/week was most frequently used (29.7% compared to >15mg MTX/week: 22.2% and <15mg MTX/week: 18.7%). The respective EULAR-good/moderate-response rates at 6 months were: 82.7% (110/368), 78% (82/368) and 78.3 % (69/368). Moreover the good clinical response rates were concordant with the improvement of functionality and the quality of life. At 6 months 31.1% of the pts showed no/minimal functional impairment (HAQ-DI≤0.5) and the EQ-5D increased from 0.49 to 0.67 (37%).

Conclusion: German pts showed continuous clinical improvement rates over 6 months when treated with GLM, regardless to the chosen concomitant LEF/MTX-therapy. The collected data concerning EULAR-(DAS28-ESR)-response, quality of life and safety profile were comparable to those of the multinational GO-MORE-study. This validates the applicability of

the data from the multinational GO-MORE-study to German clinical practice. **Reference:** * Combe B, et al. Ann Rheum Dis 73:1477–1486

Disclosure: H. Schulze-Koops, MSD, 5; **J. Wollenhaupt**, MSD, 5,MSD, 8; **M. Winnemöller**, MSD Sharp Dohme GmbH, 3; **I. Klaudius**, MSD Sharp Dohme GmbH, 3; **H. Löffler**, MSD Sharp Dohme GmbH, 3.

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Abstract Number: 612

Long-Term Sustainability of TNF-Blocker Injection Spacing in Rheumatoid Arthritis: Results of a 3-Year Long-Term Observational Follow-up of a Tapering randomised Controlled Trial

Johanna Sigaux[1], Florian Bailly[2,3], Frédérique Gandjbakhch[1,3], Violaine Foltz[1,3], Florence Tubach[4,5], Laure Gossec[1,6] and Bruno Fautrel[1,7], [1]Rheumatology, Pitié Salpêtrière Hospital, Paris, France, [2]rheumatology, Pitié Salpêtrière Hospital, paris, France, [3]Sorbonne Universités, UPMC Univ Paris 06, Paris, France, Paris, France, [4]Aix-Marseille University, Marseille, France, [5]Université Pierre et Marie Curie (UPMC)-Paris 6; APHP, Pitié Salpêtrière Hospital, Département Biostatistics and Public health, Pharmacoepidémiology center (Cephepi), 7501875013, Paris, France ;, Paris, France, [6]Sorbonne Universités, UPMC University Paris 06, Paris, France, Paris, France, [7]GRC08, Sorbonne Universités, UPMC Univ Paris 06, Paris, France, Paris, France

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Tapering of TNF blockers (TNFb) in rheumatoid arthritis (RA) patients in sustained remission is feasible in short-term randomized controlled trials (RCT). Less data are available on the sustainability of such a strategy over a longer term in real life settings. The main objective was to assess the probability of sustained dose reduction or discontinuation of TNFb in a 3-year long-term observational follow-up of the *Spacing of TNFb injections in Rheumatoid ArthritiS Study (STRASS)*. This trial compared the effect of progressive spacing of TNF-blocker injections (S arm) to their maintenance (M arm) for patients with established RA in remission for at least 6 months.

Methods: The STRASS investigators of the STRASS trial were contacted between April and October 2015, i.e., 3 years after the end of the trial, to collect evolution data at 1, 2 and 3 years after trial completion of patients having completed the RCT. During this long-term follow-up period, physicians were free to either keep the same regimen as in the arm patients were initially randomized or change injections frequency or drugs. The main endpoints were the rate of patients with spaced TNFb injections, the rate of TNFb-free patients and the mean TNFb dose compared to full dose or dose quotient (as a % of full dose).

Results: Ninety-six patients (76.2% of the completer population) had data available up to 3 years. At this term, mean DAS28 was 2.6±1.3 (respectively 2.7±1.4 in the initial Maintenance-arm, 2.6±1.2 in the initial Spacing-arm, p=0.89) and 72.9% were in low disease activity or remission (respectively 72.1% and 73.0%, p=0.93) (Table 1). Thirty patients (31.2%) had a tapered regimen (respectively 30.8% and 31.8%, p=0.96) and 11.5% (respectively 5.8% and 18.2%, p=0.07) discontinued TNFb (Figure 1). The mean TNFb dose quotient among the 96 patients was 72% of full dose (respectively, 77 and 66%, p=0.16). Eighteen (30.2%) had structural damage progression during the follow-up (respectively 25.0% and 36.8%).

Conclusion : Sustained TNFb de-escalation (injection tapering or discontinuation) is achievable in only 43% of patients over 3 years with limited dose reduction (28% on average). More optimal strategies remain needed to durably maintain remission in patients for whom bDMARD have been tapered or discontinued. Table 1 Patient outcome over 3 years of follow up

	Baseline	**3-year follow-up**		
	Total (n=96)	Total (n=96)	Initial M-arm (n=52)	Initial S-arm (n=44)
Disease activity				
Tender joint count (28 joints)	2.4±4.9	1.5±2.5	1.8±2.9	1.1±1.9
Swollen joint count (28 joints)	1.0±1.9	1.1±2.5	1.2±2.8	0.9±2.1
ESR, mm/1st hour	15.9±11.7	17.8±15.7	18.8±2.8	16.6±10
CRP, mg/L	3.8±5.2	5.6±12.5	7.4±16,2	3.6±4.6
Normal acute phase reactant , n (%)	59 (61.5)	54 (56.2)	30 (57.7)	24 (54.5)
DAS28	2.4±1.2	2.6±1.3	2.7±16,2	2.63±1.2
bDMARD intake				
Any TNFb	82 (85.4)	72 (75.0)	41 (78.8)	31 (70.4)
ADA, n (%)	35 (36.5)	30 (31.2)	17 (32.7)	13 (29.5)
ETA, n (%)	47 (48.9)	42 (43.7)	24 (46.1)	18 (40.9)
Other bDMARD, n (%)	2 (2.1)	13 (13.5)	8 (15.4)	5 (11.4)
Full dose, n (%)	60 (62.5)	44 (45.8)	27 (51.9)	17 (38.6)
Tapered regimen, n (%)	21 (21.9)	30 (31.2)	16 (30.8)	14 (21.8)
Discontinuation, n (%)	12 (12.5)	11 (11.5)	3 (5.8)	8 (18.2)
Switch from another bDMARD	4 (4.2)	18 (18.7)	10 (19.2)	8 (18.2)
Dose quotient, mean (sd)	0.75±0.37	0.72±0.36	0.77±0.33	0.66±0.39

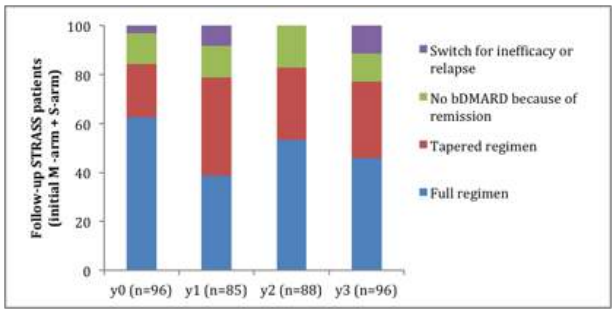

Figure 1 bDMARDs intake over time

Disclosure: J. Sigaux, None; **F. Bailly**, None; **F. Gandjbakhch**, None; **V. Foltz**, None; **F. Tubach**, None; **L. Gossec**, None; **B. Fautrel**, None.

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Abstract Number: 613

Immunogenicity of Anti-TNF Therapies in Patients with Inflammatory Rheumatic Diseases and Secondary Failure: A Multicentre Study of 570 Patients

Alejandro Balsa[1], Raimon Sanmarti[2], José Rosas[3], Susana Gomez Castro[4], Ana Cabez[4], Victor Martin[4] and María Montoro[4], [1]Rheumatology, IdiPAZ, Hospital Universitario La Paz, Madrid, Spain, [2]Rheumatology Department, Hospital Clínic de Barcelona, Barcelona, Spain, [3]Rheumatology, Hospital Marina Baixa, Villajoyosa (Alicante), Spain, [4]Pfizer, Madrid, Spain

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Session Time: 9:00AM-11:00AM

Abstract

Immunogenicity of anti-TNF therapies in Patients with inflammatory rheumatic Diseases and secondary failure: a multicentre study of 570 patients.

Background/Purpose: The treatment of rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA) has been greatly improved by the introduction of TNF inhibitors (TNFi). However, a proportion of patients receiving these biologic therapies still persist with active disease, either because the treatment fails to initiate a response (primary failure), or initial responsiveness gives rise to non-response (secondary failure). One of the potential reasons for secondary failure is the development of anti-drug antibodies. The **primary objective** of the study was to evaluate the prevalence of anti-drug antibodies in patients with RA or SpA who had a secondary failure to anti-TNF therapy. **Secondary** objectives included the evaluation of the relationship between anti-TNF concentration, presence of antibodies against anti-TNF, and clinical response. The study **also aimed** to evaluate the relationship between presence of antibodies against anti-TNF and concomitant use of DMARDs, **and** the correlation of antidrug antibody positivity and RF and anti-CCP status in patients with RA.

Methods: Cross-sectional, observational study in 45 rheumatology centers across Spain between November 2012 and July 2014. Patients were eligible for inclusion if they were aged ≥18 years, had active RA or SpA (including PsA), and had received and complied with anti-TNF [etanercept (ETN), infliximab (INF) or adalimumab (ADA))] treatment. Patients with secondary failure to anti-TNF at the time of the study visit were consecutively included. Secondary failure was defined as: good response during at least three months (Disease Activity Score (DAS28) ≤3.2, Ankylosing Spondylitis Disease Activity Score [ASDAS] ≤ 2.1 or Bath Ankylosing Spondylitis-Disease Activity Index [BASDAI] < 4) to the current anti-TNF and current moderate-to-high disease activity (DAS28 >3.2 or ASDAS >2.1 or BASDAI ≥ 4). Concomitant non-biologic DMARDs during the observation period was permitted. Trough serum anti-TNF concentration and serum anti-drug antibody concentration were measured with two-site enzyme-linked immunosorbent assay (ELISA) using the Promonitor® (Proteomika) kits. All assays were performed in a central reference laboratory. Tests were considered positive when serum drug levels and anti-drug antibody concentrations exceeded stated limits (INF: 50µg/ml and 37 AU/ml; ADA 4 µg/ml and 35 AU/ml; ETN: 52 µg/ml and 138 AU/ml, respectively). Demographic and clinical characteristics were summarised using descriptive statistics. Quantitative variables were analysed using measurements of central tendency and of dispersion. Qualitative variables were defined according to their absolute and relative frequencies. Student's t-test, Mann-Whitney-U test or Kruskall Wallis H test were used to compare quantitative variables and Pearson's chi-square or Fisher exact tests for qualitative variables.

Results: A total of 583 patients with secondary failure were recruited into the study and 570 were considered evaluable (RA, n=276; SpA, n=294). Patient demographics and patient characteristics were significantly different between patients with RA and SpA at baseline. Patients with RA were majority female (80%), older and took longer to obtain good clinical disease control; more patients with RA than SpA were taking concomitant DMARDs (83 vs 47%), but approximately 75% of patients in both groups took concomitant methotrexate. 114/570 (20.0%) patients with secondary treatment failure developed anti-drug antibodies (Table 1). 51/188 (27.1%) patients were found to be positive for anti-INF antibodies and 63/217 (29.0%) patients for anti- ADA antibodies. Significantly more patients with SpA had anti-INF antibodies than those with RA (23% vs 15.9%; P=0.015). Antibodies were not detected in patients treated with ETN. In patients treated

with ADA and INF, the majority of patients with no detectable drug levels also had anti-drug antibodies (Table 2). Low serum drug levels were detected mainly in patients with no anti-drug antibodies, though some patients with antibodies still had low but measurable levels of drug. Of the 114 patients who developed anti-drug antibodies, 81% of them had no detectable drug levels in their serum. The proportion of patients with anti- ADA and anti-INF antibodies was statistically lower in patients receiving concomitant DMARDs versus those on monotherapy ($p<0.05$). No statistically significant differences were observed between groups of patients with or without anti-drug antibodies, and positive levels of RF or anti-CCP antibodies for any biologic treatment for RA

Conclusion: In this observational study of patients diagnosed with RA or SpA, we found that antibodies against TNFi were present in 20% of patients (28% of those treated with monoclonal antibodies [63/217 (29%) treated with ADA; 51/188 (27%) treated with INF and in any patient treated with ETN] who developed secondary failure to TNFi. Most patients with antidrug antibodies had no detectable trough drug serum levels. The development of anti-drug antibodies is a a major contributor to secondary treatment failure in patients treated with monoclonal antibodies, immunogenicity could not explain a significant proportion of secondary failures in this population. Further investigations are needed to determine all possible causes of failure to anti-TNF therapy

Table 1. Prevalence of anti-drug antibodies (whole cohort; n=570)

	SpA	RA	P-value	Total
N Anti-drug antibodies, n (%)	294 70 (23.8)	276 44 (15.9)	0.015	570 114 (20.0)
N Anti-adalimumab antibodies, n (%)	107 35 (32.7)	110 28 (25.5)	0.221	217 63 (29.0)
N Anti-etanercept antibodies, n (%)	75 0	90 0	-	165 0
N Anti-infliximab antibodies, n (%)	112 35 (31.3)	76 16 (21.1)	0.014	188 51 (27.1)

Table 2. Serum drug levels according to the presence of anti-drug antibody status (whole cohort; n=570)

			Anti-drug antibodies, n (%)		
			Yes	No	Total
Serum drug concentration N=565*	Adalimumab	No drug	52 (82,5)	3 (2,0)	55 (25,6)
		Low levels	10 (15,9)	22 (14,5)	32 (14,9)
		Normal levels	1 (1,6)	127 (83,6)	128 (59,5)
		Total	63	152	215
		P-value	0,000		
	Etanercept	No Drug	-	4 (2,5)	4 (2,5)
		Presence of drug	-	159 (97,5)	159 (97,5)
		Total	0	163	163
		P-value	-		
	Infliximab	No drug	40 (78,4)	19 (14,0)	59 (31,6)
		Low levels	10 (19,6)	50 (36,8)	60 (32,1)
		Normal levels	1 (2,0)	67 (49,3)	68 (36,4)
		Total	51	136	187
		P-value	0,000		

*There are no drug level data available in 5 patients

Disclosure: A. Balsa, None; **R. Sanmarti**, None; **J. Rosas**, None; **S. Gomez Castro**, Pfizer Inc, 3; **A. Cabez**, Pfizer Inc, 3; **V. Martin**, Pfizer Inc, 3; **M. Montoro**, Pfizer Inc, 3.

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Abstract Number: 614

Canadian Study of Outcomes in Adalimumab (HUMIRA®) Patients with Support for Adherence – Results from the Companion Study

Sebastien Gerega[1], Brad Millson[1], Louis Bessette[2], John Marshall[3], Gerald Lebovic[4,5], Michael Sung[1], Driss Oraichi[1], Sandra Gazel[6], Tania Gaetano[6], Martin Latour[6] and **Marie-Claude Laliberté**[6], [1]IMS Brogan, Kirkland, QC, Canada, [2]Centre Hospitalier de l'Université Laval, Quebec, QC, Canada, [3]Department of Medicine, Division of Gastroenterology, Farncombe Family Digestive Health Research Institute, McMaster University, Hamilton, ON, Canada, [4]Applied Health Research Centre, St. Michael's Hospital, Toronto, ON, Canada, [5]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada, [6]AbbVie, Inc., St.Laurent, QC, Canada

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Background/Purpose: Adalimumab (ADA) is a TNF-alpha inhibitor indicated for use in various inflammatory autoimmune diseases including rheumatoid arthritis (RA), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). Patients receiving ADA in Canada are eligible to enroll in a patient support program (PSP) providing personalized services including tailored interventions. This retrospective cohort study assessed the impact of specific factors, including PSP services and patient characteristics, on persistence and adherence to ADA.

Methods: An algorithm based on probabilistic matching was developed to link patients in the ADA PSP database to the IMS Health longitudinal pharmacy transaction database. Patients that started ADA therapy between July 2010 and August 2014 were selected and their prescriptions were evaluated for a period of 12 months after the index date to calculate days until end of persistence (defined by a gap in therapy of ≥90 days), censored for patients who remained on therapy through month 12. Cox proportional hazards modelling provided hazard ratios (HR) for the association between persistence and patient characteristics and PSP services. Adherence, measured by medication possession ratio (MPR), was calculated and multivariable logistic regression provided adjusted odds ratios (OR) for the relationship between high adherence (MPR >= 80%) and patient characteristics and PSP services.

Results: The linkage algorithm yielded a final sample of 10,857 patients (2,067 RA; 2,499 AS or PsA). Statistically significant differences in the hazard rate of discontinuation and the odds of high adherence were identified across multiple variables. Male patients demonstrated 20% less likelihood of discontinuation (HR = 0.801, $p<0.0001$) and had a significantly greater odds of adherence (OR = 1.118, $p<0.015$). Relative to the 30-39 year category, older age groups had significantly greater odds of adherence (40-49, 50-59, 60-69, 70+; OR = 1.247, 1.234, 1.323, 1.411, $p<0.01$). Patients receiving ongoing motivational interventions, in the form of nurse-provided phone calls, were 72% less likely to cease therapy when compared to those that did not receive the interventions (HR = 0.282, $p<0.0001$) and were also more adherent (OR = 1.483, $p<0.0001$). Treatment abandonment (failure to initiate therapy after enrolment in the PSP) was >80% more frequent in patients that did not receive a pre-ADA intervention ($p<0.0001$).

Conclusion: Ongoing motivational interventions, as provided by the ADA PSP, were found to have a large and statistically significant association to greater patient persistence and adherence over the first 12 months of treatment. These results may help refine interventions aiming at improving treatment adherence.

Disclosure: S. Gerega, AbbVie, 5; **B. Millson**, AbbVie, 5; **L. Bessette**, Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Lilly, Novartis, 8,Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Celgene, Lilly, Novartis, 5,Amgen, BMS, Janssen, Roche, UCB, AbbVie, Pfizer, Merck, Celgene, Sanofi, Lilly, Novartis, 9; **J. Marshall**, AbbVie, 8,AbbVie, 5; **G. Lebovic**, None; **M. Sung**, AbbVie, 5; **D. Oraichi**, AbbVie, 5; **S. Gazel**, AbbVie, 3,AbbVie, 1; **T. Gaetano**, AbbVie, 3,AbbVie, 1; **M. Latour**, AbbVie, 3,AbbVie, 1; **M. C. Laliberté**, AbbVie, 3,AbbVie, 1.

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Abstract Number: 615

Pharmacokinetic Similarity of ABP 710 Relative to Infliximab: Results from a Randomized, Single-Blind, Single-Dose, Parallel Group Study in Healthy Subjects

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Background/Purpose: ABP 710, a biosimilar candidate to infliximab, has the same amino acid sequence as infliximab, an anti-TNF therapy. Analytical and biofunctional comparisons between ABP 710 and infliximab have been conducted and completed. This report describes the results of a study comparing pharmacokinetics (PK) of ABP 710 and infliximab sourced from the United States.

Methods: This was a single-blind, single-dose, parallel-group study among healthy adults, 18 to 45 years of age and with a body mass index of 18 to 30 kg/m^2. Subjects were randomized to receive a 5 mg/kg intravenous (IV) infusion of either ABP 710 or infliximab after pretreatment with an antihistamine and acetaminophen 30 minutes prior to the start of the infusion. The primary objective was demonstration of PK similarity of ABP 710 to infliximab based on area under the serum concentration-time curve from time 0 extrapolated to infinity (AUC_{inf}; primary endpoint). PK equivalence was deemed achieved if the geometric mean (GM) ratio and its 90% confidence interval (CI) fell within the range of 0.80 and 1.25. Secondary endpoints included maximum observed serum concentration (C_{max}), safety, and immunogenicity.

Results: Pharmacokinetics: A total of 49 subjects received ABP 710 and 50 subjects received infliximab. Following a single dose, the adjusted least square (LS) GM of AUC_{inf} and C_{max} for ABP 710 were 33559 µg·h/mL and 123 µg/mL. The adjusted LS GM of AUC_{inf} and C_{max} for infliximab were 37523 µg·h/mL and127 µg/mL. Ratios of adjusted LS GM (90% CIs) between ABP 710 and infliximab for AUC_{inf} and C_{max} were 0.894 (0.812–0.985) and 0.972 (0.917–1.030). The 90% CIs of these ratios were fully contained within the 0.80 to 1.25 interval, confirming PK similarity between ABP 710 and infliximab. Safety: There were no deaths, serious adverse events, or treatment-emergent adverse events (TEAEs) leading to discontinuation from the study. The incidence of TEAEs was similar in the two treatment groups (ABP 710: 83.7%; infliximab: 86.0%). The majority of TEAEs were mild or moderate. The most frequently reported TEAEs were somnolence, headache, nasopharyngitis, upper respiratory tract infection, nausea, and lethargy. Immunogenicity: All subjects tested negative for antidrug antibody (ADA) prior to dosing. At the end of study (Day 57), 40% subjects in the ABP 710 group and 32% in the infliximab group were positive for binding ADAs, and 13% subjects in the ABP 710 group and 10% in the infliximab group were positive for neutralizing ADAs.

Conclusion: Results of this phase 1 study demonstrate PK similarity between ABP 710 and infliximab following a single 5 mg/kg IV infusion in healthy subjects. The safety and immunogenicity profile were similar among the treatment groups.

Disclosure: P. Kaur, Amgen, 3,Amgen, 1; **V. Chow**, Amgen, 3,Amgen, 1; **N. Zhang**, Amgen, 3,Amgen, 1; **E. Krishnan**, Amgen, 3,Amgen, 1.

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Abstract Number: 616

ABP 501 Long-Term Safety/Efficacy: Interim Results from an Open-Label Extension Study

Stanley Cohen[1], Jose L. Pablos[2], Nan Zhang[3], Warren Rizzo[4], Gerhard Muller[5], Devi Padmanaban[6], Alan Kivitz[7], Alan K. Matsumoto[8] and Primal Kaur[9], [1]Metroplex Clinical Research Center and University of Texas Southwestern Medical Center, Dallas, TX, [2]Grupo de Enfermedades Inflamatorias y Autoinmunes, Instituto de Investigación Hospital 12 de Octubre (i+12), Madrid, Spain, [3]Biosimilars, Amgen, Inc., Thousand Oaks, CA, [4]Advanced Arthritis Care & Research, Scottsdale, AZ, [5]Dept of Nephrology and Rheumatogy, University Medical Center Göttingen, Göttingen, NIEDERSACHSEN, Germany, [6]Biosimilars, Amgen, Thousand Oaks, CA, [7]Altoona Center for Clinical Research, Duncansville, PA, [8]Rheumatology, Arthritis & Rheumatism Associate, Wheaton, MD, [9]Amgen, Thousand Oaks, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose: ABP 501 is a biosimilar candidate to adalimumab, a fully human recombinant monoclonal antibody. Totality of evidence to date suggests that ABP 501 is similar to adalimumab. Subjects receiving either ABP 501 or adalimumab in the active-controlled comparative pivotal phase 3 study in rheumatoid arthritis continued on to this ongoing open-label extension (OLE) study if they had completed the week 26 visit of the active-controlled pivotal phase 3 study (parent study) and met study entry criteria. Objective: To report results from the interim analysis of this OLE study.

Methods: This was a single-arm OLE of the parent study; the objective was to assess long-term safety and efficacy of ABP 501. The study design included 68 weeks of treatment followed by an assessment at week 70 and an end of study visit at week 72. All subjects received 40 mg ABP 501 every other week; starting earliest at the week 26 visit of the parent study.

Results: Of the 466/467 treated subjects, 237 transitioned from adalimumab to ABP 501. At the time of this interim analysis one (0.2%) subject had completed the OLE study and 37 (7.9%) had terminated early, mostly due to consent withdrawal. Demographics and disease characteristics were balanced between subjects who transitioned from adalimumab and those who continued on ABP 501. The incidence of treatment-emergent adverse events (TEAEs) was 57.1% (266/466) and that of grade ≥3 TEAEs was 6.2% (29/466); incidence of TEAEs leading to discontinuation of investigational product was 1.7% (8/466). The most frequently reported TEAEs included nasopharyngitis (8.2%), upper respiratory tract infection (7.3%), and bronchitis (4.3%). No fatal adverse events were reported; 6.9% (32/466) subjects experienced serious adverse events (SAEs), of which 1.9% (9/466) experienced musculoskeletal and connective tissue disorders. There were 2 SAEs of interest (infections: n=1; malignancies: n=1). The overall exposure-adjusted incidence rate for SAEs occurring in the OLE study was 8.4 per 100 patient-years (32 subjects/382.4 total subject exposure-time [patient-year]). At the time of this interim analysis, 45.9% (214/466) subjects had developed binding antidrug antibodies (ADAs), 11.6% (54/466) had developed neutralizing ADAs in the OLE study. The rates of TEAEs and ADAs were similar between subjects with single transition from adalimumab and those who continued on ABP 501. The ACR20 response rate (using the parent study baseline) was 73.3% (340/464) at the OLE study baseline, 77.6% (361/465) at week 4, 74.2% (336/453) at week 24, 76.5% (224/293) at week 48. The overall mean DAS28-CRP change from parent study baseline was −2.25 (n=440) at the OLE study baseline, −2.36 (n=463) at week 4, −2.41 (n=450) at week 24 and −2.52 (n=292) at week 48. Efficacy was similar in subjects who transitioned from adalimumab as compared with the subjects who continued on ABP 501.

Conclusion: In this ongoing OLE study of ABP 501, efficacy was maintained with no new safety findings. Long term safety and efficacy results were similar between subjects who transitioned from adalimumab and those who continued on ABP 501.

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Abstract Number: 617

Therapy in Patients with Rheumatoid Arthritis (RA) with Inadequate

Response to Tumor Necrosis Factor Alpha Inhibitors (TNFi): A Systematic Review and Meta-Analysis of Randomized Controlled Trials (RCTs

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Background/Purpose: Up to one-third of the patients who receive TNFi lose responsiveness over time. Options available to these patients include treatment with an alternative TNFi (cycling strategy) or switching to another therapy with a different mode of action (swapping strategy). We conducted a systematic review and meta-analysis of RCTs to compare the efficacy of various approaches.

Methods: Five electronic databases were searched (MEDLINE, EMBASE, Cochrane Library, and Web of Sciences). Sources of gray literature (unpublished records) were searched through clinicaltrials.gov and other websites. The search was broad in scope to capture all available evidence. The selection process was performed by two independent reviewers. We included studies evaluating the efficacy and safety of targeted therapies in RA that included only adult patients with failure to respond to at least one TNFi. We excluded non randomized studies, RCTs with no separate data for TNFi failures, evaluating retreatments (e.g. rituximab or tocilizumab vs. placebo after one or two cycles of rituximab or tocilizumab), with insufficient data to evaluate the outcomes of interest, or comparing a brand-name product with a biosimilar (with no control group). Outcomes included: 50% improvement according to the American College of Rheumatology criteria (ACR50), serious adverse events, and withdrawals.

Results: Out of 44,651 citations we found 13 studies (with multiple publications n=68). The mean age of patients ranged between 45.1 and 58.2 years. The majority of the patients were females (82%) with a disease duration ranging between 8.6 and 13.2 years and a baseline disability score ranging from 1.1 to 1.9. Cycling strategies included: golimumab, certolizumab, adalimumab, etanercept or infliximab in patients failing any other TNFi. Swapping strategies included rituximab, tocilizumab, abatacept, or tofacitinib. Four studies were head-to-head comparisons, one compared two different doses of tocilizumab combined with methotrexate with tocilizumab monotherapy, one compared nonTNFi plus TNFi versus TNFi only and the remaining studies compared a targeted agent combined with a disease modifying anti-rheumatic drug (DMARD) versus DMARD monotherapy (with or without placebo). Three studies (n=898) for the cycling strategy and four studies (n=1,774) for the swapping strategy were suitable for direct meta-analysis. When an alternative TNFi was used in combination with DMARD, ACR50 response rates were statistically significantly improved at 12 to 24 weeks compared to the DMARD alone group (pooled for all TNFi = RR 2.6 (95% CI 1.6 to 4.3). Improvements were also observed with each swapping strategy (pooled RR including rituximab, abatacept, tocilizumab, or tofacitinib was 6.1 (95% CI 4.1 to 8.9)). No differences were observed in the rates of withdrawals due to adverse events or serious adverse events between groups for any of the strategies.

Conclusion: Current evidence from RCTs shows that cycling to a different TNFi after failure can be effective, and can be considered before switching to a different targeted therapy, suggesting that many patients fail a specific agent and not TNFi as a class.

Disclosure: M. A. Lopez-Olivo, Rheumatology Research Foundation, 2; **A. Matusevich**, None; **M. Suarez-Almazor**, National Institute for Musculoskeletal and Skin Disorders, 2,Pfizer Inc, 2.

Abstract Number: 618

Do Canadian Rheumatologists Actually Treat to Target Once a Biologic Has Been Initiated? an Analysis from a Prospective, Observational Registry

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Background/Purpose: The objective of this analysis was to assess the frequency of treatment optimization in cases where treatment target was not achieved, and to describe the type of changes made in RA patients initiating treatment with infliximab or golimumab in Canadian routine clinical care.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, or psoriatic arthritis with infliximab, golimumab or ustekinumab. RA patients enrolled during 2002-2014 and with available CDAI information at both months 6 and 12 were included. DA was defined according to the CDAI criteria (remission: ≤2.8; low: >2.8 to ≤10; moderate: >10 to ≤22; high: >22). The association between treatment changes and target achievement was assessed with the Chi-square test.

Results: A total of 498 patients were included, with a mean (SD) age and disease duration of 56.4 (13.2) and 8.6 (8.6) years, respectively. The majority of patients were female (74.1%) and treated with infliximab (74.5%). After 6 months of treatment, 46% of patients had achieved treatment target of remission or low DA, and 54% were still at moderate/high DA. Among the latter, treatment was adjusted in 36.4% (34.7% when looking only at patients enrolled since 2011) and was significantly associated with target achievement at month 12 (46.9% vs. 31%; P=0.009). The frequency of treatment changes by type were: DMARD switch/add-on (11.9% of patients), biologic up-titration (10%), DMARD up-titration (8.2%), steroid initiation (7.8%), NSAID initiation (5.6%), and DMARD initiation (3%). Among patients at moderate/high DA at both visits for whom no treatment adjustment was made, mean (SD) disease parameters at 6 months were: SJC28 = 5.7 (5.0); TJC28 = 8.6 (6.5); MDGA = 3.8 (2.0); PtGA = 4.5 (2.4). In comparison, among patients with treatment adjustment, disease parameters were: SJC28 = 5.8 (4.2); TJC28 = 9.4 (7.0); MDGA = 4.7 (2.3); PtGA = 5.8 (2.1). Among patients at moderate/high DA at 6 months who achieved target at month 12 without treatment adjustment, disease parameters at month 6 were: SJC28 = 4.7 (4.5); TJC28 = 5.5 (5.1); MDGA = 3.2 (1.7); PtGA = 4.3 (2.5). Among those with a treatment adjustment, disease parameters at month 6 were: SJC28 = 3.5 (3.0); TJC28 = 5.1 (3.3); MDGA = 4.2 (2.2); PtGA = 4.7 (2.8).

Conclusion: These results suggest that a considerable portion of patients on biologics are not treated to a CRA recommended target in Canada. Treatment adjustment was found to be mainly associated with the physician's global

assessment of disease activity and resulted in better outcomes. PtGA and TJC28 were also significantly higher in those receiving treatment adjustments, while SJC did not correlate with treatment adjustments. The reasons for lack of treatment adjustment in patients not at DA target levels should be further explored.

Disclosure: P. Baer, Janssen Inc., 5; **A. Chow**, Janssen Inc., 5; **M. Starr**, Janssen Inc., 5; **B. Haraoui**, Janssen Inc., 5; **R. Arendse**, Paid Consultant of Janssen Inc., Canada, 5; **M. Teo**, Janssen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **A. J. Lehman**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3.

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Abstract Number: 619

Concomitant Treatment Use during Treatment with Golimumab in Patients with Rheumatoid Arthritis

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Background/Purpose: Previous studies have shown that, when sustained good clinical response has been achieved with a biologic therapy, traditional disease-modifying anti-rheumatic drugs (DMARDs) and other treatments can be reduced or discontinued. The aim of this analysis was to assess the discontinuation of concomitant treatment and DMARD tapering in rheumatoid arthritis (RA) patients treated with golimumab (GLM) in Canadian routine clinical practice.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for RA, ankylosing spondylitis, psoriatic arthritis with infliximab or GLM as first biologics or after having been treated with a biologic for <6 months. Patients with RA treated with GLM who were enrolled between 2010 and 2014 were included in this analysis. DMARD, steroid and NSAID discontinuation were defined as no use of any drugs in these categories. Time to treatment discontinuation or tapering was assessed both with descriptive statistics and the Kaplan Meier estimator of the survival function.

Results: 273 RA patients treated with GLM (mean dose = 50 mg s.c. monthly) were included in the analysis; 72.2% were female, mean (SD) age was 57.4 (13.5) years and disease duration was 8.1 (8.6) years. Mean (SD) disease parameters at baseline were: DAS28 = 5.1 (1.7), CDAI = 27.8 (15.9), SJC28 = 7.9 (5.9), TJC28 = 8.9 (7.0), HAQ-DI = 1.3 (0.7), MDGA (0-10 NRS) = 5.5 (2.2), PtGA (mm VAS) = 54.6 (27.9). At baseline, 74.7% were taking concomitant DMARDs, 30.8% were on NSAIDS, and 21.2% on corticosteroid. Mean (SD) available follow-up was 13.8 (9.4) months. Upon

treatment with GLM, 11.8% of the patients on a DMARD at baseline discontinued DMARD treatment after a mean (SD) of 15.3 (10.0) months. Furthermore, 56.9% and 86.7% of patients completely discontinued steroid and NSAID treatment after a mean (SD) follow-up of 8.9 (5.4) months and 6.2 (1.3) months, respectively. DMARD dose tapering was documented for 32.4% of patients on DMARDs after a mean (SD) follow-up of 11.2 (8.9) months.

Conclusion: The results of this Canadian longitudinal observational study have shown that treatment with GLM was associated with discontinuation of concomitant DMARD, steroid, and NSAID treatment as well as DMARD tapering in RA patients. The long-term benefits of this practice for patients have to be determined.

Disclosure: P. Baer, Janssen Inc., 5; **M. Bell**, Paid Consultant of Janssen Inc., Canada, 5; **B. Haraoui**, Janssen Inc., 5; **L. Bessette**, Janssen Inc., 5; **J. Kelsall**, Janssen Inc., 5; **M. Sheriff**, Janssen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **F. Nantel**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3.

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Abstract Number: 620

Clinical Activity, Ultrasound Assessment and Drug Monitoring in Rheumatoid Arthritis Patients Receiving Anti-TNF-α Therapy with Extended Interval of Administration

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Background/Purpose: To assess clinical activity, ultrasound synovitis and drug levels in rheumatoid arthritis (RA) patients receiving anti-TNFα therapy with extended interval of administration (EIA).

Methods: Prospective observational study. Population: Patients diagnosed with RA, in clinical remission, receiving adalimumab (ADL) or etanercept (ETN) with EIA. Clinical activity was assessed by DAS28-ESR, DAS28-CRP, CDAI (Clinical Disease Activity Index) and SDAI (Simple Disease Activity Index) scores at each visit. Twelve-joint ultrasound assessment (elbows, wrists, 2nd and 3rd metacarpo-phalangeal, knees and ankles) was performed evaluating synovitis through B-mode (BM) and Color Doppler signal (CD). A BM and CD score was calculated summing the highest score from each joint to a maximum of 36 points. The sonographer was blinded to the clinical and laboratory data. Serum drug levels were measured using Promonitor® ELISA kits (Progenika Biopharma - Grifols, Spain).

Results: A total of 34 patients were included since February 2011 to January 2016. One patient was excluded due to blindness violation and 2 patients never reduced anti-TNFα due to low drug levels. 27 patients were women (79,4%)

and the mean age was 61 years. Most patients were RF positive (85,3%) and ACPA positive (74,2%). 18 patients were with ADL treatment and 16 with ETN. 28 patients (82,35%) were with DMARD concomitant treatment (14 MTX, 11 LEF, 2 HCQ, 1 SSZ) and 7 patients were with low-dose CS. Mean time from diagnosis was 15,19 years (range 2,15 – 52,31) and Mean time with current biologic drug was 4,11 years (range 1,39 – 11,07). Nine patients (26,5%) returned to standard interval due to worsening of clinical activity and one discontinued treatment due to septic arthritis.

Clinical activity scores, ultrasound scores and drug levels are summarized in table 1.

Table 1. Clinical activity scores, ultrasound scores and drug levels.

	Basal visit	6 months	12 months
n	30	26	17
DAS28-ESR	2,0 (0,94)	1,77 (0,81)	1,49 (0,58)*
DAS28-CRP	1,17 (0,53)	1,76 (0,47)**	1,57 (0,34)**
SDAI	4,23 (2,63)	4,11 (2,81)	2,99 (1,27)*
CDAI	3,82 (2,48)	3,61 (2,33)	2,76 (1,3)
BM score	3,9 (4,65)	3,96 (3,93)	5,41 (4,29)
CD score	0,86 (0,79)	1,44 (1,8)	1,35 (1,46)
BM score (%)	80,95%	92,00%	100,00%
CD score (%)	61,90%	52,00%	58,82%
ADL	12,38 (7,37)	9,17 (5,51)	6,96 (2,84)*
ETN	4,16 (2,74)	3,59 (2,9)	3,03 (0,84)

BM: B-mode; CD: Color Doppler; ADL: adalimumab; ETN: etanercept; *p<0,05; **p<0,005. All results mean (SD) otherwise specified.

Conclusion : 1. Clinical remission was sustained in most patients receiving ADL or ETN in extended interval of administration. 2. Some patients (26,5%) returned to standard interval of administration due to clinical worsening. 3. Some patients show subclinical ultrasound synovitis in B-mode or Color Doppler from baseline, although we found no significant worsening over time. 4. Drug levels decrease over time as we extend interval of administration. 5. It would be advisable to perform periodic ultrasound and monitoring of anti-TNFα levels to maintain clinical remission in patient with extended interval of administration.

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Abstract Number: 621

Effectiveness and Safety of CT- P13 (Biosimilar Reference Infliximab) in a Real-Life Setting in 151 Patients with Rheumatoid Arthritis and Ankylosing Spondylitis: A Mid-Term Interim Analysis

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Background/Purpose: Over the past decade, the use of biologics has significantly changed the management of rheumatoid arthritis (RA) and ankylosing spondylitis (AS). However, the high cost of biologics imposes limits on their use, particularly in developing countries. The development and commercialization of biosimilars can help address unmet medical needs by improving access to well-established therapeutic interventions while improving healthcare affordability. CT- P13 was the first monoclonal antibody biosimilar approved in the EU, as well as recently by the FDA. The study objective was to demonstrate the safety and effectiveness of CT- P13 when administered in a real-life setting in adults with active RA or AS.

Methods: This multicenter, non-interventional, observational study was conducted in Romania, Czech Republic and Bulgaria in patients with severe, progressive RA (with inadequate response to methotrexate /other DMARDs) or severe AS (with inadequate response to conventional therapy). Study investigators determined specific doses/timing of infusions based on the CT- P13 SPC. Patients received CT- P13 at baseline (visit 1), week 2 (visit 2), week 6 (visit 3), between weeks 12 and 14 (visit 4: month 3). Safety was assessed by early dropouts and adverse events (AEs). Effectiveness was assessed at baseline and visit 4 (month 3) using the Disease Activity Score (DAS28) for RA patients and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) for AS patients.

Results: At 14 June 2016, 151 subjects (47% male, mean [SD] age 48.9 [14.1] years) have been enrolled (median follow-up 159 days). At visit 4 (month 3), mean (SD) CT- P13 doses were 240 (61) mg/3.3 (0.6) mg/kg for RA, and 384 (87) mg/5.0 (0.5) mg/kg for AS. There were 31 AEs: 5 definitely related, 0 probable related, 5 possibly related, and 21 unrelated to CT- P13. Among the AEs related to CT- P13 treatment 5 were mild, 3 moderate and 2 severe. Altogether 16 patients have been withdrawn prematurely from the study so far, and in 6 cases AE was listed as reason for dropout. Last available observation were carried forward (LOCF) for patients who did not have effectiveness measurement at visit 4 due to early termination. Thus, 111 patients (RA: 61; AS: 50) have baseline and follow-up primary effectiveness measurements at month 3 so far. After 3 months of CT- P13 treatment, patients showed significant improvements in disease activity relative to baseline in terms of DAS28 (baseline: mean [SD]=5.8 [1.0], month 3: mean [SD]=3.6 [1.6]; t=10.5, df=60, $p<0.0001$, Cohen's d=1.7) and BASDAI (baseline: mean [SD]=6.8 [1.7], month 3: mean [SD]=3.4 [2.3]; t=11.6, df=49, $p<0.0001$, Cohen's d=1.7). Patients with RA and AS analyzed together showed a significant decrease in C-reactive protein (CRP) levels after 3 months. (baseline: mean [SD]=26.3 [23.6], month 3: mean [SD]=10.2 [17.6]; t=6.0, df=105, $p<0.0001$, Cohen's d=0.8).

Conclusion: CT- P13 (biosimilar reference infliximab) is safe and effective in a real-life setting in patients with RA or AS.

Abstract Number: 622

Efficacy after Transition to SB5 from Reference Adalimumab (Humira®) Vs. Continuation of SB5 or Reference Adalimumab By Antibodies Developed after Transition from a SB5 Phase III Study

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Background/Purpose : SB5 has been developed as a biosimilar of the reference adalimumab (ADL). The 52-week efficacy and safety results were reported previously. [1] Here we report the efficacy results by anti-drug antibody (ADA) during the transition period.

Methods : Patients with moderate to severe rheumatoid arthritis (RA) despite methotrexate treatment were randomly assigned to receive 40 mg of either SB5 or ADL administered subcutaneously every other week. After 24 weeks of treatment, patients in the ADL group were re-randomized (1:1) to either be transitioned to SB5 (ADL/SB5) or continue on ADL (ADL/ADL) up to Week 50. Patients receiving SB5 continued to receive SB5 (SB5/SB5) but they followed the randomization procedure for blinding purposes. Efficacy, safety, and immunogenicity were assessed up to Week 52. Patients with detectable ADA were those who newly developed ADA or developed ADA with increased titer after transition.

Results : The proportion of patients with detectable ADA after transition was 15.7% vs. 16.8% vs. 18.3% for SB5/SB5, ADL/SB5, and ADL/ADL, respectively. In all treatment groups, the mean DAS28 tended to improve in patients without ADA while it tended to worsen in patients with detectable ADA between Week 24 and Week 52 (Figure). The mean change in DAS28 from Week 24 was comparable across treatment groups within each ADA subgroup. In other efficacy parameters such as EULAR response rates, proportion of patients with low disease activity and remission based on DAS28, there was a trend towards decreased efficacy in patients with detectable ADA compared to those without ADA (Table).

Conclusion : Patients with detectable ADA after transition were more likely to have reduced efficacy compared to those without ADA. Efficacy was comparable across treatment groups within patients with detectable ADA and within patients without ADA.

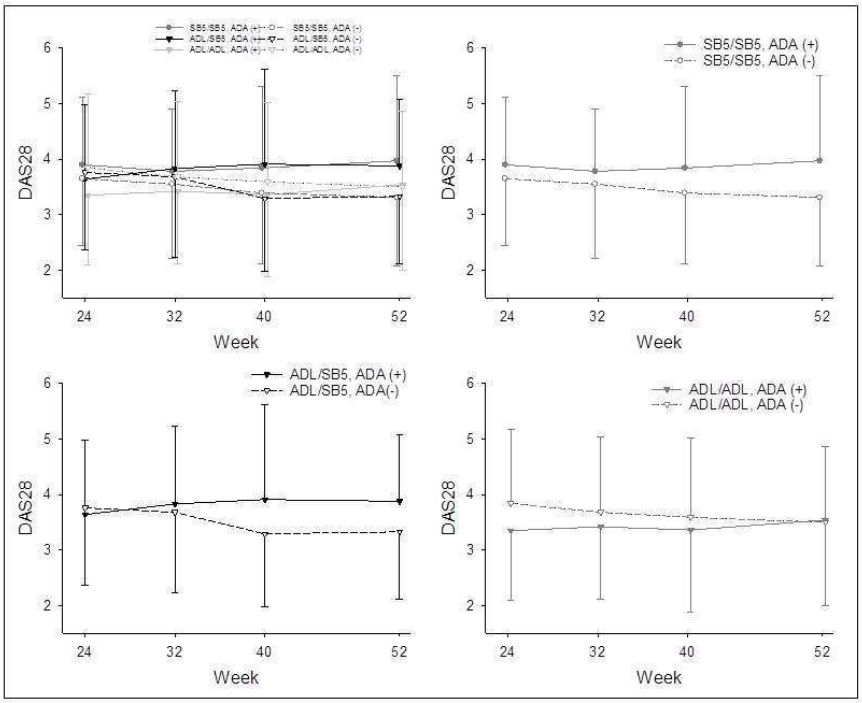

Figure. Mean and Standard Deviation of DAS28 by ADA Status after Transition

Table. Efficacy Results at Week 52 by ADA Status

	SB5/SB5		ADL/SB5		ADL/ADL	
	ADA (+)	ADA (–)	ADA (+)	ADA (–)	ADA (+)	ADA (–)
ACR20	26/40 (65.0%)	167/208 (80.3%)	15/20 (75.0%)	78/98 (79.6%)	18/23 (78.3%)	73/101 (72.3%)
ACR50	17/40 (42.5%)	107/208 (51.4%)	9/20 (45.0%)	55/98 (56.1%)	14/23 (60.9%)	49/101 (48.5%)
ACR70	13/40 (32.5%)	66/208 (31.7%)	5/20 (25.0%)	26/98 (26.5%)	10/23 (43.5%)	25/101 (24.8%)
EULAR response						
Good	16/40 (40.0%)	102/207 (49.3%)	5/20 (25.0%)	50/98 (51.0%)	12/23 (52.2%)	45/101 (44.6%)
Moderate	18/40 (45.0%)	95/207 (45.9%)	13/20 (65.0%)	43/98 (43.9%)	7/23 (30.4%)	49/101 (48.5%)
No response	6/40 (15.0%)	10/207 (4.8%)	2/20 (10.0%)	5/98 (5.1%)	4/23 (17.4%)	7/101 (6.9%)
LDA	16/40 (40.0%)	102/207 (49.3%)	5/20 (25.0%)	50/98 (51.0%)	12/23 (52.2%)	45/101 (44.6%)
Remission	6/40 (15.0%)	69/207 (33.3%)	3/20 (15.0%)	31/98 (31.6%)	7/23 (30.4%)	29/101 (28.7%)

LDA, low disease activity
Data are presented in n/n' (%)
LDA as DAS28 ≤ 3.2 and remission defined as DAS28 < 2.6.

Reference 1. Weitnblatt ME et al. *Ann Rheum Dis* 2016;75(Suppl2): 487

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Abstract Number: 623

WITHDRAWN

Abstract Number: 624

Association Between Methotrexate Use and Effects of Treatment with a Second Biologic Agent in Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
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Session Time: 9:00AM-11:00AM

Background/Purpose: In general, the concomitant use of methotrexate (MTX) and biologic disease-modifying antirheumatic drugs (bDMARDS) plays an important role in treating bio-naïve patients with rheumatoid arthritis (RA); however, whether concomitant use of MTX is associated with the effects of second bDMARDS treatment in RA patients for whom first bDMARDS treatment has failed remains unclear.

Methods: We used demographic and clinical data obtained from the Tsurumai Biologics Communication Registry, which comprises the Nagoya University and 20 affiliated hospitals in Japan. Patients aged 20–80 years who fulfilled the ACR 1987 revised or the 2010 ACR/EULAR classification criteria for RA were selected, and only those switching to second bDMARDS treatment were included. Linear multiple regression analysis was used to assess the association between MTX use and effects of second bDMARDS treatment, as defined by DAS28-ESR improvement at week 24. Unstandardized coefficients were calculated. Adjustment variables included sex, age, DAS28 at pre-treatment with second bDMARDS, tumor necrosis factor inhibitor (TNFi) or non-TNFi in RA treatments with first and second bDMARDS, MTX use with first bDMARDS, and glucocorticoid use with second bDMARDS.

Results: Table 1 summarizes the baseline demographic and disease characteristics of the patients. Some characteristics differed between patients with MTX use and non-use; however, they were adjusted using linear multiple regression analysis. Table 2 presents the unstandardized coefficients. The value of interest was 0.67 ($P < 0.05$), suggesting that DAS28 improvement in second bDMARDS treatment with MTX is superior to that without MTX. Other variables affecting the treatment effects were sex and TNFi or non-TNFi with second bDMARDS, which are well-known influential factors for biologic therapy.

Conclusion: This study demonstrated that the concomitant use of MTX was independently associated with increased effects of second bDMARDS treatment.

Table 1. Baseline characteristics of patients with MTX use and non-use

	MTX non-use (n = 49)	MTX use (n = 136)	P value
Age, Mean ± SD years	62.9 ± 15.1	57.5 ±12.7	<0.05
DAS28ESR at pre-treatment	5.24 ± 1.33	5.02 ± 1.42	0.33
Sex, % female	83.7	86.0	0.65
MTX use with first bDMARDS, %	49.0	95.6	<0.05
TNFi as first bDMARDS, %	77.6	97.1	<0.05
TNFi as second bDMARDS, %	26.5	61.0	<0.05
Oral steroid use with second bDMARDS, %	65.3	66.9	0.86

MTX: methotrexate, bDMARDS: biologic disease-modifying antirheumatic drugs, TNFi: tumor necrosis factor inhibitor

Table 2. Coefficients of variables in relation to effects of second bDMARDS treatment

	Estimate	Standard error	P value
(Intercept)	−0.20	0.87	0.82
MTX use with second bDMARDS	0.67	0.28	<0.05
MTX use with first bDMARDS	−0.21	0.31	0.50
DAS28ESR at pre-treatment with second bDMARDS	0.66	0.072	<0.01
Sex (male as reference)	−0.61	0.28	<0.05
Age	−0.013	0.0075	0.08
TNFi or non-TNFi as first bDMARDS (TNFi as reference)	0.058	0.38	0.88
TNFi or non-TNFi as second bDMARDS (TNFi as reference)	0.43	0.21	<0.05
Oral steroid use with second bDMARDS	0.023	0.21	0.91

MTX: methotrexate, bDMARDS: biologic disease-modifying antirheumatic drugs, TNFi: tumor necrosis factor inhibitor

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Disclosure: Y. Ogawa, None; **N. Takahashi**, None; **T. Kojima**, None; **N. Ishiguro**, None.

Abstract Number: 625

Efficacy and Safety of Intravenous Golimumab Plus Methotrexate in Patients 65 Years and Younger and Those Greater Than 65 Years of Age-a Post-Hoc Analysis

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Session Type: ACR Poster Session A

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Background/Purpose: There is a paucity of data on the use of anti-TNF therapy in patients >65 years. In this sub-analysis of GO-FURTHER, we compare the safety, efficacy, prednisone use, and discontinuation rates in patients age ≤65 years vs those >65 years through 2 years of treatment with intravenous (IV) golimumab (GLM) plus methotrexate (MTX) in an open-label extension of a Phase III trial of pts with active rheumatoid arthritis (RA) despite MTX therapy.

Methods: In this Phase III, double-blind, randomized, placebo-controlled GO-FURTHER trial, 592 patients with active RA were randomized (2:1) to IV GLM 2 mg/kg plus MTX (Group 1) or placebo (PBO) plus MTX (Group 2) at weeks 0 and 4, then every 8 weeks thereafter. PBO patients crossed over to GLM at week 16 (early escape) or week 24 (crossover by design). The final GLM infusion was at week 100. Assessments included ACR 20/50/70 response criteria. Safety was monitored through week 112.

Results: In total randomized patients, 523 patients aged ≤65 years and 69 patients >65 years were analyzed in the intention-to-treat population with last observation carried forward through week 100. Clinical response by ACR 20/50/70, respectively, was observed in 62%, 34.2%, and 17.5% of those ≤65 years at week 24 (primary endpoint) and was similar

(67.9%, 39.6%, and 17%) in those >65 years of age. The ACR response rates were significantly higher ($p<0.001$) in GLM+MTX group compared with the PBO + MTX group in both age groups. At week 52 and week 100, ACR 20/50/70 values for patients ≤65 years and patients >65 years remained similar to those at week 24 (Table). Mean baseline prednisone dose (mg) was higher in the ≤65 (7.04±2.47) vs the >65 years age group (6.76±2.69). Discontinuation rates were similar among patients aged ≤65 years who received PBO + MTX and GLM + MTX, respectively, at week 24 (2.8% vs 2.9%). Among patients >65 years, discontinuation rates were higher in the GLM + MTX group vs PBO + MTX, respectively, at week 24 (11.3% vs 6.3%). The 2 most common reasons for discontinuation in both age groups for PBO + MTX and GLM + MTX were adverse events and withdrawal of consent. Serious adverse events (SAEs) were numerically higher in patients aged >65 years (26.4%) vs those ≤65 years (18.7%) with infections, gastrointestinal disorders, and fractures being the most commonly reported events in the >65 years age group.

Conclusion: Clinical response to IV GLM + MTX were significantly higher than PBO + MTX in both age groups and the response was maintained through week 100 in those patients who were ≤65 years and those >65 years. Mean prednisone dose was slightly higher in patients ≤65 years, but prednisone use based on percentage was similar in both groups. SAEs were higher in patients >65 years vs ≤65 years, but no increase in unexpected events was observed in those >65 years. These data suggest IV GLM + MTX treatment in patients >65 years is not associated with loss of clinical response or an increase in unexpected adverse events vs patients ≤65 years.

Table 1 Improvement in ACR through Week 100 for patients ≤ 65 and > 65

	Patients ≤ 65 years of age		**Patients > 65 years of age**	
	PBO+MTX N=181	GLM 2mg/kg+MTX N=342	PBO+MTX N=16	GLM 2mg/kg+MTX N=53
Week 24*				
ACR20	31.5	62.0 p<0.0001	31.3	67.9 p=0.0182
ACR50	13.8	34.2 p<0.0001	6.3	39.6 p=0.0137
ACR70	4.4	17.5 p<0.0001	0.0	17.0 p=0.1044
Week 52	Crossed over to GLM at Week 24		Crossed over to GLM at Week 24	
ACR 20/50/70	61.9/32.6/15.5	66.7/39.5/18.7	56.3/18.8/6.3	60.4/34.0/15.1
Week 100				
ACR 20/50/70	65.7/42.5/24.9	69.0/45.3/24.3	68. 8/25.0/12.5	69.8/43.4/17.0
*Primary endpoint, (%)				

Disclosure: J. Tesser, Janssen Scientific Affairs, LLC, 2; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **R. J. DeHoratius**, Janssen Scientific Affairs, LLC, 3; **S. Xu**, Janssen Research Development, LLC, 3; **K. L. Tang**, Janssen Research & Development, LLC, 3; **E. C. Hsia**, Janssen Research Development, LLC, 3; **A. Turkiewicz**, Janssen Scientific Affairs, LLC, 2.

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Abstract Number: 626

Switching Biologic Therapy in a Population of Rheumatoid Arthritis Patients

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Background/Purpose: Evaluate the reason of exchange of biologic therapy in patients with rheumatoid arthritis and describe the frequency of remission or low activity, according to the disease activity score (DAS28).

Methods: A retrospective study including patients with rheumatoid arthritis, according to the ACR/EULAR 2010 criteria, age over 18 years, who were using any biologic therapy. We collected demographic and therapy data, disease duration, presence of rheumatoid factor and bone erosion on X-rays, reasons for exchange of biologic therapy: primary failure, secondary failure or adverse events and assessment of disease activity, according DAS28.

Results: 94 patients were included, 40% had moderate activity disease and 60% had high activity disease at the beginning of biologic therapy. Anti-TNF was the first choice therapy in 85 patients: 37% were using adalimumab, 36% etanercept, 13% infliximab, and 4% golimumab. Abatacept was the first choice therapy in 5% of the patients and tocilizumab in 4% of the patients. The mean follow-up was 8 years. In this period, we found 103 exchanges of biologic therapy. The reason for switching was primary failure in 26% of the patients, secondary failure in 43% and occurrence of adverse events in 31%. There was no need of switching in all 5 patients who started abatacept as first choice therapy. At the end of follow-up 28% achieved remission of disease ($p < 0.05$) and 18% achieved low activity disease ($p < 0.05$). 54% remained in moderate or high activity ($p < 0.05$). At this time, 59% were using anti-TNF (27% Adalimumab, 19% Etanercept, 3% Infliximab, 7% certolizumab and 2% golimumab), 19% abatacept, 9% Tocilizumab and 14% Rituximab. Table – Reasons for switching biologic agent in 94 RA patients in a mean follow-up of 8 years.

	ADA	*ETA*	*INFL*	*GOL*	*CERT*	*ABATA*	*TOCI*	*RITUX*	*Total*
Primary failure	***4***	***9***	***3***	***3***	***0***	***5***	***1***	***2***	***27***
Secondary failure	***15***	***16***	***8***	***3***	***0***	***0***	***1***	***1***	***44***
Adverse effects	***12***	***11***	***4***	***1***	***0***	***0***	***4***	***0***	***32***
Total	***31***	***36***	***15***	***7***	***0***	***5***	***6***	***3***	***103***

ADA: Adalimumab; ETA: Etanercept; INFL: Infliximab; GOL: Golimumab; CERT: Certolizumab; ABATA: Abatacept; TOCI: Tocilizumab; RITUX: Rituximab; RA: rheumatoid arthritis

Conclusion: In this population there were 103 exchanges of biologic agents. The average of follow-up was 8 years. At the end of follow-up, we found 28% remission and 18% of low disease activity, but 54% of patients remained in high or moderate activity.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/switching-biologic-therapy-in-a-population-of-rheumatoid-arthritis-patients

Abstract Number: 627

Clinical and Immunogenicity Outcomes after Switching Treatment from Innovator Infliximab to Biosimilar Infliximab in Rheumatic Diseases in Daily Clinical Practice

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Biosimilar infliximab is registered in Europe for the same therapeutic indications as innovator infliximab. In 2015, four rheumatology departments in the Netherlands decided to switch from innovator infliximab to biosimilar infliximab based on comparable results in randomized controlled trials and favourable costs. Since data on switching to biosimilar infliximab in daily clinical practice were still scarce, we decided to collect clinical outcomes in a large observational multicentre prospective cohort study. The objective of our study was to investigate the effects of switching treatment from innovator infliximab to biosimilar infliximab on efficacy, safety and immunogenicity in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondylarthritis (SpA).

Methods: Of all innovator infliximab-treated patients, 192/211 (91%) agreed to switch to biosimilar infliximab and were eligible for inclusion in this study. Primary outcome was change in DAS28-CRP (for RA and PsA) and BASDAI (for SpA) after 6 months of treatment. Secondary outcomes included C-reactive protein (CRP), adverse events and infliximab trough levels. Antidrug antibodies against infliximab were measured if the trough level was below 1 µg/ml.

Results: In total, 75 patients with RA, 50 with PsA and 67 with SpA who switched treatment to biosimilar infliximab were included. 44/192 (23%) patients discontinued biosimilar infliximab during 6 months follow-up, respectively due to experienced inefficacy (n=35), adverse events (n=23) or an infusion reaction (n=2). Most frequently reported adverse events resulting in biosimilar discontinuation were fatigue (n=10), malaise (n=5) and headache (n=3). No serious adverse events occurred. 34 patients restarted innovator infliximab, 7 patients switched to another biological (2 adalimumab, 3 etanercept, 1 golimumab, 1 rituximab) and 3 patients maintained biological-free. In RA and PsA patients, mean DAS28-CRP remained stable from month 0 to 6: 2.19 [SD 0.89] to 2.22 [SD 0.84] (p=0.51). In SpA patients, mean BASDAI increased from 3.8 to 4.3 (change +0.5, 95% CI 0.12-0.89, p=0.01). CRP levels at baseline (median 1.5 mg/l [p25-p75:0-5]) and 6 months (median 1.0 mg/l [p25-p75: 0-5]) were not statistically different (p=0.60). To date, 138 baseline samples and 129 follow-up samples have been analyzed. Median infliximab trough levels were similar: 2.05 µg/ml versus 2.00 µg/ml (p=0.18). Antidrug antibodies were detected in 15/32 (47%) patients at baseline and in 10/26 (38%) patients after 6 months.

Conclusion: In the majority of RA, PsA and SpA patients innovator infliximab can be switched to biosimilar infliximab without changes in efficacy, safety and immunogenicity during 6 months follow-up. However, 23% of the patients discontinued biosimilar infliximab, mainly due to a subjective increase in BASDAI score and/or adverse events, possibly explained by nocebo and/or attribution effects rather than pharmacological differences.

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outcomes-after-switching-treatment-from-innovator-infliximab-to-biosimilar-infliximab-in-rheumatic-diseases-in-daily-clinical-practice

Abstract Number: 628

Analysis of Baseline Characteristics of Rheumatoid Arthritis Patients Treated with Abatacept Compared to Those Treated with Tumor Necrosis Factor Inhibitors in Clinical Practice

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Background/Purpose: Currently, the most widely used biological agents for rheumatoid arthritis (RA) patients are the inhibitors of the tumor necrosis factor (TNFi), although other biological agents with different mechanisms of actions, such abatacept, have been approved in the recent years. Although all these drugs are indicated in RA, there is limited data on their use in clinical practice. Our objective is to analyze if there are differences in baseline characteristics of RA patients treated with abatacept, a T-cell costimulation inhibitor, compared with those treated with a TNFi

Methods: All BIOBADASER 2.0 register patients diagnosed with RA and treated with abatacept from January 2008 to December 2014 were selected. Baseline sociodemographic and clinical characteristics were analyzed compared them with RA patients treated with TNFi during the same period. Variables analyzed: age; gender; disease duration; positivity of rheumatoid factor (RF); disease activity at index time (time when the biological drug was initiated) measured by the DAS28-ESR score; number of previous biological agents (0, 1, ≥ 2); and concomitant glucocorticoid treatment. Differences between groups (abatacept vs TNFi) in the baseline DAS28-ESR were analized according to the number of previous biological drugs received

Results: From January 2008 to December 2014, 252 RA patients treated with abatacept and 640 with TNFi were included in the BIOBADASER 2.0 register. Baseline characteristics are shown in Table 1. At baseline, patients treated with abatacept were significantly younger [52.2 (± 13.1) vs 54.6 (± 13.7) years, p=0.018]; had a longer disease duration [12.1 (± 8.1) vs 7.3 (± 8.0) years; p<0.001] and had received a higher number of previous biologics (28.2% vs 7.8% had received one previous biologic; p<0.001; 61.1% vs 1.88% had received ≥ 2 previous biologics; p<0.001). When baseline DAS28-ESR was analyzed, both clustered and stratified according to the number of previous biologics, higher DAS28-ESR was found in RA patients treated with abatacept compared with those treated with anti-TNF, that was statistically significant in patients who had received one previous biologic [DAS28-ESR: 5.20 (± 1.53) vs 4.09 (± 1.95); p<0.001]. No differences were found in gender, positivity of RF and concomitant treatment with glucocorticoids between groups.
Table 1. Baseline Characteristics of Abatacept and TNF inhibitors patients in BIOBADASER 2.0 Registry

Variable Number of patients		Total	Abatacept group	TNF inhibitor group	p-value*
		(n= 892)	(n=252)	(n= 640)	
Age at index date** (years), mean (SD)		55.3 (13.5)	52.2 (13.1)	54.6 (13.7)	**0.018**
Women, n (%)		705 (79.0)	208 (82.5)	497 (77.6)	0.107
Disease duration (years), mean (SD)		8.7 (8.3)	12.1 (8.15)	7.3 (8.0)	**<0.001**
Number of previous biological agents	0	605 (67.8)	27 (10.7)	578 (90.3)	**<0.001**
	1	151 (13.6)	71 (28.2)	50 (7.8)	
	≥ 2	166 (18.6)	154 (61.1)	12 (1.9)	
Concomitant glucocorticoids (%)		512 (57.4)	134 (53.2)	378 (59.1)	0.109
Rheumatoid factor (%)		752 (84.3)	214 (84.9)	538 (84.1)	0.751
Basal DAS28 score, mean (SD)	Clustered	4.74 (1.63)	4.86 (1.74)	4.73 (1.63)	0.597
	Number of previous bDMARD = 0	n= 667*** 4.70 (1.63)	n= 44*** 4.86 (1.74)	n= 623*** 4.69 (1.63)	0.495
	Number of previous bDMARD = 1	n= 490*** 4.28 (1.93)	n= 71*** 5.20 (1.53)	n= 419*** 4.09 (1.95)	**<0.001**
	Number of previous bDMARD ≥ 2	n= 484*** 4.74 (4.17)	n= 137*** 4.99 (1.46)	n= 347*** 4.59 (5.17)	0.412

*p<0.05 **Index date: Age at the time of start of the first biologic ***Number of treatments started in every group available to calculate the DAS28 mean.

Conclusion: Patients with RA treated with abatacept have higher baseline inflammatory activity, a significantly longer disease duration, and have failed more previous biological agents than those treated with TNF inhibitors

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Disclosure: M. V. Hernández, None; **C. Sánchez-Piedra**, None; **J. D. Cañete**, None; **F. Sanchez-Alonso**, None; **J. Manero**, None; **A. M. Ortiz Garcia**, None; **E. Pérez-Pampin**, None; **R. Roselló**, None; **C. Rodriguez-Lozano**, None; **R. Sanmarti**, None; **J. J. Gómez-Reino**, None.

Abstract Number: 629

Golimumab Improves Patient-Reported Outcomes and Socio- and Health-Economic Parameters in Patients with Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA), and Ankylosing Spondylitis (AS): Results from a Non-Interventional Clinical Evaluation in Germany

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster I
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Background/Purpose: Golimumab (GLM) has shown its efficacy and safety in various randomized clinical trials with patients eligible for clinical studies. Data from patient-reported outcomes (PROs) and socio- and health-economic parameters in daily clinical practice in Germany are still lacking.

Methods: Patients were enrolled in the non-interventional prospective study GO-NICE at 158 German sites to explore the disease activity by DAS28, PsARC and BASDAI, the quality of life, fatigue, days of sick leave, quality of work, as well as safety.

Results: 1,613 patients were enrolled. A total of 1,458 (90.4%) patients had a baseline assessment and at least one additional visit and were thus eligible for final analysis. Proportions of patients who completed the study and were still on treatment with GLM at the end of month 24 were as follows: RA (44.9%), PsA (54.6%), and AS (59.2%). At baseline (BL): RA: n=474, mean age 54.9 yrs, 72.8% female, 64.7% biologic-naïve, PsA: n=501, mean age 50.5 yrs, 54.1% female, 56.5% biologic-naïve AS: n=483, mean age 43.6 yrs, 66.5% male, 61.0% biologic-naïve. An improvement of quality of life (EQ-5D-3L) was seen after 6 months and was maintained over 24 months. The patients' health state today (EQ VAS) improved from 51.0 (BL) to 63.4 (RA-), from 48.4 to 64.3 (PsA-) and from 46.8 to 66.5 (AS-patients), the functional ability (FFbH) improved significantly ($p<0.0001$ vs. BL) from baseline 68.2 to 76.1 points (RA-), from 69.0 to 76.8 (PsA-) and from 69.0 to 78.5 (AS-patients), and the mean FACIT-Fatigue score increased significantly ($p<0.0001$ vs. BL) from baseline 32.4 to 38.3 points (RA), from 30.0 to 35.9 points (PsA), and from 29.9 to 37.9 points (AS) over the time until month 24. Days of absenteeism from work due to the underlying disease in the last 6 months were evaluated at BL and after 2 years of treatment. These dropped from 16.2 to 4.1 (RA), from 10.6 to 2.0 (PsA) and from 14.7 to 3.9 days (AS). Days with reduced productivity dropped in patients with RA from 64.5 days (BL) to 29.9 days (month 12) to 23.1 days (month 24), in patients with PsA from 66.6 to 26.6 to 19.8 days, and in patients with AS from 66.3 to 26.1 to 17.3 days within the past six months. The disease impact on quality of work, determined by 0 (no impact) to 10 (very severe impact) decreased within 24 months of treatment from 4.8 to 2.4 (RA-), from 4.8 to 2.2 (PsA-) and from 4.8 to 2.0 (AS-patients) referred to the past 6 months. The proportion of patients who required hospitalization decreased from 10.6% to 1.6%, physiotherapy from 28.8% to 16.6%, and massage treatment from 10.9% to 6.4% within the two years of treatment. The safety profile of GLM was consistent with that observed in other studies of GLM. 4 deaths occurred: 1 patient unlikely related and 3 patients not drug-related to the treatment of GLM

Conclusion: GLM SC once monthly was an effective treatment in patients with RA, PsA and AS in a real-life setting in Germany. Treatment with GLM showed remarkable improvements in clinical effectiveness, patient-reported quality of life parameters and socio- and health economic and. No new safety signals were detected.

Disclosure: K. Krüger, AbbVie, BMS, Celgene,Janssen Biologics, Pfizer, Roche, Sanofi-Aventis, 5; **G. Burmester**, UCB, 2,AbbVie, 5,BMS, 5,Hexal, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,MSD, 5,MadImmune, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,AbbVie, 8,BMS, 8,Hexal, 8,MSD, 8,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **S. Wassenberg**, AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 5,AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 8; **M. Bohl-Buehler**, AbbVie, Hexal, MSD, Roche, UCB, 5; **M. H. Thomas**, MSD Sharp Dohme GmbH Germany, 3.

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Abstract Number: 630

Strategies for Biological Drug Quantification in Biological Drug Immune Responses

Michael Kruse Meyer[1,2], Marlene Andersen[1,3], Troels Vindbæk Stausbo[4], Tue Bjerg Bennike[4,5], Grethe Neumann Andersen[1,6] and Allan Stensballe[3,4], [1]Department of Rheumatology, North Denmark Regional Hospital, Hjørring, Denmark, [2]Laboratory for Medical Mass Spectrometry, Aalborg University, Aalborg, Denmark, [3]Department of Health Science and Technology, Aalborg University, Aalborg, Denmark, [4]Laboratory of Medical Mass Spectrometry, Aalborg University, Aalborg, Denmark, [5]Research Unit for Molecular Diagnostic and Clinical Research, Harvard Medical School, Boston, MA, [6]Center for Clinical Science, Aalborg University, Hjørring, Denmark
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Session Type: ACR Poster Session A
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Background/Purpose: The development of the biological DMARDs has benefitted patients, who previously had no treatment options. Currently no method for stratifying patients to these drugs exist. The biochemistry profile of the patients varies (Meyer et. al. 2016), suggesting that patients need an individualized biochemistry evaluation to improve the stratification process. This is, however, a long term and challenging goal, that will possibly reduce the overall cost of treatment and reduce side effects. Meanwhile, patients in current treatment could benefit today by optimizing their current treatment, through drug concentrations measurements in addition to immune response evaluation. This can be done my immunoassays, but these are not readily scalable, thus we apply targeted proteomics. This requires sequence information of the biological drug, which might not be available. Thus, we present strategies for de-novo sequencing prior to analysis, and show that this proteomics approach readily transfers between biosimilar drugs. The aim of this study was to develop generic scalable and multiplexed targeted mass spectrometry assays to measure four selected biological drugs abatacept, tocilizumab, infiliximab, and biosimilar infliximab in patient sera for therapeutic drug monitoring in RA patients.

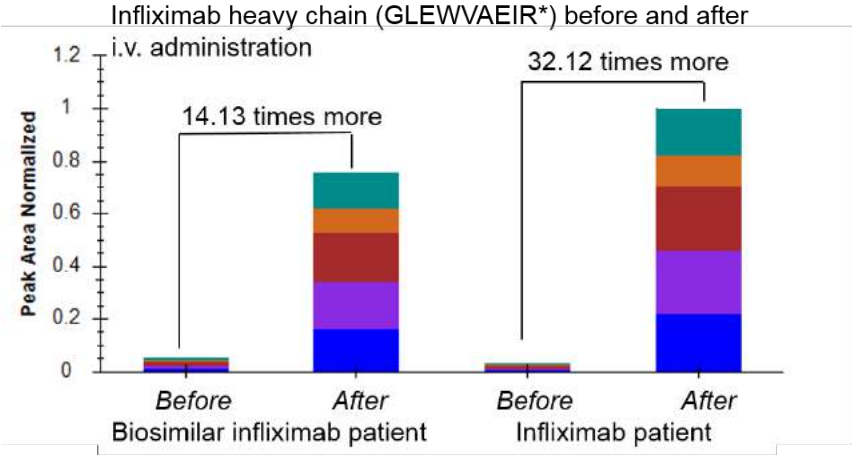
Methods:

30 patients with rheumatoid arthritis in stable i.v. treatment with the four selected biological drugs, are being enrolled in this study and sampled before and after administration of drug. Tandem mass spectrometry, i.e. MALDI-TOF lift-mode, and LC-MS/MS on pure biological drug samples were used to de-novo sequence peptides, build spectral libraries, and subsequently utilized for patient analysis. A parallel-reaction monitoring (PRM) LC-MS/MS assay was developed and applied to targeted peptides unique to the biological drugs.

Results:

Peptides were readily sequenced using MALDI-TOF, and the resulting data, i.e. unique peptide sequences of the four biologics, molecular mass, charge, and chromatographic retention time were used for quantitative targeted PRM on patient samples.

Using the exact preparation and analysis method on infliximab, and biosimilar infliximab provides the same result, due to the shared peptide sequence (Figure 1). This indicates that future biosimilar drugs can be readily quantified with targeted proteomics with no method modifications.



*Peptide target was originally published by Willrich et. al. 2015 (doi:10.1016/j.intimp.2015.07.007)

Conclusion:

Our targeted strategy highlights the strength of proteomics, and targeted proteomics for therapeutic drug monitoring in RA patients. This data-driven strategy will be important in personalized rheumatic medicine by enabling treat-to-concentration therapy.

Disclosure: M. K. Meyer, None; **M. Andersen**, None; **T. V. Stausbo**, None; **T. B. Bennike**, None; **G. N. Andersen**, None; **A. Stensballe**, None.

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Abstract Number: 631

Biologic Free Remission Rate with Etanercept in Rheumatoid Arthritis: A Potential Role of Gender

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Session Time: 9:00AM-11:00AM

Biologic free remission rate with etanercept in rheumatoid arthritis: a potential role of gender A.M. Lurati and A. Laria, D. Mazzocchi, K.A. Re, M. Marrazza, M. Scarpellini Rheumatology Unit, Fornaroli Magenta Hospital, Milan, Italy

Abstract

Background/Purpose: Etanercept is a subcutaneous antiTNF inhibitor approved to treatment of Rheumatoid Arthritis (RA). In literature there are few data about the achievement of a biological free remission in patients treated initially with a combined therapy (i.e. MTX plus antiTNF agent) and there are no data about influence of gender on clinical response to biological or DMARD therapy. Aims of our study were to evaluate the Òbiologic-freeÓ sustained remission rate in patient with RA that achieved a persistent DAS28< 2.6 with a combined therapy MTX plus etanercept and to evaluate the possible influence of gender or menopausal status on clinical response to etanercept.

Methods: A cohort of 169 Italian patients with active (DAS28 >5.1) rheumatoid arthritis (RA) attending the outpatient clinics of the Division of Rheumatology of Fornaroli Magenta Hospital (Milan, Italy) from January 2000 to January 2005 were enrolled in this study and treated with Etanercept as first line biological therapy (50mg/weekly) combines with methotrexate (MTX) (7.5-15 mg/weekly). All patients were prospectively followed every 3 months until now. When a clinical remission (DAS28-ESR <2.6) was obtained and sustained for at least 12 months, the patient interrupted biological treatment. Clinical, laboratory and disease activity measures were obtained at 3, 6 and 12 months after biological discontinuation. If after 12 months a DAS28-ESR worsening > 1.2 was observed, then etanercept was reintroduced and the patient was categorized as relapsed, otherwise the patient was considered as in persistent remission. Statistical Analysis was performed with a Cox regression model based on clinical variables collected was used to predict the odds of develop a biologic free remission status and the cumulative probability of persistent remission

Results: 169 patients were enrolled (37 males, 132 females). Mean etanercept treatment duration was 3.01± 2,7 (0,08-11,35) years. Mean disease duration from diagnosis to last follow up was 15 years ± 8.4. Mean disease duration from diagnosis to enrolment was 8±7.7 years. During the study 34 patients (20.12%) obtained a biologic free persistent remission (25% observed in 3.9 years of treatment, 50% observed in 6.59 years of treatment, 75% observed in 7.8 years of treatment) (Figure 1). Our model showed a increased risk of disease relapsing in women (odd ratio of 1.306, p=0.01) and in long standing disease (odd ratio of 1.11, p=0.03) (Figure 2) (Figure 3). The 50% of remission in males were observed in 2.8 years of treatment with etanercept, in females in 4.1 years.

Conclusion: In our study we observed a significant rate of biologic free persistent remission with etanercept. Gender seems to influence the clinical response with a lower probability of persistent remission in females. Others study are necessary to confirm these data in the future.

Disclosure: A. Lurati, None; **M. Scarpellini**, None; **K. A. re**, None; **M. Marrazza**, None; **D. Mazzocchi**, None; **A. Laria**, None.

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Abstract Number: 632

Comparative Improvement in Health-Related Quality of Life for RA Patients Between TNF-α Inhibitors, Other Biologics, and Tofacitinib: Results from a US-Wide Observational Study

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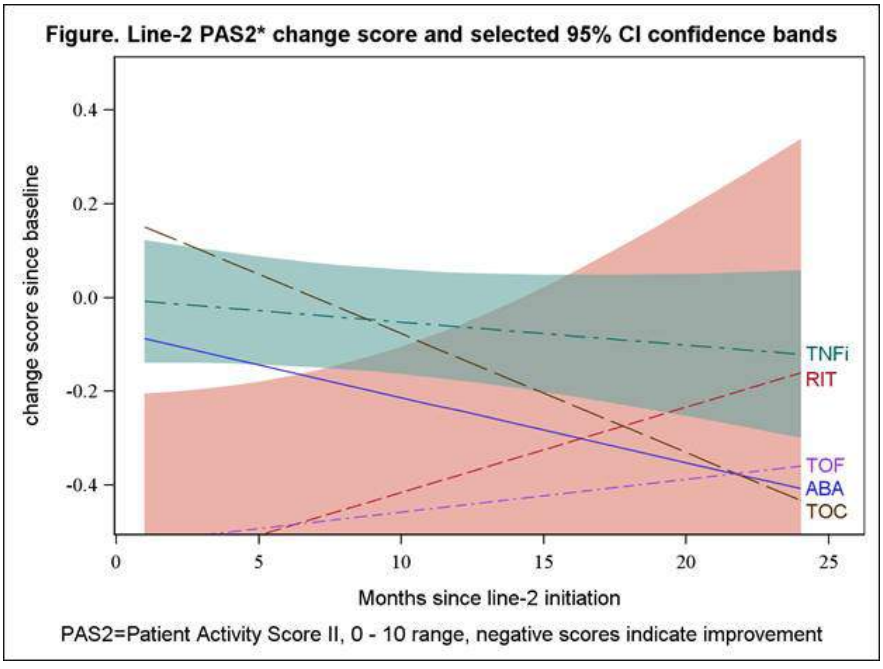
Session Time: 9:00AM-11:00AM

Background/Purpose: We compared changes from baseline for 8 health-related quality of life (HR-QOL) outcomes over two years for patients with rheumatoid arthritis (RA) treated with TNF-α inhibitors (TNFi), non-TNFi biologics (Abatacept (ABA), Rituximab (RIT), and Tocilizumab (TOC)), and Tofacitinib (TOF).

Methods: Participants were patients with RA initiating 1st- and 2nd-line biologic treatment from 2004 to 2015 in the National Data Bank for Rheumatic Diseases, a US-wide observational study that assesses outcomes and medications semi-annually. Over a 2-year period, we evaluated changes in 8 HR-QOL measures (Global assessment [Global], Health Assessment Questionnaire-II [HAQ2], Pain VAS [Pain], Patient Activity Scale-II [PAS2], Short Form 36 Physical [PCS] and Mental [MCS] Component Summary, EuroQOL US [EuroQOL], and Fatigue VAS [Fatigue]). 1st-line therapy was defined as initiation of a TNFi for which the patient was na•ve to any biologic or TOF; 2nd-line therapy was the initiation of the next biologic or TOF after first-line therapy. We calculated change scores for assessments completed after drug initiation by subtracting the baseline (observation before drug initiation) score. Our predictors of change in outcomes were study drug and time since drug initiation. We used mixed models to include fixed effects for drug and random effects for the intercept and slope of time for each individual. The interaction between drug and time was also included. To account for the non-randomization of drug groups, several covariables were added including: baseline age, sex, race, marital status, body mass index (BMI), Rheumatic Disease Comorbidity Index (RDCI), RA duration, and concomitant use of methotrexate and/or prednisone.

Results: The 913 patients analyzed for 1st-line therapy were 79% female with a baseline mean±SD age of 59 ±12 years, RA duration of 16±13 years, and RDCI of 1.7±1.5. There were no statistically significant differences in HR-QOL change scores among TNFis for 1st-line therapy. The 2nd-line cohort (N=2612) was 84% female with mean±SD age and RA duration of 60±12 and 18±12 years, and RDCI of 1.9±1.6. Analyses showed statistically significant superior improvement of Pain (0 – 10) for RIT vs. TNFi (differences of 1.0 at month 1 and ending at 0.6 at month 8) and vs. TOC (differences of 1.6 at month 1 and ending at 1.2 at month 5). RIT also showed significant improvement vs. TNFi at months 1 – 7 for PAS2 (0 – 10), with differences starting at 0.6 at month 1 and ending at 0.4 at month 7 (See Figure).

Conclusion: Results suggest that for 2nd-line therapy, RIT may be superior to TNFi and TOC during the first 5 to 8 months for pain, and during the first ~7 months when compared to TNFi for improving patient activity. For both lines of treatment, most medications were associated with modest improvement for the majority of outcomes in at least part of the study period.



Disclosure: M. G. Cisternas, Pfizer Inc, 5; **K. Michaud**, Rheumatology Research Foundation, Pfizer, 2.

Abstract Number: 633

High Similarity Between Ex-Vivo Inhibited Cytokine Profiling By Golimumab and Adalimumab As a Putative Explanation for Inferior Treatment Response to Golimumab after Adalimumab Failure in Rheumatoid Arthritis

L. Tweehuysen[1], K. Schraa[2], M.G. Netea[3], F.H.J. van den Hoogen[4,5], L.A.B. Joosten[3] and A.A. den Broeder[4], [1]Sint Maartenskliniek, Nijmegen, Netherlands, [2]Internal Medicine, Radboudumc, Nijmegen, Netherlands, [3]Internal Medicine, Radboud University Medical Center, Nijmegen, Netherlands, [4]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [5]Rheumatology, Radboudumc, Nijmegen, Netherlands

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Session Time: 9:00AM-11:00AM

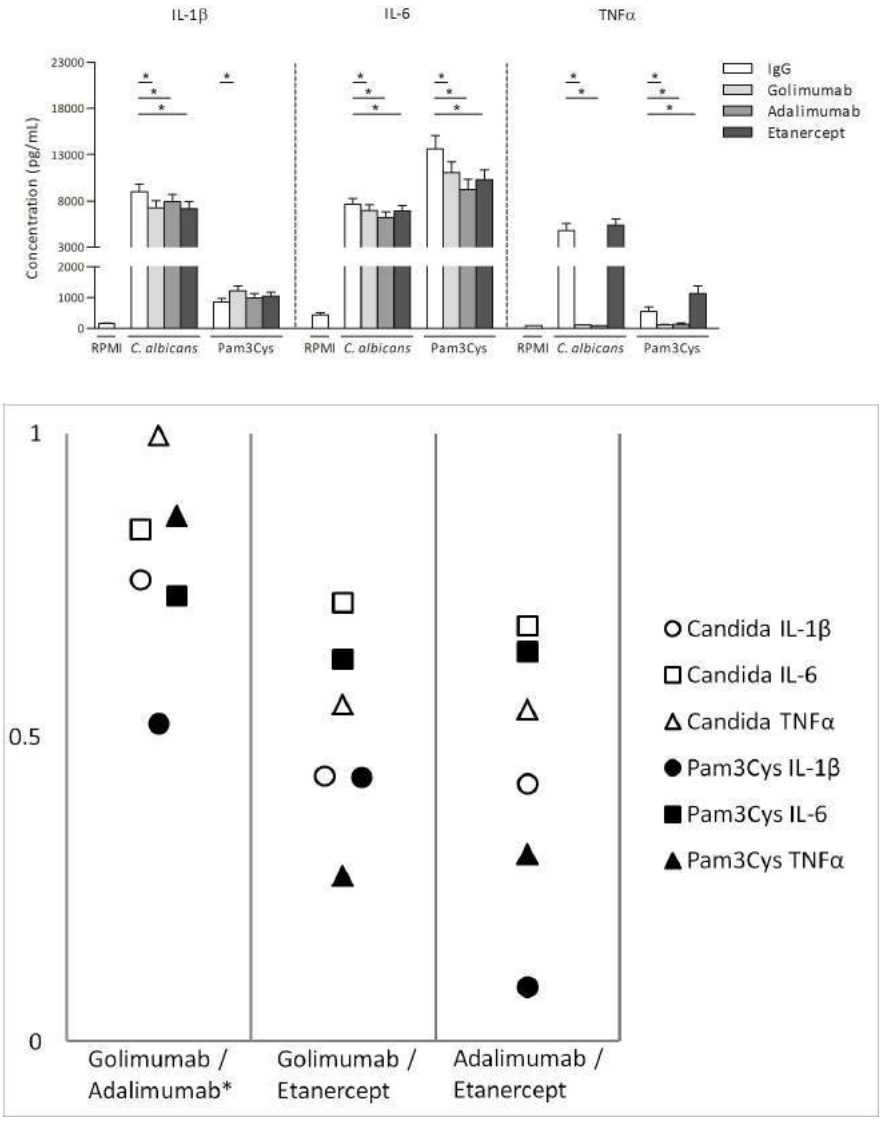
Background/Purpose: Better prediction of treatment response to biologics in rheumatoid arthritis (RA) would contribute to optimal individualized treatment. Clinical data suggest that the response of RA patients to treatment with golimumab is much lower among those who switched from adalimumab than among those who switched from etanercept.[1] To elucidate the mechanism behind this difference in response to sequential biologic treatment, we examined the effect of TNF inhibitors on ex-vivo cytokine production.

Methods: In a prospective longitudinal cohort study, blood samples were obtained from patients at baseline (before start biologic). Peripheral blood mononuclear cells (PBMCs) were isolated, washed and pre-incubated for 1 hour with the therapeutic in-vivo concentration of adalimumab, etanercept or golimumab and stimulated for 24 hours with heat killed *Candida albicans* or Pam3Cys. Cytokine concentrations of IL-1β, IL-6 and TNFα were determined by ELISA. Absolute changes in cytokine levels after inhibition by each TNF inhibitor were calculated and analyzed by means of Spearman rank correlations (r_s).

Results: Ex-vivo cytokine profiling was performed in 71 patients: 66% female, age (mean ± SD): 58 ± 11 years, disease duration (mean ± SD): 10 ± 8 years. Golimumab, adalimumab and etanercept significantly ($p<0.01$) decreased *Candida albicans*-induced cytokine production of IL-1β and IL-6 and Pam3Cys-induced cytokine production of IL-6. In contrast to etanercept, golimumab and adalimumab decreased the concentration of TNFα below the detection limit (Figure 1). Absolute changes in cytokine levels after inhibition by golimumab or adalimumab were all strongly correlated (r_s 0.52 – 0.99, $p<0.001$). These correlations were much lower or non-significant between etanercept and either golimumab or adalimumab (Figure 2).

Conclusion: High similarity between ex-vivo inhibited cytokine profiling by golimumab and adalimumab provides a putative explanation for the previously found inferior treatment response to golimumab after adalimumab failure in RA. This suggests that RA patients who are non-responsive to adalimumab should preferably not switch to golimumab and vice versa. **References:** 1. Smolen JS, Kay J, Matteson EL, et al. Insights into the efficacy of golimumab plus methotrexate in patients with active rheumatoid arthritis who discontinued prior anti-tumour necrosis factor therapy: post-hoc analyses from the GO-AFTER study. *Ann Rheum Dis* 2014;73(10):1811-8. **Figure 1** Ex-vivo cytokine production. Data are

presented as mean+SEM.* p<0.01. **Figure 2** Spearman rank correlations of cytokine profiles.* all correlations p<0.001.



Disclosure: L. Tweehuysen, None; **K. Schraa**, None; **M. G. Netea**, European Research Council, 9; **F. H. J. van den Hoogen**, Celltrion, 9,Sandoz, 9,Biogen Idec, 9; **L. A. B. Joosten**, None; **A. A. den Broeder**, Amgen, 5,ABBVIE, 9,Roche Pharmaceuticals, 9.

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Abstract Number: 634

Use of Biosimilars in Clinical Practice: A Swedish National Register-Based Assessment

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Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [5]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden, [6]Department of Rheumatology, Lund University, Lund, Sweden, [7]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [8]Rheumatology Unit, Karolinska University Hospital, Stockholm, Sweden, [9]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden
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Background/Purpose: In March 2015 the first infliximab biosimilars CT-P13 (Remsima™; Inflectra™), entered the Swedish market. The aim of this study was to evaluate the uptake and factors associated with use of the originator product (Remicade®) and its biosimilars.

Methods: Data from the Swedish Rheumatology Quality register (SRQ) was used to identify all patients with a rheumatic disease who started a treatment with the originator product or with its biosimilars between 1st March 2015 and 29th February 2016. Demographic and disease characteristics were collected and tabulated; and differences were assessed using linear and logistic regression models adjusted for age, gender and residential region. Kaplan-Meier curves were used to visualize survival on drug.

Results: During the study period, 1044 patients started treatment with infliximab; 318 started Remicade, 118 started Inflectra and 608 started Remsima (Table 1). Most patients (68%) who started a biosimilar did so following a switch from the originator product. There were large geographical variations in the relative use of originator vs. the biosimilars. Comparing the relative use across indications, the odds of being treated with a biosimilar was higher among patients with RA (OR: 1.54 (1.09-2.17)) as compared to all the other rheumatic diagnosis. There was no statistically significant difference between patients treated with originator vs. biosimilar regarding age, gender, DAS28 at start of treatment, and duration between start of symptoms and disease diagnosis. By contrast, there was a 35% decreased odds of receiving biosimilar for each unit increase in HAQ (OR: 0.64 (0.44-0.94)), that was not statistically significant after stratification by line of treatment. Biosimilars were preferred over the originator product as second or third line of treatment (OR: 1.69 (1.18-2.41)) compared to other lines of treatment and they were more likely to be prescribed among patients whose most recent biologic was Remicade as compared to other biologic drugs (OR: 4.96 (2.98-8.39)). The Kaplan-Meier curve did not show any difference in survival on drug between the originator product and the biosimilars.

Conclusion: In Sweden, during the 1st year of marketing, most prescriptions of infliximab were made up by the biosimilars products than by the originator product. The choice to prescribe a biosimilar instead of the originator product varied more with contextual factors than with the disease.

Table 1. Baseline characteristics of Swedish patients initiating a biological DMARD Infliximab or a biosimilar CT-P13 therapy, 1 March 2015- 29 February 2016

	Original (Remicade)	Biosimilar (Remsima or Inflectra)
N patients	**318**	**726**
Demographics	318 (30.5%)	726 (69.5%)
Age at start of follow-up (median, IQR)	51 (38-63)	53 (42-65)
Gender (% males)	194 (61.0)	416 (57.3)
Indication (%)		
RA	117 (27.4)	310 (72.6)
PsA	50 (26.3)	140 (73.7)
SpA	65 (32.5)	135 (67.5)
AS	54 (40.0)	81 (60.0)
Other	32 (34.8)	60 (65.2)
Swedish Region (%)		
Norra	20 (74.1)	7 (25.9)
Stockholm	30 (17.0)	146 (83.0)
Sydöstra	65 (62.5)	39 (37.5)
Södra	35 (8.7)	366 (91.3)
Uppsala-Örebro	78 (41.1)	112 (58.9)
Västsvenska	90 (61.6)	56 (38.4)
Number of previous biologics		
0	216 (67.9)	289 (39.8)
1-2	73 (23)	358 (49.3)
3+	29 (9.1)	79 (10.9)
Type of last biologic		
Original (Remicade)	20 (19.6)	297 (68.1)
Biosimilar (Remsima or Inflectra)	11 (10.8)	1 (0.2)
Other TNFi	62 (60.8)	111 (25.5)
Non-TNFi	9 (8.8)	27 (6.2)
Reason for discontinuing previous biologic		
Safety, of those with information (%)	17 (16.7)	22 (5.5)
Inefficacy, of those with information (%)	46 (45.1)	84 (20.8)
Other, of those with information (%)	39 (38.2)	297 (73.7)

Disease characteristics	**1st biological (n=216)**	**≥2nd biological (n=102)**	**1st biological (n=289)**	**≥2nd biological (n=437)**
Disease duration (median, IQR)	6.7 (1.8-16.1)	13.8 (7.9-23.4)	5.4 (2.1-13.7)	15.6 (8.6-25.2)
HAQ (median, IQR)	0.9 (0.5-1.4)	1.0 (0.8-1.3)	0.9 (0.4-1.3)	0.9 (0.4-1.4)
DAS28-ESR (median, IQR)	4.0 (3.0-5.6)	4.3 (3.3-5.1)	4.1 (3.3-4.9)	2.9 (2.2-4.2)
Concomitant MTX (%)	99 (63.1)	31 (47.0)	123 (61.5)	160 (56.5)
Concomitant non-MTX DMARDs (%)	27 (17.2)	4 (6.1)	34 (17.0)	25 (8.8)
Oral steroids (%)	51 (32.5)	24 (36.4)	61 (30.5)	68 (24.0)
NSAIDs (%)	42 (26.8)	29 (43.9)	55 (27.5)	89 (31.4)

Disclosure: D. Di Giuseppe, None; **T. Frisell**, None; **S. Ernestam**, None; **H. Forsblad D'Elia**, None; **E. Lindqvist**, None; **U. Lindström**, None; **J. Askling**, UCB, Roche, Merck, Pfizer, and Abbvie, 2.

Abstract Number: 635

Factors Associated to Lack of Adherence to Subcutaneous Biological Medications in Patients with Rheumatoid Arthritis from Spain. Arco Study

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SESSION INFORMATION

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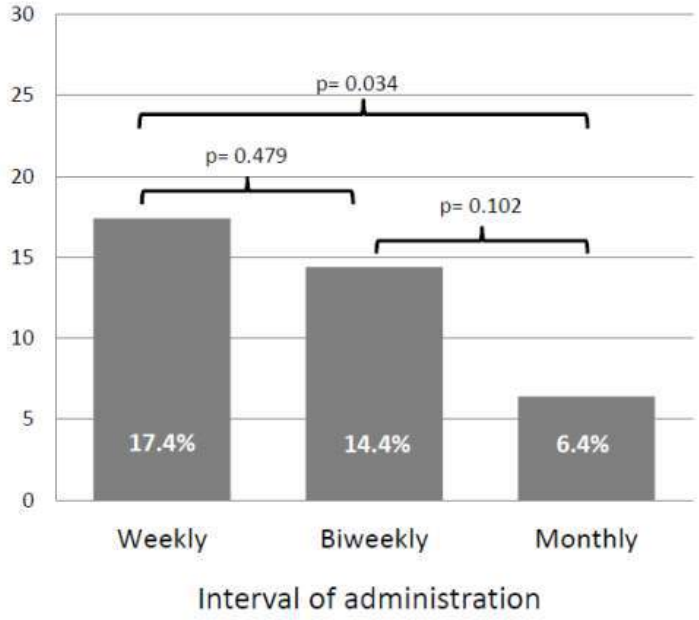
Background/Purpose: To investigate the variables associated to lack of adherence to subcutaneous (SC) biological drug in patients with rheumatoid arthritis (RA) after 1 year of starting therapy.

Methods: ARCO was a retrospective study in RA patients ≥18 years-old from 42 Spanish hospitals, who started a new SC biological drug 12 to 18 months prior to the study visit. Adherence was evaluated through the Medication Possession Ratio (MPR) (number of days covered by the taken medication / days of study period). The number of days covered was calculated with the vials taken by the patient from the hospital pharmacy, taken into account the prescribed interval of administration, changes in this interval and if induction was prescribed. The number of days was the study period, subtracting drug suspension periods. Patients with MPR ≤ 80% were considered non-adherent. Variables associated with non-adherence were studied in a multivariable model that included age, gender, RA duration, interval of administration, induction, order of administration, and changes in the interval of administration.

Results: 364 patients were included (age 54.9 years [12.5]; 77.5% women, median RA duration 7.8 years). The initial interval of administration was weekly (44.2%), biweekly (39.1%) and monthly (17.3%); the median duration of the period studied 14.8 months. A total of 52 patients were non adherent (MPR ≤ 80%) to the prescribed schedule (14.3%; 95% CI: 11.1 – 18.3). Non adherence was more frequent in patients with weekly administration (17.4%) and in those receiving induction (21.6% vs 12.5% without induction, p= 0.068) and less frequent in those with monthly administration (6.4%, figure). The multivariable analysis identified RA duration, induction and interval of administration as independently associated to lack of adherence (table).

Conclusion: Non-adherence to SC biological drugs occurred in 14.3% of patients with RA and was associated to RA duration above the median, weekly interval of administration and prescription of induction.

Figure. Percentage of non-adherent patients (MPR ≤80%) and administration intervals.



Multivariable analysis. Variables associated with non-adherence.			
	Odds ratio	**95% CI**	**p-value**
RA duration above median (>7.8 years)	1.63	0.89–3.05	0.117
No induction (vs. induction)	0.41	0.18–0.93	0.033
Biweekly administration (vs. weekly)	0.54	0.24–1.16	0.125
Monthly administration (vs. weekly)	0.32	0.09–0.87	0.042

Disclosure: J. Calvo-Alen, None; **I. Monteagudo**, None; **G. Salvador Alarcón**, None; **E. Raya Álvarez**, None; **L. Carmona**, None; **L. Cea-Calvo**, Merck Sharp and Dohme, 3; **C. Marras Fernandez-Cid**, None.

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Abstract Number: 636

Prospective, Intervention, Multicenter Study of Utility of Biologic Drug Monitoring with Respect to the Efficacy and Cost of Adalimumab Tapering in Patients with Rheumatic Diseases (34-week descriptive data)

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Background/Purpose: Adalimumab (ADL) dose tapering based on clinical assessment is a usual practice especially in patients who have achieved clinical remission. The primary aim of this study is to analyze how personalized management guided by biological drug monitoring (BDM) in moderate to severe rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) patients impacts the annual direct costs of these patients to the Health System and the quality-adjusted life year with respect to conventional practice in Spain. Secondly, to evaluate the effectiveness of BDM in the reduction of the number of days with high disease activity compared with conventional practice. Follow up will be completed in December 2016; here we present partial descriptive data at 34 weeks.

Methods: Adult patients with RA, PsA or AS treated with ADL who have remained clinically stable for at least 6 months were recruited in three sites. Patients were grouped in Control and Intervention groups according to the recruiting site. All patients were treated with 40 mg of subcutaneous ADL and treatment frequency was adjusted based on physician criteria. All patients are assessed at 8 timepoints (8 visits) for up to 18 months. Trough ADL and anti-drug antibodies levels are measured with Promonitor-ADL and Promonitor-ANTI-ADL (Progenika, Spain). BDM data are released only to the Intervention group, and blinded to the Control group (managed according to clinical assessment only). Physicians in the Intervention group are not obliged to follow any therapeutic algorithm based on BDM results but can use tests to alter doses based on their judgement. Endpoints include DAS28, BASDAI, BASFI and HAQ-DI scores at every timepoint. Criteria for assessing disease scores are identical in the three sites. Cost-effectiveness will be evaluated according to associated costs and QALY.

Results: A total of 169 patients have been recruited (Disease, N Intervention, N Control groups, %) (RA, 30, 33, 37.3%; PsA, 33, 21, 32%; and AS, 46, 6, 30.8%). Median disease duration was 117, 98.5 and 101.5 months for RA, PsA and AS, respectively. At baseline, 10 (16.7%) and 29 (26.6%) patients had low disease activity and 50 (83.3%) and 80 (73.4%) patients were in remission in the Control and Intervention groups respectively, with median trough ADL levels 5.5 and 5.3 mg/L in the Control and Intervention groups respectively. At week 34 median trough ADL levels were 5.2 and 5.5 mg/L in the Control and Intervention groups respectively. Out of the total number of patients who were in remission at baseline (n=117), 69.6% (32/46) and 76.1% (54/71) remained in remission at week 34 in the Control and Intervention groups, respectively. Out of the patients who had low disease activity at baseline (n=35), 28.6% (2/7) and 35.7% (10/28) were in remission at week 34 in the Control and Intervention groups, respectively.

Conclusion: Partial descriptive data point towards a positive effect of BDM-complemented management compared to conventional practice only. This study will provide evidence on the clinical utility of personalized management of patients based on clinical assessment and biological drug monitoring (drug and anti-drug antibody levels) for adalimumab in rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis compared to management based on clinical assessments alone.

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Abstract Number: 637

Biologic Initiation Patterns Among Rheumatoid Arthritis Patients in Moderate or High Disease Activity While Using Conventional Disease Modifying Anti-Rheumatic Drugs

Natalie Boytsov[1], George W. Reed[2], Leslie R Harrold[2,3], Xiang Zhang[1], Carol L Gaich[1], Cynthia J Larmore[1], Ying Shan[2], S Rebello[4] and Andre B. Araujo[1], [1]Eli Lilly and Company, Indianapolis, IN, [2]Corrona, LLC, Southborough, MA, [3]UMass Medical School, Worcester, MA, [4]Epidemiology, Corrona, Southborough, MA

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Background/Purpose: The purpose of this study was to describe biologic initiation patterns over a 1-year follow-up period in rheumatoid arthritis (RA) patients with moderate or high disease activity (M/HDA) while on conventional disease modifying anti-rheumatic drugs (cDMARDs).

Methods: Biologic-naïve RA patients on cDMARD were selected in a US national observational cohort (Corrona RA registry) between 1/1/2006 and 1/31/2016. All patients selected were in M/HDA based on the Clinical Disease Activity index (CDAI >10) and had ≥ 1 year of follow-up and no change in the treatment during 3 months prior to the index date. Index date was the earliest visit the patient met the inclusion criteria. Patients were excluded if their age of RA onset was <18y, or they were exposed to biologics prior to the index date. Patients' demographics, RA disease characteristics, and biologic initiation patterns were described. Baseline demographic and clinical characteristics were compared, using descriptive statistics, between patients who initiated a biologic during the follow-up vs. those who did not.

Results: Out of 11874 cDMARD users in Corrona, 3345 (28%) were in M/HDA and 2217 (19%) met the study inclusion/exclusion criteria. Most patients were female (78%), white (88%) and 64 years of age on average [SD=12]. The mean duration of RA was about 11 years [SD=10] with mean CDAI score of 20 [SD=10] at the index date. About a quarter (n=537) of the patients initiated a biologic, on average, 4 months [SD=3] after the index date. Of biologic initiators, most (85%) received a TNF-inhibitor as their first biologic. There were significant differences between the biologic initiators and non-initiators in baseline demographic and clinical characteristics (Table 1). The initiators were younger, had shorter duration of RA, had fewer comorbidities, but had higher CDAI scores and a higher proportion reported morning joint stiffness. Other RA disease baseline characteristics indicated more severe RA for the initiator group (Table 1). Most (92%) of these patients had M/HDA at the time of the biologic initiation. Among those who did not initiate a biologic, two-thirds remained on their index cDMARD therapy. Of the non-initiators, 11% had unknown disease activity status during the follow-up; among those who had disease activity reported, 53% had achieved LDA and 16% had achieved remission on at least 1 visit during the follow-up; 32% remained in M/HDA.

Conclusion: A minority (24%) of cDMARD users in M/HDA initiated a biologic therapy during the 1 year follow-up. Factors associated with biologic initiation were younger age, shorter duration of RA, less cancer and cardiovascular disease, more severe RA at baseline and higher disease activity during the follow-up.

Table 1. Demographic & clinical characteristics of M/HDA RA patients at the index date

	Treatment status during 1-year follow-up		
	Remained on cDMARD	Initiated a biologic	p*
	n=1680	n=537	
Female, n (%)	1320 (78.6%)	412 (76.7%)	0.167
Age in years, mean (SD)	65.3 (12.2)	59.8 (12.2)	<0.001
Duration of RA in years, mean (SD)	11.6 (10.9)	8.3 (8.6)	<0.001
mHAQ (range: 0 to 3), mean (SD)	0.5 (0.5)	0.6 (0.5)	0.268
Morning Joint Stiffness			
Yes, n (%)	1338 (80.6%)	458 (86.7%)	0.001
Minutes, mean (SD)	104.2 (205.1)	136.9 (255.6)	0.006
Patient Pain[1], mean (SD)	43.3 (28.6)	49.9 (28.3)	<0.001
Fatigue[1,2], mean (SD)	44.7 (28.2)	49.8 (28.5)	0.020
CDAI, mean (SD)	18.2 (8.8)	24.3 (10.9)	<0.001
Rheumatoid Arthritis			
Factor Positivity (RF+), n (%)	979 (64.9%)	241 (68.7%)	0.193
CCP Positivity, n (%)	484 (57.9%)	173 (66.5%)	0.014
Comorbidities			
Malignancies, n(%)	223 (13.3%)	50 (9.3%)	0.015
CVD[3], n (%)	231 (13.8%)	46 (8.6%)	0.002

Abbreviations: mHAQ: modified Health Assessment Questionnaire; CDAI: Clinical Disease Activity Index; RF: Rheumatoid Factor; CCP: Cyclic Citrullinated Peptide antibody; CVD: Cardio-Vascular Disease

[1] Data collection instrument: Horizontal 100-mm Visual Analog Scale (VAS).

[2] Patient reported fatigue was not included in the Corrona RA questionnaire until Version 9 (October 2013) to present

[3] Cardio-Vascular Disease included: myocardial infarction, stroke, acute coronary syndrome, coronary artery disease, congestive heart failure, revascularization procedure including percutaneous coronary intervention, coronary artery bypass grafting or coronary artery stents, ventricular arrhythmia, cardiac arrest, unstable angina, peripheral ischemia, peripheral arterial disease, hypertension, deep vein thrombosis, and transient ischemic attack.

* Significance testing was performed with t-test for continuous variables difference between means and chi-square test of association for categorical variables.

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Abstract Number: 638

A Randomized, Open-Label, Single-Dose, Parallel-Group Trial to Determine the Pharmacokinetics, Safety and Immunogenicity of GP2017, a Proposed Adalimumab Biosimilar, Following a Single Subcutaneous Injection By an Autoinjector or Prefilled Syringe in Healthy Male Subjects

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Background/Purpose: The purpose of this study was to describe the pharmacokinetics (PK), safety and immunogenicity of GP2017, a proposed adalimumab biosimilar, administered as a single subcutaneous injection by autoinjector (AI) or prefilled syringe (PFS).

Methods: This was a single-center, open-label study in healthy male subjects with body weights (BW) ranging from 50 to 140 kg. Subjects were stratified by BW category and randomized 1:1 to treatment with GP2017 40 mg administered by AI or PFS, with follow-up until Day 72. The primary objective was to describe area under the curve (AUC_{0-360h}) and maximum drug concentration (C_{max}) of GP2017 after administration by AI or PFS in subjects with BW between 50.0 and 94.9 kg. Secondary objectives included characterisation of AUC up to the last measurable concentration (AUC_{0-last}) and total AUC (AUC_{0-inf}) for the 50.0–94.9 kg BW category. PK parameters were also characterized in the 50–64.9, 65.0–79.9, 80–94.9 and 95–140 kg BW categories. Safety, immunogenicity and local tolerance were assessed in all treated subjects.

Results: A total of 108 subjects (aged 18 to 55 years) received GP2017 administered by AI (n=54) or PFS (n=54). Of these, 45 and 44, respectively, were in the 50.0–94.9 kg BW category. Demographics and baseline characteristics were well balanced across the treatment groups. For subjects in the 50.0–94.9 kg BW category, 90% confidence intervals (CI) for the ratio of geometric means between treatment groups were contained within standard bioequivalence limits (0.8 to 1.25) for primary and secondary PK parameters (Table). For subjects in the 50.0–140.0 kg BW category, 90% CI were contained within bioequivalence limits for C_{max}, AUC_{0-360h}, AUC_{0-last} and AUC_{0-inf}. The incidence of antidrug antibody (ADA) development was similar for the AI and PFS treatment groups: 69% and 72% of subjects, respectively. The proportion of subjects with neutralizing antibodies was also similar; 57% in the AI group and 59% in the PFS group. As expected, mean serum concentrations of GP2017 decreased at a faster rate in ADA-positive subjects than in ADA-negative subjects, irrespective of whether treatment was administered by AI or PFS. Overall, the incidence of treatment-emergent adverse events (AE) was similar in the AI and PFS treatment groups (reported by 74% and 76% subjects, respectively). Only one serious AE (appendicitis) was reported following administration by PFS, which was considered unrelated to treatment. Five subjects had a mild-to-moderate injection site reaction (n=3 in the AI group and n=2 in the PFS group). Most subjects had no pain, as assessed by the visual analogue scale.

Table. PK comparisons of AI and PFS for subjects with body weights between 50.0 and 94.9 kg.

			Ratio AI/PFS; 90% CI		
PK parameter	AI (n=45)	PFS (n=44)	Estimate	Lower	Upper
C_{max}, µg/mL	4.23	4.46	0.9501	0.8785	1.0275
AUC_{0-360h}, h×µg/mL	1219	1328	0.9176	0.8501	0.9905
AUC_{0-last}, h×µg/mL	2799	2755	1.0159	0.8839	1.1677
AUC_{0-inf}, h×µg/mL	3101	3002	1.0329	0.8946	1.1925

Conclusion: The primary objective of the study was met. Primary and secondary AUC parameters were similar for GP2017 40 mg administered by AI or PFS across a wide range of body weights. GP2017 was well tolerated by healthy male subjects, with no clinically relevant differences between the two treatment groups.

Disclosure: E. Schuck, Hexal AG, 3; **J. Jauch**, Hexal AG, 3; **A. Balfour**, Hexal AG, 3; **J. Storck**, Hexal AG, 3; **M. Rieger**, Hexal AG, 3; **P. Martin**, Hexal AG, 3; **A. Skerjanec**, Hexal AG, 3; **M. Velinova**, PRA Health Services, 3.

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Abstract Number: 639

Switching to Biosimilars in Rheumatology: Evidence-Based Practice

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Background/Purpose: Biosimilars of originator biologic therapeutics are entering the market, and health care professionals and patients need a clear understanding of these new treatments. The advantage of biosimilars is the greater patient access which will follow the probable lower costs, although financial savings will vary between regions. With lower costs, switching from originators to biosimilars will probably be considered. However, clinical and real-word data on the effects of switching are currently limited to transition studies of approved biosimilars. This constitutes a gap in our understanding of the switching process (both originator→biosimilar and between different biosimilars). This study was carried out to summarize the current literature on switching.

Methods: A MEDLINE/Web of Science search identified studies where healthy volunteers or patients receiving infliximab (INF), etanercept (ETN), adalimumab (ADA), or rituximab (RTX) switched between originator biologics and biosimilars.

Results: Switching data was available for 12 studies in rheumatic diseases (Table): INF/CT-P13 (4^{1-4}), INF/SB2 (1^{5}), INF/unidentified biosimilar ($2^{6,7}$), ETN/SB4 ($2^{8,9}$), ETN/GP2015 (1^{10}), ADA/SB5 (1^{11}), and RTX/CT-P10 (1^{12}). The INF/CT-P13 studies showed efficacy and safety of INF and CT-P13 to be similar in switch and maintenance groups, and similar pre- and post-switch. Immunogenicity was assessed in 3 studies and did not change post-switch. In the INF/SB2 study, switch and maintenance groups had similar safety, efficacy, and immunogenicity profiles; comparisons pre- and post-switch were not made. The other 2 INF/biosimilar switch studies showed no difference in efficacy or safety 6 months post-switch. The ETN/SB4 and ETN/GP2015 Phase 1 studies showed similar PK parameters for ETN and the 2 biosimilars. In patients with RA, similar safety, efficacy, and immunogenicity profiles were seen between ETN/SB4 (switch) and SB4/SB4 (maintenance) groups. The ADA/SB5 study showed clinical measures of efficacy, safety, and immunogenicity to be similar in the switch and maintenance groups; comparisons pre- and post-switch were not made. The RTX/CT-P10 study showed clinical measures of efficacy and safety to be similar in the switch and maintenance groups. Efficacy pre- and post-switch could not be compared.

Conclusion: Switching data is starting to become available; mostly with INF but also emerging for other drugs. The one-way switch (originator→biosimilar) with observations ranging from 24 to 56 weeks seems to be the typical design. While initial transition data confirm maintenance of efficacy and safety, additional data from clinical and real-world switching studies, especially of switching between biosimilars, are required, as is continuing pharmacovigilance. Any switching should remain a clinical decision made jointly by the treating physician and patient on an individual patient basis supported by scientific evidence.

Originator/Biosimilar	Study design (Phase)	Indication(s)	No. of patients	Type of switch	Follow-up post-switch	Reference (Study name)
Infliximab/CT-P13	OL extension of DB RCT (3)	RA	302	One-way, bo→bs	48 weeks	[1] Yoo D. H. et al, Ann Rheum Dis 2016 Apr 29 [epub] (PLANETRA)
Infliximab/CT-P13	OL extension of DB RCT (1)	AS	174	One-way, bo→bs	48 weeks	[2] Park W. et al, Ann Rheum Dis 2016 Apr 26 [epub] (PLANETAS)
Infliximab/CT-P13	Observational single-center study	RA, SpA, PsA, JIA, chronic reactive arthritis	39	One-way, bo→bs	variable	[3] Nikiphorou E. et al, Expert Opin Biol Ther 2015;15:1677-83
Infliximab/CT-P13	Observational registry	RA, SpA, PsA, other (not defined)	96	One-way, bo→bs	2-4 months	[4] Glintborg B. et al, EULAR 2016 abstract THU0123
Infliximab/SB2	DB RCT (3)	RA	396	One-way, bo→bs	24 weeks	[5] Smolen J. S. et al, EULAR 2016 abstract FRI0162
Infliximab/Biosimilar	Retrospective single-center study	Inflammatory arthritis	34	One-way, bo→bs	variable	[6] Abdalla A. et al, EULAR 2016 abstract THU0120
Infliximab/Biosimilar	Multi-center study	AS, PsA, SpA, enteropathic arthritis	31	One-way, bo→bs	6 months	[7] Batticciotto A. et al, EULAR 2016 abstract SAT0381
Etanercept/SB4	SB crossover (1)	-	138	One-way, bo→bs, bs→bo	20 days	[8] Lee Y. J. et al, Br J Clin Pharmacol 2016 Mar 11 [epub]
Etanercept/SB4	OL extension of DB RCT (3)	RA	245	One-way, bo→bs	48 weeks	[9] Emery P. et al, EULAR 2016 abstract THU0150
Etanercept/GP2015	Two-way crossover (1)	-	54	One-way, bo→bs, bs→bo	28 days	[10] Afonso M. et al, EULAR 2016 abstract THU0145
Adalimumab/SB5	DB RCT (3)	RA	508	One-way, bo→bs	28 weeks	[11] Weinblatt M. et al, EULAR 2016 abstract FRI0161
Rituximab/CT-P10	OL extension of RCT (1)	RA	87	One-way, bo→bs	56 weeks (maximum)	[12] Yoo D. H. et al, ACR 2015 abstract 1675

OL, open-label; DB, double-blind; RCT, randomized controlled trial; RA, rheumatoid arthritis; bo, biologic originator; bs, biosimilar; AS, ankylosing spondylitis; SpA, spondyloarthritis; PsA, psoriatic arthritis; JIA, juvenile idiopathic arthritis; SB, single-blind

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Abstract Number: 640

Clinical Responses and Synovial Vascularity in Obese Rheumatoid Arthritis Patients Treated with Adalimumab and Methotrexate

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Background/Purpose: Obese rheumatoid arthritis (RA) patients (pts) may have higher levels of inflammatory mediators, greater joint swelling and tenderness, and suboptimal response to therapy. We assessed disease activity and treatment response in obese RA pts, using ultrasonography (US) and clinical measures.

Methods: This *post hoc* analysis used observed data from the MUSICA trial which evaluated the efficacy of high [20 mg/week (wk)] or low (7.5 mg/wk) doses of methotrexate (MTX) in combination with adalimumab (ADA) for 24 weeks (wks) in RA pts with previous inadequate response to MTX who initiated ADA. Pts were grouped according to body mass index (BMI) at baseline (BL): normal BMI<25; overweight BMI ≥25-<30; obese BMI ≥30. Synovial vascularity and hypertrophy were measured by Power Doppler US and Greyscale respectively, bilaterally, at metacarpophalangeal (MCP) joints 2, 3, 5, metatarsophalangeal joint 5 (MTP5) and wrists. Swollen joint count (SJC) of 66 joints, tender joint count (TJC) of 68 joints, 28-joint count Disease Activity Score using C-reactive protein (DAS28-CRP), and numbers of pts reaching American College of Rheumatology (ACR) criteria, Clinical Disease Activity Index [CDAI] low disease activity (LDA,<10), DAS28-CRP low disease activity (LDA; DAS<3.2), were assessed at wks 12 and 24.

Results: Out of 308 pts at BL, 69 pts (22.4%) had BMI <25,102 pts (33.1%) had BMI ≥25-<30 and 137 pts (44.5%) had BMI ≥30. Disease characteristics and ultrasound disease assessments were similar for the 3 BMI subgroups at BL**.** At wks 12 and 24, compared with pts in the normal and overweight categories, obese pts tended to have numerically smaller mean changes from BL in SJC66, TJC68, DAS28-CRP, synovial hypertrophy and synovial vascularity **(table)**. Compared to pts in the normal and overweight categories, significantly fewer obese pts reached ACR20/50 at wks 12 and 24. Significantly fewer obese pts reached CDAI LDA and DAS28-CRP LDA at wk 12; this difference was driven by those obese pts receiving low dosage of concomitant MTX (7.5 mg/wk), although by wk 24, the differences were no longer significant. There was low to no correlation between synovial vascularity/hypertrophy and clinical findings of swelling and tenderness. The proportion of pts with synovial vascularity=0 in the 3 BMI subgroups at wks 12 and 24 was not statistically different.

Conclusion: Among obese RA pts initiating ADA, those on low dosage of concomitant MTX had poorer responses than pts in the normal and overweight categories, as measured clinically and by ultrasound imaging, although this effect was partly overcome by wk 24. Obese RA pts may have an improved clinical benefit if ADA is initiated with high (20 mg/week), rather than low dosage of concomitant MTX.

	week 12			week 24		
MTX mg/wk	**Normal (BMI <25)**	**Overweight (BMI ≥25-<30)**	**Obese (BMI ≥30)**	**Normal (BMI <25)**	**Overweight (BMI ≥25-<30)**	**Obese (BMI ≥30)**
Mean change from baseline in SJC66						
7.5	-8.7 (1.45)	-10.2 (1.24)	-7.3 (1.11)	-8.3 (1.70)	-11.2 (1.37)	-7.2 (1.23)
20	-12.1 (1.58)	-8.3 (1.26)	-9.3 (1.04)	-13.9(1.76)	-11.6(1.37)	-10.3 (1.16)
Overall	-10.4 (1.08)	-9.2 (0.88)	-8.3 (0.76)	-11.1 (1.22)	-11.4 (1.0)	-8.7 (0.85)
Mean change from baseline in TJC68						
7.5	-16.0 (2.24)	-14.5 (1.87)	-14.2 (1.67)	-16.7 (2.36)	-19.6 (1.90)	-15.8 (1.71)
20	-16.5 (2.38)	-15.44 (1.91)	-13.6 (1.58)	-18.1 (2.44)	-19.4 (1.91)	-17.3 (1.62)
Overall	-16.2 (1.64)	-15.0 (1.33)	-13.9 (1.15)	-17.4 (1.70)	-19.5 (1.35)	-16.6 (1.18)
Mean change from baseline in synovial hypertrophy						
7.5	-1.1 (0.91)**	-2.9 (0.73)**	0.7 (0.67)**	-1.8 (0.88)	-2.1 (0.71)	0.3 (0.66)
20	-2.0 (0.94)	-1.0 (0.75)	-0.8 (0.61)	-0.8 (0.95)*	-1.3 (0.71)*	1.0 (0.60)*
Overall	-1.55 (0.65)*	-2.0 (0.52)*	-0.1 (0.45)*	-1.3 (0.65)	-1.7 (0.50)	-0.34 (0.44)
Mean change from baseline in synovial vascularity						
7.5	-1.7 (0.64)	-1.3 (0.52)	-0.7 (0.47)	-2.0 (0.59)	-1.2 (0.47)	-1.6 (0.44)
20	-2.3 (0.66)	-1.6 (0.53)	-1.5 (0.43)	-2.1 (0.64)	-1.3 (0.48)	-1.7 (0.40)
Overall	-2.0 (0.46)	-1.4 (0.37)	-1.1 (0.32)	-2.0 (0.43)	-1.3 (0.34)	-1.7 (0.30)
Patients reaching ACR 20, n/N (%)						
7.5	20/34 (58.8)*	29/48 (60.4)*	23/60 (38.3)*	21/30 (70.0)**	32/46 (69.6)**	25/57 (43.9)**
20	18/30 (60.0)	24/47 (51.1)	33/69 (47.8)	18/28 (64.3)	30/46 (65.2)	36/63 (57.1)
Overall	38/64 (59.4)*	53/95 (55.8)*	56/129 (43.4)*	39/58 (67.2)	62/92 (67.4)	61/120 (50.8)
Patients reaching ACR 50, n/N (%)						
7.5	10/34 (29.4)*	13/48 (27.1)*	5/60 (8.3)*	14/30 (46.7)	17/46 (37.0)	12/57 (21.1)
20	13/30 (43.3)	14/47 (29.8)	15/69 (21.7)	11/28(39.3)	20/46 (43.5)	20/63 (31.7)
Overall	23/64 (35.9)**	27/95 (28.4)**	20/129 (15.5)**	25/58 (43.1)	37.9 (40.2)	32/120 (26.7)
Patients reaching DAS28-CRP LDA, n/N (%)						
7.5	10/31 (32.3)	10/46 (21.7)	7/57 (12.3)	12/29 (41.4)	16/46 (34.8)	13/55 (23.6)
20	8/25 (32.0)	14/42 (33.3)	10/67 (14.9)	7/24 (29.2)	19/44 (43.2)	22/58 (37.9)
Overall	18/56 (32.1)**	24/88 (27/3)**	17/124 (13.7)**	19/53 (35.8)	35/90 (38.9)	35/113 (31.0)

P values for comparison between BMI subgroups. **p* <.05, ** <.001. Chi-squared test was used for categorical variables, ANCOVA adjusting for baseline, treatment and BMI group was used for continuous variables.

Disclosure: G. S. Kaeley, AbbVie, 5; **V. K. Ranganath**, Genentech, Pfizer, 8,BMS, 9; **D. K. MacCarter**, AbbVie, 8,AbbVie, 5; **A. L. Pangan**, AbbVie, 1,AbbVie, 3; **X. Wang**, AbbVie, 1,AbbVie, 3; **J. Kalabic**, AbbVie, 1.

Abstract Number: 641

Reduction of Concomitant Oral Methotrexate or Corticosteroids in Combination Treatment with Adalimumab Does Not Affect Effectiveness in Patients with Rheumatoid Arthritis

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Background/Purpose: In rheumatoid arthritis (RA) patients (pts) receiving corticosteroids (CS) or methotrexate (MTX) with an anti-TNF, such as adalimumab (ADA), the concomitant CS or MTX dose may be reduced if pts respond well or have side-effects. The objective of the study was to assess treatment effectiveness in pts whose MTX or CS oral dose was reduced over 10 years (y) of open label (OL) ADA treatment.

Methods: This was observed data from OL extensions (OLE) of the PREMIER and DE019 trials.[1,2] In PREMIER, MTX-naïve, early RA pts received ADA/MTX/ADA+MTX for 2y, and optional OL ADA for upto 8y. In DE019, biologic-naïve, established RA pts received 20 mg ADA+MTX/ 40mg ADA+MTX/PBO+MTX for 1y and optional OL ADA+MTX for upto 9y. In both OLEs, MTX could be added/adjusted at the investigator's discretion, and oral CS dose could be tapered in pts who responded. Effectiveness at final visit (FV) was assessed by the numbers of pts achieving TJC68 = 0, SJC66 = 0, improvement from baseline in HAQ-DI ≥0.5 (HAQ-DI 0.5), ACR20/50/70 criteria and 28-joint disease activity score based on C-reactive protein (DAS28-CRP)<2.6. Additionally, in PREMIER, modified EULAR remission (REM) criteria [DAS28-CRP<2.6, TJC68 ≤1, SJC66 ≤1], "Good EULAR response" [DAS28-CRP<3.2 with a change from baseline ≤-1.2] were used.

Results: In **PREMIER,** by the pt's FV, out of 375 pts who had any oral CS, 220 (58.7%) were on ongoing CS; 155 (41.3%) had stopped. Among the 375 pts, 32% had a stable CS dose and 26.1% had a CS dose reduction. Dose reduction did not affect the proportion of pts reaching ACR criteria, HAQ=0.5 and DAS28-CRP<2.6 by FV **(table)**. Out of 497 pts in the OLE, 261 (52.5%) used concomitant MTX in the OLE, 236 pts did not. With/without MTX, the number of pts with DAS28-CRP<2.6 increased from 2- 10y, and the proportion of pts with SJC or TJC=0, good EULAR response, or modified EULAR REM criteria and the HAQ-DI scores were comparable in the +/- MTX groups. In **DE019,** by the pt's FV, out of 352 pts who received any oral CS, 207 (58.8%) were on ongoing CS and 145 (41.2%) had stopped CS. Among the 352 pts, 141 (40%) had a stable CS dose and 82 pts (23.3%) had a dose reduction. Out of 550 pts on MTX during the study, 497 (90.4%) were receiving MTX, and 53 (9.6%) had stopped by FV; 345/550 pts (62.7%) had stable MTX and 158 (28.7%) had a reduction. Reduction of CS or MTX did not affect the proportion of pts who reached the ACR criteria, HAQ DI 0.5 and DAS28-CRP<2.6 by FV.

Conclusion: Overall, effectiveness associated with continuous ADA treatment was not sacrificed in pts in whom concomitant oral CS or/and MTX doses were reduced or discontinued, although many of these pts were likely responding well at the time of taper. **References:** 1. Keystone et al. J Rheum 2013;40:1487-97 2. Keystone et al. J Rheum, 2014;41:5-

14

Table: Impact of dose changes in concomitant oral corticosteroids or MTX on effectiveness by final visit, n/N (%)		
PREMIER		
	Stable CS dose	**Decreased CS dose**
ACR20	66/117 (56.4)	71/98 (72.4)
ACR50	44/117 (37.6)	55/98 (56.1)
ACR70	26/117 (22.2)	42/98 (42.9)
HAQ-DI 0.5	48/118 (40.7)	48/98 (49.0)
DAS28-CRP <2.6	47/119 (39.5)	57/98 (58.2)
	With MTX use	**Without MTX use**
TJC68=0	97/261 (37.2)	115/234 (49.1)
SJC66=0	114/261 (43.7)	129/234 (55.1)
Modified EULAR REM criteria	87/261 (33.3)	113/233 (48.5)
"Good" EULAR-CRP	169/259 (65.3)	177/232 (76.3)
Mean HAQ-DI at final visit	0.7 (0.7)	0.6 (0.7)
DE019		
	Stable CS dose	**Decreased CS dose**
ACR20	164/323 (50.8)	98/153 (64.1)
ACR50	109/323 (33.7)	75/153 (49.0)
ACR70	63/323 (19.5)	57/153 (37.3)
HAQ-DI 0.5	137/342 (40.1)	75/158 (33.5)
DAS28-CRP <2.6	100/323 (31.0)	188/524 (35.9)
	Stable MTX dose	**Decreased MTX dose**
ACR20	57/128 (44.5)	45/78 (57.7)
ACR50	31/128 (24.2)	38/78 (48.7)
ACR70	18/128 (14.1)	26/78 (33.3)
HAQ-DI 0.5	54/139 (38.8)	37/82 (45.1)
DAS28-CRP <2.6	29/128 (22.7)	35/80 (43.8)
MTX, methotrexate; CS, corticosteroid; ACR, American College of Rheumatology; HAQ-DI, health assessment questionnaire- disability index; DAS28-CRP, 28-joint count disease activity score based on c-reactive protein; TJC68, tender joint count at 68 joints; SJC, swollen joint count at 66 joints.		

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Abstract Number: 642

Quality of Life Outcomes Following Therapy with Chs-0214 and Etanercept (Enbrel): Randomized, Double-Blind Study in Subjects with Rheumatoid Arthritis

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Background/Purpose: CHS-0214 is in development as a proposed biosimilar of etanercept. This Phase III confirmatory, safety and efficacy study randomized and dosed 644 subjects with rheumatoid arthritis (RA) in 13 countries. Health-related quality of life (QOL) outcomes were based on the Health Assessment Questionnaire – Disability Index (HAQ-DI), Subject Pain Assessment (SPA), Subject Global Assessment (SGA), and Physician Global Assessment (PGA).

Methods: Subjects had moderate/severe RA and an inadequate response to methotrexate (MTX). Subjects were randomized 1:1 to CHS-0214 or etanercept (commercial European-sourced) at 50 mg SC QW for 24 weeks (Part 1) and then received CHS-0214 50 mg SC QW open-label for 24 weeks (Part 2). Subjects continued on their stable dose of MTX throughout the study.

Results: The evaluable population for efficacy analysis in Part 1 included 512 subjects of mean age (50.6 vs 51.4 years), most of whom were female (81% vs 81%) and white (73% vs 71%) or Asian (25% vs 26%) for CHS-0214 vs etanercept, respectively. At baseline, subjects had a mean duration of RA of 6.9 vs 6.8 years and a mean DAS28-CRP(4) of 5.4 vs 5.4 for CHS-0214 vs etanercept, respectively. The primary endpoint of the study, ACR20 response at 24 weeks, was met in 91.0% vs 90.6% of subjects for CHS-0214 vs etanercept, respectively. The 95% CI of the treatment difference (0.41%) was [-4.55%, 5.37%], which fell within the predefined margin for equivalence of [-15%, 15%]. Mean scores on the HAQ-DI were 1.2 vs. 1.2 at Baseline with CHS-0214 and etanercept, respectively, and decreased 53% vs. 51% to 0.6 vs. 0.6 at Week 24. Mean scores on the SPA were 58.5 vs. 57.4 at Baseline with CHS-0214 and etanercept, respectively, and decreased 64% vs. 64% to 20.2 vs. 19.9 at Week 24. Mean scores on the SGA were 59.8 vs. 58.8 at Baseline with CHS-0214 and etanercept, respectively, and decreased 66% vs. 64% to 19.9 vs. 20.6 at Week 24. Mean scores on the PGA were 60.2 vs. 58.1 at Baseline with CHS-0214 and etanercept, respectively, and decreased 72% vs. 69% to 17.1 vs. 17.7 at Week 24. Overall, treatment emergent adverse events in Part 1 were reported in 60.8% of 324 subjects in the CHS-0214 treatment arm and 65.0% of 320 subjects in the etanercept treatment arm. The majority of adverse event were mild or moderate in severity. No deaths were reported.

Conclusion: This randomized, double-blind, active-control, global study demonstrated equivalence of CHS-0214 to etanercept based on the primary endpoint. The levels of improvement in health-related QOL measures were similar in both treatment groups.

Disclosure: A. J. Kivitz, Coherus, 9; **J. R. O'Dell**, Coherus, Medac, Lilly, BMS, GSK, 9; **T. Takeuchi**, Astellas, BMS, Celtrion, Chugai, Daiichi-Sankyo, Eisai, Mitsubishi Tanabe,Nipponkayaku, Pfizer, Sanofi-Aventis, Santen, Takeda, Teijin Pharma, AbbVie, Asahi Kasei Pharma, Taisho Toyama, Janssen, Astra Zeneca, Eli-Lilly Japan, and Novartis, 5; **Y.**

Tanaka, Abbvie, Chugai, Astellas, Takeda, Santen, Mitsubishi-Tanabe, Pfizer, Janssen, Eisai, Daiichi-Sankyo, UCB, GSK, BMS, MSD, and Novartis, 5; **S. Nakashima**, Daiichi Sankyo, 3; **C. Kelleher**, Coherus BioSciences, 3,Coherus BioSciences, 1; **J. Hodge**, Coherus BioSciences, 1,Coherus BioSciences, 3; **B. Finck**, Coherus Biosciences, 1.

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Abstract Number: 643

Exposure-Response Analyses of Efficacy of ABT-122, a Dual-Variable Domain Immunoglobulin (DVD-Ig™) Targeting TNF-α and IL-17A, Compared with Adalimumab in Subjects with Rheumatoid Arthritis and Background MTX

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Background/Purpose: ABT-122 is a novel dual-variable domain immunoglobulin (DVD-IgTM), which specifically neutralizes both TNF alpha (TNFα) and interleukin-17A (IL-17). Both cytokines are expressed at increased levels in rheumatoid synovial tissue and are believed to contribute to joint inflammation and structural damage to bone and cartilage that are hallmarks of rheumatoid arthritis (RA). Drugs individually neutralizing TNFα and IL-17 have demonstrated efficacy in patients with RA. The objective of this work was to quantitatively characterize the relationship between ABT-122 serum concentrations and time course of ACR20/50/70 and DAS28 (CRP) response following treatment with ABT-122 in subjects with RA who had an inadequate response to methotrexate in a Phase 2 study.

Methods: ABT-122 doses of 60 mg every other week (EOW; N=55), 120 mg EOW (N=56) and 120 mg every week (EW; N=55) were evaluated in this 12-week Phase 2, randomized, double blind, active comparator [adalimumab, 40 mg EOW (N=56)] study. Serial ABT-122 and adalimumab serum concentrations, collected every week and time course of efficacy data collected at baseline and weeks 2, 4, 6, 8, and 12, were analyzed using non-linear mixed-effects modeling. The relationships of ABT-122 and adalimumab average serum concentrations (C_{avg}) during the dosing interval and ACR20/50/70 responses were characterized using a Markov model, where active therapies enhanced transition of the status of patients to higher levels of response (e.g. no response to ACR20, ACR20 to ACR50, ACR50 to ACR70). For DAS28 (CRP), indirect response models with ABT-122 and adalimumab suppressing the DAS28 (CRP) scores were utilized.

Results: ABT-122 dose of 120 mg EOW provided comparable molar serum exposures to adalimumab 40 mg EOW, whereas the 60 mg EOW dose and the 120 mg EW doses provided exposures lower and higher than adalimumab, respectively. The EC_{50} (the concentration associated with 50% of maximal effect) on the transition rates to higher ACR response for ABT-122 and adalimumab were estimated to be 2.6 nM and 7.2 nM, respectively, with largely overlapping confidence intervals. The IC_{50} values, the concentrations associated with 50% of maximal reduction of DAS28 (CRP) scores for ABT-122 and adalimumab were both estimated to be 8 nM, with maximum inhibition of the baseline DAS28(CRP) level fixed to 60% based on observed data. These analyses indicate that the ACR20/50/70 and DAS28 (CRP) responses of ABT-122 plateau at exposures associated with 120 mg EOW dose in RA patients.

Conclusion: ABT-122 dose range evaluated in this Phase 2 study was adequate to describe the exposure-response relationships for ACR and DAS28 (CRP). ABT-122 and adalimumab potency values were not distinguishably different and Week 12 efficacy was comparable for the two agents at similar molar exposures (i.e. after pharmacokinetic differences are accounted for, both agents appear to provide similar efficacy). No significant increment in ABT-122 efficacy is estimated at doses higher than 120 mg EOW in patients with RA.

Disclosure: A. Khatri, AbbVie, 1,AbbVie, 3; **B. Klunder**, AbbVie, 1,AbbVie, 3; **M. Minocha**, AbbVie, 1,AbbVie, 3; **H. T. Mansikka**, AbbVie, 1,AbbVie, 3; **A. A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 644

Seroprevalence and Its Impact on Radiographic Damage in Korean Rheumatoid Arthritis Patients Starting Biologics

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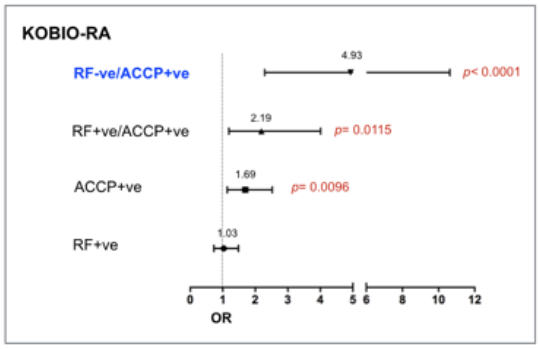
Background/Purpose: High titers of rheumatoid factor (RF) and anti-cyclic citrullinated peptide antibody (ACCP) are poor prognostic factors for rheumatoid arthritis (RA) patients. Only few studies have investigated the detailed clinical subtypes or radiographic changes based on serologic status; double (RF/ACCP) positive (+ve), RF or ACCP +ve, double negative (-ve) (seronegative, SN). We aimed to analyze the clinical and radiographic features of RA patients with robust disease activity, based on their serologic status.

Methods: RA patients registered in the Korean College of Rheumatology Biologics Registry (KOBIO), a nationwide inception cohort, were analyzed. Data regarding patient demographics, comorbidity, disease activity, medication, imaging and laboratory exams were utilized. After adjusting for gender, age, disease duration, and smoking history, we analyzed the association of seropositivity and bony erosion (hands and feet X-ray), and the association of the ACCP titer and joint damage, both at baseline (initiation of biologics) presented as odd ratio (OR) and its 95% confidence interval [95% CI].

Results: Data of 1198 RA patients were investigated. Mean age was 57.2 years, and disease duration was 8.3 +/- 7.6 years. Mean DAS28-ESR was 5.71, and erosion were found in 40.1% of patients. Being ACCP+ve was significantly associated with bony erosions (OR 1.69 [95% CI 1.13-2.52], p= 0.0096), compared with RF+ve (OR 1.03 p= 0.83), or RF+ve/ACCP+ve (OR 2.19 [95% CI 1.19-4.01], p= 0.012). Of note, being ACCP+ve/RF-ve was strongly associated with radiographic damage (OR 4.93 [95% CI 2.29-10.61], p< 0.0001) in our analysis (figure). In contrast, a multivariate logistic regression analysis showed that baseline ACCP titers were not positively associated with joint damage; a multivariate linear regression model revealed disease duration (estimate -3.95, p< 0.0001) and RF titer (estimate +0.0665, p= 0.0157) were associated with ACCP titers.

Conclusion: Our data demonstrate the significance of ACCP in predicting radiographic damage in established Korean RA patients with persistently high disease activity. Longitudinal studies would be needed to clarify the impact of ACCP titers on radiographic progression.



Disclosure: K. Shin, None; **S. Ha**, None; **I. Jung**, None; **H. A. Kim**, None; **S. S. Lee**, None.

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Abstract Number: 645

Prospective Observational Real-Life Study (STRATEGE) Shows the Efficacy of Treat-to-Target Strategy and Methotrexate Monotherapy Optimization in Patients with Established Rheumatoid Arthritis

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Background/Purpose: Current guidelines consider MTX as initial gold standard treatment for patients (pts) with RA. They also propose various strategies for MTX inadequate responders, among which the most frequent are optimization of MTX therapy (alone or in combination with other csDMARDs or biological treatment). The objective of the trial was to explore the strategies applied in daily practice in RA pts with inadequate response to MTX.

Methods: STRATEGE is a prospective, observational, multicenter study. Main inclusion criteria were: confirmed RA diagnosis (ACR 1987 or ACR/EULAR 2010 criteria) and treatment by MTX monotherapy with clinical, structural, functional and/or therapeutic evolution leading to therapeutic management modification. Data were obtained at 2 time-points: baseline and 6-month follow-up.

Results: Between Sept 2014 and July 2015, 176 rheumatologists, at 90% with private practice, included 854 pts, 801 of

which composed the analyzable baseline set. Pts baseline characteristics were [mean (SD)]: age: 57.4 (13.7) yrs; RA duration: 5.3 (6.7) yrs; DAS28: 4.0 (1.1), with the following distribution: <2.6 for 10%, >3.2 for 74% and >5.1 for 16%; HAQ: 1.1 (0.84); and extra-articular features and erosive disease for respectively 10.5% and 39.9% of pts. All pts were receiving MTX monotherapy, orally for 67.6% and at mean (SD) dose of 14.2 (4.1) mg/wk for oral and 16.6 (3.8) mg/wk for parenteral administration. Auto-injections were performed by 50.7% of pts treated parenterally. Concomitant treatment included corticosteroids for 45.8% of pts, at a mean (SD) dose of 8.2 (6.3) mg/d, and folic acid for 90.0%. After the inclusion visit, MTX prescription has been identically maintained (dose and route) for 28.1% of pts, interrupted for 1.9% and modified for 70.0%. Changes included dose increasing for 50.2%, dose tapering for 1.8% and a route modification for 21.4% (88.2% oral -> parenteral). After inclusion visit, MTX oral versus (vs) parenteral balance was respectively 49.8% at mean (SD) dose 16.2 (4.0) mg/wk vs 45.8%, 18.0 (3.9) mg/wk. Biologic treatment was initiated for 14.6%, in association with MTX for 95.7%. Other csDMARD treatment was initiated for 1.2% in monotherapy and for 3.6% in association with MTX. The reasons for treatment modification were mainly active RA (72.0%), worsening of clinical and biologic parameters (31.4%), radiographic progression (14.5%), remission not achieved (12.4%), steroid dependence (11.3%), and MTX intolerance 5.0%. Six-month follow-up results show that all the active treatment strategies were significantly and equally successful in improving disease activity (Table).

	N	DAS28 Baseline	DAS28 M6	D DAS28	*p*
MTX unchanged (Ref.)	126	3.4 (1.3)	2.5 (1.0)*	- 0.8 (1.2)	-
MTX optimization	519	4.0 (1.0)	2.9 (1.2)*	- 1.1 (1.3)	0.10
bDMARDs	117	4.6 (1.1)	3.2 (1.1)*	- 1.4 (1.3)	0.22
csDMARDs	39	4.3 (1.2)	3.1 (1.3)*	- 1.3 (1.4)	0.37

Data presented: mean (SD) * $p < 0.0001$ (M6 *vs* baseline), ANCOVA, adjusted for DAS28 at baseline

Conclusion: Consistently with all current guidelines, results of the large prospective observational French study STRATEGE reveal an important place held by initial MTX treatment optimization before initiation of a biotherapy and emphasize the importance of treat-to-target strategy.

Disclosure: R. M. Flipo, Nordic Pharma, 5; **C. Gaujoux-Viala**, Nordic Pharma, 5; **C. Hudry**, Nordic Pharma, 5; **E. Zinovieva**, Nordic Pharma, 3; **E. Leutenegger**, Nordic Pharma, 5; **H. Herman-Demars**, Nordic Pharma, 3.

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Abstract Number: 646

Population Pharmacokinetics of ABT-122, an Immunoglobulin Targeting Both TNF-α and IL-17A: Analyses Across Phase 1 Studies in Healthy Volunteers and Phase 2 Studies in Subjects with Rheumatoid or Psoriatic Arthritis

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Background/Purpose: ABT-122 is a novel dual-variable domain immunoglobulin (DVD-Ig™), which specifically neutralizes both TNF alpha (TNFα) and interleukin-17A (IL-17). Drugs individually neutralizing TNFα or IL-17 have demonstrated efficacy in patients with RA and PsA. The objective of this work was to characterize the pharmacokinetics of ABT-122 and the effect of patient-specific covariates on ABT-122 exposures using available Phase 1 and 2 data in healthy volunteers (HV) and subjects with RA and PsA.

Methods: ABT-122 serum concentrations (approximately 4400 samples) from two Phase 1 single-dose studies in HV (N=72 subjects; ABT-122 doses: 0.1 to 10 mg/kg administered intravenously [IV] and 0.3 to 3 mg/kg administered subcutaneously [SC]), two Phase 1 multiple-dose studies in subjects with RA (N=31 subjects; ABT-122 doses: 1 mg/kg SC every other week [EOW] and 0.5 to 3 mg/kg SC every week [EW] for 8 weeks) and two Phase 2 studies, one each in subjects with RA (N=165 subjects; ABT-122 doses: 60 mg SC EOW to 120 mg SC EW for 12 weeks) and PsA (N=144 subjects; ABT-122 doses: 120 mg SC EW to 240 mg SC EW for 12 weeks) were included in this analysis. The effect of clinically relevant covariates on ABT-122 exposures were evaluated. Data were analyzed using non-linear mixed-effects modeling.

Results: ABT-122 serum concentrations were characterized using a two-compartment pharmacokinetic model with a combination of first-order (linear) and saturable (non-linear) eliminations. For reference intravenous administration, ABT-122 linear clearance and steady-state volume of distribution were 0.419 L/day and 6.0 L, respectively. The contribution of saturable elimination was negligible in the dose range evaluated in Phase 2 studies (range of 60 mg EOW to 240 mg EW SC). ABT-122 absolute SC bioavailability ranged from about 35% to 55% for different formulations and studies. ABT-122 terminal elimination half-life was approximately 9 days. Subjects with bodyweights of 42 and 137 Kg (lowest and highest in the dataset) were estimated to have about 30% lower and 60% higher ABT-122 clearance, respectively, relative to a 70 kg individual. ABT-122 clearance increased with the increase in ABT-122 anti-drug antibody titers, with an anti-drug antibody titer of 100 units estimated to result in 5-fold increase in ABT-122 clearance. In Phase 2 studies, incidence and titers of ABT-122 anti-drug antibodies decreased as the dose increased.

Conclusion: ABT-122 clearance is estimated to be approximately 3-fold faster than the well characterized values for adalimumab, leading to 3-fold higher ABT-122 dose needed to provide equivalent serum exposures to adalimumab. The developed pharmacokinetic and covariate models for ABT-122 enabled integrated exposure-response analyses across ABT-122 development program, allowing better understanding of the responses to dual TNF and IL-17 inhibition with this novel DVD.

Disclosure: A. Khatri, AbbVie, 1,AbbVie, 3; **A. A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 647

Genomic and Epigenetic Bioinformatics Demonstrate Dual TNF-α and IL17A Target Engagement By ABT-122, and Suggest Mainly TNF-α–Mediated Relative Target Contribution to Drug Response in MTX-IR Rheumatoid Arthritis Patients

Robert W. Georgantas III[1], Melanie Ruzek[2], Justin Wade Davis[1], Feng Hong[1], Elizabeth Asque[1], Kenneth Idler[1], Heikki T. Mansikka[1], Benoit Guerette[1] and Jeffrey F. Waring[1], [1]AbbVie Inc., North Chicago, IL, [2]Immunology Discovery, AbbVie, Worcester, MA

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Background/Purpose: ABT-122 is a dual variable domain (DVD-Ig) biologic which inhibits TNF-α and IL17A. In a 12-wk phase 2 study (NCT02141997) in MTX-IR patients (pts) with RA, ABT-122 120 mg administered either every other week (eow) or every week (ew) (but not 60 mg eow) had efficacy at least comparable to adalimumab (ADA) 40 mg eow. However, dual inhibition was not significantly differentiated from TNF-α inhibition alone. Biomarker investigations were designed to assess the on-target effects of ABT-122 and the contribution of the anti-TNF-α and anti-IL17A components to pts ACR20 response at wk-12 in this trial.

Methods: Consenting pts provided whole blood and Paxgene blood tube samples (baseline [BL], wk-4) and serum samples (BL, wk-4, wk-12). Gene expression (Affymetrix GeneChip Human Gene 2.0 ST arrays), DNA methylation (Illumina Infinium Human Methylation 450K BeadChips), and multiplex serum protein (Milliplex or Myriad-RBM) analyses were conducted in 132 ACR20, 96 ACR20, and 30 ACR20 responders, respectively. Cell populations were estimated from DNA methylation profiles in whole blood (*Genome Biol.* 15:R31). Wk-4 changes in gene expression and DNA methylation were correlated with wk-12 continuous DAS28 change. Ingenuity Pathway Analysis software was used for pathway analysis. Repeated measures analysis of log-transformed serum protein changes used linear mixed models.

Results: Wk-4 changes in expression of genes associated with IL17A signaling (eg, IL23, MMP9, S100A8, S100A9, LCN2) indicated inhibition of IL17A by ABT-122. Serum protein changes (S100A8/A9, LCN2) were seen at wk-4 and wk-12 of ABT-122 treatment. Expression of 3756 genes was changed significantly at wk-4 in responders. Few genes (eg, MMP9, NAMPT; associated mostly with IL17A signaling) showed statistically significant differences in the ABT-122 arms vs the ADA arm. Differentially expressed genes plotted for ABT-122 responders were highly concordant with those from ADA responders. Pathway analysis of the nearest neighbor genes to these CpG sites indicated that ABT-122 inhibited IL17A pathways. Upstream driver pathway analysis of nearest neighbor genes and DAS28 found strong correlation with TNF-α responsive pathways (second highest rank) and weak correlations with IL17A- and IL17 receptor-responsive pathways (223rd and 1691st ranks, respectively). ABT-122 and ADA drove similarly robust changes in several protein biomarkers (eg, MMP3, CXCL13, CXCL9, IL6, S100A8/A9), suggesting TNF-α–driven effects. Methylation signatures in whole blood indicated significant changes in CD4 T-cell and granulocyte populations in ABT-122 vs ADA responders, indicating ABT-122–mediated inhibition of IL17A. Methylation of 6190 CpG sites was significantly correlated with DAS28 in responders at wk-4 (false detection rate <5%).

Conclusion: ABT-122 successfully engaged TNF-α and IL17A qualitatively, compared with adalimumab. However, correlation of wk-4 changes in gene expression and DNA methylation with wk-12 DAS28 response indicated that response to ABT-122 in pts with MTX-IR RA was primarily driven by TNF-α inhibition, with little added contribution from IL17A inhibition.

Disclosure: R. W. Georgantas III, AbbVie, 3,AbbVie, 1; **M. Ruzek**, AbbVie, 3,AbbVie, 1; **J. W. Davis**, AbbVie, 3,AbbVie, 1; **F. Hong**, AbbVie, 3,AbbVie, 1; **E. Asque**, AbbVie, 3,AbbVie, 1; **K. Idler**, AbbVie, 3,AbbVie, 1; **H. T. Mansikka**, AbbVie, 3,AbbVie, 1; **B. Guerette**, AbbVie, 3,AbbVie, 1; **J. F. Waring**, AbbVie, 3,AbbVie, 1.

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Abstract Number: 648

ABT-122, an Anti-TNF/Anti-IL-17 Dual Variable Domain Antibody, Alters T Cell Responses in Human Subjects

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Background/Purpose: ABT-122 is a dual variable domain antibody which neutralizes both TNF and IL-17 and is in Phase II trials for rheumatoid arthritis (RA) and psoriatic arthritis. Because anti-TNF treatment in RA patients has been reported to increase IL-10^{+}CD4 T helper cells and Th17 cells, we evaluated whether the dual neutralization of TNF and IL-17 by ABT-122 would have additional effects on T cell cytokine production and T helper phenotypes in subjects receiving ABT-122.

Methods: In a Phase 1 study peripheral blood mononuclear cells (PBMCs) were taken from healthy volunteers at baseline, day 15, day 36 and day 57 following a single 1.5mg/kg dose of ABT-122 and cryopreserved. The PBMCs were thawed and either stimulated with anti-CD3/CD28 for 48hrs and supernatants evaluated for cytokine levels (Milliplex MAP technology) or stimulated with PMA/ionomycin for 4hrs and performed cytometric time of flight (CyTOF) analysis for T helper cell populations, including cytokine and transcription factor expression. Serum from 80 MTX-IR RA patients in a Phase II clinical trial with ABT-122 (60mg/EOW, 120mg/EOW, 120mg/EW) or anti-TNF (adalimumab, 40mg/EOW) was also evaluated for several cytokines that drive or are produced by T helper populations, including IL-23, IL-13, IFNγ, IL-22, IL-12, IL-10 and TGF-β (Myriad-RBM, Singulex, MSD or Milliplex).

Results: The PBMC of healthy volunteers produced significantly lower levels of the cytokines IFNγ, IL-4, IL-2, GM-CSF, and IL-22 following ex vivo stimulation withanti-CD3/CD28 after a single dose of ABT-122 compared to pre-dose levels. In contrast, IL-1RA and IL-21 were significantly elevated in stimulated PBMC cultures, whereas IL-17A, IL-17F, IL-6, IL-1β and IL-10 levels were unchanged. To explore whether these alterations in cytokines reflect a shift in T helper cell populations, PBMCs from these Phase 1 studies were further evaluated with CyTOF. Decreases in IL-22+ T helper cells and increases in IL-21+ T helper cells were confirmed by the CyTOF analysis, but other ex vivo cytokine changes, including decreased IFNγ, IL4 and GM-CSF were not reflected in either proportion of cells or magnitude of expression. Similar to reports with anti-TNF in RA patients, there were increased percentages of Th17 cells following ABT-122 administration, but minimal changes in percentages of Th1, Th2 and Treg cells. From Phase 2 RA subjects, the levels of serum IL-23, a cytokine that promotes Th17 development, trended higher with ABT-122 compared to adalimumab treatment. Conversely, there was a significant increase in serum IL-10 levels, an immunoregulatory cytokine, with ABT-122 compared to adalimumab treatment, suggesting promotion of both Th17 and regulatory pathways with the dual neutralization.

Conclusion: While circulating Th17 cells increase following administration of ABT-122, there appears to be a compensatory regulatory mechanism that restrains proinflammatory cytokine production following T cell receptor stimulation that may contribute to the dual mechanisms of action of ABT-122 in modulating pathogenic inflammation.

Disclosure: M. Ruzek, AbbVie, 3,AbbVie, 1; **M. Konrad**, AbbVie, 1; **D. Conlon**, AbbVie, 3; **K. M. Grebe**, AbbVie, 3; **A. Slavin**, AbbVie, 3; **H. T. Mansikka**, AbbVie, 3,AbbVie, 1; **C. Cuff**, AbbVie, 3; **R. J. Padley**, AbbVie, 3.

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Abstract Number: 649

Clinical Evaluation Usefulness of Standardized Protocol Strategies of Dose Reduction in Patients with Rheumatoid Arthritis in Clinical Remission

Treated with Biologic Therapies. the Optibio Study

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Background/Purpose:

The OPTIBIO study is a clinical trial whose primary endpoint is to evaluate the proportion of patients that after one year are maintained in clinical remission with a dose reduction treatment regimen of biological therapy in patients with Rheumatoid Arthritis (RA), and to evaluate if the proportion of patients in remission with new regimen dose of treatment is not inferior to patients in remission with standard dose regimen. In our present work, we describe the preliminary results obtained so far.

Methods:

Open, randomized and controlled study of patients in clinical remission (DAS 28 <2.6 or SDAI <5 or ACR/EULAR 2011 criteria) at least 6 months followed in Third level Hospital Rheumatology Department. Patients treated with TNF inhibitors therapies (Etanercept, Infliximab, Adalimumab, Certolizumab, Golimumab), Tocilizumab and Abatacept. Patients are assigned to two groups randomly. Intervention group: according to a standardized protocol of dose reduction of biological therapies, Control group: according to standard dose regimen. Flare is considered when DAS28>2.6 or SDAI>5 or ACR/EULAR criteria are not fulfilled. Patients are following during after a minimum period of one year and maximum period of 3 years. The frequency of visits is every 12 weeks.

Results:

66 patients have been included from 14 April 2014 to 28 April 2016. Fifty-five women (83.33%) and 11 men (16.66%) with a mean age of 59.68 ± 11.72 years. Thirty-four patients in standard regimen dose and 32 patients in dose reduction regimen with comparable baseline characteristics for both groups. Positive Rheumatoid Factor (RF) in 80.30%. Forty-seven patients have erosive disease. None of the patients had tender or swollen joints at the beginning. At baseline, ESR and CRP values were 16.65 ±10.48 mm/1hour y 0.22 ± 0.23 mg/dl respectively, DAS 28-ESR value was 1.83 ±0.72 and DAS28-CRP was 1.35 ± 0.26. SDAI baseline value was 1.36 ± 1.00. Eighteen patients have presented a flare: 20.58 % in control group and 34.37 % in intervention group without statistical signification (p=0.209) with a Relative Risk (RR) 1.66 [0.73 - 3.77]. Baseline characteristics of the patients are described in tables 1 and 2

TABLE 1	BASELINE CHARACTERISTICS REMISSION (48 PATIENTS)	BASELINE CHARACTERISTICS FLARE (18 PATIENTS)
AGE (years)	Mean: 60.21 ± 11.48 Median: 59.00 (32 - 85)	Mean: 58.28 ± 12.54 Median: 58.50 (34 - 80)
SEX	42 ♀ (87.50%) 6 ♂ (12.50%)	13 ♀ (72.22%) 5 ♂ (27.77)
TIME FROM RA DIAGNOSIS TO BASELINE DATE (months)	Mean: 170.40 ± 107.12 Median: 157 (38 - 448)	Mean: 153.28 ±88.06 Median: 143.50 (35 - 435)
TIME FROM BASELINE DATE TO FLARE DATE (months)	----------	Mean: 12.33 ± 4.98 Median: 12.50 (5 - 21)
POSITIVE RF	85.41% (n=41)	66.67% (n=12)
EROSIVE DISEASE	70.83% (n=34)	72.22% (n=13)
ESR mm/1ºhour	Mean: 16.13 ± 9.87 Median: 17. 50 (1 - 35)	Mean: 18.06 ± 12.15 Median: 19.00 (1 - 39)
CRP mg/dl	Mean: 0.19 ± 0.19 Median: 0.17 (0.01 - 0.75)	Mean:0.30 ± 0.32 Median: 0.21 (0.01 - 1.14)
DAS 28-ESR BASELINE	Mean: 1.93 ± 0.89 Median: 2.12 (0.04 - 2.57)	Mean: 1.82 ± 0.84 Median: 2.18 (0.08 - 2.58)
DAS 28-CRP BASELINE	Mean: 1.32 ± 0.26 Median: 1.31 (0.96 - 1.94)	Mean: 1.43± 0.27 Median: 1.41 (0.96 - 2.04)
SDAI	Mean: 1.28 ± 0.86 Median: 1.14 (0.02 - 4.38)	Mean: 1.58 ± 1.11 Median: 1.35 (0.08 - 3.81)

TABLE 2	FLARE (18 PATIENTS)		REMISSION (48 PATIENTS)	
	CONTROL GROUP (n=7)	INTERVENTION GROUP (n=11)	CONTROL GROUP (n=27)	INTERVENTION GROUP (n=21)
AGE (years)	Mean: 59.57± 10.83 Median: 58 (49 - 80)	Mean: 57.45 ±13.97 Median: 61 (34 - 75)	Mean: 58.59 ± 12.19 Median: 57 (32 - 85)	Mean: 62.29 ± 10.44 Median: 61 (37 - 79)
SEX	5 ♀ (71.42%) 2 ♂ (28.57)	8 ♀ (72.72%) 3 ♂ (27.27%)	25 ♀ (92.60%) 2 ♂ (7.40%)	17 ♀ (80.95%) 4 ♂ (19.05%)
TIME FROM RA DIAGNOSIS TO BASELINE DATE (months)	Mean: 106.43 ± 43.24 Median: 99 (50 - 183)	Mean: 183.09 ± 112.75 Median: 163 (35 - 435)	Mean: 155.15 ± 110.89 Median: 120 (38 - 421)	Mean: 190.00 ± 101.31 Median: 167 (42 - 448)
TIME FROM BASELINE DATE TO FLARE DATE (months)	Mean: 12.43 ± 3.99 Median: 14 (8 - 19)	Mean: 12.27 ± 5.71 Median: 11 (5 - 21)	----------	----------
POSITIVE RF	100% (n=7)	45.45% (n=5)	77.78% (n=21)	95.23% (n=20)
EROSIVE DISEASE	85.71% (n=6)	63.64% (n=7)	59.25% (n=16)	85.71% (n=18)
ESR mm/1ºhour	Mean: 19.00 ± 11.85 Median: 25(1 - 31)	Mean: 17.45 ± 12.99 Median: 15 (1 - 39)	Mean: 15.56 ± 10.27 Median: 18 (1 - 35)	Mean: 16.86 ± 9.64 Median: 14 (1 - 33)
CRP mg/dl	Mean: 0.47 ± 0.47 Median: 0.21 (0.06 - 1.14)	Mean: 0.20 ± 0.12 Median: 0.21 (0.01 - 0.38)	Mean: 0.19 ± 0.21 Median: 0.14 (0.01 - 0.75)	Mean: 0.19 ± 0.16 Median: 0.17 (0.01 - 0.58)
DAS 28-ESR BASELINE	Mean: 1.86 ± 0.93 Median: 2.34 (0.06 - 2.58)	Mean: 1.80 ± 0.82 Median: 1.98 (0.11 - 2.56)	Mean: 1.79 ± 0.76 Median: 2.15 (0.04 - 2.67)	Mean: 1.89 ± 0.69 Median: 2.10 (0.13 - 2.53)
DAS 28-CRP BASELINE	Mean: 1.52 ± 0.39 Median: 1.54 (0.96 - 2.04)	Mean: 1.37 ± 0.14 Median: 1.40 (1.07 - 1.56)	Mean: 1.32 ± 0.27 Median: 1.31 (0.96 - 1.94)	Mean: 1.31 ± 0.23 Median: 1.27 (0.97 - 1.69)
SDAI	Mean: 1.78 ± 1.40 Median: 1.44 (0.06 - 3.81)	Mean: 1.47 ± 0.93 Median: 1.28 (0.38 - 3.76)	Mean: 1.48 ± 1.06 Median: 1.42 (0.02 - 4.38)	Mean: 1.01 ± 0.74 Median: 0.87 (0.13 - 2.87)

Conclusion: Preliminary results show that dose reduction of biological therapies with a standardized protocol it does not seem to increase reactivation risk of disease activity,

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Abstract Number: 650

ABT-122, a Tnf– and IL-17–Targeted Dual Variable Domain (DVD)–Ig™ in

Rheumatoid Arthritis Patients with Inadequate Response to Methotrexate: Results from a Phase 2 Trial

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster I

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Tumor necrosis factor (TNF) and interleukin 17 (IL-17) appear to independently contribute to the pathophysiology of rheumatoid arthritis (RA), synergistically inducing inflammatory mediators leading to joint destruction. Selective dual neutralization of TNF and IL-17 confers superior protection compared with inhibition of either target in a mouse collagen-induced arthritis model. ABT-122 is a novel dual variable domain immunoglobulin (DVD-Ig™) targeting both human TNF and IL-17A, hypothesized to provide greater clinical responses in RA patients (pts). The objective of this study was to investigate the safety and efficacy of ABT-122 in RA pts with inadequate response to methotrexate (MTX).

Methods: Two hundred twenty-two pts were enrolled in this 12-week (wk) phase 2, randomized, double-blind, active-controlled, parallel group, study in active RA pts receiving concomitant MTX. Pts were randomized in a 1:1:1:1 ratio to receive ABT-122 (60 mg every other wk [eow], 120 mg eow, 120 mg every wk [ew]) or adalimumab (ADA, 40 mg eow) subcutaneously. The primary efficacy endpoint was the American College of Rheumatology (ACR) 20 response at wk 12. Additional secondary efficacy endpoints included responses of ACR50/70, low disease activity (LDA) and clinical remission (CR) based on DAS28 (hsCRP) or CDAI. The analysis presented here used non-responder imputation for missing data.

Results: ACR20 responses for ABT-122 demonstrated dose-dependence, with numerically higher responses for the 120 mg ew dose compared with 40 mg eow ADA. These ACR20 responses were consistent with the secondary efficacy endpoints suggesting that ABT-122 at doses ≥120 mg eow has efficacy at least comparable to ADA 40 mg eow **(Table 1)**. Treatment-emergent adverse events (AEs) were similar across all treatment groups with the majority being of mild or moderate severity. Across all treatment groups, there were no discernable differences in serious AEs or discontinuations; infection rates were similar for all treatment groups with no serious infections reported. There were no systemic hypersensitivity reactions reported with ABT-122. There were no dose-limiting or clinically-concerning laboratory abnormalities.

Conclusion: Efficacy data showed at least comparable efficacy of ABT-122 at doses ≥120 mg eow to 40 mg eow ADA in RA pts on concomitant MTX over 12 wks. With dual inhibition of TNF- and IL-17, there were no observed increases in safety findings. These results demonstrate that dual inhibition of TNF and IL-17 with a DVD-Ig provides an acceptable safety profile at the doses tested. Dual inhibition cannot be differentiated from TNF inhibition alone based on this dataset.

Table 1. Results From ABT-122 Phase 2 Study M12-963

	ADA 40 mg eow (n = 56)	ABT-122 60 mg eow (n = 55)	ABT-122 120 mg eow (n = 56)	ABT-122 120 mg ew (n = 55)
Baseline MTX dose, mg/wk, mean	16.8	17.5	17.1	16.7
Responders at wk 12, NRI, n (%)				
ACR20	38 (67.9)	34 (61.8)	42 (75.0)	44 (80.0)
ACR50	27 (48.2)	19 (34.5)	26 (46.4)	26 (47.3)
ACR70	12 (21.4)	12 (21.8)	10 (17.9)	20 (36.4)
DAS28 (hsCRP) <3.2 (LDA or CR)	25 (44.6)	18 (32.7)	29 (51.8)	30 (54.5)
DAS28 (hsCRP) <2.6 (CR)	17 (30.4)	12 (21.8)	21 (37.5)	23 (41.8)
CDAI ≤10 (LDA or CR)	22 (39.3)	18 (32.7)	24 (42.9)	30 (54.5)

ACR=American College of Rheumatology; ADA=adalimumab; CDAI=Clinical Disease Activity Index; CR=clinical remission; DAS28 (hsCRP)=Disease Activity Score using high-sensitivity C-reactive protein; eow=every other week; ew=every week; LDA=low disease activity; MTX=methotrexate; NRI=non-responder imputation; wk=week.
ABT-122 molar serum exposures at 60 mg eow, 120 mg eow, and 120 mg ew were approximately half lower, comparable, and 2-fold higher, respectively, compared with the exposure for ADA 40 mg eow.

Disclosure: M. C. Genovese, AbbVie, Eli Lilly, Janssen, Novartis, and UCB, 2,AbbVie, Eli Lilly, Janssen, Novartis, and UCB, 5; **M. Weinblatt**, Amgen, Bristol Myers Squibb, Crescendo Bioscience, and UCB Pharma, 2,AbbVie, Amgen, Bristol Myers Squibb, Janssen, Pfizer, Roche, and UCB Pharma, 5; **J. A. Aelion**, AbbVie, Ardea Biosciences, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Galapagos, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Mesoblast, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi-Aventis, Takeda, and UCB Pharma, 2,AbbVie, Boehringer Ingelheim, Celgene, and Eli Lilly, 5; **H. T. Mansikka**, AbbVie, 3,AbbVie, 1; **P. M. Peloso**, AbbVie, 3,AbbVie, 1; **K. Chen**, AbbVie, 3,AbbVie, 1; **Y. Li**, AbbVie, 3,AbbVie, 1; **A. A. Othman**, AbbVie, 1,AbbVie, 3; **A. Khatri**, AbbVie, 3,AbbVie, 1; **N. S. Khan**, AbbVie, 3,AbbVie, 1; **R. J. Padley**, AbbVie, 3,AbbVie, 1.

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Abstract Number: 651

Calprotectin Serum Levels Strongly Predict Disease Flare in RA and Psa

Patients with Low Disease Activity Treated with TNF Inhibitors. a One-Year Prospective Cohort Study

Jose Inciarte-Mundo[1], M. Victoria Hernández[1], Virginia Ruiz-Esquide[1], Sonia Cabrera-Villalba[1], Julio Ramirez[1], Andrea Cuervo[1], Mariona Pascal[2], Jordi Yagüe[2], Juan D. Cañete[1] and Raimon Sanmarti[1], [1]Rheumatology Department, Hospital Clínic de Barcelona, Barcelona, Spain, [2]Immunology Department, Hospital Clinic de Barcelona, Barcelona, Spain

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Session Type: ACR Poster Session A

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Background/Purpose: An increasing number of RA and PsA patients achieve low levels of disease activity under biological therapy. Thus, new biomarkers are needed to stratify disease activity, guiding therapeutic decisions. Calprotectin is a major S100 leucocyte protein, is associated with disease activity in this group of patients. Calprotectin is a potentially biomarker more sensitive of disease activity than conventional acute-phase proteins

Methods: Prospective 1-year follow-up, single center study (INMUNOREMAR cohort). RA (ACR 1987) and PsA (CASPAR) patients in clinical remission (**CR**) (DAS28-ESR <2.6) or low disease activity (**LDA**) (DAS28-ESR <3.2) in ≥2 consecutive visits treated with adalimumab (**ADA**), etanercept (**ETN**) or infliximab (**IFX**) for ≥3 months were included. Demographic data, disease duration, time to initiate csDMARD and bDMARD, time to achieve remission, remission duration, autoantibody status, radiological data, concomitant csDMARD therapy, dose and duration of biological therapy were collected. Clinical and laboratory assessment was made every 4 months and at the time of flare. Calprotectin serum levels (ELISA Kit Calpro AS®) and TNFa trough serum levels (ELISA Kit Promonitor®, Progenika) were determined. Disease flare was defined as DAS28-ESR>3.2 and increase in ΔDAS28-ESR >0.6. Univariate and multivariate regression models were used to identify predictors of disease flare.

Results: 103 patients (47RA, 56PsA) were included. Mean Age 57 (30–81) years. 78 (75.8%) had CR and 25 (24.2%) LDA. Mean CR/LDA duration was 58 (4–163) months. 36 patients had received treatment with ADA, 50ETN, and 17IFX. Mean biologic treatment duration 61 (7–166) months. 47.4% patients were on monotherapy, 47% on reduced dose, and 17.9% received steroids. 84 patients (91%) remained in CR/LDA for 12 months, and 12 patients (13%; 8 RA, 4 PsA) experienced flares. Patients with flares had a longer time to achieve CR/LDA [CR/LDA (n=81) 3.1 (1–6) months vs. Flare (n=12) 20 (5–31) months, p<0.001], a shorter CR/LDA duration [CR/LDA (n=81) 59 (5–163) months vs. Flare (n=12) 25 (3–134) months, p=0.031], higher calprotectin levels [CR/LDA (n=81) 1.4 (0.6–3.7) µg/mL vs. Flare (n=12) 6 (4.5–7.9) µg/mL, p<0.001], and lower drug trough serum levels at baseline [CR/LDA (n=83) 2.6 (0.6–12) µg/mL vs. Flare (n=12) 0.6 (1–1.2) µg/mL; p<0.001], even when analyzed by biologic [ADA CR/LDA (n=30) 7 (0.2–12) µg/mL vs. Flare (n=4) 0.5 (0.4–1) µg/mL; p=0.003; ETN CR/LDA (n=44) 1.5 (0.7–4.7) µg/mL vs. Flare (n=5) 0.8 (0.9–1.2)µg/mL; p=0.039; IFX CR/LDA (n=14) 3.1 (0.5–7.7) µg/mL vs. Flare (n=3) 0.1 (0–1) µg/mL; p=0.021]. Baseline TNFi trough serum levels [hazard ratio (**HR**) = 0.47], steroid treatment (HR=3.21), time to CR/LDA (HR=1.17), and baseline calprotectin levels (HR=2.38) significantly predicted flare in the univariate analysis. However, only baseline calprotectin levels significantly predicted flare in the multivariate analysis [HR=2.74 (1.74–4.31); p<0.0001].

Conclusion: Calprotectin was a strong independent predictor of flare in RA and PsA patients treated with TNF inhibitors with low levels of disease activity.

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Abstract Number: 652

The Reasons for Discontinuation of Combination Therapy with Methotrexate and Tumor Necrosis Factor Inhibitors Versus Triple Therapy Differ Significantly Because of Higher Adverse Events with Triple Therapy

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Session Type: ACR Poster Session A

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Background/Purpose: We recently reported that real-world persistence in Veteran's Affairs (VA) patients was lower in Rheumatoid arthritis (RA) patients receiving triple therapy [methotrexate (MTX), sulfasalazine (SUL) and hydroxychloroquine (HCQ)] at 17.5% in comparison to patients receiving MTX-Tumor necrosis factor inhibitor (TNFi) combination therapy at 45.2%. ($p<0.001$). This study reports and compares the specific reasons for discontinuation of these two combination regimens.

Methods: In this historical cohort study, US Veterans with RA enrolled in VA between January 1, 2006 to December 31, 2012 were identified using clinical and administrative data. Patients receiving MTX monotherapy to which either a TNFi (MTX-TNFi) or the simultaneous addition of HCQ/SUL (triple Rx) were followed over 12 months after initiating the combination. Discontinuation of combination therapy was defined as discontinuing any of the combination medications with a >90day gap and/or starting new drug treatments for RA. Patients discontinuing triple Rx or MTX-TNFi were matched to each other on age (±5 years), sex and site of care. The specific drugs discontinued and the reasons for discontinuing the combination therapy were determined by medical record review with the reason for cessation classified as one of the following: lack of efficacy, adverse drug event, or other (step-down therapy, preoperative discontinuation, noncompliance, lost to follow-up).

Results: There were 50 matched pairs between the two combination therapy groups evaluated. The drugs discontinued (table 1) and reasons for discontinuation (table 2) are shown below. The absolute rates for discontinuation by cause were estimated by extrapolating data over the entire cohort for the two combination treatment groups. Comparing discontinuation of triple therapy discontinuation of MTX-TNFi, the triple Rx group was associated with more discontinuations due to adverse drug events by both absolute and relative comparisons. Discontinuation due to lack of efficacy and other reasons for discontinuation were similar for the two groups. Methotrexate had the lowest discontinuation frequency in either group, with sulfasalazine being the most common drug discontinued in the triple Rx group.

Conclusion: The differences in persistence between the MTX-TNFi and Triple Rx groups in this real world observation cohort study appear to be primarily related to adverse drug events. The most common drug associated with adverse drug events was sulfasalazine, which was also the drug most frequently discontinued.

Table 1 Number of patients discontinuing specific drugs alone or in combination at termination of combination therapy (n=50 matched pairs)

	Triple Rx	MTX+ TNFi
Single drug Discontinued (n= 60)		
TNFi	N/A	34
MTX	2	10
SUL	13	N/A
HCQ	1	N/A
One or more drugs discontinued simultaneously (n = 40)		
SUL +HCQ	19	N/A
MTX+HCQ	2	N/A
All drugs of the combination	13	6
Total discontinuations (n=100)	50	50

Table 2 - Reasons for termination of combination therapy (n=50 matched pairs)

	Triple Rx		MTX+ TNFi	
Lack of Efficacy	6 (12%)		13 (26%)	
Adverse Drug Event	25 (50%)		17 (34%)	
GI toxicity		9		0
Rash		4		2
Infection		3		3
Other adverse drug event		9		12
Other	19 (38%)		20 (40%)	
Step down of therapy following clinical improvement		6		2
Discontinued prior to surgery		0		5
Lost to follow-up/unknown		13		13
Total discontinuations	50		50	
Estimated absolute percentages for discontinuation of combination therapy for entire cohort during 12 months of observation.				
	Triple Rx		MTX+ TNFi	
Overall combination termination rate in initial study	82.5%		54.8%	
Lack of Efficacy	10.8%		15.4 %	
Adverse Drug Event	39.4%		19.1 %	
Other	32.3%		20.2 %	

Disclosure: D. Erhardt, None; **B. C. Sauer**, Amgen, 2; **C. C. Teng**, Amgen, 2; **T. R. Mikuls**, Roche Pharmaceuticals, 2,Pfizer Inc, 5; **J. R. Curtis**, Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, Bristol-Myers Squibb, Crescendo, AbbVie, 2,Roche, Genentech, UCB Pharma, Janssen, CORRONA, Amgen, Pfizer, Bristol-Myers Squibb, Crescendo, AbbVie, 5; **G. W. Cannon**, Amgen, 2.

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Abstract Number: 653

Thrombospondin-1 Is Highly Expressed By Salivary Gland Epithelial Cells of Sjögren's Syndrome Patients, Both Constitutively and upon Exposure to Necrotic Cells Debris

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sjögren's syndrome (SS) patients manifest inflammation in salivary glands (SG) (lymphocytic infiltration of salivary and lachrymal glands) and evidence of intrinsic activation in the salivary epithelial cells (SGEC). Recent evidence from this laboratory has indicated that the aberrant exposure of SGEC of SS patients to necrotic debris may be a major cause of inflammatory reactions via the activation of inflammasome and may hold a key role in the pathogenesis of the disorder. Thrombospondin (TSP-1) is a matricellular glycoprotein with proinflammatory, antiangiogenic and proapoptotic properties. TSP-1 also activates TGF-β1 and has been shown to be involved in TH-17 response. It was originally characterized as an α-granule glycoprotein in platelets, although can be synthesized and released by a variety of cell types, including epithelial cells. Herein, we assessed the expression of TSP-1 in cultured ductal SGEC lines obtained from SS patients and controls. We also sought to investigate the effect of necrotic cell debris (NEC) on mRNA synthesis and release of TSP-1, in healthy epithelium.

Methods: non neoplastic SGEC lines from SS patients and non-SS controls (healthy) were comparatively evaluated for the constitutive expression of TSP-1 and IL-1β (both at mRNA and protein level in culture supernatants). In addition, SGEC lines treated with NEC were evaluated for the mRNA and protein expression of TSP-1 and IL-1β, by RT-PCT and ELISA, respectively.

Results: SS patients (n=14) displayed significant upregulation of TSP-1 mRNA levels in cultured epithelial cells, compared to controls (n= 10, p=0.0005), that correlated with the severity of histopathologic lesions (tarpley score of the respective Salivary Gland tissue biopsy) (Kruskal-Wallis test, p=0.001). SS-SGEC (n=16) were also found to secrete constitutively more TSP-1 and IL-1β in their culture supernatants, compared to non-SS SGEC (n=15) (p=0.0001 and p=0.06, respectively). There was a positive correlation among the constitutively expressed levels of TSP-1 and IL-1β (Spearman's r= 0.66 for mRNA and r=0.41 for protein). Treatment of healthy SGEC lines (n=4) with NEC led to the induction of TSP-1 and IL-1β mRNA (2.1-fold and 2-fold increase, respectively), as well as protein in culture supernatants (3.0-fold and 2.5-fold increase, respectively) (for all comparisons, $p<0.05$), that were abrogated upon pre-treatment of NEC with DNase1.

Conclusion: Preliminary results suggest for the first time that salivary gland epithelial cells from SS patients manifest increased TSP-1 and IL-1β levels that correlate with severe lymphocytic infiltrates in salivary glands. Chronic exposure to necrotic cells debris may hold a key pathogenetic role in the tissue inflammatory reactions of SS patients and may also explain the "intrinsic activation status" that characterizes the epithelia of these patients.

Disclosure: A. G. Vakrakou, None; **M. D. Patsouras**, None; **P. G. Vlachoyiannopoulos**, None; **A. G. Tzioufas**, None; **M. N. Manoussakis**, None.

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Abstract Number: 654

The Level of B-Cell Active Cytokines and Soluble B-Cell Activating Factor/a Proliferation-Inducing Ligand Receptors in Patients with Primary Sjogren's Syndrome

You Jung Ha[1], Jaehyung Hur[1], Sang Wan Chung[1], Eun Ha Kang[2], Yeong Wook Song[3,4] and Yun Jong Lee[5], [1]Division of Rheumatology, Department of Internal Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea, The Republic of, [3]WCU Department of Molecular Medicine and Biopharmaceutical Sciences, Medical Research Institute, WCU Department of Molecular Medicine and Biopharmaceutical Sciences, Medical Research Institute, Seoul National University College of Medicine, Seoul, Korea, The Republic of, [4]Department of Internal Medicine, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

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SESSION INFORMATION

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Session Type: ACR Poster Session A

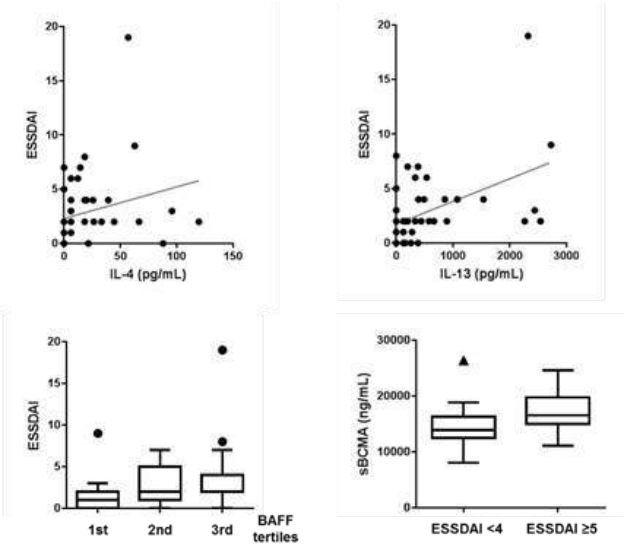
Session Time: 9:00AM-11:00AM

Background/Purpose: Primary Sjögren`s syndrome (pSS) is an autoimmune diseases characterized by lymphocytic infiltration of exocrine glands and dysregulated proliferation and differentiation of B cells. Two TNF ligand superfamily members (B cell activating factor [BAFF] and a proliferation inducing ligand [APRIL]) and their receptors (BAFF-receptor, B-cell maturation antigen [BCMA], and transmembrane activator and cyclophilin ligand interactor [TACI]) are involved in the regulation of B-cell activation. Soluble BCMA (sBCMA) or TACI (sTACI) was recently reported to be increased in body fluids of several lymphoproliferative or chronic inflammatory diseases. We measured plasma levels of B cell-targeted cytokines, sBCMA and sTACI and investigated their correlations with clinical parameters of pSS patients.

Methods: Blood samples were collected from 45 pSS patients who satisfied the American-European Consensus Group (AECG) criteria and 16 age- and gender-matched healthy controls. The plasma concentrations of IL-4, IL-13, BAFF, APRIL, sBCMA, and sTACI, were measured by using magnetic bead-based multiples assays. Disease activity was assessed by the European-SS disease activity index (ESSDAI).

Results: Plasma levels of IL-4, IL-13, and BAFF were significantly increased in patients with SS, compared with healthy controls (p=0.037, p=0.010, and p=0.004 respectively). There were no differences in the levels of APRIL, sBCMA, and sTACI between two groups. pSS patients with extraglandular manifestations had higher levels of higher levels of BAFF than those without (6.46 [4.79~ 7.65] vs. 5.03 [4.02~6.15], p= 0.042). Total IgG and beta2-microglobulin levels were found to be correlated with the levels of IL-4, IL-13, and sBCMA, while BAFF was correlated with only beta2-microglobulin. IL-4 and IL-13 levels showed significant correlations with ESSDAI (r=0.432, p=0.003, and r=0.446, p=0.002, respectively). ESSDAI scores tended to increase across BAFF tertiles (p=0.031 by by Jonckheere-Terpstra test). pSS patients with ESSDAI score >= 5 showed higher levels of sBCMA than those without (16.56 [14.99~19.76] versus 13.92 [12.48~16.29], p=0.029).

Conclusion: Circulating levels of IL-4, IL-13, and BAFF was elevated in pSS patients but sBCMA and sTACI levels were not. These findings suggest that pSS may have a less efficient negative feedback exerted by soluble BAFF/APRIL



receptors.

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Abstract Number: 655

Comprehensive Immuno-Phenotyping of Follicular Helper T Cells and B Cell Subpopulations in Primary Sjögren's Syndrome

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by immune cell infiltration in the salivary glands resulting in ocular and oral dryness. Abnormalities in B cell activation and skewing of T cell polarization toward Th2 and T follicular helper (TFH) associated with ectopic germinal center formation in the salivary gland are observed in pSS. However, the interplay between B cell subsets, T cells, and other immune abnormalities, as well as relationship to disease status, has yet to be fully elucidated. In this study, we evaluated changes in peripheral blood B and T cell populations in pSS patients compared to disease and healthy controls.

Methods: Two cohorts of patients with pSS according to European-American Consensus and ACR criteria and age-

matched healthy controls (HC) were recruited (Rochester, USA and Strasbourg, France). The Rochester cohort also included rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (n=9 and 10 respectively) classified based on ACR criteria. PBMCs were isolated by Ficoll-Hypaque and the frequencies of B and T subpopulations measured by multi-parameter flow cytometry as further defined in the results. Data are reported as median [25^{th}-75^{th} quartile].

Results: pSS patients from the Rochester cohort had a higher frequency of circulating TFH (CXCR5+ICOS+PD1+) than HC (pSS (n=15): 5.83 [4.38-8.13]%; HC (n=27): 4.18 [2.95-4.58]%, p=0.002). Although there was no significant difference in the relative frequency of TFH subpopulations (TFH1, TFH2, TFH17 and TFH1-17) between pSS, HC, RA, and SLE, the frequency of TFH1 ICOS+ PD1+ cells was significantly higher in pSS than HC (pSS (n=15): 7.29 [5.51-10.8]%; HC (n=27): 4.44 [3.2-5.86]%, p=0.001). pSS patients from the Strasbourg cohort had an increase in the frequency of circulating TFH (CD4+CD45RA- CXCR5+) in comparison to HC (pSS (n=48): 27.65 [20.45-34.1]%; HC (n=217): 21.70[18.02-26.11]%, p=0.02). The frequency of TFH1 cells was significantly higher in pSS than HC (pSS (n=48) 29.1 [25.5-33.9]; HC (n= 24): 24.01 |19.7; 31.5]%, p= 0.04). In the Rochester cohort, we characterized B cell populations. pSS patients had a significant reduction in switched memory (SM) B cells (CD27+IgD-) compared to HC (pSS (n=16): 3.94 [2.68-7.18]; HC (n=28): 8.95 [6.2-14.22]% of B cell, p=0.001). In similar fashion, the frequency of unswitched memory B cell (CD27+IgD+) in pSS was significantly lower than HC (pSS (n=16): 8.69 [4.71-13.99]; HC (n=28): 16.91 [12.98-21.36]% of B cell, p=0.003). We also observed significant reductions in frequencies of CD95+ SM B cells (pSS (n=16): 1.87 [0.93-2.88]; HC (n=28): 3.29[2.13-5.11]% of B cell, p=0.0037) and ICOSL+ SM B cells (pSS (n=16): 0.075 [0.05-0.28]; HC (n=28): 0.28 [0.17-0.84]% of B cell, p=0.01).

Conclusion: Our data highlight the significant abnormalities in the peripheral TFH and B cell compartment in pSS and further suggest the critical role of TFH- B cell interactions. The decrease in ICOSL+ SM B cells suggests their interaction with ICOS+ T cells in germinal center-like structures in salivary glands. Relationship to clinical parameters and pathologic and ultrasound abnormalities in salivary glands are currently under investigation.

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Abstract Number: 656

ERdj5 Function Is Involved in Inflammatory Manifestations of Sjögren's Syndrome in the Salivary Glands

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Background/Purpose: Sjögren's syndrome is a chronic autoimmune disorder that affects mainly the exocrine glands. The

initiation and causative agents are still unknown. Endoplasmic Reticulum (ER) stress proteins have been suggested to participate in autoimmune and inflammatory responses, either by acting as autoantigens themselves, or by modulating factors in inflammatory responses.ERdj5 is anER-resident chaperone proteinwith a disulfide reductase activityand is required for the translocationof misfolded proteins across the ERfor proteasomaldegradation. In this study we sought to investigate the role of ERdj5 in the salivary glands, in associationwith inflammation and autoimmunity.

Methods: *In situ*expression of ERdj5 was studied immunohistochemically in minor salivary gland tissues (MSG) from primarySjögren's Syndrome (SS)-patients and non-SS sicca-complaining controls. Submaxillary glands and sera from both male and female ERdj5-knockoutmice andage-matched wild types were collected at 6,34 and 52 weeks of age. Tissue samples were analyzed microscopically, while sera were screened for anti-nuclear antibodies(ANAs).

Results: Human MSGs expressed ERdj5,with higher stain intensity in MSGs of SS patients with severe inflammatory lesions.Mice deficient in ERdj5 spontaneously developed SS-like inflammation in submaxillary glands and ANAssystemically. Inflammation was characterized by T and B infiltrating lymphocytes. Notably, female ERdj5-knockout mice developed severe chronic periductal inflammation in contrast to the much milder phenotype found in male littermates.

Conclusion: Salivary glands of ERdj5-knockout mice resemble the pathologic lesions of human Sjögren's syndrome whereasERdj5 wasinduced in MSGs of SS patients. Our findings suggest a critical connection betweenthe function of the ER stress chaperone protein ERdj5 andautoimmune inflammatory responses in the salivary glands.

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Abstract Number: 657

Expression of Type-III Interferons (IFNλs) and Their Receptor in Sjögren's Syndrome

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Background/Purpose: Type-III IFNs or IFNλs(IFNλ1/IL29, IFNλ2/IL28A and IFNλ3/IL28B) consist a recently identified group of IFNs,initiallyimplicated inseveral human diseases, including cancer and autoimmunity. In this study, we sought to investigatethe expression of type-III IFNs (IFNλ1/IL29, IFNλ2/IL28A and IFNλ3/IL28B) and their common receptor IFNλR1/IL28Ra in Sjögren's Syndrome (SS).

Methods: The *in situ* expression of all molecules was studied immunohistochemically in minor salivary gland tissues (MSG) from primary SS-patients (n=46) and sicca-complaining controls (n=17). Expression in peripheral blood

mononuclear cells (PBMCs) and sera was investigated by ELISA and real-time PCR, respectively. Expression in resting or TLR-stimulated salivary gland epithelial cells (SGEC) was assessed by both qPCR and ELISA.

Results: All type-III IFN family members were detected in ductal and acinar epithelia of MSGs from both SS-patients and sicca-controls.IFNλ2/IL28A and IFNλ3/IL28B were also expressed in infiltrating mononuclear cells (MNCs). In SS-patients with intermediate MSG lesions, the epithelial expression of IFNλ2/IL28A was more intense ($p<0.05$) compared to sicca-controls. The receptor IFNλR1/IL28Ra was detected in all types of cells except fibroblasts and was exceptionally strong in plasmatocytoid dendritic-cells, indicating that they are susceptible to type-III IFN-mediated regulation.Although none of the type-III IFNs was constitutively expressed in SGECs, they were all readily induced by TLR3 stimulation, suggesting that the *in situ*epithelial expression can be attributed to local microenvironment. Type-III IFN-mRNAs were not expressed in PBMCs, whereas only IFNλ1/IL29 was detected in the sera and was significantly elevated in SS patients with intermediate MSG inflammatory lesions compared to sicca-controls ($p<0.0053$).

Conclusion: Type-III IFNs are expressed in the MSGs and their expression is likely subjected to micro-environmental regulation. Our findings suggest that they may be implicated in SS pathogenesis.

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Abstract Number: 658

Decreased Expression of Ten Micro-RNAs in Plasmacytoid Dendritic Cells of Patients with Primary SS Indicates Dysregulation on Multiple Levels

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Background/Purpose: Plasmacytoid dendritic cells (pDCs) are indicated to be key players in the pathogenesis of primary Sjögren's syndrome (pSS) and important producers of type-1 interferon (IFN). This is based on their increased presence in pSS salivary glands, potential role in experimental animal models and the presence of an IFN signature in pSS patients, which is associated with disease activity measures. MicroRNAs are key regulators of cellular function and play a pivotal role in cellular function. To study potential dysregulation of pDCs of pSS patients, we investigated the expression of micro-RNAs (miRNA) in these cells in patients with pSS.

Methods: Two independent cohorts (discovery and validation) were established including a total of 30 pSS patients who were classified according to the 2002 criteria. 15 healthy controls (HC) were included as control group and divided over the two cohorts. CD304-expressing cells were isolated from peripheral blood using MACS and profiling of 758 miRNA was performed using the OpenArray platform. miRNAs found to be differentially expressed in the discovery cohort ($p<0.05$, with at least a difference between the groups of log2) were subsequently measured in an independent validation cohort using a custom made array. Experimentally supported targets of validated miRNAs were used to perform pathway enrichment in order to assess the functional role of the dysregulated miRNAs.

Results: Twenty-four miRNAs were significantly downregulated in pSS patients versus HC in the discovery cohort. 15 of these miRNAs were selected to be measured in the validation cohort, of which ten miRNAs were subsequently validated ($p<0.05$). Pathway enrichment indicated that these miRNAs are mainly involved in regulation of growth factor signalling and cell cycle (FDR corrected, $p<0.05$). We are currently studying the involvement of these miRNAs in pDC function and their correlation with their experimentally supported targets.

Conclusion: Ten miRNAs are expressed at lower levels in pDCs of patients with pSS as compared to healthy controls. Considering the potential of miRNAs in regulation of cell function, these data suggest a significant contribution to pDC function of miRNA dysregulation. Further analysis of the pathways in which these miRNAs are involved will expand our understanding on the role of pDCs in pSS.

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Abstract Number: 659

Low Dose IL-2 Therapy Can Restore the Balance of Th17 and Treg Cells in Refractory Patients with Sjogren's Syndrome

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Background/Purpose: The therapy for sjogren's syndrome (SS) focuses on biological agents, immune inhibitors and glucocorticoid which can't correct the problem of unbalance of Th17 and Regulatory T (Treg) cells in refractory patients. It was reported that IL-2 had a critical effect on homeostatic maintenance of the Th17 and Treg cells and the ratio of them. The study is to explore the effect of low dose IL-2 therapy on the balance of Treg and Th17 cells in refractory patients with SS and observe the efficiency and side effects of the therapy.

Methods: SS patients (n=18) (from march 1st to may 30thin 2016, both outpatients and inpatients in our department, according to American-European Consensus Group criteria for SS) with decreased Treg cells (18/18) and increased ratio of Th17/Treg (16/18), who were refractory to standard therapy including glucocorticoid, immune-suppressants, biological agents or combination of them, were given low-dose IL-2 (50 WIU/day for 5 days) by hypodermic injection. Laboratory indicators were compared before and after IL-2 treatment. The side effects were observed in the course of therapy.

Results: The number of Treg cells significantly increased after the treatment and returned to normal range in 89% (16/18) of patients by 1 week (12.24±3.95 vs. 48.10±33.21, $p<0.01$). At the same time, there was a significantly decrease in the ratio of Th17/Treg cells (0.66±0.52 vs. 0.36±0.41, $p<0.1$), which returned to normal range in 7 patients and was lower in 14 patients. Besides, Th17 cells were also increased (8.11±6.72 vs. 12.91±10.04, $p<0.1$). Clinical manifestations were improved after the combitional treatment of IL-2 and traditional drugs. No obvious adverse reactions were observed.

Conclusion: Low dose IL-2 therapy can restore and maintain the balance of Th17 and Treg cells in the refractory patients with SS. Manifestation improved after the combitional therapy. The therapy is safe. More research is needed to investigate long term efficiency of the therapy and the prognosis of the patients.

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Abstract Number: 660

Expression of the Chemokine Receptor CXCR5 Is Decreased in the Periphery of Patients with Primary Sjogren's Syndrome

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Background/Purpose: CXCR5 is a chemokine receptor expressed on B and T cell subsets, which binds the CXCL13 ligand produced by follicular dendritic cells. It is involved in cell migration and germinal centre reactions. The latter is observed ectopically in the salivary gland (SG) target organ of the rheumatic autoimmune disease primary Sjögren's syndrome (pSS). Further, genome-wide association studies have linked polymorphisms of CXCR5 to pSS, making the pathway important to explore for identification of novel treatment targets and for understanding disease pathogenesis. In this study we aimed to investigate the expression of CXCR5 in the peripheral blood and minor SG biopsies of pSS patients.

Methods: Flow cytometry was performed for cell populations and activation markers on PBMCs acquired from 14 untreated pSS patients, 10 pSS patients treated with the antimalarial drug hydroxychloroquine, and 15 sex and age matched healthy controls. Moreover, minor paraffin-embedded SG biopsies from the same pSS patients were stained for the detection of CXCR5+ cells using immunohistochemistry.

Results: HLA-DR expression was significantly increased in the untreated pSS patients compared to controls, on both CD19+ B cells ($P < 0.04$) and CD14+ monocytes ($P < 0.001$), with a significant decrease in expression following treatment on both CD19+ B cells and monocytes ($P < 0.009$). A trend towards a decreased percentage of CXCR5+ cells as well as CXCR5 cell surface expression was observed for most B and T cell subsets in untreated patients with pSS, reaching statistical significance in CD19+CD27+IgD+ marginal zone ($P < 0.001$) and CD19+CD27+IgD- memory ($P < 0.006$) B cells as well as in CD3+CD4+CCR6+ Th17 cells ($P < 0.03$). These observations were not reversed, but rather aggravated by hydroxychloroquine treatment. Meanwhile, immunohistochemical staining of SG biopsies revealed high numbers of CXCR5+ cells both within the focal infiltrates and interstitially in the target organ of these patients.

Conclusion: We conclude that the decrease of CXCR5 levels in the periphery of patients with Sjögren's syndrome result from homing of B and T cells to the autoimmune target organs. Hydroxychloroquine treatment appears not to be efficient in inhibiting the factors driving the trafficking, although it decreases the MHC class II expression. Therapeutic drugs targeting the CXCR5/CXCL13 axis may be useful in pSS.

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Abstract Number: 661

Epitope Specificity and End-Organ Susceptibility Dictates Anti-Ro52 Mediated Salivary Gland Dysfunction

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Background/Purpose: Circulating autoantibodies reactive against Ro52 are detected in the sera of 70% of patients with Sjögren's syndrome (SS), and their presence has been associated with higher severity of the disease. Previous work from our laboratory has demonstrated that interaction between anti-Ro52 and activated innate immunity induces salivary gland (SG) dysfunction in the New Zealand Mixed (NZM) 2758 strain of mice. This study was undertaken to investigate the mechanisms involved in anti-Ro52 mediated salivary gland dysfunction.

Methods: To determine the role of B cell epitope specificity in glandular dysfunction, NZM 2758 mice (5-10 per group) were immunized with recombinant fusion proteins representing the 3 structural domains of Ro52: Ring-B-Box (amino acids 16-123), Coiled-coil (amino acids 128-238) and SPRY (amino acids 268-465). Control mice were immunized with Maltose-binding protein (MBP). All immunization used Alum as the adjuvant. Antibody reactivity was analyzed by immunoprecipitation assay employing 35S-Met labeled Ro52, and by flow cytometry, using mouse ductal cell line SCA9-15. The ability of antibodies to penetrate live SCA9-15 cells was investigated by immunofluorescence. To determine end-organ susceptibility, anti-Ro52 serum generated in rabbits was passively transferred into either untreated or alum treated NZM2758 and lupus-prone NZM2328 mouse strains. SG function was assessed by measuring pilocarpine stimulated saliva.

Results: All groups of NZM2758 mice, except the MBP immunized control mice, generated IgG antibodies capable of immunoprecipitating whole Ro52. While antibodies in the sera from most of the coiled-coil immunized mice (7/8) penetrated live SCA9-15 cells, only 1/5 SPRY and 0/10 Ring-B-box immunized mice had cell penetrating antibodies. This antibody uptake was not dependent on the Fc gamma receptor expression. Only mice immunized with the coiled-coil domain showed a significant drop ($p=0.0027$) in saliva production. Passive transfer of rabbit anti-Ro52 readily induced SG dysfunction in NZM2758 mice, which was further amplified, if the mice were pretreated with alum. No such functional loss was observed in the lupus-prone NZM2328 mice.

Conclusion: Our study demonstrates that anti-Ro52 mediated salivary gland dysfunction is regulated by antibody epitope specificity and the genetic susceptibility of the end-organ. Our data provides an explanation for the lack of concordance between the presence of anti-Ro52 and the extent of dry mouth observed in some patients. Thus, in SS patients, measuring the relative levels of anti-Ro52 domain reactive antibodies might be more informative than just determining the presence or absence of anti-Ro52.

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Abstract Number: 662

The Unusual Cross-Reactivity of Anti Muscarinic Receptor 3 Monclonal Antibodies Derived from Salivary Glands of Sjögren's Syndrome Patients to Ro Peptides

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Background/Purpose: Sjogrens syndrome (SS) is a chronic autoimmune inflammatory disease the characterisitic features of which includes hypofunction of exocrine glands leading to decrease in salivation (dry mouth) and lacrimation (dry eyes). The presence of antibodies against Ro and La autoantigens serves as one of the hallmarks in the diagnosis of SS. Anti-muscarinic receptor 3 antibodies are another set of antibodies also found in SS patients. Muscarinic receptor 3(M3R) is a parasympathetic end organ seven transmembrane GPCR present on salivary and lacrimal glands, the stimulation of which is known to produce salivation and lacrimation. M3R has three extracellular domains (ECD) that plays an essential role in ligand binding and stimulation of the receptor. We found that monoclonal antibodies derived from salivary glands of SS patients that are positive for 2^{nd} and 3^{rd} ECDs of M3R are highly reactive to Ro peptides.

Methods: Monoclonal antibodies (MAbs) from salivary glands: Patients having dry eyes and dry mouth were classified according to AECG criteria into SS group and Do not meet criteria group (DNMC-Control). Plasmablasts (antibody secreting cells) with CD3- CD4- CD8- CD19+ CD27high CD38high IgG+ surface markers were sorted out using FACS from the salivary glands obtained following biopsy. The variable(V),diversity(D),joining(J), complementarity determining region(CDR) portions of heavy and light chain from each individual plasmablast were sequenced, amplified by PCR, cloned into a vector, transfected and expressed in HEK293A cell line. Ro and M3R Experiments: Reactivity of each Mab towards Ro were tested either by Bioplex 2200 or invitro transcription/translation system employing Ro52 and Ro60 labeled with ^{35}S-methionine and biotinylated-Lys or both methods. Reactivity to M3R peptides were determined by ELISA employing peptides encoding either 2nd (A.A. 213-218) or 3rd ECD (A.A.514-527) respectively.

Results: In the SS group, 23 Mabs were positive for Ro. 9 mabs were postive for 2nd ECD and 5 were positive for 3rd ECD of M3R. 4 Mabs were positive for both the M3R domains. (Cutt off 2 S.D. above DNMCs average O.D.). We found that 7/9 (77%) of ECL2 +ve MAbs were positive for Ro whereas 4/5 (80%) of ECD3 +ve MAbs were positive for Ro. Four Mabs that were positive for both 2nd and 3rd ECD, all (100%) were positive for Ro. None of the Mabs in the DNMC group were positive for 2nd ECD.

Conclusion: We have found a sequence similarity between Ro and M3R ECDs. This high cross reactivity of anti-M3R antibodies with Ro possibly suggests a mechanism where antibodies formed against these shared portion of Ro with M3R could cross react with M3R and may cause inhibition of the receptor leading to major symptoms observed in SS. We are further studying functional aspects of anti-M3R antibodies on the receptor function and getting a significant higher

inhibition from Mabs from SS when compared to DNMCs. Our future studies are also aimed at discovering the functional aspects of anti-M3R monoclonal antibodies on lacrimation and salivation when passively transferred to mice.

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Abstract Number: 663

Cytokine and Chemokine Levels in Serum and Tears As Disease Activity Biomarkers in Patients with Primary Sjögren´s Syndrome

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Background/Purpose: Evidence suggests that levels of different cytokines in primary Sjögren´s syndrome (pSS) are associated with cell infiltration degree within lacrimal and salivary glands and severity of the disease. Chemokines appear to contribute to the pathogenesis of pSS. Purpose: To evaluate the association between serum and tear Th1/Th2/Th17 cytokine and chemokine levels and disease activity in patients with pSS.

Methods: Case-control study including 19 patients with pSS and 13 healthy controls. Disease activity was assessed by EULAR Sjögrens´s Syndrome Disease Activity Index (ESSDAI); serum and tear IFN-γ, TNF. IL-2, IL-4, IL-6, IL-10, IL-17, IP10, MCP-1, MIG, RANTES and IL-8 levels were measured by bead-based assays following the sandwich immunoassay principle (BD Cytometric Bead Array; BD Biosciences). Differences between groups were analyzed using the Mann-Whitney U test. Correlation was estimated by Spearman´s correlation coefficient.

Results: TNF, IL-2, IL-4, IL-6, IL-10, IP-10, MCP-1, RANTES and IL-8 tear levels were statistically different between controls and patients with pSS ($p<0.005$). A significant correlation ($p>0.005$) was shown in patients between serum IL-6 and serum IL-2 (r=0.652), IL-4 (r=0.731; serum IL-2 and serum IP-10 (r=0.640); serum IL-2 and tear IL-2 (r=0.614, IL-8 (r=0.723), IP-10 (r=0.795), MIG (r=0.755); serum IL-4 and tear IL-8 (r=0.696), MIG (r=0.707); serum IP-10 and serum MIG (r=0.847), RANTES (r=0.626); serum IP-10 and tear IP-10 (r=0.619); serum MIG and serum RANTES (r=0.719); serum MIG and tear IL-17 (r=0.619); serum RANTES and tear IL-2 (r=0.628), IL-4 (r=0.619), IL-6 (r=0.736), IL-8 (r=0.770), IP-10 (r=0.687), MCP-1 (r=0.566), MIG (r=0.740).

Conclusion: Increased tear Th1/th2 cytokine levels were found in pSS. No correlation was found between serum or tear cytokine and chemokine levels and pSS disease activity.

Disclosure: A. A. Castillo-Ortiz, None; **R. E. Barbosa-Cobos**, None; **L. Becerril-Mendoza**, None; **G. Lugo-Zamudio**, None; **V. Lima-Gómez**, None; **A. Moreno-Eutimio**, None; **N. Nieto-Velázquez**, None; **A. Tzec-Pérez**, None.

Abstract Number: 664

Regulation of Interferon Signaling By a Calcium-Induced miRNA in Primary Human Salivary Gland Epithelial Cells

Shyh-Ing Jang, NIDCR, NIH, Bethesda, MD
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SESSION INFORMATION
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Background/Purpose: Sjögren's syndrome (SS), an autoimmune disease that targets the salivary and lacrimal glands which causes dry eyes (xerophthalmia) and dry mouth (xerostomia) phenotypes. In the salivary gland, the reduction or complete loss of saliva secretion has been attributed to acinar cell dysfunction. Although the underlying mechanisms are unclear, more than 50% of SS patients display high activity of type I and II interferon (IFN) responses.

Methods: We established primary human salivary gland epithelial cell culture (phSG) conditions that either retains highly proliferative growth or display differentiated acinar-like phenotype. Whole Transcriptome profiling (RNA-Seq) revealed calcium-regulated and differentially expressed miRNAs.

Results: One of these differentially expressed miRNAs, miR-1248, increases more than 8-fold in phSG cells after calcium switch. Transfection of miR-1248 mimics into phSG cells results in up-regulation of Stat1 (6-fold), Stat2 (3-fold), JAK1 (2.5-fold) and JAK2 (4-fold). Also interferon-stimulated genes (ISG) of MX1, OAS1 and ISG15 were markedly elevated indicating the involvement of miR-1248 in regulation of IFN signaling pathway. Knockdown of IFNAR1/IFNAR2 in miR-1284 mimic-transfected phSG cells showed greatly reduced MX1 induction. IFN-b and -g were detected in culture media in miR-1248 mimic-transfected phSG and primary T cells, respectively, confirmed the production and secretion of these cytokines. Digital PCR assays revealed that the level of endogenous miR-1248 in human salivary glands biopsy from SS patients was higher than that in healthy control.

Conclusion: our data provide a potential underlying mechanism for the elevation of IFN responses regulated by differentially expressed miRNA in Sjögren's syndrome patients.

Disclosure: S. I. Jang, None;

Abstract Number: 665

Salivary Gland Secretome: A Novel Tool to Identify Biomarkers of Dryness and Immunopathology in Primary Sjogren's Syndrome and Non-Autoimmune Sicca Patients

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SESSION INFORMATION

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Background/Purpose: Salivary gland biopsy is essential in primary Sjögren's syndrome (pSS) diagnostics. However, tissue analysis using the traditional method has several limitations including inaccuracy of quantification of lymphocytic infiltration and poor correlation with dryness. To perform biomarker identification in the target organ, tissue would have to be sacrificed. By performing saliva proteomics the biopsy tissue can be saved, but this technique has not yielded consistent biomarkers and is limited by the absence of saliva production in many sicca patients. We explored whether Luminex analysis of a multitude of cytokines in salivary gland secretomes could provide biomarkers to stratify sicca patients and insights in pathogenesis.

Methods: Labial salivary gland (LSG) tissues were rinsed after biopsy and incubated in 200µL of saline for 1h at room temperature. Tissue supernatants were rendered cell-free, frozen in liquid nitrogen and stored at -80°C. Hundred and four soluble mediators were measured in supernatants from pSS and non-Sjögren's sicca (nSS) patients by Luminex. Tissue supernatants from 8 pSS and 8 nSS patients were selected for analysis based on matched biopsy weights. Findings from this discovery cohort were validated in an additional cohort (n=34 nSS, 26 pSS) and correlations with clinical parameters were assessed.

Results: Levels of 20 cytokines were significantly different between the nSS and pSS patients in the discovery cohort (all at least $p<0.05$). These 20 and 13 additional cytokines based on a trend towards statistical significance ($p<0.10$) were measured in an additional cohort. Weights of the biopsies did not significantly differ between the groups (65.9±8.0mg versus 66.5±5.5mg). Fifteen out of the 20 significantly different cytokines were validated and an additional 7 cytokines were significantly elevated in pSS as compared to nSS patients without autoimmune features (including IL-21, IFN-γ, CXCL10, CXCL13 and sIL-7R, all $p<0.05$). Interestingly, CXCL10 and MIP-3β were also significantly elevated in nSS patients with signs of autoimmunity (eg. CXCL10 nSS: 0.9±0.5pg/mL, nSS with LFS>0 and/or anti-SSA: 7.8±4.4pg/mL, pSS 41.0±21.0pg/mL). In pSS patients numerous cytokines strongly correlated with each other and significantly correlated with lymphocytic focus scores, serum IgG levels and interestingly Schirmer's tests (n=11, 23 and 3, respectively). Additionally, various cytokines were associated with autoimmunity including elevation in anti-SSA+ versus anti-SSA- patients (n=11, all at least $p<0.05$).

Conclusion: Reproducible detection of aberrant cytokine expression in LSG secretomes seems a valuable novel tool to unravel cytokine networks correlating with clinical parameters in sicca patients. This new method represents a helpful aid to provide insights in pSS immunopathology and to identify therapeutic targets and biomarkers for diagnosis, prognosis and treatment response.

Disclosure: S. L. M. Blokland, None; **M. R. Hillen**, None; **A. A. Kruize**, None; **T. R. D. J. Radstake**, None; **J. A. G. van Roon**, None.

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Abstract Number: 666

Immunoglobulin N-Glycosylation Acquired By Somatic Hypermutation As a

Potential Mechanism for Non-Specific B Cell Activation in Sjogren's Syndrome

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Background/Purpose: Sjögren's syndrome (SS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the salivary and lacrimal glands resulting in tissue destruction, pathological dry mouth and dry eyes and in increased risk for lymphoma. The presence of ectopic germinal centers, clonally related B cells and autoantibody production from antibody-secreting cells (ASCs) isolated from the salivary glands indicate that at least some of the ASCs arise from an antigen-driven immune response. Analyses of immunoglobulin sequences can be instrumental for determining somatic mutational patterns shaped by selective pressures, where positive selection in the Complementary Determining Regions (CDRs) and negative selection in the framework regions (FWRs) would indicate antigen-driven antibody production. An alternative would be a non-specific mode of B cell activation. Immunoglobulin variable region N-linked glycosylation acquired by somatic hypermutation (AcN-glycs) has been strongly correlated to follicular lymphoma. Bacterial lectins can bind and activate B cells via AcN-glycs - a possible non-specific mechanism for antibody production and proliferation of B cells.

Methods: To explore immunoglobulin selective pressures in our cohort, we single cell-sorted IgG+ ASCs isolated from the minor salivary glands of 4 SS patients meeting the American-European combined and ACR criteria, and 5 sicca controls. The immunoglobulin variable regions were sequenced by RT-PCR. AcN-glyc motiffs were identified using the online NetNGlyc tool. An IMGT/V-QUEST sequence analysis was performed to confirm that all identified AcN-glyc motifs were introduced by somatic mutation and not germline-encoded. To analyze for antigen-driven selection we utilized BASELINe Version 1.3, an online tool for predicting positive or negative selective pressures.

Results: We sequenced 56 variable regions from 3 SS and 21 sicca control immunoglobulins. Analysis of heavy and light chain sequences revealed SS patients had an increased frequency of AcN-glycs motifs in the FWRs and a decreased frequency in the CDRs as compared to controls (20% vs 5%; 4% vs 10%). The BASELINe analysis showed positive selection in the CDRs and negative selection in the FWRs of sequences from both SS patients and controls. When the selection strengths for immunoglobulins based on glycosylation status were compared (regardless of classification), we found that heavy chains with CDR AcN-glycs and light chains with FWR AcN-glycs had significantly less positive selection than those without AcN-glycs ($p=0.05$ and $p=0.04$, respectively).

Conclusion: Overall, immunoglobulins from ASCs infiltrating the minor salivary glands of SS patients and sicca controls in our cohort undergo positive selection in the CDRs and negative selection in the FWRs, indicating antigen-driven immune

responses. Immunoglobulins with AcN-glycs have lower positive and negative selection pressures in the heavy chain CDRs and FWRs as compared to those that are non-glycosylated, indicating a potential non-specific mechanism for activation in these ASCs that could potentially give rise to autoreactive proliferations or lymphoproliferative neoplasms.

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Abstract Number: 667

Cytokine and Chemokine Levels in Serum and Saliva As Disease Activity Biomarkers in Patients with Primary Sjögren's Syndrome

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Session Title: Sjögren's Syndrome - Poster I: Translational Science

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Background Evidence suggests that levels of different cytokines in primary Sjögren's syndrome (pSS) are associated with cell infiltration degree within salivary and lacrimal glands and severity of the disease. Chemokines appear to contribute to the pathogenesis of pSS. **Objectives** To evaluate the association between serum and salivary Th1/Th2/Th17 cytokine and chemokine leves and disease activity in patients with pSS.

Methods: Case-control study including 18 patients with pSS and 13 healthy controls. Disease activity was assessed by EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI); serum and salivary IFN-γ, TNF, IL-2, IL-4, IL- 6, IL-10, IL-17, IP10, MCP-1, MIG, RANTES and IL-8 levels were measured by bead-based assays following the sandwich immunoassay principle (BD Cytometric Bead Array; BD Biosciences). Differences between groups were analyzed using the Mann-Whitney U test. Correlation was estimated by Spearman´s correlation coefficient.

Results: IL-17, IL-2, IL-4, IFNγ, MIG and RANTES salivary levels were statistically different between controls and patients with pSS ($p < 0.005$). A significant correlation ($p < 0.005$) was shown in patients between serum IL-6 and serum IL- 12 (r=0.004), IL-10 (r=0.006); serum IL-12 and serum RANTES (r=0.008); serum IP-10 and serum MIG (r=0.000), RANTES (r=0.003); serum MIG and serum RANTES (r=0.014); salivary IL-17 and salivary IL-2 (r=0.004), IL-4 (r=0.001), INFγ (r=0.000), TNF (r=0.002), IL-10 (r=0.000); salivary IL-6 and salivary IL-2 (r=0.000), IL-4 (r=0.000), TNF (r=0.000), IL- 10 (r=0.000), IL-8 (r=0.0003), MCP-1 (r=0.007); salivary IL2 and salivary IL4 (r=0.000), INFγ (r=0.006), TNF (r=0.001), IL10 (r=0.000); salivary IL4 and sallivary TNF (r=0.001), IL10 (r=0.000), MCP-1 (r=0.009); salivary TNF and salivary INFγ (r=0.002), IL-10 (r=0.000), IP-10 (r=0.006); salivary MCP-1 and salivary TNF (r=0.000), IL-10 (r=0.001), IL-8 (r=0.003).

Conclusion: Increased salivary Th1/Th2/Th17 cytokine and chemokine levels were found in pSS. No correlation was found between serum or salivary cytokine and chemokine levels and pSS disease activity.

Disclosure: A. Tzec-Pérez, None; **R. E. Barbosa-Cobos**, None; **G. E. Lugo-Zamudio**, None; **L. T. Becerril-Mendoza**,

None.

Abstract Number: 668

The TNFAIP3 F127C Coding Variation in Sjogren's Syndrome: Results from a Greek Cohort

Adrianos Nezos[1], Theodora Gioka[2], Michael Koutsilieris[3], Michael Voulgarelis[4], Athanasios G Tzioufas[5] and **Clio P. Mavragani**[3], [1]Physiology, Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [2]Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, Athens, Greece, [3]Department of Physiology, School of Medicine, National Kapodistrian University of Athens, Athens, Greece, [4]Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [5]Department of Pathophysiology, Department of Pathophysiology, School of Medicine, University of Athens, Greece, Athens, Greece

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Session Time: 9:00AM-11:00AM

Background/Purpose: TNFAIP3 gene encodes the A20 protein which is an important negative feedback regulator of the NF-κB pathway. A coding TNFAIP3 polymorphism, namely rs2230926, has been previously found to be associated with primary Sjogren's syndrome (SS) related lymphoma in French and UK populations. In this study we aimed to determine the prevalence of rs2230926 in a Greek primary SS cohort and to investigate possible associations with clinical and laboratory disease characteristics.

Methods: The rs2230926 polymorphism was genotyped in 327 primary Greek SS patients, according to European American classification criteria and 448 Greek healthy controls (HC) of similar age and sex distribution. Ninety-one patients were complicated by lymphoma development. Clinical and laboratory characteristics were also recorded and gene expression of relevant genes of the NF-κB pathway was quantitated by real-time PCR in whole peripheral blood of 165 primary SS patients. Statistical analysis was performed by SPSSv.22.

Results: The prevalence of rs2230926 mutant variant was higher in both SS-lymphoma and SS-non lymphoma subgroups compared to HC [8/91 (8.8%) and 18/236 (7.6%) versus 16/448 (3.6%), p= 0.04 and p=0.03, respectively] and found to be associated with earlier age of SS diagnosis, elevated LDH levels and lower white blood cell and neutrophil number at baseline. Of interest, when patients were divided according to age of SS diagnosis, only primary SS with age at SS onset ≤ 40 years complicated by lymphoma had increased frequency of the rs2230926 compared to HC [4/22 vs 16/448, 18.2% vs 3.6%, OR 95%(CI): 6.0 (1.8-19.8, p=0.01 by Fisher's exact test]. Whole peripheral blood transcript levels of the anti-apoptotic gene BCL2L1 were significantly higher in SS patients carrying the variant compared to non-carriers (p=0.02).

Conclusion: The TNFAIP3 rs2230926 polymorphism increases lymphoma risk among primary Greek SS patients with early disease onset possibly through deregulation of the NF-κB pathway.

Disclosure: A. Nezos, None; **T. Gioka**, None; **M. Koutsilieris**, None; **M. Voulgarelis**, None; **A. G. Tzioufas**, None; **C. P. Mavragani**, GSK, 2.

sjogrens-syndrome-results-from-a-greek-cohort

Abstract Number: 669

RNA-Sequencing Reveals Sjogren's Syndrome Anti-Ro Negative Patients Share Similar Pathways to Multiple Sclerosis Patients

Indra Adrianto[1], John Ice[1], Astrid Rasmussen[2], Courtney Montgomery[1], R. Hal Scofield[1], Gabriel Pardo[1], Kathy Sivils[1], Robert Axtell[1] and Christopher Lessard[1], [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, USA, Oklahoma City, OK

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sjögren's syndrome (SS) is an autoimmune disease characterized by autoantibodies to Ro and/or La proteins and lymphocytic infiltration into exocrine glands. Multiple sclerosis (MS) is an inflammatory and degenerative disorder of the central nervous system characterized by damage to the myelin sheath. Even though SS and MS have different clinical manifestations, genetic studies have suggested that the underlying etiology is common in both diseases. We used RNA-seq to compare the expression of (DE) protein-coding and non-coding transcripts in 15 MS patients to SS anti-Ro positive (n=27) and SS anti-Ro negative (n=30) patients as well as 27 healthy controls.

Methods: Whole blood RNA samples were isolated using the NuGEN Encore kit. Sequencing was performed using the Illumina HiSeq 2000. Raw FASTQ files were aligned to the human genome using Tophat. The read counts per transcript were generated using easyRNASeq in R. DE transcripts were determined using DESeq with a false discovery rate q-value of 0.05 and a fold change (FC) of >2 or <0.5.

Results: We observed 1638, 3324, and 4052 DE transcripts when comparing each group of SS anti-Ro positive, SS anti-Ro negative, and MS patients versus healthy controls, respectively. Relevant pathways from MS DE transcripts included synaptic transmission, nervous system development, and cell differentiation among others (P<0.0001) similar to those of SS anti-Ro negative patients. Using DE transcripts relevant to distinguish two groups of SS patients, we also found MS patients clustered together with SS anti-Ro negative patients in the principal components analysis plot. In addition, we observed the expression of interferon-inducible genes and the B-cell cytokine, APRIL, were significantly higher in SS anti-Ro positive patients compared to MS patients and to healthy controls (P<0.01).

Conclusion: Our analysis shows that RNA profiles of MS patients are more similar to SS anti-Ro negative patients than the SS anti-Ro positive patients. This suggests that MS treatments may be beneficial for SS anti-Ro negative patients. Furthermore, these data have identified several putative DE in both coding and lncRNA regions in SS and MS. Further comparisons of different SS and MS subtypes are needed to confirm and expand these findings.

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Abstract Number: 670

Identification and Characterization of Sjogren's Syndrome-Associated Genetic Variants in the IL12A and DDX6-CXCR5 Loci

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Background/Purpose: Sjögren's syndrome (SS) is an autoimmune-mediated disease with hallmark features of dry eyes/mouth and autoantibodies. Genetic susceptibility to SS involves many loci, including the previously identified association of variants at the *IL12A* and *DDX6-CXCR5*loci.

Methods: Fine mapping and imputation were used to enrich existing datasets. To improve resolution, additional data was added to total 1916 SS cases and 3684 controls. Improved imputation reference panels increased the number of variants 10-fold in the *IL12A* region and nearly 2-fold in the *DDX6-CXCR5*interval. Functional significance was studied using electrophoretic mobility shift assays (EMSA) with DNA probes encompassing the variant regions and nuclear extracts from cell lines. Bands were quantified and paired t-tests performed with replicates across multiple cell lines comprising T and B lymphocyte and monocyte lineages, as well as a non-lymphoid cell control.

Results: In the region of *IL12A*, rs485497 remained the most statistically significant variant. This variant links two haplotypes upstream and downstream of this polymorphism. The downstream haplotype was an eQTL for the *IL12A* locus, peaking at rs4680536. Variant rs4680536 and SNP rs485789 were shown to be in high linkage disequilibrium (r^2=0.88). Database prediction of rs485789 revealed interaction of this variant with multiple immune-relevant transcription factors, changes in consensus transcription factor binding, and altered expression of *IL12A*. In the *DDX6-CXCR5* region, imputation showed a pattern of association spanning beyond the length of the *DDX6* coding sequence to the proximal promoter of *CXCR5*. The top associated variants (rs7125066 and rs7119038) did not yield evidence of regional functionality. However, 46 other variants that span the region of association were identified, and four variants predicted to affect gene binding or expression were selected for further study. DNA probes for variants rs4938572, rs12365699, rs57494551, and rs10892294 were used to test for altered protein binding in EMSA assays. Across all probe sets, three distinct nuclear protein complexes were observed in both the reference and alternate alleles, with the majority of signal in the two lower sized bands. Of the 4 probe sets, the rs4938572 variant was the only one to show a significant difference in binding between the reference and alternate alleles, with increased binding by the alternate allele. The major complexes showed significantly increased binding ($p<0.05$) of the alternate relative to the reference allele in 5/6 lymphocytic cell lines, but no difference in non-lymphoid cells. The most prominent differences were observed in assays using cell extracts from less differentiated cell lines.

Conclusion: Genetic variants in the *IL12A* and *DDX6-CXCR5* loci associated with SS are likely functionally impacting genes in these loci. This study adds further evidence that genetic variants in the *IL12A* and *DDX6-CXCR5* loci are functionally involved in the etiology of SS.

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Abstract Number: 671

Steered Screening for Sjögren Syndrome in Patients with Sicca Syndrome. Role of Salival Beta-2 Microglogulin

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SESSION INFORMATION

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Background/Purpose:

Sicca Syndrome patients represent a diagnostic challenge for the wide variety of etiologies that can afford it. Beta-2 Microglogulin (B2MG) is a non-glycosylated protein, found in all nuclear cells and it is release from an inflammatory stimuli [1]. The use of B2MG to differentiate between subjects with presence of autoimmunity, of those who do not, is under study. Objective: Evaluate the performance of the B2MG in distinguishing Sicca Syndrome of Sjšgren's from those with non- Sjšgren«s syndrome origin.

Methods:

This is a comparative, cross-sectional study, of diagnostic test type, registered by the local IRB (Registry number RE14-009). We included made four groups of patients: Group 1: Primary Sjšgren Syndrome (pSS), according to the 2002/2012 AECG/ACR classification criteria, Group 2: Secondary Sjšgren Syndrome to Rheumatoid Arthritis or Systemic Lupus Erythematosus, Group 3: Sicca of non-Sjšgren«s syndrome origin, Group 4: Healthy controls. Clinical test included determination of Rheumatoid factor (IgA, IgG and IgM), Anti- Ro/SSA and Anti- La/SSB levels. We record the results of patients who had biopsy of minor salivary gland. We obtained saliva according to Fleissig et al [2]. Salival B2MG was measured using a Human ELISA kit abcam¨. Medians and interquartile ranges were assessed to describe the characteristics of the groups. Finally, we categorize patients into 2 groups: SS (group 1 and 2) and No-SS (groups 3 and 4) for ROC curves.

Results:

Demographic and serological variables from the 256 subjects included in this study are shown in Table 1. In Figure 1 we showed a graphic that compares the performance of different auxiliary diagnostic methods for the SS. A value of B2MG of 0.28 µg/mL (95% CI 0.64 to 0.76), with a sensitivity of 88% and a specificity of 31% can distinguish between SS and non-SS.

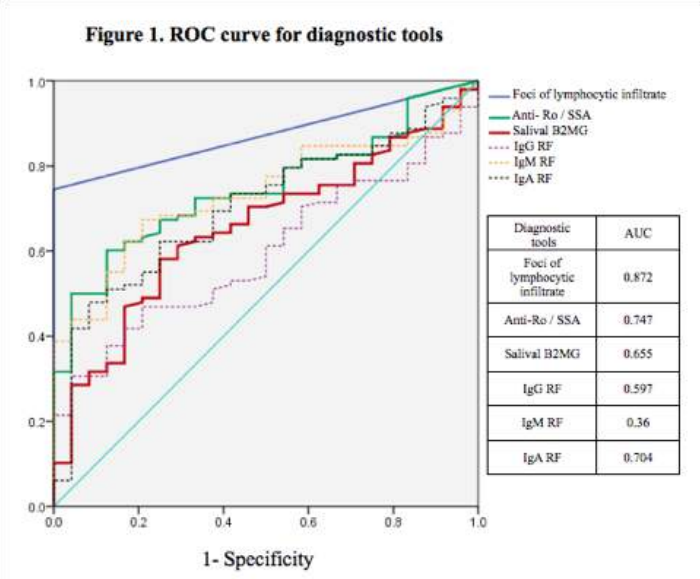
Conclusion:

We propose that salival B2MG is an easy, non-invasive tool, as a first-step on a steered screening to differentiate patients with Sjšgren Syndrome of Sicca Syndrome from others etiologies.

Table 1.Demographic and serologic patient variables

n= 256	Group 1 n=64	Group 2 n=64	Group 3 n=64	Group 4 n=64
Age (IQR)	50 (15)	54 (17)	55.5 (18)	47 (18)
Female gender, n (%)	64 (100%)	64 (100%)	62 (97%)	63 (98%)
Use of xerogenic drugs, n (%)	28 (44%)	23 (35.9%)	46(72%)	-
Use of steroid drugs, n (%)	18 (28%)	27 (42.2%)	5 (8%)	-
Use of hydroxychloroquine, n (%)	30 (47%)	19 (29.7%)	9 (14%)	-
Use of methotrexate, n (%)	15 (23%)	30 (46.9%)	1 (2%)	-
Use of biologic drugs, n (%)	0 (0%)	4 (6.2%)	1 (1.6%)	0
SSA/Ro *, n (%)	44 (69%)	10 (17.9%)/56	0 (0%)/32	-
SSB/La *, n (%)	14 (22%)	4 (7.3%)/55	0 (0%)/32	-
Schirmer test positive*, n (%)	52 (81%)	44 (71%)/62	40 (63%)/63	-
LSG biopsy positive*, n (%)	54 (87%)/62	24 (58.5%)/41	0 (0%)/25	-
Salivary flow (IQR)	0.06 (0.06)	0.06 (0.06)	0.08 (0.07)	-
Salivary b2MG (IQR)	0.71 (0.75)	0.71 (0.75)	0.52 (0.55)	0.35 (0.35)
Serum b2MG (IQR)	0.77 (0.36)	0.99 (0.73)	0.97 (0.58)	0.87 (0.26)

IQR: interquartilerange, Labialsalivaryglandbiopsy, b2MG:Beta2MicroglogulinXerogenicdrugs:tramadol, H1antihistamines, anticholinergics, betablockers, calciumchannelblockers, benzodiazepines, diuretics, selectiveinhibitorsofserotoninreuptake.SSA/Ro:Positive >25U/mL,SSB/La:Positive >25 U/mL.Schirmertestpositive:<10mmin5minutes,LSGbiopsypositive:exhibiting focallymphocyticsialadenitiswithafocusscore³1focus / 4 mm^2.*Positive/patientswithvariabledetermination



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Abstract Number: 672

Sjogren Big Data Project: Influence of Geolocation on the Phenotypic Expression at Diagnosis in 8310 Patients (North-to-South Gradient)

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Background/Purpose: To analyse the influence of geolocation (North-to-South gradient) on the clinical presentation of primary Sjögren syndrome (SjS) at diagnosis.

Methods: The Big Data Sjögren Project Consortium is an international, multicentre registry designed in 2014. By January 2016, 20 centres from five continents were participating. Patients were classified according to the geolocation of the country of the diagnosing hospital. Patients were first classified by continent, with an additional north-south sub-classification according to latitude in continents including patients from > 1 country (latitude > or < 50'N in Europe, equator > or < in America and latitude > or < 30'N in Asia).

Results: We included 7748 (93%) women and 562 (7%) men, with a mean age at diagnosis of primary SjS of 53 years. Multivariate analysis adjusted by age and gender showed that northern European patients (latitude > 50´N) had a lower frequency of ocular dryness (OR=0.39, 95%CI 0.29-0.53), abnormal ocular tests (OR=0.51, 95%CI 0.40-0.65), ANA (OR=0.59, 95%CI 0.47-0.73) and Ro/La autoantibodies (OR=0.71, 95%CI 0.58-0.88) and a higher frequency of abnormal oral tests (OR=1.62, 95%CI 1.26-2.11) and RF (OR=1.86, 95%CI 1.55-2.23) compared with southern European patients. North American patients had a lower frequency of abnormal oral tests (OR=0.55, 95%CI 0.35-0.84) and positive salivary biopsy (OR=0.43, 95%CI 0.18-0.91), and a higher frequency of ANA (OR=1.56, 95%CI 1.03-2.35), Ro/La autoantibodies (OR=2.92, 95%CI 1.95-4.41) and low C4 levels (OR=6.02, 95%CI 1.78-37.63) compared with South American patients. Northern Asian patients had a lower frequency of dry mouth (OR=0.47, 95%CI 0.26-0.83), dry eyes (OR=0.35, 95%CI 0.20-0.59), abnormal ocular tests (OR=0.34, 95%CI 0.19-0.60) and positive salivary biopsy (OR=0.43, 95%CI 0.25-0.74), and a higher frequency of ANA (OR=2.95, 95%CI 1.78-4.97) compared with southern Asian patients.

Conclusion: These results suggest, for the first time, that geolocation may influence the phenotypic expression of primary SjS at diagnosis, including significant geoepidemiological variations in the prevalence of dryness, the frequency of

abnormal diagnostic tests and the positivity of the main immunological markers. Geoepidemiology and ethnicity should be considered as key variables that should be analysed in multi-ethnic studies of patients with primary SjS.

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Abstract Number: 673

Sjögren's Syndrome (SS): The Role of Traditional (SS-A/SS-B) and Novel Antibodies in Diagnosis

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SESSION INFORMATION

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Session Title: Sjögren's Syndrome - Poster I: Translational Science

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose:

Diagnosing SS is often challenging, particularly distinguishing patients with primary SS from xerostomia and xerophthalmia (sicca). Recently, an IL-14 transgenic murine model led to the discovery of autoantibodies directed against exocrine gland antigens. These antibodies termed salivary protein-1 (SP-1), carbonic anhydrase VI (CA-6), and parotid secretory protein (PSP) were found to precede traditional antibodies and normalize once the diagnosis is established. Our goal is to explore the initial diagnostic role of these antibodies in patients suspected of having SS.

Methods:

Serum concentrations of SS-A, SS-B, and SP-1, CA-6, PSP isotypes (IgG/A/M) were examined in 94 patients being evaluated for SS. The results were recorded and analyzed. Charts were reviewed. Patients were divided among four antibody patterns: I) novel and traditional Ab +, II) novel Ab - traditional Ab +, III) novel Ab + traditional Ab -, and IV) novel and traditional Ab -. The relationship of these antibody patterns was examined in relation to diagnosis. Patients with primary SS met American-European Consensus criteria, whereas patients labeled "sicca" had nonspecific ocular and oral symptoms.

Results:

Among 94 patients, 43 (45.74%) had abnormal novel antibodies of any isotype. 27 (28.7%) were CA6+, 18 (19.10%) were SP-1+, and 15 (16.0%) were PSP+ , The IgG isotype response was the strongest: Anti CA-6 IgG was 10.4 (+/- 0.9) EU/ml, whereas SP-1 and PSP IgG were 5.1 (+/- 0.8) and 4.8 (+/- 0.6) EU/ml, respectively (P<0.0001; K-W test). The antibody patterns differed significantly between the diagnostic groups (P <0.0001,- Fisher's exact test). The traditional antibodies showed a sensitivity, specificity, PPV, and NPV of 86.53%, 92.85%, 93.75%, 84.78% compared to 32.69%, 35.71%, 38.63%, 42.85%, for the novel antibodies. Patients with abnormal novel antibodies had significantly (P<0.05; K-W test) shorter duration of symptoms in years (6.1 +/- 1.4) compared with abnormal traditional antibodies (12.8 +/-1.5).

Conclusion:

The pattern of Sjögren's associated antibodies differs between primary SS and xeropthalmia/xerostomia. Traditional antibodies have excellent sensitivity and specificity for patients clinically diagnosed with primary SS, however, novel antibodies are more prevalent in the xerophthalmia/xerostomia group and may identify a subset with early SS.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/sjogrens-syndrome-ss-the-role-of-traditional-ss-ass-b-and-novel-antibodies-in-diagnosis

Abstract Number: 674

Targeting Glandular IL-21-Production in Primary Sjogren′s Syndrome Patients By Immunomodulatory Treatment

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Interleukin-21 plays a central role in plasma cell differentiation and germinal center (GC) formation and is likely involved in the pathogenesis of primary Sjögren's syndrome (pSS). T follicular helper (Tfh)-cells are the main producers of this cytokine. Interleukin-21 protein and mRNA are present in minor salivary glands of pSS patients. Also serum levels of IL-21 are increased, compared with healthy controls. However, effects of immunomodulatory treatment on local IL-21 levels in pSS patients remain unknown. Treatment of pSS with rituximab or abatacept modulates B-T cell interaction and reduces numbers of circulating Tfh-cells. The objective of this study is to investigate if IL-21-producing cells in parotid gland tissue of pSS patients are also targeted by immunomodulatory treatment with rituximab or abatacept.

Methods: Ten pSS patients treated with rituximab (n=5) or abatacept (n=5) were included. Paraffin-embedded parotid gland tissue sections were available before and after treatment (16 weeks after the first dose of rituximab, 25 weeks after the first dose of abatacept). Sections were deparaffinized, heat-induced antigen retrieval was performed and slides were

incubated with rabbit anti-human IL-21 and goat anti-rabbit IgG-AF594. Slides were analyzed by immunofluorescence. Serum levels of rheumatoid factor (RF), anti-SSA, anti-SSB, IL-21 and numbers of circulating Tfh (cTfh)-cells were available before and after treatment.

Results: Interleukin-21-positive cells were found in parotid glands of nine out of ten patients at baseline. Baseline numbers of glandular IL-21-positive cells/mm^2 correlated strongly with serum IL-21 levels (ρ=0.83, P=0.008) and moderately with RF levels (ρ=0.60, P=0.073). Numbers of IL-21-positive cells/mm^2 were significantly higher (P=0.032) in patients with GC(s) in their biopsies (n=5), compared with GC-negative patients (n=5). No difference in age, disease duration or ESSDAI score was observed between GC-positive and GC-negative patients. After treatment with rituximab or abatacept, a decrease in IL-21-positive cells/$mm^2$was observed in all GC-positive patients, but this was not evident for GC-negative patients, possibly due to low numbers of IL-21-positive cells in GC-negative biopsies at baseline. In the whole study population a trend towards lower serum levels of IL-21 and a significant decrease in cTfh-cell numbers (P=0.023) was observed after treatment. Furthermore, treatment resulted in reduced titers of RF, anti-SSA and –SSB in all patients.

Conclusion: This pilot study shows that pSS patients with GC-positive biopsies have high numbers IL-21-positive cells in their glands. Numbers of IL-21-positive cells/mm^2 correlate strongly with serum levels of IL-21 in all patients. This study further indicates that interference with T-B-cell interaction, either by B-cell depletion or inhibition of T cell co-stimulation in pSS can abrogate the pathogenic IL-21-pathway, with a concomitant decrease in systemic autoantibody levels.

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Abstract Number: 675

Association Between Structural Lesions in the Sacroiliac Joints and Spinal Inflammatory Lesions in Patients with Non-Radiographic Axial Spondyloarthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: The relevance of structural lesions in non-radiographic axial SpA (nr-axSpA) is unclear, particularly without signs of MRI inflammation. In a post hoc analysis we evaluated the association between structural lesions in the sacroiliac joints (SIJ) and spinal inflammatory lesions on MRI in early nr-axSpA. We hypothesized that structural lesions indicate a more extensive disease phenotype that includes early spinal involvement visible on MRI.

Methods: The EMBARK study (ClinicalTrials.gov: NCT01258738) enrolled patients 18-49 yrs old with axial SpA per ASAS imaging or clinical criteria without meeting modified New York radiographic criteria. Patients had symptoms for >3 months and <5 yrs, BASDAI score ≥4, and had failed ≥2 NSAIDs. Bone marrow edema (BME) in the SIJ and spine at baseline (BL) was assessed on short tau inversion recovery (STIR) scans by 2 independent readers using Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ and 23-DVU scores, respectively. BL structural lesions were evaluated on T1 weighted spin echo scans blinded to STIR scans, using the SPARCC MRI SIJ structural score (SSS). Univariate analysis evaluated the relationship between BL spinal inflammation and these BL characteristics: gender, presence/absence of any structural MRI lesions in the SIJ (SSS>0 or =0), presence/absence of specific MRI SIJ structural lesions, and SPARCC SIJ ≥2 or <2. Multivariate stepwise regression analysis evaluated the relationship between spinal inflammation and MRI SIJ lesions after including age, gender, and symptom duration.

Results: BL MRI scans were available for 185 patients. Mean (standard deviation [SD]) age was 32.0 (7.8) yrs, 60.5% were male, mean (SD) symptom duration was 2.4 (1.8) yrs, 133/182 (71.9%) patients were human leukocyte antigen B27+ and 152 (82.2%) met ASAS MRI imaging criteria. At BL, mean (SD) SPARCC MRI 23-DVU spinal score was 4.0 (8.0); 128/183 (69.9%) patients had SPARCC SIJ BME scores ≥2 and 55/183 (30.1%) had scores <2. A total of 77/185 (41.6%) patients had ≥1 structural lesion on MRI comprised of erosion (65/185, 35.1%), backfill (26/185, 14.1%), fat metaplasia (15/185, 8.1%) and ankylosis (4/185, 2.2%). Higher spine 23-DVU scores were observed in males, in the presence of definite SIJ inflammation (SPARCC SIJ ≥2, p=0.01), and in the presence of any one of the SIJ structural lesions, Table. Multivariate analysis indicated that erosion and backfill are independent factors associated with spinal inflammation; parameter estimates (SE): erosion: 2.9 (1.3), p=0.03; backfill: 3.9 (1.8), p=0.03.

Conclusion: MRI structural lesions in the SIJ occur in a substantial proportion of patients with nr-axSpA and their presence suggests a more extensive phenotype of disease associated with early spinal involvement.

Table. Univariate analysis of the relationship between spinal inflammation and select baseline characteristics, including MRI SIJ structural lesions, in patients with nr-axSpA

			SPARCC spine score* at baseline		
Baseline characteristic	Subgroup	N	Mean (SE)	Median (Q1, Q3)	*P*-value†
Gender	Female	76	2.4 (0.4)	1.0 (0, 3.0)	0.057
	Male	114	5.5 (0.9)	2.0 (0, 6.5)	
Ankylosis	0	170	4.3 (0.6)	1.5 (0, 5.0)	0.584
	>0	4	9.0 (6.7)	3.8 (0.5, 17.5)	
Erosion	0	112	3.0 (0.4)	1.5 (0, 4.0)	0.055
	>0	62	6.9 (1.5)	2.0 (0.5, 7.0)	
Any lesion	0	100	3.0 (0.4)	1.5 (0, 4.0)	0.082
	>0	74	6.3 (1.3)	2.0 (0.5, 7.0)	
Backfill	0	148	3.6 (0.5)	1.5 (0, 4.8)	0.237
	>0	26	8.8 (3.0)	2.3 (0.5, 12.0)	
Fat metaplasia	0	159	4.3 (0.7)	1.5 (0, 5.0)	0.338
	>0	15	5.5 (1.9)	3.0 (0.5, 8.0)	
SPARCC SIJ	<2	58	2.4 (0.5)	0.8 (0, 3.2)	0.013
	≥2	132	5.1 (0.8)	2.0 (0.5, 6.3)	

*SPARCC 23-dicovertebral units (DVU), 0-414 †from Wilcoxon-Mann-Whitney test Q, quartile; SE, standard error; SIJ, sacroiliac joint; SPARCC, Spondyloarthritis Research Consortium of Canada

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5,Celgene, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Sanofi-Aventis Pharmaceutical, 5,UCB, 5,Amgen, 5.

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Abstract Number: 676

Syndesmophytes in the Thoracic Spine in Ankylosing Spondylitis As Detected By Computed Tomography and Association with Lumbar Radiographic Involvement

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

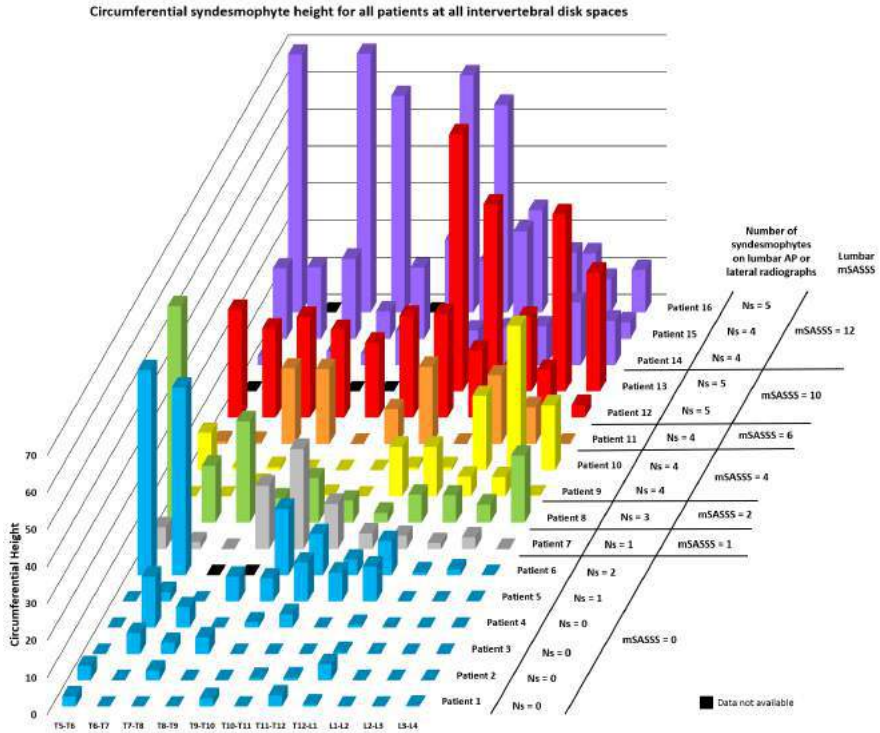
Background/Purpose: Because the thoracic spine has traditionally been excluded from radiographic examinations of spinal damage in ankylosing spondylitis (AS) due to poor visualization, little is known about the extent and degree of involvement of the thoracic spine with syndesmophytes. In particular it is not known if thoracic syndesmophytes are often present in the absence of lumbar syndesmophytes. We used computed tomography (CT) to investigate the presence of syndesmophytes in the thoracic spine, and examined the concordance between thoracic syndesmophytes in CT scans and syndesmophytes on lumbar radiographs.

Methods: Sixteen patients with modified Stoke AS Spine Score (mSASSS) in the lumbar spine ranging from 0 to 12 underwent thoracic and lumbar spine CT scans and lumbar radiography. Using a validated semi-automated computer algorithm, we quantitated syndesmophytes in 11 intervertebral disk spaces (IDS) from T5-T6 to L3-L4 on CT scans. We measured syndesmophyte height in 72 angular sectors of 5 degrees around the vertebral rim. In each angular sector, we recorded the height of the tallest syndesmophyte and normalized it to the IDS height (a score of 0 indicating no syndesmophyte and a score of 1 indicating bridging). The 72 angular sectors were summed to form the circumferential height for each IDS (a score of 72 indicating complete fusion). Anterior-posterior and lateral radiographs of the lumbar spine were read for the presence or absence of syndesmophytes and bridging in lumbar IDSs.

Results: 94% of all patients had syndesmophytes at the thoracolumbar junction (Table). Syndesmophytes were slightly more frequent in the thoracic than lumbar spine. In the thoracic spine the average frequency of IDSs with syndesmophytes was 73%, compared to 69% in the lumbar spine. Bridging was more frequent and extensive in the more superior vertebral levels ($p<0.005$). There was low concordance between thoracic syndesmophytes on CT scans and lumbar syndesmophytes seen on radiographs (Figure). All 16 patients had thoracic syndesmophytes on CT but only 12 had visible lumbar syndesmophytes on radiographs. All 6 patients with lumbar mSASSS of 0 had thoracic syndesmophytes.

Conclusion: Syndesmophytes are common in the thoracic spine in AS, and are often present among patients without lumbar syndesmophytes on radiographs. The low concordance between thoracic syndesmophytes detected on CT and lumbar syndesmophytes seen on radiographs suggests that studies that rely on radiographic measures such as the mSASSS may underestimate the extent of bone proliferation, which may confound biomarker discovery.

	Proportion of patients with any syndesmophyte	Mean (std) circumferential height (0-72)	Proportion of patients with any bridging	Mean (std) extent of bridging (0-360)
T5/T6	73%	23.4 (25.9)	60%	137 (130)
T6/T7	71%	13.5 (15.6)	50%	83 (86)
T7/T8	79%	16.9 (20.5)	50%	117 (115)
T8/T9	64%	16.4 (17.4)	50%	92 (89)
T9/T10	71%	11.6 (9.17)	50%	70 (34)
T10/T11	67%	17.2 (18.7)	47%	92 (103)
T11/T12	88%	17.3 (21.2)	38%	149 (123)
T12/L1	94%	12.4 (14.0)	44%	81 (76)
L1/L2	75%	9.84 (7.66)	13%	43 (11)
L2/L3	69%	15.8 (15.2)	38%	88 (68)
L3/L4	63%	9.97 (10.4)	19%	33 (19)
P_{trend}	0.96	0.16	0.003	0.005



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Abstract Number: 677

Low Functional Relevance of Radiographic Spinal Progression in Patients with Early Axial Spondyloarthritis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

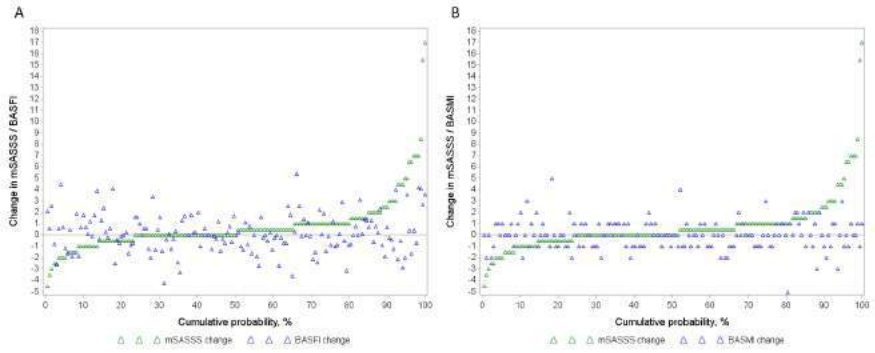
Background/Purpose: It has been shown in the past that radiographic spinal progression is an important determinant of the functional outcome in patients with advanced axial spondyloarthritis (SpA). The objective of the current study was to investigate functional relevance of structural damage development in the spine in patients with early (up to 10 years symptom duration) axial SpA.

Methods: Altogether 210 patients with early axial SpA from the German Spondyloarthritis Inception Cohort (GESPIC) were included. Clinical data reflecting disease activity (BASDAI), functional status (BASFI), and spinal mobility (BASMI) were collected at baseline and every 6 months thereafter. Structural damage in the spine was assessed on spinal radiographs at baseline and after two years according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS).

Results: The association between the mSASSS and BASFI status scores at baseline was rather weak: the BASDAI-adjusted parameter estimate (b) in the linear regression analysis was 0.04 (95%CI 0.02-0.07). At the same time, BASDAI itself was strongly associated with BASFI at baseline: b=0.87 (95%CI 0.78-0.96). For the mSASSS change score after 2 years, the parameter estimate b was 0.04 (95%CI -0.05-0.21), meaning that radiographic progression in 25 mSASSS points over 2 years would be responsible for a 1-point difference in BASFI (adjusted for the BASDAI change and mSASSS at baseline). The cumulative probability plot (figure) also shows a week association between mSASSS change and BASFI change values. Similar results were obtained for the association between mSASSS and BASMI: b=0.09 (95%CI 0.07-0.12) for the status scores and b=0.01 (95%CI -0.08-0.09) for the change scores. Results of the linear regression analysis were confirmed in the mixed model analysis: the BASDAI-adjusted parameter estimates for the association between mSASSS and BASFI / BASMI were 0.06 (95%CI 0.04-0.08) and 0.08 (95%CI 0.05-0.11), respectively. In contrast, BASDAI change score demonstrated a strong association with the BASFI change score: b=0.61 (95%CI 0.50-0.71); association with the BASMI change score was weaker: b=0.16 (95%CI 0.05-0.26).

Conclusion: The functional relevance of the structural damage development in the spine in the majority of patients with early axial SpA seems to be low, while disease activity has a major impact on the function of the spine and should be, therefore, considered as the primary treatment target in these patients.

Figure. Association between progression of structural damage in the spine (mSASSS change) and change in the functional status (BASFI) – **A** – or spinal mobility (BASMI) – **B** – over 2 years in patients with early axial spondyloarthritis.



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Abstract Number: 678

Additional Information from CT or MRI Imaging Can Increase Rheumatologists' Consensus on Grading Sacroiliitis By Radiography: Results of the Trimage Project

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The diagnosis of ankylosing spondylitis (AS) is anchored on definitive changes of sacroiliits by radiography. This is relevant not only to clinical diagnosis, but also for reimbursement and access to treatment modalities such as TNF inhibitors. However, radiographic grading of sacroiliitis is plagued by lack of interrater reliability. This study evaluated the impact of additional information from sacroiliac MRI or CT images on rheumatologists correctly identifying definite sacroiliitis by radiography.

Methods: Pelvis images from all three modalities (X-ray, CT and MRI) performed within a period of 1 year were available , from 50 patients with chronic back pain. Consensus reads for radiographic sacroiliitis, based on the interpretation of all three imaging modalities by four spondyloarthritis experts (one radiologist and 3 rheumatologists) was the gold standard grading. In the TRIMAGE project 6 rheumatologists and 2 rheumatology fellows scored radiographs online in a random order for the presence of radiographic sacroiliitis, in the first round before and after viewing the MRI images and in the second round before and after viewing the CT images. The same set of images were scored again one month later, following a two day training meeting, which included lectures for each imaging modality and supervised scoring exercises on a training set of 15 patients. Intrarater agreement, was computed for each rheumatologist before and after training. Kappa statistic and percent agreement were used to compare agreement between the expert consensus scoring and those of the rheumatologists/fellows. Sensitivity and specificity of the radiographic ratings by the rheumatologists/fellows were calculated using the final expert consensus classification as the gold standard.

Results: Based on expert consensus grading, 32 of the 50 patients (64%) had radiographic sacroiliitis. The results are summarized in Table 1 and Table 2.

Table 1. Performance of rheumatologists/fellows before and after training for diagnosing radiographic sacroiliitis when the expert consensus scoring is taken as the gold standard						
	BEFORE TRAINING			AFTER TRAINING		
	Assessment with X-ray	Assessment with X-ray & MRI	Assessment with X-ray & CT	Assessment with X-ray	Assessment with X-ray & MRI	Assessment with X-ray & CT
Intrarater agreement, mean/median	0.412 / 0.422	-	-	0.512 / 0.521	-	-
Kappa score, mean/median	0.228 / 0.253	0.305 / 0.296	0.556 / 0.554	0.363 / 0.422	0.465 / 0.480	0.533 / 0.565
Overall agreement (%), mean/median	56.5 / 58.0	62.0 / 63.0	78.3 / 78.0	67.0 / 70.0	73.8 / 75.0	78.3 / 78.0
Positive agreement (%), mean/median	51.3 / 54.3	59.6 / 61.6	81.2 / 81.7	67.1 / 72.8	75.6 / 79.0	82.1 / 82.1
Negative agreement (%), mean/median	59.8 / 60.6	62.5 / 62.6	73.3 / 73.7	63.6 / 67.5	68.3 / 68.3	69.2 / 74.7
Sensitivity, mean/median	37.9 / 40.6	48.1 / 46.9	75.4 / 75.0	59.8 / 65.6	71.5 / 73.5	80.1 / 76.6
Specificity, mean/median	89.6 / 91.7	86.8 / 91.7	83.3 / 88.9	79.9 / 83.4	77.8 / 86.1	75.0 / 86.1

Table 2. Kappa scores before and after training for the agreement between the rheumatologists/fellows and experts at different rounds of scoring						
	BEFORE TRAINING			AFTER TRAINING		
	Assessment with X-ray	Assessment with X-ray & MRI	Assessment with X-ray & CT	Assessment with X-ray	Assessment with X-ray & MRI	Assessment with X-ray & CT
Rheumatologist 1	0.178	0.205	0.503	0.491	0.491	0.327
Rheumatologist 2	0.288	0.363	0.707	0.468	0.525	0.55
Rheumatologist 3	0.11	0.492	0.399	0.045	0.478	0.33
Rheumatologist 4	0.258	0.288	0.684	0.528	0.532	0.769
Rheumatologist 5	0.363	0.413	0.826	0.376	0.48	0.579
Rheumatologist 6	0.288	0.304	0.32	0.335	0.443	0.595
Fellow 1	0.247	0.247	0.604	0.595	0.669	0.632
Fellow 2	0.093	0.126	0.407	0.069	0.168	0.481

Conclusion: Compared to expert consensus, rheumatologists/fellows had poor to fair performance in identifying radiographic sacroiliitis on plain radiographs, but most of them improved with training. Availability of CT images improved their diagnostic performance even before training while MRI improved it only after training.

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E. Dalkilic, None; **S. Donmez**, None; **O. N. Pamuk**, None; **Y. Pehlivan**, None; **S. Pay**, None; **H. Yarkan**, None; **G. Kenar**, None; **N. Akkoc**, None.

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Abstract Number: 679

Diagnostic Value of MR Enterography As a Complementary Intervention to Colonoscopy in Axial Spondylarthritis Patients with Chronic Non-Bloody Diarrhea

Ilkay Ergenç[1], Ali Ugur Unal[2], Zeynep Erturk[3], Gulsum Oguz[4], Yasemin Yalcinkaya[5], Nese Imeryuz[6], Rabia Ergelen[7], Gazanfer Ekinci[8], Nevsun Inanc[5], Cigdem Celikel[9], Haner Direskeneli[10], Hakan Akin[11] and Pamir Atagunduz[5], [1]Internal Medicine, Marmara University School of Medicine, Istanbul, Turkey, [2]Marmara University, School of Medicine, Rheumatology, Istanbul, Turkey, [3]Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [4]Rheumatology, Marmara University School of Medicine, Istanbul, Turkey, [5]Department of Rheumatology, Marmara University Faculty of Medicine, Istanbul, Turkey, [6]Gastroenterology, Marmara University, Istanbul, Turkey, [7]Radiology, Marmara University School of Medicine, Istanbul, Turkey, [8]Marmara University Faculty of Medicine Department of Radiology, Istanbul, Turkey, [9]Pathology, Marmara University School of Medicine, Istanbul, Turkey, [10]Rheumatology, Marmara University, School of Medicine, Istanbul, Turkey, [11]Gastroenterology, Marmara University School of Medicine, Istanbul, Turkey

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Chronic intermittent diarrhea (CID) is a common clinical problem in axial spondylarthritis (axSpA) patients and eventually up to 13% of these are diagnosed with inflammatory bowel disease (IBD). Magnetic resonance (MR) enterography, i.e., MRE with the highest accuracy for Crohn's disease (CD) lesions is becoming the recommended complimentary intervention to ileocolonoscopy in patients with suspected CD. We aimed to determine if a complimentary MRE (a) may change the rate of CD diagnosis in axSpA and (b) may be used as a non-invasive screening test for CID.

Methods: A total of 820 consecutive axSpA patients meeting the ASAS classification criteria (Mean disease duration of 4.3 years (6 months - 25 years) were screened for the presence of CID. Patients with a prior diagnosis of IBD, Celiac disease, inflammatory bowel syndrome (IBS) and amyloidosis were excluded. The cause of CID was investigated in 44 patients (mean age 39.5 years, 25 female) by: MRE (mural disease, bowel wall thickening and extra-luminal complications of Crohn's disease) gastro-duodenoscopy, ileocolonoscopy with histopathologic assessment, testing for Celiac disease, bacterial and parasitic agents. MRE findings assessed were Four patients refused MRE and in additional three patients had contrast medium intolerance. And seven patients refused endoscopy. Patients with either intervention missing at the time of statistical analysis were excluded from the study.

Results: Thirty-seven patients with a non-bloody, mucous diarrhea (200-400 ml / per defecation, with a monthly duration of ≥ 2 - 3 days, four times a day accompanied by stomachache) were analyzed. Mean duration of diarrhea was 21 months (3 – 120 months) Thirty-six percent were smokers, 55% were NSAID users, and 20% were under anti-TNF treatment. Nine teen percent (n=6/32) were HLA-B27 positive, only. Family history of IBD was present in one patient.IBD was

diagnosed in 12 patients; Ten with CD and two with Ulcerative colitis (UC). Four patients had normal histopathology, MRE and endoscopic findings. Remaining 21 had no conclusive diagnosis as no parasitic infections were detected by direct microscopy and stool cultures, as well as Entamoeba, clostridium difficile-, giardia antigens and celiac antibodies were negative in all patients. MRE was positive in all CD patients but abnormal endoscopic findings were detected in six CD patients, only. Both UC patients were diagnosed by ileocolonoscopy, i.e. MRE were negative. In the remaining patient group with non-specific chronic histopathologic changes and normal ileocolonoscopy only one had non-specific MRE findings.

Conclusion: Complimentary MRE increased the number of CD diagnosis in axSpA patients with CID. Evaluation of mural and extramural findings of the small intestine adds valuable information for diagnosis. Biopsy proven CD cases being all MRE positive may suggest a value of MRE as a non-invasive screening tool and larger clinical trials may be necessary.

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Abstract Number: 680

Development and Preliminary Validation of the Computed Tomography Sacroiliac Structural Score for Assessment of Structural Lesions in Axial Spondyloarthritis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Computed tomography (CT) is considered the imaging benchmark for the assessment of certain structural lesions in the sacroiliac joints (SIJ) of patients with axial spondyloarthritis (axSpA). Availability of low dose radiation techniques may lead to more widespread use, potentially as a structural endpoint in clinical trials research. We aimed to validate a new CT-based scoring method, the CT Sacroiliac Structural Score (CT-SSS), for assessing structural lesions in the SIJ.

Methods: CT scans of the SIJ from 44 patients (26 females, mean age 49.4 years, mean symptom duration 9.1 years) were reconstructed in the semicoronal plane parallel to the superior border of the sacrum and scoring of lesions was confined to this plane. Structural lesions were scored in consecutive slices in SIJ quadrants (erosion, sclerosis) or SIJ halves (ankylosis) on a dichotomous basis (present/absent) using the same anatomical principles as developed for the SPARCC MRI SIJ inflammation and structural scores. The most anterior slice is defined as visible joint >1cm vertical height and when <3 cm is defined as having only upper iliac and sacral quadrants. A visible joint >3cm vertical height is defined as

having 4 quadrants. At the posterior aspect of the SIJ, there is a natural separation of iliac and sacral cortical bone by structures in the ligamentary portion. Scoring is terminated when <1cm of iliac and sacral bone is appositional. Two readers independently scored CT scans without a prior calibration exercise and using direct online data entry onto a schematic of the SIJ. Reliability was assessed by kappa statistics, intra-class correlation coefficient (ICC), and Bland-Altman limits of agreement.

Results: Scoring was feasible (5-10 minutes per scan) and both ankylosis (ICC=0.95) and erosion (ICC=0.81) were scored to a high degree of reliability (Table). Sclerosis was less reliably scored (ICC=0.39). Presence/absence of ankylosis was reliably detected irrespective of whether this was based on a single slice (κ=0.77) or 3 consecutive slices (κ=0.81). Reliable detection (presence/absence) was lower for erosion (κ=0.50 for 1 or 3 slices) and sclerosis (κ=0.44 and 0.48 for 1 and 3 slices, respectively). Bland-Altman graphs illustrate reliability across the range of scores for ankylosis and erosion (Figure).

Conclusion: The CT-SSS method is feasible and reliable for scoring ankylosis and erosion with minimal calibration. Sclerosis requires further standardization and calibration.

	Mean (SD) score		**Median (IQR) score**			
	R1	**R2**	**R1**	**R2**	**ICC**	**95% L of A**
Erosion	4.4 (9.7)	6.5 (11.5)	0 (25.5)	0 (21)	0.95	-10.7, 13.5
Ankylosis	7.5 (14.1)	6 (13.6)	0 (12)	0 (12)	0.81	-16.2, 12.2
Sclerosis	6.6 (14.4)	7.4 (18.2)	0 (20)	0 (24.5)	0.39	-34.5, 33.0
IQR interquartile range L of A Limits of Agreement						
Table. Descriptive and Reliability data for CT-SSS score.						

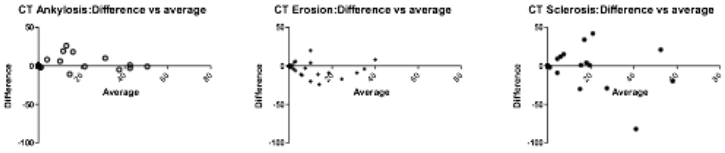

Figure.

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Abstract Number: 681

Can Bridging Syndesmophytes Independantly Affect Spinal Mobility?

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: One of the hallmark characteristics of the disease is new bone formation that manifests as syndesmophytes and spinal fusion. Spinal fusion results from bridging syndesmophytes extending across a discovertebral unit. The true impact of radiographic spinal fusion on function and spinal mobility is still debated. We studied the location and number of bridging syndesmophytes and their relation to spinal mobility measures.

Methods: The following patients were included from a longitudinal observational AS cohort: (i) patients who met the NY criteria for AS, (ii) who had complete sets of X-rays, and (iii) who had available spinal mobility measures including cervical rotation, lateral lumbar flexion and Schober's test. Schober's test and lateral lumbar flexion reflects thoracolumbar spine mobility. Cervical rotation reflects cervical spine mobility. Trained rheumatologists did all spinal measurements. Bridging syndesmophytes were scored in the anterior corners of cervical and lumbar vertebrae. Two expert rheumatologists scored X-rays. A third expert reader settled discordant results. Demographics, clinical data and BASDAI were recorded. The independent effects of bridging syndesmophytes on mobility were assessed by multivariable regression after controlling for other clinical variables.

Results: From the cohort of 800 AS patients, 113 had bridging syndesmophytes in the cervical or lumbar or both vertebrae. Ninety-two patients had cervical and 47 had lumbar bridging syndesmophytes. The mean age and disease duration of the patients was 47±11.3 and 21.6±11.4 years respectively. 86.7% of the patients were male and B27 was present in 75%. The number of cervical bridging syndesmophytes showed moderate negative correlations with cervical rotation in patients with both active and inactive disease states (r=-0.56 and -0.59 respectively). Similarly lumbar bridging syndesmophytes had moderate inverse correlations with lateral flexion and Schober's measurements (r=-0.41 and -0.38 respectively). The total number of syndesmophytes and the degree of limitation of the spine both cervical and lumbar movements showed restrictions as the number increased (Table 1). In regression models where age, sex, disease duration, increased acute phase response and B27 was included the strongest predictor for the cervical rotation, lumbar lateral mobility and Schober's was the number of cervical (β=-0.59) or lumbar bridging syndesmophytes (β=-0.42 for lumbar side flexion and -0.37 for Schober's).

Conclusion: Bridging syndesmophytes independently influenced spinal mobility. The study also provides reference values regarding the location and number of syndesmophytes and their respective impact on spinal mobility. **Table 1:**Association between localization, number of bridging syndesmophytes and degree of limitation

Number of Syndesmophtes (N)	Cervical rotation (Degrees)	Number of Syndesmophtes (N)	Lumbar lateral flexion (cm)	Schober's (cm)
0, (21)	74 (36-88)	0, (45)	10 (1-22)	3 (0-8)
2, (23)	45 (2-80)	2, (15)	6 (2-13)	1.5 (0-4)
4, (12)	54 (0-75)	4, (7)	5 (3-10)	2 (0-3)
6, (15)	35 (5-60)	6, (2)	2 (2-3)	1.25 (1-2)
8, (11)	26 (0-65)	8, (5)	4 (4-13)	1 (1-1)
10, (12)	26 (0-65)	10, (6)	5 (3-7)	0.35 (0-2)
12, (18)	20 (0-60)	12, (10)	4.7 (0-14)	1 (1-4)

* Continuous variables are presented with median (min-max) values

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Abstract Number: 682

Which Is the Most Reliable Imaging Method for Detection of Structural Changes in the Sacroiliac Joints of Patients with Ankylosing Spondylitis? a Cross-Sectional Study Comparing MRI, CT and Conventional Radiographs

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Session Type: ACR Poster Session A

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Background/Purpose: Magnetic resonance imaging (MRI) is the gold standard for detection of inflammation and fat metaplasia in the sacroiliac joints (SIJ) and the spine of patients with axial spondyloarthritis (axSpA). Structural changes (erosions, sclerosis and ankylosis) assessed by conventional radiographs (CR) or computed tomography (CT) are characteristic for ankylosing spondylitis (AS). Direct comparisons of these imaging techniques have not been performed to date. In this study we compare the reliability of CR and MRI as compared to CT for detection of structural changes in SIJs of AS patients.

Methods: Complete sets of MRI, CT and CR of SIJs of 69 AS patients and 49 age- and gender-matched controls in whom CTs had been performed for other reasons than back pain were analyzed. Two readers evaluated the images independently and blinded to diagnosis and clinical characteristics in random order. Assessment of lesions was performed based on SIJ-quadrants (SQ). Only definite erosions, sclerosis and ankylosis were recorded, and only SQ changes for which readers agreed on were used for analysis.

Results: The mean age of AS patients was 44.6 years, 72.5% were male, 85.5% were HLA-B27 positive, the mean time since diagnosis was 4.8±5.8 years (range 1 14 years), the mean BASDAI was 4.9±1.8 and the mean CRP was 1.9±2.3mg/dl. In total, 552 SQ (276 pairs) were analyzed. *Erosions* were found in 131 (23.7%) SQ by CR, 141 (25.5%) by CT and in 167 (30.3%) SQ on T1-MRI. Agreement for erosions was seen for 64 SQ assessed by CR/CT, 100 SQ by CT/MRI and 70 SQ by CR/MRI, with 48.9% of SQ detected by CR also seen on CT and 45.4% detected on CT also seen by CR. The corresponding numbers for CT/MRI were 70.9% and 59.9% and for CR/MRI 53.5% and 41.9%, respectively. Disagreement for erosions was found in 144 (26.1%), 108 (19.6%) and 158 (28.6%) SQ, respectively. *Sclerosis* was seen in 86 SQ on CR (15.6%), 91 SQ on CT (16.5%) and 63 on T1-MRI (11.4%). Agreement was found in 31 SQ on CR/CT, 22 SQ on CT/MRI and 45 SQ on CR/MRI, with 36.0% SQ detected on CR also seen on CT and 34.1% detected on CT also seen by CR. The corresponding numbers for CT/MRI were 24.2% and 34.9% and for CR/MRI 52.3% and 71.4%. Disagreement for sclerosis was found in 95 (17.2%), 72 (13.0%) and 66 (12.0%) SQ, respectively. *Ankylosis* was seen in 91 SQ pairs on CR (33,3%), 130 SQ pairs on CT (47,1%) and 106 SQ pairs on MRI (38,4%). Agreement was found in 87 SQ pairs on CR/CT, 94 SQ pairs on CR/MRI and 72 SQ pairs on CT/MRI, with 95.6% SQ detected on CR also seen on CT and 66.9% detected on CT also seen by CR. The corresponding numbers for CT/MRI were 72.3% and 88.7% and for CR/MRI 79.1% and 67.9%. Disagreement for ankylosis was seen in 47 (17.0%), 48 (17.4%) and 53 (19.2%) SQ pairs, respectively. In controls, 392 SQ were analyzed. Erosions were found in only 19 (4.8%) SQ and sclerosis in 23 (5.9%) SQ, while no patient showed ankylosis.

Conclusion: Erosions and ankylosis are more common than sclerosis in SIJs of AS patients and rarely seen in controls. The agreement between methods was rather limited. Compared to CT, less erosions were detected by MRI and CR when only erosions agreed on were counted. CT and MRI were more reliable than CR for the detection of ankylosis. The superiority of MRI to detect erosions may be related to early disease stages, while erosions seen on CT seem to be due to detection in later stages of AS.

Disclosure: X. Baraliakos, None; **F. Hoffmann**, None; **X. Deng**, None; **Y. Wang**, None; **F. Huang**, None; **J. Braun**, None.

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Abstract Number: 683

Risk Factors of Uveitis in Ankylosing Spondylitis

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Uveitis is the most common extra-articular manifestation in patients with ankylosing spondylitis (AS).The prevalence and characteristics of uveitis in AS have been studied in previous literatures while its associated risk factors have not been clarified. Therefore,this study analysed the risk factors of uveitis in patients with AS.

Methods:

A total of 390 patients with AS who fulfilled the modified New York criteria were enrolled from January to December in 2015.The history of uveitis was accepted only if diagnosed by ophthalmologists.The medical records of the patients were retrospectively reviewed and associated information was collected,such as disease duration,HLA-B27 and the number of peripheral arthritis.Hip-joint lesion was identified by imaging examination.Meanwhile, biochemical examinations were performed to determine the patient's physical function.

Results: Of 390 patients with AS (80.5% male, mean age 33.3 years), 38 (9.7%) had experienced one or more episodes of uveitis. The incidence rate for hip-joint lesion was obviously higher for patients with uveitis than the non-uveitis group (44.7% vs 22.2%; $P<0.01$). The number of peripheral arthritis was also larger for the uveitis group than non-uveitis group (2.18±0.23 vs 0.55±0.04; $P<0.001$). Meanwhile, patients with uveitis had a significantly higher level of antistreptolysin O (ASO) and circulating immune complex (CIC) than those without ($P<0.05$ and $P<0.0001$, respectively). However, there were no significant differences in disease duration, HLA-B27, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) between the two groups. Binary logistic regression results showed that ASO (OR=12.2, 95% CI:3.6-41.3, $P<0.01$) and the number of peripheral arthritis (OR=4.1, 95%CI:2.6-6.3, $P<0.01$) are significantly associated with uveitis in AS.

Conclusion: This study provides some evidence that hip-joint lesion, the number of peripheral arthritis, ASO and CIC may be associated with higher rates of uveitis in AS. The results of this comprehensive analysis suggest that the possible occurrence of uveitis in AS should not be neglected if the patients have those concomitant risk factors.

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Abstract Number: 684

Subchondral Bone Sclerosis on Computed Tomography – Does It Have Any Value in the Diagnosis of Inflammatory Sacroiliitis or Is It a Non-Specific Finding?

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Sclerosis in the sacroiliac joints (SIJ) on radiography and computed tomography (CT) is common but widely considered a non-specific finding of sacroiliitis due to an association with degeneration and osteitis condensans ilii, despite little formal study. Availability of low dose radiation (CT) may lead to more widespread use for diagnostic evaluation. We standardized the definition of sclerosis on CT and then aimed to determine whether this lesion could be reliably detected and its diagnostic utility.

Methods:

215 CT scans were obtained from patients with a history of low back pain. 107 patients had a clinical diagnosis of spondyloarthritis (SpA) and 108 patients were clinically proven not to have SpA. Both groups were age and gender matched (140 males, 75 females). The mean age was 45 years. Three musculoskeletal radiologists, blinded to patient demographics and diagnosis, scored the CTs after standardization of lesion definitions and calibration. Erosions, sclerosis, and ankylosis were graded by size and number of articular surfaces/ joints involved. Sclerosis was considered definite if located along the cartilaginous compartment, measured >5mm in all 3 planes, and present >5mm from the joint surface. Discrepant scores were arbitrated and inter-reader reliability calculated by intra-class correlation coefficient (ICC). Diagnostic utility of CT lesions was determined by calculating sensitivity and specificity for the clinical diagnosis and by logistic regression.

Results:

Inter-observer reliability for scoring sclerosis for each articular surface ranged from 0.65-0.76, 0.71-0.78 for erosion, and 0.87-0.95_ for ankylosis. Sclerosis occurred in 87(81%) cases with SpA and 25 (23%) controls. For a single articular surface the specificity for sacroiliitis ranged between 88-94%, and for any two articular surfaces 95-100%. If all 4 articular surfaces were affected, specificity was 100%. Sensitivity ranged from 14% (4 articular surfaces) to 55% (either ilium). Erosion and ankylosis had a similar specificity range of 91-100% and 92–93%, respectively depending on number of joint surfaces involved. The odds ratio was 4.9 for absence/presence of sclerosis, increasing to 12.55 where there was bilateral joint involvement. For erosion the odds ratio increased to 84.2 for bilateral disease and 22.79 for bilateral ankylosis.

Sclerosis of articular surface(s) involved	**Specificity, with 95% confidence intervals**	**Sensitivity, with 95% confidence intervals**
Single articular surface	Single ilium: 88% (85-93%) - 93% (89-96%)	Single ilium: 46% (39 - 52%) - 51% (44 - 58%)
	Single sacrum: 94% (91-98%) – 94% (91-98%)	Single sacrum: 20% (14 – 25%) - 21% (15 – 26%)
Any two articular surfaces	95% (93-98%) – 100% (100-100%)	14% (9-19%) – 41%(35-48%)
All four articular surfaces	100% (100-100%)	14% (9% - 19%)
Subchondral erosion of articular surface(s) involved	**Specificity, with 95% confidence intervals**	**Sensitivity, with 95% confidence intervals**
Single articular surface	Either ilium: 91% (87-96%)	Either ilium: 74%(67 – 80%)
	Either sacrum: 94% (91-98%)	Either sacrum: 58% (51 – 66%)
Any two articular surfaces	93% (90-97%) – 100% (100-100%)	34% (27-41%) - 60% (53 – 67%)
All four articular surfaces	100% (100-100%)	34% (37-41%)
Ankylosis of articular surface(s) involved	**Specificity, with 95% confidence intervals**	**Sensitivity, with 95% confidence intervals**
Single joint involved	92% (88 – 95%)	56% (49-62%)
Both joints involved	93% (89 – 96%)	54% (47-60%)

Table demonstrating the specificities and sensitivities with 95%CI of subchondral sclerosis, erosion, and ankylosis.

Conclusion:

When sclerosis measures > 5mm in three planes and is located > 5mm from a joint perimeter, it has high specificity for sacroiliitis, regardless of how many articular surfaces are involved, with similar specificity to erosion.

Disclosure: O. Azmat, None; **R. G. Lambert**, None; **Z. Jibri**, None; **W. Maksymowych**, AbbVie, Janssen, Pfizer, 2,AbbVie, Amgen, UCB, Pfizer, Merck, Janssen, Eli Lilly, Celgene, Sanofi, Boehringer Ingelheim, Novartis, 5.

Abstract Number: 685

Paradoxical Psoriasis Secondary to Anti-Tnfa Agents in Patients with Ankylosing Spondylitis: A Nationwide Population-Based Cohort Study

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Anti-tumor necrosis factor-alpha (anti-TNFa) agents are established as the mainstay of treatment for ankylosing spondylitis (AS). Recently, paradoxical induction or exacerbation of psoriatic skin reaction during anti-TNFα therapy has been reported. The aim of this study is to investigate the incidence of psoriatic skin reaction in AS patients following anti-TNFa therapy and to compare the risk across anti-TNFα agents.

Methods: A nationwide population-based cohort study was performed using the Korean National Health Insurance Claims database. All patients with AS were collected between 2009 and 2013. The case group (anti-TNFα therapy group) included all AS patients who had been treated with anti-TNFα agents for over 6 months, and an age- and sex-matched control group (conventional therapy group) was selected randomly, with two controls per case, from AS patients who had not been administered an anti-TNFα agent. Newly-developed psoriasis and palmoplantar pustulosis after 1-year washout period of 2009 were assessed and compared between the two groups using multivariable logistic regression models.

Results: Among a total of 36,311 AS patients, 5,838 and 11,676 patients were enrolled in the anti-TNFα and conventional therapy groups, respectively. The incidence rates of psoriasis and palmoplantar pustulosis in the anti-TNFα therapy group were significantly higher than those of conventional therapy group (1.66% vs. 0.80% for psoriasis and 0.48% vs. 0.13% for palmoplantar pustulosis, all P <0.0001). After adjusting for age and sex, the anti-TNFα therapy group had increased risks of psoriasis (odds ratio [OR] 2.112, 95% confidence interval [95% CI] 1.586–2.812) and palmoplantar pustulosis (OR 4.343, 95% CI 2.248–8.392). Infliximab (OR 2.801, 95% CI 1.793–4.375) had the highest association with incident psoriasis, followed by adalimumab (OR 1.980, 95% CI 1.359–2.886) and etanercept (OR 1.906, 95% CI 1.278–2.843).

Conclusion: The use of anti-TNFα agents was significantly associated with the development of paradoxical psoriasis and palmoplantar pustulosis in patients with AS.

Disclosure: K. J. Kim, None; **J. M. Bae**, None; **Y. B. Joo**, None; **I. W. Baek**, None; **K. S. Park**, None; **C. S. Cho**, None.

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Abstract Number: 686

Development and Evaluation of the Combined Ankylosing Spondylitis Spine Score (CASSS) for the Assessment of Spinal Radiographic Outcome

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Spinal radiographic progression is a highly variable process in ankylosing spondylitis (AS). Our aim was to develop a combined AS spine score (CASSS) in which the cervical facet joint score is combined with the mSASSS, and to investigate the additional value of the CASSS in the evaluation of spinal radiographic progression in AS patients.

Methods: Baseline and 4-year radiographs from 98 consecutive AS patients treated with TNF-α inhibitors in the GLAS cohort were scored by two readers; vertebral bodies according to mSASSS (0-72) and cervical facet joints (C2-C7) according to the method of de Vlam (0-15). The CASSS was calculated by summing up the total scores of both methods (range 0-87) and was compared to mSASSS (gold standard) using three aspects of the OMERACT filter: feasibility, discrimination, and truth.

Results: *Feasibility:* Scoring cervical facet joints took a few minutes, no additional radiographs were necessary. The CASSS could be calculated in 91 (93%) and mSASSS in 94 (96%) patients. *Discrimination:* Both scoring methods had very good inter-observer reliability (ICC's status scores >0.99, progression scores 0.92). Measurement error was similar for CASSS and mSASSS, smallest detectable change was 1.9 and 1.8, resp. Sensitivity to change was moderate for both methods with a standardized response mean of 0.63 for CASSS and 0.59 for mSASSS. *Truth:* The use of CASSS resulted in 41 (46%) patients with higher baseline scores and 22 (25%) with higher progression scores compared to mSASSS. Baseline damage of facet joints was moderately correlated with damage of vertebral bodies (rho=0.49). Radiographic progression of facet joints was not correlated with progression of vertebral bodies (rho=0.16).

Conclusion: According to the OMERACT filter, the new CASSS performed similar to mSASSS in respect to feasibility and discrimination. The CASSS showed better truth value since it provides a broader range of structural changes and captures more AS patients with progression which is very important in the evaluation of radiographic outcome in this heterogeneous and slowly progressing disease.

Disclosure: F. Maas, None; **A. Spoorenberg**, Abbvie, Pfizer, UCB, 2,Abbvie, Pfizer, MSD, UCB, and Novartis, 5; **E. Brouwer**, Roche Pharmaceuticals, 5; **H. Bootsma**, None; **R. Bos**, None; **F. Wink**, Abbvie, 5; **S. Arends**, Pfizer, 2.

Abstract Number: 687

Safety and Efficacy of Certolizumab Pegol over 204 Weeks in Patients with Axial Spondyloarthritis, Including Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: RAPID-axSpA (NCT01087762) investigated the efficacy and safety of certolizumab pegol (CZP) in patients (pts) with axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic (nr)-axSpA. Previously, CZP treatment has been shown to improve the signs and symptoms of axSpA over 96 weeks (wks).[1]

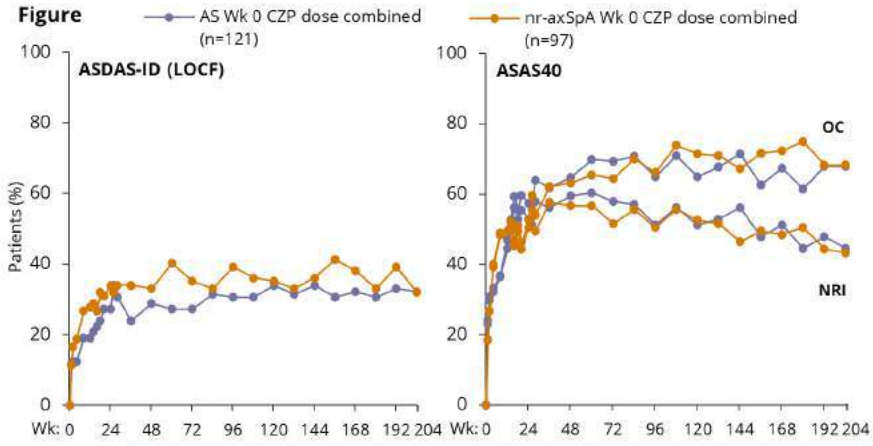
Methods: RAPID-axSpA was double-blind and placebo-controlled to Wk 24, dose-blind to Wk 48 and open-label (OL) to Wk 204. Pts fulfilled ASAS criteria and had active axSpA with positive sacroiliac joint MRI and/or raised CRP (>7.9 mg/L). Pts randomized to CZP (200 mg Q2W or 400 mg Q4W) continued their assigned dose in the OL period. Efficacy data are presented for pts originally randomized to CZP (combined doses) as observed case (OC) and with imputation: NRI for categorical measures; LOCF for continuous measures. The safety set included all pts treated with ≥1 dose of CZP.

Results: 218/325 pts were randomized to CZP from Wk 0, of whom 65% (n=142) completed to Wk 204 (AS: 67% [n=81]; nr-axSpA: 63% [n=61]). In the OL period, 9.2% of pts withdrew due to an adverse event and 1.4% due to lack of efficacy. The proportion of pts achieving ASAS20/40 and partial remission (PR) responses at Wk 24 was maintained to Wk 204 in pts remaining in the study (Figure/Table). All other clinical and patient-reported outcomes also showed maintenance of efficacy to Wk 204, with similar improvements in AS and nr-axSpA pts (Table) and in both CZP dose regimens (data not shown). Spinal mobility (BASMI-linear) and function (BASFI) also improved in both subpopulations, improvements that were maintained until Wk 204. Nr-axSpA pts had lower scores at Wk 204, but also lower levels of impairment at baseline (BL). 148 pts had BL enthesitis (MASES >0). Increasing proportions of this group who completed to Wk 204 achieved complete enthesitis clearance (MASES=0; OC): 39.6% at Wk 12, 52.5% at Wk 24, and 63.5% at Wk 204. Similarly, of 52 pts with BL heel enthesitis (tenderness at proximal insertion of ≥1 Achilles tendon; OC), 48.0%

achieved clearance at Wk 12, 65.3% at Wk 24, and 74.3% at Wk 204. Pts in the safety set (N=315) had a total CZP exposure of 981 patient-years (PY), with a serious adverse event rate per 100 PY of 10.4. Event rate for serious infections was 2.3/100 PY, for malignancies 0.5/100 PY and for serious cardiovascular events 0.4/100 PY. No new safety signals were identified from Wk 96 to Wk 204, and no deaths were reported over 4 years.

Conclusion: The RAPID-axSpA trial is the first study to report on the efficacy of an anti-TNF across the broad axSpA population, including both AS and nr-axSpA pts. Long-term data from this study show that pts from both subgroups treated with CZP were able to maintain improvements in disease activity, measured both clinically and by patient-reported outcomes, with no new safety signals, over 4 years of treatment. **References:** 1. Sieper J. Arthritis Rheum 2015;67:668–

Figure



Table

	Wk 0 CZP (dose combined: 200 mg Q2W + 400 mg Q4W)								
	axSpA			AS			nr-axSpA		
(%)	Wk 24 (NRI) n=218	Wk 204 (NRI) n=218	Wk 204 (OC) n=135	Wk 24 (NRI) n=121	Wk 204 (NRI) n=121	Wk 204 (OC) n=75	Wk 24 (NRI) n=97	Wk 204 (NRI) n=97	Wk 204 (OC) n=60
ASAS20	68.3	54.1	83.7	68.6	56.2	85.3	68.0	51.5	81.7
ASAS40	51.8	44.0	68.1	52.9	44.6	68.0	50.5	43.3	68.3
ASAS PR	30.3	23.4	36.5 [a]	28.1	21.5	32.5 [b]	33.0	25.8	41.7
Mean [c]	BL n=218	Wk 24 (LOCF) n=218	Wk 204 (LOCF) n=218	BL n=121	Wk 24 (LOCF) n=121	Wk 204 (LOCF) n=121	BL n=97	Wk 24 (LOCF) n=97	Wk 204 (LOCF) n=97
ASDAS	3.8	2.1	2.0	3.9	2.1	2.0	3.8	2.0	1.9
ASDAS-ID (%)	–	30.3	32.1	–	27.3	32.2	–	34.0	32.0
BASDAI	6.4	3.3	3.0	6.4	3.4	3.0	6.6	3.3	2.9
BASFI	5.3	3.0	2.7	5.6	3.3	3.0	5.0	2.6	2.2
BASMI-linear	3.8	3.2	3.1	4.2	3.6	3.6	3.2	2.6	2.5
MASES	3.5	1.6	1.2	3.0	1.1	0.9	4.0	2.3	1.6
Back Pain (NRS)	7.0	3.8	3.3	7.0	3.8	3.4	7.0	3.8	3.3
Nocturnal Back Pain (NRS)	6.9	3.3	3.0	6.8	3.3	3.1	7.0	3.2	2.9
MOS Sleep Scale [d]	48.1	31.8	29.9	46.4	33.0	30.1	50.2	30.4	29.6

[a] n=137; [b] n=77; [c] Unless otherwise noted; [d] Sleep disturbance. ASAS PR: ASAS Partial Remission; ASDAS-ID: ASDAS Inactive Disease (<1.3); BL: baseline; LOCF: last observation carried forward; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score; MOS: Medical Outcomes Study; NRI: non-responder imputation; NRS: numerical rating scale; OC: observed case.

77

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Abstract Number: 688

Spondyloarthritis Research Consortium of Canada (SPARCC) Baseline MRI SI Joint Score ≥2 Better Predicts Response to Golimumab Than Does Assessment of Spondyloarthritis International Society (ASAS) MRI Positivity in Nonradiographic Axial Spondyloarthritis

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Golimumab (GLM) was shown to be effective for nonradiographic axial spondyloarthritis (nr-axSpA) in a randomized, double-blind, placebo-controlled, phase 3 study (GO-AHEAD; NCT01453725).[1] The SPondyloArthritis Research Consortium of Canada (SPARCC MRI index for SI joint (SIJ) inflammation score assesses inflammation in a dichotomous manner in SIJ quadrants. Both Assessment of SpondyloArthritis international Society (ASAS) MRI SIJ positivity and the SPARCC SIJ score cut-off of ≥2 reflect positivity for MRI in nr-axSpA, yet each relies on different methodologies with different levels of scientific precision. We analyzed whether the SPARCC SIJ score cut-off of ≥2 is a better predictor of treatment responsiveness to GLM in the GO-AHEAD trial than is ASAS MRI SIJ positivity.

Methods: Patients with nr-axSpA (ASAS criteria, centrally read SIJ X-rays, disease duration ≤5 years, chronic back pain ≥3 months, high disease activity, and inadequate response or intolerance to NSAIDs) were randomized (with ASAS-defined MRI sacroiliitis by a single central reader [yes, SIJ+; no, SIJ–] and CRP level [≤ULN or >ULN] as stratification factors) to GLM 50 mg SC or placebo Q4W for 16 weeks. Baseline ASAS MRI SIJ positivity was assessed by one blinded reader. The SPARCC SIJ score was scored by two independent blinded readers. SPARCC SIJ adjudicated score

(if it existed) was used. If no adjudication was required, the mean of the two independent readers' score assessments was used.

Results: In total, 197 patients were treated (GLM=97; placebo=100). Treatment-group differences in ASAS 20, ASAS 40, ASAS PR, BASDAI 50, and SPARCC SIJ score responses were greater in patients with baseline SPARCC SIJ score ≥2 than in those with ASAS-defined MRI SIJ positivity (Tables). By contrast with the ASAS MRI–negative group, no GLM treatment benefit was observed in patients with baseline SPARCC SIJ score <2. Results should be interpreted with caution given the small subgroups, absence of multiplicity control, and post-hoc nature of the analysis.

Conclusion: Compared with ASAS MRI SIJ positivity, the categorization of patients according to a more standardized definition of MRI positivity, as defined by the SPARCC ≥2 cut-off, may provide a more accurate reflection of responsiveness to GLM in patients with nr-axSpA. **Reference**

1. Sieper J, et al. *Arthritis Rheum*. 2015;67,2702–12.

Table 1: Subgroup Analysis of Responses at Week 16 in the GO-AHEAD Trial by Baseline Stratification Factors

	Evidence of SIJ Inflammation Based on MRI at Baseline							
	ASAS MRI sacroiliitis (+)		**ASAS MRI sacroiliitis (−)**		**SPARCC MRI SIJ Score ≥2**		**SPARCC MRI SIJ Score <2**	
Endpoint	Golimumab 50 mg	Placebo	Golimumab 50 mg	Placebo	Golimumab 50 mg	Placebo	Golimumab 50 mg	Placebo
ASAS 20 at Week 16 Responders, n/N (%)	47/61 (77.0%)	24/64 (37.5%)	20/30 (66.7%)	15/32 (46.9%)	49/60 (81.7%)	25/64 (39.1%)	18/31 (58.1%)	14/32 (43.8%)
Difference in % vs Placebo Estimate (95% CI)*	39.5 (22.6, 54.1)		19.4 (-5.4, 41.6)		42.2 (25.6, 56.6)		16.4 (-8.7, 39.0)	
P value*	<0.0001		0.1257		<0.0001		0.2012	
ASAS 40 at Week 16, Responders; n/N (%)	36/61 (59.0%)	15/64 (23.4%)	17/30 (56.7%)	8/32 (25.0%)	39/60 (65.0%)	14/64 (21.9%)	14/31 (45.2%)	9/32 (28.1%)
Difference in % vs Placebo Estimate (95% CI)*	35.5 (18.6, 50.6)		31.3 (6.8, 52.6)		42.5 (25.5, 57.1)		19.1 (-5.1, 41.2)	
P value*	<0.0001		0.0125		<0.0001		0.1215	
ASAS PR at Week 16, Responders, n/N (%)	17/61 (27.9%)	12/64 (18.8%)	13/30 (43.3%)	6/32 (18.8%)	19/60 (31.7%)	11/64 (17.2%)	11/31 (35.5%)	7/32 (21.9%)
Difference in % vs Placebo Estimate (95% CI)*	9.1 (-5.9, 24.0)		24.0 (1.4, 45.3)		14.0 (-1.2, 29.1)		17.1 (-5.1, 38.3)	
P value*	0.2308		0.0373		0.0704		0.1294	
BASDAI 50 at Week 16, Responders, n/N (%)	33/61 (54.1%)	19/64 (29.7%)	19/30 (63.3%)	10/32 (31.3%)	36/60 (60.0%)	19/64 (29.7%)	16/31 (51.6%)	10/32 (31.3%)
Difference in % vs Placebo Estimate (95% CI)*	24.3 (7.3, 40.2)		31.8 (6.7, 53.2)		29.1 (11.8, 44.9)		22.5 (-2.2, 44.5)	
P value*	0.0053		0.0131		0.0011		0.0744	

*Derived based on the stratified Miettinen and Nurminen method with screening CRP level (≤ upper limit of normal or > upper limit of normal) as stratification factors.

ASAS, Assessment of SpondyloArthritis International Society; ASAS 20, 20% improvement in response; ASAS 40, 40% improvement in response; ASAS PR, Partial remission is defined as achieving ≤20 mm score in all 4 ASAS domains; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASDAI 50, At least 50% improvement from baseline in BASDAI score; CI, confidence interval; MRI, magnetic resonance imaging; SIJ, sacroiliac joint; SPARCC, SPondyloArthritis Research Consortium of Canada.

Table 2: Change from Baseline in the SPARCC MRI SIJ Score at Week 16 in the GO-AHEAD Trial by Baseline Stratification Factors

Treatment	N	Baseline Mean	Baseline Median	Week 16 Mean (SD)	Change from Baseline at Week 16 Mean (SD)	Difference vs Placebo* Mann-Whitney Score	Difference vs Placebo* *P* value
ASAS MRI sacroiliitis (+)							
Golimumab 50 mg	51	13.4	10.5	6.3 (8.81)	-7.1 (8.42)	-3.7	0.0002
Placebo	59	17.7	12.0	16.3 (15.42)	-1.4 (10.09)		
SPARCC MRI SIJ Score ≥2							
Golimumab 50 mg	50	14.5	11.5	6.8 (8.87)	-7.7 (8.32)	-3.9	<0.0001
Placebo	59	18.5	13.0	17.1 (15.21)	-1.4 (10.35)		
ASAS MRI sacroiliitis (−)							
Golimumab 50 mg	23	2.0	0	0.8 (3.15)	-1.1 (3.17)	-2.5	0.0125
Placebo	28	2.0	0	2.0 (6.50)	0 (3.45)		
SPARCC MRI SIJ Score <2							
Golimumab 50 mg	24	0.2	0	0.1 (0.34)	-0.1 (0.29)	-1.4	0.1562
Placebo	28	0.3	0	0.3 (0.70)	0 (0.43)		

*Derived based on Mann-Whitney test.
Includes subjects with MRI SI joint measurements at baseline and week 16.
ASAS, Assessment of SpondyloArthritis International Society; MRI, magnetic resonance imaging; SD, standard deviation; SIJ, sacroiliac joint; SPARCC, SPondyloArthritis Research Consortium of Canada.

Disclosure: W. Maksymowych, AbbVie, Janssen, Pfizer, 2,AbbVie, Amgen, UCB, Pfizer, Merck, Janssen, Eli Lilly, Celgene, Sanofi, Boehringer Ingelheim, Novartis, 5; **A. Tzontcheva**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **G. Philip**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **G. Bergman**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **S. Huyck**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1; **S. P. Curtis**, Merck & Co., Inc., Kenilworth, NJ, USA, 3,Merck & Co., Inc., Kenilworth, NJ, USA, 1.

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Abstract Number: 689

Relationship Between Infliximab Serum Concentrations and Risk of Infections in Patients Treated for Spondyloarthritis

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Tumour necrosis factor alpha inhibitors are effective in reducing inflammation in rheumatic diseases while increasing the risk of infections. We aimed to study the relationship between trough serum concentrations of infliximab (CIFX) and the risk of a first infectious episode (IE) in treated patients.

Methods: We retrospectively included all patients who started infliximab treatment in our department. Patients were followed-up based on recommended infliximab infusions schedule. We studied the relationship between the occurrence of a first IE requiring hospitalization, anti-infectious treatment or infliximab infusion deferral, and the last CIFX and mean of 3 last CIFX (mean-CIFX) measured before the IE.

Results: From 201 patients retrieved, 173 spondyloarthritis patients with a mean age of 46 (±12) years and disease duration of 6.2 (±6.1) years were included in the analysis. During a median follow-up of 1.1 year, 87 patients had at least one IE. Using Cox models we found that the probability of survival without IE was significantly higher in patients with a mean-CIFX under the median (<11.3 mg/L) than in patients above the median (log-rang p=0.048). Glucocorticoid use and CIFX were significantly associated with the risk of a first IE in the multivariable analysis (p=0.004 for both). The risk of IE was significantly increased in the highest quartile of mean- CIFX (>20.3 mg/L, HR=2.65, 95%CI [1.14, 6.14], p=0.023; see figure 1)

Conclusion: We showed that a high infliximab concentration was correlated with a higher risk of a first infectious episode in spondyloarthritis. This finding needs to be replicated in further prospective studies.

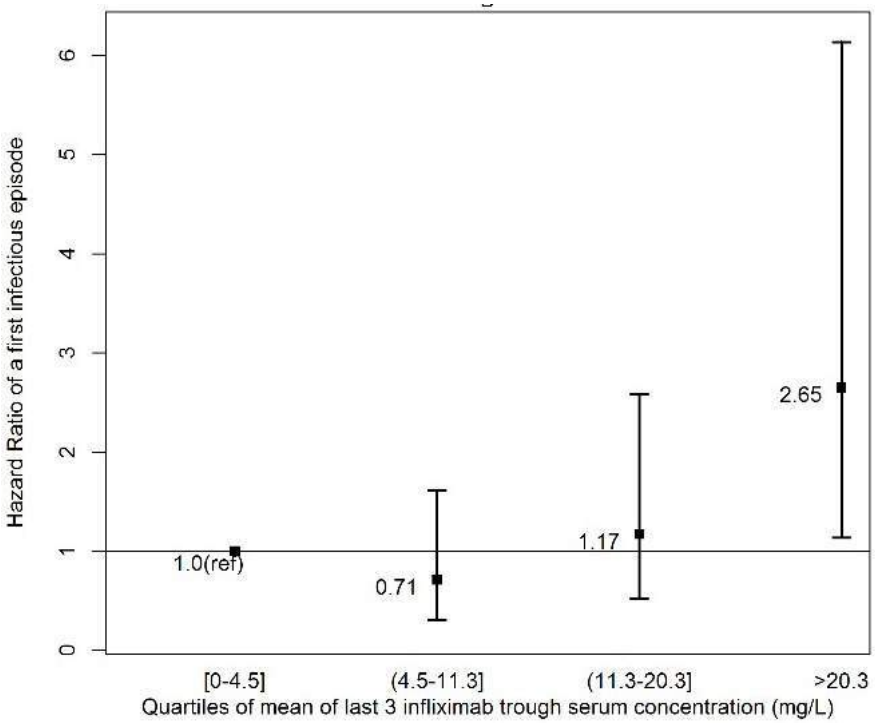

Figure 1: Estimated Hazard Ratios (points) and 95% CI (vertical segments) for a first infectious episode in quartiles of the last 3 infliximab trough serum concentrations, adjusted for weight, CRP, ESR, disease activity, presence of ATI, methotrexate and glucocorticoid use.

Disclosure: T. Bejan-Angoulvant, None; **D. Ternant**, Sanofi and Amgen, 5; **F. Daoued**, None; **F. Medina**, None; **L. Bernard**, None; **S. Mammou**, None; **G. Paintaud**, Novartis, Roche Pharma, Genzyme, MSD, Servier, Pfizer and Chugai, 2; **D. Mulleman**, Nordic Pharma, 2,Pfizer Inc, 5,MSD, Janssen-Cilag, 9.

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Abstract Number: 690

Increase in Serum Leptin Levels Is Associated with Radiographic Progression of Male Patients with Ankylosing Spondylitis: A 2-Year Longitudinal Study

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Background/Purpose: The immunomodulatory effects of adipokines have been extensively studied in rheumatic diseases, there is a paucity of information regarding their effects on bone metabolism. Our study aimed to investigate the relationship between changes in serum adipokines levels and radiographic progression in patients with ankylosing spondylitis (AS).

Methods: Twenty male patients with AS naïve to biologics and 11 age- and gender-matched male healthy subjects were consecutively recruited at a university-affiliated rheumatology center. Serum levels of leptin, adiponectin, resistin, TNF- α, IL-6, and DKK-1 were assessed by enzyme-linked immunosorbent assay at baseline and 2 years later. AS patients underwent lateral cervical and lumbar spine radiography baseline and 2 years later. Radiographic progression was defined as worsening of modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) by ≥ 2 units over the 2 years from baseline.

Results: Baseline serum leptin and adiponectin levels in AS patients did not differ significantly from those in the controls; however, AS patients had a significantly higher resistin levels (5.5 [3.8-7.7] ng/ml) compared to controls (3.8 [1.9-5.1] ng/ml) at baseline (p=0.049). Baseline serum leptin, adiponectin and resistin levels were not correlated with disease activity, functional, metrological indices or mSASSS. Two years later, a significant increase in serum leptin and resistin levels and mSASSS was observed in AS patients, whereas serum DKK-1 levels significantly decreased. Seven (35%) of the 20 AS patients showed radiographic progression after 2 years. Median changes of serum leptin levels during the 2-year follow-up in AS patients with radiographic progression was significantly higher than in those without this feature (1.6 [0.7-7.1] ng/ml vs -0.2 [-0.6-0.5] ng/ml, p=0.002). In multivariable logistic regression models, the magnitude of changes in serum leptin levels over the 2-year period was significantly associated with radiographic progression in AS patients (OR=8.24, 95% CI=1.1-61.6, p=0.04). Additionally, changes in serum adiponectin, resistin, TNF- α, IL-6 and DKK-1 levels were not related to radiographic progression.

Conclusion: Increase in serum leptin levels over a 2-year period significantly correlated with radiographic progression in AS patients. Our findings suggest that leptin may be involved in the pathogenesis of new bone formation in AS. Table 1. Logistic regression models for the radiographic progression in patients with ankylosing spondylitis

Variables	Crude OR (95% CI)	p	Adjusted OR [a] (95% CI)	p
Changes in leptin levels, ng/ml	8.24 (1.1-61.6)	0.04	8.24 (1.1-61.6)	0.04
Age, years	1.12 (0.99-1.21)	0.083	-	-
Disease duration, months	0.99 (0.98-1.02)	0.999		
TNF-α blocker use	0.64 (0.11-4.01)	0.64	-	-
Changes in BMI, kg/m^2	1.4 (0.73-2.71)	0.311		

TNF-α; tumor necrosis factor- α, BMI; body mass index [a]Estimated using multivariable logistic regression model with backward selection including changes in leptin levels, age and TNF-α blocker use

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Abstract Number: 691

ASAS Health Index for Patients with Spondyloarthritis: Translation into Spanish, Validation, Reliability and Construct Validity

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The aim of the study was to develop and validate a Spanish-language translation of the ASAS Heath Index (ASAS-HI) testing its reliability, construct validity and responsiveness in Colombian patients with SpA

Methods: Translation was done using a standardized operating procedure (forward-backward procedure). Patients fulfilling ASAS classification criteria for either axial (axSpA) or peripheral SpA (pSpA) participated. Test-retest reliability was assessed by intraclass correlation coefficient (ICC) in patients without treatment changes (stable disease state). In patients who required a therapeutic change because of high disease activity, responsiveness was assessed using a standardized response mean (SRM). Construct validity against other health outcomes was evaluated by Spearman

correlation. Internal consistency (Cronbachs-α) and discriminative ability between ASAS-HI and ASDAS were assessed

Results: In total 50 patients were included: 54% male, mean (SD) age 44.8 (13.1) years, symptom duration 15.8 (9.7) years, BASDAI 4.6 (2.2), BASFI 4.7 (2.5), ASDAS-CRP 2.2 (1.0). The diagnosis of axSpA was established in 44 patients (AS =30, nr-axSpA =14) and pSpA in 6 patients. The total score of the ASAS-HI was 8.2 (5.1). The test-retest reliability (n=18) was good ICC: 0.84 (95%CI 0.71 to 0.93, p<0.001). Sensitivity to change was tested in 10 patients and SMR was 2.58 (1.75 to 3.37), and 2.94 (2.13 to 4.24) for those patients receiving TNFi (n=7). Construct validity showed a good correlation with clinical parameters (r≥0.60) for pain, BASDAI, BASFI, and ASDAS (Table 1). A high internal consistency was found with a Cronbachs-α of 0.91. The ASAS-HI discriminated well between patients with different stages of disease activity and function irrespective of the tool applied (BASDAI, BASFI and ASDAS) Table 2

Conclusion: The Spanish-language translation of the ASAS Health index was found relevant and comprehensive by patients with SpA. This version is available to evaluate the state of health and functioning in these patients and can be used in clinical practice **Table 1** Correlation coefficient (95%IC) between ASAS-HI and clinical characteristics

	Spearman correlation coefficient	
Characteristics	ASAS-HI	P value
Age	-0.007 (-0.28-0.27)	0.959
Symptom duration	-0.11 (-0.38-0.19)	0.428
Patient global (0-10 NRS)	0.58 (0.34-0.73)	≤0.0001
Pain (0-10 NRS)	0.61 (0.38-0.75)	≤0.0001
Spinal pain (0-10 NRS)	0.59 (0.35-0.73)	≤0.0001
BASDAI	0.66 (0.46 - 0.79)	≤0.0001
BASFI	0.62 (0.41-0.76)	≤0.0001
ASDAS	0.65 (0.43-0.79)	≤0.0001
EQ-5D	0.75 (0.60-0.85)	≤0.0001
SF-36 (physical)	0.72 (0.55-0.83)	≤0.0001
SF-36 (mental)	0.74 (0.58-0.84)	≤0.0001
HAD-S Anxiety	0.65 (0.45-0.78)	≤0.0001
HAD-S Depression	0.69 (0.50-0.81)	≤0.0001

ASAS HI, The Assessment of Spondyloarthritis international Society Health Index; BASDAI, Bath ankylosing spondylitis activity disease indez; BASFI, Bath ankylosing spondylitis functional index; ASDAS, Ankylosing Spondylitis Disease Activity Score; NRS, numerical rating scale; EQ-5D, EuroQol standardized instrument; SF-36, Short form Health Survey 36 items; HAD-S, Hospital Anxiety and Depression Scale **Table 2** Discriminant ability of ASAS-HI stratified by disease activity (mean±SD)

	ASDAS status groups			
	Inactive (n=8)	Moderate (n=12)	High (n=19)	Very high (n=5)
ASAS-HI	2.5 ± 5.9	5.9 ± 3.0	9.4 ± 3.9	13.6 ± 2.0
BASDAI	1.2 ± 0.5	3.6 ± 1.0	5.8 ± 1.5	6.8 ± 0.4
BASFI	1.3 ± 0.9	3.6 ± 1.6	5.9 ± 2.0	6.6 ± 1.0

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Abstract Number: 692

Efficacy and Safety of Biological Therapy and Target Synthetic Dmards: A Systematic Literature Review Informing the 2016 Update of the ASAS/EULAR Recommendations for the Management of Axial

Spondyloarthritis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: As part of the update of the ASAS/EULAR recommendations for the management of axSpA, we performed a systematic literature review to assess the efficacy and safety of biological (b) and targeted synthetic (ts) DMARDs in patients with axSpA published since the last SLR in 2009.

Methods: We searched in Medline, EMBASE, and Cochrane Central databases (2009-2016), supplemented by searches in 2014-2015 EULAR and ACR abstracts, for randomized clinical trials (RCT) and controlled CTs, including long-term extensions, strategy trials, and observational studies (only for safety assessment and as long as a comparator group was included). Interventions were any bDMARD, tsDMARD and biosimilar. All relevant efficacy and safety outcomes were included and meta-analyses performed whenever appropriate.

Results: Of 10,244 articles and 428 conference abstracts screened, 76 papers and 26 abstracts fulfilled the inclusion criteria. A Cochrane review confirmed the efficacy and safety of etanercept, infliximab, adalimumab and golimumab in patients with r-axSpA. In addition, we found large treatment-effects both in r-axSpA and nr-axSpA for these drugs and also for certolizumab pegol (table 1). For nr-axSpA, results were better among those with objective signs of inflammation (either sacroiliitis on MRI or CRP) before treatment start (table 2). Secukinumab has shown good efficacy results in two large phase 3 RCTs [ASAS 20 pooled RR (95% CI) at week 16: 2.1 (1.7; 2.7) for 150 mg; NNT: 3.1] and overall good safety data. Ustekinumab, apremilast and tofacitinib have shown good (preliminary) results in phase 2/proof of concept trials; Rituximab, IL-6 antagonists (tocilizumab and sarilumab) and abatacept failed to do so. Infliximab biosimilar (CT-P13) proved to be as effective and safe as the infliximab originator. Although long-term observational safety data are still scarce, no new safety signals were identified.

Conclusion: New evidence strengthens the efficacy and safety of TNFi both in patients with r-axSpA and nr-axSpA. Secukinumab is the first drug targeting a new pathway showing efficacy and safety in axSpA.

Table 1. Effect of TNFi on ASAS 20 and ASAS 40 responses in patients with r-axSpA and nr-axSpA

	r-axSpA (mNY criteria)			nr-axSpA (ASAS criteria)		
Outcome Drug (dose)	N patients (Studies)	Pooled RR (95% CI)	NNT	N patients (Studies)	RR (95% CI)	NNT
ASAS 20 ≤24W†						
Etanercept	163 (2 studies)	2.16 (1.48; 3.15)	3.1	215 (1 study)	1.45 (1.06; 1.90)	6.2
Infliximab	76 (1 study)	1.81 (1.02; 3.22)	3.8	-	-	-
Adalimumab	261 (1 study)	2.42 (1.78; 3.29)	2.5	185 (1 study)	1.67 (1.17; 2.40)	4.8
Golimumab	254 (2 studies)	2.45 (1.68; 3.57)	3.3	198 (1 study)	1.86 (1.43; 2.43)	2.9
Certolizumab	122 (1 study)	2.03* (1.36; 3.04)	2.8	96 (1 study)	2.72* (1.59; 4.65)	2.3
ASAS 40 ≤24W‡						
Etanercept	82 (1 study)	1.87 (0.99; 3.59)	4.9	215 (1 study)	2.25¥ (1.33; 3.81)	5.5
Infliximab	76 (1 study)	5.69 (1.83; 17.74)	2.6	40 (1 study)	3.46¥ (1.16; 10.31)	2.3
Adalimumab	344 (1 study)	4.66 (2.61; 8.32)	2.9	185 (1 study)	2.43 (1.40; 4.25)	4.7
Golimumab	-	-	-	198 (1 study)	2.48 (1.67; 3.70)	2.9
Certolizumab	122 (1 study)	3.02* (1.57; 5.79)	2.7	96 (1 study)	4.09* (1.94; 8.40)	2.7

* Data from the same study (direct comparison); † time-point: 12 weeks for etanercept, infliximab and adalimumab; golimumab (r-axSpA: 24 weeks and nr-axSpA: 16 weeks); certolizumab: 24W; ‡ time-point: 12 weeks for etanercept and adalimumab; infliximab (r-axSpA: 12W and nr-axSpA: 16W); golimumab: 16W; certolizumab: 24W.

Table 2. Effect of TNFi on ASAS 20 and ASAS 40 outcomes according to the CRP/MRI status at baseline in patients with nr-axSpA

	MRI - AND CRP -			MRI + AND/OR CRP +		
Outcome Drug (study)	N patients	RR (95% CI)	NNT	N patients	RR (95% CI)	NNT
ASAS 20 ≤24W†						
Etanercept (EMBARK)	25 (1 study)	3.82 (0.95; 15.36)	2.5	77 (1 study)	1.48* (0.97; 2.27)	4.7
Adalimumab (ABILITY-1)	-	-	-	-	-	-
Golimumab (GO-AHEAD)	39 (1 study)	0.95 (0.50; 1.81)	NE	53 (1 study)	2.08 (1.22; 3.55)	2.5
Certolizumab (RAPID-axSpA)	NA	NA	NA	96 (1 study)	2.72 (1.59; 4.65)	2.3
ASAS 40 ≤24W†						
Etanercept (EMBARK)	25 (1 study)	6.25 (0.33; 118.2)	NE	76 (1 study)	2.09* (1.04; 4.18)	4.1
Adalimumab (ABILITY-1)	42 (1 study)	1.14 (0.35; 3.65)	36.7	142 (1 study)	2.96 (1.56; 5.63)	3.7
Golimumab (GO-AHEAD)	-	-	-	-	-	-
Certolizumab (RAPID-axSpA)	NA	NA	NA	96 (1 study)	4.09 (1.94; 8.40)	2.7

† Time-point: etanercept: 12W; adalimumab: 12W; golimumab: 16W; certolizumab: 24 weeks;
* Both MRI and CRP positive. NA, not applicable; NE, not possible to estimate.

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UCB, and Wyeth, 5,Director of Rheumatology Consultancy BV, 6,Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB and Wyeth, 8; **F. van Den Bosch**, AbbVie, Celgene, Janssen, Pfizer, and UCB, 5,AbbVie, Celgene, Janssen, Pfizer, and UCB, 8; **S. Ramiro**, None.

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Abstract Number: 693

The Prevalence of Axial and Peripheral Spondyloarthritis in Inflammatory Bowel Disease: A Systematic Review & Meta-Analysis

Maren C. Karreman[1,2], Jolanda J. Luime[3], Johanna M.W. Hazes[2] and Angelique E.A.M. Weel[1], [1]Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, [2]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands

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Session Type: ACR Poster Session A

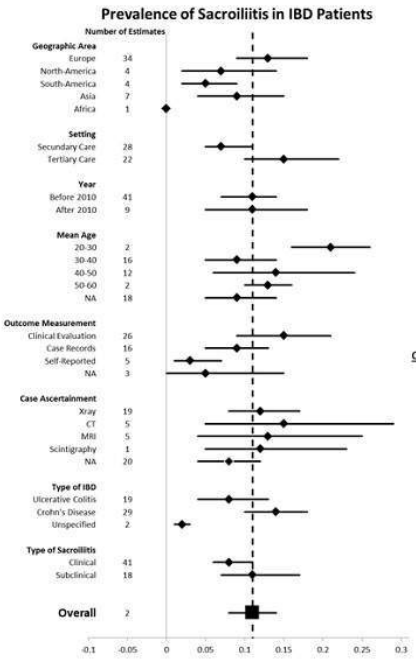
Session Time: 9:00AM-11:00AM

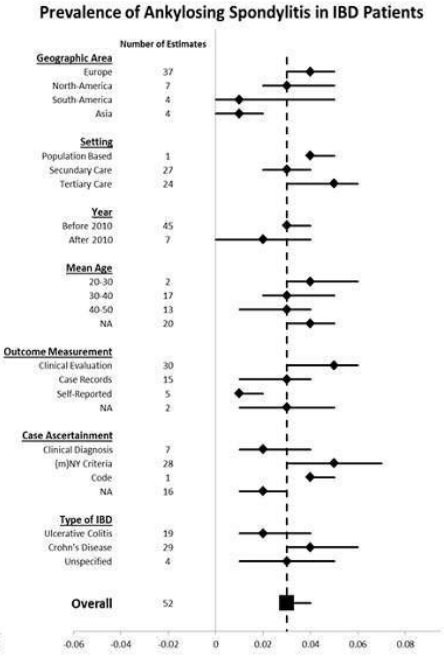
Background/Purpose: Inflammatory Bowel Disease (IBD) is a chronic disease that affects up to 0.5% of the population, comprising both Crohn's Disease (CD) and ulcerative colitis (UC). Various extra-intestinal manifestations can occur, among which spondyloarthritis (SpA). SpA can manifest with both axial and peripheral manifestations, but prevalence estimates of these manifestations differ widely. The objective of this study therefore was to provide a pooled estimate of the prevalence of axial and peripheral manifestations of SpA in patients with IBD and to identify factors that might influence the prevalence estimates.

Methods: We systematically searched Embase, Pubmed, OvidSP, Scopus and Web-of-science databases from inception to May 2014. All articles addressing the prevalence of axial and/or peripheral manifestations of spondyloarthritis in adult IBD patients were included. Risk of bias was assessed using a quality assessment tool including items on selection bias, non-response bias, sample size and misclassification of SpA diagnosis.

Results: Out of 4846 studies, 60 studies were included. Sample size varied from 9 to 4454. Methodological quality of the included studies was moderate, with only a slight majority scoring positively on the individual items of the quality assessment tool. With regard to axial manifestations, the pooled prevalence of sacroiliitis was 0.11 (95% CI 0.08-0.014), whereas the pooled prevalence for ankylosing spondylitis was 0.03 (95% CI 0.03-0.04). For peripheral arthritis the pooled prevalence was 0.14 (95% CI 0.12-0.16). Few estimates were available for the prevalence of enthesitis (range from 0.01 to 0.54) and dactylitis (range from 0 to 0.04). For both axial and peripheral manifestations, the prevalence was higher in patients with CD than in patients with UC. Heterogeneity between studies was large, which might be explained by methodological quality as well as difference in geographic area, clinical setting and the use of criteria for case ascertainment as shown for the prevalence of SI and AS.

Conclusion: Spondyloarthritis is a common extraintestinal manifestation in IBD. Peripheral arthritis is slightly more common with a pooled prevalence of 0.14 than axial manifestations as sacroiliitis (pooled prevalence 0.11) and ankylosing spondylitis (pooled prevalence 0.03). For both axial and peripheral manifesations, the prevalence is higher in patients with CD than in patients with UC.





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Abstract Number: 694

Diagnostic Delay Leads to Worse Response to Treatment

Marijn Vis[1], Kim Wervers[2], Ilja Tchetverikov[3], Mark R. Kok[4], Lindy-Anne Korswagen[5], Andreas H. Gerards[6], Hans van Groenendaal[7], Jozien Veris[8], Wiebo L. van der Graaff[9], Cathelijne W. Y. Appels[10], Johanna M.W. Hazes[11] and Jolanda J. Luime[1], [1]Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands, [2]Erasmus Medical Centre, Rotterdam, Netherlands, [3]Albert Schweitzer Hospital, Dordrecht, Netherlands, [4]Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, [5]Sint Franciscus Gasthuis, Rotterdam, Netherlands, [6]Rheumatology, Vlietland Hospital, Schiedam, Netherlands, [7]Rheumatology, ReumaZorg ZuidWest nederland, Roosendaal, Netherlands, [8]Rheumatology, Reumazorg Zuid West Nederland, Goes, Netherlands, [9]Rheumatology, Rivas hospital, Gorinchem, Netherlands, [10]Rheumatology, Amphia Hospital, Breda, Netherlands, [11]Department of Rheumatology, Erasmus University Medical Centre, Rotterdam, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Is there a clinical patient profile for PsA Patients with a diagnostic delay?

Background/Purpose: Psoriatic arthritis (PsA) is a progressive inflammatory musculoskeletal disease. Several recent studies have shown that a delay in diagnosis leads to a worse outcome. Haroon et al showed that a delay of more than 6 months from symptom onset contributes to the development of erosions and worse long-term physical function. [1] In this study we will investigate the patient profile of PsA patients with a diagnostic delay.

Methods: Data of incident PsA patients was used from the Dutch South-West Psoriatic Arthritis Registry (DEPAR) study between August 2013 and March 2016. The DEPAR includes newly diagnosed PsA patients from 8 hospitals in the South-West of the Netherlands. Patients are followed every 3 months during the first year. PsA core measurements were collected: Swollen and Tender join count (66/68), enthesitis (LEI and MASES), dactylitis (LDI) and psoriasis (PASI). In addition measures of quality of life (SF-36) and health (HAQ) are collected The groups with symptom duration longer than 6 months and shorter than 6 months were compared using parametric and non-parametric tests where appropriate.

Results: In total, 316 patients had a baseline assessment. Average age was 50.4 years (SD 13.7) and 50% were male. The median duration of complaints to diagnosis was 11.6 months (range 0-586). The median time from first visit to the general practitioner to diagnosis was 4.4 months (range 0-374). Patients with symptom duration shorter than 6 months were slightly older (52.7 (SD 14.6) vs. 49.1 (SD13.3) $p<0.05$) were more frequently male (60% vs 40%, $p<0.05$) and had less enthesitis (39% vs 52%, $p<0.05$). There was no difference in the other disease features nor quality of life or health. (table 1) Patient with a shorter symptom duration than 6 months seemed to have a better response to treatment as shown by the lower PASDAS and CPDAI scores at 3 and 6 months.

Conclusion: PsA patients with diagnostic delay for more than 6 months were more likely to be female and enthesitis more frequently and seemed to have a higher disease during follow-up as measured by CPDAI and PASDAS at 3 and 6 months.

Reference 1. Haroon M. et al, diagnostic delay of more than 6 months contributes to a poor radiographic and functional outcome. Ann Rheum Dis 2015;74:1045-1050

	Baseline		3 months		6 months	
N	109	207	93	176	83	148
	short	long	short	long	short	long
Female (%)	40%	60%*				
Age mean (SD)	52.7 (14.6)	49.1 (13.3)*				
swollen joints median (range)	2 (0-21)	2 (0-21)	1 (0-11)	1 (0-16)	0 (0-13)	0 (0-14)
tender joints median (range)	3 (0-23)	3 (0-58)	2 (0-30)	1 (0-21)	0 (0-13)	1 (0-30)*
Dactylitis (%)	14%	11%	9%	4%	7%	4%
Enthesitis (%)	39%	52% *	31%	43%	21%	43% **
PASI median (range)	2.4 (0-21)	1.8 (0-20)	1.2 (0-14)	1.0 (0-13)	1.65 (0-19)	2.0 (0-20)
SF-36 PCS mean (SD)	40.2 (8.4)	39.7 (8.5)	43.0 (8.6)	41.29 (8.9)	42.6 (9.2)	42.4 (9.2)
SF-36 MCS mean (SD)	48.2 (10.8)	47.1 (10.2)	48.1 (11.3)	45.6 (11.0)	49.4 (10.4)	47.23 (10.9)*
HAQ median (range)	5.0 (0-18)	6 (0-18)	4.0 (0-18)	5.0 (0-24)	3.5 (0-19)	5 (0-21)
PASDAS mean (SD)	4.01 (1.2)	4.1 (1.1)	3.2 (1.1)	3.45 (1.1)*	2.97 (1.1)	3.2 (1.3)
CPDAI mean (SD)	5.7 (2.2)	6.1 (2.5)	4.4 (2.0)	5.0 (2.4)	3.73 (2.1)	4.8 (2.4)*

* $p<0.05$ and ** $p < 0.001$ compared to short disease duration Enthesitis: LEI and MASES, Dactylitis: LDI

Disclosure: M. Vis, None; **K. Wervers**, None; **I. Tchetverikov**, None; **M. R. Kok**, None; **L. A. Korswagen**, None; **A. H. Gerards**, None; **H. van Groenendaal**, None; **J. Veris**, None; **W. L. van der Graaff**, None; **C. W. Y. Appels**, None; **J. M. W. Hazes**, None; **J. J. Luime**, None.

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Abstract Number: 695

Secukinumab Sustains Individual Clinical Responses over Time in Patients with Active Ankylosing Spondylitis: 2-Year Results from a Phase 3 Randomized Placebo-Controlled Trial

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

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Background/Purpose: The assessment of achieving, maintaining, and improving clinical response to biologics in Ankylosing Spondylitis (AS) is part of treat-to-target recommendations aimed at optimizing treatment goals. Here we present patient-level secukinumab data to assess the likelihood of achieving an Assessment of Spondyloarthritis international Society (ASAS) response and maintaining or improving that response from Week (Wk) 2 (early response) to Wk 16 (primary endpoint) and from Wk 16 to Wks 52 and 104 (sustained effect) in patients with active AS from the MEASURE 2 trial.[1]

Methods: This was a *post-hoc* analysis of AS patients originally randomized to secukinumab 150 mg (currently approved dose) who completed the 16-wk double-blind treatment period, followed by long-term uncontrolled treatment. Shift analyses on ASAS responses between Wks 2 and 16 and Wks 16 and 52/104 were performed for subgroups of secukinumab-treated patients, based on response at the earlier time point (non-responders for ASAS 20 or ASAS 40 [ASAS NR], ASAS 20 only, or ASAS 40 only) by evaluating whether these responses were decreased, maintained, or improved at the later time point using observed data.

Results: Overall, 65, 61, and 59 AS patients treated with secukinumab 150 mg had available data to determine ASAS responses for shift analyses from Wks 2 to 16, Wks 16 to 52, and Wks 16 to 104, respectively. At baseline, mean age was 41.9 ± 12.5 years, mean time since diagnosis was 7.0 ± 8.2 years, and mean Bath Ankylosing Spondylitis Disease Activity Index score was 6.6 ± 1.5. Approximately half of the ASAS NR patients at Wk 2 or 16 subsequently developed an ASAS response at the later time point of Wk 16 or 52, respectively. A majority (71% and 67%) of ASAS 20 responders at Wk 2 or 16 showed improved responses to ASAS 40 by Wk 16 or 52, respectively, whereas 21% and 16% of ASAS 20 responders maintained their response by Wk 16 or 52, respectively. A majority (64% and 84%) of ASAS 40 responders at Wk 2 or 16 maintained this response by Wk 16 or 52, respectively. Similar trends were observed in shift analyses of ASAS responses from Wks 16 to 104 (Table).

Conclusion: In this *post-hoc* analysis of patients with active AS, the majority of patients on secukinumab treatment maintained or improved their ASAS responses over time, consistent with the sustainability of group-level ASAS responses

reported previously.[1] In particular, the vast majority of patients who achieved either an ASAS 20 or ASAS 40 response at Wk 2 or 16 maintained or improved their response by Wks 16, 52, or 104, respectively. Reference: 1. Baeten D et al. *N Engl J Med.* 2015;373:2534–48.

Table: ASAS Shift Analyses for AS Patients on Secukinumab 150 mg from Wk 2 to Wk 16 and from Wk 16 to Wk 104 in MEASURE 2

Wk 2 (N = 65)	Wk 16# (N = 65)			Wk 16 (N = 59)	Wk 104# (N = 59)		
	ASAS NR n (%)	ASAS 20 n (%)	ASAS 40 n (%)		ASAS NR n (%)	ASAS 20 n (%)	ASAS 40 n (%)
ASAS NR (N1 = 37)	19 (51.4)	12 (32.4)	6 (16.2)	**ASAS NR (N1 = 17)**	7 (41.2)	3 (17.6)	7 (41.2)
ASAS 20 (N2 = 28)	2 (7.1)	6 (21.4)	20 (71.4)	**ASAS 20 (N2 = 42)**	5 (11.9)	12 (28.6)	25 (59.5)
ASAS 40 (N3 = 14)	0 (0.0)	5 (35.7)	9 (64.3)	**ASAS 40 (N3 = 25)**	2 (8.0)	4 (16.0)	19 (76.0)

ASAS NR = patients who are NR for ASAS 20/40 endpoints; N = number of patients at Wks 2 and 16 and Wks 16 and 104 with ASAS 20/40 endpoints; N1 = number of patients who were non-responders at Wk 2 or 16; N2 = number of patients who achieved ASAS 20 at Wk 2 or 16; N3 = number of patients who achieved ASAS 40 at Wk 2 or 16; N1 to N3 is the denominator for ASAS 20/40 endpoints at Wks 16 and 104. #At Wks 16 and 104, patients were counted only once between ASAS 20/40 to the maximum response achieved. NR, non-responder to ASAS 20 and 40

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Abstract Number: 696

Significantly Reduced Recurrence Rate of Acute Anterior Uveitis in Ankylosing Spondylitis during Treatment with Golimumab

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Background/Purpose: Acute anterior uveitis (AAU) is common in ankylosing spondylitis (AS) (1). Golimumab, a tumor necrosis factor alpha (TNF-α) blocker, has proven to be effective in the treatment of AS (2). We have shown earlier that treatment with adalimumab, another TNF-α blocker, leads to a significant decrease in the recurrence rate of AAU (3) in AS. At present, the effect of golimumab on the recurrence rate of AAU in AS is unknown. The objective was to investigate the effect of golimumab treatment on the recurrence rate of AAU attacks in AS patients.

Methods: Consecutive AS patients were enrolled who all fulfilled the 1984 Modified New York criteria, and fulfilled the criteria for initiating treatment with a TNF-α blocker in the Netherlands. All patients were treated with golimumab 50mg once a month for 12 months. During treatment, all occurring AAU attacks were assessed. The historic presence of AAU attacks was assessed from the year before baseline for non-biological treated patients, or the year before the first treatment with a TNF-α blocker in case of a switch from another TNF-α blocker to golimumab. Disease activity was measured with the Ankylosing Spondylitis Disease Activity Score – C-reactive protein (ASDAS). Response to treatment was assessed with the ASAS-20.

Results: In total, 93 patients (65% male) were evaluable as per protocol, with a mean age of 44±13 years and a median disease duration of 7 (0-53) years. Fifty-one patients (55%) were TNF-α blocker naive. Median ASDAS score at baseline was 3.1 (0.7-5.5), which decreased to 1.9 (0.1-5.1) at 12 months. ASAS-20 response was achieved by 36% of patients at month three ($p<0.001$), and by 49% of patients at month twelve ($p<0.001$). Six patients (7%) had a prior history of AAU with a total of nine attacks in the year prior to the first TNF-α blocker use (9.8/100 patient years). During golimumab treatment, the rate of recurring AAU attacks was reduced to two new attacks (2.2/100 patient years), a significant reduction of 78% ($p<0.001$). These two AAU attacks occurred in two separate patients, of whom one had no history of AAU.

Conclusion: Treatment of AS patients with golimumab leads to a significant decrease in disease activity. Simultaneously, the rate of recurring AAU attacks decreased significantly during golimumab treatment. (1) Stolwijk C, van TA, Castillo-Ortiz JD, Boonen A. Prevalence of extra-articular manifestations in patients with ankylosing spondylitis: a systematic review and meta-analysis. Ann Rheum Dis 2015 Jan;74(1):65-73. (2) Inman RD, Davis JC, Jr., Heijde D, Diekman L, Sieper J, Kim SI, et al. Efficacy and safety of golimumab in patients with ankylosing spondylitis: results of a randomized, double-blind, placebo-controlled, phase III trial. Arthritis Rheum 2008 Nov;58(11):3402-12. (3) van Denderen JC, Visman IM, Nurmohamed MT, Suttorp-Schulten MS, van der Horst-Bruinsma IE. Adalimumab significantly reduces the recurrence rate of anterior uveitis in patients with ankylosing spondylitis. J Rheumatol 2014 Sep;41(9):1843-8.

Disclosure: S. C. Heslinga, None; **M. T. Nurmohamed**, None; **A. H. Gerards**, None; **E. Griep**, None; **C. Koehorst**, None; **M. R. Kok**, None; **A. Schilder**, None; **M. Verhoef**, Merck Sharp & Dohme, 3; **I. E. Van der Horst - Bruinsma**, Pfizer, MSD and AbbVie, 2,AbbVie, MSD, UCB, 5.

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Abstract Number: 697

Does Axial Spondyloarthritis Phenotype Correlate with Imaging Morphotype?

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Background/Purpose: Traditionally, radiographic imaging was used to describe morphological differences between various types of axial SpA (axSpA). MRI has advanced understanding of disease, enabled earlier diagnosis and visualization of structural changes, and facilitated the identification of non-radiographic axial SpA (nr-axSpA). The magnitude of the pathologic changes in the axial skeleton is used to quantify inflammatory and structural outcomes in clinical trials and treatment of patients with axSpA. **Objectives:** To examine the MRI morphology of sacroiliitis (SI) and vertebral corner lesions in primary axSpA (1º) patients vs. secondary axSpA (2º) patients with concomitant psoriasis.

Methods: This posthoc analysis was performed on data from patients with axSpA enrolled in the EMBARK trial (NCT01258738). Patients with no baseline MRI lesions were excluded. Symmetric and asymmetric SI, structural lesions, and corner inflammatory lesions were analyzed in 1º axSpA vs. 2º axSpA patients with psoriasis. Data were analyzed using one-way analysis of variance for continuous parameters, Fisher's exact tests for categorical parameters, Fisher's exact chi-square for small sample sizes, and parametric and non-parametric approaches for structural lesions.

Results: The baseline demographics and disease characteristics between the 122 patients with 1º axSpA and 19 with 2º axSpA were similar. Asymmetric sacroiliitis was seen in significantly fewer 1° (43%) vs. 2° (68%) axSpA patients. There were no differences in mean SpondyloArthritis Research Consortium of Canada (SPARCC) scores between 1° and 2° axSpA for any of the 4 SI joint (SIJ) quadrants. However, the lower iliac quadrants had the highest SPARCC SIJ score and the upper iliac quadrants had the lowest SPARCC SIJ scores. When analyzing the 4 spine quadrants (lower/upper anterior and lower/upper posterior), 1° patients had higher total SPARCC spine scores than 2° patients for all 4 quadrants at baseline (Table). Collapsing the 4 quadrants shows that 1° axSpA patients had higher SPARCC MRI of the entire spine (23 discovertebral units (DVU); mean=5.6) compared with 2° axSpA patients (mean=2.2).

Conclusion: We found 1° axSpA patients had more symmetric sacroiliitis and extensive spinal bone marrow edema compared with 2° axSpA patients. In addition, women appeared to have more asymmetric sacroiliitis. These data may help physicians accurately diagnose patients and decide best treatment options.

Table:

Parameter	Total (n=141)	1° axSpA with			2° axSpA with			Overall p-value
		Symmetric sacroiliitis (n=63)	Asymmetric sacroiliitis (n=52)	Non-sacroiliitis (n=7)	Symmetric sacroiliitis (n=4)	Asymmetric sacroiliitis (n=13)	Non-sacroiliitis (n=2)	
Age, y, mean (SD)	32.1 (7.4)	30.9 (6.8)	32.5 (7.8)	35.3 (7.3)	29.3 (7.9)	33.5 (6.2)	47.0 (2.8)	0.2132
Male, n (%)	92 (65.3)	46 (73.0)	27 (51.9)	4 (57.1)	4 (100)	9 (69.2)	2 (100)	0.0896
Symptom duration, y, mean (SD)	2.6 (1.9)	2.4 (2.2)	2.6 (1.5)	2.7 (1.6)	1.8 (1.5)	3.2 (1.6)	2.9 (1.6)	0.2944
SPARCC MRI SIJ score, mean (SD)	10.5 (9.9)	15.9 (10.4)	5.4 (5.1)	2.1 (0.2)	27.5 (10.2)	5.9 (4.1)	2.5 (0.7)	0.0007
Left SPARCC SIJ, mean (SD)	5.2 (6.0)	7.9 (6.1)	3.1 (5.3)	0.8 (0.3)	10.4 (7.4)	1.8 (2.1)	1.3 (0.4)	0.0004
Right SPARCC SIJ, mean (SD)	5.4 (6.2)	8.0 (7.0)	2.3 (2.5)	1.4 (0.2)	17.1 (6.3)	4.0 (5.0)	1.3 (0.4)	0.0542
SPARCC MRI 6 DVU spinal score, mean (SD)	4.7 (7.0)	6.5 (8.8)	3.8 (5.5)	2.4 (2.1)	1.6 (3.3)	2.7 (3.6)	0.8 (1.1)	0.0141
SPARCC MRI 23 DVU spinal score, mean (SD)	5.1 (8.9)	7.3 (11.8)	3.9 (5.6)	2.4 (2.1)	1.6 (3.3)	2.5 (3.2)	0.8 (1.1)	0.0180
Fat metaplasia, mean (SD)	0.5 (1.6)	0.3 (0.9)	0.9 (2.5)	0 (0)	0.3 (0.5)	0.7 (1.1)	0 (0)	0.6805
Erosions, mean (SD)	2.6 (3.5)	4.2 (4.0)	1.1 (2.0)	0.3 (0.4)	3.1 (1.8)	1.0 (1.9)	0 (0)	0.0002

Author Disclosures: · All co-authors must agree with the submitted results and conclusions, and consent to being listed as authors. · The abstract must not have been submitted in identical format to any other international meeting. · Work involving humans or animals, or material derived from them must have been approved by an institutional ethics committee. · All authors must complete a Disclosure of Conflicting Relationships declaration form – Stock, stock options or bond holdings in a for-profit corporation or self-directed pension plan – Research grants – Employment (full or part-time) – Ownership or partnership – Consulting fees or other remuneration (payment) – Non-remunerative positions of influence such as officer, board member, trustee or public spokesperson – Receipt of royalties – Speakers' bureau – Other – None - if none of the above apply

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Performance of Modified Minimal Disease Activity (MDA) in Patients with Peripheral Spondyloarthritis

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Background/Purpose: Due to lack of validated outcome measures in non-psoriatic peripheral spondyloarthritis (pSpA), recent studies in this patient (pt) population have used varying endpoints [1]. Thus, developing new pSpA-specific indices may be worthwhile. Minimal Disease Activity (MDA) has been validated in psoriatic arthritis but not in pSpA. The objective of this study is to evaluate the performance of a modification of the MDA criteria (excluding psoriasis) in pSpA patients (pts) from the ABILITY-2 study [2].

Methods: This post-hoc analysis evaluated the validity of a modified MDA (mMDA) in pSpA. ABILITY-2 was a 12-week trial comparing adalimumab (ADA) with placebo (PBO) in pSpA followed by a 144 week extension. The mMDA for pSpA was defined as achieving at least 4 or 5 out of the following 6 criteria: (1) tender joint count (TJC, 78 joints) ≤ 1; (2) swollen joint count (SJC, 76 joints) ≤ 1; (3) pt pain visual analog scale (VAS) ≤ 15 of 100 mm; (4) pt global activity (PtGA) VAS ≤ 20 of 100 mm; (5) health assessment questionnaire–disability index (HAQ-DI)≤ 0.5; and (6) tender entheseal points ≤ 1. Enthesitis was assessed by the Leeds Enthesitis Index (LEI) or the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index for this analysis. The proportion of pts achieving the 4 different versions of mMDA were evaluated (either 4 or 5 of 6 using LEI and either 4 or 5 of 6 using SPARCC). The correlations between mMDA and the novel pSpA response criteria [PSpARC] remission from ABILITY-2 and Ankylosing Spondylitis Disease Activity Score Inactive Disease [ASDAS ID] were evaluated by tetrachoric correlation (r_{tet}).

Results: Of the 163 pts (82 ADA, 81 PBO) who completed wk 12, significantly greater proportion of pts receiving ADA achieved mMDA (regardless of the definition) compared with PBO (P<0.001 for all comparisons, **Table 1a**). The proportion of mMDA responders at yrs 1, 2, and 3 was numerically higher in pts initially randomized to ADA. The mMDA response showed a stronger positive correlation with PSpARC remission (r_{tet} > 0.9) than ASDAS ID (r_{tet} > 0.75) at wk 12, and yrs 1-3. Among pts who fulfilled the 4/6 criteria (LEI or SPARCC), approximately 20-30% of pts did not meet TJC and SJC criterion (**Table 1b)**. However, the 5/6 criteria (LEI or SPARCC) were more stringent with approximately 5% and 13% not meeting the TJC and SJC criterion, respectively.

Conclusion: All 4 versions of mMDA discriminated between ADA and PBO treatment groups; both entheseal indices performed similarly. The mMDA (particularly the 5/6 versions which closely represents the concept of MDA) could be an appropriate treatment target in pSpA pts. **References:**

1. Turina, M.C., et al., Ann Rheum Dis, 2015. *(*doi: 10.1136/annrheumdis-2014-207235).

2. Mease, P., et al., Arthritis Rheumatol, 2015. 67(4): p. 914-23.

Table 1a. Proportion of patients achieving modified MDA[a]

Modified MDA	Week 12 (DB)		Year 1 (OLE)		Year 2 (OLE)		Year 3 (OLE)	
	ADA (n=82)	PBO (n=81)	ADA (n=71)	PBO>ADA (n=74)	ADA (n=62)	PBO>ADA (n=68)	ADA (n=54)	PBO>ADA (n=58)
4/6 LEI	33 (40.2)	11 (13.6)	44 (62.0)	35(47.3)	44 (71.0)	34 (50.0)	37 (68.5)	29 (50.0)
	***				*		*	
5/6 LEI	23 (28.0)	4 (4.9)	30 (42.3)	30 (40.5)	37 (59.7)	29 (42.6)	29 (53.7)	37 (46.6)
	***							
4/6 SPARCC	29 (35.4)	10 (12.3)	43 (60.6)	34 (45.9)	43 (69.4)	33 (48.5)	35 (64.8)	28 (48.3)
	***				*			
5/6 SPARCC	22 (26.8)	4 (4.9)	30 (42.3)	29 (39.2)	36 (58.1)	27 (39.7)	29 (53.7)	27 (46.6)
	***				*			

P-values for difference between ADA and PBO treatment groups: ***, P<0.001; **, P<0.01; *, P<0.05.

Table 1b. Criteria not met in modified MDA responders receiving ADA at week 12[a]

Modified MDA	Modified MDA criterion					
	TJC78 > 1	SJC76 > 1	Pt Pain VAS > 15	PtGA VAS > 20	HAQ-DI > 0.5	Enthesitis index > 1
4/6 LEI (n=33)	9 (27.3)	10 (30.3)	2 (6.1)	3 (9.1)	3 (9.1)	0 (0.0)
5/6 LEI (n=23)	1 (4.3)	3 (13.0)	0 (0.0)	1 (4.3)	2 (8.7)	0 (0.0)
4/6 SPARCC (n=29)	6 (20.7)	7 (24.1)	1 (3.4)	2 (6.9)	3 (10.3)	3 (10.3)
5/6 SPARCC (n=22)	1 (4.5)	3 (13.6)	0 (0.0)	1 (4.5)	1 (4.5)	2 (9.1)

[a] n (%)

Abbreviations: MDA=Minimal Disease Activity; DB=double-blind period; OLE=Open-Label Extension; ADA=Adalimumab; PBO=Placebo; LEI=Leeds Enthesitis Index; SPARCC=Spondyloarthritis Research Consortium of Canada; TJC78=Tender Joint Count (78 joints); SJC76=Swollen Joint Count (76 joints); Pt Pain=Patient global assessment of Pain; VAS=Visual Analog Scale; PtGA=Patient Global assessment of disease Activity; HAQ-DI=Health Assessment Questionnaire-Disability Index based on 20 questions.

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Abstract Number: 699

In Contrast to Men, Women with Nonradiographic Axial Spondyloarthritis Have Lower Response Rates to TNF Inhibitors Than Women with Ankylosing Spondylitis

Adrian Ciurea[1], Monika Hebeisen[2], Ulrich Weber[3,4], Giorgio Tamborrini[5], Raphael Micheroli[1], Lukas Wildi[1], Pascal Zufferey[6], Michael J. Nissen[7], Peter M. Villiger[8], Juerg Bernhard[9], Désirée van der Heijde[10], RBM Landewé[11,12], Almut Scherer[2] and Pascale Exer[13], [1]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [2]SCQM Foundation, Zurich, Switzerland, [3]Institute of Regional Health Research, University of Southern Denmark, Odense, Denmark, [4]Department of Research, King Christian 10th Hospital for Rheumatic Diseases, Graasten, Denmark, [5]Department of Rheumatology and Musculoskeletal Ultrasound, Bethesda Hospital Basel, Basel, Switzerland, [6]Rheumatology, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, [7]Rheumatology, Geneva University Hospital, Geneva, Switzerland, [8]Rheumatology, Clinical immunology & Alllergology, University Hospital Bern, Bern, Switzerland, [9]Rheumatology Center, Buergerspital, Solothurn, Switzerland, [10]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [11]Division of Clinical Immunology and Rheumatology, Academic Medical Center / University of Amsterdam, Amsterdam, Netherlands, [12]Zuyderland Medical Center, Heerlen, Netherlands, Heerlen,

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Response to tumor necrosis factor inhibition (TNFi) has been shown to be similar in nonradiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS) in patients with objective signs of inflammation, such as an elevated C-reactive protein (CRP) and/or sacroiliitis on MRI. As men and women with axSpA differ with regard to the proportion of patients with elevated CRP and acute inflammation observed on MRI, we aimed at comparing response to TNFi in nr-axSpA versus AS after stratification by sex.

Methods: Patients within the Swiss Clinical Quality Management cohort fulfilling the Assessment of Spondyloarthritis international Society (ASAS) classification for axSpA were included in the current study if they a) had a baseline pelvic X-ray, b) started a first TNFi after inclusion in the cohort and c) had a follow-up visit at 1 year (± 6 months). We excluded patients with known fibromyalgia as a co-morbidity. The proportion of patients achieving the ASAS criteria for 40% improvement (ASAS40) as well as Ankylosing Spondylitis Disease Activity Score (ASDAS) improvement criteria and status scores were evaluated at 1 year. Patients having discontinued the TNFi were considered non-responders.

Results: Baseline characteristics of 152 women and 267 men included in the analyses are shown in Table 1, stratified by classification status. In contrast to men, the proportions of patients with elevated CRP levels, peripheral arthritis and enthesitis were similarly distributed in nr-axSpA versus AS in women starting a first TNFi. The proportion of patients with different numbers of classifying axSpA features was comparable in AS versus nr-axSpA in both genders. With regard to response to TNFi, similar proportions of men with nr-axSpA and AS achieved an ASAS40 response (38% versus 45%; odds ratio (OR) 0.75, 95% confidence interval (CI) 0.35-1.56, p=0.49), as well as all ASDAS response criteria (Table 2). By contrast, a significantly lower proportion of women with nr-axSpA compared to women with AS achieved a clinical response according to the different criteria assessed (ASAS40 response of 17% versus 42%, OR 0.28, 95% CI 0.10-0.70, p=0.004 in women with nr-axSpA versus AS, respectively).

Conclusion: While men with nr-axSpA have similar response rates as men with AS, significantly lower response rates are found in women with nr-axSpA in comparison to women with AS. The results are in line with randomized controlled trials of adalimumab and golimumab in nr-axSpA, showing lower response rates in women compared to men. **Table 1. Baseline characteristics in women and men with nr-axSpA versus AS at start of first TNF inhibitor**

	Women			Men		
Parameter	**Nr-axSpA N = 57**	**AS N = 95**	**P**	**Nr-axSpA N = 51**	**AS N = 216**	**P**
Age, years	37.6 ± 11.3	40.0 ± 11.3	0.28	35.7 ± 10.9	40.5 ± 11.5	0.01
Symptom duration, years	9.8 ± 10.6	13.2 ± 9.7	0.003	8.0 ± 8.3	15.5 ± 10.9	<0.001
HLA-B27 positive, %	73.5	74.1	1.00	75.0	87.1	0.04
BASDAI	6.0 ± 1.7	5.8 ± 2.0	0.72	5.4 ± 2.0	5.5 ± 2.0	0.79
ASDAS-CRP	3.4 ± 0.7	3.5 ± 1.1	0.78	3.4 ± 0.9)	3.6 ± 0.9	0.09
CRP (mg/l)	8.9 ± 8.2	17.4 ± 25.4	0.14	14.9 ± 23.6	18.5 ± 20.8	0.02
Elevated CRP, %	48.1	60.0	0.22	44.4	66.3	0.01
BASFI	3.2 ± 2.3	4.4 ± 2.6	0.009	3.8 ± 2.4	4.4 ± 2.4	0.12
BASMI	1.4 ± 1.3	2.0 ± 1.7	0.07	1.3 ± 1.5	3.1 ± 2.3	<0.001
EQ-5D	56.5 ± 17.9	54.9 ± 21.4	0.68	52.6 ± 22.7	53.8 ± 21.4	0.87
Peripheral arthritis, %	52.8	45.0	0.39	45.1	29.5	0.04
Number of swollen joints	1.6 ± 3.1	1.5 ± 4.1	0.33	0.8 ± 1.5	0.7 ± 1.9	0.10
Enthesitis, %	83.0	77.7	0.53	80.4	65.5	0.04
Modified MASES	3.6 ± 3.5	3.1 ± 3.5	0.28	2.5 ± 3.0	2.2 ± 2.8	0.47

Table 2. Response rates after 1 year of treatment with a first TNF inhibitor

		nr-axSpA N (%)	**AS N (%)**	**OR**	**95% CI**	**P**
Women	ASAS40	8 (16.7)	35 (42.2)	0.28	0.10-0.70	0.004
	ASDAS clinically important improvement	8 (19.0)	35 (51.5)	0.22	0.08-0.59	0.001
	ASDAS <2.1	10 (22.7)	37 (49.3)	0.31	0.12-0.74	0.006
	ASDAS major improvement	2 (4.8)	17 (25.0)	0.15	0.02-0.70	0.008
	ASDAS <1.3	3 (6.8)	14 (18.7)	0.32	0.06-1.25	0.10
Men	ASAS40	16 (38.1)	84 (45.2)	0.75	0.35-1.56	0.49
	ASDAS clinically important improvement	18 (52.9)	100 (59.2)	0.78	0.35-1.75	0.57
	ASDAS <2.1	18 (42.9)	91 (50.3)	0.74	0.35-1.54	0.40
	ASDAS major improvement	6 (17.6)	52 (30.8)	0.48	0.15-1.29	0.15
	ASDAS <1.3	8 (19.0)	44 (24.3)	0.73	0.27-1.77	0.55

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Abstract Number: 700

Incidence of Inflammatory Bowel Disease Events in Adalimumab (HUMIRA) Clinical Trials Across Indications

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Adalimumab (ADA) is approved for treatment of Crohn's disease (CD) and ulcerative colitis (UC); therefore, it is postulated that new onset or flare of inflammatory bowel disease (IBD) is a rare occurrence in ADA clinical trials for non-IBD indications. The purpose of this analysis was to determine the rates of IBD adverse events (AEs) in ADA clinical trials, particularly in spondyloarthritis (SpA) patients (pts) who are at higher risk of IBD as a feature of SpA.

Methods: The rates of IBD AEs in 73 phase 2–4 interventional ADA clinical trials in rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (pJIA), pediatric enthesitis-related arthritis, uveitis (non-infectious intermediate, posterior, or pan-uveitis), hidradenitis suppurativa (HS), adult and pediatric psoriasis (Ps), psoriatic arthritis (PsA), non-PsA peripheral SpA (pSpA), non-radiographic axial spondyloarthritis (nr-axSpA), and ankylosing spondylitis (AS) were analyzed (trials in UC, CD, and intestinal Behcet's disease [BD] were excluded). The search criteria for IBD events included the following standardized MedDRA queries preferred terms: inflammatory bowel disease (IBD), ulcerative colitis (UC), Crohn's disease (CD), IBD-not otherwise specified (NOS), and ulcerative proctitis. The incidence rates (IR) for events of IBD (combined new onset and flare) in interventional clinical trials of ADA are reported as events per 100 pt-years (PY). 95% confidence intervals (CI) were based on exact Poisson confidence limits.

Results: ADA was administered to 23735 pts, representing 36404.6 PY of exposure. Overall, the IR for IBD events in all interventional ADA trials included in this analysis was 0.1/100PY (**Table**). The rates of IBD events varied across therapeutic indications from <0.1 to 0.8/100PY. There were no reports of IBD events in pediatric pts. The IR for IBD events in RA, uveitis, HS, and Ps trials were <0.1, 0.2, 0.4, and <0.1/100 PY. In SpA, the overall rates of IBD were 0.5/100 PY, while the rates were 0, 0.8, 0.5, and 0.7/100 PY in PsA, non-PsA pSpA, nr-axSpA, and AS, respectively. 2216 pts with axSpA (AS: 2026, nr-axSpA: 190) were exposed to ADA; in AS, 14 IBD events (7 new onset and 7 flares) were reported in 12 pts (7 new onset and 5 flares), while in nr-axSpA, 2 IBD events were reported in 1 pt (2 flares).

Conclusion: The rates of IBD AEs in ADA clinical trials were generally low across all indications, with all events occurring in adult pts. In AS pts, who are at increased risk of manifesting IBD, the rates of IBD for pts treated with ADA (0.7/100 PY [95% CI, 0.4–1.1]) were similar to published placebo rates pooled across multiple clinical trials (1.3/100 PY [95% CI, 0.2–4.8]).[1] In pts at risk for IBD requiring biologic therapy, ADA is a reasonable therapeutic option based on the observed low IBD event rates in ADA clinical trials and its demonstrated efficacy in treating UC and CD pts.

References:

1. Braun, J. et al., *Arthritis & Rheum*, 2007; 57:639-47.

Table. Incidence of IBD events in patients from ADA clinical trials.

Indication	N (PYs)	All IBD AEs, n[§]	IR/100 PY (95% CI)
All ADA trials[†]	23735 (36404.6)	40	0.1 (0.1 – 0.2)
Rheumatoid Arthritis	15152 (24813.0)	16	<0.1 (0.0 – 0.1)
Uveitis	387 (538.8)	1	0.2 (0.0 – 1.0)
Hidradenitis suppurativa	733 (836.3)	3	0.4 (0.1 – 1.1)
Psoriasis	3500 (5268.7)	1	<0.1 (0.0 – 0.1)
All SpA[‡]	3218 (3919.9)	19	0.5 (0.3 – 0.8)
PsA	837 (997.5)	0	0.0 (0.0 – 0.4)
Non-PsA pSpA	165 (390.7)	3	0.8 (0.2 – 2.2)
All axSpA[‖]	2216 (2531.7)	16	0.6 (0.4 – 1.0)
nr-axSpA	190 (412.2)	2	0.5 (0.1 – 1.8)
AS	2026 (2119.5)	14	0.7 (0.4 – 1.1)

[§]No IBD events were reported in pediatric patients.
[†]All ADA adult and pediatric patients in all interventional studies excluding Crohn's disease, ulcerative colitis, and intestinal Behcet's disease.
[‡]All ADA patients in all interventional studies of PsA, non-PsA pSpA, nr-axSpA, and AS.
[‖]All ADA patients in all interventional studies of nr-axSpA and AS.
Abbreviations: IBD = inflammatory bowel disease; ADA = adalimumab; PY = patient years; AEs = adverse events; IR = incidence rates; CI = confidence interval; SpA = spondyloarthritis; PsA = psoriatic arthritis; pSpA = non-PsA peripheral spondyloarthritis; axSpA = axial spondyloarthritis; nr-axSpA = non-radiographic axSpA; AS = ankylosing spondylitis.

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Abstract Number: 701

In Patients with Ankylosing Spondylitis Treated with Adalimumab, Combination Therapy with DMARD, Increase the Serum Level of Adalimumab and Decrease Immunogenicity

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In patients with rheumatoid arthritis, methotrexate (MTX), improves the clinical efficacy of anti-TNF (TNFi), among other reasons, for reducing the immunogenicity. However, there are doubts of their benefit in patients with ankylosing spondylitis (AS) The purpuse of this study is to evaluate the influence of combined treatment with DMARD in clinical efficacy in patients with AS treated with adalimumab (ADL).

Methods: Prospective, observational study was done in 62 consecutive patients diagnosed with axial AS, treated with ADL, receiving DMARD, according to clinical practice, at the discretion of the rheumatologist. Epidemiological patient data (age, gender, body mass index), type of concomitant DMARD, EA characteristics (time of evolution of disease, presence of psoriasis or inflammatory bowel disease, HLA-B27), were collected, and information of ADL, too (order of introduction of TNFi treatment and time, and presence of serum anti-ADL antibodies). Clinical response was assessed using the Spanish version of BASDAI and ASDAS-ESR index. Serum concentrations of free ADL (trough level) and anti-ADL antibodies (Ab), were measured using Promonitor-ADL and Promonitor Anti-ADL Ab ELISA kits (Progenika Grifols SA, Spain), as standardised conditions, specified by the manufacturer, cut-off value were >0.024 mg/L for the serum levels of ADL and >3.5 AU/mL for positive anti-ADL Ab. The anti-ADL Ab and ADL serum level were determined by ELISA (Progenika, Grifols SA, Spain). Cut-off level for ADL were <0.004 mg/L and anti-ADL Ab >3.5 AU/mL. Samples was obtained just before subcutaneous (s.c.) injection of ADL (trough level) and was stored at -80 °C until analysis.

Results: Of the 62 patients with axial involvement included, 31 (50%) were women, with a mean age of 46±10.years and a mean BMI of 27.47±4.49. The average time of evolution of the AS was 9.5±9.25 years. HLA-B27 was positive in 74%. DMARD was combined to ADL in 14 (23%) patients (methotrexate: 10, sulfasalazine: 3 and azathioprine 1 patient). In 47 (76%) patients, they were not associated with another extraskeletal manifestation of AS, but 12 (19%) patients had AS associated with inflammatory bowel disease and 3 (5%) patients, with psoriasis. ADL was the first TNFi in 66% of patients. The average duration of treatment with ADL was 1.33±1.44 years (median: 1 year). The average serum level of ADL was 8.62±8.59. In 19 (31%) patients were detected anti-ADL Ab, all of them (100%), in the group of patients not receiving DMARD. When comparing the group of patients treated with ADL combined with DMARD and those without (Table 1), the group treated without DMARD only presented significantly the presence of anti-ADL Ab (40% vs 0%; p <0.0001) and trend to lower serum level ADL (10.82±02.05 mg/L vs 7.59±5.5 mg/L; p=0.064). The group with anti-ADL Ab versus those without anti-ADL Ab, showed levels of ADL almost undetectable (mean: 0.082±0.16 vs 10.32±4.49; p <0.0001) and significant loss of clinical efficacy by BASDAI and ASDAS: mean: 5.53±2.0 vs 3.59±2.0 (p <0.0001) and 3.2±2.1 vs 1.92±0.74 (p = 0.038), respectively.

	DMARD Yes (n: 14/23%)	DMARD No (n: 48/77%)	p
ADL monitoring, n (%)	34 (31)	79 (69)	
Age (years): mean (SD) Median	48,07 (10.80) 48.5	46.13 (10.75) 45.0	0.56
Male, n (%)	8 (57)	23 (49%)	0.69
BMI (kg/m^2): mean (SD) Median	28.12 (3.89) 28.16	27.18 (4.73) 27.51	0.46
Time of disease evolution (years): mean (SD) Median	7.45 (7.09) 6,25	10.46 (9.87) 5.33	0.22
HLA B27 positive, n (%)	10 (71)	36 (77)	0.69
ADL order of treatment, n (%): First TNFi Second TNFi Third TNFi	8 (57) 4 (29) 2 (14)	33 (70) 14 (26) 3 (4)	0.48 0.90 0.68
Time (years) on ADL: mean (SD) Median	1.67 (1.57) 1.0	1.36 (1.27) 0.91	0.51
ADL serum level, mg/L: mean (SD) mediana	10.82 (5.16) 11.25	7.59 (5.5) 8.34	**0.064**
anti-ADL Ab, AU/L, n (%):	0 (0)	19 (40)	**0.0001**
BASDAI: mean (SD) Median	4.09 (2.14) 4.1	3.98 (2.20) 4.05	0.86
BASFI: mean (SD) Median	3.67 (2.0) 4.05	3.87 (2.40) 3.90	0.75
ASDAS: mean (SD) Median	2.09 (0.62) 2	2.23 (1.40) 2.1	0.60

Conclusion: 1) The prevalence of anti-ADL Ab in AS is 31%. 2) In our cohort, 100% of patients with AS who have immunogenicity, were been treated with ADL in monotherapy. 3) Patients with anti-ADL Ab has ADL levels almost undetectable and loss of efficacy. **Funding**: The study was supported by a research grant from the Spanish Foundation of Rheumatology (2012) and the Association for Research in Rheumatology of Marina Baixa (AIR-MB). Conclusion:

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Abstract Number: 702

Treatment with Golimumab or Infliximab Reduces Health Resource Utilization and Increases Work Productivity in Patients with Ankylosing

Spondylitis in a Large, Prospective Real-Life Cohort

Pascal Claudepierre[1], Filip van Den Bosch[2], Piercarlo Sarzi-Puttini[3], Shiva Sajjan[4], N Vastesaeger[5], Marinella Govoni[6] and Sumesh Kachroo[7], [1]Hôpital Henri Mondor, Créteil, France, [2]Rheumatology, Ghent University Hospital, Ghent, Belgium, [3]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milano, Italy, [4]Merck & Co., Inc., Kenilworth, NJ, [5]Merck Sharp & Dohme, Belgium, Brussels, Belgium, [6]Via Tasso 14, Merck Sharp & Dohme, Italy, Cento, Italy, [7]CORE, Merck & Co., Inc., Kenilworth, NJ

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: We evaluated the effect of the anti-tumor necrosis factor (TNF) agents, golimumab (GLM) and infliximab (IFX), on healthcare resource utilization (HCRU) and work productivity in patients with ankylosing spondylitis (AS) in the QUality of Life as Outcomes and its VAriation with DIsease States (QUO-VADIS) study.

Methods: This was a prospective observational study in bionaïve AS patients (modified New York criteria) newly treated with GLM or IFX (originator) in a clinical practice setting. Patients were followed-up for ~6 months of treatment with GLM or IFX and data was collected at baseline (BL), and at 3 and 6 months. The assessment of HCRU was done by evaluating data on the use of concomitant medications, hospitalizations (inpatient care or acute care) and visits in day care and outpatient settings; HCRU data reflected the prior 3 months for each timepoint. Work productivity and activity impairment (WPAI) was assessed by the number of work days missed as well as quantifying absenteeism, presenteeism, work impairment, and activity using the WPAI instrument adapted to Spondylarthritis (WPAI-SpA)(1); WPAI was based on the 7 days prior to the administration of the questionnaire.

Results: 963 patients received ≥ 1 dose of medication. The vast majority (78%, n=751) was treated with GLM, while the rest (22%, n=212) received IFX. Mean age of the patients was 42.7 years, 61.4% were male. Concomitant medication usage for AS treatment was reported by 84.3% of patients, the vast majority of whom received NSAIDs, followed by analgesics, DMARDs and corticosteroids. At BL, the percent of patients who reported hospitalizations (inpatient care) in the prior 3 months was 13.6%, which decreased to 3.1% at 6 months, while outpatient care in the 3 months prior to BL was reported by 39.4% of patients, which decreased to 19.0% at 6 months. The percent of patients receiving acute emergency care in the 3 months prior to BL reduced from 1.6%0.3% at 6 months. Further details on HCRU at BL and at 6 months are shown in the Table. The mean (SD) number of days at work, missed due to AS, was reduced from 6.3 (31.1) days at BL to 2.7 (12.3) days at 6 months. Results for WPAI-SpA assessment are presented in the Table.

Conclusion: In patients with AS newly treated with GLM (almost 80% of the study population) or IFX for 6 months, HCRU was reduced, as shown by the shorter mean duration of hospitalizations and the proportion of patients receiving acute, inpatient or outpatient care. Additionally, work productivity and activity increased, and patients reported fewer days of work missed due to AS after 6 months of treatment. **References:** Tang et al. *Arthritis Care Res* 2011; 63: S337-349 **Table: Health Care Resources Utilization and WPAI-SpA Scores**

Mean (SD) Health Care Resource Utilization Among All Patients		
	Baseline	**6 months**
Acute Care (duration of stay, hours)	13.7 (32.5)	3.3 (2.08)
Acute Care (number of admissions)	1.1 (0.3)	1.3 (0.6)
Hospitalization (duration of stay, days)	7.3 (6.1)	4.1 (4.5)
Outpatient/Day Care (number of visits)	2.4 (1.8)	2.1 (2.7)
Mean (SD) Work Productivity and Impairment Among All Patients[(1)]		
Absenteeism	16.4 (32.3)	6.3 (19.8)
Presenteeism	51.9 (30.6)	28.0 (26.0)
Work Impairment	48.3 (34.0)	25.1 (26.4)
Activity	62.5 (24.7)	36.1 (26.9)

Score interpretation: For all 4 WPAI outcomes, greater scores (range 0–100%) indicate greater impact of health [(1)]

Disclosure: P. Claudepierre, None; **F. van Den Bosch**, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, UCB Pharma, 5,AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, Pfizer, UCB Pharma, 8; **P. Sarzi-Puttini**, None; **S. Sajjan**, Merck & Co., Inc., 3; **N. Vastesaeger**, Merck Sharp & Dohme, Belgium, 3; **M. Govoni**, Merck Sharp & Dohme, Italy, 3; **S. Kachroo**, Merck & Co., Inc., 3.

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Abstract Number: 703

Performance of a New Spinal Mobility Index for Patients with Axial Spondyloarthritis

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: ASAS recommends using BASMI for evaluation of axial mobility in patients with Axial Spondyloarthritis (axSpA). The EDASMI (Edmonton Ankylosing Spondylitis Metrology Index) is another index of spinal mobility which includes cervical rotation (CR), chest expansion (CE), lumbar flexion (LF) and internal rotation of the hips (IRH). This method does not require the use of goniometer, it would be less influenced by the position of the cervical spine and includes the measurement of chest expansion, which is not consider by BASMI. Our objective was to evaluate the performance of EDASMI in patients with axSpA.

Methods: Patients with axSpA ≥18 years old according mNY 1984 AS and/or ASAS 2009 axSpA criteria belonging to ESPAXIA (Estudio de Espondiloartritis Axial, IREP Argentina) cohort were studied. Data regarding sociodemographic characteristics (age, sex), disease duration, treatment, disease activity (BASDI, ASDAS-ESR, SASDAS, global patient VAS), functional capacity (BASFI), quality of life (ASQoL), enthesitis (MASES), tender and swollen 44/46 joint count, CRP and ESR were assessed. Axial mobility using a measuring tape and goniometer whenever appropriate was performed by a single trained physician and included all measures for calculating BASMI-2, BASMI-10 and EDASMI. The time to perform and calculate both indexes was evaluated. X-rays from cervical and lumbar spine, pelvis and sacroiliac joints were taken and scored by mSASSS and BASRI, by a blinded reader.

Results: 30 patients were included, 86.7% male, with a median age of 48 years (IQR 34.7-56.2) and a median disease duration of 24.5 (IQR 16.7-32.5). 90.9% were *HLA-B27* positive. Measurements of axial mobility: median BASMI-2 was 5 (IQR 3-7), median BASMI-10 4.8 (IQR 3.7-6.5) and median EDASMI 12 (IQR 8.7-13.2). EDASMI had very good correlation with BASMI-2 and BASMI-10 (Rho= 0.80 and Rho= 0.84, respectively p= 0.0001) and good correlation with mSASSS (Rho= 0.5, p= 0.006) and BASRI (Rho= 0.5, p= 0.004) and did not correlate with BASDAI, SASDAS-ESR, SASDAS-CRP, BASFI, ASQoL and morning stiffness. BASMI-2 and BASMI-10 had similar performance to that observed with the EDASMI. The mean time for measurement was significantly lower with EDASMI, compared with BASMI-2 and BASMI-10 (1.8 ±0.23 minutes vs 2.64 ±0.23 and 2.67 ±0.34 minutes, p= 0.02 and 0.01, respectively).

Conclusion: EDASMI is a valid alternative index to measure the axial mobility in patients with axSpA. It incorporates the measurement of chest expansion. It is easy to perform and calculate and does not require the use of a goniometer.

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Abstract Number: 704

Does Change in Disease Activity over One Year Result in Change in Health-Related Quality of Life in Early Axial Spondyloarthritis Patients?

Miranda van Lunteren[1], Zineb Ez-Zaitouni[1], Pauline Bakker[1], Hanne Dagfinrud[2], Robert Landewé[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Floris van Gaalen[1] and Désirée van der Heijde[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Rheumatology, Academic Medical Center, Amsterdam, Netherlands, [4]Rheumatology, Groene Hart Ziekenhuis, Gouda, Netherlands, [5]Rheumatology Unit, University of Padova, Padova, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In axial Spondyloarthritis (axSpA), treatment is targeted at reducing disease activity with the aim of improving the health-related quality of life (HRQoL). Therefore, it is very important to know if a change in disease activity is indeed related to a change in HRQoL. The aim is to assess the association between the change in disease activity and change in HRQoL between baseline and one year in patients with early axSpA.

Methods: The Spondyloarthritis Caught Early (SPACE) study is a prospective cohort study in patients with chronic back pain (≥3 months, ≤2 years, onset <45 years) recruited from various rheumatology centers across Europe. The 36-item Short-Form (SF-36) was completed by patients to assess HRQoL at baseline and one year. Physical (PCS) and Mental Component Summary (MCS) scores were calculated (adjusting converted scale scores for country, gender, and age) and were compared to the general population mean of 50 with a standard deviation (SD) of 10. The Ankylosing Spondylitis Disease Activity Score (CRP based; ASDAS) was calculated to assess disease activity. Linear regression models were made with change of ASDAS between baseline and one year (DASDAS) as a determinant and the change of PCS (DPCS) or MCS (DMCS) as an outcome. The models were adjusted for age. Fulfilment of the imaging or clinical arm and gender were tested for interaction.

Results: A total of 94 patients fulfilled the ASAS axSpA criteria; 51 patients fulfilled the clinical arm and 43 patients the imaging arm. Mean age was 29.4 years (SD 7.2), 50.0% was male, and mean duration of back complaints was 14.8 months (SD 8.9). As the MCS was not different from the general population (baseline: 50.1 (SD 13.0); one year: 50.3 (SD 11.7), only the effect of ASDAS on PCS was determined. Patients had a mean PCS of 26.4 (SD 17.1) and mean ASDAS of 2.5 (SD 1.0) at baseline (Table 1). Differences in ASDAS between men (2.2) and women (2.8) and in PCS between clinical arm (28.3) and imaging arm (24.0) were found. DPCS was different between men and women, clinical and imaging arm. In the univariable model, a decrease of one unit of ASDAS between baseline and one year resulted in an improvement in PCS of 9.2 (SE 1.6) over one year. Fulfilment of the clinical or imaging arm (p=0.036) and gender (p=0.082) were effect modifiers in the model for PCS. Results were stratified for these variables. The effect of DASDAS on DPCS was most pronounced in men (β=-13.0; SE 2.7) and patients fulfilling the imaging arm (β-12.3.8; SE 2.7). It was also significant in women (β= -6.5; SE 1.6) and patients fulfilling the clinical arm (β=-6.6; SE 1.8) but the effect sizes were smaller.

Conclusion: In axSpA, a decrease in disease activity is associated with a clear improvement in health-related quality of life, but the effect is the highest in men and patients with imaging abnormalities.

Table 1: Association between the change in ASDAS and the change in Physical Component Summary (PCS) at baseline and one year among axial Spondyloarthritis patients in the SPACE-cohort (n=94)

	n	$ASDAS_{baseline}$ (SD)	ΔASDAS (SD)	$PCS_{baseline}$ (SD)	ΔPCS (SD)	β	SE	p-value
ΔPCS								
Univariable model								
ΔASDAS	94	2.5 (1.0)	-0.4 (1.0)	26.4 (17.1)	8.6 (16.9)	-9.2	1.6	<0.001
Model for gender								
Men								
ΔASDAS	47	2.2 (1.0)	-0.4 (0.9)	26.5 (21.5)	9.5 (20.7)	-13.0	2.7	<0.001
Women								
ΔASDAS	47	2.8 (0.9)	-0.5 (1.0)	26.3 (11.5)	7.8 (12.1)	-6.5	1.6	<0.001
Model for ASAS classification								
Fulfilment of the clinical arm								
ΔASDAS	51	2.5 (1.1)	-0.5 (0.9)	28.3 (15.7)	7.2 (12.8)	-6.6	1.8	0.001
Fulfilment of the imaging arm								
ΔASDAS	43	2.4 (1.0)	-0.4 (1.0)	24.0 (18.6)	10.3 (20.7)	-12.3	2.7	<0.001

Abbreviations: Physical Component Summary, PCS; Ankylosing Spondylitis Disease Activity Score, CRP-based, ASDAS; coefficient, β; standard deviation, SD; standard error, SE

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Abstract Number: 705

Is a Positive Family History of Spondyloarthritis of Value in Patients with Chronic Back Pain? Results from Two Large Early Back Pain Cohorts

Zineb Ez-Zaitouni[1], Laure Gossec[2], Inger Jorid Berg[3], Robert Landewé[4], Maikel van Oosterhout[5], Mariagrazia Lorenzin[6], Maxime Dougados[7], Désirée van der Heijde[8] and Floris van Gaalen[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Paris 06 University and AP-HP, Hôpital Pitié Salpêtrière, Paris, France, [3]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Amsterdam Medical Center, Amsterdam, Netherlands, [5]Rheumatology, Groene Hart Hospital, Gouda, Netherlands, [6]Rheumatology Unit, Department of Medicine DIMED, Rheumatology Unit,University of Padova, Padova, Italy, [7]Paris-Descartes University, Paris, France, [8]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: To assess whether presence of spondyloarthritis (SpA) manifestations in first- and second-degree relatives of patients with chronic back pain (CBP) is associated with higher risk for axial spondyloarthritis (axSpA).

Methods: The SPACE cohort includes patients with CBP (≥ 3 months, ≤ 2 years, onset <45 years) from various European rheumatology centers. DESIR is a French prospective multi-center cohort of patients with inflammatory back pain (IBP; ≥ 3 months, < 3 years, onset < 50 years), suggestive of axSpA. Patients underwent a full diagnostic work-up at baseline including MRI and radiographs of sacroiliac joints (local reading), laboratory assessments (e.g. HLA-B27), and assessment of all other SpA-features. Patients were asked about the presence of SpA manifestations in first- and second-degree relatives. A positive family history (PFH) was defined as having a positive family history in first- and second-degree relatives for at least one of the following SpA manifestations: ankylosing spondylitis (AS), psoriasis, uveitis, inflammatory bowel disease (IBD), and reactive arthritis. First, we assessed the association between PFH manifestations and HLA-B27 positivity in patients. Secondly, we assessed the association between PFH manifestations and axSpA using fulfilment of the ASAS axSpA classification criteria as a proxy for diagnosis. This approach circumvents circular reasoning in diagnosis but allows only assessment of the relative contribution of the various manifestations.

Results: In total, 438 patients from the SPACE cohort and 647 patients from the DESIR cohort with complete information on SpA manifestations in relatives were analysed. In the SPACE and DESIR cohort mean age (SD) was 31.3 (8.3) years and 33.6 (8.6) years, 38% and 47% of patients were male, and mean symptom duration was 13.4 (7.4) and 18.1 (10.5) months, respectively. In 20.6% and 19.6% of patients AS was reported in first- and second-degree relatives, psoriasis in 19.0% and 19.9%, uveitis in 6.2% and 4.5%, IBD in 7.5% and 5.0%, and reactive arthritis in 3.2% and 0.9%. Any PFH was reported in 42.2% and 38.5% of SPACE and DESIR patients, respectively. In both the SPACE and DESIR cohort AS (OR 5.9 [3.5-9.9] and OR 3.3 [2.1-5.2]), uveitis (OR 9.8 [3.3-28.9] and OR 21.6 [2.9-160.1]), and any PFH (OR 2.5 [1.7-3.8] and OR 1.4 [1.0-2.0]) were significantly associated with presence of HLA-B27 in CBP and IBP patients, respectively (Table 1). Fulfilment of the ASAS-criteria showed similar results: AS (OR 3.3 [2.0-5.3] and OR 2.1 [1.3-3.3]), uveitis (OR 7.4 [2.5-21.7] and OR 5.0 [1.5-16.7]). No association was found for psoriasis, IBD, or reactive arthritis in both cohorts. Multivariate regression analysis showed the same trends for both cohorts (not shown).

Conclusion: These data suggest that in the diagnostic work-up of patients with chronic back pain suspected of axSpA only a positive family history for AS or uveitis is of value.

Table 1 Univariate regression analysis of the presence of family history manifestations for both HLA-B27 status and the fulfilment of ASAS axSpA criteria in patients with chronic back pain in the SPACE cohort (n=438) and in patients with recent inflammatory back pain in the DESIR cohort (n=647).

	HLA-B27 positivity			
	SPACE		**DESIR**	
	OR (95% CI)	*P*- value	OR (95% CI)	*P*- value
Any FH	**2.5 (1.7-3.8)**	**<0.001**	**1.4 (1.0-2.0)**	**0.032**
AS	**5.9 (3.5-9.9)**	**<0.001**	**3.3 (2.1-5.2)**	**<0.001**
Psoriasis	1.1 (0.6-1.8)	0.750	0.8 (0.5-1.2)	0.225
Uveitis	**9.8 (3.3-28.9)**	**<0.001**	**21.6 (2.9-160.1)**	**0.003**
IBD	0.9 (0.4-1.8)	0.666	0.8 (0.4-1.6)	0.551
Reactive arthritis	0.8 (0.3-2.5)	0.745	0.1 (0.01-1.2)	0.075
	ASAS axSpA criteria			
	SPACE		**DESIR**	
	OR (95% CI)	*P*- value	OR (95% CI)	*P*- value
AS	**3.3 (2.0-5.3)**	**<0.001**	**2.1 (1.3-3.3)**	**0.001**
Psoriasis	1.2 (0.8-2.0)	0.388	1.2 (0.8-1.8)	0.464
Uveitis	**7.4 (2.5-21.7)**	**<0.001**	**5.0 (1.5-16.7)**	**0.009**
IBD	1.1 (0.5-2.2)	0.798	0.8 (0.4-1.6)	0.521
Reactive arthritis	0.6 (0.2-1.9)	0.421	0.3 (0.05-1.5)	0.132

HLA-B27, human leukocyte antigen B27; any FH, any family history manifestation in first- and second-degree relatives; AS, ankylosing spondylitis; IBD, inflammatory bowel disease; ASAS axSpA criteria, Assessment of Spondyloarthritis international Society criteria for axial Spondyloarthritis; OR, odds ratio; 95% CI, 95% confidence interval. *P*-values under 0.05 were considered significant.

Disclosure: Z. Ez-Zaitouni, None; **L. Gossec**, None; **I. J. Berg**, None; **R. Landewé**, None; **M. van Oosterhout**, None; **M. Lorenzin**, None; **M. Dougados**, None; **D. van der Heijde**, None; **F. van Gaalen**, None.

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Abstract Number: 706

Performance of the ASAS Classification Criteria for Axial and Peripheral Spondyloarthritis – a Systematic Literature Review and Meta-Analysis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The Assessment of SpondyloArthritis international Society (ASAS) has developed and validated classification criteria for axial spondyloarthritis (axSpA) and peripheral SpA (pSpA). Following their release, the ASAS criteria have been 'challenged' in different cohorts, thus warranting a review of the so-far accumulated evidence on the criteria validity and applicability. Our aim was to summarize the evidence on the performance of the ASAS classification criteria for axSpA (also imaging and clinical arm separately), pSpA and the entire set of SpA, when tested against the Rheumatologist's diagnosis ('reference standard').

Methods: A systematic literature review was performed to identify eligible studies. Only studies with full-text available

were included and, thereafter, raw data was obtained from the authors of the selected publications. A meta-analysis was performed to obtain pooled estimates for sensitivity, specificity, positive (LR+) and negative (LR-) likelihood ratios, by fitting random effects models. With a series of sensitivity analyses we assessed the possible effects of: i) target population (original validation study inclusion criteria *vs* different inclusion criteria); iii) setting (hospital *vs* community); and iii) disease duration (< 2 years *vs* ≥ 2 years).

Results: Of the 1,647 retrieved articles, 8 fulfilled the inclusion criteria (N=5,042 patients). The entire set of the ASAS SpA criteria yielded a high pooled sensitivity (73%) and specificity (88%), but with limited available data (Table). Similarly good results were found for the axSpA criteria (sensitivity: 82%; specificity: 88%) in a larger number of studies. Splitting the axSpA criteria in 'imaging arm only' and 'clinical arm only' resulted in much lower sensitivity (30% and 23% respectively) but retaining very high specificity (97% and 94% respectively). The 'imaging arm only' compared to the 'clinical arm only' had a much higher LR+ (9.6 *vs* 4.5, respectively). The pSpA criteria were less tested than the axSpA and have shown a similarly high pooled specificity (87%) but lower sensitivity (63%). Sensitivity analyses yielded consistently good results for the axSpA criteria (sensitivity (range): 78%-86%; specificity (range): 86%-93%). For pSpA there were few studies therefore hampering sensitivity analyses.

Conclusion: Accumulated evidence from more than 5,000 patients confirms the good performance of the various ASAS SpA criteria as tested against the Rheumatologist's diagnosis. The clinical and imaging arm have high specificity but lack sensitivity if applied separately, indicating that the full set of axSpA criteria is the preferred set.

Table. Results of the meta-analysis

	Number of studies	Number of patients	LR + (95% CI)	LR – (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
ASAS SpA criteria	2	1,750	6.3 (3.2; 12.4)	0.31 (0.13; 0.70)	0.73 (0.47; 0.89)	0.88 (0.81; 0.93)
ASAS pSpA criteria	3	749	4.7 (3.5; 6.3)	0.43 (0.30; 0.62)	0.62 (0.47; 0.76)	0.87 (0.81; 0.91)
ASAS axSpA criteria	6	4,293	6.9 (3.8; 12.4)	0.19 (0.15; 0.27)	0.82 (0.76; 0.87)	0.88 (0.79; 0.94)
axSpA criteria (imaging arm +/-clinical arm)	5	3,426	13.6 (4.8; 38.7)	0.45 (0.37; 0.56)	0.57 (0.47; 0.66)	0.96 (0.88; 0.99)
axSpA criteria (clinical arm +/- imaging arm)	5	3,426	6.0 (2.9; 12.4)	0.56 (0.43; 0.72)	0.49 (0.34; 0.64)	0.92 (0.82; 0.96)
axSpA criteria (imaging arm only)	5	3,426	9.6 (4.4; 20.7)	0.72 (0.59; 0.88)	0.26 (0.16; 0.40)	0.97 (0.94; 0.99)
axSpA criteria (clinical arm only)	5	3,426	4.5 (2.3; 8.8)	0.81 (0.72; 0.91)	0.23 (0.17; 0.29)	0.94 (0.89; 0.96)

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Abstract Number: 707

Anti-TNF Drugs Are Not Associated with Increasead Risk of Hzv Infections in Patients with Spondyloarthritis (SpA): Results from the GISEA Registry

Fabiola Atzeni[1], Marco Sebastiani[2], Valentina Panetta[3], Fausto Salaffi[4], Florenzo Iannone[5], Elisa Gremese[6], Antonio Carletto[7], Antonio Marchesoni[8], Roberto Gorla[9], Marcello Govoni[10], Rosario Foti[11], Ennio G. Favalli[12], Roberta Ramonda[13], Pier Carlo Sarzi-Puttini[14], Giovanni Lapadula[15] and Gianfranco Ferraccioli[16], [1]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milano, Italy, [2]SC Reumatologia, Dipartimento di Medicine, Medicina d'Urgenza e Specialità Mediche, Azienda Ospedaliero-Universitaria di Modena, Modena, Italy,

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Background/Purpose: Herpes zoster virus (HZV) reactivation disproportionately affects patients with systemic rheumatic diseases and it is commonly described in short- and long-term use of anti-Tumor Necrosis Factor (TNF) drugs. However, it is unclear whether anti-TNF therapy elevates herpes zoster risk in patients with spondyloarthritis (SpA). The aim of this study was to evaluate the incidence of HZV infections in the TNF-inhibitors-treated SpA patients in the Gruppo Italiano Studio Early Arthritis (GISEA) Registry, and assess the predictors of their occurrence.

Methods: The Registry, which is designed to collect real-world clinical data concerning RA and SpA patients receiving biological drugs as part of routine care, was approved by local Ethics Committees, and enrols patients aged ≥18 years who have given their written informed consent. The baseline information includes demographics, disease duration, HAQ, DAS28, BASDAI, BASFI and BASMI scores, steroid use (defined as actively receiving oral steroids at the time of recruitment), smoking history and comorbidities.

Results: The analysis involved 3321 SpA patients (1731 males, 52.2%; mean age 47±13 years; median disease duration three years, interquartile range [IQR] 0, 8 years): 1065 (32%) treated with infliximab (IFN), 1052 (32%) with adalimumab (ADA), and 1204 (36%) with etanercept (ETN). Two thousand, one hundred and five (63.4%) had a median of one comorbity (IQR 0, 2], the most frequent being hypertension (701), thyroid diseases (281), diabetes mellitus (207), cardiopathy (189), and osteoporosis (145). In combination with the biological drug, 919 patients (27.7%) received steroids and 2451 (79.9%) at least one DMARD. The median follow-up was three months (IQR 1, 2 years) 12 years. Herpes zoster involed 21 patients (0.6%). Crude incidence rates among anti-TNF users were 2.4 per 1000 patient years (95% CI, 1.5-3.6). Univariate analysis showed that female gender (p=0.512) and comorbidities (p=0.861) were not associated with a high risk of HVZ reactivation, and that the use of IFN rather than the use of ETN and ADA (p=.133 and p=00.129) was not associated with a higher risk of HVZ reactivaction. Furthermore, univariate models showed that the HAQ (HR 3.71 p=0.012) and BASFI (HR=1.39 p=0.004) were statistically significant predictors of HVZ infections.

Conclusion: These data add to currently available evidence suggesting that anti-TNF therapy is not associated with a increased risk of HZV infections in SpA patients.

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Abstract Number: 708

Development of Spondyloarthritis-Features in Patients with Chronic Back Pain over a One-Year Course: Data from the Spondyloarthritis Caught Early (SPACE)-Cohort

Zineb Ez-Zaitouni[1], Miranda van Lunteren[1], Pauline Bakker[1], Inger Jorid Berg[2], Robert Landewé[3], Maikel van Oosterhout[4], Augusta Ortolan[5], Désirée van der Heijde[1] and Floris van Gaalen[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Clinical Immunology and Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]Rheumatology, Groene Hart Hospital, Gouda, Netherlands, [5]Rheumatology Unit, Department of Medicine DIMED, Rheumatology Unit,University of Padova, Padova, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Little is known on the development of spondyloarthritis (SpA)-features over time in patients with recent onset chronic back pain (CBP). The aim was to explore whether patients with suspicion of axial spondyloarthritis (axSpA) develop SpA-features over time in the SPACE-cohort, and to study the effect of gaining features on the clinical diagnosis and classification according to the Assessment of SpondyloArthritis international Society (ASAS)-criteria for axSpA.

Methods: SPACE is an inception cohort study in which CBP patients (≥ 3 months, ≤ 2 years, onset < 45 years) from various rheumatology centres across Europe are included. Baseline (BL) and one-year (FU) data were used for this study. Patients underwent a full diagnostic work-up consisting of MRI and radiographs of the sacroiliac joints (MRI-SI and X-SI), acute phase reactants, HLA-B27, and assessment of all other SpA-features. For the purpose of this study positive SpA-features were accumulated according to the principle of "once a feature always a feature" meaning patients were not able to 'lose' features over time. Total number of SpA-features was calculated excluding sacroiliac imaging and HLA-B27 status. Clinical diagnosis (axSpA yes/no) of patients was provided by the treating rheumatologist with use of local reading and the ASAS-criteria for axSpA (based on central scoring and agreement of 2/3 readers) were used for classification.

Results: A total of 270 patients with CBP with both baseline and one-year follow-up visits were included: 36.7% were male, mean age (SD) at inclusion was 31.2 (8.0) years, mean number of SpA-features (SD) at BL and one-year FU were 2.8 (1.5) and 3.5 (1.6), respectively. After one year 49.3% of patients had gained one or more features. Most common features were IBP (BL: 77.0%, FU: 88.2%), good response to NSAIDs (BL: 48.5%, FU: 70.6%), elevated CRP/ESR (BL: 29.5%, FU: 43.3%), and positive family history for SpA (BL: 48.9%, FU: 52.6%). For 16 out of the 270 patients information on diagnosis at either BL or FU was missing. In the remaining 254 patients, rheumatologists diagnosed 150 (59.1%) and 66 (26.0%) patients with axSpA and no axSpA at both time points, respectively (Figure 1). In 15.0% (38/254) of patients the diagnosis changed; 16 patients with no axSpA diagnosis at BL were diagnosed with axSpA at FU of which 11/16 (68.8%) had acquired one or more features. In 22 patients with axSpA at BL rheumatologists reconsidered their diagnosis at FU. In the 150 patients diagnosed with axSpA, 108/150 (72%) of patients already fulfilled the ASAS-criteria at BL and 79/150 (52.7%) patients gained a minimum of one feature, which led to a new axSpA classification for 9 patients at FU.

Conclusion: In patients with CBP of short duration almost half developed at least one new SpA-feature within one year, however the impact on diagnosis and classification was limited.

Figure 1. Number of acquired SpA-features (after medical history taking, physical examination and measurement of acute phase reactants; excluding sacroiliac imaging and HLA-B27 status) at one-year follow-up (FU) in patients with and without axSpA diagnosis.

	Number of features gained after one year					
Diagnosis	0	1	2	3	>3	**Total**
AxSpA baseline and FU	71	50	18	9	2	150
AxSpA only at FU	5	9	2	-	-	16
AxSpA only at baseline	11	8	2	1	-	22
No AxSpA baseline and FU	40	23	2	1	-	66
Total	127	90	24	11	2	254

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Abstract Number: 709

Development of a Novel Medication Adherence Prediction Model for Patients with Ankylosing Spondylitis Based on Results from a Global Clinical Study

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Adherence to systemic therapies, such as tumor necrosis factor inhibitors (TNFi's), is affected by various factors and may be critical for optimal disease outcomes in patients (pts) with inflammatory diseases such as ankylosing spondylitis (AS). An adherence prediction model may help rheumatologists identify pts with AS at high risk of non-adherence to systemic therapies.

Methods: The global cross-sectional non-interventional ALIGN study enrolled >7000 adult pts with 6 immune-mediated inflammatory diseases, including AS as diagnosed by treating physician, currently being treated with conventional systemic therapies and/or TNFi's. Validated questionnaires, including the 4-item Morisky Medication Adherence Scale (MMAS-4©) and the Beliefs about Medicines Questionnaire (BMQ), were administered to pts at a routine visit. The objective of this analysis was to identify an accurate adherence prediction model by 1) identification of factors significantly associated with high medication adherence (MMAS-4 = 4) in multiple regression analysis based on backward selection and dichotomization of quantitative variables for simplicity reasons, 2) selection of the model, consisting of up to 10 variables, with the highest cross-validated area under the receiver operating characteristic curve (AUROC), and 3) visual

representation of certain pt profiles in the adherence probability matrix based on the best model.

Results: A total of 812 pts with AS were analyzed (mean age, 42.5 y; disease duration, 9.3 y; prior TNFi therapy, 51%; male, 71%). Based on MMAS-4 items, more pts with csDMARD or NSAID vs TNFi monotherapy admitted forgetting to take their medication (32 49% vs 18%) or stopping medication when feeling better (20 48% vs 17%). The best model had an AUROC of 0.7492 and included the following variables: age, ethnicity, sex, type of treatment, medication necessity beliefs (BMQ-Specific *Necessity* score), illness perception (Brief Illness Perception Questionnaire scores), and number of prior treatments. According to the model, the highest predicted probability of full adherence was seen in pts with AS ≥44 years of age, with high treatment necessity beliefs and TNFi treatment (especially in combination; **Table)**. The predicted probability of full adherence was higher in Caucasian pts compared with non-Caucasian pts with the same characteristics.

Conclusion: Results from the first medication adherence prediction model for pts with AS suggest that the majority of pts with NSAID or csDMARD treatment are not completely adherent to their therapy. The developed prediction model visualizes the impact of factors on medication adherence in pts with AS, which could help clinicians identify pts at high risk of non-adherence to systemic treatment. Further studies need to confirm the developed model.

Table. Predicted Probability of High Adherence* to Maintenance Treatments According to the Final Model for Average† Caucasian vs Non-Caucasian Patients With Ankylosing Spondylitis

		Predicted full adherence* probability (lower to upper 95% CI) in patients with AS‡			
		Non-Caucasian patients (%)		Caucasian patients (%)	
Age	Treatment#§	Low BMQ-Specific *Necessity* score (<19)	High BMQ-Specific *Necessity* score (≥19)	Low BMQ-Specific *Necessity* score (<19)	High BMQ-Specific *Necessity* score (≥19)
≥44 y	TNFi in csDMARD-TNFi combination	67.6 (44.3–84.6)	84.4 (68.3–93.2)	87.1 (72.9–94.4)	94.6 (87.8–97.7)
	TNFi in NSAID-TNFi combination#	37.9 (18.1–62.8)	61.3 (37.7–80.6)	66.3 (44.0–83.1)	83.6 (68.1–92.4)
	TNFi in monotherapy	54.6 (34.0–73.6)	75.7 (58.6–87.3)	79.5 (66.0–88.5)	90.9 (84.0–95.0)
	csDMARD in csDMARD-TNFi combination	21.8 (9.8–41.6)	42.0 (22.8–63.9)	47.3 (28.3–67.1)	70.0 (51.4–83.7)
	csDMARD in NSAID-csDMARD combination	10.1 (3.1–28.4)	22.6 (7.9–49.9)	26.6 (10.1–53.9)	48.5 (23.0–74.7)
	csDMARD in monotherapy	9.9 (2.0–37.6)	22.2 (5.1–60.5)	26.2 (6.7–63.7)	47.9 (15.8–81.8)
	NSAID in NSAID-TNFi combination	8.5 (3.0–22.2)	19.5 (7.7–41.1)	23.1 (10.2–44.2)	43.8 (23.7–66.1)
	NSAID in NSAID-csDMARD combination	8.1 (2.4–24.0)	18.7 (6.2–44.2)	22.2 (8.0–48.1)	42.5 (18.9–70.1)
	NSAID in monotherapy	7.9 (2.5–22.3)	18.1 (6.6–41.1)	21.6 (8.6–44.5)	41.6 (20.6–66.2)
<44 y	TNFi in csDMARD-TNFi combination‖	45.7 (26.0–67.0)	68.6 (48.5–83.5)	73.1 (52.9–86.8)	87.6 (74.8–94.4)
	TNFi in NSAID-TNFi combination	19.7 (9.0–38.0)	39.0 (21.2–60.2)	44.2 (25.1–65.1)	67.3 (47.5–82.4)
	TNFi in monotherapy	32.6 (19.0–50.0)	55.7 (39.1–71.1)	60.9 (45.5–74.4)	80.2 (69.2–88.0)
	csDMARD in csDMARD-TNFi combination	10.1 (4.3–21.7)	22.6 (10.9–41.1)	26.6 (13.5–45.6)	48.4 (29.2–68.2)
	csDMARD in NSAID-csDMARD combination	4.3 (1.3–13.8)	10.5 (3.3–28.9)	12.8 (4.2–33.0)	27.5 (10.3–55.8)
	csDMARD in monotherapy	4.2 (0.8–19.4)	10.3 (2.1–38.1)	12.5 (2.7–42.0)	27.0 (6.8–65.2)
	NSAID in NSAID-TNFi combination	3.6 (1.3–9.9)	8.9 (3.4–21.3)	10.8 (4.4–24.2)	23.9 (11.0–44.3)
	NSAID in NSAID-csDMARD combination	3.4 (1.0–11.4)	8.5 (2.6–24.5)	10.3 (3.2–28.2)	23.0 (8.1–50.1)
	NSAID in monotherapy#	3.3 (1.0–10.1)	8.2 (2.8–21.6)	10.0 (3.6–24.7)	22.3 (9.3–44.7)

AS, ankylosing spondylitis; BMQ, Beliefs about Medicines Questionnaire; combination, combination therapy; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug(s); NSAID, nonsteroidal anti-inflammatory drug(s); TNFi, tumor necrosis factor inhibitor.
*High/full medication adherence: 4-item Morisky Medication Adherence Scale = 4.
†Male pts with AS, median scores for Brief Illness Perception Questionnaire questions 1 and 8 on how much life being affected by illness and how much being affected emotionally by disease (ie, 5), and ≤3 prior treatments.
‡With or without concomitant glucocorticoid.
§Some combinations are not recommended according to ASAS/EULAR.

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Abstract Number: 710

Patient-Reported Quality of Life in Patients with Baseline Objective Signs of Inflammation and Active Nonradiographic Axial Spondyloarthritis Treated with Golimumab: Results of the Open-Label Extension of a Randomized, Double-Blind Study

Walter Maksymowych[1], Maxime Dougados[2], Joachim Sieper[3], Jürgen Braun[4], G Bergman[5], Sean P. Curtis[6], Anjela Tzontcheva[6], George Philip[6], Susan Huyck[6] and Désirée van der Heijde[7], [1]Medicine, University of Alberta,, Edmonton, AB, Canada, [2]Paris-Descartes University, Paris, France, [3]Rheumatology Department, Charité – University Medicine Berlin, Berlin, Germany, [4]Rheumazentrum Ruhrgebiet, Herne, Germany, [5]Merck & Co., Inc., Whitehouse Station, NJ, [6]Merck & Co., Inc., Kenilworth, NJ, [7]Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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SESSION INFORMATION

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Session Type: ACR Poster Session A

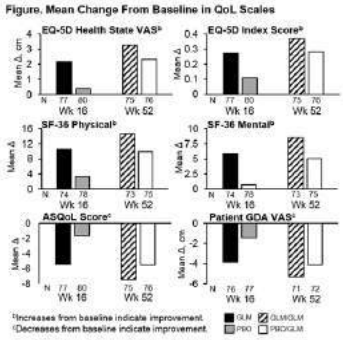
Session Time: 9:00AM-11:00AM

Background/Purpose: In an open-label extension (OLE) of a 16-week, randomized, double blind (DB), placebo (PBO)-controlled, phase 3 study (GO-AHEAD; NCT1453725) in patients with nonradiographic axial spondyloarthritis (nr-axSpA)[1], we assessed quality of life (QoL) in patients with objective signs of inflammation at baseline.

Methods: Patients received GLM 50mg Q4W during the 44-week OLE (36-week efficacy period; 8-week safety follow-up). QoL evaluations were specified in patients with objective inflammation (MRI sacroiliitis+ and/or C-reactive protein >upper limit of normal) and included Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), 36-item Short Form Health Survey (SF 36), and EuroQol Group 5 Dimensions Health Questionnaire (EQ-5D) Index and Health State (0–10cm VAS), and Work Productivity and Activity Impairment (WPAI) at weeks 16 and 52 and the Patient's Global Disease Assessment (PGDA; 0–10cm VAS) at weeks 16, 20, 24, 32, 40, and 52.

Results: There were 153 patients with objective inflammation at baseline (of the DB period: GLM=76; PBO=77) who were then treated in the OLE. At week 52, patients continuing GLM and those switched from PBO to GLM in the OLE demonstrated improvement in QoL parameters (Figure) Mean (SD) change from baseline in Overall Work Impairment scores were -21.2 (24.7) (GLM) and -8.4 (28.5) (PBO) at week 16; at week 52, mean (SD) changes were -31.1 (GLM/GLM) and -26.5 (27.2) (PBO/GLM).

Conclusion: Among patients with objective inflammation before treatment in the DB phase, those who continued GLM in the OLE had continued benefits in QoL and work productivity, and those who switched to GLM in the OLE from PBO in the DB phase had notable improvement in QoL and work productivity. **Reference:** 1. Sieper J, et al. *Arthritis Rheum.*



2015;67(10):2702-2712.

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Abstract Number: 711

The Diagnostic Value of the Symptom of Inflammatory Back Pain in the Rheumatology Setting

Denis Poddubnyy[1], Inge Spiller[1], Joachim Listing[2], Jürgen Braun[3], Joachim Sieper[1] and Martin Rudwaleit[4], [1]Charité Medical University, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Klinikum Bielefeld Rosenhöhe, Bielefeld, Germany

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Inflammatory back pain (IBP) as a symptom has been shown to perform effectively for selecting patients in primary care / orthopaedic settings for referral of chronic back pain patients to the rheumatologist for further diagnostic work-up. IBP is also being used as a diagnostic test of axial spondyloarthritis (axSpA) by rheumatologists, but

no validations studies have been performed so far with IBP as a diagnostic tool. The aim of the DIVERS study was to evaluate the diagnostic value of the IBP symptom in axSpA in the rheumatology setting.

Methods: A total of 405 consecutive patients referred to a rheumatologist because of chronic back pain starting at an age <45 years and suspicion of axSpA were included in this multicentre study. A questionnaire containing all relevant IBP parameters was first answered by the patient, followed by a rheumatologist blinded for presence or absence of other SpA features and for the diagnosis, and finally by the rheumatologist responsible for the diagnosis. A global evaluation of IBP by rheumatologists, and IBP according to the previously published Calin's, Berlin and ASAS criteria as well as single items of IBP were compared regarding their diagnostic performance.

Results: The diagnosis of definite axSpA was made in 180 (44.4%) patients (88 with ankylosing spondylitis and 92 with non-radiographic axSpA). The sensitivity, specificity and the positive likelihood ratio of IPB for the axSpA diagnosis was 81%, 44%, and 1.5, respectively, if globally assessed by the blinded rheumatologist, and 90%, 58% and 2.2, respectively, if globally assessed by the diagnosing rheumatologist - table. There was no clear superiority of any of the three criteria sets regarding sensitivity for the axSpA diagnosis with an overall sensitivity of about 80% and specificity between 25% and 45% if symptoms were assessed by a rheumatologist - table. The performance of the criteria sets based on patient's own evaluation of IBP symptoms was generally lower. No single IBP parameter showed superiority regarding sensitivity or specificity in comparison to the criteria sets.

Conclusion: IBP demonstrated high sensitivity but rather modest specificity for the diagnosis of axSpA among patients with chronic back pain referred to a rheumatologist. A resulting moderate diagnostic value of IBP in the rheumatology setting is likely to be counterbalanced by increase in the pre-test probability of axSpA in this patients population.

Table. Sensitivity, specificity, a positive and a negative predictive value (PPV and NPV) of inflammatory back pain (IBP) for the diagnosis of axSpA.

Assessor	IBP according to...	Sensitivity, % (95% CI)	Specificity, % (95% CI)	PPV (95% CI)	NPV (95% CI)	LR+	LR-
Blinded rheumatologist	Global evaluation	81.1 (75.4-86.8)	44.0 (37.4-50.5)	53.9 (48.0-59.8)	74.2 (66.8-81.7)	1.5	0.4
	Calin's criteria	79.4 (73.5-85.4)	24.9 (19.2-30.5)	45.8 (40.3-51.4)	60.2 (50.3-70.2)	1.1	0.8
	Berlin Criteria	81.1 (75.4-86.8)	32.4 (26.3-38.6)	49.0 (43.3-54.7)	68.2 (59.4-77.1)	1.2	0.6
	ASAS criteria	74.4 (68.1-80.8)	39.6 (33.2-45.9)	49.6 (43.7-55.6)	65.9 (57.9-73.9)	1.2	0.7
Diagnosing rheumatologist	Global evaluation	90.0 (85.6-94.4)	58.2 (51.8-64.7)	63.3 (57.4-69.2)	87.9 (82.6-93.2)	2.2	0.2
	Calin's criteria	85.0 (79.8-90.2)	26.7 (20.9-32.4)	48.1 (42.6-53.6)	69.0 (59.2-78.7)	1.2	0.6
	Berlin Criteria	83.9 (78.5-89.3)	44.9 (38.4-51.4)	54.9 (49.0-60.8)	77.7 (70.5-84.9)	1.5	0.4
	ASAS criteria	83.9 (78.5-89.3)	35.6 (29.3-41.8)	51.0 (45.3-56.7)	73.4 (65.1-81.7)	1.3	0.5
Patient	Calin's criteria	75.1 (68.8-81.5)	20.4 (15.1-25.7)	43.0 (37.5-48.6)	50.6 (40.2-61.0)	0.9	1.2
	Berlin Criteria	86.4 (81.4-91.5)	18.6 (13.4-23.7)	46.0 (40.6-51.3)	63.1 (51.3-74.8)	1.1	0.7
	ASAS criteria	74.0 (67.6-80.5)	31.2 (25.1-37.3)	46.3 (40.5-52.1)	60.0 (51.1-69.0)	1.1	0.8

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Abstract Number: 712

Efficacy of Golimumab for Nonradiographic Axial Spondyloarthritis (nr-axSpA): Subgroup Analysis By Baseline MRI and C-Reactive Protein Status

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Efficacy of golimumab (GLM) for nr-axSpA was demonstrated in a randomized, double-blind (DB), placebo (PBO)-controlled, phase 3 study (GO-AHEAD; NCT01453725).[1] In a subgroup analysis, we now investigate the effects of GLM based on presence or absence of objective inflammation (sacroiliitis on MRI and/or C-reactive protein [CRP] > upper limit of normal [ULN]) at baseline.

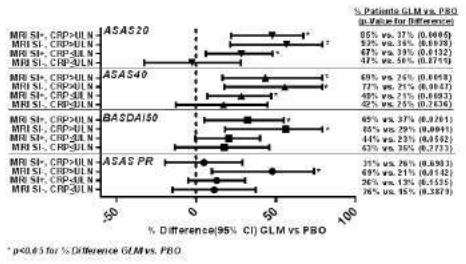
Methods: Patients with nr-axSpA (ASAS criteria, centrally read SI joint X-rays/MRIs, disease duration ≤5 years, chronic back pain ≥3 years, high disease activity, and inadequate response or intolerance to NSAIDs) were randomized (with ASAS-defined MRI sacroiliitis by single central reader [yes, SI+; no, SI–] and CRP level [≤ULN or >ULN] as stratification factors) to GLM 50 mg SC or PBO Q4W for 16 weeks. The primary endpoint was ASAS20 response at week 16. Estimated between-group differences in response at week 16 on ASAS20, ASAS40, BASDAI50, and ASAS partial remission (PR) were compared for four patient subgroups (MRI SI+ & CRP >ULN; MRI SI– & CRP >ULN; MRI SI+ & CRP ≤ULN; MRI SI– & CRP ≤ULN) by Miettinen-Nurminen methods; no multiplicity control was used.

Results: In total, 197 patients were treated (GLM=97; PBO=100). Treatment-group differences in ASAS20, ASAS40, BASDAI50, and ASAS PR response were greater in patients with baseline objective inflammation (Figure). Results should be interpreted with caution, given the small subgroups and absence of multiplicity control.

Conclusion: In the GO-AHEAD trial, responses to GLM (vs PBO) were greater in patients with objective inflammation (particularly with CRP >ULN) at baseline.

Reference 1. Sieper J, et al. *Arthritis Rheum*. 2015;67(10),2702–2712.

Figure: Subgroup Analysis of Response by MRI SI Status and CRP Level at Baseline



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Abstract Number: 713

Predictors of Treatment Retention Among Patients with Rheumatoid Arthritis or Ankylosing Spondylitis Treated with Remicade® (Infliximab) for Long-Term in Canadian Real-World

Michael Starr[1], Edward Keystone[2], Rafat Faraawi[3], Louis Bessette[4], Boulos Haraoui[5], Wojciech Olszynski[6], John Kelsall[7], Raman Joshi[8], Andrew Chow[9], Algis Jovaisas[10], J Carter Thorne[11], Emmanouil Rampakakis[12], Eliofotisti Psaradellis[13], Marilise Marrache[14], Brendan Osborne[15], Karina Maslova[16], Francois Nantel[17], Allen J Lehman[16] and Cathy Tkaczyk[15], [1]Rheumatology, Mcgill University, Pointe-Claire,, QC, Canada, [2]Mt. Sinai Hospital, University of Toronto, Toronto, ON, Canada, [3]McMaster University, Hamilton, ON, Canada, [4]Rheumatology, CHUL de Quebec, Quebec, QC, Canada, [5]Centre hospitalier de l'Université de Montréal, Montreal, QC, Canada, [6]103 Midtown Professional Center, Rheumatology Associates of Saskatoon, Saskatoon, SK, Canada, [7]Mary Pack Arthritis Centre, Vancouver, Vancouver, BC, Canada, [8]William Osler Health Centre-Brampton Civic Hospital, Brampton, ON, Canada, [9]Credit Valley Rheumatology, Mississauga, ON, Canada, [10]Capital North Therapeutics & Research, Ottawa, ON, Canada, [11]Southlake Regional Health Centre, Newmarket, ON, Canada, [12]JSS Medical Research, St-Laurent, QC, Canada, [13]JSS Medical Research, Montreal, QC, Canada, [14]Medical Affairs, Janssen Inc, Toronto, ON, Canada, [15]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [16]Janssen Inc., Toronto, ON, Canada, [17]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Remission has become a target to achieve in rheumatic diseases and it also could be linked to treatment retention. The aim of this analysis was to identify independent predictors of retention in patients with RA or AS treated with infliximab (IFX).

Methods: BioTRAC is an ongoing, prospective registry of patients (pts) treated with IFX or golimumab. This analysis included RA and AS pts treated with IFX, and that had at least 2 years of follow-up. Independent predictors of retention were assessed with multivariate cox regression. Receiver operator curve (ROC) analysis was used to determine the optimal cut-off points of CDAI and ASDAS for long-term retention.

Results: A total of 490 RA and 201 AS pts were included in the analysis. Table 1 summarizes the disease parameters and characteristics at IFX initiation. With respect to disease activity, mean CDAI score was 35.9 in RA pts and ASDAS was 3.8 in the AS group. Table 2 presents the probability of retention over time by indication. In univariate analysis, among RA pts at baseline (BL): CDAI [HR (95% CI): 0.99 (0.99-1.00)], DMARD use [HR (95% CI): 0.70 (0.51-0.97)], steroid use [HR (95% CI): 1.23 (0.99-1.52)], at 24 months: CDAI [HR (95% CI): 1.02 (1.00-1.03)], and DMARD use [HR (95% CI): 0.82 (0.66-1.01)] were identified as potential predictors (P<0.150) of retention. No significant impact was observed for age, gender, disease duration, prior biologic experience, enrolment period, and steroid use at 24 months. In multivariate analysis, CDAI score at 24 months was the only significant (P=0.013) independent predictor of treatment retention [HR (95% CI): 1.02 (1.00-1.03)]. ROC analysis showed that the optimal 24-month CDAI cut-off score for downstream (non-)discontinuation was 11.7. In AS pts, ASDAS levels at 24 months were the only significant predictor of subsequent treatment discontinuation, with higher ASDAS score being associated with an increased hazard for discontinuation [HR (95% CI): 1.63 (1.12-2.38)]. Maintaining an ASDAS score of 2.7 or less at 24 months was associated with optimal retention on treatment long-term. **Table 1. Baseline Disease Parameters and Patient Characteristics**

	RA (N=490)	**AS (N=201)**
Age, years, mean (SD)	56.4 (13.0)	46.8 (11.8)
Disease duration, years, mean (sd)	9.4 (9.5)	9.8 (10.0)
Female gender, %	73.9%	35.1%
Enrolment period, n (%)		
2002-2004	43.1%	0.0%
2005-2007	25.5%	40.8%
2008-2014	31.4%	59.2%
Biologic naïve, n (%)	90.0%	91.5%
DAS28	5.8 (1.5)	
CDAI	35.9 (16.8)	
28-SJC	12.5 (8.1)	
28-TJC	10.8 (7.3)	
HAQ-DI	1.63 (0.72)	1.22 (0.64)
ASDAS		3.8 (1.0)
BASDAI		6.4 (2.1)

Table 2. Kaplan-Meier Survival Point Estimates* of Retention

	Retention Probability (%)	
Time point (months) post 2 years of stable treatment	**RA (N=490)**	**AS (N=201)**
6	92%	94%
12	85%	89%
18	76%	85%
24	71%	79%
30	66%	73%
36	62%	70%
42	59%	65%

** Values represent n at risk, retention probability (standard error)*

Conclusion: Results have shown that, among pts remaining on IFX after 2 years, disease activity at 2 years is the single determinant of subsequent long-term retention on IFX treatment both in RA and AS pts, highlighting the importance of the

treat-to-target strategy to achieve remission but also maintaining it over time in order to ensure optimal treatment benefits.

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Abstract Number: 714

Functional Relevance of Structural Damage in the Sacroiliac Joints in Patients with Axial Spondyloarthritis – Results from the German Spondyloarthritis Inception Cohort

Mikhail Protopopov[1], Hildrun Haibel[1], Jürgen Braun[2], Martin Rudwaleit[3], Joachim Sieper[1] and **Denis Poddubnyy**[1], [1]Charité Medical University, Berlin, Germany, [2]Rheumazentrum Ruhrgebiet, Herne, Germany, [3]Klinikum Bielefeld Rosenhöhe, Bielefeld, Germany

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Background/Purpose: To analyze the association between the presence of structural damage in the sacroiliac joints and physical function / spinal mobility in patients with axial spondyloarthritis (SpA), which has not been investigated so far.

Methods: A total of 210 patients with early axial SpA (105 patients with radiographic axial SpA and symptom duration up to 10 years and 95 patients with non-radiographic axial SpA and symptom duration up to 5 years) from the German Spondyloarthritis Inception Cohort (GESPIC) were included in this cross-sectional analysis. Pelvic radiographs were scored by two trained readers (DP, HH) in a concealed and randomly selected order according to the grading system of the modified New York criteria (grade 0 to 4). For the current analysis, a mean of two readers score was calculated for each sacroiliac joint. A sum of two sacroiliitis grades (left and right sacroiliac joints) was calculated for each patient giving a total sacroiliitis score between 0 and 8. Structural damage in the spine was assessed by the same readers according to the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Disease activity was assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and C-reactive protein (CRP), functional status by the Bath Ankylosing Spondylitis Functional Index (BASFI), and spinal mobility - by the Bath Ankylosing Spondylitis Metrology Index (BASMI).

Results: In the univariable linear regression models, the crude parameter estimates for the association between sacroiliitis score and BASFI / BASMI were 0.09 (95%CI -0.07 to 0.25) and 0.23 (95%CI 0.11 to 0.33), respectively. After adjustment for parameters, which could be associated with radiographic sacroiliitis and might have an impact on the outcome (function / spinal mobility) – structural damage in the spine (mSASSS), disease activity (BASDAI and CRP), and gender – the parameter estimates indicating an association between sacroiliitis score and BASFI / BASMI changed to 0.10

(95%CI -0.01 to 0.21) and 0.12 (95%CI 0.01 to 0.23), respectively. These data indicates that change by one radiographic sacroiliitis grade in one joint is associated with a BASFI / BASMI worsening by 0.10 / 0.12 points irrespectively of structural damage in the spine and disease activity.

Conclusion: Presence of structural damage in the sacroiliac joints has an impact on functional status spinal mobility independently of structural damage in the spine and disease activity in patients with axial SpA, an association which had been mostly neglected previously.

Disclosure: M. Protopopov, None; **H. Haibel**, None; **J. Braun**, None; **M. Rudwaleit**, None; **J. Sieper**, None; **D. Poddubnyy**, None.

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Abstract Number: 715

Are Patients with Ankylosing Spondylitis Willing to Pay for Treatment with Infliximab?

Casper Webers[1,2], Ivette Essers[1,2], Astrid van Tubergen[1,2], Jürgen Braun[3], Frank Heldmann[4], Xenofon Baraliakos[5] and Annelies Boonen[2,6], [1]Department of Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]School for Public Health and Primary Care (CAPHRI), Maastricht University, Maastricht, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Zeisigwaldkliniken Bethanien, Chemnitz, Germany, [5]Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Herne, Germany, [6]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: In view of the continuous pressure of biologicals on healthcare budgets, it is essential to assess the value of biologicals for patients from different perspectives. A Willingness To Pay (WTP) represents the patients' preference for health as a consequence of treatment in monetary terms. The aim of this study was to investigate WTP for treatment with infliximab by patients with ankylosing spondylitis (AS) and explore factors associated with WTP.

Methods: Data were used from patients participating in the European AS Infliximab Cohort (EASIC) open-label extension of the AS Study for the Evaluation of Recombinant Infliximab Therapy (ASSERT). Demographics, clinical data (including BASDAI, BASFI, BASMI, BAS-G and Assessment of SpondyloArthritis International Society 20 (ASAS20) response) and data on WTP were collected at baseline of EASIC. WTP comprised a hypothetical scenario exploring whether the patient would be willing to pay for beneficial effects of infliximab and, if so, what amount they would be willing to pay per administration. To investigate factors associated with WTP, a series of models were explored using a zero inflated negative binomial regression (ZINB) technique.

Results: Eighty-five patients completed the WTP. Average age was 43.4 years, 67 patients (78.8%) were male and 62 patients (72.9%) had achieved an ASAS20 response. Sixty-three patients (74.1%) were willing to pay, and among these patients the mean (median) [Interquartile Range] amount willing to pay was €275 (100) [50-200] per administration. Multivariable ZINB analysis showed that ASAS20 response was associated with a 7-fold increase in the likelihood to be

willing to pay (OR=6.91, 95%-confidence interval [95%CI] 1.40-34.07) and a 3-fold increase in the amount willing to pay (exp(B)=3.32, 95%CI 1.44-7.69). In addition, country of residence was associated with willingness to pay (residence in the Netherlands vs. other participating countries: OR=0.07, 95% CI 0.02-0.36), while increased age was associated with the amount willing to pay (exp(B)=1.05, 95%CI 1.01-1.09).

Conclusion: In a hypothetical scenario, three quarter of patients with AS stated to be willing to pay an out-of-pocket contribution for treatment with infliximab. Treatment response contributed to the willingness as well as to the amount patients were willing to pay. Despite its limitations, the WTP method seems a valuable addition to the common approaches used for investigating treatment benefits in AS.

Table 1. Final multivariable ZINB regression model exploring determinants of willingness to pay for infliximab treatment in AS

Possibly willing to pay[§]	OR[‡]	95% CI OR	p
Gender (male)	0.41	0.06-2.68	0.35
Age	0.94	0.86-1.03	0.17
ASAS20 response	6.91	1.40-34.07	0.02
Country of residence (Netherlands)[¥]	0.07	0.02-0.36	<0.01
Amount willing to pay*	**Exp(B)[†]**	**95% CI Exp(B)**	**p**
Gender (male)	1.76	0.79-3.94	0.17
Age	1.05	1.01-1.09	<0.01
ASAS20 response	3.32	1.44-7.69	<0.01

[§]Logistic model part, predicting willingness to pay (the amount willing to pay not being certainly zero).
[‡]Factor change in odds for unit increase in independent variable.
[¥]Country of residence being Netherlands vs other (Belgium, Finland, France, Germany, United Kingdom).
*Negative binomial model part, predicting expected amount willing to pay.
[†]Factor change in expected amount willing to pay for unit increase in independent variable.
ZINB = zero-inflated negative binomial; OR = odds ratio; ASAS = Assessment of SpondyloArthritis international Society; 95% CI = 95% confidence interval.

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Abstract Number: 716

Radiographic Progression and Changes in Inflammation and Structural Damage on Serial MRI Examinations over 5 Years in Patients with Ankylosing Spondylitis Treated with TNF-Alpha Inhibitors

Susanne Juhl Pedersen[1], Ulrich Weber[2], Roula Said Nahal[3], Inge Juul Sorensen[1], Anne Gitte Loft[4], Niels Tvede[1], Gina Kollerup[1], Lars Juul[1], Gorm Thamsborg[1], Ole Rintek Madsen[1], Jakob M. Møller[5], Lone Balding[6], Anne Grethe Jurik[7] and Mikkel Østergaard[8], [1]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark, [2]Department of Research, King Christian 10th Hospital for Rheumatic Diseases, Graasten, Denmark, [3]Ambroise Paré Hospital, Boulogne-Billancourt, France, [4]Departments of Rheumatology at Vejle and Aarhus Hospitals, Vejle and Aarhus, Denmark, [5]Department of Radiology, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark, [6]Department of Radiology, Copenhagen University Hospital Herlev and Gentofte, Copenhagen, Denmark, [7]Dept. of Radiology, Aarhus University Hospital, Aarhus, Denmark, [8]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark, Copenhagen, Denmark

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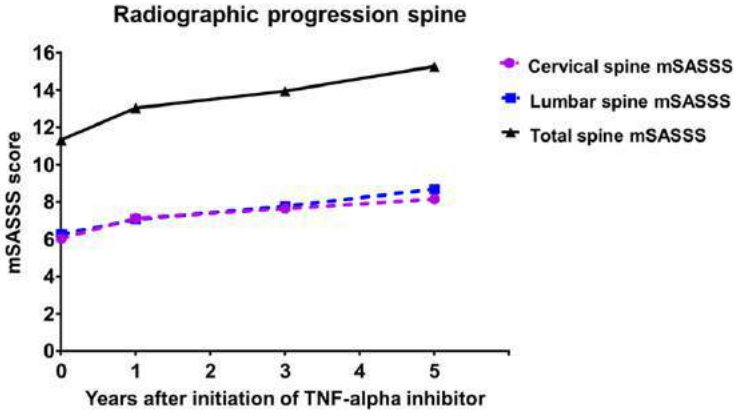
Session Time: 9:00AM-11:00AM

Background/Purpose: Only few studies have investigated long-term radiographic progression in the spine of patients with ankylosing spondylitis (AS). Moreover, no studies have reported changes in MRI lesions of inflammation and structural damage in the sacroiliac joints (SIJs) and spine assessed with annually repeated scans over 5 years. The aim was to investigate radiographic progression and evolution of MRI inflammation and structural lesions during treatment with TNFα inhibitors over 5 years assessed with serial examinations.

Methods: The study included 33 patients with AS followed for 5 years. All patients had participated in the BIOSPA study(1), which included 60 patients initiating treatment with TNFα inhibitor (infliximab, etanercept or adalimumab). Spinal radiographs were obtained 4 times (at week 0, 46, year 3 and 5) and MRIs of the SIJs and the lower spine (Th9-S1) were acquired 7 times (at week 0, 22 and 46 and annually to year 5), respectively. The images were evaluated in known time order without other information available. The SPARCC Sacroiliac and Spine Inflammation Index and Structural Scores (SSS) (2) and the Canada-Denmark (CanDen) scores of inflammation, fat(3), erosions and new bone formation (4,5) were used for the MRI evaluations. The modified Stoke AS Spine Score (mSASSS)(6) were used for the evaluation of the radiographs.

Results: During 5 years of TNFα inhibitor treatment, mSASSS increased significantly at all study visits ($p<0.01$) (Figure 1), and the structural MRI spine score SASSS increased significantly from year 2 ($p<0.05$). The mSASSS progression rate was significantly lower from week 46 to year 3 (0.45 units/year) than from week 0 to 46 (1.71 unit/year), whereas there was no difference in the progression rate from week 0 to 46 versus year 3 to 5 (0.66 units/year, $p=0.055$). MRI inflammation decreased significantly in SIJ ($p<0.05$) and spine from week 22 ($p<0.01$, except for year 5), together with a significant decrease of SIJ erosion from week 46 ($p<0.05$) and throughout the study. Conversely, the SIJ and spinal MRI fat ($p<0.05$) and SIJ ankylosis scores increased significantly from week 22 ($p<0.05$). Only minor changes were observed for SIJ backfill and spine erosion score.

Conclusion: Radiographic progression decreased significantly after the first year of treatment with TNFα inhibitor. Spine and SIJ MRI inflammation and structural scores changed significantly short after initiation of treatment, and thereafter the scores remained statistically unchanged except. References: 1. Pedersen et al. Ann Rheum Dis ; 2. Maksymowych et al. J Rheumatol 2014; 3. Pedersen et al. Arthritis Res Ther 2014; 4. Lambert et al. J Rheumatol 2009 5. Østergaard et al. J Rheumatol 2009; 6. Averns HL et al. Br J Rheumatol 1996



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Abstract Number: 717

NSAID Use and Functional Impairment in Ankylosing Spondylitis

Mark Hwang[1], Seth Eisen[1], MinJae Lee[2], Michael Ward[3], Lianne S. Gensler[4], Prabha Ranganathan[5], Johnathan Jia[6], Amirali Tahanan[2], Matthew A. Brown[7], Mohammad H. Rahbar[2], Michael Weisman[8] and John D. Reveille[9], [1]Internal Medicine-Rheumatology, Washington University in Saint Louis, School of Medicine, Saint Louis, MO, [2]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas-McGovern Medical School, Houston, TX, [3]NIH/NIAMS, Bethesda, MD, [4]Medicine/Rheumatology, UCSF, San Francisco, CA, [5]Washington University in Saint Louis, School of Medicine, Saint Louis, MO, [6]University of Texas-McGovern Medical School, Houston, TX, [7]The University of Queensland Diamantina Institute, Brisbane, Australia, [8]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [9]Rheumatology, University of Texas-McGovern Medical School, Houston, TX

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease with significant burden to patients and society. NSAIDs are the first line pharmacologic therapy in AS with proven efficacy. This efficacy is class-wide and we hypothesize a higher effect with more use of medication. An important aspect of treatment efficacy is its effect on functionality. -This study aims to identify the effect of NSAID use in AS as defined by the percent of the full inflammatory dose taken over time (the NSAID Index) on functional impairment

Methods: A prospective cohort of 823 AS patients who met the modified New York criteria were followed for at least 2 outpatient visits from multiple sites. Patients underwent a comprehensive clinical evaluation including assessment of functional impairment by the Bath AS Functional Index (BASFI) in addition to demographic, social, and psychological variables collected. Medications taken concurrently, inflammatory markers and radiographs were taken at each visit. NSAID use was captured by self-report of numbers of pills taken in the last week, month, and 6 month interval. Longitudinal multivariable analyses using mixed effect negative binomial regression models that account for the correlation of repeated measures over time were conducted to assess associations between NSAID use (NSAID index of 0%, >0 & ≤50%, and >50%) and BASFI while controlling for other variables.

Results: . Of the 5456 visits included in this analysis, 40%, 28% and 25% had an NSAID index of 0%, >0 & ≤50%, and >50% respectively. No significant differences were found analyzing the data over a one month and six month interval. Table 1 shows the longitudinal associations between NSAID use and other covariables over a 6 month period on BASFI scores. We found that NSAID use was significantly associated with higher BASFI (overall p=0.002); patients who had high NSAID index (>50%) and low NSAID index (>0 and ≤50%) were more likely to have higher BASFI compared to patients with no NSAID use (ARR=1.13; p=0.0019 and ARR=1.08; p=0.0172, respectively). There was no association of NSAID use with BASFI when we compared patients with high NSAID index to those with low NSAID index (ARR= 1.05;

p=0.1948).. C-reactive protein (CRP), Disease duration, baseline radiographic disease, depression (defined by Center for Epidemiologic Studies Depression Scale (CESD) score>16), comorbidty and opioid use were positively associated with BASFI.

Conclusion: We found an association between any NSAID use and higher functional impairment, while high vs. low NSAID use was not associated. This may be due to AS patients with higher functional impairment taking more NSAIDs. Our findings also hint at a modest treatment effect of NSAIDs in AS as high vs. low use was not associated with change in functional impairment. Table 1. NSAID Use and Covariables Associated with Longitudinal Functional Impairment in Multivariable Regression Modeling

Variable	Adjusted Rate Ratio (95% CI)	p-value
NSAID (last 6 months) use: High (>50) Low= (>0 &≤50) and no use (0)		
Low vs. No use	**1.08 (1.02, 1.16)**	**0.0125**
High vs. No use	**1.13 (1.04, 1.22)**	**0.0021**
High vs, Low use	**1.04 (0.97, 1.11)**	**0.2560**
TNFi use vs, No use	0.88 (0.82, 0.96)	0.0022
Male vs. Female	0.91 (0.80, 1.05)	0.1958
Education ≥ college vs. <college	0.72 (0.61, 0.86)	0.0003
White Race vs. other	0.80 (0.69, 0.94)	0.0057
Disease duration ≥10 vs. <10 years	1.27 (1.10, 1.47)	0.0011
CRP abnormal vs. normal	1.14 (1.09, 1.20)	<.0001
baseline mSASSS ≥ 4[a]	1.65 (1.44, 1.90)	<.0001
CESD total >16 vs. <16[b]	1.25 (1.17, 1.34)	<.0001
# comorbidity≥1 vs, 0	1.25 (1.08, 1.44)	0.0022
History of Smoking vs. No Smoking	1.06 (0.93, 1.20)	0.3653
Opioid Use vs. No use	1.19 (1.09, 1.30)	0.0001

a. modified Stoke Ankylosing Spondylitis Spinal Scores (mSASSS).

b. Center for Epidemiologic Studies Depression Scale (CESD)

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Abstract Number: 718

Radiographic Progression of Hip Arthritis in Patients with Ankylosing Spondylitis Treated with TNF Inhibitors

Maria Konsta[1], Michael Nurmohamed[2], J.C. van Denderen[3], Ingrid Visman[4] and I.E. Van der Horst - Bruinsma[5], [1]Amsterdam Rheumatology and Immunology Center,VUmc and Reade, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center | Reade, Amsterdam, Netherlands, [3]Center for Rheumatology and Rehabilitation, Jan van Breemen Institute, Amsterdam, Netherlands, [4]Amsterdam Rheumatology and Immunology Center, VUmc and Reade, Amsterdam, Netherlands, [5]GENRA Consortium, Amsterdam, Netherlands
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SESSION INFORMATION

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Session Type: ACR Poster Session A

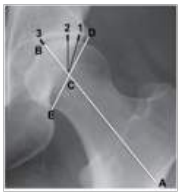
Session Time: 9:00AM-11:00AM

Background/Purpose: Although current evidence suggests that anti-TNF treatment may not inhibit spinal radiographic progression, its effect on hip involvement in AS is not known. The aim of this study is to assess the impact of long-term anti-TNF treatment on radiographic progression of hip arthritis in AS, by adding a quantitative scoring method, previously applied in hip osteoarthritis, to BASRI-hip score.

Methods: 205 consecutive AS patients (136 men, age: 49±11years, disease duration: 23±11 years) under anti-TNF treatment were included in this retrospective study. Anteroposterior X-rays of pelvis and lateral spine X-rays were scored blindly, by 2 independent readers at 3 time points: at baseline (i.e. prior anti-TNF treatment initiation), 2.6±0.7 and 7.2±2.4 years after anti-TNF initiation. Both hips were scored using: a) BASRI-hip score, b) mean joint space width (MJSW), estimated by measurement of 3 distinct points of interbone distance: 2 mm inner of the external end of the acetabulum, vertical line through femoral head center, head-neck center line(Figure). Spinal X-rays were scored by the mSASSS. Hip involvement was assessed clinically (pain, reduced range of motion and intermalleolar distance) and radiographically, as BASRI-h score ³ 2 at baseline anteroposterior pelvis X-rays. The significance of changes was tested by mixed models for longitudinal data.

Results: Definite hip involvement at baseline, was detected in 67/205(33%) patients, who had significantly higher BASRI-hip score[2(2-2.5)median(IQR) vs. 0.5(0-1) p<0.0001] and lower MJSW (3.6±0.7 vs. 4.5±0.7, p<0.0001), compared to those without. In AS patients with hip arthritis at baseline, both BASRI-h score and MJSW remained unchanged during follow up, regardless of gender. In patients without hip arthritis, the BASRI-hip score remained unchanged after 2.6±0.7 years, but increased significantly after 7.2±2.4 years compared to baseline. In particular, the BASRI-hip score showed significant increase in AS males without hip arthritis at the two intervals, compared to correspondence females, who had significant increase only at follow-up end. In contrast, the MJSW in patients without hip arthritis remained unchanged at the three time points, both in males and females. The mSASSS raised significantly during the follow-up period, regardless of gender and hip involvement (table).

Conclusion: One third of the AS patients suffer from radiographic hip involvement, that appears to stabilize during long-term anti-TNF treatment. The new scoring system may contribute to detect minor changes in contrast to BASRI-hip scoreÕ rough estimation.



Variables		Baseline	After 2.6±0.7 years	After 7.2±2.4 years	P
All pts(n=205)	BASRI-hip, median(IQR)	1(0-2)	1(0-2)	1(0-2)	<0.0001
	MJSW(mm), mean±SD	4.2±0.8	4.17±0.8	4.17±0.7	NS
	mSASSS, median(IQR)	4(0-21)	7.5(1-27)	9(2-29)	<0.0001
pts with hip involvement(n=67)	BASRI-hip, median(IQR)	2(2-2.5)	2(2-2.5)	2(2-2.5)	NS
	MJSW(mm), mean±SD	3.6±0.7	3.5±0.7	3.6±0.7	NS
	mSASSS, median(IQR)	8(2-34)	11.5(2-37.5)	14(2-38)	<0.0001
pts without hip involvement(n=138)	BASRI-hip, mean±SD	0.46±0.5	0.5±0.5	0.57±0.6	<0.0001
	MJSW(mm), mean±SD	4.5±0.7	4.5±0.6	4.4±0.6	NS
	mSASSS, median(IQR)	3.5(0-14)	6(0-21)	9(2-24)	<0.0001
Males with hip involvement (n=44)	BASRI-hip, median(IQR)	2(2-2.5)	2(2-2.5)	2(2-2.5)	NS
	MJSW(mm), mean±SD	3.6±0.7	3.5±0.8	3.6±0.7	NS
	mSASSS, median(IQR)	16(4-42)	19.5(4-46.5)	22.5(9-46)	<0.0001
Females with hip involvement (n=23)	BASRI-hip, median(IQR)	2(2-2)	2(2-2)	2(2-2)	NS
	MJSW(mm), mean±SD	3.5±0.5	3.5±0.6	3.4±0.6	NS
	mSASSS, median(IQR)	2.5(1-19)	4.5(1-26.5)	3(1-27)	<0.0001
Males without hip involvement (n=92)	BASRI-hip, mean±SD	0.55±0.5	0.6±0.5	0.6±0.56	0.003
	MJSW(mm), mean±SD	4.5±0.7	4.5±0.7	4.5±0.5	NS
	mSASSS, median(IQR)	8(2-24)	11(3-30)	13(4-35)	<0.0001
Females without hip involvement (n=46)	BASRI-hip, mean±SD	0.3±0.4	0.34±0.46	0.5±0.6	0.02
	MJSW(mm), mean±SD	4.4±0.6	4.4±0.6	4.35±0.6	NS
	mSASSS, median(IQR)	0(0-3)	2(0-4)	2(0-7)	<0.0001

Disclosure: M. Konsta, None; **M. Nurmohamed**, None; **J. C. van Denderen**, None; **I. Visman**, None; **I. E. Van der Horst - Bruinsma**, Pfizer, MSD and AbbVie, 2,AbbVie, MSD, UCB, 5.

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Abstract Number: 719

Prevalence and Incidence of Comorbidities in Patients with Ankylosing Spondylitis Versus General Population

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

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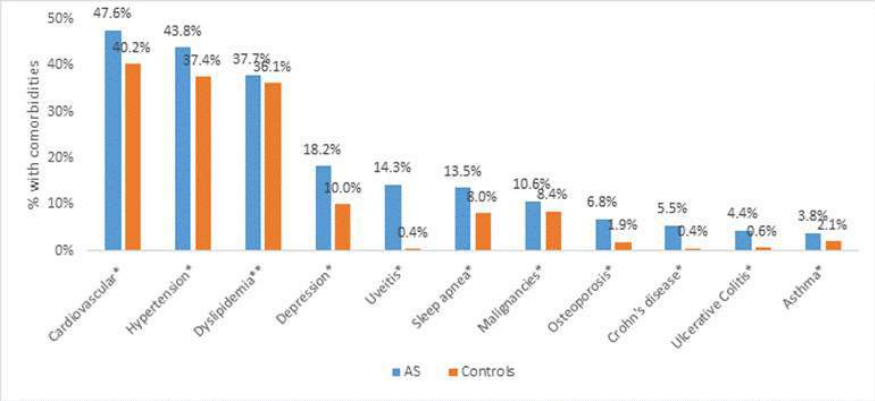
Background/Purpose: Comorbidities associated with ankylosing spondylitis (AS) have been inadequately studied in American populations. This study used a large US national claims database to compare prevalence and incidence of comorbidities of AS patients and general population.

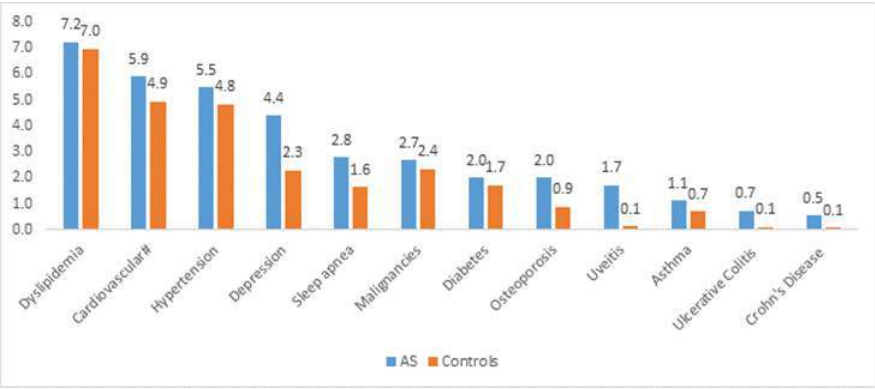
Methods: Adults with ≥1 inpatient or 2 outpatient diagnoses of AS (ICD-9-CM 720.0) in 1/1/2008 - 6/30/2014 were extracted from MarketScan Commercial and Medicare Databases. Of those identified, patients with ≥1 AS diagnosis in 2013 were included in the study, with the first AS diagnosis in 2013 set as the index date. Patients had ≥12 months pre-period and were followed for ≥12 months until patient death or the end of the study (6/30/2015). The prevalence of comorbidities was evaluated in a prevalent AS cohort. The incidence of new comorbidities (not present in a 24-month pre-

period) was evaluated in an incident AS cohort with newly diagnosed AS (no AS in the 12-month pre-period). General population included patients with no AS diagnosis in 2007-2015 and were matched to the AS patients on calendar year, age, gender, and geographic region.

Results: The prevalent AS cohort had 6,679 AS patients and 19,951 matched general population (mean age: 50.8 years for AS vs. 51.7 for general population; male: 60.5% vs. 60.8%; mean length of follow up period: 2.0 vs. 2.0 years). Compared with general population, a significantly higher proportion of AS patients had cardiovascular disease, hypertension, dyslipidemia, depression, sleep apnea, uveitis, malignancies, Crohn's disease, ulcerative colitis, osteoporosis, and asthma (Figure 1). The proportion of patients with diabetes was similar between AS patients and general population (11.8% vs. 13.6%, p=0.343). The incident AS cohort included 6,370 newly diagnosed AS patients and 14,998 matched general population. Incidence rates of newly diagnosed comorbidities were higher in incident AS patients than in general population (Figure 2). Figure 1. Proportion of Patients with Comorbidities: Prevalent AS vs. General Population



*p<0.001; ** p=0.017. Figure 2. Incidence Rates per 100 Person-Years of Top New Comorbidities for Incident AS vs. General Population



Conclusion: AS patients had significantly more comorbidity burden than general population in the US. Understanding these comorbidity profiles will help evaluate the impact of comorbid conditions on patients' health outcomes and healthcare utilizations. Future research is needed to determine optimal screening and management strategies for comorbidities in AS patients.

Disclosure: J. Walsh, Novartis Pharmaceutical Corporation, 5,AbbVie, 5; **X. Song**, None; **G. Kim**, None; **J. Park**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 720

Impact of HLA-B27 on Patient Profile and Treatment Response in As

Patients Treated with Anti-TNF in Canadian Real-World

Isabelle Fortin[1], Maqbool Sheriff[2], Proton Rahman[3], Michael Starr[4], Wojciech Olszynski[5], Sanjay Dixit[6], Viktoria Pavlova[7], Derek Haaland[8], Emmanouil Rampakakis[9], Eliofotisti Psaradellis[10], Brendan Osborne[11], Karina Maslova[12], Allen J Lehman[12], Francois Nantel[13] and Cathy Tkaczyk[11], [1]Centre de Rhumatologie De l'Est du Quebec, Rimouski, QC, Canada, [2]Nanaimo Regional General Hospital, Nanaimo, BC, Canada, [3]Rheumatology, St Claires Mercy Hospital, St Johns, NF, Canada, [4]Rheumatology, Mcgill University, Pointe-Claire,, QC, Canada, [5]103 Midtown Professional Center, Rheumatology Associates of Saskatoon, Saskatoon, SK, Canada, [6]Rheumatology, McMaster University Hamilton, Burlington, ON, Canada, [7]Ancaster Medical Centre, Ancaster, ON, Canada, [8]Rheumatology, Clinical Immunology & Allergy, McMaster University, Barrie, ON, Canada, [9]JSS Medical Research, St-Laurent, QC, Canada, [10]JSS Medical Research, Montreal, QC, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [12]Janssen Inc., Toronto, ON, Canada, [13]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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SESSION INFORMATION

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The human leukocyte antigen (HLA)-B27 allele is one of the strongest known genetic factors associated with the development of ankylosing spondylitis, however, previous studies have shown that approximately 10-25% of AS patients are HLA-B27 negative (HLA-). The aim of this analysis was to compare the profile of HLA - and HLA+ AS patients initiating anti-TNF treatment in Canadian routine clinical care.

Methods:

BioTRAC is an ongoing, prospective registry of patients initiating treatment with infliximab (IFX) or golimumab (GLM) for RA, AS, or PsA, or with ustekinumab for psoriasis. Patients eligible for this analysis included AS patients treated with IFX or GLM, enrolled since 2005 and 2010, respectively with available information on HLA B27 status. Descriptive statistics were used to assess patient and disease characteristics at Baseline and Month 12. Multivariate general linear models were used to assess the impact of HLA status on BASFI, BASDAI and ASDAS at Month 12 while adjusting for age, gender, disease duration, anti-TNF type, and baseline scores.

Results:

A total of 147 HLA+ and 78 HLA- AS patients were included, of which 93 had available data at Month 12 (62 HLA+, 31 HLA-). Table 1 summarizes the baseline patient characteristics and disease parameters by HLA status. HLA+ patients were significantly younger compared to HLA- patients both at diagnosis (32.2 vs. 46.8 years; P=0.001) and at anti-TNF initiation (42.1 vs. 48.2 years; P=0.002). Furthermore, HLA+ patients had significantly higher disease duration (7.7 vs. 3.9 years; P=0.002) and were more likely to be male (69.0% vs. 42.1%; P<0.001). Geographic distribution was comparable between HLA+ and HLA- groups (P=0.886). With respect to disease parameters, baseline BASDAI, BASFI and ASDAS were significantly higher in the HLA- group ($P < 0.05$), as was the proportion of HLA- patients reporting very high ASDAS disease activity (62.5% vs. 38.2%). Mean baseline CRP levels, although higher in HLA- patients compared to HLA+ patients (16.7 vs. 10.5 mg/L), were not found to be significantly different between groups (P=0.085).

Upon adjusting for potential confounders, HLA+ patients experienced greater improvements from baseline to Month 12 in BASDAI (-2.13 vs. -0.24; P=0.008), BASFI (-1.64 vs. 0.11; P=0.030), and ASDAS (-0.95 vs. -0.26; P=0.067). At Month 12, ASDAS DA categories were found to be statistically comparable across both groups (P=0.396), although a lower proportion of HLA - patients reported inactive-moderate disease (30.0% vs. 51.2%).

Table 1. Patient and Disease Characteristics at anti-TNF Initiation by HLA Status

Parameter	HLA+ (N=147)	HLA- (N=78)	P-value
Age, years, mean (SD)	42.1 (13.2)	48.2 (13.4)	0.002
Age at diagnosis, mean (SD)	32.2 (9.0)	46.8 (14.0)	0.001
Disease duration, years, mean (SD)	7.7 (10.3)	3.9 (4.4)	0.002
Gender, male, n (%)	98 (69.0)	44 (31.0)	< 0.001
Anti-TNF at baseline			
Infliximab, n (%)	27 (18.4)	15 (19.2)	0.504
Golimumab, n (%)	120 (81.6)	63 (80.2)	
CRP levels, mg/L, mean (SD)	10.5 (20.2)	16.7 (29.2)	0.084
BASDAI, mean (SD)	5.9 (2.2)	6.6 (1.7)	0.022
BASFI, mean (SD)	5.0 (2.6)	5.9 (2.2)	0.026
ASDAS, mean (SD)	3.2 (0.96)	3.7 (0.90)	0.002
ASDAS Disease Activity (DA), %			
Inactive DA	2.7	0.0	
Moderate DA	5.5	3.6	0.022
High DA	53.6	33.9	
Very high DA	38.2	62.5	

Conclusion: In this Canadian real-world cohort, HLA- AS patients were found to be demographically distinct from HLA+ patients and present with more advanced disease at baseline. Furthermore, HLA- was identified as an independent predictor of worse treatment outcomes, highlighting the importance of early diagnosis and management of HLA- AS patients.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-hla-b27-on-patient-profile-and-treatment-response-in-as-patients-treated-with-anti-tnf-in-canadian-real-world

Abstract Number: 721

Safety and Efficacy of Switching from Originator to CT-P13 Infliximab Biosimilar in Patients Affected By Spondyloarthritis. a 6-Month Observational Study

Alberto Batticciotto[1,2], Marco Antivalle[2], Francesca Li Gobbi[3], Simone Parisi[4], Rossella Talotta[2], Valentina Varisco[2], Maurizio Benucci[3], Enrico Fusaro[4] and Piercarlo Sarzi-Puttini[1], [1]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milano, Italy, [2]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milan, Italy, [3]Rheumatology Unit, Ospedale S. Giovanni di Dio, Florence, Florence, Italy, [4]Department of Rheumatology, University Hospital Città Della Salute e della Scienza di Torino, Turin, Italy

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Biosimilar infliximab (INX) was recently approved by the European Medicine Agency based on comparable pharmacokinetics, safety and efficacy profile to innovator INX for the treatment of Rheumatoid Arthritis, Ankylosing Spondylitis (AS), Crohn's disease, Ulcerative Colitis, Psoriatic Arthritis (PsA), and psoriasis. (1,2) Switching from originator to biosimilar INX offers cost savings but, up to now, limited evidence (from conference abstracts of open-label extension studies suggesting similar clinical efficacy) and no guidelines are available.(3) Aim of the study was to investigate efficacy and safety of switching from originator to biosimilar INX in patients affected by spondyloarthritis (SpA) in real life clinical practice.

Methods: Thirty-six patients (18 with diagnosis of AS, 7 with enteropathic arthritis, 8 with PsA and 3 with undifferentiated SpA), from three Italian Rheumatologic centers with a previous diagnosis of SpA, treated for more than 6 months with originator infliximab (in according with the ASAS/EULAR guidelines) and clinically with an inactive or moderate disease activity (ASDAS-CRP < 2.1), were switched to biosimilar infliximab for pharmacoeconomic reasons. A six months evaluation of BASDAI, BASFI, ASDAS-CRP, DAS28-CRP (if peripheral disease), MASES, VAS pain and collection of adverse events (AE) were performed.

Results: At switch, patients had a median age of 51.8 years (range 23-80 yrs), with a median disease duration of 137,1 months (range 14-372) and median ongoing treatment with originator INX of 76.4 months (range 14-372). After 6 months of biosimilar INX therapy we cannot find any statistical difference in terms of median values of BASDAI (2.66 ± 1.6 Vs 2.5 ± 1.4 p= 0.31), BASFI (2.3 ± 1.3 Vs 2.2 ± 1.2 p= 0.051), ASDAS-CRP (1.39 ± 0.4 Vs 1.38 ± 0.4 p= 0.8), DAS28-CRP (2.66 ± 0.69 Vs 2.67 ± 0.34 p= 0.93), MASES (0.33 ± 0.66 Vs 0.2 ± 0.4 p= 0.08), VAS pain (18.1 ± 14.7 Vs 16.7 ± 11.3 p= 0.55). During the first six months of biosimilar INX a very low number of patients experienced an AE without a significance difference with the AE collected the six months before the switch (Fisher Test p=0.13). Two patients (5.5%) stopped biosimilar INX therapy, after the first two administrations, for the appearance of de novo psoriasis.

Conclusion: No statistically significant differences in terms of BASDAI, BASFI, ASDAS-CRP, DAS28-CRP, MASES, VAS pain values and number of adverse events were found six months after the switch from originator to biosimilar INX in an SpA multicentre Italian cohort. **References.**

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Abstract Number: 722

Impact of Aerobic Fitness on Axial Spondyloarthritis Activity: Systematic Review and Meta-Analysis of Controlled Studies

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Session Type: ACR Poster Session A

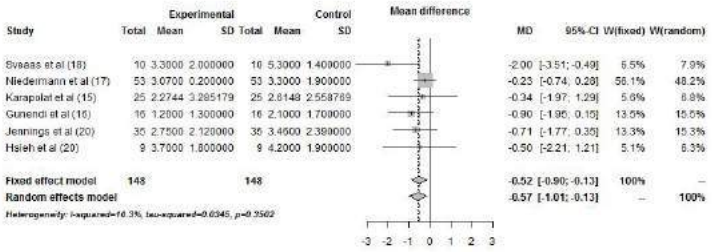
Session Time: 9:00AM-11:00AM

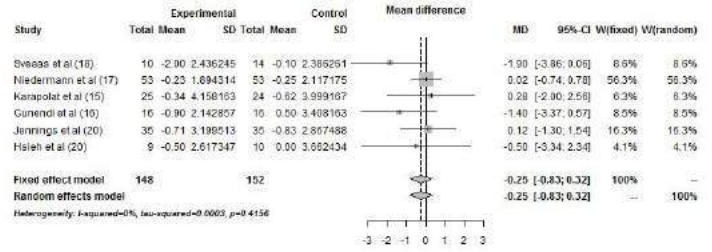
Background/Purpose: The current ASAS recommendations for the management of the ankylosing spondylitis suggest, beside pharmacological therapy, a significant part of physical therapy with supervised exercises. The importance and the beneficial impact of the physiotherapy and spa-therapy is known for a long time and numerous studies confirmed this. The impact of the aerobic fitness on the disease is not clear. The objective of this work is, after a systematic review of the literature and meta-analysis, to evaluate the impact of an aerobic fitness program on disease activity, defined by the BASDAI, and the function, defined by the BASFI, in case of axial spondyloarthritis.

Methods: A systematic review of the literature, following the prisma recommandations, was performed by two reviewers on the PubMed and Embase databases with the following keywords: ("Ankylosing spondylitis"OR "Spondyloarthritis") AND ("Physical activity" OR "Aerobic fitness"). The diagnosis axial spondyloarthritis was meeting the New York criteria and/or the ASAS criteria. Aerobic fitness was defined as an exercise performed at 50–90% of the maximal heart rate or between 50% and 80% VO2 pick.

Results: 520 abstracts were identified and, 93 abstracts were analysed. 8 studies were meeting the selection criteria and 6 were finally included in this work because of the presence of a control group. Both groups were similar in terms of age, sex ratio, disease duration. Aerobic fitness provides in the intervention group (148 patients) a positive impact on the BASDAI (weighted mean difference (WMD): - 0.52 [95% CI -0.9; -0.13]) (I^2: 10.3%, P=0.35). When compared to a control group (152 Patients) aerobic exercise does not provide a more positive impact on the BASDAI (WMD : - 0.25 [95% CI -0.83; 0.32]) (I^2: 0%, P=0.41). Aerobic exercise does not provide in the intervention group a positive impact on the BASFI (WMD: - 0.31 [95% CI -0.73; 0.1]) (I^2: 0 %, P=0.79). When compared to a control group, aerobic fitness does not provide a more positive impact on the BASFI (WMD -0.41 [95% CI -1.09; 0.27]) (I^2: 0 %, P= 0.62)

Conclusion: Aerobic exercise did not provide beneficial effects neither on disease activity nor on physical function when compared to a control group.





Disclosure: F. Verhoeven, None; **X. Guillot**, None; **C. Prati**, None; **N. Tordi**, None; **C. Demougeot**, None; **D. Wendling**, None.

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Abstract Number: 723

Hip Disease Treatment and Progression in Ankylosing Spondylitis

Daphne Scaramangas-Plumley[1], MinJae Lee[2], Mohammad H. Rahbar[2], Lianne S. Gensler[3], John D. Reveille[4] and Michael Weisman[1], [1]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [2]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas-McGovern Medical School, Houston, TX, [3]Medicine/Rheumatology, UCSF, San Francisco, CA, [4]Rheumatology, University of Texas-McGovern Medical School, Houston, TX

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory disease that affects the spine, sacroiliac joints, hips and peripheral joints. Clinical hip involvement is a common manifestation seen in many AS patients. 5% of AS patients have severe hip disease requiring total hip arthroplasty (THA). NSAIDs and TNFi are the pharmacologic standard of care in AS. Little is known about the impact of any treatment on hip disease while some studies have shown TNFi to be associated with less spinal radiographic progression. It is not clear whether TNF inhibitors (TNFi) prevent radiographic hip progression. Our hypothesis to be tested is that TNFi delays radiographic hip progression in AS patients.

Methods: We included 613 AS patients meeting the modified New York criteria and had at least 2 sets of hip radiographs. Using the Bath Ankylosing Spondylitis Radiologic Index (BASRI) for the hips, a progressor was defined as having hip scores change by at least two units between the first and last visits. We included patients with BASRI hip scores below 4 (n=579) for the progression analysis and selected a grade-2 BASRI score change to eliminate concerns associated with reliability for reading grade-1 scores. We performed a logistic regression analysis evaluating multivariable associations between TNFi use (defined as those who used TNFi for more than 50% of their follow-up period) and hip progressors after controlling for other factors such as follow-up period, baseline hip scores, baseline TNFi use, NSAID index over follow-up period, study sites and clinical/demographic variables (disease duration, sex, education level, race, current smoking status, BASDAI, CRP and comorbidities).

Results: Of the 576 patients analyzed, 551 were deemed to be non-progressors and 25 were progressors (median follow-up years=3). TNFi use was related to a lower probability of being a hip disease progressor (adjusted OR=0.02; p=0.003 – Table 1). There was not a significant interaction between NSAID and TNFi use.

Conclusion: TNFi use was associated with less radiographic hip progression in our cohort of patients with AS. There was no significant interaction effect found between NSAID and TNFi use.

Variable	Adjusted Odds Ratio (95% CI)	P
TNFi use (Yes vs. No)	**0.02 (0.001, 0.24)**	**0.0027**
NSAID index (%) ≤50 & >0 vs. 0 (low vs. no)	0.76 (0.10, 5.63)	0.7853
>50 vs. 0 (high vs. no)	1.54 (0.23, 10.31)	0.6570
>50 vs. ≤50 & >0 (high vs. low)	2.03 (0.40, 10.30)	0.3910
Baseline Hip score (Continuous)	1.61 (1.07, 2.43)	0.0225
Disease duration (>10 years vs. ≤10 years)	1.45 (0.26, 7.97)	0.6695
Sex (Male vs. Female)	2.15 (0.35, 13.02)	0.4060
Race (White vs. Others)	0.62 (0.09, 4.16)	0.6250
Education (higher than college vs. Others)	0.52 (0.07, 4.07)	0.5350
current smoke (Yes vs. No)	0.99 (0.10, 9.91)	0.9943
# comorbidity (>=1 vs. None)	1.67 (0.22, 12.53)	0.6159
BASDAI (>=40 vs. <40)	2.84 (0.55, 14.60)	0.2107
CRP (abnormal vs. normal)	0.48 (0.08, 2.86)	0.4224
Baseline TNFi use (Yes vs. No)	6.84 (1.21, 38.54)	0.0293
Follow-up years (Continuous)	0.97 (0.72, 1.29)	0.8223

Disclosure: D. Scaramangas-Plumley, None; **M. Lee**, None; **M. H. Rahbar**, None; **L. S. Gensler**, AbbVie, Amgen, Janssen, Novartis, UCB, 5; **J. D. Reveille**, None; **M. Weisman**, None.

Abstract Number: 724

Diminished Spinal Radiographic Progression during Long-Term Treatment with TNF-α Inhibitors in Ankylosing Spondylitis Patients at Risk of Poor Radiographic Outcome

Fiona Maas[1], Suzanne Arends[1,2], Freke Wink[2], Reinhard Bos[2], Hendrika Bootsma[3], Elisabeth Brouwer[1] and **Anneke Spoorenberg**[1,2], [1]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [2]Rheumatology, Medical Center Leeuwarden, Leeuwarden, Netherlands, [3]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, The Netherlands, Groningen, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: In AS, spinal radiographic progression shows a very heterogeneous course. Our aim was to

investigate which patient characteristics are of influence on the course of spinal radiographic progression in AS patients treated long-term with TNF-α inhibitors.

Methods: Consecutive patients from the Groningen Leeuwarden AS (GLAS) cohort who started TNF-α inhibitors, with baseline and biannual spinal radiographs until 6 years of follow-up were included. Radiographs were scored using mSASSS by two independent readers. Generalized estimating equations (GEE) were used to explore the associations between baseline characteristics and radiographic damage over time. The course of radiographic progression was investigated with different time functions (linear and non-linear), stratified for significantly associated patient characteristics. In case of missing radiographic data at one or more intermediate follow-up visits, single linear imputation was used.

Results: 80 AS patients reached 6 years of follow-up (mean mSASSS 8.2±12.9) of which 53 patients had complete radiographic data at all 2-year time points. Baseline syndesmophytes, male gender, older age, longer disease duration, and higher BMI were significantly associated with more radiographic damage over time. Baseline syndesmophytes was the only independent risk factor. GEE analysis in patients with these characteristics revealed that mSASSS progression followed a non-linear course; mean mSASSS progression rate reduced from maximal 2.8 units over 0-2 years to minimal 0.9 units over 4-6 years (Table 1). A linear course with overall lower progression scores over the 2-year intervals (≤1 mSASSS units/2yrs) was found in patients without risk factors (Table 1). Complete case analysis in 53 patients revealed similar results.

Conclusion: AS patients who are at risk of poor radiographic outcome showed the largest but diminishing spinal radiographic progression over time during long-term treatment with TNF-α inhibitors. Only little and linear progression was observed in patients without risk factors such as no syndesmophytes, shorter symptom duration, and normal BMI.

Table 1. Radiographic damage at baseline and estimated mean spinal radiographic progression scores over time of AS patients stratified for baseline risk factors.

		n	Baseline mSASSS	Best time model	mSASSS progression scores		
					0-2 year	2-4 year	4-6 year
Total group		80	8.7±13.3	Non-linear	1.7	1.5	1.0
Syndesmophytes	**Yes**	43	15.8±14.9	Non-linear	2.8	2.5	1.6
	No	37	0.4±0.8	Linear	0.4	0.4	0.4
Gender	**Male**	56	10.9±14.6	Non-linear	2.1	1.9	1.3
	Female	24	3.5±7.4	Linear	0.7	0.7	0.7
Age	**≥40 years**	43	12.3±15.2	Non-linear	2.3	2.0	1.3
	<40 years	37	4.5±9.1	Linear	0.9	0.9	0.9
Symptom duration	**≥10 years**	52	12.3±15.2	Non-linear	2.3	2.0	1.3
	<10 years	25	2.1±3.1	Linear	0.6	0.6	0.6
Time since diagnosis	**≥5 years**	44	11.4±15.2	Non-linear	2.2	1.9	1.3
	<5 years	36	5.4±9.8	Linear	1.0	1.0	1.0
BMI	**≥25 kg/m^2**	26	14.2±17.1	Non-linear	2.5	2.1	0.9
	<25 kg/m^2	22	3.5±6.8	Linear	0.9	0.9	0.9

Disclosure: F. Maas, None; **S. Arends**, Pfizer, 2; **F. Wink**, Abbvie, 5; **R. Bos**, None; **H. Bootsma**, None; **E. Brouwer**, Roche Pharmaceuticals, 5; **A. Spoorenberg**, Abbvie, Pfizer, UCB, 2,Abbvie, Pfizer, MSD, UCB, and Novartis, 5.

progression-during-long-term-treatment-with-tnf-%ce%b1-inhibitors-in-ankylosing-spondylitis-patients-at-risk-of-poor-radiographic-outcome

Abstract Number: 725

Long-Term Anti-TNF Treatment Is Associated with Reduction of Progression of Radiographic Changes in the Sacroiliac Joints in Patients with Non-Radiographic Axial Spa: Six-Year Results of the Esther Trial

Valeria Rios Rodriguez[1], Joachim Sieper[1], Kay-Geert Hermann[2], Hildrun Haibel[1], Christian Althoff[2], Beate Buß[1], Olaf Behmer[3] and Denis Poddubnyy[1], [1]Rheumatology, Charité Universitätmeidzin Berlin, Berlin, Germany, [2]Radiology, Charité Universitätmeidzin Berlin, Berlin, Germany, [3]Pfizer Pharma, Berlin, Germany

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Session Type: ACR Poster Session A

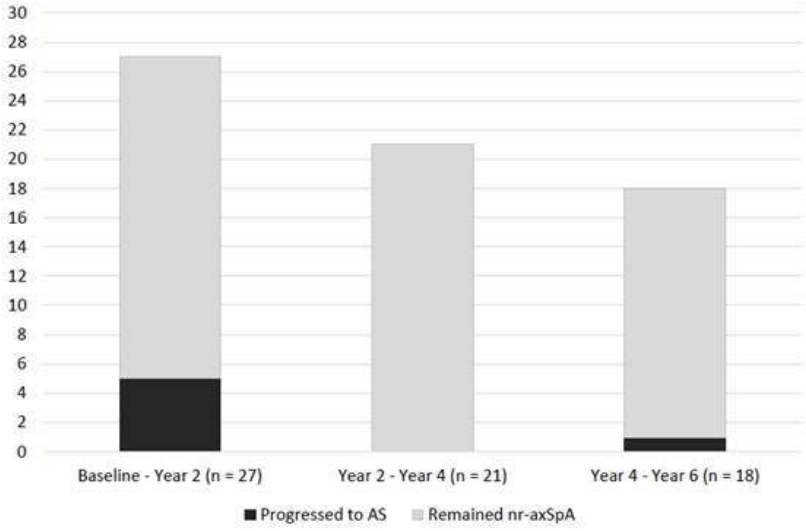
Session Time: 9:00AM-11:00AM

Background/Purpose: Data from observational studies suggests a 10-12% biannual rate of progression from non-radiographic axial SpA (nr-axSpA) to ankylosing spondylitis (AS)[1] in patients not treated with tumor necrosis factor α (TNF) blockers. It is not known, whether anti-TNF treatment might be able to prevent such a progression in patients with nr-axSpA. To assess the radiographic progression in the sacroiliac joints (SIJ) during long-term (up to 6 years) treatment with the TNF-blocker etanercept in patients with early axSpA.

Methods: In the ESTHER trial[2] a total of 76 patients with early (=<5 years symptom duration) and active axSpA were randomized to be treated with either etanercept or sulfasalazine for one year. At year 1, all patients who were not in remission continued with etanercept directly; patients in remission discontinued their therapy and were followed-up until year 2, in case of disease flare the etanercept therapy was (re)-introduced and continued until the end of year 6. X-rays of SIJ were collected at baseline and every 2 years thereafter. Two trained readers (VRR and DP), who were blinded for all clinical data, scored independently the SIJ y-rays in a concealed and randomly selected order, according to the grading system of the modified New York (mNY) criteria for AS. Patients were classified as having AS if both readers recorded the presence of definite radiographic sacroiliitis according to the mNY criteria. Active inflammatory and fatty lesions on magnetic resonance imaging (MRI) of SIJ were assessed according to the Berlin MRI scoring system (KGH and CA).

Results: A total of 55 patients from the 76 patients of ESTHER trial were included in the current analysis due to the availability of x-rays of SIJ. 19 patients (34.5%) were classified at baseline as AS and 36 (65.5%) as nr-axSpA based on the independent reading results with a fair agreement between both readers (k=0.33, p=0.01). Radiographic progression from nr-axSpA to AS was observed mainly between baseline and year 2 – in 18.5% (5/27) of the patients classified as nr-axSpA at baseline with available SIJ x-rays at year 2. There were no patients who progressed to AS between year 2 and year 4 and only one patient (5.6%, 1/18) progressed to AS between year 4 and year 6 – Figure. Treatment arm in the first year (etanercept or sulfasalazine) had no significant impact on progression from nr-axSpA to AS. Elevated C-reactive protein – CRP (>=5mg/l) at baseline was associated with a higher odds for progression: odds ratio = 7.0 (95%CI 0.7-73.9). There was no difference in the baseline osteitis score on MRI of SIJ between progressors and non-progressors (since MRI inflammation was an entry criterion), however, progressors had higher fatty lesions score at baseline as compared to non-progressors: 10.3±7.1 vs. 4.9±5.8, respectively, p=0.064.

Figure. Progression from nr-axSpA to AS in patients treated with etanercept for up to 6 years in the ESTHER trial.



Conclusion: In the ESTHER trial, there was a substantial reduction of radiographic sacroiliitis progression between year 2 and year 6 of anti-TNF treatment. Higher baseline CRP and higher MRI fatty lesions score demonstrated a positive association with progression from nr-axSpA to AS. **References**

1. Poddubnyy D, et al. Ann Rheum Dis 2011;70:1369-74.

2. Song IH, et al. Ann Rheum Dis 2011;70:590-6.

Disclosure: V. Rios Rodriguez, None; **J. Sieper**, Abbvie,BMS,Janssen,MSD,Pfizer, 2; **K. G. Hermann**, None; **H. Haibel**, Abbvie,MSD, 5,Abbvie,MSD,Pfizer,UCB, 8; **C. Althoff**, None; **B. Buß**, Abbvie,UCB, 5; **O. Behmer**, Pfizer Pharma, 3; **D. Poddubnyy**, Abbvie,Boehringer,MSD,Pfizer,Novartis, 5,Abbvie,BMS,Lilly,Janssen,MSD,Novartis,Pfizer,Roche,UCB, 8.

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Abstract Number: 726

Comparison of Infliximab Immunogenicity in Inflammatory Arthritis Versus Inflammatory Bowel Disease Patients in Routine Clinical Practice

Marianne Guirgis[1], Melanie Favre dit Jeanfavre[2], Charles Benaim[3], Matthieu Perreau[4], Pierre Michetti[5], Michel Maillard[1] and **Pascal Zufferey**[6], [1]gastroenterology, Lausanne, Switzerland, [2]DAL, RHU, Lausanne, Switzerland, [3]DAL, MPR, Lausanne, Switzerland, [4]Medecine /CHUV, Immunology, Lausanne, Switzerland, [5]La Source-Beaulieu, Lausanne, Switzerland, [6]Rhu /Dal .Chuv, Rheumatology, Lausanne, Switzerland

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Infliximab is a biological agent frequently used for inflammatory arthritis (IA) such as spondyloarthritis, rheumatoid arthritis, psoriatic arthritis as well as for the inflammatory bowel diseases (IBD) such as Crohn's disease or ulcerative colitis. A major limitation to infliximab is loss of response due to the development of anti-drug antibodies (ADABs).However, It is unclear if the underlying medical condition influences antibody development. The first aim was to compare the prevalence of ADABs IA patients to IBD patients receiving treatment with infliximab. The second aim was to evaluate the correlation between ADABs and trough levels. The final objective was to determine if there were any clinical predictors of the development of ADABs.

Methods: A retrospective study was performed of all patients with IA and IBD treated with maintenance infliximab. A trough level and ADABs were obtained prior to the next infusion and drug monitoring was performed in a pro-active manner at certain. Reproducibility was confirmed in exposed and unexposed patients. Clinical data was extracted from a central database and patient medical records. Clinical predictors of ADABs development were analyzed using regression analysis. They comprised: gender, age, duration of the disease, duration of the treatment, co-medication, doses of infliximab and schedule, previous biologic exposure.

Results: A total of 166 evaluated of whom 76 were treated for IA and 90 for IBD. IBD patients were significantly younger than IA patients (mean: 37 versus 51 years) with shorter disease duration (mean: 6.9 versus 9.4 years) and a shorter duration of treatment (median: 18 versus 44 months). Overall, ADABs were detected in 35 patients (21 %) and markedly elevated (defined as >200 ug/ml) in 21 patients (12 %). There was a trend to higher prevalence of ADABs in IA patients (26%) compared to IBD patients (26% vs 15%; p= 0.08). A markedly elevated ADAB level was significantly more prevalent in IA compared to IBD (17% versus 6%; p=0.035). In both groups ADAB were highly correlated with undetectable through level.

	total	ADABs+			ADABs>200			ADABS-			P : <0.05
Type of disease	Total	total	IA	IBD	*Total*	IA	IBD	total	IA	IBD	
	N=166	N=35	N=21	N=14	*N=21*	N=15	N=6	N=131	N=56	N=76	
ADAB+ (%)		21%	27%	15%	12%	17%	6%				0.08/0.035*
Age	45	48	50	45	47	49	44	44	52	38	0.1
Gender (F ,.%)	43%	28%	28%	28%	23%	26%	16%	49%	40%	51%	0.02/0.07*
Duration of illness (years)	8.1	8.4	9.5	6.9	8.3	7.8	8.6	8	9.9	6.8	0.8
Duration of treatment (months)	37	41	51	24	33	38	27	36	48	27	0.5
Combination therapy (%)	25%	22%	28%	12%	27%	24%	16%	18%	36%	13%	0.6/0.9*
Dosage : mg	440	412	380	460	390	370	460	450	400	500	0.6/0.9*
Dose Interval.: weeks	7	7.7	8	7.5	7.8	7.8	8	7	7	7	0.9
Previous biologics : yes:%	60%	67%	83%	71%	68%	-	-	53%	-	-	0.1
Trough level +	79%	27%	14%	38%	10%	7%	16%	95%	92%	96%	P<0.0001

*:ADABs+ versus ADABs- / ADAB>200 versus ADABs - In the overall cohort, no predictive factors for the development of ADABs were found (table). This was also the case when analyzing IBD or IA patients separately (table).

Conclusion: In this cohort of IA and IBD patients treated with maintenance infliximab, who received pro-active, trough level and ADABs monitoring, the prevalence of ADAB was higher in IA patients than in IBD patients. This may be explained by differences in baseline clinical characteristics. No clear predictive factors could be identified in either group.

Disclosure: M. Guirgis, None; **M. Favre dit Jeanfavre**, None; **C. Benaim**, None; **M. Perreau**, None; **P. Michetti**, None; **M. Maillard**, None; **P. Zufferey**, None.

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Abstract Number: 727

Effects of Nsaids on Disease Activity in Ankylosing Spondylitis

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Brown[6], Johnathan Jia[7], Amirali Tahanan[3], Mohammad H. Rahbar[3], Michael Weisman[8] and John D. Reveille[9], [1]Internal Medicine-Rheumatology, Washington University in Saint Louis, School of Medicine, Saint Louis, MO, [2]Washington University in Saint Louis, School of Medicine, Saint Louis, MO, [3]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas-McGovern Medical School, Houston, TX, [4]NIH/NIAMS, Bethesda, MD, [5]Medicine/Rheumatology, UCSF, San Francisco, CA, [6]University of Queensland Diamantina Institute, Brisbane, Australia, [7]University of Texas-McGovern Medical School, Houston, TX, [8]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [9]Rheumatology, University of Texas-McGovern Medical School, Houston, TX

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: NSAIDs are the first line pharmacologic therapy in ankylosing spondylitis (AS). Several NSAIDs are efficacious in AS without superiority demonstrated by any particular drug. The literature frames NSAID use in terms of type, dose and duration through the NSAID index. This study aims to identify the effect of NSAID use in AS as defined by the percent of the full inflammatory dose taken over time (the NSAID Index) on disease activity over time.

Methods: A prospective cohort study of 755 AS patients who met the modified New York criteria were followed for at least 2 visits from multiple sites. Patients underwent a comprehensive clinical evaluation including assessing their disease activity by the Bath AS Disease Activity Index (BASDAI) in addition other demographic, social, and psychological variables collected. . Medications taken concurrently, inflammatory markers and radiographs were taken at each visit. NSAID use was captured by self-report of numbers of pills taken in the last week, month, and 6 month interval. Longitudinal multivariable analyses using mixed effect Poisson regression models that account for the correlation of repeated measures over time were conducted to assess associations between NSAID use (NSAID index of 0%, >0 & ≤50%, and >50%) and BASDAI in tandem with other covariables..

Results: Of the 5101 visits included in this analysis, 41%, 29% and 26% had an NSAID index of 0, >0 & ≤50, and >50 respectively. Table 1. show the longitudinal associations between NSAID use and other covariables over a 6 months period on BASDAI scores. We found that NSAID use was significantly related to higher BASDAI (overall $p<0.0001$); the patients who had high NSAID index (>50%) and low NSAID index (>0 and ≤50%) were more likely to have high BASDAI compared to the ones with no NSAID use (ARR=1.21; $p<0.0001$ and ARR=1.15; $p<0.0001$, respectively). This effect was attenuated when we compare patients with high versus low NSAID index (>50% vs. >0 and ≤50%) (ARR= 1.05; $p=0.0809$). Smoking, C-reactive protein (CRP), baseline radiographic disease, depression (defined by Center for Epidemiologic Studies Depression Scale (CESD) score>16) and opioid use were positively associated with disease activity. Negative associations were seen with TNF inhibitors (TNFi), male gender, higher education. associated with disease activity (ARR=0.9; $p=0.007$). Nearly identical results were found if only the NSAID index of the previous month was considered.

Conclusion: We found a positive association between any NSAID use and higher disease activity, while high vs. low NSAID use was not associated. This may be due to AS patients with higher disease activity taking more NSAIDs. Our findings also hint at a modest treatment effect of NSAIDs in AS as high vs. low use was not associated with change in disease activity. Table 1. NSAID Use and Covariables Associated with Longitudinal Disease Activity in Multivariable Regression Modeling

Variable	Adjusted Rate Ratio (ARR) (95% CI)	p
NSAID index (last 6 months) >0 &≤50 vs. 0 (low vs. no use)	**1.15 (1.10, 1.22)**	**<.0001**
>50 vs. 0 (high vs. no use)	**1.21 (1.14, 1.28)**	**<.0001**
>50 vs. >0 &≤50 (high vs. low NSAID index)	**1.04 (0.99, 1.09)**	**0.0809**
TNFi use (Yes vs. No)	0.90 (0.85, 0.96)	0.0007
Gender (Male vs. Female)	0.90 (0.82, 0.98)	0.0109
Education (≥college vs. <college)	0.83 (0.75, 0.92)	0.0003
Race (White vs. other)	0.94 (0.85, 1.03)	0.1929
Disease duration (≥10 vs. <10)	1.02 (0.94, 1.12)	0.5947
CRP (abnormal vs. normal)	1.14 (1.09, 1.18)	<.0001
first observed mSASSS (≥ 4 vs. <4)	1.11 (1.02, 1.21)	0.0169
Depression (by CESD) (>16 vs. ≤16)	1.33 (1.26, 1.39)	<.0001
# comorbidity (≥1 vs. <1)	1.08 (0.98, 1.18)	0.1268
History of Smoking (Yes vs. No)	1.08 (1.00, 1.17)	0.0480
Opioid Use (Yes vs. No)	1.20 (1.13, 1.27)	<.0001

a. modified Stoke Ankylosing Spondylitis Spinal Scores (mSASSS).

b. Center for Epidemiologic Studies Depression Scale (CESD)

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Abstract Number: 728

Correlation Between the Spinal MRI Findings and the Serum Level of DKK-1 in Patients with Spondyloarthritis Treated with TNF Antagonist

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose : Recent prospective data suggest that spinal inflammatory damage in patients with ankylosing spondylitis will eventually convert into fat. In these complex inflammatory lesions, bone formation and inflammation are not synchronized. The molecular basis responsible for new bone formation in SpA patients is still unclear. Serum level of

dickkopf-1 (Dkk-1), the natural inhibitor of WNT protein, is a main factor in limiting new bone formation. In this study, we aimed to assess the correlation between the secreted protein Dkk-1 and abnormal findings on spinal MRI through a prospective study of SpA.

Methods: Thirty patients with active axial SpA (axSpA) who fulfilled the ASAS axSpA criteria were enrolled. All patients received an injection of recombinant human TNF receptor-antibody fusion protein (YISAIPU) at a dosage of 50 mg/week for 6 months. Patient report outcome measure questionnaires and physical examination, blood tests were completed according to the study protocol. All patients were scored for bone marrow edema and fat infiltration on spinal MRI imaging. The spinal MRI imaging of the patients before and after the treatment were blindly reviewed and scored using the SPARCC scoring system by two individuals who were familiar with the system.

Results: There are 28 male and two female patients (mean age: 31 +/- 5.5 yrs, range: 22-41; mean duration: 93.5 +/- 75.8; HLA-B27(+): 96.7% (29/30)). In patients who finished the 6 month anti-TNF treatment, the ESR, CRP, BASDAI, BASFI, BASMI and ASDAS-CRP were significantly decreased ($P < 0.01$). Serum Dkk-1 concentration was also significantly decreased ($P < 0.05$), as were the edema measurements of spinal bone marrow ($P < 0.05$). (Table1). Correlation analysis found that serum Dkk-1 concentration before treatment was significantly correlated with spinal bone marrow edema scores ($P < 0.01$). The differences in serum Dkk-1 levels significantly correlate with differences in spinal MRI bone marrow edema scores after treatment ($P < 0.05$).(Figure 1 and 2).

Table 1 Clinical indexes, serum Dkk-1 and spinal imaging scores before and after treatment

	Before treatment	After treatment
ESR (mm/h)	23.78 ± 22.27	5.03 ± 4.63**
CRP (mg/dl)	2.59 ± 2.90	0.40 ± 0.52**
BASDIA	6.23 ± 1.29	2.52 ± 1.84**
BASFI	5.78 ± 1.44	2.69 ± 1.72**
BASMI	2.46 ± 1.91	0.69 ± 1.21**
ASDAS-CRP	3.77 ± 0.83	1.58 ± 0.74**
DKK-1 (ng/ml)	98.23 ± 113.41	51.88 ± 41.90*
Spinal-BME	20.27 ± 23.53	6.08 ± 8.09**
Spinal-FAT	10.08 ± 10.38	13.81 ± 15.34

* $P < 0.05$; ** $P < 0.01$

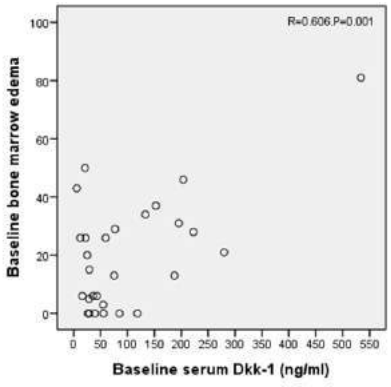

Figure 1. Serum Dkk-1 level is correlated with bone marrow edema at baseline

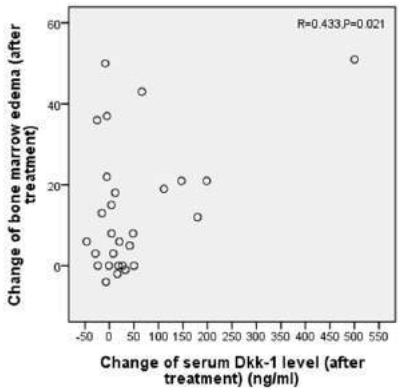

Figure 2. After treatment，the change of serum Dkk-1 level is correlated with change of bone marrow edema

Conclusion: Spinal marrow edema may have a role in predicting new bone formation in the spine, since the change of serum Dkk-1 level is correlated with change of spinal marrow edema. And Dkk-1 may participate in the molecular basis of the TNF inhibitor¡¯s blockade of new bone formation. Further research is needed on patients who have received long-term TNF antagonist treatment to find the time points when serum Dkk-1 level reaches a stabilized plateau. Increased knowledge in this area will be helpful when assessing a predictive marker for the timing of treatment withdrawal.

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Abstract Number: 729

Does the Presence of Multiple Spondyloarthritis-Features in Patients with Chronic Back Pain Always Lead to Diagnosis of Axial Spondyloarthritis?

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The number of clinical spondyloarthritis (SpA)-features plays an important role in the Assessment of SpondyloArthritis international Society (ASAS) modified Berlin algorithm for the diagnostic work-up of patients with a suspicion of axial SpA (axSpA). Therefore, we investigated whether all patients with short duration chronic back pain (CBP) and multiple SpA-features are always diagnosed as axSpA by rheumatologists and to describe the features of these patients.

Methods: The SPondyloArthritis Caught Early (SPACE)-cohort includes CBP patients (≥ 3 months, ≤ 2 years, onset < 45 years) from various rheumatology centers. Following a fixed protocol all patients underwent a full diagnostic work-up consisting of performance of MRI and radiographs of sacroiliac joints, acute phase reactants, HLA-B27, and assessment of other SpA-features (inflammatory back pain (IBP), good response to NSAIDs, family history for SpA, peripheral arthritis, dactylitis, enthesitis, uveitis, inflammatory bowel disease (IBD), and psoriasis). Each center interpreted the MRI-SI and X-SI on presence of sacroiliitis (yes/no) using global assessment as part of routine clinical practice. Total number of SpA-features was calculated after medical history taking, physical examination and measurement of acute phase reactants, excluding sacroiliac imaging and HLA-B27 status. The treating rheumatologist provided clinical diagnosis of patients and the ASAS-criteria for axSpA were used for classification.

Results: A total of 500 baseline patients were analysed in this study: 159 (31.8%) patients had ≤1 SpA-feature, 143 (28.6%) patients had 2 SpA-features, 79 (15.8%) patients had 3 SpA-features, and 119/500 (23.8%) patients had ≥4 SpA-features (Table 1). IBP, good response to NSAIDs, and positive family history for SpA were most common in all subgroups (≤1 feature: 27.0%, 8.2%, and 16.4%; 2 features: 72.0%, 35.0%, 39.9%; 3 features: 89.9%, 59.5%, 54.4%; ≥4 features: 94.1%, 82.4%, 67.2%). Of the patients with 2 and 3 SpA-features without radiographic sacroiliitis 20/127 (15.7%) and 9/74 (12.2%) did not have axSpA diagnosis despite being HLA-B27+. All patients with ≥4 SpA-features and radiographic sacroiliitis (n=28) were diagnosed with axSpA. In contrast to what would be expected by following the modified Berlin algorithm for patients with ≥4 SpA-features 18/91 patients (19.8%) with negative imaging, 4 of whom were HLA-B27+, were not diagnosed with axSpA. In the majority of patients there was concordance between fulfilment of the ASAS classification criteria and axSpA diagnosis, however 40 patients who met the criteria were not diagnosed with axSpA.

Conclusion: In this cohort of CBP patients neither the mere presence of numerous SpA-features nor fulfilment of the ASAS classification criteria did automatically lead to axSpA diagnosis. Positive imaging was the main driving factor to diagnosis

Table 1 Diagnosis and classification of patients (n=500) with ≤1, 2, 3 and ≥4 spondyloarthritis (SpA)-features after medical history taking, physical examination and measurement of acute phase reactants, followed by sacroiliac imaging and HLA-B27 testing.

Number of SpA-features	X-SI status	HLA-B27/MRI status	Rheumatologist SpA diagnosis yes	Rheumatologist SpA diagnosis no	ASAS axSpA classification yes	ASAS axSpA classification no
0-1 n=159	X-SI+ n=9	HLA-B27+/MRI+	4		4	
		HLA-B27+/MRI-	1	1	2	
		HLA-B27-/MRI+	1		1	
		HLA-B27-/MRI-	2		2	
	X-SI- n=150	HLA-B27+/MRI+	6	1	7	
		HLA-B27+/MRI-	7	16		23
		HLA-B27-/MRI+	15	6	14	7
		HLA-B27-/MRI-	2	97		99
Mean level of confidence regarding diagnosis (SD)			6.9 (2.3)	7.5 (2.4)		
2 n=143	X-SI+ n=16	HLA-B27+/MRI+	14		14	
		HLA-B27+/MRI-	1		1	
		HLA-B27-/MRI+	1		1	
		HLA-B27-/MRI-				
	X-SI- n=127	HLA-B27+/MRI+	15		15	
		HLA-B27+/MRI-	15	20	35	
		HLA-B27-/MRI+	5	2	7	
		HLA-B27-/MRI-	11	59		70
Mean level of confidence regarding diagnosis (SD)			7.6 (1.9)	6.7 (2.3)		
3 n=79	X-SI+ n=5	HLA-B27+/MRI+	3		3	
		HLA-B27+/MRI-	1		1	
		HLA-B27-/MRI+	1		1	
		HLA-B27-/MRI-				
	X-SI- n=74	HLA-B27+/MRI+	17		17	
		HLA-B27+/MRI-	11	9	20	
		HLA-B27-/MRI+	8		8	
		HLA-B27-/MRI-	8	21		29
Mean level of confidence regarding diagnosis (SD)			8.0 (1.9)	7.1 (2.0)		
≥4 n=119	X-SI+ n=28	HLA-B27+/MRI+	15		15	
		HLA-B27+/MRI-				
		HLA-B27-/MRI+	8		8	
		HLA-B27-/MRI-	5		5	
	X-SI- n=91	HLA-B27+/MRI+	16		16	
		HLA-B27+/MRI-	21	4	25	
		HLA-B27-/MRI+	8		8	
		HLA-B27-/MRI-	28	14		42
Mean level of confidence regarding diagnosis (SD)			8.0 (2.0)	7.3 (1.7)		

X-SI, radiograph of sacroiliac joints; HLA-B27, human leucocyte antigen B27; MRI-SI, magnetic resonance imaging of sacroiliac joints; Imaging according to global assessment radiologist/rheumatologist (local reading). Diagnosis based on information after full diagnostic work-up: medical history, physical examination, imaging, and laboratory testing. ASAS axSpA criteria, Assessment of SpondyloArthritis international Society criteria for axial spondyloarthritis. Mean level of confidence regarding diagnosis: 0 (not confident at all) through 10 (very confident).

of axSpA.

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Abstract Number: 730

Clinical and Quality of Life Improvements Observed with Golimumab and Infliximab in a Large Real-Life Ankylosing Spondylitis Population

Filip van Den Bosch[1], Rene-Marc Flipo[2], Jürgen Braun[3], Shiva Sajjan[4], N Vastesaeger[5], Sumesh Kachroo[6] and Marinella Govoni[7], [1]Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Rheumatology, University Hospital, Lille, France, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Merck & Co., Inc., Kenilworth, NJ, [5]Merck Sharp & Dohme, Belgium, Brussels, Belgium, [6]CORE, Merck & Co., Inc., Kenilworth, NJ, [7]Via Tasso 14, Merck Sharp & Dohme, Italy, Cento, Italy

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose : We assessed baseline parameters associated with health-related quality-of-life (HRQoL) improvement in AS patients with anti-TNF treatment (golimumab [GLM]; infliximab [IFX; originator]) in the QUality of Life as Outcomes and its VAriation with DIsease States (QUO-VADIS) study

Methods: This prospective observational study included bio-naïve AS patients (modified New York criteria) newly treated with GLM or IFX (originator). Patients were followed-up for ~6 months (data collected at BL, 3, and 6 months). Demographic and clinical characteristics, disease activity and HRQoL were summarized accordingly. The Classification and Regression Trees (CART) analysis evaluated the association of BL parameters (demographic, clinical, disease severity) with change in HRQoL at 6 months, measured by an improvement of ≥ 5 points of the Short-Form 36 (SF-36) Physical Component Summary (PCS) score. Clinical parameters included Bath AS Disease Activity Index (BASDAI), Bath AS Functional Index (BASFI), and AS Disease Activity Scores (ASDAS).

Results: 963 patients received ≥ 1 dose of medication; 78% received GLM and 22% received IFX. Mean age was 42.7 years, 61.4% were male, and 65.3% had ≥ 1 comorbidity. Mean symptom and diagnosis duration were 11.6 and 5.3 years, respectively, and 63.8%of patients were Human Leukocyte Antigen (HLA)-B27 positive. At BL, mean BASDAI, ASDAS-CRP and BASFI scores were 6.21, 3.59 and 5.34, respectively. High and very high ASDAS disease activity was observed in 41.4% and 49.3% of patients, respectively. Clinical and HRQoL improvements were shown in all collected measures following 6 months of treatment with GLM or IFX, as documented in the Table. PCS response at 6 months (improvement of ≥ 5 points from BL) was achieved in 52.3% (n=504) of patients. Using CART analysis, the baseline parameters, and their cutoff values, associated with HRQoL improvement as measured by SF-36 PCS response at 6 months were ASDAS (≥ 3.48), C-Reactive Protein (CRP) (≥ 8.55 mg/L), age (≤ 35.5 years), and BASFI (≥ 1.15). This algorithm correctly identified 57.5% (sensitivity) of the patients who had improvement on PCS >=5 points and 61.0% (specificity) of the patients who had improvement on PCS <5 points with ROC-AUC=0.61.

Conclusion: The QUO-VADIS study demonstrated clinical and HRQoL improvements over 6 months in a large, real-world population of AS patients newly treated with GLM or IFX, with results similar to clinical studies [(1)]. The study also demonstrates, for the first time, the association of parameters such as higher ASDAS, elevated CRP and younger age with improvements in HRQoL and with a more robust response. The use of these predicting factors may aid clinicians in better evaluating which patients to start on antiTNF therapy with GLM or IFX. **References:** Inman et al. *Arthritis Rheum.* 2008 Nov; 58(11): 3402-12.

Table: Improvement in Clinical and QoL Parameters Following 6 months of Treatment

	Overall population N=963	Golimumab-only cohort N=751
Mean (SD) BASDAI change from BL	-2.7 (2.3)	-2.6 (2.3)
Mean (SD) BASFI change from BL	-2.1 (2.3)	-2.2 (2.2)
BASDAI50 Response	39.5%	39.9%
ASAS20 Response	50.6%	52.6%
ASDAS Major Improvement	26.6%	26.0%
ASDAS Disease Activity Category Inactive (<1.3) Moderate (≥1.3 to ≤2.1) High (>2.1 to ≤3.5) Very High (>3.5) Missing	19.9% 21.2% 29.4% 7.0% 22.5%	20.4% 22.2% 29.6% 5.1% 22.8%
SF36 PCS responders (improvement of ≥ 5 points from BL)	52.3%	53.3%

Disclosure: F. van Den Bosch, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, UCB Pharma, 5,AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, Pfizer, UCB Pharma, 8; **R. M. Flipo**, Ipsen Pharma, 2,Menarini France, 2,Savie, 2; **J. Braun**, Abbott, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 5,Abbott, Bristol-Myers Squibb, Celgene, Celltrion, Chugai, Johnson & Johnson, MSD, Novartis, Pfizer, Roche, UCB Pharma, 2; **S. Sajjan**, Merck & Co., Inc., Kenilworth, NJ, USA;, 3; **N. Vastesaeger**, Merck Sharp & Dohme, Brussels, Belgium, 3; **S. Kachroo**, Merck & Co., Inc., Kenilworth, NJ, USA;, 3; **M. Govoni**, Merck Sharp & Dohme, Rome, Italy, 3.

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Abstract Number: 731

High Prevalence of Hip Arthritis in Patients with Ankylosing Spondylitis Treated with TNF Inhibitors

Maria Konsta[1], Michael Nurmohamed[2], J.C. van Denderen[3], Ingrid Visman[4] and I.E. Van der Horst - Bruinsma[5], [1]Amsterdam Rheumatology and Immunology Center,VUmc and Reade, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center | Reade, Amsterdam, Netherlands, [3]Center for Rheumatology and Rehabilitation, Jan van Breemen Institute, Amsterdam, Netherlands, [4]Amsterdam Rheumatology and Immunology Center, VUmc and Reade, Amsterdam, Netherlands, [5]GENRA Consortium, Amsterdam, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Hip involvement is the most frequent extraspinal arthritic manifestation of Ankylosing Spondylitis (AS) and a common cause of disability. It is present in 24% to 36% of AS patients, leading to total hip replacement (THR) in 5%. The purpose of this study was to examine the prevalence of hip arthritis in AS, to identify predictors of its development and possible gender differences.

Methods: 241 consecutive AS patients (162 men, age: 48.6±11years (mean±SD), disease duration: 23.6 ±11.2 years) were included in this cross-sectional study. The patients received initially: etanercept (n=117), adalimumab (n=89) infliximab (n=25), or golimumab (n=10). Anteroposterior X-rays of the pelvis, obtained before anti-TNF treatment initiation (i.e. baseline), were scored according to BASRI-hip scoring system. In parallel, the lateral x-rays of cervical and lumbar spine were scored using the mSASSS. The patients' disease activity and functional limitation, prior entering anti-TNF treatment, were recorded by BASDAI, ASDAS-CRP/ESR, BASFI and BASMI. Mann-Whitney, two-sample t-test and logistic regression analysis were applied. The groups averages are expressed as mean±SD, or median(IQR) according to the normality of data.

Results: Hip involvement was assessed both clinically (as pain, reduced range of motion and intermalleolar distance) and radiographically, as BASRI-h score ≥ 2 at baseline anteroposterior pelvis X-rays. Definite hip involvement was detected in 85/241(35%) patients. Bilateral THR and unilateral THR underwent 10/241(4%) and 6/241(2.5%) patients respectively. No gender difference was observed (females: 25/85(30%) vs. males 54/156(35%). The patients with hip arthritis had significantly higher BASDAI-scores (6.1± 1.7 vs. 5.4± 1.9, p=0.03), ASDAS-CRP (3.9± 0.8 vs. 3.4± 0.9, p<0.0001), CRP [12.4(4.2-32) median(IQR) vs. 7(2.5-21), p=0.001], ESR [26(8-39) vs. 14(7-30), p=0.006], compared to those without. Additionally, the aforementioned patients had higher BASFI-score (6.2±1.9vs. 4.8± 2.3, p<0.0001), BASMI-score (5±2.3vs. 3.3± 1.9, p<0.0001) and reduced intermalleolar distance (88±23 vs. 104±19 cm, p<0.0001). AS patients with hip arthritis had also higher mSASSS-scores [13.5 (2- 38.5) vs. 3(0-14), p<0.0001] and increased percentage of presence of syndesmophytes [52/84 (62%) vs.58/153 (38%), p=0.001] and peripheral arthritis [48/83 (58%) vs. 66/155 (42%), p=0.001). According to multivariate logistic regression analysis, independent risk factors for hip arthritis in AS are: ASDAS-CRP (OR:1.8, CI: 1.2-2.8), presence of syndesmophytes (OR: 2.4, CI: 1.2-5) and intermalleolar distance(OR: 0.97, CI: 0.95-0.9).

Conclusion: The prevalence of hip arthritis in AS is very high (1/3) and related to high disease activity and a high mSASSscore. No gender difference in prevalence of hip arthritis was found. Considering the large impact on function, this manifestation might need more attention.

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Abstract Number: 732

Long-Term Effect of TNF Inhibitors on Radiographic Progression in Ankylosing Spondylitis Is Associated with Syndesmophytes at Baseline and Time-Averaged CRP Levels

Maria Konsta[1,2], Grigorios Sakellariou[3], Alexios Iliopoulos[4], PETROS P SFIKAKIS[5] and I.E. Van der Horst - Bruinsma[6], [1]Amsterdam Rheumatology and Immunology Center,VUmc and Reade, Amsterdam, Netherlands, [2]First Department of Propaedeutic and Internal Medicine, Laikon Hospital, Athens University Medical School, Greece, Athens, Greece, [3]Rheumatology, Veterans Administration Hospital, Athens, Greece, [4]Department of Rheumatology, Veterans Administration Hospital, Athens, Greece, [5]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [6]GENRA Consortium, Amsterdam, Netherlands

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Although the radiographic progression in AS is associated with both baseline and time-averaged level of CRP in TNF naïve patients, the effect of level of acute phase reactants on radiographic progression in anti-TNF treated patients has not yet been investigated. The purpose of this study is to investigate whether the impact of long-term treatment with TNF inhibitors on radiographic progression in AS is associated with the level of acute phase reactants.

Methods: Seventy consecutive AS patients with long-standing anti-TNF treatment [47 men; age: 49 ± 11years (mean±SD); disease duration: 25 ± 12 years] were included in this retrospective study. Lateral X-rays of cervical and lumbar spine obtained before anti-TNF initiation were compared to those obtained after a period of 7±2.3 (range: 3-12) years. The levels of CRP and ESR were evaluated at least every 6 months. The radiographic damage was assessed by the mSASSS. New syndesmophyte formation or ΔmSASSS-score/year ≥1 unit/year was defined as radiographic progression. As ΔmSASSS-score/year was defined the difference between mSASSS at last visit and mSASSS at baseline, accounting for the time gap between radiographs. Mann-Whitney test was used to test for the differences in continuous variables between two groups, and Spearman's coefficient was used for correlations between continuous variables. Additionally, logistic regression analysis was applied.

Results: Thirty-eight AS patients (54%) showed radiographic progression. ΔmSASSS score/year was positively correlated with baseline CRP (r=0.44, p=0.0001) and baseline ESR (r=0.35, p=0.004), as well as with time-averaged CRP (r=0.3, p=0.004). Furthermore, ΔmSASSS score/year was significantly greater (p<0.0001) in patients with syndesmophytes at baseline [1 (0.6-1.8), median (IQR)] compared to those without [0 (0-0.4)]. In multivariate logistic regression analysis, independent risk factors for spinal radiographic progression during anti-TNF treatment were the presence of syndesmophytes at baseline (OR: 9.8, CI: 3-33) and the time-averaged CRP >5mg/L (OR: 6.4, CI: 1.9-21).

Conclusion: In AS patients with long-term anti-TNF treatment, radiographic progression is associated with elevated levels of time-averaged CRP. Furthermore, patients with syndesmophytes at baseline have greater radiographic progression.

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Abstract Number: 733

Efficacy and Safety of Non-Biological Therapy (Non-Biological Drugs and Non-Pharmacological Interventions): A Systematic Literature Review for the 2016 Update of the ASAS/EULAR Recommendations for the Management of Axial Spondyloarthritis

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: As part of the 2016 update of the ASAS/EULAR recommendations for the management of axSpA, we performed a systematic literature review (SLR) to assess the efficacy and safety of non-biological therapy in patients with axSpA published since the last SLR in 2009.

Methods: This SLR was performed in Medline, Embase and Cochrane databases (2009-2016) and also in 2014-2015 EULAR and ACR abstracts and included randomized controlled trials (RCT), clinical controlled trials (for efficacy and safety) and observational studies with a comparator (for safety). Any non-biological drugs or non-pharmacological therapies were eligible. All important efficacy and safety outcomes were analysed. Risk of bias was assessed according to the Cochrane and Hayden tools. Due to heterogeneity no meta-analyses were performed. When possible the Cohen´s Effect size was calculated for non-pharmacological treatments.

Results: Of 10,244 articles and 428 conference abstracts, we included 42 papers and 3 abstracts [non-biological drugs (table 1): 15 trials, 1 Cochrane review; non-pharmacological therapies: 29 trials]. A Cochrane review strengthened the efficacy and safety of NSAIDs for the treatment of axSpA. This was confirmed by two additional studies (table 1). NSAIDs used continuously compared with on-demand did not reduce the mSASSS mean change over 2 years in AS-patients with normal CRP (≤5mg/l) [1 negative RCT (0.9 vs. 0.8; p=0.62)]; while for patients with high CRP an unclear effect was found [1 positive RCT (0.2 vs. 1.7; p=0.003), 1 negative RCT (1.68 vs. 0.96; p=0.28)]. Based on 4 observational studies, there were no new findings on safety of NSAIDs. No efficacy was shown for two different doses of systemic glucocorticoids in short-term treatment (BASDAI50 week 2: 8% PBO; 27% prednisolone (PDN) 20mg; 33% PDN 50mg). No new trials on conventional synthetic (cs) DMARDs were found. Studies on non-pharmacological therapies were very heterogenous regarding type of therapy, study duration, group size and outcome parameters. All studies included patients fulfilling the mNY-criteria, only one followed the ASAS criteria. Overall they show that regular exercises can improve disease activity, function and spinal mobility in axSpA, but mostly with small improvements (table 2).

Conclusion: Efficacy and safety of NSAIDs in axSpA is confirmed. No data is found on csDMARDs. Glucocorticoids did not demonstrate efficacy in axSpA. Regular exercises can improve outcomes, but with modest effects.

Table 1 Characteristics of pharmacological non-biological studies assessing efficacy

Study	Intervention	n	Primary endpoint	Primary endpoint in each group	Time point of primary endpoint	Trial	Risk of bias
NSAIDs							
Balazcs ACR 2015	Naproxen 1000 mg/d	143	Δ Spinal Pain Intensity (VAS 0-100)	-30.6	6 weeks	(+)	unclear
	Etoricoxib 60 mg/d	660		-29.0			
	Etoricoxib 90 mg/d	144		-31.2			
Huang 2014	Celecoxib 200 mg/d	117	Δ PatGA of Pain Intensity (VAS 0-100)	-23.7 (20.6)	6 weeks	(+)	unclear
	Diclofenac 75 mg/d	115		-26.7 (22.9)			
Zheng 2014	Palisade sacroiliac joint radiofrequency neurotomy	82	Global Pain Intensity (VAS 0-10)	2.5 (2.2; 3.0)	12 weeks	(+)	high
	Celecoxib 400 mg/d	73		4.4 (4.0; 4.9)			
Sieper 2015	Diclofenac continous 150 mg/d	62	Δ mSASSS	1.28 (0.7; 1.9)	2 years	(-)	low
	Diclofenac on-demand	60		0.79 (0.2; 1.4)			
Glucocorticoids							
Haibel 2014	Placebo	13	BASDAI 50	8.0 %	2 weeks	(-)	low
	Prednisolone 20 mg/d	11		27.0 %			
	Prednisolone 50 mg/d	12		33.0 %			

(+), positive trial; (-), negative trial

Table 2 Cohen´s Effect size (mean change in score divided by the baseline standard deviation) for various outcomes of non-pharmacological interventions

Study	Intervention	n	Duration of intervention (weeks)	Primary endpoint	BASDAI	BASFI	BASMI	Pain global	ASDAS	Risk of bias
Exercises / Rehabilitation										
Dundar 2014	Aquatic exercises	35	4	NS	0.68	0.34	1.07	0.96	--	unclear
	Land-based exercises	34			0.52	0.39	0.77	0.57	--	
Kjeken 2013§	Rehabilitation program	29	3	BASDAI (+) BASFI (-)	--	--	--	--	--	unclear
	„treatment as usual"	34			--	--	--	--	--	
Niedermann 2013	Nordic walking + flexibility	53	12	Physical work capacity on bicylce (+)	0.24	-0.07	0.18	--	-0.29	unclear
	Attention control + flexibility	53			0.21	0.00	0.07	--	0.07	
Sveaas 2014	Endurance + strength training	10	12	ASDAS (-)	1.43	0.50	0.20	--	0.83	unclear
	No exercises	24			0.08	0.00	0.06	--	0.13	
Education										
Rodriguez-Lozano 2013	Education + exercises	381	24	BASDAI (+)	0.28	0.22	--	0.27	--	unclear
	Standard care*	375		BASFI (+)	0.16	0.08	--	0.15	--	
Other interventions										
Annegret 2013	Radon Spa therapy	20	4	Pain (+)	--	0.12	--	--	--	low
	Tap water baths	19			--	0.05	--	--	--	
Aydin 2013§	Low-Level Laser Therapy	19	2	NS	--	--	--	--	--	unclear
	Placebo Laser	18			--	--	--	--	--	
Stasinopoulos 2016	Laser Therapy + stretching	24	8	NS	--	0.84	--	2.48	--	unclear
	Placebo Laser + stretching	24			--	-0.11	--	0.12	--	
Turan 2014§	Magnetotherapy + exercises	35	2	Harris hip assessment index (-)	--	--	--	--	--	low
	Placebo Magnetotherapy	31			--	--	--	--	--	

Only studies with a low or an unclear risk of bias are presented. § Cohen´s ES could not be calculated for 3 studies as the results are not shown as mean (standard deviation)
*pharmacological and non-pharmacological interventions; (+), positive trial; (-), negative trial

Cohen´s Efffect size:	< 0.0 worsening	< 0.5 small change	< 0.8 moderate change	≥ 0.8 large change

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Abstract Number: 734

Lateral Spine BMD Measurement and Trabecular Bone Score Can Represent a Bone Loss in Patients with Advanced Ankylosing Spondylitis

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First publication: September 28, 2016

SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

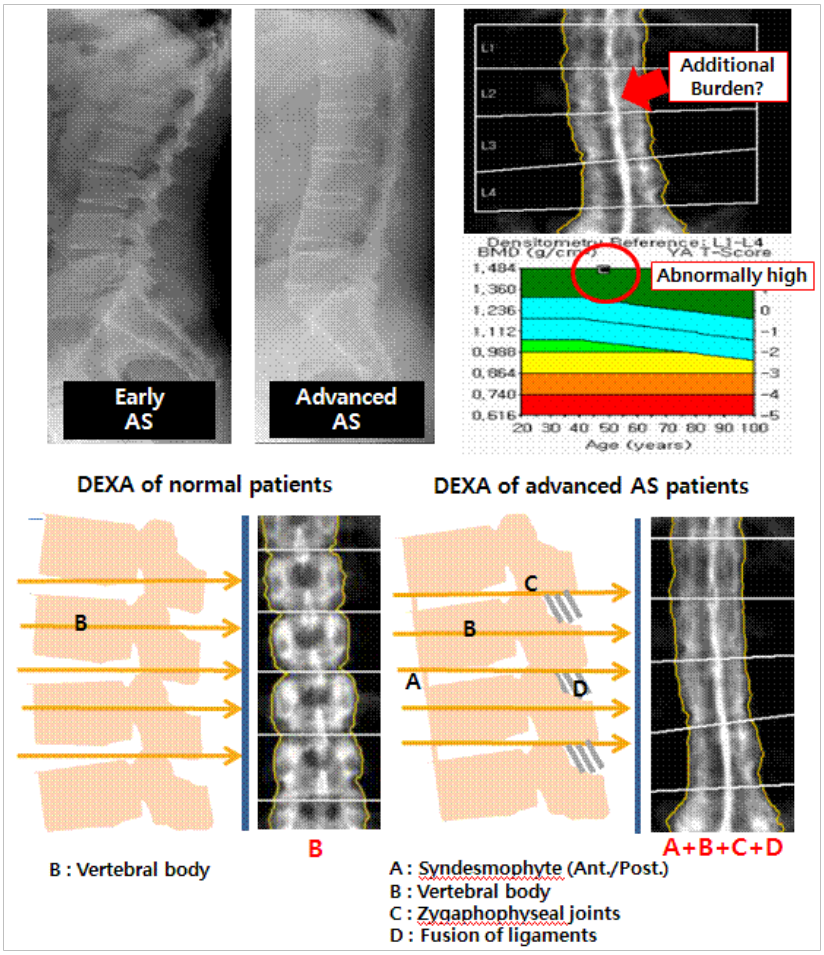
Session Time: 9:00AM-11:00AM

Background/Purpose: It is well known that osteoporosis is paradoxically common in patients with ankylosing spondylitis (AS) in spite of their new bone formation and extraosseous calcification. However, some features of advanced disease such as syndesmophyte can cause overestimation of bone marrow density (BMD) resulting normal or high BMD values even when osteoporosis is present. The aim of this study was to evaluate lateral spine BMD and trabecular bone score (TBS) as the methods to measure actual bone loss and thus redeem the obstacles of conventional BMD in patients with advanced AS.

Methods: Fifty-four patients with AS (38 males, 16 females) who assessed BMD using dual-energy X-ray absorptiometry (DXA) were retrospectively reviewed. BMD was measured by anterior-posterior (AP) lumbar (L)1-L4, lateral (Lat) L2, L3, and proximal femur projection. Trabecular bone score (TBS) L2-L4 which provides an indirect index of trabecular microarchitecture was calculated by reanalyzing AP lumbar spine image. Radiologic variables including Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s) score, modified Stroke Ankylosing Spondylitis Spine Score (mSASSS), and the presence of syndesmophyte were determined. AS patients were divided into mild, moderate, and advanced stages according to each radiologic variables, and the BMD measured by different methods were compared among those 3 groups using ANOVA.

Results: Radiologic progression of AS patients represented by BASRI-s, mSASSS, and the number of syndesmophyte was negatively correlated with Lat-L3 BMD (r=-0.431, r= -0.364, r=-0.464) and with TBS (r=-0.352, r=-0.355, r=-0.382). Moreover, patients in advanced stage (BASRI-s¡Ã3, mSASSS¡Ã10, syndesmophyte¡Ã1, respectively) showed significantly lower Lat-L3 BMD (*P*=0.047, *P*=0.012, *P*=0.006) and TBS (*P*=0.050, *P*=0.014, *P*=0.090) compared with those in mild stage, while they displayed no difference in conventional BMD from AP and femur DXA.

Conclusion: The Lat-L3 BMD and TBS have higher potency to mirror a bone loss in AS patients independent of their radiologic changes. Further studies evaluating TBS cutoff value for expecting vertebral fracture are needed.



Disclosure: **M. K. Chung**, None; **S. H. Kim**, None; **H. Kim**, None; **J. H. Koh**, None; **J. Lee**, None; **S. K. Kwok**, None; **S.**

H. Park, None; **J. H. Ju**, None.

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Abstract Number: 735

Impact of Time Since Diagnosis, Age, and Number of Prior Non-Steroidal Anti-Inflammatory Drugs on Response to Adalimumab (HUMIRA) in Patients with Ankylosing Spondylitis

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) patients (pts) were found to respond better to TNF inhibitors (TNFi) if treated early in the disease course. The objective of this analysis was to examine the impact of time since diagnosis, age, and number of prior NSAIDs as surrogates for disease duration on clinical outcomes in AS pts treated with adalimumab (ADA) in ATLAS trial.

Methods: ATLAS[1,2] was a phase III randomized double-blind trial comparing safety and efficacy of ADA with placebo (PBO) in pts with active AS who failed NSAID therapy. In this post hoc analysis, pts were categorized by baseline (BL) (1) time since diagnosis (<2 vs ≥2, <5 vs ≥5, and <10 vs ≥10 years [yrs]), (2) age (<35, 35 – 45, and >45 yrs), and (3) number of prior NSAIDs (≤ 2 vs >2). The effect of time since diagnosis, age and number of prior NSAIDs on AS outcome measures at week (wk) 12 was determined in pts who received at least one dose of ADA during the PBO-controlled period or open label extension and received prior NSAID(s) at BL.

Results: Of the 301 pts included in this analysis, a majority of them had ≥5 yrs since AS diagnosis (205 [68.1%]), were <45 yrs of age (182 [60.5%]), and had ≤2 prior NSAIDs (170 [56.5%]). Pts with shorter time since diagnosis were generally younger, while those with longer time since diagnosis were more frequently HLA-B27+. There were more men than women across all subcategories. CRP was numerically higher in patients with ≤2 prior NSAIDs. The BL disease activity measures were however numerically similar across most categories (**Table 1**). At wk 12, the proportions of pts achieving ASAS20 and ASAS40 responses were numerically higher and mean decreases in BASDAI and BASFI scores from baseline larger in subcategories with shorter time since diagnosis, lower age, and fewer prior NSAIDs (**Table 2**). The differences in the clinical outcomes were significant between <35 and >45 yrs age categories (ASAS20: P<0.001; ASAS40: P=0.003; BASDAI: P=0.002; BASFI: P=0.012).

Conclusion: Shorter time since diagnosis, younger age, and lower number of prior NSAIDs resulted in numerically greater clinical responses and improvements in disease activity and functionality following ADA treatment in pts with AS. The younger age (<35 yrs) had the largest positive impact on the clinical outcomes as compared with higher age (>45 yrs), suggesting its closest association with the actual disease duration. Overall, the results support the need for early effective treatment intervention in AS pts to improve clinical outcomes. **References:**

1. Van der Heijde, D. et al., *Ann Rheum Dis*, 2007; 67:1218-21.

2. Sieper, J. et al., *Ann Rheum Dis*, 2012; 71:700-6.

Table 1. Baseline patient demographic and disease characteristics categorized by time since diagnosis, age, and prior NSAID(s).

Characteristic	Time since diagnosis (years)						Age (years)			Prior NSAID(s)	
	<2 (n=58)	≥2 (n=243)	<5 (n=96)	≥5 (n=205)	<10 (n=163)	≥10 (n=138)	<35 (n=88)	35 – 45 (n=94)	>45 (n=119)	≤2 (n=170)	>2 (n=131)
Age, years, *mean (SD)*	37.3 (12.7)	43.5 (11.0)	38.3 (12.1)	44.2 (10.9)	38.4 (11.5)	46.8 (9.9)	28.6 (4.1)	40.1 (3.3)	54.2 (5.6)	42.5 (11.5)	42.0 (11.7)
Gender, *male : female*, %	75.9 : 24.1	75.7 : 24.3	67.7 : 32.3	79.5 : 20.5	71.8 : 28.2	80.4 : 19.6	77.3 : 22.7	71.3 : 28.7	78.2 : 21.8	78.2 : 21.8	72.5 : 27.5
HLA-B27+, *n (%)*	40 (69.0)	197 (81.1)	62 (64.6)	175 (85.4)	117 (71.8)	120 (87.0)	75 (85.2)	73 (77.7)	89 (74.8)	134 (78.8)	103 (78.6)
AS duration, years, *mean (SD)*	0.6 (0.5)	13.3 (9.0)	1.7 (1.4)	15.2 (8.8)	3.8 (3.0)	19.2 (7.7)	5.6 (5.2)	9.7 (7.4)	15.7 (11.0)	10.9 (9.8)	10.9 (9.2)
CRP, mg/dL, *mean (SD)*	2.1 (3.0)[a]	1.9 (2.4)[b]	2.1 (2.9)[d]	1.8 (2.2)[e]	1.9 (2.5)[g]	1.9 (2.4)[i]	1.7 (2.1)[k]	2.1 (2.8)[l]	1.9 (2.5)[m]	2.1 (2.9)[o]	1.6 (1.7)[q]
Total back pain[†], *mean (SD)*	69.5 (19.4)	64.4 (21.2)	67.5 (20.5)	64.5 (21.1)	66.9 (19.2)	63.6 (22.6)	61.5 (20.3)	66.1 (19.3)	66.2 (22.3)	64.0 (22.2)	67.2 (19.0)
PtGA[†], *mean (SD)*	66.4 (21.2)	62.7 (20.4)[f]	65.5 (21.0)	62.5 (20.4)[j]	64.3 (19.7)	62.5 (21.7)[r]	60.2 (20.4)	65.5 (19.6)	64.2 (21.5)[n]	62.2 (21.7)[p]	65.0 (19.1)
PhGA[†], *mean (SD)*	59.5 (18.9)	56.6 (18.6)[c]	59.4 (17.8)	56.1 (19.0)[h]	56.9 (18.0)[k]	57.4 (19.4)	55.4 (17.8)	58.4 (19.0)	57.4 (18.0)[n]	57.5 (18.9)[p]	56.6 (18.3)
BASDAI[§], *mean (SD)*	6.6 (1.8)	6.2 (1.7)	6.5 (1.7)	6.2 (1.7)	6.4 (1.6)	6.1 (1.8)	6.0 (1.7)	6.6 (1.6)	6.3 (1.7)	6.2 (0.8)	6.4 (1.5)
BASFI[§], *mean (SD)*	5.0 (2.2)	5.4 (2.2)	5.1 (2.2)	5.5 (2.2)	5.1 (2.2)	5.6 (2.3)	4.3 (2.1)	5.6 (2.1)	6.0 (2.1)	5.5 (2.3)	5.2 (2.1)

[†]Visual analog scale (VAS) 0-100 mm; [§]Visual analog scale (VAS) 0-10 cm.
[a]n=55; [b]n=241; [c]n=242; [d]n=93; [e]n=203; [f]n=204; [g]n=160; [h]n=162; [i]n=136; [j]n=137; [k]n=87; [l]n=92; [m]n=117; [n]n=118; [o]n=167; [p]n=169; [q]n=129.
Descriptive statistics and frequency distribution are reported in as observed population.
Abbreviations: NSAID = Non-Steroidal Antiinflammatory drug; HLA-B27 = Human Leukocyte Antigen B27; AS = Ankylosing Spondylitis; CRP = C-Reactive Protein; VAS = Visual Analog Scale; PtGA = Patient Global Assessment; PhGA = Physician Global Assessment; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index.

Table 2. Clinical responses at week 12 in patients categorized by time since diagnosis, age, and prior NSAID(s).

Outcome measure	Time since diagnosis (years)						Age (years)			Prior NSAID(s)	
	<2 (n=58)	≥2 (n=243)	<5 (n=96)	≥5 (n=205)	<10 (n=163)	≥10 (n=138)	<35 (n=88)	35 – 45 (n=94)	>45 (n=119)	≤2 (n=170)	>2 (n=131)
ASAS20, *n (%)*	37 (63.8)	130 (53.5)	59 (61.5)	108 (52.7)	98 (60.1)	69 (50.0)	61 (69.3)	53 (56.4)	53 (44.5)	100 (58.8)	67 (51.1)
ASAS40, *n (%)*	28 (48.3)	83 (34.2)	40 (41.7)	71 (34.6)	66 (40.5)	45 (32.6)	42 (47.7)	36 (38.3)	33 (27.7)	67 (39.4)	44 (33.6)
ΔBASDAI, *mean (SD)*[‡]	-2.7 (2.7)	-2.3 (2.3)	-2.6 (2.5)	-2.3 (2.3)	-2.5 (2.5)	-2.2 (2.2)	-2.9 (2.4)	-2.5 (2.5)	-1.9 (2.2)	-2.6 (2.3)	-2.2 (2.5)
ΔBASFI, *mean (SD)*[‡]	-1.8 (2.2)	-1.6 (1.9)	-1.7 (2.1)	-1.6 (1.9)	-1.7 (2.0)	-1.5 (1.8)	-2.0 (2.1)	-1.7 (1.9)	-1.3 (1.6)	-1.8 (2.0)	-1.4 (1.9)

[‡]Change from baseline to week 12.
Descriptive statistics and frequency distribution are reported in as observed population.
Abbreviations: NSAID = Non-Steroidal Antiinflammatory drug; ASAS = Assessment of SpondyloArthritis international Society classification criteria; BASDAI = Bath Ankylosing Spondylitis Disease Activity Index; BASFI = Bath Ankylosing Spondylitis Functional Index.

Disclosure: J. Sieper, AbbVie, Merck, Pfizer, and UCB., 9; **A. A. Deodhar**, AbbVie, Amgen, Eli Lilly, Glaxo-Smith-Kline, Merck-Sharp-Dohme, Novartis, Pfizer, Sun Pharma, and UCB., 9; **M. Hojnik**, AbbVie, 3,AbbVie, 1; **Y. Zhang**, AbbVie, 3,AbbVie, 1; **M. Dougados**, AbbVie, Lilly, Merck, Novartis, Pfizer, Sanofi, and UCB., 9.

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Abstract Number: 736

A Multi-Center, Open Label, Randomized Clinical Tries of Etanercept and Celecoxib Alone/Combined Treatment in Effectiveness and Safety of Ankylosing Spondylitis

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster I: Axial and Peripheral Spondyloarthritis – Clinical Aspects, Imaging and Treatment

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: To compare the clinical、radiographic and magnatic resonance imaging change in active

ankylosing spondylitis patients with etanercept and celecoxib alone/combined treatment，and to evaluate the effectiveness and safety on clinical and structural change of AS patients with different treatments after 24 weeks.

Methods:

A total of 92 active ankylosing spondylitis patients were included, disease activity was defined as the following three aspects: BASDAI ≥ 4 or ASDAS≥ 2.1；CRP＞6 mg/L or ESR 28 mm/1st hour；more than 2 and less than 16 syndesmophyts between cervical spine and lumber spine detected by X-ray. All patients were randomly assigned （1：1：1）to one of the three treatment groups：celecoxib 200mg bid，etanercept 50mg qw and combined therapy for 24 weeks. Disease activity was assessed with BASDAI and ASDAS, ASAS response rate was used for the evaluation of clinical efficacy. Structural change was detected using the mSASSS and SIJ SSS, and inflammation was assessed by SIJ SPARCC.

Results: A total of 92 active AS patients were included, the average age was 32.02 with mean disease duration of 9 years, the positive rate of HLA-B27 was 94.8%. The average syndesmophyts was 5.61 per patient, mSASSS and SIJ SPARCC score was 8.76 and 15.13 respectively in baseline. Erosion, fat metaplasia, backfill and ankylosis score of SSS was 3.26, 5.26, 1.09 and 3.26. After completing 24 weeks' treatment, the ASAS20 response in celecoxib, etanercept and combined group are 69.2%, 71.8% and 88.2% respectively. Of the three groups, 46.1%, 65.6% and 70.6% of patients fulfilled ASAS40 response, and almost half of patients acquired ASDAS major change. The back pain score, BASDAI, BASFI and ASDAS of three different treatment groups decreased as time extend, the combined therapy group obtained most significant change. After 24 weeks, SIJ and spine SPARCC inflammation score decreased sharply, and no statistical difference was found between three groups in four indexes of SSS. Adverse events such as upper respiration infection and slightly elevated ALT were more seen in the combined group and no SAE occurred during the research.

Conclusion: Etanercept and celecoxib alone/combined treatment were efficacious and safe in improving the symptom and sign of active AS patients, combined therapy group had the best result. The use of etanercept can alleviate inflammation detected by MRI, there were no difference of structural change between the three groups.

Disclosure: J. Gu, None; **L. Tu**, None; **M. Zhao**, None; **Z. Lin**, None; **Z. Liao**, None; **S. Cao**, None; **Q. Yu**, None; **Z. Ye**, None.

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Abstract Number: 737

Hydroxychloroquine Whole Blood Levels Do Not Associate with Hydroxychloroquine Retinopathy

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster I: Clinical Trial Design and Current Therapies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The American Academy of Ophthalmology guidelines on hydroxychloroquine retinopathy were

recently revised (Ophthalmology 2016;1-9). These guidelines recommend optical coherence tomography (OCT) with multifocal electroretinogram (mfERG) and fundus autoflorescence (FAF) as corroboratory tests. These tests can be subject to interpretation differences and require validation and repeat testing. Whether hydroxychloroquine blood levels predict retinopathy is currently unknown.

Methods: SLE patients on hydroxychloroquine underwent screening with OCT, mfERG and FAF. Hydroxychloroquine retinopathy, possible or definite, was determined by retina specialists. Patients had hydroxychloroquine blood levels (Clarke et al) determined at every clinic visit.

Results: Among the 117 patients, 95.7% were female; 50% Caucasian and 44% African-American. 12 had definite and 7 possible hydroxychloroquine retinopathy. 83.8% had no hydroxychloroquine retinopathy. Table 1: HCQ Retinopathy by HCQ Blood Level

Highest HCQ level (ng/mL)	No toxicity N (%)	Possible Toxicity N (%)	confirmed toxicity N (%)	Total
Greater than 2,000	25 (83.3)	2 (6.7)	3 (10.0)	30
1,500 to 1,999	23 (79.3)	4 (13.8)	2 (6.9)	29
1,000 to 1,499	30 (85.7)	1 (2.9)	4 (11.4)	35
500 to 999	13 (100)	0 (0)	0 (0)	13
Less than 499	7 (70.0)	0 (0)	3 (30.0)	10

Pair-wise comparison using t test with pooled Standard deviation showed that the average highest HCQ levels were not significantly different among the three groups (No vs. Possible vs. Yes) After grouping those with “confirmed” and “possible” toxicity, the average highest HCQ level was 1511.6 ng/mL vs 1591.1 ng/mL in those with vs. without retinopathy. The difference between these two groups is not significant (P = 0.7094) using t test.

Conclusion: We confirm a much higher frequency of hydroxychloroquine retinopathy (when defined by preclinical testing) than expected based on previous reports. Some SLE patients have high hydroxychloroquine levels, while on appropriate dosing by real weight. This does not correlate with current hydroxychloroquine retinopathy. Further followup will be able to prove if hydroxychloroquine blood levels predict future retinopathy.

Disclosure: M. Petri, None; **W. Fu**, None; **S. M. Shah**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hydroxychloroquine-whole-blood-levels-do-not-associate-with-hydroxychloroquine-retinopathy

Abstract Number: 738

Preventive Effect of Combined Treatment with Bisphosphonate and Vitamin D on Atherosclerosis in Patients with Systemic Lupus Erythematosus

Kazumasa Ohmura, Masaru Kato, Toshiyuki Watanabe, Ryo Hisada, Masatoshi Kanda, Sanae Shimamura, Ikuma Nakagawa, Yuka Shimizu, Kenji Oku, Toshiyuki Bohgaki, Olga Amengual, Tetsuya Horita, Shinsuke Yasuda and Tatsuya Atsumi, Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster I: Clinical Trial Design and Current Therapies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Premature atherosclerosis is one of the major complications of systemic lupus erythematosus (SLE). Preventing atherosclerosis is a key objective while monitoring patients with SLE. Recently, the biological linkage between atherosclerosis and osteoporosis has garnered much attention. The aim of this study was to explore and evaluate associations between development of atherosclerosis and anti-osteoporotic treatment. We focused on the combined treatment with bisphosphonate and vitamin D (BP+VD) on atherosclerosis and performed an unbiased cross-sectional and longitudinal study using inverse probability of treatment weighting (IPTW) based on propensity score.

Methods: Two hundred and twenty one SLE patients who received glucocorticoids (GC) at Hokkaido University Hospital between January 2012 and August 2014 were examined. Of these patients, patients who underwent carotid ultrasonography to assess subclinical atherosclerosis in clinical practice were enrolled in this study. Carotid ultrasonography was performed at baseline and during the follow-up period. Carotid plaque and plaque scores were defined as surrogate markers of subclinical atherosclerosis. Propensity score was calculated for each patients as the probability of receiving BP+VD treatment, using 8 baseline covariates including age, postmenopausal state, duration of disease, duration of GC use, current dose of GC, statin use, bone mineral status and SLEDAI-2K.

Results: A total of 108 consecutive patients with SLE were included in this study. Thirty-seven (34%) were receiving BP+VD, 26 (24%) BP alone, 29 (27%) VD alone, and 16 (%) other agents to treat or prevent osteoporosis. In 12 out of 108 patients, the propensity score could not be estimated due to unavailability of the baseline covariates. Eighty-three out of 108 patients underwent a re-evaluation of carotid ultrasonography after 104±21 months (mean ± SD). After adjustment with IPTW, the prevalence of carotid plaque at baseline was significantly less frequent in BP+VD than other treatment groups (p=0.03, McNemar test). The progression of plaque scores between baseline and follow-up was also significantly less frequent in BP+VD group (p=0.006).

Conclusion: Combined treatment with BP+VD may prevent atherosclerosis in patients with SLE. This study suggested that the new strategy in terms of preventing atherosclerosis and reducing morbidity and mortality in SLE patients might include those anti-osteoporotic medications.

Disclosure: K. Ohmura, None; **M. Kato**, None; **T. Watanabe**, None; **R. Hisada**, None; **M. Kanda**, None; **S. Shimamura**, None; **I. Nakagawa**, None; **Y. Shimizu**, None; **K. Oku**, None; **T. Bohgaki**, None; **O. Amengual**, None; **T. Horita**, None; **S. Yasuda**, None; **T. Atsumi**, None.

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Abstract Number: 739

Safety and Efficacy of Rituximab in the Treatment of Refractory Systemic Lupus Erythematosus: Results from a National Register

Stephanie Nesbit[1,2], John A. Reynolds[3], Emily Sutton[4], Eric F Morand[2], Ian N. Bruce[3] and BILAG Biologics Register Consortium, [1]University of Manchester, Manchester, United Kingdom, [2]Centre for Inflammatory Diseases, Monash University, Melbourne, Australia, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [4]University of Manchester, Manchester Academic Health Science Centre, Arthritis Research UK Centre for Epidemiology, Manchester, United Kingdom

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SESSION INFORMATION

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Session Type: ACR Poster Session A
Session Time: 9:00AM-11:00AM

Background/Purpose: Response to the anti-CD20 agent rituximab (RTX) in SLE is variable but it is still widely used for refractory SLE. Our aim was to describe the rate of response and adverse events to RTX in a large multicentre cohort.

Methods: We established a national multicentre prospective registry of patients with SLE. Patients are recruited who receive either standard therapy or a biologic, including RTX. BILAG 2004 and SLEDAI-2K are collected at baseline, 3, 6 and 12 months, then annually. We included patients who received RTX before November 2015. For efficacy analysis, we analysed those who had active SLE at baseline according to the national RTX prescribing guidelines (≥1 BILAG A or ≥2 BILAG B scores or a SLEDAI-2K ≥6 or oral steroids ≥20mg daily) and who had BILAG 2004 and SLEDAI-2K at baseline and 6 months. The primary endpoint was a modified BILAG-Based Composite Lupus Assessment (BICLA) endpoint defined as: improvement of active systems on BILAG 2004 with no worsening in other systems (all BILAG As at entry to B/C/D, all Bs to C/D, no new As, <2 new Bs); no worsening of SLEDAI-2K; no increase in oral steroid dose at 6 months. Secondary endpoints included change in global BILAG 2004 score; change in SLEDAI-2K score; change in steroid dose from baseline. We also explored a Major Clinical Response (MCR) defined as BILAG 2004 C/D/E only; SLEDAI-2K ≤4; daily oral steroid dose ≤7.5mg.

Results: 167 prospective patients commenced RTX before November 2015. 158 fulfilled ≥4 of 11 ACR criteria for classification of SLE, 3 of the remaining 9 had lupus nephritis. Baseline demographics and disease activity are shown in Table 1. The commonest RTX regime was 2x1000mg dose 14 days apart, given to 134/136 patients (98.5%) for whom dosing schedules were available. 118 patients have complete baseline and 6 month disease activity data. A BICLA response at 6 months was achieved in 57(48.3%). Over 6 months, mean global BILAG 2004 fell from 20.4 to 9.6 (mean difference 10.8, 95%CI 9.0 – 12.6, p <0.01). Mean SLEDAI-2K fell from 9.6 to 4.5 (mean difference 5.1, 95%CI 4.2 – 6.1 p<0.01) and mean daily oral steroid dose reduced from 17.0 to 11.6mg (mean difference 5.4 95%CI 3.2-7.6 p<0.01). Twelve (10.2%) patients discontinued oral steroids by 6 months and 2 commenced oral steroids. MCR was achieved in 18(15.2%) patients. In the first 6 months, 189 adverse events were reported in 90/167(54%) patients. There were 10 infusion reactions and 90 infections in 53(32%) patients including 14 serious infections. Four deaths occurred: one due to infection, two of organ failure, one of cause unknown.

Conclusion: In a large national cohort of SLE patients receiving RTX, disease activity and steroid use reduced significantly by 6 months and 48.3% achieved a BICLA response. Steroid withdrawal and MCR was evident by 6 months in some, suggesting excellent early responses in a subset warranting further characterisation.

	All patients N = 167 (%)
Age, median (IQR)	39.5 (30 – 51)
Number females (%)	154 (92.2)
Disease duration , median (IQR) years	6.8 (2.1-14.8)
Ethnicity n (%)	
Caucasian	96/156 (61.5)
Previous medications	
Hydroxychloroquine n (%)	153 (91.6)
Azathioprine	119 (71.3)
IV cyclophosphamide	42 (25.2)
Ciclosporin	19 (11.4)
Mycophenolate mofetil	118 (70.7)
Methotrexate	62 (37.1)
Current medications	
Oral steroids	145/165 (87.9)
Current oral steroid dose, median (IQR) mg	15 (10-20)
Immunological Involvement	
ANA positivity	137/145 (94.48)
dsDNA positivity	94/148 (63.5)
Low C3	50/159 (31.5)
Low C4	77/159 (48.4)
Ro positivity	80/141 (56.7)
La positivity	38/138 (27.5)
Sm positivity	47/137 (34.31)
Organ involvement	
Constitutional	28/164 (17.1)
Mucocutaneous	116/164 (70.7)
Neuropsychiatric	18/164 (11.0)
Musculoskeletal	132/164 (80.5)
Cardiorespiratory	48/164 (29.3)
Gastrointestinal	11/164 (6.7)
Ophthalmic	11/164 (6.7)
Renal	63/164 (38.4)
Haematological	94/164 (57.3)
SLEDAI median (IQR) at baseline (N=161)	8 (4-12)

Table 1: Baseline demographics and disease activity

Disclosure: S. Nesbit, None; **J. A. Reynolds**, None; **E. Sutton**, Roche Pharmaceuticals, 2,GlaxoSmithKline, 2; **E. F. Morand**, None; **I. N. Bruce**, GlaxoSmithKline, 2,Roche Pharmaceuticals, 2.

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Abstract Number: 740

Patient Adherence with Mycophenolate Mofetil Therapy in a Systemic Lupus Erythematosus Cohort: A Multi-Factorial Assessment

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lack of adherence to treatment recommendations is a serious confounder to assessment of treatment efficacy for systemic lupus erythematosus (SLE). Estimates of nonadherence with medications for SLE patients range from 10%-60%.

Methods employed to assess medication adherence in the SLE population include patient self-report questionnaires, pharmacy refill record review, physician impressions of patient adherence, and therapeutic drug monitoring; however, few studies undertake a multifactorial methodology. Mycophenolate mofetil is a viable option for induction and maintenance of lupus nephritis which lacks the gonadotoxic side effects of cyclophosphamide. However, treatment adherence is a concern. This study utilized all four methods of adherence assessment to determine the most reliable predictor of adherence for SLE patients on MMF. Methods: Adult SLE patients enrolled under the Pathogenesis and Natural History of SLE protocol receiving mycophenolate mofetil at a stable dose ranging from 0.5 grams to 1.5 grams twice daily for at least six weeks from the NIH Clinical Center Pharmacy were included in this study. Patient self-assessment of adherence was quantified using a modified Medication Adherence Self-Report Inventory (MASRI); a study tool that has been validated in SLE patients. Physicians (blinded to the patient's MASRI scores) scored patient adherence using a Likert scale with 0 being completely noncompliant and 10 being 100 % compliant. Pharmacy refill percentage for one year or from the initial date of prescription of MMF was calculated; a refill percentage greater than 80% was considered "adherent." As an objective measure of adherence, serum trough mycophenolic acid (MPA) levels were drawn with undetectable levels considered nonadherent. Patients were surveyed for demographic information and other mediators possibly related to low adherence.

Results: Adherence was assessed on 30 patients; 20 patients were considered adherent by resultant detectable MPA levels. In a univariate regression model, pharmacy refill percentage had the strongest correlation with detectable MPA levels (Pearson's Correlation r value=0.464, p-value=0.0128), while both the MASRI and the physician rating showed only modest correlations with MPA level (Pearson's Correlation r values of 0.227 and 0.202, respectively). There was a statistically significant (p=0.0041) difference in the refill percentages, with majority of the adherent cohort (80%) having refill percentages of 80% or greater. Patients in the adherent group were slightly older, with a mean age of 40.8 (p=0.0473) and were more likely to be married (p=0.0187).

Conclusion: Refill percentage was the best predictor of a detectable serum MPA level and patient adherence. Older age and being married also influenced adherence to the treatment regimen. Factors such as medication side effects, total number of medications prescribed, physician's assessment of patient adherence and educational status were not found to be significant predictors of patient adherence. Future studies are needed to more completely define specific contributors to patient nonadherence to MMF in the SLE population.

Disclosure: M. Ghaderi-Yeganeh, None; **A. Biehl**, None; **Z. G. Manna**, None; **A. Fike**, None; **S. Hasni**, None.

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Abstract Number: 741

Hydroxychloroquine Is Not Associated with Hemolytic Anemia in Glucose-6-Phosphate Dehydrogenase (G6PD) Deficient Patients

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Session Time: 9:00AM-11:00AM

Background/Purpose: Hydroxychloroquine (HCQ) is frequently used to treat autoimmune diseases. The HCQ package insert and online drug information resources report an increased risk of hemolytic anemia in patients with G6PD deficiency. However, no published studies quantify this potential risk, and the genetic forms of severe G6PD enzyme deficiency are very rare in the United States. A single abstract reported a 170 chart review, finding one G6PD deficient patient on HCQ with no adverse event. Through a retrospective chart review, we aimed to quantify the percentage of G6PD deficient patients with clinically significant hemolysis attributed to HCQ.

Methods: The Duke Medicine IRB granted approval for this study. We used a clinical search engine (Duke Enterprise Data Unified Content Explorer [DEDUCE]) to identify all patients who had a clinical visit with Duke Rheumatology, HCQ usage, and a G6PD level checked at Duke Health since 1996. A retrospective chart review was performed on all identified patients, recording demographics, G6PD levels, laboratory values consistent with hemolysis, etiology of hemolysis, and outcome of HCQ use. Data were analyzed using simple statistics.

Results: Two hundred seventy five patients met inclusion criteria by having a prior G6PD level and a prescription for HCQ. Our study population included 232 (84%) females and 43 (16%) males; 126 (46%) African Americans, 131 (48%) Caucasians, and 18 (6%) others. The leading diagnoses included 88 (32%) patients with lupus, 80 (29%) patients with rheumatoid arthritis, and 37 (14%) patients with other forms of inflammatory arthritis. Of the 275 charts reviewed, 11 (4%) of patients were G6PD deficient. The G6PD deficient patients had a total of 711 months of exposure to HCQ. One of the 11 G6PD deficient patients (9%) was found to have sulfamethoxazole/trimethoprim (TMP/SMX) induced hemolysis prior to the initiation of HCQ. This patient was later started on HCQ with no clinical adverse events noted. In 3 of 11 G6PD deficient patients, HCQ was discontinued: one after discovering G6PD deficiency (< 3 months HCQ exposure), one self-discontinued (24 months HCQ exposure), and one discontinued by hematology due to neutropenia (108 months exposure). Of the 264 patients with normal G6PD levels, 14 (5%) had hemolytic anemia at some point, caused by TTP (n=4), autoimmune hemolytic anemia (n=9), and pure red cell aplasia (n=1).

Conclusion: This is the largest study to date evaluating G6PD deficiency with concurrent use of HCQ. Among 11 patients with G6PD deficiency, only 1 had evidence of hemolytic anemia, induced by TMP/SMX prior to successfully tolerating HCQ for SLE without further hemolysis episodes. In this cohort, no G6PD deficient patients developed hemolytic anemia attributable to HCQ during 711 months exposure to the drug. These data do not support routine G6PD level measurement prior to initiating HCQ therapy.

Disclosure: S. Mohammad, None; **M. E. B. Clowse**, Pfizer, Janssen, 2,UCB Pharma, 5; **A. Eudy**, None; **L. Criscione-Schreiber**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hydroxychloroquine-is-not-associated-with-hemolytic-anemia-in-glucose-6-phosphate-dehydrogenase-g6pd-deficient-patients

Abstract Number: 742

A Pivotal Phase III, Randomized, Placebo-Controlled Study of Belimumab in Patients with Systemic Lupus Erythematosus Located in China, Japan, and South Korea

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: SLE is an autoimmune disease associated with elevated levels of B Lymphocyte Stimulator (BLyS). This study assessed the efficacy and safety of belimumab (BLyS-specific inhibitor) 10mg/kg when added to standard of care therapy compared with placebo over 52 weeks (wks) in patients with SLE located in NE Asia (China, Japan, and S. Korea).

Methods: 707 patients with SLE age ≥18 yrs with a Safety of Estrogen in Lupus National Assessment (SELENA) SLE Disease Activity Index (SLEDAI; SS) disease activity score of ≥8 at screening were randomized (2:1) 10mg/kg belimumab or placebo (NCT01345253, study BEL113750). Patients were dosed on Days 0, 14, 28 and then every 28 days through Wk 48, with a final evaluation at Wk 52. The primary endpoint was the SLE responder index (SRI) response rate at Wk 52 (reduction ≥4 points in SS score; no worsening (<0.3 increase) in Physician's Global Assessment (PGA); no new British Isles Lupus Assessment Group (BILAG). A domain score or 2 new BILAG B domain scores vs baseline. Secondary endpoints included percent of patients with ≥4 point reduction in SS score over baseline at Wk 52, SRI7 responders (SRI and ≥7 points reduction in SS) at Wk 52, number of days of daily prednisone dose ≤7.5mg and/or reduced by 50% over 52 wks, and time to first severe modified SLE Flare Index (SFI) flare.

Results: The primary endpoint was reached as an SRI response at Wk 52 was achieved in 242/446 (54.3%) evaluable patients receiving belimumab vs 87/217 (40.1%) of placebo patients [odds ratio 2.03 (95% CI 1.43, 2.88), p<0.0001]. Benefits of belimumab therapy were also observed for all 4 secondary endpoints. 55.7% of patients receiving belimumab achieved a ≥4 point reduction in SS at Wk 52 vs 42.2% on placebo (odds ratio 2.00 (95% CI: 1.41, 2.83), [p=0.0001]). An SRI7 response rate of 32.7% was achieved on belimumab vs 23.5% for placebo (odds ratio 1.78 (95% CI: 1.15, 2.77) [p=0.0099]). Among 536 patients receiving >7.5 mg/day prednisone at baseline, the median number of days prednisone was reduced to ≤7.5 mg/day and/or by 50% from baseline over 52 wks was zero for both treatments, and the 75% percentile was larger for belimumab; 213.5 days vs 172 days, rank ANCOVA p=0.0288. Belimumab patients had a 50% lower risk of experiencing a severe SFI flare relative to placebo patients (hazard ratio=0.50, 95% CI: 0.34, 0.73), p=0.0004. The overall incidence of AEs was similar between placebo (75.7%) and belimumab (74.9%). The incidence of SAEs was higher for placebo (18.3%) vs belimumab (12.3%). There were similar rates of infectious SAEs in placebo patients (5.5%) and in belimumab patients (5.3%). There was one fatality reported in the placebo group and none in the belimumab group.

Conclusion: This is the fourth pivotal belimumab trial in SLE which has achieved statistical significance for the primary endpoint. All 4 pre-specified secondary endpoints also reached statistical significance. The safety profile of IV belimumab in this NE Asia population is consistent with belimumab IV and subcutaneous data to date; no new safety issues are identified. **Disclosures:** Study funded by GSK. Submission support provided by Louisa Pettinger, Fishawack Indicia Ltd, funded by GSK.

Disclosure: F. Zhang, None; **S. C. Bae**, None; **D. Bass**, GSK, 1,GSK, 3; **M. Chu**, GSK, 1,GSK, 3; **S. Egginton**, GSK, 1,GSK, 3; **D. Gordon**, GSK, 1,GSK, 3; **D. Roth**, GSK, 1,GSK, 3; **Y. Tanaka**, Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, 2,Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline, 8; **J. Zheng**, None.

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Abstract Number: 743

Long-Term Hydroxychloroquine Therapy and Low-Dose Aspirin May Have an Additive Effectiveness in the Primary Prevention of Cardiovascular Events in Patients with Systemic Lupus Erythematosus

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Hydroxychloroquine (HCQ) is a mainstay of treatment in patients with SLE. It has been demonstrated to reduce disease activity and prevent damage accrual and suggested to give benefits on thrombosis prevention [1-2]. We have recently pointed out a role of low dose aspirin (ASA) in the primary prophylaxis of cardiovascular disease (CVD) in SLE [3]. In that study, we did not detect any time and dose-independent protective effect of antimalarials. The present analysis was performed to investigate the role of distinct HCQ cumulative dosages and treatment durations.

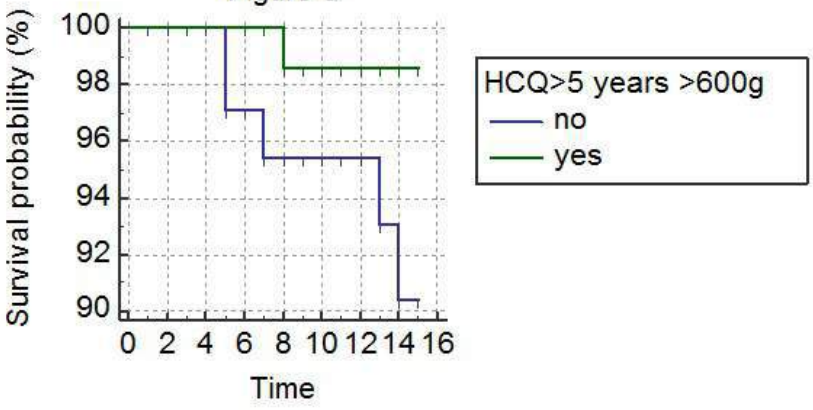
Methods: patients consecutively admitted to a tertiary center, who, at baseline, satisfied 1992 ACR and/or 2012 SLICC classification criteria for SLE and had not experienced any CV event, were enrolled. ASA treatment, daily and cumulative dosages of HCQ and treatment duration were noticed. A number of attempts were performed to identify the dosage of HCQ and its treatment duration associated with a lower incidence of CV events as assessed by evaluating CV events free survival by Kaplan-Meier curves.

Results: 189 consecutive SLE patients were enrolled and followed up for a median of 13 years (range 1-15 years). Out of them, 80.9% (153/189) had ever used HCQ, with a median treatment duration of 4 years (range 1-15). 80/153 (52.2%) had a treatment duration >5 years and 83/153 (54.2%) patients had cumulative HCQ dosages>600g. Out of the 189 patients, 31(16.4%) were treated with ASA alone and 134 (70.8%) were treated with both ASA and HCQ. During follow-up, there were 10 CV events (1 stroke, 5 TIA, and 4 MI). CV event-free rate was higher in patients treated with HCQ for more than 5 years (log-rank test $\chi 2 = 6.10$; $p= 0.01$) and in patients with a cumulative HCQ dosage >600g (log-rank test $\chi 2 = 6.45$; $p= 0.01$) [figure1-2]. Comparing the 76 patients treated by ASA and HCQ with a cumulative dosage>600g and a treatment duration >5 years with 87 the patients treated by ASA and either no HCQ or HCQ of a dosage<600g and a treatment

duration <5 years, a nearly significant difference was detected in CV events free rates (p=0.069) [figure 3].

Conclusion: Antimalarials, when administered for more than 5 years at a cumulative dosage>600g, may furtherly reduce the CV risk in SLE patients. Larger, prospective studies are needed to fully address this topic.

Figure 3



Number at risk
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Group: yes
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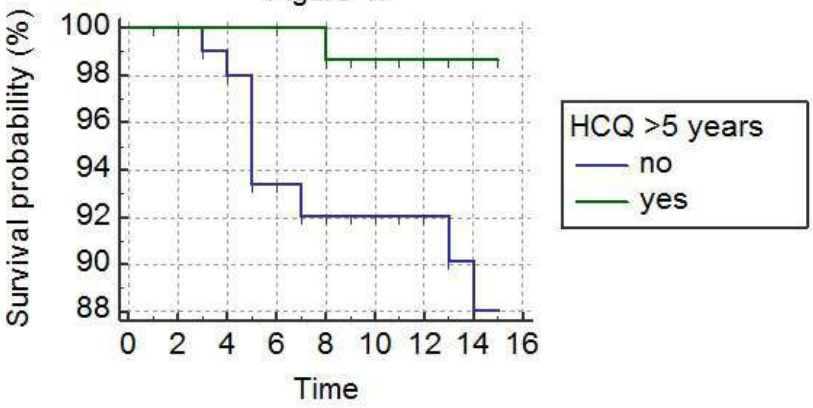
Figure 1.



Number at risk
Group: no
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Group: yes
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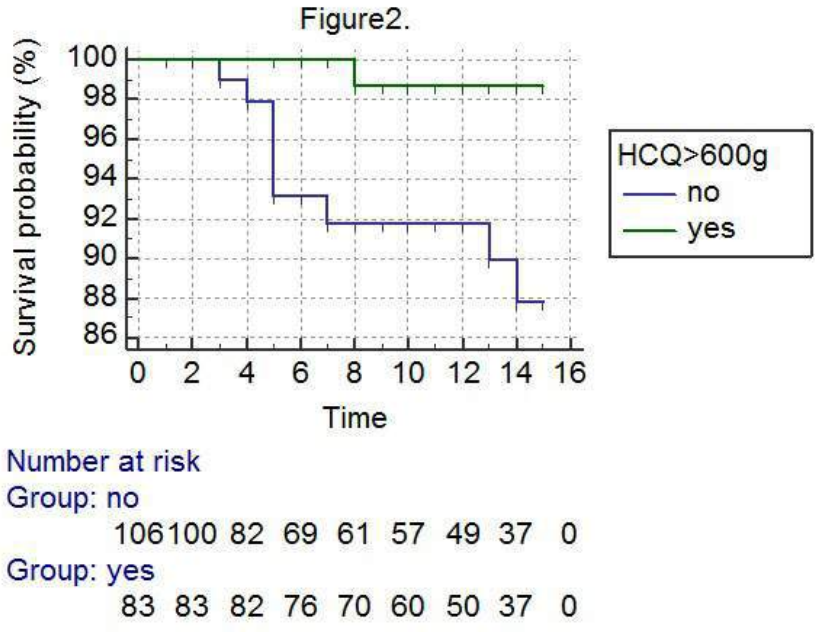

Disclosure: S. Fasano, None; **M. Iudici**, None; **I. Pantano**, None; **L. Pierro**, None; **G. Valentini**, None.

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Abstract Number: 744

Factors Related to Blood Hydroxychloroquine Concentration in Patients with Systemic Lupus Erythematosus

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Background/Purpose: To identify factors associated with blood concentrations of hydroxychloroquine (HCQ) and its major metabolite, N-desethylhydroxychloroquine (DHCQ), in patients with systemic lupus erythematosus (SLE) receiving long-term oral HCQ treatment.

Methods: SLE patients who had been taking HCQ for more than 3 months were recruited. Various clinical characteristics, laboratory values, and SLE disease activity index (SLEDAI) scores were examined. The concentration of HCQ and DHCQ ([HCQ] and [DHCQ]) was measured by liquid chromatography-mass spectrometry, and the relationship between [HCQ], [DHCQ], and [HCQ]/[DHCQ] ratio to various factors was investigated.

Results: In total, 189 SLE patients on long-term HCQ treatment were included in the analysis. The median [HCQ] was 515 (353~720) ng/ml, the median [DHCQ] was 417 (266~591) ng/ml, and the median [HCQ]/[DHCQ] ratio was 1.3 (1.0~1.7). [HCQ] was closely associated with [DHCQ] (r=0.81, p<0.0001). The weight-adjusted oral HCQ dose was strongly associated with both [HCQ] (p<0.001) and [DHCQ] (p<0.001). Time from last dose was associated with [HCQ] (p<0.001). No statistically significant association was found between renal function or smoking and [HCQ] or [DHCQ]. Additional use of immunosuppressants increased both [HCQ] and [DHCQ] after adjusting for possible confounders (p=0.04, 0.03). The lower SLEDAI score was significantly related to higher [HCQ] after adjusting for age, gender, weight adjusted HCQ dose, time from last dose, number of other immunosuppressants, and smoking status (p=0.007) (see table).

Conclusion: Various factors affected [HCQ], [DHCQ], or the [HCQ]/[DHCQ] ratio in the blood of SLE patients on long-term oral HCQ treatment. Notably, a higher [HCQ] was associated with a lower SLEDAI score, in our typical outpatient clinic population with lupus.

Table. Association between several factors and HCQ, DHCQ concentrations

	[HCQ]‡		**[DHCQ]‡**		**[HCQ]/[DHCQ]‡**	
	Estimate	p-value	Estimate	p-value	Estimate	p-value
Smoking[2]	0.28	0.10	0.29	0.16	-0.01	0.94
Smoking[6]	0.31	0.08°	0.28	0.17	0.02	0.85
# other meds[2]						
1	0.14	0.09°	0.18	0.07°	-0.04	0.54
2	0.18	0.40	0.38	0.13	-0.21	0.20
# other meds[5]						
1	0.16	0.04*	0.21	0.03*	-0.05	0.44
2	0.21	0.32	0.41	0.11	-0.19	0.24
Corticosteroid dose [2]						
<=2.5mg/d	reference		reference		reference	
>2.5, <=5mg/d	0.03	0.70	0.03	0.77	0.003	0.97
>5, <=7.5mg/d	-0.05	0.66	-0.20	0.15	0.15	0.08°
>7.5mg/d	-0.19	0.10	-0.24	0.08°	0.05	0.55
Corticosteroid dose [7]						
<=2.5mg/d	reference		reference		reference	
>2.5,<=5mg/d	0.06	0.49	0.02	0.86	0.04	0.54
>5, <=7.5mg/d	-0.03	0.77	-0.23	0.11	0.19	0.04*
>7.5mg/d	-0.11	0.38	-0.23	0.12	0.12	0.19
SLEDAI score[1]	-0.002	0.9	0.01	0.50	-0.01	0.17
SLEDAI score[2]	-0.03	0.03*	-0.02	0.27	-0.01	0.28
SLEDAI score[3]	-0.04	0.007**	-0.03	0.09°	-0.01	0.39
SLEDAI score[4]	-0.03	0.03*	-0.02	0.35	-0.02	0.16

HCQ, hydroxychloroquine; DHCQ, desethylhydroxychloroquine

ǂLog transformed for analyses

°p<0.10

*p<0.05

**p<0.01

[1]Unadjusted.

[2]Adjusted for age, gender, dose/kg/day, and time from last dose.

[3]Adjusted for age, gender, dose/kg/day, time from last dose, number of other immunosuppressants, and smoking status.

[4]Adjusted for age, gender, dose/kg/day, time from last dose, number of other immunosuppressants, smoking status, and corticosteroid dose.

[5]Adjusted for age, gender, dose/kg/day, time from last dose, SLEDAI score, smoking status, and corticosteroid dose.

[6]Adjusted for age, gender, dose/kg/day, time from last dose, number of other immunosuppressants, SLEDAI score, and corticosteroid dose.

[7]Adjusted for age, gender, dose/kg/day, time from last dose, number of other immunosuppressants, SLEDAI score, and smoking status.

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Abstract Number: 745

Clinical and Laboratory Correlates of Response in a Phase 3 Clinical Trial of Belimumab or Placebo Administered Subcutaneously Plus Standard Care to Patients with Systemic Lupus Erythematosus (SLE)

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Background/Purpose: The SRI (SLE responder index) is a composite measure established as a primary endpoint in SLE clinical trials. However, it has been questioned whether the SRI response represents a clinically meaningful change in disease state. Therefore, in order to clarify the clinical relevance of achieving the SRI, we studied clinical and laboratory correlates of the response.

Methods: Patients with SELENA-SLEDAI (SS) score ≥8, receiving stable standard of SLE care (SoC) for ≥30 days were randomized (2:1) to weekly belimumab (BEL) 200 mg or placebo (PBO), subcutaneously (prefilled syringe), plus SoC in the BLISS-SC clinical trial (BEL112341; NCT01484496). The primary endpoint of the trial was the SRI response at week 52 (≥4-point SS reduction, no worsening [<0.3 increase] in Physician's Global Assessment, and 0 new BILAG A or ≤1 new BILAG B organ domain scores, all vs baseline). Regardless of treatment received, SRI responders were compared with SRI non-responders based upon changes in clinical and laboratory parameters assessed at week 52 using the Fisher's exact test, logistic regression, analysis of covariance, and Cox regression, as appropriate.

Results: Of the 833 patients who reached week 52, 475 were SRI responders and 358 were SRI non-responders (observed population). SRI responders had statistically significantly better outcomes in multiple domains: improvements in the individual SRI components, number of improved SS and BILAG organ domain systems, reduction in prednisone use, less SFI flares (overall and severe), improvement in the FACIT-Fatigue score, and improvements in complement and anti-dsDNA antibody levels. CD20+ B cells were similar between the two groups. These results are summarized in **Table 1**. Similar observations have been seen in the Phase 3 BLISS trials following intravenous administration of belimumab or

Table 1. A comparison of changes from baseline to week 52 in clinical and laboratory parameters between SRI responders and non-responders (based upon observed population unless indicated otherwise).

	SRI responders	SRI non-responders	p-value
Patients, n	475	358	
≥4-point SELENA-SLEDAI reduction, n (%)	475 (100%)	7 (2%)	<0.0001
≥7-point SELENA-SLEDAI reduction, n (%)	231 (48.6%)	3 (0.8%)	<0.0001
BILAG improvement (no new As; ≤1B), n (%)	475 (100%)	180 (50.3%)	<0.0001
Number of organ domains improved per patient among those with organ involvement at baseline			
SELENA-SLEDAI, mean ± SE	2.08 ± 0.03	0.42 ± 0.03	<0.0001
BILAG (improvement from A or B score), mean ± SE	1.61 ± 0.03	0.45 ± 0.04	<0.0001
No worsening in PGA, n (%)	475 (100%)	178 (49.7%)	<0.0001
% change in PGA from baseline in patients, mean ± SE[a]	-64.4 ± 1.4	-23.2 ± 2.1	<0.0001
Prednisone >7.5 mg/day at week 52 in patients with baseline prednisone ≤7.5 mg/day, n/N (%)[a]	6/187 (3.2%)	20/144 (13.9%)	0.0009
Prednisone reduction by ≥25% from baseline to ≤7.5 mg/d during weeks 40–52 in patients with baseline prednisone >7.5 mg/d, n/N (%)	61/288 (21.2%)	20/214 (9.3%)	0.0002
Patients with SFI flares (all), n (%)	272 (57.3%)	256 (71.5%)	
Time to first SFI flare, median days (Q1, Q3)	223 (85, -)	113 (57, 330)	<0.0001
Patients with no SFI severe flares, n (%)	459 (96.6%)	260 (73.7%)	<0.0001
% change in FACIT-Fatigue score from baseline, mean ± SE	35.4 ± 4.0	24.7 ± 5.7	0.0102
Anti-dsDNA shifts from baseline to week 52			
Positive to Negative, n/N (%)	71/336 (21.1%)	9/140 (6.4%)	<0.0001
Negative to Positive, n/N (%)	4/127 (3.1%)	8/67 (11.9%)	0.0251
% change in anti-dsDNA from baseline, median (Q1, Q3)	-46.7 (-68.3, -10.7)	-16.7 (-49.5, 5.5)	0.0171
C3 complement shifts from baseline to week 52 Low to Normal/High, n/N (%)	87/205 (42.4%)	14/78 (17.9%)	<0.0001
% change in C3 complement from baseline, median (Q1, Q3)	6.3 (-6.8, 21.8)	-2.1 (-10.9, 12.2)	0.0024
C4 complement shifts from baseline to week 52 Low to Normal/High, n/N (%)	59/120 (49.2%)	14/45 (31.1%)	0.0523
% change in C4 complement from baseline, median (Q1, Q3)	16.7 (0, 44.4)	5.9 (-14.3, 24.1)	0.0540
% change in CD20+ B cells, median (Q1, Q3)	-44.8 (-69.5, -5.5)	-40.6 (-68.0, 3.4)	0.849

Anti-dsDNA=anti-double stranded DNA; BILAG=British Isles Lupus Assessment Group; PGA=Physician's Global Assessment; SFI=SLE Flare Index; SLEDAI=Systemic Lupus Erythematosus Disease Activity Index; FACIT=Functional Assessment of Chronic Illness Therapy; SE=standard error.

[a]Based on last observation carried forward.

placebo plus SoC (1).

Conclusion: Patients who were SRI responders in this trial, regardless of treatment, had numerous clinical and serological

benefits versus non-responders, providing strong support that the SRI response represents a clinically meaningful outcome for patients with SLE.

Reference

1. Furie R et al. *Lupus Sci Med* 2014;1:e000031.doi:10.1136/lupus-2014-000031. **Disclosures**: GlaxoSmithKline/Human Genome Sciences sponsored and conducted this clinical trial.

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Abstract Number: 746

Discrepancy in Rituximab-Induced B-Cell Depletion in Peripheral Blood and the Kidney and Relationship with Clinical Response in Patients with Lupus Nephritis

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Background/Purpose: Patients with lupus nephritis (LN) achieve variable clinical response following Rituximab (RTX) based B-cell depletion therapy, with rituximab treatment aiming to decrease the use of cyclophosphamide rescue therapy. In LN, the presence of interstitial B cells is known to be associated with renal dysfunction and active lesions. However, data on renal B-cell depletion and the clinical response to RTX in LN is limited. Therefore, we investigated the relationship between B-cell depletion in peripheral blood and the kidney, and clinical response to RTX in LN.

Methods: Six patients with LN (2 male, 4 female) had a renal biopsy performed following treatment with RTX (2 x 1g, a week apart) for on-going disease activity. Patients underwent a renal biopsy for the following reasons: decline in renal function (n=4) and nephrotic syndrome (n=2). 5 of the 6 patients had a previous renal biopsy, with 3/5 of the patients having a preceding renal biopsy in the year (between 5-8 months) prior to rituximab therapy. B-cell depletion in peripheral blood was assessed by measurement of CD19+ cells by flow cytometry. Renal B-cells were investigated using immunohistochemistry (IHC) on formalin-fixed paraffin-embedded sections using 2 different monoclonal antibodies against 2 different B-cell markers: anti-PAX-5 and anti-CD79.

Results: Patient characteristics including treatment prior to renal biopsy, serum creatinine, urine protein-creatinine ratio (PCR) and the histological type of LN are shown in Table 1. The patients had renal biopsies a median of 3 months (range 0.5 to 5 months) following rituximab. *Anti-CD79 immunohistochemistry* Five of six patients had detectable interstitial B cells with anti-CD79 staining. These patients had: (i) progressive chronic kidney disease, (ii) required 3 months of dialysis and subsequently recovered renal function but had progressive CKD and 6 years post-biopsy is approaching end-stage renal disease (ESRD) (iii) commenced peritoneal dialysis within 6 months of the renal biopsy. (iv) stable chronic kidney disease (CKD) (v) had predominantly sclerosed glomeruli with little B-cell staining and subsequently did not recover renal function and remained dialysis dependent. The 6th patient without detectable staining had a Class V LN with normal renal function at follow-up in complete disease remission. *Anti Pax-5 immunohistochemistry* Immunohistochemistry with anti-Pax-5 showed similar staining patterns to that with anti-CD79 in 4 patients. The 2 patients without detectable staining with anti-Pax-5 had Class V (patient 2) and Class VI (patient 4), Therefore staining was only present in proliferative glomerular lesions. *Peripheral B-cells* Four patients had less than 0.002 x 10^9 CD19+ cells/L; 1 patient CD19 0.042 x 10^9 cells/L and 1 patient with a Class V and with no detectable B cell infiltration, had a CD19 count of 0.03 x 10^9 cells/L at the time of renal biopsy.

Conclusion: This retrospective study demonstrates clinically relevant discrepancy in B-cell depletion between peripheral blood and the kidney in patients with LN with the persistence of interstitial B-cells suggesting resistance to rituximab-induced B-cell depletion and on-going renal inflammation. This, was associated with progressive CKD and end-stage renal failure in four patients whereas the patient with preserved renal function had no detectable B cells in the kidney. Therefore, we consider that improving B-cell depletion in the kidney may enhance clinical response to B-cell depletion therapy in lupus nephritis. Table 1. Renal biopsy data and parameters before and after rituximab.

Patient	Previous Renal biopsy Class	Previous treatment	Duration between biopsies	Class of renal biopsy after RTX	Creatinine µmol/L	PCR mg/mmol
1	IV+V	CS, CYC, MMF, Aza, CYA	7 years	V	66	371
2	n/a	CS, Aza, MMF, CYA	N/A	V	54	637
3	IV	CS, CYC	11 years	IV-GA/C	764	969
4	IV G/A	CS, CYC, MMF	8 months	VI	394	883
5	IV+V	CS, MMF	5 months	IV	461	85
6	IV-G+V	CS, CYC	5 months	IV-GA/C, V	356	627

CS-corticosteroids; CYC, cyclophosphamide; MMF, mycophenolate mofetil; Aza, Azathioprine;

Disclosure: R. J. Pepper, None; **V. Reddy**, None; **S. Henderson**, None; **M. J. Leandro**, None.

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Abstract Number: 747

The Long-Term Outcomes on Leflunomide Treatment in Patients with Lupus Nephritis: A Twelve-Year Follow-up Study

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Background/Purpose:

Leflunomide(LEF) is an effective immunosuppressant. In China, one phase III study has reported that compared with cyclophosphamide, LEF in combination with prednisone was effective in the induction therapy of proliferative lupus nephritis (LN). In 2009, The China Food and Drug Administration(CFDA) has approved LEF(leflunomide tablets, Cinkate) in the treatment of LN. However, long-term data of LEF in the maintenance treatment of LN are lacking.

To investigate the long-term outcomes of LEF in the maintenance treatment of LN in an open-label extension of a prospective multi-centre observational study.

Methods:

As the registration study, 70 patients were enrolled into LEF induction group with a loading dose of 50mg/day for 3 days, followed by 30mg/day for six months. The partial and complete remission rate was 52% and 21%. Among them, 15 patients voluntarily entered an open labeled extension study.

Results:

A total of 15 patients (mean age 39.9±7.7years) were treated with LEF for >12 months,the mean duration of LEF treatment was 11.5 years (range 8.0–13.6 years); 86.6% (13/15) of the patients were female. The mean disease duration was 14.2±3.5 years (range 8.5–23.4 years). During a median follow-up period of 11.9 years, 1 patient died from sepsis, 4 patients developed renal flare, none of patients developed in sustained doubling of serum creatinine or end-stage renal failure. The 12-year cumulative survival rates for the composite end point of death and chronic renal failure were 93.3% and 100%, respectively. At the final follow-up, the complete remission rate in the remaining patients was 64.28%(9/14), the partial remission rate was 35.72%(5/14),the mean proteinuria leval was 0.47g/day(range 0.09–1.62g/day), and the mean serum creatinine leval was 66.1umol/L(range 46-90umol/L).

Conclusion:

Our data suggest that a remission-inducing regimen of LEF followed by maintenance therapy with LEF resulted in good long-term patient survival and renal preservation. LEF can be considered as a option as maintenance therapy for patients with lupus nephritis, but its role as a long-term maintenance agent warrants further investigation.

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Abstract Number: 748

A Phase 4, Multicenter, Randomized, Open-Label Study to Evaluate the Effect of Belimumab on Vaccine Responses in Patients with Systemic Lupus

Erythematosus

Winn Chatham[1], Aneureka Chadha[2], James Fettiplace[3], Christi Kleoudis[4], Damon Bass[5], David Roth[5] and David Gordon[5], [1]University of Alabama at Birmingham, Birmingham, AL, [2]Austin Regional Clinic, Austin, TX, [3]GSK, Uxbridge, Middlesex, United Kingdom, [4]Parexel, Raleigh-Durham, NC, [5]GSK, Philadelphia, PA

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Background/Purpose: Intravenous (IV) belimumab 10 mg/kg is approved in patients with active, autoantibody-positive systemic lupus erythematosus (SLE) as add-on to standard SLE therapy (SoC). This study aimed to assess the impact of belimumab on immune response to pneumococcal vaccination in patients with SLE.

Methods: This Phase 4, randomized, open-label study (GSK Study 115470; NCT01597492) was conducted at 13 centers in the United States. Patients were randomized (7:9) to receive a 23-valent pneumococcal vaccination 4 weeks prior to (pre-belimumab cohort) or 24 weeks after (concurrent belimumab cohort) commencing 4-weekly belimumab 10 mg/kg IV treatment. All patients received SoC. All analyses of vaccine titer were performed on the as-treated population, defined as all patients who received ≥1 dose of belimumab. The primary endpoint was the proportion of patients with positive antibody responses (≥2-fold increase from pre-vaccination levels or post-vaccination level ≥0.6 µg/mL if pre-vaccination levels were unquantifiable) to ≥1 of the 23 pneumococcal vaccine serotypes 4 weeks post-vaccination. Other endpoints included the proportion of patients with positive antibody responses to ≥2 to ≥10 of the serotypes. Safety was assessed by monitoring adverse events (AEs).

Results: A total of 79 patients were enrolled and randomized to receive the pneumococcal vaccine (pre-belimumab cohort, n=34, concurrent belimumab cohort, n=45). The majority (87.3% [69/79]) completed the study; 10 patients (12.7%) withdrew (patient request, n=3; AEs, n=3; lost to follow-up, n=2; other, n=2). At Week 4 post-vaccination, 97.0% (32/33) of patients in the pre-belimumab cohort and 97.6% (40/41) in the concurrent belimumab cohort had a positive response to ≥1 of the 23 pneumococcal serotypes (as-treated population). Similarly, little difference was observed across a broader response, with 87.9% (29/33) of patients in the pre-belimumab cohort and 85.4% (35/41) in the concurrent belimumab cohort responding to ≥10 of the serotypes. The proportion of patients with an AE considered by the investigator to be treatment-related was 23.5% (8/34) in the pre-belimumab cohort and 8.9% (4/45) in the concurrent belimumab cohort. There were seven patients with non-fatal serious AEs (pre-belimumab cohort, 11.8% [n=4], concurrent belimumab cohort; 6.7% [n=3]), and no deaths were reported.

Conclusion: The proportion of patients generating a response to ≥1 pneumococcal serotype did not differ between those who were vaccinated prior to commencing belimumab and those who were vaccinated after treatment with belimumab for 24 weeks. No significant difference was also observed across a broader response (from ≥2 serotypes to ≥10 serotypes). Study funded by GSK and Human Genome Sciences, Inc. Nicole Cash, MRes, PhD, Fishawack Indicia Ltd, UK, provided submission and editorial assistance, funded by GSK.

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Abstract Number: 749

Evaluation of the Efficacy, Safety, and Tolerability of BIIB023 As an Adjunct to Standard of Care in Subjects with Lupus Nephritis

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Background/Purpose: TNF-related weak inducer of apoptosis (TWEAK) promotes renal inflammation, mesangial proliferation, tubular cell death and fibrosis in lupus nephritis (LN). TWEAK acts through its receptor, Fn14, which is upregulated in inflamed tissue but not expressed on T or B cells. We postulated that blocking the TWEAK/FN14 pathway in lupus nephritis with BIIB023, a humanized monoclonal antibody against TWEAK, would attenuate inflammation and enhance the renal response to standard-of-care (SOC) therapy without compromising safety.

Methods: ATLAS is a phase II, placebo controlled, double blind, RCT to determine whether the addition of BIIB023 (3 mg/kg or 20 mg/kg q4wk) to MMF and steroids could increase the 52-week complete or partial renal response (RR) rates in patients with proliferative lupus nephritis. Patients had centrally verified biopsies demonstrating ISN/RPS class III or IV LN and urine protein creatinine ratio (UPCR) >1 mg/mg. All patients were induced with MMF and steroids during the run-in period, but only patients with persistent UPCR >0.5 mg/mg at week 12 were eligible for the addition of BIIB023 or placebo to SOC.

Results: The study enrolled 276 subjects and randomized 188 subjects. 38 (14%) subjects completed run-in but did not qualify for randomization. The trial was prematurely terminated with 145 completing BIIB023/placebo infusions through wk 44. This group was designated the modified-ITT group, with 48 patients on placebo, 49 patients on 3 mg/kg and 48 patients on 20 mg/kg. At wk 52, complete and partial RR were: placebo: 25% (95% CI 15-35); BIIB023 3 mg/kg: 16% (8-25), and BIIB023 20 mg/kg: 31% (20-42). There were no differences between placebo and BIIB023 in time to RR or duration of RR. Dose-dependent reductions of serum and urinary TWEAK were observed. Treatment emergent adverse events were reported in 76% and 85% of placebo and BIIB023-treated subjects respectively. Serious adverse events were reported in 11% and 17% of placebo and BIIB023-treated patients, respectively.

Conclusion: The addition of an anti-TWEAK monoclonal antibody to SOC LN therapy did not improve 52-week RR rates in proliferative LN despite observed pharmacodynamic effects. This unique LN trial design, which excluded subjects who responded rapidly to SOC, requires additional assessment in order to determine the merits of studying a cohort enriched in potentially less responsive patients.

Disclosure: R. Furie, Biogen, 5; **A. Malvar**, None; **S. V. Navarra**, None; **K. Smirnakis**, Biogen, 1,Biogen, 3; **J. Kong**, Biogen Idec, 3; **N. Franchimont**, Biogen, 1,Biogen, 3; **F. Shih**, Biogen Idec, 3.

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Abstract Number: 750

Predictors of Corticosteroid Use in the Systemic Lupus International Collaborating Clinics Inception Cohort – a Multivariate Analysis

Jayne Little[1,2], Mark Lunt[3], Ben Parker[2,3], Ian N. Bruce[2,4] and The Systemic Lupus International Collaborating Clinics (SLICC), [1]Centre for Musculoskeletal Research, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [4]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

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Session Time: 9:00AM-11:00AM

Factors Associated With Oral Glucocorticoid Use in Systemic Lupus Erythematosus :

Results From a Large International Inception Cohort. Jayne Little[1], Mark Lunt[1], Ben Parker[1], Ian N. Bruce[1] and The Systemic Lupus International Collaborating Clinics (SLICC) Group, [1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, MAHSC, The University of Manchester, Manchester, United Kingdom

Background/Purpose: Glucocorticoids (GCs) are widely used in systemic lupus erythematosus (SLE). Whilst there is significant variability in how they are used, little is known about factors that explain this variability. We aimed to examine factors associated with oral GC use in a large international inception cohort.

Methods: From 2000-11, we recruited patients within 15 months of developing four or more 1997 American College of Rheumatology (ACR) criteria for SLE. Data including disease characteristics and treatment were collected at enrolment and annually thereafter. Univariate analyses were performed to explore the cross-sectional relationship between predefined demographic and clinical (independent) variables and two measures of GC use at enrolment: 1) Taking oral GCs (yes/no) and 2) Current average daily dose of oral GCs (prednisolone equivalent). For each GC outcome, independent variables significant in univariate analysis ($p<0.20$) were entered into multivariate models using backwards selection to create the final models. **Results:** We studied 1700 patients at enrolment including 1506 (88.6%) women of whom 1189 (70.0%) were taking oral GCs at a median (IQR) dose of 20 (10-30) mg daily. Over the period of study recruitment (2000-11, there was no significant temporal trend in the proportion of patients taking GC at enrolment nor in the doses used. As can be seen in Tables 1 and 2, a number of factors were independently associated with GC use including male sex, younger age, the use of immunosupressants, renal disease and higher SLEDAI2K. In addition, race/ethnicity was independently associated with higher GC use. Compared to Caucasians, the OR (95%CI) for being on GCs were 3.32 (CI: 2.14-5.15), 6.56 (CI: 4.02-10.71) & 2.80 (CI: 1.96-4.01) for patients of Hispanic, Asian and African descent respectively (table 1). Hispanics and patients of African ancestry were taking an average (CI) 3.57 (1.19-5.96)mg and 2.49 (0.16-4.82)mg more GC per day than Caucasians respectively (table 2).

		Mutivariate logistic regression analysis		
		OR	CI	p value
Age (years)		0.981	0.971 – 0.991	0.000
Sex (c.f. female)	Male	2.395	1.517 – 3.783	0.000
Race / Ethnicity (c.f. Caucasian)	Hispanic	3.319	2.138 – 5.153	0.000
	Asian	6.559	4.018 – 10.709	0.000
	African	2.804	1.959 – 4.013	0.000
	Other	1.291	0.682 – 2.443	0.433
Disease duration at diagnosis (days)		0.999	0.998 – 0.999	0.044
Active renal disease (yes/no)		2.099	1.351 – 3.263	0.001
SLEDAI-2K score		1.052	1.017 – 1.089	0.003
On immunosupressants (yes/no)		7.190	5.176 – 9.987	0.000
Diastolic BP (mmHg)		1.016	1.004 – 1.029	0.010

Table 1: Multivariate logistic analysis of factors associated oral GC prescription at enrolment (yes/no). Smoking, systolic blood pressure & diabetes were found to be non-significant in univariate analysis (p values of 0.327, 0.682 and 0.639 respectively). Date of diagnosis, use of antimalarials and BMI were removed from the multivariate model through backwards elimination (p=0646, 0 .231 & 0.084 respectively).

		Multivariate linear regression analysis		
		Beta Coefficient	CI	p value
Age (years)		-0.136	-0.206, -0.065	0.000
Race / Ethnicity	Hispanic	3.572	1.189, 5.955	0.003
	Asian	0.350	-1.956, 2.654	0.766
	African	2.491	0.161, 4.821	0.036
	Other	0.605	-3.867, 5.077	0.791
Disease duration at diagnosis (days)		-0.034	-0.041, -0.027	0.000
Active renal disease (yes/no)		5.431	3.246, 7.617	0.000
SLEDAI-2K score		0.275	0.100, 0.451	0.002
On antimalarials (yes/no)		-5.154	-6.971, -3.337	0.000
On immunosupressants (yes/no)		5.585	3.847, 7.324	0.000
Systolic BP (mmHg)		0.0864	0.034, 0.139	0.001

Table 2: Multivariate linear analysis of factors associated with outcome 2 (average daily dose of oral GC at enrolment). Date of diagnosis was non-significant at univariate analysis (p=0.196). BMI, sex & diastolic BP were removed from the multivariate model through backwards elimination (p=0.879, 0.257 & 0.189 respectively).

Conclusion: Standard of care therapy for SLE remains inadequate and over the period of study recruitment there was no significant change in how GCs were used in this cohort. A number of factors independent of disease activity and phenotype correlate with GC use and GC dose taken including race / ethnicity. A better understanding of the sources of this variation (including disease factors, socioeconomic factors, access to healthcare and physician and patient choice) may help to reduce GC use in SLE.

Disclosure: J. Little, UCB Pharma, 2; **M. Lunt**, None; **B. Parker**, None; **I. N. Bruce**, UCB Pharma, 2.

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Abstract Number: 751

Complement C4d Split Products on Erythrocytes Are Associated with Composite Measure of Disease Activity in Systemic Lupus Erythematosus Subjects Receiving Methotrexate and Hydroxychloroquine

Michelle Petri[1], Ying Qu[2], John Conklin[3], Kelley Brady[4], Robert Apilado[5] and Thierry Dervieux[6], [1]Rheumatology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Exagen Diagnostics, Vista, CA, [3]1261 Liberty Way Suite C, Exagen Diagnostics, Vista, CA, [4]R&D, Exagen Diagnostics, Vista, CA, United Kingdom, [5]Exagen Diagnostics, vista, CA, United Kingdom, [6]Research and Development, Exagen Diagnostics, Vista, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose:

We evaluated the relationships between disease activity measures and C4d split products on erythrocytes (EC4d) in SLE subjects from a subset of the Hopkins Lupus cohort treated with methotrexate (MTX) and hydroxychloroquine (HCQ). We also determined compliance by determining blood levels of these medications.

Methods:

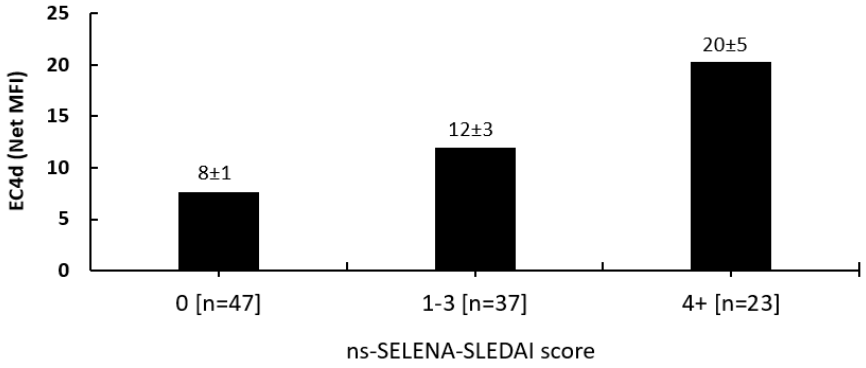
All subjects enrolled in this longitudinal study received MTX and HCQ for at least 6 months. Disease activity was assessed at each visit using the Physician Global Assessment (PGA) and the non-serological SELENA-SLEDAI (without low complement and anti-dsDNA components). Whole blood HCQ levels and red blood cells (RBC) methotrexate polyglutamate ($MTXPG_3$) levels were determined using liquid chromatography and communicated to the clinicians within 4 days of blood collection. Serum C3 and C4 levels were determined using standard immunochemistry techniques while EC4d was measured by quantitative flow cytometry (expressed as net mean fluorescence intensity [MFI] and log normalized for the analysis). Clinicians were blinded to EC4d levels throughout the study. Statistical analysis consisted of a linear mixed effects model with random intercept and fixed slope. Kruskall Wallis ANOVA was used as appropriate. Estimates are shown as average ± SEM.

Results:

Twenty-three subjects (all females, 56±3 years, average [SEM]) were enrolled and followed prospectively for at least two consecutive visits (average 4.5 visits per subject, total of 107 study visits). At baseline, whole blood HCQ levels were 1245±115 ng/ml (average dose 379±10 mg/day) and average RBC $MTXPG_3$ levels were 35±5 nmol/L (average dose 13.5±1.1 mg/week). Serum complement C3 was 105±6 mg/dl, C4 was 22±2 mg/dl, and EC4d density was 14±6 net MFI. Average ns-SELENA-SLEDAI and PGA were low in this population of SLE (1.3±0.3 and 0.6±0.1 points, respectively). Complete non-compliance to HCQ treatment (HCQ<50 ng/ml) was detected in one subject who was also not compliant to MTX therapy (RBC MTXPG<5 nmol/L). Following consultation, compliance to treatment improved as demonstrated by HCQ and $MTXPG_3$ levels rising to 539 ng/mL and 22 nmol/L at subsequent visits, respectively. Changes in C3, C4, EC4d were not associated with the change in PGA ($p>0.15$). In contrast, the change in EC4d was associated with the change in ns-SELENA-SLEDAI (intercept: 0.2±0.6, slope estimate [Log net MFI]: 0.7±0.2, $p=0.007$). Of the 107 study visits, 23 presented with active disease (ns-SELENA-SLEDAI score of 4 points or above), and 47 presented with inactive disease (ns-SELENA-SLEDAI score of 0 point). As presented in the Figure, heightened EC4d expression was associated with higher disease activity ($p<0.01$).

Conclusion:

This pilot study indicates that complement C4d split products deposited on erythrocytes are associated with the ns-SELENA-SLEDAI. Further investigations are required to establish the utility of this marker in the management of SLE.



Disclosure: M. Petri, None; **Y. Qu**, Exagen, 3; **J. Conklin**, Exagen, 3; **K. Brady**, Exagen, 3; **R. Apilado**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Abstract Number: 752

Anti-Ro Positivity Is a Predictor of Responsiveness to Topical Steroids or Hydroxychloroquine in Patients with Discoid but Not Subacute Cutaneous Lupus

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Background/Purpose: Cutaneous lupus erythematosus (CLE) lesions are difficult to treat and medications are often chosen based only on provider experience. Thus, we chose to assess the role of autoantibodies in predicting the response to disease modifying medication in subjects with subacute (sCLE) and discoid (DLE) lupus.

Methods: 306 subjects with a biopsy proven CLE diagnosis at the University of Michigan (168 sCLE; 138 DLE) between 2000-2015 were studied. Subjects with more than 2 visits with either Rheumatology or Dermatology were included in this study to assess treatment response. Demographics, clinical, immunological and SLE-related medications, including topical corticosteroids and hydroxychloroquine (HCQ) were collected. The 1997 ACR SLE criteria were used to determine the presence or absence of systemic disease at the time of CLE diagnosis. Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) for either activity or damage were assessed at the time of diagnosis and on the subsequent follow-up visit to assess response. Univariate and multivariate logistic regression analysis was used to evaluate the role of anti-Ro positivity in CLASI activity, response to HCQ and topical steroids in DLE and sCLE patients.

Results: A female predominance was observed in both groups (sCLE: 84% and DLE: 79%) with a higher percentage of

whites in the sCLE (85%) and more African Americans in the DLE (38%) subset. Age at the time of skin biopsy was (mean ± SEM) 50±17 for sCLE and 46±12 for DLE; p=0.01. ACR criterion for SLE was met in 59% of subjects with sCLE and in 28% in DLE (P<0.01). In DLE, but not sCLE, patients,simple linear regression and multivariate linear regression adjusting for age, gender, race, SLE diagnosis, lupus nephritis, the ACR criterion, marriage status, thyroid cancer status, malignancy, ANA status, Anti-sm status, APS status, and dsDNA revealed that the presence of Anti-Ro Ab is associated with higher levels of CLASI activity at the time of biopsy (simple linear regression estimate for difference between Anti-Ro positive and Anti-Ro negative: 1.83, 95% CI for difference: 0.51-3.16; P=0.007 and multivariate estimate for difference 2.27, 95% CI 0.55-4; P=0.01). Univariate logistic regression revealed that the presence of Anti-Ro in DLE is associated with decreased response to HCQ (OR: 0.34, CI: 0.14-0.83; P= 0.02) and topical steroids (OR: 0.12, CI: 0.02-0.61; P= 0.01) but is associated with increased treatment response in sCLE patients for HCQ (OR: 2.28, CI: 1.20-4.39; P=0.01). Multivariate logistic regression adjusting for age, gender, SLE diagnosis, smoking, ANA status, and Anti-sm status suggested a trend toward increased response to topical steroids in the sCLE group (OR: 3, CI: 0.81-12.94,; p=0.11). No significant predictive value for anti-Ro was noted when patients were categorized as CLE-only vs. systemic lupus.

Conclusion: Sub-classification of CLE patients by cutaneous lesion subtype and anti-Ro antibody status may help to predict which patients will respond to first line treatments such as topical steroids or hydroxychloroquine. This knowledge may help to lower the threshold for changing or modifying treatment in patients with a higher risk of non-response.

Disclosure: R. Namas, None; **C. Powell**, None; **J. M. Kahlenberg**, None.

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Abstract Number: 753

Vitamin D Improves Systolic Blood Pressure in SLE

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Background/Purpose: Vitamin D insufficiency/deficiency is common in SLE. Both a cohort study and a randomized clinical trial have proven that Vitamin D supplementation improves SLE global activity and the urine protein/cr ratio. We assessed whether there was an association between serum Vitamin D and blood pressure.

Methods: This analysis is based on clinic visits of a large SLE cohort after May 2009 when serum 25-hydroxyvitamin D was measured regularly. 1305 different patients were observed from 1 to 32 visits (the median was 10). The patients were 92% female, 50% Caucasian, 41% African American. Age ranged from 17 to 89. When the 25-OH Vitamin D level was below 40 mg/ml, the patient was prescribed supplemental vitamin D, usually 50,000 IU weekly.

Results: The “between-person” analysis addressed the question of whether those who tend to have low vitamin D also tend to have high systolic blood pressure. Among patients whose mean vitamin D was under 40, those whose mean vitamin D was 10 points higher had a mean SBP that was 3.8 mmHG lower (p<0.0001). For example, comparing those with a mean of vitamin D of 25 to those with a mean vitamin D of 35, we found a 3.8 mmHG lower mean SBP in the latter group

(Table 1). There was no evidence of an association between vitamin D levels and SBP among those with mean vitamin D greater than 40 (p=0.27 or p=0.31 for unadjusted or adjusted analysis respectively). Table 1: Difference in person-specific mean SBP per 10 ng/ml difference in person-specific mean vitamin D

Range of mean Vitamin D	Unadjusted		Adjusted[1]	
	Estimated difference in mean SBP per 10 ng/ml difference in mean Vitamin D (95% CI)	P-value	Estimated difference in mean SBP per 10 ng/ml difference in mean Vitamin D (95% CI)	P-value
0-40 ng/ml	-3.8 (-4.9, -2.8)	<0.0001	-3.5 (-4.5, -2.4)	<0.0001
40+ ng/ml	-0.7 (-2.0, 0.5)	0.27	-0.6 (-1.8, 0.6)	0.31

[1] Adjusted for age, age-squared, sex, race, proportion of time on Plaquenil, mean prednisone dose, mean BMI. The "within-person" analysis addressed the question of whether a person tends to have higher SBP when his/her vitamin D is lower than his average vitamin D (Table 2). Table 2: Difference in SBP at each visit per 10 ng/ml difference in the person's vitamin D at that visit and the person's average vitamin D.

Range of Vitamin D	Unadjusted		Adjusted[1]	
	Estimated difference in SBP (relative to a person's average SBP) as a function of differences in a person's Vitamin D levels (relative to that person's average Vitamin D levels)	P-value	Estimated difference in SBP (relative to a person's average SBP) as a function of differences in a person's Vitamin D levels (relative to that person's average Vitamin D levels)	P-value
0-40 ng/ml	-1.3 (-1.7, -1.0)	<0.0001	-1.3 (-1.7, -0.9)	<0.0001
40+ ng/ml	-0.1 (-0.3, 0.1)	0.48	0.1 (-0.4, 0.1)	0.30

[1] Adjusted for age, age-squared, sex, race, proportion of time on Plaquenil, mean prednisone dose, mean BMI. If a person's vitamin D was higher than her mean vitamin D by 10 ng/ml and she had vitamin D below 40 ng/ml, then the expected blood pressure will decrease by 1.3 mmHG (p<0.0001).

Conclusion: Both the "between person" and "within person" analyses provide evidence that among those with vitamin D below 40 ng/ml, a higher vitamin D level was associated with lower systolic BP. As with disease activity, achieving a level above 40 ng/ml did not lead to further improvement. Vitamin D supplementation has now been seen to help not just disease activity but also the most important traditional cardiovascular risk factor, hypertension.

Disclosure: M. Petri, None; **E. Barr**, None; **L. S. Magder**, None.

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Abstract Number: 754

The Duration of Anti-Malarial Agent Intake in the First 5 Years of the Disease and Prognosis in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Anti-malarial agents (AM) prevent damage in patients with systemic lupus erythematosus (SLE). We aimed to examine whether the duration of AM therapy early in the disease was associated with a reduced disease activity and the development of early damage in SLE.

Methods: An inception cohort was identified from among SLE patients, followed prospectively in a single Clinic between 1970 and December 2015. We identified the patients who had a minimum of 5 years of follow-up after the diagnosis of SLE. Duration of AM therapy was based on the percentage of the time that the patients took the medication. They were divided into three groups: patients who took AM more than 60% of the time (group A), those who took AM for less than 60% of the time (group B), and those who did not receive AM (group C) during the 5 years of follow-up. We compared the demographic, disease activity, and treatment variables among the three groups. The outcomes were measured between the baseline and the 5-year follow-up. These outcomes included the change of SLICC/ACR damage index (SDI), flare event (defined by any increase of SLE disease activity index-2K (SLEDAI-2K) between 2 consecutive visits), low disease activity at year 5 (defined by a clinical SLEDAI-2K score of 1-2 regardless of serology), adjusted mean SLEDAI-2K over 5 years of follow-up, and AM related retinal toxicity. Regression analysis models were constructed to identify the predictors of the outcomes in multivariate models controlling for gender, age, disease duration, ethnicity, disease activity, and treatment.

Results: A total of 459 patients were identified, 236 (51.4%) in group A, 88 (19.2%) in group B, and 135 (29.4%) in group C. At enrollment, gender, ethnicity, age, SLE duration, SLEDAI-2K and SDI were comparable in the three groups. The patients in group A had significantly lower cumulative dose of glucocorticoids (GC) compared to the patients in the other groups ($P<0.001$). Multivariate analysis revealed that the patients in group A had a lower risk of increasing SDI (relative risk = 0.71; 95% confidence interval (CI): 0.52, 0.95; $P = 0.02$) and were more likely to achieve low disease activity at year 5 (odd ratio = 1.96; 95% CI: 1.18, 3.26; $P = 0.01$) compared to the patients in group C. The patients taking AM more consistently had a lower cumulative dose of GC over the 5 years of follow-up ($P<0.0001$). There was only one patient with AM related retinal toxicity in each group.

Conclusion: Longer duration of anti-malarial therapy within the first 5 years of disease is associated with less disease activity and reduced risk of early progressive damage in patients with SLE.

Disclosure: R. Pakchotanon, None; **D. D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 755

Hydroxychloroquine Blood Level Monitoring in a Predominantly Hispanic Systemic Lupus Erythematosus Cohort

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Session Time: 9:00AM-11:00AM

Background/Purpose**:** Hydroxychloroquine (HCQ) is recommended for all patients with SLE. While patient reported adherence rates are between 51-64%, blood HCQ level testing may be a more accurate measure of compliance. This study aimed to evaluate the role and feasibility of blood HCQ level monitoring in a predominantly Hispanic, socioeconomically disadvantaged SLE cohort.

Methods : This is a cross-sectional study of SLE patients treated with HCQ 200–400 mg/day at the Columbia University Lupus Center. HCQ levels were measured from samples obtained during routine blood draws by high performance liquid chromatography (Avise HCQ, Exagen Diagnostics ©). Patients on HCQ for ≥ 6 months were included; patients who admitted to non-adherence before testing were excluded. Differences in demographic and clinical features between patients with therapeutic and sub-therapeutic levels were evaluated.

Results : 55 patients had blood HCQ levels tested. 50 (90.9%) were women, 41 (74.5%) Hispanic, and 8 (14.5%) Black. 46 (83.6%) resided in the Bronx or Washington Heights; 41 (74.5%) were insured by public assistance programs. 28 (50.9%) were on additional immunosuppressants; 8 (14.6%) had abnormal renal function. The mean SLEDAI was 4.7 (range 0-20). Therapeutic blood HCQ is considered to be ≥ 1000 ng/mL based on prior data; in this cohort, median HCQ level was 722 (range 0-2466 ng/mL); 34 (61.8%) patients had sub-therapeutic levels (mean 346.6 ng/mL), and 10 (18.2%) had undetectable levels. Hispanic ethnicity and normal renal function were associated with sub-therapeutic HCQ. Patients on mycophenolate mofetil (MMF) for any indication were more likely to have therapeutic HCQ (Table). In a subset of patients on MMF with concurrent mycophenolate levels (n=7), the two drug levels correlated (r=0.544). Median SLEDAI scores were 2 in patients with therapeutic HCQ vs. 5 in sub-therapeutic patients (p=0.066). SLEDAI scores inversely correlated with HCQ levels (r= -0.326).

Conclusion : 62% of SLE patients in this cohort had sub-therapeutic HCQ levels despite self-reported adherence, suggesting that blood HCQ testing may be more accurate at assessing compliance. Low HCQ levels were associated with increased SLE activity; routine testing of HCQ levels and compliance counseling—especially when immunosuppression is withdrawn—is likely to improve outcomes. Future studies are needed to identify how genetics, renal clearance, and MMF might affect HCQ's pharmacokinetics.

	Total Population with SLE	Therapeutic (≥1000ng/mL)	Sub-therapeutic (<1000ng/mL)	p-value
Number of patients	55	21	34	
HCQ level (ng/ml) ± SEM	765.6 ± 85.1	1444.0 ± 54.3	346.6 ± 78.2	
HCQ level = 0 n (%)	10 (18.2)		10 (29.4)	
HCQ dosage				
400mg n (%)	50 (90.9)	21 (100)	29 (85.3)	
200-300mg n (%)	5 (9.1)	0 (0)	5 (14.7)	
Age (years) ± SEM	38.3 ± 1.8	37.0 ± 2.4	39.1 ± 2.7	NS
Female n (%)	50 (90.9)	20 (95.2)	30 (88.2)	NS
Ethnicity				
Hispanic n (%)	41 (74.5)	12 (57.1)	29 (85.3)	**0.020**
Non-Hispanic n (%)	14 (25.4)	9 (42.9)	5 (14.7)	
Body mass index (kg/m2) ± SEM	28.8 ± 0.8	29.3 ± 1.1	28.5 ± 1.3	NS
New York City Neighborhood				
Bronx n (%)	22 (40.0)	9 (42.9)	13 (38.2)	NS
Washington Heights n (%)	24 (43.6)	8 (38.1)	16 (47.1)	NS
Other n (%)	9 (16.4)	4 (19.0)	5 (14.7)	NS
Smoking n (%)	6 (10.9)	3 (14.3)	3 (8.8)	NS
Normal eGFR >60 n (%)	47 (85.5)	15 (71.4)	32 (94.1)	**0.020**
SLEDAI (IQR)	3 (0.5, 7)	2 (0,5)	5 (2,8)	0.066
Rheumatologist				
Attendings n (%)	19 (34.5)	9 (42.9)	10 (29.4)	NS
Fellows n (%)	36 (65.5)	12 (57.1)	24 (70.6)	
Insurance				
Private n (%)	14 (25.5)	8 (38.1)	6 (17.6)	0.091
Public n (%)	41 (74.5)	13 (61.9)	28 (82.4)	
Immunosupressants n (%)	28 (50.9)	14 (66.7)	14 (41.2)	0.066
MMF	16 (29.1)	10	6	**0.017**
MTX	3 (5.5)	0	3	NS
AZA	6 (10.9)	3	3	NS
Other	3 (5.5)	1	2	NS
Prednisone n (%)	19 (34.5)	10 (47.6)	9 (26.5)	NS

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Abstract Number: 756

Pharmacokinetics and Exposure-Response Relationship of Belimumab Administered Subcutaneously to SLE Patients

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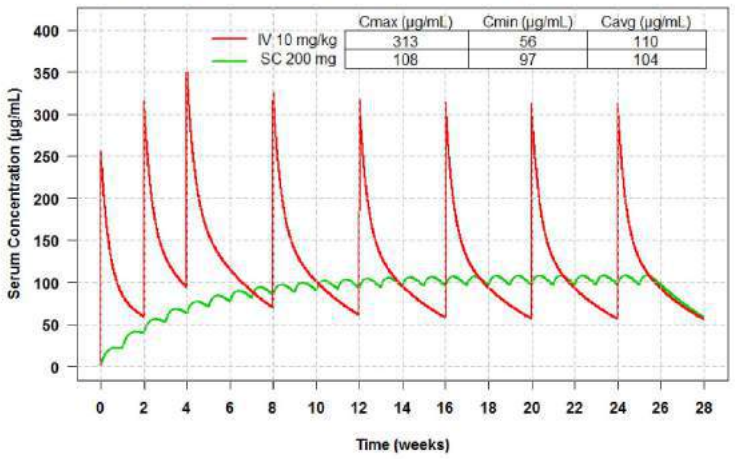
Background/Purpose: Monthly (q4w) intravenously (IV) administered belimumab 10 mg/kg is approved for the treatment of adults with active, autoantibody-positive SLE receiving standard therapy. The present analysis was conducted to characterize the exposure and exposure-response of belimumab administered subcutaneously (SC) in adult SLE patients.

Methods: Belimumab PK (n=554) and clinical response data from the SC SLE Phase 3 trial (BEL112341/NCT01484496) combined with serially sampled PK data in healthy volunteers from two Phase 1 trials (n=134; BEL114448/NCT01583530, BEL116119/NCT01516450) were analyzed with a population PK/PD (popPK/PD) approach. Following popPK model development, typical PK profiles were simulated using population parameters from this analysis and the IV popPK. A logistic regression model for efficacy response (SRI; SLE Responder Index) was developed to characterize dependencies of SRI response to individual exposures and other patient characteristics.

Results: The PK of belimumab administered SC was best described by a linear 2-compartment model with first order absorption and absorption lag time with a terminal half-life of 18.3 days. Body weight, BMI, albumin and IgG had statistically significant effects on the PK parameters, albeit with a minor effect size compared to random exposure variability. Simulations with PK parameters from this and the IV popPK analysis, demonstrated that the weekly 200 mg SC regimen results in steady-state Cavg equivalent to the 10 mg/kg IV every 4 weeks regimen (Fig.1). In the final SRI logistic regression model exposure (Cavg) was not statistically significant (α=0.05); only baseline disease activity (SELENA-SLEDAI), proteinuria (>0.5 g/day), African-American and American-Indian/Alaskan-Native race categories were identified as significant predictors of responder status.

Fig. 1: Comparison of simulated PK profiles and steady-state PK parameters for proto-typical subject receiving belimumab IV 10 mg/kg 3xq2w then q4w vs. SC 200 mg qw



Conclusion: 200 mg SC qw dosing in SLE patients resulted in steady-state belimumab Cavg comparable to the Cavg for 10 mg/kg IV q4w dosing, the approved belimumab IV dosing regimen. The popPK/PD analysis showed that exposure did not have a statistically significant impact on the SRI response. These results confirm that 200 mg qw belimumab is appropriate for subcutaneous administration to SLE patients and that no dose adjustment is required for adult patients to maintain efficacy and safety demonstrated in BLISS-SC. **Disclosure:** GSK funded this study.

Disclosure: H. Struemper, GSK, 1; **M. Thapar**, None; **D. Gordon**, GSK, 1,GSK, 3; **D. Roth**, GSK, 1,GSK, 3.

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Abstract Number: 757

Measures of Disease Activity in Patients with Persistently Active Systemic Lupus Erythematosus (SLE): Results from a Two-Part 52 Week Pilot Study of Repository Corticotropin Injection (H.P. Acthar® Gel)

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Background/Purpose: Multiple outcome measures have been utilized in SLE clinical trials. Consistency of response assessed by different instruments enhances confidence in the efficacy of pharmacologic interventions. We recently reported results from both phases of a two-part pilot study [8 week double-blind (DB) placebo (PBO)-controlled phase followed by a 44 week open-label extension (OLE)] of repository corticotropin injection (RCI) in subjects with persistent SLE disease activity requiring corticosteroids. Although the primary endpoint of the DB phase (a novel responder index described below, assessed at Week 4) was not met, RCI therapy led to improvement in several measures of disease activity by week 8. This post hoc analysis evaluated the efficacy of RCI over the entire 52 week study, as assessed by multiple standard disease activity indices (DAIs) and by a novel composite measure of organ-specific disease activity.

Methods: Thirty eight subjects with active SLE including rash and/or arthritis despite moderate dose corticosteroids were randomized to RCI (n=26) or PBO (n=12) for the DB period; 33 completed through Wk 8 and entered the OLE (RCI/RCI n=22, PBO/RCI n=11), and 20 completed through Week 52 (RCI/RCI, n=13; PBO/RCI, n=7). There were 36 subjects in the mITT population (RCI/RCI, n=25; PBO/RCI, n=11). Efficacy of RCI was assessed every 4 weeks by total BILAG, SLE responder index (SRI), Cutaneous Lupus Disease Area & Severity Index (CLASI) Activity, Tender & Swollen Joint Count, Physicians Global Assessment (PGA), severe flare by SFI, and by hybrid SLEDAI (hSLEDAI) score every 2 weeks for the first 8 weeks, then every 4 weeks for the remainder of the combined 52 week study. A novel organ-specific composite responder index, defined as decrease in hSLEDAI score from 4 to 0 for arthritis OR decrease in hSLEDAI score from 2 to 0 for rash AND no BILAG worsening in any other organ systems as compared to study baseline, was also evaluated at 4 week intervals. RCI dose was defined by the protocol during the DB phase (Weeks 1-8), but could be adjusted within specified parameters by the investigator to achieve stable improvement in disease activity during the OLE (Weeks 9-28). Corticosteroid dose was required to remain stable through Week 20, after which taper was encouraged.

Results: See Table

Conclusion: Disease activity, reflected by several standard outcome measures, was generally concordant at both Weeks 8 and 52, with improvement in most DAIs seen at Week 8 for subjects randomized to RCI, but not PBO, during the DB phase, and for all subjects in the OLE at Week 52. Directional trends in the novel organ-specific responder index employed were similar to those for standard DAIs at week 8 but did not seem to mirror other DAIs at Week 52. Inconsistency between the novel organ-specific responder index and standard DAIs at Week 52 likely relate to a higher BILAG threshold to be considered a responder for the novel index.

		Wk 0 (DB baseline)	Wk 8 (OLE baseline)	Wk 52
RCI/RCI				
Total hSLEDAI	Mean (SD)	10.0 (3.32)	5.8 (3.02)	3.5 (3.53)
Total BILAG-2004	Mean (SD)	15.7 (5.93)	6.8 (4.31)	4.6 (6.01)
CLASI Activity score*	Mean (SD)	6.7 (6.31)	3.9 (4.26)	1.3 (1.55)
Tender & Swollen Joint Count*	Mean (SD)	7.4 (5.79)	1.4 (2.32)	0.9 (2.51)
PGA	Mean (SD)	54.4 (13.04)	28.7 (21.05)	15.6 (16.46)
Novel Responder Index	Proportion (%)	n/a	11/25 (44.0)	3/25 (12.0)
Novel Responder Index revised**	Proportion (%)	n/a	15/25 (60.0)	12/25 (48.0)
SRI	Proportion (%)	n/a	13/25 (52.0)	10/25 (40.0)
hSLEDAI decrease ≥ 4	Proportion (%)	n/a	15/25 (60.0)	10/25 (40.0)
Prednisone ≤ 7.5 mg/day	Proportion (%)	n/a	n/a	9/25 (36.0)
Severe flare (SFI)	Proportion (%)	n/a	2/25 (8.0)	4/25 (16.0)
PBO/RCI				
Total hSLEDAI	Mean (SD)	9.8 (2.09)	9.1 (3.42)	3.3 (2.50)
Total BILAG-2004	Mean (SD)	15.4 (9.55)	13.5 (8.82)	2.6 (2.88)
CLASI Activity score*	Mean (SD)	7.4 (6.60)	7.0 (7.00)	0.5 (0.84)
Tender & Swollen Joint Count*	Mean (SD)	5.1 (4.86)	2.2 (3.19)	1.6 (2.61)
PGA	Mean (SD)	52.6 (12.52)	39.1 (27.24)	11.7 (13.19)
Novel Responder Index	Proportion (%)	n/a	3/11 (27.3)	4/11 (36.4)
Novel Responder Index revised**	Proportion (%)	n/a	4/11 (36.4)	6/11 (54.5)
SRI	Proportion (%)	n/a	1/11 (9.1)	6/11 (54.5)
hSLEDAI decrease ≥ 4	Proportion (%)	n/a	1/11 (9.1)	6/11 (54.5)
Prednisone ≤ 7.5 mg/day	Proportion (%)	n/a	n/a	3/11 (27.3)
Severe flare (SFI)	Proportion (%)	n/a	1/11 (9.1)	3/11 (27.3)
*Calculated for those with score > 0 at DB baseline **Novel responder index calculated using SRI definition for BILAG worsening				

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Abstract Number: 758

Relationship Between Corticosteroids and Adverse Events in SLE –Data from the Clinical Trial Belimumab in Subjects with Systemic Lupus Erythematosus

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Session Time: 9:00AM-11:00AM

Background/Purpose: Corticosteroids (CSs) are widely used in Systemic Lupus Erythematosus (SLE) patients, but have side-effects when used for prolonged periods of time. Our aim was to obtain a better understanding of the relationship between exposures to CSs and adverse events (AEs) in a large trial.

Methods: We used data from the BLISS-76 trial, phase 3 randomized, placebo-controlled study of belimumab[1]. Reported AEs were grouped according to medical relevance. The frequencies of these groups were compared between the lowest versus the highest tertile of cumulative CS doses. Additionally, we studied the relationship between AEs and patients with and without CSs at baseline.

Results: 991 AEs were reported in 819 patients of the trial. Of 714 patients (86%) treated at least once with CSs prior/during the trial, 235 were in the lowest tertile of cumulative CS dose(<5.3g) and 236 in the highest (≥10.5g) tertile. The following AEs: viral upper respiratory tract infection, viral gastroenteritis, allergic rhinitis, sinusitis, arthralgia, dental caries and bronchitis were more frequent in the lowest as compared to the highest tertile of CS doses. Only tachycardia and proteinuria were significantly more frequent in the highest tertile (Table1). Eight groups of AEs were more frequent in the lowest tertile as compared to the highest (Table2). At baseline, 76% of patients were treated with CSs. The frequencies of 4 AEs (anaemia, pyrexia, oral herpes and malaise) were significantly higher compared to those not treated with CSs. Conversely, the frequencies of several AEs was higher in patients without CSs at baseline (Table 3), most notably; asthma, infusion related reaction, nausea, seasonal allergy, sinusitis and viral upper respiratory tract infection.

Conclusion: Our study demonstrates the association of CSs with CS-specific AEs in a large RCT and highlights the feasibility of post-hoc analysis of data from RCT to extract valuable safety signals. Contrary to expectations, there were also associations between lower cumulative CS dosage and a range of AEs.

AEs	AEs with Cumulative CS Dose (%)		P value
	Lowest tertile (< 5.3 g) N=235	Highest tertile (≥ 10.5 g) N=236	
Tachycardia	0	6 (2.5)	0.03
Proteinuria	0	8 (3.4)	0.007
Viral Upper respiratory tract infection	20 (8.5)	5 (2.1)	0.002
Viral gastroenteritis	17 (7.2)	4 (1.7)	0.004
Allergic rhinitis	12 (5.1)	2 (0.9)	0.007
Sinusitis	38 (16.2)	13 (5.5)	<0.001
Arthralgia	53 (22.6)	30 (12.7)	0.005
Nasopharyngitis	37 (15.7)	20 (8.5)	0.02
Dental Caries	8 (3.4)	1 (0.4)	0.02
Bronchitis	29 (12.3)	15 (6.4)	0.03

Table 1. The frequency of AEs in lower vs. higher cumulative CS dose.

AE groups	% with lower CS cumulative dose(<5.3g) N=235	% with higher CS cumulative dose(≥10.5 g) N=236	P value
Arthritis, Arthralgia, Bacterial arthritis, Arthropathy, Gout, Joint crepitation, Joint effusion, Joint stiffness, Joint swelling, Meniscus lesion, Metatarsalgia, Myofascial pain syndrome, Periarthritis, Periostitis, Plantar fasciitis, Polyarthritis, Sacroiliitis, SLE arthritis, Synovitis, Temporomandibular joint syndrome	73 (31.1)	47 (19.9)	0.006
Nasopharyngitis, Pharyngitis, Bacterial pharyngitis, Streptococcal pharyngitis, Pharyngotonsillitis	51 (21.7)	29 (12.3)	0.007
Bronchitis, Bacteria bronchitis, Viral bronchitis, Sinobronchitis, Bronchopneumonia, Haemophilus infection, Lower respiratory tract infection, Productive cough	34 (14.5)	17 (7.2)	0.01
Fatigue, Malaise	31 (13.2)	17 (7.2)	0.03
Disseminated cytomegaloviral infection, Hand-foot-and-mouth disease, Mumps, Oral viral infection, Viral diarrhoea, Viral pharyngitis, Viral upper respiratory tract infection	23 (9.8)	11 (4.7)	0.03
Rhinitis, Bacterial rhinitis, Rhinitis allergic, Rhinitis seasonal, Rhinorrhoea, Vasomotor rhinitis, Viral rhinitis, Postnasal drip	24 (10.2)	11 (4.7)	0.02
Dry eye, Dry lip, Dry mouth, Dry skin, Dry throat, Keratoconjunctivitis sicca, Nasal dryness, Sialoadenitis, Sicca syndrome, Sjögrens' syndrome, Vulvovaginal dryness, Xerophtalmia	11 (4.7)	3 (1.3)	0.03
Conjunctivitis, Allergic Conjunctivitis, Bacterial Conjunctivitis, Infective conjunctivitis, Viral conjunctivitis, Conjunctival irritation	15 (6.4)	5 (2.1)	0.02

Table 2. The frequency of groups of AEs in lower vs. higher cumulative CS dose

AEs	CS		P value
	With N=623 (%)	Without N=196 (%)	
Anaemia	35 (5.6)	3 (1.5)	0.02
Malaise	13 (2.1)	0	0.046
Oral herpes	31 (5.0)	3 (1.5)	0.04
Pyrexia	63 (10.1)	10 (5.1)	0.03
Astma	1 (0.2)	6 (3.1)	0.001
Flank pain	5 (0.8)	6 (3.1)	0.03
Gastroenteritis viral	19 (3.1)	13 (6.6)	0.03
Infusion related reaction	8 (1.3)	9 (4.6)	0.009
Meniscus lesion	1 (0.2)	3 (1.5)	0.045
Nausea	76 (12.2)	40 (20.4)	0.007
Nephrolithiasis	4 (0.6)	5 (2.6)	0.04
Non cardiac chest pain	21 (3.4)	14 (7.1)	0.04
Rash pruritic	6 (1.0)	6 (3.1)	0.04
Seasonal allergy	10 (1.6)	11 (5.6)	0.007
Sinusitis	55 (8.8)	34 (17.4)	0.002
Sjögrens syndrome	1 (0.2)	3 (1.5)	0.045
Viral upper respiratory tract infection	22 (3.5)	20 (10.2)	<0.001

Table 3. Significant AEs in patients with and without CS at baseline

Disclosure: S. Emamikia, None; **C. Gentline**, None; **M. Backheden**, None; **K. Chatzidionysiou**, None; **L. Arnaud**, GSK, 5; **R. F. van Vollenhoven**, AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB,Biotest,Crescendo,Janssen, Lilly, Merck, Vertex, 9.

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Abstract Number: 759

Gene Signature for Glucocorticoid, from in Vitro to In Vivo

Yanhua Sarah Hu[1], Somnath Bandyopadhyay[1], Deborah Furst[1], A Johnsen[1], Robert Latek[1], Steven G. Nadler[2] and Julie Carman[3], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Immunosciences Translational Research, Bristol-Myers Squibb, Princeton, NJ, [3]Discovery Translational Sciences Group, Bristol-Myers Squibb, Princeton, NJ

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Background/Purpose: Steroids are widely used in clinical practice for treating systemic lupus erythematosus (SLE), and can have a strong effect on immune cells in Whole Blood (WB), especially B cells and T-cells. Steroids are often used as background medication during clinical trials of SLE drugs and therefore can easily confound efficacy end points associated with therapies targeting B cells and T cells in the trials. Moreover, response to steroids might vary from individual to individual and might not completely agree with protocol steroid usage. Our goal is to create a gene signature as an objective measure of steroid response that can be used in SLE trials to aid in the interpretation of potential confounding steroid effects.

Methods: We conducted 5 in vitro experiments where PBMCs from normal healthy volunteers were treated with prednisolone. Differential gene expression analysis identified genes that were up regulated by prednisolone treatment, and 64 common genes were identified as a potential prednisolone gene signature. Composite scores of the prednisolone signature were calculated using the Single-sample Gene Set Enrichment Analysis (ssGSEA) algorithm (Barbie et al., 2009) for WB samples treated in vitro with prednisolone. The same was done for whole blood samples from normal healthy subjects who had in vivo administration of either a selective glucocorticoid receptor agonist (SEGRA) or prednisolone in a phase I study. The prednisolone signature was further investigated in baseline WB samples of SLE patients from a multicenter, exploratory, phase IIb randomized, double-blind, placebo controlled trial, and signature scores were compared to neutrophil counts and protocol steroid usage.

Results: Both the in vitro and in vivo studies showed the high specificity of the prednisolone signature. When applied to WB gene expression data from SLE patients, the prednisolone signature scores were positively correlated with neutrophil counts (CBC) in WB, and negatively correlated with in vitro derived T cell and B cell signature scores. Both of these observations can be explained by the steroid mechanism of action. Steroid signature scores did not completely correlate with protocol steroid usage.

Conclusion: We identified a highly specific steroid gene signature that can be used to account for effects of steroids in global clinical trials where PAX gene tubes are routinely collected.

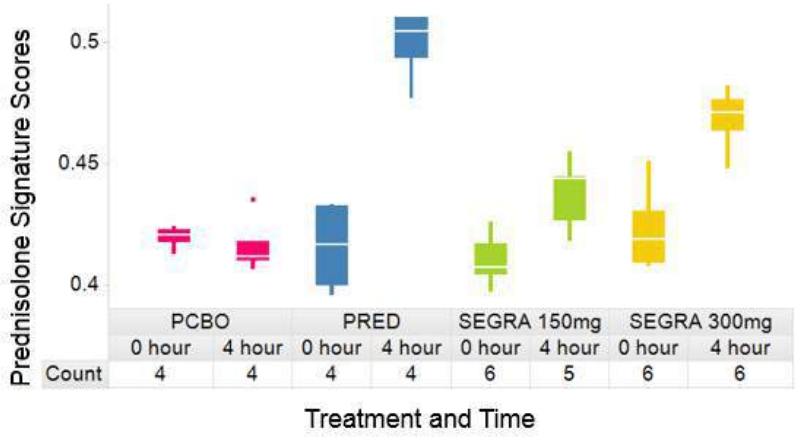

Figure 1: Prednisolone signature scores increased in a dose responsive manner in GR compound trial.

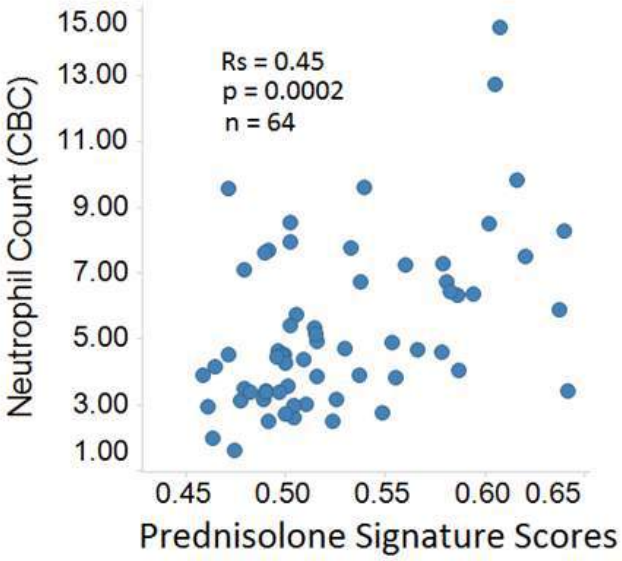

Figure 2: Prednisolone signature scores significantly correlate with netrophil counts in WB from baseline SLE patients

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Disclosure: Y. S. Hu, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Bandyopadhyay**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **D. Furst**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **A. Johnsen**, Bristol-Myers Squibb, 3; **R. Latek**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. G. Nadler**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. Carman**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3.

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Abstract Number: 760

Effects of Type I Interferon Inhibition on Blood Leukocyte Subsets in Patients Treated in a Phase IIb Clinical Study of Anifrolumab in SLE

Geoffrey Stephens[1], Rong Zeng[2], Xiang Guo[2], Steve Eck[3], Yuling Wu[3], Liangwei Wang[3], Gabor Illei[3] and **Wendy White**[2], [1]Cellcion, Clarksburg, MD, [2]Translational Sciences, MedImmune, LLC, Gaithersburg, MD, [3]MedImmune, LLC, Gaithersburg, MD

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster I: Clinical Trial Design and Current Therapies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: A Phase IIb randomized controlled study (NCT01753193) was conducted with anifrolumab, a fully human, anti-interferon (IFN)–α receptor (IFNAR1) specific antibody in adults with moderate to severe systemic lupus erythematosus (SLE). Anifrolumab binds to subunit 1 of the IFNAR and inhibits the activity of all type I IFN. A complete blood count (CBC) analysis demonstrated that anifrolumab reversed leukopenia. However, the types of peripheral immune cells affected following treatment have not been reported. To better understand how changes in the immune cell repertoire may be associated with SLE severity, the type I IFN test status (IFN high vs. IFN low), and treatment with anifrolumab, we performed flow cytometry to assess several peripheral blood cell types: dendritic cells (myeloid and plasmacytoid), B cells (naïve, memory, and plasma cells), neutrophils, and T cells (CD4, CD8, naïve, memory, central memory, and effector).

Methods: Patients were randomized to anifrolumab at 300, 1,000 mg, or placebo (PBO) every 4 weeks for 48 weeks. Peripheral blood was collected from a subset of patients (91 total) on days 1 (prior to first dose), 85, 141, 169, 253, 337, and 365. Patients were approximately evenly distributed between the treatment and PBO groups. Baseline absolute immune cell numbers were compared over treatment course in the context of SLEDAI scores, the type I IFN test, and response to therapy. Statistics were calculated using the Student's t-test, and p-values ≤ 0.05 were considered significant.

Results: At baseline, several blood cell types were lower for patients with SLEDAI $\geq$10 including naïve B cells, and memory T and B cells. In IFN-high patients, neutrophils, memory T cells, and plasmacytoid dendritic cells (pDCs) were significantly decreased. Anifrolumab led to significant increases in absolute numbers of T-cell subsets in the blood of IFN-high patients. In contrast, no significant changes were observed for IFN-low patients. Observed increases were within normal reference ranges. The alterations did not appear to be secondary to tapering of oral corticosteroids, as these cell types were not significantly different in PBO groups, regardless of tapering. Patients with $\geq$6-point SLEDAI reductions following anifrolumab demonstrated significant increases in total CD4 and CD8 T cells, and decreases in memory B cells Significant increases in pDCs were also evident. Anifrolumab did not cause significant differences in the other cell types measured.

Conclusion: Memory T cells numbers, among other cell types, were significantly reduced in patients with SLEDAI $\geq$10 and those classified as IFN-high at baseline suggesting that, for patients with more severe disease, type I IFN may be involved in cell migration into the peripheral tissues from the blood. Consistent with this, we found that neutralization of type I IFN with anifrolumab promoted immigration and/or prevented emigration of potentially pathologic immune cells between the tissues and the blood. These data suggest that some of the effects observed following anifrolumab treatment might be a result of altering the migration patterns of T and other immune cells, which may partially explain its biological activity.

Disclosure: G. Stephens, AstraZeneca, 1; **R. Zeng**, AstraZeneca, 1; **X. Guo**, AstraZeneca, 1,AstraZeneca, 3; **S. Eck**, AstraZeneca, 1; **Y. Wu**, AstraZeneca, 1; **L. Wang**, AstraZeneca, 1; **G. Illei**, AstraZeneca, 1; **W. White**, AstraZeneca, 1.

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Abstract Number: 761

Exposure-Response Analysis for Selection of Optimal Dosage Regimen of Anifrolumab in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Anifrolumab is a fully human IgG_1 monoclonal antibody directed against subunit 1 of the type I interferon–α receptor (IFNAR1) currently in development for the treatment of systemic lupus erythematosus (SLE). An exposure-response (E-R) model was developed to support the rational dosage selection for the pivotal anifrolumab studies.

Methods: In the Phase IIb MUSE study (NCT01438489),[1] adult patients with seropositive moderate to severe SLE, who had inadequate responses to standard-of-care (SOC) medications, were randomized 1:1:1 to receive anifrolumab 300 or 1,000 mg or placebo intravenously every 4 weeks, in addition to SOC medications, for 48 weeks. Patients were stratified by interferon (IFN) test status as IFN high or IFN low based on a validated 4-gene expression assay, dosage of oral corticosteroid (<10 or ≥10 mg/day of prednisone or equivalent), and SLEDAI–2K score (<10 or ≥10) at screening. A mechanistic target-mediated drug disposition model, previously developed for a first-in-human study in scleroderma patients,[2] was used to describe the pharmacokinetics (PK) of anifrolumab. The dichotomous efficacy endpoint, SLE responder index [SRI(4)], was modeled using logistic regression. A dropout hazard function was introduced to describe the voluntary patient withdrawals during the treatment period. Clinical simulations were conducted to evaluate different dosing scenarios in patients with SLE.

Results: There was no PK difference between patients classified as IFN high or IFN low. SRI(4) modeling suggested there was no treatment effect of anifrolumab in IFN-low patients, although the interpretation of this result could be limited by the small sample size. In IFN-high patients, a log-linear logistic model was selected to describe the treatment effect of anifrolumab. Patient dropouts were more likely in nonresponders. Clinical simulations demonstrated dosages less than 300 mg would result in inadequate PK exposure and suboptimal efficacy in some patients with SLE. In contrast, simulations indicated minimal improvement in efficacy for dosages higher than 300 mg, consistent with the outcome observed in the Phase IIb MUSE study.

Conclusion: Based on E-R analyses and overall risk assessment, an every-4-week 300-mg intravenous dosage regimen is recommended for pivotal anifrolumab trials in patients with SLE. References: [1]Furie R et al. *Arthritis Rheumatol* 2015;67(Suppl 10):Abs 3223. [2]Wang B et al. *Clin Pharmacol Ther* 2013;93(6):483-92.

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Abstract Number: 762

Pragmatic Treatment of Patients with Systemic Lupus Erythematosus with Rituximab: Long-Term Effects on Serum Immunoglobulins

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Background/Purpose: B cell depletion therapy based on rituximab is a therapeutic option for refractory disease in patients with Systemic Lupus Erythematosus (SLE). Hypogammaglobulinemia can be an important adverse outcome of B-cell depletion therapy with rituximab (a chimeric anti-CD20 monoclonal antibody). However, the probability of, and factors associated with, the incidence of persistent hypogammaglobulinemia after rituximab in the routine clinical setting, has not been explored. The aim of this observational study was to explore long-term effects on B cell function by following serum immunoglobulin levels in patients with SLE treated with rituximab in routine clinical practice.

Methods: In this cross-sectional observational study, we included 57 consecutive patients with SLE treated with rituximab and concomitant/sequential immunosuppressants and measured serum total IgG, IgM, and IgA and IgG anti-dsDNA antibodies over a median of 48 months most recent follow-up. Flow cytometry was used prospectively to assess B-cell phenotypes in 17/57 patients.

Results: Lupus Nephritis was diagnosed in 29/57 (51%) patients with similar percentages in each group (7/12 (58%) in the low IgM group and 22/45 (49%) in the normal IgM group). All patients had received previous treatment with at least 2 different immunosuppressants not including corticosteroids, which were continued at a low dose (<10mg/day prednisolone). We noted a hierarchy in percentage reduction, IgM > IgG > IgA (-18.4%; -2.8% ; 10.3%). Twelve patients (22%) had persistent IgM hypogammaglobulinemia (<0.4 g/L) and 3/55 (5%) had low IgG (<7g/L) at most recent follow-up (range 12-144 months). This was not associated with serious adverse events or high anti-dsDNA antibodies (≥1000IU/ml; normal<50IU/ml). Factors predictive of low serum IgM included: baseline serum IgM ≤0.8g/L (receiver-operated-curve analysis) and subsequent therapy with mycophenolate mofetil (MMF) (odds ratio=6.8 compared with other immunosuppressants). In patients maintaining normal IgM levels (9/17 included), the frequency of circulating IgD+CD27+ B cells was significantly higher (*p=0.05*). 7/30 SLE patients with baseline anti-dsDNA≤1000 IU/ml lost seropositivity 12 months after rituximab.

Conclusion:

- In SLE patients at long-term follow-up after multiple cycles of rituximab IgG hypogammaglobulinaemia was rare
- Rituximab normalized raised IgG in the majority of patients
- Low levels of serum total IgM presented in a quarter of SLE patients and were associated with low baseline levels, older age and sequential therapy with mycophenolate mofetil
- Low IgM was not associated with persistently high levels of antibodies to dsDNA

Therefore, lower baseline serum IgM levels and sequential therapy with MMF are predictive of IgM hypogammaglobulinemia after rituximab in SLE, but this was not associated with higher levels of anti-ds DNA antibodies or an increased risk of infections. This provides useful directions for clinicians regarding rituximab and sequential immunosuppressive treatment for patients with SLE.

Disclosure: V. Reddy, None; **L. Martínez-Estupiñán**, None; **D. A. Isenberg**, None; **M. J. Leandro**, None; **G. Cambridge**, None.

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Abstract Number: 763

Rituximab As a Corticosteroid-Sparing Agent in Patients with Systemic Lupus Erythematosus

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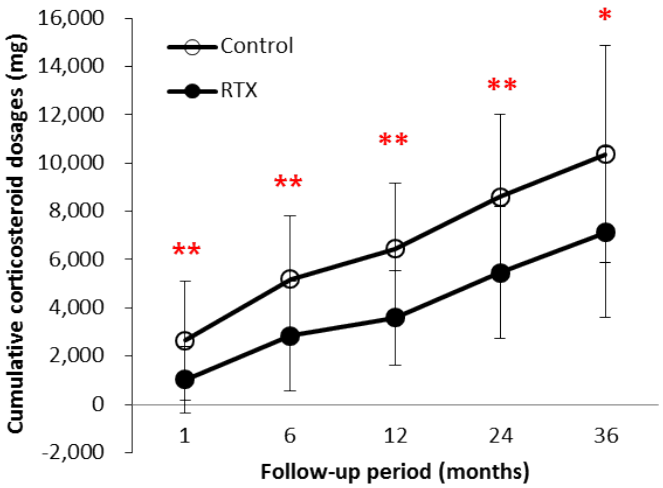
Background/Purpose : The treatment of active systemic lupus erythematosus (SLE) remains problematic because the current treatment regimen based on corticosteroids and immunosuppressive agents have significant side effects. Rituximab (RTX), a chimeric monoclonal antibody that selectively targets CD20-positive B cells, has proven optimistic results in a number of open-label trials, despite the fact that two randomized controlled trials in SLE did not meet the primary end points. In this study, we evaluated the efficacy of RTX as a steroid sparing drug in patients with moderate to severe SLE.

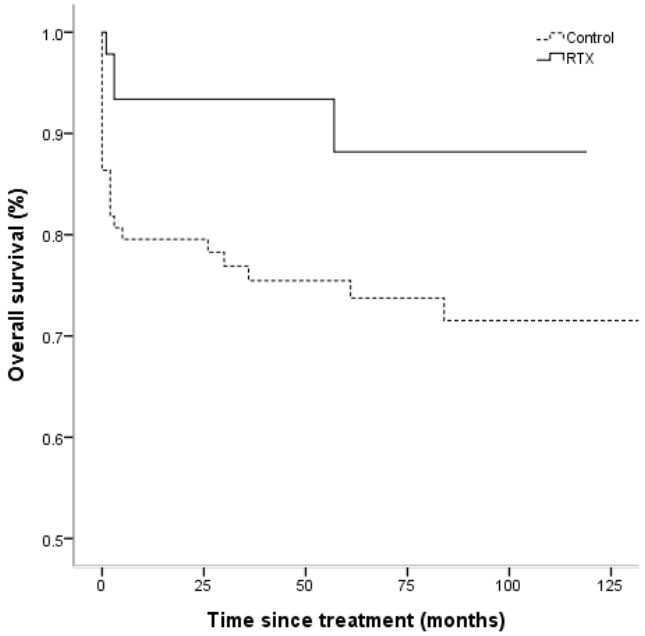
Methods : All patients satisfied the American College of Rheumatology 1997 revised criteria for SLE. Forty-six patients who were treated with immunosuppressive regimen including RTX (RTX group) were enrolled in this retrospective study. To compare the outcomes, SLE patients who were treated with immunosuppressive regimen that did not include RTX were matched for SLE Disease Activity Index (SLEDAI) score in 2:1 ratio compared to RTX group. Data of the disease activity, infection rate and mortality, treatment modalities, and cumulative dosages of corticosteroid and cyclophosphamide were collected at baseline and at 1-, 6-, and 12-month, then every 12 months up to 36 months of follow-up.

Results : Disease activity was similar in the RTX and control groups with mean SLEDAI scores of 22.3 ¡¾ 12.0 and 22.2 ¡¾ 12.0, respectively at baseline and 4.5 ¡¾ 6.2 and 3.5 ¡¾ 3.1, respectively at 36 months of follow-up. The cumulative corticosteroid doses at month 1 and 36 in the RTX group (1020.5 ¡¾ 1379.2 and 7130.1 ¡¾ 3548.7 mg, respectively) were significantly lower that those of the control group (2640.9 ¡¾ 2450.8 and 10371.7 ¡¾ 4489.7 mg, respectively). The difference in cumulative corticosteroid dosages at each visit, remained significant at all follow-up time points.



$^{**}p < 0.001$, $^{*}p = 0.002$

The mean cumulative dose of cyclophosphamide was lower in the RTX group compared with that in control group (2639.2 ¡¾ 3085.5 mg vs. 4169.5 ¡¾ 2464.0 mg, $p = 0.028$). Frequency of infection was significantly lower in RTX group (1.3 ¡¾ 1.5 vs. 1.9 ¡¾ 1.7 in control group, $p = 0.040$). The survival rate was significantly higher in RTX group compared with that in control group (91.3% vs. 73.9%, $p = 0.022$).



Conclusion : These data indicate that addition of RTX in standard immunosuppressive regimen revealed steroid-sparing effects for the treatment of moderate to severe SLE while it significantly improved the mortality and morbidity. Further studies with larger number of patients are needed to confirm the value of RTX.

Disclosure: N. R. Kim, None; **J. S. Eun**, None; **J. W. Kang**, None; **E. J. Nam**, None; **Y. M. Kang**, None.

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Abstract Number: 764

Atacicept: Integrated Safety Profile from Phase II Randomized Placebo-Controlled Studies in Autoimmune Diseases

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Session Time: 9:00AM-11:00AM

Background/Purpose: Atacicept, a recombinant fusion protein, targets both BLyS (B lymphocyte stimulator) and APRIL (a proliferation-inducing ligand), B cell activating factors involved in the pathogenesis of B cell-driven autoimmunity. This study aims to summarize safety data from double-blind, placebo-controlled, phase II studies of atacicept in autoimmune diseases.

Methods: Safety data were pooled from 7 studies of atacicept 25, 75 or 150 mg in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), multiple sclerosis (MS), optic neuritis (ON), and lupus nephritis (LN).

Results: A total of 1262 subjects were included (RA, n=513 [41%]; SLE, n=455 [36%]; MS, n=254 (20%); ON, n=34 (3%); LN, n=6 [1%]); 30% received placebo (PBO), and 10.2%, 22%, and 37.1% received atacicept 25, 75, or 150 mg, respectively. Treatment-emergent adverse events (TEAEs) were similar across groups (atacicept: 75.2%, 77.7% and 75.6% with 25 mg, 75 mg and 150 mg; PBO: 72.3%) (Table 1). Infections/infestations were the most frequent TEAE (atacicept: 33.3%, 47.9% and 49.1% with 25 mg, 75 mg and 150 mg; PBO: 43.1%) and were reported in subjects with SLE (62.4%, 60.4% with 75 mg and 150 mg; PBO: 55.2%), RA (34.8%, 19.4%, 37.4% with 25 mg, 75 mg and 150 mg; PBO: 32.7%), MS/ON (31.7%, 39.7%, 62.2% with 25 mg, 75 mg and 150 mg; PBO: 40.0%), and LN (75% with 150 mg; PBO: 0%). Pneumonia was the most common serious TEAE (atacicept: 0%, 2.1% and 1.1% with 25 mg, 75 mg and 150 mg; PBO: 1.0%) and the most common severe TEAE (atacicept: 0%, 1.1%, 0.9% with 25 mg, 75 mg and 150 mg; PBO: 0.5%). SLE subjects accounted for the majority of serious and severe pneumonia cases (80% and 67%, respectively). Six treatment-emergent deaths were reported (n=3, 2, 1 in RA, SLE, MS), atacicept n = 1, 1, and 3 with 25 mg, 75 mg and 150 mg, PBO n=1; mortality rate/100 subject-years was atacicept 1.05 vs. PBO 0.43. Herpes zoster (HZ) infections were mild/moderate and infrequent (1.3%) but occurred more commonly with atacicept (1.6% vs 0.8%, with atacicept [n=14] vs PBO [n=3]). All 3 PBO-treated subjects and 57% atacicept-treated subjects with HZ had SLE. The proportion of subjects experiencing HZ by dose was: 25 mg (0.8% overall); 75 mg (1.8% overall; 2.5% SLE); and 150 mg (1.7% overall; 2.8% SLE). No serious HZ infections were reported with atacicept.

Conclusion: TEAE rates were similar between atacicept and PBO groups, with infections the most commonly reported. Subjects with SLE appeared more likely to develop infection-related TEAE (ie, HZ) and serious/severe TEAE (ie, pneumonia). Numbers of deaths were low and were observed across the diseases. The safety profile of atacicept appears to be similar to other B cell-targeted therapies, and is being further evaluated in clinical studies of SLE patients. **Table 1. Overall analysis set**

	Placebo (n=383)	Atacicept 25 mg (n=129)	Atacicept 75 mg (n=282)	Atacicept 150 mg (n=468)	All atacicept-treated subjects (n=879)	All subjects (n=1262)
TEAEs, n (%)	277 (72.3)	97 (75.2)	219 (77.7)	354 (75.6)	670 (76.2)	947 (75.0)
Serious TEAEs, n (%)	39 (10.2)	15 (11.6)	42 (14.9)	55 (11.8)	112 (12.7)	151 (12.0)
Severe TEAEs, n (%)	23 (6.0)	10 (7.8)	38 (13.5)	52 (11.1)	100 (11.4)	123 (9.7)
TEAEs leading to treatment discontinuation, n (%)	24 (6.3)	14 (10.9)	25 (8.9)	40 (8.5)	79 (9.0)	103 (8.2)
Thromboembolic events*, n (%)	10 (2.6)	1 (0.8)	6 (2.1)	6 (1.3)	13 (1.5)	23 (1.8)
Non-opportunistic infections, n (%)	277 (72.3)	97 (75.2)	218 (77.3)	351 (75.0)	666 (75.8)	943 (74.7)
Herpes zoster, n (%)	3 (0.8)	1 (0.8)	5 (1.8)	8 (1.7)	14 (1.6)	17 (1.3)
PML, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injection site reactions, n (%)	31 (8.1)	27 (20.9)	62 (22.0)	108 (23.1)	197 (22.4)	228 (18.1)
Treatment-emergent deaths, n (%)	1 (0.3)	1 (0.8)	1 (0.4)	3 (0.6)	5 (0.6)	6 (0.5)

*Includes myocardial infarction. TEAE, treatment-emergent adverse event; PML, progressive multifocal leukoencephalopathy

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Disclosure: P. Fraser, EMD Serono, 1,EMD Serono, 3; **W. Chin**, EMD Serono, 3; **A. Kao**, EMD Serono, 3.

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Abstract Number: 765

High Baseline B Lymphocyte Stimulator (BLyS) Levels Predict Response While Smoking and Organ Damage at Baseline Predict Failure to Belimumab in Three Swedish Clinical Practice Settings

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Background/Purpose: Belimumab is a biologic drug approved to treat Systemic Lupus Erythematosus (SLE). The efficacy of belimumab has been demonstrated in phase III clinical trials. Here, we provide results from real-life

experiences in three Swedish clinical practice settings, with focus on predictors of treatment response. As smoking is coupled with unfavourable prognosis and treatment outcomes, we particularly looked at the effects of smoking on treatment response to belimumab.

Methods: Fifty-eight patients from Karolinska (n=30), Skåne (n=19), and Linköping (n=9) University Hospitals treated with belimumab were enrolled and followed longitudinally. Global disease activity was assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K), British Isles Lupus Assessment Group (BILAG) index, and a 100 mm Visual Analogue Scale (VAS) for Physician's Global Assessment (PGA). Organ damage was evaluated using the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI). Response to treatment was defined in line with the SLE responder index (SRI) as a reduction of ≥4 points in SLEDAI-2K, no new BILAG A or ≤1 new BILAG B, and no deterioration in PGA by ≥30 mm. B lymphocyte stimulator (BLyS) levels were determined by ELISA (R&D Systems).

Results: SLEDAI-2K decreased over time (median baseline score: 8.0; IQR: 4.0–13.8; p<0.0001), corresponding to a decrease of 3.9 over one year and 5.5 over three years. PGA decreased also (p<0.0001), corresponding to a decrease of 28.2 over one year and 39.7 over three years. We also observed decreasing prednisone equivalent dosages (p<0.0001), corresponding to a decrease of 6.3 mg/day over one year and 8.9 mg/day over three years (median baseline dose: 10.0 mg/day; IQR: 7.5–15.0). SDI scores remained stable (p=0.16). We found that a baseline SLEDAI-2K score ≥10 yielded a 2.5-fold increase in the probability of SRI response (HR: 2.553; 95% CI 1.339–4.896; B: 0.937; p=0.004). Baseline prednisone equivalent dosages also predicted SRI response (HR: 1.029; 95% CI 1.003–1.056; B: 0.029; p=0.029). An SDI score >1 at baseline yielded a >2-fold decrease of the probability to attain SRI response (HR: 0.449; 95% CI: 0.208–0.967; B: -0.801; p=0.041). After adjustment for baseline SLEDAI-2K scores and prednisone equivalent dosages, ever smokers had a decreased probability to attain SRI response compared with never smokers (HR: 0.460; 95% CI: 0.223–0.951; B: -0.776; p=0.036), and current smokers showed also a lower probability to attain SRI response compared with non-current smokers (HR: 0.103; 95% CI: 0.025–0.427; B: -2.276; p=0.002). Moreover, higher baseline BLyS levels predicted SRI response after adjustment for the same items (HR: 1.609; 95% CI: 1.149–2.252; B: 0.475; p=0.006).

Conclusion: In this real-life observational study, disease activity and corticosteroid usage decreased while damage remained stable during treatment with belimumab. Higher baseline SLEDAI-2K scores, corticosteroid dosages and BLyS levels predicted treatment response, whereas smoking and established damage at baseline predicted failure to belimumab treatment. Our results might contribute to a better selection of patients who are likely to respond to belimumab treatment.

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Abstract Number: 766

Withdrawal of Mycophenolate Mofetil after Maintenance Treatment of SLE Nephritis Associated with Renal Relapse

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Background/Purpose: Current ACR and EULAR evidence based guidelines provide recommendations for therapeutic choices to induce and maintain remission of lupus nephritis, however, the appropriate duration of maintenance treatment remains unclear. Data from the ALMS, MAINTAIN, and NIH-funded clinical trials in support of duration greater than three years is absent. In an effort to balance drug toxicities with the desire to prevent late disease recurrence some authors recommend maintenance therapy for as long as five years. There is an active NIH sponsored clinical trial for randomization of MMF maintenance withdrawal in SLE patients in remission, however, these results are not yet available. We analyzed the prevalence of renal flare after MMF maintenance therapy withdrawal in NYUÕs large, multi-ethnic cohort of SLE patients.

Methods: We queried the NYU SAMPLE Lupus Registry and biorepository to identify SLE nephritis patients with complete response who experienced renal flare within 12 months of discontinuing maintenance MMF therapy. The NYU SLE SAMPLE registry was initiated in September 2013 and includes 612 patients fulfilling ACR and/or SLICC criteria for SLE of which 42% have clinical nephritis.

Results: The NYU SAMPLE registry has 612 SLE patients (90% female; mean age 43.0±0.9 years), 54% Caucasian, 31% African American, 15% Asian; 30% Hispanic white, 5% Hispanic Black and 256 patients (42%) have nephritis. Of the 256 SLE nephritis we identified four patients with renal relapse within 12 months of MMF withdrawal summarized in Table 1. Table 1. Characteristics of patients with renal flare after MMF maintenance treatment withdrawal

	Case 1	Case 2	Case 3	Case 4
Age (years)	38	35	64	48
Gender	Female	Female	Female	Female
SLE Diagnosis Date	2001	2008	1995	2007
SLE ACR Criteria	Malar rash, photosensitivity, arthritis, GN, AN, DNA	Arthritis, rash, cytopenias, GN, ANA, DNA, Sm	DLE, arthritis, GN, leukopenia, ANA, DNA	malar rash, photosensitivity, arthritis, GN, ANA, DNA
WHO Classification of GN	III/V	III/V	II/III	N/A
Induction treatment	MMF	MMF	MMF	MMF
Duration MMF maintenance treatment (years)	4.5	5.8	8	4
Time to renal flare after MMF withdrawal (days)	102	288	206	63*
At Time of Withdrawal				
dsDNA Ab (IU/mL)	95	56	33	10*
C3 (mg/dL)	87	80	128	70 *
C4 (mg/dL)	13.4	7.0	39	11 *
Creatinine (mg/dL)	0.6	0.6	1.5	0.6*
Urine Protein:Creatinine (g)	0.1	0.6	0.2	0.4*
Albumin (g/dL)	4.0	4.0	4.1	4.2*
At Time of Flare				
dsDNA Ab (IU/mL)	274	340	>300	9
C3 (mg/dL)	63	52	44	70
C4 (mg/dL)	6.6	5.7	6.0	9.0
Creatinine (mg/dL)	0.5	0.8	2.9	0.5
Urine Protein:Creatinine (g)	3.9	3.6	7.5	2.2
Albumin (g/dL)	3.4	2.8	3.0	4.1
Medications continued after MMF withdrawal	HCQ	HCQ, ARB	ARB	HCQ, ACE

*Patient with renal flare within 2 months upon the initiation of MMF tapering from 2g to 0.5mg daily.

Conclusion: In the two year period between 3/2014 and 3/2016 we identified 4 patients with a renal relapse within 12 months of maintenance therapy withdrawal. All of the patients were on MMF for maintenance and for a duration >4 years of treatment. Based on this experience we recommend that maintenance of SLE GN with MMF absent contraindication should be at least 5 years and in the interval after withdrawal at any juncture careful monitoring and laboratory studies should be performed no less often than every 3 months for at least 2 years from time of maintenance therapy withdrawal. The occurrence of a renal flare during tapering, also highlights the need for guidelines regarding the rate of withdrawal. Determining risk factors for renal flare after maintenance withdrawal is necessary to facilitate clinicians identifying

candidates for discontinuations or instances when to exercise caution.

Disclosure: H. M. Belmont, None; **A. Berhanu**, None.

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Abstract Number: 767

Hydroxychloroquine Induced Retinopathy in SLE

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SESSION INFORMATION

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Session Type: ACR Poster Session A

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Background/Purpose: Retinal toxicity from hydroxychloroquine (HCQ), has been recognized for many years. But poor compliance of HCQ might confound results of previous studies. Therefore, we tried to understand HCQ induced retinopathy by investigating association between retinopathy and HCQ serum level.

Methods: 117 patients with HCQ toxicity report and HCQ level measured were included in the analysis. Patients were then followed quarterly since cohort entry. HCQ level were measured at each visit and patients taking HCQ were referred to Ophthalmologists for eye exams.

Results: Among 117 patients, 112 (95.7%) were female. Majority (49.6%) were Caucasian, 44.4% African American. 12 of them have HCQ toxicity confirmed while 7 were possible and majority (83.8%) don't have HCQ toxicity. Table 1 showed HCQ toxicity in each HCQ group. Table 1: HCQ toxicity in each HCQ group

Highest HCQ level (ng/mL)	No toxicity N (%)	Possible Toxicity N (%)	confirmed toxicity N (%)	Total
Greater than 2,000	25 (83.3)	2 (6.7)	3 (10.0)	30
1,500 to 1,999	23 (79.3)	4 (13.8)	2 (6.9)	29
1,000 to 1,499	30 (85.7)	1 (2.9)	4 (11.4)	35
500 to 999	13 (100)	0 (0)	0 (0)	13
Less than 499	7 (70.0)	0 (0)	3 (30.0)	10

Pair-wise comparison using t test with pooled Standard deviation showed that average highest HCQ levels are not significantly different among three groups (No vs. possible vs. Yes) After grouping people with "confirmed" toxicity and "possible" toxicity together, average highest HCQ level is 1511.632 ng/mL. While highest HCQ level is 1591.051 ng/mL on average among those who didn't show HCQ toxicity. The difference between these two groups is not significant (P = 0.7094) using t test.

Conclusion: Retinopathy is not associated with highest HCQ level.

Disclosure: M. Petri, None; **W. Fu**, None.

Abstract Number: 768

7-Year Safety and Efficacy of Belimumab in Patients with Systemic Lupus Erythematosus

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Background/Purpose: The availability of published long-term data from systemic lupus erythematosus (SLE) clinical trials is limited [1]. To complement existing belimumab data, we examined the long-term safety and efficacy of belimumab plus standard SLE therapy (SoC) in patients who participated in the open-label extension that followed BLISS-76.

Methods: This was a multicenter, continuation study (GSK study 112233; NCT00724867) of patients who completed BLISS-76 in the US. In this study patients received the same dose of belimumab as in BLISS-76 (1 or 10 mg/kg IV, every 28 days) plus SoC; patients who had previously received placebo received belimumab 10 mg/kg IV. Following licensing of belimumab, the dose for patients who received 1 mg/kg was increased to 10 mg/kg. Primary outcome measures included long-term safety, assessed by adverse event (AE) frequency and Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) evaluated every 48 weeks (Study Year). Other assessments included SLE Responder Index (SRI), prednisone use, B cell levels, and flare rates (modified SLE Flare Index [SFI]).

Results: 268 patients comprised the modified intent-to-treat (MITT) population; 140 patients completed the continuation study (52.2%), and 128 (47.8%) withdrew (patient request, 24.2%; AE, 19.5%). At baseline, the mean (SD) Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score was 7.8 (3.86), and the mean (SD) SDI score was 1.2 (1.51). The incidence of overall AEs, treatment-related AEs, and serious AEs remained stable or declined through Study Year 7 (**Table**). The mean (SD) SDI score increased by 0.4 (0.68) from

Table: Incidence of treatment-emergent AEs by Study Year

Number (%) of patients[a]	Any time post-baseline (N=268)	Year 1 (N=268)	Year 2 (N=259)	Year 3 (N=244)	Year 4 (N=219)	Year 5 (N=202)	Year 6 (N=192)	Year 7 (N=130)	Year 8+ (N=65)
At least 1 AE	267 (99.6)	260 (97.0)	235 (90.7)	206 (84.4)	184 (84.0)	167 (82.7)	145 (75.5)	87 (66.9)	31 (47.7)
At least 1 treatment-related AE[b]	145 (54.1)	89 (33.2)	55 (21.2)	40 (16.4)	35 (16.0)	30 (14.9)	32 (16.7)	13 (10.0)	3 (4.6)
At least 1 serious AE	112 (41.8)	33 (12.3)	30 (11.6)	25 (10.2)	22 (10.0)	24 (11.9)	16 (8.3)	13 (10.0)	3 (4.6)
At least 1 AE resulting in study agent discontinuation	26 (9.7)	3 (1.1)	4 (1.5)	7 (2.9)	8 (3.7)	0	2 (1.0)	2 (1.5)	0
All infections of special interest	43 (16)	14 (5.2)	13 (5.0)	8 (3.3)	6 (2.7)	7 (3.5)	11 (5.7)	6 (4.6)	0
Serious	5 (1.9)	1 (0.4)	1 (0.4)	1 (0.4)	6 (2.7)	1 (0.5)	1 (0.5)	0	0
All opportunistic infections[c]	16 (6.0)	3 (1.1)	3 (1.2)	4 (1.6)	0	3 (1.5)	6 (3.1)	2 (1.5)	0
Serious	0	0	0	0	0	0	0	0	0
Herpes zoster	27 (10.1)	9 (3.4)	6 (2.3)	4 (1.6)	4 (1.8)	5 (2.5)	7 (3.6)	3 (2.3)	0
Opportunistic[d]	9 (3.4)	1 (0.4)	2 (0.8)	2 (0.8)	0	2 (1.0)	5 (2.6)	2 (1.5)	0
Recurrent	8 (3.0)	1 (0.4)	2 (0.8)	2 (0.8)	0	2 (1.0)	4 (2.1)	2 (1.5)	0
Malignant neoplasms (including NMSC)	13 (4.9)	1 (0.4)	2 (0.8)	4 (1.6)	2 (0.9)	0	0	3 (2.3)	1 (1.5)
Any depression/suicide/self-injury	73 (27.2)	25 (9.3)	22 (8.5)	17 (7.0)	6 (2.7)	8 (4.0)	3 (1.6)	4 (3.1)	1 (1.5)
Deaths	2 (0.7)	0	1 (0.4)	0	1 (0.5)	0	0	0	0

[a]Patients reporting multiple AEs within a Study Year are only counted once in each of the appropriate categories; [b]Possibly, probably, or definitely related; [c]Per GSK adjudication; [d]Recurrent, or disseminated (more than three adjacent dermatomes affected or crossing the midline). AEs, adverse events; NMSC, non-melanoma skin cancer;

baseline to Study Year 7 (MITT population).

An SRI response was achieved by 41.9% (96/229) of patients overall at Study Year 1 Midpoint (Week 24), increasing to 75.6% (90/119) at Study Year 7 Midpoint. At Study Year 7 Midpoint, relative to baseline, 78.2% (93/119) of patients overall achieved a ≥4-point SELENA-SLEDAI score reduction, 98.4% (125/127) had no new British Isles Lupus Assessment Group (BILAG) 1A/2B organ domain scores, and 93.7% (119/127) of patients had no worsening in Physician's Global Assessment (PGA). The median decrease in prednisone dose from baseline was 47.1% (n=77, those receiving prednisone), and the median change in CD20+ B cells was -83.2%, at Study Year 7 Midpoint. Severe SFI flare was experienced by 20.6% (55/267) of patients through Study Year 7 Midpoint.

Conclusion: Long-term exposure to belimumab was generally safe and well tolerated. The incidence of AEs remained stable or declined throughout the study. These results are consistent with data from the Phase 2 extension study and the known profile of belimumab in patients with SLE. Study funded by GSK/Human Genome Sciences, Inc. Nicole Cash, PhD, Fishawack Indicia Ltd, UK, provided editorial assistance, funded by GSK. 1. Ginzler EM, et al. *J Rheumatol.* 2014;41(2):300–9

Disclosure: R. A. Furie, GSK, 5; **D. J. Wallace**, GSK, 5; **C. Aranow**, GSK, UCB, Janssen, Rencor, 2,Celgene, GSK, Mallinckrodt, Takeda, 5; **J. Fettiplace**, GSK, 1,GSK, 3; **B. Wilson**, GSK, 1,GSK, 3,GSK, 7; **P. Mistry**, GSK, 3; **D. A. Roth**, GSK, 1,GSK, 3; **D. Gordon**, GSK, 1,GSK, 3.

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Abstract Number: 769

Response to Belimumab in SLE Patients with High Disease Activity: Data from a Multicentric Clinical-Practice Based Study Cohort

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Background/Purpose: To investigate effectiveness and identify predictors of response to belimumab in patients with active SLE in clinical practice setting.

Methods: One hundred eighty eight active SLE (ACR criteria) patients with positive anti-dsDNA antibody and low C3 and/or C4, from 11 Italian prospective lupus cohorts, were treated with belimumab (10 mg/kg day 0, 14, 28 and then every 28 days), as add-on therapy. They were 174 (92.6%) females, mean age 40.7+-10.1 years, mean disease duration 12.7±8.5 years. SLEDAI-2K, anti-dsDNA, C3, C4, prednisone daily dose, DAS-28, 24-hours proteinuria, CLASIa (Cutaneous LE Disease Area and Severity Index Activity) were recorded at baseline, at month 12 and 24. Anti-dsDNA levels were measured by ELISA in 98 patients, IIF in 62 patients, Farr assay in 28 patients. The following variables were included in the univariate and multivariate analysis to determine baseline predictors of response (according to SLE Responder Index-4, SRI-4) at 12 and 24 months: gender, age, disease duration, disease activity pattern (relapsing remitting or chronic active), SLEDAI-2K ≥10, prednisone dose >7,5 mg/day, concomitant immunosuppressants (yes/no), polyarthritis, skin rash, glomerulonephritis (GN), hematologic involvement. Pattern of disease activity was identify as chronic active disease in patients with a SLEDAI-2K ≥2 excluding serology in at least two out of the three annual visits and relapsing-remitting disease in patients with a SLEDAI-2K ≥2 excluding serology in one out of three annual visits. Statistics were performed by pairs T-test, chi-square test and multiple logistic regression analysis using SPSS package (version 22.0).

Results: Mean follow-up period was 17.5+-10.6 months (range 3-36). Active manifestations which required the use of belimumab were polyarthritis in 45.7%, skin rash in 26.1%, GN in 13.8%, and hematologic involvement in 14.4% of cases. Clinical and serological variables at baseline and after 12 and 24 months of follow-up are reported in Table. SRI-4 was achieved by 71.3% and 68.7% of patients at 12 and 24 months, respectively. Baseline independent predictors of response by logistic regression at month 12 were: SLEDAI-2K ≥10 (OR 25.8, 4.19-159.2) and polyarthritis (OR 8.33, 1.88-36.78). Predictors at month 24 were: SLEDAI-2K ≥10 (OR 12.11, 1.63-89.80), polyarthritis (OR 32.56, 2.94-360.56), and prednisone dose >7.5 mg/day (OR 7.88, 1.02-61.48). Discontinuation was observed in 49 patients (26.1%) after 9±7 months of follow-up. Twenty seven patients (55.1%) discontinued for disease activity, 13 (26.5%) for adverse events, 5 (10.2%) for pregnancy. Retention rate was 89.4% at 6 months, 81.4% at 12 months, 76.1% at 18 months, 75.0% at 24 months.

Conclusion: SLEDAI ≥10, polyarthritis and prednisone dose >7,5 mg/day at baseline were the best predictors of response

in our cohort of patient with active SLE.

Table. Variation of clinical and serologic disease activity variables at 12 and 24 months of follow-up in 188 patients with active SLE and high disease activity treated with belimuma

	Baseline	12 months		24 months	
Patients (n.)	188	74		52	
SLEDAI-2K	8.3±3.3	4.2±2.7	p=0.063	4.0±2.8	**p<0.001**
Anti-dsDNA (ELISA, KIU/L)	376.1±768.2	153.2±210.3	**p=0.003**	124.8±145.7	p=0.054
Anti-dsDNA (Farr method, IU/mL)	97.1±194.4	33.4±65.3	p=0.782	23.0±23.5	p=n.s
C3 (g/l)	0.71±0.21	0.79±0.19	**P<0.001**	0.83±0.20	**p<0.001**
C4 (g/l)	0.11±0.06	0.15±0.07	**P<0.001**	0.16±0.07	**p<0.001**
Prednisone daily dose (mg/day)	11.1±7.6	5.0±2.9	**p=0.004**	4.2±3.8	**p<0.001**
DAS-28	4.2±1.1	2.2±1.0	**p=0.014**	1.8±1.0	**p<0.001**
CLASIa	5.5±4.4	1.4±2.9	**p<0.001**	1.8±2.8	**p=0.005**
24-hours proteinuria (g)	1.1±0.74	0.64±0.54	p=0.056	0.53±0.61	**p=0.045**

p calculated using pair T-test

CLASI: Cutaneous Lupus erythematosus Area and Severity Index Activity

Table. Variation of clinical and serologic disease activity variables at 12 and 24 months of follow-up in 188 patients with active SLE and high disease activity treated with belimuma *p calculated using pair T-test CLASI: Cutaneous Lupus erythematosus Area and Severity Index Activity*

Disclosure: L. Iaccarino, None; **S. Bettio**, None; **R. Reggia**, None; **G. Emmi**, None; **F. Ceccarelli**, None; **C. Tani**, None; **M. Gerosa**, None; **M. Govoni**, None; **A. Bortoluzzi**, None; **S. De Vita**, None; **G. De Marchi**, None; **R. De Angelis**, None; **A. Di Matteo**, None; **C. Salvarani**, None; **G. Pazzola**, None; **E. Bartoloni-Bocci**, None; **L. Andreoli**, None; **M. Zen**, None; **F. Conti**, None; **M. Mosca**, None; **P. L. Meroni**, None; **R. Gerli**, None; **A. Tincani**, None; **A. Doria**, None; **L. Emmi**, None.

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Abstract Number: 770

Introducing a Novel SLE-Specific IFN-I Inhibitor CNTO 6358: Laying the Groundwork for Precision Medicine in Lupus

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Background/Purpose: The type I interferon (IFN-I) family of cytokines signal through a ubiquitously expressed heterodimeric receptor (IFNAR) composed of IFNAR1 and the high-affinity binding chain IFNAR2 eliciting antiviral, antiproliferative, and immunomodulatory effects. IFN-I is thought to play a central role in the pathogenesis of systemic lupus erythematosus (SLE) and therapeutic approaches to down-modulate this pathway have demonstrated efficacy in SLE clinical trials. The IFN-I pathway is composed of multiple closely related IFN-α subtypes and single functional molecules for IFN-β, IFN-ε, IFN-κ and IFN-ω. Some members of the IFN-I family are thought to contribute to SLE pathogenesis,

while others may be more relevant for host defense. We developed a fully-human monoclonal antibody (CNTO 6358) to selectively neutralize the most prevalent soluble IFN-Is expressed in SLE, while retaining the functions of IFN-β, including critical antiviral contributions to host defense. Here we illustrate *in vitro* bioactivity using endogenous SLE patient-derived IFN-I preparations, including immune complexes and serum/plasma from racially diverse SLE populations, providing evidence that the neutralization and potency profile of CNTO 6358 may enable potent suppression of IFN-Is prevalent in SLE without suppression of other IFN-Is more essential for other host defense processes. We further describe an *in vitro* assay that may enable the prediction of responders and non-responders with CNTO 6358, providing a transformational framework for SLE precision medicine.

Methods: Pooled SLE serum and plasma or conditioned media from cells exposed to pooled SLE patient immune complexes or recombinant human IFN-Is were utilized as stimuli in an ISRE reporter gene assay (RGA) in the presence of CNTO 6358 or control. SLE patient whole blood was incubated *in vitro* for 24 hours in the presence or absence of CNTO 6358 and the impact of inhibitor treatment on gene expression was determined by RNA-Seq relative to untreated healthy donor samples. All patient samples were collected under informed consent.

Results: IFN-I activity present in plasma and serum preparations from multiple SLE cohorts and activity present in conditioned media from PBMCs exposed to SLE patient immune complexes was neutralized to levels seen in healthy control samples. The *in vitro* addition of CNTO 6358 to blood from individual SLE patients enabled the identification of donors having robust normalization of baseline elevated IFN-I signature gene expression and those having moderate to minimal transcriptional changes.

Conclusion: Our SLE IFN-I inhibitor CNTO 6358 exhibited potent neutralization of multiple SLE patient-derived IFN-I preparations, demonstrating a bioactivity profile targeting the most prevalent IFN-I subtypes elevated in SLE patients, while preserving the functionality of other IFN-Is which may be more important for host defense. Furthermore, our *in vitro* assay and *in silico* methodologies may enable prediction of responders to our treatment, providing a transformational framework for SLE precision medicine.

Disclosure: J. Jordan, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **M. Cesaroni**, Janssen Research and Development, LLC, 3; **J. Schreiter**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **C. Huang**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **T. Cash-Mason**, Janssen Research and Development, LLC., 9; **M. Chevrier**, Janssen Research and Development, LLC., 1,Janssen Research and Development, LLC., 3; **J. Benson**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1.

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Abstract Number: 771

Preventive Effects of Glucocorticoids on Progression of Atherosclerosis in Japanese Patients with SLE

Hisaji Oshima[1], Masaki Iwasaki[1], Ikuko Tanaka[2], Misako Higashida[3], Mari Ushikubo[4], Eriko Takei[5], Kumiko Akiya[3] and Keisuke Izumi[6], [1]Department of Connective Tissue Diseases, National Tokyo Medical Center, Tokyo, Japan, [2]NAGOYA Rheumatology Clinic, Nagoya, Japan, [3]Connective Tissue Diseases, National Tokyo Medical Center, Tokyo, Japan, [4]Department of Connective Tissue Disease, National Tokyo Medical Center, Tokyo, Japan, [5]Connective tissue disease, National Tokyo Medical Center, Tokyo, Japan, [6]Connective Tissue Dseases, National Tokyo Medical Center, Tokyo, Japan

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Background/Purpose: Several cross-sectional studies have shown a progression of atherosclerosis in SLE was associated with activities of SLE but not with glucocorticoid therapy. However, a few evidence showed correlations between the progression of atherosclerosis in SLE and glucocorticoid therapy in longitudinal studies. Moreover, races and regions are known to be important in atherosclerosis. We conducted a longitudinal cohort study to clarify relevant clinical factors to influence the progression of atherosclerosis in Japanese patients with SLE.

Methods: In our cohort of the patients with SLE who regularly visit our department, the patients who underwent echography of the carotid arteries twice or more, with an interval of two years or more, were enrolled into the present study. Atherosclerosis was evaluated with echography of the carotid arteries. A mean of the bilateral intimal carotid artery media thickness (mIMT) was measured with the three-point method (TOSHIBA Xario200, Aplio400). The annual progression rate of mIMT (mIMT/y) was calculated from the difference between the baseline and the subsequent echo studies. We analyzed clinical factors associated with mIMT and mIMT/y using multiple regression analysis. For mIMT, clinical factors assessed in the analysis were as follows: age, disease duration, smoking habits, comorbid conditions, total cumulative prednisolone dosage (tPSL), history of other medications including HMG-CoA inhibitors, SLICC/ACR damage index (SDI), Ankle-Brachial Index, Cardio-Ankle Vascular Index, HbA1c, C-reactive protein, serum creatinine, high density lipoprotein cholesterol, and low density lipoprotein cholesterol at baseline. For mIMT/y, in addition to the factors above, we assessed mean daily prednisolone dosage during the follow-up period (mPSL) and other medications during the follow-up period. The analysis was performed by SPSS version 22. Data were represented as median (25-75 percentile).

Results: Thirty-nine Japanese patients with SLE were recruited in our study. Of these, 35 were women; age, disease duration, tPSL at baseline, and daily prednisolone dosage during the follow-up period (mPSL) were 60 (48-65) years, 25 (12-32) years, 58 (36-82) g and 5.0 (4.0-7.5) mg/day, respectively. The intervals of echo studies were 4.0 (2.7-6.1) years. At baseline, the mIMT was 0.60 (0.50-0.75) mm. Age (B=0.005, SE=0.002, p=0.011) and SDI (B=0.05, SE=0.02, p=0.019) were selected as positive contributory factors for mIMT, while tPSL was selected as a negative factor (B=-0.002, SE=0.001, p=0.007). For mIMT/y, mPSL (B=-0.005, SE=0.002, p=0.004) was a negative contributory factor, and diabetes mellitus requiring medical therapy was a positive factor (B=0.032, SE=0.014, p=0.035).

Conclusion: These results suggested that glucocorticoid therapy might be protective against the progression of atherosclerosis in Japanese patients with SLE.

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Abstract Number: 772

Effect of HMG-CoA Reductase Inhibitor Drugs (Statins) on Systemic Lupus Erythematosus Disease Activity: A Systematic Review and Meta-Analysis

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster I: Clinical Trial Design and

Current Therapies

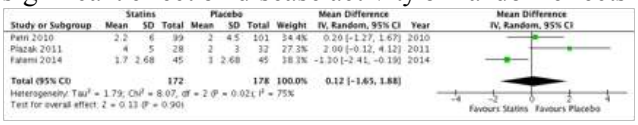
Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Statins have been shown to have anti-inflammatory and immunomodulatory effects. In vitro studies show that these drugs inhibit inflammatory cells, decrease the expression of major histocompatibility complex (MHC), decrease adhesion molecules and inflammatory cytokines (IL6 and IL10), that are also implicated in SLE pathogenesis. In terms of immunomodulary effects, animal studies demonstrate that statins exacerbate/trigger cellular apoptosis and induce a shift in the Th1/Th2 balance leading to B-cell reactivity and production of pathogenic autoantibodies. Whether statins have clinical effects in SLE have not been widely studied. In terms of disease activity, these studies show contradicting results. **Objective:** To determine the effect of statins on the disease activity of SLE based on the best available evidence.

Methods: A systematic literature search of PubMed, Scopus, and Cochrane databases was done with no date and language restrictions. Included studies were on adult SLE patients and randomized controlled trials that used statins as intervention and reported SLE disease activity as an outcome measure. Two reviewers did quality appraisal, risk bias assessment, and data extraction.

Results: Three studies met the eligibility criteria and were included in this review. Quantitative synthesis was done. The pooled analysis of these studies suggests that statins have no significant effect on disease activity on random effects model with an overall effect of 0.13 (P=0.90, 95% CI -1.65, 1.88).



Conclusion: Statins neither increased nor decreased SLE disease activity; therefore possibly it can be safely given to SLE patients without the risk of triggering or exacerbating a flare.

Disclosure: G. M. Garcia, None; **A. Urbano**, None; **E. Salido**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/effect-of-hmg-coa-reductase-inhibitor-drugs-statins-on-systemic-lupus-erythematosus-disease-activity-a-systematic-review-and-meta-analysis

Abstract Number: 773

Risk Factors for Severe Infections in Rituximab Treated Patients: Comparison of Systemic Lupus Erythematosus and Inflammatory Myositis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: The use of Rituximab (RTX) in patients with autoimmune diseases has been associated with an increased incidence of infection and risk factors for this complication are not well established. The aim of our study was to compare the incidence of infections and its related factors in the first six months after RTX infusion in two rheumatic diseases: systemic lupus erythematosus (SLE) and inflammatory myopathies (IM).

Methods: From August 2009 to March 2015, a total of 48 SLE and 39 IM consecutive patients were longitudinally followed in the biologic therapy center of Rheumatology Division of a tertiary university hospital using a standardized electronic database protocol including demographic data, clinical and laboratorial findings and treatment. RTX is regularly administered in our center with infectious screening and the protocol consisted of either 4 weekly doses of 375mg/m^2 or two doses of 1g (day 0 and 14). IM standard treatment also included the recommendation of IVIG 2-4 weeks pre RTX infusion, whereas IVIG was only indicated for lupus for severe refractory activity. Severe infection was defined as episode that required the use of intravenous antibiotics or hospitalization.

Results: SLE patients presented a significant higher incidence of overall (50.0 vs. 7.7%, p<0.001) and severe (22.9 vs. 0%, p<0.001) infections than IM patients in the first 6 months after RTX infusion. SLE and IM patients had similar age (38.0±13.3 vs. 41.5±13.2, p=0.230) and frequency of female gender (93.8 vs. 82.1%, p=0.105). At baseline, both groups had similar mean IgG level (1168.8±527.0 vs. 1346.3±397.0 mg/dL, p=0.087). With regard to treatment, mean prednisone dose (32.0±21.1 vs. 22.3±15.4mg/day, p= 0.018) was higher in SLE but the frequency of patients with associated immunosuppressants was lower in SLE (79.2 vs. 97.4%, p=0.020). IVIG infusion (2g/Kg) before RTX infusion was less often used in SLE than in IM patients (14.6 vs.69.2%, P<0.001). Previous history of severe infection 6 months before RTX was alike in SLE and IM (10.4 vs. 2.6%, p=0.218). Further analysis of 11 severe infection episodes revealed that they only occurred in SLE, more than half (64%) were sepsis and they were observed at a mean of 3.6 months (range 1 – 5 months) post infusion. At baseline, these patients were under a mean prednisone dose of 41.4±30.2mg/day and their mean IgG level was 1361.5±753.1 mg/dL.

Conclusion: We observed that SLE was associated with an unexpected higher incidence of overall and severe infections than IM patients in spite of adequate and comparable baseline IgG levels. Risk factors identified were high glucocorticoid dose and less use of pre-RTX IVIG infusion. Further studies are necessary to determine if the recommendation of IVIG pre-RTX treatment will reduce severe early infection in SLE.

Disclosure: C. Medeiros, None; **L. Seguro**, None; **F. H. C. de Souza**, None; **N. E. Aikawa**, None; **E. Bonfa**, None.

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Abstract Number: 774

BIIB059, an Anti-BDCA2 Monoclonal Antibody, Demonstrates Acceptable Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamic (PD) Effects in a Phase 1 Study with Single Ascending Doses (SAD) in Healthy Volunteers

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Session Time: 9:00AM-11:00AM

Background/Purpose: Type I interferons (IFN-I) are implicated in the pathogenesis of systemic lupus erythematosus (SLE). In SLE, immune complexes stimulate plasmacytoid dendritic cells (pDCs) to secrete large amounts of IFN-I. BDCA2 is a pDC-specific surface receptor that has been demonstrated to inhibit the production of IFN-I when engaged. Targeting BDCA2 therefore represents an attractive therapeutic strategy for inhibiting pDC-derived IFN-I and may be an effective therapy for the treatment of SLE. BIIB059, an investigational anti-BDCA2 monoclonal antibody, has been shown to engage BDCA2, and this interaction leads to BDCA2 internalization and the consequent in vitro inhibition of TLR-induced IFN-I by pDCs *(Pellerin et. al 2015)*. This first-in-human study aimed to assess the safety, tolerability, PK and PD profiles of single ascending doses of BIIB059 in healthy volunteers (HV).

Methods: A randomized, double-blinded, placebo-controlled, single ascending dose-escalation study was conducted in adult HV. In cohorts 1-7 HV were randomized to receive single IV doses of 0.05, 0.3, 1, 3, 10, or 20 mg/kg or one 50 mg SC dose of BIIB059. Each cohort had an active:placebo ratio of 2:1 or 3:1. Blood samples were obtained before and after dose administration up to week 16. Target modulation of BDCA2 and serum BIIB059 concentrations were measured using flow cytometry, and an enzyme-linked immunosorbent assay (ELISA), respectively, and anti-drug antibodies (ADA) were measured using a bridging ELISA.

Results: 54 HV were assigned to cohorts 1-7 (38 BIIB059: 16 placebo). BIIB059 demonstrated non-linear PK consistent with target mediated drug disposition. Bioavailability of SC administration was ~50%. Treatment with BIIB059 led to rapid and complete down-modulation of BDCA2 on the surface of pDCs at all dose levels. Time to reappearance of BDCA2 on pDC cell surface correlated with circulating levels of BIIB059, establishing an in vivo pharmacokinetic/pharmacodynamic (PK/PD) relationship. Single dose administration of BIIB059 was well tolerated across all dose levels. All AEs were mild to moderate in severity with no serious AEs. There were no clinically significant changes in laboratory assessments, physical examinations, or electrocardiogram (ECG) values. Anti-drug antibodies were detected at low levels in a small number of BIIB059-treated subjects. Responses were largely transient and demonstrated no impact on BIIB059 exposure or association with any safety event.

Conclusion: This first-in-human study demonstrated acceptable safety/tolerability and PK profile in healthy subjects and supports further multiple-dose studies with BIIB059. BIIB059 treatment showed dose-dependent target engagement and internalization of BDCA2 establishing a PK/PD correlation *in vivo* on circulating pDC. These data support further evaluation of clinical efficacy and safety of BIIB059 as a potential novel therapy in SLE patients.

Disclosure: D. Martin, Biogen, 1,Biogen, 3; **L. Stevenson**, Biogen, 1,Biogen, 3; **P. Prasad**, Biogen, 1,Biogen, 3; **K. Smirnakis**, Biogen, 1,Biogen, 3; **A. Kao**, Biogen, 1,Biogen, 3; **D. Rabah**, Biogen, 1,Biogen, 3; **W. Wang**, Biogen, 1,Biogen, 3; **N. Franchimont**, Biogen, 1,Biogen, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/biib059-an-anti-bdca2-monoclonal-antibody-demonstrates-acceptable-safety-tolerability-pharmacokinetics-pk-and-pharmacodynamic-pd-effects-in-a-phase-1-study-with-single-ascending-doses-sad-in

Abstract Number: 775

Evaluation of Use of Belimumab in Clinical Practice Settings: Results in Argentina

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Session Time: 9:00AM-11:00AM

Background/Purpose: Studying clinical effectiveness of belimumab treatment in real world clinical practice of Systemic Lupus Erythematosus (SLE) is relevant in assessing external validity of randomized controlled trials.

Methods: Retrospective chart review in 14 sites, including 58 patients. Primary objective: change in overall clinical manifestations assessed by a 6-point scale similar to PGA. Secondary objectives: change in SELENA SLEDAI; number of flares by mSS Flare index; steroid dose; other drugs and evaluation of health economic parameters, all assessed 6 months before and 6 (n: 58), 12 (n: 52) & & 18 (n: 25) months after treatment with 10±1 mg/Kg of belimumab. GSK sponsored this study #201282 (OBSErve).

Results: These results evaluate the use of Belimumab in the clinical practice setting in Argentina for up to 18 months. Baseline parameters: Age 41±13 yrs; female 91%; SLE duration ≥ 5 yrs 59%; hypocomplementemia 72%; high anti-dsDNA 64%; steroid dose ≥ 7.5 mg/day 77% and SELENA SLEDAI >10, 53%. Change in overall manifestations and secondary objectives are shown below:

Overall change in PGA	Worsened	No change	Improved			
			<20%	20-49%	≥ 50-79%	≥ 80%
6 months	0%	5%	10%	16%	48%	21%
12 months	2%	6%	8%	8%	25%	52%
18 months	0%	0%	0%	4%	36%	60%

	SELENA SLEDAI score (SD)	Number of Flares mean/6months (SD)	Steroid dose mg/day (SD)	Steroid Sparing Effect mg/day (SD)
Baseline	11,6 ±6,3	1,1 ±0,7	16,3 ±13,5	Not applicable
6 months	5,1 ±4,5*	0,2 ±0,4*	6,6 ±4,5*	-10 ±11,3*
12 months	4,1 ±5,0*	0,1 ±0,4*	5,3 ±6,6*	-11,5 ±13,8*
18 months	4,1 ±5,0*	0,3 ±0,6°	4,4 ±3,0°	-10,9 ±10,7°

**p<0.001 ° 0,001 vs baseline (Wilcoxon)*

The overall rate of suspension of steroids, azathioprine and belimumab after 18 months was 31%; 42% & 24% respectively. Key health economic parameters assessed did not vary after treatment although a tendency to reduced hospital admissions was observed (15,5% 6 months before treatment vs 6,7% pooled q6month after treatment, p: 0.09).

Conclusion: More than two thirds of patients obtained ≥ 50% overall response with relevant reductions in SELENA SLEDAI, number of flares, steroid and azathioprine treatment with sustained effects through 18 months follow up. Results are consistent with randomized controlled trials and similar observational real word studies performed in US and Europe therefore supporting the use of belimumab in our clinical practice.

Disclosure: A. Babini, None; **M. A. García**, None; **J. C. Barreira**, None; **B. Pons-Estel**, None; **M. Iglesias**, GlaxoSmithKline, 3; **G. Streger**, GlaxoSmithKline, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluation-of-use-of-belimumab-in-clinical-practice-settings-results-in-argentina

Abstract Number: 776

Eurolupus and Low Steroid Regimen in Proliferative Lupus Nephritis:

Retrospective Evaluation of 38 Patients in the Black Population of Martinique

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Background/Purpose: There is no data on the efficacy of the EUROLUPUS regimen associated with initial low steroids daily dose in African descent patients with proliferative lupus nephritis (LN). Here we report the 3 years prognosis of LN in black Martinican patients treated with low dose of cyclophosphamide and low dose steroids.

Methods: All patients suffering from LN in our unit have the choice after information to receive mycophénolate or IV cyclophosphamide (CY) as attack treatment. In the absence of rapidly progressive glomerulonephritis and severe extra-renal manifestations (mainly CNS involvement, auto-immune anemia or thrombocytopenia), the patients received no prednisolone assault, 6 IV 500mg fortnightly CY pulses and an initial 0.5 mg/kg/d daily dose of prednisone. On 117 consecutive SLE Afro-Caribbean patients biopsied with LN (ISN-RPS class III, IV) from 11/2008 until 9/2015, 38 living in Martinique were treated in our unit and retrospectively evaluated for complete remission (CR, daily proteinuria < 0.5 g, no urine sediment, no > 10% increasing creatininemia), partial remission (PR, same criteria than CR except for daily proteinuria < 1g), treatment failure (persistance of nephrotic proteinuria or creatininemia < 114 microM if initially < 228 microM or no decrease under half the initial creatininemia level if > 228 microM), dialysis, All patients were followed the same way. Maintenance treatment was azathioprine (n=8), mycophenolate (n=30). No patient was excluded on a creatininemia level or incompliance basis (based on self declaration).

Results: Mean (+/-SD) age at LN diagnosis was 30 (+/-9.5) years. 44.7% of patients had LN recurrence. The renal biopsy classes were: III+/-V (39.5%), IV+/-V (60.5%). Mean (+/-SD) follow up time was 49.8 (+/-27.3) months. Mean (+/-SD) baseline parameters were: glomerular filtration rate 74.75 (+/-44.17) ml/min/1.73 m^2, proteinuria 2.92 (+/-2.17) g/d, high blood pressure (57.9%), mean initial prednisone daily dose 32.2 (+/-13.2) mg/d. Five patients (13.1%) received initially at least one 1g prednisolone assault. Total remission (CR+PR) rates were 21.1% at 3 months (CR15.8%, PR 5.2%), 52.6% at 6 months (CR 34.2%, PR 18.4%), 68.4% at 1 year (CR 50%, PR 18.4%), 78.9% at 2 year (CR 65.8%, PR 13.2%), 81.6% at 3 year (CR 71.1%, PR 10.5%). No patient died and none were lost to follow up. Treatment failure was 15.8% at 3 years, 5/6 (83.3%) being non compliant. At 3 years, 5 patients were on dialysis.

Conclusion: Despite inclusion of non compliant patients, our results suggests that EUROLUPUS with low steroid use can be an effective regimen in African descent patients with proliferative LN.

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proliferative-lupus-nephritis-retrospective-evaluation-of-38-patients-in-the-black-population-of-martinique

Abstract Number: 777

a Singlecenter Experience of Rituximab Treatment in 86 Patients with Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with diverse clinical and serological manifestations. B-cell-targeted therapies have been promising new treatments for SLE. Despite the failure of randomized controlled trials, a considerable number of studies report good clinical efficacy of Rituximab, an anti-CD20 monoclonal antibody, in patients with SLE. Herein, we aimed to analyse the effects of Rituximab in lupus patients with involvement of different domains.

Methods: This a retrospective analysis of 79 lupus patients treated with rituximab at the rheumatology outpatient clinic. Disease activity was assessed using SLE disease activity index (SLEDAI) and treatment response was defined according to the system involved: A partial response was defined as ≥ 50% improvement in renal parameters, in cutaneous lesions or vasculitis, in the number of painful and/or swollen joints, increase in hemoglobin by at least 2 g/dl, doubling of basal platelet levels or platelet count between 50-100x10^9/mm^3. A complete response was defined as proteinuria<0.5/day, normal urinary sediment, normal hemoglobin levels, >100x10^9/mm^3 platelets, disappearance of cutaneous manifestations or arthritis. For patients with general disease activity a reduction of SLEDAI score at least by half was defined as partial and a score ≤2 as complete response.

Results: Cyclophosphamide(Cy) was used in 64% of the patients as previous treatment, mycophenolate mofetil(MMF) in 62%, azathioprine(AZA) in 63%, methotrexate(MTX) in 23%, calcineurin inhibitors(CNI) in 5%, leflunomide in 4% and intravenous immunoglobulin in 5% of the patients. Treatment response at 6 months revealed a complete response in 27%, 60%, 67%, 43% and 88% in patients with lupus nephritis (LN), thrombocytopenia/AIHA, arthritis, vasculitis and general disease activity respectively. In the LN group there were more partial and non responders compared to other domains. 50% of those patients went into remission and mean time to remission was 10+/-1.7 months. Concomitant treatment with Rituximab included MMF in 46, %, AZA in 13%, CNI in 5% and MTX in 10 % of patients. Comparison of treatment response between proliferative and membranous subtypes of LN revealed a a significantly higher number of complete responders (CR) in class IV whilst there were no CR among patients with membranous nephritis at the 6^{th}month of treatment. Comparison of baseline mean SLEDAI scores, antidsDNA positivity rate, C3 levels and mean daily steroid dose to 6th month of treatment favored rituximab use. Overall there were 9 infusion reactions: angioneurotic edema in 4, serum sickness in 2, rhabdomyolysis and fever in 1, urticarial rash and fever in 1 and thrombocytopenia in 1. 4 patients had zona zoster, 3 pneumonia, 3 urinary tract infections, 1 infective endocarditis and 1 tooth abscess. 3 needed to be hospitalized and 2 received intravenous immunoglobulin.

Conclusion: Regardless of the discouraging results of randomized controlled trials with Rituximab in lupus patients, our

clinical experience also shows that it still remains as a therapeutic option, especially in severe and refractory cases.

Disclosure: B. Artim-Esen, None; **B. Toz**, None; **B. Erer**, None; **S. Kamali**, None; **A. Gul**, None; **L. Ocal**, None; **M. Inanc**, None.

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Abstract Number: 778

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/apremilast-in-patients-with-lupus-rashes

Abstract Number: 779

Factors Determining Hydroxychloroquine Serum Levels in a Cohort of Chinese Patients with Systemic Lupus Erythematosus

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Session Time: 9:00AM-11:00AM

Background/Purpose: To study the factors determining the hydroxychloroquine (HCQ) serum concentration in a cohort of Chinese patients with systemic lupus erythematosus (SLE).

Methods: Consecutive patients who fulfilled ≥4 of the 1997 ACR criteria for SLE and had received HCQ for 6 months or more were recruited from our lupus clinic and hospital admissions in a 9-month period starting from November 2011. Patients were prescribed HCQ at fixed daily dosages of 400 mg, 300 mg, 200mg or less than 200mg (eg. 200mg 3 or 5 times per week) at the discretion of their attending doctors according to disease activity, organ manifestations and risk factors for HCQ toxicities. Blood was assayed for the serum levels of HCQ by an in-house technique using the tandem mass spectrometry (SPE-MS/MS). Factors affecting HCQ serum concentrations were studied by univariate and multivariate linear regression analyses. Covariates being tested in the regression models included age, sex, body mass index (BMI), prescribed dosage of HCQ, SLE disease activity score (SLEDAI), ever smoking, estimated glomerular filtration rate (eGFR) and concomitant prednisolone.

Results: 276 SLE patients were studied (94% women; mean age 41.0±13.8 years; SLE duration 8.7±6.6 years). HCQ was primarily used for the treatment of mucocutaneous or musculoskeletal manifestations, or both, in 73%, 78% and 93% of the patients, respectively. Patients were stratified into 3 groups according to the HCQ levels: (1) Total non-compliance (<10 ng/ml); (2) Sub-therapeutic (10-500 ng/ml); and (3) Therapeutic (≥500 ng/ml). The proportion of patients with HCQ levels

of <10, 10-500, ≥500 ng/ml was 11%, 77% and 12%, respectively. Patients with total non-compliance to HCQ were more likely to be in clinical and serological remission when compared to the remaining patients (42% vs 24%; p=0.04). However, no difference in the clinical manifestations could be observed between patients with total non-compliance and other patients. After excluding patients with total non-compliance to HCQ therapy, the mean and median HCQ serum concentration of the remaining 245 patients was 300±87ng/ml and 276ng/ml (interquartile range 167-401), respectively. Univariate linear regression revealed that the prescribed HCQ dosage (beta 0.47; p<0.001) and the SLEDAI score at the time of recruitment (beta 0.16; p=0.02) were the significant factors associated with the HCQ serum concentrations. Multivariate linear regression with all the factors being considered in the model showed that the prescribed HCQ dosage (beta 0.50; p<0.001) and eGFR (beta -0.14; p=0.02) were independent factors associated with HCQ serum levels. Age, sex, BMI, smoking, SLEDAI score and concomitant prednisolone were not significantly associated with the HCQ serum concentrations.

Conclusion: Non-compliance and sub-therapeutic HCQ serum levels were frequent in our cohort of SLE patients, which was related to the low prescribed dosage for maintenance treatment in those with clinical and serological remission. Patients with lower eGFR or receiving higher doses of HCQ were more likely to achieve higher HCQ serum concentrations. Thus, HCQ level monitoring and dosage adjustment may be helpful in SLE patients with impaired renal function to reduce the risk of toxicities.

Disclosure: C. C. Mok, None; **L. Y. Ho**, None; **P. Jannetto**, None.

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Abstract Number: 780

Belimumab Use in African-American Patients in an U.S. Academic Medical Center

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Background/Purpose: Belimumab is an anti-BAFF monoclonal antibody approved for the treatment of auto-antibody positive patients with SLE. In two large phase 3 clinical trials, belimumab plus standard of care reduced SLE disease activity compared with standard of care alone. However, African-American SLE patients in these studies had no such improvements resulting in clinicians unsure of the efficacy of belimumab in this group. This study examines the effect of belimumab on clinical outcomes and disease activity in a cohort of African- American patients with SLE being treated at an academic medical center.

Methods: All SLE patients who were African-American and who had been prescribed belimumab as part of their medical care at our center were identified in a retrospective chart review. Data was analyzed for up to 24 months of therapy. Patient demographics, disease manifestations, medication usage, and labs were recorded for visits at Day 0 (day of initial belimumab infusion), and at months 3, 6, 12, 18, and 24. Whenever all appropriate labs, clinical exam and history were

available, a SLEDAI was calculated. For any patient who discontinued belimumab therapy at any time point prior to 24 months, additional information as to reason was recorded.

Results: 23 African-American SLE patients were identified; mean age 38.9 years (22-58), 87% female, with a mean duration of disease of 12.7 years (4-31). At the time of their initial belimumab infusion, 91.3% of the patients were on prednisone at an average dose of 20 mg /day (5-60), 78.3% of patients were taking lupus DMARDs, and 91.3% were on HCQ. The mean SLEDAI score was 8.5 (2-20) with 39% of patients having a score ≥10. 65% of patients were hypocomplementemic (low C3/C4) at baseline, 60% had elevated anti-dsDNA titers, and 47% had both. The most common clinical disease manifestation at belimumab initiation was arthritis (56.5%) followed by cutaneous (47.8%). Over the subsequent observation period, 5 patients (22%) discontinued belimumab therapy at a mean duration of 8.4 months, 2 due to inefficacy, 1 secondary to abnormal LFTs, one patient moved away, and 1 patient self-discontinued secondary to feeling well. For the remainder of the patients, by month 3 the mean SLEDAI had decreased 3.6 points (8.5 to 4.9) and by month 24 the mean SLEDAI was 3.5 ($p < 0.001$). Prednisone dose among those still taking the medication also decreased, going from a mean of 20 mg/day to 8.06 mg/day by month 24 ($p < 0.001$). Four patients came off of prednisone completely. 53.8% of those patients with low C3/C4 normalized their levels and 25% of those with elevated anti-dsDNA titers became undetectable. One patient was hospitalized for community acquired pneumonia during the observation period but no other major infections were noted.

Conclusion: Belimumab is well tolerated and may be effective in African-American patients with SLE. Prednisone doses as well as SLEDAI scores decreased significantly and were maintained through 2 years of treatment in most patients. Ongoing prospective placebo controlled studies with belimumab in African-American SLE patients will hopefully provide more definitive answers.

Disclosure: P. Alejandro, None; **A. Pillarisetty**, None; **C. E. Collins**, None.

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Abstract Number: 781

The Use of Rituximab in Newly Diagnosed Systemic Lupus Erythematosus Patients: Long Term Steroid Saving Capacity and Clinical Effectiveness

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Session Time: 9:00AM-11:00AM

Background/Purpose: To assess the long term steroid saving capacity and clinical effectiveness of B-cell depletion therapy (BCDT) in newly diagnosed SLE patients.

Methods: Sixteen female SLE patients were treated at, or shortly after diagnosis, with BCDT aiming to minimize the routine use of oral steroids. Post-treatment, most patients were given hydroxychloroquine (n=14) and azathioprine (n=10). The BILAG disease activity index was used for clinical assessment. Serum anti-dsDNA antibodies, complement (C3),

ESR, circulating B lymphocytes (CD19+) and total inmmunoglobulins were tested every 2-6 months for an average of 4.5 years (SD 2) post-treatment. Disease activity and steroid requirement over the follow-up period (ranging from 1 to 7 years) were compared with three SLE patients treated conventionally, each carefully matched for ethnicity, sex, age, clinical features, disease duration at diagnosis and length of follow up.

Results: All patients given rituximab achieved B-cell depletion. The mean number of flares during the follow-up period (defined as a new BILAG A or B) was 2.63 (SD 3) in the BCDT group and 4 (SD 3.6) in the control group (NS, p=0.14). Post-BCDT, mean anti- dsDNA antibody level fell from 1,114 U/ml (SD 1,699.3) to 194 (SD 346.7) for 18 months (p= 0.043), mean serum ESR fell by >70% at 6 months maintained during the follow-up and serum C3 level normalized during the follow-up in 8 patients. The mean time to complement normalization was 12.75 months after treatment. At diagnosis, the mean of the Inmunogloblulin G levels in the BCDT group was 17.8 +/- 6.09 g/L and 17.8 +/- 4.3 g/L in the HC (p = 0.98). These values were decreasing progressively to a final average of 10.34 +/- 5.4 g/L in the BCDT group and 12.14 +/- 3 g/L in the HC at 2 years of follow-up and 5.2 +/- 9.35 g/L and 10.2 +/- 2.2 g/L respectively on the fifth year. The mean cumulative prednisolone dose at 60 months for the BCDT patients (n=11) was 4,745.67 mg (SD 6,090 mg) vs 12,553.92 mg (SD 12,672 mg) for the controls (p=0.01). At the end of the follow-up, the SLICC/ACR Damage Index scale showed that the BCDT group had a mean of 1.06 (SD 1.4) and HC a mean of 1.35 (SD 1.5) (p = 0.9).

Conclusion: Early treatment of SLE patients with BCDT is safe, effective and enables a reduction in the overall steroid burden. The accumulated damage in both groups measured by SLICC/ACR Damage Index showed a trend to a lower score in the BCDT group although this did not reach statistical significance. These results support the idea that the use of rituximab as a first-line treatment has similar efficacy to long term conventional treatment but with significantly lower prednisolone dose requirement.

Disclosure: B. D. C. Gracia Tello Sr., None; **D. A. Isenberg**, None; **A. Ezeonyeji**, None.

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Abstract Number: 782

Can We Identify Who Benefits from Mycophenolate Mofetil in Systemic Lupus Erythematosus? a Systematic Review

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Session Time: 9:00AM-11:00AM

Background/Purpose: Mycophenolate mofetil (MMF) is widely used in the treatment of SLE however little is known about factors that may predict response or other outcomes following MMF therapy. We aimed to undertake a systematic review to (1) identify predictors of outcomes to MMF in SLE (in randomized clinical trials (RCTs); and (2) to identify

'risk factors' for clinical outcomes following MMF treatment for SLE in observational cohorts.

Methods: We searched Medline, Embase, Web of Science and Cochrane Central Registers for Controlled Trials up to November 2015 for relevant studies. Two reviewers independently assessed the methodological quality of the RCTs using the Cochrane Collaboration risk of bias tool and cohort studies using the Quality In Prognosis Studies tool. The quality of subgroup analysis was also evaluated. The Grading of Recommendations Assessment, Development, and Evaluation working group approach summarized the quality of evidence (QoE), considering the risk of bias, imprecision, inconsistency, indirectness, and publication bias.

Results: The QoE for the prognostic value of age at study entry, gender and race was low, mainly due to exploratory or insufficient subgroup analysis, risk of bias and imprecision. The prognostic value of baseline laboratory parameters (glomerular filtration rate, proteinuria, serum creatinine) and changes during treatment (complement, proteinuria, anti-dsDNA) is very low due to post hoc subgroup analyses, risk of bias, indirectness and imprecision. One low QoE observational study showed that concomitant membranous lupus nephritis (LN) on biopsy may be an independent factor for no remission. This was not confirmed by subgroup analysis of RCT or other observational cohorts. Concomitant HCQ therapy and MMF treatment for less than 18 months were associated with response and relapse, respectively; MMF dose was not associated with adverse events (reduced IgG levels) in very-low to low QoE studies. One small cohort study found that a mycophenolic acid area under the curve ≥30 mg·h·L-1 was associated with renal response but not with side effects (infections).

Conclusion: In SLE, evidence for predictors of outcomes with MMF is limited and is mainly from secondary and post-hoc analyses. We identified between-study heterogeneity and a high risk of bias across studies. Well-designed studies are required to confirm whether demographic factors, LN biopsy class, concomitant therapy or pharmacokinetic markers truly predict MMF responses and adverse events in SLE. **Study supported by CONACYT Table 1** Characteristics of studies on prognostic factors

Study ID	Design	No. part.	Follow-up	Prognostic factor	Outcomes	Adjustment for confounders
Alexander 2014	prospective	34	12 m	MPA AUC MPA trough plasma concentrations	Renal response Adverse events	No
Cortes-Hernandez 2010	prospective	70	24 m	Age, serum albumin Anti-dsDNA Hypocomplementaemia Histopathological class	Renal response Renal relapse Treatment failure	No
Kasitanon 2006	retrospective	29	12 m	Concomitant HQC use	Complete renal remission in MLN	Presence of anti-ds-DNA antibody
Kasitanon 2008	retrospective	29	12 m	Mixed MLN	Complete renal remission	No
Laskari 2011	retrospective	44	30 m	Duration of MMF	Relapse Side effects	No
Lu 2008	prospective	213	24 w	Baseline serum creatinine, Histopathological class	Renal remission	No
Mino 2012	prospective	34	13 m	Plasma concentration of MPA or MPAG	Changes in disease markers	No
Nannini 2009	retrospective	29	14.8 m	Concomitant HQC use	Disease flares	No
Riskalla 2003	retrospective	54	12.4 m	Baseline serum creatinine, MMF dose	Side effects	No
Rivera 2012 £	retrospective	90	36 m	Gender, Poor renal function, Histopathological class.	Complete response Infectious	Age, gender, eGFR, LN class and proteinuria
Rivera 2013£	retrospective	56	24m	Gender, Proteinuria, Poor renal function Histopathological class	End-stage disease Mortality	Gender, baseline eGFR, proteinuria and LN class
Tselios 2016	retrospective	177	12 m	Renal involvement	Extrarenal manifestation improvement	No
Yap 2014*	Retrospective cohort	46	12 m	Proteinuria, serum creatinine, Anti-dsDNA and C3, White cell count Lymphocyte count at 6 m, MMF dose	Circulating IgG level	Same used for each prognostic factor

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Disclosure: C. Mendoza Pinto, None; **C. Pirone**, None; **B. Parker**, None; **I. N. Bruce**, None.

Abstract Number: 783

Review of SLE Cohort to Identify Predictors of Response to B Cell Depletion in Patients with Active SLE

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Background/Purpose:

The use of Rituximab (RTX) has been documented via published cohort data from over 20 sites worldwide (1,2) demonstrating its useful role in the treatment of Systemic Lupus Erythematous (SLE). UCLH have been using RTX for SLE since 2000 and have records from the 139 patients treated to date. The aim of this retrospective review of this cohort data to was determine if there are any relatively simple clinical aspects or bio markers that can help the clinician anticipate the likely response to B Cell depletion with Rituximab.

Methods:

Patients in the UCLH cohort are included once they meet ACR criteria for a diagnosis of SLE. During their routine clinic visits they have prospective data collected which was utilised in this review. Patient files were then reviewed to collect the available laboratory results. From this retrospective analysis 139 patients were identified as having received Rituximab, 121 patients were used in the analysis. We excluded 3 patients due to follow up time <6months and 15 due to missing BILAG scores for the times of interest. We compared the responders (defined using BILAG scores - Complete Response (CR) loss of all A's or Bs; Partial Response (PR) loss of some A's and B's but not all, at 6 month follow up) versus Non-Responders (NR) these do not meet criteria for CR/PR, developed a new A or B during 6months follow up or had died. We only analysed the first dose of RTX with response for each patient.

The cohort is described in table 1.

	Responders		**Non-Responders**
	Complete Responder **(n = 52)**	***Partial Responder*** **(n=32)**	**(n=37)**
Female	50 (96%)	28 (87.5%)	37 (100%)
Age at diagnosis	26.3 (8-69)	25.2 (10-59)	26.9 (8-51)
Age at RTX	34.4 (16-69)	33.2 (15-73)	34.9 (19-57)
Caucasian	29 (56%)	11 (34%)	13 (35%)
Ro	24 (47%)	17 (53%)	24 (64%)
La	11 (21%)	5 (16%)	10 (27%)
Sm	13 (25%)	11 (34%)	11 (30%)
RNP	23 (45%)	17 (53%)	16 (43%)
Fatigue	15 (29%)	8 (25%)	18 (49%)
Raynauds	9 (17%)	6 (19%)	8 (22%)
Photosensitivity	2 (4%)	1 (3%)	1 (3%)
Rash	31 (60%)	12 (38%)	25 (62%)
Alopecia	10 (19%)	8 (25%)	16 (43%)
Oral ulcers	10 (19%)	8 (25%)	10 (27%)
Arthritis	33 (63%)	25 (78%)	31 (84%)
Serositis	13 (25%)	9 (28%)	7 (19%)
Renal	18 (35%)	17 (53%)	15 (41%)
Neurological	4 (8%)	3 (9%)	6 (16%)
Haematological	12 (23%)	9 (28%)	11 (34%)
B Symptoms	8 (15%)	6 (19%)	8 (22%)
Lymphadenopathy	2 (4%)	5 (16%)	2 (6%)
Vasculitis	9 (17%)	6 (19%)	5 (14%)
Sicca Syndrome	3 (6%)	1 (3%)	2 (6%)
Myositis	1 (2%)	2 (6%)	0
No Steroids and ≥ 1 immunossupressor	5 (10%)	0	3 (8%)
Steroids	2 (4%)	2 (6%)	2 (6%)
Steroids and 1 immunosuppression	7 (13%)	4 (12%)	6 (16%)
Steroids and >1 immunosuppression	38 (25%)	26 (81%)	26 (70%)
dsDNA pre-treatment			
mild elevation <5xULN,	17 (33%)	6 (19%)	7 (19%)
moderate elevation >5xULN	14 (27%)	17 (53%)	13 (35%)
CD19 depletion at 3 months	38 (73%)	27 (84%)	26 (70%)

Variables including age, sex, ethnicity, age at diagnosis, age at first dose of rituximab, clinical phenotype, ENA, previous medications, C3 levels pre and at 6months, dsDNA levels pre and 6months, CD19 count pre and at 3 months were examined via univariable analysis to determine if there was a statistically significant correlation.

Results:

Alopecia and fatigue presence were inversely correlated with response to treatment (p value 0.014 and 0.023, respectively) however for fatigue this was not maintained in the sub group analysis (comparison between complete responders and non- responders only). In this cohort there were no statistically significant association between response and CD19 depletion, dsDNA or C3 levels pre and post-Rituximab.

Conclusion:

During this retrospective review of the SLE cohort from UCLH we were unable to identify any routine laboratory

biomarkers to predict response. In this cohort the only clinical feature was alopecia which was inversely correlated with response.

References:

1. Favas C, Isenberg DA. Nature Rev Rheum 5; 711-6; 2009.

2. Beckwith, H, Lightstone, L. Nephron Clin Pract 2014;128:250–254 Hannah Beckwith Liz Lightstone

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Abstract Number: 784

Drivers of the SLE Responder Index (SRI) Endpoint in Clinical Trials of SLE

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Background/Purpose: SRI is a composite endpoint designed to ensure that clinical improvement (measured by SLEDAI) is not accompanied by deterioration in other organ systems (measured by BILAG and PGA). This novel endpoint, coupled with trial completion and adherence to treatment rules, has defined response in many SLE trials. The current investigation sought to identify those components of the SRI that were critical to defining response. Additionally, individual organ systems were examined to determine those which impacted SLEDAI improvement.

Methods: Data were analyzed from two large phase 3 multinational trials that evaluated the impact of an anti-BAFF antibody or placebo, when added to *s*tandard of *c*are (SOC) on SLE disease activity using the SRI-5 endpoint (combined n=2262 SLE patients) (1,2).

Results: The overall SRI-5 response rate was 32.8% (743/2262). Non-response due to lack of a 5-point SLEDAI improvement, conmed violation or dropout were observed in 31% (702/2262), 16.5% (373/2262) and 19.1% (433/2262), respectively. In contrast, only 0.5% (7/2262) failed to meet responder criteria due to deterioration by BILAG or PGA after achieving ≥ 5 point reduction in SLEDAI, trial completion and adherence to concomitant medication rules. As expected,the predominant individual SLEDAI organ systems involved at baseline were mucocutaneous (90.6%), musculoskeletal (82.9%) and immunologic (71.6%) In the mucocutaneous organ system, the baseline prevalence of rash was 69.2%;

alopecia 58.2%; mucosal ulcer 32.5%. In the musculoskeletal system, the baseline prevalence of arthritis was 82.6%; myositis 1.1% SLEDAI organ systems with low prevalence and high point value (≥ 4 pts/feature) were also examined. At baseline, 18.1% of patients in Trial 1 and 17.2% in Trial 2 had renal, vascular or CNS organ involvement. SRI-5 response rates for placebo + SOC were CNS: 66.7%, 57.1%; renal: 45.2%, 53.3%; and vascular: 56.7%, 48%, in Trials 1 and 2, respectively. SLEDAI improvement for the 4 most common individual features was examined in the placebo plus SOC population (analysis based on observed data). Response rate for arthritis: 58.4%, 66.5%; rash: 47.8%, 54.3%; alopecia: 43.1%, 48.4%; and mucosal ulcer 85.4%, 74.7% in Trials 1 and 2, respectively.

Conclusion: The primary drivers of SRI-5 response in these trials were SLEDAI improvement, concomitant medication adherence and trial completion, which have intrinsic clinical meaningfulness. When SLEDAI scores improved by ≥ 5 points at wk 52 in pts with stable SOC, worsening in other disease activity instruments was rare, making their contribution less relevant to the outcome of a trial. Patients with infrequent yet severe manifestations had high placebo group response rates. Thus, for clinical trials that are intended to study new therapeutics in SLE patients with non- major organ threatening disease manifestations, a simple, dichotomous improvement in SLEDAI score, coupled with successful trial completion and medication stability, may provide a simple and potentially more clinically relevant approach to assess outcome.

1. Merrill et al., Ann Rheum Dis (2016) 75:332-40.
2. Isenberg et al., Ann Rheum Dis (2016) 75:323-31

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Abstract Number: 785

What Is the Prevalence of Cognitive Impairment in Lupus and Which Instruments Are Used to Measure It? a Systematic Review and Meta-Analysis

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Background/Purpose: To systematically review literature on: 1) the prevalence of Cognitive Impairment (CI) in SLE patients in the presence or absence of neuropsychiatric involvement (NPSLE), 2) the metrics of CI and 3) the relative risk (RR) for CI in SLE compared to Rheumatoid Arthritis (RA) and healthy individuals.

Methods: This review was prepared with a protocol following the Preferred Reporting Items for Systematic Reviews and

Meta-Analysis-Protocols statement. Literature search (1900-2016) in Ovid Medline, Embase and Psyc INFO for articles on the prevalence of CI in adult SLE patients using a specified neuropsychological instrument of cognitive function (CF) was conducted. Included studies were critically appraised and analyzed. The prevalence of CI was studied for all instruments and whenever possible Pooled Prevalence (PP) was determined in the commonly used instruments [standardized batteries, Modified Mini–Mental State Exam (MMSE), Automated Neuropsychological Assessment Metric (ANAM) and Montreal Cognitive Assessment (MoCA)].

Results: Of 3422 references, 670 were selected for detailed review and 84 were included in the final analysis. Standardized batteries (including ACR battery) were utilized in 41 studies in 3338 patients and found a PP of CI of 34% (95% CI: 28-40%) (Figure 1). CI was higher in NPSLE with PP of 41 (95% CI: 26-57%) (Pooled from 13 studies in 647 NPSLE patients). ANAM was utilized in 9 studies in 773 patients and yielded a PP of CI of 37% (95% CI: 20-55%). MMSE was utilized in 9 studies in 766 patients and yielded a PP of CI of 19% (95% CI: 10-30%). MoCA was utilized in 2 studies in 100 patients and yielded a PP of CI of 45% (95% CI: 14-77%). A large variability in the prevalence of CI and a high statistical heterogeneity (I^2> 75%) among studies was identified. This could have resulted because of: 1-the lack of standardization in the metrics and definitions of CI in SLE, 2) heterogeneity in the studied sample size (which involved patients with and without NPSLE) and 3) variability in other demographics such as patients age, education levels and others factors. _ The RR for CI in SLE was 1.77 (95% CI: 1.19-2.64) compared to RA (data from 6 studies of 343 lupus and 193 RA patients. The RR for CI in SLE compared to healthy individuals was 2.57 (95% CI: 1.62-4.08) (data from 10 studies of 529 SLE patients and 328 healthy individuals).

Conclusion: Patients with lupus have a high prevalence of CI ranging from 2.7–80% and largely depending on the metrics and the presence or absence of NPSLE. There is a lack of a standardized approach on how to measure and define CI in SLE. ANAM and standardized batteries (including ACR) yielded similar CI prevalence, while MMSE carried the lowest prevalence. NPSLE patients are as well at a higher risk for CI compared to non-NPSE. Lupus patients are at a higher risk to develop CI compared to RA and healthy individuals. **Figure 1. Forest Plot of CI in SLE patients using standardized batteries including ACR**

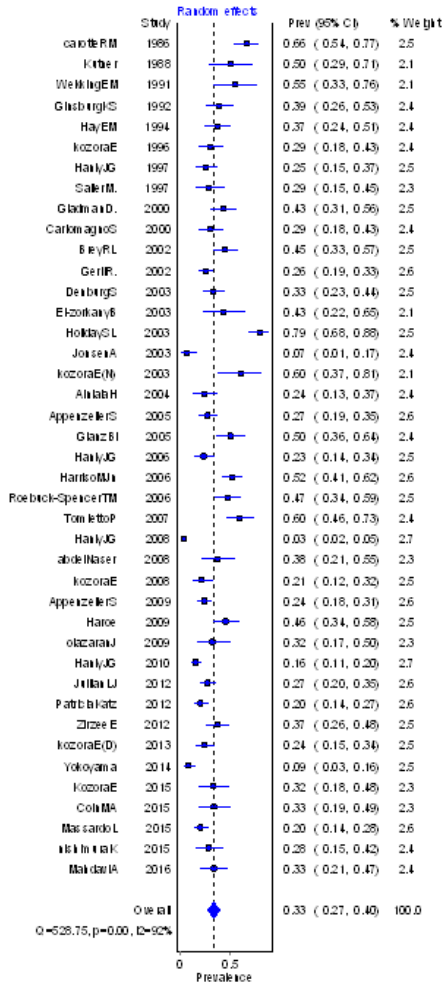
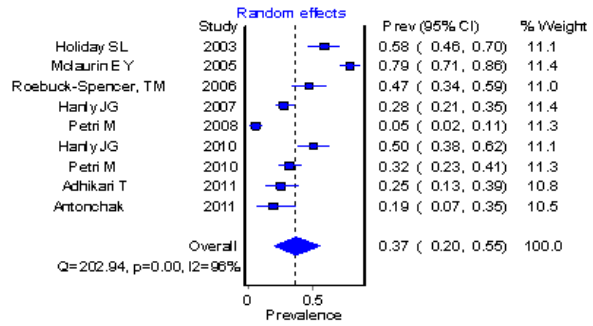


Figure 2. Forest Plot of CI in SLE patients using ANAM test:



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Abstract Number: 786

Complement Split Product iC3b and C3 Blood Levels Best Associate with

Active and Clinically Meaningful Changes in SLE Disease Activity

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Session Time: 9:00AM-11:00AM

Background/Purpose: A major unmet need in SLE is the identification of a biomarker that consistently tracks with disease activity. One current approach is measuring complement activation by evaluating consumption of serum C3 and C4. However, since they are acute phase reactants, interpretation of these levels is challenging as serum levels may not decrease until late in a disease flare. iC3b is a proteolytically derived molecule of C3b, and increases with complement activation. iC3b/C3 ratio measures complement consumption relative to production, which may provide for a more accurate assessment of complement activation. We hypothesize that blood iC3b and iC3b/C3 levels will provide a more specific and reliable marker of complement activation and disease activity in SLE.

Methods: 137 adult SLE patients were enrolled in this prospective, longitudinal, observational study. 79 patients with 3-7 study visits were used for this longitudinal analysis. C3 and C4 were measured by nephelometry; iC3b by a lateral flow assay using an investigational medical device. SLE disease activity was measured using the SLEDAI 2K Responder Index-50 instrument. Multilevel regression models were performed to examine associations for SLE disease activity. Ordinal logistic regression models with generalized estimating equation modeling (GEE) were used to examine associations for clinically meaningful changes since the outcome variable is ordinal (i.e. clinical deterioration, stability, and improvement). Odds ratios and 95% confidence intervals for iC3b, C3, iC3b/C3 ratios, C4, ESR, CRP, dsDNA values, prednisone usage, and race were estimated using Proc GLIMMIX and Proc GENMOD (SAS v9.4).

Results: Blood levels of iC3b, C3, iC3b/C3 ratio, C4, dsDNA, and prednisone use each correlated with SLE disease activity. Multilevel multiple logistic regression analysis revealed only iC3b/C3 ratio, dsDNA levels, and prednisone use were significant predictors of disease activity (Table 1A). To determine whether iC3b/C3 ratio can predict clinically meaningful changes in SLE disease activity, we evaluated the interpatient longitudinal associations between clinical deterioration, stability, and improvement and iC3b/C3 ratios. Only iC3b/C3 ratio and prednisone use significantly predicted clinically meaningful changes in disease activity (Table 1B).

Conclusion: In this prospective, longitudinal study, blood iC3b/C3 ratios are predictive of active SLE disease. Furthermore, iC3b/C3 ratio is predictive of clinical meaningful changes in SLE disease activity. These data warrant further investigation of iC3b/C3 ratio as a potential biomarker for SLE disease activity.

Table 1. Univariate and multivariate logistical regression analyses of variables predictive of active and clinically meaningful changes in SLE disease activity

A) Active SLE

Univariate

Predictor Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
iC3b (Δ1 µg/mL)	1.20	1.03	1.40
iC3b/C3 ratio (Δ 1 unit)	1.30	1.15	1.48
C3 (Δ10 mg/dL)	0.80	0.70	0.92
C4 (Δ5 mg/dL)	0.72	0.57	0.91
dsDNA Ab (Δ10 IU/mL)	1.06	1.02	1.10
ESR (Δ10 mm/hr)	1.18	0.997	1.39
CRP (Δ10 mg/L)	1.02	0.74	1.41
Prednisone (Yes vs No)	3.69	1.62	8.39
Race (White vs AA)	0.90	0.32	2.54
Visit #	0.89	0.74	1.07

Multivariate

Predictor Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
iC3b/C3 ratio (Δ 1 unit)	1.29	1.01	1.64
dsDNA Ab (Δ10 IU/mL)	1.04	1.01	1.08
Prednisone (Yes vs No)	3.88	1.74	8.63
Visit #	0.71	0.56	0.91

B) Clinically meaningful change in SLE disease activity

Univariate

Predictor Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
iC3b (Δ1 µg/mL)	1.10	0.99	1.23
iC3b/C3 ratio (Δ 1 unit)	1.06	1.03	1.10
C3 (Δ10 mg/dL)	0.98	0.90	1.07
C4 (Δ5 mg/dL)	0.98	0.86	1.12
dsDNA Ab (Δ10 IU/mL)	1.02	0.99	1.03
ESR (Δ10 mm/hr)	1.14	1.05	1.24
CRP (Δ10 mg/L)	1.18	0.87	1.60
Prednisone (Yes vs No)	0.79	0.52	1.18
Race (White vs AA)	1.05	0.73	1.53
Visit #	1.16	1.02	1.33

Multivariate

Predictor Variable	Odds Ratio	Lower 95% CI	Upper 95% CI
iC3b/C3 ratio (Δ 1 unit)	1.07	1.03	1.10
Prednisone (Yes vs No)	0.67	0.45	0.99

Disclosure: A. Kim, Kypha, Inc., 2,Amgen, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5; **D. Sen**, None; **V. Strand**, Abbvie, Amgen, AstraZeneca, BiogenIdec, Boehringer Ingelheim, Celltrion, Crescendo, Genentech/Roche, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Regeneron, Samsung, Sanofi and UCB, 5; **Q. J. Fu**, Kypha, Inc., 5; **N. Mathis**, Kypha, Inc., 5; **R. Bruchas**, Kypha, Inc., 3; **N. Staten**, Kypha, Inc., 3; **M. Schmidt**, Kypha, Inc., 3; **P. Olson**, Kypha, Inc., 3; **C. Stiening**, Kypha, Inc., 3; **J. Atkinson**, None.

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Abstract Number: 787

Using the American College of Rheumatology and Systemic Lupus International Collaborating Clinics Criteria to Measure Disease Severity in Discoid Lupus Erythematosus

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster I: Clinical Trial Design and Current Therapies

Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Discoid lupus erythematosus (DLE) progresses to systemic lupus erythematosus (SLE) in up to 28% of cases. The Systemic Lupus International Collaborating Clinics (SLICC) SLE criteria were developed to improve the American College of Rheumatology (ACR) criteria, but have not been assessed in DLE patients.

Methods: This was a retrospective study of 172 DLE patients enrolled in a cutaneous lupus database at the University of

Pennsylvania. Patients were assessed for the presence of ACR and SLICC criteria using the database and respective electronic medical records. The Fischer's exact test was used for each criterion in the ACR and SLICC to determine a difference between patients with DLE/SLE and DLE-only disease.

Results: Using the ACR criteria, 74 patients (52%) were classified as DLE/SLE and 68 (48%) as DLE-only, compared with 66 (46%) DLE/SLE and 76 (54%) DLE-only patients using the SLICC criteria (p=0.08). This net increase of 8 patients meeting ACR criteria was due to the presence of the photosensitivity criterion and fewer immunologic criteria under ACR. Due to the immunologic criteria requirement under SLICC, it can be challenging to determine an SLE diagnosis retrospectively. Overall, DLE/SLE patients were more likely than DLE-only patients to exhibit significant systemic symptoms with regard to arthritis (ACR 73% *vs.* 9%, p<0.0001; SLICC 70% *vs.* 18%, p<0.0001), serositis (ACR 22% *vs.* 0%, p<0.0001; SLICC 22% *vs.* 3%, p<0.0001), and renal disorder (ACR 27 % *vs.* 2%, p<0.0001; SLICC 33% *vs.* 0%, p<0.0001). SLE was more common in generalized DLE than in localized DLE using ACR (p=0.0001) and SLICC (p=0.0068) criteria. DLE/SLE patients were more likely to have worse skin disease compared to DLE-only patients when classified according to ACR criteria, with 40.5% of DLE/SLE patients having CLASI^{TM} activity ≥ 10 and 25.0% of DLE-only patients having CLASI^{TM} ≥ 10 (Table 1).

Conclusion: DLE/SLE patients have more significant internal disease than DLE patients who do not meet SLE criteria. Our findings trended toward the ACR criteria classifying more DLE patients with SLE than the SLICC criteria, particularly in patients without extensive laboratory testing. DLE-only patients may have significant skin disease with approximately 25% of DLE-only patients having moderate to severe skin disease.

	DLE with SLE n (%)	DLE without SLE n (%)	P-value
CLASI^{TM} ≥ 10	30 (40.5)	17 (25.0)	0.0493*
CLASI^{TM} < 10	44 (59.5)	51 (75.0)	

Table 1A. Skin activity in DLE/SLE vs DLE-only patients using ACR criteria. DLE/SLE patients are more likely to have worse skin disease compared to DLE-only patients when classified according to the ACR criteria.

	DLE with SLE n (%)	DLE without SLE n (%)	P-value
CLASI^{TM} ≥ 10	27 (40.9)	20 (26.3)	0.0653
CLASI^{TM} < 10	39 (59.1)	56 (73.7)	

Table 1B. Skin activity in DLE/SLE vs DLE-only patients using SLICC criteria. There is a trend of DLE/SLE patients having worse skin disease compared to DLE-only patients when classified according to the SLICC criteria.

Disclosure: J. K. Presto, None; **J. S. Haber**, None; **V. P. Werth**, None.

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Abstract Number: 788

Unresolving C4 Hypocomplementemia Associates with a Different Spectrum of Disease in SLE and Is More Important Than Transiently Low Levels

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Background/Purpose: Hypocomplementemia is common in systemic lupus erythematosus (SLE) and is included in classification criteria and disease activity indices. Whether persistently low complement levels (C3, C4 and both) are more important as serological markers, than levels which transiently drop in SLE is unknown. This work was undertaken to characterize SLE patients with persistent hypocomplementemia and to compare them to those with intermittently low levels.

Methods: Patients were identified as part of a longitudinal lupus cohort. Levels of C3 and C4 were measured quarterly, by nephelometry. Patients were considered with complement levels (either C3, C4 or both), which never returned to the normal range on longitudinal follow-up. Further analysis included those with intermittently low levels. To assess associated clinical manifestations, univariate and multivariate logistic regression were used. The multivariate analysis controlled for ethnicity, and gender.

Results: 2399 SLE patients, 53% Caucasian and 38% African-American, were evaluated. A history of ever having had low C3 was present in 55% and low C4 in 47%. There were 83 (4.0%) patients with persistently low C3, which never normalized and 65 (3.2%) individuals with persistently low C4. The clinical manifestations associated with persistent hypocomplementemia are outlined in Table 1 whilst those associated with transiently low levels are in Table 2. Persistently low C3 associates with renal, hematologic and serologic abnormalities with similar manifestations in those with intermittently low C3. Contrarily, chronically low C4 associates with a myriad of abnormalities, serologic and hematologic whilst intermittently low levels associate only with a positive anti-double stranded DNA, anticardiolipin and a false positive rapid plasma reagin. Persistently low C3 and C4 in combination associated with serologic abnormalities and the presence of antiphospholipid antibodies, whilst in those with transiently low levels there was cutaneous, neurologic, hematologic and immunologic dysfunction demonstrated.

Conclusion: Low complement is an important finding in SLE. Transiently low C4 is a weak marker which associates with few clinical manifestations. However, chronically low C4, which may represent a subset of patients with genetic deficiency, associates with a different spectrum of disease and has different, more severe, clinical implications.

SLE manifestation		Persistently low C3	P value	Persistently low C4	P value	Persistently low C3 and C4	P value
Malar rash		1.02 (0.6,1.75)	0.9380	0.83 (0.44,1.56)	0.5591	1.54 (0.67,3.54)	0.3083
Discoid rash		1.35 (0.71,2.55)	0.3607	1.34 (0.57,3.12)	0.5009	1.03 (0.34,3.1)	0.9629
Photosensitivity		0.74 (0.43,1.27)	0.2770	1.04 (0.54,2)	0.8948	0.82 (0.36,1.88)	0.6435
Oral/Nasal Ulcers		0.92 (0.54,1.58)	0.7647	0.85 (0.45,1.61)	0.6217	0.53 (0.23,1.25)	0.1495
Arthritis		1.54 (0.81,2.91)	0.1885	0.93 (0.47,1.84)	0.8427	1.75 (0.64,4.78)	0.2738
Serositis	**Pleurisy**	1.17 (0.69,2.01)	0.5583	1.29 (0.68,2.43)	0.4301	1 (0.43,2.33)	0.9946
	Pericarditis	1.67 (0.91,3.06)	0.0994	1.88 (0.89,3.94)	0.0959	0.47 (0.11,2.05)	0.3163
Renal disorder		3.15 (1.39,7.15)	**0.0061**	0.67 (0.09,5.06)	0.7007	2.04 (0.46,9.07)	0.3492
Neurologic	**Seizures**	1.14 (0.47,2.75)	0.7675	0.81 (0.24,2.69)	0.7307	0.45 (0.06,3.38)	0.4376
	Psychosis	1.19 (0.27,5.16)	0.8200	1.09 (0.14,8.31)	0.9345	1.69 (0.22,13.11)	0.6181
Hematologic	**Hemolytic anemia**	1.51 (0.62,3.7)	0.3627	5.01 (2.32,10.82)	**<.0001**	0.59 (0.08,4.49)	0.6125
	Leukopenia	3.57 (2.02,6.32)	**<.0001**	2.7 (1.43,5.11)	**0.0022**	2.61 (1.14,5.98)	**0.0238**
	Lymphopenia	1.96 (1.15,3.35)	**0.0140**	2.88 (1.5,5.53)	**0.0014**	1.12 (0.48,2.59)	0.7956
	Thrombocytopenia	2.3 (1.27,4.19)	**0.0063**	2.54 (1.26,5.12)	**0.0093**	1.57 (0.57,4.33)	0.3791
Immunologic	**Anti-dsDNA**	10.21 (4.34,24.05)	**<.0001**	2.99 (1.5,5.97)	**0.0018**	8.3 (2.45,28.12)	**0.0007**
	Anti Sm	6.1 (3.39,10.97)	**<.0001**	4.77 (2.24,10.16)	**<.0001**	3.08 (1.15,8.23)	**0.0247**
Anti-phospholipid	**Anti-cardiolipin**	1.58 (0.92,2.72)	0.0961	2.34 (1.21,4.51)	**0.0114**	1.52 (0.65,3.56)	0.3360
	Anti- B2 Glycoprotein	4.71 (2.16,10.27)	**0.0001**	2.3 (0.73,7.2)	0.1542	2.83 (0.78,10.35)	0.1152
	False positive RPR	3.08 (1.5,6.31)	**0.0021**	2.75 (1.2,6.28)	**0.0166**	4 (1.23,12.96)	**0.0209**
	Lupus Anticoagulant	2.11 (1.2,3.72)	**0.0095**	2.03 (1.05,3.91)	**0.0348**	1.45 (0.58,3.62)	0.4246

SLE manifestation		Low C3 Only OR (CI)	P Value	Low C4 only OR (CI)	P value	Both Low C3 and Low C4 OR (CI)	P value
Malar rash		0.96 (0.75,1.24)	0.7617	0.89 (0.63,1.26)	0.5172	1.29 (1.08,1.54)	**0.0058**
Discoid rash		1.33 (0.97,1.82)	0.0770	0.71 (0.42,1.18)	0.1826	1.3 (1.03,1.62)	**0.0255***
Photosensitivity		0.68 (0.53,0.88)	**0.0034**	0.87 (0.62,1.24)	0.4474	0.83 (0.69,0.99)	**0.0351***
Oral/Nasal Ulcers		0.68 (0.53,0.87)	**0.0028**	0.97 (0.69,1.38)	0.8778	0.75 (0.63,0.9)	**0.0020**
Arthritis		0.75 (0.57,0.98)	**0.0329**	1.17 (0.79,1.74)	0.4404	1.23 (1,1.5)	**0.0476**
Serositis	**Pleurisy**	1.18 (0.91,1.52)	0.2131	1.03 (0.72,1.47)	0.8802	1.59 (1.32,1.9)	**<. 0001**
	Pericarditis	1.19 (0.86,1.65)	0.2914	0.82 (0.5,1.34)	0.4180	1.94 (1.56,2.41)	**<. 0001**
Renal disorder		3.02 (1.89,4.82)	**<. 0001**	0.99 (0.41,2.38)	0.9803	2.94 (2.02,4.28)	**<. 0001**
Neurologic	**Seizures**	1.19 (0.75,1.88)	0.4585	1.21 (0.65,2.24)	0.5513	1.67 (1.22,2.28)	**0.0012**
	Psychosis	1.36 (0.66,2.8)	0.4090	1.07 (0.37,3.13)	0.9017	1.77 (1.07,2.93)	**0.0272**
Hematologic	**Hemolytic anemia**	2.25 (1.37,3.7)	**0.0013**	1.33 (0.61,2.91)	0.4702	4.32 (3.01,6.19)	**<. 0001**
	Leukopenia	1.92 (1.49,2.49)	**<. 0001**	1.24 (0.87,1.78)	0.2373	2.75 (2.28,3.31)	**<. 0001**
	Lymphopenia	1.38 (1.06,1.8)	**0.0183**	1.21 (0.83,1.75)	0.3152	2.54 (2.11,3.06)	**<. 0001**
	Thrombocytopenia	1.8 (1.3,2.51)	**0.0005**	1.43 (0.89,2.28)	0.1407	2.65 (2.09,3.36)	**<. 0001**
Immunologic	**Anti-dsDNA**	2.2 (1.7,2.85)	**<. 0001**	2.05 (1.44,2.92)	**0.0001**	8.2(6.61,10.6)	**<. 0001**
	Anti Sm	2.08 (1.46,2.97)	**0.0001**	0.99 (0.55,1.79)	0.9744	4.23 (3.28,5.45)	**<. 0001**
Anti-phospholipid	**Anticardiolipin**	1.42 (1.1,1.84)	**0.0076**	1.64 (1.16,2.34)	**0.0057**	2.08 (1.73,2.5)	**<. 0001**
	Anti- b2 GP 1	1.8 (1.25,2.59)	**0.0015**	1.59 (0.95,2.66)	0.0791	2.2 (1.7,2.86)	**<. 0001**
	FP RPR	1.73 (1.11,2.71)	**0.0162**	3.93 (2.4,6.44)	**<. 0001**	3.47 (2.53,4.76)	**<. 0001**
	Lupus anticoagulant	1.29 (0.96,1.74)	0.0920	1.33 (0.89,1.98)	0.1661	1.64 (1.33,2.02)	**<. 0001**

Disclosure: L. Durcan, None; **W. Fu**, None; **M. Petri**, None.

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Abstract Number: 789

Use of Nominal Group Technique to Determine Candidate Items for SLE Classification Criteria Development

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Background/Purpose: Criteria for the classification of SLE are being developed with the support of EULAR and ACR. Two independent exercises (expert-based Delphi exercise and data-driven cohort evaluation of early SLE and controls) were undertaken to generate candidate criteria, and then reduce them to a smaller set. The objective of this study was to select a set of items that maximizes the likelihood of accurate classification of SLE, particularly early disease.

Methods: In the Delphi exercise, 120 international SLE experts proposed 196 items useful for the classification of a broad spectrum of SLE, including early and late stage disease.[1] Features distinguishing early SLE (<3 years) and controls were also evaluated in a cohort from 2 European and 2 North American centers.[2] The candidate criteria were rated, and low ranking and redundant criteria were removed, leaving 41 criteria.[1] An independent panel of seven international SLE experts (reflecting practice in Spain, France, Germany, United States, Canada and Mexico) was asked to rank the 41 candidate criteria. The ranking was presented at a face-to-face meeting of the expert panel and steering committee. A consensus meeting using nominal group technique (NGT) was conducted to reduce the list of criteria for consideration.

Results: The expert panel NGT exercise reduced the candidate criteria for SLE classification from 41 to 21. The panel distinguished potential “entry criteria”, which would be required for classification, from other potential “additive criteria”, summarized in Table 1. Potential entry criteria were ‘ANA ≥1:80 (by HEp 2 immunofluorescence)’ and ‘low C3 and/or low C4.’ The use of low complement as an entry criterion was considered potentially useful in cases with negative ANA. **Table 1.** Additive Criteria

Lupus nephritis by renal biopsy with immune deposits
Rash with dermoepidermal interface changes and/or immunoglobulin and/or complement deposition on immunofluorescence
Anti-dsDNA antibody
Anti-Smith antibody
Presence of multiple autoantibodies*
Anti-phospholipid antibodies (*lupus anti-coagulant, anti-cardiolipin, anti-beta2GPI, or prolonged RVVT*)
Leukopenia (<4000/mm^3 on 2 or more occasions)
Thrombocytopenia <100,000 on 2 or more occasions
Autoimmune hemolytic anemia
Active urine sediment (without UTI)
Persistent proteinuria (≥0.5g/day)
Acute cutaneous lupus: SLICC definition (includes subacute cutaneous lupus)
Chronic cutaneous lupus: SLICC definition
Alopecia with associated scalp inflammation
Arthritis*
Serositis *(pleural, pericardial effusion, pleurisy, pericarditis, peritonitis)*
Oral mucosal lesions on the hard palate
CNS manifestations *(seizures, psychosis, chorea, myelitis, optic neuritis, stroke or acute confusional state*)
Fever*

* to be defined. Additional work is needed to refine definitions, to evaluate their independence and relationships within domains, and to ascertain item weights.

Conclusion: The expert panel's NGT exercise resulted in 21 candidate SLE classification criteria. Refinement of definitions, ability to cluster criteria into domains and weighting of criteria will be ascertained in the next phase.

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Abstract Number: 790

Assessment of the Construct Validity of the Lupus Low Disease Activity State (LLDAS) – an Expert Opinion Case Study

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Background/Purpose: Systemic lupus erythematosus (SLE) has historically lacked clear treat-to-target definitions. The recently reported Lupus Low Disease Activity State (LLDAS) definition, combining disease activity and treatment domains, was shown to be associated with protection from damage accrual in a longitudinal cohort study. Before acceptance in clinical practice and research, any new measure should undergo rigorous validation including face, content, construct and criterion validity. The objective of this study was to assess the construct validity of LLDAS by testing the operational definition against SLE expert opinion.

Methods: Fifty SLE case summaries based on real patients and without manipulation were prepared by experts in 4 countries in the Asia Pacific. Each case detailed past history, current disease features, current treatment and investigation results. Fifty rheumatologists with expertise in SLE, from multiple centres and countries, but with no prior involvement in the LLDAS project, responded to a survey in which they were asked to categorise the current disease activity state of each case as either remission, low, moderate or high, without reference to the operational definition. Two investigators independently assessed whether each case met the operational definition of LLDAS. Agreement between expert opinion and the operational definition of LLDAS was assessed using Cohen's Kappa.

Results: In total, 2500 unique responses were collected. Overall agreement between expert opinion and the operational definition of LLDAS was 77.96% (95% CI 76.34 – 79.58%), with a Cohen's Kappa of 0.57 (95% CI 0.55 – 0.61). Of the cases (22 of 50) that fulfilled the operational definition of LLDAS, only 5.34% of responders classified the cases as moderate/high activity. In contrast, of the cases that did not fulfill the operational definition of LLDAS (28 of 50), 35.14% of responders classified the cases as remission/low activity. Common reasons for this discordance were assignment to remission/low activity of cases with higher corticosteroid doses than defined in LLDAS (prednisolone ≤ 7.5mg) or serological activity (high anti-dsDNA antibody and /or low complement).

Conclusion: LLDAS has good construct validity with high overall agreement between the operational definition of LLDAS and expert opinion. Discordance of results suggests that the operational definition of LLDAS is more stringent than expert opinion at defining a low disease activity state, and that expert definition of acceptable corticosteroid dose in SLE varies.

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The International Consensus on Standardized Nomenclature of Antinuclear

Antibody HEp-2 Cell Patterns (ICAP) Initiative – Update and Its Impact

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Background/Purpose: The indirect immunofluorescence (IIF) pattern observed in the antinuclear antibody (ANA) test provides an initial assessment of autoantibody responses in candidate patients who have or may be at risk of developing systemic autoimmune rheumatic diseases (SARD). Despite its wide clinical use, a universal nomenclature to describe ANA IIF patterns has not been adopted. The International Consensus on ANA Patterns (ICAP) Initiative originated workshops that began in Sao Paulo (2014), followed by the 2nd workshop in Dresden (2015). The goal of ICAP is to promote harmonization of ANA pattern nomenclature and provide guidelines for ANA interpretation, thereby optimizing adoption in diagnostic laboratories and extended to patient care.

Methods: A working committee addressed collective issues on ANA nomenclature that were raised by participants representing research, clinical, and diagnostic laboratories. Post-workshop exchanges were held with the goal of reaching consensus on key issues.

Results: ANA IIF patterns were separated into three major categories (nuclear, cytoplasmic, and mitotic patterns) and each pattern was defined and described in detail. Consensus was achieved for 28 IIF patterns that were designated with an alpha-numeric code (AC-1 to AC-28) and summarized under a nomenclature and classification tree (ANApatterns.org). Important findings include, e.g., the Homogeneous and Coarse Speckled nuclear patterns are linked to autoantibodies strongly associated with SARD whereas the Dense Fine Speckled (DFS) nuclear pattern in isolation virtually rules out a SARD diagnosis. ICAP initiatives include translation of the website into other languages, establishing guidelines in ANA reporting, and programs for continuing education. The translation initiative promotes the establishment and dynamic engagement of a worldwide network. To date, the website displays its content in English, Spanish, Portuguese, Italian and German while, Chinese, Japanese and French translations are ongoing. Continuous education courses aim to spread and update the ICAP nomenclature/conceptual framework and to promote competency in ANA interpretation.

Conclusion: ICAP has provided a common platform to address issues that are of great interest to the community. The establishment of a consensus on ANA reporting will require interaction with committees in charge of establishing disease classification and diagnostic criteria. Future goals include building collaborative data on ANA IIF patterns, selection of new consensus patterns, and establishment of an interpretative clinical description for each AC pattern for clinical use. The 3rd and 4th ICAP workshops are planned for Kyoto (October 2016) and Dresden (September 2017).

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Systemic Lupus Erythematosus (SLE) Responder Index [SRI(4)] Response Is Associated with Global Benefit in Patients with Moderate to Severe SLE

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Background/Purpose: *Post-hoc* analysis of two Phase III studies of belimumab[1] showed that an SRI(4) response is associated with clinically meaningful benefits, irrespective of treatment assignment. Confirmation of these findings in independent cohorts will enhance the acceptance of SRI(4) as a measure of clinically meaningful improvement. This analysis assessed global clinical benefit represented by an SRI(4) response.

Methods: Changes from baseline in clinical, laboratory, and patient-reported outcome measures at Day 365 were compared between SRI(4) responders (n=396) and non-responders (n=340) in the combined dataset of two Phase IIb studies evaluating sifalimumab and anifrolumab (MUSE) in moderate to severe SLE.

Results: Baseline demographics were similar between the studies. At Day 365, a greater percentage of responders than non-responders had ≥7-point reduction in SLE Disease Activity Index 2000 (SLEDAI-2K) and had their oral corticosteroid dose reduced to ≤7.5 mg/day (Table). Responders also had greater percentage changes from baseline in clinical SLEDAI scores, and greater improvements in Physician's Global Assessment (PGA) score and number of SLEDAI-2K organ domains with improvement. British Isles Lupus Assessment Group (BILAG) "A" or "2B" flare rates were lower in SRI(4) responders. A larger percentage of responders with ≥8 swollen and ≥8 tender joints at baseline had ≥50% improvement in swollen and tender joint counts. In patients with moderate to severe skin disease at baseline, defined as Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score ≥10, more responders had ≥50% improvement in CLASI. In patients with detectable anti–double-stranded DNA (anti-dsDNA) antibodies at baseline, responders had greater improvements in anti-dsDNA concentrations; however, in patients with low complement concentrations at baseline, the improvements in complement C3 and C4 concentrations were similar between responders and non-responders. Responders also had greater improvements in patient-reported outcomes: percentage change from baseline in Patient Global Assessment, and absolute change in Short Form 36 Health Survey (SF-36; Physical Component Summary, Mental Component Summary, Vitality) and Functional Assessment of Chronic Illness Therapy (FACIT)–Fatigue scores.

Conclusion: SRI(4) response in patients with moderate to severe SLE was associated with broad improvements in clinical and patient-reported outcomes. SRI(4) response in this analysis was driven by clinical components and confirm previous findings suggesting SRI(4) response is associated with global clinically important benefits. References: [1]Furie R, et al. *Lupus Sci Med* 2014;1:e000031. First presented at EULAR 2016.

Table. Changes from baseline in outcome measures compared between SRI(4) responders and non-responders at Day 365

	Responders (n=396)	Non-responders (n=340)	*P*-Value[a]
Day 365			
SLEDAI-2K ≥7 point reduction, n (%)[b]	223/360 (61.9)	1/306 (0.3)	<0.001
Reduction of oral corticosteroid dose to ≤7.5 mg/day, n (%)[c]	76/235 (32.3)	10/188 (5.3)	<0.001
Percentage change in Clinical SLEDAI, mean (SD)	-80.5 (21.5)	-14.4 (29.1)	<0.001
Percentage change in PGA, mean (SD)	-71.7 (26.6)	-13.6 (27.7)	<0.001
Organ domains with improvement on SLEDAI-2K, mean (SD)	2.19 (0.73)	0.29 (0.59)	<0.001
BILAG "A" or "2B" flares, n (%)[d]	20 (5.1)	73/333 (21.9)	<0.001
≥50% improvement in joint counts, n (%)[e]	136/143 (95.1)	26/143 (18.2)	<0.001
≥50% improvement in CLASI, n (%)[f]	90/104 (86.5)	19/100 (19.0)	<0.001
Percentage change in serology, mean (SD) [n]			
anti-dsDNA[g]	-13.5 (69.8) [200]	6.0 (90.8) [112]	0.051
Complement C3[h]	11.4 (25.4) [148]	13.0 (29.1) [77]	0.676
Complement C4[h]	31.7 (92.5) [86]	36.6 (68.0) [50]	0.728
Change in SF-36, mean (SD)			
PCS	6.3 (9.5)	1.3 (5.8)	<0.001
MCS	4.3 (11.1)	-0.1 (6.9)	<0.001
Vitality	5.2 (9.3)	0.1 (5.5)	<0.001
Change in FACIT–Fatigue, mean (SD)	6.5 (11.3)	0.7 (7.4)	<0.001

[a]*P*-value is from 2-sample t-test for continuous variables and chi-square test for categorical variables; [b]In patients with SLEDAI-2K ≥7 at baseline; [c]Reduction of OCS dose at Day 365 to ≤7.5 mg/day in patients who were receiving ≥10 mg/day of prednisone or equivalent at baseline; [d]Percentage of patients with ≥1 BILAG "A" or "2B" flares at any time during the study up to Day 365; [e]≥50% decrease in swollen and tender joint count from baseline in patients with ≥8 swollen and ≥8 tender joints at baseline; [f]≥50% improvement in CLASI from baseline in patients with CLASI ≥10 at baseline; [g]Improvement in patients with detectable anti–double-stranded DNA antibodies at baseline; [h]Improvement in patients with low complement concentrations at baseline. Anti-dsDNA, anti–double-stranded DNA; BILAG, British Isles Lupus Assessment Group; CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; Clinical SLEDAI, at least a 4-point reduction in clinical components (no laboratory components) of Systemic Lupus Erythematosus Disease Activity; FACIT, Functional Assessment of Chronic Illness Therapy; MCS, Mental Component Summary; OCS, oral corticosteroid; PCS, Physical Component Summary; PGA, Physician's Global Assessment; SD, standard deviation; SF-36, Short Form 36 Health Survey; SLE, systemic lupus erythematosus; SLEDAI−2K, Systemic Lupus Erythematosus Disease Activity Index 2000; SRI, Systemic Lupus Erythematosus (SLE) Responder Index

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Multi-Parametric Model Development for Assessing Lupus Nephritis and Disease Activity

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Multi-parametric model development for assessing lupus nephritis and disease activity Christopher Sjöwall[1], Chelsea Bentow[2], Mary Ann Aure[2], Gabriella Lakos[2], Peter Martis[2], Michael Mahler[2] [1]AIR/Rheumatology, Department of Clinical and Experimental Medicine, Linköping University, Linköping, Sweden [2]Research and Development, Inova Diagnostics, San Diego, CA, USA

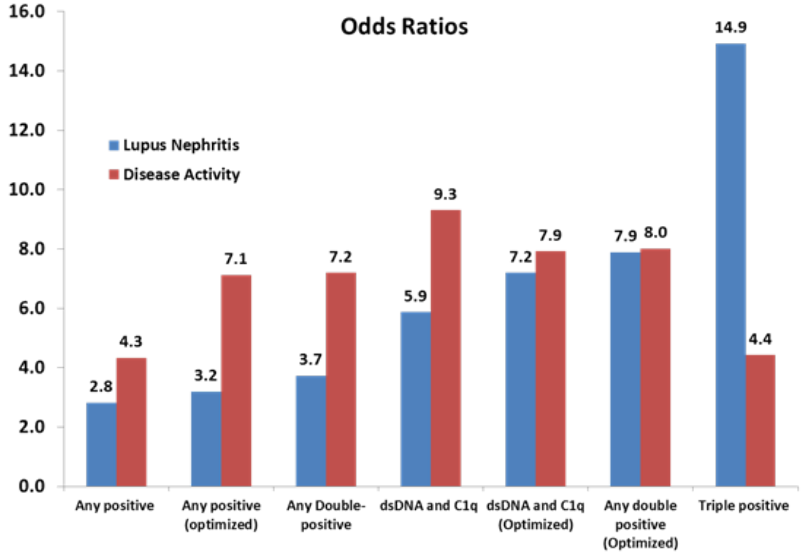
Background/Purpose: The clinical complications and symptoms of systemic lupus erythematosus (SLE) can vary widely with the individual and appropriate management is critically dependent upon the proper assessment of disease activity and organ damage. Although antibodies such as anti-dsDNA have been shown to correlate with disease activity and the likelihood of nephritis in lupus patients, the additive effect of combined biomarkers is not widely implemented. Using a cohort of well characterized SLE patients, this study investigated the utility of developing an SLE assessment model using a combination of biomarkers, namely anti-dsDNA, anti-C1q, and anti-Ku antibodies.

Methods: Samples from 261 SLE patients from Linköping University (Sweden) were tested using chemiluminescent immunoassays (CIA) for anti-dsDNA and anti-Ku (research use only) antibodies as well as by anti-C1q ELISA (all methods Inova Diagnostics, San Diego, USA). Of these 261 SLE patients, 69 (26.4%) had lupus nephritis (LN) at the time of the blood draw, or had the history of LN. The SLE disease activity index-2K (SLEDAI) scores were available for all patients and a cut-off >4 was used to define active disease (50/261, 19.2% active). The data were statistically evaluated using Analyse-it software (Version 3.90.1; Leeds, UK). The multi-parametric analysis was performed at both the manufacturer's cut-off for the methods as well as optimized cut-off points based on likelihood plots to increase the odds ratio.

Results: In the total cohort, all three antibodies (dsDNA, C1q, and Ku) demonstrated markedly higher prevalence and quantitatively higher antibody levels in active SLE patients versus inactive patients and in LN patient versus non-LN patients (see table).

	Anti-dsDNA		Anti-C1q		Anti-Ku	
	Antibody titer level	Antibody prevalence	Antibody titer level	Antibody prevalence	Antibody titer level	Antibody prevalence
Active *vs.* Inactive	$p<0.0001$	$p<0.0001$ Odds ratio = 4.2	$p<0.0001$	$p<0.0001$ Odds ratio = 6.9	$p=0.0012$	$p=0.3343$ Odds ratio = 1.8
LN *vs.* non-LN	$p<0.0001$	$p=0.0002$ Odds ratio = 2.9	$p<0.0001$	$p<0.0001$ Odds ratio = 4.4	$p=0.0213$	$p=0.1625$ Odds ratio = 2.1

When multi-parametric analysis was performed by combining biomarker results, the likelihood of nephritis and patients with active disease increased with dual positivity and triple positivity (see figure).



Conclusion: This study demonstrates the utility of a multi-parametric model approach using biomarkers for assessing SLE patients for more active and severe disease, especially for patients that may develop lupus nephritis. Furthermore, the results hold promise for the benefit of combined autoantibody profiling for the clinical management of patients.

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Development and Initial Validation of a Novel Lupus Disease Activity Index to Account for Glucocorticoids: Sledai-2K Glucocorticoids Index (SGI)

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Background/Purpose: It is challenging to describe disease activity in SLE in the context of multiple levels of glucocorticoids (GC) treatment. We aim to develop and validate a new index, SLEDAI-2K Glucocorticoids Index (SGI), to accurately describe disease activity while accounting for GC doses.

Methods: The first 2 phases focused on to the development of the index. Phase 1: identification of scenarios of real patients seen prospectively in a longitudinal cohort at the centre in the last 20 years. Phase 2: derivation of an equation that explains the association between SLEDAI-2K and GC dose while using physician global assessment (Likert scale [LS] 0-7) as the gold standard. Phase 3 was to validate the new index, SGI, against SLEDAI-2K in a cohort of active patients on standard of care treatment. ***Phase 1*** Scenarios were identified using 2 data sampling approaches. First, the top 13 most common organ involvement combinations were identified. From each of these combinations, random scenarios with a wide spectrum of GC doses were selected. Second, patients in the entire database were grouped into 7 categories based on the GC dose [5, 10, 15, 20, 30, 50 and 60 mg/day] and 10 patients were selected randomly from each category. Scenarios included information on patients' SLEDAI-2K score, organ involvement combination and GC dose. ***Phase 2*** 3 rheumatologists ranked disease activity with LS. The sample size calculation was on the assumption of reliability with ICC ≥0.80 and required a minimum of 46 scenarios. ***Phase 3*** An independent cohort was used for the validation. We hypothesized that in patients with improvement and worsening (SLEDAI-2K decrease ≥4 and increase >4 respectively), the change in SLEDAI-2K and SGI scores will move in the same direction.

Results: **1-**The first approach yielded 29577 visits in 1400 patients and 51 scenarios. The second approach yielded 18178 visits in 1086 patients and 80 scenarios. **2-** 131 scenarios were summarized and ranked by 3 rheumatologists leading to 393 records. A perfect agreement in LS was achieved; ICC (2, k) of 0.89 (95% CI: 0.83, 0.89). A quadratic linear regression model relating GC and SLEDAI-2K was structured in this equation: SGI score =SLEDAI-2K score + [3.65 + 0.29 * GC – 0.0027 (GC * GC)]. The weight score of GC doses was derived and represented in table 1. For instance, SLEDAI-2K of 6 on 10 mg of GC provides SGI of 9. The application of SGI is illustrated in table 1. **3-** Concurrent Construct Validity: Of the 158 patients studied, 109 patients improved, 38 remained unchanged, and 11 worsened at 9-12 months follow up. At follow up SLEDAI-2K and SGI correlated highly (r= 0.87) and changed in the same direction in patients with improvement and worsening proving the validity of SGI.

Conclusion: We developed and validated a novel lupus disease activity index, SGI, that describes disease activity while accounting for GC dose.

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Low Disease Activity in Systemic Lupus Erythematosus: An Achievable Goal?

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Background/Purpose: To date, there is no generally accepted definition for remission in SLE, thus a possible goal in the treat-to-target strategy might be low disease activity. Lupus Low Disease Activity State (LLDAS) is a consensus-based definition of minimally acceptable disease activity in SLE patients (1). This definition has been initially tested for criterion validity in a multi-ethnic cohort of patients showing that it is associated with improved patient outcomes.
The aims of this study are: i) to evaluate what proportion of patients fulfils the definition of LLDAS in a monocentric cohort of Caucasian SLE patients; ii) to evaluate the effect of LLDAS attainment on damage accrual over a period of 5 years.

Methods: This is a retrospective analysis of data prospectively collected in a longitudinal observational cohort of SLE patients established in our centre in 2011; patients fulfilling the 1997 ACR classification criteria who attended the last visit from January 2016 and May 2016 were enrolled in the study. Among patients regularly followed from 2012 and 2016, those with at least one visit per year and
complete clinical and serological data available were included in this analysis. The definition of LLDAS was applied to each patient for each visit; organ damage was calculated with the SLICC/DI score (SDI) at study entry and at last observation.

Results: One hundred and six patients were eligible for the study (96.2% females, mean age at last visit 47.1±13, mean disease duration at last visit 17.5±9.3 years). At last observation the mean SELENA-SLEDAI score was 2.7 ±2.5;
84 patients (79.2%) were on treatment for SLE (glucocorticoids and/or immunosuppressants and/or biologics), 22 (20.7%) were off treatment or were taking only antimalarials drugs. According with all the items of the definition, at last observation LLDAS was present in 83 patients (73%); among these, 22 patients (20.8%) maintained a stable LLDAS during the 4.5 years of follow-up (LLDAS fulfilled for all visits). Twenty-seven patients (25.4%) accrued organ damage during the follow-up; in the cohort as a whole the mean increase in SDI was 0.3 (±0.6) resulting in a mean final SDI of 1.2 (±1.7). Patients who maintained LLDAS were younger ($p<0.02$), had a lower disease activity score at study entry ($p<0.001$) and were more likely GC-free at last observation ($p=0.005$). No differences in term of major organ involvement were present in LLDAS versus non-LLDAS patients. Patients who maintained LLDAS accrued less organ damage (ΔSLICC=0.27 vs 0.33) but this difference did not reach statistical significance.

Conclusion: In our cohort, a high percentage of patients fulfils the proposed definitions for LLDA at last visit but only a minority maintained this state for all the follow-up period. A minimally acceptable
disease activity state is an achievable target in clinical practice; it is associated with a successful GC tapering and, probably, better long-term outcomes. Reference:
Franklyn K, et al. Definition and initial validation of a Lupus Low Disease Activity State (LLDAS). Ann Rheum Dis. 2015; 0:17

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Establishment of an International Autoantibody Standard for Anti-DFS70/LEDGF Antibodies: Proof-of-Concept Study for a Novel Strategy for the Setting up of International Autoantibody Standards

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Session Time: 9:00AM-11:00AM

Background/Purpose: Robust, certified, and traceable reference material for autoantibody testing is vital for the validity of results obtained in the clinical laboratory. International standards for qualitative and quantitative immunologic assays are traditionally based on large batches of serum/plasma obtained from a single individual. However, autoantibodies from one single individual may not appropriately represent the vast heterogeneity of autoantibodies observed in human species. Autoantibodies to the 70/75kDa Lens Epithelium-Derived Growth Factor (LEDGF) yield a characteristic nuclear dense fine speckled (DFS) pattern on the ANA assay on HEp-2 cells. Anti-DFS70/LEDGF75 antibodies must be appropriately identified because they virtually rule out the diagnosis of systemic autoimmune rheumatic diseases. Herein we propose pooling up samples from hundreds of individuals with the characteristic DFS pattern at high titer and specific anti-DFS70/LEDGF75 reactivity. This approach should provide a reference reagent that better represents the heterogeneity within human species regarding anti-DFS70 autoantibodies.

Methods: Serum samples with the characteristic DFS pattern at titer ≥1/640 were sequentially selected in the laboratory ANA practice and kept at -80^{o}C. Validation of samples and pools included agreement on the characteristic ANA DFS pattern by 3 independent examiners and demonstration of the typical 75kDa band on western blot and moderate/strong anti-DFS70 reactivity in 2 independent methods [ELISA (cut-off>1.0) and chemiluminescent assay (CLIA; cut-off>20)]. A progressive pooling strategy included the formation of PENTA pools (5 validated samples), ICOSA pools (4 validated PENTA), SEMI-FINAL pools (3-5 validated ICOSA) and the FINAL POOL (8 validated SEMI-FINAL). The FINAL POOL was serially diluted in fetal bovine serum (FBS) to verify the linearity and increase the volume adjusting to moderate reactivity.

Results: The 760 validated samples (CLIA median 337.7U; 26.1–3,547.0) yielded 152 validated PENTA (CLIA:

420.6U; 60.4-3,518; ELISA: 5.5U; 2.8-6.8). The 152 PENTA yielded 38 validated ICOSA (CLIA: 407.2U; 77.5-1,823.3; ELISA: 5.5U; 3.7-6.7), 8 SEMI-FINAL pools (ELISA 5.2U; 3.8-6.2) and FINAL pool (ELISA 5.1U). Intermediary pools and the FINAL pool exhibited the characteristic DFS pattern and a clear-cut 75kDa band in WB. Serial dilution in FBS resulted in a linear decreasing reactivity in all methodological platforms.

Conclusion: This proof-of-concept study indicates that pooling samples from hundreds of individuals with high titer anti-DFS70 reactivity preserves the original reactivity of individual samples encompassed, as judged by the ANA, CLIA, ELISA, and WB assays. The present anti-DFS70 standard will integrate the panel of ANA standards of the Autoantibody Standardization Committee affiliated with the International Union of Immunology Societies (IUIS), to be distributed by the Centers for Disease Control. The extrapolation of this model to other autoantibody specificities must be validated by appropriate studies.

Disclosure: A. Dellavance, None; **D. Baldo**, None; **L. E. C. Andrade**, None.

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Abstract Number: 797

Randomized Clinical Trials of Systemic Lupus Erythematosus: Evaluating Differences in the Enrolled Populations

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Background/Purpose: Randomized controlled trials (RCTs) in SLE identify specific populations of interest for eligibility, but still vary in the recruited populations. These differences may include the baseline disease activity level, laboratory findings, baseline treatment medication use, and racial mix. Previously presented data highlight regional differences in SLE populations which in turn may influence treatment responses. This study analyzed the demographics and baseline disease characteristics of randomized SLE patients across three different RCTs conducted through our organization.

Methods: We evaluated combined screening data from three recently enrolled SLE RCTs post hoc. Eligibility criteria were targeted at the enrollment of patients with active SLE meeting ACR classification criteria (SELENA-SLEDAI ≥8 for two studies of ~700 and 850 patients each, and SLEDAI-2K ≥6 for the third study of ~300 patients). Two studies were globally recruited, one was regional. Patients with varying degrees of severely active lupus nephritis or neuropsychiatric SLE were excluded. Differences between each combination of two study populations were evaluated via a two-tailed t-test for disease duration, corticosteroid use, immunosuppressant use, complement and anti-dsDNA status.

Results: Of the 1854 randomized patients, 50.1% were Asian; 38.8%, white; and 5.7%, black; and 93.4% were female. Details regarding treatment medications (corticosteroids, immunosuppressants, antimalarials), SLEDAI scores (total, clinical); anti-dsDNA, ANA, and C3/C4 status are presented in Table 1 and regarding subjects meeting each SLEDAI criterion in Table 2. Mycophenolate (20.0%) was the most common immunosuppressant used, followed by azathioprine

(15.8%) and then methotrexate (9.5%). Differences existed between each study population at the $p<0.001$ level for the percentage of subjects on corticosteroids, on immunosuppressants (except for a nonsignificant difference between the two global studies); with hypocomplementemia, with elevated anti-dsDNA titers or with both.

Conclusion: SLE patients enrolled in RCTs, despite having similar levels of disease required by the SLEDAI, varied in critical baseline laboratory characteristics and standard of care medications. These differences may have resulted from variables such as study size and regional aspects, e.g., racial mix, standard of care; and may impact treatment responses. Further differences in disease activity by region and race are being evaluated. Understanding such differences may influence the design of SLE RCTs moving forward.

Table 1. Screening Characteristics of All Randomized SLE Subjects

Characteristic	**Results (N=1854)**
Age, years, mean (SD)	36.0 (11.7)
Disease duration, years, mean (SD)	6.2 (6.2)
Positive ANA (≥1:80 titer or equivalent), %	97.4
Elevated anti-dsDNA ≥30 IU/mL, %	70.8
Hypocomplementemia (low C3 and/or C4), %	55.5
Elevated anti-dsDNA and hypocomplementemia, %	47.5
Oral corticosteroids, %	90.3
Oral corticosteroids ≥10 mg prednisone equivalent, %	43.3
Oral corticosteroid dose, mg, mean (SD) in subjects using corticosteroids (prednisone equivalent)	14.2 (9.3)
Antimalarials, %	70.1
Immunosuppressants, %	54.3
Corticosteroids and immunosuppressants, %	50.9
Corticosteroids, antimalarials and immunosuppressants, %	33.0
No corticosteroids, antimalarials or immunosuppressants, %	1.2
SLEDAI score ≥8, %	95.3
SLEDAI score>10, %	37.6
Clinical SLEDAI score ≥6, %	84.7
SLEDAI ≥8 and Clinical SLEDAI score ≥6, %	82.6
Proteinuria >1g/day, %	18.3
SD=standard deviation	

Table 2. Subjects Meeting Each SLEDAI Criterion at Randomization			
SLEDAI Item	**Subjects, % (N=1854)**	**SLEDAI Organ System**	**Subjects, % (N=1854)**
Seizure	.	Neuropsychiatric	0.6
Psychosis	.		
Organic Brain Syndrome	.		
Visual Disturbance	0.2		
Cranial Nerve Disorder	.		
Lupus Headache	0.5		
CVA	.		
Vasculitis	9.9	Vascular	9.9
Arthritis	64.8	Musculoskeletal	65.0
Myositis	0.6		
Urinary Casts	0.3	Renal	23.1
Hematuria	6.5		
Proteinuria	20.0		
Pyuria	3.7		
Rash	66.6	Mucocutaneous	87.1
Alopecia	60.9		
Mucosal Ulcers	32.7		
Pleurisy	3.2	Serosal	4.0
Pericarditis	1.1		
Low Complement	55.8	Immunologic	79.3
Increased DNA Binding	72.1		
Fever	1.6	Constitutional	1.6
Thrombocytopenia	2.0	Hematologic	7.5
Leukopenia	5.9		

Disclosure: N. Goel, Quintiles, 3; **B. Barrett**, Quintiles, Inc., 3; **A. Duncan**, Quintiles, Inc., 3; **M. B. Gallagher**, Quintiles, Inc., 3; **M. Mackey**, Quintiles, Inc., 3.

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Abstract Number: 798

Oxidized Phospholipids,Lipoprotein(a) and Glycosphingolipid Associated B-1,4 Galactosyltransferase in a Johns Hopkins Cohort of Patients with Systemic Lupus Erythematosus

Subroto Chatterjee[1], Michelle Petri[2], Steven Jones[3] and Vignesh Sadras[1], [1]Pediatrics-Cardiology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD
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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Oxidized Phospholipids, Lipoprotein (a) and Glycosphingolipid Associated B- 1,4 Galactosyltransferase in a Johns Hopkins cohort of patients with Systemic Lupus Erythematosus.

Background/Purpose: Systemic lupus erythematosus(SLE) is an autoimmune disease wherein the patient's immune system attacks apparently healthy tissue. These patients develop atherosclerotic plaques,and have high rates of coronary events mostly in premenopausal women. Chronic inflammation, lipid oxidation, and production of reactive oxygen species may attribute to atherosclerosis in these patients but this relationship has not been tested. We have previously shown that oxidized phospholipids(Ox-PC) could activate B-1,4galactosyltransferase to generate a glycosphingolipid, lactosylceramide which in turn, produces reactive oxygen species in vascular cells implicated in cell proliferation, angiogenesis, and migration-hallmarks in the pathophysiology of atherosclerosis.

Methods: SLE patients form the Johns Hopkins University cohort were assessed for disease activity using the Physician Global Assessment, the SELDA, and organ involvement assessments (the SLICC/ACR Damage index). Further, laboratory tests were condcuted to ascertain organ damage, and cardiovascular risk factors. Hopkins institutional board approval was obtained for this study. The SLE patients serum(N=50) were 50% Caucasian and 40% African American women with mean age of 38. Control serum(N=50) was obtianed from 90% Caucasian and 10% African American women with the mean age of 38. Serum levels of Ox-PC per apoB-100particle (Ox-PC-apoB) was measured by ELISA using a murine monoclonal antibody EO6,which binds to the phosphorylcholine group of oxidized phospholipids but not to native phospholpipids. By the use of apoB antibody an equal number of apoB particles in serum were captured first and then Ox-PC level was measured. The serum levels of lipoprotein a(Lp(a) and B-1,4galactosyltransferase(B-1,4GalT-V) were also measured by ELISA using corresponding antibody raised against these antigens.

Results: We observed that there were more Ox-PC molecules per apoB protein in the serum of SLE patients as compared to control serum. This was highly statistically significant($p<0.0001$). Since Lp(a) on apoB protein is the major carrier of OX-PC,it was not surprising to observe that the level of Lp(a) were also significantly increased in SLE serum ($p< 0.0001$). An unexpected finding was that the B-1,4GalT-V mass was also increased ($p<0.0001$) in SLE serum relative to control serum.

Conclusion: This study demonstrates that increased level of Ox-PC,Lp(a) and B-1,4GalT-V predict the pro-atherogenic and pro-inflammatory potential of these biomarkers in SLE.

Disclosure: S. Chatterjee, None; **M. Petri**, None; **S. Jones**, None; **V. Sadras**, None.

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Abstract Number: 799

Biomarker Identification & Molecular Sub-Classification in Systemic Sclerosis for Precision Medicine Using RNA-Seq

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics - Poster I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is a complex and highly heterogeneous disease with multi-organ involvement. Accurate tools for disease sub-classification are lacking. In most patients, skin and subcutaneous tissue are affected, and circulating immune cells are activated. We performed what is to our knowledge the first RNA-Seq on simultaneously obtained skin, intradermal white adipose tissue, and peripheral blood mononuclear cells (PBMCs) from patients with well-characterized SSc.

Methods: We obtained PBMCs and skin biopsies from healthy controls and individuals with limited cutaneous systemic sclerosis (lcSSc), diffuse cutaneous systemic sclerosis (dcSSc), and scleroderma sine scleroderma (SSS). Intradermal adipose tissue was separated from skin. Patients were followed longitudinally, and PBMCs and skin were obtained serially with repeat clinical phenotyping. We then performed stranded, total RNA-Seq for transcriptome profiling.

Results: We found increased expression of *COMP*, *THY1*, and *IGFBP4* in SSc skin biopsies with resolution to the specific differentially expressed (DE) gene isoform. In contrast, we detected a marked decreased expression of *SPAG17*, part of the ciliary axoneme central pair complex, in SSc skin. A limited set of DE genes can perfectly separate SSc from control skin. Genes with lower expression in SSc skin were enriched for the selenocysteine synthesis pathway. On the other hand, genes with increased expression in SSc skin were substantially enriched for both extracellular matrix and immune response pathways, and in particular interferon signaling. Microbial species on the skin can also be detected using *de novo* assembly. Remarkably, we found that number of DE genes and magnitude of their changes in PBMCs from SSc vs. controls was modest compared to differences detected in the skin. This dataset allows us to correlate skin scores with the transcriptome profiles of different tissues simultaneously obtained from the same individual.

Conclusion: In this initial RNA-Seq of simultaneously obtained skin, intradermal adipose tissue, and PBMCs, novel patterns of gene expression differences can be revealed that could not be recognized by earlier microarray-based transcriptome approaches. It is unclear at this time whether the matrix & immune activation signatures in the skin samples represent different SSc types, or different stages of SSc evolution. Ideally this technique could be applied to further serial biopsies to observe SSc evolution over time. Broad transcriptome profiling has excellent potential for unsupervised classification of different SSc types for further study and correlation with clinical phenotypes.

Disclosure: E. D. O. Roberson, None; **L. Cao**, None; **D. J. Morales-Heil**, None; **B. Korman**, None; **J. Varga**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/biomarker-identification-molecular-sub-classification-in-systemic-sclerosis-for-precision-medicine-using-rna-seq

Abstract Number: 800

An Altered Cardiovascular System Development Gene Expression Signature in Skin is a Hallmark of Limited Cutaneous Systemic Sclerosis

Emma C. Derrett-Smith[1,2], Viktor Martyanov[3], Cecilia B. Chighizola[4], Pia Moinzadeh[5], Korsa Khan[6], Tammara A. Wood[3], Pier Luigi Meroni[7], David Abraham[8], Voon H. Ong[9], Michael Whitfield[3] and Christopher Denton[8], [1]Centre for Rheumatology and Connective Tissue Diseases, UCL Division of Medicine, London, United Kingdom, [2]Rheumatology,

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics - Poster I

Session Type: ACR Poster Session A

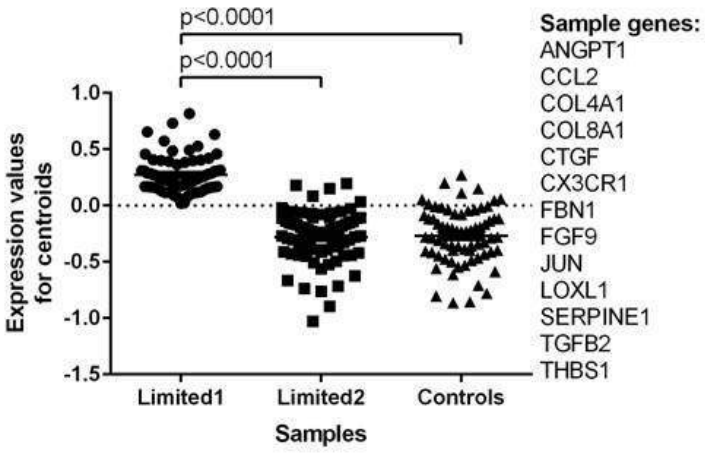
Session Time: 9:00AM-11:00AM

Background/Purpose: Limited cutaneous SSc (lcSSc) is characterised by less extensive skin fibrosis but patients can develop major internal organ complications and vascular manifestations. Gene expression analysis of SSc biopsies has been used to define molecular subsets of the disease and provide mechanistic insight into pathobiology. Clinically uninvolved skin in the diffuse cutaneous subset has closely replicated gene expression signatures compared with biopsies from clinically involved skin and a number of vasoactive genes have been identified this way. We have investigated the gene expression abnormalities in the more prevalent lcSSc subset through detailed transcriptional analysis of skin biopsies taken from uninvolved forearm skin.

Methods: Total RNA was extracted from skin biopsies from 15 patients with SSc fulfilling 2013 EULAR/ACR classification criteria with the limited subset of disease and 8 healthy controls (HC). Demographic, clinical and serological parameters were representative of the recruitment cohort but purposefully broad. Gene expression profiling was performed on a DNA oligonucleotide microarray chip. Differentially expressed genes (DEG) were identified using Significance Analysis of Microarrays (SAM). Functional enrichment analysis of gene signatures was done via g:Profiler.

Results: There were 218 DEG between lcSSc and HC samples (False Discovery Rate<10%). 181/218 DEG were upregulated in lcSSc samples. Hierarchical clustering of DEG suggested the presence of 2 separate groups of lcSSc samples: ‘limited 1’ and ‘limited 2’. The ‘limited 1’ group (13 samples, 10 unique patients) showed upregulation of genes involved in *cell adhesion*, *cardiovascular system* (CVS) *development* (Figure 1) and *extracellular matrix* as well as *immune* and *inflammatory response*. The CVS development signature was of particular interest as its genes showed very strong enrichment in *response to wounding*, *response to TGF-β* and *kinase cascade*. Neither ‘limited 2’ group (6 samples, 5 unique patients) nor HC samples showed functional enrichment. There were no significant differences in demographic or clinical parameters between these two groups including the presence of significant microvascular involvement and hallmark antibody reactivities.

Conclusion: Our study suggests the presence of molecular subsets in lcSSc that overlap with other clinical and serological features based on gene expression profiling of biopsies from uninvolved skin. This may reflect important differences in pathogenesis within these patient groups. We identify differential expression of a subset of genes that relate to CVS and are enriched in fibrotic signalling. This may shed light on underlying mechanisms of vascular disease in SSc. The enrichment in profibrotic profile is striking and suggests that dysregulated gene expression may contribute to vasculopathy and fibrosis in different disease subsets.



Disclosure: E. C. Derrett-Smith, None; **V. Martyanov**, None; **C. B. Chighizola**, None; **P. Moinzadeh**, None; **K. Khan**, None; **T. A. Wood**, None; **P. L. Meroni**, None; **D. Abraham**, None; **V. H. Ong**, None; **M. Whitfield**, None; **C. Denton**, GSK, Celgene, Actelion, Bayer, Sanofi, Roche-Genentech, Inventiva, 5,CSL Behring, GSK, Actelion, Roche-Genentech, Inventiva, 2.

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Abstract Number: 801

Multi-Tissue Gene Expression Pathway Analysis of Emerging Therapeutics in a TGFβ Dependent Mouse Model of Systemic Sclerosis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: We have previously investigated the interplay between TGFβ, BMP, VEGF and endothelin in SSc using the TβRIIΔk-fib strain, a transgenic mouse model in which there is balanced upregulation of TGFβ signalling. The pivotal role of endothelin within this multifaceted pathology was confirmed using macitentan, a licensed endothelin receptor antagonist of proven efficacy, to prevent and treat pulmonary hypertension in this model. We have extended these studies to examine whether cellular pathways targeted by modern therapies currently undergoing clinical trials in SSc are altered in this model of constitutive skin fibrosis and pulmonary vasculopathy.

Methods: RNA was isolated from cultured skin and lung fibroblasts and aortic smooth muscle cells (SMCs) explanted from adult transgenic and wildtype littermate control mice and subjected to gene expression analysis using the Illumina microarray platform (n=3 each group). Arrays were analysed for differential expression of genes involved in inflammatory, vascular and fibrotic cellular pathway components targeted by therapeutic agents undergoing multicentre clinical trial evaluation in SSc. Differential expression was defined as a 2-fold average change from wildtype with $p<0.05$.

Results: There were between 50 and 400 differentially expressed genes from the cell lines described. These gene lists were then examined to identify genes involved in the nitric oxide synthase pathway and downstream mediators (riociguat); IL-6 receptor and downstream pathways (tocilizumab) and PDGFR, FGFR and VEGFR axes (nintedanib). Several genes involved in nitric oxide metabolism were altered in lung fibroblasts, including NOS2 (inducible nitric oxide synthase), PTGIS (prostaglandin I2 synthase) and GUCY1A3 (guanylate cyclase isoform alpha 3). Genes also involved in vasoconstriction were differentially expressed in SMCs, including upregulation of multiple phosphodiesterases and PTGS-1 (prostaglandin endoperoxide synthase 1; COX-1). IL-6 gene expression was upregulated in transgenic skin and lung fibroblasts, as was STAT1, STAT3 (fold change 36:1, $p<0.004$ in skin fibroblasts) and JAK1 expression. In contrast, gp130, STAT3 and PIAS3 (protein inhibitor of STAT3) were all downregulated in SMCs. Pathways related to the mechanism of action of nintedanib are more complex since several of these downstream mediators form the non-canonical signalling pathways of TGFβ and are known to be altered in this strain. We identified multiple genes involved in these axes, for instance, upregulation of PDGFRA (fold change 137:1, $p<0.02$), FGF10, FGFR1 and downregulation of Ras and related proteins in SMCs.

Conclusion: Identification of multiple alterations in pathways targeted by potential therapeutics for SSc underpins the utility of this strain in pre-clinical investigation of candidate treatments and demonstrates the importance of selecting the most appropriate model for in vivo assessment of emerging molecular therapies in SSc. Pathways involved in vasoconstriction and inflammation are altered in relevant tissues in this TGFβ dependent strain. It is validated as a platform for experimental therapeutic studies particularly in pulmonary complications of SSc.

Disclosure: E. C. Derrett-Smith, None; **S. Xu**, None; **R. K. Hoyles**, None; **C. Denton**, GSK, Celgene, Actelion, Bayer, Sanofi, Roche-Genentech, Inventiva, 5,CSL Behring, GSK, Actelion, Roche-Genentech, Inventiva, 2.

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Abstract Number: 802

Whole Transcriptome Profiling through RNA Sequencing Reveals Differentially Expressed Sense-Antisense Gene Pairs in Patients with Systemic Sclerosis

Tobias Messemaker[1,2], Loubna Chadli[3], Varshna Goelela[3], Maaike Boonstra[4], Annemarie Dorjee[4], Stefan Andersen[3], Harald Mikkers[2], Tom WJ Huizinga[4], Zhenghui Li[5], Guoshuai Cai[5], Michael Whitfield[6], René Toes[7], Jamil Aarbiou[3], Jeroen De Groot[3], Jeska K. de Vries-Bouwstra[4] and Fina Kurreeman[4], [1]Department of Rheumagoloty, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Molecular cell Biology, Leiden University Medical Center, Leiden, Netherlands, [3]Charles River Nederland B.V., Leiden, Netherlands, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Department of Genetics, Geisel School of Medicine at Dartmouth, Hanover, NH, [6]Department of Molecular and Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, [7]Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by fibrosis of skin and multiple organs. Morbidity and mortality are high and pathogenesis is poorly understood. Previous global gene expression studies have shown skin gene profiles with fibrotic as well as inflammatory signatures. Available treatment options are mainly based on suppression of inflammation and are only partially effective. Understanding the basis of the development and progression of SSc is therefore important to lead to deeper understanding of the disease process and to investigate better treatment options. In the current study, we aimed to identify gene expression changes in coding and non-coding RNAs in skin tissue of SSc patients as compared to healthy individuals, with a specific focus on anti-sense RNAs.

Methods: Skin biopsy-derived RNA from fourteen SSc patients and six healthy individuals was sequenced using ion-torrent next generation sequencing technology. Both protein-coding and non-coding genes annotated in Gencode V7 (GRCh38, Ensemble 83) were analysed. Validation of differentially expressed genes was performed by reverse transcriptase qPCR, comparison with a public microarray RNA dataset and validation in an independent SSc skin RNA-sequencing dataset. We focussed on non-coding RNAs and more specifically the dysregulation of non-coding antisense RNAs and their sense-stranded counterpart genes.

Results: We found 619 genes that are consistently differentially expressed and overlapped with a previously published microarray-based study. More than 95% of genes showed the same directionality of expression. Overall we find an enrichment of induced genes in immunological, cell adhesion and keratin related processes. Further analyses of specific genesets revealed induced expression of 80% of the keratin genes and an induction of genes associated with interferon and alternatively activated macrophage gene signatures. Analysis of non-coding RNAs reveals 676 deregulated non-coding genes of which a majority are classified as antisense genes. Antisense genes have shown regulatory roles on gene expression of often sense-stranded genes and for 62 differentially expressed antisense genes a coding sense gene was identified. Interestingly, a significant proportion of these sense genes (26 out of 62) were also deregulated in patients suggesting a link within these sense-antisense gene pairs which might have a role in the underlying mechanisms contributing to the disease.

Conclusion: Our data highlight significant differences between anti-sense non-coding genes expressed in SSc tissue as compared to healthy individuals. To our knowledge, our data provide for the first time evidence for the role of anti-sense genes in the regulation of differential gene expression in SSc patient-derived tissue.

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Abstract Number: 803

Multi-Organ RNA-Sequencing of Systemic Sclerosis (SSc) Patients Shows Reproducible Gene Expression Profiles Across Organ Systems

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Background/Purpose: While a hallmark of systemic sclerosis (SSc) is skin fibrosis, internal organ involvement is the primary cause of mortality. Pulmonary Arterial Hypertension (PAH), Interstitial Lung Disease (ILD) and gastrointestinal dysfunction are common in these patients. Here we tested the hypothesis, generated from meta-analysis of ten different SSc datasets, that any single SSc patient would have the same molecular signatures across multiple organ systems, consistent with the systemic nature of the disease. Asking the question, "if a patient shows an inflammatory signature in skin, do they show that same signature in esophagus, fundus, duodenum, lung or blood?" To test this, we performed RNA-seq on biopsy samples for up to four different tissues from each patient.

Methods: All patients met 2013 ACR/EULAR criteria for SSc. Biopsy samples were collected from skin, esophagus, fundus, duodenum, lung and blood from 12 SSc patients. Additional tissues, from our current cohort and other SSc patients, are continuing to be collected. Lung biopsies lacked at least two paired tissues and so were excluded from current analyses. Only patients from whom at least skin, esophagus and fundus were collected were analyzed, resulting in 9/12 patients used for the analysis. 4/9 patients also had duodenum analyzed. RNA was sequenced by 75bp paired-end RNA-seq at >80 million reads per sample and aligned to the reference genome. Bioinformatic analyses were performed to determine if intrinsic gene expression subset signatures found in one tissue, were found in other tissues of the same patient.

Results: Tissue of origin showed the most robust signal with each tissue having distinct, tissue-specific gene expression signatures. Batch biases from library preparation were not significant ($p = 0.979$). Analysis of skin and esophagus from the same patient was able to recapitulate the previously defined inflammatory intrinsic gene expression subset. The fibroproliferative subset was most clearly observed in skin (n = 4/9 patients). Furthermore, for the first time, the inflammatory subset was found in the fundus (n = 5/9) and duodenum (n = 2/4) of SSc patients. 5/9 patients showed concordant intrinsic assignment across three tissues, one of whom showed concordance across all four tissues, possibly because all four tissues were collected on the same date.

Conclusion: This is the first molecular analysis of biopsies from multiple organs within an individual SSc patient. Our data suggests that molecular subsets in SSc are reproducible across organs within the same patient. We cannot rule out the possibility that pathogenic mechanisms of disease activity and progression are discordant in time in each organ, consistent with clinical observation. Further analysis of the skin, esophagus, fundus and duodenum coupled with lung and blood will provide additional insights into the progression of this systemic disease.

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Combined-Phenotype Meta-GWAS in Systemic Sclerosis and Rheumatoid Arthritis Identifies IRF4 As a New Common Susceptibility Locus

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Background/Purpose: Genome-wide association studies (GWASs) have revolutionized our understanding of the genetic component of complex autoimmune diseases (ADs) by the identification of thousands of susceptibility loci associated with autoimmunity. The vast majority of these loci are shared risk factors for at least two or more ADs, pointing to a common genetic background underlying autoimmune processes. One approach that has been developed for the identification of common loci is to perform a combined-phenotype GWAS, that is, to combine genome-wide genotype data from two autoimmune diseases. In the present study we applied this strategy to systematically search for new common loci for systemic sclerosis (SSc) and rheumatoid arthritis (RA), two complex traits that share clinical and immunological features, and a considerable proportion of its genetic background.

Methods: The complete set of individuals enrolled for this study comprised a total of 8,830 SSc patients, 16,870 RA patients and 43,393 controls of European ancestry. First, we performed a meta-analysis combining GWAS datasets of SSc and RA using a strategy that allowed identification of loci with both same-direction and opposing-direction allelic effects. Those SNPs that showed a P-value < 5 x 10-^{6} in the combined-phenotype analysis and nominal significance in the GWA study for each disease (P-value < 0.05) were followed-up in independent SSc and RA case-control replication cohorts. Subsequently, we performed a meta-analysis of the initial GWAS screening and replication stages. Association tests were performed by the means of logistic regression. Meta-analyses were performed with inverse-variance method based on population specific logistic regression results.

Results: The cross-disease meta-analysis of the GWAS datasets identified several loci with nominal association signals (P-value < 5 x 10-^{6}), which also showed evidence of association in the disease-specific GWAS scan. These loci included several genomic regions not previously reported as shared loci, besides risk factors associated with both diseases in previous studies. The follow-up of the putatively new SSc-RA loci identified IRF4 as a shared risk factor for these two diseases ($P_{combined}$ = 3.29 x 10-12). In addition, the analysis of the biological relevance of the known SSc-RA shared loci pointed to the type I interferon and the interleukin 12 signaling pathways as the main common etiopathogenic factors.

Conclusion: The present study has identified a novel shared locus, *IRF4*, for SSc and RA. The identification of these pleiotropic autoimmunity loci may point to common pathogenic pathways, which ultimately may represent a clinical advantage, thus providing support for drug repositioning.

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HLA Class II Functional Motifs Associated with Severe Systemic Sclerosis (SSc) and Sclerotic Graft Versus Host Disease (sclGVHD): The Shared Epitopes of Fibrosis

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Background/Purpose: Single Nucleotide polymorphisms within the HLA region have been strongly associated with the occurrence of SSc and sclGVHD. However, specific studies on the amino acidic sequences of the HLA antigen presenting regions are scanty. Such approach has been very informative in predicting severity of rheumatoid arthritis (Shared Epitope). The aim of our study was to explore the presence of HLA class II functional motifs associated with severe skin fibrosis in SSc and sclGVHD (shared epitopes of fibrosis). The study was designed with a discovery cohort analysed by 4-digit HLA class II typing and a validation cohort of imputated HLA typing from GWAS data of 1000 SSc patients and controls. Here we present the results of the discovery cohort.

Methods: The discovery cohort comprised 70 SSc patients (15 with diffuse (dSSc) and 55 with limited (lSSc) subset) fulfilling 2013 ACR classification criteria and 43 sclGVHD patients with severe skin fibrosis involving >50 % of body surface area recruited from the observational clinical trial on chronic GVHD (04-C-0281). Four-digit HLA class II typing and β chain hypervariable region amino acidic sequence alignment was performed for HLA-DP and HLA-DR alleles in all patients. The obtained sequences were compared between sclGVHD patients and SSc patients with severe skin fibrosis characterized by maximum modified Rodnan skin score ≥ 25 (fibrotic phenotype group) and lSSc controls (non-fibrotic phenotype group). For the qualitative analysis amino acids were classified according the polarity, charge and hydrophobicity.

Results: Prevalence of hydrophobic and non-polar side chains was higher in patients with fibrotic phenotype compared to patients with non-fibrotic phenotype at position 26 of HLA–DQ β chain ($p = 0.047$) and lower at position 11 of HLA- DP β chain ($p = 0.026$). Comparison between two groups showed a lower prevalence of the following amino acidic motifs in patients with fibrotic phenotype compared with those with non-fibrotic phenotype: VVDE at positions 8,36,55 and 56 of HLA-DP β chain and FD at positions 67 and 70 of HLA-DR β chain ($p = 0.013$ and 0.0007, respectively). They were defined as non-permissive for fibrosis. More importantly "non-permissive" amino acids F and D at positions 67 and 70 of HLA-DR β chain were present in at least one copy in 75% of patients with non-fibrotic phenotype vs 40% of the patients with fibrotic phenotype ($p=0.0004$). Similarly, a second non permissive sequence VVDE at positions 8,36,55 and 56 of HLA-DP β chain was present in 53% of patients in the non-fibrotic group vs only 29% of the fibrotic group ($p=0.018$).

Conclusion: This is the first study which describes common sequences (shared epitopes), codified by three of the most important genes associated with SSc that seem to display a protective effect against severe fibrotic involvement in SSc and sclGVHD. We identified two non-permissive motifs within the hypervariable regions of β chains of HLA – DP, HLA – DQ and HLA – DR molecules that warrant validation in the large imputation cohort. Validation of these findings will be crucial to stratify patients diagnosed with SSc or candidate to bone marrow transplant for their risk of severe fibrosis.

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Single Cell Rnaseq Defines a Unique Transcriptome Profile for Myofibroblasts in the Skin of Patients with Systemic Sclerosis

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Background/Purpose: Fibrosis in systemic sclerosis (SSc), as well as a wide variety of other fibrotic diseases, is largely driven by myofibroblasts. Myofibroblasts are known to selectively produce high amounts of collagen and are found in the deep reticular dermis of patients with diffuse cutaneous SSc (dcSSc). However, our understanding of myofibroblast biology has been limited to mixed cultures of myofibroblasts due to the lack of a unique marker for their selection.

Methods: Skin biopsies from a patient with dcSSc and a healthy control were enzymatically digested and cells sorted into individual wells of a 96 well plate. Libraries were prepared according to the SmartSeq2 protocol and RNAseq performed. Data from individual cells was deconvoluted by barcode and aligned using Tophat. Transcripts were quantified using the Cufflinks. Cuffnorm files were mean centered, normalized, clustered by complete linkage using Cluster 3.0, and visualized using Java Treeview. T-distributed stochastic neighbor embedding (t-SNE) was implemented in R using the Sincell Bioconductor package

Results: Clustering showed different cell types in the dcSSc skin that were easily identified through known markers: keratinocytes, endothelial cells, macrophages, T cells and B cells. In addition, a group of cells was found that expressed smooth muscle actin (SMA/ACT2 gene) and type 1 collagen. On the basis of previously described marker genes and clustering, these cells could be divided into three well-defined groups: pericytes, smooth muscle cells and a third cell type. This third cell type uniquely expressed high levels of integrin alpha 8 (ITGA8), an integrin previously associated with myofibroblasts in mice. This cell type also uniquely expressed a series of other genes including Disintegrin and metalloproteinase domain-containing protein 12 (ADAM12). Mice deleted of cells expressing ADAM12 show severely blunted fibrosis in murine models. t-SNE analysis supported the cell groupings, showing a discrete cellular grouping for the ACTA2/ITGA11/ADAM12-expressing cells. Immunohistochemical staining revealed that several of the unique gene markers associated with the third SMA-expressing cell type co-stained with SMA, staining deep reticular myofibroblasts, and confirming the myofibroblast identity of these cells. The unique markers on these cells correlated closely with the modified Rodnan skin score.

Conclusion: Myofibroblasts have a unique transcriptome profile that provides new insights into the function of these cells. The high correlation between transcriptome markers expressed by these cells with the MRSS supports the key importance of dermal myofibroblasts in SSc skin fibrosis.

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Abstract Number: 807

A Novel Multi-Network Approach Reveals Tissue-Specific Cellular Modulators of Fibrosis in Systemic Sclerosis, Pulmonary Fibrosis and Pulmonary Arterial Hypertension

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Background/Purpose: Systemic sclerosis (SSc) is characterized by multi-organ involvement and clinical heterogeneity. “Big data” approaches have yielded powerful tools to infer tissue-specific pathobiology. Large amounts of SSc gene expression data have been generated from different tissues and patient samples with distinct SSc clinical pathology. We performed an integrative meta-analysis of ten different SSc gene expression datasets that identified common disease drivers and tissue-specific distinctions in macrophage (MØ) phenotypes.

Methods: We developed and employed a novel data mining procedure that identified conserved coexpression patterns between ten datasets from four different tissues (skin, lung, esophagus, blood) with multiple clinical manifestations (pulmonary arterial hypertension [PAH], PF, limited and diffuse subtypes). We identified genes and processes that were conserved across all solid tissues and were highly expressed in pulmonary manifestations of SSc. We used these modules to query tissue-specific gene-gene interaction networks and analyzed the resulting lung- and skin-specific networks to infer common and tissue-specific fibrotic and inflammatory pathways.

Results: We identified a common gene signature indicative of an immune fibrotic process (IFP) composed of alternatively activated MØs that contribute to the extracellular matrix (ECM) remodeling processes. This signature was found in PAH and PF in lung, as well as the inflammatory molecular subsets in skin and esophagus. Analysis of the tissue-specific networks revealed a coupling of inflammatory and ECM processes in solid tissues that was absent in PBMC samples. We then rigorously contrasted the lung- and skin-specific gene interaction networks to identify a distinct lung resident MØ signature (LR-MØ) associated with lipid stimulation and alternative activation. Distinct MØ alternative activation transcriptional programs were observed in SSc-PF lung and SSc inflammatory skin.

Conclusion: We find evidence for alternatively activated MØs in multiple SSc tissues. However, there are subtle differences in the MØ transcriptional programs detected in skin and lung uncovered through multi-network systems analyses. In particular, different microenvironments likely provide distinct stimuli to infiltrating MØs that determine the pro-fibrotic character of these cells. This work suggests that the plasticity of this lineage is central to the divergence of fibrotic processes in multiple SSc-affected tissues and is a central component of an immune-fibrotic process driving disease.

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Abstract Number: 808

Down-Regulation of microRNA-126 in Scleroderma Microvascular Endothelial Cells (MVECs) Is Associated with Impaired Responses to Vascular Endothelial Growth Factor (VEGF) and Defective Angiogenesis

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Background/Purpose: Impaired angiogenesis in SSc is a crucial component of disease pathology that occurs in spite of upregulation of VEGF and other proangiogenic factors. MicroRNA-126 (miR-126) is expressed mainly in MVECs throughout the capillaries. MiR-126 regulates angiogenic signaling and responses to VEGF by direct repression of negative regulators of VEGF signalling pathway, including the Sprouty-related protein-1 (Spred1), and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2). In this study we investigated the expression levels of miR-126 and VEGF responses in SSc and control MVECs.

Methods: <span'arial','sans-serif';">MVECs were isolated from involved SSc skin and matched healthy subjects. The expression of miR-126 was measured by qPCR. The expression levels of VEGF inhibitors Spred1 and PIK3R2 were examined by qPCR and western analysis. The angiogenic potentials of MVECs were tested in a matrigel-based tube formation assay and in scratch test migration assay. <span'arial','sans-serif';">The expression of miR-126 was inhibited in control-MVECs by transfecting cells with has-miR-126 inhibitor and enhanced in SSc-MVECs by transfecting cells with has-miR-126 Mimic.

Results: miR-126 expression levels in SSc-MVECs and exosomes were significantly down regulated by over 10 folds in SSc-MVECs and 5 folds in SSc-exosomes (1.2 x10^7 miR-126 molecules/1million RNU44 molecules in control-MVECs and 8x10^5 in SSc-MVECs). Increased mRNA expression levels of Spred1 (2.5 folds ±0.2) and PIK3R2 (3.4±0.3 folds) in SSc-MVECs were noted by qPCR and confirmed by western analysis. Addition of VEGF (50ng/ml) to control-MVECs resulted in robust tube formation with and average branch length of (246.83±28.69 um) whereas diminished responses were seen in SSc-MVECs (88.58±15.46uM). Addition of VEGF enhanced control-MVECs migration and resulted in 50% wound closure in 6 hours, while this response was significantly diminished in SSc-MVECs (5%). Control-MVECs transfected with miR-126 inhibitor repressed miR-126 expression levels by 78% for up to 96 hours as measured by qPCR. This was associated with significant upregulation of mRNA and protein expression levels of Spred1 and PIK3R2 and reduced angiogenic capacity to levels comparable to that of SSc-MVECs. has-miR-126 Mimic transfection to SSc-MVECs resulted in upregulation of miR-126 expression, reduced expression of Spred1 and PIK3R2, and enhanced angiogenic potentials to levels comparable to control-MVECs.

Conclusion: <span'arial','sans-serif';">The data demonstrate impaired angiogenic potential of SSc-MVECs and diminished response to VEGF that was associated with significant down regulation of miR-126 in SSc-MVECs. Inhibition of miR-126 in control-MVECs resulted in impaired responses to VEGF, whereas forced expression of miR-126 in SSc-MVECs upregulated VEGV responses and normalized the angiogenic potential of SSc-MVECs. The data suggest that down regulation of miR-126 play a major role in impaired angiogenesis potential of SSc-MVECs.

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Abstract Number: 809

Microrna Targeting the Wnt Signalling Pathway in Black African Patients with Diffuse Cutaneous Systemic Sclerosis

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SESSION INFORMATION

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Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease involving the immune system, vasculature and extracellular matrix [1]. Dysregulation of the Wnt pathway has been implicated in the development of fibrosis in SSc and is proposed to contribute to a failure to maintain tissue homeostasis and appropriate immune response [2]. The objective of this research study was to explore the role of altered microRNA expression in the skin of affected individuals and their role in the dysregulation of Wnt pathway in the development of fibrosis in black South African SSc patients with early, diffuse disease (dcSSc).

Methods: Skin biopsies from eight black South African patients with dcSSc who fulfilled the 1987 ACR classification criteria, samples from both the forearm (affected skin) and the back (unaffected skin), and eight ethnically matched healthy control skin samples were examined. sRNA sequencing libraries were prepared for 50bp single-end sequencing on the Illumina HiSeq machine. The alignment software used was TopHat and Cufflinks [3], with downstream analyses done using mirDeep and SMARTAR [4]. Count data was analysed using DESeq2 [5]. Differential expression was considered significant if the adjusted p-value was <0.05 (Benjamini–Hochberg rule). For this study both TargetScan and miRanda were used to identify the Wnt pathway gene targets of the significantly differentially expressed miRNAs.

Results: The sRNA-seq data showed differential expression of 31 miRNAs that target the Wnt pathway genes, including miR-335 and miR-204 that are important regulators of normal tissue development. Ten miRNAs were differentially expressed only in the affected SSc skin samples when compared to controls. One of these miRNAs, miR-194- 5p was predicted to target 6 Wnt pathway genes, *CCND2, EP300, FRZB, MMP7, PRICKLE1* and *WIF1*. Another, miR-326 was predicted to target five of the Wnt pathway genes, *WNT5A, LEF1, NKD1, TCF7L1* and *WIF1*.Other significantly differentially expressed miRNAs included miR-15a-5p, miR-15b-5p, miR-375, miR-18b-5p and miR20b-5p, all of which are predicted to target Wnt pathway genes and have previously associated with fibrosis, autoimmunity or SSc. Table 1 summarises the main miRNA differential expression data. Experimental evidence suggests that perfect seed-region paring of the miRNA with the target mRNA is not necessarily a reliable predictor for miRNA interactions and could explain why some of the sites predicted *in-silico* are non-functional [6] and why validation of the outcome pf differential miRNA expression is essential.

Conclusion: This study revealed a number of miRNAs were differentially expressed between SSc patients and controls indicating that epigenetic changes play an important role in the pathogenesis, progression and clinical features of the disease. These changes may be triggered by environmental changes and in the context of a disease susceptible genotype. This is consistent with the multifactorial nature of scleroderma. Thedifferentially expressed miRNAs are predicted to target genes within the Wnt pathway and could result in dysregulated gene expression disrupting the Wnt pathway. This highlights the potential for these miRNAs to be investigated as biomarkers of SSc and as potential novel targets for therapeutic intervention. **References:**

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Table 1.Significantly differentially expressed miRNAs in affected and unaffected SSc skin compared to controls that are predicted to target Wnt pathway genes.

miRNA-sequencing data						
	Affected skin			Unaffected skin		
Gene	miRNA	Fold Change	Adj p-value	miRNA	Fold Change	Adj p-value
AXIN1	miR-15b-5p	-2.68	*0.001*	miR-144-5p	-3.66	*0.0005*
	miR-15b-3p	-1.96	*0.029*	miR-15b-5p	-2.63	*0.0009*
	miR-18b-5p	-4.44	*0.029*			*0.035*
DKK1	miR-335-3p	3.93	*0.00001*	miR-335-3p	4.48	*0.0000001*
	miR-543	2.47	*0.006*	miR-543	2.04	*0.03*
FZD8	miR-18b-5p	-4.44	*0.02*			
WNT10A	miR-130b	1.91	*0.05*	miR-485-5p	2.32	
	miR-485-5p	2.11	*0.01*			*0.03*
WNT3A	miR-15b-5p	-2.68	*0.001*	miR-15b-5p	-2.63	*0.0009*
	miR-335-3p	3.93	*0.00001*	miR-335-3p	4.48	*0.0000001*
	miR-15b-3p	-1.96	*0.02*	miR-15b-3p	-2.11	*0.01*
WNT7A	miR-15b-5p	-2,68	*0.001*	miR-15b-5p	-2.63	*0.009*
	miR-15b-3p	-1.96	*0.02*	miR-15b-3p	-2.11	*0.01*
	miR-15a-5p	-2.05	*0.02*	miR-15a-5p	-2.28	*0.007*
	miR-16	-1.93	*0.03*	miR-16	-1.98	*0.03*
LEF1	miR-543	2.47	*0.006*	miR-543	2.04	*0.03*
	miR-20b-5p	-2.46	*0.03*	miR-20b-5p	-2.70	*0.01*

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Abstract Number: 810

Microrna-125b As a Potential Anti-Fibrotic and Anti-Apoptotic Regulator in Systemic Sclerosis

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Background/Purpose: MicroRNAs (miRs) are a class of small, noncoding RNAs that regulate many biological processes. Some microRNAs are involved in skin fibrosis. Here, we aimed to analyze the differential expression and regulation of miR-125b and its pathophysiological role in systemic sclerosis (SSc).

Methods: Low density array was run on pooled RNA from 3 SSc and 3 healthy controls' fibroblasts. Further validation was performed by qPCR on RNA derived from cultured fibroblasts as well as from whole skin biopsies. Fibroblasts were stimulated with pro-inflammatory cytokines such as TGFβ, IL-1β, -4, -13, -17A, and PDGF. In order to identify downstream effects of miR-125b, knockdown with anti-miR-125b (or scrambled controls) in healthy controls' (HC) fibroblasts was performed to mimic the condition of SSc patients. RNA was isolated from healthy fibroblasts (n=4) after 24 hours of knockdown and was proceeded to deep sequencing using Ilumina HiSeq2000. After bioinformatic analysis, validation of the sequencing data was performed with qPCR on the RNA of the same as well as additional HC fibroblasts. Apoptosis was assessed by Caspase-Glo 3/7 assay.

Results: Screening presented miR-125b as one of the candidate miRs differently expressed in SSc. That was further validated by qPCR in primary dermal fibroblasts (SSc patients = 11, HC = 8), where it was downregulated by 47% (median 53%, first quartile 33%, third quartile 70%; $p<0.01$). Additionally, miR expression was measured in skin biopsies of both SSc patients (n=4) and HC (n=5). In patients' samples, miR-125b was downregulated by 35.5% (median 64.5%, first quartile 60.5%, third quartile 77.5%; $p<0.05$). To localize the expression of miR-125b, we separately measured the expression in dermis and epidermis of paraffin fixed tissues. In both cases, expression of miR-125b was downregulated. MiR-125b expression appeared to be independent from main pro-inflammatory cytokines action. RNA sequencing identified > 3500 differentially expressed genes with $p<0.05$. More than half of the highly expressed genes with at least 15% change were predicted targets of miR-125b by TargetScan and MiRWalk, indicating successful functional inhibition of miR-125b. Bioinformatic analysis revealed extracellular matrix organization and apoptosis regulation as the two main clusters of differentially expressed genes. Among them, BAK1 and BMF are participants of the BCL2 apoptosis pathway and predicted targets of miR-125b. Consistent with the sequencing results, qPCR showed upregulation of these genes after knockdown of miR-125b. Interestingly, BCL2 which by itself is an anti-apoptotic factor and also a target of miR-125b, was not changed after knockdown. This indicates that physiological miR-125b expression prevents cells form apoptosis. Accordingly, miR-125b knockdown resulted in 70% more apoptosis compared to either untreated cells or scrambled controls.

Conclusion: This is the first time microRNA-125b is shown to be differently expressed in SSc skin and primary dermal fibroblasts. Its downregulation increases apoptosis and might be a potential compensatory mechanism to prevent fibrosis.

Disclosure: **A. Kozlova**, None; **E. Pachera**, None; **F. Renoux**, Swisslife, 2; **M. Rudnik**, None; **B. Maurer**, AbbVie, Protagen, EMDO, 2, 9,Roche, Actelion, 9; **A. Jüngel**, None; **J. H. W. Distler**, Actelion Pharmaceuticals US, 5,BMS, 5,Celgene, 5,Bayer Pharma, 5,Boehringer Ingelheim, 5,JB Therapeutics, 5,Sanofi-Aventis, 5,Novartis Pharmaceutical Corporation, 5,UCB, 5,GSK, 5,Array Biopharma, 5,Active Biotech, 5,Galapagos, 5,Inventiva, 5,Medac, 5,Pfizer Inc, 5,Anamar Medical, 5,RuiYi, 5,4D Science GmbH, 1; **G. Kania**, Bayer, 2; **O. Distler**, Bayer, Sanofi, Ergonex, Boehringer Ingelheim, Actelion, Pfizer, 2,4 D Science, Actelion, Active Biotec, Bayer, BiogenIdec, BMS, Boehringer Ingelheim, EpiPharm, Ergonex, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Pharmacyclics, Pfizer, Serodapharm, Sinoxa, 5.

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Basophils Are Activated and Stimulate Both B Cells and Fibroblasts in Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) is a rare multisystem connective tissue disease characterized by skin and internal organs fibrosis and vascular abnormalities, along with the presence of autoantibodies. Basophils, which have long been associated with allergy and parasitic infections, are now identified as having the ability to promote fibrosis, stimulate B cells and increase autoantibodies production. Herein we investigated the potential role of basophils in SSc.

Methods: Peripheral basophils from patients with SSc who did not receive glucocorticoids or immunosuppressants and healthy controls (HC) were analyzed using flow cytometry and basophil activation test. The impact of the KU812F basophil cell line on both B cells and fibroblasts isolated from SSc patients were assessed using flow cytometry and xCelligence assay.

Results: Sixty-five consecutive SSc patients and 38 HC were recruited. The proportion of CD203c-positive basophils was higher in SSc patients than in HC (37.5 % [24.3 – 59.0] vs 25.6% [13.6 – 41.7]; $p < 0.001$). Compared to HC, basophils from SSc patients had higher mean fluorescence intensity (MFI) quantifications of CD154 (854 [541 – 1334] vs 485 [147 – 871]; $p < 0.05$) and intracellular B cell activating factor (1551 [1001 – 4373] vs 857 [722 – 1498]; $p < 0.05$). Activated KU812F basophils were able to decrease the proportion of CD95-positive B cells (10.5% [8.4 – 12.6 vs 14.8% [14.4 – 21.5]; $p < 0.05$), to increase the production of interleukine-6 (21.2% [16.5 – 29.9] vs 14.9 [12.3– 16.7]; $p < 0.05$) and transforming growth factor-β (5.6% [4.7 – 7.2] vs 4.1 [2.6– 5.4]; $p < 0.05$) producing B cells and to enhance the proliferation of fibroblasts from patients with SSc. Lastly, the expression of CRTH2 on basophils correlated with patients' disease characteristics and was able to discriminate those with or without pulmonary hypertension (PAH). Indeed, CRTH2 MFI quantification among basophils positively correlated with patients' diffusing capacity of the lungs for carbon monoxide ($r = 0.60$, $p < 0.05$), negatively correlated with patients' modified Rodnan skin score ($r = - 0.77$, $p < 0.01$) and was lower in SSc patients with PAH than in SSc patients without PAH (31476 [30213 – 31633] vs 59576 [41312 – 67788]; $p < 0.001$).

Conclusion: Peripheral basophils are activated and are able to simulate both B cells and fibroblasts in patients with SSc, suggesting a key role of basophils in the pathophysiology of SSc.

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Monocytes/Neurotrophins/Myofibroblasts As a Novel Axis in Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease, which is characterized by inflammation, fibrosis and vasculopathy in multiple organs, mainly in the lung, heart and skin. Neurotrophins (NTs) are a family of proteins promoting neuron growth and survival; however their profibrotic and proangiogenic actions were recently discovered in fibroblasts and endothelial cells. Elevated number of monocytes and their activation state has been already reported in SSc, but detailed roles of monocytes in multiorgan fibrogenesis in SSc remain unclear. We aimed to determine the contribution and the role of circulating monocytes in the onset and progression of multiorgan fibrosis in SSc. Additionally, we investigated the involvement of neurotrophin-3 (NT-3) and neurotrophins receptors in the fibrogenesis in SSc.

Methods: Endomyocardial biopsies from SSc patients and healthy controls were screened by immunohistochemistry. $CD14^+$ monocytes isolated from peripheral blood of SSc patients and healthy donors were differentiated towards the myofibroblast phenotype by stimulation with TGFβ1, IL-4, IL-10 and IL-13. In addition, $CD14^+$ monocytes were co-cultured with dermal fibroblasts originated from SSc patients

and healthy subjects, and with adult cardiac fibroblasts. After 7 days, myofibroblast gene expression and cytokine secretion profiles were evaluated by qPCR, Western blot, protein array and ELISA. Healthy and SSc dermal or cardiac fibroblasts were stimulated with NT-3 and induction of profibrotic genes was analysed by qPCR and immunofluorescence.

Results: Myocardium of SSc patients revealed the presence of CD45-expressing infiltrates, extended collagen I deposition and the presence of CD14-expressing elongated cells in the fibrotic tissue. Stimulated monocytes acquired myofibroblast-like phenotype with increased expression of collagen I ($p<0.0001$), fibronectin ($p<0.05$), and α smooth muscle actin (α-SMA) in comparison to untreated cells. Similarly, $CD14^+$ monocytes exposed to dermal or cardiac fibroblasts acquired spindle shape and expressed higher levels of profibrotic genes. The process of monocyte to myofibroblast differentiation employed TGFβ/SMAD signalling. Blocking of the TGFBR1 receptor and canonical SMAD-dependent pathway with inhibitors resulted in the abrogation of extracellular matrix secretion by monocytes. $CD14^+$ monocytes from SSc patients were characterised by higher secretion of CXCL10 ($p<0.001$), CCL20, CCL22, Leukemia Inhibitory Factor (LIF) and NT-3. SSc fibroblasts revealed higher expression of TrkB and $p75^{NTR}$ receptors. Moreover, elevated level of α-SMA was observed in SSc fibroblasts after stimulation with NT-3.

Conclusion: Here we demonstrated the capability of peripheral blood monocytes to differentiate towards the functional myofibroblast phenotype, indicating these cells as one of the potential sources of pathological tissue myofibroblasts in SSc. Additionally, SSc monocytes secreted NT-3, which induced fibroblast to myofibroblast differentiation. Further studies of TGFβ induced NT-3 expression in monocytes and its effects on fibroblast to myofibroblast differentiation might lead to novel treatment strategies.

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Abstract Number: 813

Identifying and Assessing Subgroups in Systemic Sclerosis Patients Based on Comprehensive Autoantibody Profiling

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Background/Purpose: Systemic sclerosis (SSc) is a remarkably heterogeneous autoimmune disease, for which effective disease-modifying therapies are still lacking. The most widely used classification divides SSc into two major subsets diffuse cutaneous (dcSSc) and limited (lcSSc) SSc by the extent and severity of skin fibrosis. However, not all patients fit into these subsets. This has created great interest to examine disease heterogeneity at the molecular level to uncover unrecognized SSc subtypes that may differ with regard to clinical manifestations, prognosis or therapy response. In large-scale “omics”-type autoantibody (AAB) profiling studies we have recently identified novel SSc-associated autoantigens. Here, we describe the development of a 20 marker multiplexed AAB assay and explored its utility for SSc patient subgroup analysis.

Methods: A Luminex bead-based AAB assay was designed by combining 8 connective tissue disease (anti-centromere, anti-Scl70, U1-snRNP, SSB, Ro52, Ro60, SmB, anti-ribosomal P) antigens with 12 novel antigens (including BICD2, JMJD3/KDM6B, and PPP1R2). Novel AAB targets were previously detected in SSc patients with a p-value <0.05 (Mann-Whitney-U-test) and frequency >15%. AAB reactivity was analysed in 100 SSc patients (dcSSc: n=32, lcSSc: n=50, SSc overlap: n=9, other: n=9). The mean modified Rodnan skin score (MRSS), mean disease duration (month), and mean age (years) of the SSc cohort was 10.51, 162.5 and 56.94, respectively. To analyze the individual-level patient similarity of AAB reactivity, the total number of AABs reactive in each patient was calculated and referenced to the number of all available antigens in percent. Hierarchical cluster analysis of marker co-prevalence and patient signature overlap was performed.

Results: Based on their AAB reactivity pattern, the SSc sample cohort can be decomposed into four main clusters. Cluster 1 includes 87% of all lcSSc patients characterized by an extended AAB repertoire (including BICD2, KDM6B and PPP1R2), MRSS below the average and longer disease duration. Cluster 2 includes 56% lcSSc and 26 % dcSSc patients characterized by MRSS above the average and anti-U1-snRNP antibodies. Cluster 3 includes SSc-overlap, lcSSc and dcSSc with higher MRSS compared to Cluster 1 and 2 and variable AAB profile. Cluster 4 includes mainly dcSSc patients with anti-Scl70 AAB and highest number of patients with MRSS above the average (83%).

Conclusion: The multiplexed analysis of AABs in SSc enables defining an AAB reactivity score and patient clusters. This might support to subclassify SSc beyond lcSSc and dSSc.

Disclosure: P. Budde, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **H. Göhler**, Protagen AG, 3; **K. Marquart**, Protagen AG, 3; **P. Schulz-Knappe**, Protagen AG, 3; **M. Schneider**, Protagen AG, 5; **N. Hunzelmann**, None.

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The Regulatory B Cells Ameliorate Skin Sclerosis, Lung Fibrosis, and Autoimmunity Via an Anti-Oxidative Effect in Systemic Sclerosis Model Mice

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Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease characterized by vascular damage, excessive deposition of extracellular matrix, and fibrosis in the several organs, including skin and lung, on an autoimmune background. Although the pathogenesis of SSc remains unknown, it has been proposed that oxidative stress play an important role in disease development. Many previous studies have confirmed that production of free radicals is enhanced in human SSc patients, due to ischemia and reperfusion injury following Raynaud's phenomenon, an initial clinical manifestation. Recent studies indicated that specific B cell subsets can negatively regulate T cell immune responses, and have been termed regulatory B cells. Human and mouse regulatory Bcells with the ability to express the inhibitory cytokine interleukin (IL)-10 have been identified. Although rare, regulatory B cells are potent negative regulators of antigen-specific inflammation and T cell dependent autoimmune diseases in mice. However, how IL-10 producing regulatory B cells regulate antigen-specific immune responses in vivo without inducing systemic immunosuppression is unknown. In this study, we focused on the effect of antigen-specific regulatory B cells on oxidative stress.

Methods: In this study, bleomycin (BLM)-induced SSc model mice were used. CD5+ and CD1dhi regulatory B cells were obtained from BLM or PBS treated mice respectively and adoptively transferred to BLM-induced SSc mice. To assess the effect of regulatory B cells, serum levels of 8-isoprostane, a marker of oxidative stress, were measured. Furthermore, we assessed skin and lung fibrosis histologically. Protein and mRNA levels of profibrogenic cytokines, such as IL-4, IL-6, and IL-17, were measured using ELISA and real-time RT-PCR.

Results: The regulatory B cells reduced skin and lung fibrosis and serum levels of profibrogenic cytokines in BLM-induced SSc model mice. Especially, serum levels of 8-isoprostane were decreased by adoptively transferred ex vivo-induced regulatory B cells compared with PBS injection. In addition, regulatory B cells significantly inhibited free radical production from inflammatory cells cultured with BLM. Interestingly, the regulatory B cells obtained from BLM-treated mice had more inhibitory effects than those from PBS-treated mice.

Conclusion: These results suggest that the regulatory B cells inhibited free radical production from inflammatory cells, results in ameliorating the disease manifestations of SSc. These inhibitory effects of regulatory B cells may exert via the antigen-specific manner. Although further studies are needed, the autoantigen-specific regulatory B cell can be a novel therapeutic tool for treatment for SSc.

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Abstract Number: 815

The Novel Anti-BICD2 Autoantibody Potentially Predicts a Favorable Disease Course in SSc

Johannes Schulte-Pelkum[1], Daniel Wirtz[1], Petra Budde[1], Hans-Dieter Zucht[1], Peter Schulz-Knappe[1], Prof. Dr. Matthias Schneider[2], Suzana Jordan[3], Oliver Distler[3], Britta Maurer[3] and Nicolas Hunzelmann[4], [1]Protagen AG, Dortmund, Germany, [2]Department of Rheumatology, Univ. Duesseldorf, Duesseldorf, Germany, [3]Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, [4]Department of Dermatology, University of Cologne, Cologne, Germany
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Session Time: 9:00AM-11:00AM

Background/Purpose: To evaluate clinical associations of our recently discovered systemic sclerosis-specific auto-antigen BICD2 in clinically well characterized systemic sclerosis (SSc) cohorts from two tertiary referral centers.

Methods: Serum samples were obtained from the biobanks of the Department of Rheumatology, University Hospital Zurich, Zurich, Switzerland, and Department of Dermatology, University of Cologne, Cologne. The analysis included samples collected from patients suffering from SSc (n=302) systemic lupus erythematosus (n=39), Sjogren's syndrome (n=11), rheumatoid arthritis (n=20), myositis (n=20) and healthy volunteers (n=99). Clinical annotation data, including age, gender, disease duration, MRSS, detailed information on organ involvement making up to a total of either >50 or >100 clinical data points (depending on the site) was available for more than 80% of all SSc serum samples included in this study. All samples were analyzed on the novel Multilisa BICD2 (CE), an ELISA for the semi-quantitative detection of anti-BICD2 antibodies in human serum or plasma.

Results: We found anti-BICD2 with a prevalence of 28% and 32% in the groups of SSc patients of the respective cohort, and only in 4.2% in cohorts with other rheumatic diseases or healthy controls (OR=8.702). Anti-BICD2 autoantibodies were present in a subgroup of SSc patients where skin fibrosis was either from the limited cutaneous subtype (p=0.0002) or restricted to sclerodactyly (p=0.0037). Within this line, anti-BICD2 autoantibodies showed a significantly higher titer in patients with moderate skin involvement reflected by low MRSS-stages (p=0.001). Analysis of pulmonary involvement revealed elevated anti-BICD2 titers in the group of patients *not* suffering from lung fibrosis measured by high resolution computer tomography (HCRT) (p=0.0001). Of note, the highest a-BICD2 values were observed in the group of patients having a residual transfer capability of 61-80% (DLCO stage 1 of 4). Anti-BICD2 autoantibodies were also found to be more prominent in the group of patients having a disease duration of more than 3 years.

Conclusion: In this study, we were able to further confirm the diagnostic value and high specificity of the newly discovered BICD2 autoantigen. Anti-BICD2 autoantibodies were found to be elevated in patients suffering from limited SSc, and anti-BICD2 reactivity was found to be related to clinical observations of a moderate course of disease.

Disclosure: J. Schulte-Pelkum, Protagen AG, 3; **D. Wirtz**, Protagen AG, 3; **P. Budde**, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **P. Schulz-Knappe**, Protagen AG, 3; **P. D. M. Schneider**, Protagen AG, 5; **S. Jordan**, None; **O. Distler**, None; **B. Maurer**, AbbVie, Protagen, EMDO, 2, 9,Roche, Actelion, 9; **N. Hunzelmann**, None.

Abstract Number: 816

Clinical Response to Treatment with Belimumab and Mycophenolate Mofetil Is Associated with Decrease in B Cell, TGF-β and PDGF Signaling in Systemic Sclerosis

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Background/Purpose: While B cell signaling is thought to be important in the pathogenesis of systemic sclerosis (SSc), the experience with B cell targeting therapies in SSc clinical trials has been mixed. Belimumab is a monoclonal antibody that inhibits B cell survival. We investigated gene expression changes of skin biopsy specimens of patients with early diffuse cutaneous (dc) SSc treated in the context of a randomized controlled pilot trial of belimumab versus placebo in patients on background mycophenolate mofetil (MMF) therapy (NCT01670565).

Methods: Biopsies of lesional forearm skin were obtained from 18 patients prior to randomization and after 52 weeks of treatment with belimumab or placebo. Patients were defined as improvers if they had a modified Rodnan Skin Score improvement ≥20% post-treatment. Using this criterion, 7/9 patients in the belimumab/MMF group were improvers, and 3/9 in the placebo/MMF group were improvers. Expression data from skin biopsies were analyzed for differentially expressed genes ($p \leq 0.05$, paired/unpaired t-test) which were investigated for functional enrichment via g:Profiler ($p \leq 0.05$, corrected for multiple testing). Differentially expressed pathways were determined genome-wide using Gene Set Enrichment Analysis (False Discovery Rate ≤5%).

Results: In the belimumab/MMF group, clinical improvers showed downregulation of genes involved in *B cell mediated immunity*, *extracellular matrix (ECM), collagen formation* and *response to TGF*-β. Decreased pathways included *IL4/IL6 signaling* as well as *B cell signaling*, *ECM, TGF*-β and *PDGF signaling* (Figure 1). Comparison between baseline samples of improvers and non-improvers showed that patients who improved were characterized by the increased baseline expression of *ECM* and *TGF*-β *signaling* genes and pathways. In the improvers from placebo/MMF group, we observed decreased expression of genes and pathways involved in *TCR signaling*, e.g. *T cell activation* and *T cell aggregation*, consistent with the mechanism of MMF as well as *Toll-like receptor signaling*. In both treatment arms, non-improvers were characterized by a small number of differentially expressed genes with no functional enrichment, consistent with the lack of clinical response.

Conclusion: Decrease in *B cell signaling* genes and pathways was observed only in patients with improved skin score in belimumab/MMF but not placebo/MMF group. While attributable to the pharmacologic effect of the drug, this was not seen in patients who did not improve. Improvers from belimumab/MMF group showed high baseline expression and significant post-treatment decrease of fibrotic genes and pathways i.e. *ECM, TGF*-β and *PDGF signaling*. This finding suggests that treatment effect may be influencing the interplay between immune activation and fibrosis linked to clinical manifestations of SSc such as skin fibrosis.

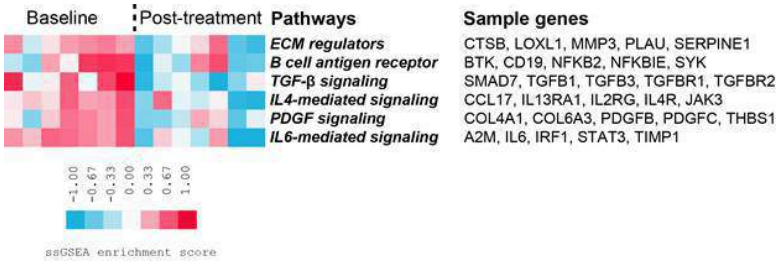

Figure 1. Sample pathways downregulated in improvers from belimumab/MMF group (GSEA FDR≤5%)

Disclosure: V. Martyanov, None; **J. K. Gordon**, None; **T. A. Wood**, None; **R. F. Spiera**, GlaxoSmithKline, 2,Roche Pharmaceuticals, 2,Boehringer Ingelheim, 2,PRISM, 2,Cytori, 2,Corbus Pharmaceuticals, 2,GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Boehringer Ingelheim, 5; **M. L. Whitfield**, GlaxoSmithKline, 5,Celdara Medical LLC, 4.

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Abstract Number: 817

RNA and Protein Cargo of Exosomes Isolated from Serum of Systemic Sclerosis Patients Induce a Profibrotic Phenotype in Cultured Normal Human Dermal Fibroblasts: A Potential Mechanism for the Initiation and Progression of a Profibrotic

Phenotype in SSc

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Background/Purpose: Exosomes are lipid bilayer-bound microvesicles that contain various macromolecules including numerous microRNA (miRNA) and proteins. Exosomes mediate intercellular communication by fusing and releasing their macromolecular content into target cells. The mechanism of the establishment and progression of a profibrotic phenotype in Systemic Sclerosis (SSc) is not currently well understood. Here, we characterized the miRNA content of exosomes isolated from the serum of SSc patients and analyzed the ability of exosomal RNA and protein components to induce a profibrotic phenotype in normal human dermal fibroblasts *in vitro*.

Methods: Exosomes were isolated from serum from normal individuals and from patients with either limited cutaneous or diffuse cutaneous SSc employing a highly specific polymer precipitation procedure. The isolated exosomes were characterized by Nanosight Particle Tracking Analysis and transmission electron microscopy and the levels of nine pro-fibrotic and nineteen antifibrotic miRNA were assessed by semiquantitative real time PCR. Cultured normal human dermal fibroblasts were incubated with untreated exosomes isolated from the serum of SSc patients or normal donors or with isolated exosomes previously treated with Triton X-100, or with RNAseA, or proteinase K, alone or in combination with Triton X-100 to selectively deplete miRNAs or proteins, respectively. The expression levels of several profibrotic genes in the dermal fibroblasts treated with exosomes isolated from serum of normal individuals or SSc patients were assessed.

Results: Nanosight particle tracking analysis and transmission electron microscopy confirmed the isolation of microvesicles in the size range expected for exosomes and an exosome protein array verified that the isolated particles contained exosome-specific proteins and were not contaminated by Golgi-associated proteins. The content of six antifibrotic miRNAs was decreased whereas the content of three profibrotic miRNAs was increased in serum exosomes from both groups of SSc patients compared to normal serum exosomes. Furthermore, the levels of four miRNA were significantly different between the two SSc clinical subsets. Untreated exosomes isolated from the serum of patients with limited or diffuse SSc induced the expression of profibrotic genes in cultured normal human dermal fibroblasts whereas the establishment of this profibrotic phenotype could be partially abrogated by treatment of the exosomes with either RNAse A or proteinase K.

Conclusion: The content of profibrotic/antifibrotic miRNA of serum exosomes from SSc patients is different from that of normal serum exosomes and displays an overall profibrotic phenotype. SSc patient-derived exosomes can induce a profibrotic phenotype in target cultured normal dermal fibroblasts. The induction of this profibrotic phenotype is mediated by both the RNA and protein content of the exosomes. Since exosomes are involved in intercellular communication these observations suggest a mechanism for transmission of a profibrotic molecular program to normal target cells leading to the extension of the fibrotic process to non-affected tissues. Supported by NIH Grants AR055660 and AR065638 to SAJ.

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Abstract Number: 818

The Role of Endothelin 1 in Activation of Vascular Smooth Muscle Cells in Systemic Sclerosis; Increased Cell Proliferation and Resistance to Apoptosis Mediated By Endotehlin B Receptors

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by activation of the immune system, vascular dysfunction and tissue fibrosis. Vascular dysfunction in SSc is one of the most prominent features of the disease that manifest by Raynaud's phenomenon in the early stages and by proliferative vasculopathy that affect all involved organs and progress throughout the disease course. Endothelin 1 (ET-1) is overexpressed in SSc as illustrated by elevated circulating levels and increased tissue expression in involved organs. We previously reported increased proliferative capacity of SSc- vascular smooth muscle cells (vSMCs) in association with resistance to apoptosis in comparison to control cells. In this study, we sought to examine the role of ET-1 and its signaling pathways in the generation of the activated vSMCs phenotype.

Methods: We isolated vSMCs from 4mm punch skin biopsies from 3 patients with SSc and 3 healthy controls. We evaluated the expression levels of *EDN1, EDNRA* and *EDNRB,* which encodes for ET-1, Endothelin Receptor A (ERA) and ERB, respectively, in vSMCs from SSc patients and controls. We treated vSMCs with ET-1, in the presence or absence of selective ETA antagonist (BQ123), selective ETB antagonist (BQ788) or dual ETA+B antagonist (PD145065). Under these conditions, we examined the effects of ET-1 on cell proliferation using BrdU assay, viability by MTT assay and apoptosis by Tunel assay.

Results: SSc-vSMCs overexpressed *EDN1* compared to control vSMCs (120 fold). Furthermore, and compared to control-vSMCs, *EDRA* expression levels were significantly increased in SSc-vSMCs while *EDNRB* expression levels were lower than control values. At baseline, SSc-vSMCs exhibited 1.8-fold increase in cell proliferation compared to control vSMCs (P= 0.0031). Upon treating control-vSMCs with 10nM ET-1, we demonstrate increased vSMCs proliferation by 1.6 folds (P= 0.03) in association with decreased cell apoptosis by 36%. The addition of selective ETB antagonist (BQ788) or dual ETA+B antagonist (PD145065) reduced vSMCs proliferation by 72% and 69%, respectively (P<0.05), but we did not find significant effect for selective ETA antagonist (PD156707) on cell proliferation (P>0.05). Moreover, BQ788 and PD145065 increased apoptosis of vSMCs. We did not see this effect using the selective ETA antagonist.

Conclusion: We provide an experimental evidence for increased proliferation, viability and decreased apoptosis of vSMCs by ET-1 *in vitro*, and we demonstrate that this effect is mediated by ETB receptors. Selective ETB and non-selective ETA+B receptor antagonists have a theoretical advantage over selective ETA antagonists in reducing the effect of ET-1 on proliferation of cells in tunica media, and that ET-1 have an important role in the development of vascular remodeling in SSc.

Disclosure: S. Nada, None; **Y. Wang**, None; **N. Altorok**, None; **B. Kahaleh**, None.

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Abstract Number: 819

Impaired Adiponectin Signaling in SSc Contributes to Myofibroblast Differentiation and Organ Fibrosis

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Session Time: 9:00AM-11:00AM

Background/Purpose: In systemic sclerosis (SSc) patients, skin fibrosis is accompanied by involution of dermal white adipose tissue

(dWAT), a prominent source of adiponectin (APN). We hypothesize that impaired APN activity due to loss of dWAT underlies the progression and persistence of skin fibrosis in SSc. To tests our hypothesis, we investigated APN pathway deregulation in SSc and used transgenic mice and APN-mimetic peptides.

Methods: APN pathway activation was evaluated in SSc skin biopsies using expression microarray and immunohistochemistry. Experimental skin and peritoneal fibrosis was investigated in ΔGLY-APN transgenic mice.

Results: Interrogating skin biopsy transcriptome data, we found that a subset of SSc patients showed reduced APN pathway activation ($p=0.04$), representing a novel molecular subset of SSc. Moreover, SSc skin biopsies ($n=20$) had significantly reduced levels of phospho-AMP protein kinase in dermal myofibroblasts compared to healthy controls ($p=0.01$), indicating attenuation of local APN signaling. To assess the effect of systemic APN, fibrosis was induced in ΔGLY-APN transgenic mice. A 2-3-fold increase in levels of circulating APN in these mice was associated with significantly attenuated skin fibrosis induced by bleomycin as well as by constitutively-active TGF-ß. Moreover, transgenic mice showed partial preservation of dWAT during early-stage fibrogenesis, and reduced influx of macrophages. Attenuation of skin fibrosis was accompanied by evidence of defective focal adhesion assembly in dermal cells. Levels of circulating APN in these mice were negatively correlated with dermal thickness ($r=-0.747$, $p<0.001$) and collagen content ($r=-0.586$, $p<0.001$). Chronic treatment of C57BL6/J mice with short APN mimetic peptides prevented and reversed experimentally-induced dermal fibrosis. ΔGLY-APN mice also showed robust protection from chlorexidine gluconate-induced peritoneal fibrosis ($p=0.05$) and myofibroblast accumulation ($p=0.02$). Cell fate-mapping studies showed that >65% of myofibroblasts within fibrotic peritoneal tissue derived from APN-positive progenitor cells resident in the mesothelial sub-lining.

Conclusion: Our results implicate defective APN production and activity in skin fibrosis in a subset of patients with SSc. APN protected mice from experimental skin and peritoneal fibrosis, and circulating levels correlated with dermal thickness. Myofibroblasts within fibrotic tissue largely derive from adipocytic lineage cells resident in the dWAT (skin) or peritoneal mesothelium. These findings suggest that restoring normal APN signaling and normal adipogenesis represent innovative therapeutic approaches to SSc.

Disclosure: R. G. Marangoni, None; **B. Korman**, None; **F. Fang**, None; **M. Hinchcliff**, None; **L. Otvos**, None; **P. E. Scherer**, None; **W. Tourtellotte**, None; **J. Varga**, None.

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Abstract Number: 820

EZH2 Modulates Angiogenesis and Fibrosis in Scleroderma

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Session Time: 9:00AM-11:00AM

Background/Purpose: Scleroderma (SSc) is a complex disease that involves activation of the immune system, vascular complications, and tissue fibrosis. Although the pathogenesis of this disease is largely unknown, epigenetic dysregulation has been implicated to play a role. In this study, we focused on the histone methyltransferase enhancer of zeste homolog 2 (EZH2), which is the catalytic component of the polycomb repressor complex 2. It mediates trimethylation of lysine 27 of histone 3, which acts as a repressive epigenetic mark. It has been reported that EZH2 regulates angiogenesis, and it is also involved in fibrosis. We hypothesize that EZH2 contributes to impaired angiogenesis and enhanced fibrosis in SSc.

Methods: Dermal endothelial cells (ECs) and fibroblasts were isolated from biopsies from healthy subjects or patients with diffuse cutaneous SSc. EZH2, collagen 1a1 (Col1a1), α-smooth muscle actin (ACTA2), fos-related antigen 2 (Fra2), and peroxisome proliferator-activated receptor gamma (PPARG) expression were determined by qPCR. EZH2 expression was also determined by Western blotting. EZH2 was overexpressed using an EZH2 vector. Inhibition of EZH2 was achieved by using EZH2 inhibitor DZNep (0.2μM-5μM) or EZH2 siRNA. Angiogenesis was assessed by an *in vitro* Matrigel tube formation assay. The scratch wound assay was used to evaluate fibroblast migration. A paired t-test was used to compare differences between groups, and a p-value of <0.05 was considered significant. Genome-wide DNA methylation status was evaluated using the Illumina Infinium Methylation EPIC BeadChip Array and the Illumina GenomeStudio platform was used to analyze the methylation data.

Results: The expression of EZH2 was significantly elevated in both SSc ECs and fibroblasts compared to healthy controls. To evaluate the effect of EZH2 on EC angiogenesis, EZH2 was overexpressed in normal ECs. This led to a significant decrease in tube formation on

Matrigel compared to sham-transfected cells. In contrast, silencing of EZH2 in SSc ECs restored normal angiogenesis. In normal fibroblasts, overexpression of EZH2 led to increase in Col1a1 and Fra2 mRNA expression. In contrast, SSc fibroblasts treated with DZNep showed a dose-dependent reduction in Cola1a and Fra2 mRNA expression, suggesting that inhibiting EZH2 attenuates profibrotic potential in SSc fibroblasts. In addition, we observed a dose-dependent reduction in mRNA expression of the myofibroblast marker ACTA2 in SSc fibroblasts treated with DZNep, but this did not reach statistical significance. The antifibrotic PPARG decreased at lower doses of DZNep but increased significantly at the highest dose (5μM) compared to untreated SSc fibroblasts. In the scratch wound assay, EZH2-overexpressing normal fibroblasts showed an increase in cell migration while DZNep-treated SSc fibroblasts showed wider wound width at 48 hours post-injury compared to untreated SSc fibroblasts. Genome-wide DNA methylation changes after manipulation of EZH2 expression were used to identify additional EZH2-regulated targets, which will help to further mechanistically understand the angiogenic and fibrotic effects of EZH2 in SSc.

Conclusion: Our results uncovered an important role for EZH2 in SSc. EZH2 is overexpressed in SSc ECs and fibroblasts, and this overexpression is profibrotic and results in impaired angiogenesis in this diseases. Targeting EZH2 or EZH2-regulated genes may open new therapeutic avenues for patients with SSc.

Disclosure: P. S. Tsou, None; **P. Coit**, None; **D. Khanna**, None; **A. H. Sawalha**, None.

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Abstract Number: 821

IL-31 Is an Inflammatory Pro-Fibrotic Factor Elevated in a Subset of Scleroderma Patients with Severe Pruritus

Bahja Ahmed Abdi[1], Sara Zafar[2], Zeinab Taki[3], Nikita Arumalla[4], Shiwen Xu[5], Christopher Denton[4], David Abraham[4] and Richard J. Stratton[6], [1]Division of Medicine, Centre for Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [2]Centre of Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [3]Department of Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [4]Division of Medicine, Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [5]Division of Medicine, Centre for Rheumatology and Connective tissue disease, University College London, London, United Kingdom, [6]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom
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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune rheumatic disease associated with fibroblast activation in the skin and visceral organs. In SSc, refractory pruritus is a common symptom in a subgroup of patients. IL-31, a Th2 cell derived cytokine, is implicated in causing pruritus in conditions including atopic dermatitis and T cell lymphoma. T-lymphocyte-derived factors provide a possible mechanistic link between autoimmune inflammation and the fibrosis reported in SSc. In this study we measured IL-31 levels in SSc tissue fluid and plasma, and sought correlation with itch severity and clinical parameters. In addition, recombinant IL-31 was investigated for its capacity to influence fibroblast and mesenchymal stem cell (MSC) activity.

Methods: Dermal blister fluid (BF) was obtained by a suction blister method from the involved skin of SSc patients or matched site of healthy controls synchronous to plasma sampling (SSc n=28, controls n=15) and IL-31 measured by ELISA. SSc and control fibroblasts lysates, MSC lysates, and tissue biopsied from involved skin lesions or control samples were analysed by qPCR for IL-31 receptor expression. Normal skin fibroblasts as well as MSCs were cultured and treated with IL-31 and phenotypic changes were assayed by protein assays, and next generation sequencing. Dermal fibroblast and MSC migration was assessed through scratch wound assay.

Results: IL-31 levels were higher in dermal blister fluid from SSc patients compared to controls (99.4pg/ml in SSc vs 2.3pg/ml in controls, $p<0.0003$) as well as in plasma samples (1370 vs 196pg/ml, $p<0.01$). Dermal BF IL-31 levels correlated strongly with itch severity ($R=0.72$, $p<0.0038$) and elevated BF IL-31 was characteristic of a subgroup of mainly diffuse cutaneous SSc patients with severe pruritus. SSc fibroblasts showed a higher IL-31 receptor mRNA expression compared to healthy controls (relative copy number 6.4 and 1.4 respectively, $p<0.01$), whereas the epidermal tissue extracts showed a non-significant increase in SSc (18.4 vs 8.2 respectively, p=ns). Treating fibroblasts with IL-31 led to induction of type I collagen but not CTGF, and promoted fibroblast and MSC migration dependent on

the PI3kinase pathway. Furthermore, recombinant IL-31 induced major changes in gene expression profile of both fibroblasts and MSCs.

Conclusion: We have shown that an increased expression of IL-31 correlates with severe itch in SSc patients. IL-31 receptor was expressed in SSc fibroblasts and epidermal tissues at increased levels, and recombinant IL-31 protein induced major phenotypic changes in fibroblasts and MSCs. IL-31 may link T-cell autoimmune responses to fibroblast and fibroblast precursor activation in SSc. Blocking IL-31 therapeutically may provide effective treatment in a subgroup of SSc patients identified clinically by severe pruritus.

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Abstract Number: 822

Pulmonary Fibrosis in Mixed Connective Tissue Disease – Results from an Unselected Longitudinal Cohort

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Background/Purpose: Mixed Connective Tissue Disease (MCTD) is a chronic, immune-mediated disorder defined by the combined presence of serum anti-ribonucleoprotein (RNP) antibodies and selected clinical features of Systemic Sclerosis, Systemic Lupus Erythematosus, Rheumatoid Arthritis and Polymyositis. The prevalence of Interstitial Lung Disease (ILD) in MCTD has been variously reported by previous studies [1]. It is considered to be a major complication in MCTD patients, yet knowledge is scarce regarding the long term progression of ILD in established MCTD.

Methods: Baseline and follow up high-resolution computed tomography (HRCT) of the lungs were systematically reviewed in 113 MCTD patients from the previously described nationwide Norwegian cohort [2]. Patients were included in the cohort if they had a clinical diagnosis of MCTD verified by a rheumatologist; positive serum anti-RNP antibody test and fulfilment of at least one of the following criteria sets: the modified Sharp's criteria, the Alarcón-Segovia criteria and the Kasukawa critera. The presence of fibrosis was evaluated according to the CT criteria of ILD recommended by The Nomenclature Committee of the Fleischner Society. The extent of fibrosis was determined in 10 HRCT sections and expressed as % of total lung volume.

Results: The mean (SD) time between baseline and follow up lung HRCT in the 113 patients was 7.0 (1.8) years. Mean (SD) disease duration at baseline was 10.0 (8.1) years. Pulmonary fibrosis was present at baseline in 36.3% and at follow-up in 38.0% of the patients. Median (IQR) extent of fibrosis % of total lung volume was 4.0 (7.3) at baseline and 6.3 (14.0) at follow up. There were only two new cases of pulmonary fibrosis at follow up resulting in an incidence proportion of 2.8%. Progression of fibrosis from baseline to follow-up was evident in 20 patients (17.7%). In these 20 patients the median (IQR) annual pulmonary fibrosis progression rate was 0.9 (1.4) % of total lung volume. Univariable logistic regression revealed that no prior arthritis at baseline was predictive of progressive lung disease.

Conclusion: Pulmonary fibrosis is present in a substantial portion of MCTD patients. These results suggest that pulmonary fibrosis generally appears early in the disease and the progression of pulmonary fibrosis years after diagnosis is generally mild and non- or slowly progressive. However a subset of MCTD patients has deteriorating progressive pulmonary fibrosis. The absence of arthritis was found to be a predictor of progressive pulmonary fibrosis.

Disclosure: S. Reiseter, None; **T. M. Aalokken**, None; **R. Gunnarsson**, None; **M. B. Lund**, None; **J. Haydon**, None; **Ø. Molberg**, None.

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disease-results-from-an-unselected-longitudinal-cohort

Abstract Number: 823

A Phase 2 Study of Pomalidomide (CC-4047) to Evaluate Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Effectiveness in Subjects with Systemic Sclerosis with Interstitial Lung Disease

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SESSION INFORMATION

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Background/Purpose: Pomalidomide (POM) is an IMiD compound, structurally similar to thalidomide. POM binds to cereblon and facilitates Ikaros and Aiolos degradation, resulting in immunomodulation of myeloid and lymphocyte cell responses. POM exhibits anti-fibrotic activity in preclinical models of dermal fibrosis. To examine the effect of POM on systemic sclerosis with interstitial lung disease [SSC-ILD], the safety and efficacy of POM on forced vital capacity (FVC), modified Rodnan Skin Score (mRSS), and gastrointestinal symptomatology as measured by the University of California, Los Angeles (UCLA) Scleroderma Clinical Trial Consortium Gastrointestinal Tract (SCTC GIT) 2.0 instrument total score compared to placebo in subjects with SSC-ILD was assessed over 52 weeks of treatment (NCT01559129).

Methods: 23 SSC-ILD adult subjects were randomized 1:1 POM:placebo (PBO) with 22 subjects dosed. Subjects were required to have a diagnosis of SSc based on the American College of Rheumatology (ACR) 1980 criteria with onset of the first non Raynaud's manifestation of SSc within 7 years of screening. Diffusion lung capacity for carbon monoxide (DLco) ≥ 35% and ≤ 80% was required at screening along with abnormalities on high resolution computed tomography (HRCT) consistent with SSc lung involvement. Subjects were required to meet at least one of the following 2 pulmonary-related criteria to be eligible: (1)FVC readings ≥ 45% and < 70% at Screening and Baseline (Visit 2); or (2) FVC readings ≥ 70% and ≤ 80% at Screening and Baseline with a documented history of either or both: (a) A ≥ 5% decrease in FVC in the 24-month period prior to Baseline; (b) An HRCT fibrosis score > 20%. Subjects received either 1 mg POM capsule PO QD or placebo.

Results: The mean change from Baseline in predicted FVC% at Week 52 was -5.2 and -2.8 in the POM and PBO arms, respectively; for the mRSS at Week 52 was -2.7 and -3.7 in the POM and PBO arms, respectively; and for the UCLA SCTC GIT 2.0 instrument total score at Week 52 was 0.1 and 0.0 in the POM and PBO arms, respectively. In both groups there was deterioration in FVC and improvement in mRSS, and the observed changes in all three co-primary efficacy endpoints favored placebo. Overall treatment emergent adverse events (TEAEs) were comparable across both treatment arms. The most frequently reported TEAEs (in ≥ 3 subjects) in the POM arm were constipation and arthralgia. There were no deaths in the study. Severe, serious, or TEAEs leading to discontinuation in the POM arm occurred in four (40%) of the 10 subjects each. In the PBO arm, severe and serious TEAEs were each reported in one (8.3%) of the 12 subjects.

Conclusion: In this study, POM was well tolerated with an AE profile consistent with the known safety for POM use in other diseases. The study did not meet its primary endpoints of improvement in FVC, mRSS, nor for the UCLA SCTC GIT 2.0 total score at Week 52. The study

			Placebo (N=12)			Pomalidomide 1 mg QD (N=10)		
Parameter	Visit		Baseline	Value at Visit	Change from Baseline	Baseline	Value at Visit	Change from Baseline
Predicted FVC (%)	Baseline[a]	n		12			10	
		Mean (±SD)		60.9 (8.6)			53.7 (7.3)	
		Min, Max		47, 77			45, 67	
	Week 24	n[b]	10	10	10	8	8	8
		Mean (±SD)	63.2 (7.3)	61.9 (8.6)	-1.3 (3.3)	53.6 (8.1)	55.9 (13.6)	2.3 (12.6)
		Min, Max	55, 77	52, 78	-7, 4	45, 67	45, 86	-8, 32
	Week 52[a]	n[b]	11	11	11	8	8	8
		Mean (±SD)	60.7 (9.0)	57.9 (10.0)	-2.8 (4.0)	53.2 (8.2)	48 (8.6)	-6.2 (5.3)
		Min, Max	47, 77	41, 77	-8, 5	45, 67	40, 61	-15, 4
mRSS	Baseline	n		11			10	
		Mean (±SD)		20.5 (10.0)			17.1 (9.4)	
		Min, Max		2, 32			4, 30	
	Week 24	n[b]	10	10	10	8	8	8
		Mean (±SD)	19.6 (10.1)	16 (9.8)	-3.6 (5.7)	15 (9.0)	13 (10.5)	-2 (3.4)
		Min, Max	2, 32	3, 28	-13, 3	4, 27	2, 29	-6, 3
	Week 52	n[b]	11	11	11	10	10	10
		Mean (±SD)	20.5 (10.0)	16.7 (10.9)	-3.7 (7.0)	17.1 (9.4)	14.4 (10.1)	-2.7 (5.7)
		Min, Max	2, 32	1, 31	-15, 7	4, 30	2, 30	-9, 10
UCLA SCTC GIT 2.0	Baseline	n		12			10	
		Mean (±SD)		0.2 (0.18)			0.5 (0.29)	
		Min, Max		0, 1			0, 1	
	Week 24	n[b]	10	10	10	8	8	8
		Mean (±SD)	0.2 (0.19)	0.3 (0.32)	0.1 (0.23)	0.5 (0.28)	0.4 (0.24)	-0.1 (0.2)
		Min, Max	0, 1	0, 1	0, 0	0, 1	0, 1	0, 0
	Week 52	n[b]	12	12	12	10	10	10
		Mean (±SD)	0.2 (0.18)	0.3 (0.2)	0 (0.18)	0.5 (0.29)	0.5 (0.39)	0.1 (0.29)
		Min, Max	0, 1	0, 1	0, 0	0, 1	0, 1	0, 0

[a] FVC Baseline: average of Screening and Baseline. FVC Week 52: average of Week 48 and Week 52.
[b] At a post-baseline time point for Baseline and Change from Baseline column, n = number of subjects with a Baseline value and a post-baseline value at the time point.

was terminated for lack of efficacy.

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Abstract Number: 824

Mycophenolate Versus Placebo for the Treatment of Systemic Sclerosis-Related Interstitial Lung Disease

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Background/Purpose: Compared with placebo, treatment with cyclophosphamide (CYC) improved lung function and dyspnea in patients with systemic sclerosis-related interstitial lung disease (SSc-ILD).[1] While treatment with mycophenolate (MMF) is also associated with improvements in lung function,[2] no studies have directly compared mycophenolate with placebo for the treatment of SSc-ILD.

Methods: Participants enrolled in the placebo arm (N=79) of Scleroderma Lung Study (SLS) I and the MMF arm of SLS II (N=69) were included in these analyses. SLS I randomized participants to oral CYC versus placebo for 1 year, while SLS II randomized participants to MMF for 2 years versus oral CYC for 1 year followed by 1 year of placebo. Eligibility criteria for SLS I and II were nearly identical. The primary outcome was FVC%-predicted and key secondary outcomes included the DLCO%-predicted and quantitative radiographic extent of ILD. FVC and DLCO were measured every 3 months. Because radiographic imaging outcomes were evaluated at 12 and 24 months for SLS I and SLS II, respectively, we could not directly compare these outcomes. Mixed models were created to evaluate the treatment effect on the course of the FVC, DLCO, and patient-reported outcomes, over 12-months while controlling for baseline disease severity.

Results: SLS II participants assigned to MMF had similar baseline characteristics compared with SLS I participants assigned to placebo in terms of gender (65% vs. 70%), disease duration (mean [SD] years: 2.6 [1.7] vs. 3.1 [1.8]), SSc subtype (62% vs. 57% diffuse), and FVC%-predicted (mean [SD]: 66.5 [8.3] vs. 68.6 [13]), respectively. SLS II MMF patients were slightly older (mean [SD] years: 52.6 [9.7] vs. 48.1 [12.4]; P=0.015) and had a higher DLCO%-predicted (mean [SD]: 54.0 [11.1] vs. 46.2 [13.3]; P=0.0002) than SLS I placebo participants. After adjusting for baseline quantitative lung fibrosis in the zone of maximum involvement (QLF-ZM) and baseline FVC%-predicted, treatment with MMF was associated with an improved course of FVC%-predicted over 12 months (P=0.0008; Table 1a). Treatment with MMF was also associated with an improved course of DLCO%-predicted over 12 months (P=0.038; Table 1b), after adjusting for baseline QLF-ZM and baseline DLCO%-predicted.

Conclusion: Although there are inherent limitations in comparing participants from two different trials, the baseline characteristics of the SLS I and SLS II participants were relatively similar. Compared with placebo, treatment with MMF was associated with improved course of the FVC and DLCO over 12 months in patients with SSc-ILD, and this treatment effect appeared more robust than the treatment effect reported in SLS I comparing CYC with placebo. These results further substantiate the use of MMF for the treatment of SSc-ILD.

References:

1. Tashkin DP, et al. NEJM 2006;354:2655-66.

2. Tashkin DP, et al. *Lancet Resp Med* 2016 (In press).

Table 1a. Treatment with MMF is associated with improved course of FVC%-predicted over 3-12 months compared with placebo

Variable	Estimate	Standard Error	P-Value
Baseline FVC	0.85	0.03	<0.001
Baseline QLF-ZM	-0.05	0.01	<0.001
Treatment Group x Time*	0.37	0.11	0.0008

Table 1b. Treatment with MMF is associated with improved course of DLCO%-predicted over 3-12 months compared with placebo

Variable	Estimate	Standard Error	P-Value
Baseline DLCO	0.96	0.04	<0.001
Baseline QLF-ZM	0.09	0.03	0.0027
Treatment Group x Time*	0.56	0.27	0.038

**Reference group is placebo; MMF participants had improved course of FVC and DLCO.*

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Abstract Number: 825

KL-6 and Not CCL-18 Is a Predictor of Early Progression in Systemic Sclerosis Related Interstitial Lung Disease

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Pneumoproteins are attractive biomarker candidates in systemic sclerosis (SSc) related interstitial lung disease (ILD) because they are easily obtainable and lung-specific. KL-6 and CCL-18 (PARC) have been previously reported as predictive biomarkers. Our goal was to determine the predictive significance of these two pneumoproteins for forced vital capacity % (FVC) decline within the first year of follow-up in patients with early SSc-ILD, in order to inform individualized care in routine clinical practice and facilitate enrichment strategies in clinical trials.

Methods: GENISOS (Genetics versus ENvironment In Scleroderma Outcome Study) cohort patients who had ILD verified by imaging and available pulmonary function tests at enrollment plus 12-18 months thereafter, were included in this study. All patients had disease duration ≤ 5 years at enrollment. FVC, expressed as percentage of predicted value was used as surrogate for severity of ILD. Annualized percent change in FVC at one year follow up was calculated using the formula ((FVC% PFT1 – FVC%PFT0)/FVC%PFT0)/(timePFT1-timePFT0). Baseline demographic, clinical variables and two pneumoproteins, KL-6 and CCL-18 were investigated. KL-6 and CCL-18 were measured by commercially available, validated ELISA kits. Linear regression with baseline clinical and demographic variables as independent variables was performed in univariable and multivariable models.

Results: A total of 84 patients with SSc-ILD were included, 19 were male, 19 African-American, and 46 had diffuse disease. Mean disease duration was 2.3 years. Rate of FVC% predicted change over time ranged from -0.23 to 0.38, indicating a highly variable course. Baseline KL-6 levels were higher in patients than in controls (p<0.0001, see Figure 1a). Baseline higher KL-6 levels (as a continuous variable) were predictive of a faster rate of FVC% decline at the one year follow-up (b=-0.03, *p*=0.04). Upon categorizing KL-6 using a cut-off of 1273 u/mL based on the optimal cut-off previously determined by a Japanese study (Kuwana M et al, J Rheumatol, in press), the predictive significance of KL-6 remained in both the univariate (p=0.01, see Figure 1b) and multivariable analyses after accounting for African-American race, disease duration, age, and treatment with immunosuppressive agents (b=-0.06, *p*=0.03). Twenty nine (34.5%) patients had KL-6 levels equal or above 1273 u/mL. Although CCL-18 was higher in patients than controls (<0.0001), its levels did not predict rate of FVC decline (p=0.4).

Conclusion: KL-6 but not CCl-18 is predictive of early SSc-ILD progression. In this study, we also validated the proposed cut-off of 1273 for KL-6 in an independent cohort. KL-6 is a promising pneumoprotein that can inform individualized clinical care and contribute to enrichment strategies in clinical trials of SSc-ILD.

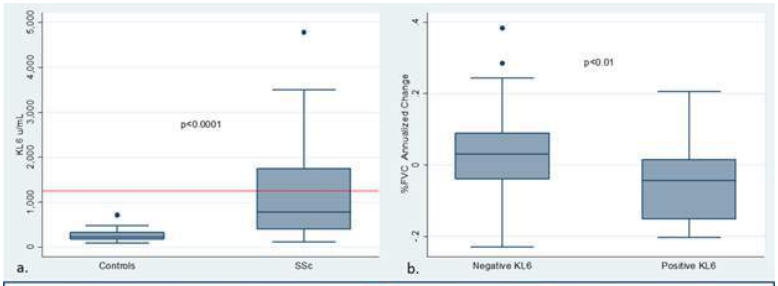

Figure 1. a) KL-6 levels (u/mL) in SSc patients versus controls (— = 1273 cut-off). b) %FVC annualized change in KL-6 positive versus negative patients based on a cut-off of 1273 u/mL. Lower values in %FVC change correspond to a faster FVC decline.

Disclosure: G. Salazar, None; **M. Kuwana**, None; **M. Wu**, None; **J. Ying**, None; **J. Charles**, None; **M. D. Mayes**, None; **S. Assassi**, Boehringer Ingelheim, 5,Genentech and Biogen IDEC Inc., 2,Bayer HealthCare, 2.

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Abstract Number: 826

Exercise Echocardiography Predicts Future Development of Pulmonary Hypertension in a High-Risk Cohort of Scleroderma Patients

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Background/Purpose: Pulmonary hypertension (PH) is the leading cause of scleroderma related deaths and is often detected late in the disease course. Early identification of patients with PH will lead to earlier treatment and may improve survival. The purpose of this study is to evaluate if a positive EE predicts future development of PH in a high-risk cohort of scleroderma patients.

Methods: This study included 100 scleroderma patients with features placing them at increased risk for pulmonary hypertension, including dyspnea on exertion, DLCO <60% of predicted, FVC <60% of predicted, FVC%/DLCO% >1.6, or resting right ventricular systolic pressure (RVSP) 30-50 mm Hg. In this prospective cohort study, all patients had baseline EE performed by the standard Bruce stress echocardiogram protocol with re-measurement of RVSP within 1 minute of stopping exercise. A positive EE was defined as an increase of at least 20 mmHg in the RVSP with exercise. All patients had at least one repeat echocardiogram at least one year after baseline EE. Patients were followed per standard of care and right heart catheterization (RHC) was performed in patients with a positive EE result or if PH was suspected based on symptoms. Time to follow up was defined as months to the development of resting PH, or in patients who did not develop PH, months from initial EE to the last echocardiogram.

Results: In our patient population, 12 patients were excluded as they did not have a repeat echocardiogram and 3 additional patients were excluded as they were being treated for exercise PH at the time of EE. Table 1 shows in the remaining cohort, 43 patients had a positive EE and 42 patients had a negative EE. There were no clinical demographic differences or differences in cardiopulmonary parameters between groups. In the positive EE cohort, 10 patients (23%) developed resting PH on RHC, a mean of 4 years after EE (4 with pulmonary arterial hypertension (PAH), 5 with pulmonary venous hypertension (PVH), and 1 with pulmonary hypertension associated with lung fibrosis (PH-ILD), whereas in the negative EE group, only 3 (7%) patients developed pulmonary hypertension (1 PAH, 2 PVH) (p=0.039). Of the remaining 33 patients with positive EE who did not develop resting PH, most (51%) patients continued to have a positive EE, with a mean of 5.3 years of follow up. This included 18 patients who had exercise induced pulmonary hypertension as documented on RHC, but who did not develop worsening symptoms, or changes on the echocardiogram over time.

Conclusion: While a positive EE does predict the future development of resting PH, it is not necessarily PAH, even in high-risk scleroderma patients. PVH also is associated with a positive EE. Many patients with a positive EE may have a persistently positive exercise echocardiogram without progression to resting pulmonary hypertension. A persistently negative EE may identify patients at low risk for future PH. Table 1:

	Positive ExEcho N=43 (49%)	Negative ExEcho N=42 (48%)	P-value
Age (years)	54.7 ± 12	50.6 ± 13	NS
Race	White: 22 (51%) AA: 19 (44%) Other: 2 (5%)	White: 24 (57%) AA: 15 (36%) Other: 3 (7%)	NS
ANAs, %	Anti-centromere: 28% Anti-scl 70: 12% Anti-nucleolar ANA:26%	Anti-centromere: 32% Anti-scl 70: 20% Anti-nucleolar ANA:20%	NS
SSc type (limited scleroderma), %	60 %	68 %	NS
FVC % ± SD	81 ± 21	85 ± 22	NS
DLCO % ± SD	66 ± 22	65 ± 20	NS
FVC(%)/DLCO(%) ± SD	1.35 ± 0.48	1.44 ± 0.5	NS
Baseline 6MWT (m) ± SD	435 ± 104	455 ± 102	NS
Baseline RVSP (mm Hg)	33 ± 7	31 ± 6	NS
Time to follow up (years) ± SD	5 ± 2.4	4.6 ± 2.4	NS
Developed PH	**10 (23%)**	**3 (7%)**	**0.039**

Disclosure: K. A. Quinn, None; **T. Kuru**, None; **S. Wappel**, None; **V. D. Steen**, None.

Abstract Number: 827

Severe Gastrointestinal Disease in Early Systemic Sclerosis Is Associated with an Increased Risk of Mortality

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Background/Purpose: Studies of severe gastrointestinal (GI) disease in systemic sclerosis (SSc) are limited by small, selected samples composed largely of subjects with prevalent disease. We undertook this study to examine the morbidity and mortality associated with severe GI disease in SSc in a large, unselected inception cohort.

Methods: A retrospective cohort of subjects with < 3 years of disease duration and without severe GI disease at baseline study visit was identified from the Canadian Scleroderma Research Group registry. Severe GI disease was defined using a previously published definition (Steen and Medsger, A and R 2000) as follows: malabsorption, hyperalimentation, pseudo-obstruction, or either antibiotics for bacterial overgrowth or esophageal stricture requiring dilatation with ≥10% associated weight loss. Subjects who developed severe GI disease during follow-up were compared to those who did not using descriptive statistics. Morbidity was assessed with the Medical Trust Short Form 36 (SF-36) physical (PCS) and mental (MCS) component summary scores. Mortality rates between subjects with and without severe GI disease were compared by dividing the number of deaths per person-years of observation in each group.

Results: Data was available for 306 subjects with < 3 years of disease duration; of these, 21 (7%) had severe GI disease at baseline study visit. Severe GI disease over a mean follow-up time of 3.8 years developed in an additional 18% (50/285) of subjects: 84% female, mean age 53 years, mean disease duration at baseline 1.6 years and proportion with limited/diffuse cutaneous SSc 54%/46%. Subjects who developed severe GI disease were more likely to have digital ulcers (52.0% vs 35.7%, p=0.03) and worse skin scores (15.7 ± 12.0 vs 12.1±10.9, p=0.003) at baseline study visit. Physical health status was more impaired at baseline in subjects with compared to without severe GI disease (SF-36 PCS 35.4 ± 11.3 vs 39.0 ± 10.9, p=0.05). There were no difference in mental health status between the 2 groups at baseline (SF-35 MCS 47.1 ± 11.3 vs 48.6 ± 12.2, p=0.30). There were 10 deaths in 137 person-years of observation among those with, compared to 21 in 1040 person-years of observation among those without severe GI disease, for a mortality rate of 3.7.

Conclusion: Severe GI disease was common in this inception cohort, affecting approximately 25% of subjects within the first 5 years of disease. It was associated with considerable impairment in physical health status and a striking increase in the risk of mortality. Baseline predictors of severe GI disease included markers of more severe vasculopathy and fibrosis. These findings provide compelling evidence to identify interventions that target selected pathophysiological pathways to reduce the burden of severe GI disease in SSc.

Disclosure: N. Richard, None; **M. Hudson**, None; **M. Wang**, None; **M. Baron**, None; **G. Gyger**, None.

Abstract Number: 828

Survival and Health-Related Quality of Life in Incident Systemic Sclerosis Related Pulmonary Arterial Hypertension: A Multicentre Australian Cohort Study

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Background/Purpose: Pulmonary arterial hypertension (PAH) is the leading cause of systemic sclerosis (SSc) related mortality. We sought to determine survival, predictors of mortality, and health related quality of life (HRQoL) of PAH in a large SSc cohort followed from the time of PAH diagnosis in the modern era of PAH-specific vasodilator therapy.

Methods:

Patients enrolled in a SSc longitudinal cohort between 2009 - 2015 were included. Group 1 PAH was diagnosed on right heart catheterization (RHC) (mPAP ≥25 and PAWP <15 mmHg). Other causes of pulmonary hypertension were excluded. Summary statistics, chi-square tests and survival methods were used to determine survival rates and identify predictors of mortality. HRQoL was measured using the Medical Outcomes Study Short Form 36 (SF-36).

Results: Among 132 SSc-PAH patients, 84.9% were female and 68.9% had limited disease subtype. The mean (±SD) age at diagnosis of PAH was 62.3 (±10.5) years and disease duration at PAH diagnosis was 14.1 (±11.9) years. Over a median (IQR) follow-up of 3.7 (1.6-5.8) years, 60 (45.5%) patients died, with a median survival time from PAH diagnosis of 3.7 years. The standardized mortality ratio for patients with SSc-PAH compared with the general population was 5.8 (95%CI 4.3-7.8). The years of life lost with SSc-PAH was 15.22 years (95%CI 12.3-18.1). Kaplan-Meier survival curves (Figure 1) showed a survival advantage with combination PAH therapy and anticoagulation. Older age at PAH diagnosis (p=0.03), coexistence of mild ILD (p=0.01), worse WHO functional class (p=0.03), higher mean pulmonary arterial pressure at PAH diagnosis (p=0.001) and presence of digital ulcers (p=0.01) during follow-up were predictive of PAH mortality (Table 1). Combination therapy together with anticoagulation provided the most significant survival advantage, with a 72% reduction in mortality compared with pulmonary vasodilator monotherapy without anticoagulation (Figure 1). Patients with SSc-PAH had consistently poorer HRQoL scores in all domains of the SF-36 form except mental health than the general population.

Conclusion: Despite advanced therapy, the median survival in SSc PAH is less than 4 years. The addition of anticoagulation to standard combination therapy is associated with a significant survival advantage, pointing to mechanisms involving endothelial abnormalities and small vessel thrombosis in the pathogenesis of PAH.

Table 1. Independent predictors of mortality in SSc-PAH determined by multivariable hazard regression analysis

Characteristic	Hazard Ratio (95% CI)	p-value
Age at diagnosis of PAH, years	1.05 (1.0-1.1)	0.03
ILD (FVC > 60%)	2.83 (1.4-5.6)	0.01
WHO functional class	2.01 (1.1-3.9)	0.03
Pulmonary arterial pressure, mmHg	1.06 (1.0-1.1)	0.001
Digital ulcers present	3.12 (1.4-7.2)	0.01
Specific PAH therapies and anticoagulation: Vasodilator monotherapy only Vasodilator monotherapy and anticoagulation Vasodilator combination therapy only Vasodilator combination therapy and anticoagulation	reference 0.39 (0.1-1.2) 0.49 (0.2-1.2) 0.28 (0.1-0.7)	reference 0.09 0.10 0.007

Abbreviations: PAH pulmonary arterial hypertension, WHO world health organization, ILD interstitial lung disease, 6MWD six minute walk distance, mRAP mean right atrial pressure, mPAP mean pulmonary arterial pressure, HCQ Hydroxychloroquine

Figure 1: Kaplan-Meier survival curves in SSc-PAH

Figure 1a

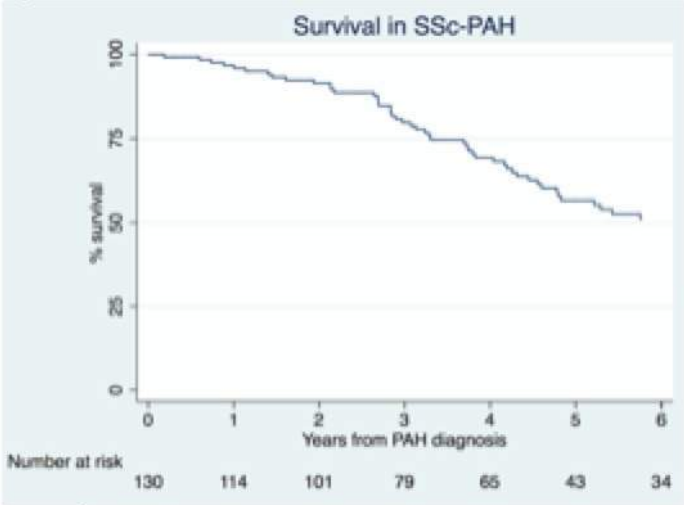


Figure 1b

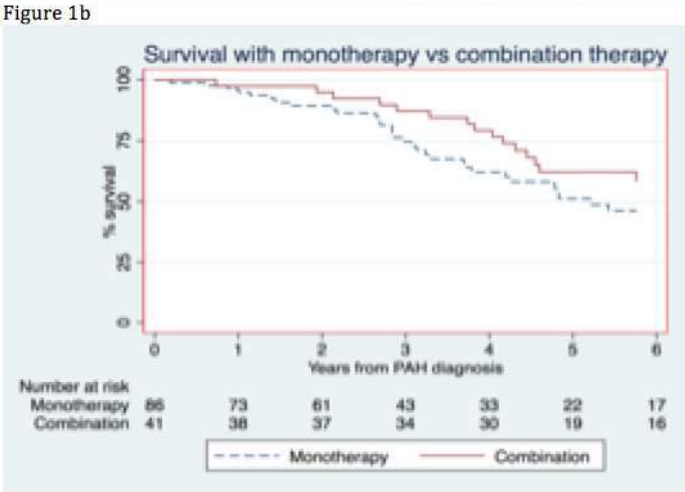
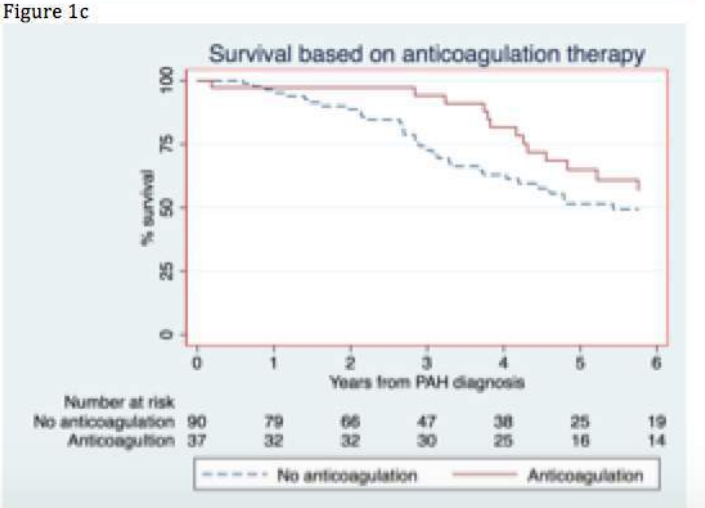


Figure 1c



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Abstract Number: 829

High Level of Chemokine CCL2 Is Associated with Lung Fibrosis Progression and Reduced Survival in Two Independent Systemic Sclerosis Cohorts

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Background/Purpose: Markers for early identification of progressive interstitial lung disease (ILD) in systemic sclerosis (SSc) are in demand. The proto-typical inflammatory chemokine CCL2 has been linked to lung fibrosis in SSc. Here, we aimed to: (i) To explore CCL2 in two independent SSc cohorts, including serum from a large and unselected SSc cohort and lung homogenates at time of lung transplant from patients with SSc-ILD. (ii) To assess associations between CCL2 in sera and lung fibrosis, lung function and survival. (iii) Determine cellular origin of CCL2 and its receptor CCR2 in lung tissue from SSc patients.

Methods: Sera from the Oslo University Hospital (OUH) SSc cohort and healthy controls were analysed for CCL2 at baseline by enzyme immunoassay. High CCL2 (>0.66 ng/ml) was defined using mean value +2SD in control sera as cut-off. Paired clinical data, pulmonary function tests and the extent of fibrosis on HRCT images were obtained at baseline and follow-up. Lung tissue was collected at the time of lung transplantation from SSc and donor lungs at the UCLA. Concentrations of CCL2 in lung homogenates were determined by Luminex technology and expression of CCL2 and CCR2 in SSc tissue were assessed by immunohistochemistry (IHC).

Results: CCL2 was elevated in sera from the OUH cohort (n=298) compared to healthy controls (n=100): 0.65 ng/ml (SD 0.80) versus 0.42 ng/ml (0.54), p=0.008. High serum CCL2 was identified in 79/298 SSc patients (27%). Extent of fibrosis, FVC% and DLCO% differed significantly between high and low CCL2 subsets (Table 1), as well as the total lung fibrosis progression rate (3.4% (SD 9.2) and 1.1% (SD 4.2, p=0.041). In multivariate analyses, CCL2 was associated with severe lung fibrosis >20% (OR 2.5, 95%CI 1.04-6.08, p=0.041), total fibrosis progression >5% (OR 2.7, 95%CI 1.14-6.19, p=0.024) and annual fibrosis progression >2.5% (OR 5.2, 95%CI 1.6-16.5), p=0.005). CCL2 was associated with increased mortality (HR 1.8 95%CI 1.02-3.27, p=0.043). Survival analyses showed that patients with high CCL2 had reduced 5- and 10-year cumulative survival compared to cases with low CCL2 (89% and 77%, compared to 95% and 88%, p=0.02). In the UCLA cohort, CCL2 was elevated in lung homogenates (n=12) compared to donor lungs (n=12) (0.61 ng/ml (SD 0.48) and 0.17 ng/ml (SD 0.23), p=0.007). IHC demonstrated a CCL2 co-localization with reactive type II pneumocytes, alveolar macrophages and infiltrating mononuclear cells. CCR2 was predominantly expressed on infiltrating mononuclear cells and on alveolar macrophages.

Conclusion: We have demonstrated an association between elevated levels of CCL2 and lung fibrosis progression, severe lung fibrosis and survival in SSc. Within the lungs, CCL2 is predominately co-localized with infiltrating mononuclear cells. The results reinforce the notion that high CCL2 may serve as a marker for progressive ILD in SSc and may potentially also represent a target for therapy in this disorder.

	No. (%)	Low CCL2 (219)	High CCL2 (79)	p-value
Male	55 (18.5)	38 (17.4)	17 (21.5)	n.s
dcSSc	78 (26.2)	43 (19.6)	35 (44.3)	<0.001
Deceased	58 (19.5)	39 (17.8)	19 (24.1)	n.s
ATA	47 (17.4)	28 (13.8)	19 (29.7)	0.003
Age at onset	48.3 (15.4)	47.4 (15.7)	50.5 (14.3)	n.s
Disease duration	6.9 (7.7)	7.13 (8.2)	6.11 (6.2)	n.s
PH	55 (18.8)	37 (16)	18 (28)	0.031
PH-ILD	21 (7)	10 (18.2)	11 (20)	
PAH	34 (11.4)	27 (49)	7 (12)	0.015
	% (SD)			
Baseline fibrosis	6.4 (12.5)	4.6 (9.9)	10.8 (16.5)	0.005
Follow up fibrosis	8.2 (14.5)	5.7 (11.6)	14.3 (18.4)	<0.001
Annual fibrosis progression	0.47 (2.3)	0.41 (1.9)	0.62 (3.9)	n.s
Baseline FVC%	94.7 (20.5)	96.7 (20.4)	89.2 (19.8)	0.003
Follow up FVC%	90.1 (23.3)	92.8 (23.3)	82.9 (22.2)	0.001
Annual FVC % decline	-1.9 (7.8)	-1.6 (8.6)	-2.7 (5.2)	n.s
Baseline DLCO%	68.2 (21.7)	69.9 (20.7)	63.5 (23.9)	0.025
Follow up DLCO%	59.7 (21.0)	61.5 (20.1)	54.7 (22.7)	0.016
Annual DLCO% decline	-1.7 (5.3)	-1.5 (4.9)	-2.4 (6.1)	n.s

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Abstract Number: 830

Cardiopulmonary Disease Development in Anti-RNA Polymerase III Positive Systemic Sclerosis; Comparative Analyses from an Unselected, Prospective Patient Cohort

Anna Hoffmann-Vold[1], Anders Heiervang Tennøe[2], Oyvind Midtvedt[2], May Brit Lund[3], Torhild Garen[2], Fadi El-Hage[4], Trond Mogens Aalokken[5], Eli Taraldsrud[4] and Øyvind Molberg[2], [1]Division of Rheumatology, Oslo University Hospital, Oslo, Norway, [2]Rheumatology, Oslo University Hospital, Oslo, Norway, [3]Respiratory Medicine, Oslo University Hospital, Oslo, Norway, [4]Oslo University Hospital, Oslo, Norway, [5]Radiology, Oslo University Hospital, Oslo, Norway

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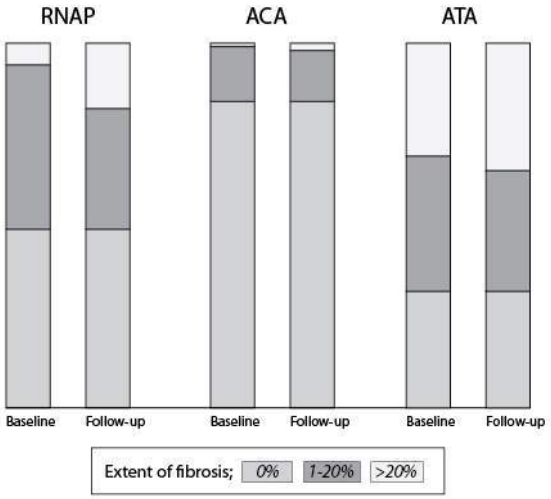
Background/Purpose: Extensive skin disease and renal crisis are hallmarks of anti-RNA polymerase III (RNAP) positive systemic sclerosis (SSc), while data on lung and heart involvement are conflicting. Here, the aims were to perform time-course analyses of interstitial lung disease (ILD) and pulmonary hypertension (PH) in the RNAP subset in a prospective unselected SSc cohort with longitudinal follow up data and use the other auto-antibody subsets as comparators. <>

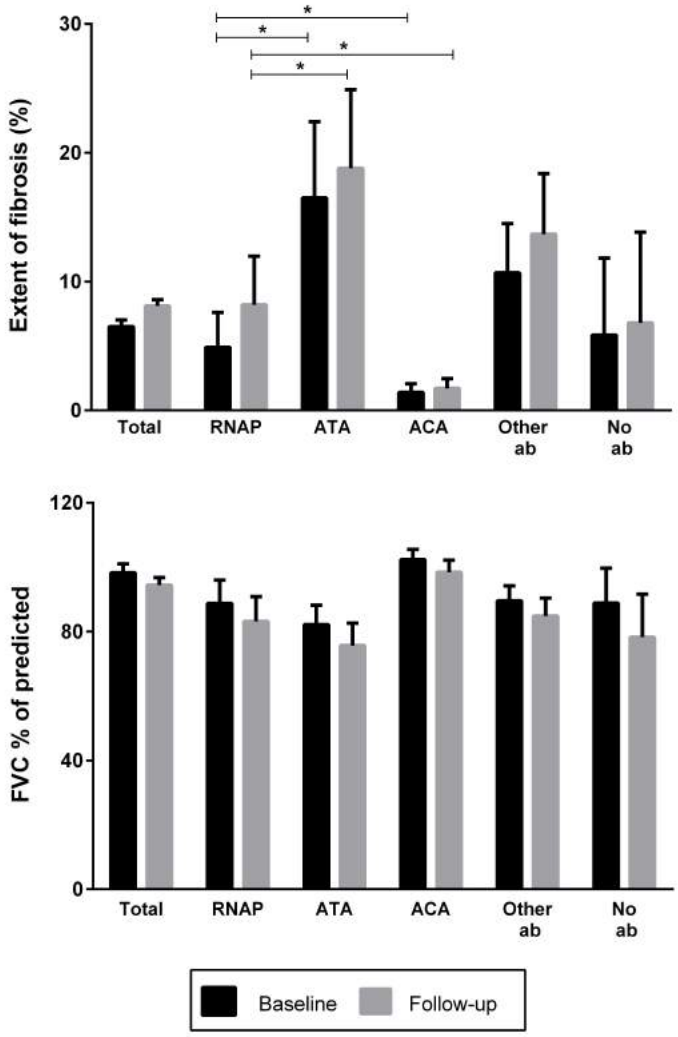
Methods: The study cohort included 276 SSc patients from the observational Oslo University Hospital cohort with complete data on (A) SSc-related auto-antibodies, (B) paired, serial analyses of lung function and extent of fibrosis by lung HRCT at baseline and follow-up, and (C) PH verified by right heart catheterization. All patients in the SSc cohort met the 2013 ACR/EULAR classification criteria.

Results: RNAP was positive in 33/276 patients (12%), of which 79% had diffuse cutaneous SSc. Patients with RNAP had higher modified Rodnan Skin Score, developed more frequently scleroderma renal crisis and gastric antral vascular ectasia than anti-Topoisomerase 1 (ATA) and anti-centromere antibody (ACA) positive patients. Pulmonary findings in the RNAP subset were heterogeneous; 49% had no signs of ILD, while 33.3% had moderate fibrosis (1-20% fibrosis) and 18.2% had severe fibrosis at follow up (>20% fibrosis); (Figure 1

and 2). The annual fibrosis progression rate was higher in RNAP (1.2% SD 2.0) compared to ATA (0.5%, SD 5.0) and ACA (0.7%, SD 1.4) but did not reach statistical significance. Forced Vital Capacity at follow up was <80% in 39% of the RNAP subset; comparable to the anti-topoisomerase subset (ATA: 47%), but higher than anti-centromere (ACA: 13%). The accumulated frequency of PH in the RNAP subset (12 %) was lower than in ACA (18 %). The 5- and 10 year survival rates in RNAP cases were 93% and 78%, respectively. The survival of RNAP positive patients was comparable to the ATA and ACA subsets, but significantly higher than in the ANA negative patient subset.

Conclusion: In this cohort, the RNAP subset was marked by cardiopulmonary heterogeneity with progression to extensive ILD in 18 %, and PH development in 12 %. These data indicate that cardiopulmonary risk stratification early in the disease course is particularly important in RNAP positive SSc.





Disclosure: **A. Hoffmann-Vold**, None; **A. Heiervang Tennøe**, None; **O. Midtvedt**, None; **M. B. Lund**, None; **T. Garen**, None; **F. El-Hage**, None; **T. M. Aalokken**, None; **E. Taraldsrud**, None; **Ø. Molberg**, None.

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Abstract Number: 831

Immunosuppression May Prevent Interstitial Lung Disease in Systemic Sclerosis

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Background/Purpose: Interstitial lung disease (ILD) is a leading cause of premature mortality in systemic sclerosis (SSc). Immunosuppression is used for treatment of established disease. However, little is known about whether immunosuppression might prevent ILD in SSc. The aim of this study was to determine if, in SSc patients without ILD, immunosuppression (given for other manifestations) was associated with a lower risk of new onset SSc-ILD.

Methods: A retrospective cohort of 887 SSc patients without ILD at baseline was studied, using data from the Canadian Scleroderma Research Group registry. The primary exposure of interest was immunosuppression with methotrexate, cyclophosphamide, mycophenolate and/or azathioprine. The primary outcome variable was new onset ILD defined using a published algorithm (Steele, ACR 2012). Time to primary outcome was compared between exposed and unexposed subjects, modeled as a time-dependent exposure variable, using an unadjusted Kaplan-Meier model and a marginal structural model incorporating inverse probability of treatment weights (IPTW) to account for confounding. Weights were constructed using variables most likely to influence a decision to initiate immunosuppression, namely age, sex, ethnicity, disease duration, anti-centromere, anti-topoisomerase I, and anti-RNA polymerase III status, modified Rodnan skin scores, C-reactive protein levels, forced vital capacity, presence of inflammatory arthritis, presence of inflammatory myositis, and exposure to immunosuppressive therapy in the past. Subjects were censored at the visit when ILD was first recorded, or time of death, permanent study drop-out or last study visit. Both robust asymptotic and non-parametric bootstrap confidence intervals were constructed.

Results: The study included 218 subjects exposed to immunosuppression at baseline or during follow up and 669 unexposed subjects. Baseline characteristics of exposed and unexposed subjects are presented in Table 1. In unadjusted Kaplan Meier analysis, the observed risk of ILD was higher in exposed compared to unexposed subjects (log rank $p < .0001$), consistent with confounding. However, in a multivariate analysis incorporating IPTW, subjects exposed to immunosuppression had a lower estimated risk of developing ILD compared to unexposed subjects: weighted hazard ratio (HR) 0.50 (95% CI 0.28, 0.90, $p=0.021$), and, after bootstrapping, 0.50 (95% CI 0.17, 0.99).

Conclusion: To our knowledge, this is the first study to demonstrate a role for immunosuppression in preventing SSc-ILD in an observational cohort using modern causal statistical methods. In subjects perceived to be at increased risk for developing ILD, there may be value in initiating immunosuppression early, as this may alter disease course and potentially outcomes. Table 1. Baseline characteristics of the cohort separated by exposure status (N=887)

	Non-exposure to treatments (N=669)		Exposure to treatments (N=218)		p values
	Mean (SD) or N (%)	Missing	Mean (SD) or N (%)	Missing	
Female	601 (89.8%)	0	186 (85.3%)	0	0.067
Age, years	55.4 (12.0)	0	50.8 (12.3)	0	<.001
Disease duration from first non-Raynaud, years	11.3 (9.5)	2	6.6 (7.5)	0	<.001
Caucasian	567 (88.3%)	27	173 (83.6%)	11	0.076
Current or ever smoking	399 (62.0%)	25	117 (56.0%)	9	0.125
Modified Rodnan skin score (0-51)	7.0 (7.7)	10	13.7 (10.8)	3	<.001
Anti-centromere, %	307 (51.3%)	71	54 (29.2%)	33	<.001
Anti-topoisomerase, %	55 (9.2%)	71	38 (20.5%)	33	<.001
Anti-RNA polymerase III, %	67 (11.2%)	71	43 (23.2%)	33	<.001
Erythrocyte sedimentation rate, mm/hr	18.8 (18.4)	79	22.0 (20.9)	33	0.067
C-reactive protein, mg/L	7.1 (14.2)	119	9.5 (19.0)	52	0.014
FVC, % predicted	97.9 (16.3)	77	92.6 (18.1)	25	<.001
TLC, % predicted	99.3 (15.1)	112	96.6 (16.2)	39	0.016
DLCO, % predicted	75.0 (18.6)	132	72.2 (19.7)	51	0.091
Inflammatory arthritis	167 (25.8%)	21	92 (43.4%)	6	<.001
Myositis	39 (5.9%)	3	39 (18.1%)	2	<.001
Exposure to immunosuppression prior to baseline	47 (7.0%)	1	39 (17.9%)	0	<.001

Disclosure: S. Hoa, None; **M. Hudson**, None; **M. Wang**, None; **R. Steele**, None; **M. Baron**, None.

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Abstract Number: 832

Defining Skin Ulcers in Systemic Sclerosis: A Systematic Literature Review of Skin Ulcer Definitions and a Preliminary Consensus-Based New SSc Skin Ulcer Definition

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Background/Purpose: Skin ulcers in SSc are a major clinical challenge and there are various un-validated definitions of skin ulcers utilized in SSc-related clinical trials. We wanted to better delineate a precise definition for skin ulcers in SSc to be used in clinical trials. Objective: To conduct a systematic literature review (SLR) regarding definitions of skin ulcers. The results were used to develop a consensus definition for SSc-skin ulcers.

Methods: A systematic literature search for SSc-skin ulcer definitions was conducted in PubMed, Web of Science, and Cochrane for articles published from inception to January 1st, 2016. For better generalizability we included related autoimmune diseases where skin ulcers are seen: SLE, RA and vasculitis. Diabetic ulcers were also included as more data is available when defining diabetic ulcers. Inclusion criteria were: studies reporting a definition of skin ulcer, adults, English language, skin ulcer as a study outcome, diseases as outlined above. Exclusions included: not in humans, pressure ulcers, reviews and case reports <10 pts. PRISMA recommendations were followed where applicable. The extracted definitions were categorized into relevant descriptive terms (Table 1) and formed the basis for a consensus definition. SSc experts discussed the definitions using a nominal process and voted for the pertinent definition terms, during the Scleroderma World Congress (SWC). A consensus was attained when agreement was > 70%. Photographs of 11 SSc skin lesions were evaluated before and after definition development to examine the face validity and general feasibility of the definition and to allow further refinement of the definition.

Results: A total of 3464 publications were screened in abstract and title and 446 articles were fully evaluated. Of these, 66 met eligibility criteria and skin ulcer definitions were extracted. Twelve SSc experts (11 rheumatologists, 1 dermatologist) from North America (n=6) and Europe (n=6) discussed, refined and voted on the consensus definition. Descriptive terms and mitigating factors (site, size etc.) were used to develop our new definition and exclusions were decided for its utilization in clinical trials. *The preliminary SWC consensus-derived definition of SSc- skin ulcer for clinical trials is: " Loss of epidermal covering with a break in the basement membrane (which separates dermis from epidermis). It appears clinically as visible blood vessels, fibrin, granulation tissue and/or underlying deeper structures (e.g. muscle, ligament, fat) or as it would appear on debridement"*

Conclusion: Using an SLR and a modified nominal technique, a preliminary consensus-based definition of SSc-skin ulcers was developed. Further validation steps are warranted.

Definition categories	Number of times used
Loss of Epidermis	11
Loss of Epidermis and Dermis(full thickness)	34
With Depth	4
Denuded	4
Unclear/non-specific (as follows):	27
• Ischemic necrotic ulcer	
• Open sore, loss of tissue	
• Open wound	
• Skin break	
• Necrotic lesions	

Table 1: showing the relevant descriptive terms used in various extracted definitions.

Disclosure: **Y. A. Suliman**, None; **C. Bruni**, None; **S. R. Johnson**, None; **E. Praino**, None; **M. Alemam**, None; **N. Borazan**, None; **L. Cometi**, None; **B. Myers**, None; **D. Khanna**, None; **Y. Allanore**, Actelion , pfizer, 9; **M. Baron**, None; **T. Krieg**, None; **A. L. Herrick**, None; **S. Kafaja**, None; **C. Denton**, GSK, Celgene, Actelion, Bayer, Sanofi, Roche-Genentech, Inventiva, 5,CSL Behring, GSK, Actelion, Roche-Genentech, Inventiva, 2; **M. Matucci Cerinic**, None; **D. E. Furst**, Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 2,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, Janssen, Gilead, GSK, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 5,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, Janssen, Gilead, NIH, Roche/Genentech, 9,Abbott, Actelion, UCB Pharma, 8.

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Abstract Number: 833

A Small Proportion of Patients with Systemic Sclerosis with Suspected Pulmonary Hypertension Meet the Published Inclusion/Exclusion Criteria for Two Systemic Sclerosis Associated Pulmonary Arterial Hypertension Screening Algorithms– Results from a Single Center Cohort

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Pulmonary arterial hypertension (PAH) is one of the leading causes of mortality in patients with systemic sclerosis (SSc). Active screening detects SSc-PAH earlier and may improve survival. Our objective was to evaluate the predictive accuracy of 2012 Australian Scleroderma Interest Group (ASIG) and 2013 DETECT when applied to all patients with SSc with suspected pulmonary hypertension (PH) versus application to only those patients with SSc with suspected PH who met the published inclusion/exclusion criteria for ASIG and DETECT (Table 1).

Methods: Subjects with a diagnosis of SSc based on 2013 ACR/EULAR classification criteria with suspected PH based on the 2013

recommendations for screening and detection of connective tissue disease (CTD)-associated PAH undergoing right heart catheterization (RHC) were evaluated (Khanna et al. Arth Rheum. 2013). Those with non-PH or PAH on RHC had ASIG and DETECT applied. Contingency table analysis was used to evaluate sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV).

Results: Approximately 281 subjects underwent screening for PH, and out of those 281 subjects, 113 subjects underwent RHC based on 2013 recommendations for CTD-PAH or clinical opinion of the referring physician (Figure 1). The prevalence of PAH was 17% (Figure 1). DETECT and ASIG performed similarly with 100% sensitivity and NPV in subjects who met and who did not meet the inclusion/exclusion criteria for ASIG or DETECT (Table 2). However, only approximately 10% of subjects met the original published inclusion/exclusion criteria. The most common reason for not meeting the inclusion/exclusion criteria was a higher DLco value; during ASIG application, 36 subjects did not have a DLco < 50 % predicted and during DETECT application, 29 subjects did not have a DLco < 60 % predicted.

Conclusion: In a well-defined SSc- PH cohort, ASIG and DETECT work well as screening tools when applied to a broad population of subjects with SSc. If only the published inclusion/exclusion criteria for ASIG AND DETECT are used, a large proportion of subjects (87 to 88%) with suspected PH would have been missed.

Table 1. Inclusion/Exclusion Criteria for ASIG and DETECT

ASIG	
Inclusion	RVSP ≥ 40 mmHg. DLCO < 50% predicted with FVC > 85% predicted.[1]
Exclusion	FVC < 40% predicted. Abnormal LV systolic or diastolic function. Abnormal LA size. No TR jet. Estimated GFR < 30ml/min.[1]
DETECT	
Inclusion	Disease duration > 3 years. DLco < 60 % predicted.[2]
Exclusion	PH diagnosis prior to RHC. FVC < 40 % predicted. Left heart disease. Advanced PH therapy. Renal insufficiency. Pregnancy.[2]

[1]Thakkar V et al. Arthritis Res Ther. 2012. [2]Coghlan JG et al. Ann Rheum Dis. 2014.

Figure 1. Subjects Screened for PH

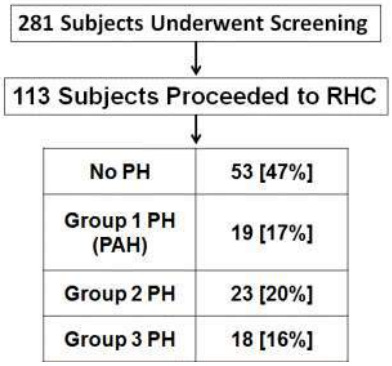

Table 2. Comparison of SSc-PAH Detection Methods

	ASIG	DETECT	ASIG Inclusion/Exclusion Criteria[1]	DETECT Inclusion/Exclusion Criteria[2]
# of Subjects	52	59	7	7
Sensitivity	1.0	1.0	1.0	1.0
Specificity	0.52	0.33	0.83	0.25
NPV	1.0	1.0	1.0	1.0
PPV	0.28	0.28	0.5	0.57

Disclosure: A. Young, None; **V. Moles**, None; **V. Nagaraja**, None; **S. H. Visovatti**, None; **V. McLaughlin**, None; **D. Khanna**, Bristol-Myers Squibb, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,BAYER, 5,CYTORI, 5,EMD Serono, 5,Roche Pharmaceuticals, 2,Actelion Pharmaceuticals US, 5.

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Abstract Number: 834

Distinctive Clinical Phenotype of Anti-Centromere Antibody Positive Diffuse Systemic Sclerosis

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Background/Purpose: Although anti-centromere antibodies (ACA) typically associate with limited cutaneous subset of systemic sclerosis (lcSSc) this reactivity is also seen in some cases with diffuse skin disease (dcSSc). Since both antibody specificity and disease subset may influence clinical features and organ manifestation, we explored the impact of ACA on outcome in dcSSc, as it has previously been reported protective for renal crisis (RC) and interstitial lung disease (ILD). Objectives: We describe clinical characteristics of dcSSc patients with ACA positivity (ACA+diffuse), and compare with ACA positive lcSSc (ACA+limited) and ACA negative dcSSc (non-ACA diffuse).

Methods: First, we identified all ACA positive systemic sclerosis cases in our cohort (n=1313). Those with dcSSc (n=36, 2.7%) were compared with representative groups of consecutive patients ACA+limited (n=160) and consecutive patients non-ACA diffuse (n=260). Long-term survival and frequency of major organ based complications were compared.

Results: The peak modified Rodnan skin score (mRSS) was not significantly different between the dcSSc subgroups with or without ACA (respectively 24.0±9.9 vs 27.4±10.4, p=0.07), but peak mRSS occurred later in disease in ACA+diffuse (88.8±77.2 vs 30.7±33.1 months, p<0.001). Survival in ACA+ was similar for both subsets with survival rates at 5, 10 and 15 years of 96%, 84% and 73% in ACA+limited and 94%, 80% and 72% in ACA+diffuse. Comparing with ACA+diffuse, non-ACA diffuse had significantly lower survival of 85%, 72% and 55% at 5, 10 and 15 years respectively (p=0.002). ACA+diffuse had higher incidence of ILD than ACA+limited (p=0.018), but significantly lower than non-ACA diffuse (p=0.003). Non-ACA diffuse developed ILD mostly in the first 5 years from disease onset, while in ACA+diffuse it occurred later in disease course. During follow-up at 5 years, 15% of ACA+diffuse developed ILD (3% - ACA+limited; 36% - non-ACA diffuse), and at 15 years, 26% had ILD (5% - ACA+limited; 49% - non-ACA diffuse). More patients had pulmonary hypertension (PH) in ACA+diffuse (27.8%), than in the other groups (12.5% - ACA+limited; 11.9% - non-ACA diffuse), though this was mainly due to their longer follow-up. Cumulative incidence of PH in ACA+diffuse was not different from the other groups (at 5 years: 8% - ACA+diffuse, 6% - ACA+limited, 6% - non-ACA diffuse; at 15 years: 24%, 20% and 18% respectively). Similarly, cardiac involvement was more frequent in ACA+diffuse (8.3%) vs 1.9% in ACA+limited and 6.5% in non-ACA diffuse, but differences were not significant adjusting for time of follow-up. In contrast, incidence of RC was higher in non-ACA diffuse (13.9%), affecting only 2 patients in ACA+diffuse (5.6%) and none in ACA+limited.

Conclusion: Although uncommon, ACA+diffuse has a distinct clinical phenotype. These patients have more insidious onset of skin and major organ involvement, which may allow early therapeutic intervention. We confirm that even in dcSSC, ACA appears protective for organ-based complications, namely ILD and RC, and associates with a better survival than expected in dcSSc. Therefore, ACA or factors determining its development, may act as a phenotype modifier in dcSSc.

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Abstract Number: 835

A Normal Pulmonary Diffusion Capacity Is Rare in Pulmonary Artery Hypertension in Systemic Sclerosis

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Background/Purpose: The Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma (PHAROS) cohort is a prospective longitudinal study of patients with systemic sclerosis (SSc) who are at risk for developing pulmonary arterial hypertension (PAH) or who have already been diagnosed with pulmonary hypertension (PH). Although PAH in SSc is usually associated with a very low diffusing capacity for carbon monoxide (DLCO) we identified some patients with a normal DLCO. The purpose of this study was to look at the subset of PAH patients with a normal DLCO defined as ³ 70% predicted at the time of diagnosis of PAH compared to those with expected low DLCO defined as < 70%. We compared demographics, BNP level, pulmonary function tests (PFT), echocardiogram, and right heart catheterization findings in these groups.

Methods: Entry criteria into PHAROS for SSc patients with Group 1 PAH were a right heart catheterization (RHC) with a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg. We examined demographics (age, gender and ethnicity), echocardiogram variables (presence of pericardial effusion and left atrial size), PFT (FVC, FEV1/FVC, FVC%/DLCO%), BNP levels (<100 versus 100 pg/mL) and RHC findings and outcomes in PAH patients who had DLCO % predicted recorded near the time of RHC. We used Fisher's exact test to examine associations between two categorical variables and Kolmogorov-Smirnov test for continuous variables. Significance was assigned at $p < 0.05$.

Results: In the PAH patients (n=202), only 11 patients (5.4%) had a normal DLCO of > 70% (mean 78%) versus 191 patients (94.6%) who had a low DLCO <70% (mean 39%). There was no difference in demographics, other PFT results, echocardiogram findings, or RHC features between the normal DLCO and the low DLCO patients, The left atrium in the normal DLCO patients was slightly larger at 4.1cm than in the low DLCO group (3.7cm), but it was not statistically different, and the PCWP were the same on RHC. There were no differences in survival between these two groups. Finally, on follow up testing in10 of these11 patients, seven had subsequently developed a low DLCO.

Conclusion: Only 5% of this large cohort of SSc-PAH patients had a normal DLCO >70% predicted at the time of diagnosis. The majority of these fell below normal values on follow up testing. There were no identified differences in these patients to suggest why they maintained a normal DLCO compared to the vast majority of SSc –PAH with abnormal low DLCO. Although a low DLCO is almost always seen in SSc patients with PAH, PHAROS data suggests that in rare situations, a patient may develop PAH with a preserved DLCO.

Disclosure: R. Overbury, None; **T. M. Frech**, None; **M. Murtaugh**, None; **V. D. Steen**, None.

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Abstract Number: 836

Comprehensive Characterization of Calcinosis in a Multicenter International Cohort of Patients with Systemic Sclerosis

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Background/Purpose: Calcinosis cutis is a debilitating complication of systemic sclerosis (SSc) affecting one quarter of patients. Repetitive trauma may be involved in the pathogenesis of calcinosis, and a prior single-center study found that the thumbs were most commonly affected, supporting this hypothesis. We sought to confirm this finding and to characterize the complications associated with calcinosis in a multi-center, international cohort of SSc patients.

Methods: We established a prospective cohort specifically to study calcinosis in SSc. We have to date enrolled 233 consecutive SSc patients who fulfill 2013 revised ACR/EULAR criteria at 9 centers within the United States, Canada, Australia, and Mexico. We performed a thorough physical exam of the entire body to assess for the presence of calcinosis, and collected detailed information on associated features. Calcinosis was defined as radiological or physical exam evidence of subcutaneous calcium deposition, or a clear history of extruded calcium.

Results: Our cohort was 88% female, and racial distribution was 64% Caucasian, 29% Hispanic, and 4% Asian. 55% had limited cutaneous disease. Mean disease duration from first non-Raynaud phenomenon (RP) symptom was 11.1 ± 9.3 years. Calcinosis was present in 90 patients (39%). Calcinosis developed 8.4 ± 9.0 years after first non-RP symptom. From 31 patients who had x-rays of the hands available, 21 (68%) had only radiographically detectable calcinotic lesions. The most common location of calcinosis was the hands (71%), followed by the elbows (19%), and the arms and/or forearms (16%). Within the hands, calcinosis most commonly affected the thumbs with decreasing frequency moving from the thumb to the little finger (50% thumbs, 37% index, 34% middle, 22% ring, and 18% in the little finger). Within patients with calcinosis of the hands, 25% had only right hand involvement, 11% had only left hand involvement, and 64% had bilateral hand involvement. 87% patients had multiple calcinotic lesions, and the median number of lesions was 2.5 per patient (range 1-13). 21% of patients had lesions >1 cm. The most common complications from calcinosis were tenderness (34%) and spontaneous extrusion of calcinosis through the skin (27%). Ulceration and infection were more rare (8% and 3% respectively). In patients with calcinotic lesions >1 cm, ulceration was more frequent (21% vs. 4%, p=0.015).

Conclusion: The majority of SSc patients with calcinosis presents with multiple, sub-centimeter lesions affecting the hands, most frequently in the right hand and in the thumb. Assuming that the dominant hand and the thumb are exposed to the most trauma, our study supports a role for trauma in the pathogenesis of calcinosis in SSc. Ulceration and infection are rare complications, but patients with larger lesions are more likely to suffer from ulceration of calcinosis.

Disclosure: A. Valenzuela, None; **J. K. Gordon**, None; **T. S. Rodriguez-Reyna**, None; **S. Proudman**, None; **M. Baron**, None; **M. Hinchcliff**, None; **D. Khanna**, None; **A. Young**, None; **F. V. Castelino**, None; **S. R. Schoenfeld**, None; **V. D. Steen**, None; **D. Fiorentino**, None; **L. Chung**, None.

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Abstract Number: 837

Development of a Skin-Specific Scleroderma Patient Reported Outcome Instrument

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Background/Purpose: Skin fibrosis is the hallmark of SSc and may lead to significantly reduced quality of life in ways that may not be directly proportional to the area and severity of skin involvement such as that captured by the modified Rodnan skin score (mRSS). We developed a patient reported outcome instrument (PRO) to assess specifically the skin-related quality of life in patients with SSc for use in routine practice and clinical trials.

Methods: We conducted 3 focus groups (N=12) with SSc participants on how their skin condition affected their lives. Analysis of transcripts resulted in themes, which were conceptually encapsulated into four constructs: physical symptoms, physical limitations, emotional effects and social effects. 56 items for the Scleroderma Skin PRO (SSPRO) were created or adapted from existing PROs to assess each of these constructs. Input from an expert panel as well as cognitive interviews with 10 SSc participants led to removal of items with 22 remaining. The 22-item SSPRO was administered to 140 participants who also completed other PROs and rated their global skin severity. An mRSS and a global disease severity rating were also completed by a physician. Psychometric analysis included test-retest reliability, internal consistency, construct validity, exploratory and confirmatory factor analyses.

Results: Participants (N=140) primarily had lcSSc (67.1%), were female (82.1%) and Caucasian (92.9%) with mean age of 53.4 years and disease duration of 6.4 years. Mean mRSS was 9.3 (SD 10.8). Self-reported skin severity was mild (45%), moderate (48.5%), and severe (5.7%). Factor analysis supported 4 underlying factors in the SSPRO corresponding to the 4 hypothesized constructs. Removal of 4/22 items that contributed most to cross loading resulted in acceptable fit statistics in a confirmatory analysis. Test-retest reliability was moderate to high (ICC = 0.61–0.83) and internal consistency (CronbachÕs alpha = 0.89-0.96) was high. SSPRO correlated strongly with other patient reported measures suggesting construct validity, and less well with physician assessed outcomes (Table). SSPRO scores were also able to discriminate between participant-reported skin severity levels (Figure), as well as between limited and diffuse disease providing further evidence of construct validity.

Conclusion: SSPRO has been developed with extensive patient input and demonstrates reliability as well as face and construct validity. It is complementary to existing measures of SSc skin involvement with emphasis on the patientÕs experience. Further research is needed to assess its sensitivity to change.

Table. Association of SSPRO with other outcome measures

Outcome Measure*	Pearson's Correlation Coefficient†
mRSS	0.38
Cochin Hand Function Scale	0.73
Skindex-29	0.88
HAQ-DI	0.59
SHAQ VAS Intestinal	0.36
SHAQ VAS Breathing	0.44
SHAQ VAS Raynaud's	0.58
SHAQ VAS Finger Ulcer	0.48
SHAQ VAS Patient Disease Severity	0.63
Patient global assessment of skin severity	0.75
Physician global assessment of overall disease	0.40
Physician global assessment of skin severity	0.31

*Data used for correlations included only measures completed within 30 days of SSPRO.
†All correlations were significant at p<0.05
mRSS, modified Rodnan skin score; HAQ-DI, Health Assessment Questionnaire Disability Index; SHAQ VAS, Scleroderma HAQ Visual Analog Scale

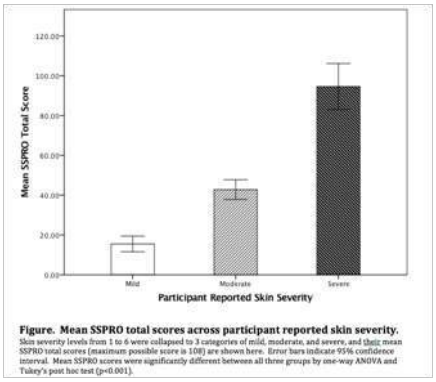

Figure. Mean SSPRO total scores across participant reported skin severity.
Skin severity levels from 1 to 6 were collapsed to 3 categories of mild, moderate, and severe, and their mean SSPRO total scores (maximum possible score is 100) are shown here. Error bars indicate 95% confidence interval. Mean SSPRO scores were significantly different between all three groups by one-way ANOVA and Tukey's post hoc test (p<0.001).

Disclosure: **A. Man**, None; **J. K. Correa**, None; **J. Ziemek**, None; **D. T. Felson**, None; **R. Lafyatis**, None.

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Abstract Number: 838

Esophageal Dysmotility and Interstitial Lung Disease in Patients with Scleroderma: A Retrospective Study

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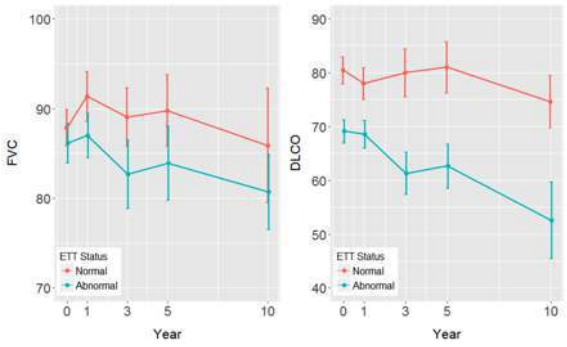
Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease with pulmonary involvement seen in 75% of patients and esophageal involvement in 90% of the patients. Pulmonary disease has overtaken renal disease as the leading cause of death. There is conflicting evidence about the association between esophageal dysmotility and lung involvement. We aimed to evaluate the relationship between esophageal dysmotility and lung disease by correlating the results of Esophageal transit time (ETT) with pulmonary function test (PFT).

Methods: Charts of SSc patients fulfilling 2013 ACR/EULAR classification criteria seen in Rheumatology from 2004 to 2015 were reviewed. Patients demographics, laboratory, results of ETT, High resolution CT (HRCT) of lung and PFT were collected at baseline, years 1, 3, 5 and 10. Patients were divided based on their initial ETT findings. Using the linear mixed effects model, we tested the effect of ETT status on forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCo) and estimated the progression rates in two groups. We adjusted for relevant covariates such as disease sub type, smoking, obesity and medications.

Results: 130 patients were identified with either LcSSC (109) or diffuse SSc (21). ETT was normal in 67(52%) and abnormal in 63(48%) patients. At baseline, years 1,3,5 and 10, the mean DLCo was significantly different between the groups while the mean FVC was not. An error bar graph indicating mean and standard error of mean at each year is provided for each outcome. Abnormal ETT group have a significantly worse progression of DLCo, both in unadjusted (p=0.023) and adjusted (p=0.019) models but FVC progression was significantly worse in adjusted (p=0.018) model only. The estimated progression rates per year are provided in Table 1a. The effect of ETT status on FVC is statistically insignificant for both unadjusted (p= 0.1608 and adjusted (p= 0.133) but significant for DLCo (unadjusted p= 0.0004, adjusted p=0.0175). The means and 95% confidence intervals for the two groups are provided in Table 1b. Patients with baseline abnormal HRCT had significantly lower DLCo but did not have worse progression rate.

Conclusion: Our results show that presence of abnormal ETT correlates with reduced mean DLCo and worsening of FVC and DLCo over a period of 10 years. Presence of abnormal HRCT at baseline did not indicate progression of FVC or DLCo. Larger prospective studies need to be done to find a causal relationship. References: 1. Steen VD et al: Ann Rheum Dis 66, 2007.



2. Christmann RB et al: Semin Arthritis Rheum. 2010 Dec; 40(3).

Table 1a Progression Rate Comparisons

			Estimated Progression Rate Per Year		
Outcome	Group Comparison	Model	Normal	Abnormal	P-value
FVC	ETT Normal:Abnormal	unadjusted	0.74	-0.37	0.054
FVC	ETT Normal:Abnormal	adjusted	0.66	-0.66	**0.018**
DLCO	ETT Normal:Abnormal	unadjusted	-0.09	-1.95	**0.023**
DLCO	ETT Normal:Abnormal	adjusted	-0.16	-2.25	**0.019**
FVC	HRCT Normal:Abnormal	unadjusted	0.40	-0.07	0.392
DLCO	HRCT Normal:Abnormal	unadjusted	-1.00	-1.08	0.924

Table 1b Mean Comparisons

			Least-Square Mean (95% CI)		
Outcome	Group Comparison	Model	Normal	Abnormal	P-value
FVC	ETT Normal:Abnormal	unadjusted	89.94 (85.68, 94.20)	85.60 (81.23, 89.96)	0.1608
FVC	ETT Normal:Abnormal	adjusted	88.96 (78.61, 99.33)	83.85 (74.59, 93.11)	0.1330
DLCO	ETT Normal:Abnormal	unadjusted	80.10 (75.46, 84.74)	65.40 (60.62, 70.18)	**< 0.0001**
DLCO	ETT Normal:Abnormal	adjusted	77.25 (65.10, 89.40)	63.05 (52.37, 73.72)	**0.0004**
FVC	HRCT Normal:Abnormal	unadjusted	90.21 (86.12, 94.30)	84.10 (79.39, 88.82)	0.0550
DLCO	HRCT Normal:Abnormal	unadjusted	76.02 (71.21, 80.83)	67.15 (61.66, 72.63)	**0.0175**

Disclosure: S. Kishore, None; **S. Lakshminarayanan**, None; **C. L. Kuo**, None; **R. Mandhadi**, None.

Abstract Number: 839

Immunosuppression Does Not Prevent Severe Gastrointestinal Disease in Systemic Sclerosis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Severe gastrointestinal (GI) disease is associated with considerable morbidity and high mortality in systemic sclerosis (SSc). There are no known preventative treatments. We wished to test the hypothesis that exposure to immunosuppression (for skin, lung, joint or muscle condition) in early disease could modify the risk of severe GI disease in SSc.

Methods: Subjects with < 3 years of disease duration (since the onset of the first non-RaynaudÕs disease manifestation) and without severe GI disease at baseline study visit were identified from the Canadian Scleroderma Research Group registry. Severe GI disease was defined using a previously published definition (Steen and Medsger, A and R 2000) as follows: malabsorption, hyperalimentation, pseudo-obstruction, or either antibiotics for bacterial overgrowth or esophageal stricture requiring dilatation with >10% associated weight loss. A retrospective cohort study was performed with immunosuppression to methotrexate, azathioprine, mycophenolate and/or cyclophosphamide as the exposure of interest and severe GI disease as the outcome. Descriptive statistics were used to compare the baseline characteristics of the subjects, according to exposure status. The risk of severe GI disease in exposed versus unexposed subjects was estimated using a Cox proportional hazard model, with exposure to immunosuppression modeled as a time-dependent variable and including inverse probability of treatment weights (IPTW) to account for confounding. The model was adjusted for potential demographic and disease-related confounders.

Results: This study included 285 subjects, 84% female, mean age 53 years old, mean disease duration at baseline 1.6 years, proportion limited/diffuse cutaneous SSc 54%/46%. During a mean follow-up time of 3.8 years, 152 (53%) subjects were exposed to immunosuppression and 133 (47%) were not. In univariate analyses, subjects exposed to immunosuppression were more likely to have diffuse disease (62.5% vs 26.3%, $p<0.001$), interstitial lung disease (37.8% vs 18.9%, $p<0.001$), inflammatory myositis (14.6% vs. 1%, $p<0.001$) and worse skin scores (16.5 ± 11.2 vs 8.4±9.5, $p<0.001$) at baseline study visit. In a multivariate Cox proportional hazard analysis modeling immunosuppression as a time-dependent variable and incorporating IPTW, exposure to immunosuppression did not modify the risk of developing severe GI disease: hazard ratio 0.71, 95% confidence interval 0.32, 1.58 (Table).

Conclusion: Contrary to our hypothesis, exposure to immunosuppression did not prevent severe GI disease. Further research is required to identify effective prevention and treatment interventions for severe GI disease in SSc.

Table 1. Cox proportional hazard model to identify predictors of severe GI disease in SSc, including exposure to immunosuppression (IS) modeled as a time-dependent variable and inverse probability of treatment weights (IPTW)

	Hazard Ratio	95% confidence interval		P values
Exposure vs non exposure (time-dependent)	0.71	0.32	1.58	0.397
Exposure to IS prior to baseline visit	1.43	0.30	6.85	0.654
Disease duration	0.97	0.55	1.72	0.970
Caucasian	1.60	0.49	5.23	0.437
Antibodies				
Anticentromere vs others	0.39	0.15	1.00	0.049
Antitopoisomere vs others	0.59	0.21	1.61	0.298
Anti-RNA polymerase vs others	0.71	0.24	2.15	0.549
Modified Rodnan Skin Score	1.02	0.98	1.06	0.367
C-reactive protein (log)	1.24	0.92	1.67	0.167
Interstitial lung disease	0.95	0.39	2.30	0.910
Digital ulcers	0.93	0.49	1.79	0.836
Inflammatory arthritis	1.38	0.60	3.16	0.448
Inflammatory myositis	1.25	0.29	5.47	0.769

Disclosure: N. Richard, None; **M. Hudson**, None; **M. Wang**, None; **M. Baron**, None; **G. Gyger**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immunosuppression-does-not-prevent-severe-gastrointestinal-disease-in-systemic-sclerosis

Abstract Number: 840

Time Trends in Incidence and Mortality of Systemic Sclerosis in Denmark from 1995-2011: A Nationwide Cohort Study

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Session Time: 9:00AM-11:00AM

Time Trends In Incidence And Mortality Of Systemic Sclerosis In Denmark From 1995-2011: A Nationwide Cohort Study

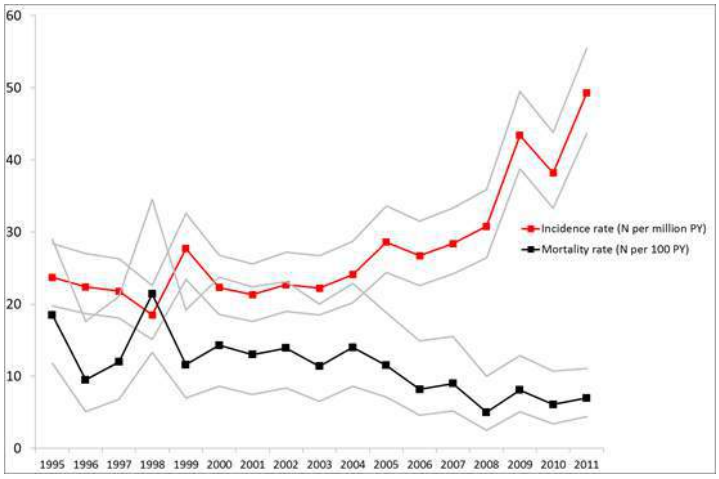
Background/Purpose: Epidemiological studies have documented an increasing incidence of several autoimmune disorders over the last few decades, but little is known about the temporal trends of systemic sclerosis (SSc). We aimed to improve our understanding of the epidemiology of SSc by evaluating over time the incidence and mortality in a registry-based nationwide analysis.

Methods: Using the Danish National Patient Registry (NPR) we identified all persons aged ≥ 18 with a first-time diagnosis of SSc (International Classification of Diseases 10th edition code M34 except for M34.2) between 1995 and 2011. Incidence rates (per million person-years) and first-year 1-year mortality rates (per 100 person-years) associated with SSc were calculated. Confidence intervals were

estimated under the assumption of a Poisson distribution. Age- and sex-adjusted Cox regression models were used to investigate the association of SSc with mortality, compared with the background population.

Results: Within the total Danish population (spanning from 4.939.465 individuals in 1995 to 5.419.512 persons in 2011), the total number of unique SSc cases increased from 117 in 1995 to 267 in 2011. The mean age of onset remained unchanged throughout the study period; 54.2 years (range: 22.6- 85.6) in 1995 and 55.1 years (range: 18.5-98.6) in 2011. The proportion of women fell from 82% in 1995 to 75% in 2011. The incidence rate per 1,000,000 showed an increasing trend from 23.7 (95% CI 19.8-28.4) in 1995 to 49.3 [95% CI 43.7-55.5) in 2011. Similar trends were observed when stratified by sex and various age groups. The all-cause 1-year mortality rate per 100 person-years showed a decreasing trend from 18.5 (95% CI 11.8-29.0) in 1995 to 7.0 (95% CI 4.4-11.1) in 2011. The age and sex-adjusted hazard ratio compared with the background population fell from 16.4 (95% CI 10.5-25.6) in 1995 to 8.2 (95% CI 5.2-13.0) in 2011, respectively.

Conclusion: Our data show that the incidence of SSc was increasing and 1-year mortality rates falling during the study period. Mechanisms underlying our findings remain to be determined, but it cannot be excluded that the increasing incidence estimates may in part be explained by increased physician awareness and more sensitive ascertainment methods identifying earlier and less severe cases of SSc. This could possibly also explain a higher survival rate associated with SSc in recent years. Further studies are needed to investigate the mechanisms underlying our findings and furthermore outcomes on 5- and 10-year survival.



Disclosure: S. Butt, None; **C. Andersson**, None; **S. Jacobsen**, None; **G. Gislason**, None; **C. Torp-Pedersen**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/time-trends-in-incidence-and-mortality-of-systemic-sclerosis-in-denmark-from-1995-2011-a-nationwide-cohort-study

Abstract Number: 841

Low Nucleoside Triphosphate Pyrophosphohydrolase Activity Contributes to Pathologic Mineralization in Systemic Sclerosis

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: Calcinosis is a major source of morbidity in patients with systemic sclerosis (SS). In addition, increased coronary calcification has been reported in patients with SS and other inflammatory diseases. The etiology of pathologic calcification in SS is unclear. Circulating levels of inflammatory cytokines, including interleukins, are elevated in SS patients compared to controls. IL-1β can induce calcification in vitro. The mechanism of this effect was recently shown to involve modulation of nucleoside triphosphate

pyrophosphohydrolase (NTPPPH) activity. This critical ecto-enzyme hydrolyzes extracellular ATP to produce pyrophosphate (PPi). PPi functions as a potent inhibitor of calcification. Thus, low levels of NTPPPH reduce PPi levels and permit increased mineralization. We sought to test the hypothesis that circulating NTPPPH enzyme activity levels are reduced in SS patients.

Methods: After obtaining informed consent, 20 ml of blood was collected from 42 well-characterized SS patients and 17 healthy controls with similar mean age and gender. For completeness, we measured serum activity levels of three enzymes involved in PPi metabolism. PPi is generated from ATP through the action of NTPPPH. PPi is degraded by alkaline phosphatase (Alk Phos) to Pi. 5'- nucleotidase (5'NT) drives PPi production by metabolizing AMP to adenosine and Pi. **Specific activities of Alk Phos (Sigma) and 5'NT (BQ Kits) were measured per manufacturers' directions and** NTPPPH activity levels were measured with a colorimetric assay.

Results: Characteristics of the patients are shown in table 1. The mean values of PPi-metabolizing enzyme activity levels in sera of patients with SS are shown in the scatter plots in figure 1. NTPPPH levels were significantly lower (p= <0.0001) in SS patients compared to controls. There were no significant differences in levels of Alk Phos (p=0.11) and 5'NT (p=0.181).

Conclusion: NTPPPH activity levels are significantly lower in patients with SS compared to controls, leading to lower PPi levels and more pathologic calcification. This work provides additional support for the important connection between inflammation and mineralization, and identifies NTPPPH enzymes as potential targets for novel therapies for SS-associated calcification. Table 1. SS patient characteristics

Patient Characteristics	
Age (years)	Mean 55.5 (range 21-78)
Women/Men	34/8
Disease Duration (years)	Mean 10.8 (range 1-31)
Limited	15
Diffuse	20
Systemic sclerosis sine scleroderma	2
Overlap	5

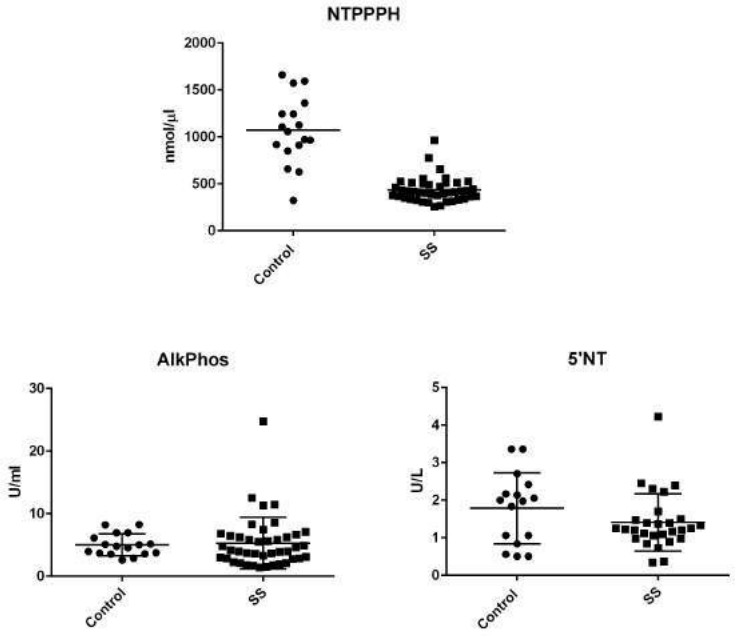

Figure 1. Scatter plot of activity levels of PPi-metabolizing enzymes in SS patients and controls.

Disclosure: Y. Ding, None; **S. Yeturi**, None; **C. Gohr**, None; **M. E. Csuka**, None; **A. K. Rosenthal**, None.

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Abstract Number: 842

Aminaphtone Treatment Increases Skin Blood Perfusion and Related Clinical Symptoms in Patients Affected By Raynaud's Phenomenon: A Pilot Study Based on Laser Speckle Contrast Analysis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Aminaphtone is an oral vasoactive drug used to treat microvascular impairement since 30 years, and recently suggested to down-regulate endothelin-1 production by endothelial cells, and to improve Raynaud's phenomenon (RP) symptoms (1-3). Laser speckle contrast analysis (LASCA) is a validated technique to measure skin blood perfusion (4,5). The aim of this longitudinal study was to evaluate skin blood perfusion changes and clinical symptoms during aminaphtone treatment in patients affected by RP.

Methods: Thirty-seven patients with active RP were enrolled during routine clinical assessment in November 2015: 10 primary (PRP) and 27 secondary RP (SRP) to systemic sclerosis. Aminaphtone was administered as clinical practice 75 mg twice daily (off label) in addiction to current treatments (patients were on stable drug regimen from at least two months, and they did not modify it during follow-up). Blood perfusion was measured by LASCA as perfusion units (PU) at baseline (T0), after one (T1), four (T4) and twelve weeks (T12) of treatment, at the level of fingertips, periungual areas, dorsum and palm of hands, tip of noise, zygoma, forehead, and perioral regions. Raynaud condition score (RCS) and both Raynaud's attack frequency and duration were also assessed at the same times. Statistical analysis was performed by non-parametric tests.

Results: A progressive statistically significant increase of blood perfusion was observed from T0 to T12 in all skin areas as in PRP as in SRP patients (median PU at T0, T1, T4, T12 respectively: fingertips 52, 86, 92, 104 for PRP, and 53, 91, 102, 107 for SRP; periungual areas 50, 74, 90, 91 for PRP, and 42, 80, 90, 91 for SRP; dorsum of hands 42, 59, 69, 75 for PRP, and 33, 66, 74, 78 for SRP; palm of hands 54, 76, 87, 101 for PRP, and 57, 88, 98, 97 for SRP; whole face 120, 125, 142, 150 for PRP, and 127, 128, 144, 148 for SRP; $p<0.001$ for all). In particular, all patients treated with aminaphtone showed an increase of blood perfusion from T0 to T1, and 28 out of 35 patients from T1 to T12 had a further increase of blood perfusion. A progressive statistically significant decrease of RCS (median at T0, T1, T4, T12: 7, 5, 4, 4 for PRP, and 8, 6, 4, 3 for SRP; $p<0.0001$), Raynaud frequency (median at T0, T1, T4, T12: 2, 2, 1, 1 for PRP, and 2, 2, 1, 1 for SRP attacks/day; $p<0.0001$) and duration (median at T0, T1, T4, T12: 20, 20, 10, 7 for PRP, and 20, 20, 10, 4 for SRP minutes; $p<0.0001$) was also observed from T0 to T12. The results were similar for both primary and secondary RP. Two patients had to stop the drug due to headache, and one patient was lost during follow-up.

Conclusion: This study demonstrates that aminaphtone treatment increases in short-time skin blood perfusion, as well as seems to ameliorate RP symptoms. A randomized clinical trial including larger number of control subjects need to confirm these results and to assess the possible role of aminaphtone in the treatment/prevention of systemic sclerosis related clinical complicantions. **References.** 1. Parisi S, et al. Am J Int Med 2015;3;204-9. 2. Scorza R, et al. Drugs R D 2008;9:251-7. 3. Salazar G, et al. Eur J Pharmacol. 2016;782:59-69. 4. Ruaro B, et al. Ann Rheum Dis. 2014;73:1181-5. 5. Ruaro B, et al. Microvasc Res. 2016;105:119-24.

Disclosure: B. Ruaro, None; **S. Paolino**, None; **C. Pizzorni**, None; **M. Cutolo**, Actelion, BMS, Sanofi-Aventis, 2,Actelion, BMS, Sanofi-Aventis, 5; **A. Sulli**, None.

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Abstract Number: 843

Forced Vital Capacity Predicts Outcome in Scleroderma Associated Interstitial Lung Disease with Concomitant Pulmonary Hypertension: Data from the Pharos Registry

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Session Time: 9:00AM-11:00AM

Forced vital capacity predicts outcome in scleroderma associated interstitial lung disease with concomitant pulmonary hypertension: Data from the PHAROS registry

Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in scleroderma and is often accompanied by secondary pulmonary hypertension (Group 3 PH). The objectives of this study were to characterize the Group 3 PH population of PHAROS, compare them to those with Group 1 PH (pulmonary arterial hypertension), and identify specific variables with prognostic significance.

Methods: PHAROS is a prospective multi-center registry of scleroderma patients at high risk for, or with definite PH based on right heart catheterization (RHC) within six months of enrollment. In this study, we included those considered by PHAROS investigators to have Group 3 PH as defined by the presence of moderately-severe ILD (as determined by a forced vital capacity [FVC] < 65% predicted and/or significant ILD by chest computed tomography scan) along with RHC-confirmed mean pulmonary artery pressure of ≥ 25 mmHg and pulmonary capillary wedge pressure < 15 mmHg and compared them to PHAROS subjects considered to have Group 1 PH (pulmonary arterial hypertension). Baseline demographics and clinical characteristics at the time of RHC were assessed, and univariate analyses (STATA, version 14.0) were performed to identify variables predictive of outcome.

Results: Sixty-three Group 3 PH patients were identified. Baseline demographics and clinical characteristics are displayed in the Table. Patients with Group 3 PH were more likely to be African-American, have diffuse skin involvement, anti-Scl70 positivity and more severe impairment on pulmonary function testing, but with better cardiac hemodynamics. With a median follow-up period of 913 days (interquartile range 383, 2158), 41% of the Group 3 PH cohort expired; with ILD progression as the most frequent cause of death (12 of 26, 46%). The 5-year survival was similarly poor for both groups: Group 1 PH 58% vs. Group 3 PH 61%. On univariate analysis of Group 3 PH patients, the only variable associated with survival time, was FVC (HR 0.967, 95% CI: 0.939-0.997; p=0.03): the lower the FVC, the higher the risk of death.

Conclusion: Moderate-severe ILD with concomitant PH is associated with a poor prognosis and the degree of physiologic restriction, as measured by FVC, is associated with worse survival time.

	Group 1 PH n=214	Group 3 PH n=63
Age (mean) **	60.3±10.5	52.6±11.1
Female gender	84%	77%
Race % African-American **	11%	25%
Diffuse skin involvement **	26%	45%
Anti-Scl-70 positive **	6%	37%
Isolated nucleolar ANA	24%	19%
Anti-centromere positive	39%	6%
Cigarette smoking history	N/A	36%
History of treatment with MMF or CYC	N/A	56%
Total lung capacity, % predicted **	81.4 (68.8, 91.8)	54.5 (47.9, 61.3)
Forced vital capacity, % predicted **	79.2 (71.1, 90.0)	49.9 (43.1, 58.9)
Diffusing capacity for carbon monoxide, % predicted **	38.8 (31.9, 51.8)	28.2 (22.6, 36.5)
Mean pulmonary artery pressure *	35 (29. 43)	30 (26, 38)
Pulmonary capillary wedge pressure	10 (8, 12)	10 (7, 14)
Cardiac output	5 (3.9, 6.1)	5 (4.6, 5.8)
Pulmonary vascular resistance *	370 (263, 658)	321.5 (223.7, 462.5)

*p<0.01 ** p<0.001 Categorical values are expressed as median (interquartile range) unless otherwise specified

Disclosure: J. S. Lee, None; **J. K. Gordon**, None; **J. Szymonifka**, None; **V. Steen**, None; **A. Fischer**, Gilead Sciences, 5,Bristol-Myers Squibb, 5,Genentech and Biogen IDEC Inc., 2,Boehringer Ingelheim, 5,Genentech and Biogen IDEC Inc., 5,GlaxoSmithKline, 5,Actelion Pharmaceuticals US, 5,Gilead Sciences, 5,Bristol-Myers Squibb, 5,Boehringer Ingelheim, 2,GlaxoSmithKline, 5,Boehringer Ingelheim, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/forced-vital-capacity-predicts-outcome-in-scleroderma-associated-interstitial-lung-disease-with-concomitant-pulmonary-hypertension-data-from-the-pharos-registry

Abstract Number: 844

Bardoxolone Methyl Produces Durable Benefits in Participants with Pulmonary Arterial Hypertension: Data from an Open-Label Extension Study

Ron Oudiz[1], Colin Meyer[2], Melanie Chin[2], Jeremy Feldman[3], Angie Goldsberry[2], John McConnell[4], Peter A. McCullough[5], Megan O'Grady[2], Victor Tapson[6], Fernando Torres[7], Aaron B. Waxman[8] and R. James White[9], [1]Los Angeles Biomedical Research Inst. at Harbor-UCLA Medical Center, Torrance, CA, [2]Reata Pharmaceuticals, Irving, TX, [3]Arizona Pulmonary Specialists, Phoenix, AZ, [4]Kentuckiana Pulmonary Associates, Louisville, KY, [5]Baylor University Medical Center, Dallas, TX, [6]Cedars-Sinai Medical Center, Los Angeles, CA, [7]University of Texas, Southwestern Medical Center, Dallas, TX, [8]Harvard Medical School, Boston, MA, [9]University of Rochester Medical Center, Rochester, NY

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Session Time: 9:00AM-11:00AM

Background/Purpose: Bardoxolone methyl (BARD), an activator of the transcription factor Nrf2, and inhibitor of NF-kB, targets dysfunctional inflammatory, metabolic, and bioenergetic pathways. In an initial analysis of 24 patients enrolled in a Phase 2 study of BARD in WHO Group I pulmonary hypertension (PAH) patients receiving one or more background PAH therapies, a statistically significant 22 m increase in 6-minute walk distance (6MWD) compared to placebo was seen after 16 weeks of treatment[1]. A subset of six participants enrolled with connective tissue disease-associated PAH (CTD-PAH) demonstrated numerically larger changes in 6MWD than those with other forms of PAH. The current analysis reports longer-term safety and efficacy data for patients in the initial report through 32 weeks total weeks of treatment (16 weeks of blinded treatment followed by 16 weeks of treatment during the open-label extension) of the ongoing LARIAT study.

Methods: WHO Group 1 PAH patients (n = 24) were randomized in a 1:3 ratio to receive once-daily placebo or bardoxolone methyl at doses of 2.5, 5, or 10 mg for 16 weeks. Participants who completed the 16-week treatment period were eligible to continue in an open-label extension study and received BARD individually adjusted up to a maximum once-daily dose of 10 mg. The primary efficacy variable, 6MWD, was measured at baseline and at Weeks 4, 8, 12, 16, 20, and 32. Investigators and participants remain blinded to their initial treatment assignment.

Results: Overall, 18 (75%) subjects (14 bardoxolone methyl, 4 placebo) entered the extension study and completed Week 32 of the study at doses of 2.5 mg (n = 5), 5 mg (n = 5), and 10 mg (n = 4). The previously reported gain in 6MWD was sustained through 32 weeks of extended treatment with BARD. BARD-treated participants with CTD-PAH (n = 6/14) had similar sustained increases in 6MWD through Week 32. Additionally, the metabolic effects at Week 16 observed with BARD (decreased weight and creatine kinase) were sustained through Week 32. Fewer adverse events were reported during the extension study than during the first 16 weeks of treatment. The most frequently reported adverse events that occurred in >10% of patients treated with BARD during the extension study were fatigue, arthralgia, muscle spasms, nausea, and sinus congestion.

Conclusion: Bardoxolone methyl was well tolerated in patients with PAH and led to sustained improvements in 6MWD for up to 32 weeks without evidence of attenuation. References:

1. Oudiz. Initial Data Report from 'LARIAT': a Phase 2 Study of Bardoxolone Methyl in PAH Patients on Stable Background Therapy. Presented at CHEST 2015.

Disclosure: R. Oudiz, Reata Pharmaceuticals, 5; **C. Meyer**, Reata Pharmaceuticals, 3; **M. Chin**, Reata Pharmaceuticals, 3; **J. Feldman**, Reata Pharmaceuticals, United Therapeutics, Gilead, Bayer, Actelion, 5; **A. Goldsberry**, Reata Pharmaceuticals, 3; **J. McConnell**, Reata, Actelion, Gilead, United therapeutics, Bayer Pharmaceuticals, Eiger Pharmaceuticals, Genentech, 5; **P. A. McCullough**, Reata PHarmaceuticals, 5; **M. O'Grady**, Reata Pharmaceuticals, 3; **V. Tapson**, Actelion, Bayer, Gilead, Reata Pharmaceuticals and United Therapeutics, 5; **F. Torres**, Reata Pharmaceuticals, 5; **A. B. Waxman**, Reata Pharmaceuticals, 5; **R. J. White**, Reata Pharmaceuticals, 5.

Abstract Number: 845

Current Use of Off-Label Therapies in Systemic Sclerosis-Associated Interstitial Lung Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Sclerosis (SSc) is a connective tissue disease that is often complicated by secondary interstitial lung disease (SSc-ILD). Due to its high morbidity and mortality, there is an on-going effort to find a specific therapy for SSc-ILD. The standard of therapy in recent years has been an immunosuppressive therapy (IST) with cyclophosphamide (CYC). Although increasing data suggest the efficacy of mycophenolate mofetil (MMF) and other ISTs, there have been very few randomized controlled trials (RTCs) to show their efficacy. In this study we will analyze the current standard of therapy in SSc-ILD in SSc centers that participated in the DeSScipher Project on SSc-ILD.

Methods: 1,447 adult SSc patients, who participated in the DeSScipher Project, met the ACR/EULAR 2013 classification criteria and had a diagnosis of SSC-ILD proven by chest X-ray or computed tomography were included in our study. Clinical parameters, medical therapies and lung function were assessed at baseline and 12 +/- 3 months later.

Results: Out of the 1,447 patients included in the study, 781 patients (54%) received ISTs. Of those only 95 patients (12%) received CYC, either as monotherapy (47, 6%) or as combination therapy (48, 6%) (combination therapy referring to any additional IST excluding glucocorticoids (GCs) < 8 mg/day or anti-malaria agents). MMF was more prevalent with 239 patients (31%), 169 (22%) on monotherapy and 70 (9%) on combination therapy. Newer therapies such as rituximab (RTX) were less frequent with 50 (6%) patients, 14 (2%) on monotherapy and 36 (5%) on combination therapy. For Tocilizumab (TOC) we found 19 (2%) patients in total, 6 (1%) on monotherapy and 13 (1%) on combination therapy. Out of the patients with SSc-ILD receiving IST there was a total of 239 (31%) patients receiving IST combination therapy. Comparing patients receiving CYC +/- other IST to patients receiving MMF, RTX or TOC either as monotherapy or as combination therapy, they are similar in age (53.7±12.7 yrs vs. 54.2±12.8 yrs in CYC), but have shorter disease duration regarding SSc (5.9±6.9 yrs in CYC vs. 8.7±6.9 yrs, $p<0.001$) and ILD (3.3±5.7 yrs in CYC vs. 5.9±7.8 yrs, $p<0.001$), similar FVC (80.8±21.4% in CYC vs. 83.1±21.5%) and higher mRSS (13.3 in CYC vs. 8.9±8.7, $p<0.001$). Interestingly, over the course of 1 year +/- 3 months patients on any combination therapy showed slightly better results in terms of FVC and mRSS compared to patients on monotherapy (ΔFVC 2.3% vs. 1.5%; ΔmRSS -1.7 vs. -0.9).

Conclusion: This study highlights the heterogeneity of ISTs in current clinical practice for the treatment of SSc-ILD. There is a high prevalence of immunosuppressive combination therapies that are not supported by any RTCs. Such combination therapy seems to have a beneficial effect on both FVC and mRSS. However, the difference is below a clinically meaningful improvement of 5% FVC. Also, these data have to be interpreted with caution, because groups are not yet adjusted for baseline characteristics.

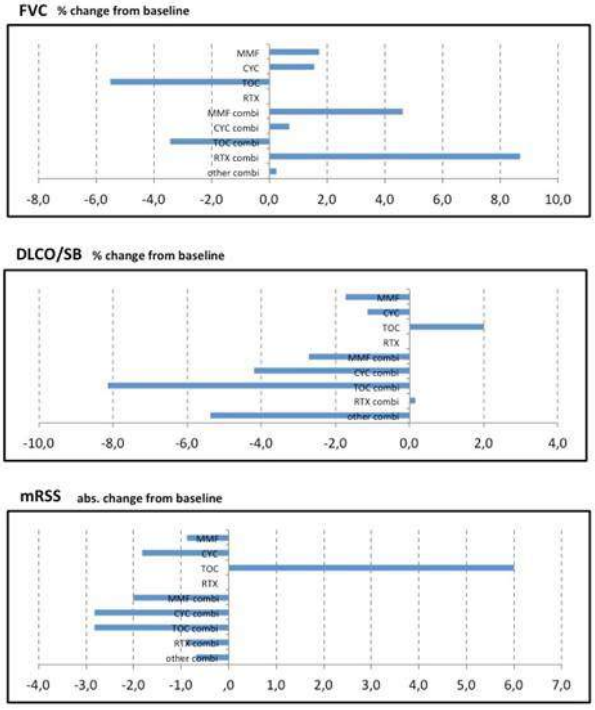

Table 1 Comparing outcomes in lung function parameters (mean changes in FVC and DLCO/SB) and skin involvement (mean changes in mRSS) after 1 year ± 3 months of IST in 141 SSc-ILD patients enrolled in the DeSScipher Project.

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Abstract Number: 846

Progression of Left Ventricular Myocardial Dysfunction in Systemic Sclerosis: Using Speckle Tracking Strain Echocardiography to Identify Patients at Risk

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Background/Purpose: Cardiac involvement is a main cause of mortality in systemic sclerosis, although reported prevalence of cardiac involvement is low and detection of cardiac involvement remains challenging. Speckle-tracking strain analysis of echocardiographic images can detect subtle myocardial dysfunction in systemic sclerosis patients. **Objectives:** This study evaluated: 1. changes in cardiac performance over time including echocardiographic myocardial speckle tracking strain analysis in a large cohort of systemic sclerosis

patients, not selected for disease severity, and 2. baseline characteristics associated with deterioration of cardiac function.

Methods: 235 systemic sclerosis patients (197 female, 52±14 years), all fulfilling ACR 2013 or Leroy 2001 criteria for systemic sclerosis, were evaluated at baseline and follow-up (2.3 years, interquartile range 1.3-3.8), including complete physical examination and screening for organ involvement with at least high resolution computed tomography of the thorax, pulmonary function test, cardiopulmonary exercise test, electrocardiography and echocardiography.

Results: Left ventricular ejection fraction did not change significantly (62%±7 vs 61%±8,p=0.148) while global longitudinal strain decreased significantly (-21%±2 vs -19%±2, p<0.001). 39 patients showed progression of left ventricular dysfunction as defined by ≥15% decline in longitudinal strain. These patients showed significant worsening of left ventricular diastolic function and Tricuspid Annular Plane Systolic Excursion (TAPSE ; 22mm±4 versus 19mm±4, p=0.003) and 6% developed pulmonary hypertension. Multivariate analysis showed that at baseline proximal muscle weakness (Odds Ratio: 3.7; interquartile range:1.3–10.4), diffusing capacity of carbon monoxide (Odds Ratio: 0.97 [0.95–1.00]) and Left ventricular diastolic dysfunction (Odds Ratio: 2.25 [1.02–4.95]) were associated with progression of left ventricular dysfunction as reflected by strain analysis.

Conclusion: In this large cohort of systemic sclerosis patients, decline of left ventricular function was detected by speckle tracking strain analysis, and increase of percentage of patients with diastolic dysfunction. At baseline, proximal muscle weakness, diffusing capacity of carbon monoxide, and left ventricular diastolic function may identify patients at higher risk for deterioration of cardiac function and in need of closer cardiac monitoring by means of annual repeated echocardiography. Table 1. Echocardiographic parameters at baseline and follow-up; n= 235 Abbreviations: LEVF= Left Ventricular Ejection Fraction; GLS= Global Longitudinal Strain; LV= Left Ventricular; sPAP= systolic Pulmonary Arterial Pressure; PAH= Pulmonary Arterial Hypertension; TAPSE = Tricuspid Annular Plane Systolic Excursion; PE= pericardial effusion

	Baseline	Follow-up	P value
LEVF%, mean (SD)	62 (7)	61 (8)	0.148
Global Longitudinal Strain (GLS) %, mean, (SD)	-20.91 (2.01)	-19.31 (2.47)	< 0.001
Decline in GLS >= 15%, n (%)	-	39 (17)	-
Diastolic dysfunction, n (%)	73 (31)	108 (46)	<0.001
LV diastolic dysfunction de novo, n (%)	-	31 (13)	-
LV diastolic dysfunction increase, n (%)	1	48 (20)	-
sPAP mmHg, mean (SD)	26 (8)	28 (12)	0.060
New PAH at follow-up, n (%)	-	13 (6)	-
Persistent PAH, n (%)	-	14 (6)	-
TAPSE mm, mean (SD)	23 (4)	22 (4)	0.006
Pericardial Effusion (PE), n (%)	9 (4)	17 (7)	< 0.001
New PE at follow-up, n (%)	-	12 (5)	-

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Abstract Number: 847

Forced Vital Capacity Predicts Lung Fibrosis Progression and Mortality in Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) carries high risk for progressive interstitial lung disease (ILD), but there are no valid methods for early detection of SSc-ILD or algorithms for ILD progression available. The aim of this study was to assess the impact of baseline FVC on lung fibrosis, fibrosis progression and mortality.

Methods: Paired pulmonary function tests (PFT) and high resolution computed tomography (HRCT) images were obtained at baseline and follow-up in consecutive SSc patients (n=305) from the prospective Oslo University Hospital (OUH) cohort. All patients met the 2013 ACR/EULAR classification criteria. Extent of fibrosis was scored on 10 sections from every HRCT and expressed as percentage of total lung volumes. The annual fibrosis progression was defined as the difference in extent of fibrosis between the baseline and follow-up HRCT divided by the actual follow-up period in years.

Results: At baseline, 186/305 patients (61%) had a baseline FVC <100% (Table 1). Lower baseline FVC (<90, 80 and 70%) was associated with male gender and higher extent of fibrosis at baseline and follow up (Table 1). In multivariate cox regression analyses, all baseline FVC thresholds (<100, 90, 80 and 70%) were significantly associated with mortality (Table 2). Other parameters significantly associated with mortality were age at onset (HR 1.1, 95% CI 1.1-1.2, p-value<0.001) and diffuse cutaneous SSc (HR 2.2, 95% CI 1.2-3.6, p-value 0.002). All baseline FVC thresholds were also associated with annual fibrosis progression in univariate cox regression analyses (Table 2). In multivariate analyses, only baseline FVC <80% was associated with annual fibrosis progression (HR 1.8, 95% CI 1.0-3.0, p-value 0.042), as well as male gender (HR 1.9, 95% CI 1.1-3.4, p-value 0.023) and anti-Topoisomerase I (HR 2.2, 95% CI 1.3-3.9, p-value 0.006). Of the 119 patients with baseline FVC>100%, 56 had no lung fibrosis. These 56 patients were predominantly female (90.4%); most of them had limited cutaneous SSc (91%) and anti-centromere antibodies (76%) and 18% died during the observation period.

Conclusion: These prospective cohort data suggest that baseline FVC%, including normal range values, predict mortality and fibrosis progression in SSc. Based on these data, we suggest that all SSc patients should be assessed with PFT and HRCT at baseline, and followed with PFTs on a regular basis. **Table 1:** Demographics, extent of fibrosis at baseline and follow-up, annual fibrosis progression and pulmonary function segregated by baseline FVC% in 305 SSc patients

	Baseline FVC					
	>100% 119 (39)	90-100% 60 (20)	80-90% 48 (16)	70-80% 32 (11)	<70% 46 (15)	p-value[1]
Age at onset, yrs	51 (12.9)	46[1](16.3)	49(16.5)	47(17.9)	45[1] (14)	n.s.
Gender, no (%)	15 (13)	11 (18)	9 (19)	8 (25)	20 (44)	<0.001
Follow-up duration, yr	3.9 (2.8)	4.1 (3.6)	3.4 (2.3)	3.8 (2.7)	3.9 (3.2)	n.s.
Disease duration, yr	10.2 (6.6)	11.9(9.1)	10.6(6.7)	10.3(9.1)	11.8 (8.6)	n.s.
Deceased, no (%)	19 (16)	14 (23)	16 (33)	10 (31)	22 (48)	<0.001
lcSSc, no (%)	102 (86)	40 (68)	30 (64)	21 (68)	21 (47)	<0.001
ACA, no (%)	82 (69)	22 (37)	17 (35)	12 (37)	6 (13)	<0.001
Any fibrosis, n (%)	63 (53)	36 (60)	31 (65)	22 (69)	45 (98)	<0.001
Baseline fibrosis %	1.6 (3.8)	4.7 (9.3)	5.3 (7.8)	5.3(10.9)	25.7(14.9)	<0.05
Follow up fibrosis %	2.1 (4.9)	6.5(11.7)	6.7 (9.2)	8.3(15.4)	28.8(20.9)	<0.05
Annual fibrosis progression%	0.1 (1.1)	0.7 (2.5)	0.6 (1.8)	1.0 (3.1)	1.0 (3.5)	n.s.
Annual FVC decline	1.8 (5.7)	1.9 (6.1)	2.2 (7.8)	2.8 (9.5)	2.6 (5.4)	n.s.
Baseline DLCO %	77.2(20.1)	65.8(15.9)	65.5(15.7)	62 (14.9)	43.6(14.9)	<0.05
Annual DLCO decline	2.9 (4.3)	0.7[1](15.5)	1.8 (6.4)	4.7 (9.1)	2.5 (6.8)	n.s.

[1]:p-value < 0,05 compared to baseline FVC>100%, n.s. not significant except for values marked: x[1] (p-value<0.05), (SD) if not stated differently **Table 2:** Univariate cox regression analyses with mortality and annual fibrosis progression as outcome measures

	N (%)	Mortality HR (95% CI)	p-value	Annual fibrosis progression HR (95% CI)	p-value
Baseline FVC<100%	186 (61)	2.1 (1.3-3.6)	0.005	1.8 (1.0-3.2)	0.045
Baseline FVC <90%	126 (41)	2.0 (1.2-3.2)	0.004	2.2 (1.3-3.7)	0.003
Baseline FVC <80	98 (32)	2.0 (1.2-3.2)	0.006	2.3 (1.4-3.9)	0.001
Baseline FVC <70%	46 (15)	2.5 (1.4-4.5)	0.003	2.1 (1.2-3.6)	0.012

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Abstract Number: 848

Efficacy of Prucalopride in the Treatment of Systemic Sclerosis-Related Intestinal Involvement: Results from an Open Label Cross-over Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: The gastrointestinal tract (GIT) is frequently affected in SSc patients as a consequence of a reduction in enteric propulsive forces. Due to intestinal involvement, patients may experience diarrhea, constipation, bloating, weight loss and a general reduction in well-being. The use of prokinetics proved effective in treating some SSc patients with GIT. Serotonin (5-HT4) receptor agonists with only moderate affinity for the 5-HT4 receptors were however withdrawn due to cardiac toxicity. Prucalopride is a high-affinity 5-HT4 receptor agonists with no major cardiac issues, whose efficacy in SSc has not been assessed yet.

Methods: Forty patients with self-reported mild-to-moderate enteric symptoms were enrolled in a cross-over 2 x 2 study. Subjects were given prucalopride 2 mg/day or no treatment for one month and vice versa after a 2 weeks washout period, according to the ABBA sequence. Before and after each sequence the patients compiled the UCLA GIT 2.0 questionnaire and Likert scales to rate the severity of GIT involvement or constipation; the number of complete intestinal movements and the number of used laxatives were also recorded. Mixed linear models, were used to compare responses correcting for the number of laxatives.

Results: Seven patients did experience side effects (headache and dizziness, diarrhea, abdominal pain) and 4 patients were not compliant to study procedures (inadequate drug intake); 29 subjects did complete the study. Baseline GIT parameters and main results are reported in the Table. Prucalopride treatment was ranked as moderately-to-extremely effective by 22 patients (72.4%).

Conclusion: The safety profile of Prucalopride in SSc is similar to what had already reported in the literature. In SSc patients with mild-to-moderate GIT problems, prucalopride may be effective in treating dismotility symptoms, increasing the number of complete bowel movements, partially reducing reflux disease and improving the patents' well-being.

Variable	Baseline	Change* after prucalopride	Change* after no drug	p
Bowel movements	NA	26,96 ± 13,84**	15,63 ± 10,54**	5*10-6
Likert GIT	2,24 ± 0,74	-0,68 ± 0,72	0 ± 0,29	7.4*10-5
Likert Constipation	2,24 ± 0,64	-1,32 ± 0,9	0,19 ± 0,79	8.1*10-8
GIT	0,99 ± 1,28	-0,15 ± 0,39	0,02 ± 0,21	0.032
GIT Constipation	1,27 ± 0,67	-0,67 ± 0,76	0,08 ± 0,26	6.3*10-5
GIT Subscales Reflux Bloating Fecal soilage Diharrea Social activities Emotional well-being	1,01 ± 0,69 1,48 ± 0,9 0,51 ± 0,91 0,22 ± 0,41 0,72 ± 0,59 0,77 ± 0,78	-0,41 ± 0,57 -0,42 ± 0,47 -0,1 ± 0,91 0,36 ± 0,62 -0,12 ± 0,7 -0,22 ± 0,49	0,01 ± 0,39 -0,08 ± 0,43 0,08 ± 0,28 0,09 ± 0,24 0 ± 0,38 0,02 ± 0,46	0.003 0.010 0.346 0.053 0.388 0.041

*Negative values indicate improvement **Total number of spontaneous bowel movements/arm

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Abstract Number: 849

Collagen Formation/Degradation Neoepitopes Are Promising Biomarkers for Systemic Sclerosis

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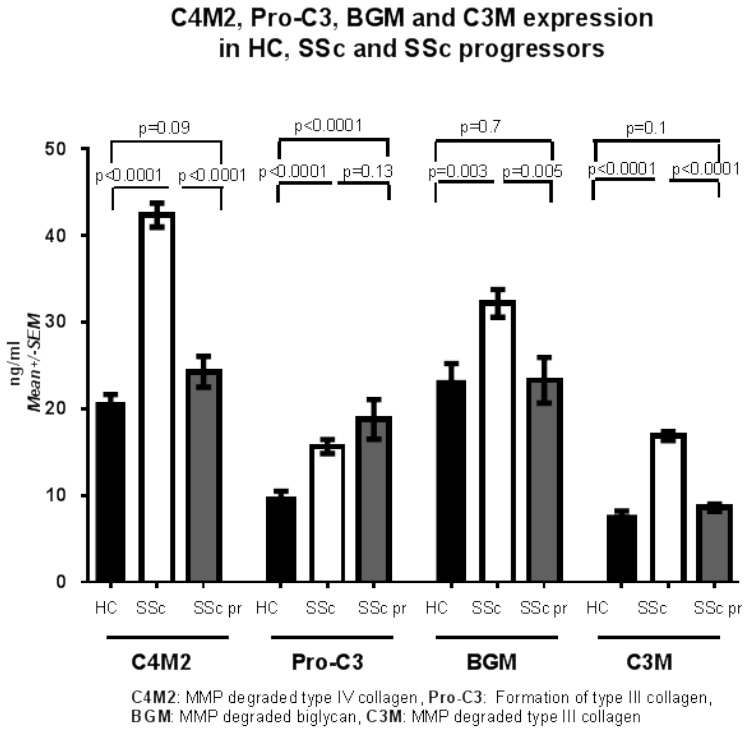
Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease with extensive fibrosis of the skin and internal organs in which extracellular matrix (ECM) remodeling is a key pathogenic process. Given the clinical heterogeneity and the individual disease course of SSc, biomarkers to allow personalized medicine are highly needed. We evaluated the potential of selected ECM neoepitopes as serological biomarkers for diagnosis, prognostic of progression and prediction of clinical outcomes.

Methods: Stable SSc patients (n=151), SSc progressors (n=21, either 10% decrease in FVC% predicted or increase in mRSS ≥25% and 5 points on 1 year clinical follow up) meeting the ACR/EULAR classification criteria and healthy controls (HC; n=29) were analyzed. Longitudinal clinical assessment, data recording and sera collection were done according to EUSTAR standards. ECM-degradation (C3M,

C4M2, BGM, VICM) and ECM-formation biomarkers (P1NP, Pro-C3, Pro-C6) were measured in serum using ELISA-based assays. Differences in biomarker levels were analyzed with respect to several fibrosis-related clinical outcomes as well as the Valentini disease activity score (VDAS). Statistical analysis was performed by Man-Whitney U, Kruskal-Wallis and Spearman tests, as well as multivariate logistic regression, adjusted for sex and age. Biomarkers' sensitivity and specificity was examined by ROC analysis.

Results: The expression of C4M2, Pro-C3, BGM and C3M was significantly increased in SSc patients compared to HC ($p<0.0001$, AUC=0.93; $p<0.0001$, AUC=0.74; $p=0.003$, AUC=0.67; $p<0.0001$; AUC=0.93, respectively). Furthermore, Pro-C3, VICM and Pro-C6 levels were significantly higher in SSc progressors vs. HC ($p<0.0001$, AUC=0.85; $p=0.003$, AUC=0.75; $p=0.0002$, AUC=0.81, respectively), whereas P1NP was significantly lower ($p=0.04$, AUC=0.67). Interestingly, ECM-degradation markers C4M2, BGM and C3M were significantly lower in SSc progressors vs. SSc patients ($p<0.0001$; $p<0.005$; $p<0.0001$, respectively), whereas the formation marker Pro-C3 was slightly higher, but without reaching statistical significance (Figure 1). Pro-C3 was significantly higher in patients with DLCO SB <70% ($p=0.03$), moderate-severe dyspnea ($p=0.02$) and active disease (VDAS ≥3, $p=0.02$) and showed a mild correlation to the VDAS ($r= -0.29$; $p=0.000$).

Conclusion: These data indicate that ECM neoepitopes could not only differentiate between HC and SSc patients but, even more, could help identify patients prone to progress at 1 year clinical follow up. The significant decrease in ECM-degradation markers in SSc progressors compared to stable patients suggests an impairment of collagen degradation in this group. ECM neoepitopes arise as potential new biomarkers in SSc. Figure 1.



Disclosure: R. Dobrota, None; **S. Jordan**, None; **P. Juhl**, Nordic Bioscience Diagnostic, 3; **L. Wildi**, None; **B. Maurer**, AbbVie, Protagen, EMDO, 2, 9,Roche, Actelion, 9; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 1; **A. S. Siebuhr**, Nordic Bioscience Diagnostic, 3; **O. Distler**, 4D Science, Actelion, Active Biotec, Bayer, BiogenIdec, BMS, Boeringer Ingelheim, EpiPharm, Ergonex, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly,medac, MedImmune, Pharmacyclics, Pfizer, Serodapharm, Sinoxa, 5,Actelion, Bayer, Boeringer Ingelheim, Ergonex, Pfizer, Sanofi, 2,mir-29 for the treatment of systemic sclerosis, 9.

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Abstract Number: 850

A Multicentre Reliability Study of Laser Speckle Contrast Imaging and Thermography in Patients with Raynaud's Phenomenon Secondary to Systemic Sclerosis

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Background/Purpose: Effective treatments for systemic sclerosis (SSc) related Raynaud's phenomenon (RP) are badly needed but clinical trials have been hampered by the lack of objective outcome measures. Laser speckle contrast imaging (LSCI) and thermography are two non-invasive measures of blood flow that show excellent potential but require further investigation to prove their suitability as outcome measures in multi-centre clinical trials. The main aim of this multi-centre study was to determine the validity and reliability of LSCI and thermography. This abstract reports the first step in a more comprehensive analysis; the repeatability of the techniques as assessed by a local assessor at each site.

Methods: 158 patients with RP secondary to SSc were recruited from 6 specialist SSc centres in the UK. Patients attended their local centre on 2 consecutive days. They underwent a cold challenge; 15^{o}C water submersion of gloved hands for 1 minute, then un-gloved reperfusion and rewarming at 23^{o}C room temperature. Baseline and changes in blood flow and temperature over 15 minutes post challenge were imaged simultaneously using LSCI (relative perfusion) and thermography (skin temperature, an indirect measure of perfusion), respectively. Parameters for both perfusion and temperature were calculated locally and data analysis was performed centrally. The distal dorsal differences (DDD) of each hand were calculated from baseline images. The area under curve (AUC), maximum value (MAX), and gradient (GRAD) in first two minutes were calculated from the post challenge data of the fingers. Data were averaged across 8 digits for each patient to obtain a single measurement for each parameter for each technique at both visits. Test-retest reliability was assessed using intra-class correlation coefficients (ICC) using linear mixed models (R version 3.2.3) where an ICC of 0.60 is regarded as substantial reliability (Landis and Koch 1977).

Results: Median age was 63.3 years (IQR 53.8–69.8), 84% were female, median SSc symptom duration was 9.6 years (IQR 4.5 – 17.4), and 77% had limited cutaneous SSc. Both techniques had substantial reliability for AUC. Thermography reliability across all parameters varied from moderate to strong (GRAD 0.56 to MAX 0.72) and LSCI varied from moderate to substantial (GRAD 0.46 to AUC 0.67) (table 1). Reliability of the two techniques has higher overall ICCs for thermography, suggesting marginally greater reliability of thermography in this sample.

Conclusion: This is the first multi-centre study examining reliability of LSCI and thermography in patients with RP secondary to SSc, and these are the preliminary findings from local analysis. The results and analysis are encouraging, overall, LSCI and thermography demonstrated moderate to strong reliability (and therefore good potential as outcome measures of digital vasculopathy), although thermography appears to be marginally superior to LSCI. **Table 1.** ICCs (Logged for non-normality where necessary) for summary measures of response to cold challenge under LSCI and thermography.

ICCs	LSCI	Thermography	Difference (LSCI-Thermography)
AUC	0.67 (0.54 to 0.76)	0.68 (0.58 to 0.80)	-0.01 (-0.17 to 0.11)
DDD	0.67(0.56 to 0.76)	0.66 (0.56 to 0.76)	0.01 (-0.12 to 0.11)
MAX	0.64 (0.52 to 0.75)	0.72 (0.64 to 0.81)	-0.09 (-0.21 to 0.03)
GRAD	0.46 (0.40 to 0.69)	0.56 (0.40 to 0.74)	-0.09 (-0.24 to 0.18)

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Perioral Autologous FAT Transplantation Is More Effective THAN Hyaluronic Acid Filler on Scleroderma Skin Fibrosis: Results from a LONG TERM Controlled Study

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Background/Purpose: Autologous fat tissue grafting (AFTG) has been successfully used in the treatment of different sclerotic conditions, including scleroderma. We evaluated in patients with SSc who complained of a reduced mouth opening, the long-term efficacy of AFTG of the lips in improving mouth opening in comparison with hyaluronic acid (HA) filler. We also investigated whether these procedures may induce some changes in the microvascular architecture and dermal structure of the treated skin area.

Methods: We studied 36 patients with dcSSc, (median age 37+12 yrs, disease duration 11+8yrs): 18 were treated by topical perioral AFTG according to Coleman technique and 18 by HA filler. The filler was repeated after 3 months. Baseline and after treatment (at months 3, 6, and 12) mouth opening changes were assessed by measuring inter-incisal distance and oral perimeter. Pre- and post-treatment modifications of microvascular architecture were assessed by counting capillaries in the inferior lip videocapillaroscopy (VC) images. Similarly, histological sections of perioral skin biopsy were examined at baseline and 3 months to evaluate dermo-epidermic junction (DEJ), the collagen content (by Masson's Trichrome staining) and microvessel density (MVD) (by anti-CD34/CD31staining).

Results: . 3 months after treatment both the inter-incisal distance and oral perimeter significantly increased ($p < 0.001$). At the same time, a significant skin neovascularization became evident, both considering the VC images ($p < 0.001$) and MVD scores in IH sections ($p < 0.0001$). Finally, some skin histological aspects also improved, as shown by the significant changes in DEJ flattening scores ($p < 0.0001$) and collagen content with less abnormal and denser collagen bundles. At 6 and 12 months, despite the disappearance of filling effect, both the functional improvement in mouth opening and the increased number of capillaries were maintained. No effect either on the mouth opening, VC images and skin histological aspects was observed in SSc patients treated by HA filler.

Conclusion: The present study shows that, in SSc patients, AFTG can improve mouth opening, induce a neovascularization, and partially restore the skin structure. All these effects were confirmed in the long-term observation. The lack of functional and biological effects in the control group treated by HA filler, suggests that the observed therapeutic effect of lipostructure may be specifically ascribed to the on site transplantation of fat tissue.

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Targeting Fibroblastoid-like Cells By Drug Loaded Engineered Gold Nanoparticles As a Novel Approach for ILD-SSc Treatment

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Background/Purpose: Systemic Sclerosis (SSc) is an autoimmune fibrotic disorder characterised by collagen and extracellular matrix deposition in the skin and internal organs, such as the lung. Interstitial lung involvement (ILD) is frequent in SSc and represents the most frequent cause of death. Gold nanoparticles (GNPs) have a great potential in biomedical applications among which drug-delivery. Previously, we proved that GNPs containing everolimus and functionalized with anti-CD44 antibody targeted to mesenchymal cells from patients with chronic lung allograft rejection (CLAD) specifically inhibited these cells. We proved that also fibroblastoid-like cells (FLCs) isolated from bronchoalveolar lavage (BAL) of ILD-SSc patients express CD44. Here, we loaded in the same nanoparticles the drug imatinib (GNP-HCim) with the aim to specifically inhibit FLCs from ILD-SSc patients.

Methods: GNPs with imatinib and exposing an anti-CD44 antibody were engineered. GNP-HCim were incubated 2h with FLCs from three patients with ILD-SSc. Cell apoptosis (Annexin V) and proliferation (CFSE) were evaluated at different times by flow cytometry. Cell viability was assessed by MTT test. As control, functionalized GNPs without imatinib (GNP-HC) or imatinib alone (IM) were used. Fluorescent GNP-HC were generated to assess cell uptake by confocal microscopy and flow cytometry. Statistical differences were evaluated using ANOVA by Graph Prism 5.0 program.

Results: Fluoresce experiments showed that only HC-functionalized nanoparticles were entered into FLCs within 1 h. The results showed that GNP-HCim inhibited cell proliferation without significant differences between the three cell lines. In particular, the effect of GNP-HCim was significant at 48 ($p<0.001$) and 72h ($p<0.01$). A significant inhibition was also observed in presence of GNP-HC both after 48 ($p<0.01$) and 72h ($p<0.05$). These results suggest that an unspecific effect of the nanoparticles itself or, by interaction with the antibody anti-CD44. No changes were produced by IM alone. MTT assay confirmed the results obtained by CFSE since a significant reduction ($p<0.001$) of cell viability was observed with GNP-HCim and GNP-HC starting from 48 h. IM treatment affected the FLCs viability ($p<0.05$ at 48h; $p<0.001$ at 72h). Functionalized nanoparticles were able to significantly increase apoptosis after 8 ($p=0.0051$) and 24 h ($p<0.001$) compared to uFLCs. However, only drug-loaded nanoparticles still significantly increase apoptotic rate after 48 h ($p=0.004$).

Conclusion: We proved that specifically engineered GNPs significantly inhibit proliferation and induce apoptosis of FLCs from ILD-SSc patients, as already described for CLAD patients. FLCs treatment with imatinib alone was not effective as GNP-HCim demonstrating the superiority of the nanoparticles. These experiments confirm the possibility to use engineered nanoparticles to develop a new pharmacological treatment for patients with pulmonary fibroproliferative disorders.

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Clinical Associations of Anti-Eukaryotic Initiation Factor 2B (anti-eIF2B) Antibodies in a Large Cohort of Patients with Anti-Nuclear Antibody Negative Systemic Sclerosis

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Background/Purpose: Autoantibodies can be characterized in up to 95% of patients with systemic sclerosis (SSc) and provide enormous diagnostic and prognostic value in the clinical setting. We have recently identified a novel autoantibody in patients with SSc targeting Eukaryotic Initiation Factor 2B (anti-eIF2B). Earlier work identified an association with diffuse cutaneous systemic sclerosis (dcSSc) and interstitial lung disease (SSc-ILD), although the majority of samples had originated from a large tertiary referral respiratory unit managing patients with SSc-ILD. Anti-eIF2B positive sera has a cytoplasmic staining pattern on indirect immunofluorescence (IIF), but anti-nuclear antibody (ANA) staining is negative. The objectives of this study were to explore the prevalence and clinical associations of anti-eIF2B antibodies in ANA-negative samples obtained from a large US prospective study of SSc.

Methods: ANA-negative samples from the Scleroderma Family Registry and DNA Repository were tested by routine serological techniques followed by radiolabelled protein immunoprecipitation (IPP). Sera that immunoprecipitated a 30kDa band (consistent with anti-eIF2) underwent immunodepletion studies to confirm antigen specificity for eIF2B. The clinical phenotype of patients carrying anti-eIF2 was assessed.

Results: Of the 128 ANA-negative samples, a 30kDA band was identified on IPP in 10 samples (7.8%). Immunodepletion studies confirmed eIF2B as the antigen target in 9 samples. No other SSc-specific autoantibodies were identified in these 9 samples (suggesting mutual exclusivity). The clinical features of anti-eIF2B positive patients are presented (Table). All patients had Raynaud's phenomenon (9/9, 100%). The majority of patients had dcSSc (8/9, 89%) although the mean modified Rodnan Skin Score (documented 7/9, 78%) was only 17.7. All patients with previous chest imaging (7/9, 78%) had radiographic evidence of SSc-ILD; either on computed tomography (6/6, 100%) and/or plain radiograph (4/4, 100%). Pulmonary function tests (documented in 7/9, 78%) revealed a mean FVC of 63.4% predicted and mean DLco of 64.3% predicted. The prevalence of digital ulcers and gastro-esophageal reflux disease was low (2/9, 22% for each). No patients had evidence of pulmonary arterial hypertension on echocardiography or right heart catheterization (when reported).

Conclusion: Anti-eIF2B is a novel, rare (estimated total prevalence in SSc ~1%) and mutually exclusive cytoplasmic autoantibody identified in approximately 7% of ANA-negative samples of patients with SSc. Our findings would support the previously reported clinical association of anti-eIF2B autoantibodies with dcSSc and SSc-ILD in a larger and more representative SSc patient population. **Table. Clinical phenotype and outcome of pulmonary investigations of anti-eIF2B positive SSc patients** * na, not available

	Ethnicity	Disease subset	Modified Rodnan skin score	FVC % predicted	DLco % predicted	SSc-ILD on CXR	SSc-ILD on CT
Patient 1	Non-hispanic white	Diffuse	na	84	86	Yes	na
Patient 2	Non-hispanic white	Diffuse	34	68	64	na	Yes
Patient 3	Non-hispanic white	Diffuse	18	na	na	Yes	na
Patient 4	Non-hispanic white	Diffuse	11	66	62	na	Yes
Patient 5	Non-hispanic white	Limited	15	42	67	Yes	Yes
Patient 6	Non-hispanic white	Diffuse	11	na	na	No	na
Patient 7	Non-hispanic white	Diffuse	12	79	79	na	Yes
Patient 8	Non-hispanic white	Diffuse	na	56	28	na	na
Patient 9	Black	Diffuse	23	49	na	Yes	Yes

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The Ducas: Proposal for a Digital Ulcer Assessment Score in Scleroderma

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Background/Purpose:

No objective measure is presently available to assess digital ulcer (DU) in SSc patients apart from “healed/non healed” and experience-based clinical judgment. The aim of the current study is to propose a composite DU clinical assessment score (DUCAS) and to lend it, test

its face validity by correlating it with commonly used disease related patient-reported outcomes (PROs) and physician evaluation.

Methods:

SSc patients presenting at least one DU and attending the Rheumatology Wound Care Clinic of the Florence University Hospital or the London Royal Free Hospital were enrolled. Patients were assessed with HAQ-DI, Cochin scale, Visual analogic scale (VAS) for DU-related pain (DU_pain, 0-100 mm), patient VAS for global DU status (ptGDU, 0-100mm) and patient global assessment (PtGA, 0-100 mm) as PROs and physician VAS for DU status (phyGDU, 0-100mm). The DUCAS included 7 DU related variables selected by a committee of 8 SSc DU experts - they are outlined in table 1. Each variable was weighted on a clinical basis and the DUCAS score was the sum of the values for the 7 variables (max=19,5). Spearman's correlation tests were calculated for to examine face validity. A linear regression model with forward and backward stepwise analysis was used to determine the relationship of individual variables with the primary clinical parameter, phyGDU.

Results:

44 SSc patients (9 males, mean age 54,3±15,6 years, mean disease duration 9,9±5,8 years) were enrolled in the study. Mean phyGDU was 44,3±23mm, mean ptGDU was 54±30mm (Wilcoxon p=0.022, phyGDU VAS vs ptGDU) and mean DUCAS score was 4,2±2. Overall DUCAS showed significant positive correlations with all PROs, but when all the individual clinician and patient's variables were modelled, only the overall DUCAS significantly predicted PhyGDU; after backwards stepwise analysis overall DUCAS and ptGDU best predicted PhyGDU, with an adjusted R^2=0,437 and AIC=380,3 (Table 2).

Conclusion:

DUCAS is a newly proposed clinical score for SSc related DU which has face validity and which may reflect DU statusas judged by SSc experts. Further validation of this score will be undertaken.

DUCAS			
1	**Number of Digital Ulcers**	None	0
		1 DU	1
		2 DUs	2
		More than 3 Dus	3
2	**New Digital Ulcers**	YES	1
		NO	0
3	**Gangrene**	YES	3
		NO	0
4	**Surgical approch to DU (above standard care)**	YES	3
		NO	0
5	**Infection of DU**	None	0
		Requiring systemic antibiotics	1
		Osteomyelitis	2
		Septicemia	3
6	**Unscheduled hospitalisation for DU**	YES	3
		NO	0
7	**Analgesics to control DU pain**	No pain	0
		Non requiried analgesics	0,5
		Non-opioids analgesics	1
		Minor opioids	2
		Major opioids	3
		dose increased since last visit	*+0.5*
		dose decreased since last visit	*-0,5*
		TOTAL SCORE	

A	Linear Regression for DUCAS		B	Linear Model to PhyGDU			Linear Model to PhyGDU after backwards stepwise		
	Pearson Correlation	p		Estimate	SE	p	Estimate	SE	p
PtGA	0,56	<0,001	PtGA	0,011	0,199	0,955			
PtGDU	0,54	<0,001	PtGDU	0,171	0,233	0,467	0,272	0,101	0,01
DU_Pain	0,44	0,003	DU_Pain	0,048	0,182	0,793			
HAQ-DI	0,44	0,003	HAQ-DI	4,58	7,563	0,549			
COCHIN	0,51	<0,001	COCHIN	0,035	0,252	0,891			
PhyGDU	0,63	<0,001	DUCAS	4,636	1,617	0,007	4,841	1,489	0,002

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Abstract Number: 855

The Relationship Between Systemic Sclerosis and Breast Cancer and the Effects on

Treatment Outcome

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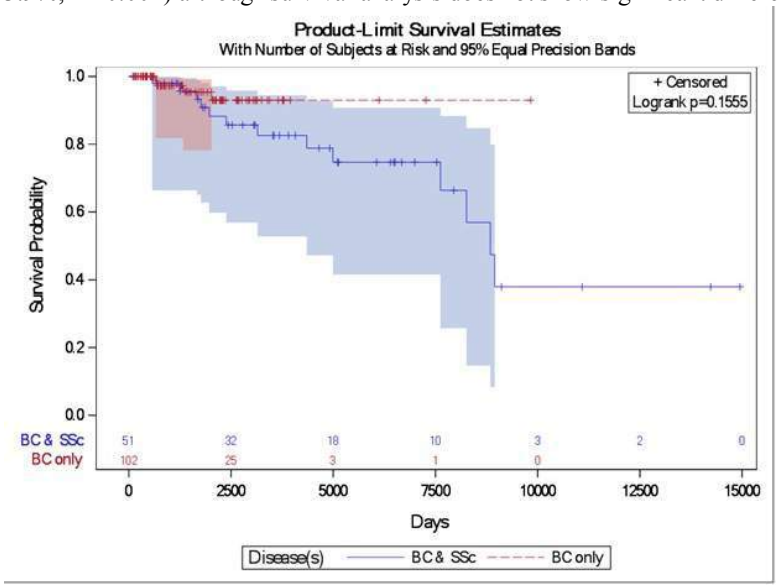
Background/Purpose: Breast cancer has been shown to be more prevalent in patients with systemic sclerosis (SSc) compared to that in the general population. A close temporal correlation between the onset of SSc and breast cancer has been demonstrated, particularly in patients with anti-RNA polymerase III antibody, suggesting a possible pathogenic or paraneoplastic association in this subset of patients. Certain chemotherapeutic agents and radiotherapy may be avoided in patients with SSc. The goal of this study was to demonstrate the impact of scleroderma on breast cancer treatment options and outcomes. We also wanted to assess the association of SSc to the specific histopathologic subtype, hormone receptor status and human epidermal growth factor receptor 2 (HER2) oncogene status of breast cancer.

Methods: A retrospective chart review was performed to compare patients with breast cancer with and without SSc that were seen within the last 10 years at our institution. For comparison, a random number generator was used to select 102 out of 9157 breast cancer patients without SSc who were diagnosed and treated at our institution over the same time period. Data on demographics, clinical characteristics, breast cancer treatments, and survival rate were collected. Numerical variables are compared between groups using ANOVA and two sample t-tests. Categorical variables were compared using either Pearson's chi-squared test or Fisher's exact test. Survivor functions were estimated using the Kaplan-Meier method and differences in survivor functions were tested for with log-rank tests.

Results: Fifty-one patients with SSc with a history of breast cancer were identified; 43.1%, 3.9% and 7.8% of patients with SSc had anti-centromere, anti-Scl-70 and anti-RNA polymerase III antibodies respectively. Patients with RNA polymerase III antibody had shorter interval between SSc and breast cancer onset compared to the patients with anti-Scl-70 (11.7 vs 51.2 months, P 0.43) and anti-centromere (11.7 vs 66.5 months, P 0.07) antibodies. Patients with breast cancer and SSc less frequently had invasive ductal carcinoma compared to breast cancer patients without SSc (47.1% vs 63.7%, P 0.049). The percentage of estrogen and progesterone receptor positivity as well as HER2 oncogene positivity were similar in the two groups. There was a trend towards receiving less radiotherapy in patients with SSc and breast cancer (52.9% vs 68.6%, P 0.058). The decision to receive chemotherapy, hormonal therapy and immunotherapy were similar between the two groups. Mortality rate was much higher in breast cancer patients with SSc compared to those without SSc (25.5% vs 3.9%, P <0.001) although survival analysis does not show significant difference (Figure1).



Conclusion: Breast cancer patients with SSc have higher mortality rate compared to those without. Further studies are needed to identify specific treatment strategies for this group of patients.

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Rho Kinase Ezpression in Giant Cell Arteritis: Validating Perm Intensity Score As a Method of Increasing Sensitivity of Temporal Artery Biopsy

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
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Session Type: ACR Poster Session A
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Background/Purpose: Aberrant rho-kinase (ROCK) activity is implicated in pathogenesis of several vascular and immunologic disorders. We previously demonstrated evidence of increased ROCK activity in histopathologically negative temporal artery biopsies (TAB) of subjects with clinical giant cell arteritis (GCA) compared to those without GCA. The aim of this study was to validate a ROCK activity score in a large cohort of GCA patients.

Methods: TAB obtained as part of an international study examining the role of ultrasound in GCA were utilized. Only histologically negative TABs were used for this study. Subjects were categorized into 2 groups, those who were diagnosed with GCA despite negative TAB at 6 months after biopsy and those with negative TAB ultimately felt not to have GCA. Paraffin-embedded TAB were stained for phosphorylated ezrin/radixin/moesin (pERM), a surrogate of ROCK activity, and reviewed by a pathologist blinded to clinical diagnosis. Three areas of the vessel (intima, adventitial and vasa vasorum) were scored for staining intensity on a scale of 0–2, with a maximum possible score of 6 for each TAB. As determined a priori, scores ³4 were considered a high pERM intensity score suggesting ROCK activity. TAB sections were also stained for unphosphorylated ERM, the inactive protein.

Results: Biopsies of 36 subjects with TAB-negative GCA were identified and compared to biopsies of 43 subjects without GCA. There were no differences between the 2 groups in age, sex and corticosteroid dose. The mean pERM intensity score in non-GCA subjects was 3.9 ± 1.4 compared to mean pERM intensity score of 5.0 ± 1.4 in those with GCA, p = 0.002. Using the predetermined cut-off of 4 to define high pERM intensity, subjects with GCA were nearly4 times more likely to have a high pERM intensity score compared to non-GCA, OR 3.67, 95%CI :1.19,11.36; p= 0.019. The sensitivity of high pERM intensity score for the diagnosis of GCA in histologically negative TAB was 86%, 95%CI: 70,95. In GCA subjects, the ERM staining was less intense in all areas of the TAB specimens compared to the pERM staining, suggesting activation of the ROCK pathway.

Conclusion: In this large cohort of well characterized subjects, those with GCA and negative biopsies had significantly higher pERM intensity scores in TAB specimens compared to subjects without GCA. These results are concordant with previously published pilot data. pERM staining has diagnostic significance in enhancing the sensitivity of TAB, and helps to define the clinically important group of biopsy-negative GCA. The ROCK pathway warrants further investigation in GCA and may be a potential therapeutic target.

Disclosure: L. Lally, None; **N. Narula**, None; **N. Goodfellow**, None; **R. Luqmani**, None; **R. F. Spiera**, None.

Abstract Number: 857

Ultrasound Cut-Off Values for Intima-Media Thickness of Temporal, Facial and Axillary Arteries in Giant Cell Arteritis

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Abstract

Background/Purpose: Ultrasound (US) is increasingly used in the diagnosis of giant cell arteritis (GCA). US findings mainly rely on morphology ("halo-sign" and "compression sign"). Increasing resolution of modern US probes allows exact intima-media thickness (IMT) measurement of normal and vasculitic temporal arteries. No data have yet been published on IMT of temporal, facial and axillary arteries in GCA patients compared to healthy controls.

Methods: Fourty newly diagnosed GCA patients of a fast-track GCA clinic and 40 age- and sex-matched controls were included between October 2014 and December 2015. The diagnosis of GCA was established by two very experienced rheumatologists (WAS or AJ) on the basis of clinical presentation, laboratory tests and US results. The diagnosis was confirmed after 6 months in patients who were included until July 2015. IMT measurement was performed at or within 24 hours after the first visit. The common superficial temporal arteries with their frontal and parietal branches and the facial arteries were bilaterally examined with a 10–22 MHz probe (Esaote MyLab Twice). A 6–18 MHz probe was used for both axillary arteries. In total, IMT measurement was performed at 800 sites. The mean IMT values of the different arteries were compared between controls and patients with active vasculitis of the corresponding artery by means of a Mann-Whitney test. ROC analysis was performed to determine the best cut-off value, balancing sensitivity and specificity, to discriminate between a normal and a vasculitic artery.

Results: Both groups consisted of 40 participants each and included 27 females. The mean age was 72 years (SD 9). Of the 40 GCA patients, 22 (55%) had indurated temporal arteries on clinical examination, 16 (40%) had symptoms of polymyalgia rheumatica. The mean duration of symptoms was 15 weeks (SD 19). Five patients (13%) had visual impairment (anterior ischaemic optic neuropathy, 3; amaurosis fugax, 1; diplopia, 1). Twenty-eight patients (70%) described headache; and 17 (43%) had jaw claudication. The mean ESR was 82 mm/h (SD ± 28); and the mean CRP was 107 mg/l (SD 79). In 26 patients (65%) the axillary arteries were involved of whom 9 had no involvement of temporal arteries. Table 1 shows IMT of affected arteries in GCA patients compared to controls and cut-off values for distinguishing normal from inflamed arteries.

Artery	Vasculitic arteries considered	IMT patients in mm (SD)	Control arteries considered	IMT controls in mm (SD)	Cut-off (mm)	Sensitivity	Specificity	Correctly classified
Common superficial temporal arteries	44	0.65 (0.18)	80	0.23 (0.04)	0.42	100%	100%	100%
Frontal branches	42	**0.54 (0.18)**	80	0.19 (0.03)	0.34	100%	100%	100%
Parietal branches	36	**0.50 (0.17)**	78	**0.20 (0.03)**	0.29	97.2%	98.7%	99.3%
Facial arteries	24	**0.53 (0.16)**	80	**0.24 (0.05)**	0.37	87.5 %	98.8%	96.2%
Axillary arteries	46	**1.72 (0.41)**	80	**0.59 (0.10)**	1.0	100%	100%	100%

Conclusion: IMT measurement of temporal, facial and axillary arteries can correctly distinguish vasculitic from normal arteries in suspected GCA in addition to morphological parameters. Data for wall diameters are needed for future longitudinal trials to monitor GCA treatment.

Abstract Number: 858

Is There a Place for Repetitive 18f-Fluorodeoxyglucose Positron Emission Tomography in Giant-Cell Arteritis with Large-Vessel Involvement?

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Background/Purpose: Positron emission tomography combined with computed tomography (PET/CT) with ^{18}F-fluorodeoxyglucose (FDG) can be used to assess large-vessel inflammation in giant-cell arteritis (GCA) and has demonstrated high sensitivity in detecting extra-cephalic forms of the disease, notably in patients without vascular-related symptoms. Few data exist on the merits of repeating this procedure as part of treatment monitoring during follow-up. It remains to be seen whether a repeated procedure during patient follow-up for GCA-related large-vessel involvement demonstrated on FDG-PET/CT is clinically helpful. Our aim was to determine the value of repetitive FDG-PET/CT in giant-cell arteritis (GCA) with large-vessel involvement.

Methods: We conducted a retrospective multicenter study between 2000 and 2015. Patients were included if 1) GCA was diagnosed according to the American College of Rheumatology criteria. 2) large-vessel involvement was demonstrated on FDG-PET/CT at diagnosis; 3) FDG-PET/CT was repeated at least once during follow-up. We separated the cohort into two groups, according to the indication of the repeated procedure, i.e. for evaluating vascular uptake in patients with disease remission or with disease relapse.

Results: Thirty-seven patients (24 [65%] women, median age: 68 [55-85]) with large-vessel inflammation on baseline FDG-PET/CT were included. During a median clinical follow-up of 50 [12-162] months, 63 new FDG-PET/CT were performed, including 34 scans in 25 patients with controlled disease and 29 scans in 22 relapsing patients. In patients with controlled disease, repeated FDG-PET/CT showed fewer involved vascular territories than on the previous one in only 15/34 (44%) scans (median involved territories: 2 [0-4] vs. 4 [1-6], respectively; $p<0.001$), including five (15%) with total disappearance of vascular uptakes, 12 [6-63] months after diagnosis. At the end of the study, 20 patients (80%) still had vascular uptakes on repetitive scans, which did not alter the therapeutic decision unless clinical symptoms and/or an elevated acute phase had resumed. Of the patients with disease relapse, the PET/CT showed increased number of vascular uptakes in 5 cases (17%), whereas the others showed reduced or unchanged vascular uptakes.

Conclusion: In patients with GCA-related large-vessel involvement, repetitive FDG-PET/CT during follow-up did not provide any reliable additional information, beside clinical and laboratory assessment. Therapeutic management was actually not influenced by the PET/CT results. A prospective study is required to confirm these findings.

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Abstract Number: 859

Long-Term Outcomes of Renal Artery Involvement in Takayasu Arteritis

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Long-term Outcomes of Renal Artery Involvement in Takayasu Arteritis

Background/Purpose: Takayasu arteritis (TA) involving the renal artery can result in hypertension, renal dysfunction, and premature death. Some patients with renal artery stenosis underwent revascularization procedures including stent insertion. The aim of this study was to investigate the long-term outcomes and factors that predict outcomes in TA patients with renal artery stenosis.

Methods: The medical records of patients diagnosed with TA between January 1997 and December 2014 were reviewed retrospectively. Renal artery involvement was based on CT and/or angiography findings. Poor outcome was defined as uncontrolled hypertension, chronic renal insufficiency, or death.

Results: Of the 62 TA patients with renal artery involvement, 11 (17.7%) underwent renal artery revascularization. Younger age, male gender, and more severe (>70%) stenosis were associated with vascular intervention. After a median follow-up of 90.6 months, 11 (17.7%) of the 62 patients had uncontrolled hypertension and six (9.7%) had chronic renal insufficiency, but these outcomes were not significantly associated with vascular intervention. Renal insufficiency (5/15 [33.3%] vs 3/47 [6.4%], p=0.016) and bilateral involvement (12/15 [80.0%] vs 23/47 [48.9%], p = 0.041) were significantly more frequent in patients with poor than good outcomes. Multivariate Cox analysis revealed that renal insufficiency at presentation (hazard ratio [HR]=13.778, 95% confidence interval [CI]=3.530–53.786; p=0.000) and bilateral renal artery involvement (HR=5.053, 95% CI=1.179–21.661; p=0.029) were significant risk factors for poor outcomes at follow-up, but revascularization procedure was not (HR=0.663, 95% CI=0.176–2.498; p=0.543) (Table 1).

Conclusion: Bilateral lesions and renal functional impairment at presentation, but not implementation of revascularization procedures, were significant factors for outcomes in TA patients with renal artery involvement.

Table 1. Multivariate analysis of clinical factors predictive of poor outcome in TA patients with renal artery involvement

	HR	95% CI	P-value
Renal impairment at presentation[a]	13.778	3.530–53.786	**0.000**
Bilateral involvement	5.053	1.179–21.661	**0.029**
Revascularization	0.663	0.176–2.498	0.543

[a]Renal insufficiency was defined as an estimated glomerular filtration rate < 60 ml/minute. CI: confidence interval; HR: hazard ratio.

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Abstract Number: 860

Assessment of the Frequency of Cardiovascular Risk Factors in Patients with Takayasu's Arteritis

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Background/Purpose: Accelerated atherosclerosis associated with chronic inflammation is one of the major complications of systemic inflammatory diseases. Takayasu arteritis (TAK) is a rare, systemic large-vessel vasculitis predominantly affecting the aorta and its major branches. The prevalence of atherosclerotic risk factors and cardiovascular (CV) disease in patients with TAK has not been well defined. The purpose of this study was to assess the frequency of CV risk factors and the incidence of CV events (CVE) in patients with TAK.

Methods: Patients fulfilling the 1990 American College of Rheumatology criteria for TAK from Mayo Clinic, Rochester, USA and Marmara University, Istanbul, Turkey were included in this retrospective cohort study. Data on CV risk factors at the time of TAK diagnosis and incident CVE during follow-up were abstracted from the medical records. Patients with TAK were compared to age, sex and calendar year–matched controls from the same geographic region without TAK. The 2008 Framingham 10-year general CV risk score (FRS) was used for the evaluation of CV risk at the time of TAK incidence/index date. For patients without lipid profiles, the office-based FRS, which does not require lipid values, was computed according to previously published algorithms.

Results: A total of 175 patients with TAK and 175 non-TAK controls were included in the study (115 from Mayo Clinic, 60 from Marmara University for each group). Among patients age ≥ 30 years at index date (107 TAK,109 non-TAK), complete data to calculate FRS were available in 93 (87%) TAK and 91 (83%) non-TAK subjects. Hypertension diagnosis and lipid-lowering treatment were significantly more frequent in the TAK group compared to non-TAK. Prior to the incidence/index date, the occurrence of CVE was significantly higher in the TAK group The overall Framingham 10-year CV risk score was significantly higher in the TAK group compared to non-TAK at incidence/index date (Table 1). After excluding patients with prevalent CVE, 18 TAK and 3 non-TAK patients developed CVE during a mean follow-up of 7.4 years in TAK and 7.9 years in non-TAK groups. The cumulative incidence of CVE was 16.4% at 10 years in TAK group vs. 6.0% in non-TAK group and the risk of CVE was increased among patients with TAK (hazard ratio: 4.52; 95% CI: 1.29, 15.78 adjusted for age, sex and country).

Table 1: Baseline characteristics of TAK and non-TAK cohorts in index dates.

	TAK (n=175)	Non-TAK (n=175)	P value
Age (Years)*	34.1±32.7	34.9±32.9	0.70
Sex (female/male)	157 / 18	160 / 15	0.58
Hypertension, n (%)	69 (40%)	22 (13%)	**<0.001**
Diabetes mellitus, n (%)	12 (7%)	8 (5%)	0.35
Lipid profile (mg/dl)*			
Total cholesterol, mg/dL	200±50 (n=113)	190±37 (n=60)	0.23
Low density lipoprotein, mg/dL	119±42 (n=101)	108±35 (n=51)	0.12
High density lipoprotein, mg/dL	52±17 (n=103)	54±15 (n=53)	0.50
Triglycerides, mg/dL	137±90 (n=108)	126±96 (n=60)	0.13
Lipid lowering treatment, n (%)	22 (13%)	7 (4%)	**0.004**
Obesity (BMI >30 kg/m^2), n, (%)	32 (22%)	37 (23%)	0.78
Smoking status, ever, n, (%)	80 (47%)	70 (41%)	0.36
Framingham risk score, %†	3.6 (2.2-10)	2 (1.2-5)	**0.001**
Any prior atherosclerotic vascular event	37 (21%)	6 (3%)	**<0.001**

*Mean ±SD †Median (Interquartile range); BMI, body mass index; n = number; SD = standard deviation; TAK = Takayasu arteritis; bolded p-values statistically significant at <0.05

Conclusion: CV risk factors are more common in patients with TAK, and the Framingham 10-year cardiovascular risk score is higher in patients with TAK at the time diagnosis compared to non-TAK subjects of similar age and sex. The cumulative incidence of CVE was also significantly higher during follow-up in the TAK group. Patients with TAK should undergo careful assessment of CV risk factors, and an aggressive risk modification approach is warranted.

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Abstract Number: 861

Efficacy of Methotrexate in Giant Cell Arteritis

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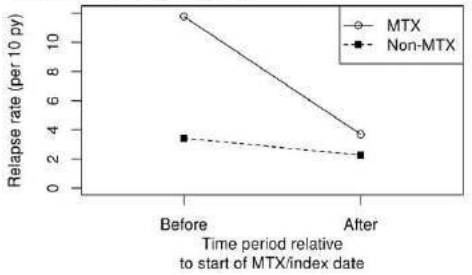
Background/Purpose: Prospective trials evaluating methotrexate (MTX) as adjunct immunosuppression in giant cell arteritis (GCA) have provided evidence of a modest benefit for reducing risk of relapse and decreasing glucocorticoid (GC) use. Limited information is available regarding the use of MTX in routine clinical practice. The purpose of this study was to determine the effect of MTX on relapse risk and GC use in a large, single-institution cohort of patients with GCA.

Methods: A retrospective review of patients diagnosed with GCA from 1998-2013 was performed. Patients diagnosed with GCA were ≥ 50 years and had either a temporal artery biopsy (TAB) that was consistent with GCA or radiographic evidence of large-vessel vasculitis. Each patient with GCA treated with adjunct MTX (case) was matched to a similar GCA patient without MTX (control). Cases and controls were matched on age, sex, disease duration at start of MTX and initial GC dose. Each control was assigned an index date that matched the start date of MTX in cases. Baseline demographics, disease characteristics and relapse events were abstracted. GC requirements and relapse events before and after MTX initiation (or corresponding index date) were compared using rate ratios.

Results: A total of 84 patients with GCA receiving MTX were identified and compared to 84 patients with GCA receiving only prednisone. Mean age at diagnosis 69.5±7.0 years in cases and 70.3±6.9 in controls. No significant differences in demographics, laboratory parameters or baseline disease characteristics were observed between groups. Mean initial prednisone doses were similar (53.5±15.8 mg/day in cases, 55.0±13.5 mg/day in controls). The median (interquartile range [IQR]) time from GCA diagnosis to MTX initiation in cases was 0.7 (0.3, 1.6) years and the median (IQR) starting dose was 13.5 (10, 15) mg per week.

Prior to MTX initiation the observed relapse rate was 11.8 relapses per 10 person-years and decreased to 3.69 relapses per 10-person years following initiation. The rate ratio comparing relapse rates observed after MTX to the rate prior to MTX initiation was significantly reduced; rate ratio (95% CI): 0.31 (0.24, 0.41). In the control group the relapse rate was 3.42 relapses per 10 person-years before the index date and 2.27 relapses per 10 person-years following the index date [rate ratio (95% CI); 0.66 (0.45, 0.99). Although both groups had a reduction in relapse rate ratios, the rate of decrease in relapse rate was significantly greater in patients on MTX than those not on MTX (p=0.002) [Figure]. Patients receiving MTX discontinued GC significantly later than patients without adjuvant MTX (p=0.014).

Figure: Rate of decrease in relapse rate is greater in patients on methotrexate (MTX) than those not on MTX (interaction p=0.002).



Conclusion: In this large single-institution cohort, the addition of MTX to GC decreased the rate of subsequent relapse by 2-fold compared to patients on GC alone. MTX should be considered as adjunct therapy in patients with relapsing GCA to decrease the risk of further relapse events.

Disclosure: M. J. Koster, None; **C. S. Crowson**, None; **C. Labarca**, None; **F. Muratore**, None; **K. J. Warrington**, None.

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Utility of 18f FDG Positron Emission Tomography (PET) As a Diagnostic Test and Marker of Disease Activity in Large Vessel Vasculitis

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Background/Purpose: FDG-PET may have a role in diagnosing and monitoring disease activity in large vessel vasculitis (LVV). Studies that assess the diagnostic accuracy of PET in LVV often use patients with cancer as a comparator group. There are limited data regarding use of serial FDG-PET imaging to monitor disease activity, and most assessments are performed during periods of clinically apparent disease. This study assesses the diagnostic performance of PET to differentiate LVV from mimics of vasculitis, examines the role of PET as a measure of disease activity, and determines the clinical characteristics associated with abnormal vascular FDG uptake.

Methods: 42 patients with LVV and 50 comparators (15 with systemic inflammation, 35 with atherosclerosis) were recruited in this prospective, observational cohort. Patients with LVV underwent FDG-PET every 6 months. Clinical and imaging assessments were performed blinded to each other and to levels of acute phase reactants. FDG-PET/CT was performed with 120 min uptake time (256 matrix, 3 mm slice). Active vasculitis on PET was defined by agreement of two nuclear medicine experts and inter-rater agreement was assessed by the kappa statistic. Multivariable regression, adjusted for repeated measures, assessed associations between active vasculitis on PET and clinical characteristics.

Results: 125 FDG-PET scans were performed in 92 patients: giant cell arteritis (n=22; mean age 68.4±9.4 years; disease duration 2.4±2.5 years), Takayasu arteritis (n=20, mean age 34.9±11.2 years; disease duration 13.4±11 years) and comparators (n=50, mean age 53.6±15.3 years). Inter-rater agreement was high (kappa = 0.84). In patients with LVV with clinically active disease, the performance characteristics of PET as a diagnostic test were good (sensitivity 90%; specificity 86%); however, 17% of patients with atherosclerosis had PET scan findings indistinguishable from active vasculitis. 26 of 45 PET scans (58%) performed in patients with LVV during apparent clinical remission suggested ongoing active vasculitis. Clinically apparent active disease and shorter disease duration were significantly associated with an abnormal PET scan. There was no association between levels of acute phase reactants and PET abnormalities; treatment with immunomodulating medications had a non-statistically significant protective effect (Table).

Conclusion: FDG-PET is useful to distinguish active LVV from mimics of vasculitis, but patients with atherosclerosis can have PET scan findings that closely resemble LVV. The majority of patients with LVV have abnormal PET scans while in clinical remission. An inverse association between disease duration and PET abnormalities suggests that scan abnormalities observed during clinical remission are not due to accrued vascular damage. FDG-PET may be an important modality to detect and monitor subclinical inflammation in LVV.

Table: Clinical Predictors of Abnormal FDG-PET Scan in Large Vessel Vasculitis

	Univariable		Multivariable	
	Odds Ratio	**P value**	**Odds Ratio**	**P value**
Disease Status (Active vs. Remission)	6.58 (1.74 – 24.90)	<0.01	9.29 (1.89 – 45.68)	<0.01
Disease Duration (Per year)	0.99 (0.99-1.00)	0.02	0.99 (0.99 – 1.00)	0.03
Diagnosis (GCA vs. TAK)	2.38 (0.86 – 6.67)	0.09	7.32 (0.35 – 151.69)	0.20
Age (Per Year)	1.02 (0.01 – 2.74)	0.10	1.05 (0.98 – 1.12)	0.20
Prednisone (Per 1mg / day)	0.99 (0.96 – 1.03)	0.72	0.96 (0.92 – 1.01)	0.10
Other Immune Medications (Yes vs. No)	0.56 (0.11 – 1.61)	0.28	0.56 (0.15 – 2.13)	0.39
Sex (Male vs. Female)	2.13 (0.62 – 7.25)	0.23	Not included in Multivariable model	
Patient Global Assessment (Range 0-10)	1.11 (0.90 – 1.38)	0.32		
Fibrinogen (Per 10)	1.02 (0.99 - 1.07	0.50		
ESR (Per 10 mm/h)	1.06 (0.92 – 1.35)	0.67		
CRP (Per 10 mg/L)	1.02 (0.91 - 1.26)	0.85		
Endothelin 1 (Per 1 mg/dl)	0.99 (0.88 – 1.12)	0.86		

GCA: giant cell arteritis; TAK: Takayasu's arteritis;
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

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Abstract Number: 863

Arterial Lesions in Giant Cell Arteritis

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SESSION INFORMATION

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Background/Purpose: This study aimed to describe large arterial lesions among patients with giant cell arteritis (GCA) and to understand what clinical characteristics are associated with development of new arterial lesions during follow-up.

Methods: Patients with GCA enrolled in a prospective, multicenter, longitudinal study and/or a clinical trial were included. All patients were followed with standardized clinical assessments, including data from arterial imaging (stenoses, occlusions, aneurysms, and dissections). New lesions were defined as any new findings in a previously unaffected arterial segment.

Results: Data on imaging of the aorta and its branches were available for 187 patients with GCA: 146 (78%) female, mean (±SD) age at diagnosis 68.5 (±8.5) years. Mean (±SD) duration of follow-up was 3.8 (±2.3) years. Disease duration at entry into the cohort was within 1 year for 124 subjects (56%). At least one arterial lesion was present in 110 (58%) patients on entry into the cohort; 72 patients (65%) with disease duration <1 year. Subclavian (62 patients, 33%) and axillary arteries (47 patients, 25%) were the most frequently involved (**Table 1**). Serial imaging was available in 108 (58%) of the entire cohort; 76 (69%) of 110 with any lesion at baseline. Median (range) number of imaging studies was 3 (1-10). New arterial lesions were noted in 39 (36%) with new axillary and/or subclavian artery involvement being the most frequently observed (**Table 1**). Only 33% of 18 patients with new subclavian and/or axillary lesions had symptoms of upper extremity claudication since the prior visit or at the time of the visit. Clinical symptoms of any active disease since the last visit or at the day time of the visit were present only in 14 of the 56 visits (25%) where a new angiographic lesion was first reported. There were no differences in age, sex, disease duration, duration of follow-up, or presence of any disease activity during follow-up between patients with and without new lesions (**Table 2)**. Medication use including adjunctive immunosuppressive treatment at last follow-up is in **Table 2.**

Conclusion: New arterial lesions on serial imaging are common in patients with GCA, especially among patients with established large-vessel involvement. The majority of new lesions identified through use of serial angiography occur in patients who do not have symptoms of active disease at the time new findings were noted. Additional studies are needed to further understand the role of serial imaging, significance of new arterial lesions, and impact of treatment on large-vessel disease in patients with GCA.

Table 1: Distribution and frequency of arterial involvement at first and on follow-up imaging in patients with giant cell arteritis

Arterial Territory	Number of patients with any involvement on baseline imaging (Total = 187)	Number of patients with any *new* lesions on follow-up imaging (Total = 108)
Thoracic Aorta (overall)	20	6
· Thoracic Root	13	6
· Arch	6	2
· Descending Thoracic Aorta	6	1
Abdominal Aorta (overall)	6	1
· Suprarenal Abdominal Aorta	2	0
· Infrarenal Abdominal Aorta	6	1
Common carotid	13	9
External Carotid	3	2
Internal Carotid	16	4
Vertebral	17	4
Innominate	7	4
Subclavian	62	16
Axillary	47	15
Mesenteric	14	6
Renal	20	6
Iliac	15	5

Table 2: Comparison of patients with giant cell arteritis with and without new arterial lesions on follow-up imaging.			
Variable	**New lesions (N=39)**	**No new lesions (N=69)**	**p-value**
Mean age	67.4 years	67.0 years	0.78
Mean disease duration	1.42 years	1.43 years	1.0
Disease duration ≤1 year	14 (36%)	25 (37%)	1.0
Mean duration of follow-up	4.0 years	4.2 years	0.44
Female	33 (85%)	60 (87%)	0.78
Positive biopsy	14/17 (82%)	32/45 (71%)	0.52
Median number studies	4.5 (1-10)	2.5 (2-7)	<0.01
Any lesion at first imaging	37 (95%)	48 (70%)	<0.01
Any activity	14 (35%)	29 (42%)	0.55
Aspirin use at last follow-up	25 (64%)	31 (45%)	0.07
Prednisone use at last follow-up	33 (85%)	34 (49%)	<0.01
Methotrexate use at last follow-up	10 (24%)	12 (17%)	0.33
Azathioprine use at last follow-up	2 (5%)	2 (3%)	0.62

Disclosure: **T. A. Kermani**, GlaxoSmithKline, 2; **S. Diab**, None; **A. Sreih**, Bristol-Myers Squibb, 2,Celgene, 2,Chemocentryx, 2,Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Krog and Partners, 5; **D. Cuthbertson**, None; **R. Borchin**, None; **S. Carette**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2; **L. J. Forbess**, None; **G. S. Hoffman**, None; **C. L. Koening**, None; **C. A. McAlear**, None; **P. A. Monach**, Genentech and Biogen IDEC Inc., 2,Bristol-Myers Squibb, 2,MedScape, 5,GlaxoSmithKline, 2,Vasculitis Foundation Board of Directors, 6,Editorial Board of Arthritis and Rheumatology, 6; **L. W. Moreland**, Genentech and Biogen IDEC Inc., 2,Pfizer Inc, 2,questcor, 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 5,Boehringer Ingelheim, 5,Acerta, 5,CVS/Caremark, 5,Smith Kline Beecham, 5; **C. Pagnoux**, Chemocentryx, 5,Chemocentryx, 9,Roche Pharmaceuticals, 9,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,Hoffmann-La Roche, Inc., 8; **P. Seo**, None; **R. F. Spiera**, GlaxoSmithKline, 2,Roche Pharmaceuticals, 2,Boehringer Ingelheim, 2,PRISM, 2,Cytori, 2,Corbus Pharmaceuticals, 2,GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Boehringer Ingelheim, 5,Bristol-Myers Squibb, 2; **K. J. Warrington**, GlaxoSmithKline, 2; **S. R. Ytterberg**, Sanofi-Aventis Pharmaceutical, 5; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Bristol-Myers Squibb, 2; **N. A. Khalidi**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **P. A. Merkel**, Bristol Myers Squibb, 2,CaridianBCT, 2,Celgene, 2,Chemocentryx, 2,Genentech/Roche, 2,GlaxoSmithKline, 2,Kypha, 2,Bristol-Myers Squibb, 5,Chemocentryx, 5,Genentech/Roche, 5,GlaxoSmithKline, 5,PrinicipioBio, 5,Auven, 5,Proteon Therapeutics, 5.

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Takayasu Arteritis Developed over the Age of 40 Has Lower Levels of Interferon Gamma and Interleukin 17 at Disease Onset and Fewer Subsequent Relapses

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SESSION INFORMATION

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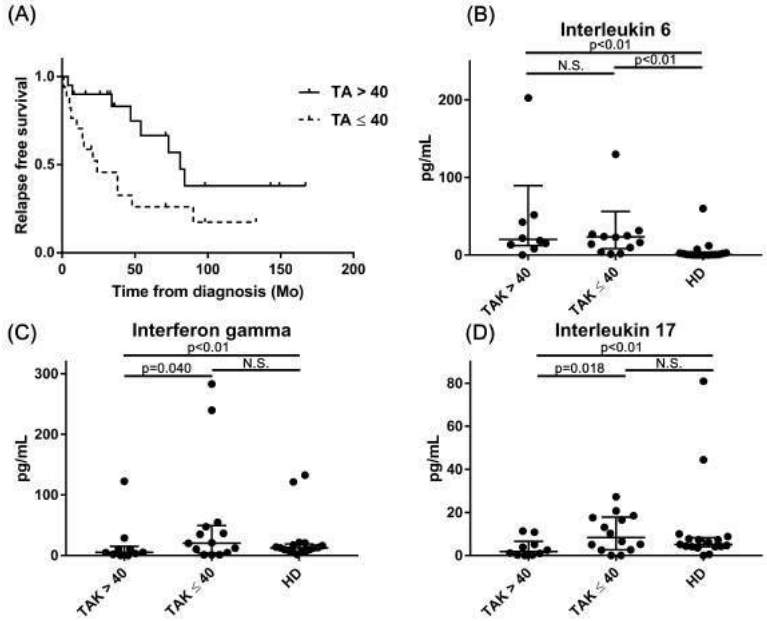
Background/Purpose: The American College of Rheumatology 1990 criteria for the classification of Takayasu arteritis (TAK) include age at disease onset ≤ 40 years. We aimed to investigate the clinical characteristics of TAK that developed over the age of 40 (TAK > 40).

Methods: We retrospectively analyzed 43 patients with TAK in three foundation hospitals from April 2000 to March 2016. We collected baseline variables at diagnosis including clinical symptoms and laboratory data, and subsequent relapses using medical records. We compared the above indices of TAK > 40 to those of TAK ≤ 40 years old at disease onset (TAK ≤ 40). Multiplex cytokine/chemokine bead assays were performed using preserved sera supernatants of 24 patients with TAK at disease onset (10 TAK > 40 and 14 TAK ≤ 40) of total 43 patients and Milliplex MAP Human Cytokine/Chemokine Panel 1 Pre-mixed 41Plex (Merck Millipore, Darmstadt, Germany) analyzed with a Bio-Plex® MAGPIX™ Multiplex Reader (Bio-Rad, Hercules, CA). Seventeen sera samples of healthy donors (HD) were used to compare to sera of patients with TAK.

Results: Of 43 patients, twenty patients were TAK > 40. TAK > 40 had significantly fewer orthostatic hypotension, carotid bruit and chest pain at disease onset compared to TAK ≤ 40 (2 [10%] (TAK > 40) vs. 10 [43%], p=0.019, 7 [35%] vs. 16 [70%], p=0.034, 0 [0%] vs. 6 [26%], p=0.023). There are no differences in C reactive protein, erythrocyte sedimentation rate, angiographic classification types, frequency of positive HLA-B52, chronic renal diseases, surgical interventions and aortic regurgitation in both groups. Initial prednisolone dose was lower in TAK > 40 [median, 30 mg vs. 40mg per day, p=0.024]. Body weight at disease onset and tapering speed of prednisolone were not different in both groups. Assessed by a log-rank test, the relapse free survival rate after remission was significantly higher in TAK > 40 (p=0.029) (Figure 1A). Median interleukin 6 levels of TAK > 40, TAK ≤ 40 and HD were 26.9 pg/mL, 23.4 pg/mL and 0.7 pg/mL, respectively (TAK > 40 vs. HD: p<0.01, TAK ≤ 40 vs HD: p<0.01, TAK > 40 vs. TAK ≤ 40: p=0.98) (Figure 1B). Median interferon gamma levels were 3.1 pg/mL, 20.5 pg/mL and 12.6 pg/mL, respectively (TAK > 40 vs. HD: p<0.01, TAK ≤ 40 vs HD: p=0.77, TAK > 40 vs. TAK ≤ 40: p=0.040) (Figure 1C). Median interleukin 17 levels were 1.1 pg/mL, 8.4 pg/mL and 5.1 pg/mL, respectively (TAK > 40 vs. HD: p<0.01, TAK ≤ 40 vs HD: p=0.77, TAK > 40 vs. TAK ≤ 40: p=0.018) (Figure 1D).

Conclusion: Our study suggested that TAK > 40 years old can be treated with lower prednisolone dose for remission and had fewer relapses after remission compared to TAK ≤ 40. Decreased levels of interferon gamma and interleukin 17 at disease onset were seen in TAK > 40. Difference of cytokine profiles at disease onset may associate with clinical characteristics of TAK > 40.



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Abstract Number: 865

Poor Predictive Value of Isolated Adventitial and Periadventitial Infiltrates in Temporal Artery Biopsies for Diagnosis of Giant Cell Arteritis

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Background/Purpose: Histological findings of intima-media or transmural inflammation in temporal artery biopsies (TABs) have undisputed high value for diagnosis of giant cell arteritis (GCA). Conversely, the diagnostic significance of isolated adventitial or periadventitial cell infiltrates (e.g., inflammation limited to the adventitia [ILA], vasa vasorum vasculitis [VVV], and small vessel vasculitis [SVV])-remains unclear. We investigated the diagnostic value of isolated ILA, VVV or SVV in TABs for GCA and for the combined GCA/polymyalgia rheumatica (GCA/PMR) spectrum because of the close clinical connection of GCA and PMR.

Methods: All TABs performed in a single center over 7 years (2009–2015) were independently reviewed by 2 experienced pathologists blinded to the clinical diagnoses and with particular attention to isolated (peri)adventitial cell infiltrates. VVV was defined as a perivascular infiltrate within or in close contact with the adventitia and SVV as infiltrates of a periadventitial vessel. Medical charts were reviewed and diagnoses were classified as GCA, PMR and other by the final clinical diagnosis, with a follow-up of at least 6 months, as the gold standard. For TABs that did not show a classical histological picture of GCA with intima-media or transmural inflammation, we calculated the specificity and positive predictive value (PPV) of ILA, VVV or SVV for GCA and for GCA/PMR diagnoses. These variables were calculated for findings observed by at least 1 or by both pathologists. Cohen's kappa statistics were used to measure inter-observer agreement.

Results: We analyzed TABs for 100 patients; 6 were discarded because they did not allow for proper morphologic analysis of all vessel layers and 19 had classical histological features of GCA. For the remaining 75 TABs (mean age of patients, 69±12 years, 59% female), the diagnosis was GCA (n=8), PMR (n=7) and non-GCA/PMR (n=60). The frequency of (peri)adventitial TAB findings and their respective specificities and PPV for clinical diagnosis of GCA or GCA/PMR are in the Table. Inter-observer agreement was good for ILA (kappa 0.63 [95% CI 0.42–0.84]) and fair for SVV (0.31 [95% CI 0.09–0.52]) and VVV (0.21 [95% CI -0.01–0.43]).

	GCA (n=8) vs. non-GCA (n=67)			**GCA/PMR (n=15) vs. non-GCA/PMR (n=60)**		
	Frequency	Spec (95% CI)	PPV (95% CI)	Frequency	Spec (95% CI)	PPV (95% CI)
ILA						
At least 1 reader	2/8 vs. 10/67	85% (74–93)	17% (2–48)	4/15 vs. 8/60	87% (75–94)	33% (10–65)
Both readers	1/8 vs. 5/67	93%(84–96)	17% (0–64)	1/15 vs. 5/60	92% (82–97)	17% (0–64)
VVV						
At least 1 reader	0/8 vs. 7/67	90% (80–96)	0% (0–41)	0/15 vs. 7/60	88% (77–95)	0% (0–41)
Both readers	0/8 vs. 1/67	99% (92–100)	0% (0–98)	0/15 vs. 1/60	98% (91–100)	0% (0–98)
SVV						
At least 1 reader	2/8 vs. 27/67	60% (47–72)	7% (1–23)	7/15 vs. 22/60	63% (50–75)	24% (10–44)
Both readers	1/8 vs. 8/67	88% (78–95)	11% (0–48)	4/15 vs. 5/60	92% (82–97)	44% (14–79)

ILA: isolated inflammation of the adventitia, PPV: positive predictive value, Spec: specificity, SVV: small vessel vasculitis, VVV: vasa vasorum vasculitis

Conclusion: Isolated (peri)adventitial infiltrates in a TAB do not reliably predict a diagnosis of GCA and should not be considered relevant GCA-defining histological criteria. More general consensus is needed on the histological criteria defining GCA.

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Abstract Number: 866

Perivascular Inflammation in Temporal Artery Biopsies That Are Negative for Arteritis: Incidental or Harbinger?

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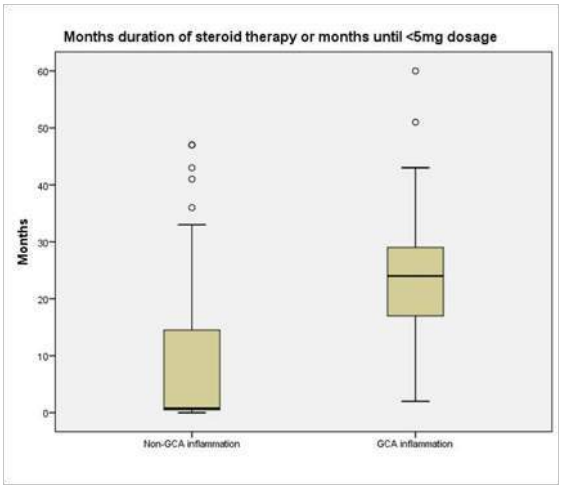
Background/Purpose: The diagnosis of giant cell arteritis (GCA) by temporal artery (TA) biopsy requires pathologic identification of arterial inflammation, usually with giant cells. However, some biopsies may show lymphocytic infiltrates without arterial involvement (nonGCA-i). The prognostic significance of these findings is uncertain and virtually no long term follow-up studies have been done.

Methods: We identified 218 TA biopsies performed from 2010-2012 and 123 were available for blind slide review by a pathologist (RLH). Of these cases, 88 had medical records reviewed for long-term outcome. Chart review included: demographics, comorbidities, clinical presentation (constitutional symptoms, craniofacial symptoms, PMR symptoms, change in vision), and laboratory parameters. Using SPSS software, the associations between two categorical variables were analyzed with Chi-Square or FisherÕs Exact test. Mann-Whitney U test was used to analyze continuous variables.

Results: Based on assessment of symptoms at presentation and during long-term follow-up, patients with nonGCA-i were significantly less likely to have constitutional symptoms, craniofacial symptoms, CRP elevation, and vision loss ($P<0.05$). The frequency of temporary or permanent vision loss of any etiology among the 3 groups was as follows: 8/18 (44.4%) patients with TA biopsy positive for GCA, 1/34 patients with nonGCA-i, (2.9%) and 5/35 (14.3%) patients with negative TA biopsy. There was a trend towards less PMR among patients with nonGCA-i ($P=0.088$). The frequencies of the 3 groups meeting the 1990 ACR classification criteria (excluding biopsy result) were as follows: 16/18 (88.8%) patients with TA biopsy positive for GCA, 25/35 (71.4%) patients with nonGCA-i, and 19/35 (54.3%) patients with negative TA biopsy. Patients with nonGCA-i received a shorter duration of corticosteroids compared to those with positive TA biopsy ($P = 0.001$). While 13/33 (39.4%) patients with non-GCA-i and 13/35 (37.1%) patients with negative biopsy were treated with steroids for at least 4 months, all 14 patients with TA biopsy positive for GCA were treated for at least 4 months (excluding patients lost to follow-up or deceased).



Conclusion: In this cohort, patients with nonGCA-i rarely developed clinically evident GCA-like symptoms requiring corticosteroid therapy >= 4 months. Most importantly, patients with nonGCA-i did not develop complications of visual loss acutely or in long-term follow-up. Based on our findings, nonGCA-i in a temporal artery biopsy is an incidental finding and is not a harbinger of GCA clinically, even with long-term followup. Treatment on the basis of nonGCA-i alone may expose the patient to unnecessary corticosteroids. No new cases of GCA were identified in the pathological review. However, dose and duration of corticosteroid therapy for patients with nonGCA-i should always be guided by clinical judgement.

Disclosure: Y. Zarbalian, None; **K. P. Liang**, None; **R. L. Hamilton**, None; **L. Wang**, None; **D. Winger**, None.

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Abstract Number: 867

Termination of Tocilizumab-Treatment in Giant Cell Arteritis: Follow-up of Patients after the RCT (ClinicalTrials.gov registration number: NCT01450137)

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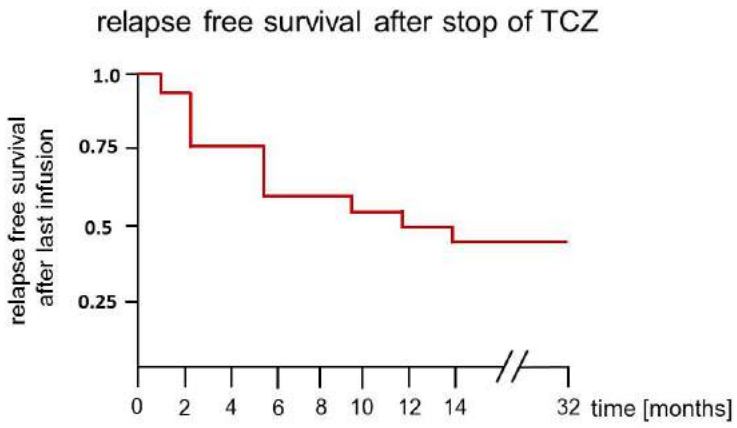
Background/Purpose: As published in The Lancet online, March 4, 2016, the first RCT about tocilizumab (TCZ) in GCA showed clinical efficacy of the anti-IL-6 biologic agent in the induction and maintenance of remission for up to 52 weeks. This study analyzed the long-term outcome after termination of the RCT.

Methods: 30 patients with Giant Cell Arteritis (GCA) were randomized in this RCT in a 2:1 ratio into receiving intravenously (i.v.) TCZ 8mg/kg bodyweight plus Glucocorticoids (GC) or Placebo (PB) plus GC. They received infusions in 4-weekly intervals for 52 weeks. Thereafter TCZ medication was stopped, further treatment was prescribed by the treating physicians, patients were followed up clinically.

Results: By week 52 of the RCT all patients of the TCZ arms were in sustained complete remission, of these 18 without GC co-medication. 2/20 patients received GC after the last infusion due to premature stop of TCZ, one patient with Stevens-Johnson-syndrome and one with diverticulitis. Median follow-up time was 12.5 months (range 3-32). After the last infusion of TCZ 11/20 patients relapsed with a median time to relapse of 5 months (range 2-14). In the placebo arm all but one patient relapsed and/or continued GC treatment. Remarkably, 1/10 PB patients remained in remission throughout the study and was without medication at last follow-up, 10 months after the end of study. None of the relapsing patients experienced blindness, aortic rupture, aortic stenosis or other major vascular complications. In case of

relapse, dose of GC was 1mg/kg bodyweight in signs of major relapse and 20-40 mg/d in minor relapse according to the average dose during the study period that was sufficient to control symptoms in PB patients prior to relapse. Additionally, in 6/11 TCZ patients relapsing after the last study infusion, TCZ was re-administered with 8mg/kg bodyweight i.v. in monthly intervals after a median time of 6.5 months (range 3-14). In 2/6 patients with TCZ re-introduction, TCZ was stopped after 4 and 6 months, respectively, with lasting remission. In 1/6 patients TCZ was again given for 2 months, stopped in remission yet had to be re-introduced 6 months later due to a second relapse.

Conclusion: Clinical and serologic remission in response to TCZ for 52 weeks does not result in relapses-free survival after termination of treatment. Although IL-6 blockade using TCZ controls clinical disease, it may not control pathogenesis in all cases. The fact that 45% of patients remained in lasting remission may help to design treatment protocols to determine appropriate maintenance dosage regimens of TCZ after achievement of remission.



Disclosure: S. Adler, None; **S. Reichenbach**, None; **S. Kuchen**, None; **F. Wermelinger**, None; **D. Dan**, None; **M. Seitz**, None; **P. M. Villiger**, None.

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Abstract Number: 868

Infections and the Risk of Incident Giant Cell Arteritis: A Population-Based, Case-Control Study

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Vasculitis - Poster I: Large Vessel Vasculitis and Polymyalgia Rheumatica

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Background/Purpose : Alterations in the immune system and infections are suspected to increase susceptibility to giant cell arteritis (GCA). Recently herpes zoster has been raised as a potential candidate pathogen for GCA. We examined the association between prior infections, in particular herpes zoster, and incident GCA in a population-based cohort.

Methods : A nested case-control study was performed using The Health Improvement Network (THIN) database, an electronic database originating from general practices in the United Kingdom. Cases with newly-diagnosed GCA were identified using a validated algorithm and compared to age-, sex-, and practice-matched controls using incidence density sampling. Patients with a prior diagnosis of polymyalgia rheumatica were excluded. Infections, including herpes zoster, that occurred prior to the onset of GCA were identified using diagnostic codes. Conditional logistic regression was used to examine the relationship between any infection or herpes zoster infection on the development of GCA and expressed as incidence rate ratios (IRR). All analyses were adjusted for prior use of glucocorticoid and non-glucocorticoid immunosuppressive therapies, alcohol use, smoking history, and the Charlson Comorbidity Index. Patients were analyzed according to the time period prior to index date in which the infection occurred to determine if recent infections were more strongly associated with GCA compared to earlier infections. A sensitivity analysis excluding patients who previously received at least 1 prescription for an oral glucocorticoid or immunosuppressive medication was performed.

Results : There were 4,559 cases of GCA and 22,795 controls. Any prior infection and herpes zoster was associated with incident GCA (IRR 1.26 [1.16, 1.36] and 1.17 [1.04, 1.32], respectively) (**Table 1**). A greater number of infections was associated with a higher risk of developing GCA. A sensitivity analysis excluding patients who received immunosuppressive medications produced similar results. The risk of developing GCA was greatest among those who experienced an infection within a year of the index date but was also significantly associated with infections that occurred in earlier time periods (**Table 2**).

Conclusion : Antecedent infections and, to a lesser extent, herpes zoster infections are modestly associated with incident GCA. These data provide population-level support for the hypothesis that longstanding alterations of the immune system are associated with susceptibility to GCA and suggest that herpes zoster is unlikely to play a major causal role in the pathogenesis of GCA.

Table 1: The Association of Infections with Incident Giant Cell Arteritis

Exposure	Unadjusted IRR (95% CI)	*P*-value	Adjusted IRR (95% CI)*	*P*-value
Herpes zoster infection	1.24 (1.10, 1.39)	< 0.01	1.17 (1.04, 1.32)	< 0.01
Herpes zoster infection AND antiviral therapy	1.16 (0.99, 1.36)	0.05	1.09 (0.93, 1.28)	0.27
Any infection	1.44 (1.34, 1.56)	< 0.01	1.26 (1.16, 1.36)	< 0.01
Number of infections	1 (reference)	--	1 (reference)	--
0	1.38 (1.27, 1.50)	< 0.01	1.28 (1.18, 1.40)	< 0.01
1	1.88 (1.71, 2.08)	< 0.01	1.60 (1.44, 1.77)	< 0.01
2-4	2.94 (2.58, 3.36)		2.18 (1.90, 2.51)	< 0.01
5 or more				
	Test for trend	< 0.01	*Test for trend*	< 0.01

*Adjusted for Charlson Comorbidity Index, alcohol use, smoking history, prior use of immunosuppressive therapies, and prior use of oral glucocorticoids if applicable.

IRR = incident rate ratio; CI = confidence interval.

Table 2: The Association of Any Infection and Herpes Zoster Infection with Incident Giant Cell Arteritis Stratified by Time Period Prior to Index Date

	Any Infection		Herpes Zoster Infection	
	Adjusted IRR (95% CI)*	*P*-value	Adjusted IRR (95% CI)*	*P*-value
<1 year	1.66 (1.54, 1.79)	< 0.01	1.32 (0.95, 1.82)	0.10
1-2 years	1.32 (1.22, 1.43)	< 0.01	1.11 (0.79, 1.56)	0.55
2-3 years	1.19 (1.09, 1.29)	< 0.01	1.00 (0.70, 1.43)	0.99
3-4 years	1.19 (1.09, 1.30)	< 0.01	0.92 (0.63, 1.36)	0.69
4-5 years	1.14 (1.05, 1.25)	< 0.01	1.15 (0.77, 1.70)	0.49
5-10 years	1.26 (1.17, 1.35)	< 0.01	1.36 (1.14, 1.64)	< 0.01
> 10 years	1.22 (1.13, 1.32)	< 0.01	1.18 (0.99, 1.42)	0.07

* Adjusted for Charlson Comorbidity Index, alcohol use, smoking history, prior use of immunosuppressive therapies, and prior use of oral glucocorticoids.

IRR = incident rate ratio; CI = confidence interval.

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Abstract Number: 869

Low Numbers of CD16+ Monocytes Predict Shorter Time to Relapse in Polymyalgia Rheumatica

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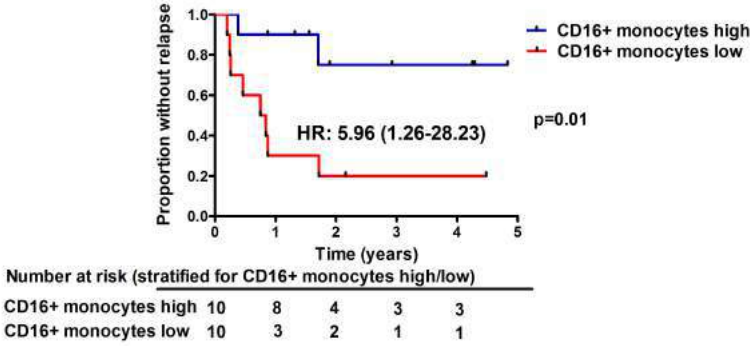
Background/Purpose: Polymyalgia rheumatica (PMR) is the most frequent inflammatory disorder in persons older than 50 years of age. Biomarkers like ESR and CRP may be associated with a relapse [1-2] but are not disease-specific. Monocytes play an important role in the pathogenesis of PMR and are detected in inflamed tissues (synovia and bursa) of PMR patients. The expression of CD16 (FcR-III) identifies pro-inflammatory monocytes that increase with age, produce IL-6, and are prone to migrate to areas of tissue damage [3]. We hypothesized that down-modulation of peripheral CD16+ monocytes is associated with an emerging relapse in PMR.

Methods: Twenty consecutively recruited, newly-diagnosed, steroid naïve PMR patients fulfilling the Chuang/Hunder criteria were included. Patients were prospectively followed for a median of 3.12 years (range 0.87-4.83 years). Relapses were defined as recurrence of PMR signs and symptoms associated with an increase in ESR (>30mm/h) and/or CRP (>10mg/L) which could not be explained otherwise. Peripheral CD16+ monocytes were enumerated by flowcytometry. Patients were divided into 2 groups based on the median value of CD16+ monocyte counts.

Results: ESR was significantly higher in the group with low CD16+ monocytes compared to the group with high CD16+ monocytes. Therefore, the relation between the numbers of CD16+ monocytes and the ESR was examined and a significant inverse correlation was found (Spearman's rho=-0.51, $p<0.05$). Also, PMR patients with low CD16+ monocyte counts were 6-fold more likely to relapse than patients with high CD16+ monocyte counts (HR: 5.96) (Figure 1).

Conclusion: PMR patients with low CD16+ monocyte counts demonstrated a shorter time to relapse. **References** 1. Kremers HM, Reinalda MS, Crowson CS, Zinsmeister AR, Hunder GG, Gabriel SE. Relapse in a population based cohort of patients with polymyalgia rheumatica. J. Rheumatol. 2005;32(1):65-73 2. Salvarani C, Cantini F, Niccoli L, et al. Acute-phase reactants and the risk of relapse/recurrence in polymyalgia rheumatica: A prospective followup study. Arthritis Care Res. 2005;53(1):33-38 3. Merino A, Buendia P, Martin-Malo A, Aljama P, Ramirez R, Carracedo J. Senescent CD14+ CD16+ monocytes exhibit proinflammatory and proatherosclerotic activity. J. Immunol. 2011;186(3):1809-15



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Abstract Number: 870

Contemporary Prevalence Estimates for Giant Cell Arteritis and Polymyalgia Rheumatica, 2015

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Session Type: ACR Poster Session A

Session Time: 9:00AM-11:00AM

Background/Purpose: There are no estimates of the prevalence of giant cell arteritis (GCA) or polymyalgia rheumatic (PMR) in a United States population in the current millennium. The purpose of this work was to estimate the 2015 point prevalence of GCA and PMR in a population-based study performed in a US population.

Methods: Study populations of incident cases of GCA in 1950-2009 and incidence cases of PMR in 1970-2014 were previously identified among residents of a well-characterized geographically defined area. Prevalence estimates were obtained from the incidence rates assuming no increased mortality associated with GCA or PMR, which has been previously shown, and assuming migration in and out of the geographically defined area was independent of disease status. Age, sex and calendar year specific indigence rates and population lifetables were used to derive prevalence estimates. Prevalence estimates were age- and sex-adjusted to US white 2010 population aged ≥50 years. Bootstrap sampling was used to obtain 95% confidence intervals [CI] for the prevalence estimates.

Results: A total of 248 incident cases of GCA were diagnosed in 1950-2009 and 790 cases of PMR were diagnosed in 1970-2014. The

overall age and sex adjusted prevalence rate of GCA on January 1, 2015 was 204 (95% CI: 161, 254) per 100,000 population aged 50 years and older. The prevalence rate of GCA among women was 304 (95% CI: 229, 375) per 100,000 population aged 50 years and older and among men was 91 (95% CI: 46, 156) per 100,000 population aged 50 years. The overall age and sex adjusted prevalence rate of PMR on January 1, 2015 was 744 (95% CI: 694, 793) per 100,000 population aged 50 years and older. The prevalence rate of GCA among women was 907 (95% CI: 824, 994) per 100,000 population aged 50 years and older and among men was 557 (95% CI: 475, 638) per 100,000 population aged 50 years.

Conclusion: Prevalence rates of GCA and PMR in the new millennium to 2015 are similar to previously published prevalence estimates in the late 1990s. For GCA this reflects the fact that the incidence of GCA has been stable for the past 20 years. For PMR there have been slight increases in incidence of PMR in recent years, which have not yet affected the prevalence of PMR, but may lead to future increases in the prevalence of PMR. The health burden of these diseases among older persons continues to be substantial and reflects the need for continued efforts to better manage it.

Disclosure: C. S. Crowson, None; **E. L. Matteson**, None.

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Abstract Number: 871

Interleukin 33 Critically Regulates Angiogenesis and Inflammation in Large Vessels Vasculitis

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Background/Purpose: Large vessels vasculitis (LVV) include Takayasu disease (TD) and Giant Cell Arteritis (GCA). Interleukin 33 (IL-33) is a cytokine which controls immune responses and has also an important vascular impact. We aimed to analyse the role of IL-33 and its receptor ST2 in the pathogenesis of LVV.

Methods: TD and GCA patients fulfilling the ACR criteria, with active or inactive disease and age-matched controls (HD) were included. We performed quantitative measurement of IL-33 in sera by ELISA, analysis of cytokine production by flow cytometry and Luminex. Immunohistochemical analysis of inflamed aorta and temporal arteries from TD and GCA patients was also performed.

Results: IL-33 and soluble ST2 were overexpressed in sera of LVV patients as compared to age-matched controls ($p=0.03$ in TD and $p=0.013$ in GCA for IL-33 and $p=0.0002$ in GCA for ST2). By immunofluorescence in inflamed vessels, we found endothelial IL-33 expression pattern mainly in the adventice together with the expression of its receptor ST2 restricted to inflammatory infiltrate. In both diseases, we highlighted in the vascular inflammatory lesions, the expression of Th2 cytokines (IL4) and of IL10. We have shown that IL-33 induced an increase of CD4+ T cells secreting IL-4 after 3 and 5 days of culture in GCA patients ($p=0.01$). In both disease, we have found that IL-33 led to an increased IL-5 and IL-13 secretion in the supernatants of mononuclear cell cultures. Besides anti-inflammatory properties of IL-33 in LVV, we demonstrated in mice that IL-33 led to an increased vascular permeability in both diseases ($p=0.004$). As

mast cells represent one of the main targets of IL-33, we have repeated a Miles assay in mice KO for mast cells. Vascular permeability was significantly decreased in KO mice injected with the same TA patients as compared to WT mice (p=0.007). In vitro, the exposure of TA sera to HUVECS led to the increase of VeCad phosphorylation compared to controls sera (p=0.03). Sera from TD patients also significantly increased the migration of endothelial cells whereas the exposure of serum to anti-IL-33 significantly decreased the number of transmigrated cells.

Conclusion: These findings open new perspectives for the role of IL-33 in the pathogenesis of LVV. IL-33 may regulate the inflammatory immune response by promoting Th2-polarization and increases vascular permeability, though mast cells.

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Abstract Number: 872

New Insights into the Pathogenesis of Giant Cell Arteritis through a Genome-Wide Association Study

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Background/Purpose: Giant cell arteritis (GCA) is an immune-mediated polygenic disease characterized by inflammatory lesions in medium- and large-sized arteries. The aim of the present study was to perform the first unbiased genome-wide association study (GWAS) of GCA in order to identify the most relevant genetic factors contributing to disease predisposition.

Methods: We obtained genome-wide genotypes of 2,134 cases of GCA and 9,125 unaffected controls from 10 different populations of European ancestry (Spain, UK, North America, Italy, Germany, France, Norway, Netherlands, Switzerland, and Ireland). After imputation and tight quality filters, a total of 1,844,133 single-nucleotide polymorphisms were analyzed by logistic regression under an additive model using sex and ten first principal components as covariates. The inverse variance weighted method under fixed effects was used to meta-analyze the different studies.

Results: Two independent signals within the HLA class II region were strongly associated with GCA: rs9268905 (P = 1.94E-54, OR = 1.79, 95% CI = 1.67-1.93), located between the *HLA-DRA* and *HLA-DRB1* genes, and rs9275592 (P = 1.14E-40, OR = 2.08, 95% CI = 1.87-2.32), located between *HLA-DQA1* and *HLA-DQA2*. Outside the HLA region, different genetic variants of plasminogen (*PLG*) and prolyl 4-hydroxylase subunit alpha 2 (*P4HA2*), which encode proteins with relevant roles in vascular remodeling and neoangiogenesis, were associated at the genome-wide level of significance (top hits: *PLG* rs4252134, P = 1.23E-10, OR = 1.28, 95% CI = 1.19-1.39; and *P4HA2* rs128738, P = 4.60E-09, OR = 1.32, 95% CI = 1.20-1.45). Using publicly available functional annotation data, we observed that the associated signals correlated with eQTLs and histone marks specific for cell types and tissues involved in GCA pathology.

Conclusion: Consistent with previously published data, our results confirm the HLA class II as the most relevant genetic region for GCA. Additionally, we have identified *PLG* and *P4HA2* as novel GCA risk *loci*, highlighting the importance of the angiogenesis processes in the development of this form of large vessel vasculitis.

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Abstract Number: 873

Interleukin-23 Stimulates Inflammatory and Proliferative Pathways in Giant Cell Arteritis

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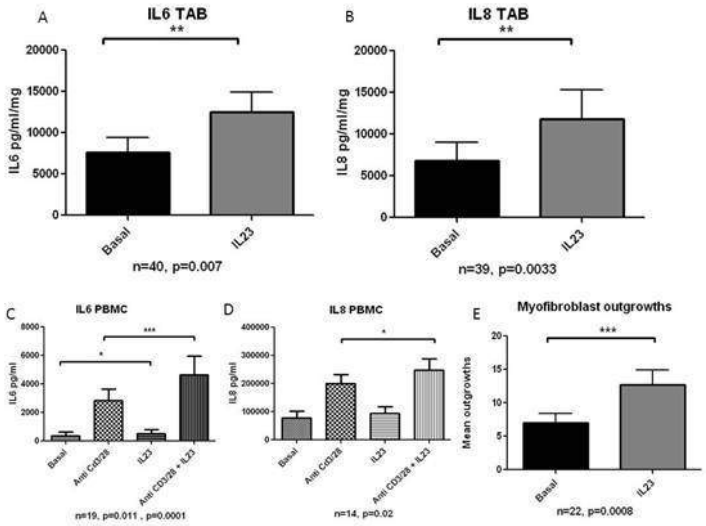
Background/Purpose: Giant cell arteritis (GCA) is the most common form of systemic vasculitis. The pathogenesis of GCA remains incompletely understood. Current evidence suggests that dendritic cells are key regulators of the inflammatory pathways involved in GCA. Dendritic cells secrete the T-cell regulating cytokine interleukin-23 (IL-23) which stimulates Th17 cells. The aim of this study was to evaluate the effect of IL-23 on inflammatory and proliferative pathways in GCA.

Methods: Temporal artery (TA) explant, peripheral blood mononuclear cell (PBMC), and myofibroblast outgrowth models were established from patients with GCA. All patients met the ACR classification criteria for GCA. TA explants were stimulated for 24 hours with recombinant IL-23 (10ng/ml). PBMCs were stimulated with recombinant IL-23 (10ng/ml) after priming with anti CD3 (0.5μg/ml) and anti-CD28 (1μg/ml). Levels of the pro-inflammatory cytokines IL-6 and IL-8 were quantified by ELISA. Myofibroblast outgrowths were established from TAs embedded in Matrigel, stimulated with IL-23 (10ng/ml) with media changed every 3 days, and number of outgrowths per high-power field (hpf) counted after 28 days. Data were reported as mean (standard deviation (SD)). Wilcoxon Signed Rank test was used to compare between group differences. Statistical significance was set at $p<0.05$. Analyses were performed using SPSS.

Results: IL-23 stimulated IL-6 from TA explants from a basal level of 7595 (11726) to 12468 (15194) pg/ml/mg ($p=0.007$, $n=40$), and IL-8 from a basal level of 6859 (13454) to 11820 (21685) pg/ml/mg ($p=0.003$, $n=39$). IL-23 stimulated IL-6 from PBMCs from a basal level of 2830 (3568) to 4637 (5739) pg/ml ($p=0.0001$, $n=19$), and IL-8 from a basal level of 201075 (116367) to 248228 (152195) pg/ml ($p=0.02$, $n=14$). IL-23 significantly increased the number/hpf of myofibroblast outgrowths compared to basal conditions from 7.01 (6.66) to 12.71 (10.55) ($p=0.0008$, $n=22$). Results are demonstrated in Figure 1.

Conclusion: IL-23 upregulated pro-inflammatory cytokines in temporal artery explants and PBMCs from GCA patients, including IL6, suggesting that IL23 may be upstream of IL-6 in the pathogenesis of GCA. IL-23 may play a central role in stimulating inflammatory and proliferative pathways and constitutes a therapeutic target in GCA. Figure 1: (A) IL-6 levels in IL-23 stimulated TA biopsies; (B) IL-8 levels in IL-23 stimulated TA biopsies; (C) IL6 levels in IL-23 stimulated PBMCs; (D) IL-8 levels in IL-23 stimulated PBMCs; (E) Myofibroblast outgrowths from IL-23 stimulated TA sections.



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Abstract Number: 874

Expression and Function of IL-12/23 Related Cytokine Subunits (p35, p40 and p19) in Giant-Cell Arteritis Lesions. Potential Role of p40 in Promoting Th1 -Mediated Pathways

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Background/Purpose: GCA has been considered a Th1-mediated disease. In recent years it has become apparent that Th17-mediated mechanisms may also play a role in GCA pathogenesis. Interleukin-12 is a heterodimeric cytokine (p35/p40) involved in Th1 functional differentiation of T lymphocytes. When combining with p19 subunit, p40 compose IL-23, a powerful pro-inflammatory cytokine that promotes Th17 response. P40, p35 and p19 are known to be expressed in GCA lesions but their distribution, association and functional roles have not been investigated. The aims of this study were 1) to investigate IL12p40, IL12p35 and IL23p19 subunit expression in GCA lesions and their combination to conform different cytokines 2) to investigate the effect of glucocorticoid treatment on subunit expression 3) to explore functional roles of p40 by culturing temporal artery sections with a neutralizing anti-human IL12/IL23p40 antibody.

Methods: IL-12/IL23p40, IL12p35 and IL23p19 mRNA were measured by qRT-PCR in temporal arteries from 50 patients with biopsy-proven GCA and 20 patients with negative temporal artery biopsies, eventually diagnosed with other conditions. 36 patients were treatment naïve and 14 had received glucocorticoid treatment for 7 days (range 2-12) before the performance of temporal artery biopsy. Cytokine subunit distribution was assessed by immunofluorescence. Proximity ligation assay (PLA) was used to assess spatial relationship between subunits to conform different cytokines. Temporal arteries from 10 patients and 10 controls were cultured on 3D-matrix (Matrigel) and exposed to a neutralizing goat anti-human p40 antibody (R&D Systems) or dexamethasone (0.5 µg/mL) .Mann-Whitney test was used for statistical analysis.

Results: p40 and p19 mRNA concentrations were significantly higher in patients than in controls .No significant differences were found in constitutively expressed p35 mRNA levels between patients and controls. P40 and p19 mRNA expression was significantly decreased in treated GCA patients versus those treatment-naïve. Interestingly, immunofluorescence staining revealed intense p19 expression by inflammatory cells, independent from p40 expression. Although p40 expression was less abundant than other subunits, association between subunits to conform IL-23 could be confirmed by PLA in GCA lesions. Neutralization of IL-12/IL-23p40 tended to reduce IFNg mRNA production in cultured temporal arteries from GCA patients with no effect on IL-17, TNFa or IL-6. Dexamethasone significantly down-regulated IFNg, IL-17, TNFa and IL-6 in cultured arteries.

Conclusion: p40 and p19 mRNA expression are increased in active lesions from patients with GCA and decrease with glucocorticoid treatment. P19 subunit is much more expressed than p40 in GCA temporal arteries, indicating an independent role for p19 or its potential association with unidentified subunits. Neutralization of IL12/IL23p40 seems to mainly inhibit the Th1-mediated pathway by reducing IFNg levels. Supported by SAF 2014 57708-R , PIE13/00033 and FEDER.

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Abstract Number: 875

Pericardial Involvement in Biopsy-Proven Giant-Cell Arteritis (GCA) Patients Detected By CT Angiography (CTA): Prevalence at Diagnosis and Outcome with Glucocorticoid (GC) Treatment

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Background/Purpose: In GCA, cranial artery involvement is particularly frequent and underlies the classical manifestations and complications of the disease. Symptomatic pericarditis has been occasionally described as part of the presenting symptoms. However, the frequency of imaging-detected pericardial involvement has not been systematically evaluated. The aim of our study was to assess the prevalence of pericardial involvement detected by CTA in patients with newly diagnosed GCA, as well as the potential relationship with pericardial symptoms, GCA manifestations, laboratory data, or the presence of large-vessel vasculitis (LVV). The outcome of pericardial involvement with GC treatment was also analyzed.

Methods: From July 2007 to January 2015, 63 patients diagnosed with biopsy-proven GCA at our institution were subjected to CTA according to a defined protocol as part of a prospective study assessing LVV [*Prieto-González S et al; Ann Rheum Dis 2012*]. These patients were treatment-naïve or had received GC for ≤ 3 days. A follow-up CTA was scheduled to evaluate the outcome of imaging-detected lesions with GC treatment. Post-hoc assessment of CTA images was performed in order to detect pericardial abnormalities including pericardial thickening (thickness of the pericardial membrane of at least 4mm) and/or pericardial effusion (presence of liquid between the pericardial membrane and the heart). Specific GCA symptoms and laboratory features, as well as classical pericardial manifestation were recorded.

Results: Among the 63 patients included, 45 were women and 18 men, aged 78 years (range 56-92). At the time of GCA diagnosis, pericardial involvement was present in 18 patients (29%), consisting of thickening (4-7mm) in 8 patients (13%) and effusion (4-18mm) in 10 (16%). Forty-six patients completed the follow-up CTA assessment after a median follow-up of 16 months (range 12-135). At the

second imaging, 8 of them (17%) still had pericardial involvement: thickening in 5 (11%) and effusion in 3 (6%). All patients were asymptomatic regarding classical pericarditis symptoms. No relationship was observed between the presence of pericardial involvement and GCA manifestations, laboratory data or the detection of LVV.

Conclusion: In our series, about one third of patients with newly diagnosed GCA have pericardial involvement, consisting of a subclinical mild to moderate pericardial thickening or effusion that improves during the follow-up with GC treatment. Supported by SAF14/57708-R.

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Abstract Number: 876

Long Term Efficacy of Ustekinumab for the Treatment of Giant Cell Arteritis

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Background/Purpose: Giant cell arteritis (GCA) requires treatment with high dose corticosteroids with attendant significant adverse events. There is a critical need for alternative therapies. Interleukins 12 (IL-12) and 23 (IL-23) stimulate Th1 and Th17 responses respectively, both hypothesized to be important in GCA pathogenesis. We have recently reported preliminary evidence of efficacy of IL-12/23 blockade with ustekinumab in 14 GCA patients. In this study we report outcomes in a larger cohort of 25 patients.

Methods: We performed a prospective open label study of ustekinumab in patients with refractory GCA. Ustekinumab was administered subcutaneously at a dose of 90mg at week 1 and week 4 followed by every 12 weeks. Patients underwent standardized clinical assessments. Disease activity was based on a combination of clinical assessment, acute phase reactants (ESR, CRP) and available imaging studies. Descriptive statistics were reported as mean and standard deviation (SD), median and interquartile range (IQR) or number (n) and percentages as appropriate, Wilcoxon Signed Rank test was used to compare between group differences. Statistical significance was set at $p<0.05$. All patients gave written informed consent and ethical approval obtained.

Results: 25 patients commenced ustekinumab having failed to taper corticosteroids and a median of 1 other immunosuppressant, with a median (IQR) of 2 (1, 3) prior relapses of GCA. 84% had experienced significant corticosteroid side effects. Full demographic and clinical details are shown in Table 1. Median (IQR) duration of ustekinumab treatment at last follow-up was 15 (6, 22) months. Efficacy outcomes are detailed in Table 2. Median (IQR) steroid dose decreased significantly from 15mg (5, 20) to 5mg (3.8, 10) ($p=0.002$). 7 patients with large vessel vasculitis had follow-up imaging performed with improvement of wall thickening in all and no new stenoses or aneurysms. No patients experienced a relapse of GCA during ustekinumab treatment. 11 adverse events were recorded, 2 respiratory tract infections, and 1 case each of pancreatitis with infected pseudocyst, bell¡¯s palsy, thyroid goitre, alopecia, parasthesia, tinea pedis, urinary tract infection, dental abscess, and cold extremities. 3 patients discontinued ustekinumab due to adverse events or personal preference, 2 subsequently had flares of polymyalgia rheumatica.

Conclusion: Ustekinumab led to significant reductions in steroid dose and acute phase reactants in patients with refractory GCA. The efficacy of ustekinumab in GCA warrants investigation in a randomized controlled trial.

Table 1: Characteristics and prior treatment of 25 GCA patients treated with ustekinumab

Age, years, mean (SD)	70 (7.3)
Female, n (%)	20/25 (80)
Met 1990 ACR criteria for GCA, n (%)	21/25 (84)
Biopsy positive, n (%)	19/25 (76)
Temporal Artery Ultrasound positive, n (%)	6/18 (33)
CT Angiogram positive, n (%)	9/13 (69)
Cranial-Ischaemic complications, n (%)	5/25 (20)
Vasculitis Damage Index, median (IQR)	1 (0, 2)
Charlson co-morbidity index, median (IQR)	1 (1, 2)
Disease duration, months, median (IQR)	29 (11.5, 36.5)
Relapses, median (IQR)	2 (1, 3)
Clinical presentation at last relapse	
Cranial, n (%)	10 (40)
Polymyalgia rheumatica, n (%)	8 (32)
Constitutional, n (%)	9 (36)
Large vessel vasculitis, n (%)	9 (36)
Prior treatment	
Glucocorticoids, n (%)	25 (100)
Glucocorticoid adverse events, n (%)	21 (84)
Other immunosuppressant, n (%)	17 (68)
Other immunosuppressant's failed, median (range)	1 (0, 1)
Methotrexate, n (%)	16 (64)
Duration methotrexate, months, median (IQR)	15 (3.5, 44.5)
Dose methotrexate, mg/week, median (IQR)	20 (13.8, 20)
Azathioprine	3 (12)
Leflunomide	1 (4)
Adalimumab	1 (4)

Table 2

Outcome	Pre-ustekinumab	Last follow-up	p-value
Prednisolone dose, mg, median (IQR)	15 (5, 20)	5 (3.8, 10)	0.002
ESR, mm/hr, median (IQR)	29 (11, 43)	12 (8, 20)	0.020
CRP mg/L, median (IQR)	12.9 (5.3, 42)	4.5 (2, 14)	0.001
BVAS, median (IQR)	1 (0, 2)	0 (0, 0)	<0.001
Stopped glucocorticoids, n (%)	-	5 (20)	-
Stopped other immunosuppressant, n (%)	-	15 (94)	-

<>

Disclosure: R. Conway, None; **L. O'Neill**, None; **P. Gallagher**, None; **E. O'Flynn**, None; **G. M. McCarthy**, None; **C. Murphy**, None; **D. J. Veale**, None; **U. Fearon**, None; **E. S. Molloy**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/long-term-efficacy-of-ustekinumab-for-the-treatment-of-giant-cell-arteritis

Abstract Number: 877

Risk of Coronary Artery Disease in Patients with Polymyalgia Rheumatica: A

Systematic Review and Meta-Analysis

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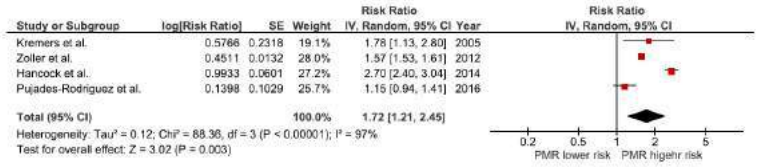
Risk of Coronary Artery Disease in Patients with Polymyalgia Rheumatica: A Systematic Review and Meta-analysis

Background/Purpose: Several chronic inflammatory disorders, such as rheumatoid arthritis and systemic lupus erythematosus, are associated with an increased risk of coronary artery disease (CAD) as a result of accelerated atherosclerosis. However, the data on polymyalgia rheumatica (PMR), one of the most common chronic inflammatory disorders in older adults, remain unclear due to limited number of epidemiological studies. To further investigate this possible association, this systematic review and meta-analysis of observational studies was conducted to compare the risk of CAD in patients with PMR versus participants without it.

Methods: Two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2016 using the terms "polymyalgia rheumatica" combined with the terms for coronary artery disease. A manual search of references of selected retrieved articles was also performed. The inclusion criteria were: (1). observational studies published as original studies to evaluate the risk of CAD among patients with PMR; (2). published odds ratios (OR), relative risk (RR) or hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence intervals (CI) in the studies. Study eligibility was independently determined by the two investigators noted above. The quality of each study was assessed using Newcastle-Ottawa scale. RevMan 5.3 software was used for data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between-study variance, random-effect model rather than fixed-effect model was used. Statistical heterogeneity was assessed using the Cochran's Q test and I^2.

Results: Out of 176 potentially relevant articles, four studies (three retrospective cohort studies and one cross-sectional study) with 34,569 patients with PMR were identified and included in this meta-analysis. The pooled risk ratio of CAD in patients with PMR was 1.72 (95% CI, 1.21 to 2.45). The statistical heterogeneity of this meta-analysis was high with an I^2 of 97%.

Conclusion: The risk of CAD among patients with PMR is 70% higher than in patients without PMR. This finding has importance for the assessment and management of cardiovascular disease in these patients.



Disclosure: P. Ungprasert, None; **M. J. Koster**, None; **K. J. Warrington**, None; **E. L. Matteson**, None.

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Abstract Number: 878

Giant-Cell Arteritis Related Stroke: A Retrospective Multicentre Case-Control Study

Hubert de Boysson[1], Eric Liozon[2], Delphine Lariviere[3], Maxime Samson[4], Jonathan Boutemy[1], Gwénola Maigné[1], Nicolas Martin Silva[1], Achille Aouba[1], Karim Sacre[3] and Boris Bienvenu[5], [1]Department of Internal Medicine, Caen University Hospital, Caen, France, [2]Departement of Internal Medicine, Limoges University Hospital, Limoges, France, [3]Department of Internal Medicine, Bichat Hospital, Paris, France, [4]Dijon University Hospital, Dijon, France, [5]Caen University Hospital, Caen, France

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Background/Purpose: Our aim was to describe patients with Giant-Cell Arteritis (GCA)-related stroke and to compare them to a control group of GCA patients without cerebrovascular involvement.

Methods: We created a retrospective multicenter cohort of patients with 1) GCA diagnosed according to the American College of Rheumatology (ACR) criteria between 1995 and 2015; 2) stroke revealing vasculitis or occurring within four weeks of starting GCA therapy. The control group comprised GCA patients with no history of stroke from patient-reporting centers. For each patient included with stroke, five randomised patients without stroke were included in the control group. All of them satisfied the ACR criteria

Results: Forty patients (21 (53%) women, median age 78 [60-91] years) with GCA-related stroke were included and were compared to 200 control patients with GCA. The stroke revealed GCA in 29 (73%) patients, whereas it occurred after diagnosis in 11 patients, 6 [1-14] days after the initiation of glucocorticosteroids (GC). No differences were observed between patients whose stroke revealed GCA and those suffering a stroke following GCA diagnosis. Vertebrobasilar territory was involved in 29 (73%) patients. Seven patients died within a few hours or days following a stroke. Compared to the control group, the stroke patients were older (78 [60-91] vs. 74 [50-94] years old, p=0.03), displayed more ophthalmic ischemic manifestations (25 (63%) vs. 50 (25%), p<0.001), had fewer anemia (22/37 (59%) vs. 137/167 (79%), p=0.03) and a higher level of hemoglobin at diagnosis (12.0 [9.4-16.1] vs. 11.1 [7.8-15.8] g/dl, p=0.02). Conversely, PMR was less frequent (8 (20%) vs. 76/198 (38%), p=0.03) and biological inflammatory parameters were lower at GCA diagnosis in patients with GCA-related stroke (ESR: 68 [10-119] mm vs. 80 [10-140], p=0.003; CRP: 61 [28-185] mg/l vs. 99 [6-400], p=0.04). Multivariate logistic regression revealed that the best predictors for the occurrence of stroke were the presence of ophthalmic ischemic manifestations at diagnosis (OR = 5, 95% CI, 2.14—12.33; p=0.0002) and absence of anemia (OR = 0.39, 95% CI, 0.16—0.99; p=0.04).

Conclusion: Stroke, especially in the vertebrobasilar territory, is more likely to occur in GCA patients who experience recent ophthalmic ischemic manifestations and who display low inflammatory parameters.

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Abstract Number: 879

Associated Inflammatory Diseases in Takayasu's Arteritis: The Many Faces of a Disease

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Background/Purpose: Case reports and series suggest that Takayasu's arteritis (TA) can co-exist with various inflammatory disorders.

Inflammatory bowel disease [(IBD; Crohn's disease (CD) or ulcerative colitis (UC)] has been the most common association. We conducted a formal study to look specifically at the frequency of such inflammatory disorders in a large cohort of TA followed by a single tertiary center.

Methods: There were 226 (200 F/ 26 M) patients registered with a diagnosis of TA. Of these, 17 (8 %) had died and 15 (7 %) were lost to follow-up. The remaining 194 patients were called back at the outpatient clinic for an interview and for a physical examination. A standardized form sought whether the patient was also diagnosed as IBD, ankylosing spondylitis (AS), Behçet's syndrome (BS), amyloidosis, uveitis, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), systemic sclerosis (pSS), Sjögren's syndrome, psoriatic arthritis, inflammatory myositis, small vessel vasculitis, autoimmune/demyelinating or any other inflammatory disorder. In addition to the self-reported information, patient charts and all medical documentation available were used as a source of information.

Results: 153 (136 F/ 17 M) patients were studied. The mean age at the onset of symptoms was 31±11 years and at the time of TA diagnosis was 34 ± 12 years. Subclavian artery was the most common involved artery (83%), followed by common carotids (75%) and aorta (64%). Currently, while 25 (16%) patients were off treatment, 72 (47%) patients were using glucocorticoids, 47 (31%) azathioprine, 32 (21%) methotrexate and 44 (29%) biological agents. We identified in total 31 (20 %) patients with inflammatory diseases (IBD: n= 11; AS: n = 11; and BS: n = 9). Table shows their demographic characteristics. Among the remaining 122 patients, inflammatory back pain was present in 44 (36 %) recurrent oral ulcers were present in 19 (16%), erythema nodosum in 13 (11%), arthritis in 12 (10%), papulo-pustular lesions in 5 (4%), uveitis in 5 (4%) and genital ulcer in 1. It was noted that inflammatory back pain was mostly located on the dorsal area (n=40). Apart from these diseases, we also observed secondary amyloidosis (n=3), psoriasis (n=3), autoimmune hepatitis (n=2), RA (n=1) and morphea (n=1). None of the patient had SLE, Sjögren's or myositis.

Conclusion: TA does co-occur with IBD, AS or BS in about 1/5 of the patients, at least in a hospital setting and without a clear temporal pattern. This could be due to the close association of TA with MHC class-1 diseases. In addition, the high prevalence of inflammatory back pain in the dorsal spine in TA needs further scrutiny.

Table. Demographic features of 31 TA patients with inflammatory bowel disease (IBD), ankylosing spondylitis (AS) or Behçet's syndrome (BS)

Concomitant disease	F/M	Mean age at TA diagnosis (SD)	Mean age at concomitant disease (SD)	The time of TA diagnosis in relation to concomitant disease
AS (n=11)	9/2	31 ±8	27±11	TA preceded (n=6) AS preceded (n=5) Simultaneous (n=6)
IBD (n=11)	10/1	33±9	31±9	TA preceded (n=2) IBD preceded (n=3) Simultaneous (n=4)
BS (n=9)	7/2	35±13	32±13	TA preceded (n=1) BS preceded (n=4)

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Abstract Number: 880

Pilot Study of Microbubble Contrast-Enhanced Vascular Ultrasonography: A Novel Method of Detecting Large Vessel Vasculitis?

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Session Time: 9:00AM-11:00AM

Background/Purpose: A key unmet need in the monitoring of disease activity in large vessel vasculitides (LVV), i.e., giant cell arteritis (GCA) and Takayasu arteritis (TAK), is the ability to differentiate active vasculitic disease activity from atherosclerotic damage through the use of noninvasive imaging modalities. In LVV, the inflammatory process begins at the vasa vasorum in the adventitia, with vasa vasoritis and inflammatory cell recruitment. Thickened adventitia and medial fibrosis are key features that differentiate vasculitis from atherosclerosis. A novel imaging modality that can noninvasively detect increased neovascularization and thickening in large vessels' adventitia is microbubble contrast-enhanced carotid ultrasonography (CU). In animal and human studies using CU, higher densities of vasa vasorum correlated with plaque vulnerability and atherosclerosis progression. Our objective was to establish feasibility of measuring adventitial vasa vasorum density (aVVD) in LVV patients; to compare aVVD in clinically active vs. inactive LVV patients; and to examine various serum vascular and inflammatory biomarkers in these patients.

Methods: We performed a preliminary analysis of an ongoing cross-sectional study of 7 LVV patients (2 active, 5 inactive) to illustrate feasibility of the novel CU technique. All subjects met ACR criteria for GCA or TAK. All subjects underwent CU with measurement of carotid intima-media thickness (cIMT, using maximum of both sides) and mean common carotid artery (CCA) adventitial to lumen videointensity ratio (using maximum of both sides) to quantify aVVD. Data on demographics and disease characteristics were collected on all subjects. Serum biomarkers of CD40L, matrix metalloproteinase-9, myeloperoxidase, E-selectin, intercellular adhesion molecule-1, and vascular cell adhesion molecule-1 were measured in all subjects by enzyme-linked immunosorbent assay (ELISA). The inflammatory markers high sensitivity C-reactive protein and erythrocyte sedimentation rate were also measured in all patients.

Results: Table 1 shows results of type of LVV, disease activity status, demographic data, cIMT, and aVVD of all 7 subjects. The mean cIMT of the two active LVV subjects was 1.23 mm, and the mean cIMT of four inactive subjects was 0.91 mm. The maximal aVVD of the CCA's far wall for the two active LVV subjects was 0.58, versus 0.50 for the five inactive LVV subjects. Wide variation in serum biomarker levels were seen in the inactive subgroup, and statistical testing will be performed when the study of n=20 participants is completed to compare if the levels are higher in the active vs. inactive subgroups.

Conclusion: Measurement of aVVD in LVV patients is feasible utilizing the novel CU technique. In this pilot study, the aVVD was slightly higher in active vs. inactive subjects. Our study is ongoing, with plans for targeted enrollment of larger numbers and comparison with control (non-LVV) subjects. **Table 1.**

Subject Number	Type of LVV	Active vs. Inactive	Age (years)	Gender	BMI (kg/m^2)	cIMT (mm)	Left aVVD	Right aVVD
LV01	GCA	Inactive	64	Female	35.1	0.65	0.095	0.276
LV02	TAK	Inactive	54	Female	25.1	1.23	0.402	0.234
LV03	TAK	Active	20	Female	22.6	1.61	0.575	0.393
LV04	GCA	Active	62	Male	25.5	0.84	0.585	0.329
LV05	GCA	Inactive	71	Female	22.8	0.91	0.98	1.04
LV06	TAK	Inactive	43	Female	44.3	Unobtainable*	0.22	0.17
LV07	TAK	Inactive	59	Female	30.5	0.84	0.57	0.51

LVV = large vessel vasculitis; GCA = giant cell arteritis; TAK = Takayasu arteritis; BMI = body mass index; cIMT = carotid intima media thickness; aVVD = ratio of adventitial to lumen vasa vasorum density *Unobtainable bilaterally due to Goretex graft in right CCA and occlusion of left CCA

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Abstract Number: 881

Cardiopulmonary Involvement in Takayasu Arteritis

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Session Type: ACR Poster Session A

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Background/Purpose:

Takayasu arteritis (TAK) is an inflammatory large-vessel vasculitis of unknown etiology affecting the proximal aorta and its primary branches. Heart disease is a major cause of death in patients with TAK but studies evaluating coronary/pulmonary artery involvement and myocardial dysfunction in this population have been limited.

Methods:

A retrospective cohort of patients with newly diagnosed TAK from 1984 to 2009 was assembled. All patients included met 1990 American College of Rheumatology classification criteria for TAK. Demographics, baseline disease characteristics, relapse events, surgeries and mortality were abstracted from direct medical record review. Angiograms (invasive and non-invasive), echocardiograms, nuclear medicine scans, and electrocardiograms (ECG) were reviewed for evidence of CP involvement. For the purpose of this study, CP abnormalities were defined as coronary or pulmonary artery vasculitis, left ventricular (LV) dysfunction, left atrial (LA) enlargement, moderate-severe valvular disease, pulmonary arterial hypertension (PAH), regional wall hypokinesis/akinesis, LV hypertrophy or persistent ECG axis deviation. Cox models with time-dependent covariates were used to assess the association between CP involvement and outcomes.

Results:

A total of 117 patients with TAK were identified. Forty-five (38%) patients had at least one objective CP abnormality observed within 6 months of TAK diagnosis. Age at diagnosis was higher in those with CP involvement than those without (34.6 vs 30.1 yrs, respectively; p=0.04). Baseline characteristics and symptoms were similar, except shortness of breath, which was more frequently observed at TAK diagnosis in patients with CP involvement compared to those without (53% vs 21%, respectively; p=0.001). PAH was identified in 7, pulmonary arteritis in 9, coronary arteritis in 3, aortic valve insufficiency in 10 (6 moderate, 4 severe), LV systolic heart failure in 4, LV enlargement in 17, and LA atrial enlargement in 17 patients. Seventy-seven patients had at least 1 year of follow-up [median (IQR): 5.5 (2.9-10.1) years]. Of these 77 patients, 44 had at least one vascular or valvular surgery during the follow-up period. Composite CP involvement was not associated with risk of first surgery [Hazard ratio (95% CI): 1.21 (0.64-2.30); p=0.56]. However, PAH on echocardiogram was significantly associated with risk of first surgery [HR (95% CI): 12.9 (1.86-89.14); p=0.01]. During follow-up 7 patients died. CP involvement was not significantly associated with mortality [HR (95% CI): 2.51 (0.45-14.02); p=0.29].

Conclusion:

Cardiopulmonary abnormalities in TAK are common. In this population, the presence of PAH predicted a 13-fold increased risk for vascular or valvular surgery. In this cohort, the presence of CP involvement did not increase mortality.

Abstract Number: 882

Polymyalgia Rheumatica Activity Score without C-Reactive Protein

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Background/Purpose: Disease activity of polymyalgia rheumatica (PMR) (1, 2) may be evaluated using the PMR activity score (PMR-AS). For patients without measure of CRP, or patients having a treatment modifying its measure (i.e. anti-IL6), the PMR-AS could be unmeasurable or biased. Three options should be suggested: 1-to use ESR instead CRP but anti IL6 may also modify ESR; 2- to use PMR-AS without CRP (clin-PMR-AS) as an item but its validation is mandatory; 3- to replace CRP by a virtual value imputed on the basis of the other parameters (CRP-imputed-PMR-AS). Our goal was to build a PMR-AS using imputed value of CRP.

Methods: We used two independent cohorts of patients: the CRI cohort (137 visits of 89 PMR patients without any treatment or treated by corticosteroids) (2) and the TENOR cohort (20 patients, 20 visit at inclusion without any treatment, 20 visit at W4, 8, 12 during tocilizumab infusions, and 20 visit at 16, 20 and 24 weeks with treatment by steroids) (2). In the CRI cohort, we evaluated the correlation (Spearman) between the items of the PMR-AS to define which of them may be the best to perform an imputation of CRP. Then we built a scatter plot representing PMR-AS and clin-PMR-AS. Their correlation could be represented by an equation y=ax+b. We verified that the CRP-imputed-PMR-AS in patients of the TENOR cohort without treatment by tocilizumab gave a good correlation with PMR-AS with CRP. Finally, we evaluated the difference of PMR-AS without CRP and the CRP-Imputed-PMR-AS in the TENOR cohort during the visit 4, 8 and 12.

Results: On the CRI cohort, we observed a good correlation between the items of the PMR-AS, the clin-PMR-AS and PMT-AS. Agreement between PMR-AS with and without CRP was excellent (using cut off 0-7-17-∞; only 5/137 were discordant, kappa: 0.93) but as anticipated, the clin-PMR-AS was lower than the PMR-AS. On a scatterplot representing the PMR-AS (y) according to the clin-PMR-AS (x), a straight line y=1.12 x clin-PMR-AS + 0.26 represented their association, and with use it for CRP imputation. The mean +/- SD was very close between the PMR-AS, clin-PMR-AS, and CRP-imputed-PMR-AS, respectively. Using cut off 0-7-17-∞, we obtained a slightly higher concordance for the CRP-imputed-PMR-AS (kappa=0.95). This suggested that it was not really necessary to do an imputation to separate patient in groups of PMR-AS except for high clin-PMR-AS. The replication in the TENOR cohort before and after treatment by tocilizumab confirmed that CRP-imputed-PMR-AS did not modify the results using the original PMR-AS (during treatment by tocilizumab, means for PMR-AS, clinPMR-AS, and CRP-Imputed-PMR-AS were 11.3+/-8,1, 11+/-8.1 and 12.0+/-9, respectively).

Conclusion: This study supplies evidence that a CRP-imputed-PMR-AS may be used to monitor PMR activity for patients without available CRP or treated by anti IL6. Nevertheless, use of PMR-AS (or Clin-PMR-AS) in patients treated by tocilizumab lead to a very small proportion of false classification of patient splited in low-disease activity or high-disease activity. References: 1- Leeb et al. Ann rheum Dis 2004;63:1279-83. 2- Binard A et al, Arthritis Rheum, 2008, 59:263-269 3-Devauchelle-Pensec V, 2016, feb 29

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Abstract Number: 883

Folate Receptor Beta and Endothelin Receptor Beta Macrophage Subtypes Are Differentially Expressed in the Vascular Compartments of the Intima and Media/Adventitia in Giant Cell Arteritis: A Pilot Study

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Background/Purpose: Giant cell arteritis (GCA) is a chronic immune-mediated vasculitis of large and medium vessels characterized by a chronic relapsing course with no good biomarkers that can predict activity and response to treatment. Fortunately, the accessibility of the temporal artery for tissue biopsy allows novel mechanistic studies that can characterize pathogenic macrophages which possess pro-inflammatory and pro-angiogenic properties which depend on their cross talk between the microenvironment of the compartments/layers of the vessel wall. The localization of particular activated macrophage subtypes (AMs) in a particular vessel compartment can provide insight on how AMs influence endothelial activation in the intima, and neoangiogenesis in the media and adventitia. In this pilot study, we evaluated the expression of 2 novel AM subtypes- folate receptor beta (FRB) and endothelin receptor beta (ETB) which are potential pathogenic populations and druggable targets for existing medications like methotrexate/new generation antifolates and endothelin receptor blockers We assessed their predominant distribution across the intima media and adventitial layers.

Methods: Formalin-fixed paraffin embedded hematoxylin-eosin stained tissue sections were examined from 6 patients with GCA and 2 controls with no disease and normal temporal artery biopsies. Immunohistochemical stains were performed using FRB, CD68 and CD3 antibodies to enhance recognition of AMs, their distribution along the intima media and adventitial layers and composition of inflammatory infiltrates. We compared the expression of FRB and ETB in GCA versus controls and mild (no visual loss) versus severe disease (positive visual loss).

Results: In GCA patients, overall inflammation was moderate to severe with >90% destruction of the internal elastic lamina. AMs comprised 36.3 ± 4.1% of total leukocyte infiltrate while CD3(+) lymphocytes accounted for 61.7 ± 4.1%. FRBs were selectively expressed in AMs, which predominantly localized in the media/adventitia with a median of 9.8 cells/hpf (IQR = 7-12). ETBs were expressed predominantly in intimal macrophages- with a median of 20.5 cells/hpf (IQR = 15.2 – 21.5), smooth muscle and endothelial cells. There were no macrophages nor FRB expression demonstrated in the controls. A trend towards higher FRB and ETB expression was seen in GCA with complications of vision loss versus those without but did not reach statistical significance.

Conclusion: FRBs macrophages are potential biomarkers that localize to the media/adventitia and may contribute to vasa vasorum angiogenesis. ETB is more ubiquitously expressed, and ETB macrophages localize to the intima where they may affect endothelial activation. FRB and ETB macrophages should be analyzed for pathogenicity, antifolate-binding properties and clinically correlated in larger samples in future and prospective studies.

Disclosure: S. Albano-Aluquin, None; **N. J. Olsen**, None; **J. Malysz**, None.

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Abstract Number: 884

Health-Related Quality of Life in Giant Cell Arteritis

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Background/Purpose: To evaluate health-related quality of life (HRQoL) in a large cohort of patients with giant cell arteritis (GCA) as measured by the 36-item Short Form Health Survey (SF-36).

Methods: Patients with GCA enrolled in a multicenter, longitudinal cohort were included. Subjects were followed with standardized clinical assessments which include symptoms attributed to vasculitis at diagnosis and follow-up, physician global assessment (PGA, 0-10 visual analogue scale), patient global assessment (PtGA, 0-10 visual analogue scale), vasculitis damage index (VDI), SF-36. Physical component scores (PCS) and mental component scores (MCS) were calculated from SF-36 and normalized to the general population (mean ± SD=50 ± 10) with lower scores indicating poorer outcomes. Active disease at a study visit was defined as presence of any symptom attributable to vasculitis in the prior 28 days.

Results: Data from 281 patients with GCA were included: 197 (70%) women; mean age at diagnosis = 72.1±8.4 years. Median (25^{th}, 75^{th} quartiles) time from diagnosis to entry in the cohort was 25 (7, 88) weeks. 108 subjects (39%) were enrolled into the cohort ≤ 12 weeks from diagnosis. Manifestations at time of diagnosis: positive temporal artery biopsy 180 of 224 (80%) patients in whom it was performed; visual manifestations in 109 patients (38%); limb claudication (upper or lower) in 59 patients (20%). VDI at entry into the cohort was 1 (0-2) with 149 subjects (60%) having at least 1 item of damage. Means±SD PCS and MCS were lower in patients with GCA compared to the general population at 39±11 and 47±13, respectively. Mean PCS was significantly lower in women, patients with active symptoms on the day of evaluation, those with elevated inflammatory markers, those with at least 1 damage item on VDI, and patients with PtGA ≥ 1 and/or PtGA ≥ 3 (**Table**). Mean MCS was lower in patients with active symptoms or with a PtGA≥1 or PtGA ≥ 3 (**Table**). Subjects with newly-diagnosed disease had similar PCS but lower MCS compared to the patients with established disease. When analysis was restricted to the subset with newly-diagnosed GCA, PCS was statistically lower in women, those with elevated acute phase reactants and the subset presenting with limb claudication or PtGA ≥ 3 while MCS was similar across these comparisons (**Table**). PCS and MCS was similar in patients with visual symptoms at diagnosis even when restricted to subjects with newly-diagnosed disease.

Conclusion: Patients with GCA have reduced HRQoL, as measured by the SF-36. PCS appears sensitive to changes in disease status or health status while MCS did not appear to differentiate between the variables measured. SF-36 may be a useful tool in assessing patient reported outcomes in patients with GCA. These findings highlight the importance of measuring the burden of disease from the patient's perspective when evaluating GCA.

Association between clinical variables and SF-36 physical component and mental component scores in 281 patients with giant cell arteritis						
Variable	**PCS**			**MCS**		
	Yes	No	p-value	Yes	No	p-value
Female sex	39.1	42.6	0.02	47.0	47.4	0.82
Positive TAB	41.2	37.5	0.08	46.9	44.5	0.31
Active symptoms on day of visit	37.8	41.3	0.01	45.0	48.6	0.02
ESR ≥ 20 mm/hour or CRP ≥ 5 mg/L	37.7	43.8	<0.01	47.0	47.5	0.76
Vision loss at diagnosis	40.1	40.0	0.94	48.1	46.7	0.36
Limb claudication at diagnosis	39.1	40.3	0.51	46.2	47.5	0.49
VDI ≥1	38.0	41.8	0.01	47.6	45.7	0.26
PtGA≥1	38.6	45.5	<0.01	45.8	52.3	<0.01
PtGA≥3	34.9	45.2	<0.01	44.0	50.3	<0.01
New diagnosis*	39.2	40.7	0.29	44.9	48.6	0.02
Female sex*	36.5	43.6	<0.01	44.1	46.1	0.43
Positive TAB*	39.9	37.6	0.49	43.9	48.8	0.16
Active symptoms on day of visit*	37.8	41.2	0.18	44.9	44.4	0.86
ESR ≥ 20 mm/hour or CRP ≥ 5 mg/L*	36.6	42.8	0.02	45.1	43.8	0.61
Vision loss at diagnosis*	40.1	38.5	0.50	46.7	43.3	0.20
Limb claudication at diagnosis*	32.0	40.1	0.03	41.6	45.2	0.36
VDI ≥ 1*	36.7	40.6	0.12	44.8	43.7	0.66
PtGA ≥ 1	38.4	42.5	0.20	44.2	48.4	0.19
PtGA ≥ 3	34.0	45.8	<0.01	44.5	45.5	0.70
Yes/No indicates whether variables under study were present. PCS: SF-36 physical component score; MCS: SF-36 mental component score; TAB: temporal artery biopsy; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VDI: Vasculitis Damage Index; PtGA: patient global assessment; *restricted to subset enrolled within 12 weeks of diagnosis						

Disclosure: **T. A. Kermani**, GlaxoSmithKline, 2; **A. Sreih**, Bristol-Myers Squibb, 2,Celgene, 2,Chemocentryx, 2,Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Krog and Partners, 5; **G. Tomasson**, None; **D. Cuthbertson**, None; **S. Carette**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2; **G. S. Hoffman**, None; **N. A. Khalidi**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **C. L. Koening**, None; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Bristol-Myers Squibb, 2; **C. A. McAlear**, None; **P. A. Monach**, Genentech and Biogen IDEC Inc., 2,Bristol-Myers Squibb, 2,MedScape, 5,GlaxoSmithKline, 2,Vasculitis Foundation Board of Directors, 6,Editorial Board of Arthritis and Rheumatology, 6; **L. W. Moreland**, Genentech and Biogen IDEC Inc., 2,Pfizer Inc, 2,questcor, 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 5,Boehringer Ingelheim, 5,Acerta, 5,CVS/Caremark, 5,Smith Kline Beecham, 5; **C. Pagnoux**, Chemocentryx, 5,Chemocentryx, 9,Roche Pharmaceuticals, 9,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,Hoffmann-La Roche, Inc., 8; **P. Seo**, None; **K. J. Warrington**, GlaxoSmithKline, 2; **S. R. Ytterberg**, Sanofi-Aventis Pharmaceutical, 5; **P. A. Merkel**, Bristol Myers Squibb, 2,CaridianBCT, 2,Celgene, 2,Chemocentryx, 2,Genentech/Roche, 2,GlaxoSmithKline, 2,Kypha, 2,Bristol-Myers Squibb, 5,Chemocentryx, 5,Genentech/Roche, 5,GlaxoSmithKline, 5,PrinicipioBio, 5,Auven, 5,Proteon Therapeutics, 5.

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Abstract Number: 885

Giant Cell Arteritis and Malignancy – More Than Just a Coincidence?

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Background/Purpose: Malignancy associated vasculitis represents 2–5% of systemic vasculitides. While there have been reports of increased incidence of malignancy in patients with giant cell arteritis (GCA) no definite association has yet been established. Our objective was to determine the proportion patients with GCA and past/concurrent/subsequent malignancy.

Methods: We conducted a prospective longitudinal analysis of patients diagnosed with GCA from September 2011 to May 2016 at a single secondary/tertiary rheumatology centre. The proportion of patients with past, concurrent, and successive malignancy (diagnosed within 1 year of follow-up) was determined. Crude incidence rate (CIR) of malignancy in general population aged 50 years and above from the same geographical region in year 2011 and 2012 (final accessible reports based on complete yearly data) was acquired from Slovenian Cancer Registry for comparison.

Results: During the observation period 119 new GCA cases were identified (median age 73.8 (IQR 70.0–78.8) years, 71% female, 39.5% ever smokers). Ninety-eight (82.4%) patients fulfilled the 1990 ACR classification criteria for GCA; the remaining 17.6% had imaging evidence of large vessel vasculitis. Thirteen patients (10.9%) had past history of malignant disease; one of these patients had an active urinary bladder cancer at the time of GCA diagnosis. There was 1 death due to cancer during the follow-up. In 8 patients (6.7%) malignant disease was found concurrently with GCA (4/8) or within one year of follow-up (4/8) (Table 1). With respect to location of the 8 newly diagnosed malignancies, there were 3 cases (2.5%) of urinary bladder cancer (Table 2). CIR for malignancy in population aged 50 years and above of the same geographical region was 1.51%, with specific CIR for bladder cancer of 0.04%.

Table 1. Age-stratified comparison of malignancy incidence rate in GCA patients vs. the general population.

Age group (years)	No. of patients with malignancy			No. of GCA patients with C/S malignancy	Total No. of GCA patients	Incidence rate (C+S)	CIR for general population
	P	C	S				
50–59	1	1	0	1	7	14.3 %	0.75 %
60–69	2	1	2	3	35	8.6 %	1.59 %
70–79	6	0	2	2	55	3.6 %	2.31 %
80+	4	2	0	2	22	9.5 %	2.56 %
Total (50+)	**13**	**4**	**4**	**8**	**119**	**6.7 %**	**1.51 %**

Legend: P – past; C – concurrent; S – successive; CIR – Crude Incidence Rate

Table 2. Location of malignancy and temporal relationship to GCA.

Location	P	C	S
Renal	1	0	0
Bladder	1	2	1
Stomach	0	1	1
Colon	3	0	0
Ovarian/uterine	3	0	0
Haematologic	1	1	0
Breast	2	0	1
Prostatic	1	0	0
Melanoma	1	0	1
Total	**13**	**4**	**4**

Conclusion: In our study, incidence rate of malignant disease was distinctly higher in GCA patients compared to general population for all age groups; ultimately, 6.7% of GCA patients were diagnosed with concurrent/successive malignant disease – compared to 1.5% of

similarly aged general population. Additionally, we detected an increased incidence of urinary bladder cancer in our GCA cohort.

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Abstract Number: 886

Vascular Inflammation Assessed By 18f-Fludeoxyglucose Positron Emission Tomography (FDG-PET) Is Modified By Treatment in Patients with Large Vessel Vasculitis

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Background/Purpose: FDG-PET can be used to detect vascular inflammation in large vessel vasculitis (LVV). The study objective was to determine if therapies currently used to treat LVV impact vascular FDG uptake.

Methods: Patients with giant cell arteritis (GCA) or Takayasu's arteritis (TAK) were recruited into a prospective, observational cohort of LVV. All patients underwent FDG-PET/CT at 6-month intervals (256 matrix, 3mm slice, 2 hour uptake time). Change in cumulative glucocorticoid (GC) dose between interval visits was calculated. Treatment status between interval visits was categorized as increased, decreased, or unchanged. Change in treatment was defined as change in average daily dose of prednisone over past 7 days by $\geq$ 5 mg, addition of a new DMARD or biologic agent or a 50% change from the baseline dose. Standardized uptake values (SUVs) were measured in 3 regions: 1) ascending aorta and arch; 2) descending aorta; and 3) liver. Vascular FDG uptake was quantified as a target to background ratio (TBR) standardized to the liver (TBR = SUV_{max} Aorta Region / SUV_{mean} Liver). Change in TBR in each region of the aorta was calculated between interval study visits. Kruskal-Wallis test was performed to compare change in TBR across treatment status categories. Spearman correlation between change in TBR, change in cumulative GC dose, and change in methotrexate (MTX) dose was calculated. Linear regression was performed to evaluate relationship between change in MTX and GC dose with change in TBR.

Results: FDG-PET/CT was performed in 20 patients with LVV (GCA=14; TAK=6) over 49 study visits. 15 patients were treated with GCs, 10 patients were treated with MTX, and 8 patients received another DMARD or biologic during the study. Increased therapy was recorded over 11 visit intervals, decreased treatment was noted in 5 visit intervals, and there was no change in therapy for 11 visit intervals. There was a simultaneous decrease in the GC dose with increase of DMARD over 2 treatment intervals, which were excluded from further analysis. Change in TBR of the descending aorta significantly differed among the 3 treatment categories (p=0.01). Post hoc analysis showed significant reduction in TBR in the group with increased treatment versus the unchanged treatment group. A similar trend was observed in the TBR of the ascending aorta and arch among the 3 treatment groups but differences between groups were less pronounced and did not reach statistical significance (p=0.08). There was no change in the SUV_{mean} of the liver with change in treatment. Change in TBR of the descending aorta was inversely correlated with change in cumulative dosage of GC (r=-0.40, p=0.03) and with change in daily dose of methotrexate (r=-0.67; p=0.01). In multivariable regression, change in GC dose and change in methotrexate dose were independently associated with a change in TBR of the descending aorta ($p<0.05$).

Conclusion: Therapies commonly used to treat LVV, including glucocorticoids and methotrexate, can reduce FDG vascular uptake in the aorta. Interval change in PET activity is more pronounced in the descending aorta compared to the ascending aorta and arch. FDG-PET might be useful to monitor vascular disease activity as an outcome measure in clinical trials of LVV.

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Abstract Number: 887

Fatigue and Physical Functioning in Patients with Giant Cell Arteritis

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Background/Purpose: Physical function is an established outcome measure for many rheumatic diseases and fatigue is a common disease manifestation across most, if not all, systemic inflammatory diseases. These two domains are often rated among the most important disease manifestations by patients. For giant cell arteritis (GCA), there exists limited data as to how the disease affects health-related quality of life, including fatigue and physical functioning.

Methods: Data from subjects with GCA participating in a multicenter longitudinal cohort from December 2014 to April 2016 were used. Fatigue and physical functioning were assessed using the Patient-Reported Outcomes Measurement Information System (PROMIS) instruments administered through computer adaptive testing (CAT). PROMIS instruments are calibrated so that scores are normally distributed with a mean of 50 and standard deviation of 10 in the US population. Higher scores signify better physical functioning and increased fatigue. Active disease was defined as physician global assessment > 0. Scores were compared to age-stratified population norms and a one sample t-tests was done. To assess whether PROMIS measures discriminated between active disease and remission in GCA, a mixed linear model was constructed with a random intercept introduced for each study subject.

Results: Data from 194 subjects that came for 435 study visits were used. The mean age of the participants was 73.7 (sd 7.9) years and 135 (70%) were women. At baseline 167 patients with GCA were in disease remission but nonetheless had substantially reduced physical functioning and increased fatigue compared to age-stratified population norms (Table). Thirteen patients had a total of 25 visits with active disease. Active disease was associated with a higher score of fatigue by 5.69 points (95% CI: 2.65; 8.73) and lower score of physical functioning by -1.76 points (95%CI: 4.14; 0.61).

Conclusion: Patients with GCA have substantially increased fatigue and reduced physical functioning compared to age-stratified population norms. PROMIS measures for fatigue and physical functioning can discriminate between active disease and remission in GCA. These

results highlight the benefit of combining patient-reported outcomes with physician-reported assessments in the evaluation of patients with GCA. **Table. Age-stratified scores for PROMIS instruments among patients with GCA during remission**

	Patients with GCA	Population Norms	P-value
Fatigue			
45-54	---	51.6	
55-64	54.6	49.7	0.04
65-74	52.9	48.1	0.001
≥75	53.8	48.0	<0.001
Physical functioning			
45-54	---	49.0	
55-64	42.4	47.5	0.03
65-74	42.6	47.2	<0.001
≥75	39.6	45.2	<0.001

PROMIS = Patient Reported Outcome Measurement Information System; GCA = giant cell arteritis

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Prevalence of Takayasu Arteritis in Young Women Presenting with Acute Ischemic Heart Disease

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Background/Purpose: Ischemic heart disease (IHD) is classically considered a disease of older men. However, 10% of myocardial infarctions occur in patients aged <45; also, in up to 25% of cases, these young patients are females. Classic atherosclerosis represents the most common etiology in young patients with IHD; additional causes include coronary vasospasm, coronary artery dissection, or vasculitis. Takayasu arteritis (TA) is a rare, large vessel vasculitis characterized by granulomatous inflammation of the aorta and its major branches, usually occurring in female patients aged ≤40. Purpose of this study was to evaluate the prevalence of TA in young women presenting with acute IHD in the Emergency Department.

Methods: We evaluated the hospital records of 172,790 consecutive young female patients (aged <45), who accessed the Emergency Department of our institution, a University Hospital serving a population of 1.5 million, over 8 consecutive years (2007-2015). The diagnosis at discharge was confirmed by either outpatient clinic or a telephone interview. Diagnosis of TA was established based on the 1990 ACR criteria.

Results: We identified 2,090 women aged <45 who presented with chest pain, dyspnea, palpitations, angina, heart failure, or cardiac arrest. Of these patients, 40 had IHD, as confirmed by elevated serum troponin T and compatible electrocardiographic changes. Seven additional patients, who died either before or shortly after accessing the Urgent Care department and in whom autopsy was not performed, were excluded from the study since their cause of death was not univocally identifiable. The etiology of IHD was 'classic' atherosclerosis in 24 cases, TA in 4 cases, vasospasm and sympathomimetic drug abuse in 3 cases each, coronary artery dissection and microvascular angina in 2 cases each, Takotsubo and radiation-induced cardiomyopathy in 1 case each.

Conclusion: In spite of an extremely low incidence in the general population (1-3 new cases/million/year in Europe or the United States), TA accounted for 10% of cases of acute IHD in female patients aged <45 in our study group. Since our Institution serves a population of 1.5 million, and coronary involvement may appear in up to a third of TA patients, the number of observed cases is compatible with the *a priori* expectations based on TA estimated incidence. Although 'classic' atherosclerosis remains the leading cause of IHD, in our study cohort TA was more frequent a cause than vasospasm and drug abuse. This finding is important, as while the latter two etiologies are commonly considered in young patients with cardiac ischemia, TA is very likely to be overlooked. Our data indicate that TA is not infrequent in younger females presenting with acute IHD. The development of TA in a young woman marks the onset of a severe, chronic disease characterized by recurrences and significant morbidity and mortality in the most productive years of life. Thus, it is crucial that a diagnosis of TA is not overlooked in a young woman presenting with IHD, in order to provide optimal care of the patient besides the management of the acute event.

Disclosure: G. Cavalli, None; **A. Tomelleri**, None; **E. Baldissera**, None; **L. Dagna**, None.

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Abstract Number: 889

The Utility of Patient-Reported Outcomes in Predicting Disease Activity in Patients with Takayasu's Arteritis

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Background/Purpose: Takayasu's arteritis (TAK) is a relapsing large vessel vasculitis. There are currently no reliable predictors of disease relapse. This study explored whether changes in patient-reported outcomes (PROs) during periods of remission are associated with future disease relapse in TAK.

Methods: Data from patients with TAK participating in a longitudinal cohort and/or a clinical trial in TAK were available for this analysis; quarterly assessments were made. Patients completed a patient global assessment (PtGA) on a 100-mm visual analog scale with higher scores indicating worse disease activity, and the 36-item Short Form Health Survey (SF-36) from which the physical component

scores (PCS) and mental component scores (MCS) were calculated and normalized to the general population (mean ± SD=50 ± 10) with lower scores indicating worse outcomes. ESR and CRP were measured at each visit. Physicians determined disease state (remission or active) at each visit and whether a relapse had occurred since last visit. The 2 visits preceding relapse (remission visits) and the study visit following or concurrent with relapse (relapse visit) were used for analysis. Robust generalized estimating equations in logistic regression models evaluated associations between changes in PtGA, PCS, MCS, ESR, and CRP in the 2 remission visits preceding relapse and disease relapse, adjusting for intra-subject correlations, age, and sex.

Results: 207 patients with TAK were seen at a total of 1,077 study visits (881 remission and 196 relapse visits); 97% were female with a mean age at entry (± SD) of 38.7 ± 12.9 years. Table 1 shows the mean PtGA, PCS, MCS, ESR and CRP during remission and relapse visits. An increase of 10 mm in PtGA or a decrease in PCS scores by 1 point between the 2 visits preceding relapse were associated with disease relapse (OR [95% CI]= 1.23 [1.05-1.45], p=0.011 for PtGA and 1.07 [1.02-1.13], p=0.016 for PCS). Changes in MCS, ESR, or CRP were not associated with disease relapse (OR=1.10 [0.96-1.05, p=0.638, OR=1.01 [0.97-1.04], p=0.546, OR=1.00 [0.95-1.03], p=0.864 for MCS, ESR and CRP respectively).

Conclusion: Changes in patient global assessment and the SF-36 physical component scores, but not the SF-36 mental component scores, during periods of remission are associated with future disease relapse. Changes in ESR or CRP during periods of remission do not predict future disease relapse. These findings suggest that patients are good predictors of disease relapse and the current measures of disease activity and definitions of relapse in TAK are problematic and should incorporate patient-reported outcomes.

Table 1. Measurements of patient-reported outcomes and acute phase reactants during periods of remission and relapse among patients with Takayasu's arteritis

Assessment	Remission visits (n=881)	Relapse visits (n=196)	p value
PtGA (mm) (mean ± SD)	28 ± 22	45 ± 23	<0.001
PCS (mean ± SD)	43.3 ± 10.1	39.0 ± 10.0	<0.001
MCS (mean ± SD)	46.5 ± 12.3	47.0 ± 11.0	0.593
ESR (mm/hr) (mean ± SD)	21.0 ± 17.9	25.6 ± 24.6	0.002
CRP (mg/dl) (mean ± SD)	5.8 ± 10.1	10.1 ± 19.2	<0.001

PtGA: Patient Global Assessment; SD: standard deviation;
PCS: SF-36 Physical Component Score; MCS: SF-36 Mental Component Scores;
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein

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Abstract Number: 890

Health-Related Domains of Importance to Patients with Takayasu's Arteritis

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Background/Purpose: The need to include patients' perspectives as key outcomes in clinical research is now widely recognized. This project was designed to describe the experience and burden of disease in patients with Takayasu's arteritis (TAK) during remission and active disease, and determine its effect on their daily lives.

Methods: Patients with TAK from the United States and Turkey were recruited to participate in semi-structured, one-on-one interviews or focus groups. The interviews and group sessions were recorded, transcribed, and entered into an Nvivo database. Patient-reported outcome themes were identified. Patients in the USA were invited to free-list terms that they associated with disease states. The Smith's Salience Index (SSI) was used to identify the most salient terms. SSI Scores range from 0 to 1 with higher scores indicating terms frequently mentioned and highly ranked by patients.

Results: 31 patients with TAK were involved in the qualitative research. 12 patients participated in individual interviews in the US and a total of 19 patients participated in three focus groups in Turkey. The most common themes that emerged were pain and discomfort, fatigue and low energy levels, and emotional impact. 75% of the study patients reported additional disease-specific domains of illness, most of which were similar between the two countries and only differed with regards to impact on finances (Table 1). The most salient terms identified by free-listing and ranking were pain/discomfort and emotional effects (SSI=0.51 and 0.37, respectively) during remission and pain/discomfort and fatigue/energy levels (SSI=0.56 and 0.33, respectively) during active disease (Figure 1).

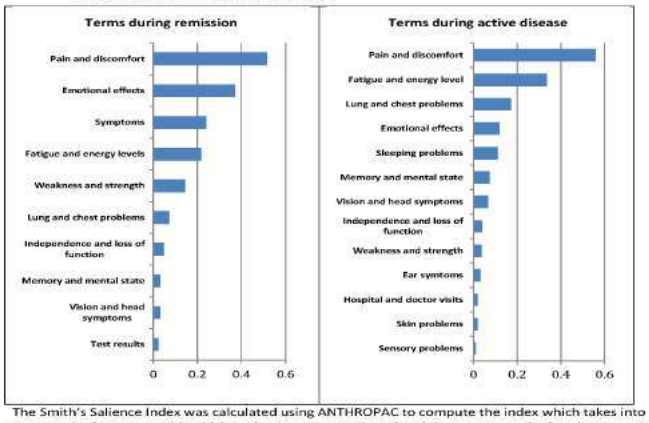
Conclusion: Patients with TAK report a range of disease-specific symptoms across different cultures and disease states that are generally not well or specifically captured by generic patient-reported outcome tools currently used in research and not at all addressed by physician-reported outcome measures. Patients identify different outcomes that are important during periods of active disease. Developing methods to capture outcomes of high importance to patients would advance research methodology to best capture the full spectrum of disease activity in TAK.

Table 1: Domains of illness commonly reported by patients with Takayasu's arteritis in the United States and Turkey

Domain	Definition	United States	Turkey
Pain/discomfort	Pain and discomfort associated with TAK	✓	✓
Fatigue/Low-energy	Fatigue and reduced energy felt secondary to having TAK	✓	✓
Impact on participation	Symptoms of TAK affect ability or desire to participate in activities	✓	✓
Impact on self-care	Symptoms of TAK affect ability to conduct personal care activities	✓	✓
Impact on finances	Financial burden associated with insurance/medication related to TAK	✓	
Impact on future	How TAK affects patient's future and plans for the future	✓	✓
Impact on school or work	Symptoms of TAK affect performance or ability to carry out specific tasks at work.	✓	✓
Limited interactions	Impact of TAK limits quantity or quality of interactions with family members or friends	✓	✓
Depression and anxiety	Impact of TAK leads to depression or anxiety	✓	✓
Stress and frustration	Stress and or frustration brought on by symptoms, diagnosis, or treatment of TAK	✓	✓

TAK: Takayasu's arteritis; "✓" indicates whether patients in that country mentioned the domain

Figure 1. Smith's Salience Indices of patients' free-listed and ranked terms in remission and active disease in Takayasu's arteritis



The Smith's Salience Index was calculated using ANTHROPAC to compute the index which takes into account the frequency with which each term was mentioned and the average rank of each term on an individual list. Scores range from 0 to 1 with higher scores indicating terms more frequently mentioned and highly ranked.

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Clinal Characterisitics and Diagnosis of Patients with Negative Temporal Artery Biopsy and without a Final Diagnosis of Giant Cell Arteritis

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Background/Purpose: To describe the characteristics and diagnosis of patients with negative temporal artery biopsy (TAB) for whom a final diagnosis of giant cell arteritis (GCA) was excluded.

Methods: We performed a prospective bicentric cohort study from January 2010 until December 2014. Patients with a clinical suspicion of GCA who underwent TAB were included. ACR criteria for the diagnosis of GCA, clinical and biological parameters, final diagnosis and glucocorticoids treatment were collected. Patients final diagnosis was (1) GCA with histological proof (TAB^+-GCA) ; (2) GCA without an histological proof (TAB^--GCA); (3) isolated polymyalgia rheumatica (PMR) and (4) another diagnosis (neither GCA nor PMR) (GCA^-PMR^-).

Results: 248 patients with a mean age of 73.7 years were included. Among them, 69 patients (27.8 %) had a final diagnosis of TAB^+-GCA; 65 patients (26.2%) had TAB^--GCA; 23 patients (9.2%) had PMR and 91 patients (36.7%) had another diagnosis (GCA^-PMR^-).

Among GCA$^-$PMR$^-$ patients, 9.8% fullfilled 3/5 ACR Criteria for the diagnostic of GCA. GCA$^-$PMR$^-$ patients less often had clinical signs of GCA: headaches (37% vs 65.8%, p <0.0001), scalp tenderness (18.6 % vs 39 %, p=0.0019), jaw claudication (13.7% vs 30%, p=0.0073) and temporal artery abnomalities (2.3% vs 18.9%, p=0.0006). These patients presented a lower C-reactive protein (CRP) and erythrocyte sedimentation rate (51.7 vs 70.5 mg/L, p=0.03; 53.6 vs 74 mm/hour, p=0.0003 respectively). The proportion of patients with CRP < 5 mg/L was more important in GCA$^-$PMR$^-$ patients (27.4% vs 10.8%, p=0.0014). The main final diagnoses for these patients were ophthalmologic (17%, n=16), systemic inflammatory (16.7%, n=15) and infectious diseases (13.1 %, n=12). No diagnosis was made in 20 of them (21.9%). Ophthalmologic causes included: non-arteritic anterior ischemic optic neuropathy (n=4), isolated ocular nerve palsy (n=4), papilledema, optic atrophy and macular degeneration (n=2 for each), retrobulbar neuritis and central retinal artery occlusion (n=1 each). Systematic diseases included: connective tissue diseases (Sjögren's syndrome (n=2), Sharp syndrome (n=1), Antiphoslipid syndrome (n=1)); systemic vasculitis (ANCA vasculitis (n=4), Takayasu arteritis (n=2), cryoglobulinemia (n=2)), Still's disease (n=2) and a diffuse infiltrative pneumonia. Infections consisted of intracellular infections (n=4), endocarditis, cellulitis, dental infection, urinary tract infection and pneumonia (n=1 each) and three suspected infections without documentation. Glucocorticoids were prescribed in 45% of GCA$^-$PMR$^-$patients.

Conclusion: Data available on the clinical characterisitics and diagnosis of GCA$^-$PMR$^-$ patients are scarse. Ophthalmologic signs and persistent inflammatory syndrome were the two main circumstances leading to a clinical suspicion of GCA. GCA$^-$PMR$^-$ patients have a significantly lower rate of specifical symptoms of GCA than TAB$^+$-GCA and more often a normal CRP. In almost half of these patients, glucocorticoids were initiated in the setting of an ophthalmologic emergency or suspected systemic disease. An algorithm combining GCA symptoms and CRP rate could be helpful to decide if TAB should be performed in patients with a clinical suspicion of GCA.

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Abstract Number: 892

FDG-PET CT Evaluation By Visual Grading Is Not Sufficiently Discriminative to Assess Disease Activity in Takayasu's Arteritis Patients with 'Persistent' Disease

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Background/Purpose: Takayasu arteritis (TAK) is a large-vessel vasculitis in which assessment of disease activity is challenging. Recent studies support that 18F-fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) is useful for disease activity assessment in TAK. In this study, we examined FDG/PET CT activity in clinically active, persistent and inactive TAK patients according to the physician's global assessment (PhGA).

Methods: A total of 42 FDG/PET CT images of 31 TAK patients (F/M: 25/6, mean age 41±15 yrs, disease duration 90±71 months) from were evaluated by visual and semiquantitative analysis (vascular SUV_{max}/liver SUV_{max}) for vascular inflammation. For the visual analysis using the liver as reference, 18F-FDG uptake was graded from grade 0 to 3. No uptake (grade 0) or any uptake lower than liver (grade 1) in major vessels were regarded as "inactive". Any uptake that is equal to or higher than liver (grade ≥2) was accepted as "active". PhGA, Kerr's criteria, and ITAS2010 and ITAS-A (both with ESR and CRP) were used for disease activity assessment. Persistent disease is defined as either elevated acute phase reactants (APR) without any clinical signs or symptoms or presence of only one of the Kerr's criteria regardless of the APR.

Results: At the time of FDG/PET CT imaging 14 (33.3%), 22 (52.4%), and 6 (14.3%) patients were regarded as active, persistent and inactive, respectively. Overall, 24 patients (57.1%) were active by FDG/PET CT visual grading with a median (range) of 2 (1-8) active vascular lesions per patient. Comparison of clinical and FDG/PET CT findings of patients who were regarded as active, persistent and

inactive by physician's assessment revealed higher ITAS2010 and ITAS-A scores, ESR and CRP levels in active and persistent patients (*Table*). PET-positivity by visual grade was observed in 78.6%, 45.5% and 50% of clinically active, persistent and inactive patients, respectively. In semiquantitative analysis, parallel with the clinical disease activity, an increasing trend was observed in SUV_{max} (inactive: 2.26, persistent: 3.22, active: 3.44) and SUV_{max} ratios (inactive: 1.00, persistent: 1.25, active: 1.43). When PET-positive and negative patients were compared, except for APR, no difference in disease activity by ITAS2010 scores were observed.

Conclusion: FDG/PET CT evaluated by visual analysis is useful in demonstrating vascular inflammation and its extent in active TAK patients. However, visual grading of FDG/PET CT is not sufficient enough to differentiate persistent and inactive patients. In these patients semiquantitative analysis should also be considered for further information about vascular inflammation. Further research is also needed to determine whether the increased FDG/PET uptake observed in persistent and inactive patients is associated with actual vascular inflammation that may lead to vascular damage.

Table. Clinical and FDG/PET CT findings according to disease activity by physician's assessment

	Active, n=14	**Persistent, n=22**	**Inactive, n=6**	**p value**
Age, years	41±14	40±14	38±15	0.94
Disease duration (months)	75±73	108±64	109±78	0.34
ESR (mm/h)	61±29	48±21	25±14	0.013
CRP (mg/L)	37.6±38.9	22.5±13.4	3.7±1.6	0.022
Prednisone, n (%)	6 (43.9)	17 (77.3)	3 (50)	0.095
Dose, median (IQR) mg/day	7.5 (5-50)	5 (5.7.5)	7.5 (5-20)	0.078
Other immunosupressives, n (%)	5 (35.7)	18 (81.8)	4 (66.7)	0.019
Methotrexate	1 (7.1)	4 (18.2)	2 (33.3)	
Azatioprine	4 (28.6)	10 (45.5)	2 (33.3)	
Leflunomide	0	4 (18.2)	2 (33.3)	
Biologics	2 (14.3)	1 (4.5)	0	
Active disease with Kerr's criteria, n (%)	14 (100)	0	0	-
ITAS2010 (0-51)	4.9±3.7	1.1±1.4	1.7±1.5	<0.001
ITAS-A (0-54)	7.1±4.2	3.1±1.7	2.0±1.7	<0.001
ITAS-ESR	7.0±4.3	3.3±1.6	1.8±1.3	
ITAS-CRP				
FDG/PET CT disease activity by visual grade, n (%)	11 (78.6)	10 (45.5)	3 (50)	0.14
Active	3 (21.4)	12 (54.5)	3 (50)	
Inactive				
Vascular SUVmax (highest of all vessels)	3.34±1.46	3.22±1.66	2.26±0.42	0.31
FDG/PET CT disease activity (SUVmax ratio) by using semiquantitative analysis¶	1.43±0.51	1.25±0.77	1.00±0.11	0.39
Number of active vascular lesions by visual grading of FDG/PET CT. median (range)	2 (0-7)	0 (0-8)	0.5 (0-2)	0.057

**The values are presented as mean±SD, unless indicated otherwise. ¶Observed maximum uptake (vascular SUV_{max}/liver SUV_{max}) among the vessels evaluated.*

Disclosure: A. U. Unal, None; **F. Dede**, None; **T. Y. Erdil**, None; **T. Ones**, None; **F. Alibaz-Oner**, None; **H. Direskeneli**, None.

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Preliminary Results of a Multi Modal Imaging Study Suggests a Better Accuracy for the Diagnosis of Giant Cell Arteritis

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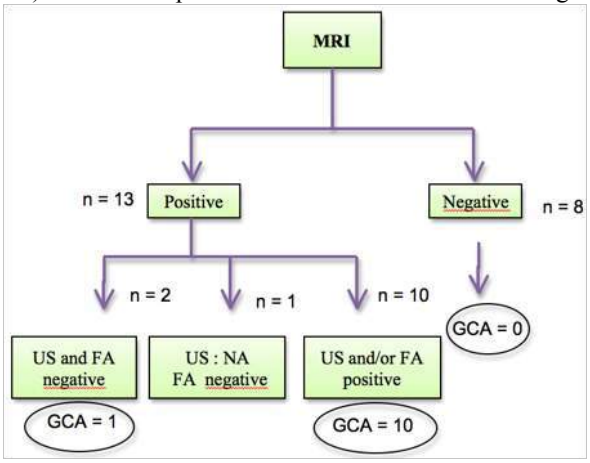
Background/Purpose: Giant Cell Arteritis (GCA) is the most common systemic vasculitis in patient over 50 years of age. It is a medical emergency as it may lead to ischemic complications, including permanent visual loss in 20 % of untreated patients. Early diagnosis enabling a rapid initiation of treatment is of critical importance. Positive Temporal Artery Biopsy (TAB) is the gold standard test. However, a negative TAB does not rule out the disease. Encephalic high-field MRI, temporal arteries ultrasonography (US) or fluorescein and indocyanine green angiogram (FA) have been widely studied as diagnostic tests. However, there is currently no consensus nor clearly identified algorithm for their use in a current practice, either alone or in combination. Our objective was to evaluate the accuracy and potential diagnostic value of a multi-modal imaging combination of encephalic high-field (3T) MRI, ultrasonography and fluorescein and indocyanine green angiogram (FA).

Methods: All patients referred for suspected GCA at our center between Dec 2014 and Mar 2016 were prospectively included in this study. The study was approved by an official external Ethical Review Board. PatientÕs informed consent was obtained upon inclusion. For each patient, encephalic 3T MRI, cervical and temporal arteries US and fluorescein and indocyanine green angiogram (FA) were performed. Subsequently, a TAB was performed. TAB-positive patients were considered cases of GCA ; TAB-negative patients files were reviewed by an expert in internal medicine using to determine (based on ACR criteria) whether they were not cases of GCA, or cases of TAB-negative GCA. Diagnostic accuracy of the combination of MRI, US and ICGA was statistically evaluated against this gold standard, first separately for each imaging modality, then using a multimodal classification tree.

Results: Twenty-two patients were included in this preliminary analysis. GCA was diagnosed in 11 patients. Fourteen patients presented a partial vision loss and 7 a visual acuity < 1/10, reflecting severe disease. MRI was positive in 13/22 patients and negative in 8/22 patients. No patient with negative MRI had GCA. When MRI was positive, if either US and/or FA was also positive, all patients were GCA (10/13 patients) (p=0,001). If MRI was positive and both US and FA were negative, final diagnosis was undetermined (two cases, one GCA and one no GCA).



Conclusion: This preliminary analysis suggests that a negative encephalic high-field MRI might be sufficient to rule out GCA, whether in cases of positive MRI the addition of the two other imaging modalities may have a good accuracy to rule-in the disease in cases at least one of them is positive. Such preliminary results have to be confirmed in the final analysis of the ongoing study.

Disclosure: A. Lecler, None; **S. Bidot**, None; **F. Charbonneau**, None; **S. Derrien**, None; **H. Picard**, None; **G. Clavel**, None.

Abstract Number: 894

Laboratory Tests in Giant Cell Arteritis – Do They Make the Cut?

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Background/Purpose: The initial suspicion of Giant cell arteritis (GCA) is often made in the setting of primary care or casualty by a non-rheumatologist. Whilst temporal artery biopsy (TAB) is the gold standard for diagnosis, this is not readily available and can be difficult to organise outside a teaching hospital setting. Furthermore, the reliability of this test is reduced by concomitant steroid use and the presence of skip lesions in vessel wall inflammation. Clinical features combined with biochemical markers of inflammation are often the most important tools in the diagnosis of giant cell arteritis. In this study, we evaluate the association of CRP, ESR, platelet count and alkaline phosphatase (ALP) with the results of temporal artery biopsy in a regional setting involving three District General Hospitals in the UK. As it has been over 5 years since the British Society for Rheumatology guidelines were published, we also audited whether our local practice follows them. Particularly, with regard to biopsy length which has been shown to influence the sensitivity of the test.

Methods: A retrospective analysis of all patients referred with suspected temporal arteritis to three centres in South East England between Feb 2010 and May 2015 was performed. Data regarding age, sex, date of biopsy, length of biopsy, biopsy result and ESR, CRP, platelet count and Alkaline Phosphatase (ALP) within 14 days prior to biopsy was collected.

Results: 542 patients were referred with suspected giant cell arteritis between Feb 2010 and May 2015. 119 patients were excluded owing to inconclusive biopsy findings and lack of laboratory results within 14 days prior to TAB. The majority of excluded patients had blood tests performed at other sites. 422 patients (131 men 291 women) were included. Mean age was 72.4. 95 TABS were positive and 327 negative. Mean biopsy length was 13.9mm. 32.2% of biopsies were less than 10mm. The mean ESR for positive biopsies was 58.6 versus 40.1 in negative biopsies ($p < 0.001$). 84.3% of patients with a positive temporal artery biopsy were associated with an ESR >10. The mean CRP in those with positive biopsies was 91.1 compared with 50.3 in those with a negative TAB ($p < 0.001$). 95.8% of patients with a positive TAB had a CRP >10. Patients with positive TABS also had higher platelet counts: mean platelet count was 424 in positive biopsies versus 334 in negative biopsies ($p < 0.001$). There was no statistical difference in ALP between those with positive and negative biopsies.

Conclusion: Laboratory correlates of inflammation remain good predictors of a positive temporal artery biopsy. A positive biopsy is associated with increased CRP, ESR and platelets. Our study shows that improvements need to be made locally to ensure the recommended temporal artery biopsy length (>10mm) is taken.

Disclosure: A. Jones, None; **J. Li**, None; **C. Li**, None.

Abstract Number: 895

Incidence of Osteoporotic Mayor Fractures in a Cohort of Patients with Polymyalgia Rheumatica

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Background/Purpose: Polymyalgia rheumatica (PMR) is an inflammatory disease associated with older age and long term use of glucocorticoids. As such a high incidence of osteoporosis and osteoporosis related fractures is expected. There is scarce information on incidence of osteoporotic-fractures in PMR in developing countries.The objective of this study was to identify the incidence rate and risk factors for osteoporotic-fractures in PMR patients.

Methods: we retrospectively reviewed electronic medical records (EMR) of patients registered in a large University hospital between years 2000-2015 with the diagnosis of PMR. Patients fulfilling ACR PMR 2012 criteria or with a clinical diagnose made by a rheumatologist were included. Patients with previous history of fractures, or with traumatic fractures were excluded. The major osteoporotic fractures (hip, wrist, and clinical spine) retrieved from the EMR, during the follow up period were taken as the endpoint event. Global, and sex-specific incidence rate with their 95% CI was calculated. A Cox proportional hazards models was fitted to analyze variables associated with suffering a fracture, including age, sex, smoking, hypertension, obesity, time on steroids, and steroids initial dose.

Results: 998 patients contributing a total of 4283 patient-years were included. Patient characteristics are shown in the table. During follow up 93 fractures were observed, for an overall incident rate (cases per 1000 patient-years) of 21.7 (95% CI: 17.7-26.6), 26.3 (95% CI: 21.2-32.5) for women, and 8.3 (95% CI: 4.3-15.9) for men. Forty-three incident osteoporotic hip fractures were observed for an overall incident rate of 10 (95% CI: 7.4-13.5) per/1000 patient-years, 12.5 (95% CI: 9.2-17) for women, and 2.8 (95% CI: 0.9-8.5) for men. The incident rate (cases per 1000 patient-years) for wrist and clinical vertebral fractures were: overall: 7 (95% CI: 4.9-10); 9 (95% CI: 6.3-13) for women, and 0.9 (95% CI: 0.13-6.5) for men; and 4.7 (95% CI: 3-7.2), 4.7 (95% CI: 2.8-7.8) for women, and 4.6 (95% CI: 1.9-11) for men, respectively. In the univariate analysis patients with fractures were significantly more females, of older age, and received steroids for a longer period (table). In the multivariate Cox proportional hazards model, the only variables associated with osteoporotic fractures were female sex (HR: 2.7 (95% CI: 1.6-4.6), and older age at diagnosis (HR: 1.1 (95% CI: 1-1.1).

Conclusion: There was a high incidence rate of major osteoporotic fractures among patients with PMR. Females and patients with older age were at higher risk. This risk should be taken into account when treating this disease. **Table 1** Patients characteristics

Variable	Patients with Fractures (n=93)	Patients without Fractures (n=905)	P Value
Females, n (%)	84 (90)	654 (72)	<0.001
Mean age at diagnosis (SD)	77.1 (6.6)	75.3 (7.9)	0.0280
Bilateral shoulder aching, n (%)	92 (99)	878 (97)	0.259
Bilateral pelvic girdle (hip) aching	64 (69)	616 (68)	0.885
Peripheral synovitis (distal swelling, tenosynovitis or arthritis	8 (8.7)	118 (13)	0.234
Mean erythrocyte sedimentation rate (SD)	59.4 (25.3)	56.4 (25.4)	0.3024
Mean Methyilprednisone initial dose (SD)	9.3 (4.47)	9.3 (4.4)	0.8825
Mean months on steroid treatment (SD)	27.7 (21.3)	23.4 (18.5)	0.0187

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Abstract Number: 896

Risk for Cardiovascular Disease in Giant Cell Arteritis and Polymyalgia Rheumatica

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Background/Purpose: chronic inflammatory diseases are at a substantially increased risk of cardiovascular events (CVE). Scarce data is available in patients with Giant cell arteritis (GCA) and Polymyalgia Rheumatica (PMR). Our objective was to analyze the incidence of CVE in these patients seen at a large University hospital.

Methods: we retrospectively reviewed electronic medical records (EMR) of patients registered between years 2000-2015 with the diagnosis of GCA or PMR. Patients fulfilling ACR 1990 criteria for GCA or ACR PMR 2012 criteria or with a diagnose made by a rheumatologist were included. Patients with history of CVE before diagnosis were excluded. Data regarding smoking status, blood pressure, obesity, diabetes, dyslipidemia, disease characteristics and treatments were recorded. CVE such as stroke or transient ischemic attack, coronary and peripheral vascular disease were identified from the EMR, during follow up. For patients with more than one CVE only the first one was considered for global incidence. Aortic aneurism (AA) was considered separately. Incidence rate with 95% CI of CVE is reported. In PMR patients a Cox proportional hazards models was fitted to analyze variables associated with CVE including age, sex, smoking, hypertension, diabetes mellitus, obesity, total cholesterol level, time on steroids, and use of aspirin.

Results: 872 PMR and 105 GCA were included . Demographic characteristics are shown in table 1. Among the 872 PMR patients (3945 patient-years (pt-yrs) of follow up)76 CVE occurred: incidence rate (cases per 1000 pt-yrs) : 19.3 (95% CI: 15.4-24.1); Females (F): 18 (14-23) and males (M): 24 (15-37). 46 patients suffered AA: incidence rate: 11.3/per 1000 pt-yrs (95% CI: 8.5-15); M: 22.3 (14.2-35) and F: 8.3 (5.7-12.2). Among the 105 ACG patients, 15 CVE occurred (501 pt-yrs of follow up): incidence rate: 29.9/per 1000 pt-yrs (95% CI: 18 - 49.6); M: 31.3 (7.8-125.3) and F: 29.7 (17.2-51.2). Nine patients had AA: incidence rate per 1000 pt-yrs: 17.9 (95% CI: 9.3–34.4); M: 30.4 (7.6-121.6) and F: 16 (7.6-33.6). The incidence rate of different CVE by gender, are shown in table 2. In the multivariate Cox proportional hazards model, variables associated with CVE were: diabetes mellitus: HR 3.3 (95% CI: 1.8-6.1), age at diagnosis: HR: 1.05 (95% CI: 1.01-1.08) and time on steroids (months of use): HR: 1.01 (95% CI: 1-1.02).

Conclusion: There was a high incidence of CVE and AA, in both patients with PMR and ACG. Diabetes, older age at diagnosis and prolonged use of steroids were significantly associated with more CVE. Table 1. Patient characteristics

Variable	PMR (n=872)	ACG (n=105)
Females, n (%)	678 (78)	88 (84)
Mean age at diagnosis (SD)	75.2 (7.9)	76.5 (5.9)
Mean time follow up (years), (SD)	4.8 (3.7)	12.1 (6.1)
Mean erythrocyte sedimentation rate (SD)	56.8 (25.4)	70.6 (25)
Polymyalgia symptoms, n (%)	872 (100)	59 (56)
Hypertension at baseline, n (%)	599 (68)	73 (69.5)
Diabetes at baseline, n (%)	64 (7.3)	10 (9.5)
Obesity at baseline (BMI (weight(kg)/Height(m)2)>30, n (%)	137 (16)	11 (10.5)
Smoking, n (%)		
Never	676 (77.5)	83 (79)
Former	144 (16.5)	12 (11.4)
Current	52 (5.9)	10 (9.5)
Median time on steroids (months) (IQR)	18 (12-29)	27.5 (18-42)

Table 2. Incidence rate of CV events by gender

	PMR (n=872)	ACG (n=105)
CV Event	Incidence rate/1000 patients-year (95 % CI)	Incidence rate/1000 patients-year (95 % CI)
CV Deaths		
Global	7.9 (5.6 -11)	13.3 (6.3 – 27.9)
Males	9.1 (4 – 18)	14.4 (2 – 102.3)
Females	7.6 (5.2 – 11)	13.1 (5.9 – 20.2)
Myocardial infarction		
Global	7.6 (5.3 – 11)	9.5 (3.9 – 22.8)
Males	12.6 (7.0 – 22.8)	14.6 (2.1 – 103.6)
Females	6.2 (4.0 –9.6)	8.7 (3.3 – 23.3)
Cerebrovascular accident		
Global	4.2 (2.8 – 6.3)	9.7 (4.1 – 23.4)
Males	2.8 (0.92 - 8.8)	14.7 (2.1 – 104.3)
Females	4.5 (2.9 – 7.0)	8.9 (3.4 – 23.9)
Peripheral vascular disease		
Global	4.4 (2.8 - 6.9)	9.8 (4.1 – 23.6)
Males	5.8 (2.4 – 13.9)	0
Females	4.0 (2.3 – 6.9)	11.3 (4.7 – 27)

Disclosure: F. B. Mollerach, None; **E. Bertiller**, None; **M. D. L. A. Gallardo**, None; **M. J. Martinez**, None; **M. Scolnik**, None; **J. Rosa**, None; **L. J. Catoggio**, None; **E. R. Soriano**, Abbvie, 2,Pfizer Inc, 3,UCB, 2,Janssen Pharmaceutica Product, L.P., 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Abbvie, 5,Pfizer Inc, 5,UCB, 5,Janssen Pharmaceutica Product, L.P., 5,Roche Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,Bristol-Myers Squibb, 5.

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Abstract Number: 897

Discordance Rates of Bilateral Temporal Artery Biopsies: A Retrospective Analysis

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Background/Purpose: Previous retrospective studies have suggested that simultaneous bilateral temporal artery biopsy (TAB) may lead to increased detection rates of giant cell arteritis (GCA). The term discordance represents one unilateral positive biopsy combined with one contralateral negative biopsy. Cases of discordance, through identification of false negatives, support the rationale for obtaining bilateral TAB. Reported discordance rates vary, ranging from 3 to 15 percent. Given the serious outcomes of untreated disease, including permanent blindness, establishing a consensus approach that increases detection of GCA is necessary. We aimed to identify cases of discordant temporal artery biopsies and to examine the role of performing simultaneous bilateral TAB in increasing the diagnostic yield of GCA.

Methods: Procedure codes for TAB were used to identify patients who underwent simultaneous bilateral temporal artery biopsies at three hospitals between the years 2009 and 2013. The following data was collected: biopsy results and length, age, gender, ESR and CRP levels. Patient data and biopsy results were compared based on their respective group: bilateral positive biopsies, bilateral negative biopsies and discordant biopsies. A combined positive biopsy group (bilateral positive biopsies and discordant biopsies) was additionally compared to the bilateral negative biopsy group. A separate chart review was performed for discordant biopsies to identify cases in which bilateral TAB may have increased the diagnostic yield of GCA.

Results: 181 patients were identified that had undergone simultaneous bilateral TAB. The mean age of the positive bilateral biopsy group was 78.2 years compared to 70.3 years for the negative bilateral biopsy group ($p < 0.001$). The mean age of the combined positive biopsy group was 77.1 years compared to 70.3 years for the biopsy negative group ($p<0.001$). 38/181 (21%) of patients had biopsy proven GCA. The overall discordance rate was 3.8% (7/181), comprising 18.4% (7/38) of the biopsy positive group. Biopsy lengths did not differ between groups. Average CRP values for the combined positive biopsy group were 6.4 mg/dL when compared to the biopsy negative group of 5.5 mg/dL ($p=0.04$). When considering localizing symptoms of the discordant group, bilateral TAB would have increased the yield of diagnosis definitively in one case (1/181 (0.5%) or 1/38 (2.6%) combined positive biopsy category alone). This may have increased to 3.3% (6/181) overall or 15.8% (6/38) as part of the combined positive group when considering best possible outcomes.

Conclusion: Bilateral TAB in patients with suspected giant cell arteritis may increase the diagnostic yield in a small number of overall cases. This increase may be more significant when considering the low prevalence of GCA diagnosis. Our results are consistent with previously reported discordance rates. The potential increase in diagnostic yield by performing bilateral TAB may have clinical significance given the negative implications of untreated disease and the side effects of long-term glucocorticoid therapy. Increasing age and CRP values may be associated with an increased likelihood of temporal arteritis.

Disclosure: J. Golenbiewski, None; **A. Halalau**, None.

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Abstract Number: 898

Treatment and Outcome of Patients with a Diagnosis of Healed Arteritis on Temporal Artery Biopsy

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Background/Purpose: Temporal artery biopsy (TAB) is the gold standard for the diagnosis of Giant Cell Arteritis (GCA), yet is limited by the presence of skip lesions and atypical pathological features. The entity of “healed arteritis” (HA) has been described in the literature as having focal to complete loss of internal elastic lamina, irregular intimal thickening, medial fibrosis or neovascularization, and usually scant, if any, inflammation.We analyzed the treatment patterns and outcomes in patients with a diagnosis of HA on TAB, compared with positive and negative biopsies in patients suspected of GCA.

Methods: We identified 18 patients with TAB pathology report indicating HA, and matched these to 27 with classically positive biopsies (POS), and 29 with negative biopsies (NEG). Statistical analysis compared corticosteroid (CS) management among these 3 cohorts.

Changes in CS dose immediately following TAB report were recorded. The 90 day CS requirements were expressed as area under the curve (AUC). Rheumatologists' pre-biopsy clinical suspicion for GCA, clinical and laboratory parameters, remission rates, and steroid-related adverse events were also analyzed.

Results: In the immediate post-biopsy follow-up period, HA and POS were both less likely to have dose decreases compared to NEG ($p<0.001$). However, the mean 90 day cumulative steroid dose AUC was significantly lower in HA versus POS (2663 mg vs 4206 mg; $p=0.01$), and were similar to NEG (2663 mg vs 2088mg; $p=0.34$). At long term follow up (mean 3.4 +/- 0.41 years), patients with HA tended to more often be in remission (defined as off steroids or tapering with quiescent disease). Both HA and NEG had fewer adverse effects from CS (29 and 14%, respectively) compared to POS (48%) ($p=0.02$). When patients with HA were compared to POS, they were significantly more likely to have a low-moderate (vs. high) pre-biopsy clinical index of suspicion for GCA ($p=0.0032$). Pre-biopsy duration and cumulative CS dose was similar among all groups, as was frequency of polymyalgia rheumatica (PMR). Mean erythrocyte sedimentation rate was significantly higher in the POS group compared to the HA and NEG groups (87 vs. 54 and 66 mm/hr, $p=0.023$ and 0.01 respectively), while not statistically different between the HA and NEG groups ($p=0.32$).

Conclusion: Although a report of HA on TAB did not result in immediate reductions in CS, our study shows that ultimately a lower 90 day cumulative dose of CS was utilized in HA. Our data suggests that patients with "healed arteritis" on pathology required less steroid and may be more aggressively tapered without adverse consequence.

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Abstract Number: 899

Disparities in Disease Characteristics, Treatment Pattern and Comorbidities in 1,858 Patients with Polymyalgia Rheumatica, Giant Cell Arteritis or Both Diseases

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Background/Purpose: To evaluate disease characteristics, treatment patterns and comorbidities in patients with polymyalgia rheumatica (PMR) to those with giant cell arteritis (GCA), or with both diseases (PMR+GCA).

Methods: Patients enrolled in the national database of the German Collaborative Arthritis Centres between 2007 and 2014 were stratified to PMR, GCA, PMR+GCA. They were compared with regard to patient characteristics, treatment and comorbidities, subdivided by disease duration. Logistic regression analyses were performed to evaluate the risk of having PMR+GCA and the association of this condition with malignant neoplasms. To put the prevalence of malignant neoplasms into perspective, patients of the three groups were matched with patients with rheumatoid arthritis (RA) by age, sex and disease duration.

Results: Data of 1,858 patients with PMR/ GCA/ PMR+GCA (n=1,420/ n=177/ n=261) were available for analysis. Mean age (73 years in each group) and disease duration (4.2/3.6/4.4 years) were comparable between these groups. Patients with PMR only were less often female (63/74/72%). PMR+GCA patients had the highest mean ESR value (21/23/26 mm/h), and more frequently hypertension (49/54/59%) and malignant neoplasms (7/7/12%). Osteoporosis was most prevalent in GCA (17/26/21%). PMR+GCA patients were most often current smokers, especially at disease onset (10/13/20%, $p<0.01$). They received the highest mean prednisone dose (5.9/6.1/9.6 mg/d) and had the highest analgesics use (14/24/39%). Multivariate analyses confirmed smoking to be associated with an increased risk of having PMR+GCA (OR=3.6, $p<0.001$), and identified patients with PMR+GCA to suffer from a higher malignancy risk (OR=2.0, $p=0.002$). When compared to RA patients, PMR and GCA patients showed a prevalence of malignancies similar to their matched RA counterparts (PMR 6.6% vs. RA 6.7%, 95% CI of the difference [-0.9; 1.2] , n=1,299 pairs, and GCA 6.5% vs. RA 7.6%, 95% CI [-2.0; 4.5], n=155 pairs), while patients with PMR+GCA had a significantly higher prevalence (PMR+GCA 12.3% vs. RA 6.7%, 95% CI [-7.6; -

3.4], n=235 pairs). Thereby the frequency of smoking did not differ significantly between the corresponding groups.

Conclusion: Patients with PMR+GCA had higher inflammatory activity, the highest need of glucocorticoids and a high comorbid burden. The observed associations of PMR+GCA with smoking on the one hand and with malignant neoplasms on the other should be further investigated, since both would significantly affect patient education and GCA management.

Disclosure: D. Huscher, None; **K. Albrecht**, None; **F. Buttgereit**, None; **M. Aringer**, None; **G. Hoese**, None; **W. Ochs**, None; **K. Thiele**, None; **A. Zink**, None.

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Abstract Number: 900

The Phenotype of Macrophages in the Inflamed Vascular Wall of Giant Cell Arteritis Resembles the Phenotype of Non-Classical Monocytes

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Background/Purpose: Macrophages are critical tissue destructive cells in the immunopathology of patients with giant cell arteritis (GCA). Macrophage precursors, monocytes, can be subclassified in three subsets: classical ($CD14^{bright}CD16-$) monocytes and the more pro-inflammatory intermediate ($CD14^{bright}CD16+$) and non-classical ($CD14^{dim}CD16+$) monocytes. Tissue migration of different monocyte subsets is determined by differential expression of chemokine receptors. Our previous data showed an altered distribution of monocyte subsets in newly diagnosed GCA patients. We therefore assessed the phenotype of macrophages in temporal arteries of GCA patients. Furthermore, we investigated expression of defined chemokine receptors and their ligands in temporal arteries of GCA patients.

Methods: We studied 16 positive temporal artery biopsies (TABs), all obtained from GCA patients fulfilling the ACR 1990 criteria . Twelve patients were without any treatment at the time of biopsy , 4 patients started corticosteroid treatment 2-14 days before the biopsy was taken. The phenotype of macrophages in the different layers of the TAB was studied by immunohistochemistry and by double staining using immunofluorescence-labeled antibodies. Expression of chemokines in TABs was determined by digitally analyzing the diffuse positive staining. Cellular staining was assessed by semi-quantitative scoring methods.

Results: All GCA TABs studied showed transmural inflammation, as CD68 expressing macrophages were detected throughout the vessel wall. Non-classical monocyte markers CD16 and CX3CR1 were strongly expressed at macrophage rich areas and immunofluorescent double staining confirmed that these macrophages co-expressed CD16 and CX3CR1. CCR2, a marker of classical monocytes, was less abundantly expressed and immunofluorescent double staining confirmed that most CD16+ cells did not express CCR2. Both CCR2 ligand CCL2 and CX3CR1 ligand CX3CL1 were readily detected in the GCA TAB.

Conclusion: The phenotype of macrophages in the TAB of GCA patients resembled the phenotype of non-classical monocytes. CD16 and CX3CR1 were co-expressed on tissue macrophages therefore indicating that migration of CD16+ non-classical monocytes to the GCA lesion may be driven by the CX3CR1-CX3CL1 axis.

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Abstract Number: 901

Clinical Features of Takayasu's Arteritis from an Inception Cohort: Early Disease Is Characterized By 'systemic Inflammation'

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Background/Purpose: There is only retrospective and very limited data for the long term prognosis of Takayasu's Arteritis (TAK), a rare large-vessel vasculitis. In this study, we aimed to present the preliminary results of a Takayasu Inception Cohort settled for long term, prospective follow-up of only newly-diagnosed patients with TAK.

Methods: Patients fullfilling the ACR 1990 criteria for TAK and diagnosed in the last 12 months were included to the study. Patients' data were recorded in an electronic database of an international "Takayasu's Arteritis Registry" requiring baseline and at least annual visits. Data is compared with an historical Turkish cohort previously published by Turkish Takayasu Arteritis Study Group(*Bıçakçıgil, et al, 2009)*.

Results: The study included 128 patients (age: 38.9±13.1 years,F/M: 112/16) with TAK from 15 tertiary Rheumatology centers in Turkey and one center from Japan. The mean symptom duration was 5.2 years at diagnosis. According to the angiographic classification, 59.2% of the study group had type I and only 17.2% had type V disease. When we compared our results to our retrospective cohort, constitutional symptoms (72.2% vs 66%) and limb claudication (62.3% vs 48%) were observed to be more frequent, whereas pulselessness (35.6% vs 88%) was less in the inception cohort.(Table 1) Carotidynia was present only in the inception cohort. Similarly, mucocutaneous symptoms also seem to be a feature of newly-diagnosed disease (26.4% vs 8.8%).Regarding comorbidities at diagnosis, the rate of dyslipidemia was 22%, diabetes mellitus 6%, smoking 28.5% and obesity (BMI>30) 15.8% among TAK patients. All patients were givenoral corticosteroid (CS) therapy (0.5-1 mg/kg) at diagnosis, 10 patients (7.8%) also having CS pulses. In addition to CSs, 55 patients (43 %) were given methotrexate, 14 patients (11%) azathioprine and 5 (4%) cyclophosphomide at disease-onset.

Conclusion: Our results suggest that, in an inception cohort, signs and symptoms of 'systemic inflammation' is more prominent in newly-diagnosed TAK patients, whereas vascular extent and damage accumulates during the disease course. The long term follow-up of our inception cohort will better show the actual course and predictors of prognosis in TAK. Table 1: Clinical characteristics of Inception and Retrospective Cohorts from Turkey.

	Inception Cohort (n=128)	Retrospective Cohort (*Bıçakçıgil, et al*) (n=248)
Constitutional symptoms	91/126 (72.2%)	163/248/ (66%)
Limb claudication	66/106 (62.3%)	119/248 (48%)
Carotidynia	26/104 (25%)	-
Pulseless	37/104 (35.6%)	218/248 (88%)
Musculoskeletal manifestations	66/124 (53.2%)	104/248 (42%)
Mucocutaneous manifestations	32/121 (26.4)	22/248 (8.8%)
Respiratory manifestations	40/122 (32.8%)	22/184 (12%)
Neurologic manifestations	58/124 (46.8%)	156/248 (63%)
Cardiac involvement	23/106 (21.7 %)	141/248 (57%)
Ophthalmologic involvement	29/125 (23.2%)	57/248 (36%)

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Abstract Number: 902

High Disease Activity Scores and Leptin Levels in Takayasu Patients with Overweight and Obesity

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Background/Purpose: We aimed to determine the prevalence of overweight, obesity and metabolic syndrome (MetS) and leptin levels in patients with Takayasu arteritis (TA) and their associations with disease activity.

Methods: This cross-sectional study included 32 patients with TA followed up at a Rheumatology clinic of a university hospital. 25 age- and gender-matched patients with systemic lupus erythematosus (SLE) were enrolled as controls. According to the TA follow-up protocol of the Rheumatology and Radiology Board of our hospital, the patients were followed using 3-6 monthly B-mode/Doppler USG examinations and 6-12 monhtly magnetic resonance angiography (MRA). Disease activity was assessed by using the Indian Takayasu Clinical Activity Score 2010-A (ITAS2010-A), radiological activity parameters, and acute-phase reactants (AFR). We used carotid intima media thickness (IMT) measurements and the presence of atheromatous plaques in carotid arteries as indicators of atherosclerosis. We also searched serum leptin and ghrelin levels and their relationship with obesity, overweight and MetS in Takayasu patients.

Results: 32 patients (28 females; mean age: 43 years) who fulfilled the American College of Rheumatology (ACR) criteria for TA were enrolled in this study. The prevalences of overweight (body mass index (BMI) between 25 and 30 kg/m^2), obesity (BMI ≥30 kg/m^2) and MetS (The National Cholesterol Education Program Adult Treatment Panel III criteria), were 26.5%, 17.6% and 23.5%, respectively. These prevalences were similar in TA and SLE patients. TA patients with obesity/overweight had higher ITAS2010-A scores compared with those without obesity/overweight and those with MetS had higher radiological activity scores compared with those without MetS although they had similar AFR levels. TA patients with obesity/overweight had also higher leptin levels. The frequency of atheromatous

plaque was found to be higher in patients with MetS than those without MetS although there was no difference in carotid IMTs between the groups (Table 1).

Conclusion: This study showed that TA patients had similar prevalences of obesity/overweight and MetS to those found in SLE patients. It also suggested that there was a relationship between disease activity and obesity/overweight and MetS in TA patients. TA patients with greater BMIs had also increased leptin levels.

Table 1. Clinical and laboratory features in Takayasu patients with overweight/obesity and MetS

		Metabolic syndrome		P value	Overweight and obesity		P value
		(+) (n=8)	(-) (n=24)		(+) (n=15)	(-) (n=17)	
ITAS2010-A	Active(n)	1	4	>0.05	5	0	0.015*
	Inactive(n)	7	20		10	17	
Radiologic activity	Active(n)	5	6	0.04*	6	5	>0.05
	Inactive(n)	2	17		8	11	
CRP (mg/L)		11.5	11.4	>0.05	13.6	9.6	>0.05
ESR (mm/h)		35.0	26.0	>0.05	30.7	27.1	>0.05
Presence of atheromatous plaque (n)		4	1	0.04*	3	2	>0.05
Leptin (ng/mL)		58	79	>0.05	100	53	0.05*
Ghrelin (pg/mL)		295	284	>0.05	249	317	>0.05

Disclosure: G. Kenar, None; **H. Yarkan**, None; **B. Zengin**, None; **G. Can**, None; **M. Birlik**, None; **N. Akkoc**, None; **F. Onen**, None.

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Abstract Number: 903

Temporal Arteritis: Is There Any Correlation Between Ultrasonographic Arterial Wall Involvement and the Inflammatory Cellular Infiltrate at Histological Examination?

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Background/Purpose: Ultrasonographic alterations such as the halo sign and the compression test are now accepted as surrogate markers of artery inflammation. No data have yet been published on the correlation between the ultrasonographic grading of arterial wall inflammation and the grading of cellular infiltrate. To compare a semiquantitative ultrasonographic grading (USG) of TA involvement (halo sign and media-intima thickness) with a semiquantitative grading of the inflammatory burden in patients with giant cell (temporal) arteritis (GCA).

Methods: fiftheen consecutive patients with new onset clinical symptoms and satisfiing ACR criteria for GCA, with positive halo sign in the frontal branch and positive temporal artery biopsy have been enrolled. For each patients we performed power Doppler ultrasonography of temporal artery with a 18-6 MHz linear probe (Esaote MyLab 70) and measured the maximum halo thickness of TA frontal branch in a quantitative and semiquantitave (0-3) grade of involvement (0= < 0.37 mm, 1= in between 0.38-0.44, 2 = 0.45- 0.6 mm, 3 = > 0.6). TA biopsy was done in the same frontal branch evalutaed with US. Then we compared the ultrasonographic data with a semiquantitative (0: absent, 1: mild, 2: moderate, 3: severe) grading of the trasmural cellular inflammatory infiltrate and with the intima-media thickness of the TA biopsy specimen. Moreover US results were correlated with the other patterns of histological alterations (giant cells, calcifications, laminar necrosis). Correlation between variables was done by Rho of Spearman method.

Results: 15 patients, 6 males and 9 females (mean age 71.6± 7 years - duration symptoms at onset 1.7 ± 1.3 months - mean ESR 60 mm/h ±29 - mean CRP 8 mg/dl ± 5.2) entered the study. US halo sign was bilateral in 10/15 (66,7%). The mean halo thickness was 0.53 mm ± 0.12. Five patients had USG =1, six patients =2 and four patients =3. The hystological inflammatory grade 1 was present in seven pts, grade 2 in four and grade 3 in four pts. No significant correlation were found between USG and histological inflammatory grade, nor with the presence of giant cells, calcifications, laminar necrosis and intima-media thickness.

Conclusion: No correlation has been found between the size of the halo sign and the hystological inflammatory grading.

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Abstract Number: 904

Clinical Features and Mortality of 411 Chinese Takayasu's Arteritis Patients

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Background/Purpose: To investigate the clinical features and long-term outcome of Chinese Takayasu arteritis (TAK) patients.

Methods: Medical records of 411 Chinese TAK in-patients (325 female, 86 male) who fulfilled 1990 ACR classification criteria during 1990 to 2014 were retrospectively reviewed. Clinical manifestations, angiographic presentations, and causes of death were collected and analyzed.

Results: The median age at disease-onset was 23(18, 30) years old, and the median disease duration was 21(6, 60) months. Aortic aneurysm, renal dysfunction, and heart failure were more likely to be found in patients with heart involvement, while weight loss and arthralgia were more likely occur in patients without. Pulse deficit were more likely to be found in patients with cerebral artery involvement, while pericarditis, ischemic heart disease, and fever were more likely occur in patients without. No difference were found in patients with and without renal, or pulmonary arteries involvement (See Table 1). Subclavian(79%), carotid(64%), abdominal aorta(38%), vertebral(29%), mesenteric(28%), thoracic aorta(21%), innominate(20%), iliacofemoral(11%), ascending aorta(10%), and aortic arch(8%) were most commonly involved. Stenosis (93%) and occlusion (59%) were much more common than dilation (20%) and aneurysm (6%) (Table 2). Analysis of 10 deceased patients found heart failure (42%), hemorrhage (17%), and pulmonary infection (17%) were the top 3 direct causes of death, and congestive heart failure, secondary hypertension, and long disease duration were risk factors for poor prognosis in TAK (Table 3).

Conclusion: The clinical manifestations, blood vessel involvement, and angiographic presentations in Chinese TAK patients are different from reports in the literature. Heart failure is the leading cause of death in these patients and are the risk factor of poor prognosis.

Table 1 Major characteristics of 411 Chinese TAK patients and comparisons between different groups Patient Number (%)

	Total	Heart lesions			Cerebral arteries involvement			Renal arteries involvement			Pulmonary arteries involvement		
	N (%)	With	Without	*P*	With	Without	*P*	With	Without	*P*	With	Without	*P*
N	**411**	**164**	**247**		**199**	**212**		**198**	**213**		**30**	**381**	
Gender				0.537			0.036			0.176			0.204
Female	325(79.1)	127(77.4)	198(80.2)		166(83.4)	159(75.0)		151(76.3)	174(81.7)		21(70.0)	304(79.8)	
Male	86(20.9)	37(22.6)	49(19.8)		33(16.6)	53(25.0)		47(23.7)	39(18.3)		9(30.0)	77(20.2)	
Age at onset (years)	23*	23*	23*	0.893	23*	23*	0.484	22*	25*	0.008	25*	23*	0.234
	(18,30)	(17,30)	(18,31)		(18,30)	(17,30)		(17,28)	(19,32)		(19,33)	(18,30)	
Duration of disease at onset (months)	21*	24*	16*	0.001	36*	11*	<0.001	24*	18*	0.668	24*	21*	0.782
	(6.0,60)	(7.3,84)	(4.0,48)		(10,96)	(4.0,36)		(5.0,72)	(6,60)		(8.5,50)	(5.5,60)	
Constitutional findings													
Fever	128(31.1)	45(27.4)	83(33.6)	0.186	45(22.6)	83(39.2)	<0.001	58(26.8)	75(35.2)	0.065	10(33.3)	118(31.0)	0.788
Malaise	122(29.7)	51(31.1)	71(28.7)	0.609	62(31.2)	60(28.3)	0.527	58(26.8)	69(32.4)	0.212	16(53.3)	106(27.8)	0.003
Weight loss	82(20.0)	41(25.0)	41(16.6)	0.037	34(8.3)	48(22.6)	0.159	36(18.2)	46(21.6)	0.387	10(33.3)	72(18.9)	0.057
Skin rash	32(7.8)	11(6.7)	21(8.5)	0.506	12(2.9)	20(9.4)	0.198	14(7.1)	18(8.5)	0.602	2(6.7)	30(7.9)	1.000[†]
Joint pain	37(9.0)	7(4.3)	30(12.1)	0.006	18(5.9)	21(9.9)	0.509	12(6.1)	25(11.7)	0.045	3(10.0)	34(8.9)	0.743[†]
Claudification													
Upper limbs	60(14.6)	20(12.2)	40(16.2)	0.261	33(16.6)	27(12.7)	0.270	21(10.6)	39(18.3)	0.027	6(20.0)	54(14.2)	0.418[†]
Lower limbs	57(13.9)	22(13.4)	35(14.2)	0.828	28(14.1)	29(13.7)	0.909	44(22.2)	13(6.1)	<0.001	3(10.0)	54(14.2)	0.783[†]
Carotid arteries bruit	257(62.5)	109(66.5)	148(59.9)	0.180	133(32.4)	124(58.5)	0.081	119(60.1)	138(64.8)	0.327	21(70.0)	236(61.9)	0.380
Pulse deficit	101(24.6)	41(25.0)	60(24.3)	0.870	68(31.7)	33(17.9)	0.001	35(17.7)	66(31.0)	0.002	4(13.3)	97(25.5)	0.137
Aortic regurgitation murmur	64(15.6)	38(23.2)	26(10.5)	0.001	30(15.1)	34(16.0)	0.788	25(12.6)	39(18.3)	0.112	6(20.0)	58(15.2)	0.441[†]
Heart lesions													
Heart failure	36(8.8)	31(18.9)	5(2.0)	<0.001	19(9.5)	17(8.0)	0.584	23(11.6)	13(6.1)	0.048	7(23.3)	29(7.6)	0.010[†]
Valval lesions	137(33.3)	137(83.5)	0	<0.001	61(30.7)	76(35.8)	0.264	75(37.9)	62(29.1)	0.059	17(56.7)	120(31.5)	0.005
Ischemic heart disease	14(3.4)	14(8.5)	0	<0.001	5(2.5)	9(4.2)	0.024	6(3.0)	8(3.8)	0.685	3(10.0)	11(2.9)	0.074[†]
Myocardial infarction	3(0.7)	3(1.8)	0	0.063	1(0.5)	2(0.9)	1.000[†]	2(1.0)	1(0.5)	0.611	1(3.3)	2(0.5)	0.204[†]
Pericarditis	30(7.3)	30(18.3)	0	<0.001	9(4.5)	21(9.9)	0.036	15(7.6)	15(7.0)	0.835	3(10.0)	27(7.1)	0.555
Systemic hypertension	165(40.1)	81(49.4)	84(34.0)	0.002	86(43.2)	79(37.5)	0.219	132(66.7)	33(15.5)	<0.001	8(26.7)	157(41.2)	0.118
Hypertrophy of left ventricle in ECG	59(14.4)	38(23.2)	21(8.5)	<0.001	30(20.4)	29(18.4)	0.907	43(28.7)	16(11.2)	<0.001	6(20.0)	53(13.9)	0.234[†]
Stroke	22(5.4)	5(3.0)	17(6.9)	0.091	22(11.1)	0	<0.001	7(3.5)	15(7.0)	0.115	0	22(5.8)	0.391[†]
Renal dysfunction	13(3.2)	11(6.7)	2(0.8)	0.001	7(3.5)	6(2.8)	0.691	9(4.5)	4(1.9)	0.123	1(3.3)	12(3.1)	1.000[†]
Aortic aneurysm	17(4.1)	11(6.7)	6(2.4)	0.034	5(2.5)	12(5.7)	0.109	12(6.1)	5(2.3)	0.059	3(10.0)	14(3.7)	0.119[†]
Laboratory findings													
ESR at baseline	26*	28*	26*	0.825	25*	31*	0.021	26*	26.5*	0.173	21*	27*	0.494
(mm/hr)	(11,65)	(11,69)	(11,65)		(11,52)	(12,80)		(11,55)	(11,80)		(11,56)	(11,66.5)	
hs-CRP at baseline	8.8*	10.0*	7.0*	0.017	5.7*	10.0*	0.001	6.5*	10*	0.022	10.0*	8.8*	0.095
(mg/L)	(2,12.5)	(2.9,26.0)	(1.8,10)		(1.7,10)	(2.4,27.6)		(1.7,10.0)	(2.3,22.1)		(5.1,55.2)	(2.0,11.1)	
Count of WBC before	8.2*	8.5*	8.0*	0.213	8.2*	8.1*	0.979	7.7*	8.4*	0.387	9.4*	8.2*	0.380
GCs ($*10^9$/L)	(6.6,11.0)	(6.7,11.4)	(6.5,10.6)		(6.5,11.1)	(6.6,11.0)		(6.5,11.3)	(6.7,10.7)		(7.1,11.2)	(6.5,11.0)	
Numano's angiographic classification													
Type I	91(22.1)												
Type IIa	16(3.9)												
Type IIb	16(3.9)												
Type III	12(2.9)												
Type IV	26(63)												
Type V	250(60.8)												

TAK: Takayasu's arteritis, ESR: erythrocyte sediment rate, hs-CRP: high sensitive C-reactive protein, WBC: white blood cell, GCs: glucocorticoids.
* Median (quantiles). [†] P < 0.05. [‡] Fisher's exact test

Table 2 The manifestations of vessels involved in 411 Chinese Takayasu's patients

Vessels	Stenosis	Occlusion	Dilatation	Aneurysm	Sum (n=411)	Mwipatayi *et al* [n=272][1]	X^2	*P*-value
Subclavian artery	232 (56.4%)	130 (31.6%)	11 (2.7%)	5 (1.2%)	**326 (79.3%)**			
Carotid artery	235 (57.2%)	112 (27.3%)	17 (4.1%)	3 (0.7%)	**262 (63.7%)**	83 (30.5%)	72.313	<0.001
Renal artery	182 (44.3%)	43 (10.5%)	6 (1.5%)	2 (0.5%)	**198 (48.2%)**			
Abdominal aorta	134 (32.6%)	12 (2.9%)	16 (3.9%)	10 (2.4%)	**158 (38.4%)**	186 (68.4%)	58.69	<0.001
Vertebral artery	82 (20.0%)	46 (11.2%)	10 (2.4%)	1 (0.2%)	**117 (28.5%)**			
Mesenteric artery	90 (21.9%)	33 (8.0%)	1 (0.2%)	0	**116 (28.2%)**	101 (37.1%)	5.992	0.014
Thoracic aorta	73 (17.8%)	0	14 (3.4%)	3 (0.7%)	**86 (20.9%)**	158 (58.1%)	98.45	<0.001
Innominate artery	61 (14.8%)	16 (3.9%)	8 (1.9%)	1 (0.2%)	**81 (19.7%)**	43 (15.8%)	1.675	0.196
Iliocefemoral artery	39 (9.5%)	18 (4.4%)	0	4(1.0%)	**44 (10.7%)**	74 (27.2%)	31.181	<0.001
Ascending aorta	4 (1.0%)	0	37 (9.0%)	3 (0.7%)	**39 (9.5%)**	65 (23.9%)	26.323	<0.001
Aortic arch	25 (6.1%)	0	7 (1.7%)	1 (0.2%)	**32 (7.8%)**	90 (33.1%)	71.422	<0.001
Pulmonary artery	17 (4.1%)	13 (3.2%)	1 (0.2%)	0	**25 (6.1%)**	24 (8.8%)	1.846	0.174
Coronary artery	14 (3.4%)	4 (1.0%)	0	0	**14 (3.4%)**			
Total	**381 (92.7%)**	**241 (58.6%)**	**84 (20.4%)**	**24 (5.8%)**				

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1. Mwipatayi BP, Jeffery PC, Beningfield SJ, et al. (2005) Takayasu arteritis: clinical features and management: report of 272 cases. ANZ J Surg 75: 110-117.

Table 3 Demographic data and clinical features of deceased group and control group, and analysis of risk factors for TAK prognosis by the model of binary logistic regression

	Deceased group (n=10)	Control group (n=40)	*P*-value
Gender	Male 2 / Female 8	Male 8 / Female 32	
Age at admission or decease (years)	30.5 (17.8, 62.8)	27.5 (20.3, 40.5)	0.636
Age at onset (years)	18.5 (14.0, 26.3)	22.0 (16.3, 30.0)	0.238
Age at diagnosis (years)	20.0 (15.5, 34.8)	25.0 (19.0, 38.5)	0.409
Disease duration / Survival time# (months)	102.5 (46.0, 242.5)	36.0 (12.0, 63.0)	0.017*
Disease duration / Survival time# (years)	8.5 (3.8, 20.2)	3.0 (1.0, 5.3)	0.017*
With active TAK disease	4 (40%)	32 (80%)	0.020*
Angio-graphic type			
I	1	9	
IIa	0	5	
IIb	1	4	
III	0	1	
IV	0	3	
V	8	18	
Direct cause of death			
heart failure	5 (41.7%)		
hemorrhage	2 (16.7%)		
pulmonary infection	2 (16.7%)		
sudden death	1 (8.3%)		
postoperative complication	1 (8.3%)		
end-stage malignancy	1 (8.3%)		
Serious complications			
Aortic regurgitation	4 (40%)	8 (20%)	0.225
Secondary hypertension	8 (80%)	12 (30%)	0.004*

Retinal involvement	2 (20%)	1 (2.5%)	0.098
Aneurysm	2 (20%)	4 (10%)	0.586
Group			
I	1 (10%)	21 (52.5%)	
II	3 (30%)	14 (35%)	
III	6 (60%)	5 (12.5%)	
Cardiovascular system manifestations			
Congestive heart failure	5 (50%)	6 (15%)	0.017*
Pulse deficiency	8 (80%)	25 (62.5%)	0.296
Claudication	3 (30%)	17 (42.5%)	0.720
Vessel bruit	8 (80%)	29 (72.5%)	0.629
Carotidynia	3 (30%)	3 (7.5%)	0.086
Stenosis of renal arteries	5 (50%)	16 (40%)	0.567
Coarctation of the aorta	5 (50%)	13 (32.5%)	0.302
Imbalance of blood pressure in upper limbs	9 (90%)	28 (70%)	0.197
Nerve system manifestations			
Dizziness	6 (60%)	23 (57.5%)	0.886
Headache	3 (30%)	17 (42.5%)	0.720
Blurred vision	1 (10%)	17 (42.5%)	0.073
Loss of vision	0	8 (20%)	0.184
Pulmonary hypertension	4 (40%)	10 (25%)	0.436
Pulmonary arteries involvement	1 (10%)	8 (20%)	0.665
Systemic manifestations			
Fever	7 (70%)	16 (40%)	0.089
Weight loss	5 (50%)	10 (25%)	0.123
Fatigue / malaise	8 (80%)	27 (67.5%)	0.440
Mucocutaneous lesions	2 (20%)	11 (27.5%)	1.000
Skeletomuscular system manifestations	2 (20%)	10 (25%)	1.000
operations or procedures for TAK	6[$] (60%)	14 (35%)	0.149
	Odds ratio	**95% CI**	***p*-value**
Secondary hypertension	9.333	1.721 – 50.614	0.010
Congestive heart failure	5.667	1.248 – 25.734	0.025
Disease duration / Survival time (months)	1.007	1.001 – 1.014	0.027
Disease duration / Survival time (years)	1.090	1.010 – 1.177	0.027
With active TAK disease	0.167	0.038 – 0.735	0.018
Retinal lesion	9.750	0.786 – 120.950	0.076
Carotidynia	0.189	0.032 – 1.136	0.069
Blurred vision	6.652	0.768 – 57.624	0.085
Fever	0.286	0.064 – 1.272	0.100

[#] Duration between onset of TAK and admission to (or decease in) our center.

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Abstract Number: 905

Platelet Activation, As Measured By Plasma Soluble Glycoprotein VI, Is Not Associated with Disease Activity or Ischaemic Events in Giant Cell Arteritis

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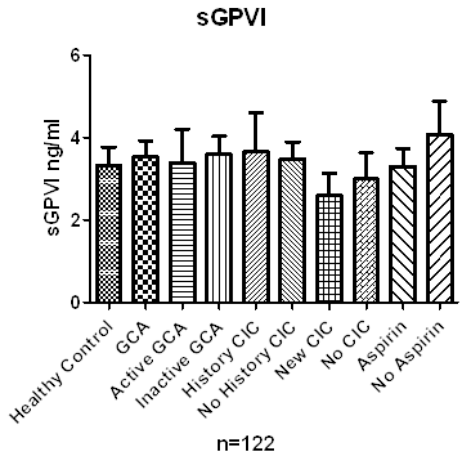
Background/Purpose: Patients with Giant Cell Arteritis (GCA) have an increased risk of devastating cranial ischaemic complications including vision loss and stroke. The BSR guidelines recommend platelet inhibition with aspirin to reduce the risk of ischaemic complications in GCA. Thrombosis occurs following platelet activation. The glycoprotein VI (GPVI) receptor is found exclusively on platelets and megakaryocytes. The proteolytic cleavage of GPVI occurs following platelet activation and is detectable in the plasma as soluble GPVI (sGPVI). Therefore elevated plasma sGPVI is a marker of platelet activation and a risk marker for adverse cardiovascular outcomes. Enhanced platelet activation is observed in inflammatory arthritis. We hypothesized that GCA would also be associated with platelet hyperreactivity which might support the rationale for aspirin use in GCA.

Methods: Following ethics approval and informed consent, blood samples were taken from patients with GCA. Healthy control samples were obtained from volunteers. Demographic and clinical data were collected for all participants. Blood samples were processed as double spun platelet poor plasma. sGPVI levels were measured using ELISA. sGPVI levels were compared between patients with GCA and healthy controls, between active and inactive GCA, and between those with and without cranial ischaemic compications. Mann-Whitney U test was used to compare groups. Spearman¡¯s Rank Correlation Coefficient was used to assess for associations between sGPVI levels and demographic and clinical markers. GraphPad Prism and SPSS were used for data analysis.

Results: 122 patients were included in the study, 70 with GCA and 53 healthy controls. Of the GCA patients, 19 had active disease and 19 had had cranial-ischaemic complications. There was no difference in sGPVI levels between GCA and healthy controls , median (IQR) 2.32 ng/ml (1.60, 4.21) vs 2.19 ng/ml (1.72, 3.31) (p=0.76). sGPVI levels were similar in GCA patients with active and inactive disease, median 2.31 ng/ml (1.86, 4.21) vs 2.33 ng/ml (1.57, 4.21) (p=0.93). sGPVI levels were similar in GCA patients with and without a history of cranial ischaemic complications, median 2.04 ng/ml (1.33, 4.21) vs 2.37 ng/ml (1.88, 4.21) (p=0.85). sGPVI levels taken from patients at initial presentation with and without cranial ischaemic complications were no different, median 2.31 ng/ml (1.33, 4.21) vs 2.27 ng/ml (1.72, 3.22) (p=0.91). Aspirin therapy did not significantly affect sGPVI levels, median 2.22 ng/ml (1.40, 4.20) vs 2.74 ng/ml (2.01, 4.64). There was no correlation between sGPVI levels and CRP (r=0.16), ESR (r=0.10), or prednisolone dose (r=-0.21).

Conclusion: We found no evidence of increased platelet activation in patients with GCA. There was no association between platelet activation and disease activity or cranial ischaemic complications in GCA. **Figure 1: sGPVI levels in GCA**



Disclosure: R. Conway, None; **A. Madigan**, None; **L. Helbert**, None; **N. Redmond**, None; **E. Dunne**, None; **E. S. Molloy**, None; **D. Kenny**, None; **G. M. McCarthy**, None.

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Abstract Number: 906

Treatment with Methotrexate and Risk of Relapses in Patients with Giant Cell Arteritis in Clinical Practice

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Background/Purpose: Several Clinical trials indicate that Methotrexate (MTX) could be considered as a feasible option in addition to corticosteroids for patients with GCA, but there is a need to corroborate these results in clinical practice. We want to assess the risk of relapses in GCA patients treated with MTX (since and after the diagnosis) and without MTX. Other factors associated were also investigated.

Methods: An inception cohort of GCA was assembled. We included patients from the date of diagnosis (January 1991 until September 2013) and followed-up in the out-patient clinic at Hospital Clinico San Carlos until September 2014. Main outcome: relapses defined as after an objective improvement (absence of symptoms of GCA and normalization of laboratory values) patient had again presence of symptoms or signs of GCA with high ESR and the need to increase corticosteroids at least 7.5mg. The independent variable was exposure to MTX (no exposure, exposure in the first month from the time of diagnosis, and exposure after). Covariables: 1) Sociodemographic, 2) Clinical symptoms and analytical data at diagnosis 3) Treatment: including concomitant corticoids, aspirin 4) Calendar time. Incidence rates of relapses (IR) per 100 patient-years with their respective 95% confidence interval [CI] were estimated using survival techniques. The time of exposure comprised the period from diagnosis until the occurrence of any of the following cut off points: lost of follow-up, main outcome, exposure to MTX or the end of the study. MTX influence on IR was analyzed by multivariable Cox models.

Results were expressed as hazard ratio (HR) and [CI]. Results: We included 168 patients (675 patient-years). Most of the patients were female (80%), with a mean age of 76±7 years. The mean dose of corticoids at starting was 55±15 mg/day. 65% of the patients were on MTX, and 45% of them started in the first month after the diagnosis. The mean dose was 10mg / week, being the maximum dose 20mg / week. 32.7% of patients (n=55) had 93 relapses during follow-up with an IR of 20.8[15.8-27.4]. The median [p25-75] number of relapses was 1[1-2], with a median lag time of 1.8 [0.6-5.8] years. In the multivariate analysis, after adjusting by age, gender, corticoids and calendar time, exposure to MTX in the first month had less risk of relapses compared to non exposed (HR: 0.44[0.2-0.9], p=0.02), whereas exposure to MTX after the first month of diagnosis (p=0.6) did not achieve statistical significance. Other variables in the model were: clinical debut with headache (HR: 4.6 [1.6-13.5], p=0.004), and visual alterations (HR: 2.3 [1.3-4.1], p=0.004). Taking aspirin during the follow- up (HR: 0.6 [0.3-1.1], p=0.1), and haemoglobin value (HR: 0.8 [0.7-1.0], p=0.1) did not achieve signification.

Conclusion: Early use of MTX seems to decrease the risk of recurrences. The treatment with aspirin involves a tendency to lower risk of relapses. We have also found other factors that can influence on the risk of recurrences.

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Abstract Number: 907

Rituximab in Patients with Takayasu Arteritis: A Single Center Experience on Five Patients

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Background/Purpose: Takayasu arteritis (TAK) is a large vessel vasculitis involving the aorta and its major branches in patients younger than 40 years. Glucocorticoids (GCs) are the mainstay of treatment for TAK, but relapses and GC dependence are seen in more than two-thirds of patients. Increasing evidence supports a role for B cells in the pathogenesis of TAK. Circulating plasmablasts and memory B cells are increased, while naive B cells are decreased in patients with active TAK as compared with inactive and control patients [1]. These findings suggest a potential role for B cell depleting therapy in TAK. Our aim was to assess the efficacy of Rituximab (RTX) in a single center series of patients with TAK.

Methods: We conducted a prospective, single center, open-label study on 5 TAK patients treated with RTX. All patients satisfied the American college of Rheumatology classification criteria for TAK. Four of the 5 patients had a refractory disease and had received high dose GCs and synthetic and/or biological immunosuppressive (IS) agents before RTX. One new diagnosed, treatment naïve TAK patient refused GCs and received RTX in monotherapy. RTX was administered according to rheumatoid arthritis scheme (2 infusions of 1.000 mg, 15 days apart). Clinical evaluation, laboratory tests (full blood count, ESR, CRP) and imaging modalities (CTA or MRA, and PET/CT) were performed at first RTX administration and every 6 months thereafter. Disease activity was assessed using Kerr index. Radiographic disease progression was defined as new or worsening lesions at follow-up CTA or MRA. PET/CT was considered positive for active disease if two or more large vessels showed grade 2 FDG uptake or higher.

Results: Five patients (4 female) were included in the study. Mean (SD) age was 30.4 (17.4) years. At first RTX administration, all patientshad active disease according to Kerr index (≥2), and had evidence of active disease at PET/CT. Table 1 summarizes the main results of our study. Despite RTX treatment, 4 of the 5 patients had evidence of persistent disease activity and/or radiographic disease progression at follow-up CTA or MRA. Only one patient experienced long-term remission (30 months to date) after two courses of RTX.

Conclusion: Our data do not support a role for RTX in refractory TAK patients. **References:** [1] Hoyer BF et al. Takayasu arteritis is characterised by disturbances of B cell homeostasis and responds to B cell depletion therapy with rituximab. Ann Rheum Dis 2012;71:75–9. Table 1.

Case	Age/Sex	Disease duration (y)	Previous therapy	ESR/CRP at first RTX (mm/h, mg/dl)	PDN dose at first RTX (mg/day)	Concomitant IS therapy	RTX courses	ESR/CRP 6 months after last RTX (mm/h, mg/dl)	Imaging (CTA/MRA) 6 months after last RTX	PET/CT 6 months after last RTX	Kerr index 6 months after last RTX	Outcome at last visit
1	20/F	2	MTX	38/6.2	25	MTX 20 mg/weekly	2	68/4.7	No disease progression	Positive	2	Active disease
2	32/F	0	None	49/4.6	0	None	1	61/3.4	Disease progression	Positive	3	Disease progression
3	21/F	1	MMF	12/2.7	50	MMF 2 gr/day	1	16/2.8	Disease progression	Positive	3	Disease progression
4	60/M	22	MTX, MMF, ADA, IFX	66/2.0	25	MMF 2 gr/day	2	18/0.5	No disease progression	Negative	0	Remission
5	19/F	5	MTX, AZA, TCZ, IFX, ADA	98/11.5	50	None	2	78/4.0	Disease progression	Positive	3	Disease progression

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Abstract Number: 908

Utilization of Multiple Acute Phase Proteins and Biomarkers for Giant Cell Arteritis – Insight into Diagnosis and Clinical Complications

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Background/Purpose: Giant Cell Arteritis (GCA) is considered an urgent condition in Rheumatology, due to high risk of permanent vision loss and cerebro-vascular insults. No diagnostic or prognostic markers are yet known for GCA. While erythrocyte sedimentation rate (ESR) is part of the ACR 1990 GCA classification criteria, other acute phase proteins could represent an added value for distinguishing between GCA/non-GCA and GCA remission/recurrence. The **aims**of our cross-sectional study were to a) measure serum levels of 40 selected biomarkers in 95 patients with GCA and 42 nonGCA patients, b) determine the associations of the biomarkers with GCA diagnosis, clinical complications and disease relaps.

Methods: Sera were collected from newly diagnosed (still steroid naive) GCA patients and nonGCA controls at time of first visit. GCA patients were followed carefully for the first year looking at signs and symptoms of relapsing disease. Sera proteins (Chitinase-3 Like-1, ICAM-1, VCAM-1, IL-1α, IL-1β, IL-1RI, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, IL-17, IL-22, IL-23, IL-33, MMP-1,-2, -3, -9, -12, TNFα, Leptin, Resistin, IFN-γ, CD62L, TNFRI,IP-10, LIF, MIG, α-Fetoprotein, MCP-1) were measured by Luminex platform. SAA, CRP, haptoglobin, fibrinogen, ferritin, hemopexin, orosomucoid, albumin were measured by nephelometry.

Results: Acute phase proteins SAA, CRP, haptoglobin, ferritin, hemopexin, orosomucoid and albumin all showed significant association with GCA diagnosis, in addition to elevated ESR, leukocyte and thrombocyte counts (Table). The highest diagnostic value was observed for SAA and CRP (n=92/93 and n=94/95, both 98.9%), followed by ESR (n=93/95, 97.9%). Patients with afterward visual disturbances had significantly lower levels of acute phase proteins: SAA (median (IQR):143 (51-290) vs. 270 (95-680) g/l), CRP (51 (28-86) vs. 73 (41-139) g/l), haptoglobin (3.7 (3-5.8) vs. 5.1 (3.6-6.5) g/l), and ESR (70 (52-88) vs. 89 (61-111) mm/h), while showing significantly elevated levels of VCAM-1 (824 (629-965) vs 502 (326-677) ng/ml) as compared to patients without visual disturbances. Among all the markers tested VCAM-1 had the highest area under ROC curve (AUC) (0.818) for visual disturbances. VCAM-1 was also significantly associated with extracranial artery disease. GCA patients who relapsed during follow-up, had significantly higher levels of SAA (311 (177-765) vs. 154 (41-418) g/l), CRP (86 (48-141) vs. 55 (32-120) g/l), ESR (94 (70-108) vs. 70 (52-90) mm/h), leukocyte counts (10.3 (8.7-12.3) vs. 9.1 (7-10.4)*10^9/l) at the disease onset.

Conclusion: Testing multiple acute phase proteins with additional blood parameters and biomarkers can represent an added value to earlier diagnosis, as well as optimize prediction of relapses and complications, such as visual disturbances and extracranial artery involvement. Table: Association of biomarkers with diagnosis GCA

Name of biomarker Cut off	Median (IQR) GCA	Median (IQR) non GCA	p	Diagnostic sensitivity (% positives in patients)	OR (95% CI)	AUC under ROC for diagnosis
SAA 6.4 g/l	205.3 (26-474) N=93	23 (2.0-220.5) N=30	**<0.001**	98.9	33.5 (4.0-281.6)	0.281
CRP 5 g/l	66 (35-124) N=95	14.5 (5-56) N=42	**<0.001**	98.9	37.6 (4.6-301.3)	0.320
Haptoglobin 2 g/l	4.9 (3.4-6.2) N=82	3.0 (1.45-4.25) N=17	**<0.001**	96.3	18.4 (4.09-82.9)	0.195
Fibrinogen 3.5 g/l	7.6 (6.3-8.5) N=56	6.9 (5.1-8.2) N=15	0.155	98.3	/	/
Ferritin F 120; M 300 µg/l	331 (158-482) N=86	271 (131-637) N=39	0.874	69.3	/	/
Hemopexin 1.15 g/l	1.4 (1.2-1.5) N=43	1.2 (1.1-1.3) N=15	**0.005**	90.7	4.8 (1.1-21.6)	0.220
Orosomucoid (α1-acid glycoprotein) 1,2 g/l	2.0 (1.6-2.6) N=43	1.5(1.0-1.7) N=15	**0.005**	95.3	10.3 (1.73-60,8)	0.224
Albumin 32-55 g/l	33 (29-36) N=92	38 (34-42) N=41	**<0.001**	[a]43.6	4.7 (1.8-12.2)	0.774
IL-6 8 ng/l	22.5 (7.0-42.3) N=90	7 (1.0-16.5) N=30	**0.002**	71.1	1.8 (0.8-3.95)	0.440
ESR F 21; M15 mm/h	81 (58-105) N=95	44 (25.7-66.3) N=42	**<0.001**	97.9	9.3 (1.84-46.9)	0.212
Leukocytes $10*10^9$ /l	9.2 (7.3-11.1) N=95	8.1 (6.8-9.7) N=42	**0.041**	38.9	2.7 (1.1-6,5)	0.477
Trombocytes $360*10^9$ /l	362 (291-443) N=95	263 (217-346) N=42	**<0.001**	57.9	3.8 (1.7-8.6)	0.106
PCT 0.5 µg/l	0.08 (0.04-0.01) N=56	0.07 (0.04-0.11) N=17	0.901	3.6	/	/

a–positives have lower albumin serum concentration than 32 g/l

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Disclosure: B. Burja, None; **K. Lakota**, None; **T. Kuret**, None; **P. Žigon**, None; **R. Jese**, None; **M. Tomsic**, None; **Z. Rotar**, None; **S. Praprotnik**, None; **T. Svec**, None; **S. Čučnik**, None; **S. Sodin Semrl**, None; **A. Hocevar**, None.

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Abstract Number: 909

A "Yellow Card" Reporting System for Sight Loss in Giant Cell Arteritis

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Background/Purpose: It is reported that 15-25% patients with GCA present with visual complications. Sight loss (SL) in the elderly is associated with considerable morbidity. There is evidence for reducing this by implementing a fast track pathway nationwide. However, data on the burden of SL due to GCA is lacking. The aim of this study is to estimate the incidence of visual complications in GCA and the factors that contribute to it.

Methods: This is an on-going observational study of new cases of SL attributable to GCA. In order to correctly estimate the incidence of SL, information is collected by participating ophthalmologists and rheumatologists on all patients with new or relapsing GCA with or without SL. Only patients that present with signs and symptoms fulfilling 1990 ACR criteria for classification of GCA or fulfilling 2/5 criteria along with positive imaging (PET-CT or vascular ultrasound) substituting for biopsy are recruited. SL is defined as symptomatic loss of acuity or field of vision, as diagnosed by an ophthalmologist. When a patient with definite visual complications of GCA is identified, an initial reporting “yellow card” will be completed electronically and either posted or emailed to the investigators. The primary statistical analysis is the estimation of the percentage incidence as well analysis risk factors using binary logistic multiple regression methods.

Results: Yellow cards and detailed reports have been sent regarding 105 patients so far from 13 centres. We plan to recruit 250 patients. Patients who developed SL had symptoms for 23.2 days preceding the diagnosis vs. 37.97 days in the non-sight loss group. 27 (25.71%) presented with visual disturbances. Mean age at presentation was 79.96 (57-93) sight loss vs. 72.86 (50-95) non-sight loss group. Interestingly, GCA patients with sight loss had a higher ESR value (60.04 vs. 50.78, p=0.025, 95 %CI 2.47-11.18) and a lower Haemoglobin level (99.98 vs. 118.91, p=0.03, 95% CI -36.087 to -1.767). There was no statistically significant difference between the two groups in terms of symptoms including headaches, jaw claudication or constitutional symptoms or risk factors (p>0.05). 70.47% of the recruited patients had temporal artery biopsy. There was no difference with regards to biopsy results (14 vs 32; OR 0.8750, CI 95%0.2903 to 2.6378, p=0.81) or USS (7 vs 26; OR 3.2308, CI 95% 0.3565 to 29.2791, P=0.29). 18.51% of the SL had a previous diagnosis of GCA or PMR compared to 8.97% (RR 0.66, CI 95% 0.1667 to 2.6657, p=0.56).

		Sight Loss n=27	No sight loss n=78	p-value
	Age, mean	79.96 (93-57)	72.86 (50-95)	P=0.0007
	Male, %	25.92	20.51	P=0.45
	Female, %	74.07	79.48	
Symptoms	Headache, n	14	71	p=1.2
	Scalp tenderness ,n	15	51	p=0.38
	Jaw claudication, n	15	32	p=0.36
	Tongue claudication, n	0	4	p=0.571
	Muscle pain, n	4	24	p=0.13
	Fevers, n	3	12	p=0.75
	Weight loss, n	4	12	p=1
	Stroke	0	1	p=1
Risk factors	Smoking, n	3	10	p=0.49
	Diabetes, n	1	7	p=0.32
	Hypertension, n	12	23	p=0.14
	Lipid disorder, n	6	10	p=0.25
	Previous stroke, n	1	2	p=0.13
	Previous MI, n	0	4	p=0.31
	CKD. n	1	2	p=0.62
	AF, n	1	5	p=0.49
	Obesity, n	0	3	p=0.42
Ischemic complications	CRON, n	2	0	p=0.06
	AION, n	6	0	P=0.002

Table 1. Patient demographics, symptoms and risk factors; AF atrial fibrillation, CKD chronic kidney disease, MI myocardial infarction, AION (acute ischemic optic neuropathy; CRON central retinal occlusion

Conclusion: Our study shows a major delay associated with the diagnosis of GCA in the UK. This may be related to the high percentage of SL seen in all participating centres. The study confirms that patients with SL have higher inflammatory markers suggesting a more active disease. Our results highlight the need for implementing the fast track GCA pathway to improve outcome and reduce ischemic complication.

Disclosure: B. Dasgupta, None; **A. Khan**, None; **D. Merinopoulos**, None; **S. Banerjee**, None; **D. Gayford**, None; **P. Stapleton**, None; **F. Laskou**, None; **G. Statache**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-yellow-card-reporting-system-for-sight-loss-in-giant-cell-arteritis

Abstract Number: 910

Survival Benefit of Statin Use in Ankylosing Spondylitis and Psoriatic Arthritis: A General Population-Based Cohort Study

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Background/Purpose: Recent studies have shown an increase in cardiovascular and all-cause mortality in ankylosing spondylitis (AS) and psoriatic arthritis (PsA).[1] The hypothesized dual role of statins in both lowering lipids and reducing inflammation may thus lead to survival benefits in patients with these seronegative spondyloarthropathies. We examined the potential survival benefit of statin use in AS and PsA within a general population context.

Methods: We performed an incident user cohort study with time-stratified propensity score matching using a UK general population database. The population studied included patients with AS or PsA between January 1, 2000 and December 31, 2014. To account for potential confounders, we compared propensity score-matched cohorts of statin initiators and comparators (non-initiators) within 1-year cohort accrual blocks. 50 variables were used to create propensity scores, including but not limited to the disease duration, socio-economic status, BMI, lifestyle factors, and medication use.

Results: 2,904 patients with AS or PsA who initiated statins compared to 2,904 propensity matched-comparators with AS or PsA that were not started on statins. 271 died during the follow up (mean = 5.3 years), whereas among the propensity-matched non-initiators, 376 patients died during the follow up (mean = 5.15 years) (**Figure 1**). This corresponds to incidence rates of 17.62/1000 and 25.14/1000 person-years (PY), respectively. The baseline characteristics were well balanced in the two groups. Statin initiation was associated with a 33% reduction of all-cause mortality (HR=0.68, 95% CI 0.57-0.81). When we compared the unmatched cohorts to determine the effectiveness of our propensity score matching, the statin initiators (n=3,389) actually showed a 44% higher risk of mortality (HR=1.44, 95% CI 1.22-1.70) than non-initiators (n=3,389 randomly selected) due to confounding by indication (**Figure 2**).

Conclusion: This general population-based cohort study indicates that statin initiation is associated with a 33% lower risk of mortality for patients with AS or PsA. The magnitude of the inverse association appears to be larger than that observed in population-based cohort studies of patients with rheumatoid arthritis (21%)[2] and in meta analyses of randomized trials of the general population (9-14%)[3], potentially due to the dual benefits of statin use (i.e. lipid lowering and anti-inflammatory effects) in patients with seronegative spondyloarthropathies. References: 1. Haroon et al. Ann Int Med 2015. 2. Schoenfeld et al. Ann Rheum Dis 2015. 3. Mihaylova et al. Lancet 2012.

Figure 1. Propensity Score Matched Analysis

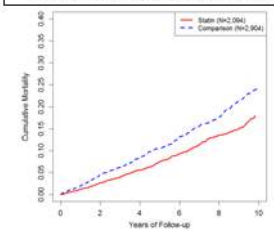
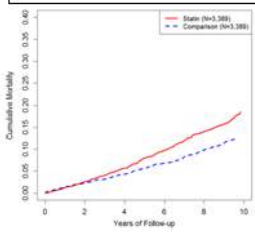


Figure 2. Unmatched Analysis



Disclosure: **A. Oza**, None; **N. Lu**, None; **H. K. Choi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/survival-benefit-of-statin-use-in-ankylosing-spondylitis-and-psoriatic-arthritis-a-general-population-based-cohort-study

Abstract Number: 911

Efficacy and Safety of Tocilizumab in Patients with Giant Cell Arteritis: Primary and

Secondary Outcomes from a Phase 3, Randomized, Double-Blind, Placebo-Controlled Trial

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SESSION INFORMATION

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Background/Purpose: The efficacy and safety of tocilizumab (TCZ), an IL-6 receptor-alpha inhibitor, was evaluated in patients with giant cell arteritis (GCA) in GiACTA, a randomized, double-blind, placebo-controlled trial with blinded glucocorticoid regimens of variable dose and duration (*Int J Rheumatol.* 2013:912562). Data up to week 52, the time of primary outcome measurement, are presented.

Methods: Patients aged ≥50 years had active GCA previously confirmed by temporal artery biopsy or cross-sectional imaging and documented acute-phase reactant elevation attributable to GCA. Randomization was stratified by baseline prednisone dose (≤30 or >30 mg/day). Patients were randomized 1:1:2:1 to 4 groups: A, short-course prednisone (26-week prednisone taper + weekly subcutaneous [SC] placebo); B, long-course prednisone (52-week prednisone taper + weekly SC placebo); C, weekly SC TCZ 162 mg + 26-week prednisone taper; D, every other week SC TCZ 162 mg + 26-week prednisone taper. The baseline prednisone dose (20-60 mg/day) was selected by the investigator. Prednisone doses <20 mg/day were blinded. Patients who flared or could not adhere to the protocol-defined tapering schedule received open-label prednisone escape therapy but continued on double-blind TCZ/placebo. Sustained remission was defined at week 52 as the absence of flare and normalization of C-reactive protein after week 12, combined with adherence to the protocol-defined prednisone taper. The primary and key secondary end point was the proportion of patients in sustained remission, comparing both TCZ groups (C, D) with the short-course prednisone group (A) and with the long-course prednisone group (B), respectively, at a significance level of 0.005. A dose hierarchy of statistical testing was implemented. Cumulative prednisone exposure was a secondary end point.

Results: Of 251 patients randomized, the mean ± SD age was 69 ± 8.2 years, and 75% were female. In the primary comparison, 56% of patients in the weekly TCZ group and 53.1% in the every other week TCZ group achieved sustained remission at 12 months compared to only 14% in the short-course prednisone group ($p < 0.0001$). In the key secondary efficacy comparison, the percentage of patients in sustained remission in each TCZ group was also superior to that of patients in the long-course prednisone group (17.6%) ($p \leq 0.0002$). The median cumulative steroid exposure in both TCZ groups was less than half that of those in the long-course prednisone group (Table). The incidence of adverse events was similar among the 4 treatment arms. No deaths and no new vision loss occurred over the period of observation.

Conclusion: TCZ plus a 26-week prednisone taper was superior to both short- and long-course prednisone tapers for the achievement of sustained remission at 52 weeks. The addition of TCZ to prednisone also led to a substantial reduction in the cumulative prednisone doses required to control GCA.

Table. Efficacy and Safety During GiACTA Part 1

	A) Short-course prednisone n = 50	B) Long-course prednisone n = 51	C) Weekly SC TCZ n = 100	D) Every other week SC TCZ n = 49
Patients in sustained remission at 52 weeks, n (%)	7 (14.0)	9 (17.6)	56 (56.0)	26 (53.1)
TCZ groups vs short-course prednisone Unadjusted difference in proportion of responders (99.5% CI)	—	—	42.0 (18.0, 66.0) $p < 0.0001$	39.1 (12.5, 65.7) $p < 0.0001$
TCZ groups vs long-course prednisone[a] Unadjusted difference in proportion of responders (99.5% CI)	—	—	38.4 (17.9, 58.8) $p < 0.0001$	35.4 (10.4, 60.4) $p = 0.0002$
Cumulative CS dose, median (min-max)	3296.00 932.0-9777.5	3817.50 822.5-10697.5	1862.00 630.0-6602.5	1862.00 295.0-9912.5
AEs Patients with event, n (%)	48 (96.0)	47 (92.2)	98 (98.8)	47 (95.9)
Withdrawals Patients withdrawn from study, n (%)	6 (12.0)	5 (9.8)	15 (15.0)	9 (18.4)
Withdrawals due to an AE, n (%)	2 (4.0)	0	7 (7.0)	3 (6.1)
SAEs Patients with event, n (%)	11 (22.0)	13 (25.5)	15 (15.0)	7 (14.3)
Infection SAEs Patients with event, n (%)	2 (4.0)	6 (11.8)	7 (7.0)	2 (4.1)

AE, adverse event; CI, confidence interval; SAE, serious adverse event.
Patients who receive escape therapy, withdraw, or do not achieve remission by week 12 are classified as nonresponders.
Patients who have 2 consecutive CRP elevations >1 mg/dL from week 12 or have >100 mg additional steroids from week 12 are classified as nonresponders.
p values for superiority of the primary and key secondary end points were compared to a significance level of 0.005 to account for multiplicity; all other secondary end points are compared to 0.01.
p values for superiority calculated using a Cochran-Mantel-Haenszel test adjusting for starting prednisone dose (≤30 mg/day, >30 mg/day).
[a]Noninferiority margin of −22.5 was used to compare TCZ groups with long-course prednisone group using 99.5% CIs.

Disclosure: J. H. Stone, Roche Pharmaceuticals, 2,Roche Pharmaceuticals, 5; **K. Tuckwell**, Roche Products Ltd., 3; **S. Dimonaco**, Roche Products Ltd., 3; **M. Klearman**, Genentech/Roche, 1,Genentech/Roche, 3; **M. Aringer**, Roche, Chugai, 3,Roche, Chugai, 8; **D. Blockmans**, None; **E. Brouwer**, Roche Pharmaceuticals, 5; **M. C. Cid**, None; **B. Dasgupta**, Roche, GSK, Servier, Mundi Pharma, 5,Napp, 2,UCB, 8; **J. Rech**, None; **C. Salvarani**, None; **R. F. Spiera**, Roche/Genentech, 2,Roche/Genentech, 5; **S. H. Unizony**, None; **N. Collinson**, Roche Products Ltd., 3.

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Abstract Number: 912

Urate Lowering Therapy in Moderate to Severe Chronic Kidney Disease

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Urate Lowering Therapy in Moderate to Severe Chronic Kidney Disease Levy G, Cheetham C, Shi J, Rashid N

Background/Purpose: To determine if urate lowering therapy (ULT) can improve Chronic Kidney Disease (CKD) function when patients achieve a serum uric acid (sUA) <6mg/dL (Goal). To determine if baseline CKD stage influences the benefits when attaining Goal with

ULT.

Methods: A retrospective cohort study was conducted from 1/1/2008 to 7/31/2014 within an integrated healthcare delivery system. A sUA > 7mg/dL was necessary for inclusion and the first occurrence sUA >7mg/dl was defined as the index date. In addition, patients were required to have an estimated Glomerular Filtration Rate (eGFR) in the 6 months preceding the index date, and at least one sUA and eGFR during follow-up, from 3 months to 12 months post index. Patients were required to be ULT naïve, ≥ 18 years of age, and have Chronic Kidney Disease Stages 2, 3 or 4 at index. Continuous health plan enrollment with a drug benefit during the entire study period was required. Exclusions included active treatment for cancer, dialysis or kidney transplant. Outcomes were defined as either a 30% decrease or a 30% improvement in eGFR from baseline to the last available value. Pairwise differences in proportion were compared using Chi-square test and 95% Confidence Interval (CI) were reported for the differences.

Results: Of the 12, 751 patients meeting inclusion criteria; 2, 690 received ULT during the study period and 10,061 did not. Goal sUA was achieved in 1,118 (42%) patients on ULT. A 30% improvement in eGFR was seen in 17.1% achieving Goal versus 10.4% of patients who did not reach sUA goal (Difference = 6.7% (95% CI = 4.0%, 9.4%), p<0.001). Pairwise comparison of CKD stages showed patients at or below Goal were more likely to have a 30% improvement in eGFR: in CKD 2: 7.1% v 3.3%, (Difference = 3.8% (95% CI = 0.7%, 7.0%), p=0.015) , in CKD3: 19.9% v 10.0%, (Difference = 9.9% (95% CI = 6.1%, 13.6%), p<0.001) and CKD 4: 30.0% v 22.2%, (Difference = 7.8% (95% CI = -1.1%, 16.8%), p=0.080).

Conclusion: This study suggests that patients who achieve ACR Goal of sUA of <6mg/dl on ULT have higher rates of eGFR improvement (≥ 30% improvement). This effect is seen across the CKD spectrum from Stage 2 through Stage 4 with the most pronounced effect in CKD 3 patients.

TABLE 1: eGFR change related to ACR sUA Goal

Patients not at Goal of <6mg/dl

	30% Decrease		No Change		30% Increase		
	n	%	n	%	n	%	
CKD II	24	5.58	392	91.16	14	3.26	
CKD III	54	6.29	718	83.68	86	10.02	
CKD IV	30	10.56	191	67.25	63	22.18	
totals	108		1301		163		1572
% of total	6.9%		82.8%		10.4%		

Patients with sUA at Goal <6mg/dl

	30% Decrease		No Change		30% Increase		
	n	%	n	%	n	%	
CKD II	15	4.24	314	88.7	25	7.06	
CKD III	20	3.21	480	76.92	124	19.87	
CKD IV	21	15	77	55	42	30	
totals	56		871		191		1118
% of total	5.0%		77.9%		17.1%		

Disclosure: G. D. Levy, None; **C. Cheetham**, None; **N. Rashid**, None; **J. Shi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/urate-lowering-therapy-in-moderate-to-severe-chronic-kidney-disease

Abstract Number: 913

Aggregatibacter Actinomycetemcomitans-Induced Hypercitrullination Links Periodontal Infection to Autoimmunity in Rheumatoid Arthritis

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SESSION INFORMATION

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Session Title: Plenary Session I: Discovery 2016

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

Background/Purpose: A bacterial etiology of rheumatoid arthritis (RA) has been suspected since the beginnings of modern germ theory. Recent studies implicate mucosal surfaces as sites of disease initiation, particularly the gingiva, the gut and the lungs. The common occurrence of periodontal dysbiosis in RA suggests that oral pathogens may trigger the production of anti-citrullinated protein antibodies (ACPAs) and arthritis in susceptible individuals. Here, we studied the periodontal microenvironment in health and disease to define mechanisms underlying mucosal inflammation and autoimmunity in RA.

Methods: Gingival crevicular fluid (GCF) from patients with periodontitis and healthy subjects without periodontitis was analyzed by immunoblotting to detect citrullinated proteins (AMC). Mass spectrometry (MS) was employed to define the microbial composition and antigenic repertoire of GCF in periodontal disease and oral health. Isolated human neutrophils were analyzed by AMC immunoblotting and MS after incubation with periodontal pathogens (*Aggregatibacter actinomycetemcomitans* [*Aa*], *P gingivalis*, *T forsythia*, *T denticola*, *F nucleatum*, *P micra*, *P intermedia*, *S intermedius*) and purified *Aa* leukotoxin A (LtxA). Neutrophils incubated alone or with LtxA were stained with SYTOX Green, anti-citH3, and ACPA-positive RA serum. Antibodies against *Aa* and LtxA were quantified in patients with RA (n=196) and healthy controls without periodontitis (n=37) by ELISA.

Results: Periodontitis was characterized by the presence of citrullinated autoantigens that are primary immune targets in RA. The citrullinome in periodontitis mirrored patterns of cellular hypercitrullination observed in the rheumatoid joint, implicating this mucosal site in RA pathogenesis. Proteomic signatures of several microbial species were detected in hypercitrullinated periodontitis samples. Among these, *Aa*, but not other candidate pathogens or commensals, induced hypercitrullination in host neutrophils. We identified the pore-forming toxin LtxA as the molecular mechanism by which *Aa* triggers dysregulated activation of citrullinating enzymes in neutrophils, mimicking membranolytic pathways known to sustain autoantigen citrullination in the RA joint. Moreover, LtxA induced changes in neutrophil morphology suggestive of extracellular trap formation, thereby releasing the hypercitrullinated cargo. Exposure to *Aa* was confirmed in RA patients (43% vs 8% of controls without periodontitis; $p<0.0001$) and significantly associated with both ACPAs and rheumatoid factor (RF). The effect of RA susceptibility alleles (the HLA-DRB1 *shared epitope*) on ACPA and RF positivity was surprisingly conditioned on patient exposure to LtxA (Table 1), suggesting a two-hit model of RA pathogenesis.

Conclusion: These studies identify the periodontal pathogen *Aa* as a candidate bacterial trigger of autoimmunity in RA.

	Anti-LtxA negative RA (n=112)			**Anti-LtxA positive RA (n=82)**			
	SE negative (n=33)	**SE positive (n=79)**	***P***	**SE negative (n=25)**	**SE positive (n=57)**	***P***	***P-interaction***
Anti-CCP positivity, n (%)	20 (61)	62 (78)	0.051	14 (56)	54 (95)	*<0.001	*0.035
ACPA positivity, n (%)	21 (64)	54 (68)	0.63	16 (64)	52 (93)	*0.002	*0.025
RF positivity, n (%)	22 (67)	57 (72)	0.56	17 (68)	55 (96)	*<0.001	*0.015

Table 1: The association of ACPAs and RF with *shared epitope* alleles is conditioned on *Aggregatibacter actinomycetemcomitans* LtxA exposure in patients with RA.

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Abstract Number: 914

Longitudinal Blood Transcriptomics Uncovers Immune Networks Associated with Complications in Lupus Pregnancy

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Background/Purpose: SLE is a systemic autoimmune disease that predominantly affects women in reproductive years. SLE pregnancies result in higher rates of adverse outcomes compared with healthy pregnancies.

Methods: To understand the molecular mechanisms underlying SLE pregnancy, we characterized the blood transcriptome of 135 pregnant (92 SLE and 43 healthy) subjects from the PROMISSE Study and 54 non-pregnant (NP) (20 SLE and 34 healthy controls) women by microarray. Blood was drawn at 4 time points during pregnancy (P1: <15 weeks gestation; P2: 16-23 wks; P3: 24-31 wks; P4: 32-40 wks) and 8-20 wks postpartum (PP). Poor pregnancy outcomes were classified as preeclampsia (SLE-PE) or other complications (SLE-OC) that included fetal or neonatal death, preterm delivery (<36 wks because of IUGR or placental insufficiency), and growth restriction (<5th %ile). SLE pregnancies included 24 SLE-PE, 22 SLE-OC, and 46 non-complicated (SLE-NC). Data were analyzed using a linear mixed model accounting for disease, complication groups and visit time point.

Results:

We first identified transcriptional signatures associated with healthy pregnancy. Using healthy NP controls as baseline, 9,687 transcripts were differentially expressed in healthy pregnancy; these included upregulation of neutrophil, myeloid inflammation and erythropoiesis signatures and downregulation of immune pathways linked to lupus pathogenesis, such as IFN and plasma cells **(Fig. 1A)**. We then assessed how the signature was affected in SLE-NC compared to healthy NP women. SLE-NC pregnancies displayed the dynamic features similar to healthy pregnancies **(Fig. 1B)**. However, while the plasma cell signature was decreased to levels lower than those of SLE-NP and healthy NP controls, the IFN signature remained patent through the course of pregnancy compared to healthy NP controls (green line). Finally, we identified complication-related transcriptional signatures by comparing SLE-PE and SLE-OC to SLE-NC **(Fig. 2)**. Both SLE groups with complications failed to downregulate IFN and plasma cell signatures to SLE-NC levels throughout the pregnancy. In addition, SLE-PE displayed early upregulation of neutrophil signatures. Network analysis at P1 identified neutrophil- (AZU1, CTSG, ELANE) related signaling pathways as early biomarkers of preeclampsia.

Conclusion: Blood transcriptomics reveals systemic changes during healthy and SLE pregnancies and highlights the neutrophil signature as a potential early biomarker of preeclampsia.

Figure 1

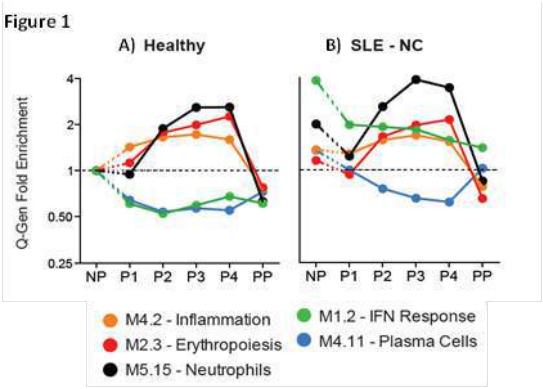
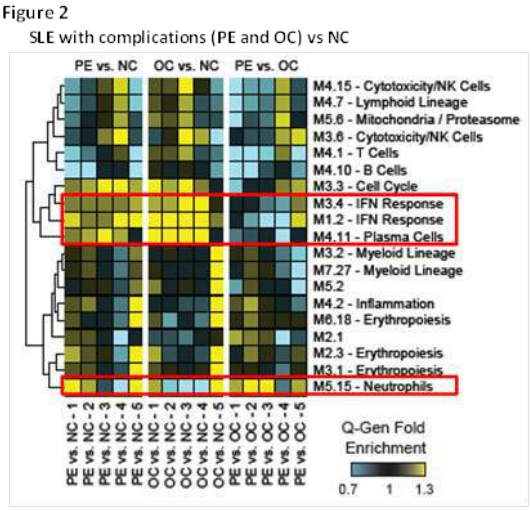


Figure 2



Disclosure: S. Hong, None; **R. Banchereau**, None; **M. M. Guerra**, None; **J. E. Salmon**, None; **V. Pascual**, None.

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Abstract Number: 915

Establishment of a Powerful Method to Identify Autoantigens Expressed on the Cell Surface

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Session Time: 2:30PM-4:00PM

Background/Purpose: Autoantibodies which recognize integral membrane proteins are generally accepted as pathogenic. However, it had been technically difficult to identify plasma membrane proteins as autoantigens by conventional methods including proteomics. Anti-endothelial cell antibodies (AECAs) are autoantibodies against cell surface molecules on the endothelium, and play important roles on promoting vascular inflammation. Most of the reported autoantigens were intracellular molecules, and their target antigens on endothelium were poorly understood. In order to identify cell-surface autoantigens, we constructed a Serological identification system for Autoantigens using a Retroviral vector and Flow cytometry (SARF).

Methods: cDNA library of human umbilical vein endothelial cells (HUVECs) were generated and inserted into the retroviral vector. Retroviruses possessing the cDNA library were generated and infected into the rat myeloma cells. Rat myeloma cells which have different HUVEC cDNA were stained with serum IgG from patients with AECA-positive collagen diseases, and AECA-positive fraction was sorted by flow cytometry. After cloning of an AECA-positive cell, cDNA inserted into each clone was identified by DNA sequencing and microarray.

Results: The identified molecules included fibronectin leucine rich transmembrane protein 2 (FLRT2), ephrin type-B receptor 2 (EphB2), and Pk antigen for systemic lupus erythematosus, and intercellular adhesion molecule-1 (ICAM-1) for rheumatoid arthritis. Expressions of these molecules on ECs were confirmed by flow cytometry and AECA IgGs bound specifically to the cells which were transfected with each of the molecules. Importantly, anti-FLRT2 antibody induced complement-dependent cytotoxicity against FLRT2 expressing cells including HUVECs. Clinical manifestations of each autoantibody-positive patient were associated with the distribution of autoantigens in different cell types, indicating that AECAs can act not only on ECs but also on other target cells. We further identified autoantigens in Takayasu arteritis, in which no definite autoantigens were reported. The autoantigens in Takayasu arteritis play important roles for the coagulation and lipid metabolism, suggesting that AECAs can directly modify vascular inflammation in Takayasu arteritis.

Conclusion: We successfully identified membrane proteins as autoantigens against AECAs by using SARF and confirmed the usefulness of SARF. Moreover, identified molecules were associated with the clinical manifestations of patients, suggesting direct contributions of AECAs for promoting pathological conditions. Using this system, it is possible to achieve a comprehensive analysis of autoantibody-mediated injury in inflammatory diseases and develop more specific interventions.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/establishment-of-a-powerful-method-to-identify-autoantigens-expressed-on-the-cell-surface

Abstract Number: 916

Novel Immunosignature Stratifies Patients with Rheumatoid Arthritis into Distinct

Disease Sub-Groups and Predicts Response to Anti-Tnfα Therapies

Laura Magill[1], Marsilio Adriani[1], Victoria Howard[2], Jessica Manson[2], Elizabeth Jury[3] and **Claudia Mauri**[4], [1]University College London, London, United Kingdom, [2]University College London Hospitals NHS Trust, London, United Kingdom, [3]Division of Medicine, Centre for Rheumatology Research, University College London, London, United Kingdom, [4]Division of Medicine, Centre for Rheumatology Research, University College London, University College London, London, United Kingdom

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SESSION INFORMATION

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Session Title: B Cell Biology and Targets in Autoimmune Disease I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Autoimmune rheumatic diseases, including rheumatoid arthritis (RA), have multifactorial pathogenesis associated with failure of immune tolerance. Advances in understanding the disease immunopathology have led to the development of biological drugs targeting components of the immune response that drive disease progression (including TNFα, IL-6, and B cells). However, these drugs are not effective in all individuals and many patients fail to respond for unknown reasons. The ability to predict patient responses to conventional and to biological treatment would provide a crucial step change improvement in the clinical management of patients with RA. We proposed a novel immunophenotyping approach to identify unique 'signatures' that could stratify patients for a more personalised approach to treatment of this complex disease.

Methods: We optimised a novel high through-put immunophenotyping platform, LEGENDScreen^{TM}, measuring the expression of 332 cell surface markers on B-cell and T-cell populations. We used this multi-dimensional approach to screen 50 RA patients, either treated with DMARDs or with anti-TNFα treatments, compared to patients with MS, SLE and healthy donors (HCs) as controls. The antigen-specific fluorescence intensity for each subset was examined. Differentially expressed markers (DEMs) between patient groups were determined using multiple unpaired *t*-test analysis ($p<0.05$). The results guided us to further stratify the data looking at B cell subsets, disease activity and immunogenicity (presence or absence ADA, measured by ELISA).

Results: We identified phenotypic markers specific for anti-TNFα-treatment-naïve RA patients, developing an "immune-signature" that differentiates these patients from HCs, RA patients treated with anti-TNFα-treatment, and from patients with MS or SLE. We observed that the majority of DEMs, with significantly different expression between patient groups, were on $CD19^+$ B-cells rather than $CD4^+$T-cells, confirming the contribution of B-cells in the pathogenesis of RA. Comparing HCs to anti-TNFα-treatment-naïve patients we identified 31 DEMs that were significantly differentially expressed on B-cells but only 2 DEMs on T-cells. Further stratification of B-cells, looking at immature, mature, and memory subsets, identified 40 and 41 DEMs on immature and mature B-cells respectively, and only 20 DEMs on memory B-cells. We identified a unique immune-phenotype associated with the lack of response to anti-TNFa and the development of ADA.

Conclusion: We have developed a new strategy, which clustered patients based on shared immune-phenotypes and distinguished between patients who developed anti-drug antibodies (ADA+) and those with active vs inactive disease. The predictive capacity of these immune-signatures is being validated in a prospective cohort of patients treated with anti-TNFα, which will also predict response to switching therapies (e.g. from anti-TNFα to rituximab). We proposed to use this novel immunophenotyping signature for a more personalised approach to treatment of this complex disease. Conducted as part of the ABIRISK consortium.

Disclosure: L. Magill, None; **M. Adriani**, None; **V. Howard**, None; **J. Manson**, None; **E. Jury**, None; **C. Mauri**, None.

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Abstract Number: 917

B Cells Inhibit Osteoblast Differentiation in Inflammatory Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is frequently associated with bone loss due to imbalanced bone resorption and formation. B cell depletion therapy (BCDT) attenuates bone erosion in a subset of RA patients. B cells promote osteoclast formation, but their role in osteoblasts (OB) in RA has not been well studied. Here, we used B cells from TNF-transgenic (TNF-Tg) mice and mice with Collagen-Induced Arthritis (CIA), mouse models of RA, and from RA patients to investigate if RA B cells inhibit OB differentiation and the mechanisms involved.

Methods: B cells were isolated using CD19 magnetic beads from bone marrow (BM) and subchondral BM (SB) of TNF-Tg and CIA mice, and from peripheral blood of RA patients with active disease, but not on biologics. Immunofluorescent (IF) staining, RNA sequencing, co-cultures of mesenchymal precursor cells (MPCs) and B cells, and BCDT were performed.

Results: To study the distribution of B cells and their relationship with OBs, we performed IF on frozen bone sections from TNF-Tg and CIA mice with anti-B220 Ab for B cells and anti-osteocalcin Ab for OBs. B cells were enriched in the SB and endosteal BM areas of RA mice and were adjacent to OBs. To investigate if RA B cells produce OB inhibitors, we performed RNA sequencing of BM and SB B cells from TNF-Tg mice. Compared to WT BM B cells, TNF-Tg BM B cells expressed about 2-fold higher levels of OB inhibitors, including CCL3, TNF, and Dkk3. SB B cells expressed much higher levels of these inhibitors compared to their BM counterparts, and this was confirmed by qPCR (fold increase in TNF-Tg SB/TNF-Tg BM: CCL3 x12, TNF x4, Dkk3 x12; in CIA SB/CIA BM: CCL3 x20, TNF x10, Dkk3 x38). To determine if RA B cells directly affect OBs, we co-cultured B cells with WT MPCs in OB-inducing medium. RA B cells significantly inhibited OB differentiation (ALP+ area: 7±1 in TNF-Tg vs. 16±2 mm^2 in WT; 7±2 in CIA vs. 20±2mm^2 in non-CIA). To investigate potential signal pathways responsible for OB inhibition, expression of NF-kB, ERK and b-catenin in MPCs after co-culture with B cells was examined. RA B cells increased expression of NF-kB and pERK in MPCs.The effect of RA B cells on OB inhibition and NF-kB/ERK activation in MPCs was partially blocked by a CCL3 or TNF neutralizing Ab. To examine the overall effect of BCDT on bone mass and OB function, we treated TNF-Tg mice with murine anti-CD20. BCDT increased SB bone volume (BV/TV: 40±2 vs. 31±1% in IgG) and OBs (#/mm bone surface: 26±5 vs. 16±3 in IgG). BM cells from BCDT-treated mice had increased OB differentiation (CFU-ALP#: 53±9 vs. 21±5 in IgG). To determine if B cells from RA patients have a similar OB inhibitory effect, we co-cultured peripheral blood B cells from RA patients with MPCs. RA B cells inhibited OB differentiation and this was partially blocked by CCL3 or TNF neutralization. Furthermore, IF of synovial specimens from RA patients showed expansion of CCL3 and TNF-producing B cells.

Conclusion: B cells are enriched in the SB area of RA joints and are adjacent to OBs. RA B cells produce multiple OB inhibitors, including CCL3 and TNF, which inhibit OB differentiation. BCDT reduces bone loss and stimulates OB function. Thus, B cells may directly target OBs, and thus contribute to bone loss and joint erosion in RA.

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Abstract Number: 918

Anergic B Cells May Preserve Peripheral Tolerance in Lupus-Prone Congenic Mice

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Background/Purpose: Anergic autoreactive B cells are thought to play a critical role in systemic lupus erythematosus (SLE), a chronic autoimmune disease where breach of tolerance to nuclear antigen leads to the production of pathogenic anti-nuclear autoantibodies (ANA). There is evidence that anergic B cells survive longer and are less tolerized in SLE patients and lupus-prone mice; however, their exact contribution to SLE pathogenesis remains unclear. Our laboratory has used congenic derivatives of the lupus-prone New Zealand Black mouse to parse the B and T cell defects involved in SLE, uncovering a B cell defect required for ANA production (in the 170.8-181 Mb interval on chromosome 1 [C1d]) as well as T cell defects (in the 124-181 Mb interval [C1b-d]) that exacerbate disease. Since these defects were sufficient to breach B cell anergy to the neo-self antigen hen egg lysozyme, we hypothesized that a similar breach would occur in the Vκ8/3H9 model of anergy, a better analogue for human SLE.

Methods: The 3H9 heavy chain and Vκ8 light chain were knocked into their correct loci in the C1d and C1b-d strains to generate mice with homogeneous, ssDNA-specific, anergic B cell repertoires. ANAs in female 8 month old non-autoimmune (B6), C1d and C1b-d wild type (WT) and double knock-in (dKI) mice were measured by ELISA, while splenic B and T cells were examined using flow cytometry. Adoptive transfer of B6 or C1d dKI B cells into B6 or C1d WT recipients was conducted to assess the effect of the anergic milieu on B cell activity; recipients were sacrificed after 7 days and splenocytes analyzed via flow cytometry.

Results: C1b-d WT mice had significantly increased anti-ssDNA IgG and IgM, and higher proportions of germinal centre (GC) B cells, $CD86^+$ B cells and T follicular helper (T_{FH}) cells than B6 WT mice, with C1d WT mice also trending to significance. Surprisingly, the autoimmune B cell phenotype was attenuated in both C1 dKI strains, such that C1 dKI mice were equivalent to B6 counterparts. While the levels of T_{FH} cells remained significantly higher in C1 dKI mice than in B6, they were significantly decreased compared to C1 WT mice, suggesting that the attenuated breach of B cell tolerance could result from insufficient T cell priming. This explanation was supported by the observation that anergic C1d dKI B cells adoptively transferred into C1d WT mice showed similar trends to increased GC and $CD86^+$ B cells as in C1d WT mice. Finally, while the proportion of T_{FH} cells was significantly decreased in C1b-d dKI mice compared to their WT counterparts, the proportion of T follicular regulatory (T_{FR}) cells remained similar to WT levels, suggesting that selective survival or induction of T_{FR} cells in the dKI congenic strains may play a role in their decreased autoimmune phenotype.

Conclusion: Our results demonstrate that while the B and T cell defects in New Zealand Black congenic mice generate autoimmunity in an unconstrained immune system, these defects are not sufficient to robustly breach tolerance to endogenous nuclear antigen when the B cell repertoire is predominantly anergic, possibly due to modulation of T cell activation or regulatory cell fate.

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Abstract Number: 919

IL-17 Receptor a Signaling Impedes NF-κB p50/p50 Repressor and Subverts B-Cell Anergy in BXD2 Mice

Jennie Hamilton[1], Qi Wu[2], PingAr Yang[3], Bao Luo[4], Woongjai Won[5], Shanrun Liu[6], Jun Li[7], Hui-Chen Hsu[2] and John D. Mountz[8,9], [1]Medicine/Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [3]Department of Medicine, Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]Division of Clinical Immunology and Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [5]University of Alabama at Birmingham, Birmingham, AL, [6]Biochemistry & Molecular Genetics, University of Alabama at Birmingham, Birmingham, AL, [7]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [8]Birmingham VA Medical Center, Birmingham, AL, [9]Department of Medicine, University of Alabama at Birmingham, birmingham, AL

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Background/Purpose: In autoimmune prone BXD2 mice, abnormally upregulated IL-17 acts through NF-κB p65 role to promote the spontaneous germinal center response and autoantibody production. Recently, a pre-germinal center defect in the early transitional B cell

development of autoimmune BXD2 mice was identified. This defect was characterized by accelerated B cell development, a feature which was normalized by IL-17RA deficiency on the BXD2 background. The hypothesis of this work is that IL-17 induced NF-κB regulates transitional B cell development

Methods: Using a B cell antigen tetramer, La_{13-27} autoreactive B cells from the spleens of B6, autoimmune wild-type (WT) BXD2, and BXD2-*Il17ra*$^{-/-}$ mice were analyzed by FACS for the development of CD93^{+} transitional B cell subsets. Intracellular phospho-flow was used to determine levels of phospho-p65 (p-p65) and total phospho-tyrosine following anti-IgM (5 µg/mL) stimulation at different time points. Super-resolution molecular imaging (STORM) was carried out to visualize p65 and p50 in BXD2-*Il17ra*$^{-/-}$ B cells. WT BXD2 and BXD2-*Il17ra*$^{-/-}$ were treated *in vivo* with AdIL-17 or AdIL-17RA:Fc to enhance or block endogenous IL-17RA signaling, respectively. Activation vs anergic responses were assessed by Dojindo cell survival assay following anti-IgM stimulation.

Results: There was an enhanced BXD2-*Il17ra*$^{-/-}$ transitional B cell anergy phenotype *in vivo*, which was characterized by a normalized La_{13-27}^{+} transitional B cell development compared with WT BXD2. BXD2-*Il17ra*$^{-/-}$ B cells further exhibited strong anergic responses to BCR or TLR7 stimulation *in vitro*. The strong anergic phenotype of BXD2-*Il17ra*$^{-/-}$ mouse B cells was associated with a dramatically enhanced nuclear expression of NF-κB1 (p50) and down-modulation of NF-κB p-p65. Super-resolution imaging supported increased p50 homodimer presence in the nucleus of BXD2-*Il17ra*$^{-/-}$ B cells relative to WT BXD2. *In vivo* injection of AdIL-17 in pre-disease BXD2 mice enhanced anti-IgM induced survival and anergy loss. Surprisingly, despite normal expression of BAFF-R on transitional and mature B cell subsets, BlyS cannot reverse the anergic response of BXD2-*Il17ra*$^{-/-}$ B cells to BCR stimulation. Analysis of the expression of IL-17RA in the B-cell subsets in BXD2 mice showed that IL17RA is strongly upregulated in transitional T2 (CD93^{+}IgM^{+}CD23^{+}) and germinal center (PNA^{+}Fas^{+}) B cells. Single cell analysis of T2 B cells revealed the co-expression of *Il17ra* with B-cell activation gene, *Bclxl*.

Conclusion: Our results suggest that, in BXD2-*Il17ra*$^{-/-}$ B cells, the anergy phenotype is established at the transitional stage. In these B cells, stimulus-specific transcription repressive p50/p50 homodimers may act as a master transcriptional regulator to counteract pro-activation/survival NF-κB signaling provided by other major B-cell stimulators. Reagents that can promote the NF-κB p50/p50 repressome complex may be a novel strategy to enhance B-cell tolerance for autoimmunity. *(Supported by NIH R01AI071110, R01AI083705, P30AR048311, T32 AI007051, VA Merit Review grant 1I01BX000600, Lupus Research Institute, Lupus Foundation of America. *Il17ra*$^{-/-}$ mice were a generous gift from Amgen).

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Abstract Number: 920

Autoantigen-Specific T Cell and Antibody Reactivity to a Human Gut Commensal in Antiphospholipid Syndrome

William Ruff[1], Carina Dehner[2], Alex Roth[1], Silvio M. Vieira[1], Cassyanne L. Aguiar[3,4], Andrew Goodman[5], Doruk Erkan[6] and Martin Kriegel[1], [1]Immunobiology, Yale School of Medicine, New Haven, CT, [2]Immunobiology, Yale School of Medicine, new haven, CT, [3]Pediatric Rheumatology, Hospital for Special Surgery, New York, NY, [4]Cohen Children's Medical Center of New York/ Hofstra Northwell School of Medicine, Pediatric Rheumatology, New York, NY, [5]Microbial Pathogenesis, Yale School of Medicine, New Haven, CT, [6]Rheumatology, Hospital for Special Surgery- Weill Cornell Medicine, New York, NY
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Autoantigen-specific T Cell and Antibody Reactivity to a Human Gut Commensal in Antiphospholipid Syndrome

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Background/Purpose: Antiphospholipid syndrome (APS) is a serious autoimmune clotting disorder of unknown etiology but with a well-defined major autoantigen, β_2-glycoprotein I (β_2GPI). Infectious triggers have been implicated in transient autoantibody production, but the persistent stimuli for anti-β_2GPI antibodies remain unknown. Given the vast antigenic potential of the gut microbiota, we hypothesize that human gut commensal bacteria induce and sustain autoreactivity via cross-reactivity. To this end, we characterized APS β_2GPI-specific T cell and autoantibody reactivity to *in silico* candidates.

Methods: NCBI BLAST was used to identify microbial protein sequences with high homology to major β_2GPI epitopes. Sorting of IgA-coated fecal microbiota followed by 16S rDNA sequencing (IgA-Seq) was performed on APS and control microbiomes. Human-derived candidate and control strains were cultured anaerobically. Blood and stool samples were collected from APS patients and controls. A novel strain-specific real-time PCR strategy was developed and validated using isolated strains and defined fecal microbiomes. Memory $CD4^+$ T cells specific to β_2GPI were cloned using a T cell library assay and a monoclonal antibody specific to the RGGMR domain I epitope of β_2GPI was expressed for cross-reactivity studies.

Results: Systematic *in silico* searches revealed *Roseburia intestinalis* as a major candidate with high homology to the main B and T cell epitopes of β_2GPI. *R. intestinalis* colonization load was abundant and persistent throughout the study population. IgA-Seq showed IgA coating of the genus *Roseburia*. APS PBMC proliferated significantly more to protein extracts from *R. intestinalis* versus control subjects (p=0.0002), and also compared to the phylogenetically related, but mimic-deficient gut commensal *Eubacterium rectale* (p=0.02). APS memory CD4+ T cells specific for a T cell epitope in domain V cross-react with *R. intestinalis* mimic peptide. Further, an APS patient-derived anti-domain I β_2GPI monoclonal antibody bound significantly to *R. intestinalis* lysates whereas a control antibody against an unrelated β_2GPI epitope did not.

Conclusion: We have identified a common gut commensal, *R. intestinalis,* as a potential chronic cross-reactive trigger in APS. *Roseburia* is IgA-coated in APS microbiomes suggesting adaptive immune responses to the candidate *in vivo*. *In vitro* studies support cross-reactivity of β_2GPI-specific CD4 memory T cells and a pathogenic autoantibody with *R. intestinalis*. This study provides a concept for common human gut commensals as chronic cross-reactive triggers in genetically susceptible autoimmune hosts such as APS patients.

Disclosure: W. Ruff, None; **C. Dehner**, None; **A. Roth**, None; **S. M. Vieira**, None; **C. L. Aguiar**, None; **A. Goodman**, None; **D. Erkan**, None; **M. Kriegel**, None.

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Abstract Number: 921

The Anti-IL-17A Antibody Secukinumab (Cosentyx®, AIN457) Diminishes the Expression of the NFκB Pathway Modulator Ikbζ

Robert Hennze[1], Thomas Schlitt[1], Thomas Peters[1], Irina Koroleva[2], Rebecca Torene[2], Xiaoyu Jiang[3], Marija Curcic Djuric[1], Anis Mir[1], Frank Kolbinger[1] and **Christine Huppertz**[1], [1]Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, Switzerland, [2]Novartis Institutes for BioMedical Research, Novartis Pharma AG, Cambridge, MA, [3]Novartis Institutes for BioMedical Research, Novartis Pharma AG, Cambdrige, MA

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Background/Purpose: In order to better understand the IL-17A signaling pathway we have analyzed the effects of IL-17A in human primary synovial fibroblasts (SF), a major source of inflammatory mediators in rheumatoid arthritis (RA), as an example of stromal cells. We could show that IL-17A alone and in combination with TNF induces NFKBIZ encoding the NFκB pathway modulator IκBζ. In this study we assessed the role of NFKBIZ/IκBζ as a signaling node downstream of IL-17A by NFKBIZ siRNA knockdown. Since NFKBIZ has recently been identified as a psoriasis susceptibility locus, and shown to drive inflammation in psoriasis-like mouse models and in human keratinocytes, we analyzed the mRNA levels of NFKBIZ and of selected target genes in skin biopsies from psoriasis patients that have been treated with the anti-IL-17A antibody secukinumab (approved for the treatment of psoriasis and psoriatic arthritis).

Methods: Human primary RA-SF (Cell Application Inc.) were transfected with control or NFKBIZ siRNA (24h) before stimulation with IL-17A alone or in combination with TNF (18h). mRNA levels of inflammatory mediators (e.g. IL-6, CSF3/G-CSF, CXCL-1) were determined by qPCR, and released protein levels by AlphaLISA or homogeneous time resolved fluorescence. Secukinumab was added prior to TNF/IL-17A to determine its neutralizing activity. The mRNA levels of NFKBIZ and target genes in lesional and nonlesional skin biopsies from psoriasis patients at baseline and after 12 week treatment with secukinumab (n=19) or placebo (n=9) were determined by Nanostring.

Results: IL-17A stimulation induced marked levels of NFKBIZ and IκBζ in SF, which were further increased by TNF/IL-17A costimulation. We achieved a > 90% knockdown by NFKBIZ siRNA transfection, and could show that the expression of several inflammatory mediators induced synergistically by TNF/IL-17A, e.g. IL-6, CXCL-1, CSF3/G-CSF, were significantly reduced both on mRNA and protein level, suggesting that NFKBIZ represents an important node controlling several pro-inflammatory genes. Secukinumab potently inhibited the TNF/IL-17A induced release of these mediators at picomolar concentrations. We observed that NFKBIZ mRNA levels were upregulated in lesional versus nonlesional skin from psoriasis patients and that the increased expression of NFKBIZ was reduced after 12 week treatment with the anti-IL-17A antibody secukinumab. The expression of main biomarkers for the efficacy of secukinumab was also decreased, including CXCL-1 and the gene encoding β-defensin2 which is specifically expressed in keratinocytes and described to depend on NFKBIZ.

Conclusion: We show that NFKBIZ is induced in psoriatic lesional skin and by IL-17A alone and in combination with TNF in synovial fibroblasts. We demonstrate that NFKBIZ controls the expression of IL-17A-stimulated main inflammatory mediators. We also observe that mRNA levels of NFKBIZ, CXCL-1 and of the gene encoding β-defensin2 are reduced in lesional skin from psoriasis patients after secukinumab treatment. These data suggest that the therapeutic effect of secukinumab seen in psoriasis and potentially other indications may be mediated at least in part by the downregulation of the NFKBIZ signaling node.

Disclosure: R. Hennze, Novartis Pharma AG, 3; **T. Schlitt**, Novartis Pharma AG, 3; **T. Peters**, Novartis Pharma AG, 3; **I. Koroleva**, Novartis Pharma AG, 3; **R. Torene**, Novartis Pharma AG, 3; **X. Jiang**, Novartis Pharma AG, 3; **M. Curcic Djuric**, Novartis Pharma AG, 3; **A. Mir**, Novartis Pharma AG, 3; **F. Kolbinger**, Novartis Pharma AG, 3; **C. Huppertz**, Novartis Pharma AG, 3.

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Abstract Number: 922

Negative Regulation of IL-17 Receptor Signaling By Regnase-1 Limits Immunopathology in a Mouse Model of Psoriatic Skin Disease

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Background/Purpose: IL-17 cytokines have emerged as drivers of autoimmunity. Indeed, the IL-17A-targeting antibody secukinumab (Cosentyx) was recently approved for treatment of plaque psoriasis, and shows efficacy in psoriatic arthritis and ankylosing spondylitis. IL-17 family members signal through a dimeric receptor composed of a common subunit, IL-17RA, and a variant co-receptor. Both IL-17A and IL-17C have been implicated in psoriasis pathology, but while IL-17A signals through IL-17RA and IL-17RC, IL-17C is reported to act

through an IL-17RA/IL-17RE heterodimer. To date, little is known about the regulatory mechanisms that control the amplitude of inflammation mediated by IL-17 cytokines, particularly in the context of autoimmunity. Not surprisingly, numerous mechanisms have evolved to restrict IL-17 signaling to limit bystander tissue damage. The endoribonuclease Regnase-1 [also known as MCP1-Induced Protein 1 (MCPIP1), encoded by *Zc3h12a*] is a key regulator of inflammation. We previously showed that Regnase-1 downregulates IL-17A signaling, including expression of IL-6 and IkBz. Consequently, Regnase-1-deficient mice had exacerbated CNS inflammation in the experimental autoimmune encephalomyelitis model. Here, we assessed the impact of MCPIP1 in a murine model of psoriasis, and verified its presence in human psoriatic lesions.

Methods: Psoriatic inflammation was induced by application of imiquimod (IMQ). *Zc3h12a*$^{+/-}$, *Il17ra*$^{-/-}$, *Il17c*$^{-/-}$, *Il17re*$^{-/-}$and intercrossed mice or littermates were subjected to IMQ-induced psoriasis for 1-5 days. Disease was assessed by measurement of ear thickening, H&E staining of skin sections, immune cell infiltration by flow cytometry, and gene expression by qPCR. Bone marrow chimeras were made by adoptive transfer into irradiated recipients. De-identified skin biopsies were stained for Regnase-1 by IHC.

Results: During IMQ-induced inflammation, *Zc3h12a* mRNA was elevated in mouse skin. Consistently, *ZC3H12A* was more highly expressed in human lesional skin than in non-lesional or healthy skin biopsies. Consistent with its recognized role as a feedback inhibitor, mice deficient for Regnase-1 (*Zc3h12a*$^{+/-}$) showed more dermal inflammation following IMQ-induced psoriasis induction than littermate controls, whereas *Il17ra*$^{-/-}$ mice were fully resistant to disease. Genes associated with Regnase-1-induced inflammation included prototypical IL-17 target genes such as *Il6* and *Lcn2*. Bone marrow chimeras indicated that the inhibitory activity of Regnase-1 in IMQ-psoriasis was restricted to the non-hematopoietic compartment, which was also consistent with an IL-17-dependent pathogenesis. Further evidence to support this model was the finding that *Zc3h12a*$^{+/-}$*Il17ra*$^{-/-}$ mice were fully protected from disease. Surprisingly, neither *Zc3h12a*$^{+/-}$*Il17c*$^{-/-}$ nor *Zc3h12a*$^{+/-}$*Il17re*$^{-/-}$mice were protected, suggesting that Regnase-1 activity is restricted to IL-17A in this setting.

Conclusion: Regnase-1 negatively regulates IL-17A but not IL-17C or IL-17RE in the context of autoimmune skin inflammation. Regnase-1 is overexpressed in active dermal inflammation, but is nonetheless insufficient to control disease.

Disclosure: S. L. Gaffen, Novartis Pharmaceutical Corporation, 2,Janssen Pharmaceutica Product, L.P., 2,UCB Celltech, 5,Janssen Pharmaceutica Product, L.P., 5,Amgen, 9; **L. Monin**, None; **N. Ward**, None; **J. Gudjonsson**, None; **A. Garg**, None; **A. Mathers**, None; **P. Kolattukudy**, None.

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Abstract Number: 923

Retinoic Acid Inhibits Expression of Interleukin 9 By Altering Enhancer Architecture

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SESSION INFORMATION

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Session Title: Cytokines, Mediators, Cell-Cell Adhesion, Cell Trafficking and Angiogenesis I

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Vitamin A and its major metabolite, retinoic acid (ATRA), modulate T cell function and fitness to shape immune responses. Vitamin A deficiency causes increased susceptibility to infection, leading to the death of an estimated 250,000-600,000 children per year. Osteoarthritis has been linked to variants in the ALDH1A2 gene, which metabolizes Vitamin A to ATRA. Retinoic acid is an essential positive regulator of T effector cell responses, yet retinoids can also dampen immune responses through inhibition of effector cytokine production. Moreover, ATRA induces expression of the transcription factor Foxp3, which is necessary for immune tolerance. This multifaceted effect of ATRA complicates dissection of the molecular mechanisms that elicit negative immunoregulatory functions.

Methods: We aimed to evaluate the direct effects of retinoic acid induced immunomodulation that are not dependent on enhancing T regulatory cell function. We performed RNA-seq and compared the transcriptomes of ATRA-treated and untreated T helper cell subsets.

We used Chromatin Immunoprecipitation-sequencing (ChIP-seq) and Assay for Transposase-Accessible Chromatin-sequencing (ATAC-seq) to characterize ATRA-induced changes in chromatin architecture.

Results: We characterized an ATRA-regulated gene signature that was independent of CD4 T cell subset. We identified IL-9 as the cytokine whose gene expression is most strongly inhibited. Using Foxp3-mutant (Scurfy) mice, we demonstrated that ATRA's immunomodulatory effects, including IL-9 inhibition, are Foxp3-independent. We confirmed that retinoic acid potently inhibits IL-9 in T cells *in vitro*, and in T cells and Type 2 innate lymphoid cells (ILC2s) in an *in vivo* model of allergic lung disease. We mapped chromatin accessibility of the *Il9* locus by ATAC-seq and enhancer marks by ChIP-seq, which led us to identify several novel *Il9* enhancers. We observed that RAR-alpha binds directly to the *Il9* locus, reduces chromatin accessibility, and disrupts looping between the *Il9* promoter and associated enhancers.

Conclusion: Our observation suggests that ATRA-RAR-alpha directly suppresses IL-9 by modifying enhancer architecture, which may serve as a paradigm for the mechanism by which retinoic acid modulates cytokine expression.

Disclosure: D. Schwartz, None; **F. Meylan**, None; **H. W. Sun**, None; **H. Y. Shih**, None; **K. Jiang**, None; **F. Petermann**, None; **R. M. Siegel**, None; **A. Laurence**, None; **J. J. O'Shea**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/retinoic-acid-inhibits-expression-of-interleukin-9-by-altering-enhancer-architecture

Abstract Number: 924

Intestinal Dysbiosis Influences Gut-Joint Lymphocyte Trafficking

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Session Time: 2:30PM-4:00PM

Background/Purpose: Intestinal microbiome studies in IBD and AS have shown significant bacterial dysbiosis (i.e., a substantial alteration of the individual species) in similar populations, as compared to healthy controls. However, *the mechanistic linkage between the microbiota, changes in mucosal immunology, and the subsequent pathogenic targeting of the spine has not been defined.* Intraepithelial lymphocytes (IELs) are a unique population of antigen-experienced T cells which are anatomically associated with intestinal epithelial cells and function to protect the host from microbial invasion and maintain epithelial homeostasis. Our ongoing studies have revealed that dysbiosis in patients with IBD and mouse models alters the function of IELs. We hypothesize that resident bacteria educate IELs, which in turn, traffic systemically and cause arthritis under dysbiotic conditions.

Methods: Dysbiosis is modeled by administration of broad-spectrum antibiotics (ampicillin, neomycin, metronidazole, and vancomycin) in the drinking water for one week; recolonization of mice is done by cohousing with unmanipulated littermates for one week. KikGR mice contain a transgene for a photoconvertible green-to-red fluorescent protein. Endoscopy-guided violet light allowed photoconversion of distal colonic IELs in vivo. $TNF^{\Delta ARE/+}$ mice contain a mutation in the AU-rich element of the TNF-α gene resulting in increased mRNA stability and systemically elevated TNF-α. As a result, these mice develop ileitis and arthritis beginning around 8 weeks of age. Microbial analysis was performed on fecal pellets via high-throughput 16S rRNA gene sequencing. Trafficking of photoconverted lymphocytes was determined by flow cytometry of tissues.

Results: One week following photoconversion of the distal colon lymphocytes in KikGR mice, labeled intestinal lymphocytes were detected systemically in tissues including the spleen, liver, lungs, and Achilles entheses; few lymphocytes remained in the colon. Treatment of mice with antibiotics following photoconversion resulted in substantially reduced trafficking to distal tissues as well as a depletion of the colonic population. After recolonization, labeled colonic lymphocytes substantially increased in the colon while few remained in distal tissues. Our analysis of $TNF^{\Delta ARE/+}$ mice demonstrates significant dysbiosis occurs as mice age and develop disease compared to $TNF^{+/+}$ littermates.

Conclusion: Manipulation of intestinal bacteria through antibiotic use alters intestinal lymphocyte trafficking to extra-intestinal tissues. We have generated $TNF^{\Delta ARE/+}$ X KikGR mice, and our future studies will link dysbiosis, lymphocyte trafficking, and disease. Our goal is to identify triggers for systemic IEL trafficking from the intestine during health and IBD-related SpA and define the role of trafficked IELs

in the target tissue. Through understanding these mechanisms we hope to identify biomarkers of gut-joint trafficking to diagnose patients earlier and/or treatment strategies to improve disease outcomes for SpA.

Disclosure: K. Kuhn, None; **H. Schulz**, None; **J. Hendrickson**, None; **N. Ohri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/intestinal-dysbiosis-influences-gut-joint-lymphocyte-trafficking

Abstract Number: 925

Complement C5a Receptor Is the Key Initiator of Neutrophil Adhesion and Inflammation in Immune Complex-Induced Arthritis

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Session Time: 2:30PM-4:00PM

Background/Purpose: Inflammatory arthritis, including rheumatoid arthritis, is characterized by neutrophil (PMN) recruitment into the joint in a highly regulated process controlled by chemoattractants (CAs). Four different chemoattractant receptors (CAR), BLT1, CCR1, CXCR2 and C5aR, are required and collaborate to mediate PMN recruitment into the joint in immune-complex (IC) induced arthritis. However, the precise role for each CA in the process of PMN recruitment into the joint *in vivo* remains unclear. This process begins with the capture of free-flowing leukocytes to the vessel wall, followed by *rolling* and then *arrest* on the vessel wall, release from adhesion and then *crawling* in all directions on the vessel to locate a receptive location for *transendothelial migration* (TEM) into the joint.

Methods: Multiphoton intravital imaging (MP-IVM) was performed to analyze the migratory behavior of wild-type (WT) and CAR-deficient (KO) PMNs in the joint of WT and CAR-KO-LysM-GFP mice, in which endogenous PMNs and macrophages express GFP, on day 7 after K/BxN serum transfer (KST). We analyzed the ability of WT and CAR-KO PMNs to enter the joint in short term adoptive transfer assays on day 7 after KST. We also analyzed joint tissue for the expression of C5a using immunohistochemistry and synovial fluid (SF) for the levels of CKs by ELISA. We analyzed the expression of CARs by flow cytometry on PMNs isolated from the bone marrow (BM), blood and SF. Lastly, we generated mixed bone marrow chimeric (BMC) mice with WT and CAR-KO BM cells transferred into lethally irradiated WT mice to analyze PMN recruitment into the joint through the entire course of arthritis development. Finally, the effect of CXCR2 ligands on SF PMN survival was evaluated.

Results: In the inflamed joint of WT- LysM-GFP mice, abundant PMN adhesion and TEM was observed. However, PMN adhesion and TEM were not observed in the joint of C5aR-KO-LysM-GFP mouse. PMN adhesion was observed in the joints of BLT1-KO-, CCR1-KO- and CXCR2-KO-LysM-GFP mice but PMN TEM was either not observed or was markedly diminished. Short term adoptive transfer assays demonstrated a decrease in the adhesion and TEM of C5aR-KO PMNs, whereas BLT1-KO, CCR1-KO and CXCR2-KO PMNs were able to adhere to the endothelium but had a decrease in TEM into the inflamed joint. 40% adoptively transferred C5aR-KO PMNs that arrested on the endothelium detached, while 20% of CCR1-KO PMNs that crawled on the endothelium detached. WT arrested and crawling PMNs were not observed to detach from the endothelium. C5a deposition was observed on the endothelium and cartilage in arthritic joints. C5a was detected in the joint on day 1, whereas the other CAs were detected at later time points. In mixed BMC mice with arthritis, CXCR2-KO PMNs were not observed in joint and CXCR2 ligands prevented SF neutrophils from undergoing apoptosis.

Conclusion: Our data demonstrate that C5a is the critical initiator of PMN adhesion on joint endothelium and is required to initiate joint inflammation in IC-induced arthritis. In addition, we have found that CCR1 contributes to the interaction of PMNs with the joint endothelium and that PMNs self-propagate their recruitment and survival via CXCR2 in the joint space.

Disclosure: Y. Miyabe, None; **C. Miyabe**, None; **T. Murooka**, None; **E. Kim**, None; **N. Kim**, None; **T. R. Mempel**, None; **A. D. Luster**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/complement-c5a-receptor-is-the-key-initiator-of-neutrophil-adhesion-and-inflammation-in-immune-complex-induced-arthritis

Abstract Number: 926

Increased Concentration of Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) Predate Onset of Rheumatoid Arthritis

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Session Time: 2:30PM-4:00PM

Background/Purpose: Receptor activator of nuclear factor κB ligand (RANKL) an important regulator of bone metabolism has a key role in local bone destruction and osteoporosis in rheumatoid arthritis (RA). The aim of this study was to investigate the relationships between RANKL and biomarkers (anti-citrullinated peptide antibodies (ACPA), anti-carbamylated (anti-CarP) antibodies and cytokines) in individuals before symptom onset of RA and their association to radiological findings at disease onset.

Methods: A case-control study with 470 (334 women/136 men) pre-symptomatic individuals (mean age±SD 52.3±9.4) who had donated blood samples before symptom onset and 96 (60 women/36 men) population based controls was performed within the Medical Biobank of Northern Sweden. The median (IQR) predating time before symptom onset was 5 (5.1) years. Radiographs of hands and feet performed when diagnosed with RA were grade using Larsen score. ELISAs were used for analysing RANKL (BioVendor, Karasek, Czech Republic), anti-CCP2 antibodies (Eurodiagnostics, Sweden), anti-CarP antibodies (in-house ELISA in collaboration with L Trouw, NL) and ACPA using multiplex ISAC platform (PhaDia AB, Sweden) in plasma. Cytokines were analysed using Meso Scale Discovery V-plex methods (Maryland, USA). The cut-off for RANKL was set at 95% according to the ROC curve.

Results: The concentration of RANKL was significantly higher in the pre-symptomatic individuals compared with controls, mean±SEM 0.50±0.03 nmol/L versus 0.22±0.02 nmol/L, ($p<0.001$). The RANKL concentration increased gradually over time the closer to onset of symptoms samples were collected. Anti-CCP2 positive pre-symptomatic individuals had higher levels of RANKL compared with sero-negative individuals, as for rheumatoid factor positive individuals ($p<0.001$). Concentrations of RANKL were significantly associated with several ACPA specificities, anti-CarP antibodies, interleukin (IL)6 and IL10 concentrations in pre-symptomatic individuals. RANKL concentrations were related to higher Larsen score at RA diagnosis in men ($p<0.05$). Combination of positivity of RANKL and anti-CarP antibodies yielded increased risk for higher Larsen score at RA diagnosis compared with being negative for both as a reference, ß= 6.23 (95%Cl 0.96, 11.50, $p<0.021$).

Conclusion: RANKL concentrations were increased several years before symptom onset of RA and associated with Larsen score when RA was diagnosed in men. Combination of positivity of both RANKL and anti-CarP antibodies yielded the highest Larsen score at disease onset. These findings provide new insight into some of the key mechanism of RANKL in bone destruction in individuals already years before onset of symptoms of RA.

Disclosure: L. Johansson, None; **L. Ärlestig**, None; **H. Kokkonen**, None; **S. Rantapaa-Dahlqvist**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-concentration-of-receptor-activator-of-nuclear-factor-kappa-b-ligand-rankl-predate-onset-of-rheumatoid-arthritis

Abstract Number: 927

2015 ACR/ARHP Workforce Study in the United States: Pediatric Rheumatologist Supply and Demand Projections for 2015-2030

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Session Title: Health Services Research I: Workforce and Quality of Care in Rheumatology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The 2015 ACR Workforce study updated the current and projected pediatric rheumatology workforce for the next 15 years.

Methods: The 2015 ACR/ARHP Workforce Study was completed using several primary and secondary data sources, including, ACR member data, state licensure registries, 2005 ACR workforce study, professional organizations, and other medical literature. These data were supplemented with a web-based survey to collect information about work settings, practice patterns, retirement planning, and demographics. Utilizing an integrated workforce modeling methodology, supply and demand projections were computed for pediatric rheumatologists from 2015-2030. The factors affecting supply included the current pediatric rheumatology workforce, demographic changes, completed fellowships, retirement trends, patient workload and practice settings. Multivariate regression modeling was used to determine significant factors affecting demand. These included healthcare utilization, provider practice trends, disease prevalence, population demographics, per capita income and access to care trends. Clinical FTE was defined as 1.0 FTE for private practice and 0.5 FTE for academic practice and compared to actual projections (Figure 1), assuming 95% of the pediatric rheumatology workforce was in academic practice vs. 5% in private practice.

Results: The 2015 ACR current pediatric workforce is estimated to be 300 providers (287 Clinical FTE). The majority (56%) of pediatric rheumatologists are in the Northeast, Mid-Atlantic and Great Lakes Regions. There are two states that have no board-certified practicing pediatric rheumatologists (Alaska, New Mexico) and many states where there is only 1-3 covering the entire state. A 20% reduction in supply coupled with a 21% increase in need results in a projected excess demand of about 100% pediatric rheumatologists by 2030 (461-231=230) (Figure 2). Projected need is much greater when compared to that projected in 2005.

Conclusion: This severe shortage of pediatric rheumatologists is likely due to several factors, including increases in projected patient population, coupled with the decrease in clinical FTE due to increases in females, part-time, and millennial workers. Additionally, the number of unfilled fellowship positions average 40% each year contributing to the shortage. As a result, patients in need have severely limited access to the care. Regional and innovative recruitment strategies will be necessary to help increase the supply, manage access to care and reduce barriers to care for pediatric rheumatology patients.

Figure 1. Comparison Total Numbers vs. Clinical FTE Pediatric Rheumatologists

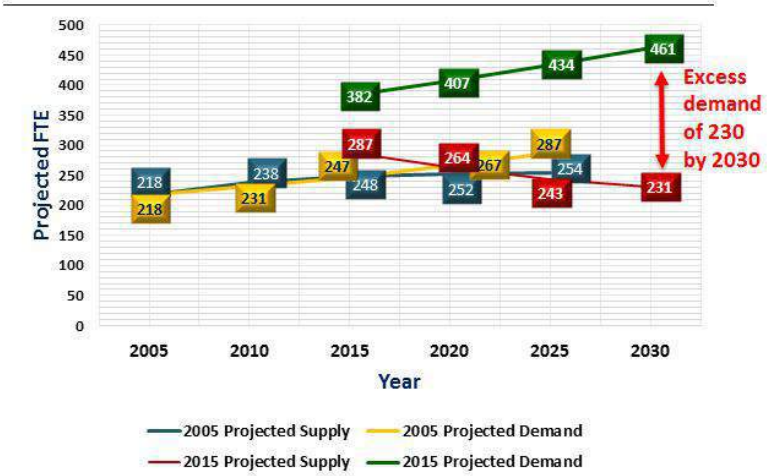

Figure 2. Comparison of Projected Supply and Demand of Pediatric Rheumatology Workforce

Disclosure: D. Battafarano, None; **S. Monrad**, None; **M. Ditmyer**, None; **L. Imundo**, None; **M. Klein-Gitelman**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/2015-acrarhp-workforce-study-in-the-united-states-pediatric-rheumatologist-supply-and-demand-projections-for-2015-2030

Abstract Number: 928

2015 ACR/ARHP Workforce Study in the United States: A Maldistribution of Adult Rheumatologists

Katrina Lawrence-Wolff[1], Bernard Hildebrand[1], Seetha Monrad[2], Marcia Ditmyer[3], John Fitzgerald[4], Alan Erickson[5], Anne R. Bass[6] and Daniel Battafarano[7], [1]Rheumatology, San Antonio Military Medical Center, San Antonio, TX, [2]Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [3]University of Nevada, Las Vegas, NV, [4]Rheumatology, UCLA, Los Angeles, CA, [5]University of Nebraska, LaVista, NE, [6]Rheumatology, Hospital for Special Surgery, New York, NY, [7]Medicine, San Antonio Military Medical Center, San Antonio, TX

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: The 2015 ACR/ARHP Workforce Study assessed the current and projected rheumatology workforce and the regional distribution of rheumatologists. Over the next 10 years, a declining rheumatology workforce resulting from significant “baby boomer” retirements, millennial ascendency and a gender shift toward women will be met with an increasing patient demand. We analyzed regional workforce differences and retirement trends within the context of population expansion to better understand the impact of workforce changes in the decade of 2015-2025.

Methods: The 2015 ACR/ARHP Workforce Study was completed using several primary and secondary data sources, including the ACR member database, state licensure registries, 2005 ACR workforce study results, professional organization information and peer-reviewed literature. These data were supplemented with a web-based survey assessing work settings, practice patterns, retirement planning and demographics. A clinical FTE was defined as 1.0 FTE for private practice and 0.5 FTE for academic practice to determine rheumatologists actually treating patients vs. total number of physicians. Population growth estimates were obtained using U.S. Census Bureau data.

Results: The U.S. ranks 3rd in projected population growth in the world with an anticipated growth of 16.5% by 2030. Thirty-two percent of ACR members responded to the survey (1996/6342).The highest concentrations of rheumatologists are found in the Northeast and Mid-Atlantic regions (Table 1). Response rates ranged from 17% in the Northeast to 54% in the Southwest/South Central regions (Table 1). The estimated total number of rheumatologists in the U.S. workforce in 2015 by FTE is 4,933 with a projected decrease to 3,645 by 2025. Combining the projected growth rates by region coupled with the projected retirement rates, the three regions with the greatest increase of

adult to physician ratio would be the Northwest (148%), North Central (136%), and South Central (102%) (Figure 1). The overall adult-to-physician is projected to be 99,177 by 2025 (Table 1).

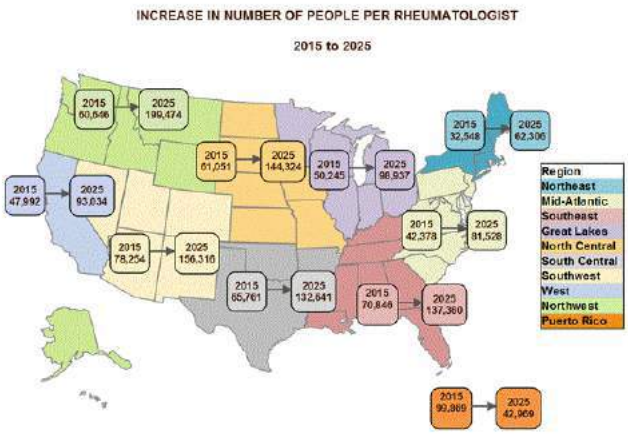
Conclusion: There is a regional maldistribution of rheumatologists in the United States, and disparities will increase with anticipated retirements and regional population growth estimates. The South Central, North Central and Northwest regions will experience the greatest change in population to provider ratios. The challenge of an increasing demand for rheumatology care requires novel solutions, processes and a multidisciplinary approach to ensure timely access to care for rheumatology patients.

Table 1. 2015-2025 Projected Regional Distribution of Rheumatologists with Population Growth

Region	Absolute number of Rheum 2015		Reported Active Rheum 2015*		Survey Respondents Response Rate**		Adult per Rheum Ratio 2015	% Projected Retired 0-10 Years#	Projected Rheum in 2025*	Projected Adult per Rheum Ratio 2025
	N	%	N	%	N	%				
Northeast	1261	21.1	1,036	21	219	0.17	32,548	0.44	767	63,306
Mid-Atlantic	1028	17.2	839	17.1	251	0.25	42,378	0.44	628	81,528
Puerto Rico	64	1.1	64	1.1	---	---	42,969	0.38	38	99,869
West	742	12.4	641	12.4	292	0.39	47,992	0.5	496	93,034
Great Lakes	957	16	789	16	187	0.2	50,245	0.45	581	98,937
Northwest	262	4.4	197	4.4	126	0.48	60,646	0.47	147	119,474
North Central	255	4.3	197	4.3	48	0.19	61,051	0.26	105	144,324
South Central	493	8.2	395	8.2	264	0.54	65,761	0.44	282	132,641
Southeast	698	11.9	592	11.6	133	0.19	70,846	0.5	458	137,360
Southwest	233	3.9	197	3.9	125	0.54	78,254	0.45	143	156,316
Total	5993		4,997		1,184		50,626		3645	99,469

Sources: AMA, ABIM, ABP; RNS, AAPA, & ACR Workforce Study Survey Results. ABIM most current numbers of active rheumatologists (February 2016) minus Puerto Rico. Numbers were pulled from mid-level provider associations' information and other published literature. *Numbers reflect Clinical FTE. **Numbers represent those who reported zip codes. Only US zip codes were included. #Percentages based on survey response data.

Figure 1. Adult Rheumatologists per Population, 2015 compared to 2025



Disclosure: K. Lawrence-Wolff, None; **B. Hildebrand**, None; **S. Monrad**, None; **M. Ditmyer**, None; **J. Fitzgerald**, None; **A. Erickson**, None; **A. R. Bass**, None; **D. Battafarano**, None.

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Abstract Number: 929

Retinal Examinations Among SLE Patients Newly-Initiating Hydroxychloroquine in a U.S. Medicaid SLE Population, 2000-10

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Session Time: 2:30PM-4:00PM

Background/Purpose: U.S. Medicaid provides medical benefits to low-income people. Although the Federal government establishes guidelines, each state sets vision benefits. The American Academy of Ophthalmology recommends a baseline retinal examination at hydroxychloroquine (HCQ) initiation and periodically thereafter, but there is lack of real-world practice information. We investigated the proportion of SLE Medicaid patients newly-initiating HCQ who receive indicated retinal exams and identified factors associated with receiving this care.

Methods: We conducted a retrospective cohort study of SLE patients 18-65 years old in Medicaid Analytic eXtract (MAX) from the 29 most populated U.S. states, 2000-2010. SLE patients were identified by ≥ 3 codes for ICD-9 710.0, each ≥ 30 days apart, in hospital discharge diagnoses and physician visit claims. HCQ new-users were identified by a new HCQ prescription fill (index date) after 1st SLE code, with no HCQ use in the prior 12 months. We restricted to those with ≥12 months of continuous enrollment before and after index date to assess both ophthalmologic and retinal exams, identified by CPT and HCPCS codes. Comorbidities and healthcare utilization were collected from the 12 months before index date. Examination rates were calculated across calendar years and by comorbidity and healthcare utilization subgroups. Differences between patients with and without exams were detected by the difference in means or proportions of a variable divided by a pooled estimate of the standard deviation of the variable.

Results: We identified 12,755 SLE patients newly starting HCQ. Proportions of patients undergoing exams 1 year before or after initial HCQ prescription ranged from 35.8 to 42.8% for ophthalmologic exams and 4.7 to 7.7% for retinal exams during year 2001-2009. Patients who received ophthalmologic exams, compared to those who had not, were older (40.8 ± 12.1 vs. 37.5 ± 11.5 years), more were White/Hispanic/Asian vs. Black. They also had more comorbid conditions and had received more SLE-related lab tests (ANA, anti-dsDNA, C3, C4) in the pre-index period. The proportions of lupus nephritis patients (35.2%) and pregnant patients (32.6%) who had *any* ophthalmologic exam were among the lowest. Overall, a high proportion of SLE patients newly starting HCQ did not have *any* Medicaid claims for retinal exams (92.7%) or even for *any* ophthalmologic exam (55.2%) in the 1 year before and 1 year after HCQ initiation. (**Table**)

Conclusion: The proportions of U.S. Medicaid SLE patients starting HCQ who received ophthalmologic and retinal exams were extremely low overall, possibly due to state-dependent vision coverage. SLE patients may not be getting these indicated exams or they may be paying out-of-pocket or through supplemental vision insurance. Future studies will examine state-to-state variation in retinal exam rates and Medicaid vision coverage.

Table. Proportions of 12,755 SLE Patients Newly-Initiating HCQ who Received Ophthalmologic and Retinal Exams in the Year prior to or following First HCQ Prescription Fill

	Ophthalmologic Exams	Retinal Exams
Any baseline exams[a], %	22.8	2.8
Baseline exams only, %	13.8	2.2
Exams both before and after HCQ initiation, %	9.0	0.6
After HCQ initiation only[b]	22.1	4.5
No exams both before and after HCQ initiation	55.2	92.7

a During the one year prior to initial HCQ prescription fill b During the one year on or after initial HCQ prescription fill Codes for any ophthalmologic exams: CPT codes: 92002,92004,92012,92014,92018,92019,92225,92227,92228,92250,92230,92235,92240,92250,92260 HCPCS: S0620,S0621,S0625,S3000 Codes for retinal exams:

CPT-4 code(s) : 92225, 92227,92228, 92250 HCPCS: S0625 and S3000

Disclosure: **T. C. Lin**, None; **C. Feldman**, None; **H. Guan**, None; **S. Chen**, None; **M. Barbhaiya**, None; **K. H. Costenbader**, UpToDate, 7.

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Abstract Number: 930

How to Implement Cardiovascular Disease Risk Assessment for Patients with Inflammatory Joint Diseases in Daily Rheumatology Practice: An Overview of a

Nationwide Norwegian Project

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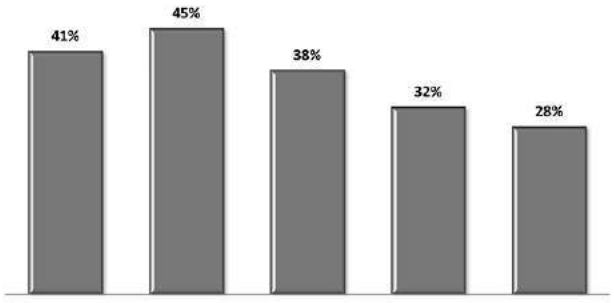
Background/Purpose: The EULAR recommendations for cardiovascular disease (CVD) risk management in patients with inflammatory joint diseases (IJD) states that CVD risk assessment should be considered annually in this patient population, and emphasizes that such assessment can be easily incorporated into a routine rheumatology visit; but they are rarely implemented. The aim of the NOrwegian Collaboration on Atherosclerosis in patients with Rheumatic joint diseases (NOCAR) was to design a program of annual CVD risk assessment for IJD patients that could be implemented into routine visits in rheumatology outpatient clinics.

Methods: NOCAR was started in April 2014 for quality assurance purposes, and comprises 11 rheumatology centres across Norway. All IJD patients >30 years registered in the electronic patient journal program GoTreatIt® Rheuma (GTI) are eligible. The CVD risk factors recorded in NOCAR are imputed directly into the GTI journal and are collected in a multidisciplinary manner: 1) Patients self-report CVD risk factors, 2) non-fasting lipids are ordered by health secretaries in addition to routine laboratory tests and 3) rheumatology nurses perform blood pressure measurement. Based on the Systematic COronary Risk Evaluation (SCORE) algorithm, GTI automatically calculates the patient's 10-year risk of a fatal CVD event. If the SCORE estimate is ≥5%, the rheumatologist forwards a note to the patient's primary physician to inform that there is indication for initiation of CVD-preventive measures (e.g. medication and lifestyle changes). Additionally, the rheumatologists and rheumatology nurses are instructed in how to deliver brief advice regarding smoking cessation and healthy diet. We report the initial capture rate in 3 NOCAR centres from which visit data was extracted in October 2015. We evaluated how many of the eligible patients who had received a CVD risk evaluation during these first 1.5 years of the NOCAR project. A CVD risk assessment was defined as having recoded all of the CVD risk factors included in the SCORE algorithm (total cholesterol, systolic blood pressure, smoking status, age and sex).

Percent of eligible patients for whom all CVD risk factors included in the SCORE algorithm were recorded



	ALL	RA	AS	PsA	SpA
Eligible patients	6150	3504	1107	1108	431
Patients who received CVD risk assessment	2519	1569	418	350	122

Results: Of the 6150 IJD patients (Rheumatoid arthritis [RA]: 3504, ankylosing spondylitis [AS]: 1107, psoriatic arthritis [PsA]: 1108, and other spondyloarthritides [SpA]: 431) who were eligible for the NOCAR project, 2519 (41%) patients received a CVD risk assessment during this 1.5 year interval (RA: 1569 [45%]), AS: 418 [38%], PsA: 350 [32%], SpA: 122 [28%]). The major obstacles to successful implementation encountered in NOCAR were time scarcity; defining a date for annual CVD risk assessment and making sure that lipids were measured before seeing the rheumatologist.

Conclusion: To our knowledge, this is the first multi-centre clinical project to show that incorporation of CVD risk assessment into routine rheumatology visits is feasible.

Disclosure: E. Ikdahl, None; **S. Rollefstad**, None; **G. Wibetoe**, None; **A. Salberg**, None; **D. M. Soldal**, None; **I. C. Olsen**, None; **T. K.**

Kvien, None; **G. Haugeberg**, Go Treat IT, 4; **A. G. Semb**, None.

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Abstract Number: 931

Rates of Lipid Testing and Statin Prescriptions Among SLE and Diabetes Mellitus Patients in a Nationwide Medicaid Cohort

Sarah K. Chen[1], Medha Barbhaiya[2], Michael A. Fischer[3], Hongshu Guan[4], Tzu-Chieh Lin[2], Candace H. Feldman[5], Brendan M. Everett[6] and Karen H. Costenbader[2], [1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Rheumatology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [5]Social and Behavioral Sciences, Harvard T. H. Chan School of Public Health, Boston, MA, [6]Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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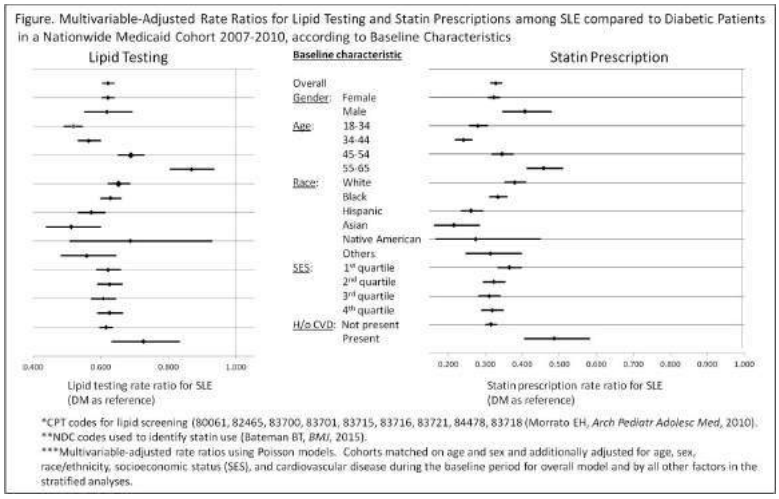
Background/Purpose: We have recently found that rates of myocardial infarction (MI) are similar among individuals with SLE and those with diabetes mellitus (DM) in a nationwide cohort of Medicaid recipients. Given high cardiovascular disease (CVD) risks in both SLE and DM patients, lipid testing is widely advocated for both groups. We investigated rates of lipid testing and statin prescriptions among SLE and DM patients within Medicaid.

Methods: Within Medicaid Analytic eXtract (MAX), with billing claims from 2007-2010 for patients from the 29 most populous US states, we identified patients aged 18-65 years with prevalent SLE (>3 ICD-9 codes for SLE, >30 days apart), and a 1:2 age- and sex-matched DM cohort (>3 ICD-9 codes for DM, >30 days apart). We required 6 months of continuous Medicaid enrollment (baseline period) prior to the 3rd diagnosis code (index date). Subjects were followed from index date until death, Medicaid disenrollment or end of follow-up (12/31/2010). Within claims, we used CPT codes to identify lipid testing and NDC codes to identify statin prescriptions. We calculated rates per 100 person-years for lipid testing (>1 per person) and statin prescriptions (> 1 per person), and rate ratios (with 95% CIs) adjusted for baseline demographics and CVD using Poisson regression to compare rates (DM=referent).

Results: 32,089 SLE patients were matched to 64,178 DM patients; 92% were female and mean age was 41.3 (+ 12.1) years in both cohorts. Mean years of follow-up from index date was 1.68 (+1.03) for SLE, and 1.81 (+1.08) for DM. Baseline CVD covariates for SLE vs. DM cohorts were similar for MI (0.90 vs. 0.67%), angina (2.19 vs. 2.08%), old MI (0.89 vs. 0.67%), PCI (2.29 vs. 1.61%), CABG (0.18 vs. 0.12%), CVA (2.23 vs. 0.14%), and presence of any any CVD (4.62 vs. 3.57%). Rates (per 100 person years) of lipid testing increased from 22.2 to 44.1 for SLE and 38.2 to 59.1 for DM and statin prescription increased from 7.0 to 23.4 for SLE and 24.6 to 57.9 for DM between 2007 and 2010. Unadjusted rates (per 100 person years) for lipid testing were 25.8 (95% CI 25.3-26.3) for SLE and 41.6 (95% CI 41.1-42.0) for DM, and for statin prescription were 9.1 (95% CI 8.8-9.4) for SLE and 27.6 (95% CI 27.3-28.0) for DM. The highest rates of lipid testing and statin prescriptions were found among Asians and lowest rates were seen among Native Americans for both SLE and DM. After adjusting for age, race/ethnicity, sex, region, socioeconomic status, calendar year, and CVD at baseline, the rate ratios in SLE compared to DM patients were 0.61 (95% CI 0.60-0.63) for lipid testing and 0.32 (95% CI 0.31-0.34) for statin prescriptions.

Conclusion: Rates for lipid testing and statin prescriptions increased in both SLE and DM cohorts during the study period and were highest among older patients and those with baseline CVD. Although DM and SLE confer similar risk of CVD, in this cohort, lipid testing rates were 40% lower and statin prescription rates were 70% lower in patients with SLE compared to DM.



Disclosure: S. K. Chen, None; **M. Barbhaiya**, None; **M. A. Fischer**, None; **H. Guan**, None; **T. C. Lin**, None; **C. H. Feldman**, None; **B. M. Everett**, None; **K. H. Costenbader**, UpToDate, 7.

Abstract Number: 932

High Symptom Prevalence and Under-Utilisation of Palliative Care at End-of-Life of Patients with Systemic Rheumatic Diseases

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Background/Purpose: Patients with rheumatic diseases may have systemic complications from disease as well as therapy and often suffer symptoms towards the end-of-life comparable to patients with advanced cancer. Palliative care in this group of patients has not been well evaluated due to a lack of data in the current literature. The aims of this study were to: (i) describe the multidimensional symptom profile and prevalence and (ii) analyze the factors associated with symptom prevalence and referral to palliative care services in patients with systemic rheumatic diseases in the last 1 year of life.

Methods: The electronic records of patients with systemic rheumatic diseases who died at the National University Hospital, Singapore from 2012 to 2016 were reviewed. Patients with crystal arthritis, septic arthritis, osteoarthritis and fibromyalgia were excluded. Symptom prevalence was assessed by summation of the number of symptoms experienced by the patients in the last 1 year of life. Charlson Comorbidity Index (CCI) and its predicted 1-year survival were constructed from the medical records. Linear and logistic regressions were used to identify independent predictors for symptom prevalence and referral to palliative care services.

Results: In total, 70 deceased patients with systemic rheumatic diseases were identified. The mean age at death was 66.2 years (standard deviation 14.5), 52 (74.3%) were females. The majority of patients had rheumatoid arthritis (30.0%) and systemic lupus erythematosus (25.7%), 58.6% of the deceased patients had active disease. The most common cause of death was infection (45.7%). Table 1 summarizes the symptom profile and prevalence of the deceased patients. Only 5.7% had advance care planning and 15.7% were referred to palliative care services. Active rheumatic disease was associated with escalation of immunosuppression ($p < 0.001$) but not with recurrent infections or symptom prevalence ($p > 0.05$, respectively). Among the various symptoms examined, only depression was associated with referral to palliative care services ($p = 0.013$). Predicted 1-year survival ($\beta = -0.104$, SE = 0.027, $p < 0.001$) was independently associated with

symptom prevalence. When considering only patients with active rheumatic diseases, predicted 1-year survival (β = -0.089, SE = 0.030, p = 0.005) and recurrent infections (β = 1.866, SE = 0.749, p = 0.017) were independently related to symptom prevalence. Predicted 1-year survival (OR = 0.902, 95% CI 0.825-0.986, p = 0.023), but not symptom prevalence (p > 0.05), was independently associated with referral to palliative care services.

Conclusion: This is the first study to describe the symptom profile and prevalence in patients with systemic rheumatic diseases in their last 1 year of life. Predicted 1-year survival using the CCI may be used to identify patients in earlier need of palliative care.

Table 1: Cumulative Symptom Prevalence Over Last 1 Year of Life

No. of Symptoms, Median (Min-Max)	Pain No. (%)	Dyspnoea No. (%)	Delirium No. (%)	Peripheral Edema No. (%)	Functional Decline No. (%)	Falls No. (%)	Decubitus Ulcers No. (%)	Bleeding No. (%)	Depression No. (%)	Weight Loss No. (%)
7 (2-14)	57 (81.4)	53 (75.7)	29 (41.4)	29 (41.4)	50 (71.4)	18 (25.7)	15 (21.4)	18 (25.7)	13 (18.6)	40 (57.1)
Anorexia No. (%)	**Nausea or Vomiting No. (%)**	**Dysphagia or Aspiration No. (%)**	**Constipation No. (%)**	**Diarrhoea No. (%)**	**Any Abdominal Symptom No. (%)**	**Terminal Secretions* No. (%)**	**Pyrexia* No. (%)**	**Carer Stress No. (%)**	**Recurrent Infections No. (%)**	**Recurrent Admissions No. (%)**
54 (77.1)	15 (21.4)	18 (25.7)	23 (32.9)	12 (17.1)	56 (80.0)	34 (48.6)	45 (64.3)	12 (17.1)	38 (54.3)	60 (85.7)

*Symptom prevalence for terminal secretions and pyrexia were collected only at the terminal admission.

Disclosure: J. Cho, None; **D. Lo**, None; **A. Mak**, None; **J. Zhou**, None; **S. H. Tay**, None.

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Abstract Number: 933

Erosion Patterns in Seropositive and Seronegative Rheumatoid Arthritis: A Joint-By-Joint Approach

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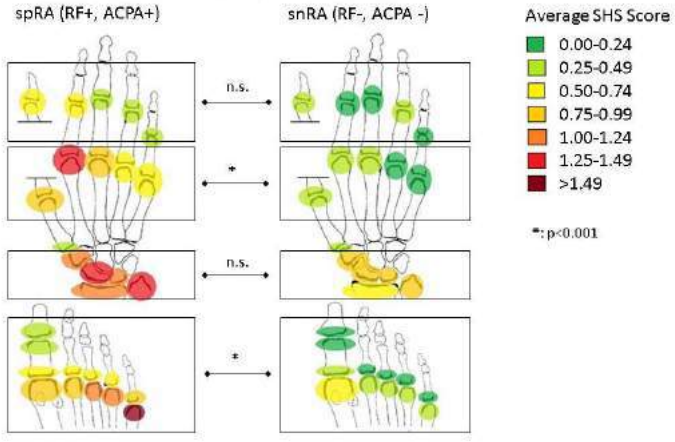
Background/Purpose: Rheumatoid arthritis (RA) can be differentiated according to rheumatoid factor (RF) and citrullinated peptide antibodies (ACPA). It is unclear whether seropositive RA (spRA) and seronegative RA (snRA) are different forms of the same disease or separate entities. Differing manifestation patterns between spRA and snRA on hand radiographs were first described by Burns/Calin in 1983[1]. To our knowledge, this observation has not been pursued further.

Methods: Hand and foot radiographs of 54 patients with RF negative, ACPA negative, erosive RA (snRA) were evaluated according to the Sharp-van-der-Heijde score (SHS) and compared with radiographs of 55 age-matched, RF-positive, ACPA-positive, erosive RA (spRA) patients. The average SHS for both cohorts was determined for the entire set of radiographs, for the carpal, MCP, PIP and foot compartments and for each single joint separately. We also evaluated the relative erosion score for each compartment (compartment SHS/total SHS). The results were transferred to a ‘heat map’ for visual representation. All data are given as mean± SD.

Results: Total SHS was significantly higher in spRA than in snRA (SHS 47.4± 53.5 vs. 20.6± 24.7, p=0.0012). The difference in SHS was significant in the MCP (8.5± 11.3 vs. 2.6± 4.7, p<0.001) and foot (20.9± 26.3 vs. 6.1± 14.8, p<0.001) but not in the PIP (4.9± 9.7 vs. 2.2± 5.4) or carpal (12.2± 14.4 vs. 8.8± 12.5, p=0.192) compartments (Fig.1). The greatest single-joint difference was found in MCP 2 (1.26± 1.60 vs. 0.27± 0.48) and proximal MTP 5 (2.11± 1.48 vs. 0.44± 0.89, p<0.0001 respectively). Significant differences in relative erosion score were found in the carpal (28± 23% vs. 42± 33%, p=0.017) and foot (44± 26% vs. 27± 34%, p=0.004) compartments.

Conclusion: Sharp-van-der-Heijde score (SHS) is higher in seropositive RA (spRA) than in seronegative RA (snRA). The difference in SHS is significant for the MCP and foot, but not for the carpal or PIP compartments. The single joint difference is greatest in MCP 2 and proximal MTP 5. Considering the relative erosion score (compartment SHS/total SHS), spRA shows a predilection for the foot and snRA for the carpal compartment. The different erosion patterns suggest that pathophysiological processes differ between the forms.

Fig. 1: Erosion distribution between different compartments (PIP, MCP, carpal and foot) for seropositive (spRA) and seronegative (snRA) Rheumatoid Arthritis



[1] Burns T, Calin A. The hand radiograph as a diagnostic discriminant between seropositive and seronegative 'rheumatoid arthritis': a controlled study. Annals of the Rheumatic Diseases, 1983, 42, 605-612

Disclosure: O. Gadeholt, None; **K. Hausotter**, None; **H. Eberle**, None; **H. P. Tony**, Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 5,Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 8; **M. Schmalzing**, None; **T. Klink**, None.

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Abstract Number: 934

Magnetic Resonance Imaging (MRI) Joint Space Narrowing Is an Independent Predictor of Radiographic and MRI Damage Progression in Patients with Early Rheumatoid Arthritis

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Background/Purpose: Magnetic Resonance Imaging (MRI) osteitis and synovitis have been identified as predictors of structural damage progression in rheumatoid arthritis (RA)[1,2], but the predictive value of MRI joint space narrowing (JSN, a measure of cartilage damage) and tenosynovitis needs further investigation. The purpose was to investigate the predictive value of baseline MRI inflammatory and damage parameters on 2 year MRI and X-ray damage progression in an early RA (eRA) cohort following a non biologic treat-to-target strategy.

Methods: In 129 eRA (<6months) patients from the double-blind randomized CIMESTRA trial (randomized to receive methotrexate, intraarticular betamethasone and cyclosporine (CYA)/placebo CYA) contrast-enhanced MRIs of the non-dominant wrist and X-rays of hands and feet were performed at baseline and after 2 years. MRIs were evaluated according to the RAMRIS scoring system for osteitis, synovitis, erosion, JSN, and for tenosynovitis according to Haavardsholm et al[3]. X-rays were evaluated according to the Sharp/van der Heijde method. MRIs and X-rays were read with known chronology by two experienced radiologists. Potential predictive baseline variables (MRI osteitis, synovitis, tenosynovitis, erosion, JSN, X-ray erosion and JSN, DAS28, gender, age, anti-CCP, smoking status) were tested in univariate linear regression analyses with 2-year change in MRI total damage score, Total Sharp Score (TSS), and MRI and X-ray JSN and erosion scores as dependent variables. Significant variables ($p<0.05$) were included in multiple regression analyses with backward selection.

Results: Independent predictors of structural damage progression are presented in table 1. If MRI JSN was not included in the model, MRI osteitis score was statistically significant independent predictor of X-ray progression (coefficient 0.32, p=0.001, vs. TSS progression).

Table 1

Final Models

	Dependent variables					
	MRI variables			X-ray variables		
	MRI erosion	MRI JSN	MRI total damage score	X-ray erosion	X-ray JSN	TSS
Explanatory variables	Coefficient(CI)	Coefficient(CI)	Coefficient(CI)	Coefficient(CI)	Coefficient(CI)	Coefficient(CI)
MRI synovitis	0.23 (0.06-0.31) p=0.006		0.18 (0.03-0.36) p=0.023			
MRI JSN	0.39 (0.27-0.68) p<0.001	0.66 (0.35-0.54) p<0.001	0.54 (0.66-1.17) p<0.001	0.41 (0.89-2.15) p<0.001	0.24 (0.12-0.83) p<0.001	0.39 (1.10-2.82) p<0.001

MRI total damage score: sum score of MRI erosion and JSN; CI: Confidence Interval

Conclusion: This trial is the first to report that MRI JSN independently predicts both X-ray and MRI damage progression in early RA. Further studies are needed to confirm early MRI-determined cartilage damage as predictor of progressive joint destruction in RA.
References: 1. Hetland et al, Ann Rheum Dis 2009;**68**(3) 2. Boyesen et al, Ann Rheum Dis 2011;**70**(3) 3 Haavardsholm et al, Ann Rheum Dis 2007;**66**(9)

Abstract Number: 935

Pretreatment Plasma IL-6 Levels Are Responsible for Bone Erosion Progression on Magnetic Resonance Imaging in Patients with Rheumatoid Arthritis

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SESSION INFORMATION

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Background/Purpose: Plasma cytokines include tumour necrosis factor (TNF)-ƒ¿, interleukin (IL)-1 and IL-6 play important roles in the pathogenesis of rheumatoid arthritis (RA) causing not only joint inflammation but also joint destruction. On the other hand, magnetic resonance imaging (MRI) can visualize fine distinction in the inflamed joint sensitively, and bone erosions on MRI are well relevant with prospective tangible erosions on X-ray. The aim of this study is to examine the relationship of pretreatment plasma inflammatory cytokines with MRI bone erosion progression in patients with RA patients.

Methods: We enrolled 89 newly diagnosed, untreated patients with RA. Contrast MRIs of the dominant hand and X-ray of hands and feet at baseline and 1 year later were performed. MR images were scored according to the latest OMERACT rheumatoid arthritis magnetic imaging score (RAMRIS) for synovitis, osteitis, bone erosions. Changes in MRI erosion scores (DRAMRIS erosion) from baseline to 1 year were calculated. X-ray were also assessed using the modified total Sharp score (mTSS). Plasma levels of ten cytokines were measured by electrochemiluminescence assay.

Results: The median age and symptom duration were 58 years and 3.2 months, respectively. The mean DAS28 decreased from 4.8 at baseline to 2.4 at 1 year. Progression in bone erosion were observed more frequently in MRI than in X-ray (54% in MRI vs 21% in X-ray, p = 0.005). Multiple linear regression model with baseline DAS28, seropositivity (positive for anti-CCP or RF), CRP and cytokines including IL-6, VEGF and IL-1ƒÀ as an independent variable revealed that baseline IL-6 levels and seropositivity were independent predictive factors for 1 year DRAMRIS erosion score. Receiver operating characteristic curve found the baseline IL-6 level of 7.6 pg/ml discriminated MRI erosion progression during 1 year with AUC of 0.82 with sensitivity of 69% and specificity of 95% (figure 1). We divided the patients into 4 groups (high, moderate-high, moderate-low and low) according to baseline IL-6 levels. The RAMRIS erosion progression was significantly dependent on baseline IL-6 concentration (p<0.001). While erosions in MRI significantly increased in high and moderate-high IL-6 groups (p < 0.05), mod-low and low IL-6 group showed slight improvement of MRI erosion at 1 year (figure 2)

Conclusion: In newly diagnosed, untreated RA patients, baseline plasma IL-6 levels predict 1-year MRI bone erosion progression in patients with RA. Figure 1

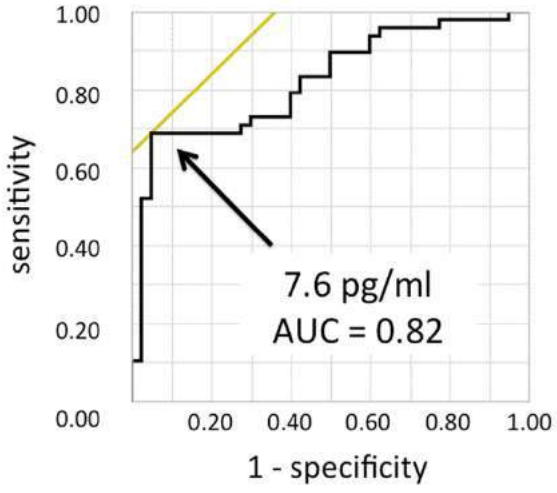
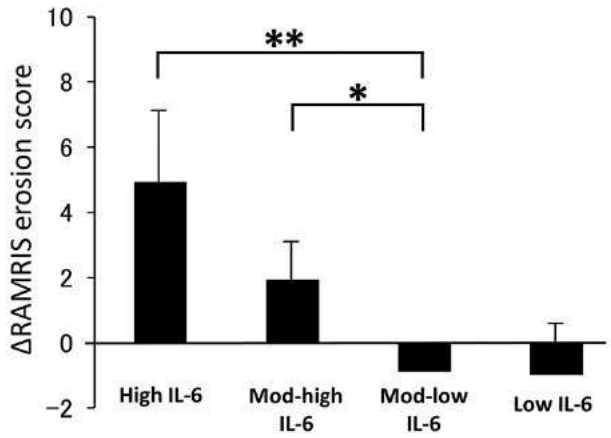


Figure 2



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Abstract Number: 936

Reliability and Responsiveness of an Omeract Tenosynovitis Magnetic Resonance Imaging Scoring System for the Rheumatoid Arthritis Wrist and Hand

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Background/Purpose: Tenosynovitis in the hand occurs frequently and early in rheumatoid arthritis (RA) and sensitive outcome measures are important to assess and monitor the inflammatory activity. Magnetic resonance imaging (MRI) can visualize tenosynovitis and a semiquantitative scoring system for tenosynovitis in the hand has previously been suggested[1]. In a multi-reader exercise, we aimed to assess the intra- and inter-reader agreement and responsiveness of a proposed OMERACT MRI tenosynovitis scoring system in the wrist and metacarpophalangeal (MCP) flexor tendons in the hands of RA patients.

Methods: Axial T1-weighted pre- and post-contrast fat-sat MRIs (0.8mm slice thickness) of the hand of 43 patients initiating rituximab therapy were obtained at baseline and after 3 (n=5), 6 (n=8), 9 (n=15) or 12 (n=15) months. The MRIs were read and scored twice on separate days with intermediate re-anonymization by 4 readers blinded to patient data but not to chronology. The tendons of 6 extensor and

3 flexor tendon compartments of the wrist and 4 flexor tendon compartments of the 2nd to 5th MCP joints were assessed. Tenosynovitis was defined as peritendinous effusion (PE) or post-contrast tenosynovial enhancement (PTE) on 3 consecutive slices. Pathologies were measured perpendicularly to the tendon at the thickest point of the effused or enhanced tenosynovium. Tenosynovitis was scored as follows: 0: no, 1: >0 but <1.5mm, 2: ≥1.5 but <3mm, 3: ≥3mm PE or PTE. Change in score over time was assessed using descriptive statistics and the Wilcoxon signed-rank test. Intra- and inter-reader agreement was calculated using intra-class correlation coefficients (ICC), percentage of exact and close agreement (PEA and PCA) and the smallest detectable change (SDC). Responsiveness to change was assessed using standardized response mean (SRM).

Results: The mean (SD) change in score between baseline and follow-up was -1.38 (2.84) for wrist, -0.94 (1.85) for MCP flexor tendons and -2.31 (4.63) for total score (all p<0.01). Intra- and inter-reader ICC for status scores were very good in all readers, except baseline scores in the MCP region in 1 reader. Intra-reader ICC for change scores were good to very good in all readers, and inter-reader ICC for status and change scores were very good in all readers. Intra-reader PEA for status and change scores was above 57% and PCA above 95% for all parameters. Inter-reader PEA was above 40% and PCA above 81% for all parameters. Intra-reader SDC was equal or below 3.0 and inter-reader SDC was below 2.0 in all readers. SRM was small to moderate (table 1).

Conclusion: The proposed OMERACT tenosynovitis scoring system showed high intra- and inter-reader agreement and small to moderate responsiveness for the wrist and MCP tendons and is a reliable tool for MRI-assessment of tenosynovitis in the RA hand. [1]Haavardsholm et al. Ann Rheum Dis 2007;66(9):1216-20

Table 1 Intra- and inter-reader agreement and responsiveness to change for the wrist, metacarpophalangeal (MCP) flexor tendons and total score

INTRA-READER		Wrist			MCP flexor tendons			Total score		
		Baseline	Follow-up	Change	Baseline	Follow-up	Change	Baseline	Follow-up	Change
Reader 1	SmICC	0.91	0.82	0.82	0.88	0.88	0.81	0.90	0.90	0.86
	PEA	82.5	79.0	79.3	75.4	76.5	75.0	80.3	78.8	78.0
	PCA	99.3	99.2	99.3	100	100	99.4	99.6	99.3	99.3
	SDC			1.8			1.1			2.1
	SRM			0.36			0.44			0.42
Reader 2	SmICC	0.93	0.84	0.88	0.88	0.91	0.83	0.94	0.92	0.93
	PEA	86.9	76.8	80.3	73.8	80.8	78.5	79.4	78.1	79.7
	PCA	97.7	97.8	97.3	97.7	96.4	97.7	97.7	96.6	97.4
	SDC			2.0			1.2			2.7
	SRM			0.48			0.42			0.48
Reader 3	SmICC	0.84	0.81	0.76	0.79	0.86	0.68	0.87	0.86	0.84
	PEA	61.7	63.2	65.1	62.2	67.4	57.6	64.9	68.5	62.8
	PCA	97.6	96.6	96.3	100	99.4	96.3	98.3	97.3	96.3
	SDC			2.9			1.8			3.0
	SRM			0.44			0.54			0.56
Reader 4	SmICC	0.94	0.91	0.64	0.92	0.92	0.87	0.95	0.94	0.80
	PEA	88.6	83.4	76.5	82.0	79.1	78.4	88.0	82.0	74.5
	PCA	98.5	98.2	98.5	100	100	98.3	98.9	99.1	97.0
	SDC			2.9			1.8			2.9
	SRM			0.52			0.47			0.58
INTER-READER	AvmICC	0.94	0.90	0.91	0.96	0.97	0.94	0.96	0.94	0.94
	PEA	42.5	48.1	59.0	41.6	48.7	42.4	42.6	48.6	47.8
	PCA	81.1	83.2	84.0	86.9	89.8	87.2	82.9	86.5	85.0
	SDC			1.7			0.8			1.8
	SRM			0.44			0.47			0.50

Single measure intra-class correlation coefficients (SmICC) and average measure intra-class correlation coefficients (AvmICC) were calculated for intra-reader and inter-reader agreement respectively. An ICC ≥0.50 was considered good and an ICC ≥0.80 was considered very good. Percentage of exact agreement (PEA) was defined as the percentage of tendons given the same score within and between the readers (expressed as the average percentage for wrist, MCP tendons and total scores). Percentage of close agreement (PCA) was defined as the percentage of tendons given scores that differed ≤1 within and between the readers (expressed as the average percentage for wrist, MCP tendons and total scores). Smallest detectable change (SDC) was calculated for change scores and expresses the minimal amount of change that can be deemed as true change and not measurement error. Standardized response mean (SRM) was calculated by dividing the mean change score with the standard deviation of the change score.

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Abstract Number: 937

Distal Interphalangeal Joint Erosions Assessed By HR-pQCT in Patients with Psoriatic Onycholysis

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Background/Purpose: A third of cases of skin psoriasis are complicated by potentially incapacitating psoriatic arthritis (PsA). Nail psoriasis, especially onycholysis, is present in more than 70% of PsA and the risk of developing PsA is significantly higher in patients with nail involvement (OR = 2.24; 95% CI [1.26-3.98]) (*Wilson FC. Arthritis Rheumatism 2009*). In this study, we wanted to test the hypothesis that onycholysis, in patients without PsA, may be a potential clinical marker of subclinical distal pathogenic enthesopathy and thus may present early bone microstructural alterations of the distal interphalangeal joint.

Methods: We compared bone microstructural damages (erosions, osteophytes) of the distal interphalangeal joint using High Resolution Peripheral Quantitative Computed Tomography imaging HR-pQCT (XtremCT Scanco, Switzerland®) in patients with psoriatic onycholysis without PsA (ONY) and in patients with cutaneous psoriasis only without PsA or nail psoriasis (PsO). We used, as reference for bone features, patients with peripheral psoriatic arthritis (PsA) and healthy gender/age-matched controls. Ultrasonography of the target distal interphalangeal joint was used to assess enthesopathy (finger extensor tendon thickness), synovitis, and nail apparatus (nail plate and matrix).

Results: Between 2013 and 2016, 80 patients were recruited in the four following groups (20 per group): controls, ONY, PsO and PsA. Mean±SD age of the participants was 45.7±4.3 years. Nail plate thickness, matrix and finger extensor tendon thickness were increased in ONY versus PsO patients. Erosions and synovitis were observed in respectively 8.3% and 4.1% of ONY patients but never in PsO patients. By HR-pQCT, ONY patients were associated with a mean number of 3.6±0.77 erosions of the distal interphalangeal joint versus only 0.21±0.1 in PsO patients (p=0.035). PsA patients presented several V-shaped, Omega-shaped, U-shaped erosions and osteophytes.

Conclusion: We describe for the first time the existence of bone erosions in interphalangeal distal joints of patients with psoriatic onycholysis. These findings support the pathogenic role of enthesopathy in joint involvement of PsA. These data underly the potential severity of onycholysis compared to isolated cutaneous psoriasis only. Onycholysis may be considered as a clinical marker for patients with psoriasis who have an increased risk of joint destruction.

Disclosure: A. P. VILLANI, None; **S. Boutroy**, None; **H. Marotte Sr.**, None; **L. Barets**, None; **M. C. Carlier**, None; **R. Chapurlat**, None; **D. Jullien**, None; **C. B. Confavreux**, None.

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Abstract Number: 938

Prevalence of Non-Radiographic Axial Spondyloarthritis in Psoriatic Arthritis – a Single Center Observational Study

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Background/Purpose: Sacroiliitis, as detected by plain radiographs of the sacroiliac joints (SIJ), has been reported in a third of the psoriatic arthritis (PsA) population. (1) Referred to as radiographic axial spondyloarthritis (r-axSpA), this finding represents a late axial disease. For detection of an *non –radiographic* (nr-axSpA) axial disease in the presence of normal pelvic XR (non-radiographic axSpA – nr-axSpA), MRI is commonly applied. Yet, there is limited data on the frequency of nr-axSpA in the PsA population. The purpose of our study was to establish the prevalence of nr-axSpA in a consecutively recruited observational cohort of PsA.

Methods: Adult PsA patients from the Tel Aviv Medical Center Rheumatology Clinic were consecutively recruited into the study. All patients underwent clinical evaluation, CRP and HLA-B27 tests, plain XR of the SIJs and MRI of the entire spine and SIJs. Spinal sagittal T1-W and STIR images of the spine and semi-coronal T1-W and T2-W with fat saturation of the SIJs were performed. Radiographs were independently read by two musculoskeletal radiologists (NY criteria)(2), and MRI examinations were interpreted by a third musculoskeletal radiologist using ASAS criteria and global (both structural and acute) SIJ scoring(3), all blinded to the clinical data. Data were analyzed by SPPS Version 20.0. Categorical descriptive data were presented as absolute values with percentages and continuous data as mean (standard deviation). Group comparisons of categorical data were performed by χ^2-tests and of continuous data by the Mann-Whitney U-test.

Results: Sixty-nine patients were recruited into the study. For 51 patients, all imaging set was available at the time of the interim analysis. Demographic and clinical data is presented in Table 1. All patients but two were HLA-B27 negative. Inter-reader agreement between the two XR readers was good (κ=0.73). Nr-axSpA was detected in 20% of the cohort, and r-axSpA was detected in 23%. 12% of patients demonstrated false positive sacroiliitis by XR not confirmed by MRI. MRI positive sacroiliitis (ASAS/Global) was detected in 29%/43%, respectively. Extensive psoriasis assessed by PASI was associated with global MRI sacroiliitis presence (*p 0.03*). Clinical indices of peripheral and spinal disease activity did not correlate with MRI sacroiliitis. There was no difference in the sacroiliitis prevalence among male and female sub-groups. Biologic naïve patients demonstrated similar rates of sacroiliitis as patients exposed to biologic therapies.

Conclusion: This is the first study to report the frequency of nr-axSpA (20%) in an observational PsA cohort. Our study also emphasizes the limitations of pelvic XR in diagnosing clinical sacroiliitis. **Table 1. Cohort demographics and clinical data.**

Age (mean, yr)	50±13
Gender M:F	37:32
BMI	27±5.6
Psoriasis duration (mean, yr) PsA duration (mean, yr)	21±14 10±9
PASI	2.9±7.6
ASDAS-CRP	2±1
Current DMARD therapy Past DMARD therapy	46% 59%
Current biologic therapy Past biologic therapy	44% 38%
Back pain (%) Back pain duration (mean, yr)	71% 6±8
Inflammatory back pain (%)	28%
BASDAI	3.7±2.4
BASMI	2.7±1.2
BASFI HAQ	3±2.3 0.7±0.6

References: 1.Gladman D. Axial disease in psoriatic arthritis. Curr Rheumatol Rep 2007. 9 (6):455 -60. 2. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum1984;27:361–8. 3. Song IH et al. Relationship between active inflammatory lesions in the spine and sacroiliac joints and new development of chronic lesions on whole-body MRI in early axial spondyloarthritis: results of the ESTHER trial at week 48. Ann Rheum Dis. 2011 Jul;70(7):1257-63

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Abstract Number: 939

Circulating IgG4 Antibody Secreting Cells Are Better Biomarker of Disease Activity Compared to Serum IgG4 Levels in Patients with IgG4-Related Disease

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Background/Purpose: IgG4-related disease (IgG4-RD) is a fibro-inflammatory condition with a consistent set of pathological features that affect multiple organ systems. Patients with IgG4-RD typically present with mass lesions in different organs. Clinical and radiologic findings usually resemble malignancy, infection, or other autoimmune diseases making the diagnosis challenging. Up to now, the best marker of the disease is elevated serum IgG4 concentrations; however, many different studies find that this analyte is not a reliable disease biomarker, measured by current immunoassays. We hypothesized that reliance on elevated serum IgG4 concentration fails to identify a significant fraction of patients, at least partly due to assay limitations. Here we describe the direct measurement of IgG4 production by circulating antibody secreting cells (ASCs) as a more reliable biomarker for diagnosis and disease activity monitoring in patients with IgG4-RD.

Methods: This study compared serum IgG4 levels measured by nephelometry assay with frequency of IgG4 ASC in blood measured with IgG4 ELISpot (Enzyme-linked immunospot) assay. We enrolled 30 IgG4-RD patients with various degrees of disease activity, 4 patients with diseases mimicking IgG4-RD, and 7 healthy controls. Using the IgG4-RD Responder Index (RI), where an RI $\geq$ 3 is regarded as active disease, we had 21 patients with active disease. We used multivariate analysis and Pearson correlation for statistical comparison.

Results: Serum IgG4 concentration was elevated in 10 IgG4-RD patients (33%) while increased IgG4/IgG percentages in ELISpots (>5% IgG4/IgG) occurred in 23 patients (76%). All IgG4-RD patients who had serum elevation showed IgG4/IgG >5 % in the ELISpot assay. Among patients who had normal serum IgG4 by nephelometry but elevated number of IgG4 on the ELISpot, 11 out of 13 had active IgG4-RD with IgG4-RD responder index score of $\geq$ 3. Of the patients with active IgG4-RD with RI $\geq$ 3, 16 of 21 (76%) had elevated IgG4/IgG ASC percentages > 5% compared with only 5 out of 21 (23%) with elevated serum IgG4 (r=0.23 P=0.18). Furthermore, among the control group, one subject had elevated serum IgG4 at 176 mg/dl (normal 0-89 mg/dl) but normal Elispot IgG4/IgG percentages 1.2 % (<5%) showing improved specificity.

Conclusion: Circulating IgG4/IgG ASC percentages > 5% is a more sensitive and reliable marker for disease activity in patients with IgG4-RD both for diagnosis and disease activity monitoring. This method overcomes spurious low serum IgG4 levels due to the prozone phenomenon, cell binding and other unknown phenomena. This preliminary study shows that IgG4 ASC ELISpots are sensitive markers for IgG4-RD.

Abstract Number: 940

A Trial of XmAb®5871, a Reversible Inhibitor of CD19+ Cells, in IgG4-Related Disease

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Background/Purpose: IgG4-related disease (IgG4-RD) is an immune-mediated condition responsible for fibro-inflammatory lesions that can lead to irreversible damage. No approved therapies for IgG4-RD exist. We report the use of a novel monoclonal antibody, XmAb5871, in IgG4-RD. XmAb5871 is a humanized anti-CD19 antibody with an Fc portion engineered for increased affinity (200- to 400-fold over native IgG) to FcgRIIb, the only Fc receptor on B cells. Co-ligation of CD19 and FcgRIIb leads to downregulation and inhibition of B lineage cells bearing these targets. Reversible inhibition of B cell function without B cell ablation is one potential advantage of this approach.

Methods: The trial is an open-label investigation of XmAb5871 in active IgG4-RD, defined as an IgG4-RD Responder Index of ≥3. XmAb5871 (5 mg/kg) is administered IV every 14 days for 12 doses. Positron emission tomography (PET) scans are performed at baseline and at three months. The primary outcome measure is the proportion of patients on day 169 with decrease in the IgG4-RD RI ≥2 compared to baseline. Glucocorticoids are permitted but not required at entry and must be discontinued by two months. Other immunosuppressive medications are not allowed. Mechanistic studies are performed at baseline and at selected intervals.

Results: The first patient was infused in March 2016. As of June 2016, 8 of the targeted 15 patients have been enrolled. The mean age among the 8 patients enrolled to date is 58 years (range: 47 to 77 years). Four patients are male, 4 female. All are Caucasian. Seven of the 8 patients had elevated serum IgG4 concentrations at screen, with a mean serum IgG4 of 526 mg/dL (range: 27 – 1877; normal < 86 mg/dL). The mean baseline IgG4-RD RI score was 12.4 (range: 3 – 22), with active inflammatory disease in at least one organ system (range: 1-8, mean 5). The organs most commonly affected were submandibular glands (7 patients), parotid glands (6), lymph nodes (6), lacrimal glands (5). Two patients had bile duct involvement and kidneys, lungs, pancreas were affected in 1 each. Six of the 8 patients are being treated with XmAb5871 alone. One patient was started on prednisone 40 mg/day concomitantly with enrollment because of serious IgG4-related kidney disease (tubulointerstitial nephritis; serum Cr 2.6 mg/dL). PET scans at baseline identified disease involvement of organs that had not been suspected by other diagnostic means in 5 of 8 patients. Six of 6 patients with major salivary or lacrimal gland enlargement on physical examination demonstrated improvement on follow-up, some as early as one week. One patient had been on glucocorticoid treatment for 2 years and was on prednisone 15 mg/day at baseline, but was able to discontinue prednisone by 2 months after baseline treatment. Three patients experienced minor, transient gastrointestinal side-effects during the 1st infusion. One patient had GI symptoms on the 5thinfusion. This patient also developed symptoms suggestive of serum sickness and has discontinued the study.

Conclusion: XmAb5871, which targets the B cell lineage through reversible co-ligation of CD19 and FcgRIIb, may be a promising treatment approach for IgG4-RD.

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An International, Multi-Specialty Validation Study of the IgG4-Related Disease Responder Index

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Background/Purpose: IgG4-related disease (IgG4-RD) is an immune-mediated condition responsible for fibro-inflammatory lesions that can affect nearly any organ and lead to irreversible damage. To evaluate the efficacy of treatments, a tool understood and adopted by many types of specialists that can assess disease activity accurately and reliably across various organs is necessary. The IgG4-RD Responder Index (RI) was developed for this purpose. We sought to validate the RI among an international, multi-specialty group of IgG4-RD experts.

Methods: The RI requires participants to assess disease activity in 25 domains (24 disease sites and 1 domain for constitutional symptoms). Completing the instrument takes approximately three minutes per patient visit. Scoring incorporates higher weights for "urgent" manifestations and those that worsened despite treatment. After completing a training exercise, 25 participants were asked to review 12 written cases describing patients with diverse manifestations of IgG4-RD. The vignettes were supplemented by photographs, radiology images, and pictures of pathology findings. For each case, participants calculated the RI as well as a physician global assessment (PGA) of disease activity on a 100mm scale. We then assessed: 1) consistency (the inter-observer reliability) of the RI and PGA using intra-class correlation coefficients (ICCs); 2) precision (the inter-observer variation) by applying the signed rank test to the differences between the coefficients of variation for the RI and PGA of each case; 3) construct validity by determining the correlation between the RI and the PGA using the Spearman's rank correlation coefficient; 4) and sensitivity to change (discriminant validity) using a paired T-test comparing RI scores before and after treatment in six consecutive real-life cases as well as by assessing the Spearman's rank correlation coefficient when comparing the change in RI and PGA before and after treatment.

Results: Twenty five participants completed the study, including 11 rheumatologists, 5 gastroenterologists, 4 immunologists, 2 pulmonologists, 2 nephrologists, and 1 internist. Experts from the Canada, China, Italy, France, Japan, South Korea, Turkey, the UK, and the US participated. Correlations (construct validity) between the RI and PGA were high ($r=0.9$, $P<0.0001$). The consistency (interobserver reliability) was higher for the RI ($r=0.88$) than the PGA ($r=0.83$) as assessed using ICCs. The precision (interobserver variation) of the RI and PGA was similar ($P=1$). The RI was sensitive to change (discriminant validity). Following treatment (median 46.5 days, IQR 38-54 days), there was a significant improvement in the RI ($P=0.007$) and a high correlation between the change in RI and PGA ($r=0.8$, $P=0.04$).

Conclusion: In this international, multi-specialty study, we found that the RI is a valid and reliable disease activity assessment tool for IgG4-RD. The performance of the RI was assessed in patients with diverse manifestations of IgG4-RD in both cross-sectional and longitudinal phases. The RI can be used to determine the response to treatment and will be an important tool for international studies investigating the effectiveness of IgG4-RD treatment.

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A Nationwide Experience with the Off Label Use of Interleukin 1 Targeting Treatment in Familial Mediterranean Fever Patients

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Background/Purpose: Familial Mediterranean fever (FMF) is the most common autoinflammatory disease and colchicine is the mainstay of treatment. Around 30-45% of FMF patients were reported to have attacks despite the colchicine treatment. Currently the data regarding the treatment of colchicine unresponsive or intolerant FMF patients is limited and the most promising alternatives seem to be anti-interleukin-1 (IL1) agents. Herein we report our experience in the off-label use of anti-IL1 agents in a large group of FMF patients.

Methods: This study was conducted by the means of Turkish Multi-centered Investigations Platform in Rheumatology (TULIP). Twenty-one centers from different geographical regions of Turkey were included in the study. Medical records of all FMF patients who used anti-IL1 treatment for at least 6 months were reviewed. Demographics, disease related clinical and laboratory data were collected by a web based structured questionnaire.

Results: In total 135 FMF patients (69 [51%] male, mean age 34.1 [range; 18-67] years) were included in the analysis. In our FMF patients the mean age at symptom onset was 12.3 (range; 1-45) and at diagnosis was 20.1 (3-60) years. 98 patients were carrying M694V mutation. The mean colchicine dose was 1.8 (1.0-4.0) mg/day and attack frequency was reported to be decreased from a mean of 26/years (3-96) to 13.9/years (0-96). 116 out of 135 patients were put on anakinra and 19 on canakinumab treatment due to colchicine resistance in 114 patients, amyloidosis in 15 and other reasons in 4 patients. During the median 14.5 (6-69) months of treatment period; yearly attack frequency was significantly reduced (P<0.001), and 74 (54%) patients reported no FMF attacks. Besides serum levels of C-reactive protein, erythrocyte sedimentation rate, and 24 hours urinary protein excretion were significantly reduced, as shown in table. Although serum creatinine levels were also improved with anti-IL1 treatment, it was not reached to statistical significance.

Conclusion: The results of this large study showed that anti-IL1 treatment is an effective alternative for not only controlling the attacks but also decreasing the proteinuria in quite challenging FMF patients.

	Before treatment	After treatment	*P*
Attacks/year, mean (range)	16.8 (0-96)	2.1 (0-24)	**<0.001**
CRP level (mg/L), mean (range)	34.5 (0.14-220)	6.6 (0-52)	**<0.001**
ESR (mm/h), mean (range)	45.2 (2-129)	15.6 (0-154)	**<0.001**
24 hour urinary protein (mg), mean (range)	2746.7 (20-19610)	1769.6 (0-18500)	**<0.001**
Serum creatinine (mg/dL), mean (range)	1.68 (0.3-10.2)	1.18 (0.4-7.7)	0.907

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Efficacy and Safety of IL-1 Inhibitors in Amyloidosis Associated with Familial Mediterranean Fever Who Underwent Kidney Transplantation

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Background/Purpose: Familial Mediterranean fever (FMF) is a hereditary autoinflammatory disease characterized by self-limiting febrile attacks associated with serosal or synovial inflammation as well as increased risk for AA-amyloidosis. There are limited data about kidney transplantation (KT) in FMF patients with amyloidosis regarding the post-transplant course of FMF and amyloidosis. This study aims to investigate the efficacy, safety and long term outcome of IL-1 receptor antagonist (IL-1RA, anakinra) treatment in FMF patients with amyloidosis who underwent KT. **Methods:** We screened our database for FMF patients diagnosed with amyloidosis between 1978-2016, and reviewed charts of those who underwent kidney transplantation (KT). Seventeen FMF patients with KT and receiving anakinra constituted the study group. All patients were also receiving colchicine treatment. All patients were on maintenance immunosuppressive therapy. Partial response was defined as ≥50% decrease in proteinuria whereas complete response was defined as <0.3 gr/d proteinuria.

Results: Demographic features of the patients are shown in Table. The percentage of irregular/inadequate colchicine use in patients who developed amyloidosis was 41%. Mean age of transplant recipients at the time of transplantation was 32±7 (22-51). The reasons to start anakinra treatment in the post-transplant FMF group included inadequate response to colchicine treatment (n=13), persistently elevated CRP (n=8), and persistence of proteinuria (n=3). Recurrence of renal amyloidosis in transplant kidney was noted in four patients. Mean GFR at the last follow-up was 62±30(15-142) mL/min. Attack frequency was significantly decreased in patients after anakinra treatment Table2. After initiation of anakinra treatment, CRP decreased to normal values in 50% of the patients, and partial and complete response were achieved in only two patients with proteinuria. The proteinuria levels remained stable in three patients under colchicine and anakinra treatment. Serious infection required hospitalization was observed in two patients (pneumonia and pyelonephritis) treated with anakinra on

top of other immunosuppressives, and the patient with pneumonia died due to septic shock. Severe neutropenia (<500/mm^3) developed in one patient after three years of anakinra therapy without serious complications. **Table-1.** Demographic and Clinical Parameters of FMF Patients Who Underwent KT.

Male/Female ratio (n)	12/5
Age (mean±SD, range)	39±10 (24-59)
Age of onset (mean±SD, range)	10±7 (2-26)
Age of diagnosis (mean±SD, range)	21±11 (8-48)
Family history of FMF, n (%)	10 (58%)
Family history of amyloidosis, n (%)	1 (6%)
Disease follow-up duration (mo)	32±50 (3-216)
Time to diagnosis (mo)	140±137 (6-504)
Arthritis at presentation n(%)	9 (53%)
MEFV mutation, n (%)	M694V, 11 (100%)
Duration of IL-1RA (mo)	21±16 (4-51)
High CRP rate during attack free periods n (%)	9 (53%)
Mean colchicine doses after KT (mg)	1.1±0.4 (0.5-2)

Abbreviations: FMF, Familial Mediterranean Fever; mo, months; CRP, C-reactive protein; KT, kidney transplantation **Table-2. Attack frequency under anakinra treatment**

Patients	Anakinra Duration (months)	Before anakinra attack frequency /month	After anakinra attack frequency / /month
1	3	1	0
2	3	2	0
3	4	0	0
4	4	0,5	0
5	4	0	0
6	7	1	0
7	11	0	0
8	14	1	0
9	15	1	0
10	24	1	0
11	27	0	0
12	31	3	1
13	36	2	0
14	36	1	0
15	37	0,7	0
16	48	1	0
17	51	1,3	0

Conclusion: Anakinra treatment seems to be effective and safe in refractory FMF patients with amyloidosis who underwent KT

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A New Syndrome in the Spectrum of Cryopyrin-Associated Periodic Syndromes (CAPS) Caused By the Novel R918Q NLRP3 Mutation

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Background/Purpose: Mutations in *NLRP3* cause 3 different dominantly inherited autoinflammatory syndromes: familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID). All three manifest urticarial rash and episodic or in some cases continuous elevation of acute phase reactants. Here we describe a novel *NLRP3* mutation that has been identified in two separate families and presents with a predominantly neurological phenotype.

Methods: Two families presented to the NIH Otolaryngology Clinic with a history of sensorineural hearing loss. Patients from both families underwent genetic testing, a thorough rheumatologic evaluation, measurements of acute phase inflammatory markers, and cytokine profiling. Patients underwent evaluation by neuro-otology, MRI of the inner ear with the fluid-attenuation inversion recovery (MRI-FLAIR) protocol, and audiograms. Neurology evaluation and lumbar puncture was performed on patients with neurological symptoms. Peripheral blood leukocytes from patients and matched healthy controls were studied for constitutive NLRP3 inflammasome activation.

Results: Dideoxy sequence analysis of *NLRP3* identified a heterozygous transition c.2753G>A in exon 7, predicted to result in the missense substitution p.Arg918Gln (also known as p.Arg920Gln) in the leucine rich repeat domain of the NLRP3 protein, that co-segregated with hearing loss in both families. Patients from both families had either mildly elevated or normal inflammatory markers in the peripheral blood. Affected members of the first family had no dermatologic or rheumatologic manifestations while those in the second family exhibited urticariform maculopapular rash, oral ulcers, and lymphadenopathy. MRI of the inner ear showed active and chronic inflammation in the labyrinth and cochlea of all patients, and audiograms from the second family had worsened in the last year. A member of the first family with progressive lower extremity weakness showed a strong predominance of innate immune activation, but no evidence of intrathecal activation of adaptive immunity in the cerebrospinal fluid. Patients from both families exhibited evidence of constitutive NLRP3 inflammasome activation. Based on these findings, the father and two older siblings from the second family were started on treatment with anakinra. Follow up audiograms three months after treatment was started showed improvement in all three patients. The most severely affected member of the first family was started on anakinra and within three weeks started to normalize her deep tendon reflexes.

Conclusion: The R918Q *NLRP3* mutation is associated with a distinct phenotype, relative to other patients with CAPS. Nevertheless, initial data suggest a favorable response to IL-1 inhibition.

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When and Where Musculoskeletal Ultrasound Might Replace Magnetic Resonance in the Assessment of Patients with Juvenile Idiopathic Arthritis?

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Background/Purpose: Magnetic resonance imaging (MRI) is the most attractive imaging modality for the investigation of patients with juvenile arthritis (JIA). Musculoskeletal ultrasound (MSUS) has intuitive advantages over MRI including noninvasiveness, low cost, ability to scan multiple joints at once, repeatability and high patient acceptability. The aim of the study was to compare these imaging modalities and to evaluate whether MSUS might replace MRI in the management of JIA in a daily setting.

Methods: All consecutive JIA patients who performed a joint MRI at the study unit over the last 2 years were included. The main clinical indications for MRI were: 1) to quantify disease activity, 2) to confirm disease remission, 3) to evaluate structural damage. The joint assessed by MRI was scanned on the same day with MSUS; the sonographer was blind to MRI's results. MR and MSUS pathological findings were assessed based on the OMERACT RAMRIS and MSUS definitions and scores. Concordance between MR and MSUS was tested using Cohen's kappa coefficient and Bland and Altman.

Results:

A total of 101 JIA patients (median age 13.5 years, median disease duration 7.2 years) were included. Overall, 33 patients were imaged in the ankle, 26 in the wrist, 20 in the hip, 10 in the temporomandibular joints (TMJs), 10 in the knee and 2 in the shoulder. Fifty patients had clinically active arthritis; both imaging modalities confirmed active disease in 36/50 (72%) patients; 14/50 (28%) patients had no signs of active disease on MSUS, but only 9 of them showed inactivity on MRI. Concordance between MRI and MSUS for evaluating disease activity was substantial (k=0.72) for the joint recesses and almost perfect (k=0.81) for the tendons. The mean differences (95 %-limits of agreement) between MRI and MSUS were 0.56 (-7.1 to 8.21) for the wrist and 4.8 (-5.85 to 15.38) for the ankle, resulting in an acceptable agreement of these imaging techniques in quantifying disease activity. The concordance was moderate (k=0.56) for the hip. In 51 patients, the imaged joint was clinically inactive. MRI and MSUS confirmed remission in 23/51 (45%) patients, whereas both imaging modalities revealed active disease in 16/51 (31%) patients. In the remaining 12 (24%) patients, persistent synovitis was detected only on MRI. Concordance between MRI and MSUS for evaluating remission was moderate (k=0.53). Major discrepancies between MRI and MSUS were found for the TMJ and hip joints. MRI and MSUS agreed on the presence of structural damage in 11 out of 13 patients (85%) for which MRI was requested for evaluating joint damage.

Conclusion: In patients with clinically active disease, MSUS performs as well as MR not only in detecting but also in quantifying disease activity, especially in the wrist. In patients in remission the concordance between MSUS and MR was acceptable, suggesting the use of MSUS as a first-line imaging modality. In patients with long disease duration and established structural damage MSUS is as sensitive as MR in detecting bone damage. References Colebatch-Bourn AN et al. EULAR-PReS points to consider for the use of imaging in the diagnosis and management of juvenile idiopathic arthritis in clinical practice. Ann Rheum Dis. 2015;74:1946-57.

Disclosure: S. Lanni, None; **F. Magnaguagno**, None; **E. Ricci**, None; **A. Pistorio**, None; **C. Bava**, None; **A. Martini**, None; **C. Malattia**, None.

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Abstract Number: 946

Comparative Effectiveness of Second-Line Treatment Strategies for Lyme Arthritis in Children

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Session Type: ACR Concurrent Abstract Session
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Background/Purpose: First-line treatment for Lyme arthritis is fairly standardized, but second-line strategies are more variable. We compared the effectiveness of oral antibiotics, intra-articular glucocorticoid injections (IAGC), and intravenous (IV) antibiotics in second-line regimens for pediatric Lyme arthritis.

Methods: We performed a retrospective cohort study of children age ≤18 seen in 3 pediatric rheumatology clinics for Western blot-confirmed Lyme arthritis. We limited the cohort to children who began second-line therapy ≤4 months after starting antibiotics, a timeline consistent with usual practice at these sites. Second-line strategies were: 1) a second course of oral antibiotics alone, 2) IAGC with or without oral antibiotics, or 3) a course of IV antibiotics. The primary outcome was development of antibiotic-refractory Lyme arthritis (ARLA), defined as persistent arthritis ≥2 months after completing ≥56 days of oral antibiotics or ≥14 days of IV antibiotics, per IDSA/Red Book guidelines. The secondary outcome was rate of clinical resolution of arthritis. We compared second-line treatment strategies using logistic regression for ARLA and Cox regression for rate of resolution, adjusted for confounders.

Results: There were 129 children with second-line treatment for Lyme arthritis, of whom 42 (33%) developed ARLA: 29/83 (35%) on oral antibiotics alone; 3/18 (17%) with IAGC ± oral antibiotics; and 10/28 (36%) after IV antibiotics. Children who received second-line IAGC or IV antibiotics were more likely female (Table 1). Children whose arthritis markedly worsened after antibiotic initiation were more likely to receive second-line IV antibiotics (P<0.01). After adjusting for sex and worsening arthritis, children who received IAGC ± oral antibiotics appeared to have a decreased risk of developing ARLA compared with children receiving second-line oral antibiotics alone, but this did not meet traditional levels of significance (aOR 0.4, 95% CI 0.1, 1.4, P = 0.14) (Table 2). Similarly, second-line IAGC was associated with non-significantly increased rates of resolution of arthritis (aHR 1.6, 95% CI 0.9, 2.9, P = 0.11). There was no significant difference in the risk of developing ARLA (P=0.55) or rate of resolution (P=0.46) between groups receiving second-line IV or oral antibiotics (Table 2). Results were similar after excluding children whose disease worsened after antibiotic initiation.

Conclusion: Use of second-line intra-articular glucocorticoid injection may hasten the resolution of Lyme arthritis and prevent chronic Lyme arthritis in children. Further study of this strategy in larger cohorts is warranted.

Table 1. Clinical and treatment characteristics of children who received second-line treatment for Lyme arthritis					
Characteristic	**(1) Oral antibiotics alone (N=83)**	**(2) IAGC ± oral antibiotics (N=18)**	**P-value (2) vs. (1)**	**(3) IV antibiotics (N=28)**	**P-value (3) vs. (1)**
Age in years, median (IQR)	12.1 (9.4, 14.5)	11.2 (8.3, 13.7)	0.38	12.2 (10.2, 14.2)	0.77
Male sex, N (%)	64 (77)	10 (56)	0.06	15 (54)	0.02
Duration of initial joint symptoms in days, median (IQR)	7 (4, 28)	3 (3, 21)	0.26	14 (7, 28)	0.36
More than 1 joint involved,[1] N (%)	12 (14)	3 (17)	0.81	5 (18)	0.67
Non-knee joint involved, N (%)	11 (13)	2 (11)	0.81	2 (7)	0.39
Marked clinical worsening ≤6 weeks after antibiotic initiation,[2] N (%)	10 (12)	0	0.12	10 (36)	<0.01
First antibiotic course ≥28 days in duration, N (%)	55 (66)	11 (61)	0.68	19 (68)	0.88
First antibiotic course dose correct per guidelines, N (%)	58 (70)	12 (67)	0.79	22 (79)	0.38
Second-line antibiotics, N (%)			<0.01		<0.01
Doxycycline	61 (73)	10 (56)		0	
Amoxicillin	17 (20)	3 (17)		0	
Cefuroxime	4 (5)	1 (6)		0	
Other oral antibiotic	1 (1)	0		0	
Ceftriaxone	0	0		28 (100)	
None	0	4 (22)		0	
IAGC, intra-articular glucocorticoid injection; IQR, interquartile range; IV, intravenous. [1] Two knees would count as two joints [2] New massive effusion, joint capsule rupture, or joint recruitment					

Table 2. Multivariable analysis comparing second-line regimens for pediatric Lyme arthritis				
	Risk of developing antibiotic-refractory Lyme arthritis		Rate of clinical resolution of arthritis[1]	
Treatment strategy	**aOR[2] (95% CI)**	**P-value**	**aHR[2] (95% CI)**	**P-value**
Oral antibiotics alone (reference)	1.0	-	1.0	-
IAGC ± oral antibiotics	0.4 (0.1, 1.4)	0.14	1.6 (0.9, 2.9)	0.11
IV antibiotics	0.7 (0.3, 2.0)	0.55	1.2 (0.7, 2.1)	0.46
aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; IAGC, intra-articular glucocorticoid injection; IV, intravenous. [1]Presence of mild, asymptomatic joint swelling was considered compatible with clinical resolution if there was no subsequent worsening or recurrence of symptomatic arthritis [2] Multivariable models also adjusted for male sex and marked worsening on antibiotics, defined as a new massive effusion, joint capsule rupture, or joint recruitment within 6 weeks of antibiotic initiation				

Disclosure: D. B. Horton, None; **A. J. Taxter**, None; **B. Groh**, None; **D. D. Sherry**, None; **C. D. Rosé**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparative-effectiveness-of-second-line-treatment-strategies-for-lyme-arthritis-in-children

Abstract Number: 947

A Multi-Center, Open-Label Study to Assess the Pharmacokinetics, Efficacy and Safety of Certolizumab Pegol in Children and Adolescents with Moderately to Severely Active Polyarticular-Course Juvenile Idiopathic Arthritis: Week 24 Results

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Background/Purpose: Juvenile idiopathic arthritis (JIA) often requires biologic medication to control polyarticular disease courses. This study assesses the pharmacokinetics (PK), efficacy and safety of certolizumab pegol (CZP)±MTX in children and adolescents with moderate to severe polyarticular-course JIA.

Methods: PASCAL (NCT01550003) is an ongoing, multi-center, open-label study for patients (pts) aged 2–<18 years (yrs), weight ≥10 kg, with signs and symptoms of JIA for ≥6 months and prior history of DMARD use. Pts were enrolled from 7 PRCSG-PRINTO countries in North/South America and Russia. Original CZP doses were weight-adjusted based on simulations from a population PK model (adult rheumatoid arthritis [RA] data): pts 10–<20kg received a loading dose (LD; Week [Wk] 0, 2, 4) of CZP 100 mg and maintenance dose (MD; Q2W) of CZP 50 mg; 20–<40 kg, LD CZP 200 mg and MD CZP 100 mg; ≥40 kg, LD CZP 400 mg and MD CZP 200 mg. Interim analyses revealed higher CZP plasma trough concentrations than the target range (C_{trough} geometric mean in adult RA pts: 15.7 µg/mL [95% CI: 14.0–17.7]). Thus, MD was reduced by 50% and additional pts were enrolled with 50% reduction in LD and MD. Non-responder imputation and last observation carried forward were used for binary and continuous efficacy endpoints, respectively.

Results: Of 163 pts: 78 enrolled on the Original Dose Regimen (ODR) with dose reduction as early as Wk 12; 85 pts enrolled on the Reduced Dose Regimen (RDR). Overall, 68.7% were female, median (min, max) age of 12.0 (3, 17) yrs, 2.0 (0.5, 14.7) yrs since diagnosis. At Wk 12, C_{trough} values were higher than target range for ODR pts but largely within range for RDR pts, with lower exposure in 10–<20 kg pts. 15.4% of ODR pts and 28.2% of RDR pts were anti-CZP antibody positive, with no apparent impact on efficacy or safety. At Wk 16, JIA ACR30 responses were achieved by 79.2% of ODR pts and 80.0% of RDR pts. JIA ACR 50/70/90 responses were similar across the two dosing regimens (Table A). Clinically inactive disease (CID) was seen in 2.6% of ODR pts and 9.4% of RDR pts. Improvements were also observed in JADAS-71 score for ODR and RDR pts. Efficacy improvements were maintained through Wk 24 (Table A). The incidence rate (IR) of AEs was similar for ODR and RDR pts, with no new safety signals (Table B). The most common class of AE was infection and infestation. There were 2 deaths among RDR pts (CZP 100 mg): 1 was a road traffic accident in a 16 yr old pt considered unrelated to CZP±MTX, the other occurred post Wk 24 in an 18 yr old Mexican pt and is described by the investigator as hepatic tuberculosis and septic shock, considered related to CZP±MTX treatment at the time of onset.

Conclusion: For JIA pts on RDR, distribution of CZP plasma concentrations fell largely within the range seen in adult RA pts. Clinically-relevant JIA improvement was observed across all weight groups by Wk 16 and maintained to Wk 24. The safety profile of CZP seemed in

Table A: Efficacy outcomes for PASCAL study patients at Week 16 and Week 24 (Full analysis set)

	Original Dose Regimen [a], N=78 [b]		Reduced Dose Regimen, N=85 [c]	
	Wk 16 (n=77)	Wk 24 (n=76)	Wk 16 (n=85)	Wk 24 (n=85)
JIA ACR30, % responders	79.2	72.4	80.0	81.2
JIA ACR50, % responders	68.8	65.8	75.3	80.0
JIA ACR70, % responders	46.8	52.6	61.2	63.5
JIA ACR90, % responders	20.8	28.9	28.2	40.0
CID, % responders	2.6	5.3	9.4	17.6
JADAS-71 change from baseline, median (min, max)	-19.9 (-59.7, 9.4)	-21.1 (-64.4, 5.7)	-14.2 (-65.0, 16.9)	-14.6 (-63.8, 16.6)

[a] Refers to Original Dose Regimen prior to dose reduction; [b] 66 and [c] 78 completed to Wk24. JIA ACR: American College of Rheumatology JIA improvement based on a 30%, 50%, 70%, 90% improvement from baseline in ≥3/6 core measures, with no more than 1 of the remaining worsened by >30%; CID: clinically inactive disease (based on the Wallace method); JADAS-71: juvenile arthritis disease activity score 71-joint.

Table B: Safety data for PASCAL study patients by dose regimen and weight group (Safety set)

	Weight group 10–<20 kg	Weight group 20–<40 kg	Weight group ≥40 kg	Total
Original Dose Regimen – Overall [a], n (%) [IR/100 PY (95% CI)] [b]				
	n=6	n=28	n=44	N=78
Total PY at risk	12.8	65.2	93.6	171.7
Any AEs	4 (66.7) [84.4 (23.0, 216.1)]	25 (89.3) [175.4 (113.5, 258.9)]	43 (97.7) [270.7 (195.9, 364.6)]	72 (92.3) [206.4 (161.5, 260.0)]
SAEs	0 (-) [n/a]	5 (17.9) [8.4 (2.7, 19.6)]	3 (6.8) [3.4 (0.7, 9.9)]	8 (10.3) [5.0 (2.1, 9.8)]
Reduced Dose Regimen, n (%) [IR/100 PY (95% CI)] [b]				
	n=10	n=29	n=46	N=85
Total PY at risk	6.7	29.2	47.5	83.4
Any AEs	7 (70.0) [168.0 (67.5, 346.1)]	21 (72.4) [151.2 (93.6, 231.2)]	38 (82.6) [266.8 (188.8, 366.2)]	66 (77.6) [204.4 (158.1, 260.0)]
SAEs	0 (-) [n/a]	2 (6.9) [6.9 (0.8, 25.0)]	3 (6.5) [6.4 (1.3, 18.6)]	5 (5.9) [6.1 (2.0, 14.1)]
SAEs of Interest (by SOC) for Any Dose Regimen, n (%) [IR/100 PY (95% CI)] [b]				
	n=16	n=57	n=90	N=163
Total PY at risk	19.5	94.4	141.2	255.1
Any SAEs	0 (-) [n/a]	7 (12.3) [7.9 (3.2, 16.3)]	6 (6.7) [4.4 (1.6, 9.6)]	13 (8.0) [5.3 (2.8, 9.1)]
Blood and lymphatic system disorders	0 (-) [n/a]	1 (1.8) [c] [1.1 (0.0, 5.9)]	0 (-) [n/a]	1 (0.6) [0.4 (0.0, 2.2)]
General disorders and administration site conditions	0 (-) [n/a]	2 (3.5) [2.2 (0.3, 7.9)]	0 (-) [n/a]	2 (1.2) [0.8 (0.1, 2.9)]
Immune system disorders	0 (-) [n/a]	1 (1.8) [1.1 (0.0, 5.9)]	0 (-) [n/a]	1 (0.6) [0.4 (0.0, 2.2)]
Infections and infestations	0 (-) [n/a]	1 (1.8) [1.1 (0.0, 5.9)]	3 (3.3) [d] [2.2 (0.4, 6.3)]	4 (2.5) [1.6 (0.4, 4.1)]
Psychiatric disorders	0 (-) [n/a]	0 (-) [n/a]	1 (1.1) [0.7 (0.0, 4.0)]	1 (0.6) [0.4 (0.0, 2.2)]
Renal and urinary disorders	0 (-) [n/a]	1 (1.8) [1.09 (0.0, 6.1)]	0 (-) [n/a]	1 (0.6) [0.40 (0.0, 2.2)]

[a] Longer duration of exposure of Original Dose Regimen compared to Reduced Dose Regimen; [b] IR of new cases per 100 PY, and associated 95% CI; [c] refers to a case of anemia; [d] including 1 case of opportunistic infection: hepatic tuberculosis. CI: confidence interval; IR: incidence rate; PY: patient-years; SAEs: serious adverse events; SOC: system order class.

line with that of other anti-TNFs approved for JIA.

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Abstract Number: 948

Subcutaneous Abatacept in Patients with Polyarticular-Course Juvenile Idiopathic

Arthritis and Inadequate Response to Biologic or Non-Biologic Disease-Modifying Antirheumatic Drugs: Pharmacokinetics, Efficacy and Safety

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Background/Purpose: IV abatacept (ABA) 10 mg/kg every 4 weeks was well tolerated and effective in reducing the signs and symptoms of polyarticular-course juvenile idiopathic arthritis (pJIA) in patients aged 6–17 years (yrs).[1] SC ABA 125 mg weekly has equivalent therapeutic efficacy and comparable safety to IV ABA in adult patients with RA. Here we assessed SC ABA treatment in patients with active pJIA aged 2–17 yrs.

Methods: Two age cohorts (2–5 and 6–17 yrs) of patients with pJIA with an inadequate response/intolerance to ≥1 DMARD were enrolled in this single-arm, open-label (OL), Phase III pharmacokinetic study (NCT01844518) and received OL SC ABA weekly for 4 months (M) based on body weight tier (10–<25 kg [50 mg ABA]; 25–50 kg [87.5 mg ABA]; >50 kg [125 mg ABA]). JIA-ACR criteria 30 (JIA-ACR30; ACR Pediatric 30) responders at 4M could receive ABA for another 20M. Primary endpoint was ABA steady-state blood trough concentration (C_{minss}) at 4M in the 6–17-yr cohort.

Results: Patients were aged 2–5 yrs (n=32; interim analysis) or 6–17 yrs (n=173; complete 4M/interim 20M analysis; Table 1). Mean (SD) drug exposure duration was 9.8 (4.12) and 11.7 (4.33) M in the 2–5- and 6–17-yr cohorts, respectively (latter comparable to IV ABA exposure)[1]. The target therapeutic C_{minss} of 10 µg/mL at 4M was achieved in the 2–5-yr cohort (mean [SD] C_{minss}: 50.1 [14.2] µg/mL) and the 6–17-yr cohort[2] (42.1 [14.7] µg/mL; Figure). Robust JIA-ACR30/70 and inactive disease (no active joints, physician's global assessment of disease activity <10 mm, CRP <0.6 mg/dL) responses, respectively, were seen at 4M in the 2–5-yr cohort: 86.7, 70.0 and 51.7%, and in the 6–17-yr cohort:[2] 80.9, 52.6 and 29.5%. Safety data are presented in Table 2; no laboratory abnormalities or unexpected safety concerns were reported. Immunogenic responses (anti-drug antibodies) were seen in 3/31 (0 persistent [≥2 consecutive visits]) and in 3/171 (2 [1.2%] persistent) patients in the 2–5- and 6–17-yr cohorts, respectively.

Conclusion: The target therapeutic exposure for SC abatacept of C_{minss} of 10 µg/mL was achieved, and exceeded, in patients with pJIA aged 2–17 yrs (observed>predicted values), with marked improvements in JIA-ACR responses and no new safety concerns compared with that observed in adults or with IV abatacept in pJIA. 1. Ruperto N, et al. *Lancet* 2008;**372**:383–91. 2. Ruperto N, et al. *Ann Rheum Dis* 2016;**75** (Suppl): 138.

Table 1. Baseline demographics and disease characteristics		
	Patients aged 2–5 years (n=32)	**Patients aged 6–17 years (n=173)**
Age, years	5.0 (2.0, 5.0)	13.0 (6.0, 17.0)
Female, n (%)	19 (59.4)	136 (78.6)
Weight, kg	18.6 (13.3, 25.4)	45.0 (16.0, 146.3)
Number of active joints	7.0 (2.0, 27.0)	10.0 (2.0, 42.0)
MTX use, n (%)	27 (84.4)	136 (78.6)
MTX dose, mg/m^2/week	13.3 (6.8, 17.7)	11.6 (1.6, 24.5)
MTX dose, mg/week	10.0 (5.0, 15.0)	15.0 (2.1, 30.0)
JIA disease onset, n (%)		
Polyarthritis RF–	22 (68.8)	94 (54.3)
Polyarthritis RF+	3 (9.4)	43 (24.9)
Extended oligoarthritis	4 (12.5)	18 (10.4)
Persistent oligoarthritis*	1 (3.1)	5 (2.9)
Systemic arthritis	0	5 (2.9)
Other†	1 (3.1)	4 (2.3)
Enthesitis-related arthritis	0	3 (1.7)
Undifferentiated arthritis	0	1 (0.6)
Psoriatic arthritis	1 (3.1)	0

Data represent median (min, max) unless otherwise specified *Protocol deviation †2–5 years: diagnosed with disease category 'Other' and presented with mild intensity for all six JIA core set components; 6–17 years: misclassified polyarticular, RF negative (n=3); diagnosis of sarcoid arthritis (n=1) JIA= juvenile idiopathic arthritis

Table 2. Summary of AEs during the combined initial 4-month and 20-month extension period (all treated patients)		
AEs, n (%)	**Patients aged 2–5 years (n=32)**	**Patients aged 6–17 years (n=173)**
Deaths	0	0
All AEs	26 (81.3)	127 (73.4)
Related AEs	11 (34.4)	45 (26.0)
AEs leading to discontinuation	0	4 (2.3)*
SAEs	0	8 (4.6)
Related SAEs	0	1 (0.6)
SAEs leading to discontinuation	0	2 (1.2)†
AEs of special interest		
Infections‡	22 (68.8)	90 (52.0)
Malignancies	0	1 (0.6)
Autoimmune disorders	0	3 (1.7) §
Systemic reactions related to study drug	0	2‖
Local injection-site reactions	0	10 (5.8)

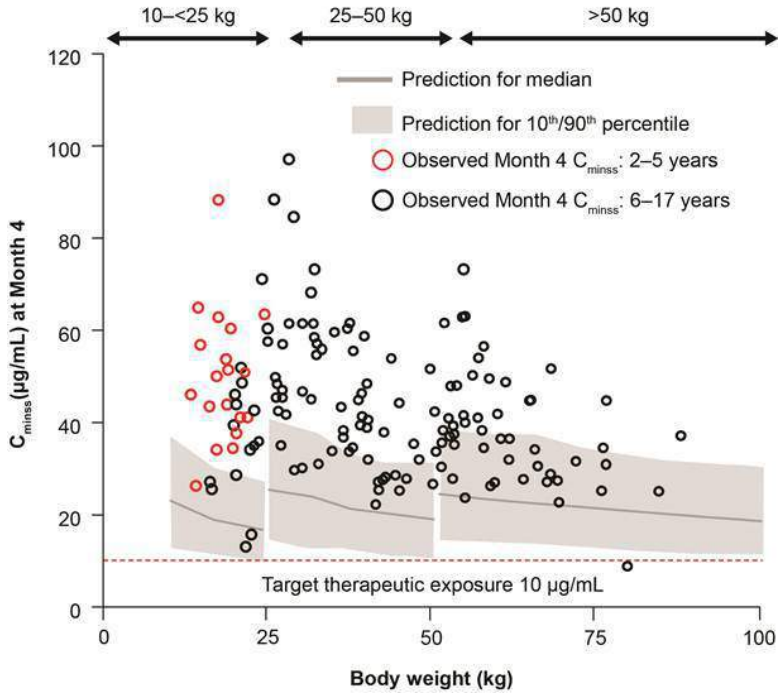
*Exanthema (n=1) and fatigue (n=1), both related to study drug (as well as the two SAEs leading to discontinuation)

†Sepsis (n=1), related to study drug; stage III ovarian germ cell teratoma (n=1), not related to study drug

‡The most common infections were nasopharyngitis and upper respiratory tract infections §Episcleritis (n=1), Raynaud's phenomenon (n=1) and psoriasis (n=1)

‖Nausea (n=1) and dizziness (n=1) SAE=serious adverse event

Figure. Predicted and observed steady-state blood trough concentration (C_{minss}) by body weight tier – evaluable pharmacokinetics population (n=131)



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Abstract Number: 949

Comparison of Treatment Response, Remission Rate and Drug Adherence in Polyarticular Juvenile Idiopathic Arthritis Patients Treated with Etanercept, Adalimumab or Tocilizumab

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
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Session Time: 2:30PM-4:00PM

Background/Purpose: Treatment response, remission rates and compliance in polyarticular JIA patients treated with adalimumab(ADA), etanercept(ETA), or tocilizumab(TCZ) were analyzed in clinical practice.

Methods: Data from the German BIKER registry were analyzed in all patients with polyarticular JIA who started treatment with ETA, ADA or TCZ from 2011-2015. Baseline patient characteristics, treatment response, safety and drug survival were compared.

Results: : In total 236 patients started ADA, 419 ETA and 74 TCZ, with several differences in baseline patient characteristics (table 1). The baseline JADAS10 scores (mean +/-SD) in the ADA/ETA/TCZ cohorts were 12.1+/-7.6, 13.8+/-7.1 and 15.1+/-7.4, respectively (ADA vs ETA $p<0.004$), and the CHAQ-disability index scores were 0.43 +/-0.58, 0.59 +/- 0.6 and 0.63+/-0.55 (ADA vs ETA $p<0.001$). Uveitis history was more frequent in the ADA cohort (OR 5.73; $p<0.0001$). PedACR30/50/70/90 criterion improvement after 3 months of treatment was achieved by 69%/60%/42%/24% in the ETA cohort, 68%/61%/44%/27% in the ADA cohort and 61%/51%/33%/ 25% in the TCZ cohort. At 12 months, JADAS minimal disease activity was achieved in 57.2%/68.6%/60.5% and JADAS remission in 30.3%/44.4%/21.1% patients in the ADA/ETA/TCZ cohorts, respectively. ETA was used as a first biologic for 374 patients, ADA for 122 patients and TCZ for 13 patients. There were no important differences in efficacy between first and second-line use of the biologics. A total of 60.4%/49.4%/31.1% patients discontinued ADA/ETA/TCZ, respectively (OR for ADA 1.73; $p= 0.006$; OR for TCZ 0.46; $p=0.004$). The drug survival rates did not differ significantly for patients on biologic monotherapy compared with combination therapy with methotrexate. Over 4 years of observation in the ETA/ADA/TCZ cohorts 996/386/103 adverse events, and 148/119/26 serious adverse events, were reported.

Conclusion: In clinical practice, ETA is most frequently used as first-line biologic. ADA/ETA/TCZ showed comparable efficacies toward polyarticular JIA. Remission was achieved more frequently with ETA and TOC than with ADA. Overall, tolerance was acceptable. Interestingly, compliance was highest with TCZ and lowest with ADA. Because the patient cohorts differed at baseline, these results are preliminary and demonstrate the need for well-controlled head-to-head studies for confirmation. **Table 1 Patient characteristics and response**

	Etanercept cohort N=419	Adalimumab cohort N=236	Statistical comparison#	Tocilizumab cohort N=74	Statistical comparison#
Female, n (%)	332 (79.2%)	192 (81.4%)	OR=1.1 (0.7-1.5); p=0.78	51 (68.8%)	OR=0.6 (0.4-0.9); p=0.027
Age at baseline, mean+/- SD	10.49+/-4.36	11.8 +/-4.0	p<0.0001	13.9+/-3.6	p<0.0001
JIA Category, n (%)					
RF+PA	37 (8.8%)	23 (9.7%)	n.s.	9 (12.2%)	n.s.
RF-PA	224 (53.5%)	128 (54.2%)	n.s.	47 (63.5%)	n.s.
ExOA	158 (37.7%)	85 (36.0%)	n.s.	18 (24.3%)	OR=0.58 (0.4-0.99); p=0.03
Uveitis before start of biologic, n (%)	23 (5.5%)	59 (25%)	OR=5.73 (3.4-6.0); p=0.0001	0	n.a.
Use as first biologic, n (%)	400 (95.5%)	122 (51.7%)	OR=0.08 (0.05-0.1); p<0.0001	15 (20.3%)	OR=0.02 (0.01-0.03); p<0.0001
Co-Med MTX, n (%)	309 (73.7)	127 (53.8)	OR=0.5 (0.4-0.7); p<0.0001	34 (45.9)	OR=0.4 (0.3-0.7); p=0.0004
JADAS10 [0-40], mean +/-SD	13.8+/-7.1	12.1+/-7.6	p= 0.004	15.1+/-7.4	n.s
Median (IQR)	13.6 (8.8-19.0)	11.7 (6.1-17.5)		14.8 (9.2-19.8)	
JADAS10 MDA at month 12 (ITT-population), n (%)	68.6%	57.2%	OR=0.61 (0.4-0.95); p=0.03	60.5%	n.s.
JADAS10 remission at month 12 (ITT-population), n (%)	44.4%	30.3%	OR=0.55 (0.35-0.85) p=0.007	21.1%	OR=0.33 (0.15-0.76) p=0.007

Compared with the ETA cohort, n.a. not applicable, n.s. not significant. **Table 2: Rates and reasons for discontinuation**

Reason for discontinuation	Etanercept N=419	Adalimumab N=236	Odds ratio # (95% CI); p	Tocilizumab N=74	Odds ratio # (95% CI); p
Discontinuations N (%)	207 (49.4)	142 (60.4)	1.55 (1.12-2.14); 0.008	23 (31.1)	0.46 (0.27-0.78); 0.004
Inefficacy N (%)	50 (11.9)	52 (22.0)	2.03 (1.32-3.11); <0.001	9 (12.2)	1.01 (0.47-2.15); n.s.
Remission N (%)	54 (12.9)	22 (9.3)	0.69 (0.41-1.17); n.s.	2 (2.7)	0.19 (0.05-0.79); 0.01
Intolerance N (%)	15 (3.6)	15 (6.4)	1.83 (0.88-3.81); n.s.	2 (2.7)	0.75 (0.17.3.34); n.s.
Others* N (%)	88 (16.0)	53 (22.4)	n.a.	10 (13.4)	n.a.

* Others included patient/parent decision, # Compared with the ETA cohort n.a. not applicable; n.s. not significant

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Kuemmerle-Deschner, None; **J. P. Haas**, None; **T. Hospach**, Pfizer, Abbvie, Roche, 9,Pfizer, Abbvie, Roche, 9.

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Abstract Number: 950

Flares after Withdrawal of Biotherapies in JIA: Clinical and Laboratory Correlates of Remission Duration

Gabriele Simonini[1], Erika Scoccimarro[1], Irene Pontikaki[2], Giovanna Ferrara[3], Teresa Giani[1], Andrea Taddio[3], Pier Luigi Meroni[4] and Rolando Cimaz[1], [1]Pediatric Rheumatology Unit, Anna Meyer Children's Hospital-University of Florence, Firenze, Italy, [2]Rheumatology Department, Gaetano Pini Institute, University of Milan, Milano, Italy, [3]Institute for Maternal and Child Health - IRCCS "Burlo Garofolo", University of Trieste, Trieste, Italy, [4]Rheumatology Department, University of Milan, Istituto Ortopedico Gaetano Pini, Milano, Italy
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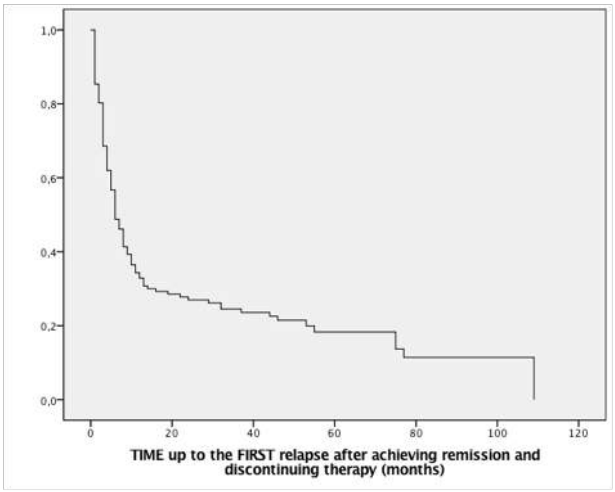
Background/Purpose: Information regarding the history of patients with JIA after systemic treatment withdrawal would be helpful in driving the choice of duration therapy. While some informations in this regard exist for second-line drugs (eg methotrexate), studies on biologics are lacking. Aim of our study was to assess the time on remission after discontinuing biologic therapy in a retrospective, comparative, multicenter, cohort study of patients with JIA,

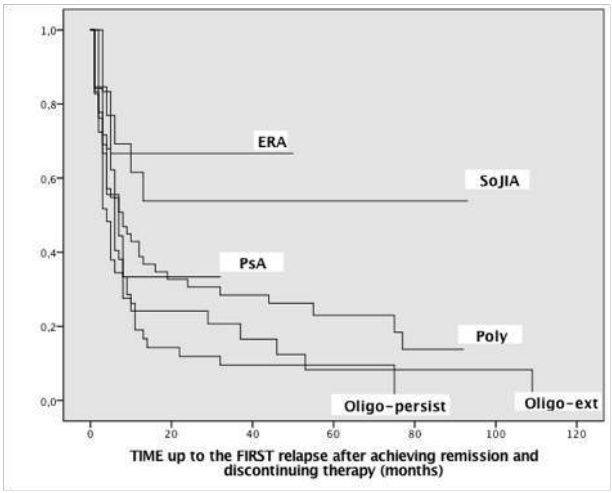
Methods: Among 349 JIA patients followed in three tertiary care centres and treated with biologics (started before age 18 y), 135 (103 F, 32 M; median age 15 years) achieved remission and could discontinue such treatment. Only first cycle of biologics was considered for this study: 87 received Etanercept, 27 Adalimumab, 12 Infliximab, 7 Anakinra, 1 Rituximab, and 1 Abatacept. Primary outcome was to assess, once remission was achieved, the time on remission up to the first flare after discontinuing treatment. Time to achieve remission once biologic drug was started, corticosteroid usage, and time on remission on therapy before discontinuing all treatments were also considered, along with demographic, clinical, and laboratory data. Mann–Whitney U-test, Wilcoxon signed-rank test for paired samples, chi-square, and FisherÕs exact test, when appropriate, were used to compare data. Pearson and Spearman correlation tests were used to determine correlation coefficients for different variables. In order to identify predictors of outcome Cox regression model and Kaplan–Meier curves were constructed, each one at mean of entered covariates.

Results: The vast majority of enrolled patients flared after stopping treatment with biologics (102/135, 75.6%) with a median follow-up time on remission of 6 months (range 1–109) [Figure1]. Considering the time point one year after treatment discontinuation 43/135 (31.9%) patients were still in remission. For this group, remission lasted for a median period of 53 months (range 12-109): 30/48 with polyarticular onset, 7/27 oligoarticular extended, 6/35 oligoarticular persistent, 2/6 enthesitis-related arthritis (ERA), 2/7 psoriatic arthritis, and 8/12 systemic onset JIA. A higher probability of maintaining remission after discontinuing treatment was present in systemic onset disease and in ERA compared to the rest of JIA patients (Mantel-Cox χ^2 14.58, $p<0.012$) [Figure 2]. ANA positivity was associated with a higher probability of flare (Mantel-Cox χ^2 4.17, $p<0.04$). Patients who received biologics > 2 years after achieving remission had a higher probability of maintaining such remission off therapy (median 21.74 ±3.4 months vs 13.4 ±2.3; Mantel-Cox χ^2 6.86, $p<0.009$). No other clinical variable, including total length of treatment and type of treatment, resulted significantly associated with a long-lasting remission.

Conclusion: Even if in a retrospective study, we showed that patients with ANA positivity and those who stop treatment before two years of remission have a higher chance of relapsing after biologic withdrawal, and that patients with systemic onset disease and ERA are less



likely to flare.



Disclosure: G. Simonini, None; **E. Scoccimarro**, None; **I. Pontikaki**, None; **G. Ferrara**, None; **T. Giani**, None; **A. Taddio**, None; **P. L. Meroni**, None; **R. Cimaz**, None.

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Abstract Number: 951

A Nationwide Non-Medical Switch from Originator to Biosimilar Infliximab in Patients with Inflammatory Arthritis. Eleven Months' Clinical Outcomes from the Danbio Registry

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First publication: September 28, 2016

SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: According to national guidelines issued in May 2015, a non-medical switch from originator infliximab (IFX) (Remicade) to biosimilar Remsima was conducted in all Danish patients with inflammatory rheumatic diseases treated in routine care. We aimed to investigate the clinical outcomes in Remicade-treated patients (pts) with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthrits (AxSpA) who were switched to Remsima and monitored prospectively in the Danish nationwide quality registry, DANBIO.

Methods: Patients who switched from Remicade to Remisma before Feb 1st 2016 and who had available data on treatment outcomes in DANBIO were included. In each patient, disease activity at 3 mths before switch (pre-switch) (defined as between minus 180 and minus 30 days before switch), at the time of switch (-30 days before to 6 days after), after 3 mths (70 to 120 days after switch) (post-switch) and changes over time (Dpre-switch and Dpost-switch) were calculated. Disease flare was defined as DDAS28≥0.6, DDAS28≥1.2 (in RA and PsA) or DASDAS≥1.3 (AxSpA). Reasons for withdrawal (adverse events (AE), lack of effect (LOE) or other) were registered. Multivariable Cox regression analyses stratified according to diagnosis (RA, PsA or AxSpA) were used to identify baseline characteristics (gender, age, use of methotrexate (yes-no), Remsima dosing interval, Remsima dose (mg/kg), patient's global score (Visual analogue scale from 0-100mm, VAS)) associated with Remsima treatment adherence. Numbers are medians (interquartile ranges) unless otherwise stated.

Results: 768 of 792 switching pts (97%) had available data regarding disease activity after switching. 52% were women, age (56 (46-66)yrs) (Table). Prior Remicade treatment duration was 6.6 (3.9-9.4) yrs, and in 75% of patients it was the first biological treatment. Median follow-up time after switching was 336 (297-357) days. Disease activity and disease flare rates remained largely unchanged 3 months prior to versus after the switch (Table 1). At the latest visit after switch, disease activity was for RA: DAS28 2.2 (1.7-3.0) and for axSpA: ASDAS 2.0 (1.2-2.9). Proportion of patients with disease flare pre-/post switch was 25%/21% (DDAS28≥0.6, RA+PsA)(p=0.4), 10%/10% (DDAS28≥1.2,RA+PsA) (p=0.8) and 2%/2% (AxSpA)(p=1.0) (related samples McNemar test). Overall, 117 patients (15%) stopped Remsima treatment between switch and end of follow-up (AE 34, LOE 51, remission 1, death 2, cancer 1, pregnancy 1, other 27). Prior Remicade treatment duration in those who withdrew was 6.0 (2.6-8.9) years and disease activity in those who stopped due to LOE was for RA: DAS28 4.3 (3.1-4.9) and for AxSpA: ASDAS 3 (2.6-3.8). Treatment adherences were similar in RA, PsA and AxSpA (Figure). In multivariable Cox regression analysis, lower baseline VAS patient's global and use of methotrexate was associated with better treatment adherence in RA (Table 2) whereas in AxSpA it was lower baseline VAS global and lower IFX doses (Table 2). No significant baseline predictors were found in PsA.

Conclusion: In 768 patients with inflammatory rheumatic diseases treated with Remicade for >4 years, disease activity was largely unaffected in the majority of patients after non-medical switch to biosimilar Remsima, and the fluctuations 3 months after the switch were comparable to the fluctuations observed in the 3 months prior to the switch. However, several patients (15%) stopped treatment. This warrants further investigation before such a non-medical switch can be recommended.

TABLE 1

BASELINE DEMOGRAPHICS AND OUTCOMES ACCORDING TO DIAGNOSIS

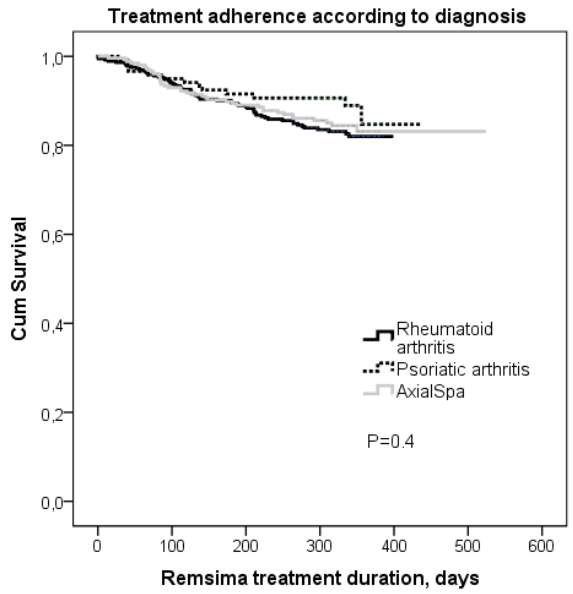
	RA	**PsA**	**AxSpA**	**Other**
Number of patients included, n	364	119	256	29
Baseline Remsima dose, mg/kg	3.8 (3.1-4.9)	4.9 (3.8-5.1)	4.9 (4.1-5.2)	4.8 (3.1-5-5)
Baseline dose interval, wks	8 (7-8)	7 (6-8)	8 (6-8)	8 (7-8)
Concomitant methotrexate, n (%)	307 (84%)	81 (68%)	80 (31%)	9 (31%)
Withdrawal of Remsima during follow-up N (%)	60 (16%)	13 (10%)	39 (15%)	5 (17%)
Prior Remicade treatment duration in withdrawers (years)	7.2 (4.1-9.8)	7.7 (2.6-10.2)	3.8 (1.6-6.1)	3.3 (0.5-4.6)

DISEASE ACTIVITY 3 months prior to vs. 3 months after the switch

	Disease activity			Delta-values		P*
	3 months pre-switch	Switch	3 months post-switch	Pre-switch	Post-switch	
RA and PSA						
DAS28	2.3 (1.7-3.0)	2.3 (1.8-3.1)	2.3 (1.8-3.2)	0.0 (-0.3-0.5)	0.0 (-0.3-0.3)	0.4
HAQ (0-3)	0.6 (0.1-1.1)	0.6 (0.1-1.1)	0.6 (0.1-1.1)	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.9
CRP, mg/l (<10mg/L)	4 (2-8)	4 (2-8)	5 (2-9)	0 (-1-2)	0 (-2-3)	0.09
VAS pt's global, mm	28 (10-53)	27 (12-57)	27 (11-56)	0 (-7-8)	0 (-7-9)	0.2
AxSpA						
BASDAI, mm	26 (11-46)	26 (11-46)	24 (10-47)	0 (-4-5)	0 (-3-6)	0.5
CRP, mg/l	4 (1-7)	4 (1-9)	4 (1-8)	0 (-1-1)	0 (-2-2)	0.4
Pt's global VAS, mm	27 (13-55)	33 (16-58)	24 (11-58)	1 (-6-9)	-1 (-8-4)	0.4
ASDAS	1.9 (1.3-2.7)	2.0 (1.4-2.7)	1.9 (1.3-2.7)	0 (-3-4)	0 (-4-2)	0.6

*delta values for disease activity pre-switch vs. post-switch, Wilcoxon matched-pair signed rank test. Numbers are medians (interquartile ranges) unless otherwise stated.

TABLE 2				
BASELINE FACTORS ASSOCIATED WITH TREATMENT ADHERENCE Multivariable Cox regression analyses stratified by diagnosis				
	Rheumatid arthritis		**AxSpA**	
	Hazard Ratio	p	Hazard Ratio	p
Gender, women vs. men	1.08 (0.51-2.17)	0.8	1.68 (0.65-4.37)	0.3
Methotrexate use, no vs. yes	2.47 (1.22-5.01)	0.01	2.87 (0.88-9.41)	0.08
Age, years	1.00 (0.97-1.02)	0.9	1.01 (0.97-1.05)	0.7
VAS patient's global, mm	1.02 (1.00-1.03)	0.03	1.02 (1.00-1.04)	0.04
Remisma interval, weeks	0.97 (0.76-1.23)	0.8	0.72 (0.50-1.03)	0.07
Remisma dose, mg/kg	1.06 (0.80-1.41)	0.7	1.76 (1.12-2.79)	0.02
Multivariable Cox regression analyses stratified by diagnosis. Numbers are Hazard ratios (95% confidence intervals). Age, VAS patient's global, Remsima interval and dose are continuous variables. PsA: no significant baseline predictors were found, data not shown				



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Abstract Number: 952

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study Evaluating Treatment Strategies (Continuation Versus Withdrawal) for Maintaining Low Disease Activity after 1 Year of Certolizumab Pegol in DMARD-Naive Patients with Early and Progressive, Active RA

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
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Session Time: 2:30PM-4:00PM

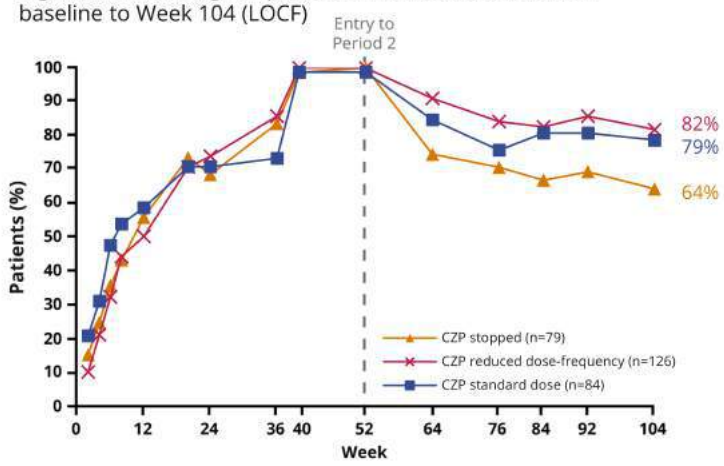
Background/Purpose: There is interest in tapering or stopping biologic DMARD therapy in RA patients (pts) who have achieved sustained disease control.[1] We report the results from C-EARLY Period 2 (P2), in which pts continuing on certolizumab pegol (CZP; standard and reduced dose-frequency) were compared with pts stopping CZP.

Methods: Pts from C-EARLY Period 1 (P1; NCT01519791)[2] treated with dose-optimized MTX and CZP (200 mg Q2W) or placebo (PBO) who achieved sustained low disease activity (sLDA; DAS28[ESR] ≤3.2 at both Weeks [wks] 40 and 52) entered P2 (NCT01521923),[1] a randomized, double-blind dose withdrawal study. CZP-treated pts were randomized 2:3:2 to CZP standard dose (200 mg Q2W+MTX), reduced dose-frequency (200mg Q4W+MTX) or CZP stopped (PBO+MTX). The primary endpoint was the percentage of pts in maintained (Wks 52–104 without flares) LDA. The hierarchical testing scheme compared CZP standard dose vs CZP stopped; if $p<0.05$ was achieved, then CZP reduced dose-frequency vs CZP stopped was compared. Data presented use imputation: NRI for primary endpoint; LOCF for continuous variables; linear extrapolation for mTSS.

Results: The study was powered assuming 455 CZP-treated pts would achieve sLDA in P1 and enter P2; however, only 293 pts (64%) were eligible and entered P2. 49% CZP standard and 53% reduced dose-frequency pts in sLDA were able to maintain LDA to Wk 104 vs 39% CZP stopped pts ($p=0.112$ and $p<0.05$, respectively; the study did not achieve its primary endpoint). 44% CZP standard and 43% reduced dose-frequency pts were able to maintain remission (DAS28[ESR] <2.6) to Wk 104 vs 33% CZP stopped pts. Overall, a higher proportion of CZP-treated pts (standard and reduced dose-frequency) achieved LDA at Wk 104 vs CZP stopped pts (Figure A). At Wk 104, more pts continuing CZP (standard and reduced dose-frequency) had radiographic non-progression (change from baseline mTSS ≤0.5) vs CZP stopped and MTX alone pts (Figure B). The safety profiles of all 4 groups were similar, with no new safety signals for pts continuing CZP treatment up to 2 years.

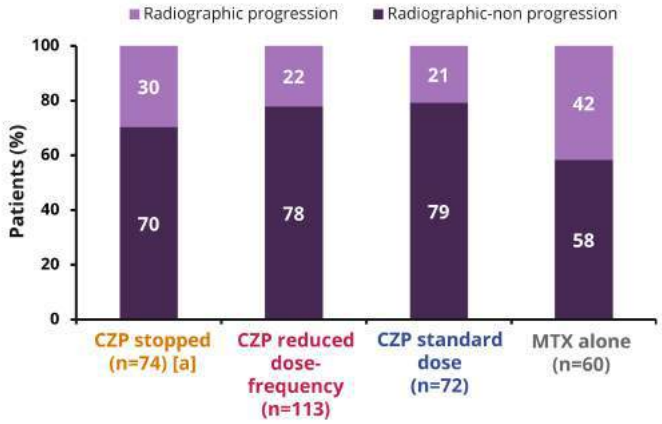
Conclusion: The study did not achieve its primary endpoint of maintained LDA at all visits in CZP-treated pts (standard and reduced dose-frequency) vs those who stopped CZP; however, there was a numerical difference between these groups. One possible reason may have been that 36% fewer pts were eligible for P2 than planned, based on the entry criteria. A higher proportion of CZP-treated pts (standard and reduced dose-frequency) achieved LDA and radiographic stabilization compared with those who stopped CZP. Additionally, despite clinical improvement, more pts treated with MTX alone experienced radiographic progression than pts treated with CZP over 2 years.
References: 1. Emery P. Ann Rheum Dis 2016;75(S2):143; 2. Emery P. Ann Rheum Dis 2016;doi:10.1136/annrheumdis-2015-209057

Figure A: Percentage of patients in DAS28(ESR) LDA from baseline to Week 104 (LOCF)



293 patients were randomized: 84, 127, and 82 patients to CZP standard, reduced dose-frequency, and CZP stopped; P2 full analysis set data shown (all patients with a valid post-Week 52 efficacy measurement within P2 for the primary efficacy assessment, DAS28[ESR]). LDA: DAS28(ESR) ≤3.2.

Figure B: Percentage of patients with radiographic non-progression at Week 104 (linear extrapolation)



Radiographic set (those patients with valid radiographs at baseline, Week 52, and Week 104/Withdrawal visit). Radiographic non-progression: change from baseline in mTSS ≤0.5 based on linearly extrapolated scores. [a] 1 outlier excluded from analysis in this group. MTX alone data from a post-hoc analysis.

Disclosure: M. Weinblatt, Amgen, Bristol-Myers Squibb, Crescendo Bioscience, UCB Pharma, 2,AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Crescendo Bioscience, Eli Lilly, MedImmune, Merck, Novartis, Pfizer, Roche, UCB Pharma, 5; **C. Bingham III**, UCB Pharma, 5; **G. R. Burmester**, AbbVie, MSD, Pfizer, Roche, and UCB Pharma, 5; **V. P. Bykerk**, AbbVie, Bristol-Myers Squibb, Pfizer, Roche/Genentech, Regeneron, and UCB Pharma, 5; **D. E. Furst**, Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 2,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, Janssen, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, UCB Pharma, 5,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, Janssen, Gilead, NIH, Roche/Genentech, UCB Pharma, 9; **X. Mariette**, Pfizer, GlaxoSmithKline, and Roche, 2,Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma and Sanofi-Aventis, 5; **D. van der Heijde**, AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, Vertex, 5,AbbVie, Amgen, AstraZeneca, Augurex, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Chugai, Covagen, Daiichi, Eli-Lilly, Galapagos, GlaxoSmithKline, Janssen, Merck, Novo-Nordisk, Otsuka, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, Vertex, 2,Director of Imaging at Rheumatology BV, 3; **R. van Vollenhoven**, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, and UCB Pharma, 2,AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli-Lilly, Merck, Pfizer, Roche, UCB Pharma, and Vertex, 5; **B. VanLunen**, UCB Pharma, 3; **C. Ecoffet**, UCB Pharma, 3; **C. Cioffi**, UCB Pharma, 3; **P. Emery**, Pfizer, MSD, AbbVie, UCB Pharma, Roche, Bristol-Myers Squibb, Schering-Plough, Novartis, and Samsung, 5.

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Abstract Number: 953

Comparison of 10-Years Disease Outcomes of Rheumatoid Arthritis Patients with Continued Low Disease Activity on Methotrexate with or without Initial Combination Therapy with Infliximab or Prednisone and Sulfasalazine

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Session Date: Sunday, November 13, 2016

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Session Time: 2:30PM-4:00PM

Background/Purpose: Low disease activity and remission in rheumatoid arthritis (RA) patients is achieved earlier and in higher frequency when the initial treatment includes a combination of methotrexate (MTX) with corticosteroids or a biologic disease modifying anti-rheumatic drug than MTX alone. However, it is unknown whether persistently good responders to MTX monotherapy have similarly good long-term outcomes than persistently good responders to initial combination therapy. The aim was to compare 10 years disease outcomes of RA patients with persistent low disease activity on MTX monotherapy with patients on initial combination therapy with infliximab or prednisone and sulfasalazine.

Methods: RA patients with 10 years follow-up from the BeSt study were analyzed. RA patients fulfilling the American College of Rheumatology 1987 criteria with <2 years symptom duration were 'treated to target' aiming at disease activity score (DAS) ≤2.4, assessed with 3-monthly intervals. Patients in arms 1 and 2 started MTX monotherapy, patients in arm 3 started MTX, sulfasalazine and prednisone and patients in arm 4 started MTX and infliximab. All had DAS ≤2.4 from t=6 months until t=10 years and therefore stayed on initial treatment, with patients in arms 3 and 4 tapering to monotherapy within 10 months. Patients in arms 1 and 2 were compared with patients in arms 3 and 4. Between-group differences over time were compared using (generalized) linear mixed model analyses, for the outcomes DAS, Health Assessment Questionnaire (HAQ), erythrocyte sedimentation rate (ESR), visual analogue scale (VAS) patient global health (range 0-100), % patients in remission and drug free remission and % patients with Sharp/van der Heijde score progression ≥1.

Results: At t=10 years 28/247 (11%) patients in arms 1 and 2 had continued DAS≤2.4 compared to 68/261 (26%) patients in arms 3 and 4. Patients in arms 1 and 2 were less often ACPA positive (46% versus 54%), had shorter symptom duration at baseline [median (range) 14 (1-191) versus 18(4-263) weeks] and less radiologic damage progression after 10 years [0 (0-16) versus 2.5 (0-26)] than patients in arms 3 and 4. No between-group differences were found over time. Significant group-time interactions were found for DAS, ESR, VAS patient's global health, percentage remission, but not HAQ and percentage drug free remission, with slightly worse results over time for arms 3 and 4 compared to arms 1 and 2 (table 1).

Conclusion: More patients achieved persistent low disease activity on initial combination therapy with prednisone or infliximab than on MTX monotherapy, but additional benefits of combination treatment strategies for patients who have continued DAS ≤2.4 could not be found. These results strongly suggest that rapid achievement of remission/LDA itself, rather than how you achieve it, is crucial for determining long-term outcome in RA.

Table 1: Linear mixed model and generalized linear mixed model analyses to assess differences over time between MTX monotherapy responders (n=28) and combination therapy responders (n=68).

Linear mixed models				
HAQ				
	β	**SE**	**P**	**95% CI**
Treatment group[a]	0.038	0.075	0.611	-0.11; 0.19
Time	-0.007	0.002	<0.001	-0.010; -0.003
Treatment group*Time	0.002	0.001	0.075	-0.00019; 0.004
Constant	0.344	0.133	0.010	0.083; 0.60
DAS				
	β	**SE**	**P**	**95% CI**
Treatment group[a]	-0.031	0.11	0.776	-0.24; 0.18
Time	-0.029	0.004	<0.001	-0.037; -0.021
Treatment group*Time	0.0056	0.0022	0.013	0.0012; 0.010
Constant	1.94	0.19	<0.001	1.56; 2.31
ESR				
	β	**SE**	**P**	**95% CI**
Treatment group[a]	-3.30	2.14	0.122	-7.50; 0.89
Time	-0.19	0.060	0.002	-0.31; -0.072
Treatment group*Time	0.11	0.034	0.002	0.041; 0.17
Constant	20.42	3.78	<0.001	13.00; 27.84
VAS patient global health				
	β	**SE**	**P**	**95% CI**
Treatment group[a]	-4.07	2.74	0.139	-9.45; 1.32
Time	-0.42	0.077	<0.001	-0.57; -0.27
Treatment group*Time	0.090	0.043	0.038	0.0048; 0.17
Constant	30.60	4.86	<0.001	21.07; 40.12
Generalized linear mixed models				
Sharp / van der Heijde score progression				
	OR	**SE**	**P**	**95% CI**
Treatment group[a]	0.78	0.43	0.654	0.26; 2.32
Time	0.71	0.11	0.017	0.54; 0.94
Group*Time	1.18	0.093	0.041	1.01; 1.37
Constant	0.40	0.40	0.354	0.057; 2.79
Remission				
	OR	**SE**	**P**	**95% CI**
Treatment group[a]	0.91	0.34	0.795	0.44; 1.87
Time	1.09	0.017	<0.001	1.05; 1.12
Treatment group*Time	0.98	0.0085	0.019	0.96; 1.00
Constant	0.81	0.53	0.747	0.22; 2.92
Drug free remission				
	OR	**SE**	**P**	**95% CI**
Treatment group[a]	0.28	0.26	0.171	0.047; 1.72
Time	1.11	0.044	0.011	1.02; 1.20
Treatment group*Time	0.98	0.023	0.367	0.94; 1.03
Constant	0.17	0.27	0.258	0.0080; 3.65

[a]Difference between treatment groups, MTX monotherapy responders as reference group , SE = standard error, 95% CI = 95% confidence interval

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Abstract Number: 954

Effectiveness of Different Dosages of Retreatment of Rituximab in Combination with Leflunomide: Results from a Multicenter Randomized Placebo Controlled Investigator Initiated Clinical Trial in Active Rheumatoid Arthritis (Amara-Study

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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Use of biologicals such as Rituximab (RTX) in Rheumatoid Arthritis (RA) is effective and often only licensed in combination with Methotrexate (MTX). In cases of contraindications to or intolerances of MTX, other cDMARDs are frequently used in routine care without data from RCTs. In addition, in daily practice different strategies for retreatment with RTX are used. The objective of this study was to demonstrate safety and efficacy of RTX in combination with Leflunomide (LEF) and compare effectiveness of therapy for different dosages of RTX as retreatment at week 24 in a multicenter randomized placebo (PLA) controlled clinical trial in Germany.

Methods: A total of 189 patients with active RA (DAS28 > 3.2 and at least 3 SJC and 3 TJC) despite stable LEF treatment were screened for a 52-weeks randomized double-blind placebo controlled multicenter clinical trial, separated into two parts: in part I, patients were randomized to receive either two times 1000mg RTX i.v. followed by two times 1000 (RTX-RTXhigh) or 500 mg (RTX-RTXlow) at week 24 or PLA, followed by a second course of RTX of either two times 1000 (PLA-RTXhigh) or 500 mg(PLA-RTXlow) at week 24 in part II. The primary endpoint of part II of the study for the retreatment was change in DAS28 at week 52. Adult patients who had inadequate response to more than one antiTNF or failed more than three cDMARDs were excluded. Disease activity as well as patient reported outcomes were measured at each visit until week 52. For safety evaluation, frequency and severity of adverse events were documented.

Results: Of 189 screened patients 148 were randomized. The mean age was 56 years; the mean body weight 76 kg and 74% were female. The disease activity (DAS28) at baseline was 5.57 for RTX and 5.54 in the PLA group. All baseline-characteristics were well balanced between the treatment groups. A superior response for ACR 20 and 50 of RTX vs PLA was seen at week 16 in Part I with 51.6% vs 23.4% ($p<0.05$) and 31.2% vs 14.9% ($p<0.05$). For retreatment in part II in patients treated with RTX (2x1000mg) (n=60) at baseline no differences were seen for both groups (RTX-RTXhigh and RTX-RTXlow) with a change in DAS 28 to week 52 of -2.46 and -2.42 respectively. In patients who initially responded to placebo and therefore entered Part II (n=24) a clear difference for two times 1000 mg (PLA-RTXhigh) vs two times 500 mg (PLA-RTX low) could be detected with changes in DAS28 to week 52 of -2.68 and -2.32 respectively. A total of 372 adverse events (AE) were observed during the one-year study period, only 14 were classified as severe (10 in RTX and 4 in PLA). 43 serious adverse events were reported, 28 of them in the RTX treatment group during the placebo controlled period.

Conclusion: Here we report for the first time data of a RCT of combination of RTX with LEF. The treatment with RTX in combination with LEF demonstrated significant efficacy compared to PLA in part I. Retreatment with two times 500mg RTX after standard first course of RTX (two times 1000mg) is comparable to two times 1000mg while clear differences were seen after PLA-treatment. This illustrates the importance of two times 1000mg as initial therapy while retreatment with the lower dose seems equally effective after regular induction therapy. The combination of RTX and LEF demonstrated a reasonable safety profile.

Disclosure: F. Behrens, AbbVie Deutschland, Roche, Janssen, 5,Chugai, 8; **T. Rossmanith**, Pfizer, Roche Janssen, 2; **M. Koehm**, Pfizer, Janssen, 2; **R. Alten**, Roche Pharmaceuticals, 5; **M. Aringer**, Roche, Chugai, 3,Roche, Chugai, 8; **G. Burmester**, UCB, 2,AbbVie, 5,BMS, 5,Hexal, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,MSD, 5,MadImmune, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,AbbVie, 8,BMS, 8,Hexal, 8,MSD, 8,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **E. Feist**, None; **K. Krüger**, AbbVie, BMS, Celgene,Janssen Biologics, Pfizer, Roche, Sanofi-Aventis, 5; **U. Müller-Ladner**, Boehringer Ingelheim, 9; **A. Rubbert-Roth**, Roche Pharmaceuticals, 5; **S. Wassenberg**, AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 5,AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 8; **H. P. Tony**, Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 5,Abbvie, BMS, Chugai, Janssen, Lilly, MSD, Novartis, Roche, Takeda, UCB, 8; **H. Kellner**, Roche Pharmaceuticals, 5; **M. Backhaus**, Roche Pharmaceuticals, 5; **H. Burkhardt**, AbbVie Deutschland, BMS, Chugai, Janssen, Pfizer, UCB, 5,Pfizer Inc, 2.

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Abstract Number: 955

Tocilizumab Infusion Intervals Can be Extended to 5 or 6 Weeks in RA Patients Who Sustained Low Disease Activity By 4 Weeks Interval of Tocilizumab Infusion

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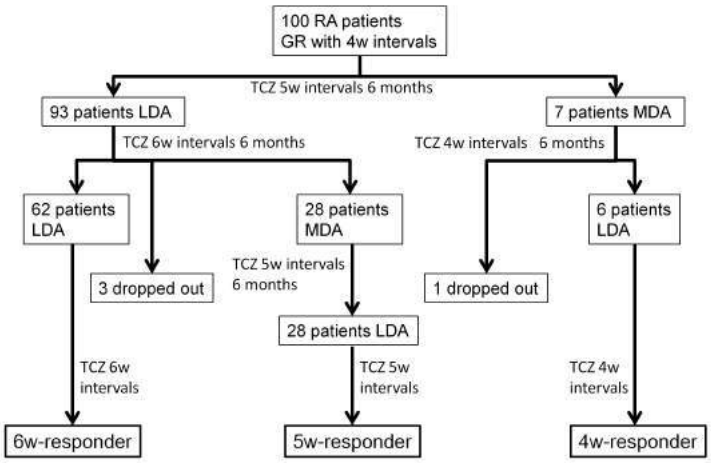
Background/Purpose: A period of 4 weeks (w) has been recommended as the interval between tocilizumab (TCZ) infusions. The cost of TCZ is very high, which makes it difficult for all patients to receive TCZ because of the associated expenses. Treating the patients with TCZ, we experienced that longer intervals than 4w were also effective. We examined whether the intervals between TCZ infusions could extend from 4w to 6w or 5w.

Methods: The RA patients who had shown good response and sustained low disease activity (LDA) with 8mg/kg of TCZ infusions at 4w intervals were enrolled in the study. To the eligible patients, the intervals between TCZ infusions were extended to 5w at the same TCZ dose (8mg/kg). For the patients who could maintain LDA for 6 months and more at 5w interval of TCZ infusion, the intervals between TCZ infusions were extended to 6w. We followed the patients up for 2 years and more. Good response and LDA was defined as DAS-28CRP EULAR criteria.

Results: One hundred patients were enrolled in the present study, and 96 patients completed the study. 93 patients maintained LDA with 8mg/kg of TCZ infusion every 5w for 6 months and more and the rest of 7 patients could not keep LDA and the intervals between TCZ infusions were shortened to 4w. The 93 patients who maintained LDA with 8mg/kg of TCZ infusion every 5w were received 8mg/kg of TCZ infusion every 6 weeks, and 62 patients maintained LDA with 6w-interval. After 2 years follow-up, 96 patients could maintain LDA and 4 patients were dropped from the study. Among 96 patients who could maintain LDA, the intervals between TCZ intervals were 6w in 62 patients, 5w in 28 patients, and 4w in 6 patients, indicating that 90% of patients who had shown good response and sustained LDA with 4w intervals could extend the intervals between TCZ infusions from 4w to 5w or 6w. The mean baseline DAS28-CRP score in patients who could maintain LDA with TCZ infusions at 6w intervals were 2.2 and was significantly lower than that at 4 weeks interval (2.6). The frequency of adverse events with TCZ infusions at 6 weeks intervals was lower than that at 4 weeks intervals.

Conclusion: The present study provides evidence that most of RA patients who showed good response to TCZ infusions at 4w and sustained LDA could extend the intervals to 6w or 5w. This finding should be of great interest for both financial and labor reasons.



Disclosure: H. Uda, None; **O. Saiki**, None.

Abstract Number: 956

The Effect of Treatment Adjustments Aimed at DAS Remission on Physical Functioning in Undifferentiated and Rheumatoid Arthritis Patients in Low Disease Activity

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Background/Purpose: Should we aim at remission if patients are in low disease activity (LDA)? We assessed if rheumatoid or undifferentiated arthritis (RA, UA) patients who achieved LDA benefit with better functional ability from treatment intensification aimed at DAS remission.

Methods: In the IMPROVED study 610 patients with early RA (ACR 2010) or UA were 'treated to target' aimed at DAS remission, assessed every 4 months. Initial treatment was methotrexate (MTX) + tapered high dose prednisone. Patients with DAS≤1.6 tapered treatment. Patients with DAS>1.6 were randomized to MTX + hydroxychloroquine + sulphasalazine + prednisone or to MTX + adalimumab. Over 5 years, patients with DAS>1.6 were required to increase, change or restart medication. HAQ was measured 4-monthly. A linear mixed model analysis with random intercept and independent covariance matrix was performed to test the relationship between changes in therapy and HAQ over time. Patients in LDA with DAS>1.6 with and without (i.e. protocol violation) treatment change were compared. ΔHAQ and ΔDAS at each visit compared to the previous visit were calculated. We tested the interaction effect between change in treatment and follow-up time adjusted for possible confounders.

Results: Over 5 years DAS and HAQ showed a statistically significant and clinically relevant decrease [Baseline HAQ mean (SD) 1.2 (0.7), ΔHAQ -0.59, 95% CI -0.61, -0.57; Baseline DAS mean (SD) 3.2 (1.7), ΔDAS -1.77, 95% CI -1.79; -1.75]. The number of patients in LDA per visit ranged from 88 to 146, of which 26% to 73% had no treatment change, with an increase in such protocol violations towards the end of study. We found a statistically significant but not clinically relevant effect of treatment change on ΔHAQ, corrected for baseline HAQ, age, gender and treatment arm (model 1, β -0.085, 95% CI -0.13, -0.044). When ΔDAS was added (model 2), treatment change was partly explained by ΔDAS and the effect of treatment change was no longer statistically significant (β -0.022, 95% CI -0.060; 0.015). When the interaction between treatment change and time in follow-up was added (model 3), a statistically significant interaction was found (β 0.0098, 95% CI 0.0010; 0.019), indicating a lower improvement in HAQ after treatment change if follow-up time increased (table 1).

Conclusion: During 5 years of DAS remission steered treatment in early RA or UA patients, treatment intensification or change for patients already in LDA resulted in a statistically significant but not clinically relevant improvement in HAQ, which was partly explained by ΔDAS. The effect decreased with increasing follow-up time. This supports the call for rapid treatment start to suppress disease activity in order to restore physical functioning. Remission may be the optimal goal, but when patients are in longer follow-up and HAQ is acceptably low, it might be sufficient to accept LDA rather than continue treatment changes aiming at remission.

Table 1. Linear Mixed Model analysis to assess the effect of treatment change on change in HAQ (n visits = 1532, n patients = 482)

	β	SE	P	95% CI
Model 1				
Medication change	-0.085	0.021	<0.001	-0.13; -0.044
Follow-up time[a]	0.0057	0.0024	0.019	0.00094; 0.010
Baseline HAQ	-0.028	0.015	0.059	-0.056; 0.0010
Gender	0.050	0.022	0.023	0.0070; 0.093
Age	0.0024	0.00079	0.003	0.00082; 0.0039
Treatment arm	0.028	0.0097	0.004	0.0086; 0.047
Constant	-0.29	0.067	<0.001	-0.42; -0.16
Model 2				
Medication change	-0.022	0.019	0.245	-0.060; 0.015
Follow-up time[a]	0.0022	0.0022	0.312	-0.0021; 0.0066
DAS change	0.23	0.013	<0.001	0.21; 0.26
Baseline HAQ	-0.036	0.013	0.006	-0.063; -0.010
Gender	0.031	0.020	0.123	-0.0084; 0.070
Age	0.0019	0.00072	0.009	0.00048; 0.0033
Treatment arm	-0.0013	0.0090	0.884	-0.019; 0.016
Constant	-0.090	0.062	0.149	-0.21; 0.032
Model 3				
Medication change	-0.10	0.041	0.013	-0.18; -0.021
Follow-up time[a]	-0.0034	0.0034	0.322	-0.010; 0.0033
Medication change * follow-up time	0.0098	0.0045	0.029	0.0010; 0.019
DAS change	0.23	0.013	<0.001	0.21; 0.26
Baseline HAQ	-0.038	0.013	0.005	-0.063; -0.011
Gender	0.029	0.020	0.144	-0.010; 0.068
Age	0.0019	0.00072	0.009	0.00048; 0.0033
Treatment arm	-0.0021	0.0090	0.814	-0.020; 0.016
Constant	-0.034	0.067	0.618	-0.17; 0.098

HAQ = health assessment questionnaire, SE = standard error, CI = confidence interval.
[a]Follow-up time is added to the model as visit number, with time between visits being 4 months.

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Abstract Number: 957

International Patient and Physician Consensus on Psoriatic Arthritis Outcomes for Clinical Trials

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Session Time: 2:30PM-4:00PM

Background/Purpose: A psoriatic arthritis (PsA) core domain set to be measured in randomized controlled trials (RCT) was developed by Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) and endorsed by Outcome Measures in Rheumatology (OMERACT) in 2006. Over the past 2 years, the GRAPPA-OMERACT PsA working group conducted research projects with the objective to update the PsA core domains set to reflect patients' and physicians' priorities and evolving PsA research.

Methods: We conducted: 1) a systematic literature review (SLR) of domains assessed in PsA RCTs and longitudinal observational studies (LOS); 2) international qualitative focus groups on five continents to identify domains important to patients with PsA; 3) international surveys with patients with PsA and physicians to prioritize domains; and 4) an international face-to-face consensus meeting among patient research partners (PRPs) and physicians using the nominal group technique (NGT) method to draft a PsA core domain set. Patient research partners (PRPs) were involved in each phase and one co-chaired the working group.

Results: Thirty-nine unique PsA domains were identified through the SLR (24 domains) and focus groups (34 domains). Patients (n=50) and physicians (n=75) completed electronic surveys rating the importance of the 39 domains for inclusion in the core set (Figure 1). At the consensus meeting, 12 patients and 12 physicians used these data to agree upon 10 domains for inclusion in PsA clinical trials, one strongly recommended to be measured at least once during the development of a new medication (middle circle) and four domains for the research agenda. These domains were rated in a second international survey with patients (n=49) and physicians (n=71) (Figure 1). The results were presented at the OMERACT conference in May 2016 and voted upon for endorsement. The updated PsA Core Domain set endorsed at OMERACT 2016 with 90% vote includes: musculoskeletal disease activity (peripheral arthritis, enthesitis, dactylitis, and spine symptoms), skin disease activity (skin and nail disease), pain, patient global, physical function, health-related quality of life, fatigue, and systemic inflammation (Figure 2).

Conclusion: The updated PsA Core Domain Set incorporates patients' and physicians' priorities and evolving PsA research. Next steps include identifying outcome measurement instruments that adequately assess these domains. **Figure 1: Survey results from patients and**

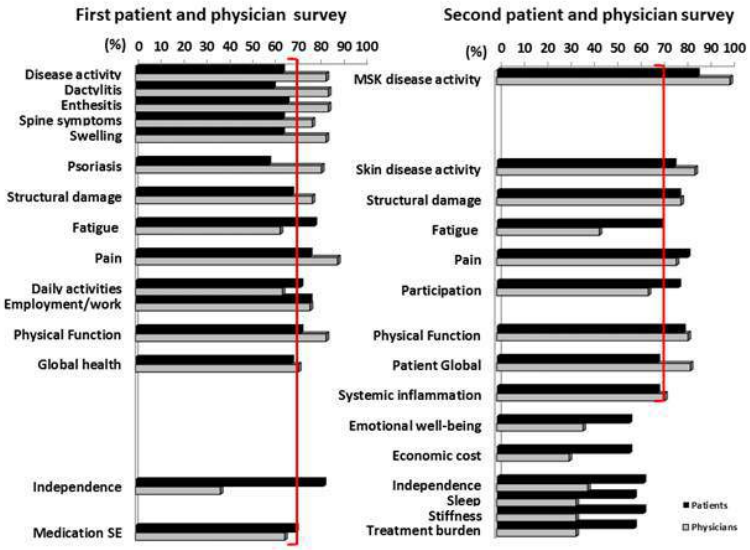
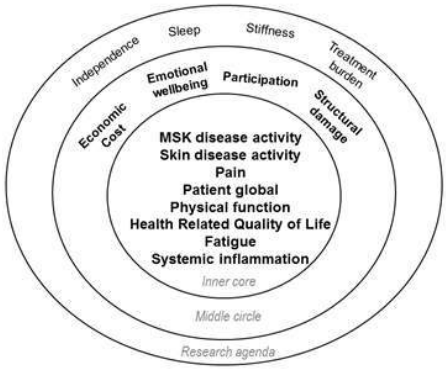


Figure 2: 2016 Psoriatic Arthritis Core Domain Set.



physicians.

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Abstract Number: 958

Safety and Efficacy of ABT-122, a TNF and IL-17–Targeted Dual Variable Domain (DVD)–Ig™, in Psoriatic Arthritis Patients with Inadequate Response to

Methotrexate: Results from a Phase 2 Trial

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Background/Purpose: Since inhibition of either Tumor Necrosis Factor (TNF) or interleukin 17 (IL-17) alone has demonstrated efficacy in psoriatic arthritis (PsA) on both joint and skin features, dual inhibition of TNF and IL-17 holds the promise for a superior therapeutic profile. ABT-122 is a dual variable domain immunoglobulin (DVD-Ig™) inhibitor of TNF and IL-17A that has shown an enabling safety profile from phase 1 studies. The purpose of this study was to investigate the safety and efficacy of ABT-122 in PsA patients (pts) with inadequate response to methotrexate (MTX).

Methods: Pts with active PsA (N=240) on background MTX were randomized in a 3:3:3:1 ratio to receive ABT-122 (120 mg every week [ew], or 240 mg ew), adalimumab (ADA) 40 mg every other week (eow), or matching placebo (PBO) subcutaneously in a 12-week (wk) double-blind, parallel group study. The primary efficacy endpoint was the ACR20 responses versus PBO at week (wk) 12. Additional efficacy endpoints included ACR50/70, low disease activity (LDA) and clinical remission (CR) based on DAS28 (hsCRP), and PASI 75/90 responses in pts who had psoriasis ≥3% body surface area at baseline.

Results: ACR20 responses for both ABT-122 dose groups were statistically superior to PBO and comparable to ADA (**Table 1**). ACR50 and ACR70 responses were superior to PBO for all active dose arms, with numerical superiority for ABT-122 240 mg dose versus ADA. LDA or CR rates based on DAS28 (hsCRP) were superior to PBO across all active dose arms, but did not differ between ABT-122 and ADA. All active dose arms showed higher PASI 75 and PASI 90 response rates than PBO. PASI 75 responses for both ABT-122 doses were numerically greater than ADA; but PASI 90 responses were similar. Treatment-emergent adverse events (TEAEs) were similar across active treatment groups (**Table 2**), with no differences in serious AEs (SAEs) or discontinuations; infection rates were higher in active treatment groups than PBO, however no serious infections were reported in any treatment group. There were no reports of drug-related SAEs, systemic hypersensitivity reactions, severe injection site reactions, or dose-limiting or clinically-concerning laboratory abnormalities in any dose arms.

Conclusion: Efficacy of ABT-122 over 12 wks was superior to PBO on all clinical outcomes. ACR20 and PASI 90 responses for both ABT-122 doses were similar to ADA, but ACR50/70 and PASI 75 responses for 240 mg ABT-122 were numerically superior versus ADA. ABT-122 had an acceptable safety profile in PsA pts on background MTX. Dual neutralization of TNF and IL-17 with a DVD-Ig offers similar infection rates to ADA, but does not have differentiated efficacy over 12 wks in PsA pts.

Table 1. Efficacy results (NRI) at week 12 from ABT-122 Phase 2 study (M14-197)‡

Efficacy Endpoint	n (%) Responders (NRI)‖			
		Adalimumab	ABT-122§	
	Placebo (N = 24)	40 mg eow (N = 72)	120 mg ew (N = 71)	240 mg ew (N = 73)
ACR 20	6 (25.0)	49 (68.1)	46 (64.8)***	55 (75.3)***
ACR 50	3 (12.5)	27 (37.5)	26 (36.6)*	39 (53.4)***,+
ACR 70	1 (4.2)	11 (15.3)	16 (22.5)*	23 (31.5)**,+
DAS28 (hsCRP) <3.2 (LDA or CR)	10 (41.7)	41 (56.9)	43 (60.6)	50 (68.5)*
DAS28 (hsCRP) <2.6 (CR)	4 (16.7)	29 (40.3)	32 (45.1)*	38 (52.1)**
PASI 75†	3 (27.3)	19 (57.6)	32 (74.4)**	38 (77.6)**,+
PASI 90†	2 (18.2)	15 (45.5)	21 (48.8)	23 (46.9)

P-values for comparison versus placebo: ***, P <0.001; **, P <0.01; *, P <0.05.

P-values for comparison versus adalimumab: +, P <0.05.

‡16 (6.7%) pts had prior exposure to TNF inhibitors.

‖4 pts withdrew from the study (1 ADA 40 mg eow, 2 ABT-122 120 mg ew, and 1 ABT-122 240 mg ew).

§Molar serum exposures for the ABT-122 120 mg ew and 240 mg ew doses were about 2- and 4-fold higher, respectively, compared with the exposure for ADA 40 mg eow.

†N = 11, 33, 43, and 49 for placebo, adalimumab, 120 mg ABT-122, and 240 mg ABT-122 patients, respectively, with psoriasis ≥3% body surface area at baseline.

Abbreviations: NRI = non-responder imputation; eow = every other week; ew = every week; ACR = American College of Rheumatology; DAS28 (hsCRP) = change from baseline in Disease Activity Score using high-sensitivity C-Reactive Protein; LDA = low disease activity; CR = clinical remission; PASI = Psoriasis Area and Severity Index, calculated in patients with psoriasis (body surface area ≥3%).

Table 2. Safety results (n [%] TEAEs) from ABT-122 Phase 2 study (M14-197)

Treatment-emergent adverse events TEAEs, n (%)	Placebo (N = 24)	Adalimumab 40 mg eow (N = 72)	ABT-122 120 mg ew (N = 71)	ABT-122 240 mg ew (N = 73)
Any AEs	11 (45.8)	38 (52.8)	33 (46.5)	31 (42.5)
Drug-related AEs[†]	0	13 (18.1)	15 (21.2)	14 (19.2)
Serious AEs	1 (4.2)	0	0	1 (1.4)[§]
Drug-related serious AEs[†]	0	0	0	0
Severe AEs	0	1 (1.4)	0	1 (1.4)[§]
AE leading to discontinuation	0	0	0	0
Infection	5 (10.8)	20 (27.8)	14 (19.7)	15 (20.5)
Serious infection	0	0	0	0

[†]Investigator assessed AE as possibly or probably related to study drug.
[§]Non-drug related decreased heart rate/syncope was reported in 1 pt.
Abbreviations: eow = every other week; ew = every week.

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Abstract Number: 959

Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis: 52 Week Results from a Phase 3 Study

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Background/Purpose: Ixekizumab (IXE) is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. In this phase 3 study (SPIRIT P1), IXE was superior to placebo (PBO) in achieving ACR20 response at Week 24 in biologic DMARD-naive (bDMARD-naive) patients with active PsA1.The objective of this analysis was to evaluate efficacy and safety of IXE over 52 weeks in patients with active PsA.

Methods: A total of 417 bDMARD-naive patients with active PsA were randomized 1:1:1:1 to IXE 80 mg once every 4 weeks (Q4W) or once every 2 weeks (Q2W) including a 160 mg starting dose, to 40 mg adalimumab (ADA), or to PBO (all subcutaneous dosing) during the Double-Blind Treatment Period (DBTP: Weeks 0 to 24). Of these, 381 patients completed the DBTP and entered the Extension Period (EP: Weeks 24 to 52) where they were assigned to 80 mg IXE Q4W or Q2W. Patients randomized to IXE at Week 0 continued the same dose regimen in the EP. Patients randomized to PBO or ADA at Week 0 were re-randomized (1:1) to 80 mg IXE Q4W or Q2W at Week 16 (inadequate responders) or 24. Those patients who initially received PBO started IXE at Week 16 or 24; patients who initially received ADA started IXE at Week 24 or 32 after an 8 week wash out period. Efficacy measures included ACR20/50/70 response, HAQ-Disability Index (HAQ-DI) Score, Disease Activity Score 28 diarthrodial joint count based on C-reactive protein (DAS 28-CRP), Psoriasis Area and Severity Index 75, 90, 100 (PASI 75/90/100), Leeds Enthesitis Index (LEI), and Leeds Dactylitis Index-Basic (LDI-B). Efficacy and safety were analyzed using the EP population defined as all patients who received at least 1 dose of study drug in the EP. Missing values were imputed by nonresponder imputation for categorical data and modified baseline observation carried forward for continuous data.

Results: A total of 304 patients completed the EP. Efficacy and safety results in the EP population are summarized in Table 1.

Improvements from baseline in ACR20/50/70, HAQ-DI, DAS 28-CRP, PASI 75/90/100, LEI and LDI-B were observed at Week 52. The frequency of treatment-emergent adverse events (AEs) in the EP was similar to that observed in the DBTP; the majority were mild or moderate in severity. Serious AEs occurred in 12 patients and no deaths occurred in the EP population.

Conclusion: IXE demonstrated clinically significant improvement in signs and symptoms of PsA including arthritis, dactylitis and enthesitis as well as skin manifestations across treatment groups in the EP. The safety profile of IXE observed in the EP was similar to that observed in the DBTP and other phase 3 studies of IXE in patients with plaque psoriasis (UNCOVER studies). 1Philip J. Mease et al. *2015 ACR/ARHP Annual Meeting*, 6-11 November, San Francisco, CA 2015; [abstract 977]

Table 1. Efficacy and Safety Outcome Measures at Week 52a (Extension Period Population)

	IXEQ4W/ IXEQ4W (N=97)	IXEQ2W/ IXEQ2W (N=96)	ADA/ IXEQ4W (N=49)	ADA/ IXEQ2W (N=48)	PBO/ IXEQ4W (N=45)	PBO/ IXEQ2W (N=46)	Total IXEQ4W (N=191)	Total IXEQ2W (N=190)
ACR20, n (%)	67 (69.1)	66 (68.8)	34 (69.4)	28 (58.3)	26 (57.8)	33 (71.7)	127 (66.5)	127 (66.8)
ACR50, n (%)	53 (54.6)	51 (53.1)	29 (59.2)	21 (43.8)	19 (42.2)	21 (45.7)	101 (52.9)	93 (48.9)
ACR70, n (%)	38 (39.2)	38 (39.6)	17 (34.7)	14 (29.2)	9 (20.0)	14 (30.4)	64 (33.5)	66 (34.7)
HAQ-DI, Mean (SD) CFB	-0.53 (0.56)	-0.55 (0.52)	-0.47 (0.48)	-0.42 (0.47)	-0.38 (0.53)	-0.42 (0.60)	-0.48 (0.53)	-0.48 (0.53)
DAS 28-CRP, Mean (SD) CFB	-2.29 (1.28)	-2.36 (1.28)	-2.16 (1.26)	-2.13 (0.93)	-1.92 (1.21)	-2.11 (1.09)	-2.17 (1.26)	-2.24 (1.15)
PASI 75, Nb,	66	55	34	33	31	29	131	117
n (%)	52 (78.8)	45 (81.8)	22 (64.7)	22 (66.7)	19 (61.3)	19 (65.5)	93 (71.0)	86 (73.5)
PASI 90, Nb,	66	55	34	33	31	29	131	117
n (%)	44 (66.7)	43 (78.2)	17 (50.0)	17 (51.5)	16 (51.6)	18 (62.1)	77 (58.8)	78 (66.7)
PASI 100, Nb,	66	55	34	33	31	29	131	117
n (%)	37 (56.1)	37 (67.3)	12 (35.3)	15 (45.5)	15 (48.4)	13 (44.8)	64 (48.9)	65 (55.6)
LEI, Nc,	67	54	28	25	22	26	117	105
Mean (SD) CFB	-1.9 (1.65)	-1.8 (1.56)	-2.0 (1.91)	-1.1 (2.29)	-1.1 (2.18)	-1.7 (2.00)	-1.8 (1.84)	-1.6 (1.87)
LEI (0), Nd,	65	52	28	23	22	26	115	101
n (%)	36 (55.4)	26 (50.0)	14 (50.0)	6 (26.1)	9 (40.9)	11 (42.3)	59 (51.3)	43 (42.6)
LDI-B, Ne,	48	35	11	11	16	19	75	65
Mean (SD) CFB	-57.9 (103.9)	-43.4 (55.5)	-96.5 (125.5)	-93.1 (102.5)	-47.7 (62.6)	-21.3 (21.7)	-61.9 (100.2)	-45.3 (63.0)
LDI-B (0), Nf,	35	24	8	10	10	14	53	48
n (%)	30 (85.7)	21 (87.5)	6 (75.0)	7 (70.0)	7 (70.0)	8 (57.1)	43 (81.1)	36 (75.0)
TEAE, n (%)	54 (55.7)	54 (56.3)	20 (40.8)	21 (43.8)	28 (62.2)	27 (58.7)	102 (53.4)	102 (53.7)
SAE, n (%)	4 (4.1)	0	5 (10.2)	1 (2.1)	1 (2.2)	1 (2.2)	10 (5.2)	2 (1.1)
Discontinued due to AE, n (%)	1 (1.0)	0	0	0	1 (2.2)	1 (2.2)	2 (1.0)	1 (0.5)

Abbreviations: ACR20/50/70=American College of Rheumatology 20/50/70 index; ADA=adalimumab 40 mg; AE=adverse event; CFB=change from baseline; DAS 28-CRP=Disease Activity Score 28 diarthrodial joint count based on C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; IXE=ixekizumab; IXEQ2W=ixekizumab 80 mg once every 2 weeks; IXEQ4W=ixekizumab 80 mg once every 4 weeks; LDI-B=Leeds Dactylitis Index-Basic; LEI=Leeds Enthesitis Index; N=number of patients in the analysis population; n=number of responders; PASI 75/90/100= Psoriasis Area and Severity Index 75/90/100; PBO=placebo; SAE=serious adverse event; SD=standard deviation; TEAE=treatment-emergent adverse event.

[a]For efficacy analyses, baseline was defined as the last non-missing assessment recorded on or prior to the date of first injection of study treatment at Week 0. For analyses of TEAEs, baseline was defined as AEs which started prior to the study drug injection at Week 24 with an exception of patients who were randomized to ADA during the entire Double-Blind Treatment Period and started IXE at Week 32 where baseline was defined as AEs which started prior to the study drug injection at Week 32.

[b]Only patients with psoriatic lesions ≥3% of BSA at baseline were included in the analysis.

[c]Only patients with enthesitis at baseline were included in the analysis.

[d]Only patients with enthesitis and LEI ≥0 at baseline were included in the analysis.

[e]Only patients with dactylitis at baseline were included in the analysis.

[f]Only patients with dactylitis and LDI-B ≥0 at baseline were included in the analysis.

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Abstract Number: 960

Ultrasonographic Improvement of Peripheral Subclinical Enthesopathy in Therapy-Naive Patients Treated with Ustekinumab for Chronic Plaque Psoriasis: A 52-Week, Prospective, Open Label, Controlled Cohort Study

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Background/Purpose: Subclinical enthesopathy is recognised in up to 50% of psoriasis patients and is thought to precede inflammatory

PsA. It is not known if effective treatment in the asymptomatic phase can reduce inflammation and damage. Studies have assessed enthesitis only as a secondary endpoint in established PsA. This study used ultrasound to investigate the effect of ustekinumab on subclinical enthesopathy in asymptomatic treatment-naive patients with psoriasis.

Methods: 73 new patients with severe psoriasis (PASI>10) and no PsA (absence of inflammatory arthritis to satisfy the CASPAR criteria) were screened using ultrasound. Exclusion criteria included rheumatological disease, RF or ACPA positivity and prior treatment with DMARDs. Patients were eligible if they exhibited inflammatory sonographic changes that fulfilled the OMERACT definition of enthesopathy in at least one peripheral enthesis and met the screening requirements for biologic therapy. 23 psoriasis patients received ustekinumab at week 0, 4, 16, 28 and 40 and underwent further sonography of 26 entheses at week 0, 12, 24 and 52. The same protocol was used once only in 23 healthy controls for comparison. The primary endpoint was the change in sonographic enthesopathy inflammation score (extrapolated from the GUESS score) at 24 weeks. This was a prospective proof-of-concept study (no power calculation). Analysis was primarily descriptive with effect size (Cohens d) and paired t-tests provided for enthesopathy scores.

Results: 24% of 598 entheses in patients at week 0 (median (IQR) 6 (4,9) out of 26 per patient) had at least one inflammatory entheseal abnormality (thickening, hypoechogenicity, PD signal) compared to 5% in controls, reducing to 14% and 10% after 24 and 52 weeks of treatment respectively (fig. 1). Mean inflammation scores reduced by 42% to week 24 (mean (95% C.I.) reduction -4.2(-6.3,-2.1) d=1.2 p<0.001) and by 47.5% (-4.7 (-7.1,-2.3) d=1.3 p=0.001) to week 52. Of 187 inflammatory abnormalities found at week 0, 116 (62%) resolved, 4 (7%) improved, 55 (29%) remained unchanged and 2 (1.1%) worsened by week 24. 38 new abnormalities developed on treatment. There were no differences in scores between those achieving PASI90 (n=17) and those not at week 24 (difference -0.3 95% C.I.-4.5,3.8). Chronic damage abnormalities (calcification, enthesophytes, erosions, bone cortex irregularities) did not improve with therapy. 16% entheses at week 0 had at least one abnormality compared to 6% in controls, increasing to 19% and 20% after 24 and 52 weeks of therapy respectively (fig. 1). Mean chronicity scores increased by 17% to week 24 (1.3 (-0.2,2.7) d=0.5 p<0.082), and by 10% (0.8 (-1.6,3.1) d=0.2 p=0.512) to week 52.

Conclusion: This study suggests that ustekinumab therapy for psoriasis suppresses the inflammatory features of subclinical enthesopathy supporting the concept that early intervention may prevent arthritis evolution.

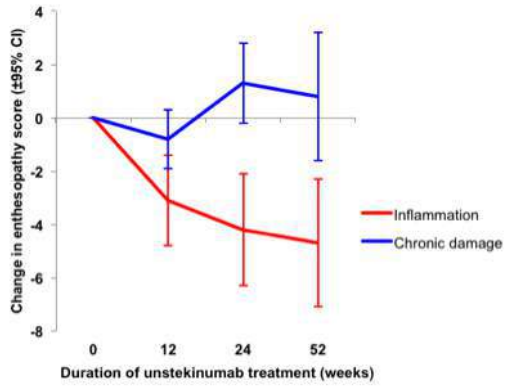

Figure 1: Change over time in total enthesopathy scores for inflammatory and chornic damage abnormalities in patients treated with ustekinumab

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Disclosure: L. Savage, None; **M. Goodfield**, None; **E. M. A. Hensor**, None; **P. Emery**, None; **D. McGonagle**, None.

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Abstract Number: 961

Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Psoriatic Arthritis through 3 Years: Efficacy and Safety Results from a Phase 3 Trial

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Background/Purpose: Secukinumab, an anti–interleukin-17A monoclonal antibody, provided rapid and significant improvements in the key clinical domains of psoriatic arthritis (PsA) in the FUTURE 1 study (NCT01392326) with improvements sustained through 2 years.[1] Here, we present efficacy and safety results through 3 years in the extension of the FUTURE 1 study.

Methods: A total of 606 adults with active PsA were randomized to receive secukinumab or placebo (PBO). Secukinumab patients (pts) received a 10 mg/kg i.v. loading dose at baseline (BL), Weeks (Wks) 2 and 4, and then either 150 mg s.c. (IV→150 mg) or 75 mg s.c. (IV→75 mg) every 4 wks. PBO was given on the same dosing schedule. At Wk 16 or Wk 24, based on Wk 16 clinical response, PBO-treated pts were re-randomized to receive secukinumab 150 or 75 mg s.c. At Wk 104, pts could enter the extension phase of the study. Efficacy results at Wk 156 are presented for pts that were originally randomized to secukinumab (n = 308). Clinical assessments at Wk 156 included: ACR20/50/70, PASI 75, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Multiple imputation was applied to missing binary variables. Summary statistics are based on relative frequencies for binary variables and mean (±SD) for continuous variables. Analyses stratified by anti-TNFα status (anti–TNFα-naïve and anti-TNFα inadequate response [IR]) were pre-specified and reported as observed. Safety analysis is based on exposure adjusted incidence rate (EAIR). All pts (n = 587) who received ≥1 dose of study treatment through 156 wks were included in the safety analysis.

Results: Overall, 457 of the original 606 pts entered the extension study (including 308 originally randomized to secukinumab) of which 435 pts completed 156 wks (151 pts in IV→150 mg group; 142 in IV→75 mg group; 142 in PBO → secukinumab groups). At Wk 156, ACR 20/50/70 response rates were 76.8/54.9/32.9% with IV→150 mg and 65.2/39.0/26.0% with IV→75 mg, respectively. Sustained clinical improvements through Wk 156 were observed across other clinically important domains of PsA. Improvements were sustained in both anti–TNFα-naïve and anti–TNFα-IR pts (Table). Over the entire study period (mean [± SD] exposure to secukinumab of 1025.1 ± 372.7 days) the type, incidence and severity of adverse events (AEs) were consistent with those reported previously.[1] EAIRs for serious infections/infestations, candida infections, Crohn's disease, malignant/unspecified tumors, and major adverse cardiac events with secukinumab were 1.7, 1.2, 0.1, 0.9, and 0.7 per 100 pt-years, respectively.

Conclusion: Secukinumab provided sustained improvements in signs and symptoms and multiple clinical domains of active PsA in pts who completed 3 years of therapy. Secukinumab was well tolerated with a safety profile consistent with that previously reported. References: 1. Mease PJ, et al. *Arthritis Rheumatol*. 2015; 67 (suppl 10).

Table. Summary of Efficacy Results at Week 156				
Variables	**Secukinumab IV→150 mg (n = 161)**		**Secukinumab IV→75 mg (n = 147)**	
ACR 20/50/70[a] (% responders)	76.8/54.9/32.9		65.2/39.0/26.0	
PASI 75[a,b] (% responders)	75.6		58.6	
DAS28-CRP[c], mean change (SD)	–1.94 (1.3)		–1.85 (1.5)	
SF-36 PCS[c], mean change (SD)	6.0 (8.5)		5.5 (7.3)	
HAQ-DI[c], mean change (SD)	–0.43 (0.6)		–0.42 (0.6)	
Resolution of dactylitis[a,d] (%)	88.1		86.8	
Resolution of enthesitis [a,d] (%)	76.7		74.8	
Analysis by anti-TNFα status[c]				
	Anti–TNFα-naïve		**Anti-TNFα-IR**	
	Secukinumab IV→150 mg (n = 120)	**Secukinumab IV→75 mg (n = 110)**	**Secukinumab IV→150 mg (n = 41)**	**Secukinumab IV→75 mg (n = 37)**
ACR20/50/70 (% responders)	81.0/62.9/38.8	67.3/43.0/28.0	61.5/35.9/17.9	55.6/27.8/19.4
PASI 75 (% responders)	76.2	60.0	75.0	56.3

[a]Multiple imputation (missing binary variables); [b]Analysis performed in psoriasis subset pts, i.e. pts with psoriasis ≥3% body surface area at time of randomization (n = 89 in secukinumab IV→150 mg and n = 82 in secukinumab IV→75 mg); [c]Observed data; [d]Data from the pts with these symptoms at BL (dactylitis, n = 83 in secukinumab IV→150 mg and n = 77 in secukinumab IV→75 mg and enthesitis, n = 99 in secukinumab IV→150 mg and n = 91 in secukinumab IV→75 mg). ACR, American College of Rheumatology response criteria; BL, baseline; DAS28-CRP, Disease Activity Score 28 using C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; IV, intravenous; n, number of pts in the extension study; PASI, Psoriasis Area-and-Severity Index; SF-36 PCS, short form-36 physical component summary

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No Increased Risk of Inflammatory Bowel Disease Among Secukinumab-Treated Patients with Moderate to Severe Psoriasis, Psoriatic Arthritis, or Ankylosing Spondylitis: Data from 14 Phase 2 and Phase 3 Clinical Studies

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Background/Purpose: Secukinumab, a fully human anti–interleukin-17A monoclonal antibody, has been evaluated and approved for the treatment of moderate to severe psoriasis, active psoriatic arthritis (PsA) and active ankylosing spondylitis (AS). Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is commonly associated with psoriasis, PsA and AS.[1,2] The risk of CD in moderate to severe psoriasis patients (pts) is ~2–4-fold higher than that in the general population,[1,3,4] occurring at a rate of up to 0.25 cases per 100 pt-years.[4] CD has been reported at a rate of 0.06 cases per 100 pt-years among pts with PsA,[3] and 0.7 cases per 100 pt-years among placebo-treated pts in AS trials.[5] Endoscopic subclinical inflammation occurs in up to 50% of AS pts.[2] Here, we report the incidence of CD and UC among secukinumab-treated pts in the psoriasis, PsA, and AS clinical trial programs.

Methods: This analysis included data from 10 Phase II and Phase III studies in moderate to severe psoriasis, 2 Phase III studies in active PsA, and 2 Phase III studies in active AS, pooled per indication. Most studies included short-term, placebo treatment arms; 1 psoriasis study included an etanercept active comparator arm. Pts with prior history of, but not active, IBD could be enrolled. Study durations varied; data from all pts receiving ≥1 secukinumab dose up to Week 52 (psoriasis studies) or Week 112 visit (PsA/AS studies) were included. Data are reported as crude frequency rates (%) in the short-term (Week 12 in the psoriasis studies and Week 16 in the PsA/AS studies) and exposure adjusted incidence rates (EAIR; per 100 pt-years) over the entire treatment period.

Results: Overall, 3430, 974, and 571 pts received ≥1 secukinumab dose in the psoriasis, PsA, and AS studies, respectively. Adverse events of CD or UC were reported infrequently amongst secukinumab-treated pts in both the short- and long-term treatment periods (Table). Rates of CD and UC were similar across the psoriasis and PsA cohorts, and rates with secukinumab were similar to those seen with etanercept in psoriasis pts. Across all indications, there was no dose dependency with respect to the incidence of CD or UC with secukinumab, and no pattern in time-to-onset (data not shown).

Conclusion: Events of CD and UC in the 14 clinical studies were reported infrequently in secukinumab-treated pts with psoriasis, PsA, or AS; rates were similar across the psoriasis and PsA cohorts. EAIR rates of CD and UC observed in secukinumab-treated pts are consistent with those reported in the literature in psoriasis, PsA, and AS populations. **References:** 1. Li et al. *Ann Rheum Dis* 2013;72:1200–5; 2. Rudwaleit et al. *Best Pract Res Clin Rheumatol* 2006;20:451–71; 3. Egeberg et al. *Br J Dermatol* 2016; E-pub ahead of print; 4. Scosyrev & Primatesta. Poster P068, 5th Congress of the Psoriasis International Network, 7–9 July 2016, Paris, France; 5. Braun et al. *Arthritis Rheum* 2007;57:639–47

Table: Incidence of CD and UC Across the Psoriasis, PsA and AS Secukinumab Clinical Trial Programs							
Short-term period, n (%)							
	Psoriasis Studies			**PsA Studies**		**AS Studies†**	
	Any SEC (N=2877)	**PBO (N=793)**	**ETN (N=323)**	**Any SEC (N=703)**	**PBO (N=300)**	**Any SEC (N=394)**	**PBO (N=196)**
Mean exposure, days	83.2	81.2	82.6	112.0	110.1	112.1	108.6
Crohn's disease	1 (0.03)	0	0	0	1 (0.3)	2 (0.5)	0
Exacerbations[b]	1	0	0	0	0	2	0
Ulcerative colitis	1 (0.03)	0	1 (0.3)	0	0	1 (0.3)	0
Exacerbations[b]	0	0	0	0	0	0	0
Entire treatment period, n (EAIR per 100 pt-years) [95% CI]							
	Psoriasis Studies			**PsA Studies**		**AS Studies**	
	Any SEC[a] (N=3430)	**ETN (N=323)**		**Any SEC[a] (N=974)**		**Any SEC[a] (N=591)**	
Mean exposure, days	290.1	331.9		542.4		670.0	
Crohn's disease	3 (0.11) [0.02–0.32]	0 [0–1.26]		1 (0.07) [0.00–0.39]		8* (0.77) [0.33–1.51]	
Exacerbations[b]	3	0		0		3	
Ulcerative colitis	4 (0.15) [0.04–0.38]	1 (0.34) [0.01–1.90]		2 (0.14) [0.02–0.50]		3 (0.29) [0.06–0.84]	
Exacerbations[b]	2	0		1		1	

†There was 1 report of IBD not classified as Crohn's disease or ulcerative colitis in a SEC-treated pt in the AS program *Final diagnosis was not confirmed in 2 cases; [a]Includes pts switched from placebo (PBO); [b]Exacerbations count to the overall incidence rate; AS, ankylosing spondylitis; CI, confidence interval; EAIR, exposure adjusted incidence rate; ETN, etanercept; IBD, inflammatory bowel disease; PsA, psoriatic arthritis; pt, patient; SEC, secukinumab

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Abstract Number: 963

Treatment of Homocysteine Improves Urine Protein/Cr Ratio in SLE

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment I: Nephritis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Homocysteine is a proven prospective risk factor for stroke and arterial thrombosis in SLE. However, checking for

homocysteine and treating high levels is actually discouraged, because randomized clinical trials in the general population did not show a reduction in coronary events.

Methods: 1623 SLE patients (92% female; 52% Caucasian and 40% African-American) were studied. For the first homocysteine measurement, 85.6% were below 15 umol/L. High levels were treated with folic acid or Folbic. We used GEE to estimate the association between homocysteine and the urine protein/cr ratio using serial tests of homocysteine.

Results: The same day homocysteine > 15 was associated with the same day urine protein/cr ratio (p=0.0008). Homocysteine was associated with serum creatinine (p>0.0001). Among 829 patients, 604 had at least two homocysteine measurements, 272 had three or more. A 10 umol/L decrease in homocysteine within a person corresponds to an average 0.011 (95% CI: 0.006 to 0.015) unit decrease in urine protein/creatinine ratio (P < 0.0001), after adjusting for sex and ethnicity. The association remained significant (0.004 (95% CI 0.002 to 0.007), P = 0.0005) when we only included patients with a first homocysteine greater or equal to 15 umol/L and a same day urine protein/creatinine ratio greater or equal to 0.2. In addition, the association was not changed if we adjusted for the serum creatinine. Table 1. Association of a 10 umol/L Decrease in Homocysteine with Lower Urine Protein/Cr

All patient analysis	0.011 decrease (95% CI 0.006 – 0.015	P<0.0001
Homocysteine > 15 and urine p/c > 0.200	0.004 decrease (95% CI 0.002 – 0.007)	P< 0.007

Conclusion: High homocysteine levels, when treated, resulted in significant lowering of the urine protein/cr ratio, that was independent of serum creatinine.

Disclosure: W. Fu, None; **M. Petri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/treatment-of-homocysteine-improves-urine-proteincr-ratio-in-sle

Abstract Number: 964

Tubulointerstitial Damage Is an Independent Predictor of End Stage Renal Disease in Lupus Nephritis Patients with Mild to Moderate Renal Impairment

Bojana Jovanovic[1], Hina N. Khan[1], Wenzhu Mowrey[1], Peter M. Izmirly[2], Daniel Schwartz[1], Jill P. Buyon[3], Chaim Putterman[1], Beatrice Goilav[1] and Anna R. Broder[1], [1]Albert Einstein College of Medicine/Montefiore Medical Center, New York, NY, [2]New York University School of Medicine, New York, NY, [3]Medicine, New York University School of Medicine, New York, NY
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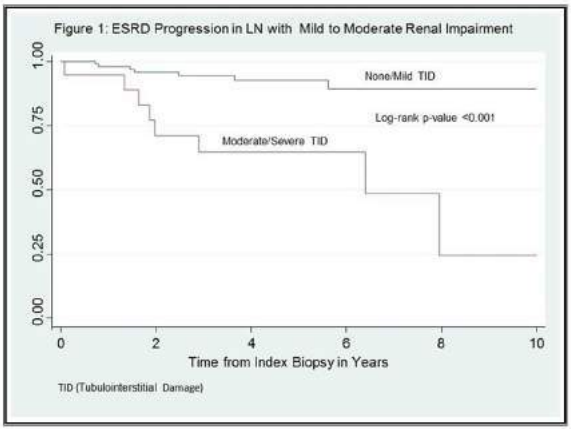
Background/Purpose: Tubulointerstitial damage (TID) is considered to be a later sequela of lupus nephritis (LN). The clinical significance of TID in patients with only mild to moderate renal impairment at the time of biopsy has not been studied. The objective of this study was to determine if TID predicts progression to end-stage renal disease (ESRD) in LN patients with mild to moderate renal impairment.

Methods: We identified all adult and pediatric SLE patients (by ACR and/or SLICC criteria) with who had an index biopsy consistent with LN (>6 glomerulai examined) between January 2005 and July 2015. Renal impairment was defined as mild (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73m^2) or moderate (eGFR≥30 and <60 mL/min/1.73m^2) at index biopsy. Demographic data, comorbidities, medications, laboratory data, ESRD onset, and deaths through December 2015 were ascertained from medical chart reviews, the United States Renal Data Systemic Report, and National Death Index. TID was defined as the presence of moderate to severe tubular atrophy and/or interstitial fibrosis as reported on the renal biopsies in accordance with the 2003 ISN/RPS criteria. Time to ESRD onset was defined as time from the index biopsy date to incident ESRD date; non-ESRD patients were censored at time of death or the last visit. Kaplan-Meier survival curves and Cox proportional hazards models were used to evaluate whether TID was predictive of ESRD progression adjusting for eGFR (as a continuous variable) and LN class.

Results: Of the 155 patients with renal biopsies, 131 (85%) had baseline eGFR>30 mL/min/1.73m^2: 8(6%) Class II, 58(44%) Class

III/IV, 38(29%) Class V, and 27(21%) mixed; 16 (12%) progressed to ESRD. Eighty six percent of ESRD progressors had proliferative or mixed LN vs. 51% of non-ESRD, p=0.02. ESRD and non-ESRD groups were similar with respect to age, sex, race, comorbidity scores, complement levels, anti-dsDNA, and protein to creatinine ratio at index biopsy. Median (IQR) baseline eGFR was 65 (51, 75) mL/min/1.73m^2 in the ESRD group and 97 (69, 127) mL/min/1.73m^2 in the non-ESRD group, p=0.001. TID was present in 12% of biopsies with eGFR≥60 mL/min/1.73m^2 and in 35% of biopsies with GFR between 30 and 60 mL/min/1.73m^2. Moderate to severe TID was associated with a high risk of ESRD progression (Figure 1, log-rank p-value<0.001), HR=8.3, 95% CI: (2.6, 27), p-value<0.001, adjusted for eGFR and proliferative or mixed LN. Similarly, TID remained a significant predictor in the subgroup with eGFR>60 mL/min/1.73m^2, HR= 5.6, 95% CI: (1.3, 22.9), p=0.02.

Conclusion: TID was highly prevalent among LN patients with mild to moderate renal impairment. TID was a strong predictor of ESRD progression in these patients independent of eGFR or biopsy class. Identifying factors associated with the presence of TID early in the disease may lead to the development of effective prevention strategies to decrease the risk of ESRD.



Disclosure: B. Jovanovic, None; **H. N. Khan**, None; **W. Mowrey**, None; **P. M. Izmirly**, None; **D. Schwartz**, None; **J. P. Buyon**, None; **C. Putterman**, None; **B. Goilav**, None; **A. R. Broder**, None.

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Abstract Number: 965

Clinical and Serologic Variables Associated with Renal Response Among Lupus Nephritis Phase III Trial Patients Treated with Standard of Care Immunosuppression

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Background/Purpose: Lupus nephritis (LN) is associated with high treatment failure rates and the development of new therapies for LN is limited by the lack of validated predictors of clinical response. Recent analyses have identified early predictors of renal outcome in LN.[1,2] The combined placebo control arms of two multi-center, double blinded placebo controlled trials in LN patients (LUNAR and BELONG), where standard of care immunosuppression was given, provide the opportunity to explore the association of clinical variables with renal response.[3,4]

Methods: The analysis population included 146 patients given standard of care immunosuppression plus placebo infusions. Response was assessed in the following 3 mutually exclusive categories at one year: complete renal response (CRR), defined as urine protein/creatinine

ratio (UPCR) <0.5 on 24-hour urine collection and serum creatinine ²25% above baseline; partial renal response (PRR), defined as ³50% reduction in UPCR, reduction of UPCR to <3 if screening value >3, and serum creatinine ²25% above baseline; and nonresponse (NR), no CRR or PRR. Multivariate logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) for the associations between independent variables and renal response. These associations were examined in univariate and multivariate models to identify variables independently associated with response.

Results: All patients had biopsy-proven ISN/RPS 2003 class III or IV LN with 38 (26%) having concomitant class V. Mean UPCR was 4.1 ± 2.9 and mean estimated glomerular filtration rate (eGFR) was 87 ± 38 mL/min/1.73 m^2 at baseline. 85% were treated with mycophenolate mofetil and 15% with the Euro-Lupus cyclophosphamide regimen. In multivariate analysis (Table 1), baseline UPCR (OR 1.18 for each 1 unit decrease, 95% CI 1.01 to 1.37) and the presence of concomitant class V nephritis (OR 2.8, 95% CI 1.17 to 6.7) were associated with achievement of CRR. ³25% reduction in UPCR at week 8 was associated with CRR in univariate but not multivariate models. ³25% reduction in UPCR at week 8 (OR 0.33, 95% CI 0.15 to 0.76) and the presence of concomitant class V nephritis (OR 0.32, 95% CI 0.13 to 0.79) were associated with a decreased likelihood of NR.

Conclusion: In this pooled population from two phase III randomized trials of LN treated with standard of care immunosuppression, baseline UPCR, concomitant class V LN, and achievement of 25% reduction in UPCR at week 8 were independently associated with renal response. These findings build upon an emerging literature of early predictors of clinical response in LN with the ultimate goals of individualizing treatment decisions based on patient risk and accelerating the development of new therapeutics for LN. References:

1. Dall'era M *Arthritis Rheumatol* 2015

2. Dall'era M *Lupus Sci Med* 2015

3. Rovin B *Arthritis Rheumatol* 2012

4. Mysler E *Arthritis Rheumatol* 2013

Table 1: Adjusted odds ratios and 95% confidence intervals for the association between selected variables and renal response at one year

Variable	Complete renal response OR (95% CI)	Nonresponse OR (95% CI)
Disease duration ³1 year	0.47 (0.21, 1.08)	1.91 (0.88, 4.1)
Concomitant biopsy class V LN	2.8* (1.17, 6.7)	0.32* (0.13, 0.79)
Baseline UPCR (per 1 unit decrease)	1.18* (1.01, 1.37)	1.02 (0.89, 1.16)
Baseline abnormal eGFR	0.58 (0.27, 1.25)	0.68 (0.32, 1.43)
Baseline low C4	0.69 (0.26, 1.82)	0.80 (0.32, 1.99)
Baseline anti-dsDNA titer >75 IU/mL	1.43 (0.61, 3.4)	0.88 (0.39, 1.99)
Week 8 ³25% reduction in UPCR from baseline	2.2 (0.89, 5.2)	0.33** (0.15, 0.76)

* P < 0.05, ** P < 0.01

Disclosure: M. D. Cascino, Genentech, Inc., 2; **P. Lambert**, Genentech, Inc., 3; **A. Decker**, Genentech, Inc., 3; **T. Katsumoto**, Genentech, Inc., 3; **J. Garg**, Genentech, Inc., 3; **P. Brunetta**, Genentech, Inc., 3; **M. Dall'Era**, None; **L. L. Dragone**, Genentech, Inc., 3.

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Abstract Number: 966

Renal Activity in Lupus (RAIL) Urinary Biomarkers Predict Treatment Response

Gaurav Gulati[1], Michael Bennett[2], Khalid Abulaban[3,4], Qing Ma[5], Marisa S. Klein-Gitelman[6], Kelly A. Rouster-Stevens[7], Christopher Haffner[5], Kasha Wiley[8], Stacy P. Ardoin[9], Jun Ying[10], Prasad Devarajan[11] and Hermine I. Brunner[8], [1]Division of Immunology, Allergy

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Renal Activity In Lupus (RAIL) Urinary Biomarkers Predict Treatment Response

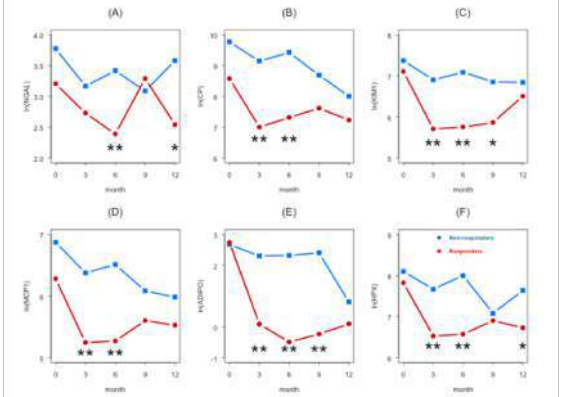
Background/Purpose: We have previously demonstrated the strong predictive value of the Renal Activity In Lupus (RAIL) algorithm, using 6 urinary biomarkers (UBMs), in children (RAIL) and adult (A-RAIL) populations. The purpose of the present study was to prospectively study these six UBMs in relation to the response to therapy for lupus nephritis.

Methods: Patients with a diagnosis of Systemic Lupus Erythematosus (SLE) with new biopsy proven class III/IV lupus nephritis were enrolled. In addition to routine lab work, including anti-dsDNA antibody levels, complement levels, and urinalysis, the patientsÕ serial urine samples were collected during the 12 months of treatment with immunosuppressive medications. The six RAIL biomarkers, namely neutrophil gelatinase associated lipocalin (NGAL), ceruloplasmin (CP), kidney injury molecule 1 (KIM 1), monocyte chemotactic protein 1 (MCP 1), adiponectin (ADIPO) and hemopexin (HPX), were measured longitudinally using standardized ELISA-based assays during the patientsÕ course. Patients were treated with standard induction regimen using cyclophosphamide versus mycophenolate mofetil, and categorized as responders or non-responders, based on the American College of Rheumatology (ACR) lupus nephritis response criteria. Longitudinal patterns of RAIL biomarkers were assessed and compared between visits (0, 3, 6, 9 and 12 months) and groups (Responders versus Non-responders) using mixed effect models.

Results: A total of seventy-two patients were enrolled in this longitudinal prospective study, with 32 responders and 40 non-responders. About 80 percent in each group were females, and non-Caucasian race was predominant (13 out of 32 responders; 19 out of 40 non-responders, respectively). At 6 month follow up since induction therapy, all 6 UBMs showed significantly lower levels among responders when compared to non-responders (Figure 1). The differences were also significant for all except NGAL at 3 month follow up. At 12 months of treatment, the responders and non-responders did not continue this trend and differences in biomarkers became largely non significant, except NGAL and HPX, which showed significant differences.

Conclusion: The RAIL UBMs demonstrate strong value in predicting response to therapy, can be used as a reliable surrogate in predicting treatment response, and will be highly valuable in making therapeutic changes and clinical decisions.

FIGURE 1: RAIL UBMs: Changes after response to Induction Therapy



LEGEND: The symbol "*" and "**" denotes a *p value* of 0.05 and 0.01 respectively for difference between the two groups for the given time point. The RAIL biomarkers ((A) NGAL, (B) Ceruloplasmin, (C) KIM-1, (D) MCP-1, (E) Adiponectin, and (F) Hemopexin) are represented as standardized log transformed concentration values. Non-responder values are marked with blue, and responders with red.

Disclosure: G. Gulati, None; **M. Bennett**, None; **K. Abulaban**, None; **Q. Ma**, None; **M. S. Klein-Gitelman**, None; **K. A. Rouster-**

Stevens, None; **C. Haffner**, None; **K. Wiley**, None; **S. P. Ardoin**, None; **J. Ying**, None; **P. Devarajan**, N/A, 9; **H. I. Brunner**, N/A, 9,NIH, 2.

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Abstract Number: 967

Using a Hazard Index Tool Based on Short Term Renal Parameters to Predict Long Term Outcomes in Lupus Nephritis: A Novel Way to Assess New Therapies

Meggan Mackay[1], Joanna Fishbein[2], Maria Dall'Era[3], Kenneth Kalunian[4], Martin Lesser[5] and Brad H. Rovin[6], [1]Autoimmune & Musculoskeletal Disorders, The Feinstein Institute for Medical Research, Manhasset, NY, [2]Biostatistics Unit, The Feinstein Institute for Medical Research, Manhasset, NY, [3]Division of Rheumatology, University of California, San Francisco, San Francisco, CA, [4]Center for Innovative Therapy, UCSD School of Medicine, La Jolla, CA, [5]Biostatistics, Feinstein Institute for Medical Reasearch, Manhasset, NY, [6]Ohio State University Medical Center, Columbus, OH

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Background/Purpose: Variability in response criteria for lupus nephritis (LN) clinical trials (CTs) has compromised the legitimacy and generalizability of CT results, primarily because short term response, however defined, does not necessarily equate to good long term kidney function. The aim of this study was to examine associations between short term renal parameters and long term renal outcomes to establish novel endpoints for LN CTs that predict long term kidney health.

Methods: A database of 944 patients with LN flare (baseline) and extended follow-up was established from 12 multinational clinical centers and 3 CTs. Performance of clinical variables at 12 months was assessed for predicting development of new or progressive chronic kidney disease (CKD), defined as a sustained decrease in eGFR ≥30%. Treatment was standard of care or as dictated by CT protocol. Statistical analyses included Kaplan-Meier curves for comparison of survival times using the log-rank test between categorical grouping variables and univariate Cox proportional hazards regression for continuous variables; Bonferroni correction was used for multiple comparisons. Factors significantly associated with CKD on univariate analysis ($p<0.10$) were included in a multivariable Cox regression analysis to build a prognostic model for time to CKD.

Results: Accounting for inclusion criteria and missing data, final analyses included 558 subjects (**Table** 1). 75 events of CKD occurred in 558 subjects; follow-up time ranged 22-317 months. Urine RBCs at baseline and 12 months, age, race (binary variable Black/non-Black), ISN Class, SCr at baseline and 12 months, proteinuria at 12 months and % change (%Δ) in SCr and proteinuria from baseline to 12 months were significantly associated with CKD by univariate analysis. The final multivariate model for significant predicators of CKD included the log (%Δ in proteinuria, $p<0.0001$), log (SCr at 12 months, $p<0.0001$) and race ($p=0.04$). The hazard ratios (HR) for CKD were 1.86 (95% CI: 1.52, 2.65) for log (%Δ proteinuria), 5.11 (3.04, 8.58) for log SCr and 1.65 (1.003, 2.70) for race. These predictors were combined into a "Hazard Index Tool" formula for developing CKD: $\text{Hazard Index}_i = 0.61859*X_1 + 1.63100*X_2 + 0.49870*X_3 + 13$, where X_1= log (%Δ proteinuria), X_2=log (SCr 12 months), X_3=1 if Black; 0 if non-Black.

Conclusion: Evaluation of a longitudinal cohort of patients with LN flare demonstrates that race and 12 month measures of proteinuria and SCr predict risk for development of CKD, whereas urine RBCs do not. HRs derived from multivariable analysis of these clinical variables were used to develop a Hazard Index Tool that predicts hazard of developing CKD. This tool can be used in CTs to evaluate superiority of new LN drugs in preventing future development of CKD (i.e., comparison of mean Hazard Index scores between treatment and placebo groups). Tool validation studies are planned. **Table 1.**Subject characteristics and predictor variables at baseline and 12 months stratified by development of CKD defined as a sustained decrease in eGFR≥30% after month 12.

N = 558	Mean ± SD or Frequency			
	Baseline		12 months	
	CKD+ (n=75)	CKD- (n=483)	CKD+ (n=75)	CKD- (n=483)
Gender				
Female	66 (88%)	422 (87%)		
Male	9 (12%)	61 (13%)		
Age	36 ± 14.5	33 ± 11.8		
Race				
Black	26 (35%)	67 (14%)		
Non-Black	49 (65%)	416 (86%)		
Follow-up time (months)	80.5 ± 59.4	48.9 ± 25.3		
ISN Class				
Class II/V or V	17 (23%)	72 (15%)		
Class III/V or IV/V	4 (5%)	53 (11%)		
Class III	13 (17%)	76 (16%)		
Class IV	40 (53%)	271 (56%)		
Not done	1 (1%)	11 (2%)		
Proteinuria [1]	3.9 ± 2.8	4.1 ± 3.4	2.8 ± 3.9	.88 ± 1.25
SCr (mg/dL)	1.45 ± 0.85	1.15 ± .69	1.3 ± 0.74	.89 ± .36
eGFR (CKD-EPI)	68.8 ± 33.5	82.5± 34.5	74.7 ± 32.3	97.9 ± 27.8
Urine RBC				
>5/HPF	34 (45%)	276 (57%)	22 (29%)	131 (27%)
Absent	15 (20%)	109 (23%)	26 (35%)	252 (52%)
Not Done	26 (35%)	98 (20%)	27 (36%)	100 (21%)

[1]Proteinuria was measured either as random urine protein/Cr ratios or 24 hour collections Methods: Results: Conclusion:

Abstract Number: 968

Urinary Soluble CD163, an M2 Macrophage Marker, Reflects the Renal Disease Activity in Lupus Nephritis: A Cross Sectional and Longitudinal Assessment

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment I: Nephritis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Alternatively activated (M2) macrophages are the major macrophage subtype infiltrating the glomeruli in lupus nephritis (LN). CD163 is a marker of M2 macrophages. In urine, soluble CD163 (sCD163), which is the shed form of CD163, may reflect the activation of M2 macrophages in kidney. Thus, it may serve as a biomarker for identification and assessment of treatment response in patients with LN.

Methods: Patients with SLE with active nephritis (AN), active disease without nephritis (active non-renal; ANR) and inactive disease (ID) were enrolled. Disease activity was assessed using SLEDAI and renal SLEDAI (rSLEDAI). Patients in AN group were treated according to the ACR guidelines and followed up every 3 months for 1 year. Urine and plasma samples were collected at baseline for all and every 3 months in AN group. Urine samples from 25 healthy subjects (HC) and 20 patients of rheumatoid arthritis (RA) served as controls. Plasma sCD163 (pCD163) and urinary sCD163 were measured using ELISA and urinary values were normalized for creatinine excretion.

Variables are expressed as median (range) and non-parametric tests were used for analysis.

Results: A total of 122 SLE patients (females 114) were enrolled. At baseline, normalized urinary sCD163 (uCD163) was significantly higher in AN group as compared to ANR, ID, HC and RA (p-value <0.001 for all). uCD163 showed good correlation with protein:creatinine ratio (r=0.55; p-value <0.001), rSLEDAI (r=0.47, p-value <0.001) and SLEDAI (r=0.3, p-value <0.001) but not with pCD163 levels (r=0.23). uCD163 but not pCD163 could differentiate between AN and ANR groups (Table 1) and on ROC analysis, uCD163 (AUC=0.76) performed better than pCD163, C3, C4 and anti-ds DNA antibodies. In the longitudinal study, with reduction in disease activity, uCD163 also decreased significantly at all follow-up visits as compared to baseline (p-value <0.001) (Table 2). pCD163 also decreased significantly but had an erratic and irregular trend. uCD163 and not pCD163 showed a rise before conventional markers in 4 patients who relapsed within 1 year of follow-up.

Conclusion: uCD163 is a potential biomarker of LN disease activity. Among patients with active SLE, it helps differentiate between patients with and without LN. It shows modest correlation with renal disease activity and has a potential to predict relapse of LN.

Table1: Baseline characteristics of SLE patients in the three categories

	Active Nephritis (AN)	Active Non-Renal (ANR)	Inactive Disease (ID)
Number	57	23	42
F:M	55:2	18:5	41:1
Median age (yrs)	27 (12 – 50)	29 (15 – 50)	28 (14 – 48)
rSLEDAI	8 (4 – 16)	0 (0)	0 (0)
SLEDAI	18 (6 – 28)	10 (5 – 20)	2 (0 – 4)
C3 (mg/dl)	47.1 (<16.9 – 156)	48.6 (17.3 – 139)	113.5 (34.2 – 194)
C4 (mg/dl)	7.6 (<5.6 – 56)	9.4 (<5.6 – 26)	22.1 (6 – 45)
Anti-ds DNA (IU/ml)	200 (24 – >300)	185 (<6.25 – >300)	59.95 (<6.25 – 200)
U_{Pr}/U_{Cr} ratio	3.37 (0.3 – 20.25)	0.38 (0.03 – 1.46)	0.09 (0 – 10.69)
Serum Creatinine (mg/dl)	0.9 (0.4 – 3.87)	0.82 (0.6 – 1.25)	0.8 (0.4 – 1.3)
Plasma sCD163 (ng/ml)	2837.1 (701.3 – 7433.2)	2759 (619.8 – 9931)	1503.6 (564.5 – 3142.8)***
U_{CD163}/U_{Cr} (x 100 pg/mg)	127 (0 – 1435)	3.82 (0 – 179)***	10.34 (0 – 1923)***

p-value ***= <0.001 as compared to AN group Table 2. Change in different disease activity parameters, plasma and normalized urinary sCD163 in the active nephritis group with treatment over 1 year

	Baseline	3 months	6 months	9 months	12 months
rSLEDAI	8 (4 – 16)	0 (0 – 12)	0 (0 – 4)	0 (0 – 8)	0 (0 – 8)
SLEDAI	18 (6 – 28)	2 (0 – 14)	2 (0 – 6)	2 (0 – 10)	2 (0 – 15)
C3 (mg/dl)	47.1 (<16.9 – 156)	85.9 (7 – 161)	93.9 (47.1 – 174)	89.7 (33.4 – 168)	103 (35 – 165)
C4 (mg/dl)	7.6 (<5.6 – 56)	17.4 (<5.6 – 73.7)	19.6 (<5.6 – 61.1)	20.1 (<5.6 – 76.5)	19.6 (<5.6 – 79)
Anti-ds DNA (IU)	200 (24 – >300)	60.4 (6.1 – >300)	54.6 (<6.25 – 300)	67.45 (<6.5 – 300)	53.4 (<6.5 – 300)
U_{Pr}/U_{Cr} ratio	3.37 (0.3 – 20.25)	0.35 (0 – 13.55)	0.4 (0 – 8.69)	0.3 (0 – 6.98)	0.25 (0 – 6.25)
Serum Creatinine (mg/dl)	0.9 (0.4 – 3.87)	0.77 (0 – 4.12)	0.8 (056 – 1.7)	0.79 (0.4 – 1.3)	0.81 (0.4 – 1.3)
Plasma SCD163 (ng/ml)	2837.1 (701.3 – 7433.2)	1409.5 (393.7 – 4162.1)***	1071.6 (246.6 – 2753.8)***	1307.7 (555.9 – 3580)***	1141.7 (398 – 4124)***
U_{SCD163}/U_{Cr} (x 100 pg/mg)	127 (0 – 1435)	19.7 (0 – 534.9)***	12.7 (0 – 580.5)***	11.9 (0 – 113)***	7.2 (0 – 378)***

p-value ***= <0.001 as compared to baseline values

Disclosure: R. Gupta, None; **A. Yadav**, None; **A. Aggarwal**, None.

Abstract Number: 969

Safety and Efficacy of Subcutaneous Tocilizumab in Early Systemic Sclerosis: Results from the Open-Label Period of a Phase 2 Randomized, Controlled Trial

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics I
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Systemic sclerosis (SSc) is a debilitating disease with few treatment options. Interleukin-6 (IL-6) appears to play a

role in SSc pathogenesis (*J Rheumatol* 1998;25:308; *Pathobiology* 1993;61:239). Data from the 48-week, double-blind (DB), placebo (PBO)-controlled period of the faSScinate trial of subcutaneous (SC) tocilizumab (TCZ) in patients with SSc have been published (*Lancet* 2016: doi: 10.1016/S0140-6736(16)00232-4). Herein we present data on the safety and efficacy of TCZ in SSc patients during 48 weeks of open-label (OL) TCZ treatment.

Methods: Patients ≥18 years of age with active SSc (≤5-year duration, modified Rodnan skin score [mRSS] 15-40, and elevated acute-phase reactants) diagnosed according to 1980 ACR criteria received OL TCZ 162 mg SC weekly from week 48 to week 96. Change from baseline in mRSS, patient-reported outcomes (PROs), and forced vital capacity (FVC) at week 96 were exploratory measures. Observed means used all available data.

Results: In total, 27 of 43 (63%) TCZ and 24 of 44 (55%) PBO patients completed week 96. Baseline (BL) characteristics were similar at BL and at entry into the OL period. Patients who switched from PBO→OL TCZ showed improvement in observed mean change from BL in mRSS at week 96 (–9.4) compared with the end of the 48-week DB period (–3.1). In patients initially randomly assigned to TCZ (TCZ→OL TCZ), mean change in mRSS was –5.6 at week 48 and –9.1 at week 96. In the OL period, improvements in PROs were noted at week 96 compared with week 48 in the PBO→OL TCZ group (mean [SD] change from BL at week 96 vs week 48 in HAQ-DI: –0.3 [0.4] vs 0.2 [0.4]; Patient Global VAS: –23.8 [36.0] vs –4.0 [24.0]; FACIT-Fatigue: 11.3 [12.8] vs 1.4 [7.6]). Of patients who completed the study, none experienced a >10% decline in % predicted FVC during the OL period on TCZ therapy. Rates (95% CI) of serious adverse events/100 patient-years (PY) in the DB period were 76.1 (50.6, 110.0) in PBO patients and 66.7 (42.3, 100.1) in TCZ patients and were 36.0 (18.0, 64.4) in PBO→OL TCZ patients and 16.5 (5.4, 38.5) in TCZ→OL TCZ patients in the OL period. Rates (95% CI)/100PY of serious infections in the DB period were 10.9 (3.0, 27.9) in PBO patients and 34.8 (18.0, 60.8) in TCZ patients. In the OL period they were 19.6 (7.2, 42.7) in PBO→OL TCZ patients and 0.0 (0.0, 12.2) in TCZ→OL TCZ patients. No deaths occurred in the OL period (deaths in DB period: 3 TCZ, 1 PBO).

Conclusion: Although OL data have to be interpreted with caution, efficacy and safety in PBO-treated patients who switched to OL TCZ were generally similar to those observed in patients randomly assigned to TCZ in the DB period. Results over 96 weeks of TCZ treatment suggest maintenance of the clinical response for mRSS in SSc patients. Rates of serious infection increased in PBO patients after they switched to OL TCZ. Long-term safety was consistent with the natural history of SSc and the safety profile of TCZ.

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Abstract Number: 970

The Serotonin Receptor 2 Inhibitor Terguride Has Beneficial Effects on Skin Fibrosis: Results from a Phase 2 Proof of Concept Study

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics I

Session Type: ACR Concurrent Abstract Session

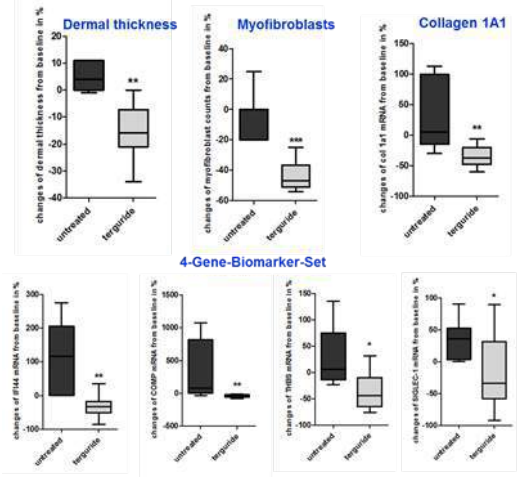
Session Time: 2:30PM-4:00PM

Background/Purpose: Circumstantial evidence from preclinical studies indicates a key role of serotonin (5-HT) signaling via the 5-HT-2B receptor in the development of fibrosis. Terguride is an orally available 5-HT-2 receptor inhibitor that has shown beneficial effects in different animal models of systemic sclerosis (SSc). **Objectives:** To evaluate the efficacy of Terguride for the treatment of fibrosis in patients with SSc in an investigator initiated phase 2 proof of concept study.

Methods: Main inclusion criteria were fulfillment of ACR classification criteria and diffuse cutaneous SSc (dcSSc). Patients with end-stage organ involvement and treatment with potentially disease modifying agents including immunosuppressives were excluded. Patients were treated with Terguride at up to 3 mg/d p.o. or standard of care (post hoc control) for three months. Primary efficacy endpoints were changes of pre-defined skin biopsy biomarkers over the three months treatment period. Secondary efficacy endpoints included change of mRSS and lung function parameters. Serious adverse events (SAEs) and AEs were coded using MedDRA. The study was externally monitored.

Results: Twelve patients were recruited into the Terguride group and 6 patients into the control group. The primary endpoints, skin biopsy biomarkers, showed a consistent and statistically significant down-regulation compared to the control group (Figure) for dermal thickness, myofibroblast counts and mRNA levels of col1a1, col1a2 as well as for the Lafyatis 4-gene biomarker set (COMP, THSP-1, SIGLEC-1, IFI-44). This was accompanied by a reduction in mRSS of - 32.3% versus baseline in the Terguride group versus stable values in the control group ($p < 0.05$). Lung function parameters did not change significantly. Overall, 33 AEs (n=27 mild and n=6 moderate) and one SAE (pyelonephritis, not related) occurred in the Terguride group, most often consisting of nausea and vomiting (9% and 13% of patients respectively).

Conclusion: Terguride was well tolerated in patients with dcSSc. Strong and consistent effects on fibrosis related skin biopsy biomarkers could be observed in this open-label controlled phase 2 proof of concept study, which was further supported by a significant improvement of the mRSS over the control group. These data justify further investigation in an upcoming randomized placebo controlled phase 3 study.



Figure

Disclosure: O. Distler, D Science, Actelion, Active Biotec, Bayer, BiogenIdec, BMS, Boehringer Ingelheim, EpiPharm, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Pharmacyclics, Pfizer, Sanofi, Serodapharm, Sinoxa, 5,Actelion, Bayer, Boehringer Ingelheim, Pfizer, Sanofi, 2,mir-29 for the treatment of systemic sclerosis, 9; **B. Maurer**, AbbVie, Protagen, EMDO, 2, 9,Roche, Actelion, 9; **S. Vettori**, None; **S. Blumhardt**, None; **D. Frey**, None; **A. Distler**, None; **C. Beyer**, None; **J. H. Distler**, None.

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Abstract Number: 971

Reliability and Minimal Clinically Important Differences (MCID) of Forced Vital Capacity: Post-Hoc Analyses from the Scleroderma Lung Studies (SLS-I and II)

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Background/Purpose: Forced vital capacity (FVC) is used as a primary outcome measure in clinical trials of systemic sclerosis-related interstitial lung disease (SSc-ILD). Minimally Clinically Important Difference (MCID) can help interpret whether changes in outcomes are meaningful and can potentially lead to management changes. Our objective was to define inter-rater reliability and MCID of FVC using SLS-I and II data.

Methods: SLS-I and II patients (pts) were adults with SSc with disease duration of ≤7 years, FVC between 45-85 %-predicted and symptomatic ILD. In SLS-1, pts were randomized to daily oral cyclophosphamide (CYC) or matching placebo for 1 year. SLS-II pts were randomized to either mycophenolate mofetil (MMF) for 2 years or daily oral CYC for 1 year followed by 1 yr of placebo. Spirometry was assessed at 3-month intervals. We evaluated the test-retest reliability for FVC between the screening and baseline visits using intra-class correlation (ICC). An ICC of ≥0.90 was considered acceptable. MCID estimates were calculated in the pooled SLS I and II data using SF-36 health transition question: "Compared to one year ago, how would you rate your health in general now?" Pts answering "a *little better" or "a little worse*)" were defined as the MCID changed subgroup. We also assessed the association of MCID for improvement and worsening of FVC (absolute change in % predicted from baseline) with the patient reported outcomes (PROs): HAQ-DI, Mahler's Transition Dyspnea Index (TDI), Saint George's Respiratory Questionnaire (SLS II only), computer-assisted quantitation of extent of fibrosis (QLF) and of total ILD (QILD) on HRCT (12-0 month in SLS-1 and 24-0 month in SLSII). Student's t-test compared the mean difference in outcomes between the MCID improvement/ worsening and "no change" group. P-values < 0.05 were considered statistically significant.

Results: FVC reliability was 0.90 for SLS I, 0.97 for SLS II pts and 0.93 for the combined database. The MCID estimate for improvement in FVC% predicted, after adjusting for "no change" group, was a mean change of 2.97% and -3.32% ($p<0.05$) for worsening. For easy interpretation, FVC% change of >3% was used as the MCID estimate for improvement and >3.3% for worsening. When FVC improved by ≥3%, trends toward significant improvement were noted for SGRQ, SF-36 MCS and QLF, while statistically significant improvement was noted for SF-36 PCS, TDI, HAQ-DI and QILD (Table 1). For negative FVC changes ≥3.3%, worsening was noted in all PROs with statistically significant worsening in SGRQ, TDI, QILD and QLF scores.

Conclusion: Reliability of FVC measurement was acceptable. Our analysis supports an absolute change of +3% for improvement and -3.3% for worsening in FVC% predicted as the MCID estimates for improvement and worsening in SSc-ILD. Estimates correspond to changes in the PROs as well as HRCT quantification of ILD. This needs to be validated in future SSc-ILD trials. **Table 1. Change in PROs, HRCT-QILD and QLF based on MCID estimates of FVC %**

	Improvement > +3% FVC			+ 3% FVC to – 3% FVC			Worsening > -3% FVC		
	N	Mean difference	P-value	N	Mean difference	P-value	N	Mean difference	P-value
SF-36 PCS§	72	4.32	<0.001	70	-0.56	ref	41	-1.56	0.53
SF-36 MCS§	72	3.36	0.34	70	1.70	ref	41	0.14	0.44
TDI§	77	2.61	<0.001	85	0.20	ref	62	-1.37	0.003
HAQ-DI¶	85	-0.13	0.01	89	0.04	ref	65	0.09	0.54
Total SGRQ¶	51	-5.72	0.23	39	-2.34	ref	17	5	0.046
HRCT QLF ¶	71	-2.52	0.07	55	-1.46	ref	51	9.45	0.009
HRCT QILD¶	71	-5.61	0.033	55	-1.09	ref	51	5.55	0.011

§ Positive score denotes improvement in health**;** ¶ Negative score denotes improvement in health**; Ref** refers to reference level.

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Abstract Number: 972

Outcome of the Scleroderma Population "at Risk" to Develop Pulmonary Hypertension in the Pulmonary Hypertension Assessment and Recognition of Outcomes in

Scleroderma Cohort Study

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ABSTRACT:

Background/Purpose: We investigated predictors of outcome, including mortality and cardiopulmonary hospitalizations in the Òat riskÓ group for pulmonary hypertension in PHAROS, a prospective longitudinal cohort study to understand the natural history of pulmonary hypertension (PH) in systemic sclerosis (SSc).

Methods: The **Ò**at riskÓ population for PH was defined by the following entry criteria: echocardiogram (echo) systolic pulmonary arterial pressure (sPAP) >40mmHg, or diffusion lung capacity of carbon monoxide (DLco) <55% predicted or ratio of % forced vital capacity (FVC) /%DLco >1.6 measured by pulmonary function testing (PFT) (1), were followed annually between 2005 and 2015. The population was stratified into 2 groups: those who developed PH, confirmed by right heart catheterization (RHC), and those who remained Òat riskÓ. Associations of baseline predictors with all-cause mortality and cardio-pulmonary hospitalizations were assessed using Kaplan Meier plots and Cox proportional hazards models adjusted for age, gender, race and disease duration.

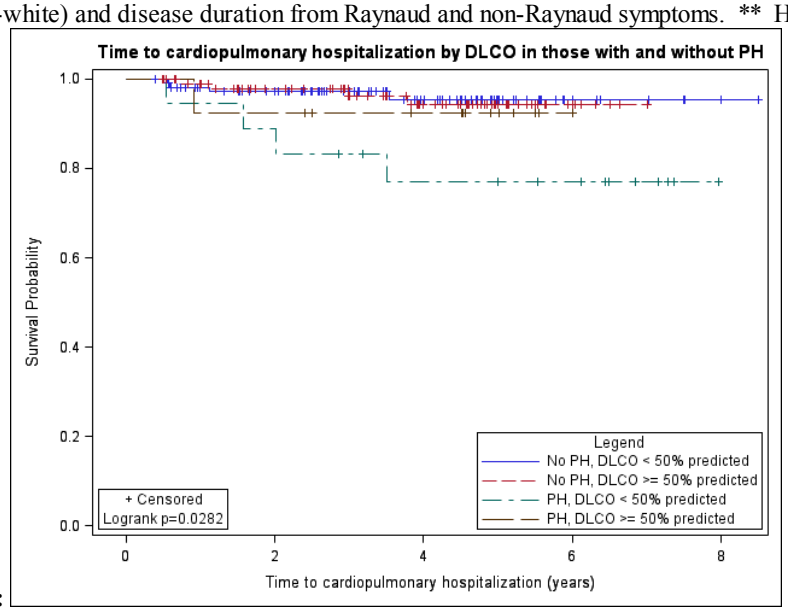
Results: In total, 266 Òat riskÓ SSc patients were followed for a median of 4 years (range 0.4-8.5 years). The median overall survival was 84.6% at 5 years and nearly 80% at 8.5 years. Thirty four patients Òat riskÓ developed PH and 232 remained Òat riskÓ. Though median survival was similar in both groups, 45% deaths in the Òat riskÓ group were due to cardio-pulmonary complications versus 70% in the PH group. In the Òat riskÓ group (Table 1), lower risk of mortality was significantly associated with female sex, higher %DLCO, and no exercise oxygen desaturation, whereas higher mortality risk was significantly associated with anemia, higher UCSD scores, and presence of pericardial effusion. Moreover, higher UCSD scores and presence of pericardial effusion were associated with elevated risk of cardiopulmonary hospitalizations. Stratified analysis showed that PH patients with DLCO<50% had higher risk of cardiopulmonary hospitalizations as compared to other groups (figure 1). No other significant differences were observed in the associations of predictors with cardiopulmonary hospitalization risk comparing PH and Òat-riskÓ groups.Ó .

Conclusion: This is one of the largest prospective study of SSc patients Òat riskÓ for PH. Though survival was better than those with incident PH (2, 3), male sex, low %DLCO, exercise oxygen desaturation and pericardial effusion, were similarly associated with worse outcomes.

Table 1: Predictors of overall mortality and cardiopulmonary hospitalizations in the Òat-riskÓ group, N=232

Overall Mortality				
Predictors	**Crude model**		**Adjusted model***	
	Hazard ratio (95% CI)	***P value***	***Hazard ratio (95% CI)***	***P value***
Female vs. Male	0.23 (0.10, 0.52)	0.0004	0.19 (0.08,0.49)	0.0005
%DLCO**	0.59 (0.47, 0.75)	<0.0001	0.61 (0.47, 0.79)	0.0002
Exercise oxygen desaturation***	0.04 (0.01, 0.14)	<0.001	0.07 (0.02, 0.26)	<0.0001
Pericardial effusion (yes vs. no)	5.79 (2.38, 14.07)	0.0001	7.79 (2.88, 21.05)	<0.0001
Hemoglobin <11.2	2.71 (1.16, 6.35)	0.0216	2.71 (1.02, 7.17)	0.0451
UCSD scores (>2 vs. ²2)	2.25 (0.92, 5.46)	0.0746	2.66 (1.03, 6.89)	0.044
Cardiopulmonary hospitalizations				
	Crude model		**Adjusted model***	
UCSD scores (>2 vs. ²2)	6.93 (0.85,56.36)	0.0701	6.20 (0.74, 52.22)	0.0934
%DLCO**	0.64 (0.43, 0.96)	0.0317	0.63 (0.04, 0.99)	0.0441
Pericardial effusion (yes vs. no)	4.38 (0.08, 23.92)	0.0884	6.77 (1.06, 43.17)	0.0432

* Adjusted for age, gender, race (white versus non-white) and disease duration from Raynaud and non-Raynaud symptoms. ** HRs per 10% increase *** HRs per 40% increase **Figure 1:**



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Abstract Number: 973

Clinical Characterization of Patients with World Health Organization Group 2 Pulmonary Hypertension in the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Cohort

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics I

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Background/Purpose: Pulmonary hypertension (PH) is a leading cause of death in patients (pts) with Systemic Sclerosis (SSc). The World Health Organization (WHO) classifies PH into groups: pulmonary arterial hypertension (PAH, WHO1); PH secondary to left heart dysfunction or isolated post-capillary PH (WHO2); and PH secondary to pulmonary disease (WHO3). The purpose of this study was to describe the clinical characteristics and outcomes of those pts in the PHAROS cohort categorized as WHO2.

Methods: Pts were enrolled in PHAROS within 6 months of the diagnosis of PH. PH was defined by a mean pulmonary artery pressure (mPAP)≥25 mmHg on right heart catheterization (RHC.) Pts were categorized as WHO2 if they had a pulmonary capillary wedge pressure (PCWP)>15 mmHg. Pts with Interstitial Lung Disease (ILD) as defined by a forced vital capacity (FVC) <65% predicted and/or significant fibrosis on chest CT with a normal PCWP were included in WHO3. Clinical expertise from the treating centers was also used to categorize pts best, as individuals may have features of more than one group. Statistical analysis was carried out using Shapiro-Wilk, Kruskal-Wallis, Kaplan-Meier and stratified log-rank tests.

Results: There are 335 pts with PH in the PHAROS database: WHO1 - 215, WHO2 – 57, and WHO3 –63. As shown in table 1, WHO2 pts are different from WHO1 but similar to WHO3 pts in that they are more likely to be African American, to have diffuse SSc and to be scl70 positive. WHO2 pts had lower FVC and FVC%/DLCO% ratio than WHO1 pts. They had normal ejection fractions but significantly larger left atrial measurements. WHO2 patients by definition have higher PCWP, which is associated with a lower pulmonary vascular resistance on RHC. Stratified log-rank tests did not show a significant difference in time to death between the groups, p=0.28. Survivals for 1, 3, and 5 years are shown below in table 2. WHO2 patients had a significantly higher proportion of deaths related to scleroderma than WHO1 (95% v. 70%, p=0.02). The most common cause of death among WHO2 pts was PH (37%) followed by multifactorial causes (26%.) WHO I pts died most commonly from PAH (50%), while the most common cause among WHO III patients was pulmonary fibrosis (46%, p<0.001).

Conclusion: Patients with WHO2 PH have different features that help to separate them from WHO1 pts. Overall survival in the PH pts enrolled in PHAROS has improved over historical values. WHO group classification did not affect survival in these incident patients. However, pts with WHO2 PH were more likely to die from scleroderma-related causes.

Table 1. Demographics and Clinical Characteristics

Variable	WHO 1 (n=215)	WHO 2 (n=57)	WHO 3 (n=63)	p-value (overall)	p-value (1 v 2)	p-value (1 v 3)	p-value (2 v 3)
Age, yr – mean ±SD	**60.3±10.5**	**56.9±11.8**	**52.6±11.1**	**<.001**	**0.039**	**<.001**	**0.045**
Female – n (%)	177 (84%)	42 (76%)	46 (77%)	0.265	0.193	0.196	0.969
Race – n (%)				**0.012**	**0.022**	**0.022**	0.519
Caucasian	**170 (81%)**	**34 (62%)**	**35 (59%)**				
Hispanic	**11 (5%)**	**3 (5%)**	**6 (10%)**				
Black	**24 (11%)**	**15 (27%)**	**15 (25%)**				
Antibody– n (%)				**<.001**	**0.008**	**<.001**	0.067
Negative	**9 (4%)**	**6 (11%)**	**4 (6%)**				
Anticentromere	**82 (39%)**	**9 (17%)**	**4 (6%)**				
Scl 70	**12 (6%)**	**9 (17%)**	**23 (37%)**				
U1RNP	**8 (4%)**	**2 (4%)**	**3 (5%)**				
Isolated nucleolar pattern	**51 (24%)**	**15 (28%)**	**12 (19%)**				
Polymerase III	**9 (4%)**	**4 (7%)**	**1 (2%)**				
Mixed or other	**39 (19%)**	**9 (17%)**	**15 (24%)**				
Scleroderma subtype– n (%)				**<.001**	**0.001**	**<.001**	0.536
Limited	**152 (71%)**	**24 (44%)**	**27 (44%)**				
Diffuse	**55 (26%)**	**27 (50%)**	**28 (45%)**				
Other	**8 (4%)**	**3 (6%)**	**7 (11%)**				
Disease duration, yr	8.2 [3.4, 16.0]	6.8 [3.5, 10.4]	6.8 [3.6, 12.4]	0.305	0.146	0.410	0.625
Echo parameters							
sPAP, mmHg – median [IQR]	**55.5 [41.0, 72.0]**	**50.0 [39.5, 63.0]**	**48.5 [40.0, 60.0]**	**0.028**	0.072	**0.021**	0.873
Jet velocity – median [IQR]	3.5 [3.0, 4.1]	3.2 [2.7, 3.7]	3.1 [2.9, 3.9]	0.101	0.067	0.148	0.676
Ejection fraction, % - – median [IQR]	60.0 [55.0, 65.0]	60.0 [55.0, 65.0]	60.0 [57.5, 65.0]	0.840	0.588	0.761	0.765
Left atrial measurement, cm - – median [IQR]	**3.7 [3.2, 4.2]**	**4.1 [3.5, 4.6]**	**3.5 [3.1, 3.9]**	**0.013**	**0.037**	0.081	**0.005**
Pericardial effusion present– n (%)	**70 (38%)**	16 (33%)	**13 (23%)**	0.129	0.564	**0.044**	0.251
PFT parameters							
FVC % predicted – median [IQR]	**79.2 [71.1, 90.0]**	**72.0 [55.2, 80.5]**	**49.9 [43.1, 58.6]**	**<.001**	**<.001**	**<.001**	**<.001**
DLCO % predicted – median [IQR]	**38.8 [31.9, 51.8]**	**40.6 [33.2, 51.1]**	**28.2 [22.9, 36.4]**	**<.001**	0.506	**<.001**	**<.001**
TLC % predicted – median [IQR]	**81.4 [68.8, 91.8]**	**73.9 [62.6, 92.8]**	**53.9 [47.6, 60.8]**	**<.001**	0.080	**<.001**	**<.001**
FVC:DLCO ratio - – median [IQR]	**2.1 [1.6, 2.6]**	**1.7 [1.4, 2.2]**	**1.9 [1.4, 2.3]**	**0.002**	**<.001**	0.056	0.210
RHC Parameters							
sPAP, mmHg – median [IQR]	**55.0 [45.0, 72.0]**	**46.0 [40.0, 56.0]**	**47.0 [43.0, 64.0]**	**0.003**	**0.003**	**0.026**	0.470
mPAP, mmHg – median [IQR]	**35.0 [29.0, 43.0]**	**32.0 [28.0, 38.0]**	**30.0 [26.0, 38.0]**	**0.008**	0.063	**0.005**	0.347

PCW, mmHg - – median [IQR]	**10.0 [8.0, 12.0]**	**19.0 [17.0, 23.0]**	**10.0 [7.0, 14.0]**	**<.001**	**<.001**	0.760	**<.001**
Cardiac Output, L/min – median [IQR]	5.0 [3.9, 6.1]	5.6 [4.3, 6.5]	5.0 [4.6, 5.8]	0.201	0.088	0.503	0.248
Pulmonary Vascular Resistance, dynes-sec-cm-5 – median [IQR]	**370 [263, 658]**	**180 [138, 335]**	**322 [224, 463]**	**<.001**	**<.001**	**0.021**	**<.001**

Table 2. 1-, 3- and 5-year survival estimates by WHO Group

WHO Group	n deaths / N (%)	1-year survival estimate (95% CI)	3-year survival estimate (95% CI)	5-year survival estimate (95% CI)
1	86/215 (40%)	92.5% (88.1% - 95.3%)	73.8% (67.0% - 79.5%)	58.1% (50.0% - 65.4%)
2	19/57 (33%)	86.0% (73.9% - 92.7%)	67.5% (52.8% - 78.6%)	64.5% (49.1% - 76.3%)
3	26/63 (41%)	85.6% (74.1% - 92.2%)	68.4% (54.4% - 78.9%)	61.1% (46.3% - 73.0%)

Disclosure: J. K. Gordon, None; **J. Szymonifka**, None; **M. R. Lammi**, None; **V. D. Steen**, None.

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Abstract Number: 974

Diffuse Scleroderma, Male Sex, and Myopathy Are Associated with Severe Gastrointestinal Dysmotility in Scleroderma

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Background/Purpose: Despite the fact that up to 90% of scleroderma (SSc) patients are affected by gastrointestinal (GI) dysmotility, features associated with severe GI disease are not well-defined. We sought to identify such features by studying a large cohort of SSc patients requiring parenteral nutrition (TPN) for severe GI dysmotility and SSc controls with mild or no GI symptoms.

Methods: Patients were selected from the Johns Hopkins Scleroderma Center cohort database (clinic visits from 1991-2015) and met either 1980 American College of Rheumatology criteria or at least three of five features of the CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, telangiectasia) syndrome for SSc. All patients with SSc who required TPN for SSc GI dysmotility, and all patients with SSc and mild or no GI symptoms (modified GI Medsger score of 0 or 1) were included in this study. Demographic and clinical data were obtained on each patient at the time of the clinical visit when they were first assigned their maximum GI score. Myopathy was defined by the presence of abnormal muscle enzymes (CK, aldolase), an irritable myopathy on EMG, and/or muscle biopsy findings associated with SSc. In the cross-sectional analysis, associations between dichotomous variables were assessed using Chi-square or

Fischer's exact tests. T-tests were applied to parametric data to evaluate for significant differences in the means of continuous variables between two groups. Univariate logistic regression analyses further explored associations between disease characteristics and severe GI dysmotility. Significant findings from the univariate analyses and potential confounders were then included in a multivariable model to determine whether associations remained significant after adjusting for relevant covariates.

Results: There were 59 TPN dependent SSc patients, and 1,744 SSc patients with mild or no GI symptoms. 1,456 (81%) of patients were female and 347 (19%) of patients were male. In the univariate analysis, we identified male sex (OR 2.2, CI 1.28, 3.86; p = 0.005), diffuse cutaneous disease (OR 2.62, CI 1.53, 4.45; p = <0.001), and black race (OR 2.5, CI 1.42, 4.39; p = 0.001), as features associated with severe GI dysmotility in SSc. Myopathy was also found to associate with severe SSc GI dysmotility (OR 4.5, CI 2.61, 7.79; p = <0.001). After adjusting for potential confounders (age, disease duration, and history of diabetes), male gender (OR 2.6, CI 1.17, 5.90; p=0.02), diffuse disease (OR 2.79, CI 1.20, 6.47; p = 0.017), and myopathy (OR 3.6, CI 1.54, 8.33; p = 0.003), all remained significantly associated with severe GI dysmotility.

Conclusion: We utilized the largest reported cohort to date of TPN-dependent SSc patients to define phenotypic features associated with severe GI dysmotility. Our results demonstrate that male sex, diffuse cutaneous disease, and myopathy are significantly associated with severe SSc GI dysmotility. As myopathy is a complication associated with severe SSc GI dysmotility, defining autoantigens common among smooth and skeletal muscle may provide insight into disease pathogenesis.

Disclosure: Z. McMahan, Scleroderma Research Foundation, 2,Jerome L. Greene Foundation, 2; **L. Casciola-Rosen**, Scleroderma Research Foundation, 2; **F. M. Wigley**, CSL Behring, 2,Allergan, Inc., 2,Cytori, 2,Corbus, 2,Boehringer Ingelheim, 2.

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Abstract Number: 975

Maintenance Therapy Improves Long-Term Outcomes in Patients with Primary Angiitis of the Central Nervous System

Hubert de Boysson[1], Caroline Arquizan[2], Grégoire Boulouis[3], Nicolas Gaillard[4], Alexis Regent[5], Antoine Néel[6], Olivier Detante[7], Emmanuel Touzé[8], Achille Aouba[1], Boris Bienvenu[9], Loïc Guillevin[10], Olivier Naggara[3], Mathieu Zuber[11] and Christian Pagnoux[12], [1]Department of Internal Medicine, Caen University Hospital, Caen, France, [2]Department of Neurology, Hôpital Gui de Chauliac, Université Montpellier, Montpellier, France, [3]Department of Neuroradiology, Hôpital Sainte-Anne, Paris, France, [4]Department of Neurology, CH Perpignan, Perpignan, France, [5]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [6]Department of Internal Medicine, Nantes University Hospital, Nantes, France, [7]Department of Neurology, Centre Hospitalier Universitaire de Grenoble, Grenoble, France, [8]Department of Neurology, Cane University Hospital, CAEN, France, [9]Caen University Hospital, Caen, France, [10]Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, Paris, France, [11]Department of Neurology, Groupe Hospitalier Saint-Joseph, Université Paris Descartes, Paris, France, [12]Division of Rheumatology, Mount Sinai Hospital, University Health Network, University of Toronto, Toronto, Canada, Toronto, ON, Canada

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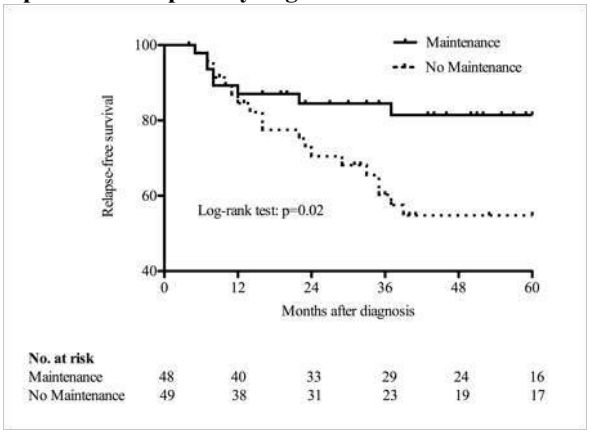
Background/Purpose: To evaluate the effect of maintenance therapy on the outcomes of adult patients with primary angiitis of the central nervous system (PACNS).

Methods: We analyzed long-term outcomes (relapse, survival and functional status) of adult patients enrolled in the French multicenter cohort of PACNS who achieved remission under induction treatment and with at least 12 months of follow-up (or who died earlier after having achieved remission), according to whether or not they received maintenance therapy. Good functional outcome was defined as a modified Rankin scale (MRS) inferior or equal to 2 at last news.

Results: Ninety-seven patients [46 (47%) female, median age: 46 [18-78] years-old at diagnosis] were included and followed for a median of 55 [5-198] months. Induction treatment consisted of glucocorticoids (GC) in 95 (98%) patients, combined with an immunosuppressant in 80 (83%), mostly cyclophosphamide (CYC, median of 6 [2-12] pulses for 6 [2-10] months). Maintenance therapy

was prescribed in 48 (49%) patients, including 42 with previous CYC treatment. Azathioprine (AZA), mycophenolate mofetil (MMF) and methotrexate (MTX) were chosen in 38, 4 and 6 patients, respectively. Maintenance therapy was started 4 [2-18] months after GC initiation and was prescribed for a median duration of 24 [6-72] months. Thirty-two (33%) patients relapsed, 4 of whom died. At last follow-up, patients who had received maintenance therapy, compared to those who did not, had better median MRS (1 [0-6] vs. 3 [0-6], p<0.0001) and had less disease relapse (10 (22%) vs. 22 (45%), p=0.01; Figure 1). At the time of relapse, 6/10 of the former patients had stopped maintenance therapy (3-6 months before). In multivariate analysis, maintenance therapy was the strongest predictor of good functional outcomes (OR = 8.17 [3.03—24.91], p<0.0001), and had a protective effect against relapse (OR=0.23 [0.07—0.67], p=0.01).

Conclusion : The results of this long-term follow-up study suggest that maintenance therapy in patients with PACNS improves functional outcomes and lowers relapse rate. It should thus be prescribed after induction treatment. **Figure 1**. **Kaplan-Meier curves of relapse-free survival in patients with primary angiitis of the central nervous system, according to whether or not they received maintenance therapy.**



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Abstract Number: 976

Efficacy and Safety of Tocilizumab in Patients with Refractory Takayasu Arteritis: Results from a Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial in Japan

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Background/Purpose: Glucocorticoids (GC) are the mainstay of treatment options for patients (pts) with Takayasu arteritis (TAK); however, long-term GC therapy is associated with adverse events (AEs). TAK pts have elevated IL-6 levels, which correlates with TAK disease activity (*Rheumatology*. 2006;45:545-48). Tocilizumab (TCZ), a humanized anti–IL-6 receptor antibody, was investigated for the treatment of relapsing TAK.

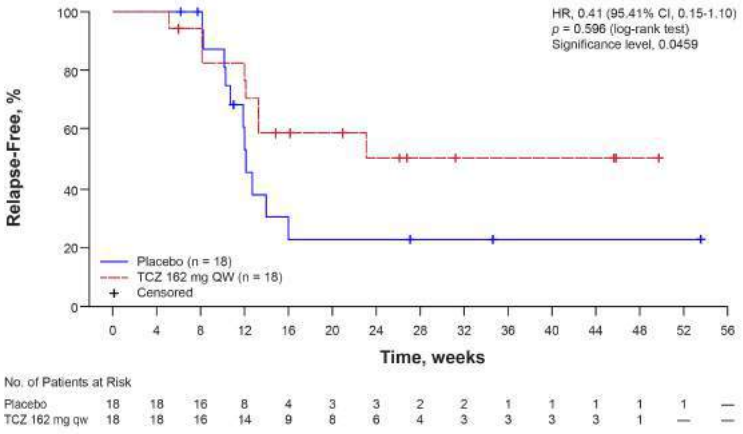
Methods: Pts ≥12 y with TAK (*Circ J*. 2011;75:474-503) receiving GC (≥0.2 mg/kg/d prednisolone equivalent) who had relapsed ≤12

weeks (wks) before enrollment were randomly assigned 1:1 to subcutaneous (SC) TCZ 162 mg or placebo (PBO) every wk (QW). Pts had to be receiving a stable GC dose at ≥2× dose at relapse and to be in remission for 1 wk before randomization. During the double-blind (DB) period, which lasted until relapse occurred in 19 pts, background GC were tapered by 10%/wk from wk 4, which is more rapid than in a general clinical setting. The primary end point was time to first relapse of TAK per protocol-defined criteria in the intent-to-treat (ITT) population estimated with the Kaplan-Meier analysis method and analyzed with the log-rank test stratified by age (<18 y, 18–64 y, ≥65 y). Time to relapse by Kerr's definition (*Ann Intern Med.* 1994;120:919-29) was a secondary end point.

Results: The ITT and safety populations included 18 TCZ pts and 18 PBO pts; median disease duration was 3.33 y and 2.89 y, respectively; mean ± SD GC dose at randomization was 0.57 ± 0.19 (TCZ) and 0.52 ± 0.16 (PBO) mg/kg/d; 38.9% of TCZ and 72.2% of PBO pts were HLA-B52 positive; 86.1% of pts were female. The per-protocol (PP) population included 16 TCZ and 17 PBO pts. No pts withdrew during the DB period. In the ITT population, 8 (44.4%) TCZ and 11 (61.1%) PBO pts relapsed. Estimated relapse-free rates at wk 24 were 50.6% and 22.9%, respectively, no statistical difference of time to first relapse between groups was seen (Figure; hazard ratio [HR], 0.41 [95.41% CI, 0.15-1.10]; $p = 0.0596$). Results were the same with Kerr's definition. In the PP population, for relapse according to protocol-defined criteria, HR was 0.34 and $p = 0.0345$ (95.41% CI, 0.11-1.00), favoring TCZ. In addition, TCZ showed favorable trends in each sign of relapse, including objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular lesions, and ischemic symptoms accompanied by organ lesions (ITT population). AEs were reported in 14 (77.8%) TCZ and 11 (61.1%) PBO pts, and serious AEs were reported in 1 pt and 2 pts. Infections were the most frequent AEs. No pts died.

Conclusion: There was a trend toward relapse suppression favoring TCZ, though the primary end point was not met. The safety of TCZ was consistent with the current safety profile for TCZ in RA/JIA. TCZ may be a promising treatment option for rapidly tapering GC in TAK pts.

Figure. Time to first relapse[a] (Kaplan-Meier analysis; ITT population)



[a]Defined as ≥2 of 5 signs of relapse present, including objective systemic symptoms, subjective systemic symptoms, elevated inflammation markers, vascular lesions, ischemic symptoms accompanied by organ lesions. Relapse was also considered to have occurred if there was severe aortic valve incompetence accompanied by symptoms of cardiac failure or if there were ischemic symptoms accompanied by organ lesions ≥grade 2 or ≥grade 3 for myocardial infarction. TAK had to be medically confirmed as the cause of relapse by eliminating causes other than TAK on ≥2 consecutive assessments.

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Abstract Number: 977

Tocilizumab As an Add-on Therapy to Glucocorticoids during the First 3 Months of Treatment of Giant Cell Arteritis: Results of a French Multicenter Prospective Open-Label Study

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Background/Purpose: Giant cell arteritis (GCA) is a large-vessel vasculitis usually treated with glucocorticoids (GC). GC are effective but responsible for substantial morbidity and mortality. Tocilizumab (TCZ) is a humanized monoclonal antibody against interleukin-6 receptor (IL-6R) that has recently been shown to be effective for the induction and maintenance of remission in GCA when used monthly for 1 year (1). However, data concerning the course of GCA after TCZ discontinuation are lacking and the optimal duration of this expensive immunosuppressive therapy in GCA is unknown. Our study therefore aimed to evaluate TCZ as an add-on therapy to GC during the first 3 months of GCA treatment (2).

Methods: Patients affected by GCA, as defined by the 1990 ACR criteria and a positive temporal artery biopsy (TAB) or CT-scan or PET-scan-proven aortitis were included in this French multicenter prospective open-label study. GC were started at 0.7 mg/Kg/day and then tapered according to a standardized protocol (2) with the aim to reach 0.1 mg/Kg/day at week 24 (W24). All patients received 4 infusions of TCZ (8 mg/Kg/4 weeks) after inclusion (W0, W4, W8 and W12). The primary endpoint was the percentage of patients in remission with a dose of prednisone ≤0.1 mg/Kg/day at W26. Patients were followed for 26 weeks and data about relapses and adverse events were prospectively recorded. Quantitative data are presented as mean±SD. This trial was registered with ClinicalTrials.gov, number NCT01910038.

Results: Twenty patients (15 women, 19 new-onset GCA) were included in this study between March 2014 and June 2015. Age at diagnosis was 72.6±7.6 years. TAB was positive in 17/19 (90%) patients and 7/16 (44%) had aortitis. Remission was obtained in all the cases, at W4 for 18/20 (90%) patients and at W8 and W12 for the two others. At W26 (14 weeks after last TCZ infusion), 5 patients (25%) had relapsed, 24.5±2.3 weeks after inclusion and at a mean dose of prednisone of 6.4±2.1 mg/day. One of these relapses was limited to a slight increase in the CRP (10 mg/L) and fibrinogen (4.6 g/L) level at W24; GC were briefly increased but the primary endpoint was reached at W26 without subsequent relapse. One patient died suddenly at W26 and was not considered to have reached the primary endpoint in the final analysis. Finally, 15 (75%) patients met the primary endpoint at W26, which is higher than previously reported with the same GC tapering i.e. 50% in the placebo group from the HECTHOR trial (2). Prednisone cumulative dose at W26 was 3,524±811 mg. After 26 weeks, 60 adverse events were reported in 19 patients and 20 were considered directly related to the study, the most common being hypercholesterolemia (n=8), infections (n=7 [3 before week 16]), and hepatic cytolysis (n=1).

Conclusion: Four TCZ infusions as an add-on therapy to GC for GCA treatment allowed rapid GC tapering and persistent remission with a low dose of GC (0.1 mg/Kg/day) after 6 months of follow-up. However, relapses can occur after TCZ discontinuation and further studies are needed to identify predictive factor of relapse after TCZ discontinuation. **REFERENCES** 1. Villiger PM et al. Lancet 2016; 387:1921-7 2. Seror R et al. Ann Rheum Dis 2014; 73:2074-81.

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A Randomized Clinical Trial of CCX168, an Orally Administered C5aR Inhibitor for Treatment of Patients with ANCA-Associated Vasculitis

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Background/Purpose: Complement 5a (C5a) is involved in the pathogenesis of anti-neutrophil cytoplasm antibody (ANCA)-associated vasculitis (AAV). CCX168 is an orally administered, small molecule selective inhibitor of the C5a receptor (C5aR). It was shown to be effective and safe in a randomized clinical trial (CLEAR) in patients with AAV, and safely substituted for treatment with prednisone without a loss of efficacy. In the current trial (named CLASSIC), conducted in the USA and Canada, CCX168 was added to full-dose glucocorticoids plus either rituximab (RTX) or cyclophosphamide (CYC) to investigate the safety profile of CCX168 in addition to standard of care (SOC) treatment.

Methods: Patients with new or relapsing AAV and PR3 or MPO ANCA were eligible. Patients were randomized into one of three groups: i. SOC+placebo (N=13), ii. SOC+10 mg CCX168 twice daily (N=13), or iii. SOC+30 mg CCX168 twice daily (N=16) and were treated for 12 weeks with CCX168/placebo. Two patients, one in each of the CCX168 groups, were excluded from the intention to treat analysis but included in the safety analysis: one did not receive any study drug and one received only 2 weeks of study drug and thus did not have any on-treatment disease activity assessment. All patients received either RTX (375 mg/m^2 IV weekly for 4 weeks) or CYC (15 mg/kg IV up to 1.2 g, on Days 1, 15, 29, 57, and 85) at investigators' discretion. The starting dose of prednisone for all patients was 60 mg/day, tapered to 10 mg/day by week 12. Since CCX168 was added to full-dose glucocorticoid SOC treatment, the primary endpoint was safety measured by comparison of the incidence of adverse events (AEs) among the groups. Efficacy was mainly assessed based on clinical response, defined as a decrease of Birmingham Vasculitis Activity Score (BVAS) from baseline to week 12 of at least 50%, and no worsening in any body system; however, the study was not powered to detect differences among groups.

Results: Forty-two patients with AAV were enrolled. Presenting features were typical of AAV and well balanced across groups. Mean ±SD age: 58±13 years; female/male: 55%/45%; newly-diagnosed/relapsing AAV: 64%/36%; PR3/MPO-ANCA: 50%/50%; BVAS: 15.3±6.6, eGFR: 59±27 mL/min/1.73 m^2; RTX/CYC use: 93%/7%. A total of 7 patients had serious adverse events, 2 of 13 patients in the SOC+placebo group, 2 of 13 in the SOC+10 mg CCX168 group, and 3 of 16 in the SOC+30 mg CCX168 group. These included 4 infection-related SAEs: toe gangrene (1), cellulitis and skin abscesses (1), and sepsis and urinary tract infection (1 each) in the three groups, respectively. Total AEs occurred in 13, 11, and 15 patients in the three groups, respectively. Response at week 12, based on BVAS, was achieved in 10, 11, and 12 patients, respectively, in each group. Early remission (BVAS = 0 at week 4) was achieved in 2, 1, and 5 patients, respectively. eGFR mean change from baseline to week 12 was 0.8, -0.8, and 3.1 mL/min/1.73 m^2, respectively, in each group.

Conclusion: CCX168 was found to be safe when added to SOC high-dose glucocorticoids and either RTX or CYC. Based on these results and the prior CLEAR trial, 30 mg CCX168 twice daily appears to be an appropriate and safe dose for further study in patients with AAV.

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A Randomized Double-Blind Trial of Abatacept and Glucocorticoids for the Treatment

of Takayasu's Arteritis

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Background/Purpose: Takayasu's arteritis (TAK) is a large-vessel primary systemic vasculitis that affects the aorta, its branches, and the pulmonary arteries. Despite treatment with glucocorticoids, relapse with treatment- and disease-related morbidity occurs in a high percentage of patients. Several other immunosuppressive agents have been used to treat TAK, but their use is based solely on open-label experience. T-cell activation has been implicated in the pathophysiology of TAK. A multi-center, randomized, double-blind, placebo-controlled, withdrawal design trial was conducted to examine the efficacy and safety of treatment with abatacept (CTLA4-Ig) combined with prednisone in patients with TAK.

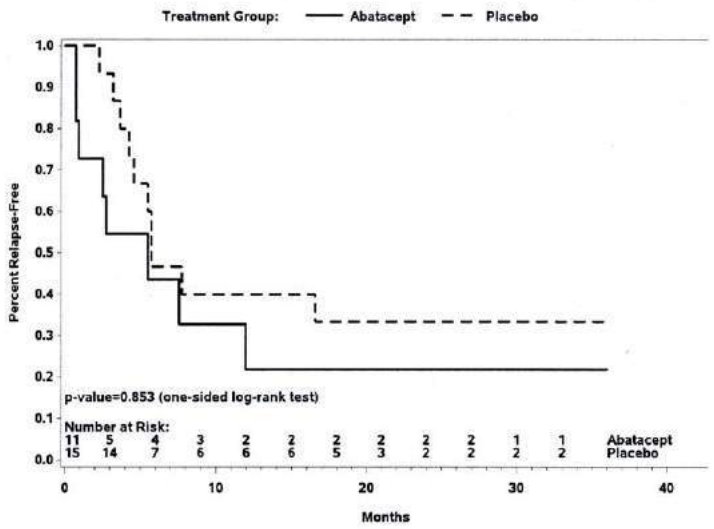
Methods: Patients with newly-diagnosed or relapsing TAK were eligible for the trial. All patients were treated with abatacept 10 mg/kg IV on days 1, 15, 29, and week 8, together with prednisone. At week 12 patients in remission underwent a double-blinded randomization to continue monthly abatacept or be switched to placebo together with a standardized prednisone taper reaching discontinuation at week 28. Patients remained on their randomized assignment until meeting criteria for early termination or until the common closeout date, 12 months after enrollment of the last patient. The primary endpoint was duration of remission (relapse-free survival, RFS). A planned sample size of 30 patients was based on detecting a 30% improvement in RFS utilizing a one-sided alpha = 0.1. Kaplan-Meier curves were constructed and differences in treatment arms compared using the log-rank test in an intent-to-treat analysis.

Results: 34 eligible patients received study drug with 26 reaching the week 12 randomization. Disease characteristics of the 26 randomized patients are outlined in Table 1. The RFS at 12 months was estimated to be 22% for those receiving abatacept and 40% for those receiving placebo (p= 0.853), Figure 1. Treatment with abatacept in patients with TAK enrolled in this study was not associated with a longer median duration of remission (abatacept 5.5 months, placebo 5.7 months). 114 adverse events occurred in 28 patients including 23 serious adverse events in 15 patients. There was no difference in the frequency or severity of adverse events between treatment arms, including the rate of infection.

Conclusion: In this study, which was the first randomized, double-blind trial conducted in TAK, the addition of abatacept to prednisone did not reduce the risk of relapse in patients with TAK. Concurrent abatacept was not associated with a higher rate of toxicity compared to prednisone alone.

Table 1. Baseline characteristics of the study population with Takayasu's arteritis			
	Abatacept N=11	Placebo N=15	
	N (%)	N (%)	p-value
Patient demographics			
Age at enrollment (years), median (range)	30.2 (18.9-58.9)	28.6 (19.5-57.0)	0.92
Age at diagnosis (years), median (range)	25.1 (16.9-52.2)	28.5 (15.9-56.9)	0.47
Sex			
Female	9 (81.8%)	13 (86.7%)	1.00
Male	2 (18.2%)	2 (13.3%)	-
Diagnosis category at enrollment			
Newly diagnosed	0 (0%)	4 (26.7%)	0.11
Relapsing	11 (100%)	11 (73.3%)	-
Disease duration (years), median (range)	5.1 (0.4-19.0)	0.91 (0-17.0)	0.10
Race			
Asian	1 (9.1%)	3 (20%)	0.35
Black or African-American	1 (9.1%)	0 (0%)	-
Unknown/not reported	1 (9.1%)	0 (0%)	-
Caucasian	8 (72.7%)	12 (80%)	-
Active disease characteristics at enrollment			
Sustained fever of > 38° C for > 1 week	0 (0%)	1 (6.7%)	1.00
Vascular pain or tenderness	2 (18.2%)	3 (20%)	1.00
Headache	2 (18.2%)	3 (20%)	1.00
Ischemic retinopathy or visual loss	0 (0%)	1 (6.7%)	1.00
Tongue/jaw pain or claudication	1 (9.1%)	1 (6.7%)	1.00
Extremity claudication	5 (45.5%)	9 (60%)	0.46
Musculoskeletal symptoms	4 (36.4%)	5 (33.3%)	1.00
Malaise/fatigue + ESR > 40 mm/hour	6 (54.6%)	6 (40%)	0.46
New vascular stenosis or aneurysm	4 (36.4%)	7 (46.7%)	0.70
Other features attributed to TAK	1 (9.1%)	3 (20%)	0.61
Prior non-glucocorticoid immunosuppressive treatment			
Adalimumab	2 (18.2%)	2 (13.3%)	1.00
Azathioprine	2 (18.2%)	3 (20%)	1.00
Cyclosporine	1 (9.1%)	1 (6.7%)	1.00
Cyclophosphamide-daily	0 (0%)	1 (6.7%)	1.00
Cyclophosphamide-intravenous	1 (9.1%)	0 (0%)	0.42
Etanercept	0 (0%)	2 (13.3%)	0.49
Infliximab	4 (36.4%)	1 (6.7%)	0.13
Leflunomide	1 (9.1%)	0 (0%)	0.42
Methotrexate	9 (81.8%)	8 (53.3%)	0.22
Mycophenolate	2 (18.2%)	2 (13.3%)	1.00
Tacrolimus	0 (0%)	1 (6.7%)	1.00
ESR: erythrocyte sedimentation rate; TAK: Takayasu's arteritis			

Figure 1. Relapse-free survival comparing treatment with abatacept to placebo in patients with Takayasu's arteritis



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5,Boehringer Ingelheim, 5,Acerta, 5,CVS/Caremark, 5,Smith Kline Beecham, 5; **M. Weisman**, Bristol-Myers Squibb, 2; **C. L. Koening**, Bristol-Myers Squibb, 2; **A. G. Sreih**, Alexion Pharmaceuticals, Inc., 1,Bristol-Myers Squibb, 2,Celgene, 2,Chemocentryx, 2,Roche Pharmaceuticals, 2,GlaxoSmithKline, 2,Kropp and Partners, 5; **R. F. Spiera**, GlaxoSmithKline, 2,Roche Pharmaceuticals, 2,Boehringer Ingelheim, 2,PRISM, 2,Cytori, 2,Corbus Pharmaceuticals, 2,GlaxoSmithKline, 5,Roche Pharmaceuticals, 5,Boehringer Ingelheim, 5,Bristol-Myers Squibb, 2; **C. A. McAlear**, None; **K. J. Warrington**, GlaxoSmithKline, 2; **C. Pagnoux**, Chemocentryx, 5,Sanofi-Aventis Pharmaceutical, 5,Hoffmann-La Roche, Inc., 8; **K. Maksimowicz-McKinnon**, None; **L. J. Forbess**, None; **G. S. Hoffman**, None; **R. Borchin**, None; **J. Krischer**, Bristol-Myers Squibb, 2; **P. A. Merkel**, Bristol Myers Squibb, 2,CaridianBCT, 2,Celgene, 2,Chemocentryx, 2,Genentech/Roche, 2,GlaxoSmithKline, 2,Kypha, 2,Bristol-Myers Squibb, 5,Chemocentryx, 5,Genentech/Roche, 5,GlaxoSmithKline, 5,PrinicipioBio, 5,Auven, 5,Proteon Therapeutics, 5.

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Short-Course Glucocorticoids in ANCA-Associated Vasculitis: A Proof of Concept Study

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Background/Purpose: Despite therapeutic advances in ANCA-associated vasculitis (AAV), patients continue to be exposed to considerable treatment morbidity from long-term glucocorticoid (GC) use. The optimal duration of GC treatment has not been studied in AAV. We conducted an open-label, proof of concept study investigating whether an 8-week GC taper, in combination with rituximab (RTX), would be sufficient to control AAV in a subset of patients who have a more favorable prognosis. Such an approach would reduce the cumulative GC dose by at least 45%, thereby diminishing the potential for GC toxicity.

Methods: Patients with granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) who had newly diagnosed or relapsing disease with a BVAS/WG of 3 or more were eligible to participate. Patients with diffuse alveolar hemorrhage requiring intubation, MPO-ANCA-positive patients with severe renal involvement (GFR < 30 ml/min/1.73m^2) and PR3-ANCA-positive patients with glomerulonephritis were excluded. Subjects were treated with RTX 375mg/m^2 weekly for four weeks and an 8 week GC taper (60mg x 2 weeks, 40mg x 2 weeks, 30mg x 1 week, 20mg x 1 week, 10mg x 1 week and 5mg x 1 week then off). Patients on chronic GCs prior to trial entry were permitted to taper to their pre-relapse dose. The primary outcome was no disease activity (BVAS/WG = 0) and being off prednisone (or at baseline dose for those on chronic GCs prior to trial entry) at 6 months.

Results: Eighteen patients have enrolled and 14 have completed the study to date (Table 1). The mean age was 59.7 and 66% were female. Sixty-seven percent had GPA, 39% were PR3-ANCA-positive and 44% had relapsing disease. Mean BVAS/WG at study entry was 5.6. Nine of fourteen patients (64%) successfully reached the primary endpoint. Of the 5 patients who failed the primary endpoint, 2 had flares of glomerulonephritis, one had relapse of diffuse alveolar hemorrhage, one of mononeuritis multiplex and one had recurrent meningitis. All of these patients reached remission after treatment according to best medical judgment. There were no relapses of clinical features associated with granulomatous inflammation. Vasculitis damage index at study entry was 0.9 and 1.5 at the completion of the study.

Conclusion : A 2-month course of prednisone in combination with rituximab resulted in 64% of patients reaching and maintaining complete remission at 6 months, similar to rates reported in the Rituximab in ANCA-associated Vasculitis (RAVE) trial. Relapses were primarily due to manifestations associated with vasculitis rather than granulomatous inflammation. Further study of this protocol in larger numbers of patients should be considered.

Table – Demographic characteristics and organ involvement at baseline

Characteristic	N (%)
Age (years)	59.7
Sex (female)	12 (67%)
GPA	12 (67%)
MPA	6 (33%)
PR3-ANCA	7 (39)
MPO-ANCA	9 (50%)
ANCA negative	2 (11%)
Relapsing disease	8 (44%)
BVAS/WG at baseline	5.7
Organs involved	
General	9 (50%)
Cutaneous	7 (39%)
Mucous membranes/eyes	2 (11%)
Ear, nose, throat	10 (56%)
Pulmonary	11 (61%)
Renal	4 (22%)
Neurologic	5 (28%)
Other	2 (11%)

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Effectiveness of a Six-Week Hand Osteoarthritis Program in a Primary Care Setting

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Background/Purpose: Hand Osteoarthritis (hand OA) is highly prevalent among women and men aged 55 and older. It often causes pain, reduced range of motion and grip strength which, in turn, reduce hand function and cause activity limitations in daily life. Effects of structured hand OA programs in primary care settings, including both patient education and exercise, are sparsely reported. The aim of the study is to evaluate the effectiveness of a six-week hand OA primary care program on hand function and activity limitation in individuals with hand OA.

Methods: Individuals with diagnosed hand OA that began a hand OA program at a primary care unit in southeastern Sweden were enrolled consecutively between 2008 and 2011. In total 64 individuals agreed to participate, of which 15 did not fulfill the program. The remaining 49 (92% female, mean age 69, range 47-89 years) performed the hand OA program starting with a theoretical part with two lectures of 1.5 hours each. The program continued with group based hand exercises including paraffin treatment twice weekly during the six-week period. Outcome measures were the Grip Ability Test (GAT), the Signal of Functional Impairment (SOFI) and the JAMAR (grip strength). To assess activity limitation the Patient Specific Functional Scale (PSFS) and the Quick Disabilities of the Arm, Shoulders and Hand (Quick-DASH) were used. The evaluations were performed at baseline, after three months and after one year by occupational therapists trained in

using the study specific outcome measures. The study was conducted in accordance with the ethical principles of the Helsinki declaration.

Results: The participants and the drop-outs were comparable with the exception that patients in the drop-out group were working to a higher extent (p=0.005). The comparisons based on non-parametric analyses showed that the participants' hand function, concerning grip strength (JAMAR), range of motion (SOFI - hand) and grip ability (GAT) improved significantly from baseline to the three-month follow-up (p<0.001- 0.011), as well as when comparing baseline with the one year follow-up (p<0.001-0.004). Activity limitations (PSFS and Quick-DASH) also decreased during the same periods (0.001- 0.008 and 0.001- 0.013 respectively).

Conclusion: The result indicates that a structured hand OA program, including both patient education and hand exercises, is a useful non-pharmacological group treatment in primary care as it improves hand function and activity limitation with a retentive effect up to one year after completion of the intervention.

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High Financial Strain, but Not Poverty or Lower Education, Increases the Risk of Incident Depression in Systemic Lupus Erythematosus (SLE)

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Session Time: 2:30PM-4:00PM

Background/Purpose:

Depression is common in women with SLE. Low socioeconomic status (SES) has been associated with prevalent depression, but the longitudinal relationship between SES and onset of depression has not been examined. We assessed poverty, income, education, and subjective financial strain (FS) as predictors of incident depression in the UCSF Lupus Outcomes Study (LOS).

Methods: Data were from the 2010-2015 cycles of the LOS, obtained through annual structured phone interviews of individuals with confirmed SLE. Depression was assessed with the Center for Epidemiological Studies Depression Scale (CESD), using a validated cutoff value (≥ 23) for major depressive disorder. Women interviewed in ≥ two consecutive cycles, with scores < 23 in the first cycle (T1), were included. Participants' level of FS was classified as High, Moderate, or None based on responses to 3 questions on current and anticipated FS (Table 1). Generalized estimating equations were used to assess the impact of educational attainment, poverty (≤ or > 125% of federal poverty level), income, and FS at T1 on the risk of incident depression the next year (T2), while adjusting for age, race, marital status, current smoking, obesity, physical functioning, disease duration, and T1 CESD score, self-reported disease activity (Systemic Lupus Activity Questionnaire; SLAQ) and damage (Brief Index of Lupus Damage; BILD).

Results:

682 women (mean age 51±13.6, SLE duration 18 ±8.9 years) contributed 2,097 observations. 45% were college graduates; 13% were living in poverty. 19% had High FS, 47% Moderate FS, and 34% No FS. High FS was reported by 61% of those in poverty, but also 13% of those not in poverty (Table 1).

166 women had 184 episodes of incident depression (rate=8.8/100 person-years). Depression occurred in 40% of those with High FS at T1, 24% with Moderate FS, and 16% with No FS. In univariate analysis, poverty, lower income and education, higher T1 SLAQ, BILD, and CESD scores, and high FS were each associated with onset of depression (Table 2); race/ethnicity was not. Neither poverty, income, nor education remained significant in multivariate analyses, but FS did. In the final model, odds of developing major depression were nearly two times higher for those with High FS compared with None (OR=1.89, 1.09-3.28).

Conclusion:

In this community-based cohort of SLE, the annual incidence of depression was 9%, and high financial strain (FS) was a significant predictor, even after controlling for disease factors and other measures of SES. Determining specific, modifiable sources of FS in SLE patients may help identify those with elevated risk of depression.

Table 1: Levels of Financial Strain by Poverty Status and Educational Attainment

	High Financial Strain[a]	Moderate Financial Strain[b]	No Financial Strain[c]
All Participants	130 (19%)	320 (47%)	232 (34%)
Poverty Status[1]			
Poverty	54 (61%)	28 (32%)	6 (7%)
Not in poverty	74 (13%)	287 (50%)	218 (38%)
Educational Attainment			
No college degree	92 (25%)	190 (51%)	93 (25%)
College degree	38 (12%)	130 (42%)	139 (45%)

[1] Missing for 15 individuals: two high-strain, five moderate-strain, eight no-strain [a] Responded as "Very Likely" to experience actual hardships (i.e. inadequate food, housing, or medical attention) in the next two months; OR "Very Likely" to need to reduce standard of living to the bare necessities in the next two months; OR "Very or Extremely Difficult" to live on current household income. (Vinokur A, Caplan RD. J Appl Soc Psychol. 1987 Dec;17(12):1007–24)

[b] Responses were a combination of "Somewhat Likely or Not Too Likely", "Not at all Likely", "Difficult or Somewhat Difficult", and "Not at all Difficult" [c] Responded as "Not At All Likely" to experience actual hardships (i.e. inadequate food, housing, or medical attention) in the next two months; AND "Not At All Likely" to have to reduce standard of living to the bare necessities in the next two months; AND "No Difficulty" living on your current household income

Table 2: Predictors of the Development of Depression over One Year[a]

	Univariate analyses, OR (95% CI)	Multivariate analysis[b], OR (95% CI)
Age	1.00 (0.99-1.01)	1.00 (0.98-1.02)
Poverty Status		
Living in poverty (≤ 125% of federal poverty level)	2.33 (1.53-3.54)*	1.00 (0.57-1.73)
Not in poverty (reference)	-	-
Education		
No college degree	1.60 (1.13-2.26)*	1.01 (0.67-1.53)
College degree (reference)	-	-
Financial Strain		
High	2.53 (1.81-3.52)*	1.89 (1.09-3.28)*
Moderate	1.16 (0.87-1.53)	1.42 (0.93-2.18)
None (reference)	-	-

*significant at $p < 0.05$ [a] Other significant predictors were disease activity (SLAQ score) and baseline CES-D score; race/ethnicity was not significant

[b] Covariates were race/ethnicity (White, Hispanic, African-American, Asian-American, or Other), marital status, obesity (BMI ≥ 26.8 kg/m^2), current smoking status, SF-36 physical functioning score, SLE disease duration, baseline CES-D score, disease activity (SLAQ score), and disease damage (BILD score)

Disclosure: N. McCormick, None; **L. Trupin**, None; **E. H. Yelin**, None; **P. P. Katz**, None.

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Abstract Number: 983

Objectively Assessed Sedentary Behaviour and Light Physical Activity Are Associated with Long-Term Cardiovascular Risk in People Living with Rheumatoid Arthritis Independently of Moderate-to-Vigorous Physical Activity

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Rheumatoid Arthritis (RA) can result in functional disability and is associated with an increased risk of cardiovascular disease (CVD). In healthy adults and patient populations, light physical activity (LPA) engagement is reported to confer benefits to cardiovascular health and physical function, with time spent sedentary (i.e., activities ≤ 1.5 METS whilst sitting/lying) demonstrated to be adversely related to these health outcomes. Studies also indicate the manner in which sedentary time is accumulated (i.e., sedentary time, bouts, breaks) to hold implications for CVD profile and physical function. However, it is not known whether sedentary behaviour patterns and LPA are relevant to CVD risk and functional ability in RA. The aims of this study were therefore to investigate relationships between objectively assessed sedentary behaviour patterns and LPA with (1) 10-year risk of CVD, and (2) individual CVD risk factors and functional disability in RA. A secondary aim was to determine if associations were independent of moderate-to-vigorous physical activity (MVPA) engagement**.**

Methods: Patients with RA (N = 61) provided a fasted blood sample and underwent physical assessments to evaluate factors associated with their cardiovascular health. Ten-year CVD risk was computed via the Q-risk-score. Individual CVD risk factors were determined from fasted blood samples (Table 1), and functional disability assessed via the Stanford Health Assessment Questionnaire (HAQ). Sedentary behaviour patterns, LPA and MVPA were measured via 7-days of accelerometry. Sedentary time, LPA and MVPA (min/day) were defined as <100, 100 – 2019, and ≥2020 counts per minute, respectively. Sedentary breaks (number/day) were calculated as interruptions in sedentary time for ≥1 minute. Sedentary bout variables (number/day, average length) were derived by determining the number and length of consecutive zeros recorded above a ≥20 zero-count threshold.

Results: Regressions analyses were conducted to answer study aims. Models were adjusted as appropriate for age, gender and accelerometer-wear time (Model 1). Where significant associations were observed, models were further adjusted for daily MVPA engagement (Model 2). Results revealed significant positive associations between sedentary time and the number of sedentary bouts per day ≥20 minutes with 10-year CVD risk, with the reverse true for LPA participation (model 1; sedentary time, $\beta = .38$, $p < .01$, sedentary bouts, $\beta = .37$, $p < .01$, LPA, $\beta = -.45$, $p < .01$). Associations were independent of MVPA engagement (model 2; β change = .01 to .03). Sedentary behaviour patterns and LPA were not related to individual CVD risk factors or functional disability.

Conclusion: Promoting LPA participation and restricting sedentary time to bouts <20 minutes may attenuate long-term CVD risk in RA, independent of MVPA engagement.

Table 1. Descriptive statistics

	Male (N = 20)	**Female (N = 41)**	**Total (N = 61)**
Age (years)	58.85 ± 9.44	53.00 ± 13.28	54.92 ± 12.39
Height (m)	1.73 ± .10	1.63 ± .06	1.66 ± .09
Weight (kg)	78.13 ± 10.33	76.81 ± 19.42	77.23 ± 16.94
RA duration (years from diagnosis)	5.05 ± 5.44	7.97 ± 10.34	6.96 ± 9.01
Accelerometer data			
Average valid wear time (hours/day)	12.99 ± .74	13.12 ± .77	13.08 ± .76
Sedentary time (min/day)	505.40 ± 71.45	493.52 ± 67.24	497.42 ± 68.28
LPA (min/day)	251.14 ± 71.79	278.23 ± 67.22	269.35 ± 69.35
MVPA (min/day)	22.65 ± 22.53	15.70 ± 13.77	17.98 ± 17.26
Sedentary behaviour patterns			
Number of Sedentary breaks/day)	79.59 ± 16.89	86.52 ± 11.94	84.32 ± 14.02
Number of Sedentary bouts ≥ 20 minutes/day	6.37 ± 2.41	5.45 ± 1.91	5.75 ± 2.11
Average time per Sbouts ≥ 20 (min)	31.08 ± 2.07	30.64 ± 2.75	30.78 ± 2.54
10 year risk of CVD			
Qrisk (% risk of 10 year CVD)	24.14 ± 14.82	12.54 ± 11.05	16.33 ± 13.45
Individual CVD risk factors			
C-reactive protein (mg/l)	6.72 ± 8.12	7.66 ± 9.58	7.35 ± 9.09
Erythrocyte sedimentation rate (mg/l)	10.00 ± 8.12	16.55 ± 16.50	14.37 ± 14.52
Fibrinogen (mg/l)	4.64 ± 0.90	4.60 ± 1.20	4.62 ± 1.10
Total cholesterol (mg/l)	4.77 ± .70	5.01 ± 1.09	4.93 ± .98
HDL-cholesterol	1.26 ± .32	1.54 ± .36	1.45 ± .37

(mg/l)			
LDL-cholesterol (mg/l)	2.88 ± .80	2.99 ± .93	2.95 ± .88
Triglycerides (mg/l)	1.39 ± .83	1.05 ± .52	1.16 ± .65
Systolic-blood pressure (mm HG)	138.07 ± 19.45	132.32 ± 16.98	134.08 ± 17.77
Diastolic-blood pressure (mm HG)	83.13 ± 9.96	79.18 ± 8.58	80.39 ± 9.11
Plasma insulin (mg/l)	57.35 ± 26.68	59.32 ± 55.82	58.67 ± 47.99
Plasma glucose (mg/l)	4.65 ± .38	4.80 ± 1.21	4.75 ± 1.01
HOMA status	1.70 ± .82	2.11 ± 3.34	1.97 ± 2.77
Functional Disability			
¶HAQ	1.74 ± .63	1.64 ± .56	1.67 ± .58

Disclosure: S. Fenton, None; **J. Veldhuijzen van Zanten**, None; **G. D. Kitas**, None; **J. Duda**, None; **P. Rouse**, None; **C. A. Yu**, None; **G. Metsios**, None.

Abstract Number: 984

Clinical Characteristics of Inflammatory Myopathies Associated with Cancer: A Report from the Remicam Registry

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Background/Purpose: To describe the clinical presentation and associations of patients with IM associated with cancer in a large group of inflamatory myopathy (IM) from the multicentric REMICAM registry

Methods: A multicenter retrospective study from the REMICAM registry was performed. Patients older than 40 years at diagnosis were selected. All patients were diagnosed with IM according to Bohan and Peter criteria, followed between Jan 1980 and Dec 2014 and classified into 7 different clinical subgroups: primary dermatomyositis (DM), primary polymyositis (PM), cancer associated myositis (CAM), overlap myositis (OM), inclusion body myositis (IBM) and necrotizing myositis (NM). Only cancers diagnosed within 3 years of IM diagnosis were considered as CAM. Descriptive statistics, univariate and multivariate analysis were performed. Kaplan Meyer curves with long-rank analysis were used for survival.

Results: From 283 patients (72% w, 60±11 y at diagnosis, 9±7 y of follow-up, 39% DM, 61% PM), 64 (23%) presented any type of cancer: 11 lung, 8 hematological, 8 skin, 7 breast, 4 colon, 4 stomach, 4 ovary, 4 bladder, 3 endometrium, 3 prostate and 8 others. Median time between IM and cancer was 5 months. In multivariate analysis, patients with cancer were more frequently men (p<.0001), with DM (p=.005) and presented more ischemic lesions (p<.0001). No other clinical findings were different between patients with or without cancer. Mortality was higher in patients with cancer, with a median survival of 10±3 years, compared to 22±3 years for patients without cancer (p<.0001). From the CAM group, 41 (64%) patients died, mainly as a consequence of cancer.

Conclusion: In our registry, over 20% of patients older than 40 years presented IM associated with cancer. This type of IM is more common in men and present as dermatomyositis with ischemic lesions. As expected, mortality is highly increased in IM patients with cancer.

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Abstract Number: 985

Effectiveness of a Web-Based Personalized Rheumatoid Arthritis Risk Tool with or without a Health Educator for Knowledge of RA Risk Factors

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Background/Purpose: Much progress has been made in identifying risk factors for RA, but it is unclear whether individuals at risk for RA have knowledge of these factors. Potential educational interventions include reading materials, interactive web-based tools, and sessions with health educators. We assessed the effect of these educational interventions on RA risk factor knowledge among first-degree relatives (FDRs) of patients with RA using a randomized controlled trial.

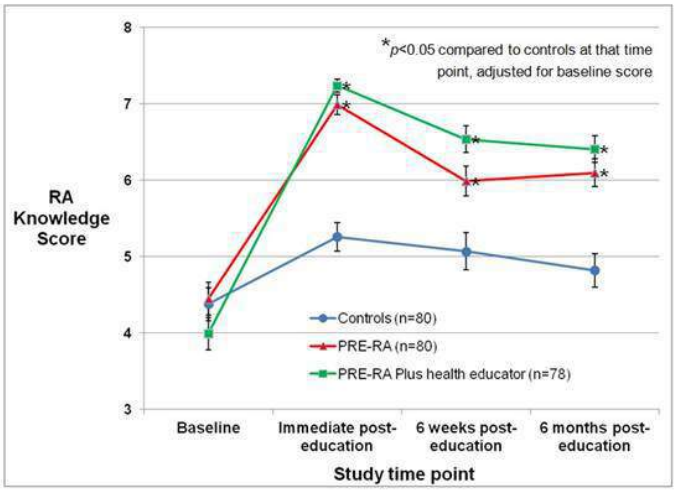
Methods: We developed a web-based tool, the Personalized Risk Estimator for Rheumatoid Arthritis (PRE-RA), which collects data on an individual's age, sex, family history, and risk-related behaviors; presents genetic and autoantibody results; displays relative risk and

absolute risk of RA; and provides personalized education about RA risk. We randomly assigned FDRs without RA to 1 of 3 educational interventions: 1) Control group that received standard education about RA (n=80), 2) PRE-RA group that received personalized education via the web-based PRE-RA tool (n=80), and 3) PRE-RA Plus group that received PRE-RA and a one-on-one session with a health educator (n=78). We assessed RA knowledge at baseline and immediately, 6 weeks, and 6 months after education using the validated Illness Perception Questionnaire modified for RA. We calculated an RA knowledge score by summing the number of 8 RA risk factors that a subject agreed were related to RA. We used linear regression to compare RA knowledge scores from PRE-RA and PRE-RA Plus vs. controls at each time point adjusted for baseline score. We additionally evaluated the impact of the health educator in PRE-RA Plus vs. PRE-RA alone at each post-intervention time point as well as change in RA knowledge compared to baseline.

Results: Among 238 randomized FDRs at baseline, mean age was 45.6 years (SD 14.4), 76% were female, 88% were college educated, and mean RA knowledge score (possible range 0-8) was 4.3 (SD 1.9). At baseline, only 31% agreed smoking was a risk factor for RA, but this increased to 77% at 6 months after PRE-RA (p<0.001). Those who received PRE-RA or PRE-RA Plus had higher mean RA knowledge scores immediately (7.1 [SD 1.0]) and 6 months (6.3 [SD 1.6]) after personalized education compared to controls (immediate 5.3 [SD 1.7] and 6 months 4.8 [SD 2.0]; p<0.001, **Figure**). Compared to only the PRE-RA tool, those who also met with a health educator had similar RA knowledge 6 months after education (improvement of 1.7 [SD 1.8] for PRE-RA; 2.4 [SD 1.9] for PRE-RA Plus, p=0.16).

Conclusion: Despite being both familiar with and at increased risk for RA, FDRs had low baseline knowledge about RA risk factors. We created an interactive, web-based personalized tool that educated FDRs about RA, and this increased knowledge persisted for 6 months. While there may be some additional benefit by also using a health educator, the PRE-RA tool alone is an effective method to educate individuals about RA risk factors to encourage positive health behaviors.

Figure. Mean RA knowledge scores for subjects by randomized group at baseline and immediately, 6 weeks, and 6 months after educational intervention (n=238).



The RA knowledge score was calculated by summing the number of 8 established risk factors for RA that a subject agreed was related to RA (range 0-8, higher scores with more knowledge): smoking, diet, being overweight/obese, poor dental health, personal behavior, heredity/genetics, aging, and altered immunity.

PRE-RA (Personalized Risk Estimator for Rheumatoid Arthritis) is a web-based risk assessment tool that uses an individual's genetics (shared epitope), autoantibodies (CCP and RF), age, sex, family history, and RA risk-related behaviors to provide personalized education on their RA risk.

Disclosure: **M. G. Prado**, None; **R. Miller Krooouze**, None; **Z. Yu**, None; **M. D. Iversen**, None; **N. A. Triedman**, None; **S. S. Kalia**, None; **K. D. Deane**, Inova Diagnostics, Inc., 9; **K. H. Costenbader**, UpToDate, 7; **B. Lu**, None; **R. C. Green**, Invitae, 5,Prudential, 5,Illumina, 5,AIA, 5,Helix, 5,Roche Pharmaceuticals, 5; **E. W. Karlson**, None; **J. A. Sparks**, None.

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Abstract Number: 986

Sex-Specific Associations Between Improvement in Gait Mechanics and Improvement in Pain, Function, and Abductor Strength after Total Hip Arthroplasty

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Background/Purpose: There are sex disparities in both utilization and outcomes of total hip arthroplasty (THA).[1] Identification of sex-specific biomechanical factors related to outcomes could lead to new perioperative rehabilitation strategies to ultimately reduce disparities. We have previously shown that gait mechanics are associated with self-reported function and pain.[2] The purpose of this secondary analysis was to test the hypothesis that these associations differ by sex. We also hypothesized that associations between abductor strength and pain or function differ by sex.

Methods: 124 subjects (age 61 ± 10; 64 Female; BMI 29 ± 5) from an IRB approved repository, were assessed before and ~1 year after THA. Dynamic sagittal plane hip range of motion (ROM) and peak 3D hip external moments, averaged from trials at subjects' self-selected normal walking speeds, were analyzed. Hip abductor strength was assessed using manual muscle testing. Function and pain were assessed using Harris Hip Score (HHS) subscores. To test our hypotheses, we used first-order partial correlations to identify relationships between changes in HHS and changes in gait variables, controlling for speed. Next we used Pearson correlations to identify relationships between changes in HHS and muscle strength. Men and women were analyzed separately. We compared the associations by sex.

Results: We found several sex-specific associations (Table 1). There were no associations between improved function and either gait or strength in men. By contrast, improved function was significantly correlated with increased hip ROM, peak adduction and external rotation moments, and abductor strength, in women. Improved pain was associated with increased ROM and decreased peak adduction moment, in men. Improved pain was associated with increased external rotation moment in women. There were no other associations ($p > 0.112$).

Conclusion: Sex-specific associations among improvement in self-reported pain and function, and improvement in gait mechanics and strength, suggest that sex-specific rehabilitation may be helpful. Although these findings are preliminary, they may indicate that women could benefit from interventions to improve dynamic sagittal plane ROM, and frontal and transverse plane hip mechanics, as well as hip abductor strength. Further research should investigate the feasibility and effectiveness of sex-specific rehabilitation protocols.

References:

1. Borkhoff CM, et al. *Clin Orthop Relat Res*. 2011;469(7):1829-37.

2. Behery OA, Foucher KC. *Clin Orthop Relat Res*. 2014;472:3452-61.

Table 1. Statistically significant associations between pre-to-post THA changes in self-reported outcomes and changes in hip mechanics and abductor strength.

	Change in Dynamic Hip ROM		**Change in Peak Hip Adduction Moment**		**Change in Peak Hip External Rotation Moment**		**Change in Peak Hip Abductor Strength**	
Male Reported Change in HHS	Function	**Pain**	Function	**Pain**	Function	Pain	Function	Pain
	$R_{\|speed}$ = 0.202	$R_{\|speed}$ = 0.284	$R_{\|speed}$ = -0.209	$R_{\|speed}$ = -0.261	$R_{\|speed}$ = 0.146	$R_{\|speed}$ = 0.128	R = 0.214	R = 0.068
	p = 0.124	p = 0.029	p = 0.112	p = 0.046	p = 0.272	p = 0.333	p = 0.184	p = 0.675
Female Reported Change in HHS	**Function**	Pain	**Function**	Pain	**Function**	**Pain**	**Function**	Pain
	$R_{\|speed}$ = 0.474	$R_{\|speed}$ = 0.119	$R_{\|speed}$ = 0.437	$R_{\|speed}$ = 0.189	$R_{\|speed}$ = 0.360	$R_{\|speed}$ = 0.336	R = 0.318	R = -0.030
	p < 0.001	p = 0.354	p < 0.001	p = 0.138	p = 0.004	p = 0.007	p = 0.033	p = 0.846
Shading indicates a significant relationship between self-reported outcome and hip mechanic variable or abductor strength.								

Disclosure: J. H. Brunner, None; **K. C. Foucher**, None.

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Abstract Number: 987

Pesticide Exposure and Risk of Rheumatoid Arthritis in Licensed Male Pesticide Applicators in the Agricultural Health Study

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Session Time: 4:30PM-6:00PM

Background/Purpose: Studies suggest an association between farming and risk of rheumatoid arthritis (RA), but knowledge on the role of pesticides is sparse. Two prior studies have reported use of insecticides may increase risk of RA in women, but associations of RA with specific pesticides in men and in farmers are not known.

Methods: We investigated associations between specific pesticides and RA in a cohort of licensed male pesticide applicators/farmers in the Agricultural Health Study (AHS). Of 30,316 participants enrolled in 1993-97 who completed at least one follow-up questionnaire through 2014, 358 (138 prevalent; 220 incident) cases of RA were confirmed by medical records or self-reported use of disease modifying anti-rheumatic drugs. We evaluated associations between RA and ever-use and intensity-weighted lifetime days of use for 46 pesticides with at least 5 exposed cases, comparing confirmed cases and non-cases (n=27,744) who did not self-report RA using logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), adjusted for age at enrollment, state, smoking pack-years, and education.

Results: Incident RA was associated with ever using the insecticides fonofos (OR: 1.70; 95%CI: 1.22-2.37) and carbaryl (OR: 1.51; 95%CI: 1.03-2.23), and use of the herbicide chlorimuron ethyl (OR: 1.45; 95%CI: 1.01-2.07), while overall (prevalent + incident) RA was associated with having used the insecticides terbufos (OR: 1.27; 95%CI: 1.01-1.60) and DDT (OR: 1.38; 95%CI: 1.01-1.89) and the overall insecticide class of organophosphates (OR: 1.51; 95%CI: 1.02-2.23). Statistically significant exposure-response trends were observed for incident RA, confirming the association with fonofos (trend p=0.005), and also showing associations with the insecticide toxaphene (trend p=0.02) and the herbicide atrazine (trend p=0.01). For RA cases overall, exposure-response relationships were confirmed for terbufos (trend p=0.02) and DDT (trend p=0.04), and were also observed for the herbicides alachlor (trend p=0.03) and glyphosate (trend p=0.02).

Conclusion: Our results provide evidence of associations between use of specific pesticides and risk of RA in men, including organophosphate insecticides. Our findings also replicate an association of RA risk with the organochlorine insecticide DDT, recently described in female spouses of farmer/applicators in the AHS cohort. The immunotoxic effects of pesticides are complex, and the potential role of specific pesticides in the development of RA warrants further investigation in other samples and mechanistic studies.

Disclosure: A. Meyer, None; **D. Sandler**, None; **L. Beane-Freeman**, None; **J. Hoffman**, None; **C. G. Parks**, None.

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Abstract Number: 988

Risk of Rheumatoid Arthritis after Transfusion of Blood from Donors Later Diagnosed with Rheumatoid Arthritis: A Retrospective Cohort Study

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Epidemiology and Public Health I: Inflammatory Arthritis – Risk and Impact

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Rheumatoid Arthritis (RA) is a disease that can have a long sub-clinical phase. During this phase the person with pre-RA could have factors in the peripheral blood, that could confer a risk of developing RA to a blood recipient. One factor could be anti-citrullinated peptide/protein antibodies (ACPA), which has a high specificity for RA and has been found in blood donors to precede the clinical RA by several years (1). In experimental murine models it has been shown that ACPA can not only induce but also enhance arthritis (2). Previous studies on risk of RA and blood transfusion have been few and inconclusive, and none of them described the blood donor population. Based on these findings we speculated whether blood products from a donor with subclinical RA at the time of donation, could be a risk factor of RA development in the recipient.

Methods: We used the Scandinavian Donations and Transfusions database (SCANDAT2) linked with Danish and Swedish nationwide health outcomes registers to attain complete follow-up for up to 47 years regarding hospital care, cancer, and death. In 2015 the database contains 25.523.334 donation records, 21.318.794 transfusion records, and 3.692.653 unique persons with valid identification, presently followed over 40 million person-years(3). Incident RA was defined as having two registered RA diagnoses in the national health registers within a two-year period. Taking a look-back approach, we first identified all donors in SCANDAT2 diagnosed with RA subsequent to their earliest registered donation. We then followed all recipients in SCANDAT2 for the occurrence of RA, starting follow-up one year after first registered transfusion. In analyses, we then assessed the occurrence of RA in recipients according to blood donor characteristics, e.g. whether exposed to donors with subsequent RA or not. Rate ratios adjusted for patient age, sex, ABO blood group, birth cohort, geographic region, and number of transfusions were calculated.

Results: We identified 55 recipients who developed RA during 72017 person-years of follow-up after receiving blood from donors who developed RA (55 events/72017 person-years). For comparison, we identified 9370 recipients who developed RA during 11,733,459 person-years of follow-up after receiving blood from donors who remained free of RA. These figures corresponded to a rate ratio of 1.01 (95% confidence interval 0.73-1.39). Detailed data on recipient RA occurrence by time since transfusion and according to donor rheumatoid factor status, age and sex will be presented.

Conclusion: We found no evidence that a pre-RA condition in the blood donor contributes significantly to a higher risk of developing RA in the transfusion recipients. References:

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2. van Venrooij WJ, et al. Anti-CCP antibodies: the past, the present and the future. Nat Rev Rheumatol. 2011;7(7):391-8.

3. Edgren G, et al. The new Scandinavian Donations and Transfusions database (SCANDAT2): a blood safety resource with added versatility. Transfusion. 2015;55(7):1600-6.

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Abstract Number: 989

A Randomized Controlled Trial of Rheumatoid Arthritis Risk Disclosure Personalized to Genetics, Autoantibodies, and Lifestyle Among Unaffected First-Degree Relatives: The Personalized Risk Estimator for RA (PRE-RA) Family Study

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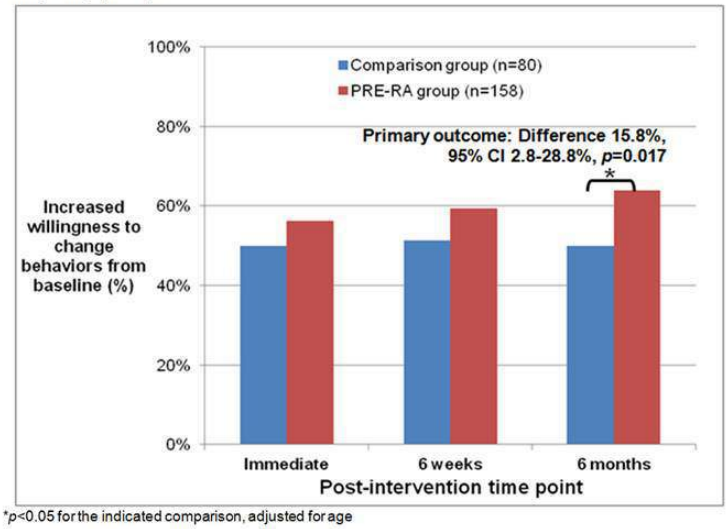
Background/Purpose : Disclosure of genetic risk information alone has had limited impact on changing health behaviors in research trials. Prior studies have not evaluated whether disclosure of risk personalized to genetics, biomarkers, and lifestyle factors may motivate changes in health behaviors. We performed a randomized controlled trial to test the effect of personalized RA risk disclosure, including genetics and autoantibodies, on willingness to change RA behavioral risk factors among a high-risk population of first-degree relatives (FDRs).

Methods : We developed the Personalized Risk Estimator for RA (PRE-RA) tool as a web-based intervention for use in the PRE-RA Family Study. PRE-RA provides summary estimates of absolute and relative RA risks and educates individuals about their RA risk factors —including *HLA-DRB1* genotype results, CCP and RF autoantibody results, lifestyle risk factors (smoking, overweight/obesity, low fish intake, periodontitis), and demographics. We recruited asymptomatic FDRs without RA at a single center and randomized them to receive PRE-RA education alone (n=80) or PRE-RA education with health educator guidance (n=78; total n=158, PRE-RA group), or to receive standard education about RA (n=80, comparison group). We measured willingness to change behaviors based on Prochaska's Stages of Readiness for Change using validated ladder scales (range 0-10, higher score indicating more willingness to change) at 4 time points: baseline and immediately, 6 weeks, and 6 months after intervention. The primary outcome for willingness to change behaviors was defined as an increase in any ladder scale for 4 modifiable RA risk factors (exercise, diet, dental care, and smoking among current smokers) 6 months after intervention compared to baseline using intention-to-treat (ITT) analysis. Secondary analyses investigated differences among the three study arms.

Results : Among the 238 randomized subjects, 87% were White and 77% were female. The PRE-RA intervention group was older (mean 46.7 years [SD 14.4]) than the comparison group (mean 43.4 years [SD 14.7]). In the primary ITT analysis, 63.9% of the PRE-RA group met the primary outcome, compared to 50.0% in the comparison group (age-adjusted difference 15.8%, 95%CI 2.8-28.8%, p=0.017, **Figure**). Within the PRE-RA group, the addition of a health educator resulted in no additional effect on willingness to change behaviors beyond the web-based PRE-RA education tool alone (p=0.54 at 6 months after intervention).

Conclusion : Disclosure of RA risk to FDRs personalized to genotype, autoantibody results, and lifestyle risks resulted in increased willingness to change behaviors related to RA. Personalized risk education incorporating factors beyond genetics may motivate health behavior changes in those at risk for chronic disease and could be widely disseminated using a web-based tool.

Figure. Proportion of unaffected first-degree relatives who had increased willingness to change RA-related behaviors according to those randomized to receive RA risk disclosure personalized to genetics autoantibodies, and lifestyle (PRE-RA group) or standard RA education (comparison group) in the PRE-RA Family Study (n=238).



*$p<0.05$ for the indicated comparison, adjusted for age

The primary outcome for increased willingness to change behaviors was defined as an increase after intervention compared to baseline in any ladder scale for 4 modifiable RA behavioral risk factors (exercise, diet, dental care, or smoking).

PRE-RA (Personalized Risk Estimator for Rheumatoid Arthritis) is a web-based risk assessment tool that uses an individual's genetics (*HLA-DRB1* shared epitope), autoantibodies (CCP and RF), age, sex, family history, and RA risk-related behaviors to provide personalized education on their RA risk.

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Abstract Number: 990

Autoimmunity to Multiple Antigens Is Expanded in at-Risk Family Members Beyond the Disease Specific Patterns of the SLE or RA Proband

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Session Time: 4:30PM-6:00PM

Background/Purpose: Certain autoantibodies (aabs) are highly disease specific, can be detected prior to the onset of clinically apparent disease and oftentimes increase in number and titer up to disease classification. Whether preclinical autoreactivities are already specific for the eventual clinical disease, or if they initially cross specificity boundaries but become more disease-specific closer to diagnosis, is unknown. First-degree relatives (FDRs) provide an ideal group to examine aabs prior to disease classification. We tested samples from nearly 1,700 patients, unaffected FDRs , and unaffected controls from SLE, RA and Type 1 Diabetes (T1D) cohorts to categorize both non-specific and disease-specific autoreactivities.

Methods: Previously collected cohorts of disease-specific autoantibody (aAb) positive patients with SLE (n=187), RA (n=200), and T1D (n=188), disease-specific aab positive (aAb+) and negative (aAb-) FDRs of SLE (n=136 aAb+, n=186 aAb-) and RA (n=198 aAb+ and n=194 aAb-) patients, and unaffected controls from the SLE (n=198) and T1D sites (n=200) were used. All individuals were tested for 8 SLE (dsDNA, Chromatin, Ro, La, Sm, SmRNP, RNP, and aRibo P by Bioplex2200; IF ANA), six RA (CCP2, CCP3.1, RF IgA, RF IgM, RF IgG, RF-neph), and three T1D (GADA, IA2 and mIAA) aabs. 38 Anti-citrullinated protein/peptide antibodies (ACPA) were measured using a bead-based array.

Results: Higher rates of SLE aabs, Ro/La and Sm/SmRNP/RNP, were seen in RA patients (8.0% and 4.0%), RA aAb+ FDRs (5.0% and 4.0%), and RA aAb- FDRs (5.1% and 5.7%) than T1D patients (1.1% and 1.6%) and T1D controls (1.5% and 2.0%). Overall positivity rates for any SLE aab in the RA groups (patients: 16.1%, aAb+ FDRs: 14.7%, aAb- FDRs: 15.5%) were twice as high as those of the T1D cohort (7%). All SLE groups were more likely to be positive for any of the RA aabs than the T1D groups, but a higher percent of SLE aAb+ FDRs were positive for RA aabs than SLE patients (CCP3.1: 9.6% vs 2.7%; RF Neph: 16.9% vs 11.8%; RF IgM: 20.6% vs 12.8%). ACPA were highly RA patient specific, although a higher percent of SLE patients (43.0%) and SLE aAb+ FDRs (31.1%) were positive for any citrullinated antigen, more than RA aAb+ FDRs (20.2%). Using logistic regression, we estimated the probability of an individual testing positive for an alternate autoantibody. Compared to RA FDRs, SLE FDRs are more likely to test positive for other aabs (OR= 3.4). In patients and FDRs who tested positive for aabs associated with the familial autoimmune diseases, males are less likely to have aabs associated with other autoimmune disease than females (OR = 0.63).

Conclusion: Limited but detectable evidence of autoimmunity expanding beyond the familial disease specificity was found in FDRs. RA and SLE patients and FDRs exhibit more autoantibody specificities than T1D patients. Male FDRs are more likely to only have antibodies associated with the familial disease, whereas female FDRs more often have antibodies across autoimmune diseases. Understanding the clinical relevance of detecting other aabs in unaffected FDRs will require additional prospective study.

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Abstract Number: 991

Familial Aggregation of Rheumatoid Arthritis in Sarcoidosis: A Register-Based Case-Control Study in Sweden

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Background/Purpose: Sarcoidosis is an inflammatory disease with unknown etiology that primarily affects the lungs and lymph glands. Sarcoidosis shares some features with rheumatoid arthritis (RA), such as joint involvement and genetic susceptibility related to HLA class II alleles. The aim of this study was to estimate the familial co-aggregation of sarcoidosis with RA.

Methods: A case-control study using Swedish national registers was performed. Adults with sarcoidosis (cases) were identified from the National Patient Register (NPR) and required to have at least two visits listing a sarcoidosis ICD code 2001-2013. Population controls matched 10:1 on age, sex and county who were living in Sweden with no history of sarcoidosis at the time the case was diagnosed (index date) were identified from the Total Population Register. The Multigeneration Register was used to identify parents, siblings and children. Family members with at least two visits listing an ICD code for RA were identified from the NPR (2001-2013). A subset was identified who had any listing of seropositive RA (M05, M08.0). Mean number of first degree relatives (FDR) was calculated for cases and controls

to assure that family structures did not differ by case status. Familial relative risks for sarcoidosis associated with having a family history of RA were estimated using odds ratios and 95% confidence intervals (OR 95%CI) from conditional logistic regression models. Models were stratified by sex of the proband. In a sensitivity analysis, cases and controls with comorbid RA were excluded.

Results: 11,669 sarcoidosis cases and 115,581 controls were identified. The average age at diagnosis was 50 and 55% were male. Cases and controls had a similar mean number of FDRs (4.8 and 4.7, respectively). A higher proportion of cases had a family history of RA compared to controls (4.4% vs. 3.3%). The OR for sarcoidosis comparing any family history of RA to no family history was 1.4 (95%CI 1.2, 1.5). The OR associated with a family history of seropositive RA was similar (OR 1.3; 95%CI 1.1, 1.6). The OR was higher for male probands (OR 1.5; 95%CI 1.3, 1.7) compared to females (OR 1.2; 95%CI 1.0, 1.4). When excluding cases and controls with comorbid RA (2% and 1%, respectively), the OR was 1.3 (95%CI 1.2, 1.5).

Conclusion: There exists a 40% increased risk for sarcoidosis associated with a family history of RA. This indicates that, to some extent, the two diseases share a common etiology and an overlap in genetic risk.

Disclosure: E. V. Arkema, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/familial-aggregation-of-rheumatoid-arthritis-in-sarcoidosis-a-register-based-case-control-study-in-sweden

Abstract Number: 992

The Impact of Inflammatory Arthritis (rheumatoid arthritis, spondyloarthritis, psoriatic arthritis, reactive arthritis) on Maternal and Neonatal Outcomes: A Population-Level Analysis

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Background/Purpose: The impact of inflammatory arthritis (IA) including rheumatoid (RA), psoriatic (PsA), and spondyloarthritis (SpA) on maternal, obstetrical and neonatal outcomes is not well described at the population level. Accordingly, we compared maternal and neonatal outcomes of women with and without IA in a contemporary pregnancy-birth cohort in a defined geographic area (province of Alberta, Canada) with universal health care.

Methods: The patient population consisted of 316,458 women who delivered singleton, live babies between 01/01/05 and 12/31/2014. Only the first birth for each woman during the study time period was included in the analysis. Previously established International Classification of Disease (ICD) version 9 or 10 was used to identify women with IA. A woman was considered to have IA if the diagnosis was present in a hospitalization, or in two outpatient records within 2 years that were at least 2 months apart. Women with IA were further categorized as RA and other IA . Other IA included psoriatic arthritis, spondyloarthritis, and reactive arthritis. Psoriasis patients were included in “other IA” due to the overlapping ICD 9/10 codes between PsO and PsA.

Results: There were 577 women with RA; 2281 with other IA; and 313600 with neither. Although statistically significantly different, maternal age did not differ substantially across groups (Table 1). Babies of women with RA were more likely to be small for gestational age (SGA). Maternal and neonatal outcomes in the other IA group were similar to those in women with neither disease (no IA). Rates of caesarean section and preterm delivery were significantly higher among women with RA (Table 1).

Conclusion: Our study provides novel data on the prevalence of RA and other IA in a contemporary cohort of pregnant women. We find that RA is associated with a higher likelihood of undergoing a caesarean section, preterm delivery and of having an SGA infant; however, other IA had no impact on maternal and neonatal outcomes. Our study highlights the need for peripartum counselling of women with RA.

Neonatal Outcome	No Inflammatory Arthritis	Rheumatoid Arthritis	Other Inflammatory Arthritis	P-value
Mean Maternal Age (years) (SD)	28.6 (5.6)	29.9 (5.7)	29.4 (5.4)	<0.0001
Mean Birthweight (grams) (SD)	3335.7 (565.6)	3203.1 (592.8)	3348.5 (563.0)	<0.0001
Small for gestational age (SGA) (n (%))	37826 (12.1%)	93 (16.1%)	261 (11.5%)	0.0074
Preterm Delivery (< 37 weeks) (n (%))	22779 (7.3%)	85 (14.7%)	170 (7.5%)	<0.0001
Caesarean section (n (%))	87956 (28.0)	196 (34.0)	665 (29.2)	<0.001

TABLE 1. Neonatal outcomes in Albertan women with "no inflammatory arthritis" (no IA), "rheumatoid arthritis" (RA) and "other inflammatory arthritis" (psoriatic arthritis, psoriasis, spondyloarthritis, reactive arthritis)

Disclosure: S. Keeling, None; **A. Savu**, None; **P. Kaul**, None.

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Abstract Number: 993

Chronic Widespread Pain Associated with Premature Mortality in a UK National Prospective Study

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SESSION INFORMATION

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Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes

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Session Time: 4:30PM-6:00PM

Background/Purpose: A small number of studies have examined the long-term consequences of having chronic widespread pain (CWP). Most report premature mortality, but the magnitude and type of excess mortality has varied considerably between studies. We report the largest study to examine mortality, and possible lifestyle mediators of premature mortality, amongst person with CWP.

Methods: UK Biobank involves 502,627 persons aged 40-69 years recruited in 2006-10. At recruitment, participants completed touch-screen questionnaires about health and lifestyle, including questions on pain. Those who reported "pain all over the body" that had lasted >3 months were defined as having CWP. Body mass index (BMI) was determined by measuring height and weight. Lifestyle factors measured included days of moderate/vigorous physical activity in a typical week; frequency of alcohol consumption; amount of fruit and vegetables consumed; smoking status. Vital status was determined through record linkage to national registers up to 2015. The relationship between CWP and mortality was analysed by Poisson regression and expressed as Mortality Rate Ratio (MRR) with 95% Confidence Intervals.

Results: The prevalence of CWP was 1.4% (female v. male 1.7%, 1.1%; peak prevalence 50-59 years 1.7%) and at the time of current follow-up 12,799 persons had died after a mean of 46.5 months. Mortality was higher amongst those with CWP compared to those without chronic pain (5.7% v 2.5%; $MRR_{adj\ age/sex}$ 2.4 95% CI 2.1,2.6). The difference was attenuated after adjustment for markers of lifestyle ($1.6_{adj\ full}$ 1.4,1.8) but did not further change excluding deaths occurring in the first two years of follow-up. Specific causes which were in excess included death from cardiovascular disease ($2.9_{age/sex\ adj}$, $1.9_{full\ adj}$ 95% CI (1.5,2.4)), respiratory disease ($5.0_{age/sex\ adj}$, $2.4_{full\ adj}$ 95% CI (1.7, 3.5)) and cancer ($1.7_{age/sex\ adj}$, $1.2_{full\ adj}$ 95% CI (1.01,1.4)).

Conclusion: This study provides the strongest evidence to date that persons with CWP experience long-term excess mortality. An important part of this excess risk is explained by lifestyle factors which should be targets for intervention, alongside current best care.

Disclosure: G. J. Macfarlane, Pfizer Inc; AbbVie; UCB, 2; **G. T. Jones**, Pfizer Inc, AbbVie, UCB, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/chronic-widespread-pain-associated-with-premature-mortality-in-a-uk-national-prospective-study

Abstract Number: 994

Validation Studies of the American College of Rheumatology (ACR) 2010 Fibromyalgia Diagnostic Criteria and the 2011 Self-Report Modification for Survey and Clinical Research

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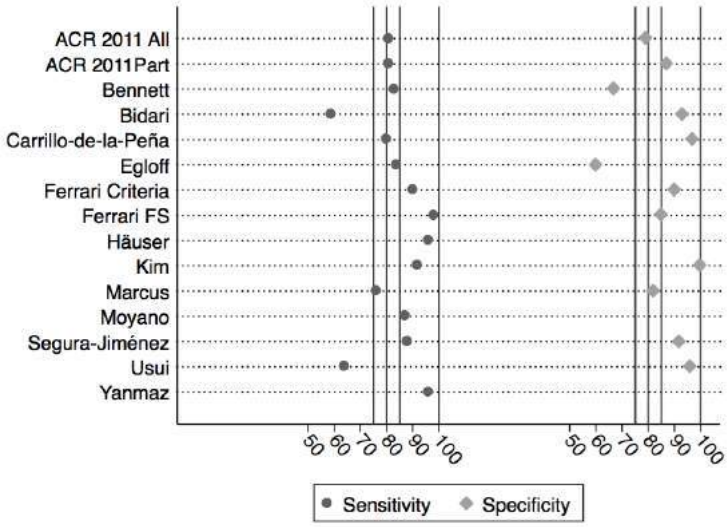
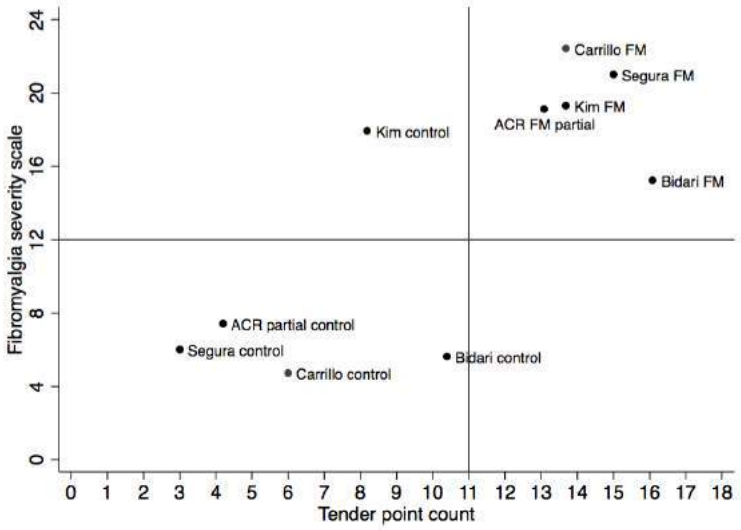
Background/Purpose: The provisional criteria of the American College of Rheumatology (ACR) 2010 and the 2011 self-report modification for survey and clinical research are widely used for fibromyalgia diagnosis. To determine the validity, usefulness, potential problems and modifications required for the criteria, we assessed multiple research reports published in 2010-2015 in order to provide a 2016 update to the criteria.

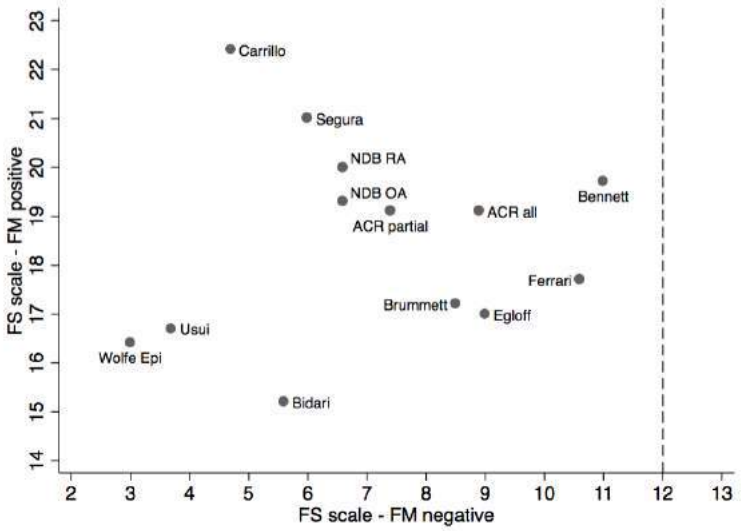
Methods: We reviewed 14 validation studies that compared 2010/2011 criteria with ACR 1990 gold standard classification and clinical criteria, as well as epidemiology, clinical and databank studies that addressed important criteria-level variables, including the polysymptomatic distress (PSD) scale - also known as the fibromyalgia severity (FS) scale. Based on definitional differences between 1990 and 2010/2011 criteria, we interpreted 85% sensitivity and 90% specificity as excellent agreement.

Results: Against 1990 and clinical criteria, the median sensitivity and specificity of the 2010/2011 criteria was 86% and 90% (Figure 1). There was a strong association between ACR 1990 tender point levels in cases and controls, and among 2010/2011 PSD/FS scale results (Figure 2). Data from the ACR 2010 study indicated the correlation between tender points and PSD/FS scale was 0.781. Plotting the levels of PSD in FM (+) and FM (-) cases (Figure 3) provided further insight into the effect of symptom severity on diagnosis. Fibromyalgia is milder in population studies. Studies of fibromyalgia criteria are sensitive to selection issues and severity, and to characteristics of control subjects. Various study authors were uncertain as to how to interpret criteria in the presence of other medical disorders. 2010/2011 criteria led to misclassification when applied to regional pain syndromes, but when a test modified widespread pain criterion was added misclassification was eliminated.

Conclusion: The fibromyalgia criteria have good sensitivity and specificity, and were perceived as useful and easy to use. Results of these analyses will be incorporated into revised criteria to eliminate observed problems.







Disclosure: F. Wolfe, None; **D. J. Clauw**, Pfizer, Lilly, Tonix, Zynerba, Apptinix, Cerephex, IMC, 5,Paizer, Lilly, Cerephex, Tonix, 2; **M. FitzCharles**, None; **D. Goldenerberg**, None; **W. Häuser**, None; **R. S. Katz**, None; **P. J. Mease**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun, UCB Pharma, 2,Abbive, Amgen, BMS, Celgene, Crescendo, Corrona, Dermira, Janssen, Lilly, Merck, Novartis, Pfizer, Sun, UCB Pharma, Zynerba, 5,Abbvie, Amgen, BMS, Celgene, Crescendo, Genentech, Janssen, Novartis, Pfizer, UCB Pharma, 8; **A. Russell**, None; **I. J. Russell**, None; **B. Walitt**, None.

Abstract Number: 995

Use of Opiate Diminished the Treatment Benefits of Motivational Interviewing for Fibromyalgia

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Background/Purpose: Opiate is not indicated in the treatment of fibromyalgia (FM). In fact, chronic use of opiate may even worsen the symptoms of fibromyalgia. There are reports in other pain conditions that long term use of opiate may even contribute to pain chronicity or the persistence of pain. Given the known medical complications from opiate (e.g., cognitive dysfunction) we hypothesized that the use of opiate may modify (or diminish) the effects of motivational interviewing (MI) treatment intervention on FM-relevant clinical outcomes.

Methods: This is a secondary data analysis of a 36-week randomized clinical trial to assess the efficacy of MI to promote physical activity among patients with FM. Participants were randomized to 1 of 2 treatment arms: 6 phone-based MI sessions (n=107) or an equal number of FM self-management instructions (attention control/AC, n=109). Subjects were evaluated at 4 time points: baseline, week 12 (post-intervention), week 24 and week 36. In the previous main outcome analyses†, MI was marginally superior (p=0.06) to AC in improving global FM symptom severity (as measured by Fibromyalgia Impact Questionnaire/FIQ total) from baseline to week 36. For the current analyses, the clinical outcomes were changes in FIQ total and SF36 physical function scores, from baseline to each follow-up visit. At study entry, subjects were categorized as opiate users vs. non-users. Repeated measures ANOVA were used to assess treatment effects within each category.

Results: Approximately 5 subjects in MI and 8 subjects in the AC group had missing data; and therefore, were not included in the analyses.

	MI	AC	p-value
Improvement in global FM severity (FIQ total)			
Opiate **users**	-9.90 (1.78), n=35	-9.21 (1.73), n=35	0.781
Opiate **non-users**	-15.42 (1.23), n=66	-11.90 (1.20), n=66	0.042*
Improvement in SF36 physical function			
Opiate **users**	9.84 (2.00), n=35	7.38 (1.93), n=35	0.375
Opiate **non-users**	14.04 (1.35), n=67	10.08 (1.33), n=66	0.037*

Values are means (standard errors) Stratifying the data based on the use of anticonvulsant (i.e., pregabalin or gabapentin) at study entry, we found the reverse (data not shown). Specifically, treatment benefits from MI were observed among anticonvulsant users, but not among non-users.

Conclusion: In contrast to opiate users, opiate non-users reported greater treatment benefits from MI. Based on our findings, a hypothesis can be made that opiate interferes with the (biological and/or psychological) mechanisms of psychoeducational treatment intervention for FM. If replicated in future studies, opiate status may guide clinician on when best to offer MI for patients with FM. †Ang DC et al. Research to Encourage Exercise for Fibromyalgia. Clin J Pain 2013; 29:296-304

Disclosure: D. Ang, None; **J. Slaven**, None.

Abstract Number: 996

Use of a Shared Medical Appointment for Patients with Fibromyalgia in a Rural, Academic Medical Center: A Process Improvement Initiative for the Development of a New Care Model

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Background/Purpose: Fibromyalgia is a complex chronic pain condition with patients often presenting with multiple somatic complaints that are difficult to address in standard new patient visit. Primary care providers have considerable discomfort in diagnosing fibromyalgia due to the lack of specific diagnostic modalities prompting a referral for verifying the diagnosis. The increased demand in rheumatologic consultation, compounded by the constraints in staffing, necessitated the creation of a new care model for patients with fibromyalgia. We describe a fibromyalgia shared medical appointment (SMA) that evaluates, educates, enhances timely access, and improves patient satisfaction.

Methods: We assembled an interdisciplinary team of a rheumatologist, 2 nurse practitioners, a chaplain and a secretary. All referrals, notes, and ancillary studies, with an indication of myalgia or fibromyalgia were reviewed by a staff rheumatologist (NMO). Eligible patients were called using a standardized script by the secretaries explaining the visit details. A patient history questionnaire was mailed prior to the appointment. Primary care providers were notified by letter about the SMA and its format, and asked to perform specific labs if not performed already. Patients arrive simultaneously to our clinic on the visit day with nursing staff measuring vital signs and reconciling medications. Each patient is examined individually for confirmation of the diagnosis. A facilitated discussion by a trained chaplain followed by a short presentation by the clinician permits ensuing time for discussion and questions among the group. The session concludes with a demonstration of mindfulness techniques by the chaplain for managing chronic pain.

Results: The SMA format was designed between January and April 2015 and implemented in June 2015. Between June 1st, 2015 and June 30, 2016, 67 patients have been evaluated. The visit length was 2.5 hours. Using Plan-Do-Study-Act methodology, we made incremental changes to the session including location, length, flow, content of the presentation and different mindfulness techniques. Post-session surveys identified uniform themes. First, all patients strongly agreed/agreed that the SMA would assist in managing their condition. Most patients (95%) found that interacting with others in a peer-to-peer support environment with the same condition was extremely helpful. Longer appointment times were welcomed by patients to allow for additional question/answer time than would be offered during routine new patient visits. Clinical efficiency in assessing multiple new patients in a defined period of time was observed. The SMA improved wait times for fibromyalgia patients from 3 months to 1 month. The SMA also freed up new patient consultation slots for other conditions. Estimated additional work Relative Value Units (wRVUs) generated as a result of the SMA since its inception is 113.

Conclusion: Considerable benefits were observed in the use of a SMA in an academic, rural consultative rheumatology practice. Future work will enhance and optimize the visit, expand its use, address referring provider satisfaction and examine post-visit resource utilization.

Disclosure: N. M. Orzechowski, None; **D. Lloyd**, None; **K. Tuthill**, None; **J. Puttgen**, None; **R. Bergeron**, None.

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2016 Revisions to the 2010/2011 Fibromyalgia Diagnostic Criteria

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Background/Purpose: The provisional criteria of the ACR 2010 and the 2011 self-report modification for survey and clinical research are valid, reliable and widely used for fibromyalgia diagnosis. In this 2016 fibromyalgia criteria update, we address identify problems and provide further guidelines for use.

Methods: Based on analysis of criteria studies and clinician and researchers comments, we identified problematic areas, including a) misclassification in asymmetric pain disorders, b) inconsistent and unclear instructions in the presence of other medical conditions, c) different clinician (2010) and self-report criteria (2011), d) unclearly defined pain assessment regions.

Results: Based on the above data and clinic usage data, we developed a (2016) revision of the 2010/2011 fibromyalgia criteria. Fibromyalgia may now be diagnosed in adults when all of the following criteria are met:

1) Widespread pain index (WPI) ≥7 and symptom severity scale (SSS) score ≥5 OR WPI 4–6 and SSS score ≥9.

2) Generalized pain, defined as pain in at least 4 of 5 regions, is present.

3) Symptoms have been present at a similar level for at least 3 months.

4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.

The revision makes the following changes:

1) Changes criterion 1 to "Widespread pain index (WPI) ≥7 and Symptom Severity Scale (SSS) score ≥5 OR WPI 4–6 and SSS score ≥9." (WPI minimum must be ≥4 instead of previous ≥3)

2) Adds a generalized pain criterion (Criterion 2) that is defined as pain in at least 4 of 5 regions (Left upper, right upper, left lower, right lower, axial). In this definition, jaw, chest and abdominal pain are not evaluated as part of the generalized pain definition.

3. Standardizes and makes 2010 and 2011 criterion (criterion 3) wording the same: "Symptoms have been generally present for at least 3 months."

4) Removes the exclusion regarding disorders that could (sufficiently) explain the pain (criterion 4) and adds the following text: "A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses."

5) Adds the Fibromyalgia Symptom (FS) [or polysymptomatic distress (PSD)] scale as a full component of the fibromyalgia criteria.

6) Creates one set of criteria (2016) instead of having separate physician (2010) and patient (2011) criteria by replacing the physician estimate of somatic symptom burden with ascertainment of the presence of headaches, pain or cramps in lower abdomen, and depression during the previous 6 months.

Conclusion: This revision combines physician and questionnaire criteria, minimizes misclassification of regional pain disorders, and eliminates the previously confusing recommendation regarding diagnostic exclusions. The physician-based criteria are valid for individual patient diagnosis. The self report version of the criteria are not valid for clinical diagnosis in individual patients, but are valid for research studies. The changes to the criteria allow them to function as diagnostic criteria, while still being useful for classification.

Disclosure: F. Wolfe, None; **D. J. Clauw**, Pfizer, Lilly, Tonix, Zynerba, Apptinix, Cerephex, IMC, 5,Paizer, Lilly, Cerephex, Tonix, 2; **M. FitzCharles**, None; **D. Goldenerberg**, None; **W. Häuser**, None; **R. S. Katz**, None; **I. J. Russell**, None; **P. J. Mease**, Abbvie, Amgen, BMS, Celgene, Janssen, Lilly, Novartis, Pfizer, Sun, UCB Pharma, 2,Abbive, Amgen, BMS, Celgene, Crescendo, Corrona, Dermira, Janssen, Lilly, Merck, Novartis, Pfizer, Sun, UCB Pharma, Zynerba, 5,Abbvie, Amgen, BMS, Celgene, Crescendo, Genentech, Janssen,

Novartis, Pfizer, UCB Pharma, 8; **A. Russell**, None; **B. Walitt**, None.

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Brain Responses to Other's Pain in Fibromyalgia – a Magnetoencephalography (MEG) Study

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Background/Purpose: Fibromyalgia Syndrome (FMS) is a disorder characterized by the presence of widespread pain and tenderness, which is now believed to be, at least in part, a disorder of central pain processing producing hyperalgesia and allodynia. These phenomena might be caused by defective top-down sensorimotor regulation. In order to test this notion, we activated the pain matrix in a top-down manner by presenting pictures of painful situations while recording brain activity using Magnetoencephalography (MEG). We hypothesized that FMS patients will show different responses to pain pictures and will not show normal alpha desynchronization.

Methods: 19 FMS patients (ACR 1990 criteria) and 14 age-matched healthy controls (age 20-60) were recruited from the community as well as from a specialized fibromyalgia clinic. Participants were shown photographs of right hands and feet in situations depicting pain and in control situations with no depiction of pain and were instructed to judge the painfulness of each situation (painful vs. not-painful). A total of 160 pictures (80 each) were presented in random order, displayed for 200ms followed by a "?" that remained on screen until the response was made. A whole-head, 248-channel magnetometer array (4-D Neuroimaging, Magnes 3600 WH) was used in a magnetically shielded room. The data were digitized with a sample rate of 1017Hz and an online 1-400Hz band-pass filter. Data were filtered offline (1-40Hz), segmented into 2s epochs with a 800ms pre-stimulus baseline. Segments containing excessive artifacts were removed. Sources were localized with beamforming (SAM) using alpha-band filtered data from all segments to derive the covariance matrix and weights. Normalized alpha (10-11Hz) power was then estimated separately for each condition and group. Functional images were co-registered with a template MRI adapted to individual head shapes. Statistical analyses were performed using AFNI (3dMVM).

Results: In healthy controls exposure to pictures depicting painful situations induced a decrease in alpha activity (10-12Hz) which was significantly more pronounced than the one induced by non-painful content. However, FMS patients did not show decreased alpha for pain relative to no-pain pictures, indicating abnormal regulation of sensorimotor cortex. Reduction in alpha power at 100-500ms was significant at right Precentral and Postcentral regions, only in the healthy control group [$p<0.05$, cluster size=37]. Overall, FMS patients showed more alpha activity in bilateral visual areas , left Fusiform, right Precentral and right Inferior Frontal, left Middle Frontal and Anterior Cingulate Gyri [$p<0.05$, clusters size>20].

Conclusion: Consistent with previous findings, healthy participants displayed stronger alpha desynchronization for pain pictures, indicating automatic disinhibition of the sensorimotor cortices in response to the observation of pain in others. We found evidence for a deficient modulation of sensorimotor cortex in FMS patients. The lack of differential response suggests that they perceived relatively neutral pictures as potentially painful, at least in this setting. Our findings suggest that defective top-down regulation may play a role in the pathogenesis of FMS.

Disclosure: A. Goldstein, None; **M. Wolf**, None; **J. N. Ablin**, None.

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Abstract Number: 999

Utility of Neutrophil CD64 Expression & sTREM-1 in Distinguishing Bacterial

Infection from Disease Flare in SLE and ANCA Associated Vasculitis

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Background/Purpose: Fever is a common presenting manifestation of systemic lupus erythematosus (SLE) and ANCA associated vasculitis (AAV). Treating physician is challenged to differentiate between disease activity *vs.* infection as to the cause of fever. Presently, there is no clinical or serological biomarker that may reliably differentiate between these two. We aimed to determine the usefulness of CD64 (FcγR1) glycoprotein expression on the surface of neutrophils and sTREM-1 (soluble triggering receptor expressed on myeloid cells) levels in serum in distinguishing bacterial infection from disease flare in SLE and AAV patients

Methods: In this descriptive, cross sectional, observational study 20 healthy control and adult patients of SLE and AAV admitted to our unit either with disease flare or bacterial infection were recruited over a period of 1 year. Neutrophil CD64 expression was measured by flowcytometry and sTREM by ELISA from blood samples collected on the day of admission. Other parameters such as Total Leukocyte Count (TLC), erythrocyte sedimentation rate (ESR), C-Reactive Protein (CRP), C3, and C4 were noted.

Results: Among the 45 patients included in the study 29 (SLE-18 and AAV-11) had disease flare while 16 (SLE-12 and AAV-4) had infection**.** 62% had fever at presentation. Percentage of neutrophil with CD64 expression and their mean fluorescence intensity in patients with infection were significantly ($p<0.05$) higher as compared to those without infection and healthy controls (Table-1). CD64 expression as a marker for differentiation between disease flare and infection had a sensitivity of 94% and specificity of 88% at cut off of 30% (percentage of neutrophil expressing CD64). In contrast to CD64 expression on neutrophils, serum sTREM-1 level was not significantly different in patients with disease flare when compared to patients with infection. Though, CRP was significantly higher in patients with infection compared to those with disease flare ($p<0.05$), however, sensitivity and specificity of CRP to differentiate disease flare with infection was 53% and 79% respectively. TLC, ESR, C3, C4 levels were not significantly different between disease flare and infection group. On subgroup (Table-2) analysis patients of SLE with infection had a higher CRP and TLC compared those with disease flare ($p<0.5$). Sensitivity and specificity of TLC to differentiate SLE disease flare with infection was 54% and 77% respectively.

Conclusion: CD64 expression on neutrophils is helpful in differentiating bacterial infection from disease flare in patients with SLE and AAV.

Table 1 Comparison of various parameters between healthy controls, patients with disease flare and infection

Variable	Disease flare (n=29)	Infection (n=16)	Healthy controls (n=20)
CD64 expression on neutrophils (%)	3.01(1.2-16)	76.24(59.9-93.9)*	7.05(1.4-9.5)
Mean fluorescence intensity of CD64	198.5(82.5-287)	1610(955.7-2563.75)*	99.5(54.7-140.7)
sTREM-1 (pg/ml)	1131.59(666.54-1645.45)**	1041(546-1618.25)**	255.1(95.1-634.8)
CRP (mg/dl)	1.49(0.6-6.6)	9.2(1.7-20.4)***	-
TLC (cells/mm^3)	10000(4825-12475)	11650(6200-17125)	-
ESR (mm/hr)	75(28-107)	70(28-107)	-
C3 (mg/dl)	58(36.8-114.3)	46.6(23.2-63)	-
C4 (mg/dl)	9.3(6.2-16.7)	9.8(6.4-28.3)	-

*$p<0.05$ vs. disease flare group & healthy controls
**$p<0.05$ vs. healthy controls
***$p<0.05$ vs. infection group
All values have been expressed as median (25^{th}-75^{th} Interquartile range)
Abbreviation used- CRP- C-reactive protein, ESR- Erythrocyte sedimentation rate, TLC- Total leucocyte count, sTREM- Soluble triggering receptor expressed on myeloid cells.

Table 2 Subgroup analysis of patients with SLE and ANCA associated vasculitis

Variable	SLE disease flare (n= 18)	SLE with Infection (n=12)	AAV with disease flare (n=11)	AAV with infection (n=4)
CRP (mg/dl)	0.8(0.33-1.52)	9.2(1.24-16.7)*	6.6(2.05-8.72)	11.7 (2.08-20.85)
TLC (cells/mm^3)	5500(2800-9400)	12300(4750-18200)*	11000(10500-16000)	12000(10,300-20100)

*p<0.05 vs. SLE with disease flare
All values have been expressed as median (25th-75th Interquartile range)
Abbreviation used- AAV- ANCA associated vasculitis, CRP- C-reactive protein, TLC- Total leucocyte count.

Disclosure: S. Ajmani, None; **H. Singh**, None; **S. Chaturvedi**, None; **M. K. Rai**, None; **V. Agrawal**, None.

Abstract Number: 1000

Subclinical Cytomegalovirus Viremia Is Associated with Increased Nosocomial Infections and Prolonged Hospitalization in Patients with Systemic Autoimmune Diseases

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Background/Purpose: Both subclinical cytomegalovirus (CMV) viremia and CMV disease have been associated with adverse outcomes in select immunosuppressed populations, including an increased incidence of other infections, prolonged hospitalization, and mortality. We examined the incidence and impact of subclinical CMV viremia in hospitalized patients with systemic autoimmune diseases (AD) [systemic lupus erythematosus (SLE) or anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV)] using the Investigation Use Only (IUO) Abbott RealTi*me*CMV assay (RT assay).

Methods: Prospectively collected blood samples were obtained from AD hospitalized patients at study entry with a second sample collected 1 week later or at discharge from the hospital, whichever occurred first. Controls included age- and gender- matched inpatients without AD and rheumatology clinic outpatients with vasculitis or SLE without active infection. All plasma samples were tested in batch using the IUO RT assay with a LLOD (LLOQ) at 21 IU/mL (32 IU/mL).

Results:

Twenty-three inpatients (10 SLE, 8 AAV, 5 controls), and 31 outpatient controls were recruited. Detectable CMV viremia by the RT assay was found in 61% (11/18) of inpatient AD subjects, 3% (1/31) of outpatient AD subjects, and in none of the five inpatient controls (p<0.001). Average CMV viremia for AD patients at entry was 51.8 IU/mL (33.1 copies/mL) and at 7 days was 175.3 IU/mL (112.4 copies/mL). CMV IgG titers were similar between controls, AD patients, and AD patients with CMV viremia (2.90 vs. 3.01 vs. 3.75, p=0.54). CMV viremia was associated with increased length of ICU stay (25 vs. 5 days, p=0.033), length of hospital stay (35 vs. 10 days,

p=0.014), increased nosocomial infections (7 vs. 1, p=0.007) and trends towards increased frequency of disease flare (3 vs. 0) and renal failure requiring hemodialysis at hospital discharge (4 vs. 1). Two AD patients developed overt CMV disease, neither of which was receiving immunosuppressive therapy at the time of hospitalization. CMV viremia was not associated with the overall severity of illness at study entry (as measured by SOFA and APACHE II scores) nor with disease-specific activity (as measured by SLEDAI or BVAS scores).

Conclusion: More than half of hospitalized AD patients in our cohort had subclinical CMV viremia, which was associated with increased length of hospital stay and nosocomial infections, with trends suggesting a possible impact on disease activity and severity. This low level CMV viremia would be missed by most currently used clinical CMV assays, and occurred even in patients with detectable anti-CMV antibodies. These data suggest that subclinical CMV viremia may wield significant adverse effects in hospitalized patients with SLE and AAV, and that further study of the Immunomodulatory effects of CMV in AD is warranted.

Disclosure: J. McKinnon, Abbott Molecular, 2; **J. Zhou**, None; **J. Hudy**, None; **S. Hegab**, None; **K. Maksimowicz-McKinnon**, Abbott Molecular, 2.

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Abstract Number: 1001

Cytomegalovirus Reactivation in Connective Tissue Disease By Immunosuppressive Therapy Predicts Severe Infection and High Mortality

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Background/Purpose: Intensive immunosuppressive treatment for remission induction in connective tissue diseases (CTDs) sometimes causes serious infection. Cytomegalovirus (CMV) is a herpesvirus remaining latent after primary mild or asymptomatic infection, and the reactivation of CMV is one of the problematic opportunistic infections in immunocompromised patients. This study was to investigate the relationship between CMV reactivation and other infections.

Methods: All hospitalized patients with CTD who started immunosuppressive agents as induction therapy from January 2012 until March 2016 were retrospectively reviewed. Clinical information including history of all infection until June 2016 were collected from their medical charts. CMV reactivation was defined by the detection of CMV PP65 antigen in polymorphonuclear leukocytes from peripheral blood. We defined severe infection as infections which required hospitalization. The relationship between CMV reactivation and other infections were statistically analyzed.

Results: A total of 179 CTD cases with CMV PP65 measured during the remission induction therapy were enrolled in the analysis. Mean age was 57.1±17.0 years old and the female ratio was 68.7%. The CTDs were 48 systemic lupus erythematosus (26.8%), 35 antineutrophil cytoplasmic antibody-associated vasculitis (19.6%), 23 polymyositis/dermatomyositis (12.8%), 21 rheumatoid arthritis (11.7%), 10 adult-onset Still's disease (5.6%), and others 42 (23.4%). 118 cases (65.9%) were new-onset. All cases were treated with moderate to high dose of glucocorticoid (mean prednisolone (PSL) dose, 50.0±11.0 mg/day). Methylprednisolone (mPSL) pulse therapy was conducted in 55 (30.7%), and concomitant immunosuppressants were used in 129 (72.1%). CMV was reactivated in 71 (39.7%) including 18 CMV infection (bone marrow suppression 14, pericarditis 2, liver injury 1, retinitis 1) following the initiation of remission induction therapy. During the immunosuppressive treatment, severe infection occurred in 28 cases (15.6%), and it was more frequent in the CMV-positive cases than the CMV-negative cases with statistical significance (31.0% vs. 5.6%. p<0.001). The incidence of severe lung infection (18.3% vs. 3.7%. p=0.002) and sepsis (8.5% vs. 0.0%. p=0.003) were significantly higher in the CMV-positive cases than the CMV-negative cases. The mortality rate were 14.1% in the CMV-positive cases compared with 1.9% in the CMV-negative cases (p=0.002). The relapse-free survival rate for CTD was significantly lower in the CMV-positive cases by log-rank test (p=0.001).

Conclusion: CMV reactivation in connective tissue disease by immunosuppressive therapy predicts severe infection and high mortality. The cases with CMV reactivation require particular attention to other severe infection.

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Abstract Number: 1002

Pneumocystis Jiroveci in Rheumatic Disease: A 20 Year Single-Center Experience

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Background/Purpose: Pneumocystis jiroveci (PJP) is an opportunistic infection associated with high mortality in patients with rheumatologic conditions. Given the paucity of data, clinical guidelines to initiate PJP prophylaxis are based on expert opinion and identify patients on >20 mg daily prednisone for >4 weeks duration for treatment. Herein we describe the PJP experience over a 20-year period at a single academic center.

Methods: We conducted a retrospective review of all patients admitted to a tertiary academic institution who received an ICD-9 code for Pneumocystis jiroveci (PJP) or Pneumocystis carinii (PCP) (136.3) from 1/1/1996-9/30/2015. Records were abstracted for clinical information including underlying disease, immunosuppressive regimen, lymphocyte count on admission, and outcome. Patients with underlying oncologic diagnoses or organ transplant history were excluded. Summary statistics were performed using Stata v.14.

Results: A total of 21 cases with confirmed PJP were reviewed, averaging to a rate of approximately one case per year. The most common underlying rheumatologic conditions with PJP infection were inflammatory myopathy, systemic lupus erythematosus (SLE), and granulomatosis with polyangiitis (GPA). None of these 21 patients was receiving PJP prophylaxis upon admission. The average time from rheumatologic disease diagnosis to PJP diagnosis was 50 ± 50 months. Data on duration of therapy prior to diagnosis were unavailable. All but three patients were lymphopenic upon presentation (absolute lymphocyte count 558 ± 449, range 40-1580, normal 1100-4800/mm^3). Seventeen patients (81%) were receiving >20 mg prednisone at the time of diagnosis. Of the 4 who were receiving <20 mg prednisone, all received concomitant immunosuppressive medications, including 3 with cyclophosphamide (Table 1). For those patients with available lung function data (pulmonary function testing and/or high-resolution CT imaging, n=12), half had a history of ILD. There was a 43% (9/21) mortality rate overall.

Conclusion: PJP is a largely preventable complication of rheumatic disease treatment with a high mortality, and often occurs years after the initial rheumatologic disease is diagnosed. No patient developed PJP while on less than 20 mg prednisone monotherapy; however, lower doses were noted in those who developed PJP while on concomitant cyclophosphamide. While expert guidelines recommend PJP prophylaxis with patients on >20 mg prednisone for >4 weeks, consideration should be made for patients receiving any dose of prednisone who are also receiving cyclophosphamide, regardless of the underlying rheumatic disease. Table 1. Patients who developed PJP on less than 20 mg of prednisone

Patient	Disease	Prednisone (mg/day)	Other Immunosuppressant
1	SLE	10	CYC
2	Sarcoidosis	10	CYC
3	SSc	5	CYC, MTX
4	RA	1	MTX, TNFi

SLE = systemic lupus erythematosus, SSc = systemic sclerosis, RA = rheumatoid arthritis, CYC = cyclophosphamide, current or in past 12 months, MTX = methotrexate, TNFi = tumor-necrosis factor inhibitor, NR = not reported

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Ultrasonography Changes during the Course of Septic Arthritis ARE Associated with Functional Outcome

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Background/Purpose: Ultrasonography (US) is useful to study the joints and the synovial tissue. It allows the evaluation of the synovial membrane thickness and inflammation. It can depict effusions and help to assess the surrounding soft tissues. Therefore, US could be of interest in the monitoring of septic arthritis. The main goal of this study was to describe the US changes observed during the course of septic arthritis and their association with clinical and functional outcomes.

Methods: We included all patients seen for a native joint infection in 3 different hospitals between January 2014 and July 2015. We collected baseline demographic, clinical, biological and microbiological characteristics. Patients were followed up prospectively with clinical and US evaluation at Day 0, 4, 15 and at 3 months (M3). US exam included the study of synovial membrane thickness, Power Doppler and involvement of the periarticular tissue. Evolution of the synovial thickness was compared to baseline (% of change). X-Ray of the joint was made at baseline and M3. Functional outcome was assessed at M3 (range of motion; SF-36 score).

Results: Thirty four patients were included, mean age 63.7 (range 22-90) with 24 men (70.6%). Most of the time, septic arthritis occurred in patients with pre-existing joint disease (n=24; 70.6%) and the knee was mostly affected (n=19; 55.9%). Predominant causative organism was Staphylococcus Aureus (n=15; 44.1%). Twelve patients (35.3%) underwent joint lavage mean time 4.2 days (range 0-13) after the diagnosis with synovectomy in 2 cases (5.9%). US synovitis was present in 96.4% of the cases at D0, 100% at D15 but was less frequent at M3 (77.8%; p=0.051). The synovial thickness increased at D4 and D15 compared to baseline (respectively median +17.3%, +20%, p = 0.015) and significantly decreased at M3 (median -31.5%; p = 0.015). Doppler signal was frequent (64.3% (D0); 66.7% (D4); 61.3% (D15)) and decreased significantly at M3 (25.9%; p = 0.04). The effusion was present at D0 (92.8%), D4 (88.9%), D15 (80.6%) and significantly less frequent at M3 (55.6%, p =0.001). Periarticular abscess or cellulitis was rare (10.7% and 3.7% at D0 respectively). At M3, one patient died (2.9%) and 5 (14.7%) patients were lost to follow-up. Twenty (58.8%) patients had a decreased joint range of motion. A high total Sharp score and a high joint space narrowing score at M3 was associated with a late start antibiotic treatment (respectively p=0.048, p=0.03). We found no correlation between US characteristics and any of the baseline clinical or biological parameters. In contrast, joint limitation at M3 was associated with an increase of the synovial thickness between D0 and M3 (p=0.024) and with the persistence of Doppler at D15 and at M3 ((p=0.033; p=0.002).

Conclusion: Septic arthritis have a poor functional outcome in more than half of the cases. US synovitis remains present at 3 months in most patients but with a significant decrease in synovial thickness compared to baseline. Doppler signal persists in a quarter of the cases at M3. Persistence of Doppler signal and a thickened synovial tissue at 3 months are associated with a poor clinical outcome.

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Abstract Number: 1004

Herpes Zoster Virus Infection in Patients Treated with Biological Therapies (BIOBADASAR)

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Rossana Quintana[20], Eduardo Mussano[21], Santiago Scarafia[22], Carolina Costi[23], Mercedes De La Sota[24], Monica Patricia Diaz[25], Edson Javier Velozo[26], Santiago Aguero[27], Cristina Battagliotti[28], Sidney Soares de Souza[29], Emilia Cavillon[30], Analia Bohr[31], Andrea Smichowski[32], Alejandro Benitez[33], Daniela Vidal[34], Dora Pereira[35], Liliana Martinez[36], Luis Somma[37], Marta Zalazar[38], Pablo Finucci Curi[39], Leandro Carlevaris[40], Guillermo Berbotto[41] and Veronica Saurit[1], [1]Rheumatology, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [2]Rheumatology Unit, Hospital Privado Centro Médico de Córdoba, Argentina, Córdoba, Argentina, [3]Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [4]Rheumatology, Hospital Privado Centro Médico de Córdoba, Cordoba, Argentina, [5]Reumatología, Hospital Privado Centro Médico de Córdoba, Córdoba, Argentina, [6]SAR, CABA, Argentina, [7]Sociedad Argentina de Reumatologia, CABA, Argentina, [8]Section of Rheumatology an, SAR, CABA, Argentina, [9]IREP, CABA, Argentina, [10]Hospital Italiano de Buenos Aires, CABA, Argentina, [11]Centro Integral Reumatológico, Tucuman, Argentina, [12]Sanatorio Parque, Córdoba, Argentina, [13]Hospital Tornú, CABA, Argentina, [14]Sanatorio Allende, Cordoba, Argentina, [15]Hospital Penna, Bahía Blanca, Argentina, [16]Centro Platense de Reumatología, La Plata, Argentina, [17]Hospital Clínica José de San Martín, CABA, Argentina, [18]Hospital Cesar Milstein, CABA, Argentina, [19]Hospital Provincial, Rosario, Argentina, [20]Sanatorio Parque, Rosario, Argentina, [21]Córdoba, Hospital Nacional de Clínicas, Córdoba, Argentina, [22]Hospital Bernardino Rivadavia, CABA, Argentina, [23]Hospital San Martín, LaPlata, Argentina, [24]Consultorios, Bahia Blanca, Argentina, [25]Hospital Zonal Bariloche, Bariloche, Argentina, [26]Rheumatology, Sanatorio Adventista del Plata, Entre Rios, Argentina, [27]Sanatorio Pasteur, Catamarca, Argentina, [28]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [29]Ramallo 1851, REUMAR, CABA, Argentina, [30]Consultorio, Cordoba, Argentina, [31]Hospital de Rehabilitación Rocca, CABA, Argentina, [32]Atención Integral de Reumatología, CABA, Argentina, [33]CEIM, CABA, Argentina, [34]Hospital de Niños de Córdoba, Córdoba, Argentina, [35]Centro Raquis, Buenos Aires, Argentina, [36]Hospital Fernandez, CABA, Argentina, [37]SOMMA, Buenos Aires, Argentina, [38]Hospital Pirovano, CABA, Argentina, [39]Centro Médico Mitre, Entre Rios, Argentina, [40]IARI, CABA, Argentina, [41]Sanatorio Británico, Rosario, Argentina
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Background/Purpose: Biologic therapies (bDMARDs) have improved the treatment of rheumatic diseases; however, the risk of herpes zoster (HZ) virus infection or reactivation in patients treated with these drugs remains a concern. Objectives: We investigated the clinical characteristics and prognostic factors of HZ in an Argentine registry of rheumatic diseases patients treated with bDMARDs.

Methods: Database included demographics of patients, type and duration of treatments and clinical information of adverse events. A control group was included for comparison consisting of patients not treated with bDMARDs but similar demographics. Values are expressed as mean±standard deviation, median (ranges), and frequencies (percentages), as appropriate. Multivariate logistic and regression analysis were used to identify variables associated with the occurrence of HZ; OR and 95% CI were calculated by exponentiation of regression coefficients.

Results: As of January 2016, 3483 patients, 4762 treatments and 2580 adverse events were studied. 2748 (78.9%) patients were women, mean age was 56.1±15.7 years. Patients were treated with non-bDMARDs in 2011 (57.7%) and 1472 (42.3%) with bDMARDs. BIOBADASAR included 2706 (77.7%) patients with rheumatoid arthritis (RA), 293 (8.4%) with psoriatic arthritis (PsA), juvenile idiopathic arthritis (JIA) and SLE with 117 (3.36%) each. Most frequent biological drugs were etanercept 1193 (41.4%), adalimumab 626 (21.7%), and abatacept with 282 (9.8%). Of 3483 patients, 25 (0.72%) developed HZ infection as an adverse event, their mean age was 59.44±19.31 years. The mean time between treatment and HZ infection was 10.5 (range 1.6 - 251.5) months. Twenty two (88%) patients with HZ received bDMARDs (5 patients developed HZ after more than one biological treatment) and 3 (12%) patients received only non-bDMARD treatments. Ten (40%) patients developed HZ infection during treatment with etanercept. Severities of HZ infections were: non-serious in 21 (84%) and serious in 4 (16%) cases. In comparison with patients treated with non-bDMARDs, patients with bDMARDs showed a high risk of development of HZ infection; incidence rate ratio (IRR) of HZ in the bDMARDs group was 9.084 (95% CI 2.72-47.40; $p<0.001$). The risk was higher for those who used concomitant corticoids (HR 2.97, CI95% 1.55–8.66) and bDMARDs (HR 2.48, CI95% 1.37–15.5) than for those who used methotrexate (HR -3.42, CI95% 0.10–0.53); statistical differences were found in the univariate analysis, and confirmed by the multivariate models. The outcomes of HZ infection were: recovered without sequelae in 21 (84%), not recovered at time of report in 3 (12%) and recovered with sequelae in 1 (4%) case.

Conclusion:

A higher frequency of HZ was seen in patients treated with bDMARDs and concomitant corticoids whereas use of methotrexate has a protective effect. However, results should be interpreted cautiously because of registries inherent limitations.

G. Casado, None; **G. Gomez**, None; **J. Roberti**, None; **O. L. Cerda**, None; **M. D. L. A. Gallardo**, None; **A. Quinteros**, None; **I. Exeni**, None; **J. M. Bande**, None; **P. Astesana**, None; **A. Alvarez**, None; **A. Granel**, None; **A. Peluzzon**, None; **A. Capuccio**, None; **R. Nieto**, None; **R. Quintana**, None; **E. Mussano**, None; **S. Scarafia**, None; **C. Costi**, None; **M. De La Sota**, None; **M. P. Diaz**, None; **E. J. Velozo**, None; **S. Aguero**, None; **C. Battagliotti**, None; **S. Soares de Souza**, None; **E. Cavillon**, None; **A. Bohr**, None; **A. Smichowski**, None; **A. Benitez**, None; **D. Vidal**, None; **D. Pereira**, None; **L. Martinez**, None; **L. Somma**, None; **M. Zalazar**, None; **P. Finucci Curi**, None; **L. Carlevaris**, None; **G. Berbotto**, None; **V. Saurit**, None.

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Abstract Number: 1005

Biallelic Hypomorphic Mutations in a Linear Deubiquitinase Define Otulipenia, an Early-Onset Systemic Autoinflammatory Disease

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Background/Purpose: Autoinflammatory diseases are caused by mutations in genes regulating innate immune responses. More than 20 genes have been associated with various monogenic autoinflammatory disorders.

Methods: We performed whole-exome and candidate gene sequencing in the patients and their unaffected family members. We used an NF-κB luciferase assay and overexpression experiments in 293 cells to confirm the causality of mutations. Patient samples were analyzed using immunoprecipitation, immunoblotting, gene expression and cytokine profiling.

Results: We studied 3 unrelated families, one of Pakistani and two of Turkish ancestry, with neonatal-onset systemic inflammation, neutrophilic dermatitis/rash, and lipodystrophy. We identified three novel homozygous mutations in the *FAM105B*gene, which encodes OTULIN, the only deubiquitinase that specifically hydrolyzes Met-1 linked ubiquitin chains. The p.Leu272Pro and p.Tyr244Cys mutations are located near the linear ubiquitination binding region, and they reduce OTULIN protein stability, while the p.Gly174Aspfs*2 mutation truncates the protein. The three mutations do not disrupt OTULIN interaction with LUBAC. Over-expressed mutant OTULIN plasmid p. Leu272Pro and p.Gly174Aspfs*2 failed to restrain NF-κB activity compared to WT OTULIN. Patient-derived PBMCs and fibroblasts sustained higher levels of phosphorylated IKKα/IKKβ and IκBα, and showed increased phosphorylation of P38 and JNK MAP-kinases compared to healthy controls. These results demonstrate enhanced signaling of the NF-κB and MAPK pathways in OTULIN deficient patients. Transfected OTULIN mutant plasmids showed decreased enzyme activity and a substantial defect in deubiquitination of target molecules NEMO, RIPK1, TNFR1 and ASC. This defect could be partially rescued by cotransfecting the mutation proteins with wild type OTULIN. Stimulated patients' fibroblasts and PBMCs showed a higher linear-ubiquitinaton level of NEMO, RIPK1, TNFR1, and ASC. These results indicate that inefficient deubiquitination of OTULIN target proteins might explain increased NF-κB activity in mutant cells. OTULIN-deficient patients' cells showed a strong inflammatory signature. We observed an excessive production of IL-1β, IL-6, IL-12, IL-18, and IFN-γ in stimulated patient whole blood and patients' serum. Purified patient's monocytes had significantly higher secretion of IL-1β, IL-6, IL-16, IL-18, and TNF in response to LPS, TNF, or IL-1β stimulation relative to controls. Intracellular staining for TNF and IL-6 from Patient 1 and 3 was higher at basal levels in monocytes, dendritic cells and T cells than in controls.

Conclusion: A new disorder caused by loss-of-function mutations in OTULIN expands the spectrum of autoinflammatory diseases caused by defects in deubiquitination and proteasomal degradation.

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Abstract Number: 1006

Immune Complex-Mediated TLR8 Activation Shifts Neutrophils from Phagocytosis to Netosis through Furin-Dependent Shedding of Fcgriia

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Background/Purpose: Neutrophils participate in host defense through mechanisms including phagocytosis and formation of neutrophil extracellular traps (NETs), a neutrophil cell death process in which DNA is extruded together with cytoplasmic and granular content to trap and kill pathogens. Immune complex (IC)-mediated NET formation has emerged as a mechanism that may increase the autoantigenic burden as well as promote type I interferon production in patients with the autoimmune disease, systemic lupus erythematosus (SLE). Although TLR agonists, such as nucleic acids, have been shown to enhance phagocytosis by macrophages and dendritic cells, the role of TLR signaling in neutrophil phagocytosis of RNA-containing ICs has not been extensively studied. The aim of the current study was to explore the cross-talk between TLRs and FcgRs in the regulation of IC-mediated phagocytosis and NETosis.

Methods: Neutrophils, isolated from healthy individuals, were incubated with RNA-ICs and analyzed for phagocytosis and NETosis by flow cytometry and fluorimetry, respectively, in the presence of FcgR blocking antibodies or TLR8 inhibitors (oligonucleotides, RNase). FcgRIIA cleavage on neutrophils was assessed on ex vivo isolated neutrophils from healthy controls (n=7) and SLE patients (n=19) as well upon serum incubation, using two antibody clones recognizing full length or cleaved FcgRIIA, and the results related to clinical data.

Results: Both FcgRIIA- and TLR8-engagement were required for induction of NETosis by RNA-ICs, as demonstrated by FcgR blocking antibodies as well as RNase treatment. While degradation of RNA inhibited NETosis as expected, surprisingly, removal of the TLR ligand by RNase markedly increased the phagocytosis of RNA-ICs by neutrophils ($p<0.0001$), suggesting that TLR activation suppressed phagocytosis. Consistent with this hypothesis, addition of TLR8 agonist (R848) inhibited phagocytosis of ICs ($p<0.0001$), but not of latex beads, by neutrophils. Mechanistically, TLR8 activation mediated furin-dependent proteolytic cleavage of the most N-terminal part of FcgRIIA, reducing the phagocytic capacity, while promoting progression into NETosis. Interestingly, the opposite was also true, namely that phagocytic stimuli (beads) could suppress IC-mediated NETosis ($p<0.01$) while promoting phagocytosis ($p<0.05$), suggesting plasticity of the neutrophils in adapting into specific effector cell functions. Importantly, ex vivo isolated neutrophils from SLE patients demonstrated increased shedding of FcgRIIA ($p<0.0001$), which correlated with neutrophil activation ($r=-0.73$, $p=0.003$) and the presence of anti-Sm/RNP antibodies ($p<0.001$), consistent with the in vitro data.

Conclusion: Neutrophils are not terminally differentiated cells but can mature into phagocytic or NETosing cells, partly regulated by a cross-talk between TLR8 and FcgRIIA. SLE patients have ongoing shedding of neutrophil FcgRIIA, demonstrating the in vivo relevance of our observation. Therapeutic approaches aimed at degrading the TLR8 ligand would be predicted to increase the uptake of circulating ICs, while disarming their inflammatory potential and ability to induce NETs.

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Interferon Regulatory Factor 1 Is the Key Driver of Inflammasome Activity in Systemic Lupus Erythematosus

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Background/Purpose: *The inflammasome complex has recently emerged as a driver of organ damage in systemic lupus erythematosus (SLE). This complex, via its enzymatic subunit caspase-1, is responsible for the cleavage and activation of the inflammatory cytokines* IL-1β *and IL-18. While type I interferons (IFNs) are well established as mediators of SLE pathogenesis, their role in inflammasome activation has not been assessed in this disease. In this study, we examine type I IFNs as regulators of inflammasome activation, and identify interferon regulatory factor-1 (IRF-1) as the critical intersection between the two pathways.*

Methods *:* All patients and controls gave written, informed consent and were treated according to the declaration of Helsinki. SLE patients fulfilled >4 ACR criteria and were recruited from the University of Michigan Lupus Cohort. Primary monocytes were isolated from SLE patients or healthy controls by negative selection. To study inflammasome activation, monocyte cultures were treated with or without lipopolysaccharide (LPS) and adenosine tri-phosphate (ATP). The effects of IFNα on inflammasome activation were measured by pre-treating with IFNα overnight before or concurrently with inflammasome activators. IL-1β secretion was measured by ELISA. Expression levels of caspase-1, STAT1, STAT2, and IRF-1 were assessed by Western blotting. IRF-1 expression was specifically downregulated by siRNA transfection.

Results: Expression of inflammasome (caspase-1, NLRP3, ASC, IL-1β) and interferon-regulated genes (IFI44, MX1, IRF-1) was tightly and significantly correlated in lupus, but not control, monocytes. Indeed, lupus monocytes exhibited increased expression and enhanced activation of the inflammasome by ATP when compared to control monocytes. Importantly, inflammasome activity was increased in control and SLE monocytes with prolonged, but not brief, exposure to IFNα. IFNα treatment resulted in robust upregulation of caspase-1 and IRF-1, a known transcription factor of caspase-1. Reduction of IRF-1 expression via siRNA blocked caspase-1 upregulation after treatment with IFNα. Importantly, hyperactivity of the inflammasome in lupus monocytes was significantly reduced after knock-down of IRF-1.

Conclusion: Prolonged type I IFN exposure, as seen in SLE patients, primes monocytes for robust inflammasome activation in an IRF-1-dependent manner. IRF-1 inhibition may serve as a novel target for treatment of SLE-associated inflammation and organ damage.

Disclosure: J. Liu, None; **J. M. Kahlenberg**, None.

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Abstract Number: 1008

Advantageous Effect of an Endogenous Retroviral Envelope Protein in Systemic Lupus Erythematosus with Ex Vivo and In Vivo Anti-Inflammatory Potential

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Background/Purpose: Human Endogenous Retroviruses (HERVs) are remnants of retroviral infections in the human germline. Most, but not all, HERV genes have become inactive by accumulation of mutations. The presence of open reading frames (ORFs) in a few select HERV genes, suggest an evolutionary advantage for the host in maintaining the protein coding capacity. We investigated whether differences could be detected between upregulation of a panel of ENV-proteins in patients with Systemic Lupus Erythematosus (SLE) compared to healthy controls. Further, we examined a peptide form of the highest upregulated ENV-protein for an anti-inflammatory potential *in vitro*, *ex vivo* and *in vivo*

Methods: 45 patients fulfilling the ACR criteria for SLE and 50 age and gender matched blood donors, were included consecutively. By real time PCR, we analyzed the transcriptome of 11 genes with coding capacity for complete envelope protein. Subsequently, we cloned the *Env59* gene to examine if it retained its retroviral fusion protein activity. Sequence analysis of the protein identified an immune suppressive domain (ISD). A corresponding peptide was synthesized and examined *in vitro* for immune suppressive activity on stimulated experimental cell lines and *ex vivo* on human PBMCs from patients with SLE and Rheumatoid Arthritis. Next, in two separate treatment experiments, we tested the anti-inflammatory potential of the peptide *in vivo* in an experimental model of arthritis, the Sakaguchi mouse (first experiment n=15, second n=40). Mice were treated daily for 4 weeks. Arthritis scoring was performed blinded. At termination, hind paws were fixated in ethanol for histology and stained with Masson-Golden trichrome.

Results: We found that the HERV-H derived *Env* gene (Env59) was highly expressed in SLE patients. Further, that expression of Env59 showed negative correlation with the central inflammatory protein IL-6 (P=0.0065). The peptide version of the Env59 ISD had anti-inflammatory activity and ability to lower IL-6 levels *in vitro* and *ex vivo*. Lastly, in two independent *in vivo* experiments of experimental arthritis, we illustrated the peptide significantly lowered arthritis score ($p<0.05$) in treated versus untreated mice. The reduction in arthritis was confirmed measuring serum amyloid A3 as a biomarker for inflammation and by histology in mice treated with saline compared to peptide-treated mice.

Conclusion: We demonstrated an upregulation of *Env59* in SLE patients compared to healthy controls, and that ENV59 expression was negatively correlated to IL-6 expression in SLE patients. With a synthetic peptide derived from the ISD domain of the retroviral gene we illustrated an anti-inflammatory potential of the peptide *in vitro, ex vivo and in vivo*. We propose the peptide represents a possible new treatment strategy for inflammatory diseases.

Disclosure: **A. Troldborg**, StemGuard aps, 4; **M. J. Laska**, StemGuard aps, 3; **E. M. Hauge**, None; **S. Bahrami**, CEO of StemGuard aps, 3; **K. Stengaard-Pedersen**, StemGuard aps, 4.

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Abstract Number: 1009

Plasmacytoid Dendritic Cells Are Activated in Systemic Sclerosis and Contribute to the Disease By Inducing Ifnα and CXCL4

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Background/Purpose: Plasmacytoid Dendritic Cells (PDCs) are key immune cells involved with anti-viral responses due to their ability to produce large amount of type I IFN in response to Toll-like receptor (TLR)7 and TLR9 signaling. Several studies have reported that PDCs play a role in autoimmune diseases, including lupus, and inflammatory skin diseases such as psoriasis or dermatomyositis. Although the role of PDCs in Systemic Sclerosis (SSc) is less clear, several parallels studies suggest that mechanisms of innate immune dysfunction

operating in SLE may also be important in SSc. Both diseases are associated with presence of autoantibodies to nucleic acid-binding proteins, e.g topoisomerase I and centromere and with increased expression of interferon-responsive genes by peripheral blood mononuclear cells, suggesting the participation of PDC in SSc. Recently, CXCL4 (Chemokine CXC motif ligand 4) was identified as a major protein secreted by PDC and as a biomarker of SSc as its level correlated with the presence of lung and skin fibrosis. The aim of this study is to investigate the role of PDC and the mechanisms by which these cells participate to the pathogenesis of SSc.

Methods: Blood was obtained from 55 SSc patients or 14 healthy volunteers (HV) and PBMC isolated by density gradient. PDC were then isolated from PBMC by positive selection with BDCA4 magnetic beads or by cell sorting. PBMC was analyzed by flow cytometry. In addition, PDC were cultivated for 24h and IFNα and CXCL4 secretion were analyzed by ELISA.

Results: We observed a decrease in the percentage of PDC in SSc PBMC as compared to HV PBMC (0.25±0.02 vs 0.51±0.09; p=0.003). SSc PDC spontaneously secreted excessive IFNa as opposed to HV (10-fold, p=0.03). On the other hand, no difference was observed in the expression of co-stimulatory molecules, CD86, CD83 and CD80 (46.5±10.5, 108.8±16.7 and 9.3±1.5 vs 54.9±5.9, 101±7.6, 18.4±4.9) as well as in the secretion of IL-6 in HV and SSc PDC (1.1±07 vs 8.3±3.1 pg/ml, p=0.2). We also confirmed an increased secretion of CXCL4 in SSc PDC (6903±662 in HV vs 17111±1855 pg/ml; p=0.001), which we showed is dependent on PI3Kδ. We also demonstrated that the increase of CXCL4 in patients is solely due to the secretion of this chemokine by PDC, and not by other cells in PBMCs. Moreover, we show that the CXCL4 and IFN pathways are intertwined in SSc as CXCL4 synergized with TLR9 signaling in PDC to induce enormous levels of type I IFN.

Conclusion: Taken together our data provide evidence of a role of PDC in the pathogenesis of SSc. Decrease in number of PDC in SSc blood suggest an activation of PDC and their migration to the site of disease, probably the skin. We also show that SSc PDC exhibit a non-mature state, with high production of IFNα and low expression of maturation molecules. CXCL4 secretion is dependent on PI3Kδ pathway and contribute to increased IFNa secretion through TLR9 activation.

Disclosure: M. D. Ah Kioon, None; **E. Pelrine**, None; **R. F. Spiera**, None; **J. K. Gordon**, None; **F. J. Barrat**, None.

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Abstract Number: 1010

Elucidating the Activation Profile of Systemic Sclerosis Macrophages

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Background/Purpose: Genome-wide gene expression studies implicate macrophages (MØs) as mediators of fibrosis in systemic sclerosis (SSc) and our data indicate that MØs constitute the dominant inflammatory signature in SSc tissue. Because MØs are plastic and subject to modulation by local micro-environmental factors, *in vivo*MØ polarization spans a broad spectrum of activation states. Therefore, SSc MØ activation is likely shaped by the interplay of many factors, resulting in the development of an immuno-phenotype that supports disease development and progression. In this study, we define the activation profile of human SSc MØs as pro-fibrotic, and provide direct evidence that SSc MØs elicit activation of NFkappaB signaling pathways and proliferation in fibroblasts.

Methods: Plasma and PBMCs were obtained from whole blood of 14 SSc patients (disease duration <5 years) and from 5 healthy age and gender-matched control subjects following informed written consent. $CD14^{+}$monocytes were isolated from PBMCs using magnetic bead selection, and were cultured with either autologous or allogeneic plasma for 7 days to differentiate the cells into MØs. Immune activation studies were performed using 10 ng/ml LPS. For reciprocal activation studies, SSc MØs were co-cultured with fibroblasts using Transwells. RNA expression in MØs and fibroblasts was analyzed using genome-wide analysis and RT-PCR, and protein expression and secretion were monitored using flow cytometry and by ELISA.

Results: Genome-wide expression profiling of human SSc MØs shows up-regulation of signaling pathways involved in antigen presentation and extracellular matrix organization. SSc MØs show an alternatively activated phenotype based on expression of cell surface markers, and express higher levels of TGF-beta and IL-6 under both basal and LPS-stimulated conditions. Differentiation of healthy MØs with SSc plasma results in enhanced TGF-beta and IL-6/JAK/STAT3 signaling pathway activation, and SSc-differentiated MØs co-cultured with dermal fibroblasts show enrichment of inflammatory and proliferation expression signatures. Dermal fibroblasts co-cultured with SSc-differentiated MØs show an activated phenotype.

Conclusion: The activation profile of SSc-differentiated MØs is pro-fibrotic. We demonstrate that SSc MØs are activated under basal conditions, and that these cells release mediators associated with both alternative and inflammatory MØ activation. For the first time, we show that co-culture of SSc MØs with fibroblasts induces fibroblast activation and proliferation. Intriguingly, these data suggest that activation of SSc MØs arises from soluble factors in local microenvironments. Collectively, these studies implicate MØs as likely drivers of fibrosis in SSc and suggest therapeutic targeting of these cells may be beneficial in ameliorating disease in SSc patients.

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Abstract Number: 1011

Correlations Between B Cell Epitope Specificity and Clinical Features in Patients with Jo-1 Antibodies and the Anti-Synthetase Syndrome

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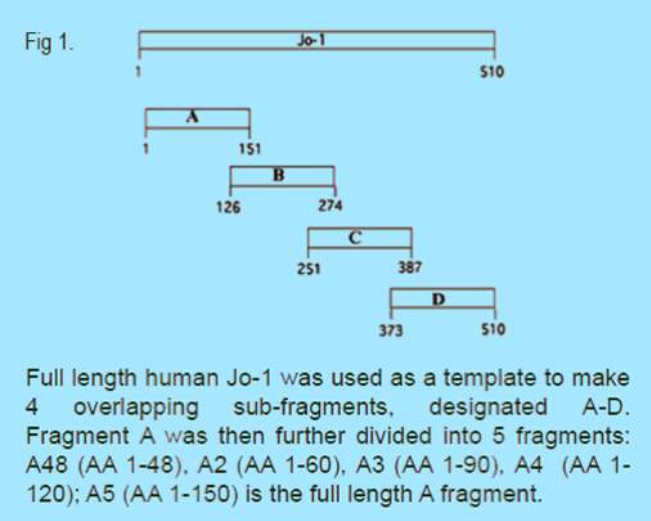
Correlations Between B Cell Epitope Specificity and Clinical Features in Patients with Jo-1 Antibodies and the Anti-Synthetase Syndrome

Background/Purpose: Idiopathic inflammatory myopathy (IIM) is an autoimmune disorder characterized by muscular as well as extra-muscular organ pathology. The anti-synthetase syndrome is specifically associated with auto-antibodies directed against amino-acyl-tRNA synthetases and encompasses a clinical spectrum comprised of myositis, interstitial lung disease, Raynauds's phenomenon, symmetric non-erosive arthritis, mechanic's hands, and fever. The most common autoantibody is anti-Jo-1 which targets histidyl-tRNA synthetase (HRS). Previous work assessing the reactivity of serum anti-Jo-1 antibodies with full length recombinant HRS demonstrated cross-sectional as well as longitudinal correlations with serum creatinine kinase levels, myositis visual analogue scale (VAS), arthritis VAS, and different components of the Myositis Intention to Treat Activity Index (MITAX). In the current study, we aimed to refine these correlations through more detailed assessment of the relationship between HRS epitope specificity and clinical features of the anti-synthetase syndrome.

Methods: We assessed serum reactivity (via ELISA) against overlapping sub-fragments of HRS/Jo-1 protein (Fig 1) in 139 patients with anti-Jo-1 antibodies and different patterns of organ involvement. Use of Mann U Whitney and Kruskal Wallace testing permitted statistical correlations of epitope specificity with various clinical features encompassed by the Myositis Disease Activity Assessment Tool (MDAAT).

Results: Our results indicate that defined clinical features such as joint swelling and Raynaud's are associated with enhanced antibody binding of amino-terminal HRS sub-fragments—with a trend toward preferential antibody affinity for sub-fragments containing amino acids 90-150 (A3-A5). While reactivity to A3-A5 generally overlapped in different patient subsets, reactivity to A2 (aa 1-60) was frequently lower than that of larger subfragments encompassed by A3-A5. Patients with joint swelling had significantly increased reactivity to fragments A2 ($p = 0.0036$), A3 ($p = 0.0015$), A4 ($p = 0.0014$) and A5 ($p = 0.0016$) relative to patients without joint swelling. Patients with Raynaud's also had significantly increased reactivity to fragments A2 ($p = 0.0147$), A3 ($p = 0.0497$), A4 ($p = 0.0209$) and A5 ($p = 0.0225$) compared to patients without Raynaud's.

Conclusion: This work not only confirms that the amino terminal portion of HRS/Jo-1 contains an immunodominant B cell epitope, but also suggests that fine specificity mapping may provide useful biomarkers for different patterns and/or severity of organ involvement. More broadly, these results support the possibility that tissue-specific alterations in antigen presentation are linked to disease pathogenesis.



Full length human Jo-1 was used as a template to make 4 overlapping sub-fragments, designated A-D. Fragment A was then further divided into 5 fragments: A48 (AA 1-48), A2 (AA 1-60), A3 (AA 1-90), A4 (AA 1-120); A5 (AA 1-150) is the full length A fragment.

Disclosure: J. LaConti, None; **F. Kippelen**, None; **R. Aggarwal**, None; **D. P. Ascherman**, None.

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Abstract Number: 1012

WITHDRAWN

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Abstract Number: 1013

The Risk of Colchicine Associated Myopathy in Gout: Influence of Concomitant Use of Statin

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Background/Purpose: To investigate the risk of concomitant use of statin on the development of myopathy in gout patients who received colchicine.

Methods: We included patients with gout at a tertiary medical center in Korea from January 2000 to March 2016, who received colchicine with or without statin. Clinical characteristics including comorbidities such as hypertension, diabetes mellitus, chronic kidney disease, and

liver cirrhosis were collected. Myopathy was defined as the presence of muscle symptoms with elevation of creatinine phosphokinase (CPK) and/or myoglobin. Multivariate Cox analysis was performed to identify risk factors of developing myopathy. And by combining inverse probability of treatment weighting (IPTW) to Cox analysis, we evaluated whether concomitant statin use was associated with increased myopathy.

Results: Of the total 674 patients with gout, 486 received colchicine alone and 188 received colchicine with statin. The rate of myopathy was not higher in patients who received colchicine with statin than in those who received colchicine alone (2.7% vs 1.4%, p=0.330). In multivariate Cox analysis, following factors were associated with increased risk of myopathy: chronic kidney disease (hazard ratio [HR] 29.056, 95% confidence interval [CI] 4.387-192.450, p<0.001), liver cirrhosis (HR 10.676, 95% CI 1.279-89.126, p=0.029), colchicine dose increment (HR 20.960, 95% CI 1.835-239.481, p=0.014) and concomitant CYP 3A4 inhibitor use (HR 12.027, 95% CI 2.743-52.725, p=0.001). Concomitant use of statin, however, was not associated with increased risk of developing myopathy even after adjusting for confounders using IPTW (Multivariate-adjusted HR 1.123 [95% CI 0.262-4.814, p=0.875] and IPTW adjusted HR 0.321 [95% CI 0.077-1.345, p=0.120]).

Conclusion: In patients with gout, concomitant use of colchicine with statin was not associated with increased risk of myopathy compared to use of colchicine alone. The increased risk of myopathy was significantly associated with the following variables: chronic kidney disease, liver cirrhosis, colchicine dose increment and CYP 3A4 inhibitor use. Thus, concomitant use of statin with colchicine seems to be safe from myotoxicity in patients with gout.

Table 1. Analysis of clinical factors associated with myopathy in gout patients who received colchicine

Univariate analysis			
	Unadjusted hazard ratio	95% CI	p-value
Female	3.822	0.488-29.927	0.202
Age	1.043	0.995-1.094	0.078
Baseline creatinine	4.083	0.369-45.232	0.252
Colchicine dose	7.068	0.622-80.343	0.115
Hypertension	3.431	1.088-10.820	0.035
Diabetes mellitus	5.033	1.361-18.612	0.015
Chronic kidney disease	6.286	1.991-19.844	0.002
Coronary artery disease	8.816	2.641-29.435	0.000
Heart failure	4.475	0.979-20.461	0.053
Cerebrovascular event	4.057	0.522-31.522	0.181
Cancer	1.181	0.152-9.184	0.874
Fatty liver	1.009	0.130-7.855	0.993
Liver cirrhosis	7.015	0.905-54.379	0.062
Nephrotic syndrome	0.049	N/A	0.838
CYP 3A4 inducer	0.049	N/A	0.813
CYP 3A4 inhibitor	7.922	2.144-29.270	0.002
Statin	2.006	0.636-6.322	0.235
Multivariate analysis			
	Adjusted hazard ratio	95% CI	p-value
Chronic kidney disease	29.056	4.387-192.450	0.000
Liver cirrhosis	10.676	1.279-89.126	0.029
Colchicine dose	20.960	1.835-239.481	0.014
CYP 3A4 inhibitor	12.027	2.743-52.725	0.001
Statin	1.123	0.262-4.814	0.875

Disclosure: O. C. Kwon, None; **B. Ghang**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

Abstract Number: 1014

Juvenile Dermatomyositis: What Comes Next?

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Background/Purpose: Few studies describe the natural course and long term outcomes of myositis in childhood in large, prospectively-followed patient cohorts, treated in the modern era. We aimed to describe long term patient-reported outcomes in adolescents and young adults (≥ 16 y) who had myositis in childhood and to find outcome predictors from data in the Juvenile Dermatomyositis Cohort and Biomarker Study, UK and Ireland (JDCBS)

Methods: Participants in the JDCBS, previously diagnosed with idiopathic inflammatory myopathy and now aged 16 years or over, completed the SF36 v2, HAQ and a newly developed questionnaire to collect information on current disease features and damage, medication use and side effects, and education and employment opportunities.

Results: Of 205 sets of questionnaires sent, 84 (41%) were returned. Average age of respondents was 21.5 years (maximum 30.8y). Average disease duration was 11.8 y (SD 5.1), age at onset 9.2y (SD 4.3) and female to male ratio 4.25:1. Most patients were white (82.1%) and had a diagnosis of Definite Juvenile Dermatomyositis (69%). Of the 68 who had Myositis-Specific Autoantibody testing, eight (11.8%) had TIF1γ and eight had NXP2. Six (8.8%) were positive for Mi2. Nine (13.2%) had unknown bands and 14 (20.6%) were negative. Of note, 49 (59%) reported persistently active disease and 54 (65%) were still taking immunosuppressive medication for myositis. Among respondents at school or in higher education, 13 out of 29 (44.8%) reported that their academic results were adversely affected by myositis, and that time missed, muscle weakness and fatigue were all significant contributors. Around two-thirds of respondents found that myositis had made it difficult to study. Fourteen of 50 (28%) reported career compromise caused by myositis; of these, 10/37 (27%) were employed and 4/13 (30.8%) were unemployed. Among 47 patients aged 18 to 24 there were 21 (44.7%) who were employed; patients in this study were twice as likely to be unemployed compared to the corresponding age group in the UK population (p=0.001, OR 0.456, 95% CI 0.24, 0.84). SF36 Physical Composite Scores (PCS) were significantly better in those who did not report current myositis (p=0.0003) arthritis (p=0.002) or muscle weakness (p=0.0001). Mental Composite Scores (MCS) were also better in those who did not report current arthritis (p=0.03) or muscle weakness (p=0.013). Intensity indices were calculated for skin DAS, CMAS and MMT by dividing area under the curve (AUC) of score trajectories by the duration (y) of study follow-up. There was significant correlation between MCS and MMT index scores (p=0.007, *rho* 0.328). This association remained significant after fitting a quantile regression model to predict changes in the median MMT intensity score as a function of MCS after adjusting for education/employment status.

Conclusion: We found high patient-reported rates of persistently active disease and medication use in long term follow-up of juvenile myositis, although response bias exists. The young people had reduced rates of employment compared to the UK general population. Persistent muscle disease affected quality of life outcomes in this cohort.

Disclosure: C. A. Boros, None; **L. J. McCann**, None; **N. Ambrose**, None; **M. Cortina-Borja**, None; **S. Simou**, None; **C. Pilkington**, None; **L. R. Wedderburn**, None.

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Abstract Number: 1015

Pro-Inflammatory Cytokines Produced By Different Subsets of Peripheral Blood Mononuclear Cells Are Associated with Ro52/TRIM21 Deficiency in Patients with

Inflammatory Myopathies

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Session Time: 4:30PM-6:00PM

Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of rare, heterogeneous autoimmune diseases of unknown etiology. Different physiopathogenic mechanisms have been proposed, including the production of autoantibodies and pathogenic cytokines. Ro52/TRIM21 is a ubiquitin ligase, and antibodies against this molecule have been described in different autoimmune diseases, including IIM. The aim of this study was to assess if there is a differential production of cytokines, associated with Ro52/TRIM 21 levels, in patients with recent-onset IIM.

Methods: We included patients within the first month of IIM diagnosis according to Bohan and Peter's criteria. They all had active disease, had no treatment, and were seen at a tertiary care center between 2013 and 2015. Patients with diagnosis of dermatomyositis (DM), polymyositis and antisynthetase syndrome, as well as age and gender-matched healthy donors were recruited. PBMCs were isolated by Ficoll-Hypaque. $CD4^+$ T cells and monocytes ($CD14^+$) were purified by magnetic selection. Effector T cells were stimulated with PMA plus ionomycin and monocytes with LPS. Supernatants were collected and cytokine levels were measured. Levels of IFN-α were determined by ELISA, and the other cytokines were assessed by cytometric bead array. The expression of TRIM21 in different PBMC subsets was evaluated by Western Blot.

Results: We included 15 patients with IIM and 15 healthy controls. DM was the most prevalent IIM (73.3%). Most patients were female (66%), with a mean age of 43 ± 15 years. After stimulation, T cells from IIM patients had a higher production of IL-17 (80.22 ± 28.57 *vs* 14.7 ± 5.47, p=0.017) and TNF-α (2325.1 ± 405.14 *vs* 1055.62 ± 235.21, p=0.005) than healthy controls. After being stimulated with LPS, monocytes from IIM patients produced more IL-6 (8441.2 ± 1801.03 *vs* 1996.6 ± 650.58, p=0.003) and IFN-α (85.27 ± 13.78 vs 13.3 ± 0.87, p=0.002) than control monocytes. Also, patients with IIM showed a decreased protein expression of TRIM21 in comparison to healthy controls in different PBMC subsets: total PBMC (0.971 ± 0.603 *vs* 1.849 ± 0.927 p=0.016), $CD4^+$ lymphocytes (0.797 ± 0.54 *vs* 2.413 ±0.786, p=0.017), and monocytes (0.875 ± 0.358 *vs*1.89 ±0.209, p<0.001).

Conclusion: Our findings suggest that patients with IIM are characterized by a higher production of proinflammatory cytokines, associated with decreased levels of TRIM21. The deficiency in TRIM21 could potentially lead to decreased IRF ubiquitination and degradation, enhancing type-1 IFN signaling. Along with the higher IFN-α production, this could contribute to the IFN signature found in IIM patients. Also, the specific cytokine profile could represent a potential biomarker for IIM, particularly DM patients.

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Abstract Number: 1016

Soluble BAT-3: A New Biomarker for Antisynthetase Syndrome

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Background/Purpose: Antisynthetase syndrome (ARS) is an inflammatory myopathy (IM) commonly associated to interstitial lung disease (ILD) and different anti-tRNA-synthetase autoantibodies. The immune mechanisms leading to ARS are yet poorly understood. Recently, we have shown an infiltration of NK cells inside target tissues associated to a specific decrease of peripheral NK cells expressing the natural cytotoxicity receptor-3 (NKp30). These events resulted in a down-modulation of NK cell functions in active ARS patients, suggesting a contribution of NK cells to ARS pathogenesis. In patients with certain tumor subtypes, down-modulation of NKp30 has also been reported and correlated with an abnormal expression of NKp30 ligands, namely B7-H6 and BAT3. These two stress molecules are also expressed or secreted by monocytes/macrophages. In the present study we evaluated the possible impact of the soluble forms of B7-H6 and BAT3 in ARS.

Methods: From 2013-16, 53 treated or untreated patients with ARS were included (15 men = 28%; median age 48, range 18-77; 40 with Jo-1 auto-antibody = 75%) and grouped according to the disease activity (27 active and 26 inactive patients). Patients were compared to 17 healthy donors (2 men = 12%, median age 29, range 22-44) and to 20 patients with non-ARS active IM (8 men = 40%; median age 48, range 25-78; with 12 dermatomyositis = 60%, 7 auto-immune necrotizing myopathy = 35% and 1 overlaping myopathy = 5%). Serum IL-2 & IL-15 were quantified using Quantikine-ELISA-kits (R&D systems), as were soluble forms of NKp30 ligands sB7-H6 and sBAT3 (EIAab & Cusabio, respectively). Statistical analyses were performed using appropriate tests.

Results: Whereas sB7-H6 median concentration was similar in ARS patients and healthy donors, sBAT3 titers were significantly increased in patients with ARS (250 *vs.* 134 and pg/mL, p=0.0002, Figure 1). Importantly, sBAT3 strongly correlated with ARS activity: median sBAT3 concentration reached 340 pg/mL in active patients *vs.* 160 pg/mL in inactive patients (p<0.0001). Furthermore, in patients with increased sBAT3 who were tested twice longitudinally, sBAT3 decreased under treatment in 5/6 (83%) cases (from 472 to 259 pg/mL, p=0.06). sBAT3 increase was highly specific for ARS, as only 1/20 (5%) patients with non-ARS active IM showed a sBAT3 titer above 2 times the healthy donors range (median concentration in patients with non-ARS active IM = 178 pg/mL, p<0.0001). The mechanism of sBAT3 increase remains unknown and sBAT3 level did not correlate with inflammatory cytokine IL2 and IL15 serum concentrations.

Conclusion: The significant and specific increase of sBAT3 in patients with active ARS and its decrease under treatment suggested that this stress molecule may be involved in ARS pathogenesis and could also be considered as a new biomarker for ARS patients.

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Abstract Number: 1017

Statistical Simulation Using Data from the Foundation for the National Institute of Health/Osteoarthritis Initiative Biomarkers Consortium to Evaluate the Clinical Utility of Prognostic Knee Osteoarthritis Biomarkers in Designing a Knee Osteoarthritis Clinical Trial

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Background/Purpose: Development of disease-modifying osteoarthritis drugs (DMOADs) for knee osteoarthritis (OA) has been challenging, partially owing to lack of prognostic biomarkers. Our objective was to identify baseline (BL) biomarkers of rapid OA progression and estimate the potential value and cost of using biomarkers in a knee OA trial.

Methods: The Foundation for the National Institute of Health/Osteoarthritis Initiative (fNIH/OAI) Biomarker Consortium included 600 patients (pts) with knee OA. Pts with nonprogression (n=200), pain progression (n=100), x-ray progression (n=100), and pain/x-ray progression combined (n=200) had knee x-rays, MRIs, and blood and urine biomarkers of bone and cartilage damage. BL biomarkers associated with progression were identified using receiver operator characteristics and multivariate models (Random Forest, Neuro-Network, and Monte Carlo empowered LASSO). To identify subgroups, Patient Rule Induction Method and the Adaptive Index Model were used. To evaluate the value of implementing biomarkers in a trial, we simulated biomarker data based on the OAI population, from which fNIH samples were selected. We estimated potential benefit (reduction in sample size) and cost (screen failure rate) of the biomarker strategy for conducting a knee OA trial.

Results: BL urine CTX-II was the best soluble biomarker predicting OA progression in 12 of 25 multivariate models tested, although predictive power was low (AUROC <60%; **Table 1**). Use of urine CTX-II during the screening phase of a DMOAD trial enriched the number of pts with OA progression by 13% and reduced sample size by 45%; screen failure rate was 83% **(Fig; Table 2)**. The number of medial tibiofemoral subregions affected by MRI bone marrow lesion (BML) was one of the best imaging predictors of OA progression. BL MRI BMLs enriched the number of pts with OA progression by 20% and reduced sample size by 62%; screen failure rate was 78% **(Fig; Table 2)**.

Conclusion: A novel approach combining statistical analysis of fNIH/OAI data with clinical simulations indicated that stratification using urine CTX-II and MRI BML would reduce the sample size needed for a DMOAD clinical trial. However, use of CTX-II and MRI BML could increase the screen failure rate and preclude their implementation as stratification biomarkers in clinical trials.

Table 1. Multivariate Analyses Exploring a BL Prognostic Biomarker Signature to Predict Rapid Progression of OA

Observed Statistics	Random Forest	Neuro-Network	MC-LASSO
Number of predictors most likely to be selected by final multivariate model in 10 runs (frequency)	1 (7/10)	3 (4/10)	1 (5/5)
Most common top predictor likely to be selected by final multivariate model in 10 runs (frequency)	CTX-II (4/10)	CTX-II (3/10)	CTX-II (5/5)
Other notable predictors (selected as the top predictors more than once)	BTI Coll 2-1 NO_2	None	None
Best AUROC of multivariate models in all runs	56.6%	56.4%	56.8%

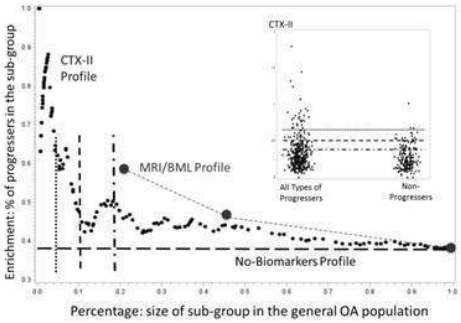
AUROC, area under the receiver operating characteristic; BL, baseline; BTI, bone trabecular integrity; Coll 2-1 NO_2, nitrated fragment from α-helical region of type 2 collagen; CTX-II, C-telopeptide of type 2 collagen; MC-LASSO, Monte Carlo empowered LASSO; OA, osteoarthritis.

Table 2. The Incremental Value and Cost of Implementing a Test of BL Urine CTX-II and MRI/BML in a Future Clinical Study*

Assumptions and Design Parameters	Without Biomarker	With Biomarker	
		CTX-II	MRI (BML)
Screen-failure rate in general OA population, %	0	83	78
Enrichment: pts with rapid OA progression in the subgroup, %	38	51	58
Sample size calculation per arm	1535	850	585

BL, baseline; BML, bone marrow lesion; CTX-II, C-telopeptide of type 2 collagen; MRI, magnetic resonance imaging; OA, osteoarthritis; pts, patients.
*The efficacy was defined as the difference of relative changes from BL between treatment and placebo. A 25% minimum efficacy was assumed for pts with rapid OA progression. The SD of the efficacy is set to 75% of mean. For the sample size estimation, 5% type 1 error and 80% power are assumed.

Figure. Potential benefit* and cost† of using urine CTX-II, MRI/BML, or no biomarker (reference) in a future knee OA trial. BML, bone marrow lesion; CTX-II, C-telopeptide of type 2 collagen; MRI, magnetic resonance imaging; OA, osteoarthritis. *Enrichment of progressers; †Size of subgroup or screen failure rate.



Disclosure: S. Feng, AbbVie, 3,AbbVie, 1; **Z. Liu**, AbbVie, 3,AbbVie, 1; **F. Hong**, AbbVie, 3,AbbVie, 1; **J. Medema**, AbbVie, 3,AbbVie, 1; **R. Kamath**, AbbVie, 3,AbbVie, 1; **M. C. Levesque**, AbbVie, 3,AbbVie, 1.

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Abstract Number: 1018

Dietary Intake of Fiber and Risk of Knee Osteoarthritis

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Background/Purpose: Dietary fiber reduced risks of metabolic diseases in part by reducing systemic inflammation and body weight. These factors are both likely to contribute to causing osteoarthritis (OA) and both are more strongly associated with painful OA than with radiographic disease. In this study, we assessed the relationship between dietary fiber and risk of knee OA.

Methods: We used data from the Osteoarthritis Initiative, a prospective, multicenter cohort of 4,796 U.S. men (41.5%) and women [mean (SD) age: 61.2 (9.2) years and BMI: 28.6 (4.8) kg/m^2] with or at risk of knee OA. Dietary fiber was estimated using a validated food frequency questionnaire at baseline and sex-specific quartiles of dietary fiber were created. Total dietary fiber was the sum of fibers from grains, fruits and vegetables, and nuts and legumes. Incident radiographic OA (ROA), symptomatic OA (SxOA), and knee pain worsening were followed annually until 48 months. Incident ROA was defined as a knee newly developing Kellgren and Lawrence grade ≥2. Incident SxOA was defined as a new onset of both ROA and a painful knee on most days in past month. Knee pain was estimated used the WOMAC pain subscale ranging from 0 (no pain) to 20 (most pain) points, and pain worsening was defined if the score difference between the baseline and each annual exam ≥ 14% of the base score according to the published estimates for the minimal clinical important difference in WOMAC. We used Generalized Estimating Equations to account for the correlation between two knees individually and for analysis of pain worsening for each exam. We further assessed to what extent the association between fiber and OA was mediated by BMI using a marginal structural model.

Results: At 48 months, we identified 869 knees with incident SxOA, 152 knees with incident ROA, and 1,964 knees with pain worsening among 5,752 / 3,350 / 7,951 eligible knees, respectively (**Table**). Dietary total fiber was inversely associated with SxOA and pain worsening (p- trend <0.01); grain fiber was similarly associated with pain worsening (p-trend<0.02). Approximately 34% of the association between total fiber and SxOA and 22% between total fiber and pain worsening was through the mediation by BMI. As a secondary analysis, adjustment for baseline BMI yielded similarly significant results. No associations were found for dietary fiber with ROA or for other fiber with OA phenotypes.

Conclusion: This is the first study demonstrating that dietary fiber is associated with lower risks of symptomatic OA and pain worsening in the knee that may be partially mediated through reduced BMI. The strongest association was found at the highest quartile of fiber intake, which is in line with the recommended daily fiber of 25 grams for Americans.

Table. Relative risk (95% CI) to estimate total effect of dietary fiber on knee incident symptomatic (Sx) OA (n=2,876 persons), incident radiographic (R) OA (n=1,675 persons), and knee pain worsening (n=3,976 persons) for all eligible participants

Fibers		**Q1**	**Q2**	**Q3**	**Q4**	**P-trend†**
Total fiber (g/d)						
Median (IQR)		8.6 (6.4,11.3)	12.5 (9.9, 15.5)	15.1 (12.4, 18.9)	20.6 (16.2, 26.3)	
SxOA	knees*	208/1,346	256/1,440	206/1,472	199/1,494	
Model 1††		1.00	1.14 (0.90,1.45)	0.83 (0.65,1.07)	0.78 (0.61,1.00)	<0.02
Model 2†††		1.00	1.12 (0.87,1.42)	0.79 (0.61,1.03)	0.70 (0.52,0.94)	<0.002
ROA	knees	29/796	44/828	44/864	35/862	
Model 1		1.00	1.51 (0.85,2.68)	1.44 (0.83,2.48)	1.11 (0.61,2.02)	0.93
Model 2		1.00	1.41 (0.78,2.55)	1.24 (0.69,2.24)	0.83 (0.40,1.73)	0.46
Pain worsening	knees	526/1,970	512/1,988	514/1,994	412/1,999	
Model 1		1.00	0.95 (0.85,1.07)	0.92 (0.81,1.03)	0.77 (0.68,0.87)	<0.001
Model 2		1.00	0.96 (0.85,1.08)	0.94 (0.83,1.06)	0.81 (0.71,0.94)	0.005
Grain fiber (g/d)						
Median (IQR)		2.8 (1.9, 4.0)	4.5 (3.5, 5.9)	6.0 (4.6, 7.6)	8.4 (6.4, 11.1)	
SxOA	knees	211/1,348	226/1,420	215/1,450	217/1,534	
Model 1		1.00	1.03 (0.82,1.31)	0.96 (0.76,1.22)	0.88 (0.69,1.12)	0.26
Model 2		1.00	1.04 (0.81,1.32)	0.98 (0.76,1.24)	0.87 (0.68,1.13)	0.29
ROA	knees	38/774	36/838	42/850	36/888	
Model 1		1.00	0.89 (0.53,1.50)	1.02 (0.61,1.73)	0.81 (0.48,1.36)	0.38
Model 2		1.00	0.92 (0.55,1.56)	1.09 (0.65,1.84)	0.78 (0.46,1.35)	0.34
Pain worsening	knees	554/1,975	474/1,974	480/1,998	456/2,004	
Model 1		1.00	0.91 (0.81,1.03)	0.92 (0.82,1.04)	0.83 (0.73,0.93)	<0.002
Model 2		1.00	0.92 (0.82,1.04)	0.94 (0.83,1.06)	0.86 (0.76,0.97)	<0.02

* Number of OA affected /total number of knees in each quartile of dietary fiber; †Test for trend based on variable containing median value for each quartile; ††Model 1 adjusted for age (years), sex (men vs. women), race (white vs. non-white), and total energy intake (kcal); †††Model 2 further adjusted for education (<college vs. ≥college), tobacco use (never, former, current smokers), physical activity (PASE, continuous), intake of other dietary factors including polyunsaturated fat (g/day), vitamin C (mg/day), vitamin D (IU/day), vitamin E (mg α-TE/day), vitamin K (µg/day), dairy products (servings/day), and fats, oils, sweets and soda (serving/day), and NSAID use (yes vs. no for pain worsening).

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Abstract Number: 1019

The Impact of Hip and Knee Osteoarthritis on the Subsequent Risk of Incident Diabetes: A Population-Based Cohort Study

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Background/Purpose: Osteoarthritis (OA) and diabetes commonly co-occur. Potential explanations include common risk factors (aging, obesity) and the effects of OA-related functional limitations on diabetes risk factors (e.g., sedentary behavior exacerbates metabolic syndrome). However, whether or not there is a causal relationship between OA and diabetes is unclear. In a large population-based cohort free of diabetes at baseline, we examined the relationship between self-reported hip and knee OA and incident diabetes.

Methods: A population cohort aged ≥55 years was recruited from 1996-98 and followed through provincial health administrative data to 2014. Subjects with baseline diabetes, rheumatic diseases, and medical conditions associated with functional disability were excluded.

Age, sex, height, weight, joint complaints and functional limitations were collected. Hip and knee OA were defined as swelling, pain, or stiffness in any joint lasting 6 weeks in the past 3 months and indication on a joint homunculus that a hip or knee was "troublesome". Comorbidities were defined using validated algorithms for health administrative data. Using Cox-regressions, we examined the relationship of baseline hip/knee OA (0-2 hips; 0-2 knees) with subsequent incident diabetes as defined from health administrative data (sensitivity - 86%, specificity - 97%), incrementally controlling for age, sex, BMI, preexisting hypertension and cardiovascular disease (CVD), income and prior primary care exposure, and finally walking limitation.

Results: 16,362 participants without baseline diabetes were included: median age 68 years, 61% female and median BMI 25.3 kg/m^2. 1,637 (10%) individuals met criteria for hip OA, 2,431 (15%) for knee OA, and 3,908 (24%) for walking limitation. Over a median follow-up of 13 years, 3,539 individuals (22%) developed diabetes. Controlling for baseline age, sex, income, BMI, preexisting hypertension and CVD, and prior primary care exposure, a significant dose-response relationship was observed between number of hip/knee joints with OA and incident diabetes: HR for two vs. no OA hips 1.25, 95% CI: 1.08-1.44 (p=0.003); HR for two vs. no OA knees 1.16, 95%CI: 1.04 -1.29 (p=0.008). Further adjustment for walking limitation resulted in attenuation of these relationships, which became non-significant.

Conclusion: In a large population cohort aged ≥55 years free of diabetes at baseline and after controlling for multiple confounders, the presence and burden of hip and knee OA was a significant independent predictor of incident diabetes. This association was explained largely by OA-related walking limitation. Increased attention to management of hip and knee OA with a view to improving mobility has potential to reduce risk of incident diabetes.

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Abstract Number: 1020

Risk Factors Can Classify Individuals Who Develop Accelerated Knee Osteoarthritis

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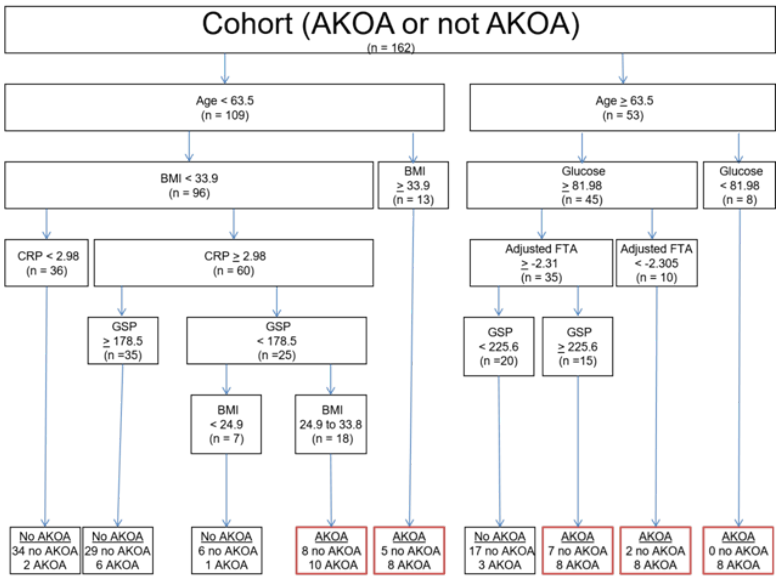
Background/Purpose: Accelerated knee osteoarthritis (KOA) is a painful disorder and associated with several risk factors: greater age, greater body mass index (BMI), static knee alignment, and coronal tibial slope. While no single risk factor can accurately predict who is at risk for accelerated KOA, it would be beneficial to recognize the combinations of risk factors that identify people at risk for accelerated KOA. Hence, we assessed which combinations of risk factors can classify adults who develop accelerated KOA or not and which risk factors are most important.

Methods: We conducted a case-control study using data from baseline and the first 4 annual visits of the Osteoarthritis Initiative. Eligible participants had no radiographic KOA at baseline (Kellgren-Lawrence [KL] < 2). We classified 3 groups: 1) accelerated KOA: ≥ 1 knee progressed to advance-stage KOA (KL 3 or 4) within 48 months, 2) typical onset of KOA: ≥ 1 knee increased in radiographic scoring within 48 months (excluding those defined as accelerated KOA), and 3) No KOA: no change in KL grade by 48-months. We did 1:1:1 matching for the 3 groups based on sex. A laboratory blinded to group assignment conducted serum assays in duplicate for CRP, GSP, and glucose concentrations. Staff recorded age, sex, and BMI based on standardized protocols. Weight-bearing, fixed flexion posterior-anterior knee radiographs were obtained at baseline and follow-up visits. One reader manually measured baseline coronal tibial slope (ICC = 0.87). Baseline femorotibial alignment angle was measured on the radiographs using a semi-automated program software tool. We performed classification and regression tree (CART) analysis to determine rules for classifying individuals as accelerated KOA or not (no KOA and gradual onset) based on baseline age, BMI, coronal tibial slope, static alignment, serum measures, and sex.

Results: Based on the CART analysis, the most important baseline variables for classifying individuals with incident accelerated KOA (in order of importance) were BMI, glucose concentrations, and age (Figure 1). Individuals < 63.5 years of age were likely not to develop accelerated KOA, except when they were overweight. Individuals ≥ 63.5 years of age were more likely to develop accelerated KOA unless their glucose levels were > 81.98 mg/dL, had varus malalignment, and had GSP concentrations < 225.6 nMol/mL. The relative error (unexplained variance) of the CART = 63%.

Conclusion: Age, BMI, and serum assays may enable the classification of individuals who will develop accelerated KOA in the subsequent 4 years. Future studies should explore other novel risk factors that may help classify individuals at risk for accelerated KOA and recognize the complex inter-play between risk factors. **Figure 1. Classification and Regression Tree for Accelerated Knee Osteoarthritis (AKOA) versus those without AKOA**



Disclosure: J. Driban, None; **T. E. McAlindon**, None; **M. Amin**, None; **L. L. Price**, None; **C. B. Eaton**, None; **J. Davis**, None; **B. Lu**, None; **G. H. Lo**, None; **J. Duryea**, None; **M. Barbe**, None.

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Abstract Number: 1021

Maintaining Sufficient Serum Vitamin D Levels over 2 Years Is Associated with Reduced Knee Structural and Symptomatic Changes in Patients with Knee Osteoarthritis

Shuang Zheng[1], Xingzhong Jin[1], Flavia M Cicuttini[2], Xia Wang[1], Zhaohua Zhu[1], Anita E Wluka[3], Weiyu Han[1], Tania Winzenberg[1], Leigh Blizzard[1], Graeme Jones[4] and Changhai Ding[4], [1]Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia, [2]Monash University, Department of Epidemiology and Preventive Medicine, Melbourne, Australia, [3]Australia, Armadale, Australia, [4]Musculoskeletal Unit, Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia
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Session Time: 4:30PM-6:00PM

Background/Purpose: To examine whether those maintaining sufficient serum vitamin D levels have reduced knee structural changes and

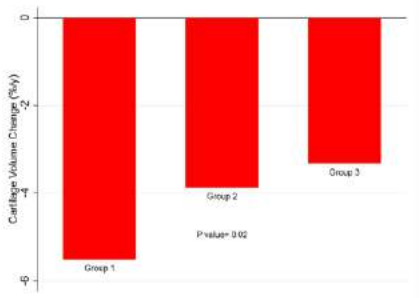
symptomatic improvement compared with those not maintaining sufficient serum vitamin D levels over 2 years in patients with knee osteoarthritis (OA).

Methods: Participants (n= 413, age 63.2; 50% females) with symptomatic knee OA and vitamin D insufficiency were enrolled in a multicentre, parallel randomized, placebo-controlled and double-blind clinical trial. 340 participants (82.3%) completed the study as well as 25-hydroxyvitamin D [25(OH)D] measurements at month 3 and month 24. In the post-hoc analyses, participants were classified as maintaining insufficient vitamin D group (Group 1, serum 25(OH)D≤50nmol/l at month 3 and month 24, n=45), fluctuating vitamin D group (Group 2, 25(OH)D>50nmol/l only at one point, n=68) and maintaining sufficient vitamin D group (Group 3, 25(OH)D>50nmol/l at month 3 and month 24, n=226). Serum 25(OH)D were measured at baseline, month 3 and month 24 using direct competitive chemiluminescent immunoassays. Knee structural changes including cartilage volume, cartilage defects, bone marrow lesions (BML) and effusion-synovitis volume were assessed using magnetic response imaging (MRI) at baseline and month 24. Knee pain was assessed at baseline, month 3, 6 12 and 24 using Western Ontario and McMaster Universities Arthritis Index (WOMAC) and visual analogue scale.

Results: Patients in Group 3 had significantly less tibial cartilage volume loss per year (β: 2.2, 95% CI: 0.4, 4.0) and change in effusion-synovitis volume per year (β: -69.5, 95% CI: -133.4, -5.6) than participants in Group 1 (*Figure 1 and Figure 2*). The differences remained significantly after further adjustment for age, sex, BMI and season of blood sampling (β: 2.1, 95 CI%: 0.3, 3.9 and β: -61.8, 95 CI%: -121.9, -1.7, respectively). There were no significant differences in changes of tibiofemoral cartilage defects and BML between Group 3 and other two groups. Patients in Group 3 had significantly less loss of WOMAC physical function (β: -94.8, 95% CI: -183.1, -6.6) than others two groups in the mixed-effect models.

Conclusion: Patients maintaining sufficient serum vitamin D at month 3 and 24 had less cartilage volume loss, less increase in effusion-synovitis volume and more improvement in physical function compared with those not maintaining sufficient serum vitamin D over 2 years in symptomatic knee OA patients with vitamin D insufficiency. These findings suggesting that maintaining sufficient 25(OH)D is beneficial for structural change and functional improvement in knee osteoarthritis.

Figure 1. Tibial Cartilage Volume Change (%/y) in knee OA patients with or without sufficient serum vitamin D levels over 24 months.

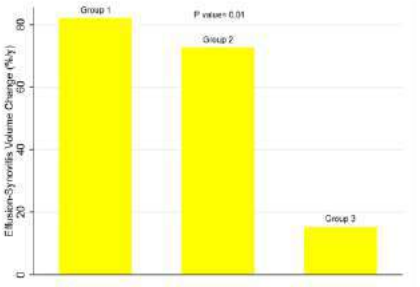


Group 1: maintaining insufficient vitamin D (serum 25-OHD≤ 50nmol/l at both month 3 and 24);

Group 2: fluctuating vitamin D group (serum 25-OHD> 50nmol/l only at one time point);

Group 3: maintaining sufficient vitamin D (serum 25-OHD> 50nmol/l at both month 3 and 24);

Figure 2 Effusion-Synovitis Volume Change (%/y) in knee OA patients with or without sufficient serum vitamin D levels over 24 months.



Group 1: maintaining insufficient vitamin D (serum 25-OHD≤ 50nmol/l at both month 3 and 24);

Group 2: fluctuating vitamin D group (serum 25-OHD> 50nmol/l only at one time point);

Group 3: maintaining sufficient vitamin D (serum 25-OHD> 50nmol/l at both month 3 and 24);

Disclosure: S. Zheng, None; **X. Jin**, None; **F. M. Cicuttini**, None; **X. Wang**, None; **Z. Zhu**, None; **A. E. Wluka**, None; **W. Han**, None; **T. Winzenberg**, None; **L. Blizzard**, None; **G. Jones**, None; **C. Ding**, None.

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Abstract Number: 1022

The Risk of Symptomatic Knee Osteoarthritis after Arthroscopic Meniscus Repair Vs Partial Meniscectomy Vs the General Population

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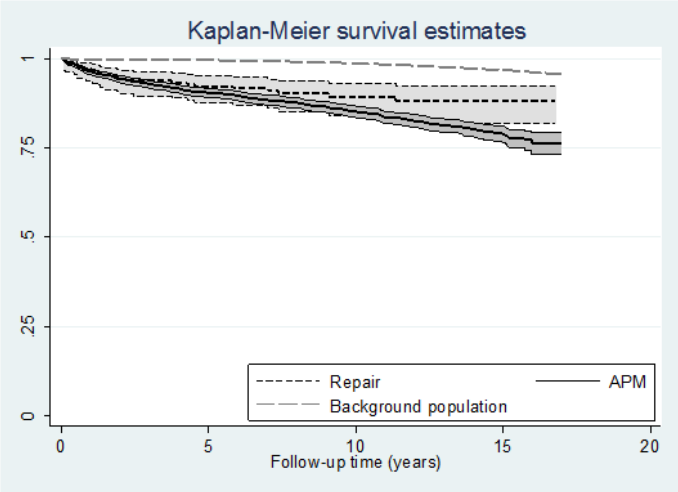
Background/Purpose: Traumatic meniscus injury is associated with increased risk of developing knee osteoarthritis (OA). The purpose of meniscus repair, beyond short time symptom relief and restoration of knee biomechanics, is to reduce the risk of later knee OA. However, the long-term consequences of meniscus repair have not been sufficiently investigated. Thus, our objective was to compare the consultation rate for symptomatic knee OA in patients after meniscus repair, arthroscopic partial meniscectomy (APM), and in the general population.

Methods: We identified patients aged 16-45 years having had meniscus surgery due to acute meniscus tear in 1998-2009 in southern Sweden by a healthcare register. All patients were followed from the time of first meniscus surgery until a diagnosis of knee OA, relocation outside the Skåne region, death, or December 31st, 2014. We studied the consultation rate for knee OA compared to the general population as well as calculated the age- and sex-adjusted hazard ratio (HR) for knee OA consultation after meniscus repair vs. APM.

Results: We identified 2409 patients with an acute meniscus tear (mean [SD] age 30.5 [8.6] years); 211 (8.8%) of them had had meniscus repair. The absolute risk of having consulted for knee OA during the study period was 16.4% after APM, 10.0% after meniscus repair, and 2.1% in the general population (Figure). The age- and sex-standardized incidence of knee OA was 110/10 000 person-years after meniscus repair, 165/10 000 person-years after APM, and 19/10 000 person-years in the general population. The HR for knee OA after repair vs APM was: 0.79 (95% confidence interval [CI] 0.51, 1.24). A sensitivity analysis, excluding cases with OA within the first 2 years post-surgery, yielded the HR of 0.53 (95% CI 0.27, 1.04).

Figure. The survival estimates for doctor-diagnosed knee osteoarthritis among persons aged 16 to 45 years in patients having had arthroscopic partial meniscectomy (APM), meniscal repair or in the general population.



Conclusion: The point estimates suggests about 20-50% lower risk of knee OA in patients after meniscus repair as compared to patients with APM. However, the consultation rate for OA after repair was still at least 2.5 times higher as compared to the general population.

Disclosure: M. Englund, None; **A. Turkiewicz**, None; **D. Bergkvist**, None; **P. Neuman**, None; **F. Persson**, None.

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Abstract Number: 1023

Fracture Risk Reduction with Romosozumab: Results of a Phase 3 Study in Postmenopausal Women with Osteoporosis

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Background/Purpose: Romosozumab (Romo) is an investigational bone-forming monoclonal antibody that binds sclerostin and has a dual effect, increasing bone formation and decreasing bone resorption. Here, we report results of the FRActure study in postmenopausal woMen with ostEoporosis (FRAME) (NCT01575834).

Methods: This multicenter, randomized, double-blind, placebo-controlled study enrolled postmenopausal women aged 55 to 90 years with osteoporosis (BMD T-score ≤ –2.5 at the total hip or femoral neck). Subjects were randomized 1:1 to subcutaneous placebo (Pbo) or 210 mg Romo monthly for 12 months, followed by subcutaneous denosumab (DMAb) every 6 months for 12 months in both groups. The co-primary endpoints were subject incidence of new vertebral fracture through month (M) 12 and M24. Secondary endpoints included clinical (nonvertebral plus symptomatic vertebral) and nonvertebral fracture, and BMD.

Results: A total of 7180 women (mean age 71 years, mean total hip T-score –2.5) were enrolled. At M12, Romo reduced new vertebral fracture, with a relative risk reduction (RRR) of 73% (subject incidence of fracture: 1.8% Pbo vs 0.5% Romo; $P < 0.001$). In subjects who

received Romo in year 1, vertebral fracture risk reduction persisted through M24 after both groups transitioned to DMAb (2.5% Pbo/DMAb vs 0.6% Romo/DMAb; RRR 75%; $P < 0.001$). Romo reduced clinical fracture risk at M12 (2.5% Pbo vs 1.6% Romo; RRR 36%; $P = 0.008$). Nonvertebral fracture incidence through M12 was 2.1% for Pbo (lower than expected) vs 1.6% for Romo (RRR 25%; $P = 0.096$), with a similar risk reduction through M24 (Pbo/DMAb vs Romo/DMAb RRR 25%; nominal $P = 0.029$, adjusted $P = 0.057$). A preplanned analysis revealed a significant interaction between treatment and geographic region for nonvertebral fracture at M12 ($P = 0.042$). Nonvertebral fracture incidence in Central/Latin America was 1.2% for Pbo vs 1.5% for Romo, whereas a 42% RRR in nonvertebral fracture was observed in rest-of-world ($P = 0.012$). Compared to Pbo, Romo increased BMD by 12.7% and 5.8% at the lumbar spine and total hip, respectively, at M12 ($P < 0.001$). Adverse events were generally balanced between groups, with injection-site reactions in 2.9% of Pbo subjects and 5.2% of Romo subjects during year 1. One atypical femoral fracture and 2 osteonecrosis of the jaw events were positively adjudicated in the Romo group through M24.

Conclusion: In postmenopausal women with osteoporosis, Romo 210 mg monthly was well tolerated and reduced vertebral and clinical fracture risk vs Pbo at M12; vertebral fracture risk reduction persisted in Romo subjects through M24 after both groups transitioned to DMAb. The sequence of Romo followed by DMAb may be a highly effective treatment for postmenopausal women with osteoporosis.

Disclosure: F. Cosman, Amgen, Eli Lilly, 2,Amgen, Eli Lilly, 8,Amgen, Eli Lilly, Merck, Radius, Sermonix, 5; **D. Crittenden**, Amgen, 3,Amgen, 1; **J. Adachi**, Amgen, Eli Lilly, Pfizer, 2,Amgen, Eli Lilly, 5,International Osteoporosis Foundation, Osteoporosis Canada, 6,Amgen, Eli Lilly, 8; **N. Binkley**, Amgen, GE Healthcare, Lilly, Merck, Opko Ireland, 2,Amgen, Astellas, Bristol-Myers Squibb, Lilly, Merck, Nestle, 5; **E. Czerwinski**, Amgen, 2,Amgen, 9; **S. Ferrari**, MSD, 2,Amgen, MSD, UCB, 5; **L. Hofbauer**, Amgen, Novartis, 2,Alexion, Amgen, Eli Lilly, Merck, UCB, 5; **E. Lau**, None; **E. Lewiecki**, Amgen, Merck, Lilly, 2,Amgen, Merck, Lilly, Shire, Alexion, 5,Shire, 8; **A. Miyauchi**, Amgen Astellas BioPharma K.K., 5; **C. Zerbini**, Pfizer, Lilly, Amgen, Merck, Sanofi, 2,Pfizer, Lilly, Sanofi, 5; **C. Milmont**, Amgen, 3,Amgen, 1; **L. Chen**, Amgen, 3,Amgen, 1; **J. Maddox**, Amgen, 3,Amgen, 1; **P. Meisner**, UCB Pharma, 3,UCB Pharma, 1; **C. Libanati**, UCB Pharma, 1,UCB Pharma, 3; **A. Grauer**, Amgen, 3,Amgen, 1.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/fracture-risk-reduction-with-romosozumab-results-of-a-phase-3-study-in-postmenopausal-women-with-osteoporosis

Abstract Number: 1024

Superior Gains in Bone Mineral Density and Estimated Strength at the Hip for Romosozumab Compared with Teriparatide in Women with Postmenopausal Osteoporosis Transitioning from Bisphosphonate Therapy: Results of a Phase 3, Open-Label Clinical Trial

B Langdahl[1], C Libanati[2], DB Crittenden[3], MA Bolognese[4], **JP Brown**[5], NS Daizadeh[3], K Engelke[6], HK Genant[7], S Goemaere[8], Lars Hyldstrup[9], E Jodar-Gimeno[10], TM Keaveny[11], D Kendler[12], P Lakatos[13], J Maddox[3], J Malouf[14], FE Massari[15], JF Molina[16], MR Ulla[17] and A Grauer[3], [1]Aarhus University Hospital, Aarhus, Denmark, [2]UCB Pharma, Brussels, Belgium, [3]Amgen Inc., Thousand Oaks, CA, [4]Bethesda Health Research Center, Bethesda, MD, [5]Laval University and CHU de Québec (CHUL) Research Centre, Quebec City, QC, Canada, [6]BioClinica Inc., Hamburg, Germany, [7]Department of Radiology, University of California San Francisco, San Francisco, CA, [8]Ghent University Hospital, Gent, Belgium, [9]Hvidovre University Hospital, Hvidovre, Denmark, [10]Servicio de Endocrinología, Hospital Universitario Quirón, Madrid, Spain, [11]University of California at Berkeley, Berkeley, CA, [12]University of British Columbia, Vancouver, BC, Canada, [13]Department of Medicine, Semmelweis University, Budapest, Hungary, [14]Universitat Autònoma de Barcelona, Barcelona, Spain, [15]Instituto de Investigaciones Metabólicas, Buenos Aires, Argentina, [16]Reumalab Centro Integral de Reumatologia, Medellin, Colombia, [17]Instituto Latinoamericano de Investigaciones Médicas, Córdoba, Argentina

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Background/Purpose: STRUCTURE was a phase 3, open-label study evaluating the effect of romosozumab or teriparatide for 12 months in women with postmenopausal osteoporosis transitioning from bisphosphonate therapy (NCT01796301).

Methods: This multicenter, active-controlled study enrolled women with postmenopausal osteoporosis who had taken an oral bisphosphonate for ≥ 3 years prior to screening and alendronate (70 mg weekly or equivalent) in the year prior to screening; had a bone

mineral density (BMD) T-score ≤ –2.5 at the total hip, lumbar spine, or femoral neck; and had a history of nonvertebral fracture after age 50 or vertebral fracture. Subjects received daily calcium and vitamin D and were randomized to receive subcutaneous romosozumab 210 mg once monthly or teriparatide 20 µg once daily. The primary endpoint was percent change from baseline in BMD by DXA at the total hip through month 12 (the average at months 6 and 12). Secondary endpoints included percent change from baseline at months 6 and 12 in BMD by DXA at the total hip, lumbar spine, and femoral neck; hip integral and cortical BMD by quantitative computed tomography (QCT); and estimated hip strength by finite element analysis. Imaging assessments were done blinded to treatment.

Results: A total of 436 women, with a mean age of 72 years, were randomized to receive romosozumab (N = 218) or teriparatide (N = 218). Baseline mean total hip, lumbar spine, and femoral neck T-scores were –2.2, –2.9, and –2.5, respectively. Through 12 months, the mean (95% CI) percent change from baseline in total hip BMD by DXA was 2.6% (2.2, 3.0) with romosozumab and –0.6% (–1.0, –0.2) with teriparatide ($p < 0.0001$ between groups). Total hip BMD changes at months 6 and 12 were significantly larger with romosozumab than with teriparatide ($p < 0.0001$): month 6, 2.3% (1.9, 2.7) vs –0.8% (–1.2, –0.4); month 12, 2.9% (2.5, 3.4) vs –0.5% (–0.9, 0), respectively. Romosozumab also resulted in significantly larger BMD gains at the lumbar spine at months 6 and 12 vs teriparatide ($p < 0.0001$): month 6, 7.2% (6.6, 7.8) vs 3.5% (2.9, 4.0); month 12, 9.8% (9.0, 10.5) vs 5.4% (4.7, 6.1), respectively. QCT assessments of the hip demonstrated significantly greater gains in integral and cortical BMD with romosozumab vs teriparatide at months 6 and 12 ($p < 0.0001$). Estimated hip strength gains were also significantly larger with romosozumab at both time points ($p < 0.0001$) and declined from baseline in teriparatide-treated subjects at month 6. The subject incidences of treatment emergent adverse events and adverse events of interest were generally balanced between treatment groups.

Conclusion: In subjects transitioning from bisphosphonate therapy, romosozumab was well-tolerated and was associated with significant BMD gains at both the hip and spine compared with teriparatide. BMD gains in the cortical compartment contributed to the greater treatment effect of romosozumab at the hip. Estimated hip strength improved with romosozumab over 12 months but decreased early with teriparatide. A global phase 3 program evaluating romosozumab for the treatment of postmenopausal osteoporosis is ongoing.

Disclosure: B. Langdahl, Eli Lilly, Novo Nordisk, Orkla Health, 2,Amgen, Eli Lilly, Merck, UCB,, 5,Amgen, Eli Lilly, Merck, 8; **C. Libanati**, UCB, 1,UCB Pharma, 3; **D. Crittenden**, Amgen Inc., 1,Amgen Inc., 3; **M. Bolognese**, Amgen Inc., 8; **J. Brown**, Amgen Inc., Eli Lilly, 2,Amgen Inc., Eli Lilly, Merck, 5,Amgen Inc., Eli Lilly, 8; **N. Daizadeh**, Amgen Inc., 1,Amgen Inc., 3; **K. Engelke**, German Research Organizations, 2,Bioclinica (part time), 3,Amgen Inc., Radius, 5; **H. Genant**, Agnovos, Amgen Inc., BioClinica, Biomarin, Clementia, Daiichi, Janssen, Lilly, Merck, Novartis, Medtronic,Pfizer, 5; **S. Goemaere**, Amgen Inc., 8; **L. Hyldstrup**, Amgen, Eli-Lilly, 8; **E. Jodar-Gimeno**, Amgen Inc., MSD, 2,Amgen Inc., Lilly, MSD, 5,Amgen Inc., Lilly, 8; **T. Keaveny**, Agnovos, Amgen Inc., and O.N. Diagnostics, 5,O.N. Diagnostics, 1; **D. Kendler**, Amgen Inc., Astalis, Astra Zeneca, Eli Lilly, 2,Amgen Inc., Eli Lilly, Merck, 5,Board representative to Doctors of BC, 6,Amgen Inc., Eli Lilly, Merck, 8; **P. Lakatos**, None; **J. Maddox**, Amgen Inc., 1,Amgen Inc., 3; **J. Malouf**, Amgen Inc., Lilly, Gruenenthal, Mundipharma, 5,Amgen Inc., Lilly, Gruenenthal, Mundipharma, 8; **F. Massari**, None; **J. Molina**, Amgen Inc., 2; **M. Ulla**, None; **A. Grauer**, Amgen Inc., 1,Amgen Inc., 3.

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Abstract Number: 1025

Assessment of the Effects of Switching Bisphosphonates to Denosumab or Daily Teriparatide in Patients with Rheumatoid Arthritis

Kosuke Ebina[1], Makoto Hirao[2], Jun Hashimoto[3], Masao Yukioka[4], Takaaki Noguchi[5] and Hideki Yoshikawa[6], [1]Orthopaedic Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [2]Orthopaedic Surgery, Osaka University, Graduate School of Medicine, Suita, Japan, [3]Dept of Rheumatology, Osaka-Minami Medical Center, Kawachinagano City, Japan, [4]Orthopedic Surgery, Yukioka Hospital, Osaka, Japan, [5]Orthopaedic Surgery, Osaka University, Graduate School of Medicine, Osaka, Japan, [6]Department of Orthopedics, Osaka University Graduate School of Medicine, Suita Osaka, Japan

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Background/Purpose: The efficacies of switching bisphosphonate (BP) to denosumab (DMAb), an anti-RANKL antibody which strongly inhibits bone resorption, or daily teriparatide (TPTD), a bone anabolic agent which induce bone formation, has been reported in primary osteoporosis. However, its adaptation and efficacies in patients with rheumatoid arthritis (RA) still lack reliable evidence and also no

previous reports directly compared the results of these two switching treatments.

Methods: 194 patients with RA treated by BP [177 female, 65.9 years old, disease duration 17.8 years, RF positivity 77.8%, DAS28-CRP 2.3, 75.8% with oral prednisolone (PSL) 3.6mg/day, 23.2% with biologics, prior BP duration 40.0 months, prior vertebral fracture rate 41.8%, T-scores: lumbar spine (LS) -1.8, femoral neck (FN) -2.3, total hip (TH) -2.0] were allocated to either the (1) BP-continued group (BP; n=80), (2) switched-to-DMAb group (DMAb; n=74), or (3) switched-to-TPTD group (TPTD; n=40) based on each physicians' decision and followed up for 12 months by monitoring bone mineral density (BMD), trabecular bone score (TBS), bone turnover markers, and fracture incidence.

Results: At baseline, TPTD group showed significantly lower T-scores than BP group in all resions ($P<0.05$), while no significant differences were observed between DMAb and BP group, and DMAb and TPTD group. Changes of BMD from baseline→6→12 months were as follows. (1) BP group: LS; 0→1.1→2.5%, TH; 0→0.3→0.2%, FN; 0→0.5→0.8%, (2) DMAb group: LS; 0→2.8→4.9%, TH; 0→1.5→3.0%, FN; 0→2.0→3.9%, (3) TPTD group: LS; 0→4.2→6.0%, TH; 0→-1.4→1.4%, FN; 0→-1.1→2.1%. TBS changed from baseline to 12 months as follows. (1) BP group: -1.4%, (2) DMAb group: 0.4%, (3) TPTD group: 2.7%. DMAb group showed significant increase in LS, TH, and FN BMD ($P<0.01$) and maintained TBS ($P<0.01$) compared to BP group at 12 months, and TPTD group showed significant increase in LS BMD ($P<0.01$) and TBS ($P<0.001$) compared to BP group at 12 months. TPTD group showed similar increase in LS, TH, and FN BMD, while significantly increased TBS ($P<0.05$) compared to DMAb group at 12 months. Changes of bone turnover markers were as follows. (1) BP group: bone resorption marker, TRACP-5b; 0→-3.5→1.4%, bone formation marker, PINP; 0→-9.6→-13.4%, (2) DMAb group: TRACP-5b; 0→-28.5→-27.9%, PINP; 0→-14.5→-17.6%, (3) TPTD group: TRACP-5b; 0→77.1→77.6%, PINP; 0→296.5→227.7%. DMAb group showed significant decrease in TRACP-5b ($P<0.001$), and TPTD group showed significant increase in TRACP-5b and PINP ($P<0.001$) compared to BP and DMAb group at 12 months. The fracture incidence during this period was (1) BP group: 3.8% (1 vertebra, 1 forearm, and 1 humerus), (2) DMAb group: 1.4% (1 rib), (3) TPTD group: 2.5% (1 toe). DMAb and TPTD group showed no major fractures during this period.

Conclusion: Switching oral BP to DMAb significantly increased LS, TH, and FN BMD, and decreased TRACP-5b, while switching to TPTD increased LS BMD, TBS, and total bone turnover at most compared to continuing BP at 12 months. Our results indicate that switching BP to DMAb or TPTD by determining treatment target may provide useful treatment option in RA associated osteoporosis.

Disclosure: K. Ebina, Daiichi Sankyo, 8; **M. Hirao**, None; **J. Hashimoto**, None; **M. Yukioka**, None; **T. Noguchi**, None; **H. Yoshikawa**, None.

Abstract Number: 1026

Morphea-like Skin Lesions Reported in the Phase 3 Long-Term Odanacatib Fracture Trial and Extension in Postmenopausal Women with Osteoporosis

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Background/Purpose: Odanacatib (ODN) is a selective oral inhibitor of cathepsin K (CatK) in development for the treatment of osteoporosis. Because of reports with the CatK inhibitor balicatib, morphea-like skin lesions were deemed Events of Clinical Interest in the Phase 3 Long-Term Odanacatib Fracture Trial (LOFT; NCT00529373).

Methods: LOFT was a double-blind, placebo-controlled trial. Women ≥65 years with total hip (TH) or femoral neck (FN) bone mineral density (BMD) T-score ≤-2.5, or with a radiographic vertebral fracture and T-score ≤-1.5 at TH or FN, were randomized (1:1) to ODN 50 mg/week or placebo. In a preplanned double-blind extension, 51% of patients continued on their originally assigned treatment up to 5 years. As part of the safety evaluation, external adjudication committees evaluated specific adverse event (AE) categories, including AEs with skin changes suggestive of morphea or systemic sclerosis.

Results: Of 16,713 participants randomized at 388 centers in 40 countries, 16,071 were included in the safety analysis; of these, 12,290 completed the base study, 8,257 continued into and 6,047 completed the extension. Adjudication confirmed morphea-like skin lesions occurred in 13 patients (0.16%) treated with ODN versus 3 patients (0.04%) treated with placebo. The time of onset varied from Study Day 115 to 1315, with 3 cases occurring in the first year of the study and 10 cases occurring within the first two years. Lesions were characterized most consistently as indurated (often termed “hardened” or “thickened”), with pallor, pruritus, and erythema reported less frequently. Although histopathology was generally consistent with that of spontaneous (idiopathic) morphea, atypical features included pandermal involvement and occasionally dense eosinophilic infiltrates. Most lesions affected the trunk or lower extremities. There were no reports of accompanying constitutional symptoms or systemic involvement. All ODN-treated patients were negative for autoantibodies. Study medication was discontinued in all but one patient (ODN). As of the last follow-up, 12/16 cases (10 ODN, 2 placebo) were reported as fully recovered (including the patient who continued on ODN), 3/16 (3 ODN) as improved or recovering, and the remaining patient (placebo) declined further contact.

Conclusion: Confirmed morphea-like skin lesions were uncommon but occurred more often with ODN than placebo. Although the gross features and histopathology of these lesions were generally consistent with those of spontaneous morphea, in all patients in whom follow-up was obtained improvement or full recovery was reported.

Disclosure: K. G. Saag, Amgen, Lilly, Merck, 2,Amgen, Lilly, Merck, 5; **T. de Villiers**, Pfizer, Merck, Abbott, Adcock Ingram, 5,Pfizer, Merck, Abbott, Adcock Ingram, Bayer, 8; **P. Alexandersen**, CCBR, 3; **H. Jacobe**, Merck Co., 5; **C. Kovarik**, Merck Co., 5; **V. P. Werth**, Amgen, Rigel, Janssen, Novartis, Invion, 2,Medimmune, Genentech, Novartis, Pfizer, Cephalon, UV Therapeutics, Rigel, Biogen, Lupus Foundation of America, Sanofi-Aventis, Stiefel, Merck, RPS, Idera, Canfield, Celgene, 5,Amgen, Merck, 8,UV Therapeutics, 1,Philadelphia VAMC and University of Pennsylvania - employment;, 3,Head MAB, International Pemphigus and Pemphigoid Foundation - non-remunerative, 9; **A. Leung**, Merck Co. - former employee, 3; **A. Desai-Merchant**, Merck Co., 3; **J. Mattaliano**, Merck Co., 3; **D. Gurner**, Merck Co., 3.

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Abstract Number: 1027

Odanacatib Efficacy and Safety in Postmenopausal Women with Osteoporosis: 5-Year Data from the Extension of the Phase 3 Long-Term Odanacatib Fracture Trial

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Background/Purpose: Odanacatib (ODN) is a selective oral inhibitor of cathepsin K in development for the treatment of osteoporosis. The randomized, double-blind, placebo (PBO) controlled, event-driven, Phase 3 Fracture Trial (Long-Term Odanacatib Fracture Trial [LOFT]; NCT00529373) evaluated efficacy and safety of ODN in postmenopausal women with osteoporosis. In a planned double-blind

extension to LOFT, eligible patients continued on their originally assigned treatment for up to 5 years. We present efficacy and safety data for the entire 5-year double-blind period.

Methods: Women ≥65 years of age with BMD T-score ≤–2.5 at total hip (TH) or femoral neck (FN), or with radiographic vertebral fracture (VFx) and T-score ≤–1.5 at TH or FN, were randomized (1:1) to ODN 50 mg/week or PBO. All received vitamin D_3 (5600 IU/week) and calcium as required. Endpoints included morphometric VFx, hip fracture, non-VFx, clinical VFx, and safety and tolerability. Specific adverse events (AEs) were adjudicated.

Results: Of 16,071 patients (8043 ODN, 8028 PBO) in LOFT, 12,290 (6092 ODN, 6198 PBO) completed the study. Among these, 8,257 (4297 ODN, 3960 PBO) who were eligible and consented entered the extension and 6,047 (3432 ODN, 2615 PBO) completed it. Mean (SD) age at randomization was 72.8 (5.3) years, 46.5% had prior VFx, and mean BMD T-scores were lumbar spine (LS) –2.7, TH –2.4, and FN –2.7. Mean (SD) follow-up was approximately 44 (18) months. Compared with PBO, ODN treatment over 5 years resulted in relative risk reductions of 52% for morphometric VFx, 48% for hip fracture, 26% for non-VFx, and 67% for clinical VFx (all p<0.001). Compared with PBO, ODN treatment led to progressive mean percent increases (95% CI) in BMD of 10.9% (10.5, 11.2) at LS and 10.3% (10.0, 10.6) at TH (both p<0.001) at 5 years. Incidences of AEs and serious AEs overall were balanced for ODN vs PBO (88.3 vs 88.2% and 30.3 vs 30.4%, respectively). Deaths reported in patients being followed on study were 378 (4.7%) vs 327 (4.1%), ODN vs PBO, respectively (HR 1.12 [95% CI: 0.97, 1.30]); more complete ITT analysis of deaths among all patients, including those who discontinued from study, showed 682 (8.5%) vs 660 (8.2%), respectively (HR 1.04 [95% CI: 0.93, 1.16]). Delayed fracture union occurred in 18 patients in each group. Femoral shaft fractures occurred more often with ODN (26 patients [0.3%] vs 7 [0.1%]), of which 10 (0.1%) on ODN and none on PBO met criteria for atypical femoral shaft fractures (AFFs). No cases of osteonecrosis of the jaw (ONJ) were confirmed. Morphea-like skin lesions occurred more often with ODN (13 [0.2%] vs 3 [<0.1%]), most with onset within 2 years and 15 of 16 improved or fully recovered. Systemic sclerosis occurred in 2 (<0.1%) with ODN vs 1 (<0.1%) with PBO. Independent adjudication of CV events is ongoing and will be presented separately.

Conclusion: Consistent with the results of LOFT, treatment with ODN for up to 5 years reduced the risk of hip, vertebral and non-vertebral fractures. Overall incidence of AEs, including serious AEs, was generally balanced between ODN and PBO. Femoral shaft fractures, including AFFs, and morphea-like skin lesions were uncommon but more frequent with ODN.

Disclosure: M. R. McClung, Amgen, Merck, 5; **B. Langdahl**, Lilly, Novo Nordisk, Orkla, 2,Amgen, Lilly, Merck, UCB, 5,Merck, Amgen, Lilly, 8; **S. Papapoulos**, Amgen, Axsome, Merck, Mereo Biopharma, UCB, 5; **K. G. Saag**, Amgen, Lilly, Merck, 2,Amgen, Lilly, Merck, 5; **H. Bone**, Amgen, Merck, 2,Merck, Amgen, Novartis, Grunenthal, Radius, 5,Amgen, Shire, 8; **D. P. Kiel**, Merck, Lilly, 2,Merck, Lilly, Amgen, Novartis, 5,Wolters Kluwer, 9; **K. Lippuner**, Amgen, Lilly, Merck, 5; **T. Nakamura**, MSD, Amgen, Asahi-Kasei, Chugai, 5; **I. Reid**, Amgen, Merck, Novartis, 2,Lilly, Merck, Novartis, Amgen, 5; **N. Heyden**, Merck Co., 3; **C. DaSilva**, Merck Co., 3; **B. B. Scott**, Merck Co., 3; **R. Massaad**, MSD Europe Inc., 3; **K. D. Kaufman**, Merck Co., 3; **S. A. Stoch**, Merck Co., 3; **A. Santora**, Merck Co., 3; **D. Gurner**, Merck Co., 3; **A. Lombardi**, Merck Co., 3.

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Abstract Number: 1028

Discontinuation of Denosumab and Associated Vertebral Fracture Incidence: Analysis from a Phase 3 Placebo-Controlled Study of Denosumab and Its Open-Label Extension

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Background/Purpose: Denosumab (DMAb) treatment has been shown to decrease fracture (Fx) risk. Unlike bisphosphonates, DMAb is a

monoclonal antibody against RANKL. Discontinuation is characterized by reversal of effect, including transient increases in bone turnover markers to above-baseline (BL) levels returning to BL within 2 yr and loss of bone mineral density (BMD) to BL levels. An analysis from FREEDOM showed similar subject incidence of Fx in DMAb and placebo (PBO) groups upon discontinuation. Recent reports describe isolated cases of multiple (≥2) vertebral Fx (VFx) after DMAb cessation (Aubrey-Rozier *OI* 2015; Anastasilakis *OI* 2015; Popp *OI* 2016). To better understand VFx incidence—particularly multiple VFx—upon DMAb cessation, we describe VFx risk and possible determinants in subjects who discontinued DMAb during the 3-yr FREEDOM or 7-yr Extension.

Methods: Subjects who received ≥2 doses of investigational product (IP; DMAb 60 mg Q6M or PBO) and discontinued IP but stayed in study ≥7 M after the last dose were included in the analysis. Subjects who discontinued DMAb from FREEDOM or Extension were analyzed as one group. A logistic regression model explored covariates related to off-treatment new VFx or multiple new VFx.

Results: Of 1001 subjects who discontinued DMAb during FREEDOM or Extension, 56 (5.6%) sustained new VFx. Upon DMAb discontinuation, new VFx incidence increased relative to the on-treatment period but stayed within the range of those who discontinued PBO, ie, had never been treated (Table). The same pattern was seen in subjects with prior VFx, who had higher on- and off-treatment VFx rates than the overall population. Among subjects with off-treatment new VFx, a greater percentage of those who discontinued DMAb (34/56 [60.7%]) than PBO (10/29 [34.5%]) sustained multiple new VFx. Logistic regression models found prior VFx before or during treatment to be the strongest predictor of off-treatment new VFx, including multiple VFx (odds ratio 2.1-3.4). Off-treatment femoral neck BMD loss was a weak covariate.

Conclusion: Discontinuation of DMAb is associated with an increase in VFx rate to levels comparable to PBO. Among subjects who sustained new VFx after DMAb cessation, there was a greater incidence of multiple new VFx than in PBO. Subjects with prior VFx are at high risk for off-treatment new VFx and should continue osteoporosis therapy. Consequently those who discontinue DMAb should transition to another therapy after the 6-M dosing interval. **Table. Off-treatment vertebral fracture incidence in subjects who discontinued IP in FREEDOM or its Extension**

	FREEDOM	FREEDOM + Extension
	Placebo	Denosumab
All subjects	N = 470	N = 1,001
Off-treatment new VFx, n (%)	29 (6.2%)	56 (5.6%)
Off-treatment multiple new VFX, n (%) [among all subjects]	10 (2.1%)	34 (3.4%)
Off-treatment multiple new VFX, n (%) [among all subjects with new VFx]	10 (34.5%)	34 (60.7%)
On-treatment new VFx (per 100 subject-years)	7.0	1.2
Off-treatment new VFx (per 100 subject-years)	8.0	7.1
Subjects with prior VFx before treatment	N = 122 (26%)	N = 255 (25%)
Off-treatment new VFx, n (%)	12 (9.8%)	19 (7.5%)
Off-treatment multiple new VFx, n (%) [among subjects with prior VFx]	5 (4.1%)	15 (5.9%)
Off-treatment multiple new VFx, n (%) [among subjects with prior VFx and new VFx]	5 (41.7%)	15 (78.9%)
On-treatment new VFx (per 100 subject-years)	11.6	1.9
Off-treatment new VFx (per 100 subject-years)	14.4	12.1

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Abstract Number: 1029

Functional Genetics of PTPN2 in Rheumatoid Arthritis: Haploinsufficiency of PTPN2 Promotes Severity of Th17-Cell Mediated Autoimmune Arthritis

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Background/Purpose: Genome-wide association studies have linked polymorphisms in the *PTPN2* locus to rheumatoid arthritis (RA). *PTPN2* encodes the tyrosine phosphatase TC-PTP, an important regulator of cytokine signaling. Disease-associated variants of *PTPN2* result in a partial loss of expression. To model the functional genetics of *PTPN2* in mice, we studied the effect of *PTPN2* haploinsufficiency in the SKG mouse, a spontaneous $CD4^+$ T-cell-driven model of autoimmune arthritis.

Methods: Development of spontaneous and/or mannan-induced arthritis was evaluated in SKG mice. $CD4^+$ T-cells isolated from SKG mice were transferred to $RAG2^{-/-}$ mice. Clinical scoring of arthritis was followed by histological and micro-CT analysis. Flow cytometry was used to assess T-cell development and T-cell effector populations. Gene expression was analyzed using qPCR. Statistical differences were calculated using the Mann-Whitney or un-paired T tests.

Results: Haploinsufficiency of *PTPN2* caused increased severity of spontaneous *(P=0.003)* and mannan-induced (*P=0.007*) arthritis in SKG mice, with high expression of *TNF (P=0.056)*, *IL-1b* (*P=0.020*), *IL-6 (P=0.026)* and *RANKL (P=0.007)* in arthritic joints. $PTPN2^{+/-}$ mice showed an increased presence of ectopic lymphoid-like structures within arthritic joints, correlating with an increased expression of *Cxcl13 (P=0.035)*. Increased susceptibility to arthritis could be transferred to $RAG2^{-/-}$ mice by $PTPN2^{+/-}$ $CD4^+$ T-cells (*P=0.011 vs* $PTPN2^{+/+}$ $CD4^+$ T-cells). Next we generated a novel C57BL/6 mouse carrying the SKG mutation and the $H2^d$ haplotype (B6.$H2^d$.SKG), which showed similar arthritis development as BALB/c SKG mice. B6.$H2^d$.SKG carrying T-cell specific haploinsufficiency of *PTPN2* (Lck-Cre^+.$PTPN2^{floxed/wild\ type}$) developed increased severity of arthritis (*P=0.002*) when compared to WT mice. Further investigation into the effect of *PTPN2* haploinsufficiency in T-cell function revealed no alterations in thymocyte development or selection; however, $PTPN2^{+/-}$ SKG mice had an increased accumulation of Th17 cells (*P=0.027*) in arthritic joints which correlated to an increased sensitivity to IL-6 stimulation in $PTPN2^{+/-}$ CD4+ T-cells.

Conclusion: Haploinsufficiency of human RA-associated *PTPN2* mediates autoimmune arthritis in mice by rendering $CD4^+$ T-cells more susceptible to IL-6 stimulation and promoting expansion of pathogenic Th17 cells in arthritic joints. We validate our newly generated B6.$H2^d$.SKG model as a novel powerful tool for mechanistic studies of RA pathogenesis.

Disclosure: M. N. D. Svensson, None; **K. M. Doody**, None; **C. Sacchetti**, None; **D. J. Wu**, None; **G. Kim**, None; **A. Hellvard**, None; **B. Bergum**, None; **P. Mydel**, None; **M. Kronenberg**, None; **M. L. Tremblay**, None; **N. Bottini**, None.

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Abstract Number: 1030

Synovial Tissue Resident Macrophages Play the Protective Role in the Development of Inflammatory Arthritis in CD11c-Flip-KO Mice

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Synovial Tissue Resident Macrophages Play the protective role in the Development of Inflammatory Arthritis in CD11c-Flip-KO Mice

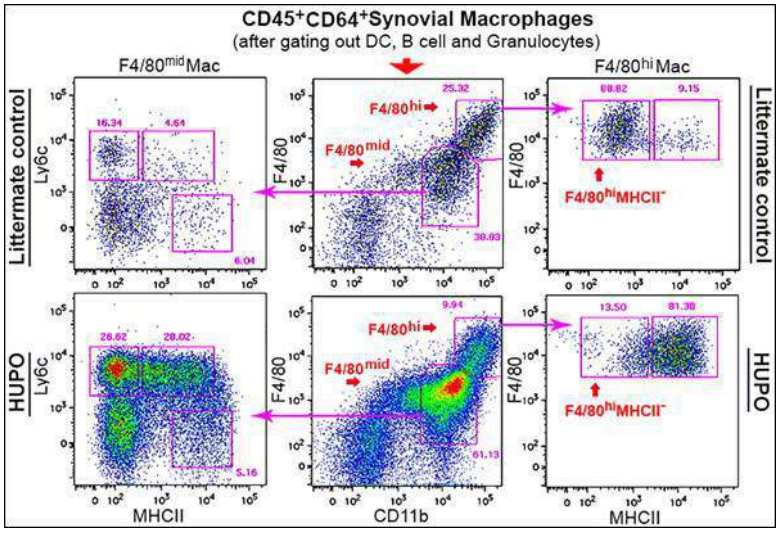
Qi-Quan Huang[1], Renee Doyle[1], Robert Birkett[1] and Richard M. Pope[1]

Background/Purpose: We have generated a CD11c-Flip-KO (HUPO) mouse line that spontaneously develops erosive arthritis resembling rheumatoid arthritis. Arthritis spontaneously developed beginning at 5weeks of age in ~10% of HUPO, progressing to ~80% incidence at ≥20 weeks. HUPO mice crossed with Rag-/- mice developed a mild non-progressive arthritis due to macrophage infiltration, supporting an important role for macrophages in disease pathogenesis. This study examined the phenotype of macrophages in the joints of littermate control mice and of ≥ 20 week old HUPO mice with and without arthritis.

Methods: Ankle joint cells were dissected and digested with collagenase. Cells were analyzed by flow cytometry employing multicolor fluorochrome-antibodies. Arthritis were evaluated by clinical score for the inflammation, joint deformity and grip strength, ranging from 0-28.

Results: Under homeostatic conditions in control mice synovial macrophages are defined as $CD11b^+CD64^+F4/80^+$, about 90% co-express $CD11c^+$. Further, macrophages may be defined as $F4/80^{hi}$ or $F4/80^{mid}$ (Figure). The $F4/80^{mid}$ $Ly6C^+$ $MHCII^-$ are macrophages recently differentiated from peripheral blood monocytes. Increase of MHCII and loss of Ly6C represents progressive stages of macrophage differentiation. The percent $F4/80^{mid}$ $Ly6C^+$ $MHCII^-$ macrophages were increased ($p < 0.001$) in ankles of HUPO mice with arthritis, compared with littermate controls. The $F4/80^{hi}$ macrophages are $Ly6C^-$, and either $MHCII^+$ or $MHCII^-$. During homeostasis, the $F4/80^{hi}$ $MHCII^-$ macrophages are considered as tissue resident macrophages. $F4/80^{hi}$ $MHCII^-$ tissue resident macrophages are greatly reduced and $F4/80^{hi}$ $MHCII^+$ macrophages increased ($p < 0.01$-0.001) in HUPO mice with arthritis, compared with littermate controls or HUPO mice without arthritis. $F4/80^{hi}$ $MHCII^-$ macrophages were also decreased in the joints of HUPO mice at 4 weeks, before arthritis onset. In HUPO mice the $F4/80^{hi}$ $MHCII^-$ macrophages were inversely correlated ($p = 0.023$) with arthritis severity, while the $F4/80^{hi}$ $MHCII^+$ macrophages were positively correlated ($p = 0.024$). Further supporting the role of $F4/80^{hi}$ $MHCII^-$ macrophages in suppressing inflammation, the percent $F4/80^{hi}$ $MHCII^-$ macrophages was strongly, inversely correlated ($r = -0.874$, $p<0.001$) with the percent granulocytes in the synovial tissue.

Conclusion: In HUPO mice the reduction of synovial tissue resident macrophages, which are also $CD11c^+$, was highly associated with inflammation and the onset and severity of arthritis. The influx of peripheral blood monocytes and their differentiation into macrophages was observed in HUPO arthritis. Approaches to preserve tissue resident macrophages or to decrease influx of peripheral blood monocytes may be effective therapeutically in HUPO, and potentially other forms of inflammatory arthritis.



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Abstract Number: 1031

Glucocorticoid Receptor Dimerization in Stromal Cells Modulates Macrophage Polarization during Serum Transfer-Induced Arthritis

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Session Time: 4:30PM-6:00PM

Background/Purpose: Rheumatoid arthritis is commonly treated with potent anti-inflammatory glucocorticoids (GC), despite severe side effects such as osteoporosis and insulin resistance associated with chronic dosing of GCs. The prevailing view is that GCs solely rely on repression of cytokines and elimination of immune cells for their anti-inflammatory effects. However, we now show that these direct effects on immune cells are insufficient. GCs modulate transcription by activating the glucocorticoid receptor (GR), a ligand activated transcription factor that binds DNA either as a monomer or dimer. Whereas previously the anti-inflammatory actions of the monomeric GR were considered to be sufficient for immune suppression, we demonstrate for a variety of disease models including arthritis, that GR dimerization is essential to reduce inflammation.

Methods: We induced serum transfer-induces arthritis (STIA) in wild type (wt) mice and in mice with impaired GR dimerization (GR^{dim}) and treated them with Dexamethasone (Dex) or PBS after the onset of STIA. To test the importance of immune cells, we generated bone marrow chimeric GR^{dim} mice, reconstituted with wt hematopoietic cells (wt/GR^{dim}) and wt/wt littermates, induced STIA and treated with Dex or PBS as a control. Disease severity was assessed clinically and histologically and inflamed ankles were analysed by flow cytometry, iTRAQ proteomics and qPCR. Co-culture of wt and GR^{dim} fibroblast-like synoviocytes (FLS) and bone marrow derived macrophages (BMDM) were used to analyse the interplay of FLS and BMDM *in vitro*.

Results: GR^{dim} mice are not able to resolve the infiltration of immune cells in STIA after Dex treatment in contrast to wt control mice. Unexpectedly, we show that wt/GR^{dim}-chimeras, with impaired GR dimerization in non-immune, radio-resistant cells are resistant to Dex treatment in STIA, too. Flow cytometry analysis of inflamed ankles of wt/wt- and wt/GR^{dim}-chimeras with STIA reveals a reduction of leukocytes (70%) in wt/wt but not in wt/GR^{dim}-chimeras treated with Dex. Moreover, Dex induced non-classical, non-activated M2-like macrophages (F4/80+, Ly6C-, MHCII-) are only evident in wt/wt- (+70% compared to wt/wt-chimeras treated with PBS) but not wt/GR^{dim}-chimeras. Proteomics and gene expression analysis of inflamed ankles confirmed the induction of known M2 polarization markers of macrophages, such as CD163, CD36 and MerTK after Dex treatment of STIA in wt/wt-chimeras, which was absent in wt/GR^{dim}-chimeras. We corroborated our findings in an in vitro co-culture system of GR^{dim} FLS with wt primary BMDMs. Concomitant TNF/Dex treatment induced CD163 in wt co-cultures, but not in GR^{dim}FLS co-cultured BMDMs.

Conclusion: Taken together, we discovered a novel anti-inflammatory mechanism of corticosteroids that involves GR dimerization dependent gene regulation in non-immune cells to control M2 polarization of macrophages for resolution of arthritis.

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Abstract Number: 1032

Early In Vivo Induction of Mouse Interferon-alpha1 Overexpression Triggers an Expansion of Highly Suppressive Regulatory T Lymphocytes Protecting Against Experimental Arthritis

Katarzyna Matyja[1,2], Matthieu Ribon[1,2], Roxane Hervé[1,2], Delphine Lemeiter[1,2], Ken Tsumiyama[3], Natacha Bessis[1,2], Shunichi Shiozawa[3], Marie-Christophe Boissier[1,2,4] and **Patrice Decker**[1,2], [1]Li2P, University of Paris 13, Sorbonne Paris Cité, Bobigny, France, [2]UMR 1125, Inserm, Bobigny, France, [3]Department of Medicine, Rheumatic Diseases Unit, Kyushu University Beppu Hospital, Beppu, Japan, [4]Rheumatology Department, Assistance Publique – Hôpitaux de Paris (AP-HP), Avicenne Hospital, Bobigny, France
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Background/Purpose: Type I interferons (IFN-I) can be both anti- and pro-inflammatory. Among them, IFN-α inhibits normal Th17 differentiation, whereas it is pathogenic in lupus. The role of IFN-I is also controversial in rheumatoid arthritis (RA) and experimental models. An IFN-I signature has been reported in RA patients, the signification of which is unclear. In mice, IFN-I enhance or inhibit arthritis development according to the IFN subtype, arthritis model and the kinetics. Because of the reported IFN-I/TNF cross-regulation, and TNF being a key pathogenic cytokine in RA, we have evaluated the therapeutic effect of early IFN-α production in collagen-induced arthritis (CIA).

Methods: CIA was induced by 2 immunizations with collagen/CFA. Disease development was studied in conditional transgenic mice over-expressing mouse IFN-α1 after cessation of doxycyclin (Dox) administration (Tet-off system). IFN-α1-negative littermates were used as controls. All mice express endogenous IFN-α. All mice were treated with Dox. Arthritis was followed by clinical evaluation. Inflammation/bone destruction were estimated by histology. Plasma cytokines and anti-collagen antibodies were measured by Luminex/ELISA. Leukocytes sub-populations and Th1/Th2/Th17 polarization were analyzed by flow cytometry. Bone marrow cells were cultured with M-CSF/RANKL to evaluate osteoclast differentiation and activity. $CD4^+CD25^+$ regulatory T cells (Treg) and $CD4^+CD25^-$ effector T cells (Teff) were purified by magnetic sorting. Treg ATPase activity was determined in vitro by a luminescent assay. Treg inhibition of Teff proliferation/activation was measured by flow cytometry/ELISA in co-cultures. The in vivo therapeutic capacity of purified Treg was estimated by adoptive transfer.

Results: Induction of mouse IFN-α1 production before the first or even before the second immunization resulted in CIA protection. Both immunized IFN-$\alpha1^-$ and IFN-$\alpha1^+$ mice produced anti-collagen antibodies, however the latter produced less. Likewise, IFN-$\alpha1^+$ mice produced less IL-6 but more IL-5. Protection was associated with decreased polarization to Th17 and increased polarization to Th1 and Th2 lymphocytes. Moreover, IFN-$\alpha1^+$ mice showed increased levels of IFN-γ-positive NK cells. On the contrary, osteoclastogenesis and osteoclast activity were decreased in IFN-$\alpha1^+$ mice. Particularly, CIA protection in IFN-α1-overexpressing mice was associated with an expansion of Treg with a higher CD39 expression, higher ATPase activity and a higher capacity to inhibit Teff. Most importantly, adoptive transfer of those highly suppressive Treg purified from CIA IFN-$\alpha1^+$ mice impaired CIA development in recipients in comparison to adoptive transfer of Treg purified from CIA IFN-$\alpha1^-$ mice.

Conclusion: This is the first study analyzing the impact of IFN-α on CIA development. Induction of IFN-α1 production before immunization or even after the first immunization nearly completely protects against arthritis. Protection is associated with an expansion of more suppressive Treg able to confer protection upon adoptive transfer. This work better defines the role of IFN-α and shows its potent modulatory effect in inflammatory arthritis.

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Abstract Number: 1033

Targeting Notch-Activated M1 Macrophages Attenuates Joint Tissue Damage in a Mouse Model of Inflammatory Arthritis

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Background/Purpose: Increased expression of Notch signaling molecules has been reported in synovial samples of patients with rheumatoid arthritis (RA). However, the identity of the cell type(s) in RA joints with Notch activation or how they might contribute to RA pathogenesis is unknown. Here, we used GFP+ cells from *Hes1*-GFP/TNF transgenic (TNF-Tg) mice (a model of RA) to identify Notch-activated cells, i.e., those with high Hes1 expression, in the joints of these mice and to study the source and effect of the deletion of GFP+ cells on joint tissue damage.

Methods: *Hes1*-GFP/TNF-Tg mice were generated by crossing *Hes1*-GFP reporter mice and TNF-Tg mice. Immunofluorescent (IF) staining, flow cytometry and bone marrow (BM) transplantation assays were used. BM macrophages (BMM) were generated by culturing BM cells with M-CSF. M1 inflammatory macrophages (M1s) and M2 anti-inflammatory cells (M2s) were induced from BMM by TNF and IL-4, respectively. Thapsigargin (Thap), a recently recognized Notch inhibitor, was used.

Results: To determine the cell type(s) with high Hes1 expression in RA joints, we performed flow cytometry of BM and synovial cells from 6-m-old *Hes1*-GFP/TNF-Tg mice when they had developed severe RA joint damage. Compared to *Hes1*-GFP control (Ctl) mice, *Hes1*-GFP/TNF-Tg mice had significantly more GFP+ cells, especially in the synovial tissue (Ctl BM 2±0.6% vs. *Hes1*-GFP/TNF-Tg BM 5±0.7% vs. synovium 12±4%). Synovial GFP+ cells comprised 60% F4/80+, 2% B220+, 5% CD3+, 0.7% CD31+, and 3% CD45-Sca1+ cells. Significantly more of the F4/80+/GFP+ cells expressed the M1 marker, iNOS than the M2 marker CD206 (75+6% M1s vs. 25+6% M2s). IF staining showed that M1s were located mainly in the inflamed synovial tissue. To study if synovial M1s came from BM, we transferred *Hes1*-GFP/TNF-Tg BM cells into irradiated TNF-Tg and WT recipient mice. Chimeric mice were sacrificed 8 wks post-BM transfer. IF staining indicated numerous GFP+ cells in the synovium of TNF-Tg mice, but there were few GFP+ cells in the BM of the same mice. No GFP+ cells were detected in the synovium of WT recipient mice. To determine if Notch inhibition could reduce M1s and attenuate joint tissue damage in RA, we demonstrated that TNF treatment of *Hes1*-GFP BMMs promoted GFP+/iNOS+ M1s, while IL-4 promoted GFP-/CD206+ M2s. Thap reduced Hes1 expression and switched TNF-induced M1s to M2s (M1s: 32±18% vs. 79±11%; M2s: 63±14% vs. 23±11% in PBS). More importantly, the inhibitory effect of Thap on TNF-induced M1s was abolished in BMMs from mice carrying a constitutively active Notch intracellular domain. In vivo, Thap treatment of *Hes1*-GFP/TNF-Tg mice significantly reduced bone resorption (subchondral BV/TV: 30±3 vs. 20±4% in Ctl), inflammation area (0.7±0.3 vs. 1.3±0.2mm^{2}in Ctl), synovial M1s and GFP+ cells (M1s: 35±28 vs. 78±16 % in Ctl; GFP+: 6±1 vs. 11±2% in Ctl).

Conclusion: M1s derived from BM are the main cells with activated Notch signaling in the inflamed synovial tissues of TNF-Tg mice. Switching Notch-activated M1s to M2s by Thapsigargin attenuated joint inflammation and erosion; thus targeting Notch-activated M1s may represent a new therapeutic approach for patients with inflammatory arthritis.

Disclosure: W. Sun, None; **H. Zhang**, None; **H. Wang**, None; **Y. G. Chiu**, None; **C. T. Ritchlin**, None; **A. Kiernan**, None; **B. Boyce**, None; **L. Xing**, NIH AR48697, AR63650, 2.

Abstract Number: 1034

Microrna-146a Controls Local Bone Destruction By Regulating Fibroblast Induced Osteoclastogenesis in Inflammatory Arthritis

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Background/Purpose: MicroRNA (MiR-) 146a plays an important role in the regulation of the innate immune response and has also been shown to suppress cancer development in myeloid cells. Although in late stages of arthritis elevated expression of miR-146a in synovial tissue of rheumatoid arthritis patients was detected, the level of this miRNA was found to be down regulated in early disease, but its role in the development of inflammatory arthritis is still elusive.

Methods: To induce arthritis we used the chronic inflammatory hTNFtg disease model, therefore we crossed miR-146a deficient into hTNFtg mice. Disease severity was assessed clinically and histologically. Serum cytokine levels were measured by Elisa. Synovial fibroblasts were isolated from metatarsal bones. Proliferation of fibroblasts was analysed histologically and by ^{3}[H]thymidine incorporation. RNA expression levels were measured by qPCR

Results: When we crossed miR-146a$^{-/-}$ into hTNFtg mice, histological examination revealed a significant increase in synovial inflammation and even more striking a more than twofold increase in local bone destruction, due to increased generation of osteoclasts in the tarsal joints in miR-146a$^{-/-}$/hTNFtg mice compared to hTNFtg mice. Interestingly, systemic bone loss was comparable in hTNFtg compared to miR-146a$^{-/-}$/hTNFtg mice, suggesting an important local role of miR-146a. Indeed, we detected increased levels of IL-1β, TRAF6, a major target of miR-146a and RANKL, in addition the expression level of OPG was decreased locally in the paws of miR-146a$^{-/-}$/hTNFtg compared to hTNFtg mice. By performing bone marrow transplants we could indeed show a pivotal role for miR-146a in mesenchymal cells in controlling local osteoclast generation and bone destruction. Analysis of important mesenchymal cells in arthritis, the synovial fibroblasts exhibited enhanced proliferation if miR-146a is missing, *in vitro* and *in vivo*. Moreover stimulation of these cells with IL-1β, a prominent cytokine in arthritis which was also shown to be negatively regulated by miR-146a, led to increased expression of RANKL and TRAF6 in miR-146a deficient synovial fibroblasts.

Conclusion: These data demonstrate an important mitigating role of the miR-146a in inflammatory arthritis, most importantly in local bone destruction, by controlling mesenchymal expression of osteoclastogenic factors. This shows an important anti-inflammatory role of miR-146a, which might possibly be exploited for therapeutic purposes.

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Abstract Number: 1035

The Prognostic Value of Different Auto-Antibodies for Arthritis Development in Patients with Clinically Suspect Arthralgia

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Session Time: 4:30PM-6:00PM

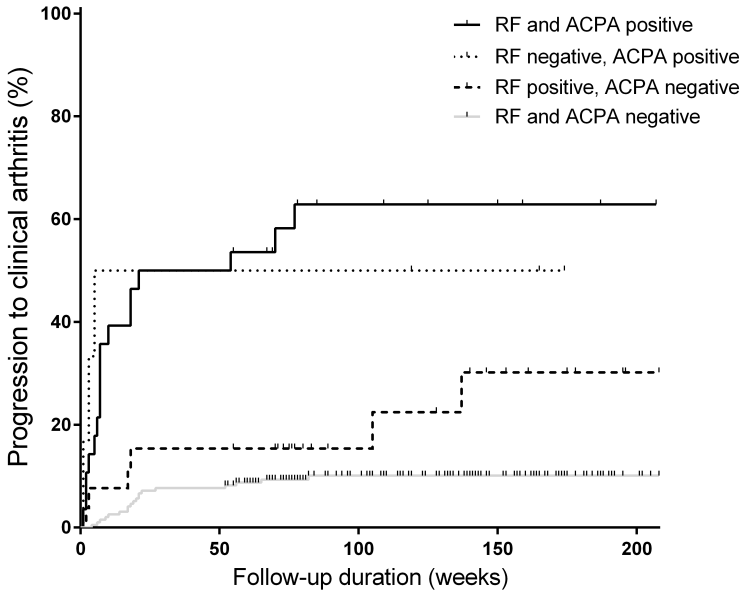
Background/Purpose: Previous longitudinal studies in arthralgia patients studied Rheumatoid Factor (IgM-RF) and Anti-Citrullinated Protein Antibodies (ACPA) in relation to arthritis development. Participants in these studies were often selected on the presence of at least one autoantibody and consequently the predictive values of different autoantibodies were evaluated relative to each other. This study evaluated the association of RF, ACPA and anti-carbamylated protein antibodies and arthritis development in arthralgia patients that were selected based on the clinical suspicion to progress to RA (Clinically Suspect Arthralgia).

Methods: 255 Clinically Suspect Arthralgia patients were included in our cohort. Patients had arthralgia for <1 year, without clinical arthritis and were considered at risk for RA based on clinical presentation by their rheumatologists. RF, ACPA and anti-carbamylated protein status determined at baseline were studied in relation to the development of clinical arthritis during a median follow-up of 96 week using univariable and multivariable Cox regression analyses.

Results: 45 patients developed clinical arthritis. In univariable Cox regression analyses, presence of RF (HR=4.8, 95%CI=2.7-8.7), ACPA (HR=7.9, 95%CI=4.4-14.3) and anti-carbamylated protein (HR=3.7, 95%CI=1.9-7.3) antibodies were all shown to have a significant association with arthritis development. In multivariable Cox regression including RF, ACPA and anti-carbamylated protein, only ACPA-seropositivity was significantly associated with arthritis development (HR=5.0, 95%CI=1.9-12.9). When stratifying the patients in groups with different combinations of RF and ACPA (see Figure 1), Cox regression revealed the highest hazard ratio for RF-positive ACPA-positive patients (HR=9.5, 95%CI=4.9-18.3, compared to RF-negative ACPA-negative patients). No significant differences were observed for RF-negative ACPA-positive compared to RF-positive ACPA-positive patients. Although nearly 70% of ACPA-positive RF-positive patients progressed to clinical arthritis, 30% did not develop clinical arthritis during a median follow-up duration of 96 weeks.

Conclusion: Within Clinically Suspect Arthralgia patients, presence of ACPA alone or in combination with RF, is associated with an increased hazard on progression to clinical arthritis. However, although still 30% of patients that have both antibodies did not develop arthritis within 96 weeks follow-up and patients without antibodies also developed arthritis suggest that information on autoantibodies alone is not sufficient for optimal risk stratification.

Figure 1. Kaplan-Meier One Minus Survival plots for combinations of Rheumatoid Factor and Anti-Citrullinated Protein antibodies and progression to clinical arthritis.



Glossary: Kaplan-Meier one minus survival plot showing cumulative progression to clinical arthritis for Clinically Suspect Arthralgia patients, according to being positive for either positive for anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) positive (N=28), single ACPA-positive (N=6), single RF-positive (N=26) and double negative patients (N=195). Cox regression of combinations of RF- and ACPA-positivity revealed that the presence of both ACPA and RF yielded the highest HR of 9.5 (95%CI=4.9–18.3) for arthritis development compared to the group negative for both autoantibodies, as shown in figure 1. The hazard ratio of single ACPA-positivity was 8.1 (95%CI=2.4–27.4), compared to the group that was negative for both RF and ACPA. The hazard ratio for single RF-positivity was 2.5

(95%CI=1.0–6.3) compared to the group that was negative for both RF and ACPA.

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Abstract Number: 1036

Dominant B-Cell Receptor Clones in Peripheral Blood Predict Onset of Arthritis in Individuals at Risk for Rheumatoid Arthritis

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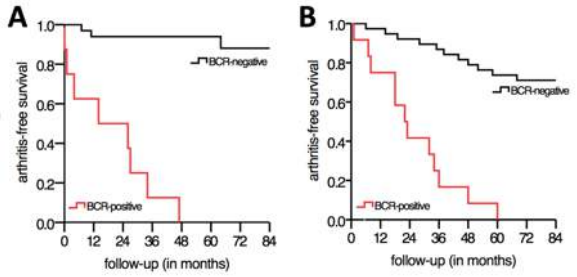
Background/Purpose: The onset of seropositive rheumatoid arthritis (RA) is preceded by the presence of specific autoantibodies in the absence of synovial inflammation. Only a subset of these *at-risk* individuals will develop clinical disease. This impedes efforts to implement early interventions that may prevent onset of clinical disease. Here we analyze whether clonal changes in the B-cell receptor (BCR) repertoire can reliably predict onset of clinical disease.

Methods: In a prospective cohort study in 21 individuals *at-risk* for RA, the BCR repertoire of paired peripheral blood and synovial tissue samples was analyzed using RNA-based next-generation BCR sequencing. BCR clones that were expanded beyond 0.5% of the total repertoire were labeled dominant. The relative risk for onset of arthritis was assessed, using a cut-off of presence of 5 or more dominant BCR clones. Findings in peripheral blood were validated in an independent prospective cohort of 50 *at-risk* individuals. Based on the test cohort, individuals in the validation cohort were considered BCR positive if peripheral blood at study entry showed 5 or more dominant BCR clones.

Results: Both in the test and validation cohort, the presence of 5 or more dominant BCR clones in peripheral blood was significantly associated with arthritis development (validation cohort relative risk (RR) 6.3, 95% confidence interval (CI) 2.7 - 15, $p < 1*10^{-4}$). Figure A and B show the arthritis-free survival curves of BCR negatives (black) and BCR positives (red) for the test and validation cohort respectively. After adjustment for the recently described clinical prediction rule the association remained intact (relative risk 5.0, 95% CI 1.2 - 20, $p = 0.024$). When individuals developed arthritis, dominant BCR clones disappeared from peripheral blood and appeared in synovial tissue, suggesting a direct role of these clones in disease pathogenesis.

Conclusion: Dominant BCR clones in peripheral blood predict onset of clinical symptoms of RA in *at-risk* individuals with high accuracy.

Our data suggest that during onset of RA these clones shift from peripheral blood to target tissue.



Disclosure: P. P. Tak, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries. Author is currently employee of GSK, but was not involved in data analysis., 7; **M. E. Doorenspleet**, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries., 7; **M. de Hair**, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries., 7; **P. L. Klarenbeek**, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries., 7; **M. van Beers-Tas**, None; **A. H. C. van Kampen**, None; **D. van Schaardenburg**, None; **D. M. Gerlag**, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries. Author is currently employee of GSK, but was not involved in data analysis., 7; **F. Baas**, None; **N. de Vries**, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries., 7.

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Abstract Number: 1037

Evaluation of 14-3-3η As a Tool for Diagnosis of Early RA in a European Cohort

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Background/Purpose: Early diagnosis of rheumatoid arthritis (RA) coupled with an effective treatment strategy is a key imperative in the effective management of disease. Anti-citrullinated peptide antibodies (ACPA) and antibodies against rheumatoid factor (RF) are two serological markers cited in the 2010 RA classification criteria that are commonly used in routine clinical practice. 14-3-3η protein is a mechanistic marker which seems to have a biologic role in the joint erosive process, that assists with the diagnosis of RA. The aim of this study, was to assess the clinical utility of 14-3-3η in the European EIRA (Epidemiological Investigation of Rheumatoid Arthritis) cohort.

Methods: 14-3-3η levels were measured in a total of 505 patient samples, 305 early RA patients samples and 200 control samples from the EIRA cohort using the 14-3-3η ELISA test (Augurex). Control samples included patients with various autoimmune conditions, infections, malignancies, osteoarthritis and healthy subjects. The specificity and sensitivity of 14-3-3η was assessed using the manufacturer's suggested positivity cut-off of ≥ 0.19 ng/ml and at 2 and 4x of the diagnostic cut-off. The added value of 14-3-3η to CCP2 (Eurodiagnostica) in the diagnosis of RA was determined by examining the additional patients captured by 14-3-3η.

Results: As shown in the Table below, CCP2 had a sensitivity of 66.2% and a specificity of 96.5%. For 14-3-3η with a serum cutoff of ≥ 0.8 ng/ml the sensitivity was calculated to 47.2% and the specificity to 94.5%. Adding 14-3-3η resulted in a sensitivity of 74.1% compared to 66,2% for CCP2 alone. Depending upon the selected cut-off, up to 50.5% of the CCP-negative patients within the EIRA cohort could be identified by 14-3-3η.

	CCP2 IgG (E/ml)	14-3-3η (ng/ml)		
Cut off	≥ 25 E/ml	≥ 0.19	≥ 0.40	≥ 0.80
Sensitivity %	66.2	68.2	59.3	47.2
Additional No of Positives to CCP2		52	37	24
Added Cohort Sensitivity %		17.0	12.1	7.9
Added sensitivity of CCP -ve patients %		50.5	35.9	23.3
Specificity	96.5	83.0	90.5	94.5
Loss of cohort specificity %		16.0	9.5	4.5

Conclusion: Based on past publications the 14-3-3η protein is more frequently increased in established RA patients than in early RA patients. Nevertheless, even in our early RA cohort we could identify a considerable added value of increased sensitivity compared to CCP2. The 14-3-3η protein used in conjunction with CCP2 improves diagnostic sensitivity in the early diagnosis of RA.

Disclosure: M. Hansson, None; **L. Mathsson-Alm**, None; **A. Marotta**, Augurex Life Sciences Corpt, 3; **S. Swiniarski**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/evaluation-of-14-3-3%ce%b7-as-a-tool-for-diagnosis-of-early-ra-in-a-european-cohort

Abstract Number: 1038

Functional Disability in Patients Presenting with Clinically Suspect Arthralgia and Progression to Clinical Arthritis

Robin M ten Brinck[1], Hanna W van Steenbergen[1], Lukas Mangnus[2], Leonie E Burgers[1], Monique Reijnierse[3], Tom WJ Huizinga[1] and Annette HM van der Helm-van Mil[4], [1]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Radiology, Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology, Rheumatology, Leiden University Medical Center, Leiden, Netherlands
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SESSION INFORMATION
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Session Time: 4:30PM-6:00PM

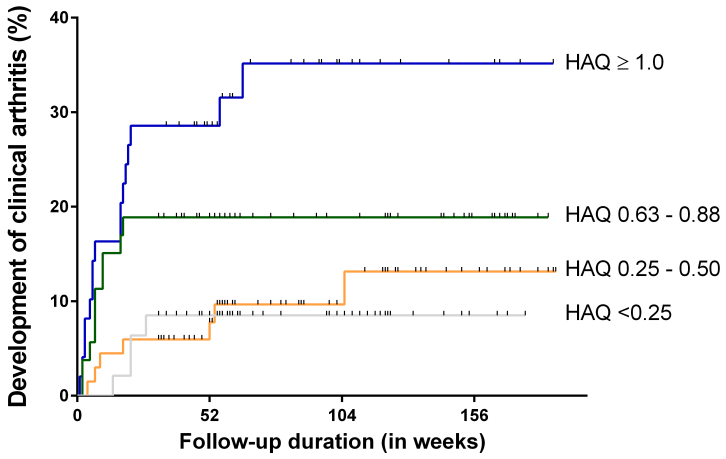
Background/Purpose: A phase of arthralgia precedes the emergence of rheumatoid arthritis (RA). It is unknown if patients have functional limitations in this phase. We assessed functional disability in patients with Clinically Suspect Arthralgia, its association with MRI-detected subclinical inflammation and with progression to clinical arthritis.

Methods: From April 2012 to April 2015, 255 CSA-patients had arthralgia for <1 year and were, based on clinical presentation, considered at risk for RA by their rheumatologists. At baseline, functional disability was assessed using HAQ-scores. Subclinical inflammation was assessed using unilateral 1.5Tesla MRI of MCP, wrist and MTP-joints. Synovitis, tenosynovitis and bone marrow edema scores were summed in the total MRI-inflammation score. Patients were followed on arthritis development.

Results: Median HAQ-score at presentation was 0.50. Higher total MRI-inflammation scores were associated with higher HAQ-scores (β=0.017, 95%CI=0.004-0.030). During median 61 weeks follow-up, 41 patients progressed to clinical arthritis. HAQ-scores ≥1.0 were associated with arthritis development (HR=4.60, 95%CI=1.54-13.75). Within converters, median HAQ-scores did not increase from

presentation with Clinically Suspect Arthralgia to arthritis development (0.88 and 0.75, p-value=0.59).

Conclusion: Functional limitations already exist during the symptomatic pre-arthritis phase, with a similar severity as in the early clinical arthritis-phase. HAQ-scores ≥1.0 were associated with progression to clinical arthritis. **Figure 1**. Kaplan-Meier One Minus Survival plot showing cumulative progression to clinical arthritis for CSA-patients divided in four groups based on their baseline HAQ-score.



Glossary: Patients were appointed into quartiles according to their total HAQ-score to create four subgroups with equal numbers, see supplementary file 2. Each line represents one HAQ-score quartile and cumulative progression to clinical arthritis. The lowest quartile contains patients with HAQ-scores <0.25 with N=49. The second quartile contains HAQ-scores 0.25–0.50 (N=67), with a HR for progression to clinical arthritis of 1.2 (95%CI=0.37–4.3). Patients in the third quartile had HAQ-scores 0.63–0.88 (N=53) with a HR for progression to clinical arthritis of 2.4 (95%CI 0.77–7.8). Finally, the quartile with the highest HAQ-scores contains HAQ-scores ≥ 1.0. (N=49).The hazard ratio for this quartile (HR=4.60, 95%CI=1.54–13.75) was significantly elevated, compared to the lowest quartile.

Disclosure: R. M. ten Brinck, None; **H. W. van Steenbergen**, None; **L. Mangnus**, None; **L. E. Burgers**, None; **M. Reijnierse**, None; **T. W. Huizinga**, None; **A. H. van der Helm-van Mil**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/functional-disability-in-patients-presenting-with-clinically-suspect-arthralgia-and-progression-to-clinical-arthritis

Abstract Number: 1039

Estimation of the Risk of Developing Rheumatoid Arthritis in High-Risk Subjects : Systematic Review and Meta-Analysis

François Vercruysse[1], Vincent Germain[1], Thomas Barnetche[2], Marie-Elise Truchetet[3] and Thierry Schaeverbeke[2], [1]Rheumatology, CHU Pellegrin, Bordeaux, France, BORDEAUX, France, [2]Rheumatology, CHU Pellegrin, Bordeaux, France, Bordeaux, France, [3]CHU Pellegrin, Bordeaux, France, Bordeaux, France

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Background/Purpose: Identifying individuals at risk for rheumatoid arthritis (RA) development is a prerequisite to understand preclinical events and to develop prevention. Based on a systematic review of the literature, our goals were to determine the risk of RA in first degree relatives (FDR) of RA patients (Q1), to study the serological status of FDR (Q2), to determine risk of developing RA among asymptomatic subjects seropositive either for RF or anti-CCP (Q3) and to determine whether being seropositive for RF or anti-CCP increases RA risk among subjects complaining of arthralgia (Q4).

Methods: 3185 articles were screened using various databases until june 2016 and data was extracted independently by two authors. Meta-analysis were performed to assess odds-ratios (OR) for each studied group using the inverse variance approach to estimate pooled OR with their 95% confidence interval. Heterogeneity was assessed according to Cochran Q-test and I^2 values. Calculations were made with

the Cochrane RevMan 5.3 software. P-values less than 0,05 were considered as significant.

Results: For Q1 : FDR of RA patients have a two to fourfold risk of RA, compared to controls. For Q2 : IgM-RF were positive among 14,4% of FDR and 5,7% of unrelated controls, resulting in an OR 3,19 (1,27-8,01 ; I^2=66%). Anti-CCP were found among 4,4% of FDR and 2,1% of unrelated controls, resulting in an OR 2,42 (IC95% 1,22-4,79 ; I^2=0%) (figure 1). For Q3 : the risk of developing RA among asymptomatic seropositive subjects was OR 7,89 (IC95% 4,54-13,72; I^2=54%) when positive for IgM-RF, and OR 21,60 (IC95% 5,8-80,37 ; I^2=92%) when positive for anti-CCP, compared to seronegative subjects (figure 2). For Q4 : arthralgia subjects showed an increased risk for arthritis with an OR 3,53 (IC95% 1,49-8,39; I^2=88%) if these subjects were positive for IgM-RF and OR 12,67 (IC95% 5,37-29,90; I^2=61%) when positive for anti-CCP, compared to seronegative arthralgia subjects (figure 3).

Conclusion: Our study allows to quantify the increased risk conferred by a family history of RA, and a seropositivity for IgM-RF or anti-CCP among asymptomatic and arthralgia subjects. These results should help the physician to answer questions often asked by RA patients, and should help him to better define and to monitor closely at risk subjects with the aim of early screening and earlier treatment

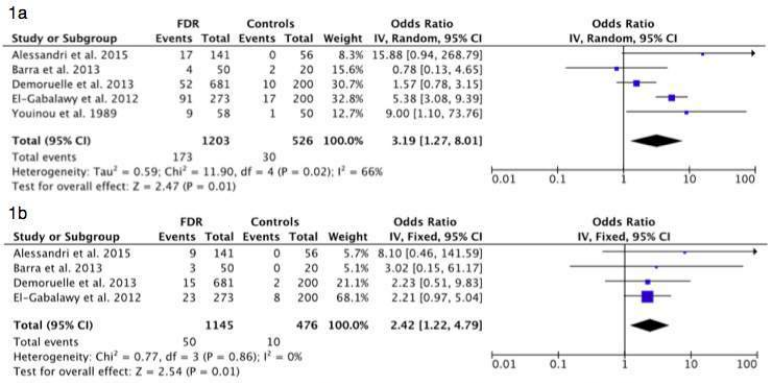

Figure 1. Risk of seropositivity among FDR for IgM-RF (1a) and anti-CCP (1b) compared to unrelated controls

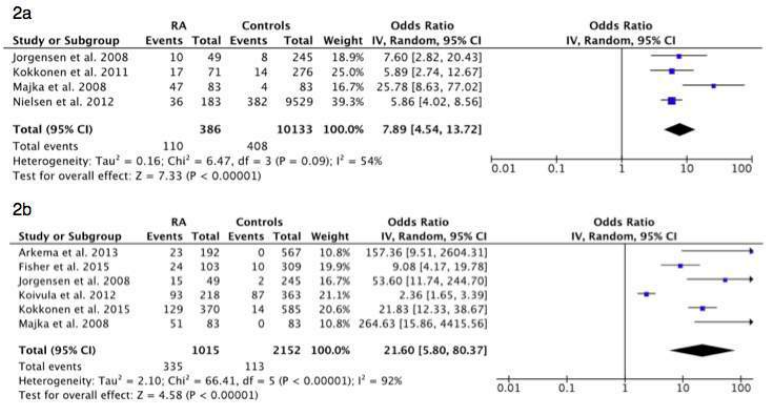

Figure 2. RA risk among asymptomatic subjects when positive for IgM-RF (2a) and anti-CCP (2b) compared to seronegative subjects

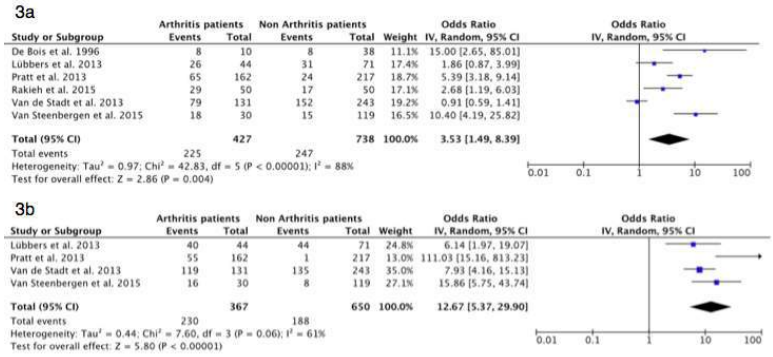

Figure 3. Risk of arthritis among arthralgia subjects when positive for IgM-RF (3a) or anti-CCP (3b) compared to seronegative subjects

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Abstract Number: 1040

Stressful Life Events : A Trigger for Rheumatoid Arthritis Onset within a Year. a Case-Control Study

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Background/Purpose: To assess the association between recent stressful life events and rheumatoid arthritis (RA) onset.

Methods: We conducted a monocentric case-control study of in and out patients. Cases were RA patients fulfilling ACR EULAR criteria and controls were osteoarthritis (OA) patients. With face-to-face interviews, we assessed stressful life events occurring during the year before rheumatoid arthritis onset according to the Social Readjustment Rating Scale (SRRS), which provided a life change unit (LCU) score representing the level of stress experienced. Patients were classified in 3 subgroups by life change unit score: 0-40, 41-100 and 101-300.

Results: Overall, 69 RA and 65 OA patients were included (71% were women). Cases and controls did not differ in characteristics except age, with younger age for RA than OA patients. RA onset within a year was increased with SRRS ≥100 (OR=15.31 [95% CI 6.00-39.09], p<0.0001) and 41 to 100 (OR=4.99 [1.87-13.32], p=0.001) as compared with 0-40. High LCU score remained associated with RA onset within a year on multivariable analysis adjusted for age, sex, disease duration and current depression: > 100 (OR=16.05 [5.44-47.32], p<0.001) and 41–100 (OR=5.46 [1.82-16.37], p=0.002).

Conclusion: We found a strong association between stressful life events and RA onset within a year. The more the patient experienced stress, the greater was the risk of RA developing. Clinicians should look for stressful life events in the history-taking of patients with early arthritis.

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Abstract Number: 1041

Abatacept in the Treatment of Active Psoriatic Arthritis: 24-Week Results from a Phase III Study

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Session Time: 4:30PM-6:00PM

Background/Purpose: Abatacept (ABA), a selective T-cell co-stimulation modulator, showed promise for the treatment of PsA in a Phase II trial.[1] This prompted the conduct of the Phase III Active pSoriaTic aRthritis rAndomizEd triAl (ASTRAEA; NCT01860976); key results are presented here.

Methods: In this international, double-blind, multicenter study, patients (pts) with PsA were randomized (1:1) to SC ABA 125 mg wkly or placebo for 24 wks, and then treated with open-label SC ABA up to 24 mths. Pts had active disease (≥3 tender and ≥3 swollen joints), ≥2 cm target lesion of plaque psoriasis and inadequate response or intolerance to ≥1 non-biologic DMARD. Randomization was stratified by MTX use, prior TNFi use and skin involvement ≥3% of body surface area (BSA). Pts not achieving ≥20% improvement in SJC and TJC at Day 113 were switched to open-label ABA (early escape). Primary endpoint: ACR20 response at Wk 24. Key secondary endpoints at Wk 24: HAQ response (change from baseline ≥0.35); ACR20 response in the TNFi-naïve and -exposed subgroups; radiographic non-progression (PsA-modified total Sharp/van der Heijde score; change from baseline ≤0). Other secondary/exploratory endpoints included: ≥50% improvement in Psoriasis Area and Severity Index score (PASI50) in pts with ≥3% BSA; change in HAQ score; safety. Comparisons were performed using a 2-sided Cochran–Mantel–Haenszel chi-square test, adjusted for stratification criteria. Pts designated as early escape or with missing data were imputed as non-responders/radiographic progressors. Change in HAQ score was analyzed using a longitudinal repeated measures model (early escape pts set to missing at Days 141 and 169). Primary and key secondary endpoints were tested using a hierarchical approach.

Results: Of 424 pts enrolled, 213 received ABA and 211 placebo; 76 were early escape pts in ABA and 89 in placebo; 12 pts discontinued in ABA and 24 in placebo. Table 1 shows baseline characteristics. Most (>60%) pts had prior exposure to TNFis. ABA significantly improved the proportion of pts achieving an ACR20 response at Wk 24 ($p<0.001$) (Table 2). The proportion of HAQ responses was numerically higher with ABA vs placebo ($p=0.097$). Higher proportions of pts receiving ABA vs placebo had an ACR20 response in the TNFi-naïve and -exposed subgroups, and radiographic non-progression (nominal $p<0.05$), with modest numerical improvement in PASI50. Efficacy was maintained at 1 year. The safety profile of ABA was similar to placebo, with no new safety signals.

Conclusion: Abatacept improved disease and was well tolerated in pts with active PsA, regardless of prior exposure to TNFis.

1. Mease P, et al. *Arthritis Rheum* 2011;**63**:939–48.

Table 1. Baseline characteristics

	Abatacept (n=213)	Placebo (n=211)
Age, years	51.0 (10.7)	49.8 (11.3)
Female, n (%)	121 (56.8)	112 (53.1)
PsA duration, years	8.3 (8.1)	8.8 (8.3)
Prior TNFi use, n (%)	129 (60.6)	130 (61.6)
Concomitant MTX, n (%)	129 (60.6)	127 (60.2)
DAS28 (CRP)	5.0 (1.1)	4.9 (1.1)
Tender joint count	21.0 (13.4)	19.3 (13.1)
Swollen joint count	12.1 (7.8)	11.1 (7.2)
HAQ score	1.3 (0.7)	1.3 (0.7)
Patient Global Assessment of disease activity, 0–100 mm VAS	61.1 (23.5)	62.6 (22.6)
Physician Global Assessment of disease activity, 0–100 mm VAS	53.9 (18.8)	55.0 (19.6)
Patient Global Assessment of pain, 0–100 mm VAS	64.2 (23.5)	64.4 (21.8)
CRP, mg/L	14.0 (20.9)	14.3 (30.3)
PsA-modified total SHS	20.0 (46.8)	17.7 (39.6)
Psoriasis covering ≥3% BSA, n (%)	146 (68.5)	148 (70.1)
PASI score*	7.4 (8.0)	7.2 (7.8)

Data are mean (SD) unless indicated otherwise *For patients with psoriasis covering ≥3% of BSA BSA=body surface area; HAQ=Health Assessment Questionnaire; PASI=Psoriasis Area and Severity Index; SHS=Sharp/van der Heijde score; VAS=visual analog scale

Table 2. Outcomes at Week 24				
	Abatacept	**Placebo**	**Estimated difference (95% CI)**	**p value**
ACR20 responders	39.4 (84/213)	22.3 (47/211)	17.2 (8.7, 25.6)	<0.001
ACR20 responders – TNFi naïve	44.0 (37/84)	22.2 (18/81)	21.9 (8.3, 35.6)	0.003*
ACR20 responders – TNFi exposed	36.4 (47/129)	22.3 (29/130)	14.0 (3.3, 24.8)	0.012*
HAQ responders†	31.0 (66/213)	23.7 (50/211)	7.2 (–1.1, 15.6)	0.097
HAQ, change from baseline, mean (SD)	–0.33 (0.04)	–0.20 (0.05)	–0.13 (–0.25, –0.01)	NC
Radiographic non-progressors	42.7 (91/213)	32.7 (69/211)	10.0 (1.0, 19.1)	0.034*
PASI 50	26.7 (39/146)	19.6 (29/148)	7.3 (–2.2, 16.7)	0.137*

Data are % (n/N) unless indicated otherwise A hierarchical testing procedure was applied to the primary and key secondary endpoints in the following order: ACR20 responders, HAQ responders, ACR20 responders – TNFi naïve, ACR responders – TNFi exposed, radiographic non-progressors. Early Escape patients and other patients with missing data at Day 169 were imputed as non responders/radiographic progressors at Day 169 *Nominal p value †HAQ response was defined as a score reduction of ≥0.35 from baseline NC=not calculated; PASI 50=≥50% improvement in Psoriasis Area and Severity Index score

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Disclosure: P. Mease, AbbVie, 2,AbbVie, 5,AbbVie, 8; **A. Gottlieb**, Amgen Inc.; Astellas, Akros, Centocor (Janssen), Inc., Celgene Corp., Bristol-Myers Squibb Co., Beiersdorf, Inc., Abbott Labs. (AbbVie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Karyoph, 5,Centocor (Janssen), Amgen, Abbott (AbbVie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck, Xenoport, Dermira, Baxalta, 2; **D. van der Heijde**, AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, 5,Imaging Rheumatology bv Director, 9; **O. FitzGerald**, AbbVie, Pfizer, BMS, 2,AbbVie, Pfizer, BMS, Celgene, Janssen, Novartis, UCB, Lilly, 5; **A. Johnsen**, Bristol-Myers Squibb, 3; **M. Nys**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Banerjee**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **D. Gladman**, AbbVie, Amgen, Celgene, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 5.

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Abstract Number: 1042

Four Year Imaging Outcomes in Patients with Axial Spondyloarthritis Treated with Certolizumab Pegol, Including Patients with Ankylosing Spondylitis and Non-Radiographic Axial Spondyloarthritis

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Session Time: 4:30PM-6:00PM

Background/Purpose: RAPID-axSpA (NCT01087762) was a long-term study in patients (pts) with axial spondyloarthritis (axSpA) treated with certolizumab pegol (CZP). This is the first report of 4-year imaging results in CZP-treated axSpA pts, including ankylosing spondylitis (AS) and non-radiographic (nr-)axSpA.

Methods: RAPID-axSpA[1] was double-blind, placebo (PBO)-controlled to Wk 24, dose-blind to Wk 48 and open-label to Wk 204. Pts fulfilling ASAS axSpA criteria were stratified according to presence/absence of radiographic sacroiliitis (AS/nr-axSpA) at randomization, and had active disease. Wk 0 CZP-randomized pts (200 mg Q2W/400 mg Q4W) continued assigned dose; PBO pts received CZP after Wk 16 or 24. Lateral X-rays of cervical/lumbar spine at BL, Wk 96 and 204 were assessed using mSASSS (average of 2 independent central readers blind to timepoint). SI joint X-rays were scored for sacroiliitis by 2 independent central readers (3rd reader adjudicated grade scoring differences) at BL and Wk 204. MRI scans using STIR sequences were performed at BL, Wk 12, 48, 96 and 204, and were assessed using SPARCC for SI joints and Berlin score for spine. Data are shown for CZP-treated pts (including those starting on PBO). mSASSS data were estimated for all pts by MMRM analysis covering all available observations. MRI data at each timepoint are shown as observed for pts with a valid assessment at that timepoint. SI joint X-ray data were assessed in pts with valid assessments at both BL and Wk 204.

Results: Of 315 CZP-treated pts, 196 had available spinal X-rays and were included in MMRM analysis (BL mean mSASSS: 9.47). 158 pts had MRI assessments and were included in this reading campaign (BL mean SPARCC: 8.17 [n=151]; Berlin: 6.10 [n=153]) and 137 pts had SI Joint X-rays at BL and Wk 204 (BL: 67.9% radiographic sacroiliitis). In AS pts, mean mSASSS change between BL and Wk 204 was 0.98 (95% CI: 0.34–1.63); 0.67 (0.21–1.13) from BL to Wk 96 and 0.31 (0.02–0.60) from Wk 96 to Wk 204. These numbers were 0.06 (-0.17–0.28), -0.01 (-0.19–0.17), and 0.07 (-0.07–0.20) respectively for nr-axSpA (**Table**). MMRM estimates were similar to observed values (axSpA Wk 204 mean change: 0.62 and 0.70 respectively). Limited changes in SI joint X-ray grading were observed to Wk 204: only 2/44 pts (4.5%) progressed to AS, while 4/93 (4.3%) shifted from an AS classification to nr-axSpA. MRI assessments showed maintained improvements in SPARCC and Berlin scores from Wk 12 to Wk 204 (**Table**).

Conclusion: This is the first report of imaging data from a clinical trial including both AS and nr-axSpA pts over 4 years. Limited spinal radiographic progression was observed in CZP-treated pts with lower progression between Wk 96 and Wk 204, compared to the first 96 wks. Limited change in radiographic sacroiliitis was observed and scores were even similar in both directions. Early reductions in MRI inflammation were maintained to Wk 204. References: 1. Landewé R. Ann Rheum Dis 2014;73:39

Table A: Mixed-effects model repeated measures (MMRM) estimates of mSASSS to Week 204 of the RAPID-axSpA study for all patients treated with CZP

	Baseline	Week 96		Week 204	
	LS mean score (95% CI)	LS mean score (95% CI)	LS mean change from BL (95% CI)	LS mean score (95% CI)	LS mean change from BL (95% CI)
axSpA (n=196)	9.47 (7.20 – 11.73)	9.86 (7.52 – 12.21)	0.40 (0.11 – 0.69)	10.08 (7.71 – 12.46)	0.62 (0.22 – 1.01)
AS (n=113)	13.17 (9.79 – 16.56)	13.84 (10.35 – 17.34)	0.67 (0.21 – 1.13)	14.16 (10.61 – 17.71)	0.98 (0.34 – 1.63)
nr-axSpA (n=83)	4.42 (2.02 – 6.82)	4.41 (1.97 – 6.84)	-0.01 (-0.19 – 0.17)	4.47 (2.06 – 6.88)	0.06 (-0.17 – 0.28)

Table B: MRI outcomes to Week 204 of the RAPID-axSpA study for all patients treated with CZP (observed values)

	Baseline		Week 204			
	N	Mean score (SD)	N	Mean score (SD)	N	Mean change from BL (SD)
SI Joint Inflammation – SPARCC						
axSpA	151	8.17 (13.08)	72	1.90 (5.00)	72	-4.70 (9.40)
AS	91	8.50 (13.83)	41	1.84 (5.60)	41	-4.35 (8.49)
nr-axSpA	60	7.66 (11.93)	31	1.97 (4.18)	31	-5.16 (10.60)
Spinal Inflammation – Berlin						
axSpA	153	6.10 (8.68)	82	2.13 (4.46)	82	-4.84 (8.33)
AS	92	7.38 (8.80)	50	2.62 (5.23)	50	-5.51 (7.61)
nr-axSpA	61	4.17 (8.21)	32	1.36 (2.75)	32	-3.78 (9.38)

Data shown for all CZP-treated patients with valid assessments (including patients re-randomized from PBO at Week 16 or 24)

Disclosure: D. van der Heijde, AbbVie, Amgen, Astellas, AstraZeneca, Bristol-Myers Squibb, Celgene, Daiichi, Eli Lilly, Galapagos, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB Pharma, 5,Director of Imaging Rheumatology bv, 3; **X. Baraliakos**, AbbVie, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer and UCB Pharma, 2,AbbVie, Bristol-Myers

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Abstract Number: 1043

Safety and Efficacy of Intravenous Golimumab in Adult Patients with Active Ankylosing Spondylitis: Results through Week 28

Atul A. Deodhar[1], John D. Reveille[2], Diane D. Harrison[3], Lilianne Kim[4], Kim Hung Lo[4] and Elizabeth C. Hsia[5,6], [1]Division of Arthritis & Rheumatic Diseases OP09, Oregon Health & Science University, Portland, OR, [2]Rheumatology, University of Texas-McGovern Medical School, Houston, TX, [3]Janssen Research & Development, LLC., Horsham, PA, [4]Janssen Research & Development, LLC., Spring House, PA, [5]Janssen Research & Development, LLC, Spring House, PA, [6]University of Pennsylvania, Philadelphia, PA
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Background/Purpose: Subcutaneous (SC) golimumab (GLM) is currently approved for adult patients (pts) with RA, PsA, and AS. The GO-ALIVE study was designed to evaluate the safety and efficacy of IV GLM in adult pts with active AS.

Methods: GO-ALIVE is a Phase 3, multicenter, randomized, double-blind, placebo (PBO)-controlled trial. Pts (aged ≥18 yrs) had a diagnosis of definite AS (per modified New York criteria) and BASDAI ≥4, total back pain visual analogue scale ≥4, and CRP ≥0.3mg/dL. Pts were randomized (1:1) to IV GLM 2mg/kg at weeks (wks) 0, 4, and every 8 wks or PBO at wks 0, 4, and 12, with crossover to GLM at wk16. Up to 20% of pts could have had a prior anti-TNF agent (other than GLM), and up to 10% of pts could have complete ankylosis of the spine. The primary endpoint was ASAS20 at wk16. Major secondary endpoints were ASAS40, BASDAI50, and change in BASFI score at wk16. Other statistically-controlled assessments were BASMI, ASAS partial remission, SF-36 PCS/MCS, and ASQoL. Pts were monitored for adverse events (AEs). Data through wk28 are reported here. All investigators and some sponsor personnel will remain blinded to the treatment group assignments through the end of the study (wk60); thus treatment group assignments for individual pts are not reported here.

Results: 208 pts were randomized and received study agent (PBO: 103; GLM: 105). Baseline demographic and disease characteristics were similar between treatment groups. 78% of pts were male, mean age was 39 yrs; mean disease duration was 5.5 yrs, 89.9% were HLA-B27 positive, 5.8% had complete ankylosis of the spine, 14.4% used a prior anti-TNF. At wk16, significantly greater proportions of GLM pts vs PBO had ASAS20 (73.3% vs. 26.2%), ASAS40 (47.6% vs. 8.7%), and BASDAI 50 (41.0% vs. 14.6%) responses (all $p<0.001$; Table). Reductions in BASFI were also significantly greater with GLM. Improvements in SF-36 PCS/MCS and ASQoL were significantly greater in the GLM group vs PBO at wk16. ASAS20 was significantly higher with GLM than PBO as early as wk2 (37.1% vs 19.4%; $p=0.005$). Responses in the GLM group were maintained through wk28. PBO pts who crossed over to GLM at wk16 had improvements in clinical response at wk20 that were maintained through wk28. Through wk16, 23.3% of PBO pts and 32.4% of GLM pts had ≥1 AE. Infections were the most common AE (PBO, 7.8%; GLM, 11.4%). Through wk28, 34.8% of all GLM-treated pts had ≥1 AE; nasopharyngitis (5.4%) was the most common. Two pts (1.0%) had SAEs (pancreatitis, n=1; pneumonia, n=1).There were no opportunistic infections, malignancies, or deaths through wk28. The rate of infusion reactions was low (1.4%). 3 pts had 4 reactions; none were serious or severe.

Conclusion: IV GLM 2mg/kg was efficacious in reducing the signs and symptoms of AS compared with PBO. GLM was well-tolerated

through wk28; the safety profile was consistent with other anti-TNFs, including SC GLM.

Table. Efficacy at week 16.

	Placebo	Golimumab 2 mg/kg
Patients randomized, n	103	105
Clinical efficacy		
ASAS20, n (%)	27 (26.2%)	77 (73.3%)**
ASAS40, n (%)	9 (8.7%)	50 (47.6%)**
BASDAI 50, n (%)	15 (14.6%)	43 (41.0%)**
Change from baseline in BASFI		
n	98	105
mean (SD)	-0.5 (2.0)	-2.4 (2.1)**
ASAS partial remission, n (%)	4 (3.9%)	17 (16.2%)*
Change from baseline in BASMI (linear)		
n	96	100
mean (SD)	-0.1 (0.5)	-0.4 (0.6)**
Health-related quality of life		
Change from baseline in SF-36 PCS score		
n	98	104
mean (SD)	2.9 (6.2)	8.5 (7.5)**
Change from baseline in SF-36 MCS score		
n	98	104
mean (SD)	0.8 (10.0)	6.5 (9.1)**
Change from baseline in ASQoL		
n	98	104
mean (SD)	-1.8 (4.6)	-5.4 (5.0)**

* $p < 0.01$; ** $p \leq 0.001$ ASAS20/40, ≥20%/40% improvement in ASsessment in Ankylosing Spondylitis (ASAS) International Working Group criteria; ASQoL, Ankylosing Spondylitis Qualify of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; SD, standard deviation; SF-36 PCS/MCS, 36-item Short-Form Health Survey Physical/Mental Component Summary

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Abstract Number: 1044

Treatment with Tofacitinib Is Associated with Clinically Meaningful Reductions in Axial MRI Inflammation in Patients with Ankylosing Spondylitis

Walter Maksymowych[1], Désirée van der Heijde[2], Xenofon Baraliakos[3], Atul A. Deodhar[4], Matt Brown[5], Sarah Sherlock[6], David Li[7], Dona Fleishaker[8] and Thijs Hendrikx[7], [1]Department of Medicine, University of Alberta, Edmonton, AB, Canada, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Rheumazentrum Ruhrgebiet, Herne, Germany, [4]Division of Arthritis and Rheumatic Diseases, Oregon Health and Science University, Portland, OR, [5]Institute for Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia, [6]Pfizer Inc, Cambridge, MA, [7]Pfizer Inc, Collegeville, PA, [8]Pfizer Inc, Groton, CT

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor. Minimum clinically important differences (MCID) for SPondyloArthritis Research Consortium of Canada (SPARCC) MRI SI joint and spine scores (SIJ, spine) are ≥2.5 and ≥5, respectively.[1] We assessed whether MCID in SIJ and spine can discriminate between tofacitinib and placebo (PBO) in patients (pts) with AS and whether this is concordant with clinical responses.

Methods: In this 16-week (wk), Phase 2, double-blind, dose-ranging study (NCT01786668),[2] 207 adult pts meeting modified New York AS criteria were randomized 1:1:1:1 to PBO or tofacitinib 2, 5, or 10 mg twice daily (BID) for 12 wks. Clinical response endpoints included in this post-hoc analysis were: Assessment of AS 20% improvement (ASAS20) and ASAS40 response rates, AS disease activity score major improvement (ASDAS MI), ASDAS <1.3, Bath AS disease activity index (BASDAI), Bath AS functional index (BASFI). Pts (%) achieving MCID in SIJ, spine, both SIJ and spine, in tofacitinib and PBO groups were summarized based on observed data and pooled tofacitinib vs PBO were compared using Fisher's exact test. Concordance between achieving MCID and Wk 12 clinical responses was assessed. Wk 12 clinical responses were compared between pts achieving/not achieving MCID.

Results: MRI data for 164 pts were evaluated. Baseline demographics were generally balanced between treatment groups and typical of AS populations. All tofacitinib doses improved SIJ and spine scores vs PBO; proportion of pts achieving MCID in SIJ or spine was ~3 times higher in pooled tofacitinib group vs PBO (Table 1; $p<0.05$ for SIJ, $p<0.01$ for spine). Achieving MCID in SIJ and spine correlated with clinical response. In pts on tofacitinib, ASAS20, ASAS40, ASDAS MI, and ASDAS <1.3 responses were more likely in pts achieving MCID in SIJ, spine (Table 2), or both SIJ and spine vs not achieving MCID. Compared with not achieving MCID, pts on tofacitinib achieving MCID in SIJ had larger improvements in BASDAI, BASFI, and back pain.

Conclusion: Tofacitinib-treated pts with AS experienced clinically meaningful reductions in axial MRI inflammation. Pts achieving MCID for MRI inflammation had increased clinical response rates. **References** 1. Maksymowych WP et al. J Rheumatol 2012; 39: 1666-1674. 2. van der Heijde D et al. Arthritis Rheumatol 2015; 67: Abstr 5L.

Table 1. Week 12 SPARCC scores and proportion of patients achieving MCID

	Placebo	Tofacitinib 2 mg BID	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	All tofacitinib
Change from baseline to Week 12 SPARCC SIJ scores	N=34	N=42	N=44	N=44	N=130
Mean (range)	-0.7 (-9.5, 6.5)	-2.2 (-22.0, 10.5)	-3.5 (-34.5, 11.0)	-3.6 (-29.0, 0.5)	NA
Median (Q1, Q3)	0.0 (-1.0, 0.0)	0.0 (-3.0, 0.0)	0.0 (-5.0, 0.0)	0.0 (-3.5, 0.0)	NA
Change from baseline to Week 12 SPARCC spine score	N=34	N=41	N=44	N=44	N=130
Mean (range)	0.8 (-8.0, 14.0)	-3.2 (-34.5, 20.5)	-5.5 (-36.5, 8.0)	-6.7 (-32.5, 7.5)	NA
Median (Q1, Q3)	0.0 (-1.5, 2.5)	-0.5 (-5.5, 0.0)	-2.0 (-9.5, 0.0)	-1.8 (-11.3, 0.0)	NA
	N=34	N=42	N=44	N=44	N=130
n (%) meeting MCID SPARCC SIJ score	4 (11.8)	12 (28.6)	17 (38.6)	13 (29.6)	42 (32.3)
	N=34	N=41	N=44	N=44	N=129
n (%) meeting MCID SPARCC spine score	4 (11.8)	12 (29.3)	16 (36.4)	18 (40.9)	46 (35.7)
	N=34	N=41	N=44	N=44	N=129
n (%) meeting MCID SPARCC SIJ and spine score	0	3 (7.3)	8 (18.2)	3 (6.8)	14 (10.9)

SPARCC SIJ score MCID is an improvement from baseline ≥2.5

SPARCC spine score MCID is an improvement from baseline ≥5

BID, twice daily; MCID, minimum clinically important difference; NA, not available; SD, standard deviation; SIJ, sacroiliac joints; SPARCC, SPondyloArthritis Research Consortium of Canada

Table 2. Relationship between Week 12 clinical response rates and achievement of MCID

	Pooled tofacitinib					Placebo				
	N	ASAS20 n (%)	ASAS40 n (%)	ASDAS MI n (%)	ASDAS <1.3 n (%)	N	ASAS20 n (%)	ASAS40 n (%)	ASDAS MI n (%)	ASDAS <1.3 n (%)
SIJ ≥MCID (2.5)	42	33 (78.6)	25 (59.5)	15 (35.7)	8 (19.1)	4	3 (75.0)	1 (25.0)	0	0
SIJ <MCID (2.5)	88	54 (63.5)	36 (42.4)	17 (19.5)	13 (14.9)	30	14 (48.3)	6 (20.7)	3 (10.7)	3 (10.7)
Spine ≥MCID (5)	46	36 (81.8)	26 (59.1)	16 (35.6)	8 (17.8)	4	3 (75.0)	2 (50.0)	2 (50.0)	1 (25.0)
Spine <MCID (5)	83	51 (62.2)	35 (42.7)	16 (19.3)	13 (15.7)	30	14 (48.3)	5 (17.2)	1 (3.6)	2 (7.1)

ASAS, ASessments in Ankylosing Spondylitis; ASDAS, ankylosing spondylitis disease activity score; MCID, minimum clinically important difference; MI, major improvement; SIJ, sacroiliac joints

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2016 Update of the ASAS-EULAR Management Recommendations for Axial Spondyloarthritis

Désirée van der Heijde[1], Sofia Ramiro[2], Robert Landewé[3], Xenofon Baraliakos[4], Filip van Den Bosch[5], Alexandre Sepriano[2], Andrea Regel[6], John D. Reveille[7] and Jürgen Braun[6], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Clinical Immunology and Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [4]Rheumazentrum Ruhrgebiet Herne, Ruhr-University Bochum, Herne, Germany, [5]Rheumatology, Ghent University Hospital, Ghent, Belgium, [6]Rheumazentrum Ruhrgebiet, Herne, Germany, [7]Rheumatology, University of Texas-McGovern Medical School, Houston, TX

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Background/Purpose: In 2010 the latest ASAS-EULAR recommendations for AS and the ASAS recommendations for the use of TNF-inhibitors (TNFi) have been published. Since then new treatments for axSpA have become available. We aimed to update and integrate the two sets of recommendations into one set applicable to patients with axSpA.

Methods: The EULAR Standardised Operating Procedures have been followed. First, two Systematic Literature Reviews have been performed to update the evidence on all treatment options (pharmacological and non-pharmacological) since 2009. The results have been presented during a one-day meeting of the task force. Thereafter, overarching principles and recommendations were updated by a process of achieving consensus and voting.

Results: A total of 5 overarching principles and 13 recommendations have been formulated (Table). The first 3 recommendations deal with personalised medicine including treatment target and monitoring. Recommendation 4 deals with non-pharmacological management. Recommendation 5 describes the central role of NSAIDs as first pharmacological treatment. Recommendations 6 to 8 define the limited place of analgesics, glucocorticoids and conventional synthetic DMARDs. Biological DMARDs (bDMARDs) include TNF- and IL17-inhibitors and are indicated in patients diagnosed with axSpa by a rheumatologist, who have radiographic sacroiliitis and/or inflammation on MRI and/or an elevated CRP-level. Patients should also have high disease activity despite the use of -or intolerance for- at least 2 NSAIDs. High disease activity is defined as an ASDAS ≥2.1 or BASDAI ≥4 and an indication to start a bDMARD by a rheumatologist (Figure). The continuation of a bDMARD should be considered if an improvement of ASDAS ≥1.1 or BASDAI ≥2 has been achieved after at least 12 weeks. Current practice is to start with a TNFi. Switching to another TNFi or an IL-17i is recommended in case of failure of TNFi treatment. Tapering -but not stopping- of a bDMARD can be considered in patients with sustained remission. The final two recommendations deal with surgery and fractures.

Conclusion: The 2016 ASAS-EULAR recommendations provide up-to-date guidance on management of patients with axSpA.

Table: 2016 update of the ASAS-EULAR management recommendations
Overarching principles of the management of axSpA
Axial Spondyloarthritis (axSpA) is a potentially severe disease with diverse manifestations, usually requiring multidisciplinary management coordinated by the rheumatologist
The primary goal of treating the patient with axSpA is to maximize health related quality of life through control of symptoms and inflammation, prevention of progressive structural damage, preservation/normalisation of function and social participation.
The optimal management of patients with axSpA requires a combination of non-pharmacological and pharmacological treatment modalities.
Treatment of axSpA should aim at the best care and must be based on a shared decision between the patient and the rheumatologist.
axSpA incurs high individual, medical and societal costs, all of which should be considered in its management by the treating rheumatologist
Recommendation 1
The treatment of patients with axSpA should be individualised according to the current signs and symptoms of the disease (axial, peripheral, extra-articular manifestations) and the patient characteristics including comorbidities and psychosocial factors
Recommendation 2
Disease monitoring of patients with axSpA should include patient reported outcomes, clinical findings, laboratory tests and imaging, all with the appropriate instruments and relevant to the clinical presentation. The frequency of monitoring should be decided on an individual basis depending on symptoms, severity, and treatment.
Recommendation 3
Treatment should be guided according to a predefined treatment target.
Recommendation 4
Patients should be educated about axSpA and encouraged to exercise on a regular basis and stop smoking; physical therapy should be considered.
Recommendation 5
Patients suffering from pain and stiffness should use an NSAID as first line drug treatment up to the maximum dose, taking risks and benefits into account. For patients who respond well to NSAIDs continuous use is preferred if symptomatic otherwise.
Recommendation 6
Analgesics, such as paracetamol and opioid-(like) drugs, might be considered for residual pain after previously recommended treatments have failed, are contraindicated, and/or poorly tolerated.
Recommendation 7
Glucocorticoid injections directed to the local site of musculoskeletal inflammation may be considered. Patients with axial disease should not receive long-term treatment with systemic glucocorticoids.
Recommendation 8
Patients with purely axial disease should normally not be treated with csDMARDs; Sulfasalazine may be considered in patients with peripheral arthritis.
Recommendation 9
bDMARDs should be considered in patients with persistently high disease activity despite conventional treatments (box1); current practice is to start with TNFi therapy
Recommendation 10
If TNFi therapy fails, switching to another TNFi or IL17i therapy should be considered.

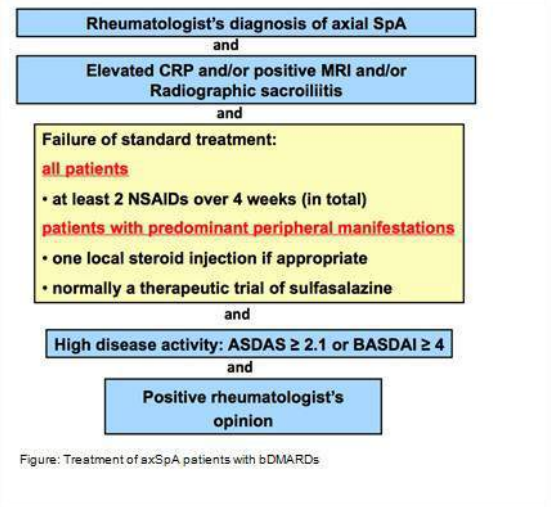

Figure: Treatment of axSpA patients with bDMARDs

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Abstract Number: 1046

Anti-TNF Therapy in Axial Spondyloarthritis: Prediction of Therapeutic Responses Using Immunological Signatures

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Background/Purpose: The introduction of anti-TNF therapy has proven effective to reduce inflammation and clinical symptoms in several chronic inflammatory diseases. However, TNF-blockers are effective only in a subpopulation of patients and can be associated with serious side effects. Despite intense efforts, it is currently not possible to predict responsiveness of patients to anti-TNF treatment. To address this issue, we have asked whether the analysis of the immune functions of patients will allow us to define biomarkers that can predict therapeutic responses to TNF blockers. The goals of this project were to define (i) the impact of anti-TNF therapy on immune responses to microbial challenges and stimuli targeting specific immune pathways in axial spondyloarthritis (axSpA) patients and (ii) to identify immunological correlates associated with therapeutic responses to TNF blockers before the initiation of therapy.

Methods: We have recently developed a set of whole-blood, syringe-based assays to assess innate or adaptive immune responses to stimuli targeting different signaling pathways (e.g. cytokines and TLR/NLR agonists), or mimicking infections in patients (1). This “TruCulture” system is designed to capture immune cell activity in response to specific stimuli without introducing sample collection and manipulation variables. Using this assay system, we have investigated immune responses to 20 different stimuli in a pilot study involving 12 axSpA patients before and 3 months after initiation of anti-TNF therapy. We are currently validating our findings in a replication cohort.

Results: We noted a highly significant reduction of the secretion of IL-1ra, IL-1β, and MIP-1β in response to selected stimuli after treatment with TNF-blockers. In contrast, TNF blockers had only minor effects on cytokine/chemokine production in unstimulated cultures, indicating that the effects of anti-TNF therapy can be measured when immune cells are challenged, but not at steady state. We also tested whether there is a correlation between the responses of immune cells to specific stimuli and the clinical response to TNF-blockers. For this, we calculated the “Ankylosing Spondylitis Disease Activity Score” (ASDAS) before treatment and 3 months after initiation of anti-TNF therapy and determined the “Improvement Score”. We found that axSpA patients who secreted the highest levels of inflammatory cytokines and chemokines in response to specific immune stimuli before initiation of anti-TNF therapy had the best therapeutic responses (highest improvement score).

Conclusion: Our results show that TruCulture assays are an efficient and robust tool to monitor immune functions in patients and that anti-TNF therapy induces specific changes in immune responses to selected stimuli. Our data also indicate that analyzing immune responses in patients before therapy is a promising strategy to develop biomarkers predicting therapeutic efficacy of TNF-blockers. Reference: (1) Duffy et al., Immunity. 2014 Mar 20;40(3):436-50

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Abstract Number: 1047

Negative Results of Antinuclear Antibody (ANA) Testing in Clinical Trials of Systemic Lupus Erythematosus (SLE) May be Due to Assay Variability

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Background/Purpose: SLE clinical trials typically require that patients have either a positive ANA serology at a central laboratory during screening or have prior positive results. The definition of positive serology has varied among trials but, in all cases, a pre-specified titer of ANA has been sufficient to meet entry criteria. Studies that have allowed patients to enter with historically positive ANA serologies have been criticized because of concerns that these patients may not truly have lupus. Inconsistencies in the performance of ANAs and lack of standardization among the assays used in these trials may, however, contribute to the variability in ANA assay results.[1] To further evaluate this issue, we have analyzed different ANA assays using samples collected in a Phase 2 randomized clinical trial which evaluated the efficacy and safety of an IL-6 mAb for the treatment of SLE.[2] All potentially eligible subjects underwent a careful review of serology and clinical laboratory findings (ANA, anti-dsDNA, anti-Sm, anti-RNP, anti-SSA, anti-SSB, C3, and C4), medical history, and current lupus symptoms at screening. Those without a current positive ANA (Kallestad HEp-2 Cell Line Substrate) or anti-dsDNA by the central laboratory were also reviewed by an independent panel of lupus experts to confirm that the subject had both a positive historical ANA and clinically active lupus prior to randomization. Of the 183 patients enrolled, there were 43 (23.8%) who had <1:80 ANA titer at screening from the central laboratory.

Methods: 181 samples collected at baseline in the clinical trial were evaluated using 5 commercially available HEp-2 ANA indirect fluorescent antibody (IFA) assays. All assays were performed according to the manufacturers' protocols. Samples at 1:40 and 1:80 dilutions were run with each manufacturers' positive and negative controls, and visualized using an EVOS FL Cell Imaging System.

Results: Overall, the EuroImmun assay resulted in the greatest percentage of positive results at a 1:80 dilution (99.4%). The Kallestad and Immunoconcepts assays had the lowest number of positive results of 86% and 72%, respectively. When combined, the EuroImmun and Nova Lite or Zeus assays yielded the maximum number of positive responses (100%). All 43 subjects with a <1:80 ANA titer during screening were ≥1:80 in 1 or more assays during this analysis.

Table 1. HEp-2 ANA Assay Results from Five Commercial Assays

	EuroImmun	Nova Lite	Zeus	Kallestad	Immunoconcepts
Positive Samples at 1:80, n (%)	180 (99.4)	175 (96.7)	171 (94.5)	156 (86.2)	131 (72.4)
Negative Samples at 1:80, n (%)	1 (0.6)	6 (3.3)	10 (5.5)	25 (13.8)	50 (27.6)

Assays: ANA IFA: HEp-20-10 Test (Euroimmun, Boonton Township, NJ), Nova Lite Hep-2 ANA (INOVA Diagnostics, San Diego, CA), the ANA/HEp-2 Cell Culture IFA test System (Zeus Laboratories, Raritan, NJ), the Kallestad HEp-2 Cell Line Substrate (Bio-Rad Laboratories, Hercules, CA), and the HEp-2000 Fluorescent ANA-Ro Test System (ImmunoConcepts, Sacramento, CA)

Conclusion: In a well characterized lupus population, there was a large variation in the frequencies of positive samples depending on the ANA assay. These results suggest that careful consideration should be applied in the selection of an ANA assay for the purpose of establishing clinical trial eligibility. Preference may be given to assays that exhibit high sensitivity in patients with established SLE and using 2 sensitive assays may provide additional evidence for patient enrollment in SLE trials. 1. Copple SS et al. Am J Clin Pathol 2012;137:825-830. 2. Wallace D et al. ACR Annual Meeting 2014.

Disclosure: D. Pisetsky, Pfizer Inc, 5; **D. Thompson**, None; **J. Wajdula**, Pfizer Inc., 3,Pfizer Inc., 1; **A. Diehl**, Pfizer Inc, 3,Pfizer Inc, 1; **S. Sridharan**, Pfizer Inc, 9.

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Abstract Number: 1048

Differences in Clinical Manifestations of SLE Across Four Racial/Ethnic Groups: The

California Lupus Surveillance Project (CLSP)

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Background/Purpose: The CLSP is a population-based registry of individuals with SLE residing in San Francisco County, California from 2007 – 2009. The registry has a special focus on improving our understanding of SLE in Asian/Pacific Islander (PI) and Hispanic individuals, two groups previously understudied in population-based epidemiologic investigations. We used CLSP data to analyze differences in 1) lupus manifestations by sex and race/ethnicity and 2) time to development of these manifestations after disease onset.

Methods: Relative risks (RR) of SLE manifestations were calculated using Poisson regression models adjusted for race/ethnicity, sex, age at SLE diagnosis, and duration of SLE disease. Kaplan-Meier and Cox proportional hazards methods were used to analyze time to development of severe manifestations of SLE, with higher hazard ratios (HR) indicating a shorter time to development of specific manifestations.

Results: 724 prevalent cases of SLE were identified with the following distribution by race/ethnicity: white (26.2%), Black (18.8%), Asian/PI (36.9%), Hispanic (15.5%), missing (2.6%). For lupus manifestations, Blacks, Asians/PIs, and Hispanics had increased prevalence of lupus nephritis relative to whites (RR 1.78, RR 1.74, and RR 1.46, respectively). Furthermore, Blacks had increased neurological manifestations (RR 1.50), Asians/PIs had increased mucocutaneous manifestations (RR 1.16), and both Blacks and Asians/PIs had increased hematologic manifestations (RR 1.08 and RR 1.07, respectively). For time to development of manifestations, statistically significant differences in lupus nephritis ($p < 0.001$), thrombocytopenia ($p = 0.006$), and neuropsychiatric abnormalities ($p = 0.042$) were observed by race/ethnicity, though this was not the case in the analysis of antiphospholipid (APS) ($P = 0.092$). Blacks, Asians/PIs, and Hispanics had earlier development (higher hazards) of lupus nephritis, thrombocytopenia, and APS relative to whites. Men had earlier development of lupus nephritis and thrombocytopenia relative to women (Table).

Table. Factors associated with earlier occurrence (higher hazards) of manifestations of SLE in multivariate cox proportional models, among prevalent SLE cases in San Francisco County, 2007 – 2009.

Variables	Lupus Nephritis* HR (95% CI)	Thrombocytopenia HR (95% CI)	Neuropsychiatric** HR (95% CI)	APS HR (95% CI)	Combined HR (95% CI)
Race/ethnicity					
White, non-Hispanic	reference	reference	reference	reference	reference
Black, non-Hispanic	2.4 (1.5 – 3.7)	2.6 (1.4 – 4.6)	1.3 (0.7 – 2.2)	2.6 (1.0 – 6.5)	1.7 (1.3 – 2.3)
Asian/PI, non-Hispanic	4.1 (2.8 – 6.0)	2.5 (1.5 – 4.2)	0.8 (0.5 – 1.4)	3.9 (1.8 – 8.9)	2.3 (1.7 – 3.0)
Hispanic	2.3 (1.4 –3.7)	2.9 (1.6 – 5.3)	1.0 (0.5 – 2.0)	5.1 (2.1 – 12.2)	1.6 (1.1 – 2.3)
Sex					
Female	reference	reference	reference	reference	reference
Male	1.6 (1.1 – 2.3)	1.8 (1.1 – 2.9)	1.6 (0.9 – 2.9)	1.8 (1.0 – 3.3)	1.8 (1.3 – 2.4)
Age, yr at diagnosis					
≤18	1.0 (0.7 – 1.4)	1.2 (0.7 – 2.0)	1.0 (0.5 – 1.8)	1.0 (0.5 – 1.9)	0.9 (0.7 – 1.2)
19-29	reference	reference	reference	reference	reference
30-39	0.8 (0.5 – 1.2)	0.9 (0.5 – 1.6)	0.8 (0.4 – 1.5)	0.8 (0.4 – 1.5)	0.8 (0.6 – 1.1)
40-49	0.9 (0.6 – 1.3)	0.6 (0.3 – 1.1)	1.1 (0.5 – 2.2)	0.9 (0.4 – 1.8)	0.9 (0.7 – 1.3)
50+	1.0 (0.7 – 1.5)	1.9 (1.2 – 3.1)	2.1 (1.1 – 3.8)	0.8 (0.4 – 1.7)	1.4 (1.0 – 1.9)

SLE = systemic lupus erythematosus; APS = antiphospholipid antibody syndrome; Combined outcome = any of lupus nephritis, thrombocytopenia, neuropsychiatric, or APS
**Any of the following surrogate labs were used to define lupus nephritis: 24 hour urine for protein > 300mg, 24 hour urine protein/creatinine ratio > 0.5, or spot protein/creatinine ratio > 0.5.*
***Neuropsychiatric manifestations studied include: seizures, psychosis, and acute confusional state.*

Conclusion: This analysis represents the first epidemiologic study comparing lupus manifestations among four major racial/ethnic groups and includes large numbers of Asians/PIs and Hispanics. We found 1) dramatic differences in the prevalence of several clinical SLE manifestations among race/ethnicities and 2) that Blacks, Asians/PIs, and Hispanics are at increased risk of developing many manifestations earlier than whites following initial SLE diagnosis. Men also developed lupus nephritis and thrombocytopenia earlier than women with SLE.

Abstract Number: 1049

High Titer ANA Not Necessarily a Valid Criterion for Lupus – Proposal of a Modification to the Criteria for Classification of SLE

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Background/Purpose: A positive ANA test is one of ACR Revised Criteria for Classification of SLE, as well as the SLICC classification. The ANA test provides a direct initial assessment of autoantibody response in candidate patients of systemic autoimmune rheumatic diseases (SARD). As a follow-up to the International Consensus on ANA Patterns (ICAP) initiative (ANApatterns.org), which aims to promote harmonization of ANA pattern nomenclature and provides guidelines for ANA interpretation, thereby optimizing usage in patient care, the relevance of each ANA pattern is being re-evaluated. An important observation is that, while the Homogeneous (AC-1) and Coarse Speckled nuclear (AC-5) patterns are linked to autoantibodies strongly associated with SARD, the Dense Fine Speckled (DFS) nuclear pattern (AC-2) virtually rules out a SARD diagnosis. A clear-cut DFS pattern is usually present when anti-DFS70 is the only predominant autoantibody. DFS is the most common pattern in high titer ANA+, apparently healthy, individuals. Although DFS has been reported in a wide variety of chronic inflammatory diseases, it is not associated with SARD even when present at very high titer.

Methods: ANA test at 1/80 screening dilution was performed in 269 sequentially selected patients with SLE diagnosis, 918 healthy individuals, and 558 patients with non-SARD conditions (arterial hypertension, diabetes mellitus, dyslipidemia, various cancers, psychiatric diseases, and HCV/HIV infection). ANA interpretation was the consensus of 3 independent readers using 2 HEp-2 cell slide brands at 400x mag. Conversely, sequentially selected individuals presenting >1/640 titer DFS ANA pattern in a large clinical laboratory within a 2-year period had the diagnosis assessed by interview with the respective physician.

Results: Among 269 consecutive SLE patients, 96.3% had a positive ANA with the following principal nuclear patterns: homogeneous (29.3%), coarse speckled (14.7%), fine speckled (40.1%). One patient (0.3%) had the DFS pattern and the reactivity to DFS70 confirmed by ELISA. Conversely, among 118 ANA+ healthy individuals and 102 ANA+ patients with miscellaneous non-SARD conditions, 33.1 and 16.7% presented the DFS pattern, respectively. In addition, the 327 consecutive high-titer DFS individuals presented mostly non-SARD conditions or non-specific clinical presentation. Only 7 had possibly SARD-related presentations: 1 anti-phospholipid syndrome, 1 “possible” SLE (polyarthritis, arthritis, chronic urticaria), 1 WG, 1 DLE, 1 primary biliary cirrhosis, and 1 RA.

Conclusion: Well-defined anti-DFS ANA, confirmed by antigen-specific reflex testing, should not be considered a criterion for SLE - either in the ACR or SLICC classification criteria.

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Abstract Number: 1050

Defining Low Disease Activity in Systemic Lupus Erythematosus

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Background/Purpose: Remission is a desirable but not a common enough outcome in systemic lupus erythematosus (SLE) and therefore additional measures are needed to evaluate new therapies. Our aims were: 1. to define and identify a group of SLE patients with low disease activity (LDA) in a prospective cohort; 2. To examine whether the LDA group was similar to a remission group and whether these 2 groups were different from a high disease activity group (HDA) in short term outcomes.

Methods: The study population included patients with SLE who were followed according to a standard protocol from 1970 to 2015 and who had visits no more than 18 months apart. The LDA group was defined as Systemic Lupus Erythematosus Disease Activity Index (SLEDAI-2K) of 2 or less (with or without positive serology) based on the presence of only 1 clinical manifestation of: rash, alopecia, mucosal ulcers, pleurisy, pericarditis, fever, thrombocytopenia or leukopenia. The patients could be taking antimalarial, but not corticosteroids or immunosuppressives. The remission group was defined as inactive clinical manifestations while only antimalarials were allowed and the HDA group was defined as SLEDAI-2K>6. The minimal time for inclusion in each group was 1 year.

Results: Of 620 patients with active disease who were seen during this period 80 (12.9%) patients fulfilled the criteria for LDA, 191 (30.8%) for remission and 349 (56.3%) for HDA. The LDA patients with positive serology (30 patients) were similar to the LDA patients without serology (50 patients) in baseline and prior disease manifestations, co-morbidities, treatments and in the distribution of the defined SLEDAI-2K items at baseline. After 2 years of follow-up, the LDA and remission groups were similar in their adjusted mean SLEDAI score (AMS), organ involvement (including central nervous system, vasculitis, renal and musculoskeletal), SLICC score, mortality and different treatments (Table 1). After 2 and 4 years of follow up, the HDA group had higher AMS, more major organ involvement, higher SLICC score, more mortality and was given more treatments compared to the LDA and remission groups. Further comparison according to these categories between the HDA group and a combined group of LDA and remission groups, showed the same trend of worse outcome and prognosis for the HDA group (Table 2).

Conclusion: SLE patients with LDA were defined and identified in a large SLE cohort. The LDA and remission groups had similar short term outcomes and both had better outcomes and prognosis than the HDA group. LDA may be used as an outcome measure in therapeutic trials or in treat to target regimens.

Table 1: Disease activity and prognosis of the LDA and the remission groups at 2 years from the definition year

Characteristic	Remission (N=139)	LDA (n=68)	P value
Adjusted mean SLEDAI (AMS)	2.4 ± 2.3	2.9 ± 1.8	0.09
Flares, n (%)	7 (5)	3 (4.4)	0.8
Organ involvement:			
CNS, n (%)	9 (6.5)	4 (5.9)	0.9
Vasculitis, n (%)	3 (2.2)	2 (2.9)	0.7
Renal, n (%)	20 (14.4)	7 (10.3)	0.4
MSK, n (%)	21 (15.1)	9 (13.2)	0.7
Comorbidities:			
CVS (atherosclerosis), n (%)	2 (1.4)	0	0.3
AVN, n (%)	1 (0.7)	2 (2.9)	0.5
Osteoporosis, n (%)	0	0	NA
Mean SDI	0.1 ± 0.5	0.2± 0.5	0.18
Mortality, n (%)	1 (0.5)	2 (2.5)	0.15
Treatment:			
Cumulative dose of GCS (g/d)	0.5 ± 1.9	0.04 ± 0.2	0.2
Anti-malarial medications, n (%)	10 (7.2)	3 (4.4)	0.2
Immunosuppressive drugs, n (%)	1 (0.7)	1 (1.5)	0.6

LDA – low disease activity, SDI– SLICC/ACR damage index, CNS- central nervous system, CVS – cardiovascular system, AVN – avascular necrosis, GCS – glucocorticsteroids, N/A – not applicable

Table 2: Disease activity and prognosis of the Remission/LDA and HDA groups at 2 years from the definition period			
Characteristic	Remission +LDA (n=207)	HDA (n=247)	P value
Adjusted mean SLEDAI (AMS)	2.6 ± 2.1	8.6 ± 4.6	<0.001
Flares, n (%)	11 (4.1)	41 (11.7)	<0.001
Organ involvement:			
CNS, n (%)	13 (6.3)	78 (31.6)	<0.001
Vasculitis, n (%)	5 (2.4)	30 (12.1)	<0.001
Renal, n (%)	27 (13)	156 (63.2)	<0.001
MSK, n (%)	30 (14.5)	47 (19)	0.2
Comorbidities:			
CVS (atherosclerosis), n (%)	2 (1)	12 (4.9)	0.02
AVN, n (%)	3 (1.4)	13 (5.3)	0.03
Osteoporosis, n (%)	0	16 (6.5)	<0.001
Mean SDI	0.15 ± 0.5	0.52± 1	<0.001
Mortality, n (%)	3 (1.4)	17 (6.9)	0.02
Treatment:			
Cumulative dose of GCS (g/d)	0.33 ± 1.5	15 ± 9	<0.001
Anti-malarial medications, n (%)	13 (6.3)	41 (16.6)	<0.001
Immunosuppressive drugs, n (%)	2 (1)	74 (30)	<0.001
LDA – low disease activity, HDA – high disease activity, SDI– SLICC/ACR damage index, CNS- central nervous system, CVS – cardiovascular system, AVN – avascular necrosis, GCS – glucocorticosteroids			

Disclosure: **A. Polachek**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 1051

Determining the Minimal Clinically Important Difference for Improvement for Systemic Lupus Erythematosus Disease Activity Index-2000 Responder Index-50 (S2K RI-50)

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Background/Purpose: Systemic Lupus Erythematosus Disease Activity Index-2000 Responder Index-50 (S2K RI-50) is a reliable and valid index able to measure ≥ 50% improvement in disease activity. We aimed to determine the Minimal Clinically Important Difference (MCID) for improvement for S2K RI-50.

Methods: Analysis was conducted on patients seen during 2010-2012 at a single lupus centre. The S2K RI-50 data retrieval form was completed at each visit. Physician global assessment was determined at baseline visit on a visual analogue scale (0-10) and at follow up visits on a 7-point Likert scale (LS) (1-3 reflects worsening, 4 unchanged, 5 slightly improved, 6 moderate improved (≥ 50%) and 7 much

improved). This analysis is focused on the first follow up visit. LS was collapsed into 2groups; LS 6-7 and LS 1-5. The change of SLEDAI-2K scores was calculated between baseline and follow up. The change of S2K RI-50 was calculated between baseline SLEDAI-2K and follow up S2K RI-50 scores. MCID was determined with the anchor-based and the distribution-based approaches. *Anchor-based approach using the whole cohort*: we modeled the 1st follow up LS ≥ 6 as the outcome variable, and continuous S2K RI-50 change as the predictor in Logistic Regression model. Area Under the Curve (AUC) was obtained to determine the predictive power of S2K RI-50. We also derived the best S2K RI-50 cutoff based on optimal sensitivity/specificity in receiver operating characteristic (ROC) determined by the Youden index. *Distribution-based approach*: Standardized Response Mean (SRM) was used to confirm the effect size. The Standard Error of Measurement (SEM) was derived based on the following equation: SEM = $Pooled\ SD_{Baseline} \times \sqrt{(1 - test - retest\ reliability\ coefficient}$

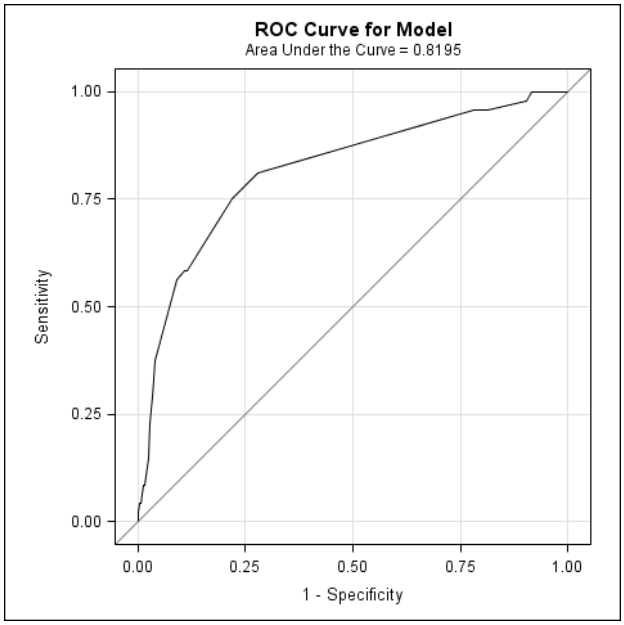
[S2K RI-50 test-retest reliability = 0.98 based on a previous publication from the same centre]

Results: 509 patients were studied (age and lupus duration at baseline visit were 44.3 ± 14.7 and 15.2 ± 11.0 years respectively). 48 patients had an improvement (LS 6 or 7). The characteristics of the patients with LS 6-7 and LS ≤5 are represented in table 1. **Anchor-based approach**: MCID of improvement is equal to 1 based on the ROC analysis [AUC 0.82 (95% CI: 75-89), sensitivity 81% and specificity 72%] (Figure 1). **Distribution-based approach**: SRM of S2K RI-50 for LS 6-7 was -0.97 (95% CI: -1.3, -0.6) which is considered a large effect size. SEM was equal to 0.96 from the previous equation.

Conclusion: The estimated MCID of S2K RI-50 derived from both ROC analysis and SEM confirmed that it is close to 1. Thus a reduction of S2K RI-50 of 1 represents a relevant change in disease activity.

Table 1. Characteristics of the patients with LS 6-7 and LS ≤5

VARIABLE		LS≤5 N=461	LS 6-7 N=48	p
Sex	F	411 (89.2%)	44 (91.7%)	0.59
	M	50 (10.8%)	4 (8.3%)	
Age at baseline	Mean ± SD	44.11 ± 14.90	45.60 ± 14.22	0.50
SLE duration at baseline	Mean ± SD	15.27 ± 11.21	13.32 ± 8.70	0.24
SLEDAI-2K baseline	Mean ± SD	2.93 ± 3.54	7.33 ± 4.85	<.001
SLEDAI-2K at 1st follow up	Mean ± SD	3.26 ± 4.06	4.71 ± 4.08	0.01
SLEDAI-2K change	Mean ± SD	0.32 ± 2.74	-2.63 ± 4.15	<.001
S2K RI-50 at 1st follow up	Mean ± SD	2.90 ± 3.88	3.19 ± 2.53	0.61
S2K RI-50 change	Mean ± SD	-0.04 ± 3.15	-4.15 ± 4.24	<.001



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Abstract Number: 1052

Longitudinal Patterns in SLE Response to Standard of Care Therapy: Implications for SLE Clinical Trial Design

Mimi Kim[1], Joan T Merrill[2], Kenneth Kalunian[3], Bevra H. Hahn[4], Anita Roach[5], **Peter M. Izmirly**[6] and the Lupus Foundation of America Collective Data Analysis Initiative Group., [1]Biostatistics and Research Design Resource, Albert Einstein Coll Med, Bronx, NY, [2]OMRF, Oklahoma, OK, [3]Center for Innovative Therapy, UCSD School of Medicine, La Jolla, CA, [4]Division of Rheumatology, UCLA David Geffen School of Medicine, Los Angeles, CA, [5]Education & Research, Lupus Foundation of America, Washington, DC, [6]New York University School of Medicine, New York, NY

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment II: Clinical Trial Design

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Most clinical trials of new treatments for systemic lupus erythematosus (SLE) have shown weak discrimination between investigational agents and placebo when added to standard of care (SOC). Given that targeted biologics are unlikely to be effective in all patients, it is challenging for these experimental therapies to exceed the high response rates observed with SOC alone in placebo arms. The design of future SLE trials may be improved by considering strategies for reducing placebo response rates and obtaining a better understanding of the within-patient variability in disease activity during follow up. The goal of this study was to evaluate longitudinal patterns of response in SLE patients who received placebo plus SOC in two completed 52-week clinical trials. Baseline characteristics discriminating early and persistent responders from non-responders to SOC were also examined to identify patient populations who may benefit most from experimental therapies and could be targeted for enrollment in future trials.

Methods: Data was obtained from the Collective Data Analysis Initiative (CDAI) of the Lupus Foundation of America and included 147 patients from the placebo plus SOC arms of two randomized Phase II/III trials in moderately-to-severely active lupus patients without acute nephritis. A BILAG-based response was evaluated at weeks 12, 24, 36, 48, and 52. Both cross-sectional and longitudinal analyses of response patterns were performed. Clinical variables, including background medications and baseline factors associated with disease severity, that discriminated persistent responders from non-responders were identified using logistic regression.

Results: The cross-sectional response rates ranged from 37% - 46% between 12 - 52 weeks for patients treated with placebo plus SOC, similar to the placebo response rates estimated in most non-nephritis lupus trials. The response rate decreased to 14.3% (95% CI: 8.6% - 19.9%) when the criterion was complete response, i.e., response at all visits between 12 - 52 weeks. Agreement between response status at 12 weeks and 36-52 weeks was low (kappa = 0.15 - 0.25); furthermore only 31% of initial 12 week responders maintained response at all subsequent visits. Factors contributing to non-response to SOC at all visits included more severe disease, as suggested by more organ systems active at baseline, and low C3 levels at baseline. Less aggressive immunosuppression was also associated with non-response.

Conclusion: An endpoint based on a sustained rather than cross-sectional response may reduce high placebo response rates in SLE trials that continue aggressive SOC and may improve discrimination between effective experimental treatments and SOC. Although there is increasing interest in conducting efficient 12 or 24 week early phase trials, the observed lack of stability in response to SOC over time highlights a potential weakness with shorter studies that use an endpoint of improvement. Our data also confirm earlier reports that the likelihood of response in the placebo group depends on the severity of disease and the aggressiveness of background treatments.

Disclosure: M. Kim, None; **J. T. Merrill**, Aspreva, 5,Genentech and Biogen IDEC Inc., 5; **K. Kalunian**, Bristol-Myers Squibb, 5,Genentech, 5; **B. H. Hahn**, Bristol-Myers Squibb, 2; **A. Roach**, None; **P. M. Izmirly**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/longitudinal-patterns-in-sle-response-to-standard-of-care-therapy-implications-for-sle-clinical-trial-design

Abstract Number: 1053

Evaluating the Charla De Lupus (Lupus Chat)® Program's Teen, Young Adult and Parent Support Group: Reaching the Hispanic/Latino Community through a Family Model of Support

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SESSION INFORMATION

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Session Title: ARHP II: Healthcare Disparities and and Psychosocial Impact on Rheumatic Disease

Session Type: ARHP Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Research shows that chronic illnesses such as SLE have multi-level impact on the family; it can be challenging for both patients & caregivers to cope with & manage the illness. An analysis of session evaluations was conducted for a monthly psychoeducation group, ongoing since 2001, for teens & young adults with SLE & their loved ones with a focus on Hispanic/Latino communities. The bilingual groups provide support & education strategies to manage & cope with SLE. Each 2-hour evening program occurs at a hospital site where many patients receive care & includes a professionally-led presentation, workshop or open discussion on a SLE-related topic.

Methods: A 16-item evaluation with Likert scale, multiple choice & open-ended questions was distributed after each of the 7 groups (2015-2016) focused on a SLE-related topic, such as Medications, Nutrition, Research & Doctor-Patient Communication. Items included demographics, overall satisfaction, knowledge, coping & disease management. There were 148 surveys distributed. Separate analyses were conducted for teens/young adults (T/YAs) < age 30 & parents/caregivers (Ps). Responses were also stratified by Hispanic (H) ethnicity. Fisher's exact tests were used to examine differences.

Results: There were 141 surveys (95%) submitted. Respondents were 50% T/YAs & 73% female. Over half (68%) were Hispanic, 29% African American, 28% some other race, 23% White & 13% Asian. Hispanic ethnicities included 32% Puerto Rican & 13% Dominican. Most (99%) respondents were satisfied overall with the program; 94% agreed that the program increased their understanding of SLE-related issues; 88% agreed that the program helped them cope with SLE; 90% agreed that they could apply what they learned to manage lupus; 95% agreed that the program met their expectations; 98% agreed that the presenter was clear & informative; 96% agreed that they would recommend this program. Ps reported ↑ agreement than T/YAs across 6 relevant Likert questions, with a significant difference in applying what they have learned to manage SLE (95% vs. 84% respectively, p=0.044). Differences in agreement for Hispanics (Hs) vs. Non-Hispanics (NHs) were significant across 6 Likert questions using Fisher's exact tests. Hs reported ↑ agreement (99%) than NH (82%) that the program increased knowledge of SLE, p=.001. This was similarly found in coping (95% vs. 73%, p=.005), disease management (94% vs. 79%, p=.024), meeting expectations (99% vs. 85%, p=.004), presenter clarity (100% vs. 93%, p=.032) & recommending the

program (99% vs. 90%, p=.042). Responses to open-ended questions, such as learning “how to manage my portions,” “how to explain lupus to others” & “how to communicate with doctors,” underscored substantial increases in knowledge and coping strategies.

Conclusion: Despite a limited sample size, our results demonstrate the value of the groups & our success in engaging patients. The significant differences found when stratified by Hispanic ethnicity speak to the positive impact the program has on the target community & indicate a need to further monitor this trend. This evaluation underscores the relevance of the family model of support when serving chronically ill diverse T/YAs with SLE & their caregivers.

Disclosure: M. T. Flores, None; **J. A. Rose**, None; **P. Toral**, None; **R. Horton**, None; **D. M. Pichardo**, None; **L. Mendez**, None; **L. F. Imundo**, None.

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Abstract Number: 1054

Self-Reported Psychological Impact and Coping Strategies of Men with RA

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Session Time: 4:30PM-6:00PM

Background/Purpose: Current RA research reflects the preponderance of women with the condition (30% male). Research in other conditions suggests men need their own health strategy. Our previous Q-methodology study (qualitative and quantitative approach to grouping people according to subjective opinion) found a sample of men with RA (n=30) formed two groups (termed ‘Factors’ in Q-methodology): Factor 1 ("accept and adapt") take control of other areas of their lives to enable them to accept and adapt to their RA. However, Factor 2 ("struggling to match up") try to continue masculine activities without accepting physical help or emotional support. The aim is to investigate the existence, distribution, coping strategies and psychological impact of these two groups in the wider male RA population.

Methods: Q-survey methods investigated the distribution of the Q-methodology factors from our previous study in the wider male RA population. Men with RA completed numerical rating scales (NRS) of the statements that define each factor and were assigned to a factor based on a weighted averaging of their scores[2]. Validated scales were used to measure disease severity (Patient-based DAS: PDAS), coping strategies; acceptance of illness; perceived stress; anxiety; depression and emotional well-being. The survey was sent to a random sample of 620 men with RA. Chi[2], ANOVA and t-tests were used to compare responses between the factors (groups) of men.

Results: 293/620 male patients (47%): mean age 66yrs (SD 10.9), dis dur 14yrs (SD 11.3), HAQ 0.56 (SD 0.57), PDAS 4.13 (SD 1.10) Of the 293 men, 12 had missing data, thus 281 were included in the analysis. Of these 61 (22%) were assigned to Factor 1 ("accept and adapt") and 120 (43%) were assigned to Factor 2 ("struggling to match up") and 99 (35%) were unassigned due to insufficient difference (<1SD) between the weighted averaged NRS scores The two factors differed significantly on measures of disease status, coping strategies and psychological status. Factor 2 reported higher scores on PDAS, confrontation, avoidance and resignation coping strategies; and perceived stress. Factor 2 had significantly more cases or borderline cases of anxiety and depression than Factor 1. Factor 1 reported higher scores on acceptance of illness and mental well-being (Table 1).

Conclusion: Some men seem able to accept and adapt to their RA, but others (43%) report severe disease, poor coping and poor psychological status. Future research needs to identify effective and appealing support for men with RA, particularly for those who seem to be struggling (Factor 2). References: [1]Flurey et al. (In Press) Identifying different typologies of experiences and coping strategies in men with rheumatoid arthritis: A Q-methodology study. BMJ Open. [2]Baker et al (2010) Connecting Q and surveys: Three methods to explore factor membership in large samples. Operant Subjectivity. 34 (1): 38-58

Variable	Factor 1: "Accept and adapt" Mean (SD) / % n=61	Factor 2: "Struggling to match up" Mean (SD) / % n=120	Unassigned Mean (SD) / % n=99
Age	68 (10.1) yrs	64 (10.9) yrs	67 (11.0) yrs
Disease duration	15 (10.1) yrs	15 (11.1) yrs	14 (12.2) yrs
Co-morbidities	61%	71%	68%
Marital status	69% married	77% married	77% married
Employment status	66% retired	54% retired	62% retired
Patient Global	18.32 (17.3)	51.02 (25.0)[a]	35.2 (26.3)
MHAQ	0.17 (0.33)	0.85 (0.57)[a]	0.49 (0.54)
PDAS	3.29 (0.62)	4.70 (1.00)[a]	4.02 (1.07)
DMARDs	79%	83%	80%
Biologics	18%	40%[b]	29%
Steroids	26%	28%	31%
No medication	8%	4%	5%
Confrontation coping	15.98 (3.39)	17.28 (3.41)[c]	17.09 (3.71)
Avoidance coping	13.48 (3.31)	15.74 (3.04)[a]	14.5 (3.54)
Resignation coping	7.25 (1.03)	8.83 (1.67)[a]	7.74 (1.52)
Acceptance of illness	35.03 (5.23)	21.55 (6.66)[a]	28.93 (7.01)
Depression	2% case 2% borderline	22% case[a] 23% borderline[a]	12% case 14% borderline
Anxiety	2% case 2% borderline	22% case[a] 23% borderline[a]	13% case 15% borderline
Perceived stress	2.48 (2.75)	6.64 (3.30)[a]	4.33 (3.13)
Mental well-being	27.74 (4.92)[a]	21.74 (4.25)	25.07 (5.12)

[a]P=<.000; [b]p=.010; [c]p=.015

Disclosure: C. Flurey, Arthritis Research UK, 2; **S. Hewlett**, None; **K. Rodham**, None; **A. White**, None; **R. Noddings**, None; **J. Kirwan**, None.

Abstract Number: 1055

Physical Activity Behavior in Men with Inflammatory Arthritis: A Cross-Sectional Register Based Study of Physical Activity Correlates, Motivators, Barriers and Preferences

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Session Time: 4:30PM-6:00PM

Background/Purpose: While physical activity (PA) has been recommended as a part of the non-pharmacological management of inflammatory arthritis (IA), previous research within this area has strong predominance of women and thus knowledge of the men's PA behavior is lacking. Accordingly, the aim was to examine PA behavior in men with IA, and the association between selected clinical and demographic variables and engagement in regular physical activity. Also men's motivation, barriers and preferences for PA was explored.

Methods: A cross-sectional study based on the Danish nationwide DANBIO registry covering patient with IA treated in routine care. Men, ≥18 years and rheumatoid arthritis (RA), psoriatic arthritis (PsA) or ankylosing spondylitis (AS) recruited consecutively from one hospital. PA level was determined using the patient-reported Saltin-Grimby PA Level Scale, categorized into groups of low PA (level 1 and 2 on the scale: mainly sedentary or only light physical activity) or regular PA (moderate-vigorous PA min. 2 h/w; level 3 and 4). Other measures included VAS for global, pain and fatigue, C-reactive protein (CRP) level, Clinical Disease Activity and Health Assessment Questionnaire (HAQ). Logistic regression analyses were performed to identify factors associated with engagement in regular physical activity.

Results: In total, 325 were included in the analyses (47% RA, 29% AS and 25% PsA); median age 55 y, 10 y median disease duration. Totally, 129 (40%) reported regularly physically active (i.e. recommended level), 196 (60%) reported mainly sedentary or engage in only light PA. Those regularly physically active were significantly younger, smoked less ($p<0.05$), reported less pain, fatigue and global ($p<0.01$) compared to the group who reported PA at a suboptimal level. Also a better score on physician's global, lower disease activity and a better functional status than the less active ($p<0.01$). Only VAS fatigue remained independently associated with engagement in regular PA (OR=0.814, 95%CI=0.741-0.895); $p<0.001$) (multivariable logistic regression analysis). The most frequently reported motivators for PA were to maintain/improve health (62%), be in shape (50%) and maintain/reduce weight (42%), whereas the most frequently reported barriers were being too tired (29%), lacking energy (27%) and prioritizing work/studies (23%). In total, 42% stated they would be motivated for participating in an intervention or other initiative aiming at promoting PA in men with IA. Most preferred interventions including strength training (43%), swimming (34%) or road cycling (20%). 41% would like the training to be individual and 30% to exercise in groups.

Conclusion: A majority of men with IA are not meeting the recommendations of regular engagement in PA. This group seems to perform worse than their more active counterparts on clinical, subjective and objective parameters. Fatigue seems to play a crucial role in explaining motivation and barriers for PA. However, a causal relationship cannot be established. Taking into account preventive and general health promoting effects of physical activity, further focus on strategies to increase the engagement in PA in men with IA is needed.

Disclosure: N. M. Hammer, None; **J. Midtgaard**, None; **M. Lund Hetland**, AbbVie, BMS, MSD, Roche, Pfiser, UCB, Crescendo, 2; **N. S. Krogh**, None; **B. A. Esbensen**, None.

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Abstract Number: 1056

Mind-Body Skills Training and Supportive Counseling for Depression in SLE: Positive Effects in a Randomized Controlled Trial

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Background/Purpose: Although depressive symptoms are prevalent in persons with SLE, no studies to date have evaluated psychotherapy approaches in persons with SLE who also have comorbid depression.

Methods: Ninety persons with SLE with comorbid depression were randomly assigned to receive 8 weekly individual sessions and 3

monthly booster sessions of Mind-Body Skills Training (MBST, n=45) or Supportive Counseling/Symptom Monitoring (SCSM, n=45). SLE was defined by 1997 ACR criteria and depression was defined by Quick Inventory of Depressive Symptomatology – clinician interview version (QIDS-C) diagnostic criteria and Center for Epidemiology Studies Depression (CESD) scale score of >/=16. The MBST protocol included elements of cognitive-behavioral therapy and mindfulness meditation methods and principles. The SCSM protocol resembled traditional supportive, non-directive counseling but with a focus on topics of particular interest to persons with SLE, such as living with chronic illness, and communication with family and heathcare providers. Both interventions included information on SLE and depression as well as goal setting, and were delivered by trained, experienced psychotherapists. Participants completed study evaluations at baseline, mid-treatment, end of intervention, and 6 and 12 month follow-up. Mental health outcomes (CESD, QIDS) are reported here. Data were analyzed using generalized mixed effects models.

Results: The average age of participants was 49 years (+/- 12), 92% were females, and 23% were African American or other non-white race. Of the 90 persons enrolled, 73 (81%) completed the study. Levels of depressive symptoms in the two groups did not differ at baseline, and were in the range of moderate to severe (MBST CESD=29.7 +/- 6.4, SCSM CESD=30 +/- 6; MBST QIDS=12 +/- 3.4, SCSM QIDS=11.6 +/- 3). Both MBST and SCSM resulted in improvement in self-reported depressive symptoms (CESD) [time effect $F(4,286)=44$, $p<.001$] with a marginally significant group x time effect in favor of SCSM [$F(4,286)=2$, $p=.07$]. Likewise, both groups improved on QIDS [time effect $F(4,284) = 78$, $p<.001$], and there was not a significant group x time effect. At the 12 month follow-up evaluation, CESD scores averaged 21.3 (SD=8) for MBST and 20.2 (SD=6.5) for SCSM, indicating that, despite improvement, participants continued to report some symptoms consistent with depression and/or chronic illness. QIDS scores at 12 month follow up averaged 5.5 (SD=4.6) for MBST and 3.6 (SD=2.6) for SCSM, which is consistent with ‘no’ to ‘mild’ depression.

Conclusion: We found that both MBST and SCSM resulted in improvement in depressive symptoms in persons with SLE. Skills training was not superior to supportive counseling. Clinical diagnostic interviews indicated ‘no depression’ to ‘mild’ levels of depression at follow-up, whereas participants continued to self-report symptoms at follow-up, perhaps due to overlap between SLE and depressive symptoms such as lack of energy and difficulty concentrating. Psychotherapy approaches tailored to SLE may benefit many SLE patients who experience comorbid depression.

Disclosure: C. Greco, None; **L. W. Chen**, None; **Y. Cheng**, None; **C. McFarland**, None; **S. Manzi**, None.

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Abstract Number: 1057

Effect of Quantitative Information Concerning Medication Side-Effects on Risk Perception

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Background/Purpose: The Food and Drug Administration (FDA) requires that patients prescribed a bisphosphonate to treat osteoporosis receive an FDA-approved Medication Guide that warns of the risk of unusual thigh fracture. These Medication Guides state: "Some people have developed unusual fractures in their thigh bone. Symptoms of a fracture may include new or unusual pain in your hip, groin, or thigh". However, no information is given concerning the probability of experiencing an unusual thigh fracture. We hypothesized that providing quantitative information concerning the probability of fracture would: (1) increase willingness to use the medication, (2) increase perceptions of medication safety, and (3) decrease perceptions of the likelihood of experiencing an unusual thigh fracture.

Methods: Participants (N=258) were recruited using Amazon Mechanical Turk. Using an internet-based survey design, each participant was randomly assigned to 1 of 3 groups that viewed a medication fact sheet with general information about a fictional bisphosphonate called, Bonemax. The fact sheet included information about medication benefits and the risk of atypical femoral fractures. For atypical femoral fractures, one format presented only non-numeric risk information, modeled after Medication Guides, while the other 2 formats presented numeric risk information for differing durations of therapy (0-2 years and 2+ years). The risk of atypical femur fracture was reported as 2 in 10,000 in the 0-2 year duration group and 8 in 10,000 in the 2+ year duration group. All 3 formats presented the same benefit information. The primary outcome variables were: 1) Likelihood of taking the medication if recommended by one's physician; 2) Medication safety; and 3) Likelihood of causing an atypical femoral fracture. All responses were recorded on 7-point rating scales and

statistical significance was set at alpha=0.05. Statistical analyses were performed using SAS®9.4.

Results: All three hypotheses were supported. Participants in the non-numeric group reported being less likely to use the medication (Mean=3.15) compared to those in either of the other two groups (Means=4.14 and 3.96 in the 0-2 year and 2+ year duration groups respectively, both p's < 0.01). Participants in the non-numeric group rated the medication as less safe (M=2.79) compared to those in either of the other two groups (Means=3.89 and 3.74 in the 0-2 year and 2+ year duration groups, both p's < 0.001). Participants in the non-numeric group believed that the medication was more likely to cause an atypical femur fracture (Mean=3.20) compared to those in either of the other two groups (Means=1.71 and 1.56, respectively, both p's < 0.001). None of the variables significantly differed between the numeric risk information groups.

Conclusion: Study findings suggest that the addition of numeric risk information to Medication Guides may facilitate patient decision making.

Disclosure: S. J. Blalock, None; **M. Dixon**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/effect-of-quantitative-information-concerning-medication-side-effects-on-risk-perception

Abstract Number: 1058

Adjustment Profiles Comprising Objective and Subjective Measures in Fibromyalgia Patients

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Background/Purpose: Only one-third of FM patients obtain benefits after receiving one of the available therapy modalities. Insights into the heterogeneous picture of FM might improve therapy effectiveness. The present study aimed to examine 1) whether it is possible to differentiate between clinically meaningful profiles (subgroups) and 2) whether these profiles differ in terms of FM severity.

Methods: The al-Ándalus project allowed us to perform a comprehensive cross-sectional approach including assessments of physical, psychological, and cognitive adjustment in a total of 510 FM patients, who met either the 1990 or the modified 2010 ACR FM criteria. Measurements included objective (e.g., neuropsychological tests) and subjective data (i.e., questionnaires). Analyses of these assessments involved a two-step approach of exploratory factor analysis and cluster analysis.

Results: The first (factor analyses) step yielded 8 factors; 3 including objective measures (*declarative memory, performed physical fitness, and active lifestyle*) and 5 including subjective measures (*fatigue, psychological distress, catastrophizing, resilience, and subjective physical fitness*). In cluster analyses, the combination of these 8 factor scores yielded 5 profiles. An *Adapted* profile (*n*=88, 17%) showing low *psychological distress*, *catastrophizing*, and *physical fatigue* as well as high *resilience* and (both *objective* and *subjective*) *physical fitness*. A *Fit* profile (*n*=96, 19%) characterized by an *active lifestyle* and enhanced *objective physical fitness*. A *Positive* profile (*n*=116, 23%) in which *catastrophizing* was low. An *Unfit* profile (*n*=91, 18%) characterized by poor *subjective physical fitness*. A *Maladapted* profile (*n*=119, 23%) characterized by poor *resilience* and (*objective* and *subjective*) *physical fitness* as well as increased levels of *psychological distress*, *catastrophizing*, and *physical fatigue*. One-way analyses of variance showed that the mean score (standard deviation) of FM severity at the Revised FM Impact Questionnaire was 47 (13), 60 (15), 65 (13), 66 (14), and 79 (11) for *Adapted, Fit, Positive, Unfit*, and *Maladapted* profiles, respectively. After Student-Newman-Keuls posthoc tests, significant differences emerged between all the profiles; the only one exception was between *Positive* and *Unfit* groups.

Conclusion: Our study suggested the existence of 5 adjustment profiles that were differentially associated with FM severity. Future research using longitudinal designs should examine whether these profiles are associated with the prognosis of FM and the effectiveness of interventions, which would enhance the development of interventions customized to the adjustment profiles of FM patients. **Funding**: The Spanish Ministry of Economy and Competitiveness (I+D+i DEP2010-15639, I+D+i DEP2013-40908-R, BES-2014-067612, and BES-

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Abstract Number: 1059

Quality of Life in Patients with Antiphospholipid Syndrome Is Related to Disease Burden and Anticoagulant Therapy

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Background/Purpose: Few studies have reported impaired health related quality of life (HRQoL) in patients with primary antiphospholipid syndrome (APS); however the causes of this outcome have been scarcely explored. Our aim was to evaluate HRQoL in patients with primary APS and to correlate it with a crude estimate of accrual organ damage, comorbidity and treatment.

Methods: We registered demographics, criteria and non-criteria APS features, comorbidities (diabetes mellitus, hypertension, dyslipidemia) and use of oral anticoagulation, immunosuppressors and prednisone. We assessed HRQoL with the SF-36 as a generic instrument and in the absence of a specific HRQoL questionnaire for APS, we used the Spanish version LupusQoL. We also evaluated the disease burden with a modified SLICC/ACR SDI including four additional items (livedo racemosa, adrenal infarcts requiring chronic treatment, permanent Greenfield filter replacement and multiple sclerosis-like disease). As controls we used SF-36 data from Mexican general population within the same age range.

Results: We included 50 patients (86% women), mean age 47.6 ± 14.5 years, median disease duration 9.4 years, median SLICC/ACR score of 1 point. Eighty percent had thrombotic events, 28% pregnancy morbidity and 72% non-criteria APS features (non-exclusive groups). APS patients had lower HRQoL than controls (SF-36= 66.1 ± 22.4 vs. 96.3 ± 29.8, p=0.0001). The results of each domain of SF-36 and LupusQoL are shown at Table 1. We found a positive correlation between SF-36 and LupusQoL (r=0.85, p<0.0001). The SLICC/ACR DI correlated negatively with both LupusQol and SF-36, specifically the peripheral vascular domain (r=-0.29, p=0.03, for both instruments). Patients on anticoagulant therapy (n=37) had lower LupusQoL physical functioning, intimate relationships, burden to the others and pain scores than patients without them. They also had a lower SF-36 physical functioning score. We did not find differences in HRQoL regarding comorbidities, prednisone and immunosuppressors use. **Table 1.**

	SF-36		LupusQoL
Total score	66 ± 22.4		69 ± 29.36
Comparable domains			
Physical functioning	71.9 ± 27.5	Physical health	77.6 ± 19.7
Mental health	64.6 ± 19.4	Emotional health	78.1 ± 18.1
Bodily pain	68.8 ± 25.5	Pain	81.3 ± 23.7
Vitality	54.8 ± 21.5	Fatigue	74.1 ± 19.5
Non Comparable domains			
Role physical	71.5 ± 40.7	Planning	82.3 ± 23.8
General health	56.9 ± 22.5	Intimate relationships	77.9 ± 35.5
Social functioning	78.8 ± 22	Burden to others	67.1 ± 30.8
Role emotional	60.6 ± 44.6	Body image	79.1 ± 24.2
Physical component summary score	64.6 ± 22.6	Not applicable	Not applicable
Emotional component summary score	67.6 ± 26	Not applicable	Not applicable

Conclusion: HRQoL in APS is related to burden of the disease specifically at the vascular peripheral area and use of anticoagulation treatment.

Disclosure: G. Hernandez-Molina, None; **I. Gonzalez-Pérez**, None; **C. Pacheco**, None; **A. R. Cabral**, None.

Abstract Number: 1060

Antiphospholipid Antibodies and Related Clinical Events Following Infection in Children: A Systematic Review of Case Reports

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Background/Purpose: A systematic review of case reports to summarize existing evidence in the literature regarding the association of APS and infection during childhood. Our aims were to identify all possible presumed infections that may predispose to elevation of aPL antibodies, and related clinical events.

Methods: Medline, EMBASE, Web of Science, PubMed ePubs, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched with no restriction through June 2016. References cited in the included articles were searched manually. We included case reports describing children who developed elevated aPL antibodies after a prior infection. One positive laboratory test for anticardiolipin, lupus anticoagulant, or anti-β2-GPI antibodies after a previous diagnosis of infection was required for inclusion. We extracted data on the infectious agent identified, pre-existing conditions, aPL antibody profile, clinical manifestations, treatment required, and reported outcome. Patients with systemic lupus were excluded.

Results: A total of 2,740 unique citations were identified through the databases and hand-searched bibliographies. Of these, 72 publications met inclusion criteria, reporting on 87 cases. The age of the cases ranged from 6 months to 18 years; 48 children (55.2%) were female. Cases were classified into four groups according to the clinical presentation reported following infection: 1) patients fulfilling criteria for diagnosis of APS (13.8%) including three cases with catastrophic antiphospholipid syndrome (CAPS), 2) patients with transient

thromboembolic events, not fulfilling APS criteria (31.0%), 3) patients developing hemorrhage rather than thrombosis (31.0%), and 4) patients with elevated aPL antibodies but no clinical manifestations (24.2%). Viral infection was the most frequent preceding infections across all groups (56.3%), followed by bacterial infection (26.0%). Ten different viral and bacterial agents were reported in group 1, with *Escherichia coli*, *Pseudomonas aeruginosa*, and *Parvovirus B19* recognized in the three cases who developed CAPS. *Varicella Zoster* and *Mycoplasma Pneumonia* were mainly identified in group 2, *Adenovirus* in group 3, and both *Adenovirus* and *Parvovirus B19* were equally reported in group 4. Infection was the sole precipitating factor in 85.1% of the reported cases; 8.1% had pre-existing autoimmune diseases such as juvenile idiopathic arthritis, or celiac disease, where *Parvovirus B19* was the predominant infection. Thirty nine (44.8%) cases developed thromboembolic events, predominantly hematologic, followed by skin manifestations, peripheral thrombosis, and stroke. Splenic infarction and other non-typical presentations were also reported. Positive lupus anticoagulant was most frequently reported in (81.7%). Anticoagulation or antiplatelet therapy were required for the majority of cases in groups 1 and 2. While complete recovery was achieved in the majority of cases, 37.5% of patients in group 1 reported persistent APS, and 25.0% died.

Conclusion: Development of aPL antibodies, APS and CAPS can occur in children after an infection. Further studies are needed to determine the risk and long-term outcomes of aPL-related events following infection.

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Identifying Clinical and Epidemiological Risk Factors Associated with Thrombosis and Pregnancy Morbidity in a Large Cohort of Chinese APS Patients

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Background/Purpose: It is well known that anti-phospholipid antibodies (aPL) are associated with an increased risk of arterial and venous thrombosis and pregnancy loss/morbidity. However, assessment of the risk associated with various antibody profiles, risks associated with aPL in the setting of other risk factors, and the evaluation of risk in individual patients are challenging issues. Our study aims to investigate the clinical and epidemiological characteristics of patients in a large APS cohort and to identify potential predictors of thrombosis and pregnancy morbidities.

Methods: This study included 180 consecutive patients who attended the rheumatology clinic at People's Hospital of Beijing University Health Science Center. All patients fulfilled the 2006 revised APS criteria. The criteria aPL profiles [anticardiolipin (aCL), anti-β2glycoprotein-I (anti-β2GPI) and lupus anticoagulant (LA)] were assessed with an in-house assay. Complement (C3/C4) and platelet levels were assessed in a University laboratory. Hypertension (HTN) was classified based on 8th Joint National Committee (JNC-8) guidelines. Hyperlipidemia (HLD) was defined as fasting total cholesterol >200 mg/dl. Diabetes (DM) is defined as Hemoglobin A1c >7. Pearson Chi-squared or Fisher's exact test univariate analysis with two tailed P value was used to evaluate correlation between different cardiovascular and epidemiological risk factors and clinical manifestations.

Results: 180 patients who met 2006 revised APS criteria were analyzed. There were 135 females and 45 males with a mean age of 42.85 (+/- 15.72). 66 (36.7%) patients had primary APS and 114 (63.3%) had secondary APS. Among those patients 141(78%) had thromboembolic events and 60 (33.3%) patients had recurrent thrombosis. 54 (30%) patients had pregnancy related morbidities. 59 (32.8%) patients had HTN and 28 (15.6%) were smokers. 102 (56.7%) patients exhibit hypocomplementemia and 81 (45%) exhibit thrombocytopenia. 24 (13.3%) had Raynaud's phenomenon. Age >50 (OR=9.548, 95%CI 2.206- 41.3, P<0.00002), HTN (OR=4.221, 95%CI 1.6 – 11.4, P<0.003), and smoking (OR=19.84, 95%CI 1.182 – 332.8, P<0.0038) were significantly associated with thromboembolic events (Fig 1). HLD, DM, hypocomplementemia, and thrombocytopenia did not demonstrate significant correlation with thrombosis. Only double positive antiphospholipid antibodies (defined as patients have at least two positive criteria aPLs) were significantly associated with pregnancy morbidity. None of the other analyzed clinical characteristics showed significant correlation with obstetric manifestations.

Conclusion: A high frequency of thrombocytopenia and hypocomplementemia were observed in APS patients. Age >50, HTN, and smoking are predictors of thromboembolic events while double positive aPLs is a predictor for pregnancy morbidities in Chinese APS patients.

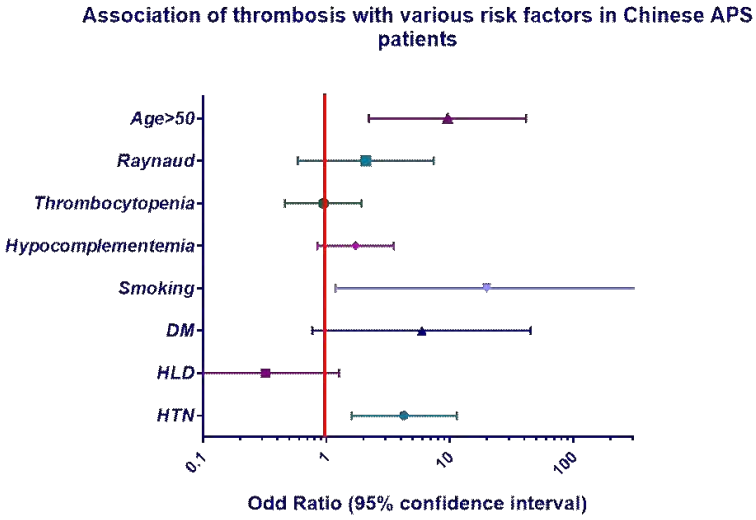

Fig 1:

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Abstract Number: 1062

Non-Conventional Antiphospholipid Antibodies in Patients with Clinical Obstetrical APS: Prevalence and Pregnancies Treatment Efficacy

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Background/Purpose: To describe the prevalence of non-conventional APL in patients with obstetrical APS pregnancy adverse outcome without conventional APL and the impact of treatment on pregnancy outcome.

Methods: The inclusion criteria were: (1) ≥3 early miscarriages less than 10 weeks of gestation; (2) intrauterine fetal death ≥10 weeks of gestation; (3) preeclampsia, prematurity <34 weeks of gestation related to placental insufficiency; (4) absence of inherited thrombophilia (V Leiden and II homozygous mutations, proteins C, S, ATIII deficiencies) and of conventional APL (LA, ACL IgG/M, anti- β_2GPI IgG/M). 96 patients with clinical obstetrical APS criteria were tested for anti-phosphatidylethanolamine (aPE) IgG/M, anti-prothrombin/phosphatidylserine (anti-PS/PT) IgG/M and anti-annexin V IgG. Pregnancies losses rates were compared between APS, non-conventional APS and non-APL and in untreated pregnancies to treated ones for each group. A control group of 47 healthy pregnant patients without any pregnancy complication have been selected from Bichat Hospital, without any age difference with clinical APS and without conventional APL (31±6 versus 33±4 years; p>0.05). A control group of patients with confirmed APS (Sydney criteria) (n=83) was also

selected.

Results: Using the cut-offs (ROC), 65/96 (68%) patients have been considered as non-conventional APS and compared to 83 APS and 31 patients without APL. Among these 65 non-conventional APS, recurrent miscarriage was noted in 44 (46%) cases, intrauterine fetal deaths in 38 (40%) cases, premature term<34 weeks of gestation in 25 (27%) cases, preeclampsia and/or HELLP syndrome in 25 (26%) cases and thrombosis in 14 (15%) cases. The obstetrical history in non-conventional APS did not differ in comparison to confirmed APS. The frequencies of anti-annexin V IgG antibodies tended to be more frequent in non-conventional APS (88% versus 73%; p=0.06), and those of anti-PE IgG and M were similar. The anti-PS/PT IgG and M antibodies were more frequent in confirmed APS than in non-conventional APS (63% and 37% versus 4% and 5%, p<0.0001). Overall 261 pregnancies in patients with non-conventional APS were compared to 81 pregnancies of confirmed APS and 132 pregnancies from non-APL group. 136/474 (29%) patients have been treated during pregnancies and treatment significantly increased the rate of live birth (26% in untreated versus 72% in treated pregnancies, p<0.0001). In univariate analyses, treatment effect on pregnancies losses was similar in patients with APS and non-conventional APS, with odds ratio at 3.3 [95% CI; 1.8 to 6.1] and 6.9 [95% CI; 3.9 to 12.3] (p=0.49) and significantly more important for the 2 APS groups pooled versus non-APL group (OR at 1.9 [95% CI; 1.1 to 3.5] for non-APL group versus 5.3 [95% CI; 3.5 to 8.1] for APS groups, p=0.0025).

Conclusion: In this study 68% of patients with clinical criteria for obstetrical APS seronegative for conventional APL have non-conventional APL. These patients have a significant decrement of pregnancy losses if they receive treatment for APS during their pregnancy.

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Abstract Number: 1063

A Systematic Review of Direct Oral Anticoagulant Use in Antiphospholipid Syndrome

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Background/Purpose: Oral direct oral anticoagulants (DOACs) are approved for the treatment of venous thrombosis and the prevention of venous/arterial thrombosis. There is growing information from case reports and series where DOACs have been used in antiphospholipid syndrome (APS) patients with controversial results. Thus, our objective was to systematically review the literature for DOAC use in APS.

Methods: We reviewed the literature (Pubmed, Cochrane Library, congress abstracts books, and the reference lists of studies) without language restrictions. Medical subject heading terms were: “antiphospholipid syndrome”, “direct oral anticoagulants”, “oral direct inhibitors of thrombin”, “oral direct inhibitors of factor Xa”, “rivaroxaban”, “dabigatran”, “apixaban”, and “edoxaban”. In a systematic fashion, we recorded the type of the study, DOACs used, indication for DOAC use, follow-up time, and outcomes.

Results: As of April 2016, we identified seven case reports and four case series, which included 99 APS patients (primary APS: 38; APS associated with lupus: 23; and unspecified: 38) treated with DOACs (rivaroxaban: 84; dabigatran: 14; and apixaban: 1) (Table). Direct oral anticoagulants were used due to: international normalized ratio (INR) lability in 69 patients; recurrent thrombosis on warfarin in 12; first line therapy in 12; and life-threatening bleeding on warfarin in 5. The follow up time varied between 1- 39 months (mean ± SD: 12.9 ± 8.6 months) (not specified in two studies). Recurrent vascular events (including two superficial venous thrombosis and one transient ischemic attack) were reported in 17 (17%) patients; and minor bleeding in 4 (4%) patients. The frequency of recurrence was not different between the patients who used rivaroxaban (18%) or dabigatran (14%) (p: 0.85), or between the patients with (30%) or without (16%) a previous history of recurrence (p: 0.43).

Conclusion: Based on our systematic literature review of DOAC-receiving APS patients, approximately 20% of patients develop thrombosis during a mean follow-up of 12 months. Given the publication bias and also the low evidence level study designs, e.g., case reports and series, it is difficult to have strong clinical recommendations based on the current literature. Ongoing randomized controlled

clinical trials evaluating DOACs in APS will determine if these agents can be incorporated into the management of APS patients. **Table:** Direct Oral Anticoagulated (DOAC)-treated APS Patients

Reference (1st Author/Year)	N (PAPS/SAPS)	DOAC (Dose)	Mean F/U time (range)	Recurrence
Schaefer K, 2014	3 (2/1)	Rivaroxaban (20mg QD): 2 Dabigatran (150mg QD): 1	5.7±0.6m (5-6m)	100% (2 AT, 1 DVT)
Win K, 2014	3 (NR/NR)	Rivaroxaban (20mg QD):2 Dabigatran (150mg BID):1	9±4.2m (6-12m)	100% (2 SVT, 1 AT)
Bachmeyer C, 2014	1 (1/0)	Rivaroxaban (20mg QD)	NR	No
Son M, 2015	12 (8/4)	Rivaroxaban (20mg QD)	11.4±4.4m (2-16m)	16.7% (2 DVT)
Sugie M, 2015	1 (1/0)	Rivaroxaban (15mg QD)	7m	No
Delgado MG, 2015	1 (1/0)	Rivaroxaban (NR)	3m	100% (AT)
Reshetnyak, 2015	1 (1/0)	Dabigatran (NR)	NR	No
Sciascia S, 2015	35 (NR/NR)	Rivaroxaban (20mg QD)	10 m* (6-24m)	No
Betancur JB, 2016	8 (4/4)	Rivaroxaban (20mg QD): 7 Apixaban (5mg QD): 1	19±10.7m (2-36m)	No
Noel N, 2016	26 (12/14)	Rivaroxaban (15-30mg QD): 15 Dabigatran (150mg BID): 11	19.2±11.7m (1-39m)	3.8% (AT)
Signorelli F, 2016	8 (8/0)	Rivaroxaban (20mg QD)	5-365 days**	88% (4 AT, 2VT, 1 TIA)

PAPS: primary antiphospholipid syndrome; **SAPS**: APS associated with other autoimmune diseases; **NR**: no report; **AT**: arterial thrombosis; **VT**: vein thrombosis; **SVT**: superficial vein thrombosis; **TIA:** transient ischemic attack; **m**: months; f/u: follow-up; QD: daily; BID: twice a day; * median; **: only time to recurrence was reported (median: 90days;

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Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking Registry Analysis: Direct Oral Anticoagulant Use Among Antiphospholipid Syndrome Patients

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Background/Purpose: Direct oral anticoagulants (DOACs) are approved for the treatment of venous, and prevention of venous/arterial thrombosis. There have been case reports/ series where DOACs have been used in antiphospholipid syndrome (APS) with controversial results. Our objective was to describe the clinical characteristics of and thrombosis risk in APS patients treated with DOACs.

Methods: A web-based data capture system stores patientsÕ clinical and laboratory characteristics in the context of the Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) Clinical Database and Repository (ÔRegistryÕ), which has been created to study the natural course of persistently aPL-positive patients with/without autoimmune diseases (AIDx) over 10 years. The inclusion criteria are aPL positivity according to the Updated Sapporo Classification Criteria. For this descriptive study, we analyzed the demographics, clinical characteristics, and outcomes of aPL-positive patients who have been treated with DOACs.

Results: As of 4/2016, 627 aPL-positive patients were recruited (aPL/APS without any other AIDx: 410 [thrombotic APS with/without obstetric APS: 286]; and aPL/APS associated with another AIDx: 217 [thrombotic APS with/without obstetric APS: 142]). Of 428 thrombotic APS patients, 19 (4.4%) were current or past DOAC users (rivaroxaban: 17; dabigatran: 2).Of 19 patients, 17 (90%) had history of thrombosis; however only seven [37%] had single venous thrombosis. The indications for DOAC use were: INR lability (n:3); recurrent thrombosis or adverse events on warfarin (n: 4); first line therapy for thrombosis treatment (n:2) and prevention (n:2); clinical trial (n:5); and patientsÕ request (n: 3). The follow up time on DOACs was 1- 84m (mean ± SD: 23.3 ± 22.3m). Recurrent vascular events were reported in six patients (32%) (including 1 microthrombosis; 4 retrospective; and 2 prospective) (Table). One of two patients with prospective follow-up had cardiovascular disease risk factors at the time of the event. The annual incident thrombosis risk was 16.2% (for comparison, the risk was 2.1% for warfarin-users).

Conclusion: Based on a descriptive analysis of a large-scale international aPL/APS registry, less than five percent of patients receive a DOAC, mostly rivaroxaban. One-third of these patients developed recurrent events during the two-year follow-up; however, in approximately 60% of these patients the DOAC use was not as per licensed indications aside from the APS diagnosis. Although the small number of patients and the retrospective/prospective nature of the data collection might have resulted in a relatively high recurrence rate, DOAC use in APS should be guided by the results of appropriate randomized clinical trials. Currently no recommendations can be made against or for the use of DOACs in APS.

Table : Clinical Data on DOAC-treated APS Patients

#	Age*/Sex/Race	Thrombosis History	aPL Profile	Warfarin History**	DOAC Indication	DOAC Duration	Outcome
1	48/M/W	AT, VT#	aCL+ aB2GPI	No	DVT	R x 17m	Stroke
2	31/F/AA	VT, MT#	LA	Yes (84m)	DVT+PE	R x 34m	Stroke
3	24/M/W	VT	Triple aPL	Yes (33m)	PP	R X 22m	DVT - ? MI
4	54/F/W	VT	Triple aPL	Yes (6m)	TIA	D x 1m	TIA
5	27/F/NR	VT#	LA+aCL	Yes (77m)	PP	R X 3m	Microthrombotic skin ulcer
6	58/M/W	AT, VT#	aCL+ aB2GPI	Yes*** (34m)	ICT	D X 21m	Stroke/Ischemic Optic Neuritis

*At the time of the recurrent event

**Prior to DOAC - Duration of warfarin use is in parentheses

***Acenocoumarol

History of recurrent thromboses

AT: Arterial Thrombosis; **AA:** African American; **D:** Dabigatran; **DOAC:** Direct Oral Anticoagulant; **DVT:** Deep Vein Thrombosis; **F:** Female; **ICT:** Intracardiac Thrombus; **m:** month; **M:** Male; **MI:** Myocardial Infarction; **MT:** Microthrombosis; **NR:** Not Allowed to Record; **PE:** Pulmonary Embolism; **PP:** Patient Preference; **R:** Rivaroxaban; **TIA:** Transient Ischemic Attack; **VT:** Venous Thrombus; **W:** White

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Abstract Number: 1065

A Practical Application of Antiphospholipid Antibodies Profiles in the Diagnosis and Managements of Antiphospholipid Syndrome: The Modified Antiphospholipid Score

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Background/Purpose: The clinical scoring systems to quantify the probability for the diagnosis of antiphospholipid syndrome (APS) or future thrombosis, have been proposed as to reflect the diverseness of antiphospholipid antibodies (aPL) profiles into the clinical judgments: They are the Antiphospholipid Score (APLS) and the Global Antiphoshpholipid Syndrome Score (GAPSS). However, the clinical applications of these scores have been obstructed mainly of its burdensome procedure of performing more than 10 aPL tests routinely. The aim of this study is to confirm the function of modified APLS (mAPLS) with reduced number of needed aPL tests.

Methods: This study comprised 261 consecutive patients with autoimmune diseases including APS who visited Hokkaido University Hospital Rheumatology Clinic between 2002 and 2003 and has been followed more than five years afterwards. Five lupus anticoagulant assays (three mixing studies and two confirmatory tests) and six ELISAs (IgG/M of anticardiolipin antibodies, anti-b2-glycoprotein I antibodies and phosphatidylserine dependent antiprothrombin antibodies) were performed in all subjects. All of the aPL were calculated of their hazard ratio for developing thrombosis on definition of the APLS. Using those original data, mAPLS was constituted of the aPL tests that had high odds ratio over 5.0 for thrombotic events. The functions of mAPLS were compared with those of APLS and GAPSS. To evaluate the diagnostic powers, area under the curve (AUC) of receiver operating characteristic (ROC) curves were calculated. Cox proportional hazard regression analyses were performed separately to evaluate the powers of thrombosis prediction. To evaluate and compare the predictive powers of the two scores, Somer's d coefficient was calculated.

Results: The diagnostic values of the three scores were similar(AUC of the ROC curve: APLS vs mAPLS vs GAPSS : 0.853 vs 0.810 vs 0.831). The Cox multivariate proportional hazard regression analyses revealed that three scores have functions of predicting future thrombotic events. However, Somer's d coefficient revealed that the APLS and mAPLS have similar power of predicting thrombosis while GAPSS showed lower predictive value(0.50 vs 0.48 vs 0.40, $p<0.01$). Moreover, when these scores were evaluated in patients with SLE, exactness of accuracy for diagnosis fell rapidly in every scores (APLS(0.91 for non-SLE, 0.80 for SLE), mAPLS(0.90 for non-SLE, 0.85 for SLE), GAPSS(0.85 for non-SLE, 0.80 for SLE)) and predictive value of future thrombosis was only confirmed by mAPLS; these phenomenon possibly reflecting the pseudo-positive aPL occasionally found in SLE patients.

Conclusion: Modified APLS with its high performances on APS diagnosis and thrombosis prediction, along with its simplified calculation, may be an available option in general practice.

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Abstract Number: 1066

History of Lupus Nephritis Is an Independent Risk Factor for Thrombosis in Systemic Lupus Erythematosus Patients with Antiphospholipid Antibodies

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Background/Purpose:

Few studies have analyzed the risk factors for thrombosis in Systemic Lupus Erythematosus (SLE) patients with antiphospholipid

antibodies (aPL) and most had small sample sizes and homogenous patient populations. We examined whether a history of nephritis is an additional risk factor for thrombosis on a large multi-ethnic SLE cohort database.

Methods:

The NYU SLE SAMPLE biorepository and registry was initiated in September 2013 and includes 612 patients fulfilling ACR and/or SLICC criteria for SLE. Within SAMPLE, we identified patients with a positive aPL test (lupus anticoagulant, IgG or IgM anti-β_2-glycoprotein-I antibodies and/or IgG or IgM anticardiolipin antibodies) and determined if these patients had also ever fulfilled nephritis criteria. We reviewed each patient's medical record for presence/absence of venous and arterial thrombosis, and obstetric events as well as the non-criteria manifestations such as thrombocytopenia or valvulitis. We compared the prevalence of antiphospholipid syndrome (APS) manifestations in SLE patients with and without a history of lupus nephritis.

Results:

Of the initial 612 SLE patients (90% female; mean age 43.0±0.9 years), 54% were Caucasian, 31% African American, 15% Asian; 30% Hispanic white, and 5% Hispanic Black. Of the 612 patients, 105 had aPL, including 93 females and 12 males (mean age 43.0±0.2 years), 56% Caucasian, 33% African American, 11% Asian, 24% Hispanic white and 4% Hispanic Black. The total number of patients with thrombotic events was 45/105 (43%), including 26/43 (60%) in the nephritis subset and 19/62 (30%) (p=0.04) among patients without prior renal involvement. The most common thrombotic event was deep vein thrombosis (DVT) followed by stroke.

Conclusion:

The prevalence of APS criteria in the NYU SLE SAMPLE was 17%. Within this group, adverse events were more common among the patients with, versus without, a prior history of renal involvement (60% vs 30%). It remains uncertain if this association can be explained by, for example, by the presence of other accompanying findings that distinguish nephritis from non-nephritis SLE (e.g. anti-dsDNA, complement consumption) or drug treatment. This observation provides further support for the universal use of hydroxychloroquine in SLE, especially in those with current or previous nephritis and suggests that event-free aPL positive patients with a prior history of nephritis may be at increased risk for future thrombosis. Further studies are needed to determine whether such patients could benefit from prophylaxis with low-dose aspirin, statins or even other mild anti-thrombotic agents.

Disclosure: V. Domingues, None; **J. Nwaukoni**, None; **J. P. Buyon**, exagen, 2; **H. M. Belmont**, None.

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Abstract Number: 1067

History of Thrombocytopenia Is Associated with Lower Prevalence of Thrombotic Events in Systemic Lupus Erythematosus Patients with Antiphospholipid Antibodies

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Background/Purpose: Thrombocytopenia is a common feature of both systemic lupus erythematosus (SLE) and antiphospholipid syndrome (APS) and in the former most frequently results from antiplatelet antibodies (i.e., AITP) or aPL antibodies. Patients with AITP paradoxically have an increased risk of thrombosis and it has been speculated that this can result from co-presence of aPL. Primary APS is associated with both thrombosis and thrombocytopenia. We assessed whether there was an association between a history of thrombocytopenia and the prevalence of a thrombotic event in a large, multiethnic cohort of SLE patients.

Methods: We analyzed the NYU SLE SAMPLE registry, consisting of patients fulfilling ACR and/or SLICC criteria for SLE. We identified 105 patients whose SLE criteria included the presence of one or more of the following aPL antibodies: lupus anticoagulant, IgG or IgM anti-β_2-glycoprotein-I, and/or IgG or IgM anticardiolipin antibodies; and determined whether these patients had thrombocytopenia

(<100,000/μL) recorded among their SLE classification criteria. We reviewed each patient's medical record to identify the prevalence of arterial or venous thrombosis (defined as DVT, PE, stroke, arterial occlusion with gangrene or amputation), and/or obstetric events. We compared the prevalence of thrombotic events in SLE patients with and without history of thrombocytopenia.

Results:

The NYU SLE SAMPLE currently includes 612 patients (90% female, mean age 43.0±0.9 years, and mean age of 41.0±0.3 years in the males); 54% of the subjects were Caucasian, 31% African American, 15% Asian, 30% Hispanic White, and 5% Hispanic Black: 17% had aPL antibodies, of whom 89% were female and 11% male (mean age 43.0±0.2 years, 56% Caucasian, 33% African American, and 11% Asian, 24% Hispanic white and 4% Hispanic Black). The total numbers of patients with thrombotic events were 45 (43%), with 5/21 (23%) in the SLE patients with aPL and prior history of thrombocytopenia and 40/84 (47%; p=0.042) in the patients without thrombocytopenia. The most common thrombotic event was DVT followed by stroke.

Conclusion:

The prevalence of aPL in the NYU SLE registry was 17%, and adverse thrombotic events were less common in the patients with prior history of thrombocytopenia (5/21, 23%) as compared to those without (40/84, 47%). This unexpected finding could be explained by protective benefit of anti-platelet antibodies when co-occur with aPL in SLE, or less thrombogenic aPL in SLE when there is concomitant thrombocytopenia. Additionally, our data suggest that there might be different consequences of aPL between primary APS patients and SLE patients with aPL.

Disclosure: V. Domingues, None; **J. Nwaukoni**, None; **J. P. Buyon**, exagen, 2; **H. M. Belmont**, None.

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Abstract Number: 1068

Recurrence of Thrombosis Despite Negativization of Antiphospholipid Antibodies in Primary Antiphospholipid Syndrome. a Follow-up to 5 Years

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Background/Purpose: In some antiphospholipid syndrome (APS) patients, the antiphospholipid antibodies (aPL) becomes persistently negative. Discontinuation of anticoagulation has been proposed, however the long term follow-up after negativization is uncertain**.**The purpose of this study is to evaluate the clinical outcome after aPL negativization in primary APS patients.

Methods: From a cohort of 70 patients diagnosed with primary APS, we selected patients with positive aPL determinations at onset and ≥2 subsequent negative aPL determinations during the last 5 years. In order to corroborate the immunologic profile, a cross-sectional analysis was made. We determined IgG/IgM aCL antibodies, IgG/IgM antiβ2GPI, anti-annexin A5 antibodies (Enzyme Linked Immunosorbent Assay,ELISA) and lupus anticoagulant (LA) (Russell viper venom). All patients continued treatment with oral anticoagulants. We reviewed clinical charts to obtain clinical data and aPL determinations at onset and after negativization. Statistical analysis: descriptive statistics and Kaplan-Meier analysis.

Results: We found 24 patients with persistently negative aPL, including the last immunologic profile, 17 females, 7 males, mean age 51.7, disease evolution 16.3 years, mean of 4 aPL previous positive determinations. aCL was found positive at onset in 87.5% and 21% had double aPL positivity at onset (aCL/LA). Deep venous thrombosis (DVT) was the most frequent manifestation at onset in 33%,ischemic stroke in 29% and pulmonary embolism in 12%. INR range: 2-3.The most frequent concomitant cardiovascular risk factors

were dyslipidemia (29%), overweight (20.8%) obesity (16.7%). Mean time with aPL positive 109.4± 80.7 months. The median of thrombotic events was 2 (range 2-19). After 60 months of follow-up since negativization of aPL, Kaplan-Meier analysis: 40% of patients presented thrombosis recurrence, of these, DVT was observed in 29.2%, and ischemic stroke in 4,2%, despite optimal anticoagulant treatment. Other non-thrombotic APS manifestations were chronic ulcers in lower extremities in16.7%, and severe thrombocytopenia in 8%

Conclusion: This study suggest, that in primary APS, persistent negativization of aPL, is not an indication to interrupt oral anticoagulant therapy. Additional risk factors and other aPL can contribute to the recurrence of thrombosis.

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Abstract Number: 1069

The Predictive Value of Acl and Anti-β2GPI in Patients with Acute Deep Vein Thrombosis

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Background/Purpose: Acute deep vein thrombosis (DVT) is generally treated with anticoagulants for 3 to 6 months. Antiphospholipid syndrome (APS) is an important cause of DVT. However, APS can be diagnosed only 24 weeks after DVT according to the current APS classification criteria.[1] Thus, undiagnosed APS patients, who cease anticoagulant therapy after 3 months, might be exposed to a greater risk for recurrent thromboembolic event. Studies evaluating the significance of positive antiphospholipid antibody (aPL) test immediately after acute DVT are lacking. Our aim was to evaluate whether positive aPL test at the time of acute DVT diagnosis is predictive of APS.

Methods: Patients with acute DVT, confirmed by compression ultrasound, were included into a 24-month prospective study. All patients were given anticoagulants according to the current DVT treatment guidelines. Anticardiolipin antibodies (aCL) and *anti-beta2-glycoprotein* I antibodies (anti- β2GPI) were determined first at inclusion and then every 4 weeks for the first 24 weeks. The last aPL measurement was performed 24 months after inclusion into the study. APS was confirmed if a patient tested positive (medium or high positive aCL and/or presence of anti-β2GPI) 12 and 24 weeks after DVT. Lupus anticoagulants (LA) were tested 4 weeks after anticoagulation therapy had been stopped. aCL IgG/IgM and anti-β2GPI IgG/IgM/IgA antibodies were determined by our in-house ELISA.[2]

Results: 157 patients (91 male, 66 female, age 52.6 ±15.8) who were included in the study had aPL titer assessed at least 5 times. 20 patients ultimately fulfilled APS classification criteria. Among these, 15/20 (75%) patients had medium or high titer aPL, 4 of whom had multiple positive aPL, already at the time of acute DVT, 2/20 (10%) had low positive aCL IgG and 1/20 (5%) had low titer aCL IgM. 2/20 (10%) were negative for aPL, but had later fulfilled APS criteria due to positive LA. APS was not established in 137/157 (87.3%) patients. Among these, 114/137 (83.2%) patients were negative for aPL at inclusion, while 2/137 (1.5%) had low titer aCL IgM and 21/137 (15.3%) had low titer aCL IgG. Altogether, diagnostically important aCL IgG/IgM and/or anti- β2GPI titer at the time of acute DVT had 93.7% specificity and 75% sensitivity for APS. Isolated low titer aCL IgG were not more frequent in patients with APS than in patients without APS (P=0.059, χ^2). Completely negative aCL IgG/IgM aCL and anti-β2GPI at the time of acute DVT had a negative predictive value of 98.3%.

Conclusion: Here we show that in patients with acute DVT positive medium or high titer aCL IgG/IgM or anti-β2GPI is suggestive of APS. These patients should therefore continue with anticoagulant therapy beyond the initial 3 to 6 months required for DVT. Our results also indicate that patients with negative aPL at the time of acute DVT do not need further aPL testing; however, LA should be determined. Low

aPL titer at the time of acute DVT deems further testing imperative. References: 1. Miyakis S et al.Thromb Haemost 2006; 4: 295–306.2. 2. Cucnik S, et al. Clin Chem Lab Med 2000; 38: 777-783.

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Abstract Number: 1070

Performance and External Validation of the Damage Index in Antiphospholipid Syndrome in Primary and Secondary APS Patients

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Background/Purpose: In APS, irreversible organ damage may result of disease activity, medications, or comorbid illnesses. To assess it, different methods have been used including the SLICC index which tends to underestimate APS-related damage (Arthritis Rheum. 2011;3:Abstract). Recently, a new instrument to evaluate organ damage in APS, the Damage Index in Antiphospholipid Syndrome(DIAPS), was constructed and internally validated by adding items specific of APS that are not included in the SLICC (Lupus.2015;9:927).

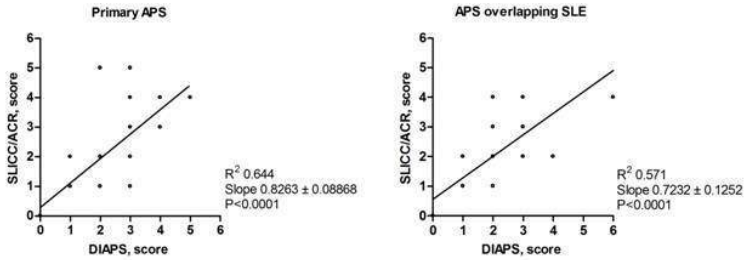
Our aim was to externally validate the DIAPS in a large cohort of primary APS patients and compare its performance against the SLICC index.

Methods: A total of 77 patients with an established APS diagnosis (either primary or secondary to SLE) were recruited in our Rheumatology clinic from March to June 2016. Main demographic, clinical and laboratory data were collected and both DIAPS and SLICC indexes were simultaneously scored. In addition, anxiety (GAD-7) and depression (PHQ-9) scales were measured as surrogate of quality of life. Data were expressed as frequencies and medians (interquartile range) or means (± standard deviation) as corresponded. Differences were assessed by either Fisher's exact or Mann-Whitney tests, while linear regressions were performed to assess linearity between DIAPS and SLICC scores. The GraphPad Prism 4.02 software was used for calculations.

Results: Out of the 77 patients included, 50 had primary APS and 27 had SLE-associated APS. Basal characteristics were similar in both groups, except for an older age (46.8±12.4 years *vs* 39.1±9.7 years; p=0.007) and a longer disease duration (9.6±6.4 years *vs* 6.0±4.8 years, p=0.01) in primary APS. Similar median DIAPS scores were found in primary APS patients as compared to secondary APS patients (2, 1 to 2.75 *vs* 2, 1 to 3; p=0.3); similar results were observed for the SLICC index (2, 1 to 2 *vs* 2, 1 to 3; p=0.3). No differences were observed for the GAD-7 (5, 2 to 6 *vs* 4, 1 to 5; p=0.4) and PHQ-9 (4.5, 2 to 6.25 VS 5, 2 to 6; P=0.9) indexes. No correlation was observed between the DIAPS index and either GAD-7 or PHQ-9 scores.

Finally, a linear association (see the Figure) between the DIAPS and the SLICC indexes was found both in primary APS patients (r^2=0.64; p=0.0001) and in patients with SLE-associated APS (r^2=0.57;p=0.0001).

Conclusion: Our cross-sectional study externally validates the DIAPS index as a useful instrument to evaluate cumulative organ damage in primary APS. However, it also suggests that the advantage of this current version of DIAPS over the SLICC index to assess organ damage in APS patients is marginal at best.



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Abstract Number: 1071

Anti-β2GP-I-Domain 3 and Aps/PT-IgG Antibodies Identify Primary APS Patients with Both Thrombotic and Hematological Manifestations

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Background/Purpose: Thrombocytopenia and hemolytic anemia (HA) are considered non-criteria clinical manifestations by the Sydney revised criteria for APS. These features can precede, follow a thrombotic event or remain as such. We aimed to evaluate the serological phenotype of patients with both conditions

Methods: We included 77 consecutive patients with primary APS according the Sydney classification criteria and/or patients with hematological features (thrombocytopenia and HA). Patients from both groups fulfilled the Sydney laboratory criteria for APS. We registered demographics, disease duration and type of manifestation. aCL (IgG and IgM), antibodies to purified human anti-β2GP-I (IgG and IgM) and IgG and IgM anti-phosphatidylserine/prothrombin (aPS/PT) antibodies were assessed by ELISA. Lupus anticoagulant (LA) was determined by LA/1 screening reactant and a confirmatory test LA/2 according to published guidelines. The reactivity of IgG antibodies to domains 1-5 of β2GP-1 genetically engineered in our laboratory were determined by immunoblotting.

Results: Most patients were females (75.3%), mean age 45.3 ± 15 and mean disease duration 9.6 ± 6.5.The most prevalent antibody was aCL-IgM (87%) followed by anti-β2GP-l IgG (81.8%), anti-β2GP-I IgM (80%), aCL-IgG (79.2%) and LA (70%); 33% of patients were triple-positive. The prevalence of aPS/PT antibodies was 61.3% (both isotypes). Of the 62 IgG anti-β2GP-I-positive patients 31 (50%) had only thrombotic features, 14 (22.5%) hematological manifestations and 17 (27.4%) had both. They were not different in gender, age, disease duration, nor in the prevalence of aCL (both isotypes), LA, anti-β2GP-I IgM, aPS/PT–IgM or anti-D 1, 2, 4 and 5. In contrast, we found a significant difference in the prevalence of aPS/PT-IgG (70% thrombotic vs. 35.7% hematological and 87.5% both, p=0.01) and anti-domain 3 antibodies (64.5% thrombotic vs. 78.6% hematological and 33.3%, p=0.01). The logistic regression analysis of patients with both manifestations (n=17) vs. those with only one (n=45) showed that anti-D3 (OR 0.16 95% CI 0.35-0.76, p=0.02) and aPS/PT-IgG antibody (OR 11.7 95% CI 1.02-133.6, p=0.04) remained associated.

Conclusion: We identified a serological phenotype that discriminates APS patients with both thrombotic and hematological features. This finding further supports our contention that thrombocytopenia and hemolytic anemia are part of the APS. Future studies in other cohorts are

needed to validate this finding.

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Abstract Number: 1072

Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking Registry Analysis: Cardiovascular Risk Factors Among Different Groups of Antiphospholipid Antibody-Positive Patients

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Traditional cardiovascular disease (CVD) risk factors increase the risk of thrombotic clinical manifestations in antiphospholipid antibody (aPL)-positive patients. The prevalence of CVD risk factors has not previously examined in a large cohort of aPL-positive patients. Our objective was to examine the prevalence of CVD risk factors among aPL-positive patients with or without lupus.

Methods: A secure web-based data capture system is used to store patientsÕ clinical and laboratory characteristics in the context of the APS ACTION International Clinical Database and Repository (ÒRegistryÓ), created to study the natural course of persistently aPL-positive patients (according to the Updated Sapporo Classification Criteria) with or without autoimmune disorders over 10 years. Patients with systemic lupus erythematosus (SLE) fulfilled the American College of Rheumatology SLE Classification Criteria. Based on the enrolment data, CVD risk factors included in the analysis were hypertension, diabetes, and hyperlipidemia requiring medications, smoking (ever/current), estrogen use, obesity (BMI>30), family history, and sedentary lifestyle.

Results: As of April 2016, 627 persistently aPL-positive patients were recruited from 24 centers. Fifty-two patients were excluded due to the diagnosis of other systemic autoimmune diseases and 4 patients due to missing data. Of the remaining 571, 124 (21.7%) were asymptomatic carriers. The prevalence of CVD risk factors was not different between aPL-positive patients with or without SLE, except current smoking (15.9% vs 9.2%, p: 0.01) and hypertension (35.5% vs 27.3%, p: 0.05) that were more frequent in SLE patients. In a subgroup analysis of aPL-positive patients with thrombosis, hypertension (44.7% vs 31.5%, p: 0.01), and obesity (26.8% vs 36.8 %, p: 0.05) were significantly higher in those with SLE compared to those without SLE. Among all patients, thrombotic APS patients had significantly higher frequencies of hypertension, hyperlipidemia, obesity, and sedentary lifestyle compared to those with only obstetric APS and asymptomatic aPL carriers (Table).

Conclusion: The prevalence of CVD risk factors was similar between aPL-positive patients with or without SLE except current hypertension and smoking, supporting the need for awareness for these risk factors in both SLE and non SLE patients. Cardiovascular disease risk factors were more frequent among patients with thrombotic APS than those with only obstetric APS or asymptomatic aPL carriers. This suggests that the physicians should also be vigilant about the CVD risk factors and manage them well in order to decrease the risk of thrombosis in aPL-positive patients.

Table: Cardiovascular Risk Factors in aPL- positive patients with or without SLE, and among the groups of Thrombotic APS, Obstetric APS, and Asymptomatic aPL-positive carriers

Variables	aPL (with/without APS) without SLE (n=402)	aPL (with/without APS) with SLE (n=169)	p	Thrombotic APS (n=393)	Obstetric APS only (n=54)	Asymptomatic aPL carriers (n=124)	p
Hypertension	110 (27.3%)	60 (35.5%)	0.05	139 (35.3%)	9 (16.6%)	22 (17.7%)	< 0.001
Diabetes	20 (4.9%)	7 (4.1%)	0.66	22 (5.5%)	1 (1.8%)	4 (3.2%)	0.32
Hyperlipidemia	95 (23.6%)	34 (20.1%)	0.35	108 (27.4%)	3 (5.5%)	18 (14.5%)	< 0.001
Smoking ever	148 (36.8%)	73 (43.1%)	0.15	155 (39.4%)	13 (24%)	53 (42.7%)	0.054
Smoking current	37 (9.2%)	27 (15.9%)	0.01	40 (10.1%)	6 (11.1%)	18 (14.5%)	0.41
Estrogen use	3 (0.7%)	2 (1.1%)	0.6	3 (0.7%)	1 (1.8%)	1 (0.8%)	0.72
Obesity	101 (25.1%)	54 (31.9%)	0.09	117(29.7%)	8 (14.8%)	30 (24.1%)	0.048
Family history	62 (15.4%)	17 (10%)	0.09	58 (14.7%)	9 (16.6%)	12 (9.6%)	0.29
Sedentary lifestyle	188 (46.7%)	79 (46.7%)	0.99	202 (51.3%)	20 (37%)	45 (36.2%)	0.004

Disclosure: O. Unlu, None; **D. Erkan**, None; **M. Tektonidou**, None; **O. B. O. A. A. .**, None.

Abstract Number: 1073

Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking (APS ACTION) Clinical Database and Repository Analysis: The Comparison of Real World and Core Laboratory Antiphospholipid Antibody ELISA Results

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Background/Purpose: The APS ACTION International Clinical Database and Repository ("Registry") was created to study the natural course of disease over 10 years in persistently aPL-positive patients with/without other systemic autoimmune diseases. The network consists of five international core laboratories created to confirm aPL-positivity and for mechanistic studies. In this study we aimed to assess the agreement between inclusion and core laboratory anticardiolipin (aCL) and anti-β2glycoprotein I antibodies (aβ2GPI) ELISA

Methods: A secure web-based data capture system is used to store patient information including demographics, aPL/APS history, and aPL data. The inclusion criteria are positive lupus anticoagulant (LA) test based on the ISTH recommendations and medium-to-high titer aCL and/or aβ2GPI tested at least twice within one year prior to enrollment. The baseline samples of registry patients were re-tested for aCL and aβ2GPI (IgG, IgM and IgA with the QUANTA Lite® ELISA kits, Inova Diagnostics) at five different core laboratories. As part of this validation exercise, two different cut off values assays for aPL ELISA were arbitrarily used (20 and 40 GPL/MPL/APL for IgG, IgM and

IgA, respectively). Data was analysed using SPSS (IBM Software, NY).

Results: Four hundred and ninety-seven patients were included. Categorical agreement between the baseline values at inclusion vs. core laboratory results is summarized in Table 1. Cohen's kappa coefficients ranged between 0.61 and 0.80 (as substantial agreement). Overall, the correlation between quantitative results in the aCL and aβ2GPI was better for IgM and IgA compared to IgG (Spearman rho 0.789 and 0.666 vs. 0.600 for aCL and rho 0.892 and 0.744 vs. 0.432 for aβ2GPI).

Conclusion: aCL and aβ2GPI results showed very good categorical agreement between aPL testing at inclusion and core laboratories results. This agreement increases when considering high titer samples (>40 units). Based on the evaluations performed by the APS ACTION core laboratories, different ELISA tests used for inclusion displayed substantially equivalent performance for the detection of aCL and aβ2GPI. However, some non-substantial misclassification in terms of titers can be observed, especially for IgG isotype. **Table 1: Categorical agreement between the baseline values (BV) at inclusion vs. core laboratory (CR) results**

		cut off 40 %(BV/CR)	cut off 20 %(BV/CR)
aCL	**IgG**	81.7% (368/450)	81.6% (367/450)
	IgM	85.2% (381/447)	79.2% (354/447)
	IgA	90.8% (99/109)	83.5% (91/109)
aβ2GPI	**IgG**	82.2% (287/349)	79.7% (278/349)
	IgM	88.9% (346/389)	86.1% (335/389)
	IgA	88.5% (108/122)	82.2% (100/122)

Disclosure: S. Sciascia, None; **R. Willis**, None; **V. Pengo**, None; **S. Krilis**, None; **D. Andrade**, None; **D. Erkan**, None; **M. L. Bertolaccini**, None; **O. B. O. A. A. .**, None.

Abstract Number: 1074

The Risk of Obstetric Complications and the Effects of Treatment in Women with Low Titer and Medium-High Titer Anti-Phospholipid Antibodies

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Background/Purpose: The association of low titer anti-phospholipid antibodies (aPL) with obstetric anti-phospholipid syndrome (APS) is increasingly acknowledged, even though some studies have showed conflicting results. To raise further evidence on the relevance of low titer aPL in pregnancy morbidity (PM), we retrospectively reviewed the clinical records of pregnant women attending a joint obstetric/rheumatology clinic over the years 2009-2016.

Methods: Patients were included when positive in at least one criteria aPL assay, at any titer, in two occasions minimum 12 weeks apart. Statistical analysis was performed using R package.

Results: 111 women (338 pregnancies) were identified. 51 women displayed low-titer aPL, with 160 pregnancies. 60 patients carried aPL at medium-high titers, with 178 pregnancies. 4 patients (4%) had thrombotic APS, 27 (24%) obstetric APS, 7 (6%) thrombotic and

obstetric APS, 15 (14%) medium-high titer aPL and non criteria PM, 7 (6%) medium-high titer aPL and no PM, 18 (16%) low titer aPL and non criteria PM and 15 (14%) low titer aPL and no PM. Low-titer aPL were significantly associated with pregnancy complications (c^2=8.82, p=0.003). Considering 245 untreated pregnancies, a significant difference in PM distribution was noted for low titer and medium-high titer aPL (p=0.003, **Table 1**). Among patients with low titer aPL, treatment with low molecular weight heparin [LMWH] + low-dose aspirin [LDASA] significantly improved pregnancy outcomes (p<<0.001, odds ratio [OR]=0.07, 95% CI=0.007–0.300), leading to a 14.3-fold reduction of obstetric complications. Hydroxychloroquine [HCQ] was not associated with a significant improvement in live birth rate (p=0.079). Among women with medium-high titer aPL, the standard therapeutic approach with LMWH+LDASA resulted in a significant improvement of obstetric outcome (p<<0.001, OR=0.20, 95% CI=0.100–0.400). HCQ treatment significantly improved obstetric outcome, carrying a 3-fold increase in the live birth rate (p=0.025, OR=0.34, 95% CI=0.117–0.894).

Conclusion: According to our data, low titer aPL are significantly associated with aPL-associated obstetric complications, with a lower prevalence of premature birth compared to medium-high titer aPL. Treatment with LDASA+LMWH led to a higher increase of live birth rate in women with low titer aPL compared to those with medium-high titer aPL. Additional treatment such as HCQ were effective in women with medium-high titer aPL but not those with low titer aPL. **Table 1. Obstetric outcomes (defined according to Miyakis et al, 2006) in 245 untreated pregnancies in women with low titer and medium-high titer anti-phospholipid antibodies.**

	Live birth	Early loss	Late loss	Premature birth	Total
Low titer aPL	57 (42%)	60 (45%)	16 (12%)	1 (1%)	134
Medium-high titer aPL	31 (28%)	59 (53%)	13 (12%)	8 (7%)	111

Disclosure: C. B. Chighizola, None; **M. G. Raimondo**, None; **C. Comerio**, None; **F. Pregnolato**, None; **C. Sobrino**, None; **L. Trespidi**, None; **B. Acaia**, None; **M. Gerosa**, None; **W. Ossola**, None; **P. L. Meroni**, None.

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Abstract Number: 1075

CD40-Pathway Activation in Ectopic Lymphoid Structure (ELS)-Resident B Cells Contributes to Disease Pathology in Primary SjöGren's Syndrome

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SESSION INFORMATION

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Session Title: B Cell Biology and Targets in Autoimmune Disease - Poster I: SLE and Sjögren's

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: T cell-dependent activation of B lymphocytes is a key effector arm of the adaptive immune system, resulting in protective antibody responses and long-lived humoral immunity. Such B cell responses often occur in germinal centers (GCs); specialized anatomical locations within secondary lymphoid organs. Similar GC-like structures can also be found in involved tissue in various autoimmune diseases, including the salivary glands of primary Sjögren's syndrome (pSS) patients. Previous work has implicated CD40-CD154 pathway-dependent processes in regulating B cell survival and function in GCs, and we wanted to investigate whether this costimulatory pathway might be linked to ELS formation and function in pSS

Methods: Histological analysis of minor salivary gland biopsies from pSS patients revealed evidence of CD40 and CD154 expression on ELS-resident B and T cells respectively, co-locating receptor and ligand positive cells in affected tissue. These results suggested that there might be ongoing T-B cell collaboration in these ELS and we therefore wanted to examine whether there was evidence of CD40 pathway activation *in situ*. To do this we first generated a CD40-pathway gene signature in primary human B cells following recombinant CD154 stimulation *in vitro*

Results: Using a published microarray dataset generated using parotid gland biopsies we could demonstrate upregulation of a portion of the B cell CD40 gene signature in biopsies from pSS patients but not from healthy donors or individuals with Sicca symptoms, suggesting that CD40 pathway activation was occurring within disease-relevant tissue in lymphocytes implicated in disease pathology. To better understand the role of CD40-CD154 interactions in ELS, we examined salivary glands in CD40 knockout NOD mice. Wild-type NOD mice

develop sialadenitis, anti-SSA/SSB autoantibodies, and display evidence of ELS in salivary glands. In contrast, there was no evidence of ELS, sialadenitis or autoantibodies in CD40 deficient NOD mice up to one year of age. Further, anti-CD154 treatment resulted in disaggregation in splenic GCs as well as established ELS in NOD mice and resulted in decreased levels of IgG secreting cells in salivary glands

Conclusion: Collectively our data indicate that CD40 pathway signalling is essential for formation and maintenance of salivary gland ELS and suggest that CD40 pathway signalling is active in established ELS from pSS patients, supporting the notion that blockade of CD40-CD154 interactions may provide therapeutic benefit in patients suffering from this autoimmune exocrinopathy

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Disclosure: G. Wieczorek, Novartis Pharmaceuticals Corporation, 3; **M. Bigaud**, Novartis Pharmaceuticals Corporation, 3; **S. Pfister**, Novartis Pharmaceuticals Corporation, 3; **S. Hoersch**, Novartis Pharmaceuticals Corporation, 3; **K. McMichael**, Novartis Pharmaceuticals Corporation, 3; **C. Afatsawo**, Novartis Pharmaceuticals Corporation, 3; **M. Hamburger**, Novartis Pharmaceuticals Corporation, 3; **C. Texier**, Novartis Pharmaceuticals Corporation, 3; **C. Cojean**, Novartis Pharmaceuticals Corporation, 3; **M. Henry**, Novartis Pharmaceuticals Corporation, 3; **J. S. Rush**, Novartis Pharmaceuticals Corporation, 3.

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Abstract Number: 1076

BAFF Receptor Antagonists Suppress Differentiation of B Cells in Vitro and Are Drug Candidates for Primary SjöGren's Syndrome

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: We have reported that soluble BAFF (sBAFF) robustly increases IL-6 production in vitro by peripheral monocytes of patients with primary Sjögren's syndrome (pSS) as compared to healthy controls. In an attempt to elucidate the underlying mechanism, we have found that the expression level of BAFF receptor (BR3) is elevated in pSS monocytes and that the level is significantly and positively correlated with serum IgG level of pSS patients. These data collectively suggest that the elevated expression of BR3 on monocytes is involved in the pathogenesis of pSS which is often accompanied with hypergammaglobulinemia, and that BR3 is a possible therapeutic target to treat pSS. We have also successfully discovered two low-molecular weight compounds, pyrrolopyrimidine derivatives, BIK-12 and BIK-13, as BAFF receptor antagonists. The compounds inhibit BAFF-binding to BR3 and suppress both IL-6 production by BAFF-stimulated peripheral pSS monocytes and IgG production by peripheral pSS B cells co-cultured with BAFF-stimulated monocytes. In this study, we investigate the mechanisms of action of these compounds.

Methods: Peripheral monocytes were stimulated with sBAFF and cultured in vitro in the presence of BIK-12 or BIK-13. PBMC were stimulated with a mixture of sBAFF, recombinant human IL-21 (rhIL-21), and anti-IgM and anti-CD40 antibodies (multiple B cell activation) in the presence of BIK-12 or BIK-13. The expression levels of CD80/CD19/CD38/IgD and NF-kB/AID (Activation-induced cytidine deaminase) in the cells were analyzed by FACS and quantitative PCR, respectively. The amounts of IL-6 and IgG produced in the culture supernatants were measured by ELISA.

Results: sBAFF-induced IL-6 production by peripheral monocytes was significantly suppressed by BIK12 and BIK13 in a dose dependent manner. The elevated expression of CD80 and NF-kB, the markers of activated monocytes, in sBAFF-stimulated monocytes was also suppressed by the compounds. Interestingly, increased IgG production by activated PBMC was suppressed by BIK12 and BIK13. FACS analysis of PBMC indicated that differentiation of B cells into plasma blasts and/or plasma cells was inhibited by these compounds in a dose dependent manner. In addition, the expression level of AID was also suppressed by these compounds, suggesting that an IgG class switching was impaired.

Conclusion: Our results suggest that BAFF receptor antagonists suppress not only activation of monocytes but also IgG production by B

cells possibly by impairing differentiation and an IgG class switching of B cells. Our findings strongly suggest that BIK-12 and BIK-13 are drug candidates for hyper-activated B cell-related autoimmune diseases, such as pSS.

Disclosure: K. Yoshimoto, None; **N. Seki**, Mitsubishi Tanabe Pharma Corporation, 3; **K. Suzuki**, None; **K. Sugahara**, Mitsubishi Tanabe Pharma Corporation, 3; **T. Takeuchi**, Mitsubishi Tanabe Pharma Corporation, 2.

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Abstract Number: 1077

Increased Expression of B-Cell Lipid Rafts in Patients with Primary Sjogren's Syndrome Correlated Positively with Disease Activity Score, Suggesting a B Cell Activated State Potentially Relevant for the Disease Pathogenesis and Response to Biologic Therapies

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SESSION INFORMATION
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Session Type: ACR Poster Session B
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Background/Purpose: Recent research indicates that lipid rafts play an important role during B-cell activation and could be defective in patients with primary Sjögren's syndrome (pSS). No previous comparisons between the lipid raft profile in patients with lupus (SLE), SLE and secondary Sjögren's syndrome (SLE/SS) and pSS are available. Our study aimed to: 1. identify peripheral B and T cell abnormalities in patients with pSS compared to SLE and SS/SLE patients and correlate them with immune phenotype with clinical features and serological abnormalities. 2. investigate lipid raft expression in different B cell populations and their correlations with disease activity scores (ESSDAI and BILAG).

Methods: Blood samples and clinical and laboratory parameters from 34 patients with pSS, SLE and SS/SLE and 13 age/sex matched healthy controls (HC) were obtained. We used flow-cytometry to perform B-cell immunophenotyping and analysis of lipid-raft expression (marker of B-cell activation). In vitro cultures assessed lipid-raft expression in response to BAFF. We used ImageStream cytometry to characterise the interaction between lipid rafts and IgD and BAFF receptor (BAFF-R).

Results: Figure 1 presents the heatmaps assessing the expression of T and B cell populations in HC compared to patients with SS, SLE and SS/SLE. Lipid rafts were significantly elevated in B cells from patients with SS and SLE but not SLE/SS. Figure 2 shows the correlation between different immune cell populations and clinical and laboratory parameters. Figure 3 shows altered colocalisation of BAFF-R, Ig D and lipid rafts in patients with pSS, SLE and SS/SLE compared to HC.

Conclusion: This is the first comprehensive immunophenotype analysis performed in patients with pSS and SS/SLE, which identified that the SS/SLE patient group is immunologically distinct from pSS and SLE patients. The SS/SLE group had the most striking B cell phenotype abnormalities compared to patients with pSS or SLE (increased Bm2 cells and decreased early and late Bm5 cells). These abnormalities suggest a disturbance of B cell trafficking in the patient groups, and a possible bias towards plasma cell differentiation (as all disease groups had low memory B cells). The significant correlation between lipid raft expression and disease activity (ESSDAI score) in patients with pSS suggests abnormal B cell signalling. This could be relevant for the variability of patients' response to biologic treatments in SLE compared to pSS, as B cell targeted monoclonal antibodies are internalised within the lipid rafts.

Figure 1: Immunophenotyping

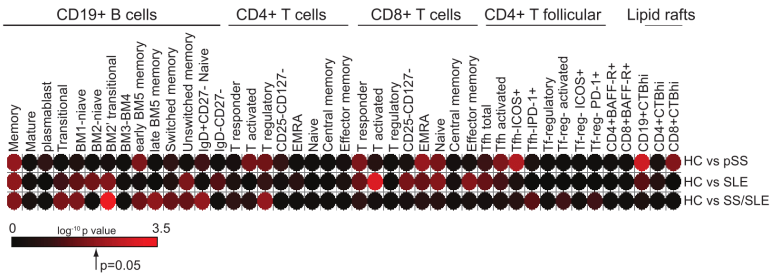


Figure 2: B cell phenotype vs clinical characteristics of patients

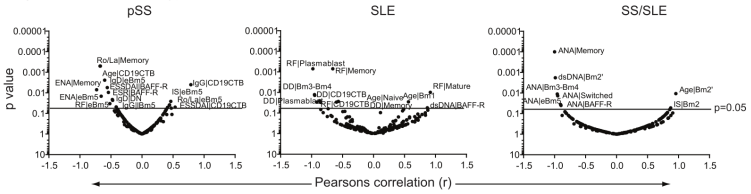
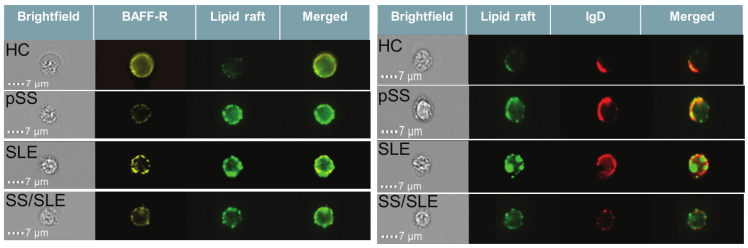


Figure 3: Imagestream analysis of lipid raft and BAFF-R/BCR co-association



Disclosure: **N. Thompson**, None; **A. Gandhi**, None; **R. Radmore**, None; **S. Cho**, None; **D. A. Isenberg**, None; **E. Jury**, None; **C. Ciurtin**, None.

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Abstract Number: 1078

Elevated Proportion of CD38highIgD+ b Cells in Peripheral Blood Is Related to Disease Activity in Patients with Primary SjöGren's Syndrome

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Background/Purpose: Primary Sjögren's syndrome (pSS) is well recognized as an autoimmune disease accompanied by hypergammaglobulinemia and production of autoantibodies such as anti-Ro/SSA and anti-La/SSB antibodies. Although these serological aberrations suggest that abnormally activated B cells play a key role in the pathogenesis of pSS, the possible involvement of hyperactivated

B cells in the development of pSS has not been fully understood. In this study, we tried to identify B cell subsets in peripheral blood which may be responsible for disease activities of pSS.

Methods: Peripheral blood was collected from pSS patients (n = 34) and gender- matched healthy controls (HC, n = 20), and the proportion of B cell subsets characterized by anti-CD19, anti-IgD and anti-CD38 antibodies was analyzed by flow cytometry. $CD19^{+}$B cells prepared from pSS patients and HC by using CD19-microbeads were stimulated in vitro with a mixture of an anti-IgM antibody, recombinant human CD40 ligand, recombinant human IL-4 and recombinant human soluble BAFF (B cell stimulation). IgG production by the cells was measured by ELISA. Disease activities of the pSS patients were quantified based on the European League against Rheumatism (EULAR) Primary Sjögren's syndrome disease activity index (ESSDAI). The serological data of the patients were collected by clinical records.

Results: The proportion of $CD19^{+}$ B cells was significantly increased in pSS patients as compared with HC. In addition, IgG production by $CD19^{+}$ B cells in vitro upon B cell stimulation was also significantly increased in pSS patients. Moreover, the IgG production was positively and significantly correlated with serum IgG levels of the patients. Interestingly, FACS analysis of whole blood samples revealed that both $CD38^{high}IgD^{+}$ and $CD38^{high}IgD^{-}$ B cells were significantly increased in pSS patients compared with HC. Moreover, the number of $CD38^{high}IgD^{+}$ B cells was significantly higher than that of $CD38^{high}IgD^{-}$ B cells in the patients. In addition, the proportion of $CD38^{high}IgD^{+}$ B cells to $CD19^{+}$B cells was positively and significantly correlated with ESSDAI, serum levels of IgG, anti-Ro/SSA and anti-La/SSB antibodies.

Conclusion: Our results suggest that $CD38^{high}IgD^{+}$ B cells, which are known as activated B cells, are involved in overproduction of IgG and associated with disease activity of pSS. Our findings may shed light on the mechanism of pathogenesis of pSS.

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Abstract Number: 1079

Discovery of Novel Autoantigens in Sjogren's Syndrome with Potential for Subgrouping of Disease

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a common autoimmune disease with exocrine gland dysfunction and multi-organ involvement. With the growing interest in conducting clinical trials in pSS, there is a need for new biomarkers that can be used to diagnose pSS, identify clinical subsets of pSS, predict treatment outcome and assessment of disease activity. Activation of B-cells and dysregulation of the cytokine network plays a critical role in the pathophysiology of pSS. In the exocrine glands, elevated levels of cytokines, such as type I interferon (IFN), tumor necrosis factor alpha (TNF), interleukin 12 (IL-12) and B cell activating factor (BAFF) can be found. Dysregulated pathways of the innate and adaptive immune system lead to loss of tolerance and the production of organ-specific and non-specific autoantibodies. Current diagnostic criteria for pSS utilize autoantibodies directed to nuclear antigens (ANA), especially to SS-A/Ro (TRIM21, TROVE2) and La (SSB), but those are not specific, and can be identified as well in SLE and even in healthy volunteers. Several studies have shown that not all patients with pSS are tested positive for Ro and La autoantibodies, but suggested the existence of additional autoantibodies in pSS. This autoantibody burden is not well understood for the importance of disease progression, for its role in patient segmentation, or for response to treatments. The discovery of autoantigens may provide a deeper understanding of mechanisms of actions for pSS drugs, and may be useful to stratify patients.

Methods: The autoantibody reactivity pattern of pSS serum patients was analyzed using a Luminex bead-based antigen array (SeroTag) and 1,600 selected human protein antigens from our hPEX protein library of 8,000 recombinant proteins. We screened over 2,000 serum samples from patients with autoimmune diseases as active controls targeting Sjögren's Syndrome (n= 70), SLE (n= >500), SSc (n= >250), RA (n= >500), and over 1,000 healthy individuals to confirm known and to discover novel autoantibodies.

Results: Apart from clear confirmation the known benchmark autoantigens known for many years we have discovered a small set of additional, novel autoantibodies, which were detected in frequencies of 8 to >20% in pSS. Accumulation of autoantibody reactivities allows for a first subgroup definition of Sjögren's, and for clear segregation of SjS/SLE overlap syndrome patients.

Conclusion: A set of novel autoantigens for diagnosis and subgroup definition in Sjögren's syndrome was discovered by high content screening using a Luminex bead-based array platform. Validation in additional, large patient cohorts is ongoing.

Disclosure: P. Schulz-Knappe, Protagen AG, 3; **P. Budde**, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **H. Göhler**, Protagen AG, 3; **K. Marquart**, Protagen AG, 3; **P. D. M. Schneider**, Protagen AG, 5; **T. Witte**, None.

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Abstract Number: 1080

B-Cell Clonal Expansions in Parotid Glands of Sjogren's Patients Are Associated with Increased Numbers of N-Glycosylation Motifs in the Immunoglobulin Heavy Chain Genes

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by chronic inflammation of salivary and lacrimal glands. Patients with pSS have increased clonal expansions of B-cells in glandular tissue. The driving force for this expansion is unknown. Previous Ig heavy chain (IGHV) analysis studies of both parotid and labial glands revealed that there are no indications for an antigen driven expansion. However, our sequence analysis of RNA transcripts encoding for IGHV3 (IGHV3) genes derived from parotid pSS B-cell clones revealed significantly higher incidence of acquired N-glycosylation sites due to somatic hypermutation, suggesting a role for N-glycosylation motifs (N-glycs) in the selection of Ig producing cells. The aim of this study was to assess clonal expansions with Next Generation Sequencing (NGS) technology for all IGHV family genes in parotid gland tissue derived from pSS and non-pSS sicca patients.

Methods: mRNA was isolated from biopsies of parotid glands of 5 pSS patients diagnosed according to the AECG criteria and 5 non-pSS sicca patients. IGHV sequences of all IGHV families were amplified and sequenced using NGS. The Ig sequences were analyzed for IGHV gene usage, somatic hypermutation, CDR3 length and rearrangement by alignment with germline gene sequences of the IMGT reference directory. Sequences with the same CDR3 region (amino acids) and shared mutations within the Ig variable region were referred to as clonally related. Clones composed of more than ≥0.3% of the total amount of productive sequences were referred to as dominant clones. These clones were analyzed for expansion patterns, signs of antigen selection and acquired N-glycs.

Results: From each patient 1800-4000 unique sequences were recovered. We observed no difference in IGHV gene usage or CDR3 length between the pSS and non-pSS IGHV sequences. A total of 70 dominant clones (mean 14.0±5.6 clones) was found in pSS biopsies, whereas in non-pSS biopsies a significantly lower (p=0.0079) number of 15 dominant clones was detected (mean 3.0±1.6 clones). No difference in

percentage of mutations was seen between dominant clones from pSS and non-pSS patients. Analysis of dominant clones showed that in 4 of the 5 pSS patients, and in none of the clones of the non-pSS patients, the germline sequence was present in some of the clones. There was no evidence for antigen driven selection in the dominant clones. We observed that the IGHV sequences of dominant clones in pSS patients had acquired significantly more N-glycs compared to non-pSS sicca patients. These N-glycs were not restricted to IGHV3 genes. Remarkably, the majority of N-glycs was seen in the framework 3 region of IGHV3.

Conclusion: The presence of germline and heavily mutated IGHV sequences in dominant clones in parotid gland tissue of Sjögren patients is direct evidence that naïve B-cells entering the parotid gland expand and differentiate locally into plasma cells. Lack of evidence for antigen-driven clonal expansion in conjunction with significantly higher incidence of N-glycs, outside the antigen-binding site, in these clones suggests an alternative selection of Ig producing B-cells in pSS. We postulate that there might be a possible role for lectins in this process.

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Abstract Number: 1081

The CRL4CRBN E3 Ubiquitin Ligase Modulator CC-220 Inhibits BAFF-Mediated Plasmablast Differentiation and Immunoglobulin Secretion from Class Switched CD27+IgD- Memory and Lupus-Associated CD27-IgD- Double Negative B-Cells

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Background/Purpose: Changes in the ratio of circulating memory, naive, and double negative $CD27^{-}IgD^{-}$ B cell subsets are associated with a higher disease activity index in systemic lupus erythematosus (SLE) patients. Little is known about the soluble factors that may induce plasmablast differentiation from B-cell subtypes infiltrating inflamed tissue environments where they have proximity to, but often spatially separated from T-cells. We investigated the potential for SLE-associated soluble BAFF, IL-2 and IL-21 to drive plasmablast differentiation from B-cell subsets in a T-cell contact independent manner and whether CC-220, a Cullin Ring Ligase 4 Cereblon ($CRL4^{CRBN}$) E3 Ubiquitin Ligase Modulator, has an impact on generating potential autoantibody producing cells. The objective of the study was to determine the potential of BAFF, IL-2 and IL-21 to induce plasmablast differentiation from memory, naive, and lupus-associated double negative B-cell subsets and to determine the impact of CC-220 on differentiation and proliferation within these B-cell populations.

Methods: We investigated the effects of CC-220 on plasmablast differentiation from purified B-cell subsets in *in vitro* models mimicking germinal center T cell contact dependent (CD40L, IL-2, IL-21) and extra-germinal center T-cell contact independent (BAFF, IL-2, IL-21) systems. Plasmablast differentiation and antibody secretion was measured 5 days post treatment of $CD27^{+}$ memory B-cells and $CD27^{-}$ naive B-cells. Sorted B-cell subsets based on the CD27 memory and the IgD class switch markers were also tested: $CD27^{-}IgD^{+}$ naïve; $CD27^{+}IgD^{-}$ switched memory (SMe); $CD27^{+}IgD^{+}$ non switched memory (NSM); and $CD27^{-}IgD^{-}$ double negative (DN) B cells. Plasmablast differentiation and antibody production in the absence or presence of CC-220 were analyzed by flow cytometry and ELISA, respectively.

Results: BAFF, IL-2, and IL-21 in combination induced proliferation and plasmablast differentiation in SMe and DN B-cells, but not NSM or naive B-cells. Induced IgG secretion by BAFF, IL-2, and IL-21 was observed only from SMe and DN B-cells. Induced IgM secretion by BAFF, IL-2, and IL-21 was observed from SMe, to a lesser degree DN, but not from NSM or naive B-cells. CD40L, IL-2, and IL-21 induced B-cell proliferation and differentiation from all four subpopulations, with SMe producing the largest amount of IgG secretion followed by DN and DP and little from naive B-cells. Similar to IgG, IgM secretion was induced most from SMe, followed by NSM and DN in the CD40L, IL-2, IL-21 system. CC-220 inhibited plasmablast differentiation and antibody production in all cases, with different

efficacy depending on the B-cell subpopulations and stimuli.

Conclusion: In the presence of IL-2 and IL-21, BAFF induced proliferative and plasmablast differentiation effects are only observed on class switched $CD27^{+}IgD^{-}$ memory and DN $CD27^{-}IgD^{-}$ B-cells. This is in contrast to CD40L, IL-2, and IL-21,which drives B-cell proliferation and differentiation in all four subpopulations tested. In all conditions used to induce B-cell proliferation and plasmablast differentiation, CC-220 inhibited these processes at clinically relevant concentrations (1-10 nM).

Disclosure: Y. Nakayama, Celgene, 3; **J. Kosek**, Celgene, 1,Celgene, 3; **L. Capone**, Celgene, 1,Celgene, 3; **P. H. Schafer**, Celgene, 1,Celgene, 3; **G. Ringheim**, Celgene, 3,Celgene, 1.

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Abstract Number: 1082

Type I/II Interferon Commits to Abnormal Expression of Chemokine Receptor on B Cells in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by an expanded population of peripheral memory B cells. However, little is known about the qualitative abnormality of B cells associated with the pathogenesis of SLE. We assessed the subset of B cells by expression of chemokine receptors in patients with SLE and performed in vitro analysis to assess the differentiation mechanisms of those subsets.

Methods: PBMCs obtained from subjects with 56 patients with SLE, 31 patients with rheumatoid arthritis (RA) and 20 healthy donors (HD) were analyzed. Circulating B cell subsets were categorized by expression of chemokine receptors such as CXCR3 and CXCR5. Additionally, pan B cells obtained from HDs were cultured 4 days under stimulation with B cell receptor, co-stimulatory molecules and cytokines such as IL-21 and type I/II interferons (IFNs), and we assessed the expression of chemokine receptors such as CXCR3 and CXCR5 and transcription factors such as T-bet and Bcl-6 by multi-color flow cytometry.

Results: 1) The proportion of effector memory B cells (EM B cells; $CD19^{+}CD20^{+}IgD^{-}CD27^{-}$) has significantly increased in SLE compared to HD and RA ($p<0.01$). 2) The proportion of $CD19^{+}CD20^{+}CXCR5^{-}CXCR3^{-}$ B cells and $CD19^{+}CD20^{+}$ $CXCR5^{-}CXCR3^{+}$ B cells has significantly increased in SLE, compared to HD and RA, which were remarkably noted in $CD19^{+}CD20^{+}IgD^{-}CD27^{+/-}$ memory B cells ($p<0.01$). 3) CXCR5 expression was decreased in cultured B cells stimulated by BCR, CD40 ligands and IFN-β ($p<0.05$). By contrast, CXCR3 expression was increased in cultured B cells stimulated by BCR, CD40 ligands and IFN-γ ($p<0.05$). 4) T-bet expression was increased in cultured B cells stimulated by BCR, CD40 ligands and IFN-γ ($p<0.05$).

Conclusion: The results indicated that abnormality of B cell in SLE is characterized by not only quantitative increase in peripheral memory B cells but also unique expression pattern of chemokine receptors with down-regulation of CXCR5 and up-regulation of CXCR3 in EM B cells, indicating a potential of preferential migration into peripheral organs. Furthermore, in vitro experiments revealed that type I/II IFNs are a potent inducer of EM B cells involving abnormal chemokine receptor expression, suggesting an importance of these cytokines for the pathogenesis of SLE.

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Abstract Number: 1083

Discovery and Subsequent Diagnostic Verification of Autoantibodies Against the Major Vault Protein (MVP) in Systemic Lupus Erythematosus

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Background/Purpose: In systemic lupus erythematosus (SLE), early diagnosis and prognostic stratification are still great challenges. The broad characterization of the autoantibody repertoire in SLE is an emerging tool to supporting a personalized disease management approach. We have recently conducted autoantibody profiling studies of SLE, systemic autoimmune diseases (AID), and healthy controls to identify biomarkers for improving lupus diagnosis and patient stratification. Here we describe the identification of autoantibodies against the major vault protein (MVP) in SLE and its subsequent development into an ELISA based assay.

Methods: A large-scale Luminex bead-based autoantibody screen was conducted by combining diagnostic with putative antigens. In the discovery phase the autoantibody reactivity of serum samples from 130 SLE patients, 794 AID patients (systemic sclerosis, rheumatoid arthritis/RA, early RA, ankylosing spondylitis) and 343 healthy controls were tested against 6,912 recombinant human proteins. Following validation in independent SLE samples (n=101), consistent autoantibody reactivity against 46 antigens was found (p-value <0.05). The newly discovered autoantigen was developed into a prototypical ELISA format and analyzed for diagnostic performance using a medium sized control cohort consisting of n=93 serum samples (24 healthy controls, 42 SLE, 14 SSc, and 13 Sjögren syndrome (SjS) serum samples).

Results: A data base search of 46 known and novel SLE-associated antigens revealed that the expression of ten proteins is upregulated by type I interferon (INF) (http://www.interferome.org). Beyond known antigens (TRIM21/Ro52, SSB), we identified a novel autoantibody target MVP with a frequency of 20 % in SLE. Initial findings of the Luminex based screening results were verified by the results of the ELISA test; the newly discovered MVP autoantigen revealed sensitivity and specificity of 26% and 98% respectively. Anti-MVP antibodies were also found in SLE patients tested negative for dsDNA, Sm, and Ribosomal P. Interestingly, MVP is the major constituent of the vault particle, which is a cytoplasmic organelle and the largest known ribonuclear protein complex. Although the exact biological function of MVP is not well understood, literature data suggest that MVP is a virus-induced host factor, which up-regulates type I INF production [1].

Conclusion: Anti-MVP autoantibodies represent a useful marker in SLE and, in combination with anti-dsDNA, anti-Sm and anti-ribosomal P, optimizes the strategy for autoantibody testing. Furthermore, although more studies are needed, our findings suggest a previously undescribed linkage of type I INF and autoantibody targets in SLE. Liu S et al. (2012). Hepatology. 56(1):57-66.

Disclosure: P. Budde, Protagen AG, 3; **J. Schulte-Pelkum**, Protagen AG, 3; **D. Wirtz**, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **H. Göhler**, Protagen AG, 3; **S. Vordenbäumen**, None; **P. Schulz-Knappe**, Protagen AG, 3; **M. Schneider**, Protagen AG, 5.

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Abstract Number: 1084

Antibodies to Native Vimentin in Lupus: Characterization, Isotypes, Origins, and

Associations with Other Autoimmune Pathways

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Background/Purpose: Severe lupus tubulointerstitial nephritis (TIN) is prognostic of renal failure and characterized by tertiary lymphoid organogenesis. We have previously demonstrated that the dominant target of monoclonal antibodies (mAbs) cloned from B cells isolated from TIN biopsies was vimentin and not nuclear antigens. Probing bovine lens vimentin coated arrays confirmed anti-vimentin antibody (AVA) reactivity and serum IgG AVA titers correlated with TIN severity. Vimentin is an abundant secreted antigen in inflamed tissue. Citrullinated vimentin comprises a low proportion of the antigen, yet high titers of anti-citrullinated protein antibodies (ACPAs) are specific features of rheumatoid arthritis. However, it is not known if in situ selected AVAs in TIN target citrullinated vimentin. Furthermore, the origin of AVAs, and how they are selected in situ, is not clear.

Methods: Recombinant human vimentin was made in E.coli and used as substrate by ELISA. Eight TIN mAbs (with high vimentin reactivity) from six different TIN biopsies were probed for reactivity with unmodified and in vitro citrullinated vimentin. Predicted germ-line reversions of the respective TIN mAbs, 23 mAbs from healthy naïve and 20 mAbs from anergic B-cells, were also assayed for vimentin reactivity. Lupus serum samples from 101 subjects were screened for IgM, IgG, IgA and IgE AVAs. Other routinely assayed autoantibodies were titrated using commercially available ELISAs.

Results: In vitro citrullination of human vimentin, confirmed by mass spectrometry, inhibited TIN mAb binding. Germline reversion of seven of eight somatically hypermutated TIN mAbs diminished but did not ablate AVA activity. Vimentin immunoreactivity was, surprisingly, a common feature of the naïve and anergic repertoires. Furthermore, the range of relative affinities between reverted AVAs and anergic antibodies with AVA activity was similar. IgM and IgA AVAs could be readily detected in the serum of some patients with SLE. High titers of one AVA isotype did not categorically determine high titers of another isotype.

Conclusion: These studies demonstrated that the AVAs associated with SLE and the ACPAs associated with RA are different. It also appeared that AVAs are selected in situ from preexisting repertoires of AVA and are common through the spectrum of antibody isotypes associated with SLE. These data suggest that loss of tolerance to vimentin, and selection of high affinity and potentially pathogenic AVAs, is a common feature of SLE.

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Abstract Number: 1085

The Anti-CD38 Monoclonal Antibody TAK-079 Depletes Antibody Secreting Cells from Normal and SLE Patients

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by expanded antibody secreting cells (ASCs) and the production of a variety of autoantibodies. Depletion of B cells by the anti-CD20 monoclonal antibody, Rituximab, has been widely used in autoimmune disease therapy. However, ASCs express low levels of CD20 and are poorly targeted. In this study, we examined the ability of TAK-079, a monoclonal against CD38 which is expressed at high levels by ASCs, to inhibit antibody production.

Methods: TAK-079 was provided by Takeda California, in collaboration with XOMA Corporation. Mononuclear cells were isolated from bone marrow aspirates or blood from healthy control (HC) and SLE patients. B cell subset frequencies were measured by flow cytometry following *ex vivo* depletion with TAK-079. To determine the frequency of ASCs, ELISpot was used to enumerate total IgG-producing and autoantigen specific cells. In some cultures NK cells were added to purified B cells to effect target cell killing.

Results: The addition of TAK-079 *in vitro* depleted 80% of plasma cell populations, which were characterized by the expression of CD27, CD38, and CD138 using flow cytometry. More importantly, with intracellular staining, cells positive for plasma cell markers BLIMP1 and IRF4, were also significantly reduced. Furthermore, TAK-079 depleted both short-lived plasma cells (CD19+ plasma cells), and long-lived plasma cells (CD19- plasma cells) from bone marrow. ASCs measured directly by ELISpot were also reduced in both HC and SLE patient samples. In HC samples, with TAK-079 treatment there was 70% reduction in the number of IgG producing cells from both blood samples and bone marrow samples. Similar depletion was seen in SLE patient samples. Additionally, the number of cells producing autoantigen specific antibodies was also dramatically reduced, including: VH4-34 9G4+ antibodies (70% reduction), anti-Ro antibody (70% reduction), and anti-dsDNA antibody (80% reduction). We elucidated the mechanism of plasma cell depletion and found that antibody-dependent cell-mediated cytotoxicity (ADCC) is an essential mechanism of plasma cell lysis *in vitro* by TAK-079. Purified B cells alone were unaffected by TAK-079 mAb, whereas addition of NK cells elicited TAK-079 dependent depletion of ASCs.

Conclusion: Our results highlight the potential of TAK-079 monoclonal antibody for treating SLE via plasma cell depletion. By targeting CD38, a molecule highly expressed on all plasma cells, TAK-079 effectively depleted both short lived and long-lived ASCs. Furthermore SLE ASCs producing antibodies against self-antigens were also efficiently depleted through NK cell and TAK-079 mediated ADCC *in vitro*.

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Abstract Number: 1086

Analysis of the Naive B Cell Repertoire in Belimumab Treated SLE Patients

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Background/Purpose: BAFF is a TNF-like cytokine that supports the survival and differentiation of B cells. The anti-BAFF antibody belimumab is the only new drug that has been approved by the FDA for the treatment of lupus in the last 50 years. While it is clear that BAFF inhibition depletes B cells and can alter selection of the naïve B cell repertoire in mice, especially in the absence of competition from non-autoreactive B cells, some autoreactive VH genes are unaffected by belimumab and can subsequently enter and expand in the germinal center. A single study in humans did not show exaggerated loss of autoreactivity between the transitional and naïve compartments in belimumab treated patients. Furthermore, it is still not certain that altered selection is the mechanism by which BAFF inhibition achieves its therapeutic effect either in mice or humans. The purpose of this study was to determine how belimumab treatment alters the VH

repertoire of the naïve B cell repertoire in SLE patients.

Methods: Blood was collected from 14 SLE patients who had received and responded to belimumab for > 3years and from 10 SLE patients matched for age, ethnicity, disease duration, disease activity and other medications. Blood was also collected from 5 patients before and 6 months after starting belimumab therapy. PBMCs were analyzed by flow cytometry for B cell phenotype and naïve B cells ($CD3^-/CD11b^-/CD56^-/CD19^+/CD27^-/CD10^-$) were sorted as pellets. RNA was generated from the isolated cells and libraries were made for next generation sequencing using iRepertoire primers. Multiplexed libraries were sequenced using miSeq.

Results: Naïve B cells were depleted in all chronic belimumab treated patients with up to 90% depletion in treated patients 6 months after treatment initiation. 60-100 x 10^3 cells were sorted from belimumab treated patients and 350-700 x 10^3 cells were sorted from control SLE patients. 120-600 x 10^3reads were obtained from each sample. The number of distinct CDR3 regions was two to three-fold less in belimumab treated patients compared with either SLE or pre-treatment controls. The D50, calculated as a percent of dominant B cell clones that cumulatively account for 50% of the total CDR3s per sample was lower in the chronic belimumab patients compared with the SLE controls ($p<0.02$) but was not different in the pre-treatment vs. 6 month post-treatment belimumab samples. Each patient had a unique distribution of VH genes. Little difference was observed in the overall distribution of VH genes in patients examined before and 6 months after belimumab treatment. Since VH3-23 and VH4-34 are autoreactive genes it might be expected that naïve B cells expressing these genes would be preferentially deleted by belimumab therapy. However no difference was observed in the frequency of either of these two VH genes in pre vs. 6 month post belimumab treated samples or in chronic belimumab vs. SLE controls. Furthermore, belimumab did not preferentially delete the “naïve activated” B cell population that preferentially expresses VH4-34.

Conclusion: Treatment with belimumab depletes approximately 90% of naive B cells with a modest decrease in diversity over a long time period. However at 6 months after treatment initiation, when B cell depletion has already occurred, belimumab treatment does not result in significant skewing of the overall VH repertoire. Belimumab does not induce preferential deletion of naïve B cells expressing the autoreactive VH3-23 or VH4-34 genes even after three years of treatment. These data suggest that loss of autoreactivity in the naïve B cell compartment is not a sufficient explanation for the therapeutic efficacy of belimumab.

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Abstract Number: 1087

Nonmemory B Cell Signature Alterations in Belimumab Patients

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Background/Purpose: Insight into B cell subset dynamics and homeostasis can provide a biological rationale for use of B cell targeted therapies in SLE patients. Using our B cell signature (BCS) approach we wanted to assess whether treatment with Belimumab would result in a unique BCS that reflects a reduction in B cell subsets that are most sensitive to B cell activating factor (BAFF) depletion. Our BCS used the CD21/CD24 model that delineates analogous mouse and human nonmemory B cell subsets. Mouse studies have used CD21 and CD24 co-expression to identify which subsets are susceptible to BAFF depletion.

Methods: PBMCs were isolated from healthy donors, and SLE patients on Belimumab or standard of care therapy (SCT). Cells were stained for flow cytometry to identify nonmemory and memory subsets. BCS were determined based on the frequency of each B cell subsets within the nonmemory and memory pools and compared across treatment groups. One-way ANOVA test and Tukey’s post-hoc test were used for statistical analysis.

Results: Our evaluation of BCS showed that Belimumab (n=13) patients had significantly higher proportions of nonmemory transitional 1 cells ($p = 0.0062$) compared to SCT (n=24) patients and healthy controls (n=14). Alternately, Belimumab patients had significantly lower

proportions of nonmemory transitional 2 subset (p=0.0014) compared to healthy controls. FM (naïve) cells displayed no significant differences between the three groups. When we assessed the ratio of T1 to T2, Belimumab B cells had a larger ratio compared to both healthy and SCT (p=0.0033), but healthy and SCT were not significantly different. We also evaluated total transitional B cells to FM cells and noted no significant differences.

Conclusion: Our results show that B cell subsets must be stringently assessed as indicated by the transitional B cell subset data. BCS from Belimumab patients display unique profiles compared to both SCT and healthy donors. Our future studies will consist of a longitudinal evaluation of BCS in pre-Belimumab treatment and at subsequent time points in order to correlate BCS alterations with specific patient clinical characteristics.

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Abstract Number: 1088

Expansion of Transitional B Cells in SLE Patients Correlates with Increased Toll-like Receptor 7 Expression

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Background/Purpose: B cell hyperactivation and autoantibody (auto-Ab) production are hallmarks of SLE. Auto-Abs, reactive to RNA-containing antigens are found in a fraction of SLE patients, particularly those with severe disease activity. Toll-like receptor 7 (TLR7), an intracellular TLR that recognizes ssRNA, has been highly implicated in the generation of pathogenic anti-RNA autoantibodies in SLE, however the cellular origin of anti-RNA Ab–secreting cells is not well defined. Human transitional (TR) B cells have been previously shown to be enriched in polyreactive specificities and increase of TR B cells have been described in SLE patients. This study was undertaken to determine a possible link between the transitional B cell expansion and increase in *TLR7* expression in SLE.

Methods: Human peripheral blood mononuclear cells (PBMCs) were collected from both SLE patients and healthy donors (HDs) and analyzed by multicolor flow cytometry. Frequencies of TR B cells within the $CD19^+$ cell population were determined based on the relative expression of IgD, CD10, CD24, CD27, and CD38 surface markers. Expression levels of *TLR7* and *TLR9* were measured by real-time PCR. Additionally, $CD19^+$ $CD38^{++}CD24^{++}$ TR B cells from human cord blood were isolated by cell sorting. These cells were stimulated with IFNα, followed by stimulation with anti-IgM and/or TLR7 agonist R848. Changes in mRNA levels of *TLR7* were analyzed 3-6 hours post-stimulation. Plasma cell differentiation was assessed by flow cytometry after 5 days of *in vitro* cell culture; antibody production was analyzed by ELISA, and the expression of cytokines was measured by bead-based immunoassay.

Results: Analysis of the B cell compartment revealed a significant increase in the frequencies of circulating $CD19^+CD27^-IgD^+CD10^+CD38^{++}CD24^{++}$ TR B cells in SLE patients, compared to HDs. We found a significant positive correlation between the levels of *TLR7,* but not *TLR9* expression, and the frequencies of circulating TR B cells. SLE patients who carry a risk G allele (TLR7 polymorphism rs3853839, associated with increased *TLR7* expression) show a trend toward increased TR cell frequencies compared to non-risk allele carriers. SLE patients with high frequencies of TR B cells were also more likely to been found positive for pathogenic Sm/RNP auto-Abs in the clinic. IFNα treatment induced a nearly 10-fold increase in the expression of *TLR7* and *IRF7* in TR B cells isolated from umbilical cord blood. IFNα-primed TR B cells become highly responsive to *in vitro* stimulation with R848 and differentiated into $CD27^{++}CD38^{++}CD24^-$plasmablast in the absence of any other stimuli. Stimulation of TR B cells with R848 promoted IgM production, whereas stimulation with anti-IgM plus R848 induced IFN-γ, IL-6 and IL-10 cytokines.

Conclusion: Our findings show a direct correlation between *TLR7* expression levels and the expansion of TR B cells in SLE patients. Upon IFNα exposure, human TR B cells become hyper-responsive to stimulation through TLR7. Our study suggest that human TR B cells might be

an important source of auto-Abs and provide a new link between innate IFN and TLR7 signaling and B cell activation in SLE.

Disclosure: T. Wang, None; **J. Marken**, None; **K. Cerosaletti**, None; **N. V. Giltiay**, None.

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Decreased B Cell Activation-Induced Apoptosis in Cells Overexpressing Interferon Regulatory Factor 5 (IRF5), a Gene Associated with Risk for Systemic Lupus Erythematosus and Other Autoimmune Diseases

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Background/Purpose: The transcription factor Interferon Regulatory Factor 5 (IRF5) plays a crucial role in the functioning of several cell types such as macrophages, dendritic, and B cells. In Systemic Lupus Erythematosus (SLE), the IRF5 gene locus has been identified as a risk factor with various single nucleotide polymorphisms (SNPs) that demonstrate a strong correlation with disease development. It has been demonstrated that these polymorphisms cause increased production of IRF5 protein. In this study we investigate the effects of IRF5 overexpression in B cells on apoptosis. We hypothesized that overexpression of IRF5 would decrease activation-induced apoptosis. This would reduce tolerance and likely contribute to the development of lupus or other autoimmune diseases.

Methods: A lentivirus transduction system was engineered by cloning the human IRF5 gene into the bicistronic lentivirus pUltra-Chili, which expresses the reporter dTomato along with IRF5. Naïve B cells were isolated from healthy donors and transduced with our lentivirus construct with and without IRF5. The cells were then stimulated with IgG anti-Igm to induce activation. As an added control, a population of un-transduced naïve B cells was also stimulated. Forty-two hours post stimulation, apoptosis was measured by Annexin V staining and flow cytometry, with naïve B cell populations being gated on dTomato expression. Statistical analysis was done using the Wilcoxon signed-rank and p values with an alpha less than 0.05 were considered significant.

Results: Anti-IgM treated naïve B cells showed increased apoptosis compared to non-stimulated samples as expected. Comparing naïve B cells overexpressing IRF5 with naïve B cells treated with the empty vector, the IRF5 overexpressing cells demonstrated, on average, 46.5 % less apoptosis ($p < 0.05$).

Conclusion: These results support our hypothesis that overexpression of IRF5, which is a result of lupus-associated IRF5 SNPs, decreases apoptosis in activated B cells after B cell receptor engagement. This could provide a greater risk of breaking self-tolerance in individuals with the IRF5 risk haplotype.

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Abstract Number: 1090

CpG-Stimulated B Cells Require Glutaminolysis for Glycolysis, Mitochondrial Respiration, and Cytokine Production

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Background/Purpose: B cells contribute to disease pathophysiology through several mechanisms, including cytokine secretion. A wide variety of stimuli can activate B cells to produce cytokines including B cell receptor and Toll-like receptor engagement. Recently, numerous observations have established the role of metabolic pathways in the diverse array of immune cell functions. It is unknown though how these metabolic pathways influence B cell cytokine production. We sought to elucidate the metabolic programs required for B cell cytokine production.

Methods: B cells were isolated from the spleens of C57Bl/6J mice and activated overnight individually by the following agents: anti-μ antibody, anti-CD40 agonist antibody, poly(I:C), LPS, loxoribine, and CpG. Supernatants were collected and analyzed for the quantification of cytokines using the Milliplex cytokine kit (EMD Millipore). Real-time analysis of extracellular acidification rates and oxygen consumption rates of activated B cells were performed using the XF-96 Extracellular Flux Analyzer (Seahorse Bioscience). Three or more consecutive measurements were obtained under basal conditions and after the sequential addition of 1 μM oligomycin, to inhibit mitochondrial ATP synthase; 1.5 μM FCCP (fluoro-carbonyl cyanide phenylhydrazone), a protonophore that uncouples ATP synthesis from oxygen consumption by the electron-transport chain; and 100 nM rotenone plus 1 μM antimycin A, which inhibit the electron transport chain. To assess 3-carbon sources for oxidative phosphorylation, inhibitors to fatty acid oxidation (etomoxir, which irreversibly inhibits carnitine palmitoyltransferase-1), pyruvate transfer to mitochondria (UK-5099), and glutamine usage (BPTES, which inhibits mitochondrial glutaminases) were used.

Results: CpG stimulation of mouse splenic B cells increased both glycolysis and mitochondrial respiration to a larger extent that by other stimuli such as LPS or B cell receptor alone. These processes are highly dependent on glutamine, as inhibition of glutaminolysis with BPTES significantly reduced both processes. Importantly, production of TNF-α, IL-6, and IL-10 by CpG-stimulated B cells also heavily relied on glutaminolysis.

Conclusion: B cells undergo metabolic reprogramming when stimulated with CpG, requiring glutaminolysis. Cytokine production is intrinsically linked with this reprogramming. These data are the among first to demonstrate a relationship between B cell effector function and metabolic reprogramming, and suggest that B cell cytokine secretion can be manipulated by altering the local metabolic environment. Manipulating metabolic pathways may represent an interesting therapeutic approach for modulating B cells in autoimmune diseases.

Disclosure: M. Cheung, None; **D. Huang**, None; **D. Wu**, None; **E. Pearce**, None; **A. Kim**, Kypha, Inc., 2,Amgen, 5,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5.

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Abstract Number: 1091

Synergistic Immunoregulatory Effects of IL-10 and TGF-β on Humoral Immunity

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Background/Purpose: We have previously identified $CD4^{+}CD25^{-}Foxp3^{-}$ regulatory T cells (Treg) that characteristically express lymphocyte-activation gene 3 (LAG3) produce IL-10. Recently we reported that these Treg regulate humoral immunity and ameliorate lupus pathologies in MRL/*lpr*mice with producing large amounts of TGF-β3. However, the immunological significance of the co-existence of IL-10 and TGF-β3 has not been elucidated. Here we examined the synergistic role of IL-10 and TGF-β3 in the control of lupus pathogenesis.

Methods: *In vivo*, 4-hydroxy-3-nitrophenylacetyl (NP)- keyhole limpet hemocyanin (KLH) immunized C57BL/6 mice were intravenously injected with plasmid pCAGGS-Mock, pCAGGS-Il10, pCAGGS-Tgfb1, or pCAGGS-Tgfb3 vectors. NP-specific antibody titers were quantified by ELISA. Lupus-prone MRL/*lpr* mice were also injected with each pCAGGS-Mock, pCAGGS-Tgfb1, or pCAGGS-Tgfb3 vectors and comparative analyses of splenomegaly, autoantibody production, and renal pathology were conducted. *In vitro*, B cells stimulated with lipopolysaccharides (LPS) were cultured in the presence or absence of IL-10 and TGF-β3, and the proliferation and antibody production were assessed. Further, the comprehensive gene expression analyses by next generation sequencing (NGS) analysis and immunoblotting in each condition were conducted.

Results: NP-specific IgG antibody titer was significantly suppressed in NP-KLH immunized mice only in cases with simultaneous administration of pCAGGS-Il10 and pCAGGS-Tgfb3. In MRL/*lpr* mice whose serum IL-10 levels were quite higher than MRL/+ mice, not pCAGGS-Tgfb1, but pCAGGS-Tgfb3 ameliorated lupus-like phenotypes, such as splenomegaly, glomerulonephritis, and anti-dsDNA antibody production. In *in vitro*experiments, although LPS stimulated B cells either with IL-10 or TGF-β3 enhanced the proliferation and antibody production, conversely, the simultaneous addition of IL-10 and TGF-β3 suppressed them. Hierarchical clustering of NGS data revealed that the genes of "stimulated B cells with IL-10 and TGF-β3" and "no stimulated B cells", but not "stimulated B cells either with IL-10 or TGF-β3", located within the same cluster. Immunoblot analyses confirmed the specific down-regulation of mammalian target of rapamycin (mTOR) target molecules in "stimulated B cells with IL-10 and TGF-β3".

Conclusion: We revealed that IL-10 and TGF-β3 synergistically suppressed humoral immune responses through suppressing mTOR signaling. Also, in lupus pathology, TGF-β3 exhibited the superior therapeutic effects compared to TGF-β1. The combination of IL-10 and TGF-β, especially TGF-β3, could be a novel therapeutic approach to systemic autoimmune diseases including lupus.

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Abstract Number: 1092

Expansion of Age Associated B Cells in Murine Lupus Is Regulated By DEF6 and Its Homologue Swap-70

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Background/Purpose: Age-associated B cells (ABCs) are a novel B cell subset, which expresses CD11c and preferentially accumulates with age in female mice. Increased expansion of ABCs has also been observed in some autoimmune-prone mice. ABC differentiation is promoted by T cell help and TLR7 stimulation. Although the generation of ABCs is known to rely on the transcription factor T-bet, the molecular mechanisms regulating this novel B cell subset are poorly understood. Our laboratory previously identified a protein termed

DEF6, which shows significant homology to only one other protein, SWAP-70. Notably, the human DEF6 locus has recently been identified as a new SLE risk variant and mice deficient in both DEF6 and SWAP-70 (DKO mice) spontaneously develop a lupus-like disease on a C57BL/6 background. Similarly to human SLE, the lupus-like disorder in DKO mice preferentially affects the female sex. Autoimmunity in DKO mice is characterized by a number of T cell abnormalities including accumulation of T_{FH} cells and increased IL-21 production. Here we have investigated whether DEF6 and SWAP-70 regulate the ABC subset.

Methods: Presence of $CD11c^+CD11b^+B220^+CD19^+$ B cells (ABCs) was evaluated by FACS in WT and DKO mice as well as in DKO mice concomitantly lacking either IL-21 or SAP. ABCs were FACS-sorted from spleens and stimulated *in vitro* with TLR7 ligands or generated *in vitro* by culturing $CD23^+$ follicular B cells with aIgM, aCD40, and IL-21±TLR7 ligands. ABC markers and gene expression were analyzed by FACS, qPCR and western blot.

Results: We have found that DKO mice exhibit a marked accumulation of ABCs in the spleen but not in the draining lymph nodes or bone marrow. ABC expansion was higher in DKO female mice as compared to DKO male mice. ABC expansion in DKO mice was dependent on both DEF6 and SWAP-70 since mice lacking only DEF6 or only SWAP-70 did not show accumulation of ABCs. Expansion of ABCs in DKO mice was dependent on both IL-21 and T-B cell interactions as demonstrated by a significant reduction of ABCs in DKO mice concomitantly lacking either IL-21 or SAP. *In vitro* stimulation of $CD23^+$ B cells with aBCR, aCD40, +/- IL-21, furthermore, demonstrated increased frequencies of $CD11c^+CD11b^+Tbet^+$ ABCs from DKO B cells stimulated with IL-21. FACS-sorted ABCs from DKO mice stimulated *in vitro* with TLR7 ligands produced high levels of IgG2a/c anti-dsDNA autoantibodies compared to follicular B cells, confirming that ABCs are capable of producing autoantibodies.

Conclusion: Our study demonstrate that the absence of DEF6, a genetic risk factor for lupus, leads to the aberrant expansion of ABCs, a novel B cell subset previously associated with the development of autoimmunity. We also show that accumulation of ABCs in murine lupus is dependent on T-B cell interactions and IL-21. Finally, we demonstrate that ABCs may contribute to SLE pathogenesis by producing high levels of anti-dsDNA IgG2a/c antibodies.

Disclosure: M. Manni, None; **S. Gupta**, None; **E. Ricker**, None; **Y. Chinenov**, None; **R. Jessberger**, None; **A. B. Pernis**, None.

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Abstract Number: 1093

DNA Methylation Defines Joint Specific Differences in Synovial Fibroblasts from OA and RA Patients

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Background/Purpose: Recent studies revealed epigenetic changes in DNA methylation associated with rheumatoid arthritis (RA) synovial fibroblasts (SF). In addition, we have shown that SF exhibit large anatomic differences in their epigenome, transcriptome and function. Here, we investigated the role of DNA methylation in the regulation of joint specific gene expression.

Methods: RNA and DNA were isolated from cultured SF obtained from hands (n= 1 OA/4 RA), shoulders (n = 3 OA/4 RA) and knees (n = 1 OA/4 RA) of RA and OA patients. RNA sequencing (Illumina HiSeq2000) of SF was used to identify differentially expressed genes (n=3 for each joint and condition). DNA from the same samples was subjected to the Illumina HumanMethylation 450 array. After quality control, we calculated differentially methylated CpG sites and islands using the COHCAP Bioconductor package (version 3.3) in R statistical program.

Results: We compared the methylation profile of the following joints shoulder-hand, knee-hand and knee-shoulder. The analysis identified 66, 32 and 64 differentially methylated CpG sites, respectively (methylated beta > 0.7 and unmethylated beta <0.3, $p<0.05$, FDR <0.05). Principal component analysis showed clustering of samples in relation to the joint localization. In detail, we found 40 CpG sites to be

hypomethylated and 26 hypermethylated in hand compared to shoulder SF. Of these, 13 and 6 CpG sites were hypomethylated on the CpG island of lncRNAs HOXA11AS and LOC145845. 8 hypermethylated CpG sites were found on the CpG island of MEIS1 in hand. In hand versus knee SF 28 CpG sites were hypomethylated and 4 hypermethylated. Of these, 5 CpG sites were hypomethylated on the gene body of the lncRNA HOTAIR and 4 CpG sites along the region of HOXC6, C5, C4 genes in hand. Last, we compared SF of shoulders versus knees and identified 51 hypomethylated and 13 hypermethylated CpG sites. Of these, 4 CpG sites were hypomethylated on the CpG island of HAND2 and 5 hypomethylated CpG sites were spread along the MEIS1 gene body in shoulders. Functional annotation analysis revealed that the majority of differential methylated genes are associated with limb development. The grade of DNA methylation matched the expression of most but not all differentially methylated genes, pointing to other regulating mechanisms of joint specific transcription. HOXA11-AS was higher (log2 ratio 2.89, $p=1.18x10^{-23}$) and MEIS1 lower expressed in hand than in shoulder SF (log2 ratio -1.63, $p=2.77x10^{-21}$). Expression of LOC145845 was not detectable. HOTAIR and HOXC6, C5, C4 were however overexpressed in knee compared to hand SF (log2 ratios 5.85, 3.04, 3.23, 3.08, $p<5.6x10^{-21}$). Expression of HAND2 (log2 ratio 3.13, $p=3.53x10^{-8}$) and also MEIS1 (log2 ratio 0.94, $p=1.52x10^{-5}$) was increased in shoulder compared to knee SF.

Conclusion: We show that DNA methylation regulates the expression of genes in a joint specific manner. These results point towards a fundamental role of epigenetics in maintaining location specific identities in joint stromal cells. We suggest that these joint specific differences in gene expression mediate the occurrence of distinct patterns of joint involvement in the development of arthritides.

Disclosure: E. Karouzakis, None; **M. Frank Bertoncelj**, None; **K. Klein**, None; **C. Kolling**, None; **R. E. Gay**, None; **S. Gay**, None; **C. Ospelt**, None.

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Abstract Number: 1094

A Dual Role of Bromodomain Containing 1 Protein in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: Bromodomain proteins (BRD) contain conserved acetyl-lysine binding domains that specifically recognize ε-N-lysine acetylation motifs, a key event in the reading process of epigenetic marks. We have identified a single nucleotide polymorphism in the BRD1 locus that is associated with the progression of joint destruction in rheumatoid arthritis (RA) in stage-I of a genome-wide association study (Knevel et al., Ann Rheum Dis. 2014). In the current study we investigated the role of BRD1 in the regulation of gene expression levels and functional properties in rheumatoid arthritis synovial fibroblasts (RASF).

Methods: RASF (n=8-10) were transfected with siRNAs targeting BRD1, or scrambled siRNAs as a control. 24 hours later cells were stimulated with TNFα (10 ng/ml), IL1β (1 ng/ml), or the Toll-like receptor (TLR) 2 agonist Pam3 (100 ng/ml), the TLR3 agonist pIC (10 µg/ml) or the TLR4 agonist LPS (100 ng/ml). Knockdown of BRD1 was verified by quantitative RT-PCR and Western blotting. Expression levels and secretion rates into cell culture supernatants of MMP1, MMP3, IL6 and IL8 were evaluated by RT-PCR and ELISA, respectively. The enrichment of histone 3 (H3) lysine 14 acetylation (H3K14ac) levels, a histone mark associated with BRD1 function (Mishima et al., Blood, 2011), in promoter regions of MMPs, IL6 and IL8 were determined by Chromatin Immunoprecipitation (ChIP, n=4) and analyzed relative to input DNA. Proliferation (n=6) properties of RASF after silencing of BRD1 were analyzed using an impedance-based system for real-time cell-based proliferation and adhesion (xCELLigence System) in presence and absence of TNFα.

Results: Silencing of BRD1 increased the TNFα and LPS-induced secretion rates of MMP3 (TNFα $p<0.01$, LPS $p=0.056$), IL8 (TNFα $p<0.01$, LPS $p<0.01$) as well as LPS-induced levels of IL6 ($p<0.01$). In contrast, basal MMP1 ($p<0.05$) secretion levels were decreased by BRD1 silencing. Similar results were obtained on mRNA levels. After stimulation of RASF with other inflammatory stimuli silencing of BRD1 had no effect on secretion rates of MMP1, MMP3, IL6 and IL8. ChIP analysis showed no differences in H3K14ac levels in TNFα treated compared to untreated RASF in promoter regions of MMP1, MMP3, IL6 and IL8. However, we detected strongly reduced levels of total histone 3 (H3) levels in IL6 and IL8 ($p<0.05$) but not MMP promoter regions after TNFα stimulation, indicating that histone eviction is

involved in the cytokine response induced by TNFα. Furthermore, silencing of BRD1 reduced proliferation rates ($p<0.05$) and increased the doubling time ($p<0.05$) of RASF both in presence and absence of TNFα without changing the adhesion properties of RASF towards plastic.

Conclusion: Our results demonstrate that BRD1 has a dual role in RASF by inducing proliferation rates but limiting expression levels of matrix degrading enzymes and cytokines specifically in TNFα and LPS-induced pathways. The anti-inflammatory role of BRD1 should be kept in mind in the drug development of bromodomain inhibitors. **Acknowledgements:** IMI-BT Cure (Pfizer), IAR Epalinges, euroTEAM, EMDO Stiftung, Novartis Stiftung, Jubiläumsstiftung

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Abstract Number: 1095

Periarticular Bone Loss in Arthritis Is Induced By Autoantibodies Against Citrullinated Vimentin

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Background/Purpose: Periarticular bone loss is a long known and early but yet insufficiently understood phenomenon in patients with rheumatoid arthritis. This study investigated whether autoimmunity against citrullinated proteins is causally involved in triggering focal trabecular bone loss by modifying a standard experimental model of periarticular bone loss in the context of arthritis.

Methods: Antigen induced arthritis (AIA) was induced by methylated bovine serum albumin (mBSA) and modified by mutated citrullinated vimentin (MCV). Periarticular bone loss, subchondral osteoclastogenesis as well as expression of PAD enzyme, bone associated genes and cytokines, were assessed after arthritis induction. Immune cell and osteoclast precursor infiltration were detected in the periarticular bone marrow and the local lymph nodes. In addition, periarticular bone loss was assessed upon challenge of mice with anti-MCV antibodies.

Results: Despite inducing a milder form of arthritis than mBSA, MCV triggered significant periarticular bone loss associated with an increased infiltration of osteoclast precursors and mature osteoclasts in the periarticular bone marrow. MCV enhanced the expression of the osteoclast inducers RANKL and MCSF, the cytokines IL-8, IL-1, IL-6 and TNF-α as well as PAD2 and PAD4 enzymes in the focal bone marrow. In addition, also anti-MCV antibody challenge induced significant periarticular bone loss and osteoclastogenesis in the bone marrow of mice.

Conclusion: Autoimmunity against citrullinated vimentin triggers periarticular bone loss by osteoclast activation in the bone marrow. These findings may explain why periarticular bone loss is already found very early in the disease course of rheumatoid arthritis patients.

Disclosure: C. Engdahl, None; **H. Bang**, Orgentec Diagnostika, 3; **K. Dietel**, None; **S. C. Lang**, None; **U. Harre**, None; **G. Schett**, None.

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Abstract Number: 1096

Augmentation of Wnt Signaling By IL-1β in Fibroblast-like Synoviocytes

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Background/Purpose: Wnt family proteins canonically stabilize β-catenin to activate T-cell factor (TCF) for the transcription of several genes, including *Runx2*, which is important for osteoblastogenesis. *Wnt* transcripts are highly expressed in RA synovia (Am J Pathol. 2005; 167: 97–105), suggesting the role of Wnt signaling in bone metabolism during articular disease development. Interestingly, fibroblast-like synoviocytes (FLS) also produce remarkable amount of Dickkopf1 (DKK1), a soluble protein that blocks Wnt pathway. Therefore, FLS have both positive and negative effects on Wnt signal activation. It is plausible that a change in WNT and DKK1 expression can affect the strength of Wnt signaling and regulate bone metabolism and joint destruction in articular diseases. In this study, we aimed to determine the cytokines that regulate Wnt signaling in FLS.

Methods: The mRNA expression levels of *Wnt1*, *2*, *3*, *3a*, *4*, *5a*, *5b*, *7b*, *8b*, *10A*, *10B*, *11*, *DKK1*, and *Runx2* in FLS were quantified by SYBR green real-time PCR after treatment with cytokines (TNFα, IL-1β, IL-6, IL-17, and IFNγ). Activity of Wnt pathway was assessed by luciferase assay using TCF reporter plasmid, which was transfected to U2OS, an osteosarcoma cell line that lacks DKK1 expression. The concentration of DKK1 in the culture media was measured by ELISA. Anti-DKK1 antibodies were used to neutralize DKK1 in FLS culture medium.

Results: FLS expresses mRNA of *Wnt2*, *3*, *4*, *5A*, *5B*, *7B*, *8B 10A*, *10B*, *11*, and *DKK1*. DKK1 secreted by FLS was functional, as it blocked the activation of TCF luciferase activity induced by recombinant Wnt3a, and was effectively blocked by anti-DKK1 antibody. TNFα and IL-6 induced *Wnt2*, *4,* and *Wnt4* mRNA levels in FLS, respectively, whereas, IL-1β increased *Wnt2*, *5A*, *7B*, *10A*, *10B*, and *11* mRNA levels. Importantly, IL-1β dampened *DKK1* mRNA expression in FLS, but TNFα and IL-6 did not alter its expression. Consistent with these results, luciferase activity was induced by the supernatant of FLS treated with IL-1β, but not with other cytokines. In addition, *Runx2* mRNA expression in FLS was induced by only IL-1β.

Conclusion: Our data indicates that IL-1β has the highest potential to enhance Wnt signaling, among the tested cytokines. It is already known that IL-1β induces phosphorylation of glycogen synthase kinase-3β for the activation of transcriptional factor TCF. Our findings demonstrate that IL-1β also activates the canonical Wnt signaling pathway by changing the expression pattern of Wnt family proteins and DKK1 in FLS. It is suggested that IL-1β, but not the other cytokines, changes the gene expression pattern of Wnt family and DKK1 in FLS to up-regulate Wnt signaling in the joint during aberrant bone formation.

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Abstract Number: 1097

Tankyrase Regulates Osteoclastogenesis Via SH3BP2

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Background/Purpose: Tankyrase is a poly (ADP-ribose) polymerase that leads to ubiquitination and degradation of target proteins. Axin, a regulatory protein of Wnt/β-catenin signaling, is one of the target proteins of tankyrase, therefore tankyrase inhibitors function as a Wnt/β-

catenin inhibitor. Tankyrase has recently been reported to degrade an adaptor protein SH3BP2 (SH3 domain-binding protein 2). We have previously reported that SH3BP2 gain-of-function mutation in murine bone marrow-derived macrophages enhances RANKL-induced osteoclastogenesis. Though the interaction between tankyrase and SH3BP2 has been reported, it is not fully elucidated whether tankyrase is involved in osteoclastogenesis. In this study, we investigated the role of tankyrase in bone metabolism.

Methods: Primary murine bone marrow-derived macrophages and murine preosteoclastic RAW264.7 cells were treated with RANKL in the presence of tankyrase inhibitors (IWR1 or XAV-939) and Wnt inhibitors (ICG001 or IWP2). Osteoclasts were visualized by a tartrate-resistant acid phosphatase (TRAP) staining, and TRAP-positive multinucleated cells (TRAP+ MNCs) were counted as osteoclasts. Expression levels of osteoclast-associated genes (*Cathepsine K, Oscar, Acp5 and Dc-stamp*) were measured by quantitative PCR analysis. Osteoclastic function was assessed by resorption assay. To determine the intracellular mechanisms, protein expression patterns of SH3BP2, NFATc1, and Syk were examined by western blotting.

Results: Both IWR1 and XAV-939 enhanced RANKL-induced TRAP+ MNCs formation, osteoclast-associated genes expression, and mineral resorbing activity. SH3BP2 protein levels were elevated in cells treated with tankyrase inhibitors but not with Wnt inhibitors. Tankyrase inhibitors significantly augmented nuclear localization of NFATc1 and phosphorylation of Syk in response to RANKL. Finally, FK506, an NFATc1 inhibitor, fully abolished the promoting effect of tankyrase inhibitors on osteoclast formation.

Conclusion: These findings suggest that the inhibition of tankyrase enhances osteoclastogenesis through activating Syk and NFATc1 via elevated SH3BP2 expression. Our findings highlight the undetermined effect of tankyrase inhibition in addition to its suppressive effect on Wnt/β-catenin signaling. Modulating tankyrase activity could be a novel therapeutic option of bone destructive diseases including osteoporosis and rheumatoid arthritis.

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Abstract Number: 1098

ZCCHC6/TUT7 Negatively Regulates Osterix Activity and Influences Osteoblast-Mediated Regulation of Osteoclastogenesis

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Background/Purpose: Mechanisms associated with intrinsic mRNA regulation are important players in development and disease processes. The terminal uridylyl transferases (TUT) are a family of enzymes involved in the regulation of mRNA turnover and apoptosis-mediated global mRNA decay. However, their role in skeletal homeostasis has not been explored. In this study, we investigated the role of ZCCHC6/ TUT7 in osteogenesis and bone homeostasis in mice.

Methods: RNA and protein expression were analyzed using SYBR green-based qPCR and Western blotting respectively. Osteoblasts (OB) and osteoclasts (OC) were generated following our published protocols. TUT7KO mice were generated by gene targeting and their skeletal phenotype was characterized using DXA, mCT, histology and histochemistry. Osteocalcin (OCN), OPG and RANKL were quantified by ELISA. Promoter activity was assessed by Luciferase assays.

Results: TUT7 showed an age-dependent differential pattern of expression in osseous tissues with expression being high in calvaria and

long bones of newborn mice which declined with aging. Next, we generated TUT7KO mice and characterized their skeletal phenotype. Deletion of TUT7 was not lethal and neonatal TUT7KO mice developed normal similiar to wildtype (WT) littermates. However, at 8 weeks of age TUT7KO mice showed significantly increased bone mass compared to WT as determined by DEXA, mCT, and histomorphometric analyses. Serum analyses revealed an increase in OCN and OPG levels as well as a decrease in RANKL suggesting an overall increase in bone mass. *Ex vivo* analysis of bone marrow derived osteoprogenitor cells and primary calvarial OBs from TUT7KO mice demonstrated increased matrix mineralization as shown by von Kossa staining. These data suggest that TUT7 plays an important role in OB function. Interestingly, osteoclasts derived from TUT7KO mice showed no significant difference in differentiation and function as determined by TRAP staining and osteoclast activity assay. Co-culture of osteoblast and osteoclast precursors from WT and TUT7KO mice revealed that TUT7KO osteoblasts inhibited the generation of TRAP positive osteoclasts. This suggests that the role of TUT7 in bone homeostasis is predominantly mediated by the osteoblasts. Expression analyses of genes known to be important in osteogenesis showed that constitutive expression of master transcription factor osterix (Osx) was significantly upregulated in OB derived from TUT7KO mice compared to OB derived from WT littermates. Importantly genes known to be regulated by Osx were also expressed at significantly higher levels in OB derived from TUT7 KO mice. Regulation of Osx activity by TUT7 was demonstrated using an Osx reporter activity assay and inhibition of the promoter activity by overexpression of TUT7 in OB derived from TUT7 KO mice.

Conclusion: Overall, our data demonstrate that TUT7 is a negative regulator of bone formation through suppression of Osx activity in OB and influencing osteoblast-mediated regulation of osteoclastogenesis. This study is the first to demonstrate the role of TUT7 in bone formation and identifies a potential target for therapeutic interventions.

Disclosure: G. Sondag, None; **M. Khan**, None; **M. Ansari**, None; **N. Hussein**, None; **S. Haynie**, None; **F. Safadi**, None; **T. M. Haqqi**, None.

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Abstract Number: 1099

Synovial Exosomes Induce Osteoclast Differentiation in Rheumatoid arthritis

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Background/Purpose: Exosomes are small membrane vesicles (40-150 nm) of endocytic origin secreted by many types of cells and engage in cell-to-cell communication by transferring proteins, microRNAs, mRNA, and lipid to recipient cells. Exosomes are also identified in various biological fluids including blood, urine, amniotic fluid, saliva, malignant ascites, and synovial fluid. We investigated the effect of synovial exosomes on osteoclast differentiation in inflammatory arthritis.

Methods: Synovial exosomes were isolated from SF of rheumatoid arthritis (RA, n=16), ankylosing spondylitis (AS, n=7), gout (n=9), and osteoarthritis (OA, n=8) patients. The size and morphology of synovial exosomes was evaluated by transmission electron microscopy. The number of synovial exosomes was assessed by acetylcholinesterase activity and CD81-ELISA. Monocytes isolated from healthy peripheral blood mononuclear cells (PBMCs) were differentiated into macrophages by treatment of macrophage colony-stimulating factor (M-CSF). Then, macrophages were incubated with synovial exosomes without M-CSF and receptor activator of nuclear factor kappa-B ligand (RANKL). Cell proliferation was determined using cell counting kit-8 assay. Osteoclast differentiation was evaluated by tartrate resistant acid phosphatase (TRAP) stain. Cellular uptake of CFSE-labeled exosomes was analyzed by confocal microscopy.

Results: The size of synovial exosomes ranged from 20 to 150 nm. The number of exosomes in the same volume of synovial fluid was higher in SF of RA ($p=0.0235$), AS ($p=0.0135$), and gout ($p=0.2245$) patients compared to OA patients. Exosomes from RA ($p=0.8639$), AS ($p=0.0823$), or gout ($p=0.2571$) SF induced higher macrophage proliferation compared to those from OA SF but the difference was not significant. Exosomes from RA or AS SF induced osteoclastogenesis in the absence of M-CSF and RANKL. Osteoclast formation was

significantly increased in the presence of RA (p=0.01) exosomes compared to OA exosomes, but not in AS or gout. Synovial exosomes labeled with CFSE were internalized by macrophage and enriched in perinuclear space.

Conclusion: The number of exosomes was increased in SF of RA and AS compared to OA. Exosomes from SF of RA induced osteoclast differentiation.

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Abstract Number: 1100

Tenofovir, a Nucleoside Analog Reverse Transcriptase Inhibitor for Treatment of HIV, Promotes Osteoclast Differentiation and Decreases Osteoblast Formation By a Mechanism Depending on ATP Release and Adenosine

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Background/Purpose: Human Immunodeficiency Virus (HIV) infection devastates the immune system but also affects tissues and organs such as kidney, liver, central nervous system, heart and bone. Bone alterations have been observed in HIV disease for nearly two decades, in particular a higher risk of low bone mineral density (BMD) and fragility fractures. Treatment of patients with tenofovir alone or in combination (as part of HAART), leads to changes in bone catabolism markers and significant reductions in BMD in children and young adults. Tenofovir is taken up by cells and phosphorylated; tenofovir-phosphate inhibits HIV-reverse transcriptase by mimicking AMP. We have recently found that tenofovir inhibits Pannexin-1/Connexin-43-mediated ATP release from cells and decreases extracellular adenosine levels and fibrosis in murine models. As adenosine and ATP are key regulators of bone homeostasis, we determined whether tenofovir directly affects bone by an adenosine- or ATP-dependent mechanism.

Methods: M-CSF/RANKL-induced osteoclast (OC) and stimulated osteoblast (OB) differentiation were studied in primary murine bone marrow culture as the number of TRAP-positive or Alizarin Red-positive cells, respectively, after challenge with tenofovir (1nM-100mM) alone or in combination with dipyridamole (1nM-100mM), an agent that increases extracellular adenosine by blocking cellular adenosine uptake. Pannexin-1 and Connexin-43 expression were permanently knocked down by lentiviral infection with appropriate shRNA or scrambled shRNA and these cells were induced to differentiate into OC by RANKL. Male C57Bl/6 (WT), A2AKO and A2BKO mice received tenofovir 75mg/Kg/day for 4 weeks. Double labelling of bone with calcein (15mg/Kg)/Alizarin Red (30mg/Kg) was performed and long bones prepared for mCT and histology.

Results: There was a dose-dependent increase in OC differentiation after treatment with Tenofovir (EC50=44.5nM), that was reversed by dipyridamole (IC50=0.3μM). Moreover, tenofovir inhibited OB differentiation (IC50=0.4μM) which was also reversed by dipyridamole (EC50=10nM). When both Pannexin-1 and Connexin-43 were absent, tenofovir did not increase OC number. Tenofovir treatment reduced bone formation in WT-mice (49±8μm vs 110±7μm untreated $p<0.0005$) but not in A2AKO (72±6μm vs 71±5μm untreated, p=ns) and A2BKO mice (64±8μm vs 86±9μm untreated, p=ns). mCT revealed decreased BMD and both cortical and trabecular bones were affected. TRAP-staining showed increased OCs *in vivo* in tenofovir-treated WT mice (21±1 vs 16±1 OC/hpf in untreated, $p<0.005$). There are increased osteoclasts in A2AKO mice and this was unaffected by tenofovir treatment (24±1 OC/hpf, vs 22±1 OC/hpf in untreated p=ns) and osteoclast number in A2BKO mice was unchanged (19±1 OC/hpf, vs 18±1 OC/hpf in untreated, p=ns). Similar results were obtained for Cathepsin K.

Conclusion: These results indicate that tenofovir enhances osteoclast differentiation and inhibits osteoblast differentiation by an

adenosine-dependent mechanism and suggests that treatment with agents that increase local adenosine concentrations, like dipyridamole, might prevent bone loss following tenofovir treatment.

Disclosure: A. Mediero, CP15/0053, 2, 9,Patent for the use of adenosine A2AR agonists to prevent prosthesis loosening. Patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **P. Llamas**, None; **S. Portal-Nuñez**, None; **R. Largo**, None; **G. Herrero-Beaumont**, None; **B. Cronstein**, Canfite Pharma, 1,Celgene, AstraZeneca, Takeda, 2,Revive Therapeutics, 5,Always hopeful, 9.

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Adalimumab:TNF Complexes Induce a Divergent Proteomic Profile in Human Osteoclast Precursors to That Resembling a Monocytic Cell

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Background/Purpose: TNF has been shown to contribute to osteoclastogenesis independently and in conjunction with M-CSF or RANKL, two key cytokines involved in osteoclast (OC) development. We have previously demonstrated that TNF enhances the kinetics of RANKL-induced human osteoclastogenesis and that its effects are mitigated more effectively by the anti-TNF biologic adalimumab (ADA) as compared to etanercept (ETN). To determine the mechanism responsible for the difference in effectiveness between the two biologics, a label-free quantitative proteomics study was conducted on TNF-activated human OC upon biologic treatment using an EASY Nano LC1000/ QExactive Plus LC/MS system.

Methods: Human OC precursors (OCP) were exposed for up to 5 days to M-CSF, M-CSF+RANKL (RANKL) alone or in combination with 100 ng/mL TNF +/- 5 ug/mL ADA, ETN or human IgG1 (IGG) as a pre-formed complex. OC differentiation was confirmed by measuring tartrate-resistant acid phosphatase 5b (TRAP 5b) activity. Peptides from cell lysates were generated using modified Filter Aid Sample Preparation. Sample pooling (sham) was used to minimize false discovery by applying a cut off value (ratio >150% or <66.7%) based on reproducibility between sham samples. Data was analyzed with a 3 database search algorithm through Proteome Discoverer (PD) 2.0 and a 4th algorithm using MaxQuant. Protein IDs were aggregated in Scaffold software. Relative quantification was achieved using precursor ion area extraction function within PD. Data is expressed as percentage based on ratio of ion counts of each condition to that of RANKL with differences considered significant if >150% only for proteins whose percentage between TNF and IGG conditions are similar. Flow cytometry analysis for monocyte-related markers was performed on day 4 OCP cultures.

Results: Ten OC-related proteins were identified (e.g. OSTF1, NFATC1, ACP5, CTSK, MMP9, TCIRG1, ATP6V0D2), 5 of which (underlined) were induced by TNF (>161%), decreased by ADA (<77%), but unaffected by ETN. Overall, TNF upregulated the levels of 110 proteins as compared to RANKL. A greater proportion of these proteins had levels reduced following ADA treatment as compared to ETN (69% and 20%, respectively) concordant with a greater reduction in OC maturation with ADA as to that of ETN (TRAP 5b levels of 11 and 40U/L, respectively). In addition to lowering TNF-induced protein levels concordant with neutralization by ADA, we observed indications for OCP development toward an alternative myeloid lineage based on its >1.5-fold induction of 25 proteins that are typically expressed in monocytic cells (e.g. PSMB9, DPP7 & IFI30) including 2 proteins reportedly shown to negatively regulate OC development (LGMN & ZFAND5). Moreover, several monocyte-related markers (CD14, CD163 & CD206) were increased by the ADA:TNF complex as compared to RANKL based on flow cytometry.

Conclusion: Our *in vitro* findings demonstrate that ADA treatment, unlike exposure to ETN, dramatically reduces the TNF-induced protein levels in human OC and moreover, that the ADA:TNF complex may potentially alter their proteome to a profile resembling that of a monocytic cell through an increase in negative regulators of OC development.

Disclosure: B. P. Harvey, AbbVie, Inc, 3,AbbVie, Inc., 1; **C. Hu**, AbbVie, Inc., 3,AbbVie, Inc., 1; **D. Wang**, AbbVie, Inc., 3,AbbVie, Inc., 1; **Y. Tian**, AbbVie, Inc., 3,AbbVie, Inc., 1; **Z. Kaymakcalan**, AbbVie, Inc., 3,AbbVie, Inc., 1.

Abstract Number: 1102

Differentiation of Spongiosa-Derived Mesenchymal Stromal Cells from Osteoporosis and Osteoarthritis Patients Are Influenced By Adipokines

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Background/Purpose: Osteoporosis is characterized by bone loss, increased fracture risk and reduced regeneration ability. Age-related bone loss leading to osteoporosis correlates with increased bone marrow fat infiltration and is characterized by an inverse relationship between bone mass and bone marrow adiposity. Bone marrow adipose tissue releases immunmodulatory (e.g. adipokines) and matrix-degrading proteins (e.g. matrix metalloproteinases, MMP) which promote bone loss observed in osteoporosis and osteoarthritis. Bone marrow adipocytes share mesenchymal stem cell (MSC) as precursors with osteoblasts. Therefore, adipocyte-derived factors might influence differentiation of bone marrow-derived MSC and be involved in the shift of differentiation from osteoblasts to adipocytes observed in osteoporosis. The aim was to analyze the presence of adipokines in the bone marrow cavity and their effects on MSC differentiation.

Methods: Spongiosa from femoral heads containing bone marrow were collected (hip replacement of osteoarthritis patients or after osteoporotic femoral neck fracture). Primary spongiosa-derived mesenchymal stromal cells (hMSC) and commercially obtained 'normal' MSC were cultured in adipogenic and osteogenic media 3 weeks with/without adipokines. Adipogenic differentiation was confirmed using Oil Red O staining. Realtime PCR for adipokines, bone marker genes, TIMP, MMP as well as of bone samples was performed. Matrix produced was stained and quantified using Alizarin S. Proinflammatory factors were measured by ELISA.

Results: Visfatin and leptin level were increased in osteoporotic bone (n=14) vs. non-osteoporotic bone (n=13). Visfatin induced the secretion of proinflammatory factors during both, osteogenic and adipogenic differentiation but not leptin or resistin (IL-6, IL-8, MCP-1). While MMP2 was reduced by stimulation of all adipokines during osteogenesis (n=3), visfatin reduced MMP13 expression during osteogenic differentiation (e.g. day 21: -55-fold) as well as TIMP1, -2 and RunX2 (e.g. day 21: -2.86-fold) / -3.17-fold / -5.85-fold, respectively) while leptin and resistin did not affect these parameters. Visfatin significantly increased matrix production during osteogenic differentiation. During adipogenesis, visfatin but not leptin or resistin stimulation of hMSC significantly increased MMP13 (e.g. day 21: 72-fold).

Conclusion: Visfatin and leptin were increased and resistin reduced in osteoporotic bone. MMP production was specifically reduced by visfatin during adipogenesis. Therefore, visfatin might promote bone destruction during increased adipogenic differentiation in osteoporosis. Of note, the shift towards osteogenic differentiation may be beneficial as visfatin appears to reduce MMP production during osteogenesis. Leptin had no direct effects on MSC differentiation *in vitro,* but could indirectly modulate bone degradation by affecting inflammatory cells.

Disclosure: L. Tsiklauri, None; **J. Werner**, None; **K. W. Frommer**, None; **U. Müller-Ladner**, None; **S. Rehart**, None; **S. Wenisch**, None; **E. Neumann**, None.

Abstract Number: 1103

Gingival Tissue-Derived MSC Cells (GMSC) Suppress Osteoclastogenesis and Bone Erosion in Collagen-Induced Arthritis Thought CD73 Signal Pathway

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Background/Purpose: Rheumatoid arthritis (RA) is characterized by chronic inflammatory synovitis leading to joint destruction and systemic bone loss. Osteoclasts are responsible for bone destruction in rheumatoid arthritis (RA). GMSCs have been demonstrated to suppress T cell responses and suppress the progress of experimental collagen induced arthritis model. This study aims to determine whether GMSCs also directly suppress osteoclastogenesis and bone erosion in collagen induced arthritis (CIA).

Methods: Osteoclasts were induced from bone-marrow cells with RANKL and M-CSF stimulation, and assessed with tartrate-resistant acid phosphatase (TRAP) staining. For human cells, osteoclasts were induced from human $CD14^+$cells. GMSCs were isolated from the volunteer donors and were generated understand a standard protocol. GMSCs were added to cultures with different ratios with BM cells. Transwell, antibody or inhibitors blockade experiments were performed to define the mechanisms of action. NF-κB activation as well as RANKL expression was determined by western blot and qRT-PCR. 2×10^6 GMSCs or fibroblast cells were adoptively transferred to DBA1/J mice on day 14 after immunization with CII/CFA. CIA onset and severity were monitored, osteoclast expression and distribution in CIA model was analyzed by TRAP stain, and bone erosion was examined by micro CT scan.

Results: GMSCs but not fibroblast cells markedly suppressed osteoclastogenesis *in vitro* for human and mice. GMSCs injected after immunization and before of onset of CIA significantly suppressed disease development. Treatment with GMSCs dramatically decreased the levels of NF-κB p65/p50 in osteoclasts *in vitro* and P65/50 and RANKL expression by synovial tissues *in vivo*. Blockade of CD73 signal significantly revised the effect of GMSCs on osteoclast formation and bone erosion.

Conclusion: We demonstrate that GMSCs dramatically and directly inhibited NF-kB- and RANKL-mediated osteoclast formation, as well as bone erosion in CIA. Manipulation of GMSCs may have therapeutic effects on rheumatoid arthritis and other bone erosion related diseases.

Disclosure: Y. Zheng, None; **J. Wang**, None; **N. J. Olsen**, Mallinckrodt Pharmaceuticals, 2; **L. Rong**, None; **S. G. Zheng**, None.

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Abstract Number: 1104

Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) As a Potential Topical Treatment for Chronic Tendinopathy

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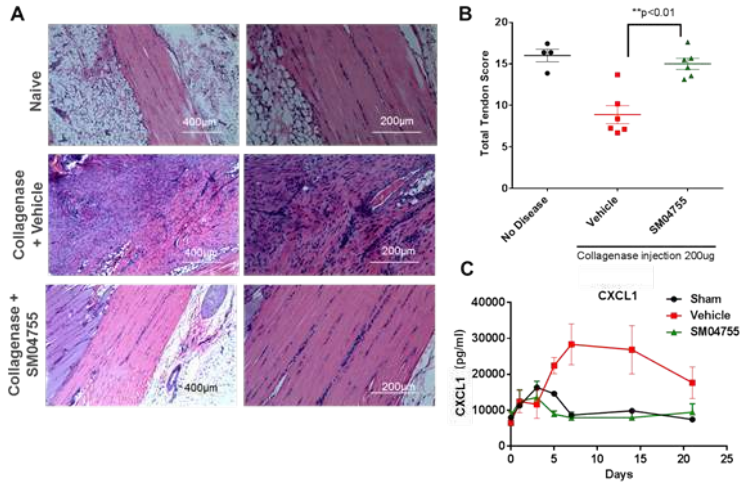
Background/Purpose: Chronic tendinopathy is an inflammatory and degenerative condition caused by injuries or overuse. Current therapeutic options focus on alleviating the symptoms and pain rather than treatment of the underlying causes. The Wnt pathway plays an important role in tenocyte differentiation, and is upregulated in chronic tendinopathy. SM04755, a novel, topical, small-molecule Wnt pathway inhibitor, was evaluated in preclinical studies to determine its potential to inhibit inflammation, reduce fibrosis and increase tenocyte differentiation, thereby promoting tendon healing.

Methods: Wnt pathway inhibition was measured via cell-based reporter assay. Anti-inflammatory activity was evaluated by measuring TNFα and IL-6 secretion using ELISA in lipopolysaccharides (LPS)-stimulated THP-1 monocytes and anti-CD3/anti-CD28-stimulated peripheral blood mononuclear cells (PBMCs). Histological expression of scleraxis A (SCXA), tenomodulin and tenascin C were measured using high-content imaging to evaluate differentiation of human mesenchymal stem cells (hMSCs) to tenocytes. Pharmacokinetics were evaluated by topical application in rats, dogs and mini-pigs, followed by analysis of compound concentrations in tendon and plasma. *In vivo* efficacy of topical SM04755 was evaluated in an intra-tendon collagenase-induced rodent tendinopathy model by scoring (range 5-20) several histological indicators of tendon health. Inflammation in the rodent model was measured by chemokine ligand 1 (CXCL1) levels in plasma by ELISA and other inflammatory markers in the tendon by qPCR. Tendon regeneration was evaluated by qPCR based gene expression of tenocyte differentiation markers- SCXA and tenascin C.

Results: SM04755 demonstrated potent (EC_{50}=152nM) and selective inhibition of Wnt signaling. SM04755 inhibited both LPS and anti-CD3/anti-CD28 induced TNFα and IL6 secretion (EC_{50}=500nM) in THP-1 cells and PBMCs. SM04755 induced differentiation of hMSCs into SCXA, tenomodulin, and tenascin C expressing tenocytes (EC_{50}=200nM). A single topical application of SM04755 resulted in tendon concentrations >EC50 for up to 24hrs, with minimal systemic drug exposure or toxicity. In the collagenase-induced model, SM04755 treatment significantly increased the mean tendon health score ($p<0.01$, n=6), decreased the plasma levels of CXCL1 ($p<0.05$), reduced gene expression of pro-inflammatory markers (IL-6, TNF-a, IL-1b, INF-g, IL-8) ($p<0.05$), and increased expression of SCXA and tenascin C in tendon compared to vehicle.

Conclusion: Topical SM04755 reduced tendon inflammation and an inflammatory marker in plasma, showed evidence of tendon regeneration, and increased tendon health scores compared to vehicle in a rodent tendinopathy model. Plasma exposure and systemic toxicity were minimal. SM04755 demonstrates potential to promote tendon healing in chronic tendinopathy.

Figure. SM04755 inhibited inflammation and promoted tendon healing in a rat collagenase-induced tendinopathy model



Disclosure: V. Deshmukh, Samumed, LLC, 3; **T. Seo**, Samumed, LLC, 3; **M. Ibanez**, Samumed, LLC, 3; **L. Dellamary**, Samumed, LLC, 3; **J. Stewart**, Samumed, LLC, 3; **J. Hood**, Samumed, LLC, 9; **Y. Yazici**, Samumed, LLC, 3.

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Abstract Number: 1105

Bone Metabolism in Rheumatic Diseases May be Affected By Free Fatty Acids

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Background/Purpose: Obesity is associated with an increased risk of osteoarthritis also in non-weight bearing joints and increased amounts of visceral fat are associated with lower bone density. This observation and the association of chronically elevated free fatty acid (FFA) serum levels with a number of inflammatory cardiovascular and metabolic diseases suggest that FFA may also play a role in inflammation-related bone loss. We therefore analyzed the effect of FFA on the central cells of bone metabolism, i.e. osteoblasts and osteoclasts, in the context of rheumatic diseases.

Methods: Primary osteoblasts (OB) were isolated from cancellous bone of OA and RA patients undergoing knee joint surgery. Osteoclasts (OC) were differentiated from peripheral blood mononuclear cells (PBMC). OB and OC were stimulated with the saturated FFA palmitic acid (PA) and the unsaturated FFA linoleic acid (LA). Immunoassays were used to quantify protein secretion. mRNA expression levels were quantified by real-time PCR. Mineralization activity was quantified using Alizarin Red S staining, differentiated OC were quantified by counting TRAP-positive multinuclear cells. Toll-like receptor (TLR) 4 and TLR2 were blocked by neutralizing antibodies.

Results: OB secreted increased amounts of the proinflammatory cytokine IL-6 (up to 9-fold) as well as the chemokines IL-8 (up to 221-fold), GRO-a (from below detection level to detectable levels) and MCP 1 (up to 16-fold) upon stimulation with PA or LA. The degree of response was highly dependent on the patient. RANKL as well as OPG, important regulators of osteoclastogenesis and OC activity, remained unaffected by FFA on protein and mRNA level. OB activity appeared unaffected because alkaline phosphatase (ALP) and collagen type I mRNA expression as well as production of inorganic matrix was not altered. Differentiation markers of OB (e.g. osteocalcin) also remained unchanged after FFA stimulation. PA-induced IL-8 secretion by OB could be significantly reduced by TLR4 blockade (by 93%), while blocking TLR2 had no effect. Secretion of IL-8 by RA OC was increased by FFA, while MMP-9 was reduced. The number of TRAP positive multinuclear cells decreased (by around 50%). However, markers of osteoclast activity (CLCN7, CTSK, TCIRG) remained unchanged at the mRNA level.

Conclusion: Our results clearly suggest a pro-inflammatory effect of certain FFA on osteoblasts and osteoclasts. While this can indirectly contribute to bone loss, the reduced number of mature OC after FFA stimulation suggests an inhibitory effect on bone resorption. The effect of FFA on cells of bone metabolism therefore appears to be divergent. The effects on osteoblasts are at least in part mediated by TLR4, while TLR2 is not involved.

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Abstract Number: 1106

Test of the Spleen Tyrosine Kinase Inhibitor Fostamatinib in a Translational Joint Tissue Model Show Significant Effect on Bone, but Not on Synovial Tissue

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Background/Purpose: The Spleen tyrosine kinase (Syk) inhibitor fostamatinib was not approved as treatment for rheumatoid arthritis (RA) due to insufficient effect on joint structure in the phase III OSKIRA-1 study. Here we use a translational model system to investigate the direct effect of Fostamatinib on the extracellular matrix (ECM) of the target tissues (cartilage, bone, and synovium) for a better understanding of the insufficient effect in joint structure found in OSIKRA-1.

Methods: Human mature osteoclasts (HOC) seeded on bone, bovine cartilage explants (BEX) and human synovial explants (SME) were treated with the active metabolite of Fostamatinib, R406, at 5μM-0.05μM. Osteoclasts were co-stimulated with 25 ng/ml M-CSF and RANKL, while BEX and SME were co-stimulated with TNFα 2 ng/mL and OSM 10 ng/mL (O+T) or TNFα 10 ng/mL, respectively. CTX-1 and Calcium (Ca^{2+}) were measured in conditioned medium (CM) from HOC. Metabolic activity of HOC was assessed with Alamar Blue®. C2M and AGNx1 were measured in CM from BEX, while acMMP3, C1M, and C3M were measured in CM from SME. The biomarkers in BEX and SME CM were measured at 4 time points and the total release were quantified by area under the curve (AUC). CTX-1, C2M, AGNx1, acMMP3, C1M, C2M and C3M were measured with ELISA. $Ca^{2+}$was measured with ADVIA Chemistry system. Statistical differences of metabolic activity was calculated with One-way ANOVA with Dunnett's multiple comparison test. Statistical differences between biomarkers levels or AUC were calculated with Kruskall Wallis test with Dunn's multiple comparision test.

Results: R406 decreased the release of CTX-1 (Fig 1A) and Ca^{2+} in a dose-dependent manner, with a significant decrease at 1μM ($P<0.01$). This might be due to a toxic effect of R406 on HOC (Fig 1B) ($P<0.05$). In cartilage, R406 decreased the total release of C2M and AGNx1 in a dose-dependent manner. C2M was inhibited a concentrations down to 1.25μM ($P=0.034$), and AGNx1 down to 5μM ($P=0.012$). In synovial explants, R406 tended to decrease release of C3M (Fig 1e), C1M and acMMP3 (Fig 1f) at 5μM, but this was not significant.

Conclusion: Serum-based biomarkers of the joint ECM turnover were measured in CM from HOC, cartilage and synovial explant cultures. R406 decreased bone resorption and HOC metabolic activity in a dose-dependent manner, together with the MMP-mediated degradation of type II (C2M) collagen and aggrecanse degradation of aggrecan (AGNx1) in cartilage. However, R406 had limited effect on the inflammation driven MMP-mediated degradation of type I (C1M) and III (C3M) collagen and activation of MMP-3. From these data it is expected that Fostamatinib would have some effect on bone and cartilage, but not on inflammation driven degradation of the synovium.

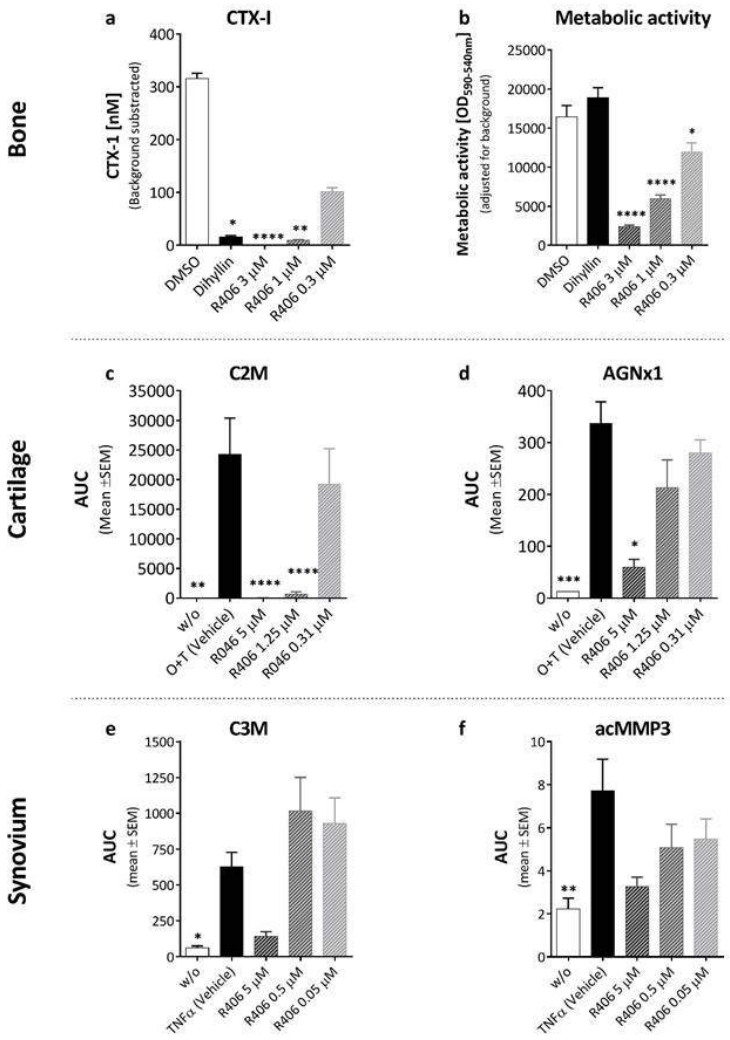

Figure 1

Disclosure: C. F. Kjelgaard-Petersen, None; **A. C. Bay-Jensen**, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2; **T. G. Christiansen**, None; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3; **P. Hägglund**, None; **C. S. Thudium**, Nordic Bioscience A/S, 3.

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Abstract Number: 1107

Combining Scaffold-Free Cartilage Transplants to Controlled Gene Expression for Therapeutic Application in Rheumatic Disorders

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Background/Purpose:

Cartilage destruction is accompanied by a tremendous loss of life quality due to deprivation of agility, flexibility and pain. Additionally, increased catabolic mediators such as inflammatory cytokines, matrix-degrading enzymes or bioenergetic-relevant proteins play a crucial role in the pathogenesis of rheumatic disorders such as OA and RA. However, therapeutic approaches including the cartilage restoration or replacement combined with anti-inflammatory properties are still elusive. Therefore, promising approaches link tissue engineering to gene therapy. To overcome critical challenges such as transient therapeutic effects as well as undesirable long-lasting overexpression of transgenes, several approaches focus on the expression control and optimization of viral vectors applied either directly or by a cell therapeutic approach.

Therefore, we aimed at engineering scaffold-free cartilage transplants (SFCTs) using the transgenic expression of the chondroprotective IL-4 under the control of the cyclooxygenase-2 promoter (pCox-2) being activated by the presence of and inactivated in the absence of inflammatory mediators and co-expressing the green fluorescence protein (GFP).

Methods:

First, the gene therapeutic approach (pCox-2 and IL-4) was tested by transient transfection of primary equine chondrocytes, subsequent activation with IL-1β and TNF-α and detection of inflammatory marker and matrix degrading enzyme gene expression (*IL1B, TNFA, IL6, IL8, COX2* and *MMP1, MMP3*). Secondly, the equine and human sequences of pCox-2 and IL-4 were subcloned into a lentiviral-based GFP-co-expressing vector backbone. Thirdly, to assess the durability of GFP-expression SFCTs were generated from primary chondrocytes, transduced and monitored for up to 4 months. Finally, to simulate OA, SFCTs were stimulated with IL-1β and TNF-α for 3 weeks and cultivated afterwards under non-stimulating conditions to determine the regenerative potential. Subsequently SFCTs were analyzed with regard to the inflammatory marker / matrix degrading enzyme gene expression and histological changes (Collagen I/II).

Results:

Feasibility and functionality of the gene therapeutic approach including the genetic switch was demonstrated by IL-4 mediated inactivation of inflammatory marker gene expression and matrix degrading enzyme gene expression. Generated SFCTs achieved diameters up to 1 cm. GFP-expression within transduced SFCTs was stable for up to 4 months. After stimulation of SFCTs with IL-1β and TNF-α, the inflammatory marker gene expression and matrix degrading enzyme gene expression was increased as compared to the untreated controls. The histological findings showed increased softening and wateriness of the tissue. A histological redistribution of Collagen I and II production could be demonstrated. The observed effects were reversible after 3 weeks of regeneration.

Conclusion:

First results show the feasibility and functionality of the gene therapeutic approach, promising features (stability and integrity) of our new generation cartilage transplants combined with gene therapy where the therapeutic gene will be expressed in a disease responsive way. Further investigations are needed to test and optimize the system.

Disclosure: J. Neuhaus, None; **I. Ponomarev**, None; **F. Buttgereit**, None; **T. Gaber**, None; **A. Lang**, None.

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Abstract Number: 1108

Protein Citrullinations By PAD Enzymes Promote Dendritic Cell Transdifferentiation into Osteoclast and Generate Targets for RA-Specific Antibodies

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Background/Purpose: Immature dendritic cells (DCs) can develop into osteoclasts (OCs), however, the mechanisms regulating this differentiation switch are not yet understood. We have shown that protein citrullination can play important roles in OC differentiation, both at steady state and in rheumatoid arthritis (RA) when anti-citrulline protein antibodies (ACPAs) induce bone erosion through an IL-8 mediated induction of OC development. In the present study we analyzed how protein citrullination and ACPAs regulate differentiation plasticity towards the OC lineage in DCs.

Methods: We have previously shown that the endogenously produced lactic acid (LA), a glycolysis side product, can increase the ability of developing DCs to differentiate into osteoclasts in dense cell cultures, whereas sparse cultures, associated with low LA levels, promoted the development of immunostimulatory DCs with little ability to form OCs. By exploiting this mechanism we generated different monocyte-derived DC types in parallel with macrophages and cultured these cells in presence of M-CSF and RANKL to induce OC development. Mass spectrometry was applied to analyze protein expression and citrullination at different stages of OC differentiation. Activity of peptidylarginine deiminases, the enzymes responsible for protein citrullination, was measured by ELISA, cytokine levels were analyzed using CBA technology. We studied in detail the autocrine effects of IL-8 in OC cultures.

Results: Citrullinated-actin peptides were identified in all stages DC-OC transdifferentiation and citrullinated-vimentin peptides were identified in mature OCs. Expression of PAD2 and PAD4 increased during DC differentiation and PAD activity was detected in both DCs and OCs. Interestingly, the efficiency of DC-OC transdifferentiation correlated with the level of PAD activity and with higher detection of citrullinated peptides in DCs. The PAD inhibitor Cl-Amidine efficiently interfered with OC development form DC precursors. Polyclonal and certain monoclonal ACPAs increased osteoclastogenesis from DCs and the intensity bone resorption. DC-derived OC differentiation was inhibited by Cl-Amidine in the presence of ACPAs. The IL-8 receptors CXCR1 and CXCR2 were present on immature DCs and the increased osteoclastogenesis was associated with elevated IL-8 levels in ACPA-treated cultures. IL-8 neutralization blocked the ACPA-mediated increase of OC development.

Conclusion: Our results indicated that DCs are heterogenic in their ability to form OCs and the differentiation plasticity towards the OC lineage might be influenced by protein citrullination. The increase of LA at sites of immune activation might play an important role in the reprogramming DCs and increasing OC development. Antibodies that target citrullinated proteins and have been suggested to play an improtant pathogenic role in RA-associated bone destruction ACPAs can further increase osteoclastogenesis from DCs through an IL-8 dependent mechanism, which further support OC development in an autocrine manner. Blocking IL-8 and PAD activities represent important therapeutic possibilities that might interfere with DC transdifferentiation into OC and ACPA-induced bone damage.

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Abstract Number: 1109

Targeting IL-8 and CXCR1/2 Abrogates RANKL- and ACPA-Mediated Osteoclastogenesis

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Background/Purpose: Increased circulating levels of Interleukin-8 (IL-8) have been linked to the bone loss associated with breast cancer metastasis. Recently, we have shown that anti-citrullinated protein antibodies (ACPAs) can induce bone loss and pain-like behavior in mice through an IL-8 dependent mechanism. We aimed to further investigate the role of IL-8 and the IL-8 receptor molecules CXCR1 and

CXCR2 in osteoclasts (OC) development in the presence or absence of ACPAs.

Methods: ELISA was used to measure IL-8 in the serum of ACPA-positive patients with arthralgia and seronegative healthy controls and in the synovial fluid of RA and spondylarthropaty patients. Peripheral blood CD14-positive monocytes were used to generate OCs in the presence of M-CSF and RANKL. Expression levels of IL-8 and CXCR1/2 were measured during OCs maturation using ELISA, RT-PCR, flow cytometry and immunostaining. Inhibition of IL-8 and its receptors were performed in OC cultures using IL-8 neutralizing antibodies and small molecule CXCR1 and CXCR2 antagonists (Reparixin, SCH-527123, SB-332235), in the presence or absence of ACPAs. OC numbers were counted using light microscope after TRAP staining. Cytotoxicity was monitored with Cell counting kit 8 (CCK8).

Results: Serum IL-8 levels were significantly higher in the serum of ACPA-positive patients with arthralgia, as compared to ACPA-negative healthy individuals. Synovial fluid of ACPA-positive RA patients contained significantly higher levels of IL-8 as compared to spondyloarthritis patients. Endogenous IL-8 increased gradually in the maturing OC supernatants and exogenous IL-8 dose dependently increased RANKL-mediated OC development. IL-8 neutralizing antibodies inhibited OC differentiation with or without ACPAs. Reparixin and SCH-527123 significantly inhibited the RANKL-mediated osteoclastogenesis at doses as high as 80µM concentration, without inducing detectable toxicity. SB-332235, an inhibitor characterized by higher selectivity towards CXCR2, inhibited OC development at a concentration of 10µM. CXCR1 and CXCR2 expressions were detectable on the cell membrane of macrophages and decreased during OC differentiation. Expression of the CXCR1 and CXCR2 genes in developing OCs was weak and variable. Immunohistochemistry stainings confirmed the cell surface expression of CXCR1, and to a lesser extent of CXCR2, with high amounts of both of these receptors being present intracellularly during OC maturation.

Conclusion: Serum IL-8 is a potential biomarker for ACPA-positive arthralgia and possibly for the bone loss described in these patients. Small molecule CXCR2 antagonists might provide novel therapeutic tools for targeting OCs in RA.

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Abstract Number: 1110

Inactive Rhomboid Family Member 2/Tnfα Convertase/Tnfα Pathway Is Essential to the Pathogenesis of Haemophilic Arthropathy

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Background/Purpose: A major manifestation of Hemophilia A, an X-linked bleeding disorder, is hemophilic arthropathy (HA), a debilitating degenerative joint disease that is caused by intraarticular bleeding. HA typically begins with haemophilic synovitis (HS), hypertrophy of synoviocytes with inflammation of the synovium and a neovascular response, followed by joint erosion and, ultimately, arthropathy with cartilage destruction and erosion of the underlying bone. HS has features in common with inflammatory arthritides such as rheumatoid arthritis (RA). The pro-inflammatory TNFα is a major target for treatment of RA. TNFα is synthesized as a membrane-anchored precursor that is released by the TNFα convertase (TACE, also referred to as ADAM17). We have recently uncovered a crucial role for TACE and its regulator, inactive Rhomboid family member 2 (iRhom2), in the pathogenesis of inflammatory arthritis in mice. Since RA is caused, at least in part, by inappropriate release of TNFα, we hypothesize that iRhom2/TACE/TNFα also have pivotal roles in promoting HA.

Methods: To determine whether blood cells induce TNFα shedding, we exposed macrophages from WT and iRhom2-/- mice to intact and lysed red blood cells (RBC) and measured TNFα in supernatants. We used a joint puncture model in *Fviii-/-*, *Fviii-/-Tnfa-/-*, *Fviii-/-iRhom2-/-* and *Fviii-/-* etanercept-treated mice to simulate intra-articular bleeding. TNFα in the joint was measured on day 2 after puncture, and histological analyses and microCT were performed at 2 weeks.

Results: Treatment of WT macrophages with intact and lysed RBC *in vitro* activated TNFα shedding, but not in macrophages lacking iRhom2. *In vivo* studies of *Fviii-/-* mice subjected to knee joint puncture showed severe hemarthrosis and high elevated levels of TNFα on day 2 and synovial invasion with enhanced neovascularization in the joint space and cortical thickening of bone on day 14 compared to WT. MicroCT analysis showed a significant decrease in trabecular bone volume (-75%±12, n=8 mice), number of trabeculae (-40%% ±10), and a significant increase in trabecular separation (+71%%±35) in the punctured knee compared to the contralateral non-puncture knee. Inactivation of TNFa in *Fviii-/-* mice using TNFα-/-, iRhom2-/- and etanercept-treatment dramatically and significantly ($p<0.01$, n=7-9 per group) reduced the osteopenia in the HA/HS model and improved bone trabecular parameters compared in *Fviii-/-* mice. TRAP staining demonstrated that the bone loss in *Fviii-/-* mice was mainly caused by a local increase in osteoclast number (+132%±63) and osteoclast surface per bone surface which was abrogated in *Fviii-/-Tnfα-/-, Fviii-/-iRhom2-/-* and *Fviii-/-* etanercept-treated mice. Immunohistochemistry studies showed that although all of mice developed synovitis, the number of macrophages in the synovial membrane was markedly reduced in *Fviii-/-Tnfα-/-* and *Fviii-/-iRhom2-/-* compared *to Fviii-/-*.

Conclusion: Our results support the hypothesis that the iRhom2/ADAM17/TNFα signaling pathway contributes to the pathogenesis of HA/HS and the associated osteopenia observed in HA/HS patients and suggest that this pathway as a target for treatment.

Disclosure: C. Haxaire, Bayer, 2; **N. Hakobyan**, Bayer, 2; **J. E. Salmon**, Bayer, 2; **C. Blobel**, Bayer, 2.

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Abstract Number: 1111

Huntingtin Interactin Protein 1 (HIP1) Regulates Receptor Tyrosine Kinases Mediated Activity and Cell Invasiness in Fibroblast-like Synoviocytes

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Background/Purpose: Huntingtin-interacting protein 1 (Hip1) is a new arthritis severity gene recently identified in the Pristane and Collagen-induced arthritis (PIA, CIA) quantitative trait locus Cia25/Pia42 on rat chromosome 12. This study aimed to characterize the mechanism of action of Hip1 in arthritis.

Methods: Synovial tissues and fibroblast-like synoviocytes (FLS) were obtained from DA and DA.ACI(Cia25/Pia42) subcongenic R6 (R6) rats (day 21 after the onset of PIA). FLS from DA and the DA.ACI(Cia25/Pia42) subcongenic R6 (R6) were treated with PDGF, EGF, 10% FBS or 0.1% FBS and studied for a) *in vitro* invasion in a two-chamber assay through Matrigel, b) proliferation, c) gene expression (qPCR) analysis. DA and rheumatoid arthritis (RA) FLS were also studied following siRNA knockdown of Hip1. Tissues from Hip1 knockout mice were used for qPCR.

Results: Synovial tissues from DA rats expressed higher levels of Hip1 compared with DA.ACI(Cia25/Pia42) (1.78-fold). FLS from DA were five-fold more invasive than FLS from protected DA.ACI(Cia25/Pia42)-R6 subcongenics. Hip1 siRNA knockdown reduced the invasiveness of DA FLS and RA FLS by 60% and 50%, respectively demonstrating a critical role for Hip1 in cell invasion. Hip1 is known to interact with receptor tyrosine kinases (RTKs). Therefore, we examined 84 PDGF pathway genes in FLS and detected 16 up and 12 down in DA, compared with R6 subcongenics, including PDGFR, IGFR and EGFR. siRNA knock down of Hip1 in DA FLS reduced the levels of these RTKs to nearly zero, with similar reductions in expression levels detected in tissues from Hip1 knock-out mice. We examined cell invasion in response to PDGFb and detected a more pronounced increase on mean DA FLS invasiveness (12-fold) compared with R6 FLS (7-fold). In the presence of low serum conditions (0.1% FBS) DA FLS also had increased growth rate compared with R6 subcongenic FLS, a characteristic previously reported in Hip1 transfected cells.

Conclusion: We describe new evidence suggesting increased expression and activity of Hip1 in arthritis-derived FLS. Our results suggest that Hip1 regulates different aspect of FLS behavior favoring survival and proliferation, as well as invasivess in FLS from arthritic rats and from patients with RA. Hip1 also regulates the expression levels and activity of RTKs and their response to ligands such as PDGFb. These new discoveries provide new understanding about event regulating FLS behavior in arthritis and have the potential to generate a new prognostic biomarkers and a new intra-cellular target for therapy.

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Abstract Number: 1112

Hypoxia Modulates Neutrophil Integrin Expression, Adhesion and Trans-Endothelial Migration

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Dysregulation of neutrophil activation is important in the pathogenesis of various inflammatory and autoimmune rheumatic diseases (ARDs), including RA, SLE and APS. Neutrophils are exquisitely sensitive to their environment and neutrophil function can be modulated by numerous factors including cytokines, circulating IgG and localised tissue hypoxia (0.5-2.7% O_2). One mechanism of neutrophil activation results in the release of a meshwork of chromatin fibres decorated with antimicrobial proteins, called neutrophil extracellular traps (NETs). Aberrant NETosis has been described in various ARDs. We have previously shown that purified IgG and hypoxia promotes NETosis, however the underlying mechanism is unknown. Integrin engagement modulates several aspects of neutrophil function including: adhesion, cytokine production, NETosis and reactive oxygen species (ROS) generation. Therefore, we investigated the effects of hypoxia upon neutrophil integrin expression, adhesion to immobilised ligands and endothelial cells and trans-endothelial migration (TEM) to better understand the effects of hypoxia upon the stages preceding NETosis.

Methods: Neutrophils were isolated from whole blood donated by healthy controls (HC) and cultured under normoxia (21% O_2) or hypoxia (1% O_2). NETosis was visualised by immunofluorescence (IF) staining for histone H3. Levels of surface integrin expression of α_1 (CD49a), α_4 (CD49d), α_5 (CD49e), α_L (CD11a), α_M (CD11b), α_X (CD11c), β_1 (CD29) and β_2(CD18) were measured by flow cytometry. Assessment of 2',7'-bis-(2-carboxyethyl)-5-(and-6)-carboxyfluorescein, acetoxymethyl ester (BCECF-AM)-labelled neutrophil adhesion to immobilised fibrinogen, fibronectin and intercellular adhesion molecule (ICAM)-1 and human umbilical cord endothelial cells (HUVEC) was measured using a fluorescent plate reader. Neutrophil TEM across HUVEC monolayers was measured by flow cytometry.

Results: IF studies found that NETosis was inhibited by EDTA treatment, indicating cation-dependent integrin involvement. Moreover, NETosis could be induced by integrin activation with either Mn^{2+} or macrophage-1 antigen (Mac-1, $\alpha_M\beta_2$)-specific activation with leukadherin-1. Hypoxia significantly increased expression of α_M ($p<0.001$) and α_X($p=0.038$) in HC neutrophils compared to normoxia ($n=7$). Adhesion to immobilised fibrinogen, fibronectin and ICAM-1 were all significantly reduced under hypoxia ($p<0.01$, $p<0.01$ and $p<0.01$ respectively). In contrast, hypoxia enhanced both unstimulated ($p<0.01$) and LPS-stimulated ($p<0.001$) adhesion to and TEM across HUVEC monolayers ($p<0.05$) compared to normoxic controls.

Conclusion: Hypoxia significantly increased neutrophil: expression of α_M and α_X integrin subunits; adhesion to HUVEC but not immobilised integrin ligands; and TEM across HUVEC monolayers. Further work is currently underway to dissect the molecular and signalling mechanisms that regulate neutrophil function under hypoxia and whether ARD-IgG further modulate these responses.

Disclosure: **A. A. Khawaja**, None; **C. Pericleous**, None; **V. M. Ripoll**, None; **J. C. Porter**, None; **I. Giles**, None.

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Abstract Number: 1113

Leptin Promotes Distribution of Mast Cells in Salivary Glands of Patients with Primary Sjogren's Syndrome

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Background/Purpose: Mast cells (MCs) are immune cells that produce and secrete a variety of mediators and cytokines, which influence various inflammatory and immune processes. It has become clear that MCs were not only related to allergic reactions, but also involved in several autoimmune diseases. However, the role and precise mechanism of MCs on the pathogenesis of primary Sjogren¡¯s syndrome (pSS) is not completely understood. Leptin is a protein secreted by adipose tissue, which has an important role in metabolism and immunity. MCs were found to express leptin receptors. It is therefore plausible that leptin, through its effects on MCs, may play an important role in the development of pSS. The present study aimed to investigate the distribution of MCs in labial salivary glands in an attempt to elucidate a possible role of MCs in the pSS pathogenesis. Furthermore, this work explored the correlation between MCs and leptin in the pSS.

Methods: All recruited patients fulfilled the American-European Consensus Group criteria for primary SS. The labial salivary glands were obtained from patients with pSS. Mast cell count in labial salivary glands was studied by toluidine blue stain and immunohistochemical staining using monoclonal antibody against tryptase. Serum leptin and tryptase were measured by enzyme-linked immunosorbent assay.

Results: Serum leptin and trypase in pSS patients were significantly higher than that of healthy control. The leptin concentrations were positively correlated with trypase levels in pSS patients (Fig 1). Both the toluidine blue and immunohistochemical stain showed that distribution of MCs was absent from lymphocyte foci, and was preference for location in the connective tissue. MCs were more common in salivary glands in pSS patients than in healthy controls. The MCs were more frequent in labial salivary glands with severely lymphocytic infiltration than those with slightly lymphocytic infiltration, which indicated the number of MCs positively correlated with the disease activity (Fig 2).

Conclusion: Our findings suggested that the proinflammatory role of MCs in the pathogenesis of SS was related to leptin. Treatment with leptin antagonists might be a potential target to control inflammatory activities of MCs in SS. **Figure 1**

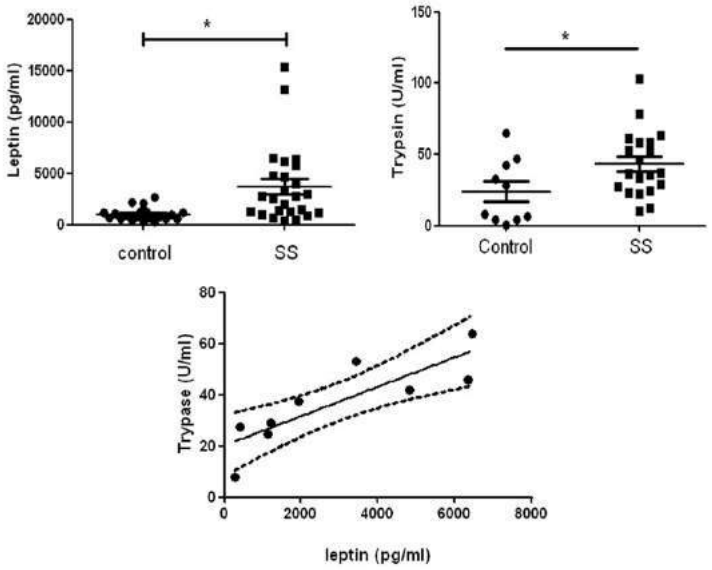
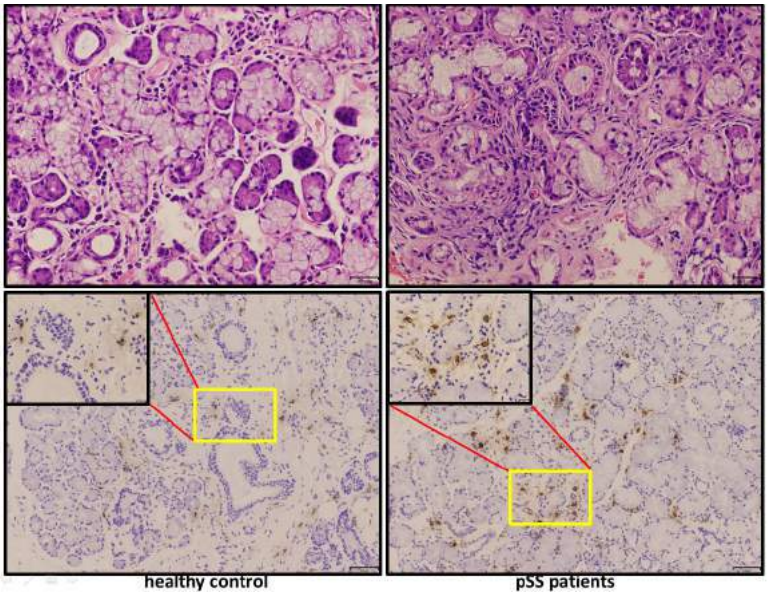


Figure 2



Disclosure: **G. Yao**, None; **J. Qi**, None; **B. Shi**, None; **W. Chen**, None; **X. Tang**, None; **W. Li**, None; **D. Wang**, None; **L. Sun**, None.

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Abstract Number: 1114

Extracellular Vesicles in the Circulating of Rheumatoid Arthritis Patients Are Pro-Inflammatory

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Background/Purpose: Rheumatoid arthritis (RA) is a progressive and degenerative joint disease with chronic synovial inflammation in multiple joints. Interestingly, the symmetry and spreading of the disease to multiple joints are clinically significant signs of RA, but not fully understood. Our hypothesis is that circulating extracellular vesicles (cEVs) obtained from blood of RA patients contribute to the polyarticular and systemic involvement of this disease. In this study we measured cytokines in platelet free plasma (PFP) and plasma EVs from RA patients and healthy controls (HC). Furthermore, we analyzed the biological activity of cEVs using functional studies in human monocytes (THP-1).

Methods: cEVs were obtained sterile from PFP of 21 RA patients or 15 HC (age matched) by size exclusion chromatography (SEC). Protein content of cEVs was measured by micro-BCA and characterized by Nanoparticle Tracking Analysis and electron microscopy. Level of TNFα, IL-1β, IL-6, IL-8, IL-10 and MCP-1 in PFP and cEVs were measured by Luminex. To study the functionality, 50.000 THP-1 cells were incubated for 24h with RA- or HC-cEVs and cytokine production was measured in supernatant by Luminex.

Results: The particle size and concentration of RA-cEVs (105 nm, 4.74 $x10^{10}$ particles/ml) were not different from HC-cEVs (106 nm, $4.40x10^{10}$ particles/ml). Protein content was also not significant different (RA;211 µg/ml, HC;176 µg/ml). In RA-cEVs the levels of TNFα, IL-1β, IL-6, IL-10 and MCP-1 were significant enhanced (RA-cEVs: 71,8,30,22 and 26 pg/ml ; HC-cEVs: 1,0,3,0 and 9 pg/ml resp.) while in PFP only levels of IL-1β and IL-6 were significant increased (RA-cEVs: 15 and 112 pg/ml, HC-cEVs: 1 and 5 pg/ml resp.). THP-1 cells exposed to cEVs were activated shown by enhanced production of IL-8. Cells incubated with RA-cEVs showed significant higher protein production of MCP-1 (45%) while TNFα, IL-1β and IL-6 were undetectable.

Conclusion: This study showed that cEVs obtained from platelet free plasma of RA patients contains cytokines and were able to stimulate THP-1 cells to release pro-inflammatory proteins. For that, it is plausible that cEVs contribute to the systemic nature of this disease.

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Abstract Number: 1115

Non-Esterified Fatty Acids Are Associated with Clinical Features and an Enhanced Th1 Response in Rheumatoid Arthritis: Towards Disease Profiling

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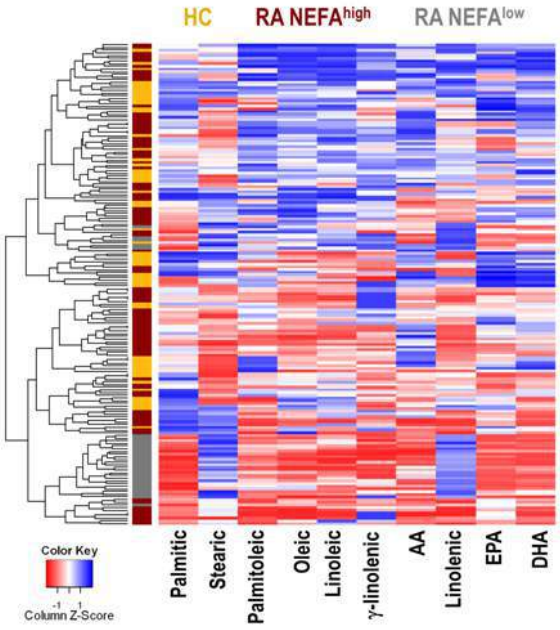
Session Time: 9:00AM-11:00AM

Background/Purpose: Non-Esterified Fatty Acids (NEFA) are important lipid mediators which can play a role in a number of biological functions other than energy supply. NEFA are known to regulate gene expression in monocytes and macrophages, as well as to modulate of $CD4^+$ T-cell function. Thus, we hypothesized that altered NEFA levels may underlie rheumatoid arthritis (RA) pathogenesis.

Methods: NEFA serum levels (palmitic, stearic, palmitoleic, oleic, linoleic, g-linoleic, arachidonic –AA–, linolenic, eicosapentaenoic –EPA– and docosahexaenoic –DHA–) were quantified by LC-MS/MS after methyl-*tert*-butylether (MTBE)-extraction in 124 RA patients (all fulfilling 2010 ACR/EULAR RA criteria, 61.2% RF+, 59.6% ACPA+) and 56 healthy controls (HC). Moreover, 13 prospectively-followed RA patients undergoing TNFa-blockade were recruited. $CD4^+$ T-cell phenotype was studied by flow cytometry. TNFa, IL-8, VEGF, GM-CSF, IFNg, IL-17, MCP-1, IP-10, leptin and resistin serum levels were quantified by immunoassays. The effect of NEFA on IFNg production by PBMC was evaluated in vitro.

Results: Lower levels of palmitic ($p<0.0001$), palmitoleic ($p=0.002$), oleic ($p=0.010$), arachidonic ($p=0.027$), EPA ($p<0.0001$) and DHA ($p<0.0001$) were found in RA, some NEFA being altered at onset. No differences in total NEFA level were observed ($p=0.157$), thus pointing to an altered NEFA profile in RA. Cluster analysis identified a FFA profile ($NEFA^{low}$) characterized by increased stearic and decreased EPA and DHA levels to be overrepresented in RA patients compared to HC ($p=0.002$) (Figure 1). $NEFA^{low}$ profile was associated with clinical features (RF, shared epitope and erosions), increased IFNg expression in $CD4^+$ T-cells ($p=0.002$) and a Th1-enhanced serum milieu (IFNg, MCP-1 and IP-10, all $p<0.005$). In vitro assays demonstrated that imbalanced NEFA could underlie IFNg production by $CD4^+$ T-cells. Finally, changes on NEFA levels were associated with clinical response upon TNFa-blockade, decreasing EPA and DHA being related to a poor clinical outcome.

Conclusion: An altered NEFA profile can be found in RA patients associated with clinical characteristics of aggressive disease and Th1-enhanced response. Impaired NEFA levels may underlie a poor clinical outcome upon TNFa-blockade. A complex NEFA profile was observed, specific NEFA being altered independently of their chemical properties. These results support the relevance of lipidomic studies in RA and provide a rationale for new therapeutic targets.



Disclosure: J. Rodríguez-Carrio, None; **M. Alperi-López**, None; **P. López**, None; **F. J. Ballina-García**, None; **A. Suárez**, None.

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Abstract Number: 1116

Anti-Citrullinated Protein Antibodies Promote Synovial Fibroblasts Migration and Adhesion through a Peptidylarginine Deiminases (PAD) Dependent Pathway

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Background/Purpose:

Synovial fibroblasts (SFs) contribute to rheumatoid arthritis (RA) pathogenesis by growing into the synovial space and by producing pro-angiogenic and tissue remodelling factors, chemokines and inflammatory cytokines that recruit and stimulate various immune cells. We have recently demonstrated that anti-citrullinated proteins antibodies (ACPAs) promote osteoclastogenesis through an interleukin-8 (IL-8) dependent autocrine mechanism. In the present work we investigated alterations of synovial fibroblast morphology and behaviour in response to ACPAs, including signalling transduction, cytokine production and mobility.

Methods: SFs were isolated from synovial tissue of RA patients by enzymatic digestion. Polyclonal ACPA and others non-ACPA IgGs were separated from peripheral blood of RA patients by affinity purification on cyclic citrullinated peptide (CCP)-2 column. SF migration capacity were tested by scratch-assays in presence of various stimuli, including ACPAs, non-ACPA IgGs, TNF and IL-8 using starved

cells. The results were evaluated by NIH ImageJ software. SF adhesion was analyzed by xCELLigence System Real-Time Cell Analyzer (ACEA bioscience). Cytokine production was detected in supernatant by cytometric bead array. Signaling cascades were targeted using inhibitors of phosphoinositide 3-kinase (PI3K), phosphatase and tensin homolog (PTEN), G-protein coupled receptors (GPCRs), focal adhesion kinase (FAK) and peptidylarginine deiminases (PAD) in scratching assays. Protein phosphorylations were monitored by western blot.

Results: Polyclonal ACPAs but not non-ACPA IgGs induced migration (a fold increase of 2.6±0.5, mean±SD, $p<0,05$) and adhesion (a fold increase of 1.3±0.1 at 6 hours, $p<0.05$) after starvation. The cytokines TNF and IL-8 synergistically increased SF migration in presence of ACPAs. By inhibiting PADs, the enzymes responsible for protein citrullination, we showed that PAD activity is needed for the ACPA effects but not for baseline SF mobility. GPCR and PI3K blocking inhibited the effects of ACPAs whereas PTEN blocking enhanced migration, indicating important roles for GPCR and PI3K in the ACPA-mediated SF modulation. Immunoblot analysis revealed an increased AKT phosphorylation in ACPA-treated cells, further suggesting the involvement of PI3K in the ACPA-mediated signals.

Conclusion: ACPAs promote SFs migration and adhesion acting synergistically with IL-8 through a PAD-dependent pathway. Our findings suggest that SFs might have an active role in the ACPA-dependent disease propagation from the bone marrow to synovial tissue during RA.

Disclosure: M. Sun, None; **V. Joshua**, None; **A. Krishnamurthy**, None; **Y. Liu**, None; **A. Hensvold**, None; **S. B. Catrina**, None; **C. Ospelt**, None; **V. Malmström**, None; **K. Amara**, None; **J. Steen**, None; **M. S. Mia**, None; **M. Engström**, None; **H. Wähämaa**, None; **J. Ytterberg**, None; **B. Rethi**, None; **A. I. Catrina**, None.

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Abstract Number: 1117

EGCG Down-Regulates TNF-α-Induced Mcl-1 Expression By Modulating Mule/Huwe1, β-TrCP, and USP9X Ubiquitin/De-Ubiquitin Ligases in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: Myeloid cell leukemia (Mcl-1) phosphorylation at Ser64 position (p-Mcl-1^{Ser64}) has been shown to enhance Mcl-1's stability and resistance to proteasomal degradation. However, the role of p-Mcl-1^{Ser64} in rheumatoid arthritis synovial fibroblasts (RASFs) resistance to TNF-α-induced apoptosis and the influence of ubiquitin and de-ubiquitin ligases in regulating Mcl-1 resistance is not yet studied in RA. This study was undertaken to understand the posttranslational mechanism of Mcl-1 regulation by epigallocatechin-3-gallate (EGCG), a potent anti-inflammatory molecule found in green tea, in human RASFs.

Methods: The expression of p-Mcl-1^{Ser64} and of the Mcl-1-specific ubiquitin ligases (Mule/Huwe1 and β-TrCP), and de-ubiquitin ligase (USP9X) was determined in SFs from RA, osteoarthritis (OA), and non-diseased (NL) SFs. Efficacy of an acute EGCG concentration (50 μM) or physiologically-achievable chronic concentrations (0.1-1 μM) were tested in regulating these posttranslational modifications in RASFs using Western blotting and immunoprecipitation methods. $P<0.05$ was considered significant.

Results: The levels of p-Mcl-1^{Ser64}, which enhances its anti-apoptotic property, was markedly upregulated in human RASFs compared to OASFs or NLSFs ($p<0.05$). Pretreatment of RASFs with EGCG (50 μM) for 24 h markedly inhibited p-Mcl-1^{Ser64}and total Mcl-1 expression and enhanced the expression of pro-apoptotic proteins (Bak and Bax) in TNF-α stimulated RASFs. Western blotting evaluation of the posttranslational processes showed a significant decrease in the expression of Mcl-1-specific ubiquitin ligases Mule/Huwe1 (~82%) and β-TrCP (~75%) in RASFs compared to NLSFs ($p<0.05$). However, the expression of Mcl-1-specific de-ubiquitin ligase, USP9X, was not significantly different between RASFs and NLSFs. Interestingly, Western blot analysis of samples immunoprecipitated with Mcl-1 antibody showed a reduced association with β-TrCP and an increased association with USP9X in RASFs compared to NLSFs. EGCG treatment significantly induced the expression of Mule/Huwe1 and β-TrCP in TNF-α-stimulated RASFs. In addition, Mcl-1

immunoprecipitation in the EGCG treated RASFs showed a marked decrease in Mcl-1-associated USP9X and an increase in Mcl-1-associated β-TrCP in TNF-α-stimulated RASFs compared to TNF-α alone group. The majority of beneficial effects of a single-dose EGCG (50 μM) were mimicked by the repeated RASF treatment for 7 days with EGCG (1 μM) to attain physiological concentrations of EGCG, if consumed in the form of green tea supplement.

Conclusion: This study provides a novel evidence that EGCG induces Mule/Huwe1 and β-TrCP ubiquitin ligases and inhibits USP9X de-ubiquitin ligase that are Mcl-1-specific, thereby, facilitating Mcl-1 degradation in RASFs and possibly regulating tissue invasion and destruction in RA.

Disclosure: N. Akhtar, None; **S. Umar**, None; **D. Fox**, None; **S. Ahmed**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/egcg-down-regulates-tnf-%ce%b1-induced-mcl-1-expression-by-modulating-mulehuwe1-%ce%b2-trcp-and-usp9x-ubiquitinde-ubiquitin-ligases-in-rheumatoid-arthritis-synovial-fibroblasts

Abstract Number: 1118

Increased Population of Myeloid Dendritic Cells and Upregulated Gene Expression of Tnfα Is Associated with Poor Response to Hydroxychloroquine

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Background/Purpose: Cutaneous lupus erythematosus (CLE) is an autoimmune disease with various subsets and wide-ranging clinical manifestations. T lymphocytes are the predominant cell type found in lesions, but plasmacytoid dendritic cells (pDCs) and myeloid dendritic cells (mDCs) also play a pivotal role in the pathogenesis. Although antimalarials are the primary treatment for CLE, the exact mode of action is still not completely understood. To figure out the determining factor of treatment response to antimalarials in CLE patients, inflammatory cell infiltrates and cytokine profiles in lesional skin of CLE patients were evaluated.

Methods: Thirty-two skin biopsies of CLE patients (SCLE; n=13, DLE; n=19) were immunohistochemically investigated for the presence of pDCs, mDCs, neutrophils, and macrophages by employing antibodies against CD123, CD11c, MPO, and MAC387 respectively. Skin sections were examined by light microscopy and positive stained cells were quantified at x400 magnification in five non-overlapping adjacent microscopic fields in the dermis. The results were expressed as mean number of cells. RNA extracted from formalin-fixed paraffin-embedded (FFPE) skin samples from 21 CLE patients were analyzed by qRT-PCR for gene expression of type I IFN signature genes (LY6E, OAS1, OASL, ISG15, and MX1) and inflammatory cytokines TNFα. The patients were grouped according to their response to antimalarial treatment; 1) Hydroxychloroquine (HCQ) group, who were responsive to HCQ; and 2) HCQ + Quinacrine (QC) group, who were refractory to HCQ and responded to additional QC. The Mann-Whitney test was used to compare the number of each cell type and gene expression between HCQ and QC responsive groups.

Results: The number of mDCs was significantly higher (p=0.0106) in HCQ+QC group patients (19 cases) compared to those in HCQ group (13 cases) (Figure). The mean number (standard error) of pDCs, mDCs, neutrophils, and macrophages in each group of patients is summarized in the table. Gene expression of type I IFN signatures were significantly upregulated in the HCQ group compared to the HCQ+QC group (LYE p=0.0037; OAS1 p=0.0002; OASL p=0.0067; ISG15 p=0.01; and MX1 p=0.0083), while TNFα levels were significantly higher in the HCQ+QC group (p=0.003).

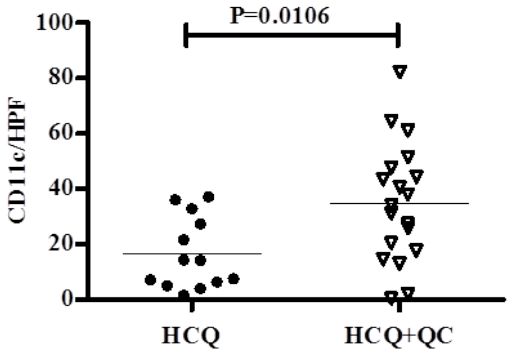
Conclusion: Increased numbers of mDCs together with higher TNFα expression might be responsible for refractoriness to HCQ and better response to QC. Our data suggest that the increased number of mDCs in CLE patients may be used as a predictive factor of refractoriness to HCQ and responsiveness to QC.

Table

CLE	CD123 Mean (SE)	CD11c Mean (SE)	MPO Mean (SE)	MAC387 Mean (SE)
HCQ (n=13)	29.4 (5.8)	16.6 (3.6)	16 (3.7)	25.3 (4.9)
HCQ+QC (n=19)	27.9 (5.1)	34.7 (4.9)	13.4 (1.8)	24.6 (3.1)

*SE: Standard Error; HCQ: Hydroxychloroquine group; HCQ+QC: Hydroxychloroquine + Quinacrine group

Figure



Disclosure: M. Zeidi, None; **H. J. Kim**, None; **V. P. Werth**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-population-of-myeloid-dendritic-cells-and-upregulated-gene-expression-of-tnf%ce%b1-is-associated-with-poor-response-to-hydroxychloroquine

Abstract Number: 1119

The Enhanced Expression of mRNA for Calgranulins, S100A8, S100A9 and S100A12, in CD34+ Cells of the Bone Marrow in Rheumatoid Arthritis

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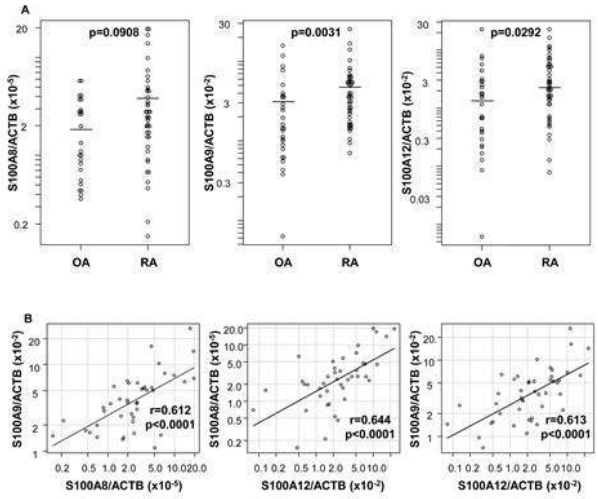
Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory arthritis of unknown etiology. A subset of S100 proteins known as calgranulins (S100A8, S100A9 and S100A12) are constitutively expressed at high levels in neutrophils and monocytes and play a critical role in inflammation as they can activate the innate immunity pathway sensed by Toll-like receptors. Notably, recent studies have revealed that the expression of calgranulins was about 10-fold higher in RA synovial fluid (SF) versus osteoarthritis (OA) SF. However, the mechanisms for such upregulation of the expression of calgranulins in RA SF remain unclear. We have previously demonstrated that the expression of mRNAs for various genes in BM CD34+ cells, including nuclear factor kappa B1, is higher in RA patients than in OA patients. It is thus possible that the expression of mRNAs for calgranulins might be also upregulated in RA BM CD34+ cells. The current study therefore examined the mRNA expression of S100A8, S100A9 and S100A12 in BM CD34+ cells from RA patients versus OA patients.

Methods: BM samples were obtained from 45 patients with RA (5 males and 40 females: mean age 59.0 years) and 28 patients with OA (3 males and 25 females: mean age 70.8 years), who gave informed consent, during joint operations via aspiration from iliac crest. CD34+ cells were purified from the BM mononuclear cells by positive selection with magnetic beads. The expression of mRNAs for S100A8,

S100A9 and S100A12 was examined by quantitative reverse transcription PCR and is shown as the ratio of the copy numbers to those of b-actin mRNA.

Results: The expression of mRNAs for S100A9 and S100A12 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells. The expression of mRNA for S100A8 in RA BM CD34+ cells appeared to be increased compared to OA BM CD34+ cells, although it did not reach the statistical significance. (Fig. A). The mRNA expression levels of S100A8, S100A9 and S100A12 were not correlated with serum C-reactive protein or with the administration of methotrexate or oral steroid. Finally, the level of S100A8 mRNA as well as that of S100A9 mRNA was significantly correlated with the level of S100A12 mRNA in RA BM CD34+ cells (Fig. B).

Conclusion: These results indicate that the mRNA expression of S100A8, S100A9 and S100A12 is upregulated in RA BM CD34+ cells independently of the systemic inflammation or treatment regimen. Thus, the data account for the upregulation of the enhanced expression of calgranulins in RF SF compared with that in OA SF.



Disclosure: T. Nagai, None; **Y. Matsueda**, None; **T. Tomita**, None; **H. Yoshikawa**, None; **S. Hirohata**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-enhanced-expression-of-mrna-for-calgranulins-s100a8-s100a9-and-s100a12-in-cd34-cells-of-the-bone-marrow-in-rheumatoid-arthritis

Abstract Number: 1120

Interleukin-1β Stabilize CXCL2 mRNA and Increase Its Expression

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Background/Purpose: Changes in gene expression are closely related to inflammation and joint destruction in RA. Recently, it has been recognized that post-transcriptional regulation of the gene expression of various cytokines is important to the immunological process. In this study, we attempted to identify cytokines that regulate the metabolism of RA-related mRNA through unique AU rich elements (ARE), which are characterized by AUUUA repeats in their 3′ untranslated regions (3′UTR).

Methods: We generated dual luciferase reporter plasmids to study the influence of cytokines on the stability of transcripts associated with RA. The 3′-UTR sequences of RA-related genes (*CXCL2*, *PIM1*, *CSF2*, *IL12B*, *IL1B*, *TNF*, *TNFRSF10B*, *HIF1A*, *ARHGEF2*) with ARE were inserted into the 3′ end of the firefly luciferase gene in the pmirGLO Dual-Luciferase miRNA Target Expression Vector. *Renilla* luciferase in the plasmid was used as a control reporter for normalization. U2OS cells were transfected with these plasmids 2 hours before cytokine treatment. The transfected cells were stimulated with cytokines for 12 hours and were lysed using a passive lysis buffer for luciferase activity analyses with the Dual-Glo Luciferase Assay System and Infinite 200 PRO. TIA1, TIAR, TTP, or HuR were co-

transfected with the reporter. The expression of *CXCL2* mRNA in fibroblast-like synoviocytes (FLS) was examined by RT-PCR. In mRNA decay experiments, actinomycin D was used to stop RNA polymerase II dependent transcription in FLS.

Results: Various cytokine treatments affected the reporter luciferase activities. In particular, IL-1β and IL-17A increased the luciferase activities of the reporters harboring the 3′-UTR of *CXCL2* mRNA in a dose-dependent manner. Addition of IL-1β remarkably upregulated the *CXCL2* mRNA expression in FLS. The half-life of *CXCL2* mRNA was significantly longer in IL-1β treated FLS (21.7 hours) than that in untreated FLS (3.3 hours). ARE-harboring mRNA is potentially regulated by RNA binding proteins including TIA1, TIAR, TTP, and HuR. Among these, co-transfection of TTP with the reporter plasmid suppressed the luciferase activity with the 3′UTR of *CXCL2* mRNA.

Conclusion: Our data suggest that the metabolism of *CXCL2* mRNA is stabilized by IL-1β, leading to a remarkable increase in *CXCL2* mRNA in FLS. CXCL2 is a chemokine that is secreted from various cells for chemotactic attraction of polymorphonuclear leukocytes and is involved in the pathogenesis of infections and autoimmune diseases. Therefore, it is possible that IL-1β signaling stabilizes *CXCL2* mRNA by regulating RNA binding proteins like TTP, for the recruitment of neutrophils at the inflamed joint.

Disclosure: S. Yamasaki, Eli Lilly and Company, 2; **Y. Yoshida**, None; **E. Sugiyama**, Eli Lilly and Company, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 2,Chugai, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/interleukin-1%ce%b2-stabilize-cxcl2-mrna-and-increase-its-expression

Abstract Number: 1121

IFN Regulatory Factor-5 Signaling Increases IFN-Gamma Production and Suppresses IL-2 Production from CD4+ T Cells, and Controls IgG Production in B Cells

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Background/Purpose: Recent studies of human genetics and mouse models have shown that interferon regulatory factor-5 (IRF5) is associated with the development of autoimmune disease. However, the role of IRF5 in their pathogenesis is not fully understood.

Methods: We generated dendritic cells (DCs) with Fms-related tyrosine kinase 3 ligand (Flt-3L) using bone marrow cells from wild type mice or IRF5-/- mice. We stimulated the DCs with toll-like receptor (TLR) ligands and cultured them with CD4+ T cells. We measured T cell cytokines (IFN-gamma, IL-17, IL-4 and IL-2) in the culture supernatant. In separate experiments, we stimulated B cells from wild type mice and IRF5-/- mice with TLR ligands in the presence of IFN-gamma, IFN-beta, IL-4 and IL-17.

Results: TLR7-IRF5 signaling in DCs stimulated CD4+ T cells to release large amounts of type II IFN (IFN-gamma). Concomitantly, IL-2 production from CD4+ T cells was suppressed. This balance of cytokine production was controlled by modulating IL-12 and type I IFN expression through IRF5. By neutralizing IL-12p40 and blocking IFN receptors, production of IFN-gamma was suppressed while that of IL-2 was increased. IFN-gamma enhances IgG2a/c and IgG2b production from B cells stimulated with TLR7 and TLR9 through IRF5-dependent pathways. In addition, dual activation of BCR and TLR7 induces IRF5-dependent enhancement of T-bet, which is responsible for IgG2a production in B cells.

Conclusion: IRF5 promotes Th1-type T cell responses and the production of pathogenic IgG isotypes. In adidition, our results provide a mechanism to explain the low level of T cell IL-2 expression that has previously been linked to lupus pathogenesis.

Disclosure: K. Yasuda, None; **P. Shukla**, None; **R. G. Bonegio**, None; **I. Rifkin**, None.

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Abstract Number: 1122

Infliximab Suppresses the Monocyte Chemotaxis in Human TNF-Transgenic Mice

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Background/Purpose: Macrophages in rheumatoid arthritis (RA) synovium produce high levels of inflammatory cytokines/chemokines and play the pivotal role in promoting inflammation and joint destruction. Treatment of patients with RA with infliximab results in a rapid reduction of synovial tissue macrophages, which is a reliable biomarker of clinical response. Since the mechanism for reduction of macrophages has not been clearly defined, studies were performed with human TNF transgenic (hTNF-tg) mice to determine if the initial reduction of macrophages was due to increased cell death, increased efflux of macrophages or decreased influx of monocytes.

Methods: hTNF-tg mice and littermate controls at 5-6 week old were employed. Administration of infliximab was performed intraperitoneally (10mg/kg), 2 doses over 3 days. The clinical severity of the arthritis was defined as the sum score of inflammation, deformity and grip strength, ranging 0-28. Inflammation and bone destruction were assessed by ankle histology. The immune cell phenotypes and apoptosis were determined by flow cytometry. Monocyte migration into ankles was documented following intravenous administration of $CD115^+$ monocytes from $CD45.1^+$donors into the synovial tissue of hTNF-tg mice with or without the infliximab treatment. Ankle joint homogenizes were analyzed for cytokines/chemokines by quantitative ELISA.

Results: Arthritis in 5 week old CD45.2 hTNF-tg mice was significantly improved after 2 dosages of infliximab evaluated clinically and histologically, which demonstrated reduction of inflammation and bone erosion. In addition, the $Ly6C^+$ synovial tissue monocyte-derived macrophages ($CD64^+CD11b^+$ $F4/80^{mid}$ $Ly6C^+$) were sighnificantly reduced by infliximab ($p<0.001$), determined by flow cytometric analysis. No increase of macrophage apoptosis was identified following treatment, although there was a modest reduction neutrophil apoptosis. There was no increase of any subset of macrophages in the draining peritoneal lymph nodes (pLNs) of the treated mice. In fact the $Ly6C^+$ macrophages were actually reduced in the pLNs following treatment. The adoptive transfer CD45.1 monocytes was employed to track the influx of monocytes. The influx of $CD115^+$circulating monocytes into the synovial tissue of hTNF-tg mice was significantly ($p < 0.001$) reduced in the mice that received 2 doses of infliximab, one 24h before and another at the time of monocyte transfer, or just one dose simultaneously with monocyte administration ($p<0.001$). Ankle joint homogenizes demonstrated greatly reduced the CCL2 ($p<0.001$), but not Cx3CL1 ($p>0.05$), following treatment.

Conclusion: The initial effect of infliximab on macrophages in the joints of hTNF-tg mice was the reduction of Ly6C+ macrophages. The decrease was not due to increased efflux from the joint or increased apoptosis but due to decreased influx of circulating Ly6C+ monocytes, which are also CCR2+. These observations provide a potential explanation for the rapid reduction of synovial tissue macrophages observed in patients with RA treated with infliximab.

Disclosure: Q. Q. Huang, None; **R. Birkett**, None; **E. L. Roberts**, None; **R. M. Pope**, None.

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Abstract Number: 1123

Targeted Mutations Identify the Active Site of Glucocorticoid-Induced Leucine Zipper (GILZ)

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Background/Purpose: Glucocorticoids (GC) have been used to treat inflammatory disease for more than six decades, but the broad spectrum of therapeutic effects is accompanied by significant metabolic adverse effects. Recent studies suggest that glucocorticoid-induced leucine zipper (GILZ) mimics the anti-inflammatory effects of GC, including inhibiting the activation of macrophage, B cells, Th1 and Th17 cells, but lacks GC adverse effects. However, little is known about molecular mechanisms of GILZ action that could empower drug discovery.

Methods:

Expression of GILZ and acetylated GILZ was measured by Western blotting in murine bone marrow-derived macrophages. WT and mutated GILZ plasmids were co-transfected with an NF-κB luciferase reporter into human microvascular endothelial cells (HMECs). IL-6 and MCP-1 were measured by ELISA. NF-κB activity was measured using a NF-κB luciferase reporter assay. Interactions between GILZ and p65/NF-κB were detected by Fluorescence lifetime imaging (FLIM)/ Fluorescence Resonance Energy Transfer (FRET).

Results: GILZ acetylation was detected in macrophages, and TSA, a deacetylase inhibitor, increased GILZ acetylation in a time-dependent manner. WT GILZ was constructed in the pcDNA3.1 expression plasmid and overexpression of GILZ significantly inhibited NF-κB activity and IL-6 and MCP-1 expression. Using an acetylation substrate-binding site alignment approach, we predicted three potential GILZ acetylation sites at K37, K77 and K108. Acetylation of GILZ was lost when K77, but not K37 or K108, was mutated to arginine (K77R). Mutation at K77 aborgated GILZ inhibition of NF-κB activity, and IL-6 and MCP-1 expression. Co-IP and FLIM/FRET demonstrated that GILZ mutation at K77 prevented interaction with p65/NF-κB.

Conclusion: Acetylation of GILZ at K77 is required for its interaction with NF-κB and anti-inflammatory effects. This suggests a potential target for enhancing the anti-inflammatory effects of GILZ as a GC mimic via inducing K77 acetylation.

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Abstract Number: 1124

IL37 Rescues Human OA Cartilage Explants from GAG Release

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Background/Purpose: In healthy cartilage, there is a balance between anabolic and catabolic activities of chondrocytes that maintains the functional integrity of the extracellular matrix. However, during osteoarthritis (OA), chondrocytes become more catabolically active and express matrix degrading enzymes, such MMPs and ADAMTSs. This process results in a net loss of the extracellular matrix and therefore leads to cartilage damage. Previously we found, that the anti-inflammatory cytokine Interleukin 37 (IL37) is able to counter-regulate the catabolic status of chondrocytes by reducing the IL1β-driven expression of pro-inflammatory cytokines and catabolic enzymes. The goal of this study was to investigate the effect of IL37 on content and synthesis of extracellular matrix molecules in human OA cartilage explants.

Methods: Human cartilage was obtained from sixteen OA patients undergoing total knee or hip arthroplasty. Biopsy punches of 4 mm in diameter were made to equalize explant size. After culturing overnight, explants were incubated for 48 h with three doses (1-10 ng/ml) of

recombinant-IL37 (rec-IL37). Sulfated glycosaminoglyans (GAG) were measured in the supernatant with the DMB assay and RNA was extracted from explants to analyze gene expression of extracellular matrix molecules and cartilage degrading enzymes. In addition, nitric oxide (NO) was measured in the supernatant using Griess reagens, because NO is an important effector molecule that may suppress cartilage matrix synthesis.

Results: Adding rec-IL37 (100ng/ml) to OA cartilage explants caused a significant reduction in GAG release in the supernatant of, on average, 32% in sixteen donors. Gene expression of the extracellular matrix molecules aggrecan and collagen type II was not different between rec-IL37 treated groups and controls in the five patients analyzed so far. This indicates that rec-IL37 does not inhibit GAG release by inhibiting the synthesis of the proteoglycan aggrecan. We did observe a reduction in the gene expression of the matrix degrading enzyme MMP3 after stimulation with 1 ng/ml rec-IL37. However, high doses of rec-IL37 did not significantly reduce MMP3 expression. Furthermore, we did not observe an effect of rec-IL37 on gene expression of MMP13 and ADAMTS5, which suggests that rec-IL37 does not inhibit GAG release by inhibiting expression of these enzymes. Another mechanism to prevent GAG release is via inhibition of NO synthesis, but NO levels in the supernatant were comparable between rec-IL37 treated groups and the control group. However, we did observe a trend towards increased gene expression of the metalloproteinase inhibitor TIMP3 in rec-IL37 treated groups, as a possible mechanism for reduced GAG release.

Conclusion: Our data show that rec-IL37 reduces GAG release out of OA cartilage explants. The mechanism behind this process is most likely positioned downstream of catabolic gene expression, and possibly runs via modulation of matrix degrading enzyme activity. Our results indicate that IL37 can maintain cartilage matrix integrity under OA conditions.

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Abstract Number: 1125

Targeted Lipidomics Reveals Incomplete Activation of Resolution Pathways in Knee Osteoarthritis

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Background/Purpose: Persistent inflammation is a characteristic of several joint diseases, including OA. It is nowadays appreciated that this could be a result of a failure to (optimally) activate inflammation resolution pathways. Therefore, we investigated the presence of specialized pro-resolving lipid mediators (SPM) and their precursors as pathway markers of the resolution process in the joint of OA patients and controls.

Methods: SF was obtained from knee OA (2 populations) and rheumatoid arthritis (RA) patients fulfilling the ACR criteria for OA and RA, respectively, and healthy controls. Lipid mediators (LMs) were determined by targeted lipidomics using liquid-chromatography mass spectrometry. Sixty different lipids including pro-inflammatory (e.g. prostaglandins, leukotrienes) and anti-inflammatory/pro-resolving LM (e.g. SPM), as well as their precursors can be detected with our technique.

Results: SF from 24 OA and 12 RA patients were first studied. Thirty-seven lipids were detected in the soluble fraction of SF, including

polyunsaturated fatty acids (PUFA) and their lipoxygenase (LOX) and cyclooxygenase (COX) pathway markers in both OA and RA patients. Among these, pro-inflammatory LM such as PGE_2 and thromboxane B2, as well as the pathway markers of resolution and precursors of SPM, 17-HDHA and 18-HEPE, were detected. Except for the LOX products of arachidonic acid: 15-HETE, 6-trans-LTB_4 and 20-OH- LTB_4, which were lower in OA than in RA SF, all other lipid mediators and PUFA were comparable between OA and RA samples. Ratios of metabolites to their precursors indicated that both pro- (e.g. LTB_4) and anti-inflammatory LOX products (e.g. 17-HDHA) are more efficiently generated in RA than in OA patients, while no differences were observed in COX products. Interestingly, the SPM resolvin D2 (RvD2) could also be detected, but only in the insoluble fraction (cells and undigested matrix), indicating that the resolution pathways are activated in OA. This expands our previous publication showing activation of resolution in RA patients. To assess the efficiency of activation of resolution in OA, we have performed targeted lipidomics on total SF in an additional study with 32 OA patients and 10 healthy controls. Confirming earlier data, most LMs were also detected in this study, including the pro-inflammatory PGE_2, the SPM precursors 17-HDHA and 18-HEPE, and the SPM RvD2. Additionally, we detected 18S-resolvin E3 (18S-RvE3). Remarkably, both the absolute concentrations of the SPM RvD2 and 18S-RvE3, and the ratio to their precursors, 17-HDHA and 18-HEPE, were lower in OA compared to healthy SF, indicating less efficient generation of SPM in OA compared to healthy joints. In contrast, the pro-inflammatory lipid $PGE_2$was higher in OA than in healthy SF, indicating that the lower activation of resolution is paired by a higher inflammatory load in OA compared with healthy individuals.

Conclusion: By using a state-of-the-art technique, we show for the first time that resolution pathways are activated in OA patients. Importantly, resolution seems to be less efficiently activated than in healthy individuals, which could account for the persistent inflammation observed in OA and RA patients.

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Abstract Number: 1126

Interleukin-1 Is Not Involved in Synovial Inflammation and Cartilage Destruction in Collagenase-Induced Osteoarthritis

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Background/Purpose: Osteoarthritis (OA) is characterized by severe cartilage destruction, with a putative role for synovial macrophages. Up to 50% of the patients also show low grade joint inflammation reflected by a thickened synovial lining and elevated release of macrophage-derived mediators like interleukin-1 (IL-1) and S100A8/A9. The deteriorating role of S100A8/A9 in OA has been studied extensively, but the contribution of IL-1 to OA pathology is still unclear. IL-1 mediates cartilage destruction by degrading existing proteoglycans through stimulating degradative enzyme production, and by inhibiting new formation of proteoglycans. However, treatment of OA patients with IL-1 inhibitors has so far been disappointing. Here we investigated the role of IL-1α and IL-1βin synovitis and cartilage destruction during collagenase-induced OA (CiOA).

Methods: CiOA was induced by intra-articular injection of collagenase in WT and IL-1$\alpha\beta^{-/-}$mice. In addition, IL-1 signaling was inhibited in WT mice with CiOA using osmotic pumps containing IL-1RA. Histology of total knee joints was used to assess synovitis and cartilage destruction with a modified Pritzker score. Activity of cartilage-degrading enzymes was determined using antibodies against aggrecan neo-epitopes VDIPEN and NITEGE. Synovial gene expression was analyzed using qRT-PCR. Serum protein levels were measured with Luminex. S100A8/A9 protein levels were determined with a sandwich ELISA.

Results: At early stage (day 7) of CiOA, gene expression of IL-1β within inflamed synovium was significantly elevated when compared to synovium of naïve control knees. In later stages (day 21 and 42), IL-1β expression levels showed a steep decline. This is in contrast to pro-

inflammatory mediators like S100A8 and S100A9 which remained elevated on day 21. Remarkably, synovial inflammation on day 7 in IL-1αβ$^{-/-}$ mice was not different from WT controls (2.9±0.2 vs. 2.7±0.4), suggesting that IL-1 does not aggravate synovitis. Absence of IL-1α and IL-1β had no effect on the synovial gene expression levels of pro-inflammatory factors KC, S100A8 and S100A9. IL-6 mRNA levels, however, were significantly decreased in the synovium of IL-1αβ$^{-/-}$ mice. The lack of IL-1α and IL-1β also did not affect gene expression of anti-inflammatory cytokines IL-10 and iNOS. Moreover, serum protein levels of KC, IL-6, IL-10 and S100A8/A9 on day 7 of CiOA in IL-1αβ$^{-/-}$ mice were not different when compared to WT mice. No difference was found in MMP and ADAMTS activity on day 7 between WT and IL-1αβ$^{-/-}$ mice. In line, cartilage destruction on day 42 was not significantly different between both strains (mean OA score of 59.2±25.4 and 74.8±27.0, respectively), which was supported by our finding that IL-1RA treatment in WT mice with CiOA did not alter joint destruction (mean OA score of 44.7±33.3 in treated mice vs. 56.2±20.5in untreated mice).

Conclusion: IL-1α and IL-1β are not involved in synovial inflammation and cartilage destruction during collagenase-induced osteoarthritis, implicating that other mediators are responsible for the joint damage.

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Abstract Number: 1127

Extracellular Macrophage Migration Inhibitory Factor Is Essential for Hypoxia-Induced Angiogenesis in a Hypoxia Inducible Factor Independent Manner

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Background/Purpose: Angiogenesis is a hallmark of the pathogenesis of rheumatoid arthritis (RA) but also of other inflammatory processes, tissue regeneration and progressing tumors. In RA, the neovascular network is dysfunctional and fails to restore tissue oxygen homeostasis, so that the inflamed joint remains markedly hypoxic. The hypoxia-induced multifunctional and pro-inflammatory protein macrophage migration inhibitory factor (MIF) participates in the regulation of hypoxia-induced angiogenesis. At cellular level, hypoxia is detected by a mechanism that regulates the amount of the oxygen-sensitive α-subunits of the transcription factors, hypoxia-inducible factor (HIF)-1 and -2, which activate a gene program associated with angiogenesis and glycolysis. Here, we focus on the role of MIF and its mechanism of action in the process of hypoxia-induced angiogenesis and in the regulation of HIFs.

Methods: Therefore, we developed a specific knockdown of MIF and its receptor CD74 in Human Microvascular Endothelial Cell (HMEC) using lentiviral-based shRNA technology allowing us to analyse the role of MIF in hypoxia-induced angiogenesis. We investigated the adaption of these cells towards pathophysiologic hypoxic conditions (1% O_2) analysing protein-levels of HIF-1α and HIF-2α, HIF-target gene expression, angiogenesis and VEGFA release. To further identify the underlying mechanisms angiogenesis assay was performed with HMECs treated with anti-CD74-IgG, rhMIF and 4-IPP, a small molecule inhibitor of MIF.

Results: Lentiviral-mediated reduction of MIF in HMEC led to significantly decreased angiogenesis ($p<0.01$) which could be restored by adding extracellular rhMIF. Interestingly, reduction of MIF did not influence hypoxia-induced (i) protein-levels of HIF-1α and HIF-2α, respectively, and (ii) HIF-target gene expression of *PGK1*, *GAPDH* and *VEGFA* but (iii) induced secretion of pro-angiogenic VEGFA and IL8. Moreover, addition of 4-IPP also decreased angiogenic response of non-transduced HMECs but enhanced the hypoxia-induced HIF-target gene expression of *PGK1* and *VEGFA*. Inhibiting MIF-signalling by the addition of extracellular anti-CD74-IgG also reduced angiogenic potential of HMEC ($p<0.001$), which was not restorable by the addition of extracellular rhMIF. Furthermore, lentiviral-mediated reduction of CD74 in HMEC also decreased angiogenesis ($p<0.01$) again without influencing HIF-target gene expression of *PGK1*, *GAPDH* and *VEGFA*.

Conclusion:

Our findings reveal an essential regulatory function of MIF upon the angiogenic potential of HMECs. Hypoxia-induced MIF-dependent induction of angiogenesis is independent of HIF-mediated activation of a gene program associated with angiogenesis and glycolysis including VEGFA secretion. These findings open new possibilities for therapeutic approaches in RA and other inflammatory disorders by targeting specific MIF-mediated signalling events.

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Abstract Number: 1128

Anti-Fractalkine Monoclonal Antibody Inhibits Cartilage Destruction and Bone Erosion in Collagen-Induced Arthritis Model

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease leading to joint destruction. In the previous Phase 1/2 clinical study, E6011, a novel humanized anti-fractalkine (FKN) monoclonal antibody (mAb) demonstrated a promising efficacy in active RA patients who were inadequately controlled by MTX and/or TNF-a inhibitors. However, the effect of anti-FKN mAb on joint destruction remains to be elucidated. In RA, synovium-infiltrated monocytes/macrophages cause synovitis and cartilage damage by the induction of matrix metalloproteases and inflammatory cytokines. Osteoclasts are generated from osteoclast precursor cells (OCPs) and cause bone erosion. FKN is expressed on endothelial cells and fibroblast-like synoviocytes in synovium in both experimental arthritis model and RA patient. Moreover, it is reported that FKN expressed by osteoblasts in neonatal mouse calvariae. CX3CR1, the receptor for FKN, is expressed on monocytes/macrophages and OCPs. Therefore, the interaction of FKN and CX3CR1 might play important roles in migration, differentiation and activation of these cells, leading to cartilage damage and bone erosion. In this study, we examine the efficacy of anti-FKN mAb on collagen-induced arthritis (CIA) in mice, especially on joint destruction.

Methods: For the induction of CIA, DBA/1J mice were immunized with intradermal injections of bovine type II collagen on days 0 and 21. Four hundred micrograms of anti-FKN mAb or control IgG intraperitoneally injected twice a week from the day of the 1stimmunization (for the prophylactic treatment) or after the onset of CIA (for the therapeutic treatment). The clinical arthritis score was defined as the sum of the scores of four paws. Plasma concentration of Tartrate-Resistant Acid Phosphatase type 5b (TRAP-5b), Cartilage Oligomeric Matrix Protein (COMP), Matrix Metalloproteinase 3 (MMP-3) were measured using ELISA. Radiological score was measured by the soft x-ray for limb bones. For histopathological analysis, Alcian blue/Alizarin red and Tartrate-Resistant Acid Phosphatase (TRAP) staining were performed using frozen sections of ankle joints.

Results: The prophylactic treatment of anti-FKN mAb significantly reduced the clinical arthritis score, soft x-ray score and plasma levels of TRAP-5b, COMP and MMP-3, compared with the treatment of control IgG. Histopathological analysis demonstrated almost complete suppression of synovitis, pannus formation, cartilage degradation and bone erosion by the treatment of anti-FKN mAb. The number of TRAP-positive cells was also dramatically decreased in anti-FKN mAb–treated mice. Importantly, therapeutic treatment of anti-FKN mAb significantly ameliorated clinical arthritis score and soft x-ray score compared with the treatment of control IgG.

Conclusion: Anti-FKN mAb demonstrated a remarkable efficacy in established mouse CIA and completely inhibited the cartilage damage and bone erosion with the reduction of osteoclasts. These results indicate that inhibition of FKN/CX3CR1 axis by a humanized anti-FKN mAb, E6011, is an attractive therapeutic strategy for the treatment of both inflammatory synovitis and joint destruction of RA.

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Abstract Number: 1129

Tumor Necrosis Factor Receptor 2 Is Crucial for Regulatory T Cells Activity with Consequences in a Model of Chronic Inflammation and in Anti-TNF Treated Rheumatoid Arthritis

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Background/Purpose: $CD4^+FoxP3^+$ regulatory T cells (Tregs) are essential for maintaining immune homeostasis, and are functionally defective in rheumatoid arthritis (RA) and other chronic inflammatory diseases. In RA, effective anti-TNF treatment was found to modify Tregs phenotype and restore their suppressive function. Tregs express the two TNF receptors (TNFR): TNFR1 and TNFR2. Nevertheless, the respective roles of TNFR1 and TNFR2 in mediating the effect TNF on Tregs are still unclear. Likewise, whether TNF blockade may affect Tregs via the TNF receptors, is not clearly established. To dissect the role of the TNF-TNFR2 system on Tregs in chronic inflammatory diseases by **:** 1) determining the effect of the interaction between TNF and TNFR2 on cultured mouse Tregs 2) studying the effect of TNFR2 deficiency in a model of chronic inflammation 3) analyzing the influence of anti-TNF therapy on TNFR2 expression on Tregs in RA patients

Methods: Tregs were purified by magnetic separation from mice spleen and their frequencies and phenotype were analyzed by flow cytometry. TNFR2 deficient mice were used. Psoriasis-like skin inflammation was induced by imiquimod skin application. Tregs from blood of RA patients were studied by flow cytometry.

Results: TNF induces Foxp3 maintenance in cultures of purified mouse Tregs. With two models of TNFR2 inactivation (a TNFR2-blocking antibody and a TNFR2 knock-out mouse) we showed that this effect was mediated by TNF-TNFR2 -and not TNFR1- interaction. Moreover, compared to Tregs from wild type (WT) mice, TNFR2-deficient Treg showed reduced suppression of effector T cells (Teff) proliferation and Teff interferon-g production. TNF decreased CD39 expression and ATP hydrolysis activity in cultured Tregs. Additionally, TNFR2-deficient Tregs were less effective in hydrolyzing ATP than Tregs from WT mice. In parallel, we evaluated the consequences of TNFR2 deficiency in a model of skin inflammation, namely imiquimod-induced psoriasis. In TNFR2- deficient mice, Tregs frequencies were lower and the clinical signs of psoriasis were aggravated, compared to WT mice. Moreover, in the peripheral blood of RA patients treated with anti-TNF agents there was both an increase in total Tregs frequencies, and in the frequency of Tregs expressing TNFR2 at 3 months of treatment vs. the baseline.

Conclusion: The integrity of the TNF-TNFR2 system is critical for Treg survival and suppressive activity *in vitro*. TNFR2 deficiency aggravates a model of chronic skin inflammation. Three-month anti-TNF treatment is associated with an increase of TNFR2-expressing Tregs in the peripheral blood of RA patients. These data suggest that the effect of TNF blockade on Tregs may rely on the activation of the TNF-TNFR2 system.

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Abstract Number: 1130

Aminopeptidase N/CD13 Induces Monocyte Migration in Vitro and In Vivo and Signals through GPCR, Erk1/2, Jnk, Src, and NFκB

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Background/Purpose: Aminopeptidase N/CD13 is a metalloproteinase expressed on the surface of fibroblast like synoviocytes (FLS). It is found in soluble form in serum and rheumatoid arthritis (RA) synovial fluid (SF). We have shown that CD13 induces T cell migration and FLS proliferation. In this study, we determine the role of CD13 in monocyte (MN) migration, signaling mechanisms involved and its role in acute inflammatory arthritis.

Methods: To examine the functional significance of CD13, we performed an *in vitro* migration assay using normal human MNs and U937 cells. We examined the signaling mechanisms involved in CD13-induced MN migration using signaling inhibitors and pertussis toxin (PT). To assess whether its enzymatic activity contributes to CD13-induced phosphorylation of signaling molecules and MN migration, we generated enzymatically inactive (mutant CD13) and active (WT CD13). MN chemotaxis was performed with CD13-depleted RA SF supplemented with mutant or WT CD13. To examine the role of CD13 in RA, MN migration was performed with CD13- and sham-depleted RA SF. To determine the crosstalk between CD13-induced signaling intermediates, RA FLS, MN, and U937 cells were treated with or without signaling inhibitors or PT before CD13 stimulation. To test the arthritogenicity of CD13 *in vivo*, CD13 or PBS was injected into mouse knees. Joint circumference was measured at 0 and 24h. Pro-inflammatory mediators in knee joint homogenates were measured by ELISA.

Results: We found that CD13 is a potent chemoattractant for MNs and U937 cells. Chemotaxis was significantly decreased by inhibitors of Erk1/2, Src, NFκB, and Jnk, and was strongly inhibited by PT, a G-protein coupled receptor (GPCR) inhibitor, indicating the role of these molecules in CD13-mediated MN migration. CD13-depleted RA SF induced significantly less MN migration than sham-depleted, while addition of mutant or WT CD13 to CD13-depleted RA SF restored MN migration similar to the sham-depleted. CD13 and WT and mutant CD13 had similar effects in activating signaling molecule phosphorylation, indicating that enzymatic activity had no effect on these CD13 functions. CD13 induced Erk1/2, Src, NFkB and Jnk phosphorylation in MNs and U937 cells. In RA FLS, phosphorylation of Erk1/2, Src, and NFκB showed similar results, but there was no phosphorylation of Jnk. We found that the GPCR inhibitor, PT, decreased CD13-stimulated phospho-Erk1/2 in MNs, U937, and RA FLS, suggesting that GPCRs are upstream in CD13-mediated signaling pathways. In an acute model of inflammation, there was a significant increase in the knee circumference in mice injected with CD13 compared to PBS, indicating that CD13 contributes to acute inflammatory arthritis. MCP-1/CCL2 and IL-1β were significantly higher in CD13-injected knee joint homogenates, while TNFα and IL-6 were not.

Conclusion: CD13 is strongly chemotactic for MNs and U937 cells. CD13 contributes to MN migration independent of its chemotactic activity. CD13 induces MN migration through Erk1/2, Src, NFkB, Jnk, and GPCR. CD13 plays an important role in RA SF mediated MN migration. CD13 contributes to acute inflammatory arthritis by increasing MCP-1/CCL2 and IL-1β. CD13 may be a potential therapeutic target in RA.

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Abstract Number: 1131

Regulation of Rheumatoid Arthritis Synovial Fibroblast Cytokine Production By Inhibitor of DNA Binding-1 Via Crispr/Cas9 Transfection

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Inhibitor of DNA binding-1 (Id1) is a nuclear protein actively transcribed in endothelial progenitor cells (EPCs) and synovial fibroblasts. We previously identified Id1 as a soluble inflammatory protein that displays elevated expression in rheumatoid arthritis (RA) synovial tissues (STs) and effusions, contributing to angiogenesis, vasculogenesis and cellular migration. We and others have shown that RA fibroblasts display unchecked growth and are a major source of cytokine production. In this study, we investigated the mechanisms of Id1 regulation of synovial fibroblast cytokine production, trans-cellular activity and cellular growth in the RA joint.

Methods: RA STs and K/BxN mouse ankles were analyzed histologically for correlation of Id1 expression and disease severity. Exosomes from fibroblast supernatants and synovial fluids (SFs) were purified via differential centrifugation. Exosome fractions were then subjected to 0.5% Triton X-100 for lysis and measured for Id1 by ELISA. RA fibroblasts were transfected with a clustered regularly interspaced short palindromic repeats (CRISPR)/Cas9 plasmid, containing a GFP insert, via electroporation to induce error-prone non-homologous end joining repair (NHEJ), causing a nonsense mutation and removal of the targeted Id1 gene. To validate transfection efficiency, Tracking of Indels by Decomposition (TIDE) analysis was performed to verify CRISPR/Cas9 activity in the transfected fibroblasts. GFP-positive cells deleted of Id1 were then sorted by FACS, cultured for 24 hours, and measured for cytokine release and cell proliferation.

Results: Histologic analysis revealed positive correlations of Id1 expression and disease severity by Pearson's Correlation Coefficient in RA STs ($r=0.74$, $p<0.05$, $n=12$) and K/BxN mouse ankles ($r=0.87$, $p<0.05$, $n=10$). RA compared to osteoarthritis (OA) fibroblast culture supernatants contained greater amounts of exosomes, and >80% of the Id1 released by RA fibroblasts was encapsulated within exosomes. Correspondingly, exosomes isolated from SFs have abundant levels of Id1 with a two-fold higher amount of Id1 in RA compared to OA SFs. We targeted Id1 to determine the function of Id1 on RA fibroblast growth and cytokine production. TIDE analysis confirmed CRISPR/Cas9-mediated NHEJ at the Id1 gene, resulting in Id1 deleted cells. Id1 deleted RA fibroblasts showed a 40% decrease in cell proliferation, and four and 100 fold increases in IL-6 and IL-8 production respectively, compared to transfected control plasmids and sham transfected (no plasmid) cells. Epithelial-derived neutrophil-activating peptide 78 (ENA-78)/CXCL5 did not show an increase in the Id1 deleted RA fibroblasts. The attenuated fibroblast growth in the RA fibroblasts can be explained, in part, by a significant increase in IL-6, a known inhibitor of fibroblast growth.

Conclusion: We show that Id1 is upregulated and packaged within RA fibroblast exosomes for trans-cellular distribution. Id1 deletion by CRISPR/Cas9 transfection significantly slows RA fibroblast growth and induces elevated production of IL-6 and IL-8. Our data indicate that Id1 is an active regulator of both fibroblast growth and proinflammatory cytokine production in the RA joint.

Disclosure: R. A. Ohara, None; **G. Edhayan**, None; **T. L. Saunders**, None; **T. M. Lanigan**, None; **R. Morgan**, None; **W. A. Stinson**, None; **P. L. Campbell**, None; **J. Graham**, None; **D. A. Fox**, None; **J. H. Ruth**, None.

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Abstract Number: 1132

The Musculoskeletal Master Educator Training Program: A New Resource and Professional Development Opportunity for Leaders in Medical Education

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Background/Purpose: In response to the Veterans Access, Choice, and Accountability Act of 2014, the Veterans Health Affairs (VHA) Simulation Learning, Education and Research Network (SimLEARN) National Simulation Center launched the Musculoskeletal (MSK) Master Educator program. This initiative aims to improve veteransÕ access to appropriate care by strengthening training in the evaluation and management of common MSK conditions. This report describes the first year of the SimLEARN MSK Master Educator program.

Methods: The 2-day course was held at the SimLEARN facility in Orlando, and focused on evaluation and management of shoulder and knee pain in primary care. Opportunity to attend was communicated through national, regional, and local VHA organizational networks. Curriculum was introduced through didactics, reinforced in small-group hands-on sessions enhanced by peer-teaching and simulation via standardized patients and joint injection task-trainers. Pre- and post-course self-assessments were collected, using a 5-point response scale. Competence was assessed using a previously validated objective structured clinical examination (OSCE). Finally, participants rotated through an observed structured teaching experience (OSTE), where they practiced roles of simulated patients, evaluators and learners. Data were analyzed using SPSS.

Results: Twenty-five participants completed the program in 2016 (15 physicians, 7 nurse practitioners (APRN), 2 physician assistants (PA), 1 nurse). Participants consistently gave high ratings to the importance of competence in the evaluation and management of MSK conditions, and self-reported competence ratings were significantly higher after the course (Table 1). Mean OSCE score was 83% (SEM = 3); statistical description of OSCE scores is reported in Table 2. There were no significant differences in OSCE score across disciplines or years of experience.

Conclusion: The SimLEARN MSK Master Educator course is a new professional development workshop for clinical educators, providing content instruction, external assessment of competence, a portable curriculum, and structured practice teaching and evaluating peer learners in an OSTE. Participants from a broad range of disciplines and experience levels reported significant increases in confidence and competence in evaluating and managing MSK problems. Next steps will involve dissemination of this opportunity to leaders in medical and health professions education, and implementation of adaptations of the training program at educatorsÕ local institutions.

Table 1. Self-Reported Survey Results

	Pre-course Mean	Post-course Mean	Mean Paired Difference (p)
How *confident* are you in your ability to:			
Evaluate shoulder pain	3.2	4.4	1.2 (<0.0001)
Perform a subacromial injection	2.3	3.8	1.5 (<0.0001)
Evaluate knee pain	3.2	4.2	1.0 (<0.0001)
Perform a knee injection	2.7	3.9	1.2 (<0.0001)
How *competent* are you to:			
Perform a subacromial injection	2.5	3.9	1.4 (<0.0001)
Perform a knee injection	2.9	3.9	1.0 (<0.0001)
How *important* is it to be competent to:			
Evaluate shoulder pain	4.7	4.8	0.1 (0.185)
Perform subacromial injections	4.2	4.3	0.1 (0.425)
Evaluate knee pain	4.7	4.8	0.1 (0.185)
Perform knee injections	4.2	4.4	0.2 (0.382)

Table 2

Statistical Results of Objective Structured Clinical Examination (OSCE)						
		N	Mean OSCE Score (%)	Std. Error	Minimum	Maximum
Discipline	Primary Care Physicians	12	83	3	60	100
	Specialty Care Physicians	3	87	3	80	100
	PA/APRN	10	82	5	40	100
Years of Experience	< 3 years	4	73	11	40	90
	3 - 5	3	80	6	70	90
	6 - 10	3	90	0	90	90
	11 - 20	8	86	3	70	100
	> 20	7	84	5	60	100
Overall Total		25	83	3	40	100
ANOVA Results						
		Sum of Squares	df	Mean Square	F	Sig.
Discipline	Between groups	0.005	2	0.003	0.143	0.867
	Within groups	0.389	22	0.018		
	Total	0.394	24			
Years of Experience	Between groups	0.071	4	0.018	1.098	0.385
	Within groups	0.323	20	0.016		
	Total	0.394	24			

Disclosure: **A. M. Barker**, None; **Y. Okuda**, None; **P. Bruno**, None; **B. Peplinski**, None; **A. Artino**, None; **J. La-Rochelle**, None; **G. W. Cannon**, Amgen, 2; **M. J. Battistone**, None.

Abstract Number: 1133

Can Patient Videos in Lectures Increase Interest and Improve Learning in Rheumatology Among Second Year Medical Students?

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Given the expanding aging population and burden of rheumatic diseases, along with an anticipated shortage of rheumatologists, there is increasing urgency to develop curriculums that properly train and attract new fellows. A recent study showed a low level of self assessed confidence in rheumatology knowledge and skills among internal medicine residents despite increasing years of training1. Increased patient exposure can potentially increase students' interest in becoming rheumatologists. It remains to be tested whether videos featuring patients can be an effective teaching tool. The aim of this study is to assess whether videos featuring real patients can increase interest and improve learning in rheumatology among second year medical students.

Methods:

A rheumatologist gave a PowerPoint lecture on rheumatoid arthritis (RA) followed by short video segments featuring real patients talking about their experiences with RA. The rheumatologist explained and demonstrated physical findings characteristic of RA. Prior to filming, the patients completed informed consents stating that the videos will only be used for educational purposes. Immediately after lecture, students rated their confidence in taking a history from patients with joint pain, forming differential diagnoses for patients with joint pain and identifying physical exam findings associated with RA. The survey included a comments section to gather students' perception of the videos.

Results:

TABLE 1. Demographic Characteristics of Second Year Medical Students and their Interest in Rheumatology (n=61)

Gender	
Male	30 (49%)
Female	31 (51%)
Age	24 (median)
Career Plan	
Internal Medicine	0 (0%)
Internal Medicine Subspecialty	15 (24.6%)
Surgical Specialty	15 (24.6%)
Other	25 (41%)
Undecided	5 (8.2%)
Have you had a medical school lecture in rheumatology?	
Yes	53 (86.9%)
No	8 (13.1%)
Did this lecture increase your interest in taking a rheumatology elective?	
Yes	31 (51%)
No	15 (24.5%)
Undecided	15 (24.5%)
Do you have an interest in rheumatology as a career?	
Yes	1 (1.6%)
No	35 (57.4%)
Undecided	25 (41%)
Did this lecture increase your interest in pursuing rheumatology as a career?	
Yes	10 (16.4%)
No	31 (50.8%)
Undecided	20 (32.8%)
Do you have adequate exposure to rheumatology in two years of medical school?	
Not at all	6 (9.8%)
A little bit	12 (19.7%)
Somewhat	20 (32.8%)
Adequate	23 (37.7%)
Very Adequate	0 (0%)

TABLE2. Comparison of confidence rating based on self-reported impact from video exposure

Video Impact	N (%)	Average Rating┼ (+/- S.D.)	P value*
Patient History Gathering			
Increased confidence	31 (51%)	3.5 +/- 0.6	**<0.01**
No change in confidence	30 (49%)	2.5 +/- 0.7	
Forming Differential Diagnosis			
Increased confidence	23 (38%)	3.3 +/- 0.6	**<0.01**
No change in confidence	38 (62%)	2.5 +/- 0.8	
Identifying RA Physical Exam Findings			
Increased confidence	46 (75%)	3.8 +/- 0.7	**<0.01**
No change in confidence	15 (25%)	2.9 +/- 0.5	
Board Exam Preparation			
Helpful	27 (45%)	3.2 +/- 0.8	**<0.01**
Did not help	33 (55%)	2.5 +/- 0.9	

┼Rating on a (1) to (5) scale: (1) not at all (2) a little bit (3) somewhat (4) moderately (5) extremely

*p-values were obtained using the Mann-Whitney-Wilcoxon test

Among students who reported that watching the videos increased their confidence in history gathering, forming differential diagnoses, identifying RA physical findings in patients with joint pain, they also reported higher level of confidence in those areas compared to

students who did not report increase in confidence from watching the videos. In the comments section, students reported the videos were 'helpful', 'personable', 'memorable', and useful in recalling 'landmark manifestations more easily' and in realizing the drastic changes of RA on patients' lives.

Conclusion:

This study suggests that including patient videos in lectures may generate interest in rheumatology and increase self perceived confidence in taking a history and physical from patients with joint pain. More rigorous studies are needed to evaluate the role of patient videos in medical school curriculum.

Reference:

1. Kroop SF, Chung CP, Davidson MA, et al. Rheumatologic skills development: what are the needs of internal medicine residents? Clin Rheumatol. 2015

Disclosure: S. Wang, None; **M. Meltzer**, None.

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Abstract Number: 1134

Confidence and Competence of Medicine Trainees' Musculoskeletal Skills: A Report of the Relationship from a Large Multi-Year, Multidisciplinary Cohort

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: The Musculoskeletal (MSK) Education Week for medical students, residents, fellows, and trainees of other health professions has been sustained since 2011. The objective of this study was to examine the relationship between self-reported measures of confidence and observed measures of competence in this multi-year, multidisciplinary cohort of trainees.

Methods: The MSK Education Week emphasized the evaluation and management of shoulder and knee pain. Self-reported confidence was captured utilizing a 5-point Likert scale at the start and conclusion of the program. Competence was measured at the end of the program by a validated 2-station objective structured clinical examination (OSCE) with a rater unaware of the self-reported confidence. Self-report ratings of 3 (neutral) or lower were categorized as ÒlessconfidentÓ; performance on the OSCE was categorized as ÒlowÓ for those lower than 2 standard deviations from the mean. Chi-square was calculated for dichotomized self-assessment ratings and OSCE scores, and PearsonÕs correlation was performed on all data.

Results: Since 2013, 233 trainees have participated in the MSK education week. Response rates producing complete data sets were 86% for shoulder and 80% for knee. Confidence ratings by participants across all disciplines increased after the course (Table 1). Mean OSCE score was 92% for the shoulder and 86% for the knee. Table 2 shows the relationship of dichotomized confidence ratings and OSCE scores; there was no significant difference between the groups (shoulder $X^2 = 1.22$, $p = .269$; knee $X^2 = 0.18$, $p = .672$). PearsonÕs coefficient indicated no correlation between confidence and competence for the shoulder (r = 0.02) or the knee (r = 0.1).

Table 1

Postgraduates	N			Total (%)	Mean Rating		
	2013 – 2014	2014 – 2015	2015 – 2016		Pre-course Confidence	Post-course Confidence	OSCE
					Shoulder / Knee		
Internal medicine							
PGY-1	31	33	35	99 (42)	2.6 / 3.0	4.4 / 4.4	4.6 / 4.2
PGY-2	2	...	...	2 (1)	2.8 / 3.1	4.3 / 5.0	4.8 / 5.0
PGY-3	1	...	...	1	2.4 / 4.0	...	...
PM&R							
Preliminary PGY-1	1	3	4	8 (3)	3.2 / 3.3	4.6 / 4.6	4.7 / 4.3
PGY-3	4	3	5	12 (5)	3.7 / 3.9	4.6 / 4.6	4.4 / 4.5
Occupational medicine	1	5	5	11 (5)	3.4 / 3.7	4.4 / 4.4	4.4 / 4.2
Physical therapy residents	...	4	4	8 (3)	4.1 / 4.2	4.4 / 4.4	4.7 / 4.4
Neurology (preliminary PGY-1)	1	...	6	7 (3)	2.6 / 2.9	4.3 / 4.4	4.4 / 4.4
Orthopaedics (PGY-1)	4	2	...	6 (3)	3.7 / 4.1	4.6 / 4.7	4.2 / 4.2
Rheumatology (PGY-4)	2	1	2	5 (2)	3.6 / 4.0	4.9 / 5.0	4.5 / 4.7
Pharmacy residents	...	5	...	5 (2)	1.4 / 1.3	3.9 / 3.5	4.1 / 3.2
Geriatrics (PGY-4)	1	...	2	3 (1)	3.3 / 3.3	...	...
Family medicine	...	...	3	3 (1)	3.9 / 4.2	4.8 / 4.8	4.5 / 5.0
Anesthesia pain (PGY-4)	...	...	1	1	4.2 / 4.6	...	...
Students							
Physician assistant	10	12	12	34 (15)	3.0 / 3.2	4.4 / 4.3	4.6 / 4.3
Advance practice nursing	9	7	1	17 (7)	2.0 / 2.8	4.4 / 4.4	4.6 / 4.5
Medicine (MS 4)	4	7	...	11 (5)	2.8 / 3.1	4.4 / 4.4	4.6 / 4.4
Total	71	82	80	233 (100)	2.9 / 3.2	4.4 / 4.4	4.6 / 4.3

Abbreviations: PGY, postgraduate year; PM&R, physical medicine and rehabilitation; MS 4, fourth year medical student.

Table 2 – Relationship of Dichotomized Confidence Rating and OSCE Score

		OSCE Performance		
		Low	High	Total
Shoulder	Less Confident	0 (0%)	17 (9%)	17 (9%)
	Highly Confident	11 (6%)	172 (86%)	183 (92%)
	Total	11 (6%)	189 (95%)	200 (100%)
				$X^2 = 1.22$, $p = .269$
Knee	Less Confident	1 (1%)	13 (7%)	14 (7%)
	Highly Confident	8 (4%)	165 (88%)	173 (93%)
	Total	9 (5%)	178 (95%)	187 (100%)
				$X^2 = 0.18$, $p = .672$

Conclusion: The MSK Education Week is a sustainable program that has demonstrated effectiveness across a range of disciplines and learner levels for over 3 years. Following the program, the majority of participants were both highly confident and highly competent. A small number of participants whose observed competence was low were nonetheless highly confident. The lack of correlation between self-report and objective measures supports the continued development and use of meaningful external measures of competence for trainees in medical education and health professions programs.

Disclosure: A. M. Barker, None; **G. W. Cannon**, Amgen, 2; **M. J. Battistone**, None.

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Abstract Number: 1135

Long-Term Impact of an Enhanced Rheumatology Curriculum for Internal Medicine Residents

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Background/Purpose: Internal medicine (IM) residents need to be trained in the diagnosis and care of patients with rheumatologic disease. Our prior data show that a multimodal simulation training session (MSTS) enhanced curriculum improves post graduate year (PGY) 1 IM residents' self-confidence in rheumatologic history taking, physical exam, ordering and interpreting laboratory test results, procedures and patient care. To assess if this enhanced curriculum has a long-term impact on trainees' self-confidence, we compared self-assessment surveys of PGY3 IM residents who received this MSTS curriculum while PGY1 residents to those who had not.

Methods: Since 2014, all PGY1 IM residents participate in a MSTS enhanced curriculum during the ambulatory rheumatology block which includes direct observation , discussion and feedback of their evaluation of a standardized patient with knee pain as well as knee aspiration training using a mannequin model. All PGY3 residents are invited to complete a web-based survey assessing confidence (0=not confident, 100=extremely confident) in performing a rheumatologic history, exam and common rheumatologic procedures (injection and aspiration of the knee and shoulder and trochanteric bursa injection), in ordering and interpreting rheumatologic lab tests (ESR, CRP, RF, CCP, ANA) and in caring for patients with OA, SLE, RA, gout, and fibromyalgia. The survey also includes demographics and participation in additional rheumatology electives. We compared the PGY3 survey results between those who had participated in the MSTS enhanced curriculum 2 years prior during their PGY1 year (Group 1) with an historical control group who did not have the enhanced curriculum (Group 2)using the Wilcoxon Signed Rank test. The Institutional Review Board approved the study.

Results: 33/42 (79%) PGY3 IM residents from the MSTS enhanced group (Group 1) and 67/85 (79%) from the control group completed the survey. 48% of respondents were female in Group 1 and 55% were female in Group 2. 14/33 (42%) in group 1 and 30/67 (45%) in group 2 took an additional rheumatology elective during training. There was a significantly higher self-assessed confidence in ordering and interpreting ANA and RF in those residents that had participated in the MSTS enhanced curriculum (Group 1) compared to controls (Group 2). There was no significant difference in self-assessed confidence in all other metrics (Table).

Conclusion: Our MSTS enhanced curriculum during the PGY1 ambulatory rheumatology block was associated with higher self-assessed confidence two years later at the PGY3 level in ordering and interpreting ANA and RF, but not in the other metrics measured. This suggests that repeat or additional rheumatology specific training may be necessary during the later years of residency to improve IM residents' confidence in all aspects of the diagnosis and care of patients with rheumatologic disease.

Table: PGY3 IM resident self-rated confidence survey results. Visual analogue scale (1-100).

	Group 1 MSTS Enhanced median (IQR)	Group 2 Historical controls median (IQR)	p-value
Self-rated confidence in performing			
Rheumatology history taking	68 (50-77)	64 (37-73)	p=0.25
Rheumatologic exam	61 (50-72)	58 (36-66)	p=0.32
Knee injection	21 (5-36)	27 (9-59)	p=0.25
Knee aspiration	23 (7-68)	48 (12-64)	p=0.47
Shoulder injection	7 (2-19)	11 (2-31)	p=0.34
Trochanteric bursa injection	14 (4-25)	10 (0-27)	p=0.55
Self-rated confidence in ordering and interpreting			
ESR	76 (68-86)	71 (63-83)	p=0.14
CRP	76 (68-86)	73 (67-83)	p=0.28
ANA	70 (57-85)	61 (48-73)	p<0.05
RF	71 (63-83)	68 (52-77)	p<0.05
Anti- CCP	79 (67-88)	75 (61-85)	p=0.16
Self-rated confidence in care of patients with			
Osteoarthritis	76 (70-85)	73 (63-84)	p=0.31
Rheumatoid Arthritis	53 (33-64)	54 (40-68)	p=0.26
Gout	76 (65-88)	74 (62-84)	p=0.29
Systemic Lupus Erythematosus	43 (24-57)	42 (31-64)	p=0.65
Fibromyalgia	52 (38-69)	55 (38-68)	p=0.78

Disclosure: S. F. Kroop, None; **C. P. Chung**, None; **M. A. Davidson**, None; **L. A. Skaug**, None; **D. A. Johnstone**, None; **C. M. Dewey**, None.

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Abstract Number: 1136

Clinician Training in Motivational Communication Skills: The Impact of the Language

of Change Program Among Rheumatologists from Across Canada

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Background/Purpose: Motivational communication (MC) is an evidenced-based communication style designed to enhance patients' intrinsic motivation to engage in a healthy lifestyle and adhere to treatment. Due to its efficacy and popularity, the demand for physician training has risen markedly over the past decade. Despite the widespread dissemination of these programs, there is little empirical data on the extent to which they impact physician knowledge and attitudes. This study assessed the impact of 2 1.5 hour MC workshops (phase 1 and 2 of the Language of Change Program) on MC attitudes among rheumatologists.

Methods: This was a single group pre-post intervention trial. The MC training program, called The Language of Change, was developed by rheumatologists and a behavior change expert. The program being assessed consisted of 2 live workshops (1.5 hour sessions, held roughly 6 months apart) delivered by an MC expert alongside a rheumatologist, to 67 rheumatologists from across Canada. Participants completed a battery of validated questionnaires measuring MC motivation, self-efficacy, outcome expectancies, and short term (30 day) intention to change, at baseline and after each of the Module 1 and 2 sessions. T-tests were conducted to assess the effects of the introductory workshop on each questionnaire.

Results: Analyses revealed significant post-introductory workshop effects on motivation to use MC (+.86, p<.0001), MC self-efficacy (+1.26, p<.0001), outcome expectancies (including perceived program usefulness [+.59, p<.0005], pertinence [+.48, p<.003], effectiveness [+.81, p<.00001], potential to benefit physicians [+.54, p<.0001], potential to benefit patients [+.65, p<.0002], and short term (30 day) intention to change (pre=43%, post=66%).

Conclusion: This study indicates that two 1.5 hour workshops on MC significantly increased motivation to use MC and MC self-efficacy, and had a uniformly positive impact on outcome expectancies and intention to use MC in practice. Results suggest that even a small amount of MC training may impact healthcare professional attitudes and intention to change.

Disclosure: K. L. Lavoie, Paid Consultant of Janssen Inc., Canada, 5; **M. Bell**, Paid Consultant of Janssen Inc., Canada, 5; **T. Taylor**, Paid consultant of Janssen Inc., Canada, 5; **R. Arendse**, Paid Consultant of Janssen Inc., Canada, 5; **M. Saum**, Employee of Janssen Inc., Canada, 3; **D. Faucher**, Employee of Janssen Inc., Canada, 3; **M. Shawi**, Janssen, 3,Johnson & Johnson, 1; **M. Camerlain**, Paid consultant of Janssen Inc., Canada, 5.

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Abstract Number: 1137

Enhancing Pediatric Rheumatology Education through Computer-Assisted Fellow-Taught Case Modules

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Background/Purpose: Teaching is an ACGME milestone for pediatric subspecialty fellows. Despite this expectation, there is little literature regarding how to empower fellows to teach residents. In a recent survey, 100% of Stanford Pediatric Rheumatology fellows were either extremely or very dissatisfied with the teaching they provide. Corroborating fellows' perceptions, Stanford pediatric residents rated the rheumatology rotation the lowest overall in 2014-2015, with teaching identified as a primary weakness. The objective of this study was to evaluate the effect of a novel resident curriculum on resident education and fellow teaching of core pediatric rheumatology topics.

Methods: This is an IRB-exempt, single site, prospective interventional study. Four existing pediatric rheumatology didactic lectures were converted into interactive, computer-assisted, case-based learning modules using e-learning software. Modules were designed to encourage fellow and resident interaction at each clinical decision point. Fellows led didactic sessions on four consecutive Thursdays during the rotation. Study participants included 27 residents and 5 pediatric rheumatology fellows during academic year 2015-2016. 15 residents in the pre-intervention group received 4 existing lectures. So far, 9 of 12 residents in the intervention group have received interactive, computer-assisted, case-based teaching modules. All residents received a pre- and post-rotation knowledge assessment and survey. The primary outcome was resident evaluation of fellow teaching. Secondary outcomes included fellow self-evaluation of teaching, resident knowledge of rheumatologic conditions, and resident evaluation of the Rheumatology rotation.

Results: 10/15 residents (66.6%) in the pre-intervention group and 7/9 residents (77.8%) in the post-intervention group completed the post-rotation survey. Pre-intervention feedback included desire for case-based instruction, a structured approach to rheumatologic diagnoses, and increased teacher-learner interaction. After the intervention, resident rating of fellow lectures improved from 2.75 to 3.60 on 4-point Likert scale ($p<0.05$) and amount of interaction/discussion improved from 2.63 to 3.60 ($p<0.05$). Pre and post-rotation knowledge assessment analysis was limited by suboptimal completion rates. Data collection regarding fellow self-evaluation of teaching and resident rotation evaluation will be completed by July 1, 2016.

Conclusion: Residents on the pediatric rheumatology rotation value case-based, interactive modules, which improve satisfaction and guide teacher-learner discussions about the complex clinical reasoning process in rheumatology. Additionally, this study suggests that computer-assisted case-based modules may be an effective, standardized and easily accessible modality to enhance fellows' teaching of residents.

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Rheumapalooza Update: Applying a Flipped Classroom Instructional Model to an Intensive Rheumatology Curriculum for Second Year Medical Students

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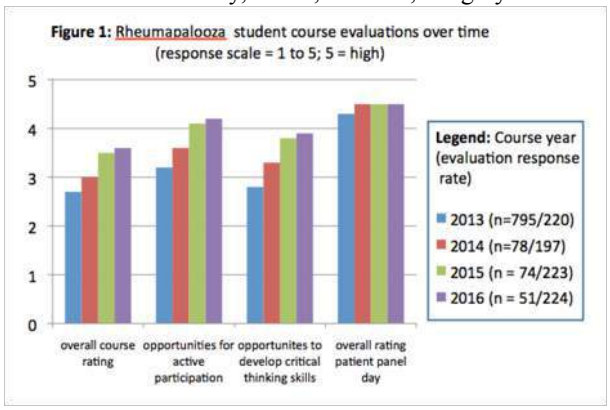
Background/Purpose: Rheumapalooza was implemented in 2008 as a 2 half-day elective course with support from an ACR/REF Clinical Scholar Educator Award. Course evaluation demonstrated significant increases in studentÕs knowledge of rheumatologic disorders and high student satisfaction ratings.[1] Rheumapalooza was incorporated into the required UW Medical School 2nd year curriculum in 2010 and expanded to 3 half days. In 2015 a flipped classroom instructional model was applied to 1 half day of content. We describe lessons learned from ongoing curriculum review with emphasis on increasing opportunities for learner engagement.

Methods: The course now consists of 3 consecutive half-day sessions. Day 1 is structured as a series of foundational didactic lectures.[1] Day 2 was initially delivered in large-group lecture format. Revisions in 2015 put more emphasis on basic rheumatologic disorders and opportunities for active learning. Students were given required reading and 4 case studies to prepare prior to class. Cases reinforce key

aspects of RA, gout, JIA, and SLE. Faculty facilitate student discussion of cases in a small-group format. On day 3, students rotate through 14 stations, including adult and pediatric rheumatology patients, demonstrations of physical therapy, pathology specimens and imaging modalities. Multiple choice exams assess mastery of course material. Students complete annual course evaluations including overall rating, achievement of learning objectives, ratings of specific lectures and days. Numerical and qualitative responses were recorded.

Results: The patient panel day has received consistently high student ratings (Figure 1). Feedback on the lecture days revealed opportunities for improvement. Students reported the lectures felt overloaded and requested more opportunities for cementing knowledge. Modification of the 2nd day to a small-group flipped classroom model was associated with improvement in studentÕs rating of active learning opportunities and overall satisfaction (Figure 1). However, student comments indicated concern about less coverage of rare rheumatologic disorders and inconsistencies between small group instructors.

Conclusion: Integration of a case-based flipped classroom model into the Rheumapalooza curriculum was associated with improved student satisfaction, however, the breadth of information covered decreased. These findings have important ramifications for future medical school curricula development given increasing emphasis on active learning delivery models and shorter duration of pre-clinical teaching hours. Future work will focus on partnership with clinical year course directors to envision adequate coverage of essential rheumatologic concepts across the medical school curriculum. SHAPE * MERGEFORMAT Reference: 1. Emery, Helen, Gardner, Gregory. [abstract]. Arthritis Rheum 2010;62 Suppl 10 :1433 DOI: 10.1002/art.29199.



Disclosure: K. Hayward, None; **G. Gardner**, None; **H. M. Emery**, None.

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The Virtual Rheumatology Clinic: Virtual Patients for Resident Education in Rheumatology

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Background/Purpose: Rheumatology topics can be challenging for residents to master during training. In our program, a survey of residents completing a 2- or 4-week rheumatology elective in 2014-15 demonstrated that many still felt unprepared to provide primary care (67%) or inpatient care (46%) for patients with rheumatologic disease, and for board exams (56%). Residents were confident in their ability to diagnose rheumatologic conditions (71%) but less confident in management of these conditions (47%). We aimed to assess the role of the Virtual Rheumatology Clinic, an online self-study tool developed to supplement resident education in rheumatology through virtual exposure to several common rheumatologic diagnoses, in enhancing the education of the resident.

Methods: Four virtual patient cases were developed to introduce evaluation and management options for patients presenting with

symptoms commonly seen in primary care: 1) monoarticular swelling in an adult, 2) joint swelling in a child, 3) fatigue and unexplained fever, and 4) back pain. Each case begins with the complaint and proceeds through several stages. Learners' decisions shaped the virtual patient's course, allowing the trainee to practice longitudinal decision making and experimentation in a safe environment. Activities included drag-and-drop quizzes, script concordance testing, procedure simulation, and matching exercises, and offer immediate feedback to enhance learning. Links to images, videos, review articles, and primary literature were embedded as well. Modules were available to residents on the web via any computer or tablet. Rotating residents were given time to complete these modules during their elective. Participating residents were asked to complete a pre-test, a post-test associated with each module, and a final survey.

Results: Ten residents rotating in 2015-16 completed the pretest and survey, 7 completed at least one module post-test, and 16 completed the final survey. On post-tests, residents scored higher on knowledge-based multiple choice questions than on key features questions, (76% vs 64% average score). On a 0-10 scale, residents who completed at least one module rated these as helpful (8.8), easy to use (8.7), and realistic (8.1). They were rated as more useful in learning to care for patients in a primary care setting (8.7) or in the hospital (8.3) than for board study (7.4). Residents who completed modules were more confident in their ability to manage rheumatologic conditions and expressed greater interest in caring for patients with these conditions than those who did not complete any modules.

Conclusion: The Virtual Rheumatology Clinic is a an online self-study tool developed to provide virtual exposure to common rheumatologic diagnoses likely to present in primary care. Participants in the pilot cohort found it helpful, easy to use, and realistic, and useful for a variety of settings. It is unclear whether participation increased interest in rheumatology or whether participants are self-selecting. Future work may be able to better assess knowledge acquisition and clinical reasoning skills by random selection of questions to be completed either before or after completion of each module.

Disclosure: B. A. Marston, None; **D. Siegel**, None; **A. P. Anandarajah**, None; **V. Lang**, None.

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Abstract Number: 1140

The Future of Rheumatology: Pediatric and Adult Fellows-in-Training Results from the 2015 ACR/ARHP Workforce Study

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Background/Purpose:

Caring for children and adults with rheumatic diseases in the future requires training an adequate number of rheumatologists today. As part of the 2015 Workforce Study, rheumatology fellows-in-training (FITs) were surveyed to obtain insight into factors affecting the selection of rheumatology as a specialty and their expected career tracks.

Methods:

FITs completed an electronic survey assessing demographics, fellowship information, student debt, and career decisions. Missing responses were excluded from analysis and percentages were calculated based on the number of respondents answering each question.

Results:

Of 497 pediatric and adult FITs in the US, 415 completed the survey (83.5% response rate). FIT demographics are shown in Table 1. Most FITs were women; almost half (48.9%) were international medical graduates (IMGs). 70% of US graduates had student loan debt.

The most common reasons to choose rheumatology were intellectual interest, lifestyle/work hours, and clinical rotations; the least common

reason was income potential. Rheumatologists commonly inspired trainees to pursue rheumatology training, usually during residency.

FITs' career interests are shown in Figure 1. Although private practice was the most commonly preferred career path overall, it was significantly more common for men than women (51.1% vs 38.2%, p=0.0154). Women were more interested than men in the clinician educator track (37.8% vs 22.0%, p=0.0012).

Upon fellowship completion, 11.3% (n=47) of FITs were planning to work part-time, more commonly by women than men (15.9% vs. 2.8%, p=0.0001). 17.5% (n=72) of FITs plan to practice outside the US, the majority being IMGs, as compared to FITs from US medical schools (33% vs. 2.8%, p<0.0001).

Conclusion:

The current study sheds light on challenges facing the future of rheumatology in the US. Rheumatology fellowships are failing to attract graduates from US medical schools, these graduates also have significant student loan debt. Eleven percent of FITs plan to work part time, and 33% of IMGs plan to work abroad, contributing to a potential shortage of rheumatologists.

This study also highlights opportunities to increase the number of future rheumatologists. These include recruiting underrepresented minorities, increasing rheumatology exposure in medical school and residency, encouraging practicing rheumatologists to mentor trainees, providing incentives with loan repayment programs, and encouraging IMGs to stay in the US after fellowship.

	Total N (%)	US graduates N (%)	International graduates N (%)	P value
Gender				
Male	144 (34.7)	75 (35.4)	69 (34.0)	-
Female	270 (65.1)	137 (64.6)	133 (65.5)	-
Other	1 (0.2)	0	1 (0.5)	-
Race				
American Indian / Alaskan Native	3 (0.7)	1 (0.5)	2 (1)	-
Asian	163 (39.9)	66 (31.3)	97 (49) *	p=0.0003
Black or African American	12 (2.9)	4 (1.9)	8 (4)	-
Native Hawaiian / Pacific Islander	4 (1)	2 (0.9)	2 (1)	-
White	210 (51.3)	130 (61.6)	80 (40.4) *	p=0.0001
Two or more races	17 (4.2)	8 (3.8)	9 (4.5)	-
Ethnicity				
Hispanic	26 (6.5)	14 (6.7)	12 (6.2)	-
Not Hispanic	377 (93.5)	194 (93.3)	183 (93.8)	-
Age				
25-30	132 (33.3)	86 (41.7)	46 (24.2) *	p=0.0001
31-35	207 (52.3)	104 (50.5)	103 (54.2)	-
36-40	46 (11.6)	13 (6.3)	33 (8.3)	-
41-45	6 (1.5)	2 (1)	4 (2.1)	-
>45	5 (1.3)	1 (0.5)	4 (2.1)	-
Year of Medical School Graduation				
2011-2013	192 (48.1)	133 (64.3)	59 (25.5)	p=0.0001
2006-2010	145 (36.3)	69 (33.3)	76 (39.6)	-
2000-2005	52 (13.0)	5 (2.4)	47 (24.5)	p=0.0001
Before 2000	10 (2.5)	0	10 (5.2)	p=0.0006
Type of Fellowship				
Pediatrics	66 (15.9)	34 (16)	32 (15.8)	-
Adult	342 (82.4)	171 (80.7)	171 (84.2)	-
Med-Peds	7 (1.7)	7 (3.3)	0	p=0.015
Length of Fellowship				
Two years	296 (71.2)	134 (63.2)	162 (79.4)	p=0.0003
Three years	97 (23.3)	61 (28.8)	36 (17.6)	p=0.0077
Four years	16 (3.8)	13 (3.1)	3 (1.5)	p=0.0193
Uncertain	7 (1.7)	4 (1.9)	3 (1.5)	-
Current year in training				
First year	138 (33.3)	70 (33.3)	68 (33.5)	-
Second year	226 (54.5)	113 (53.3)	113 (55.7)	-
Third year	44 (10.6)	26 (12.3)	18 (8.9)	-
Fourth year	7 (1.7)	3 (1.4)	4 (2)	-
Student Loan Debt				
Yes	198 (48.1)	149 (70.6)	49 (24.5)	p<0.0001
<$50,000	21 (10.6)	16 (10.7)	5 (10.2)	-
$50-99,999	26 (13.1)	15 (10.1)	11 (22.4)	p=0.0480
$100-199,999	56 (28.3)	39 (26.2)	17 (34.7)	-
$200-299,999	53 (26.8)	42 (28.2)	11 (22.4)	-
>$300,000	42 (21.2)	37 (24.8)	5 (10.2)	p=0.0424

Table 1. FIT Demographics. P-values represent comparisons between US and international medical graduates. Only significant p-values are reported.

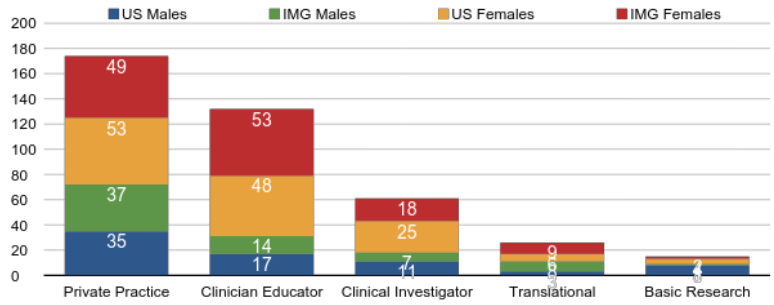

Figure 1. FIT career interests for US and international medical graduates (IMGs).

Disclosure: J. S. Hausmann, None; **S. Monrad**, None; **M. Ditmyer**, None; **M. B. Bolster**, None; **L. F. Imundo**, None; **D. Battafarano**, None.

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Abstract Number: 1141

Mentoring the Pediatric Rheumatology Community through the American College of Rheumatology/Childhood Arthritis and Rheumatology Research Alliance Mentoring Interest Group Network: A Five-Year Status Update

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Background/Purpose: The American College of Rheumatology (ACR)/Childhood Arthritis and Rheumatology Research Alliance (CARRA) Mentoring Interest Group (AMIGO) is a subspecialty-wide inter-institutional mentorship program launched in 2011 to target mentorship gaps within pediatric rheumatology. AMIGO provides an annual opportunity for fellows and junior faculty to be paired with a more senior faculty based on career interests. These ongoing mentorship dyads last for a 3-year cycle. Initial survey of the pediatric rheumatology community after the first 3-year cycle revealed measurable increases in reported access to mentorship beyond the home institution and perceived benefit from AMIGO in specific domains, including career development, scholarship, work-life balance, and connectedness to the pediatric rheumatology community. We describe the sustainability and spread of the AMIGO mentoring network over the past five years (2011-2016).

Methods: A quality improvement framework was used to report on outcomes associated with annual cycles. ACR database and surveys were used to obtain data.

Results:

1) Process outcomes: Figure 1 demonstrates the number of new dyads entering the AMIGO network each year and the cumulative number of active dyads which reached 141 in 2015. 2011 and 2012 cohorts are now retired, for 75 dyads that have completed the program.
2) Participant experiences and perceptions: Participants have responded favorably to faculty development sessions held annually at the ACR and CARRA scientific conferences. Highlights from programmatic evaluations are shown in Table 1.

3) Outcomes for organizational effect: As of spring 2016, 252 unique individuals have participated in AMIGO as mentees, mentors or

both. The 2015 American Board of Pediatrics Workforce Survey identifies 325 pediatric rheumatologists with active board certification and 96 pediatric or medicine-pediatrics rheumatology fellows. Thus, participation in AMIGO has reached almost 60% (252/421) of the U.S. pediatric rheumatology community.

Conclusion: AMIGO continues to provide much needed access to mentorship for pediatric rheumatologists. Over the span of 5 years, more than half of the U.S. pediatric rheumatology community has been involved in this program. Exit survey of retired dyads and repeat survey of the pediatric rheumatology community are planned to identify factors contributing to mentorship success and areas for improvement.

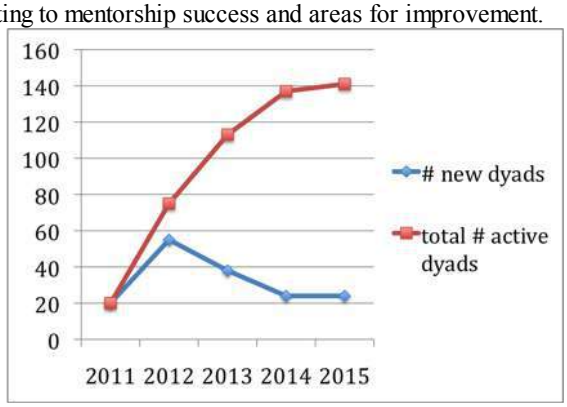

Figure 1: Number of AMIGO mentorship dyads (new and total active) over time \s

Table 1: Program Evaluations at Annual Pediatric Rheumatology Meetings

AMIGO Event	Assessment Question	Rating (Scale: 1-5)	Respondents (n)**
2014 CARRA session	*Overall assessment of the potential value of the AMIGO program?*	1.6*	57
2015 CARRA session ÒPromotions BootcampÓ	*Understanding of promotion domains after session?*	4.3	43
	Grasp of career development documentation after session?	4.1	43
2015 ACR breakfast ÒMentorship Resource FairÓ	*Value of todayÕs mentorship resource fair?*	4.7	33
	Value of encouraging mentorship networks?	4.8	33
2016 CARRA session ÒMentorship 360ºÓ	Talk: ÒMentoring 360Ó	4.7	43
	Overall assessment of the potential value of a mentoring program as envisaged by AMIGO?	4.8	43

* highest rating = 1 (for this session only) **responses from session attendees, sessions were open to AMIGO participants and non-participants

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Disclosure: K. Hayward, None; **A. Grom**, Novartis Pharmaceutical Corporation, 5,novimmune, 5; **E. Muscal**, None; **P. Nigrovic**, None; **K. Rouster-Stevens**, None; **L. N. Moorthy**, None.

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a-five-year-status

Abstract Number: 1142

Impact of a Student Led Rheumatology Interest Group on Medical Student Interest in Rheumatology

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Impact of a Student Led Rheumatology Interest Group on Medical Student Interest in Rheumatology

Background/Purpose: Based on data from the 2005 Rheumatology Workforce Study the demand for rheumatologists will continue to increase in the coming decades. Demand for rheumatologists outstrips the current supply of trained rheumatologists. The American College of Rheumatology has implemented several strategies to try to increase medical student interest in Rheumatology including programs such as Choose Rheumatology! The purpose of this observational study was to investigate impact of development of a student led Rheumatology Interest Group and the Choose Rheumatology! program on medical student interest in Rheumatology at a single institution.

Methods: In April 2015 a student led Rheumatology Interest Group was established at our institution. As part of the inaugural meeting the "Choose Rheumatology!" team presented on careers in rheumatology, several faculty gave testimonials on why they had chosen Rheumatology, and patients spoke on the impact their rheumatologist had on their lives. Follow up meetings included a meeting on finding research projects and two joint injection workshops. To assess medical student interest in rheumatology we retrospectively collected data from the two years before initiation of the interest group (2012-2014) and the year following initiation of the interest group (2015-16) based on four parameters: the number of medical student abstract submissions to the GW Research Day, the number of medical students enrolling in the rheumatology elective, and the number of manuscripts published by faculty with medical students. In order to account for the variable time periods in the pre and post intervention groups, the mean number of student-rheumatology interactions per 6 months in the pre and post intervention periods was assessed for each parameter. Data analysis was performed using GraphPad Prism version 5.00 for Windows (GraphPad Software, San Diego, CA).

Results: Student interest in the rheumatology elective significantly increased following the Interest Group intervention with a mean number of students per 6 months of 2.0±0.36 in the pre intervention period and 7.5±3.5 in the post intervention period (p=0.021). The number of abstract submissions also significantly increased with 0.5±0.34 in the pre-intervention period compared to 7.0±4.0 in the post-intervention period (p=0.017). The number of manuscripts submitted by student-faculty dyads has also increased from 0.16±0.16 to 1.5±0.5 (p=0.013).

Conclusion: A simple and low cost intervention of development of a student led interest group coupled with a Choose Rheumatology! Campus visit has dramatically impacted student interest in Rheumatology at a single institution.

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Abstract Number: 1143

Adressing Medical Students' Concerns in the Patient/Physician Interaction with People with Rheumatic and Musculoskeletal Diseases Leading to Handicap – a Pilot Experience Including Student Focus Groups and Interactions with Patient Associations

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Background/Purpose: Physicians may have difficulties dealing with patients with chronic rheumatic and musculoskeletal diseases, in particular due to bias against handicap. There may be preconceived ideas about these diseases associated with disabilities, leading to altered patient-physician interactions. In other specialties, the technique of focus groups (FG) including medical students who can discuss their preconceived ideas, followed by interactions with patients, has been used [1]. The objective of this study was to explore the usefulness of FG and interactions with patient associations during undergraduate training for medical students.

Methods: This was a pilot experience in one French University. Five FG were organized during spring 2016. Students in the fourth year of medical studies volunteered in one 3-hours FG, about one of the following themes: handicap (2 sessions), obesity (2 sessions) or mental health. The discussion groups were moderated by a neutral coordinator (Assistant Professor), attended by an observer and a transcriber. In the 2 handicap FG, the students first discussed together about 3 pre-defined questions: 1) which perception do you have about handicap and disabled people? 2) Do you have difficulties when you are faced with clinical examination of disabled people? 3) According to you, what do the handicapped people expect from medical doctors? After one-hour discussion, the students met the representatives of patient associations and shared the main elements resulting from the FG. Satisfaction was assessed through anonymous likert-scale questionnaires comprising 10 questions (final score 0-100%).

Results: Of the 375 students initially contacted by the University, 70 volunteered, and 5 FG of 14 students were organized: 2 FG (28 students) were centered on handicap. Preconceptions of undergraduates included difficulties to examine handicapped patients and to take care of them, with an uncomfortable feeling about how to look at them and how to behave, and the fear to harm them. The interaction with the patient associations allowed the students to compare their bias to the truth of living with a handicap. Satisfaction ratings among students were very high (mean value 93%). All the students (100%) reported that discussing about preconceived ideas was useful, and 92% declared that the FG helped them to observe the importance of social representations in the care of disabled patients. Interestingly, 54 % of the students estimated that medical training on handicap was not sufficient before attending the FG. The satisfaction rating of the patient association was 100%.

Conclusion: FG followed by a moment for dialogue and exchange with patients allow medical undergraduate students to express their bias against handicap, and to compare them with the truth of living with a handicap. This method, leading to high levels of satisfaction in our pilot study, may help in future teaching of patient-physician relationships and interactions around handicap. Long-term impact on care relationship remains to be studied. **References:** 1. Stalmeijer RE, Mcnaughton N, Van Mook WN. Using focus groups in medical education research: AMEE Guide No. 91. Med Teach. 2014;36(11):923-39.

Disclosure: S. Mitrovic, None; **C. Poitou-Bernert**, None; **R. Haddad**, None; **M. Ferrari**, None; **M. C. Renaud**, None; **A. Duguet**, None; **L. Gossec**, None.

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Abstract Number: 1144

Impact of Decision-Making Role Preferences in the Efficacy of a Multimedia Patient Education Tool for Patients with Common Rheumatologic Conditions

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Background/Purpose: A preference for shared decision-making among patients with chronic conditions has been associated with better health outcomes. We compared the impact of a multimedia patient education tool (MM-PtET) compared to a written booklet with the same information in patients with passive vs active decision-making role preference.

Methods: Patients were recruited from 5 centers and through advertisement. Inclusion criteria were: (i) age ≥18 years (ii) diagnosis of rheumatoid arthritis (RA), knee osteoarthritis, or osteoporosis/osteopenia (OP) (iii) adequate cognitive status and, (iv) ability to communicate in English or Spanish language. Participants with RA had a disease duration ≤10 years and all patients with OP were women. Our primary outcome was disease knowledge and secondary measures included decisional conflict, self-efficacy and disease management. Assessments were conducted before and after viewing MM-PtET, at 3 and 6 months. The Control Preference Scale (CPS) was used to characterize participants according to their preferred role in decision making (passive/uninformed vs active/informed role).

Results: 665 participants were randomized (331=MM-PtET, 334=written booklet). Mean age was 59.8±12.1 years, 87% were female, 65% non-White, 20% had inadequate health literacy levels and 26% answered the questionnaire in Spanish. Thirty-three percent had a diagnosis of OA, 34% OP, and 33% RA; 472 (232=MM-PtET, 240=booklet) and 522 (257=MM-PtET, 265=booklet) participants returned their questionnaires at 3 and 6 months, respectively. Most patients reported an active decision-making role preference in the intervention (48% active, 36% shared, and 15% passive) and control (47% active, 36% shared, 17% passive) groups. Greater knowledge scores were observed after viewing the MM-PtET compared reading the booklet in patients with a shared role preference (p=0.04). Compared to patients in the control group, patients in the intervention group with a passive role preference had less decisional (p=0.04) and better decision management (p=0.02) at 3 months. However, at 6 months improvements from baseline were only significant for patients with an active (decisional conflict, p=0.04) and shared role preference (disease management, p=0.03). Univariate analysis showed that greater improvements in knowledge (regardless of assignment) were associated with passive role preference compared to active (p=0.001, pre&post; p=0.03, pre&6-month) and shared role (p=0.01) preference.

Conclusion: Our MM-PtET improved outcomes after intervention, 3 and 6 months. However, the benefits varied according to the decision-making role preference. Given the observed differences, it is important that educational interventions are tailored to the patients' preferences about their involvement in the decision-making processes.

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Abstract Number: 1145

#Rheumjc: Impact of Invited Authors on a Twitter Based Rheumatology Journal Club

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Background/Purpose: Twitter is an increasingly popular platform for discussion and engagement among healthcare professionals. #RheumJC is a Twitter-based international rheumatology journal club which occurs approximately once a month. One novel aspect of #RheumJC has been to include principal authors of the discussed manuscripts, whenever possible. Here we describe participant analysis and survey results from the past 18 months of this initiative with a focus on how the presence of authors has impacted the journal club and

participants.

Methods: A #RheumJC development team was created to help define the structure and moderate the online discussions. Prior to each journal club, principal authors of the selected manuscripts were invited to participate. A total of 10 different online journal clubs were conducted between January 29th, 2015 and June 2nd, 2016, each consisting of two "live" one hour chats, as well as a full 24 hrs to allow for asynchronous participation. In 4 of the 10 journal clubs, principal authors of the chosen manuscripts participated in the online discussion. An analysis of all the sessions was performed to assess participant demographics and participation rates. A follow up survey was conducted after the 10th journal club to both #RheumJC participants as well as the invited authors to assess metrics of satisfaction and identify additional strengths or barriers.

Results: In total, 433 individuals from 36 different countries participated in at least one #RheumJC session. For the 4 journal clubs during which principal authors were present, compared to sessions without an author present, there were a significantly greater number of participants (46 ± 11.5 vs 26 ± 13.3 respectively, p=0.039) and tweets (462 ± 103.5 vs 306 ± 111.0, p=0.048) suggesting the presence of principal authors was a popular feature. 35 individuals from 11 different countries responded to a survey and indicated they had participated or followed along in at least one journal club session. The majority (88%) indicated they were either satisfied or very satisfied with the #RheumJC initiative. Additionally, 37.5% of respondents indicated that their participation in #RheumJC had influenced practice decision making. When asked which sessions resulted in practice changes, 71% of the responses highlighted sessions where authors were available as discussants. Of interest, 7% of respondents indicated they had joined Twitter solely because of #RheumJC, and another 37% stated that #RheumJC had increased their use of Twitter as a tool for medical education. A survey of the invited authors revealed that they found their experience very rewarding and all of them indicated that they would be highly likely to participate again.

Conclusion: #RheumJC is a novel and popular approach to the traditional medical journal club. The involvement of manuscript authors has proven to be a particularly well received aspect of this initiative. The inclusion of authors in the discussion increases user engagement and possibly can influence practice decision making by journal club participants. We encourage authors to participate in this novel educational activity to potentially broaden the impact of their research.

Disclosure: I. Amigues, None; **P. Sufka**, None; **S. Bhana**, None; **J. Campos**, None; **C. Collins**, None.

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Reducing Imaging Tests for Low Back Pain: Can Patients Choose Wisely?

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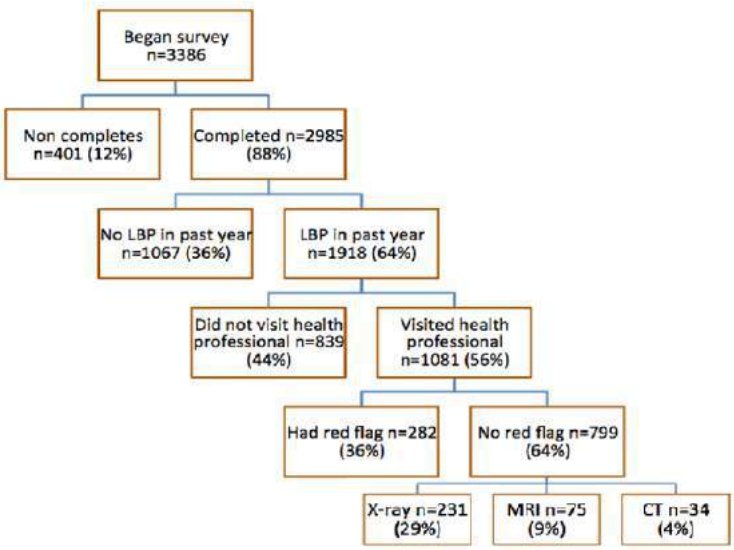
Background/Purpose: Management of nonspecific acute low back pain (LBP) is complicated by many patients' belief that imaging tests will be useful. Choosing Wisely is a campaign that represents a physician-driven effort to create conversations between physicians and patients around overuse and waste. The objective of this study was to determine the potential impact of the Choosing Wisely educational pamphlet on patients' behavioural intentions for future imaging tests.

Methods: We recruited a cohort representative of the Canadian adult general population to a web survey in English and French to consider the impact of the Choosing Wisely campaign for LBP. We first ascertained respondents' experiences of LBP, and baseline behavioural intentions for a future LBP episode, including attitudes, beliefs and knowledge on LBP and imaging tests. We next asked respondents to read the Choosing Wisely pamphlet before asking follow-up questions to understand the pamphlet's potential impact.

Results: Of the 3386 respondents that began the survey, 2985 completed all questions and were included in the analysis. Respondents broadly matched the age and gender of the Canadian population, with 7% completing the survey in French. 1918 (64%) of respondents reported an episode of LBP in the past year, of which 1081 (56%) visited a health professional. Of the 799 who reported they had no red

flag, 336 (42%) received an imaging test for their LBP, predominantly X-ray. Overall, 37% and 39% of respondents stated that they would want or expect an imaging test for future LBP. After reading the Choosing Wisely educational pamphlet, this reduced from 39% to 24% ($p<0.001$) for wanting, and 37% to 22% ($p<0.001$) for expecting an imaging test. Similar improvement was seen in knowledge questions about the need and potential risks of imaging tests, and for alternative management strategies.



Conclusion: The Choosing Wisely pamphlet for LBP was effective in changing some individuals' behavioural intentions around imaging tests. Simple extrapolation implies in Canada each year there are over 2 million inappropriate x-rays and 700,000 inappropriate MRIs for LBP. This costs between $300-$600 million per year. Conservative estimates suggest implementing the Choosing Wisely campaign could save $30 million per year. Future analysis will explore subgroups where the influence of the Choosing Wisely pamphlet is most and least. Follow-up studies are planned to assess whether respondents stated changes in behavioural intentions.

Disclosure: N. Bansback, None; **J. Chiu**, None; **S. Kerr**, None; **R. McCracken**, None; **B. Forster**, None.

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Abstract Number: 1147

A Novel Survey Tool to Assess Inpatient Consult Service Performance

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Background/Purpose: The role of subspecialty consultation in inpatient medicine is increasing. Effective consultation services have an important impact on the quality and efficiency of patient care as well as care transitions. Within academic medical centers, successful resident-fellow interactions during consultation positively affect resident and student education and may influence their career choice. Therefore, enhancing the performance of subspecialty inpatient consultation services may have a broad reaching impact. To our knowledge, an instrument designed to measure consult service performance has not been described. We developed a consult service evaluation tool and evaluated its psychometric properties at a large academic center.

Methods: The instrument was developed by the investigators and Internal Medicine (IM) subspecialty fellowship program directors at a single academic center. It asked IM residents to evaluate ten IM subspecialty consult services (rheumatology, cardiology, etc.) on the following items (5-point scale): overall satisfaction, communication, professionalism, teaching and pushback (reluctance or resistance to perform the consult). The instrument was administered in May 2015 and May 2016 to all IM residents. Pearson correlation coefficients

were used to summarize the relationship between measured items and overall satisfaction. To take into account the repeated measures data structure, linear regression models with Generalized Estimating Equations were used to compare across post graduate year (PGY), year of survey administration or consult service.

Results: One hundred and thirteen residents responded (47 in 2015 and 66 in 2016 [45 PGY-I, 35 PGY-II and 33 PGY-III or IV], combined response rate 35%). Each of the four items measured (communication, professionalism, teaching, pushback) significantly correlated to the overall satisfaction rating in univariate analyses (all with $p<0.01$), suggesting internal validity. Multivariate analyses demonstrated that each item independently contributed to the overall satisfaction score (communication [r=0.68], professionalism [r=0.64], teaching [r=0.42] and pushback [r=0.47], all with $p<0.01$). There were no differences in ratings across PGY year or year of survey administration demonstrating reliability of the instrument (Table). There was considerable variation in ratings among the 10 services evaluated (all with $p<0.01$, Table) signifying that consult services are perceived differently, even within a single academic center.

Conclusion: We describe the development and evaluation of an instrument designed to evaluate subspecialty consult service performance. Our results suggest that perception of consult services varies considerably among residents. This tool can be utilized to assess consult services and measure the effect of interventions designed to improve consult service performance. **Table – Ratings of Internal Medicine Subspecialty Consult Services and Comparisons by PGY Year and Year of Survey Administration**

	Overall Satisfaction		Communication		Professionalism		Pushback		Teaching	
Subpecialty Service	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**	**Mean**	**Std**
Service 1	4.4	0.7	4.5	0.6	4.5	0.7	4.0	0.8	4.2	0.9
Service 2	4.3	0.7	4.2	0.8	4.4	0.8	4.4	0.7	3.7	1.3
Service 3	4.2	0.8	3.9	0.9	4.1	0.9	3.2	1.0	3.8	1.1
Service 4	4.1	0.8	4.0	0.8	4.4	0.7	4.1	0.8	3.7	1.2
Service 5	4.0	0.9	4.1	0.8	4.3	0.9	4.3	0.7	3.6	1.3
Service 6	4.0	1.0	4.3	0.8	4.4	0.7	2.9	1.3	3.4	1.3
Service 7	3.8	0.9	3.8	1.0	4.1	1.0	3.9	1.2	2.7	1.5
Service 8	3.8	0.9	3.8	0.8	4.2	0.9	3.3	1.0	3.5	1.2
Service 9	3.5	0.9	3.4	1.0	3.8	1.1	2.8	0.9	3.8	1.2
Service 10	3.5	1.0	3.6	1.0	3.9	1.0	3.6	1.1	2.9	1.2
By PGY year (p-value)	0.83		0.56		0.43		0.67		0.11	
By year survey administered (p-value)	0.92		0.78		0.20		0.74		0.18	

Disclosure: E. Miloslavsky, None; **Y. Chang**, None.

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Abstract Number: 1148

Implementation of a Gout Knowledge Based Assessment Tool in an Inter-Professional, Multi-Disciplinary Musculoskeletal Training Program

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Background/Purpose: The Musculoskeletal (MSK) Education Week is an interprofessional, multidisciplinary, multilevel training initiative launched in 2012. In 2015, this program was expanded to include a written assessment of participants' knowledge regarding the evaluation and treatment of patients with gout. Our objective was to examine the initial experience in implementation and compare the self-assement versus standardized questions scores.

Methods: The week-long course is held monthly at a VA Medical Center affiliated with a university training program. The curriculum includes didactics, technology-enhanced simulation, peer-teaching, and culminates in ambulatory clinical experiences and reflective practice. All interns from categorical internal medicine, preliminary neurology and physical medicine and rehabilitation programs, residents and fellows from occupational medicine, family medicine, geriatric and rheumatology programs, and students from the physician assistant and advance practice nursing programs participate each year. Evaluations include self-assessments and a 2-station observed structured clinical examination (OSCE). In 2015-16, a 40-item multiple-choice test, which included 28 questions relating to gout, was developed and incorporated into the existing scheme of pre- and post-course assessments.

Results: In 2015-16 to date, 70 trainees have participated in the MSK Education Week. Response rates for the pre-course and post-course gout knowledge assessment were 96% (n = 67) and 93% (n = 65) respectively. Mean pre-course score for questions related to gout were 50% and mean post-course score was 85% with p-value for pre- vs. post-course scores <0.001. Response rates for the pre-course, post-course and retrospective self-assessment surveys were 97% (n = 68), 83% (n = 58), and 53% (n=37) respectively; these results are shown in the Table below as well as a correlation with the objective test scores at completion of the course. Our analysis was limited to the subjects who completed all pre- and post-course self and knowledge assessments.

	Mean Pre-course Ratings		Mean Post-course Ratings	Spearman's rank correlation coefficient for Gout-# self-rating vs Post-course multiple choice test score n = 34
	Prospective (range, s.d)	Retrospective		
Gout-1: I can perform an appropriate evaluation of patients with gout	3.3*** (1-5, 0.9)	2.8*** (1-4, 1.8)	4.3 (3-5, 0.7)	-0.09
Gout-2: I can develop an appropriate plan for patients with gout	3.2*** (1-5, 1.0)	2.8*** (1-4, 1.0)	4.3 (3-5, 0.6)	-0.15
Gout-3: I understand when to refer patients with gout for specialty care	3.0*** (1-5, 1.0)	2.6*** (1-4, 1.1)	3.9 (2-5, 0.7)	0.05

*** P<0.0001 in comparison to post course

Conclusion: Increases in self-assessment of knowledge, as well as in written test scores, were observed following participation in the MSK Education Week. There was no correlation between improvement in these two measures, which may be attributable to a ceiling effect associated with nearly universal high self-assessment ratings at the end of the course.

Disclosure: E. Jaffe, None; **A. M. Barker**, None; **G. W. Cannon**, Amgen, 2; **M. J. Battistone**, None.

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Abstract Number: 1149

Rheumatology Elective Time in a 4+1 Residency Structure: Evaluating Impact of a Novel Residency Schedule Structure on Rheumatology Resident Education

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Background/Purpose: Models of residency education in the United States are evolving nationwide to limit conflicting care responsibilities and enhance the outpatient internal medicine resident experience. One newer model of training is known as the X+Y model with X (inpatient) weeks to Y (ambulatory clinic) weeks (e.g. 4 inpatient weeks followed by 1 outpatient week) repeated in a continuous cycle over the course of residency. [1] Despite the increasing adoption of an X+Y training model, little is known about how it impacts subspecialty rheumatology elective time and resident rheumatology education needs. This needs assessment sought to determine how

residents at The George Washington University (GWU) felt rheumatology education was impacted in the new X+Y structure.

Methods: Two surveys, were conducted utilizing Survey Monkey in March of 2015 and again in June of 2016. [2] Surveys consisted of 9-10 questions with responses via Likert scale or multiple choice with section for free text response.

Results: 27/98 (27%) of residents responded to the March 2015 survey conducted in the first year of the 4+1 residency structure, 19/27 (69%) of residents reported extreme or moderate dissatisfaction with rheumatology exposure in the 4+1 residency structure. 0/27 (0%) felt they had adequate time for electives in the new structure. 18/27 (66%) rated themselves as likely or definite in their plans to seek rheumatology elective. 16/27 (59%) resident respondents reported decreased opportunity for rheumatology exposure in a 4+1 structure. To achieve rheumatology education, the requested models for education included addition of a rheumatology half day clinic to their +1 week (9/27 (33%)) with the second most popular choice being the addition of more rheumatology noon conference lectures (7/27 (25%)), however 12/27 (44%) felt noon conference was not an effective training method. 17/25 (68%) third year residents responded to the 2016 follow up survey. 4/17 (24%) of residents found subspecialty elective time decreased in the newer residency model with majority of residents 13/17 (64%) noting elective time the same or increasing. 8/17 (47%) of residents felt satisfied with the amount of rheumatology exposure they receive in the new 4+1 structure with 9/17 (53%) feeling dissatisfied or unsure if they had sufficient exposure. 6/17 (35%) reported an educational half-day within their +Y week would best meet their rheumatology education needs. 6/17 (35%) cited more morning report cases as the optimal rheumatology learning format. Only 3/17 (18%) felt rheumatology elective time would best satisfy their learning needs.

Conclusion: Dissatisfaction with degree of rheumatology training and exposure were evident in both surveys. Traditional rheumatology elective was not cited as a popular way for residents to meet their rheumatology education needs. Rheumatology educators need to consider novel ways of adopting internal medicine resident rheumatology education to evolving residency structures.

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2. Monkey, S.; Available from: https://www.surveymonkey.com/home/.

Disclosure: N. Taylor, None; **E. McBride**, None.

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Abstract Number: 1150

Advocacy 101: Engaging Rheumatology Fellows in Health Policy and Advocacy

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Background/Purpose: Healthcare delivery and health policies in the United States are evolving rapidly. Rheumatology fellowship programs lack formal curricular content to educate trainees about legislative and regulatory healthcare policies that will have a profound impact on the future of academic and community practices.

Methods: A web-based survey was sent via the American College of Rheumatology (ACR) Fellows in Training (FIT) listserve in June and July 2015. The survey queried fellows enrolled in U.S. rheumatology training programs about their knowledge of and participation in health policy and advocacy. Survey results guided the design of an educational session called Advocacy 101 for fellows and program directors in October 2015 in conjunction with the ACR Advocates for Arthritis fly-in. Curriculum included introduction to state and federal legislative and regulatory policies as well as education on how to be an effective advocate. Participants were asked to take educational content from the event and hold a teaching session at their home institution. Participants also shared their experiences at the 2015 ACR Annual Meeting FIT roundtable sessions and the 2016 ACR State of the Art meeting Advocacy Workshop. A second survey was sent to fellows in April 2016.

Results: Survey response rates increased from 19% to 39% between 2015 and 2016. The majority of respondents were in adult training programs with nearly half (46% in 2015, 47% in 2016) reporting plans for a career in academics. Forty percent (up from 35% in 2015) reported that they were aware of advocacy efforts through the ACR. The top reason (64%) for non-participation in health policy and advocacy efforts in 2015 was lack of knowledge on how to get involved. This decreased to 39% of respondents reporting the same barrier in 2016. Other barriers to participation in 2016 included lack of time and familiarity with the issues. Only 7% felt their participation would have no effect, down from 16% the previous year. The health policy issues that 2016 participants identified as most important were patient access to medication (83%), patient access to insurance (68%) and physician reimbursement (58%). Fellows preferred in-person teaching sessions and online modules to email correspondence for education on these topics. The percentage of individuals who were familiar with and contributed to RheumPAC increased.

Conclusion: Engagement in health policy and advocacy efforts is critical to continued recruitment of trainees into the field of rheumatology, support for education and research, and advancement of clinical practice. Current training program curricula do not prepare fellows for the new challenges of our changing health care system. Advocacy 101 is the first program designed to educate and engage rheumatology fellows in health policy and advocacy endeavors. Fellows express an interest in becoming involved but view their lack of time and knowledge of the issues as their biggest barriers. Fellows indicate that ACR-sponsored events and formal curricula would be an effective way to gain knowledge on health policy and advocacy. Advocacy 101 is the first step in addressing this need.

Disclosure: S. Doaty, None; **S. L. Kolasinski**, None; **W. F. Harvey**, None; **A. Cooper**, None; **E. B. Solow**, None.

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Abstract Number: 1151

A Pediatric Rheumatology Fellow Educating Pediatric Primary Care and Emergency Room Providers about Pediatric Lupus: A Local, Pilot Adaptation of the Lupus Education Advancement Project (LEAP)

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Background/Purpose: Pediatric systemic lupus erythematosus (SLE) accounts for approximately 10-20% of all cases of SLE. It is more common in African American and Hispanic patients, who together comprise the majority of our Bronx population. It can be a challenging diagnosis for providers to make but early recognition is especially important, as pediatric patients typically have more severe disease than adults. The objectives of this project are for pediatric primary care and emergency room providers to be able to recognize the symptoms and signs of lupus, to initiate a work-up, and to identify high-risk patients who would benefit from prompt referral to pediatric rheumatology.

Methods: First, a comprehensive, interactive presentation on pediatric lupus and a relevant knowledge assessment tool, consisting of 9 multiple-choice questions, were developed. These new materials were tested on a small group of providers affiliated with a nearby, community hospital. Then, formal seminars were scheduled with groups of providers affiliated with The Children's Hospital at Montefiore during regular, weekly meeting times. These included pediatric primary care, adolescent medicine, and pediatric emergency medicine providers. At the seminars, participants were asked to complete voluntary, de-identified pre and post assessments, and were informed about completing an online version in 4-6 weeks (follow-up assessment). Paired t-tests were used to calculate the changes in knowledge for matched data. Participants were also asked to comment on their intent to make practice changes.

Results: Eighty-one providers attended the 8 seminars, and 57 matched pre and post assessments were collected. Of participants who completed the post-assessment, 94.9% agreed that the seminar improved their medical or practice knowledge. Of those with matched responses, 96.4% demonstrated an increase in knowledge on the assessment tool, with a score difference of 3.02 on a 9-point scale ($p < .001$). In addition, of participants who completed the post-assessment, 90.4% indicated that they will make changes that will benefit patient care as a direct result of the seminar. The mean follow-up assessment scores remained higher than the pre-assessment scores for 7

out of 9 questions. Lastly, of those who completed the follow-up assessment, 40% indicated that they are more likely to think of lupus in the differential diagnosis.

Conclusion: After a brief educational intervention, pediatric primary care and emergency room providers demonstrate knowledge gains, some of which are sustained. Importantly, they are also more likely to consider lupus in this high-risk population.

Table 1. Knowledge Assessment Tool Scores, On a 9-Point Scale

(Includes Matched and Unmatched Data)

	N	Mean Score	Std. Deviation	Minimum Score	Maximum Score
Pre	60	4.63	1.64	1.00	9.00
Post	60	7.65	1.23	4.00	9.00
Follow-up	5	6.40	1.52	4.00	8.00
Total	125	6.15	2.07		

Disclosure: K. Steigerwald, None; **A. Caron**, None; **D. Gross**, None; **Z. Naqvi**, None; **Y. Sterba**, None.

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Abstract Number: 1152

Implementation of a Musculoskeletal Ultrasound Teaching Program Is Not Determined By Fellowship Program Size

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Background/Purpose: In 2008, 18% of rheumatology fellowship program (RFP) program directors (PDs) included musculoskeletal ultrasound (MSUS) in their training programs. Overall goal of this study was to assess the current state and ascertain the needs for MSUS education among RFPs. The objective of this study was to determine if fellowship program size impacts inclusion of MSUS in training.

Methods: Out of two surveys sent via Qualtrics™ in 2015, a 13-item needs assessment survey was sent to all RFP PDs determining implementation of MSUS teaching including machine accessibility, faculty training, and institutional support. The second survey assessed teaching and evaluation methods used. For the first survey, Fischer's Exact Test was used to test differences between fellowship programs based on size. Small programs were defined as programs with 1-2 fellows yearly, while big programs were those with at least 3 fellows yearly.

Results: Out of 113 RFPs, 103 (91%) PDs responded to the needs assessment survey. In total, 94% of RFPs are currently offering some form of MSUS training. Of 73 small programs, 91.8% offered MSUS training; 97.1% of big programs offered MSUS training. By large, there was no statistically significant difference between small and big programs (p=0.429). Majority of both small and big programs (81.8 vs. 93.9%) cited at least one faculty who was competent in performing MSUS (p=0.212). Majority of the teaching was done by a key clinical faculty member other than the PD (39.7% vs. 54.5%). Majority owned an US machine (72.1 vs. 87.9%; p=0.037). When asked if they wanted MSUS to be part of the Rheumatology fellowship training curriculum, majority wanted its inclusion however most wanted it

only to be optional (66.2% vs. 66.7%), as compared to those wanted it to be a standard requirement (29.4% vs. 30.3%).

Conclusion: MSUS has become prevalent among RFPs. The size of a fellowship program is not a factor in determining inclusion of a MSUS teaching program. Small programs have comparable capacity to include MSUS in teaching programs when compared to big programs. There is openness to including MSUS in Rheumatology fellowship training, whether as an optional or standard part of the curriculum.

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Abstract Number: 1153

Exploring Perceptions of a Rheumatoid Arthritis Specific Smoking Cessation Programme

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Background/Purpose: Premature mortality rates in individuals with rheumatoid arthritis (RA) are significantly higher in current smokers compared to those who have never smoked, making smoking cessation an important consideration in RA management. The aim of this study was to determine which aspects of a novel three-month RA smoking cessation intervention were most useful and to identify areas for improvement.

Methods: Thirty-eight current smokers (19 intervention and 19 control) with RA were enrolled in a pilot randomized controlled trial involving a novel three-month psychosocial smoking cessation intervention delivered by two community based Arthritis Educators. Nicotine replacement therapy (NRT) was offered to all participants as usual care regardless of randomization. Despite no significant difference in smoking cessation rates (26% intervention vs 21% control; p=0.70), there was a high quitting rate among all participants. Here we examine the efficacy through interviews with the participants and Arthritis Educators, using a mixed qualitative methodology. There were three sources of data: 1) interview notes from contacts between the Educators and 19 intervention participants during the smoking cessation intervention; 2) interview notes from the two follow-up interviews at three and six months post-randomization between the researcher and all study participants; and 3) exit interviews between the researcher and the two Educators. Interview data was analyzed thematically using a combination of deductive and inductive approaches to identify themes.

Results: Sixteen intervention and 19 control participants completed the six month follow-up. Support was individualized for each participant and their support choices were monitored by the Educators. A comparison between the acceptance and usefulness of individual intervention components as informed by the participants who accepted each component is shown in Figure 1. The individualized support and advice from the Educators were the key intervention components most valued by the participants and the Educators alike. This was followed by the generic smoking cessation components and education about the links between smoking and RA. The use of NRT as a common treatment to both intervention and control groups was the most commonly reported facilitator of smoking cessation. Participants who identified as being ready to quit smoking had more success at smoking cessation. The Educators were positive about ongoing provision of the smoking cessation intervention with minor changes.

Conclusion: This research highlights the strategies that can be focused on for improving smoking cessation rates in people with RA. Successful quitters were ready and motivated to quit smoking regardless of their randomization status. Support offered by the Educators was critical from the viewpoint of participants who received the intervention.

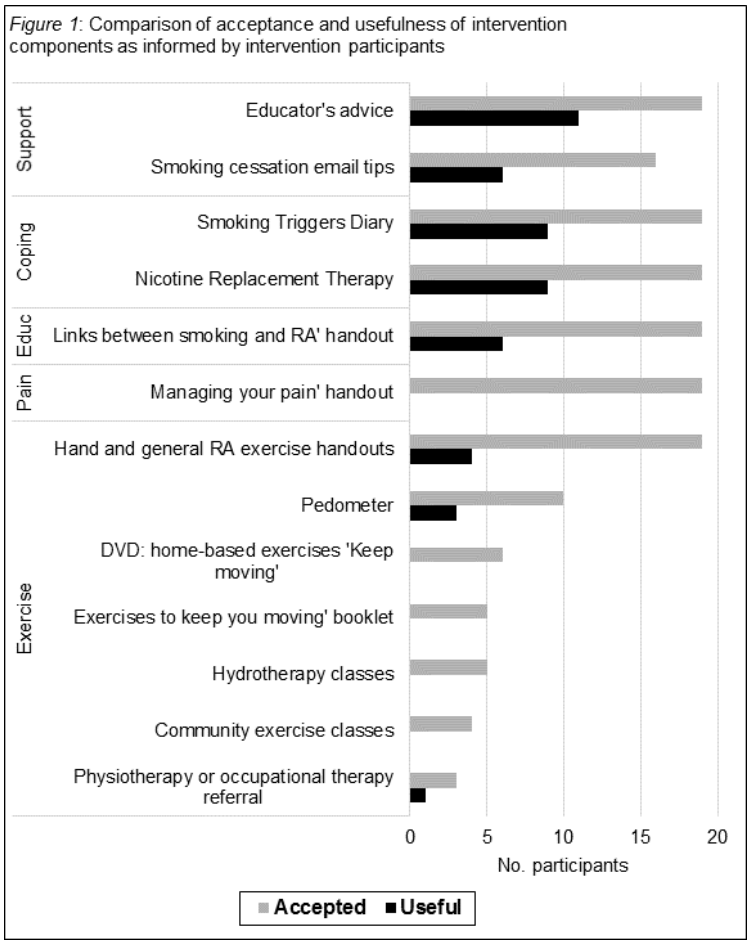

Figure 1: Comparison of acceptance and usefulness of intervention components as informed by intervention participants

Disclosure: P. Aimer, None; **L. K. Stamp**, None; **S. Stebbings**, None; **V. Cameron**, None; **S. Kirby**, None; **G. Treharne**, None.

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Promoting Self-Management Techniques for Osteoarthritis Pain: a Pilot Study of Nurse Practitioner Led Coping Skills Training

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Background/Purpose: Arthritis is the leading cause of chronic pain and disability in the United States. Two thirds of patients report inadequate pain control. Coping Skills Training (CST), a well recognized self-management program traditionally delivered by mental health providers, decreases pain and disability and improves self-efficacy. Yet, access to CST remains limited. The purpose of this pilot study is to evaluate the feasibility and effectiveness of nurse practitioners (NPs) delivering group CST in a suburban rheumatology private practice.

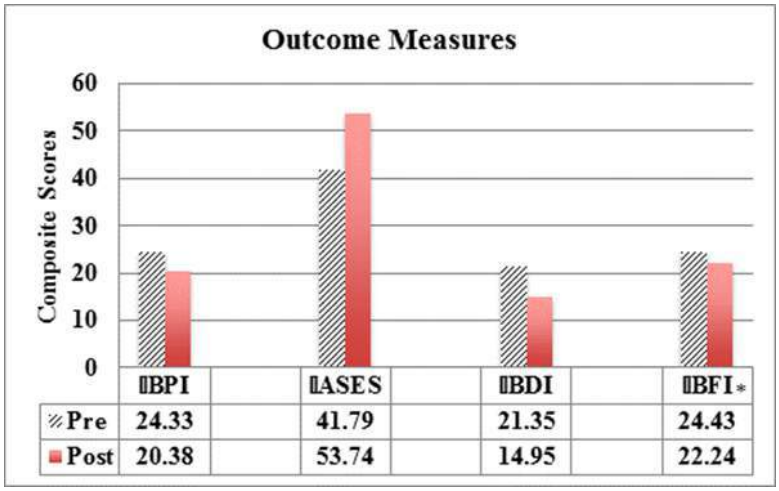
Methods: A convenience sample of 39 osteoarthritis patients with chronic pain participated in a 10-week CST program delivered by a

trained adult NP. There were approximately 10 patients in each of 4 groups. The feasibility of delivering group CST was measured through completion of at least 50% of the program. Effectiveness was assessed through change scores from pre and post treatment measures of pain, depression, coping, and self-efficacy using paired t-tests.

Results: The sample was primarily Caucasian (92%), female (87%), 60 years of age with 13 years of moderate to severe osteoarthritis (71.8%) and most carrying co morbid rheumatologic conditions (72%). Overall, subjects reported being very satisfied with the program, group process, content and leadership by the NP. Non-completers (n=17) were not statistically different at baseline than completers and described mostly logistical issues and medical problems as reasons for attrition. For those who completed the program (n=22), there was a significant improvement in pain, depression, coping, and self-efficacy. Table 1 Feasibility of Group Process for 10 Week Program, N=22

Item	**Mean**
Likert Scale: 0= Not at all, 6= Very	
Importance of Group	**5.57**
Usefulness of hearing others	**5.85**
Comfortable discussing issues	**5.78**
How adequate was the length?	**5.30**
Were your needs met?	**5.40**
Difficulty getting to sessions	**2.80**
Average # Sessions Attended	**8.2(range 6-10)**
	%
Completion (n=22)	**56**
Non Completers (n=17)	**44**

Figure 1 Outcome Measures



BPI: Brief Pain Inventory, ASES: Arthritis Self Efficacy Scale, BDI: Beck Depression Inventory, BFI: Brief Fatigue Inventory. P value < .05 for all except Fatigue. * There was no significant change on this measure.

Conclusion: This pilot study provides preliminary evidence to support the use of adult health NPs to deliver CST to patients with chronic pain seen in private practice settings. Additionally, it has the potential to broaden the scope of advanced practice nursing and dramatically increase access to this important self-management technique.

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Abstract Number: 1155

The Effect of Nurse-Led Follow-up in Rheumatoid Arthritis. a Systematic Review and Meta-Analysis of Randomized Controlled Trails

Annette de Thurah[1,2], Bente Appel Esbensen[3,4], Ida K Roelsgaard[4], Tove F Frandsen[5] and Jette Primdahl[6,7], [1]Department of Rheumatology, Aarhus University Hospital, Aarhus, DK, Aarhus, Denmark, [2]Department of Clinical Medicine, Aarhus University, Aarhus, DK, Aarhus N, Denmark, [3]Copenhagen Center for Arthritis Research (Copecare), Rigshospitalet, Copenhagen, DK, Copenhagen, Denmark, [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, DK, Copenhagen, Denmark, [5]The knowledge Center of Odense University Hospital, Odense University Hospital, Odense, DK, Odense, Denmark, [6]King Christian X's Hospital for Rheumatic Diseases, Graasten, Hospital of Southern Jutland, DK, Graasten, Denmark, [7]Institute for Regional health Research, University of Southern Denmark, Odense, DK, Odence, Denmark
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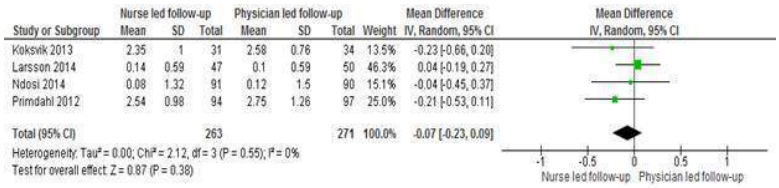
Background/Purpose: Due to a longer life expectancy in general, the treatment burden of RA is growing, and although treatment is generally becoming more effective and better tolerated, many countries experience an unmet demand for rheumatologists and a current demand for greater cost-effectiveness. For this reason alternatives to conventional outpatient physician-led follow-up have been investigated, i.e. nurse-led follow-up. Thus, the aim was to conduct a systematic review and meta-analysis, investigating the efficacy of nurse- versus physician-led follow-up in the treat to target strategy in RA.

Methods: A systematic literature search was performed using the databases: Medline, Embase, the Cochrane Central Register of Controlled Trials, PsycINFO, CINAHL, Web of Science, Scopus, and. Eligible trials were all randomized controlled trails reporting on the effect of nurse-led follow-up in managing disease control in RA in comparison to physician-led follow-up at hospitals or medical clinics. This implied nurse-led follow-up for out-patients with RA where nurses performed assessment of tender and swollen joints, evaluated blood-samples and monitored the medical treatment in order to evaluate the patients' disease activity as part of the consultation. Nurses included rheumatology nurses, nurse practitioners, clinical nurse specialists and advanced nurse practitioners. Physicians included rheumatologists and younger physicians involved in follow-up care of patients with RA.

Results: Eight articles, reporting five studies with 1044 participants in total, were included. All but one study included stable patients who were in remission at baseline. Overall, no difference in disease activity was found after 48-52 weeks (MD -0.07 (95% CI: -0.23; 0.09)) (Figure 1). After 84-104 weeks a small statistical, but not clinical relevant difference, was seen in favor of nurse-led follow-up (MD -0.29 (95% CI: -0.53; -0.04). No difference in patient satisfaction was seen after 48-52 weeks (SMD -0.17 (95% CI: -1.00; 0.67). After 84-104 weeks a statistical significant difference was found in favor of nurse consultations.

Conclusion: Overall no difference was found on the effect of disease activity whether RA patients were offered nurse- or physician led follow-up, but the patients tended to become more satisfied over time in nurse-led follow-up. This evidence supports the understanding that routine disease monitoring of RA patients in stable phase can include specialist nurses. PROSPERO id:CRD42015026151 Figure 1 Forest plot: pooled mean differences for disease activity after one year



Disclosure: A. de Thurah, None; **B. A. Esbensen**, None; **I. K. Roelsgaard**, None; **T. F. Frandsen**, None; **J. Primdahl**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-effect-of-nurse-led-follow-up-in-rheumatoid-arthritis-a-systematic-review-and-meta-analysis-of-randomized-controlled-trails

Abstract Number: 1156

Development of a Taxonomy of Patient Engagement in Health Research

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Development of a Taxonomy of Patient Engagement in Health Research

Background/Purpose: The emergent practice of patients engaging in the conduct and decision-making aspects of health research has been accentuated in this decade. Its practice deems to improve the relevance, appropriateness, and knowledge translation of research by incorporating the patient perspective. However, systematic reviews (SRs) have highlighted a lack of common language across studies reporting this practice,[1, 2] making it challenging to examine the evidence in this area. To address this shortcoming, this study aimed to develop a taxonomy of patient engagement in research.

Methods: We systematically searched 6 electronic databases for relevant documents published January 1980 – July 2015. We also searched 4 key journals, reference lists, and the grey literature. Eligible documents were in English, with information relevant to patient engagement in research. We targeted theories, frameworks and models as well as SRs and commentaries related to the practice, to base our taxonomy. Content analysis was performed using 3 predetermined categories: 1) *Who* are the patients?; 2) *How* do patients engage?; and 3) *When* do patients engage?, that were formed based on prior readings. For example, one article emphasized that these 3 categories cover the context and process of patient engagement in research.[3] The first author reviewed, extracted, and organized the data under each category. The data was analyzed for unique descriptors, then combined into themes. The descriptors were then defined and their relationships explored.

Results: A total of 29 documents (21 frameworks/models, 4 SRs, 1 commentary, and 3 empirical studies) contributed descriptors to the taxonomy. Each document provided descriptors in some themes, but none provided descriptors in all themes. Some documents contributed to defining and explaining the interconnections of the descriptors. These documents included models of information flow and communication between patients/public and researchers, community/patient/public engagement continuum, and the division of control and power over the research process. The results, summarized in Table 1, contain the categories '*Who?'* described by type of affiliation; '*How?*' described by the initiation, mechanism, and degree of engagement; and '*When?*' described by the stage of research cycle divided across three research phases.

Conclusion: This taxonomy presents descriptors for diverse forms of patient engagement in research. Researchers could use this taxonomy to select options of patient engagement in research to plan their studies, then use its descriptors to communicate the context-specific contributions of patients. Future research should validate this taxonomy.

1. Shippee et al. *Health Expect* 18:1151-66,2015. 2. Domecq et al. *BMC Health Serv Res* 14:1-9,2014. 3. Esmail et al. *J Comp Eff Res* 4:133-145, 2015.

Table 1. Descriptors in the taxonomy of patient engagement in research

Who? (Who are the patients who engage in research?)	***How?*** (How do patients engage in research?)	***When?*** (When during the research process do patients engage?)
Type of Affiliation[a] 1. Individual 2. Group	**Initiation of Engagement**[b] 1. Patient-initiated 2. Researcher/funder-initiated (other-initiated) 3. Joint patient and other-initiated **Mechanism of Engagement** 1. Complete Interview/Survey (such as focus group and Delphi) 2. Attend Meeting (such as a town hall meeting) 3. Perform Research-Team Activity (includes deliberation and organizational participation) **Degree of Engagement**[c] 1. Informed-patient A passive recipient of information, within a research team. 2. Consultant Provides solicited information to inform decision-making in research, but does not have the authority to decide whether his/her expressed perspective contribute to the research process and outcome. 3. Partner Engage in active communication with the research team, and has continuously shared power over decision-making and knowledge-use in the research process. 4. Lead: Co-lead, Delegated-lead, and Full-lead Has the authority to make the determinative decisions in research-related matters.	**Stage of Research Cycle** 1. Preparation Phase 1.1 Identifying and Prioritising 1.2 Commissioning 2. Execution Phase 2.1 Study Designing and Managing 2.2 Undertaking 3. Translation Phase 3.1 Disseminating 3.2 Implementing 3.3 Evaluating Impact

[a] Authors should had further context by providing individual patient or group characteristics, such as diagnosis, disease duration, sex, age, education level, the nature of the group (e.g. patient advisory board), and that number of patients in the group. [b] When the patient is the funder, use

the patient descriptor. [c] Degree of engagement by patient increase from informed-patient through lead.

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Abstract Number: 1157

Using Goutpro to Make Medical Trainees Gout Pros

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Background/Purpose: Gout is the most common type of inflammatory arthritis in the U.S., affecting 4% of the population. Gout also has a large impact on health care costs in the U.S. with $6 billion dollars spent annually. Over 2 million visits to primary care providers (PCP) each year are gout related. Despite modern advancements and the availability of reference tools, the current care from PCPs is felt to be suboptimal in the U.S. Barriers to improving care in gout include limited education during medical training, perception of non-importance by providers, and the lack of PCP continuing medical education. In an attempt to address limited education during training, we developed a digital adjunctive teaching tool, GoutPro, on the topic of gout. Utilizing a clinically integrative model proposed by *Khan et al*, it takes into consideration different learning styles, current guidelines on gout, interactive activities and clinical problem solving. The overall the goal of our teaching intervention is to improve medical trainee knowledge and interest in gout.

Methods: 15 medical residents and students from the University of Minnesota participated in a 1 hour GoutPro teaching session. The session was a Fellow led didactic using our GoutPro software. GoutPro is a hybrid software that incorporates presentation ability, audience participation, clinical simulation and mini-games. GoutPro is structured with lecture content on slides with multiple choice questions integrated evenly throughout. Within the lecture content, we also incorporated competitive scored mini-games to increase audience participation and satisfaction. At the end of the session, there was a simulation in which participants made clinical decisions based on an evolving scenario. Feedback was provided on choices participants made at the end. Participants utilized their smart devices to operate GoutPro as a means of interacting anonymously during the session. Our primary outcome measure was participant satisfaction assessed by post-session survey. Our secondary outcome measure was level of interest in the topic of gout, educational value of the tool, and usefulness of the tool also assessed by a post-session survey. A descriptive analysis of the data was performed.

Results:

Table 1. GoutPro Feedback	1 Strongly Disagree	2 Somewhat Disagree	3 Neutral	4 Somewhat Agree	5 Strongly Agree
I was satisfied with the GoutPro session	-	-	-	4	11
My level of interest in the topic of gout care has increased	-	-	-	6	9
The GoutPro session was fun	-	-	-	-	15
The GoutPro session was interactive	-	-	-	8	7
My knowledge base on the topic of gout has increased	-	-	-	2	13
The GoutPro session is likely to change my future management of gout	-	-	-	1	14

Conclusion: In conclusion, the GoutPro session was effective, fun, interactive and educational. All participants were satisfied with the session. Our study demonstrates that GoutPro can be used as a teaching tool to increase participant satisfaction and interest. Further studies will be needed to assess change in knowledge and quality measures.

Disclosure: L. Ngo, None; **P. A. Valen**, None; **A. Duran**, None.

Abstract Number: 1158

Effects of an Educational Program Using Treat to Target Strategy in Korean Patients with Rheumatoid Arthritis

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Background/Purpose:

The purpose of this study was to investigate the effects of an educational program using T2T (Treat RA to Target, T2T) strategy on Korean patients with moderate to severe rheumatoid arthritis

Methods:

Patients with moderate-severe RA were randomly assigned to an educational intervention group or conventional care group. The intervention was a nurse-delivered 9 month educational program consisting of 3 monthly sessions lasting 30~40 minutes each and monthly telephone counseling. Assessments occurred at baseline and every 3 months with both two groups, but only intervention group was completed 9 month- education follow up. Primary outcome variables were as follows: disease activity (DAS28), pain (VAS 100mm), functional disability (Korean Health Assessment Questionnaire, KHAQ), fatigue (FACIT-Fatigue scale), illness perception (Brief Illness Perception Questionnaire, BIPQ), self-esteem (self-esteem questionnaire) and quality of life (Short form Health Survey 36, SF-36). We used the ANOVA test with repeated measures to evaluate the outcome variables in comparison between groups and follow-up times.

Results: Patients in the interventional group (n=33) had significant improvement in disease activity (DAS28) (p=.029), pain(p=.023), fatigue(p=.019), illness perception(p=.000), quality of life (physical function: p=.028, role physical: p=.035, bodily pain: p=.007, general health: p=.003, vitality: p=.009, social function: p=.001, mental health: p=.037) compared to patients in conventional care group(n=33). There was no significant difference between the groups and follow-up times in functional disability, self-esteem and SF-36 subscale of role emotion

Conclusion: This patient educational program using T2T strategy consisting of nurse-delivered individual session had statistically significant benefits for disease activity, pain, fatigue, illness perception and quality of life in Korean patients with moderate to severe rheumatoid arthritis. The results suggested that patient educational program using T2T strategy contribute to positive clinical outcome as a good practical nursing intervention.

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Abstract Number: 1159

Use of Rheumatology-Specific Patient Navigators for DMARD Adherence: Results from a Pilot Intervention

Candace H. Feldman[1], Alyssa Wohlfahrt[2], Anarosa Campos[3], Joshua Gagne[4], Maura D. Iversen[5], Elena Massarotti[6], Ichiro Kawachi[7] and Daniel H. Solomon[8], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [2]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [3]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [4]Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, [5]Northeastern University, Department of Physical Therapy, and Brigham & Women's Hospital, Harvard Medical School, Boston, MA, [6]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [7]Social and Behavioral Sciences, Harvard T. H. Chan School of Public Health, Boston, MA, [8]Rheumatology Immunology & Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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Background/Purpose: Adherence to DMARDs is suboptimal and declines over time, preventing patients from reaching remission. Patient navigators, non-health professionals trained in advocacy, care coordination and basic disease management, have been shown to improve diabetes and heart failure control and cancer screening. We piloted a 6-month intervention, Med Assist, to assess whether rheumatology patient navigators could improve DMARD adherence.

Methods: We enrolled patients ≥18 years old at an academic rheumatology center with a systemic rheumatic disease, initiating a new oral DMARD within the prior 6 months. Two patient navigators communicated by phone or in person with patients every 2-4 weeks depending on need, for 6 months. Navigators assessed medication use and barriers to care and provided tailored strategies to improve medication adherence. Patients completed validated surveys at baseline and at 6 months. These included the Morisky Medication Adherence Scale (MMAS-8, <6=poor adherence, 6-<8=borderline, 8=high), Mental Health Inventory (MHI-5, <68 indicates depressive symptoms), Beliefs about Medicines Questionnaire, Brief Illness Perception Questionnaire (cognitive and emotional representations of illness), and disease activity indices (SLAQ for SLE, RADAI for RA). We used paired t-tests to compare baseline and 6-month survey scores. We examined the association of age, race/ethnicity, insurance and MHI-5 with change in MMAS-8 score using multivariable linear regression.

Results: We studied 69 patients with rheumatic diseases who engaged with the navigator and completed baseline and 6-month MMAS-8 surveys. The mean age was 55 (±16) years, 93% were female, 50% were white, 11% Hispanic and 7% black; 14% had Medicaid, 32% Medicare and 37% commercial insurance. The mean baseline MMAS-8 score was 6.7 (± 1.3), indicating borderline adherence, and the mean MHI-5 was 60.8 (± 9.1), suggesting prevalent depressive symptoms (**Table**). At 6 months, there was no significant change in MMAS-8 or MHI-5, or in measures of RA or SLE disease activity. We observed stronger beliefs about medicine efficacy (p=0.03) and a higher illness perception score (p=0.01) at 6-months compared to baseline. Our multivariable model demonstrated a small but statistically significant change in MMAS-8 for each 5-year increase in age (β=0.14, p=0.02).

Conclusion: While this pilot demonstrated the feasibility of a rheumatology-specific navigator, we did not find a significant improvement in DMARD adherence at 6 months. We observed enhanced beliefs about DMARD efficacy, but also a more negative view of the impact of rheumatic diseases on patients lives. A randomized, controlled trial of a rheumatology-specific navigator with longer follow-up is needed to determine whether stable DMARD adherence may demonstrate a beneficial effect, compared to the usual trend in the literature of poorer DMARD adherence over time.

Table. Survey results for baseline and 6-month post rheumatology-specific patient navigator intervention			
Survey*	**Baseline** - Mean (SD)	**6-month Follow-up** - Mean (SD)	**p-value****
Morisky Medication Adherence Scale (MMAS-8, N=69)	6.7 (1.3)	6.4 (1.6)	0.09
Mental Health Inventory (MHI-5, N=48)	60.8 (9.1)	60.5 (8.9)	0.83
Beliefs about Medicines (N=48)	11.8 (4.7)	11.6 (4.9)	**0.03**
Brief Illness Perception (N=47)	45.7 (9.8)	47.1 (8.0)	**0.01**
*MMAS-8 range 0-8, <6 is poor adherence, 6-<8 borderline and 8 is high; MHI-5 range 0-100, <68 signifies depressive symptoms; Beliefs about Medicines Questionnaire range 5-25, higher scores indicate stronger beliefs in DMARD efficacy; Brief Illness Perception Questionnaire range 0-80, higher scores indicate a more threatening view of the rheumatic disease. **Determined using paired t-tests			

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Development of a Shared Decision Making Tool for Osteoporosis Treatment

Sonam Kiwalkar, Internal Medicine, Rochester General Hospital, Rochester, NY
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Background/Purpose: In this era of modern medicine, health care providers and patients are partners in making decisions about treatment. It is imperative that evidence-based medicine be translated into a patient-friendly format, in which pros and cons of treatment options are compared. A simple-to-follow decision aid allows integration of patient preferences, values and circumstances with up to date science, keeping in mind the challenge of integrating this system in a busy clinical practice. Previous studies have shown that this approach enhances patient and provider satisfaction.

Methods: Several prior studies have explored the factors that matter when patients make treatment choices—these include adverse effect profile, efficacy, cost of medication, and opinion of heath care provider. Currently there is no decision aid available for osteoporosis that incorporates all the treatment options approved by the Food and Drug Administration (FDA) and considers the American College of Rheumatology (ACR) – Glucocorticoid Induced Osteoporosis 2010 guidelines. We included clinical risk factors for development of osteoporosis, computed a list of osteoporosis medications approved by FDA, searched through meta-analyses for evidence based efficacy and effect (odds ratio), cost, and side effects of the agents. We referenced National Osteoporosis Foundation Guidelines (NOF) and US

Preventive Services Task Force (USPSTF) for screening and treatment guidelines, and for glucocorticoid induced osteoporosis we referred the ACR 2010 guidelines.

Results: We created a personalized evidence-based shared decision making tool, envisioned to be used at an outpatient visit in primary care or specialty center. The clinician and patient start by documenting clinical risk factors, after which, with the help of a computer algorithm, the 10 year risk of a major osteoporotic fracture or hip fracture is calculated. A personalized report is generated which uses NOF guidelines to determine whether initiation of medication is advised. Next, the patient and provider review efficacy of medications tailored specifically to the patient's risk of an osteoporotic fracture within 10 years and how it would be altered by taking a particular medication (Fig 1). The side effect profile, form, frequency and cost of medications are included. Finally, after the patient makes an informed decision in conjunction with the clinician, an individualized report can be printed and be given to the patient with specific instructions at the end of visit.

Conclusion: We developed an interactive, colorful, easy to follow, online tool, integrating evidence based medicine and patient preferences, which has the potential to help providers in delivering optimal patient care. We are in the process of validating the tool and gathering patient and provider satisfaction scores at our institution.

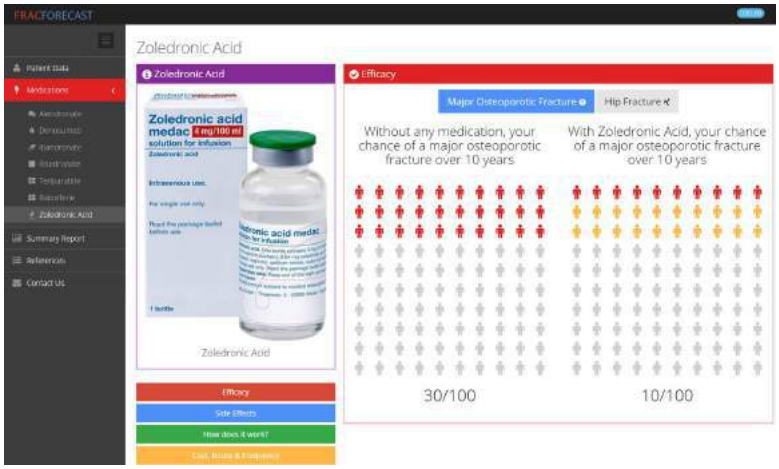

Figure 1: Screenshot from Shared Decision Making tool for Osteoporosis Treatment options.

Disclosure: S. Kiwalkar, None;

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Abstract Number: 1161

Systematic Development of a Patient-Centered Strategy to Improve Tight Control in Daily Clinical Practice

Marieke J. de Jonge[1], Sofie H.M. Manders[1], Anita M.P. Huis[1], Mart A.F.J. van de Laar[2], Piet L.C.M. van Riel[1,3] and Marlies E.J.L. Hulscher[1], [1]Radboud university medical center, Radboud Institute for Health Sciences, IQ healthcare, Nijmegen, Netherlands, [2]University of Twente, Department of Psychology, Health and Technology, Enschede, Netherlands, [3]Bernhoven, Department of Rheumatology, Uden, Netherlands

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Background/Purpose: Patients are not aware of the important role of disease activity in Rheumatoid Arthritis (RA) for long term clinical outcomes. This not only prevents them from taking a more central role in the care for their own health, it also hinders rheumatologists in adhering to the tight control principle. In order to improve daily clinical practice, an improvement strategy should address patient-level barriers to tight control adherence.

Methods: The strategy was developed through a step-wise approach, in collaboration with all stakeholders and by addressing barriers to tight control on patient level. Strategies that have already proven to be successful in other chronic diseases were taken into consideration. First patient-level barriers to tight control were defined and evidence and example materials were explored. Next, a draft version was developed and improved through applying the International Patient Decision Aids Standards (IPDAS) criteria. Then, the draft was further improved by consulting an expert panel, patient research partners, and rheumatology professionals several times. The layout of the strategy was developed by consulting laymen, hospital communication departments, and patients.

Results: The DAS-pass strategy consists of two components. The first component, decision supportive information for patients, includes an informational leaflet and a patient held record. The leaflet is designed to educate patients about tight control and its importance for clinical outcomes. It aims to increase patients knowledge on tight control, to empower patients to be more involved in their own disease management, and to improve patients' medication beliefs. With the patient held record, patients can keep track of their own disease activity scores, their RA medication (changes), and on topics to be discussed with their physician. The patient held record aims to increase understanding of the tight control principle by increasing involvement and information uptake. The second component is guidance by a specialized rheumatology nurse. By discussing the decision supportive information (component 1) during an individual consult with each patient, the nurse aims to stimulate patients to communicate about their disease activity during visits, to individualize the decision supportive information to the patients' needs, and to offer the opportunity to ask questions or ask for additional support.

Conclusion: The DAS-pass strategy is a patient centered-strategy that was developed to improve tight control in daily clinical practice. By empowering and educating patients, it aims to improve communication about tight control between patients and rheumatologists, and to enable patients to take the initiative in tight control. We consider the DAS-pass strategy promising as it was developed systematically: theory based and in cooperation with the stakeholders. Research on the evaluation of the effects of the DAS-pas strategy in a Randomized Controlled Trial is currently ongoing. Acknowledgements*:* The input of all stakeholders that have helped in the development of the DAS-pas strategy is very much appreciated.

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Abstract Number: 1162

How Ehealth Technologies Are Changing the Office Visit: Perspectives from Healthcare Professionals in Rheumatology

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Background/Purpose: eHealth is a broad term referring to the application of information and communication technologies in the health sector, ranging from health records to telemedicine and multiple forms of health education, support, and tools. By providing increased and anytime access to information, opportunities to exchange experiences with others, and self-management support, eHealth has been heralded as transformational, creating informed, engaged, and empowered "patients as partners," equipped to take part in shared decision-making, and effectively self-manage chronic illness.1 The objective of our study is to examine how eHealth affects patient-provider relationships, and its ethical and practical ramifications.

Methods: We interviewed healthcare professionals (HCPs) about their experiences with eHealth and its impact on the office visit. Eligible participants had a caseload with >25% of patients with arthritis and multi-morbidity, in order to address issues of managing complex chronic conditions and coordination of care. In-depth interviews used a flexible, semi-structured discussion guide, and follow-up

interviews served to clarify and expand upon initial discussions. All interviews were audiotaped and transcribed verbatim. Constant comparisons and a narrative approach guided the analyses and a relational ethics conceptual lens was applied to the data to identify emergent issues.

Results: 12 HCPs (nurses, fellows, physician; 6 male, 6 female) participated. Years of practice varied from one to 29 (median = 13), and all worked in an urban or suburban setting. eHealth tools accessed most frequently were online educational resources for patients (used by all participants in some form), followed by online resources for HCPs like curated scientific summaries on diagnostic criteria, clinical therapies, and dosage calculators. HCPs generally did not see how social media could be useful to their practice. Analysis revealed 3 emergent themes: 1) HCPs shared some commonalities in how they conceptualized an "ideal" engaged patient as medically literate, bringing "useful" data to consultations, and whose evolution is largely a product of the rise of eHealth; 2) Fears of eHealth technology disrupting existing practice habits and uncertainty about liability and confidentiality issues were a barrier to the adoption of new technology; 3) Most HCPs saw eHealth tools as facilitating a shift towards a patient-provider relationship where shared decision-making is the new norm. Perceptions on the usefulness and impact of eHealth technologies varied from doubtful to enthusiastic. All declared a primary concern for best possible patient outcomes, and some saw eHealth as integral to reaching that goal.

Conclusion: HCPs see eHealth technologies broadly as agents of change, for better or for worse, however, the perceived direction of that change is neither clear nor uniform given the varied experiences of this group. The value of these technologies was largely assessed through a relational ethics perspective, as the patient-provider relationship and its outcomes remained the primary concern of all HCPs. [1]Townsend A et al. *JMIR Res Protoc* 2013;2(2):e38

Disclosure: G. Macdonald, None; **A. F. Townsend**, None; **L. Li**, None; **S. Kerr**, None; **P. Adam**, None; **M. McDonald**, None; **C. L. Backman**, None.

Abstract Number: 1163

Impact of E-Learning on Perceived Social Role Participation of Patients with Axial Spondyloarthritis: Results from a Longitudinal Randomized Control Trial

Daeria Lawson[1], Laura Passalent[2,3], Rita Kang[4], Christopher Hawke[2,5], Ahmed Omar[6,7], Arane Thavaneswaran[1], Nigil Haroon[8,9] and Robert D Inman[6,10], [1]Toronto Western Hospital, Toronto, ON, Canada, [2]Allied Health, Toronto Western Hospital, Toronto, ON, Canada, [3]Physical Therapy, University of Toronto, Toronto, ON, Canada, [4]Patient and Family Education, Toronto Western Hospital, Toronto, ON, Canada, [5]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada, [6]Rheumatology, Toronto Western Hospital, University of Toronto, Spondylitis Clinic, Toronto, ON, Canada, [7]Rheumatology, University of Toronto, Toronto, ON, Canada, [8]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [9]Medicine, Rheumatology, University of Toronto, Toronto, ON, Canada, [10]University of Toronto, Toronto, ON, Canada

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Background/Purpose: Individuals impacted by arthritis have identified social role participation (e.g. relationships, leisure activities, employment) as an important quality of life outcome. There is evidence that education programs are effective for patients with arthritis in terms of improved function and quality of life. The Toronto Western Hospital Spondyloarthritis Program developed a novel interactive e-Learning education program for patients with axial Spondyloarthritis (axSpA) with input from patients and an interdisciplinary team of health care professionals. The purpose of this study was to measure the impact of the axSpA e-Learning patient education program on patients' perception of social roles and participation.

Methods: Fifty-six adult patients with axSpA attending a tertiary academic spondyloarthritis clinic were randomly assigned to one of two groups: 1) e-Learning intervention, in addition to usual care, where patients were emailed a link to the online patient education module to be completed at their leisure; or, 2) usual care (i.e. control group). All patients completed outcomes measuring Social Role and Participation (SRPQ, Gignac et al. 2011) at baseline, immediately after completing the e-Learning module, and at 6 to 12 months thereafter. The SRPQ includes 12 role domains with 3 dimensions: 1) role importance, 2) restriction to role participation, and 3) satisfaction with social role performance. Univariate and bivariate analyses were conducted on SAS version 9.2.

Results: Twenty-three patients with axSpA completed the e-Learning module and thirty-three patients continued with usual care. Overall, mean (SD) age was 42.3 (12.9) years, 69.6% were male, mean (SD) disease duration was 12.9 (10.2) years and 75% had a post-secondary education. Comparison by study group at baseline showed that importance of "relationship with other family members" was lower in the intervention group compared to controls ($p = 0.02$). Otherwise there were no significant differences between groups at baseline. Immediate follow-up measures indicated lower perceived importance in the intervention group with respect to: "plan/attend social events" ($p = 0.007$); "having a paid job" ($p = 0.005$); "relationship with other family members" ($p = 0.02$); and "fully participating in all aspects of life" ($p = 0.02$) The intervention group reported lower satisfaction with "type of paid work that you are able to have" ($p = 0.03$). Otherwise, no significant differences were noted between control and intervention groups at immediate follow-up. At 6-12 months follow-up, the intervention group reported less physical difficulty "participating in hobbies" ($p = 0.04$) and "engaging in activities with children/grandchildren" ($p = 0.04$). In addition the intervention group identified "intimate relationships" ($p = 0.02$) and "fully participating in all aspects of life" ($p = 0.02$) as less important.

Conclusion: Although there are significant differences in the levels of importance of several social role subscales, the reported differences are relatively small. Long-term findings of less physical difficulty with some social role subscales indicate potential long-term benefits of the e-Learning module to patients with axSpA.

Disclosure: D. Lawson, None; **L. Passalent**, Abbvie Canada, 8; **R. Kang**, None; **C. Hawke**, None; **A. Omar**, None; **A. Thavaneswaran**, None; **N. Haroon**, None; **R. D. Inman**, None.

Abstract Number: 1164

Impact of E-Learning on Knowledge, Self-Efficacy and Exercise Behaviours of Patients with Axial Spondyloarthritis: Results from a Longitudinal Randomized Control Trial

Laura Passalent[1,2], Rita Kang[3], Daeria Lawson[4], Christopher Hawke[1,5], Ahmed Omar[6,7], Arane Thavaneswaran[4], Nigil Haroon[8,9] and Robert D Inman[7,10], [1]Allied Health, Toronto Western Hospital, Toronto, ON, Canada, [2]Physical Therapy, University of Toronto, Toronto, ON, Canada, [3]Patient and Family Education, Toronto Western Hospital, Toronto, ON, Canada, [4]Toronto Western Hospital, Toronto, ON, Canada, [5]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada, [6]Rheumatology, University of Toronto, Toronto, ON, Canada, [7]Rheumatology, Toronto Western Hospital, University of Toronto, Spondylitis Clinic, Toronto, ON, Canada, [8]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [9]Medicine, Rheumatology, University of Toronto, Toronto, ON, Canada, [10]University of Toronto, Toronto, ON, Canada

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Background/Purpose: There is a growing body of evidence to support the effectiveness of education programs for patients with arthritis. Despite this, there has been little development or investigation into education strategies specifically for patients with axial spondyloarthritis (axSpA). A number of studies examining education strategies for patients with various forms of arthritis have involved an interdisciplinary approach and suggest positive impact on disease activity, function and overall health. Furthermore, the use of an electronic format for education has been shown to be preferred over other methods of education for patients with axSpA. As such, the Toronto Western Hospital Spondylitis Program developed an interactive web-based e-Learning education module for patients with axSpA with input from patients and an interdisciplinary team of health care professionals and consists of evidence-based topics including diagnosis, treatment and self-management for axSpA. The purpose of this study was to measure the effect of the axSpA e-Learning patient education module with respect to: 1) knowledge of axSpA; 2) chronic disease self-efficacy, and 3) exercise behaviour.

Methods: Fifty-six adult patients with axSpA attending a tertiary academic spondylitis clinic were randomly assigned to one of two groups: 1) e-Learning intervention, in addition to usual care, where patients were emailed a link to the online patient education module and were asked to complete the module at their leisure; or, 2) usual care (i.e. control group). All patients completed outcome questionnaires at baseline, immediately after the completion of the e-Learning module and at 6-12 months thereafter. Outcome measures included: the Ankylosing Spondylitis (AS): "what do you know" knowledge questionnaire; Stanford Chronic Disease Self-Efficacy Scale, and the Stanford questionnaire for Exercise Behaviours.

Results: Twenty-three patients with axSpA completed the e-Learning education module, in addition to usual care, and 33 patients continued with usual care. Overall, mean (SD) age was 42.3 (12.9) years, 69.6% were male, mean (SD) disease duration was 12.9 (10.2) years and 75% had a post-secondary education. There were no statistically significant differences in the above outcome measures between the two groups at baseline or immediately following the completion of the e-Learning module. At the 6-12 month follow-up there was an overall increase in the number of minutes dedicated to all types of exercise the week prior to completing the outcome measures in the intervention group compared to controls, with a significant increase in the average minutes dedicated to bicycling as a form of exercise from a mean of 5.2 minutes to 34.6 minutes, p=0.02.

Conclusion: The results of this study demonstrate the addition of the axSpA e-Learning patient education module to usual care is equivalent to usual care provided at a tertiary academic spondylitis clinic and has potential to provide benefit to patients with axSpA who have limited access to specialty care. Long-term results suggest a significant impact on exercise behaviours in patients with axSpA who completed the e-Learning module.

Disclosure: L. Passalent, Abbvie Canada, 8; **R. Kang**, None; **D. Lawson**, None; **C. Hawke**, None; **A. Omar**, None; **A. Thavaneswaran**, None; **N. Haroon**, None; **R. D. Inman**, None.

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Abstract Number: 1165

The Development of an Interdisciplinary Treatment Program for Fibromyalgia in a Tertiary Medical Center Focused upon Rheumatology and Internal Medicine

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Background/Purpose: Fibromyalgia syndrome (FMS) appears to be undertreated despite the mounting evidence to support the efficacy of interdisciplinary treatment. Why are patients not receiving effective care? Practice needs included a lack of standardized assessment and treatment for patients with Fibromyalgia, inefficient management of patients being referred to Rheumatology for Fibromyalgia creating less availability of Rheumatologists on the consult service as well as reducing availability of appointments for other rheumatologic patients needed for resident teaching as well as low satisfaction for physicians employed in the care of these patients without the support of an interdisciplinary team. The present study was designed to describe the development of a successful interdisciplinary treatment program for Fibromyalgia patients and provide clinical information on the first 600 patients treated in this program between October 2014 and April 2016.

Methods: The collaborative structure of the interdisciplinary team and the goals of the program are illustrated. Patients referred to a tertiary medical center for evaluation of fibromyalgia symptoms, which were subsequently diagnosed with FMS by meeting the 2010 ACR criteria, enrolled in a 2-day interdisciplinary treatment program, served as subjects in this study. All patients in this study met the ACR Classification Criteria for Fibromyalgia. Patients completed the Fibromyalgia Impact Questionnaire - Revised (FIQR), the Center for Epidemiological Studies Depression Scale (CES-D), and the Pain Catastrophizing Scale (PCS) at the time of admission to the program. Patients were seen in a collaborative care model with trained psychiatric nurses and physicians for diagnosis and then received cognitive behavioral strategies and education in a 2-day course led by health psychologists and nurses.

Results: Physician feedback revealed that at one year, rheumatology consults had significantly greater availability, a varied patient population was now being seen in the residency program, and physician satisfaction was very high. Of the 600 patients that participated in the Fibromyalgia Treatment Program, the average age of patients was 49 years with a range from 17 to 92. The majority was female (90%). Duration of fibromyalgia symptoms on average was 10 years at the time of referral. Forty-three percent of the patients were regional, 32% national, 24% local and 1% international. The FIQR results revealed severe levels of impairment (62.08); CESD scale scores indicated significant depressive symptoms with an average score of 26; and PCS scores were at elevated levels of pain catastrophizing with an average score of 25. Patient and family satisfaction was uniformly high.

Conclusion: A successful interdisciplinary program can be developed in a medical practice. The improvement in physician and patient satisfaction in this care model is substantial. Large numbers of patients with Fibromyalgia are still not receiving interdisciplinary care locally producing continued difficulties in functioning and psychological distress.

Disclosure: J. Gehin, None; **A. Abril**, None; **F. Rivera**, None; **B. Wang**, None; **B. Bruce**, None.

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Abstract Number: 1166

Survey on the Understanding and Practice of T2T for Nurses Engaged in Medical Treatment of Rheumatoid Arthritis

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Background/Purpose: In order to achieve treatment goals in patients with rheumatoid arthritis (RA), the guidance for "treatment to target (T2T) by measuring disease activity and adjusting therapy accordingly" was proposed.[1)] However, patients with RA also face various other problems such as side effects of drugs, psychological problems and issues of daily living. These problems cannot be resolved by doctors alone and, therefore, collaboration with medical staff, especially nurses, is essential. As a first step toward better rheumatic care, the nurses understanding of T2T is considered to be important.We evaluated the understanding and practice of T2T for nurses engaged in rheumatic care.

Methods: This is a cross-sectional survey conducted in Japan. Registered nurses consulting patients with RA were selected randomly for this study between May and September 2013. A self-administered survey was carried out to check the understanding of T2T, DAS28 and patient guidance. A series of data analyses were performed based on the Wilcoxon rank sum test and Pearson chi-square.

Results: 103 nurses (one male and 102 female) were enrolled. While 19 (18.4%) of the nurses knew the concept of T2T precisely, 47 (45.6%) understood partially and 37 (35.9%) did not know it at all. In comparison with 37 nurses who did not know about T2T, 66 nurses who knew about T2T showed higher knowledge about DAS28 ($p<0.0001$). The ratio of experience of the DAS calculation was also statistically significantly higher in nurses with knowledge of T2T compared with those without T2T knowledge ($p<0.0001$). Nurses with thorough knowledge of T2T statistically significantly engaged in guidance of daily life ($p=0.018$), therapeutic agent ($p<0.0001$) and health care system ($p=0.004$) compared with those who did not. Regarding the explanation of RA, there is no statistically significant difference between nurses with and without the knowledge of T2T ($p=0.126$).

Nurses who did not know about T2T statistically showed a significant tendency to consider that doctors should assess patients' joints scores compared with those with a thorough knowledge of T2T ($p=0.045$). However, both nurses agreed that the benefits of the assessment of joint scores by nurses is broadening nursing care and saves time for doctors and promotes awareness of the patients' condition before consultation. Most nurses think that they can assess joint scores technically with sufficient training.

Conclusion: This study indicates that understanding the concept of T2T is necessary to expand the role of nurses and to develop the technical knowhow for nurses involved in rheumatic care, leading to better QOL for patients with RA. [1] Smolen JS, et al. Ann Rheum Dis. 2010; 69: 631-7.

Disclosure: M. Fusama, None; **K. Higashi**, None; **K. Maeda**, None; **N. Murata**, None; **H. Nakahara**, None.

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Abstract Number: 1167

Incidence of Primary Chronic Cutaneous Lupus Erythematosus in a Metropolitan Area of the Southeastern United States: The Georgia Lupus Registry

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Background/Purpose: Chronic cutaneous lupus erythematosus CCLE is a group of immune mediated inflammatory disorders of the skin that often induce permanent disfigurement, leading to a substantial negative impact on patientsÕ quality of life. CCLE comprises discoid lupus erythematosus (DLE), lupus erythematosus profundus or lupus panniculitis (LEP), lupus erythematous tumidus (LET) and chilblain lupus erythematosus (CHLE). Relative to SLE, epidemiologic studies on CCLE are rare and limited to populations without racial diversity. This study provides minimum estimates of the incidence of DLE in particular, and CCLE in general, in a predominantly white and black population in the Southeastern United States.

Methods: The Georgia Lupus Registry is a Centers for Disease Control and Prevention-funded registry conducted to estimate the burden of lupus in a large diverse population of the Southeastern United States. Multiple sources, including dermatology and rheumatology practices, multispecialty healthcare facilities, and dermatopathology reports were used to ascertain potential new cases of CCLE from 2002 through 2004. Cases with a clinical or clinical-histological diagnosis of DLE were classified as definite DLE. Cases ascertained exclusively from dermatopathology reports were categorized as probable DLE. Age-standardized rates were determined and stratified by race and sex for DLE in particular and CCLE in general.

Results: The overall age-adjusted incidence of definite and combined (definite and probable) DLE were 2.9 and 3.7/100,000 person-years, respectively. Overall age-adjusted estimate for combined CCLE was 3.9/100,000 person-years. Black-to-white and female-to-male incidence ratios were 5.4 and 3.1 for definite DLE.

Incidence of DLE and CCLE in Fulton/DeKalb, Georgia (01/01/2002-12/31/2004)

	Definite DLE			*Combined DLE (definite and probable)*			*Combined CCLE (definite and probable)*		
Race/Sex	*N Cases*	*Crude Rate (95% CI)*	*Age-adjusted rate (95% CI)*	*N Cases*	*Crude Rate (95% CI)*	*Age-adjusted rate (95% CI)*	*N Cases*	*Crude Rate (95% CI)*	*Age-adjusted rate (95% CI)*
Overall	139	2.9 (2.5,3.5)	2.9 (2.4,3.4)	178	3.8 (3.2,4.3)	3.7 (3.2,4.3)	190	4.0 (3.5,4.6)	3.9 (3.4,4.5)
Female	105	4.3 (3.6,5.2)	4.3 (3.5,5.2)	131	5.4 (4.6,6.4)	5.3 (4.5,6.3)	137	5.7 (4.8,6.7)	5.6 (4.7,6.6)
Male	34	1.5 (1.0,2.0)	1.4 (1.0,2.0)	47	2.0 (1.5,2.7)	1.9 (1.4,2.6)	53	2.3 (1.7,3)	2.2 (1.7,2.9)
Black	113	4.9 (4.0,5.9)	4.9 (4.1,5.9)	135	5.8 (4.9,6.9)	5.8 (4.9,6.9)	143	6.2 (5.2,7.3)	6.2 (5.3,7.3)
Black Female	83	6.7 (5.4,8.3)	6.6 (5.3,8.2)	100	8.1 (6.6,9.8)	7.9 (6.5,9.6)	104	8.4 (6.9,10.2)	8.3 (6.8,10)
Black Male	30	2.8 (1.9,4.0)	2.8 (1.9,4.0)	35	3.2 (2.3,4.5)	3.3 (2.4,4.5)	39	3.6 (2.6,4.9)	3.7 (2.7,5)
White	20	0.9 (0.6,1.4)	0.9 (0.6,1.4)	33	1.5 (1.1,2.1)	1.4 (1,2)	37	1.7 (1.2,2.3)	1.6 (1.2,2.3)
White Female	17	1.6 (1.0,2.5)	1.6 (1,2.5.0)	24	2.2 (1.5,3.3)	2.2 (1.5,3.3)	26	2.4 (1.6,3.5)	2.4 (1.6,3.5)
White Male	3	0.3 (0.1,0.8)	0.2 (0.1,0.7)	9	0.8 (0.4,1.5)	0.7 (0.4,1.4)	11	1.0 (0.5,1.7)	0.9 (0.5,1.6)

Incidence rates are per 100,000 person-years (95% confidence intervals [95%CI]). Age-adjusted rates used the 2000 projected US population. The definite definition for discoid lupus erythematosus (DLE) consisted of cases with a clinical or clinical-pathological diagnosis of DLE. The combined definition for DLE included cases validated as definite and those ascertained through pathology reports (probable). Combined chronic cutaneous lupus (CCLE) included definite and probable cases of all types of CCLE, including DLE. Three cases of Asian race and 7 of unknown race were excluded from the estimates by race

Conclusion: Our findings underscore striking racial disparities in the susceptibility for CCLE, with black people experiencing between three and five-fold increased incidence of CCLE in general and DLE in particular, compared to white people. Gender differences were consistent with those reported previously, with a 3 times higher risk of DLE in females compared to males.

Disclosure: C. Drenkard, None; **S. Parker**, None; **C. Gordon**, None; **C. Hemlick**, None; **L. Aspey**, None; **G. Bao**, None; **S. S. Lim**, None.

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Abstract Number: 1168

The Epidemiology of Individuals Not Fully Meeting Classification Criteria for Systemic Lupus Erythematosus (SLE): The Georgia Lupus Registry

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Background/Purpose: Identifying individuals as early as possible in the development of an autoimmune disease may lead to important opportunities. This study utilizes an established population-based registry to evaluate the burden of individuals who do not meet criteria for SLE but may be at higher risk of being diagnosed later.

Methods: The Georgia Lupus Registry (GLR) is designed to more accurately estimate the incidence and prevalence of SLE in Atlanta, Georgia. The state allowed investigators and trained abstractors to access protected health information without patient consent. Sources of potential cases included hospitals (20), rheumatologists (35), nephrology groups (10), dermatology groups (20), commercial labs, and population databases. Databases were queried for the International Classification of Diseases, Ninth Revision, (ICD-9) code 710.0 (SLE), as well as 695.4 (discoid lupus), 710.8 (other specified connective tissue disease), and 710.9 (unspecified connective tissue disease), as well as serologies and pathology results suggestive of SLE. Antiphospholipid antibody syndrome was searched for if a consistent code was used at a particular facility. Those with less than 4 American College of Rheumatology (ACR) criteria for SLE and without a final physician diagnosis of a specific connective tissue disease were analyzed. Rates were determined for incidence (2002-2004) and prevalence (2002) and age adjusted using the 2000 US population. Age adjusted estimates and 95% confidence intervals were calculated by the direct method using R (routine ageadjust.direct).

Results: 220 individuals were prevalent in 2004 with an overall age-adjusted rate of 14.2 per 100,000 person-years. 99 individuals were incident in 2002-04 with a rate of 2.1. Similar to SLE, the highest rates were in women and blacks. The rate ratio of prevalent women to men was 4.9 and was 2.2 in blacks to whites, lower than seen in SLE. (Table 1) The most frequent ACR criteria manifestations were ANA (56.4% and 57.6% in prevalent and incident individuals, respectively), hematologic disorder (39.1%, 35.4%), and arthritis (30%, 32.3%). There were no statistically significant differences between blacks and whites.

Conclusion: This is the first population-based evaluation of those not fully meeting ACR criteria for SLE in the US. The prevalence and incidence rates were 15% and 30%, respectively, of that which were seen in those validated as having SLE from the same general population. This suggests a significant population at higher risk of being diagnosed with SLE in the future can be identified. Studies are ongoing to determine the outcomes of these patients.

Rates of individuals not fully meeting classification criteria for systemic lupus erythematosus in Atlanta, Georgia, categorized by race/sex* (prevalence in 2004, incidence in 2002-04)

Race/Ethnicity, sex	Catchment population (person-years)	No. of cases	Crude rate (95% CI)	Age-adjusted rate (95% CI)
PREVALENCE				
Overall	1610314	220	13.7 (12,15.6)	14.2 (12.5,16.1)
Women	822408	185	22.5 (19.5,26)	22.5 (19.5,26)
Men	787906	35	4.4 (3.2,6.2)	4.6 (3.3,6.3)
Black	783405	131	16.7 (14.1,19.8)	18.2 (15.5,21.5)
Women	418297	114	27.3 (22.7,32.7)	28.4 (23.8,34)
Men	365108	17	4.7 (2.9,7.5)	5.1 (3.3,8.1)
White	753526	65	8.6 (6.8,11)	8.3 (6.5,10.7)
Women	368338	52	14.1 (10.8,18.5)	12.8 (9.6,17)
Men	385188	13	3.4 (2,5.8)	3.4 (2,5.9)
INCIDENCE				
Overall	4742264	99	2.1 (1.7,2.5)	2.1 (1.7,2.6)
Women	2424592	78	3.2 (2.6,4)	3.2 (2.5,4)
Men	2317672	21	0.9 (0.6,1.4)	1.0 (0.7,1.5)
Black	2321302	58	2.5 (1.9,3.2)	2.8 (2.2,3.5)
Women	1239819	47	3.8 (2.9,5)	3.9 (3,5.2)
Men	1081483	11	1.0 (0.6,1.8)	1.4 (0.9,2.3)
White	2210389	27	1.2 (0.8,1.8)	1.1 (0.8,1.7)
Women	1082131	20	1.8 (1.2,2.9)	1.6 (1,2.6)
Men	1128258	7	0.6 (0.3,1.3)	0.6 (0.3,1.3)

* Rates are per 100,000 person-years (95% confidence intervals [95% CIs]).
* Age-adjusted rates used the 2000 US population.

Disclosure: P. Saxena, None; **G. Bao**, None; **C. Drenkard**, None; **S. S. Lim**, None.

Abstract Number: 1169

A Systematic Review of Rheumatic Disease Epidemiology in the Indigenous Populations of Canada, the United States, Australia and New Zealand

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Background/Purpose:

Two important reviews have summarized the epidemiology of rheumatic disease (Peschken 1999) and RA (Ferucci 2005) in Indigenous populations of North America. Our objective was to update these reviews, incorporate non-medical databases, and expand the scope to include Indigenous populations of New Zealand and Australia.

Methods: A systematic search was performed in medical (Medline, EMBASE, CINAHL), Indigenous and conference abstract databases (to June 2015). Search terms for Indigenous populations were combined with terms for inflammatory arthritis conditions, connective tissue disorders, crystal arthritis, and osteoarthritis. Studies were included if they reported on the incidence or prevalence of rheumatic disease in Canadian, American, Australian or New Zealand Indigenous populations.

Results:

A total of 5,269 titles and abstracts were reviewed, of which 504 underwent full-text review and 88 met inclusion criteria. Prevalence rates of RA in Alaskan Native populations ranged from 0.6 to 2.4%, mostly similar to those estimated in the general population. RA prevalence was estimated at 2.2 to 6.8% in Blackfeet, Chippewa and Pima American Indian populations, higher than in the general population of the United States. Reported rates in Canadian First Nations ranged from 1.0 to 7.1%, increased compared to the general population by at least two-fold. The prevalence of RA in Australian Indigenous populations was 2.7% compared to 1.9% in non-Indigenous people. New Zealand Maori RA prevalence was estimated at 3.3%. Contemporary studies of SLE found prevalence rates to be 149-159 per 100,000 in Alaskan Natives and 138-263 per 100,000 in Native American populations, increased from historical studies. Canadian Indigenous SLE prevalence was 42-348 per 100,000, and in Australian Indigenous populations was 13-93 per 100,000, at least double that of non-Indigenous populations. Incidence rates of SLE (per 100,000) were 7 in Alaska Natives, up to 30 in American Indians, 11 in Australian Indigenous and up to 7 in Canadian First Nations populations. Spondyloarthropathies affected 0.2-2.7% of Alaska Native populations, and <0.04% of American Indian populations studied; in Canadian Inuit, spondyloarthropathy prevalence was estimated at 0.9%. Ankylosing spondylitis prevalence was estimated at 3.0% in Pima American Indian populations, and 2.3% in Canadian Haida populations, but just 0.4% in First Nations in Alberta, and 0% in New Zealand Maori. Crystal arthropathy prevalence is comparatively low in Alaska Native and Canadian First Nations in contrast to New Zealand Maori populations, where prevalence was 6.4 to 11.1%, significantly higher than non-Maori or European populations. Osteoarthritis prevalence was estimated at 6-22% in Canadian First Nations, 1.5% in Canadian Inuit, 7-32% in Australian Indigenous populations, and 4-6% in New Zealand Maori over 50 years of age.

Conclusion: Rheumatic disease prevalence in North American, Australian and New Zealand Indigenous populations is significantly higher than that of non-Indigenous populations, but with variation in estimates across tribal ancestry relevant to health services planning.

Disclosure: C. McDougall, None; **K. Hurd**, None; **C. Barnabe**, None.

Abstract Number: 1170

Month of Birth Affects the Risk of Rheumatic Diseases: A Nationwide Case-Control

Study

Seo Hwa Kim[1], **Jennifer Lee**[2], Haneul Kim[3], Seung-Ki Kwok[4], Sung-Hwan Park[5] and Ji Hyeon Ju[5], [1]Division of Rheumatology,, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, The Republic of, [2]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, The Republic of, [4]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose: There have been several studies which demonstrated the impact of birth on the risk of certain diseases such as asthma or cardiovascular diseases. However, rheumatic diseases have not yet been thoroughly investigated in terms of association with birth month. In this study, we sought to determine whether birth month or season could affect the risk of rheumatologic diseases.

Methods: The birth month patterns of patients with rheumatic diseases were compared with to those of general population. We utilized the claims data of Health Insurance Review and Assessment Service (HIRA) which covers nearly 90% of total population in Korea. The associations between birth month/season and 32 diseases were investigated using logistic regression.

Results: Our dataset included 17,247,458 (male 8,224,670; female 9,022,788) individuals from HIRA database from January, 1997 to August, 2015. Among 27 rheumatic diseases, 8 diseases including Crohn's disease (CD), ulcerative colitis (UC), rheumatoid arthritis (RA), systemic lupus erythematosus, polymyalgia rheumatica(PMR), ankylosing spondylitis (AS), multiple sclerosis, gout, fibromyalgia (FMS) were significantly associated with birth month ($P<0.05$). In terms of seasonality, CD, UC, RA, Sjogren's syndrome, PMR, AS, Gout, and FMS demonstrated significant difference. CD, UC and AS showed higher prevalence in individuals born in winter and lower prevalence in summer. On the other hand, people who were born in summer showed higher possibility to have gout and FMS compared to those born in winter. In consistent with previous reports, type 1 diabetes is more prevalent in those born in winter. Angina and myocardial infarction showed higher prevalence in patients born in spring and lower in fall. This consistency reflects the relevance of our dataset and methodology.

Conclusion: We found significant impacts of birth month/season on various rheumatic diseases. Seasonal variation of infective agents, sun exposure or food ingestion during gestation or early infancy may explain the association between birth month/season and certain disease development.

Disclosure: S. H. Kim, None; **J. Lee**, None; **H. Kim**, None; **S. K. Kwok**, None; **S. H. Park**, None; **J. H. Ju**, None.

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Abstract Number: 1171

Obesity and the Risk of Systemic Lupus Erythematosus in the Nurses' Health Studies

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Background/Purpose: Obesity has become alarmingly common over the past four decades in the U.S., with a notable rise in obesity prevalence starting in the late 1980s. Obesity is related to increased risk of several autoimmune diseases, likely via generation of inflammatory adipokines, but prior studies have not evaluated obesity as a risk factor for SLE. We aimed to prospectively evaluate whether obesity is associated with increased SLE risk, particularly during the years in which obesity prevalence was rising most drastically.

Methods: We conducted a prospective cohort study of women in the U.S. Nurses' Health Studies (NHS, 1976-2012, aged 30-55 at baseline; NHSII, 1989-2013, aged 25-42 at baseline). Incident SLE was confirmed by ACR 1997 criteria. Body mass index (BMI, kg/m^2) was reported at baseline and on biennial questionnaires. We excluded women who did not report BMI at baseline. Cumulative average BMI category, updated every two years, was the primary exposure: 18.5 to <25 (normal [reference]), 25 to <30 (overweight), ≥30 (obese). Cox proportional hazards models estimated HRs (95% CIs) for SLE by cumulative average BMI category, adjusting for time-varying age, race, smoking, alcohol intake, household income, age at menarche, oral contraceptive use, menopausal status and post-menopause hormone use. Analyses were conducted separately in each cohort, and results were meta-analyzed with a DerSimonian-Laird random effects model. We performed a median trend test for SLE risk across increasing BMI categories. In secondary analyses, follow-up started in 1988 (NHS)/1989 (NHSII) when obesity prevalence in the U.S. was increasing most dramatically.

Results: We identified 154 SLE cases in NHS and 113 cases in NHSII. Obesity was present at enrollment in 8.4% (NHS) and 11.8% (NHSII). Mean age at enrollment was 42.7 years (SD 7.1) in NHS and 34.4 years (SD 4.6) in NHSII. 92% of subjects were White in each cohort. At SLE diagnosis, 46.1% (NHS) and 61.1% (NHSII) were anti-dsDNA positive. Obesity was significantly associated with SLE risk in NHSII (HR 1.86, 95% CI [1.17-2.94], p trend 0.02), but did not increase SLE risk in NHS (HR 1.09, 95% CI [0.64-1.84], p trend 0.47). Meta-analysis of NHS+NHSII revealed a significant trend for increased SLE risk by increasing BMI category (p trend 0.03) (**Table**). When follow-up started in the late 1980s, meta-analysis of NHS+NHSII revealed increased SLE risk among obese women (HR 1.78, 95% CI 1.21-2.63, p trend <0.01).

Conclusion: We observed a significant risk of SLE among obese women in NHSII, which started enrollment later than NHS. Obese women were at 78% elevated risk of developing SLE when follow-up started in both cohorts in the late 1980s, suggesting that secular trends in obesity prevalence were associated with increased SLE risk.

SLE risk by cumulative average BMI category: Meta-analysis of Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII)

	Cumulative Average BMI, kg/m^2			
	18.5 to <25	25 to <30	≥30	p trend
Primary analysis **(NHS 1976-2012, NHSII 1989-2013)**				
Cases/person-years	154/3,357,896	66/1,475,564	47/774,433	
Adjusted HR (95%CI)*	1.00	1.01 (0.61-1.68)	1.44 (0.86-2.43)	0.03
Sensitivity analysis **(NHS 1990-2012, NHSII 1989-2013)**				
Cases/person-years	95/2,468,571	45/1,171,617	40/648,533	
Adjusted HR (95%CI)*	1.00	1.13 (0.50-2.56)	1.78 (1.21-2.63)	<0.01

*Meta-analyzed HRs adjusted for age in months, questionnaire cycle, race (White/non-White), annual household income (<$60,000 vs. ≥$60,000), smoking (never/past/current), alcohol intake (none, >0 to <5, ≥5 grams/day), oral contraceptive use (ever/never), age at menarche (≤10 vs. >10 years), menopausal status and post-menopause hormone (PMH) use (pre-menopausal, post-menopausal/never used PMH, post-menopausal/ever used PMH)

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Abstract Number: 1172

Azathioprine and Mycophenolate Mofetil Adherence in a Nationwide Medicaid Cohort with Systemic Lupus Erythematosus

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Background/Purpose: Azathioprine (AZA) and mycophenolate mofetil (MMF) are commonly used immunosuppressants for moderate-to-severe SLE. Overall adherence among SLE patients has been shown to be poor but few studies examine adherence patterns over time by specific immunosuppressant. We applied an innovative method, group-based trajectory modeling (GBTM), to investigate longitudinal, dynamic patterns and predictors of adherence among new users of AZA and MMF in a U.S. nationwide cohort of Medicaid enrollees with SLE.

Methods: We identified prevalent SLE patients in the Medicaid Analytic eXtract, which includes demographics, claims and pharmacy data for enrollees from most U.S. states (2000-2010). We determined new use of AZA or MMF based on ≥6 months of enrollment with no prior use, and required ≥1 year of follow-up after first dispensing (index date). Predictors were determined during the 6 months pre-index date. We assessed overall adherence using the proportion of days covered (PDC ≥80%=adherent) and used logistic regression adjusting for age, sex and race/ethnicity to compare adherence to MMF vs. AZA. We applied GBTM to examine monthly nonadherence patterns (≥80% days covered/month=adherent), beginning at the index date. Multivariable multinomial logistic regression models adjusted for sociodemographics, comorbidities, medication and healthcare use, preventive care, state and year, were used to determine predictors of adherence trajectory patterns.

Results: There were 2360 new users of AZA and 2135 of MMF. Mean age of AZA users was 36 (±12), 92% were female, 47% black, 25% white and 20% Hispanic; mean age of MMF users was 34 (±12), 90% were female, 45% black, 24% white and 21% Hispanic. 14.9% of AZA users were adherent (PDC ≥80%) vs. 17.7% of MMF users (p=0.01); the odds of adherence (PDC ≥80%) were 1.25 times higher (95% CI 1.06-1.47) for MMF vs. AZA. For both AZA and MMF, 4-group trajectory models had the lowest BIC and posterior probabilities >80% indicating the best fit (**Figure**). 46% of AZA users and 23% of MMF users were persistent nonadherers (group 1); 17% of AZA users and 20% of MMF users were persistent adherers (group 4). Multivariable multinomial regression models (persistent nonadherers (group 4)=ref) demonstrated that females vs. males, younger vs. older ages and black race and Hispanic ethnicity vs. white had significantly increased odds of nonadherence to AZA, but not to MMF. More emergency department visits and ever corticosteroid use increased the odds of nonadherence to MMF, but not to AZA.

Conclusion: In this cohort, persistent adherence to either AZA or MMF in the first year of use was rare. We observed even poorer overall adherence among AZA users compared to MMF with distinct nonadherence patterns for each drug and different associated demographic and utilization predictors. Further studies are needed to determine whether drug-related characteristics contribute and whether adherence should factor into prescribing choice.

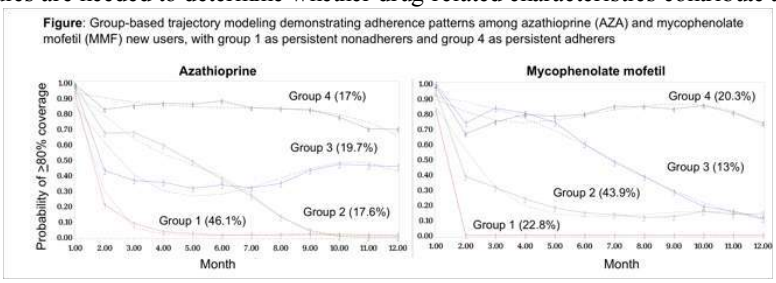

Figure: Group-based trajectory modeling demonstrating adherence patterns among azathioprine (AZA) and mycophenolate mofetil (MMF) new users, with group 1 as persistent nonadherers and group 4 as persistent adherers

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Abstract Number: 1173

Screening for Depression and Anxiety in an Outpatient Rheumatology Clinic Using Validated Self-Applied Questionnaires

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Background/Purpose: Anxiety and depression are often present in chronic rheumatic diseases. Recognition of these psychological disorders is fundamental for proper patient management. The absence of screening leaves more than >50% of patients with depression unidentified. Patient Help Questionnaire-9 (PHQ-9) and General Anxiety Disorder-7 (GAD-7) are two validated self-applied questionnaires that are appropriate to assess the presence of, depression and anxiety, respectively. Objectives. 1) To assess the prevalence of depression and anxiety in a hospital based outpatient Rheumatology clinic and 2) To provide the attending physician with appropriate instruments that allow a rapid orientation on the psychological status of her/his patient.

Methods: Consecutive patients that attended our outpatient Rheumatology clinic from March to June 2016 were invited to participate in this cross-sectional study. Participants filled out PHQ-9 and GAD-7 in the waiting room. The prevalence and severity of anxiety and depression were calculated for the most prevalent diagnoses.

Results: A total of 410 patients were recruited; 339 (82.8%) were female. Overall, 191 (46.6%) patients reported depressive symptoms (PHQ-9 >5). Of them, 87 (21.2%) were classified as having moderate depression or higher (PHQ-9 >10). Prevalence of depression and anxiety among study participants according to each rheumatic disease is depicted in Table 1. Prevalence of moderate or severe depression was significantly different among various rheumatic diseases (p = 0.001). Regarding anxiety symptoms, they were reported in 168 (40.7%); 67 (16.2%) of them had moderate or severe anxiety.

Conclusion: This cross-sectional study shows that anxiety and depression are frequent in the Rheumatology clinic. We demonstrated that the use of a self-applied screening tool can help clinicians to properly detect depression and anxiety associated with diverse rheumatic diseases. Special attention should be paid to patients with fibromyalgia and osteoarthritis.

Disease	N	Moderate or severe depression	Moderate or severe anxiety
SLE	99 (24.1 %)	16 (16.2 %)	12 (12.1 %)
RA	107 (26.1 %)	26 (24.3%)	17 (15.9%)
FM	87 (21.3 %)	**30 (34.5 %) p= 0.001**	**27 (31 %) p=0.001**
OA	69 (16.8 %)	**25 (36.2 %) p= 0.001**	**22 (31.9 %) p=0.001**
SSc	18 (4.4 %)	13 (26 %)	8 (16 %)
Inflammatory myopathies	14 (3.4 %)	4 (28.6 %)	2 (14.3 %)
Osteoporosis	49 (12 %)	14 (28.6 %)	9 (18.4 %)
APS	42 (10.2 %)	**1 (2.4 %) p= 0.001**	3 (7.1 %)

Table 1. Prevalence of depression and anxiety among study participants according to each rheumatic disease. (SLE – Systemic lupus erythematosus, RA – Rheumatoid Arthritis, FM – Fibromyalgia, OA – Osteoarthritis, SSc – Systemic sclerosis, APS – Antiphospholipid syndrome.

Disclosure: L. F. Perez-Garcia, None; **V. Rivera**, None; **M. Moreno Ramirez**, None; **J. Loaiza Felix**, None; **L. A. Martinez-Martinez**, None; **A. Vargas Guerrero**, None; **L. H. Silveira**, None; **L. M. Amezcua-Guerra**, None; **M. Martínez-Lavín**, None.

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Abstract Number: 1174

Perceived Stress and Reported Cognitive Symptoms Among Patients with Systemic Lupus Erythematosus

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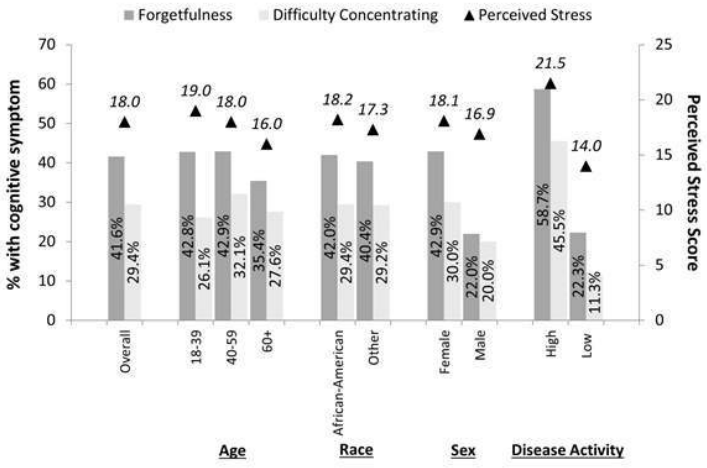
Background/Purpose: Higher stress is associated with lower cognitive functioning in many populations. We examined associations of perceived stress with cognitive symptoms among adults with systemic lupus erythematosus (SLE), a chronic, complex autoimmune disorder.

Methods: We obtained cross-sectional data for 799 Atlanta-area SLE patients ≥18 years old on scores from the validated Perceived Stress Scale (PSS; range, 0-40 with higher scores=higher stress) and two self-reported cognitive symptoms: forgetfulness [severe/moderate vs. mild/none; from the Systemic Lupus Activity Questionnaire (SLAQ)] and difficulty concentrating (all/most vs. some/little/none of the time; from the Lupus Impact Tracker). We estimated mean PSS scores and percentages of patients with cognitive symptoms, overall and by age (18-39, 40-59, and 60+), race, sex, and high vs. low disease activity [≥ vs. < median SLAQ score (=15), after excluding the forgetfulness item]. We used multivariable logistic regression to estimate the odds ratios (ORs) for the associations between PSS score (minimal clinically important difference=0.5*SD=4.0 points) and cognitive symptoms.

Results: Overall, 41.6% and 29.4% of participants reported forgetfulness and difficulty concentrating. Women were twice as likely to report forgetfulness (P=0.004) and those with high vs. low disease activity were ~3- and 4-fold more likely to report forgetfulness (P<0.001) and difficulty concentrating (P<0.001), respectively (Figure). Mean PSS scores were lower in the oldest SLE patients (P=0.002) and those with low disease activity (P<0.001). With adjustment for age, race, sex, education, income, and disease activity, each 4.0-point increase in PSS score was associated with 1.3- and 2.1-fold higher prevalence of forgetfulness (OR=1.33, 95% CI 1.21-1.47) and difficulty concentrating (OR=2.12, 95% CI 1.83-2.44). No substantial differences in this association by age, race, sex, or disease activity were noted, and interaction terms were not statistically significant.



Conclusion: SLE patients, particularly those with high disease activity, report a substantial burden of cognitive symptoms. These symptoms are associated with higher perceived stress, regardless of disease activity or other patient characteristics. This relatively young patient population may be susceptible to cognitive symptoms often linked with geriatric syndromes, for which stress may represent a modifiable risk factor.

Disclosure: L. Plantinga, None; **C. Drenkard**, None; **C. B. Bowling**, None; **S. S. Lim**, None.

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Thirty Day Readmission Rates for Patients Diagnosed with Systemic Lupus Erythematosus: Analysis at a Tertiary Care Center

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic illness that has been associated with high hospital readmission rates. Based on a recently published (Arth Rheumatol (2014) 66:2828) electronic database analysis of Medicare/Medicaid hospital discharges, 16.5% of patients with the ICD-9-CM code 710.0 for SLE were readmitted to any hospital within thirty days. We propose a retrospective, observational study to assess the rate of and predictive factors influencing a thirty-day hospital readmission for adult patients with SLE.

Methods: All index admissions, defined as hospital admissions from adult patients (≥ 18 years of age) who had a primary or secondary ICD-9-CM diagnosis of 710.0 from October 1, 2012 to December 30, 2014, were discovered through data mining. Individual electronic patient charts from these admissions were manually reviewed to determine if the patient fulfilled the 1997 ACR revised criteria for SLE. Hospitalizations were excluded if they were scheduled admissions, resulted in a discharge to acute rehab, maternity related or resulted in death. The remaining hospitalizations were analyzed to determine if they resulted in a thirty-day readmission, using the same methods of determining thirty-day readmission counts performed in the benchmark study of readmission rates in Medicare's fee-for-service program.

Results: 1003 index admissions (obtained from 433 unique patients) met our inclusion criteria. Only 196 of the 433 patients (45.3%) fulfilled criteria for SLE. The other 237 patients (54.7%) did not meet criteria: 185 patients had an inappropriate diagnosis of SLE (i.e., chart review contained sufficient data to support an alternate diagnosis), 34 patients had limited cutaneous lupus, and 18 patients had insufficient data to either confirm or refute a diagnosis of SLE. After application of exclusion criteria, 88 patients remained, accounting for 293 admissions, broken down into 221 index admissions (75.4%) and 72 thirty-day readmissions (24.6%). Of the 88 patients, 33 patients (37.5%) had ≥1 thirty-day readmission. Demographic data including age (p=0.92), gender (p=0.75), race/ethnicity (p=0.82), median household income by zip code (p=0.078) and primary expected payer (p=0.322) was compared between the groups. Of those with ≥1 thirty-day readmission, 11 were deceased (33.3%) compared to 3 deceased in those without a thirty-day readmission (5.5%) (p=0.0005).

Conclusion: We discovered a 37.5% rate of thirty-day readmission in patients meeting the 1997 revised criteria for the diagnosis of SLE. Among patients with ≥1 thirty-day readmission, a lower mean household income per zip code (p=0.078) was observed, approaching significance. All cause mortality was significantly increased in patients with SLE and ≥1 thirty-day readmission (p=0.0005). Additionally, our study revealed a 54.7% rate of miscoding of hospital records for adult patients with a primary or secondary diagnosis of SLE designated by the ICD-9-CM code 710.0, questioning the validity of using ICD-9-CM codes to identify patients with SLE.

Disclosure: S. Ali, None; **S. Mullis**, None; **N. Emejuaiwe**, None; **D. Ang**, None.

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Abstract Number: 1176

Prevalence of Influenza and Pneumococcal Polysaccharide Vaccine Administration and the Factors Affecting Vaccine Uptake in a Population of Patients with Autoimmune Inflammatory Rheumatic Diseases in a Brooklyn Clinic

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Background/Purpose: Patients with autoimmune inflammatory rheumatic diseases (AIIRDs) are at increased risk for developing infections. The pathophysiology of the primary disease process, as well as the immunosuppressive agents used in management of these conditions both contribute to this increased risk. Routine vaccine administration can prevent severe infections in this patient population.

Our aim was to determine the rates of influenza and pneumococcal polysaccharide vaccine administration in the patients followed in the rheumatology clinics at SUNY Downstate Medical Center (SUNY DMC), as well as the factors associated with vaccine uptake.

Methods: A retrospective chart review was performed on 296 eligible patients during the period between October 2014 and January 2015. Demographic data including age, gender, number of clinic visits during the period, autoimmune rheumatic diagnosis, frequency of primary care follow-up and immunization status with influenza and pneumococcal vaccines were collected. An additional survey was administered to 39 established clinic patients over the period covering March 8 to April 4, 2016. Data collected included age, sex, ethnicity, level of education, influenza and pneumococcal vaccination status, physician referral for vaccination and reasons (if applicable) for refusal of immunization.

Results: Of the 296 participants, 271 (91.6%) were female, with 266 (89.9%) on immunosuppressive therapy. The majority of the patients had the diagnosis of systemic lupus erythematous (n=165; 55.74%) and rheumatoid arthritis (n=97; 32.77%). The prevalence of influenza virus and pneumococcal vaccination were low at 18.92% (n=56) and 14.53% (n=43) respectively. Among the participants surveyed, the most common reason for refusal of the influenza vaccination (60%) was concerns about subsequent illness.

Conclusion: This study demonstrated that the rates of influenza and pneumococcal vaccination in patients with AAIRDS followed at SUNY DMC rheumatology clinic are lower than that of the general population. The main factor affecting the rate of immunization was found to be concerns for acquired illness from the vaccines. This information can be used by clinicians to develop interventions to ensure increased vaccine uptake, including improved verbal patient education as well as the dissemination of printed materials with important facts about immunization.

Disclosure: D. A. Williams, None; **R. Hardie**, None; **A. Anderson**, None; **O. Dvorkina**, None.

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Abstract Number: 1177

Pneumocystis Jirovecii Pneumonia in Systemic Autoimmune Inflammatory Diseases

Shafay Raheel[1], Eric L. Matteson[1], Cynthia S. Crowson[2], Andrew Limper[3], Eva M. Carmona Porquera[3], Ulrich Specks[4] and Misbah Baqir[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, MN, [4]Mayo Clinic, Rochester, MN, [5]Pulmonary/Critical Care, Mayo Clinic, Rochester, MN
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Background/Purpose: *Pneumocystis jirovecii* pneumonia (PJP) is most frequently associated with AIDS, however, this infection also occurs in a variety of rheumatologic conditions in the context of immunosuppressive therapy. The mechanisms of immune compromise in patients without AIDS who have PCP are usually multifactorial, related to underlying cytotoxic therapy and malnutrition. PCP infection has been extensively studied among AIDS patients, however, not many studies have evaluated its occurrence in the setting of underlying rheumatologic diseases.

Methods: The study cohort included a consecutive series of patients without AIDS and malignancy or organ transplantation who were assessed at a single institution for a first episode of PCP infection. Medical records were examined to determine underlying immunosuppressive disorders, corticosteroid dosage, associated infections, and subsequent respiratory failure and in-hospital mortality.

Results: The study included 54 patients (mean age at presentation 62.8 years; 54% male) with mean follow up of 2.5 years. Conditions associated with a first episode of PCP were rheumatoid arthritis (30%), inflammatory bowel disease (17%), systemic lupus erythematosus, polymyalgia rheumatic (7%) and giant cell arteritis (6%). Regardless of the underlying condition, corticosteroids had been administered systematically in 45 patients (83%) within 3 months before the diagnosis of PCP. The median daily corticosteroid dose was 27.5 mg. Predominant symptoms on presentation were cough (78%) and shortness of breath (76%). The majority of the patients (87%) on immunosuppressive therapy did not receive any prophylaxis for PCP infection. There were 25 patients (46%) that improved upon institution of therapy while 14 patients (26%) died as a result of infection.

Conclusion: In this large consecutive series, systemic administration of corticosteroid therapy, even in the moderate doses may increase

susceptibility to PCP infections. Consideration should be given to instituting PCP prophylaxis (when not contraindicated) in patients for whom prolonged systemic corticosteroid therapy is prescribed.

Disclosure: S. Raheel, None; **E. L. Matteson**, None; **C. S. Crowson**, None; **A. Limper**, None; **E. M. Carmona Porquera**, None; **U. Specks**, Genentech, 5; **M. Baqir**, None.

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Abstract Number: 1178

Is Subclinical Atherosclerosis Prevalent in a French Patient Cohort with Systemic Lupus Erythematosus?

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Background/Purpose: Systemic lupus erythematosus (SLE) seems associated with an increased risk of cardiovascular disease. These data are mainly based on studies mostly from North America. The aim of this study was to investigate the prevalence of subclinical atherosclerosis in a large cohort of SLE patients in France.

Methods: In this retrospective cohort study, 282 SLE patients underwent screening for subclinical atherosclerosis from January 2014 to April 2016. The presence of subclinical atherosclerosis was evaluated using a carotid ultrasound examination with measurement of intima media thickness (IMT) and electron-beam computed tomography to screen for coronary artery calcification (CAC). CAC was divided in 4 categories: 0; 1- 99; 100 – 399 and ≥ 400. SLE characteristics and cardiovascular risk factors were included in a regression analysis to determine the importance of SLE specific features in the occurrence of subclinical atherosclerosis in the female subpopulation.

Results: From the eligible cohort of 282 patients, 19 patients (6.7%) were excluded because of the presence of prior cardiovascular events. 263 (240 women, 91.3%) patients free from cardiovascular disease were included. The mean age of the study population was 42.6 +/- 13.2 years. 35.4% suffered from arterial hypertension, 20.6% were current smokers, 5.3% had diabetes, 26.2% had a dyslipidemia and 2.3% had a familial history of cardiovascular disease. The mean BMI was 24.8 kg/m² +/- 5.4. 58.8 % of the study population had disease duration of at least 10 years and 25.5% had a SLICC score > 0. 89% of the patients were treated with hydroxychloroquine, 53.6% with corticosteroids and 28.5% with at least one other immunosuppressive agents. The prevalence of carotid plaques was 20.3% (19.2% in women and 32% in men, p = 0.17). The median value of the IMT was 0.53 mm (IQR [0.47; 0.60]). 25% of the patients had a CAC > 0: 17.3% between 1 – 99; 5.2% between 100 - 399 and 2.4% ≥ 400. Using multivariable logistic regression analysis the presence of carotid plaques in women was significantly associated with age with an adjusted Odds ratio (OR) for each supplementary year of 1.12 (95%CI, 1.07;1.16), controlling on smoking habit. CAC score > 0 in women was significantly associated with age (OR per year = 1.14, 95% CI [1.09; 1.19]) and current treatment with immunosuppressive drugs (OR = 2.70; 95%CI [1.08; 6.71]), controlling on smoking habit. IMT was significantly associated with age, with the presence of diabetes and lupus nephritis. Patients with diabetes had a mean IMT that was 116 µm (95% CI, 49;184) higher than those without diabetes. Treatment with glucocorticosteroids and the presence of an antiphospholipid antibody syndrome was not associated with an increased risk for subclinical atherosclerosis.

Conclusion: In this retrospective cohort, the CAC and IMT did not seem to be elevated compared to published series of SLE patients. Besides an expected association with classical atherosclerotic risk factors including age, diabetes, and smoking, disease-related factors such as treatment with immunosuppressive agents and lupus nephritis are associated with subclinical atherosclerosis.

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Abstract Number: 1179

The Impact of Autoimmune Disease in the Management and Prognosis of Acute Coronary Syndrome

Nuria Lozano-Rivas[1], Carlos Marras Fernandez-Cid[2], Francisco Jose Pastor Perez[3], Pedro Flores-Blanco[4], Miriam Gomez-Molina[4], Alberto Bermudez[5], Luis Francisco Linares[2], Javier Martinez Ferrin[2], Francisco Andrés Martinez-Angosto[1], Pablo Mesa del Castillo[2] and Sergio Manzano-Fernandez[4], [1]Rheumatology, Hospital Virgen de la Arrixaca, murcia, Spain, [2]Rheumatology, Hospital Virgen de la Arrixaca, Murcia, Spain, [3]Cardiology, Hospital Virgen de la Arrixaca, Murcia, Spain, [4]Cardiology, Hospital Virgen de la Arrixaca, murcia, Spain, [5]Hospital Virgen de la Arrixaca, Molina de Segura (Mu, Spain
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Background/Purpose: Patients with autoimmune diseases (AID) have a high burden of cardiovascular disease leading to premature morbidity and mortality. But it is unclear if it is due to a higher prevalence of cardiovascular disease, to a worse case fatality or to a different management after an index event. The primary aim of the study is to assess the prognostic implications of the presence of AID both during the hospitalization and after discharge after an acute coronary syndrome (ACS). The secondary objectives included the assessment of the prevalence of AID in patients with ACS, their clinical profile and the management of this index event

Methods: The study included consecutive patients admitted after ACS from January 2011 to December 2015 at the University Hospital Virgen de la Arrixaca, Murcia (Spain). For AID patients, in-hospital management and ACS presentation was compared to non-AID patients. We also compared in-hospital and major adverse events during follow-up (death, recurrent non-fatal myocardial infarction, stroke and major bleeding, between groups). A multivariate Cox regression model was performed to assess the independent role of the presence of AID in the occurrence of the events of interest.

Results: Of 2236 patients included with ACS, 78 had AID (3.3%): 24 rheumatoid arthritis, 10 inflammatory bowel disease, 7 ankylosing spondylitis, 6 psoriatic arthritis, 5 polymyalgia rheumatica, 2 systemic lupus erythematosus and 20 miscellanea. Mean age of AID patients was 67 ± 13 years and median evolution of the disease was 10 [4-14] years. Seventy percent of AID patients were taking corticosteroids, 50% disease modifying antirheumatic drugs, 22% non-steroidal anti-inflammatory drugs and 8 biological theraphy. No significant differences were found in clinical and demographics characteristics between groups except for a higher percentage of atrial fibrillation and chronic obstructive pulmonary disease in AID patients. Compared to non-AID patients, AID patients had similar clinical ACS presentation and no differences were found with respect to revascularization strategies or medical treatment at discharge. With respect to prognosis the two groups had comparable rates of adverse events during hospitalization (10% vs 10%, p=0.920) with no statistically significant differences in any single event studied. However after a follow-up of 397 [375-559] years, AID patients had higher rate of combined adverse events (44% vs 28% p<0,001). After multivariate adjustment the presence of AID was associated with increased total mortality (hazard ratio 2.1, 95% CI 1.2 to 3.7, p=0.008) and it was also a borderline risk factor for higher bleeding complications (hazard ratio 2.2, 95% CI 0.9 to 5.5). The presence of AID was not an independent risk factor for neither stroke or recurrent non-fatal myocardial infarction.

Conclusion: The presence of AID did not change ACS presentation and clinical management. Although AID is not associated with worse outcomes during hospitalization it is independently linked to higher total mortality and a trend to an increased risk of major bleeding during follow-up

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Disclosure: N. Lozano-Rivas, None; **C. Marras Fernandez-Cid**, None; **F. J. Pastor Perez**, None; **P. Flores-Blanco**, None; **M. Gomez-Molina**, None; **A. Bermudez**, None; **L. F. Linares**, None; **J. Martinez Ferrin**, None; **F. A. Martinez-Angosto**, None; **P. Mesa del Castillo**, None; **S. Manzano-Fernandez**, None.

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Abstract Number: 1180

Class V Lupus Nephritis Results in Significant Numbers of End Stage Renal Disease and Death in a Population-Based Registry

Jennifer Brandt[1], Cristina Drenkard[2], Jason Cobb[3], Gaobin Bao[4] and S. Sam Lim[4], [1]Department of Rheumatology, Emory University School of Medicine, Atlanta, GA, [2]Emory University School of Medicine, Atlanta, GA, [3]Department of Nephrology, Emory University School of Medicine, Atlanta, GA, [4]Medicine, Emory University School of Medicine, Atlanta, GA

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Background/Purpose: Although the diagnosis of pure class V lupus nephritis (LN) is generally thought to portend a favorable prognosis, outcomes on a population-level are not well known. We evaluated the outcomes of those with only class Va/b and class Vc/d disease with a focus of end stage renal disease (ESRD) and death on a population level.

Methods: The Georgia Lupus Registry (GLR) is a population-based registry designed to more accurately estimate the incidence and prevalence of systemic lupus erythematosus (SLE) in Atlanta, Georgia, by partnering with the state health department, allowing records to be reviewed without patient consent. Trained abstractors documented demographic and clinical information from potential SLE patients who were prevalent in 2002 and incident in 2002-04. Renal biopsy results (WHO criteria) were obtained from the medical record as well as local and regional commercial nephropathology labs. Those with a concurrent LN class other than V were excluded. Patients were matched to the state death certificate database through 2013 and the United States Renal Data System for ESRD through September 2012.

Results: Among prevalent patients with class V LN, many resulted in ESRD 35/129 (27.1%) and death 34/129 (26.4%). Among incident patients with class V LN, 3/31 (9.7%) developed ESRD and 6/31 (19.4%) died. There was no significant difference in age, race, ACR criteria manifestations, or outcomes between Va/b and Vc/d in prevalent and incident SLE patients. There were significantly more females with class Vc/d compared to Va/b in prevalent patients. Though not statistically significant in incident patients, more females had class Vc/d compared to Va/b (81.3% vs. 66.7%).

Conclusion: This is the first population-based evaluation of class V only SLE with surveillance for outcomes up to 13 years. Individuals with pure class V LN have relatively high prevalence of ESRD and death with no difference in outcomes between Va/b and Vc/d. Differences in age, race, and ACR manifestations were not seen between the two groups. There were significantly more females with class Vc/d compared to Va/b in prevalent patients. More study is required to understand the factors responsible for poor health outcomes among persons with class V nephritis.

Prevalent SLE With Class V Only Lupus Nephritis				
Characteristic	**Overall (n = 129)**	**Class Va/b (n=80)**	**Class Vc/d (n=49)**	**P Value**
Age at diagnosis, Mean +/- SD	28.4 ± 12.2	29.9 ± 12.3	26.0 ± 11.8	0.084
Gender (female), n (%)	108 (83.7)	61 (76.3)	47 (95.9)	0.0033
Race, n (%) Black	120 (93.0)	76 (95.0)	44 (89.8)	0.18
White	7 (5.4)	4 (5.0)	3 (6.1)	
Other	2 (1.6)	-	2 (4.1)	
Malar rash, n (%)	45 (34.9)	25 (31.3)	20 (40.8)	0.27
Discord rash, n (%)	28 (21.7)	20 (25.0)	8 (16.3)	0.25
Photosensitivity, n (%)	24 (18.6)	15 (18.8)	9 (18.4)	0.96
Oral ulcers, n (%)	25 (19.4)	16 (20.0)	9 (18.4)	0.82
Arthritis, n (%)	86 (66.7)	51 (63.8)	35 (71.4)	0.37
Serositis, n (%)	65 (50.4)	39 (48.8)	26 (53.1)	0.63
Neurologic disorder, n (%)	24 (18.6)	11 (13.8)	13 (26.5)	0.07
Hematologic disorder, n (%)	112 (86.8)	68 (85.0)	44 (89.8)	0.43
Immunologic disorder, n (%)	96 (74.4)	61 (76.3)	35 (71.4)	0.54
ESRD, n (%)	35 (27.1)	19 (23.8)	16 (32.7)	0.27
Death (by 12/31/2013), n (%)	34 (26.4)	20 (25.0)	14 (28.6)	0.65
Age at death, Mean +/- SD	42.3 ± 16.5	46.5 ± 17.2	36.4 ± 13.8	0.079
Median(IQR)	40.0 (30.7-54.8)	46.2 (35.7-57.1)	35.7 (26.1-42.2)	
Incident SLE With Class V Only Lupus Nephritis				
Characteristic	**Overall (n=31)**	**Class Va/b (n=15)**	**Class Vc/d (n=16)**	**P Value**
Age at diagnosis, Mean +/- SD	33.2 ± 13.0	32.9 ± 12.8	33.4 ± 13.6	0.92
Gender (female), n (%)	23 (74.2)	10 (66.7)	13 (81.3)	0.43
Race, n (%) Black	26 (83.9)	13 (86.7)	13 (81.3)	>0.99
White	2 (6.5)	1 (6.7)	1 (6.3)	
Other	3 (9.7)	1 (6.7)	2 (12.5)	
Malar rash, n (%)	4 (12.9)	3 (20.0)	1 (6.3)	0.33
Discord rash, n (%)	2 (6.5)	1 (6.7)	1 (6.3)	>0.99
Photosensitivity, n (%)	2 (6.5)	2 (13.3)		0.23
Oral ulcers, n (%)	4 (12.9)	1 (6.7)	3 (18.8)	0.6
Arthritis, n (%)	13 (41.9)	6 (40.0)	7 (43.8)	>0.99
Serositis, n (%)	12 (38.7)	7 (46.7)	5 (31.3)	0.47
Neurologic disorder, n (%)	5 (16.1)	2 (13.3)	3 (18.8)	>0.99
Hematologic disorder, n (%)	21 (67.7)	11 (73.3)	10 (62.5)	0.7
Immunologic disorder, n (%)	21 (67.7)	10 (66.7)	11 (68.8)	>0.99
ESRD, n (%)	3 (9.7)	2 (13.3)	1 (6.3)	0.6
Death (by 12/31/2013), n (%)	6 (19.4)	4 (26.7)	2 (12.5)	0.32
Age at death, Mean+/- SD	46.0 ± 9.9	47.8 ± 7.8	42.3 ± 16.4	0.83
Median(IQR)	49.4 (37.0-53.9)	49.4 (42.4-53.1)	42.3 (30.7-53.9)	

Disclosure: J. Brandt, None; **C. Drenkard**, None; **J. Cobb**, None; **G. Bao**, None; **S. S. Lim**, None.

Abstract Number: 1181

Risk Factors for Incident Fractures in Patients with Systemic Lupus Erythematosus on Dialysis

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Background/Purpose: Osteoporosis and osteoporotic fractures are significant comorbidities in patients with systemic lupus erythematosus (SLE). Hip fractures are being increasingly recognized as a complication of dialysis raising concern for similar events among patients with SLE who progress to end-stage renal disease (ESRD). The intention of this study was two-fold: (1) to compare the frequency of incident osteoporotic fractures in patients with ESRD with and without SLE, and (2) to identify risk factors for osteoporotic fractures in patients with SLE and ESRD.

Methods: A retrospective cohort of adults starting dialysis between 2006-2008 enrolled in Medicare Part D without a previously filled prescription for osteoporosis medications were selected from the U.S. Renal Data System (USRDS). The International Classification of Diseases, 9th Revision (ICD-9) codes were used to identify patients in the hospital claims dataset with a diagnosis of SLE prior to starting dialysis. A 5% control sample was randomly selected for comparison due to a sizable proportion of patients without a diagnosis of SLE. Potential risk factors for osteoporotic fractures including demographic and clinical factors and medication use were determined using ICD-9 codes from hospital claims, Medical Evidence Report and Medicare Part D. Incident fracture was defined as an ICD-9 code for a non-traumatic, non-pathologic fracture within 5 years of follow-up. Fractures were grouped by location: upper extremity, lower extremity (excluding hip), hip and vertebral.

Results: There were 1,311 (0.5%) patients starting dialysis between 2006-2008 with a diagnosis of SLE. After applying exclusion criteria and including random selection of 5% of controls, there were 649 patients with SLE and 3,992 patients in the control group. Fractures occurred in 10.5% of SLE patients compared to 11.9% of controls. In multivariable analyses, there was no significant difference in the incidence of osteoporotic fractures in patients with SLE compared with controls (p=0.08, RR 0.40, CI 0.66-1.08). Among patients with SLE, fractures of the hip were most common (46%) followed by those of the upper extremity (21%), vertebrae (19%) and lower extremity (14%). In the control group, fractures of the hip (49%) outnumbered those of the lower extremity (25%), upper extremity (17%) and vertebrae (9%). In multivariable adjusted analyses, female gender (p=0.05, RR 2.08, CI 1.00-4.32) and older age (p=0.03, RR 1.02, CI 1.00-1.04) were associated with increased fracture risk. However, race, ethnicity, dialysis type, tobacco and alcohol use, BMI, Charlson Comorbidity Index, prevalent fractures or medication use (corticosteroids, opioids, selective serotonin reuptake inhibitors, proton pump inhibitors, anticonvulsants, diuretics, sedatives, oral hypoglycemics) (p>0.10 for all) were not significantly associated with fracture risk.

Conclusion: Patients with SLE and ESRD do not have an increased risk for osteoporotic fractures compared to patients with ESRD alone. Hip fractures are the most common fracture site in patients with SLE and ESRD. In patients with SLE and ESRD, female gender and older age are associated with increased fracture risk.

Disclosure: B. Le, None; **J. Waller**, None; **R. Radhakrishnan**, None; **S. J. Oh**, None; **M. Bethel**, None; **C. Rice**, None; **L. Carbone**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-factors-for-incident-fractures-in-patients-with-systemic-lupus-erythematosus-on-dialysis

Abstract Number: 1182

Opiod Use and Death in Chronic Pain Patients with Systemic Lupus Erythematosis

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Background/Purpose: Chronic pain is one of the most common symptoms reported in patients with SLE. Treating pain in these individuals can be complex and difficult to manage and often require opioid therapy. The present research, to our knowledge, is the first investigation into the impact of opioid use in the management of patients with SLE and chronic pain.

Methods: This prospective 5 year longitudinal outcome study of 275 SLE patients at the University of New Mexico included 24% (chronic opioid use) and 76% (no opioid use). Inclusion criteria were patients fulfilling ACR criteria for SLE, aged18-80. Patients diagnosed with any other autoimmune disease were excluded. Outcomes were determined at 5 years after enrollment in the study. Statistical differences were determined with Student t-test and categorical data with Fisher's exact method. Associations were determined initially with univariate regression analysis and then multivariate models were created to determine independent and dependent variables.

Results: No statistical signficance was observed in age, age of onset, disease duration, race, family history of autoimmune disease, alcohol use, ANA titer, dsDNA titer, aPL positivity, anti-ribosomal P, RNP, anti-Smith, Ro/SSA, La/SSB, Scl-70, Coombs, active or chronic kidney disease, or joint pain between opioid and non-opioid SLE groups. SLE patients that used opioids had a signficantly higher rate of tobacco use and duration, criteria average for SLE diagnosis, average pain scores, morning stiffness, SLICC and SLEDAI indices, cocaine use, non-compliance, and total deaths. Logistic regression analysis predicting death revealed hazard ratios 2.6 and 1.1, when comparing opioid use and total SLEDAI respectively; and hazard ratios 2.5, 1.1, and 1.6, when comparing opiod use, total SLEDAI, and non-compliance respectively. Univariate Cox Model estimated the probability of death in SLE patients revealed statistical significance for opioid use and non-compliance, hazard ratios 3.2 and 1.8 respectively. Multivariate Cox Model analysis estimating the probability of death with covariates; opioid use and total SLEDAI (both statistically significant, hazard ratios 2.6 and 1.1 respectively), opioid use and alcohol use (only opioid use was statistically significant, hazard ratio 3.3), opioid use, cocaine use, and alcohol use (only opioid use and cocaine use were statistically significant, hazard ratios 3.0 and 3.2 respectively), and lastly opioid use, non-compliance, and total SLEDAI (only opioid use and non-compliance were statistically significant, hazard ratios 2.5 and 1.1 respectively). The marginal survival for SLE patients not taking opioids was 88% (12% dead) versus 65% (35% dead) patients taking opoiods. The Kaplan-Meir survival curve revealed higher probability of survival for SLE patients that did not use opioids.

Conclusion: This study indicates that opioid use in SLE is associated with higher mortality, total SLICC and SLEDAI disease activity scores, increase cocaine use, and non-compliance. These data suggest the need for education and safe opioid prescribing strategies in SLE patients with chronic pain.

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Abstract Number: 1183

Lack of Awareness of Sexual Health in Rheumatology. High Prevalence of Sexual Dysfunction Among Women with Rheumatic Diseases

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Background/Purpose:

Rheumatic diseases comprise a diverse group of about 150 degenerative, autoimmune and autoinflammatory diseases. Sexual dysfunction affects about 70% of patients with rheumatic diseases and is related to both anxiety and depression. However there are few studies which analyze in depth the sexuality of patients with rheumatic diseases.

Methods:

A cross-sectional study where the patients enrolled in two clincal settings (public heatlh insurance and social security service). We evaluated every patient with a rheumatic disease by the classification criteria ACR / EULAR which may apply. The presence of sexual dysfunction was assessed with the questionnaire 'Female Sexual Function Index (FSFI)' proposed by Rosen. The FSFI is a self-administered aimed at assessing female sexual response questionnaire in six domains: sexual desire, sexual arousal, vaginal lubrication, orgasm, sexual satisfaction and pain. The FSFI contains 19 questions that assess sexual function in the last four weeks. A total of ≤26 indicates sexual dysfunction . An historical comparison with an aged matched control group was conducted.

Results:

We included 356 women with a mean age of 48.9 years (SD 13.2). The 76.7% of those evaluated were represented by the following diseases: Rheumatoid Arthritis (195, 54.8%) Systemic Lupus Erythematosus (43, 12.1%), Osteoarthritis (21, 5.9%) and Primary Sjögren's syndrome, (14, 3.9%). The median FSFI score was 14.1 (IQR 12), the percentage of women with sexual dysfunction was 94.9%. Median and IQR scores of every item were as follows: Desire 4.8 (2.4), Excitation 1.5 (3.3), Lubrication 2.4 (2), Orgasm 1 (3.6), Satisfaction 2.4 (1.2) and Pain 0.2 (4.4). There was no difference between the different rheumatic diseases studied and FSFI score or the percentage of patients with sexual dysfunction. There is a negative correlation (Spearman rho -0.31 p = 0.01) between age and the total score; and a positive one (0.434 p = 0.01) with the Desire item and negative (-0.391 p = 0.01) for pain item. The was statistical diference between the rheumatic cohort and the historical aged matched control group (14.1 vs 25.2 (p = 0.001)).

Conclusion:

Compared with other reports on the prevalence of rheumatic diseased sexual dysfunction is high and the score is very low compared with healthy. It is necessary to investigate and act on this problem that had family and psychosocial implications in our patients.

Disclosure: A. Garza-Alpirez, None; **D. Vega-Morales**, None; **W. Orzua-de la Fuente**, None; **A. Arana-Guajardo**, None; **D. Flores-Alvarado**, None; **J. Esquivel-Valerio**, None; **M. A. Garza-Elizondo**, None; **L. Pérez-Barbosa**, None.

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Abstract Number: 1184

Projected 2015 Prevalence of Physician-Diagnosed Primary SjöGren's Syndrome Based on 1976-2005 Annual Incidence Rates in a Well-Defined U.S. Population

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Background/Purpose: Estimates of prevalence of primary Sjögren's syndrome (pSS) are conflicting, ranging from 1 to more than 8 cases

per 10,000 according to different population-based studies. No prevalence data for the U.S. population are available so far. The objective of this work was to estimate the 2015 point prevalence of primary Sjögren's syndrome (pSS) in a population-based study performed in the United States.

Methods: This study was performed in a well-defined U.S. population which counted approximately 157,000 inhabitants as of January 1, 2015. Individual medical record review of all cases was previously performed to obtain the total number of incident pSS cases by physician diagnosis from 1976-2005 (1). Prevalence estimates for this study are based on the same source population, assuming that the disease was not associated with excess mortality, as previously shown, and that migration in or out of the census population was independent of disease status. Annual incidence rates were stable for the 1976-2000 period but increased over time between 2000 and 2005 (figure). Therefore, different prevalence estimates were computed according to stable or increasing incidence rate scenarios between 2006 and 2015. Prevalence was age- and sex-adjusted to US white 2010 population.

Results: A total of 105 pSS cases were diagnosed in this population between 1976 and 2005, with annual incidence rates varying between 2 and 8 cases/100,000/year (figure). Using several scenarios for incidence estimates between 2006 and 2015 based upon previous data (table), the projected 2015 prevalence in this population ranged between 9.5 and 36.9 per 10,000. The prevalence was estimated between 0.6 and 3.1 per 10,000 in males and between 18.0 and 69.1 per 10,000 in females.

Conclusion: Our estimated prevalence range is substantially higher than previously published population-based pSS prevalence studies conducted in other geographical area. This finding could reflect important variations of physician diagnosis during the 40-year period during which incidence rates were previously assessed in this population. New epidemiological population-based studies are warranted, using validated and consensual classification criteria for case ascertainment. **Reference:** (1) Nannini C et al, BMJ Open. 2013 Nov 25;3(11):e003569.

Figure. Annual pSS incidence rates 1976-2005, adapted from reference 1.

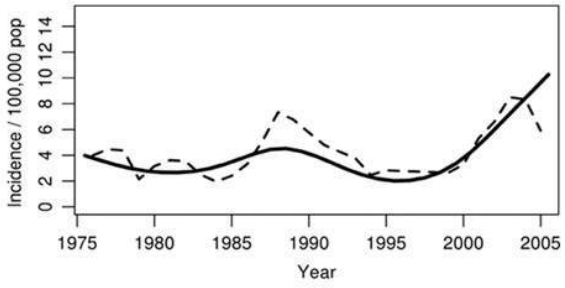

Table. Estimates of 2015 point prevalence of pSS in a US population according to different projections of annual incidence rate for the 2006-2015 period.

	Prevalence rate per 10,000 population* (95% confidence interval)		
Prevalence estimate based on:	**Female**	**Male**	**Overall**
Age and sex specific incidence rates for 1976-1999 (incidence rates were stable in this time period)	18.0 (14.2, 23.2)	0.6 (0.0, 2.0)	9.5 (7.5, 12.3)
Age and sex specific incidence rates for 1976-2005 (this rate is a bit higher due to the increase in incidence rates after 1999)	20.0 (16.2, 25.2)	1.5 (0.0, 2.9)	11.0 (9.0, 13.8)
Age sex and calendar year specific incidence rates for 1976-2005 (projecting flat rate after 2005)	28.5 (21.5, 36.2)	3.0 (1.0, 7.3)	16.0 (12.2, 20.1)
Age sex and calendar year specific incidence rates for 1976-2005 (projecting increasing rate after 2005 based on trajectory from 2000-2005)	69.1 (42.4, 165.4)	3.1 (1.5, 1984.4)	36.9 (20.4, 933.6)

*Age and sex adjusted to US white 2010 population

Disclosure: D. Cornec, None; **E. L. Matteson**, Genentech and Biogen IDEC Inc., 2; **C. S. Crowson**, Genentech and Biogen IDEC Inc., 2.

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Abstract Number: 1185

Increased Risk of Osteoporotic Fractures in Patients with Primary SjöGren Syndrome: A Nationwide Population-Based Study in Taiwan

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Background/Purpose: Primary Sjögren syndrome (pSjS) is an autoimmune disease involved multiple organs, including exocrine glands, lungs, and bone marrow. Patients with pSjS are vulnerable to fatigue and pain over extremities with deterioration of life quality. However, the risks of osteoporotic fracture remain unclear. We performed this cohort study In order to evaluate the incidence rate (IR) and risk factors of osteoporotic fractures in patients with pSjS.

Methods: A cohort study was performed by using the Taiwan National Health Insurance database. pSjS was classified as a catastrophic illnesses after verifying by a review committee. Patients with pSjS with catastrophic validation after 1997 were enrolled. Patients with other autoimmune diseases (systemic lupus erythematous, rheumatoid arthritis, etc.) or operation of fracture before enrollment, were excluded from analysis. Age and gender-matched controls without pSjS were selected as control group. The primary endpoint was the first time of osteoporotic fracture. Other risks factors, including comorbidities and medications history, were examined by using Cox proportional model.

Results: Total 3367 pSjS patients (mean 53.23 years, female 85.5%) and 22182 age, gender matched patients without pSjS were evaluated. The median follow-up time was 9.76 years. Among pSjS group, 243 patients had vertebral fractures (IR 71.18 per 1,000 person-years), 84 patients had hip fractures (IR 24.15 per 1,000 person-years), and 40 patients had radius fractures (IR 11.46 per 1,000 person-years). The incidence rate ratios of vertebral fractures (1.54, 95% CI 1.30-2.39, p<0.001) and hip fractures (1.41, 95% CI 1.10-1.79, p=0.005) revealed significant differences, but not of radius fractures (1.13, 95% CI 0.79-1.58, p=0.463). pSjS patients experienced fractures at older ages compared with control group (p<0.001). Multivariable Cox regression analyses revealed that older age, female, end-stage renal disease, and using higher doses of corticosteroid (>7.5mg per day) were associated with increasing risks of developing fractures.

Conclusion: pSjS patients had higher IR of vertebral and hip fractures, but not of radius fractures. Patients who were older, female, in end stage renal disease, or using higher doses of corticosteroid, were of elevating risks in developing fractures.

Disclosure: Y. P. Tsao, None; **Y. S. Chang**, None; **C. C. Lai**, None; **W. S. Chen**, None; **C. Y. Tsai**, None.

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Abstract Number: 1186

The Use of Clinical Mucosal Manifestations to Differentiate Patients with Lupus and Dermatomyositis: Transversal, Retrospective and Analytical Study of 116 Patients

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Background/Purpose: There are few studies comparing oral manifestations in patients with Cutaneous Lupus (CL), Systemic Lupus Erythematosus (SLE) and Dermatomyositis (DM). Our objective was to determine signs in the oral cavity that could allow us to guide a particular diagnosis

Methods: Two dermatologists described the semiological findings of photographs of the oral cavity of a total of 116 patients (96 patients with Lupus and 20 patients with DM). All patients with SLE fulfilled at least 4 ACR classification criteria. We analyzed 4 areas: gums, soft palate, hard palate and buccal mucosa. For each of these areas the evaluators described the presence of the following clinical findings: red macules, red dots, telangiectasias, pigmented light brown macules, pigmented dark brown macules, discoid lesions, whitish streaks, white patches, mucosal folds, fine cobblestone and thick cobblestone (Fig. 1, 2, 3). We tried to find mucosal clinical features that differentiate

patients with strictly CL with those with CL and SLE, and with those with strictly SLE. Also we compared oral features of patients with SLE (with or without skin involvement) of those with DM, since sometimes these 2 clinical entities are very similar. Patients were divided into 3 different groups: SLE with and without cutaneous involvement; CL with and without systemic manifestations and subjects with DM and SLE with or without cutaneous manifestations. X^2 or Fisher exact test was used. A p value < 0.05 was considered significant

Results: Of all 84 patients with CL (with or without SLE), discoid mucous patches were only seen in patients with CL with SLE (15.4% vs 0%, p=0.008). Light and dark brown macules on gums were more frequent in patients with CL without SLE (48.3% vs 23.1% p=0.033 and 27.6% vs 7.7% p=0.033, respectively). Of all 38 SLE patients (with or without CL), red spots on hard palate and thick cobblestone on gums were more common in patients with SLE with CL (69.2% vs 33.3% p=0.037 and 53.8% vs 16.7 % p=0.031, respectively). White mucous streaks were more frequent in patients with SLE without CL (41.7% vs 3.8%, p=0.008). When comparing 38 SLE patients and 20 patients with DM, the mucosal folds on hard palate were only in SLE patients (15.8% vs 0%, p=0.084)

Conclusion: There are signs in the oral cavity that help us to differentiate CL from SLE, and SLE from DM

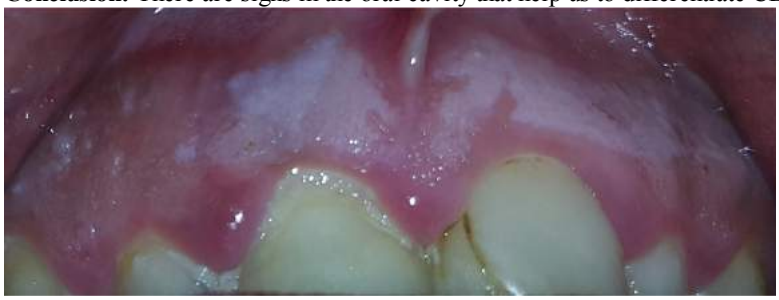

Fig 1: white patch

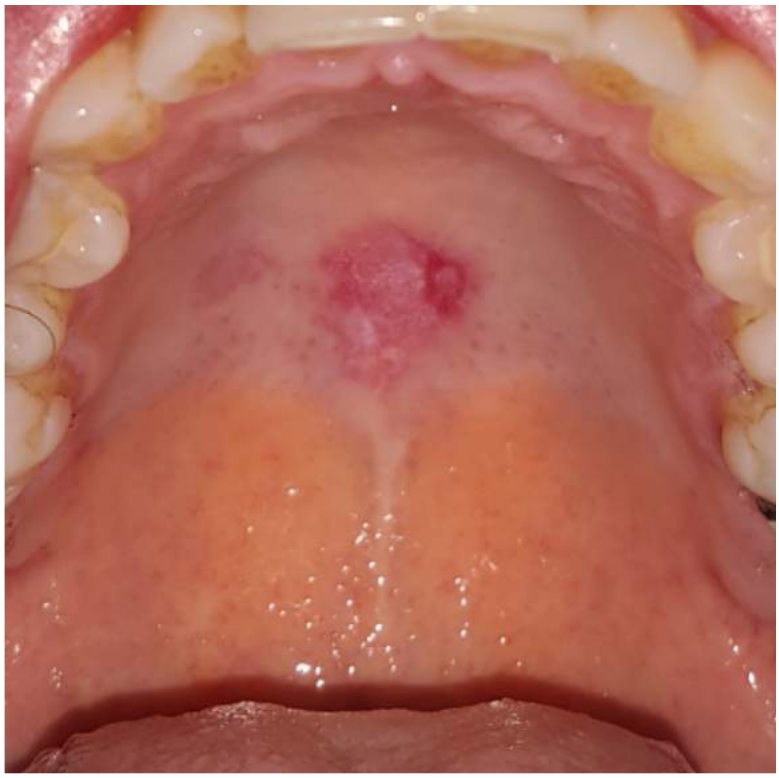

Fig 2: discoid lesion

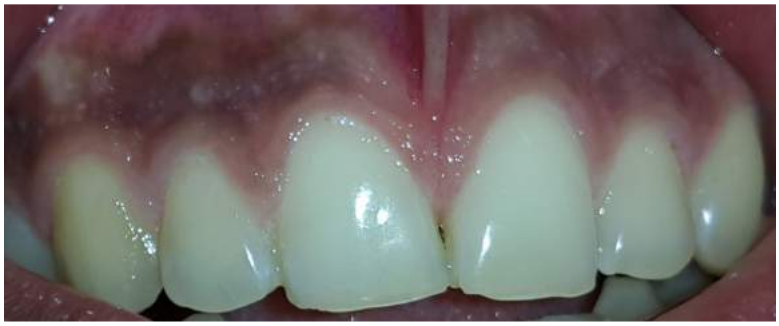

Fig 3: fine cobblestone

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differentiate-patients-with-lupus-and-dermatomyositis-transversal-retrospective-and-analytical-study-of-116-patients

Abstract Number: 1187

Ultraviolet Radiation Exposures Are Associated with Dermatomyositis in a National Myositis Registry

Christine G. Parks[1], Jesse Wilkerson[2], Kathryn M. Rose[2], Abdullah Faiq[3], Payam Noroozi Farhadi[3], Craig S. Long[4], Nastaran Bayat[3], Hermine I. Brunner[5], Bob Goldberg[6], John McGrath[2], Frederick W. Miller[3] and Lisa G. Rider[3], [1]Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, Durham, NC, [2]Social and Scientific Systems, Inc., Durham, NC, [3]Environmental Autoimmunity Group, National Institute of Environmental Health Sciences, NIH, Bethesda, MD, [4]NOAA/National Weather Service, National Centers for Environmental Prediction Climate Prediction Center, College Park, MD, [5]Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [6]The Myositis Association, Alexandria, VA
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Background/Purpose: Previous studies suggest exposure to ultraviolet (UV) radiation may be a risk factor for dermatomyositis (DM) and autoantibody phenotypes, based on differences in prevalence associated residential environmental UV levels in proximity to diagnosis. However, the role of individual determinants of exposure and susceptibility is unknown.

Methods: We analyzed data from adult patients (ages 18-65) in a national myositis patient registry (including 658 dermatomyositis [DM], 451 polymyositis [PM], and 309 inclusion body myositis [IBM]) diagnosed through 2011. A questionnaire collected data on geographic residence, sun sensitivity (tendency to experience severe or painful sunburns), history of sunburn in the 12 months prior to diagnosis, and history of specific jobs, longest job and hobbies (specified as outdoor and other) prior to diagnosis. Using a job-exposure matrix and consensus review blinded to myositis subgroup, jobs and hobbies were rated for sun exposure intensity (high, moderate, low, or none), with a certainty level assigned to each estimate (high or low). Maximum residential UV exposures were identified for the 12 months prior to diagnosis for cases diagnosed after 1990, using data on UV-B Erythemal irradiances from the NASA Total Ozone Mapping Spectrometer (TOMS). Comparing DM with PM and IBM patients, odds ratios (OR) and 95% confidence intervals (CI) were estimated for sunburn and UV exposures in the year prior to diagnosis using logistic regression models adjusted for age, skin tone, and sex. Stratified models explored the potential modifying role of maximum residential UV levels and sun sensitivity on recreational/occupational exposures.

Results: Sunburn in the year prior to diagnosis was reported by 41% of DM compared with 28% of PM/IBM patients (OR=1.55: 95%CI 1.22, 1.96). DM was associated with high or moderate sun exposures from outdoor recreation or hobbies in the year prior to diagnosis (OR=1.38: 95%CI 1.08, 1.76, vs. PM/IBM), and together, high or moderate recreational or occupational sun exposure was associated with DM vs. PM/IBM (high OR=1.61: 95%CI 1.08, 2.42; moderate OR=1.37: 95%CI 1.05, 1.79). The association of DM with moderate recreational/occupational exposures was most apparent in patients with higher environmental UV levels (OR=1.56: 95%CI 1.06, 2.30) and those who reported being less likely to have severe sunburns (OR=1.62: 95%CI 1.16, 2.26). Sensitivity analyses showed the associations with occupational or recreational exposures remained after excluding patients reporting any sunburn in the year prior to diagnosis, and in analyses limited to high certainty exposure estimates.

Conclusion: These findings suggest that sunburn and high intensity sun exposures from recreational or occupational activities within a year prior to diagnosis may be associated with greater risk of developing DM compared to other myositis subtypes. Results support investigation of the role of sun exposures in relation to environmental UV, individual susceptibility and protective behaviors, in the risk of DM.

Disclosure: C. G. Parks, None; **J. Wilkerson**, None; **K. M. Rose**, None; **A. Faiq**, None; **P. Noroozi Farhadi**, None; **C. S. Long**, None; **N. Bayat**, None; **H. I. Brunner**, The Myositis Association, 2; **B. Goldberg**, Centers for Disease Control, 2; **J. McGrath**, None; **F. W. Miller**, None; **L. G. Rider**, None.

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Abstract Number: 1188

Major Comorbidities of Idiopathic Inflammatory Myositis: A Population-Based Study Using 10 Years of Follow up from the National Health Insurance in Korea

Jeong Seok Lee[1], **Min Jung Kim**[2], Hee Young Lee[3], So Yeon Ahn[4], Yeong Wook Song[5], Eun Bong Lee[6], Eun Young Lee[7], Yun Jong Lee[8] and Eun Ha Kang[9], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Departmenf of Internal Medicine, Seoul National University Hospital, Seoul, Korea, The Republic of, [3]Center for Preventive Medicine and Public health, Seoul National University Bundang Hospital, Seongnam, Korea, The Republic of, [4]Medical Research Collaborating Center, Seoul National University Bundang Hospital, Seongnam, Korea, The Republic of, [5]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, Republic of Korea, Seoul, Korea, The Republic of, [6]Division of Rheumatology, Department of Internal Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea, Seoul, Korea, The Republic of, [7]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [8]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [9]Division of Rheumatology, Department of Internal Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, Korea, The Republic of

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Major comorbidities of idiopathic inflammatory myositis: A population-based study using 10 years of follow up from the national health insurance in Korea

Jeong Seok Lee[1], Min Jung Kim[1], Hee Young Lee[2], So Yeon Ahn[3], Yeong Wook Song[1], Eun Bong Lee[1], Eun Young Lee[1], Yun Jong Lee[4], Eun Ha Kang[4].

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Background/Purpose: Patients with idiopathic inflammatory myositis (IIM) suffer from comorbidities such as interstitial lung disease (ILD), cancer, and infections related to immunosuppressive agents. We evaluated incidence rate ratio (IRRs) and characteristics of major comorbidities in IIM compared to non-IIM Koreans.

Methods: A retrospective cohort study was performed using the 2005-2014 National Health Insurance Service database covering more than 99% of Korean population. Incident IIM (n = 4088) was identified by at least two visits (first visit date = index date) to the tertiary hospitals under ICD9 codes of IIM with at least 1 year devoid of such code preceding the index date. Age- and sex-matched subjects were enrolled as the unexposed at 10:1 ratio. The occurrence of ILD, cancer, herpes zoster, and tuberculosis, and death was captured using ICD9 code, disease-specific medication, and/or government-approved qualification for co-payment reduction on these outcomes.

Results: Newly diagnosed IIM patients was 4,088 (male 39.3%, age at diagnosis 51.0¡¾15.3), in 2005-2014. Most patients (> 90%) defined as such were found to have muscle biopsy, electromyogram, or multiple laboratory examinations on muscle enzymes. Their incidence rate of the above outcomes was significantly elevated; IRRs were 36.8 [95% confidence interval: 33.9-39.9] for ILD, 2.1 [2.0-2.2] for cancer, 2.2 [2.1-2.3] for herpes zoster, 3.5 [3.3-3.7] for tuberculosis, and 4.9 [4.7-5.1] for mortality. ILD and cancers were associated with shortened survival while herpes zoster and tuberculosis were not. Among cancers whose incidence rate more than 1.0 case per 1000 person-year, the most common type of cancer was metastasis of unknown origin (MUO) (6.3 [3.9-10.1]) followed by lymphoma (4.9 [3.0-7.9]) (Table 1). The temporal relationship between cancer and IIM was highest in stomach cancer showing the majority occurring within one year of IIM diagnosis (82.8%) (Fig1). Among cancers whose incidence rate more than 10.0 cases per 1000 person-year, lung cancer and metastasis of known primary cancers showed the highest incidence rate ratio and strong temporal relationship with IIM.

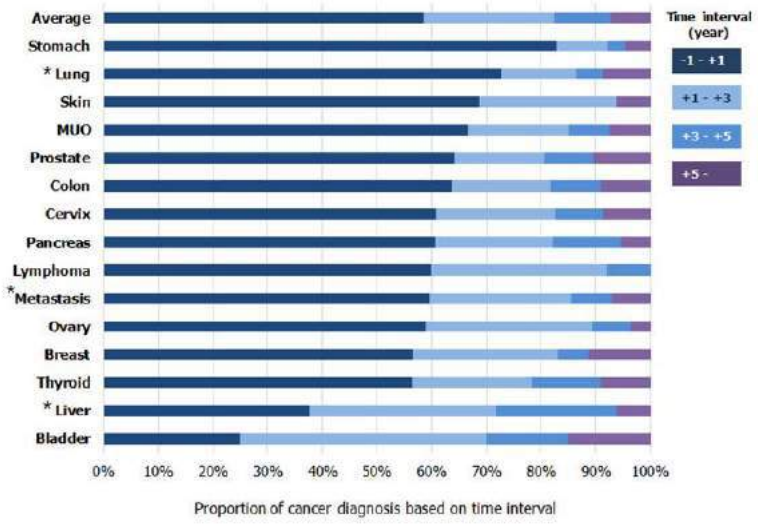
Conclusion: This is the first report of the nation-wide population based evaluation of IIM in Korea. The incidence of ILD, cancers, zoster, and tuberculosis was exceptionally higher in IIM than non-IIM. ILD and cancers were associated with worse survival. Advanced cancers with metastasis were strongly associated with IIM, showing high IRR in MUO and metastasis of known primary cancers.

Table 1. Common type of cancers in IIM patents with incidence rate higher than 1.0 case per 1000 person-year.

Organ	Incidence rate (number of cases per 1000 person-year)	Incidence rate ratio [95% confidence interval]
MUO	1.9	6.3 [3.9-10.1]
Lymphoma	1.8	4.9 [3.0-7.9]
Skin	1.1	3.5 [2.0-6.3]
Liver	17.0	3.4 [3.0-4.0]
Metastasis of known primary cancers	25.1	3.0 [2.7-3.4]
Ovary	4.0	2.9 [2.2-3.9]
Lung	10.0	2.9 [2.4-3.5]
Pancreas	4.0	1.5 [1.2-2.0]
Breast	3.8	1.4 [1.1-1.9]

MUO: metastasis of unknown origin (ICD9 code: C80). Metastasis: secondary malignant neoplasm of known primary sites (ICD9 code: C78, C79).

Figure 1. Time interval between IIM and cancer diagnosis among cancers with incidence rate of higher than 1.0 case per 1000 person-year.



MUO: metastasis of unknown origin (ICD9 code: C80). Metastasis: secondary malignant neoplasm of known primary sites (ICD9 code: C78, C79). *Cancers with incidence rate higher than 10.0 cases per 1000 person-year

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Disclosure: J. S. Lee, None; **M. J. Kim**, None; **H. Y. Lee**, None; **S. Y. Ahn**, None; **Y. W. Song**, None; **E. B. Lee**, None; **E. Y. Lee**, None; **Y. J. Lee**, None; **E. H. Kang**, None.

Abstract Number: 1189

Inpatient Trends for Adults with Scleroderma in the United States: A 20 Year Analysis

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Background/Purpose: Patients who are diagnosed with scleroderma, undergo multiple hospitalizations during their lifetime. It still remains an incurable disease, however, numerous advances in its management have improved life expectancy and quality of life in affected patients. Hence, it is important to provide an updated surveillance data of this disease burden on inpatient hospitalizations, costs and mortality rate.

Methods: The National Inpatient Sample database for adult patients with principle discharge diagnoses of Systemic Scleroderma (ICD 9-CM CODE: 710.1) from the years 1993-2013 was analyzed. Spearman's correlation technique was applied using SAS 9.3 for Windows OS to determine statistical correlation of the number of hospital discharges, length of stay and hospital costs over time during these years.

Results: Total number of patients admitted with principle discharge diagnoses of systemic scleroderma decreased from 1910 in 1993 to 1665 in 2013(rho = 0.189, p=0.41). The mean length of stay for these patients did not show any statistically significant difference. The in-hospital mortality was noted to be significantly decreased from 9.63% in 1993 to 8.40% in 2013 (rho=0.681, p =.0007). The mean charges per hospital stay for adult systemic scleroderma patients increased from $14184 in 1993 to $86080 in 2013 (rho=.987, p <.0001). The aggregate charges (i.e. the national bill) increased from $41,517,946 in 1997 for adult systemic scleroderma patients to $143,104,818 in 2013.

Conclusion: A significant decrease was noted in hospital mortality in adult patients with systemic scleroderma. This is accompanied with major increase in cost of hospitalization during this time. This change can be attributed to increase in use of pharmacologic agents including immune-modulators and anti-fibrotic therapy, increased use of hematopoietic stem cell transplantation, advances in organ based treatment e.g. use of ACE inhibitors in scleroderma renal crisis, screening of these patients leading to early detection of complications and initiation of treatment. Also, multi-disciplinary approach to management including pulmonologists, gastroenterologists, nephrologist, dietician and social worker evaluation in hospital adds to the cost burden. A decrease in total number of admissions for adult patients with systemic scleroderma was noted. This may be attributed to better outpatient management for these patients. More data is required to study the trends in hospital admissions in these patients. Further research is required on cost effective management in patients with systemic scleroderma.

Disclosure: N. Goel, None; **I. Lalani**, None; **I. Moledina**, None.

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Abstract Number: 1190

Incidence and Prevalence of Polymyalgia Rheumatic and Giant Cell Arteritis: A 15-Year Study in a Health Care Management Organization

Jose Maximiliano Martinez P[1], Florencia Beatriz Mollerach[2], Facundo Vergara[2], Ignacio Javier Gandino[2], Marina Scolnik[3], Luis J. Catoggio[4], Javier Rosa[2] and Enrique R. Soriano[2], [1]Rheumatology, Internal Medicine Service, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [2]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [3]Rheumatology Section, Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [4]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Argentina., Buenos Aires, Argentina
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Background/Purpose: There is scarce information on the epidemiology of polymyalgia rheumatic (PMR) and giant cell arteritis (GCA) in Latin America. To estimate incidence and prevalence rates of PMR and GCA in a large university hospital–based health management organization in South America.

Methods: Global, age-specific, and sex-specific incidence and prevalence rates were calculated for members of a Medical Care Program

(HIMCP), age ≥ 50 years. Incidence study followed members with continuous affiliation ≥ 6 months from January 2000 to December 2015 until he/she voluntarily left the HIMCP, PMR or GCA were diagnosed, death, or study finalization. Cases from the Rheumatology Section database, electronic medical records, laboratory database, temporal artery biopsy and pharmacy database were filtered with the 2012 EULAR/ACR criteria for PMR or the ACR 1990 criteria for GCA. Prevalence was calculated on January 1, 2015.

Results: : In the study period 176,558 persons contributed a total of 1,046,620 person-years, of who 825 developed PMR for an overall incidence rate (cases per 100,000 person-years) of 78.8 (95% CI 73.4–84.2), 90.1 (95% CI 82.9–97.2) for women, and 58.9 (95% CI 51.1–66.6) for men. Ninety persons developed GCA for an overall incidence rate of 8.6 (95% CI 6.8–10.4), 11.1 (95% CI 8.5–10.6) for women, and 4.2 (2.2–6.3) for men. On January 1, 2015, 899 prevalent PMR cases and 100 prevalent ACG cases were identified from a denominator population of 80335 HIMCP members. Prevalence rates of PMR (percentage of cases in the sample population) were 11.2 per 1000 (95% CI 10.4–11.9) overall, 12.7 (95% CI 11.8–13.7) for women, and 8.2 (95% CI 7.2–9.3) for men, and prevalence rates of GCA were 1.2 per 1000 (95% CI 1–1.4) overall, 1.5 (95% CI 1.2–1.9) for women, and 6.3 (95% CI 3.4–9.3) for men. Patient's characteristics and incidence and prevalence rates per gender and different age groups are shown in table 1 and figures 1 and 2 respectively.

Conclusion: This study's incidence and prevalence rates are in the upper range of the rates found around the world. Our peak incidence age for PMR was in the eighth decade for both sexes and for GCA was in the seventh decades for both sexes.

Figure 2. Prevalence of PMR and ACG per age groups per1000 inhabitants

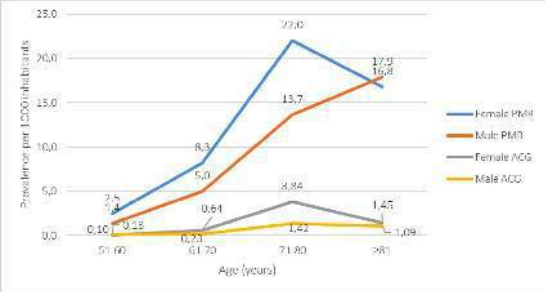
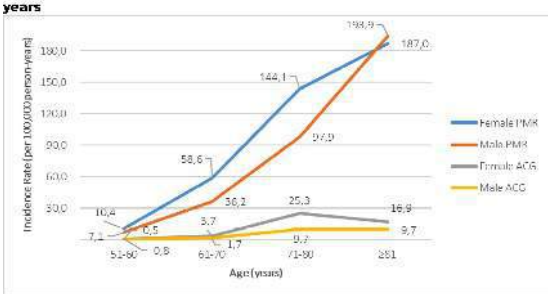


Table 1. Patient Characteristics in incident cases

Variable	PMR (n=825)	ACG (n=90)
Females, n (%)	603 (73.1)	74 (82)
Mean age at diagnosis (SD)	75.4 (7.9)	75.6 (11.1)
Bilateral shoulder aching, n (%)	798 (96.7)	-
Bilateral pelvic girdle (hip) aching, n (%)	602 (73)	-
Peripheral synovitis (distal swelling, tenosynovitis or arthritis), n (%)	107 (13)	-
PMR symptoms, n (%)	825 (100)	53 (59)
Abnormal erythrocyte sedimentation rate, n (%)	700 (85)	87 (97)
Mean erythrocyte sedimentation rate (SD)	56.7 (25.3)	69.8 (25.1)
Median Methylprednisolone initial dose (IQR)	8 (0-8)	40 (20-40)
Median months on steroid treatment (IQR)	20 (13-31)	29 (19-40)
Jaw claudication, n (%)	-	48 (54)
Headaches, n (%)	-	70 (78)
Visual impairment, n (%)	-	36 (40)

Figure 1. Incidence rate of PMR and ACG per age groups per 100,000 person-years



Disclosure: J. M. Martinez P, None; **F. B. Mollerach**, None; **F. Vergara**, None; **I. J. Gandino**, None; **M. Scolnik**, None; **L. J. Catoggio**, None; **J. Rosa**, None; **E. R. Soriano**, Abbvie, 2,Pfizer Inc, 3,UCB, 2,Janssen Pharmaceutica Product, L.P., 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Abbvie, 5,Pfizer Inc, 5,UCB, 5,Janssen Pharmaceutica Product, L.P., 5,Roche Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,Bristol-Myers Squibb, 5.

and-giant-cell-arteritis-a-15-year-study-in-a-health-care-management-organization

Abstract Number: 1191

Retinal Vessel Morphometry Associations with Polymyalgia Rheumatica; Findings from the European Prospective Investigation of Cancer (EPIC) in Norfolk

Max Yates[1], Shabina Hayat[2], Robert N. Luben[3], Roshan Welikala[4], Alicja Rudnicka[5], Christopher Owen[5], Sarah Barman[4], Eoin O'Sullivan[6], Sarah Mackie[7], Richard Watts[1], Paul Foster[8], Kay-Tee Khaw[3], Nick Wareham[3] and Alex J Macgregor[9], [1]Norwich Medical School, University of East Anglia, Norwich, United Kingdom, [2]Strangeways Research Laboratory, University of Cambridge, Cambridge, United Kingdom, [3]Department of Public Health and Primary Care, University of Cambridge School of Clinical Medicine, Cambridge, United Kingdom, [4]Faculty of Science, Engineering and Computing, University of Kingston, London, United Kingdom, [5]Population Health Research Institute, St George's University of London, London, United Kingdom, [6]Ophthalmology, Kings College Hospital, London, United Kingdom, [7]NIHR-Leeds Musculoskeletal Biomedical Research Unit and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, University of Leeds, Leeds, United Kingdom, [8]Division of Epidemiology and Genetics, University College London, London, United Kingdom, [9]Rheumatology, Norfolk and Norwich University Hospital, Norwich, United Kingdom
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Background/Purpose: Increasing evidence suggests that characteristic changes in retinal vessel morphometry are biomarkers for vascular health. Polymyalgia Rheumatica (PMR) has been associated with increased risk of vascular disease in some epidemiological studies, but to date there are limited data on objective changes in blood vessels in patients with this condition. This study examines the retinal vessel morphology of individuals with PMR in a population-based cohort.

Methods: The study was conducted in participants diagnosed with PMR identified from the EPIC-Norfolk cohort, a population-based study of 25,639 men and women aged 40-79 years, recruited between 1993-1997. Diagnoses of PMR were established through electronic linkage to laboratory, hospital care episodes and questionnaire responses, supplemented by chart reviews during follow-up to 2015. In 2006-2011 digital retinal photography was undertaken and analysed using a validated automated system, which measures vessel width in arterioles and venules respectively. Gaussian modelling was used to determine vessel widths. An ensemble classifier of bagged decision trees was used to classify vessels into probabilities of being either venules or arterioles. Associations were analysed using multi-level linear regression, adjusted for gender and age, allowing for within person clustering.

Results: In total, 10,494 good quality images were obtained from 5959 participants were analysed. Median arteriolar and venular widths were 68.5µm (5^{th} to 95^{th} centiles 49.4, 91.0µm), and 99.1µm (5^{th} to 95^{th} centiles 83.1, 116.4µm) respectively. There were 298 incident diagnoses of PMR (72.5% female) during the follow-up period. The median age at diagnosis was 75.6 years of which 140 had good quality retinal imaging. Those with PMR diagnoses showed wider venules compared to those without disease (mean difference 3.1µm. 95% CI 1.1,5.1µm); there were no appreciable differences in arteriolar diameter (mean difference 0.3µm, 95% CI -2.1,2.8 µm).

Conclusion: These results provide the first objective evidence of a biomarker for vascular health in patients with PMR, a disease in which there is an absence of adequate clinical process and outcome measures. Although limited by the cross-sectional design, the findings indicate that retinal morphometric analysis could prove a useful monitoring tool for vascular complications in patients with rheumatic disease.

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Abstract Number: 1192

Mortality and Survival of Patients Diagnosed with GCA in Bergen (Western Norway)

1972-2012

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Session Time: 9:00AM-11:00AM

Background/Purpose: Giant cell arteritis (GCA) is the most common systemic vasculitis in people ³ 50 years of age and the disease is associated with potentially life-threatening complications. Nevertheless, most studies have shown little or no significant difference in the mortality rates observed between GCA patients and non-GCA subjects. However, the epidemiology is changing as the elderly population increases. The aim of this study was to investigate the epidemiology of GCA in an expected high-incidence region over time.

Methods: This is a retrospective cohort study of patients diagnosed with GCA in the hospitals of Bergen Health Area (Helse Bergen) during 1972-2012. The International Classification of Diseases (ICD)-coding system was used to identify patients from hospital records, ICD-8 (446.4) for 1972-1987, ICD-9 (446.5) for 1987-1998 and ICD-10 (M31.5-6) for 1999-2012. The diagnosis was verified according to ACR 1990 classification criteria by review of patient charts. Patient outcomes were documented by reviewing patient charts from time of diagnosis until death or end of study (31 Dec 2012). Information on time and cause of death was collected from the Norwegian Cause of Death Registry. Standardized mortality ratio (SMR) was calculated using the observed patient mortality and the death rates of the Norwegian population (age- and gender-matched) per 100 000.

Results: Eight-hundred twenty patients satisfied the ACR classification criteria for GCA. Among these there were 71 % females and 29 % males. Five-hundred twenty-eight patients (64 %) had a positive temporal artery biopsy (TAB) and 206 patients (25 %) had a negative TAB. For the remaining 86 patients (11 %) TAB was not performed or TAB results were inconclusively or insufficiently reported. Patient characteristics are presented in table 1. Four-hundred forty-three patients (54 %) died during the follow-up period. Median survival time was 12 years (95% CI 11-13). The overall SMR was 1.1 (95% CI 1-1.2). Female sex, younger age at time of diagnosis and high (>85) ESR at the time of diagnosis were found to be associated with increased mortality. Neither TAB-result nor decade of diagnosis showed statistically significant effect on survival. SMRs and median survival times are presented in table 2.

Conclusion: We did not find statistically significant difference in the overall mortality of GCA-patients compared to the general Norwegian population, but our results indicate that gender, age and level of ESR at the time of diagnosis may have prognostic impact.

Table 1. Patient characteristics

	Overall n=820	Female n=585	Male n=235
Mean age at onset of GCA (SD)	72.9 (8.7)	73.4 (8.4)	71.7 (9.3)
ACR criteria fulfilled (%)	820 (100)		
Age ≥ 50 at disease onset (%)	816 (99.5)	583 (99.7)	233 (99.1)
New onset headache (%)	592 (72.2)	418 (71.5)	174 (74.0)
Temporal artery tenderness (%)	378 (46.1)	265 (45.3)	113 (48.1)
Decreased temporal pulse(%)	230 (28)	170 (29.1)	60 (25.5)
ESR ≥ 50 (%)	740 (90.2)	525 (89.7)	215 (91.5)
Biopsy showing vasculitis (%)	528(64.4)	378 (64.6)	150 (63.8)
Giant cells in biopsy (%)	243 (29.6)	185 (31.6)	58 (24.7)
Mean ESR (SD) n=810	84.1 (27.6)	83.7 (27.9)	85.1 (27.0)
Mean CRP (SD) n=626	90.3 (63.4)	87.5 (62.3)	97.7 (65.2)
Jaw claudication (%)	181 (22.1)	134 (22.9)	47 (20)
Polymyalgia Rheumatica (%)	246 (30)	195 (33.3)	51 (21.7)
Peripheral Arthritis (%)	35 (4.3)	25 (4.3)	10 (4.3)
Visual disturbance (%)	149 (18.2)	106 (18.1)	43 (18.3)
Blindness one or both eyes (%)	33 (4)	24 (4.1)	9 (3.8)
Scalp necrosis (%)	6 (0.7)	4 (0.7)	2 (0.9)
Number of deaths 1972-2012 (%)	443 (54)	311 (53.2)	132 (56.2)

Table 2. Standardized Mortality Ratios					
	n	SMR	95 % CI	Median survival	95 % CI
All patients	820	1.1	1-1.2	12	11-13
Sex					
Male	235	0.96	0.81-1.14	12	11-13
Female	585	1.17	1.04-1.3	12	10-14
Age at diagnosis, years					
<60	57	1.89	0.98-3.23	28	20-NA
60-69	224	1.28	1.04-1.55	17	15-19
70-79	357	1.11	0.97-1.26	11	10-12
>79	182	0.94	0.79-1.12	7	6-8
Year of diagnosis					
1972-1982	72	1.25	0.98-1.56	13	6-NA
1983-1992	175	1.16	0.99-1.35	12	11-13
1993-2002	255	0.99	0.84-1.16	12	10-15
2003-2012	318	1.09	0.84-1.39		
Temporal Artery Biopsy					
Positive	528	1.05	0.94-1.18	12	10-15
Negative	206	1.21	0.98-1.47	12	11-13
ESR					
≤ 85	407	1	0.87-1.14	12	11-13
> 85	403	1.17	1.03-1.33	12	10-14
Initial prednisone-dose, mg/day					
≤20	58	1.27	0.88-1.77	12	9-14
>20 – 40	280	1.05	0.88-1.24	13	12-15
>40 – 60	267	1.04	0.88-1.21	12	11-14
> 60	138	1.16	0.94-1.42	10	9-12
Maximum prednisone-dose before tapering, mg/day					
≤20	27	1.34	0.84-2.02	12	9-14
>20 – 40	247	1.06	0.88-1.27	13	12-14
>40 – 60	298	1.02	0.87-1.19	12	11-14
> 60	154	1.2	0.98-1.45	10	9-12

Disclosure: L. K. Brekke, None; **A. P. Diamantopoulos**, None; **B. T. Fevang**, None; **J. Aβmus**, None; **C. G. Gjesdal**, None.

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Abstract Number: 1193

Mortality Rate According to Cause in Patients with Hemophagocytic Lymphohistiocytosis: A Meta-Analysis

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Background/Purpose: Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome of excessive immune activation associated with high mortality. Early diagnosis and treatment can reduce mortality among these patients. In our study, we analyzed the rate of mortality independently and according to the cause in patients with HLH.

Methods: Pubmed database with the MeSH terms ("lymphohistiocytosis, hemophagocytic"[MeSH Terms] OR ("lymphohistiocytosis"[All Fields] AND "hemophagocytic"[All Fields]) OR "hemophagocytic lymphohistiocytosis"[All Fields] OR ("hemophagocytic"[All Fields] AND "lymphohistiocytosis"[All Fields])) AND cases [All Fields] were queried which yielded 466 results. Case series referenced from these studies were also studied. 74 studies were identified out of which the studies with a sample size smaller than 10 were excluded. 48 studies were kept with a total of 1983 patients. Meta analysis was performed to combine the mortality rates of all studies and studies of patients with the same cause. The results were presented in a Forest plot. Prior to the meta analysis, the heterogeneity test on mortalities

was conducted to choose a fixed or random effects model. I^2, a common heterogeneity measure, was reported with 25%, 50%, 75% suggesting low, moderate, and high heterogeneity.

Results: The combined mortality rate for all studies was 41.99% [95% confidence interval (CI) 36%> 49%]. In studies of patients with EBV infection (n=4), the combined mortality rate was 44% (95% CI 18%>74%) whereas the mortality rate in studies with other infections (n=4) was 46 % (95% CI 13-83%). The mortality rate in patients with hematological malignancy (n=8) was higher at 60% (95% CI 44%>74%]. For studies of patients with autoimmune diseases (n=2) and in transplant (n=4) patients, the combined mortality rate was 11% (95% CI 5%>21%) in patients with autoimmune disease and 38% (95% CI 27%>51%) in transplant patients. I^2 for the mortalities of all studies and each cause was presented as follows: $I^2 = 0\%$ (p=0.764) for autoimmune disease, $I^2 = 94.8\%$ [89.6%; 97.4%] (p<0.0001) for EBV infection, $I^2 = 75.2\%$ [50%; 87.7%] (p=0.0002) for hematological malignancy, $I^2 = 75.2\%$ [50%; 87.7%] (p=0.0002) for infection malignancy, $I^2 = 89.2\%$ [75.1%; 95.3%] (p<0.0001) for other infection, and $I^2 = 0\%$ [0%; 52.1%] (p=0.811) for transplant. The heterogeneity test result remained significant but for the causes of autoimmune disease and transplant.

Conclusion: Based on our results, mortality is higher in patients with hematological malignancy compared to patients with other causes, whereas it is lower in patients with autoimmune disease.

Disclosure: K. Sheth, None; **C. L. Kuo**, None; **D. Modi**, None; **C. Scola**, None.

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Abstract Number: 1194

Low Body Mass Index and Smoking Are Associated with a Lower Risk of Sarcoidosis: A Population-Based Nested Case-Control Study

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Low Body Mass Index and Smoking Are Associated With a Lower Risk of Sarcoidosis: A Population-Based Nested Case-Control Study

Background/Purpose: Sarcoidosis is a systemic disorder characterized by the presence of non-caseating granuloma. The etiology of sarcoidosis is unknown. It has been hypothesized that the interaction between genetic predisposition and environmental factors plays an essential role in the pathogenesis. Recent studies have found an association between body mass index, smoking and risk of sarcoidosis although the results were conflicting. Moreover, most of studies were referral-based studies that could be at risk of selection bias.

Methods: 345 patients (50% female; 90% Caucasian, 5% African-American; mean age 45.6 years) with incident sarcoidosis in 1976-2013 in a geographically well-defined population were identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology and radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. 345 sex and age-matched controls (50% female; 95% Caucasian, 1% African-American; mean age 45.4 years) were also identified from the same underlying population. Index date for controls was the same as diagnosis date of corresponding cases. Data on body weight, height and smoking status (never, prior and current smoker) were abstracted from clinical notes and health information questionnaires completed by patients. Overweight was defined as body mass index (BMI) ≥ 25 kg/m^2 but < 30 kg/m^2. Obesity was defined as BMI ≥ 30 kg/m^2. BMI within 1 year before to 3 months after index date was used in this study. Odds ratios (ORs) with 95% confidence intervals (CIs) for the association between smoking status, overweight and obesity and sarcoidosis with adjustment for age, sex and African-American race were calculated.

Results: Information on smoking status was available in 94% of subjects. Among cases, 60% were never smokers, 21% were former smokers and 19% were current smokers. Among controls, 42% were never smokers, 22% were former smokers and 36% were current smokers. Current smokers had a lower risk of sarcoidosis with adjusted OR of 0.34 (95% CI, 0.23 – 0.51) compared with participants who never smoked and adjusted OR of 0.39 (95% CI, 0.27 – 0.56) compared with participants who never smoked and former smokers.

BMI within the defined period was available in 74% of subjects. Among cases, 41% were obese, 33% were overweight and 26% had normal/low BMI. Among controls, 24% were obese, 41% were overweight and 35% had normal/low BMI. Subjects with obesity had a higher risk of sarcoidosis compared with those with normal/low BMI with adjusted OR of 2.47 (95% CI, 1.54 – 3.96). However, overweight was not significantly associated with a higher risk of sarcoidosis compared with subjects with normal/low BMI (adjusted OR 1.12; 95% CI 0.71 – 1.75).

Conclusion: Obesity was associated with a higher risk of sarcoidosis while smoking was associated with a lower risk in this cohort. The potential causal relationship of these exposures to the risk of developing sarcoidosis requires further investigation.

Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

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Abstract Number: 1195

Risk of Hospitalized Infection Among Patients with Sarcoidosis: A Population-Based Retrospective Cohort Study

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Risk of Hospitalized Infection Among Patients With Sarcoidosis: A Population-Based Retrospective Cohort Study

Background/Purpose: Increased risk of infection has been observed in several autoimmune disorders. Immune dysregulation and use of immunosuppressive agents, especially glucocorticoids, are thought to be responsible for the increased risk. It is unclear whether patients with sarcoidosis, another relatively common immune-mediated chronic inflammatory disorder characterized by the presence of non-caseating granuloma, might also be at an increased risk of infection.

Methods: 345 patients (50% female; 90% Caucasian, 5% African-American; mean age 45.6 years) with incident sarcoidosis in 1976-2013 in a geographically well-defined population were identified based on comprehensive individual medical record review. Inclusion required physician diagnosis supported by histopathology and radiologic features of intrathoracic sarcoidosis, compatible clinical presentation, and exclusion of other granulomatous diseases. 345 sex and age-matched comparators (50% female; 95% Caucasian, 1% African-American; mean age 45.4 years) were also identified from the same underlying population. Medical records of both cases and comparators were individually reviewed for first hospitalized infection for each type of infection (and not multiple infections per patient). The cumulative incidence of hospitalized infection adjusted for the competing risk of death was estimated. Cox proportional hazards models with adjustment for age, sex, calendar year, current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity were used to compare the rate of development of hospitalized infection between patients with sarcoidosis and the non-sarcoidosis comparison cohort.

Results: Hospitalized infection after index date occurred in 84 cases and 47 comparators. After adjusting for age, sex and calendar year, the risk of at least one hospitalized infection after index date was significantly increased among patients with sarcoidosis with adjusted hazard ratio (HR) of 2.00 (95% CI, 1.41 – 2.84). Further adjustment for current smoking, diabetes mellitus, hypertension, dyslipidemia and obesity yielded adjusted HR of 2.09 (95% CI, 1.33 – 3.28). Sensitivity analysis including only hospitalized infection that occurred at least 6 months after index date to reduce the likelihood of detection bias was also performed. When only these cases were considered, the adjusted HR was essentially unchanged (HR 1.97; 95% CI, 1.38 – 2.82). Patients in this cohort were at significantly increased risk especially for some types of infections including pneumonia, gastrointestinal and soft tissue infections as shown in table 1.

Conclusion: Risk of hospitalized infection is increased among patients with sarcoidosis. How this risk should be addressed in clinical practice requires further investigations.

Subtype of infection	HR (95% CI) for all events after index , adjusting for age, sex and calendar year	HR (95% CI) for events that occurred at least 6 months after index date, adjusting for age, sex and calendar year
Sepsis	1.66 (0.78 – 3.56)	1.74 (0.79 – 3.84)
Septic arthritis	4.43 (0.42 – 46.94)	4.43 (0.42 – 46.94)
Osteomyelitis	3.31 (0.34 – 31.95)	3.31 (0.34 – 31.95)
Pneumonia	1.99 (1.15 – 3.43)	1.97 (1.13 – 3.45)
Pyelonephritis	1.62 (0.78 – 3.34)	1.62 (0.78 – 3.34)
Soft tissue infection	2.39 (1.04 – 5.51)	2.27 (0.98 – 5.27)
Gastrointestinal infection	2.66 (1.32 – 5.38)	2.57 (1.27 – 5.22)
Intra-abdominal infection	3.23 (0.33 – 31.4)	3.23 (0.33 – 31.4)

Disclosure: P. Ungprasert, None; **C. S. Crowson**, None; **E. L. Matteson**, None.

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Abstract Number: 1196

AA Amyloidosis: An Evaluation of Epidemiology and Prevalence in the US and EU5 Countries

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Background/Purpose: AA amyloidosis (AAA) is a rare, systemic form of amyloidosis, which mostly occurs secondary to chronic inflammatory conditions, predominantly systemic arthritides. AAA is characterized by abnormal deposition of amyloid A proteins, which can be deposited in a variety of organs, most often the kidneys. While there is currently no approved treatment for AAA, treatment of the inflammation can reduce manifestations of AAA in some patients[1]. As with most rare diseases, understanding the epidemiology and prevalence of the disease is difficult, but is critical to improving the ability to diagnose the disease in a timely manner such that optimal treatment can be provided to patients[2]. As there is no clear source that defines the prevalence of AAA, we sought to evaluate prevalence in the US and EU5.

Methods: Five different methodologies were evaluated for use in the estimation of prevalence of AAA, three of which were chosen as robust approaches for regionally specific estimations. The methodologies used included: 1) Evaluation of AAA diagnosis rate via renal biopsy with extrapolation to that regional population based on overall rate of renal biopsy, 2) Assessment of multiple regional centers of excellence with patient registries or databases, with extrapolation to those regional populations, and 3) A survey of 270 US physicians, including nephrologists, rheumatologists, and gastroenterologists, to assess numbers and rates of AAA patient diagnoses.

Results: Estimates suggest that there are 9,100-15,500 AAA patients currently under the care of a physician in the US and approximately 6,200 patients in the EU5. Data reveal that 40-68% of the primary conditions in AAA patients are arthritic in nature, and suggest that US rheumatologists are managing close to 30% of AAA patients. Approximately half of US rheumatologists are currently managing AAA patients. Rheumatologists are generally more aware than other specialists of the signs of AAA, the first sign of which is typically the development of kidney disease. Patients are then referred to a nephrologist for confirmation of the diagnosis, which is most often done by renal biopsy. Compared to the US, care in the EU5 is more highly centralized and patients are often referred to an AAA center of excellence.

Conclusion: Understanding the prevalence of a rare disease is typically difficult due in large part to the small numbers of patients spread

out across the globe. Other reasons are low awareness of the disease and regional variations in clinical practice. In addition, global registries are not in place for most rare diseases. This research suggests an AAA prevalence of 9,100-15,500 patients in the US and approximately 6,200 in the EU5. In the US, rheumatologists are managing a large portion of the patients. Bringing together centers of excellence and thought leaders to develop a global patient registry would help to further define the epidemiology and prevalence of AAA, and increase awareness of this rare but devastating disease. References: [1]Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol 2006;17:3458-3471. [2]Lachmann HJ et al. Natural history and outcome in systemic AA Amyloidosis. NEJM 2007;356:2361-71.

Disclosure: W. Andrews, Auven Therapeutics, 5; **D. Garceau**, Auven Therapeutics, 5; **T. Sablinski**, Auven Therapeutics, 3; **P. Zhang**, Auven Therapeutics, 5; **T. Waldman**, Auven Therapeutics, 5.

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Abstract Number: 1197

Certain Serum Micro-RNAs Are Associated with Osteoarthritis

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Background/Purpose: Sensitive and specific blood biomarkers to detect the initial stages of osteoarthritis (OA) and to predict the future development of the disease are not available in clinical routine. Consequently, there is a considerable interest in the identification of new markers. In OA, studies investigating the altered expression of regulatory RNA that may be used clinically are scarce. MicroRNAs (miRs) are small non-coding RNAs of approximately 22 nucleotides in length that can silence gene expression by binding to complementary sequence on target messenger RNA transcripts resulting in translational repression or target degradation. They are easily accessible and stable. So, we studied the differential expression of circulating miRs in subjects with and without OA in the OFELY cohort.

Methods: The study group included French women belonging to the population-based cohort OFELY (Os des FEmmes de LYon). Expression levels of serum miR were measured in 10 healthy women without OA at any site (knee, lumbar spine, hip and hand) and in 10 women with a Kellgren & Lawrence score of 2 and 3 (early and intermediate knee OA) and OA at others sites. The evaluation of the OA disease was performed by radiography for spine disc degeneration and knee OA, by clinical examination for hand OA and by questionnaire for hip OA. These evaluations have been performed at the same visit, 8 years after recruitment of the cohort. Both groups were matched for age (healthy: 61.9 ± 3.03 and OA: 63.9 ± 3.4 p=0.17) and menopausal status. According to the manufacturer's protocol (EXIQON, Denmark) for the Next Generation Sequencing (NGS) method, RNA isolation was performed from 400 µl of serum followed by the library preparation and amplification and the µRNA sequencing (Illumina platform). Measurements were expressed as Tags per million (TPM), which is a unit used to measure expression in NGS experiments. The number of reads for a particular miR is divided by the total number of mapped reads and multiplied by 1 million (Tags Per Million, TPM).

Results: We identified 421 miRs with an expression level ≥ 1 TPM and 241 with an expression level ≥ 10 TPM. When we compared the two groups, 22 miRs showed differential expression ($p<0.05$) between controls and OA patients. After Benjamini-Hochberg False Discovery Rate (FDR) correction has-miR-139-5p, has-miR-1299 and has-miR-200a-3p remained significantly different between OA patients and controls ($p<0.05$, FDR at 5%) (Table).

names	Log Fold change	P-value	FDR	Healthy average TPM	OA average TPM
has-miR-139-5p	0.734682	0.000126	0.043432	90.1	143.3
has-miR-1299	-3.38328	0.000201	0.043432	12	0.8
has-miR-200a-3p	-1.881	0.000328	0.047335	77.2	29.4

Conclusion: With a NGS screening approach, we identified 3 miRs that are differentially expressed in women suffering from OA compared to healthy women. The next step will be the measurement of these specific miRs in the entire cohort to determine the clinical utility of these markers.

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Abstract Number: 1198

Gene Enrichment Analysis Identifies Active CD40-CD40L Signaling in Early and Established Rheumatoid Arthritis

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Background/Purpose: CD40 and CD40L (CD154) are tumor necrosis factor (TNF) family members involved in the pathogenesis of various autoimmune diseases. While this pathway is active in established RA, its activity and potential role in early disease pathogenesis is unknown.

Methods: RNA-seq analysis was used to identify the expression of *CD40* and *CD40LG* in synovial tissue biopsies from various stages (seropositive arthralgia, undifferentiated arthritis, early RA and established RA) during the progression of RA. Gene Set Variation Analysis (GSVA) was used to determine if CD40-CD40L signaling is active in the biopsies, using human immature dendritic (iDC) and B cell genes induced by soluble CD40L as reference sets.

Results: *CD40LG* and the active full-length *CD40* isoform were increased in synovial tissue biopsies from early RA, established RA, and undifferentiated arthritis cohorts in comparison to healthy donors. In contrast, levels of the dominant-negative truncated *CD40* isoform were reduced in the same synovial tissue samples. Transcriptome characterization of soluble CD40L (sCD40L)-stimulated human iDCs identified *GPR120* and *KDM6B* as novel potential targets involved in CD40-CD40L signaling. We also compared sCD40L transcriptional profiles in iDC and naïve B cells and found that different set of genes respond to sCD40L stimulation in these two cell types. Finally, using GSVA we found that CD40L-responsive genes in B cells and iDC are significantly enriched in synovial tissue mRNA from early RA, established RA and undifferentiated arthritis patients.

Conclusion: The CD40-CD40L pathway is activated in the early stages of RA, and agents inhibiting this pathway may bw effective in established RA, early RA, and undifferentiated arthritis.

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Abstract Number: 1199

A Genome-Wide Association Study of Methotrexate-Pneumonitis in Rheumatoid Arthritis: Results from the Pneumonitis Study Consortium

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Background/Purpose: Methotrexate (MTX) is associated with a rare but potentially life-threatening lung disease, MTX-pneumonitis (MTX-P). MTX-P is an idiosyncratic hypersensitivity reaction to MTX inducing inflammation, cytokine release and the activation of CD4+ T-lymphocytes within the lung parenchyma. Clinical risk factors are associated with the development of MTX-P; they are however, poorly predictive, there is therefore a need for improved markers of disease susceptibility. Epidemiological studies have provided evidence that MTX-P may be a genetically susceptible disease. To date, only one locus has been associated with MTX-P in a Japanese population (HLA-A 31:01). To identify genetic predictors of MTX-P we conducted a genome wide association study in a United Kingdom (UK) population.

Methods: Cases of MTX-P were recruited from a UK-wide multi-centre study. Cases were physician diagnosed MTX-P. Controls were recruited from the Rheumatoid Arthritis Medications Study (RAMS), a multi-centre observational study in the UK. Controls were participants with RA taking MTX for at least 1 year without the development of MTX-P and were age:sex matched 3:1 to cases. Genotyping was performed using the Illumina Infinium HumanCoreExome BeadChip array (Illumina, San Diego, USA). Bioinformatic analysis was undertaken to identify associated SNPs with potential functional significance.

Results: 65 cases and 195 controls were recruited. The study has an 80% power to detect an allele with frequency 0.30 and allelic odds ratio of 3.0. Following quality control, data for 236,308 SNPs in 62 cases and 172 controls remained. 48 cases (77%) retrospectively fulfilled either the Carson et al. or Searles et al. unvalidated criteria for MTX-P. Three SNPs were associated with MTX-P at $P<10^{-5}$. Rs6593803 ($p = 1.85 \text{ X } 10^{-7}$, OR = 3.13) maps near *GJA5* (figure 1), rs9299346 ($p = 1.76 \text{ X } 10^{-6}$, OR = 2.76) in *GRIN3A* and rs1624005 ($p = 6.54 \text{ X } 10^{-6}$, OR = 2.59) maps near *LRFN5*. rs6593803 affects *GJA5* expression, a subunit of the gap junction connexin 40. Transgenic mice deficient in connexin 40 and 43 ($cx40^{--}/cx43^{--}$) have a reduced life span due to lung abnormalities including pulmonary fibrosis, alveolar wall thickening and increased lung fibroblasts, histopathological findings similar to MTX-P.

Conclusion: 3 SNPs were associated with MTX-P at borderline significance levels. Further studies should prioritise investigating the role of rs6593803 in MTX-P.

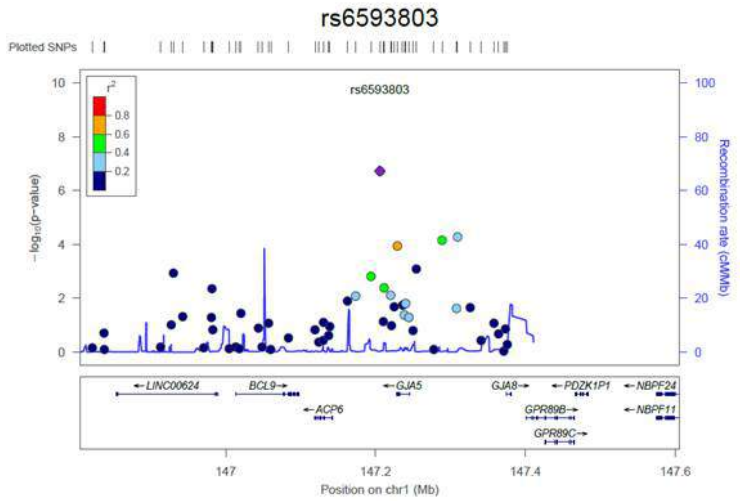

Figure 1. LocusZoom plot of SNP rs6593803.

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Abstract Number: 1200

Transcriptional Profiling of Early RA Synovial Tissue Reveals the Impact of Triple DMARD Treatment on T Cell Activation Pathways

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Background/Purpose: While several transcriptional profiling studies of synovial biopsies have been reported from RA patients with advanced disease, there is relatively little data available from patients with early disease before treatment with DMARDs or on the effects of treatment with DMARDS. Such data may advance our understanding of RA pathogenesis and promote precision-medicine based treatments for early disease.

Methods: Biopsies from subjects with early RA (<12 months from diagnosis at baseline with an average disease duration of 17.6 weeks) before and after triple DMARD (tDMARD) therapy were collected by arthroscopy (n=19 paired samples at baseline and 6 months post-treatment). These biopsies as well as those from subjects with normal synovium (n=28) or those diagnosed with osteoarthritis (n=15) were profiled by total RNA sequencing. Comparison of RA biopsies before and after treatment and comparison with non-RA controls were performed. Pathway enrichment and upstream regulator analysis were used to understand gene changes and to generate hypotheses for future experimental confirmation.

Results: Over 5000 genes were identified with differential expression between baseline RA samples and normal controls (with 5% FDR and 2 fold-change cutoffs). A subset comprising less than 500 of these genes was modulated by tDMARD treatment in the subjects (n=17) who achieved good or moderate response at 6 months as assessed by EULAR criteria. The gene set whose expression was modulated by treatment was enriched for genes involved in immune system and T cell activation pathways. Interestingly, many genes with increased expression in RA samples remained elevated after treatment compared to normal controls. Based on this finding, we also identified gene expression patterns in treated patients with low disease activity (DAS28 < 3.2) that differentiates them from normal controls. These gene

signatures may help identify novel drug targets to improve rates of treatment induced disease remission.

Conclusion: Through genome-wide transcriptomics profiling, we identified signatures that characterize synovial tissue from RA patients with early disease. Analysis of gene expression after 6 months of tDMARD treatment highlight consistent alterations in expression of genes related to immune response and T cell activation. Our results provide novel insight into the biology of joints from early RA patients and the mechanism of tDMARD action in this patient population with high unmet clinical need.

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Abstract Number: 1201

Deconvolution of Immune Cell Proportions from Whole Blood RNA Using Next-Generation Sequencing

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Background/Purpose: Measurements of immune cell proportions from whole blood can be used to detect pharmacodynamic effects, as a marker for prognosis and to aid in understanding therapeutic response in patients with disease. Profiling of immune cell types from whole blood in clinical trials is traditionally accomplished with low resolution tests such as complete blood count (CBC). Although FACS yields more comprehensive profiling it is challenging to execute in large trials. Mathematical deconvolution techniques have been developed to estimate the proportion of constituent cell types from whole blood using microarray expression profiling (Abbas et al., 2005, Newman et al., 2015) and RNA profiling by next-generation sequencing (NGS) (Gong et al., 2011). Here we extend the technique using RNA-Seq of naïve and activated immune cells to derive cell and activation specific gene signatures.

Methods: Immune cells from lymphoid and myeloid lineages were isolated from multiple healthy donors. Naïve cells were stimulated to induce an activated state. RNA from 102 samples were harvested and profiled by NGS. The deconvolution algorithm leverages a set of genes and associated expression levels to infer cell abundances. Multiple filters were used to ensure specificity and sensitivity during gene identification and matrix generation (Figure 1).

Results: We assessed the ability of the deconvolution algorithm to discriminate pure cell types (T, B, NK, Monocytes and Neutrophils) on an independent RNA-Seq dataset of cells sorted from whole blood from Systemic Lupus Erythematosus (SLE), Multiple Sclerosis and Normal Healthy subjects comprising 191 samples. It achieved an average positive predictive value of 100% and an average negative predictive value of 95% (Table 1). Further validation is planned using whole blood samples analyzed in parallel by FACS and RNA-Seq. We applied this method to a large publically available RNA-Seq dataset of 99 SLE subjects (Hung et al., 2015). We were able to identify a higher proportion of activated T-cells (defined by CD3/CD28 stimulation) in SLE subjects and those corresponded with interferon activity levels as determined by the authors (Figure 2).

Conclusion: Whole blood deconvolution using RNA-Seq may be a useful method for immuno-phenotyping by proxy when FACS is unavailable.

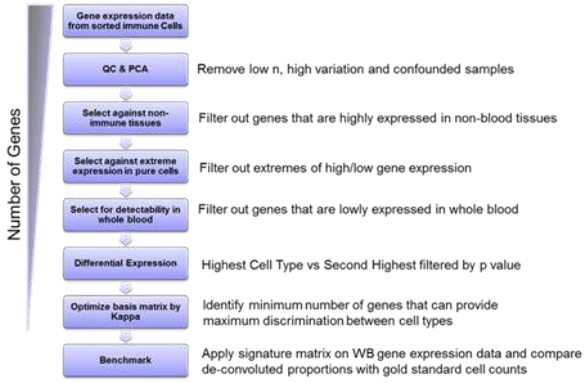

Figure 1: Gene Filtering Strategy for Deconvolution

Table 1: Deconvolution Algorithm Performance on Pure Cells

Pure Cell Type	Specificity	Sensitivity	Accuracy	PPV	NPV	Samples
T Cells	100%	97%	99%	100%	98%	67
B Cells	100%	12%	84%	100%	84%	34
NK Cells	100%	73%	97%	100%	97%	22
Monocytes	100%	97%	99%	100%	99%	34
Neutrophils	100%	85%	97%	100%	97%	34

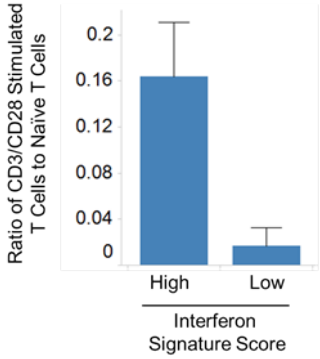

Figure 2: Activation state of T Cells inferred by deconvolution corresponds to interferon signature status
Hung et al., 2015 classified 99 SLE subjects into Interferon High (75) or Interferon Low (24) by qPCR assay of three genes (Kennedy et al., *Lupus Sci Med.* 2015). A deconvolution algorithm was used on whole blood RNA-Seq to estimate proportions of Naïve T Cells and T Cells with a CD3/CD28 activation transcriptional phenotype. Bar height represent the ratio of activated to naïve T Cell subsets; error bars are SEM.

Disclosure: O. Jabado, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Hu**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. Carman**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Suchard**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **D. Lee**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **Z. Qi**, Bristol-Myers Squibb, 3,Bristol-Myers Squibb, 1; **S. Kirov**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **R. Golhar**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **A. He**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **C. Speake**, None; **P. S. Linsley**, Bristol-Myers Squibb, 2; **S. G. Nadler**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Bandyopadhyay**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3.

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Abstract Number: 1202

Characteristic Compositional and Functional Alteration of Gut Microbiota in Patients with Behcet's Disease

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Background/Purpose: We have presented evidence that the frequency of helper T (Th)17 cells increased and the cells had already been activated in vivo in patients with Behcet's disease (BD). Major proinflammatory cytokines, such as IL-1β, IL-23 and TNFα, significantly increased IL-17 production of T cells of BD patients. Recently, some researchers clarified the relationships among several gut bacteria, skewed Th17 cell function and local inflammation in autoimmune disease models, presumably through the overproduction of several proinflammatory cytokines in the intestinal immune system. We conducted fecal metagenomic analysis of BD patients and compared the data with those of normal individuals (NI) to assess whether unfavorable compositional and functional changes of gut microbiota (Dysbiosis) exist in BD patients.

Methods: We explored fecal microbiota of 12 patients with BD and 12 NI by sequencing of 16S rRNA gene. We calculated relative abundance of bacterial taxa and the diversity of each sample (alpha diversity) and each group (beta diversity). We compared the relative abundance of bacterial taxa with fecal secretary IgA (sIgA) concentrations and a BD disease activity index in BD patients. Then we predicted metagenome functional content from the 16S rRNA gene data using a bioinformatics software package (PICRUSt).

Results: The sequencing data showed that the family Lactobacillaceae, the genera Bifidobacterium and Eggerthella increased significantly in BD. The order Clostridia and the genus Megamonas significantly increased in NI. Fecal sIgA concentrations increased significantly in BD patients compared with those in NI. None of the relative abundance of bacterial taxa correlated with fecal sIgA concentrations or the BD activity index of patients with BD. There was no significant difference in alpha diversity between BD and NI. An exploratory analysis showed a significant difference between the two groups (BD and NI) in beta diversity. Bacterial genome function analyses revealed that glycolysis/glycogenesis and fatty acid metabolic pathways exceeded in BD patients compared with NI.

Conclusion: Lactic acid producing bacteria, such as Bifidobacterium and Lactobacillus, were suggested to decrease short chain fatty acid production of microbes belonging to the class Clostridia, some of which were reported to be essential for the differentiation of regulatory type T cells. Recently, glycogen and several short chain fatty acids were reported to play a role in the activation of T cells through the regulation of metabolic pathway. We suggest that low short chain fatty acid concentrations with bacterial metabolic alterations may have a relationship with the skewed Th cell differentiation of BD.

Disclosure: N. Suzuki, None; **J. Shimizu**, None; **T. Kubota**, None.

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Abstract Number: 1203

Differential Synovial Expression Patterns in Early Osteoarthritis Predict Pain and Progression of Joint Damage

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Background/Purpose: The cause for chronic pain in OA is largely unknown. Over 50% of osteoarthritis (OA) patients show synovial

inflammation, even at early stages of the disease. However, if and how this synovial activation contributes to joint pathology and pain, is not known. We aimed to identify pathways that predict progression of cartilage damage and osteophyte (OP) formation in OA. In addition, we identified association between gene expression and pain in a cross-sectional approach.

Methods: From 25 patients with knee OA that entered the CHECK Cohort study (Cohort Hip and Cohort Knee) synovial biopsies were collected at baseline. CHECK is a prospective 10-year follow-up study on patients with early osteoarthritis-related complaints initiated by the Dutch Arthritis Foundation. Progression over 5 years was determined radiographically based on change of joint space width (JSW) and OP size in these radiographs. Pain was assessed at baseline and after 5 years by the WOMAC pain questionnaire. Synovial samples from baseline were studied using histology and microarray (affymetrix U133-plus-2.0), and Functional Annotation Clustering (FAC).

Results: We identified patients as progressors or non-progressors, either based on JSW (respectively n=13 vs n=8) or OP size (respectively n=10 vs n=11) at baseline and t=5yrs. Among the genes that were differentially expressed by OP progressors were MMP1, 2, 3, 9 and -14, which were not found in JSW-progressors. Specifically in JSW-progressors, macrophage markers (e.g. CD14, S100A8, S100A9, MHC class II genes) were positively associated with progression. This indicates that expression of these factors predict progression of cartilage damage in OA patients. Using FAC we identified inflammatory response, macrophage differentiation, blood vessel formation, ossification and cell migration to be enriched in JSW-progressors. Blood vessel formation, ossification and cell proliferation were enriched in OP-progressors. Histologically, the JSW-progressors showed a thicker synovial lining and cellularity was higher in the sublining compared to non-progressors and OP progressors. Both JSW-progressors and osteophyte-progressors showed increased vascularisation compared to non-progressors. FAC analysis pointed out that dendrite formation (p=0.036), ossification (p=0.027) and wnt signaling (p=0.0065) were annotation clusters that were related to pain at Baseline. Moreover, we found neuronprojection/dendrite formation (p=0.0044), skeletal morphogenesis (p=0.018) and neuron differentiation (p=0.038) enriched in synovium of patients with pain after 5 years. When only upregulated genes were tested these patients showed strong enrichment of inflammatory genes ($p=6.4*10^{-12}$) and axogenesis (p=0.005).

Conclusion: We found evidence for a difference in underlying processes in the synovium regarding progression of cartilage damage and progression of osteophyte formation. The presence of macrophages, in the lining layer, is associated with progression of cartilage damage, whereas synovial expression of MMPs correlated to progression of osteophyte formation. Pain at t=5 yrs was predicted by several nerve fiber related processes and strongly by inflammation.

Disclosure: A. B. Blom, None; **M. H. van den Bosch**, None; **H. Cats**, None; **F. van den Hoogen**, None; **F. P. Lafeber**, Roche Nederland BV, 2; **W. B. van den Berg**, None; **P. L. van Lent**, None; **P. M. van der Kraan**, None.

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Abstract Number: 1204

Methotrexate Is an Antibacterial Drug Metabolized By Human Gut Bacteria

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease of unknown etiology that causes inflammation and irreversible damage in joints and other organs. Methotrexate (MTX) is the first-line therapy used in the treatment of RA. However, not all patients respond to MTX, and a tool to predict MTX responders would help clinicians identify the 50-60% of patients that require additional therapy. Because MTX affects evolutionarily conserved pathways that are present in both humans and bacteria, it is plausible that the microbiome may be affected by MTX or directly metabolizes the drug, which is a folic acid analogue. Additionally, gut bacteria have been shown in prior studies to metabolize many pharmacologic drugs. We hypothesize that the microbiome contributes to inter-individual variations in clinical outcome. Here, we focus on the response of bacteria to MTX and ask whether bacteria can metabolize MTX.

Methods: First, we tested the *in vitro* growth of a panel of 25 gut bacterial isolates in response to MTX. The minimal inhibitory concentration (MIC), or the concentration of MTX required to completely suppress bacterial growth, was identified for each isolate. Second, we used HPLC to ask whether gut bacteria metabolize methotrexate. In select cases, we also used UPLC-MS-MS to learn the identity of MTX metabolites.

Results: Methotrexate inhibited the growth of 19 of the 25 isolates examined. Minimal inhibitory concentrations ranged from 2 ug/ml to >900 ug/ml *in vitro*. At the Phylum level, Bacteroidetes tended to be sensitive and Firmicutes tended to be resistant to antimicrobial effects of MTX (Fisher's exact test, p=0.03). We next asked whether these species metabolize MTX, and found that 5 possessed this ability. At least two species metabolized MTX into polyglutamated methotrexate, which is a novel finding that has not been described previously in the literature. Interestingly, there was no association between bacteria that were resistant to MTX and those that metabolized it.

Conclusion: These findings suggest that methotrexate is an antibacterial in addition to being a chemotherapeutic agent and an immunosuppressant. Additionally, gut bacteria can metabolize MTX, perhaps even before this drug enters a patient's bloodstream. The metabolite found in our study was polyglutamated MTX, which prior studies have shown to be associated with patient response. Our ongoing studies will examine the *in vivo* implications of these findings, but this supports the hypothesis that a patient's response to methotrexate may be influenced by their gut microbiome. Thus, the microbiome may be an important factor in predicting patient response to MTX and perhaps other rheumatologic medications as well.

Disclosure: R. R. Nayak, None; **C. O'Loughlin**, None; **M. Fischbach**, None; **P. J. Turnbaugh**, None.

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Abstract Number: 1205

In silico Drug Repurposing Analysis Supports Phosphoinositol 3 Kinase Inhibitors As Treatment of LUPUS

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a clinically heterogeneous disease with few treatment options. Current treatments are not fully effective and show highly variable responses. Drug repurposing is based on the comparison of gene expression signatures of blood, PBMCs or separated cell types from cases with a disease with gene expression signatures made with various cancer cell lines treated with different drugs. It has been an effective technique for the identification of new therapeutic approaches. We present a systematic drug repurposing analysis based on gene expression signatures derived from blood cells of SLE patients to discover potential new drug candidates and target genes.

Methods: We collected and processed a compendium of gene expression data sets of SLE from the NCBI Gene Expression Omnibus database. We selected data sets of adult and juvenile SLE cases from different micro-array platforms to obtain a heterogeneous group of data from which to identify a common signature. We used R to process each data set independently, making normalization, transformation to logarithmic scale, quality control, and differential expression analysis. The genetic signatures obtained were queried independently on the Lincscloud database, which contains tens of thousands of drug and genetic perturbation-caused profiles, and obtained a list of drugs and genes based on similarity scores for each SLE signature. A positive similarity score represented a genetic pattern similar to the SLE signature, and a negative similarity score represented an inverse genetic profile. A negative score was therefore considered to revert the genetic profile of SLE. The median of the similarity score of each independent experiment was then calculated to obtain a unique list of genes and drugs. Drug targets were annotated using a file created in R from three drug databases to classify the drugs into groups. The Enrichr web tool was used to obtain the pathways involved when analyzing the knock-in and knock-down experiments.

Results: We obtained drugs never or little studied to treat SLE and drugs undergoing intensive research. Results were not dependent of cell type or SLE heterogeneity, as we selected genes conserved across all SLE signatures queried. Phospoinositol 3 kinase (PI3K) and mammalian targets of Rapamycin (mTOR) inhibitors were the most significant groups of drugs obtained. When we analyzed the biological pathways obtained with the knock-in and knock-down experiments we found pathways impaired in SLE, such as the interferon and immune signaling pathway, the translational process, but also, pathways related to the PI3K signaling pathway or the Insulin signaling pathway. So, these results are complementary and consistent with those observed with the drugs. PI3K acts in important processes related to the development of SLE, such as immune signaling, the lymphocyte differentiation and proliferation or apoptotic processes.

Conclusion: Our results suggest that PI3K inhibitors affecting biological pathways impaired in SLE are the best potential therapeutic option. This work has received support from the EU/EFPIA Innovative Medicines Initiative Joint Undertaking (PRECISESADS, grant n. 115565).

Disclosure: D. Toro, None; **P. Carmona Sanz**, None; **M. Alarcón-Riquelme**, None.

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Abstract Number: 1206

A Replication Study and Meta-Analysis Demonstrate the Influence of the mtDNA Haplogroups in the Rate of Incident Knee Osteoarthritis. Functional Explanation of This Association Using Transmitochondrial Cybrids

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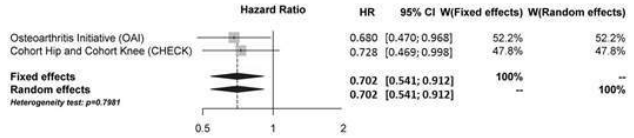
Background/Purpose: The study of the mitochondria in the context of osteoarthritis (OA) attracted much attention. In this study we aimed to evaluate the influence of the mitochondrial DNA haplogroups in the risk of incident knee OA and to explain the functional consequences of this association to identify potential therapeutic targets.

Methods: The influence of the haplogroups in the rate of incident knee OA at eight years in 2579 subjects from the Osteoarthritis Initiative (OAI) and 635 subjects from the Cohort hip and Cohort knee (CHECK) was assessed. Incident knee OA was defined as a new onset KL grade ≥ 2 during 96 months follow-up. Finally, a subsequent meta-analysis was conducted to synthetize results. Transmitochondrial cybrids carrying the haplogroups J and H were constructed to study the influence of the mitochondrial background in different OA-related features using an extracellular flux analyzer

Results: The haplogroup J associates with a decreased risk of incident knee OA in subjects from the OAI (HR=0.680; 95% CI=0.470–0.968; P<0.05) and CHECK (HR=0.728; 95% CI=0.469–0.998; P<0.05). The subsequent meta-analysis including 3214 cases showed that the haplogroup J associates with a lower risk of incident knee OA (HR=0.702; 95% CI=0.541-0.912; P=0.008) (Figure 1). Cybrids with the haplogroup H show higher mitochondrial respiration and glycolysis leading to an increased ATP production. On the contrary, haplogroup J shows a significantly lower free radical production, higher cell survival under oxidative stress conditions and lower grade of

apoptosis as well as lower expression of the mitochondrially-related pro-apoptotic gene BBC3



Conclusion: The haplogroup J reduces the risk of incident knee OA. This mitochondrial variant constitutes a protective phenotype against the development of OA and his beneficial physiological effects could be emulated to identify potential therapeutic targets to treat OA.

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Abstract Number: 1207

Design of a Multiplex Serum Proteome Assay to Monitor Biologic Drug Response in Rheumatoid Arthritis Patients

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Background/Purpose: Biologic drugs have revolutionised the treatment of Rheumatoid Arthritis (RA), however these therapies are expensive and exhibit a high non–response rate (30%). Currently there are no specific biological markers which distinguish non-response early after initiating treatment. The aim of this study was to identify serum protein levels which change when disease activity score is reduced by biologic drug treatment. These proteins may give mechanistic insight into molecular events after failed therapeutic intervention.

Methods: Sera and disease activity scores (DAS28-ESR) were collected from n=25 RA patients at baseline and six months after anti-tumour necrosis factor alpha treatment. EULAR response criteria were used. Untargeted (unbiased) label free LC-MS/MS based proteomics was used initially to discover sera proteins differentially expressed at six months in responders and non-responders. Multiple reaction monitoring (MRM) assays were designed and tested on a triple quadrupole mass spectrometer.

Results: Over 500 proteins were identified in each of the pooled serum samples using the untargeted label free LC-MS/MS approach. Statistical analysis of the data revealed a list of 155 proteins that were significantly differentially expressed between good and non-responders ($p<0.05$). 55 of these proteins were shortlisted for development of targeted MRM assays, and assays were successfully developed for 47 proteins.

Conclusion: The approach outlined here and the initial results obtained indicate the power of a combined mass spectrometry strategy for comprehensive serum proteome analysis to determine quantitative changes, discover novel protein signatures and develop a multiplexed protein assay capable of monitoring response to biologic treatments. Such biologic drug response markers could minimise the use of

expensive biologic drugs in patients who do not gain benefit and reduce adverse side effects.

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Abstract Number: 1208

High-Throughput Screening Discovers Multiple Novel Autoantibodies in Rheumatoid Arthritis, Systemic Lupus, Systemic Sclerosis and Sjogrens Syndrome

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Background/Purpose: Diagnostic biomarkers are decision-making tools in clinical lab routine and are of growing importance for clinical management of patients. In autoimmune diseases, one important class of biomarkers are autoantibodies (AAB) directed against human autoantigens. Apart from diagnostic antigens used in clinical routine, additional AAB reactivities to more than 100 human antigens relevant for disease are described in literature. Obviously, the autoimmune profile of humans covers a huge number of AABs, which display an enormous resource to identify novel marker candidates. Here, we describe a new screening platform SeroTag for discovery of novel AABs in healthy controls and autoimmune diseases. By selecting 100+ AABs a comprehensive autoimmune landscape will be outlined to define diseases and disease subgroups according to their intrinsic, highly differentiated AAB pattern.

Methods: SeroTag utilizes over 8,000 human proteins as antigen collection in bead-based suspension arrays (Luminex FlexMap 3D) to allow for high-throughput (HTS) serum sample processing with high accuracy, followed by standard and advanced data mining procedures. Recombinant antigens were covalently coupled to magnetic, color-coded beads and serum samples were incubated with several multiplex bead mixes each representing 400 different antigens. We screened over 6,000 serum samples from patients with autoimmune diseases such as SLE (n= >1,000), SSc (n= >450), RA (n= >1,500), SjS (n= >100) and over 1,000 healthy individuals to confirm known and to discover novel AABs.

Results: In SLE, SjS, SSc and RA, and also in healthy controls, novel autoantigens were discovered in several independent discovery studies and subsequently validated in separate validation studies. Antigens showing reproducible, significant reactivity compared to active and passive controls were selected in a stepwise marker refinement approach. Examples include BICD2 and KDM6B/JMJD3 as novel antigens in SSc with 20-30% prevalence, TMPO and MVP in SLE with 15-25% prevalence, and several novel protein targets of anti-citrullinated peptide antibodies.

Conclusion: HTS AAB screening is a valuable tool for “omics”-type biomarker discovery and verification in autoimmune diseases. Utilizing a technical platform capable to analyze thousands of antigens in thousands of patients, a high-resolution landscape of autoimmunity can be drawn. Over 50 novel autoantigens were discovered and validated in RA, SLE, SSc, and a set of novel autoantigens with high prevalence in healthy controls is presented. In combination with known AABs our findings show potential for improved and earlier diagnosis, differential diagnosis, and disease subgrouping. Distinct sets of AABs are utilized for biomarker support in the development of novel medicines for autoimmune diseases.

Disclosure: P. Schulz-Knappe, Protagen AG, 3; **H. D. Zucht**, Protagen AG, 3; **P. Budde**, Protagen AG, 3; **H. Göhler**, Protagen AG, 3; **D. Wirtz**, Protagen AG, 3; **J. Schulte-Pelkum**, Protagen AG, 3; **S. Vordenbäumen**, None; **T. Witte**, None; **P. D. M. Schneider**, Protagen AG, 5.

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Abstract Number: 1209

Sporadic Hemophagocytic Lymphohistiocytosis (sHLH): A Polygenic Disease? a Report of French National, Prospective, Cohort of 205 Patients

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Background/Purpose: The role of genetic factors in the occurrence and/or severity of sHLH is not yet known. Therefore, from 2010 to 2016, we performed a national, prospective, cohort study to analysis HLH-associated genes (*Lyst, perforine, Munc 13-4, syntaxine-11, STXBP-2, SH2D1, XIAP, Rab-27, Itk)* in sHLH.

Methods: We included 190 adults and 15 children fulfilling adapted Histiocyte Society criteria. Data collected included: (i) clinical and biological features, (ii) malignant, autoimmune or infectious associated diseases, (iii) treatment and evolution at M0 and M12. HLH associated-genes could be sequenced in 185 patients and analyzed in 147. Mutational profiles of Non Synonymous (NS), rare variants (frequency < 1% or 5% in reference populations) were compared to control populations issued from the "1000 genomes" project and in house repositories.

Results: Heterozygous (n=111) and homozygous (n=2) rare variants were identified in 80 patients. For 26 patients, rare variants were localized in 2 or 3 genes. Compared with control populations, overall rare variants frequency didn't differ significantly. However, rare variants (frequency < 1% or < 5%) affecting 2 or more genes in patients were significantly different from controls ($p<0.0002$ and $p< 0.03$). Combinations of rare variants were enriched with *perforin* and *RAB27a* or *STXBP2* genes. sHLH were associated with hematologic malignancies and autoimmune diseases in 51 and 20 cases respectively, and idiopathic in 75 cases with infectious trigger in half of the cases. Severity of sHLH (relapsing cases, ICU transfer, or death) is significantly correlated with the presence of combination of rare variants (p=0,0043), especially in the groups of autoimmune diseases or idiopathic.

Conclusion: In conclusion, genes of primary HLH may also be involved in sHLH physiopathology and outcome.

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Abstract Number: 1210

A Genome-Wide Association Study of Psoriatic Arthritis in Italian Population

Mariagrazia Catanoso[1], Pierluigi Macchioni[1], Salvatore D'Angelo[2], Antonio Marchesoni[3], Roberta Ramonda[4], Alberto Cauli[5], Fabio Massimo Perrotta[6], Roberto Bortolotti[7], Guseppe Provenzano[8], Giovanni Pistone[9], Katya Boito[10], Cristina Giuliani[11], Paolo Garagnani[11], Davide Gentilini[12], Mariana Lofrano[13], Laura Rotunno[14], Mariagrazia Lorenzin[15], Ignazio Olivieri[13], Alessandro Mathieu[16], Guido Valesini[17], Giuseppe Paolazzi[7], Roberto Baricchi[18], Anna Maria Di Blasio[12], Luigi Boiardi[19], Claudio Franceschi[20] and Carlo Salvarani[1], [1]Rheumatology Unit, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Rheumatology Department of

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Background/Purpose: In order to search for susceptibility loci, we undertook a genome wide association (GWA) scan to identify genetic factors predisposing to Psoriatic Arthritis (PsA) and its clinical subsets in italian population.

Methods: This is a multicenter italian study involving 9 rheumatological centres localized in the main four macro-areas of Italy. We enrolled 835 consecutive PsA patients diagnosed according to CASPAR criteria. The control group consisted of 773 sex and geographical origin matched people recruited from healthy blood donors. Each sample was genotyped using the SNPs microarray Illumina CoreExome24 BeadChip. A whole-genome screening of common variants (SNPs) and structural variants (CNVs) on each cohort was performed. Moreover PsA patients were stratified according to their clinical patterns as peripheral (PPA), axial (APA), or mixed involvement (APPA).

Results: The association studies showed 40 markers with $p<7.40\times10^{-5}$ located on chromosome 6 in HLA-B region among PsA patients vs healthy controls. We found highly significant association with rs3916765 ($p=5.39 \times 10^{-12}$, OR 2.669, 95%CI =2 – 3.56), exm-rs12191877 ($p=4.87 \times10^{-10}$, OR 1.731, 95%CI =1.46-2.06), rs13191519 ($p=7.76 \times 10^{-9}$, OR 1.609, 95%CI =1.37-1.89), exm-rs4947248 ($p=1.98 \times10^{-9}$, OR 1.56, 95%CI = 1.35-1.80). Moreover, in PsA patients we identified signals of association from a region on chromosome 15q21 harboring USP8 gene ($p=6.25 \times 10^{-9}$, OR 1.627, 95%CI =1.38-1.92). Among these identified risk variants, two were strongly associated only with PPA [exm-rs12191877 ($p=1.27 \times10^{-9}$,OR 1.76, 95%CI =1.46-2.11), rs3916765 ($p=2.55 \times 10^{-11}$, OR 2.68, 95%CI =1.99-3.61)] but not with mixed clinical pattern. Moreover , PsA patients with mixed clinical pattern did not shown associations on chromosome 6 in HlA-B region. No SNPs association was found comparing axial or mixed form with healthy controls.

Conclusion: We have confirmed a strong association with PsA and high number of loci located on chromosome 6. A new association was found on chromosome 15. We found no association with SNPs localized in HLA-C region as already observed in other GWA studies. Replication of these variants in multiple larger populations is necessary.

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Abstract Number: 1211

Allele-Dependent Binding of a Viral Protein to Autoimmune Disease-Associated Genetic Variants

Matthew T. Weirauch[1], Daniel Miller[1], Leah C. Kottyan[2], Ignacio Ibarra[3], Sayeed Syed[4], Xiaoting Chen[1], Erin Zoller[1], Arthur Lynch[1], Connor Schroeder[1], Josh Lee[1], Albert Magnussen[1], Ally Yang[5], Timothy R. Hughes[5], Joo-Seop Park[1], Charles Vinson[4] and John B. Harley[6,7], [1]Cincinnati Childrens Hospital, Cincinnati, OH, [2]Center for Autoimmune Genomics and Etiology, Cincinnati Childrens Hospital, Cincinnati, OH, [3]EMBL, Heidelberg, Germany, [4]NCI, Bethesda, MD, [5]University of Toronto, Toronto, ON, Canada, [6]US Department of Veterans Affairs Medical Center, Cincinnati, OH, [7]Center for Autoimmune Genomics and Etiology (CAGE), Cincinnati Childrens Hospital, Cincinnati, OH
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Background/Purpose : Risk factors are known for many diseases, but the etiologies of most autoimmune diseases remain unknown and are idiopathic. Pathogenesis of disease likely involves complex interplay between genetic and environmental risk factors. Specifically, Epstein Barr virus (EBV) has suggestive associations with many autoimmune diseases, and EBV infection is nearly ubiquitous in adults. The molecular mechanisms underlying these associations, however, remain unclear.

Methods: We tested the hypothesis that some autoimmune variants might act by altering the binding of the EBV-encoded transcription factor ZTA, consequently resulting in downstream changes in gene expression. To this end, we comprehensively characterized the DNA binding of ZTA to both methylated and unmethylated DNA sequences using protein binding microarrays (PBMs). Based on these data, we identified plausible causal variants for multiple sclerosis (MS), systemic lupus erythematosus (SLE), and juvenile idiopathic arthritic (JIA) predicted to alter ZTA binding. From among these, we identified variants located within likely regulatory regions in EBV-infected B cells using publically available functional genomic datasets. We screened these candidate variants using electrophoretic mobility shift assays (EMSAs) to identify general differential binding of nuclear factors, and validated differential ZTA binding using EMSA-supershift and DNA Affinity Precipitation Assays coupled with Western blots (DAPA-Westerns).

Results: These experiments revealed three genetic variants, associated with MS, SLE, and JIA, respectively, exhibiting stronger ZTA binding to the risk allele. We provide data showing that each of these variants is associated with genotype-dependent expression in EBV-transformed B cell lines. Using luciferase reporter assays, we further demonstrate that the autoimmune risk alleles result in greater promoter activity.

Conclusion: Collectively, these data demonstrate for the first time that differential binding of a viral protein to a disease-associated genetic variant can result in altered levels of host gene expression in ways that are predicted to influence autoimmune disease risk of MS, SLE, and JIA. Since ZTA is a viral protein, and is expressed throughout human life subsequent to EBV infection, but only in virus infected cells, these results offer a potential therapeutic target for multiple autoimmune diseases.

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Abstract Number: 1212

A Combined Large Scale Meta-Analysis Identifies COG6 As a Novel Shared Risk Locus for Rheumatoid Arthritis and Systemic Lupus Erythematosus

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Background/Purpose: One of the main limitations of the association studies in autoimmunity is the difficulty in identifying genetic risk variants with modest effects, given the large sample size required and the relatively low prevalence of these diseases in the general population. This limitation has been partially overcome by combining GWAS data from different pathologies as a single phenotype, thus providing the statistical power lacking in GWAS datasets of a specific disease. This approach has already been successfully applied in the study of several autoimmune diseases with common genetic backgrounds. During the last years, genome-wide association studies (GWAS) have identified a number of common genetic risk factors for rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). However, the genetic overlap between these two immune-mediated diseases has not been thoroughly examined thus far. The aim of the present study was therefore to identify novel shared risk loci between RA and SLE by performing a combined meta-analysis including previously published GWAS datasets of both diseases.

Methods: We performed a large-scale meta-analysis of GWAS data from RA (3,911 cases and 4,083 controls) and SLE (2,237 cases and 6,315 controls). Statistical analyses were performed with PLINK V.1.07. First, disease-specific meta-analyses were performed combining RA datasets, on one hand, and SLE datasets, on the other hand, by an inverse variance-weighted method. Subsequently, a combined RA–SLE meta-analysis was conducted. Those SNPs with p values lower than 1×10^{-5} in this combined meta-GWAS and p values lower than 0.01 in each disease meta-analysis were selected for replication in additional datasets comprising 13,641 RA cases and 31,921 controls and 1,957 SLE patients and 4,588 controls.

Results: The rs9603612 genetic variant, located nearby the *COG6* gene, an established susceptibility *locus* for RA, reached genome-wide significance in the combined analysis including both discovery and replication sets (P-value=2.95E-13). *In silico* expression quantitative trait *locus* analysis revealed that the associated polymorphism acts as a regulatory variant influencing *COG6* expression in monocytes. Moreover, protein-protein interaction and gene ontology enrichment analyses suggested the existence of overlap with specific biological processes, specially the type I interferon signalling pathway. Finally, genetic correlation and polygenic risk score analyses showed cross-phenotype associations between RA and SLE.

Conclusion: In summary, the present study adds COG6 to the list of risk factors shared between RA and SLE. Our results highlight the existence of a relevant genetic correlation between both diseases as well as the influence of common molecular mechanisms in their pathophysiology. Since common genetic pathways are implicated in RA and SLE, a reclassification of patients from a genetic point of view will lead to more specific and effective therapeutic procedures.

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Abstract Number: 1213

Targeted Next-Generation Sequencing of 128 Genes Associated with Rheumatoid Arthritis

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Background/Purpose: Through genome-wide association scans (GWAS), more than 120 genes have been found to be associated with rheumatoid arthritis (RA). This study aims to search for novel risk alleles in Singapore Chinese RA patients positive for anticitrullinated peptide antibodies through next-generation sequencing of these genes.

Methods: Targeted sequencing of 128 genes was performed in 48 RA cases and 45 healthy controls. These genes were selected based on RAvariome database and literature review. The target exons and 5' non-coding regulatory regions were enriched using the Nimblegen SeqCap EZ kit (Roche) followed by parallel sequencing using Miseq (Illumina). Variant detection and annotation were conducted with the Genome Analysis Toolkit (GATK) and ANNOVA. Association analysis was determined with PLINK.

Results: A dataset of 696 high quality variants consisting of 14.2% non-synonymous, 68.5% coding synonymous/UTRs and 16.6% up- or downstream of gene was obtained. We focused our analysis on rare or low frequency variants (MAF<5%) that are not reported in previous GWAS studies. Risk association analysis identified 13 de novel non-synonymous variants. Among these, in the exons of AHNAK2 (rs77454674, rs201071549, rs144426530, rs144488514), AFF3 (rs117712488), PTPRC (rs148561683), FCRL3 (rs79895668) and ARAP1 (rs2291288) are variants predicted to be deleterious. In our non-exonic analysis, we found 7 risk associated low frequency variants (P<0.05). Two variants upstream of RUNX1 (rs56151547) and CCR6 (rs6931699) are found within the chromatin activation H3K4me3 mark and may be associated with epigenetic regulation.

Conclusion: We identified novel rare variants in RA that will be validated in a larger cohort.

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Abstract Number: 1214

Autoantibody Reactivities Correlated with SLE Disease Activity Identified By the SLE-key® iCHIP® Platform

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Background/Purpose: We have developed an antigen microarray technology to study antibody profiles to elucidate and diagnose clinical

states of SLE patients – the iCHIP® SLE-key® assay[1]. Our first product is the SLE-Key® Rule-Out test with 94% sensitivity, 75% specificity, and a negative predictive value (NPV) of 93%[2]. Here our goal was to determine whether particular antibody reactivities are associated with SLE disease activity index (SLEDAI) and can be used to monitor SLE disease activity.

Methods: We analyzed data from serum samples of 232 SLE patients (SLEDAI 0-25) tested on the iCHIP® containing ~200 antigens. Intensities were measured for both IgG and IgM autoantibodies. Two types of analyses were performed. For a dichotomous analysis, we defined two groups of patients: low SLEDAI (SLEDAI ≤2 [n= 123]) compared to moderate-high SLEDAI (SLEDAI >2 [n=109]). For each of the 382 features, we fit a univariate logistic regression model and estimated the odds ratio (OR), indicating the relationship between binding to a specific antigen and the subject's SLEDAI score. An OR significantly above or below 1 indicates a strong association between the feature and the dichotomous SLEDAI variable. We calculated the FDR-adjusted p-values for each univariate test, and constructed a FDR-adjusted confidence interval for the features with an adjusted p-value < 0.05 using a confidence level of 0.995. We also calculated the Pearson correlation coefficient between the intensity score for each feature and the continuous SLEDAI score.

Results: Thirty six individual antibody reactivities successfully separated between low and moderate-high SLEDAI groups in the dichotomous analysis. Nineteen of these features displayed OR>1 (mean 1.39±0.18), while the remaining 17 features displayed OR<1 (mean 0.53 ±0.08). IgG isotype was most prominent in both groups, while IgM isotype frequency increased in the latter group. Among the serologic reactivities with the largest OR were connective tissue antigens such as collagen III (IgG), vitronectin (IgG), laminin (IgG) and collagen IV (IgG) (OR 1.64-1.78); the reactivities with the smallest odds ratios were TNF receptor (IgG; 0.39) and GLP1 (IgM; 0.42). Autoantibodies to ssDNA (IgG), dsDNA (IgG and IgM), U1snRNP (IgG), Sm (IgG), and histones (IgG), which all showed significant OR, also significantly correlated with the SLEDAI score (correlation coefficients 0.46-0.57). In addition, 13 proprietary oligonucleotide sequences correlated with disease activity, with a median SLEDAI correlation coefficient of 0.44.

Conclusion: This initial proof of concept study shows that the SLE-key® microarray can detect individual autoantibody reactivities associated with high or low SLEDAI scores. Based on these results we are using the iCHIP®microarray technology to screen hundreds of antigens from relevant molecular pathways to establish a multivariate classifier for disease activity monitoring. **References:** (1)Fattal et al; Immunology, 2010 (2)Putterman et al., Journal of Immunological Methods, 2016 **Acknowledgements**: The authors wish to acknowledge the Innovative Medicines Initiative Joint Undertaking under grant agreement n° 115308 BIOVACSAFE.

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Abstract Number: 1215

Interferon Signature Genes Are Differentially Expressed Between Microscopic Polyangiitis and Systemic Lupus Erythematosus Peripheral Blood Transcriptomes

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Background/Purpose: Interferon (IFN) signature has been established in the peripheral blood of the patients with systemic lupus erythematosus (SLE) by transcriptome analyses, indicating a role of the IFN pathway in the pathogenesis of SLE. On the other hand, contribution of the IFN pathway to anti-neutrophil cytoplasmic antibodies (ANCA) - associated vasculitis (AAV) has not been established. We previously reported association of a single nucleotide polymorphism in *interferon regulatory factor 5* (*IRF5*) gene with susceptibility to myeloperoxidase (MPO)-ANCA-positive AAV in a Japanese population, suggesting a potential role of the IFN pathway in AAV. In the present study, we conducted a transcriptome analysis to examine the contribution of the IFN pathway to AAV and compared the results with

those of SLE.

Methods: Total RNA was extracted from the whole blood of Japanese individuals including 6 patients with microscopic polyangiitis (MPA), 8 patients with SLE and 14 healthy controls using the PAXgene kit. The mRNA levels of the IFN signature genes, previously reported to be differentially expressed in SLE, were analyzed using the Agilent SurePrint G3 Human GE microarray. P values were calculated by Welch's t-test, and Benjamini-Hochberg false discovery rate (FDR) correction was applied for multiple testing.

Results: In MPA, 68 (17.3%) among the 392 probes for the IFN signature genes were upregulated (P_{FDR}<0.05 and fold change [FC] ≥1.5), showing significant enrichment when compared with 1515 (7.6%) upregulated probes among the 20053 probes in total (Fisher's exact test P value=9.8E-11). In SLE, 159 out of 392 IFN signature probes (40.6%) were upregulated. Of particular interest, although upregulation of IFN signature gene probes was observed both in SLE and MPA, the sets of upregulated genes showed substantial difference. Cluster analysis showed differential expression patterns in IFN signature genes between MPA and SLE. Principal component analysis using the IFN signature probes confirmed distinct MPA and SLE clusters. When the expression levels of each probe was compared between SLE and MPA, 3228 (16.1%) probes were upregulated in SLE compared with MPA. Among such differentially expressed genes, IFN signature genes showed significant enrichment (115 out of 392 genes, 29.3%, P=3.4E-11).

Conclusion: Although IFN signature was observed also in the peripheral blood of MPA, a substantial proportion of IFN signature genes were differentially expressed between MPA and SLE.

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Abstract Number: 1216

Sjogren's Syndrome-Associated Transcripts Show Correlation with Objective Measures of Dryness

John A. Ice[1], Indra Adrianto[1], Astrid Rasmussen[1], Kiely Grundahl[2], Michelle L. Joachims[3], Graham B. Wiley[1], Jennifer A. Kelly[1], Glen D. Houston[4], David M. Lewis[4], Lida Radfar[5], Donald U. Stone[6,7], Barbara M. Segal[8], Nelson L. Rhodus[9], Joel M. Guthridge[3], James Chodosh[10,11], Raj Gopalakrishnan[12], Andrew J.W. Huang[13], Pamela J Hughes[14], Michael D. Rohrer[15], Judith A. James[1,16,17], Courtney G. Montgomery[1], R. Hal Scofield[1,17,18], Patrick Gaffney[1], Kathy L. Sivils[3] and Christopher J. Lessard[1], [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [3]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [4]Department of Oral and Maxillofacial Pathology, University of Oklahoma College of Dentistry, Oklahoma City, OK, [5]Oral Diagnosis and Radiology Department, University of Oklahoma College of Dentistry, Oklahoma City, OK, [6]King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia, [7]Department of Ophthalmology, Johns Hopkins University, Baltimore, MD, [8]Rheumatology, Hennepin County Medical Center, Minneapolis, MN, [9]Department of Diagnostic and Biological Sciences, University of Minnesota School of Dentistry, Minneapolis, MN, [10]Ophthalmology, Massachusetts Eye and Ear Infirmary, Harvard Medical School, Boston, MA, [11]Harvard Medical School, Boston, MA, [12]Diagnostic and Biological Sciences, Division of Oral Pathology, University of Minnesota School of Dentistry, Minneapolis, MN, [13]Department of Ophthalmology and Visual Sciences, Washington University, St. Louis, MO, [14]Department of Oral and Maxillofacial Surgery, Oregon Health & Science University School of Dentistry, Portland, OR, [15]Diagnostic and Biological Sciences, University of Minnesota, Minneapolis, MN, [16]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [17]Department of Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [18]US Department of Veterans Affairs Medical Center, Oklahoma City, OK

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Background/Purpose: Sjögren's syndrome (SS) is a chronic autoimmune disorder in which exocrine dysfunction can lead to chronic, debilitating dryness. Expression studies in SS have identified the dysregulated expression of coding and non-coding transcripts enriched in

innate and adaptive immune response pathways, yet their relationship to clinical features of SS remains poorly understood. By applying statistical approaches to RNA sequencing (RNA-seq) data for 3748 differentially expressed (DE; FC>2 or <0.5, q<0.05) transcripts in SS, we sought to identify transcripts whose expression correlates with objective dryness measures used in the 2002 American-European Consensus Group (AECG) SS classification criteria, including whole unstimulated salivary flow (WUSF), lissamine green (LiG) staining, and Schirmer's (Sch) tear migration.

Methods: Normalized expression data from a whole blood SS RNA-seq study was obtained for 57 cases and 11 healthy controls who underwent multidisciplinary clinical evaluation for the 2002 AECG classification criteria. Objective dryness measures (WUSF, LiG, & Sch) were normalized by $\log_2$ transformation and correlation analysis (Spearman for WUSF and LiG; Pearson for Sch) was performed for each clinical measure against all 3748 DE transcripts. Both r or $\boldsymbol{\rho}$ and a FDR-corrected p-value, or q-value, were calculated. Significantly correlated transcripts were defined by q<0.05.

Results: For WUSF, the significant positive correlation between WUSF rate and the expression of 2 non-coding transcripts was observed: the small Cajal body-specific RNA 5 (*SCARNA5*; s=0.50, q=0.018) and the uncharacterized antisense lncRNA RP11-137H2.4 (s=0.50, q=0.018). For LiG, positive correlation was observed for 31 transcripts (0.42<s<0.51, 0.017<q<0.05) mostly represented by interferon-inducible (IFI) protein-coding genes (*e.g. IFIT3, OAS3,* and *IRF7),* although the pseudogene *ZDHHC4P1* and its neighboring IFI gene *EPSTI1* showed significant positive correlation. For LiG, the only negatively correlated transcript was the sodium bicarbonate transporter *SCL4A10* (s=-0.43, q=0.045). For Sch, 3 transcripts (*CARD16*, *HMGB2*, and *BLC2A1*) were negatively correlated (-0.51<s<-0.49, 0.018<q<0.019), while *IQCH* was positively correlated (s=0.49, q=0.019).

Conclusion: We have identified SS-associated transcripts whose expression correlates with clinical measures of dryness. For WUSF, the ncRNA *SCARNA5* is situated within an intron of the Crohn's disease-associated gene autophagy-related 16-like 1 (*ATG16L1*). Although IFI genes have previously shown correlation with WUSF, the *ZDHHC4P1* pseudogene could regulate neighboring SS-associated IFI gene *EPSTI1*. For Sch, *CARD16* is a caspase inhibitor that influences apoptotic responses that induces NF-kB activation in inflammation, while *BLC2A1* has been shown to slow apoptotic responses. Further transcript characterization will allow us to assess their potential as biomarkers or surrogates of objective clinical measures for SS.

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Abstract Number: 1217

Identification of Sjogren's Syndrome-Associated Long Non-Coding RNAs That Are Co-Expressed with Key Protein-Coding Transcripts Involved in Dysregulated Interferon Responses

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Background/Purpose: The "interferon signature", marked by transcriptional upregulation of interferon (IFN)-inducible (IFI) genes, is a common finding in Sjögren's syndrome (SS) that is associated with anti-Ro production. Recent studies have implicated long non-coding RNAs (lncRNAs) as novel transcriptional regulators of IFI genes, yet their contribution to dysregulated IFN responses in SS remains unknown. In this study, we used RNA sequencing (RNA-seq) to characterize the relationship between lncRNAs and IFN transcriptional responses in anti-Ro-positive SS (SS^{Ro+}) and to prioritize lncRNAs for functional evaluation.

Methods: We used RNA-seq to generate whole-blood transcriptional profiles for 27 SS^{Ro+} patients and 27 healthy controls (HCs). Sequences were aligned to the human genome using TOPHAT and identified differentially expressed (DE) transcripts (FC >2 or <0.5 and q<0.05) using DEseq. For those DE IFI transcripts with a coefficient of variation (CV) >100% from a subset of 64 IFI transcripts, we calculated Pearson's correlation statistic, r, against the 267 DE antisense and 793 DE long-intergenic non-coding RNAs and identified those showing positive (r >+0.70) and negative (r <-0.60) correlation with FDR-corrected significance <0.05. To confirm DE of specific targets, we utilized qRT-PCR in an independent cohort of 16 SS^{Ro+}cases and 36 HCs to determine the relative expression of specific transcripts. Statistical significance was determined using an unpaired t-test in Prism.

Results: For the 19 DE IFI transcripts with CV>100%, we identified 6 DE lncRNAs whose expression is significantly correlated with IFI transcripts, including both overexpressed [*MX1-AS1* (FC=4.12), *OAS123-AS1* (FC=3.35), *NRIR* (FC=2.73), *GBP5-AS1* (FC=2.51)] and underexpressed [*ERC1-AS1* (FC=0.45), *linc-DCP1B* (FC=0.50)] lncRNAs. For only the overexpressed lncRNAs, we noted correlated expression with DE IFI genes in their immediate proximity, such as *MX1-AS1* (*MX1*, r =0.95), *OAS123-AS1* (*OAS1*, r=0.92; *OAS2*, r=0.91; *OAS3*, r=0.86), *NRIR* (*RSAD2*, r=0.77; *CMPK2*, r=0.80), and *GBP5-AS1* (*GBP5*, r=0.96). We have replicated the finding of *NRIR* upregulation in an independent cohort of SS^{Ro+} cases and HCs (p=4.8x10^{-3}), and replication is in progress for the remaining targets.

Conclusion: In this study, we have identified 6 novel SS lncRNAs showing significant co-expression with transcripts found within the IFN signature. Previous studies have implicated *NRIR* in the negative regulation of a subset of IFI genes that include the neighboring genes *RSAD2* and *CMPK2*. The proximity of additional overexpressed lncRNAs to well-defined IFI genes known to be dysregulated in SS and other autoimmune disorders bolsters the argument that these lncRNAs have regulatory roles and mediate IFI transcriptional responses. Further elucidation of the relationship between lncRNAs and expression differences in both peripheral blood and exocrine gland tissue has the potential to identify peripheral biomarkers that define specific clinical and transcriptional features resulting from IFI gene dysregulation.

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Abstract Number: 1218

Extensive Genetic Overlap of Traits Related to Gout, Hyperuricemia and Its Comorbidities

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Background/Purpose: Gout and hyperuricemia (serum urate > 7 mg/dL) typically present in the context of one or more comorbidities including type-2 diabetes, chronic renal disease, hypertension and obesity. The joint prevalence of these comorbidities with hyperuricemia is for some trait pairs more than double their marginal prevalence in the general population. However, the extent to which this association reflects genetic or environmental sources is unknown. The purpose is to derive marker-based heritability and genetic correlation estimates between, serum urate (SU), serum creatinine (SC), systolic blood pressure (SBP), blood glucose (BG) and body mass index (BMI), using whole genome regression (WGR) models of clinical data and genotypes from single nucleotide polymorphisms (SNPs).

Methods: We computed these estimates from a subset of the Framingham Heart Study, consisting of SNP genotypes from the Affymetrix500 array and clinical data measured on a total of 8,200 combined records from cohort 0, exam 13 (N = 1,396), cohort 1, exam 6 (N = 3,237) and cohort 3, exam 1 (N = 3,567). These data were fit with Bayesian multi-trait WGR models. Briefly, the model assumed two random components, one associated to the genetic factors ($\boldsymbol{\mu_k}$, for the kth subject) of BMI, SBP, BG, SU and SC; and the other to the environmental, or random residual errors ($\boldsymbol{\varepsilon_k}$). From these random components individual trait heritabilities and their genetic correlations with 95% posterior credible regions (CR) were estimated.

Results: With the exception of age and SBP the mean values of the traits were similar among the three cohorts. The mean (SD) for SU, BMI, SC and BG was 5.3 (1.5), mg/dL, 27.2 (5.2) kg/m^2, 0.8 (0.2) mg/dL, and 98.1 (23.5) mg/dL, respectively. Individuals in cohort 3 were on average (SD) younger, 40.2 (8.9) years, and had lower SBP, 115 (14) mm Hg, than those from cohort 1: 63.0 (6.7) years, and 138 (21) mm Hg. The highest marker based estimates of heritability (CR) were for SU, 0.35 (0.29, 0.42), SC, 0.46 (0.38, 0.54) and BMI, 0.42 (0.38, 0.47). The heritability of BG, 0.21 (0.17, 0.26) and SBP, 0.28 (0.24, 0.33) were lowest of the five traits analyzed, which, with the exception of SC, were all similar to family or pedigree-based heritability estimates reported in the literature. The three highest magnitude bivariate genetic correlations (CR) involved BG, with SU, 0.32 (0.18, 0.46), with SBP, 0.28 (0.15, 0.41), and with BMI 0.41 (0.30, 0.51), and their phenotypic associations involved minimal contribution from environmental (random residual) sources. The highest magnitude environmental correlations were for BMI with SU, 0.42 (0.36, 0.47) and BMI with SBP, 0.23 (0.19, 0.27) and contributed most, compared with genetics, to the phenotypic association of these traits.

Conclusion: Genetic sources of covariance between traits associated with hyperuricemia, gout and its comorbidities are substantial and consistently involve genes associated with BG. BMI consistently accounts for the environmental portion of the phenotypic associations. Therefore the etiology of gout and hyperuricemia may have an axis involving type-2 diabetes with a significant genetic component and one involving obesity that is primarily environmental.

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Abstract Number: 1219

Differential Peripheral Blood DNA Methylation Patterns Are Predictive of Radiographic OA Progression

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Background/Purpose: Extensive evidence has correlated epigenetic alterations in articular tissues with both the presence and progression of human osteoarthritis, but data regarding extraarticular tissues are lacking. Given recent findings implicating systemic inflammation in OA, we sought to characterize the DNA methylome of OA patients' peripheral blood to ascertain whether PBMC methylation patterns were associated with rapid progression of human knee OA.

Methods: Peripheral blood mononuclear cell (PBMC) DNA was obtained from baseline blood draws of 72 OA patients enrolled in the Osteoarthritis Initiative (OAI) longitudinal study. All patients had baseline symptomatic and radiographic OA. 36 rapidly-progressive OA patients, defined as >= 1.0mm radiographic joint space loss or joint replacement within the first 24 months of follow-up were compared to 36 non-progressive OA patients defined as <= 0.5mm radiographic joint space loss over 48 months of follow-up. Sets were frequency matched for age, sex, race, BMI, and baseline K/L grade among the larger OAI cohort.

DNA methylation was quantified with Illumina HumanMethylation 450k arrays. Preprocessing was done in ChAMP, SNP-dependent and sex chromosome CpG sites were excluded from analysis, batch effects were corrected with frozen surrogate variable analysis. The estimateCellCounts function of minfi was utilized to ensure differential methylation results were not skewed by PBMC subset differences. GLMnet was used to derive machine learning-based algorithms correlating methylation of CpG sites with rapid progression, and correlations were validated on a random split of 30% of cases. This machine learning strategy was repeated 40 times and results compared. Genes associated with differential methylated sites and progression predictors were then submitted to Ingenuity (IPA) for ontological analysis.

Results: Our analysis identified 44 CpG sites as meeting our criteria for differential methylation, 35 of which were hypomethylated. Most were located within CpG islands or nearby shores or shelves, or upstream enhancers. The 14 associated genes were involved in canonical pathways including B cell development, antigen presentation, tRNA splicing, T helper cell differentiation, and IL4 signaling, among others. Many CpG sites were selected by our machine learning algorithms, the majority of predictive capability being provided by 29 CpG sites selected in at least 5 iterations of the model. Over multiple splits of data into training and testing sets, the predictive modeling strategy achieved a mean error rate of 33.3% on previously unseen validation data. The average receiver operating characteristic (ROC) curve of the model demonstrated an AUC of 0.75 for prediction of rapid progression. Ontologic analysis of genes selected by this algorithm were enriched in various pathways including the role of osteoblasts, osteoclasts, and chondrocytes in RA, NFAT signaling, EGF signaling, IL-10 signaling, TLR signaling, IL-6 signaling, and neuropathic pain signaling, among others.

Conclusion: Our data suggest that differential DNA methylation may be a readily-accessible biomarker for prediction of future radiographic progression in symptomatic knee OA patients. Further work will need to be done to confirm this pattern, and to define the specific cell populations which may be driving this differential methylation. These data further support the association of epigenetic modifications with human osteoarthritis.

Disclosure: M. A. Jeffries, None; **M. Andrews**, None; **J. A. James**, None; **M. B. Humphrey**, None; **A. H. Sawalha**, None.

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Abstract Number: 1220

Comparison of Healthcare Utilization of Patients with Rheumatoid Arthritis Who Are Anti-Cyclic Citrullinated Peptide Antibody Positive Versus Negative

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Background/Purpose: Anti-cyclic citrullinated peptide (CCP) antibody is a marker used in the diagnosis of RA, and it may be useful in identifying patients who are likely to have severe disease activity and joint damage.[1] This study compared RA-related healthcare utilization between patients with RA who are anti-CCP antibody positive versus negative.

Methods: Using electronic medical records from the Henry Ford Health System (HFHS), patients newly diagnosed with RA (International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code 714.0x) were identified between 1/1/09 and 12/31/14. The first RA diagnosis date was the index date. Patients were required to have 12 months of continuous activity in the HFHS (6 months pre- and 6 months post-index). Baseline anti-CCP test was used to categorize patients as positive or negative for anti-CCP antibodies. RA-related healthcare utilization evaluated in the post-index period included: laboratory testing (RF, CRP and ESR), outpatient visits, emergency room visits and hospitalizations. Statistical comparisons between the cohorts were conducted with chi-square tests for categorical variables and t-tests for continuous variables.

Results: The analysis included 103 anti-CCP-negative and 248 anti-CCP-positive patients with RA. Mean age was 58.5 years and 78.9% were female. The anti-CCP-positive cohort had a higher proportion of Black patients than the anti-CCP-negative cohort (44.4 vs 34.0%, p<0.0001). Joint pain was present in 39.3% of patients. Inflammatory back pain was higher in the anti-CCP-negative compared with the anti-CCP-positive cohort (14.6 vs 7.7%, p=0.0465). During follow-up, compared with the anti-CCP-positive cohort, a higher proportion of the anti-CCP-negative cohort was tested for RF (41.7 vs 19.4%, p<0.0001), CRP (71.8 vs 58.5%, p=0.0185) and ESR (66.0 vs 52.0%, p=0.0161). Among those tested, higher proportions of the anti-CCP-positive cohort than the anti-CCP-negative cohort had positive test results (RF: 83.3 vs 25.6%, p<0.0001; CRP: 68.3 vs 58.1%, p=0.1361; and ESR: 82.2 vs 60.3%, p<0.0001); significance was not reached for CRP. RA-related healthcare utilization occurred mainly in the outpatient setting. The proportion of patients with any outpatient physician office visit and the mean (SD) number of visits were highest in the anti-CCP-positive cohort compared with the anti-CCP-negative cohort (96.8 vs 88.3%, p=0.0019 and 5.3 [3.1] vs 3.6 [2.9)], p<0.0001). Most outpatient visits were to a rheumatologist, and the proportion of patients with a visit and mean (SD) number of visits were higher in the anti-CCP-positive compared with the anti-CCP-negative cohort (93.5 vs 73.8%, p<0.0001 and 4.4 [2.5] vs 3.3 [2.3], p=0.0003). Other healthcare utilization in outpatient and other settings was similar between the two cohorts.

Conclusion: Patients with RA who are anti-CCP positive had laboratory results indicative of higher inflammation and disease activity, which likely led to the higher healthcare utilization in the outpatient office setting. Future studies may evaluate differences in treatment outcomes and costs by anti-CCP serostatus. 1. Niewold TB, et al. *Q J Med* 2007;**100**:193–201.

Disclosure: L. Rosenblatt, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **K. Price**, Bristol-Myers Squibb, 3; **Y. Doleh**, Bristol-Myers Squibb, 3; **A. Szymialis**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **M. Eaddy**, Xcenda, LLC, which received research fees from Bristol-Myers for conducting this research, 3; **A. Ogbonnaya**, Xcenda, LLC, 3; **H. C. Shih**, Xcenda, LLC, 3; **L. Lamerato**, Centers for Disease Control, National Cancer Institute, Policy Analysis, Incorporated, Outcomes Research Solutions, Xcenda, LLC, eMAXHealth, Merck Pharmaceuticals, Pfizer Pharmaceuticals, Reagan Udall Foundation, 2,Henry Ford Health System, 3.

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Abstract Number: 1221

Environmental Scan of Rheumatoid Arthritis Patient Registries Around the World: An Omeract Initiative

Natalia V. Zamora[1], Maria A. Lopez-Olivo[2], Robin Christensen[3], Niti Goel[4,5], Lars Erik Kristensen[6], Vibeke Strand[7], Jeffrey R. Curtis[8], Beverly Shea[9] and Maria Suarez-Almazor[10], [1]Section of Rheumatology and Clinical Immunology, The University of Texas, MD Anderson Cancer Center, Houston, TX, [2]General Internal Medicine, The University of Texas, MD Anderson Cancer Center, Houston, TX, [3]Musculoskeletal Statistics Unit, The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [4]Rheumatology Center of Excellence, Quintiles, Durham, NC, [5]Duke University School of Medicine, Durham, NC, [6]The Parker Institute, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Copenhagen, Denmark, [7]Biopharmaceutical Consultant, Portola Valley, CA, [8]Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [9]Department of Clinical Epidemiology & Biostatistics, McMaster University, Health Science Centre Hamilton, Ontario, ON, Canada, [10]Section of Rheumatology and Clinical Immunology, Department of General Internal Medicine, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA., Houston, TX

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Background/Purpose: Patient registries both disease-and drug-based complement information obtained from clinical trials. Long-term

outcomes studies can provide information useful for patients. The Agency for Healthcare Research and Quality (AHRQ) has developed a guide to standardized registries in order to optimize their quality. Objectives: To identify worldwide registries assessing patients with rheumatoid arthritis (RA) and describe their collected and reported variables. To evaluate the reporting of quality components in RA registries.

Methods: We performed an environmental scan to identify registries collecting data on patients with RA. The sample of registries was identified through: i) Google, ii) PubMed, and iii) clinicaltrials.gov. We also manually searched the list of references of selected reviews on this topic. One author selected the registries and two additional investigators reviewed the list for accuracy and provided additional registry names and references. Registry characteristics and variables were summarized and their differences explored to provide a preliminary assessment of their current strengths and limitations. We also evaluated the quality components of each registry using the basic elements of good practice developed by AHRQ. We considered the domain as reported when at least one of the following items was provided: i) planning, ii) design iii) data elements and sources, and iv) ethics, privacy and governance. Descriptive statistics were performed.

Results: We identified 90 worldwide registries. Out of the total, 59% (53) were patient-based registries and 41% (37) drug-based registries. Drug-based registries primarily evaluating biologic therapies and 83% of them, also included patients with other inflammatory arthritis with biologic treatment. The reported information was different if it was a patient or a drug-based registry: Radiological information, seropositivity, measures of socio-economic status, work disability and patient reported outcomes such as functional capacity; were more frequently reported in patient-based registries ($p<0.05$). On the other hand, comorbidities and biologic related outcomes such as adverse events and response, were most liked to be reported in drug-based registries ($p<0.05$). We have not found any difference between both registries in reporting in: self-reported patient disease indices, quality of life, fatigue, sleep, depression and stiffness. Regarding reporting of quality domains, the domain most frequently reported in all registries was data elements and sources (82%). Planning, design and ethics, privacy, and governance were reported less frequently (12%, 19% and 27%, respectively). We have not found any significant difference in reporting between drug and patient-based registries.

Conclusion: Our preliminary results showed that a broad variety of outcomes are collected in registries of patients with RA. Efforts should be made to standardize and to enhance the quality of collecting and reporting elements of good practice for RA patient registries.

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Abstract Number: 1222

A Systematic Review of Consumer Perceived Health Service Needs Related to Osteoarthritis

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Background/Purpose: Osteoarthritis (OA) is a common cause of pain and disability. The patients' perception of health care influences their involvement in management, affecting health outcomes and health system utilisation. Thus it is important to understand the consumer's perceived health service needs in OA. The aim of this systematic review is to identify evidence regarding the consumers' perceived health service needs regarding OA.

Methods: A systematic literature review of the MEDLINE, PsychINFO, EMBASE and CINAHL databases was performed to capture information regarding consumer perceived health service needs related to OA (1990 to May 2015). Themes were identified to provide a

systematic review of the existing literature.

Results: 1053 manuscripts were identified by the search strategy, of which 18 articles were relevant. Of these, 7 studies used quantitative methods, 10 used qualitative and 1 used mixed methods. These themes emerged (> 2 papers): 1) Patients' valued being in an individualised relationship with their practitioner. Insufficient practitioner knowledge, an emphasis on analgesic therapies, rejection of alternative medicine options, and poor practitioner communication skills resulted in consumer dissatisfaction. 2) Complementary and alternative medicine use was prevalent amongst OA patients, primarily driven by desire for analgesic relief. The accessibility, empathy, interpersonal skills and holistic patient approach to care contributed to patient satisfaction with complementary and alternative medicine. 3) Attitudes towards medication use was variable. Fear of side effects was the biggest concern. Baseline pain levels and financial constrains impacted the choice of medication used. 4) Patients perceive a need for physiotherapy and exercises for OA, however accessibility was the main barrier to this. This review generated limited studies on geriatric populations and patients from developing countries or non-English speaking backgrounds. There was a paucity of data relating to patient waiting times for specialist review, specialist fees and medication costs and the ease of medication administration.

Conclusion: Health service delivery in OA is largely driven by patient perceived needs. Aligning perceived needs with health care requirements is important in order to obtain better outcomes in OA. This review revealed that many patient perceived health service needs are aligned with current OA management guidelines. It also identified the barriers to health service implementation. This review also highlights significant gaps in the literature relating to a number of consumers' perceived needs. A better understanding of these needs may guide the provision of relevant services for those with OA, with the view to optimize patient outcomes and healthcare system utilisation and efficiency.

Disclosure: **M. C. Papandony**, None; **A. E. Wluka**, Arthritis and Osteoporosis Victoria, 2,Nhmrc career development fellowship, 2; **F. M. Cicuttini**, None; **Y. Wang**, None; **L. Chou**, None; **K. L. Seneviwickrama**, None; **K. Lasserre**, None; **A. Teichtahl**, None; **A. M. Briggs**, None.

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Abstract Number: 1223

The Cost of Confronting Osteoporosis:Cost Study of a Fracture Liaison Service

Gabor Major[1,2], Rod Ling[3,4], Andrew Searles[3,4], Fiona Niddrie[5], Ayano Nakayama[6], Elizabeth Holliday[4,7], John Attia[4,7] and Nikolai Bogduk[4,6], [1]Rheumatology, Bone and Joint Institute, John Hunter Hospital NSW Australia, Newcastle, Australia, [2]Medicine, University of Newcastle, Newcastle, Australia, [3]Health Economics, Hunter Medical Research Institute, Newcastle, Australia, [4]University of Newcastle, Newcastle, Australia, [5]Rheumatology, Bone and Joint Institute,John Hunter Hospital, Newcatle, Australia, [6]Rheumatology, Bone and Joint Institute,John Hunter Hospital, Newcastle, Australia, [7]Hunter Medical Research Institute, Newcastle, Australia

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Background/Purpose: Services that actively seek out and identify patients with fractures following a minimal trauma injury have been promoted as the most effective means of addressing the wold wide increasing incidence of osteoporotic fractures. Implementation however has been hampered by the paucity of information about the cost effectiveness of this approach

Methods: *Design*: To undertake a detailed costing of operating a fracture liaison service (FLS) and compare the total direct cost of re-fracture management of a cohort of patients (n=515) processed over a 6 month period, and followed for 3 years with the refracture management costs of a contemporaneous cohort of patients (n=414) seen at a hospital without a FLS. *Determination of costs*: Components of the care and entered as a cost centre in a microcosting model created in a Microsoft® Excel workbook. The model compared costs between the FLS and Usual Care. Sensitivity analyses were performed on a number of variables that had uncertain value. Cost of labour, infrastructure and consumables were calculated from the relevant public sources. Medical consultations, investigations and treatment costs were derived from reference tables of the Australian Medical and Pharmaceutical Schedules of Benefits. Costs of re-fracture management were derived from published costing of fracture treatments in Australia. Health inflation calculations for 2015/16 were done with reference to the Total Health Price Index and Industry Wide Index (AIHW). To allow comparison of the different cohort sizes the FLS costs were spread over 3 years and given for every 1,000 patients processed.

Results: Table 1. Component costs of FLS per 1000 patients processed

Cost Centre /Activity	Cost ($ AUS)
Reviewing emergency department records	$30,143
Contacting patients	$42,732
Clinical assessment and treatment	$364,707
Follow up	$23,018
Total	**$468,601**

Table 2. Comparison of costs of treatment between a hospital with a fracture liaison service (FLS) and usual care (Per 1,000 patients)

	Re-fractures over 3 years	Total Cost	Saving
	(n)	($AUS)	($AUS)
Hospital with FLS	150	$2,883,937	
Usual Care (no additional cost)	212	$3,421,653	$537,716
5% of Usual Care patients treated	212	$3,518,584	$634,648
15% of Usual Care patients treated	212	$3,712,447	$828,510

Conclusion: From the perspective of the health system a FLS generates a significant gain, in opportunity costs with a rounded net positive of effect of $540,000 - $830,000 per 1,000 patients processed.

Disclosure: G. Major, None; **R. Ling**, None; **A. Searles**, None; **F. Niddrie**, None; **A. Nakayama**, None; **E. Holliday**, None; **J. Attia**, None; **N. Bogduk**, None.

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Abstract Number: 1224

Healthcare and Research Priorities of Adolescents and Young Adults with Systemic Lupus Erythematosus: A Mixed-Methods Study

David Tunnicliffe[1,2], Davinder Singh-Grewal[3,4,5], Jonathan Craig[1,6], Martin Howell[1,7], Peter Tugwell[8], Fiona Mackie[9,10], Ming-Wei Lin[3,11], Sean O'Neill[12], Angelique Ralph[1,6] and Allison Tong[1,6], [1]Sydney School of Public Health, University of Sydney, Sydney, Australia, [2]Centre for Kidney Research, Children's Hospital at Westmead, sydney, Australia, [3]Sydney Medical School, University of Sydney, Sydney, Australia, [4]Department of Rheumatology, The Sydney Children's Hospital Network, Sydney, Australia, [5]Faculty of Medicine, University of New South Wales, Sydney, Australia, [6]Centre for Kidney Research, Children's Hospital at Westmead, Sydney, Australia, [7]Centre for Kidney Research, Children's Hospital at Westmead, Sydne, Australia, [8]Center For Global Health, Institute of Population Hlth, Ottawa, ON, Canada, [9]School of Women's and Children's Health, University of New South Wales, Sydney, Australia, [10]Department of Nephrology, The Sydney Children's Hospital Network, Sydney, Australia, [11]Department of Immunology, Westmead Hospital, Sydney, Australia, [12]University of New South Wales, Sydney, Australia

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Background/Purpose: The care of adolescents and young adults with systemic lupus erythematosus (SLE) is particularly challenging. The disease may be severe, adolescent patients have complex medical and psycho-social needs, and they must navigate the transition to adult services. To inform patient-centered care we aimed to identify the healthcare and research priorities of adolescents and young adults with

SLE and describe the reasons underpinning their priorities.

Methods: Face-to-face, semi-structured interviews and focus groups were conducted with patients with SLE, aged from 14 to 30 years, from five centers in Australia. In five allocation exercises, participants allocated ten tokens (i.e. votes) to 1) research topics (medical management, prevention and diagnosis, lifestyle and psychosocial), 2-4) research questions associated with research topics, and 5) healthcare specialties, and discussed the reasons for their choices. Descriptive statistics were calculated for votes and qualitative data was analyzed thematically.

Results: From the 26 participants, there was an undifferentiated allocation of votes to research topics and associated research questions. They allocated their votes towards medical and mental health specialties in the management of SLE, whilst fewer votes were given to allied health. Seven themes underpinned participants' priorities: improving service shortfalls, strengthening well-being, ensuring cost efficiency, minimizing family/community burden, severity of comorbidity or complications, reducing lifestyle disruption, and fulfilling future goals.

Conclusion: Young patients with SLE value comprehensive care, in particular, rheumatology, nephrology and mental health. Research on improving psychological health and self-management of symptoms may improve treatment satisfaction and health outcomes for adolescents and young adults with SLE.

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Abstract Number: 1225

Serum Uric Acid Testing Practices over Five Years Among Incident Gout Cases

Dena H. Jaffe[1], Arriel Benis[2], Natalia M. Flores[3], Hagit Gabay[2], Robert Morlock[4], Alyssa Klein[5], Dana Y Teltsch[6], Jonathan Chapnick[7], Becca Feldman[2], **Yair Molad**[8], Shmuel M Giveon[9] and Maya Leventer-Roberts[2], [1]Health Outcomes Research, Kantar Health, Jerusalem, Israel, [2]Clalit Research Institute, Clalit Health Services, Tel Aviv, Israel, [3]Kantar Health, Foster City, CA, [4]4939 Directors Place, Ardea Biosciences, Inc., San Diego, CA, [5]AstraZeneca, Gaithersburg, MD, [6]Evidera, Lexington, MA, [7]Kantar Health, Horsham, PA, [8]Rheumatology, Rabin Medical Center, Beilinson, Petah Tikva, Israel, [9]Clalit Health Services, Tel Aviv, Israel

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Background/Purpose: Gout is a chronic inflammatory disorder associated with elevated levels of serum uric acid (sUA), resulting in urate crystal deposits in soft tissues. Uncontrolled gout can result in bone erosion, joint destruction, kidney stones, uric acid nephropathy, and other organ damage. Gout is treatable with medication and lifestyle change. Long-term sUA monitoring is needed to confirm that patients are achieving target levels (≤6 mg/dL, or <5 mg/dL in more severe cases). The study objective is to describe incident cases of gout and characterize these patients by sUA testing during the subsequent 5 consecutive years.

Methods: Data from Clalit Health Services were used to identify incident cases of gout (1/1/2003-31/12/2009) among members ≥25 years old with continuous enrollment in Clalit for 1 year prior to and 5 years subsequent to diagnosis (index date). Cases were identified based on the following criteria: a) 1 diagnosis of gout from a hospital or specialist visit; or b) ≥2 diagnoses of gout from a general practitioner (GP) visit and either elevated sUA (>6 mg/dL) or a purchase of colchicine or allopurinol. Cases were excluded if a member was concurrently diagnosed with a disease known to affect sUA (eg, renal insufficiency, cancer, Familial Mediterranean Fever). sUA testing practices during the 5-year follow-up period were defined as: full (≥1 test per year), moderate (≥1 test per year for 3 or 4 years), low (≥1 test per year for 1 or 2 years) and no testing (no tests performed). Demographics, clinical characteristics, comorbidities, concurrent medications, and healthcare utilization were examined and stratified by testing practices. Chi-square tests were used to test for differences between groups.

Results: We identified 15,598 incident gout cases meeting the inclusion criteria. Mean age was 59.3±14.5 years, 79.7% were male, and 35.7% were of higher socioeconomic status. Patients' clinical history indicated that 15.2% were current smokers and 32.4% were obese.

Prevalence of pre-existing comorbidities including CVD, diabetes and hypertension was 26.8%, 20.8%, and 52.5% respectively, and mean Charlson Comorbidity Index was 0.9±1.3. The distribution of annual sUA testing over the 5-year follow up in this cohort was: 5,445 (34.9%) patients had full testing, 6,678 (42.8%) had moderate testing, 3,196 (20.5%) had poor testing, and 279 (1.8%) had no testing. At the end of follow-up, 25.6% of patients' last documented sUA was ≤6 mg/dL. Among patients in the groups with sUA ≤6 or ≥10 mg/dL, close to 39% had full testing, while among those with sUA between 6.1-9.9 mg/dL, full testing ranged from 31.6%-35.7%.

Conclusion: Consistent with previous findings, gout patients in Clalit were on average older adults, predominately men and with concurrent comorbidities. Over three-quarters of newly diagnosed gout patients performed an annual sUA testing during at least 3 of the 5 years of follow-up. Further study is required to assess the association between regular testing and health outcomes.

Disclosure: D. H. Jaffe, Kantar Health, 3; **A. Benis**, Clalit Research Institute, 3; **N. M. Flores**, Kantar Health, 3; **H. Gabay**, Clalit Research Institute, 3; **R. Morlock**, Ardea Biosciences Inc, 3; **A. Klein**, AstraZeneca, 3; **D. Y. Teltsch**, Evidera, 3; **J. Chapnick**, Kantar Health, 3; **B. Feldman**, Clalit Research Institute, 3; **Y. Molad**, None; **S. M. Giveon**, None; **M. Leventer-Roberts**, Clalit Research Institute, 3.

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Abstract Number: 1226

Evaluation of the Association Between C-Reactive Protein and Anti-Citrullinated Protein Antibody in Rheumatoid Arthritis: Analysis of Two Clinical Practice Data Sets

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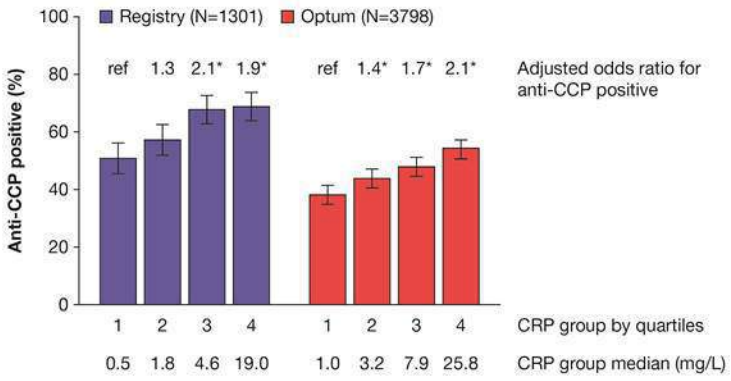
Background/Purpose: The association between inflammatory markers such as CRP or ESR and joint damage has been widely established in RA. Autoantibodies such as RF and anti-cyclic citrullinated peptide (anti-CCP) are also associated with severe joint damage. However, there are limited data on the association between markers of inflammation and autoantibodies. The objective of this analysis was to evaluate the association between CRP and anti-CCP using clinical practice data sets.

Methods: Two data sets were used: a single academic center, prospective, observational cohort registry of patients (pts) with RA, and the Optum Clinformatics Data Mart (Optum), which includes the Optum Medicare data. The registry was established in 2003 and primarily comprises pts with established RA. In Optum, pts with two ICD-9 codes for RA (714.0) and a prescription for a DMARD between Jan 2007 and Dec 2014 were identified. For inclusion in the current study, pts were required to have anti-CCP and CRP baseline values. The high normal concentration for anti-CCP was 19 U/ml in both data sets, and for CRP it was 5 mg/L in the registry and 4.9 mg/L in Optum. Pts meeting inclusion criteria were placed into CRP groups (grps) by quartiles and anti-CCP positivity was evaluated in each grp. Additional sensitivity analyses were conducted by grouping pts into two CRP grps, i.e., CRP ≥5 vs <5 mg/L. Multivariate logistic and linear regression for anti-CCP positivity were evaluated with CRP as an independent variable and controlling for baseline covariates. In the registry analysis, we adjusted for age, sex, race, BMI, Charlson co-morbidity index, RA duration, DAS28 (CRP) and treatment with biologic DMARDs. In Optum, we adjusted for age, sex, region, incident RA, co-morbidities, use of steroids, use of NSAIDs, use of salicylates and initiating a DMARD within 90 days after the index date.

Results: A total of 1309 pts from the registry and 3798 from Optum were included in the analysis. Pts in the high (vs low) CRP grps were older (mean [SD] 60.1 [13.2] vs 51.4 [14.0] yrs in the registry; 60.0 [15.7] vs 54.4 [14.9] yrs in Optum), had more males (23 vs 13% in the registry; 30 vs 21% in Optum) and a greater proportion of pts was anti-CCP positive (Figure). Based on multivariate logistic models, pts in CRP grp 3 vs grp 1 (odds ratio [95% CI] 2.08 [1.43, 3.03], p<0.001) and grp 4 vs grp 1 (1.87 [1.23, 2.84], p=0.003) had significantly higher odds of being anti-CCP positive in the registry. Similar findings were observed in Optum: grp 2 vs grp 1 (1.37 [1.15, 1.63], p<0.001); grp 3 vs grp 1 (1.68 [1.42, 2.00], p<0.001); and grp 4 vs grp 1 (2.09 [1.76, 2.48], p<0.001). The findings from the linear regression model and sensitivity analysis were consistent with those of the logistic regression model.

Conclusion: Analyses based on two independent data sources indicate that there is an association between CRP and anti-CCP levels in pts with RA. Pts with a high CRP level are more likely to be anti-CCP positive, with a higher anti-CCP level.

Figure. Percentage of anti-CCP positive patients by CRP groups in the registry and Optum



*p<0.01; anti-CCP=anti-cyclic citrullinated peptide

Disclosure: E. Alemao, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **Z. Guo**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **L. Burns**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **M. Frits**, None; **J. Coblyn**, None; **M. Weinblatt**, BMS, 2,BMS, 5; **N. Shadick**, UCB, Amgen, Crescendo Biosciences, BMS, Mallinckrodt, 2,Bristol-Myers Squibb, 5.

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Abstract Number: 1227

Clinician-Led Development of a Standardised Term Set for Rheumatic and Musculoskeletal Disorders Allows Easy Creation of Large-Scale ICD-10 and Snomed CT Mapped Datasets from Routinely Collected Clinical Data

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Background/Purpose: Clinicians use a range of different terms to describe the same clinical concept. Whilst these variations seldom lead to confusion among clinicians they make it difficult to aggregate, analyse and share clinical data. The ability to create and share large data sets has become increasingly important in the age of personalised medicine when it is not possible to collect enough data from a single centre to tease out the importance of phenotypic variations. Similar restrictions apply when studying geographical and temporal trends in case mix.

Methods: Working with the British Society for Rheumatology (BSR) the authors have developed a list of diagnostic terms (standard term set (STS)). The BSR Specialised Adult Rheumatology Specification was used as template. The principles underlying the structure of the STS are that it should reflect anticipated use cases for the collected data, the set should serve equally the needs of general rheumatology departments & highly specialised units, the set should allow broad concepts and more granular ones to be collected with equal ease and that it should be mapped to ICD 10 and SNOMED CT as fully as those instruments permit. A hierarchical structure to the STS allowed aggregation of many concepts to a single parent while retaining the ability to separate out conditions of particular interest. The STS will form the core of a much richer data model for RMDs which will include minimum data sets for each concept in the STS and capture comorbidities, phenotypic variables and outcome measures. In this phase the authors have made no attempt to capture diagnostic uncertainty, detailed phenotype, secondary diagnosis or co-morbidities. Where there was a need to reflect new knowledge or new classification of diseases the authors have also undertaken a programme of SNOMED CT content improvement in collaboration with the UK Health and Social Care Information Centre (HSCIC) to improve representation of current concepts and ring fence it for ease of future use. The authors also developed a synonym table which maps physicians combined clinical vocabulary to the matching STS. The final set for the first phase of this coding project was arrived at after a number of iterative editorial cycles with valuable input from local musculoskeletal coding leads for ICD 10, HSCIC and lead clinicians from pilot sites. The STS was released to pilot sites in early 2016

along with a detailed cover note, reference guide for users, agreed “minimal data set” and hyperlinks to ICD 10 and SNOMED CT browsers. Minimum data set in this pilot phase comprised of patient identifiers, demographics, appointment date and type, diagnosis and outcome.

Results: The first 3 months of the pilot have shown that large volumes of data can be collected and shared using the STS with minimal additional workload for the clinician. It has been successfully implemented in various clinic settings ie community, district general hospital and large teaching hospitals. It serves the purpose of both general & special interest clinics. The STS can be used to capture data using paper, electronic & digital care records. It can be used by a single user or entire department. For the first time it has allowed clinical data collected during routine outpatient consultations to be used for a variety of secondary purposes including case-mix analysis, commissioning, workforce planning, audit and identification of research cohorts. Data collection is ongoing. Results will be presented at the ACR meeting.

Conclusion: Clinicians should lead the development of health informatics solutions. Software developers should work closely with health professionals to build platforms that collect data as part of routine care using models that place data in context so as to maximise secondary use ie data collected once can be used with equal ease to provide care for an individual or study trends at a population level.

Disclosure: I. Pande, None; **I. Gaywood**, None.

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Abstract Number: 1228

Prescribing for Children with Rheumatologic Disease: Differences Between Pediatric and Adult Rheumatologists

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Background/Purpose: Rheumatologic diseases affect 300,000 children in the United States and are associated with significant morbidity.[1,2] Due to a national shortage of pediatric rheumatologists (PR),[2] an estimated half of US children with rheumatologic disease are being cared for by adult rheumatologists (AR).[2,3] However, many AR report being uncomfortable caring for children and do not perceive themselves as up to date.[4] How variations in treatment relate to subspecialty, fellowship training, and information resources are not known.

Methods: Two parallel, cross sectional mail surveys with a focus on juvenile idiopathic arthritis (JIA) were administered to a random sample of 193 PR and 500 AR using the American College of Rheumatology membership file. Bivariate analysis was conducted for items common to both surveys.

Results: The response rate was 62.1% for AR (N=306) and 72.3% for PR (N=138). Only 23% of responding AR (N=69) reported caring for children with JIA. Of these, 94% strongly agreed/agreed that they are comfortable diagnosing JIA; however, only 76% report being comfortable treating JIA. Clinical vignettes highlighted several prescribing differences (Table 1). Forty-eight percent of AR, and 31% of PR, felt medications to treat JIA did not have clear dosing guidelines. Though PR initiated DMARDs and biologics earlier, after three months the selected treatments for JIA were quite similar. Co-management of JIA patients by adult and pediatric rheumatologists is infrequent and its acceptance seems limited.

Conclusion: Nearly a quarter of surveyed adult rheumatologists care for children with JIA, with most limiting their practice to older children. There was more discomfort in treating JIA than diagnosing it, and there were significant prescribing differences. Both adult and pediatric providers reported a lack of adequate dosing/treatment resources. Easily accessible and up-to-date treatment and dosing guidelines, as well as exposure to pediatric rheumatology in fellowship, would further enhance the care of children with JIA and facilitate collaboration between adult and pediatric providers. 1. Sacks JJ. Helmick CG. Luo YH. Ilowite NT. Bowyer S. Prevalence of and annual

ambulatory health care visits for pediatric arthritis and other rheumatologic conditions in the United States in 2001-2004. *Arthritis Rheum.* 2007; 57(8): 1439-1445. 2. Duke EM. Report to Congress. The Pediatric Rheumatology Workforce: A Study of the Supply and Demand for Pediatric Rheumatologists. http://bhpr.hrsa.gov/healthworkforce/reports/ped_rheumatology/ 3. Mayer ML, Sandborg CI and Mellins ED. Role of pediatric and internist rheumatologists in treating children with rheumatic diseases. *Pediatrics* 2004; 113(3): 173-181. 4. Sherry DD, Wallace CA, Kahn S. Pediatric rheumatology in adult rheumatology practices in Washington State. *Arthritis Rheum.* 1996; 39(7):1218-1221.

Table 1: Treatment Selection by JIA Subtype Based on Clinical Vignettes

	(a) 2 yr old with Oligoarticular JIA		(b)) 6 yr old with Systemic Onset JIA		(c) 9 yr old with Polyarticular JIA		(d) 14 yr old RF+ Polyarticular JIA	
	Adult N=25	*Pediatric N=128*	*Adult N=33*	*Pediatric N=128*	*Adult N=39*	*Pediatric N=128*	*Adult N=59*	*Pediatric N=127*
NSAID (%)								
	80	89	**73**	**88#**	90	95	**79**	**93***
METHOTREXATE (%)								
Initial	**12**	**2#**	39	55	**44**	**74***	81	89
Refractory	32	52	38	27	**46**	**24#**	14	9
Total	44	54	77	82	90	98	95	98
TNF INHIBITOR (%)								
Initial	0	0	3	1	0	5	**7**	**21***
Refractory	16	9	19	32	***54**	**79***	77	74
ORAL STEROIDS (%)								
			64	69	23	25	38	42
STEROID INJECTION (%)								
Initial	48	63			23	17	17	9
Refractory	28	28						
ANAKINRA (%)								
Initial			12	10				
Refractory			**38**	**56#**				
ABATACEPT (%)								
Initial							0	0
Refractory							3	12

* p<0.01, *p<0.05

1. Sulfasalazine, hydroxychloroquine, leflunomide selected by fewer than 10% of respondents, results not shown.

2. The N for adult rheumatologist varies, as only those respondents who reported seeing children of each age were included in analyses.

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Abstract Number: 1229

Stakeholder Needs Assessment for a New Model of Care for Pediatric Rheumatology in Ontario

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Background/Purpose: Twenty-five pediatric rheumatologists (PR) service a population of 14 million Ontarians. Patients may travel up to 1500 km to be seen by a PR practising in tertiary healthcare centres. To facilitate care to patients living in distant communities we propose using a new model: local Advanced Clinician Practitioners in Arthritis Care (ACPAC) using telemedicine to engage with PRs. There are more than 50 ACPACs in Ontario who may be able to provide pediatric patient care via this model. The following are results from the first phase of this project: a stakeholders' needs assessment for a new Model of Care (MOC) for pediatric rheumatology in Ontario.

Methods: Three stakeholder groups were anonymously surveyed: (1) Adult rheumatologists' opinions on treating pediatric patients; (2) ACPACs' interest and availability to see pediatric patients; and (3) Patients'/caregivers' perception of visit burden and their knowledge and attitudes towards alternate MOCs. Surveys were distributed to patients/caregivers who travelled >25 km for their appointment one of two tertiary healthcare facilities: The Hospital for Sick Children (SickKids) in Toronto, Ontario or London Health Sciences Centre (LHSC) in London, Ontario. Quantitative data were summarized using descriptive statistics and qualitative data were analyzed using grounded theory.

Results: 91/186 (49%) adult rheumatologists responded, of which 18 (20%) indicated that they saw pediatric patients. The majority indicated that they would prefer that some or all of their pediatric patients be cared for by a pediatric rheumatologist. 27/44 (61%) ACPACs responded, of which 6 (22%) indicated that they would have salary/time to receive additional training or hold additional clinics to see pediatric patients.

Patient/ Caregiver Survey	Number of Respondents	Travelled >50km	Travelled >200km	Would use telemedicine to avoid cost of clinic visit	Not aware of availability of telemedicine	Comfortable seeing an ACPAC	Spent >$50 travelling to their appointment	Missed ≥1 day of work
Toronto	111/134 (83%)	89/111 (80%)	13/111 (12%)	36/110 (33%)	86/111 (77%)	104/111 (94%)	36/111 (32%)	53/99 (54%)
London	130/131 (99%)	103/128 (80%)	16/128 (13%)	33/119 (28%)	96/126 (76%)	125/126 (99%)	53/130 (41%)	66/116 (57%)

Several themes were identified including the importance of seeing the healthcare team in person for physical examination, hesitancy to use telemedicine due to lack of experience, and preference for an assessment closer to home. Some indicated that telemedicine may be appropriate for certain situations such as follow-up visits or bloodwork results. Those who indicated a preference for telemedicine indicated that it would reduce time away from school/work. Parents indicated that jobs were in jeopardy due to missed time and that the high cost of parking was a deterrent.

Conclusion: A MOC integrating ACPACs, telemedicine, and PRs may improve local access to pediatric rheumatology care while reducing the burden of travel and cost to families. Barriers to this new model include the lack of awareness about the role of telemedicine and how it can be combined with ACPACs to facilitate a patient appointment.

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Abstract Number: 1230

Allopurinol Use and the Risk of Stroke in the Elderly

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Background/Purpose: To assess the effect of allopurinol use on the risk of stroke in the elderly

Methods: We used the 5% random sample of Medicare beneficiaries from 2006-2012 to study the association of new allopurinol initiation and incident stroke. We used multivariable-adjusted Cox regression models adjusted for age, gender, race, Charlson index, and cardio-

protective medications (beta-blockers, ACE inhibitors, diuretics, statins) to calculate hazards ratio (HR) with 95% confidence intervals (CI). Sensitivity analyses adjusted for coronary artery disease (CAD) risk factors including hypertension, hyperlipidemia, diabetes, and smoking instead of Charlson index.

Results: Among 28,488 eligible episodes of incident allopurinol, 2,177 ended in incident stroke (7.6% episodes). In multivariable-adjusted analyses, allopurinol use was associated with 9% lower hazard ratio for stoke, 0.91 (95% CI, 0.83 to 0.99). Compared to no allopurinol use, allopurinol use durations of 181 days to 2 years, 0.88 (95% CI, 0.78 to 0.99) and >2 years, 0.79 (95% CI, 0.65 to 0.96) were significantly associated with lower multivariable-adjusted hazard of stroke. Sensitivity analyses adjusted for CAD risk factors confirmed these findings. In subgroup analyses, significant associations were noted between allopurinol use and the risk of ischemic stroke, 0.89 (95% CI, 0.81 to 0.98); no significant associations were noted for hemorrhagic stroke, 1.01 (95% CI, 0.79 to 1.29).

Conclusion: Allopurinol use was independently associated with a lower risk of stroke overall, more specifically ischemic stroke in the US elderly. This protective effect is evident after 6-months of allopurinol use, and the protective effect increases with longer duration of use. Future studies need to examine underlying mechanisms for this novel effect.

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **S. Yu**, None.

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Abstract Number: 1231

Impact of Comorbidity on Health-Related Quality of Life and Healthcare Expenditure in Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid Arthritis (RA) is known to be associated with an increased risk of comorbidity, premature mortality, and disability. We investigated the effect of comorbidity on health-related quality of life (HRQOL) and total healthcare expenditure (TE) in patients with RA.

Methods: Adult RA patients were identified from the Medical Expenditure Panel Survey 2010 to 2012 data. Twenty-six comorbid conditions were identified including cardiovascular, endocrine, respiratory, psychological, cancer, skin, vision, and gastrointestinal disorders. The Short Form (SF)-12 physical component summary (PCS) and mental component summary (MCS) scores for HRQOL, and TE (2012 USD) were summarized based on the number of comorbidity as well as type of comorbidity using descriptive statistics. Outcomes were further investigated using multivariable regression analyses. Adjusted mean PCS/MSC scores and TE were reported along with bootstrapped confidence intervals. All analyses considered sampling strata and weights in survey design.

Results: A total of 1,982 patients with RA were identified representing 18 million US population. The mean (SE) age was 61.2 (0.53) years and mean (SE) duration of RA was 17.2 (0.57) years. Approximately 30.5% had 1 to 2, 34.5% had 3 to 4 and 23.6% had ≥5 comorbid conditions. The most prevalent comorbidities were cardiovascular (73.4%) and endocrine disorders (35.6%). The mean (SE) PCS/MCS scores for RA with comorbidity were lower compared to RA without comorbidity [PCS: 32.3 (0.58) vs. 37.5 (1.93), p=0.012; MCS: 42.8 (0.59) vs. 47.3 (1.66), p= 0.013]; whereas the mean (SE) TE for RA with comorbidity was higher compared to RA without comorbidity [TE: $ 13,951 ($729) vs. $7,947 ($1,393), p<0.001]. Having multiple comorbidities was associated with a significant impact on both HRQOL and TE (Table). Adjusting for confounders, having ³ 5 comorbid conditions was associated with a decrease in PCS/MCS [PCS: -6.75 for ³ 5 comorbidities vs. none; MCS: -7.15 for ³ 5 comorbidities vs. none, respectively] and an increase in TE compared to no comorbidity [$4,637 for 3-4 comorbidities vs. none, $13,842 for ³ 5 comorbidities vs. none, respectively]. Only selected types of comorbidity were associated with changes in MCS/PCS or TE.

Conclusion: Majority of RA patients have at least one comorbidity and substantial number of patients had multiple comorbid conditions. Presence of comorbidity in RA was associated with significant impact in both HRQOL and TE. The impact was higher as the number of comorbidity increases regardless of the type of comorbidity. Table. Adjusted Means (95% Bootstrapped CI) of Health-Related Quality of Life and Total Healthcare Expenditure by Number of Comorbid Conditions

Number of Comorbid Conditions	Physical Component Score	Mental Component Score	Healthcare Expenditure (2012 USD)
None	35.2 (32.0 – 38.1)	46.8 (43.2 – 49.7)	$8,189 ($6,018 - $10,744)
1-2	35.1 (33.5 – 36.5)	42.9 (41.1 – 44.5)	$8,376 ($6,848 - $9,797)
3-4	31.6 (30.3 – 32.9)	42.8 (41.3 – 44.2)	$12,767 ($11,333 - $14,408)
5 or more	28.4 (27.1 – 29.9)	39.6 (38.0 – 41.5)	$21,329 ($18,527 - $24,845)

*adjusted for age, sex, race/ethnicity, marital status, education, insurance, and poverty

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Disclosure: **E. Nyarko**, None; **J. An**, None.

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Abstract Number: 1232

Interdisciplinary Osteoporosis Clinical Working Group and Fracture Liaison Service at Loma Linda University Medical Center (LLUMC): Laying the Groundwork

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Background/Purpose: There is an ongoing effort worldwide to effect quality improvement to address secondary prevention of fractures. Patients who have incurred fractures attributed to osteoporosis have low rates of diagnostic screening and treatment for osteoporosis. An LLUMC Osteoporosis Clinical Working Group spearheaded by the divisions/departments of Rheumatology, Endocrinology, Orthopedics and Geriatrics was established February 2016, with one of the main arms being the Fracture Liaison Service. We determined the most common problems related to primary and secondary prevention, and management. We reviewed the most recent volumes of fractures seen in the hospital through the electronic medical record (EMR).

Methods: A consensus meeting between collaborating specialties was held to discuss system-based practice challenges in managing osteoporosis issues. An October 2015-April 2016 EMR review by our Patient Safety and Reliability Office was done utilizing International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) codes to determine: 1) numbers of fracture patients seen at emergency room and/or hospital, 2) hospital stay length, 3) anatomic sites, and 4) procedural interventions done.

Results: The needs identified in our healthcare system are: 1) improving education of patients about the need to diagnose and treat osteoporosis; 2) improving access to healthcare providers committed to addressing osteoporosis and improving rates of screening and compliance with therapy among patients; 3) improving accessibility to DXA results. A High-Risk Osteoporosis (HRO) line of service generating consults for both inpatient and outpatient services, including interdisciplinary providers, is in progress. FLS certification was obtained by a rheumatologist. Four target groups identified are: 1) Patients who have sustained fractures, 2) Men with osteoporosis, 3) Postmenopausal women needing screening and 4) Patients on steroids. Steps to address solutions include: EMR coordination to optimize consult generation and DXA access, partnership development with Physical Therapy, Emergency Medicine, Hospitalist Medicine, General Medicine, Pulmonology, Ophthalmology, Obstetrics and Family Medicine. EMR review revealed 261 fracture encounters; 136 (52%) encounters for femoral fractures (134 initial, 2 subsequent), and 32 (12.3%) vertebral fracture encounters (31 initial and 1 subsequent). Six vertebral fracture encounters were coded as “age related osteoporosis”. Eight encounters were linked to steroid use codes (4 femur, 2 vertebral, 1 radius and tibia each). Most common length of hospital stay was 3 days (62 encounters; range 1-20 days).

Conclusion: A large number of patients with fractures presented to LLUMC within a seven month period. Interdisciplinary coordination to address specific patient groups with or prone to osteoporosis have been developed. Tracking of outcomes to this initial effort includes

improving bone density screening rates, education of patients, and compliance with therapy. Improving ICD10 coding by providers can help facilitate tracking of outcomes.

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Abstract Number: 1233

A Descriptive Analysis of Real-World Treatment Patterns of Innovator Infliximab (Remicade) and Biosimilar Infliximab in a Treatment NaïVe Turkish Rheumatologic Disease Population

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Background/Purpose: This retrospective healthcare claims analysis examined treatment patterns of innovator infliximab (IFX) and biosimilar infliximab (CT-P13) in a Turkish rheumatologic disease population after CT-P13 availability in July, 2014.

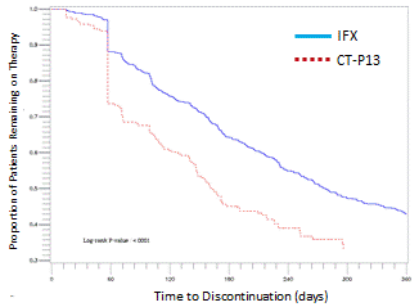
Methods: Adult patients (pts) with ≥1 diagnosis code (ICD-10-CM) for rheumatoid arthritis (RA) were identified in a national Turkish healthcare database during the study period (01DEC2010-01DEC2015). Eligible pts had continuous medical/pharmacy enrollment ≥12 months before and ≥6 months after IFX or CT-P13 initiation (index date). Patients were naïve to IFX or CT-P13 (i.e. had no IFX or CT-P13 within 12 months before the index date). Demographics, concomitant diseases and medications, and treatment patterns, eg., dose, interval, discontinuation, and switch were summarized. Confirmed discontinuation was defined as a switch to another biologic medication or the absence of an index biologic claim for ≥120 days without censoring.

Results: Key results are shown in the Table. A total of 1044 patients initiated either medication. The majority (80%; n=831) initiated IFX. The IFX cohort had a mean age of 42 years; 56% were women and mean follow up was 12 months. The CT-P13 cohort consisted of 213 pts with mean age of 43 years; 58% women; and mean follow up of 9 months. Approximately one-third of pts in each cohort had a concomitant diagnosis of ankylosing spondylitis (AS; TABLE). Other concomitant diseases and medications appeared balanced between cohorts. Pts in the IFX cohort had an average of 5.2 infusions and mean dose of 4.7 vials per infusion approximately every 8 weeks. Pts in the CT-P13 cohort had an average of 3.6 doses and mean dose of 5.8 vials per dispensing approximately 9 weeks apart. A confirmed discontinuation occurred in 55% of the IFX cohort; driven in part by switching. 24% of IFX pts had ≥ 1 biologic switch with 8% initially switching to CT-P13. Time to any discontinuation or censoring of IFX is shown in the Figure and Table. In the CT-P13 cohort, a confirmed discontinuation was observed in 63%; 31% switched to another biologic therapy; and 20% initially switched to IFX. Time to any discontinuation or censoring of CT-P13 is shown in Figure and Table.

Conclusion: These findings in a single country indicate that real world utilization patterns may differ between innovator IFX and CT-P13, with predominantly more patients initiating IFX; greater overall CT-P13 discontinuation and a higher proportion of patients switching from CT-P13 to IFX. Further studies are needed to understand the reasons for these observed differences. Table

	Innovator IFX Cohort (N= 831)		CT-P13Cohort (N=213)	
	N/Mean	%/SD	N/Mean	%/SD
Age (Mean)	42	13	43	12
Gender				
Female	465	56%	124	58 %
Average Length of Follow up Period (in Months)	12	3	9	2
Concomitant Disease During Baseline Period				
Ankylosing Spondylitis	230	28%	70	33%
Psoriatic Arthritis	130	16%	24	11%
Crohn's Disease	65	8%	11	5%
Ulcerative Colitis	64	8%	10	5%
Concomitant RA-Medications During Follow up Period				
Methotrexate	253	30%	69	32%
Sulfasalazine	147	18%	46	22%
Dosing Characteristics				
Average # of doses within follow up period	5.2	2.6	3.6	1.8
Mean # of weeks between doses	8.2	4.2	9.0	4.7
Mean # of days between 1st and 2nd dose	38	37	50	41
Mean # of days between 2nd and 3rd dose	53	33	60	38
Mean # of days between 3rd and 4th dose	65	34	67	31
Switching				
# and % of patients with ≥1 switch	203	24%	66	31%
# of patient switches between Infliximab Types				
Switch to CT-P13	64	8%		
Switch to Innovator Infliximab			42	20%
Discontinuations				
# of Patients Confirmed to Have Discontinued	453	55%	134	63%
Time to confirmed discontinuation (days)	155	93	107	66
Time to any discontinuation or censoring (days):	239	130	169	102

Figure



Disclosure: Y. Yazici, Janssen Scientific Affairs, LLC, 2; **L. Xie**, Janssen Scientific Affairs, LLC, 5; **A. Ogbomo**, Janssen Scientific Affairs, LLC, 5; **D. Parenti**, Janssen Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **A. Teeple**, Janssen Scientific Affairs, LLC, 3; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **I. Simsek**, Janssen Scientific Affairs, LLC, 2.

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Abstract Number: 1234

Does SLE Care in a Lupus Clinic Result in Higher Quality Scores Than in General Rheumatology Clinics?

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Background/Purpose: We compared the quality of care received by SLE patients at two settings within the same academic institution (lupus clinic or general rheumatology clinic) using validated SLE quality indicators (QI).

Methods: 150 consenting, consecutive patients fulfilling the ACR classification criteria for SLE receiving longitudinal care at Rush University Rheumatology outpatient clinic and subspecialty Lupus clinic were recruited. A validated QI survey was updated, modified and administered during participantsÕ routine visit. Retrospective rheumatology medical chart reviews were done for complete evaluation of performance on each QI. The overall performance rate (total number of QIs met by total number of QIs that the participants were eligible for) and performance on 20 QIs were calculated for the two groups and compared using non-parametric tests. P-value <0.05 was considered significant.

Results: 77 patients from sub-specialty lupus clinic and 73 patients from general rheumatology clinic participated. Patients receiving care at lupus clinic had longer disease duration [9.8 ± 7.1 vs. 7.0 ± 7.2 years; P= 0.02] and met more number of ACR criteria [5.3 ± 1.6 vs. 4.6 ± 1.0; P= 0.001] compared to patients from general rheumatology clinics. The overall performance rate was significantly greater among lupus clinic SLE patients [85.8% (IQR: 19.6%) vs. 70.2% (IQR: 11.5%), P= 0.001]. Differences noted among the two groups were in counseling for use of sunscreen (98.7% vs. 83.6%, p=0.001), testing for antiphospholipid antibodies (71.4% vs. 37%, p< 0.001), recommendation for pneumococcal vaccine if on immunosuppressive medication/s (84.8% vs. 48.8%, p< 0.001), bone mineral density test performance (94.2% vs. 54.5%, p<0.001), counselling about drugs (92.2% vs. 80.8%, p=0.04), prescribing a steroid sparing agent and angiotensin-converting enzyme (ACE) inhibitor if eligible(100% vs. 82%, p< 0.007 and 94.4% vs. 58.3%, p=0.03, respectively) and assessment of cardiovascular disease risk (40.3% vs. 15.1%, p=0.01) (Figure 1; Table 1). Patients from lupus clinic were less often on corticosteroids as compared to patients from general rheumatology clinic (32.5% vs. 47.9%, p=0.05).

Conclusion: SLE patients seen in the dedicated lupus clinic had better overall and specific QI performance relative to general rheumatology clinics. This may suggest greater recognition among lupus clinic physicians of the importance of preventive care and disease monitoring among SLE patients. Figure 1: Differences in performance of QIs between Lupus clinic and General Rheumatology clinic (p-value <0.05)

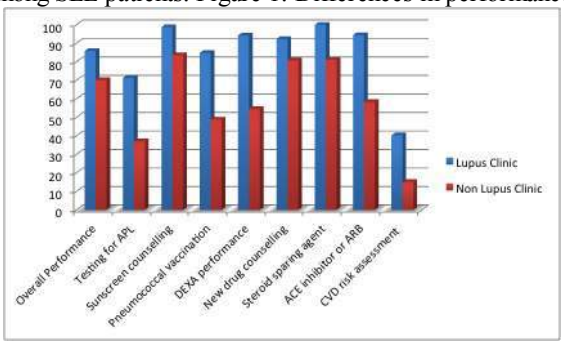

TABLE 1: PERFORMANCE ON QUALITY INDICATORS (QI)

		LUPUS CLINIC			GENERAL RHEUMATOLOGY CLINIC			P-VALUE
QI No.	Description of QI	QI eligible (N)	Met QI (n)	PP (%)	QI eligible (N)	Met QI (n)	PP (%)	
1	ANA, CBC, Platelet, Creatinine, UA at diagnosis of lupus	77	77	100	73	72	98.6	0.49
2	AntidsDNA, C3/4, APL within 6 months of diagnosis	77	55	**71.4**	73	27	37.0	**< 0.001**
3	Counselling for use of sunscreen	77	76	**98.7**	73	61	83.6	**0.001**
4	Infleunza vaccine in last year if on ISM	46	45	97.8	43	38	88.4	0.1
5	Pneumococcal vaccine if on ISM	46	39	**84.8**	43	21	48.8	**<0.001**
6	DEXA if have received ≥7.5 mg/day CS for ≥3 months	52	49	**94.2**	44	24	54.5	**< 0.001**
7	Calcium and Vitamin D if have received ≥7.5 mg/d CS for ≥3 months or is post-menopausal	59	46	78	57	41	71.9	0.45
8	Antiresorptive agent if have received ≥7.5 mg/d CS for ≥1 month & central T score ≤2.5 or h/o fragility fracture	12	12	100	7	7	100	N\A
9	Counselling about drugs at initiation	77	71	**92.2**	73	59	80.8	**0.04**
10	Baseline tests at initiation of drugs	74	73	98.6	72	67	93.1	0.11
11	Tests for drug monitoring	73	66	90.4	69	60	87	0.6
12	Steroid sparing agent if have taken ≥10 mg/day CS for ≥3 months	46	46	**100**	37	30	81.1	**0.002**
13	Follow up tests (UA, CBC, Creatinine) done for LN at every 3 months	19	14	73.7	10	6	60	0.68
14	Treatment with ISM & CS within 1 month of diagnosis of Class 3/4 LN	13	13	100	14	14	100	N\A
15	Antihypertensive if have proteinuria ≥ 300 mg/d or GFR < 60 ml/min & ≥ 2 BP readings > 130/80	15	14	93.3	15	15	100	1.00
16	ACE inhibitor or ARB if have proteinuria ≥ 300 mg/d	18	17	**94.4**	12	7	58.3	**0.03**
17	Assessment of CVD risk & counselling	77	31	**40.3**	73	11	15.1	**0.01**
18	Tests in pregnancy (AntiSSA/SSB, APL)	9	6	66.7	7	2	28.6	0.32
19	Treatment of APS in future pregnancies	1	1	100	1	1	100	N\A
20	Reproductive health counselling	29	26	89.7	20	13	65.0	0.07

Abbreviations: PP - Performance percentage, ANA - Antinuclear antibody, CBC - Complete Blood Count, UA - Urinalysis, APL - Anti-phospholipid antibodies, ISM - Immunosuppressive medications, CS - Corticosteroids, HCQ - Hydroxychloroquine, MTX - Methotrexate, MMF - Mycophenolate mofetil,LN - Lupus Nephritis, ARB - Angiotensin receptor blocker, CVD - Cardiovascular Disease, APS - Antiphospholipid antibody syndrome.

Disclosure: S. Arora, None; **A. Nika**, None; **J. Block**, None; **W. Sequeira**, None; **J. Yazdany**, None; **L. Trupin**, None; **M. Jolly**, Pfizer Inc, 9.

Abstract Number: 1235

Healthcare Utilization and Multimorbidities Among Adult Patients with Juvenile Idiopathic Arthritis

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Background/Purpose: Active juvenile idiopathic arthritis (JIA) is commonly associated with high healthcare costs in children. The disabling consequences and multimorbidities often manifest, however, in adulthood. Combining a large clinical dataset on patients at a rheumatology clinic with administrative data on healthcare utilization and costs allows investigating the disease burden to the society. Our aim was to explore the multimorbidities and detailed clinical characteristics in adult JIA patients and to investigate which factors affect their healthcare utilization.

Methods: The patients attending Jyväskylä Central Hospital rheumatology unit, Finland, are enrolled prospectively in a structured digital database, from which we identified all JIA patients. Data is collected systematically on factors such as date of diagnosis, laboratory tests, questionnaire scores, joint counts, functional capacity, and medications on most rheumatology unit visits. We combined this population-based clinical data with well-recorded administrative data on all public healthcare visits, both in primary and specialty care, on fiscal year 2014 to depict healthcare utilization. The data includes visits to physicians and allied health care professionals in outpatient care as well as inpatient care. Diagnoses are recorded as either ICPC-2 or ICD-10, and also converted to a broader disease classification. Associations between clinical characteristics and healthcare costs were investigated with logistic regression.

Results: Of 182 JIA patients (74% women, mean age 34.9 ± 13.6 (SD)), we have data on healthcare utilization from 2014 on 102 (56%) patients with 80% coding coverage. Median number of healthcare contacts (1 contact = 1 disease discussed during an appointment or inpatient episode) was 12 (min = 1, max = 212). When drawing the difference between low and high healthcare utilizors at the upper quartile (75^{th}percentile), the only factor associated with high healthcare utilization was ever having received biologics (OR 9.47, 95% CI 2.43-49.35, $p < 0.01$) compared to never received. Total healthcare costs in euros (€) did not differ between those less than 30 years of age and over 30 ($p = 0.12$). Of the healthcare contacts with recorded diagnostic codes (rheumatic diagnoses excluded), mental health disorders accounted for 1 in 4 and cardiovascular diseases for 1 in 10. The main mental multimorbidity was depression (52% of all contacts for mental disorders). The main cardiovascular multimorbidity was cardiac arrythmias (57% of all contacts for cardiovascular diseases).

Conclusion: Mental health disorders are common in adult JIA patients. Healthcare professionals should pay attention to mental wellbeing, particularly in young adults with JIA. Further analyses on utilization data from 2012 to 2014 are currently underway for investigating other factors associated with increased healthcare utilization in a larger dataset.

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Abstract Number: 1236

Rheumatoid Arthritis-Interstitial Lung Disease in the United States: Prevalence, Incidence, and Healthcare Costs

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Background/Purpose: Interstitial lung disease (ILD) is commonly associated with rheumatoid arthritis (RA) and can have significant morbidity and mortality. The objective was to calculate the prevalence, incidence and healthcare costs of RA-related ILD (RA-ILD) in the US.

Methods: We used data from the MarketScan Commercial and Medicare Supplemental Databases from 2004-2013. In each year, patients meeting 1 of the following criteria were considered to have RA-ILD: (A) ≥2 claims with a diagnosis of pulmonary fibrosis (ICD-9-CM 515, 516.3, 516.31) or rheumatic lung disease (ICD-9-CM 714.81) plus ≥2 claims with a diagnosis of rheumatoid arthritis (ICD-9-CM

714.xx excluding 714.3x and 714.4x) or (B) ≥2 claims with a diagnosis for rheumatic lung disease. Patients with 6 months of continuous enrollment prior to first RA-ILD diagnosis in the database and with no claims for pulmonary fibrosis or rheumatic lung disease during that period were classified as incident patients. Patients with evidence of other lung diseases were excluded. Demographic characteristics were measured on date of first RA-ILD diagnosis and clinical characteristics were based on diagnosis, procedure, and drug codes on claims over 12 months for patients who had 12 months of enrollment. All-cause healthcare resource utilization and costs were calculated over 5 years for incident patients with sufficient enrollment. All-cause mortality was assessed for patients who could be linked to Social Security Administration death data.

Results: Prevalence of RA-ILD ranged from 3.2 to 6.0 cases per 100,000 people (Table 1) and incidence ranged from 2.7 to 3.8 cases per 100,000 people. Mean age was 64-66 years across study years; the majority of patients were female (66%-70%). Common comorbidities included gastro-esophageal reflux disease (46%-54%), dyslipidemia (35%-52%), acute bronchitis/pneumonia (34%-38%), and hypertension (41%-61%). The majority of patients had a chest computed tomography (CT) scan (50%-59%) or chest x-ray (69%-80%) over a 12 month period. There were 750 incident patients with 5-year follow-up data; Over 5 years, 72% had an inpatient admission and 76% had an emergency room visit. Mean total 5-year costs were $173,405 per patient (SD $158,837). Annual per-patient costs were highest in years 1 and 5 (Table 2). At 5 years after first diagnosis in the data, 66.7% of patients were alive.

Conclusion: Prevalence of RA-ILD increased over time. For patients who could be followed over a 5-year period, utilization and costs were somewhat stable over time, although inpatient admissions were more common and costs were higher in year 1.

Table 1.

Year	Prevalence of RA-ILD per 100,000 People
2004	3.51
2005	3.73
2006	3.18
2007	3.39
2008	3.52
2009	4.62
2010	4.95
2011	5.35
2012	5.20
2013	5.95

Table 2.

All-Cause Healthcare Costs of Incident RA-ILD Patients

	Year 1	Year 2	Year 3	Year 4	Year 5
Inpatient admissions	$10,437	$6,379	$6,179	$9,332	$8,739
Emergency room visits	$307	$306	$345	$395	$460
Outpatient office visits	$1,987	$1,670	$1,597	$1,578	$1,579
Other outpatient services	$13,188	$12,801	$12,302	$13,404	$14,646
Outpatient pharmacy	$11,072	$11,084	$11,182	$11,116	$11,321
Total healthcare costs	$36,991	$32,240	$31,604	$35,825	$36,744

Disclosure: K. Raimundo, Genentech Inc, 3; **A. Farr**, Truven Health Analytics, 3; **A. Cole**, Truven Health Analytics, 3,UNC Chapel Hill, 3; **J. J. Swigris**, Genentech Inc, 5,Genentech Inc, 8,Boehringer Ingelheim, 5,Boehringer Ingelheim, 8.

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Abstract Number: 1237

The Economic Burden of Dermatomyositis and Polymyositis in the US

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Background/Purpose: Dermatomyositis and polymyositis (DM/PM) are inflammatory myopathies that can lead to persistent muscle weakness and disability. Although significant healthcare resource utilization (HCRU) and work loss among DM/PM patients have been reported, the economic burden to the national population has not been explored. The aim of this study was to provide a contemporary estimate of the total and incremental direct medical cost burden of DM/PM in the US. Total and incremental indirect work-loss burden attributable to DM/PM were also analyzed.

Methods: Patients aged 18-64 years with a first diagnosis of DM/PM between 1/1/1998 and 3/31/2014 were selected from a large, de-identified, privately-insured administrative claims database (OptumHealth Reporting and Insights). Propensity score (1:1) matching of DM/PM patients with non-DM/PM controls from the same database was performed to reduce baseline differences in demographic characteristics, comorbidities, HCRU, and costs. Healthcare costs (inpatient, outpatient/physician office, emergency department, other, pharmacy) and indirect work loss (disability days, medically-related absenteeism) were compared between matched DM/PM patients and controls from the payer perspective over 12 months post-diagnosis. The prevalence of DM/PM in the US was estimated from the recent literature.

Results: A total of 2,587 DM/PM patients who met the sample selection criteria were matched with a control. Overall, commercial payers incurred $23,064 in total healthcare costs per DM/PM patient during the 12-month outcome period. Relative to controls, DM/PM patients had, on average, $7,368 (47%) higher total healthcare costs ($23,064 vs. $15,695; $p<0.001$). Paired with US population statistics and estimates of DM/PM prevalence (ranging from 14.8 to 19.5 DM/PM cases per 100,000 persons), results of this analysis suggest that DM/PM patients impose a total direct medical cost burden of approximately $457 to $602 million (in 2013$) to commercial payers, or approximately $146 to $192 million in excess costs over matched controls. Further, work loss among DM/PM patients amounted to $3,621 in annual costs, $633 (21%) more than the non-DM/PM patients ($3,621 vs. $2,988; $p<0.001$).These results suggest that DM/PM patients impose an indirect cost burden of approximately $76 to $100 million to employers in work-loss costs, or approximately $13 to $17 million in excess work-loss costs compared with matched controls. The estimated total costs (direct and indirect) of DM/PM range from $533 to $702 million a year.

Conclusion: DM/PM is associated with substantial economic burden in the US population due to significantly increased healthcare costs and work loss. Moreover, results of this analysis potentially underestimate the excess burden of DM/PM because a few high-cost DM/PM patients could not be matched. Also, the actual national cost of DM/PM is likely understated as this study excluded individuals 65 years and older, out-of-pocket costs, supplemental insurer payments, and informal caregiving. Finally, only costs in the 12 months following diagnosis were assessed; costs may increase due to changes in disease severity over time.

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Abstract Number: 1238

Assessment of Mortality and Healthcare Costs Associated with Systemic Sclerosis with and without Lung Involvement

Karina Raimundo[1], Amanda Farr[2], Ashley Cole[3] and Aryeh Fischer[4], [1]Genentech, Inc., a Member of the Roche Group, South San Francisco, CA, [2]Truven Health Analytics, Cambridge, MA, [3]Truven Health Analytics, Bethesda, MD, [4]Medicine / Center for Lungs and Breathing, University of Colorado School of Medicine, Aurora, CO

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Background/Purpose: Patients with systemic sclerosis (SSc) are at high risk of developing interstitial lung disease (ILD) and/or pulmonary hypertension (PH). These two lung manifestations are associated with significant morbidity and are the leading causes of death in SSc. In this study, in addition to describing survival experience, we sought to assess the financial burden by determining all-cause healthcare costs in patients with SSc with and without coexistent ILD and/or PH.

Methods: We used data from the MarketScan Commercial and Medicare Supplemental Databases from 2004-2014. Patients with ≥2 claims with a diagnosis of SSc (ICD-9-CM 710.1) were identified. Patients with 6 months of continuous enrollment prior to first SSc diagnosis in the database and with no claims for SSc during that period were classified as incident patients. Patients with ≥2 claims with a diagnosis of ILD (ICD-9-CM 515, 516.3, 516.31, 517.2) and no diagnoses of other respiratory conditions were classified as having ILD. Patients with ≥2 claims with a diagnosis of PH (ICD-9-CM 416.0) were classified as having PH. Those without claims for these conditions in the 6 months prior to first diagnosis of ILD or PH in the database were considered incident. All-cause mortality was assessed for incident patients who could be linked to Social Security Administration death data. All-cause healthcare costs were calculated over a 5-year follow-up period for incident patients with sufficient enrollment.

Results: There were 11,752 incident SSc patients, 1,808 SSc patients with incident ILD, and 1,223 SSc patients with incident PH. Average age at first diagnosis of SSc, ILD, and PH was 55 years, 57 years, and 60 years, respectively. Among those who could be linked to death records (n=4,605; n=715; n=525), median survival time was 11.3 years, 8.8 years, and 6.0 years. Per-patient all-cause healthcare costs over a 5-year follow-up were lowest for newly diagnosed SSc patients and highest for SSc patients with newly diagnosed PH ($101,839; $191,107; $254,425). Yearly per-patient costs are presented by service type in Tables 1-3.

Conclusion: In comparison to those with SSc alone, the presence of ILD and/or PH is associated with significant increases in healthcare costs and a worse survival experience. Table 1.

All-Cause Healthcare Costs of Incident SSc Patients (N=1,957)

	Year 1	Year 2	Year 3	Year 4	Year 5
Inpatient admissions	$4,691	$3,780	$3,770	$4,492	$6,101
Emergency room visits	$337	$290	$290	$311	$261
Outpatient office visits	$1,392	$1,164	$1,153	$1,168	$1,173
Other outpatient services	$9,060	$7,779	$7,327	$7,869	$8,677
Outpatient pharmacy	$5,418	$5,822	$5,973	$6,486	$7,055
Total healthcare costs	$20,898	$18,836	$18,513	$20,325	$23,268

Table 2.

All-Cause Healthcare Costs of SSc Patients with Incident ILD (N=219)

	Year 1	Year 2	Year 3	Year 4	Year 5
Inpatient admissions	$7,693	$7,643	$3,502	$7,735	$22,609
Emergency room visits	$450	$474	$461	$425	$344
Outpatient office visits	$1,794	$1,410	$1,458	$1,455	$1,567
Other outpatient services	$14,051	$13,375	$12,387	$9,485	$14,578
Outpatient pharmacy	$11,260	$13,013	$13,476	$14,112	$16,348
Total healthcare costs	$35,248	$35,916	$31,285	$33,212	$55,446

Table 3.

All-Cause Healthcare Costs of SSc Patients with Incident PH

	(N=108)				
	Year 1	Year 2	Year 3	Year 4	Year 5
Inpatient admissions	$9,203	$5,383	$5,641	$8,317	$12,413
Emergency room visits	$789	$703	$785	$347	$365
Outpatient office visits	$1,912	$1,640	$1,508	$1,594	$1,579
Other outpatient services	$17,355	$12,984	$9,850	$13,565	$18,002
Outpatient pharmacy	$20,769	$24,294	$26,671	$27,796	$30,962
Total healthcare costs	$50,028	$45,003	$44,454	$51,620	$63,320

Disclosure: K. Raimundo, Genentech Inc, 3; **A. Farr**, Truven Health Analytics, 3; **A. Cole**, Truven Health Analytics, 3,UNC Chapel Hill, 3; **A. Fischer**, Genentech Inc, 2,Boehringer Ingelheim, 5,Genentech Inc, 5,Actelion Pharmaceuticals US, 5,Gilead Sciences, 5,Bristol-Myers Squibb, 5,GlaxoSmithKline, 5,Boehringer Ingelheim, 2.

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Optimizing Screening for Psoriatic Arthritis through a Shortened Psoriatic Arthritis Screening and Evaluation-2 (PASE-2) Tool

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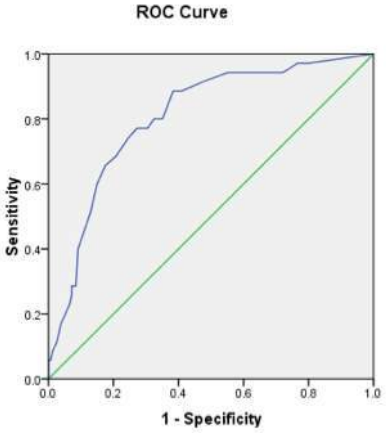
Background/Purpose: The Psoriatic Arthritis Screening and Evaluation (PASE) Tool is one of the most frequently used tools to screen psoriasis patients for signs and symptoms of psoriatic arthritis (PsA). PASE has been used in dermatology outpatient settings, in large-scale epidemiological studies, and in clinical trials and has been translated into more than 20 different languages. The original PASE included 15 questions addressing two separate domains including symptoms (7 questions) and function (8 questions). Given the demonstrated efficacy of the tool for early identification of PsA, we sought to determine the optimal cut off score and generate a shorter version in efforts to improve adoption and implementation in the clinical setting as PASE-2.

Methods: Eligible patients included those adults aged 18-85 with a diagnosis of psoriasis or psoriatic arthritis, who presented at an academic dermatology clinic. The PASE questionnaire was administered to 190 consecutive patients. From survey responses, we conducted a principal component analysis to guide revision of the tool. Principal component analysis identified a one-factor solution which accounted for 57.5% of total variance. Questions with factor loading below 0.75 were removed. A Youden index was used to guide selection of the appropriate total survey score cutoff for sensitivity and specificity for identifying inflammatory arthritis. Receiver operating characteristic (ROC) curves were calculated for individual questions and for the revised PASE-2 as a whole.

Results: 190 patients with dermatologist-diagnosed psoriasis completed the PASE tool (110 males and 80 females, median age 55). We identified 7 questions for removal, yielding an 8-item questionnaire. Remaining items inquire about joint stiffness, joint function, joint pain and/or swelling, joint warmth/erythema, migratory joint pain, work and activity-related changes. The area under the ROC curve for the 8-item tool was 0.81 (Figure). Selecting a new total score cutoff of 19 or greater provided a sensitivity of 0.84 and specificity of 0.63 for the identification of psoriasis patients at risk for PsA. This is compared to a sensitivity and specificity of 0.82 and 0.73 from the original 15-item PASE tool.

Conclusion: We conducted a principal component analysis to develop an 8-question PASE-2. The improved sensitivity of the PASE-2 highlights the potential for better screening for PsA in the psoriasis population while minimizing survey burden to physicians and patients and thereby increasing adoption of the tool. Further studies will be needed in larger populations to improve the adoption of screening to help improve patient outcomes.



Disclosure: J. Thompson, None; **M. Darwish**, None; **S. Y. Paek**, None; **J. Merola**, Biogen Idec, 2,Biogen Idec, 5,Abbvie, 5,Amgen, 5,Eli Lilly and Company, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Janssen Pharmaceutica Product, L.P., 5,Mallinckrodt, 5,Abbvie, 8,Eli Lilly and Company, 8,Biogen Idec, 9,Boehringer Ingelheim, 9,Abbvie, 9; **A. Qureshi**, Abbvie, Amgen, Centers for Disease Control, Janssen, Merck, Novartis, Pfizer, 5,Amgen, 9,PASE, 9; **M. E. Husni**, Lilly, Novartis, Abbvie, Celgene, Bristol Myers Squibb, Amgen, Janssen, & UCB pharma, 5,PASE, 9.

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Abstract Number: 1240

A Minority of Patients Utilize Most of Healthcare Resources in Rheumatoid Arthritis, Psoriatic Arthritis, Juvenile Idiopathic Arthritis, and Axial Spondyloarthritis

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Background/Purpose: Rheumatoid arthritis (RA) is associated with high healthcare costs, but little is known about how the costs compare to other chronic rheumatic diseases. We combined a large, population-based clinical dataset on patients at a rheumatology clinic with an administrative database in order to compare healthcare utilization in patients with rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, and axial spondyloarthritis.

Methods: The data is on the adult population of the City of Jyväskylä, Finland (population 135 000). Their primary care is delivered at the local healthcare centers, which rely on the Jyväskylä Central Hospital (JCH) when specialist treatment is needed. The rheumatic specialist care is served in the JCH rheumatology unit, where clinical data is systematically recorded in a structured digital database. Well-recorded administrative data with costs data in euros (€) from fiscal year 2014 includes information on all public healthcare visits to physicians and allied healthcare professionals, both in primary and specialty care. Also inpatient care is included. With the Kruskal-Wallis test, we compared costs associated with healthcare utilization for adult patients with RA, psoriatic arthritis (PsA), juvenile idiopatic arthritis (JIA),

and patients with axial spondyloarthritis or spondyloarthropathies (AS+SpA). We recognized high healthcare utilizing proportions in each and explored their clinical characteristics.

Results: The cost distribution was similar in all studied diseases (p = 0.62), and the distribution was widest in RA. The cost distribution was similar also in women (p = 0.31) and in men (p = 0.59). In RA (n = 967), 9% utilizes as much as the remaining 91%. Corresponding figures are 9% and 91% for PsA (n = 190), 10% and 90% for AS+SpA (n = 257), and 16% and 84% for JIA (n = 102). The high healthcare utilizing proportions were characterized by lower functional capacity measured with HAQ index (0-3) and higher pain (VAS 0-100), as well as higher disease activity, measured with DAS28. In addition, a larger proportion of these patients had at some point received biologics compared to patients with lower utilization. Mental health disorders were common multimorbidities in all studied diseases, particularly in young adults, as cardiovascular multimorbidities were particularly prevalent in older age groups.

Conclusion: Healthcare utilization is similar for RA, PsA, JIA, and AS+SpA. Approximately one tenth of patients utilizes as much as the remaining 90%. Higher healthcare utilization is characterized by patient perceived health measures. To limit the costs caused by healthcare utilization, disease activity should be minimized, improving functional capacity with reducing HAQ and pain. Moreover, costs of active treatment might be saved by reducing the healthcare utilization.

Disclosure: N. Mars, None; **A. M. Kerola**, None; **M. J. Kauppi**, None; **O. Elonheimo**, Employee of FCG Finnish Consulting Group Ltd, 3; **S. Huvinen**, Employee of FCG Finnish Consulting Group Ltd, 3; **T. Sokka-Isler**, None.

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Abstract Number: 1241

Understanding Lupus Patients' Ability to Work with Numbers

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Background/Purpose: Systemic lupus erythematous (SLE) is a heterogeneous disease with high morbidity and mortality affecting approximately 20-150 cases per 100,000 people. The risk of early death in patients with SLE is two times greater than the general population. Long-term SLE treatment is often complex with frequent medication changes, which are challenging especially given the cognitive and neuropsychiatric deficits affecting 25-60% of lupus patients. Across wide spectrums of educational backgrounds, patients need multiple skill sets to understand health recommendations, manage their disease, and avoid poor health outcomes. Health literacy, numeracy, and patient engagement are key components of patient proficiencies necessary to support constructive communication between physician and patient.

Methods: Through the Ohio State University IRB-approved Lupus Registry, we recruited patients to complete health literacy, numeracy, and patient activation measures. 65 patients completed measures of health literacy (sTOFLA), subjective numeracy (SNS) measuring patient's perception of their math ability, objective numeracy (ONS) that is patient's actual math ability, and patient activation (PAM) measuring patient engagement. Cronbach's alpha was used to assess reliability and internal consistency of measures; alpha above 0.7 are considered acceptable.

Results: All patients demonstrated adequate health literacy (scores above 23; Cronbach's alpha= 0.77) compared to the 12% of population as estimated by the National Assessment of Adult Literacy. Patients' ONS was low (mean score=3 out of 8 possible; Cronbach's alpha= 0.92) and consistent with mean scores for high-school-only educated individuals. PAM scores averaged at 3.3 (out of 4 possible), suggesting patients want to be engaged in their disease. See Table 1 for correlations; values are likely due to small sample size.

Conclusion: Minimal literature exists to describe health literacy in SLE patients, and even less describes numeracy and engagement. It is clear that, despite adequate health literacy and patient activation, these patients still perform poorly on math-related questions. PAM and SNS have a positive correlation suggesting that patients who are more engaged also perceive their math ability to be better. SLEDAI scores while not statistically significant are negatively correlated with PAM scores, suggesting patients who are less engaged have higher disease

activity scores. Relations with SLICC scores require more data collection, which is ongoing. These data suggest that patients with poor PAM scores have high disease activity scores; other trends are promising. These data point towards the potential to modify patient skill sets and improves outcomes in future research. Table 1:

		Health Literacy	SNS	ONS	Patient Activation
SNS	Pearson correlation coefficient r	0.35			
	P value	0.01			
	N=	63			
ONS	Pearson correlation coefficient r	0.48	0.40		
	P value	<0.0001	0.001		
	N=	60	61		
Patient Activation Measure	Pearson correlation coefficient r	0.12	0.32	0.04	
	P value	0.35	0.01	0.76	
	N=	63	64	61	
SLEDAI	Pearson correlation coefficient r	-0.15	0.1824	0.0140	-.38
	P value	0.31	0.20	0.93	0.01
	N=	50	51	48	51
SLICC	Pearson correlation coefficient r	-0.09	0.06	-0.02	-0.15
	P value	0.53	0.70	0.88	0.29
	N=	50	51	48	51

SNS= Subjective Numeracy ONS= Objective numeracy

Disclosure: A. Meara, None; **M. K. Tompkins**, None; **K. Fisher**, None; **H. Steigelman**, None; **W. N. Jarjour**, None; **S. P. Ardoin**, None; **E. Peters**, None.

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Abstract Number: 1242

Rate of Hospitalization for Heart Failure Is Lower in Patients with Controlled Gout Versus Uncontrolled Gout

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Background/Purpose: Hyperuricemia is associated with worsened outcomes in heart failure (HF) patients. However, little is known regarding the association between gout and HF itself. This analysis assesses the impact of gout control on the rate of hospitalization for acute HF in a prevalent gout population.

Methods: This retrospective database analysis used data from the Clinical Practice Research Datalink-Hospital Episode Statistics (UK) from Jan 1, 2009 to Dec 31, 2011. Patients were required to have evidence of "prevalent established gout" (ie, treated with urate-lowering therapy (ULT) or eligible for ULT based on ACR guidelines) between Jan 1, 2009 and Dec 31, 2009 and be aged ≥18 on index date (Jan 1, 2010). Follow-up extended from Jan 1, 2010 to Dec 31, 2011. HF rate was calculated as the percentage of eligible patients having at least 1 HF-related hospitalization over the course of the calendar year. In each calendar year, patients were considered to have controlled gout if they had no elevated serum urate acid (sUA; ≥6 mg/dL), no diagnosis of tophus, and no flare documented. Uncontrolled gout was defined as

at least 1 elevated sUA or 1 tophus diagnosis during the year. In this analysis patients with no documented sUA were considered not evaluable. To mitigate the limited availability of sUA data, a sensitivity analysis was conducted using an alternate definition of control status: if sUA was available, controlled was defined as no elevated sUA, no flare, and no tophi and uncontrolled was defined as ≥1 elevated sUA, tophus or flare; if sUA unavailable, controlled defined as medication possession ratio (MPR)>80% and uncontrolled defined as 0%<MPR≤80%. Here, patients with no documented sUA and MPR=0% were not evaluable. The odds ratio of HF was modeled in each post-index year using logistic regression models, with adjustment for control status (in previous or current year), gender, age, and Charlson Comorbidity index as covariates.

Results: A total of 29,758 eligible gout patients were identified. Within the subset of patients with available sUA (4,762 in 2010 and 4,385 in 2011), the HF rate was consistently lower in patients whose gout was controlled in the ongoing year (adjusted OR: 0.253 in 2010 [p=0.032]; 0.268 in 2011 [p=0.019]). The sensitivity analysis conducted using MPR as a proxy for control in a larger population (26,999 patients in 2010 and 26,176 patients in 2011) yielded similar results (OR: 0.387 in 2010 [p<0.001]; 0.462 in 2011 [p<0.001]). There was a trend for patients being controlled in the previous year to have a lower HF rate in the current year but this effect was not significant.

Conclusion: This study suggests that patients with controlled gout have a lower risk of being hospitalized for HF. Further investigations would be required to validate this finding on larger samples.

Heart Failure Rate Stratified Per Gout Control Status

Year of Heart Failure Assessment	Stratification Variable	Controlled gout N patients at risk	Controlled gout Heart Failure Rate	Uncontrolled gout N patients at risk	Uncontrolled gout Heart Failure Rate
2010	Control status in 2010 (base case)	1,937	0.15% [0.03% - 0.45%]	2,825	0.60% [0.35% - 0.96%]
	Control status in 2010 (sensitivity analysis)	18,719	0.19% [0.13% - 0.27%	8,280	0.46% [0.32% - 0.63%]
	Control status in 2009 (base case)	1,960	0.10% [0.01% - 0.37%]	5,512	0.27% [0.15% - 0.45%]
	Control status in 2009 (sensitivity analysis)	17,256	0.24% [0.17% - 0.32%]	11,546	0.29% [0.20% - 0.40%]
2011	Control status in 2011 (base case)	1,827	0.22% [0.06% - 0.56%]	2,558	0.70% [0.42% - 1.11%]
	Control status in 2011 (sensitivity analysis)	18,598	0.28% [0.21% - 0.37%]	7,578	0.57% [0.41% - 0.76%]
	Control status in 2010 (base case)	1,937	0.26% [0.08% - 0.60%]	2,825	0.57% [0.32% - 0.92%]
	Control status in 2010 (sensitivity analysis)	18,719	0.36% [0.28% - 0.45%]	8,280	0.42% [0.29% - 0.59%]

Disclosure: R. Morlock, Consulting fees, 5; **P. Chevalier**, IMS Health, 3; **A. B. Klein**, AstraZeneca, 3.

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Abstract Number: 1243

Validity of the Short Form 6D Utility Measure in Early Axial Spondyloarthritis

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Background/Purpose: The quantification of health improvements is essential, notably in the current context of increasingly expensive therapies and more and more limited resources. Preference-based measures of health have become important for estimating health states in calculating quality-adjusted life years (QALYs), an essential component of cost-utility analysis. The SF-6D is an indirect preference-based health-related quality of life instruments increasingly being used for economic evaluation of clinical interventions and health programs. Data on economic as well as QoL outcomes among early axial Spondyloarthtritis (axSpA) patients remain scarce. Objectives: To evaluate the validity of an utility measure, the SF-6D, in early axSpA especially concerning the ability of this measure to reflect the change in patients' condition over time.

Methods: DESIR (Devenir des Spondyloarthropathies Indifférenciées Récentes) is a French, multicentre, longitudinal cohort of 708 patients with early inflammatory back pain suggestive of axSpA. SF-6D utility measures were assessed in 607 patients over 1 year. To investigate whether the change in SF-6D is a valid measure of change in axSpA health status, we used Spearman's product-moment correlation to compare change scores for SF6D with those for external measures of health, the HAQ, SF36 physical component, SF36 mental component and AS-QOL from baseline to 6 and 12 months. Responsiveness was tested by the effect size (ES) at 6 and 12 months for the entire sample and subgroups by disease evolution (increase or decrease-stabilization in BASDAI). Bootstrap methods were used to estimate 95% confidence intervals [95% CI]. Sensitivity to change of the HAQ was calculated as a benchmark.

Results: At baseline, mean value of SF-6D was 0.69±0.12 (range 0.30 to 0.95). The distribution was near normal. Few missing values were observed: 2.4%. No floor or ceiling effects were evidenced. Correlations of the SF6D change with change in HAQ and physical component of SF-36 scores were moderate at 6 months (r=-0.42 and 0.44, respectively). Correlations with change in mental component of SF-36 and AS-QOL scores were good (r=0.60 and -0.60, respectively). Correlations were stable over 1 year. For the entire sample at 6 months, the SF-6D was more sensitive to change than the HAQ: ES 0.36 [95% CI 0.28;0.44] versus -0.22 [-0.28;-0.17]. The SF-6D was more responsive than the HAQ for improved condition: ES 0.45 [0.37;0.54] vs -0.32 [-0.38;-0.26] without difference for patients with deteriorated condition: ES SF-6D -0.23 [-0.41;-0.04] vs 0.33 [0.18;0.50] for HAQ. Results were similar at 12 months.

Conclusion: The SF-6D is valid and able to reflect the change in patients' condition over time, especially improvement, in patients with early inflammatory back pain suggestive of axSpA.

Disclosure: C. Gaujoux-Viala, None; **L. Gossec**, None; **C. Castelli**, None; **C. Lukas**, None; **F. Barchechath-Flaisler**, None; **J. P. Daures**, None; **M. Dougados**, None.

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Abstract Number: 1244

Establishing a Case Report Form (CRF) for Systemic Autoimmune Diseases Studies

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Background/Purpose: Systemic autoimmune diseases (SADs) are heterogeneous conditions with peculiar characteristics that share several clinical features. It is suspected that SADs share similar molecular abnormalities, however, until now, the cross-sectional study of SADs has been hampered by the difficulty to establish common a clinical groundwork. A challenge of such studies is the generation of a CRF capable of capturing similarities and diversities without being redundant with the diagnosis themselves or, conversely, too detailed. We present a framework used within the Innovative Medicines Initiative Joint Undertaking (IMI JU) project PRECISESADS to develop a CRF that balances compactness and granularity to allow the identification of diseases clusters based on molecular features. A similar decisional process can also be applied when building the data structure for registries and the CRF content we developed can be used to align registries or studies data focussing on the transversal analysis of SADs.

Methods: The following steps were performed: 1) Bioinformatics gave insight into the analysis plan and suggested the key rules for data collection. Briefly, unsupervised clustering analysis is planned; missing and redundant data are to be avoided as much as possible; yes/no answers are preferred to open entry fields; data should focus on elements necessary to implement the analysis and limit the number of extraneous ("nice to know") elements. 2) A working group of experts on SADs (RA, SLE, SSc, SjS, UCTD/MCTD/APS) was established. A first broad set of transversal items to the different diseases (n = 130) was created and divided in 8 domains (constitutional symptoms, gastrointestinal, vascular, heart and lung, nervous system, skin and glands, muscle-skeletal, therapy). 3) The items were ranked and reviewed via a Delphi technique and the top ranking items were selected after convergence was reached. 4) The core items were discussed by all the members of the consortium to gain consensus among the stakeholders, and suggestions were gathered. 5) A final set of items was

created, digitalized and pilot tested. 6) The final CRF was released along with explicit data definitions.

Results: Convergence among experts was obtained after 3 tiers and a core set of 28 items was generated. This set was enriched by additional baseline demographic and enrolment data, comorbidities, essential laboratory tests and some disease-specific clinical data. The final CRF proved to be flexible and easy to compile. The average rate of missing data (median, IQR) was 1.9% (0.83 - 7.95). Missing data were: 1.66% (1 - 2.2) in the core set and 0.83% (0.66 - 1.91) for comorbidities. Higher missing rates were observed for lab results: 10% (1.28 - 17.32) and for the additional non-transversal data: 17.03% (14.57 - 24.25).

Conclusion: We describe a seamless procedure to build a core data set transversal to different SADs. This set may be used with few modifications or integrations as data standards for studies or registries that plan to analyze different SADs at once. The generalisation of this core data set may allow a better comparison across studies and contribute to evolving medical knowledge in the field of SADs. www.precisesads.eu

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Abstract Number: 1245

Comparison of Secukinumab Vs Adalimumab in a Cost per Responder Analysis Based on a Matching-Adjusted Indirect Comparison of Efficacy Data for the Treatment of Psoriatic Arthritis at 48 Weeks from the US Perspective

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Comparison of Secukinumab vs Adalimumab in a cost per responder analysis based on a matching-adjusted indirect comparison of efficacy data for the treatment of psoriatic arthritis at 48 weeks from the US perspective Jeff Greenberg [1], Efthalia Nikoglou[2], Praveen Gunda[3], Jacqueline Palmer[4], Steffen Jugl[5] [1] New York University school of medicine, New York NY USA

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Background/Purpose: The objective of this analysis was to estimate and compare the long-term cost per responder based on the American College of Rheumatology outcomes (ACR 20/50/70) following 48 weeks of psoriatic arthritis (PsA) treatment with the anti-IL-17A antibody Secukinumab relative to the anti-TNF antibody Adalimumab.

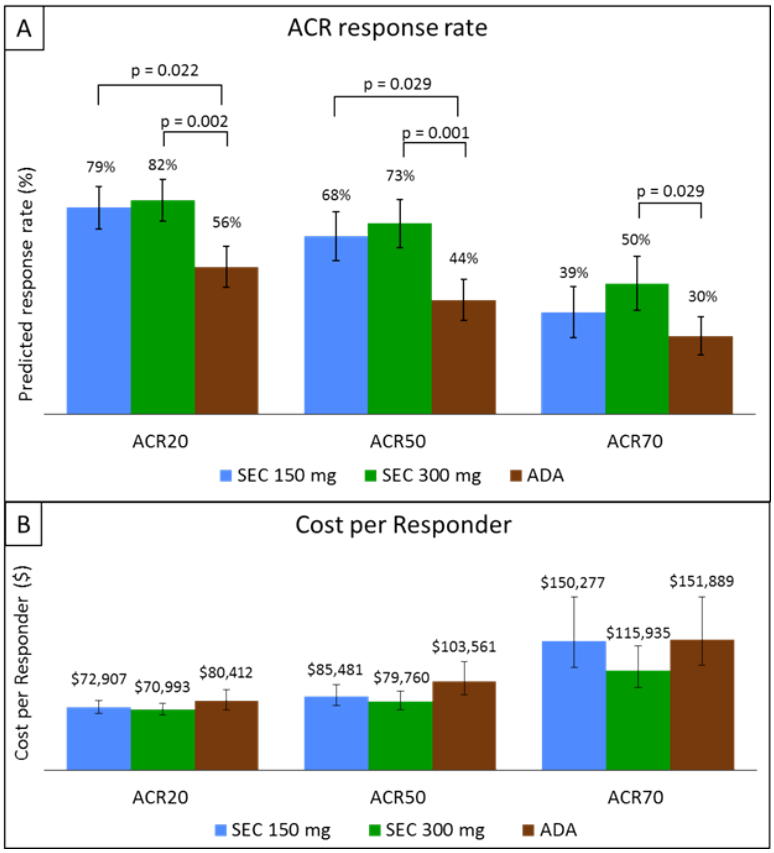
Methods: The cost per responder for each treatment, namely Secukinumab and Adalimumab was estimated by dividing the drug acquisition cost for the course of treatment with its response rate. Drug costs were estimated on the basis of the official US drug acquisition costs and the number of doses required for 48 weeks. The long-term response rates were estimated using a matching-adjusted indirect comparison (MAIC) technique based on the data from FUTURE 2 and ADEPT clinical trials of Secukinumab and Adalimumab respectively. MAIC analysis matched the age, weight, race and gender distribution, PASI score, HAQ-DI score, PsA duration (years), swollen joint count, CRP

, proportions of patients using methotrexate, with psoriasis ≥3% body surface area, presence of dactylitis, presence of enthesitis and TNF-naive at the baseline. A sensitivity analysis was also conducted by varying the choice of baseline characteristics (includes all variables except PsA duration (years), swollen joint count, and CRP) used in MAIC analysis.

Results: The effective sample sizes after matching the baseline characteristics were 15, 25 for Secukinumab 150 mg, Secukinumab 300 mg respectively, while the sample size for Adalimumab was 151. MAIC analysis showed ACR (20/50/70) response rates were significantly higher for Secukinumab 150mg and 300mg compared to Adalimumab at 48 weeks. ACR 20 response rates were 79%, 82% and 56% ACR 50 response rates were 68%, 73% and 44%, whereas the ACR 70 response rates were 39%, 50% and 30% for Secukinumab 150mg, Secukinumab 300 mg and Adalimumab respectively (**Figure 1A)**. Sensitivity analysis also showed higher response rates for Secukinumab 150mg and 300mg compared to Adalimumab. Among PsA patients, cost per ACR20 responder were $72,906, $70,993 and $80,412 cost per ACR50 responder were $85,480, $79,760 and $103,561, whereas costs per ACR70 responder were $150,276, $115,934 and $151,890 for Secukinumab 150mg, Secukinumab 300mg and Adalimumab respectively (**Figure 1B**). Sensitivity analysis also produced similar results.

Conclusion: ACR (20/50/70) response rates were significantly higher for Secukinumab 150mg and 300mg compared to Adalimumab at 48 weeks. The long term cost per responder for all ACR outcomes at 48 weeks were consistently lower for secukinumab (150,300mg) vs. adalimumab. These findings indicate that Secukinumab represents a cost-efficient treatment choice for PsA patients in the US.

Figure 1: Predicted response rate (A) and cost per responder (B) analysis of ACR (20/50/70) for Secukinumab vs Adalimumab for the treatment of psoriatic arthritis at 48 weeks in principal analysis



Disclosure: J. D. Greenberg, Novartis Pharmaceutical Corporation, 5; **E. Nikoglou**, Novartis Ireland Ltd, 3; **P. Gunda**, Novartis Healthcare Pvt. Ltd., 3; **J. Palmer**, None; **S. Jugl**, Shareholder of Novartis Pharma AG, 1,Full-time employee of Novartis Pharma GA, Basel, Switzerland, 3.

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Abstract Number: 1246

Causes and Predictors of Early Readmission in Systemic Lupus Erythematosus

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Background/Purpose : Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that is largely heterogeneous and can affect virtually any organ system. Each year about one-third of individuals with SLE are hospitalized, and it is one of the highest rated causes of readmission in the United States. We took an in-depth look at SLE patients admitted to Cedars-Sinai Medical Center (CSMC) who required early readmission to assess whether there were any opportunities that could have prevented readmission, as well as identify which patients are at highest risk for readmission.

Methods : We performed a retrospective cohort study to look at inpatient records of SLE patients at CSMC between January 2012 and July 2014. We identified patients with SLE that were readmitted within 30 days of discharge and whose primary hospitalization included an ICD-9 diagnosis of SLE (710.0). These readmitted patients were compared to patients with lupus who did not require early readmission. Finally, we used stepwise logistic regression to calculate which variables were associated with early readmission.

Results : The study group included 154 patients in the early readmission group, and 301 patients in the group that was not readmitted. The main causes for early readmission included cardiovascular, renal, and infectious complications. Age and gender did not play a significant role, however the readmission group had significantly more African American patients and more patients with publicly funded insurance. Immunosuppressive use, key laboratory values such as low hemoglobin, elevated creatinine, and lower albumin were also associated with early readmission.

Conclusion: We found higher rates of readmission among African Americans and patients with MediCal insurance. We also found that elevated creatinine, low hemoglobin, and low albumin levels were associated with readmission. Immunosuppressive use also correlated with readmission. Data collected in this study will allow for identification of patients at highest risk for early readmission, which will provide an opportunity to improve the discharge process and transitions in care in the lupus patient population.

Number of patients in cohort	
Readmitted	Not Readmitted
154	301

Disclosure: A. Nangit, None; **M. Weisman**, None; **M. Ishimori**, None; **B. Spiegel**, None; **C. Lin**, None.

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Abstract Number: 1247

Diagnostic Modeling of Rheumatoid Arthritis in Oklahoma Tribal Members Using Soluble Mediators

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Background/Purpose: Diagnosis of RA is difficult in American Indian (AI) patients who often have atypical autoantibodies (e.g. ANA) with erosive arthritis. Soluble mediators may serve as alternative markers for earlier identification of RA from other conditions affecting AI patients. This study characterized soluble mediator profiles of AI RA patients to identify pathogenic mechanisms of disease and develop early diagnostic algorithms for use by healthcare providers to direct patients toward individualized therapies.

Methods: The serum levels of RF, anti-CCP, and 26 soluble mediators from AI patients with RA (n=59), arthralgias (n=28), polyarthritis/osteoarthritis (n=31), or AI healthy controls (n=116) were measured using ELISA or multiplex assays. Comparisons were made using Kruskal-Wallis testing with Dunn's multiple comparison. To identify factors that distinguished AI RA patients from healthy controls or patients with other forms of arthritis, random forest modeling was performed using autoantibodies and soluble mediators that differed significantly between the groups. One model used autoantibodies, a second used soluble mediators and a third used both to classify AI RA patients from other AI arthritis groups. Each model was developed using 300 trees, $\sqrt{x}$ variables at each split (where x=number of incorporated variables), and a terminal node size of 1. Top predictive classifiers were identified using the prediction step of VSURF function in R 3.3.0. Sensitivity, specificity, positive and negative predictive values were calculated based on 50 random forests using the top predictive identifiers for each model.

Results: When comparing AI RA patients and controls, the soluble mediator model outperformed the autoantibody model with an accuracy of 93.2% vs 88.1%. The combined model outperformed the autoantibody model with an accuracy of 92.7%. IL-8, TGF-beta, SCF, MCP-3, and IL-1RA were identified as the top predictive classifiers when using the soluble mediator model. IL-8, RF(IgM), anti-CCP, and TGF-beta were identified as the top predictive classifiers when using the combined model. When comparing RA patients to AI patients from other arthritis groups the combined model outperformed the autoantibody model (82.5% vs 78.3%) with anti-CCP, RF (IgM), SCF, resistin, and TNFRII as top predictive classifiers. The soluble mediator model did not differentiate patients with RA from the other arthritis groups, suggesting some AI patients with polyarthritis have similar immune dysfunction without meeting classification criteria. IL-8 levels best distinguished patients and controls and SCF levels best distinguished RA patients from other diseases.

Conclusion: Adding soluble mediators to traditional autoantibodies improves the accuracy of diagnostic modeling in AI RA patients when compared to AI controls or AI patients with other forms of arthritis. These data support the hypothesis that soluble mediator profiles of AI RA patients can be used to identify mechanisms of disease and to develop early diagnostic algorithms for use by healthcare providers to direct patients toward individualized therapies. The study was funded by Native American Research Centers for Health.

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Abstract Number: 1248

Access to Care: The Patient Perspective from the 2015 ACR/ARHP Workforce Study

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Background/Purpose: The 2015 Workforce Study (WFS) sought to expand our current understanding of the rheumatology workforce utilizing an integrated, patient-centered approach to workforce modeling. Primary data from rheumatology patientsÕ perspectives was collected to help inform access to care issues.

Methods: The 2015 WFS used several primary and secondary data sources, including the ACR member database, state licensure registries, 2005 ACR workforce study results, professional organization information and peer-reviewed literature. These data were supplemented with survey data collected from adult, young adult and parents of pediatric rheumatology patients with assistance from the Arthritis Foundation. Face, content, and criterion validity was established through a team of rheumatology/survey research professionals. Overall internal reliability was established (Adult Survey: r=0.82; Pediatric/Young Adult Survey: r=0.85).

Results: Respondents were from 49 states representing all major regions of the U.S. (Adult=564; Young Adult=76; Pediatric=292); not all respondents answered every item. A majority self-identified as having private insurance. Approximately 48% (n=274) of adult, 55% (n=160) pediatric, and 40% (n=30) young adult patients were diagnosed by a rheumatologist, with the remainder diagnosed by their PCP or a non-rheumatology specialist. While a majority were able to see a rheumatologist within 3 months of onset of symptoms, there were still 30% (n=155) of adults, 26% (n=77) pediatric, and 26% (n=20) young adults who had over a 4 month wait to see a rheumatologist. When asked about the ease of obtaining regular follow-up appointments, 78% (n=430) of adults reported they were able to make routine appointments within the timeframe recommended by their rheumatologist, whereas only 57% (n=193) pediatric and young adult patients were able to do so. 50% (n=283) adults, 57% (n=165) pediatric, and 61% (n=46) young adults indicated it was somewhat to very difficult to make an urgent care appointment. 67% adults (n=372) adults and 55% (n=202) pediatric/young adults went to their PCP for urgent care if they could not see their rheumatologist. 13% (n=72) adults, 7% (n=17) young adults, and 57% (n=166) pediatric patients indicated there was not a rheumatologist within 25 miles from their home. 31% (n=90) pediatric patients reported having to travel more than 2 hours. In addition to travel time, respondents reported major travel costs related to fuel and missing work (Table 1).

Conclusion: Access to care is a substantial issue for patients, with major potential impact on quality and outcomes. There are substantial direct and indirect costs for patients in obtaining rheumatologic care, especially for pediatric patients. These data realistically enhance our understanding of access to care challenges for rheumatology patients.

Table 1. Travel Time and Costs of Patient Care

Time to get to Specialist*	Adults		Young Adult		Parent of Child	
	N	%	N	%	N	%
Between 45-60 mins	36	51.4	4	5.3	27	9.3
Between 1 to 2 hours	27	38.5	6	7.9	47	16.25
Between 2 to 3 hours	2	2.9	2	2.6	43	14.8
Between 3 to 4 hours	2	2.9	2	2.6	20	6.9
More than 4 hours	3	4.3	---	---	26	9.0
Additional Patient Costs**	**Adults**		**Young Adult**		**Parent of Child**	
	N	%	N	%	N	%
Fuel Costs	179	31.1	36	47.4	200	68.6
Overnight lodging	1.0	1.7	4	5.3	59	20.0
Missing work for appointments	181	31.5	43	56.6	210	71.7
Child care	14	2.4	6	7.9	85	29.0
Other	149	25.9	10	13.2	54	18.6

Note: *Only answered by those who reported they traveled more than 25 miles to rheumatologist. **Respondents were allowed to choose more than 1 response, thus percentages do not add up to 100%

Disclosure: S. Monrad, None; **L. Imundo**, None; **D. Battafarano**, None; **M. Ditmyer**, None.

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Abstract Number: 1249

"There Are Still a Lot of Things That I Need": A Qualitative Study Exploring Opportunities to Improve the Health Outcomes of First Nations People with Arthritis Seen at an on-Reserve Outreach Rheumatology Clinic

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Background/Purpose: A rheumatology specialty clinic embedded in a primary health care clinic on a First Nations reserve was established six years ago to improve access to care and reduce arthritis outcome inequities. Although the clinic has proved successful to achieve inflammatory arthritis physician-derived disease control targets during a 24-month follow-up period, patient-reported pain, disease severity and physical function did not significantly improve. The objective of this study was to explore remaining care needs from patient and provider perspectives, to inform enhancements to the model of care in this clinic.

Methods: A qualitative study with patients and their family members (n=10), health providers (n=14) and administrative staff (n=10) was performed. Thirty-four in-depth interviews were conducted to reach thematic saturation. Interviewing was assisted by semi-structured guides to focus on personal narratives and perceptions of needs and solutions. Interviews were audio recorded, transcribed verbatim and coded to find meaningful concepts. Concepts were then grouped into themes, which were validated using a member-checking strategy. An inductive interpretation was then conducted using "health service quality" and "cultural competency" theoretical frameworks.

Results: Four main themes of improvement areas were identified (see Table). The first three themes were related to the concept of health service quality: service organization, communication between patients and providers, and holistic patient support mechanisms integrating mainstream and traditional knowledge. Participants stressed that in order to realize treatment goals and thereby reduce health disparities, it was important to improve the administrative and inter-personal quality of existing services. Suggested strategies included administrative and organizational accommodations, health-interpreter services, cultural training and cultural immersion for providers, coordination with traditional healers, use of community health workers, culturally competent health promotion activities and involvement of family and other community members in the management of arthritis. The last theme identified was the need to enhance service availability and expand the scope of provided services beyond the health clinic, such as exercise programs and support groups.

Conclusion: Enhancements to an existing model of care needed to better meet the needs of the community, which could reduce arthritis outcome disparities in an outreach specialty clinic, were identified. Improved service organization, communication strategies, holistic patient support mechanisms and an expansion of services outside of the health clinic were suggested.

Enhancement Required	Illustrative Participant Quote
Service organization	*"There's a fragmentation and disintegration of health services on reserve." (Male, clinical services)*
Communication between providers, patients and their families	*"That (a) client agrees with you…that does not mean you know that person, you have to learn how to think Indian, think like an Indian to know that person…(we need someone)to speak for you if (you) do not understand…" (Female, RA patient)*
Support for patients to adequately manage their disease in a holistic manner, integrating mainstream and traditional knowledge	*"I need to understand more…I need to meet other people who are living this…mentally, I am traditional, I got to sweat, I leave things on creators hands… I am trying to figure out how to help her…It is a chronic disease…it is not going to get better…I want to prepare to help her anyway I can" (Male, husband of a woman with RA)*
Expansion of services outside of the health clinic	*"They do not have support groups out here for smoking, dieting, they do exercising but…even arthritis support groups that would be easier to associate with other people with arthritis cause they know exactly what are you going through… becoming more acceptable in the society to have arthritis…I think exercises for peoples needs… there are certain exercises that we can do and we cant do." (Female, client)*

Disclosure: A. Loyola-Sánchez, None; **L. Crowshoe**, None; **T. White**, None; **D. Lacaille**, None; **C. Barnabe**, None.

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Abstract Number: 1250

Mortality in Indigenous Populations of Canada, the United States, Australia, and New Zealand with Rheumatic Disease: A Systematic Review

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Background/Purpose: Indigenous populations of Canada, America, Australia, and New Zealand share similar experiences of colonization impacting their rheumatic disease clinical outcomes. The objective of our systematic review was to describe mortality in Indigenous populations with rheumatic conditions.

Methods: A systematic search was performed in medical (Medline, EMBASE, CINAHL), Indigenous and conference abstract databases (to June 2015). Search terms for Indigenous populations were combined with terms for inflammatory arthritis conditions, connective tissue disorders, crystal arthritis, and osteoarthritis. Studies were selected for data extraction if they reported measures of mortality (e.g. mortality rate, survival rates, potential years of life lost). Meta-analysis was not performed due to heterogeneity in the reporting of measures in each study, and a narrative summary was prepared.

Results: A total of 5,269 titles and abstracts were reviewed, of which 504 underwent full-text review and 12 (n=5 Canadian First Nations with SLE; n=2 Native Americans with SLE; n=1 Native Americans with RA; n=1 Native Americans with scleroderma; n=3 Australian Indigenous with SLE) were included for data extraction. First Nations ethnicity was associated with higher mortality compared to Caucasians in all Canadian SLE studies, reflected by a higher crude proportion of deaths (n=3 studies), increased risk of death after adjustment for covariates (hazard ratios 2-3, relative to Caucasians, n=2 studies), higher odds of death (n=1 study) and increased potential years of life lost (n=2 studies). First Nations people with SLE were more likely to have shorter disease duration and be younger at death, and die of SLE complications (27% vs 16%). Risk of death was 43% higher In Native Americans with SLE compared to Caucasians in age and sex adjusted models, and in models with an expanded list of covariates. Risk was highest in women ages 45-65 years. Crude death rates and causes of death were reported in the three studies of Australian Indigenous people with SLE; in these cohorts created through case-finding, Aborigines had higher death rates than Caucasians, mostly related to SLE complications. The RA study in Pima Indians included a comparison of mortality rates between RA and non-RA subjects, with an age and sex-adjusted mortality rate ratio of 1.28 (95%CI 1.01 to 1.62). The one study in Native Americans with scleroderma reported a crude death rate, with nearly all deaths related to progressive disease.

Conclusion: In Canada, America and Australia, Indigenous populations with rheumatic diseases have higher mortality rates. Several studies identified the underlying rheumatic disease as contributing to the deaths. We did not identify any studies disentangling the proportional attribution of rheumatic disease severity from the underlying higher mortality rates in Indigenous populations. The future research agenda should seek to clarify this important issue while expanding the scope to include more rheumatic diseases and populations.

Disclosure: K. Hurd, None; **C. Barnabe**, None.

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Abstract Number: 1251

Does Preconsult Electronic Exchange Affect Postconsult Diagnosis?

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Background/Purpose: Recent publications have suggested that implementation of an electronic consultation (E-Consult) system can

improve communication between primary care clinicians and subspecialists, reduce wait times, and improve access to care, particularly in safety net hospital systems. Provider-consultant-provider communication through the E-Consult system before any face-to-face interaction is termed a preconsult exchange. Preconsult exchanges can help reduce unnecessary face to face visits, but often require a substantial, potentially uncompensated, time commitment on the part of the reviewer, and have not yet been found to affect the outcome of patients who have been accepted for face-to-face consultation. As a measure of the utility of the preconsult exchange, we conducted a retrospective study to determine whether changes in diagnosis were more likely among those who had electronic exchange compared to those who did not.

Methods: Harbor UCLA is one of the safety-net hospitals of Los Angeles County, serving primarily minority uninsured and Medicaid patients. The hospitals and their community partner clinics provide integrated services for patients, and in order to facilitate subspecialty access, the Department of Health Services adopted an E-Consult system similar to one used at San Francisco General Hospital since 2007. We identified new patients to our clinic who were referred to us via the E-Consult system, then identified those for whom there was preconsult exchange and those for whom there was not. We then conducted a retrospective cohort study of patients accepted for face-to-face evaluation using available data from the E-Consult system and from our electronic medical record. The primary outcome was the odds of diagnosis change after face to face evaluation based on whether a patient had a preconsult exchange or not. Secondary outcomes examined whether a change in diagnosis was associated with a prior diagnosis of a rheumatic condition. Because E-Consult exchanges are asynchronous, obtaining sufficient information to close a consult can often take days to weeks. As an additional measure of this time cost, we compared mean times between consult initiation and face-to-face evaluation.

Results: Between November 2014 and March 2016, 230 patients were seen for face-to-face evaluation for which an E-Consult had been submitted. 68 of these E-Consults were identified as having had an exchange and 162 had not. Odds of a change in diagnosis after face to face consultation were higher for the group who received preconsult exchange but were not statistically significant (Figure 1). Odds of change in diagnosis were no different among those who had a prior rheumatologic diagnosis and also preconsult exchange versus those who did not. Patients for which there was a preconsult exchange were seen a mean 15.5 days later (mean 119.5 days between consult initiation and visit for patients with a preconsult exchange versus 104.1 days for those who did not; se = 11.6 days, p = 0.18).

Conclusion: As E-Consult systems become more widely adopted, particularly among resource limited safety net systems, providers and payers will need clarification on the benefits of preconsult exchange beyond currently available data, which primarily emphasizes improved access but does not address quality or cost (in dollars or in time). Although this study did not meet statistical significance for its endpoints, the results do suggest a trend towards utility of preconsult exchange in sorting patients who need a rheumatologist evaluation, but at a cost of delayed face to face consultation.

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Abstract Number: 1252

Socioeconomic Status and Not Race Associated with Delay in Diagnosis and Treatment of Rheumatoid Arthritis

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Background/Purpose: Ethnic disparities in outcomes of RA patients have been attributed to delayed presentation to specialty care and access to DMARDs, greater disease burden, and less years of education. Recent literature supports a role for socioeconomic status (SES) as a determinant of RA disease status, including clinical disease activity measures, mortality, seropositivity, and treatment delays. The purpose of this analysis was to delineate the association of SES to referral time and start of first DMARD in a diverse cohort of RA patients.

Methods: Ethnic Minority RA Consortium (EMRAC) participants with recorded dates of initial RA symptom, diagnosis and first disease-modifying drug (DMARD) were abstracted for analysis. Socio-demographic (age, gender, race, years of education, tobacco use), and RA disease status (disease duration, erosions, tender and swollen joints, RAPID3) at enrollment was documented. An estimate of SES was derived from the median housing income of the city of each enrollment site. Median incomes less than two-fold the 2014 poverty line ($47,700) defined lower SES status. Delays of ³ one-year for diagnosis and DMARD initiation were both defined from date of initial RA symptom. Logistic regression was used to model the association between risk factors and a one-year delay of diagnosis and DMARD initiation.

Results: 269 EMRAC participants with self-reported race/ethnicity and disease history were evaluated; 202 (75%) were female. The average values for the following parameters were: age 60.4 (±15.8) years, disease duration 13.6 (±10.8) years, and education 12.5 (±3.0) years. A majority (200 [74.4%]) of EMRAC participants were enrolled at sites serving lower than the twice poverty line. Significant differences in participantsÕ age, education years, disease activity and race were observed between SES groups (**Table**). Based upon the logistic regression model, being below the twice poverty line was significantly associated with the increased odds of ³ one-year diagnosis delay [3-fold increase; odds ratio (OR) = 4.0, 95% CI: (1.6, 10.1), P=0.003)] as well as increased odds of DMARD initiation delay [1.4 fold increase, OR = 2.4, 95% CI: (1.1, 5.06), P=0.027)]. There was no association between either diagnosis or DMARD delay and race. However tender joint counts were associated with increased odds of DMARD delay (per tender joint increase OR 1.1, 95% CI (1.01, 1.14), P = 0.028).

Conclusion: In a diverse ethnic cohort, disparity in income as an estimate of SES was a strong predictor of delay in referral to a rheumatologist and start of first DMARD. Policies that improve access to specialty care and RA medications must be paralleled by improvements in overall SES of individuals in order to minimize the impact of disease. **Table. Enrollment Characteristics by being Below or Above the Poverty Line**

	Median Below	At or Above	P
N	200 (74%)	69 (26%)	
Age (years)	58.2 (13.3)	64.5 (19.2)	**0.009**
Duration (years)	13.8 (9.9)	13.2 (13.0)	0.71
Education (years)	12.1 (2.9)	13.7 (3.0)	**<0.001**
RAPID3 [0-30]	13.5 (6.7)	11.0 (7.4)	**0.013**
Female	143 (71.5%)	59 (85.5%)	**0.020**
Race			**<0.001**
White	28 (14.0%)	33 (47.8%)	
Black	120 (60.0%)	27 (39.1%)	
Hispanic	13 (6.5%)	5 (7.3%)	
Other	39 (19.5%)	4 (5.8%)	

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Abstract Number: 1253

Evaluation of a Pre-Assessment Tool to Define the Spectrum of Autoimmune Diseases in an Underserved Environment

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Background/Purpose: American rheumatology practice patterns vary considerably. One challenge is practitioner shortage, thus a patient-self-administered screening tool would fill an unmet need if it identified patients with the highest likelihood of having an inflammatory disease (ID).

Objective: To assess the appropriateness of referral patterns and concurrently to evaluate a previously published screening tool, Early Inflammatory Arthritis-3 (EIA–3)[1].

Methods: The US rheumatology database, JointMan® captures inflammatory/non-inflammatory diagnoses of referred patients at a large Washington State rheumatology practice. All patients at the practice fill in an electronic version of the EIA-3 tool. This published screening questionnaire estimates the likelihood of having an inflammatory disease [JIA, RA–fulfilling ACR criteria, Unspecified inflammatory arthritis, SpA, CTDs, SLE] vs non-inflammatory disease [OA, FM, CPPD]. The evaluating clinician was not aware of the EIA-3 results. The results were later correlated to the clinician's diagnosis. Based on the confusion matrix, effect sizes (sensitivity, specificity and likelihood ratios) were calculated and compared to published results[2].

	Inflammatory diagnosis only	Non-inflammatory diagnosis only	Both inflammatory and non-inflammatory diagnoses
Referral Recommended	485	148	92
Referral Not Recommended	104	82	45

Confusion matrix displaying patient counts in all categories

Results: There were 956 patients with a mean age of 55; 66.32% female; 77.82% Caucasian. Of those,726 patients had inflammatory diseases [137 also had non-inflammatory disease]; 230 had non-autoimmune disease. The EIA-3 suggested referrals for 725 patients and no referral for 231.

	JointMan Effect Size		Tavares et al. 2013 Effect Size	
Sensitivity	0.823		0.855	
Specificity	0.357		0.873	
Precision	0.766		N/R	
Likelihood Ratio + (95% CI)	1.280	(1.154 - 1.419)	4.167	(4.144-1.191)
Likelihood Ratio - (95% CI)	0.495	(0.387 - 0.633)	0.158	(0.079-0.238)

Effect size table for the JointMan and Tavares datasets

Description	Count	%
Unspecified Inflammatory Polyarthropathy	235	40.73%
Rheumatoid Arthritis	177	30.68%
Osteoarthrosis	75	13.00%
Connective Tissue Disease	67	11.61%
Psoriatic Arthropathy	67	11.61%
Ankylosing Spondylitis	27	4.68%
Fibromyalgia	23	3.99%
Inflammatory Spondylopathy NOS	22	3.81%
Lupus	13	2.25%
Pauciarticular Juvenile Rheum Arthritis	10	1.73%
IBD Associated Arthritis	7	1.21%
Pseudogout (CPPD)	3	0.52%
Reactive Arthritis (Reiter's Disease)	2	0.35%
Systemic Rheumatoid Arthritis NEC	1	0.17%
Polyarticular Juvenile Rheumatoid Arthritis	1	0.17%

The diagnosis distribution for patients who were recommended for a referral to a rheumatologist. Some patients had multiple diagnoses.

Conclusion: In this study, primary care physicians adeptly referred appropriate ID patients to less accessible rheumatologists (EIA-3 use only modestly increased preselection of ID patients). It is possible that an electronic patient generated screening tool may help primary

providers referring ID patients in less preselected populations (as in the first EIA-3 trial where non-inflammatory diseases were more common).

1. Bell et al. BMC MSK Disorders 2010, 11:50

2. Tavares, R. et al. J. Rheumatol 40(4):417-424

Disclosure: G. Craig, Discus Analytics LLC., 4,Celgene, 8,UCB, 8,Genentech and Biogen IDEC Inc., 8,Novartis Pharmaceutical Corporation, 8,Bristol-Myers Squibb, 8,Novartis Pharmaceutical Corporation, 5,Bristol-Myers Squibb, 5; **K. Knapp**, Discus Analytics, 1,Discus Analytics, 3; **K. Ferguson**, Genentech and Biogen IDEC Inc., 8,Discus Analytics LLC., 4; **R. Tavares**, None; **M. Bell**, Paid Consultant of Janssen Inc., Canada, 5; **S. Schwartzman**, Genentech and Biogen IDEC Inc., 8,Genentech and Biogen IDEC Inc., 5,Abbott Immunology Pharmaceuticals, 5,Abbott Immunology Pharmaceuticals, 8,Janssen Pharmaceutica Product, L.P., 8,Janssen Pharmaceutica Product, L.P., 5,Pfizer Inc, 5,Pfizer Inc, 8,UCB, 5,UCB, 8,Regeneron, 5,Novartis Pharmaceutical Corporation, 8,Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 1254

Knee Pain and Patient Preference for Knee Replacement: Healthcare Access Matters

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Background/Purpose:

Total knee replacement (TKR) is a cost-effective intervention for end-stage knee osteoarthritis (OA). Objectives were to estimate the effect of knee pain severity on willingness to undergo TKR and the impact of healthcare access.

Methods:

The Osteoarthritis Initiative (OAI) is an observational study of participants with or at risk for knee OA. Knee pain severity in the past 30 days was assessed using a numerical rating scale (0-10). Willingness to undergo TKR was ascertained at the 72 month visit. Participants with no history of TKR were included in cross-sectional analyses. Adjusted odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models. Stratified analyses were conducted to evaluate whether healthcare access modified the association between knee pain severity and willingness to undergo TKR, as well as a likelihood ratio test for interaction between knee pain and components of healthcare access.

Results:

The 3530 participants were predominately White (81.2%) and African American (16.7%), with mean age 66.6 years (sd 9.0), and 58.6% female. More than 90% of participants had health insurance.

Participants with severe knee pain, compared to participants without knee pain, expressed less willingness to undergo TKR (OR 0.70, 95% CI 0.55-0.90) with adjustment for age and sex. This association attenuated after further adjustment for comorbidity, and depression (OR 0.80, 95% CI 0.61-1.03) and when further adjusted for health insurance, prescription coverage, healthcare provider, education, income, employment, race, and marital status (OR 0.92, 95% CI 0.68-1.24).

Among participants without health insurance coverage, severe knee pain was associated with significantly decreased odds of willingness to undergo TKR after adjustment for demographic, clinical, healthcare access, and socioeconomic factors (OR 0.08, 95% CI 0.01-0.56) (Figure 1). Similarly, among participants without prescription coverage, those with severe knee pain were significantly less willing to undergo TKR (OR 0.12, 95% CI 0.03-0.41). No association between knee pain and willingness was observed among those with health insurance (OR 1.03, 95% CI 0.73-1.38) and with prescription drug coverage (OR 1.10, 95% CI 0.79-1.53), suggesting that health insurance

and prescription drug coverage modify the association between knee pain severity and willingness to undergo TKR (interaction p=0.015 and p=0.003, respectively).

Conclusion:

Among participants with health insurance and with prescription drug coverage, no evidence of an effect of knee pain severity on willingness to undergo TKR was found. Among participants without health insurance and/or without prescription drug coverage, those reporting severe knee pain were less willing to undergo TKR. This finding reinforces the influence of health insurance on preferences and receipt of appropriate medical care.

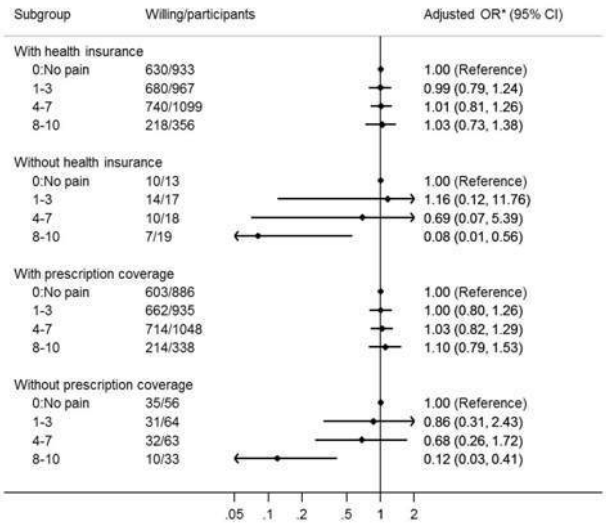

Figure 1. Willingness to undergo knee replacement and knee pain severity, by healthcare access.
P-values for interaction between: pain severity and health insurance coverage (0.003), pain severity and prescription medicine coverage (0.015)
* Adjusted for age(<65 vs. >=65), gender, education, income, current employment, comorbidity, CESD, marital status, health insurance, prescription coverage, health care provider

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Abstract Number: 1255

Medicare Part B Utilization By Rheumatology Health Care Providers As Related to Population Demographics from 2013

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Background/Purpose: In 2015, the Center for Medicare and Medicaid Services released claims data on payments to over 950,000 health care providers paid through Medicare Part B. This study investigated 2013 Part B utilization and costs among rheumatology providers in the state of Illinois, and links between utilization data and local demographics.

Methods: Publicly available 2013 Medicare Part B reimbursement data was compiled through ProPublica Treatment Tracker (https://projects.propublica.org/treatment/). Providers identified by Medicare as rheumatology providers in Illinois (n=191) with

individual practitioner payment and service data were used for analysis. Practice location as defined by Medicare-assigned zip code was used to search 2013 census data (http://www.census.gov) for geographic distributions of race/ethnicity, education, and income. Six provider level outcomes were investigated. Both services delivered and payments were examined for: A) rheumatoid arthritis (RA) biologics; B) osteoarthritis (OA) viscosupplements, and; C) totals billed to Medicare. T-tests investigated differences in mean outcomes between providers who did versus did not order services. Multivariable regression analyses investigated geographic factors associated with any ordering (0/1; logistic regressions) and continuous payments (generalized linear models; gamma family, log link) of RA biologics and viscosupplements.

Results: Total of 191 Illinois rheumatology providers were identified by Medicare for 2013. The top ten providers accounted for 26.5% of total Medicare payments and 32% total number of services. Significant differences between Part B RA biologic utilizers (n=38) and non-utilizers (n=153) existed for: total number of services (mean 42763 vs 4598, p<0.001); services per patient (81 vs 15, p<0.001); total payments ($770,342 vs 108,196, p<0.001); and payment per patient ($1,510 vs 333, p<0.001). Similar data existed for viscosupplements utilizers (n=44) vs non-utilizers (n=147) in terms of: total number of services (mean 3213 vs 6257, p<0.001); services per patient (54 vs 20, p<0.001); total payments ($600,052 vs 132,141, p<0.001); and payment per patient ($1,048 vs 423, p<0.001). There were correlations between biologic utilization for RA and viscosupplements for OA in both total payments (rho = .52, p<0.001) as well as number of services (rho = .48, p<0.001). In adjusted regression analyses, a 1% zip code-level increase in percent white race/ethnicity was associated with both a 4% increase in the odds of any RA biologics orders (p=0.002) and a 6% increase in RA biologics payments (p<0.001).

Conclusion: We observed dramatic differences in 2013 Medicare Part B utilization among rheumatology providers in Illinois for RA biologic and OA viscosupplement use. In adjusted regressions analysis, percent white race was positively associated with RA biologic use. Further research is needed to better understand health care utilization in rheumatology and its relation to population demographics. This study did not investigate quality of care or patient outcomes and did not examine medications not covered under Part B. Payments do not reflect provider profit as providers may incur substantial overhead costs.

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Abstract Number: 1256

Disparities in Total Knee Replacement: Population Losses in Quality-Adjusted Life Years Due to Differential Offer, Acceptance, and Complication Rates in African Americans

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Background/Purpose: Total knee replacement (TKR) is an effective treatment for persons with end-stage knee osteoarthritis (OA). Differences in offer, acceptance, and complication rates for TKR have been documented for racial minorities compared to Whites within the US; however, there has been no translation of these differences into population level lossess of quality-adjusted life-years (QALYs).

Methods: We used the Osteoarthritis Policy Model (OAPol), a validated computer simulation of knee OA, to estimate QALYs lost in African American (AA) men and women compared to Whites (W) due to differences in TKR offer, acceptance, and complication rates.The data on complications, offer and acceptance of TKR were derived from published literature. TKR offer ranged from 10% in AA persons with advanced knee OA to 23% in White persons. Willingness to undergo TKR (acceptance) ranged from 58% for AA men to 84% in W men (Table). Published complication rates ranged from 4.3% in Whites to 6.5% in AA persons undergoing TKR. We validated OAPol model estimates using national data on TKR utilization from the Healthcare Cost and Utilization Project. Future QALYs were discounted at 3%/year. We estimated per person QALY losses due to differential offer, acceptance, and complication rates in AA men and women and calculated population-level person-years lost by multiplying QALY losses by the number of AA men and women with advanced knee OA

in the US. Loss was defined as the QALY difference seen using AA rates of offer, acceptance, and complication, compared to W rates. The population size for those with advanced symptomatic knee OA was obtained from published data (310,000 AA men and 600,000 AA women).

Results: Current utilization of TKR leads to 16,000 QALYs gained for AA men and 50,000 QALYs for AA women (Table). The disparity between offer levels observed in AA and W populations with advanced knee OA may lead to a loss of 71,000 QALYs for African Americans. The increased complication rates experienced by the AA population could lead to a loss of 3,000 QALYs. Assessing the combined effect of lower offer rate and increased complictions for the AA population reveals a QALY loss of 20,100 for AA males and 57,100 QALYs for AA women, leading to over 77,000 QALYs lost overall.

Conclusion: Documented differences in TKR offer rates in conjunction with increased complication rates in racial minorities leads to substantial QALY losses. Increasing the offer of TKR among African American persons and decreasing the complication rates to levels observed in White populations may lead to additional 120% gains in quality-adjusted life years. Programs focused on decreasing the disparities in TKR offer and complications rates in African Americans with diagnosed advanced symptomatic knee OA are urgently needed and such efforts could result in large population-level benfits for racial minorities.

Table. Quality-adjusted life year losses due to lower rates of TKR offer and acceptance and higher rates of complications among African American men and women

				Population QALY Losses				
Cohort	Population Size	Offer	Accept	Current TKR Utilization	Lost to Low Offer	Lost to Low Accept	Lost to High Comp.	Lost to Low Offer and High Comp.
AA-M	310,000	10%	58%	15,700	18,200	7,200	1,300	20,100
AA-W	600,000	10%	63%	49,700	53,340	10,100	2,000	57,500
AA-Both				65,000	71,000	17,300	3,300	77,200

Abbreviations: AA, African American; M, men; W, women; TKR, total knee replacement; Comp., complications; QALYs, quality-adjusted life years

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Disclosure: H. Kerman, None; **S. R. Smith**, None; **J. N. Katz**, None; **E. Losina**, None.

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Abstract Number: 1257

Gender Differences in Ankylosing Spondylitis Patients Treated with Anti-TNF in Daily Practice with Ten Year Follow up

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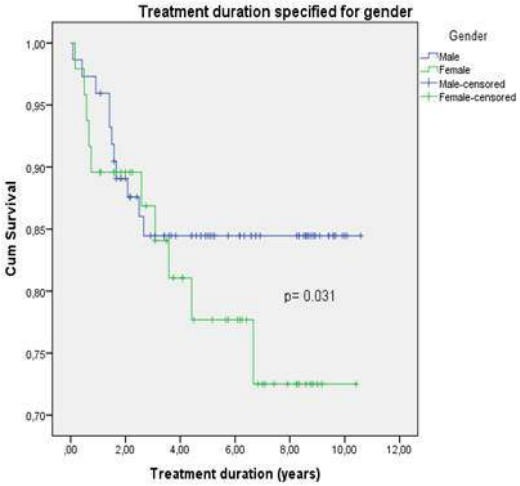
Background/Purpose: Anti-TNF treatment is available for Ankylosing Spondylitis (AS) for many years now, but the data on long term follow up in daily practice are limited. To determine treatment survival and adverse events of anti-TNF treatment in AS patients in a large peripheral hospital in daily practice. Also, gender differences in drug survival and side effects were studied.

Methods: Retrospective data were collected from AS patients treated with etanercept, infliximab and adalimumab in the period of January 2004 until January 2014 in the Kennemer Gasthuis. Statistical analyses were performed with Kaplan Meijer survival curves to describe the drug survival and occurrence of adverse events in time.

Results: In total 122 ankylosing spondylitis patients were included with 159 treatment episodes (defined as time on drug) over a 10 year time period. The mean treatment duration was 51 months (range 1-127 months). Females showed a significant shorter treatment period compared to males (33.4 vs. 44.9 months) (Figure 1). Overall, 21% of the patients stopped the TNF alpha inhibitor after a mean period of 15 months, mainly due to inefficacy (53.7%). Only 6 patients stopped because of infections (mild) and no patients had malignancies. Female patients switched more often compared to male patients (26.9% vs. 16.3%). Females had a significantly higher risk (26%) at

developing infections compared to males (19%).

Conclusion: Over a mean treatment period of 4.3 years (51 months), nearly 80% of the patients treated with anti-TNF treatment continued using these drugs. Females showed a significant shorter treatment period compared to males (33.4 vs. 44.9 months). The most important stop reason was inefficacy. Women developed significantly more often infections during anti-TNF treatment than men.



Disclosure: T. Rusman, None; **S. ten Wolde**, None; **S. M. Euser**, None; **T. van der Ploeg**, None; **O. van Hall**, None; **I. E. Van der Horst - Bruinsma**, None.

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Abstract Number: 1258

Female Gender Is Associated with a Poorer Response to TNF-Inhibitors in Ankylosing Spondylitis

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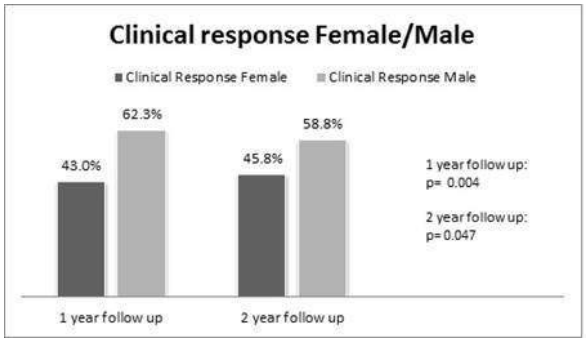

Background/Purpose: Limited data is available on the influence of smoking, Body Mass Index (BMI) and gender on disease activity and

response to TNF inhibitors in ankylosing spondylitis (AS). This study aims to determine whether these factors influence time of diagnosis, disease activity and response to TNF inhibitors.

Methods: In a prospective study, disease activity data (Ankylosing Spondylitis Disease Activity Score (ASDAS and BASDAI)) were collected from patients included in a real life observational cohort, who started or switched treatment TNF inhibitors. Data were collected at baseline, 6, 12 and 24 months. Independent T-tests and linear regression analyses were performed to assess the different factors their influence on time of diagnosis diagnosis and change in disease activity.

Results: In total 312 consecutive AS patients were included with a mean follow-up of 18.9 months. Most patients (172, 55%) showed improvement after the start of TNF inhibitors whereas, 86 patients (27.7%) had a clinically important improvement (i.e. decrease in ASDAS > 1.1) and 86 (27.7%) a major clinical improvement (decrease in ASDAS > 2.2). BMI was significantly correlated with time of diagnosis (p=0.016; 95%CI: 0.07 – 0.65): an increase of BMI with three points extended the AS diagnosis with one year. Smoking and gender were not correlated with the baseline ASDAS. BASDAI and BASMI at baseline were both influenced negatively by BMI. Gender was significantly associated with the clinical response (BASDAI50% or a 2 point decrease) to TNF treatment (p=0.041). More male patients showed clinical improvement on TNF treatment compared to female patients: at one year follow up 62.3% vs. 43.0 % and at two year follow 58.8% vs. 45.8% (figure1). Adjustment for BMI as confounder lead to a stronger statistical significance for gender difference in clinical response (p=0.022).

Conclusion: The most interesting finding was that females had a significantly lower clinical response to TNF treatment compared to males. Furthermore, high BMI not only extended the AS diagnosis up to one year, but also negatively influenced the BASDAI and BASMI scores. It seems that BMI and female gender are associated with clinical response to TNF treatment.

Disclosure: T. Rusman, None; **M. Nurmohamed**, None; **J. C. van Denderen**, None; **I. Visman**, None; **I. E. Van der Horst - Bruinsma**, None.

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Abstract Number: 1259

Factors Influencing Patient's Participation in Rheumatology Research Studies: Experience from a Single Academic Centre

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Background/Purpose: There is a drive to offer all patients the opportunity to participate in clinical research. We aimed to investigate the eligibility, screening and participation of rheumatology patients in clinical research studies in a single academic rheumatology department to identify targets for improving patient engagement with research

Methods: Methods: This study was conducted in two phases. Phase 1 was a retrospective analysis of study screening logs over 12 months. In phase 2; the outpatient population was surveyed using a questionnaire to identify the motivators and barriers to research participation. Comparisons were made using chi-squared tests and logistic regression models where appropriate.

Results: In phase 1 of the study we identified 1025 patients who were eligible for screening (median [IQR] age 47 [18-85] years; 87% female); 566 (55%) had been screened for any study. Of these, 217/566 (38%) were subsequently enrolled. Enrollment varied by ethnicity. Reasons for screen failure included study ineligibility (54%) and patient factors (29%). There was significant variation in these reasons by ethnicity (P=0.047), however this was not clearly due to patient factor (P = 0.091). Females were more likely to be ineligible (OR [95%

CI] 1.78 [1.08, 2.95]) and increased age was associated with declining research participation (OR 0.98 [0.95, 0.998]). In phase 2, 152 participants including 117 (77%) women, responded to our survey (overall response rate 25% [Caucasians 45%, Non-Caucasians 7%]). Their median [IQR] age was 50 [17-84] yrs and our sample included 111 (73%) Caucasians and 41(27%) non-Caucasian ethnicity. Overall, 50 (33%) had ever been invited to research, of whom 71% participated. The key motivational factors were to contribute to scientific knowledge (94%), to help other patients (89%) and personal health benefits (47%). The major factors for non-participation were study ineligibility (47%), stopping/changing current medication (33%), inadequate information about the study (27%) and inconvenience (27%). Overall, 87/152 (57%) were happy to participate in future studies .The main influencing factors were potential help to others (98%),contributing to scientific knowledge(96%),quality of information given about the study (79%) and understanding of what study involved (76%). Non-Caucasians were less likely to participate (p=0.052); however, main spoken language (p=0.102) and employment status (P=0.395) had no influence on deciding whether to take part in research. We also found that Caucasians were significantly more likely to be approached to research (P=0.004) and previous research experience had a positive impact to participate in future research (P=0.001).

Conclusion: Our study identified a number of barriers to research participation. Almost half of patients were never even considered or screened for research eligibility, and many failed screening. This may reflect study case mix/design; however there was also variability in participation according to ethnicity. Strategies to facilitate a universal research offer and support study involvement will need to account for ethnic variation in patient characteristics and beliefs about research.

Disclosure: M. Khan, None; **J. A. Reynolds**, None; **K. Kumar**, None; **S. Peters**, None; **C. Yemidale**, None; **I. N. Bruce**, None; **B. Parker**, None.

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Abstract Number: 1260

Association of Traditional Chinese Medicine Use and Adherence to Prescribed Western Medications in Chinese-American Rheumatology Patients

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Background/Purpose: Chinese-Americans are one of the fastest growing immigrant groups in the US. They often use Traditional Chinese Medicine (TCM), but whether that affects medication adherence is unknown. This question is important because data suggest that ethnic Chinese have more severe SLE and RA than Caucasians, and thus nonadherence could be especially problematic. This study evaluates whether TCM use is associated with nonadherence to western medicines prescribed for chronic rheumatic diseases among Chinese-American patients. Secondary aims are to explore differences in self-reported health status between TCM users and non-users.

Methods: Recruitment was from a rheumatology clinic that serves a predominantly Chinese-American immigrant population. A bilingual Mandarin/English speaker evaluated TCM use, medication adherence, patient-reported outcomes from the Patient-Reported Outcomes Measurement Information System (PROMIS), and other patient-level factors, all administered with validated instruments available in English and Mandarin. Inclusion criteria included speaking Mandarin or English, prescription of ≥ 1 medication by the rheumatologist, and being actively followed for a systemic rheumatic disease or OA of hands, knees, or hips. Those with only fibromyalgia, neck/back pain, or other soft tissue diseases were excluded. Adherence was analyzed as low, medium or high based on the 8-item Morisky Medication Adherence Scale.

Results: Seventy-three enrolled, mean age 56y (range 22-97), 59% female, 77% Medicaid, and only 21% spoke English. Diagnoses included RA (37%), spondyloarthropathies (22%), SLE (15%), SS (7%), gout/pseudogout (7%), OA (3%), and other (9%). Forty-nine percent reported TCM use in the past year, most commonly massage (53%), acupuncture (47%), and herbs (44%). There was a trend for TCM use to be more common in SLE vs. RA (65% vs. 37%, p=0.5) and TCM users had a shorter disease duration (5.3 vs. 11.2 years, p=0.03). Overall, 70% reported nonadherence to rheumatic medication. In multivariate analysis adjusting for patient characteristics, TCM

use was not associated with lower adherence (OR 0.34, 95% CI 0.09-1.26), while herb use was associated (OR 5.3, 95% CI 1.09-25.87). TCM users also had worse PROMIS scores in anxiety (mean T-score 52 vs. 46, p=0.01) and depression (mean T-score 52 vs. 46, p=0.007), and a trend for worse pain (mean T-score 58 vs. 56, p=0.2), fatigue (mean T-score 55 vs. 51, p=0.1), function (mean T-score 43 vs.47, p=0.1), and worse ability to participate in social roles and activities (mean T-score 55 vs.59, p=0.06).

Conclusion: In this group of poorly integrated Chinese-American rheumatology patients, most were non-adherent with western medicines, but only herb use was associated with non-adherence. This could reflect two divergent beliefs towards TCM. In general TCM is "complementary", but herb may be seen as an "alternative" to western medicine. In addition, TCM users had worse scores in several important self-reported health domains. This may indicate unmet needs, particularly in mental health. These associations should be explored longitudinally, including the association of TCM use and adherence on disease activity.

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Abstract Number: 1261

Reliability and Validity of the Patient Health Questionnaire-9 for Assessment of Depression in Socioeconomically Disadvantaged Latinos with Rheumatoid Arthritis Living in the United States

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Background/Purpose: Depression is highly prevalent in rheumatoid arthritis (RA). The Patient Health Questionnaire-9 (PHQ-9) is a simple screening tool widely used in medical settings and validated in multiple ethnic and linguistic groups. However, its measurement properties have not been assessed among low socioeconomic status (SES) Spanish-speaking Latinos with RA. We investigated factor structure, reliability and validity of the Spanish-language PHQ-9 in low SES Latinos with RA living in the US.

Methods: We evaluated 447 patients from a single center. On the PHQ-9, participants rated from 0 (none) to 3 (almost daily) their feelings of depressed mood and 8 other symptoms of depression (see Table 1). Total scores (0-27) correspond to depression severity levels: minimal (0-4), mild (5-9), moderate (10-14), and moderately severe to severe (>=15). Internal consistency and reliability were examined with Cronbach's alpha and corrected item-total correlations. Confirmatory factor analysis (CFA) assessed the hypothesized unidimensional factor structure. Multi-group CFA examined the generalizability of the factor structure across distinct patient subgroups. Convergent validity was explored via correlations among PHQ-9 scores and measures of health-related quality of life (Physical and Mental Components of the 36-Item Short Form Health Survey), disability (Health Assessment Questionnaire disability index), activity impairment (Work Productivity and Activity Impairment Questionnaire), fatigue VAS, pain VAS, patient and evaluator global assessments of disease activity, and Disease Activity Score 28 (DAS28-3 ESR).

Results: Patients were 89% female with a mean age of 52.6 years and mean RA duration of 10.7 years. The internal consistency of the PHQ-9 was good (a =.91) and all corrected item-total correlations reached an acceptable level (Table 1). CFA showed the one-factor solution provided a good fit to the data: S-Bx^2(27) = 67.85, p <.05, CFI =.971, TLI =.961, RMSEA =.058 with all significant factor loadings (Table 1). Multi-group CFA demonstrated the factor structure can be generalized across age groups, RA disease duration and levels of disease activity. Convergent validity was supported by significant associations of PHQ-9 scores and severity levels in the expected directions with related measures (Table 2).

Conclusion: Findings support use of the PHQ-9 as a brief, low-burden screen for depression in low SES Spanish-speaking Latinos with

Table 1. Standardized factor loadings and descriptive statistics for PHQ-9 items

PHQ-9 Item	CFA Factor Loading	Item Mean (SD)	Item-Total Correlation	α if Item Deleted
1. Anhedonia	.790*	1.11 (1.11)	.728	.893
2. Depressed mood	.867*	0.95 (1.07)	.815	.886
3. Sleep difficulties	.738*	0.98 (1.13)	.703	.895
4. Feeling tired	.800*	1.32 (1.08)	.752	.891
5. Appetite changes	.690*	0.84 (1.03)	.663	.898
6. Feelings of worthlessness	.735*	0.69 (0.98)	.706	.895
7. Concentration problems	.668*	0.64 (0.95)	.653	.899
8. Psychomotor agitation/retardation	.673*	0.58 (0.96)	.650	.899
9. Suicidal thoughts	.498*	0.24 (0.64)	.478	.909

Note. Cronbach's alpha for the PHQ-9 total score was α = .907. *p < .001.

RA.

Table 2. Evaluation of convergent validity

		PHQ-9 Depression Symptom Severity Level			
	PHQ-9 total Pearson's *r*	Minimal	Mild	Moderate	Severe
		Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
SF-36 Physical	-.528*	55.51 (25.86)[a]	44.82 (22.53)[b]	29.37 (18.89)[c]	19.43 (10.89)[c]
SF-36 Mental	-.646*	72.94 (21.65)[a]	54.39 (18.33)[b]	45.21 (17.57)[b]	30.84 (16.84)[c]
Disability (0-3)	.500*	0.75 (0.74)[a]	1.36 (0.75)[b]	1.57 (0.68)[bc]	1.83 (0.65)[c]
Activity impairment	.557*	32.31 (30.49)[a]	55.77 (27.33)[b]	63.67 (22.33)[bc]	76.48 (20.39)[c]
Fatigue VAS (0-10)	.644*	2.22 (2.52)[a]	4.54 (2.53)[b]	5.82 (2.57)[c]	7.52 (2.38)[d]
Pain VAS (0-10)	.517*	0.92 (0.73)[a]	1.40 (0.69)[b]	1.76 (0.79)[c]	2.02 (0.71)[c]
PGA (0-10)	.625*	3.03 (2.32)[a]	4.91 (2.41)[b]	6.17 (2.48)[c]	7.67 (2.08)[d]
EGA (0-10)	.238*	2.04 (2.83)[a]	3.17 (3.01)[b]	3.93 (3.15)[b]	3.88 (3.39)[b]
DAS28-3 ESR	.288*	3.41 (1.21)[a]	4.01 (1.26)[b]	4.36 (1.30)[b]	4.38 (1.47)[b]

Note. Pairwise contrasts between each PHQ-9 depression symptom severity level for a given variable were Bonferroni corrected. Values in a row sharing common superscript letters do not differ significantly (p > .05). PGA = Patient global assessment of disease activity, EGA = Evaluator global assessment of disease activity.
*p < .001.

Disclosure: S. Ormseth, None; **T. Draper**, None; **E. Hernandez**, None; **G. A. Karpouzas**, None.

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Abstract Number: 1262

Sociodemographic and Clinical Correlates of Physical Therapy Utilization in Adults with Symptomatic Knee Osteoarthritis

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Background/Purpose: Although physical therapy (PT) is recommended for managing symptomatic knee osteoarthritis (sxKOA), little is known about correlates of PT utilization among adults with sxKOA. This study aimed to: (1) describe the prevalence of PT utilization among adults with sxKOA enrolled in an exercise trial and (2) identify sociodemographic and clinical correlates of PT utilization for sxKOA.

Methods : This cross-sectional study is a secondary analysis of data from a randomized controlled trial (RCT) of 350 adults (aged >=18 years) with physician-diagnosed sxKOA (median WOMAC pain=5, range=0-20, and median WOMAC function=22.5, range =0-68) recruited from a large tertiary medical center and an ongoing prospective cohort study. Patients completed baseline demographic and medical history questions and whether they had utilized PT to manage sxKOA (yes/no). Logistic regression was used to develop a parsimonious set of correlates of PT utilization, with all models adjusted for body mass index and age. We evaluated all race by predictor and gender by predictor pairwise interactions.

Results : Of 350 patients, 249 (74%) were Caucasian, 72% female, 50% obese or very obese, mean age was 62.5 years (SD=11.3). The median duration of KOA symptoms was 10 years (<1 to 65). 147(42%) had received a knee joint injection, 175 (50%) had a prior knee injury, and 182 (52%) reported PT utilization for their KOA. Factors independently associated with increased odds of PT utilization were: female gender, having a college education, history of a knee injury, duration of KOA symptoms, and having family members with KOA. Individuals who were Caucasian and had received a joint injection were 3.69 times more likely to have utilized PT; this relationship did not exist for non-Caucasians (Table 1). Employment tended to be associated with a reduced likelihood of PT utilization.

Conclusion : Of persons with sxKOA that enrolled in an exercise intervention, roughly half reported prior PT utilization. Demographic and clinical features were associated with PT utilization for adults with sxKOA; strongest correlates were female gender, higher education, and longer duration of KOA symptoms. Differences by race in the link between joint injection and PT may reflect a reduced likelihood of health interventions for sxKOA among non-Caucasians. More research is needed to facilitate PT utilization among adults with sxKOA, especially men and those with lower educational attainment. Limitations of this study include the use of a convenience sample enrolled in an RCT, the potential for misclassification of PT utilization due to self-report and inability to determine whether lack of utilization was due to clinicians not offering PT or patients not attending PT. Diverse characteristics of the sample allowed for evaluation of PT utilization by race.

Table 1. Correlates of Physical Therapy Service Use for Managing Knee Osteoarthritis from Multivariable Logistic Regression (n=348)

		Model c statistic = 0.74	
Explanatory variable	**Odds Ratio**	**95%CI**	**p-value**
Have received a joint injection Caucasian	3.69	1.94 – 7.01	<0.0001
Non-Caucasian	1.18	0.44 – 3.18	0.748
Female	3.06	1.58 – 5.93	0.001
College educated	2.44	1.15 – 5.16	0.020
Having at least 1 Family Member with KOA	1.64	0.95 – 2.87	0.07
History of Knee Injury	1.86	1.08 – 3.19	0.025
Employed	0.58	0.36– 1.00	0.0502
Duration KOA symptoms, years > 5 to 10 > 10 Referent < 1 to 5	2.16 2.11	1.09 – 4.29 1.1 – 4.04	0.02 0.025

* P-value for interaction 0.058*

Disclosure: M. D. Iversen, None; **T. A. Schwartz**, None; **L. F. Callahan**, None; **Y. M. Golightly**, None; **A. P. Goode**, None; **C. Hill**, None; **K. Huffman**, None; **A. Pathak**, None; **K. Allen**, None.

therapy-utilization-in-adults-with-symptomatic-knee-osteoarthritis

Abstract Number: 1263

Implicit Biases Influencing Service Provision in Physical Therapy for Low Back Pain

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Background/Purpose: The management of physical therapy (PT) services may raise concerns about equity. Previous research suggests that certain individuals have less access to services and receive inferior quality care compared to others due to their age, gender or socio-economic status (SES). Insurance status may also influence the clinical practice of PT professionals. Our study aimed to determine whether patient-related factors (age, gender, SES) and the source of reimbursement for PT services (insurance status) influence waiting time, frequency and duration of PT treatment for low back pain.

Methods: We conducted an empirical cross-sectional online survey of Canadian PT professionals. 846 PT professionals completed a survey containing one of 24 different clinical vignettes (i.e., patient case scenarios with low back pain) chosen at random, and a 40-item questionnaire about how they would treat the fictional patient in the vignette, as well as details on their professional clinical practice. Each vignette described a patient with low back pain but with variations in patient characteristics (age, gender, SES) and insurance status (none, private insurance, workers' compensation board (WCB)).

Results:

The age, gender and SES of patients did not make any difference in how participants would provide service. However, patients with no insurance coverage would wait longer ($p=0.002$) for access to PT in private clinics, while patients with WCB insurance would be seen more frequently ($p<.0001$) than patients with private insurance or no insurance, in both public and private clinics. However, when explicitly asked, study participants stated that insurance status, age or chronicity of the condition were not factors associated with treatment access, frequency or duration.

Conclusion: The study findings demonstrate an implicit professional bias in favour of preferentially treating patients with low back pain who have insurance; the resulting inequity in access highlights the urgent need for national guidelines to ensure equity in access to and provision of PT services.

Disclosure: M. Laliberté, None; **B. Mazer**, None; **T. Orozco**, None; **G. Chilingaryan**, None; **B. Williams-Jones**, None; **M. Hunt**, None; **D. Ehrmann Feldman**, None.

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Abstract Number: 1264

Pilot Evaluation Points to Male Specific Educational Programming for Males with SLE

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Background/Purpose: While studies report that SLE affects primarily women, males with SLE represent 4-22% of SLE patients. Support & education has improved self-management & coping strategies, including sexual health (SH) issues. Beliefs about what it means to be a male having a "women's disease" can undermine good preventative & SH care for men with SLE. Further, despite research demonstrating higher mortality for males, males with SLE tend to seek medical attention & supportive care less often than females. A hospital-based support & education program, ongoing since 1994, conducted a pilot survey to identify self-reported needs & concerns for men with SLE.

Methods: Ten males with SLE were recruited to participate in a pilot, semi-structured 30 min phone interview; consisting of 6 scripted open-ended questions, focused on: SLE knowledge, impact, communication with doctor & partners, SH & interest in male specific programing.

Results: Three males were African-American, 3 Latino & 1 Asian; mean age 26, mean years since diagnosis 9. All males demonstrated good baseline understanding of SLE & describing it as "unpredictable" & a "women's disease." The areas of their lives most affected by SLE, included: physical limitations, personal relationships & work/school. Other themes related to masculine/cultural stereotypes, suggesting that seeking care or asking for help is "weak." "I am told to man up, seeing a therapist is taboo in my family." All males agreed these views contributed to increased physical activity despite known limitations, to combat feelings of weakness. All males reported attending primarily "female support groups"& expressed inability to relate to women's experiences with SLE due to different life concerns, "there is no sense of connection." When asked about SH concerns, fears about infertility & feeling uncomfortable talking to their doctors or partners about these issues were shared. All men were concerned about medication side effects contributing to SH & other health factors. Additionally, all males reported never talking directly with their rheumatologists regarding SH & SLE. When asked why, the majority indicated they preferred to be asked directly by providers. All expressed a desire for more tailored SH education as it relates to their SLE & a male specific support group addressing the following areas: communication issues with doctors & partners, strategies for sexual decision making & general SH topics. When asked if they would attend said programming, all replied affirmatively.

Conclusion: Despite our small sample size, our pilot shows an unmet need for this population, which potentially impacts on psychosocial, SH, disease self-management & outcomes. Despite some (primarily Web based) support forums for males with SLE, no peer reviewed literature was found reporting on the efficacy of these interventions. The next step is to develop a more robust needs assessment to address barriers & best interventions in partnership with the rheumatology community.

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Abstract Number: 1265

Ultra-High Field MRI and Biomechanical Investigation of Vertebral Bone Microarchitecture

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Background/Purpose: The purpose of this study was to investigate bone microarchitecture variables of cadaveric vertebrae using ultra-

high field MRI (7 Tesla).

Methods: Twenty four vertebrae (L2, L3, L4) from eight cadavers were studied using 7 Tesla MRI. Their Bone Mineral Density (BMD) were investigated using dual energy X Ray absorptiometry. Then, all specimens underwent mechanical compression tests to failure and the failure load (in Newton) and constraint (in Mpa) were measured. Bone Volume Fraction (BV/TV), Trabecular Thickness (Tb.Th), and Trabecular Spacing (Tb.Sp) were measured in MR images using a Digital topological analysis (Bone J). Measurements were performed by two observators in order to characterize the inter-rater reliability. Statistical analyses were performed using SPSS. Correlations between variables were analyzed using Spearman correlations and Stepwise regression. A p value of 0.05 was considered as significant.

Results: The inter-rater reliability for bone microarchitecture parameters quantification was good. Tb.Th and Tb.Sp measured using high-field MRI were 0.52±0.18 and 0.48 ± 0.10 respectively while the BV/TV fraction was 0.52 ± 0.13. The mean BMD was 0.86 ± 0.20 g/cm^2. The failure load and the constraint measured during the compression tests were 2600 ± 1267N and 1.57 ± 0.81 Mpa respectively. Interestingly, the variables measured during the mechanical tests were significantly. The failure load and constraint measured during the compression tests were significantly correlated with the BMD. Regarding the bone indices quantified using high-field MRI, a significant linear relationship was observed between the trabecular spacing and the BMD ($R^2 = 0.23$, $p = 0.01$) and the constraint values to failure ($R^2 = 0.18$, $p = 0.04$). A stepwise regression with backward elimination demonstrated that combining BV/TV and BMD improved the relationship with the constraints from an adjusted $R^2 = 0.384$ for BMD alone to an adjusted $R^2 = 0.41$ for BMD + BV/TV.

Conclusion: In the present study, we demonstrated for the first time that the variables characterizing the vertebral bone microarchitecture quantified using ultra-high field MRI were significantly correlated with biomechanical parameters. In addition, we illustrated that the vertebral bone strength was better described by a variable combining BMD and trabecular bone spacing.

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Abstract Number: 1266

Predictors of Radiographic Progression in Early Rheumatoid Arthritis Patients Treated By an Aggressive Treat-to-Target Regimen

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Background/Purpose: With implementation of tight control strategies and defined treatment targets in rheumatoid arthritis (RA) care, a majority of early RA patients may reach remission and traditional predictors of joint damage might no longer be present. The aim of our study was to identify baseline parameters predictive of 2-year radiographic progression in an early RA population treated by a semi-personalized treat-to-target strategy.

Methods: DMARD naive RA patients with <2 years from first patient reported swollen joint, who fulfilled the 2010 ACR/EULAR criteria, were included in the ARCTIC study. Patients were followed for 24 months with treatment according to an aggressive algorithm targeting clinical remission (DAS <1.6 and SJC44=0), and in half the patients an additional target was imaging remission (absence of ultrasound PD signal). Patients with risk factors for progressive joint destruction (ACPA or RF positive with baseline erosions, or MRI bone marrow edema) could be escalated more rapidly from MTX monotherapy to biologics. Radiographs were scored by two readers using the van der Heijde-Sharp score (vdHSs), with cut-off 1 unit or more change/year to be classified as progression. Potential baseline predictors were analyzed for collinearity, and remaining variables assessed by univariate logistic regression. Variables with univariate $p<0.25$ were included in the multivariate model building, and $p<0.05$ was required to remain in the model.

Results: Mean [SD] disease duration for the 222 patients was 7.2 [5.4] months, and mean DAS based on 44 joints was 3.5 [1.2]. 72% were RF and 82% ACPA positive. 41% had radiographic progression at 24 months, while DAS remission was reached by 68%. In 16%

treatment was escalated more rapidly due to baseline risk factors. In univariate models, gender, age, smoking, RF, tender joints, 44 SJC, ESR, total GS-score, total PD-score and vdHSs at baseline had p<0.25, while BMI, disease duration<3months, ACPA and patient global had p>0.25. In the multivariate model, RF positivity (OR 2.27, p=0.022), total vdHSs (OR 1.08, p=0.017) and ultrasound GS score (OR 1.03 per unit, p=0.019) were independent baseline predictors of radiographic progression at 24 months (table). Ultrasound PD was not an independent predictor in secondary models built without GS or in separate models for the two strategy arms, neither as a continuous nor dichotomized variable according to the mean (9.8) and median (7) baseline score.

Table: Multivariate model for baseline predictors of radiographic progression at 24 months (corrected for age and gender). Radiographic progression occurred in 92/222.

	Univariate		Multivariate	
Baseline variables	**OR [CI]**	**P-value**	**OR [CI]**	**P-value**
US GS-score (0-96)	**1.03 [1.01, 1.05]**	**0.005**	**1.03 [1.00, 1.05]**	**0.019**
RF positivity (IgM/IgA)	**1.78 [0.96, 3.29]**	**0.07**	**2.27 [1.13, 4.57]**	**0.022**
Total van der Heijde Sharp score	**1.11 [1.06, 1.17]**	**<0.001**	**1.08 [1.01, 1.14]**	**0.017**

Conclusion: RF positivity, radiographic joint damage and ultrasound gray-scale score were independent baseline predictors of joint damage in early RA patients treated according to an aggressive treatment regimen aiming for remission. This indicates that further individualization of treatment based on risk factors might be needed to optimize disease outcomes, also in treat-to-target strategies.

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Abstract Number: 1267

Application of the Spondyloarthritis Research Consortium of Canada Magnetic Resonance Imaging Sacroiliac Joint Structural Score in Chinese Patients with Axial Spondyloarthritis

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Background/Purpose: There is an unmet need for reliable assessment of structural progression in the sacroiliac joints (SIJ) of patients with axial spondyloarthritis (SpA), but radiography is unreliable and lacks responsiveness. The Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ Structural Score (SSS) is developed and proved to be a new reliable scoring method for evaluating structural lesions based on magnetic resonance imaging (MRI). In this study, we tried to record the features of structural lesions using SSS and to validate SSS in Chinese patients with axial SpA.

Methods: Three readers (two radiologists and one rheumatologist) investigated fat metaplasia, erosion, backfill and ankylosis seen on MR images from 423 patients. All these patients fulfilled the 2009 ASAS classification criteria for axial SpA. The SSS method for assessment of these four kinds of structural lesions was based on T1-weighted spin echo MRI, and dichotomous scoring (lesion present/absent) of five consecutive slices through the cartilaginous portion of the joint. Scoring ranges were fat metaplasia (0-40), erosion (0-40), backfill (0-20), and ankylosis (0-20).

Results: There were 342 male and 81 female patients included. The mean age of them was 26.2±8.4 years old. Their symptom duration was 4.7±6.1 years. The total SSS score (sum of four kinds of lesions) of them was 18.4 ± 9.1. 372 (88.0%) were recorded with fat

metaplasia, 343 (81.1%) patients were recorded with erosion, 246 (58.2%) were recorded with backfill, and 104 (24.6%) were recorded with backfill. There were no differences of the rates of four kinds of lesions appeared on the left or the right SIJ (all $p>0.05$). Erosion and backfill were more frequently seen in the upper half than in the lower half SIJ (both $p<0.05$). The ilium bones were with more often with erosion and fat metaplasia than the sacrum bones (both $p<0.05$). Interobserver reliability was good for fat metaplasia (ICC 0.70-0.75), also good for erosion (ICC 0.67-0.73), fair to good for backfill (ICC 0.56-0.66), and good to excellent for ankylosis (ICC 0.78-0.88).

Conclusion: The SPARCC MRI SSS method could detect structural changes in the SIJ with acceptable reliability in Chinese patients with axial SpA.

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Abstract Number: 1268

Hand Bone Loss in Early Rheumatoid Arthritis Is Independent of Adalimumab Treatment – Results from a Randomized Controlled Clinical Trial.

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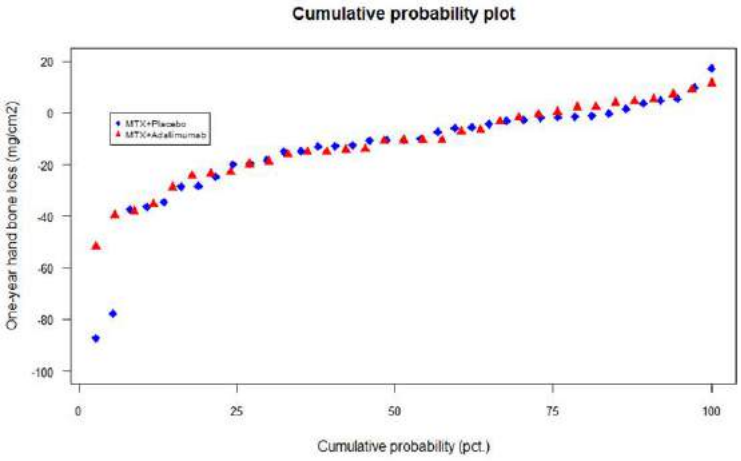
Background/Purpose: Rheumatoid arthritis (RA) is characterised by progressive destruction of joint bone and loss of periarticularbone mineral. Hand bone loss (HBL) measured by Digital X-ray Radiogrammetry (DXR) has been proposed as a sensitive outcome measure for treatment effect and as a potential predictor of subsequent radiographic progression in RA patients. We aimed to investigate the effect of adding adalimumab to a methotrexate and intra-articular triamcinolone treat-to-target strategy on one-year hand bone loss ($HBL_{one\text{-}year}$) in early rheumatoid arthritis (RA) and to determine if $HBL_{6months}$ is associated with radiographic progression after two years.

Methods: In a clinical trial (OPERA) of 180 treatment-naive early RA patients (1), bone mineral density (BMD) was estimated from hand radiographs with Digital X-ray radiogrammetry (DXR) at baseline, after 6 months (n=90) and 12 months (n=70) of follow-up. Baseline and two-year radiographs were scored according to the Sharp/van der Heijde method. Baseline characteristics and $HBL_{6months}$ (0-6 months changes in DXR-BMD) were investigated as predictors of structural damage by univariate linear (DTotal Sharp/van der Heijde Score (TSS) as dependent variable) and logistic (+/-radiographic progression (DTSS>0) as dependent variable) regression analyses. Variables with $p<0.10$ were included in multivariable models.

Results: In 70 patients with available $HBL_{one\text{-}year}$ data, $HBL_{one\text{-}year}$ was median (InterQuartileRange(IQR)) -1.9 (-3.3;-0.26 mg/cm^2) in the placebo-group and -1.8 (-3.6;0.06) mg/cm^2 in the adalimumab-group, p=0.98,Mann Whitney (Figure 1). Increased HBL (compared to general population reference values (2)) was found in 26/37 and 23/33 patients in the placebo- and adalimumab-groups, Chi-sq=0.99. In 90 patients with $HBL_{6months}$ data and two-year radiographic data, $HBL_{6months}$ was independently associated with DTSS after two years (β=-0.086 (95% Confidence Interval=-0.15;-0.025) TSS unit/mg/cm^2 increase,p=0.006), and borderline associated with presence of

radiographic progression (DTSS>0) (OR 0.96(0.92-1.0), p=0.10).

Conclusion: In early RA, adding adalimumab to a methotrexate-based treat-to-target strategy had no impact on $HBL_{one\text{-}year}$, which was increased in both treatment groups. $HBL_{6months}$ was independently associated with DTSS after two years. **References:** 1) Hørslev-Petersen et al. *Ann Rheum Dis.* 2015 doi: 10.1136/annrheumdis-2015-208166. 2) Ørnbjerg LM et al. *Arthritis Research & Therapy*.2016,



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Abstract Number: 1269

Description of Radiographic Hip Measurements By OA Status in a Large Community-Based Study of African American and White Men and Women

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Background/Purpose: There has been increasing interest in hip morphology as a risk factor for OA. There is a need for frequency estimates in the general population (Dickenson OAC 2016). We aimed to provide a description of these measures in a well-characterized community-based cohort.

Methods: This cross-sectional analysis involved data collected during 1991-1997 from the Johnston County OA Project. Hip morphology measures were defined using OxMorf software (Oxford, UK). Radiographic hip OA (rHOA) was defined, at the participant level, if at least one hip had Kellgren-Lawrence grade 2 or more. Descriptive means and 95% confidence intervals for hip measures were obtained from unadjusted regression and logit models, as appropriate, using GEE to account for within-participant hip correlation, stratified by sex and rHOA status; comparisons were qualitative.

Results: Complete data were available for 4519 hips from 2263 individuals, mean age 64 years, mean BMI 29 kg/m^2, 30% African American, 39% male. Several measures although different by sex, did not differ substantially between those with and without rHOA (triangular index height, femoral shaft angle, extrusion index, coxa profunda). Results for those without rHOA are shown in Table 1. Only crossover sign (~20%) and lateral center edge angle (CEA) <=25 degrees (~25%) were more frequently seen in the non-rHOA compared with the rHOA group. Pathologic AP alpha angles over 60 degrees were seen in 20% of men and 7% of women, while only around 1% had a triangular index sign, both signs of cam-type morphology. About a quarter had CEA <=25 degrees, consistent with mild dysplasia. In contrast, several measures were higher in those with rHOA in at least one hip (Table 2), including AP alpha angle, Gosvig ratio, the proportion with triangular index sign, CEA >40 degrees, and protrusio acetabuli. AP alpha angle > 60 degrees was twice as common in those with rHOA (26% overall; 39% of men, 20% of women) versus those without, and 5% had a triangular index sign. Other measures suggestive of cam type deformity (continuous alpha angle and Gosvig ratio) were also higher compared to the non-rHOA group. CEA > 40 degrees was about twice as frequent among men and women with rHOA versus those without. Protrusio was twice as frequent among women with versus women without rHOA, but was rare in men.

Conclusion: One out of 5 men without rHOA, and 2 out of 5 with rHOA, have a pathologic AP alpha angle in this sample. Radiographic assessment of most measures is confounded by morphologic changes due to rHOA; however, some were not. Both cam-type (alpha angle, Gosvig ratio) and pincer-type (protrusio, CEA >40 degrees) were more common in those with rHOA.

Table 1. GEE estimates of means and frequencies (with corresponding 95% confidence intervals), stratified by sex among those WITHOUT rHOA at baseline (KLG 0 or 1, n=1599)

Morphologic measure	Overall (n=1599)	Men (n=661)	Women (n=938)
AP alpha angle, mean°	48.4 (47.9, 48.9)	51.4 (50.6, 52.2)	46.3 (45.7, 46.9)
AP alpha angle >60°, %	12.4% (11.1, 13.9%)	20.2% (17.8, 22.9%)	7.0% (5.7, 8.5%)
Gosvig ratio, mean mm	0.94 (0.93, 0.94)	0.97 (0.97, 0.97)	0.91 (0.91, 0.92)
Triangular index, mean mm	22.8 (22.6, 22.9)	25.7 (25.5, 25.9)	20.7 (20.6, 20.8)
Triangular index sign, %	1.0% (0.6, 1.5%)	2.0% (1.3, 3.1%)	0.2% (0.1, 0.7%)
Femoral shaft angle, mean°	130.6 (130.3, 130.9)	129.3 (128.8, 129.7)	131.5 (131.1, 131.8)
Crossover sign, %	20.5% (18.8, 22.2%)	23.5% (20.9, 26.4%)	18.3% (16.3, 20.4%)
Extrusion index, mean mm	0.17 (0.16, 0.17)	0.19 (0.18, 0.19)	0.15 (0.15, 0.16)
CEA ≤25°, %	25.1% (23.3, 27.0%)	26.3% (23.5, 29.3%)	24.2% (21.9, 26.7%)
CEA >40°, %	5.9% (5.0, 7.0%)	4.8% (3.6, 6.4%)	6.8% (5.5, 8.3%)
Protrusio acetabula, %	3.5% (2.8, 4.3%)	0.6% (0.3, 1.4%)	5.5% (4.4, 6.8%)
Coxa profunda, %	69.9% (67.9, 71.8)	50.6% (47.2, 54.0%)	83.5% (81.5, 85.4%)

CEA: center edge angle

Table 2. GEE estimates of means and frequencies (with corresponding 95% confidence intervals), stratified by sex among those WITH rHOA at baseline (KLG 2 or more, n=664)

Morphologic measure	Overall (n=664)	Men (n=226)	Women (n=438)
AP alpha angle, mean°	54.1 (53.0, 55.3)	57.9 (56.0, 59.8)	52.2 (50.8, 53.7)
AP alpha angle >60°, %	26.0% (23.2, 28.9%)	38.5% (33.2, 44.0%)	19.5% (16.5, 22.8%)
Gosvig ratio, mean mm	0.95 (0.95, 0.96)	0.99 (0.98, 1.0)	0.93 (0.92, 0.94)
Triangular index, mean mm	22.7 (22.5, 23.0)	26.2 (25.8, 26.5)	21.0 (20.8, 21.2)
Triangular index sign, %	5.2% (4.0, 6.7%)	10.3% (7.5, 13.9%)	2.5% (1.6, 3.9%)
Femoral shaft angle, mean°	130.3 (129.8, 130.8)	129.7 (128.9, 130.5)	130.6 (130.0, 131.2)
Crossover sign, %	17.9% (15.6, 20.4%)	19.7% (15.8, 24.3%)	16.9% (14.2, 20.0%)
Extrusion index, mean mm	0.16 (0.15, 0.16)	0.20 (0.19, 0.20)	0.14 (0.13, 0.14)
CEA ≤25°, %	18.0% (15.6, 20.7%)	24.9% (20.5, 30.0%)	14.4% (11.8, 17.5%)
CEA >40°, %	11.8% (9.8, 14.1%)	7.8% (5.3, 11.1%)	13.9% (11.2, 17.0%)
Protrusio acetabula, %	6.6% (5.3, 8.3%)	0.2% (0.0, 1.6%)	10.0% (8.0, 12.4%)
Coxa profunda, %	72.1% (69.1, 74.9%)	53.5% (47.7, 59.2%)	81.7% (78.7, 84.4%)

CEA: center edge angle

Disclosure: A. E. Nelson, None; **R. Raveendran**, None; **J. L. Stiller**, None; **C. Alvarez**, None; **J. B. Renner**, None; **T. A. Schwartz**, None; **N. K. Arden**, None; **J. M. Jordan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/description-of-radiographic-hip-measurements-by-oa-status-in-a-large-community-based-study-of-african-american-and-white-men-and-women

Abstract Number: 1270

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-7

Abstract Number: 1271

Plasma Concentration of S100A8/A9 Proteins Is an Independent Biomarker for Radiological Progression in in Early Rheumatoid Arthritis

Maxime Chevreau[1], Marie Helène Paclet[2], Jean-Louis Quesada[3], Marine Clay[4], Philippe Dieudé[5,6], Olivier Vittecoq[7], Philippe Gaudin[8] and **Athan Baillet**[9], [1]Rheumatology, CHU Sud Hospital, Grenoble, France, [2]IPB _ Grenoble teaching hospital, Grenoble, France, [3]Grenoble University Hospital, France, Grenoble, France, Grenoble, France, [4]Rheumatology Grenoble, Grenoble, France, [5]Rheumatology, Bichat hospital APHP, Paris, France, [6]Rheumatology, Hôpital Bichat, Paris, France, [7]Rheumatology, Rouen University Hospital &INSERM U905, Rouen, France, [8]Grenoble University Hospital, France, Grenoble, France, [9]Rheumatology, Grenoble University Hospital, France, Echirolles, France

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SESSION INFORMATION

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Background/Purpose: Increasing body of evidence suggest that alarmins such as S100A8/A9 proteins play a critical role in Rheumatoid Arthritis pathogenesis (RA). We aimed to analyze the association between baseline S100A8/A9 protein plasma levels and radiological progression during the first 36 months of early RA.

Methods: Patients fulfilling the ACR/EULAR criteria in the early arthritis cohort ESPOIR were included in this study. S100A8/A9 (also known as calprotectin) levels were assessed in 813 patients of the early arthritis cohort ESPOIR at baseline. Total Sharp-van der Heijde score was assessed at baseline, year 1, 2 and 3. Univariate Cox regressions were used to evaluate the role of the risks factors to detect total Sharp-van der Heijde score progression ≥ 5 points /year. A multivariate risk model, comprising gender, age, baseline CRP, baseline ACPA, baseline smoking status, baseline DAS28, baseline S100A8/A9 level and treatment with biologic or synthetic DMARD , was constructed using a backward stepwise Cox model. A patient was considered under DMARD treatment when receiving methotrexate≥7.5mg/sem, sulfasalazine, leflunomide or any biological treatment at least 6 months before radiological assessment.

Results: A total of 614 patients were included and analyzed out of 813 patients of the cohort. Significant differences were found between patients with or without radiological progression, in the univariate Cox model : progressors were more likely to be ACPA positive, to be treated biologic or synthetic DMARD and to display high level of baseline CRP and S100A8/A9 proteins (**table**). In the multivariate analysis, S100A8/A9 level was the only predictor of the structural evolution over 3 years, independently of usual marker of inflammation (Hazard ratio 1.06, 95%CI [1.00-1.11], p=0,045). .

Conclusion: These results confirm that S100A8/A9 predicts radiological progression, in a large cohort of early rheumatoid arthritis. The correlation between this new biomarker and radiological progression was moderate but independent from other risk factors.

Table. Predictors of radiological progression with the first 3 years of early Rheumatoid arthritis

N=615	No radiological progression n=290	Radiological progression n=325	Hazard Ratio [95%IC]	P value
Gender, female	79.3% (230)	76.9% (250)	0.95 [0.73 ; 1.23]	0.702
Age, years	48.7 [38 ; 56.3]	52.4 [41.1 ; 58.4]	1.01 [0.99 ; 1.02]	0.082
Baseline CRP	7 [4 ; 18]	12 [5 ; 28]	1.003 [1 ; 1.01]	0.047
Baseline ACPA	29.1% (103)	53.7% (187)	1.94 [1.57 ; 2.39]	<0.001
Baseline DAS28	5.14 ± 1.23	5.25 ± 1.25	1.07 [0.98 ; 1.17]	0.148
Current smoking at baseline	48.3% (140)	46.8% (152)	1.04 [0.84 ; 1.29]	0.732
Baseline S100A8/A9	3.18 [1.83 ; 4.83]	3.85 [2.35 ; 5.31]	1.06 [1.01 ; 1.12]	0.027
DMARD treatment *	77.2% (224)	86.8% (282)	1.5 [1.09 ; 2.07]	0.013

Univariate analysis: Cox model, HR: hazard ratio [confidence interval 95%]. Percentage (Number); mean ± standard deviation or median [25th, 75th percentiles] were appropriate

* A patient was considered under DMARD treatment when receiving methotrexate≥7.5mg/sem, sulfasalazine, leflunomide or any biological treatment at least 6 months before radiological assessment.

Disclosure: M. Chevreau, None; **M. H. Paclet**, None; **J. L. Quesada**, None; **M. Clay**, None; **P. Dieudé**, None; **O. Vittecoq**, None; **P. Gaudin**, None; **A. Baillet**, None.

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Abstract Number: 1272

Can Histologically Defined Peri-Articular Vascular Channels be Identified on High-Resolution Computed Tomography? – a Study in Cadaveric Finger Joints

A. Scharmga[1], K. K. Keller[2], M. Peters[1], A. van Tubergen[1], J. van den Bergh[3], B. van Rietbergen[4], R. Weijers[5], D. Loeffen[5], E-M. Hauge[2] and P. Geusens[6], [1]Department of Internal Medicine, Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands, [2]Rheumatology, Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Internal Medicine, Viecuri Medical Center, Venlo, Netherlands, [4]Biomedical Engineering, Eindhoven University of Technology, Eindhoven, Netherlands, [5]Department of Radiology, Maastricht University Medical Center, Maastricht, Netherlands, [6]Internal Medicine/Rheumatology, Maastricht University Medical Center and Hasselt University, Biomedical Research Institute, Diepenbeek, Belgium
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Background/Purpose: Several studies have indicated that High Resolution peripheral CT (HR-pQCT) scanning is more sensitive than radiography in detecting cortical interruptions in destructive joint diseases like rheumatoid arthritis (RA)[1-3]. Cortical interruptions are also seen in healthy controls, but the exact nature of these interruptions is not known, and might represent vascular channels (VCs). No previous study has compared histology to HR-pQCT images in finger joints. We hypothesized that VCs seen on histology can also be detected by HR-pQCT imaging.

Methods: Based on HR-pQCT, 4 regions in 3 metacarpophalangeal (MCP) joints from female cadavers with an unknown medical history (mean age 84.7, SD 5.5 years) were selected. These regions were extracted, embedded undecalcified in methylmetacrylate and histologically sectioned (thickness 14µm) parallel to the axial plane. Every second section (n=478) was stained with Goldner Trichrome. VCs were identified as a cortical interruption in one histological section, which contained one or more vessels. Histological sections were matched visually to corresponding axial HR-pQCT images. Per match, it was described if a cortical interruption was observed on HR-pQCT and if this was a VC based on an interruption with a parallel structure present on 2 consecutive slices in 2 planes (axial, and/or sagittal/coronal).

Results: A total of 52 different VCs were identified on histology. All could be matched to a corresponding axial HR-pQCT image. Twenty histologically defined VCs would be defined as VC on HR-pQCT based on the parallel structure, although only 5 were present on 2 consecutive slices and 15 on less than 2 consecutive slices. Twenty-seven interruptions were observed on HR-pQCT, but did not fulfill the definition of a VC. In 5 cases no interruptions could be observed on HR-pQCT. Figure 1 demonstrates 3 examples of histology and matching HR-pQCT images.

Conclusion: VCs were frequently present in MCP joints. Only a minority of histologically defined VCs is interpreted as VC using a pre-specified definition on HR-pQCT images. Small histological VCs were often identified as an interruption but rarely considered a VC on HR-pQCT. Therefore, additional criteria in order to categorize a VC as such on HR-pQCT are warranted.

References.1.Stach 2010 2.Srikhum 2013.3.Fouque-Aubert 2010

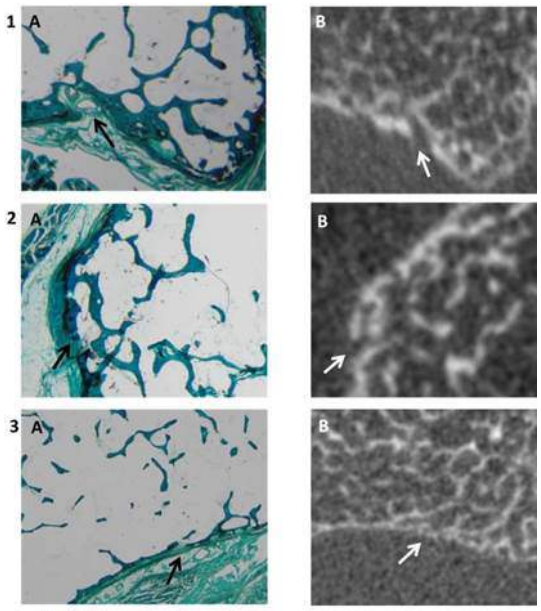

Figure 1.
Panel 1: Vascular channel on histology (A) and HR-pQCT imaging (B)
Panel 2: Vascular channel on histology (A) and a cortical break not defined as vascular channel on HR-pQCT (B)
Panel 3: Vascular channel on histology (A) but no break in cortex on HR-pQCT (B)

Disclosure: **A. Scharmga**, None; **K. K. Keller**, None; **M. Peters**, None; **A. van Tubergen**, None; **J. van den Bergh**, None; **B. van Rietbergen**, Scanco Medical A.G., 5; **R. Weijers**, None; **D. Loeffen**, None; **E. M. Hauge**, None; **P. Geusens**, None.

Abstract Number: 1273

Effect of Anti-Cyclic Citrullinated Protein Antibodies and Rheumatoid Factor on Bone Erosions in Early Rheumatoid Arthritis Patients Using HR-pQCT: A Cross-Sectional Study

JIANG YUE[1], James F Griffith[2], Lin Shi[3], Defeng Wang[2], Jiayun Shen[4], Priscilla Wong[5], Edmund LI[5], Martin Li[6], Tena K. Li[6], Tracy Y. Zhu[7], Ling qin[8] and Lai-Shan TAM[9], [1]The Prince of Wales Hospital, The Chinese University of Hong Kong, Department of Medicine and Therapeutics, HONG KONG, Hong Kong, [2]The Prince of Wales Hospital, The Chinese University of Hong Kong, Department of Imaging and Interventional Radiology, HONGKONG, Hong Kong, [3]Department of Medicine & Therapeutics, Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Shatin, Hong Kong, [4]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, China, [5]Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, Hong Kong, [6]Department Medicine and Therapeutics, The Chinese University of Hong Kong, Hong Kong, China, [7]Department of Orthopaedics & Traumatology, The Chinese University of Hong Kong, Hong Kong, China, [8]Department of Orthopedics & Traumatology, hongkong, Hong Kong, [9]Department of Medicine & Therapeutics, The Chinese University of Hong Kong, Hong Kong, Hong Kong

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Background/Purpose:

Concomitant presence of anti-cyclic citrullinated peptide antibodies (ACPA) and rheumatoid factor (RF) is associated with higher erosive disease burden in patients with established rheumatoid arthritis (RA). Even before the clinical onset of arthritis, ACPAs are associated with bone loss. Whether RF also influences bone damage in patients with RA is less well defined. In this study, we aim to determine whether there is an effect of ACPA and RF on the number and volume of bone erosions in early rheumatoid arthritis (ERA) patients.

Methods:

In this cross-sectional study, the second metacarpophalangeal joint (MCP2) in 96 patients with ERA (onset of disease within 2 years) were assessed using high-resolution peripheral quantitative CT (HR-pQCT). Data on demographic (age, sex) and disease-specific parameters including DAS 28, ESR, CRP, ACPA and RF levels were recorded. Erosions were visualized in 73 patients and the number and volume of the erosions were documented. Relationship between erosions, demographic and disease-specific data was evaluated by two multiple linear regression models.

Results:

Amongst the 96 ERA patients, 72.9% were female. The mean age was 53.1±13.8 years, disease duration was 8.0±5.6 months and DAS 28 was 5.0 ±0.9. Out of the 96 patients, 75 were both RF and ACPA positive (ACPA+/RF+), 5 were RF positive only (ACPA-/RF+), 9 were ACPA positive only (ACPA+/RF-) and 7 were double negative (ACPA-/RF-). Erosion volume was higher in the ACPA+/RF+ group compared with the non- ACPA+/RF+ (ACPA-/RF+ or ACPA+/RF- or ACPA-/RF-) group (3.99±3.16 mm^3 vs 2.50±1.24 mm^3, p=0.023). When all patients were subdivided according to RF and ACPA titer, erosion volume was significantly larger in the RF positive (>16 U) group than the RF negative (<16 U) group (4.28±3.42 mm^3 vs 2.66±1.34 mm^3, p=0.019). Similarly, erosion volume was also significantly larger in the ACPA>100U group compared to the ACPA<100U group (2.94±3.19 mm^3 vs 1.64±1.34 mm^3, p=0.010). Erosion volume was also increased in female patients (Beta=0.315, p=0.012). On the other hand, erosion number was associated with increasing age (Beta=0.359, p=0.000), ESR (Beta=0.320, p=0.001) and longer disease duration (Beta=0.251, p=0.014) in the univariate analysis. Using multiple linear regression model, independent explanatory variables associated with erosion volume included RF>16U (p=0.018) and female gender (p=0.011); while erosion number was associated with a longer disease duration (p=0.021), older age (p=0.000) and elevated ESR (p=0.007).

Conclusion:

In RA patients with recent onset of disease, the number of erosion appears to depend on disease activity, while the presence of RF may play a predominant role in the structural deterioration in terms of erosion volume. .

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Abstract Number: 1274

The Reproducibility of a Semi-Automatic Algorithm in the Detection of Cortical Breaks and Adjacent Trabecular Bone Loss in Scan-Rescan Data from Patients with Early Arthritis

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Background/Purpose: In RA bone erosions are defined as cortical breaks with adjacent trabecular bone loss. High resolution peripheral quantitative CT (HR-pQCT) is more sensitive than conventional radiography in the detection of erosions in finger joints, but the scoring of erosions on acquired images was performed manually. We thus developed and validated a semi-automatic algorithm for HR-pQCT to detect cortical breaks and adjacent trabecular bone loss. The reproducibility of our algorithm on scan/re-scan (repositioning) data is presented in this study.

Methods: Twenty one subjects (mean (SD); age 49 (11) years) with 17 early RA (n=17, diagnosis <1 year) and undifferentiated arthritis (n=4) were studied. The 2nd and 3rd MCP joints were imaged by HR-pQCT (82µm nominal isotropic voxel size) twice on the same day with repositioning in between the scans. The semi-automatic algorithm was applied to the HR-pQCT images for the detection of cortical breaks. This included automatic detection of the outer contour of the bone, which was verified manually. A cortical mask of 0.33mm from this contour was selected and the remaining inner volume was considered trabecular bone. Cortical breaks with a diameter of >0.16mm, >0.33mm and >0.50mm and trabecular cavities >0.3mm in diameter were extracted, of which only those that were connected to a cortical break remained. Reproducibility for the number of breaks detected, break surface and erosion volumes was calculated per break diameter using intraclass correlation coefficient (ICC).

Results: The algorithm enabled detection of cortical breaks and adjacent trabecular bone loss (Fig. 1). The number of breaks, break surface and erosion volume per joint detected was dependent on the minimal break diameter (Table 1). Excellent reproducibility (ICC ≥0.82) was observed for all outcomes and all break diameters, with the exception of erosion volume for breaks >0.50mm (ICC=0.11). This is explained in figure 1 where an erosion was accurately detected on the 1st scan by all break diameters. However, on the 2nd scan the erosion was not detected for breaks >0.50mm. This subsequently leads to a high discrepancy in the erosion volume.

Conclusion: Our semi-automatic algorithm is highly reproducible in the detection of cortical breaks, break surface and erosion volume in repositioning data on HR-pQCT.The use of HR-pQCT in combination with our algorithm is therefore a promising tool for early detection and monitoring of erosions in finger joints.

Table 1. The mean number of cortical breaks, break surface and erosion volume per joint detected by the algorithm on the 1st and 2nd scan.

break diameter	Number of breaks				ICC	Break Surface (mm^2)				ICC	Erosion Volume (mm^3)				ICC
	1st scan		2nd scan			1st scan		2nd scan			1st scan		2nd scan		
>0.16mm	25.0	(18.5)	25.8	(20.3)	0.93	18.9	(18.4)	19.5	(18.7)	0.95	16.9	(19.5)	16.8	(20.6)	0.88
>0.33mm	3.0	(3.5)	3.2	(3.6)	0.82	4.0	(7.0)	4.4	(7.5)	0.92	4.6	(11.9)	4.4	(11.2)	0.88
>0.50mm	0.9	(1.8)	1.3	(1.9)	0.86	1.5	(3.5)	2.3	(4.5)	0.91	1.1	(3.2)	2.9	(10.5)	0.11

Values are displayed as: mean (SD)
SD = standard deviation
ICC = intraclass correlation coefficient

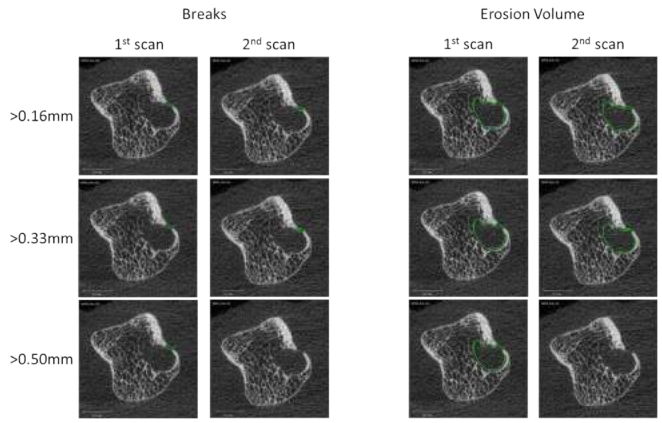

Figure 1. An example of an erosion in a 2D grayscale image. The cortical break and the adjacent trabecular bone loss of the erosion was accurately detected by the algorithm for all break diameters on the 1st scan. However, on the 2nd scan the break was not detected for breaks >0.50mm and therefore no adjacent trabecular bone loss was detected.

Disclosure: M. Peters, None; **J. de Jong**, None; **A. Scharmga**, None; **A. van Tubergen**, None; **D. Loeffen**, None; **R. Weijers**, None; **B. van Rietbergen**, Scanco Medical A.G., 5; **S. K. Boyd**, None; **C. Barnabe**, None; **K. S. Stok**, Scanco Medical AG, 3; **P. Geusens**, Pfizer, Abbott, Lilly, Amgen, MSD, Will, Bio Minerals and Roche, 2,Pfizer, Abbott, Lilly, Amgen, MSD, Will, Bio Minerals and Roche, 8; **J. van den Bergh**, None.

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Abstract Number: 1275

Evaluation of Spine and Tibia Bone Microarchitecture Using Trabecular Bone Score (TBS) and HR-pQCT in Patients with Ankylosing Spondylitis

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Background/Purpose: Ankylosing Spondylitis (AS) is a chronic inflammatory disease characterized by new bone growth that leads to syndesmophytes formation. However, AS patients present low bone mineral density (BMD) or osteoporosis that can be associated to systemic inflammation and decreased mobility. Low bone mass diagnosis in AS patients is based on data using dual-energy X-ray absorptiometry (DXA), which may present confusion factor for the presence of syndesmophytes and difficulty in patient positioning on the DXA table.Other limitation of DXA is that it cannot distinguish between bone compartments.Thus, the objective of this study is evaluate bone microarchitecture, cortical and trabecular, at spine and peripheral sites analyzing bone parameters using other images technology in AS patients. Patients and

Methods: Seventy-nine male patients with AS were evaluated compared with age-matched male controls. Demographic, anthropometric, disease duration, disease activity Score (BASDAI) and medication using were recorded. None patient was using bisphosphonates. Bone mineral density (BMD) was evaluated by using dual-energy X-ray absorptiometry (DXA-Hologic). Trabecular bone score (TBS iNsight software) was analyzed from lumbar spine measurement for vertebrae L1–L4 exactly at the same ROI as spine BMD DXA. Trabecular and cortical parameters were measured by High-resolution peripheral quantitative computed tomography (HR-pQCT- Scanco) at distal tibia.

Results: Patients with AS had a mean 42.6 ± 8.9 yrs and a mean disease duration of 17.4 ± 9.7 yrs. Bone mineral density at lumbar spine in AS patients showed higher values compared with control group (1.104 ± 0.206 vs 1.041 ± 0.117g/cm^2, p = 0.023) and lower BMD at total hip (0.951 ± 0.015 vs. 1.003 ± 0.015 g/cm^2, p= 0.017). Differently, TBS analysis showed lower values of this score in patients than control group (1.317 ± 0.121 vs. 1.396 ± 0.070, p <0.001). AS patients had lower values than controls of trabecular parameters as Tb.N (1.82 ± 0.34 vs. 1.94 ± 0.32, p=0.03), Tb.Th (0.07 ± 0.01 vs 0.08 ± 0.01, p= 0.008); cortical parameter as Ct.Th (1.24 ± 0.32 vs 1.36 ± 0.27, p=0.024) and total vBMD parameters (293.2 ± 67.69 vs. 319.15 ± 55.07, p= 0.019) at distal tibia measured by HR-pQCT. The bone strength parameters such as stiffness and stress estimated by finite element analysis were lower in AS patients than controls (p<0.001). In AS patients, TBS correlated negatively with mSASSS (r=-0.325; p=0.003). Furthermore, TBS correlated positively with trabecular thickness (Tb.Th) at tibia (r=0.228; p=0.047).

Conclusion: The TBS and HR-pQCT imaging measurements seems to be a good technologies to analysis the bone microarchitecture parameters in AS patients allowing better interpretation and possible predicting the fracture risk in these patients.

Disclosure: V. F. Caparbo, None; **C. G. S. Saad**, None; **J. C. Alvarenga**, None; **R. M. R. Pereira**, None.

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Abstract Number: 1276

Sensitive SPECT/CT Imaging of Fibroblast Activation Protein Expression after Anti-IL-22 Treatment in Experimental Arthritis

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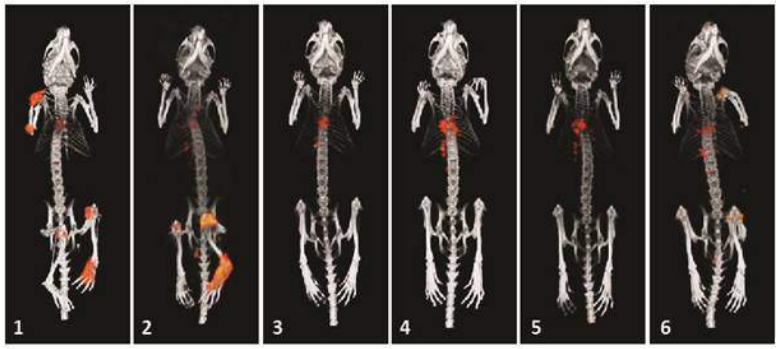
Background/Purpose: Rheumatoid arthritis (RA) synovial tissue has been demonstrated to express high levels of fibroblast activation protein (FAP) using anti-FAP-antibody 28H1. In addition, RA patients show elevated levels of IL-22 and IL-22-producing T helper cells that correlate to erosive disease, suggesting a role for this cytokine in the pathogenesis of RA. The purpose of this study was to determine the feasibility of ^{111}In-28H1 SPECT/CT imaging of FAP-expressing synovium to monitor the therapeutic potential of neutralizing IL-22 during experimental arthritis.

Methods: Collagen-induced arthritis (CIA) was induced in male DBA/1J mice. Mice were treated 3 times per week with anti-IL-22 antibodies (8 mg/kg), while the control group received rat IgG1 isotype control antibodies. To monitor the therapeutic effect after 2 weeks of treatment, SPECT/CT images were acquired 24 h after injection of ^{111}In-labeled DTPA-conjugated anti-FAP antibody, 28H1. After image acquisition, mice were euthanized and dissected. Imaging results were compared with the macroscopic arthritis scores and radiographic bone damage scores acquired by X-ray.

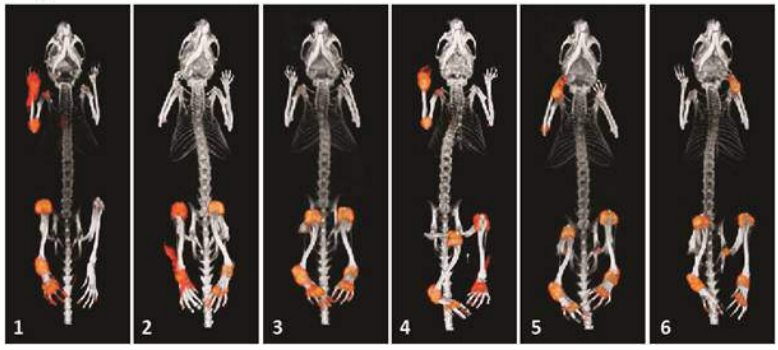
Results: Blocking IL-22 during CIA was a potent approach to prevent arthritis development, reaching a disease incidence of only 50%, versus 100% in the control group. SPECT/CT imaging using indium-labeled anti-FAP antibodies showed that joint uptake of the tracer was significantly reduced ($p = 0.03$) in anti-IL-22-treated mice (4.3 %ID/g) compared to the isotype control group (8.0 %ID/g) (See figure). This was confirmed by the corresponding macroscopic arthritis scores and radiographic bone damage scores that were significantly ($p = 0.047$ and $p = 0.017$ respectively) lower in the anti-IL-22-treated group. Besides its sensitivity, the in vivo FAP-based SPECT/CT had the great advantage to visualize sites of inflammation that were overlooked during clinical scoring, like in knee, hip, elbow and shoulder (See figure).

Conclusion: These findings demonstrate that IL-22 plays an important role in the development of experimental arthritis, and targeting this cytokine seems an attractive new strategy in RA treatment. Most importantly, SPECT/CT imaging of the inflamed synovium using the labeled anti-FAP antibody ^{111}In-DTPA-28H1 can be used to specifically monitor response to therapy in an objective and quantitative way, and is potentially more sensitive in disease monitoring compared to the standard method of clinical arthritis scoring by macroscopic inspection.

anti-IL-22 treatment



Isotype control



Disclosure: D. M. Roeleveld, None; **T. van der Geest**, None; **B. Walgreen**, None; **M. M. Helsen**, None; **T. K. Nayak**, Roche Pharmaceuticals, 3; **C. Klein**, Roche Pharmaceuticals, 3; **M. Hegen**, Pfizer Inc, 3; **P. Laverman**, None; **O. C. Boerman**, None; **M. I. Koenders**, None.

Abstract Number: 1277

WITHDRAWN

Abstract Number: 1278

Combined Positron Emission Tomography and Magnetic Resonance Imaging in Assessing Gastrointestinal Involvement in Systemic Sclerosis: A Pilot Study

Sue-Ann Ng[1], Stephanie Marchesseau[2], Yu Tien Wang[3], Josh Schaefferkoetter[2], Wanying Xie[4], David Ng[4], John Totman[2] and Andrea HL Low[1], [1]Department of Rheumatology and Immunology, Singapore General Hospital, Singapore; Duke-National University of Singapore, Singapore, Singapore, [2]Clinical Imaging Research Center, A*STAR & National University of Singapore, Singapore, Singapore, Singapore, [3]Department of Gastroenterology and Hepatology, Singapore General Hospital, Singapore, Singapore, Singapore, [4]Department of Nuclear Medicine and PET, Singapore General Hospital, Singapore, Singapore, Singapore

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Session Title: Imaging of Rheumatic Diseases - Poster II: XR/CT/PET/MRI

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Systemic sclerosis (SSc), a multi-organ fibrotic disease, affects the gastrointestinal tract (GIT) in 90% of patients. An urgent unmet need in the management of SSc GIT involvement is the availability of non-invasive investigations for early diagnosis and monitoring. Development of a new MRI sequence, T1 MOLLI (modified look-locker inversion recovery) mapping, has been applied to cardiac imaging, which enables detection and quantification of diffuse fibrosis without contrast. In this pilot study comparing SSc patients with healthy controls, we investigate FDG-PET/MRI in diagnosing SSc GIT involvement, hypothesizing that (i) MRI T1 MOLLI values, denoting fibrosis, is higher in SSc patients than healthy controls, and (ii) PET detects bowel inflammation associated with early mild GIT involvement.

Methods:

Ten patients fulfilling the 2013 ACR/EULAR criteria for SSc and 10 healthy age and sex matched controls underwent scanning. SSc patients either had early SSc <3 years and asymptomatic to mild GIT symptoms (Group A, n=5), or moderate to severe GIT symptoms regardless of disease duration (Group B, n=5), as determined by a validated questionnaire (Table 1). All subjects fasted 6 hours prior and had non-spicy low-residue diet 3 days prior. SSc patients underwent PET-MRI scan, 60 minutes after injection of 6mCi FDG tracer and immediately after injecting 10mg hyoscine butylbromide (reduce peristalsis). Breath-hold native T1 MOLLI mapping was acquired. Controls underwent the same MRI protocol. FDG uptake was quantified by specific uptake value (SUV). Student t-test and box plots were used to evaluate statistical significance ($p<0.05$).

Results:

Majority were females with a mean age of 48 years. Mean T1 values for the large and small bowels were higher in SSc patients than healthy controls (large bowel: 1206±148ms vs 869±192ms respectively, $p<0.001$; small bowel: 1425±245ms vs 1150±115ms respectively, $p=0.005$) (Table 1).

All SSc patients had high PET uptake in the bowel (on average 25% of their total bowel had SUV >1.5). PET SUV values in the large and small bowels were higher in Group A (mean GIT score 0.11) than Group B (mean GIT score 0.57) patients. In the large bowel, T1 values were higher in the regions of inflamed bowel, as defined by PET SUV >1.5 (Figure 1).

Conclusion:

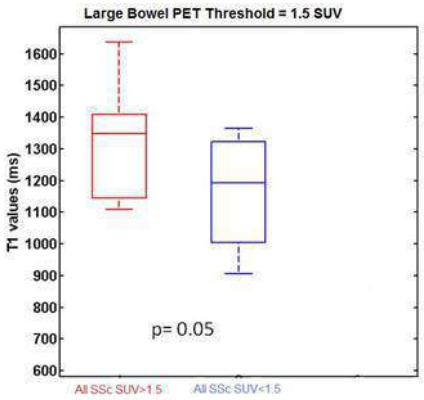
Our preliminary results suggest the feasibility of using T1 MOLLI to evaluate bowel fibrosis. FDG-PET showed uptake in all SSc cases, with increased bowel inflammation occuring in patients with early mild disease. FDG-PET/MRI is potentially a useful diagnostic and monitoring tool for SSc GIT disease.

-

Table 1

	Group A (n=5)	**Group B** (n=5)	**All SSc patients** (n=10)	**Controls** (n=10)
Demographic and clinical features				
Female sex, n (%)	5 (100%)	4 (80%)	9 (90%)	9 (90%)
Age, years	42.4 ± 15.9	54.0 ± 5.7	48.2 ± 12.8	48.0 ± 12.7
Limited/Diffuse SSc, n	2/3	5/0	7/3	Not applicable
Mean disease duration from Raynaud's phenomenon onset, years	2.6 ± 0.8	5.0 ± 4.3	3.8 ± 3.2	Not applicable
Mean disease duration from non-Raynaud's phenomenon onset, years	3.1 ± 1.0	4.7 ± 3.6	3.9 ± 2.6	Not applicable
Total GIT score	0.11 ± 0.07	0.57 ± 0.29	0.34 ± 0.32	0
T1 MOLLI and PET findings				
T1 (large bowel) (ms)	1218 ± 142 ¶	1193 ± 170 ¶	1206 ± 148 ¶	869 ± 192
T1 (small bowel) (ms)	1335 ± 112 ¶	1516 ± 320 ¶	1425 ± 245 ¶	1150 ± 115
PET SUV (large bowel)	1.31 ± 0.30	1.11 ± 0.19	1.21 ± 0.26	Not applicable
PET SUV (small bowel)	1.31 ± 0.35	1.19 ± 0.33	1.25 ±0.33	Not applicable
Total GIT: Total Gastrointestinal Tract (version 2.0) score, from University of California Los Angeles Scleroderma Clinical Trials Consortium ¶ $p < 0.05$ versus controls				

Figure 1



Disclosure: S. A. Ng, None; **S. Marchesseau**, None; **Y. T. Wang**, None; **J. Schaefferkoetter**, None; **W. Xie**, None; **D. Ng**, None; **J. Totman**, None; **A. H. Low**, None.

Abstract Number: 1279

Imaging of Ankylosing Spondylitis By [18f]Fluoride PET-CT to Assess Bone Formation Activity and to Monitor Anti-TNF Therapy

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Background/Purpose: Bone formation is an important hallmark of ankylosing spondylitis (AS). Recently, we demonstrated that axial bone formation activity in AS patients can be visualized in vivo by [^{18}F]Fluoride PET-CT. [^{18}F]Fluoride PET-CT may therefore allow monitoring of changes of bone formation in AS during treatment. Therefore we investigated **1.** changes in bone formation activity in AS patients that start anti-TNF treatment using [^{18}F]Fluoride-PET-CT and **2.** Histology of PET identified lesions in spine (small feasibility sub-study).

Methods: We included 12 AS patients (female 7/12; age 39±11) with high disease activity (BASDAI 5.5±1.1). [^{18}F]fluoride PET-CT scans were performed at baseline and 12 weeks of anti-TNF treatment. Two patients only obtained a baseline scan to identify PET^{+} lesions in spine for a subsequent biopsy procedure to collect material of these lesions for immunohistochemistry (IHC). PET scans were assessed visually by two blinded readers. Clinical response was defined according to the ASAS20 at 12 weeks.

Results: Visualization of bone formation by [^{18}F]fluoride PET-CT in spine was supported by osteoid formation and osteoclasts along with cell infiltrate in conjunction areas of bone and connective tissue in PET^{+} lesions, while largely absent in PET- lesions (Figure 1A,B). At baseline, the other 10 patients showed at least one lesion of [^{18}F]Fluoride uptake in spine and/or SI joints. In spine, a total of 94 PET^{+} lesions were observed in 6 patients (range 2-32 p.p.), and ≥1 SI PET^{+} joint in 8/10 patients (Fig. 2). After 12 weeks of anti-TNF treatment, 7/10 patients received ASAS20 response. In spine, in 6/10pts with ≥1 PET^{+} lesion at baseline, the number of PET^{+} lesions decreased from 94 to 66 in 12 weeks. Decrease of spine^{+} lesions was noticed both in clinical responders and non-responders although the remaining number of spine^{+} lesions at 12 weeks tended to be higher in non-responders than in responders (16-21 vs. 1-13, respectively). SI^{+} joints remained visually positive at 12 weeks although at variable intensity.

Conclusion: In AS patients, [^{18}F]Fluoride PET-CT visualizes multiple lesions with bone formation in SI joints and spine. Histological evaluation of PET^{+} lesions supported *in-vivo* identification of bone formation activity by [^{18}F]Fluoride PET-CT. In this preliminary visual analysis of PET data, one third of [^{18}F]Fluoride PET-CT^{+} lesions in spine disappeared after 12 weeks of a-TNF treatment. The relationship between PET outcome and clinical response will be further investigated by quantitative analysis of PET^{+} lesions and clinical follow-up up to 24 weeks, which is currently in progress.

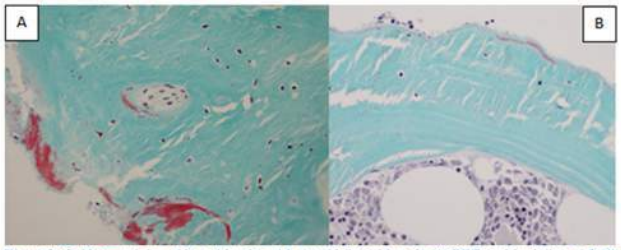

Figure 1: Goldner staining of bone biopsies with osteoid depositions in (A) PET positive lesion and (B) contralateral PET negative control biopsy.

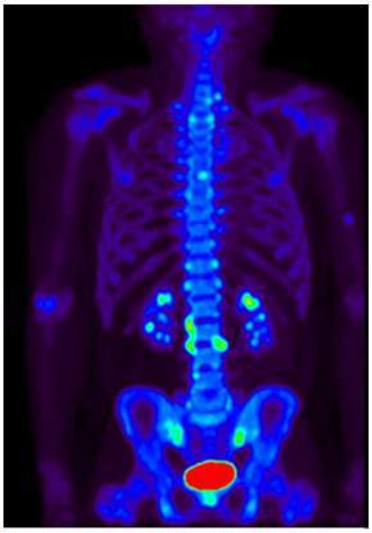
Figure 2: Whole body [18F]Fluoride PET image with tracer uptake in SI joints and spine in lumbar vertebrae.

Disclosure: S. Bruijnen, Dutch Arthritis Association, 2; **N. Verweij**, None; **L. van Duivenvoorde**, None; **D. Baeten**, None; **C. van Denderen**, None; **J. Bot**, None; **O. Hoekstra**, None; **P. Raijmakers**, None; **I. van der Horst - Bruinsma**, None; **C. van der Laken**, None.

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Abstract Number: 1280

Positron Emission Tomography Images with an Amyloid-Specific Tracer 11C-BF-227 in Systemic Amyloidosis Patients

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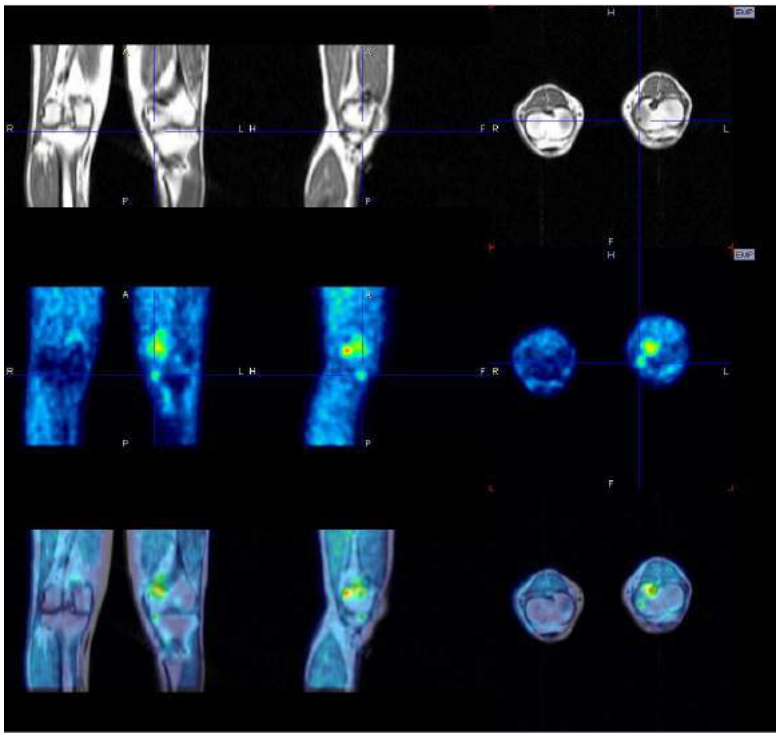
Background/Purpose: In order to visualize amyloid deposition in the specific organs, the patients with systemic amyloidosis underwent positron-emission tomography (PET) study with 11C-BF-227 that specifically binds to aggregated amyloid fibrils. A PET tracer, 11C-BF-227, was previously developed, and we had success with in vivo detection of amyloid plaques in Alzheimerfs disease brains and cardiac amyloidosis in familial transthyretin-related systemic amyloidosis (Kudo Y. et al. in J Nucl Med 8: 2007, and Furukawa K. et al. in

Circulation.125:2012, respectively).Here, we investigated additional patients with AA and AL amyloidosis, utilizing this strategy.

Methods: We obtained 6 patients who were diagnosed as amyloidosis with tissue biopsies. We got the informed consent from all study subjects. Patients were 2 female, 4 men (average age plus minus SD, 69 plus minus 5.7) , and they were 2 of Sjogrenfs syndrome, 2 of monoclonal gammopathy of undetermined significance (MGUS), 1 of Rheumatoid Arthritis, and 1 of etiology unknown. The types of amyloid are 3 of AA and 3 of AL amyloid. We also evaluated two healthy controls to compare the images. They were taken 11C-BF-227 PET imaging, then collected an anatomic Magnetic Resonance Image (MRI) sequence to identify the specific organ structures. We analyzed the data with PMOD and Dr. view software, merging the PET and MRI images from the same subject into the same three-dimensional space. The region-of-interest (ROI) was placed on individual MRI images in each organ. The ROI information was then copied onto dynamic PET standardized uptake value (SUV) images. The ratio of regional SUV to the intact lung SUV (SUVR) was also calculated.

Results: First, we confirmed the amyloid depositions by biopsies of the knee, lung nodules, skin, heart, kidney, and colon. We analyzed the PET images, and the subjects showed the accumulation of 11C-BF-227 in each organ. The representative PET and MRI image of the patient, having amyloid deposition by the knee biopsy, was shown the strong accumulation of 11C-BF-227as indicated in the Figure. His renal and cardiac functions were normal and did not have any amyloid deposition. Another patient having multiple nodules in the lung with amyloid deposition, indicated an increased SUV in those nodules in the PET image. The patients who had amyloid deposition in the kidney showed relatively higher SUVR in the kidney.

Conclusion: We clarified that our newly developed amyloid pet tracer, 11C-BF-227, can detect the amyloid deposition specifically, and 11C-BF-227-PET is a useful technology to detect the amyloid in the whole bodies, although the sensitivity might be different in each organ.



Disclosure: Y. Shirota, None; **K. Furukawa**, None; **M. Tashiro**, None; **T. Shirrai**, None; **H. Fujii**, None; **T. Ishii**, None; **H. Harigae**, None.

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Abstract Number: 1281

Feasibility and Reliability of the Spondyloarthritis Research Consortium of Canada Sacroiliac Joint Inflammation Score for Children with Spondyloarthritis

Nancy A. Chauvin[1], Walter P. Maksymowych[2,3], Robert G. Lambert[4], Jacob Jaremko[5], David M. Biko[1], Timothy G. Brandon[6], Joel Paschke[2] and **Pamela F. Weiss**[7,8], [1]Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]CaRE Arthritis, Edmonton, AB, Canada, [3]Medicine, University of Alberta, Edmonton, AB, Canada, [4]Radiology, University of Alberta, Edmonton, AB, Canada, [5]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [6]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA,

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Background/Purpose: We lack a method to quantify severity of inflammation in the pediatric sacroiliac joint. We evaluated the reliability and construct validity of the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint inflammation score (SIS) in children with suspected or confirmed juvenile spondyloarthritis (SpA).

Methods: The SIS divides the joint into quadrants and scores the presence, depth, and intensity of bone marrow edema (BME) on short tau inversion recovery (STIR) magnetic resonance imaging (MRI). Six consecutive semicoronal slices through the cartilaginous portion of the joint are scored for BME (total score 0-72). We developed a pediatric training module that included scoring instructions and examples of BME and bright subchondral signal on STIR scans easily confused with inflammation (Figure). After reviewing the module, 5 readers (1 adult and 3 pediatric radiologists, 1 adult rheumatologist), blinded to clinical details except age, scored 30 studies that included semicoronal T1-weighted and STIR sequences. Pain was recorded on a visual analogue scale (0-10). Disease activity was evaluated using the juvenile SpA disease activity (JSpADA) index (range 0-8). Inter-observer reliability was assessed using intraclass correlation coefficient (ICC). Correlation (convergent validity) of the mean SPARCC SIS developers' score with disease activity was tested using Spearman correlation. Discrimination was tested by comparing the mean SPARCC SIS developers' score between children with and without inflammatory back pain using the Mann-Whitney test.

Results: The SIS had face validity and was feasible to score in the 30 pediatric cases. 21 (70%) were male. Median age at the time of imaging was 15.5 years (IQR: 12.7-16.8). Median pain score and JSpADA index were 2 (IQR 0.5-6) and 2 (IQR: 0.5-3), respectively. Of the 150 scores submitted by 5 readers, 114 (76%) of the studies had a SIS >2. Median SIS was 13.5 (IQR: 2-28). ICC for all readers (N=5), SPARCC developers (N=2), and pediatric radiologists (N=3) were 0.69 (95% CI: 0.47-0.83), 0.89 (95% CI: 0.75-0.95), and 0.85 (95% CI: 0.72-0.92), respectively. SIS had low correlation with disease activity as measured by the JSpADA (r=-0.08) and C-reactive protein (r=0.14). SIS score did not discriminate between those with and without inflammatory back pain (p=0.16).

Conclusion: The SIS was feasible to score and had near excellent reliability, even with limited calibration. SIS did not have convergent validity with clinical measures of disease activity, highlighting that imaging and clinical evaluations provide complimentary but non-overlapping information. Responsiveness of the SIS should be evaluated in a prospective cohort of children who start biologic therapy.

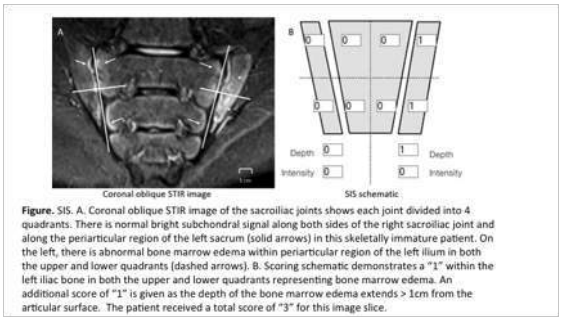

Figure. SIS. A. Coronal oblique STIR image of the sacroiliac joints shows each joint divided into 4 quadrants. There is normal bright subchondral signal along both sides of the right sacroiliac joint and along the periarticular region of the left sacrum (solid arrows) in this skeletally immature patient. On the left, there is abnormal bone marrow edema within periarticular region of the left ilium in both the upper and lower quadrants (dashed arrows). B. Scoring schematic demonstrates a "1" within the left iliac bone in both the upper and lower quadrants representing bone marrow edema. An additional score of "1" is given as the depth of the bone marrow edema extends > 1cm from the articular surface. The patient received a total score of "3" for this image slice.

Disclosure: N. A. Chauvin, None; **W. P. Maksymowych**, None; **R. G. Lambert**, None; **J. Jaremko**, None; **D. M. Biko**, None; **T. G. Brandon**, None; **J. Paschke**, None; **P. F. Weiss**, None.

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Abstract Number: 1282

Feasibility and Reliability of the Spondyloarthritis Research Consortium of Canada Sacroiliac Joint Structural Score for Children with Spondyloarthritis

Nancy A. Chauvin[1], Walter P. Maksymowych[2,3], Robert G. Lambert[4], Jacob Jaremko[5], David M. Biko[1], Timothy G. Brandon[6], Joel Paschke[3] and **Pamela F. Weiss**[7,8], [1]Radiology, Children's Hospital of Philadelphia, Philadelphia, PA, [2]Medicine, University of Alberta,

Edmonton, AB, Canada, [3]CaRE Arthritis, Edmonton, AB, Canada, [4]Radiology, University of Alberta, Edmonton, AB, Canada, [5]Radiology, Radiology, University of Alberta, Edmonton, AB, Canada, [6]Pediatrics, Children's Hospital of Philadelphia, Philadelphia, PA, [7]Department of Pediatrics, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, [8]Division of Rheumatology, Center for Pediatric Clincial Effectiveness, Children's Hospital of Philadelphia, Philadelphia, PA
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Background/Purpose: There is a critical need for measures to evaluate structural progression in the pediatric sacroiliac joint. We aimed to evaluate the precision and construct validity of the Spondyloarthritis Research Consortium of Canada (SPARCC) sacroiliac joint structural score (SSS) in children with suspected or confirmed juvenile spondyloarthritis.

Methods: The SSS assesses a spectrum of structural lesions of the sacroiliac joint on magnetic resonance imaging (MRI) including fat metaplasia, erosion, backfill, and ankylosis on 5 consecutive slices through the cartilaginous part of the joint. These components are scored 0-20 (backfill and ankylosis) or 0-40 (fat metaplasia, erosion). We developed a pediatric training module that included a detailed description of each SSS component plus sclerosis (0-40), scoring methodology, and numerous examples (Figure). After reviewing the module, 5 readers (1 adult and 3 pediatric radiologists, 1 adult rheumatologist), blinded to clinical details except age, scored 30 studies that included semicoronal T1-weighted sequences. Inter-observer reliability was assessed using intraclass correlation coefficient (ICC). We assessed correlation (construct validity) between the mean SPARCC SSS developers' scores and disease duration with Spearman correlation. Discrimination was tested by comparing the mean SPARCC SSS developers' scores between children with and without limited mobility (retained lumbar lordosis, modified Schober <20 cm, or both).

Results: The SSS had face validity and was feasible to score in the 30 pediatric cases with suspected or confirmed spondyloarthritis. 21 (70%) were male and median age was 15.5 years (IQR 12.7-16.8). Median symptom duration was 30 months (IQR 2.3-74.7). The ICCs for the SSS components are shown in the Table. Erosion, backfill, and ankylosis had good reliability (>0.40) while reliability for fat metaplasia and sclerosis were low. 27 (18%), 106 (70%), 44 (29%), 83 (55%), and 13 (9%) of studies had a score>0 for fat metaplasia, erosion, backfill, sclerosis, and ankylosis, respectively. Correlations of symptom duration with each component of the SSS were low (r range -0.13-0.26). SSS components did not discriminate between children with and without limited back mobility.

Conclusion: The SSS was feasible to score and had acceptable reliability for pediatric sacroiliac joint MRI evaluation. Low ICC for fat metaplasia may reflect low frequency of this feature in pediatric SpA or difficulty in assessment since hematopoietic marrow can appear patchy. Low ICC for fat metaplasia and sclerosis highlight the need for additional calibration.

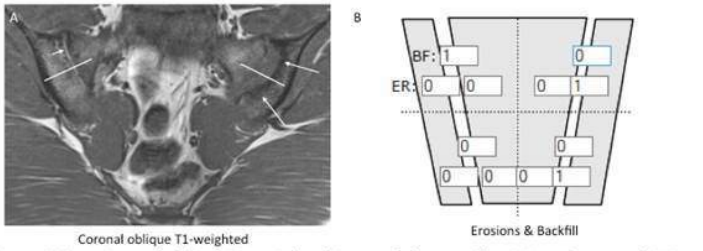

Figure. SSS. A. Coronal oblique T1-weighted image of the sacroiliac joints shows each joint divided into 4 quadrants. There is backfill along the superior aspect of the right sacroiliac joint, as demonstrated by abnormal bright T1 signal adjacent to the articular surface (short arrow). There are erosions within the upper and lower quadrants of the left iliac bone (long arrows). No sclerosis, ankylosis or fat metaplasia. B. Scoring schematic demonstrates a "1" for backfill (BF) within the upper aspect of the right sacroiliac joint and "1" within both the upper and lower quadrants of the left iliac bone representing erosions (ER).

	SSS Median (IQR), All readers	All Readers (N=5) ICC (95% CI)	Pediatric Radiologists (N=3) ICC (95% CI)	SPARCC developers (N=2) ICC (95% CI)
Fat metaplasia (0-40)	0 (0-0)	0.37 (0.21-0.56)	0.46 (0.25, 0.67)	0.89 (0.77-0.95)
Erosion (0-40)	4 (0-10)	0.47 (0.29-0.65)	0.39 (0.15, 0.61)	0.72 (0.48-0.86)
Backfill (0-20)	0 (0-1)	0.54 (0.38-0.71)	0.36 (0.14, 0.58)	0.82 (0.56-0.92)
Sclerosis (0-40)	1 (0-5)	0.39 (0.21-0.59)	0.42 (0.17, 0.65)	0.61 (0.08-0.83)
Ankylosis (0-20)	0 (0-0)	0.59 (0.43-0.74)	0.46 (0.24, 0.66)	0.72 (0.49-0.85)
Table. ICC for SSS components. ICC<0.40 is poor, 0.40≤ICC<0.75 is good and ICC≥0.75 is excellent.				

Abstract Number: 1283

Utility of FDG-PET Imaging and Serological Biomarkers for Diagnosing Lymphadenopathy of IgG4-Related Diseas

Hiroaki Dobashi, Hiroki Ozaki, Atsushi Kondo, Risa Wakiya, Hiromi Shimada, Shusaku Nakashima, Miharu Izumikawa and Tomohiro Kameda, Internal Medicine Division of Hematology, Rheumatology, and Respiratory Medicine, Kagawa University, Kagawa, Japan

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Background/Purpose: IgG4-related disease (IgG4-RD) is not rare and clinically important disease. It is difficult to confirm the diagnosis because IgG4 positive lymphocyte infiltrates various organs. Especially, lymphadenopathy is a common manifestation in IgG4-RD. However, it is difficult for the rheumatologist to distinguish its lymphadenopathy from non IgG4-RD. Elevated serum IgG4 level did not decide diagnosis of IgG4-RD. In 2011, comprehensive diagnostic criteria for IgG4-RD were established by Umehara et al. [1]. This criteria required histopathological findings to diagnose IgG4-RD definite. Recent research has shown FDG-PET/CT is useful modality to select biopsy site [2].

Methods: We enrolled 29 cases which suspected IgG4-RD with lymphadenopathy in our facility between 2008 and 2016. Serum IgG4 level was analyzed all patients which were undertaken whole-body FDG-PET/CT study and biopsy. The diagnosis for IgG4-RD was based on comprehensive diagnostic criteria for IgG4-RD. Laboratory data were retrospectively collected from their medical records. We investigated levels of serum C-reactive protein (CRP) and serum albumin, eosinophil/leukocyte ratio, serum IgG and IgG4 levels, sIL2-R levels, the size and maximum standardized uptake value (SUVmax) and distribution of lymph nodes with abnormal FDG uptake on FDG-PET/CT and pathological findings. We investigate the utility of FDG-PET imaging and serological biomarkers for diagnosing lymphadenopathy of IgG4-RD.

Results: 29 patients were diagnosed into 3 groups (IgG4-RD definite: 12, IgG4-RD possible: 10, non IgG4-RD: 7). Non IgG4-RD group was included infectious disease, systemic lupus erythematosus, eosinophilic granulomatosis with polyangiitis, Sjogren's syndrome,

Castleman's disease, and malignant lymphoma. No significant differences among 3 groups in levels of CRP or sIL-2R were found. In IgG4-RD definite group, serum IgG4 levels and serum IgG4/IgG ratio were higher than other groups. Serum albumin levels were lower in non IgG4 group compared to others. Eosinophil/leukocyte ratio was higher in IgG4-RD definite group than in possible group. We examined about lymph nodes with abnormal FDG uptake. In IgG4-RD definite group, size of lymph nodes were smaller compared to other 2 groups. There is no difference among 3 groups in SUVmax or distribution of abnormal lymph nodes. Lymph node biopsy were performed in 5 patients with IgG4-RD. In 2 patients who diagnosed IgG4-RD definite, sIL-2R levels were higher and size of abnormal lymph nodes were smaller compared with those in 3 patients diagnosed IgG4-RD possible.

Conclusion: In this study, we examined patients which suspected IgG4-RD with lymphadenopathy. Patients with IgG4-RD definite tended to show higher serum IgG4 levels and smaller size of lymph nodes with abnormal FDG uptake on FDG-PET/CT. No significant differences were found among 3 groups in levels of serum CRP, sIL2-R, SUVmax or distribution of lymph nodes with abnormal FDG uptake.
References: [1]Umehara H, Okazaki K, Masaki Y, et al. Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD), 2011. Mod Rheumatol. 2012 Feb;22(1):21-30. [2]Nakatani K. Utility of FDG PET/CT in IgG4-related systemic disease Clin Radiol. 2012 Apr;67(4):297-305.

Disclosure: H. Dobashi, None; **H. Ozaki**, None; **A. Kondo**, None; **R. Wakiya**, None; **H. Shimada**, None; **S. Nakashima**, None; **M. Izumikawa**, None; **T. Kameda**, None.

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Abstract Number: 1284

International Multi-Observer Ultrasound Reliability Study of Age Related Vascularization and Ossification in Healthy Children: The Omeract Pediatric Ultrasound Task Force

Daniel Windschall[1], Paz Collado[2], Jelena Vojinovic[3], Silvia Magni-Manzoni[4], Peter Balint[5], George A. W. Bruyn[6], Cristina Hernandez-Diaz[7], Juan Carlos Nieto[8], Viviana Ravagnani[9], Nikolay Tzaribachev[10], Annamaria Iagnocco[11], Maria Antonietta D'Agostino[12] and Esperanza Naredo[13], [1]Pediatric Clinic, Asklepios Hospital Weissenfels, Weissenfels, Germany, [2]Hospital Universitario Severo Ochoa, Madrid, Spain, [3]Dept of Pediatric Rheumatology, Faculty of Medicine, University of Nis, Nis, Serbia, [4]Pediatrico Bambino Gesù, Rome, Italy, [5]Rheumatology, National Institute of Rheumatology and Physiotherapy, Budapest, Hungary, [6]Dept of Rheumatology, MC Groep hospitals, Lelystad, Netherlands, [7]Instituto Nacional de Rehabilitación, Mexico City, Mexico, [8]Hospital General Universitario Gregorio Marañón and Complutense University, Madrid, Spain, [9]Rheumatology Clinic, University of Verona, Verona, Italy, [10]PRI - Pediatric Rheumatology Research Institute, Bad Bramstedt, Germany, [11]Sapienza Università Di Roma,, Roma, Italy, [12]Rheumatology, Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [13]Rheumatology, Hospital General Universitario Gregorio Marañón and Universidad Complutense, Madrid, Spain

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases - Poster II: XR/CT/PET/MRI

Session Type: ACR Poster Session B

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Background/Purpose: Ultrasound (US) has been demonstrated to be a very sensitive and objective tool for evaluating synovitis in children. However sometimes due to the age variability especially in the vascularization of the epiphysis and short bone cartilage, the distinction between physiological and pathological grey-scale (GS) and power Doppler (PD) findings can be difficult. The aim of the study was to test the intra- and inter-observer reliability of US detected age related vascularization and ossification grade in healthy children.

Methods: Following standardized image acquisition and machine setting protocol, 10 international ultrasound experts examined four joints (wrist, 2ndMCP, knee and ankle) in 12 healthy children (divided in four age groups: 2–4; 5–8; 9–12 and 13–16 years). GS and PD US were used to detect physiological vascularization and ossification grade. Ossification was graded as follow: grade 0 – non-ossified epiphyseal bone, short bones or patella; grade 1 - small ossification centers, dominant cartilage, visible growth plate; grade 2 - large ossification centers, thin cartilage, visible growth plate; grade 3 - completed ossification. PD was defined as any PD signal inside the joint. Kappa statistics were applied for intra- and inter-observer reliability.

Results: According to specific joint and age up to 4 solitary PD signals (mean 1.5/joint) were detected within the joint areas due to the

physiological vascularization localized predominantly in some specific anatomic positions: fat pad, epiphysis, the physis and the short bone cartilage. The kappa values for grading ossification were 0.87 (range 0.85-0.91) for intra-observer and 0.58 for inter-observer reliability respectively. Since the prevalence of the PD detected lesions was not uniformly distributed, we used the bias adjusted kappa, which was 0.71 (range 0.44-1) for intra-observer and 0.69 for inter-observer reliability.

Conclusion: Our study showed that the detection of normal findings (i.e. grading of physiological ossification in the skeletal maturation including physiological vessels) can be high reliable by using clear definitions and a standardized acquisition protocol. These data will permit to develop a reliable and standardized US approach for evaluating pediatric joint pathologies.

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Abstract Number: 1285

PET/CT Imaging in Patients with Vascular Behcet Disease

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Background/Purpose: BehetÕs disease (BD) is a multisystemic disease characterized by recurrent inflammatory manifestations. BD is classified as variable vessel vasculitis. While inflammatory thrombotic venous findings are dominant in patients with vascular-BD, arterial lesions manifesting as aneurysms and occlusive/stenotic lesions can also be seen. In addition to clinical findings, imaging studies with CT, MRI, and Doppler ultrasonography play an important role in the diagnosis of vascular involvement. PET/CT is a relatively new tool being used in the assessment of large-vessel vasculitis, and there are conflicting reports about using PET/CT in patients with BD. We herein aimed to investigate our records for the role of PET-CT in the diagnosis and follow-up of BD patients with vascular involvement.

Methods: We retrospectively reviewed the charts of BD patients who were investigated with PET/CT for any reason related to disease activity. Patients fulfilling the ISG criteria or with a preliminary diagnosis of BD were included for the analysis. Using a standard form, clinical findings, acute phase response including ESR and CRP, and additional imaging findings, such as CT or MRI, performed within the last 2-week of PET/CT scanning were recorded. Vascular FDG uptake was graded using a 4-point semi-quantitative scale. PET/CT scans were considered positive if vascular FDG uptake was ³ 2 (equal to or greater than liver).

Results: We identified 12 patients investigated with PET/CT. The mean age of the patients was 44 years, the mean disease duration was 14 years, and 11 (92%) were male. Demographic and clinical findings are summarized in Table 1. Patients underwent PET-CT due to fever of unknown origin (n=6), fatigue with unexplained high acute phase response (n=3), abdominal pain (n=1), or unexplained neck pain (n=1). Five of them fulfilled the ISG criteria, and 4 had positive PET/CT findings due to aortic involvement or bronchiolitis obliterans organizing pneumonia (n=2). No FDG uptake was detected in one patient with venous lesions. In remaining 7 patients with incomplete manifestations suggesting BD, vascular involvement documented by FDG uptake in aorta and its branches (n=2), pulmonary arteries (n=2), carotid arteries

Table-1.Demographic and clinical findings of patients with Behcet Disease

N	Sex, age	Disease duration (y)	Clinical Finding					Clinical finding before PET	Positive PET-CT findings
			Mucocutaneous	Eye	Arthritis	Vascular	CNS		
1	M,38	4	ROA, GU, PPL, EN	-	-	DVT, right ventricular thrombus	-	Fatigue, High CRP and ESH	Normal
2	M,42	18	ROA, GU, PPL	-	-	Aortitis	-	FUO	Arcus and thoracic aorta involvement
3	M,27	17	ROA, GU, PPL	Uveitis	-	Pulmonary aneurysm and thrombosis	-	FUO	Bronchiolitis obliterans organizing pneumonia
4	M,47	14	ROA, GU, PPL	Uveitis	-	Pulmonary aneurysm	-	FUO	Bronchiolitis obliterans organizing pneumonia
5	M,46	23	ROA, GU, PPL, EN	Panuveitis	-	LAD aneurysm	ACA aneurysm	Fatigue and high ESH	Abdominal aorta involvement
6	M 38	26	ROA, PPL, EN	-	Oligoarthritis	CCA and ICA aneurysm		Neck pain	Carotid involvement
7	M,37	2	ROA	-	Oligoarthritis	DVT, pulmonary aneurysm	-	FUO	Pulmonary artery involvement
8	F,61	13	ROA	-	Oligoarthritis	Arcus aort and abdominal aneurysm	-	FUO	Arcus and abdominal aorta involvement
9	M,47	12	ROA, GU	-	-	-	-	Chest and back pain	Carotid and aortic (arcus, thoracic, abdominal) involvement
10	M,46	12	ROA, GU	-	-	Arcus aort, thoracic and abdominal aneurysm	-	High CRP and ESH	Normal
11	M,59	10	ROA, PPL	-	-	Pulmonary aneurysm	-	FUO	Pulmonary artery involvement
12	M,42	16	ROA, PPL	-	-	Coronary, femoral, and splenic artery aneurysm	Parenchymal infarct	Abdominal pain	Splenic artery involvement

ROA; recurrent oral aphthous ulcers, GU; genital ulcers, PPL, papulopustular skin lesions, DVT; Deep venous thrombosis,

(n=2) and splenic artery (n=1).

Conclusion: In BD patients with unexplained acute phase response, screening for vascular involvement is important, and PET/CT may contribute to diagnostic process by documenting medium-large size arterial activity. FDG uptake by arterial aneurysms and venous involvement in PET/CT is not clear, and several factors such as the size of the vessels and the thickness of vessel wall may affect FDG uptake. Parenchymal lesions possibly induced by small vessel vasculitis may also be another reason for positive PET/CT findings. Role of PET/CT in the diagnosis of patients with incomplete BD manifestations needs to be investigated further, since other disorders with mucocutaneous and vascular findings may mimic BD and cause diagnostic uncertainty.

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Abstract Number: 1286

Inflammatory Activity of IgG4-Related Disease Lesions Assessed By Quantitative Positron Emission Tomography Correlates with Circulating Plasmablasts Levels

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Background/Purpose: IgG4-Related Disease (IgG4-RD) is a multisystemic inflammatory disease characterized by fibrous swelling and IgG4+ plasma cells infiltration of affected organs.18-Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) scan is emerging as a promising imaging technique for diagnosis and staging of IgG4-RD. We aim to correlate the intensity and distribution of FDG-PET uptake with clinical and immunological parameters in patients with active untreated IgG4-RD.

Methods: Patients with active, untreated, biopsy proven IgG4-RD were included in the study. Disease activity was assessed through clinical (IgG4-RD Responder Index (RI)) and immunological (erythrocyte sedimentation rate (ESR), C reactive protein (CRP), serum IgG4, and circulating plasmablasts) parameters. Plasmablasts, a recently characterized disease biomarker, were identified as CD19+CD20-CD27+CD38bright cells on flow cytometry. FDG-PET/CT was performed in all patients at diagnosis. Quantitative assessment of FDG uptake was measured using the mean Standardized Uptake Value corrected for the Partial Volume Effect (PVC-SUV) and with total lesion glycolysis (TLG). Lymph nodes < 1 cm of diameter were excluded from the analysis because of the risk of PVC-SUV over/under-estimation. In patients with multiorgan involvement, the IgG4-RD lesion with the highest PVC-SUV was selected to correlate FGD uptake with clinical and serological parameters.

Results: We studied 19 patients (12 males, 7 females) with a mean age of 61 years (range, 30-78 years). Eleven (58%) patients had

multiorgan IgG4-RD, with a average number of organ affected of 2.2 (range, 1-6). Involved organs were: lymphnodes (8 patients), aorta (6 patients), pancreas (4 patients); lung, parotids and submandibolar glands (3 cases each), paranasal sinuses, palate, orbits, bones and lachrymal glands (2 cases each); meninges, thyroid, subcutaneous nodule and spleen (one case each). The median IgG4-RD RI was 6 (range 6-15; normal < 3). The median levels of ESR, CRP, serum IgG4 and plasmablasts at baseline were 30 mm/h (range 4-121 mm/h, normal <20 mm/h), 9,9 mg/L (range 0.0-48.0 mg/L; normal <6mg/L), 455 mg/dL (range 80-2100 mg/dL, normal <135 mg/dL), and 5365 cells/mL (range 130-40840 cells/mL, normal <650 cells/mL), respectively. The mean PCV-SUV was 10.36 (range, 2.78-39.34) and the mean TLG was 429.24 (range, 91.37-3479.65). Significant positive correlation was found between PVC-SUV and circulating plasmablasts levels (r=.46, p=.004). No statistically significant correlation was found between either PVC-SUV or TLG and CRP, ESR, serum IgG4 levels, IgG4-RD RI at baseline (p>.05), and not even between TLG and circulating plasmablasts (p>.05).

Conclusion: We first demonstrated a positive correlation between circulating plasmablasts and inflammatory activity of IgG4-RD lesions as assessed by PVC-SUV on FDG-PET. Inflammatory markers, serum IgG4 levels, and IgG4-RD RI do not appear to correlate with metabolic activity in IgG4-RD lesions. Our results further strengthen the utility of circulating plasmablasts as a biomarker of IgG4-RD activity.

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Abstract Number: 1287

Utility of Vascular Findings By PET/CT Scan in the Diagnosis and Activity Assesment of Takayasu Arteritis

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Background/Purpose: Takayasu arteritis (TA) is a large-vessel vasculitis predominantly affecting the aorta and its main branches. Assessing disease activity is difficult and mainly based on the clinical findings, levels of acute phase reactants and angiography, but these items generally do not correlate well. The aim of the this study was to investigate the role of PET/CT in the diagnosis of the disease and assessing disease activity in TA

Methods: Thirty TA patients fulfilling ACR criteria underwent FDG-PET/CT were retrospectively assessed. Disease activity was defined according to NIH criteria. A nuclear physician who was blinded to clinical and laboratory data examined all PET/CT scans. PET/CT scans were considered negative if vascular FDG uptake relative to liver was grade 0 or 1 and positive if vascular uptake was grade 2 or 3 in at least one vessel area. The levels of C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were measured concomitantly. The correlations between CRP and ESR with SUVmax values of vessels were investigated. CRP levels and ESRs were compared in subjects with or without positive PET/CT scans. Disease activity assessed by PET/CT was compared with the NIH criteria. ROC curve analyses were performed to assess the sensitivity and specificity of CRP and ESR according to PET/CT positivity.

Results: PET/CT was performed for diagnostic purposes early in the disease course in 9 subjects and to assess disease flare in 21 subjects on follow-up. The rate of a positive PET/CT examination tended to be higher in diagnostic/early use (88.9% positive) compared with use for flare-assessment (61.9% positive), although the difference was not significant (Fisher=0.2). Median CRP and ESR tended to be higher in PET/CT positive patients compared with PET/CT negative subjects (median CRP 19 vs. 14, p=0.16; mean ESR 59.8±36.5 vs. 35.2±19.7, p=0.07). ROC curve analysis showed an ESR of 38 mm/h or higher was 68.4% sensitivity and 66.7% specificity to predict a positive PET/CT examination (positive and negative predictive values 81.6% and 50%). A CRP of 14.5 mg/L or higher was 66.7% and 55.6% specific to predict a positive PET/CT examination (positive and negative predictive values 77.8% and 41.7%). While CRP was significantly correlated with mean SUV_{max} value of aorta (r=0.41, p=0.02), ESR was weakly correlated with SUV_{max} value of aorta

(r=0.3, p=0.13). There was moderate agreement between PET-CT and NIH criteria (kappa 0.462, p=0.01, sensivity 81%, spesificity 67%)

Conclusion: These results suggested that clinical benefit of PET/CT may be higher in diagnostic use (early in the disease course) compared with use for flare assessment (after treatment) in TA. There was a moderate association between NIH activity criteria and PET/CT activity. The predictive value of increased ESR and CRP was similar for a positive PET/CT scan with lower negative predictive values. CRP levels had a better correlation with SUVmax levels of aorta compared to ESR. PET/CT is a promising tool in the diagnosis and activity assessment of TA but discrepancies with other activity parameters do exist.

Disclosure: B. Toz, None; **Z. G. Özkan**, None; **B. Artim-Esen**, None; **B. Erer**, None; **S. Kamali**, None; **A. Gul**, None; **L. Ocal**, None; **M. Inanc**, None.

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Abstract Number: 1288

Evaluating Rheumatoid Arthritis Disease Activity Using Global Assessment of 18f-FDG Uptake in the Joints

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Background/Purpose: Clinical imaging modalities in rheumatoid arthritis (RA) such as MRI and ultrasound can detect morphologic changes associated with synovial inflammation. ^{18}F-labeled fluorodeoxyglucose positron emission tomography (FDG-PET) can directly assess cellular metabolic activity and has been used to quantify joint inflammation in small studies. We developed a semi-automatic method to evaluate RA disease activity and assessed associations with measures of systemic inflammation.

Methods: Patients with RA underwent static FDG-PET 180 minutes after the intravenous administration of FDG tracer. Regions of interest were drawn around the hips, shoulders, knees, elbows, hands, and feet. An adaptive thresholding algorithm delineated and quantified regions of high tracer uptake in the regions of interest (Figure 1). Of the calculated values, the global partial volume corrected mean standardized uptake value considers all active sites proportional to their active volumes and was considered to best represent overall disease activity as an estimate of total body synovial metabolic activity. Correlations between synovial metabolic activity and systemic inflammation and clinical disease activity were assessed.

Results: A total of 18 patients (13 men) underwent FDG-PET. The average age was 57.7 (12.1) years with a mean DAS28(CRP) of 3.74 (1.29). The mean synovial metabolic activity score was 4.48 (1.78), with a range of 2.35-9.46 units. A significant correlation was observed between synovial metabolic activity and TNF-α, IL-6, and CRP (Figure 2). In contrast there was poor correlation with other measures of clinical disease such as swollen joints, tender joints, and results of the Health Assessment Questionnaire (Table). Among the 6 subjects with low clinical disease activity [DAS28(CRP) <3.2], there was a strong positive correlation between synovial metabolic activity and CRP (Rho=0.89, p=0.01) and IL-6 (Rho=0.89, p=0.02).

Conclusion: This study describes a novel semi-automated methodology to quantify synovial metabolic activity in RA using FDG-PET. This measure strongly correlates with measures of systemic inflammation, even among those with low disease activity. This methodology may have clinical and research utility in the evaluation of RA-specific systemic inflammation.

Figure: FDG-PET images of the whole-body of a patient with rheumatoid arthritis in the upper (a) and lower (b) extremities. The disease activity in these joints was assessed using ROVER software. The pvcSUVmean is presented next to each joint. The global pvcSUVmean was 5.8 for this individual.

Global pvcSUVmean = [∑ (joint pvcSUVmean × joint volume)]/(∑ joint volume)

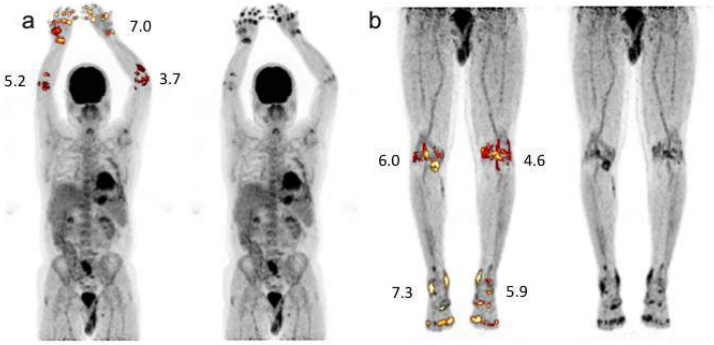
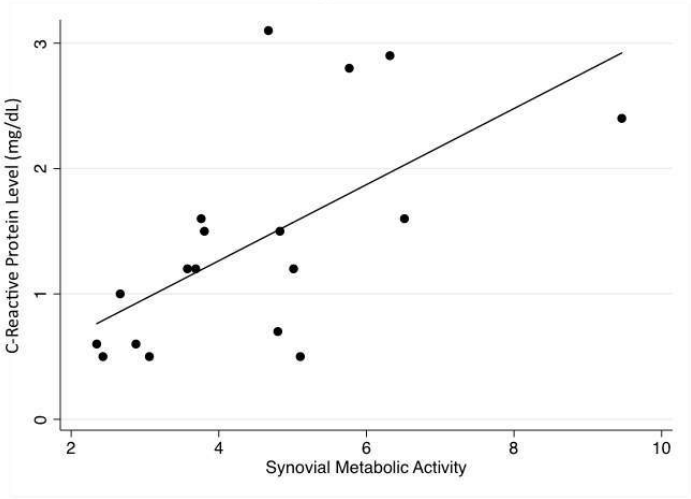


Table: Correlations between total synovial metabolic activity score and estimates of disease activity and systemic inflammation.		
	FDG PET Synovial Metabolic Activity	
	SpearmanÕs Rho	P-value
C-Reactive Protein (mg/dL)	**0.63**	0.005
Sedementation Rate (mm)	**0.44**	0.08
Interleukin-6 (pg/mL)	**0.49**	0.04
Tumor Necrosis Factor-α (pg/mL)	**0.54**	0.02
Interleukin-1 (pg/mL)	0.28	0.25
Swollen Joint Count	0.033	0.90
Tender Joint Count	-0.010	0.97
Patient Global Score	-0.19	0.44
DAS28(CRP)	0.039	0.89
Health Assessment Questionnaire	0.21	0.40

Figure: Correlation between the synovial metabolic activity score from FDG PET/CT and C-Reactive Protein Levels among patients with RA.



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Abstract Number: 1289

Comparison of Clinical Parameters and PET/MRI in Juvenile Idiopathic Arthritis

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Background/Purpose: Positron emission tomography (PET) can be used to identify inflammation using ^{18}F-fluorodeoxyglucose (^{18}F-FDG). ^{18}F-FDG uptake correlates with clinical and laboratory markers of disease activity in adults with rheumatoid arthritis and in one previous study of juvenile idiopathic arthritis (JIA). The purpose of this study was to test the feasibility of combining the metabolic data from ^{18}F-FDG PET with structural and functional data from MRI to assess disease activity in JIA.

Methods: Seven patients with polyarticular JIA according to ILAR criteria (6 RF-positive, 1 RF-negative) underwent ^{18}F-FDG PET/MRI of the whole body and a dedicated scan of 1 joint/region. Each patient had a complete joint exam on the day of the scan. Patients were scanned using a weight-based, low-dose (0.5 megabecquerel/kg) ^{18}F-FDG protocol to minimize radiation exposure, resulting in maximum effective dose less than 0.7 millisievert for patients weighing 55 kg or greater. Images were evaluated qualitatively, and joints were considered positive on PET if ^{18}F-FDG localization was increased above background.

Results: Mean age was 15.1±2.9 yrs and median disease duration was 7.5±2.4 yrs. For 4 out of 7 patients, PET showed more positive joints than physical exam (see table). For 1 patient, physical exam showed 2 positive joints but PET was negative. Joints that showed disagreement between physical exam and PET included hand/wrist, ankle/foot, knee, elbow, and shoulder (see Figure 1). Disagreement between physical exam and PET did not correlate with any clinical characteristics including ESR, BMI, or Juvenile Arthritis Disease Activity Score (JADAS). MRI allowed localization of PET signal, for example allowing diagnosis of tenosynovitis in one patient (see Figure 2).

Conclusion: We found disagreement between physical exam and PET in 5 out of 7 JIA patients. PET detected more joints with inflammation than physical exam, and notably this disagreement often occurred in joints that are easily accessible on physical exam.

Table. Clinical disease activity compared to PET findings

Subject	Clinical disease activity[a]	JADAS[b]	Active joint count by physical exam	PET positive joints
1	Inactive	3.1	0	0
2	Inactive	0	0	5
3	Inactive	4.0	0	0
4	Active	3.0	1	4
5	Active	9.0	2	0
6	Active	9.0	3	4
7	Active	10.0	3	8

[a] ACR provisional criteria for inactive disease in JIA
[b] Juvenile Arthritis Disease Activity Score: Low disease activity ≤ 2.5, Moderate 2.6 – 8.5, High > 8.5

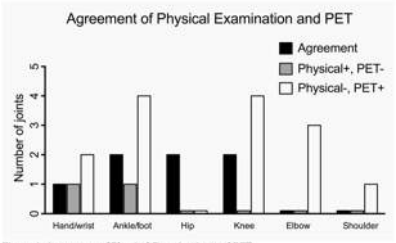

Figure 1: Agreement of Physical Examination and PET

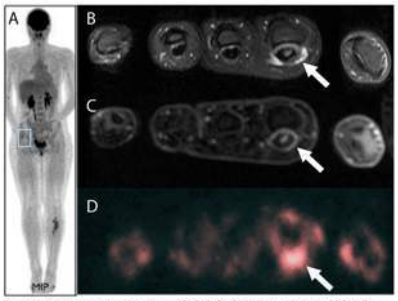

Figure 2: Maximum projection image of whole body PET in a 17-year-old female with JIA shows increased activity in the right hand (box in A). Axial images show tenosynovitis at the right index finger extensor tendon (arrows) on T2-weighted fat saturated MRI (A), T1-weighted fat saturated post-contrast MRI (B), and high resolution PET.

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Abstract Number: 1290

The Usefulness of Volumetric Parameters of FDG PET/CT for Reflecting Disease Activity in Polymyositis/Dermatomyositis Patients

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Background/Purpose: Polymyositis/dermatomyositis (PM/DM) are systemic inflammatory disorders predominantly affecting skeletal muscles and skin respectively. Although muscle biopsy is the most important to the diagnosis of PM/DM, some cases may not have inflammatory lesion in biopsy site. There are some reports that enhanced magnetic resonance imaging (MRI) is useful for decision of biopsy site. However, enhanced MRI could not detect inflammatory lesion of whole body easily.The purpose of this study was to investigate the usefulness of volumetric parameters of the whole-body FDG PET/CT for evaluating disease activity in patients with PM/DM.

Methods: A total of 21 patients with previously untreated PM/DM were examined with whole-body FDG PET/CT. The same number of age- and sex-matched control patients with non-muscular diseases were also identified. The FDG uptake was visually evaluated in 22 regions of the whole-body. Regions with FDG uptake greater than that of the mediastinum blood vessels were considered positive. The semi-quantitative analysis was also performed using a maximum standardized uptake value (SUVmax), metabolic volume (MTV), and total lesion glycolysis (TLG). PET results were compared with those of serum levels of creatine kinase (CK) and aldolase.

Results: On visual analysis, the mean ± SD of number of positive regions in patients with PM/DM was 11 ± 7. The mean value of SUVmax in patients with PM/DM was significantly higher than that in control patients ($p<0.001$). There was a significant correlation between number of positive regions and TLG ($p<0.04$). There was a significant correlation between MTV and aldolase ($p<0.04$) and between TLG and CK ($p<0.009$) and aldolase ($p<0.006$). There was no significant correlation between number of positive regions and CK or aldolase and between SUVmax and CK or aldolase.

Conclusion: These preliminary results suggest that volumetric parameters such as MTV and TLG of whole-body FDG PET/CT may be useful for evaluating disease activity in patients with PM/DM.

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Abstract Number: 1291

Performance of Magnetic Resonance Imaging and 18fluoride Sodium Positron Emission Tomography with Computed Tomography to Assess Inflammatory and Structural Abnormalities of the Sacroiliac Joint in Axial Spondyloarthritis

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Background/Purpose: We aimed to assess increased SIJ uptakes on 18-FNa (an osteoblastic tracer) PET/CT and to compare with MRI SIJ assessments for inflammation and structural damage in MRI in a population of 23 patients with SpA. (IDRCB : 2012-A00568-35).

Methods: This prospective study included 23 patients with active SpA according to ASAS and/or modified mNY criteria (males 43%, median age 43 y, median symptom duration 7.7 y, HLA-B27 30%, median CRP 8mg/L, median BASDAI 6.1). Pelvic radiograph, MRI of the SIJ and 18-FNa PET/CT were performed during the same month. For MRI, SIJ were assessed for the presence of inflammation (ASAS criteria) and were quantitatively assessed according to SPARCC methods for scoring inflammation and structural damage. On the PET, SIJ

were scored blinded to MRI and CT by two nuclear physician according to a slice by slice approach. A positive PET was defined when unilateral uptake was observed on 2 consecutive slices or bilateral uptake on a single slice. As for SPARCC MRI methods, quantitative assessment on 18-FNa PET was performed according to SIJ quadrants for six consecutive slices through the cartilaginous region of the joint (PET-activity score). The Standardized Maximal Uptake Value (SUV-max) was measured for each SIJ, corresponding to the highest uptake value of the SIJ.

Results: 7 patients had radiographic sacroiliitis, 9 had inflammatory sacroiliitis on MRI (mean SPARCC 7.65)., 9 had structural sacroiliitis on MRI The concordance between the two readers for a positive PET was good (73.9%) as well as the inter-reader reliabilities for the PET-activity score (ICC= 0.69 (95%CI: 0.40 to 0.86)). 18 patients had a positive PET with a mean PET-activity score of 15.7 (± 14). The mean SUV-max for a positive PET was 1.91 versus 1.27 for a negative one. According to a binary approach, a positive PET did not correlate to both inflammatory and structural damages on MRI. The PET-activity score (r=0.57, p=0.005) and SUV-max ($p<0.05$) correlated with the SPARCC inflammation score .Only backfill score amongst MRI structural lesions correlated negatively with the PET-activity score (r=-0.45 p=0.03). The SUV max was associated with SPARCC inflammation and backfill (r= 0.02; p=0.046) and (r= -0.1; p=0.04), respectively.

Conclusion: In axial SpA, the frequency of a positive 18-FNa PET (78.3%) was higher than the frequency of an ASAS positive MRI for inflammatory sacroiliitis (39.1%). Compared to MRI, PET SIJ uptake had a good correlation with inflammatory sacroiliitis while correlation with structural lesions was absent except for backfill.

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Abstract Number: 1292

Performance of 18fluoride Sodium Positron Emission Tomography with Computed Tomography to Assess Inflammatory and Structural Sacroiliitis Respectively on Magnetic Resonance Imaging and Computed Tomography in Axial Spondyloarthritis

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Background/Purpose: to assess increased SIJ uptakes on 18-FNa (an osteoblastic tracer) PET/CT according to a qualitative and quantitative approach and to compare with MRI SIJ assessments for inflammation and with CT-scan for structural damage in a population of 23 patients with SpA (IDRCB: 2012-A00568-35).

Methods: This single-center prospective study included 23 patients with active SpA according to ASAS and/or modified mNY criteria (males 43.5%, HLA-B27 30%, years 44, symptom duration 7.7 years, median CRP 8mg/L, median BASDAI 6.1). All patients had a pelvic AP-view radiograph, MRI of the SIJ and 18-FNa PET/CT examinations during the same month. For MRI, SIJ were assessed for the presence/absence of inflammation according to ASAS criteria and were quantitatively assessed according to SPARCC method for scoring inflammation. CT-scans were read by three readers blinded to MRI images. Structural lesions were scored in consecutive slices in SIJ quadrants (erosion, sclerosis) or SIJ halves (ankylosis) on a dichotomous basis (present/absent) using the same anatomical principles for defining SIJ quadrants as developed for the SPARCC MRI SIJ inflammation and structural scores. On the 18-FNa PET, SIJ were scored blinded to MRI and CT images by two nuclear physicians according to a slice by slice approach performed from the anterior to the posterior part of the joint. A positive PET was defined when unilateral (sacral or iliac part) uptake was observed on 2 consecutive slices or when bilateral uptake was depicted on a single slice. As for SPARCC MRI methods, quantitative assessment on 18-FNa PET was performed according to SIJ quadrants for six consecutive slices through the cartilaginous region of the joint (PET-activity score). The

Standardized Maximal Uptake Value (SUV-max) was measured for each SIJ, corresponding to the highest uptake value of the SIJ.

Results: 7 patients had radiographic sacroiliitis, 9 had inflammatory sacroiliitis on MRI (mean SPARCC 7.65). On CT-scan, inter-reader reliabilities for ankylosis, erosion and sclerosis were excellent to mild (ICC=0.95; ICC=0.81; ICC=0.39) respectively. The concordance between the two readers for a positive PET was good (73.9%) as well as the inter-reader reliabilities for the PET-activity score (ICC= 0.69 (95%CI: 0.40 to 0.86)). 18 patients had a positive PET with a mean PET-activity score of 15.7 (± 14). The mean SUV-max for a positive PET was 1.91 versus 1.27 for a negative one. According to a binary approach, a positive PET did not correlate to a positive MRI (ASAS criteria) or to a structural sacroiliitis on CT-scan. The PET-activity score (r=0.57, p=0.005) and SUV-max (r= 0.02, p=0.046) correlated with the SPARCC inflammation score but not with erosion, ankylosis and both ankylosis-erosions scores on CT-scan (ICC=-0.04; p=0.85), (ICC=-0.30; p=0.16) and (ICC=-0.19; p=0.37) respectively.

Conclusion: In axial SpA, the frequency of a positive 18-FNa PET (78.3%) was higher than the frequency of an ASAS positive MRI for inflammatory sacroiliitis (39.1%) and was also higher than the frequency of structural damages on CT-scan (39.1%). PET activity score had a good correlation with inflammatory sacroiliitis but not with structural lesion on CT-scan.

Disclosure: M. Raynal, None; **O. remy**, None; **J. Melchior**, None; **I. Chary-Valckenaere**, None; **W. Ngueyon Sime**, None; **W. P. Maksymowych**, None; **R. G. Lambert**, None; **D. Loeuille**, None.

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Abstract Number: 1293

Utility of Extremity Magnetic Resonance Imaging (eMRI) without Contrast Enhancement in Detecting Preclinical Psoriatic Arthritis

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Background/Purpose: Between 8-39% of patients with cutaneous psoriasis may develop psoriatic arthritis (PsA). Subclinical inflammatory joint disease in patients with psoriasis is common. [i,ii] This study sought to examine the utility of easily accessible office-based eMRI in evaluating inflammation and damage in a subset of psoriasis patients without arthritis, and compare the findings with PsA patients.

Methods: Psoriasis patients recruited from Dermatology and Rheumatology clinics of a tertiary care, teaching institution in southern India were divided into those without arthritis (PsO) and PsA groups. All underwent contrast eMRI of the dominant or most-affected hand. Demographic and physical examination details were noted. PsO patients completed the early arthritis in psoriasis (EARP) questionnaire. MRIs were scored by two trained readers, based on Psoriatic arthritis MRI score (PsAMRIS). One reader (AJM) read all studies and a second reader (JP) read a random subset of 40 cases to assess inter-reader reliability. Reliability of scores was determined using intra-class correlation coefficient. Proportion of patients showing any signs of MRI inflammation (synovitis, osteitis, tenosynovitis, periarticular inflammation) or damage (erosion or bone proliferation) was determined. Mann-Whitney U test was used to compare PsA with PsO patients. Significant values ($p<0.1$) were included in multivariate linear regression to assess their independent contributions to outcome.

Results: 104 patients included 62 PsO and 42 PsA, with 73% males; mean age was 42.08±11.90 years. Inter-reader reliability for all features was very good (ICC >0.7). Thirty-nine (62%) patients in the PsO group exhibited evidence of inflammation and 31 (60%) patients showed evidence of damage by eMRI (Table 1). Flexor tenosynovitis and periarticular inflammation were the most common pathologies identified. PsO patients with nail involvement showed a higher percentage of cases with MRI inflammation ($p = 0.037$). EARP ≥3 (OR 1.9; $p = 0.024$) in PsO group and NAPSI scores ≥20 in PsA group predicted higher MRI inflammation.

Conclusion: This study demonstrates a high proportion of psoriasis patients with subclinical disease and evidence of joint damage. Patients with psoriasis and nail involvement had a higher risk of subclinical disease. Office eMRI provides a potential screening tool for these at-

risk groups. [i] Freeston JE et al. Arthritis Care Res (Hoboken) 2014;66:432-9 [ii] Faustini F et al. Ann Rheum Dis doi:10.1136/annrheumdis-2015-208821 **Table 1:** PsAMRIS variables for MRI inflammation and damage in the PsO and PsA subgroups

Variable	PsO (n = 62)	PsA (n = 42)
Synovitis	11 (17.7%)	23 (54.8%)
Osteitis	3 (4.8%)	11 (26.2%)
Flexor tenosynovitis	25 (40.3%)	33 (78.9%)
Periarticular inflammation	32 (51.6%)	40 (95.2%)
Bone erosion	15 (24.2%)	26 (61.9%)
Bone proliferation	23 (37.1%)	33 (78.6%)

Disclosure: A. J. Mathew, APLAR research grant, Christian Medical College IRB fluid grant, 2; **J. Panwar**, None; **P. Bird**, None; **R. George**, None; **D. Danda**, None.

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Abstract Number: 1294

Oblique Views Radiographs Have Advantages over Antero-Posterior View Radiographs in Assessing Sacroiliitis in Patients with Early Axial Spondyloarthritis

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Background/Purpose: Antero-posterior (A-P) view radiograph of pelvis was usually used to diagnose sacroiliitis. Magnetic resonance imaging (MRI) can detect lesions in early disease before lesions can be seen on radiography. The oblique views radiographs of pelvis can provide additional information that makes it closer to the findings of MRI than A-P view radiograph. In this study, we attempted to record lesions of sacroiliac joint (SIJ) seen on A-P view and oblique views radiographs and MRI in patients with axial Spondyloarthritis (SpA), and to analyze whether oblique views are better than A-P view radiographs in assessing sacroiliitis.

Methods: All patients fulfilled the 2009 ASAS classification criteria for axial SpA. Three readers blinded (two radiologists and one rheumatologist) investigated the A-P view and oblique views radiographs and MR images from 182 patients with axial SpA. The modified New York criterion was used to grade the sacroiliitis according to the lesions seen on different imaging methods. We analyzed and calculated the sensitivity, specificity, positive and negative likelihood ratio of A-P view and oblique views radiographs for diagnosing axial SpA with MRI as the gold-standard.

Results: The total consistency was higher in oblique views and MRI than in A-P view and MRI (82.8% vs. 71.6%, $p<0.01$). The agreement rates were higher between oblique views and MRI than that between A-P view and MRI in the SIJs graded≤2, especially in patients with symptom duration less than 2 years (all $p<0.01$). But in the SIJs graded>2 and in patients with symptom duration more than 2 years, there were no differences using A-P view or oblique views to assess sacroiliitis (all $p>0.05$). Oblique views had high sensitivity, while A-P view had moderate sensitivity for diagnosing axial SpA in the SIJs graded≤2.

Conclusion: We recorded and analyzed the sacroiliitis assessed by A-P view, oblique views radiographs and MRI and found that oblique views radiographs had some advantages over A-P view radiographs in assessing sacroiliitis in patients with early axial SpA.

Disclosure: Z. Hu, None; **S. Zhu**, None; **Z. Liao**, None; **B. Zhang**, None; **J. Gu**, None.

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antero-posterior-view-radiographs-in-assessing-sacroiliitis-in-patients-with-early-axial-spondyloarthritis

Abstract Number: 1295

The Prevalence of Inflammatory and Structural Lesions on MRI of the Sacroiliac Joints in Patients with Very Early Peripheral Spondyloarthritis

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Background/Purpose: To assess the prevalence of inflammatory and structural lesions on MRI of the sacroiliac joints (SIJ) in patients with peripheral spondyloarthritis (PSpA) in a very early stage of the disease.

Methods: Baseline data originated from the double-blind RCT with golimumab in 60 patients (CRESPA), who were diagnosed with PSpA and had a symptom duration <3 months. MRI SIJ was performed at baseline. Peripheral arthritis, dactylitis or enthesitis combined with ≥1 SpA feature (uveitis, psoriasis, IBD, preceding infection, HLAB27 or sacroiliitis on imaging) was necessary for inclusion. However, all patients already fulfilled the classification criteria without data on imaging of the SIJ. Bone marrow edema (BME) of the SIJ was quantified using the Spondyloarthritis Research Consortium of Canada (SPARCC) scoring system. Besides BME of the SIJ, all MRIs were also scored for other inflammatory lesions such as enthesitis and capsulitis. Structural MRI lesions of the SIJ such as subchondral sclerosis, erosions, periarticular fat and ankylosis were also assessed. Hip evaluation consisted of the presence of joint effusion, BME, enthesitis and cortical aberrations.

Results: Although not the reason for encounter, 7 out of 60 patients reported ever having inflammatory back pain (IBP) at inclusion or in the past, with median Visual analogue scores (VAS) of 2.0 (range 0.0- 9.0) for back pain. Overall, 35% of patients (21/60) exhibited BME of the SIJ and fulfilled the definition of a positive MRI by ASAS, with median SPARCC score of 8.0 (range 2.0-37.0). Only 3 out of 7 patients with IBP exhibited BME on MRI SIJ. Therefore, almost 86% of patients (18/21) with active sacroiliitis did not exhibit symptoms of IBP. Median VAS back pain in patients with sacroiliitis compared to patients without sacroiliitis respectively reached 2.0 and 1.0 (P=NS). Pelvic enthesitis was present in 23.8% (5/21) of patients with an ASAS positive MRI SIJ and in 10.3% (4/39) of patients with negative MRI. None of the patients exhibited enthesitis of the L5 spinous process, iliac crest, anterior superior iliac spine or ramus pubis. None of the patients exhibited thorax enthesitis.

Conclusion: Even in early diagnosed peripheral SpA patients, over 1/3 exhibited BME suggestive of acute sacroiliitis and structural lesions of the SI joints. Our findings underscore the importance of sacroiliitis as the cornerstone feature within the SpA-concept, even in asymptomatic patients.

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Abstract Number: 1296

Quantitative Measurements of Cartilage, Osteophyte, and Bone Marrow Lesion Volume in Knee Osteoarthritis

Lena Franziska Schaefer[1], Ming Yin[1], Meera Sury[2], Scott Jamieson[1], Jamie E. Collins[3], Stacy Smith[4] and **Jeffrey Duryea**[1], [1]Radiology,

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Quantitative Measurements of Cartilage, Osteophyte, and Bone Marrow Lesion volume in Knee Osteoarthritis

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Background/Purpose: Clinical trials and other large studies of knee osteoarthritis (OA) require efficient and objective methods to assess disease changes. Magnetic resonance imaging (MRI) offers superb soft tissue contrast and is ideal for visualizing many structures associated with knee OA. We have developed the MRI Osteoarthritis Software Score (MOSS), a software-based method that assesses volume change of osteophytes, cartilage, and bone marrow lesions (BMLs) for knee OA. The goal of our study is to assess all 600 subjects of the OA Biomarkers Consortium FNIH Study. This will further validate the method and demonstrate its suitability for use in highly-powered studies and clinical trials of knee OA.

Methods: The OA Biomarkers Consortium FNIH Study is a case-control study of knee OA progression nested within the Osteoarthritis Initiative (OAI). The study cohort was divided into four subgroups based on radiographic and pain progression: Group 1: radiographic and pain progression (n=194) Group 2: radiographic-only progression (n=103) Group 3: pain-only progression (n=103) Group 4: no radiographic or pain progression (n=200). Double echo steady state (DESS) pulse sequences were used for cartilage and osteophytes, and turbo spin echo (TSE) for BMLs. Baseline to 24 month volume change was analyzed as a predictor of case-control status in univariate models using logistic regression. This highly-powered longitudinal study represents the result of 3,600 individual measurements of OA structures on MRI scans.

Results: Change in volume of cartilage and osteophytes were strongly associated with radiographic progression: decreasing cartilage volume was associated with an increased odds of being a case, while increasing osteophyte and BML volume were associated with an increased odds of being a case. The association of cartilage and osteophyte volume change was lower but significant for pain progression. BMLs showed marginally significant associations with radiographic and pain progression. All three measurements (cartilage, osteophytes, and BMLs) can be performed in a total time of less than 30 minutes per knee, split roughly evenly between a research assistant and an experienced reader. Table 1: Results

	Primary analysis: cases (Group 1) versus controls (Group 2, 3, and 4)		Radiographic (Group 1+2) versus non-radiographic progression (Group 3+4)		Pain progression (Group 1+3) versus no pain progression (Group 2+4)	
Variable	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Cartilage	0.55 (0.45-0.67)	<.0001	0.30 (0.22-0.39)	<.0001	0.75 (0.63-0.90)	0.0018
Osteophytes	1.53 (1.27-1.85)	<.0001	2.13 (1.69-2.69)	<.0001	1.21 (1.02-1.45)	0.0329
Bone Marrow Lesions	1.25 (1.04-1.49)	0.0169	1.23 (1.02-1.48)	0.0285	1.21 (1.01-1.44)	0.0375

Conclusion: We have demonstrated that measurements of cartilage, BML, and osteophyte volume using the MOSS method have clinical validity in a case-control study. The method is efficient and ideal for current and future large studies and clinical trials of knee OA requiring assessment of many thousands of MRI scans.

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bone-marrow-lesion-volume-in-knee-osteoarthritis

Abstract Number: 1297

Positive Sacroiliac Joint MRI in Asymptomatic Patients with Recurrent Acute Anterior Uveitis: A Proof of Concept

Thauana Oliveira[1], Walter Maksymowych[2], Robert G Lambert[3], Cristina Muccioli[1] and **Marcelo Pinheiro**[1], [1]Federal University of São Paulo, São Paulo, Brazil, [2]Medicine, University of Alberta,, Edmonton, AB, Canada, [3]Radiology, University of Alberta, Edmonton, AB, Canada

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Background/Purpose: Recurrent acute anterior uveitis (rAAU) is associated with spondyloarthritis (SpA). However, it is not known if patients with rAAU, but no back symptoms could have positive findings on sacroiliac joint (SIJ) MRI. **Aim:** To assess the prevalence of definite SpA by combined T1W/STIR MRI (global MRI), to quantify acute and chronic lesions in SIJ using MRI in patients with rAAU with and without back symptoms, and to assess which MRI lesion-based criteria optimally reflect the global MRI designation of definite SpA.

Methods: A total of 50 consecutive patients with rAAU without prior rheumatologic diagnosis were included in this cross-sectional study and were compared to 21 healthy volunteers. MRI scans were read by two rheumatologists according to the SPARCC/MORPHO protocol.

Results: rAAU patients were classified as axial SpA (Group 1, n=20), according to ASAS criteria (2009); non-specific back pain (Group 2, n=6) and asymptomatic (Group 3, n=24). The groups were similar regarding age, sex, ethnicity, age at onset of uveitis, current uveitis activity and duration of eye disease. HLA-B27 was positive in 48% of those with rAAU. Considering only group 3, nine (37.5%) patients had SIJ MRI and/or X-ray positive for axial SpA (5 MRI and x-ray, 1 MRI, 3 x-ray). MRI scans compatible with SpA in groups 1(n=12) and 3 (n=6) were similar regarding acute and chronic lesions analysed according to MORPHO. The best sensitivity/specificity criterion to define a positive global MRI assessment was bone marrow edema (BME) ≥ 3 (92%/94%).

Conclusion: This is the first study evaluating SIJ MRI in patients with rAUU without back symptoms showing positive findings for sacroiliitis, confirming a uvea-axial spine link, and BME ≥ 3 as optimal for a positive MRI.

Disclosure: T. Oliveira, None; **W. Maksymowych**, Merck Pharmaceuticals, 5; **R. G. Lambert**, BioClinica, 5,Abbvie, 8; **C. Muccioli**, AbbVie, 5; **M. Pinheiro**, None.

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Abstract Number: 1298

Development and Validation of Berlin and Sparcc MRI Sacroiliac Joint Scoring Methods for the Semi-Axial Scan Plan

Pernille Hededal[1], Mikkel Østergaard[2], Inge Juul Sorensen[3], Anne Gitte Loft[4], Jens Hindrup[3], Gorm Thamborg[3], Karsten Asmussen[3], Oliver Hendricks[5], Jesper Nørregaard[3], Jakob M. Møller[6], Anne Grethe Jurik[7], Lone Morsel-Carlsen[1], Lone Balding[8] and **Susanne Juhl Pedersen**[3], [1]Department of Radiology, Rigshospitalet, Copenhagen, Denmark, [2]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark, Copenhagen, Denmark, [3]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark, [4]Departments of Rheumatology at Vejle and Aarhus Hospitals, Vejle and Aarhus, Denmark, [5]Dep. of Rheumatology, King Christians Hospital for Rheumatic Diseases, Copenhagen, Denmark, [6]Department of Radiology, Copenhagen University Hospital Herlev and Gentofte, Herlev, Denmark, [7]Dept. of Radiology, Aarhus University Hospital, Aarhus, Denmark, [8]Department of Radiology, Copenhagen University Hospital Herlev and Gentofte, Copenhagen,

Denmark

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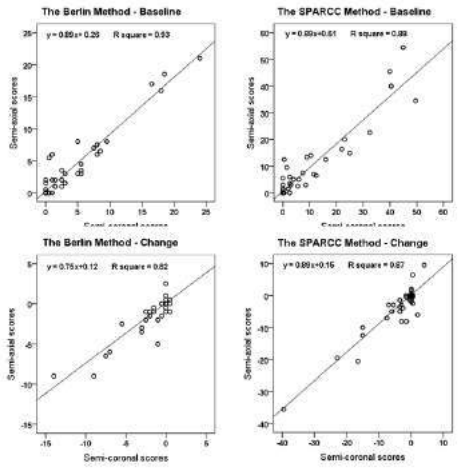
Background/Purpose: In clinical trials encompassing axial spondyloarthritis (axSpA) patients, bone marrow edema (BME) in the sacroiliac joints (SIJs) is assessed with standardized and validated semi-quantitative scoring systems such as the Berlin MRI method(1) and the SPARCC method(2), which both are based on the semi-coronal scan plane. However, in routine care the inflammation sensitive MRI sequence (e.g. STIR) is frequently obtained in the semi-axial scan plane. This limits use of routine care MRI for systematic follow-up of assessment and prediction of treatment effect in patients recorded in clinical databases. It is important to investigate such patients, since they represent a broader spectrum of the disease than patients recruited to clinical trials (3). The objective of this study was to develop semi-axial MRI scoring methods for assessment of SIJ BME in patients with axSpA, and to compare the reliability with equivalent semi-coronal scoring methods.

Methods: Two semi-axial MRI scoring methods were based on the principles of the Berlin and SPARCC MRI inflammation methods. The intra-reader and interreader reliability of the semi-axial and semi-coronal methods were assessed with intraclass correlation coefficients (ICC) and smallest detectable change (SDC) as absolute values and percentages of the highest observed score (SDC-HOS) were used to assess reproducibility and sensitivity to change, and linear regression analysis to compare the 2 methods

Results: Inter-reader and intra-reader ICCs for *status scores* were excellent for the semi-axial MRI scoring methods (Berlin: 0.88 and 0.93-0.95; SPARCC: 0.92 and 0.92-0.97) and comparable to the semi-coronal methods (Berlin: 0.92 and 0.96-0.97; SPARCC: 0.92 and 0.96). The ICCs for the semi-axial *change scores* were moderate for the Berlin method (0.50) and good for the SPARCC method (0.78), whereas it was good for the semi-coronal methods (Berlin: 0.87; SPARCC 0.89). The association between semi-axial and semi-coronal scores was high for both the Berlin and SPARCC method (linear regression, R^2=0.93 and 0.88; change: R^2=0.82 and 0.87, respectively, see Figure 1). The SDCs and SDC-HOC for the Berlin vs. SPARCC semi-axial methods were 2.6 and 12.8% vs. 5.5 and 9.8%, respectively, and for the semi-coronal methods 1.4 and 5.9% vs. 3.2 and 6.4%, respectively.

Conclusion: Detection of SIJ BME in the semi-axial scan plane is feasible and reproducible. However, slightly lower reliability and sensitivity to change of the semi-axial methods support the general practice of using the semi-coronal scan plane in therapeutic studies.
References: 1. Song IH et al. Ann. Rheum. Dis. 70, 590-596; 2. Maksymowych WP et al. Arthritis Rheum. 53, 703-709; 3. Roland M. et al. BMJ 316, 285. **Figure 1** Comparison of semi-coronal and semi-axial scores for baseline and change score for mean of readers. The



linear regression lines are shown.

Disclosure: P. Hededal, None; **M. Østergaard**, AbbVie, 2; **I. J. Sorensen**, None; **A. G. Loft**, MSD, UCB, AbbVie, Pfizer., 8; **J. Hindrup**, None; **G. Thamborg**, None; **K. Asmussen**, None; **O. Hendricks**, None; **J. Nørregaard**, None; **J. M. Møller**, None; **A. G. Jurik**, None; **L. Morsel-Carlsen**, None; **L. Balding**, None; **S. J. Pedersen**, AbbVie, 2,MSD, 2.

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Abstract Number: 1299

Can the 3D-Modified Dixon Methods Replace the Conventional Sacroiliac Joint Magnetic Resonance Imaging?

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Can the 3D-modified Dixon

Methods Replace the Conventional Sacroiliac Joint Magnetic Resonance Imaging?

ABSTRACT

Background/Purpose: The purpose of our study was to assess the diagnostic value of two-point Dixon method compared with conventional magnetic resonance imaging (MRI) including T1-weighted, T2-weighted, fat saturated (FS) T1-weighted, FS T2-weighted, and short tau inversion recovery (STIR) in diagnosing axial spondyloarthritis (SpA). Methods: A total of 67 patients with low back pain and suspected axial SpA who underwent sacroiliac joint MRI in our institution from September 2014 to October 2015 were retrospectively evaluated. Each with two data sets (modified Dixon images, conventional MRI), were independently reviewed by two radiologists as follows: 1) grading of both sacroiliac joints; 2) bone marrow edema; 3) erosion; 4) periarticular fat deposition; 5) ankylosis. Bone marrow edema was evaluated on FS T2-weighted, and STIR images. Structural change and fat deposition were evaluated on T1-weighted image. Erosion was evaluated on T1-weighted and FS T1-weighted images. All variables were determined in a thin slice 3D-Dixon images. Sensitivity, specificity, and intra- and interobserver reliabilities were calculated.

Results: Patients had a mean age of 31.7 ¡¾ 11.1 years and male were 44 (65.7%). 44 of 67 patients (65.7%) had positive HLA-B27. 62 patients were diagnosed with axial SpA based on laboratory and imaging information as well as the Assessment of Spondyloarthritis International Society (ASAS) criteria. One patient was diagnosed with osteitis condensans ilii. Four patients were diagnosed with non-specific mechanical back pain. Sensitivities and specificities of Dixon method and conventional MRI are 97.4%, 14.3% and 94.6%, 10.7%. Both Dixon method and conventional MRI had a good to excellent intraobserver (mean intraclass correlation coefficient [ICC] = 0.680-0.953, 0.886-1.000) and interobserver agreement (mean ICC = 0.860-0.986, 0.792-0.953).

Conclusion: 3D-modified Dixon method might be another practical novel imaging technique as conventional MRI. The Dixon method is more intuitive than conventional MRI to evaluate sacroiliac joint, moreover, it takes less time.

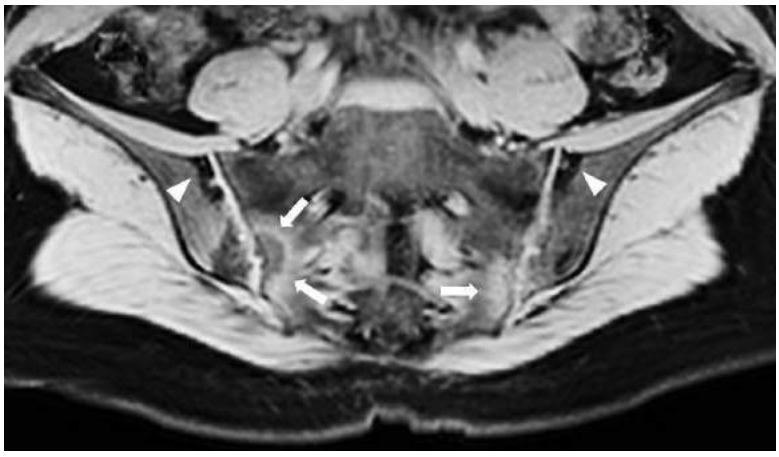

Figure 1. Bilateral sacroiliitis (grade 3) with periarticular fat deposition (arrow head), and edema (arrow) showed in 3D-Dixon methods.

Disclosure: Y. Song, None; **S. Lee**, None; **T. H. Kim**, None.

Abstract Number: 1300

MRI-Detected Inflammation Is Associated with Functional Disability in Early Arthritis – Results of a Cross-Sectional Study

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Background/Purpose: Magnetic resonance imaging (MRI) sensitively detects inflammation, but the clinical relevance of MRI-detected inflammation is undetermined in early arthritis. Therefore, this cross-sectional study investigated the association between MRI-detected inflammation of hands and feet and functional disability in early arthritis.

Methods: 514 early arthritis patients, consecutively included in the Leiden Early Arthritis Clinic, were studied. At baseline, unilateral 1.5T MRI of the wrist, metacarpophalangeal (MCP) and metatarsophalangeal-joints was made and functional disability was measured using the Health Assessment Questionnaire (HAQ). MRIs were scored for tenosynovitis, synovitis and bone marrow oedema (BME) by two readers. The sum of these types of MRI-inflammation yielded the total MRI-inflammation score. Linear and non-linear regression analyses were performed with HAQ as outcome.

Results: The total MRI-inflammation score was associated with the HAQ-score (β=0.014, $p<0.001$), as were tenosynovitis (β=0.046, $p<0.001$), synovitis (β=0.039, $p<0.001$) and BME-scores (β=0.015, $p<0.001$) separately. Analysing these three types of MRI-inflammation in one multivariable model, revealed that only tenosynovitis was independently associated with HAQ-score (β=0.039, $p<0.001$). Also when correcting for age, gender, joint counts, C-reactive protein and auto-antibodies, this association remained significant (β=0.034, $p<0.001$). MRI-detected inflammation at wrists or MCP-joints associated significantly with impairments in hand functioning (e.g. difficulties with opening milk cartons or jars). Exploring the relation between MRI-detected inflammation and HAQ-scores, suggested the presence of a ceiling effect, because after a certain inflammation-level, more inflammation was not associated with higher HAQ-scores.

Conclusion: MRI-detected inflammation, and tenosynovitis in particular, is associated with functional disability in early arthritis. This demonstrates the functional relevance of MRI-detected inflammation in early arthritis.

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Abstract Number: 1301

Analysis of Anatomical Sites Causing Dactylitis and Their Responsiveness to Change Under TNF-Therapy in Psoriatic Arthritis By High Resolution MRI

Dr. Philipp Sewerin, PD Dr. Stefan Vordenbäumen, Dr. Ruben Sengewein, Prof. Dr. Matthias Schneider and Prof. Dr. Benedikt Ostendorf, Department of Rheumatology & Hiller Research Unit, Heinrich-Heine University, Düsseldorf, Germany
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Background/Purpose: Enthesites and dactylitis are common phenomena in patients with psoriatic arthritis (PsA). Inspite of significant advances in our understanding of PsA pathophysiology in recent years, the structural changes underlying dactylitis in PsA have not been comprehensively assessed. Moreover, it is unknown which components of dactylitis respond best to immunosuppressive therapy. We therefore aim to employ most recently developed small joint MRI coils to generate high-resolution images of the fingers in PsA patients in order to analyse the contribution of the various inflammatory dactylitis lesions of PsA and analysing the responsiveness of these components to immunosuppressive therapy with highly active anti-TNF therapy.

Methods: High resolution MRI scans (3 Tesla) with use of small joint coils of the clinical dominate hand were performed before and 6 months after switch from DMARD to anti-TNF therapy in 12 PsA patients with dactylitis (age 42 ± 18; disease duration 4 ± 3.3 years).

Results: The following sites were most commonly involved in dactylitis: collateral ligament enthesitis 11/12 (92%); extensor tendons enthesitis 5/12 (42%); flexor tenosynovitis 9/12 (75%), periarticulitis (i.e. contrast enhancement in periarticular soft tissue) 9/12 (75%).After 6 months, periarticulitis was improved in 8/9 cases (89%), while residual enthesits at any site persisted in 6/11 patients (55%).

Conclusion: Dactylitis is a digital polyenthesitis with collateral ligaments and the extensor ligaments most frequently involved. Moreover periarticular contrast enhancement as well as tenosynovitis is regularly seen. Periarticulitis responds more readily to TNF-therapy than enthesitis. High-resolution MRI is a valid tool to investigate and monitor pathological findings in dactylitis in PsA patients.

Disclosure: D. P. Sewerin, None; **P. D. S. Vordenbäumen**, None; **D. R. Sengewein**, None; **P. D. M. Schneider**, None; **P. D. B. Ostendorf**, None.

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Abstract Number: 1302

Silent Progression in Patients with Rheumatoid Arthritis: Is DAS28 Remission an Insufficient Goal in RA? Results from the German Remission-PLUS Cohort

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Background/Purpose: Remission in rheumatoid arthritis (RA) arguably is the ultimate goal of an antirheumatic therapy. With modern therapeutic strategies, this goal can be achieved in the majority of patients with early RA (ERA). It is known, that the number and extend of erosions can increase instead of clinically measurable low disease activity or remission (disease activity score in 28 joints; DAS28). We therefore investigated the value of MRI for the detection of erosive changes in patients with DAS28 improvement and/or remission of the German Remission-plus cohort.

Methods: Data-sets of 80 RA patients from the REMISSION-plus study cohort who fulfilled the following criteria were retrospectively analysed: ACR/EULAR 2010 Criteria for RA according to ACR/EULAR criteria, availability of two consecutive MRI scans (low-field MRI, follow up interval 1 year) of the clinically dominant hand and wrist, and the presence of DAS28 (CRP) scores at both time points. The DAS28 was used to assess disease activity. Changes of disease activity were graded by the following classification criteria: DAS28£ 2.6 = clinical remission, £ 3.2 mild disease activity < 5.2 moderate disease activity and > 5.2 severe disease activity. Therapy response was graded by the following improvement criteria proposed by the EULAR committee DAS28 decrease >1.2 units and endpoint score <3.2 =good response, DAS28 decrease >1.2 units and endpoint score >3.2 or DAS28 decrease 0.6 – 1.2 units and endpoint score <5.1 =moderate response, DAS28 decrease <0.6 or DAS28 decrease 0.6 -1.2 units and endpoint score >5.1 =poor response.

Results: 71 of the 80 investigated patients presented a clinical improvement of the DAS28 after 12 month (T4). After 12 months 73% of the 71 patients who improved in DAS28 showed a lower RAMRIS-Score, while 24% demonstrated an increased score despite DAS28 improvement. 34 of the 71 patients who improved in DAS28 reached EULAR Remission. Despite DAS28 remission, 41% of all patients who attained remission showed in increased Erosion-Subscore in MRI after 12 month (T4). Looking at the 71 patients who improved in DAS28 after 12 month, 7 showed EULAR non-response, 19 presented moderate and 45 good EULAR responses. An increase of erosions was found in 71.4% of non-responders 52.6% of moderate responders and 31.1% of good responder at T4 compared to baseline.

Conclusion: Up to 40% of patients in this study demonstrated a progressive erosive disease course in rheumatoid arthritis detected by MRI despite DAS28 improvement or EULAR remission. These data reflects that DAS28 remission alone might be an insufficient therapy goal in rheumatoid arthritis. MRI should be considered as a secondary outcome measure in interventional therapeutic trials with subsequent observational extension including conventional x-rays to systematically assess this question.

Disclosure: D. P. Sewerin, None; **P. D. S. Vordenbäumen**, None; **A. Hoyer**, None; **R. Brinks**, None; **D. C. Buchbender**, None; **D. C. Schleich**, None; **S. Kamp**, None; **P. D. G. Antoch**, None; **P. D. M. Schneider**, None; **P. D. B. Ostendorf**, None.

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Abstract Number: 1303

Extended T2-Times in Cardiovascular Magnetic Resonance (CMR) in Patients with Systemic Lupus Erythematosus (SLE) and Persisted Dyspnoea: Is SLE-Associated Myocarditis an Underestimated Problem?

Dr. Philipp Sewerin[1], Vera Lachmann[2], Mareike Gastl[2], Patrick Behm[3], PD Dr. Rebecca Fischer-Betz[4], Prof. Dr. Benedikt Ostendorf[1], Dr. Gamal Chehab[5], Prof. Dr. Matthias Schneider[1], Prof. Dr. Malte Kelm[2] and Dr. Florian Bönner[2], [1]Department of Rheumatology & Hiller Research Unit, Heinrich-Heine University, Düsseldorf, Germany, [2]Department of Internal Medicine, Division of Cardiology, Pulmology and Vascular Medicine and Molecular Cardiology, Heinrich-Heine University, Düsseldorf, Germany, [3]Heinrich-Heine University, Düsseldorf, Germany, [4]Department of Rheumatology & Hiller Research Unit, Heinrich-Heine-University, Duesseldorf, Germany, [5]Department of Rheumatology & Hiller Research Unit, Heinrich-Heine University, 40225 Duesseldorf, Germany

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Background/Purpose: To investigate the value of cardiovascular magnetic resonance (CMR) and T2-mapping in patients with systemic lupus erythematosus (SLE) and persistent dyspnoea without sings for pulmonary involvement (conventional x-rays and pulmonary function testing) as a possible sign for myocardial involvement.

Methods: 5 women fulfilling the ACR criteria for SLE (mean age 47.4 (30-69) years, mean disease duration 10.4 (5.3 – 22) years, with persistent dyspnoea (at least NYHA II) but absence of pathological findings in electrocardiogram (ECG) or echocardiography were investigated by CMR. CMR was conducted with a 1.5 Tesla MRI-System (Achieva, Philips, Best, Netherlands) using a 32-channel coil. T2 mapping was done using a respiration navigator gated Gradient-And Spin-Echo sequence (GRASE, 15 T2 echoes separated by 10ms, res: 1x1x10mm², 3 short axis slices). Images were post-processed using software based on the LabView environment for local T2 value generation (T2 mapping). Strain analysis was conducted entering cine-images into myocardial feature tracking (FTI) analysis software (TomTec Imaging Systems, Unterschleißheim, Germany). A cohort five of age and gender matched volunteers served as controls.

Results: All patients showed significantly extended T2 times as a sign of local inflammation compared with age matched healthy controls ($p < 0.05$). Moreover, the global systolic longitudinal strain (GLS) as means by systolic function was significantly decreased. In addition, global early diastolic strain rate displayed diastolic dysfunction in comparison to controls.

Conclusion: SLE patients with persistent dyspnoea in absence of pathological findings in ECG and echocardiography showed significantly extended T2-times in MRI as a sign of local fluid content as a part of myocardial inflammation, reduced GLS and diastolic dysfunction, which would be missed by using conventional technics. CMR and T2-mapping is a possible tool for the investigation of a cardiac involvement in SLE patients and should be investigated in clinical studies.

Disclosure: D. P. Sewerin, None; **V. Lachmann**, None; **M. Gastl**, None; **P. Behm**, None; **P. D. R. Fischer-Betz**, None; **P. D. B. Ostendorf**, None; **D. G. Chehab**, None; **P. D. M. Schneider**, None; **P. D. M. Kelm**, None; **D. F. Bönner**, None.

Abstract Number: 1304

2D and 3D Measurements of Osteoarthritis Joint Space Width Have Good Agreement in Radiographically Normal Knees but Poor Agreement with Advancing Kellgren-Lawrence Grade: Data from the Osteoarthritis Initiative

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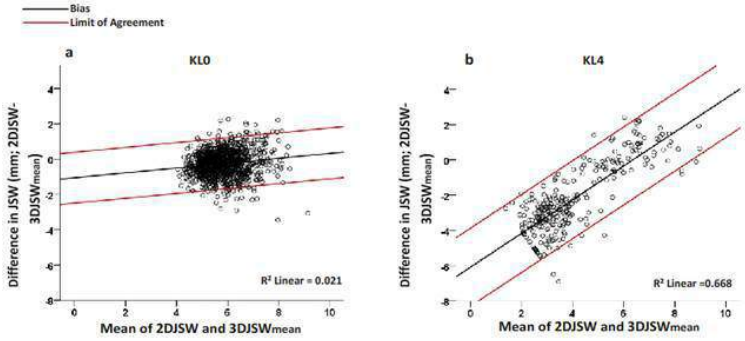
2D and 3D Measurements of Osteoarthritis Joint Space Width have Good Agreement in Radiographically Normal Knees but Poor Agreement with Advancing Kellgren-Lawrence Grade: Data from the Osteoarthritis Initiative Aaron Ray[1], Michael A Bowes[2], Bright Dube[1], Elizabeth MA Hensor[1], Andrew Barr[1], Philip G Conaghan[1] *[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds [2]Imorphics Ltd, Kilburn House, Manchester, UK;*

Background/Purpose: Joint Space Width (JSW) remains the current gold standard in OA structure modification trials, however MRI studies have suggested JS narrowing represents a group of pathologies[1]. We aimed to assess the agreement between sensitive measurements of 3DJSW and standard radiographic 2DJSW to further explore conceptually what inter-bone distance represents, using a large OA knee cohort.

Methods: Analyses were performed on 5622 knees from the Osteoarthritis Initiative. Femur and tibia bones were automatically segmented using active appearance models (AAMs). 3D JSW measurements were taken from 1700 points on the medial tibial plateau across the medial tibiofemoral joint (mTFJ), generating an average measurement ($3DJSW_{mean}$); radiographic 2DJSW was generated centrally using a trainable algorithm-based software tool. 3DJSW was compared to radiographic 2DJSW at a fixed radiographic location. SPSSv21 was used to generate Bland Altman plots and used linear regression to measure agreement between the methods.

Results: Bland Altman plots for 2D vs 3D measurements of JSW demonstrated good agreement in radiographic structurally normal knees (Kellgren-Lawrence (KL) grade 0 variation in bias=0.14 per mm; bias at 5mm = -0.36; limits of agreement (LoA) width = 2.89; see Figure 1a) but as KL grade increased and mean JSW decreased, the variation in bias with mean JSW increased and limits of agreement widened (KL4 variation in bias=0.96 per mm; bias at 5mm = -1.30; LoA width: 4.42; see Figure 1b) with a breakdown of the relationship between the 2D and 3D JSW measurements.

Conclusion: JSN comprises various pathologies that are not visualised in radiographs (which consolidate these changes into a single projection) including asymmetric cartilage loss and meniscal extrusion. Although X-ray assessment of JSW provides a comparable measure of inter-bone distance for normal knees, there is increasing discrepancy between 2D and 3DJSW with increasing KL grade. In KL4 knees, poorer agreement between the methods is seen at lower average JSWs. This suggests that radiographs underestimate JSW when compared to MRI when structural change is most advanced. When radiographs demonstrate 'bone on bone' changes, MRI is able to discern differences in JSW. **FIGURE 1: Bland Altman Plot of Fixed Radiographic JSW vs 3DJSWmean**



References:

1. Hunter et al. Arthritis Rheum 2006;54(8): 2488–2495

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Abstract Number: 1305

Enriching Rheumatoid Arthritis Trial Cohorts with Erosion Progressors By Screening for Active Erosions (Erosions with Osteitis) with MRI

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Background/Purpose: Radiography is often used in RA clinical trials to screen for bone erosions (ERO) to ensure that only patients with the erosive phenotype are enrolled. Despite this fewer than 30% of patients in most RA cohorts show significant progression of joint damage. Osteitis (OST) and synovitis (SYN) on MRI have been shown to predict ERO progression, and may thus offer further opportunity to enrich clinical trial cohorts with patients more likely to progress structurally. However, previous studies examining these MRI parameters were at the patient level, and were thus confounded by the multiplicity of individual joint score combinations that could produce a similar total score. We have examined the association between OST and SYN at baseline and the progression of ERO on follow-up at the level of individual bones and joints in an unplanned sub-analysis of the AC-CUTE trial (NCT01951170).[1]

Methods: 50 patients with active RA who had inadequate response to methotrexate (MTX) or other DMARDs and had at least one ERO on screening radiographs or MRI were included in the sub-analysis. 1.5T MRI of one hand (MCP 1-5) and wrist was acquired at baseline and 24 weeks. Two radiologists scored all images blinded to visit order using the RA MRI Score (RAMRIS); the two radiologists' scores were averaged.

Results: A total of 1245 bones were examined. ERO, OST and SYN at baseline were each associated with ERO progression, with odds ratios (OR) of 9.5, 3.7 and 3.1, respectively (Table). OST was more strongly associated with ERO progression than ERO or SYN were. Among bones with ERO at baseline, a larger proportion of those with concurrent OST, i.e., "active" ERO (OR = 1.6) but not those with adjacent SYN (OR = 1.0) progressed. At the patient level, the OR for progression with active ERO (ERO + OST) versus with ERO alone was 1.7. Screening for ERO originally excluded 6% of patients from participating in the study. Screening for at least one bone with active ERO would have excluded 28% more. Requiring patients also to have SYN adjacent to the bone with active ERO would have raised the screen failure rate to 42%.

Conclusion: Baseline ERO, OST and SYN were each associated with ERO progression at the individual bone and joint level. Screening with MRI for the presence of active ERO may enrich RA trial cohorts with likely progressors more effectively than would screening for ERO, OST or SYN alone. **References:** 1. Bird et al. EULAR 2016, (AB0368). [DOI: 10.1136/annrheumdis-2016-eular.3780]. **Table: Effect of ERO, OST and SYN at baseline on subsequent ERO progression**

MRI Feature	% Bones Involved	% ERO Progression*
- ERO	65.3	1.4
+ ERO	34.7	12.0
- OST	82.6	4.1
+ OST	18.3	14.0
- SYN	37.3	2.8
+ SYN	62.7	8.2
+ ERO - OST	20.0	10.0
+ ERO + OST	14.5	14.9
+ ERO - SYN	18.7	12.6
+ ERO + SYN	46.8	12.2

*Erosion progression defined as ≥0.5

Disclosure: C. Peterfy, Spire Sciences, Inc., 3; **P. Bird**, None; **P. Countryman**, Spire Sciences, Inc., 3; **F. Joshua**, None; **S. Hall**, None; **H. Griffiths**, None; **P. Youssef**, None; **A. Holmes**, Roche Products, Pty. Limited, 3.

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Abstract Number: 1306

Magnetic Resonance Imaging Measures of Disease Activity in Rheumatoid Arthritis Patients Treated with Multiple Regimens of DMARD Therapy

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Background/Purpose: Magnetic resonance imaging (MRI) in rheumatoid arthritis (RA) has been shown to be more sensitive than clinical and radiological parameters in evaluating disease activity levels and chronic joint damage. Few studies have illustrated the impact of conventional and biologic DMARDs on the MRI findings of RA, including osteitis (bone marrow edema), synovitis and bone erosions. The objectives of this study were to compare MRI findings among groups of RA patients treated with conventional systemic DMARD (csDMARD) monotherapy, csDMARD multi-therapy and combination biologic and conventional DMARD therapies over a two year study period.

Methods: Magnetic resonance images were acquired of the dominant hand of 51 RA patients from a single rheumatology clinic at baseline and at follow-up over an average time of 23 months. Images were obtained using a 1T magnet, 100nm cylindrical transmit and receive coil and a 3D spoiled gradient echo sequence. RAMRIS scoring for bone marrow edema, synovitis and bone erosion was performed for the 2nd through 5thMCP joints at baseline and follow-up as well as clinical disease activity scores (CDAI). DMARD (biologic and conventional) history for all patients was obtained and the patients were grouped into four categories based on their exposure: 1. DMARD mono-therapy with methotrexate (MTX), 2. DMARD mono-therapy with hydroxychloroquine (HCQ), 3. DMARD multi-therapy (multiDMARD) and 4. Biologic and conventional DMARD multi-therapy (DMARDbio). Multivariable linear regression analyses were conducted to determine differences in synovitis, edema and erosion scores at follow-up. The analyses were adjusted for baseline values.

Results: The MTX, HCQ, DMARDbio and multiDMARD groups had 12, 5, 21 and 13 patients respectively. Average CDAI scores at baseline were 10.9, 7.3, 19.0 and 36.5 for MTX, HCQ, multiDMARD and DMARDbio groups respectively. The average baseline and follow-up RAMRIS scores for all groups are listed in table 1 with asterisks denoting statistical significance ($p < 0.05$) versus MTX group.

	RAMRIS baseline				RAMRIS follow-up			
	Synovitis	Edema	Erosion	Overall	Synovitis	Edema	Erosion	Overall
MTX	3.6	3.3	11.3	18.2	2.4	3.8	8.8	15
HCQ	3.2	2.4	7.2	12.8	2.4	3	8.6	14
multiDMARD	5.2	4.2	13.5	22.9	5.8*	7.3*	15*	28.1
DMARDbio	3.2	3.9	9.8	16.9	4.5*	4.3	11.8	20.6

Table 1: RAMRIS scores at baseline and follow-up (* p value < 0.05 vs MTX)

Conclusion: In this prospective cohort of rheumatoid arthritis patients treated with four different regimens, we noted a significant difference in all RAMRIS scoring over an average 23 month period in the multiDMARD therapy group versus MTX group. The baseline CDAI score of the multiDMARD group was higher than the MTX group. The need for multiple DMARDs during this study period may have been because of the higher disease activity in this group. Despite multiple therapies, there was worsening of disease activity based on the RAMRIS scores in this group, which likely was accounted for by the significantly higher baseline disease activity. The MTX group was a suitable control considering the stable RAMRIS scores from baseline to follow-up. The DMARDbio group had higher clinical disease activity score than all other groups at baseline with a CDAI of 36.5. There was a significant difference in RAMRIS synovitis score in the DMARDbio group over the study period versus MTX group but other RAMRIS scores were not significant. This would suggest that biologic DMARD therapy has higher efficacy in suppressing disease activity versus multiple csDMARD therapy. Further studies will be needed to determine the impact of therapy on disease activity as measured by MRI studies.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/magnetic-resonance-imaging-measures-of-disease-activity-in-rheumatoid-arthritis-patients-treated-with-multiple-regimens-of-dmard-therapy

Abstract Number: 1307

Anatomical Patterns Suggest the Involvement of Biomechanical Stress in the Pathogenesis of Erosions in Rheumatoid Arthritis

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Background/Purpose: There is limited data outlining the anatomic characteristics of bone erosions of the small joints in rheumatoid arthritis (RA). In particular, there is minimal utilization of 3-dimensional imaging modalities, such as magnetic resonance imaging (MRI) for the purpose of describing erosion patterns in the metacarpophalangeal (MCP) joints. This is of particular interest for understanding the role of biomechanical forces exerted by the adjacent anatomy in contributing to erosion initiation and progression. Our objective was to describe the anatomical features of erosions in the MCP joints to explore the importance of biomechanical stress in erosion pathogenesis.

Methods: MR images of the 2nd through 5th MCP joints were acquired bilaterally from 22 patients who met early referral criterial for RA. Maximum depth and width of erosions were determined using the semi-automated segmentation software Early Erosions in Rheumatoid Arthritis (EERA). Anatomical features were recorded, including: affected hand and MCP joint, metacarpal head vs. phalangeal base involvement, radial- vs. ulnar-sided cortical breakage, and palmar vs. dorsal cortical breakage. One-way ANOVA was used to compare means across groups. Bivariate correlation between maximum erosion depth and width was calculated as an estimate of erosion geometric sphericity.

Results: Patients were 91% female with mean (SD) age of 55.9 (9.3) years, symptom duration of 4.8 (5.3) years, and disease activity score of 4.8 (1.5). Thirty right-handed and 19 left-handed erosions were identified; all involved the metacarpal head, with none involving the phalangeal base. Erosion frequencies across MCP joints 2 through 5 were: 15, 22, 7 and 5 erosions, respectively. Radial-sided cortical breakage was observed in 42 (86%) erosions, and ulnar-sided breakage was observed in 4 (8%) erosions, 3 of which were on the 5th metacarpal. Palmar cortical breakage was observed in 3 (6%) erosions, and dorsal breakage was observed in 1 (2%) erosion. Mean (SD) maximum erosion depth and width were 4.3 (1.5) mm and 4.6 (2.1) mm, respectively. Maximum depth and width correlated moderately, Pearson's $r = 0.51$ ($p < 0.05$), and with the exclusion of one large erosion outlier, only correlated weakly, $r = 0.36$ ($p < 0.05$). Neither erosion depth nor width were significantly associated with MCP joint number, or location of cortical break ($p > 0.05$ for all comparisons).

Conclusion: Predominance of erosions on the right (mostly dominant) hand, 2nd and 3rd MCP joints (higher stresses compared to 4th and 5th MCP), and the radial side of metacarpal heads (higher stabilizing stress from the adjacent radial collateral ligament) except on the 5th metacarpal, all support the hypothesis that anatomical areas subjected to greater biomechanical stress are more susceptible to erosive damage. The weak to moderate correlation between maximum depth and width reflects the geometric asymmetries and irregularities of erosions of the MCP joints. Application of MRI to characterizing other small joints in RA may provide insight to the unique ways in which biomechanical stresses influence bone erosion pathogenesis and progression.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/anatomical-patterns-suggest-the-involvement-of-biomechanical-stress-in-the-pathogenesis-of-erosions-in-rheumatoid-arthritis

Abstract Number: 1308

MRI of Bilateral Hands Prevents Clinicians from Failing to Detect Joint Damage of Patients with Rheumatoid Arthritis Compared to Scanning Unilateral Hand

Yuji Kukida[1], Akiko Kasahara[1], Takahiro Seno[1], Takuya Inoue[1], Risa Sagawa[1], Takashi Kida[1], Amane Nakabayashi[1], Hidetake Nagahara[1], Ken Murakami[1], Satoshi Morita[2], Hirotoshi Ito[3], Masataka Kohno[1] and Yutaka Kawahito[1], [1]Inflammation and Immunology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan, [2]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan, [3]Department of Radiology, Kajiicho Medical Imaging Center, Kyoto, Japan

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Session Time: 9:00AM-11:00AM

Background/Purpose: Almost all previous clinical trials investigating the drug efficacy in patients with rheumatoid arthritis (RA) on the outcome of MRI were based on scans of a unilateral hand (unilateral approach). The aim of this study is to identify the usefulness of MRI scanning bilateral hands (bilateral approach) of patients with RA in clinical practice.

Methods: Thirty-five RA patients participated in this prospective study and received intravenous abatacept treatment for 12 months. MRI of bilateral hands was performed at baseline and 12 months. MRI images were scored for synovitis, osteitis and bone erosion according to the Rheumatoid Arthritis MRI Scoring System (OMERACT-RAMRIS). Score of unilateral hand was defined as score of hand with higher synovitis score. The smallest detectable changes (SDCs) in MRI scores were calculated to estimate the measurement error and a definite change of MRI score (progression or regression) was defined as a change in the score greater than the SDC cut-off. First, we compared MRI scores between hands at baseline and explored imbalances in the imaging scores for each hand. Next, we compared the treatment results obtained by MRI with the “bilateral approach” to those obtained by MRI with the “unilateral approach”.

Results: Imbalances in the synovitis, osteitis, and erosion scores were identified at baseline in 14%, 51%, and 40% of enrolled patients, respectively. We also found that the hand with the higher synovitis score was different from the hand with the higher osteitis score in 11% of patients and from the hand with the higher erosion score in 37% of patients. After 12-month treatment, higher number of patients with progressive synovitis and osteitis scores was detected in the “bilateral approach” than was detected in the “unilateral approach” (synovitis; one case in the “unilateral approach” /four cases in the “bilateral approach”, osteitis; none case /one case, respectively). No significant difference between two approaches was observed. The number of patients with progressive erosion scores was same (six cases in both approaches).

Conclusion: Our data revealed that high prevalence of imbalances in MRI scores between hands and that MRI by the “bilateral approach” revealed higher number of patients who showed progressions in synovitis and osteitis scores compared to the “unilateral approach”. These results imply that MRI of unilateral hands could make clinicians fail to detect joint damage of the other hand and that scanning bilateral hands provides more reliable information about joint damage of patients with RA in clinical practice.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mri-of-bilateral-hands-prevents-clinicians-from-failing-to-detect-joint-damage-of-patients-with-rheumatoid-arthritis-compared-to-scanning-unilateral-hand

Abstract Number: 1309

The Incidence of Sexually Acquired Reactive Arthritis: A Systematic Literature Review

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Background/Purpose: Reactive Arthritis (ReA) is an inflammatory spondyloarthritis occurring after infection at a distant site.

Chlamydia trachomatis is proposed to be the most common cause of ReA, yet the incidence of sexually-acquired ReA (SARA) has not been well established. We carried out a systematic literature review to collate and critically evaluate the published evidence regarding the incidence of SARA.

Methods: MEDLINE and EMBASE databases were searched using free-text and MeSH terms relating to infection and ReA. The title and abstract of articles returned were screened independently by two reviewers and potentially relevant articles assessed in full. Data were extracted from relevant articles and a risk of bias assessment carried out using a validated tool. Heterogeneity of study methodology and results precluded meta-analysis.

Results: The search yielded a total of 11680 articles, and a further 17 were identified from review articles. After screening, 55 papers were assessed in full, from which 3 met the relevant inclusion criteria for the review. The studies reported an incidence of SARA of 3.0% - 8.1% and were of low to moderate quality.

Conclusion: More studies are required to address the lack of data regarding the incidence of SARA. Specific and sensitive classification criteria must be developed in order for consistent classification and valid conclusions to be drawn. In clinical practice, it is recommended clinicians discuss the possibility of ReA developing at the time of STI diagnosis, and to encourage patients to return if they experience any relevant symptoms.

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Abstract Number: 1310

Management of Chronic Post-Chikungunya Rheumatic Disease: The Martinican Experience

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Background/Purpose: To describe “chronic chikungunya (CHIK)” manifestations seen during the Caribbean outbreak from December 2013 to January 2015.

Methods: We report our experience as the only Rheumatology Department on Martinique Island. Patients were examined by a senior rheumatologist, using a standard care-report form, and CHIK was diagnosed collectively. The median time from acute CHIK to the first rheumatology consultation was calculated; severity was evaluated based on clinical scales and the degree of joint destruction. Each patient’s therapeutic strategy was recorded.

Results: The median time between acute CHIK and the first rheumatology consultation for the 147 patients analyzed was 8 months. After reviewing each patient’s chart, 19 (12.9%) had been given epidemic-influenced CHIK diagnoses. For the remaining 128 patients, with compatible history and positive serology, 4 distinct rheumatologic patterns were observed: 47 (31.9%) had reactivation of painful chronic mechanical manifestations; 9 (6.1%) had fibromyalgia; 45 (30.6%) met the criteria of spondyloarthritis, known for all before the CHIKV infection, and suffered a flare; and 27 (18.3%), with no history of joint disease, developed de novo bilateral symmetric chronic inflammatory joint disease in response to CHIKV infection.

Conclusion: The term “chronic CHIK syndrome” covers multiple etiologies. Compliance with the French Society of Rheumatology recommendations, careful history-taking and serologic verification help avoid errors inherent to the epidemic context and assure early therapeutic intervention for these patients, who should be managed by rheumatologists as early as possible to avoid late treatment onset.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/management-of-chronic-post-chikungunya-rheumatic-disease-the-martinican-experience

Abstract Number: 1311

Causative Pathogens, Antibiotic Susceptibility, and Characteristics of Patients with Bacterial Septic Arthritis over Time

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Background/Purpose: Management of septic arthritis remains a challenge. The emergence of methicillin-resistant Staphylococcus aureus (MRSA) strains with reduced vancomycin susceptibility and multi drug resistant (MDR) gram negative bacilli (GNB) further complicates treatment. However, no information is available for the incidence and outcomes of septic arthritis due to these organisms.

Methods: We performed a retrospective chart review of all inpatient cases of septic arthritis with positive synovial cultures from 2000 to 2015 at a tertiary medical center. MDR was defined for GNB as resistance to two or more classes/groups of antibiotics. We compared patient demographics, clinical information, antibiotic resistance patterns, and clinical outcomes between the early period (2000-07) and the later period (2008-2015) using Mann Whitney and chi-square tests.

Results: There were 128 cases of septic arthritis; 52 in the period 2000-2007 and 76 in the period 2008-2015. The proportion of MRSA septic arthritis did not differ significantly between the first and second period (17% vs 20% of cases, p-value 0.73) while there was a trend toward more cases of GNB in the second period (4% vs 11%, p-value 0.20). One patient had septic arthritis due to MRSA with a vancomycin minimum inhibitory concentration (MIC) $\geq$ 1.5 ug/mL in each period. There was only 1 case of MDR GNB in the later period. Median length of stay (LOS) was similar between methicillin-sensitive Staphylococcus aureus (MSSA) and MRSA (11 days vs 14 days, p=0.59), but higher than other organisms including streptococci and GNB (p=0.02). The most common joint involved was knee (55%) followed by hip (14%). Six out of 8 (75%) cases of polyarticular septic arthritis occurred in patients with MSSA. In-hospital mortality rate of MSSA and MRSA septic arthritis was 6.7% and 8.3 % respectively while no deaths occurred in patients with streptococci and GNB septic arthritis.

Conclusion: The distribution and sensitivity of pathogens causing septic arthritis, including MRSA and MDR GNB, did not differ between the two study periods in this single-center study. The patient with MDR GNB developed severe sepsis requiring intensive care unit admission. The outcomes of MRSA septic arthritis, including increased vancomycin MIC, did not differ significantly from MSSA septic arthritis. Figure

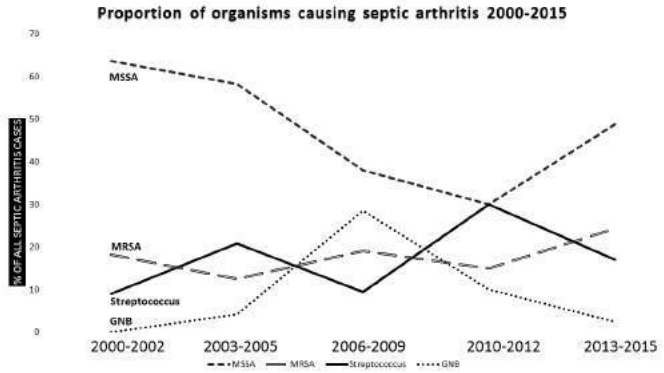

Table Outcomes of septic arthritis across different organisms

	MSSA [a] (N=60)	MRSA [b] (N=24)	CoNS [c] (N=7)	Streptococci (N=22)	Gram negative bacilli (N=10)
Concomitant Endocarditis, n (%)	6 (9.7)	2 (8.3)	0	0	0
Sepsis [d], n (%)	30 (51.7)	13 (56.5)	0	5 (22.7)	1 (10.0)
Surgical intervention	48 (81.4)	19 (82.6)	7 (100)	5 (68.2)	10 (100)
ICU stay, n (%)	15 (25.4)	7 (29.1)	1 (14.3)	5 (22.7)	1 (10.0)
Length of stay [IQR]	11 [8-16]	14 [7-19]	9 [8-11]	9 [5-14]	7 [7-12]
Death, n (%)	4 (6.7)	2 (8.3)	0	0	0

Data are no. (%) patients, unless otherwise indicated. a. MSSA: methicillin-sensitive Staphylococcus aureus. b. MRSA: methicillin-resistant Staphylococcus aureus, c. CoNS: coagulase negative staphylococci, d. two or more systemic inflammatory response syndrome criteria.

Disclosure: S. Jinno, None; **C. Sulis**, None; **M. Dubreuil**, None.

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Abstract Number: 1312

Incidence of Reactive Arthritis, Uveitis and Conjunctivitis in Japanese Patients with Bladder Cancer Following Intravesical BCG Therapy: A 20 Years' Two-Center Retrospective Study

Satoshi Inotani[1,2,3,4], Yoshinori Taniguchi[5], Takashi Karashima[6], Yasuhiko Yoshinaga[7], Hirofumi Nishikawa[8], Natsuki Maeda[9], Shimpei Fujimoto[8] and Yoshio Terada[10], [1]internal medicine, Chikamori Hospital, Kochi, Japan, [2]Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi medical school, Nankoku, Japan, [3]Urology, Kochi medical school, Nankoku, Japan, [4]Rheumatic Disease Center, Kurashiki Medical Center, Kurashiki, Japan, [5]Endocrinology, Metabolism,Nephrology and Rheumatology, Kochi University, Kochi, Japan, [6]Urology, Kochi University, Nankoku, Japan, [7]Kurashiki Medical Center, Kurashiki, Japan, [8]Endocrinology, Metabolism, Nephrology and Rheumatology, Kochi Medical School, Nankoku, Japan, [9]Endocrinology,Metabolism,Nephrology and

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Background/Purpose: To evaluate the incidence of reactive arthritis (ReA), uveitis and conjunctivitis in Japanese patients with bladder cancer following intravesical BCG therapy (iBCG).

Methods: The clinical symptoms, laboratory, and imaging findings of Japanese patients who received iBCG (n=555 (250 and 305 in Kochi Medical School Hospital (KMSH) and Kurashiki Medical Center (KMC), respectively)) for bladder cancer from March 1997 to February 2016 (for 20 years) were retrospectively assessed. Especially, the patients with ReA and conjunctivitis/uveitis were examined.

Results: The backgrounds of patients received iBCG were followings; age 73±10 and 70±11; male/female 198/52 and 240/65 in KMSH and KMC, respectively. ReA was revealed in 5/250 (2.0%) and 6/305 (2.0%), uveitis in 3/250 (1.2%) and 1/305 (0.3%), and conjunctivitis in 18/250 (7.2%) and 15/305 (4.9%) in KMSH and KMC, respectively. As the total evaluation, ReA, uveitis and conjunctivitis were revealed in 11/555 (2.0%), 4/555 (0.7%) and 33/555(5.9%), respectively. All ReA were developed after 3-times of iBCG. Clinical, ultrasound and FDG-PET/CT findings of ReA induced by iBCG showed asymmetric polyarthritis/polyenthesitis. Laboratory examinations showed high CRP (>10mg/dl) in all cases. Notably, there were significant increased frequencies of HLA-B27, B35, B39 and B51 alleles in ReA patients (16.7%, 33.3%, 33.3% and 66.7%, respectively) when compared with healthy subjects (0.3%, 17.0%, 6.0% and 16.0%, respectively).

Conclusion: Despite the positive rate of HLA-B27 in ReA induced by iBCG in our study was 16.7% suggesting lower frequency than 51 to 55% in the Western countries, the incidence of ReA induced by iBCG in Japanese population was 2.0 % which could be more than in the Western countries (0.5 to 1%) from previous reports. High positivity 66.7% and 33.3% of HLA-B51 and B39 in our study might raise the possibility that HLA-B51 or B39, besides B27, also may be associated with ReA induced by iBCG in Japan.

Disclosure: S. Inotani, None; **Y. Taniguchi**, None; **T. Karashima**, None; **Y. Yoshinaga**, None; **H. Nishikawa**, None; **N. Maeda**, None; **S. Fujimoto**, None; **Y. Terada**, None.

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Abstract Number: 1313

Rheumatologic Diseases in HIV-Infected Patients in the Post-Antiretroviral Therapy Era: The County Experience

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Background/Purpose: HIV infection has been associated with a plethora of rheumatologic diseases, however there are only few studies in the US analyzing the frequency of the different musculoskeletal conditions in patients with HIV on antiretroviral therapy

(ART). The aim of the study was to calculate the proportion of rheumatic manifestations in HIV-infected patients who were receiving antiretroviral treatment and to identify association of the HIV medications with the development of rheumatologic conditions.

Methods: We conducted a review of our electronic medical record database at Maricopa Integrated Health System during the period of 2009 to 2015 using ICD-9 and ICD-10 codes for specific morbidities. We identified 2,996 patients as having chronic HIV infection and on ART that had more than 2 visits in the HIV clinic. A chart review was performed and we identified patients with rheumatologic diseases based on the ACR and EULAR diagnostic criteria. We collected data regarding patient's demographic characteristics, co-morbidities, CD 4 count, HIV viral load and antiretroviral regimen. One hundred fifteen patients with one of the morbidities and 200 randomly selected HIV-infected patients on ART without a diagnosis of rheumatologic disease were used for the analysis. Analytical comparison was based on an aggregate group of patients with any of the four morbidities: autoimmune conditions, avascular necrosis (AVN), musculoskeletal infections, or crystal arthropathies. Group differences were statistically compared and presented using Mann-Whitney U and Fisher's exact test.

Results: Based on the medical record review, 115 out of 2996 HIV patients (3.8%) were found to have a rheumatic condition (mean age of 48.6 years, 83% male). The most frequent musculoskeletal condition was AVN in 39 (1.3%) and the most frequent autoimmune condition was psoriasis in 28 patients (1%). Seven patients had rheumatoid arthritis (0.23%), 6 (0.2%) had psoriatic arthritis and 6 (0.2%) had systemic lupus erythematosus. Ankylosing spondylitis, granulomatosis with polyangiitis and polymyositis were present in one case each. Ten patient were diagnosed with gout (0.35%) and 1 patient had pseudogout. Infectious musculoskeletal conditions were present in 15 patients (0.5%), 12 with osteomyelitis and 3 with septic arthritis. Compared with the 200 HIV patients without any diagnosis of rheumatic disease, the patients with rheumatic conditions were older (median age of 50 vs. 42 years; $p<0.01$) and had a longer duration of HIV infection (median duration of 16 vs. 8 years; $p<0.01$). Those who received integrase inhibitors were more likely (63.3%) to develop rheumatologic manifestations relative to those who never received integrase inhibitors (21.6%; $p<0.01$).

Conclusion: Our study showed that AVN is the most frequent rheumatic complication. Psoriasis was the most frequent autoimmune disease. The proportion of autoimmune rheumatic diseases in HIV patients appears to be comparable to the prevalence in the US population. Older age, longer duration of HIV infection and the use of ART regimens containing integrase inhibitors, appear to increase the risk of developing a rheumatologic condition.

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Abstract Number: 1314

Characteristics of the Musculoskeletal Symptoms Observed Among Survivors of Ebola Virus Disease (EVD) in the Postebogui Cohort in Guinea

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Background/Purpose: Previous studies showed that arthralgia and myalgia were the most common symptoms among Ebola virus disease (EVD) survivors. Nevertheless specific analyses of rheumatologic sequelea are still lacking.

Methods: The Postebogui study is a prospective multicenter cohort aiming to evaluate the long-term clinical, psychological and socio-behavioral outcomes of EVD survivors infected during the 2014-2015 outbreaks. Of the 216 participants included in October 22th 2015, 44 patients with arthralgia/myalgia underwent a complete examination by a rheumatologist. Data were collected using a

standardized questionnaire and entered in an electronic database.

Results: 43 patients reported joint pain and one patient had myalgia only. 61% were female; median age was 31.5 years; median time from Ebola Treatment Center (ETC) discharge to rheumatologic examination was 8.8 months. Pain manifestations started after Ebola infection in all patients except one. We found similar characteristics in the whole cohort without rheumatologic examination. Morning stiffness was present in 75% of patients. Patients had mechanical pain only (45%), inflammatory pain only (9%) or both (45%). 77% had low back pain and all patients had at least one peripheral joint painful. Large joints were most frequently affected than small joints (73% vs 41%). Oligo and polyarticular presentations were similar and a symmetrical pain distribution was frequent (43-81%). Furthermore, 36 patients (82%) had at least one painful 18-tender point count, most of whom had extensive pain (n=19) and symmetric distribution (91%). Diagnoses were mainly non-specific musculoskeletal disorders (59%) and mechanical back pain (52%). No polyarthritis was observed. We found a higher percentage of depressed patients 42% versus 11% in the remaining Postebogui group ($p<0.001$).

Conclusion: Our study provides an in-depth analysis of rheumatic complaints among a large cohort of EVD survivors. Compared to some other viral infections, synovitis seems rare. Importantly a strong correlation with depression was found highlighting the impact of pain symptoms among survivors

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Abstract Number: 1315

Methotrexate and TNF-Blockers for Post Chikungunya Chronic Arthritis : The Martinican Experience

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Background/Purpose: To describe treatments in patients with chronic post-chikungunya polyarthritis seen during the Caribbean outbreak (December 2013 - January 2015).

Methods: Patients were examined by senior rheumatologists, using a standard care-report form, post-CHIK polyarthritis was diagnosed collectively. Treatments were introduced following recommendation of the French Society of Rheumatology.

Results: Among 147 patients, 45 (30.6%) met criteria of spondyloarthritis. In all cases the rheumatic diseases predated CHIKV infection and exacerbated at the waning of the acute viral infection, despite NSAID(s), justifying further therapeutic intensification with DMARDs (MTX 17/45, mean dose 20 mg/w) and anti- TNF (7/45). Mean follow-up was 6.5 months, during which time the patients' mean BASDAI±SD decreased from 5.1 ± 1.5 at the first visit to 3.8 ± 1.5 at the last one. 27 patients (18.3%), developed de novo polyarthritis in response to CHIKV infection. None had CHIKV-positive PCR during polyarthritis. Biologic inflammation was moderate (mean CRP 25 ± 12 mg/liter), serologic work-up was negative for all patients. All received MTX (mean dose 21 mg/w), with good responses in 21/28, while 7/28 required anti-TNF. Mean follow-up was 7 months, during which mean DAS28score ± SD decreased from 4.8 ± 1.5 at the first visit to 3.3 ± 1.5 at the last one. They received biologics at conventional doses (etanercept 11 and adalimumab 3). Tolerance was good without any recurrence of the viral infection manifestations, as previously described (18). Efficacy

was as expected for this type of pathology.

Conclusion: The term "chronic CHIK syndrome" covers multiple etiologies. These patients should be managed by rheumatologists as early as possible to avoid late treatment onset. Compliance with the French Society of Rheumatology recommendations, assure early therapeutic intervention. *Simon F, Javelle E, Cabie A, Bouquillard E, Troisgros O, Gentile G, et al. French guidelines for the management of chikungunya (acute and persistent presentations). Méd Mal Infect 2015;45:243–63.*

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Abstract Number: 1316

Clinical Features and Outcomes of Prosthetic Joint Septic Arthritis: The Gender Effect

Mary Louise Fowler[1], Sarah B. Lieber[2], Andy Moore[3], Robert Shmerling[4] and Ziv Paz[2], [1]Boston University School of Medicine, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Division of Rheumatology, Cambridge Health Alliance, Harvard Medical School, Boston, MA, [4]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA

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Background/Purpose: In developed countries, certain health outcomes are worse among men. For example, in the US, life expectancy for men is 5 years shorter than for women and cardiovascular disease is a major contributor to this discrepancy. Little is known about how clinical features and outcomes of prosthetic joint septic arthritis (PJSA) differ between men and women. This is the first study of its kind to investigate these differences. **Objective**: To compare clinical characteristics and outcomes between women and men with surgically-treated PJSA.

Methods: We conducted a retrospective study that included all patients aged 18 and older admitted to a single, tertiary-care hospital between 1998 and 2015 diagnosed with monoarticular PJSA and treated surgically. We excluded all cases of osteomyelitis, polyarticular infection, septic bursitis, and native joint infection.

Results: Of the 225 patients with PJSA, 122 were female. The frequency of comorbid conditions was similar in men and women [Table 1]. However, a prior history of septic arthritis was more common in men (33 vs 21.3%, p=0.05). While there were no differences in rates of admission early after joint replacement (< 43 days), significantly more men developed late (>365 days after joint replacement) PJSA (59.8 vs 43.9%, p= 0.02). Women had significantly higher mean peripheral WBC counts (11.8 vs 10.3 x 10^9/L, p=0.03) and lower mean synovial fluid polymorphonuclear (PMN) cell counts (82.8 vs 89.9%, p=0.01) than their male counterparts. Males had higher rates of culture positivity (82.5 vs 69.7%, p=0.03) and presence of pus during surgery (68.9 vs 47.1%, p=0.005) but similar rates of MRSA infection [Table 2]. Finally, men were more likely to require ICU stay (17.5 vs 7.4%, p=0.02) and more frequently required multiple operations (29.4 vs 17.4%, p=0.05).

Conclusion: This study suggests there are significant gender differences in clinical features and outcomes of PJSA. Though the presentations were similar, men tended to present later (>1 year post joint replacement), have higher rates of culture positivity and worse outcomes. Further investigation is needed to better understand the causes of these differences and how they might be used to improve treatment. **Table 1. Demographic, comorbidities, and clinical features of patients with PJSA, male vs. female.**

	Female (n=122)	Male (n=103)	p-value
Age (yrs), mean (SD)	62.5 (15.5)	61.9 (13.8)	0.77
Risk Factors for Septic Arthritis			
DM, N (%)	34 (27.9)	35 (34)	0.32
HIV, N (%)	2 (1.6)	4 (3.9)	0.3
Prior History of Septic Arthritis, N (%)	26 (21.3)	34 (33)	0.05
RA, N (%)	11 (9.0)	8 (7.8)	0.74
Previous joint trauma, N (%)	7 (5.7)	8 (7.8)	0.54
Recent joint procedure, N (%)	74 (61.2)	56 (54.4)	0.31
Clinical features			
Fever (>100 F), N (%)	34 (27.9)	36 (35)	0.11
Sepsis (defined by SIRS criteria), N (%)	25 (20.5)	25 (24.3)	0.35
Mean peripheral WBC (in thousands) (SD)	11.8 (5.2)	10.3 (5)	0.03
Mean peripheral PMN (%) (SD)	77.5 (11.6)	76.0 (10.3)	0.36
Mean ESR (mm/hr) (SD)	68.9 (34.4)	77.7 (37.5)	0.11
Mean CRP (mg/L) (SD)	103.3 (94.2)	128.8 (99.3)	0.09
Mean synovial fluid WBC (in thousands), (SD)	67 (100.3)	87.7 (138.2)	0.25
Mean synovial fluid PMN (%) (SD)	82.8 (21.5)	89.9 (14.6)	0.01
Affected Joint			
Knee, N (%)	89 (73)	76 (73.8)	0.89
Hip, N (%)	30 (25)	25 (24.3)	0.96

SD: Standard deviation; DM: Diabetes Mellitus; HIV: Human Immunodeficiency Virus; RA: Rheumatoid arthritis; WBC: White blood cell; PMN: Polymorphonuclear leukocyte; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

Table 2. Outcomes of patients with PJSA, male vs. female

	Female (n=122)	Male (n=103)	p-value
MSSA infection, N (%)	71 (22.1)	129 (29.9)	0.02
Detection of pus by surgeon, N (%)	111 (55.8)	168 (65.6)	0.03
ICU stay, N (%)	9 (7.4)	18 (17.5)	0.02
Multiple operations required, N (%)	19 (17.4)	27 (29.4)	0.05
Mean LOS (days) (SD)	8.9 (5.3)	10.2 (8.5)	0.16
Readmission within 60 days, N (%)	21 (17.5)	23 (22.5)	0.3
Expiration within 30 days	2 (1.6)	2 (1.9)	0.8
Discharge to rehabilitation, N (%)	80 (66.7)	57 (56.4)	0.12

MSSA: Methicillin-sensitive staphylococcal aureus; ICU: Intensive care unit; LOS: Length of stay

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Abstract Number: 1317

Do Patients with MRSA-Positive Septic Arthritis Differ Clinically from Non-MRSA-Positive Counterparts?

Mary Louise Fowler[1], Kevin Byrne[1], Sarah B. Lieber[2], Andy Moore[3], Robert Shmerling[4] and Ziv Paz[2], [1]Boston University School of Medicine, Boston, MA, [2]Beth Israel Deaconess Medical Center, Boston, MA, [3]Division of Rheumatology, Cambridge Health Alliance, Harvard Medical School, Boston, MA, [4]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA

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Do patients with MRSA-positive septic arthritis differ clinically from non-MRSA-positive counterparts? Mary Louise Fowler[3], Kevin Byrne[3], Sarah B. Lieber[1], Andrew Moore[2], Robert H. Shmerling[1], Ziv Paz[1], [1]Beth Israel Deaconess Medical Center, [2]Cambridge Health Alliance, Harvard Medical School, [3]Boston University School of Medicine

Background/Purpose: The incidence of methicillin-resistant Staphylococcus aureus (MRSA) septic arthritis (SA) has increased over the past decade. While MRSA SA is thought to be more severe than non-MRSA SA, there is little published evidence suggesting these patients differ in their presentation and outcomes in the adult population. **Our objective:** To define the epidemiology, clinical characteristics and outcomes of patients with MRSA SA compared to non-MRSA SA patients.

Methods: We conducted a retrospective study that included all patients 18 and older admitted to a single, tertiary-care hospital between 1998 and 2015 diagnosed with culture-positive monoarticular SA and were surgically treated. We excluded cases of osteomyelitis, polyarticular infection or septic bursitis.

Results: Of the 425 patients with SA, 63 (14.8%) were due to MRSA. Compared to patients with non-MRSA SA, those with MRSA SA: were older (63.2 vs 58.3 years, p=0.04); had a higher prevalence of chronic kidney injury (p=0.004); had more end-stage liver disease (p=0.04); and were more likely to have shoulder involvement (p=0.004). In addition, MRSA SA was more likely to affect patients with recent (0-42 days) prosthetic implantation (p=0.05). There were no significant differences in rates of fever or sepsis but mean ESR (87.5 vs 74.3 mm/hour, p=0.04) and mean % of blood polymorphonuclear (PMN) (80.4 vs 77.3%, p= 0.05) were significantly higher in those with MRSA SA. Importantly, the length of hospital stay (LOS) was significantly longer for patients with MRSA SA (12.6 vs 10.4 days, p=0.05), as well as the rates of discharge to rehabilitation was higher (73.7 vs 54%, p=0.005) and expiration within 30 days (11.4 vs 4.4 %, p=0.03).

Conclusion: MRSA SA is common, representing nearly 15% of SA cases. Our study confirms that MRSA SA patients tend to be older, have more comorbidities and worse outcomes than those infected with other organisms. Despite these findings, patients with MRSA SA do not, on average, appear to be sicker at the time of presentation. Table 1. Demographic and clinical features of patients with culture-positive septic arthritis, Methicillin-Resistant Staphylococcus Aureus (MRSA) vs. non-MRSA

	MRSA (n=63)	Non-MRSA (n=362)	p-Value
Demographic Data:			
Age (yrs), mean (SD)	63.2 (19.4)	58.3 (17.8)	0.04
Female gender, N (%)	29 (46)	159 (43.9)	0.76
Risk Factors for SA:			
DM, N (%)	22 (34.9)	116 (32)	0.65
CKI, N (%)	17 (27)	47 (13)	0.004
HIV, N (%)	1 (1.6)	11 (3)	0.52
ESLD, N (%)	5 (8)	10 (2.8)	0.04
IVDU, N (%)	6 (9.5)	17 (4.7)	0.12
History of septic arthritis, N (%)	17 (27)	60 (16.6)	0.05
RA, N (%)	5 (7.9)	20 (5.5)	0.45
Previous joint trauma, N (%)	10 (15.9)	53 (14.6)	0.80
Recent procedure in joint, N (%)	29 (46)	141 (39.1)	0.30
Clinical features:			
Fever (>100 F), N (%)	23 (36.5)	129 (35.6)	0.78
Sepsis (defined by SIRS criteria), N (%)	17 (27)	121 (33.4)	0.43
Mean peripheral WBC (in thousands), (SD)	12.3 (6.1)	11.5 (5.2)	0.31
Mean peripheral PMN (%), (SD)	80.4 (9.9)	77.3 (11.1)	0.05
Mean ESR (mm/hr), (SD)	87.5 (36.4)	74.3 (37.9)	0.04
Mean CRP (mg/L), (SD)	151.5 (111.3)	135.9 (105.9)	0.40
Mean synovial WBC (in thousands), (SD)	105.6 (118.4)	83.8 (112)	0.22
Mean synovial fluid PMN (%), (SD)	89.4 (15.9)	87.1 (17.8)	0.39

SD: Standard deviation; DM: Diabetes Mellitus; CKI: Chronic Kidney Injury; HIV: Human Immunodeficiency Virus; ESLD: End Stage Liver Disease; IVDU: Intravenous Drug Use; RA: Rheumatoid arthritis; WBC: White blood cell; PMN: Polymorphonuclear leukocyte; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein

Table 2. Joints affected and outcomes in patients with culture-positive septic arthritis, MRSA vs. non-MRSA.

	MRSA	Non-MRSA	P-Value
Joint:			
Knee, N (%)	32 (50.8)	206 (56.9)	0.37
Hip, N (%)	8 (12.7)	72 (19.9)	0.18
Shoulder, N (%)	14 (22.2)	35 (9.7)	0.004
Infected 0-42 days of prosthetic insertion, N (%)	6 (30)	17 (12.8)	0.05
Infected 43-365 days of prosthetic insertion, N (%)	6 (30)	43 (32.3)	0.84
Infected >365 days since prosthetic insertion, N (%)	8 (40)	73 (54.9)	0.21
ICU, N (%)	12 (19.4)	59 (16.3)	0.56
Detection of pus by surgeon, N (%)	26 (74.3)	154 (65.8)	0.32
Mean LOS in days, N (SD)	12.6 (9.1)	10.4 (8.1)	0.05
Discharge to rehabilitation, N (%)	42 (73.7)	185 (54)	0.005

ICU: Intensive Care Unit; LOS: Length of Stay

Abstract Number: 1318

Profile of Macrophage-Derived Cytokines and Chemokines of Patients with Chikungunya-Induced Chronic Arthralgia/Arthritis

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Background/Purpose: Chikungunya virus (CHIKV) caused a large epidemic in Puerto Rico in 2014 with more than 30,000 reported cases. Many of the affected individuals developed chronic arthralgia and/or arthritis months or years after the infection. Animal and human studies have suggested that chronic arthralgia/arthritis is caused by unresolved inflammation responses in joints and persistent infection in macrophages. Thus, the main goal of this study was to identify factors released from macrophages of CHIKV-infected individuals that may play a role in the establishment of the chronic arthralgia/arthritis.

Methods: A cross-sectional study was performed in patients with and without chronic arthralgia/arthritis (chronic and control groups, respectively) associated with CHIKV infection. All patients had laboratory confirmed CHIKV infection by IgG ELISA. Demographic features, health-related behaviors, clinical manifestations, comorbidities, disease activity (per Clinical Disease Activity Index [CDAI]), functional status (per Health Assessment Questionnaire [HAQ]), patient's and physician's global disease assessments by visual analog scales, and pharmacologic treatment were determined. Monocytes-derived macrophages were cultured for 7 days for differentiation. Cytokines and chemokines levels were determined in supernatants collected 3 days after macrophage differentiation

using the Quantibody Inflammation Q3 ELISA array. Variables between chronic and control groups were compared using Fisher's Exact and Mann-Whitney tests. Additional analyses were performed with stratified CDAI data (low < 10 and moderate or high ≥ 10) using Kruskal-Wallis tests with Dunn's multiple comparisons.

Results: Twenty-four patients were studied, 15 with chronic symptoms and 9 controls. The mean age was 47 ± 17 (SD) and 52 ± 11 years old in the chronic and control groups, respectively. A significantly higher proportion of women (13/15) had chronic arthralgia/arthritis than men (2/15, p=0.042). The mean time period between CHIKV infection and study visit was 18 months for both groups. Patients with chronic symptoms had significantly higher CDAI (12.5 ± 10.1 vs. 0.1 ± 0.3, p<0.001) and HAQ scores (0.9 ± 0.66 vs. 0.1 ± 0.29, p=0.002) than the controls. Patients in the chronic group had significantly (p<0.05) lower levels of MCP-1, MCSF, MIP1alpha, TIMP1, and TIMP2 than the controls. Conversely, patients with chronic arthralgias/arthritis were more likely to have significantly (p=0.003) higher levels of I309 than those without chronic symptoms. No differences in cytokine or chemokine levels were observed in chronic patients with low or moderate/high CDAI. Eotaxin, IL-4, IL-11, and IL-12p70 were not detected in any of the samples tested in this study.

Conclusion: Higher levels of chemokines, except for I309, were observed in patients without chronic arthralgia/arthritis suggesting a protective role, in particular of the metalloproteinase inhibitors TIMP1 and TIMP2. Further studies are required to define the mechanism of action of these chemokines in preventing the development of chronic arthralgia/arthritis after CHIKV infection.

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Chikungunya Fever in Patients on Biological and on Conventional Dmards Therapy – Results from the Brazilian Register Biobadabrasil

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Background/Purpose: Chikungunya fever (CHIKF) is a systemic arboviral disease manifesting with fever, acute arthritis and rash. The acute symptoms can last for days but articular pain and edema can persist and chronify. Objectives: to analyze the clinical manifestations of CHIKF in patients with a previous established articular disease in regular biological (boDMARDs) or conventional DMARDs (cDMARDs) treatment included in BiobadaBrasil register,

Methods: an active search for CHIKF in patients with established rheumatic diseases (ACR criteria) in regular follow up in our database and living in the epidemic area (127.8CHIKFcases/100000 habitants – 18 epidemiological week) was performed; positive cases were identified and submitted to clinical exam and structured interview,

Results: from 358 patients in regular follow up at the 4 centers localized in the epidemic area, CHIKF was diagnosed in 30 (8.4%) patients based on clinical and epidemiological criteria. In this sample, 13 patients were on boDMARDs therapy (4 on adalimumab, 2 on certolizumab and 3 on etanercept, and one on abatacept, infliximabe, golimumabe and rituximab); median treatment

duration 30 months[1-70]) and 17 on cDMARDs. Nearly all patients (85%) lived in urban area, 87% were female, mean age 46(10)yrs; mean disease duration 8 (1-21).yrs. Regarding diagnosis 22 have RA, 7AS and 1 SLE. Remarkable symptoms reported in the table below as well CHIKF treatment with corticoid (CE) *p<0.05.

symptoms	fever	Joint pain	polyarticular	Swollen	Exanthema	paresthesia	CE	Daily dose(mg)
cDMARds n=17 (%)	17 (100)	17 (100)	14 (82)	13 (76)	13* (54)	9* (53)	12 (61)	16.8 (±5.8)
boDMARDs (n=13) %	13 (100)	13 (100)	11 (85)	10 (77)	7 (76)	2 (15)	8 (71)	16.2 (±6.9)

Symptons presented by more than 60% of the patients, with no difference between treatment groups were: myalgia, fatigue, GI complains (diarrhea, nausea, vomit, pain), headache, morning stiffness. Presence of exanthema, paresthesia and neuropatic pain were more frequent in cDMARds treated patients. At the moment of the CHIKF symptoms 76% of the patients in both treatment groups were considered in remission and the articular manifestations were reported as similar to the rheumatic disease only by 15% of the patients on boDMARDs and 18% of the ones on cDMARDs. The pain intensity and localization was reported as different of other acute exacerbations of the previous rheumatic disease. So far, the duration of symptoms were similar with just 23% of the patients having less than 3 months of symptoms. There were no serious complications of CHIKF in any of the treatment groups.

Conclusion: : boDMARDs does not aggravate CHIKF symptoms or persistence. The clinical manifestations of CHIKF in patients with rheumatic diseases are no different from literature reports in health individuals.

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Chikungunya Fever Outbreak in Brazil: Preliminary Assessment in a Cohort of Patients with Rheumatological Manifestations

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Background/Purpose: Chikungunya virus (CHIKV) emerged in Brazil in September 2014. Since then the infection reached epidemic proportions in the country, paticularly in the Northeast region of Brazilian territory. Clinical manifestations of CHIKV infection involve various organs (skin, gastrointestinal tract, vascular system); however, rheumatic manifestations are the most typical features. The disability present in the chronic articular disease in CHIKV infection is an emerging challenge for rheumatologists. **Objectives**: To describe clinical manifestations associated with CHIKV infection in the Brazil population, in patients with previous rheumatic diseases and without previous rheumatic diseases.

Methods: From April to June 2016, 122 patients were enrolled with clinical and epidemiological diagnosis of CHIKV infection, 75

with IGG serology positive for CHIKV (ELISA, Euroimmun®).

Results: Thirty three patients (27.0%) presented a rheumatic disease prior to CHIKV infection (19 rheumatoid arthritis, 8 ankylosing spondylitis and 6 systemic lupus erythematosus). Most of the patients were women (80.3%), non-caucasians (85.0%) and the median age was 53.5 (±11.97) years. Patients had a median time of symptons of 10.8 (±7.46) weeks at the moment of enrollment. All of the patients presented joint pain, 87.0% presented characteristic inflammatory joint stiffness and 87.7% presente arthritis, with an additive polyarticular pattern in most of the cases. Pain intensity measured by visual analogue scale (VAS) was 6.36 (±2.52) and stiffness was 7.44 (±2.11); the median number of painful joints per patient was foi 11.9 (±17.9) and swollen joitns was 7.3 (±9.10). From the 122 patients, 53 (42.63%) had positive CHIKV IgM and 13.9% had a negative result; among the positives, 44.9% retained the positivity after 12 weeks of disease onset. There was significant association between IgM positivity and the number of painful joints by physical examination (p=0.001). There was no difference in clinical manifestations between patients with prior rheumatic diseases and patients whithout prior rheumatic diseases. Most of patients with prior rheumatic diseaes (50%) were under biological therapy (mainly TNF-blockers). There was no association between biological therapy use either with time of symtpons or joint pain characteristics. No disesase complications were observed in patients under immunossuppressor treatment and under disease modifying rheumatic drugs, biological or non-biological.

Conclusion: Initial data of CHIKV infection in brazilian population with prior rheumatic diseases suggest that there are no clinical differences from individuals with no prior rheumatologic disesases. The use of biological drugs seems not to be associated with either clinical complications or changes in the characteristic features of the symptons related to CHIKV infection. The persistence of positivity for IgM beyond 12 weeks may be a factor associated with chronicity of joint symptoms in FC .

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Distinguishing Features of Polymicrobial Septic Arthritis

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Background/Purpose: Little is known about patients with polymicrobial septic arthritis (SA) and how they may differ from those with SA due to a single organism. The purpose of this study is to define the demographic features, clinical characteristics, microbiology, and outcomes of patients with polymicrobial SA as compared to those with monomicrobial SA.

Methods: We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with culture-positive, surgically treated SA affecting one or more joints. Baseline characteristics, clinical features, microbial profile, rate of operative intervention, length of hospital stay (LOS), and 60-day readmission rates were determined. Patients were stratified by presence of SA due to a single organism or more than one organism, identified either in the blood of patients with inflammatory arthritis or in synovial fluid.

Results: Of 511 patients with SA, 52 (10.2%) were found to have polymicrobial SA. Demographic features were similar in the polymicrobial and monomicrobial SA groups. Of those with polymicrobial SA, 6 had polyarticular involvement, similar to the rate of polyarticular involvement in those with monomicrobial SA. Polymicrobial SA was less commonly preceded by joint trauma (5.9% versus 18.1%; p = 0.03). Those with polymicrobial SA tended to have lower synovial fluid white blood cell counts (SF WBC) (71.2 versus 101.4 x 10^9 per liter) with significantly lower % polymorphonuclear (PMN) cells (78.1% versus 88.0%; p = 0.003). Polymicrobial SA occurred most frequently in the knee (n = 27) and hip (n = 13), but no differences in joint distribution were found as

compared to those with SA due to a single organism. Coagulase negative Staphylococcus (32.7% versus 12.0%; p < 0.001), Enterococci (33% versus 2.5%, p <0.001) and Escherichia Coli (15% versus 2.5%, p <0.001) are the three most frequently isolated organism in polymicrobial SA (Figure 1). LOS was longer in those with polymicrobial SA (13.4 versus 10.7 days; p = 0.04), and there was a trend toward more frequent Intensive Care Unit (ICU) stays (25.0% versus 15.9%; p = 0.098). Rates of endocarditis were similar in patients with polymicrobial and monomicrobial SA.

Conclusion: Patients with polymicrobial SA may differ in important ways from patients with monomicrobial SA. Despite lower SF WBC counts and many infections with bacteria of low virulence, patients with polymicrobial SA may have more severe disease, as suggested by a longer LOS and more frequent transfers to the ICU.

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Abstract Number: 1322

Use of Biologics in Arthritis Patients with Hepatitis B and C : A Multicentral Retrospective Case Series

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Use of biologics in arthritis patients with Hepatitis B and C : a multicentral retrospective case series

Abstract

Background/Purpose: Reactivation of viral hepatitis B (HBV) and C (HCV) has been reported in various case reports in arthritis patients on biological therapy. The objective of the study is to describe clinical characteristics and outcomes of arthritis patients with HBV or HCV treated with biological therapy.

.**Methods:** This is a retrospective case series including 4 centers

Results: Total of 20 arthritis patients with HBV and HCV on biological therapy were identified: 10 cases had (HBV) and 10 cases had (HCV) infection. In the HBV cohort the mean age was 51 (34-85) years, 80% were females. Most patients had Rheumatoid Arthritis (RA) 8(80%), 1 patient had RA/ Systemic lupus erythematosis (SLE) and 1 had HIV related arthritis.A total of 70% were inactive HBsAg carrier and the 3 had chronic hepatitis B. Prophylactic antiviral therapy was given in 9 patients with HBV cases: Entecavir (ETV) 7 , lamivudine and (ETV) 1 and tenofovir 1. The biologics used were Adalimumab (ADA), tociluzumab (TOC), rituximab (RIT) .and etarnercept (ETA). There were 2 cases with chronic HBV had reactivation with no elevation of the transaminases

The mean age in Hepatitis C (HCV) cohort was 54 (23-79) years, all were female RA patients. 5 had detectable HCV RNA before start of biologics. Antiviral treatment was given in 9 (90 %) patients of the hepatitis C cohort: pegylated interferone plus ribavarin (PEG-RIB) 8, PEG-RIB and sofosbuvir plus ribavirin (SOF-RIB) 1pat. The biologics that were used: (ETA, ADA, TOC, RIT, abatacept (ABA) and infliximab (INF). There were 3 patients found to have elevated HCV RNA with elevation of transaminases during followup on biologics meeting criteria for hepatitis C reactivation. All three cases were genotype 4. One of the patients with HCV reactivation was started on SOF-RIB that showed undectable HCV RNA on follow-up.

Conclusion: We report a successful and safe use of biological therapy in patients with arthritis infected with HBV or HCV. Frequent .monitoring is essential to detect reactivation that might occur

Table 1: Characteristics and treatment in 10 arthritis patients with Hepatitis B infection on biologics

No	Age/Sex	Rheumatic Disease	Duration(Months)	HBsAg	HBV markers (BL)	HBV DNA (BL) IU/ML	ALT,AST (BL)	HBV DNA before treatment	B-DMARD	Duration of biologics months	HBV Antiviral	Duration of Antiviral (Months)	HBV DNA followup	HBVr	Followup months	DMARDS	Steroids	Multiple biologics
1	61/F	RA	300	+	HBsAg HBcAb HBeAb	3288	Normal	ND	ETA	60	ETV	72	3969	Yes	71	MTX HCQ	Yes	No
2	34/F	RA SLE	58	+	HBsAg HBcAb HBeAb	ND	Normal	ND	RIT	60	LMV ETV	>30 28	ND	No	60	SSZ HCQ MMF	Yes	No
3	85/M	RA	276	+	HBsAg	26	Normal	NF	ADA ETA	38 16	ETV	52	ND	No	53	MTX HCQ	Yes	Yes
4	64/F	HIV related arthritis	52	+	HBsAg HBcAb HBeAb	4.5 million	ALT 139 AST 175	ND	ETA ADA	11 43	TFV	72	ND	No	75	HCQ	Yes	Yes
5	64/F	RA	51	+	HBsAb HBcAb	ND	Normal	ND	ADA ETA	9 28	ETV	37	ND	No	51	MTX	Yes	Yes
6	51/F	RA	43	+	HBsAb HBcAb	NF	Normal	NF	TOC	27	NO	NF	NF	No	27	MTX HCQ	Yes	No
7	52/M	RA	108	+	HBsAg HBeAb	380	Normal	NF	ETA	14	ETV	24	20 IU	No	48	HCQ SSZ	NF	No
8	54/F	RA	144	+	HBsAg	15	Normal	ND	ETA	60	ETV	60	NF	No	60	HCQ MTX	Yes	No
9	42/F	RA	48	+	HBsAg	6726	Normal	NF	ETA	11	ETV	60	6653	Yes	72	NF	NF	No
10	35/F	RA	216	+	HBsAg HBeAb	467	Normal	NF	ETA	19	ETV	14	<20	NO	19	MTX	Yes	No

F:Female ,M : Male , BL:baseline, Ast :aspartate transaminases, Alt: alanine transaminases, RA : Rheumatoid Arthritis, SLE : Systemic Lupus Erythematosus, ND : Not Detected,NF :Not Found, ETV : Entecavir, DNF : Infliximab, RTX : Rituximab, ADA : Adalimumab, ABA:Abatacept, TOC : Tocilizumab, LMV : Lamivudine, ETV : Entecavir, TFV : Tenofovir, LEF : Leflunomide , MTX : Methotrexate, SSZ : Sulfasalazine, HCQ : Hydroxychloroquine , AZA : Azathioprine , CyA : Cyclosporine A , DMARD : disease-modifying antirheumatic drug, B-DMARD : Biological disease-modifying antirheumatic drug,HBVr:HBV reactivation

Table 2:Patients characteristics of 10 arthritis patients with Hepatitis C infection on biologics

Case No.	Age/Sex years	Rheumatic Disease	Duration of RD (Months)	HCVPCR (BL) Genotype	ALT AST (BL)	HCV antiviral	HCV RNA before Biologic	B-DMARDS	Length of biologic (months)	Presence of reactivation	Follow up (months)	Follow up HCV RNA	DMARDS	Steroids	Multiple biologics
1	69/F	RA	100	Positive	Normal	PEG-RIB	ND	RIT	65	No	70	NF	MTx	No	No
2	41/F	RA	101	Positive	Normal	PEG-RIB	ND	RIT	84	No	90	NF	MTx	No	No
3	79/F	RA	178	11 m IU/mL Genotype 4	Normal	PEG-RIB (SE)	2million	INF ADA TOC ABA	NF NF 22 4	Yes Elevated HCV RNA	40	6 million	Mtx LEF	Yes	Yes
4	68/F	RA	228	8 m IU/mL Genotype 1,4	Normal	PEG-RIB non responder	2million	ADA RIT	12 8	No	36	599	Mtx LEF	Yes	Yes
5	57/F	RA	108	4 million Genotype 4	Normal	PEG-RIB	ND	RIT	50	No	52	ND	SSZ HQC	Yes	No
6	60/F	RA Cryoglobulinemia Vasculitis	168	>3 m IU/mL Genotype 3,4	ALT 197 AST 177	PEG-RIB SOF-RIB	ND	RIT ABA	26 11	Yes Elevated HCV RNA	37	<2 million	No	Yes	Yes
7	23/F	RA Sickle cell anemia	60	62340 IU/mL	ALT 49 AST 57	PEG-RIB	ND	ETA ADA RIT	10 20 2	Yes Elevated HCV RNA	41	1.2 million	MTX CyA	Yes	Yes
8	63/F	RA	180	2011883 IU/Ml	Normal	PEG-RIB	NF	ETA	48	No	52	NF	MTX SSZ HQC	NF	No
9	77/F	RA	NF	162726 IU/ml	Normal	Not given	NF	ETA ADA	72 12	No	NF	NF	HQC	Yes	Yes
10	63/F	RA	180	280861 IU/mL Genotype 1	Normal	PEG-RIB	164046	ETA	72	NF	72	NF	HQC MTX SSZ Gold	Yes	No

F:Female ,M: Male, BL:baseline,Ast :aspartate transaminases, Alt:alanine transaminases, RA :Rheumatoid Arthrit, SLE :Systemic Lupus Erythemateux, ND :Not Detected, NF : Not Found, ETN :Etanercept, INF :Infliximab, RTX :Rituximab, ADA :Adalimumab, ABA:Abatacept, TOC :Tocilizumab, LEF :Leflunomide , MTX :Methotrexate, SSZ :Sulfasalazine, HCQ :Hydroxychloroquine , AZA :Azathioprine , CyA: Cyclosporine A , DMARD :disease-modifying antirheumatic drug, B-DMARD :Biological disease-modifying antirheumatic drug, PEG-INF pegylated interferon, RBV Ribavirin, SOF Sofosbuvir

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Systemic Manifestations Associated with Parvovirus B19 Infection in Adults: A Retrospective Study in 23 Patients

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Background/Purpose: Human parvovirus B19 (HPV-B19) is well known as a cause of erythema infectiosum during childhood, pure red cell aplasia in immunocompromised persons, transient aplastic crisis in patients with hereditary hemolytic anemia, and hydrops fetalis during pregnancy. We sought to describe the characteristics and outcome of the systemic manifestations of HPV-B19 primary infection in adults, whose spectrum is poorly identified and treatment uncodified.

Methods: We conducted an observational, retrospective, multicenter study, with the help of the Société Nationale Française de Médecine Interne and the Club Rhumatismes et Inflammation. Cases was defined by at least one diagnostic criterion of recent HPV-B19 infection: IgM antibodies or viral DNA presence in blood and/or another tissue.

Results: We collected 23 observations over the period 2001-2016. Median patient age at diagnosis was 37.9 years (range: 22.7-83.4). There was a female predominance (sex-ratio: 3.6/1). Median time to diagnosis was 11 days (0-197). Only 2 patients had underlying predisposing condition (sickle cell disease, pregnancy). The most common manifestations were joint involvement (87.0%), with peripheral and symmetrical polyarthralgia in all cases and sometimes arthritis (34.8%) or axial involvement (8.7%). Cutaneous symptoms were also frequent (56.5%) and manifested predominantly by rash (21.7%) with or without classical papular-purpuric gloves and socks syndrome (17.4%); when biopsy was performed, it revealed leucocytoclastic vasculitis in 2/3 cases and neutrophilic dermatosis in 1/3 cases. Four patients (17.4%) had renal involvement, with histological documentation in 2 cases (endocapillary proliferative glomerulonephritis, membranoproliferative glomerulonephritis). Two patients (8.7%) presented with lower limbs myositis, and two others with peripheral nervous system involvement (mononeuritis multiplex, Guillain-Barré syndrome). Other disorders included hemophagocytic lymphohistiocytosis, myopericarditis, pleural effusion, lymphadenopathy and splenomegaly mimicking lymphoma, and spleen infarct. Immunologic abnormalities were frequently observed: anti-nuclear antibodies (43.5%), anti-dsDNA antibodies (21.7%), anti-phospholipid antibodies (17.4%), hypocomplementemia (21.7%), anti-neutrophil cytoplasmic antibodies (13.0%), rheumatoid factor (13.0%), and mixed cryoglobulinemia (8.7%). After 6 months, all patients survived, and 47.8% were in complete remission. In 2 patients, joint involvement evolved into rheumatoid arthritis. Only 5 patients (21.7%) received intravenous immunoglobulin (IVIg), with a good response in the 2 patients with neurological disorders but without efficacy in the 3 others.

Conclusion: HPV-B19 is responsible for a wide variety of systemic manifestations with prominent joint and skin involvement, and diagnosis can be difficult to make. IVIg therapy could be discussed in rare cases whose evolution is not spontaneously favorable, particularly in the setting of peripheral nervous system involvement, but its efficacy should be further investigated in prospective studies.

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Abstract Number: 1324

The Result of Follow-up Interferon-Gamma-Release Assays in Patients with Rheumatic Disease Receiving Biologic Agents in a Japanese Hospital

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Background/Purpose: Active tuberculosis (TB) is one of the most devastating side effects of biologic agents use. Several guidelines for the prevention of biologic agents-related infections have been published and recommended screening tests for latent tuberculosis

infection (LTBI). However, the evidence for the repeated screening tests for LTBI in areas that have a high incidence of active TB and the incidence rate of positive conversion after starting biologic agents in patients with rheumatic diseases is lacking. The value of LTBI screening in non-TNF biologics and switching biologics use are also unknown. Herein, we repot the result of follow-up interferon-gamma-release assays (IGRAs) in patients with rheumatic disease receiving biologic agents.

Methods: We studied retrospectively all patients who had received biologic agents (TNF and non-TNF agents) for the treatment of rheumatic diseases in our department from April 2007 to March 2016. To evaluate the results of follow-up IGRAs for detection of latent and newly developing tuberculosis, 406 patients with various rheumatic diseases were screened prior to biologic therapy initiation for LTBI with T-SPOT.TB and QuantiFERON-TB Gold In Tube assays.

Results : We assessed 275 patients with follow-up IGRA tests. The analysis of the data showed 2.2% (n=6) of IGRA negative conversion and 4.0% (n=11) of IGRA positive conversion (Table 1). There was no difference in patientfs characteristics between converters and non-converter (Table 2). The incidence of active TB after starting biologic agents was 0 % in this study.

Conclusion : Although the evidence for the repeated IGRA and the positive conversion after starting biologic agents in patients with rheumatic diseases is lacking, follow-up IGRA test may be useful to prevent the activation of LTBI in areas that have a high incidence of active TB such as Japan.

Table1. Results of follow-up IGRAs (QFT or T-SPOT)

		no follow up	1 year follow up	2 years follow up	3 years follow up	4 years follow up	5 years follow up	6 years follow up	7 years follow up
Total		131	48	72	50	43	31	29	2
IGRA not positive		122	39	63	41	37	27	26	2
IGRA positive≧1		9	9	9	9	6	4	3	0
QFT negative	→ T-SPOT positive	0	1	0	0	0	2	2	0
QFT indeterminate	→ T-SPOT positive	0	2	0	0	4	0	0	0
QFTpositive	→ QFTpositive	0	1	0	0	0	0	0	0
QFTpositive	→ QFT indeterminate	0	/	0	0	0	0	0	0
QFTpositive	→ T-SPOT negative	0	0	2	0	0	/	/	0
QFTpositive	→ T-SPOT positive	0	0	7	9	2	1	0	0
T-SPOT positive	→ T-SPOT indeterminate	0	/	0	0	0	0	0	0
T-SPOT positive	→ T-SPOT positive	0	3	0	0	0	0	0	0

Converters (Positive to Negative:n=6 Negative to Positive: n=11) ■Positive conversion ■Negative conversion

Table 2. Comparison between converters and non converter

	IGRA positive conversion n=11	IGRA negative conversion n=6	IGRA no conversion n=258	P-value
≧65	3 (27.3%)	0 (0%)	66 (25.6%)	0.487
Female	8 (72.7%)	4 (66.7%)	190 (73.7%)	0.908
TNF inhibitors	4 (36.7%)	5 (83.3%)	146 (56.6%)	0.180
Tocilizumab	5 (45.5%)	0 (0%)	38 (14.7%)	0.019
Abatacept	0 (0%)	0 (0%)	46 (17.8%)	0.251
Ustekinumab	2 (18.2%)	1 (16.7%)	21 (8.4%)	0.206
Tofacitinib	0 (0%)	0 (0%)	6 (2.3%)	1.000
Secukunumab	0 (0%)	0 (0%)	1 (0.4%)	1.000
Switcher	4 (36.7%)	0 (0%)	87 (33.7%)	0.287
Methotrexate	7 (63.6%)	5 (83.3%)	185 (71.7%)	0.687
Steroid	8 (72.7%)	4 (66.7%)	155 (61.1%)	0.726

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Abstract Number: 1325

Musculoskeletal Manifestations in Ebola Survivors

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Background/Purpose: Musculoskeletal complaints are common among survivors of Ebola Virus Disease (EVD) and can have clinical impacts beyond two years post-convalescence. The frequency of these manifestations has been described in several post-convalescent populations, but with very little detail. This study helps detail arthritis manifestations in EVD survivors.

Methods: EVD survivors were evaluated at an established survivors' clinic between 6/29/2015 & 7/2/2015. A trained rheumatologist formally evaluated self-selected survivors, and data were recorded on a standardized form. Summary statistics were then performed.

Results: Forty-six Ebola survivors presented to the survivors' clinic and were evaluated. The mean age was 37.8 years, ranging from 14 to 68 years of age at the time of evaluation. The survivors who presented to the clinic were 54% female and 46% male. Of those whose musculoskeletal complaints could be related to the Ebola infection (i.e., the infection preceded the symptoms), n=42, the mean number of days between being released from the Ebola Treatment Unit (ETU) and development of arthritis symptoms was 46.6 days, SD of 81.5 days. The most striking feature of the Ebola survivors' musculoskeletal symptoms is the high prevalence of enthesitis. Of those examined, 43% had enthesitis in at least one site identified for formal spondyloarthritis examinations after a mean of 202 days of symptoms. Only 7% had one or more swollen joints. Sacroiliac joint tenderness was not a common feature, with only 5% with a positive exam. Twenty-six percent espoused past or present uveitis.

Conclusion: Musculoskeletal complaints are reportedly common among EVD survivors. In a self-selected survivor population, the musculoskeletal complaints are most notable for a predominance of enthesitis with an absence of signs of inflammatory arthritis and sacroiliitis.

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Autoimmune Arthritides, Rheumatoid Arthritis, Psoriatic Arthritis, or Peripheral Spondyloarthropathy, Following Lyme Disease

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Background/Purpose: Lyme arthritis (LA) usually responds to antibiotic therapy, though immune-mediated synovitis may persist after antibiotic treatment, usually confined to a previously infected joint, without systemic symptoms. In contrast, systemic autoimmune arthritides following Lyme disease have not been described. We report here a cohort of 30 patients who developed new-onset rheumatoid arthritis (RA), psoriatic arthritis or peripheral spondyloarthropathy (PsA/SpA), after antibiotic treatment for Lyme disease.

Methods: We reviewed records of all adult patients referred to our Lyme arthritis (LA) clinic over a 13-year period in whom we diagnosed systemic autoimmune arthritis occurring within 2 years of Lyme disease, the interval in which LA may develop after erythema migrans (EM). For comparison, 43 patients enrolled in our LA cohort over a 2-year period were analyzed. IgG antibodies to *Borrelia burgdorferi* and to 3 Lyme-associated autoantigens, endothelial cell growth factor (ECGF), apolipoproteinB-100, and matrix metalloproteinase-10, were measured.

Results: We identified 30 patients who developed new-onset systemic arthritis a median of 4 months after Lyme disease; 60% were seen in the past 3 years. Fifteen had RA, 13 had PsA, and 2 had peripheral SpA. The majority (80%) had prior early Lyme disease, usually EM; all had been treated appropriately with antibiotics. In contrast, only 2 of 43 LA patients had prior EM ($P<0.0001$), and no

patient received antibiotics prior to arthritis onset. All 15 RA patients had symmetrical polyarthritis; 6 had RF or anti-CCP antibodies. The 15 PsA/SpA patients often had axial arthritis, dactylitis, or enthesitis. Of the PsA patients, 9 had skin psoriasis prior to Lyme disease, whereas 4 developed new-onset skin psoriasis and arthritis after the infection. In contrast, the LA patients had monoarticular or oligoarticular arthritis, usually of knees, without SpA features or RA autoantibodies. Most systemic autoimmune patients had positive tests for *B. burgdorferi* IgG antibodies by ELISA, but had much lower titers than LA patients ($P<0.0001$). Moreover they had lower frequencies and levels of Lyme-associated autoantibodies, particularly anti-ECGF ($P\leq0.02$). Prior to our evaluation, the patients often received additional antibiotics for presumed Lyme arthritis without benefit. We prescribed anti-inflammatory therapies, usually DMARDs, resulting in improvement.

Conclusion: Although systemic autoimmune arthritis may follow Lyme disease by chance, onset within months suggests that *B. burgdorferi* infection may be a pro-inflammatory trigger. Thus, when inflammatory arthritis develops in the context of Lyme disease, clinicians need to distinguish among three possibilities: patients who have active infection in joints, those who have post-infectious Lyme arthritis, and those who have developed another form of arthritis. Onset of polyarthritis after antibiotic-treated EM, prior psoriasis, or low-titer *B. burgdorferi* antibodies may be distinguishing features. As Lyme disease is now epidemic in parts of the U.S., awareness of this arthritis spectrum is essential in preventing delays in appropriate diagnosis and treatment.

Disclosure: S. Arvikar, RRF, 2; **J. Crowley**, None; **K. Sulka**, None; **A. C. Steere**, NIH, 2.

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Patients with Chikungunya Fever Have Increased Serum Levels of Proinflamatory Cytokines

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Background/Purpose: Chikungunya fever (CHIK) is an arboviral disease characterized by sudden onset of fever and incapacitating polyarthralgia. Some patients develop chronic articular symptoms but the mechanisms by which this occurs and possible biomarkers are poorly understood. Interleukin (IL)-17A, IL-21, IL-22, IL-27 and IL-29 have been implicated in the pathogenesis of inflammatory joint diseases, such as rheumatoid arthritis. Therefore, the purpose of this study was to assess the serum levels of these cytokines and to verify any association with clinical manifestations in CHIK-patients.

Methods: We evaluated 75 patients (58 female, mean age 52.7 ± 13.4 years old) with clinical manifestations of Chikungunya fever and sorological confirmation with IgM and/or IgG CHIK antibodies. All included patients had articular manifestation on the evaluation. From these patients, 30 had previous inflammatory rheumatologic diseases (17 rheumatoid arthritis, 6 systemic lupus erythematosus and 7 spondyloarthritis). Forty-nine age and gender matched healthy individuals served as controls.

Anti-CHIKV IgM and IgG antibodies were tested by ELISA (Euroimmun). IL-17A, IL-21, IL-22, IL-27 and IL-29 serum levels were measured with specific ELISA kits (eBioscience), according to the manufacturer's protocol. The association between cytokines levels and clinical parameters were analyzed. Statistical analyses were performed using GraphPad Prism (version 6.0) and results are expressed as the median and interquartile range.

Results: Serum IL-17A, IL-27 and IL-29 were detected in most of the patients but not in controls. Instead, IL-21 was only detected in healthy individuals' serum but not in CHIK-patients. Serum IL-22 was not detected in both groups. There were no differences in IL-17A, IL-27 and IL-29 levels between rheumatic and non-rheumatic patients.

IL-27 serum levels were higher in patients with chronic symptoms (median 395.9 [62.5-1065] pg/ml) compared with acute/subacute patients (median 62.5 [62.5-451.3] pg/ml), p=0.008). In CHIK-patients, we found significant correlations between IL-27 levels and tender joints (r=0.32, p=0.006) and swollen joints (r=0.26, p=0.03). Also IL-17A levels were associated with swollen joints (r=0.32, p=0.006). Furthermore, patients who reported arthritis had higher IL-17 A levels (median 24.14 [20.6-27.1] pg/ml) than those who did not (median 20.15 [3.9-22.5] pg/ml).

Conclusion: Increased serum levels of IL-17 A, IL-27, and IL-29 were present in CHIK-patients and there was an important association with articular manifestations. This finding may reflect the inflammatory nature of CHIK infection in patients with joint symptons and may implicate the role of these cytokines in the pathophysiology of the disease, similar to what occurs in other inflammatory arthritis.

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Abstract Number: 1328

Infective Endocarditis with Septic Arthritis: A Single-Center Experience

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Background/Purpose: Echocardiogram is frequently performed on patients presenting with septic arthritis (SA) but rarely demonstrates evidence of infective endocarditis (IE). Similarly, while patients with IE often develop musculoskeletal manifestations (including arthralgias, myalgias, and osteomyelitis) concomitant SA and IE is uncommon. The prevalence and presenting features of IE among patients with SA have not been well-defined. The purpose of this study is to describe the utilization of echocardiogram and clinical features and outcomes of patients with SA found to have endocarditis.

Methods: We conducted a retrospective cohort study of patients 18 years and older admitted to a single tertiary care center from 1998 to 2015 with septic arthritis. Baseline characteristics, clinical features, microbial profiles, rates of operative intervention, length of hospital stays (LOS), and 60-day readmission rates were determined. Patients were stratified on the basis of whether echocardiogram was performed and whether it demonstrated evidence of IE.

Results: Of 750 patients with SA, transthoracic echocardiogram (TTE) or transesophageal echocardiogram (TEE) was performed in 293 patients (39%) and found to be positive in 16 patients (2%). TTE and TEE were obtained more often in older patients (mean age 60.4 versus 56.6; p = 0.004) with higher peripheral white blood cell (WBC) counts (12.8 versus 10.6; p <0.0001) and synovial fluid WBC counts (106.8 versus 70.6; p = 0.003 (Table1). TTE and TEE were more frequently performed for those with longer LOS (13.7 versus 7.4 days; p <0.0001) who underwent operative intervention (p = 0.05), were discharged to rehabilitation (p <0.001), and died within 30 days post-discharge (p < 0.001). Presenting features, comorbidities, and outcomes did not differ significantly between those with and without IE. Echocardiograms were more frequently positive in those with SA transferred from outside hospitals as compared to those who were not (68.75% versus 31.25%; p = 0.002). Methicillin sensitive Staph aureus (MSSA) was the most bacterial cause of SA with associated endocarditis.

Conclusion: In this study of SA, we were unable to identify clinical features and outcomes that distinguished those with or without IE other than higher rates of MSSA infection and preceding outside hospital transfers. Echocardiograms were more frequently obtained in sicker patients as implied by their presentation and eventual outcomes; however, IE was not more frequently identified in such patients. Additional study is needed to determine which factors may predict the presence of IE in patients with SA and which may benefit most from echocardiography.

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Abstract Number: 1329

Efficacy and Safety of Biologics in Relapsing Polychondritis: A National Multicenter Study in France

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Background/Purpose: No study has compared the efficacy and the safety of biologics in a large relapsing polychondritis (RP) cohort. This is the aim of the present study.

Methods: We conducted a national multicenter retrospective study in France including adult patients treated with biologics for RP from 2001 until July, 2015. Data were recorded at the time of biologic exposure (T0), at 3 and 6 months, and then every 6 months. Follow-up ended at biologic discontinuation or at the date of last available data. Efficacy outcomes were the intention-to-treat rates of partial (PR, defined by clinical improvement with persistent disease activity) or complete response (CR, defined by no clinical activity) during the first 6 months of exposure, and the evolution of the corticosteroid (CS) doses between T0 and month 6 for patients having a >6-month exposure to each biologic. Adverse drug reactions (ADRs) were described. We also compared the persistence of biologics (excluding rituximab) through Kaplan-Meier curves and the reasons for discontinuation. Factors associated to a PR or CR during the first 6 months of exposure to first-line biologics were investigated using a multivariate logistic regression model.

Results: The cohort included 41 patients. Mean age was 46.9 ± 12.5 years and 53.6% were females. Median time from RP diagnosis to

first-line biologic T0 was 26.5 months. All patients satisfied to McAdam, Damiani and Michet diagnostic criteria. All but 2 patients had an active disease at first biologic prescription. Reasons for biologic initiation were CS dependency (n=28), CS resistance (n=11) or ADR to previous treatments (n=3). First-line biologics were TNF inhibitors (n=30), tocilizumab (n=5), rituximab (n=4), anakinra and abatacept (n=1 each). Twenty-eight patients were exposed to at least 2 lines of biologics (because of insufficient efficacy in14, relapses in 8 or adverse drug reactions in 9). In total, 105 biologic prescriptions were recorded (TNF inhibitors, n=60; tocilizumab, n=17; anakinra, n=15; rituximab, n=7; abatacept, n=6). Outcomes are presented in Table 1. PR or CR rate during the first 6 months was 62.9% while CR rate was 19.0%. There was only a modest reduction in the median CS dose. ADRs were mostly infections (n=42) and reaction at site of injection for subcutaneous biologics (n=12). Persistence was comparable among biologic classes (p=0.77). Among TNF inhibitors, the highest persistence was observed on adalimumab and the lowest for etanercept (log-rank test: p=0.02). In multivariate analysis, the single factor associated to PR or CR during the first 6 months of exposure to first-line biologic treatment was a history of chondro-sternal inflammation (OR: 5.75; 95% CI: 1.27-26.07; p=0.02) and there was a trend for nasal or auricular inflammation at biologic initiation (OR: 4.30; 95% CI: 0.93-19.78, p=0.09).

Conclusion: Overall, biologics are an interesting option for RP treatment.

Table 1. Efficacy and adverse drug reactions of biologics prescribed for relapsing polychondritis in 41 patients.

Biologics	PR or CR at 6 months, n (%)	CR at 6 months, n (%)	Variation in CS dose at M6, mg PEQ, median (range)	Follow-up, months, median (range)	Discontinuation of biologic				
					Overall	Insufficient efficacy	Loss of efficacy	ADR	Stable CR
Overall (n=105)	66 (62.9%)	20 (19.0%)	-5.0 (-72.5; +70.0)	6.0 (0.1-80.8)	77 (73.3%)	36 (34.3%)	19 (18.1%)	22 (20.9%)	1
TNF antagonists (n=60)	38 (63.3%)	14 (23.3%)	-5 (-53; +70)	6.0 (0.4-80.8)	47 (78.3%)	23 (38.3%)	15 (25.0%)	8 (13.3%)	1
Infliximab (n=20)	12 (60.0%)	7 (35.0%)	-5 (-50; +70)	6.5 (0.4-80.8)	16 (80.0%)	7 (35.0%)	6 (30.0%)	3 (15.0%)	0
Adalimumab (n=25)	16 (64.0%)	5 (20.0%)	-7.5 (-53; +10)	8.0 (0.4-71.7)	18 (72.0%)	6 (24.0%)	7 (28.0%)	5 (20.0%)	1
Etanercept (n=11)	8 (72.7%)	0	-5 (-50; +0)	5.5 (0.7-36.7)	11 (100%)	8 (72.7%)	2 (18.2%)	2 (18.2%)	0
Golimumab (n=3)	2 (66.7%)	2 (66.7%)	-20	3.8 (3.4-7.2)	1 (33.3%)	1 (33.3%)	0	0	0
Certolizumab (n=1)	0	0	-	2.9	1 (100%)	1 (100%)	0	1 (100%)	0
Tocilizumab (n=17)	12 (70.6%)	2 (11.8%)	-1 (-72.5; +0)	3.7 (0.4-36.2)	10 (58.8%)	4 (23.5%)	2 (11.7%)	4 (23.5%)	0
Anakinra (n=15)	8 (53.3%)	2 (13.3%)	-12.5 (-20; +0)	2.6 (0.3-63.8)	13 (86.7%)	5 (33.3%)	0	7 (46.7%)	0
Rituximab (n=7)	5 (71.4%)	1 (14.3%)	-3 (-30; +5)	6.0	3 (42.8%)	3 (42.8%)	0	0	0
Abatacept (n=6)	3 (50.0%)	1 (16.7%)	-16 (-40; +0)	9.5 (0.1-37.1)	6 (100%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	0

Abbreviations: ADR, adverse drug reaction; CR, complete response; PR, partial response.

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Abstract Number: 1330

Clinical Presentations of Relapsing Polychondritis: More Than a Swollen Ear

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Background/Purpose: Relapsing polychondritis (RP) is a rare and in some cases fatal autoimmune disease that can affect multiple organs including cartilaginous structures. The disease is unpredictable and clinical manifestations may be variable resulting in a delay to diagnosis. Patients may have involvement of organs other than the nasal bridge and ear, including larynx, tracheobronchial tree, joints, vasculature, heart valves and kidneys. In this report we present the results of the largest survey to date evaluating disease patterns in an international cohort.

Methods: Data was acquired using an internet-based questionnaire aimed at cataloguing a variety of possible clinical presentations of RP. We obtained an Office of Human Subjects Research Protections 'Exclusion from IRB Review' certificate. The data was anonymous therefore met criteria for exclusion per the requirements of 45 CFR 46 and NIH policy. The Relapsing Polychondritis Awareness and Support Foundation administered the survey by email solicitation to patients that previously agreed to be contacted and by posting the link online. The survey was open to the public on 2/23/2016 and the data for this analysis was extracted on 4/11/2016.

Results: 193 surveys total were captured and 13 were excluded either for age less than 18 or no age reported**.** 180 surveys were included in this analysis. The mean age was 49.5 (SD 11.9). 86.5% were female. 91% identified as "white" and 31.5% reported country of origin other than the USA. The approximate mean age at diagnosis was 43.4 years (SD 12.7). A non-rheumatologist physician made the diagnosed in 47.5%. 54% of the patients saw more than 3 physicians prior to establishing a diagnosis and only 15% underwent cartilage biopsy to support the diagnosis. 49% of the patients had symptoms for more than 3 year before diagnosis. 55% of patients went to the emergency room prior to diagnosis because of RP symptoms. Common initial symptoms included dizziness, eye inflammation, constochondritis, and shortness of breath, nose pain, and voice changes. Some patients also reported fatigue, flu-like symptoms, fever and difficulty swallowing as initial symptoms. Complications of RP included disability (25%), tracheomalacia (16%) and intubation related to RP (12%).

Conclusion: This is the largest RP study to collate patient and disease characteristics in an international self-reported cohort. We found that the majority was female and there was a high incidence of initial symptoms other than ear and nose inflammation. The time to diagnosis was greater than 5 years. We learned that non-rheumatologist physicians commonly encounter patients with RP and sometimes these encounters occur in the emergency room. We also found that RP could have devastating complications including tracheomalacia and disability. Physicians must be alert to underappreciated presenting symptoms such as voice changes and shortness of breath. The limitations of this study include both the inability to validate self-reported claims of a diagnosis of RP and recall bias. The strength of our study includes the anonymous web-based strategy, which enabled us to capture a larger, and less geographically constrained, population.

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Abstract Number: 1331

Disease Patterns and Long Term Outcome Amongst Patients with Relapsing Polychondritis – Single Centre Experience

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Background/Purpose: Relapsing polychondritis (RP) is a rare autoimmune disorder characterized by cartilage inflammation and damage. Chronic RP may lead to sequelae due to cartilage tissue damage. There is no diagnostic test for RP and prompt diagnosis remains a challenge due to the marked variation in initial clinical presentation. We describe disease patterns amongst patients with RP, and identify factors that correlate with diagnostic delay and poor outcome.

Methods: This was a retrospective cohort study of RP patients followed up for 20 years in our systemic vasculitis clinic. Patient data was retrieved from June 1995 until 31stDecember 2015, or until patient's last follow-up date. Data recorded include patients' demographic, initial clinical presentations, therapeutic regimes, and long-term outcome. Data analysis was performed using SPSS Version 23.0

Results: 45 patients were identified. 68.9% were female. 39 patients (86.7%) were Caucasian, 5 (11.1%) Afro-Caribbean and 1 (2.2%) Asian. Median age of disease onset was 39.0 (29.5, 54.0) years. Median age of RP diagnosis was 42.0 (34.5, 60.5) years. Median diagnosis delay was 19.0 (5.0, 65.0) months. Most had ear involvement at presentation (73.3%, n=33), followed by chest wall or peripheral joint pain (57.8%), eyes (53.3%), nose (42.2%), and airways (28.9%). Mean number of initial organ presentation was 2.6 ± 1.04. All patients received steroid as therapeutic agent. There was wide heterogeneity in terms of therapeutic agents used, including methotrexate (31.1%), azathioprine (26.7%), hydroxychloroquine (13.3%), mycophenolate (13.3%), and IV cyclophosphamide (11.1%). Mean number of drugs used at any time was 1.9 ± 1.00. Long-term sequelae involved chronic pain (64.4%) and drugs related complications (57.8%). 57.8% had ears damages, followed by eyes damages (42.2%), and airway damages (40%). Mean number of organ damages was 1.7 ± 1.37. Higher number of initial organ presentation (r= 0.34, p= 0.022) and younger age of disease onset (r= -0.40, p= 0.006) correlated with diagnosis delay. Male gender correlated with airway involvement (r= 0.42, p= 0.004). There was positive correlation between airway involvement with higher number of organ damage (r= 0.30, p= 0.047). A weak correlation was noted between initial involvement of chest wall or peripheral joint pain with chronic pain complication (r= 0.34, p= 0.024). 30 patients (66.7%) remained under active follow-up, with 11 patients (24.4%) lost to follow-up, and 4 deaths occurred with cause unknown (8.9%).

Conclusion: Our study revealed higher number of initial organ presentation, and younger age of disease onset correlated with potential diagnosis delay. Male gender with airway involvements correlated with higher number of organ damages and poorer outcome. Multicenter registries may lead to a better understanding of this disease.

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Abstract Number: 1332

Severe Complications and Immunosuppressive Treatments in 33 Patients with Relapsing Polychondritis

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Background/Purpose: Since relapsing polychondritis (RP) is a rare disease as the prevalence rate is 0.0004% in Japan, its severe

complications, prognosis and immunosuppressive therapies have not been fully understood or established. We recently reported association of disease onset and 3 HLA haplotypes (DQB1*05:02, B*67:01 and DRB1*16:02 in linkage disequilibrium) in 102 patients with RP (Terao C et al. Rheumatology (Oxford) doi: 10.1093/rheumatology/kew233), however, we did not survey clinical information such as treatment course. In the present study, we investigated detailed clinical information of 33 patients in a single center.

Methods: We examined medical records of 33 patients with RP who satisfied Damiani's criteria. HLA haplotypes and anti-type II collagen antibodies were assayed in some of these patients.

Results: Tracheobronchial (TB), central nerve system (CNS), and aortic complications were seen in 17 (51.5%), 4 (9.1%), and 2 (6.0%) patients, respectively. One (3.0%) died, and two (6.0%) with CNS lesions failed into bed-bound status. Recurrence was seen in 25 (75.8%). Positivity of HLA-DQB1 05:02 was 17.6% (3/17), higher than 2.6% in healthy Japanese. Two of the 3 patients with DQB1 05:02 had TB lesions and one needed TCZ. B 67:01 and DRB1 16:02 were positive in 2 patients (11.8%) and linked with DQB1 05:02. Anti-type II collagen antibodies were seen in 29.2% (7/24). Methotrexate (MTX), azathioprine (AZP), intravenous cyclophosphamide (IVCY), infliximab (IFX) and tocilizumab (TCZ) were used along with glucocorticoid in 10 (30.3%), 8 (24.2%), 5 (15.2%), 5 (15.2%) and 4 (12.1%), respectively. Three patients with TB lesions and 2 with CNS lesions were treated with IVCY, and response rates were 100% and 50%, respectively. IFX was used and partially effective in 1 with TB lesion, 1 with CNS lesion, and 3 patients complicated with Behçet disease. TCZ was used in 3 patients with TB lesions, and response rate was 33%.

Conclusion: The linkage with certain haplotypes of HLA and the positivity of autoantibodies (~30%) consolidate that RP is an autoimmune disease. IVCY showed a good response in patients with TB lesions in the present study. The prognosis of patients with CNS lesions was poor. Further collection of cases is required to elucidate pathophysiology and improve treatments.

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Abstract Number: 1333

Relevance of Granulomatous Presentation for the Diagnosis and Outcome of Uveitis: Retrospective Case-Control Study of 251 Patients

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Background/Purpose: Findings of ophthalmologic examination can guide the diagnostic management of uveitis. Granulomatous presentation is commonly associated with peculiar causes, including infections, eye-restricted diseases, or systemic diseases such as sarcoidosis, multiple sclerosis or bowel inflammatory diseases, but large series are lacking to confirm this trend. The present study aimed to evaluate relevance of granulomatous presentation for the etiological diagnosis of uveitis.

Methods: Single-centre retrospective study including patients referred from the Ophthalmology department to Internal Medicine practitioners for etiological diagnosis of uveitis. Uveitis related to pure ophthalmological diseases or occurring during the course of an already diagnosed pathology were excluded. Granulomatous presentation was defined by the aspect of keratic precipitates and/or the presence of iris nodules. Granulomatous uveitis were compared to non-granulomatous uveitis.

Results: One hundred and thirty-one consecutive granulomatous uveitis were compared to 120 non-granulomatous uveitis. Mains ophthalmologic findings (i.e. (bilateralism, topography, frequency of panuveitis, cystoid macular edema and chronicity)) were

comparable between both subgroups. In contrast, vitreous snowballs were more frequent in granulomatous uveitis compared to non-granulomatous uveitis (32% vs. 21%, p=0.04). Increased serum angiotensin-converting enzyme titer, a positive latent tuberculosis test (purified protein derivative skin test or Interferon-gamma releasing assay) and chest CT scan findings were comparable between both groups. The frequency of lymphocytic alveolitis on bronchoalveolar lavage and granulomas on bronchial biopsies were also similar. At the end of the diagnostic workup which was comparable between groups, the rate of uveitis of undetermined origin was similar between both groups (35% vs. 32%, p=0.68), as well as the spectrum of causes: sarcoidosis (16% vs. 10%, p=0.19) and uveitis associated with latent tuberculosis (34% vs. 23%, p=0.09). In contrast, uveitis associated with HLA B27 antigen (6% vs. 0%, p=0.006) and Behçet's disease (9% vs. 0%, p<0.001) were only observed in the non-granulomatous group. Rather than the granulomatous presentation of the anterior chamber, the combination of granulomatous uveitis with vitreous snowballs or with peripheral multifocal choroiditis was significantly associated with proven or presumed sarcoidosis (p=0.001 and p=0.006, respectively). Finally, response to treatment and relapse rate were comparable between both groups.

Conclusion: The granulomatous presentation of uveitis alone is not sufficient to guide the diagnostic management of uveitis and does not impact treatment response and outcome. In contrast, its association with vitreous snowballs or peripheral multifocal choroiditis are highly suggestive of sarcoidosis.

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Abstract Number: 1334

Contribution of Diagnostic Investigations in the Management of Uveitis: Retrospective Analysis of 300 Patients

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Background/Purpose: Uveitis represents a diagnostic and therapeutic challenge, as well as an economic one, due to its heterogeneous presentation, multiple underlying causes and lack of well-codified diagnostic procedures. Furthermore, a third of uveitis is considered idiopathic. The aim of this study was to evaluate the contribution of diagnostic investigations in the management of uveitis in a specialized centre.

Methods: Single-centre retrospective study including patients referred from the Ophthalmology department to Internal Medicine practitioners for etiological diagnosis of uveitis. Uveitis related to pure ophthalmological diseases or occurring during the course of an already diagnosed pathology were excluded. All patients had a complete ophthalmologic examination followed by clinical and paraclinical exams. All diagnoses were established according to recent international diagnostic criteria.

Results: Three hundred consecutive patients were included (mean age 48 ± 30 years, men 49%). The main features of uveitis were: bilateral 56%, anterior 33%, posterior 8%, panuveitis 30%, granulomatous 44%, chronic 39%. Forty-three percent of patients had at least one clinical extra-ophthalmologic manifestation, such as arthralgia (17%) or general symptoms (15%). Regarding paraclinical exams, chest CT scan was performed in 94% of cases, and showed abnormal findings suggestive of pulmonary or mediastinal sarcoidosis in 39%. Factors associated with having an abnormal CT scan were blood lymphocytopenia (p=0.002) and increased angiotensin-converting enzyme (ACE) over 1.5 the upper limit of normal (ULN) (p=0.007). Salivary gland biopsy, performed in 76% of cases, led to the identification of granuloma in only 6%. Bronchoscopy was performed in 61% of cases, with bronchial biopsies showing granuloma in only 8% whereas bronchoalveolar lavage fluid (BALF) analysis revealed alveolar lymphocytosis suggestive of

sarcoidosis (lymphocytes >15% and/or CD4/CD8 ratio >3.5) in 27%. Patients with granuloma on biopsies always had abnormalities on CT scan whereas 37% of patients with alveolar lymphocytosis had normal CT scan. Factors associated with having contributive BALF were vitreous snowballs (p=0.003), peripheral multifocal choroiditis (p=0.002), lymphocytopenia (p=0.03), and a >1.5 ULN ACE titer (p<0.0001). Cerebral MRI was performed in 56% of cases and was abnormal in 14%. Factors associated with abnormal MRI were retinal vasculitis (p=0.03) and a >1.5 ULN ACE titer. Lumbar puncture was performed in 44% but mainly showed non relevant abnormalities in 31%. Finally, at the end of the diagnostic workup, the main causes identified were uveitis associated with latent tuberculosis in 25%, sarcoidosis in 18% or Behçet's disease in 5%. However, 37% of uveitis remained of undetermined origin. Baseline features from the latter did not differ from those in which a specific diagnosis was retained.

Conclusion: Despite an extensive clinical and paraclinical workup, an important proportion of uveitis remains of undetermined origin. Identification of factors associated with abnormal investigations might improve the optimal diagnostic workup adapted to each patient's characteristics.

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Abstract Number: 1335

Long–Term Safety and Efficacy of Adalimumab in Patients with Non-Infectious Intermediate, Posterior, or Panuveitis in an Ongoing Open-Label Study

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Background/Purpose: To evaluate the long-term safety and efficacy of adalimumab (Humira®) in patients with non-infectious intermediate, posterior, or panuveitis (NIPPU) in an open-label clinical trial extension, VISUAL-III.

Methods: Adults who met treatment failure or study completion criteria in VISUAL-I/VISUAL-II and opted to enroll in VISUAL-III received adalimumab 40-mg every other week. Corticosteroids and/or immunosuppressive therapy were permitted as needed. Patients that discontinued VISUAL-I/VISUAL-II due to treatment failure had active disease at VISUAL-III entry. Efficacy endpoints included new inflammatory lesions, anterior chamber (AC) cell, and vitreous haze (VH) grades from study entry (week-0) through week-54 (inactive uveitis) and week-78 (active uveitis). Corticosteroid daily dose was measured over time. Adverse event rates were reported from first adalimumab dose in VISUAL-I/II/III until the data cutoff of 31-August-2015.

Results: Intent-to-treat analyses included 243 (active) and 128 (inactive) uveitis patients at study entry. At week-54, no new

inflammatory lesions relative to baseline, AC cell and VH grades of ≤0.5+ were observed in 98.5%, 98.5% and 92.6% of inactive uveitis patients, respectively. At week-78, no new inflammatory lesions relative to week-8, AC cell and VH grades of ≤0.5+ were observed in 96.3%, 91.0% and 87.8% of active uveitis patients, respectively. Mean systemic corticosteroid daily dose decreased from 12.7 to 3.68 prednisone equivalents by year 1 for patients with active uveitis and remained stable from 1.48 to 1.21 prednisone equivalents for inactive patients. Adverse events rates (577 AE/100PY and 19.6 SAE/100PY) were comparable to the VISUAL-I and VISUAL-II trials.

Conclusion: Long-term adalimumab treatment reduced ocular inflammation and corticosteroid burden in NIPPU patients and demonstrated a safety profile consistent with other indications and previous VISUAL studies.

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Abstract Number: 1336

Tocilizumab for Uveitic Cystoid Macular Edema Refractory to Other Synthetic and Biological Immunosuppressive Drugs. Multicenter Study of 25 Patients

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Background/Purpose: Our objective was to evaluate the efficacy and safety of Tocilizumab (TCZ) in a series of patients with refractory CME.

Methods: A Multicenter study of 25 patients with CME secondary to non-infectious uveitis who had inadequate response or intolerance to traditional treatment with corticosteroids and at least one conventional immunosuppressive drug including in most cases biological therapy. CME was defined by (OCT >300 µm). The outcome variables were the degree of inflammation of the anterior chamber and vitreous, visual acuity and macular thickness. Comparison of continuous variables was performed using theWilcoxon test.

Results: 25 patients (17 females/8 males) with CME were studied. Mean age of 33.6±18.9 years. The associated disease was: juvenile idiopathic arthritis (n=9), Behçet's disease (n=7), Birdshot retinochoroidopathy (n=4), idiopathic (n=4), sarcoidosis (n=1). The ocular pattern was: panuveitis (n=9), anterior uveitis (n=7), posterior uveitis (n=5), intermediate uveitis (n=4). Most patients had bilateral involvement (n=24). Prior to TCZ patients received: intraocular corticosteroids (n=22), iv. methylprednisolone (n=7), methotrexate (MTX) (n=19), cyclosporine A (CSA) (n=17), mycophenolate (n=4), azathioprine (n=2), cyclophosphamide (n=1), sulfasalazine (n=1), daclizumab (n=1), acetazolamide (n=1), thalidomide (n=1), leflunomide (n=2), infliximab (n=8), adalimumab (n=19), etanercept (n=2), golimumab (n=2), rituximab (n=2), abatacept (n=3), anakinra (n=1). TCZ administration schedule was 8 mg/kg/4 weeks iv. in all patients except in one that was administered every 2 weeks. TCZ was used in monotherapy (n=11) or combined with conventional immunosuppressive: MTX (n=6), CsA (n=5) and leflunomide (n=1). A statistically significant reduction was observed in macular thickness from 415.68±177.15 to 259.1±499.5 microns; p=0.00009 during the first year of treatment with TCZ. Most of intraocular inflammation parameters showed also a rapid improvement after initiation of TCZ (TABLE). Visual acuity improved in a statistically significant way from 0.39±0.31 at baseline to 0.54±0.33 after one year of treatment (p =0.0002). After a mean follow up of 12.7±8.34 months only minor side effects were observed: nausea (n=1), viral conjunctivitis and bullous impetigo (n=1). Remission was achieved in 14 patients. The prednisone dose was reduced from 15.9±13.6 at baseline to 3.1±2.3 after a year of treatment; p=0.002.

Conclusion: Treatment with TCZ seems an effective and safe treatment in patients with uveitic CME refractory to other synthetic and biological immunosuppressive drugs **TABLE**

	Baseline	1st week	2nd week	1st month	3rd month	6th month	1st year
Visual acuity mean ± SD	0.39±0.31	0.4±0.31	0.45±0.31*	0.51±0.3*	0.57±0.32*	0.56±0.33*	0.54±0.34*
Anterior chamber cells [median (IQR)]	1 (0-1)	0.5(0-1)*	0 (0-1)*	0 (0-0)*	0 (0-0)*	0 (0-0)*	0 (0-0)*
Vitritis [median (IQR)]	1 (0-2)	1 (0-1.5)	0 (0-1)*	0 (0-0.5)*	0 (0-0.5)*	0 (0-0)*	0 (0-0)*
OCT (microns) mean ± SD	415.68±177.15	413.3±162.9*	388.06±158.1*	330.8±104.2*	290.26±76.53*	275.07±73.8*	259.1±49.51*

* p <0.05 compared with basal data

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Effectiveness of Certolizumab Pegol in Patients with Uveitis Refractory to Other Tumor Necrosis Factor Inhibitors. Report of 22 Cases

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Background/Purpose: Refractory uveitis may requiere the use of biological therapy, especially tumour necrosis factors inhibitors (TNFi), being the most currently used infliximab and adalimumab. However, in cases of failure or adverse events related to these drugs, another TNFi such as certolizumab pegol (CZP) could be an effective option (1) as we have previously reported (2). Moreover, given that CZP does not cross the placental barrier (3), this drug could be a safer option in women considering pregnancy. Our purpose is to study the efficacy and safety of CZP in patients with uveitis refractory to other immunomodulatory treatments

Methods: Observational, multicentric, retrospective study. All the patients with a diagnosis of uveitis, confirmed by an Ophtalmologist, treated with CZP for at least 6 months were included. Variables analyzed: age, sex, diagnosis, type of uveitis and duration since the first uveitis episode; previous treatment (NSAID, disease-modifying anti-rheumatic drugs (DMARDs), immunossuppressive or biological therapy); outcome and time to follow-up

Results: Forty eyes of 22 patients (10 women); age 44.6 ± 12.6 (range 29-71 years) were included in the study. Diagnosis were: 8 ankylosing spondylitis; 5 Behçet disease; 4 psoriatic arthritis; and one of each of the following (nonradiographic axial spondyloarthritis, rheumatoid arthritis, juvenile idiopathic arthritis, punctate inner coroiditis, and idiopathic panuveitis). Type of uveitis: 10 anterior, 7 panuveitis, 4 posterior and 1 intermediate; mean disease duration of 139.8 ± 112.9 months (range 5-420). 86.4% patients had received previous biological therapy (59% ≥ 2 biological agents). 72.7% received CZP with no concomitant DMARD treatment (only 6 patients received concomitant DMARD: 3 methotrexate and 3 azathioprine). In four women CZP was indicated due to pregnancy desire. In the remaining cases CZP was started due to inefficacy to previous treatment except for 2 cases that was by adverse event. After a follow-up of 17.3 ± 11.6 months (range 6-48), 16 patients are still on CZP treatment. Eighteen eyes showed improvement of visual acuity (45%), 17 remained stable and 5 worsened. One patient had retinal vasculitis at baseline that resolved after 1 month of CZP. During the follow-up only 3 patients suffered 7 uveitis flares and 2 required switch to tocilizumab. No serious adverse events were reported. Only 4 cases withdrawn treatment: 2 due to worsening of articular symptoms but with no uveitis activity; 1 due to macular edema and 1 due to persistent uveitis activity

Conclusion: CZP has demonstrated effectiveness in patients with refractory uveitis to previous TNFi treatment, showing a safety profile that even allows its use in patients with pregnancy desire References: 1. Rudwaleit M et al Arthritis Care Res (Hoboken). 2016; 68: 838-44. 2. Llorenç V et al. Ocul Immunol Inflamm. 2016; 24: 167-72. 3. Porter C. J Reprod Immunol. 2016; 116: 7-12

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Abstract Number: 1338

Use of Subcutaneous Golimumab in Autoimmune Inner Ear Disease

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Background/Purpose: Autoimmune Inner Ear Disease (AIED) is characterized by rapidly progressive sensorineural hearing loss accompanied by tinnitus, with or without vertigo, which may progress to deafness if untreated. While corticosteroid (CS) therapy may

be effective in 50-70% of cases, there is often difficulty in tapering CS without decline in hearing and there are significant associated side effects. Multiple immunosuppressive regimens have been used with mixed results. A recent open label trial demonstrated intratympanic (TM) Golimumab, a tumor necrosis-α inhibitor, to be effective in stabilizing hearing loss and allow 7 of 10 long-term CS-dependent patients to completely taper off of prednisone. In this retrospective case series, we report our experience with the use of subcutaneous (SC) Golimumab.

Methods: Patients were diagnosed by experienced Otologists at House Ear Clinic and followed by Rheumatology at Cedars-Sinai for co-management of immunomodulatory therapy, from January 2013 to April 2016. Medication lists and hearing tests were reviewed throughout treatment with off-label SC Golimumab.

Results: Five patients were identified with AIED with hearing loss initially responsive to CS and difficulty with sustaining hearing with taper. There were 3 male and 2 female patients, with a mean age of 57.4. In 2 patients, 1 male and 1 female, there was previous success with steroid taper and hearing stability during the TM Golimumab trial in 2012. Patient 1 was steroid dependent (30 mg QD) for 7 years prior to trial and was able to taper off. Once hearing declined after 15 months, she was started on SC Golimumab. She continues to be maintained off steroids and showed improvement in left ear word recognition scores. Patient 2 was able to taper off steroids in the TM trial. He needed to restart steroids 16 months after trial at 60 mg due to worsening hearing loss and tinnitus. He started SC Golimumab and was able to taper off steroids within 13 months with improvements in both hearing loss and tinnitus. Patient 3 required steroids off and on for 8 years due to hearing loss and severe attacks of vertigo. When he started SC Golimumab he was on Prednisone 20 mg and was able to taper to 4 mg in 11 months, with improvement in speech recognition in both ears. He has been free of severe vertigo attacks, now with only mild episodes. Patient 4 had symptoms of hearing loss, tinnitus and vertigo and was on Prednisone 11 mg when she started SC Golimumab. She was able to taper off completely within 12 months, with improvement in speech discrimination score in both ears and improvement in all her symptoms. Patient 5 was on and off steroids for several years due to hearing loss and vertigo. After initiation of SC Golimumab, he noted increase in speech recognition in the 2ndmonth of therapy, improvement in vertigo and has been maintained off steroids. Golimumab was well-tolerated in all patients without significant complications or side effects to date.

Conclusion: The preliminary data suggests that treatment with SC Golimumab may be considered a therapeutic option for patients with AIED, and is useful as a steroid-sparing agent. Larger studies are warranted to further explore the therapeutic potential of Golimumab in AIED.

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Rheumatic Immune Related Adverse Events of Checkpoint Therapy for Cancer: Case Series of a New Nosologic Entity

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Background/Purpose: The introduction of immunotherapy with biologic agents targeting immunologic checkpoints (i.e. CTLA4 and PD-1/PDL-1) have yielded impressive gains for cancer patients. These agents exploit suppressor and regulatory pathways boosting integrated immunity against tumors but are attended by a spectrum of immune related adverse events (irAEs) most notably affecting dermatologic, pulmonary, gastrointestinal and endocrine systems. Reports of rheumatic complications have been sparse and not systematically reported. We have developed a multidisciplinary virtual clinic to evaluate and manage irAEs and now report our initial findings.

Methods: In February 2016 an interdisciplinary group was created to manage irAEs resulting from patients on approved and

experimental immune based therapies for cancer. Patients were identified by treating oncologist and then triaged by a designated advanced practitioner and seen in a facilitated fashion. Two designated rheumatologists saw all patients. A detailed retrospective review of the EMR was performed, including: gender, date of birth, age at diagnosis of malignancy, type and stage of malignancy, prior treatment (chemotherapy, radiation, surgery), checkpoint inhibitor (drug(s), date started, date of last dose), pre-existing autoimmune history, nosology of irAE (type, date of onset, diagnostic testing), irAE treatment and global response to treatment, prior autoimmune serologies.

Results: IrAEs were evaluated in 12 patients. 9 had no pre-existing autoimmune disease (AID) and 3 with AID (2 rheumatoid arthritis, 1 psoriatic arthritis) were evaluated pre-emptively prior to starting immunotherapy. In the group without AID average age at rheumatologic evaluation was 61.2 years. 5 patients had melanoma, 2 lung adenocarcinoma and 2 renal cell. All had previous treatments with either surgery, chemotherapy, radiation or in combination. Rheumatic irAEs included 4 inflammatory arthritis, 2 polymyalgia rheumatica, 5 sicca and 1 myositis. The majority of patients had more than one irAE, including hypophysitis, thyroiditis and rash. With the exception of one patient who experienced irAE 1 year after starting immunotherapy, the average time to irAE was 52 days. Rheumatic irAEs led to holding of immunotherapy in all but one patient. All cases were treated with glucocorticoids, and 3 required additional therapy with anti-tumor necrosis alpha, intravenous immunoglobulin or hydroxychloroquine. Treatment of irAEs led to significant improvement in 5 patients and only moderate improvement in 3. The lone patient with myositis developed life-threatening muscle involvement requiring hospitalization for aggressive immunosuppression. Of the 3 patients with pre-established AID, 2 experienced flares of their disease after starting immunotherapy.

Conclusion: Attendant to immunotherapy for malignancy are a growing number of newly defined rheumatic complications. These complications may require aggressive immunosuppression or even cessation of immunotherapy. The epidemiology, natural history and pathophysiology remains undefined. Rheumatologists must be increasingly aware of this spectrum so they may participate in optimal management.

Disclosure: C. Calabrese, None; **A. Kontzias**, None; **V. Velcheti**, Bristol-Myers Squibb, 5,Merck Pharmaceuticals, 5,Genentech and Biogen IDEC Inc., 5,Merck Pharmaceuticals, 2,Genentech and Biogen IDEC Inc., 2; **L. H. Calabrese**, Bristol-Myers Squibb, 5.

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Type and Frequency of Immune-Related Adverse Reactions in Patients Treated with Pembrolizumab (Keytruda), a Monoclonal Antibody Directed Against PD-1, in Advanced Melanoma at a Single Institution

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Background/Purpose: Although immune checkpoint inhibitors improve survival in patients with melanoma and other cancers, the alterations to the immune system induced by these medications can trigger immune-related adverse reactions. Documented immune-related adverse reactions of pembrolizumab include pneumonitis, immune-mediated colitis, hepatitis, endocrinopathies, and nephritis. The purpose of this abstract is to identify the type and frequency of immune-related adverse reactions in patients treated with pembrolizumab at our institution.

Methods: We conducted a retrospective chart review of 74 patients who received pembrolizumab therapy to treat melanoma at our institution between September 2014 and May 2016. The notes from the patients' initial oncologic evaluations and all subsequent follow-up visit notes during their treatments with pembrolizumab were evaluated. We focused on patient complaints, symptoms, physical exam results, and treatment plans. Referrals to subspecialists and hospitalization records were also reviewed if applicable and available. Complaints and adverse reactions were grouped by organ system for detailed analysis. Treatment with glucocorticoids was also recorded.

Results: Seventy-four charts were reviewed, and 69 patients had advanced melanoma and were treated with at least 1 cycle of pembrolizumab. Please refer to the table below for the type and frequency of identified immune-related adverse reactions. Rheumatology was consulted on 3 patients. One patient with a history of Raynaud's disease was evaluated for hand pain with swelling. This patient was treated with prednisone prior to evaluation, which effectively treated the pain, but there was still residual, diffuse swelling of the hands and limited extension of the wrists bilaterally, but no synovitis was identified. This patient had elevated ANA 1.1 and anti-histone antibody 1.1. Another patient had recurrent episodes of diarrhea and abdominal pain that required admission to the hospital for large-vessel vasculitis after a computed tomography scan showed thickening of the abdominal aorta and ileum as well as ileal dilation that was suggestive of ischemia due to vasculitis of the superior mesenteric artery. Finally, one patient had history of seronegative rheumatoid arthritis who was in remission and no longer taking hydroxychloroquine and had no flare ups during pembrolizumab treatment.

Conclusion: We found that the incidence of significant adverse events was higher than reported in the populations treated with pembrolizumab, including a never-reported case of large-vessel vasculitis. **Table 1: Selected Adverse Immune-Reactions Occurring in Patients Treated with Pembrolizumab**

Total Patients with Advanced Melanoma	69	
Female	27	39%
Males	42	61%
Age 25-45	5	7%
Age 51-59	10	14%
Age 60-69	20	29%
Age 70-79	24	35%
Age 80-87	10	14%
Mean Age	67	
Adverse Reaction	**All Grades # (%)**	**Grade 3-4 # (%)**
Musculoskeletal and Connective Tissue Disorders (Total 34 patients)		
Arthralgia	28 (82%)	0 (0%)
Back pain	7 (21%)	0 (0%)
Hand/wrist pain	4 (12%)	0 (0%)
Synovitis	0 (0%)	0 (0%)
Large Vessel Vasculitis	1 (3%)	1 (3%)
Treated with glucocorticoids	11 (32%)	1 (3%)
Rheumatology consulted	3 (9%)	1 (3%)
History of CTD (rheumatoid arthritis)	1 (3%)	
Total	34 (49%)	
Skin and Subcutaneous Tissue Disorders (Total 26 patients)		
Rash	19 (73%)	1 (4%)
Vitiligo	2 (8%)	0 (0%)
Pruritus	22 (85%)	0 (0%)
Lichenoid eruption	1 (4%)	0 (0%)
New onset psoriasis	1 (4%)	0 (0%)
Furunculosis a/w steroid induced acne	1 (4%)	0 (0%)
Treated with glucocorticoids	5 (19%)	1 (4%)
Total	26 (38%)	
Gastrointestinal Disorders (Total 25 patients)		
Diarrhea	12 (48%)	2 (8%)
Abdominal pain	6 (24%)	0 (0%)
Transaminitis	7 (28%)	2 (8%)
Immune mediated colitis	1 (4%)	1 (4%)
Treated with glucocorticoids	9 (36%)	4 (16%)
Total	25 (36%)	
Endocrine Disorders (Total 13 patients)		
Hypothyroidism	12 (92%)	
Hypophysitis	1 (8%)	
Total	13 (19%)	

Disclosure: O. Pinkston, None; **F. Berianu**, None; **B. Wang**, None.

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Rheumatic and Musculoskeletal Immune-Related Adverse Events Due to Immune Checkpoint Inhibitors: A Systematic Literature Review

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Rheumatic and Musculoskeletal Immune-Related Adverse Events due to Immune Checkpoint Inhibitors: A Systematic Literature Review

Background/Purpose: Immune checkpoint inhibitors (ICI) are effective treatments for advanced solid tumors that act by blocking negative costimulation of T-cells leading to an anti-tumor response. ICIs also cause non-specific immunologic activation leading to immune-related adverse events (IRAE), including colitis, pneumonitis, and hepatitis. Rheumatic and musculoskeletal events have been described in clinical trials, case reports, and observational studies, but have not been summarized or reviewed. This topic will become important to rheumatologists as the number of ICIs and indications for their use increase.

Methods: We conducted a systematic review of published literature (Medline, CENTRAL databases) reporting rheumatic and musculoskeletal IRAE secondary to inhibition of PD-1, CTLA-4, or PD-L1.

Results were screened for relevance and inclusion of original data. Studies were grouped by type: case series or reports, observational studies, and clinical trials. Data extraction was performed in duplicate. **Results**: Searches yielded 1725 unique results; 233 abstracts contained original data, which went on to full text screening. Of these, 51 mentioned a musculoskeletal or rheumatic IRAE and were included. Among 33 clinical trials, the incidence of arthralgia ranged from 1-43 %, while myalgia was reported in 2-20%. True rheumatic IRAE were reported less often in trials with rates of arthritis reported in 5/33 (incidence 1-7%) and vasculitis in 2/33 (incidence 2-3%). In 1 of 3 observational studies, the incidence of arthritis was 2% in patients receiving ipilimumab for renal cell carcinoma or melanoma. In case series and reports, inflammatory arthritis, inflammatory myopathy, eosinophilic fasciitis, vasculitis, and lupus nephritis secondary to ICIs were described (Table 1). No evidence-based information about treatment of rheumatic IRAE or studies evaluating specific pathogenesis was found.

Conclusion: Arthralgia and myalgia are common in patients treated with ICIs. The incidence of true rheumatic IRAEs, like inflammatory arthritis, is less clear from trials, partly due to lack of consensus on event coding and reporting of adverse events only of grade 3 or higher severity. There have been no prospective cohort studies to date that evaluate rheumatic IRAE, but more comprehensive data concerning pathogenesis, evaluation, and management are critical to inform rheumatologists, who will increasingly be referred patients for these complications of cancer therapy.

Table 1: Case reports and series describing rheumatic IRAE.

Author	ICI Drug	Indication	Clinical Presentation/s	Lab/imaging/biopsy	Treatment
Chan	PEM	Melanoma	2 cases polyarticular arthritis (wrist, knee, ankles; PIPs, wrist, elbow, knees)	ANA, RF, CCP negative; MRI: Synovitis/ tenosynovitis	NSAIDs. Pamidronate in 1, HCQ in 1
Conry	IPI	Melanoma	Arthralgia, myalgia, fever, neuro symptoms	ANA, dsDNA, RF negative	High dose IV steroids
De Valasco	NIVO	Renal cell	Joint pain/stiff, swan neck, uveitis	Hand X-Ray: no erosions	Arthropathy no report; Intraocular steroids
Fadel	IPI	Melanoma	Nephrotic proteinuria, microscopic hematuria, renal thrombosis	Positive ANA (1:100) and dsDNA; Biopsy: IgG, IgM, C3,C1q	Prednisone 1 mg/kg, anticoagulation
Golstein	IPI	Melanoma	2 cases PMR/GCA. 1 with arthralgia	↑ CRP; TA biopsies: intimal proliferation/lamina disruption	Prednisone 50-60 mg/d
Henderson	IPI	Melanoma	Orbital inflammation, conjunctival injection, foreign body sensation, limited ocular range of motion	MRI: proptosis, enlarged extraocular muscles	Prednisone: dose/duration not stated
Izzedine	IPI	Melanoma	2 cases Acute Interstitial Nephritis; Prior Sjogrens syndrome in 1 patient	Negative ANA; Renal biopsies: interstitial inflammation in both, tubular injury in 1	Prednisone 1 mg/kg then taper
Khoja	PEM	Melanoma	Myalgias, muscle ÒheavinessÓ, eosinophilic fasciitis, encephalopathy	Peripheral eosinophilia, MRI: fascial edema	Methylprednisolone 1 gm daily x 10 d, then taper
Manusow	PEM	Melanoma	Retinal vasculitis (in setting of ocular metastasis)	Fluoroscein angiography showed retinal vasculitis	Vitrectomy
Minor	IPI	Melanoma	Uterine lymphocytic vasculitis, pelvic mass and lymphadenopathy	ANA negative; Lymphocytic vasculitis uterine and ovarian vessels	Hysterectomy
Sheikh Ali	IPI	Melanoma	Dermatomyositis, Rash (eyelid, upper chest, back, knuckle erythema), proximal muscle weakness.	ANA 1:640 speckled; Anti-Jo1 negative; CK 1854 U/L	IV methylprednisolone 80 mg/day, then prednisone taper
Yoshioka	NIVO	Melanoma	Polymyositis, lung involvement, proximal muscle weakness, dyspnea	CK 2812 U/L; Decreased FVC	Prednisolone 30 mg/day, D/C NIVO
PEM: pembrolizumab; IPI: Ipilimumab; NIVO: nivolumab					

Disclosure: L. Cappelli, None; **A. K. Gutierrez**, None; **A. A. Shah**, None; **C. Bingham III**, Bristol-Myers Squibb, 5.

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Abstract Number: 1342

Use of Immune Checkpoint Inhibitors in the Treatment of Patients with Cancer and Preexisting Autoimmune Diseases: A Systematic Review of Case Reports

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Background/Purpose: A systematic review of case reports to summarize the existing evidence on the use of checkpoint inhibitors in patients with cancer and preexisting autoimmune diseases.

Methods: We searched Medline, EMBASE, Web of Science, PubMed ePubs, and the Cochrane Central Register of Controlled Trials (CENTRAL) through January 2016 with no restrictions. References cited in the included articles were searched manually. We included case reports describing patients with cancer and autoimmune disease diagnosed before starting treatment with the checkpoint inhibitors. We extracted data on patient's characteristics, type of checkpoint inhibitors, reported immune related adverse events (irAEs), how they were managed, and their clinical outcome, if discontinuation of immunotherapy was required, and if treatment rechallenge was reported.

Results: Fourteen publications met inclusion criteria, reporting on 45 cases. Age of the cases ranged from 30 to 80 years; 25 patients (55.6%) were male. Forty three cases (95.6%) had melanoma. Preexisting autoimmune diseases included autoimmune thyroid diseases, rheumatoid arthritis, ulcerative colitis, psoriasis (two with psoriatic arthritis), multiple sclerosis, Crohn's disease, sarcoidosis, systemic lupus, Behcet disease, inflammatory arthritis, reactive arthritis, rheumatic fever, Sjogren's syndrome, transverse myelitis, and celiac disease. Of the 45 cases, 86.8% received concomitant treatment (corticosteroids, DMARDs, and biologics) for their autoimmune disease; 53.9% were still active at the time of immune checkpoint inhibitor therapy. Most received ipilimumab (88.9%). After immunotherapy: 1) 40.0% reported de novo irAEs, 2) 28.9% reported exacerbation of the preexisting autoimmune disease, 3) 8.9% reported both, and 4) 40.0% did not report any adverse events. Hypophysitis and colitis occurred in most cases (27.8% each) with de novo irAEs. Autoimmune thyroiditis, diabetes, glaucoma, interstitial nephritis, skin itching, and toxic epidermal necrolysis were also reported. Those with exacerbation of the preexisting autoimmune disease, had manifestations similar to those occurring before checkpoint therapy, and none developed new disease features. Patients were treated with corticosteroids and hormonal replacement therapy. Therapy with azathioprine, sulfasalazine, or infliximab was also reported. Discontinuation of immunotherapy was recommended in 33.3%, and resolution of irAEs was achieved in the majority of cases. Death was reported in one case with toxic epidermal necrolysis and in another with severe colitis. Treatment rechallenge was reported in a patient with ulcerative colitis who developed exacerbation of his colitis after initial use of ipilimumab. Upon rechallenge, he reported grade III anterior panhypopitutarism and tracheobronchitis. In a patient with pulmonary sarcoidosis, ipilimumab rechallenge was not associated with significant clinical symptoms.

Conclusion: Forty percent of the cases did not experience irAE or disease exacerbation, despite many having active autoimmune disease at the time of checkpoint inhibition. Further studies are needed to establish the risk-benefit profile of this novel therapy in this population.

Disclosure: N. Abdel-Wahab, None; **M. Shah**, None; **M. Suarez-Almazor**, None.

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Abstract Number: 1343

Efficacy of Biological-Targeted Treatments in MDS-Related Systemic Autoimmune Diseases: Multicenter Retrospective Study of 28 Patients

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Background/Purpose: This study analyze the safety and efficiency of biologics (TNF-α antagonists, tocilizumab, rituximab and IL-1 inhibitors) in patients with autoimmune systemic diseases (SAIDs) associated to myelodysplastic syndrome (MDS).

Methods: In a French multicenter retrospective study, 28 patients with both MDS and SAID treated with at least one biological-targeted treatment were analyzed. Clinical, biological and overall treatment response was considered as complete (no more symptoms), partial (at least 50% improvement) or non-response. In patients with several lines of treatment, data were analyzed before and at the end of each line and pooled to compare overall response between steroids, DMARDs and biologics

Results: 28 patients with median age 66 [19-85] years, 11% of females were included. MDS most frequent subtypes were CMML (18%), AREB-1 (32%), CRDM (32%), 5q-(7%) with median marrow blasts 2% (0-10), normal karyotype in 12/24 (50%) cases and IPSS 0.5 (0-1). The associated SAIDs were arthritis (undifferentiated and rheumatoid arthritis in 3 (10%) cases each), Behcet's disease in 2 (7%) cases, cryoglobulinemic vasculitis in 2 (7%) cases, giant cell arteritis in 1 (4%), relapsing polychondritis in 8 (30%) cases, Sweet's disease in 3 (10%) cases and others (18%). During the follow-up of 3 (1.3-4.5) years, 112 lines of treatments were used, consisting in steroids alone (23%), DMARDs (25%), TNF-α antagonists (15%), anakinra (11%), rituximab (10%) and tocilizumab (7%). The median number of lines was 3 (1-9) and more than 5 lines were used in 13 (46%) of patients. Specific MDS treatment was used for SAIDs in 10 patients (9%) (azacytidine). Considering all 112 lines, overall response (complete and partial) occurred in 54% cases. Comparing the treatments, overall response was noted more frequently under steroids (76%) and rituximab (54%), than DMARDs (45%) and TNF-α antagonists, tocilizumab and anakinra (31%)($p<0.05$). Azacytidine allowed 71% response in steroid-dependent SAIDs. Steroid dependence occured in 25 cases with mean steroid dose 27 mg/day (10-120). During the follow-up, 20 (71%) patients presented at least one severe infection. Table 1

N=112	DMARDs N=29 (26%)	Biologics N=36 (32%)	Rituximab N=11 (10%)	Steroids N=26 (24%)	Azacytidine/BMT N=10 (9%)
Treatments					
Steroids	21 (95%)	36 (95%)	11(91%)	25 (100%)	10 (100%)
Prednisone (mg/day) before/at the end	25 (18-38) 25 (15-28)	25 (20-30) 22.5 (10-30)	20 (15-30) 18 (9-24)	60 (40-60) 25 (20-40)	25 (18-28) 20 (5-23)
Type of immunosuppressive agents	MTX 7 (24%)	Anakinra 14 (39%)	-	-	-
	CYC 4 (13%)	TNF-a antagonists 15 (42%)	-	-	-
	AZA 4 (13%)	Tocilizumab 7 (19%)	-	-	-
	MMF 5 (18%)	-	-	-	-
	CICLO 5 (18%)	-	-	-	-
	HCQ 4(14%)				
Treatment duration (months)	9 (4-21)	2.5 (1-7)	6 (4-32)	9 (2-12)	8 (3-22)
C-reactive protein level (mg/l) before/at the end	53 (39-140) 18 (3-200)	60 (22-90) / 60 (26-99)	18 (5-50) 30 (7-50)	90 (45-117) 32 (4-90)	53 (36-79) 9 (3-20)
SAID response					
SAIDs partial response	1/20 (5%)	8/30(25%)	4/11 (36%)	1/23 (4%)	5/7 (71%)
SAIDs complete response	8/20(40%)	2/30 (6%)	2/11 (18%)	18/23 (78%)	0
SAIDs non response	11/20 (55%)	21/30 (69%)	5/10 (46%)	4/23 (18%)	2/7 (29%)

Conclusion: This nationwide study demonstrates the efficiency of steroids for SAID associated to MDS, the frequency of steroid dependence and poor response to biologics, except rituximab. The efficiency of azacytidine for MDS-related SAIDs should be considered in patients with inefficacy of other strategies and steroid dependence.

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Characteristics, Treatment and Outcome of Severe Pulmonary Hemorrhage Related to Systemic Disease: French Multicentric Study

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Background/Purpose: pulmonary hemorrhage (PH) may complicate systemic disease. The main objective of this study was to describe characteristics, treatment and outcome of patients presenting severe PH related to systemic disease.

Methods: we performed a French multicentric retrospective study including all cases of adult patients presenting severe PH related to systemic disease from 2000 to 2016. Severe PH was defined as PH requiring intensive care unit (ICU) admission. Data concerning clinical, biological and radiological findings were collected, as well as treatments.

Results: we identified 70 patients (52.9% men) admitted with severe PH due to a systemic disease with a median age of 48 (29.8-66.3), in 7 centers. Among these patients, 21 (30%) had a past medical history of systemic disease. Main symptom for consultation was dyspnea in 69 (98.6%) cases. Patients were hospitalized 27.5 (10-66) days after the first symptoms and 6.5 (1-29) days after the beginning of respiratory symptoms. There was evidence a pulmonary-renal syndrome in 54 (78.3%) cases, articular manifestations in 9 (13.0%) cases, skin manifestations in 16 (23.2%) cases, nervous manifestations in 12 (17.4%) cases, and digestive manifestations in 5 (7.2%) cases. ICU admission occurred 4 (1-11.5) days after hospital admission. All patients presented anemia with a median hemoglobin level of 8.2 (6.9-9.4) g/dl. Median blood creatinine level was 222 (91-429) µmol/l. Chest X-ray was normal in 3 (4.6%) patients, there was bilateral alveolar condensations in 51 (78.5%) patients and bilateral interstitial pattern in 28 (43%) patients. CT-scan was realized for 50 (71.4%) patients and was never normal. Main findings included ground glass opacities in 44 (88%) cases, nodules in 11 (22%) cases, and a pleural effusion in 6 (12%) cases. Sixty-one (87.1%) patients underwent a bronchial fibroscopy showing PH for all patients (100%). Diagnosis was made 31 (10.5-62.5) days after the first symptoms and 5 (2-10) days after hospitalization. A vasculitis diagnosis was made for 40 (57.1%) patients with ANCA, IgA and cryoglobulinemic vasculitis in 33 (47.1%), 3 (5.7%), and 4 (5.7%) cases, respectively. A connective tissue disorder was diagnosed for 21 (30%) patients, mainly with lupus and antiphospholipid syndrome (APS) in 9 (12.9%) and 6 (8.6%), respectively. Anti-MBG disease (Goodpasture syndrome) was diagnosed in 9 (12.9%) cases. Steroids were used in 69 (98.6%) patients with bolus in 61 (87.1%) patients. Cyclophosphamide and Rituximab were used for 49 (70%) and 8 (11.4%) patients, respectively. Plasmapheresis was used in 38 (54.3%) patients. During ICU stay, 67 (95.7%) patients required oxygen therapy, 34 (48.6%) were intubated with a median ventilation length of 12 (6.3-25.3) days, 40 (57.1%) required renal replacement therapy, and 25 (35.7%) vasopressive drugs. Median ICU and hospital length of stay were 11 (6.8-19.3%) and 39 (21.3-64) days. Twelve (17.1%) patients died. After a median follow-up of 7.5 (2-34) months, 17 (39.5%) patients required renal replacement therapy, and 3 (7.6%) had a chronic lung disease.

Conclusion: PH is a serious complication of systemic disease accounting for 17% of deaths. Even if the use of steroids, immunosuppressive therapy, and plasmapheresis seem to be effective, the best regimen remains to be determined.

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Abstract Number: 1345

Undifferentiated Connective Tissue Disease: A 121 Patients Audit Focusing on Initial Diagnosis and Changes over Time

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Background/Purpose: The diagnosis of Undifferentiated Connective Tissue Disease (UCTD) has raised controversy over the years regarding making the diagnosis, evolution and prognosis. Le Roy et al[1] in 1980 and most recently Mosca et al[2]in 2014 proposed classification criteria for UCTD, but confusion still exists regarding making the diagnosis of UCTD, evolution and prognosis of the syndrome and how the patient should be followed up over time.

Methods: This was a retrospective study of patients followed up in a specialist clinic in a tertiary referral centre (University College London Hospitals) with a diagnosis of UCTD, focusing on clinical and serological features, treatment, follow up and disease evolution over time.

Results: A total of 121 patients were included in the study: 93% were females; the mean age at disease onset was 39 years (range 20 to 80); and the patients were followed up for at least 1 year (mean 12 years, range 1 to 40). 78% of these patients had a stable diagnosis of UCTD, while in 22% diagnosis changed over time: 9% evolved into a specific connective tissue disease (CTD) - 4 Systemic Lupus Erythematosus, 3 Sjogren's Syndrome, 1 Rheumatoid Arthritis, 1 Systemic sclerosis and 1 Anti-synthetase Syndrome -, 7% had a change of diagnosis from a specific CTD to UCTD, 4% evolved into an overlap syndrome and 2% of the patients were no longer diagnosed as having any CTD at the end of the study. The most prevalent manifestations were joint pain (arthralgia/arthritis) in 89% of the patients, fatigue 80%, Raynaud's phenomenon 63%, skin rashes 49% and sicca symptoms 45%. Lung involvement was observed in 11% of the patients within which 8% had a nonspecific interstitial pneumonia (NSIP) and 3% had a usual interstitial pneumonia (UIP) pattern. 36% of the patients were noted to have associated gastro-oesophageal reflux disease. Serological features included positive ANA in 98%, anti-RNP 33%, anti-Ro 32%, Rheumatoid Factor 20% and hypocomplementemia was observed in 19% of the patients. 7% of the patients did not require any treatment for their UCTD, but the majority of patients were treated with Hydroxychloroquine only (75%), and the rest with other immunosupressants/immunomodulators.

Conclusion: In our study the majority of patients initially diagnosed with UCTD kept this diagnosis over time but 13% of patients evolved to a defined CTD or an overlap syndrome and in 2% of patients, symptoms and serological features eventually resolved. Although, UCTD is often mild, significant major organ involvement such as interstitial lung disease can occur, as well as evolution to a defined CTD or overlap syndrome. This should guide follow up of these patients in clinic.

Disclosure: M. Leandro, None; **R. Ionescu**, None.

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Abstract Number: 1346

Factors That Influence Therapy in Patients with Undifferentiated Connective Tissue Disease

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Background/Purpose: To compare clinical and immunological characteristics in patients with undifferentiated connective tissue disease (UCTD) treated with hydroxycholoroquine (HCQ) in a large academic clinical practice.

Methods : This cross-sectional study included all patients diagnosed with UCTD according to the preliminary classification criteria(1), seen at the Columbia University Lupus Center in New York, from January to December 2015. Clinical and immunological variables were ascertained. Chi squared tests were used to compare the following characteristic between treated and untreated patients: demographic characteristics, number of ACR criteria, SLICC criteria, individual symptoms and laboratory values.

Results : Eighty-three patients were identified; 93% were female, mean age at diagnosis of 44 years ±14.9; 67% were Caucasian, 20% Hispanic and 11% Black/African American; median disease duration of 3.91 years±5.35 (1-27). The most prevalent symptoms that required medical attention are described in the Figure 1.

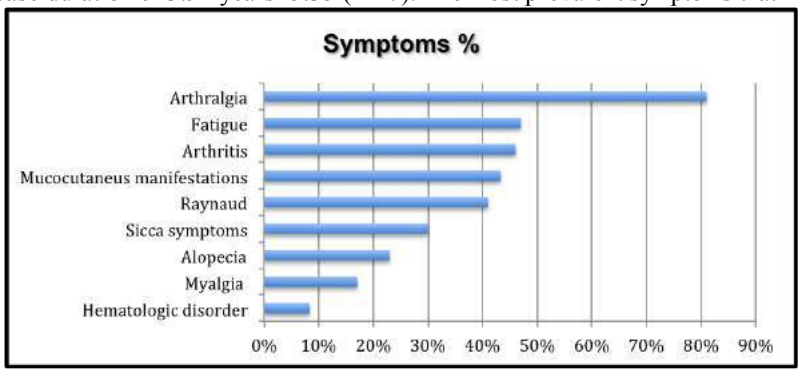

Figure 1. 49.4% of patients had a family history of autoimmune diseases. 95% of patients had positive antinuclear antibody (ANA) titers and 5% were ANA negative Ro/SSA+, 88% had titers ≥ 1:160, with speckled pattern in 69% of patients. 16% of the patients studied met SLICC SLE criteria. Half of the patients, 42(51%) were treated with HCQ and 41(49.3%) were not treated. The patients treated with HCQ were more likely to also meet SLICC criteria (10 vs. 3, respectively; p=0.03), have a history of arthralgia (38 vs. 29; p=0.02), arthritis (28 vs. 10; p=0.0001), and fatigue (25 vs. 14; p=0.02). A history of low complement was more prevalent in the treated group (12 vs. 3; p=0.01). 38 patients had folllow-up greater than 3 years; of these 18 had a strong family history of autoimmune diseases. While only 17(45%) patients had been treated with HCQ, we did not observe any increase in the titer and/or number of autoantibodies or clinical manifestations over the 3 years of follow-up in any of these 38 patients.

Conclusion : Data from this single-center cohort of patients with UCTD show that patients treated with HCQ by their rheumatologist are more likely to have multiple clinical criteria and low complement compared to those that were not treated. These data suggest that rheumatologists treat pre-clinical autoimmunity in the setting of clinical symptoms. None of patients were treated based on serologies alone. Longitudinal studies are needed to evaluate the long-term impact of HCQ on clinical and seologic outcomes of patients with UCTD. **References:** (1) Mosca M, et al. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 1999;17:615-620.

Disclosure: D. P. Pena, None; **A. D. Askanase**, None.

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Abstract Number: 1347

Steroid-Responsive Encephalopathy Associated with Autoimmune Thyroiditis: Characteristics, Treatment and Outcome in 251 Cases from the Literature

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Background/Purpose: Steroid-responsive encephalopathy and associated autoimmune thyroiditis (SREAT) is characterized by encephalopathy and the presence of antithyroid antibodies. We describe the clinical presentation, outcome and treatments for SREAT by a systematic review of the literature.

Methods: MEDLINE via PubMed, Web of Science and the Cochrane Library were searched for articles published until 2015. Inclusion criteria were unexplained encephalopathy with antithyroid antibodies.

Results: We found reports of 251 patients (median age 52 years [range 18–86], 73% females, 80 [32%] with preexisting thyroiditis). Patients presented encephalitis signs with convulsions (n=117; 47%), confusion (n=115, 46%), speech disorder (n=91, 37%), memory impairment (n=107, 43%), gait disturbance (n= 67, 27%) and persecutory delusions (n=61, 25%). 28 patients (11%) presented progressive memory impairment and 26 (10%) isolated psychiatric disorders. In serum, 34% of patients were positive for anti-thyroid peroxidase (TPO) antibodies, 7% for anti-thyroglobulin (TG) antibodies, and 69% both. Thyroid-stimulating hormone levels were usually normal, at 2 UI/ml [0.001–205]. Cerebrospinal fluid analysis showed mild to moderate hyperproteinorachia in 107/131 patients (82%), with median level 0.71 g/l [0.13–7.65]. Cerebrospinal fluid from 10/53 patients (19%) was positive for anti-TPO antibodies, 2/53 (4%) anti-TG antibodies and 28 (53%) both. Electroencephalography findings were abnormal for 82% of patients, showing diffuse slowing consistent with encephalopathy (70%) or epileptic activity (14%). The first-line treatment was steroids in 193 patients and other immunosuppressive drugs in 10 (intravenous immunoglobulin (n=4), azathioprine (n=2), plasma exchange (n=2), rituximab (n=1) or hydroxychloroquine (n=1). Among 146 patients evaluated within a median delay of 5 days [1-20], 134/146 (92%) showed neurological response. At a median final follow-up of 12 months [range 0.2–110], 91% of patients showed complete or partial neurological response, with anti-TPO and -TG antibody titers at 347 UI/ml [0–825000] and 110 UI/ml 0–50892], respectively. During follow-up, 40 patients (16%) experienced at least one relapse. Relapse was more frequent in patients with initial coma (26% vs 13%, p=0.08).

Conclusion:

SREAT is a rare syndrome with various clinical presentations that should be considered in any patient with acute or subacute encephalopathy without obvious etiology but also with progressive cognitive impairment and psychiatric signs, to quickly start corticosteroid treatment. The benefit of other immunosuppressive drugs remains to be determined. Table 1:

Table 1. General characteristics of 251 patients with steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT).

Characteristics	
Age (years), median [range] / female sex	52 [18-86] /184/251 (73)
Coma	38/249 (15)
Headaches	38/245 (16)
Convulsions	117/250 (47)
Speech disorder	91/249 (37)
Memory impairment	107/247 (43)
Confusion	115/249 (46)
Persecutory delusions	61/247 (25)
Depression	29/244 (12)
Fever	18/244 (7)
Abnormal electroencephalography findings	182/224 (81)
Serum positivity	
Anti-TPO antibodies	70/203 (34)
Anti-TG antibodies	11/168 (7)
Anti-TGO + TP antibodies	119/173 (69)
Cerebrospinal fluid positivity	
Anti-TPO antibodies	10/53 (19)
Anti-TG antibodies	2/53 (4)
Anti-TPO+TG antibodies	28/53 (53)
TSH, median [range]	2 [0.001–205]
Relapse	40/251 (16)
Death	9/141 (6)
Follow-up (months), median [range]	12 [0.2–110]

Data are no. (%) unless indicated.

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Abstract Number: 1348

Neuromyelitis Optica: Patient Characteristics and Treatment Patterns Among Rheumatologists Versus Non-Rheumatologists

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Background/Purpose: Neuromyelitis optica (NMO) is an immune-mediated inflammatory disorder of the central nervous system that has been associated with systemic autoimmunity often cared for by rheumatologists. We examined whether clinical characteristics and treatments differed among patients with NMO treated by rheumatologists compared to non-rheumatologists.

Methods: We performed a retrospective cohort study using a large national health plan database from May 1, 2000 - June 30, 2013. Data collected included inpatient, outpatient, and pharmacy claims. Subjects were identified by having at least one *International Classification of Disease, Ninth Revision, Clinical Modification* (ID-9-CM) code for NMO, receipt of glucocorticoids, and an inpatient/acute care visit within 90 days of the index date (defined as the first documented code for NMO). Subjects <1 year of age and with ≥2 codes for multiple sclerosis were excluded. Subjects required continuous health plan enrollment for 6 months prior to and 12 months after the index date. The exposed group included subjects with ≥ 1 NMO diagnosis code documented by a rheumatologist. Systemic autoimmune conditions were identified by their respective ICD-9-CM codes. Pharmacy claims (via National Drug Code) were used to identify medication use. We were unable to reliably assess intravenous medications.

Results : 156 subjects met study criteria. Subjects were predominantly adult (90%), female (63%) and Caucasian (66%). Median age among the pediatric (<18 years old) group (N=15) was 12 years (IQR: 4-15) and among the adult cohort was 49 years (IQR: 38-64). 41% of subjects had at least one systemic autoimmune condition. A rheumatologist documented at least one NMO ICD-9-CM code for 27% of the subjects (N=41). Table 1 shows demographics, clinical characteristics and treatment regimens for subjects treated by a rheumatologist versus non-rheumatologist. There was no statistically significant difference in the proportion of subjects with a concomitant systemic autoimmune disease between the two groups (all p>0.05). Use of any non-glucocorticoid immunosuppressant was more common in the rheumatologist group (p<0.01). This finding persisted when restricted to the adult cohort (p<0.01) but was not true for the pediatric cohort (p=1.00). Azathioprine and mycophenolate mofetil were significantly more common in the rheumatologist group (p=0.02 and p=0.01, respectively). Methotrexate was more common among rheumatologists (4.9% vs. 0%) but was only marginally significant (p=0.07).

Conclusion: Patients with NMO cared for by a rheumatologist were more likely to receive non-glucocorticoid immunosuppressive agents. The most commonly used medications were azathioprine and mycophenolate mofetil. Future studies should address the use and effectiveness of non-glucocorticoid medications in the rheumatologic management of pediatric NMO.

Table 1. Demographics, Clinical Characteristics and Treatment Regimens in Neuromyelitis Optica Based on Provider Type

Patient Demographics, N(%) or Median (IQR)	All (N=156)	Rheumatologist (N=41)	Non-Rheumatologist (N=115)	P-value*
Age	47 (35.0, 60.0)	44 (32.0, 57.5)	49 (36.0, 63.0)	0.25
Female^	98 (62.8)	22 (53.7)	76 (66.1)	0.21
Race				
Caucasian	103 (66.0)	32 (78.0)	71 (61.4)	0.53
Black	13 (8.3)	2 (4.9)	11 (9.6)	
Hispanic	7 (4.5)	1 (2.4)	6 (5.2)	
Asian	3 (2.0)	0 (0)	3 (2.6)	
Unknown or Missing	30 (19.2)	6 (14.6)	24 (20.8)	
Systemic Autoimmune Conditions, N (%)				
Any autoimmune disease‡	64 (41.0)	18 (43.9)	46 (0.40)	0.67
Autoimmune thyroid disease	19 (12.2)	5 (12.2)	14 (12.2)	1.00
Inflammatory arthritis	31 (19.9)	9 (22.0)	22 (19.1)	0.70
Mixed connective tissue disease	19 (12.2)	4 (9.8)	15 (13.0)	0.78
Psoriasis	8 (5.1)	2 (4.9)	6 (5.2)	1.00
Sjögren's syndrome	3 (1.9)	2 (4.9)	1 (0.9)	0.17
Systemic lupus erythematosus	5 (3.2)	2 (4.9)	3 (2.6)	0.61
Treatment Regimens, N (%)				
Any non-glucocorticoid+	23 (14.7)	12 (29.3)	11 (9.6)	**<0.01**
Azathioprine	13 (8.3)	7 (17.1)	6 (5.2)	**0.02**
Hydroxychloroquine	5 (3.2)	2 (4.9)	3 (2.6)	0.61
Methotrexate	2 (1.3)	2 (4.9)	0 (0)	0.07
Mycophenolate mofetil	9 (5.8)	6 (14.6)	3 (2.61)	**0.01**
Tacrolimus	3 (1.9)	1 (2.4)	2 (1.7)	1.00

Legend. ^Gender was missing for 1 subject. ‡ Any autoimmune disease defined as number of unique subjects with a diagnosis code for at least one of the systemic autoimmune conditions listed above. + Any non-glucocorticoid defined as number of unique subjects with at least one National Drug Code (NDC) for any treatment regimen listed above. *Differences in clinical and demographic characteristics by provider type were assessed using the Mann-Whitney, Chi-squared or Fischer's exact tests, as appropriate. p<0.05 is considered statistically significant.

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Clinical Analysis of Hypertrophic Pachymeningitis

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Background/Purpose: Hypertrophic pachymeningitis (HP) is a rare, chronic and inflammatory disorder. HP is characterized by thickening of the cranial dura mater. The cause of HP was reported to be associated with some disorders such as infectious disease, connective tissue disease (CTD) and malignant tumor[1)]. Recently, some reports showed that some patients with hypertrophic pachymeningitis may have myeloperoxidase anti-neutrophil cytoplasmic antibody (MPO-ANCA)-positive status[2)]. However, the clinical characteristics and specific treatments for CTD associated hypertrophic pachymeningitis remain elusive. Because of its low incidence of HP, clinical course such as symptom, laboratory data and treatment strategy was unclear. [1) 2)] Previous reports have shown that HP patients usually respond to glucocorticoid (GC), but not some patients were recurred during steroid tapering [3)]. We extract the clinical features and treatment regimen, and investigate the clinical characteristics of HP. We examined HP patients in our institution in order to reveal the incidence of CTD complication and the efficacy of treatment.

Methods: We enrolled the 6 patients (M/F: 2/4) with HP diagnosed and treated in our facility between 2000 and 2015. We extract the subjects as follow; initial symptom, underlying disorder, initial intervention and the efficacy of treatment.

Results: The mean age at diagnosis of HP was 43.7 years old (range; 18-73). The initial symptom of HP was headache in 5 cases, eye manifestation in 3 cases, fever in 2 cases, nausea in 1 case and tinnitus in 1 case. Underlying disorders complicated HP existed in 4 of 6 cases and all 4 cases diagnosed CTD (two only Sjögren's syndrome, one mixed connective tissue disease and Sjögren's syndrome, one granulomatosis with polyangitis). Performed meningeal biopsy was only 1 case. Infiltration of lymphocytes and anti-IgG4-positive plasma cells (IgG4/IgG≧40%), but we couldn't diagnose IgG4-related disease. The intervention was conducted with glucocorticoid (GC) treatment in all HP patients. 3 cases were taken methylprednisolone-pulse. Two third of 6 HP patients had well responded to initial GC treatment. However two patients were refractory treatment. One case treated with methotrexate combined with GC, and another case cyclosporine A.

Conclusion: In HP patients in our institution complicated with CTD, headache and eye manifestation often observed as initial symptoms. Several reports showed that serum IgG4 level was normal in IgG4-related HP as this case. Sjögren's syndrome is most frequent complication in our hospital and these HP patients are refractoriness to GC. It is necessary for refractory HP patients to treat using immunosuppressive therapy with combined GC.

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Abstract Number: 1350

Asymptomatic Coccidioidomycosis in Patients with Rheumatic Disease: 8 Years of Experience

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Background/Purpose: Coccidioidomycosis (valley fever) is an endemic fungal infection that typically causes a self-limited pulmonary illness in the Southwestern United States,. Immunosuppressed patients are at higher risk of more severe infection, and this includes patients with rheumatic disease on disease-modifying antirheumatic drugs (DMARD) or biologic response modifiers (BRM). At our institution, the routine practice is to screen patients for coccidioidomycosis before initiating BRM therapy, and then annually thereafter. Through this process, we have identified asymptomatic patients with positive serologies. This is concerning as it indicates a recent infection. A 2012 retrospective study proposed a protocol that suggested continuing antirheumatic therapy rather than stopping it in asymptomatic patients. Following this protocol has not resulted in the development of a more severe infection in asymptomatic patients.

Methods: A cohort study at two centers in Tucson, Arizona identified patients who developed coccidioidomycosis while on DMARD or BRM therapy. Several patients had asymptomatic illness as defined as a positive serology found on surveillance labs, not ordered in response to symptoms, and no concurrent signs or symptoms of active disease. Patients were seen at least once between 2007 and 2015. The study emphasized management of BRM/DMARD therapy, as well as antifungal therapy and duration.

Results: Seventy one patients with rheumatic disease were diagnosed with coccidioidomycosis, and 19 of them had positive serologies and no symptoms. Most (17/19) had rheumatoid arthritis, 1 had psoriatic arthritis, and 1 had dermatomyositis. Sixteen patients were identified during routine annual surveillance, and three were identified during pre-BRM therapy screening. Eight patients were on BRM alone, 9 on BRM with a DMARD, and 2 on a DMARD alone. Three patients were also on prednisone. Six patients stopped their antirheumatic therapy, while the rest continued without interuption. BRM therapy was restarted in 5 of these patients, most resuming therapy within 1 month of infection (range 0.5 – 12 mos). One did not resume therapy due to osteonecrosis of the jaw. Six patients received fluconazole, duration ranging from 8 to 73 months (median 30.5 mos). Ten patients neither reduced antirheumatic therapy, nor started antifungal treatment. The median follow up is 43 months, and no patients have developed symptomatic illness. Three patients have been lost to follow up, and one died from unrelated causes.

Conclusion: Positive coccidioidomycosis serologies in asymptomatic patients are concerning as they are indicative of a recent active infection. This cohort supports the management strategy of continuing DMARD and BRM therapy in patient with asymptomatic disease. It also suggests that in patients with persistently positive serologies, antifungal therapy should be considered. In the past 8 years there have been no complications in the asymptomatic cocci patients who continued BRM and DMARD. The management strategy implemented may be effective in guiding therapy.

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Mortality and Prognostic Factors of Pneumocystis Pneumonia in Patients with Connective Tissue Diseases

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Background/Purpose: Pneumocystis pneumonia (PCP) is one of the severe opportunistic infections in immunocompromised patients. PCP is still a leading cause of death in patients with connective tissue diseases treated with glucocorticoid, immunosuppressant and biologic agents. However, the mortality rate and factors related to death for PCP remain unclear. The aim of this study is to identify the prognostic factors for PCP in immunosuppressed patients with connective tissue diseases.

Methods: A total of 52 patients with connective tissue diseases developing PCP were included in this study. PCP was diagnosed by clinical symptoms, radiological findings, respiratory specimens (the microscopic demonstration of Pneumocystis jirovecii or pneumocystis-specific nested polymerase chain reaction) and serum β-D glucan. The patients were divided into two groups according to the outcome (Survivors group or Non-survivors group). Baseline demographics, treatment for the underlying connective tissue disease, laboratory findings at the diagnosis of PCP, and treatment for PCP were compared between the two groups.

Results: Of 52 patients with PCP, 6 deceased and a mortality rate was 11.5%. There were no significant differences in age, gender, type of connective tissue disease, previous immunosuppressive treatments between survivors and non-survivors. The treatment regimen for PCP was not different between the two groups. The initial trimethoprim-sulfamethoxazole treatment failure was also not statistically different between the two groups. In univariate analysis, while the levels of serum β-D glucan, KL-6, IgG and PaO2, and the number of lymphocytes were not statistically different, the lower level of serum albumin, and higher levels of serum C-reactive protein and lactate dehydrogenase were significantly associated with mortality. Multivariate analysis showed that the lower level of serum albumin was an independent poor prognostic factor for the death with PCP.

Conclusion: The low serum albumin is an independent prognostic factor for mortality in PCP developed in immunosuppressed patients with connective tissue diseases.

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Abstract Number: 1352

Predictors of Mortality in Rheumatic Disease Patients with CMV Infection

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Background/Purpose: Immunosuppressive therapy, which is frequently used to treat various rheumatic diseases, increases risk of opportunistic infection. However, few reports were available on the prognosis of CMV infection in rheumatic diseases. While prognosis of CMV infection without end-organ involvement is excellent, there is a clinical dilemma to start anti-viral treatment because it is difficult to assess end-organ involvement of CMV due to systemic manifestations of underlying disease or co-existence of other

infections. This study aimed to assess the predictors of mortality in rheumatic diseases patients with CMV infection.

Methods: We retrospectively reviewed the Severance Hospital¡¯s electronic medical records of rheumatic disease patients with CMV infection between 2005 and 2016. Clinical and laboratory data on patients including immunosuppresive treatment, CMV titer by real time PCR, anti-viral treatment were collected. Statistic analysis was done using internet based "R" software. Characterization of the features was analyzed using descriptive statistics and Fisher's exact test. Separate analyses of variance (Kai analysis) examined. Mortality was compared across the tertiles by CMV titer.

Results: A total of 68 rheumatic disease patients with CMV infection were evaluated (mean age 56.6 years, 45 women(68%), mean disease duration 6.4 years, 22 deaths). Rheumatic disease¡¯s distribution was like table 1. Mortality rate was significantly higher for the upper tertile CMV group than lower tertile CMV group (table 2, p<0.05). Comparison of the death group and the survival group revealed CMV count (239,252.2 ¡¾ 389,940.3 vs. 63,126.1 ¡¾ 197,791.7, p=0.056), lymphocyte count (917.0 ¡¾ 1,914.6 vs. 682.0 ¡¾ 911.0, P=0.589), using ganciclorvir (10 (45.5%) vs. 15 (32.6%), p=0.448) and using mechanical ventilation (13 (59.1%) vs. 3 (6.5%), p<0.0001).

Conclusion: High CMV titer is associated with mortality in rheumatic disease patients even though anti-viral treatment was not associated with mortality. It is still unknown whether high CMV titer is the direct cause of mortality or the result of critical condition. Larger studies are needed to confirm the findings.

Table 1. Distribution of Rheumatic disease

outcome	Death (N=22)	Survival (N=46)
ANCA associated GN	1 (4.5%)	1 (2.2%)
AOSD	1 (4.5%)	1 (2.2%)
Behcet's disease	0 (0.0%)	3 (6.5%)
Churg-Strauss syndrome	0 (0.0%)	2 (4.3%)
Dermatomyositis	2 (9.1%)	3 (6.5%)
Microscopic polyangiitis	1 (4.5%)	1 (2.2%)
Polymyositis	1 (4.5%)	2 (4.3%)
RA	6 (27.3%)	11 (23.9%)
Sjogren syndrome	1 (4.5%)	0 (0.0%)
SLE	6 (27.3%)	19 (41.3%)
Takayasu's disease	1 (4.5%)	0 (0.0%)
undifferentiated arthritis	0 (0.0%)	1 (2.2%)
Wegener's granulomatosis	2 (9.1%)	2 (4.3%)

Table 2. Outcome comparison of the upper and lower tertile group by CMV titer

	Upper tertile (N=22)	Lower tertile (N=22)	p
outcome			0.028
death	12 (54.5%)	4 (18.2%)	
survival	10 (45.5%)	18 (81.8%)	

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Risk Factors of Pulmonary Mycobacterium Avium-Comlex (MAC) Disease and the Significance of Anti-MAC Antibody in Patients with Rheumatic Diseases

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Background/Purpose: Pulmonary MAC disease is caused by MAC and the incidence is increasing in Japan. It is also becoming a great concern in the field of rheumatology because there are no drugs which show good anti-MAC activity. Another problem is diagnostic criteria for pulmonary MAC disease that has been revised many times, in which positive sputum culture more than twice is included. However, it takes long time to get culture positive twice. Measurement of anti-MAC antibody was developed by Kitada, et al (Am J Respir Crir Care Med 2008) and is commercially available (Capilia MAC, TM), and the sensitivity has been reported to be 70 - 80 % with very good specificity. We aimed to detect risk factors for pulmonary MAC disease in patients with rheumatic diseases and the significance of the measurement ant-MAC antibody.

Methods: Subjects were 88 patients with various rheumatic diseases whose chest CT findings showed small nodular opacities, bronchiectasis, and, in cases, cavities which are difficult to distinguish from pulmonary lesions due to rheumatic diseases itself. Sputum culture was done more than twice, and blood was drawn for anti-MAC antibody detection. PCR test for MAC in sputum samples was done in most of the patients. Fourteen clinical factors, such as age, gender, BMI, underlying diseases, dose of PSL and MTX, and others, were collected and multivariate analysis was done to find risk factors of pulmonary MAC disease.

Results: Out of 88 patients, 12 patients fulfilled the criteria for pulmonary MAC disease. However, 2 patients showed sputum culture positive once and PCR test for MAC in another sample was positive, and these patients were treated as pulmonary MAC disease resulting in good response. Therefore, we included these 2 patients into pulmonary MAC disease. Multivariate analysis found only one significant risk factor, low BMI. The mean BMI with and without pulmonary MAC disease were 17.5 +/- 2.3 and 21.3 +/- 3.7, respectively ($p < 0.0005$). In patients with BMI less than 18.5, OR of developing pulmonary MAC diseases was 12.3. Anti-MAC antibody was positive in 11 patients. In 14 patients diagnosed as pulmonary MAC disease, ant-MAC antibody was positive in 9, and 2 patients not diagnosed as MAC disease were positive for anti-MAC antibody. The sensitivity, specificity, PPV and NPV of ant-MAC antibody for pulmonary MAC disease were 64.3 %, 97.3 %, 81.8 %, and 93.9 %, respectively.

Conclusion: Low BMI was only one risk factor of developing pulmonary MAC disease in patients with rheumatic diseases, which is consistent with that in general populations. Measurement of anti-MAC antibody can be a replacement of one positive sputum culture, but further study is definitely needed.

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Abstract Number: 1354

Ultrasound Verified Inflammation and Structural Abnormalities in Patients with Hemochromatosis with and without Associated Arthropathy

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Background/Purpose: To study inflammatory and structural ultrasound lesions in patients with hereditary hemochromatosis (HH) with and without arthropathy

Methods: Cross-sectional study of 50 patients with HH [mean age 57.5 (±SD 11.6) years years, 26.0% female, median disease duration 8.8 (range 0.8-27.6) years] recruited at medical centers in Graz, Oberndorf and Vienna. HH arthropathy (HH-A) was defined as the presence of hand pain (VAS>10mm and/or ≥1 tender joint) plus ≥1 radiographic finding compatible with HH-A. Thirty-eight patients with hand osteoarthritis (HOA, according to ACR criteria) were studied for comparison [mean age, 60.1 (±SD 9.4), 89.5% female). Clinical examination was performed at 68 joints, and we retrieved data on hand function, pain and overall health status (all using a VAS), morning stiffness, ferritin levels and phlebotomy. Ultrasound was conducted at 40 joints (hand joints, hips, knees, ankles) by one rheumatologist blinded to clinical data using an ESAOTE Twice ultrasound device. Synovial hypertrophy and/or joint effusion (SH/E), Power Doppler (PD), osteophytes and erosions were subjectively graded from 0 to 3 in accordance with prior publications.

Results: Twenty-six (52.0%) HH patients were classified as HH-A. Mean age [57.1 (±SD 13.0) vs. 57.8 (±SD 9.7) years], median disease duration [7.5 (3.2-22.8) vs. 10.3 (0.8-27.6) years), median ferritin levels [83.6 (23-1060) vs. 66.1 ng/ml (14-853) as well as median duration [6.0 (0-23) vs. 6.0 (0-26) years] and number of phlebotomies/year [3 (0-5) vs. (2.5 (0-12)] were comparable between HH patients Without Arthropathy (HH-WA) and HH-A patients.<span">Patients with HH-A and HOA had a similar number of tender [4 (0-29) vs. 3 (0-40)] and swollen joints [0 (0-7) vs. 0 (0-6)], and similar scores for hand function [39.5 (0-100) vs. 47.0 (0-92) mm] and hand pain [31.0 (0-72) vs. 23.0 (0-86) mm]. These findings were absent/low in HH-WA patients by definition.Using ultrasound, we observed ≥1 erosion in 10 (41.7%) HH-WA patients, 12 (46.2%) HH-A, and 21 (55.3) HOA patients (p>0.2). Similarly, ≥1 osteophyte was observed in 23 (95.8%), 26 (100%) and 38 (100%) patients, respectively (p>0.2); median osteophyte score, however, was higher in HH-A than in HH-WA patients [19 (0-53) vs. 30 (3-69), p=0.019] and comparable between HH-A and HOA [36 (8-68)]. SH/E were observed in a high portion of HH-WA, HH-A and HOA patients [20 (83.3%), 25 (96.2%) and 38 (100%), respectively] whereas PD-findings were more common in the HH-A [n=21 (80.8%)] and the HOA [n=31 (81.6%)] than in the HH-WA group [n=12 (50.0%), p<0.05]. Also, SH/E scores were comparable between the three groups [HH-WA: 6.5 (0-25), HH-A 9 (0-32) and HOA 11.5 (1-30)] whereas PD-scores were higher in HH-A [2.5 (0-17] and HOA [2 (0-17] than in HH-WA cases [0.5 (0-9), p<0.05). In HH-A patients, there was a weak correlation between PD-score and hand function (0.23, p=0.031), whereas the other clinical parameters were unrelated to ultrasound results.

Conclusion: A high prevalence of ultrasound verified inflammatory and structural lesions were found in patients with hereditary hemochromatosis. Higher PD scores were observed in patients with arthropathy, and these were related to limited hand function.

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ASAH1 Gene Mutations Cause Acid Ceramidase Deficiency (Farber Disease), with Symptoms Including Arthritis and Subcutaneous Nodules. Patients Are Often Misdiagnosed with JIA, and Slowly Progressive Disease May Only be Diagnosed in Adulthood

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Background/Purpose: Mutations in the *ASAH1* gene cause acid ceramidase deficiency, accumulation of the pro-inflammatory and pro-apoptotic lipid ceramide, and a distinct set of clinical features, which can vary greatly in severity (Farber disease). Typically, Farber disease presents in childhood with polyarticular arthritis or joint contractures, subcutaneous nodules and a hoarse or weak voice due to nodule formation in the larynx. A recent report of patients diagnosed at over 40 years of age indicates that peripheral osteolysis can also

be caused by *ASAH1* mutations, and reinforces the fact that mild forms of the disease may only be diagnosed in adulthood. The prevalence of Farber disease is currently unknown, but it is likely underdiagnosed due to lack of awareness of the clinical presentation and of the availability of diagnostic testing. All known phenotypes are associated with autosomal recessive inheritance. Acid ceramidase enzyme replacement therapy is currently under development.

Methods: Using physician reporting and retrospective chart review, data from 22 recently diagnosed Farber disease patients has been collected to explore the spectrum of symptoms and disease severity associated with acid ceramidase deficiency. When available, data on previous diagnosis, presence of specific symptoms, age at presentation of first symptom, and time between presentation of each additional symptom was compared between patients with severe, moderate and attenuated phenotypes.

Results: Data indicates that Farber disease represents a broad clinical spectrum, with first symptoms presenting most often from infancy through late childhood, with a mean age at onset of 1.2 months for the most severe form in this group of patients, and reinforces the validity of the characteristic features of Farber disease: polyarticular arthritis, subcutaneous nodules and a hoarse or weak voice. However, there are patients who present with only one or two of these symptoms, and the spectrum of disease includes remarkably attenuated forms (mean age at onset of 4.5 years). 10 of 14 patients (71%) with moderate or attenuated disease were initially misdiagnosed with JIA. Treatment with anti-inflammatory therapies or disease modifying anti-rheumatic drugs (including biologics) may have some effect on the severity of pain and inflammation in Farber disease patients, and this can initially reinforce a misdiagnosis. Such treatments cannot resolve the major symptoms of Farber disease, or prevent disease progression.

Conclusion: The broad spectrum of phenotypes associated with *ASAH1* mutations indicate that Farber disease should be considered in the differential diagnosis of therapy resistant arthritis in childhood and adulthood, as well as in cases of peripheral osteolysis. A better understanding of the clinical symptoms associated with *ASAH1* mutations, and the availability of biochemical and genetic diagnostic testing, means that screening programs can be initiated to identify patients with Farber disease from among those currently treated by adult and pediatric rheumatologists around the world.

Disclosure: A. Solyom, Roivant Sciences, 5; **C. Simonaro**, Roivant Sciences, 2,Roivant Sciences, 6; **E. Schuchman**, Roivant Sciences, 2,Roivant Sciences, 6.

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Abstract Number: 1356

Correlation of Erythrocyte Sedimentation Rate with Glycohemoglobin Values and Other Patient Factors

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Background/Purpose: The erythrocyte sedimentation rate (ESR) is a laboratory test commonly used in clinical practice as an assessment of systemic inflammation. The glycohemoglobin (A1c) measures long-term serum glucose levels to screen for diabetes and evaluate glycemic control. Both of these tests use red blood cells to determine their values. The result of the ESR test is nonspecific and varies with factors including patient age, gender, body size, pregnancy, anemia, albumin, and more. This project sought to determine the correlation of A1c to ESR values while accounting for other relevant clinical factors.

Methods: Historical biomedical data from 2011 to 2014 were collected and analyzed. Patients with ESR values resulted within a 30-day period of glycohemoglobin values were included, with a total sample size of 22,984. Additional information was collected including age, gender, body mass index, smoking status, platelets, WBCs, C-reactive protein and hemoglobin. The dataset was then analyzed to determine the correlation of ESR values with glycohemoglobin values. Additional analyses evaluated the impact of other variables on the ESR value and construct a model based on this using forward selection methods.

Results: The correlation between ESR and A1c levels was 0.268, with a p-value of 2.2e-16 indicating a strong positive correlation.

Other variables that were significantly associated with the ESR level included hemoglobin, gender, creatinine, platelets, white blood cells (WBCs), and age (see **table 1**).

Table 1: Effect of Individual Variables on ESR Values.

Variable	Estimate	Standard Error	p-value
Intercept	37.6	1.26	<0.00001
Hemoglobin	-3.5	0.06	<0.00001
Glycohemoglobin	2.15	0.08	<0.00001
Creatinine	2.17	0.09	<0.00001
Platelets	0.02	0.001	<0.00001
WBC	0.24	0.03	<0.00001
Age	0.24	0.03	<0.00001
Male gender	-2	0.3	<0.00001

Fitting the full model using significant predicting variables yielded the following: **Model:** Expected (ESR) = 37.6 – 3.5(hemoglobin) + 2.15(glycohemoglobin) + 2.17(creatinine) + 0.02(platelets) + 0.24(WBCs) + 0.24(Age) – 2(Male) This model had an overall F-statistic of 1418 with a p-value of 2.2e-16, indicating a highly significant model. The R squared value for this model was 0.3102, indicating that 31% of the variability of ESR was explained by the model.

Conclusion: The traditional model used in interpreting erythrocyte sedimentation rates (ESR) is age divided by two plus five for males, though this is understood to be an incomplete model. It is established that many factors effect ESR values, and this project sought to quantify the effect of these variables on actual ESR values using a retrospectively collected large biomedical dataset. The variables that had a significant effect on ESR levels are shown in **table 1** and in the **model**. The most significant variable was hemoglobin, which had an inverse association with ESR. Other variables had a direct correlation to ESR. Elevated ESR values often result in referrals to rheumatology, and if there was a more accurate way to reliably interpret what an 'average' ESR level would be given a set of specific clinical factors it may help physicians and rheumatologists to frame and understand the significance of a given patients' ESR value.

Disclosure: B. LaMoreaux, None;

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Abstract Number: 1357

Clinical Description of Patients with Cytoplasmic Discrete Speckles on Indirect Immunofluorescence on HEp-2 Cells in a Universitary Hospital

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Background/Purpose: Indirect Immunofluorescence (IIF) shows different nuclear and cytoplasmic fluorescence patterns depending on the antibodies present in the cell. Cytoplasmic patterns are an unusual finding. Their study is not standardized and their clinical value is unknown. The Cytoplasmic Discrete Speckles (CDS) pattern comprises several antigens distributed in the endosomes, lysosomes and GW bodies. The purpose of this study is to describe demographic and clinical characteristics of patients with CDS pattern on IIF in a cohort of patients.

Methods: This is a retrospective descriptive study. We included all patients with a CDS pattern on IIF on HEp-2 cells with a titer equal or greater than 1/80, using a database of all IIF performed in a referral laboratory of a universitary hospital between 2007 and 2015.

We analyzed demographical and clinical information available on their clinical records. We included sex, age, health history and symptoms compatible with autoimmune diseases.

Results: In that period of time, 7085 IIF studies were performed and 21 patients showed CDS pattern (0.29%). We reviewed 17 out of 21 clinical records. We excluded 4 patients that did not have clinical records at the hospital. All patients were female, with a median age of 62 (range 50-81 years). Demographics and clinical characteristics are shown in table 1. We found no relationship between the IIF titer, health history and symptoms compatible with autoimmune diseases. Fourteen of the patients (82%) had at least one symptom of autoimmune disease. Eight of the patients (47%) had an autoimmune disease, being Hashimoto Thyroiditis the most frequent one (50%).

A high rate of respiratory symptoms was observed among these patients. Six of them (34%) referred dyspnea and dry cough. They had different underlying causes, including chronic obstructive pulmonary disease (COPD). Symptoms description is shown in table 2.

Conclusion: CDS pattern is uncommon. We found no association with any particular disease, and none of our patients had any of the diseases described in other studies. Taking into account the low prevalence of this pattern and the heterogeneity of symptoms, the study of antibodies underlying this IIF pattern seems more useful for cell biology study than for clinical use.

Table 1.

	Age	Sex	IIF titer	Health History	Sum of symptoms compatible with autoimmune disease
1	56	Female	1280	No	0
2	70	Female	1280	Hypothyroidism (antibodies lacking), gout, scleroderma, pulmonary hypertension, restrictive cardiopathy	4
4	52	Female	1280	No	1
10	62	Female	1280	No	2
16	69	Female	1280	Hashimoto Thyroiditis, 3 miscarriages	1
17	81	Female	1280	Primary Hyperparathyroidism	1
6	70	Female	640	Hypothyroidism (antibodies lacking), brain tumor	0
8	66	Female	640	Hashimoto Thyroiditis, Polymyalgia rheumatic	1
9	66	Female	640	No	0
11	53	Female	640	Mixed connective tissue disease	4
13	50	Female	640	Psoriasis, COPD, Discoid Lupus, fibromyalgia	3
3	60	Female	320	Dermatomyositis, Cryptogenic Organizing Pneumonia	3
7	52	Female	320	Hashimoto thyroiditis, Fibromyalgia, 3 miscarriages	1
12	51	Female	320	Non Hashimoto Hypothyroidism	2
15	59	Female	320	Hashimoto Thyroiditis, 3 miscarriages, dyspnea and chronic cough	1
5	72	Female	80	Hypothyroidism (antibodies lacking), Secondary Hyperparathyroidism, COPD.	1
14	71	Female	80	Asthma, Primary Hyperparathyroidism	1

Table 2.

	IIF titer	Rheum. disease	Dry eyes / Dry mouth	Morning Stiffness (over 1 hour)	Arthritis	Photo-sensitivity	Raynaud	Alopecia areata	Telangiect asia	Calci nosis	Sclero dactyly	Dyspnea /Dry cough	Muscle weakness	Rash
1	1280	No	No	No	No	No	No	No	No	No	No	No	No	No
2	1280	Sclero-derma	+	No	+	No	No	No	+	+	No	+	No	No
4	1280	No	No	-	no	No	No	No	No	No	No	No	No	No
10	1280	No	+	No	No	No	No	No	No	No	No	No	No	No
16	1280	No	No	No	No	No	No	+	+	No	No	No	No	No
17	1280	No	No	No	No	No	+	No	No	No	No	No	No	No
6	640	No	No	No	No	No	No	No	No	No	No	No	No	No
8	640	PMR	No	No	No	No	No	No	+	No	No	No	No	+
9	640	No	No	No	No	No	No	No	No	No	No	No	No	No
11	640	MCTD	No	+	+	No	No	No	No	No	No	+	+	No
13	640	Discoid Lupus	No	No	No	-	No	-	No	No	No	-	No	+
3	320	Dermato myositis	No	No	No	No	No	No	No	No	No	+	+	+
12	320	No	-	No	No	No	No	No	No	No	No	No	No	No
7	320	No	No	No	No	No	+	No	No	No	No	No	No	No
15	320	No	No	No	No	No	No	No	No	No	No	+	No	No
5	80	No	No	No	No	No	No	No	+	No	No	+	No	No
14	80	No	No	No	No	+	No	No	No	No	No	No	No	No

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Response of Hidradenitis Suppurativa to Biologic Therapy

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Response of Hidradenitis Suppurativa to Biologic Therapy

Background/Purpose: Hidradenitis suppurativa (HS) is a chronic, debilitating inflammatory disease of apocrine sweat glands, characterized by recurrent abscessing inflammation. The prevalence is around 1-4% in young adults. Despite the prevalence of HS in the US it largely unstudied and treatment is extrapolated from studies done in a northern European population. Molecular drivers of HS are poorly understood, and traditional disease modifying anti-rheumatic (DMARD) therapies have been largely ineffective. Targeted biologic therapies including TNF-α inhibitors have been used with some success. Adjuvant biologic therapy after radical resection has been shown to reduce risk of recurrence in HS. The purpose of this study is to analyze the outcomes of patients with HS followed in our dedicated HS clinic and to assess how treatment with biologic agents affects disease activity scores including Hidradenitis Sartorius Score (HSS) and Hurley Stage in a US population.

Methods: This research was conducted through the Wound Etiology and Healing Study (WE-HEAL Study), an IRB approved biospecimen and data repository. All subjects gave written informed consent for longitudinal collection of their data while they receive treatment according to standard of care. At the time of data lock, of the 565 patients enrolled in the WE-HEAL study, 67 had HS. Modified Hidradenitis Sartorius Score (HSS) and Hurley Stage were analyzed according to medication exposures.

Results: Consistent with the known demographics of HS, the mean age of HS patients in this cohort was 40.12 ± 13.82 years, and they were 67.2% female and 71.6% African American. Mean HSS score at the first visit was 62.48 ± 47.45, and 67.2% were Hurley Stage III at the time of first visit. In this cohort patients treated with TNF inhibitor showed significant reduction in HSS score after treatment (mean HSS 74.88 ± 49.87 pre-treatment and 30.48 ± 42.18 post-treatment, p=0.0002).

Conclusion: The cohort of HS patients followed in the WE-HEAL study is representative of the population affected in the US with a high prevalence of women and African Americans. Treatment with TNF-α inhibitors was associated with significant improvement in disease activity scores in this population.

Disclosure: S. Mulani, None; **S. McNish**, None; **S. Harris**, None; **V. K. Shanmugam**, None.

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New Markers for Celiac Disease: Anti-Neo-Epitope Human and Microbial Transglutaminases

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Background/Purpose: Microbial transglutaminase (mTg) and human tissue Tg (tTg) complexed to gliadin peptides present neo-epitopes. Antibodies against these complexes are called tTg neo-epitope and mTg neo-epitope. Reliability of antibodies against the

non-complexed and complexed forms of both transglutaminases to reflect intestinal damage and to diagnose the pediatric Celiac Disease (PCD) was compared.

Methods: 95 PCD patients, 99 normal children (NC) and 79 normal adults (NA) were tested using the following ELISAs detecting IgA, IgG or both IgA+IgG combined: *AESKULISA*® tTg (tTg, RUO), *AESKULISA*® tTg New Generation (tTg neo-epitope (tTg-neo)), *AESKULISA*® mTg (RUO) and *AESKULISA*® mTg neo-epitope (mTg-neo, RUO). Marsh criteria were used for the degree of intestinal injury.

Results: All anti-mTg-neo and anti-tTg-neo levels were higher ($p<0.001$) compared to the single antigens. tTg-neo IgA and IgG+IgA were higher than mTg-neo IgA and IgA+IgG ($p<0.0001$). The antibody activities reflecting best the increased intestinal damage were: mTg-neo IgA> mTg-neo IgA+IgG > tTg-neo IgG ≥ mTg-neo IgG > tTg-neo IgA> tTg-neo IgA+IgG. Taken together, mTg-neo IgG and tTg-neo IgA & IgA+IgG correlated best with intestinal pathology ($r=0.5633$, $r=0.6165$ & $r= 0.6492$; $p<0.0001$, $p<0.0001$ & $p<0.0001$ respectively).

Conclusion: The complexed forms of both transglutaminases exhibited a higher OD activity and better reflected intestinal damage in PCD, compared to the non-complexed forms. mTg is immunogenic in children with CD and by complexing to gliadin its immunogenicity and pathology reflection is enhanced.

Disclosure: T. Matthias, None; **S. Neidhöfer**, None; **P. Jeremias**, None; **A. Lerner**, None.

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Discontinuation Causes of Biological Therapies: Over a Five-Year Period. Biobadasar

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Background/Purpose: To analyze discontinuation causes of biologics therapies (bDMARDs) in patients who are registered in the database BIOBADASAR.

Methods: Database included demographics of patients, type and duration of treatments and clinical information of adverse events. A control group was included for comparison consisting of patients not treated with bDMARDs but similar demographics. Values are expressed as mean±standard deviation, median (ranges), and frequencies (percentages), as appropriate. Student's t-test and the chi-squared test were applied and Fisher's exact test was used where necessary. Multivariate cause-specific regression models were used to measure the association with discontinuation. Values of $p < 0.05$ were considered to be statistically significant.

Results: From August 2010 to January 2016, 3483 patients were registered in BIOBADASAR; mean age:56.115.7 yrs; 78.9% females; 2745 (78.6%) had RA, 395 (11.3%) PsA, 150 (4.3%) JIA, 144 (4.1%) SLE, 107 (3.07%) AS. Therapy with non-bDMARDS included 2011(57.7%) patients. Different bDMARDs were used in 1472 (42.3%) patients for a total of 2736 (1.85/patients) treatments cycles. Of these, 1184 (45.8%) were discontinued; etanercept 43.6% (521/1193), infliximab 64.1% (109/156), abatacept 43.5% (123/283), adalimumab 41.2% (262/626), rituximab 34.5% (78/226), belumimab 29.2% (7/24), golimumab 21.6% (11/51), certolizumab 16.6% (20/120) and tofacitinib 8.8% (5/57). The main reasons for bDMARD discontinuation were: Inefficacy: 450 (38%); adverse events 368 (31.1%); lack of insurance: 239 (20.2%) Discontinuation due to inefficacy was significantly higher in patients who were treated with infliximab; and tofacinitib showed a higher frequency of switching due to adverse events in comparison with the rest of biological agents (Table 1). In a logistic regression model, predictors associated with discontinuation of bDMARD treatment were: older age (OR 1.01 95% CI 1.01-1.02), concomitant use of corticoids (OR 1.72, 95% CI 1.44-2.04) and use of infliximab (OR 2.17, 95%CI 1.53-3.08). However, use of tofacitinib (OR 0.14, 95%CI 0.04-0.48, p=0.002), certolizumab (OR 0.21, 95%CI 0.11-0.39, $p \leq 0.00001$), golimumab (OR 0.34, 95%CI 0.15-0.80, p=0.014) and rituximab (OR 0.68, 95%CI 0.49-0.95, p=0.026) showed less discontinuation rate. **Table 1.** Discontinuation causes of biologics therapies in BIOBADASAR

Reason for discontinuation	Abatacept n (%)	Adalimumab n (%)	Belimumab n (%)	Certolizumab n (%)	Etanercept n (%)	Golimumab n (%)	Infliximab n (%)	Rituximab n (%)	Tocilizumab n (%)	Tofacitinib n (%)
Adverse event	32(26)	86(32.8)	1(14.3)	8 (40)	152(29.2)	5(45.5)	34(31.2)	28(35.9)	18(37.5)	4 (80) a
Unknown	1(0.8)	3(1.2)	0(0)	0(0)	8(1.5)	1(9.1)	1(0.9)	3(3.9)	1(2.1)	0(0)
Pregnancy	0(0)	3(1.2)	1(14.3)	2(10)	10(1.9)	0(0)	0(0)	1(1.3)	0(0)	1 (20)
Inefficacy	53(43.1)	106(40.5)	3(42.9)	8 (40)	192(36.9)	4(36.4)	55(50.5) b	16(20.5) c	13(27.1)	0(0)
Lack of cover	29(23.6)	44(16.8)	0(0)	2(10)	121(23.2)	1(9.1)	9(8.3) d	19(24.4)	14(29.2)	0(0)
Lost of follow up	7(5.7)	18(6.9)	0(0)	0(0)	33(6.3)	0(0)	7(6.4)	6(7.7)	0(0)	0(0)
Remission	1(0.8)	2(0.8)	2(28.6) e	0(0)	5(1)	0(0)	3(2.8)	5(6.4) f	2(4.2)	0(0)
total	123(100)	262(100)	7 (100)	20 (100)	521(100)	11(100)	109(100)	78(100)	48(100)	5 (100)

P values: a. 0.035; b. 0.005; c. 0.001; d. 0.001; e. 0.005; f. 0.008. Chi2 test or Fisher's exact test as appropriate

Conclusion: Discontinuation was significantly associated with older age, corticosteroid use and infliximab therapy. Certolizumab, Golimumab and Rituximab had protective effect against discontinuation.

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Abstract Number: 1361

The Role of Von Willebrand Factor Antigen As a Disease Biomarker in the Clinical

Assessment of Children with Juvenile Dermatomyositis

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: With the advent of new therapies, outcomes for children with juvenile dermatomyositis (JDM) have significantly improved. Accurate markers of clinically *inactive*disease are thus fundamental in the effort to reduce unnecessary prolongation of treatment. Muscle enzymes are frequently monitored, however individual enzyme levels do not always correlate with disease activity. Von Willebrand factor (vWF) antigen has been shown to be elevated in children with active JDM, albeit without specificity and absolute consistency. This study aims to evaluate the utility of normal vWF antigen as an indicator of disease quiescence, as well as the usefulness of vWF antigen levels in the assessment of disease flare.

Methods: This longitudinal, retrospective cohort study analyzed disease activity of children with JDM from January 2009 to April 2014, evaluating serial clinical and laboratory measurements. Disease flare was defined by the presence of 2 or more of the following: elevation in muscle enzymes, worsening muscle strength (manual muscle testing - MMT) or functional ability (Childhood Myositis Assessment Scale - CMAS), worsening extramuscular manifestations or worsening physician global assessment of disease activity (PhyGloVAS). Disease inactivity was defined according to modified PRINTO criteria: 3 of the 4 following elements: creatine kinase≤150, CMAS score≥48, MMT≥78 and PhyGloVAS≤0.2.

Results: A total of 357 visits were evaluated from 22 patients. The median number of visits per patient was 12 (IQR: 7-17). Using modified PRINTO criteria, 77/357 (22%) visits met criteria for disease inactivity. In multivariate analysis, the odds of children with normal vWF antigen levels to be in a state of disease quiescence was 3 times greater than the odds of those with abnormal levels after controlling for age, gender and disease duration (p<0.0001) (Table 1). Laboratory values taken from a previous visit (within 3 months duration of a flare) were assessed in separate multivariate analyses as predictors of the upcoming flare (Table 2).

Table 1: Factors predictive of disease quiescence

	OR	CI	p-value
Age (years) at visit	1.1495	1.0368, 1.2743	0.0081
Female gender	0.3924	0.2316, 0.6647	0.0005
Disease Duration	0.9969	0.9799, 1.0142	0.7232
Normal vWF antigen	3.0750	1.8009, 5.2504	<.0001

Table 2: Recent biomarker assessment as predictors of disease flare*

	OR	CI	p-value
Prior vWF antigen	2.4298	1.5287, 3.8621	0.0002
Prior LDH	3.2687	1.8245, 5.8556	<.0001
Prior CPK	1.3715	0.7933, 2.3707	0.2580
Prior AST	1.7859	1.0720, 2.9752	0.0260
Prior Aldolase	0.6452	0.4519, 0.9214	0.0159

* Individual biomarker results are each from separate multivariable analyses of which each adjusts for the other variables which are not presented in the table (age, gender and disease duration)

Conclusion: With improved therapies, clinical remission in JDM is an achievable goal. Accurately identifying children with inactive disease is critical in reducing long-term treatment toxicity and overall morbidity. This data supports the use of vWF antigen, LDH and AST as predictors of disease flare; while traditional markers, CPK and aldolase, were less reliable markers of flare. To our knowledge, this is the first study to demonstrate the utility of normalization of vWF antigen in defining clinically inactive disease.

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Abstract Number: 1362

Associations Between 25-Hydroxyvitamin D, Parathyroid Hormone, and Cathelicidin Concentrations with Inflammation and Cardiovascular Risk in Subjects with Pediatric Systemic Lupus Erythematosus

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Background/Purpose: Previous studies have shown associations between reduced serum 25-hydroxyvitamin D (25OHD) levels, inflammation, and disease activity in pediatric systemic lupus erythematosus (pSLE). The goal of this study was to assess the role of parathyroid hormone (PTH) in its relationship with vitamin D and inflammation, and to better understand the role of human cathelicidin (LL-37) in pSLE. LL-37 is upregulated by activated vitamin D and has antimicrobial and immunomodulatory properties. We examined the relationship between 25OHD and LL-37 concentrations to determine whether LL-37 concentrations are associated with the chronic inflammation seen in pSLE.

Methods: Available frozen serum samples from the 3-year APPLE study (n=221 participants) were used to determine 25OHD, PTH, and LL-37 levels at study entry. Pearson's correlations and Chi-square tests were used to evaluate the relationships between 25OHD, PTH, LL-37, inflammation, disease activity, and infection using baseline values collected as part of the study.

Results: 201/221 APPLE participants had serum available for analysis. 61/201 had vitamin D deficiency at baseline. Serum 25OHD was inversely associated with PTH, $r = -0.39$ ($p < 0.01$), but not with LL-37 ($p = 0.58$). LL-37 levels ranged from 18.3 to 289.2 ng/mL, with a mean level of 57.2 (SD 30.6) ng/mL. PTH was not associated with hsCRP, carotid IMT, or HDL- or LDL-cholesterol, but was negatively associated with lipoprotein(a) levels, $r = -0.15$ ($p = 0.03$). Despite no association with serum 25OHD, LL-37 was negatively associated with total cholesterol, HDL- and LDL-cholesterol, and positively associated with age (Table 1). There was no significant difference in mean LL-37 levels in participants with reported infection as an adverse event during the 3 years of study.

Conclusion: As expected, PTH was negatively associated with 25OHD, but interestingly, LL-37 levels were not associated with 25OHD. Serum levels may not reflect the interaction of 25OHD and LL-37 at a cellular level. Notably, many LL-37 levels were significantly elevated over normal. There may be an association between LL-37 and cardiovascular risk (via cholesterol). These exploratory results addressing the role of LL-37 levels in pSLE inflammation and infection appear worthy of future study. Table 1:

Variable 1	Variable 2	Pearson correlation coefficient	P-Value
25OHD (ng/mL)	LL-37 (ng/mL) Baseline	0.04	0.58
25OHD (ng/mL)	**PTH (pg/mL) Baseline**	**-0.39**	**<0.01**
LL-37 (ng/mL)	PTH (pg/mL) Baseline	0.07	0.30
PTH (pg/mL)	Age at Randomization (Years)	-0.10	0.14
PTH (pg/mL)	Body Mass Index (kg/m*m)	0.04	0.60
PTH (pg/mL)	SLEDAI Total	-0.01	0.93
PTH (pg/mL)	Mean-Mean IMT Common (mm)	0.01	0.84
PTH (pg/mL)	Total Cholesterol (mg/dL)	-0.13	0.06
PTH (pg/mL)	Triglycerides (mg/dL)	0.01	0.99
PTH (pg/mL)	HDL Cholesterol (mg/dL)	-0.11	0.11
PTH (pg/mL)	LDL Cholesterol (mg/dL)	-0.11	0.13
PTH (pg/mL)	**Lp(a) (mg/dL)**	**-0.12**	**0.03**
PTH (pg/mL)	Homocysteine Level (mcmol/L)	0.01	0.90
PTH (pg/mL)	High Sensitivity CRP (mg/L)	0.03	0.65
Log of LL-37 (ng/mL)	**Age at Randomization (Years)**	**0.15**	**0.03**
Log of LL-37 (ng/mL)	Body Mass Index (kg/m*m)	0.10	0.16
Log of LL-37 (ng/mL)	SLEDAI Total	-0.14	0.06
Log of LL-37 (ng/mL)	Mean-Mean IMT Common (mm)	0.01	0.98
Log of LL-37 (ng/mL)	**Total Cholesterol (mg/dL)**	**-0.22**	**<0.01**
Log of LL-37 (ng/mL)	Triglycerides (mg/dL)	-0.02	0.82
Log of LL-37 (ng/mL)	**HDL Cholesterol (mg/dL)**	**-0.19**	**<0.01**
Log of LL-37 (ng/mL)	**LDL Cholesterol (mg/dL)**	**-0.19**	**<0.01**
Log of LL-37 (ng/mL)	Lp(a) (mg/dL)	0.02	0.83
Log of LL-37 (ng/mL)	Homocysteine Level (mcmol/L)	-0.13	0.08
Log of LL-37 (ng/mL)	High Sensitivity CRP (mg/L)	-0.02	0.76

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Abstract Number: 1363

Serum Adipokines in Juvenile Dermatomyositis Are Associated with Disease Activities and Cardiac Function

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Background/Purpose: We have earlier demonstrated redistribution of adipose tissue in JDM patients. There is an increase in visceral adipose tissue (VAT), a highly active metabolic organ producing adipokines which are involved in many inflammatory responses and cardiovascular complications. We aimed to investigate serum adipokine levels in JDM patients and controls, and explore the associations with disease activity and damage, VAT and cardiac function.

Methods: Fifty-nine patients with JDM and 59 age- and sex matched controls were included in a cross sectional study median 16.8years after disease onset. Body composition was analyzed by total body dual-energy X-ray absorptiometry (DXA). VAT (g) was quantified (DXA) only in individuals above 18 years. Serum adipokines, including pro-inflammatory (leptin and visfatin) and anti-inflammatory (adiponectin and apelin-12) analyzed by ELISA, were measured in serum drawn at follow-up. Long axis strain (LAS) and early diastolic tissue velocity (E') assessed by echocardiography were used as markers for systolic and diastolic cardiac function, respectively. Inactive disease was measured by the PRINTO criteria, disease activity by DAS and disease damage by myositis damage index (MDI).

Results: Leptin levels were higher in patients compared with controls (11.0ng/ml (IQR 4.4-25.2) vs 5.8ng/ml (IQR 3,0-14.7), p=0.010). Adiponectin was lower, but not significant in patients vs. controls (IQR 4.3microgr/ml (IQR 2.7-6.1) vs 5.5microgr/ml (IQR 3.7-6.9), p 0.091). Apelin-12 (0.8 ng/ml (IQR 0.7-1.3) vs 0.7 (IQR 0.6-0.9), p=0.005) and visfatin levels (5.7ng/ml (IQR 4.1-8.1) vs 4.2 (IQR 4.0-6.0), p=0.032) were higher in patients with active than inactive disease. Disease duration, lipodystrophy and calcinosis at follow-up correlated negatively with adiponectin (rsp-0.464, p=0.000; rsp -0.447, p=0.000 and rsp-0.358, p=0.005). Leptin correlated with DAS muscle at follow-up (rsp 0.284, p=0.029). MDI total at follow-up correlated negatively with adiponectin (rsp -0.315, p=0.015). VAT correlated negatively with adiponectin in all patients, with active and inactive disease and also with controls (rsp -0.578, p=0.000; rsp -0.647, p=0.004; rsp -0.492, p=0.028 and rsp -0.445, p=0.007 respectively). LAS and E' correlated positively with both adiponectin (rsp 0.534, p=0.008 and rsp 0.435, p=0.001) and apelin-12 (rsp 0.347, p=0.007 and rsp 0.279, p=0.034). Leptin correlated with diastolic blood pressure (BP), whereas adiponectin correlated negatively with systolic and diastolic BP, numbers not given.

Conclusion: The pro-inflammatory adipokines leptin and visfatin are elevated in JDM patients and in the subgroup with active disease, respectively. Leptin is associated with higher DAS and elevated blood pressure. Lower levels of anti-inflammatory adipokines (adiponectin and apelin-12) were associated with higher VAT, higher disease activity, higher BP and impaired cardiac function. Our finding suggests that increased VAT and imbalanced adipokine secretion is involved in disease activity and cardiovascular abnormalities in JDM.

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Efficacy and Safety of Tumour Necrosis Factor Antagonists in a Large Cohort of Juvenile Dermatomyositis Patients

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Background/Purpose: Some patients with juvenile dermatomyositis (JDM) have a disease course which is refractory to multiple drug treatments. There is evidence that prolonged disease activity is associated with increased mortality and morbidity. High levels of TNFα have been reported in JDM patients with a long disease course, suggesting it may play a significant role in refractory disease. There are no published clinical trials of this therapy but some are in progress. The aim of this study was to evaluate the efficacy and safety of anti-TNF treatment in UK JDM Cohort and Biomarker Study patients.

Methods: Data were analysed from children who were recruited to the UK JDM Cohort and Biomarker Study, met Bohan-Peter criteria and were on anti-TNF treatment at the time of analysis, and had had at least 3 months of therapy. Childhood Myositis Assessment Scale (CMAS), Manual Muscle Testing (MMT8), muscle enzymes and physicians global assessment (PGA) were recorded. Skin disease was assessed using modified skin Disease activity score (DAS).

Results: 67 patients with JDM actively treated with anti-TNF agents were analyzed. 41 patients were female (61%). The median [IQR] age at disease onset was 5.2 [3.4-9.5] years and the median age at beginning of anti-TNF was 10.1 [6.5-14] years. The median disease duration at beginning of anti-TNF was 3.2 [1.8-5.3] years and the median duration on anti-TNF was of 2.55 [1.5-3.9] years. Muscle involvement significantly improved, with median [IQR] CMAS and MMT8 values at initiation of anti-TNF therapy of 45.50 [39.75-52.25] and 74 [59.5-79.5] respectively, and at current evaluation (or date of anti-TNF treatment completion) of 53 [50-53] and 79 [74.580] ($p<0.0001$ and $p=0.0097$; Mann Whitney test), respectively. For skin involvement the initial modified DAS was 4 [2-5] and final 1 [0-3] ($p<0.0001$; Mann Whitney test). Assessing global disease activity the initial PGA was 2.9 [1.3-4.3] and final 0.5 [0-1.45] ($p<0.0001$; Mann Whitney test). Sixteen patients (24%) switched their anti-TNF treatment. 62.5% of the switches were due to therapy failure, 25% due to adverse events and 12.5% for patient preference in subcutaneous administration. Of 31 adverse events registered (13.3 adverse events per 100 patient-years), 12 were considered severe. One patient died due to small bowel perforation (not felt to be related to the use of TNF antagonists). The remaining adverse reactions were not severe and 79% (n=15) of them were due to infections causes. In 5 of the mild to moderate adverse reactions the drug had to be discontinued and switched to another TNF antagonist, while in the remaining patients temporarily withholding the drug proved sufficient. No malignancies or tuberculosis were reported.

Conclusion: This study is one of the largest to explore the efficacy and safety of TNF antagonist treatment in a large independent cohort of JDM patients. Both muscle and skin involvement appeared to improve after anti-TNF treatment.

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Abstract Number: 1365

Trends in Medication Usage in Patients with Juvenile Dermatomyositis

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Background/Purpose: Juvenile dermatomyositis (JDM) is a systemic autoimmune disease with characteristic rashes and chronic muscle inflammation. Because of its rarity, most therapeutic choices are based on small trials or retrospective series. The purpose of this study was to evaluate changes in treatment over time, and factors associated with medication choices in JDM.

Methods: We performed a retrospective review of therapies received by 334 patients with probable or definite JDM enrolled in the Childhood Myositis Heterogeneity Study. Patients were diagnosed from November 1965 to September 2014 (median August 1994). We evaluated the number and type of medications received and their durations, including differences by year of diagnosis, onset severity, and myositis autoantibodies (MSAs). Logistic regression and ROC analysis determined 1997 as a cut point for increasing usage of drugs other than prednisone.

Results: The median follow-up duration was 46 months and treatment duration was 33 months. Oral prednisone (PRED) was the primary therapy used by 99.4% of JDM patients, but was used as monotherapy in only 49% of patients diagnosed after 1997 vs. 85% before 1997 (P<0.001). Other medications were used more frequently in patients diagnosed after 1997 vs. before, including methotrexate (MTX) (95% vs. 60%), Intravenous Immunoglobulin (IVIG) (64% vs. 25%), hydroxychloroquine (HCQ) (70% vs. 37%), other DMARDs (41% vs. 14%) and cytotoxics/biologics (28% vs. 6%, P<0.001 for all). Patients diagnosed after 1997 had a greater number of drug trials per year (median 2.3 vs. 1.0) and a longer percentage of follow-up time on treatment compared to patients diagnosed before 1997. The median daily maximum PRED dose was 2.0 mg/kg/d [IQR 1.2-2.0], and did not differ by onset severity or MSAs. However, the median time to half the initial PRED dose was shorter in patients diagnosed after vs. before 1997 (11 vs. 22 months, P<0.01). The median time to discontinuation of PRED was 47 months [IQ 24-104] and for MTX was 50 months [IQ 24-86] by Kaplan-Meier analysis. Thirty-seven percent of patients discontinued all medications at last follow-up, with a median time to discontinuation of 85 months. There were no significant differences in time to discontinuation of PRED, MTX, or other medications by onset severity or MSAs, but there was a longer time to discontinuation for IVMP, MTX and IVIG in patients diagnosed after 1997 (P<0.01). We examined factors for use of IVMP, MTX, IVIG, and HCQ by multiple logistic regression. All drugs had greater usage in patients diagnosed after 1997 (OR 2.2-13.4). IVMP was more frequently used in patients with severe onset (OR 3.0), with anti-p155/140 and anti-MJ Abs (OR 2.7 and 2.5), and with a higher total initial symptom score (OR 21.9). HCQ was used more commonly in patients with anti-p155/140 Abs (OR 2.2). MTX was more frequently used in older patients at diagnosis (OR 1.1).

Conclusion: PRED is the mainstay of therapy in JDM. There is increasing use of MTX, IVIG and other drugs/biologics in combination after 1997, and PRED was reduced faster for this group compared with patients diagnosed before 1997. Diagnosis year, onset severity, age at diagnosis, and MSAs were associated with specific medication usage in JDM.

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Evidence Based Criteria for Corticosteroid Tapering/Discontinuation. an Analysis of the Paediatric Rheumatology International Trials Organization (PRINTO) Trial in New Onset Juvenile Dermatomyositis

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Background/Purpose: Corticosteroids in juvenile dermatomyositis (JDM) alone or in association with other immunosuppressive drugs, namely methotrexate (MTX) and cyclosporine (CSA), represent the first-line treatment option for new onset JDM. No clear evidence based guidelines are actually available to standardize the tapering and discontinuation of corticosteroids in JDM. The purpose of the study was to provide an evidence-based approach for corticosteroid tapering/discontinuation through the analysis of the patients in the PRINTO new onset JDM trial.

Methods: New onset JDM children were randomized to receive either prednisone (PDN) alone or in combination with MTX or CSA. All children were given initially three daily pulses of intravenous methylprednisolone (30 mg/kg/pulse), and then PDN 2 mg/kg/day. After 1 month PDN was tapered to 1 mg/kg/day, from month 2 to 6 was tapered to 0.2, at month 12 to 0.1, and then discontinued at month 24. Major therapeutic changes were defined as the addition or major increase in the dose of MTX/CSA/other drugs or any other reasons for which the patient was dropped from the trial (adverse events, lost to follow-up, etc). Patients who followed the steroid tapering protocol and discontinued PDN at month 24 with no major therapeutic change (group 1) represented the reference standard for the best clinical outcome. Group 1 was compared with those following the steroid protocol, but with other major therapeutic changes (group 2), and with the group who deviated from the steroid protocol with/without major therapeutic changes (group 3). JDM core set measures (CSM) were compared in the 3 groups at 6-12-18 and 24 months (Table).

Results: 139 children were enrolled in the trial: 47 on PDN, 46 on PDN+CSA and 46 on PDN+MTX. We identified 57 (41%) patients for group 1, 24 (17%) for group 2 and 58 (42%) for group 3. At baseline all 3 groups had a high level of disease activity with no differences in the CSM. In group 1 (PND off no failure) there were 12 (21%) patients randomized to PDN alone, 21 (37%) to PDN+CSA and 24 (42%) to PDN+MTX. When we compared the three groups, significant differences were found in all CSM at each time point of analysis ($p<0.0001$). In particular Group 1, when compared to Group 2 and 3, had the lowest level of disease activity at all time points; the decrease of disease activity was primarily within the first 6 months of treatment. Group 2 and 3 were overlapping in the levels of disease activity reached at all the time points and were globally higher when compared to group 1. **Table: Core set measures values at different time points in the 3 groups of patients (only key results are reported).**

	OFF PDN Failure: No Group 1 N=57	OFF PDN Failure: Yes Group 2 N=24	PDN ON Failure Yes or No Group 3 N=58	P value
Month 6: MD global	0.5 (0-2)	2.6 (0.8-5)	3 (0.6-6)	<0.0001
Parent global	1 (0-1.8)	3.1 (0.5-5)	2.5 (0.8-5.8)	0.0002
CHAQ	0.1 (0-0.5)	0.1 (0-0.9)	0.5 (0-1.9)	0.0007
DAS	3 (0-5)	6.5 (1-11.5)	8 (4-12)	<0.0001
CMAS	47 (42-51)	45 (35-48.5)	35 (21.5-47)	0.0001
CHQ-PhS	51.8 (46.2-54.9)	47.5 (20.3-54.1)	36.3 (16.6-50.6)	<0.0001
MMT	77 (70-80)	70 (59-78.5)	64 (51-75)	<0.0001
Month 12: MD global	0 (0-1)	2.6 (1-5.5)	3 (0.6-6)	<0.0001
Month 18 DAS	0 (0-3)	6 (2.5-11.5)	9 (2-12)	<0.0001
Month 24: CMAS	50 (48-52)	42 (36-50)	36.5 (21.5-48)	<0.0001

Conclusion: The PRINTO protocol from the trial in new onset JDM might constitute the reference evidence-based approach for corticosteroid tapering for possible use in current clinical practice.

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Long-Term Outcomes and Their Predictors in Patients with Juvenile Idiopathic Inflammatory Myopathies of Adult Age: A Referral Population Study

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Background/Purpose: To investigate the long-term outcomes and prognostic factors for pts with juvenile-onset idiopathic inflammatory myopathies (JIIM) who are currently adults.

Methods: Adults with JIIM were assessed at two referral centers between 1994 and 2016. Predictor variables included demographics, clinical symptom scores, disease course, worst ACR functional status, drug therapies and co-morbid conditions. Outcomes included physician global activity (PGA) and damage (PGD), Myositis Damage Index (MDI), HAQ, muscle strength testing (MMT26), and total

number of drugs at last visit. The analysis was done in GraphPad Prysm (version 7.0a).

Results: Forty-nine pts with probable or definite JIIM (42 dermatomyositis, 5 polymyositis, 2 overlap myositis) had a median age of 22 yrs. and median disease duration of 11 yrs.; 47% were Caucasian, 82% female. Among these, 55% had a chronic course, 31% polycyclic,10% a monocyclic illness course, 4% undefined. Review of treatment revealed past use of daily prednisone in 84% and current use in 58%; 56% received IV steroids in past and 16% still required IV steroids. Methotrexate (MTX) was the most commonly used DMARD with 79% receiving it in the past and 40% with continued use; 32% used biologics or cytotoxic therapies and 7% remained on these. Median assessment scores at final visit included PGA 1.6 of 10 [IQR 1.0-3.7]; PGD 3.0 [IQR 2-4.4], HAQ 0.4 of 3, and MMT26 229 of 260 [IQR 212-257]. Damage was present in 96% with a median MDI score of 7 [IQR 4-10]. Cutaneous (80%) and muscle (78%) damage were most frequent and most severe (median cutaneous 3 [IQR 1-5], muscle 2 [IQR 1-3]). The most frequent damage features included persistent weakness (71%), muscle dysfunction (68%), contractures (67%), cutaneous scarring/atrophy (61%), calcinosis (57%), muscle atrophy (49%), and lipodystrophy (32%). The most frequent co-morbid conditions included hyperlipidemia (18%), depression or anxiety (18%), and fibromyalgia (6%). Significant univariable predictors of cutaneous damage included disease duration, ACR functional class and prior use of MTX (p 0.016–0.046), whereas for muscle damage, predictors included the past muscle symptom score, earlier year of diagnosis, and prior MTX use (p=0.004-0.025). Predictors of total MDI score included past GI symptom score, younger age at diagnosis, disease duration and ACR functional class (p=0.0004-0.032). Predictors of final PGA scores included past GI and pulmonary symptom scores, chronic disease course, and past use of biologics/cytotoxics (p=0.007-0.028). Pts were receiving a greater number of drugs at last visit if they were younger at time of enrollment, had a shorter disease duration, and had co-morbid depression or anxiety (p=0.0001-0.033).

Conclusion: This is one of the largest cohorts of patients with JIIM evaluated for long-term outcomes. Our results showed the majority of JIIM pts in this referral-based population have ongoing disease activity and significant disease damage, especially in the cutaneous and muscle systems, and frequent use of prednisone and other drug therapies as adults. Predictors of poor outcomes included disease duration, medication usage, and clinical symptom scores.

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Abstract Number: 1368

Clinical Course of Juvenile Dermatomyositis Presenting As Skin Predominant Disease

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Background/Purpose: Juvenile dermatomyositis (JDM) is a chronic inflammatory disorder of the skin and striated muscle. A subset of patients can present with rash only, labeled as *skin predominant JDM* (spJDM) for this study. The natural course of patients with spJDM and optimal treatment is unknown. The purpose of this study is to describe the clinical course of spJDM patients and assess for early indicators that may predict progression to classic JDM.

Methods: A chart review to identify patients presenting with spJDM was performed on all patients with the diagnosis code for dermatomyositis seen at 3 sites (Children's Hospital of Wisconsin, Boston Children's Hospital, IWK Health Centre). Data collected included patient demographics, presenting symptoms and exam findings, initial treatment, muscle enzymes, muscle biopsy,

electromyography, and magnetic resonance imaging (MRI). Patients were categorized as either amyopathic (no weakness on exam and no diagnostic studies consistent with myositis) or hypomyopathic (no weakness but diagnostic studies showed subclinical myositis). Follow up visits were reviewed for development of weakness.

Results: Twenty-four patients presented with spJDM: 8 (33%) were amyopathic on initial evaluation, while 16 (67%) were hypomyopathic. None of the amyopathic patients later developed weakness (follow up 3-144 months, median 31 months). Six (38%) hypomyopathic patients later evolved into classic JDM with weakness (follow up 10-85 months, median 45 months). Time to development of weakness ranged from 3 to 24 months after onset of rash. Patients who developed weakness had varying degrees of subclinical myositis as evidenced by lab or MRI. MRI was abnormal in 7 of 20 patients (35%) at baseline. Only 2 of these 7 patients (29%) later developed weakness. Patients with an abnormal MRI were more likely to receive systemic corticosteroids and/or methotrexate as part of initial therapy (43% vs 8%). The combination of hydroxychloroquine (HCQ) with a topical calcineurin inhibitor was the most common first line agent (21%). However, whether alone or in combination with a topical agent, HCQ was initiated in 46% of patients. Nine percent of patients treated with HCQ with or without topical agents developed weakness, while 50% treated with topical agents alone and 40% treated with systemic steroids developed weakness. Methotrexate was always started in conjunction with systemic steroids (4/24). Two patients with no initial treatment were later treated with HCQ or topical steroid for persistent skin disease and never had weakness.

Conclusion: Our work suggests that topical therapies do not prevent the development of weakness, but systemic treatment with HCQ may diminish the development of weakness in spJDM (50% vs 9%). No amyopathic patient progressed to develop weakness, while 38% of hypomyopathic patients developed weakness. This suggests the importance of comprehensive baseline testing using clinical, lab and MRI assessments, and that hypomyopathic patients should be followed more closely to assess for disease progression over time. Larger trials are needed to identify long term outcomes, optimal treatment, and whether treatment of spJDM prevents weakness.

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Abstract Number: 1369

Features Distinguishing Clinically Hypo- and Amyopathic Juvenile Dermatomyositis (CAJDM) from Juvenile Dermatomyositis (JDM)

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Background/Purpose: Clinically Amyopathic Juvenile Dermatomyositis **(**CAJDM) is a distinct clinical phenotype of JDM in which patients (pts) often have characteristic JDM rashes with little to no evidence of muscle involvement. Our purpose was to investigate features distinguishing CAJDM from JDM.

Methods: Demographic, clinical, laboratory, and treatment data from 13 (10 hypo- and 3 amyopathic) pts meeting Sontheimer's criteria for CAJDM and from 65 myositis autoantibody (MSA)-matched (1:5) JDM pts meeting probable or definite Bohan and Peter criteria were examined. Differences were evaluated by Fisher's exact and Mann-Whitney tests and significant univariable results were examined in multivariable logistic regression. MSAs were tested by standard immunoprecipitation methods. Scores for each organ system were based on the number of signs/symptoms present at diagnosis vs. the number assessed.

Results: Sixty-nine percent of CAJDM had anti-p155/140 Abs, 2 each (15.4%) had anti-MDA5 or were MSA negative. CAJDM more

frequently had p155/150 Abs than the full cohort of 400 JDM (37.4% p155/140 Ab, p=0.038). CAJDM were younger at diagnosis vs. Ab-matched JDM (median 4.2 vs. 8.0 yrs, p=0.004). CAJDM tended to more often have a family history of autoimmune disease compared to JDM (83% vs. 48%, p=0.07). Gottron's papules were most often the first rash in CAJDM (54% vs.14%, p=0.004) whereas combination of heliotrope and Gottron's papules was most often the first rash in JDM (82% vs. 8%, p=0.0001). CAJDM more frequently had mild illness severity at onset (77% vs. 11%, p<0.0001). There were no differences in speed of disease onset, environmental factors preceding diagnosis, or median UV index scores (average and highest) based on residential location at time of diagnosis between the two groups. CAJDM less frequently had myalgias (7.7% vs. 63%, p=0.0004), arthralgias (15.4% vs. 56.9%, p=0.013), mucous membrane lesions (7.7% vs. 45%, p=0.012), calcinosis (0 vs. 35.4%, p=0.008), and fatigue (38.5% vs. 84.6%, p=0.0012) than JDM, and no ILD. The median muscle (0.0 vs. 0.29), skeletal (0 vs. 0.5) and overall (0.07 vs. 0.20) clinical symptom scores at diagnosis were lower in CAJDM than JDM ($p \leq 0.001$ for each). Muscle enzyme levels were less frequently increased in CAJDM (10-38% vs. 60-87%, $p \leq 0.005$); peak CK levels were lower (median 158 vs. 394 U/L, p=0.005) in CAJDM. CAJDM received less treatment, including fewer drug therapies (median 2 vs. 4, p=0.003) and treatment trials (median 2.5 vs. 5, p=0.004), had shorter durations on steroids (median 3.6 vs. 24 months, p=0.003), and less frequent use of prednisone (60% vs. 100%, p=0.0003). Multivariate logistic regression revealed a lower median muscle system score (p=0.009) was the only significant predictor of CAJDM compared to JDM. At a median f/up duration of 2.5 yrs, all CAJDM were ACR functional class I, 62% had rash, and none developed clinically significant muscle weakness or calcinosis vs. JDM ($p \leq 0.03$).

Conclusion: CAJDM may be distinguished from JDM in that they more likely have p155/140 Abs, are younger at diagnosis, have fewer clinical manifestations, especially muscle symptoms, lower muscle enzyme levels, receive less therapy including oral prednisone and have more favorable outcomes.

Disclosure: G. Mamyrova, Cure JM, 2; **T. Kishi**, The Myositis Association, 2; **N. Bayat**, Cure JM, 2; **I. N. Targoff**, None; **L. Wu**, None; **O. Y. Jones**, None; **R. Curiel**, Cure JM, 2; **F. W. Miller**, None; **L. G. Rider**, Cure JM, 2.

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Abstract Number: 1370

Development and Validation of a Composite Disease Activity Score for Juvenile Dermatomyositis

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Background/Purpose: JDM is a multisystem vasculopathic disease that primarily affects the skin and muscles. Most tools for assessment of disease activity in JDM are lenghty, complex, and centered on physician's evaluation. We aim to develop a composite disease activity score for JDM and provide preliminary evidence of its validity.

Methods: A panel of experts devised the score, named Juvenile DermatoMyositis Activity Index (JDMAI), based on their clinical experience and a literature review. The JDMAI is composed of 4 clinical domains: 1) physician's global assessment of overall disease activity on a 0-10 visual analog scale (VAS); 2) parent's/child's global assessment of child's wellbeing on a 0-10 VAS; 3) muscle strength/endurance; 4) skin disease activity. Eight versions of the JDMAI were tested, which differed in the tools used to assess items 3 and 4. For item 3, two versions included the hybrid MMT/CMAS (hMC) with score in deciles (0-10), two the hMC with its original score (0-100), two the MMT-8 (0-80), and two the CMAS (0-52). For item 4, four versions included physician's global rating of skin disease activity on a 0-10 VAS, and four included the cutaneous domain of the Disease Activity Score (DAS) (0-9). Validation was conducted on 275 patients included in a multinational dataset, evaluated at baseline and at 6, 12, and 24 months. Construct validity was assessed by calculating between-subject and within-subject correlations with JDM outcome measures not included in the JDMAI; internal consistency was assessed with Cronbach α and responsiveness to change with standardized response mean (SRM).

Discriminant ability was determined in a different multinational dataset of 142 patients, by assessing the JDMAI score in patients rated in remission, low, moderate, or high disease activity by the attending physician.

Results: In between-subject exercise, all JDMAI versions showed strong (r>0.7) correlations with CHAQ (0.72-0.82), muscle VAS (0.77-0.87), muscle DAS (0.76-0.86) and total DAS (0.68-0.90), and moderate correlations (r=0.4-0.7) with pain VAS (0.50-0.57) and Myositis Damage Index (MDI) (0.51-0.60). Owing to the interrelatedness of longitudinal data from an individual patient, within-subject correlations were higher and were all strong (r=0.76-0.97). SRM was good (1.09-1.57) and was higher for JDMAI 1 and 2. Cronbach's alpha was fair (0.70 and 0.69) for JDMAI 1 and 2, and poor for other JDMAI versions. All JDMAI versions discriminated strongly between patients in different disease activity states (Kruskal-Wallis test, $p < 0.001$).

Conclusion: Overall, the JDMAI1 and JDMAI2 revealed the best measurement properties in validation analyses. The JDMAI1 (score range: 0-40) may be preferred over the JDMAI2 as it weights equally its 4 components, whereas in the JDMAI2 (score range: 0-39) items 1 to 3 are scored on a 0-10 scale and skin disease on a 0-9 scale.

JDMAI 1	JDMAI 2	JDMAI 3	JDMAI 4	JDMAI 5	JDMAI 6	JDMAI 7	JDMAI 8
Physician's global assessment (0-10)							
Parent's global assessment (0-10)							
hMC in deciles (0-10)*		hMC (0-100)*		MMT-8 (0-80)*		CMAS (0-52)*	
Skin VAS (0-10) 0-40	Skin DAS (0-9) 0-39	Skin VAS (0-10) 0-130	Skin DAS (0-9) 0-129	Skin VAS (0-10) 0-110	Skin DAS (0-9) 0-109	Skin VAS (0-10) 0-82	Skin DAS (0-9) 0-81

See text for abbreviations. *: scores were reversed for consistency with other parameters

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Abstract Number: 1371

Comparison of Patient and Physician Reported Global Disease Activity Measures in Juvenile Dermatomyositis

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Background/Purpose: Patient reported outcomes (PROs) are becoming increasingly recognized as important in the care of patients with chronic diseases, such as Juvenile Dermatomyositis (JDM); however, the correlation of PROs to physician (MD) reported scores in clinical practice is unclear. We sought to assess the correlation between patient (PT) and MD reported global disease activity in JDM and examine factors associated with disparate scores.

Methods: We identified a cohort of patients with physician-diagnosed JDM through the Childhood Arthritis and Rheumatology Research Alliance registry, an IRB approved, multi-center registry developed to capture data about children with rheumatic diseases. Data were abstracted using a standardized form, including demographics, medication history, PRO measures (global disease activity on a 10 point visual analog scale (VAS), childhood health assessment questionnaire (CHAQ), pain and overall quality of life scores), and physician reported outcome measures (global disease activity VAS, subjective weakness, muscle strength scoring, muscle enzyme

testing, examination findings and associated co-morbidities). We assessed the discordance between PT and MD global disease activity VAS, and defined ≥3 point difference as discordant. We then evaluated factors associated with discordance. Variables were compared using chi-square for categorical and Kruskal-Wallis analysis for continuous, with significance $p<0.01$.

Results: In the registry, 563 patients with JDM were identified. Mean age was 10.6 years (range 6.9-14.7) with average age of onset 5.5 (3.6-9.3). Most patients were female (403, 72%), white (442, 79%) and non-Hispanic (471, 84%). Overall, PT and MD global disease activity VAS were similar in 78% of cases. Of discordant scores, 16% of PT rated VAS ≥3 points above MD (indicating greater disease activity), while 6% of MD VAS were higher than PT VAS. When PT VAS was ≥3 points above MD, these patients had significantly worse CHAQ scores, higher pain scores, and more frequently reported poor quality of life (all $p<0.01$). When MD VAS was ≥3 points above PT, these patients had more frequent muscle enzyme abnormalities, weakness and lower strength score, rash, nail fold changes, calcinosis, joint involvement, and current steroid treatment (all $p<0.01$). Prevalence of GI/cardiac involvement tended to be higher with discordance in either direction. There was no statistical evidence that demographic factors (current age, age of onset, gender, race or ethnicity, or income level) were associated with discordant VAS scores.

Conclusion: While patients and physicians frequently agree on global disease activity VAS ratings in JDM, discordance is seen in over 20%. When patients report discordantly worse/higher scores, this is associated with worse PRO measures of functional status, pain and quality of life. When physicians report higher scores, this is associated with poorer objective measures of strength, abnormal muscle enzyme testing, more co-morbidities and physical exam findings. This study highlights the importance of incorporating PROs into the routine assessment of patients with JDM.

Disclosure: H. Tory, None; **D. Zurakowski**, None; **S. Kim**, None.

Abstract Number: 1372

Comparison of the Printo 2010 and Printo/International Myositis and Clinical Studies Group (IMACS) 2016 Improvement Criteria in the Printo Trial in New Onset Juvenile Dermatomyositis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile dermatomyositis (JDM) is a systemic autoimmune disease characterized by chronic skeletal muscle inflammation with weakness and skin involvement. The Paediatric Rheumatology INternational Trials Organisation (PRINTO) and the International Myositis and Clinical Studies Group (IMACS) developed criteria to evaluate response in clinical trials which have been recently updated and validated. We compared the PRINTO 2010 (JDM 2010 response criteria) with PRINTO/IMACS 2016 response criteria (JDM 2016 criteria) for improvement in the PRINTO new onset JDM trial.

Methods: New onset JDM children were randomized to receive either prednisone (PDN) alone or in combination with methotrexate (MTX) or cyclosporine A (CSA). Patients were evaluated at months 6, 12, 18 and 24 with different levels of JDM 2010 criteria (improvement of 20-50-70 or 90% in at least three of the 6 core set measures and worsening <30% in no more than one). The same

patients were re-analyzed with the continuous JDM 2016 criteria which evaluate absolute percent change into three categories (total score 0-100): minimal (≥30), moderate (≥45), major (≥70) improvement. Clinical trials data were analyzed according to the intention-to-treat (ITT) principle with patients discontinuing (lack of efficacy, safety, etc.) considered as non-responders from that point onwards.

Results: 139 children were enrolled in the trial: 47 on PDN, 46 on PDN+CSA and 46 on PDN+MTX. The two sets of criteria showed a similar capacity to recognize different levels of improvement of the disease at 6, 12, 18 and 24 months, after treatment with PDN, PDN+CSA or PDN+MTX as shown by the overlapping 95% CI intervals at various time points (Table). In particular, at month 6, 51% patients on PDN versus 72% on PDN+CSA or PDN+MTX achieved at least JDM 2010 20% improvement (p=0.023) as compared to 55% and 74% with the JDM 2016 minimal improvement (p=0.027). At month 24, 38% patients on PDN versus 60% on PDN+CSA or PDN+MTX achieved at least JDM 2010 20% improvement (p=0.016) as opposed to 38% and 61% with JDM 2016 minimal improvement (p=0.012). Kappa agreement between the two criteria with ITT approach were at least in the moderate range (0.61-0.8) as follows: 0.75, 0.75, 0.77, 0.79 at 6-12-18 and 24 months, respectively. The JDM 2016 criteria, similar to the 2010 criteria, confirmed the superior efficacy of combined treatment with PDN+CSA or PDN+MTX versus treatment with PDN alone. **Table 1.** 2010 and 2016 improvement criteria after 6, 18 and 24 months of treatment with PDN or PDN+MTX or PDN+CSA (only few examples are reported)

2010 or 2016 criteria of improvement	**PDN**	**PDN+CSA**	**PDN+MTX**	
	N=47	***N=46***	**N=46**	**P values**
	N (%) [95%CI]	**N (%) [95%CI]**	**N (%) [95%CI]**	
Month 6				
2010 ≥20%	24 (51%) [36-66]	32 (70%) [54-82]	33 (72%) [56-84]	**0.023**
2016 at least minimal	26 (55 %) [40-70]	34 (74%) [59-86]	34 (74%) [59-86]	**0.027**
Month 18				
2010 ≥50%	20 (42%) [28-58]	30 (65%) [50-79]	29 (63%) [47-77]	**0.015**
2016 at least moderate	21 (45%) [30-60]	30 (65%) [50-79]	30 (65%) [50-79]	**0.020**
Month 24				
2010 ≥70%	18 (38%) [24-54]	26 (56%) [41-71]	26 (56%) [41-71]	**0.042**
2016 at least major	17 (36%) [23-51]	27 (59%) [43-73]	27 (59%) [43-73]	**0.012**

Conclusion: Both response criteria have shown a similar discrimination in evaluating different levels of improvement in new onset JDM patients treated with 3 alternative treatment strategies.

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Abstract Number: 1373

Evaluation of the Reliability of the Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and Cutaneous Assessment Tool Binary Method (CAT-BM) in Juvenile Dermatomyositis Among Pediatric Dermatologists, Rheumatologists, and Neurologists

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SESSION INFORMATION

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Background/Purpose: The Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) and Cutaneous Assessment Tool-Binary Method (CAT-BM) have been shown to be reliable and valid outcome measures to assess cutaneous disease in adult dermatomyositis (DM) and juvenile DM (JDM), respectively. This study compared the CDASI and CAT-BM for use by pediatric dermatologists, pediatric rheumatologists, and pediatric neurologists in patients with JDM.

Methods: Five pediatric dermatologists, five pediatric rheumatologists, and five pediatric neurologists each evaluated 14 patients with JDM using the CDASI, CAT-BM, and skin Physician Global Assessment (PGA) scales. Inter-rater, intra-rater reliability, construct validity, and completion time were compared.

Results: Inter-rater reliability for CDASI activity and damage scores was good to moderate for pediatric dermatologists and rheumatologists, but poor for pediatric neurologists. The inter-rater reliability for CAT-BM activity scores was moderate for pediatric dermatologists and rheumatologists, but poor for pediatric neurologists and poor across all specialties for damage scores. Intra-rater reliability for the CDASI and CAT-BM activity and damage scores was moderate to excellent for pediatric dermatologists, rheumatologists, and neurologists. Strong associations were found between skin PGA activity and damage scores and CDASI or CAT-BM activity and damage scores, respectively ($p<0.002$). The CDASI had a mean completion time of 5.1 minutes versus the CAT-BM of 2.8 minutes.

Conclusion: Our data confirm the reliability of the CDASI activity and damage scores and the CAT-BM activity scores when used by pediatric dermatologists and rheumatologists in assessing JDM. Significant variation existed in the pediatric neurologistsÕ scores.

Table 1. Inter-rater reliability of Skin Assessment Tool Scores in JDM patients among pediatric specialists*

	Within pediatric dermatologists (n=5)	Within pediatric rheumatologists (n=5)	Within pediatric neurologists (n=5)
CDASI			
Activity	0.52 (0.44-0.61)	0.81 (0.76-0.85)	0.47 (0.39-0.56)
Damage	0.59 (0.51-0.67)	0.59 (0.51-0.66)	0.46 (0.37-0.54)
CAT-BM			
Activity	0.58 (0.50-0.66)	0.67 (0.60-0.74)	0.42 (0.33-0.51)
Damage	0.49 (0.41-0.58)	0.48 (0.39-0.57)	0.29 (0.20-0.38)
Skin PGA			
Activity	0.64 (0.50-0.78)	0.47 (0.39-0.56)	0.38 (0.29-0.47)
Damage	0.71 (0.65-0.83)	0.31 (0.22-0.40)	0.73 (0.67-0.79)

*Intra-class correlation coefficients (95% C.I.) Abbreviations: Abbreviations: CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; CAT-BM: Cutaneous Assessment Tool-Binary Method; PGA: Physician Global Assessment

Table 2. Intra-rater reliability of Skin Assessment Tool Scores in JDM patients among pediatric specialists*

	Within pediatric dermatologists (n=5)	Within pediatric rheumatologists (n=5)	Within pediatric neurologists (n=5)
CDASI			
Activity	0.90 (0.78-1.00)	0.91 (0.79-1.00)	0.65 (0.29-1.00)
Damage	0.97 (0.94-1.00)	0.64 (0.27-1.00)	0.78 (0.53-1.00)
CAT-BM			
Activity	0.86 (0.70-1.00)	0.88 (0.74-1.00)	0.91 (0.80-1.00)
Damage	0.93 (0.85-1.00)	0.73 (0.44-1.00)	0.89 (0.76-1.00)
Skin PGA			
Activity	0.95 (0.90-1.00)	0.50 (0.03-0.96)	0.83 (0.64-1.00)
Damage	0.84 (0.66-1.00)	0.55 (0.12-0.98)	0.96 (0.91-1.00)

*Intra-class correlation coefficients (95% C.I.) Abbreviations: Abbreviations: CDASI: Cutaneous Dermatomyositis Disease Area and Severity Index; CAT-BM: Cutaneous Assessment Tool-Binary Method; PGA: Physician Global Assessment

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Disclosure: J. Tiao, None; **R. Feng**, None; **E. M. Berger**, None; **J. F. Brandsema**, None; **C. C. Coughlin**, None; **N. Khan**, None; **E. A. Kichula**, None; **M. A. Lerman**, None; **S. Lvovich**, None; **P. J. McMahon**, None; **L. G. Rider**, None; **A. I. Rubin**, None; **L. V. Scalzi**, None; **D. M. Smith**, None; **A. J. Taxter**, None; **J. R. Treat**, None; **R. P. Williams**, None; **S. W. Yum**, None; **J. Okawa**, None; **V. P. Werth**, None.

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Abstract Number: 1374

Predictors of Changes in Disease Activity Among Children with Juvenile Dermatomyositis

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SESSION INFORMATION

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Background/Purpose: Determinants of changes in disease activity among patients with juvenile dermatomyositis (JDM) are unknown. Our objective was to develop scores to predict changes in disease activity over the next 6 months among children with active disease at baseline using the CARRA registry.

Methods: The CARRA registry included 658 subjects enrolled between May 2010 and October 2014 with definite or probably JDM defined based on Bohan and Peter criteria, which were modified to include magnetic resonance imaging. Among the 297 subjects with at least one follow-up visit between 4 and 10 months (median 6 months) after baseline, we studied the 65 subjects with active disease at baseline(defined as physician global ≥3 of 10). Linear regression models were used to build risk scores for changes in disease activity adjusted for baseline disease activity, age, sex and disease duration.

Results: The study population included 65 patients (mean age at baseline: 9.3 (SD 4.4) years; 66% female; 72% white) with median disease duration of 1.7 (range: 0.1 to 15.2) years. Disease activity improved significantly from baseline to 6 month follow-up as measured by patient global health score (median 4; IQR 2-6 at baseline vs median 2; IQR 1-5 at follow-up; p=0.008), patient pain score (median 2; IQR 0-5.5 to median 1.0, IQR 0=4; p=0.014), physician global (median: 4, IQR: 3-6 to 2, IQR 1-3; p<0.001) and Childhood Myositis Assessment Scale (CMAS) (median 41, IQR 33-47 to median 47, IQR 43-51; p<0.001). Anti-nuclear antibodies (p=0.013) and hydroxychloroquine use (p=0.045) were significant predictors of less improvement in patient global after adjusting for age, sex, disease duration and baseline patient global (R-square improved from 0.19 for adjustors alone to 0.34 for the full model). Anti-nuclear antibodies (p=0.001) and V/shawl sign (p=0.005) were significant predictors of less improvement in patient pain after adjusting for age, sex, disease duration and baseline patient pain (R-square improved from 0.29 for adjustors alone to 0.46 for the full model). There were no identified risk factors for improvement in physician global after adjustment for physician global at baseline, age, sex and disease duration. Small joint arthritis (p<0.01) predicted less improvement and dysphagia/dysphonia (p=0.033) predicted greater improvement in CMAS after adjusting for age, sex, disease duration and baseline CMAS (R-square improved from 0.73 for adjustors alone to 0.86 for the full model).

Conclusion: Disease characteristics can help identify patients who are less likely to improve over time. Risk scores to predict future changes in disease activity could be used to trigger more aggressive treatment earlier in the disease course.

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Abstract Number: 1375

A Five Year Study of 102 Children with Juvenile Myositis: Disease Course and Outcomes

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Background/Purpose: Children with juvenile myositis (JM) have a variable disease course, in part associated with myositis specific/associated antibodies (MSA). Time to off medications has not been well documented. Published reports show 18-55% develop calcifications, but little is known about disease course and damage after 60 observation months. Objective: To examine the records of children with JM at specific time points over 5 years to determine disease activity, therapy duration and evidence of damage.

Methods: After obtaining informed consent, 102 children were enrolled. 65 were treated elsewhere then transferred care (TR). 37 were diagnosed at our center, untreated at first visit (UTR). MSAs (Oklahoma Medical Research Foundation Clinical Immunology Laboratory) were determined by immunodiffusion and immunoprecipitation. Disease Activity Scores (DAS) for skin and muscle involvement, nailfold capillary end row loop (ERL) number, reported cataracts and BMI were obtained at months 0 (first visit to our center) 6, 12, 24, 36 and 60, as well as periodic bone density (DXA) evaluation. Data was analyzed using ANOVA or t tests.

Results: Table 1 describes patient features. TR and UTR groups were similar for race and age at disease onset. TR patients presented after a mean of 12.7 months of treatment (SD 17.23). At first visit, the DAS was essentially equivalent for both groups but at 60 months was significantly lower for UTR ($p=0.04$). Mean time to off medication was 3.8 years (SD 1.54). Calcifications were present in 4 (10.8%) UTR and 8 (12.3%) TR. Cataracts were reported in 13 (35.1%) UTR and 19 (29.2%) TR. TR had a lower average lumbar Z-score at months 0 and 60 than UTR, though not statistically significant. At 60 months, the mean BMI percentile of each group was 66th. ERL number improved in both groups, approaching the normal value of 7. MSA distribution was: p155/140 (29.4%), none (27.5%), Mi-2 (5.9%), MJ (3.9%), MDA5 (1%), Ro (2.9%), Ro plus another MSA (6.9%), three antibodies (12.7%) and antibodies seen in overlapping connective tissue disease ± MSA (9.8%). TR patients with ≥1 MSA trended to have the lowest lumbar Z-score ($p=0.085$) but groups were too small for further analysis.

Conclusion: Between TR and UTR patients, there were few differences at first visit and at 60 months. TR patients had a higher DAS total and muscle at 60 months, possibly reflecting more severe disease, thus prompting referral to our center. MSA distribution was similar to previously reported frequencies but only 11.8% had calcifications, much less than previously reported. Mean lumbar spine Z-scores were below average for age and cataracts occurred in 31.4% of patients, supporting the need for steroid-sparing JM treatments. Our study describes a large JM patient cohort through 60+ treatment months, a middle-term outcome rarely reported in JM literature.

Table 1. Disease Features of Untreated and Treated JM patients at first visit to the Cure JM Myositis Clinic (month 0) and 60 months

Untreated patients, mean (SD) [n=x] total N=37	Treated patients, mean (SD) [n=x] total N=65	p value	All patients, mean (SD) [n=x] total N=102	
Age of disease onset (years)	5.64 (2.87) [n=37]	6.59 (4.15) [n=65]	NS	6.24 (3.75) [n=102]
DAS total month 0 (maximum 20)	10.31 (3.30) [n=35]	10.66 (4.1) [n=64]	NS	10.54 (3.81) [n=99]
DAS total month 60 (maximum 20)	1.96 (2.53) [n=37]	3.14 (3.14) [n=63]	0.04	2.71 (2.98) [n=100]
DAS muscle month 60 (maximum 11)	0.45 (1.08) [n=37]	0.95 (1.78) [n=63]	NS	0.77 (1.57) [n=100]
DAS skin month 60 (maximum 9)	1.51 (2.21) [n=37]	2.19 (2.32) [n=63]	NS	1.94 (2.29) [n=100]
Time to medication discontinuation (years)	4.12 (1.88) [n=28]	3.53 (0.98) [n=26]	NS	3.84 (1.54) [n=54]
Lumbar Z-score at month 0	-0.18 (1.16) [n=17]	-0.48 (1.19) [n=42]	0.027	-0.39 (1.18) [n=59]
Lumbar Z-score at month 60	-0.19 (1.01) [n=28]	-0.57 (1.00) [n=46]	0.013	-0.42 (1.01) [n=74]
BMI percentile at month 0	53.64 (23.87) [n=14]	70.82 (28.58) [n=29]	NS	65.23 (28.06) [n=43]
BMI percentile at month 60	66.6 (31.29) [n=30]	66.38 (29.11) [n=59]	NS	66.46 (29.68) [n=89]
ERL number at month 0	4.45 (1.12) [n=36]	4.48 (1.21) [n=62]	NS	4.47 (1.17) [n=98]
ERL number at month 60	5.93 (1.15) [n=33]	5.63 (1.29) [n=62]	NS	5.73 (1.25) [n=95]

Disclosure: L. M. Pachman, None; **M. L. Curran**, None; **G. A. Morgan**, None; **M. C. Amoruso**, None; **I. N. Targoff**, None; **C. C. Huang**, None.

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Abstract Number: 1376

In Juvenile Dermatomyositis, Organ Damage Is Comparable after Median 13.5 and 21.5 Years Follow-up Time, Despite Sustained Disease Activity

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Background/Purpose: All previous studies of disease outcome in juvenile dermatomyositis (JDM) patients have been based on retrospective data or cross sectional examination. We aimed to examine if disease activity, muscle strength and organ damage changed over time in an unselected cohort of JDM patients reassessed after long-term follow-up.

Methods: Patients who were included in a cross-sectional examination in 2005-2008 (visit 1) were invited for a re examination in 2013-2015 (visit 2). Patients were divided in active and inactive disease by the Paediatric Rheumatology International Trials Organisation (PRINTO) criteria. Disease Activity Score (DAS) was used to measure disease activity in skin and muscle, while the myositis damage index (MDI) was used to assess cumulative organ damage. The manual muscle test (MMT) and child myositis assessment scale (CMAS) were used to measure muscle strength/endurance, respectively. Also, use of anti-inflammatory medication was assessed.

Results: 42 patients (62% female) participated in both visits. Duration between the visits was mean 7.5 (1.0) years, and disease duration from symptom onset was median 21.5 years, (range 7.6-42.7). No difference in cumulative organ damage, muscle strength / endurance or disease activity measures was found between the visits, except that DAS muscle was higher in visit 2 (Table 1). By the PRINTO criteria, 25(60%) had inactive disease at visit 2; 4 of those used anti-inflammatory medication. Of the 17 (40%) active patients, only 3 used anti-inflammatory medication. 29 patients remained in the same PRINTO category at both visits (18 inactive and 11 active), whereas 7 active patients became inactive and 5 inactive patients became active between the visits.

Conclusion: Despite 40 % of JDM patients still had active disease after median 21.5 years follow-up and the majority of active patients were not on anti-inflammatory medication, no increase in cumulative organ damage was found over a 7.5 years time period.

Table 1: Disease characteristics in 42 JDM patients at visit 1 and visit 2

	Visit 1	**Visit 2**	P value
Follow-up time, years	13.4 (2.0-34.6)	21.5 (7.6-42.7)	NA
DAS muscle (0-11)	1.2 (1.2)	1.8 (1.6)	0.007
DAS skin (0-9)	3.3 (2.2)	2.7 (2.0)	NS
DAS total (0-20)	4.5 (2.7)	4.5 (2.6)	NS
MDI (0-40)	3.5 (2.5)	3.2 (1.9)	NS
PRINTO inactive, n (%)	23 (56)	25 (60)	NS
CMAS (0-52)	50 (28-42)	49 (39-52)	NS
MMT-8 (0-80)	79 (61-80)	78 (50-80)	NS
On prednisolone, n (%)	6 (14)	3 (7)	NS
On methotrexate, n (%)	9 (21)	7 (17)	NS

Numbers are mean (SD) or median (range) if not otherwise stated; NA, not assessed; NS, non-significant

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Disclosure: K. S. Berntsen, None; **B. Flatø**, None; **I. Sjaastad**, None; **H. Sanner**, None.

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Abstract Number: 1377

The Role of Muscle MRI in Detecting a Flare-up of Juvenile Dermatomyositis

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster II: Myositis, Systemic Lupus Erythematosus, Sjögren's Syndrome

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose : The course of juvenile dermatomyositis (JDM) has improved greatly over the last 70 years with early and aggressive use of corticosteroids, immunosuppressive medications, and biologics. Yet it remains difficult to detect disease flare-up because symptoms may be mild, signs of the rash and muscle weakness vary widely and are often equivocal, and laboratory tests, including muscle enzyme levels are often normal. Electromyography and muscle biopsy are invasive and not reliable so alternative tools are needed to detect disease flare-up and decide if further treatment is needed. The objective of this study is to determine the effectiveness of muscle Magnetic Resonance Imaging (MRI) in detecting JDM flare-up and affecting physician's decision-making regarding treatment.

Methods: Approval was obtained from the Internal Review Board of Nationwide Children's Hospital. Subjects were included if they met the modified Bohan and Peter dermatomyositis criteria and were seen between 1/2005 and 6/2015. The MRI was performed on both lower extremities without contrast with the following sequences: Axial T1, axial T2 fat saturation, axial and coronal inversion recovery, and axial diffusion weighted. The physician decision that a subject with JDM was in a flare-up was considered as the gold standard, using rash, muscle weakness by childhood myositis assessment scale, muscle enzymes, and myositis on MRI. We compared the MRI result with the physician's decision of relapse or not and evaluated whether there was a concordance or discordance between the MRI findings and the subsequent treatment decision.

Results: Forty-five JDM children were identified, of which 32 were females. The median age at diagnosis was 5.8 years. Eighty percent had weakness at diagnosis, 100% typical rash, 73% typical nail fold capillary changes. At diagnosis, muscle enzymes were compatible with JDM generally (CK 52%, LDH 62%, aldolase 72%, AST 54% abnormal), EMG abnormal in 3/8, muscle biopsy typical of JDM in 10/11, and MRI abnormal demonstrating myositis in 31/40. Thirteen of the 45 subjects had a repeat MRI for a possible flare-up with differing indications: general proximal weakness in 4 subjects, hip, thigh or calf pain in 3 subjects, rash in 3 subjects, worsening nail fold changes in one subject, elevated enzymes in one subject, and to confirm remission in one subject. Three of 13 repeat MRI's were abnormal, demonstrating myositis. There was moderate agreement between the flare-up MRI findings and the physician's treatment decision (kappa=0.59); in each abnormal MRI case the physician decided to increase treatment (Bayes rule 100% agreement). When the MRI was negative for myositis in 10 patients, 7/10 physicians chose to continue same medications or to taper medications (70% agreement).

Conclusion: Our study suggests that MRI at a time of a JDM flare-up is useful, yielding a sensitivity of 50% and a specificity of 100% for flare-up using a physician's assessment of disease flare-up as the gold standard. Using Bayes rule, when an MRI shows myositis, physicians tend to treat 100% of the time and when an MRI shows no myositis, physicians in this study continued the same medications or tapered medications 70% of the time.

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Abstract Number: 1378

Pentraxin-3 Level Predicts Vasculitis and Mucocutaneous Involvement in Childhood-Onset Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a persistent or remitting-relapsing autoimmune disease that handled in the context of connective tissue diseases and also vasculitides. Although there are commonly used biomarkers of active kidney disease and central nervous system disease, there is not a specific marker for vasculitic involvement. Pentraxin-3 (PTX3) is derived primarily from vascular endothelium and innate immunity cells in response to local inflammation and plays an important role locally at the site of inflammation. Thus PTX3 seems to be a useful biomarker directly reflecting local inflammation and local vasculitis. To the best of our knowledge PTX-3 was not studied in children with SLE. In the present study, we aimed to compare the concentrations of plasma PTX-3 among childhood-onset SLE (c-SLE) patients and control groups and to assess the association of PTX-3 levels with SLEDAI-2K, clinical manifestations and laboratory results.

Methods: From October 2015 to May 2016, 76 c-SLE patients without active infection sign and symptom were eligible for this cross-sectional single center study. We have also measured pentraxin-3 level in 41 healthy and age-matched controls. Both the cumulative and current organ involvement and manifestations were recorded from patient records and from the last examination at that moment, respectively. All of the laboratory analyses were studied concurrently with PTX-3 levels. PedSDI and SLEDAI-2K scores at disease onset, at the most severe flare and at the last examination were calculated. Serum pentraxin-3 levels were measured by a commercially available enzyme-linked immunosorbent assay kit.

Results: Plasma PTX3 concentrations were measured in 76 patients with c-SLE and 41 control subjects. Plasma PTX3 concentration of the SLE patients was significantly higher than that of the healthy controls (mean 10.6 ± 8.2 vs. 2.7 ± 1.3 ng/mL, $p<0.001$). The ratio of females to males with c-SLE was 5.3:1. The mean SLEDAI scores decreased from 10.3±4.8 (at disease onset) to 5.2± 5.3 (at last examination). Additionally, only 10.5% (n=8) and 3.9% (n=3) of the cohort were displaying the signs of active nephritis and active neuropsychiatric disease at last examination. In patients with SLE, PTX3 concentrations were correlated with SLEDAI-2K ($p<0.001$), active vasculitis ($p<0.001$), Raynaud's phenomenon ($p = 0.006$) and active mucocutaneous involvement ($p<0.001$). PTX3 level was not associated with disease duration, anti-ds DNA antibody, decreased complement levels, PedSDI, active nephritis, active neuropsychiatric involvement, musculoskeletal involvement, hematological involvement, ESR,CRP, procalcitonin levels.

Conclusion: In brief, PTX3 levels were significantly correlated with SLEDAI scores. Additionally, its levels are found to be substantially increased in the presence of Raynaud's phenomenon and vasculitic manifestations. Thus predicting the vascular involvement early and quantitatively in a c-SLE patient with presumed clinically inactive, will provide a better management of the disease. In conclusion, as in other vasculitides, PTX3 may represent a potential biomarker for vascular involvement in c-SLE.

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Abstract Number: 1379

Evaluation of S100 Proteins As Potential Biomarkers of Global and Renal-Specific Disease Activity in Childhood-Onset Systemic Lupus Erythematosus

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Background/Purpose: Childhood-onset systemic lupus erythematosus (cSLE) is a heterogeneous disease with differing levels of disease activity and organ-specific disease manifestations in each individual. In particular, lupus nephritis (LN) persists as a leading cause of morbidity. We largely lack effective, non-invasive biomarkers to accurately detect LN activity and also to predict children at greatest risk for poor prognosis with LN. S100 proteins are a diverse group of calcium-binding proteins that can promote inflammation and be elevated in varied etiologies of nephritis. The purpose of this cross-sectional study was to evaluate five S100 proteins (S100A4, S100A6, S100A8/9 and S100A12) in both the serum and urine as potential biomarkers of global and renal-specific disease activity in a cohort of cSLE patients.

Methods: Patients were selected for inclusion from an ongoing cSLE Clinical and Research Database based on available serum at an active disease visit, designated by a SLE Disease Activity Index 2000 (SLEDAI-2K) ≥ 8. We then searched for an accompanying paired serum sample from a less active and ideally inactive visit if available. Serum and urine from the active and less active visits were analyzed for protein levels of S100A4, A6, A8/9 and A12 using commercial ELISAs (BÜHLMANN MRP8/14 and Circulex S100A12/EN-RAGE, S100A4, S100A6). Clinical characteristics were also collected on all patients for each visit, including demographics, standard lab values, organ specific disease activity and current medications.

Results: Serum S100 levels did not differ significantly between either paired or independent active/inactive visits, although S100A4 levels trended toward significance. Urine S100A4, A6 and A12 levels were elevated in cSLE patients with active LN, as defined by a renal SLEDAI ≥ 4, when compared to both cSLE patients with active disease but no LN and cSLE patients with inactive disease (refer to table for median S100 levels). Urine S100A4, A6 and A12 levels also differed by the degree of LN activity. In the paired sample analysis, only urine S100A4 levels differed significantly in patients with active LN, increasing by a median value of 4.98 ng/mL from inactive to active visits.

Conclusion: Higher levels of S100 proteins in the urine are associated with LN activity in our cSLE cohort. In particular, S100A4 and A6 levels are much higher in the urine than in the serum, suggesting the possibility of localized production within the kidney and a potential role in LN pathogenesis. S100 proteins could serve as novel biomarkers of LN; however, it will first be necessary to establish that elevation of urine S100 proteins is specific to LN. Further studies are required to validate urine S100 levels as a marker of LN activity in a separate cSLE cohort and to study the possible role of S100 proteins in LN pathogenesis.

Table 1. Summary Table for S100 Serum and Urine Protein Levels in Unpaired cSLE Samples

	(1)	(2)	(3)	(4)	(5)	(6)	P-value	P-value	P-value	P-value	P-value
Urine	Active (SLEDAI ≥ 8) (n=28)	Inactive (n=21)	Active LN (n=17)	Very active LN (n=9)	Less active LN (n=8)	Active SLE without LN (n=11)	(1) vs. (2)	(2) vs. (3)	(3) vs. (6)	(2) vs. (6)	(4) vs. (5)
A4 (ng/mL)	1.82 (0.63-11.21)	0.55 (0.17-1.21)	9.65 (1.62-16.63)	14.1 (9.65-24.1)	1.5 (1.03-4.56)	0.56 (0.34-1.49)	0.0053	<0.0001	0.0011	0.8518	0.0152
A6 (ng/mL)	504 (197-1184)	422 (95-542)	804 (393-1398)	1398 (1123-2082)	417 (224-605)	203 (154-418)	0.1332	0.0095	0.0049	0.6391	0.0055
A8/9 (ng/mL)	1066 (214-4185)	1420 (243-3749)	2620 (841-13434)	5474 (1362-14505)	1361 (268-2791)	217 (31-821)	0.6608	0.1006	0.0058	0.1802	0.1388
A12 (ng/mL)	7 (1.37-59.39)	5 (0.49-45)	50 (8-74)	61 (50-498)	3.87 (1.03-27.56)	3.27 (0.68-5.93)	0.3329	0.0309	0.0035	0.3312	0.036
	(1)	(2)	(3)	(4)	P-value	P-value	P-value	P-value			
Serum	Active (SLEDAI ≥ 8) (n=33)	Inactive (n=32)	Active LN (n=19)	Active SLE without LN (n=14)	(1) vs. (2)	(2) vs. (3)	(3) vs. (4)	(2) vs. (4)			
A4 (ng/mL)	0.44 (0.4-0.67)	0.39 (0.26-0.49)	0.44 (0.4-0.6)	0.46 (0.4-0.7)	0.0301	0.0569	0.7178	0.1088			
A6 (ng/mL)	166 (92-262)	124 (77-236)	165 (76-304)	195 (92-252)	0.4533	0.5812	0.9856	0.4997			
A8/9 (ng/mL)	4921 (783-6833)	2186 (327-4027)	4352 (1084-6463)	6402 (593-10725)	0.0801	0.164	0.4184	0.1426			
A12 (ng/mL)	164 (66-456)	117 (42-307)	153 (86-373)	227 (64-470)	0.2579	0.2847	0.8993	0.4631			

* Data are presented as median (interquartile range), non-parametric analyses with the Wilcoxon rank sum test were used to calculate two-sided p-values
* Very active LN was defined by a renal SLEDAI ≥ 12 and less active LN by a renal SLEDAI ≤ 8

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Abstract Number: 1380

Multicenter Prospective Study on the Role of Urinary HER2 As a Lupus Nephritis Biomarker

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Background/Purpose:

HER2 (Human Epidermal Growth Factor Receptor 2) is dramatically overexpressed in the glomeruli and in the tubular compartment of patients with lupus nephritis, but not in other proliferative glomerulonephritides. HER2 expression is also increased in NZM2410 mice and it correlates with disease activity. In human mesangial cells, α-interferon increases HER2 expression, which regulates miR-26a and miR-30b levels. These miRNAs control the expression of cell cycle related genes and consequently regulate mesangial cell proliferation. The dysregulation of this pathway contributes, therefore, to the aberrant mesangial cell proliferation seen in lupus nephritis. Furthermore, in an adult cohort, it was recently shown that urinary HER2 levels were increased in patients with active lupus nephritis and correlated with MCP-1 and VCAM-1 levels.

The goal of this study is to determine the role of HER2 as a urinary biomarker for lupus nephritis activity.

Methods: This is an interim analysis of a prospective study of patients with biopsy-proven lupus nephritis. Data were collected from one adult and four pediatric centers. Urine samples were collected from patients at every clinical visit and also from age-sex matched controls. Urine supernatants were analyzed by enzyme-linked immunosorbent assays for HER2. Clinical data were also collected. The activity of lupus nephritis was measured using renal SLEDAI.

Results: HER2 levels were significantly increased in the urine of lupus nephritis patients (N=135) when compared to controls (N=61) (p=0.003). Moreover, our preliminary prospective data from patients with lupus nephritis analyzed at different visits showed that HER2 levels tend to reflect a renal flare (N=22).

Conclusion: The urinary HER2 levels were significantly increased in patients with lupus nephritis and reflected renal disease activity. This evolving study will further analyse if HER2 levels can be clinically useful, namely if they can predict the occurrence of a flare. Finally, this work also establishes strong foundations to study the use of anti-HER2 drugs to control cell proliferation and damage in lupus nephritis.

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Abstract Number: 1381

Humoral Immune Response and Cytokine Profile after a Booster Dose with Tdap Vaccine in Juvenile Systemic Lupus Erythematosus and Controls

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Background/Purpose: Pertussis cases have increased worldwide and knowledge on immune response and cytokine profile after adult Tdap vaccine is scarce. This study evaluated the humoral and cellular response through antibodies and cytokine profile after Tdap in juvenile systemic lupus erythematosus (jSLE) and controls.

Methods: After written informed consent, jSLE (n=20) and healthy adolescents (n=8) who received three whole-cell DTP vaccine (DTwP) plus two booster doses and had lymphocytes count > 500 received a Tdap dose. Blood samples were collected immediately before and 28 days after the vaccine. *In vitro* culture was performed with whole blood stimulated with tetanus toxoid, *Bordetella pertussis* or medium. Supernatants were collected after 7 days, kept frozen and subsequently assayed for cytokines secretion by xMAP-Luminex platform. Tetanus, diphtheria and pertussis antibodies were tested by ELISA.

Results: jSLE patients group median age was 14y (9-18y) and control group, 15.2y (9-15.6y). Both control group and jSLE presented an increase in response to tetanus ($p<0.01$), diphtheria ($p<0.001$) and pertussis ($p=0.01$) antibodies after Tdap booster dose on day 28. *Pertussis cellular immune response* on day 28 was stronger in control group, with significantly higher cytokine levels for **IL-2, IL-6, IL12p70, IFN-gamma,** and **TNF-alpha**; by contrast, **IL-4** concentration was higher in jSLE. *Tetanus cellular immune response* on day 28 was also stronger in control group, with significantly higher cytokine concentrations for **IL-2, IL-4,** and **IFN-gamma**; however, **IL-12p70** and **TNF-alpha** were higher in jSLE group. The cytokine levels and p-values are shown in table 1.

Table 1 - Cytokine levels for pertussis and tetanus cellular immune response

	Pertussis				
	jSLE D0	jSLE D 28	Control D0	Control D28	D28 p-value
IL-2	2.26	0.28	1.29	1.16	0.0201
IL-4	2,276.37	1,293.05	0.83	1.1	0.0019
IL-6	281.92	265.69	1,928.02	2,913.48	0.0019
IL-10	61.16	43.92	33.88	53.24	0.5186
IL-12p70	13.36	2.34	1.69	9.33	0.014
IFN-gamma	18.99	46.16	186.21	536.04	0.0098
TNF-alpha	21.63	14.81	158.72	228.49	0.0019
	Tetanus				
	jSLE D0	jSLE D 28	Control D0	Control D28	D28 p-value
IL-2	3.19	1.59	4.33	10.22	0.0528
IL-4	2,451.86	1,323	2,291.08	3,784	0.0142
IL-6	361.79	219	172.14	359	0.1556
IL-12p70	21.73	11.61	2.16	2.25	0.0067
IL-10	49.24	41.46	24.95	57.09	0.2453
IFN-gamma	29.43	54.31	219.05	2,152.06	0.0067
TNF-alpha	18.02	12.47	2.27	1.3	0.0142

Conclusion: In this preliminary study, children and adolescents with jSLE and healthy controls showed adequate humoral immune response to tetanus, diphtheria and pertussis after Tdap. However, jSLE adolescents showed a Th2 pertussis immune response profile, what might not be adequate to control *B. pertussis* infection.

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Abstract Number: 1382

Effect of Lupus Anticoagulant on Rotational Thromboelastometry in Juvenile Systemic Lupus Erythematosus: Preliminary Data on a Single Center Cohort

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Background/Purpose: Interpretation of coagulation tests remain a challenge in jSLE with positive aPL. Lupus anticoagulant (LA) can mimic bleeding diathesis and its effect on prolonged aPTT is well documented. Rotational thromboelastometry (ROTEM) is a recently approved tool that assesses primary and secondary hemostasis. It has gained utility in the surgical setting and helps guide therapeutic transfusion decisions. The utility of ROTEM for patients with jSLE who have a positive LA has not been defined. We hypothesized that LA affects ROTEM parameters, especially clotting time (CT) and maximum clot firmness (MCF).

Methods: A prospective observational study was conducted from 12/1/15 to 05/30/16 in a pediatric rheumatology clinic after IRB approval was obtained. jSLE patients with current or previous LA positivity were included. Positive LA was defined by positivity of either a hexagonal phase neutralization procedure or dilute Russell's viper venom test. ROTEM was performed using 3 different assays reflective of coagulation pathways; INTEM (intrinsic), EXTEM (extrinsic) and FIBTEM (platelet-inhibited extrinsic pathway). When clotting time (CT) of INTEM was prolonged, the sample was incubated with phospholipids and CT measured again. Correlation between ROTEM results with standard coagulation tests were done by using Pearson's correlation coefficient. Clinical data was presented in mean ± standard deviation. We compared CT parameters in patients with and without aPL mediated clinical features (MS Excel, 2013).

Results: Twelve jSLE patients were recruited; 83% (10) were female, mean age was 16 ± 2.5 years. Ten were Hispanics, duration of disease was 3.25 ± 3 years, SLEDAI score was 3.8 ± 3. Five (42%) patients had aPL mediated clinical features: RP (1), livedo reticularis (1), thrombocytopenia (1), cutaneous ulceration (1), and pulmonary embolism (1). Two patients were on anticoagulation for history of thrombotic events. Immunomodulatory therapy as indicated by the disease severity included CYC (4), Rituximab (5), MTX (3), AZA (5) and MMF (2). All patients were on HCQ and ASA. Mean prednisone dose was 16.8 ± 15 mg/day. A total of 13 samples were obtained, 6 patients had a positive LA. In all children with strong LA, a positive correlation between aPTT and CT prolongation in both INTEM (r= 0.97; p 0.003) and EXTEM (r=0.988; p 0.001) was seen. Comparison between CT prolongation of ROTEM parameters and aPL mediated clinical features were not statistically significant. Elevation in MCF did not correlate with strong LA. Phospholipid incubation did correct all INTEM CT prolongation abnormalities (Figure 1).

Conclusion: LA affects ROTEM by prolonging clotting times as it does other traditional assays. Pediatric rheumatologists should interpret ROTEM coagulation tests with caution in jSLE patients undergoing surgical intervention or presenting with bleeding.

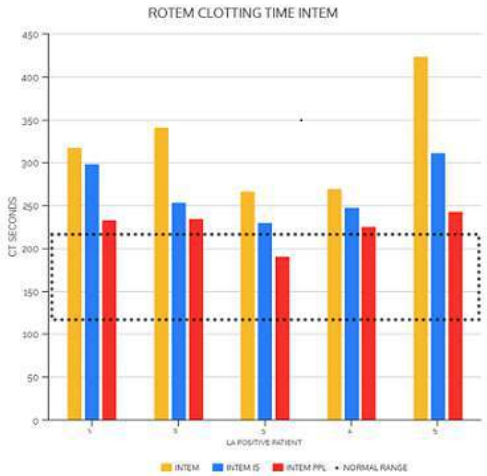

Figure 1. CT INTEM was prolonged in LA positive patients. Samples were incubated in isotonic solution (IS) and phospholipid (PPL). Shortening of CT INTEM close to upper limit resulted from PPL incubation.

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Abstract Number: 1383

ANTI-RO/SSA and/or ANTI-La/SSB Antibodies: Association with Mild LUPUS Manifestations in 645 Childhood-Onset Systemic LUPUS Erythematosus

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SESSION INFORMATION

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Background/Purpose: Anti-Ro/SSA and anti-La/SSB antibodies were reported in 30-50% and 10-30% of adult SLE patients, associated mainly with cutaneous manifestations. However, to our knowledge there are no studies assessing these autoantibodies in a large population of childhood SLE (cSLE) patients. Therefore, the aim of this multicenter cohort study was to evaluate demographic, clinical and laboratorial features in cSLE patients with and without the presence of anti-Ro/SSA and anti-La/SSB antibodies.

Methods: This was a retrospective multicenter study performed in 10 Pediatric Rheumatology services of São Paulo state, Brazil. Anti-SSA/Ro and anti-SSB/La antibodies were measured by either contraimmunoelectrophoresis or enzyme linked immuno sorbent assay (ELISA) in 645 patients cSLE patients. Other autoantibody analysis was performed according to the routine laboratory of each Center. Demographic data, cumulative clinical and laboratorial features and disease damage (SLICC/ACR-DI) at last visit were evaluated. Juvenile Sjögren's syndrome was established according to the American-European Consensus Group.

Results: Anti-Ro/SSA and anti-La/SSB antibodies were evidenced in 209/645 (32%) and 102/645 (16%) of cSLE patients, respectively. Analysis of cSLE patients with and without anti-Ro/SSA antibodies revealed higher frequencies of malar rash (79% vs. 71%, p=0.032), photosensitivity (73% vs. 65% p=0.035), cutaneous vasculitis (43% vs. 35%, p=0.046), musculoskeletal involvement (82% vs. 75%, p=0.046) in spite of long and comparable disease duration in both groups (4.25 vs. 4.58 years, p=0.973). Sjögren syndrome was rare and observed in only five patients with this antibody (2.5% vs. 0%, p=0.0035), two of them with concomitant anti-La/SSB. The presence of associated autoantibodies: anti-Sm (50% vs. 30%, p<0.0001), anti-RNP (39% vs. 21%, p<0.0001) and anti-ribossomal P protein (46% vs. 21%, p=0.002) were also significantly higher in patients with the presence of anti-Ro/SAA antibodies. Female gender, multi-organ involvement and SLICC/ACR-DI, including skin damage, were similar in both groups (p>0.05). Further evaluation of cSLE patients with the presence of anti-La/SSB antibodies compared to those without these autoantibodies showed that the frequency of alopecia (70% vs. 51%, p=0.0005) anti-Sm (59% vs. 31%, p<0.0001), anti-RNP (42% vs. 23%, p<0.0001) were significantly higher in the former group. Further evaluation of cSLE patients with and without concomitant anti-Ro/SSA and anti-La/SSB antibodies showed a lower frequency of anti-dsDNA (55% vs. 70%, p=0.009), whereas alopecia (71% vs. 51%, p=0.0008), anti-Sm (59% vs. 29%, p=0.0001) and anti-RNP (45% vs. 21%, p=0.0001) were more frequent in patients with these antibodies.

Conclusion: Our large multicenter study provided novel evidence in cSLE that anti-Ro/SSA and/or anti-La/SSB antibodies were associated with mild manifestations, particularly cutaneous and musculoskeletal. Sjögren syndrome was rarely diagnosed in these patients, in spite of the comparable frequencies of anti-Ro/SSA and/or anti-La/SSB reported for adult SLE.

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Abstract Number: 1384

Comparison of the Systemic Lupus Collaborating Clinics-Damage Index Score with a Physician Global Assessment of Damage in an International Cohort of Patients with Childhood-Onset Systemic Lupus

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Background/Purpose: Childhood-onset systemic lupus erythematosus (cSLE) is a chronic autoimmune disease, which can affect any organ system. cSLE is associated with significant morbidity, including diverse types of disease-related organ damage: up to 58% of children have apparent damage at 5 years after diagnosis. The Systemic Lupus Collaborating Clinics-Damage Index (SDI) is the only widely-used damage measure in patients with SLE (and cSLE), but was designed to list extant types of damage, not quantify severity. We sought to determine how this "listing" approach compared to a physician global assessment of disease-related damage in an international registry of cSLE patients.

Methods: The PRINTO (Pediatric Rheumatology International Trials Organization) cSLE registry includes longitudinal follow-up (mean approximately 3 years) of patients meeting revised American College of Rheumatology criteria for classification of SLE. Data from 557 patients, with a total of 1820 visits, was available for review. Data included SDI item and total scores, as well as a physician visual analog scale rating damage from 0 to 10. First, frequency of SDI summary scores was determined. The total SDI score and physician global rating of disease damage were then examined for correlation via Spearman rank-order testing. Finally, a mixed-effect model was used to determine the association of individual items with the physician damage global assessment.

Results: Out of 1820 visits, 1268 visits were assigned a SDI score of zero, while 552 (30.3%) had a non-zero score. Of non-zero scores, 331 visits received a score of one, 116 a score of two, 48 a score of three, 18 each a score of four or five, and 11 a score of six. A further 10 visits were assigned a SDI score of greater than 6. Spearman correlation of non-zero SDI scores with damage VAS was moderate at 0.496 (p value <0.0001). When visits with a SDI score of zero were included, the correlation coefficient was strong at 0.71 (p value <0.0001). Interestingly, of visits with a SDI score of zero (n=1268) 23.7% (n=301) were assigned a physician damage global greater than zero. Mixed effect analysis revealed that only 4 of the 41 SDI items were significantly associated with the physician damage global rating (Pulmonary Fibrosis, Shrinking Lung Syndrome, Chronic Pericarditis, Extensive Cutaneous Scar).

Conclusion: Our analysis revealed that a significant number of cSLE patients were found to have disease-related damage, even within the relatively limited follow-up period. It is also interesting to note the significant discrepancy between SDI scores of zero with non-zero physician global assessments, which could suggest either misunderstanding of the scale by raters, or damage items not captured by the SDI. The moderate correlation between non-zero SLICC-DI scores and the physician damage assessment suggests the need for a new or modified scale to specifically address damage severity. Finally, the lack of an association between the great majority of damage items and the physician damage assessment implies that item weightings alone would be insufficient to improve capture of damage severity.

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Abstract Number: 1385

Frequency of the Systemic Lupus Collaborating Clinics- Damage Index Items in Three Registries of Childhood-Onset Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Childhood-Onset Systemic Lupus Erythematosus (cSLE) is a chronic, multi-system autoimmune disease. In addition to active inflammation, cSLE may result in irreversible damage to affected tissues: up to 58% of children will demonstrate evidence of organ damage by 5 years after diagnosis. The Systemic Lupus Collaborating Clinics-Damage Index (SDI) lists 41 damage items, and is the only widely used measure of damage in patients with cSLE. As the index was originally created to reflect damage seen in adults, we sought to find the frequency of SDI items in three cSLE cohorts, and determine if a reduction in the number of items might be justified for cSLE.

Methods:

The United Kingdom Juvenile-onset SLE Cohort Study (UK) is a longitudinal cohort of 350 cSLE patients (1,375 visits), with a mean follow-up of 4 years. Additionally, the Cincinnati ChildrenÕs cSLE registry (Cincinnati) includes data from 163 patients (243 visits). Finally, the Pediatric Rheumatology International Trials Organization (PRINTO) cSLE cohort includes data from 559 patients (1,832 visits), with mean follow-up of 3 years. Gender distribution, as well as mean and standard deviation for age at diagnosis, disease duration, and final-visit SDI score were determined for each cohort, and the combined dataset. Age at onset, disease duration, and mean SDI score were tested for differences between cohorts via one-way ANOVA. Frequency of each SDI item was also determined, in individual cohorts and overall.

Results: *See table for detailed results.* Mean age at diagnosis was significantly higher in the Cincinnati cohort (14.45 vs. 11.98 for PRINTO and 12.02 for UK, $p < 0.0001$), as was mean disease duration (6.05 years vs. 3.46 for PRINTO and 3.82 for UK, $p< 0.0001$). Mean final-visit SDI score was significantly lower in the UK cohort (0.56 vs. 0.92 for Cincinnati and 1.16 for PRINTO, $p < 0.0001$). The mean SDI of the combined dataset was 0.93, while 602 patients (56.2%) had a final-visit SDI of zero. When SDI item scores were

considered, pulmonary infarct was the only item absent from all cohorts. When all datasets were combined, an additional 17 items were found to have occurred in fewer than 1% of the 1,072 patients, with 4 occurring in only a single case (tendon rupture, angina, myocardial infarct, and mesenteric insufficiency). The most common item in the combined dataset was proteinuria, (found in 103 patients or 9.6%), followed by alopecia (96 patients, 8.9%), and cognitive impairment (91 patients, 8.49 %).

Conclusion:

While many items are relatively rare (occurring in less than 1% of patients), all but one were observed at least once in the combined dataset. This is particularly noteworthy given the relatively brief disease duration (between 3.5 and 6.1 years), and diversity of manifestations described in the SDI. Our analyses do not support a substantial reduction in the number of SDI items considered for cSLE, but do underscore the rarity of many items in childhood-onset disease.

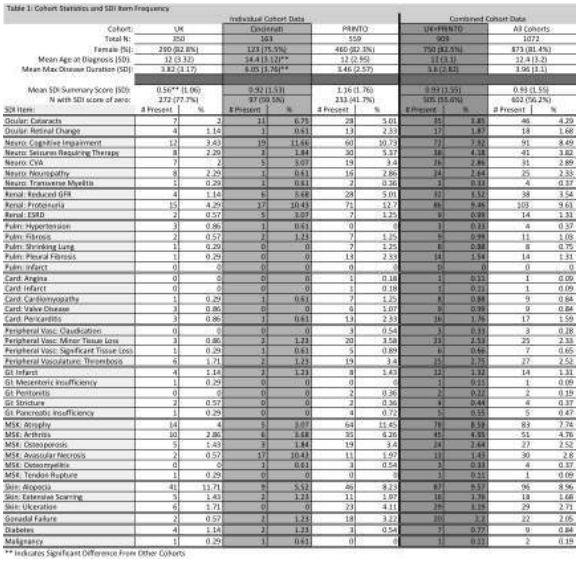

Table 1: Cohort Statistics and SDI Item Frequency

	Individual Cohort Data						Combined Cohort Data			
Cohort:	UK		Cincinnati		PRINTO		UK+PRINTO		All Cohorts	
Total N:	350		163		559		909		1072	
Female (%):	260 (82.8%)		123 (75.5%)		460 (82.3%)		750 (82.5%)		873 (81.4%)	
Mean Age at Diagnosis (SD):	12 (3.32)		14.4 (3.12)**		12 (2.95)		12 (3.1)		12.4 (3.2)	
Mean Max Disease Duration (SD):	3.82 (3.17)		6.05 (3.76)**		3.46 (2.57)		3.8 (2.82)		3.96 (3.1)	
Mean SDI Summary Score (SD):	0.56** (1.06)		0.92 (1.53)		1.16 (1.76)		0.93 (1.55)		0.91 (1.55)	
N with SDI score of zero:	272 (77.7%)		97 (59.5%)		233 (41.7%)		505 (55.6%)		602 (56.2%)	
SDI Item:	# Present	%	# Present	%	# Present	%	# Present	%	# Present	%
Ocular: Cataracts	7	2	11	6.75	28	5.01	35	3.85	46	4.29
Ocular: Retinal Change	4	1.14	1	0.61	13	2.33	17	1.87	18	1.68
Neuro: Cognitive Impairment	12	3.43	19	11.66	60	10.73	72	7.92	91	8.49
Neuro: Seizures Requiring Therapy	8	2.29	3	1.84	30	5.37	38	4.18	45	3.82
Neuro: CVA	7	2	5	3.07	19	3.4	26	2.86	31	2.89
Neuro: Neuropathy	8	2.29	1	0.61	16	2.86	24	2.64	25	2.33
Neuro: Transverse Myelitis	1	0.29	1	0.61	2	0.36	3	0.33	4	0.37
Renal: Reduced GFR	4	1.14	6	3.68	28	5.01	32	3.52	38	3.54
Renal: Proteinuria	15	4.29	17	10.43	71	12.7	86	9.46	103	9.61
Renal: ESRD	2	0.57	5	3.07	7	1.25	9	0.99	14	1.31
Pulm: Hypertension	3	0.86	1	0.61	0	0	3	0.33	4	0.37
Pulm: Fibrosis	2	0.57	2	1.23	7	1.25	9	0.99	11	1.03
Pulm: Shrinking Lung	1	0.29	0	0	7	1.25	8	0.88	8	0.75
Pulm: Pleural Fibrosis	1	0.29	0	0	13	2.33	14	1.54	14	1.31
Pulm: Infarct	0	0	0	0	0	0	0	0	0	0
Card: Angina	0	0	0	0	1	0.18	1	0.11	1	0.09
Card: Infarct	0	0	0	0	1	0.18	1	0.11	1	0.09
Card: Cardiomyopathy	1	0.29	1	0.61	7	1.25	8	0.88	9	0.84
Card: Valve Disease	3	0.86	0	0	6	1.07	9	0.99	9	0.84
Card: Pericarditis	3	0.86	1	0.61	13	2.33	16	1.76	17	1.59
Peripheral Vasc: Claudication	0	0	0	0	3	0.54	3	0.33	3	0.28
Peripheral Vasc: Minor Tissue Loss	3	0.86	2	1.23	20	3.58	23	2.53	25	2.33
Peripheral Vasc: Significant Tissue Loss	1	0.29	1	0.61	5	0.89	6	0.66	7	0.65
Peripheral Vasculature: Thrombosis	6	1.71	2	1.23	19	3.4	25	2.75	27	2.52
GI: Infarct	4	1.14	2	1.23	8	1.43	12	1.32	14	1.31
GI: Mesenteric Insufficiency	1	0.29	0	0	0	0	1	0.11	1	0.09
GI: Peritonitis	0	0	0	0	2	0.36	2	0.22	2	0.19
GI: Stricture	2	0.57	0	0	2	0.36	4	0.44	4	0.37
GI: Pancreatic Insufficiency	1	0.29	0	0	4	0.72	5	0.55	5	0.47
MSK: Atrophy	14	4	5	3.07	64	11.45	78	8.58	83	7.74
MSK: Arthritis	10	2.86	6	3.68	35	6.26	45	4.95	51	4.76
MSK: Osteoporosis	5	1.43	3	1.84	19	3.4	24	2.64	27	2.52
MSK: Avascular Necrosis	2	0.57	17	10.43	11	1.97	13	1.43	30	2.8
MSK: Osteomyelitis	0	0	1	0.61	3	0.54	3	0.33	4	0.37
MSK: Tendon Rupture	1	0.29	0	0	0	0	1	0.11	1	0.09
Skin: Alopecia	41	11.71	9	5.52	46	8.23	87	9.57	96	8.96
Skin: Extensive Scarring	5	1.43	2	1.23	11	1.97	16	1.76	18	1.68
Skin: Ulceration	6	1.71	0	0	23	4.11	29	3.19	29	2.71
Gonadal Failure	2	0.57	2	1.23	18	3.22	20	2.2	22	2.05
Diabetes	4	1.14	2	1.23	3	0.54	7	0.77	9	0.84
Malignancy	1	0.29	1	0.61	0	0	1	0.11	2	0.19

** Indicates Significant Difference From Other Cohorts

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Abstract Number: 1386

Outcome of 847 Childhood-Onset Systemic LUPUS Erythematousus Patients in Three Age Groups

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: A recent large study comparing childhood systemic lupus erythematosus (cSLE) with adult-onset SLE revealed a more aggressive and worse outcome in the former group. However, analysis of age-related differences regarding outcome focused on pediatric patients and particularly assessing early-onset cSLE patients (<6 years) is limited to very small sample size precluding a definitive conclusion about their findings. Therefore, the objective of this large multicenter study was to compare cumulative clinical/laboratory features, disease damage and death in three different age groups.

Methods: A retrospective multicenter study was performed in 847 cSLE patients from 10 Pediatric Rheumatology Divisions of São Paulo State, Brazil. Patients were divided in three age-related cSLE groups at diagnosis: A - early-onset (<6 years), B - school age (≥6 and <12 years) and C - adolescent (≥12 and < 18 years). An investigator meeting was held to define the protocol and to standardize disease parameters definitions. Demographic data, clinical and laboratorial features, disease damage (SLICC/ACR-DI) and death were evaluated at last visit.

Results: Groups of cSLE patients were divided according to the age at diagnosis: A=39 (4%), B=395 (47%) and C=413 (49%). Median disease duration was significantly higher in group A compared to groups B and C [8.3(0.1-23.4) vs. 6.2(0-17) vs. 3.3(0-14.6) years,p<0.0001]. The median SLICC/ACR-DI [0(0-9) vs. 0(0-6) vs. 0(0-7),p=0.065] was comparable in the three groups. Further analysis of organ/system damage revealed that frequencies of neuropsychiatric (21% vs. 10% vs. 7%,p=0.007), skin (10% vs. 1% vs. 3%,p=0.002) and peripheral vascular (5% vs. 3% vs. 0.3%,p=0.008) were more often observed in group A compared to B and C. Frequencies of severe cumulative lupus manifestations such as nephritis, thrombocytopenia, hemolytic anemia and vasculitis were alike in all groups(p>0.05). Death was significantly higher in group A compared to groups B and C (15% vs. 10% vs. 6%,p=0.028). Among 69 deaths, 8/33(24%) occurred at first month after diagnosis. Infection accounted for 54/69 (78%) of the overall deaths and 38/54 (70%) had concomitant disease activity. Other causes of death were nephritis (acute kidney injury or chronic renal disease) in 6 (9%), alveolar hemorrhage in 3 (4%), massive intracranial bleeding in 1 (1.4%), multiple thrombosis due to catastrophic antiphospholipid syndrome in 1 (1.4%), B-cell lymphoma in 1 (1.4%) and unknown 3 (4%).

Conclusion: This large multicenter study provided evidence that early-onset cSLE group had distinct outcomes. This group was characterized by higher mortality rate and neuropsychiatric/vascular/skin organ damages in spite of comparable frequencies of severe cumulative lupus manifestations. We also identified that overall death in cSLE was an early event mainly attributed to infection with associated disease activity.

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Abstract Number: 1387

Evaluation of Mild to Moderate SLE Flare in Patients with Childhood-Onset Disease

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SESSION INFORMATION

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Background/Purpose: One aspect of childhood SLE lacking understanding is the prediction of disease flares. The objective of this study is to identify predictors of mild to moderate flare in pediatric patients with SLE. The specific aims of this study are to investigate predictors of SLE flare in a high risk, urban, minority population. We aim to use this information to formulate a way to better predict and prevent flares among the pediatric population.

Methods: Included participants were enrolled in the pediatric Einstein Lupus Cohort (a database created in 2009 of patients meeting ACR criteria for SLE at the Children's Hospital at Montefiore), have evidence of mild to moderate flare during participation in the cohort, and have data recorded 1, 6, and 12 months prior to flare. To investigate predictors of flare within our population, we evaluated demographic variables including age, gender, race, ethnicity, education, household income, original criteria for diagnosis, and autoantibody profile. We also evaluated disease specific measures such as disease duration, medication usage, SELENA SLEDAI score, BILAG score and SLICC damage index. Laboratory variables assessed include ANA titer, anti-dsDNA antibodies, C3, C4, CBC, albumin, creatinine and urinalysis. Mild to moderate flare wass defined based on the following parameters: (1) Change in SELENA SLEDAI of ≥3 points OR (2) development of 1 new BILAG A score or 2 new BILAG B scores. All predictors identified in univariate analyses with $p<0.25$ were included into a multivariate model.

Results: We enrolled 102 pediatric patients with SLE (as defined by ACR criteria) and have data recorded for over 369 follow-up visits. General demographics for included participants are listed in Table 1. In multivariate analysis, elevated dsDNA antibodies, low WBC and sledai score were identified as independent predictors of disease flare at the next visit (within 6 months) (Table 2).

Conclusion: We have identified elevated dsDNA and low WBC count as important predictors of upcoming disease flare in pediatric patients with SLE. Interestingly, conventional markers including C3 and C4 were not found to be predictive. With this research, we hope to be able to identify flares before they manifest and ultimately be able to reduce disease burden among the pediatric SLE population.

Table 1: Demographics

Total patients enrolled	102
Total # of specimens collected	369
Mean age at Diagnosis	14.2 ± 3.7 (range 6-20)
Gender	Females: 83 (81.4%) Males: 19 (18.6%)
Race	African American: 41 (40.2%) Asian: 5 (4.9%) White: 5 (4.9%) Other: 4 (3.9%)
Ethnicity	Hispanic: 45 (44.1%) Non-Hispanic: 51 (51.0%)
Patient Level of Education	Grammar School: 11 (11%) High School: 55 (54%) College: 24 (24%)
Household Income	Less than $25,000: 21 (20.1%) $25-75,000: 12 (11.8%) Greater than $75,000: 9 (9%) Deferred: 43 (42.1%)
Patients with a family history of SLE	30 (29%)
Patients with renal disease	61 (59.8%)
Class of renal disease	Class II – 9 (8.8%) Class III – 21 (20.1%) Class IV – 15 (14.7%) Class V – 22 (21.6%)
Patients on Steroids	89 (87.3%)
Patients currently on an additional oral immunosuppressive therapy	37 (36.2%) 9% azathioprine 21% MMF 6% methotrexate
Patients previously received immunosuppressive infusions	39 (38.2%) cyclophosphamide 23 (22.5%) rituximab 7 (6.8%) IVIG 8 (7.8%) belimumab 3 (2.9%) abatacept

Table 2: Factors predictive of lupus flare			
	OR	CI	p-value
Male gender	0.896	0.343, 2.352	0.824
Hispanic ethnicity	1.269	1.668, 2.687	0.534
Black race	0.697	0.325, 1.494	0.353
Elevated dsDNA	3.053	1.393, 6.686	0.005
Low WBC	2.235	1.275, 3.918	0.005
SLEDAI score	0.934	0.877, 0.993	0.030

Disclosure: M. Peskin, None; **D. Wahezi**, None; **C. Putterman**, None; **T. Rubinstein**, Lupus Foundation of America, 2; **N. Jordan**, None.

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Distinct Clinical Correlates of Immune Thrombocytopenic Purpura at Diagnosis of Childhood-Onset and Adult SLE

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Background/Purpose: Hematologic abnormalities are common manifestations in systemic lupus erythematosus (SLE) patients. Several studies have demonstrated a higher frequency of immune thrombocytopenic purpura (ITP) in pediatric compared to adult lupus but none evaluated ITP at lupus diagnosis in both age groups. Simultaneous diagnosis of these two conditions is challenging and analysis of clinical correlates of ITP in pediatric and adults at lupus presentation may provide a more appropriate time frame from diagnosis to treatment in these patients. Therefore, the objectives of this study were to compare clinical and laboratorial features between pediatric and adult patients at concomitant diagnosis of ITP and SLE.

Methods: This was a retrospective study evaluating 336 cSLE and 1,830 aSLE patients from 1983 to 2014 regularly followed at the Pediatric Rheumatology Unit and the Rheumatology Division of the same University hospital. ITP was defined as platelets count $<100,000/mm^3$ in the absence of other causes often with the characteristic purpuric rash. Data were obtained from medical charts assessed at ITP and SLE diagnosis, including demographic characteristics, clinical and laboratorial findings of SLE, disease activity and initial treatment.

Results: The median current age was 11.6 years and 27.3 years, respectively. The frequencies of female gender and Caucasian race were similar in both groups ($p > 0.05$). cSLE had a higher frequency of ITP compared to aSLE (17% vs. 4%, $p<0.0001$) and the former group had more hemorrhagic manifestations (59% vs. 34%, $p=0.007$). Simultaneous severe lupus manifestations such as pericarditis (25% vs. 10%, $p=0.029$) and central nervous system involvement (30% vs. 14%, $p=0.029$) were more common in cSLE. Concomitant constitutional symptoms (fever and weight loss) and reticuloendothelial manifestations (adenomegaly, hepatomegaly and splenomegaly) were also more frequent in this age group ($p<0.05$), whereas cutaneous and articular involvements were less often observed in cSLE patients ($p<0.05$). A trend for a higher SLEDAI score was observed in pediatric patients (18 vs. 13, $p=0.072$). Analysis of autoantibodies showed a lower frequency of anti-Ro (11% vs. 27%, $p=0.026$) in cSLE patients compared to adults. Concerning treatment, intravenous methylprednisolone, intravenous immunoglobulin, blood transfusion and platelets transfusion were more frequently used in the pediatric population ($p < 0.05$).

Conclusion: ITP at cSLE presentation is more severe than in aSLE with distinct features characterized by major organ involvements and constitutional/reticuloendothelial manifestations. These findings reinforce the need for a more aggressive treatment in this age group.

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Abstract Number: 1389

Alterations in Nailfold Capillaroscopy in Childhood-Onset Systemic Lupus Erythematosus: The Role of Disease Activity in a Prospective Study

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Background/Purpose: The association between disease activity and nailfold capillaroscopy (NC) alterations has been described in systemic lupus erythematosus (SLE). However, data on longitudinal assessment of NC are scarce in childhood-onset SLE (cSLE), especially concerning its association with clinical and laboratory parameters. Therefore, the objectives of this study were to perform a prospective evaluation of nailfold capillaries in childhood-onset SLE (cSLE) and to assess the possible influence of clinical and laboratory manifestations, disease activity and treatment on altered NC.

Methods: This prospective study included cSLE patients regularly followed at the Rheumatology Outpatient clinic, University of Sao Paulo. NC was performed at inclusion and after 18 months and the results were classified as normal (no morphologic alterations and more than 7 loops per linear millimeter) or abnormal (slightly decreased capillary density with the presence of mild to moderate micro-hemorrhages or scleroderma pattern). Clinical and laboratory findings, disease activity score and treatment were evaluated at each NC.

Results: Forty-four patients were initially included and 33 patients repeated NC after 18 months. Thirty-eight (86%) were female and the median age at baseline was 20.4±3.7 years with mean disease duration of 7.8±4.7 years. Clinical manifestations of lupus since diagnosis included arthritis in 84% of patients, mucocutaneous involvement in 39%, hematologic in 32% and nephritis in 64%. Thirty-eight (86%) patients were positive for anti-dsDNA, 50% anti-Sm, 9% anti-RNP, 39% anti-Ro, 11% anti-La, 52% anti-P and 23% antiphospholipid antibodies. At baseline, the median of SLEDAI was 3.5 (0-16), predominantly for renal activity (30%), leucopenia (14%), positive anti-dsDNA (39%) and hypocomplementemia (45%). Thirty-four (77%) patients were under prednisone, 18% azathioprine, 11% cyclophosphamide, 50% micofenolate mofetil and 11% methotrexate. Comparison of patients with altered and normal NC showed a higher frequency of serositis in the former group (63 vs. 21%, p=0.01), particularly pericarditis (50 vs. 14%, p=0.016), as well as a trend for more cutaneous vasculitis (56 vs. 25%, p=0.054) any time since lupus diagnosis. At baseline, the group with abnormal NC had more mucocutaneous activity (19% vs. 0, p=0.042). No differences were observed in other clinical manifestations, autoantibodies profile, SLEDAI and treatment at the moment of NC (p>0.05). After 18 months, 21/33 (64%) patients maintained the same NC findings and 3/33 (9%) presented new abnormalities or intensified previous alterations. One of the latter also presented new capillary enlargement with a concomitant lupus nephritis, requiring higher doses of immunosuppressive drugs. Among the 9/33 (27%) patients who showed less alterations on NC after 18 months, six had stable disease/SLEDAI and were on prednisone tapering.

Conclusion: This study reinforces the dynamic characteristics of nailfold capillaries in lupus and strengthens the role of NC as a useful

tool for the follow-up of cSLE patients, especially concerning disease activity assessment.

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WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-9

Abstract Number: 1391

Novel Electronic Health Record-Based Method Confirms Increased Renal Disease Burden in Pediatric-Onset Vs. Adult-Onset Patients with Systemic Lupus Erythematosus

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Background/Purpose: Children with Systemic Lupus Erythematosus (SLE) are often understudied compared with adults. Using the electronic health record (EHR) can increase sample size and the diversity of SLE patients while providing longitudinal data on comorbidities. We assessed differences in comorbidities in pediatric vs. adult-onset SLE using an EHR-based phenome-wide association study (PheWAS). PheWAS is a systematic and efficient approach that compares two groups using ICD-9 codes.

Methods: We used our validated algorithm of ≥ 4 counts of the SLE ICD-9 code (710.0) and ANA positive ≥ 1:160 while excluding dermatomyositis and systemic sclerosis ICD-9 codes to identify SLE cases in a de-identified EHR called the Synthetic Derivative (SD). The SD contains over 2.5 million subjects with longitudinal clinical data. Our algorithm has an internally validated positive predictive value of 94% and a sensitivity of 86%. Pediatric-onset SLE was defined as ≤ 18 years at first use of the SLE ICD-9 code vs. adult-onset ≥ 19. PheWAS was performed in pediatric vs. adult-onset adjusting for sex and race in logistic regression models and correcting for multiple testing using Bonferroni. PheWAS excludes subjects that have a one time count for a code to minimize the effect of coding errors.

Results: We identified 93 pediatric-onset and 1005 adult-onset patients with SLE. Pediatric-onset patients had a mean age at first SLE code of 15 ± 3 years versus adult-onset at 43 ±15. Both pediatric and adult-onset patients were predominantly female (87% vs. 90%, $p = 0.34$). Pediatric-onset patients were more likely African Americans (49% African American, 40% Caucasian, 8% Asian, and 3% Hispanic) vs. adult-onset (72% Caucasian, 24% African American, 3% Hispanic, and 1% Asian), ($p < 0.001$). Adjusting for sex and race, pediatric-onset patients had 13 codes that met the Bonferroni threshold for significance ($p < 1.26 \times 10^{-4}$) including mostly nephritis codes (Table 1, Figure 1). Compared to adult-onset, pediatric-onset patients had more codes related to other SLE ACR criteria such as pleurisy/pleural effusion, pericarditis, thrombocytopenia, aplastic anemia, pancytopenia, convulsions, and non-infectious encephalitis (all $p < 0.05$).

Conclusion: Using a large EHR, pediatric-onset patients had an increased SLE disease burden with more ICD-9 codes related to ACR SLE criteria, particularly renal disease. These findings demonstrate the ability of PheWAS to replicate epidemiologic associations

within subgroups of SLE patients and to function as an efficient discovery tool in the EHR.

Table 1.

ICD-9 Codes	Code Present	Code Absent	Adjusted Odds Ratio for sex and race (95% CI)	p value
Nephritis and nephropathy without mention of glomerulonephritis (580.3)	176	664	Pediatric-onset: 4.29 (2.62 – 7.02) Adult-onset: 1.00 (ref)	$p = 0.49 \times 10^{-9}$
Nephritis and nephropathy in diseases classified elsewhere (580.31)	164	664	4.25 (2.57 – 7.03)	$p = 1.80 \times 10^{-8}$
Nephritis and nephropathy with pathological lesion (580.32)	60	664	5.99 (3.10 – 11.57)	$p = 1.04 \times 10^{-8}$
Nephritis, nephrosis, renal sclerosis (580)	215	664	3.50 (2.16 – 5.66)	$p = 3.64 \times 10^{-7}$
Abnormal findings on examination of urine (398)	135	891	3.58 (2.13 – 5.94)	$p = 8.68 \times 10^{-7}$
Other hypertensive complications (401.3)	20	566	9.66 (3.47 – 26.87)	$p = 1.38 \times 10^{-5}$
Disorders of phosphorus metabolism (275.53)	27	987	6.39 (2.76 – 14.75)	$p = 1.42 \times 10^{-5}$
Thrombocytopenia (287.3)	98	660	3.77 (2.00 – 7.09)	$p = 3.94 \times 10^{-5}$
Glomerulonephritis (580.1)	99	664	3.51 (1.91 – 6.43)	$p = 5.14 \times 10^{-5}$
Coagulation defects (286)	167	660	3.15 (1.80 – 5.50)	$p = 5.58 \times 10^{-5}$
Pericarditis (420.2)	78	922	3.47 (1.89 – 6.40)	$p = 6.42 \times 10^{-5}$
Purpura and other hemorrhagic conditions (287)	104	660	3.57 (1.90 – 6.68)	$p = 7.30 \times 10^{-5}$
Primary thrombocytopenia (287.31)	27	660	6.42 (2.48 – 16.60)	$p = 1.24 \times 10^{-4}$

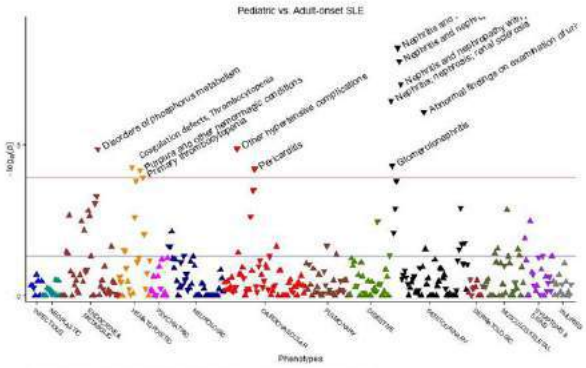

Figure 1. PheWAS of pediatric vs. adult-onset SLE.
The x axis represents the PheWAS codes that are mapped to ICD-9 codes organized by organ system. The y axis represents the level of significance. Adult-onset patients are the reference group. The lower horizontal line represents the $p < 0.05$ significance threshold. The upper horizontal line represents the Bonferroni threshold ($p < 1.26 \times 10^{-4}$). The thirteen codes that met the Bonferroni threshold are labeled above.

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Abstract Number: 1392

Familial Aggregation of Autoimmune Diseases in Childhood and Adulthood Systemic Lupus Erythematosus

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Background/Purpose: Genetic factors play a role in SLE, evidenced by the high sibling risk ratio (λs=8–29) and higher concordance rates between monozygotic twins (>35%) compared to dizygotic twins (2-5%). It is clear that the genetic basis of disease differs to some degree between ancestral backgrounds, and is less well understood in non-European ancestry subjects. In this study, we assessed the familial occurrence autoimmune disease in childhood-onset SLE (cSLE) and adult-onset SLE (aSLE) relatives in a large Brazilian cohort.

Methods: cSLE patients (disease-onset ≤18 years) and aSLE patients (disease-onset >18 years) followed in the Pediatric and Adult Rheumatology Outpatient Clinic of the State University of Campinas were included. Each patient was personally interviewed regarding history of autoimmune diseases in three family generations (grandparents, parents and uncles/aunts, cousins and siblings). Recurrence rates were then calculated for each reported disease.

Results: We included 112 cSLE patients [96 (85.7%) women] and 266 aSLE patients [247 (92.9%) women]. In cSLE patients we identified 3812 relatives. In the first-degree kinship we observed 10 relatives with SLE, with a recurrence rate of 25.3 (25-fold greater risk of SLE than the general population). In the second-degree kinship we observed 10 relatives with SLE and 1193 relatives without, with a recurrence rate of 8.3. In the third-degree kinship we observed a recurrence rate of 0.9 (no increase over general population). In aSLE patients we identified 10584 relatives. In the first-degree kinship we observed a recurrence rate of 18.8. In the second-degree kinship the recurrence rate was4.6. The most frequent non-SLE autoimmune diseases observed in the family members were: hypothyroidism, hyperthyroidism, vitiligo, rheumatoid arthritis, psoriasis, systemic sclerosis, ankylosing spondylitis, inflammatory myopathy, Sjögren syndrome, Crohn's disease.

Conclusion: SLE recurrence rate is higher among first-degree relatives in both cSLE and aSLE patients, and steadily decreases between generations as would be expected for complex inheritance. Familial tendency toward SLE was higher in families with a cSLE patient, and recurrence rates were comparable or higher than those reported in European ancestry.

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Abstract Number: 1393

Mycophenolic Acid Pharmacokinetics in Childhood-Onset Systemic Lupus Erythematosus Patients of Hispanic Ethnicity in a Single Center

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Background/Purpose: Mycophenolic acid (MPA) is the biologically active metabolite of mycophenolate mofetil (MMF), a widely used immunosuppressant in the treatment of childhood-onset systemic lupus erythematosus (cSLE). In our center, 54% of our cSLE patients are of Hispanic ethnicity. Hispanic cSLE patients are predisposed to higher SLE disease activity and risk for increased

morbidity but have also been found to respond well to MMF. Published cSLE MPA PK studies include mainly Caucasian or African-American patients. The objective of this ongoing study is to describe the pharmacokinetics (PK) of MPA in a cohort of Hispanic cSLE patients at a single center.

Methods: The PK of MPA and its glucuronide metabolites (MPA glucuronide/ MPAG and Acyl MPA glucuronide/ AcMPAG) was evaluated in cSLE patients (n=6; all female and Hispanic; age 13-18 years) on a stable MMF regimen (1,500-2,000 mg/day) (*Table 1*). Blood samples for PK analysis were collected at 4 time points: prior to MMF morning dose administration (trough), 20 minutes, 1 hour, and 3 hours post-MMF administration. Exposure to drug (PK) was measured by the area under the curve of MPA concentration plotted against time. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI).

Results: The plasma concentration-time profiles of MPA, MPAG, and AcMPAG are shown in Figure 1. The PK parameters (mean ± SD) were: maximum MPA concentration (C_{max}) of 12.8 ± 7 µg/ml (55% coefficient of variation, CV), time to reach C_{max} (T_{max}) of 0.8 ± 0.4 hrs (44.5% CV), and $AUC_{0\text{-}3\ h}$ of 23.7 ± 12.3 µg*hr/ml (51.9% CV). There was noted improvement and decline in SLEDAI scores averaged over time after MMF therapy initiation (*Table 1*).

Conclusion: Our study in an all-Hispanic cSLE patient cohort demonstrated MPA PK parameters which are consistent with currently published literature on MPA PK in cSLE patients. Substantial inter-patient variability in MPA PK was observed, highlighting the need for further studies on individualized MMF dosing strategies in cSLE.

Table 1. Demographic and clinical characteristics of patients with childhood-onset SLE at the time of the PK sampling visit.

	N	*% of total*	*Mean ± SD*	*Range*
Gender				
Female	6	100		
Ethnicity				
Hispanic	6	100		
Age (years)			17.2 ± 2.2	13.3 - 18.9
Weight (kilograms)			71.5 ± 20.7	54.9 - 104.8
Disease duration (years)			2.9 ± 2.9	0.8 - 8.5
Treatment duration with Mycophenolate mofetil (years)			1.5 ± 0.8	0.2 - 2.8
Average daily dose of Mycophenolate mofetil (mg/day)	6	100	1916 ± 204	1500 - 2000
Disease activity measures*				
MTA-SLEDAI $_{Pre\text{-}MMF}$ †			9.2 ± 2.7	
MTA-SLEDAI $_{Post\text{-}MMF}$ ‡			2.2 ± 1.5	

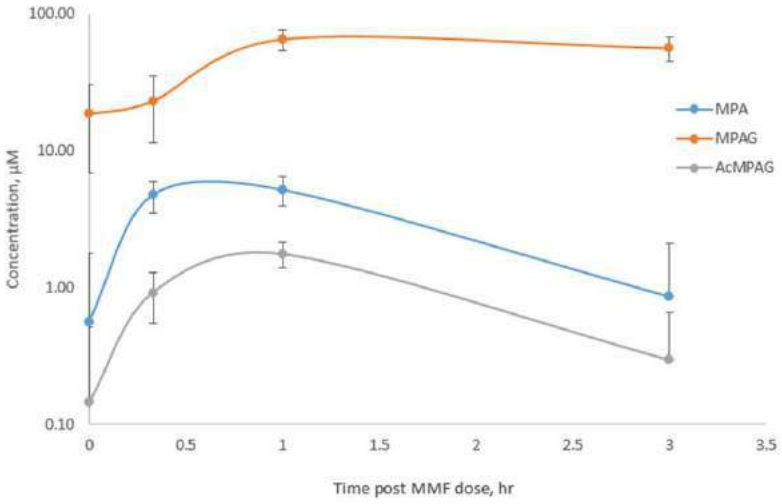
Note:

SD - standard deviation

*Change in disease activity measures averaged over time using the SLEDAI (Systemic Lupus Erythematosus Disease Activity Index)

† MTA-SLEDAI $_{Pre\text{-}MMF}$ - time-adjusted mean of SLEDAI scores measured up to 6 months prior to initiation of MMF therapy

‡ MTA-SLEDAI $_{Post\text{-}MMF}$ - time-adjusted mean of SLEDAI scores measured starting at least 2 weeks after initiation of MMF therapy until PK sampling date **Figure 1. Mean MPA, MPAG, and AcMPAG Plasma Concentration (Mean ± SE) -Time Profiles**



Disclosure: A. C. Sagcal-Gironella, Caroline Wiess Law Fund for Research in Molecular Medicine, 2; **M. De Guzman**, None; **D. Zhang**, None; **L. Agu**, None; **D. Chow**, None.

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Abstract Number: 1394

A Pilot Study of Consensus Treatment Plans for Induction Therapy in Childhood Proliferative Lupus Nephritis

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SESSION INFORMATION

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Background/Purpose: Childhood-onset systemic lupus erythematous (cSLE) patients are at higher risk for renal disease than those with adult-onset disease. Mycophenolate mofetil (MMF) and intravenous cyclophosphamide (CYC), commonly used for induction immunosuppression therapy of proliferative lupus nephritis (LN), are considered equally efficacious in adults. Comparative data in the pediatric population are lacking. To reduce treatment variability and facilitate comparative effectiveness studies, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) published a consensus treatment plan (CTP) for induction therapy in childhood proliferative LN. The CTP recommended treatment with MMF or IV CYC and one of three steroid regimens: primarily oral, primarily IV, or mixed oral/IV. We report treatment group allocation and provider adherence for induction agents and steroid regimens in a multi-center pilot feasibility study.

Methods: This observational study enrolled 41 cSLE patients from 10 CARRA sites. Subjects had new-onset biopsy proven class III or IV proliferative LN and were starting induction therapy with MMF or IV CYC and steroids. Baseline demographics, disease-related features, physician decision-making regarding choice of induction agent and steroid regimen were reported. Subjects were followed for up to 24 months. Providers reported adherence to the CTP for induction agents and steroid regimen at 3 and 6 month visits. Complete renal response (CRR), defined as normal renal function, inactive urine sediment, and urine protein to creatinine ratio of < 0.2, was reported at 6 months.

Results: A majority of participants were female (83%) with a median age of 14 years. There were no significant differences in demographics between MMF or CYC groups or among the three steroid regimens. However, 78% (18/23) of those treated with CYC had class IV nephritis versus 33% (6/18) of those treated with MMF (p = 0.004). Physicians reported adherence concerns as a reason for selecting treatment for 5 of the patients in the CYC group but none in the MMF group (22% versus 0%, p = 0.04). MMF or CYC regimen was followed as intended per the CTP in 75% of subjects at 3 months and 56% at 6 months. CRR at 6 months was achieved for 56% with MMF and 64% with IV CYC (p = 0.6); the study was not powered to evaluate treatment efficacy. Steroid regimen chosen differed significantly by induction agent; those treated with MMF were more likely to receive the primarily oral steroid regimen and those treated with CYC were more likely to receive the mixed oral/IV regimen. Steroid regimen was followed as intended per the CTP in 59% of patients at 3 months and 37% of patients at 6 months.

Conclusion: This feasibility study revealed two important issues. First, there was confounding by indication present as patients with class IV nephritis (vs class III) were more likely to receive CYC. Second, a substantial number of patients did not continue treatment according to the CTP. For future comparative effectiveness studies using observational methodologies, large sample sizes may be needed to allow sufficient adjustment for confounders and modification of the CTP regimens may needed to ensure better usability.

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Abstract Number: 1395

Regional Brain Gray Matter Volume Loss in Children and Adolescents with SLE

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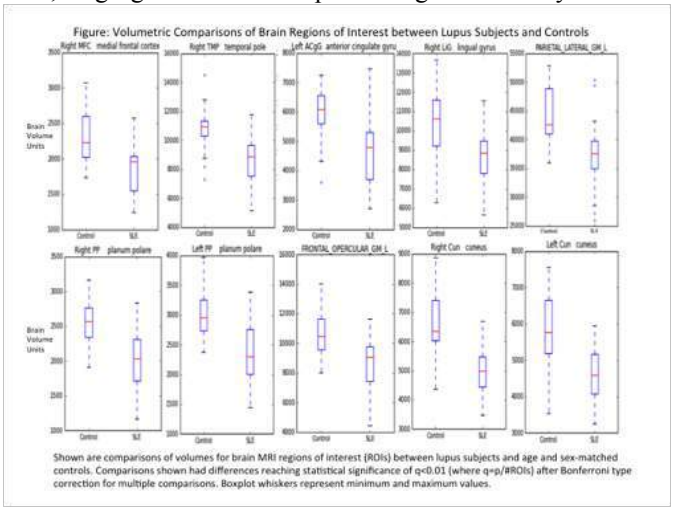
Background/Purpose: Neuropsychiatric SLE in children and adolescents presents diagnostic challenge due to limitations of conventional magnetic resonance imaging (MRI) to detect clinically relevant brain changes. We examined structural brain abnormalities in pediatric-onset SLE (pSLE) utilizing advanced MRI techniques.

Methods: We conducted a cross-sectional analysis of clinically-obtained brain MRI images from subjects with pSLE, and compared them to existing brain MRI images from age and sex-matched controls from another study. All images were obtained between 2007 and 2015 on the same scanner at 3T using a T1-weighted MPRAGE (magnetization-prepared rapid, acquisition gradient echo) protocol. We used an advanced multi-atlas segmentation algorithm to divide the brain into 154 anatomical regions of interest (ROIs), organized hierarchically within larger brain structures. We calculated volumes of individual ROIs and larger brain structures, and compared volumetric measurements from pSLE and control subjects using univariate paired t-tests. ROIs with significant group differences after Bonferroni correction for multiple comparisons ($q<0.01$, where $q=p/\#ROIs$ tested) were reported. A neuroradiologist, blinded to the volumetric results, performed conventional re-reads of MRIs for pSLE subjects.

Results: We matched 29 SLE adolescents to 29 controls, comprised of 90% females with a mean age of 15.9 (SD=3.6). Median disease duration for SLE subjects was 1.1 years (interquartile range, IQR= 0.2, 2.8), and there was a history of nephritis in 11 (39%), seizures and/or stroke in 5 (18%), anti-phospholipid syndrome in 5 (18%), depression and/or anxiety in 15 (54%). Glucocorticoids were used by 86% of pSLE subjects at the time of MRI (median prednisone dose=10 mg, IQR=6,25). Conventional pSLE MRI reads indicated T2 hyperintensities in 14 (48%) and mild diffuse volume loss in 8 (28%). Using advanced segmentation, total brain volume did not differ between groups, but volumes in specific gray matter ROIs were significantly decreased in pSLE subjects compared to controls ($q<0.01$) (Figure). These ROIs are involved in: decision-making, memory, and social cognition (right medial frontal cortex); empathy, emotional memory and processing (right temporal pole, left anterior cingulate gyrus); topographical and facial recognition (right lingual gyrus); language processing (left parietal lateral cortex, bilateral planum polare, frontal operculum); visual and spatial attention (bilateral cuneus). SLE subjects also had significantly larger lateral ventricles.

Conclusion: Compared to healthy peers, children and adolescents with SLE have decreased gray matter volumes in regions involved in executive function, social cognition, language and emotional processing. Future study should examine the functional correlates of these structural brain abnormalities.



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Cognitive Function in Children with SLE Nephritis: A Cross-Sectional Comparison to Children with Other Glomerular Chronic Kidney Diseases

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Background/Purpose: Children with lupus nephritis (LN) are at risk for cognitive impairment due to effects on the brain from systemic inflammation and from potential effects of chronic kidney disease (CKD). We aimed to determine the risk for neurocognitive dysfunction for children with LN compared to children with other etiologies of glomerular CKD, hypothesizing a higher risk for those with LN, and examined the relationship of cognitive function to quality of life (QOL).

Methods: We conducted a cross-sectional analysis of the Chronic Kidney Disease in Children (CKiD) cohort, a 54-center prospective observational study of pediatric CKD patients with mild/moderate renal dysfunction. We determined neurocognitive outcomes using baseline measures after study entry for standardized tests of intelligence, academic achievement, attention/inhibitory control, memory, and executive function. QOL was measured using parent and child reports of the Pediatric Inventory of Quality of Life Core Scales 4.0. We used inverse probability weighting in a logistic model for propensity score analysis to achieve balance between children with LN and those with other glomerular CKD for the following variables: age, sex, height, race, ethnicity, maternal education, glomerular filtration rate, proteinuria, systolic blood pressure, and anemia. We used linear regression models to: i) compare neurocognitive outcomes between exposure groups, adjusting for prednisone use (yes/no), and testing for an interaction between prednisone use and LN, and ii) test for an association between cognitive function and QOL.

Results: Compared to subjects with other glomerular CKD (n=171), those with LN (n=34) had shorter median CKD duration (1.6 vs 4.0 years) and higher prednisone use (59% vs 23%). In adjusted analyses, subjects with LN had higher intelligence (p=0.07), academic achievement (p=0.03), and better performance for attention (p=<0.01) and inhibitory control (p=0.07) (Table). There were no differences for the other cognitive measures, and no significant interactions between prednisone use and LN. Prednisone use was independently associated with better achievement (p=0.05), but worse attention (p=0.01). Lower executive function was associated with worse parent (p<0.001) and child-reported QOL (p<0.001), and lower attention (p<0.01) and inhibitory control (p<0.01) with worse child-reported QOL.

Conclusion: Contrary to our hypothesis, children with LN early in their disease course have comparable or better cognitive function than their peers with other glomerular CKD, possibly due to shorter disease duration and/or more immunosuppressive treatment. Further study should examine the association of disease duration and immunosuppression in cognitive function for children with LN, as well as strategies to mitigate adverse effects of cognitive dysfunction on QOL in children with CKD.

Table: Neurocognitive Outcomes for Children with Lupus Nephritis vs Other Glomerular Chronic Kidney Diseases				
Neurocognitive Outcome	**Median T-score (IQR)**		**Adjusted Effect of LN**	
	LN n=34	**Other CKD n=171**	**Estimate (95% CI)**	**p-value**
Intelligence (WASI)*	103 (90.5, 114)	93.5 (83, 104)	7.63 (-0.69, 15.95)	0.07
Academic achievement (WIAT-II-A)*	100 (93, 122)	89.5 (77, 100)	8.29 (-3.05, 19.64)	0.15
Memory (WISC-IV)*				
Digit span forward (verbal)	10 (5, 11)	7 (5, 10)	0.93 (-0.68, 2.55)	0.26
Digit span reverse (verbal working)	9 (8, 11)	9 (7, 11)	0.28 (-1.24, 1.80)	0.71
Spatial span forward (visual)	9.5 (8, 11)	9 (7, 11)	1.20 (-0.93, 3.32)	0.26
Spatial span reverse (visual working)	10.5 (8, 12)	10 (7, 12)	0.67 (-1.54, 2.87)	0.55
Attention & Inhibitory Control (CPT-II)**				
Detectability	50 (42, 55)	53 (45, 58)	-7.41 (-11.84, -2.98)	**<0.01**
Response time variability	48 (41, 63)	50 (43, 58)	-0.18 (-5.04, 4.68)	0.94
Errors of Commission	48 (41, 55)	49 (41, 58)	-4.74 (-9.78, 0.30)	0.07
Executive Function				
BRIEF Global Executive Composite**	46.5 (41, 58)	53 (45, 61)	-0.99 (-5.76, 3.79)	0.68
D-KEFS Achievement*	10 (8, 13)	9 (8, 11)	1.66 (0.20, 3.11)	**0.03**
D-KEFS Accuracy ratio*	9 (8, 10)	9 (7, 11)	-0.52 (-2.05, 1.01)	0.50

Shown are actual standardized T-scores for the neurocognitive outcomes. Linear regression models compared neurocognitive outcomes in children with lupus nephritis (LN) and those with other glomerular CKD (reference group), adjusting for prednisone use (yes/no). *Higher scores indicate better performance for the Wechsler Abbreviated Scales of Intelligence (WASI), Wechsler Individual Achievement Test-II-Abbreviated (WIAT-II-A) (mean=100 and SD=15), Wechsler Intelligence Scale for Children 4th Edition (WISC-IV), and Delis-Kaplan Executive Function System (D-KEFS) (mean=10 and SD =3). **Lower scores indicate better performance for the ConnersÕ Continuous Performance Test 2nd edition (CPT-II) and Behavior Rating Inventory of Executive Function (BRIEF) (mean=50 and SD =10). IQR=interquartile range

Disclosure: A. Knight, None; **M. Matheson**, None; **S. Furth**, None; **B. Warady**, None; **S. Hooper**, None; **A. Kogon**, None.

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Correlation and Responsiveness of Cutaneous Lupus Disease Area and Severity

Index (CLASI) and Skindex-29 with Cutaneous Childhood Lupus Erythematosus (cSLE)

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Correlation and Responsiveness of Cutaneous Lupus Disease Area and Severity Index (CLASI) and Skindex-29 with Cutaneous Childhood Lupus Erythematosus (cSLE) **Ashwaq AlEÕed, **Nora Al Mutairi , **Sulaiman M Al-Mayouf, $Hafize Emine Sšnmez, $Seza Ozen, Jennifer L. Huggins,*Hermine I Brunner.* *Division of Rheumatology, Cincinnati ChildrenÕs Hospital Medical Center, Department of Pediatrics, University of Cincinnati College of Medicine, Cincinnati, USA. **Department of Pediatrics Rheumatology, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia. $Department of Pediatric Rheumatology Hacettepe University Faculty of Medicine Ankara, Turkey.

Background/Purpose: Mucocutaneous lupus is a common manifestation in both adult and children with lupus (60-85%). The *Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)* allows for measuring active inflammation(CLASI-A;range 0-70)and chronic damage (CLASI_D; range 0-59)has been developed and validated for use in adults. The Skindex is a skin-specific Quality of Life (QoL; range 0–100; 100=worst QoL). Neither the CLASI nor the Skindex-29 has been validated for use in cSLE. The objective of this study was to assess the validity of the CLASI and Skindex29 in cSLE.

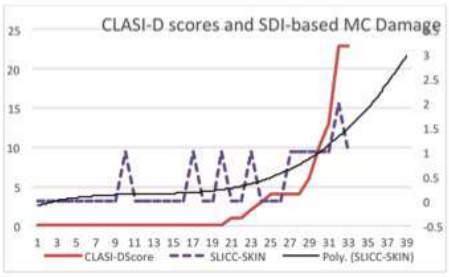
Methods : In this ongoing study, 33 cSLE patients were enrolled to date. Besides the CLASI, physicians-rated cSLE activity (SLEDAI) and completed the SLICC/ACR damage index (SDI). The Skindex was modified to a 28-item scale given difference between the adult and children life styles. PatientsÕ QoL was rated using the PedsQL Generic Core (GC) scale and the Rheumatology Module (RM) and the Skindex29.

Results: Patients (age: 3-18years; 87% females) had moderately active cSLE (mean± SD; SLEDAI 9.6 ± 7.4), 44.4% had a SDI score>0; and PedsQL-GC/RM scores 75±17.06/74.2±14.8, respectively. The mucocutaneous (MC)scores were 2.6 ± 1.5 for SLEDAI-MC and 0.36 ±0.55 for SDI-MC. As shown in **Table 1/Figure1**,cSLE activity (SLEDAI, SLEDAI-MC), damage (SDI, SDI-MC) and QoL(PedsQL-GC/MC)were moderately associated with CLASI-A, CLASI-D and Skindex scores, respectively.

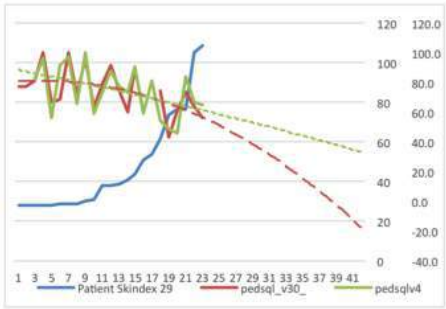
Conclusion: We found the CLASI and the modified Skindex feasible and to show construct validity when used in cSLE. Additional research is needed to confirm the responsiveness to change of these two indices when use in cSLE.

Figure 1: The relation between different scores.

a.CLASI - A score in relation to SLEDAI-MC scores



b.CLASI-D scores and SDI-based MC Damage



c. Relationahip between SKinDex and PedsQL

Table 1: Show the Correlation Coefficients between the scores.

SLEDAI	SLEDAI	SLEDAI-MC	CLASI-A	SDI	SDI-MC	CLASI-D	PedQL-RM	PedQL-GC
SLEDAI-MC	**0.54**	**1.00**	**0.54**	**0.35**	**0.40**	**0.42**	**-0.09**	**-0.20**
CLASI-A	**0.09**	**0.54**	**1.00**	**0.22**	**0.62**	**0.84**	**-0.22**	**-0.28**
SDI	**-0.16**	**0.36**	**0.36**	**1.00**	**0.47**	**0.47**	**-0.50**	**-0.66**
SDI-MC	**-0.05**	**0.17**	**0.17**	**0.47**	**1.00**	**0.69**	**-0.20**	**-0.31**
CLASI-D	**-0.06**	**-0.07**	**-0.10**	**0.47**	**0.69**	**1.00**	**-0.54**	**-0.60**
Skindex	**-0.02**	**0.29**	**0.67**	**0.55**	**0.53**	**0.41**	**0.54**	**-0.60**

Disclosure: A. Aleed, None;

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Abstract Number: 1398

Practice-Based Differences Between Pediatric Rheumatologists and Dermatologists Caring for Children with Discoid Lupus

Lisa Arkin[1], **Kaveh Ardalan**[2], Heather Brandling-Bennett[3], Yvonne Chiu[4], Benjamin Chong[5], Megan Curran[6], Raegan Hunt[7], Amy Paller[8], Victoria P. Werth[9,10], Marisa Klein-Gitelman[6], Emily von Scheven[11] and for the CARRA SLE workgroup, [1]Department of Dermatology and Pediatrics;, University of Wisconsin School of Medicine & Public Health/American Family Children's Hospital, Madison, WI, [2]Division of Rheumatology; Department of Pediatrics, Ann & Robert H. Lurie Children's Hospital of

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Background/Purpose: Discoid lupus erythematosus (DLE) is rare in children. There are no consensus guidelines for management or screening for evolution to systemic lupus erythematosus (SLE). This study compared screening and treatment practice patterns among pediatric dermatologists and pediatric rheumatologists caring for children with DLE.

Methods: A survey was e-mailed to 292 pediatric rheumatologists (Childhood Arthritis & Rheumatology Research Alliance [CARRA]) and 200 pediatric dermatologists (Pediatric Dermatology Research Alliance [PeDRA]). The survey addressed the following domains: laboratory screening for SLE (at time of DLE diagnosis); risk factors impacting screening strategy for SLE; first/second-line systemic therapies; and topical therapies. Consensus was pre-defined as ≥70% agreement from both subspecialties.

Results: Fifty-three pediatric rheumatologists and 69 pediatric dermatologists were included (18% and 35% response rates respectively). Both groups reported treating pediatric DLE (rheum n =48 [91%]; derm n= 65 [94%]), but >90% of respondents reported <10 DLE patients in their current practice. There was no consensus on the choice of labs for initial screening for SLE, but most respondents (rheum n = 42 [79%] vs derm n = 28 [41%]) chose the following panel: CBC/diff, renal/hepatic function, ESR, CRP, urine studies, complements, autoantibodies (i.e. dsDNA, SSA, SSB, RNP, Smith), anti-phospholipid antibodies. Of those who selected a partial laboratory work up (rheum n = 9 [17%]; derm n = 33 [48%]), only CBC (rheum n = 9 [100%]; derm n =32 [97%] and urinalysis (rheum n = 7 [78%]; derm n = 24 [73%]) achieved consensus as defined above. Other laboratory studies are listed in Table 1. There was consensus that the following baseline clinical features warrant more thorough SLE screening: 1st degree relative with SLE, positive autoantibodies, arthritis and nephritis. Rheumatologists more often initiated hydroxychloroquine as first-line therapy (rheum n = 24 [45%]; derm n = 9 [13%]) while dermatologists more frequently started with topical therapy (rheum n = 16 [30%]; derm n = 50 [72%]). There was no consensus regarding appropriate choice of second-line systemic agents.

Conclusion: This study reveals lack of consensus between and among pediatric dermatologists and rheumatologists caring for children with DLE, underscoring the need for future study and collaboration. Knowledge gaps include risk factors for SLE, screening for SLE, optimal therapy, and patient outcomes. Collection of robust longitudinal observational data will aid in developing consensus for management of pediatric-onset DLE. Table 1. Laboratory studies selected for partial screening

	Rheum (9) n, (%)	Derm (33) n, (%)
Complete blood count with differential**	9 (100%)	32 (97%)
Urinalysis**	7 (78%)	24 (73%)
Complement	9 (100%)	16 (48%)
ESR	7 (78%)	17 (52%)
ANA	6 (67%)	31 (94%)
Basic metabolic panel	6 (67%)	18 (55%)
Hepatic function tests	6 (67%)	21 (64%)
Anti-ds DNA	5 (56%)	24 (73%)
Ro, La, Smith, and RNP	5 (56%)	18 (55%)
Urine protein:creatinine	5 (56%)	5 (15%)
CRP	3 (33%)	9 (27%)
Anti-phospholipid antibodies	0 (0%)	1 (3%)

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Abstract Number: 1399

Transitioning Lupus Patients from Pediatric to Adult Rheumatology

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Pediatric rheumatologists have successfully improved the life expectancy and quality of life of children with systemic lupus (cSLE). cSLE has higher morbidity and mortality than adult SLE; the young adult with SLE may have severe system involvement at the time of transition. The consequences of poor transition in this at-risk population are loss of continuity in care and medication regimen, as well as worse disease activity and damage. As data are scarce on successful transition of cSLE patients to adult care, we conducted a pilot study to better understand how to facilitate this transition.

Methods: Patients with cSLE ≥14 years old who fulfilled ACR SLE criteria were evaluated using a 29-item Transition Readiness Questionnaire (SLE-TRQ) adapted from transitioning questionnaires in other chronic disease. It included medical and life skills, medical knowledge and independent living, and feelings/stress about transition. A protocol based on the American Academy of Pediatrics guidelines for successful transition was implemented for patients ≥18 years old. All patients met with the adult rheumatologist in the pediatric clinic and were accompanied to their first adult clinic visit by the Pediatric Rheumatology nurse. Successful transition was defined as ≥ 3 visits with the adult rheumatologist. All successfully transitioned patients were asked to complete a Satisfaction Questionnaire (SQ).

Results: 40 patients with a mean age of 18.4 years completed the SLE-TRQ. The mean disease duration was 5.25 years; 75% were female; 45% Hispanic, 40% African American, 7% Caucasian. There were 93% who had major organ involvement, 19 (48%) renal disease, 8 (20%) neuropsychiatric lupus, 3 (10%) abnormal pulmonary function tests and 2 (5%) anti-phospholipid syndrome. Eleven patients were on prednisone, median dose 20 mg/day at the time of enrollment. Over 50% were non-adherent at least on one occasion with medications and appointments. On the SLE-TRQ, 27 patients reported good medical and life skills, and 14 had good knowledge. However, 16/40 admitted to uneasiness/unreadiness for transition. The mean scores were: skills- 1.39, knowledge- 2.4 and feelings about transition- 2.3, where scores of 4-5 identify patients that are not ready, 2-3 patients in preparation and 0-1 ready for transition. Of the 20 patients scheduled to transition, 12 were successfully transferred, and 8 remain under pediatric care, scheduled to transition at a later date. The mean SLEDAI at the last pediatric visit was 5.6 and at the third adult visit 5.25. Three patients were on prednisone (mean dose 13.8 mg/day). Nine patients completed the SQ, reporting satisfaction with the transition process.

Conclusion: This is the first study evaluating self-reported pre-transition readiness in cSLE and satisfaction with the transition process. Patients had good medical knowledge and independent living skills but were not psychologically ready to transition. We were able to successfully transition 60% of the patients with good satisfaction. However, 40% were not transitioned, suggesting adolescents with cSLE and major organ involvement need additional support in the transition to adult rheumatology.

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Abstract Number: 1400

Preliminary Validation of the Turkish Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY) in a Single Center

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Background/Purpose: Juvenile systemic lupus erythematosus (SLE) is a chronic multisystemic disease with an episodic course which is prevalent in all cultures with wide-ranging effects on their health-related quality of life (HRQOL). In order to detect the effect of SLE on pediatric population and their parents; a disease specific HRQOL tool, called Simple Measure of Impact of Lupus Erythematosus in Youngsters (SMILEY), was developed, translated into different languages and validated in several languages. To determine the validity and reliability of the Turkish SMILEY in our center. Here we are presenting the preliminary data of our single-center research.

Methods: In our cross-sectional study, Turkish children and adolescents 8–18 years of age with SLE and their parents were enrolled. Pediatric SLE patients and parents completed child and parent reports of Turkish SMILEY and Turkish Pediatric Quality of Life Inventory (PedsQL^{TM}) Generic module. Parents also completed the Childhood Health Assessment Questionnaire (CHAQ) regarding disability which affects HRQOL. Disease activity was estimated by examining physicians with usage of the SLE disease activity index (SLEDAI) and Physician's Global Assessment of disease activity (PGA); chronic damage with the Systemic Lupus Erythematosus International Collaborating Clinics ACR Damage Index (SDI). Additional information including child's age, gender, co-morbidity, date of disease onset, disease duration and medical treatment history were also noted. Test-retest reliability, agreement between child and parent reports of the Turkish SMILEY and validity modalities were examined.

Results: 70 children with SLE (Male/Female 11/59; mean age at investigation 15.4±2.8 years, mean disease duration 41.4±29.4 months) were recruited into the study. Our patients have a median SLEDAI of 4 (range 0-23), and median SDI of 0 (0-5), and median PGA was 1 (0-4) and 80% of these were active (SLEDAI > 0). Out of 70 children, only one child didn't complete the child report SMILEY scale; but all of seventy parents were able to fulfill their corresponding report of the Turkish SMILEY. 59 child subjects and 60 parent subjects solved the Turkish SMILEY again 14 days later. The ICC for all domains and total scores of child report (0.7-0.9, P<0.001) and parent report (0.6-0.9, P<0.001) was significant, thus confirming excellent test-retest reliability. Agreement between children and their parents was found to be favoring. For the existing child-parent pairs (n=69), moderate rho (0.4-0.6, P<0.001) and significant ICC (0.6 - 0.8, P<0.001) values were seen between the child and parent SMILEY total and domain scores. For children; the mean SMILEY total score was 70.3±13.4 and the mean PedsQL^{TM} Generic module score was 78±15.7. For the parents they were calculated as 70.1±13.4 and 77±16.5 respectively. There was a significant correlation between these scores both for the children (r=0.5, P<0.001) and the parents (r=0.4, P<0.001). In our study; important Spearman's correlations were found between child report of Turkish SMILEY and factors affecting morbidity, mortality. The child SMILEY total score (n=69) correlated remarkably with the PGA (r=0.7, P<0.001), SLEDAI (r=0.4, P<0.001), and SDI (r=0.5, P<0.001). The children with lower disease activity and damage were discovered to have higher scores in their corresponding SMILEY report, hereby emphasizing better QOL. This relationship was especially noticeable in total score and the limitation domain of SMILEY.

Conclusion: This first validation study about HRQOL of pediatric SLE patients in Turkey showed that; Turkish SMILEY is a useful, valid and a reliable disease-specific questionnaire which can be further used as a beneficial research tool in our country.

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Abstract Number: 1401

Ultrasonography of Major Salivary Glands in Juvenile SjöGren's Syndrome − Preliminary Findings in a Multi-Center Study

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile Sjögren's syndrome (jSS) is a rare, poorly defined and possibly underdiagnosed condition. Mean age of diagnosis is approximately 10 years, with major salivary gland swelling as a common initial symptom. Extraglandular manifestations occur in approximately 50% of patients with jSS. Salivary gland ultrasonography (SGUS) is a non-invasive, non-irradiating imaging method. With regard to the late onset of sicca symptoms, the current lack of diagnostic criteria and the need for an alternative or supplement to the lip biopsy, a non-invasive diagnostic tool is especially important in the younger population. The aim of this study was to characterize symptoms and clinical findings of jSS and to investigate SGUS as a diagnostic method.

Methods: Patients were recruited from the Departments of Rheumatology at Haukeland University Hospital, Bergen, Norway, and Oslo University Hospital, Oslo, Norway. Patients were previously diagnosed with jSS by a specialist in rheumatology and had received the diagnosis before 18 years of age. Clinical examination, sialometry, Schirmers Itest and SGUS were performed in all patients, and information regarding autoantibodies and biopsy results obtained from the patients' medical journal. The SGUS examination of the parotid and submandibular glands was performed using a GE LogiqE9 with a linear high-frequency transducer (6-15 MHz). Representative images were stored digitally and blindly evaluated by two investigators (DH and MVJ). Glandular homogeneity and presence of hypoechogenic areas were evaluated and glands characterized as normal or SS-like.

Results: Mean age at jSS diagnosis was 13.6 years (range 7-16), with first symptoms occurring at 11 years (range 6-17). Sicca symptoms were reported in 4/10 patients. Reduced secretion of tears (Schirmer I-test ≤ 5 mm/5 minutes) was detected in 3/10 patients, and hyposalivation (unstimulated whole saliva ≤ 1.5 ml/15 minutes) in 4/10 patients. Minor salivary gland lip biopsy had been performed and focus score determined in 8/10 patients; 7/8 biopsies had a focus score ≥ 1. All patients were positive for ANA and anti-Ro/SSA; 6/10 were also anti-La/SSB positive, and 6/10 were rheumatoid factor positive. Salivary gland enlargement had been experienced by 6/10 patients; 1/6 had also experienced lacrimal gland enlargement. Lymphadenopathy was noted in 3/10 patients, and articular involvement in 3/10 patients. Current treatment with hydroxychloroquine was noted in 7/10 patients, and previous treatment in two patients. Interestingly, SGUS revealed that all investigated patients (n=10) had pathological findings consistent with pSS in at least 1 out of 4 major salivary glands, whereas the American-European Consensus Group (AECG) criteria was fulfilled by only 6/10 patients.

Conclusion: The majority of patients in this jSS cohort present with autoantibodies and pathological SGUS findings. Major salivary gland swelling was commonly reported, whereas sicca symptoms were rare. Although further studies are warranted in larger cohorts, findings indicate SGUS as a suitable imaging method in the diagnosis of jSS, possibly enabling an early diagnosis of this rare clinical condition.

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Abstract Number: 1402

Meeting the Needs of Adolescents with Autoimmune Diseases, the Development of a Clinical Transition Pathway

Margot Walter[1], Johanna M.W. Hazes[2], Radboud JEM Dolhain[3], Philomine A. van Pelt[4], A. Dijk van[5] and Sylvia S.M. Kamphuis[6], [1]Rheumatology, Erasmus Medical Center, Rotterdam, Netherlands, [2]Department of Rheumatology, Erasmus University Medical Centre, Rotterdam, Netherlands, [3]Rheumatology, University Medical Center Rotterdam, Rotterdam, Netherlands, [4]Rheumatology, Erasmus MC,

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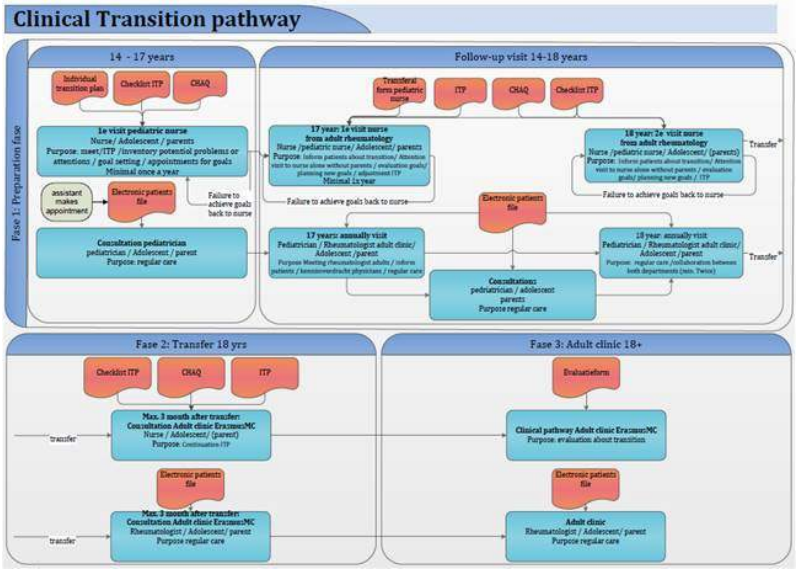
Background/Purpose: Evidence based recommendations for transitional programs are available. Despite this, half of Young People (YP) do not make a successful transfer and implementation of transitional care is not widespread. Therefore, it is important to improve transitional care for YP with an autoimmune disease (AID). A potential tool could be the institution of a clinical transition pathway (CTP). The aim of this study was i) to explore how YP with an AID and their parent(s) experience care during the preparation for the upcoming transfer to adult care, ii) to develop a CTP.

Methods: A survey was conducted among YP with an AID (n=48), age 14-20 years with a separate survey for parents (n=48). Subjects of the 38 survey-questions involved demographics, achievement of self-management skills, experience with preparation for transfer and questioning for topics that were not discussed but should have been in clinic. The CTP was built based on principles of vanHaecht & Sermeus[1], results of the surveys were incorporated into the CTP.

Results: Response rate was 67% for YP and 69% for parents. It appeared that almost all YP attended the consultation with parents (88%). Training self-management skills was neglected and only 25% of YP were ordering medication or made appointments independently (15 %). Transition was not a topic in the consultation according to half of the YP. One third of all parents had feelings of anxiety about the upcoming transfer. Almost half of the YP needed discussing topics that were never mentioned during consultation like education, vocational, and alcohol. Results were used to built the CTP (figure 1). Most important points are an early start , with focus on self-management skills and independency using an individual transition plan (ITP) for each patient, joint consultations with professionals from both pediatric and adult rheumatology departments and supporting parents in letting go. The ITP (developed using 'DREAM TEAM UK' [2]) was divided into 3 age-categories (12-14;14-16;16-18+), with final checklist regarding different domains and per category targets that needed to be met.

Conclusion: Current care in general does not meet the needs of YP in the process of transition to adult rheumatology care. The developed CTP is a tool to improve this process with provision of care appropriate to the developmental stage of YP, focus on achievement of self-management skills and self-reliance and supporting parents during this process. [1] VanHaecht et all. Clinical pathway audit tools: a systematic review. Journal of Nursing Management, 2006, 14, 529–537K. [2] McDonagh et all. Growing up and moving on in rheumatology: development and preliminary evaluation of a transitional care programme for a multicentre cohort of adolescents with juvenile idiopathic arthritis J Child Health Care. 2006 Mar;10(1):22-42.



Disclosure: M. Walter, None; **J. M. W. Hazes**, None; **R. J. Dolhain**, None; **P. A. van Pelt**, None; **A. Dijk van**, None; **S. S. M. Kamphuis**, None.

diseases-the-development-of-a-clinical-transition-pathway

Abstract Number: 1403

Systematic Appraisal of the American College of Rheumatology Clinical Practice Guidelines

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Session Time: 9:00AM-11:00AM

Background/Purpose: The ACR practice guidelines establish U.S. and international treatment recommendations. We sought to characterize the quality of the guidelines using the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument with the aim of identifying potential areas for improvement.

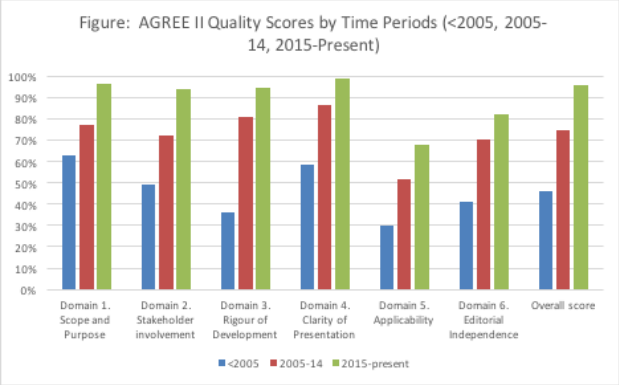
Methods: Using the AGREE II online tool, four independent reviewers appraised the ACR practice guidelines available at the ACR website and their immediate previous version. AGREE II consists of 23 questions that examine six quality domains: Scope and Purpose, Stakeholder Involvement, Rigor of the Methodology, Clarity of Presentation, Applicability and Editorial Independence. To avoid sequencing effects, the order of appraisal was randomly assigned across reviewers. The quality scores of each domain were calculated by summing up the individual item scores in a domain and then dividing that sum by the maximum possible score for that domain. We summarized the domain scores for each guideline and examined trends over time.

Results: The 9 guidelines (Glucocorticoid Induced Osteoporosis (GIOP); JIA; Gout; LN; OA; SpA; PMR; RA) listed at the ACR website as of April 2016 and 4 previous versions (SLE 1999, OA 2000, GIOP 2000 and RA 2008) were appraised using the AGREE II instrument. All guidelines were published between 1999 and 2015. The Table shows the percentages of the total possible score for each guideline. The minimum and maximum for each domain were 53-99 for Scope and Purpose; 47-99 for Stakeholder Involvement; 31-96 for Rigor of the Methodology; 50-99 for Clarity of Presentation; 26-78 for Applicability; 25-85 for Editorial Independence and 42-96 overall. The Figure displays the trend in score changes over time. The average quality of guidelines improved over each time period, especially in the Scope and Purpose, Rigor of the Methodology, Stakeholder Involvement and Clarity of Presentation. In contrast Applicability and Editorial Independence domains improved but not to the levels of the other domains. For the 4 guidelines with previous versions, the mean (SD) absolute improvements for each domain were 18 (±11) for Scope and Purpose; 13 (±8) for Stakeholder Involvement; 38 (±22) for Rigor of the Methodology ; 25 (±15) for Clarity of Presentation; 22 (±12) for Applicability; 24 (±17) for Editorial Independence and 31 (±5) overall.

Conclusion: Based on the AGREE II instrument, the quality of ACR guidelines has improved over the past 16 years. There remains potential for improvement in the applicability and editorial independence domains.

Table: AGREE II Quality Score

	Domain 1. Scope and Purpose	Domain 2. Stakeholder involvement	Domain 3. Rigor of Development	Domain 4. Clarity of Presentation	Domain 5. Applicability	Domain 6. Editorial Independence	Overall score
SLE1999	76%	51%	43%	63%	36%	25%	50%
OA2000	53%	47%	34%	50%	28%	50%	42%
GIOP2001	60%	50%	31%	63%	26%	48%	46%
RA2008	76%	79%	86%	92%	52%	73%	71%
GIOP2010	83%	60%	82%	83%	61%	69%	75%
JIA2011	82%	82%	83%	86%	53%	75%	71%
LN2012	78%	57%	84%	92%	60%	71%	83%
OA2013	81%	71%	88%	93%	49%	73%	79%
Gout1.2012	62%	66%	63%	68%	39%	57%	63%
Gout2.2012	78%	89%	81%	90%	49%	73%	83%
PMR2015	97%	99%	96%	99%	70%	83%	96%
SpA2015	99%	93%	95%	99%	76%	85%	96%
RA2015	93%	90%	93%	99%	58%	79%	96%



Disclosure: A. Duarte-Garcia, None; **M. Cavalcante**, None; **S. Arabelovic**, None; **J. B. Wong**, None.

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Abstract Number: 1404

Systematic Review and Appraisal of Quality Measures for Inflammatory Arthritis

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Background/Purpose: Quality measures are metrics health professionals can monitor to improve care delivery and patient outcomes. To be measurable they must include a specified numerator, denominator for a defined population, capture best-practices and be feasible to measure. The objective of this study was to conduct a systematic review and quality appraisal of measures for inflammatory arthritis (IA).

Methods: A search strategy was developed in consultation with a medical librarian using MeSH terms for IA (SpA [AS, PsA, ReA, and IBD-related arthritis], RA, and JIA) and quality measures. EMBASE, MEDLINE and CINAHL were searched from January 1, 2000 to Jan 17, 2016. A "grey literature" review of international arthritis organizations and quality measure libraries was also conducted. Two reviewers independently considered the papers for inclusion with disagreements resolved by consensus. A modified guideline appraisal tool (AGREE-II) was used to evaluate 6 domains of measure development on a 7 point Likert scale: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, editorial independence and an overall quality assessment which determined inclusion. Measures were abstracted in duplicate and categorized into themes, indicator type (process, structure, outcome) and based on 6 domains of quality (acceptability, accessibility, appropriateness, effectiveness, efficiency, safety).

Results: 3417 unique citations were found and 483 were selected for full-text review, 8 measurement sets were eligible for inclusion. An additional 2 sets were included that were published after the search and 5 sets from the grey literature review. Two sets did not meet AGREE II criteria leaving a total of 13 measurement sets. The measure sets were from 4 countries (USA, Canada, UK, Netherlands) and one European consortium. They included 10 sets on RA and 1 each for PsA, IA and JIA. There were a total of 161 unique individual measures (136 process, 20 structure and 5 outcome). Measures were found covering each of the 6 domains of quality. Frequent themes included assessment, management (including medications and comorbidities), wait times and education. Measure sets were developed based on systematic reviews of guidelines and measures, individual guidelines or on information from targeted literature reviews. Evaluation of development methods for the measurement sets revealed a variety of consensus techniques including: RAND-UCLA appropriateness methodology, prioritization exercises or other modified-Delphi methods. Inclusion of patients occurred

in 62% of development groups. Discussion of barriers to measurement was infrequent.

Conclusion: This review highlights that IA quality measures cover a diversity of themes encompassing process, structure and outcome measures across the 6 domains of quality. However, between organizations measure development is not standardized, highlighting the need for a standardized assessment tool for evaluation of development methods. As well, local assessment of measurement feasibility through pilot testing before implementation and use outside the original development context is recommended.

Disclosure: M. Cooper, None; **C. E. H. Barber**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/systematic-review-and-appraisal-of-quality-measures-for-inflammatory-arthritis

Abstract Number: 1405

Quality Measures in High Priority Rheumatologic Diseases: A Systematic Literature Review and Analysis

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Session Date: Monday, November 14, 2016

Session Title: Quality Measures and Quality of Care - Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: To identify published quality measures in rheumatoid arthritis (RA), osteoarthritis (OA), osteoporosis, spondyloarthropathy (SpA) and gout for the purpose of summarizing the existing measures and identifying gaps for improving care.

Methods: We performed a systematic review of English language articles in PubMed and Embase published before 2/11/2016 on the topic of quality measures in RA, OA, osteoporosis, SpA (psoriatic arthritis and ankylosing spondylitis) and gout. To be included, the quality measure applied to a clearly stated study population and had a description of its development, a measurable change, and an identifiable numerator and denominator. When articles referenced a website as the primary source of a quality measure, we reviewed the website for additional references; opinion articles were excluded. If measures were published on an annual basis, we evaluated the most recent measure set. We categorized individual measures by disease, publication year, domain (structure, process or outcome), country of origin, and endorsement. We analyzed identified quality measures across disease categories to draw summative conclusions and identify gaps.

Results: The literature search identified 4831 relevant abstracts. Detailed screening by 3 reviewers identified 22 abstracts meeting the inclusion criteria; 6 quality measure sets were found only on websites with no primary source in the scientific literature. Most of the published measures were specific for RA and OA (Table) and published after 2010 (n = 24, 62%). Not unexpectedly, most of the measures were related to the health care delivery process (82.3%), while relatively few were in the domains of structure (16%) and outcome (1.7%). Quality measures often originated from organizations and investigators in the United States (US) and United Kingdom (UK). Within the US, ACR (3 sets), Centers for Medicare and Medicaid Services (CMS) (3 sets), and the National Committee for Quality Assurance (NCQA) (2 sets) produced the greatest number of measure sets.

Conclusion: Most of the quality measures in rheumatology relate to the care of patients with RA and OA and focus on process rather than outcomes or structure. These results highlight the gaps in our ability to measure quality of care across the full spectrum of common rheumatologic diseases. Further work is needed to expand the development of quality measures to other common rheumatologic diseases and to address quality of care from the perspective of structure and outcomes.

Quality measures by High Priority Rheumatologic Disease

Disease	Year of Publication (n)	Number of Measure Sets	Number of Individual Measures	Origins of publications (n)	Domains of Individual Measures
Rheumatoid Arthritis (RA)	2004-2010 (4); 2011-2016 (9)	13	142	US (6); Canada (2); UK (2); Netherlands (1); PANLAR (1); EULAR (1)	Structure: 25 (18%) Process: 114 (80%) Outcome: 3 (2%)
Osteoarthritis (OA)	2001-2010 (5); 2011-2015 (6)	11	104	US (5); UK (2); Canada (1); Mexico (1); Belgium (1); EULAR (1)	Structure: 17 (16%) Process: 85 (82%) Outcome: 2 (2%)
Osteoporosis	2001-2010 (3); 2011-2013 (4)	7	40	US (7)	Process: 40 (100%)
Spondyloarthropathy (SpA)* and Generic Inflammatory arthritis[#]	2004-2010 (1); 2011-2016 (3)	4	38	US (2); UK (1); Canada (1)	Structure: 11 (29%) Process: 27 (71%)
Gout	2004-2010 (2); 2011-2014 (2)	4	27	US (3); UK (1)	Structure: 3 (11%) Process: 23 (85%) Outcome: 1 (4%)

*Only one paper found for spondyloarthropathy, specifically addressing psoriatic arthritis. [#] Generic Inflammatory arthritis includes: RA, psoriatic arthritis, ankylosing spondylitis and juvenile idiopathic arthritis US = United States; UK = United Kingdom; EULAR = European League Against Rheumatism; PANLAR = Pan American League of Associations of Rheumatology

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Abstract Number: 1406

Towards Harmonized Data Collection in Rheumatoid Arthritis (RA): The EULAR Task Force for Standardizing a Minimum Data Collection for RA Observational Research

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Background/Purpose: Collaborative research is compromised by heterogeneity of data collection in observational rheumatoid arthritis (RA) databases. Therefore a EULAR taskforce has been convened to develop a minimum core dataset (MCD) of data items (i.e. Ôwhat to collectÕ) and instruments for data collection (i.e. Ôhow to collectÕ) to 1) harmonize future data collection 2) act as a common data model to which existing databases can be mapped 3) serve as a template for standardized data collection for RA research in routine clinical practice.

Methods: The task force comprised a study steering committee, a task force working group and a pan-European expert panel. The project involved a multi-step process (Figure): 1) a hierarchical literature review to identify data items and instruments of existing RA cohorts and registers 2) an online survey to capture information on perceived importance of extracted items and instruments for possible inclusion 3) two face-to-face (F2F) meetings of the working group with discussion and voting on content (items) and structure (instruments) of the MCD. The voting of the F2F meetings were confirmed and consolidated by a ratification survey and work performed by the steering group between the two F2F meetings.

Results: Published articles from 67 different European registers and cohorts were included for data extraction. The number of patients recruited in each register ranged from 130 to more than 50,000. A total of 40 different items and 125 instruments were identified in literature; 7 items felt to be missing were added by the steering group. A total of 90 experts from 28 different European countries, including patients (18%), health professionals (18%), physicians (55%) and researchers or other experts (10%) participated in the online survey. 27/47 (57%) items were regarded to be important for inclusion in a MCD by >80% of responders. At the first F2F meeting 22/47 items were voted to be INCLUDED, 24/47 to be EXCLUDED in a MCD; for 2 items no consensus was reached. Ratification survey and second F2F meeting revealed consensus to include 21/47 items and their instruments (Table). Remaining work in the task force pertains to instruments for two items (ÔglucocorticoidsÕ and ÔcomorbiditiesÕ).

Conclusion: Based on the multistep process, a first draft of a MCD was developed which has to be tested for feasibility in clinical settings and applicability to answer important research questions. Figure: Flowchart of the multistep process of the project

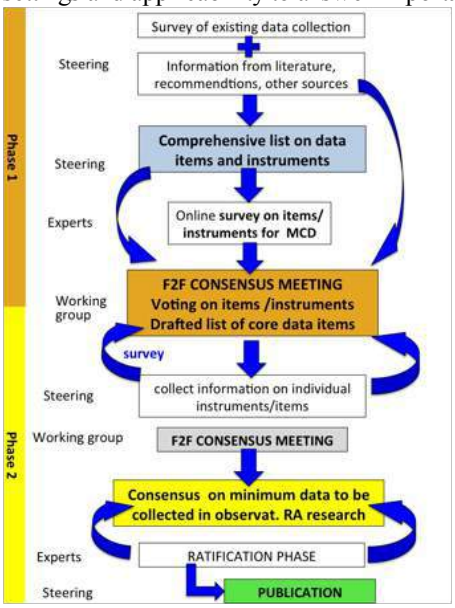

Table: Content of minimum core dataset

INCLUDED ITEM	PROPOSED INSTRUMENTS
AGE	date of birth
GENDER	male /female
DIAGNOISIS OF RA	rheumatologist reported diagnosis of RA
DISEASE DURATION	date of diagnosis
SMOKING	current / previous / never
BMI	weight / height
COMPOSITE SCORE	Clinical disease activity index (CDAI), simplified disease activity index (SDAI), disease activity score 28 joints (DAS28) EULAR and ACR response
TENDER JOINT COUNT	28 joint count
SWOLLEN JOINT COUNT	28 joint count
PATIENT GLOBAL	capture: 1) global assessment of disease activity, 2)related to arthritis,3) today and use of visual analogue scale (VAS) or numeric rating scale (NRS)
EVALUATOR GLOBAL	capture: 1) global assessment of disease activity, 2)related to arthritis,3) today and use of VAS or NRS
PAIN	capture: 1) pain, 2)related to arthritis, 3) last week and use of VAS or NRS
PHYSICAL FUNCTION	Health assessment questionnaire (HAQ)
ACUTE PHASE REACTANTS	C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
SEROLOGY	Rheumatoid factor AND ACPA
ONGOING/MOST RECENT DMARD	1) type of DMARD, 2) start and stop date, 3) reason for discontinuation (if applicable)
DMARD HISTORY	name of previous DMARD(s) (including biological, conventional synthetic and targeted synthetic DMARDs)
HEALTH RELATED QUALITY OF LIFE	Euro-Qol-5D (if available cost-free)
X-RAY HANDS AND FEET	presence of erosions on X-RAY Yes/No
COMORBIDITIES	*To be identified*
GLUCOCORTICOIDS	*To be identified*

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Abstract Number: 1407

Disease Activity Trackers to Support Treat to Target Strategies: A Needs Assessment Survey

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Background/Purpose: Custom-built software applications (apps) have become an integral part of medical practice today to help physicians be more efficient. They are being widely used for diagnostic purposes and for monitoring chronic conditions. In rheumatology, medical apps may help health professionals track disease activity and aid treatment decision in real-time to achieve optimal patient outcomes. The objective was to assess the need of a digital disease tracker to monitor disease activity in rheumatoid arthritis (RA) patients and psoriatic arthritis (PsA).

Methods: A needs assessment survey of Canadian rheumatologists was conducted in the spring of 2015. Our goals were to understand their views about Treat to Target strategies, and their perceptions of digital trackers to provide benefit to their patients and practice.

Results: Of 410 surveys sent via Survey Monkey, we received 70 responses (17% response rate). Responders were representative of the distribution of rheumatologists in Canada with the majority being in Ontario and Quebec. Among responders, 67% had practiced for 15 to 20 years and were serving predominantly urban patient populations (86%). The majority (56%) utilize both paper and electronic medical records (EMR). An additional 31% use EMR only. The vast majority (87%) accessed EMR via desktop/laptop computer with only 15.7% also utilizing tablets or smart phones. Clinical practice guidelines were widely used (87%) to make treatment decisions. CRA guidelines were mostly commonly selected, followed by ACR then EULAR. Treat to target strategies were employed by 92.86% of respondents, with swollen joint count (85.94%), physician global assessment (69.35%) and patient global assessment (57.14%) being the most common targets while DAS28 (45.45%) and SDAI (42%) were used less frequently . Over 80% of respondents do not use an RA disease tracking tool at this time. However 54.3% of respondents were very interested in having access to an efficient, user-friendly electronic device or app to help assess RA patients' disease activity at each visit, and track it over time. Many strongly believed such an app would benefit their practice (48.57%) and their patients (44.93%) and felt it was very important that the tracker be integrated with EMR (62.86%). Similar to accessing EMRs most respondents selected desktop/laptop as their preferred device for use of a digital RA Tracker.

Conclusion: Our survey found that most Rheumatologist apply Treat to Target strategies but are not currently using an RA disease tracking tools in their practice. An easy to use digital RA disease assessment tracker may be of value to Rheumatologists in Canada.

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Abstract Number: 1408

Impact of Participation in the Adalimumab (Humira) Patient Support Program on Patient Reported Outcomes Among Patients with Rheumatoid Arthritis: Passion Study

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Background/Purpose: Patient (pt) Support Program (PSP) is offered to pts who are prescribed adalimumab (ADA) for their Rheumatoid arthritis (RA). How participation in a PSP may impact pt-reported outcomes (PROs) has not been explored extensively in a prospective study. The purpose of this analysis was to assess the effect of ADA PSP participation on PROs among RA pts initiating ADA.

Methods: In this multi-country, ex-US, 78 week (wk) study, pts were offered a panel of "Core elements" (starter pack, call center/hotline, nursing services, educational material, and injection guide; offered in all participating countries) and "Other elements" (e.g, refill reminders, email, newsletters, support groups, home delivery, and financial assistance; vary by country) of PSP. Pts were divided in 2 groups on the basis of their participation in the PSP: ever (PSP users) vs never (PSP non-users). The following PROs were assessed over time to analyze the effectiveness of ADA in context of PSP utilization: Patient Activation Measure-13 (PAM-13, evaluates knowledge, skills, and confidence essential to a pt managing his/her own health; scores classified *a priori* into 4 levels [higher level = greater pt involvement in disease management]), Work Productivity and Activity Impairment (WPAI, evaluates absenteeism, presenteesism, work productivity loss, and activity impairment), Compliance Questionnaire Rheumatology (CQR, measures compliance to drug regimen), and Treatment Satisfaction Questionnaire for Medication (TSQM, evaluates convenience, effectiveness, side effects and global satisfaction). Change in pt perceptions was measured by the Beliefs about Medicines Questionnaire (BMQ, necessity and concern scales).

Results: Percentage (%) of pts that demonstrated improvement in PAM-13 levels were significantly higher among PSP users vs PSP non-users at wk 78 compared to BL (35.7% vs 28.1%, *P*=0.01). Additionally, compared to PSP non-users, PSP users had a significantly higher % of pts that started at level 4 at BL and remained at level 4 at wk 78 of ADA treatment (52.4% vs 28.9%, *P*=0.001); and % of pts that started at level 3 at BL and stayed at level 3 or improved to level 4 at wk 78 (64.5% vs 53.8%, *P*=0.028). PSP users had lower activity impairment (WPAI), higher convenience and global satisfaction (TSQM), and showed improvement in the necessity scale (BMQ) at all measured time points. Only numerical improvement in the favor of PSP users was observed for CQR **(Table)**.

Conclusion: In pts with moderate to severe RA, PSP users reported significant improvements after 78 wks of ADA initiation in managing their health and had skills and confidence to do so as evidenced by higher PAM-13 levels compared to the PSP non-users. Additionally, PSP users had significantly lower activity impairment, improved convenience and global satisfaction, and felt higher necessity for prescribed medication in comparison to the PSP non-users.

Table: Patient-reported outcomes by PSP utilization category

Patient-Reported Outcomes mean change from BL, (n)	24 weeks		52 weeks		78 weeks	
	PSP user	PSP non-user	PSP user	PSP non-user	PSP user	PSP non-user
WPAI						
Absenteeism	-2.32 (149)	-5.43 (138)	-2.80 (152)	-5.18 (147)	-5.71 (156)	-8.17 (151)
Presenteeism	-18.68 (167)	-17.06 (163)	-18.34 (169)	-17.02 (168)	-19.07 (172)	-17.75 (173)
Work productivity loss	-17.55 (148)	-18.17 (137)	-17.77 (152)	-16.69 (147)	-22.28 (156)	-19.94 (151)
Activity impairment	-23.90* (474)	-20.11 (458)	-25.06* (478)	-20.97 (466)	-26.42* (478)	-20.56 (468)
CQR	2.44 (488)	2.01 (458)	2.39 (490)	1.99 (466)	2.30 (490)	1.80 (467)
TSQM						
Convenience	6.67* (387)	3.85 (269)	7.38* (413)	4.77 (292)	7.23* (422)	4.76 (300)
Effectiveness	14.56 (368)	14.29 (262)	16.06 (392)	15.41 (286)	16.24* (401)	13.62 (294)
Side effects	8.21 (367)	8.10 (246)	8.09 (393)	8.55 (274)	8.37 (403)	8.25 (284)
Global satisfaction	11.44* (383)	10.85 (267)	12.53* (408)	11.12 (292)	11.68* (417)	9.87 (300)
BMQ						
Necessity	NC	NC	NC	NC	-0.03* (409)	-0.04 (362)
Concern	NC	NC	NC	NC	-0.12 (409)	-0.17 (361)

*P<0.05. NC = Not Collected. Data represented by LOCF imputation for intent-to-treat population for WPAI, CQR, and TSQM. Data represented as observed for BMQ. Results are adjusted for BL WPAI, CQR, TSQM, and BMQ. LOCF=last observation carried forward.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/impact-of-participation-in-the-adalimumab-humira-patient-support-program-on-patient-reported-outcomes-among-patients-with-rheumatoid-arthritis-passion-study

Abstract Number: 1409

Increase in the Use of Validated Disease Activity Scores in Current Daily Clinical Practice Compared to 2007

Marieke J. de Jonge[1], Laura W.M. Boerboom[1], Anita M.P. Huis[1], Julia M. Weijers[1], Mart A.F.J. van de Laar[2], Marlies E.J.L. Hulscher[1] and Piet L.C.M. van Riel[1,3], [1]Radboud university medical center, Radboud Institute for Health Sciences, IQ healthcare, Nijmegen, Netherlands, [2]University of Twente, Department of Psychology, Health and Technology, Enschede, Netherlands, [3]Bernhoven, Department of Rheumatology, Uden, Netherlands

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Background/Purpose: International guidelines and studies recommend rheumatologists to use validated measures to monitor disease activity, such as the Disease Activity Score of 28 joints (DAS28). However, based on previous research, that recommendation was marginally followed in daily clinical practice. Before the dissemination of the Dutch guideline, it was found that in 16% of the patient's visits a measure for disease activity was obtained.[1] Up till now it is unknown whether adherence to tight control increased since the dissemination of the Dutch guideline in 2009. This study aims to evaluate whether the use of validated disease activity scores has changed since 2007.

Methods: To increase the precision of the study, Dutch rheumatologists that participated in the study of 2007 were invited to re-enter the study, If necessary, data were supplemented with data from colleagues and 'new' rheumatologists. Per rheumatologist, data was collected from the first 30 consecutive patients that visited the outpatient clinic. Per patient, data from four consecutive rheumatologist visits were collected. Data were collected by local nurses or by a research assistant, using case record forms. Disease activity was considered to be measured when either a validated score was reported in patients' medical chart, or when the researchers could calculate a validated score from the reported data (see figure 1). To allow comparison, this definition is the same as van Hulst et al. used in their 2007 measurement.[1]

Results: At this phase of the study, a medical chart review was performed on a sample of 1044 visits, within 10 rheumatologists, within 7 Dutch rheumatology outpatient clinics. These preliminary results show that in 84.0% (877/1044) of the visits a RA disease activity score was reported. Of those visits, a DAS28 score was reported in 49.6%(435/877) of the cases, a DAS28-CRP score was reported in 13.5% (118/877) of the cases, and a DAS score was reported in 2.6% (23/877) of the cases. In the remaining 34.3% (301/877) of the cases, another disease activity score was used (see figure 1).

Conclusion: Based on the preliminary results, the use of validated disease activity scores has increased since 2007. Currently, a medical chart review on a sample of 35 Dutch rheumatologists is still ongoing. Ultimately, we will present data on their use of validated disease activity scores, as well as on medication regimen changes based on disease activity. References: 1. van Hulst LT, Hulscher ME, van Riel PL. Achieving tight control in rheumatoid arthritis. Rheumatology (Oxford, England). 2011;50(10):1729-31. Acknowledgements: We thank all participating rheumatologist and nurses for their cooperation.

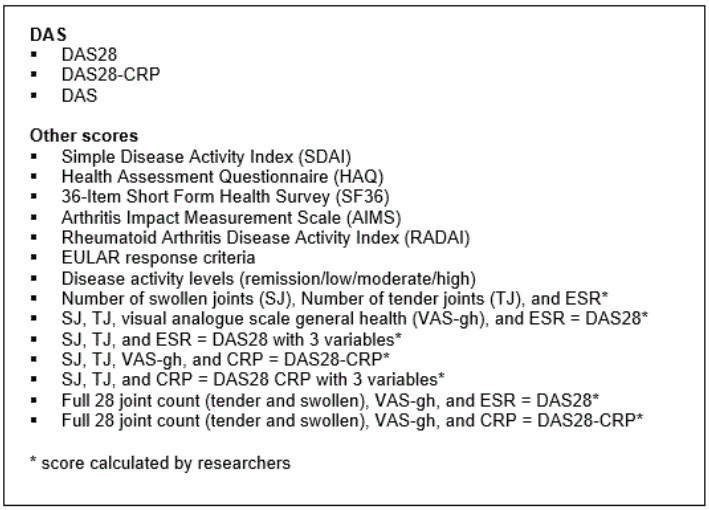

Figure 1: Definition of 'use of validated disease activity scores'

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Abstract Number: 1410

Is the Self-Assessment of Disease Activity (auto-DAS28) By Patients a Feasible and Acceptable Measure over the Long Term in Rheumatoid Arthritis (RA)? Three-Year Follow-up of a Nurse-Led Program in 771 Patients with Established RA

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Background/Purpose: Patients with RA can be trained in self-assessment of disease activity by a self-assessment of their joints and calculation of the Disease activity Score 28 (DAS28) (ref). **Objective:** To assess if such an auto-DAS assessment is a feasible measure over the long-term (i.e., do patients adhere to such an assessment?) and to determine the characteristics of patients related to adherence to auto-DAS.

Methods: This was an open long term (2-4 years) extension of the 6 month randomized controlled COMEDRA trial of patients with definite, stable RA. Patients were trained to perform auto-DAS by a nurse, using a video and teaching of self-assessment of joints (the training took approximately 30 minutes) and nurses provided the advice to perform the auto-DAS regularly in a dedicated booklet. 2-4 years after the end of the trial, patients were seen in a face-to-face interview with a nurse and the frequency of auto-DAS was assessed through the auto-DAS booklet and if unavailable, from patient questioning. Adherence to auto-DAS was defined as the performance of at least one auto-DAS more than 6 months after the end of the trial. Characteristics of adherent versus non adherent patients were compared by univariate and multivariate logistic regression analyses and included demographic and disease activity variables as well as the centre (higher versus lower than median inclusion number).

Results: Of the 970 recruited patients, 771 (79.5%) were followed up 3 years and had available data regarding auto-DAS: mean (±SD) age 61 (±11) years, median [IQR] disease duration 15 [9 - 23] years; 615 (80%) were women and 82% had received a biologic. The mean (±SD) baseline and 3-year DAS28 scores were respectively 3.1±1.3 and 2.8±1.4. After 3 years, 354 (46%) patients were adherent to auto-DAS (i.e., had at least one auto-DAS completed more than 6 months after the end of the trial). For adherent patients the median [IQR] number of auto-DAS performed was 5.4 [1.7 – 12.8] overall, i.e. 2.3 [0.8 – 5.9] per year. However among the adherent population, the number of patients who completed their autoDAS booklet at least once per year decreased over time, with 351 (99%), 162 (46%) and 118 (33%) patients respectively for 2012, 2013 and 2014 ($p<0.0001$). In the multivariate analysis, only larger inclusion centres were significantly associated to an adherent behaviour (OR [95% CI] 2.9 [2.0 – 4.1], $p<0.0001$).

Conclusion: After a short training, many of these long-standing, moderately active RA patients continued to perform an auto-DAS, though the performance of auto-DAS decreased over time in this cohort where patients did not receive any ongoing positive feedback on their auto-DAS. In the larger inclusions centres, autoDAS adherence was higher, perhaps related to more patient/physician interactions around autoDAS results. Self-assessment of disease activity is feasible in RA but positive reinforcement appears necessary. Further studies should analyse if outcomes are better for patients who self-assess.

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Abstract Number: 1411

An Electronic MDHAQ (multidimensional health assessment questionnaire) Beyond an Electronic RAPID (routine assessment of patient index data): 21.3% of Rheumatoid Arthritis Patients Identified As Having Secondary Fibromyalgia Versus 3.5% By Clinicians

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Background/Purpose: A major impediment to use of patient questionnaires in routine clinical care has been the absence of electronic entry for patients and for doctors to introduce data into electronic medical records (EMR), particularly as most EMRs are incompatible with each other. RAPID3 (routine assessment of patient index data) on a multi-dimensional health assessment questionnaire (MDHAQ) has been found as useful in rheumatoid arthritis (RA) clinical trials as indices which require a formal joint count, such as disease activity score 28 (DAS28) or clinical disease activity index (CDAI), to distinguish active from control treatments, and to monitor clinical care. RAPID3 also is informative to recognize improvement in patients with osteoarthritis, systemic lupus erythematosus, spondyloarthropathies, vasculitis, and gout. Therefore, a number of organizations have developed electronic versions of RAPID3, often for demonstration projects and to provide quality indicators in routine clinical care. Most electronic versions mimic EMRs in being incompatible with one another, and therefore not easily merged with one another to study patient courses and outcomes, and invovling considerable expense. A common electronic version of MDHAQ used by many rheumatologists can be merged easily for collaborative research, and rendered compatible with any EMR through mandated HL7 and SMART on FHIR interfaces. We sought to develop an electronic MDHAQ/RAPID3 to be compatible with any EMR, although requiring initial collaboration with the EMR vendor, for routine clinical care.

Methods: A developer was identified with expertise in HL7 and SMART on FHIR interfaces and cloud-based storage, meeting all government privacy and security requirements. The developer has worked closely with rheumatologists to develop a user-friendly electronic MDHAQ, including RAPID3 and many additional scales (Table).

Results: The electronic MDHAQ functions quite effectively, providing RAPID3 and much additional information beyond RAPID3 (Table). For example, among 287 patients with RA in one clinical setting, secondary fibromyalgia (FM) was diagnosed in the EMR by rheumatologists in 10 patients (3.5%), while scores on a MDHAQ-FM index composed of pain, RADAI self-report joint count, and symptom checklist, indicated secondary FM in 61 patients (21.2%), of whom only 6 were identified by rheumatologist. An interface with an EMR through HL7 and SMART on FHIR is available, although requiring collaborative interactions to establish the interface.

Conclusion: An electronic MDHAQ offers considerably more information then only an electronic RAPID3, with no extra work on the part of the physician, while saving time with far better documentation, particularly with establishment of an interface to the EMR through HL HL7 and SMART on FHIR. Rheumatologists and organizations are encouraged to implement an electronic MDHAQ/RAPID3, rather than simply an electronic RAPID3.

Features of electronic MDHAQ/RAPID3 for routine rheumatology care	
Feature	Advantage(s)
RAPID3	Informative in RA, OA, AS, vasculitis, SLE, gout
Fatigue	Higher in SLE, FM than RA
Psychological variables: sleep, anxiety, depression	Screen for frequent source of patient problems
RADAI Self-report joint count	Correlated r>0.04-0.06 with TJC, SJC, in range of ESR vs CRP
Symptom checklist	Most effective screening tool reported for FM -
Recent medical history	Updates recent illness, surgery, adverse events, etc. for clinician
Calculations	Calculates RAPID3, RADAI, # symptoms, psych HAQ; MDHAQ FM index of pain>6, RADAI>16, symptoms>16/60; also DAS28, CDAI, if joint count and lab test available

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Validation of the Danish Version of the Stanford Health Assessment Questionnaire Disability Index and Determination of the Minimal Clinically Important Difference in a Cohort of Rheumatoid Arthritis Patients Using the Rasch Measurement Model

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Background/Purpose: The Stanford Health Assessment Questionnaire Disability Index (HAQ-DI) is a widely used patient reported outcome for functional disability in RA. Minimal clinically important differences (MCIDs) have previously been calculated based on the original ordinal HAQ-DI scores resulting in a dependence of the MCIDs on baseline scores(1), causesing limited generalizability and validity of the proposed MCIDs. The Rasch model provides a transformation of ordinal scores to an underlying latent scale with interval scale properties. This requires adequate fit of HAQ-DI data to the model. We aimed to 1) examine internal construct validity of the Danish version of the HAQ-DI (scored without correction for devices) and 2) determine a MCID of the HAQ-DI in a cohort of RA patients initiating anti-rheumatic treatment in clinical practice based on the transformed linear logit scale.

Methods: RA patients registered in the DANBIO registry at Center for Rheumatology and Spine Diseases, Copenhagen, Denmark were included in the study if HAQ-DI and Patient Global Visual Analogue Scores (PtGl) scores were available at a baseline visit and after > three months of follow-up after initiation of a) first synthetic Disease Modifying Anti Rheumatic Drug (sDMARD) (disease duration <

12 months) or 2) first biological drug (disease duration > 12 months). The Rasch model was fitted to HAQ-DI data at baseline and follow-up and item fit evaluated in separate analyses by comparing observed and expected item-restscore correlations (2). MCID was calculated as the median changes of A) the original and B) logit HAQ-DI score in the group of patients who had improved by 15-30 mm (ie. minimal improvement) on a 0-100 mm PtGl scale.

Results: 362 RA patients were included in the study. HAQ-DI data showed acceptable fit to the Rasch model as no significant evidence of misfit was disclosed at baseline and only a single misfitting item (the "Grip" sub-item, p=0.01) was identified at follow-up. Consistent item ranking across time indicated instrument invariance. Changes in ordinal and logit HAQ-DI scores were strongly correlated (Spearmans rho = 0.935, p <0.001), but the association between them is not completely linear. Sixty-one patients had an improvement > MCID on the logit scale (0.48), but no improvement on the ordinal scale (MCID 0.250), while no patients had the opposite pattern.

Conclusion: The Danish version of the HAQ-DI scored without correcting for devices showed acceptable internal construct validity and thus a MCID based on a linear transformed scale could be calculated for this study (0.48). Application of the logit MCID classified an additional 17% of patients as having achieved a MCID compared to the MCID calculated on the ordinal scale. This finding has potential implications for the use of ordinal-based MCID and the powering of future studies. References:

1. Doganay et al.J Rheumatol. 2016 Jan;43(1):194-202

2. Kreiner S. Appl. Psychol. Meas. 2011;35(7):557-561.

Table 1 Characteristics of the study population grouped by ΔPtGl from baseline to follow-up.

	Worsened ΔPtGl > 15	Unchanged ΔPtGl > -15 < 15	Minimal improved ΔPtGl <-15 >-30	Improved ΔPtGl<-30
No. of patients	47	149	61	105
Female gender, %	88	77	78	80
Age, years	54 (46-65)	58 (48-67)	61 (49-68)	60 (46-69)
Disease duration, years	4.8 (2.5-9.1)	7.6 (2.5-14.6)	7.6 (3.2 – 18.1)	6.2 (2.1 – 12.7)
IgM-RF positive, %	57	79	75	62
PtGl, mm	43 (23-56)	51 (18-80)	57 (37-74)	77 (60-88)
Baseline DAS28	4.0 (3.25-4.75)	4.3 (2.85-4.8)	4.7 (3.6-5.2)	5.1 (4.4-5.7)
ΔDAS28	-0.1 (-0.5 -0.75)	-0.5 (-1.0 – -0.1)	-1.4 (-1.9 - -1.0)	-2.2 (-3.4 – -1.5)
Initiated bDMARD, %	69	82	80	63
Baseline HAQ-DI – original scale	0.875 (0.5-1.21)	1.0 (0.5-1.5)	1.0 (0.5-1.625)	1.25 (0.875-1.625)
ΔHAQ-DI – original scale	0.25 (0.0 - 0.5)	0.0 (-0.238 - 0.125)	-0.250* (-0.375 - 0.0)	-0.625 (0.875 – -0.25)
Baseline HAQ-DI – Logit scale	0.09 (-0.71 – 0.43)	0.07 (-0.71 – 0.73)	0.07 (-0.71 – 0.73)	0.35 (-0.15 - 0.73)
ΔHAQ-DI – Logit scale	0.26 (-0.03 – 1.02)	0.0 (-0.33 – 0.24)	-0.48** (-1.07 – 0.0)	-0.98 (-1.96 – -0.42)

Values are median (Inter Quartile Range). * Study specific MCID based on original scale; ** Study specific MCID based on logit transformed scale. IgM-RF: IgM Rheumatoid Factor, PtGl: Patient Global Visual Analogue Scale, DAS28: Disease Activity Score in 28 joints, HAQ-DI: Health Assessment Questionnaire Disability Index.

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Abstract Number: 1413

Establishing Clinical Severity for Patient Reported Outcomes Measurement Information System Measures in Adult Patients with Rheumatic Diseases

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Background/Purpose: Different patient reported outcome [PRO] measures are used for rheumatic diseases [RD], and there is lack of uniform generic illness measures across the disease spectrum. The aims of this study are – (1) Identify PROMISÒ health domains most relevant to care of patients with RD, (2) Collect T-Score metrics for these domains, (3) Identify clinically meaningful cut-points for these domains.

Methods: A convenience sample of RD patients aged 18 and over, were recruited consecutively at the time of routine clinic visits, to complete computer-adaptive tests on thirteen Patient-Reported Outcomes Measurement Information System (PROMIS®) instruments as part of an approved IRB. Based on the severity of the T-score metrics and discussion with clinical providers, four measures were chosen to be relevant to RD patients. A common educational method for establishing "proficiency" was borrowed to determine severity of the domains. Data from these patients were used to develop clinical vignettes across a range of symptom severity. Vignettes were created based on most likely item responses at different levels on the T-score metric (mean = 50; SD = 10). Vignettes were anchored at 5-point intervals (0.5 SDs). Patients with RD (N=9) and clinical providers (N=10) participated as expert panelists in separate one-day meetings. Vignettes were ordered and placed on cards. Panelists identified adjacent vignettes considered to represent upper and lower boundaries separating category cut points. In other words, for each domain these cut-points were used to classify the severity of symptoms – no symptoms, mild symptoms, moderate symptoms, and severe symptoms. Cut scores were defined as mean score for boundary vignettes.

Results: Four domains (physical function, pain interference, sleep disturbance, depression) were selected for their importance in RD, and that are actionable at the point of care, as determined in previous focus groups with clinical providers[1]. For all domains, patients set lower cut points for severity than clinical providers, by 0.5 to 1 SD (Table1). Patient and providers had the most overlap in their cut-scores for the pain interference domain.

Conclusion: We used a modified educational standard setting method to estimate clinically relevant cut points to classify severity for PROMIS measures of physical function, pain interference, sleep disturbance, and depression in patients with RD. Parallel exercises identified the cut points from the perspectives of patients with RD, and clinical providers who treat rheumatic diseases. This allows for meaningful interpretation of PROMIS® measures in a clinical setting in RD populations. Further work is focused on incorporating these cut points in clinical practice and assessing their impact on clinical care. **Table 1: Consensus cut-scores by domains and expert panel**

Domain	Severity categories	T-score cut points	
		Patient classification	Provider classification
Physical function*	No symptoms	>65	>60
	Mild symptoms	45-65	45-60
	Moderate symptoms	35-45	25-45
	Severe symptoms	<35	<25
Pain interference**	No symptoms	<50	<50
	Mild symptoms	50-60	50-60
	Moderate symptoms	60-65	60-70
	Severe symptoms	>65	>70
Sleep disturbance**	No symptoms	<35	<45
	Mild symptoms	35-45	45-55
	Moderate symptoms	45-60	55-65
	Severe symptoms	>60	>65
Depression**	No symptoms	<45	<55
	Mild symptoms	45-55	55-60
	Moderate symptoms	55-60	60-65
	Severe symptoms	>60	>65

*Higher score denotes better physical function ** Higher scores denote more [or worse] symptoms

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Abstract Number: 1414

Access to an Active, Interactive Self-Assessment e-Health Platform Improves Patient-Physician Communication in Rheumatoid Arthritis: Results of a Randomized Controlled Trial Including 320 Patients over 1 Year

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Background/Purpose: Electronic (e)-health is a rapidly evolving field. Interactive online services are available and may be useful for patients with chronic diseases such as rheumatoid arthritis (RA), but have not been properly assessed. Sanoia is a secure and independent patient e-health and mobile (m)-health platform, developed to allow self-assessment, storage of questions to ask physicians and self-monitoring of disease status. The platform offers a dedicated set of scores, patient-reported outcomes and information for diseases, including RA. The objective of the trial was to assess the effect of access to the Sanoia e-health platform on patient-physician interaction efficacy after 12 months.

Methods: This 12-month, French, multi-center, randomized controlled trial (NCT02200068) included patients diagnosed with RA, recruited by their tertiary care center physician. Patients were allocated to 2 groups: a) possibility of access to the Sanoia platform, or b) usual care (continuation of normal internet use without Sanoia access). Follow-up was performed over 12 months by a home-based e-CRF. Primary outcome was change over 12 months of Perceived Efficacy in Patient-Physician Interactions Questionnaire (PEPPI).[1] The PEPPI-5 consists of 5 items, each starting with ''How confident are you in your ability to…" (eg. "...know what questions to ask a doctor?''). Patients rated each item on an 11-point scale; 0=not at all confident, 10=very confident. Total PEPPI-5 scores range from 0–50, with higher scores representing higher perceived self-efficacy in patient-physician interactions. Other outcomes measured included numeric rating scale (NRS) to assess perceived quality of care, and RA Impact of Disease (RAID) score to assess patient-perceived impact of RA. Analyses were non-parametric comparisons and used LOCF imputation on the intention-to-treat (ITT) population.

Results: Of 320 RA patients (159 vs 161, Sanoia vs usual care), mean (SD) age was 57.0 (12.7) years, mean (SD) disease duration was 14.6 (11.1) years and 253 (79.1%) were female. DAS28 was 2.65 (1.20), 54.1% were in DAS28 remission (<2.6), 216 (67.5%) were taking a biologic and 21.9% had previous therapeutic education sessions. 12-month data were available for 244 patients (76.0%). In ITT analyses, mean (SD) changes in PEPPI from baseline to 12 months were 38.6 (8.2) to 39.2 (8.0) (delta=+0.60 [5.52]) vs 39.7 (7.3) to 38.8 (8.0) (delta=-0.91 [6.08]) in Sanoia vs control group (p=0.01). Mean (SD) changes in quality of care NRS from baseline to 12 months were 8.2 (1.7) to 8.3 (1.6) (delta=+0.06 [1.44]) vs 8.2 (1.6) to 7.8 (1.9) (delta=-0.42[1.63]) in Sanoia vs control group (p=0.02). RAID changes did not differ between groups (data not shown).

Conclusion: In this randomized trial, giving RA patients access to the interactive Sanoia e-health platform led to a statistically significant, although small, improvement in patient-perceived patient-physician interactions and patient-perceived quality of care. This confirms the usefulness of an e-health intervention complementary to physician care in RA. **References:** ten Klooster P. Patient Educ Couns 2012;87(1):125–30.

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Abstract Number: 1415

Impact of the Clinical Disease Activity Index to Treat to Target Rheumatoid Arthritis in the Ambulatory Setting

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Background/Purpose: Since 2008 the Center for Medicare and Medicaid Services (CMS) has been in the process of changing patient care to quality-valued healthcare. In order to comply with the six RA performance improvement care measures, we created the Clinical Disease Activity Index (CDAI) calculator with the efforts of a multidisciplinary team for use in the electronic medical record (EMR). The goal of this pilot study was to review the utility, adoption, and impact of the CDAI in an academic clinical practice. We investigated distribution of disease categories, the correlation and agreement of the CDAI and Simple Disease Activity Index (SDAI) values and categories, and finally examined longitudinal trends in disease activity and associated factors in our cohort.

Methods: 179 patients were analyzed over 16 months (n= 663 clinical encounters). Intraclass correlation was computed for CDAI and SDAI scores. The Kappa agreement and McNemar's test were conducted for the agreement of CDAI and SDAI disease categories. A logistic mixed effect model was used to assess the effect of the cofactors on CDAI and SDAI disease categories recorded for patients over time. The Cox proportional hazards model was used to assess the time to initial remission and low disease categories.

Results: After 3 months of launching the calculator we maintained >70 % EMR documentation rate throughout the study period. Our study was conducted in an 84.27% Hispanic population with 84.27% being female. Of total, 72% of subjects improved or remained stable in remission or low CDAI status, while 28% deteriorated or remained in high or moderate status. The intraclass correlation for CDAI and SDAI scores was found to be very high 0.99 (p-value <0.0001). The test of concordance for SDAI and CDAI categories showed no significant difference between discordant pairs (p-value 0.3352). The rate of change to remission or low stage was 7% likely to be obtained in an individual over the follow up period (OR: 1.07; 95% CI: 0.92-1.26, p=0.37). A median time to initial remission or low disease status was estimated as 5.8 months for patients in the cohort that started with either a moderate or high disease status (n=22) based on using the Kaplan-Meier method.

Conclusion: An excellent concordance was found between CDAI and SDAI, therefore CDAI could be used regardless of CRP values. Upon implementation of the CDAI in the clinic a small trend towards improvement in disease control over time could be seen, but could not reach a statistically significant level. Further analysis is needed to study the utility of clinical disease indices in the ambulatory setting. This study has established a quick and easy way to document periodic assessment of disease activity for future epidemiological review and classification of RA disease prognosis.

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Abstract Number: 1416

Sustained Improvement in Documentation of Disease Activity Measurement As a Quality Improvement Project at an Academic Rheumatology Clinic

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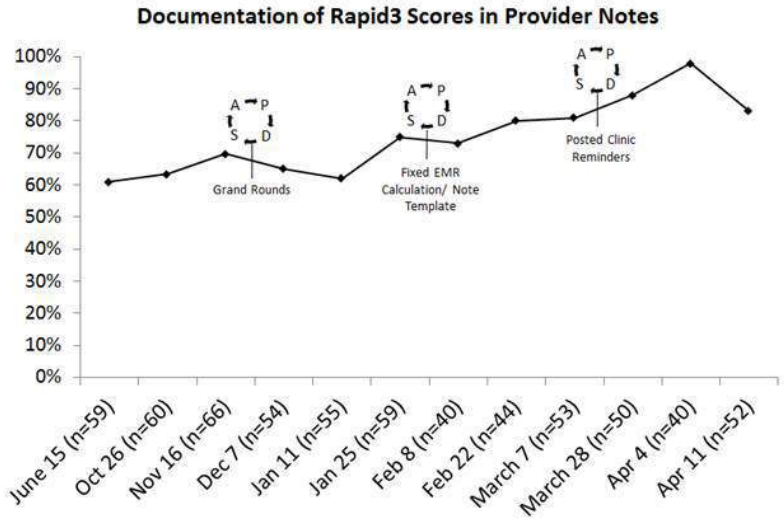
Background/Purpose: Measurement of disease activity is considered a quality measure for management of rheumatoid arthritis (RA) patients. One validated measure of RA disease activity is the Routine Assessment of Patient Index Data 3 (RAPID3) score. We developed a quality improvement project to improve our clinic's adherence to use of the RAPID3 score in our patients with RA, with the goal of increasing documentation by 25% from baseline.

Methods: In our academic practice, we surveyed providers regarding their preferred disease activity measurement; the RAPID3,

already utilized in our clinic, was preferred by the majority of providers. Patient charts were screened for presence or absence of RAPID3 score within providers' notes. Using Plan-Do-Study-Act (PDSA) methodology, we introduced the following interventions to improve provider documentation: education through Divisional Grand Rounds, direct modification of electronic medical record (EMR) templates, and posted reminders in clinic. Chart review was conducted between interventions and at the conclusion of all interventions. A repeat survey of providers assessed providers' responses to the interventions and utilization of the RAPID3 in clinical decision making.

Results: Review of 3054 charts identified 632 patients with RA. At baseline, an average of 65% of provider progress notes documented a RAPID3 score. For the 3 months following the last intervention, the provider documentation rate had increased to an average of 90%, a 38% increase from baseline (see figure). Reasons for missing RAPID3 documentation include incomplete data entry during check-in. Providers noted the most helpful interventions to be changing their note template in the EMR (40%), Grand Rounds discussions (33%), and posted clinic reminders (13%). At the conclusion of the QI initiative, 20% of providers reported using the Rapid3 for clinical decision making in 50-74% of cases, while 53% used the Rapid3 25-49% of the time, and 27% reported using the Rapid3 <25% of the time; no one reported never using the Rapid 3 for clinical decision making, and no one reported using it >75% of the time.

Conclusion: We demonstrated sustained improvement in documentation of RAPID3 scores, increasing documentation rates by 38%. One barrier to successful implementation of this score was correct calculation within the EMR, which was challenging to rectify. Once corrected, documentation of the disease activity measure increased. However, we found that the majority of clinicians reported using the RAPID3 in their medical decision making less than 50% of the time, despite stating a preference for this measure in the practice. With the RAPID3 now incorporated into our practice's daily use, assessment of overall clinical response rate will be possible along with ongoing efforts to increase utilization of this quality measure for medical decision making to improve quality of patient care in RA.



Disclosure: M. Wells, None; **R. Sadun**, None; **M. Jayasundara**, None; **N. Holdgate**, None; **S. Mohammad**, None; **J. Weiner**, None; **T. Haroun**, None; **S. Balevic**, None; **L. Criscione-Schrieber**, None; **M. Kaul**, None.

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Abstract Number: 1417

Back to Feeling Normal Again: Patients with Rheumatoid Arthritis in Remission

Linda Rasch[1], Maarten Boers[2,3], Willem F. Lems[1,2], Samina Turk[4], Dirkjan van Schaardenburg[2,5], Tessa Sanderson[6], Sarah Hewlett[6] and Lilian van Tuyl[1], [1]Amsterdam Rheumatology and immunology Center | VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [2]Amsterdam Rheumatology and immunology Center | Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [3]Epidemiology & Biostatistics, VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [4]Rheumatology, Amsterdam Rheumatology and immunology Center | Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [5]Clinical Immunology & Rheumatology F4.105, Amsterdam Rheumatology and immunology Center | Academic Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [6]Nursing and Midwifery, University of the West of England, Bristol, United Kingdom, Bristol, United Kingdom

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Session Type: ACR Poster Session B

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Background/Purpose: The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) definition of remission in rheumatoid arthritis (RA) [1] lacks information on patient perceived remission [2]. Qualitative research identified 'returning back to normal' as one of three themes of patient perceived remission [3]. A questionnaire to measure this 'normality' was developed in Bristol and investigated for its discriminative ability [4].

Objectives: This study investigated the relationship between patient perceived concepts of normality and remission, and the ability of the normality questionnaire to discriminate between remission and non-remission states.

Methods: Newly diagnosed RA patients with a high disease activity and/or unfavourable prognostic factors, were treated according a treat-to-target regime. Initially, all patients were treated with methotrexate and prednisolone, for patients not achieving a good EULAR response after 13 weeks treatment was intensified. At baseline and after 13 and 26 weeks of treatment different measures were collected, including the 'normality scale' to measure the perception of normality (7 items, range 7-36, higher scores indicating higher feeling of normality), Disease Activity Score of 28 joints (DAS28), and remission. Remission was measured in two ways: 1) patient perceived remission using the question *"Would you say that, at this moment, your disease activity is as good as gone? (yes/no)"*; and 2) ACR/EULAR Boolean-based definition of remission.

Results: Forty-seven patients completed all assessments, of whom 34 (72%) were female with a mean ± SD age of 50 ± 14 years. At baseline, mean ± SD DAS28 was 4.5 ± 1.1 and the normality score was 20 ± 7. After 13 weeks of therapy, DAS28 significantly decreased to 2.5 ± 1.0 ($p<0.001$), and further to 2.2 ± 0.7 after 26 weeks ($p<0.001$). The feeling of normality was significantly increased to 23 ± 8 in week 13 ($p=0.001$) and 24 ± 8 in week 26 ($p<0.001$) compared to baseline. As shown in Figure 1, patients in self-perceived remission had a significantly higher feeling of normality at week 13 ($p<0.001$) and week 26 ($p=0.007$) compared to patients not in self-perceived remission, while patients in Boolean remission had only a significantly higher feeling of normality at week 26 ($p<0.001$) compared to patients not in Boolean remission.

Conclusion: Self-perceived remission is significantly associated with higher normality perceptions after 13 and 26 weeks of therapy; Boolean remission only after 26 weeks of therapy. The normality scale has the ability to discriminate between patients in and not in remission.

References: [1] Felson et al. Arthritis & Rheum 2011; [2] Van Tuyl et al. J Rheumatol 2016; [3] Van Tuyl et al. ARD 2015; [4] Sanderson. Doctoral thesis 2009.

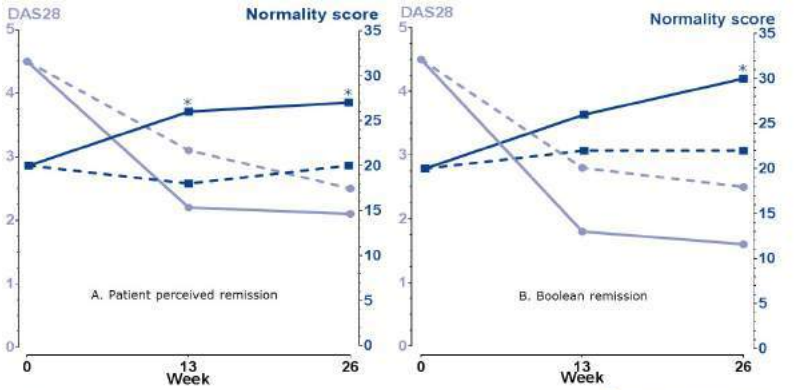

Figure 1. *DAS28 and normality scores of 47 patients, categorized by presence (y/n) of: A. patient perceived remission (week 0: 0/47; week 13: 30/47; week 26: 32/47); B. ACR/EULAR Boolean remission (week 0: 0/47; week 13: 13/47; week 26: 13/47). * significant difference in normality score between patients in remission and patients not in remission ($p<0.05$)*

Disclosure: L. Rasch, None; **M. Boers**, None; **W. F. Lems**, None; **S. Turk**, None; **D. van Schaardenburg**, None; **T. Sanderson**, None; **S. Hewlett**, None; **L. van Tuyl**, None.

Abstract Number: 1418

Rheumatologist: If You Fell Ill with Seropositive Active Rheumatoid Arthritis Yourself, What to Do!

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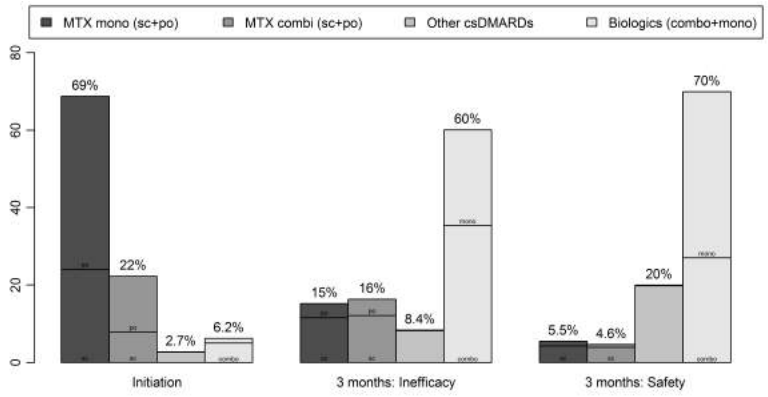
Background/Purpose: International and national bodies have given evidence-based recommendations for rheumatoid arthritis (RA) treatment. We assessed the general uptake of these recommendations by asking rheumatologists about their initial treatment preferences in case they themselves developed RA.

Methods: An online survey was disseminated to practicing rheumatologists across the continents and also made accessible on social media platforms between April and June 2016. Survey questions included following: 1. If you fell ill with seropositive active rheumatoid arthritis, what medications would you start as the first option? 2. At 3 months: if the first option does not - work, what would you take next? 3. At 3 months: if the first option would work, but you cannot really take it for disturbing side effects, what would you take next? Response options, to select one or more, included NSAIDs, Glucocorticoids (GC), and all DMARDs. Background information included age, gender, type and country of practice, and whether the participant was involved in national or international task force of guidelines/recommendations for RA.

Results: A total of 717 rheumatologists (49% female, 50% <50 years old) participated in the survey from 46 countries on 5 continents. The first preferred medication for early active seropositive RA included: MTX monotherapy 69% (sc 36%), MTX-based combination therapy 22%, another cDMARD(s) 2.7%, and biologic agent 6.2% (Figure 1). Furthermore, 53% would take NSAIDs and 84% GC including 6.3% im, 36% ia, 41% low dose GC, 28% medium dose GC, 1.8% high dose GC, and 16% would not take any GC. In case of inefficacy, options would be MTX monotherapy 15% (sc 78%), MTX-based combination 16%, another cDMARD(s) 8%, biologic agent 60%, and in case of side effects: MTX monotherapy 5.5% (sc 80%), MTX-based combination 4.6%, another cDMARD(s) 20%, biologic agent 70% (Figure 1). The EULAR 2016 recommendation of starting with MTX monotherapy and in case of inefficacy, switching to another cDMARD or adding a biologic was followed by 49% of respondents.

Conclusion: To our knowledge this is the first international effort to evaluate how rheumatologists would treat themselves if they were patients with early seropositive RA. Not surprisingly, biologics are the preferred option in the majority in the case of inefficacy or intolerance to first treatment. Sc MTX administration is preferred by 36% of rheumatologists as first option, despite rarely mentioned in recommendations. This may be a reflection of positive clinical experience using sc MTX. Limitations of the survey include a relatively small number of respondents and better coverage in many countries would be preferred. **Figure 1.** Preferred DMARD therapy for early active seropositive RA at the initiation, in case of inefficacy or side effects at 3 months, among 717 rheumatologists around the globe.



Disclosure: K. Aaltonen, None; **E. Nikiphorou**, None; **N. A. Khan**, None; **T. Sokka**, None.

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Abstract Number: 1419

Validation of the French Version of Lupus Patient Reported Outcome (LupusPRO), a Disease-Specific Patient Reported Outcome for Lupus Patients

Hervé Devilliers[1], Meenakshi Jolly[2], Maxime Samson[3], Bernard Bonnotte[4], Francois Maurier[5], Pascal Sève[6], Nadine Magy-Bertrand[7], Denis Wahl[8], Jean-Loup Pennaforte[9], Thierry Martin[10], Olivier Aumaître[11], Gilles Blaison[12], Philip Bielefeld[13], Alexis Mathian[14], Christine Binquet[15] and Zahir Amoura[14], [1]Department of Internal Medicine and Systemic Diseases, Hôpital François Mitterrand, CHU de Dijon, Dijon, France, [2]Department of Medicine, Section of Rheumatology, Rush University Medical Center, Chicago, IL, [3]Dijon University Hospital, Dijon, France, [4]Department of Internal Medicine and Clinical Immunology, Hôpital François Mitterrand, CHU de Dijon, Dijon, France, [5]Department of Internal Medicine, HP Metz Belle Isle Hospital, Metz, France, [6]Internal medicine, Internal medicine department, Hôpital de la Croix-Rousse, Hospices Civils de Lyon, Lyon, France, [7]CHU Jean-Minjoz, Service de médecine interne et immunologie clinique, Besançon, France, [8]CHU de Nancy, Vascular Medicine Division and Regional Competence Centre For Rare Vascular And Systemic Autoimmune Diseases; and UMR_S U1116 Research Unit, France, Nancy, France, [9]Internal Medicine, Internal medicine departement, CHU de Reims, Reims, France, [10]Internal medicine and clinical immunology departement, Strasbourg University Hospital, Strasbourg, France, [11]Division of internal Medicine, Centre Hospitalier Universitaire, Hôpital Gabriel Montpied, Clermont–Ferrand, Clermont–Ferrand, France, [12]Internal medicine departement, Colmar Hospital, Colmar, France, [13]Internal medicine and systemic disease unit, Dijon University Hospital, Dijon, France, [14]Department of Internal Medicine 2. Referal center for SLE/APS, Hôpital Pitié-Salpêtrière, AP-HP, UPMC Univ Paris 06 & French National Reference Center For Systemic Lupus and Antiphospholipid Syndrome, Paris, France, [15]INSERM, CIC 1432, Clinical Epidemiology Unit, Hôpital François Mitterrand, CHU de Dijon, Dijon, France

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Background/Purpose:

To assess validity and reliability of French LupusPRO in France.

Methods:

After cross-cultural adaptation and harmonization for France, the LupusPRO was administered along with a generic PRO tool (the Short Form health survey 36 [SF-36]) in a prospective, multicenter study in France. SLE patients (ACR 1997 criteria) filled the

questionnaires at baseline, and 3 months later. Demographics, disease activity and damage where recorded by the physicians at baseline. We performed a confirmatory factory analysis of the French LupusPRO and evaluated test-rest reliability and internal consistency. External validity was then explored as the correlation between LupusPRO scores and SF-36 scores or disease activity. Test-retest reliability was assessed by the mean of intra-class correlation between baseline and M3 scores among patients who did not report change in their quality of life during this period.

Results:

Among 269 patients participating to the study, 90% were women, with a mean age (SD) of 42 (12) years. Mean baseline activity was low, median (range) SELENA-SLEDAI (SS) score was 2 (0-19), 26% of patients having a moderate or severe flare at baseline according to SELENA-SLEDAI flare index revised (SFI-R). The fit of the data to the conceptual model of LupusPRO was acceptable: RMSEA, CFI, chi-square/degrees of freedom were 0.073, 0.97 and 2.6 respectively (with desirable values of <0.08, >0.95 and <3). Factor loading was over 0.7 for all items in their own dimension except for 3 out of 43 : 0.45 for item #1 ("Loss of hair" in "Lupus Symptoms" dimension), 0.36 for item #38 ("I learned to live with my lupus") , and 0.35 for item #39 ("I received comfort/strength from my religious or spiritual beliefs") , both in "coping" dimension. Cronbach's alpha (Table 1) exceeded 0.7 except for "Lupus symptoms" (alpha=0.6) and "coping" dimensions (alpha=0.4). Test retest reliability -ICC ranged from 0.4 to 0.9 between baseline and M3. External validity was supported by a significant lower score in PRO among patients reporting a low health status according to SF-36 first question ($p<0.0001$ except for "procreation", "coping", and "satisfaction with care"), a high correlation with corresponding SF-36 domains and a low but significant correlation with disease activity.

Conclusion:

The French version of the LupusPRO is valid and reliable. Further study is needed to investigate whether the low fit of the items of "coping" domain is due to cultural difference between French and US patients.

Table 1. Reliability and external validity of French LupusPRO

LupusPRO HRQOL Domains	Correlation	p-value	ICC*	Cronbach's alpha
1.Lupus Symptoms				
PGA	-0.24	<.0001		
SFI-R Flare	-0.28	<.0001	0.7	0.6
SFI-R Skin Flare	-0.13	0.032		
SFI-R Articular Flare	-0.21	0.001		
Total SLEDAI	-0.06	0.334		
2.Cognition			0.8	0.9
3. Lupus Medication			0.6	0.7
PGA				
4.Physical function, role physical				
SF-36 PF	0.63	<.0001	0.7	0.9
SF-36 RP	0.69	<.0001		
SLICC/DI	-0.13	0.041		
SFI-R Articular Flare	-0.26	<.0001		
Pain vitality				
SF-36 BP	0.84	<.0001	0.8	0.9
SF-36 VT	0.76	<.0001		
SFI-R Articular Flare	-0.33	<.0001		
Emotional function, Role emotional			0.8	0.9
SF-36 MH	0.69	<.0001		
SF-36 RE	0.58	<.0001		
Body Image				
SFI-R Flare	-0.14	0.020	0.8	0.9
SF-36 SF	0.61	<.0001		
Non-HRQOL Domains				
Desires, Goals, Plans			0.6	0.9
Procreation			0.7	0.9
Social Support			0.5	0.8
Coping			0.4	0.4
Satisfaction with Care			0.5	0.9

* Intraclass correlation to assess test-retest reliability

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Corporation, 3; **P. Sève**, None; **N. Magy-Bertrand**, None; **D. Wahl**, None; **J. L. Pennaforte**, None; **T. Martin**, None; **O. Aumaître**, None; **G. Blaison**, None; **P. Bielefeld**, None; **A. Mathian**, None; **C. Binquet**, None; **Z. Amoura**, None.

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Abstract Number: 1420

Validation of Lupuspro V1.8, Disease Targeted Patient Reported Outcome for Systemic Lupus Erythematosus

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Background/Purpose: Disease Specific Patient reported outcome measures capture unique domains relevant to patients with a specific disease. LupusPRO is targeted towards measuring health (HRQOL) and non-health related quality of life (Non HRQOL) among patients with systemic lupus erythematosus (SLE). LupusPRO V 1.7 and its translated versions in various languages have measurement equivalence and are responsive to changes in changes in patient reported changes in health and physician-based disease activity assessments. LupusPRO v1.8 has separate domains of sleep, pain and vitality, and has shown good reliability and validity among 50 SLE patients[1]. Herein, we present the confirmation of the psychometric properties of LupusPRO v1.8 in a larger sample size.

Methods: 122 consecutive SLE patients fulfilling ACR classification criteria were given self-administered surveys (MOS SF36 FACIT-Fatigue, Pain, Insomnia Severity Index for sleep, Perceived Stress Scale (PSS)-4, Patient Health Questionnaire-9 (PHQ-9) for depression, LupusPRO V 1.8) to complete at routine care visit. Disease activity and damage were assessed at visit using SELENA-SLEDAI (SS), numeric BILAG and SLICC-SDI/ACR (SDI). Internal consistency reliability (ICR) for each domain was obtained using Cronbach alpha. Convergent construct validity (CV) with corresponding domains of SF36 was tested using Spearman correlation coefficient.

Results: Mean (SD) age was 40.7±14 yrs., 90% of participants were women, and mean disease duration was 8.7 years. Ethnic background was as follows: 56% Blacks, 24% Whites, 10% Asians and 10% others. Median (IQR) values of PGA, total SS, and SDI were 0.5 (0.6), 4.0(6.0) and 0.0(1.0), respectively. Results for LupusPRO V1.8 domains descriptives, ICR and CV are shown in Table 1. Several domains, HRQOL and QOL scores were associated with disease activity. LupusPRO Sleep domain scores strongly correlated with the Insomnia severity index scores, while LupusPRO Vitality correlated strongly with FACIT-Fatigue and SF36 Vitality scores. LupusPRO Pain domain correlated strongly with the Pain score and SF36 Bodily pain domain. Lupus symptom domain (3 items) showed significant correlation with PGA and SS, but not with SDI. Similarly, LupusPRO domains of Physical and Emotional Health had good ICR and significant correlation with corresponding SF36 domains (Table 1). ICR for HRQOL and non HRQOL were 0.96 and 0.81.

Conclusion: LupusPRO V1.8 (including its sleep, vitality and pain domains) has acceptable reliability and validity. Use of lupusPRO as an outcome measure in clinical trials would facilitate responsiveness evaluation and provide important insight into patients' assessment concerning the test therapies.

Table 1: Valdity and Reliability of LupusPRO V1.8				
HRQOL	**Items**	**Median (IQR)**	**ICR**	**Conv. Validity rho (p value)**
Lupus Syptoms	1-3	75.0 (41.7)	0.82	PGA -0.40 (<0.001), SELENA-SLEDAI -0.40 (<0.001), SDI -0.001 (0.99)
Cognition	4-5	75.0 (50.0)	0.88	
Lupus Medications	6-7	87.5 (37.5)	0.69	PGA -0.23 (0.01), SELENA-SLEDAI -0.27 (0.003), Current steroid dose -0.29 (0.002), current steroid use 0.21 (0.027)
Procreation	8-9	100 (0.0)	0.66	
Physical Health	10-14	90.0 (30.0)	0.94	PF 0.43 (0.002); RP 0.39 (0.006)
Sleep	15-17	66.7 (41.7)	0.85	PGA -0.19 (0.04),INSOMNIA SCORE -0.66 (<0.001)
Vitality	18-21	68.8 (29.3)	0.95	VT 0.67 (<0.001); FACIT-FT -0.85 (<0.001)
Pain	22-25	75.0 (43.8)	0.96	**PGA -0.21 (0.025), SELENA-SLEDAI -0.23 (0.01), BP 0.78 (<0.001); PAIN INDEX -0.68 (<0.001)**
Emotional Health	26-31	62.5 (45.8)	0.91	PHQ-9 0.62 (<0.001); MH 0.37 (0.001); RE 0.38 (<0.001); PSS -0.46 (<0.001)
Body Image	32-36	80.0 (40.0)	0.94	PGA -0.31 (0.001), SELENA-SLEDAI -0.30 (0.001), PHQ9 -0.52 (<0.001), MH 0.49 (<0.001)
Total HRQOL	1-36	75.2 (26.6)	0.96	PGA -0.30 (0.002), SELENA-SLEDAI -0.31 (0.002)
Non HRQOL				
Desires-Goals	37-40	75.0 (43.8)	0.90	PGA -0.17 (0.076), SELENA-SLEDAI -0.15 (0.124)
Social-Support	41-42	75.0 (50.0)	0.84	
Coping	43-45	75.0 (41.7)	0.73	PSS -0.20 (0.039)
Satisfaction with Care	46-49	100.0 (25.0)	0.97	
Total NonHRQOL	37-49	75.0 (31.5)	0.81	
Total QOL	1-49	72.8 (22.4)		PGA -0.19 (0.067), SELENA-SLEDAI -0.21 (0.036)

PGA: Physician Global Assessment, SF-36 Domains: PF-Physical Function, RP-Role Physical, VT-Vitality, BP-Bodily Pain, MH-Mental Health.

Disclosure: M. Jolly, Pfizer Inc, 9; **N. Gandhi**, None; **W. Sequeira**, None; **J. Block**, None.

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Abstract Number: 1421

Responsiveness of Lupus Impact Tracker Among Chinese Patients with Lupus

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Background/Purpose: Lupus Impact Tracker (LIT), a 10 item, patient reported outcome tool for patients with systemic lupus erythematosus (SLE) has undergone psychometric validation and responsiveness studies in the US and Europe. Herein we report results on responsiveness of this tool among ethnic Chinese patients with SLE.

Methods: 430 patients with SLE meeting the ACR classification criteria were recruited in Hong Kong, China at a single center. LIT scores from two visits one year apart were analyzed for responsiveness and Minimal Clinically Important Difference (MCID) against patient report and physician assessed anchors of changes in health. Two patient reported anchors were used (Global change in health and item 2 of Short Form 36 form). Physician assessed anchors of change in health were disease activity (Physician global assessment-PGA, SELENA-SLEDAI) and damage (SLICC-SDI/ACR). Change in PGA of ≥ 0.3 and SELENA-SLEDAI of ≥ 4 in either direction was used to define worsening in disease activity. Analysis of variance was used to compare changes in LIT score against the anchors.

Results: Mean (SD) age of participants was 42 (14) years. Ninety five percent were women. Mean (SD) PGA, SELENA-SLEDAI and SDI at baseline were 0.5 (0.5), 2.9 (3.0) and 0.7 (1.2) respectively. Mean (SD) LIT score at baseline was 27.8 (18.2). Mean changes in LIT scores in response to worsening, no change or improvement based on patient report and physician assessments are shown in Table 1. MCID for “some worsening” were -4.0 and -3.9 on patient reported health question and SF36 question 2 respectively.

Conclusion: LIT changes in response to changes in both patient-reported and physician assessed changes in health status among ethnic Chinese SLE patients.

Table 1:

Anchor	Change	N	Mean Change in LIT	p-value
Patient Reported Change				
SF36-Q2	Worse	118	-4.7	<0.001
	No Change	153	0.3	
	Much Better	157	7.5	
Global Change in Health Status	Worse	118	-4.7	<0.001
	No Change	153	0.3	
	Better	157	7.5	
Patient Assessed Change				
PGA	Increase of ≥0.3	72	-2.8	0.02
	Stable	293	-1.8	
	Decrease of ≥0.3	104	2.7	
SELENA- SLEDAI	Increase of ≥4	48	-3.5	0.005
	Stable	348	-0.6	
	Decrease of ≥4	41	8.0	
SDI	Unchanged	405	0.1	0.005
	Increase of ≥ 1.0	21	-8.7	

Disclosure: **C. C. Mok**, None; **M. Jolly**, Pfizer Inc, 9; **J. Block**, None.

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Abstract Number: 1422

Identifying Generic and Specific Patients' Perspectives on Disease- and Treatment-Related Issues in Rheumatoid Arthritis, Psoriatic Arthritis, and Psoriasis: A Qualitative Concept Mapping Study

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Identifying generic and specific patients' perspectives on disease- and treatment-related issues in rheumatoid arthritis, psoriatic arthritis, and psoriasis: a qualitative concept mapping study

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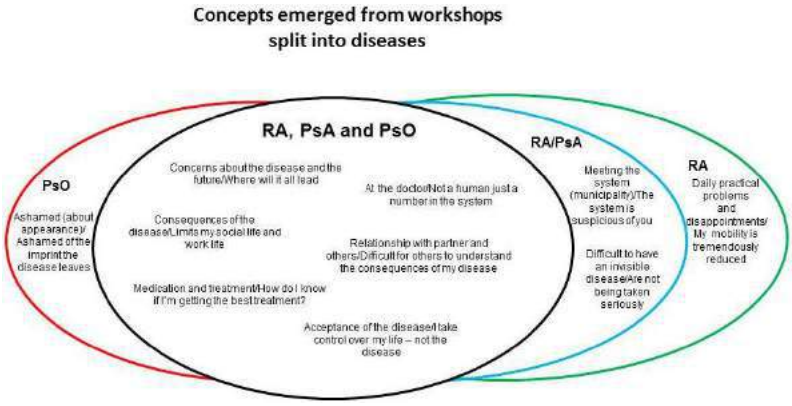
Background/Purpose: Considering the patients' perspectives is necessary to promote patient empowerment and adherence to treatment, and thereby optimizing disease management. Specifically, it is essential to identify issues of importance to patients to help guide selection of value based treatment targets and outcomes. The aim of this study was to qualitatively explore disease- and treatment-related issues and concerns experienced by patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and psoriasis (PsO), and to rate the clinical importance of these. A secondary aim was to explore whether these factors were generic or disease specific.

Methods: Concept Mapping, a structured group process, was used to identify and organize disease- and treatment-related issues and concerns. Data were elicited through a nominal group technique and then organized using participants' themes, multidimensional scaling, cluster analysis, participant validation, rating of clinical importance, and thematic analyses, to generate a conceptual model of disease-related concerns experienced in patients with RA, PsA, and PsO.

Results: 17 RA patients, 8 PsA patients, and 9 PsO patients contributed to generating the conceptual model. 8 RA clusters, 7 PsA clusters, and 7 PsO clusters, with each cluster having sub-clusters, emerged from the workshops producing 292 RA statements, 160 PsA

statements, and 187 PsO statements. Some clusters were generic: ‘concerns about the disease and the future’, ‘consequences of the disease’, ‘relationship with partner and others’, ‘acceptance of the disease’, ‘medication and treatment’, and ‘at the doctor’ (Figure). Specific clusters were; for RA: ‘Daily practical problems and disappointments’, for RA/PsA: ‘Meeting the system (municipality)’ and ‘Difficult to have an invisible disease’, and for PsO: ‘Ashamed (about appearance)’ (Figure). RA and PsA patients ranked “Meeting the system (municipality)” as being the most important concept, whereas PsO patients ranked “Ashamed (about appearance)” as being the most important concept.

Conclusion: Patients across chronic inflammatory diseases agreed largely on the concepts, with a few of them being disease specific. The relative ranking of importance showed considerable differences, highlighting the importance of patient involvement. These data offer new knowledge to guide selection of clinically relevant and value based treatment targets and outcomes for patients impacted by RA, PsA and PsO. **Acknowledgements:** This study was funded by The Oak foundation, Roche (Denmark) and Novartis (Denmark). **Disclosure of Interest:** T.S. Jørgensen has received research grants paid to institute: Roche and Novartis; L. Klokker has no disclosures of interest to this project; H. Gudbergsen has no disclosures of interest to this project; S.F. Thomsen has received research grants and speaker fee from Novartis; R. Christensen has no disclosures of interest to this project; H. Bliddal has received research grants paid to institute: Roche and Novartis; L.E. Kristensen has received research grants paid to institute: Roche and Novartis **Figure:**



Disclosure: T. S. Jørgensen, Roche Pharmaceuticals, Novartis, 2; **L. Klokker**, None; **H. Gudbergsen**, None; **S. F. Thomsen**, Novartis Pharmaceutical Corporation, 2; **R. Christensen**, None; **H. Bliddal**, Roche Pharmaceuticals, Novartis, 2; **L. E. Kristensen**, Roche Pharmaceuticals, Novartis, 2.

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Using Self-Reported Patient Experiences to Evaluate Patient Reported Outcomes (PRO) Instruments: Learnings from Digital Patient Communities in Psoriatic Arthritis

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Background/Purpose: Psoriatic Arthritis (PsA) is a debilitating disease with significant impact on patient quality of life (QoL). While patient reported outcome (PRO) instruments broadly capture patient experiences with PsA, they may not identify the full extent of issues patients face. In this study, we compared the types of experiences patients self-report online to concepts captured within commonly used PRO instruments in PsA.

Methods: We collected unguided patient narratives reported between January 2010 and May 2016 from 31 online sources. 56% of narratives were from health social networking sites, 22% from disease-specific patient forums, 9.9% from general health forums, and 0.1% from mainstream social media. Using natural language processing combined with manual curation, we evaluated patient reported experiences within narratives and categorized them into 5 high level themes: **S**ocial (e.g. family burden), **P**hysical (e.g. pain), **E**motional (e.g. anxiety), **C**ognitive (e.g. memory), and **R**ole Activity (e.g. work), or SPEC-R. For comparison, the same SPEC-R categorization was applied to 3 PRO instruments: the Psoriatic Arthritis Quality of Life tool (PsAQoL), Psoriatic Arthritis Impact of Disease tool (PSAID), and Short Form 36 Health Survey (SF-36). The instruments were then evaluated based on their capacity to capture the concepts and sub-concepts extracted from patient narratives.

Results: 15,390 narratives from 3,139 patients were qualified into the sample for analysis. Across the SPEC-R categories, Physical concepts were reported by 81.6% of patients, Emotional concepts by 60.7%, Cognitive concepts by 20.0%, Role Activity concepts by 8.1%, and Social concepts by 5.6%. In addition, 66.8% of patients reported general concepts (e.g. “Feeling unwell”) that could not otherwise be classified into the SPEC-R categories. Pain and dermatology related issues were the most reported physical sub-concepts (66% and 26%, respectively). Emotional concepts were mainly comprised of anxiety (60%) and depression (38%). Cognitive concepts were characterized by impulsive behavior (25%) and balance/coordination issues (12%). Patients reporting Role Activity concepts focused on work/school performance (55%) and parenting (17%). Among patients reporting Social concepts, family burden (50%) and relationships with spouses (27%) were most frequent. While PRO instruments capture many physical and social concepts and sub-concepts, many sub-concepts within other SPEC-R categories were not captured by either PsA-specific or general health related PRO instruments (see table).

Conclusion: This study offers insight into a variety of patient experiences with PsA. The physical and emotional impact of PsA dominates self-reported patient experiences. PROs capture many of the physical and emotional impairments of PsA, but may miss key cognitive and role activity issues that affect patient QoL. **Table 1. Fit/Gap Analysis of PsA PRO Tools with regards to Reported SPEC-R Concepts and Sub-concepts**

SPEC-R Category (% of patients)	Top 3 Reported Sub-concepts	% of SPEC-R Category	PsAQoL	SF-36	PSAID
Physical (81.5%)	Pain	65.6%	N	Y	Y
	Dermatological Issues*	25.7%	N	N	Y
	Musculoskeletal Issues*	21.7%	Y	Y	N
Emotional (50.7%)	Anxiety	60.2%	N	Y	Y
	Depression / Sadness	37.9%	Y	Y	Y
	Anger / Frustration	10.1%	Y	N	N
Cognitive (20.0%)	Impulsive Behavior*	25.3%	N	N	N
	Balance/Coordination	12.4%	N	N	N
	Memory Issues	9.9%	N	N	N
Role Activity (8.1%)	Work/School Performance	55.5%	N	Y	Y
	Parenting	17.3%	N	N	N
	Work/School Absenteeism	15.7%	N	Y	N
Social (5.6%)	Family Burden	50.0%	N	N	N
	Relationships (Partner/Spouse)	26.5%	Y	Y	Y
	Social Activities (Group)	14.5%	Y	Y	Y

* Example symptoms and impairments within selected sub-concepts: *Dermatological Issues*: rash, itching, scaling *Musculoskeletal Issues*: joint swelling, trigger finger, muscle spasms *Impulsive Behavior:* restlessness, substance abuse, eating related disorders Abbreviations: *SPEC-R*: Social, Physical, Emotional, Cognitive, Role Activity *PsAQoL*: Psoriatic Arthritis Quality of Life Instrument *PSAID*: Psoriatic Arthritis Impact of Disease *SF-36*: Short Form health survey 36-items

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Abstract Number: 1424

Acceptability of a Connected Activity Tracker in 92 Patients with Rheumatoid Arthritis (RA) or Axial Spondyloarthritis (axSpA): A 3-Months Study

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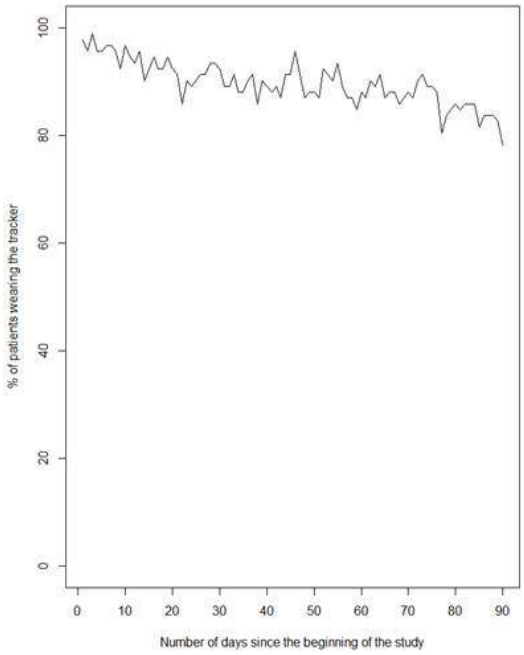
Background/Purpose: Physical activity is recommended and is an important part of the management of inflammatory arthritis and in particular RA and axSpA. Activity trackers, and in particular connected devices, are more and more used to assess physical activity and motivate people to increase their activity level in the general population, and in chronic conditions. However there may be technical issues for arthritic patients and a rapid loss of motivation. The objective of this study was to assess the acceptability of a physical activity connected device in RA/AxSpA patients.

Methods: In this prospective multicenter observational study patients had definite axSpA (ASAS criteria) or RA (ACR/EULAR criteria), and owned a smartphone. All patients were provided with an activity tracker (a watch) connected by Bluetooth and were instructed to wear it every day for 3 months. Acceptability was assessed by the mean number of days the tracker was worn over the 3 months (ie adherence). We considered that the tracker was worn a day if at least 8 hours of physical activity were recorded between the first and the last step. Then predictors of adherence were explored by comparing in univariate and multivariate analyses the adherent patients (ie bracelet worn at least 80/90 days) to non-adherent patients. Acceptability to the use of the activity tracker were assessed by a questionnaire.

Results: 92 patients (49 RA and 43 axSpA patients) were included: 39 (42.4%) were males, with a mean age of 46.6 (±12.3) and a mean disease duration of 10.8 (±7.8) years; 52 (56.5%) were receiving a biologic. RA and axSpA patients had respectively a mean DAS 28 of 2.2 (±1.0) and a mean BASDAI of 3.4 (±2.1). Patients wore the activity trackers 91.3% of the time, during 80.7 (±13.5) days on average and 64 (69.6%) patients wore it at least 80/90 days; 81 (88.0%) patients still wore the device at the end of the 3-month period (Figure). Adherent patients were more often men (OR=7.69, p<0.01), had more often RA (OR=5.56, p=0.02) and were more likely to be treated with biologics (OR=5.00, p<0.01). Overall 69 (75%) patients reported no technical issues related to the use of the device though 17 (18%) needed helped to set the device; 2 (2.2%) patients reported issues to wear the device because of their arthritis. The acceptability of the activity tracker was scored on average at 9 on a 0 to 10 scale.

Conclusion: Acceptability of a connected device in RA and axSpA is high in a population of selected patients accepting to participate in this 3 months study. Studies using connected devices in rheumatology are feasible, but long-term assessments are needed.

Figure: Proportion of patients wearing the tracker throughout the study



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Abstract Number: 1425

Validation of a Patient Reported Experience Measure (PREM) in Patients with Axial

Spondyloarthropathies (AxSpA)

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Background/Purpose: Improving patient experience is important in all diseases, but most important in patients with chronic rheumatic diseases like the axial spondyloarthropathies (AxSpa). The Commissioning for Quality in Rheumatoid Arthritis (CQRA), a British multidisciplinary group of stakeholders, developed a PREM questionnaire to evaluate patient satisfaction in rheumatology. The questionnaire comprises 8 domains that have been evidenced as being most important to patients' experiences of National Health Service (NHS) services. All questions were graded from very satisfied to very unsatisfied on a five point scale. This PREM was validated within Rheumatoid Arthritis and a variety of rheumatic conditions in a previous publication (Bosworth A et al. 2015). This has not yet been published and validated within a cohort of patients with AxSpa. Our aim was to determine the validity of the PREM questionnaire developed by the CQRA group in a single centre AxSpa clinic.

Methods: Cronbachs alpha was used to check internal consistency within groups of scores in each domain if it contained more than one question and whether it was reasonable to combine scores within groups into a numerical scale. Additionally for each question the percentage agreement with the overall assessment on the five point scale was calculated, in case of multiple questions per domain, the responses are shown as a range.

Results: 64 patients were included in the analysis (mean age 51.6 ± SD11.7; M 58/64, 87.5%). Duration of disease equated >10years in 71.9%. The Cronbach alpha co-efficients within the multi-question domains and their percentage agreement with the question on overall care are shown in the table below. **Table.** Result of Cronbach's alpha analysis and their agreement with overall care

Domain	Number of questions	Alpha Within domain	%Agreement with overall care
Needs and preferences	5	0.71	0.75
Co-ordination of care	4	0.81	0.84
Information about care	4	0.88	0.87
Daily living	2	0.25	0.52
Emotional aspects	2	0.81	0.75
Family and friends	1	NA	0.34
Access to care	1	NA	0.61

Conclusion: The PREM has good construct validity and is a valid tool for measuring AxSpa patient experience. Some domains have higher agreement with overall patient experience. This could provide a useful future tool for measuring patient experience.

Abstract Number: 1426

Using Self-Reported Patient Experiences to Understand Patient Burden: Learnings from Digital Patient Communities in Ankylosing Spondylitis

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Background/Purpose: Ankylosing Spondylitis (AS) is a chronic inflammatory disorder of the spinal joints that can lead to severe, chronic pain and discomfort. There is a substantial disease burden on AS patients as they experience reduction in physical function, increased risk of unemployment, and increased direct and indirect health costs. This study aimed to better understand AS disease burden by describing patient experiences reported online and making comparison to existing patient-reported outcome (PRO) instruments to identify potential gaps.

Methods: Patient narratives between Jan 2010 and May 2016 from 52 online sources were collected; of the online sources, 46.6% were patient health networking sites, 24.9% disease-specific patient forums, 13.5% general health forums, 8.3% treatment reviews, 6.0% Doctor Q&A, and 0.6% mainstream social media. Using a natural language processing platform and manual curation, functional impairments and symptoms related to AS were evaluated and grouped into 6 high-level concepts: Social, Physical, Emotional, Cognitive, Role Activity (SPEC-R), and General (consisting of non-specific narratives, e.g. feeling unwell). These broad categories provided a starting point for organizing the data, with additional levels of detail added through sub-concept groupings. For comparison, the same SPEC-R categorization was applied to 5 AS-specific PRO instruments: ASQoL, ASAS-HI, BASDAI, HAQ-S, and BASFI (81 PRO questions curated, 40 total sub-concepts identified). PRO Instruments were then compared to key concepts and sub-concepts extracted from patient narratives.

Results: A total of 34,780 unguided narratives from 3,449 patients were collected for analysis: 86.7% of patient narratives correlated to the Physical concept, 32.5% to Emotional, 23.6% to Cognitive, 8.7% to Role Activity, 5.6% to Social, and 69.1% to General (Table 1). Some of the common concepts reported by patients, such as pain (65%), muscle weakness (20%), and musculoskeletal impairment (20%), depression (10%), and anger/frustration (5%) were effectively captured by more than 2 of the PRO instruments. However, commonly reported emotional concepts, such as anxiety (19%), and cognitive concepts, such as mental impairment (3.2%), were not captured in the PRO instruments evaluated in this analysis.

Conclusion: Analysis of self-reported patient narratives from online sources showed that some physical and emotional concepts, such as depression and pain, are effectively addressed by existing PRO instruments. However, the analysis also uncovered some concepts that may be important in addressing disease burden in AS patients but are not currently captured in existing PRO instruments. This study helps identify opportunities to refine existing PRO instruments.

SPEC-R Category	Top 3 Reported Sub-concepts	% of Total Reports	% within SPEC-R Category	ASAS-HI	ASQOL	BASDAI	BASFI	HAQ-S
Social	Lack of Independence	1.2%	23.9%	**N**	**Y**	**N**	**Y**	**Y**
	Family Burden	0.9%	19.3%	**N**	**Y**	**N**	**N**	**N**
	Relationships	0.8%	16.5%	**Y**	**N**	**N**	**N**	**N**
Physical	Pain	65.3%	75.3%	**Y**	**Y**	**Y**	**Y**	**Y**
	Energy Levels	19.9%	23.2%	**Y**	**Y**	**Y**	**N**	**N**
	Musculoskeletal Impairment*	19.9%	22.9%	**Y**	**N**	**Y**	**N**	**Y**
Emotional	Anxiety	19.1%	58.8%	**N**	**N**	**N**	**N**	**N**
	Depression	9.9%	30.5%	**Y**	**Y**	**N**	**N**	**N**
	Anger/Frustration	5.4%	16.7%	**Y**	**Y**	**N**	**N**	**N**
Cognitive	Mental Impairment**	3.2%	13.6%	**N**	**N**	**N**	**N**	**N**
	Impulsivity	2.9%	12.4%	**N**	**N**	**N**	**N**	**N**
	Balance/Coordination	2.9%	12.1%	**Y**	**N**	**N**	**N**	**Y**
Role Activity	Performance at Work/School	3.0%	34.6%	**N**	**N**	**N**	**N**	**Y**
	Unemployment/Dropped out of School	1.7%	19.9%	**N**	**N**	**N**	**N**	**N**
	Absence from Work/School	1.3%	15.0%	**N**	**Y**	**N**	**N**	**N**

Legend: Cells with the letter "N" indicate that the listed sub-concept is not captured by the PRO tool being evaluated. Cells with the letter "Y" indicate that the listed sub-concept is captured by the PRO tool being evaluated. * "Musculoskeletal Impairment" refers to stiffness, swelling, and inflexibility. ** "Mental Impairment" does not encompass "Concentration," as that sub-concept was captured separately.

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Abstract Number: 1427

The Importance of Outcome Measures in Ankylosing Spondylitis – Validity of the Routine Assessment of Patient Index Data 3 in a Real World Cohort

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Background/Purpose: Outcome measures in AS are well established in clinical trial settings but infrequently used in real-world (RW) practice. These measures include the BASDAI, BASFI, and ASDAS. The RAPID3 is an established RA measure, but infrequently used in real world (RW) settings. It has been tested most recently in 75 patients with AS correlating RAPID3 scores with BASDAI and ASDAS-ESR[1]. The purpose is to compare RAPID3 to BASDAI, BASFI, ASDAS-(CRP, ESR), in a cross-sectional analysis of 456 AS patients enrolled in the JointMan® registry (JM), a real-world (RW) database capturing five AS outcome measures.

Methods: A retrospective review of data collected in the JM registry. These study measures were recorded in 456 patients at 1706

visits. Indices and individual measures were compared using Spearman's (ρ) and Cohen's Kappa (κ) correlations.

Results: BASDAI > 4, active AS, correlated with moderate/high RAPID3; Kappa of 0.486 (p = 0.001). ASDAS >1.3, high disease activity correlated with moderate/high RAPID3; Kappa correlation of 0.544 (p = 0.001).

Patient Characteristics	**Value**
Mean Age (SD)	52 (14.16)
Female	45.83%
White	90.57%
HLA-B27 (+)	61.90%

Spearman's correlation of RAPID3 for Specific Measures	**ρ**	**p-value**
BASDAI	0.85	< 0.0001
ASDAS-ESR	0.75	< 0.0001
ASDAS-CRP	0.81	< 0.0001
BASDAI Fatigue	0.54	< 0.0001
BASDAI Spinal Pain	0.75	< 0.0001
BASFI	0.81	< 0.0001
Acute-phase reactant ESR	0.16	< 0.0001
Acute-phase reactant CRP	0.09	< .0003
Cohen's Kappa correlation for Rapid3 (high, moderate, or low)	**κ**	**p-value**
ASDAS (High, moderate, or low)	0.455	0
BASDAI (Active)	0.235	0
Cohen's Kappa correlation for Rapid3 (High or moderate)		
ASDAS (High or moderate)	0.544	0
BASDAI (Active)	0.486	0

Conclusion: RAPID3 is the most common outcome measure utilized in RW settings for managing patients with RA. In clinical practice this outcome is frequently obtained in all patients seen in a rheumatology office at the time of registration prior to the rheumatologist's evaluation although it has only been validated in RA. In this cross sectional study of a large cohort of patients with AS, RAPID3 results had high correlations with BASDAI, BASFI, and ASDAS. This study supports the use of the RAPID3 in RW rheumatology practices for patients with AS.

1. Park et al. J. of Clin. Rheum. 2015;21(6):300-304.

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Abstract Number: 1428

Patient Attitudes Towards Being Prescribed Biosimilars in Inflammatory Autoimmune Diseases in Germany

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Background/Purpose: Our aim is to address the lack of understanding surrounding patient attitudes to being prescribed biosimilars in the real world for Rheumatoid Arthritis (RA), Axial Spondyloarthritis (AxSpA) and Psoriatic Arthritis (PsA).

Methods: The Adelphi Biosimilars Programme is a real-world, cross-sectional survey of patients receiving biosimilars or biologic originators in RA, AxSpA and PsA. Patients report their satisfaction, understanding and attitudes towards being prescribed biosimilars or bio-originators. Rheumatologists (n=50) reported matching data on patients who completed the survey.

Results: Data was collected from 174 biosimilar patients and 87 bio-originator patients. Less biosimilar patients, 78%, were satisfied that their current treatment was controlling their condition than bio-originator patients, 85%. Physician satisfaction reflected that of patients, with only 27% stating they were 'very satisfied' when prescribing a biosimilar compared to 43% a bio-originator (p=0.005). Biosimilar patients demonstrated lower understanding of their treatment, 39% felt they didn't know enough about the drug when it was initiated, vs. 28% for bio-originators. The lack of understanding of biosimilars was again observed as 42% of biosimilar patients were not aware that their treatment was based on an alternative original product. Biosimilar patients who had not previously received a bio-originator stated the most common reasons they accepted biosimilars was cost (30%) and doctor's recommendations (30%), whilst biosimilar patients who switched from a bio-originator accepted due to doctor's recommendations (73%) and cost or insurance reasons (43%).

Conclusion: These data demonstrate biosimilar patients show less satisfaction than bio-originator patients and their understanding of their treatment is lower. Whilst many patients seem unaware that biosimilars are based on existing bio-originators, they seem aware that cost is a factor behind their prescription. This may be indicative of the conversations that prescribers are having with both patients and payers when deciding on treatment options.

Disclosure: J. Piercy, Adelphi Real World, 3; **J. Waller**, Adelphi Real World, 3; **E. Sullivan**, Adelphi Real World, 3; **C. Black**, Merck and Co Inc, 3; **S. Kachroo**, Merck and Co Inc, 3.

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Abstract Number: 1429

Patient-Reported Outcomes Measures and Economical Burden of Patients with Ankylosing Spondylitis in a Chinese Prospective Cohort with Smart Management System for Spondyloarthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing Spondylitis (AS) is characterized by relatively young onset age, easily causing spinal deformity and stiffness, and seriously influencing the health related Quality of Life (QoL) and engaging heavy economical burden for the patients, their families and even the whole society. There were adequate clinical studies about the Patient-reported Outcomes (PROs), which include Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) et al. This study was designed to assess the clinical value of various PROs in a prospective cohort study of AS patients, and to evaluate the medicine cost and other treatment-related cost of patients with AS in Chinese population, and to explore the global economical burden and the factors that may affect the cost.

Methods: 517 AS patients were collected from the Department of Rheumatology, Chinese PLA General Hospital. Data were obtained from Smart Management System (SMSP) for Spondyloarthritis collected online. The Quality of Life (QoL) were assessed by SF-36 questionnaire and compared with the general Chinese population. The correlation between QoL and clinical measures of AS, including BASDAI, BASFI et al, were analysed.Meanwhile, a retrospective study of 283 AS patients and multivariate logistic regression analysis

were performed to explore the global economical burden and influence factors.

Results: BASDAI and BASFI were significantly correlated with SF-36 scores($r>0.3$, $P<0.01$). Logistic multiple regression analysis showed that BASDAI, BASFI, BASMI and education had close correlation with the baseline global QoL, physical and mental health. BASDAI variation showed the most important influence on the change of global QoL, physical health and mental health (*OR*=0.235, 0.209, 0.125; *P*<0.01). The total average medicine cost in the past year was $2654.27 per patient，of which non-steroid anti-inflammatory drugs represented 4.2% percentages, conventional disease modifying anti-rheumatic drugs represented 11.7%, biological disease modifying anti-rheumatic drugs represented 81.9%, herbal drugs represented 2.2%. The mean value of other cost correlated with the treatment of AS were laboratory examination ($260.62/year), transportation ($323.26/y), accommodation ($177.16/y), other cost ($40.21/y). Peripheral articular involvement (*OR*=2.412, 95%*CI*: 1.006~4.562, *P*=0.048) and disease duration (*OR*=0.197, 95%*CI*: 0.056~0.693, *P*=0.011) showed the most important influence on the total medicine cost.

Conclusion: SF-36 can objectively reflected the QoL of Chinese patients with AS. PROs such as BASDAI and BASFI showed great application value in this prospective cohort study of AS patients. High medicine cost directly increased the economical burden of AS patients. Peripheral articular involvement and disease duration showed the most important influence on the total medicine cost. Other indirect cost related with the therapies also increased the economical burden of AS.

Disclosure: Q. Wen, None; **X. Ji**, None; **J. Yang**, None; **J. Zhu**, None; **J. Zhang**, None; **F. Huang**, None.

Abstract Number: 1430

Adherence to the International Consensus Quality Indicators for Longitudinal Health Maintenance and Preventative Care in a Pediatric Rheumatology Clinic

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Background/Purpose: Juvenile systemic lupus erythematosus (jSLE) is a chronic disease associated with significant morbidity. Variability in the health maintenance-related management of these patients can contribute to suboptimal outcomes. International consensus quality indicators (QIs) were developed to guide management in SLE, with a subset focused on health maintenance and preventative care. We performed a retrospective chart review to assess adherence to the health maintenance-related QIs for jSLE in our clinic, with the goal of using this data to drive a quality improvement initiative to improve adherence.

Methods: A retrospective chart review was performed on patients with an active diagnosis of SLE followed in the pediatric rheumatology clinic at our institution from December 1, 2014 to April 30, 2016. Patients were included if they had a current active diagnosis of jSLE and were seen within the study period. Patients were excluded if they were no longer followed in our clinic, or received alternative diagnoses. Data were abstracted in a standardized database for analysis. To assess adherence to the health maintenance-related QIs, we calculated the percentage of patients who had documentation of performance of each measure, including: (a) Receiving antimalarial therapy (hydroxychloroquine) unless contraindicated; (b) Vaccination against influenza and encapsulated organisms; (c) Bone mineral testing; (d) Prescription for calcium and vitamin D supplementation for patients exposed to any glucocorticoid dose for longer than 3 months; (e) Annual ophthalmology evaluation; and (f) Serum lipid levels every 2 years.

Results: Sixty-six patients were identified with jSLE on initial screening, with 15 excluded based on criteria. We reviewed charts of the remaining 51 patients with an active diagnosis of jSLE seen during the study period. Mean age was 17 years (range 10-25) and 42 (83%) were female. Forty-nine (96%) were taking hydroxychloroquine. The 2 patients not taking had contraindications of allergy to medication and inability to take due to anxiety. 29 (57%) had documentation of the need for an annual ophthalmologic exam. 47 patients (92%) were on chronic steroid therapy, but only 13 (28%) were prescribed calcium and vitamin D. 7 (12%) had documentation of the necessary vaccinations and 7 (12%) had serum lipids checked within the last two years. None (0%) had bone mineral testing.

Conclusion: Adherence to the international consensus QIs for SLE in our pediatric rheumatology clinic varied considerably. Adherence was greatest for anti-malarial medication treatment and ophthalmology examination screening, and lowest for health maintenance-related measures of documentation of vaccination status, serum lipid level screening and bone mineral testing. This may reflect dissociation between routine jSLE disease management and preventive health maintenance activities. Accordingly, a standardized, system-based process that incorporates health maintenance-related activities into standard daily work may be necessary for improved adherence to recognized evidence-based QIs.

Disclosure: A. Bosk, None; **B. Edelheit**, None; **L. Zemel**, None; **H. Tory**, None.

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Abstract Number: 1431

Estimates of Global Status By Physicians and Patients Are More Likely to be Discordant in Osteoarthritis Than in Rheumatoid Arthritis

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Background/Purpose: Concordant 0-10 estimates of global status by physicians (DOCGL) and patients (PATGL) are associated with greater expectations for improvement and better outcomes[1], and appear desirable in shared decisions concerning therapy. However, previous studies have shown that physicians and their patients with rheumatoid arthritis (RA) and other rheumatic conditions have discordant global estimates in about 50% of instances[2,3]. Although recent evidence suggests that disease burden RA is similar or lesser than in osteoarthritis OA, OA generally remains regarded as being less severe than RA. We analyzed discordance between PATGL and DOCGL in OA vs RA patients seen in routine care at an academic rheumatology setting.

Methods: All patients in this setting complete a multidimensional health assessment questionnaire / routine assessment of patient index data (MDHAQ/RAPID3) at each visit, which includes 0-10 scores for physical function, pain, and PATGL compiled into a 0-30 RAPID3, as well as fatigue VAS, 60 symptom checklist, RADAI self-report joint count, and demographic data. Rheumatologists complete a RheuMetric checklist, which includes a physician global (DOCGL). Mean differences between PATGL & DOCGL were calculated. Patients with primary OA or RA were classified into 3 categories: PATGL ≥ DOCGL by 2/10 units, PATGL = DOCGL, and DOCGL ≥ PATGL by 2 units, and compared with other measures using chi-square tests, ANOVA, and logistic regression.

Results: The study included 216 patients with RA and 243 with OA. Patients with OA were older and showed higher scores for PATGL, pain, fatigue, and number of symptoms (data not shown). A higher percentage of patients with OA showed discordance with PATGL>DOCGL in comparison with RA (34% vs 18%) while concordance and discordance with DOCGL > PATGL were higher in RA patients (67% vs 56% and 15% vs 10%) ($p<0.001$). In general, patients with PATGL>DOCGL had lower formal education levels ($p<0.05$ in RA but not OA), and had higher scores for pain, function, fatigue, number of symptoms ($p<0.05$ in OA but not RA), and self-report RADAI (Table). In logistic regressions, pain was the only significant predictor of discordance in both RA [odds ration (OR) 1.47, 95% confidence interval (CI) 1.12-1.93] and OA (OR 1.40, 95% CI 1.04-1.89), but not age, gender, race, education, function, symptom checklist or self-report RADAI.

Conclusion: Patients with OA are more likely to have their clinical status underestimated by rheumatologists than patients with RA, although the burden of disease was greater in OA than in RA. The data suggest that rheumatologists and the medical and general public might revise generally held views that OA is less severe than RA. **References: 1.** *Am J Public Health* 1981, **71**(2):127-131. **2.**Arthritis Care Res (Hoboken) 2014;66:934-42. 2. **3.**Arthritis Care Res (Hoboken) 2012;64:206-14.

Table. Comparison of discordance groups in OA and RA patients.				
OSTEOARTHRITIS	**PATGL>DOCGL** **N= 82 (34%)**	**PATGL=DOCGL** **N = 136 (56%)**	**DOCGL>PATGL** **N = 25 (10%)**	**P values**
Age, years	64.7 (12.3)	64.8 (14.0)	**72.6 (12.6)**	0.02
Women, %	87.8%	91.2%	92%	0.68
Race: White Non-White	24.4% 75.6%	39.7% 60.3%	28% 72%	0.10
Education, years	12.9 (3.5)	14.3 (3.0)	13.6	0.06
Pain (0-10)	**7.7 (2.0)**	5.7 (2.8)	4.9 (3.5)	<0.001
Function (0-10)	**3.4 (1.9)**	2.6 (1.9)	2.0 (1.9)	0.004
Fatigue (0-10)	**6.3 (2.7)**	4.4 (3.0)	3.0 (2.6)	<0.001
Symptom checklist (0-60)	**12.4 (8.6)**	9.8 (7.4)	6.9 (6.1)	0.005
Self-report RADAI (48)	**16.5 (12.1)**	11.1 (9.4)	7.8 (7.5)	<0.001
RHEUMATOID ARTHRITIS	**PATGL>DOCGL** **N= 39 (18%)**	**PATGL=DOCGL** **N = 144 (67%)**	**DOCGL>PATGL** **N = 33 (15%)**	**P values**
Age, years	57.7 (15.8)	56.4 (16.8)	55.0 (17.5)	0.79
Women, %	92.3%	84.0%	81.8%	0.36
Race: White Non-White	28.2% 71.8%	44.4% 55.6%	48.5% 51.5%	0.57
Education, years	**12.7 (4.1)**	14.3 (3.4)	15.2 (3.9)	0.03
Pain (0-10)	**7.3 (1.8)**	4.3 (3.0)	2.7 (2.9)	<0.001
Function (0-10)	**3.6 (1.9)**	2.5 (2.2)	1.3 (1.6)	0.001
Fatigue (0-10)	**5.8 (2.8)**	3.8 (3.0)	1.9 (2.2)	<0.001
Symptom checklist (0-60)	9.6 (7.8)	7.4 (7.1)	6.0 (5.2)	0.09
Self-report RADAI (48)	**18.2 (10.7)**	9.4 (9.4)	4.5 (5.0)	<0.001

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Abstract Number: 1432

The EULAR Systemic Sclerosis Impact of Disease Score – a New Patient-Reported Outcome Measure for Patients with Systemic Sclerosis Under Development

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SESSION INFORMATION

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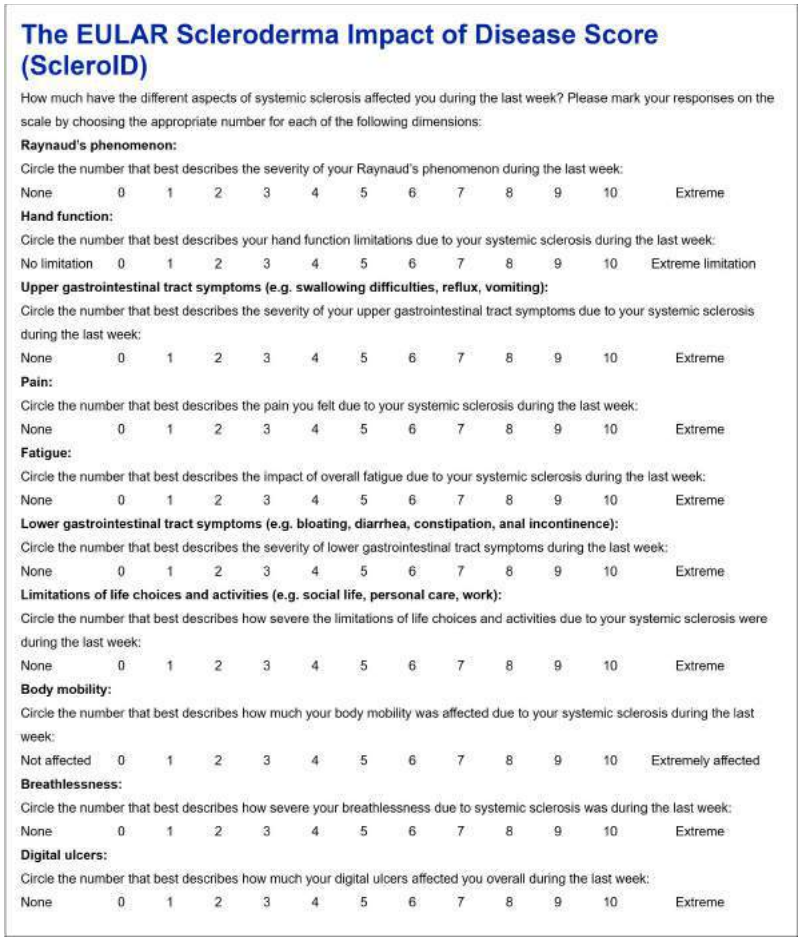
Background/Purpose: Patient reported outcome measures (PROM) are required as key outcomes in disease modifying therapeutic trials in systemic sclerosis (SSc). A PROM tool in SSc, covering the different features of this multi-organ autoimmune disease, is lacking. In this study, we aim to develop and validate a brief, disease-specific, patient-derived, composite disease impact score for scientific and clinical use in SSc.

Methods: This multi-center project endorsed by EULAR involves SSc patients and experts from 11 European countries. Firstly, using the nominal group technique, patients with SSc selected the health dimensions where the disease has the most significant impact. The dimensions were subsequently given numeric priority by an international group of SSc patients. Patients were asked to rank the dimensions in order of their importance by giving a rank from 1(most important) to 17 (least important). Each rank could only be used once. The dimensions with the top 10 median ranks, as ranked by the patients, were used to construct the ScleroID questionnaire using numeric rating scales. An observational study to weight the dimensions in order to calculate the ScleroID score and to validate the questionnaire is currently ongoing and aims to target a larger cohort of patients from all participating countries.

Results: 24 SSc patients selected 17 health dimensions in the nominal group exercise. The prioritization cohort included 108 SSc patients from 11 centers (female:male 82:25, limited: diffuse SSc subset 53:54). The top 10 health dimensions which were ranked most relevant by the patients were Raynaud's phenomenon, hand function, upper and lower gastrointestinal tract symptoms, pain, fatigue, limitation of life choices and activities, body mobility, breathlessness and digital ulcers. Based on this, the ScleroID questionnaire was constructed (Figure 1).

Conclusion: The EULAR ScleroID score is a novel, patient-derived, tool under development designed for use in clinical practice and clinical trials to display the disease impact of SSc. A large scale observational study for weighting of the dimensions and validation of this new instrument is ongoing. **Figure 1. The ScleroID questionnaire.**



The EULAR Scleroderma Impact of Disease Score (ScleroID)

How much have the different aspects of systemic sclerosis affected you during the last week? Please mark your responses on the scale by choosing the appropriate number for each of the following dimensions:

Raynaud's phenomenon:

Circle the number that best describes the severity of your Raynaud's phenomenon during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Hand function:

Circle the number that best describes your hand function limitations due to your systemic sclerosis during the last week:

No limitation 0 1 2 3 4 5 6 7 8 9 10 Extreme limitation

Upper gastrointestinal tract symptoms (e.g. swallowing difficulties, reflux, vomiting):

Circle the number that best describes the severity of your upper gastrointestinal tract symptoms due to your systemic sclerosis during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Pain:

Circle the number that best describes the pain you felt due to your systemic sclerosis during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Fatigue:

Circle the number that best describes the impact of overall fatigue due to your systemic sclerosis during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Lower gastrointestinal tract symptoms (e.g. bloating, diarrhea, constipation, anal incontinence):

Circle the number that best describes the severity of lower gastrointestinal tract symptoms during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Limitations of life choices and activities (e.g. social life, personal care, work):

Circle the number that best describes how severe the limitations of life choices and activities due to your systemic sclerosis were during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Body mobility:

Circle the number that best describes how much your body mobility was affected due to your systemic sclerosis during the last week:

Not affected 0 1 2 3 4 5 6 7 8 9 10 Extremely affected

Breathlessness:

Circle the number that best describes how severe your breathlessness due to systemic sclerosis was during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

Digital ulcers:

Circle the number that best describes how much your digital ulcers affected you overall during the last week:

None 0 1 2 3 4 5 6 7 8 9 10 Extreme

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Abstract Number: 1433

Self-Perception Reporting to Healthcare Professionals: Do Individuals with Systemic Sclerosis Report Quality of Life Changes Accurately?

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Background/Purpose: Systemic Sclerosis (SS) involves multiple systems that affect the ability to move and function. When ability is lost the individuals living with this autoimmune disorder may experience changes in day-to-day abilities. If a decline in function occurs then independence and quality of life changes; therefore an assessment of function and quality of life in persons with SS was done.

Methods: Thirty individuals (22 African-American, 6 Caucasians, 2 other) with SS were given a health literacy test before administering self-report tests on quality of life; these included the Health Assessment Questionnaire Disability Index (HAQDI), ADLs, IADLs and the St. George Respiratory Questionnaire. Additionally medical records showed the 6 Minute Walk Test had been performed on 15 of the individuals. Health literacy was assessed prior to giving the paper and pencil reports using the Rapid Estimate of Adult Literacy in Medicine (REALM).

Results: The average age was 62.5 (range 55-82). Individuals reported impairment as follows: 33% with the HAQDI, 11% ADLs, 10% IADLs. The REALM score ranked an average of 7-8th grade level. The average duration of SS diagnosis was 9.4 years. Seventeen of the participants (15 African American, 1 male) had 6-M-W scores, walking an average of 334 meters (m) with a dyspnea level of 2.5 (out of 10); 6 out of 13 had Pulmonary Function Test of Forced Vital Capacity < 80%. Only 1 individual walked the normal distance for their age group a 76 year old woman walked 820 m (normal 471 m).

Conclusion: Most individuals scored a high ability with low impairment on ADLs and IADS, with average HAQDI score of 0.98 (out of 3.0). This indicates a low impact of the disease on daily function; however more than half of the participants reported difficulty with stair climbing, meaning individuals may struggle with more challenging movements. Individuals with SS perceived they were able to perform independently at relatively high levels, 66%-90% of function on the disability and self-care reports but when it came to actual performance these individuals were not able to walk at normal age-ranked levels when walking for 6 minutes. Perhaps these individuals adjusted to lower levels of function over time and did not see themselves as having much disability. A low number of respiratory symptoms were reported on the St. George Respiratory Questionnaire yet only one individual was able to walk the norm for her age group. Another possibility is that individuals could have had difficulty understanding the self-report tests, even when assistance and explanation was offered resulting in higher scores on those tests. The health literacy scores did score at a 7-8th grade level. It is vital that health care professionals understand that individuals who are living with SS may not always accurately report their ability to function; therefore it behooves the professional to have their patient perform the skill in question so that more accurate information can be obtained and optimal intervention can be sought. Villalba WO, Sampaio-Barros PD, Pereira MC, Cerqueira EMFP, Leme Jr CA, Marques-Neto JF, Paschoal IA. Six-Minute Walk Test for the Evaluation of Pulmonary Disease Severity in Scleroderma Patients *CHEST*. 2007;131:217–222.

Disclosure: S. Hayat, None; **P. Fenter**, None; **T. GILMORE**, None.

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Abstract Number: 1434

Effect of Systemic and Local Inflammation on the Insulin Resistance and Glucose/Lipid Metabolism in Rheumatoid Arthritis: Humans and CIA Mouse Model

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Background/Purpose: Rheumatoid arthritis (RA) patients are at higher risk for insulin resistance (IR). The association between RA and IR, and its role on the different characteristics of the disease, such as duration and activity have not been well defined. In addition, there is a gap of knowledge regarding the link between systemic/local inflammation and insulin sensitivity and lipid metabolism in RA patients. **Objective:** To explore the effects of the systemic and local inflammation on the insulin sensitivity and lipid metabolism in RA patients and collagen induced arthritis (CIA) mouse model.

Methods: **Human study:** 120 RA patients and 40 healthy donors were included. IR was quantified using the homeostatic model assessment of IR (HOMA-IR) and was compared between RA patients and demographically matched non-RA controls. **Mouse model:** To investigate the mechanisms underlying the link between inflammation and insulin sensitivity and lipid metabolism in RA, a CIA mouse model was used. A total number of 20 mice were used; five mice were used as non diseased control group, and 15 were used in CIA modelling. Scoring for CIA was performed after injection of chicken collagen type II and arthritis index (AI) was calculated. Leukocytes, skeletal muscle and adipose tissue were collected for gene and protein profiling. mRNA expression of genes involved in lipid and glucose metabolism, insulin signalling and inflammation were evaluated (CD36, CPT1a, MCAD, PGC1b, PPARa, PPARg2, ACC, DGAT2, FADS1, FADS2, LPL, PLIN2, AOX, FAS, GLUT4, IRS1, IRS2, TNFa, MCP-1 and F4/80). Phosphorylation and expression of AKT and JNK as markers of insulin sensitivity and inflammation were analysed. Protein expression of IL-1b was also evaluated.

Results: Percentages of obesity, hypertension, atherogenic risk, metabolic syndrome and insulin resistance were significantly increased in the RA group. Although mean time of evolution was 8 years, no association between insulin resistance and the duration of the disease was found. Levels of HOMA-IR significantly correlated with number of swollen joints, DAS28 and C-reactive protein levels, suggesting that systemic and local inflammation might lead to the development of insulin resistance. In mice, the induction of arthritis promoted an alteration of the expression of genes involved in inflammation as well as lipid metabolism and insulin signalling in skeletal muscle, adipose tissue and leukocytes of diseased CIA mice vs. controls. Levels of phosphorylation of AKT and JNK and protein expression of IL1b were significantly increased in those tissues of the CIA mice group.

Conclusion: 1) Insulin resistance was closely associated with an increase in disease activity and systemic and local inflammation in RA patients. 2) Induction of arthritis in mice promoted an increase in inflammation markers in skeletal muscle, adipose tissue and leukocytes, and a reduction of genes involved in lipid uptake and storage, generating an insulin resistance state in those tissues. In sum, our results suggest that chronic inflammation associated with RA might directly impact relevant metabolic tissues, altering glucose and lipid homeostasis. Funded by CP15/00158 and PI2013/0191.

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Abstract Number: 1435

KCa1.1 Potassium Channels Are a Novel Therapeutic Target on Fibroblast-like Synoviocytes in Rheumatoid Arthritis

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Background/Purpose: Fibroblast-like synoviocytes (FLS) develop a high degree of invasiveness during rheumatoid arthritis (RA), leading to joint degradation. There are currently no therapeutics that specifically target the pathogenic phenotype of FLS. We have previously found that FLS from RA patients and from rats with a model of RA express higher levels of the KCa1.1 potassium channel at

their plasma membrane than FLS from patients with osteoarthritis or from healthy rats. Selectively inhibiting KCa1.1 with the small molecule paxilline reduces the *in vitro* invasiveness of FLS and reduces disease severity in multiple rat models of RA. However, KCa1.1 is expressed in a variety of tissues and systemic KCa1.1 block induces side effects that preclude paxilline's use as a potential therapeutic in humans. Here, we investigated the efficacy of the peptide KCa1.1 inhibitor iberiotoxin (IbTX), which has a limited biodistribution, in reducing disease severity in an animal model of RA, assessed IbTX's side effects, and determined the mechanism by which KCa1.1 regulates FLS invasiveness.

Methods: Starting at disease onset, rats with the pristane-induced arthritis (PIA) model of RA were given either vehicle, paxilline, or IbTX. Disease severity was measured daily using a standard scoring system. After three weeks of treatment, X-rays and histology were completed on paws of rats from each treatment group. Side effects, including incontinence and tremors, were determined in healthy rats given a single treatment of either IbTX, paxilline, or vehicle. Flow cytometry and *ex vivo* functional assays were used to assess the effects of KCa1.1 inhibition on the expression and activation of signaling molecules involved with FLS invasion.

Results: Both paxilline and IbTX significantly reduced clinical signs of disease in PIA by approximately 55% ($p<0.001$) and 65% ($p<0.001$), respectively, as determined by a standard scoring system of paw inflammation. X-rays and histological analysis of joints from each treatment group indicated that the KCa1.1 blocker-treated rats had less bone and cartilage damage and reduced synovial hyperplasia, fibrosis, and immune infiltrates compared to vehicle-treated animals. Side effects, including tremors and incontinence, were significantly reduced in IbTX-treated rats compared to those treated with paxilline. *Ex vivo* analysis of RA-FLS demonstrated that KCa1.1 inhibition alters integrin expression and activation through modulation of calcium homeostasis and Akt phosphorylation, resulting in decreased invasiveness.

Conclusion: KCa1.1 is an attractive therapeutic target for the treatment of RA by inhibiting the invasive phenotype of FLS through modulating integrin expression. The use of the selective peptide KCa1.1 inhibitor IbTX provides for a novel targeted pharmacological approach to inhibit KCa1.1 expressed on FLS while minimizing side effects. Overall, these studies emphasize the efficacy of targeting FLS in reducing disease severity and suggest selective KCa1.1 inhibitors as potential therapeutics in the treatment of RA.

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TAS8274, a Highly Selective Janus Kinase 3 Inhibitor, Demonstrates Potent Efficacy in an Animal Model of Rheumatoid Arthritis

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Background/Purpose: The family of Janus kinases (JAKs) plays important roles in signaling pathway mediated by various cytokine receptors. An aberrant activation of JAK-STAT signaling has been reported to be involved in the pathogenesis of autoimmune diseases.Non-selective JAK inhibitors have shown excellent efficacy in patient with rheumatoid arthritis (RA). However, their use is limited due to adverse effects and safety concerns by inhibiting JAK1/2 signaling. Selective inhibition of JAK3 might result in an improved safety profile while maintaining excellent efficacy. The objectives of this study were to identify pharmacological profiles of TAS8274, a novel JAK3 inhibitor with high selectivity, and to evaluate its therapeutic potential in rat adjuvant-induced arthritis (AIA).

Methods: In vitro biochemical assay was performed using available kinase assay panels. In cell-based assay, JAK3 activation was evaluated by interleukin (IL) -2-induced human peripheral blood mononuclear cells (PBMC) proliferation. IL-2–, IFN-α– and IL-3–induced phosphorylation of STAT proteins in PBMC were analyzed and quantified by a flow cytometry-based assay. Female Lewis rats were injected intradermally with adjuvant at the base of the tail. In order to evaluate the therapeutic efficacy of TAS8274 in rat AIA, treatment was initiated when the overt clinical signs of disease were observed. TAS8274 was administered orally twice daily for 2

weeks. Swelling in hind paws were measured using a plethysmometer. At the end of the experiment, the paws were removed to analyze the histopathological changes. The scoring of inflammation, pannus, cartilage and bone damage in two joints of the rat AIA was performed by a single blinded pathologist using a modified Mankin score system.

Results: TAS8274 strongly inhibited the enzymatic activity of JAK3, and showed more than 1000-fold selectivity against other JAK family members, JAK1, JAK2 and TYK2. TAS8274 inhibited the IL-2–induced proliferation of PBMC in a dose dependent manner (IC_{50} = 25.3 nM) and also potently suppressed IL-2–induced STAT5 phosphorylation (IC_{50} = 18.9 nM). On the other hand, TAS8274 showed 300-3000 fold less inhibitory effects against JAK3–independent IFN-α or IL-3–induced STAT phosphorylation than that of JAK3–dependent STAT phosphorylation. In an established rat AIA, the hind paw volume in TAS8274-treated rats was dose-dependently decreased after oral administration of TAS8274 (0.3 to 10 mg/kg). TAS8274 also significantly reduced paw histopathology scores compared with those in vehicle-treated rats.

Conclusion: Our results demonstrate that TAS8274 has the potential to elicit JAK3-mediated immunomodulatory effects without affecting the activities of JAK1, JAK2 and TYK2 and improves clinical signs of arthritis in the rat AIA. TAS8274 would be an attractive therapeutic agent for patients with autoimmune disorders such as RA, and reduce the side effects induced by inhibiting other JAK family members. TAS8274 was selected as a clinical candidate and is being evaluated for its safety profile to initiate Phase 1 study.

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Netrin-1 and Its Receptor Unc5b Are Novel Targets for the Treatment of Inflammatory Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease that causes chronic inflammation and destruction of joints. Netrin-1, a laminin-like matrix protein that acts as a chemorepulsant, plays a pathogenic role during inflammation by preventing macrophage egress from inflamed sites, and it is required for osteoclast differentiation. We asked whether blockade of Netrin-1 or its receptors (Unc5b, DCC) may be useful therapeutic targets in the treatment of inflammatory arthritis.

Methods: 8wk-old-C57Bl/6 mice were ip-injected with 0.2ml K/BxN serum twice. Murine monoclonal antibodies against Netrin-1, Unc5b or DCC (10µg/mice) were ip-injected weekly for 4wk (n=10). Clinical signs (paw swelling and thickness) were observed daily. Animals were sacrificed 2-4wk after serum transfer, and paws were prepared for microCT and histology

Results: Serum transfer induced an increase in paw inflammation that was maximal 2wk after injection. Anti-Netrin-1 or anti-Unc5b, but not anti-DCC, antibodies significantly reduced paw inflammation (clinical score of 9.8±0.8, 10.4±0.9 and 13.5±0.5 respectively vs. 16±0 for control, $p<0.001$, n=10). Same results were observed for changes in paw thickness. microCT showed bony erosions in untreated or anti-DCC-treated-mice whereas there were no erosions in anti-Netrin-1/anti-Unc5b-treated-animals. TRAPstaining demonstrated a marked decrease in osteoclasts in anti-Netrin-1/anti-Unc5b-treated-animals but not in anti-DCC-treated-mice (4±1, 3±1 and 9±2cells/hpf respectively vs.12±1cells/hpf for control, $p<0.001$ and p=ns, n=5). Immunofluorescence staining revealed a decrease Cathepsin K and CD68-positive cells in anti-Netrin-1/anti-Unc5b, but not anti-DCC-treated-animals.

Conclusion: Blockade of Netrin-1/Unc5b by treatment with murine monoclonal antibodies prevents bone destruction and K/BxN serum transfer-induced arthritis. Netrin-1 may be a novel therapeutic target for inflammatory bone destruction.

Disclosure: A. Mediero, CP15/0053, 2, 9,Patent for the use of adenosine A2AR agonists to prevent prosthesis loosening. Patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **T. Wilder**, None; **B. Ramkhelawon**, patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **K. Moore**, patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **B. Cronstein**, Canfite Pharma, 1,Celgene, AstraZeneca, Takeda, 2,Revive Therapeutics, 5,Always hopeful, 9.

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Abstract Number: 1438

Tofacitinib Restores Reverse Cholesterol Transport Inhibition Induced By Inflammation. Understanding the Lipid Paradox

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Background/Purpose: Patients with active rheumatoid arthritis (RA) have significantly increased cardiovascular (CV) morbidity and mortality, paradoxically in association with reduced circulating levels of total cholesterol (TC) and LDL-C. Tofacitinib (TOFA), an oral Janus Kinase inhibitor, improves systemic and joint inflammation in RA, increasing serum TC and LDL-C without affecting CV disease. Our aim was to study the effect of TOFA on the lipid profile of hyperlipidemic rabbits with chronic arthritis (CA) and to go deeper into the mechanisms associated to the regulation of reverse cholesterol transport (RCT) exerted by this treatment in chronic inflammation

Methods: Twenty-four male, New Zealand white rabbits fed with a high fat diet (HFD) were randomly assigned to two groups: control (n=6) and CA (n=18). CA was induced over six weeks via intra-dermal ovalbumin sensitization and four subsequent intra-articular injections. Nine CA rabbits were treated with TOFA (10mg/kg/day) for two weeks. Fully differentiated THP-1 cells were exposed to HFD rabbit serum or ox-LDL to become foam cells. Thereafter, cells were stimulated with IFNγ to reproduce the inflammatory milieu in the presence or absence of TOFA for 24 hours. Intracellular lipid accumulation was assessed by Oil Red-O staining and protein and RNA were isolated for molecular studies.

Results: CA rabbits showed lower levels of serum TC and LDL-C compared to controls (p=0.001 and p=0.012), while TC/HDL-C ratio was higher in CA+TOFA rabbits when compared with CA animals (150±15 vs. 230±17; p=0.004). Synovial inflammation and C-reactive protein (CRP) levels were increased in CA animals, and a significant reduction was shown in CA+TOFA rabbits in both parameters (p=0.015 and p=0.006). We observed an inverse correlation between serum TC and CRP (R=-0.454, p=0.029). An increased infiltration of lipid-loaded macrophages was found in the synovial membrane of CA and CA+TOFA rabbits. In vitro experiments confirmed that IFNγ further stimulates intracellular lipid accumulation in macrophages incubated with HFD rabbit serum or with oxLDL. INFγ inhibited the expression of the cellular ATP-binding cassette transporter (ABCA1) that mediates the first step of RCT. The impaired lipid accumulation was prevented in the presence of TOFA. Furthermore, TOFA restored the IFNγ-induced ABCA1 downregulation, both preventing STAT1 phosphorylation and increasing LXRα expression.

Conclusion: Our experimental model of CA perfectly replicated the lipid paradox observed in RA patients, and the increase in circulating lipids evoked by TOFA, together with an amelioration of joint and systemic inflammation. In vitro studies showed that TOFA prevented the inflammation-induced dysregulation of lipid transport in macrophages through a LXRα depending mechanism, counteracting the IFNg inhibition of RCT. Therefore, these results suggest that chronic inflammation would sequester lipids into macrophages -in the synovium and probably in other tissues- thus decreasing serum lipid levels. Taking together, our findings partially explain the effect of TOFA on the lipid profile in RA patients.

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Abstract Number: 1439

The EP4 Receptor Antagonist CR6086 Is More Effective Than Classical NSAID and DMARD Treatment in a Murine Model of Arthritis and in Human RA Synovial Explants

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Background/Purpose: CR6086 is a novel small molecule acting as a potent and selective antagonist of the prostaglandin E2 (PGE2) receptor EP4 subtype (EP4 receptor). Recent studies have shown that PGE2-EP4 signaling acts directly on type 3 innate lymphoid cells (ILCs) and T cell differentiation, and may therefore play a key role in the altered immune response observed in autoimmune diseases such as rheumatoid arthritis (RA). The **objectives** of this study were: (1) to evaluate the efficacy and immunomodulatory effects of systemic treatment with CR6086 in comparison to classical NSAID or DMARD treatment on experimental arthritis in mice; (2) to confirm the efficacy of EP4 receptor targeting in a translational setting using human RA synovial tissue.

Methods: In female C57Bl/6 mice, antigen-induced arthritis (AIA) was elicited by two immunizations with methylated bovine serum albumin (mBSA) as an antigen in Freund's complete adjuvant, and subsequently by intra-articular injection with mBSA into the right knee joint. Treatment was started two hours after the onset of arthritis, in 6 treatment groups: CR6086 (20 or 60 mg/kg/day), Naproxen (60 mg/kg/day), Dexamethasone (5 mg/kg/day), Etanercept (10 mg/kg every other day) or vehicle control. The effects of treatment were studied in vivo by ^{99m}Technetium measurements to detect joint swelling in the arthritic knee joint. At day 7 of treatment, mice were sacrificed and joints were isolated for histological analysis of inflammation and destruction. Synovial tissue was collected at day 3 to assess local cytokine and chemokine production by Luminex, and synovial gene expression by RT-QPCR. Furthermore, synovial explants of RA patients were cultured ex vivo in the presence or absence of CR6086 (300nM), Etanercept (10 µg/mL), or Tofacitinib (300nM), and the effect on spontaneous cytokine and chemokine production was analyzed by Luminex.

Results: Treatment with the EP4 receptor antagonist CR6086 significantly and dose-dependently reduced antigen-induced arthritis, as scored by macroscopic and histological scoring. Interestingly, CR6086 at 60 mg/kg/day was more effective than Naproxen, a classical NSAID, in reducing clinical inflammation scores and histological joint pathology. Furthermore, CR6086 at this dose was as effective as Dexamethasone in reducing histological inflammation, and even more potent in protecting from severe bone erosions. Regarding the immunomodulatory actions of CR6086, our study showed that CR6086 treatment reduced cytokines like IL-1beta, IL-17A, and to a lesser extent IL-6 and IFNgamma. The ex vivo experiment with human synovial tissue showed a beneficial, inhibitory effect of CR6086 on spontaneous secretion of cytokines and chemokines by synovial explants in two RA donors. In these two "responders", a comparable inhibitory effect of Etanercept was observed, whereas Tofacitinib was clearly less effective than CR6086.

Conclusion: These findings provide support for the potential therapeutic effects of the EP4 receptor antagonist CR6086 in RA patients, and point to the PGE2-EP4 receptor pathway as a rational target for the development of novel DMARDs with immunomodulatory and anti-inflammatory properties.

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Abstract Number: 1440

Anti-TNF Vaccination Protects from Experimental Arthritis without Affecting Resistance to Mycobacterium Tuberculosis or Listeria Monocytogenes infection

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Background/Purpose: Anti-TNF-alpha therapy has been a successful treatment strategy for rheumatoid arthritis (RA), but is associated with reduced resistance to infection. In mice, TNF is essential to control infection. We have developed a murine vaccine against TNF (mTNF-K) which protects mice from collagen-induced arthritis (CIA) to same extent as etanercept. We aimed at modelizing the infectious risk/benefit ratio of TNF-alpha neutralization by a vaccination strategy. Here we evaluated the consequence of TNF blockade by the mTNF-K in *Listeria* and *Mycobacterium* infection models.

Methods: Arthritis models were collagen-induced arthritis (CIA) in mice and collagen-antibodies induced arthritis (CAIA). In *Listeria monocytogenes* infection model, 4 groups of 10 C57Bl/6 mice were used and compared with a murine TNF KO group (same background). Wild type mice were treated either by mTNF-K, etanercept, KLH or PBS. Vaccines were emulsified in CFA (day 0) or IFA (days 13, 27 and 40) before injections. All groups were infected at day 44 by 10^4 cfu of *Listeria monocytogenes* (LO28 strain). Mice groups were divided in two arms: one was euthanized 4 days post-infection, survival of the lasting mice was evaluated until day 11. In Mycobacterium infection model, the same protocol was applied with same groups before infection by 10^4 cfu of *Mycobacterium tuberculosis* (H37Rv strain). Mice groups were divided in two arms: one was euthanized 28 days post-infection, the lasting mice were euthanized 56 days post-infection. Bacterial burden was evaluated in the lung. Cellular infiltration was studied by immunohistological analysis.

Results: Our vaccine was efficient in improving clinical and histological signs of arthritis in CIA and CAIA. A sustained anti-TNF-alpha antibody production was obtained in mTNF-K vaccinated mice in all experiments. At day 4 post-infection by Listeria, mTNF-K and non-targeted-TNF treatments groups (KLH, PBS) presented lower bacterial burden in liver and spleen than TNF KO and etanercept groups. At day 11, all mice of PBS and mTNF-K groups survived to infection. Large lesions in livers were observed only within TNF KO and etanercept groups. At day 28 post-infection by Mycobacterium, bacterial burden, organ weights and cellular infiltrations (Neutrophils, B cells) were similar between mTNF-K and non-targeted-TNF treatments groups. On the contrary, etanercept group presented increased surface of liver granuloma and lower lung infiltration by iNOS+ cells than mTNF-K group. At day 56, etanercept group presented higher surface of lung granuloma than mTNF-K and KLH group.

Conclusion: Together, our results indicate that anti-TNF-alpha vaccine could protect mice from inflammatory arthritis without deeply altering host immunity against infection, suggesting the existence of two distinct pathophysiologic thresholds for TNF inhibition, one for arthritis improvement, the other for infection deregulation.

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Abstract Number: 1441

Dendritic Cell-Specific Transmembrane Protein (DC-STAMP) Knockout Attenuates Arthritis Progression and Systemic Inflammation in TNF-Tg Arthritis Mouse Models

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Background/Purpose: Tumor necrosis factor-transgenic (TNF-Tg) mice develop systemic inflammatory polyarthritis. DC-STAMP, a multi-pass transmembrane protein, was originally identified from a dendritic cell library and required for cell-cell fusion between osteoclast precursors (OCPs). To examine if DC-STAMP also regulates inflammatory responses in TNFα-mediated arthritis pathogenesis, we introduced a DC-STAMP null mutation into the TNF-Tg background and examined immune responses and inflammatory-erosive arthritis progression in the presence or absence of DC-STAMP.

Methods: Two TNF-Tg lines (TNF-Tg3647 & Taconic 1006) were crossed to DC-STAMP-/- mice to generate distinct DC-STAMP genotypes (+/+, +/-, and -/-) under TNF-Tg (+ or -) background. Arthritis progression was evaluated by grip strength monthly until mice reached 4 months of age. Immune responses were evaluated by flow cytometry on cells obtained from the ascites of 4-month old mice. ELISA was performed to assess endogenous mouse and transgenic human TNF levels in sera. Immunohistochemistry (IHC) were performed to identify DC-STAMP+ cells in lung, heart and intestine.

Results: We observed the following:(1) Synthetic lethality in Taconic 1006: no live DC-STAMP-/-TNF+ pups were detected; (2) In TNF-Tg3647 background: although the majority of DC-STAMP-/-TNF+ pups died within a week after birth, several DC-STAMP-/-TNF+ pups survived; (3) In contrast to their DC-STAMP+/-TNF+ & DC-STAMP+/+TNF+ littermates where widespread inflammation (ascites, heart & lung pathology) and arthritis progression were observed, DC-STAMP-/- TNF-Tg+ mice showed attenuated joint pathology and inflammation. The grip strength of DC-STAMP+/-TNF+ & DC-STAMP+/+TNF+ mice decreased dramatically between weeks 11 & 12 (0.6±0.2N), whereas DC-STAMP-/-TNF+ mice grip strength was relatively strong at week 12 (1.6±0.3N), p=0.05 between 2 groups; (4) The protective effect of DC-STAMP null mutation on TNFα-induced arthritis progression and inflammation was independent of TNFα serum levels. Intriguingly, a higher serum TNFα level was detected in arthritis-free DC-STAMP-/-TNF+ mice compared to DC-STAMP+/+ TNF+ littermates with severe arthritis; (5) 65% of cells collected from inflammatory ascites were DC-STAMP+CD11b+ cells; (6) the lung, heart and intestine of DC-STAMP-/-Tg+ mice showed significantly less inflammation (neutrophils & CD11b+ monocytes infiltration) and attenuated pathology than their DC-STAMP+/+Tg+ littermates.

Conclusion: The absence of DC-STAMP expression in the TNFα-overexpressing mouse arthritis model was associated with suppression of both systemic inflammation and arthritis progression. The presence of DC-STAMP+ cells in ascitic fluid coupled with attenuated arthritis and systemic inflammation in DC-STAMP -/- mice provides preliminary evidence that DC-STAMP is involved in the regulation of TNF-induced immune responses. Examination of the molecular mechanism underlying the altered immune system and anti-inflammatory responses in DC-STAMP-/-TNF+ mice will provide new insights into the interplay between DC-STAMP and TNFα. Collectively, our results suggest that blockade of DC-STAMP may serve as an effective therapy for arthritis medication.

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Abstract Number: 1442

Suppression of Acute Arthritis By N-Methyl-3,4-Dichloropropionaniline (N-

MeDCPA), a Reversible Orai Calcium Channel Inhibitor

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Background/Purpose: Bone maintenance is a balance between the removal of old bone by osteoclasts (OCL) and the production of new bone by osteoblasts. In the arthritides, bone erosion by OCL occurs at normally protected sites in the joints where bone replacement does not occur. N-MeDCPA allows the regulated reduction of OCL activity, that is, control damage to joints without complete elimination of OCL activity. Thus, the balance of bone maintenance in joints can be restored. OCL maturation is suppressed when calcium-release activated calcium (CRAC) currents are blocked by targeting Orai1, the pore-forming unit of CRAC. We provide evidence that N-MeDCPA is a Orai1 antagonist that suppresses OCL maturation, without significantly affecting osteoblastogenesis or immune function.

Methods: The Orai1-blocking activity of N-MeDCPA was measured in Jurkat T cells using Fura-2. In vivo data was collected after the induction of CIA in DBA/1 mice. Animals were dosed with 0 or 21 mg/kg body weight per day N-MeDCPA via a subcutaneous 21-day continuous time-release pellet inserted at day 20 - dose equivalent to 350 mg qid as a human anti-inflammatory drug. A booster injection of collagen II was administered at day 21 and the Arthritis Index (AI) and paw swelling were measured for 20 d thereafter. Bone erosion was assessed using micro-computer tomography (m-CT). Serum anti-(mouse) collagen IgG was measured by ELISA and serum cytokine levels were measured using MSD V–PLEX panels.

Results: Orai1 activity was blocked by N-MeDCPA in a concentration-related manner. CIA measurements, by blinded observers, showed that N-MeDCPA suppressed the AI (severity) over 3 weeks. Bone and cartilage damage in sections of animal feet was reduced; overall swelling of joints was reduced by a similar amount. Effects on bone density by μ CT showed clear separation in N-MeDCPA-treated CIA animals from CIA without treatment, while differences between controls without CIA and CIA treated with N-MeDCPA differed by small amounts and in most cases were not statistically different. Response was not related to anti-collagen titers. There were no adverse effects in the treated group on animal weight or activity, consistent with low toxicity. The effect was maximal 12-17 days after collagen booster, during the rapid appearance of arthritis in untreated CIA. At 20 days after treatment (day 40), differences in arthritis score were reduced and TNF-α, IL-1, or IL-6 in the serum of the animals were similar in treated and untreated animals.

Conclusion: N-MeDCPA, a novel inhibitor of Orai1 channels, suppresses bone erosion associated with acute arthritis in mice and potentially represents a new treatment modality for acute arthritis.

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Abstract Number: 1443

A Therapeutic Peptide Vaccine Reduces Pro-Inflammatory Responses and Suppresses Arthritis in the Cartilage Proteoglycan G1 Domain-Induced Mouse Model of Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease leading to inflammatory destruction of the peripheral joints. Although pro-inflammatory T helper 1 (Th1) and/or Th17 cell responses play a central role in the immunopathology of RA, current therapies do not provide efficient inhibition of these pro-inflammatory T cells or their signature cytokines. In this study, we demonstrate that the peptide conjugate DerG-PG70 (CEL-4000) is able to inhibit Th1 and Th17 responses and can act as a therapeutic vaccine in an autoimmune mouse model of RA.

Methods: Female BALB/c mice were immunized intraperitoneally (ip) with the recombinant G1 domain of human cartilage proteoglycan (PG) aggrecan in adjuvant. This G1-induced arthritis (GIA) model of RA can display Th1- or Th17-skewed cellular responses depending on the route of immunization (ip or id/sc, respectively). We elected to focus on the more aggressive ip-induced form with a Th1 signature phenotype (IFNg). Peptide conjugates composed of an immune cell binding motif (designated DerG or J) and the arthritogenic epitope of human PG (PG70) were constructed. DerG-PG70 (CEL-4000) or J-PG70 vaccine was administered with adjuvant twice (2 weeks apart) to the mice, beginning at the early phase of arthritis. Mice treated with adjuvant only served as controls. Disease severity was monitored by visual scoring of joint inflammation. Three weeks after the second vaccination limbs were processed for histopathology and serum was collected for measurement of pro- and anti-inflammatory cytokines. Spleen cell cultures were set up to examine binding of peptide conjugates to Th cells or antigen-presenting cells (APCs) and to determine Th cell cytokine profiles using flow cytometry and Millipore's MagPix multiple cytokine assays.

Results: The CEL-4000 vaccine significantly suppressed arthritis severity and limited joint damage in the ip-induced form of GIA. The other peptide conjugate (J-PG70) or single PG70 and DerG peptides were not therapeutically effective in the disease. Increased ratios of anti-inflammatory cytokines (IL-4 and IL-10) to pro-inflammatory IL-17 were found in the serum of mice vaccinated with CEL-4000 as compared to the other treatment groups. Spleen cells from mice with ip-induced GIA and vaccinated with either CEL-4000 or J-PG70 showed reduced production of Th1 and Th17 signature cytokines as well as other pro-inflammatory mediators in vitro as compared to controls. However, this inhibitory effect was found to be more potent in cell cultures of CEL-4000-treated than J-PG70 treated animals. In vitro cell binding experiments revealed preferential binding of the CEL-4000 peptide conjugate to Th cells whereas J-PG70 bound primarily to APCs.

Conclusion: Our results suggest that while both peptide vaccines have an influence on the immune system, CEL-4000 powerfully down-modulates pro-inflammatory T-cell responses probably via direct binding to Th cells whereas J-PG70 does it indirectly, and less effectively, via binding to APCs. Robust inhibition of Th1, Th17, and pro-inflammatory pathways, as seen in mice with ip-induced GIA after receiving CEL-4000 vaccine, appears to be necessary for arthritis suppression.

Disclosure: D. Zimmerman, CEL SCI corporation, 1, 9; **H. Steiner III**, CEL SCI Corporation, 3; **R. Carambula**, CEL SCI Corporation, 1; **A. Markovics**, None; **A. Finnegan**, None; **K. Mikecz**, None; **T. Glant**, None.

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Abstract Number: 1444

Differential Expression of Wnt Inhibitors before and after Joint Inflammation Onset in Rat Arthritis Could Partly Explain Paradoxical Effect of Sclerostin Inhibition

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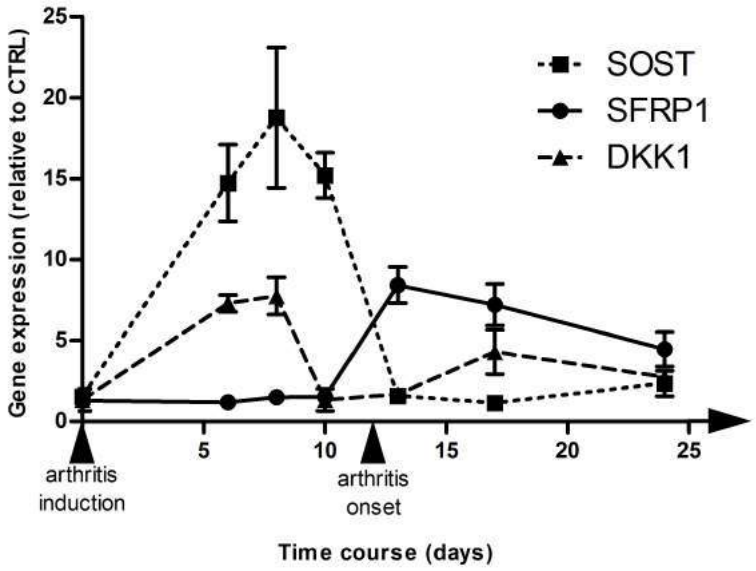
Background/Purpose: Periarticular bone loss in rheumatoid arthritis is considered to be mainly related to synovial inflammation, leading to uncoupling between decreased bone formation and increased bone resorption. However, it has been recently demonstrated a paradoxical exacerbation of joint damage when blocking sclerostin in various arthritis models. Phase specific changes in Wnt pathway activity over the course of the disease could participate in the underlying mechanisms of these results. Thus, we proposed to determine kinetic expressions of Wnt inhibitors in a classic rodent model of arthritis, the rat adjuvant induced arthritis (AIA).

Methods: Arthritis was induced (AIA, n=35) or not (CTRL, n=35) at baseline. Inflammation and loss of articular function were monitored. Periarticular bone loss and joint damage were evaluated before, during and after arthritis onset in a 7 time-point follow-up, using micro-computed tomography (µ-CT) and histomorphometry. Gene expressions were assessed by quantitative RT-PCRs at each time point.

Results: AIA onset occurred at day 12 post-induction ($p<0.001$). Surprisingly, histomorphometry and µ-CT showed bone alterations as early as day 8. Indeed, cortical porosity increased and trabecular network was significantly impaired ($p<0.01$). Moreover, these early bone alterations before arthritis onset predicted arthritis severity outcome. As expected, gene expression confirmed an early upregulation of bone resorption markers like RANKL from day 8 to day 24 ($p<0.01$). More interestingly, expression of bone formation inhibitors followed a specific pattern with SOST upregulation only before arthritis onset ($p<0.01$) and return to normal expression afterwards. However, frizzled related protein 1 (SFRP1) expression only increased after arthritis onset ($p<0.01$). Furthermore, dickkopf related protein 1 (DKK1) expression increased before and after arthritis onset with a low expression during arthritis onset.
Figure: gene expression pattern of SOST, DKK1, and SFRP1.



Conclusion: Bone alterations before arthritis onset supports the hypothesis of an early involvement of bone compartment in arthritis. The specific pattern of sclerostin expression suggested that sclerostin might play dual effects depending on arthritis phases. In addition, SFRP1 later increased expression could play a strong role in bone formation alteration related to arthritis. Since DKK-1 was highly expressed before and after arthritis onset, its blockade was already described to be efficient in mice arthritic model. We infer from our results that better deciphering Wnt pathway changes during arthritis is required before using biologics targeting this pathway for preventing periarticular bone loss.

Disclosure: G. Courbon, None; **R. Lamarque**, None; **M. T. Linossier**, None; **N. Laroche**, None; **T. Thomas**, None; **L. Vico**, None; **H. Marotte**, None.

Abstract Number: 1445

Human Umbilical Cord Blood-Derived Mesenchymal Stem Cells Ameliorate Rheumatoid Arthritis Via Regulation of Macrophage Activation and Polarization

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Background/Purpose: Immunomodulatory properties enable mesenchymal stem cells (MSCs) to be a promising alternative for the treatment of a wide range of immune-related diseases including rheumatoid arthritis (RA). However, underlying mechanisms with the perspective of systemic immune regulation are less verified. We sought to explore the therapeutic efficacy of human umbilical cord blood-derived MSCs (hUCB-MSCs) against murine collagen-induced arthritis (CIA) and to investigate distinct mechanisms mainly focused on macrophages.

Methods: CIA was induced in DBA1/J mice by the repeated immunization of bovine type II collagen with complete Freund's adjuvant. hUCB-MSCs were administered to CIA mice intraperitoneally each day for 5 days after the onset of disease, and clinical severity was assessed. Alternatively, CIA mice were given with a single intravenous injection of hUCB-MSCs at the same phase of disease progression. To verify the regulatory effects of hUCB-MSCs on macrophages, human and murine macrophages were co-cultured with hUCB-MSCs and the alteration of cytokine profile and marker expression was determined. These regulatory functions were confirmed using peripheral blood mononuclear cells (PBMCs) from patients with RA.

Results: The multiple intraperitoneal administration of hUCB-MSCs exerted significant therapeutic efficacy against CIA to a similar extent of etanercept, anti-TNF-α biologic agent. A single intravenous injection of hUCB-MSCs exerted sufficient therapeutic effect on CIA, and down-regulated the production of various pro-inflammatory cytokines concomitantly. hUCB-MSCs suppressed the classical M1 activation of macrophages, and simultaneously increased the anti-inflammatory M2 polarization. Concerted action of strengthened cyclooxygenase (COX-2) and tumor necrosis factor alpha stimulate gene 6 (TSG-6) signaling in response to TNF-α, a prominent inflammatory cytokine in RA, contributed to the regulation of macrophage plasticity by inducing M2 polarization. In addition, these immune-balancing effects of hUCB-MSCs were reproducible in PBMCs from patients with active RA.

Conclusion: The systemic application of hUCB-MSCs can effectively attenuate murine inflammatory arthritis through the regulation of macrophage plasticity. Upon TNF-α stimuli, COX-2 and TSG-6 signaling is enhanced, consequentially results in both inhibition of M1 activation and induction of M2 polarization. Therefore, our findings provide the clue that stem cell therapy using hUCB-MSCs can be an attractive candidate for the treatment of RA, especially who do not respond to current single-target biologic medications.

Disclosure: T. H. Shin, None; **K. Shin**, None; **H. S. Kim**, None; **K. S. Kang**, Kangstem Biotech, 4.

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Abstract Number: 1446

High Fat Diet Alleviates Antigen-Induced Arthritis Severity in Male Mice By Enhancing Both Treg and B10 Cells

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Background/Purpose: Obesity is associated with many chronic diseases. However, evidence regarding obesity's impact on rheumatoid arthritis (RA) initiation and development remains controversial. Recent studies indicate that obesity could reduce the risk of men developing RA. Here, we examined the role of high fat diet (HFD)-induced obesity in antigen-induced arthritis in adult male mice.

Methods: Antigen-induced arthritis (AIA) was induced in normal diet (ND) or 8-week exposure HFD mice by immunizing with mBSA in complete Freund's adjuvant. Arthritis severity was assessed by knee swelling measurement and histological evaluation. Serum anti-mBSA antibody and cytokines were detected by ELISA or Multiplex bead assay at various time points. T cell subpopulations and B regulatory cell in spleen and lymph node were evaluated *in vivo,* and their function was also examined by measuring cytokines production after phorbol ester (PMA) and Ionomycin stimulations *in vitro*.

Results: When compared to ND-mice, HFD-mice displayed less knee swelling and delayed peak arthritis. Consistent with these observations, histological assessment showed reduced infiltration of inflammatory cell and bone erosion in obese mice joints. Despite no difference in TNF-a, IL-21, IL-22 and TGF-b1 level in sera, IL-21/23p40 and anti-mBSA IgG production was significantly lower in HFD mice. Interestingly, the anti-inflammatory cytokine IL-10 level was increased in sera from HFD mice. Surprisingly, Th1, Th2 and Th17 cell population did not differ in both spleen and lymph node. Consistently, levels of IFN-g, IL-4 and IL-17A were comparable in the splenocyte supernatant from ND and HFD mice. Interestingly, a significantly increased Treg population was detected in the spleen of HFD mice but not in the lymph node. $CD19^{+}IL\text{-}10^{+}$ (B10) cells in the spleen of HFD mice were also enhanced, accompanied by higher IL-10 level in the splenocyte supernatant *in vitro*.

Conclusion: In summary, these data suggest HFD-induced obesity alleviates AIA-induced arthritis in male mice. This might due to the enhanced Treg and B10 cell population in HFD mice, which leads to increased IL-10 in sera of obese mice. This study provides a novel mechanistic link of obesity and RA.

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Abstract Number: 1447

Therapeutic Blockade of Interleukin-6 Trans-Signalling Restores Vascular Function in Murine Collagen Induced Arthritis

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Background/Purpose:

Mortality is increased in rheumatoid arthritis (RA), mainly due to cardiovascular disease (CVD). While molecular mechanisms underlining this clinical observation are unknown, systemic elevations in inflammatory cytokines such as interleukin (IL)-6 frequently correlate with increased cardiovascular risk. Importantly, IL-6 plays important roles in both immune homeostasis and driving chronic disease progression. Control of these processes is regulated by two modes of IL-6 signalling; classical IL-6 receptor signalling and IL-6 trans-signalling. Cellular responses controlled by IL-6 trans-signalling are mediated via soluble IL-6 receptor (sIL-6R) and is widely considered to promote deleterious pro-inflammatory outcomes. Importantly, a genetic polymorphism within IL6R enhances circulating sIL-6R levels and is associated with CVD incidence in the normal population. Biological drugs against IL-6 (e.g. olokizumab) or IL-6R (e.g. tocilizumab) block both classical and trans-signalling. However it is advocated that selective inhibition of IL-6 trans-signalling may reduce the incidence of clinical complications associated with a more global intervention strategy. Previously, murine collagen induced arthritis (mCIA) has been associated with vascular dysfunction, with reduced aortic constriction to 5-hydroxytryptamine (5-HT)[1]. Here, we found systemic alterations in vascular tone, as a response to mCIA, was attributable to the action of IL-6 trans-signalling.

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Methods:

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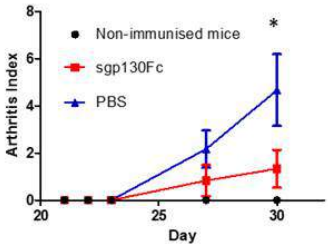
Arthritis was induced in 8 week old male DBA/1 mice by type-II collagen, as previously described[2]. Animals were intravenously administered sgp130Fc (2.5mg/kg) or PBS weekly from day 21 after immunisation with type-II collagen. Arthritis severity was monitored daily from day 21 to 30. Vasoconstriction of isolated aortic rings in response to 5-HT was monitored as an index of vascular function using isometric tension myography.

Results are expressed as mean ± SEM (n=10).

Results:



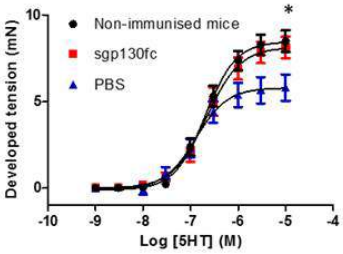


Figure 1 (A) Significant difference in Arthritis Index over time in mice administered spg130Fc compared with PBS. (B) Vasoconstriction concentration-response curves to 5-HT in aortic rings. N=10

When compared with PBS controls (Arthritis Index: 4.3±1.1), disease severity was significantly (P<0.05) reduced in sgp130Fc (1.5±0.6) treated mice (Figure1A). The induction of arthritis in PBS control animals was accompanied by reduced vasoconstriction (developed tension 8.5±0.6 mN for non-immunised mice, compared with 5.8±0.8 mN for mice with CIA; P<0.05). Significantly, improvement of disease activity observed for sgp130Fc treated animals was associated with normalisation of vascular function (developed tension 8.1±0.6 mN).

Conclusion:

Consistent with previous reports[2], sgp130Fc reduced arthritis in mCIA. Sgp130Fc also restored vascular function. Selective IL-6 trans-signaling blockade by sgp130Fc is a promising therapeutic strategy for both RA and its associated CVD. Further work is needed to elucidate the role of IL-6 trans-signalling in the pathogenesis of vascular dysfunction in both mCIA and RA.

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Abstract Number: 1448

Therapeutic Role of a Novel Histone Deacetylase 6 Inhibitor, CKD-M808, in Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) is a chronic inflammatory autoimmune disease whose etiology is unclear. Recently, upregulated HDAC (histone deacetylase) activity has been reported in peripheral blood mononuclear cell (PBMC) from RA patient. In addition, it was reported that HDAC6 inhibitor (HDAC6i) improves cancers and inflammatory diseases by suppressing cell migration and proliferation and reducing pro-inflammatory cytokines such as TNF-α. Here, we investigated the therapeutic effects of a new HDAC6 inhibitor, CKD-M808 (M808), specifically targeting catalytic domain 1 of HDAC6 in RA.

Methods: We made adjuvant induced arthritis (AIA) model by injection of complete Freund's adjuvant (CFA) subcutaneously into the tail base of Lewis rat on the 1st day of experiment. Vehicle (n=9) and M808 (10, 30, 50 and 100 mg/kg, n=9, 9, 8 and 10, respectively) were administered orally every day. Clinical score was measured at 10th, 14th and 17th days after induction. PBMC from RA patients were treated with HDAC6i (Tubastatin A and M808) for 24 hours under lipopolysaccharide (LPS) stimulation. After incubation, cell viability and the levels of cytokines including TNF-α, IL-1ß, IL-6 and IL-10 in culture supernatant were measured using CCK-8 and multiplex ELISA assay, respectively. Fibroblast-like synoviocyte (FLS) from RA patients were treated with HDAC6i for 24 hours under IL-1ß stimulation. The levels of IL-6, MMP-1 and MMP-3 were measured in culture supernatant. Cortactin and acetylated cortactin in HDAC6i-treated RA-FLS were measured by Western blotting.

Results: Clinical score of AIA model were significantly decreased as the dose of M808 increased, indicating the therapeutic effect of M808. In RA-PBMC, M808 downregulated the level of TNF-α<span 'arial','sans-serif';"="'Arial','sans-serif';"" lang="EN-US"> and upregulated the level of IL-10 without any impact on cell viability. In RA-FLS, M808 decreased the production of MMP-1 and MMP-3. M808 increased acetylation of cortactin molecule in a dose-dependent manner.

Conclusion: M808 suppressed clinical arthritis in the AIA model. M808 decreased the production of TNF-α and increased IL-10 in PBMC of RA patients. M808 also decreased MMP-1 and MMP-3 in FLS of RA patients. The novel HDAC6i, M808, may provide a new therapeutic option in RA patients.

Disclosure: S. Shon, CKD Research Institute, 2; **J. S. Park**, None; **D. Bae**, CKD Research Institute, 2; **N. Ha**, CKD Research Institute, 2; **Y. I. Choi**, CKD Research Institute, 2; **J. K. Park**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, CKD Research Institute, 2.

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Abstract Number: 1449

The Efficiency of the Regulation of Ca2+ Entry through Calcium Release-Activated Calcium Channel in the Treatment of Rheumatoid Arthritis

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Background/Purpose: The regulation of Ca^{2+} entry by targeting a store-operated calcium release-activated channel (CRAC), known as *ORAI*, has shown benefits in the treatment of rheumatoid arthritis (RA). This study was undertaken to investigate the feasibility and efficiency of CRAC inhibitors in the treatment of RA.

Methods: Peripheral T cells and B cells were obtained from RA patients and health donors. We engrafted pannus tissue from synovia, articular cartilage, bone, and peripheral blood mononuclear cells from RA patients who underwent prosthetic replacement arthroplasty for therapeutic purposes into NOD/ShiJic-scid mice (SCID-HuRAg mice) and treated them with CRAC inhibitors, including YM-58483, a specific short hairpin RNA and a monoclonal neutralizing antibody.

Results: The treatment of CRAC inhibitors suppressed the Ca^{2+} entry and the activation in peripheral cells. CRAC inhibitors declined the production of human IgG2 and IgM in SCID-HuRAg mice. According to the results of histological evaluation, treatment of SCID-HuRAg mice with CRAC inhibitors markedly suppressed invasion of synovial tissue into cartilage. A decrease in mature osteoclast activity was also observed in CRAC inhibitor-treated SCID-HuRAg mice.

Conclusion: These results indicate that the regulation of Ca^{2+} entry through CRAC channel is beneficial in the treatment of RA.

Disclosure: S. Liu, None; **H. Hasegawa**, None; **T. Kiyoi**, None; **T. Sawasaki**, None; **K. Maeyama**, None.

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Abstract Number: 1450

Regulatory Mechanisms of Mesenchymal Stem Cell Transplantation on Systemic Osteoporosis in Collagen-Induced Arthritis Mice

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Background/Purpose: To investigate the effects of umbilical cord-mesenchymal stem cell (UC-MSC) transplantation on joint damage and systemic osteoporosis in collagen induced arthritis (CIA) mice.

Methods: DBA/1 male mice were induced to CIA models by injecting type II Collagen (CII). Then CIA mice were divided into four groups, including CIA control group, UC-MSC transplantation group, anti-tumor necrosis factor alpha (anti-TNFα) treatment group and zoledronic acid (ZA) treatment group. The CIA mice were treated for 8 weeks. Arthritis score of CIA mice were evaluated every 3 days. Micro computed tomography (micro-CT) was used to analyze the bone morphology parameters. Bone marrow mesenchymal stem cells (BMMSCs) were isolated and cultured in the osteogenic medium. Osteogenic differentiation was determined by alkaline phosphatase (ALP) staining and ALP activity on day 7. The expression of the osteogenic markers ALP, Osterix and type I collagen (COL-I) were analyzed by RT-PCR and western bloton day 7 and day 14 respectively. Moreover, bone marrow monocytes (BMMs) were isolated and induced to osteoclast (OC) in the presence of macrophage colony-stimulating factor and receptor activator of nuclear factor-KB ligand. OC differentiation was determined by tartrate-resistant acid phosphatase (TRAP) staining and mRNA levels of nuclear factor of activated T cells (NFAT)2 and osteoprotegerin (OPG).

Results: The arthritis score was significantly reduced in UC-MSC transplantation and anti-TNFα treated CIA group compared with control mice. Micro-CT showed that the BMD, trabecular bone volume/total volume (BV/TV) and trabecular number (Tb.N) of the

femur were significantly decreased in CIA mice, compared with that in DBA/1 mice. H&E staining also showed a reduced Tb.N in CIA mice. Whereas these parameters were partially improved in UC-MSCs treated CIA mice compared with control mice. Impaired osteogenic differentiation functions were shown by decreased ALP activity, reduced gene and protein levels of osteogenic marker genes in CIA mice compared with DBA/1 mice. UC-MSCs treatment significantly upregulated the osteogenic differentiation ability in CIA mice. Moreover, TRAP staining and OC counting showed that OC number was increased in CIA mice compared to that in DBA/1 mice. The NFAT2 mRNA levels were elevated in CIA mice compared to that in DBA/1 mice, however the OPG mRNA levels were decreased in CIA mice. UC-MSC treatment downregulated the enhanced OC differentiation in CIA mice.

Conclusion: The present study demonstrated that CIA mice developed osteoporosis. UC-MSCs transplantation not only improved the joint damage significantly but also played a positive role in osteoporosis in CIA mice. The osteogenic differentiation ability of BMMSCs in CIA mice was impaired. The OC differentiation function of BMMs in CIA mice was enhanced. UC-MSCs transplantation could upregulate the osteogenic differentiation and downregulate the OC differentiation in CIA mice. Thus, we provide strong evidence that MSCs ameliorate inflammation-induced systemic bone loss in CIA mice by upregulating osteogenic differentiation and reducing OC differentiation.

Disclosure: C. Liu, None; **H. Zhang**, None; **X. Tang**, None; **R. Feng**, None; **G. Yao**, None; **W. Chen**, None; **W. Li**, None; **L. Sun**, None.

Abstract Number: 1451

Glutamine Metabolism Plays a Crucial Role in the Pathogenesis of Rheumatoid Arthritis

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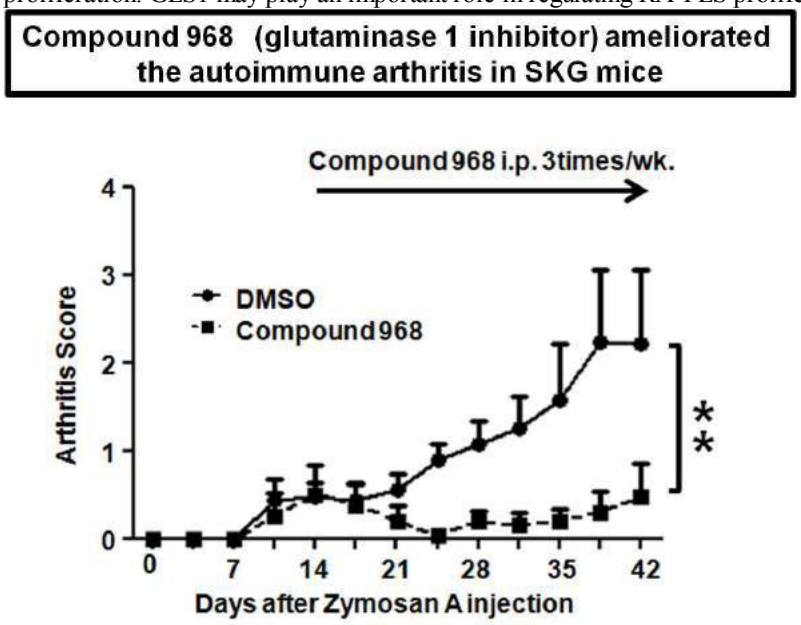
Background/Purpose: Many signaling pathways activated under inflammatory and hypoxic conditions have profound effects on intracellular metabolism to support cell growth and survival. Cancer cells consume glucose and glutamine at a high rate compared to normal cells. Recent studies have identified cancer-specific metabolic changes that provide new therapeutic targets. The microenvironment in inflamed joints in RA is also characterized by hypoxia and low concentration of nutrients, and fibroblast-like synoviocytes from RA patients (RA-FLS) is known to have several tumor-like characteristics. However, little is known about how glucose or glutamine metabolism are involved in the aberrant proliferation of RA-FLS. We aimed to evaluate the role of these metabolisms in RA-FLS, and discover a metabolic characteristics of RA-FLS.

Methods: The expression of glycolysis- or glutaminolysis-related enzymes was evaluated by real-time PCR and Western blotting. The intracellular metabolites in FLS were analyzed by gas chromatography mass spectrometry (GC/MS) and capillary electrophoresis (CE)-MS. We used glucose- or glutamine-free medium for investigating the effects of glucose or glutamine on cell growth of RA-FLS. siRNA or compound 968 was used to inhibit glutaminase 1 (GLS1). Arthritis was induced in SKG mice by zymosan A injection. SKG mice were treated with compound 968 three days per week. Ki-67-positive cells were analyzed by immunohistochemistry.

Results: GLS1 expression was increased in RA-FLS and metabolome analyses suggested that glutamine metabolism was upregulated in RA-FLS. Cell proliferation of RA-FLS was significantly decreased under the glutamine-derived condition, but not under glucose-derived condition. Cell proliferation of RA-FLS was significantly suppressed by GLS1 inhibition. The levels of GLS1 mRNA was increased by treatment with IL-17 or PDGF in RA-FLS. Administration of GLS1 inhibitor, compound 968, ameliorated autoimmune

arthritis in SKG mice. Histologic score of arthritis in compound 968-treated mice were significantly lower than those in control mice. Furthermore, immunohistochemical analysis revealed that compound 968 treatment significantly downregulated the Ki-67-positive synovial cells. The number of Th17 cells and Treg cells in spleens from compound 968-treated and control mice were not changed by compound 968 treatment.

Conclusion: Glutamine metabolism was involved in the pathogenesis of RA. Glutamine deprivation or inhibition of GLS1 inhibited cell proliferation of RA-FLS. Administration of GLS1 inhibitor ameliorated the inflammatory arthritis in SKG mice by suppressing the proliferation of RA-FLS. GLS1 inhibition directly affected the cell cycle progression of RA-FLS and suppresses the aberrant cell proliferation. GLS1 may play an important role in regulating RA-FLS proliferation, and could be a novel therapeutic target in RA.



Disclosure: S. Takahashi, None; **J. Saegusa**, None; **I. Naka**, None; **K. Tsuda**, None; **T. Okano**, None; **K. Akashi**, None; **S. Sendo**, None; **Y. Ueda**, None; **A. Onishi**, None; **Y. Kogata**, None; **A. Morinobu**, None.

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Abstract Number: 1452

18 F-FDG PET Imaging: An In Vivo quantitative Drug Screening Tool for Novel Antiinflammatory Therapies

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Background/Purpose: Collagen induced arthritis (CIA) mouse model is used for screening of new drugs for autoimmune arthritis. The conventional read outs of this model are clinical and histological scores. These read-outs have many limitations including (i) longitudinal studies in the same mouse cannot be performed (ii) clinical and histological scores are subjected to observer bias (iii) *in vivo* cellular events cannot be captured in its native environment. To meet these unmet needs here we have evaluated the utility of ^{18}F-FDG PET imaging in the CIA model.

Methods: Briefly, arthritis was induced using bovine type II collagen in 8-week old male DBA/1J mice (n=30), out of which 20 mice developed arthritis. The disease was allowed to progress till day 45 (pre-treatment time point- **Fig 1**), 5 mice were sacrificed for histological studies; 10 mice were treated with i.p anti-mouse TNF-α antibody (CNTO5048, Janssen Biotech, USA) every alternate day (300 ug/dose) for next 10 days, and 5 mice received sterile PBS (vehicle control). Mice were scored clinically and had ^{18}F-FDG PET scan on day 0, 28, 45 and 56. The maximum ^{18}F-FDG uptake (standardized uptake value normalized by body weight) was determined for each major joints to generate a comprehensive **PET score (PS).**

Results: All data represented as median with range. The median clinical score **(CS)** of the most affected limb in the vehicle treated and untreated gradually increased to 2 (range:1-2) at day 28 ($p<0.01$), 2 (range:2-3) at day 45 ($p<0.01$) and 3 (range:2-3) at day 56 ($p<0.01$) compared to day 0. The clinical observation was confirmed by histological scores **(HS).** Compared to day 0 (HS=0), the median HS on day 28 was 2 (range:1-3), day 45 was 4 (range:2-4) and day 56 was 4 (range:4-5). The PS on day 0 was 1.02 (range:0.85-1.05). PS increased to median values of 1.52 (range:1.14-2.01) on day 28 ($p<0.05$), 3.51 (range:1.23-4.76) on day 45 ($p<0.05$) and 1.76 (range:1.45-2.78) on day 56 ($p<0.05$). CNTO5048 treatment significantly reduced the median CS to 1 (range:0-2, $p<0.01$) and HS to 1 (range:1-2, $p<0.01$) compared to their respective pre-treatment levels (CS:2, HS:4). Similar to CS and HS, PS on day 56 was significantly low (median=0.97, range=0.62-2.12, $p<0.01$) compared to pre-treatment level (day 45) (median=3.51, range=1.23-4.76) (**Fig 1**).

Conclusion: Here we have validated in the CIA mouse model that ^{18}F-FDG PET is an *in vivo* preclinical drug screening tool for antiinflammatory therapies. The use of this imaging modality will allow longitudinal quantitative evaluation response in the same mouse.

Figure 1

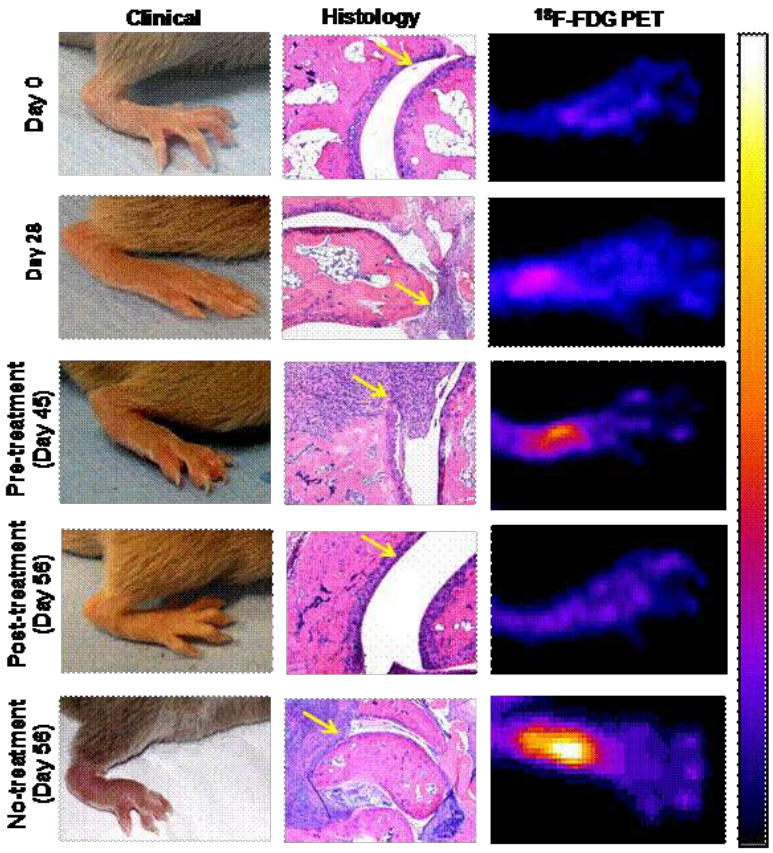

Figure 1: ^{18}F-FDG PET imaging, a quantative *in vivo* pre-clinical drug screening tool. 18F-FDG PET imaging effectively corelated with the both clinical and histopayhological (yellow arrows) therapuetic response of the anti-TNF-α (CNTO5048) antibody. The pseudo-color in PET indicates higher cellular metabolic activity, which resiprocates with the degree of inflammation.

Disclosure: S. P. Raychaudhuri, None; **S. K. Raychaudhuri**, None; **A. Mitra**, None; **A. Chaudhari**, None.

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Abstract Number: 1453

Treatment of BAFF Transgenic Mice with Anti-TNF: Monoclonals Are Associated with a Higher Risk of Lymphoma Than Etanercept

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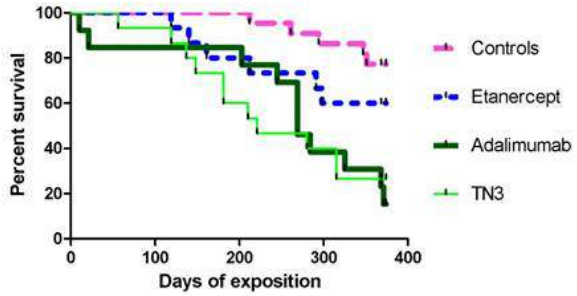
Background/Purpose: Patients suffering from rheumatoid arthritis (RA) have an increased risk of lymphoma and disease activity is the main risk factor. The impact of treatment, and notably of anti- (TNF), is unclear. They might decrease the risk of lymphoma by controlling activity. But they also might alter anti-tumor immunosurveillance. Large epidemiologic studies have demonstrated that anti-TNF were not associated with an increased risk of lymphoma. However, some data support that this risk might vary according to the type or to the dose of anti-TNF. The aim of our study was to assess if the risk of lymphoma might differ according to the type of anti-TNF, comparing monoclonals to soluble receptor. For that, we used BAFF transgenic (Tg) mice as a model of autoimmunity-associated lymphomas. They develop lupus and Sjögren and 3% of them spontaneously developed lymphoma at 12-18 months.

Methods: Six months aged BAFF-Tg mice were treated with anti-TNF for 12 months: etanercept (ETA) (n=15, 8 mg/kgx3/week), monoclonal anti-mouse TNF (TN3 19.12, n=15, 20 mg/kg/week), adalimumab(ADA) (n=13, 20 mg/kg/week) or controls (n=22). Sera were assessed monthly to monitor drug trough level and anti-drug antibodies, auto-antibodies (antinuclear factor and rheumatoid factor) and immunoglobulins (Ig). Crude mortality was compared among the different groups (log rank test). Histologic examination of kidneys and of lymphoid tissue (spleen and lymph nodes) was performed at the end of the treatment period. The Fisher's exact test was used to compare the incidence of of lymphoma among the groups.

Results: Adjunction of low dose of methotrexate during the 3 first days of treatment with biologics prevented immunization in the 3 groups of treatment for life. Mean level of ETA, TN3 and ADA were 7 µg/ml, 69 µg/ml and 105 µg/ml, respectively. The level of auto-antibodies and serum Ig did not significantly differ among the groups. However, crude mortality was significantly higher in mice treated with monoclonals compared to controls (p=0.0001 for ADA and p=0.0003 for TN3) but not for mice treated with ETA (figure). Incidence of lymphoma was higher in mice treated with monoclonals: 5/15 (33%) with TN3 (p=0.03 / controls), 4/13 (31%) with ADA (p=0.054 / controls), 0/15 with ETA and 1/22 (5%) in controls.

Conclusion: Higher mortality and increased risk of lymphoma were observed in BAFF Tg mice treated with monoclonal anti-TNF compared to etanercept. This result may be linked either to the different mechanism of action between the soluble receptor and the monoclonals or to a difference of trough level observed in the different groups and new experiments with lower dose of monoclonals are ongoing. This study demonstrates the negative impact of a prolonged anti-TNF treatment on the risk of lymphoma in the context of BAFF increase. Negative impact on NK cells might explain this finding (accompanying abstract submitted). _



_ Figure: Crude survival of BAFF Tg mice exposed to anti-TNF or controls

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Disclosure: G. Nocturne, None; **B. Ly**, None; **S. Boudaoud**, None; **R. seror**, None; **C. Nicco**, None; **C. Chereau**, None; **N. Kavian**, None; **F. Batteux**, None; **F. Mackay**, None; **F. Vincent**, None; **T. Lazure**, None; **S. Ferlicot**, None; **L. Stimmer**, None; **R. Krzysiek**, None; **S. Hacein-Bey**, None; **X. Mariette**, None.

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Abstract Number: 1454

Combination of the SYK Inhibitor, GS-9876, with a JAK Inhibitor Increases Efficacy in a Chronic Rat Model of Collagen-Induced Arthritis

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Background/Purpose: Spleen Tyrosine Kinase (SYK) mediates signaling in hematopoietic cells important for the initiation and progression of rheumatoid arthritis (RA). GS-9876 is an oral, selective SYK inhibitor being developed in RA. Janus kinase (JAK) inhibitors, have demonstrated clinical efficacy in RA and exert their biological activity principally by blockade of proinflammatory cytokine signaling. Here we demonstrate that 1) the single agent activity of GS-9876 is efficacious in a late stage rat model of collagen-induced arthritis (CIA); 2) the combination of GS-9876 with a JAK inhibitor increases efficacy in this model; and 3) the effects of targeting SYK or JAK as single agents can be functionally differentiated.

Methods: The in vivo efficacy of GS-9876 and a JAK inhibitor were tested alone or in combination in a therapeutic rat CIA model. Dosing was initiated at the peak of disease (day 17-20) and continued into the chronic phase until day 34; making the test more indicative of late treatment effects in the highly destructive macrophage-mediated phase, rather than in the acute, early neutrophil mediated phase of t this model. Efficacy evaluations were based on animal body weights, daily ankle caliper measurements, ankle diameter (expressed as area under the curve), terminal hind paw weights, and histopathology of ankles and knees. Anti-type II collagen antibody levels in terminal serum were analyzed, and PK was collected to evaluate the relationship to efficacy. Joint tissue RNA and protein were analyzed for transcriptional and protein modulation.

Results: GS-9876 demonstrated dose-responsive efficacy in the rat CIA model. GS-9876 or a JAK inhibitor alone showed efficacy on clinical and histopathology parameters. Administration of the SYK or JAK inhibitor in combination showed significantly alleviated increases in terminal paw weights, ankle swelling, and ankle histopathology scores than either agent alone. Body weight loss was also significantly reduced in the combination therapy group, and weight was increased compared to the monotherapy arms. Knee ED-1 immunopositive osteoclast counts were significantly reduced in the animals treated with GS-9876, but not a JAK inhibitor, highlighting functionally distinct effects of SYK and JAK inhibition. PK analysis of GS-9876 showed serum exposure levels similar to those achieved in human studies.

Conclusion: GS-9876 is a novel SYK inhibitor which displays in vivo therapeutic efficacy in a chronic rat CIA model. Combining GS-9876 with JAK inhibition significantly improved clinical and histopathology scores, and reduced body weight loss in this model, at exposures similar to those achieved in healthy human volunteers. These data suggest that simultaneously targeting SYK and JAK can provide an efficacious therapy for inflammatory diseases.

Disclosure: J. Di Paolo, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **D. Alonzo**, Gilead Sciences, 1; **C. Franci**, Gilead Sciences, 1; **T. Gentzler**, Gilead Sciences, 1; **L. Li**, Gilead, 3; **B. Murray**, Gilead Sciences, 1; **J. Zheng**, Gilead Sciences, 1.

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Abstract Number: 1455

Collagen-Induced Arthritis and Uveitis in Mice Lacking TNF Receptors

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Background/Purpose: Tumor necrosis factor (TNF) is a critical effector of the autoimmune inflammation in rheumatoid arthritis (RA) and uveitis. TNF inhibitors are preferably used in the treatment of these autoimmune diseases. However, TNF inhibitors are not always effective in treating RA. Moreover, previous reports showed that some TNF inhibitors may even accelerate comorbid uveitis in RA patients. Therefore, it is very important to know the precise role of TNF signaling in RA and uveitis. TNF signals are mediated by two structurally related, but functionally distinct, receptors, p55 (TNFR1) and p75 (TNFR2). It has already been shown that genetic disruption of the TNF p55 receptor in mice can reduce the severity of collagen-induced arthritis (CIA) and experimental autoimmune uveitis (EAU), murine models of autoimmune arthritis and uveitis, respectively. However, it remains unclear whether mice lacking p75 or mice lacking both p55 and p75 are also resistant to CIA and EAU. In this study, we aimed to dissect the role of TNF signaling through the TNF p55 or p75 receptor in the development of EAU and CIA.

Methods: The p55-/-, p75-/-, and p55-/-p75-/- mice on a C57BL/6 background were generated by successive backcrossing to C57BL/6 for ten generations. EAU was initiated by immunization with interphotoreceptor retinoid binding protein (IRBP) in complete Freund's adjuvant (CFA) and administration of pertussis toxin. CIA was induced by immunizing these mice with type II collagen in CFA twice. Clinical examination was performed and severities of EAU and CIA were assessed using clinical scoring system.

Results: In EAU, the severity in p55-/- mice was reduced compared to that in control WT mice, as described previously. In contrast, EAU in p75-/- mice was similar to, or slightly more severe than that in WT mice. Mice lacking both p55 and p75 did not develop a typical acute disease but exhibited delayed-onset uveitis. In CIA, p55-/- mice were protected from arthritis. In contrast, the severity of CIA in p75-/- mice tended to be increased compared to that in control WT mice. Mice lacking both p55 and p75 developed less severe arthritis than WT mice.

Conclusion: Unlike p55-/- mice, p75-/- mice retained susceptibility to CIA and EAU. TNF signaling through p75 might contribute to limit inflammation in CIA and EAU. Antagonists selective to p55 may be advantageous for the treatment of autoimmune arthritis and uveitis.

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Abstract Number: 1456

Identification of a Unique Population of B220hi B-Cells in Inflamed Lymph Nodes (Bin) As a Potential Biomarker of Arthritic Progression in the Tumor Necrosis Factor Transgenic Mouse Model of Rheumatoid Arthritis

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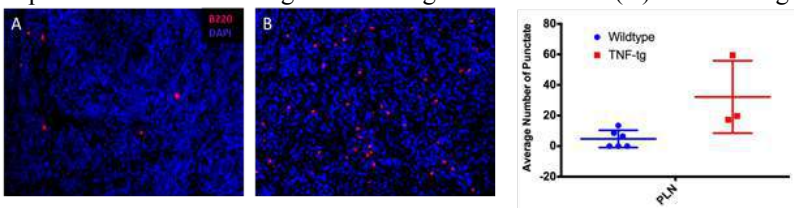
Background/Purpose: Using the tumor necrosis factor transgenic (TNF-Tg) mouse model of rheumatoid arthritis (RA), we have shown that during progression of knee synovitis, popliteal lymph nodes (PLNs) initially expand and then collapse concomitant with arthritic flare in the ipsilateral knee. In these collapsed PLNs, there is an abundance of $B220^{+}/CD23^{+}/CD21^{hi}$ B cells in inflamed lymph nodes (Bin) clogging the lymph node sinuses. We have also recently shown that TNF-Tg mice have evidence of interstitial lung disease (ILD), with large numbers of B cells. To determine the relationship between these B cells and Bin, we performed histology to phenotype B-cells in PLN versus mediastinal lymph nodes (MLN) from WT and TNF-Tg mice.

Methods: MLNs and PLNs (n=3) were harvested from 12-month old male TNF-Tg mice (3647 line in C57B6 background) with established arthritis and ILD, and their WT littermates (MLN n=3, PLN n=6). Tissues were processed for immunohistochemistry with antibodies against B220, a pan B-cell marker, and DAPI and imaged at 10 and 20x magnifications. Fluorescent images were quantified by manually counting the number of high intensity areas in three 10x fields of view on each slide. Two slides per tissue type per animal were used, with six total images averaged for one count per tissue type per animal.

Results: PLNs from both WT and TNF-Tg animals showed a distinct pattern of increased high intensity staining compared to MLNs (4.74 vs 0 for WT, $p<0.05$ and 32.16 vs 0.36, $p<0.05$ for TNF-Tg). Furthermore, TNF-Tg PLNs showed increased high intensity staining compared to WT PLNs (32.16 vs 4.74, $p<0.05$) (Fig. 1).

Conclusion: This is the first description of a $B220^{hi}$ population in PLNs of aged mice with established arthritis and ILD. Interestingly, only PLNs display an increased $B220^{hi}$ population compared to MLNs, which drain the inflamed lung. The discordant expression in MLN versus PLN tissue suggests a continuous localized response of B cells in lymph nodes draining synovial tissue. Further specific characterization of this population at earlier timepoints during arthritis development is ongoing in order to determine if expression is altered in early disease, and if B220 expression pattern could help differentiate early inflammation from established disease. Figure 1: Representative $B220^{hi}$ images at 20x magnification of WT (A) and TNF-Tg (B) PLN



Disclosure: M. Forney, None; **R. Bell**, None; **E. Schwarz**, None; **H. Rahimi**, None.

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Abstract Number: 1457

Early Onset Morbidity and Mortality in Female Tumor Necrosis Factor Transgenic Mice with Inflammatory-Erosive Arthritis and Interstitial Lung Disease

Richard Bell[1], Emily Wu[2], Ronald Wood[3], Joe Chakkalakal[2], Javier Rangel-Moreno[4], Maria de la Luz Garcia-Hernandez[2], Christopher T. Ritchlin[5], Edward Schwarz[6] and Homaira Rahimi[7], [1]Center for Musculoskelatal Research, University of Rochester, Rochester, NY, [2]University of Rochaester, Rochester, NY, [3]University of Rochester, Rochester, NY, [4]Allergy, Immunology & Rheumatology, University of Rochester Medical Center, Rochester, NY, [5]Allergy Immunology & Rheumatology, University of Rochester Medical Center, Rochester, NY, [6]Orthopedeatrics, University of Rochester, Rochester, NY, [7]Rheumatology, University of Rochester/Golisano Children's Hosp, Rochester, NY

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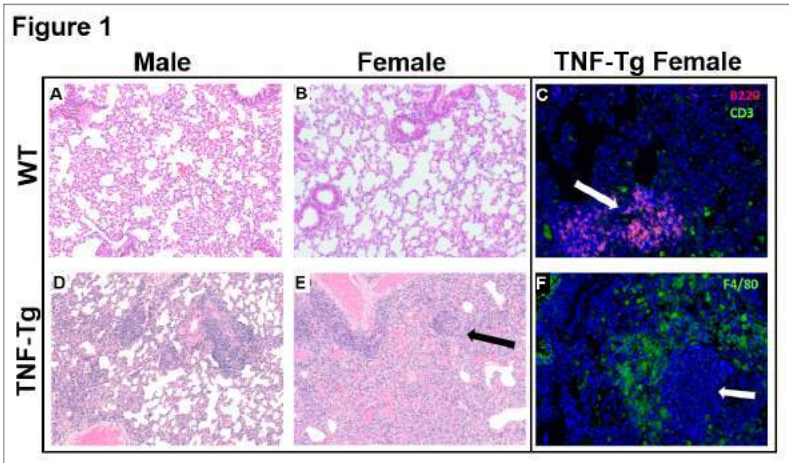
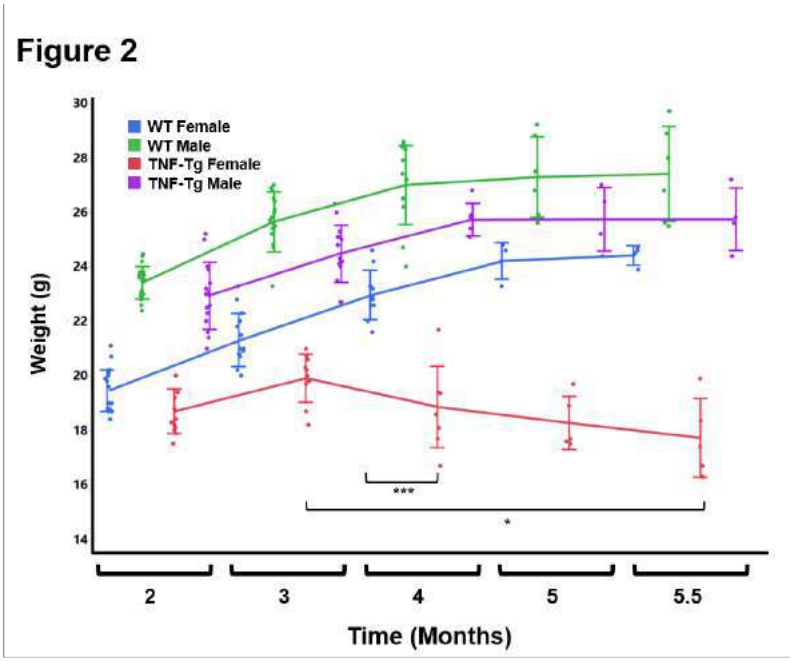


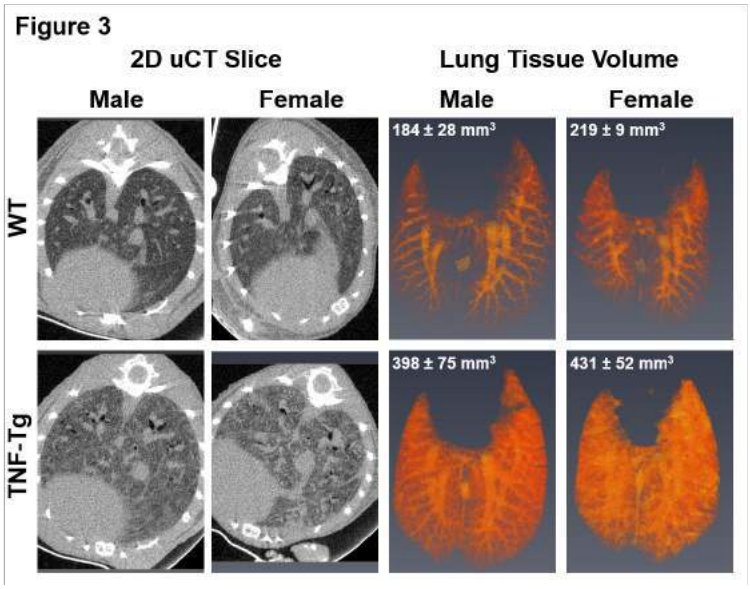
Background/Purpose: Although exacerbated morbidity and mortality in rheumatoid arthritis (RA) is frequently seen in women, the etiology of this sexual dimorphism remains unclear. Previously, we showed that the TNF-Tg mouse model of RA displays similar unexplored sex differences in the severity of inflammatory-erosive arthritis, interstitial lung disease (ILD) and early mortality from cardiopulmonary disease (female median life span = 165 vs. 226 days for males). Thus, the goal of this study was to elucidate the mechanisms that underlie these sex differences.

Methods: WT and TNF-Tg male and female mice in a C57BL/6 background (n = 3-12) were evaluated for weight and grip strength at 2, 3, 4, 5 and 5.5 months. At 5.5 months mice underwent in vivo micro-CT of the lung and a novel analysis technique was used to measure tissue (cells, fluid and ECM) volume within the lung. Mice were euthanized at 5.5 months for lung immunohistochemistry (CD3, B220 and F4/80), or flow cytometry (CD3, CD19, CD11b and CD11c).

Results: ILD lesions contained B-cells, T-cells, and macrophages, and showed signs of pulmonary arterial hypertension (Fig. 1). At 4 months, female TNF-Tg mice were significantly smaller vs. WT littermates (18.9 ± 1.5g vs. 23.0 ± 0.9g, $p<0.01$); and TNF-Tg females displayed significant weight loss from 3 to 5.5 months (19.9 ± 0.9g vs 17.7 ± 1.4g, $p<0.05$; Fig. 2). Female TNF-Tg grip strength was also significantly decreased starting at 2 months vs. WT females (1.9 ± 0.4N vs 2.2 ± 0.2N, $p<0.01$), while male WT and TNF-Tg mice did not differ until 3 months (2.0 ± 0.3N vs 2.7 ± 0.3N, $p<0.01$). Both female and male TNF-Tg mice had significantly greater tissue volume via µCT vs. WT animals (431 ± 52 vs 398 ± 75 vs 219 ± 9 vs 184 ± 28 mm^3; $p<0.05$; Fig. 3). Female and male TNF-Tg lungs also had significantly increased numbers of immune cells, in particular CD11b+/CD11c+ cells (105.5 ± 7.5, 345.0 ± 263.1 vs 8.6 ± 3.5, 4.5 ± 2.4 cells/lung x 10^3; $p<0.05$).



Conclusion: Here we describe a novel model of RA-associated ILD that recapitulates the sexual dimorphism known to occur in patients. While further work is necessary to elucidate the interactions of the comorbidities and their contributing factors, the significant weight loss observed in females may account for their early onset of arthritis and mortality.



Disclosure: R. Bell, None; **E. Wu**, None; **R. Wood**, None; **J. Chakkalakal**, None; **J. Rangel-Moreno**, None; **M. D. L. L. Garcia-Hernandez**, None; **C. T. Ritchlin**, Amgen, Janssen Pharmaceutica Product, L.P., and UCB, 2,AbbVie, Amgen, Janssen Pharmaceutica Product, L.P., Regeneron, and UCB, 5; **E. Schwarz**, None; **H. Rahimi**, None.

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Abstract Number: 1458

Intraadrenal Dendritic Cells Inhibit Corticosterone Response during Collagen-Induced Arthritis – a Role for IL-1β and CXC Chemokines?

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Background/Purpose: In rheumatoid arthritis (RA) and collagen-induced arthritis (CIA) the phenomenon of a relative insufficiency of adrenal glands to produce an adequate amount of anti-inflammatory glucocorticoids in later stages of the disease is well known (Spiess et al 2014, Wolff et al. 2015). At the same time, the presence and migration of macrophages and dendritic cells (DCs) in and into endocrine organs like the pituitary gland and the adrenal glands has been described (Glennon et al. 2015, Sato 1998, Engstrom et al. 2008). We hypothesized that resident and/or invading immune cells like DCs contribute to the inadequate secretion of endogenous glucocorticoids from adrenocortical cells during arthritis. The aim of this study is to elucidate first possible paracrine mechanisms between local DCs and adrenocortical cells and secondly to manipulate these pathways in order to prevent relative adrenocortical insufficiency in arthritis.

Methods: Cells from whole adrenal glands were harvested and cultured while DCs were differentiated from bone marrow, which was collected from healthy control and arthritic DA rats. Cytokine levels in supernatants from DCs and adrenal gland cells were analyzed by proteome profiler and ELISA. Corticosterone response upon stimulation with ACTH in a co-culture system of adrenal gland cells from control rats and DCs generated from control or arthritic rats was quantified with ELISA.

Results: Analysis of cytokine protein expression revealed a similar profile of the C-X-C ligand chemokines CINC-1, -2, -3 (Cytokine-induced neutrophil chemoattractant), LIX (LPS-induced CXC chemokine) and of the cytokine IL-1β in supernatants from DCs and adrenal gland cells. DCs generated from rats with CIA expressed significantly higher amounts of IL-1β, CINC-1, -2, -3, and LIX (all $p<0.001$) compared to DCs from control animals. Expression of IL-1β ($p<0.001$) and CINC-2 ($p=0.034$) in supernatants from arthritic adrenal gland cells was significantly higher than in supernatants from control cells. Co-culture experiments revealed an inhibitory effect of DCs from control and CIA rats on the corticosterone response of adrenal gland cells upon stimulation with ATCH.

Conclusion: DCs are present in the adrenal gland and seem to inhibit corticosterone production physiologically and during arthritis, possibly via expression of IL-1β and the CXC chemokines CINC-1,2,3 and LIX. Specific targeting of these cells and these chemokines might prevent progression of arthritis by inhibiting the relative adrenal gland insufficiency and, hence, could be a future therapy.

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Abstract Number: 1459

Enhanced Efficacy of Early Vs. Late IL-1β Antagonism in Murine Arthritis Mediated By Deficiency of the IL-1 Receptor Antagonist IL-1ra

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Background/Purpose: IL-1 blockade is highly effective for systemic juvenile idiopathic arthritis (sJIA), but clinical observations raise the possibility that initiation of treatment in a "window of opportunity" before chronic arthritis develops may be more effective than in latyers disease. We have hypothesized that sJIA is a biphasic process in which an initial IL-1β-driven systemic phase gives rise to IL-17-driven chronic inflammatory arthritis. We sought to test this hypothesis in the IL-1ra$^{-/-}$model, a spontaneous T cell-mediated murine arthritis dependent upon both IL-1β and IL-17.

Methods: IL-1ra$^{-/-}$mice were treated with anti-mIL-1β or isotype-matched IgG (5mg/kg i.p. 2 times per week) for 2 weeks, beginning either 3 days after arthritis onset (early treatment) or 3 weeks after arthritis treatment (late treatment). Arthritis score (0-3/per paw, 0-12 total) and ankle and wrist thickening measured by caliper were followed for 54 days after arthritis onset. Synovial tissue was harvested at day 54 for flow cytometry to characterize lymphocyte surface phenotype and cytokine production.

Results: Clinical indices were reduced in both treatment groups compared with isotype control, without a difference between groups. However, joint thickening was reduced in early compared with late treatment, although worsening was again noted after anti-IL-1β was discontinued. Histological injury was minimized in the early treatment group, suggesting that early IL-1β antagonism was more efficient. In support of this possibility, early anti-IL-1β abrogated accumulation of lymphocytes expressing IFN-γ and IL-17A, while treatment of established disease resulted only in modest reduction of IL-17A-expressing cells. Consistent with published findings, γδT cells represented on average slightly more than half of all synovial CD3^{+}cells. The reduction in IL-17-expressing lymphocytes paralleled the lower abundance of this population after either early or late treatment, with an intriguing trend toward greater reduction in γδT cells in the early treatment group, corresponding to the reduction in synovial lymphocytes expressing IL-17.

Conclusion: In murine IL-1ra$^{-/-}$ synovitis, early IL-1β blockade more efficiently reduces tissue injury and lymphocyte accumulation than late blockade, although both are effective. Efficacy correlated with a reduction in IL-17-producting cells, and in particular with fewer IL-17-producing gdT cells. These findings support the hypothesis that early IL-1β blockade could represent an effective strategy to modulate the development of arthritogenic T cells in IL-1-driven arthritis, a result that may inform the understanding and treatment of sJIA.

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Abstract Number: 1460

Suppression of Cholesterol Levels and Impairment in Cholesterol Efflux By HDL in K/BxN Mice Is Associated with a Specific Cytokine/Chemokine Profile

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Background/Purpose: Better understanding of lipid metabolism in active rheumatoid arthritis (RA) is needed to understand the cholesterol changes associated with active disease, as well as the increases in cholesterol which occur with common RA treatments involving specific cytokine and chemokine pathways. In the current work we used both short and long term K/BxN mouse models of RA to evaluate the relationship between active RA, lipid measures (cholesterol levels/HDL efflux and anti-oxidant function) and serum cytokine/chemokine levels.

Methods: 29 K/BxN mice were generated from cross of male KRN mice with NOD female mice expressing the MHC class II

molecule A^{g7} and arthritis was assessed regularly until sacrifice/serum collection at 21 weeks. 15/29 mice received an atherogenic diet at 11 weeks until sacrifice. 18 *C57BL/6* mice were injected intraperitoneally with either K/BxN serum (from 8 wk stock K/BxN mice) to induce inflammatory arthritis (n=9), or *C57BL/6* serum as controls (n=9), and sacrifice/serum collection occurred at 2 weeks. Serum cytokine and chemokine levels were assessed using Luminex-based 20-plex assays. HDL's cholesterol efflux and anti-oxidant functions were assessed as previously (*ARD* 2012; 71: 1157) and paraoxonase 1 (PON1) activity was assessed using both paraoxon and dihydrocumarin as substrates (*A&R* 2013; 65: 2765). Total and HDL cholesterol (HDL-C) were assessed by standard assays.

Results: At 21 weeks, male mice (n=17) had significantly worse arthritis activity compared to female mice (n=12) which was associated with significantly higher levels of GM-CSF, IFN-γ, IL-1β, IL-6, IL-12, and FGF-basic, and significantly lower levels of HDL and total cholesterol and PON1 activity (Table 1). Impairment in the cholesterol efflux capacity of HDL was associated with significantly higher levels of GM-CSF, IFN-γ, IL-17, and FGF-basic which also correlated significantly with suppression of cholesterol levels and impairment in PON1 activity (Table 2). An atherogenic diet was not associated with significant changes in lipid assessments or cytokine/chemokine panels compared to chow diet. Inflammatory arthritis of 2 weeks duration was not associated with a similar dyslipidemia or cytokine/chemokine changes.

Conclusion: Increases in GM-CSF, IFN-γ, IL-1β, and FGF-basic in K/BxN mice with inflammatory arthritis of 21 weeks duration are associated with impairment in the cholesterol efflux capacity of HDL and suppression of PON 1 activity, total and HDL-C levels. Further investigation of these pathways including the effects on accelerated atherosclerosis in RA is warranted. **Table 1. Comparison of Female and Male K/BxN Mice at 21 weeks**

	Female K/BxN Mice (n=12) 21 weeks	**Male K/BxN Mice (n=17) 21 weeks**
Hind limb Measurement (mm)	386 ± 15	408 ± 17*
Clinical Arthritis Score	7.3 ± 1.4	10.5 ± 1.5*
HDL Cholesterol (mg/dL)	64 ± 11	44 ± 23*
Total Cholesterol (mg/dL)	98 ± 17	65 ± 32*
Paraoxonase 1 Activity (nmol/min/ml)	112 ± 24	69 ± 27*
Lactonase Activity (U/ml)	22.1 ± 1.3	18.4 ± 3.6*
HDL-C Efflux Capacity (%)	12.0 ± 2.0	13.1 ± 3.8
HDL Anti-oxidant Capacity (Fluorescence units)	403 ± 68	509 ± 248
Cytokines		
GM-CSF(pg/ml)	43 ± 23	79 ± 60*
IFN-γ (pg/ml)	14.9 ± 12.7	19.2 ± 18.8*
Il-1α (pg/ml)	17 ± 24	49 ± 68
IL-1β (pg/ml)	2.6 ± 3.4	6.1 ± 4.5*
IL-2 (pg/ml)	30 ± 57	61 ± 131
IL-6 (pg/ml)	11.0 ± 24.0	13.3 ± 29.7*
IL-12 (p40/p70) (pg/ml)	4.6 ± 3.8	23.2 ± 48.3*
IL-13 (pg/ml)	24.8 ± 16.9	224.3 ± 325.0
IL-17 (pg/ml)	0.1 ± 0.1	2.7 ± 7.4
Chemokines		
KC (pg/ml)	81.3 ± 156.2	114.2 ± 261.9
MCP-1 (pg/ml)	9.8 ± 8.1	12.9 ± 12.0
Growth Factors		
FGF-basic (pg/ml)	18.7 ± 15.4	85.3 ± 123.0*

*P<0.05 for comparison. IL-4, IL-5, IL-10, TNF-α, IP-10, MIG, MIP-1α, and VEGF assessed in the multiplex panel but values too low in majority of specimens to allow reliable analysis. **Table 2. Correlations of Arthritis and Lipid Assessments with Chemokine and Cytokine Levels**

	Hind limb Score	HDL-C	TC	PON1	lactonase	% cholesterol efflux	HDL anti-oxidant capacity
Cytokines							
GM-CSF	0.64*	-0.44*	-0.50*	-0.69*	-0.69*	-0.44*	0.33
IFN-γ	0.69*	-0.44*	-0.42*	-0.55*	-0.54*	-0.45*	0.21
Il-1α	0.01	-0.24	-0.31	-0.01	0.08	-0.05	0.26
IL-1β	0.71*	-0.58*	-0.58*	-0.62*	-0.59*	-0.47*	0.35
IL-2	0.45*	-0.59*	-0.60*	-0.24	-0.35	-0.34	0.35
IL-6	0.64	-0.35	-0.43*	-0.52*	-0.45*	-0.23	0.01
IL-12 (p40/p70)	0.61*	-0.71*	-0.76*	-0.58*	-0.48*	-0.14	0.35
IL-13	-0.13	-0.10	-0.10	0.12	0.25	-0.05	0.07
IL-17	0.60*	-0.50*	-0.46*	-0.43*	-0.65*	-0.39*	0.28
Chemokines							
KC	0.04	-0.40*	-0.41*	-0.07	-0.03	-0.36	0.34
MCP-1	0.30	-0.57*	-0.60*	-0.23	-0.17	-0.10	0.38*
Growth Factors							
FGF-basic	0.57*	-0.51*	-0.52*	-0.37*	-0.39*	-0.52*	0.30

*p<0.05 for test of Spearman Correlation Coefficient. IL-4, IL-5, IL-10, TNF-α, IP-10, MIG, MIP-1α, and VEGF assessed in the multiplex panel but values too low in majority of specimens to allow reliable analysis.

Disclosure: C. Charles-Schoeman, None; **A. Shahbazian**, None; **Y. Y. Lee**, None; **B. Oganesian**, None; **V. Grijalva**, None; **A. Garcia Heredia**, None; **S. T. Reddy**, None.

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Abstract Number: 1461

Modification of Proteins with Malondialdehyde-Acetaldehyde and Citrulline Elicit Antibody Responses in DBA/1J Mice

Peter M. Maloley[1], Michael J. Duryee[2], Carlos D. Hunter[2], James R. O'Dell[3], Daniel R. Anderson[1], Ted R Mikuls[4], Geoffrey M. Thiele[1] and Lynell W. Klassen[3], [1]University of Nebraska Medical Center, Omaha, NE, [2]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [4]Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Previous studies have shown that proteins modified with malondialdehyde-acetaldehyde (MAA) and/or citrulline (CIT) co-localize in rheumatoid arthritis (RA) synovial tissues, are pro-inflammatory, and promote robust antibody responses that correlate with disease severity in RA. The interaction of MAA and CIT modifications on proteins with respect to immune responses is not currently known. Thus, the purpose of this study was to first examine the feasibility of co-modifying protein with both MAA and CIT and secondly to evaluate the impact of these modifications on antibody responses.

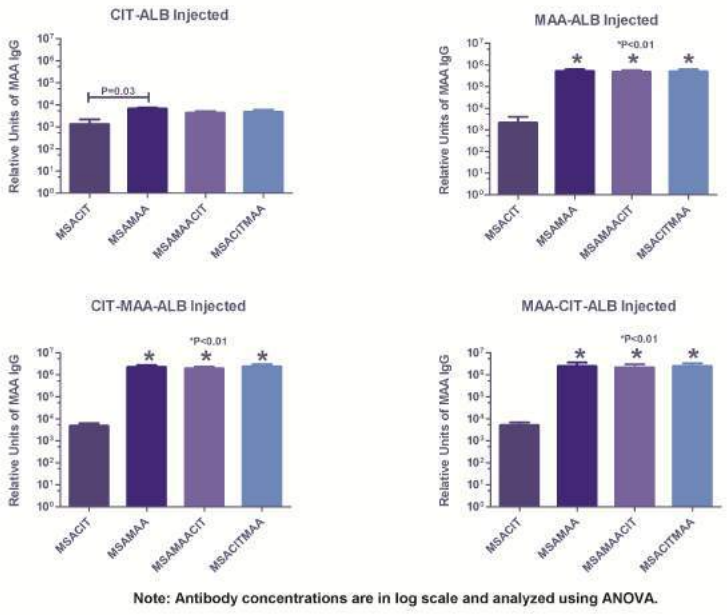
Methods: Human serum albumin (ALB) was modified with MAA (MAA-ALB), CIT (CIT-ALB), MAA then CIT (MAA-CIT-ALB), or CIT then MAA (CIT-MAA-ALB) in order to produce the unique antigens. Samples were analyzed for MAA adduction using fluorescence and CIT by Western blot. Protein concentrations were determined and separate groups of mice (n=10 per antigen) were immunized with 25 µg of MAA-ALB, CIT-ALB, MAA-CIT-ALB, or CIT-MAA-ALB weekly for 5 weeks. At week 6, serum was

tested for antibody reactivity to these modifications using ELISA with mouse serum albumin (MSA) used in place of ALB. This was done to eliminate background reactivity and to assess the reactivity specific to the MAA or CIT epitopes rather than ALB. Data is expressed in arbitrary units relative to a mouse IgG standard curve, and analyzed by one-way ANOVA.

Results: MAA levels (by fluorescence) and citrullination (by Western Blot) showed no differences with respect to the amount of modification between the different antigens, and all preparations remained soluble. Immunization with CIT-ALB produced a significant (P=0.03) antibody response to the MAA epitope with very little antibody to the CIT epitope. MAA-ALB, CIT-MAA-ALB, and MAA-CIT-ALB immunization significantly (P<0.01) increased the antibody responses to MSA-MAA, MSA-MAA-CIT, and MSA-CIT-MAA compared to immunization with CIT-ALB. Notably, immunization with CIT-MAA-ALB or MAA-CIT-ALB increased the antibody concentrations 4-fold over MAA immunization alone to all antigens except MSA-CIT.

Conclusion: Modification of protein with MAA in combination with CIT appears to form a stable protein adduct. The combination of these two modifications elicits a robust antibody response in mice to MAA or the MAA-CIT antigen regardless of which modification was performed first, but was highly dependent on the presence of the MAA modification to drive the immune response. These data provide a potential mechanism by which MAA-modification and citrullination of self-proteins conspire to promote the initiation or progression of RA. Future studies evaluating the T-cell response are under way to understand this unique immune response.

Figure 1.



Note: Antibody concentrations are in log scale and analyzed using ANOVA.

Disclosure: P. M. Maloley, None; **M. J. Duryee**, None; **C. D. Hunter**, None; **J. R. O'Dell**, Eli Lilly and Company, Medac, Coherus, BMS, GSK, 5; **D. R. Anderson**, None; **T. R. Mikuls**, None; **G. M. Thiele**, None; **L. W. Klassen**, None.

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Abstract Number: 1462

Magnesium Is a New Mediator Arthritis Severity and Joint Damage

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Animal Models - Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Given the effects of magnesium supplementation in suppressing components of the innate immunity in short-term studies, we examined the effect of dietary magnesium modifications in arthritis severity, a chronic model of autoimmune disease.

Methods: DBA1/J mice were placed on one of two short-term diets before (22-day) the induction of collagen-induced arthritis (CIA) or after disease onset (9-days): low-magnesium diet or normal diet. The diets were then discontinued and converted into a normal diet. CIA activity and arthritis severity was scored for 50 days. Spleens were used for qPCR and FACS, and synovial tissues and cells lines for qPCR.

Results: Mice on the low magnesium diets were significantly protected and had a >70% lower mean arthritis severity scores in the preventive arm. The group that started the low magnesium diet after the onset of disease also achieved a 50% reduction on their mean severity. The disease protective or ameliorating effects of the low magnesium diet persisted beyond the duration of the diet suggesting a permanent effect on a critical pathogenic pathway. The low magnesium diet mice preserved a normal joint histology without erosive changes. Mice on the low-magnesium diet had significantly reduced synovial tissue expression of IL-6, IL-17, CXCL10, RORA and RORC (genes required or implicated in the development of Th17 T cells), as well as reduced levels of MMP-2 and MMP-3, which are two key mediators of joint damage. Low magnesium concentrations also reduced synovial fibroblast expression of TNFa and IL-6. Spleens from low magnesium diet mice had reduced levels of Th17 T cells and increased numbers of FoxP3+ Treg cells and increased number of IL-10+ CD4+ T cells. *In vitro* studies demonstrated that low magnesium concentrations (0.1mM and 0.4mM) did not directly affect the differentiation of mouse naïve CD4+ T cells into Th17 T cells, nor affected the amount of IL-17 produced by these cells, suggesting an indirect effect mediated by another cell type.

Conclusion: This study revealed a novel role for magnesium in the regulation of autoimmune arthritis and opens new possibilities for the treatment of autoimmune diseases such as RA and psoriatic arthritis with short courses of dietary or drug-induced modulations of magnesium levels. We also describe a new effect of low magnesium in suppressing Th17-related genes and MMPs.

Disclosure: T. Laragione, None; **N. Azizgolshani**, None; **C. Harris**, None; **E. Gao**, None; **P. Gulko**, None.

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Abstract Number: 1463

Helminths Based Tuftsin-Phosphorylcholine Prevent Development of Mouse Collagen Induced Arthritis, While Maintaining Normal Gut Microbiota

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: , Rheumatoid arthritis (RA) is a chronic auto inflammation of the joints, with a prevalence of about 1% in Western population. Treatment with lives helminths or helminths' secreted molecules in different autoimmune diseases. Recently, the critical involvement of the microbiome in the pathogenesis of autoimmune diseases has gained appreciation. In RA, there is a shift in microbial coupled with an inflammatory response which includes an alteration in the function of anti-inflammatory regulatory T cells (Treg) and susceptibility towards autoimmunity.

The aim of the current study addresses the correlation between TPC therapeutic efficacy and the microbiome composition in a mouse model of collagen-induced arthritis (CIA).

Methods: , Arthritis was induced in DBA mice by immunization with collagen type II. The mice were treated with TPC or PBS and compared to healthy mice. Stools from the mice were collected every 3 days. DNA was extracted then sequenced using Illumina Miseq

platform. Data analysis was performed using QIIME.

Results: Significantly lower arthritis score was illustrated in TPC treated mice in comparison to mice which received vehicle. We showed that the microbial composition changes with treatment and correlated to disease severity. At the order level, *Enterobacteriales* were significantly more abundant in the healthy mice while *Clostridiales* and *Deferribacterales* were more abundant in the PBS-CIA mice. CIA mice treated with TPC maintained a "healthy" microbiota, which was similar to mice in which RA was not induced.

Conclusion: Our results provide support for a microbial link in CIA and show the importance of the microbiome in the success of the treatment.

Disclosure: Y. Shoenfeld, None; **H. Mizrahi**, None; **T. Bashi**, None; **H. Mor**, None; **M. Blank**, None; **O. Koren**, None.

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Abstract Number: 1464

Utility of Relative Cardiovascular Risk Score Scales and Vascular Age Predictors in Patients with Reumathoid Arthritis UNDER 50 YEARS of Age

Andrea Zacarias[1], Carmen Gomez Vaquero[2], Francisco Javier Narváez[3], Joan Miquel Nolla[4], Miguel Angel González-Gay[5], Carlos González-Juanatey[6] and Javier Llorca[7], [1]Hospital Universitari de Bellvitge, Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario de Bellvitge, Barcelona, Spain, [3]Rheumatology, Hospital Universitario de Bellvitge-IDIBELL, L'Hospitalet de Llobregat, Barcelona, Spain, [4]Rheumatology, Bellvitge University Hospital, Barcelona, Spain, [5]Rheumatology, Hospital Universitario Marqués de Valdecilla, IDIVAL, University of Cantabria, Santander, Spain, [6]Cardiology Division, Hospital Xeral-Calde, Lugo, Spain, [7]Department of Epidemiology and Computational Biology, School of Medicine, University of Cantabria, and CIBER Epidemiología y Salud Pública (CIBERESP), IDIVAL, Santander, Spain

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose:

Rheumatoid Arthritis (RA) is associated with a greater cardiovascular mortality than the general population of the same age and gender. Cardiovascular events prediction scales, due to its significant dependence on age, underestimate absolute cardiovascular risk (CVR) in young people. Two methods exist to address this problem: a) Cardiovascular Relative Risk, which estimates the increased risk when compared to people of the same age without CVRF. B) Vascular age, defined as the lower age with the same absolute CVR but with no CVRF. OBJECTIVE: To evaluate the utility of the relative cardiovascular risk score scales and the vascular age predictors in patients with RA, younger than 50 years of age.

Methods: Transversal prospective study developed at the Rheumatology Services in two Spanish academic hospitals. Only patients under 50 years of age who fulfilled the EULAR/ACR 2010 criteria for RA were included. They were selected consecutively when they came on regular follow-up. We registered to calculate SCORE, REGICOR, Relative Cardiovascular Risk and Vascular Age (age, gender, tobacco habits, systolic blood pressure, total serum cholesterol concentration and HDL and diabetes Mellitus). According to the EULAR 2011 recommendations, a multiplying factor of 1,5 was applied to SCORE, REGICOR and Relative Cardiovascular Risk in patients who fitted in at least two of the following criteria: a) Duration of RA > 10 years, b) positive RF or CCP , c) Presence of extra-articular manifestations.

Results: 140 patients with RA under 50 years of age were included [120 (86%) women] with an mean age of 40 ± 7 years. 64% of patients had RF+ and 56% CCP+. Regarding to EULAR multiplying factors, 30% had RA duration > 10 years, 71% had CCP or RF+, 11% had extra-articular manifestations, and 26% had 2 or more factors. None of the patients had has a previous history of cardiovascular events. The modified (after the application of the multiplying fact) mean SCORE was 1,03 ± 0,52 and modified REGICOR 1,81 ± 1,37. Mean Cardiovascular relative risk was 2,05 ± 1,33 between 2x and 10x. 54% of the patients had a relative cardiovascular risk superior to 1, and 47% had cardiovascular relative risk between 2 and 3 times higher. Mean vascular Age's was of

44 ± 10 years, 4 years more than biological age. 41% of patients, vascular age was greater than biological age, from 3 to 20 years older. Relative Cardiovascular risk identifies more patients with CVR than Vascular Age. Patients with increased relative cardiovascular risk were older (41 ± 6 vs 38 ± 9 years; p < 0,01) and had been diagnosed with RA for over10 years (40% vs 7%, p < 0,001).

Conclusion: In young patients with Rheumatoid Arthritis, the estimates of Relative Cardiovascular Risk and the assessment of vascular age allow us to identify patients with an increased cardiovascular risk, who may be overlooked by SCORE event prediction charts.

Disclosure: A. Zacarias, None; **C. Gomez Vaquero**, None; **F. J. Narváez**, None; **J. M. Nolla**, None; **M. A. González-Gay**, None; **C. González-Juanatey**, None; **J. Llorca**, None.

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Abstract Number: 1465

Utility of Relative Cardiovascular Risk Score Scales in Patients UNDER the Age of 50 and Its Association with the Presence of Carotid Atherosclerosis in the Ultrasound

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Background/Purpose:

Rheumatoid Arthritis (RA) is associated with a greater cardiovascular mortality than the general population of the same age and gender. Cardiovascular events prediction scales, due to its significant dependence on age, underestimate the absolute cardiovascular risk (CVR) in young people. Two methods exist to address this problem: a) Cardiovascular Relative Risk, which estimates the increased risk when compared to people of the same age without CVRF. B) Vascular age, defined as the lower age with the same absolute CVR but with no CVRF. **Objective**: to evaluate the presence of subclinical carotid atherosclerosis and the utility of the carotid ultrasound (US) in patients with AR under the age of 50 and compare it with relative CVR scores.

Methods: Transversal prospective study. Patients under 50 years of age who fulfilled the EULAR/ACR 2010 criteria for RA were included. They were selected consecutively when they came on regular follow-up. We registered to calculate SCORE, REGICOR, Relative Cardiovascular Risk and Vascular Age (age, gender, tobacco habits, systolic blood pressure, total serum cholesterol concentration and HDL and diabetes Mellitus) and history of previous CVR event. According to the EULAR 2011 recommendations, a multiplying factor of 1,5 was applied to SCORE, REGICOR and Relative Cardiovascular Risk in patients who fitted in at least two of the following criteria: a) Duration of RA > 10 years, b) positive RF or CCP , c) Presence of extra-articular manifestations. A carotid ultrasound was performed; Intimal medial thickness (IMT) was measured and the presence of atheromatous plaques was assessed. Database and analyzed using SPPSS-Windows 15. Sensitivity and specificity, positive and negative predictive values were calculated.

Results: 83 AR patients under the age of 50 years old were included (71 (85,5%) women) with a mean age of 39 ± 8 years. 61% had RF+ and 50% PCC+. 34% had bone erosion on X-ray and 3.6% presented rheumatoid nodules. About the CVRF: 45% were active smokers; 22% had high blood pressure; 8% were diabetics; 25 had a high LDL levels and 4% presented with hypertriglyceridemia.

Regarding to EULAR multiplying factors, 30% had RA duration > 10 years, 69% had CCP or RF+, 13% had extra-articular manifestations, and 27% had 2 or more factors. The prevalence of subclinical carotid pathology was 9.6%. The US results demonstrated that 9.6% (8 patients) had atheromatous plaque (6% unilateral and 4% bilateral). An IMT ≥0, 9 were observed in 1% (1 patient). None of the patients had had a previous history of cardiovascular events. Sensitivity and positive predictive value to identified carotid atheromatous plaques were very low for the modified SCORE and REGICOR, with the exception of the modified RCR, which presented a sensitivity of 87%. Superior specificity was observed with the modified SCORE and REGICOR than with the modified RCR. The negative predictive value was similar in the 3 scales (>90%).

Conclusion: The prevalence of subclinical atherosclerosis in RA patients under 50 years old is not small (10%). The RCR is the scale with more sensitivity and with an important negative predictive value that allow us to recognize and select the patients for a carotid ultrasound.

Disclosure: A. Zacarias, None; **C. Gomez Vaquero**, None; **F. J. Narváez**, None; **M. A. González-Gay**, None; **A. Corrales**, None; **C. González-Juanatey**, None; **J. Llorca**, None; **J. M. Nolla**, None.

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Abstract Number: 1466

Cardiovascular Risk Assessment in Persons with Rheumatoid Arthritis: A Correlative Study of Non-Invasive Arterial Health Testing with the Inflammatory Burden of Disease

Erin Scanlon[1], Rekha Mankad[2], Cynthia S. Crowson[3], Iftikhar Kullo[4], Sharon Mulvagh[2], Eric L. Matteson[1], Zoran Kvrgic[1] and John M. Davis III[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Department of Internal Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Mayo Clinic, Rochester, MN

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Persons with rheumatoid arthritis (RA) have increased morbidity and mortality attributable to atherosclerotic cardiovascular disease (ASCVD) events. It is unknown how presence of subclinical ASCVD, as measured by arterial health parameters, is affected by the current state of RA disease activity. The objective of this study was to determine the relationship between non-invasive arterial health measures and measures of both current and average disease activity over time in patients with established RA.

Methods: 50 patients with RA underwent non-invasive arterial health testing (measures of arterial stiffness: corrected aortic augmentation index; pulse wave velocity) and rheumatologic assessment of clinical disease activity (tender/swollen joint counts; the Clinical Disease Activity Index (CDAI); the Health Assessment Questionnaire (HAQ) disability index). Clinical measures of disease activity during 3 years prior to the study visit were averaged to obtain time-averaged measures. The AHA/ACC Pooled Cohort Equation (estimated 10-year CV risk %) was used to classify patients as low/intermediate/high risk. Spearman methods were used to determine the correlation between the rheumatologic disease activity scores and arterial health testing parameters.

Results: In the 50 patients (mean age: 57.5 years; 76% female, mean RA disease duration: 6.4 years), the disease activity was moderate, with mean (±SD) CDAI of 16.9 (15.3). At the study visit, the corrected aortic augmentation index correlated with the CDAI (r=0.37, p=0.009) and the HAQ (r=0.33, p=0.019). The corrected aortic augmentation index correlated with time-averaged measures of the tender joint count (r=0.37, p= 0.008); CDAI (r=0.36, p=0.01); HAQ (r=0.36, p=0.009); swollen joint count (r=0.36, p =0.01); patient global assessment (r=0.33, p=0.02); physician global assessment (r=0.35, p=0.014); and pain score (r=0.38, p=0.007). Marginally significant correlations emerged between the aortic pulse wave velocity and the time-averaged CDAI (r=0.26, p=0.07); tender joint count (r=0.26, p=0.07); and physician global assessment (r=0.28, p=0.05). Adjusted correlations between time-averaged CDAI and corrected aortic augmentation showed statistical significance (r=0.41, p=0.007) when adjusted for the pooled cohort CV risk

score, and marginal significance when adjusted for the pooled cohort CV risk score and use of prednisone, methotrexate and/or biologics (r=0.3, p=0.07).

Conclusion: The results demonstrate that measures of arterial stiffness, especially the corrected aortic augmentation index, correlate with the time-averaged burden of disease activity as well as current disease activity. The findings suggest that non-invasive arterial health testing provides a means to measure the effects of inflammatory disease burden on arterial function even after accounting for estimated CV risk scores.

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Abstract Number: 1467

Cardiovascular Risk Assessment in Persons with Rheumatoid Arthritis: Non-Invasive Arterial Health Testing to Assess Subclinical Risk of Cardiovascular Disease

Erin Scanlon[1], Rekha Mankad[2], Cynthia S. Crowson[3], Iftikhar Kullo[4], Sharon Mulvagh[2], Eric L. Matteson[1], Zoran Kvrgic[1] and John M. Davis III[5], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [3]Health Sciences Research, Mayo Clinic, Rochester, MN, [4]Department of Internal Medicine, Division of Cardiovascular Diseases, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Mayo Clinic, Rochester, MN

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Background/Purpose: Measures of arterial health may be useful in assessing the risk of atherosclerotic cardiovascular disease (ASCVD) in patients with rheumatoid arthritis (RA). The objective of this study was to determine if our innovative arterial health testing panel would identify early ASCVD that is not reflected in traditional CV risk scores in patients with RA. The AHA/ACC Pooled Cohort Equation (estimated 10-year CV risk %) is used to classify patients as low/intermediate/high risk. Our study evaluated early CV disease (plaque presence, carotid intima media thickness) using non-invasive arterial health testing in RA patients classified in the low/intermediate CV risk category.

Methods: 50 patients with RA underwent non-invasive arterial health testing (brachial artery reactivity testing, pulse wave velocity, and carotid intima media thickness [CIMT] and plaque presence) and calculation of the estimated 10 year CV risk (%) using the AHA/ACC Pooled Cohort Equation. Comparisons between non-invasive arterial health measures and the low/intermediate/high risk category as identified by the AHA/ACC Pooled Cohort Equation (10-year risk %) were performed using chi-square and rank sum tests. Descriptive statistics were examined to determine whether we could identify early CV disease (plaque presence) in patients typically classified as low or intermediate risk.

Results: In the 50 patients (mean age: 57.5 years; 76% female, mean RA disease duration: 6.4 years), the AHA/ACC Pooled Cohort Equation (10-year risk %, as measured as low <4%, intermediate 4-7.5%, and high >7.5%) was used to estimate CV risk. Carotid plaques were found in 7 of 21 (33%) patients with low AHA/ACC risk, 11 of 15 (73%) patients with intermediate AHA/ACC risk, and 2 of 8 (25%) patients with high AHA/ACC risk. Plaque in the intermediate AHA/ACC risk group was identified as mild in 9 (82%) and severe in 2 (18%) of the 11 patients with plaques. Brachial artery reactivity testing showed that hyperemic forearm flow was highest in the high risk category (median 712 compared to 510 in intermediate risk and 459 in low risk, p=0.048). No significant differences were identified with measures of arterial stiffness, such as pulse pressure, aortic pulse wave velocity, aortic augmentation index and corrected aortic augmentation index between low, intermediate, and high risk categories. The mean CIMT was highest in the high risk group (median 0.9 compared to 0.8 in intermediate and 0.7 in low risk, p=0.006), and maximal common carotid IMT highest in the high risk group as well (p=0.01).

Conclusion: Among patients with RA considered to have intermediate CV risk by the AHA/ACC Pooled Cohort Equation (4-7.5% AHA/ACC risk), non-invasive arterial health testing identified a high proportion of patients with both mild and severe carotid plaques. The presence of carotid plaques may identify early ASCVD that is not adequately predicted by standard CV risk scores calculators.

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Abstract Number: 1468

Increased Mitral and Tricuspid Valve Regurgitation Among Mexican Mestizo Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is chronic, systemic, inflammatory, multifactorial disease that mainly affects synovial joints. RA-patients have an increased risk of cardiovascular (CV) morbidity and mortality, being atherosclerotic CV disease the leading cause of death. Valvular heart disease (VHD) associated with RA has not been well characterized and its clinical predictors are undefined. Prevalence of VHD varies greatly in the published reports. Data in Mexican mestizo patients with RA is scarce.

Methods: A case-control study with 56 RA-patients aged 40 to 75 years that fulfilled the 2010 ACR/EULAR criteria and 28 matching control were included. Exclusion criteria included prior atherosclerotic cardiovascular disease and overlap syndromes. Patients were matched using age and sex. A standard transthoracic echocardiogram was performed according to the American Society of Echocardiography guidelines in our echocardiography lab using a 5 MHz linear transducer with a Vivid 9 (GE Healthcare, WI, USA), analyzing data in EchoPAC (GE Healthcare, WI, USA). Valvular regurgitation was classified as mild, moderate or severe according to the European Association of Echocardiography and American Society of Echocardiography recommendations.

Results: Clinical and demographic characteristics of both groups are shown in Table 1. Mean DAS28-CPR was 3.29 ± 1.56. As shown in table 2, VHD was reported in 45 (80.4%) RA-patients and 13 (46.4%) individuals in the control group ($p < 0.003$). Statistical difference was found in mitral and tricuspid regurgitation ($p < 0.001$ and $p < 0.003$, respectively) in RA-patients when compared with the control group. In the RA group, 5 (8.9%) showed mild aortic regurgitation; 28 had mild and 1 had moderate (50% and 1.8%, respectively) mitral regurgitation; 8 (14.3%) showed mild pulmonary regurgitation; 39 had mild and 4 had moderate (69.6% and 7.1%, respectively) tricuspid regurgitation. In the control group, 1 (3.6%) showed mild aortic regurgitation; 3 (10.7%) had mild mitral regurgitation; 1 (3.6%) showed mild pulmonary regurgitation; 12 (42.9%) had mild tricuspid regurgitation.

Conclusion: In our cohort, VHD was present in 80.4% of the RA-patients, with the tricuspid valve being the most affected (76.8%). Statistical difference was found between the RA and the control groups when comparing mitral and tricuspid valve. Prospective studies are needed to evaluate the role in morbidity and mortality of VHD in RA-patients.

Table 1. Clinical and Demographic characteristics			
	RA group (n = 56)	Control group (n = 28)	P value
Age, mean ± SD	56.01 ± 9.38	53.15 ± 6.27	0.922
Women, n (%)	54 (96.4)	27 (96.4)	0.845
BMI, mean ± SD	28.51 ± 4.61	28.49 ± 4.54	0.538
Hypertension, n (%)	22 (39.3)	4 (14.3)	0.024
Diabetes, n (%)	8 (19.0)	2 (9.5)	0.329

Table 2. Valvular heart disease			
	RA group (n = 56)	Control group (n = 28)	P value
Valvular heart disease, n (%)	45 (80.4)	13 (46.6)	< 0.003
Mitral valve, n (%)	29 (51.8)	3 (10.7)	<0.001
Tricuspid valve, n (%)	43 (76.8)	12 (42.9)	< 0.003
Aortic valve, n (%)	5 (8.9)	1 (3.6)	0.658
Pulmonary valve, n (%)	8 (14.3)	1 (3.6)	0.260

Disclosure: D. A. Galarza-Delgado, None; **J. R. Azpiri-Lopez**, None; **I. J. Colunga-Pedraza**, None; **R. I. Arvizu-Rivera**, None; **A. Martinez-Moreno**, None; **L. E. Gonzalez-Carrillo**, None; **M. A. Ramos-Guzman**, None; **F. Hervert-Cavazos**, None; **A. Cardenas-de La Garza**, None; **R. Vera-Pineda**, None; **M. A. Garza-Elizondo**, None; **M. A. Benavides-González**, None.

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Abstract Number: 1469

Coronary Territories Are Not Affected in Mexican Mestizo Patients with Rheumatoid Arthritis in Comparison to Matched Controls: Evaluation Using Speckle Tracking Echocardiography

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Background/Purpose: Atherosclerotic cardiovascular disease is the leading cause of death in patients with rheumatoid arthritis (RA). Two dimensional speckle tracking echocardiography (TSE) assess local and global myocardial function by analyzing myocardial deformation (strain). In ischemic pathologies, early strain abnormalities are observed. We aimed to analyze if longitudinal strain abnormalities occur following vascular territories, and to compare our findings in RA-patients with matched controls.

Methods: Case-control study with 53 RA-patients aged 40 to 75 years that fulfilled with 2010 ACR/EULAR criteria and 27 matching control were included. Subject with prior atherosclerotic cardiovascular disease (myocardial infarction, stroke and peripheral arterial disease) and overlap syndromes were excluded. Patients were matched using age, sex and comorbidities. A standard transthoracic echocardiogram was performed according to the American Society of Echocardiography guidelines using 5 MHz linear transducer with

a Vivid 9 (GE Healthcare, WI, USA), and EchoPAC (GE Healthcare, WI, USA) was used to analyze the data. Affection of coronary territories was compared between groups using longitudinal strain by speckle tracking according to the European Society of Cardiology and the American Society of Echocardiography recommendations.

Results: Mean age of RA-patients was 55.54 ± 9.11 years, and 51 (96.2%) were women. Mean RA disease duration was 12.45 ± 6.72 years, with mean DAS28-CRP of 3.11 ± 1.46. No statistical difference was found in age, sex, body mass index, hypertension or diabetes between RA-patients and controls (Table 1). Global longitudinal strain showed no statistical difference between RA-patients and controls (20.86 ± 2.82 vs -21.19 ± 2.46, p=0.620). Comparison between longitudinal strain values of the three vascular territories evaluated between RA-patients and controls did not reach statistical difference.

Conclusion: Global longitudinal strain values were not different in the Mexican mestizo RA-patients evaluated when compared with controls, which is not consistent with previous published evidence. Larger studies are needed to determine the utility of strain abnormalities to detect subclinical cardiovascular disease in our population.

Table 1. Clinical and Demographic characteristics

	RA group (n = 53)	Control group (n = 27)	P value
Age, mean ± SD	55.54 ± 9.11	52.81 ± 6.61	0.172
Women, n (%)	51 (96.2)	26 (96.3)	0.988
Body mass index, mean ± SD	27.53 ± 5.85	28.05 ± 4.66	0.956
Hypertension, n (%)	18 (33.96)	5 (18.5)	0.149
Diabetes, n (%)	7 (13.2)	4 (14.8)	0.844

Table 2. Longitudinal strain characteristics

	RA group (n = 53)	RA group (n = 53)	P value
Anterior descendent territory, mean ± SD	-21.16 ± 3.13	-21.64 ± 2.91	0.510
Circumflex territory, mean ± SD	-20.12 ± 3.28	-21.09 ± 3.1	0.207
Right coronary territory, mean ± SD	-18.98 ± 2.38	-18.79 ± 2.37	0.735

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Abstract Number: 1470

Moderate to Severe Disease Activity in Rheumatoid Arthritis Is Associated with Myocardial 18f-Fluorodeoxyglucose (18F-FDG) Uptake

Isabelle Amigues[1], Jon T. Giles[2], Afshin Zartoshti[3], Rachelle Morgenstern[4], Raul Flores[5], Sabahat Bokhari[6] and Joan Bathon[7], [1]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [2]Rheumatology, Columbia University Medical Center, NY, NY, [3]Rheumatology, Columbia University, College of Physicians & Surgeons, New York city, NY, [4]Cardiology, columbia university college of physicians and surgeons, New York city, NY, [5]Medicine, Columbia University, New York Presbyterian, New York city, NY, [6]Cardiology, Columbia University College of Physicians & Surgeons, NY, NY, [7]Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY

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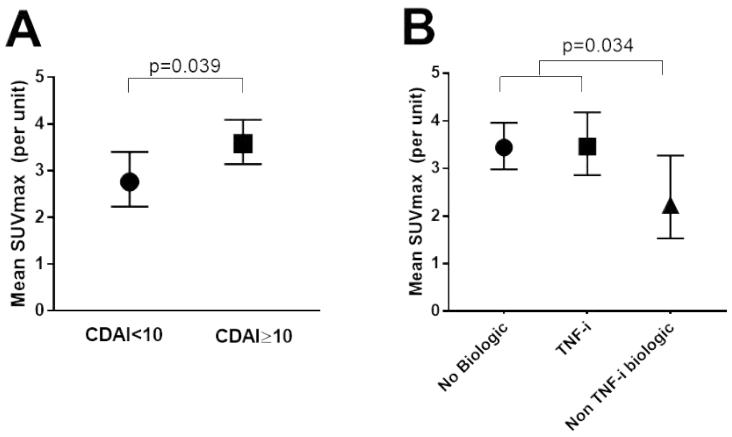
Background/Purpose: RA patients are at increased risk for developing heart failure (HF) even after controlling for coronary artery disease (CAD), indicating that factors other than flow-limiting CAD contribute to HF in RA. Chronic myocarditis may be one mechanism that contributes to HF in RA. We investigated the prevalence of myocardial inflammation in RA patients without known

cardiovascular disease (CVD) compared to non-RA controls, and evaluated its association in the RA group with disease characteristics.

Methods: RA patients without prior CVD events underwent a cardiac [18F-fluorodeoxyglucose (FDG)] positron emission-computed tomography (FDG PET-CT). A small sample of non-RA controls frequency matched on age and gender were also enrolled. Participants also underwent 3-D echocardiography to assess left ventricular (LV) mass, volumes, and systolic and diastolic function. The mean maximal standardized uptake value (SUVmax) for myocardial FDG uptake, was compared according to disease status. Generalized linear models were used to explore the associations of SUVmax with RA patient characteristics and measures of LV structure and function.

Results: A total of 118 RA patients [mean age=55 years, 81% Female, 37% non-Hispanic White, 44% Hispanic, mean BMI=28.5, median RA duration=7 years, 76% RF or anti-CCP positive, mean DAS28=3.78, CDAI was < 10 (low disease activity) in 28%] and 13 controls were scanned. Biologics were used in 45 (38%), primarily TNF inhibitors (TNFi; n=34 (29%)]. Median SUVmax was 12% higher in RA vs. controls (2.9 vs. 2.6 units; p=0.047). In univariate analyses, higher BMI and having a moderate/severe disease activity (CDAI>10) were positively associated with SUVmax in the RA group. After adjusting for BMI and RA treatment, mean SUVmax was 30% higher for those with moderate/severe disease activity (CDAI>10) compared with low disease activity (CDAI<10) (p=0.039; figure 1A). Treatment with a non-TNFi biologic was associated with a 35% lower mean SUVmax compared to patients not on biologics or on TNFi's (p=0.034; figure 1.B). SUVmax was not associated with age, gender, race, diabetes, level of CRP or IL-6, coronary flow reserve and coronary calcium score. There was no significant association between SUVmax and echocardiographically defined measures of left ventricular structure or function.

Conclusion: In patients with RA, moderate/high disease activity was associated with elevated levels of myocardial inflammation, while treatment with non-TNFi biologic DMARDs was associated with lower level. Longitudinal studies are needed to assess whether chronic myocarditis is a risk factor for HF in RA, and whether treatment of articular disease activity reduces myocardial inflammation and HF risk.



The mean of the global myocardial maximum Standardized Uptake Values (SUVmax) was not normally distributed and was log transformed for linear regression. Depicted are back-transformed means and 95% confidence intervals. Panel A was adjusted for RA treatments and BMI whereas Panel B was adjusted for BMI and RA disease group (low disease activity vs moderate/severe disease activity), all of which were the only relevant covariates retained in multivariable modeling. CDAI: Clinical Disease Activity Index, TNF-i: Tumor Necrosis Factor inhibitor.

Disclosure: I. Amigues, None; **J. T. Giles**, None; **A. Zartoshti**, None; **R. Morgenstern**, None; **R. Flores**, None; **S. Bokhari**, None; **J. Bathon**, None.

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Abstract Number: 1471

Myocardial 18f-Fluorodeoxyglucose (18F-FDG) Uptake in RA Patients without Clinical Cardiovascular Disease Is Higher Than in Controls and Decreases with

Treatment

Isabelle Amigues[1], Jon T. Giles[2], Afshin Zartoshti[3], Rachelle Morgenstern[4], Raul Flores[5], Sabahat Bokhari[6] and Joan Bathon[7], [1]Division of Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY, [2]Rheumatology, Columbia University Medical Center, NY, NY, [3]Rheumatology, Columbia University, College of Physicians & Surgeons, New York city, NY, [4]Cardiology, columbia university college of physicians and surgeons, New York city, NY, [5]Medicine, Columbia University, New York Presbyterian, New York city, NY, [6]Cardiology, Columbia University College of Physicians & Surgeons, NY, NY, [7]Rheumatology, Columbia University, College of Physicians & Surgeons, New York, NY

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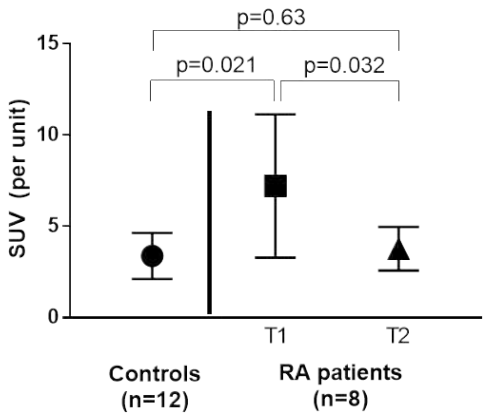
Background/Purpose: Symptomatic heart failure (HF) and HF-associated mortality rates are higher in RA compared with the non-RA population, even after controlling for coronary artery disease (CAD)[1], indicating that factors other than flow-limiting CAD contribute to HF in RA. Chronic myocarditis may be one mechanism that contributes to HF in RA. We hypothesized that RA patients without clinical cardiovascular disease (CVD) would have a higher prevalence of subclinical myocarditis compared with non-RA controls, and that it may improve with disease modifying therapy (DMARDs).

Methods : RA patients without prior CV events and with an inadequate response to methotrexate (MTX) underwent a baseline (T1) cardiac [^{18}F-fluorodeoxyglucose (FDG)] positron emission-computed tomography (FDG PET-CT) and a repeat scan six months later following initiation of step-up therapy (T2). Non-RA controls were recruited for a baseline scan only. Myocardial FDG uptake, a measure of myocardial inflammation, was assessed using INVIA Corridor 4DM software and calculated as the global maximum standardized uptake values (SUV max). Participants also underwent 3-D echocardiography to assess left ventricular (LV) mass, volumes, and systolic and diastolic function.

Results : 12 RA patients were enrolled but only 8 completed both scans. 25% received triple therapy and 75% anti-TNF therapy (with background MTX). 12 non-RA controls were enrolled and scanned. Characteristics of RA patients were: 87.5% female, mean age 61± 7.6 years; mean disease duration 5±7 months, 62% seropositive. Controls were younger (mean age 53±12.2) and with fewer women (75%). Mean DAS28-CRP decreased from 4.57±0.31 at T1 to 3.51± 0.41 at T2 (p=0.036. At T1, mean global myocardial SUV max was significantly higher in RA compared with controls (7.2 vs. 3.4 units, respectively; p=0.021). At T2, mean global myocardial SUV max decreased in the RA group, and was now not significantly different from controls at baseline (Figure). Measures of left ventricular (LV) Ejection Fraction (LVEF) and LV mass (LVM) were in normal ranges for both the RA patients and controls with no significant differences between groups. There were no significant changes in LVEF or LVM from T1 to T2 in RA patients.

Conclusion: Patients with active RA exhibited significantly higher myocardial ^{18}FDG-uptake when compared to controls. Improvements in disease activity were paralleled by improvement in myocardial FDG uptake. Larger long-term studies are necessary to determine whether myocardial inflammation is a major risk factor for myocardial dysfunction and HF. **Figure:**

Global Maximum Standard Uptake Values (SUV) of controls and RA patients before (T1) and after (T2) step up therapy.



Means and 95% confidence intervals are depicted. Controls had only one scan while Rheumatoid Arthritis (RA) patients had a scan before and 6 months after step-up therapy to either TNF-inhibitors or Triple therapy with Methotrexate/Hydroxychloroquine/sulfasalazine. T-test were used to compare global maximum myocardial Standard Uptake Values (SUV max) between T1 or T2 and Controls. In RA patients paired t-test were used to compare the RA characteristics and myocardial SUV max between T1 and T2.

[1]: Nicola, P.J., et al., Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. Arthritis Rheum, 2006. 54(1): p. 60-7.

Disclosure: I. Amigues, None; **J. T. Giles**, None; **A. Zartoshti**, None; **R. Morgenstern**, None; **R. Flores**, None; **S. Bokhari**, None; **J. Bathon**, None.

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Abstract Number: 1472

Comparison Between Carotid Plaque and Carotid Intima-Media Thickness to Detect Subclinical Atherosclerosis in Rheumatoid Arthritis

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Background/Purpose: Carotid plaque (CP) detected by ultrasonography and carotid intima-media thickness (cIMT) are useful surrogate markers for subclinical atherosclerosis and good predictors of cardiovascular disease in the general population and rheumatoid arthritis (RA). Our aim was to determine if cIMT may predict the presence of carotid plaques.

Methods: We evaluated 670 RA patients from Northern Spain without previous history cardiovascular events. Carotid

ultrasonography was performed by a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7-12 MHz linear transducer and the *automated software guided technique radiofrequency-Quality Intima Media Thickness* in *real-time* (*QIMT*, *Esaote*, *Maastricht*, *Holland*). The cIMT was determined as the average of three measurements in each common carotid artery. The final cIMT was the largest average cIMT (left or right). Carotid plaque was defined according to the Manheim Consensus Conference criteria. Based on studies reported in non-rheumatic patients, a cIMT was considered as associated with high cardiovascular risk if it was ≥ 0.90 mm.

Results: Unilateral and bilateral carotid plaque frequency and cIMT values are summarized in the **TABLE**. cIMT values were 0.619±0.105 mm in patients without plaques and 0.774±0.161 mm in those with plaques ($p<0.001$). Using 0.90 mm as the cIMT cut-off value for high cardiovascular risk, the sensitivity to detect carotid plaques was 21.2% and the specificity 99%. A ROC curve comparing the presence of carotid plaque and cIMT was performed, being the area under the curve 0.795. The best cIMT cut-off point to determine the presence of plaques was considered as the one with the highest sensitivity and specificity. According to that, 0.670 mm was found to be the best cut-off point, being sensitivity and specificity for plaque detection 71.9% and 74% respectively. Positive predictive value for a cIMT ≥0.670 mm was 78.3% in our population, being 66.8% the negative predictive value. Regarding bilateral plaques, a cIMT cut-off value of 0.90 mm had sensitivity of 0.277 and specificity of 0.966. The ROC curve showed that the best cut-off point for bilateral plaque detection was also 0.670 mm with sensitivity 79.1% and specificity 64.2%.

Conclusion: In Spanish RA patients cIMT ≥0.670 mm is a good predictor of carotid plaques. Our study suggests the possibility of considering a cIMT greater than 0.67 mm as a predictor of high cardiovascular risk in RA. **TABLE**

Variable	
Carotid plaque, n (%)	379 (56.8)
Unilateral plaque, n (%)	128 (19.2)
Bilateral plaque, n (%)	251 (37.6)
cIMT (mean ±SD) mm	0.71± 0.16

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Abstract Number: 1473

Expression of Vitamin D Receptor Associated Genes in the Aorta of Coronary Artery Disease Patients with and without Rheumatoid Arthritis

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Background/Purpose: Vitamin D has an important role in the immune system, and has been linked to inflammation, rheumatoid arthritis (RA) and coronary artery disease (CAD)[1, 2]. However, the exact mechanisms how vitamin D is involved in these processes are still unclear. Therefore, the aim of this study was to compare the expression of vitamin D receptor (VDR) associated genes in the aortic

adventitia of CAD patients with and without RA.

Methods: RNA was isolated, and Affymetrix microarray was used to determine the gene expression profile in specimens from the ascending aorta in 8 patients with CAD and 8 patients with CAD and RA from the Feiring Heart Biopsy Study. Partek Genomics Suite software was used to identify differentially expressed genes by one-way ANOVA (p<0.05; FC>1.1), and differences in expression of VDR associated genes were determined by Ingenuity Pathway Analysis.

Results: Among the 15586 transcripts that were identified, pathway analysis determined two genes within the VDR signaling pathway, Growth arrest and DNA-damage-inducible protein 45 alpha (GADD45A) (p=0.006; FC=1.474) and Nuclear Receptor Corepressor 1 (NCOR1) (p=0.005; FC=1,210), that where both up-regulated in RA patients.

Conclusion: GADD45A induces cell cycle arrest, DNA repair and apoptosis in response to various environmental stresses [3], and NCOR1 has an important role as a gene-specific integrator of positive and negative signals that control inflammation [4]. In theory, the accelerated atherosclerosis in RA might be related to the up-regulation of GADD45A and NCOR1 through the VDR signaling pathway.

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Abstract Number: 1474

Increased Levels of Lipoprotein(a) in RA Patients with Cardiovascular Disease

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Background/Purpose: Patients with various inflammatory rheumatic diseases (IRD) have increased cardiovascular morbidity caused by atherosclerosis. The aetiology of the accelerated atherosclerosis in IRD is still unclear, but both traditional cardiovascular risk factors and inflammation seem to play a role. There has been increasing attention to Lipoprotein (a) (LP(a)) as a risk factor for atherosclerotic cardiovascular disease (CVD). LP(a) exhibits homology to plasminogen, and thereby interfere with fibrinolysis.

Moreover, through binding to macrophages it may promote foam cell formation and cholesterol deposition in atherosclerotic plaques. The aim of this study was to compare levels of Lp(a) in patients with CVD with and without IRD, and in healthy controls (HC).

Methods: We examined the plasma level of LP(a) and other plasma lipids in patients included in the Feiring Heart Biopsy Study, comprising patients referred to coronary artery bypass grafting (CABG): 69 patients with IRDs and 53 sex and age matched patients without IRDs called CVD. We also examined blood samples from a group of 30 HC, matched for sex and with the same age range as the CVD-IRD group. All measurements were done by standard laboratory methods.

Results: Patients with CVD and IRD had increased plasma levels of LP(a) compared to HC (631.4 vs 335.7 mg/l, p=0.0018), while they had reduced levels of the classical atherogenic lipids, i.e. total cholesterol (TC) (4.9 vs 6.1 mmol/l, p<0.0005) and Low Density Lipoprotein cholesterol (LDL) (3.1 vs 3.9 mmol/l, p=0.002) compared to HC potentially reflecting the use of statins as most CVD patients (78 %) are on statins at the time of CABG. The levels of Lp(a) were not significantly different between IRD and non-IRD CVD patients (631.4 vs 592.5 mg/l).

Conclusion: Despite reduced levels of TC and LDL, patients with CVD regardless of IRD have higher levels of LP(a) than HC. It is likely that the reduced levels of TC and LDL are result of statin treatment which seems to not normalize Lp(a) levels. This unmask a plausible role of Lp(a) in CVD and evokes a hypothesis that there might be a need for a better control of Lp(a), e.g. by TNF inhibition, to protect from CVD at least in the IRD population.[1]

1.Hjeltnes G, *et al*, *ClinExp Rheumatol*. 2013.

Disclosure: S. Holm, None; **I. Oma**, None; **T. A. Hagve**, None; **K. Saatvedt**, None; **K. Mikkelsen**, None; **H. Rydningen**, None; **S. M. Almdahl**, None; **P. Aukrust**, None; **B. Halvorsen**, None; **I. Hollan**, None.

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Abstract Number: 1475

Comparative Risk of Cardiovascular Outcomes Between Topical and Oral Non-Selective Nsaids in Taiwanese Rheumatoid Arthritis Patients

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Background/Purpose: Topical NSAIDs (tNSAIDs) have less systemic absorption than oral NSAIDs (oNSAIDs). Thus, tNSAIDs may be associated with a reduced cardiovascular disease (CVD) risk compared with oNSAIDs. We examined risk of incident CV events associated with tNSAIDs versus oNSAIDs among Rheumatoid Arthritis (RA) patients in Taiwan.

Methods: We conducted a retrospective cohort which included incident RA patients who newly started non-selective tNSAIDs or oNSAIDs. We used the Taiwan National Health Insurance Research Database (NHIRD). The first date patients received NSAIDs was defined as the index date, and the 6 month baseline period before the index date was used to define covariates. Patients were excluded if they had NSAIDs exposures, cancer, HIV, psoriatic arthritis or ankylosing spondylitis claims during the baseline period. Treatment episodes continued until there was a treatment gap more than 30 days. Follow-up was censored at the first of any of the following: 30-days after treatment was discontinued, switch/addition of other NSAIDs category, CV outcome, death, or the end of study. Patients without any NSAID use for at least 180 days could contribute a second treatment episode. The main outcome was a CV event, including myocardial infarction, unstable angina, heart failure, stroke or revascularization. Inverse probability of treatment weight (IPTW) weighted Cox regression model was used to compare the risk of CV events between tNSAIDs and oNSAIDs, with oNSAIDs as the reference group. Sensitivity analyses included varying the length of treatment gap and subgroups.

Results: There were 10,758 and 78,056 treatment episodes for topical and oral NSAIDs indentified from our cohort. The mean age was 55.1±15.4 years in tNSAIDs users and 51.7±15.1 years in oNSAIDs users. tNSAIDs users were also more prevalent in female (82.3% vs. 76.0%), CVD risk factors and co-medications than oNSAIDs users. After weighting by IPTW, the cohorts were well balanced. 34 CV events were found during 1,854.6 person-year follow-up in tNSAIDs users, and 433 CV events in 20,205.3 person-year in oNSAIDs users. The crude CV event rate was 1.87 and 2.14 per 100 person-year in topical and oral NSAIDs groups. Results of IPTW weighted Cox regression found tNSAIDs groups had 36% lower risk for CV events as compared with oNSAID group (**table**, HR: 0.64; 95%CI: 0.43-0.95). Consistent results were found in sensitivity analyses (**figure**).

Conclusion: We found tNSAIDs users experienced a reduced risk of CV events compared with oNSAID users. If future studies with larger sample size and longer follow-up confirm these results, NSAID prescribing might change accordingly. **Table. Incidence and risk of composite CV events in topical and oral NSAIDs recipients**

	Follow-up person-year	Event (N)	Crude incidence per 100 person-year	Propensity score adjusted HR* (95%CI)
Topical NSAIDs (N=10,758)	1,855	34	1.83	0.64 (0.43-0.95)
Oral NSAIDS (N=78,056)	20,205	433	2.14	REF

* Adjusted by Inverse probability of treatment weight (IPTW), conditioning on patient demographic information (age, gender, income levels), comorbid conditions and co-medications that correlated with CVDs and traditional and biologic DMARDs patients.

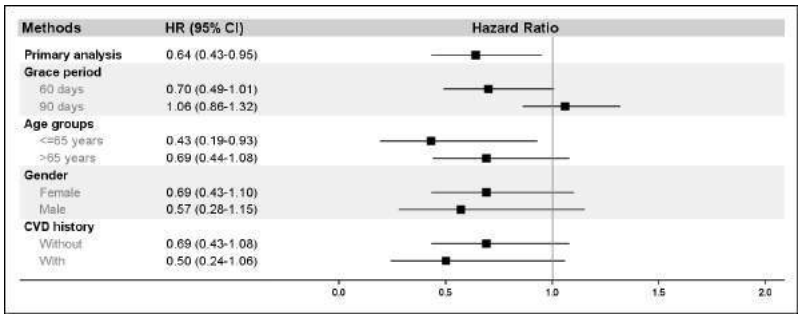

Figure. CV event risk comparing topical NSAIDs versus oral NSAIDs users in the primary analysis and in subgroups.

Disclosure: T. C. Lin, None; **D. H. Solomon**, None; **S. K. Tedeschi**, None; **K. Yoshida**, None; **Y. H. Kao Yang**, None.

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Abstract Number: 1476

Diastolic Dysfunction in Patients with Rheumatoid Arthritis: Predictors of Longitudinal Progression over Five Years

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Background/Purpose: The impairment of left ventricular (LV) relaxation and passive filling, known as diastolic dysfunction, undergirds the development of heart failure in patients with rheumatoid arthritis (RA). Little is known about factors that contribute to the progression of diastolic dysfunction over time in these patients. The objective of this study was to identify predictors of progression of LV diastolic dysfunction over five years in patients with RA.

Methods: A prospective longitudinal study of a population-based cohort of patients with RA was performed. Patients participated in research study visits at baseline and 5 years later. Clinical evaluation included the Rapid Assessment of Patient Index Data-3 (RAPID-3), Health Assessment Questionnaire (HAQ) disability index, use of disease-modifying antirheumatic drugs (DMARDs), biologics and prednisone, and measurement of C-reactive protein (CRP), rheumatoid factor (RF), and anti-cyclic citrullinated peptide antibodies (anti-CCP). At baseline and 5 years, participants underwent pulse-wave and tissue Doppler echocardiography, according to a standardized research protocol. Spearman methods were used to determine the age- and sex-adjusted correlations between the 5-year changes in echocardiographic parameters and baseline clinical variables.

Results: A total of 160 patients with RA were included in this study. The mean age at baseline was 58.5 years, and 76.3% were female. The mean (SD) values of the RAPID-3, HAQ and CRP were 6.4 (5.8), 0.47 (0.55) and 4.2 (6.3) mg/L, respectively. Previous analyses demonstrated that RA is associated with increasing mitral A velocity and decreasing E/A ratio over 5 years. The present analysis demonstrated statistically significant correlations between the 5-year increases in the mitral A velocity and higher baseline values of the RAPID-3 ($r = 0.24$, $p = 0.003$), the HAQ disability index ($r = 0.21$, $p = 0.011$), CRP ($r = 0.21$, $p = 0.011$), and baseline prednisone use ($r = 0.17$, $p = 0.039$). Similarly, 5-year decreases in the E/A ratio correlated with higher baseline values of RAPID-3 ($r = -0.17$, $p = 0.041$), HAQ disability index ($r = -0.19$, $p = 0.019$), and CRP ($r = -0.16$, $p = 0.047$). Increases in the e' velocity correlated only with higher values of CRP ($r = 0.19$, $p = 0.021$) while increases in the E/e' ratio correlated with higher values of RAPID-3 ($r = 0.19$, $p = 0.018$). There was no evidence of any significant correlations between echocardiographic parameters and RF, anti-CCP or DMARD/biologic use.

Conclusion: Higher disease activity and severity at baseline are predictive of progressive changes over time in key parameters of LV diastolic function among patients with RA. The findings suggest that disease activity is a determinant of future myocardial disease in patients with RA. Echocardiographic monitoring of LV diastolic function should be considered as an outcome measure in future clinical trials of treat-to-target strategies for RA.

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Abstract Number: 1477

Exploring the Inadequate Cardiovascular Disease Prevention in Inflammatory Joint Diseases: Results from a Nationwide Norwegian Project

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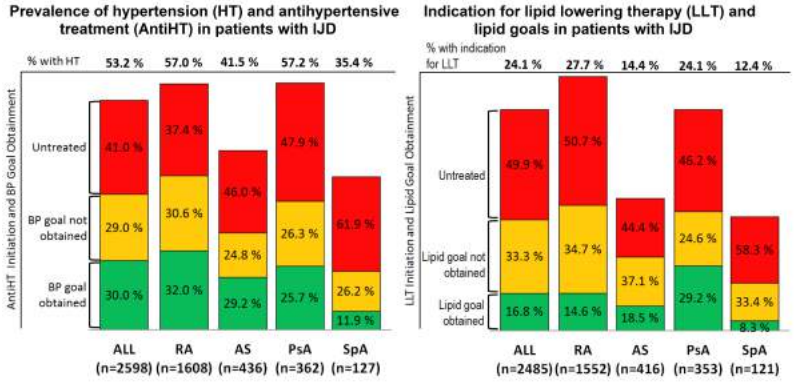
Background/Purpose: Antihypertensives (antiHT) and lipid lowering therapies (LLT) prevent cardiovascular disease (CVD)

effectively. It has been reported that patients with rheumatoid arthritis (RA) receive suboptimal CVD-prevention. Whether other inflammatory joint diseases (IJD), such as ankylosing spondylitis (AS), psoriatic arthritis (PsA) and other spondyloarthropathies (SpA), also receive inadequate CVD management remains unknown. In a large IJD cohort we aimed to evaluate 1) Rate of indications for antiHT and/or LLT, 2) rate of antiHT and/or LLT initiation, and 3) blood pressure (BP) and low-density lipoprotein cholesterol (LDL) goal attainment in patients treated with antiHT or LLT, respectively.

Methods: The present IJD cohort is derived from the Norwegian COllaboration on Cardiovascular disease in patients with Rheumatic joint diseases (NOCAR). In NOCAR, CVD risk factors are collected in daily rheumatology practice. Need for antiHT was defined as BP ≥140/90mmHg or self-reported hypertension (HT). BP levels <140/90 mmHg were recognized as BP goal attainment. Ten year risk of a fatal CVD event was estimated by the Systematic COronary Risk Evaluation (SCORE). According to guidelines, patients with diabetes, hyperlipidemia or SCORE ≥5% are at high CVD risk and should receive LLT (LDL target <2.6 mmol/L); whereas established CVD or SCORE ≥10% imply a very high CVD risk (LDL target <1.8 mmol/L). Rates were calculated for the whole cohort and compared across IJD entities using logistic regression, age and sex adjusted.

Results: Of the 2647 patients (RA: n=1696, AS: n=445, PsA: n=376, SpA: n=130), 53.2% had indication for antiHT, and this was significantly higher in RA (57.0%) and PsA (57.2%). Among patients for whom antiHT was indicated, 59.0% received treatment and half of the patients on antiHT had obtained BP goal. There was indication for LLT in 24.1%, which was comparable across the IJD entities except for AS (14.4%) (p<0.0001). In the group with indication for LLT, 55.6% had high CVD risk which was most frequently seen in PsA (p=0.02), whereas 43.7% had very high CVD risk, which was more common in AS patients (p=0.02). Half of the patients with indication for LLT received this therapy, and treatment rates were higher for patients with very high CVD risk compared to those with high CVD risk (p<0.001). In total, 16.8% had achieved LDL treatment targets; LDL goal attainment was particularly high in PsA patients (p<0.01), and higher in patients with high CVD risk than in those with very high CVD risk (p<0.001).



Conclusion: CVD-preventive medication is often indicated, but infrequently initiated in IJD patients. Moreover, when antiHT and LLT are started, quite few patients obtain treatment goals. There is a need for improving CVD risk assessment, initiation of proper CVD-prevention and careful monitoring of target achievements to successfully reduce the excess CVD risk in IJD patients.

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Abstract Number: 1478

Coronary Artery Calcification in Rheumatoid Arthritis Patients Is Not Characterized By an Increase in Genes Associated with Coronary Artery Disease in the General Population

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Background/Purpose: In the general population individuals with coronary artery disease (CAD) have a significantly increased frequency of particular susceptibility single nucleotide polymorphisms (SNPs). Since CAD is increased in rheumatoid arthritis (RA), we sought to determine whether RA patients with CAD will have an increased frequency of these SNPs compared to those without CAD, implying that RA enhances the risk for CAD by acting on established genetic pathways predisposing to CAD, or alternatively, whether RA acts to increase CAD by mechanisms independent of these genetic pathways.

Methods: CAD was assessed by coronary artery calcification (CAC) using computed-tomography in 561 patients with RA. 100 SNPs associated with CAD in the general population were genotyped or imputed and their relation to CAC established through multiple regression analysis for individual SNPs and a genetic risk score (GRS) representing their cumulative effect.

Results: Ninety-one CAD SNPs were genotyped successfully; these were not significantly associated with CAC (Agatston units) or different CAC categorizations, either individually or collectively in the GRS. Only rs6544713 (ABCG8), rs3869109 (HCG27), rs1332844 (PHACTR1), rs579459 (ABO), rs4773144 (COL4A2), rs2075650 (TOMM40) and rs9982601 (KCNE2) expressed any positive relation with CAC in one or more of the analyses. Notably, none of the group of the 12 SNPs mapping in the 53 kb region of chromosome 9p21 that are among the strongest predictors of CAD in the general population exhibited any association with CAD. Moreover, rs1333040 (CDKN2B-AS1), which in the general population is positively associated with CAD risk, showed a significant inverse association between genotype and CAC. Only rs579459 (ABO) exhibited a consistent positive association between genotype and CAC score, with a significant increase of the effect allele frequency in both homozygous or heterozygous genotype distributions. When the association of the CAD related SNPS with CAC was studied through the non weighted and weighted set of SNPs, no significant association was found. In particular, an increase in the number of homozygous cardiovascular disease related SNPs was not significantly associated with an increase in *log*CAC Agatston units. GRS was not associated with CAC both in the univariate, and in the multivariate analysis adjusted for age and sex and for traditional cardiovascular factors. Additionally, when CAD related SNPs were weighted by their effect sizes, the resulting GRS was not significantly associated with CAC. Besides, trend analysis showed no relation between GRS and log CAC Agatson units (p=0.93). Interestingly, the positive association found between DAS28 and CAC after adjusting for traditional cardiovascular risk factors was not modified by correcting for the CAD related SNPs GRS.

Conclusion: The increased risk for CAC in RA does not appear to primarily operate through established genetically regulated atherogenic mechanisms that are preponderant in the general population.

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Abstract Number: 1479

Cardiovascular Diseases and Mortality Are Independently Influenced By Carotid Plaque Presence in Rheumatoid Arthritis: The 5-Year Prospective Study

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Background/Purpose: Patients with rheumatoid arthritis (RA) have a higher risk of cardiovascular disease (CVD) and premature mortality, compared to the general population. Inflammatory burden and conventional cardiovascular (CV) risk factors contribute to the development of carotid atherosclerosis in patients with RA. We evaluated the effects of RA on the occurrence of CVD and mortality in a prospective study of an Asian population.

Methods: A total of 369 patients with RA and 160 healthy controls were followed up for 5 years or until deaths in a prospective KARRA cohort study (412 patients and 221 controls at baseline). To detect the presence and progression of carotid atherosclerosis, we performed carotid ultrasound at baseline and 5-year. We analyzed the incidence of CVD, conventional CV risk factors, RA disease activity and severity markers, medication histories, mortality rate, and causes of death.

Results: During 5-year follow-up period, the mortality rate was 5.8% (24/412) in RA patients and 0% in healthy controls ($p<0.001$), while the incidence of CVD were 6.1% (25/412) in RA patients and 0.5% (1/221) in healthy controls ($p<0.001$). Among CVD in RA patients, cerebrovascular accident (CVA) and cardiovascular event (CVE) were 8 (32%) and 17 (68%) events, respectively. Major causes of death included infection (11/24, 45.8%), CVD (6/24, 25%), and others (7/24, 29.2%). The mean age, presence and number of carotid plaques, functional class, modified Korean version of the HAQ (mKHAQ), tender joint count (TJC), swollen joint count (SJC), ESR and CRP, and conventional CV risk factors at baseline were significantly associated with mortality among RA patients. Multivariate logistic regression analysis showed that the presence of carotid plaque (OR 5.32 [95% CI 1.09-25.99; P = 0.039]), mKHAQ (OR 1.07 [95% CI 1.02-1.13; P = 0.007]), and ESR (OR 1.04 [95% CI 1.02-1.06; P < 0.001]) at baseline were independent risk factor for mortality of RA patients. In contrast, factors associated with new-onset CVD included the mean age, presence and number of carotid plaques, peak CRP, and conventional CV risk factors at baseline. Carotid plaque (OR 7.86 [95% CI 2.14-28.83; P = 0.002]) and two or more CV risk factors (OR 4.77 [95% CI 1.07-21.23; P = 0.040]) at baseline were independent predictive factors for new-onset CVD of RA patients in a multivariate logistic regression analysis.

Conclusion: This prospective study shows that a common risk factor for CVD and mortality is carotid plaque which is determined by disease activity and CV risk factors. While disease activity of RA is a critical determinant for the mortality, the development of CVD depends on conventional CV risk factors.

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Abstract Number: 1480

Determination of the Lipid Profile in Active Disease Leads to Incorrect Cardiovascular Risk Prediction in Early Rheumatoid Arthritis Patients

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Background/Purpose: Rheumatoid arthritis (RA) is associated with increased cardiovascular morbidity and mortality. This cardiovascular risk is mainly determined by the lipid profile, which may change during the course of the disease(1). For a proper cardiovascular risk assessment stable lipid values should be used and in cardiovascular risk prediction models mostly lipid ratios are applied. As the increased cardiovascular risk is already present at the time of diagnosis, it is important to initiate cardiovascular risk management as early as possible in the disease(2). However, first it is necessary to know if measurement of the lipid profile is adequate (i.e. stable lipid values) early in the disease. The aim of this study was to 1) investigate the change in lipid profile during the first 4

weeks of RA treatment 2) analyse the association between the alteration in the lipid profile and the change in ESR.

Methods: In 66 consecutive DMARD-naive early RA patients lipid profile and disease activity were measured. This was repeated after four weeks of treatment with methotrexate (3 weeks 10 mg, 4th week 17.5 mg) and prednisolone (30 mg tapered to 10 mg). Lipid profile assessment comprised TC, HDL-C, LDL-C, triglycerides and apolipoprotein A and B (Apo A and Apo B). Disease activity was assessed by the disease activity score of 44 joints (DAS44), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Patients on statins were excluded. The change in lipid profile (week 4 minus week 0) versus change in ESR was analysed in 2 patient groups: a group with high (median -31.0 mm/h) and a group with low (median -3.0 mm/h) improvement in ESR.

Results: Three patients on statins were excluded, analyses were thus performed on 63 early RA patients. All components of the lipid profile increased significantly during treatment, except for Apo B. In addition, ratios of lipid values, particularly the TC/HDL cholesterol ratio improved significantly (table 1). The group with high ESR versus the group with low ESR improvement had a significantly higher increase in TC, HDL-C, LDL-C and Apo A levels. This was 2.7% in the group with less improvement in ESR and 23.1% in the most improvement group. The spearman rho test showed a correlation between delta ESR and delta TC, HDL, LDL and Apo A of r=0.456, r=0.313, r=0.507 and r=0.281, respectively (all $p<0.05$).

Conclusion: Lipid levels increased significantly after four weeks of methotrexate and prednisolone treatment after RA diagnosis and this change is associated with the improvement in ESR. In both groups ratios of lipid values improved substantially. Hence, cardiovascular risk management in early arthritis should be postponed until low disease activity has been obtained, as assessment during active disease leads to an inappropriately high cardiovascular risk estimation. **References:** 1) Nat Rev Rheumatol 2013 Sep;9(9):513-23. 2) Arthritis Res Ther 2010;12(4):R158.

Table 1.

	Baseline samples	Week 4 samples	P-value
Total cholesterol, mmol/l (mean, SD)	4.9 (1.1)	5.6 (1.3)	P=0.000
Triglycerides, mmol/l (mean, SD)	1.3 (0.6)	1.4 (0.8)	P=0.023
HDL, mmol/l (mean, SD)	1.3 (0.4)	1.9 (0.6)	P=0.000
LDL, mmol/l (mean, SD)	3.1 (0.9)	3.3 (1.1)	P=0.020
Apo A, g/l (mean, SD)	1.4 (0.3)	1.8 (0.3)	P=0.000
Apo B, g/l (median, IQR)	0.9 (0.8-1.1)	0.9 (0.8-1.1)	P=0.740
TC/HDL ratio (mean, SD)	4.0 (1.4)	3.2 (1.1)	P=0.000
Apo B/ Apo A ratio (mean, SD)	0.7 (0.2)	0.6 (0.2)	P=0.007

Values are reported as mean (SD) or median (IQR); mmol/l: millimole per liter, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, Apo: apolipoprotein, g/l: gram per liter, TC: Total cholesterol

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Disclosure: S. A. Turk, None; **D. van Schaardenburg**, None; **W. F. Lems**, None; **M. T. Nurmohamed**, None.

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Abstract Number: 1481

Success Rate of Blood Pressure Goal Achievement in Patients with Inflammatory Joint Diseases

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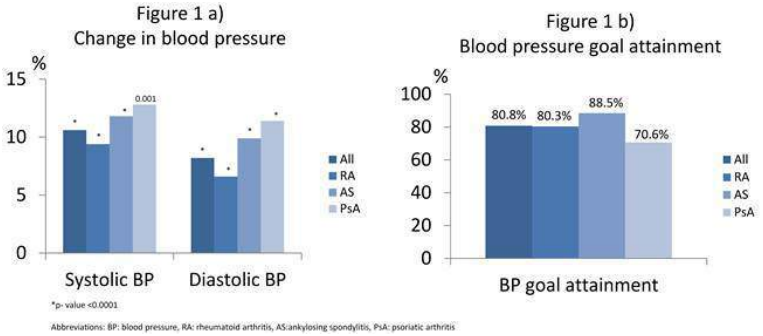
Background/Purpose: The excess risk of cardiovascular disease (CVD) in patients with inflammatory joint diseases (IJD) is attributable to several risk factors, including a high prevalence of hypertension. However, there is limited knowledge on the effect of antihypertensive treatment (a-HTT) in these patients. Our objective was to initiate a-HTT when indicated and treat to guideline recommended blood pressure (BP) goal in IJD patients. We also aimed to evaluate the effect of a-HTT in this patient population, and which factors were associated with BP goal attainment.

Methods: Patients with IJD (n=765) were referred from a rheumatology outpatient clinic or general practitioners to a preventive cardio-rheuma clinic. All patients underwent a CVD risk evaluation, including BP measurements (performed using and Omron M7 apparatus). Antihypertensive treatment was initiated in accordance with guidelines, and the BP treatment goal was <140/90 mmHg.

Results: Of the 765 IJD patients referred (rheumatoid arthritis n= 450, ankylosing spondylitis n=210 and psoriatic arthritis n=105), 104 (13.6%) had an indication for BP lowering, while 224 (29.3%) were already using a-HTT at the first consultation. For those where a-HTT was initiated at baseline (n=104), there was a highly significant change in BP from first to final consultation (Fig 1a). BP goal was achieved in 84 (80.8%) patients (Fig 1b), using mean±SD 3.1±1.7 consultations. Dose adjustments was done in 38 (36.5%) of the patients with median (IQR) a-HTT dose adjustments of 1 (1, 1.25). In 9 (8.7%) patients the a-HTT was changed. Systolic BP (p <0.0001), but not use of anti-rheumatic medication or inflammatory biomarkers at baseline, was significantly associated with BP goal attainment in age- and sex adjusted logistic regression analyses. Patients with the lowest systolic BP were more likely to achieve BP goals. For patients already on a-HTT (n=224), only 52.7% had a BP <140/90 mmHg at baseline. After up titration or change of a-HTT, the percentage of patients achieving BP goal in this group increased to 82.6%.

Conclusion: This is to our knowledge the first prospective report on success rate of BP goal achievement in patients with IJD. Approximately 80% reached BP target, which is even a higher proportion than what is shown in the general population. Treatment to BP goal is feasible in patients with IJD, and is not complicated by inflammation or use of anti-rheumatic medication.



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Abstract Number: 1482

Web-Based PILOT Intervention Study to Improve Cardiovascular Risk Knowledge Among Rheumatoid Arthritis Patients

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Background/Purpose: Cardiovascular disease (CVD) is the leading cause of mortality in rheumatoid arthritis (RA), underscoring the importance of CVD prevention. The rates of screening and intervention for modifiable traditional and RA-specific CVD risk factors are low among RA patients. The primary objective of this study was to design and test a web-based educational intervention (EI) for RA patients.

Methods: A 28-minute educational web-based video presentation was designed, recorded on CVD risk specifically for RA patients and pretested. Thirty-eight consecutive consenting RA patients completed onsite EI offered on web. Participants also completed web-based surveys assessing heart disease knowledge, unique heart disease risk factors specific to RA patients, and illness perceptions for CVD as RA patients (HDKQ; HDFQ-RA; IPQ-R) before and after EI. HDKQ and HDFQ-RA were scored using correct response ratios

(CRR). Smoking status and sedentary lifestyle were assessed by self-report, whereas chart review was used to ascertain hypertension, diabetes, dyslipidemia, weight, RA control, medication use. General linear model analyses for repeated measures were used to compare within-person changes in CVD risk knowledge post EI.

Results: The participants were 57±13 years old; 77% were women. Cardiac risks were: 21% current smokers, 44% hypertension, 21% diabetes, 63% dyslipidemia, 47% overweight, 45% sedentary, 49% poor RA control; of which 51% reported steroid and/or nonsteroidal anti-inflammatory medication (NSAIDS) use for >15 days within the past 3 months. At study initiation, patients had poor perception of increased CVD risk in context of RA. CRR was ≤ 50% on 8/30 HDKQ domains relating to recognition of CVD symptoms, role of stress, diet and exercise and treatment in CVD. Post EI, significant improvements (Table 1) were evident in 5/8 of these domains ($p<0.01$). CRR was ≤70% on 3/13 domains on HDFQ-RA, with CRR of 34% and 53% in two domains specifically related to CVD in RA (Table 1). Significant improvements after EI were noted across all three HDFQ-RA domains ($p<0.05$).

Conclusion: RA patients have poor perception and knowledge of CVD risk associated specifically with RA and RA-related medications. This brief web-based EI increased their awareness about RA-related CVD risk. This may be a step towards mitigating RA related CVD morbidity. Longitudinal study is ongoing. Table 1.

Item	Heart Disease Knowledge Questionnaire	Pre N=38 EMM*, SE	Post N=38 EMM,SE	Within person P value
7	The most important cause of heart attacks is stress.	0.37,0.08	0.55,0.08	0.006
8	Walking and gardening are considered types of exercise than can lower heart disease risk.	0.97,0.03	0.90,0.05	0.08
9	Most of the cholesterol in an egg is in the white part of the egg.	0.95,0.04	0.89,0.06	0.08
14	The healthiest exercise for the heart involves rapid breathing for a sustained period of time.	0.34,0.08	0.50,0.08	0.03
19	HDL refers to "good" cholesterol, and LDL refers to "bad" cholesterol.	0.58,0.08	0.90,0.05	<0.001
25	Margarine with liquid safflower oil is healthier than margarine with hydrogenated soy oil.	0.24,0.07	0.50,0.08	0.003
27	Men and women experience many of the same symptoms of a heart attack.	0.29,0.08	0.53,0.08	0.005

Item	Heart Disease Fact Questionnaire-RA	Pre N=38 EMM*, SE	Post N=38 EMM,SE	Within person P value
8	A person with diabetes is more likely to develop heart disease	0.68,0.08	0.87,0.06	0.050
12	Anti-inflammatory medications, such as diclofenac or ibuprofen, taken by patients with rheumatoid arthritis may increase their chance of heart disease	0.34,0.08	0.71,0.08	<0.001
13	Having lots of inflammation ('flares') of rheumatoid arthritis adds to the increased chance of heart disease	0.53,0.08	0.84,0.06	0.002

*Estimated Marginal Means and Standard Errors

Disclosure: M. Jolly, Pfizer Inc, 9; **E. Steinig**, None; **L. Walt**, None; **R. Kazkauskaite**, None.

Abstract Number: 1483

Elevated Anti-Cyclic Citrullinated Peptide Antibody Titer Is Associated with

Increased Cardiovascular Risk

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Background/Purpose: Rheumatoid arthritits (RA) patients have an increased risk of mortality from cardiovascular (CV) disease. Proposed adaptation of CV risk score models in RA patients include criteria such as anti-cyclic citrullinated peptide antibodies (ACPA) positivity. The existing literature on the association between ACPA positivity and CV risk is not definitive.[1-3]

Methods: This is a retrospective chart review of patients over 18 years of age with ACPA testing between 2007 and 2013 at a single academic center. Patients with non-RA autoimmune disease were excluded. Information about RA diagnosis and treatment, CV risk factors and CV events was collected. Statistical methods included chi-square tests, t-tests, Wilcoxon Rank Sum tests, Fisher's exact tests, simple logistic regression and multivariable logistic regression.

Results: 2,030 records were reviewed. 309 patients with non-RA autoimmune disease were excluded. The mean RA duration was 12.1 years. RA and non-RA groups were similar in gender, tobacco status, hyperlipidemia, statin use, chronic kidney disease, and diabetes; significant differences included race, BMI, and systolic blood pressure. Primary outcomes included coronary artery disease (CAD, defined as acute coronary syndrome or intervention), stroke (CVA, defined as clinical or radiographic stroke or transient ischemic attack), and a combined outcome (CAD or CVA). The combined outcome occurred in 173 patients. There was a significant association between an increasing prevalence of the combined outcome and ACPA quartile in all patients (p=0.002) and in RA patients (p=0.05). A similar trend was seen in non-RA patients but did not reach statistical significance. There was an increased odds ratio of the combined outcome with each increasing ACPA quartile in all patients (p=0.002) (Figure 1). Subgroup analyses of the RA and non-RA groups did not reach statistical significance, though the trend was preserved.

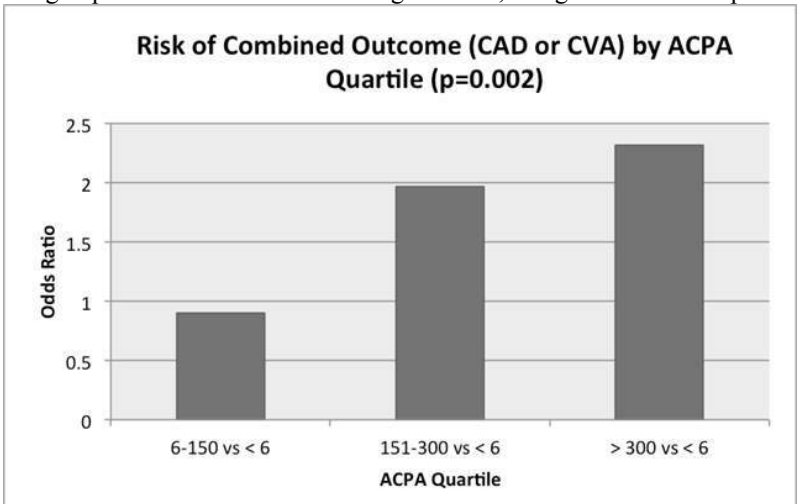

Fig 1. Odds ratio for combined outcome of CAD or CVA in all patients

Conclusion: Increased ACPA is associated with increased risk of the combined outcome of CVA or CAD. To the authors' knowledge, this is the first study to demonstrate progressively increased risk of CV disease with extent of ACPA elevation. Although statistical significance was not reached in non-RA patients, the observed trends warrant larger studies to evaluate this population. **References:**

1. López-Longo FJ, et al. Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Rheum 2009;61(4):419-24.

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Abstract Number: 1484

Exploring the Link Between RA Disease Activity, Lipid Levels, and Cardiovascular Disease in an Early Inflammatory Arthritis Cohort

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Background/Purpose: Rheumatoid arthritis (RA) has been established as a risk factor for cardiovascular disease (CVD), with systemic inflammation being linked with atherosclerosis. Traditional CVD risk indices like the Framingham Risk Score (FRS) underestimate CVD risk in RA. RA patients that develop CVD often have more inflammation yet lower levels of atherogenic cholesterol in what is labelled “the lipid paradox”. Additionally, evidence suggests RA disease activity may modify the cardioprotective function (versus the absolute value) of cardioprotective high density lipoprotein (HDL). We explore the link between CVD, disease activity, lipid levels, and apoA1 (an atheroprotective HDL subcomponent) in an early inflammatory arthritis (EIA) cohort.

Methods: Data was obtained from subjects followed in a single centre EIA cohort with systematic collection of disease activity measures, comorbidities and serum lipids. FRS scores were calculated for each patient, and new CVD (myocardial infarction, unstable angina, stroke) confirmed by chart review. Annual lipid profiles (total cholesterol (TChol), triglycerides (TG), low density lipoprotein (LDL) and HDL) were correlated with disease activity (DASESR283variable) using Spearman’s rho (first profile obtained after median (IQR) of 25 (0, 40) months follow-up). ApoA1 was measured by ELISA in serial samples from 22 patients matched for age and DAS28ER3variable (5 with new CVD) and differences in apoA1, lipid levels, and DAS28ESR-3variable over time in both non-CVD and CVD patients compared using non-parametric tests and logistic regression.

Results: 278 patients with EIA (<12months symptoms at baseline) and no prior CVD history (mean(SD) age 49(15) years, 75% female, 67% RA) were followed for a median (IQR) of 67 (25, 102) months. Considering all visits, there was modest negative correlation between DAS28ESR-3variable and HDL levels (r=-0.12, p<0.001), a trend for negative correlation with TChol level (r=-0.07 p=0.03), but no correlation for LDL and TG. CRP correlated with TChol (r=-0.12 p<0.0001), TG (r=0.14 p<0.0001), and HDL (r=-0.31 p<0.0001). A good or moderate EULAR treatment response was achieved by 70% of the cohort at last visit and there was greater increase in LDL levels in these individuals than those with no response (mean(SD) +0.24(0.7) vs +0.01(0.6), p=0.02). Five subjects developed CVD after a median (IQR) of 64(42, 104) months. FRS increased from baseline to last visit (median (IQR) 4.4(1.2, 9.1) vs 5.1(2.1,10.8) p<0.0001) however there was no difference in FRS at baseline, last visit or change in FRS between those with or without CVD. Baseline high FRS (FRS in fourth quartile) was not significant in cox-proportional hazards modelling of CVD-free survival. ApoA1 levels modestly fluctuated over time, but did not correlate with HDL or other lipids nor associate with CVD.

Conclusion: In EIA, high disease activity is associated with lower levels of pathogenic lipids, supporting the lipid paradox. Neither Framingham risk scores nor apoA1 levels adequately associate with CVD risk in these EIA patients. Alternate measures of lipid metabolism may be more predictive of CVD.

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Abstract Number: 1485

Generation of New Carotid Plaque Is Determined By the Prexisting Carotid Atherosclerosis and Ongoning Disease Activity of Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic and systemic inflammatory disease. The incidence of cardiovascular (CV) disease is increased in patients with RA compared with the general population, which is related to the fact that atherosclerosis has an inflammatory etiology. We previously have shown that synergistic interaction between inflammatory burden and conventional CV risk factors in the development of carotid atherosclerosis. In the present study, we investigated the risk factors for the progression of the carotid atherosclerosis in RA patients in the Kyungpook National University Hospital Atherosclerosis Risk in Rheumatoid Arthritis (KARRA) cohort study.

Methods: After a baseline evaluation for KARRA enrollment, all RA patients and healthy controls were prospectively followed up for 5 years or until deaths. We analyzed the demographic findings, conventional risk factors and RA disease activity. Carotid ultrasound at baseline and year 5 was performed to evaluation of the intima-medial thickness (IMT) and presence and progression of carotid plaque.

Results: A total of 417 patients with RA and 221 age- and sex- matched healthy controls were included in the baseline KARRA cohort, and 314 patients with RA and 160 healthy controls were followed for the 5 year period. Mean age and female frequency of RA patients were not different compared with those of healthy controls at year 5. At year 5, the mean carotid intima-medial thickness (IMT) of RA patients was higher than that of controls [0.85mm (S.D 0.15) vs 0.89 (S.D 0.18), p=0.032]. However, frequency and number of carotid plaque were similar in both groups, which reflects steeper increase of plaque number during 5-year follow-up in healthy controls. Factors associated with plaques at year 5 included IMT, mean blood pressure, and total and LDL cholesterols at baseline. New development of carotid plaques at year 5 in RA patients (n=90) was predicted by IMT and total and LDL cholesterols at baseline, while it was associated with IMT and DAS28-CRP at year 5. Multivariate logistic regression analysis revealed that baseline IMT (OR 36.48 [95% CI 1.66-803.62; P = 0.023]) and DAS28-CRP at year 5 (OR 1.56 [95% CI 1.06-2.30; P = 0.024]) were independent risk factors for new plaque formation in 5-year followed period.

Conclusion: This study shows that carotid plaque at year 5 is predicted by IMT and dyslipidemia at baseline, whereas formation of new plaques after long-term follow-up depends on the preexisting carotid atherosclerosis that is aggravated by suboptimal disease control.

Disclosure: J. W. Kang, None; **E. S. Lee**, None; **J. S. Eun**, None; **N. R. Kim**, None; **J. H. Kim**, None; **J. Y. Kang**, None; **E. J. Nam**, None; **Y. M. Kang**, None.

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Abstract Number: 1486

Associations Between Heart Rate Adjusted ST Segment and Heart Rate Variability in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for myocardial infarction (MI), which is often silent. Heart rate adjusted ST segment (ST/HR index) is a novel method for assessing myocardial ischemic changes during exercise testing. This index has been related to MI risk and has been shown to have greater sensitivity in detecting ischemic changes than conventional ST segment depression, which relies on reaching maximal workload intensity during exercise tolerance test (ETT). ST/HR index takes heart rate responses to exercise into account, which means that it is not necessary for study participants to reach maximal workload. This is particularly important for patients with RA, who might have limited exercise ability due to joint problems. Reduced heart rate variability (HRV) at rest is an indicator of reduced parasympathetic activity and poorer cardiac autonomic balance, and it has been suggested to contribute to the risk of developing MI. Both ST/HR index and HRV are related to MI, but little is known about their associations. Thus, this study is aimed to explore the association between resting HRV indices and ST/HR index in patients with RA.

Methods: Two minutes beat to beat R-R interval data from ECG were recorded in 96 RA patients (54.4±12.6 years, 68% women). ST/HR index was measured as the difference between ST-segment depression at rest and maximum ST-segment depression during ETT, divided by the absolute change from resting heart rate (HR) to the HR at maximum ST depression during the ETT. Low frequency (LF; 0.04-0.15 Hz) and high frequency (HF; 0.15-0.40 Hz) spectral powers, LF/HF ratio, and the normalised units (nu) of LF and HF were used as HRV indices to measure cardiac autonomic control.

Results: Mean ST/HR index was 2.6 ± 1.7v μV/beats/min. Mean or median values for HRV indices were LF (nu) [60.4 (41.7-76.1)], HF (nu) (43.0 ± 24.4), LF/HF ratio [1.5 (0.7-3.1)]. Pearson moment correlation (controlling for gender) revealed that LF/HF ratio (r (81) = .28, p= .01) and LF (r (81) = .23, p= .03) were positively and HF (r (81) = -.27, p= .01) was negatively associated with ST/HR index.

Conclusion: This is the first study to report an association between ST/HR index, parasympathetic activity and autonomic balance in patient with RA. Measuring ST/HR index during ETT could be a particularly relevant indicator for p with RA who might not be able to exercise to their maximal HR due to joint problems. Thus, the use of ST/HR index during exercise testing may help in early detection of risk for MI in people with RA. Further research is needed to explore the associations between ST/HR index and clinical cardiac endpoints.

Disclosure: A. Osailan, None; **J. J. Veldhuijzen van Zanten**, None; **J. Duda**, None; **S. Fenton**, None; **P. Rouse**, None; **N. Ntoumanis**, None; **G. D. Kitas**, None; **G. Metsios**, None.

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Abstract Number: 1487

Comparison Between Intima-Media Thickness and Coronary Artery Tomography in Subclinical Atheroesclerosis Detection in Rheumatoid Arthritis

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Background/Purpose: Intima media thickness (IMT) and coronary artery calcification (CAC) quantification using multidetector computed tomography (MDCT) scanner are useful in detecting subclinical atherosclerosis and are good surrogate markers of cardiovascular morbidity and mortality in general population and in rheumatoid arthritis (RA). A good correlation between these methods has been reported in RA, being CAC a slightly more sensitive technique **(ref. 1).** Our aim is to determine the value of IMT that better predicts the presence of coronary atherosclerosis, using CAC as reference and assuming CAC value of 100 as the cut-off point indicating high cardiovascular risk.

Methods: We evaluated 127 RA patients without previous cardiovascular events. Carotid ultrasonography was performed by a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7-12 MHz linear transducer and the *automated software guided technique radiofrequency-Quality Intima Media Thickness* in *real-time* (*QIMT*, *Esaote*, *Maastricht*, *Holland*). According to data from non-rheumatic patients and also from RA patients, an IMT≥ 0.90 mm is a good predictor of high cardiovascular risk. To determine CAC score, a CT Imaging of coronary arteries using a 32-slice MDCT scanner (Lightspeed, Pro 32, GE Healthcare, USA) was performed.

Results: Patients with IMT below 0.90 mm had CAC values of 88±210 whereas patients with IMT≥0.90 mm had mean CAC values of 190 ± 272 (p=0.066). We found a positive correlation between IMT and CAC (correlation coefficient 0,303; p=0.001). The IMT cut-off value ≥ 0.90 mm had a sensitivity of 32% for detecting CAC ≥100. ROC curve analysis showed and area under the curve of 0.664. The IMT cut-off value of 0.80 mm had a sensitivity of 40% and a specificity of 71.3%. Lowering the IMT cut-off point to 0.70, we reached a sensitivity of 76% and a specificity of 51.5% for CAC ≥100 detection. The positive predictive value for the IMT cut-off point of 0.70 mm was 76% in our population, being the negative predictive value 49.5%

Conclusion: IMT values ≥0.70 mm predict coronary artery calcification score above 100 with a sensitivity of 76%. According to that, the IMT value considered as predictor of high cardiovascular risk would be 0.70 mm instead of 0.90 mm. **TABLE:**

Variable	
Age (mean ± SD)	58. 57 ±9.7
Female sex, n (%)	92 (72.,4)
IMT ≥ 0,9 mm, n (%)	19 (15)
IMT ≥ 0.7 mm, n (%)	71 (56)
CAC score (mean ± SD)	103.4 ±222.6
CAC score ≥ 100, n (%)	26 (20.5)

(ref. 1). Corrales A et al. Ann Rheum Dis. 2013, 72: 1764-1770.

Abstract Number: 1488

Comparison Between Carotid Ultrasonography and Coronary Artery Calcification Score to Detect Subclinical Atherosclerosis in Rheumatoid Arthritis

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Background/Purpose: Carotid ultrasonography (CU) and coronary artery calcification score (CAC) evaluated by multidetector computed tomography (MDCT) scanner are useful in detecting subclinical atherosclerosis in the general population and in rheumatoid arthritis (RA) patients. A good correlation between both diagnostic tools was demonstrated in RA, being CU more sensitive for detecting subclinical atherosclerosis **(ref. 1).** Using the presence of carotid plaque as a reference, we aimed to determine the cut-off value of CAC score that better predicts subclinical carotid atherosclerosis.

Methods: We evaluated 127 RA patients without previous cardiovascular events. Carotid ultrasonography was performed by a MyLab 70 scanner (Esaote; Genoa, Italy), equipped with 7-12 MHz linear transducer and the *automated software guided technique radiofrequency-Quality Intima Media Thickness* in *real-time* (*QIMT*, *Esaote*, *Maastricht*, *Holland*). Carotid plaque was defined according to the Manheim Conference Consensus criteria. To determine CAC score, a CT Imaging of coronary arteries using a 32-slice MDCT scanner (Lightspeed, Pro 32, GE Healthcare, USA) was performed. A CAC score ≥100 was considered as a surrogate marker of very high cardiovascular risk.

Results: Unilateral and bilateral carotid plaque frequency and the mean CAC score in the different groups are summarized in the **TABLE**. Patients without carotid plaques had a mean CAC value of 23±49 [range 0-250] whereas it was 50±116 [0-569] in patients with unilateral plaque and 192±302 [0-1205] in patients with bilateral plaques, being these differences statistically significant ($p<0.001$). The sensitivity to detect unilateral carotid plaques using a CAC score ≥100 as a marker of very high cardiovascular risk was very low (28%). A ROC curve comparing the presence of carotid plaque and CAC quantification was performed, being the area under the curve 0.692. The sensitivity and specificity for the presence of unilateral carotid plaques increased (69.3% and 64.1%, respectively) when we used a CAC score value ≥1 as the cut-off value to predict high cardiovascular risk. Positive predictive value using CAC ≥1 was 81.3% in our population, being 48.1% the negative predictive value.

Regarding bilateral carotid plaques, the CAC score ≥100 had a sensitivity of 40%. ROC curve showed an area under the curve of 0.712. Using a CAC score value ≥ 1 as the cut-off value to predict high cardiovascular risk, the sensitivity to determine the presence of bilateral carotid plaques increased to 76.4% but the specificity decreased to 54.2%.

Conclusion: A CAC score value score ≥1 is a good predictor of carotid plaques, showing sensitivity close to 70%. Our data support the use of a CAC score value score ≥1 instead of a CAC score ≥100 as the cut-off value to predict high cardiovascular risk in patients with RA. **TABLE**

Variable	
Age (mean ± SD)	58.57±9.7
Female, n (%)	92 (72.4)
Plaque: no, n (%)	39 (30.7)
Plaque: yes, n (%)	88 (69.3)
Unilateral plaque, n (%)	33 (26.0)
Bilateral plaque, n (%)	55 (43.3)
CAC (media±DE)	103.4±222.6
CAC ≥1, n (%)	75 (59.0)
CAC ≥100, n (%)	26 (20.5)

(ref. 1). Corrales A et al. Ann Rheum Dis. 2013, 72: 1764-1770

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coronary-artery-calcification-score-to-detect-subclinical-atherosclerosis-in-rheumatoid-arthritis

Abstract Number: 1489

Incident Hypertension and Associated Factors in a Hispanic Group with Rheumatoid Arthritis

Mariangelí Arroyo-Ávila[1], Ruth Fred-Jiménez[2], Naydi Pérez-Ríos[3], Angel M Mayor[4], Noelia Rodríguez-Pérez[1], Grissel Ríos[1] and Luis M. Vilá[5], [1]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [2]Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico, [3]Puerto Rico Clinical and Translational Research Consortium, University of Puerto Rico Medical Sciences Campus, San Juan, PR, [4]Universidad Central Del Caribe, Puerto Rico Clinical and Translational Research Consortium, Bayamón, Puerto Rico, [5]Department of Medicine, Division of Rheumatology, University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico

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Background/Purpose: Rheumatoid arthritis (RA) is associated with an increased incidence of cardiovascular disease. Hypertension is a major cardiovascular risk factor and it is one of the most common comorbid conditions in RA patients. The incidence and associated factors of hypertension occurring during the course of RA have not been extensively studied. Thus, we determined the demographic features, clinical manifestations, and pharmacologic profile associated with incident hypertension in a cohort of Hispanics with RA.

Methods: Hispanics from Puerto Rico with RA (per 1987 American College of Rheumatology classification criteria) were studied. Hypertension was defined as a blood pressure ≥140/90 mmHg on 2 or more subsequent visits. Incident hypertension was defined as that occurring after the onset of RA, whereas prevalent hypertension was defined as that occurring at or before the onset of RA symptoms. Demographic features, health-related behaviors, clinical manifestations, comorbidities, disease activity (per Disease Activity Score 28), functional status (per Health Assessment Questionnaire), patient's and physician's global disease assessments by visual analog scales, and pharmacologic treatment were determined. Differences between patients with incident hypertension and those without hypertension were examined by bivariable (chi-square and Student t tests) and multivariable (logistic regression) analyses.

Results: The entire cohort consisted of 405 RA patients. Prevalent hypertension was present in 83 (20.5%), incident hypertension in 140 (34.6%), and 182 (44.9%) patients did not have hypertension. The mean age of the study population was 54.4 years; 88.2% were women. The mean disease duration was 16.8 years. In the multivariable analysis adjusted for age, gender, disease duration, body mass index, dyslipidemia, and type 2 diabetes mellitus, incident hypertension was associated with joint replacement (OR 3.16, 95% CI 1.46-6.85, p=0.003), presence of fibromyalgia (OR 5.99, 95% CI 1.98-18.16, p=0.002), and corticosteroid use (OR 2.70, 95% CI 1.34-5.46, p=0.006). Conversely, exercise was negatively associated with incident hypertension (OR 0.41, 95% CI 0.19-0.88, p=0.023). No associations were observed for smoking, alcohol use, joint deformities, extra-articular manifestations, disease activity, functional status, patient's or physician's global disease assessments, early therapy (within 6 months of disease onset), or exposure to nonsteroidal anti-inflammatory drugs, disease-modifying anti-rheumatic drugs, or biologic agents.

Conclusion: In this population of patients, nearly 35% developed hypertension during the course of RA. Several features including joint replacement, presence of fibromyalgia, and corticosteroid use were associated with incident hypertension, whereas exercise was associated with decreased risk. Clinicians should be aware of these associations to provide appropriate management and counseling to RA patients, especially those related to modifiable factors such as exercise and steroid use.

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Abstract Number: 1490

Metabolic and Cardio-Vascular Benefits of Hydroxychloroquine in Patients with Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Background/Purpose: Cardiovascular disease (CVD) is the leading cause of mortality in rheumatoid arthritis (RA) patients. Hydroxychloroquine (HCQ) has been shown to improve major outcomes like survival rates in other inflammatory diseases, like systemic lupus. The aim of our study was to assess currently available literature on the cardio-vascular impact of hydroxychloroquine (HCQ) in patients with RA.

Methods: We systematically searched literature (via Pubmed, Embase and abstracts from recent ACR and EULAR congresses) for studies evaluating the effects of HCQ, wether in monotherapy or in combination with other conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) on cardio-vascular outcomes or known risk factors for CVD in RA patients (lipid profiles, diabetes incidence, insulin resistance and incidence of CVD). A meta-analysis was performed with Review Manager Software, with random-effects models, whenever methodologically possible and relevant. Data were extracted by one investigator and independently checked by another.

Results: The literature search revealed 213 articles and abstracts of potential interest, and further examination resulted in 13 studies fulfilling required criteria for preplanned analyses regarding the cardio-vascular impact of HCQ in RA. For lipid profiles, the mean difference (mg/dL) between HCQ users versus non-users was -9,82 (95% confidence interval [95% CI] -14.03; -5.60) for total-cholesterol (figure 1), -10.61 [-14.17;-7.04] for low-density-lipoprotein, +4.13 [2.22;6.04] for high-density-lipoprotein, and -19.15 [-27.20; -11.10] for triglycerides (figure 2); with respectively a decrease (mg/dL) of -13.15 [-20.96; -5.34], -12.35 [-20.14; -4.36], 1.67 [-0.96, 4.31] and -12.54 [-28.94; 3.86] after HCQ initiation. Diabetes incidence was reduced in “HCQ ever users” versus “patients who never used HCQ” with a hazard-ratio of 0.59 [0.49; 0.70] (figure 3). In addition, HCQ seems to decrease insulin resistance and incidence of cardio-vascular events but data were too scarce for meta-analysis.

Conclusion: Beside its limited efficacy on disease activity, this study supports the benefit of HCQ on metabolic profile and to a lesser extent on cardio-vascular events of patients with RA, suggesting its usefulness in combination with other csDMARD.

Figure 1 – Forest plot for the mean difference (mg/dL) of total-cholesterol between HCQ users and HCQ non users

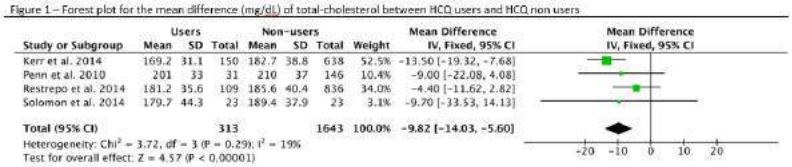


Figure 2 – Forest plot for the mean difference (mg/dL) of triglycerides between HCQ users and HCQ non users

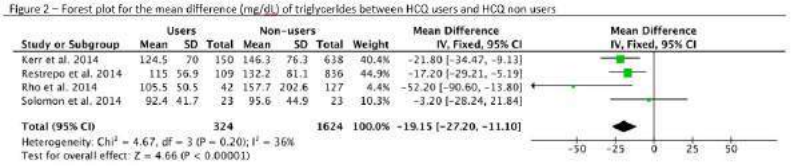
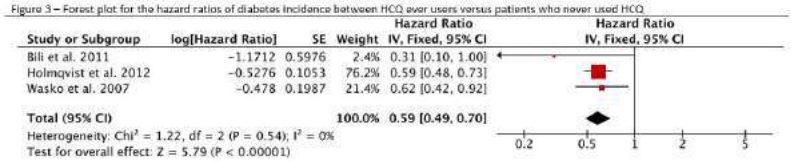


Figure 3 – Forest plot for the hazard ratios of diabetes incidence between HCQ ever users versus patients who never used HCQ



Disclosure: C. Rempenault, None; **T. Barnetche**, None; **J. Morel**, None; **C. Lukas**, None; **C. Gaujoux-Viala**, None; **B. Combe**, None; **C. Hua**, None.

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Abstract Number: 1491

M-Ficolin and MAp44 As Potential Markers of Subclinical Cardiovascular Comorbidity; Cardiac Evaluation By Coronary Computer Tomography and Myocardial Deformation of Left Ventricle in Early Rheumatoid Arthritis Patients

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Background/Purpose: The aim was to investigate M-ficolin and Map44, proteins from the lectin pathway, as prognostic markers of subclinical cardiovascular disease in untreated early rheumatoid arthritis (RA) patients. We evaluated the associations between M-ficolin, MAp44 and disease activity (DAS28, CRP and HAQ-score), the degree of coronary artery calcification and myocardial deformation of left ventricle in an inception cohort.

Methods: 79 DMARD-naïve RA patients with a disease duration < 6 months were included from an inception cohort. Clinical variables, plasma- and serum-M-ficolin and MAp44 levels, myocardial deformation analysis and coronary calcification were measured at baseline and after two years. M-ficolin and Map44 were measured with an in-house time-resolved flourometric immunoassay. Coronary calcification was evaluated by Agatston calcium-score using cardiac computer tomography. Left ventricle deformation imaging was determined by speckle tracking echocardiography. Level of statistical dependence and significance were determined with Spearman rank correlation test.

Results: Baseline serum M-ficolin was associated to CRP (r=0.26, p=0.02) and DAS28 (r=0.24, p=0.04). Further, baseline Map44 was associated to CRP in serum (r=0.25, p=0.03) and plasma (r=0.29, p=0.01). At the two-year follow-up patient's global assessment, assessment of pain, fatigue and HAQ score were associated to serum MAp44 (range p=0.002; 0.04), (range r=-0.36; -0.25). We found associations between baseline fasting insulin and M-ficolin and MAp44 (range p=0.001; 0.02). No associations were found between Agatston calcium score and MAp44 or M-ficolin. Only baseline plasma MAp44 showed association to global longitudinal strain (GLS) (r=0.27, p=0.03).

Conclusion: M-ficolin and MAp44 were associated with disease activity markers and plasma insulin at baseline and at two-year follow-up. GLS and MAp44 were positively associated at baseline.

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Abstract Number: 1492

Biomarker-Related Risk for Myocardial Infarction and Serious Infections in Patients with Rheumatoid Arthritis: A Population-Based Study

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Background/Purpose: Serious infection events (SIE) and myocardial infarction (MI) are among the most concerning adverse events that occur in rheumatoid arthritis (RA) patients. The role of RA disease activity and associated systematic inflammation has been examined only in a limited fashion as it relates to these outcomes.

Methods: Multi-biomarker disease activity (MBDA) test scores (n=77,641) were linked to Medicare claims at a patient-level for individuals with RA who had at least 12 months of Medicare coverage from 2011-2014, excluding patients with other autoimmune diseases. The 4 outcomes studied were pneumonia or sepsis as the primary reason for hospitalization (SIE-primary); any pneumonia or sepsis during hospitalization (SIE-secondary); MI; and a composite CHD outcome (MI, PCI or CABG), using previously-validated definitions defined by ICD9 and HCPCS codes. Patients were excluded from the MI/CHD analysis for prior MI. The MBDA score was analyzed in a time-varying fashion, updated with each new test result, and analyzed according to its established disease activity cutpoints and in quartiles. MBDA scores were lagged by 1 week (MI/CHD) or 2 weeks (SIE). Tests were excluded (n=10,996) for vaccination, antibiotic use, or hospitalization within the prior 21 days. Patient baseline characteristics were measured at the time of the first usable MBDA test and in the previous 12 months. Cox proportional hazards models evaluated the association between MBDA score and SIE, MI, and CHD events, controlling for age, sex, and race.

Results: A total of 17,333 patients were eligible for the SIE, and 16,796 for the MI/CHD analyses. Baseline characteristics were mean (SD) age 69 (10) years, 79% women, 80% white, and 37% disabled. RA therapies included biologics (20%), MTX (55%), other non-biologic DMARDs (40%), and oral glucocorticoids (51%). In up to 16,424 person-years of follow-up, there were 452 SIE-primary, 653 SIE-secondary, 132 MI, and 181 CHD events. The crude rates of all outcomes were associated with increasing MBDA score in a dose-response fashion (Table), using either established cutpoints or quartiles. After adjustment for age, sex, and race, higher MBDA score was associated with all outcomes of interest. Sensitivity analyses that examined the MBDA score without CRP, and separately adjusted for CRP, yielded similar findings to the main results.

Conclusion: Higher MBDA scores were associated with increased risk for hospitalized infection, MI, and CHD events in a large U.S. RA population predominantly consisting of older individuals. Use of the MBDA score to risk-stratify patients for these serious adverse events may help clinicians identify those at highest risk.

Table: Incidence Rates and Adjusted Risk of Serious Infection Events and MI/CHD Outcomes Associated with MBDA Score								
	SIE-primary		SIE-secondary		MI		CHD	
MBDA	IR*	aHR (95% CI)	IR*	aHR (95%CI)	IR*	aHR	IR*	aHR
All scores	2.75	1.47 (1.38,1.55)	4.00	1.48 (1.41,1.55)	0.82	1.20 (1.06,1.34)	1.13	1.18 (1.07,1.31)
Categorical score Low (<30) Moderate (30-44) High (>44)	0.74 1.98 4.17	referent 2.55 (1.55,4.18) 5.34 (3.31,8.63)	1.19 2.73 6.17	Referent 2.18 (1.47-3.23) 4.91 (3.36-7.18)	0.42 0.80 0.98	Referent 1.68 (0.85,3.34) 2.06 (1.05-4.03)	0.67 1.05 1.36	Referent 1.48 (0.85,2.55) 1.89 (1.11,3.24)
Quartiles Q1 (<35) Q2 (35-42) Q3 (43-52) Q4 (53-100)	1.07 2.06 3.09 4.94	Referent 1.87 (1.30,2.67) 2.78 (1.96,3.95) 4.45 (3.21,6.19)	1.58 2.79 4.62 7.28	Referent 1.71 (1.27,2.38) 2.81 (2.11-3.75) 4.44 (3.89-5.82)	0.47 0.83 0.92 1.09	Referent 1.63 (0.94,2.83) 1.78 (1.01,3.13) 2.13 (1.24,3.67)	0.67 1.08 1.34 1.42	Referent 1.56 (0.97,2.52) 1.93 (1.32,3.06) 2.02 (1.27,3.21)
SIE = Serious infection event; MI = myocardial infarction; CHD = MI, PCI, or CABG; IR=incidence rate per 100 patient years; aHR = adjusted hazard ratio, controlling for age, sex and race. aHR associated with MBDA score (first row) expressed per 10 unit change								

Disclosure: J. Curtis, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **F. Xie**, None; **L. Chen**, None; **H. Yun**, Amgen, 2.

Abstract Number: 1493

Screening Patterns for Hyperlipidemia Among Patients with Rheumatoid Arthritis Based on Patterns of Care from By Primary Care Physicians, Rheumatologists or Both

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Background/Purpose: Coronary heart disease (CHD) is increased among patients with rheumatoid arthritis (RA). Limited data suggest that there is a screening gap for hyperlipidemia, a risk factor for CHD, among RA patients. To evaluate the pattern of lipid testing among RA patients based on whether patients are receive care from a primary care physician (PCP), a rheumatologist, or both.

Methods: We used a dataset that linked commercial and public health plan claims data together over 2006 to 2010. Eligible participants were required to 1) have at least 12 months of continuous medical and pharmacy coverage (baseline), and 2) have 2+ physician diagnosis plus relevant DMARD/biologic medications to categorize them as having RA; 3) 2 years of follow-up. Patients with prevalent myocardial infarction (MI), stroke or CHD during baseline were excluded as well as patients who had baseline diagnosis of hyperlipidemia and/or were already using hyperlipidemia medications The patterns of care at baseline were characterized into 3 categories: 1) visited ONLY PCP; 2) visited ONLY Rheumatologist; 3) visited both rheumatologist AND PCP. We used logistic regression to determine the likelihood of been screened for hyperlipidemia during 2 years of follow-up based on whether RA patients received care from a PCP (only), a rheumatologist (only) or both.

Results: There were 13,319 patients with RA. Overall, 83% were women. The overall age distribution was: 26% 41-60 and 74% >65 years old. There were 18 % of the RA patients who did not see a PCP the 12-month baseline. The proportion of patients that were screened for hyperlipidemia , stratified by physician specialty pattern were: 1) care from a PCP only = 42%; 2) care from a Rheumatologist only = 40%; 3) care from both a rheumatologist AND PCP = 47% . After controlling for multiple potential confounders, there was a 32% increase in the likelihood of being screened for hyperlipidemia if RA patients received combined care between PCPs and rheumatologist (Table).

Conclusion: Screening for hyperlipidemia may not be part of the factors that rheumatologist considered as part of the care of RA patients. Improvement in coordination of care between PCP and rheumatologist s,as well as establishing which physician should be responsible for hyperlipidemia management, may increase appropriate cardiovascular risk factor screening. Table: Likelihood of RA patients being tested for hyperlipidemia in regards to visiting either a rheumatologist or primary care physician

Characteristic	% tested for hyperlipidemia	Unadjusted (95% CI)	Adjusted* (95% CI)
All patients, N	**5932 (44.5)**	**13,319**	**13,319**
Rheum only [referent]	40.0	Ref	Ref
PCP only	41.9	1.08 (0.97,1.20)	1.07 (0.96,1.20)
PCP + Rheum	46.9	1.32 (1.21,1.45)	1.32 (1.20,1.45)
*adjusted for age category, sex, race, comorbidity index, and RA medication use			

Disclosure: I. Navarro-Millán, None; **S. Yang**, None; **L. Chen**, None; **H. Yun**, None; **C. M. Bartels**, None; **A. Jagpal**, None; **A. Cherrington**, None; **L. Fraenkel**, None; **M. M. Safford**, None; **J. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 1494

Myocardial Structure, Function, and Fibrosis in Patients with Rheumatoid Arthritis and Matched Control Subjects

Michelle J. Ormseth[1], William Bradham[2], Comfort Elumogo[3], Srikanth Palanisamy[4], Chia Liu[5], Mark Lawson[2], Jonathan Soslow[2], Nadine Kawel[6], David A. Bluemke[7] and C Michael Stein[2], [1]Medicine, Vanderbilt University Medical Center, Nashville, TN, [2]Vanderbilt University Medical Center, Nashville, TN, [3]National Institutes of Health, Bethesada, MD, [4]Cornell University, Ithaca, NY, [5]National Institutes of Health, Bethsada, MD, [6]National Institutes of Health, Bethsada, TN, [7]National Institutes of Health, Bethesda, MD

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Background/Purpose: The prevalence of heart failure is increased 2-fold in RA; this is not explained by ischemic heart disease or other risk factors for heart failure. We have previously shown that N-terminal pro-brain natriuretic peptide and high-sensitivity cardiac troponin-I are elevated in RA, suggesting subtle myocardial dysfunction or chronic myocyte injury. We hypothesized that in patients with RA without known heart disease, cardiac magnetic resonance imaging (CMR) would detect altered cardiac structure, function, and

fibrosis.

Methods: We performed 1.5-T CMR in 59 patients with RA and 56 controls frequency-matched for age, race, and sex. CMR indices of structure, function, and fibrosis (late gadolinium enhancement (LGE), T1 values, extracellular volume fraction (ECV)) were compared between RA and control subjects using Mann-Whitney U tests and linear regression adjusting for age, race, and sex. Measurements were performed by CMR expert cardiologists blinded to disease or control status.

Results: Patients with RA had low to moderate disease activity (DAS28-CRP median [interquartile range] =3.16 [2.03, 4.05]. Indexed left ventricular (LV) mass, indexed LV end diastolic and systolic volumes, and left atrial size were not altered in RA. LV ejection fraction was also not significantly altered in RA. LGE was found in 2 patients with RA and 1 control subject; T1 mapping and ECV (measures of diffuse fibrosis) did not differ significantly between RA and control subjects (Table).

Conclusion: Contrary to a prior report, CMR measures of cardiac structure, function, and fibrosis were not significantly different in patients with well-controlled RA compared to a matched control group in the largest study to date.

Table. CMR findings

	Control (N=56)	RA (N=59)	Adjusted P
LVEDV indexed to BSA, ml/m2	61.1 [55.0, 66.3]	59.3 [46.9, 66.9]	0.13
LVESV indexed to BSA, ml/m2	20.9 [16.0, 26.3]	18.0 [11.7, 24.5]	0.05
LVEF, %	66.7 [60.1, 70.3]	67.9 [62.4, 74.4]	0.07
LV mass indexed to BSA, g/m2	42.2 [36.4, 48.5]	43.8 [40.0, 49.5]	0.21
LA size, mm	29 [26, 32]	29 [24, 32]	0.19
Presence of LGE, n (%)	1 (1.8)	2 (3.4)	-
Native myocardial T1, msec	978 [928, 996]	973 [945, 1001]	0.92
Post-contrast T1, msec	453 [427, 476]	457 [424, 486]	0.15
ECV, %	26.6 [24.7, 28.5]	27.5 [25.4, 30.4]	0.06

Adjusted for age, race and sex. BSA= body surface area.

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Lipoprotein(a) Concentrations in Rheumatoid Arthritis on Biologic Therapy: Results from the Cardiovascular in Rheumatology [CARMA] Study Project

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Background/Purpose: Plasma concentrations of lipoprotein (a) [Lp(a)], a lipoprotein with proatherogenic and thrombogenic properties, have a strong genetic basis, although high concentrations of Lp(a) have also been reported in the context of inflammation, as rheumatoid arthritis (RA) (1). There are few studies that evaluate the impact of biologic therapies on Lp(a) in RA (2), taking into account that with these new therapies a better control of inflammation is achieved.This study evaluate the plasma concentrations of Lp(a) in Spanish RA patients on biological therapies attending rheumatology outpatient clinics.

Methods: Baseline analysis of the CARMA project (CARdiovascular in rheuMAtology), a 10-year prospective study evaluating the risk of cardiovascular events in RA patients and other forms of inflammatory arthritis who attended rheumatology outpatient clinics at 67 hospitals in Spain. RA patients were classified into four categories: no biologic therapy, undergoing anti-TNF therapy, receiving anti-IL-6 receptor tocilizumab (TCZ), and other biologic therapies (rituximab or abatacept). A model of linear multivariate regression was built in which the dependent variable was Lp(a) concentration and the explanatory variable was biologic therapy. The model was adjusted for confounding factors.

Results: Seven hundred and seventy-five RA patients were analyzed. Total cholesterol and triglycerides concentrations were significantly higher in TCZ-treated patients. Nevertheless, no significant difference in the atherogenic index (TC/HDL-c) between TCZ-treated patients and patients without biological therapy was found. After adjusting for confounding factors, patients treated with biologic therapy had lower plasma concentrations of Lp(a) than those not undergoing biologic therapy. However, only TCZ-treated patients achieved statistically significant differences when compared with those not undergoing biologic therapy (β-coefficient: -0.303, 95% confidence interval: -0.558 to -0.047; p=0.02).

Conclusion: RA patients treated with tocilizumab, an inhibitor of interleukin 6 receptor, show lower plasma concentrations of Lp (a) compared to patients without biological therapy.

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Risk for Serious Infection in Rheumatoid Arthritis Associated Interstitial Lung Disease

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Background/Purpose: Rheumatoid arthritis (RA) associated interstitial lung disease (ILD) carries a risk for serious infection due to lung disease, immunosuppressive therapy, and RA disease itself.

Methods: All patients with RA-ILD (ACR 1987 criteria for RA) seen at a single center from 1998-2014 were identified and manually screened for study inclusion. Follow-up data were abstracted until death or December 31, 2015, including immunosuppressive

medications at and after ILD diagnosis. Serious infection was defined as an infectious process requiring both antimicrobial therapy and hospitalization. Risk of infection was analyzed by person-year (py) methods using a 30-day washout period after discontinuation of individual medications.

Results: Of the 181 included patients, 87 (48%) were female and 96% were Caucasian. The mean age at ILD diagnosis was 67.4 (±9.9) years with a median time of 4.9 (range: -10.9 to 48.1) years from RA to ILD diagnosis. Median follow-up time was 3.1 (range: 0.01 to 14.8) years. Sixty-seven (37%) were never smokers. Ninety-eight (54%) had usual interstitial pneumonia (UIP), 73 (40%) had non-specific interstitial pneumonia (NSIP), and 10 (6%) had RA-related organizing pneumonia (OP). A total of 54 serious infections were identified of which pneumonia was the most common with (3.9 per 100 py) followed by opportunistic infections (1.5 per 100 py) and septicemia (1.0 per 100 py). Overall infection risk was higher in OP (27.1 per 100 py) than UIP (7.7 per 100 py) or NSIP (5.5 per 100 py) (P<0.001), and did not differ in UIP and NSIP (p=0.24). Pneumonia and septicemia were also significantly more common among OP patients (although number with OP was small) than in UIP and NSIP (p=0.002 and p=0.007, respectively), but there were no differences between groups in opportunistic infections (p=0.63). Immunosuppressive regimens were summarized into distinct groups (see table), of which tumor necrosis factor inhibitors with or without disease modifying anti-rheumatic drug (DMARD) or glucocorticoids was the most common (163.0 py). Sulfasalazine and/or hydroxychloroquine (SSZ/HCQ) were used as the referent group for comparisons and had an infection rate of 2.9 per 100 py. The highest infection rate observed was with a daily prednisone use > 10mg per day with or without additional DMARDs with a rate of 15.4 per 100 py. There were no significant differences observed between baseline and no immunosuppression, methotrexate/leflunomide (MTX/LEF), tumor necrosis factor inhibitor (TNFi) or other DMARD combination. Prednisone > 10mg (RR: 4.40; 95%CI: 1.38, 27.7) and non-TNFi biologic (RR: 3.87; 95%CI: 1.22, 24.3) had the highest risk.

Conclusion: Patients with RA-ILD are at high risk of serious infection. Prednisone use at >10 mg per day was associated with higher rates of infection, and lowest risk was in patients on SSZ/HCQ and TNFi. Channeling bias cannot be excluded.

Table 1. Risk of Serious Infection by Medication in 181 Patients with Rheumatoid Arthritis Associated Interstitial Lung Disease

Medication Category	Number of Patients	Number of Patients with Infections	Number of Infections	Number of Person Years (PY)	Infection Rate per 100 PY
Overall	181	38	54	726.2	7.4
SSZ/HCQ alone*	36	2	2	68.3	2.9
MTX/LEF alone	54	5	8	107.4	7.4
TNFi (with any**)	59	3	3	163.0	1.8
non-TNFi biologic (with any)	38	7	11	81.2	13.5
Prednisone ≤ 10 mg per day alone*	54	4	6	54.4	11.0
Prednisone > 10 mg per day (with any**)	86	11	11	71.5	15.4
Other DMARD or combination	80	8	9	119.6	7.5
No therapy	48	4	4	60.7	6.6

*Alone: without other antirheumatic drug or glucocorticoid **with any: any other antirheumatic drug in combination.

Abbreviations: sulfasalazine (SSZ), hydroxychloroquine (HCQ), methotrexate (MTX), leflunomide (LEF), tumor necrosis factor inhibitor (TNFi), disease modifying anti-rheumatic drug (DMARD)

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Progressive Decline of Lung Function in Rheumatoid Arthritis Associated Interstitial Lung Disease

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Background/Purpose: Interstitial lung disease (ILD) is associated with substantial morbidity in rheumatoid arthritis (RA), but virtually nothing is known about the long-term of progression of pulmonary disease.

Methods: All patients with RA-ILD (ACR 1987 criteria for RA) seen at a single center from 1998-2014 with at least 4 weeks follow-up and at least 1 pulmonary function test (PFT) were identified and manually screened for study inclusion. Follow-up data were abstracted until death, 10 years follow-up or December 31, 2015, including all PFTs within 12 months of initial diagnosis and first PFT for each subsequent follow-up year. Progression was defined as a diffusing capacity for carbon monoxide (DLCO) < 40% predicted/ too ill to perform DLCO or a forced vital capacity (FVC) < 50% predicted. Time to progression was analyzed using Kaplan-Meier methods and Cox models adjusted for age and sex.

Results: Of the 167 included patients, 81 (49%) female, 97% Caucasian, mean age was 67 years (±10) at ILD diagnosis. 62 (37%) were never smokers. Median follow-up time from ILD diagnosis was 3.3 (range 0.01-14.8) years. Eighty-nine (53%) had usual interstitial pneumonia (UIP), 70 (42%) had non-specific interstitial pneumonia (NSIP), and 8 (5%) had RA-related organizing pneumonia (OP). A total of 564 PFTs were abstracted. Baseline PFTs at time of ILD diagnosis (± 6 months) included mean percent predicted FVC of 72% ± 20, forced expiratory volume (FEV1) of 72% ±21, total lung capacity (TLC) of 73% ± 16 and DLCO of 55% ±18. Mean percent predicted DLCO for UIP was 51% ±16, for NSIP 58% ±20, and for OP 74% ±13 (P=0.006). During follow-up, DLCO declined to <40% predicted or were too ill to perform the test in 57 patients, and 29 patients developed an FVC < 50%. By 5 years after ILD diagnosis, 33.2% of patients reached DLCO<40% predicted or were too ill to perform the test and 16.3% of patients reached FVC<50% predicted. Risk factors for progression to DLCO < 40% were UIP (vs NSIP) (hazard ratio [HR]: 2.22; 95% confidence interval [CI]: 1.26, 3.92) and male sex (HR: 1.63; 95% CI: 0.96, 2.75). C-reactive protein at ILD diagnosis was associated with progression to FVC<50% (HR: 1.16 per 10 mg/L increase; 95% CI: 0.97, 1.38). Higher percent predicted DLCO and FVC at baseline reduced the risk for progression to a DLCO < 40% (HR: 0.48 per 10 unit increase; 95% CI: 0.40, 0.58; HR: 0.70 per 10 unit increase; 95% CI: 0.60, 0.82; respectively) and an FVC < 50% (HR: 0.64 per 10 unit increase; 95% CI: 0.48, 0.84; HR: 0.38 per 10 unit increase; 95% CI: 0.29, 0.50; respectively). Estimated rate of change in the first 6 months for FVC was a median increase of 1.0% predicted (interquartile range: -5.0, 7.0) and for DLCO was a median loss of 1.0% (interquartile range: -6.0, 5.0). There was a significant association between the DLCO 6-month rate of change progression to DLCO < 40% (HR: 1.55 per 10-unit decrease; 95% CI: 1.10, 2.18) and between the FVC 6-month rate of change and progression to FVC<50% (HR: 2.44; 95% CI: 1.44, 4.13).

Conclusion: Progressive loss of pulmonary function is common in RA-ILD and is typically worse in patients with UIP than NSIP. A higher baseline DLCO and FVC reduced the risk of progression, but higher rates of change in the first 6 months increased the risk of severe pulmonary impairment.

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Patterns of Interstitial Lung Disease and Associated Mortality in Rheumatoid Arthritis

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Background/Purpose: To characterize a cohort of patients with rheumatoid arthritis (RA) who have interstitial lung disease (ILD) and to assess the utility of the GAP (gender, age, pulmonary function) and ILD-GAP staging system for mortality risk prediction in patients with RA-ILD.

Methods: All patients with RA and ILD seen at a single center from 1998-2014 were identified and manually screened for study inclusion and followed until death or December 31, 2015. All cases fulfilled the 1987 ACR criteria for RA. Pulmonary function test (PFT) results closest to ILD diagnosis were recorded. The GAP and ILD-GAP scores were calculated using age, sex, and lung physiology variables (forced vital capacity [FVC], diffusing capacity for carbon monoxide [DLCO]) at ILD diagnosis. Survival rates were calculated using the Kaplan-Meier method. Cox models were used to examine associations between baseline characteristics and mortality. The accuracy of risk predictions was assessed using standardized incidence ratios and c-statistics.

Results: Of the 181 included patients, 87 (48%) were female and 96% were Caucasian. The mean age at ILD diagnosis was 67.4 (±9.9) years with a median time of 4.9 (range: -10.9 to 48.1) years from RA to ILD diagnosis. Median follow-up time was 3.1 (range: 0.01 to 14.8) years. Sixty-seven were never smokers (37%) and 44 (24%) had erosive disease. Ninety-eight (54%) had usual interstitial pneumonia (UIP), 73 (40%) had non-specific interstitial pneumonia (NSIP), and 10 (6%) had RA-related organizing pneumonia (OP). Anti-citrullinated protein antibodies were present in 77% of 136 tested and rheumatoid factor in 82% of 176 tested. The baseline PFTs at time of ILD diagnosis included mean percent predicted FVC of 72% ± 20 and DLCO of 56% ±20. At last follow-up 72 had died. Pulmonary disease accounting for 21 (29%) of deaths. The five-year survival rate was 59.7% (95% confidence interval [CI] 51.5-69.2). Survival did not differ between ILD types (p=0.42). Baseline risk factors significantly associated with mortality were age at ILD diagnosis (hazard ratio [HR]: 1.34 per 10 year increase; 95% CI: 1.11-1.63) and RA disease duration at ILD diagnosis (age and sex adjusted HR 1.71 per 10 year increase; 95% CI: 1.22-2.39). Lower baseline percent predicted DLCO and FVC were associated with significantly higher mortality (HR: 2.48; 95% CI: 1.55-3.95 and HR: 1.20; 95% CI: 1.04-1.41, per 10% predicted decrease, respectively). GAP and ILD-GAP scores were calculated for 159 patients with PFTs within 6 months of diagnosis. 30 patients died within 3 years of diagnosis. The GAP model predicted 31.0 deaths and demonstrated good calibration (standardized incidence ratio [SIR]: 0.97; 95% CI: 0.68, 1.38) and discrimination (c-statistic: 0.71). The ILD-GAP score reduced the predicted mortality risk, so only 18.3 deaths were predicted within 3 years of ILD diagnosis, this demonstrated poor calibration (SIR 1.64; 95%CI 1.15, 2.35).

Conclusion: In this large single-center cohort of patients with RA-ILD, most patients were seropositive and had a history of smoking. RA-ILD is associated with decreased survival, similar for NSIP and UIP. The GAP model may be useful in informing prognosis and patient management.

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Abstract Number: 1499

Anti-Cyclic Citrullinated Peptide Antibodies and Severity of Interstitial Lung Disease with Rheumatoid Arthritis

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Background/Purpose: Serum anti-cyclic citrullinated peptide antibodies (anti-CCP2) positivity was associated with presence of interstitial lung disease and airway disease in rheumatoid arthritis (RA). This study analyze whether high resolutional CT (HRCT) and anti-CCP2 can predict the outcome of ILD in RA.

Methods: 472(Male74/Female398, age 58.9+/-14.0) cases were analyzed in this study. Participants met 2010 ACR/EULAR classification criteria of RA were followed up at least one year as newly onset RA. All patients were also performed chest radiological

examinations at the initial presentation. ILD extension Score was determined based on the presence and extent of ILD features (i.e., ground glass opacification (GGO), reticulation and honeycombing (HC) using a semiquantitative scale at the each of the three zones of each lung with a maximum total score possible of 6. HRCT parameters which include ILD extension Score and titer of anti-CCP2 at the initial presentation were retrospectively analyzed.

Results: 231 out of 472 patients (48.9%) had abnormal chest radiological findings which included bronchiectasis, bronchitis and ILD. 101 out of 472 patients (21.4%) showed ILD at initial presentation. The titer of anti-CCP2 showed statistical difference between RA only vs. RA-ILD patients(Ave. 47.8 and 164.3 U/ml, respectively, $p<0.001$). 6 out of 101 RA-ILD patients showed rapidly progressive ILD. These 6 patients had widely spread honeycombing compared to asymptomatic RA-ILD patients ($p=0.0012$). In 101 RA-ILD patients, higher anti-CCP2 levels were associated with more severe RA-ILD. Average titer of anti-CCP2 in ILD extension Score 1, 2, 3, 4, 6 showed 20.3+/-28.4, 155.0+/-49.6, 290.9+/-26.3, 693.7+/-308.9 and 1582.5+/-120.9 U/ml respectively. Higher extension score of each ILD features GGO ($p=0.0052$), reticulation ($p=0.0047$) and honeycombing ($p=0.0025$) also showed association with higher anti-CCP2.

Conclusion: Anti-CCP2 antibodies are marker of severity and extent of RA-ILD in HRCT. HRCT findings focused on ILD extension Score at the initial presentation is a useful predictor of the outcome of ILD in RA. Anti-CCP2 is one of the related factor of ILD extension Score.

Disclosure: M. Yamasaki, None;

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Concomitant Development of Interstitial Pneumonia Associated with Dermatomyositis and Rheumatoid Arthritis

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Background/Purpose: A few cases of the concomitant development of interstitial pneumonia associated with dermatomyositis (DM-IP) and rheumatoid arthritis (RA) have been reported mainly in Asia, but the details are still unclear. The possible induction of dermatomyositis (DM) and polymyositis by TNF inhibitor has been pointed out, but no conclusion has been reached. We investigated the clinical features of DM-IP which concomitantly developed during the treatment of RA.

Methods: The subjects were 14 consecutive patients with DM-IP complicating RA treated at our department between November 2005 and October 2015, and the clinical features, such as patient background, clinical symptoms, examinations, treatment, and outcome, were retrospectively investigated. RA was diagnosed using the 1987 Revised ACR classification criteria and 2010 ACR/EULAR classification criteria, and DM was diagnosed using the criteria of Bohan and Peter. For the classification of clinically amyopathic dermatomyositis (CADM), the criteria of Sontheimer and Gerami were used. IP was diagnosed using chest HRCT, and the pattern was classified following the 2013 Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias.

Results: The median (IQR) onset age of DM-IP was 62.5 years old (54-68.5). All patients were female, and 4 were smokers (29%). The duration of RA illness until the development of DM-IP was 1,095 days (577-1,580). DM-IP newly developed during RA treatment in 5 patients at our department and the incidence was 0.57%. Nine patients were transferred for IP treatment from other hospitals. ACPA was >100, 15-100, and <15 U/mL at the time of RA diagnosis in 7 (54%), 3 (23%), and 3 (23%), respectively, RF was 58 IU/mL (33-149), and radiologic damage was noted in 11 (79%). RA was treated with MTX in 6 (42.9%), PSL in 6 (42.9%), BUC in 2 (14.3%), TAC in one (7.1%), biologics in 4 (28.6%) (ETN in 3 and GLM in 1), and others in 4 (28.6%). IP exacerbated within one month in 3 (21.4%) and 1-3 months in 4 (28.6%), and a slow course taking 3 months or longer was observed in 7 (50%). At the onset

time of DM-IP (at the time of diagnosis), KL-6 was 769 U/mL (368-1,215), aldolase was 7.2 U/L (5.8-11.2), CK was 83 U/L (40-331), and ferritin was 119 (91-253) ng/mL. On chest HRCT, the NSIP and OP patterns were noted in 7 each (50%), and no honeycomb lung was seen. In all patients, dorsal lower lung field-dominant shadows newly appeared. On imaging before the development, the NSIP pattern was observed in 4 (28.6%), but no existing feature of IP was noted in 10 (71.4%). DM-IP was treated with PSL in all patients, and IVCY, CsA, and TAC were administered to 3, 9, and 3 patients, respectively. Cyclosporin was administered at 4 mg/kg in all treated cases, and cyclophosphamide was concomitantly administered to severe cases. Regarding the outcome, remission was achieved in all patients without recurrence.

Conclusion: DM-IP frequently developed concomitantly with RA in females with a high ACPA titer. Various DMARDs were used in previous RA treatment, but TNF inhibitor was used as a biological product in all cases. When NSIP and OP appear dominantly in the lower lung field during RA treatment, the concomitant development of DM-IP should be suspected.

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Abstract Number: 1501

The Incidence of Interstial Lung Disease and Malignancies in Veterans with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a systemic disease with a known association with lymphoma and interstitial lung disease (ILD). ILD is a frequent extraarticular manifestation of RA with a prevalence as low as 4% and as high as up to 68%. Additionally, patients with RA also have been documented to have an increased risk of lymphoma. It is unclear if the increased incidence of lymphoma or ILD is correlated to the disease itself or the treatment. In particular, new attention is being drawn to biologic agents being used to treat severe rheumatoid arthritis and whether these agents in particular, through immune-mediated actions, may specifically pose an increased risk of either ILD or lymphoma. This study aims to examine the incidence for ILD and malignancies in patients at the McGuire Veteran's Medical Center with a diagnosis of RA as well as to examine the whether this incidence is affected by treatment.

Methods: Patients with an ICD-9 code of RA who have received care from a rheumatologist at the McGuire VA Medical Center are included in this study. Diagnosis of malignancy and ILD was determined by ICD-9 codes as well. As of now, 275 patients have met our inclusion criteria. Baseline demographic data, data regarding diagnosis and treatment of rheumatoid arthritis, and diagnosis of cancer and/or ILD were collected.

Results: Based on our current data, compared to the general population, the incidence of malignancy in our veteran population is 49% ($p < 0.0001$). This is higher than the general population. Patients with RA diagnosed at age 65 or above have a higher chance of being diagnosed with cancer (HR 1.089). The incidence of ILD is 9%; however, this is not significant compared to general population ($p = 0.08$). Interestingly, there appears to be a protective effect of treatment with a biologic in patients diagnosed with cancer (HR 0.54).

Conclusion: This is currently an ongoing study to examine the incidence of ILD/malignancy and correlation with biologic agents in the veteran population. The data collected shows an increased risk of malignancy. This appears to be rather notable when RA is diagnosed at an older age (>65). This could imply that later onset RA needs more aggressive treatment, and the potential protective effect of biologics on development of cancer imply that late onset RA may need more aggressive treatment with biologics. More studies need to be done to determine the significance of the protective effect of biologics. Our study is ongoing and sample size should be increased for more robust data. Additionally, study duration should be increased in order to follow younger patients that have been newly diagnosed with RA.

Disclosure: K. Larson, None; **F. Siddique**, None; **S. Mohammad**, None.

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Abstract Number: 1502

Vaccination Program to Prevent Hospital Admissions Due to Serious Respiratory Infections in Rheumatoid Arthritis Patients. Prosprective Study of 294 Patients

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SESSION INFORMATION

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Rheumatoid Arthritis (RA) are at increased risk of infections, especially serious respiratory infections. Immunization is a recommended to reduce these complications. Our aim was to assess the incidence of hospitalizations due to serious respiratory infections before and after the onset a program of systematic vaccination.

Methods: Prospective study of a cohort of 294 patients diagnosed with RA who were invited to participate in a vaccination program. It included seasonal flu vaccination (from October to April), pneumococcal (combined regimen 13-valent and 23-valent vaccines) and haemophilus influenzae type B vaccine. Only 7 patients (2.94%) refused vaccination. The follow-up time of this cohort was from October 1, 2011 (starting date) to June 30, 2015. Information on serious respiratory infection episodes before and after being immunized was conducted using the hospital information system by reviewing hospital records.

Results: 287 RA patients (225 women /62 men), average age 58.1±12.7 years, were vaccinated. The main features at the time of vaccination were: Disease duration (93±95.9 months; Rheumatoid Factor positive in 154 (53.65%), erosive arthritis in 97 (33.8%), and pulmonary fibrosis in 7 cases. Also, at the timwe of vaccination 245 (85.45%) were taking disease modifying drugs, including methotrexate in 98 (34.1%) and/or anti-TNF-alpha therapy in 98 patients (34.1%). In most of the remaining patients vaccination was performed at the time of disease diagnosis. Twenty (7%) patients had required hospital admissions by serious respiratory infections, before being included in the vaccination program. After the onset of the vaccination program only 6 of the 287 patients (2.1%) required admission because of serious respiratory infections **(TABLE).** The reduction achieved from 7% to 2.1% was statistically significant ($p = 0.0017$).

Conclusion: A program that includes systematic vaccination of RA patients seems to be an effective procedure to prevent hospitalizations caused by serious respiratory infections. **TABLE**

Age	sex	Biologic therapy at the time of vaccination	Previous history of biologic therapy	Other drugs used at the time of vaccination	Rheumatoid Factor status	Serious Respiratory Infections
72	W	No	Yes	Prednisone 30 mg/24h	negative	Pneumonia (Escherichia Coli)
45	W	No	-	LFN	postive	LRTI (negative cultures)
66	M	No	Yes	CQ	negative	Pneumonia (negative cultures)
67	W	No	No	-	negative	LRTI (negative cultures)
48	W	No	No	MTX Prednisone 10 mg/24h	positive	LRTI (negative cultures)
63	M	No	Yes	MTX Prednisone 10mg/24h	positive	Pneumonia (Aspergillus Fumigatus)

Abbreviations: W: woman; M: man; LFN: leflunomide. CQ: chloroquine; MTX: methotrexate; LRTI: Lower Respiratory Tract Infections

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Abstract Number: 1503

Patterns and Factors Associated with Immunization Among Adult Patients with Rheumatic Diseases in the US

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Background/Purpose: Rates of adult vaccination are low in patients with autoimmune disease despite broad recommendations for many years. In the U.S., pneumococcal vaccination is recommended for people age 65 or older or with a risk factor (e.g. immunosuppression); herpes zoster (HZ) vaccination is recommended for adults aged 60 years and older, and influenza vaccination has been recommended for all persons aged ≥ 6 months. Despite many studies showing patients with rheumatic diseases or treated with immunosuppressive medications are at an increased risk of infections, but factors associated with receive recommended immunizations

are not well known. We evaluated the pattern of pneumococcal, HZ, and seasonal influenza vaccination and factors associated with receiving these vaccinations among patients participating in a national US. registry.

Methods: We examined patient self-reported survey responses among participants in the National Data Bank for Rheumatic Diseases (NDB) from 2006-2015. After excluding patients who never answered vaccine questions, all adult patients in the registry with a rheumatologist-diagnosed rheumatic disease were eligible for analysis. Patients <60 years old or who enrolled after 2007 were excluded from the analysis of the HZ vaccine use due to incomplete vaccine history. Vaccine administrations and potential confounders were time-varying and updated at the time of each 6 month survey. For pneumococcal and HZ vaccine, follow-up started at the first survey that all required criteria were met and ended at the earlier date of either vaccination, death, or exited the registry. For influenza, patients were allowed to have multiple vaccinations. A generalized estimating equation model with repeated measures was used to evaluate the factors associated with receipt of each vaccine.

Results: Among 21,522 patients (72.8% with RA, 16.9% with OA, 10.1% with Fibromyalgia, 7% with SLE, patients were allowed to have multiple conditions) who were eligible for pneumococcal and influenza vaccination analysis, we identified 9,162 and 84,991 vaccinations, respectively. Of the cohort, 74.7% had at least one influenza vaccination during the 10 years of study period.The proportion of patients receiving the influenza vaccine in each year is on the average of 60%.). 9,867(45.8%) patients never had pneumococcal vaccination and 5,438 (25.2%) patients never had influenza vaccination. Of 11,947 eligible patients for HZ vaccine analysis, 1,724 (14.4%) received the HZ vaccine over a median (IQR: 6 years) of 4.5 years of follow-up. After multivariable adjustment, older age, African American race, biologic use, cardiovascular disease, and prior hospitalization were significantly associated with all three vaccinations. Factors associated with each vaccine vary (see Table).

Conclusion: Overall rates of pneumococcal, HZ, and influenza vaccinations were low among patients with rheumatic diseases. For each type of vaccination, more efforts on different associated factors are needed to improve the vaccination rate. Table: Multivariable factors associated with vaccination among patients with rheumatic diseases in the NDB

Characteristics†	Vaccination		
	Pneumococcal (n=21,522)	Herpes Zoster (n=11,947)	Influenza (n=21,522)
Age, year	1.02 (1.02, 1.03)	1.0 (0.99, 1.0)	1.03 (1.03, 1.04)
Male sex	1.01 (0.94, 1.08)	1.10 (0.98, 1.24)	0.93 (0.89, 0.98)
Ethnicity			
Caucasian	Ref (1.0)	Ref (1.0)	Ref (1.0)
African American	1.24 (1.07, 1.43)	0.65 (0.45, 0.93)	0.82 (0.73, 0.92)
Hispanic	1.27 (1.06, 1.51)	0.92 (0.60, 1.42)	0.94 (0.82, 1.08)
Asian	1.11 (0.78, 1.58)	1.79 (1.10, 2.92)	0.95 (0.74, 1.23)
Other	1.10 (0.76, 1.57)	0.45 (0.15, 1.37)	0.89 (0.69, 1.15)
Alcohol use	0.84 (0.48, 1.48)	1.85 (0.77, 4.41)	1.06 (0.87, 1.30)
Smoker, current	1.02 (0.91, 1.14)	0.62 (0.47, 0.84)	0.78 (0.72, 0.85)
Rheumatoid arthritis	1.21 (1.03, 1.43)	0.75 (0.56, 1.01)	1.05 (0.93, 1.19)
Osteoarthritis	1.15 (0.99, 1.34)	0.97 (0.75, 1.24)	1.00 (0.90, 1.12)
Fibromyalgia	1.00 (0.87, 1.15)	0.95 (0.78, 1.16)	0.87 (0.79, 0.97)
Lupus	1.52 (1.31, 1.75)	0.83 (0.61, 1.13)	1.35 (1.22, 1.50)
Biologics	1.17 (1.10, 1.24)	0.53 (0.47, 0.61)	1.18 (1.13, 1.22)
Non-biologic DMARDs	1.06 (0.99, 1.13)	0.76 (0.68, 0.86)	0.99 (0.95, 1.03)
Glucocorticoids			
None	Ref (1.0)	Ref (1.0)	Ref (1.0)
≤7.5 mg/day	1.12 (1.05, 1.20)	0.77 (0.66, 0.90)	0.98 (0.94, 1.02)
>7.5 mg/day	1.13 (1.01, 1.27)	0.83 (0.64, 1.07)	0.97 (0.92, 1.03)
Nursing home residency	2.15 (1.79, 2.57)	0.81 (0.55, 1.21)	1.10 (1.01, 1.21)
Hospitalization	0.74 (0.55, 0.99)	0.38 (0.17, 0.81)	0.70 (0.62, 0.78)
Comorbidities			
Cardiovascular	1.18 (1.11, 1.25)	1.20 (1.08, 1.32)	1.23 (1.18, 1.28)
Liver	0.89 (0.70, 1.13)	0.94 (0.59, 1.51)	0.96 (0.87, 1.05)
Lung	1.55 (1.40, 1.72)	0.90 (0.74, 1.10)	1.16 (1.09, 1.22)
Stroke	1.15 (0.81, 1.62)	0.58 (0.27, 1.23)	0.94 (0.82, 1.08)
Diabetes	1.22 (1.11, 1.33)	0.99 (0.85, 1.15)	1.14 (1.09, 1.21)
Cancer	1.10 (0.93, 1.31)	0.80 (0.59, 1.09)	0.99 (0.93, 1.06)
Pneumonia	1.33 (1.18, 1.51)	N/A	N/A
Zoster	N/A	2.63 (2.05, 3.36)	N/A
Influenza	N/A	N/A	1.01 (0.96, 1.05)
†Except male sex and ethnicity, all other factors were time-varying and updated on an average of 6 months			

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Abstract Number: 1504

Fluoroquinolone Resistance in Escherichia coli Urinary Tract Infections Among Patients with Rheumatoid Arthritis: Does Use of Hydroxichloroquine Matter?

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Background/Purpose:

Rheumatoid arthritis (RA) is a chronic autoimmune disease that requires chronic immunosuppressive treatment. Urinary tract infections (UTI) are common among patients with RA. It has been suggested that hydroxichloroquine (HCQ), a drug used in the treatment of RA, may have antimicrobial activity and induce selective resistance to fluoroquinolones in bacterial species. However, this has not been well established.

To evaluate the association between use of HCQ and development of fluoroquinolone resistance in *Escherichia coli* among patients with RA and UTI.

Methods:

Retrospective case-control study. We evaluated 225 patients with RA and UTI. Cases were defined as patients receiving HCQ, and controls as those receiving a different treatment. Demographics and clinical features were assessed, and laboratory data was obtained from urine cultures and antibiotic susceptibility tests. Univariate and multivariate analyses were performed.

Results:

There were 112 subjects in the HCQ group and 113 controls. The mean±SD age in the HCQ group and controls was 51 ± 15.66, and 60 ± 15.35 years, respectively. Duration of RA was 12± 8.67 and 17± 9.48 years in the HCQ and control groups, respectively. Overall, 61% of patients received methotrexate, 50% HCQ, and 29% prednisone. Class I/II functional status was observed in 63% of patients, and class III/IV in 37%. Resistance to ciprofloxacin was found in 102 (45%) patients overall, and it was less common among the HCQ group compared with controls, although the difference was not statistically significant (43% vs. 48%, *p*-value = 0.458). The factors associated with resistance to ciprofloxacin in univariate analysis were: UTI within the last six months, previous antibiotic use, diabetes mellitus, and RA functional status. In logistic regression analysis, RA functional status class and previous antibiotic use were the only significant independent predictors of fluoroquinolone resistance.

Conclusion:

Resistance to ciprofloxacin is common among patients with RA and UTI. We found no evidence that the use of HCQ is associated with fluoroquinolone resistance in patients with RA and *Escherichia coli* UTI. RA functional status class III/IV was a significant independent predictor of fluoroquinolone resistance.

Disclosure: K. Ferez-Blando, None; **H. Fragoso-Loyo**, None; **A. Ponce de León**, None; **S. Ponce de Leon-Rosales**, None; **Y. Atisha-Fregoso**, None.

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Abstract Number: 1505

Trends in Hospitalizations for Infections in US Patients with Rheumatoid Arthritis, 1993-2013

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Background/Purpose: With the increasing uptake of RA treatments that confer infection risk, an increase in the rates of infection hospitalizations among RA patients is expected, but limited data exists. Additionally, some studies show a doubling of sepsis in the general population in recent years, possibly due in part to changes in coding practices. We sought to investigate the national trends in hospitalization for infections in US patients with rheumatoid arthritis (RA).

Methods: We conducted serial cross-sectional analyses of 1993-2013 data from the National Inpatient Sample, a nationally representative sample of all community hospitals in the US. We identified hospitalized adults with RA using an *ICD-9* codes in any secondary diagnosis field. We evaluated 5 infections as the primary diagnosis: pneumonia, sepsis, urinary tract infection (UTI), skin and soft tissue infections (SSTI), and opportunistic infections (OI). The primary outcome was the proportion of hospitalizations for each infection, among all hospitalizations with a secondary diagnosis of RA. We considered the proportion of myocardial infarction (MI) hospitalizations among RA as a control condition, since reports indicate decreased incidence. We also calculated the incidence of each infection among RA patients by year, using an estimate of the national adult RA population as 1% of the adult US census population. The Cochran-Armitage Trend Test was used to examine trends.

Results: From 1993 to 2013 there were 792,921 hospitalizations for infection with a secondary diagnosis of RA. Hospitalizations with any secondary RA code increased from 60 to 160 per 100,000 persons (US general population). Among RA patients, the proportion of hospitalizations decreased for pneumonia (5.4 to 4.6%, $p<0.001$), UTI (0.42 to 0.38%, $p=0.04$), and OI (0.44 to 0.26% ($p<0.001$). The rate for SSTI increased slightly (2.3 to 2.5%, $p<0.001$), while the proportion of hospitalizations for sepsis more than tripled (1.9 to 6.4%, $p<0.001$). Consistent with previous reports, MI hospitalizations decreased from 2.2 to 1.8%. Using the theoretical national RA population as the denominator, without accounting for the increased RA coding over the study period, there appeared to be an increase in the rates of all infections: pneumonia (0.48 to 0.96%), UTI (0.37 to 0.79%), SSTI (0.20 to 0.52%), OI (0.039 to 0.055%) and sepsis (0.17 to 1.32%); all p values <0.001.

Conclusion: Between 1993 and 2013, the proportion of hospitalizations for infections among RA patients declined for pneumonia, UTI, and OI, with a small increase in the proportion for SSTI and a marked increase in sepsis. The sepsis results are consistent with previous reports that the sensitivity of sepsis coding has increased, but still warrant confirmation in other data sets such as RA cohorts. There has been a doubling of coding for RA in hospital discharges, which should be investigated further and acknowledged in studies using hospitalization data.

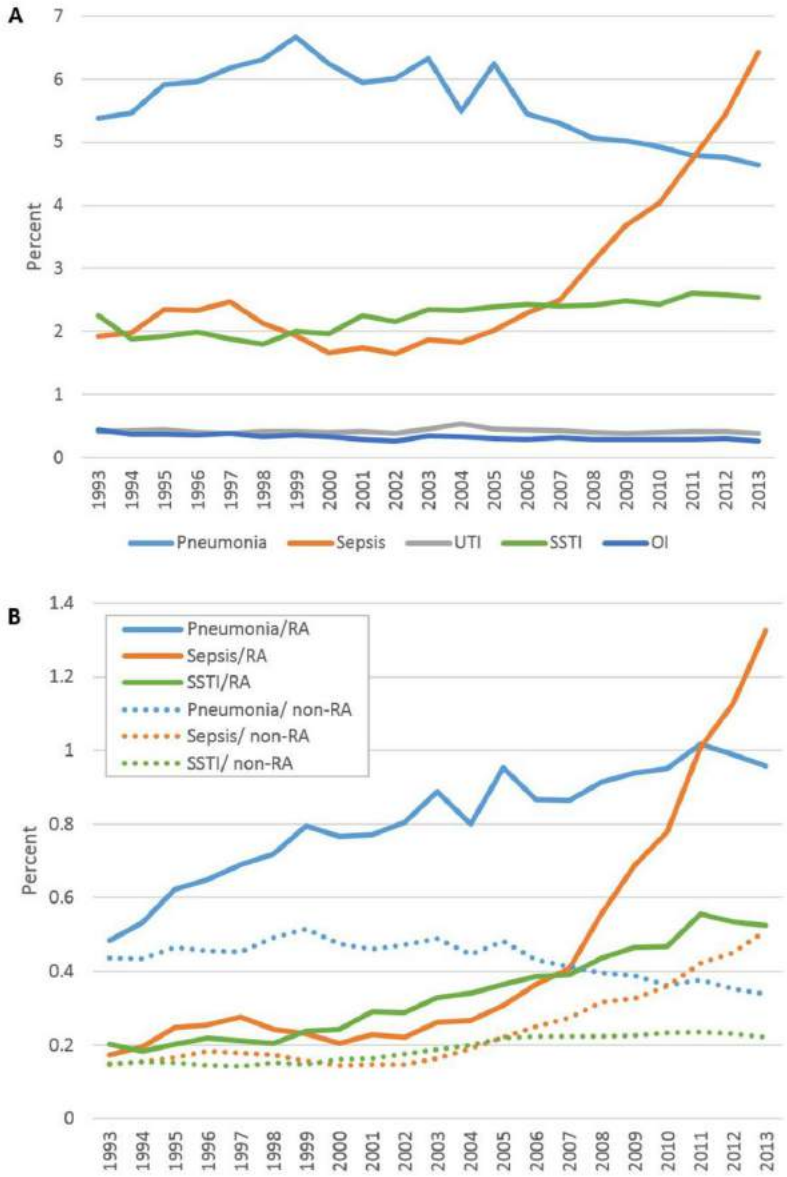

Figure. A. Proportion of all US RA hospitalizations for infection, stratified by infection type; **B.** Incidence of hospitalized infection for pneumonia, sepsis and SSTI among RA (solid lines) and non-RA (dashed lines), from 1993-2013 National Inpatient Sample.
RA: rheumatoid arthritis, UTI: urinary tract infection, SSTI: skin and soft tissue infections, OI: opportunistic infections

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Disclosure: S. Jinno, None; **N. Lu**, None; **S. R. Jafarzadeh**, None; **M. Dubreuil**, None.

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Abstract Number: 1506

One Third of Patients with Established Rheumatoid Arthritis (RA) Are Correctly Vaccinated Against Influenza and Pneumococcus and This Is Increasing: 3 Year Longitudinal Assessment of 776 Patients

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Hélène Cerato[8], Gerard H. Chales[9], Isabelle Chary-Valckenaere[10], Bernard Combe[11], Emmanuelle Dernis Labous[12], Liana Euller-Ziegler[13], Rene-Marc Flipo[14], Philippe Gaudin[15], Melanie Gilson[16], Sandrine Guis[17], Xavier Mariette[18], Gaël Mouterde[19], Sophie Pouplin[20], Pascal Richette[21], Alain Saraux[22], Thierry Schaeverbeke[23], Jean Sibilia[24], Françoise Fayet[25] and Maxime Dougados[26], [1]Rheumatology, Pitié Salpêtrière Hospital, Paris, France, [2]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [3]COMEDRA working group, Paris, France, [4]Hopital Cochin, Paris Descartes University, Paris, France, [5]Hôpital Lariboisière, Paris, France, [6]Rheumatology dept, APHP St-Antoine hospital, Univ Paris 06, Paris, France, Paris, France, [7]Purpan Hospital, Toulouse, France, [8]University Hospital, Toulouse, France, [9]CHU RENNES, Rennes, France, [10]University Hospital, Nancy, France, [11]Lapeyronie Hospital, Montpellier, France, [12]Le Mans Hospital, Le Mans, France, [13]Rheumatology, Nice, France, [14]Rheumatology, University Hospital, Lille, France, [15]Rheumatology, Grenoble University Hospital, France, Grenoble, France, [16]Hopital Sud, Grenoble, France, [17]Rheumatology 1, CRMBM-CEMEREM 7339, Aix-Marseille Université, AP-HM, CNRS, Marseilles, France, [18]Rheumatology, Rheumatology department, Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France, [19]Rheumatology Department, Hopital Lapeyronie, Montpellier, France, [20]Rheumatology Department & Inserm 905, Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [21]Rhumatologie, Hôpital Lariboisière, Paris, France, [22]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [23]Rheumatology, CHU Bordeaux, Bordeaux, France, [24]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [25]Rheumatology, CHU Gabriel-Montpied, Clermont-Ferrand, France, [26]Cochin Hospital and Paris 05 University, Paris, France
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Background/Purpose: Influenza and pneumococcal vaccinations are recommended in all patients with RA. However, it is well known that a gap exists between recommendations and their implementation in real life. As EULAR recommendations for vaccinations are now widely disseminated, we took the opportunity of assessing vaccination rates of the patients who participated in the COMEDRA study [1], both at study entry and 3 years after the trial ended, to assess the progression of vaccination rate in this long-standing RA population undergoing a nurse-led program.

Methods: This was an open long term (3 years) extension of the COMEDRA 6 month randomized controlled trial in which patients with definite, stable RA were visiting a nurse for comorbidity counselling. Vaccination status was assessed during the RCT and nurses provided advice on vaccinations, and again 3 years later, during a face-to-face interview with a nurse. Agreement with the vaccination recommendations was defined as (a) influenza vaccination performed within the last 12 months and (b) pneumococcal vaccination performed within the last 5 years. The proportion of patients in accordance with the recommendations was compared between baseline and 3-year assessment using a McNemar test for paired data. The probability to be in accordance with recommendations was assessed by logistic mixed models including in the model the patient as random effect and as fixed effects: age, gender, disease duration, DAS28, educational level, work status, any biologic at baseline, and trial group and centre.

Results: Of the 970 recruited patients, 776 (80%) were followed up at 2-4 years and 759 (78%) had available data regarding both influenza and pneumococcal vaccination status: mean (±sd) age 58 (±11) years, mean disease duration 14 (±10) years; 607 (80%) were women and 538 (70%) were receiving a biologic. The mean baseline and 3-year DAS28 scores were respectively 2.99±1.30 and 2.83±1.34. At baseline, 337 (44.4%), 459 (60.5%) and 252 (33.2%) patients were in agreement with recommendations for influenza, pneumococcal and both vaccinations, respectively. After 3 years, this agreement increased for both vaccinations, to 420 (55.3%), 499 (65.7%) and 317 (41.8%) respectively. (Table 1) Having ever received a biologic (odds ratio, OR= 4.73 [95% CI: 2.62 - 8.52]), centre size (OR=2.8 [1.04-1.7]) , university education (OR=1.79 [1.11 - 2.89]) and higher age (OR=1.07 [1.04 - 1.10]), were independently associated with being in accordance with both vaccinations recommendations .

Conclusion: the agreement with the EULAR vaccination recommendations is moderate but has increased in patients who had participated in a nurse-led program aiming at checking systematically for vaccination status.

Ref 1. Dougados M, Soubrier M, et al. Ann Rheum Dis. 2015;74(9):1725-33. **Table 1 Adherence to vaccination recommendations**

Adherence to vaccination recommendations, N (% of 759):	COMEDRA RCT study baseline (month 0 for group I and month 6 for group II)	Follow-up at 3 years	*p* value between baseline and follow up date
Influenza	337 (44.4)	420 (55.3)	p<0.0001
Pneumococcus	459 (60.5)	499 (65.7)	p<0.01
Both	252 (33.2)	317 (41.8)	p<0.0001

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Abstract Number: 1507

Our Strategy of Preventing Tuberculosis (TB) in Patients with Rheumatic Diseases Under the Treatment with Biologic Dmards

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Background/Purpose: According to the report by WHO, Japan is still in moderately-prevailing countries of TB. The annual incidence of TB in Japan is approximately 15/100,000, which is 4 – 5 times higher than those in western countries. The incidence of TB in patients with RA is reported to be 2 – 3 times higher than that of general population. Moreover the TB incidence increases 4 – 5 times when bDMARDS are used for the treatment. Therefore, the TB incidence becomes approximately 10 times higher than that of general population when prevention of TB is not done properly. We, in this study, aimed to show the effectiveness of our strategy of TB prevention in patients with rheumatic diseases under the treatment with bDMARDS.

Methods: Subjects were 235 patients with rheumatic diseases who were introduced with bDMARDS, most of them were RA. The mean age was 62 with the range of 18 – 90 years. The duration of administration of bDMARD was 0.25 – 11.8 years, including 2nd bDMARDS and thereafter, with the mean duration of 3.0 years, and the total duration of administration was 818 years. TB prevention by isoniazid (INH) was applied to patients who fit more than 1 of the following 5 items (risk factors). They are; 1. more than 70 years of age, 2. moderate or strong positive tuberculin skin test (STS), 3. positive or intermediate QuantiFerron (QFT) result (intermediate result was established by Japan Society for TB), 4. findings suggestive of old TB on chest CT, and 5. history of treatment of TB. In addition, there were patients who chose to had prevention after consulting attending physicians. The duration of INH administration was 9 months. The reasons why patients of more than 70 years of age was indicated for TB prevention are as follows; 1. more than 50 % of TB patients in Japan are more than 70 years of age, 2. TB incidence of more than 70 years of age is very high (approximately 50/100,000), and 3. compatible with the BTS guideline of TB prevention.

Results: Tb prevention was done for 166 patients (70 %). The number of patients who had 0, 1, 2, 3, 4, 5 risk factors listed above were 30, 91, 31, 6, 7, 1, respectively. Thirty patients took INH despite they did not have risk factors. In patients with one risk factor, the most risk factor was advanced age, followed by positive STS, chest CT findings, and positive QFT. Five patients did not take INH despite

that they had risk factors. Predictive value of TB development was calculated from the annual incidence stratified by age and the duration of bDMARDS administration. It was estimated to be 2.2, but no TB developed actually.

Conclusion: Our strategy of preventing TB by INH is so far working well.

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Abstract Number: 1508

Prevalence and Clinical Characteristics of Rheumatoid Arthritis in Sickle Cell Patients: A Cross-Sectional Analysis

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Title: Prevalence and Clinical Characteristics of Rheumatoid Arthritis in Sickle Cell Patients

Background/Purpose: Rheumatoid arthritis (RA) has been rarely reported in association with sickle cell disease (SCD). It was hypothesized that sickle cell-associated vasculopathy impairs angiogenesis; a key step in the formation and maintenance of the panus in RA, thus preventing the development of RA. However, there is no substantial data available on the prevalence and clinical characteristics of RA in SCD patients. We performed a cross-sectional analysis to estimate the prevalence of RA in SCD population and to describe the clinical characteristics of RA associated with SCD.

Methods: Retrospective chart review of SCD and RA patients followed at 2 large urban hospitals. Seven RA/SCD patients were identified and compared to age and sex matched cohort of SCD only and of RA only group. All patients were black.

Results: Of the 658 SCD cases, 7 (1.0%) met ACR criteria for RA (SCD-RA), 411cases were RA only group. Mean age = (41.1±2.21 (±SEM) vs 34.55± 0.13), vs.60.7±16.3 P<0.01. Compared to age and sex matched groups of RA and of SCD, RA/SCD group tended to have more frequent hospitalization and increased LOS, as well as lower hemoglobin / hematocrit values. Other clinical and biochemical characteristics were similar for the 3 groups (table1). There were also no significant differences in rheumatologic parameters between SCD/RA and RA only groups, except for increase in periarticular osteopenia and difficulty in ADL among SCD/RA cohort (table2). **Table 1 Comparison** of the Clinical and Biochemical Characteristics of SCD, SCD and RA, and RA patients.

Measurements	SCD (n=7)	SCD+RA (n=7)	RA (n=7)	P-Value
Age	41.7 ± 3.9	41.7 ± 3.9	39.8 ± 4.1	0.93
Body Mass Index	23.5 ± 0.86	20.8 ± 1.9	25.6 ± 2.1	0.17
Systolic BP	119 ± 4.7	118 ± 5.0	128 ± 4.9	0.3
Diastolic BP	70 ± 1.8	68 ± 4.3	79 ± 5.8	0.19
Hemoglobin	8.3 ± 0.6	7.4 ± 0.49	11.0 ± 0.59	**<0.01**
Hematocrit	25.7 ± 1.7	23.1 ± 1.5	34.6 ± 1.5	**<0.01**
CRP	38.6 ± 23.3	12.2 ± 5.6	38.1 ± 13.8	0.47
ESR	63.0 ± 15.4	71.6 ± 20.2	37.0 ± 10.0	0.23
Lymphocyte Count	3.0 ± 1.9	3.9 ± 2.2	1.7 ± 1.0	**0.023**
Creatinine	0.57 ± 0.057	0.72 ± 0.097	0.8 ± 0.087	0.09
Reticulocyte Count	9.5 ± 2.4	13.2 ± 2.3	-----	0.28
# of Hospitalizations	8.7 ± 3.2	9.1 ± 4.9	1.8 ± 0.14	0.26
Total length of stay in hospital	52.1 ± 24.6	88.2 ± 40.7	6.4 ± 2.2	0.13
# ED visits	30.7 ± 22.0	12.8 ± 5.4	4.5 ± 0.86	0.37
# Blood transfusions	6.2 ± 3.8	6.5 ± 3.7	0.71 ± 0.47	0.34
Acute Chest Syndrome	71.4% (5/7)	71.4% (5/7)	-----	1.0

Table 2 Comparison of Clinical Characteristics and Radiographic Profiles in patients with SCD and RA, and RA alone.

Measurements	SCD + RA (n=7)	RA (n=7)	P- Value
Rheumatoid Factor	86% (6/7)	71% (5/7)	0.46
Anti-citrullinated protein antibody	83% (5/6)	60% (3/5)	0.54
Antinuclear antibody	40% (2/5)	50% (3/6)	1.0
Prednisone	71.4% (5/7)	71.4% (5/7)	1.0
Methotrexate	42.9% (3/7)	71.4% (5/7)	0.59
Hydroxychloroquine	14.3% (1/7)	14.3% (1/7)	0.26
Biologics	14.3% (1/7)	14.3% (1/7)	1.0
Leflunomide	42.9% (3/7)	42.9% (3/7)	1.0
Duration of Morning Stiffness	127.5±18.8	55.3±34.7	0.10
Peri-articular Osteopenia	100% (5/5)	0% (0/5)	**0.01**
Erosive arthritis	50% (3/6)	17% (1/6)	0.54
Difficulty with ADLs	57 % (4/7)	0% (0/7)	**0.01**

Conclusion: The prevalence of RA among SCD patients is similar to that of the general population and is associated with increased hospitalizations and length of stay as well as difficulty in activities of daily living. This is contrary to previous reports from 1980-1990s indicating rare occurrence of RA in SCD patients. Given the increase prevalence of RA with age, our findings are likely a reflection of increased longevity among SCD patients with hydroxyurea and other modern interventions.

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Increased Fracture Risk in Patients with Early Rheumatoid Arthritis in the 1990s As Well As in the 2000s: A Prospective General Population-Matched Cohort Study

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Background/Purpose: Osteoporotic fractures represent one of the serious extra-articular manifestations of rheumatoid arthritis (RA). The aim of this study was to investigate whether fracture incidence differs between patients with early RA diagnosed in the 1990s and the 2000s, and compared to the general population.

Methods: The RA-patients were recruited from the BARFOT (Better Anti-Rheumatic FarmacO Therapy) cohort, which is a Swedish multicentre observational study of patients with early RA. All patients fulfilled the 1987 American College of Rheumatology classification criteria and were included between 1992 and 2006. For each patient four reference subjects matched for sex, age and residential area were randomly selected from the general population using data from the Swedish Central Statistics Office. Cases with new osteoporotic fractures were identified through the Swedish National Inpatients Register, the Swedish Outpatients Register and the Swedish Cause of Death Register until December 2013. Analysis were performed for the total study population and also stratified by inclusion period; 1992-1999 and 2000-2006.

Results: During a mean (SD) follow-up period of 14 (3.9) years 617 of 2751 (16.8%) patients with RA and 1901 of 11004 (13.6%) of controls had an osteoporotic fracture ($p < 0.001$). 18.2% of RA-patients included 1992-1999 (n=314) experienced a fracture (controls 14.8%; p=0,001) and 15.9% of RA-patients included 2000-2006 (n=303) experienced a fracture (controls 12.4%; p=0.002). Compared to the controls the risk HR (95%CI) of sustaining any clinical fracture in the whole RA-group was 1.33 (1.18, 1.50) ($p<0.001$). The risk was increased for both inclusion periods; 1990s 1.28 (1.09, 1.52) (p=0.003) and 2000s 1.41 (1.17, 1.70) ($p<0.001$), although the patients included later more often started treatment with DMARDs at the first visits, inclusion; 88% vs 65% ($p<0.001$) and at 3 months follow-up; 90% vs 72% ($p<0.001$).

Conclusion: Our study showed an increased risk of osteoporotic fractures in patients with early RA compared with population based reference subjects matched for sex and age and residential area. This was also shown when stratified by the 1990s and the 2000s.

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Abstract Number: 1510

Trends in the Occurrence of Malignancy in Japanese Patients with Rheumatoid Arthritis Based on the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) Cohort during a 14-Year Observation Period

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Background/Purpose: Along with increased proportions of patients using methotrexate (MTX) and biological agents (from 34.2% and 0.0% in 2000 to 77.3% and 18.8% in 2013, respectively), the proportions with DAS28 remission and low disease activity increased from 8.4% and 13.8% in 2000 to 54.7% and 20.8% in 2013, respectively, based on our observational cohort of Japanese patients with RA, the Institute of Rheumatology, Rheumatoid Arthritis (IORRA). Trends for malignancies in patients with RA have not been examined comprehensively in a specific cohort. The aim of this study is to investigate the trends in the occurrence of overall and site-specific malignancies in Japanese patients with RA over a long period.

Methods: Among Japanese patients with RA enrolled in the IORRA, all malignancies occurring from April 2000 to September 2013 were extracted from self-reported information and confirmed by medical records. Malignancies occurring in patients who dropped out

of the IORRA study during the subsequent 3 months were also collected by follow-up mailings and medical information from affiliated hospitals. For malignancies overall and at frequently involved sites (breast, malignant lymphoma, stomach, lung, colorectal), the standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) during 3 periods (pre-biologics, 2000-2003; early biologics, 2004-2007; and late biologics, 2008-2011) were calculated based on data from the general Japanese population.

Results: Among 11,106 Japanese patients with RA (68,483 person-years), 507 malignancies (72 breast cancers, 68 malignant lymphomas, 65 stomach cancers, 60 lung cancers, 54 colorectal cancers) were confirmed. The incidence of overall malignancies decreased gradually, with SIRs (95% CIs) of 0.96 (0.80-1.14) in pre-biologics, 0.95 (0.80-1.11) in early biologics and 0.91 (0.79-1.05) in late biologics, respectively (*P* for trend = 0.43 by Poisson regression). The lung cancer incidence decreased to a level comparable to that of the general Japanese population, with SIRs (95% CIs) of 1.68 (1.07-2.53), 0.60 (0.29-1.10) and 0.97 (0.60-1.48), respectively. The incidence of malignant lymphoma was markedly increased, with SIRs (95% CIs) of 4.53 (2.59-7.35), 4.06 (2.36-6.50) and 4.59 (3.00-6.72), respectively.

Conclusion: Trends in the occurrence of overall and site-specific malignancies in Japanese patients with RA did not increase with the expanding use of MTX and biological agents in this decade.

Malignancy	Pre-biologics (2000-2003) (Male, 3,376 pys; Female, 16,171 pys)	Early biologics (2004-2007) (Male, 3,482 pys; Female, 17,682 pys)	Late biologics (2008-2011) (Male, 3,502 pys; Female, 19,015 pys)
	SIR (95% CI)	SIR (95% CI)	SIR (95% CI)
Total	0.96 (0.80-1.14)	0.95 (0.80-1.11)	0.91 (0.79-1.05)
Breast	0.61 (0.30-1.09)	1.37 (0.95-1.92)	0.64 (0.40-0.97)
Malignant lymphoma	4.53 (2.59-7.35)	4.06 (2.36-6.50)	4.59 (3.00-6.72)
Stomach	0.95 (0.57-1.48)	0.90 (0.55-1.38)	0.81 (0.50-1.25)
Lung	1.68 (1.07-2.53)	0.60 (0.29-1.10)	0.97 (0.60-1.48)
Colorectal	0.44 (0.21-0.81)	0.66 (0.39-1.04)	0.68 (0.43-1.02)

pys: person-years; SIR: standardized incidence ratio; CI: confidence interval

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Abstract Number: 1511

Impacts of Disease Activity and Serum Level of Neurotrophic Factors on Depression in Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) and depression is closely associated with each other. The serum level of neurotrophic factors are related with the major depressive disorder (MDD). However, the impacts of disease activity, pro-inflammatory cytokines and neurotrophic factors on depression in RA patients have not well studied. The aims of this study were to determine the risk factors for depression and to examine the effect of disease activity, pro-inflammatory cytokines and neurotrophic factors on depression in patients with RA.

Methods: This cross sectional study was conducted from Jan, 2014 to Jan, 2015 from 3 university hospitals. Demographic and laboratory data were examined and routine assessment of patient index data 3 (RAPID 3) questionnaire and 28 joints disease activity score (DAS28-CRP) were assessed for disease activity. Depression was measured by Korean version of the Beck Depression Inventory second edition (K-BDI II). Serum level of pro-inflammatory cytokines and neurotrophic factors such as BDNF, VEGF, GDNF, and IGF-1 were assessed by ELISA.

Results: A total of 507 RA patients were recruited. The prevalence of depression was 33.1% (n=168). RAPID 3 score (OR 1.2, 95% CI 1.1-1.4, P=0.006) and severity of fatigue (OR 1.19, 95%CI 1.07-1.32, P=0.001) showed significant associations with depression in multivariate analysis. The RA patients with DAS 28-CRP $\geq$3.2 (n=126) had more risk for depression than those with DAS 28-CRP<3.2 (n=279) in multivariate analysis (OR 2.02 95% CI 1.34-3.06, p=0.006). When patients was followed up for a year after strict treatment, as DAS28-CRP decreased, BDI score also decreased (ΔDAS28-CRP: -1.4±1.6, and ΔK-BDI II: -5.4±10.1, P<0.001). There were no relationships between pro-inflammatory cytokines and depression (IL-1β: r=0.057, IL-6: r=0.169, TNF-α: r=-0.078). In the case of neurotrophic factors, only the level of BDNF showed weakly correlation with K-BDI II score (r=-0.233, P<0.001).

Conclusion: This study suggests strict control of fatigue and disease activity is important in regulating depressive symptoms in patients with RA. To evaluate psychological manifestation of RA patients, using both RAPID 3 score and DAS28 might be helpful. Larger studies of the possible role of BDNF should be conducted.

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Abstract Number: 1512

Bone Structural Deficits in Rheumatoid Arthritis: Impact of Muscle Mass and Density

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Background/Purpose: Rheumatoid arthritis (RA) is associated with muscle loss, obesity, and osteoporotic fractures. Body composition and muscle quality are important regulators of bone strength among healthy adults. This study determined if patients with RA have deficits in cortical bone thickness (CBT; a structural measure highly correlated with fracture load) and trabecular bone density (TBD; a measure of volumetric bone mineral density) relative to their body mass. The study also assessed the degree to which these deficits are related to deficits in skeletal muscle.

Methods: Participants with RA, ages 18-75 years, were recruited from academic practices (2012-2016) and compared to a reference sample of healthy controls (ages 21 to 80). Participants underwent peripheral quantitative CT (pQCT) of the tibia to measure CBT and TBD as well as muscle cross-sectional area and density and fat area. Whole-body DXA measured appendicular lean mass index (ALMI), and fat mass index (FMI). BMI and body composition measures were converted to age-, sex, and race-specific Z-Scores. Multivariable linear regression models evaluated independent associations between body composition exposures and bone outcomes in RA and controls with assessment for altered associations in RA.

Results: The study consisted of 102 RA patients (50 men) and 416 controls (192 men). Patients with RA had greater BMI (p=0.004), greater total fat mass (p=0.02) and lower adiposity-adjusted ALMI Z-Scores (p=0.004), and low muscle density Z-Scores (p<0.0001). TBD and CBT Z-Scores were similar in RA and controls. However, RA patients had lower Z-Scores for bone outcomes compared to controls with similar BMI Z-Score (**Figure**). Sequential adjustment for ALMI, FMI, and muscle density Z-Scores in linear regression models attenuated these associations. Results were similar in analyses incorporating pQCT muscle and fat cross-sectional area Z-Scores. Relationships between body composition and bone outcomes were similar in RA and controls (no interaction) (**Table**). Men with RA had lower TBD Z-Scores than women with RA (p=0.005). Disease duration >10 years was associated with lower TBD (p=0.07) and CBT (p=0.04) independent of sex, ALMI, and FMI.

Conclusion: Patients with RA have bone structure and density that is maladapted to their weight. Muscle deficits in RA likely contribute to bone deficits through a loss of mechanical loading. Deficits in muscle mass and quality are, therefore, under-recognized risk factors for maladapted bone structure in RA; potentially impacting the long-term risk of fracture.

Figure: Estimation of bone deficits (by standard deviation score) between RA and controls in sequential linear regression models.

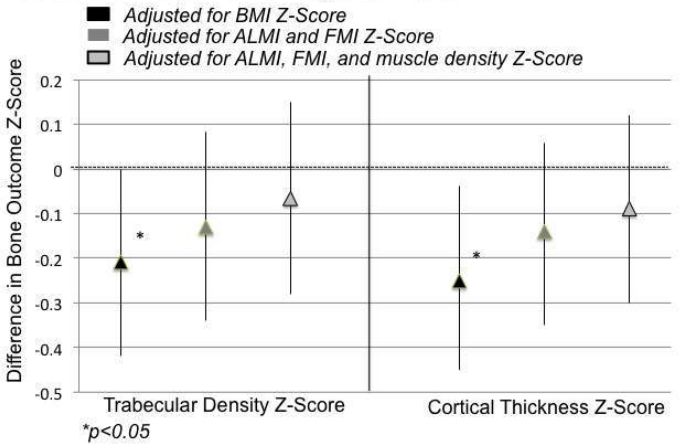

Table: Beta-coefficients representing associations between body composition and bone structure outcomes in patients with RA and controls. RA has similar relationships (no significant disease interaction) between body composition, muscle quality and bone outcomes.

	Rheumatoid Arthritis (N=102)		Controls (N=416)	
	TRABECULAR DENSITY Z-SCORE			
	β (95%CI)	p-value	β (95%CI)	p-value
ALMI Z-Score	0.33 (0.053, 0.61)	0.02	0.34 (0.21, 0.47)	0.001
FMI Z-Score	0.12 (-0.12, 0.36)	0.33	0.0062 (-0.088, 0.15)	0.90
Muscle Density Z-Score	0.099 (-0.099, 0.30)	0.33	0.10 (0.011, 0.20)	0.03
	CORTICAL THICKNESS Z-SCORE			
	β (95%CI)	p-value	β (95%CI)	p-value
ALMI Z-Score	0.35 (0.11, 0.59)	0.004	0.45 (0.33, 0.58)	<0.001
FMI Z-Score	-0.04 (-0.23, 0.17)	0.77	-0.027 (-0.15, 0.092)	0.66
Muscle Density Z-Score	0.12 (-0.039, 0.29)	0.14	0.089 (-0.0023, 0.18)	0.06

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Abstract Number: 1513

FRAX Fracture Risk in Rheumatoid Arthritis – Assessments with and without Bone Mineral Density May Lead to Very Different Results in Individual Patients

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SESSION INFORMATION

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Background/Purpose: Osteoporosis is a well-known complication in patients with rheumatoid arthritis (RA). The FRAX tool is an online computer-based algorithm developed by WHO to evaluate the 10-year risk of an osteoporotic hip fracture and major fracture (hip, clinical spine, proximal humerus or forearm fracture). Clinical risk factors include age, height and weight and dichotomized risk factors comprising prior fragility fracture, parental history of hip fracture, current tobacco smoking, ever use of long-term oral glucocorticoids, RA, other causes of secondary osteoporosis and alcohol consumption. Bone mineral density (BMD, g/cm2) of the femoral neck can be optionally included as a risk factor but FRAX does not provide recommendations on which side to measure BMD.

The usability of fracture risk assessment without BMD has been evaluated on group level, but the agreement between fracture risks assessed with and without BMD in individual patients has not met much attention. The objective of this study was to investigate the intra-individual agreement between 10-year fracture risk calculated with and without BMD in patients with RA.

Methods: Data from 50 RA patients registered in the Danish registry for biological treatment in rheumatology (DANBIO) were used for analysis. BMD of the left and right femoral neck had been measured using a Lunar iDXA-scanner (GE, Lunar) by experienced laboratory technicians. The intra-individual agreement between fracture risk assessed with and without BMDs was examined using the Bland-Altman method. 95 % lower and upper limits of agreement (LLoA and ULoA) were estimated as the mean difference (bias) in percent points (pp) between paired measurements ± 1.96SD (2.5 % - 97.5 % range for side comparison due to screwed distribution). Student's t-test was used for comparison on the group level.

Results: Mean age was 63.6 ± 11.7 (range 40-50) years, mean disease activity score (DAS28-CRP) 3.3 ± 3.5 and the mean femoral neck T-score -1.4 ± 1.2. 64 % of the patients were on oral steroids, 50 % on DMARDs and 46 % on biological treatment (±DMARD). The mean 10-year risk of a major fracture and a hip fracture calculated with BMD was 22.9 ± 15.8 % and 8.5 ± 10.8 %, respectively. The LLoA and ULoA [bias] for major fracture risk calculated with BMD (side with lowest value) and without BMD were -14.5 pp and 20.4 pp [2.93 pp, $p < 0.05$]. For hip fracture risk, LLoA and ULoA were -14 pp and 23.2 pp [4.6 pp, ($p < 0.001$)]. When calculating fracture risk based on the side with lowest versus the highest BMD-value, the LLoA and ULoA for hip fracture were 0 pp and 6.8 pp [0.8 pp, $p < 0.001$] and for major fracture 0 pp and 7.3 pp [1.0 pp, $p < 0.001$]. There was an overall trend of a greater bias, the higher the FRAX fracture risk but the bias was lower and LoA more narrow in osteopenic and osteoporotic patients compared to patients with normal BMD.

Conclusion: The FRAX 10-year fracture risk estimated with and without BMD may disagree to a substantial degree in individual RA patients and should therefore not be considered inter-changeable in the daily clinic. Choice of measurement side may also impact the fracture risk assessment, especially in the individual patient.

Disclosure: O. Rintek Madsen, None; **K. D. Elde**, None.

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Abstract Number: 1514

Symptoms of Depression and Anxiety Predict Worse Disease Activity and Functional Disability in a Cohort of Established Rheumatoid Arthritis Patients

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Background/Purpose: Depression and anxiety disorders are common in RA patients, with the most recent prevalence estimates indicating that 16.8% of RA patients have a diagnosis of depression and 25.1% of RA outpatients have screened positive for anxiety (1,2). In RA patients, depression and anxiety have been shown to be associated with increased pain, fatigue, reduced quality of life, and increased healthcare utilization use. Our aim was to examine the longitudinal impact of depression and anxiety on RA disease activity and functional status in a cohort of RA patients with established disease.

Methods: Data from a prospective longitudinal RA cohort study were analyzed and included joint exams, serological analyses, and patient reported measures. The Mental Health Index-5 (MHI-5), a validated scale that screens for depression and anxiety, was collected annually for two years. At baseline, univariate analyses were performed using MHI-5 as a dichotomous variable (scale 0-100, ≤65 positive for mood/anxiety disorder) to study the association between depression/anxiety with age, gender, ethnicity, seropositivity,

education, social support (Berkman Social Network Index), disease duration, disease activity measures (DAS28-CRP3, RADAI, CRP), and functional disability (MHAQ). To examine the association between MHI-5 and outcomes of disease activity and functional disability, linear repeated mixed model analyses were performed where the predictor variable, MHI-5 mood/anxiety disorder, was lagged by one year in relation to the outcomes.

Results: Of 992 participants analyzed, the average age was 57 (±13.6) years, most were female (82.6%), with an average disease duration of 13.8 (±11.9) years. Univariate analyses showed that MHI-5 scores were associated with DAS28-CRP3 ($p<0.0001$), MHAQ ($p<0.0001$), education ($p=0.04$), and social support ($p=0.0006$). The linear repeated mixed model analyses indicated that MHI-5 mood/anxiety disorder predicted worse DAS28-CRP3 ($p=0.0002$), worse RADAI scores ($p<0.0001$), and worse MHAQ scores ($p<0.0001$) one year later. MHI-5 score did not predict worse CRP levels overtime ($p=0.48$) (Table 1). Lower education also predicted worse DAS28-CRP3 ($p=0.03$), RADAI ($p=0.0007$), and MHAQ ($p=0.0002$) scores.

Conclusion: Symptoms of depression and anxiety defined by the MHI-5 score, predict worse disease activity and functional disability in RA patients. Ongoing monitoring and treatment of a patient's mental health is important and may impact long-term RA outcomes.

1. Matchum F et al. The prevalence of depression in rheumatoid arthritis: a systematic review and meta-analysis. Rheumatology 2013;52:2136-48.

2. Spitzer RL et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;166:1092-7.

Table 1. Using MHI-5 mood/anxiety disorder to Predict Disease Activity and Functional Disability a year later[a]

Primary Outcomes	β estimate (SE)	P-value
Higher DAS28-CRP3	0.37 (0.10)	<0.0001
Higher CRP	1.11 (1.56)	0.48
Higher RADAI score	0.56 (0.14)	<0.0001
Higher MHAQ score	0.13 (0.03)	<0.0001

[a]Primary outcome models adjusted for age, gender, seropositivity, education, and social support

Disclosure: C. Iannaccone, None; **T. G. Mahmoud**, None; **J. Cui**, None; **M. Weinblatt**, Amgen, 2,Bristol-Myers Squibb, 2,Crescendo Bioscience, 2,UCB, 2,Amgen, 5,Bristol-Myers Squibb, 5,Cresendo Bioscience, 5,UCB, 5; **N. Shadick**, UCB, Amgen, Crescendo Biosciences, BMS, Mallinckrodt, 2,Bristol-Myers Squibb, 5.

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Abstract Number: 1515

Could Increase Levels of Dickkopf-1 Protein be Considered As a Potential Biomarker for Bone Resorption in Joint and Periodontal Disease in Patients with Early Rheumatoid Arthritis?

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Background/Purpose: Periodontitis and rheumatoid arthritis (RA) are chronic destructive inflammatory diseases with significant worldwide prevalence. They are characterized by inflammatory lesions adjacent to bone destruction involving connective tissue and bone. Dickkopf-1 (DKK-1) is a major regulator of bone mass; however, their involvement in local bone resorption is largely unknown. The aim of this study was to assess the utility of DKK-1 levels in gingival crevicular fluid (GCF) and serum as a potential predictor of bone loss in periodontal disease and/or early RA

Methods: Cross-sectional study. Samples of serum and GCF (including 240 interproximal periodontal sites) were obtained from 24 patients with early RA. Adult patients were classified according to the 2010 ACR-EULAR criteria. The periodontal diagnosis was stablished according to the American Association of Periodontology and the Center for Disease Control and Prevention. Radiographs from hands and feet were taken and evaluated using the Sharp-van der Heijde score (SvH) as well as dental cone-beam computed tomography (CBCT) to evaluated interproximal sites. Serum DKK1 levels were determined by ELISA. An association analysis was made to evaluate the relationship between Dkk1 levels and periodontal, rheumatologic or radiographic scores using X2 test, and a multinomial or basic logistic regression model was performed to confirm this associations. The comparisons for Dkk1 levels and bone loss by tomography according to rheumatic scores were made by Kruskal Wallis and U Mann-Whitney tests. This study was approved by the Ethics Committee of the Institution

Results: Mean age 50±12.0 years, Bone Mass Index 25.3±3.6, C-reactive protein 4.6±20.7, ESR 15±21.7, DAS28-ESR 4.04±1.4, SDAI 17.5±22.28, HAQ 1.3±2.4, APCA IgG/IgA 130.5±7.8, RF 33.2±54.6, SvH 50.4% without the presence of erosion or decreased joint space, 66.6% periodontal diagnosis with moderate severity of 33.3% with 59.6% bone loss in interproximal sites (CBCT). GCF DKK1 levels showed a relationship with periodontal bone loss (p = 0.011). DKK1 levels were associated with both periodontal diagnosis and periodontal severity (p = 0.07 and 0.011 respectively). That condition was maintained for periodontal severity (OR: 2.58 $IC_{95\%}$ 2.28 – 7.28 p= 0.001). 47.5% of GCF DKK1 high levels had also increased DKK1 serum levels (p = 0.022 by X2; OR: 2,41 $IC_{95\%}$ 1.14 – 5.09 p= 0.021). It was observed associations between GCF-DKK1 levels and the activity score DAS28ESR (p = 0.000), HAQ (p = 0.000; RRR: 1,96 $IC_{95\%}$ 1.04 – 4.21 p= 0.035), RAPID 3 (p = 0.000) and presence of painful joints (p = 0.04). Despite that, It was not observed associations between GCF-DKK1 levels and SvH. However, feet bone erosion evaluated by SvH and juxta-articular osteopenia were associated with high levels of serum DKK-1 (p=0.009 and 0.001 respectively), showing serum levels up to 7 folds increased. Serum DKK1 levels also showed associations with SDAI (p=0.006; RRR: 2,38 $IC_{95\%}$1.03 – 5.52 p= 0.043), RAPID (p=0.000) and RF (0.018).

Conclusion: The DKK1 can be considered as a potential biomarker for bone resorption in joint and periodontal disease in patients with early rheumatoid arthritis. Seror R et al. Sci Rep. 2016; 20:18421

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Abstract Number: 1516

Evidence of Labial Salivary Gland Epithelial Cell Activation from Patients with Rheumatoid Arthritis and Sicca Symptomatology

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Background/Purpose: In primary Sjögren's syndrome (pSS), labial minor salivary gland epithelial cells (LMSGEC) inappropriately express various molecules, including B7, HLA-DR, ICAM, as assessed previously by in-situ and in-vitro studies, indicating an epithelial cell activation. Sicca symptomatology is encountered in around 30% of rheumatoid arthritis patients (RA-sicca). We previously showed that RA-sicca labial minor salivary gland (LMSG) lesions differ from those observed in pSS, primarily by displaying higher frequency of antigen presenting cells (APCs) [1]. Also, in a subgroup of RA-sicca patients, LMSGECs were found to express the B7 molecule. Interestingly patients exhibiting B7-positive LMSGECs had distinct histopathological and clinicoserological characteristics resembling those observed in pSS. We sought to further investigate if there is, indeed, evidence of a pSS-like epithelial activation in this subgroup of RA-sicca patients.

Methods: Serial sections of LMSGs from 32 RA patients (2010 ACR criteria) with sicca symptoms were evaluated with immunohistochemistry for the presence of total T cells, helper and cytotoxic T cell subpopulations, B cells, macrophages (MΦ), interdigitating (iDC) and follicular dendritic cells (fDC) and for the expression of B7, HLA-DR and ICAM molecules. Stained cells and total mononuclear cells (MNC) were counted in the entire section. Counts were expressed as cell frequency (% of cell type/total infiltrating MNC numbers) and staining for activation markers was assessed on an arbitrary scale (0-1). Correlations between epithelial cell activation status and cell frequencies or clinicoserological features were performed.

Results: LMSGECs in 16/32 patients were triple (B7.1, HLA-DR, ICAM) positive while the rest were either single, double or triple negative. Triple positive patients versus the remaining ones had more severe LMSG lesions (focus score; Mann Whitney, $p=0.05$) and exhibited lower frequencies of MΦ, iDCs and fDCs (Table 1). No differences on clinicoserological features were observed among groups. Expression of the aforementioned molecules by primary cultured LMSGECs of the same patients will be confirmed by flow cytometry.

Conclusion: A distinct subgroup was identified within the RA-sicca patients. This is characterized by expression of activation markers by their LMSGECs and also by an immunohistopathological pattern resembling pSS rather than RA-sicca. In vitro studies of primary LMSGEC cultures will confirm if these cells are indeed activated in such patients. 1. GE Fragoulis, et al. Analysis of the cell populations composing the mononuclear cell infiltrates in the labial minor salivary glands from patients with rheumatoid arthritis and sicca syndrome. J Autoimmun. 2016 (In press)

Table 1: Epidemiological, clinicoserological and histopathological features. a. Kruskal-Wallis and chi-square test for continuous and categorical variables, respectively.

Patients characteristics	Triple negative N=3	Single positive N=6	Double positive N=7	Triple positive N=16	p-value[a]
Epidemiological					
Age, median (range)	61 (56-68)	57 (41-64)	56 (44-64)	61 (32-69)	0.473
Sex female, N (%)	3 (100.0)	6 (100.0)	7 (100.0)	14 (87.5)	0.597
Total follow up, months (mean ± SD)	90.0 ± 81.2	55.1 ± 36.1	119.0 ± 63.2	71.9 ± 80.7	0.283
Criteria					
Ocular dryness (subjective), N (%)	2 (66.6)	5 (83.3)	3 (42.9)	15 (93.8)	0.105
Oral dryness (subjective), N (%)	1 (33.3)	4 (66.6)	5 (71.4)	8 (50.0)	0.351
Tarpley score, median (range)	1 (0-1)	1 (0-2)	1 (0-3)	2 (0-3)	0.836
Focus score, (mean ± SD)	0.33 ± 0.42	1.08 ± 0.76	0.79 ± 1.12	2.39 ± 3.02	0.347
Laboratory					
ANA positive, N (%)	2 (66.6)	5 (83.3)	4 (57.1)	13 (81.2)	0.206
Anti-Ro/SSA positive, N (%)	1 (33.3)	2 (33.3)	2 (28.6)	5 (31.2)	0.996
Anti-La/SSB positive, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1.000
RF positive, N (%)	3 (100.0)	5 (83.3)	4 (57.1)	13 (81.2)	0.700
Anti-CCP positive, N (%)	2 (66.6)	6 (100.0)	4 (57.1)	8 (50.0)	0.085
C3 (mg/dl), (mean ± SD)	111.0 ± 34.4	123.5 ± 18.7	121.8 ± 32.1	103.8 ± 19.8	0.413
C4 (mg/dl), (mean ± SD)	26.7 ± 3.8	23.0 ± 11.9	24.3 ± 7.2	20.3 ± 7.3	0.498
Clinical					
Fatigue, N (%)	1 (33.3)	0 (0.0)	2 (28.6)	7 (43.8)	0.317
Raynaud's phenomenon, N (%)	1 (33.3)	2 (33.3)	3 (42.9)	5 (31.3)	0.840
Morning stiffness N (%)	3 (100.)	5 (83.3)	6 (85.7)	12 (75.0)	0.339
Liver/renal/lung involvement, N (%)	0 (0.0)	0 (0.0)	1 (14.2)	2 (12.5)	0.735
Serositis, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0.823
Myositis, N (%)	0 (0.0)	0 (0.0)	1 (14.2)	0 (0.0)	0.215
Peripheral nerve involvement, N (%)	1 (33.3)	0 (0.0)	2 (28.6)	1 (6.3)	0.164
Purpura, N (%)	0 (0.0)	0 (0.0)	1 (14.2)	3 (18.8)	0.616
Salivary gland enlargement, N (%)	0 (0.0)	0 (0.0)	1 (14.2)	2 (12.5)	0.700
Lymphoma, N (%)	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.3)	0.823
Histopathological	mean±SD				
%$CD20^+$ B cells	47.9 ± 15.0	45.1 ± 7.3	35.9 ± 7.1	45.9 ± 12.6	0.457
%$CD3^+$ T cells	46.5 ± 16.2	39.7 ± 2.8	41.9 ± 6.3	44.8 ± 12.4	0.771
%$CD4^+$ T cells	24.0 ± 12.1	19.3 ± 6.8	21.8 ± 7.6	28.1 ± 7.9	0.727
%$CD8^+$ T cells	20.7 ± 5.4	18.9 ± 5.4	19.5 ± 4.2	16.8 ± 5.5	0.512
%$CD68^+$ MΦs	2.8 ± 1.7	7.3 ± 2.3	8.1 ± 3.0	4.1 ± 2.0	0.009
%$S100^+$ iDCs	1.1 ± 0.7	1.8 ± 1.0	3.5 ± 2.0	1.2 ± 1.1	0.02
%$fascin^+$ fDCs	2.2 ± 0.8	4.5 ± 2.3	6.5 ± 1.5	3.2 ± 1.7	0.02

Disclosure: G. Fragoulis, None; **J. Reilly**, None; **S. Kerr**, None; **I. B. McInnes**, None; **H. M. Moutsopoulos**, None.

Abstract Number: 1517

Does Inflammatory Arthritis Really Improve during Pregnancy? a Systematic Review and Meta-Analysis

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Background/Purpose: Disease activity is considered to improve in approximately 75% of patients with rheumatoid arthritis (RA) during pregnancy. This figure, however, is derived from historical data from mostly retrospective studies, which lack standardised and objective measures of disease activity. More recently, prospective studies have been carried out in patients with various forms of inflammatory arthritis using validated disease activity scores, which have shown a more modest improvement in disease activity during pregnancy. We carried out this systematic review of prospective studies to examine whether inflammatory arthritis truly does improve during pregnancy.

Methods: A systematic review of PubMed, EMBASE/Medline, Cochrane and LactMed databases was performed using the terms 'pregnan*', 'lactat*', 'breastfeeding', 'breast feeding', 'rheumat*', 'inflammatory arth*', 'arthritis', 'psoria*', 'spondyloarthropath*' and 'ankylosing spondylitis'. Exclusion criteria included: retrospective, <5 subjects, no validated disease activity scores and abstracts. Two reviewers independently assessed each study for quality and extracted data using a predesigned proforma. A chi-square test for heterogeneity was performed to determine whether findings were consistent between studies, and random effects meta-analysis was used to account for the heterogeneity observed. A 95% confidence interval was calculated for final data analysis.

Results: Of 762 articles screened, 86 were selected for full length review and 14 eligible for the final analysis, including 965 pregnancies (939 with RA, 6 with juvenile idiopathic arthritis (JIA), 20 with ankylosing spondylitis (AS)). A significant amount of heterogeneity between studies was noted (I^2= 76.3%). All studies utilised the DAS(3)28 (for RA), RADAI (for RA and JIA) or BASDAI (for AS) to measure disease activity. Overall, disease activity improved in 523 pregnancies (54.3% (95% CI 51.0-57.6%)); this total comprised 510 patients with RA (54.3% (95% CI 51.0-57.7%)), 5 patients with JIA (83.3% (95% CI 36.5 - 99.1%)) and 8 patients with AS (40.0% (95% CI 21.5-58.5%)). Post-partum disease activity was recorded in 808 pregnancies and flares were noted in 48.57% of pregnancies (95% CI 45.02 – 52.02%) overall, of which 47.97% (95% CI 44.4 – 51.46%) were in patients with RA (793 pregnancies), 66.6% (95% CI 24.11 – 94.0%) were in patients with JIA (6 pregnancies) and 89.9% (95% CI 50.67 – 99.42%) occurred in patients with AS (9 pregnancies). Pregnancy outcomes were only reported in 2 studies (of 303 pregnancies) with no increase in adverse events.

Conclusion: We found that half of all patients with RA had an objective improvement in disease activity during pregnancy and a similar proportion relapsed post-partum. In contrast, patients with JIA were more likely to improve during pregnancy and relapse post-partum whilst patients with AS in pregnancy were less likely to improve and far more likely to relapse post-partum. This information is vital when counselling patients with inflammatory arthritis pre-partum and considering alterations in therapy to ensure maintenance of disease control with medications that are compatible with pregnancy.

Disclosure: H. Jethwa, None; **S. Lam**, None; **C. Smith**, None; **I. Giles**, None.

Abstract Number: 1518

Immunoglobulin Binding Protein (BiP), an Antigen for CCP Sero-Positive Rheumatoid Arthritis Patients, Can Result in a False Positive Quantiferon-Gold Tuberculosis Test

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Background/Purpose: Citrullinated BiP is a newly described target for cyclic citrullinated peptide(CCP). BiP in both serum and synovial fluid is over-expressed in RA patients and correlates with CCP[1]. Serum BiP causes T cell expansion and increases interferon during incubation of the QuantiFERON-Gold tuberculosis in-tube test (QFT-G TB) which can result in a false positive TB test. The QFT-G TB has never been validated where interferon is increased, as for example RA.

Methods: Positive CCP RA patients (n=126) were tested prior to initiating biologic therapy with QFT-G TB (Cellestis). TB evaluation at baseline and annually for two years included history, physical, standard blood tests, chest radiograph, PPD and control skin testing. RA patients had CCP, RF, Wesr, CRP, DAS, wrist temperature, tender and swollen joint counts at baseline (table 1). Three healthy middle-aged female controls with no arthritis were tested with QFT-G TB. Their serum was later tested with BiP added, with 2 ug/ml, 5ug/ml, 10ug/ml, and 20ug/ml, levels seen in RA. (Sourced BiP Novus Biologicals.)

Results: Of 126 CCP+ patients, 16 tested positive for TB (13%) by QFT-G TB, despite no known risk factors for TB (no travel, low endemic rural area, no exposure history), negative chest radiograph, negative PPD with positive candida control, normal blood testing, no symptoms or signs of TB. The CDC established local TB rate is 0.0007%. All 16 had high levels of CCP and active inflammation (mean DAS-esr 6.17). With consultation of an Infectious Disease specialist, all 16 patients received biologic therapy with no INH prophylaxis. In follow up after 24 months, none developed TB and QFT-G TB reverted to negative in 5 patients, correlating with the RA control on biologic therapy. (The other 11 did not have repeat QFT-G.) Mean QFT-G interferon levels in test tubes were 1.57 IU for TB, 0.18 IU for nil, and >10 IU for the mitogen tube. Positive TB defined by the lab kit was > 0.35 IU. False TB interferon levels correlated with CCP level ($p<0.02$). Three healthy women with no arthritis or TB exposure had negative QFT-G TB. These three subjects tested positive every time for TB correlating to the dose of BiP added, at concentrations of 2 ug/ml, 5 ug/ml, 10 ug/ml, and 20 ug/ml (fig 1).

Conclusion: BiP is naturally found in the majority of CCP+RA patients and presence of BiP in serum can result in a false positive QFT-G TB. Patients with the highest CCP had the highest QFT-G TB interferon levels. Subsequent undertreatment of RA, if biologic therapy is withheld, and overtreatment of presumed latent TB may harm patients.

1. Arth Rheum 2015;67:1171-1181.

2. Arth Care Res 2015 Dec 1, on line.

False positive QFT RA patient characteristics

Age	Yrs RA	CCP	CCP3	RF	DAS-esr	DAS-crp	Jt Temp	IFN level
56 (11.8)	12 (8.8)	148 (288)	663 (848)	62 (73)	4.8 (1.2)	6.2 (1.3)	97.2 (0.1)	1.57* (2.0)

Results listed are average values (s.d.) Joint temperature is dermal skin measurement over the left wrist.[2]
* $p<0.02$ correlation between CCP and IFN level, and $p<0.02$ for CCP3 and IFN level.

Table 1

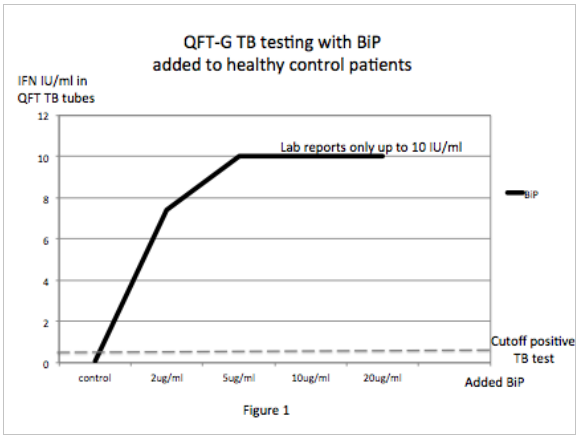

Figure 1

Disclosure: J. Ball, None; **K. Greenwald**, None; **A. A. Deodhar**, AbbVie, 2,AbbVie, 9,Amgen, 2,Amgen, 9,Boehringer Ingelheim, 2,Boehringer Ingelheim, 9,Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 9,Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 9,Pfizer Inc, 2,Pfizer Inc, 9,UCB, 2,UCB, 9; **K. L. Winthrop**, None.

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Abstract Number: 1519

How Much, and When, Does Autoimmune Thyroid Disease Increase the Risk of RA, and Does RA-Onset Impact the Risk of Autoimmune Thyroid Disease?

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Background/Purpose: Autoimmune thyroid disease (AITD) is one of the most common autoimmune diseases, and occurs more often than expected in patients with Rheumatoid Arthritis (RA). The nature (shared susceptibility or risk factors, AITD triggering RA, or vice versa) and the pattern of risks in relation to RA onset remain unknown. We therefore aimed at assessing risks and relative risks of AITD as a function of time before and after, respectively, RA onset, overall and by age and sex.

Methods: In the Swedish Rheumatology Quality Register, we identified a large cohort of patients with incident RA (symptom duration at diagnosis < 1 year) 2006 through 2013 (n=8090). For each RA-patient 10 general population controls were individually matched. (n=80 856). Incident AITD was defined as a first ever prescription of thyroxin, based linkage to the Swedish Prescribed Drug register (excluding participants with prescriptions for iodine-containing drugs and thyroid cancer. We used a case-control approach to assess relative risks (odds ratios) for AITD before RA, and a cohort approach to assess relative risks (hazard ratios) of AITD after RA.

Results: By the time of RA diagnosis, 259 (3.2%) RA patients vs. 1613 (2.0%) of the general population controls had a history of AITD (OR=1.6, 95%CI 1.4-1.9). We noted increased risks for AITD up to five years before RA onset (OR=1.4, 95%CI 1.2-1.8), with the highest relative risks 3 months or less between the onset of AITD and the RA-diagnosis (OR=5.1, 95% CI 3.6-7.2). Separate analyses revealed higher relative risk among younger and seropositive patients. Following diagnosis of RA, AITD occurred among 121 (1.7%) RA-patients and 1384 (1.9%) controls, overall HR=0.9, 95% CI 0.7-1.1. The risk of AITD was increased during the first three months following RA diagnosis (HR= 2.1, 95% CI 1.2-3.7), but decreased over time into a decreased risk two or more years after RA diagnosis (HR=0.7, 95%CI 0.5-0.99).

Conclusion: This study confirms the increased risk of incident RA among patients with AITD, and extends this observation by demonstrating that the risk of incident AITD varies with time before/after RA, and that the increased risk before RA onset is replaced

by a decrease in risk in patients with established RA. This temporal pattern of risk is compatible both with a critical link between AITD and RA onset, and with increased diagnostic intensity around the time-point of RA diagnosis. Whether the decrease in risk with increasing RA duration is a reciprocating decline after a transient increase in diagnostic intensity, or is a true protective effect e.g., via anti-rheumatic therapies, remains to be investigated.

Table 1. Relative risk of AITD before the diagnosis of RA in 8090 patients with RA compared with 80856 matched controls

	No of thyroxintreatment in RA cases/controls	OR (95% CI)	P-value
Overall	263 cases/1687 controls	1.585 (1.388-1.810)	<0.0001
treatment with iodine-containing drug	2 cases/47 controls		
lithium	1 cases/34 controls		
amiodarone	1 cases/ 13 controls		
history of thyroid cancer	2 cases/27 controls		
	No of AITD in RA cases(8086)/controls (80 782)		
Overall	259 cases/1613 controls	1.632 (1.428-1.866)	<0.0001
Sex			
women	223/1394	1.629 (1.410-1.883)	<0.0001
men	36/219	1.612 (1.124-2.313)	0.0095
RF status			
Positive(5195cases/51 871)	167/992	1.710 (1.447-2.022)	<0.0001
Negative(2609 cases/26 082	81/551	1.495 (1.178-1.898)	0.0009
NA(282 cases/ 2829 controls)	11/70	1.598 (0.834-3.064)	0.1580
Time beetween AITD and RA diagnosis			
0-<3 months	47/92	5.076 (3.567-7.226)	<0.0001
3-<12 months	49/257	1.927 (1.417-2.620)	<0.0001
12-<24 months	42/325	1.288 (0.933-1.779)	0.1244
24-<60 months	100/704	1.443 (1.168-1.784)	0.0007
>60 months	21/235	0.890 (0.568-1.394)	0.6106
Age at inclusion in SRQ			
16-49 years	89/342	2.683 (2.113-3.406)	<0.0001
50-74	136/998	1.378 (1.148-1.654)	0.0006
>74	34/273	1.254 (0.872-1.805)	0.222

Table 2. Relative risk of AITD in 7059 patients with RA and 71 350 matched controls, by time since RA diagnosis (2006-2012)

	No of AITD in RA cases/controls	HR (95% CI)	p-value
Overall	121/1384	0.901 (0.748-1.087)	0.277
Time since RA diagnosis			
0-<3 months	15/72	2.100 (1.199-3.678)	0.009
3-<12 months	26/266	1.003 (0.669-1.504)	0.987
12-<24 months	29/298	1.032 (0.703-1.516)	0.871
24-<60 months	41/580	0.722 (0.525-0.992)	0.045
>60 months	10/168	0.610 (0.321-1.160)	0.132

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Abstract Number: 1520

RA Flare after Total Hip and Total Knee Arthroplasty: Preliminary Outcomes at 1 Year

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Background/Purpose: Post-op flares are frequent for RA patients after total hip (THA) and total knee arthroplasty (TKA), when medications are discontinued to mitigate infection risk. The association of flares and patient-reported outcomes (PROs) at 1 year after THA and TKA is unknown. We aimed to describe the relationship of post-op flares with 1 year THA/TKA outcomes.

Methods : Post-op flares were identified in patients with RA undergoing TKA/THA by self-report. Patients completed a questionnaire comprised of a subset of questions from the RA Flare Questionnaire, administered weekly for 6 weeks after arthroplasty. Flare was defined by concordance between patient report ("Are you in a flare? Yes/No"), plus MD assessment of patient-reported survey data including patient reported swollen and tender joints and Rapid III. Pain and function scores (HOOS/KOOS) and disease characteristics were collected at baseline before surgery and after one year. Baseline characteristics and HOOS/KOOS scores were compared using t-tests and chi-square.

Results: One-year outcome scores were available for 20 THA and 14 TKA patients, predominantly women with established RA (Table 1). Baseline DAS-28 and CDAI were higher in TKA flarers, but not THA flarers. 20 (59%) were using biologic medications that were stopped for surgery, and 21 (61%) were flaring before or within six weeks of surgery. MTX use was similar in all groups. Despite this, flarers and non-flarers both had excellent pain and function outcomes at 1 year. There was no statistically or clinically significant difference between flarers and non-flarers, despite poorer pre-operative KOOS scores and higher disease activity for TKA flarers.

Conclusion: Although post-op flares were frequent in RA patients undergoing THA/TKA, pain and function outcomes were similar at 1 year in those who reported flare or not. While these preliminary data are reassuring that perioperative flares do not appear to affect long term functional outcomes, further validation in a larger sample of patients is needed, as well as more study in different settings to increase confidence in these findings. This study was supported by the Clinical Translational Science Center (CTSC) (UL1-TR000457-06)

	Flare Mean (SD)	No Flare Mean (SD)	P-Value
Total Hip Arthroplasty	**N = 16**	**N = 4**	
Age	57.8 (14.0)	62.9 (16.1)	.59
Sex Female	12 (75%)	3 (75%)	1.0
BMI	30.8 (6.5)	28.0 (1.9)	.17
Disease Duration	17.3 (16.6)	7.8 (6.2)	.09
Methotrexate	12 (75%)	3 (75%)	1.0
Biologic DMARD	10 (63%)	1 (25%)	.24
RF+ or CCP+	11 (69%)	2 (50%)	.58
1987 or 2010 Criteria	13 (81%)	3 (75%)	.82
Baseline			
- HOOS Symptoms	39.8 (21.7)	36.3 (27.2)	.82
- HOOS ADL Function	38.4 (15.6)	44.7 (30.8)	.71
- DAS28	3.9 (1.2)	3.4 (1.1)	.62
- CDAI	18.9 (7.6)	22.7 (7.0)	.46
1-Year			
- HOOS Symptoms	89.6 (10.8)	78.8 (20.2)	.37
- HOOS Pain	91.1 (9.5)	96.3 (5.3)	.37
- HOOS ADL Function	84.7 (18.4)	83.0 (20.8)	.89
Total Knee Arthroplasty	**N = 5**	**N = 9**	
Age	57.6 (7.5)	62.5 (9.2)	.30
Sex Female	5 (100%)	8 (89%)	.35
BMI	30.3 (11.7)	28.5 (5.8)	.76
Disease Duration	19.0 (12.7)	11.5 (6.4)	.27
Biologic DMARD	3 (60%)	6 (67%)	.83
Methotrexate	3 (60%)	6 (67%)	.89
RF+ or CCP+	2 (40%)	4 (44%)	.89
1987 or 2010 Criteria	5 (100%)	8 (89%)	.35
Baseline			
- KOOS Symptoms	15.0 (8.6)	37.3 (15.9)	**.005**
- KOOS Pain	19.5 (15.4)	40.1 (12.0)	**.04**
- KOOS ADL Function	32.0 (21.6)	43.5 (13.1)	.32
- DAS28	5.3 (1.0)	3.0 (1.3)	**.003**
- CDAI	38.0 (14.5)	14.1 (9.4)	**.04**
1-Year			
- KOOS Symptoms	78.6 (14.3)	87.7 (8.4)	.89
- KOOS Pain	78.9 (19.0)	87.4 (13.3)	.41
- KOOS ADL Function	78.3 (17.2)	84.8 (15.1)	.50

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Abstract Number: 1521

Disease Characteristics and Change of Arthritis Activity According to Treatment in Hepatitis B Surface Antigen Positive Rheumatoid Arthritis Patients

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Background/Purpose: Rheumatoid arthritis (RA) treatment may differ according to hepatitis B state and consequently bring about different outcome of arthritis. Only a small number of studies have addressed the differences in disease characteristics and treatment patterns of RA in relation to hepatitis B state. However, it has not yet been elucidated whether hepatitis B affects treatment outcome such as disease activity. We investigated possible differences in change of arthritis activity between RA patients according to concomitant hepatitis B virus (HBV) infection.

Methods: We conducted an age-matched, sex-matched and entry-time-matched cohort study using single center data, from 1 January 2000 to 31 March 2015. Up to three hepatitis B surface antigen (HBsAg)-negative rheumatoid arthritis (RA) patients were matched to each patient with HBsAg-positive RA by age, sex and year of cohort entry. The longitudinal relationship between HBsAg-positivity and RA activity was analyzed using generalized estimating equations in linear regression models. Similar analysis was performed for RA medication use within each group.

Results: One hundred fifty-two patients were included in the study; 40 were HBsAg-positive. Baseline characteristics did not differ significantly between groups. In regression analysis, RA activity showed time-dependent improvement. The reductions of swollen joint count over time were significantly larger in HBsAg-negative group (b-coefficient 7.91 [95% confidence interval (95% CI) 1.41, 14.41], P = 0.017). However, changes of disease activity score in 28 joints with 3 variables (DAS28-3), tender joint count, erythrocyte sedimentation rate and C-reactive protein level did not differ between groups. There was no difference in alanine aminotransferase level. Over all visits, HBsAg-positive patients were less likely to receive methotrexate (OR 0.09 [95% CI 0.04-0.19], P < 0.0001) and more likely to receive sulfasalazine (OR 3.67 [95% CI 1.94-6.95], P < 0.0001).

Conclusion: RA medication use was different according to HBsAg-positivity. However, the improvement of RA activity was not significantly affected by concomitant hepatitis B state.

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Abstract Number: 1522

Disease Burden in Rheumatoid Arthritis (RA) Patients Who Have Secondary Osteoarthritis (OA) Is Lower Than in OA but Higher Than in RA with No Secondary OA

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Background/Purpose: Recent data indicate that the disease burden experienced by patients with osteoarthritis (OA) is similar to or greater than in rheumatoid arthritis (RA) (EULAR meeting, 2015)(1). Many patients with RA may have secondary (2°) OA, which may affect disease burden and clinical management. We compared disease burden in patients with RA, RA with 2° OA, and OA, according to scores on a multi-dimensional health assessment questionnaire (MDHAQ) and physician RheuMetric checklist.

Methods: At one academic rheumatology center, all patients with all diagnoses complete an MDHAQ. The MDHAQ includes 0-10 scores for physical function (FN), pain (PN), and patient global estimate (PATGL), compiled into a 0-30 composite routine assessment of patient index data (RAPID3), and a 0-48 RA disease activity index (RADAI) self-report joint count. Rheumatologists complete a RheuMetric checklist, which includes four 0-10 visual analog scales (VAS) for overall physician global estimate (DOCGL), inflammation or reversible findings (DOCINF), damage or irreversible findings (DOCDAM), and patient distress unexplained by DOCINF or DOCDAM (e.g. fibromyalgia, depression) (DOCSTR). Patients were classified as RA, RA with 2° OA, and OA, according to medical record diagnoses. Measures were compared in the 3 groups by MANOVA, adjusted for age.

Results: 669 patients seen in routine care between September 2014 and June 2015 were studied, including 248 with RA, 47 with RA and 2° OA (16% of all RA), and 374 with OA. Patients with OA were significantly older, but no differences were seen in formal education level or gender. MDHAQ scores indicated substantial disease burden in all 3 diagnosis groups, although least in RA patients with no 2° OA, intermediate in RA patients with 2° OA, and greatest in patients with primary OA, e.g., RAPID3 was 11.0±7.7, 12.3±6.7, and 15.1±6.3 in the 3 groups, respectively (Table) ($p<0.001$ adjusted for age). Among RheuMetric checklist scores, DOCGL did not differ significantly in the 3 groups; DOCDAM was higher than DOCINF in all 3 groups, but differed by 0.7 /10 units in RA vs 1.6 units in RA with secondary OA and 3.2 units in patients with primary OA (Table).

Conclusion: Patients with OA appear to have a greater disease burden than those with RA; the disease burden is intermediate in RA patients who have 2° OA. The higher DOCDAM scores vs DOCINF relative in RA patients may help explain why RA remission rates are below 50%, even though inflammation appears to be effectively controlled (2). Patient MDHAQ and physician RheuMetric are useful and feasible to assess and monitor rheumatic diseases in busy clinical settings. **References: 1.** C. El-Haddad, I. Ann Rheum Dis 2015;74(Suppl2): 369. **2.** Tymms K, et al. Arthritis Care Res (Hoboken). 2014;66:190-6.

	RA N= 248	RA with secondary OA N= 47	OA N=374	P
Demographic measures				
Age, mean, years	56.8	62.4	66.3	<0.001
Education level, mean, years	13.7	14.1	13.5	0.48
Female, %	85.8%	80.6%	88.1%	0.20
MDHAQ: Mean Patient self-report scores				
MDHAQ-Function	2.4	2.8	2.8	0.12
MDHAQ-Pain	4.7	5.0	6.3	<0.001
MDHAQ-PATGL	4.2	4.5	5.6	<0.001
RAPID3 (0-30)	11.0	12.3	15.1	<0.001
RADAI (0-48)	10.7	10.5	12.1	0.32
RheuMetric: Mean Physician Estimates				
DOCGL	3.7	3.9	4.0	0.28
DOCDAM	2.9	3.4	4.1	<0.001
DOCINF	2.2	1.8	0.9	<0.001
DOCSTR	1.1	0.5	1.6	0.03

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Abstract Number: 1523

The Effect Size of Fibromyalgia on PG-VAS in Rheumatoid Arthritis Patients. Adjustment Proposal in DAS28-ESR

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Background/Purpose:

The disease activity score (DAS) is a method used to monitor disease activity in Rheumatoid Arthritis (RA). Diseases that cause chronic pain or mood disorders have been previously studied to assess their effect on the activity of RA. The aim of the study was to assess clinic, activity, and function characteristics on the DAS28-ESR in RA patients.

Methods:

This is an observational, descriptive cross-sectional study fron march 2013 to march 2014. We included patients with RA according to 2010 ACR/EULAR classification criteria. We analyzed the effect of Fibromyalgia, Knee Osteoarthritis knee, presence of Tendinopathy (any) on the status of RA activity. Evaluation of Health Assessment Questionnaire (HAQ) and Patient Global Visual Analogue Scale (PG-VAS) were included. We considered a VAS> 40 with clinical significance. All patients underwent joint count and ESR.

Results:

We analyzed 395 patients, 360 (91.1%) women , with mean age of 51.1 (SD 12.7). Table 1 shows the clinical and activity characteristics of the patients. We found in the bivariate analysis that the presence of a PG-VAS >40 was associated with a DAS28-ESR greater than 2.6 (OR: 12.47, 5.2-29 95% CI, p = 0.001). Fibromyalgia was a predictor of PG-VAS >40 (OR 3.49, 1.72-7.08 95% CI, p = 0.0001). The rest of the variables analyzed did not influence.

Conclusion:

We observed a negative effect of Fibromyalgia in the PG-VAS and therefore in the DAS28-ESR in patients with RA. The effect size of diagnostic Fibromyalgia on the DAS28 was 27%. We propose to adjust the DAS28, when the PG-VAS is above 40, by multiplying by 0.73, to consider the effect of Fibromyalgia in the evaluation.

Table 1. Clinic, activity, and function characteristics of RA patients

Variables	With FM	Without FM	p
	n= 39	n= 356	
Age, years mean, SD	55.5, 6.8	50.6, 13.3	0.02
DAS28-ESR median, IQR	3.01, 1.3	3.1, 1.4	0.5
ESR mm/Hr median, IQR	27.02, 14.8	29.1, 12	0.35
PG-VAS mm, mean , SD	**29.9, 4.7**	**22, 1.2**	**0.001**
PG-VAS > 40mm n,%	**15, 38.5**	**54, 15.2**	**0.001**
Presence of morning stiffness n,%	17, 43.6	119, 33.4	0.2
Presence of night pain n,%	39,100	336, 94.4	0.3
Functional class I n,%	32, 82.1	270, 75.8	0.14
Knee Osteoarthritis n,%	11, 28.2	61, 17.1	0.08
Tendinopathy n,%	4, 10.3	15, 4.2	0.094
HAQ-8			
- Dress yourself, including tying shoelaces and doing buttons? n,%	29, 74.4	217, 61	0.1
- Get in and out of bed? n,%	36, 92.3	337, 94.7	0.5
- Lift a full cup or glass to your mouth? n,%	36, 92.3	317, 89	0.5
- Wash and dry your entire body? n,%	36, 92.3	336, 94.4	0.5
- Bend down to pick up clothing from the floor? n,%	34, 87.2	326, 91.6	0.35
- Turn faucets/taps on and off? n,%	38, 97.4	342, 96.1	0.67
- Get in and out of a car? n,%	36, 92.3	342, 96.1	0.27
- Walk outdoors on flat ground?	34, 87.2	320, 89.9	0.5

DAS28-ESR: Disease Activity Score of 28 joints with ESR, PG-VAS: Patient Global visual analogue scale, ESR: erythrocyte sedimentation rate, IQR: interquartile range, HAQ: Health Assessment Questionnaire. Functional class I:Without limitation to activities of daily living

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Abstract Number: 1524

Suppletion Therapy May be Warranted in RA Patients with Co-Existent Subclinical Hypothyroidism

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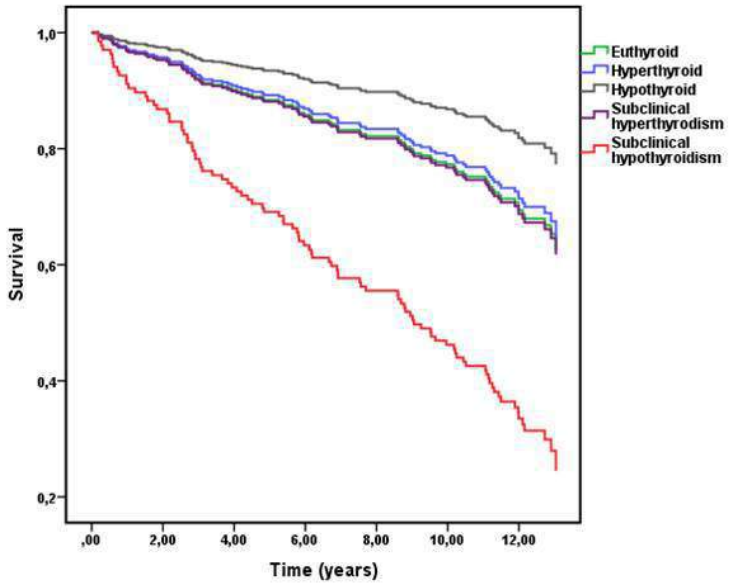
Background/Purpose: Autoimmune thyroid disease often coexists with RA and has been associated with an elevated cardiovascular (CV) risk, especially in hypothyroid patients. However, the existing studies show conflicting results and long term follow up studies are scarce. Therefore, we have investigated whether RA patients with thyroid dysfunction have an increased incidence of CV disease (CVD) compared to euthyroid RA patients.

Methods: Thyroid-stimulating hormone (TSH) and serum free thyroxine (FT4) were assessed in 348 RA patients participating in an ongoing prospective cohort study designed to assess CV risk factors, morbidity and mortality. Cox proportional hazard models were

used to calculate hazard rates (HR) for incident CVD.

Results: The participants were predominantly females (66.1%) with a mean age of 63 ± 8 years and a mean disease duration of 7 ± 4 years. At baseline 4.6% was hypothyroid (n=16, TSH >4.0 mU/L, FT4 <10 pmol/L), 4.0% was hyperthyroid (n=14, TSH <0.3, FT4 >24 pmol/L), 2.6% had subclinical hyperthyroidism (n=9, TSH<0.3 and normal FT4), 2.9% had subclinical hypothyroidism (n=10, TSH>4.0 and normal FT4) and 85.9% (n=299) was euthyroid. 99 patients (28%) developed CVD during 15 years of follow up. 50% of the subclinical hypothyroid, 25% of the hypothyroid, 44.4% of the subclinical hyperthyroid, 21.4% of the hyperthyroid and 27.4% of the euthyroid RA patients developed CVD. Compared to the euthyroid persons, age and gender adjusted HR were 0.77 (95%CI 0.24 – 2.47; P=0.65) for hyperthyroid patients, 0.75 (95% CI 0.27 – 2.09; P=0.58) for hypothyroid patients, 1.26 (95%CI 0.46 – 3.44; P=0.67) for subclinical hyperthyroidism and 2.54 (95%CI 1.03-6.30; P=0.04) for subclinical hypothyroidism. Only subclinical hypothyroidism was associated with incident CVD compared to euthyroid patients in all models, with a HR of 2.94 (95% CI 1.05 – 8.19; P=0.04) in the final model after adjustment for prevalent CV disease, metabolic syndrome, RA duration, disease activity and creatinine.

Conclusion: Coexistence of subclinical hypothyroidism with RA is associated with an increased incidence of CVD. If external validation can confirm this amplified CV risk, thyroxine supplementation and CV risk management may be warranted in this subgroup of patients.



Disclosure: R. Agca, None; **H. Raterman**, None; **S. Simsek**, None; **A. E. Voskuyl**, None; **M. T. Nurmohamed**, None.

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Abstract Number: 1525

Pain, Physical Function, and Worry (But Not Depression and Poor Sleep) Lead to Greater Fatigue in RA

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Background/Purpose: Some view fatigue as resulting from disease activity, while others see it as a natural consequence of the pain, disability, and the emotional burden of living with RA. We explored how RA symptoms and impacts contribute to fatigue.

Methods: Participants had MD-diagnosed RA, were receiving care at an academic arthritis clinic, and were enrolled in an observational study. All completed PROMIS measures of fatigue, mood (depression, anxiety), and symptoms/impacts (physical function [PF], sleep disturbance, pain interference, and participation in social roles and activities). Clinical RA indicators and self reports of exercise frequency we also obtained. Pearson correlation and multiple regression models were used to evaluate associations among variables.

Results: Data are from the baseline visit of 177 RA patients who were mostly female (82%) and white (83%) with a mean (SD) age of 56 (13) years; 24% had ≤ high school, 29% had RA ≤ 5 years with 13% ≤ 2 years, and 22% were disabled. Mean CDAI was 7.9 (7.8). Most were in CDAI remission (n=56; 32%) or LDA (n=67; 38%); 39 (22%) were in MDA, and 14 (8%) in HDA. As compared to the general US population, patients with active RA had higher disability, fatigue, and pain; only those with HDA had elevated mood, sleep disturbance and impaired participation (Table 1). Fatigue was moderately-strongly and directly associated with pain, sleep, depression, and anxiety (r's .45-.67), inversely to PF and participation (r=-.61 and -.64, respectively), weakly and directly with swollen joints (r=.27) and weakly and inversely with regular exercise (r=-.24)(p's <.001). Age and RA duration were not associated with fatigue (p's .967 and .677, respectively). VIF estimates among remaining variable ranged from 1.1–3.3. In multiple regression, pain, physical function, and anxiety were significant predictors of fatigue [F (7,157) = 28.60, p<.001, r^2=.54](Table 2).

Conclusion: In RA, fatigue is common and increases with disease activity. Pain, disability, and anxiety contributed to fatigue, whereas depression and sleep disturbance did not. Overall, anxiety was within the normal range for most (72%) except those with the high disease activity. Our data suggest that beyond pain and disability, in 28% of people with RA, anxiety may also contribute to fatigue. Stress management coaching may offer opportunities to help reduce fatigue in people whose RA is otherwise well controlled. PCORI IP2-PI0000737 and SC14-1402-10818.

Table 1. Patient reported symptoms and impacts of RA across CDAI levels (n=177).

PROMIS Measure	Remission (n=56)		Low (n=67)		Moderate (n=39)		High (n=14)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Fatigue	46.2_a	8.6	**55.7_b**	**8.3**	**58.5_b**	**6.9**	**64.0_c**	**9.6**
Pain Interference	45.6_a	7.2	**56.0_b**	**8.3**	**57.8_b**	**6.1**	**63.4_c**	**8.6**
Physical Function	50.1_a	8.8	**42.2_b**	**7.1**	**39.2_c**	**5.9**	**32.9_d**	**5.5**
Sleep Disturbance	46.6_a	8.6	$53.4_{b,c}$	8.9	52.9_b	10.7	**58.7_c**	**7.9**
Depression	45.7_a	7.9	50.1_b	8.5	50.1_b	8.8	**56.2_c**	**8.2**
Anxiety	47.6_a	7.3	52.2_b	8.5	51.3_b	7.0	**57.0_c**	**7.8**
Participation Social Roles/Activities	**55.8_a**	**8.3**	49.1_b	7.8	47.8_b	6.8	**38.8_c**	**6.8**
Regular Exercise	1.6_a	1.1	1.2_{ab}	1.3	0.9_b	1.0	1.2_{ab}	1.2

Different subscripts reflect significantly different groups (p<.05). Bolded values are ± .5 SD above US population norms.

Table 2. Predictors of fatigue in people with rheumatoid arthritis

	Unadjusted					Adjusted*				
	Beta	SE	Std Beta	t value	Sig	Beta	SE	Std Beta	t value	Sig
Swollen Joints	.813		.274	3.746	.000	.104	.169	.035	.616	.538
Pain	.707	.059	.672	12.003	.000	**.288**	**.092**	**.272**	**3.117**	**.002**
PF	-.706	.065	-.635	-10.886	.000	**-.242**	**.097**	**-.218**	**-2.505**	**.013**
Sleep	.461	.069	.453	6.726	.000	.116	.063	.115	1.841	.068
Depression	.555	.075	.487	7.362	.000	-.049	.110	-.041	-.430	.668
Anxiety	.641	.079	.523	8.093	.000	**.271**	**.120**	**.219**	**2.253**	**.026**
Participation	-.676	.067	-.607	10.039	.000	-.125	.092	-.113	-1.161	.176
Exercise	-2.036	.640	-.240	-3.180	.002	-.740	.475	-.087	-1.557	.121

Std. beta = standardized estimate. *F (7,157) = 28.60, p=.000, adjusted r^2=.541.

Disclosure: S. J. Bartlett, C-Path Institute, 5; **M. Jones**, None; **C. Bingham III**, C-Path Institute, 5.

Abstract Number: 1526

Serum y-Neuropeptide Levels and Its Relationship with Body Fat Mass and Clinical Characteristics in Rheumatoid Arthritis

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Background/Purpose: Overweight and obesity are comorbidities that may increase the risk of cardiovascular disease in rheumatoid arthritis. Increase in in body fat is observed in a high proportion of patients and increase of risk for cardiovascular diseases. Several biomarkers have been tested to be associated with cardiovascular risk. Neuropéptido-Y(NPY) is a neuroendocrine protein of anabolic signaling involved in the pathogenesis of increased body mass index and body fat mass, cardiovascular regulation and pro-inflammatory modulation. Currently, there is a lack of information regarding the clinical association of serum NPY levels in established RA.
Objective: To evaluate the association between NPY levels with disease activity, body fat mass and risk factors for the development of cardiovascular disease in RA.

Methods: In this cross-sectional study, we evaluated 110 women with diagnosis of RA according to 1987 ACR criteria. We assessed disease activity by DAS-28. Percentage of fat mass was measured by dual X-ray absorptiometry (DXA) and cardiovascular risk factors using the Framingham index. Serum levels of NPY were measured by ELISA. Pearson's test was used for the correlation between NPY with the variables of interest and multiple regression analysis in order to control for confounders

Results: The mean age was 58.5±11.2, mean disease duration 13.8±10.2, 97% of RA patients had high percentage of fat mass, and 62.7% had activity of their disease. In the correlation analysis we observed a negative correlation between NPY and body fat mass (r= -0.20, p=0.04) and a negative correlation with atherogenic index (r= -0.23, p=0.02); whereas, a positive correlation was observed between NPY with the TNF-alpha levels (r=0.52, p=0.005) and high-density lipoproteins (HDL-C) (r = 0.25, p <0.001); whereas, no correlation was observed between NPY and DAS-28, HAQ-DI or other variables. In the adjusted analysis after controlling by age, disease duration, fat mass, and other variables; the serum NPY levels were associated with increased in serum TNF-alpha levels

(p=0.006); Glucocorticoids doses or use of biologic agents were not significant as confounders in the final model.

Conclusion: Serum levels of NPY are associated with lower percentage of body fat mass, lower score of atherogenic index and greater concentrations of TNF-alpha on RA. These interesting results encourage future longitudinal studies evaluating if changes of NPY levels during the disease may be associated with a modification of important outcomes mainly the development of future cardiovascular diseases in these patients.

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Abstract Number: 1527

Anxiety Sensitivity on Indicators of Disease Severity Among Patients with Inflammatory Arthritis

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Background/Purpose: There has been growing interest in anxiety sensitivity, defined as the fear of behaviors or sensations associated with the experience of anxiety, in chronic pain research. However, few studies have investigated anxiety sensitivity in the context of inflammatory arthritis. The current study aimed to understand the relationship between anxiety sensitivity and indicators of severity in inflammatory arthritis.

Methods: Data included 148 subjects (mean age = 57.7, 72% female) drawn from a prospective longitudinal Early Arthritis Cohort (symptom less than 12 months at baseline) from 2012 to 2015. Anxiety sensitivity (AS) was assessed using the validated Anxiety Sensitivity Index (ASI). Three factors were investigated: physical AS (fear of autonomic arousal and physical symptoms), cognitive AS (fear of the cognitive aspects of anxiety), and social concerns AS (fear of social consequences of anxiety). Patients completed the ASI on their annual visits. Arthritis activity indicators included patient reported visual analogue scales for pain, fatigue, and functional status (modified health assessment questionnaire; mHAQ), physician assessed global disease activity, swollen 28 joint count, tender 28 joint count, Lansbury weighted joint count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and composite indices (DAS28ESR-3variable, Clinical Disease Activity Index (CDAI)). Bivariate correlations first examined the cross-sectional relationship between AS factors and indicators of disease severity. Adjusted linear and logistic regressions controlling for number of visits examined the longitudinal relationship between change in AS factors on indicators of severity. Only results significant at the 0.01 level are reported to adjust for multiple comparisons.

Results: Total summed mean scores significantly differed for social AS (M = 6.96, SD = 8.43), cognitive AS (M = 2.80, SD = 4.07), and physical AS (M = 3.56, SD = 4.19). The three AS factors were significantly associated with worse pain levels (r range = 0.250-0.293), fatigue (r range = 0.312-0.403), mHAQ (r range = 0.284-0.340) and CDAI (r range = 0.200-0.272). The strongest correlations were consistently indicated for the social AS. Only social (r = 0.211) and physical AS (r = 0.250) were significantly associated with physician assessed global functioning and social AS was the only factor associated with the Lansbury Index (r = 0.197). There was no significant relationship between changes in AS on disease severity; however, only higher physical AS scores at baseline significantly predicted persistence indicated by DAS28ESR > 2.6 (adjusted odds ratio = 1.150, 95%CI = 1.036-1.269, p< 0.01).

Conclusion: Anxiety sensitivity is associated with several indicators of severity among those with inflammatory arthritis; unique

findings emerged across factors and the social AS factor has a particularly strong association with arthritis severity indicators.

Disclosure: R. El-Gabalawy, University of Manitoba, 2; **M. Bernstein**, None; **C. Mackenzie**, None; **J. Sareen**, None; **C. Hitchon**, Health Sciences Centre Foundation, Manitoba Health Research Council, 2.

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Abstract Number: 1528

Incretin Axis in Non Diabetic Rheumatoid Arthritis Patients

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Background/Purpose: Incretins hormones have been found to be a function of glucose tolerance in normal subjects, individuals with impaired glucose tolerance and patients with type 2 diabetes. Similarly, chronic inflammation, and rheumatoid arthritis (RA), is associated with an insulin resistance (IR) phenomenon, a well-known risk factor for cardiovascular diseases. The aim of the present study was to examine whether incretins hormones are disrupted in RA patients and if they are related with the insulin resistance (IR) that these patients express.

Methods: Cross-sectional study that encompassed 361 non-diabetes individuals; 151 patients with RA and 210 age- and sex-matched controls. IR by homeostatic model assessment (HOMA2), insulin, C-peptide, amylin, glucagon-like peptide-1 (GLP-1), gastric inhibitory polypeptide (GIP), and dipeptidyl peptidase 4 (DPP-4) soluble form and lipoproteins serum concentrations, were assessed in patients and controls. A multivariable regression analysis, adjusted for IR related factors, was performed to evaluate the differences between patients and controls in incretins hormones and how these were related to inflammation and IR in patients and controls.

Results: RA patients, compared to controls, disclosed higher levels of HOMA-IR (2.49 ± 2.35 vs. 1.13 ± 0.58 vs, p=0.00), insulin (13.0 ± 13.4 vs. 9.8 ± 6.5 U/ml, p=0.04) and C-peptide (3.37 ± 2.94 vs. 1.53 ± 0.77 ng/ml, p=0.00). These differences remained significant after adjustment for age, sex, waist circumference, dyslipidemia, statins, antihypertensive treatment and cholesterol levels. Similarly, amylin showed superior serum levels in RA patients in the univariate analysis, however, after adjusting for confounders this relation was lost. Incretins, GIP (0.37 ± 0.40 vs. 1.78 ± 0.51 ng/ml, p=0.00) and GLP-1 (0.49 ± 1.28 vs. 0.71 ± 0.22 ng/ml, p=0.00), were higher in RA patients after multivariable analysis. Contrary, DPP4 was found to be down regulated in RA patients after adjusting for IR related factors (811 ± 459 vs. 696 ± 301 ng/ml, p=0.02). While DDP-4 was correlated with disease activity through DAS28 (r=0.18, p=0.03), DAS28-PCR (r=0.5, p=0.08) and CDAI (r=0.20, p=0.01), neither insulin, C-peptide, incretins (GLP-1 and GIP) nor amylin were found to be associated with disease activity. DPP4 serum levels were significant and negatively associated with HOMA-IR-C-peptide index (beta coef -0.03 [-0.05--0.01 ng/ml], p=0.01) in the entire sample. Interestingly, the addition of RA as an interaction term in this relation disclosed a significant association (interaction p=0.04). Patients and controls in the higher HOMA-IR-C-peptide quartile (#4) disclosed different levels of GLP-1 (mean difference 0.4 [0.3-0.5] ng/ml, p=0.00), GIP (1.7 [1.4-2.0] ng/ml, p=0.00) and DPP-4 (-220 [38-402] ng/ml); showing, therefore, a different relation of IR indexes with these molecules between patients and controls.

Conclusion: Incretin axis is disrupted in non-diabetic RA patients. These defects may participate to the development of IR in RA or arise as a consequence of IR and/or other metabolic manifestations of RA itself.

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Abstract Number: 1529

Serum Levels of P-Glycoprotein Are Associated with Disease Activity in Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) exert a wide variety of therapeutic responses to disease controlling anti-rheumatic drugs (DMARDs). P-glycoprotein (P-Gp) is involved in treatment resistance in some chronic diseases. Although, to date there is lack information to identify if high levels of P-gp are associated with low therapeutic response to s-DMARDs. The aim of the present study is analyze the association between serum P-Gp levels with the severity of disease activity despite treatment with DMARDs in RA.

Methods: We included in this cross-sectional study eighty-one patients with RA treated for at least six months with DMARD. Patients were assessed for disease activity (DAS-28), type of DMARD, as well as other drugs currently used for the treatment of their disease and other clinical characteristics. Serum P-Gp levels were measured by ELISA.

Results: The patients had a mean age of 57±10, the frequency of synthetic DMARDs received by the patients were methotrexate 59%, sulfasalazine 38%, leflunomide 30%, azathioprine 14%, chloroquine 14%, d-penicillamine 3%; whereas anti-TNF agents were received by 11% (etanercept 9%, adalimumab 1%, infliximab 1%) and rituximab 4%. Overall, patients with RA had higher serum P-Gp levels compared with controls 153 ± 187 versus 31 ± 29 ng/mL; respectively, $p<0.0001$). Patients with moderate or severe disease activity had higher serum P-Gp levels compared with patients with low-disease activity or remission (201 ± 207 versus 109 ± 156 ng/mL; respectively, $p=0.028$). Serum P-Gp levels were correlated with DAS-28 (r=0.26, $p=0.018$). There were no differences observed between patients with biologic agents vs patients with synthetic DMARDs in the serum P-Gp levels (228 ± 200 vs. 140 ± 183 ng/mL; $p=0.14$). P-Gp levels were independent of methotrexate utilization ($p=0.5$). After adjusting for age, disease duration and biologic agents' utilization, the serum P-Gp levels remain associated with moderate or severe disease activity in the logistic regression analysis ($p=0.021$, using forward conditional method)

Conclusion: Higher serum P-Gp levels are associated with the severity of disease activity despite treatment with DMARDs in RA. These serum levels can be used as biomarkers in patients with a non-therapeutic response. Further longitudinal studies should

demonstrate if these levels can be predictive of failure to therapeutic response.

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Abstract Number: 1530

Temporal Trend of Total Joint Replacement in Rheumatoid Arthritis Patients: A Survival Study

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Background/Purpose : To analyze the temporal trend of incidence rate (IR) of hip and/or knee total joint replacement in a cohort of rheumatoid arthritis (RA) patients

Methods : We performed a retrospective longitudinal study, including patients diagnosed of RA between 1994 and 2009, according to the 1986 ACR diagnostic criteria, attending the rheumatology outpatient clinic of the Hospital Clínico San Carlos (Madrid, Spain). Clinical records were reviewed in order to collect demographic and clinical information. Our main outcome was total hip or knee replacement surgery, considering only the first replacement per joint (multiple event variable). In order to ensure a similar maximum follow-up time for all included patients, regardless the moment when they were included, time of observation comprised only the first 5 year after RA diagnosis (from such date until both knees and hips were replaced, lost of follow-up or 5 years had elapsed). Total joint replacement (TJR) IR was expressed per 1000 patients-year. Kaplan Meier curves were set to account for all TJRs. Cox bivariate and multivariate regression models were constructed to assess the effect of calendar time, demographic and clinical-related variables in the IR. Three time intervals were considered, defined by the year of RA diagnosis: 1994-1999, 200-2004, and 2005-2009. Statistical analyses were performed using STATA v12.

Results : We included 1812 patients, 74% women, with a median (interquartile range) age at RA diagnosis of 60.4 (47.6-71.8) years, 85% Spaniards, 65% with rheumatoid factor (FR), and 48% with anti-citrullinated peptides antibodies (ACPA). 526 patients had been diagnosed between 1994-1999, 551 between 2000-2004 and 735 between 2005-2009. 69 total joints (25 hips and 44 knees) were replaced during a follow-up time of 7522.0 patients-years, resulting in an IR of 9.2 [7.2 to 11.6] per 1000 patients-year. We observed an incidence rate for the time periods 1994-99, 2000-04, and 2005-09 of 10.8 [7.3 to 16.2], 10.5 [7.4 to 15.7], and 6.9 [4.5 to 10.6], respectively (**Figure 1**). In the bivariate analysis, only age at RA diagnosis showed a significant association with a higher risk of TJR ($p=1.0x10^{-4}$). In the multivariate analysis (adjusted by sex, age at RA diagnosis, country of birth, presence of ACPA and FR), year of RA diagnosis was not associated with the rate of TJR (2000-2004 vs. 1994-1999: HR 0.97 [95%CI: 0.55 to 1.71], p=0.91; 2005-2009 vs. 1994-1999: HR 0.67 [95%CI: 0.37 to 1.21], p=0.18).

Conclusion : Although we observed that patient diagnosed with RA more recently had a smaller rate of TJR in our RA cohort, differences were not statistically significant. **Table 1**: Baseline demographic and clinical characteristics of the RA patients included in this study.

Variables	n = 1812
Women, n (%)	1337 (73.8)
Age of RA diagnosis, median (IQR)	60.4 (47.6 to 71.8)
Elapsed time from RA symptoms onset to diagnosis in years, median (IQR)	1.0 (0.3 to 4.6)
Follow-up time in years, median (IQR)	5 (4.1 to 5)
Presence of Rheumatoid Factor, n/N (%)	1152/1780 (64.7)
Presence of ACPA, n/N (%)	482/1002 (48.1)
Spaniard, n (%):	1534 (84.7)
Year of RA diagnosis, n (%):	
1994 - 1999	526 (29.0)
2000 - 2004	551 (30.4)
2005 - 2009	735 (40.6)

ACPA: Anti Citrullinated peptide antibodies, IQR: Interquartile range, RA: Rheumatoid arthritis.

Disclosure: L. Rodriguez-Rodriguez, None; **J. Ivorra-Cortes**, None; **L. León**, None; **B. Fernández-Gutiérrez**, None; **L. Abasolo**, None; **I. Gonzalez-Alvaro**, None.

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Abstract Number: 1531

Decrease in Bone Mineral Density during Three Months of Early RA Measured By DXR Predicts Radiographic Joint Damage after One Year

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Background/Purpose: Digital X-ray radiogrammetry (DXR) is a method to calculate peripheral bone mineral density (BMD) which calculates BMD of the hands (DXR-BMD). The aim of this study was to evaluate whether hand bone loss (HBL) during the initial three months after diagnosis predicts radiographic joint damage after 12 and 24 months in patients with rheumatoid arthritis (RA).

Methods: Patients with early RA (<12 months since symptom onset) were consecutively included from three Swedish rheumatology departments (and treated according to the Swedish guidelines). Radiographs of hands and feet were taken at baseline, 3 months (hands only), 12 and 24 months. The baseline, 12 and 24 months radiographs were evaluated according to the Larsen score by one reader at each centre. The smallest detectable change (SDC) was established for each reader individually. DXR-BMD was performed on radiographs of the hands taken at baseline and after 3 months. Changes in BMD were evaluated in metacarpals 2, 3 and 4. HBL was defined either as a moderate change in DXR-BMD (≥0,25 but <2,5 mg/cm^2 per month) or a severe change (≥2,5 mg/cm^2 per month), as defined by the device manufacturer Sectra AB, Sweden. Radiographic progression was defined as a difference in Larsen score above the SDC [of the corresponding reader]. Statistical calculations were performed using SPSS 23 software. After testing different variables in a simple regression with change in Larsen score as dependent variable, all variables with the lowest p-value ($p<0.2$) were extracted to perform univariate analysis of variance. ESR and anti-CCP were measured at baseline and DAS28 was evaluated at each visit.

Results: One hundred and sixty seven patients (64% women) with a mean disease duration of 6 months (SD 3.7) and mean age 58

years (SD 14.5) were included. 63% tested positive regarding serum anti-CCP antibodies. HBL occurred in 58.7% of the patients (44.3% moderate and 14.4% severe HBL). Thirty two patients (19.2%) had radiographic progression at 12 months and 45 (34.9%) at 24 months. Greater HBL within 3 months associated significantly (p= 0.033) with greater increase in Larsen score between baseline and 12 months, adjusted for sex and baseline values of ESR, DAS28, Larsen score and anti-CCP status. No significant association was observed between early bone loss and radiological damage at 24 months (p=0.626).

Conclusion: HBL during the initial three months is an independent predictor of radiologic joint damage at 12 months in patients with early RA, but does not predict the 24 months outcome. Thus, DXR-BMD examinations after three months may be useful to detect ongoing joint damage, but the long-term predictive ability seems to be limited.

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Abstract Number: 1532

Sleep Hygiene Practices and Associations with Patient-Reported Outcomes in Rheumatoid Arthritis

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Background/Purpose: Previous studies showed a high prevalence of sleep disturbances in Rheumatoid Arthritis (RA). Poor sleep has been associated with patient-reported outcomes (PROs) for measuring disease activity in RA. Sleep hygiene is a variety of behavioral practices important for normal, quality nighttime sleep. The relationship between sleep hygiene behaviors themselves and PROs has not been described. We evaluated associations between sleep hygiene, sleep quality, and PROs in veterans with RA.

Methods: This is a cross-sectional study of patients with RA attending a single VA rheumatology clinic. Participants were administered 3 questionnaires by telephone survey: 1) Sleep Hygiene Index (SHI), 2) Pittsburgh Sleep Quality Index (PSQI), and 3) RAPID3 (comprising the Multi-dimensional Health Assessment Questionnaire [MD-HAQ], pain and, patient global scores [0-10]). Furthermore, information about demographics, BMI, inflammatory markers within the past 6 months, RA serologies, medications, and comorbid diagnoses were collected by chart review. Correlations between sleep hygiene, sleep quality, and PRO's were performed using Spearman's correlations and linear regression analyses.

Results: The cohort consisted of 51 subjects (86% male, mean age of 63 (range 27-77), mean BMI of 28.7, 84% seropositive). The mean SHI score was 17 (6.3) and mean PSQI score was 9.23 (4.0). Only 11/51 (22%) patients had normal sleep quality (PSQI <5 units). The SHI was strongly associated with PSQI (Rho: 0.40, p = 0.004). Both SHI and PSQI were strongly correlated with all RA PROs (Table, Figure). Question 8 from the SHI, "I go to bed feeling stressed, angry, upset, or nervous" was particularly associated with PROs. Specific domains of the PSQI associated with the PROs included subjective sleep quality, habitual sleep efficiency, sleep disturbances, and daytime dysfunction. PSQI total score and SHI total score were significantly higher among those with comorbid depression, but similar among those with osteoarthritis (p>0.78). RAPID3 correlated with SHI and PSQI, but was not associated with ESR. In multivariable models adjusting for age, gender, and depression SHI was independently associated with RAPID3.

Conclusion: Sleep hygiene behaviors and sleep quality play an important role in a patient's experience of their RA and correlate with self-report of function, pain, and well-being. Sleep hygiene questions that assessed patient distress at night were most strongly associated with these PROs. This study emphasizes how sleep and sleep behavior might impact the patient reporting of disease activity.

Figure: Relationship between RA Patient-Reported Outcomes assessing disease activity and tertile of Sleep Hygeine Index Score.

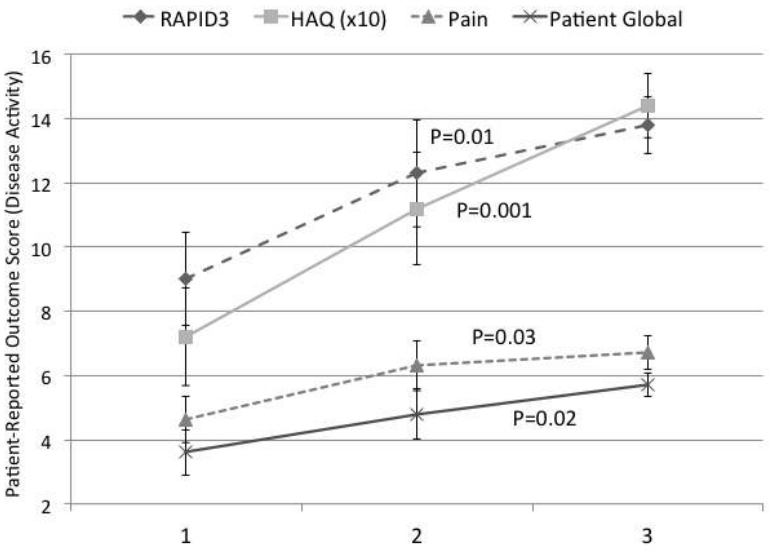

Table 1: Spearman's correlation between PROs and sleep hygiene and sleep quality indices (n = 51).				
Variable	**RAPID 3**	**Pain**	**Patient Global Status**	**Functional Status**
Sleep Hygiene Total Score	**0.38***	**0.31***	**0.34***	**0.43***
Sleep Quality Total score	**0.56***	**0.38***	**0.63***	**0.56***
Sleep Hygiene Questions				
SHI Question 1	0.25	**0.30***	0.15	0.16
SHI Question 8	**0.49***	**0.46***	**0.47***	**0.48***
SHI Question 13	**0.28***	**0.36***	0.17	**0.33***
PSQI components				
Subjective Sleep Quality	**0.71***	**0.56***	**0.76***	**0.60***
Sleep Duration	**0.31***	0.25	**0.29***	0.27
Habitual Sleep Efficiency	**0.48***	**0.37***	**0.57***	**0.43***
Sleep Disturbances	**0.43***	**0.44***	**0.36***	**0.38***
Daytime Dysfunction	**0.43***	**0.37***	**0.43***	**0.45***
ESR (n = 41)	0.17	0.17	0.13	0.17
***p<0.05**				
SHI Question 1: "I take daytime naps lasting two or more hours." SHI Question 8: "I go to bed feeling stressed, angry, upset, or nervous." SHI Question 13: "I think, plan, or worry when I am in bed."				

Disclosure: S. Sangani, None; **J. F. Baker**, None.

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Abstract Number: 1533

Pregnancy Outcomes in Women with Rheumatoid Arthritis : A Systematic Review

and Meta-Analyses

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Background/Purpose: Actually better control of rheumatoid arthritis (RA) activity leads to new interrogations and daily questions about pregnancy. Only few studies have studied pregnancy outcomes in women with RA, and results have shown some discrepancies. The objective is to determine the effect of Rheumatoid Arthritis on pregnancy outcomes, specially hypertension and preeclampsia, low birth weight, preterm birth, perinatal mortality, congenital malformation and cesarean section in women with Rheumatoid Arthritis

Methods: A litterature search was performed from Medline and Cochrane databases for articles published in english from 1955 to May 2016. Studies were eligible if they presented prevalence study, including national birth registry. Population were women with Rheumatoid Arthritis and keys terms related to pregnancy outcomes. Meta-analysis were performed to assess odds-ratios (OR) for each studied group using the inverse variance approach to estimate pooled OR with their 95% confidence interval (95% IC). Heterogeneity was assessed according to Cochran's Q-test and I2 values. Calculations were made with the Cochrane RevMan 5.3 software. P-values less than 0.05 were considered as significant.

Results: Expanded literature searche identified 1002 papers, of which 68 were eligible. Meta-analysis calculations showed a significant increased risk of prematurity with an OR of 1,42 (95% CI 1,29 to 1,56), low birth weight with an OR of 1,53(95% CI 1,35 to 1,75), small size at birth with an OR of 1,22 (95% IC : 1,00 to 1,48), perinatal mortality with an OR of 1,84(95% IC 1,25 to 2,72), preeclampsia with an ORof 1,46 (95% IC 1,06 to 1,85) , cesarean with an OR of 1,52 (95%IC 1,25 to 1,85). We did not find a higher risk of congenital malformation , hypertension or instrumental delivery. A higher risk of pregnancy outcomes seems to be showed before the disease onset. Furthermore, disease activity and drug treatment such as NSAIDs and corticosteroids should decrease fertility and increase pregnancy outcomes and specially prematurity and miscarriage.

Conclusion: A significative higher risk of several pregnancy outcomes in women with Rheumatoid Arthritis . Rheumatologist should be advised of these risks to refer women in apropriate obstectrics department.

Disclosure: A. L. Gaillard, Abbvie, 7; **T. Barnetche**, None; **T. Schaeverbeke**, Abbvie, 7.

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Abstract Number: 1534

Assessment of the Relationship of the Static and Dynamic Balance Parameters with Clinical, Functional and Radiological Findings in Patients with Rheumatoid Arthritis

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Background/Purpose: Lower extremity arthritis, proprioceptive dysfunction related to foot deformities, muscle weakness, joint restrictions, biomechanical disoerders, fatigue, sleep disorders, depression, and pain are frequently seen in patients with romatoid arthritis and may affect the balance. The aim of this study to evaluate the static and dynamic balances of the patients diagnosed with rheumatoid arthritis (RA) and also to disclose the relationship between these parameters and clinical, functional and radiological findings.

Methods: Patients diagnosed with RA according to ACR 2010 diagnostic criteria were compared with *age and gender matched* healthy controls. The age, sex and body mass index (BMI) data of the cases were recorded. DAS-28 score was calculated for determining the disease activity and the detailed rheumatologic and musculoskeletal examination was performed. Radiographic assessments of feet were done to evaluate the presence of pes planus, hallux valgus, metatarsus primus varus and splaying foot deformities. 'Foot and Ankle Outcome Score' (FAOS) was applied for foot function assessment. The level of fatigue, depression and sleep disorders of all patients were determined with 'Multidimentional Assessment of Fatigue', 'Beck Depression Inventory' and 'Pittsburgh Sleep Quality Index', respectively. The state of balance of the patients was evaluated by means of 'Berg Balance Scale' (BBS) and also 3 static (Modified Clinical Test of Sensory Interaction and Balance, Unilateral Stance , Weight Bearing Squat) and 4 dynamic (Step Up/Over, Sit to Stand, Tandem Walk, Limits of Stability) balance tests with 30 parameters were assessed via the '*Neurocom Balance Master*' device available in our clinic. Statistical analyses were performed with SPSS version 22 and p values less than 0.05 were considered statistically significant.

Results: This study included 165 cases that consist of 81 RA group (66 female, 15 male) and 84 healthy control group (70 female, 14 male). The mean age of patients and controls were 48.90±10.36 and 45.89±12.07 years, respectively. Age, sex and BMI data of both groups were similar between ($p>0.05$). The mean score of DAS28 of patients were 3,69±1,17. There were significant differences in the results of Modified Clinical Test of Sensory Interaction and Balance, Unilateral Stance, Tandem Walk, Limits of Stability, Step Up/Over tests between the patient and the control groups ($p<0.05$). Sit to Stand and Weight Bearing Squat test results were similar ($p>0.05$). It was deduced that 66.7% of patients have depression, 64.2% sleep disorders and 93.8% fatigue according to surveys; however there was no correlation between these symptoms and presence of balance disorders. Although 61% of patients were established with hallux valgus, 52% metatarsus primus varus, 33% pes planus, 26% splaying foot, these deformities were not correlated with FAOS and balance disorders. The presence of the swollen joint was determined as the most relevant factor about the balance disorders of RA patients.

Conclusion: Patients diagnosed with RA may have balance disorders as an important finding independently from other findings and symptoms during the course of the disease.

Disclosure: C. Sanal Top, None; **M. T. Duruoz**, None; **O. Hakan Gunduz**, None.

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Abstract Number: 1535

Depression in Rheumatoid Arthritis

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Background/Purpose: Depression is an important comorbidity in patients with rheumatoid arthritis (RA). Its incidence is variable (10-25%), being more frequent in women[1]. Wolfe et al. determined that pain, HAQ-DI and disease activity predict depression[2]. The main objective is to determine depression in patients with RA by the PHQ-9 questionnaire and evaluate its relationship with disease activity.

Methods: A cross-sectional study was conducted in patients with established diagnosis of RA according to the criteria of the ACR-1988, from the Luis Vernaza Hospital and a private rheumatology center. The database included demographic data, pain visual analog scale (VAS), activity index DAS-28, HAQ-DI disability index and the PHQ-9 questionnaire. Data was loaded and analyzed in the statistical program SPSS V. 22. Statistical significance used was 0.01, with a 99% reliability.

Results: 184 patients with a mean age of 51 years (20-90) were included, 90.8% women and 9.2% men. The mean age of onset of the disease was 40 years (18-49) with a delay of visit to the specialist of 26 months (1-432). 94.6% were mestizos, 3.8%, whites and 1.6% afroecuadorians, 50% were married, 16.3%, cohabiting 16.3% divorced, 9.2% single, and 8.2% widowed. The mean patient VAS was 3.4 (0-10) and physician VAS 2.8 (0-10). The mean DAS28-CRP was 3.11 (0.7-7.6), with 44% (81) in remission, 16.8% (31) low activity, 32.1% (59) moderate activity and 7.1% (13) high activity. 21.7% (40) patients had HAQ-DI disability and 1.6% (3) severe disability. The mean PHQ-9 was 5.39 points (0-24). According to this questionnaire, depression was found in 42.9% (79), 24.5% (45) mild depression, 9.8% (18) moderate, 7.1% (13) moderate-severe and 1.6% (3) severe. Of these, 89.9% (71) were women and 10.1% (8) men. Depression related to disease activity with DAS-28. 66.7% (20) of patients in remission had mild depression while 70% (7) patients with high activity had moderate to severe depression ($p = 0.009$). Mean DAS-28 for patients with moderate to severe depression was higher than those with mild depression (4.0 vs. 2.9, $p = 0.004$) Disability also related to depression levels as 40.7% (11) patients with functional disability had moderate to severe depression, compared with 35.1% (13) patients without disability ($p = 0.009$). Likewise, the average HAQ of patients with major depression was higher ($p = 0.000$). The average patient VAS in people with mild depression was 3.7, while in moderate to severe depression was 5.4 ($p = 0.000$). In the physician VAS, it was 3.1 for mild depression, and 4.6 for moderate to severe depression ($p = 0.000$). The number of tender and swollen joints was higher in patients with major depression than in those with mild depression ($p = 0.000$).

Conclusion: The presence of depression was common in our population, women were the most affected. Depression was related with disability and disease activity. The presence of depression in ecuadorian patients with RA was similar to that of other populations. This is the first study of depression in patients with RA in Ecuador.

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Disclosure: C. Ferro, None; **C. Ríos**, None; **M. Moreno Alvarez**, None; **M. J. Intriago**, None; **G. Maldonado**, None; **C. Aguirre**, None; **C. Paredes**, None; **J. Cardenas**, None; **N. Cordova**, None; **R. López**, None; **J. Martinez**, None.

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Abstract Number: 1536

Sleep Disturbance in Patients with Rheumatoid Arthritis – a Cross-Section Study

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Background/Purpose: Sleep disturbance is common in patients with rheumatoid arthritis (RA). Poor sleep can result in increased psychological distress, depression, fatigue, inability to work, socioeconomic burden and consequently significantly decreased health-related quality of life. Achievement and maintenance of tight disease control using disease-modifying anti-rheumatic drugs (DMARDs) including biologic DMARDs (bDMARDs) is associated with significant improvement in the outcome of RA as these strategies have the potential to control synovitis and to slow disease progression. The aim of this study was to assess the relationship between sleep disturbance and disease activity, pain, fatigue, health-related quality of life and treatment.

Methods: A total of 172 participants diagnosed with RA meeting the 2010 ACR/EULAR criteria were enrolled in this study, including 137 females (79.7 %) with a mean age of 44.37 ± 12.90 years. Among all the patients, 110 were treated with conventional DMARDs (cDMARDs), while 62 treated with bDMARDs (47 with tumor necrosis factor inhibitors and 15 with tocilizumab). Participants

completed the following questionnaires: Pittsburgh Sleeping Quality Index (PSQI), Health Assessment Questionnaire (HAQ), Hospital Anxiety and Depression Scale (HADS), and Fatigue Severity Scale (FSS). RA disease activity was assessed using the 28 joint disease activity score (DAS28), erythrocyte sedimentation rate, serum C-reactive protein and pain visual analog scale (VAS). Data were analyzed using SPSS v.17.0 software by descriptive statistics such as frequency, mean (SD) and inferential statistics including Wilcoxon rank sum test, Chi-square, and logistic regression.

Results were considered statistically significant when p value was less than 0.05. Results: PSQI was used to assess the quality of sleep in RA patients. Sleep disturbance was considered if PSQI score was greater than 6. Sleep disturbance was present in 46.5% (80/172) of RA patients and was associated with disease activity. Compared with RA patients without sleep disturbance, RA patients with sleep disturbance had increased pain levels, poor health-related quality of life, depression and fatigue as assessed by VAS ($p<0.01$), HAQ ($p<0.05$), HADS ($p<0.05$) and FSS ($p<0.01$) respectively. Better disease control could improve the quality of sleep in RA patients. In addition, patients treated with bDMARDs had significantly lower scores of DAS28 ($p<0.01$), PSQI ($p<0.01$) and VAS ($p<0.05$) compared to those treated with cDMARDs (Table 1).

Conclusion: High prevalence of sleep disturbance in patients with RA was observed. Sleep disturbance was associated with several measurements of health-related quality of life. Control of disease activity improved sleep disturbance. Treatment with bMARDs not only had better disease control, but also improved functional status by improving quality of sleep and pain.

Table1. Association of sleep disturbance with disease activity and other measurements of health-related quality of life in RA patients.

Variable	DAS28	VAS	HAQ	FSS	HADS	bMARDS (number of patients)	cDMARDS (number of patients)
Sleep disturbance	4.31±1.37	100.57	94.45	99.37	95.3	23	59
Non-sleep disturbance	2.64±1.07	73.68	79.26	74.77	78.73	39	51
Z/t score	8.962	3.564	2.021	3.238	2.151	9.054	6.599
P value	< 0.01	< 0.01	< 0.05	< 0.01	< 0.05	< 0.01	< 0.01

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Prevalence and Impact of Inflammatory Multimorbid Conditions on Trajectories of Disease Activity in the First Year of Follow-up in a Multi-Center Era Cohort

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Background/Purpose: Patients with rheumatoid arthritis also commonly report other chronic conditions ("multimorbidity") with higher counts of conditions associated with reduced response to treatment and persistent disease activity. However little is known about which specific conditions have stronger associations with RA outcomes. The objective of the present study was to estimate the prevalence and impact of chronic inflammatory multimorbidity on the trajectory of disease activity in the first year in patients with early rheumatoid arthritis (ERA).

Methods: We analyzed data from ERA patients (<1-year symptom duration) enrolled in a large prospective multi-center cohort study who completed a standardized clinical assessment and self-report questionnaire every 3-months in the first year of follow-up, who met 1987 or 2010 ACR/EULAR RA criteria, and had at least two DAS28 measures available in the first year. Information on physician-diagnosed chronic inflammatory conditions including cardiovascular disease (CVD), pulmonary disease, bowel disease, diabetes, cancer, obesity, psoriasis and other rheumatologic conditions was obtained by patient self-report and information on depressive symptoms from SF-12 responses (using a depressive symptom cut-off of 42). Prevalence of each condition, as well as chronic inflammatory multimorbidity counts were estimated with standard descriptive statistics. Linear growth models were used to examine individual and cumulative effects of each chronic inflammatory condition on trajectory of DAS28 disease activity in the first year adjusting for age, sex, education, race, smoking, symptom duration, and treatment.

Results: The sample included 1595 patients with a mean(sd) age of 54(15) years, symptom duration of 6(3) months, 1153 (72%) were female and 1316 (83%) were white. At baseline 1434 (92%) were treated with a conventional DMARD (majority with methotrexate (76%)) and 33 (2%) with a biologic. Multimorbid inflammatory conditions were common: 1138 (72%) reported at least 1 condition, 541 (34%) reported at least 2 conditions and 166 (10%) reported 3 or more conditions. Depressive symptoms reported in 589 (40%), obesity in 355 (32%), pulmonary disease in 220 (14%), CVD in 191 (12%) and other rheumatic conditions in 197 (12%) were most prevalent, followed by diabetes 127 (8%) and cancer 109 (7%). Bowel disease in 61 (4%) and psoriasis in 60 (4%) were least prevalent. Results of multivariable growth models showed that depressive symptoms were associated with higher baseline disease activity and both depressive symptoms and obesity were associated with less change in DAS28 over time ($p<0.05$).

Conclusion: Results of the present study showed that multimorbidity with other chronic inflammatory conditions is common in ERA patients. Integrated treatment approaches to address multimorbid rather than single inflammatory conditions may yield better outcomes.

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Abstract Number: 1538

Lower Ratings of Pain Intensity in Older Adults Lead to Underestimation of Disease Activity By Disease Activity Score 28-C-Reactive Protein (DAS28-CRP) in Patients with Rheumatoid Arthritis

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Background/Purpose: To investigate the influence of age on the components of the 28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP) in patients with rheumatoid arthritis (RA) and whether DAS28-CRP can be equally interpreted in all age groups.

Methods: For RA subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER), a cross-sectional analysis was performed. The share was expressed as a proportion and calculated by dividing the formula the DAS28 by the entire DAS28 (CRP share = [0.36 x ln(CRP +1] / DAS28, Relative of the contribution of the patient reported measures (tender joint count [TJC] and patient global assessment [PtGA] in DAS28-CRP [DAS-P] = [0.56 x sqrt (TJC) + 0.014 x PtGA] / DAS28-CRP). Share of CRP and patient reported components of the DAS28 (DAS-P) were analyzed and compared between 2 age groups (younger RA <60, older RA ¡Ã 60) using Mann-Whitney U test. Inflammatory disease burden in the joint was calculated by modified DAS28 (MDAS28 = 0.49 x ln(C-reactive protein (CRP)) + 0.15 x swollen joint count 28 (SJC) + 0.22 x physician global assessment (PhGA) +1). Multivariate analyses were used to design models best predicting the effect of age on CRP, the share of CRP, inflammation level calculated by MDAS28, DAS-P, and pain levels.

Results: CRP and the share of CRP in DAS28-CRP were not influenced by age. MDAS28 did not increase significantly with age but was associated with disease duration and anti-tumor necrosis factor (TNF) therapy. Female gender had significantly higher DAS-P, while age was associated with lower DAS-P. Pain level had significant negative association with age (Table 1). In subjects with moderate inflammation (defined by MDAS28 score above 50 percentile, N=370), older RA subjects (age >= 60, N=189) had lower pain level, tender joint count (TJC), patient and physician global assessment, DAS28-CRP than younger subjects (age < 60, n=157) (Table 2).

Conclusion: CRP, CRP share, and MDAS28 were not associated with age. However, age played a role in how subjective components of DAS28-CRP and pain level are assessed and rated in patients with RA. Disease activity could be underestimated by DAS28-CRP in older RA patients with moderate to high grade inflammation from RA.

Table 1 Multiple regression analysis of influence of age on modified disease activity score 28 (MDAS28), subjective components of DAS28 relative to the total DAS28 (DAS-P), pain level (visual analog scale, VAS) (β denotes the standardized regression coefficient, SE denotes the standard error)

Model	Variables	β	SE	p value
MDAS28	Age	.002	.002	.316
	Gender	-.076	.070	.276
	Race	.112	.094	.232
	Charlson Score	-.014	.022	.538
	Disease duration	.006	.002	.012
	Anti-TNF therapy	-.182	.062	.004
	Other biologic therapy*	-.099	.103	.336
	Glucocorticoid therapy	.157	.060	.009
	CDAI	.104	.002	.000
DAS-P	Age	-.088	.040	.030
	Gender	2.894	1.227	.019
	Race	1.443	1.659	.385
	Charlson Score	-.294	.389	.451
	Disease duration	-.036	.042	.397
	Anti-TNF therapy	1.841	1.101	.095
	Other biologic therapy*	.611	1.811	.736
	Glucocorticoid therapy	2.279	1.058	.032
	MDAS28	3.977	.350	.000
Pain (VAS)	Age	-.024	.008	.002
	Gender	.134	.236	.569
	Race	.990	.319	.002
	Charlson Score	.161	.075	.032
	Disease duration	.005	.008	.527
	Anti-TNF therapy	.241	.212	.256
	Other biologic therapy*	.395	.348	.256
	Glucocorticoid therapy	.605	.203	.003
	MDAS28Tabl	.680	.067	.000

*biologic therapy other than anti-tumor necrosis factor (TNF), CDAI: clinical disease activity index, MDAS28: modified disease activity score 28

Table 2 Comparison between 2 age groups according to the level of inflammation in the joint calculated by modified disease activity score 28 (MDAS28)

	Low grade inflammation (n=370)		P value†	Moderate to high grade inflammation (n=370)		P value†
Age groups	**Age <60**	**Age ≥ 60**		**Age<60**	**Age ≥ 60**	
Pain (VAS)	3.9±2.9	3.4±2.43	0.448	6.4±2.7	5.1±2.7	<0.001
SJC	0.9±1.7	1.1±1.8	0.884	6.8±5.9	6.8±6.0	0.963
TJC	1.3±3.0	0.8±1.6	0.884	6.7±6.7	4.2±5.5	<0.001
PhGA	1.3±1.3	1.5±1.2	0.175	4.9±2.4	4.0±2.3	<0.001
PtGA	3.3±2.5	3.2±2.4	0.884	5.6±2.4	4.4±2.5	<0.001
ESR*	11.8±10.0	18.6±16.1	0.175	26.8±21.9	33.1±26.9	0.255
CRP	0.3±0.3	0.3±0.3	0.884	1.7±2.6	1.6±1.8	0.723
DAS28-CRP	2.4±0.8	2.3±0.7	0.884	4.5±1.2	4.0±1.1	<0.001
CDAI	7.0±5.7	6.6±4.3	0.884	23.9±13.8	19.5±12.2	<0.001
SDAI	7.2±5.6	6.9±4.2	0.884	25.7±14.3	21.1±12.4	<0.001
RAPID3	8.7±6.2	8.3±5.2	0.884	14.8±6.0	12.1±6.1	<0.001
SF12-PCS	42.1±11.2	40.3±9.0	0.176	34.8±9.9	35.3±20.3	0.755
SF12-MCS	48.6±10.1	51.3±10.3	0.176	44.3±11.6	49.3±10.9	<0.001

*ESR total n for low grade inflammation group =90, high grade inflammation group n=150, † P-values were adjusted for multiple comparisons using the Benjamini-Hochberg procedure

VAS: visual analog scale, SJC: swollen joint count ,TJC: tender joint count ,PhGA: physician global assessment, PtGA: patient global assessment, ESR: erythrocyte sedimentation rate, CRP: C- reactive protein, DAS: disease activity score, CDAI: clinical disease activity index, SDAI: simplified disease activity index, RAPID3: routine assessment of patient index data 3, DAS-P: Patient reported components in the DAS28-CRP, SF12: 12-item short form health survey, PCS: physical component summary, MCS: mental component summary

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Abstract Number: 1539

Physician-Reported and Patient-Reported Anxiety and Depression in Rheumatoid Arthritis

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Background/Purpose: As many as 40% of people with rheumatoid arthritis (RA) experience significant symptoms of mood disorders. In addition to the pain, fatigue, and disability associated with RA, inflammatory mediators such as IL-1, TNF and IL-6 are thought to play a role in the aetiology of mood disorders. This study examined comorbid anxiety/depression in RA (both physician- and patient-reported), and its association with work and activity impairment.

Methods: Data were drawn from the 2014 Adelphi RA Disease Specific Programme, a cross-sectional survey in the US and 5 European countries (France, Germany, Italy, Spain, UK). Physician-reported anxiety or depression was documented as a comorbid condition for each patient. In addition, patient-reported anxiety/depression was collected using the EQ-5D health status questionnaire: anxiety and depression were rated as "none," "moderate," or "extreme." These 2 distinct markers for anxiety/depression in RA patients within the Adelphi survey were analyzed separately in univariate/multivariate analyses. Univariate analysis was initially used to identify any association between physician- and patient-rated anxiety/depression with patient-reported work productivity and activity impairment (WPAI) questionnaire scores. Controlling for patient age, gender, region, body mass index, physician-reported disease severity, number of flares (past 12 months), and physician-reported global health, multivariate regression analyses further examined the relationships between these markers and outcomes of interest.

Results: Of the total 3,379 patients, 15.3% had physician-reported anxiety/depression as a comorbid condition. 38.4% of those who completed the EQ-5D question on anxiety and depression (n=1015) had self-reported anxiety/depression of at least moderate severity at the time of the survey. Multivariate analyses demonstrated that patient-reported anxiety/depression was significantly associated with overall work impairment (among employed patients) (coefficient [95% CI], 11.04 [4.23, 17.84]; P=0.002) and activity impairment (among all patients) (14.11 [10.69, 17.54]; P<0.001). Separate multivariate analysis demonstrate that physician-reported

anxiety/depression was also borderline significantly associated with overall work impairment (6.80 [-0.01, 13.62]; *P*=0.050) and significantly associated with activity impairment (6.80 [2.89, 10.72]; *P*=0.001), respectively.

Conclusion: Both physician-reported comorbid anxiety/depression, and patient-reported anxiety/depression during EQ-5D administration were independently and significantly associated with overall work impairment as well as activity impairment. Further research on optimal management of mood disorders in RA is warranted.

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Abstract Number: 1540

"I Am Always in Pain Somewhere": Continuing Unmet Need in Rheumatoid Arthritis

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Background/Purpose: Despite advances in the RA treatment, substantial humanistic and economic burdens remain. This study of patients with RA, with moderate to severe disease activity and on active treatment, explored unmet treatment needs and the resultant impact on physical functioning and activities of daily living.

Methods: Semi-structured interviews were conducted with 46 patients with RA from Germany (n=15), France (n=15), UK (n=11), and Spain (n=5). Eligible patients had been diagnosed for 2-5 years, had a current disease activity score in 28 joints (DAS28) >3.2, and were receiving ongoing treatment. Initial questions were open-ended, followed by more focused questions to probe unmet need. Patients completed the HAQ-Disability Index and EuroQol 5 dimensions questionnaires. Interviews were conducted with 10 rheumatologists across countries, to explore their understanding of unmet need in RA.

Results: Patients had a DAS28 mean score of 4.23 (SD=1.0) and either, were eligible for but had not yet received biologic DMARDs (bDMARDs) (23/46; 50.0%), were receiving bDMARDs (12/46; 26.1%), had received >1 anti-TNF treatment previously and were now receiving a treatment with a different mode of action (3/46; 6.5%), or were receiving another treatment regimen (8/46; 17.4%). The majority of patients (44/46; 95.7%) experienced pain due to RA (Table). A high proportion of patients (37/46; 80.4%) specifically identified pain as an unmet need and experienced pain despite advances in treatments. Joint stiffness and swelling, and fatigue were experienced by 87.0% (40/46), 84.8% (39/46), and 91.3% (42/46) patients, respectively. Over half reported each symptom spontaneously, suggesting they are relevant to the symptom experience of RA. All 10 clinicians reported that patients experience each of the above mentioned symptoms. In almost all patients (45/46; 97.8%), RA had impacted their physical functioning, including walking (35/46; 76.1%), sleep (26/46; 56.5%), gripping (22/46; 47.8%), lifting/carrying (28/46; 60.9%), mobility/flexibility (34/46; 73.9%), and speed/agility (15/46; 32.6%). All patients (46/46; 100%) reported an impact on activities of daily living; 40/46 (88.9%), emotional well-being; 37/46 (80.4%), family and social relationships; and 26/46 (57.0%) experienced a financial impact.

Conclusion: Although pain, joint stiffness and swelling, and fatigue are well-known symptoms associated with RA, they persist in most patients who are eligible for, or who are receiving, bDMARDs. Pain severity showed relationships to the wider scope of impact on patients' lives. Despite the high standards of care available for patients in the countries in which this study was conducted, the level of unmet need described from both patients and clinicians is compelling.

Table: Patient experiences and clinician perceptions of pain due to RA, n (%)

	Total	Spontaneous	Probed	Not experienced	Individual experiences and perceptions of pain
Patients					
All (n=46)	44 (95.7)	37 (80.4)	7 (15.2)	2 (4.3)	
Germany (n=15)	15 (100)	14 (93.3)	1 (6.7)	0 (0)	*"the knees hurt a lot, and then I can't stand for a long time"*
France (n=15)	14 (93.3)	8 (53.3)	6 (40.0)	1 (6.7)	*"when I walk around in the morning, I have pain in putting my feet down"*
UK (n=11)	10 (90.9)	10 (90.9)	0 (0)	1 (9.1)	*"Mainly hands and wrists; yes, hands and wrists very painful."*
Spain (n=5)	5 (100)	5 (100)	0 (0)	0 (0)	*"it's that discomfort that's always there, I just get used to it"*
Clinicians					
All (n=10)	10 (100)	10 (100)	0 (0)	0 (0)	*"when the patients are on biotherapy, they still have a bit of pain or some discomfort in certain joints when they move"*

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Abstract Number: 1541

Frailty Is Associated with Decreased Physical Function in Adults with Rheumatoid Arthritis

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Background/Purpose: Reduced physical function and health-related quality of life remain common in Rheumatoid Arthritis (RA), and further studies are needed that examine potential, novel determinates of reduced physical function in RA. Frailty is a state of excess vulnerability to stressors, with reduced ability to maintain or regain homeostasis after a destabilizing event. Frailty is associated with increased risk of poor health outcomes including death. The present study examines whether frailty is associated with differences in self-reported physical function among adults with RA.

Methods: Adults (n=124) from a longitudinal RA cohort participated in the study. All measures were collected during in-person research visits. Using an established definition of frailty[1], individuals with 3 or more of the following physical deficits were classified as frail: 1) body mass index ≤ 18.5, 2) low grip strength (adjusted for sex and BMI, measured by handheld dynamometer), 3) severe fatigue (measured by the Fatigue Severity Inventory), 4) slow 4-meter walking speed (adjusted for sex and height), 5) low physical activity (measured by the International Physical Activity Questionnaire). Individuals with 1 or 2 deficits were classified as "pre-frail", and those with no deficits as "robust[1]." Self-reported physical function was assessed by the Health Assessment Questionnaire (HAQ) and the Valued Life Activities Difficulty scale (VLA), (HAQ and VLA scored 0-3). Regression analyses modeled associations of frailty category with HAQ and VLA Difficulty scores with and without controlling for age, sex, disease duration, hsCRP, use of oral steroids, and pain. Secondary analyses tested whether associations of frailty category and physical function scores were robust to using knee strength rather than grip strength in assigning frailty category and relationships between pain, frailty category, and physical function.

Results: Among adults with RA, being frail compared to being robust was associated with a 0.54 worse HAQ score (p<0.01) and a

0.63 worse VLA score (p<0.001) when the effects of all covariates are held constant (Table 1). The association of frailty category with HAQ and VLA Difficulty scores persisted when knee strength was used to assign frailty category (Table 2).

Conclusion: Frailty is common among individuals with RA. Being frail, compared to being robust, is associated with significantly worse self-reported physical function among adults with RA. Future studies should continue to advance understanding of frailty as a potential source of reduced physical function in RA.

Table 1: Linear Regression Coefficients (95% CIs) for the Effect of Frailty Category, Based on Grip Strength, on HAQ and VLA Difficulty Scores among Individuals with Rheumatoid Arthritis

	HAQ		VLA	
	Unadjusted	Adjusted[#]	Unadjusted	Adjusted[#]
Frail	**0.84 (0.49 1.20)*** **	**0.54 (0.19, 0.89)** **	**0.78 (0.54, 1.02)*** **	**0.63 (0.40, 0.86)*** **
Pre-Frail	0.18 (-0.03, 0.39)	0.13 (-0.06, 0.33)	**0.26 (0.13, 0.41)*** **	**0.23 (0.11, 0.36)*** **
Robust	Reference	Reference	Reference	Reference

[#]Model is adjusted for age, sex, disease duration, hsCRP, use of oral steroids, and pain. Frail= ³3 physical deficits, Pre-frail= 1-2 physical deficits, Robust= 0 physical deficits ([1]Fried LP et al., J Gerontol A Biol Sci Med Sci, 2001; 56:M146) *p<0.05, **p<0.01, ***, p<0.001 Both the HAQ and VLA are scored 0-3.

Table 2: Linear Regression Coefficients (95% CIs) for the Effect of Frailty Category, Based on Knee Strength, on HAQ and VLA Difficulty Scores among Individuals with Rheumatoid Arthritis

	HAQ		VLA	
	Unadjusted	Adjusted[#]	Unadjusted	Adjusted[#]
Frail	**0.81 (0.41, 1.21)*** **	**0.69 (0.28, 1.10)** **	**0.85 (0.60, 1.11)*** **	**0.69 (0.43, 0.95)*** **
Pre-Frail	0.21 (-0.01, 0.43)	0.14 (-0.07, 0.35)	**0.22 (0.08, 0.36)** **	**0.16 (0.03, 0.30)***
Robust	Reference	Reference	Reference	Reference

[#]Model is adjusted for age, sex, disease duration, hsCRP, use of oral steroids, and pain. Frail= ³3 physical deficits, Pre-frail= 1-2 physical deficits, Robust= 0 physical deficits ([1]Fried LP et al., J Gerontol A Biol Sci Med Sci, 2001; 56:M146) *p<0.05, **p<0.01, ***, p<0.001 Both the HAQ and VLA are scored 0-3.

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Abstract Number: 1542

Metabolic Syndrome and Cardiovascular Risk Factors in Brazilian Patients with Established Rheumatoid Arthritis

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Background/Purpose: rheumatoid arthritis (RA) has been stablished as an independent risk factor for cardiovascular diseases. Metabolic syndrome (MS) may provide additional link between accelarated atherosclerosis and inflammation in RA. Objective: to estimate the prevalence of MS and modifiable and non-modifiable risk factors for cardiovascular disease among patients with RA, correlating them to disease activity markers.

Methods: a cross-sectional study in patients with established RA (according to the ACR classification criteria) from three Brazilian university hospitals. Demographic and clinical data, and the presence of cardiovascular risk factors were collected. Blood pressure, weight, height and waist circumference were determined in the assessment visit and laboratory data were assessed from medical records. Disease activity was evaluated by the Disease Activity Score in 28 joints (DAS28), and patients were classified in remission <2.6; low disease activity (LDA) 2.6 to ≤3.2; moderate disease activity (MDA) >3.2 to ≤5.1; or high disease activity (HDA) >5.1. The diagnosis of MS was done according to the National Cholesterol Education Program (NCEP ATPIII 2005) and to the International Diabetes Foundation (IDF 2005). Remission was correlated to LDA, MDA and HDA in the analysis. Multiple logistic binary response analysis with Huber/White standard errors that accounted for clustering on hospitals was performed. Variables were sequentially deleted when not reaching significance equal to or less than 5%.

Results: 791 patients were included, 86.9% women, mean age 54.7 (±12) years, 59.9% Caucasian, mean disease duration of 12.8 (±8.9) years. Rheumatoid factor was positive in 75% of the patients, mean body mass index (BMI) was 27.1 (±4.9) kg/m^{2}and mean waist circumference was 93.5 (±12.5) cm. Methotrexate were used by 67.7% and prednisone in 37.4% of the patients. Dyslipidemia, DM, HBP and family history of premature cardiovascular disease occurred in 34.3%, 15%, 49.2% and 16.5% of the patients, respectively. MS prevalence was 36.4% (NCEP) and 30.7% (IDF), with 91.5% of agreement. Age, dyslipidemia, HBP, DM and body mass index were associated with MS by NCEP and IDF definitions. MS (IDF) was associated to CRP levels (OR=1.30; p<0.001), to LDA (OR=1.62; p=0.001) and to MDA (OR=1.47; p<0.001). MS (IDF) and HAD association was fairly significant (OR=1.79; p=0.093). MS (NCEP) was associated to CRP levels (OR=1.32; p<0.001) and to HDA (OR=1.52; p=0.004). Dyslipidemia was positively correlated to LDA (OR=1.71; p=0.002), MDA (OR=1.51; p=0.001) and HDA (OR=1.77; p<0.001). HBP was positively correlated to LDA (OR=1.24; p<0.001). DM was positivily correlated to MDA (OR=1.83; p<0.001) and HDA (OR=3.18; p<0.001) and BMI was positivily correlated to MDA (OR=1.69; p= p<0.039) and HDA (OR=1.36; p=0.010).

Conclusion: our results depicted the association of MS to CRP levels and to DAS28, emphasizing the relevance of inflammation control in RA. Lipid, hypertension, diabetes and weight control are relevant metabolic aspect and should be valued and point to the more comprehensive medical approach. Disclosure of Interest:none declared

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Obese Patients with RA Have a More Seropositive and a More Active Disease with Less Deformities

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Background/Purpose: An association between obesity and RA activity has been proposed in the literature. Kuwait has the highest obesity rate in The Middle East and is ranked among the top 10 most obese countries in the world. We describe obese patients with RA and study the influence of body mass index (BMI) on RA activity and severity.

Methods: Adult patients from The Kuwait Registry for Rheumatic Diseases (KRRD) who satisfied the ACR classification criteria for RA from four major hospitals were studied from February 2013 through December 2015. Patients were classified using WHO criteria to underweight (<18.5), normal (18.5-24.99), pre-obese (25-29.99) and obese (>30). Their demographic, clinical and serological features were compared. Statistical tests were applied where appropriate.

Results: A total of 425 RA patients with1615 hospital visits and available BMI were identified, 351 (82.6%) were females. The mean age was 52.6 years (18-86) and disease duration 6.7+7.2 years (0.1-46). Among them, 156 (36.7%) were obese, 177 (41.6%) were pre-obese, 89 (21%) were normal and 3 (0.7%) were underweight. Based on DAS28 scores, 257 (60.5%) were in remission or had low disease activity, 146 (34.4%) had a moderate disease activity and 22 (5.1%) had a severe disease activity. Patients with a higher BMI were diagnosed at an older age (p=0.02). BMI was positively correlated to DAS28 (p=0.03), CDAI (p=0.006), ESR (p<0.001), CRP (p=0.02), tender joint count (p=0.022), swollen joint count (p=0.012), positive rheumatoid factor (RF) (p=0.014), positive anti-citrullinated protein antibodies (ACPA) (p=0.029) and a combination of positive RF and ACPA (p<0.001). Increased BMI was associated with a lower VAS pain (p=0.022), a lower patient's global assessment of disease activity (p=0.027) and less deformities (p<0.001). There was no significant association with gender, HAQ score, sicca symptoms, rheumatoid nodules or other extra-articular features. Biologic therapy was more prescribed to patients with a higher BMI score (p=0.005).

Conclusion: The distribution of BMI among RA patients in Kuwait was similar to the general population with the majority being overweight. Patients with a higher BMI had a more seropositive and a more active RA but less deformities. We recommend that BMI is measured and approached in all RA patients and that overweight patients are aggressively managed to control disease activity.

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Abstract Number: 1544

Serum Omentin-1 Levels and Metabolic Syndrome in Women with Rheumatoid Arthritis

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Background/Purpose: Metabolic syndrome (MS) is a common comorbidity in patients with rheumatoid arthritis (RA). Several adipokines have been implied in the pathogenesis of MS on general population and rheumatic inflamatory disorders. Omentin-1 is an adipokine implied in reducing insulin resistance, and improving hypertension and dyslipidemia among general population. Nevertheless, the role of this adipokine in MS is not conclusive and there is no information about the association between serum levels of omentin-1 and the components of MS in RA. In order to test the hypothesis that serum omentin-1 levels are biomarkers of protection for MS the aim of the present study was to evaluate if serum omentin-1 levels are associated with the MS components in patients with RA.

Methods: In this cross-sectional study we included adult women with established RA (according to 1987 ACR criteria). Exclusion criteria were active infections, cancer, chronic renal failure, hepatic failure or pulmonary fibrosis. Thirty women with RA and MS (RA+MS) according to the NCEP-ATP III criteria were compared with 30 women with RA without MS (RA-MS) matched by range of age. Clinical and epidemiological characteristics were evaluated, as well as disease activity measured by DAS-28 index. Serum omentin-1 levels were determined by ELISA.

Results: Patients with RA+MS had higher body mass index compared with RA-MS (28.1 vs 24.4 kg/m^2, $p< 0.001$). Serum omentin-1 levels were similar in patients with RA+MS compared with RA-MS (794 vs 941 ng/mL, respectively, $p = 0.15$). In the correlation between specific components of MS, serum omentin-1 levels correlated with higher diastolic blood pressure (rho= 0.22, p= 0.03) and higher HDL-cholesterol levels (rho= 0.20, p=0.05). After adjusting by age and disease duration, BMI was the major risk factor for MS in this patients (OR= 1.46, 95% CI= 1.06-1.99, p= 0.02), and serum omentin-1 levels did not achieve statistical significance.

Conclusion: No significant difference in omentin-1 levels in RA patients with and without MS was observed. However serum omentin-1 positively correlated with HDL-cholesterol and diastolic blood pressure. This implies the assumption that this adipokine influences some cardiovascular risk factors and should be evaluated in future studies.

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Abstract Number: 1545

Vitamin D Insufficiency in Patients with Rheumatoid Arthritis and Healthy Controls and Correlation Between Vitamin D Levels and Disease Activity and Disability in RA Patients

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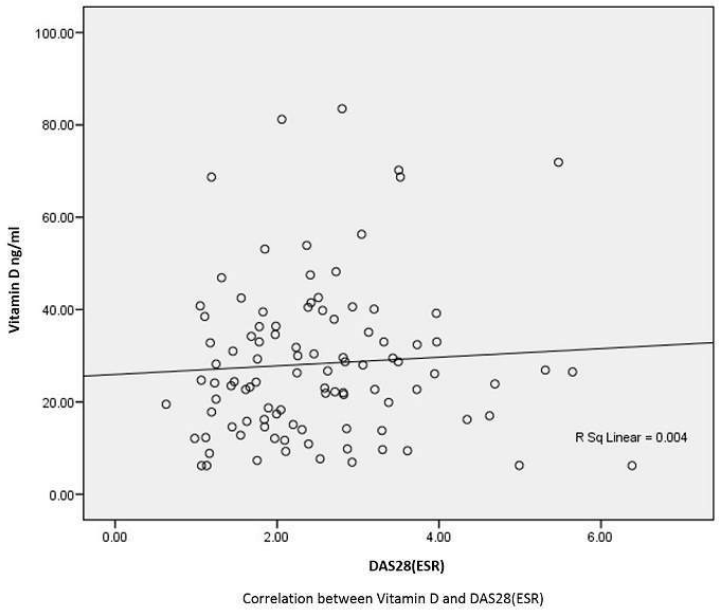
Background/Purpose: Lower serum vitamin D levels have been shown to be associated with various autoimmune disorders including Rheumatoid Arthritis (RA). We undertook this study to evaluate vitamin D status and assess the relationship if any between vitamin D levels and disease activity and disability in patients with RA.

Methods: A total of 100 adult patients (82 females, 18 males) of RA (ACR/EULAR-2010 criteria) presenting to Rheumatology department and 50 healthy controls drawn from hospital staff matched for age and gender (42 female, 8 male) were enrolled. Exclusion criteria comprised severe hepatic, and/or renal disease, uncontrolled diabetes, granulomatous disease. Disease activity and disability was evaluated by DAS28(ESR) and Indian HAQ disability index (HAQ-DI) respectively. Serum total 25(OH)D_3 levels were measured by electrochemiluminescence assay. Vitamin D insufficiency was defined as <30 ng/ml. Unpaired t-tests, chi square, ANOVA, Kruskal Wallis, Pearson and multivariate regression were applied as appropriate.

Results: The mean 25(OH)D_3 levels in cases and controls were 28.29±16.67 and 15.59±10.58 ng/ml respectively (p-value=0.000). As many as 62% of the patients and 88% (44/50) of the controls had vitamin D insufficiency (p-value<0.001). Mean serum vitamin D levels were significantly higher in patients who were on high dose (oral 60,000 IU/week or injection within last 6 months) of vitamin D supplementation (40%) (39.55±17.00 ng/ml) (p-value<0.001) compared to that of those who had received either none (23%), 250 IU/day (23%) or 500 IU/day (14%). Vitamin D levels were not significantly different in patients who were in remission, low, moderate and high disease activity (27.05±15.05, 32.44±18.52, 27.49±17.30 and 32.88±27.75 ng/ml respectively, p-value=0.709). No significant correlation was seen between mean vitamin D levels and age, BMI, SJC, TJC, ESR, General Health (GH), DAS28(ESR), HAQ-DI and serum PTH. Only duration of illness was positively correlated with vitamin D level (r=0.212, p-value=0.035). Vitamin D levels were also not different with regard to gender, menopause, deformity, hypothyroidism, RF, anti CCP status and current glucocorticoid use. On multivariate analysis, vitamin D levels were not related to various disease activity and disability variables [SJC, TJC, ESR, GH, DAS28(ESR) and HAQ-DI].



Correlation between Vitamin D and DAS28(ESR)

Conclusion: Vitamin D insufficiency was widespread both in patients with RA (62%) and in hospital staff without any disease (88%). No correlation was found between mean 25(OH)D_3 levels and disease activity, disability and other variables. Longer disease duration of RA was associated with higher vitamin D levels. This could be because of greater use of vitamin D supplements by patients with long standing disease. The healthy hospital staff had low vitamin D possibly due to greater time spent indoors.

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Abstract Number: 1546

Clinical Features at the Onset of Lymphoproliferative Disorder in Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is intrinsically associated with an increased incidence of lymphoproliferative disorders (LPDs). Although treatment with immunosuppressive agents, such as methotrexate, tacrolimus, or biological disease-modifying antirheumatic drugs (b*DMARDs*) is highly efficient, development of immunodeficiency-associated LPDs is becoming a more important issue. However, previous reports have come mainly from university or flagship hospitals, where the patient populations might differ from average RA patients. Furthermore, those studies have focused on the pathological features and regression of LPDs after withdrawal of methotrexate (MTX), and information that could allow earlier diagnosis of LPDs has been scant. Here we surveyed the clinical course of RA patients who developed LPDs seen at our hospital, focusing especially on the clinical features at LPD onset.

Methods: RA patients who had been treated at Niigata Rheumatic Center between October 2006 and April 2016 were analyzed. The patients' data were obtained retrospectively from their medical records. Data indicated are median ($IQR_{1/4-3/4}$) values.

Results: Among 2,986 RA patients, 26 patients with pathologically identified LPDs were analysed. The median patient age at the time of LPD diagnosis was 71 (62.5-78.3) years, and the duration of RA was 181 (106.5-238.3) month. Twenty-two patients were treated with MTX, 8 with bDMARDs (infliximab in 6 cases, etanercept in 1 case and golimumab switched from infliximab in 1 case), and 8 with tacrolimus. Ten patients were diagnosed as having diffuse large B cell lymphoma, 7 as having Hodgkin lymphoma, and 3 as having T cell lymphoma. The primary site of LPDs was extranodal in 11 (42.3%), and only 7 patients complained of lymph node swelling. Furthermore, even computed tomography image could not detect lymph node swelling in 6 cases. Although the C-reactive protein level (CRP) significantly rose from 0.2 (0.1 - 0.4) mg/dL at 6 months before LPD diagnosis to 2.1 (1.4 – 5.2) mg/dL after LPD diagnosis ($p<0.001$, Wilcoxon signed-rank test), neither the number of tender and swollen joints nor the matrix metalloproteinase-3 level showed any significant change (0.0 (0.0 – 0.5) vs 0.0 (0.0 – 1.3), $p=0.389$, 1.0 (0.0 – 2.0) vs 0.0 (0.0 – 2.0), $p=0.309$, and 64.2 (54.7- 108.1) to 90.3 (55.8 -125.2) ng/mL, $p=0.482$, respectively). Lactate dehydrogenase (LDH) level and total lymphocyte count changed significantly from 198.0 (184.0 – 230) to 270.5 (209.3 – 384.8) IU/L, $p=0.005$, and 1365.0 (1101.8 – 1758.0) to 1008.5 (692.8 – 1628.0) /mm^3, $p=0.032$, respectively. By June 2016, 9 patients had died, and the median survival period was 27.0 (9.0 – 45.5) months. Among the 9 patients who died, 7 had diagnosed as LPDs with poor performance status (i.e. 3 to 4).

Conclusion: Twenty-two out of 26 patients who developed LPDs were receiving MTX. MTX users might have a higher incidence of LPDs in our hospital. Patients with poor performance status had poor prognosis, and over the half of patients develops LPDs without subjective symptoms of lymph node swelling. CRP elevation that is disproportionate to RA activity, LDH elevation, and decrease of lymphocyte count might be the signs of underlying LPDs.

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Abstract Number: 1547

Antibodies Against Carbamylated Proteins in Belgian RA Patients and in Other Rheumatic Diseases

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Background/Purpose: Antibodies targeting carbamylated proteins (Anti-CarP) have been recently described in Rheumatoid Arthritis (RA) and are reported to be associated with increased disease activity and with more severe joint damage. The specificity of the antibodies has been debated due to the fact that they are present in other rheumatic conditions. The aim of this study was to assess the presence of anti-CarP in RA patients from the CAP48 early arthritis Belgian cohort, as well as established RA patients regularly followed in our department, compare them to healthy subjects and controls from other rheumatic diseases and evaluate the specificity, sensitivity and diagnostic values of the Anti-CarP antibodies.

Methods: We tested sera from a total of 103 RA patients (38 early RA and 65 established RA), classified using the ACR/EULAR 2010 criteria for RA, healthy controls (n=56) as well as 142 patients with different rheumatic conditions (Juvenile Idiopathic Arthritis (n=80), Ankylosing Spondylitis (n=25) and Sjögren's Syndrome (n=37)). Sera were obtained from the CAP48 Early Arthritis cohort and from the biobank of the Rheumatology department of Erasme Hospital. An in-house ELISA technique, as described previously by Shi et al, was used to determine the presence of IgG class antibodies against carbamylated Fetal Calf Serum. A cut off for positive response was established as the mean plus two SD of the anti-CarP reactivity of the healthy controls.

Results: In our RA patients, Anti-CarP were detected in 38 patients (37%), while 66 patients (66%) were positive for Rheumatoid Factor and 68 (68%) patients were positive for ACPA. Anti-CarP were also found in 4 patients (4%) seronegative for both RF and ACPA. In the control population, 5 healthy controls were positive, along with 12 JIA patients, 5 SA patients and 11 Sjögren Syndrome Patients. (figure 1) The sensitivity of the anti-CarP antibodies at the cut-off chosen was at 35% and the specificity at 92,8%. Overall, the Positive Predictive value of the antibodies was estimated at 88,4%, whereas the Negative Predictive value was 44%.

Conclusion: Anti-CarP antibodies were detected in the sera of RA patients in a Belgian cohort, including a subgroup of patients seronegative for ACPA and RF. The anti-CarP are not exclusive to RA, our study confirms their presence in other rheumatic diseases (JIA, Sjogren's, Ankylosing Spondylitis). Whether this reactivity can be attributed to other interfering antibodies present in the sera of the controls or whether it is predictive of a particular articular phenotype remains to be elucidated.

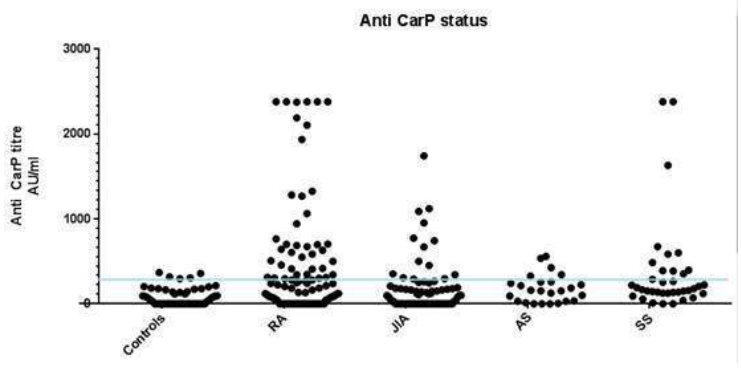

Fig 1. : Horizontal line represents the cut-off value.

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Abstract Number: 1548

Correlates of Fatigue in People Living with Rheumatoid Arthritis

Jet Veldhuijzen van Zanten[1,2], Sally Fenton[3,4], Peter Rouse[5], George Metsios[3,6], Ahmad Osailan[1,2], Chen-an Yu[2], Nikos Ntoumanis[7], Joan Duda[4] and George Kitas[1,2], [1]Department of Rheumatology, Dudley Group NHS Foundation Trust, Dudley, United Kingdom, [2]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, United Kingdom, [3]Department of Rheumatology, Russells Hall Hospital, Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [4]School of Sport, Exercise and Rehabilitation, University of Birmingham, Birmingham, United Kingdom, [5]Department for Health, University of Bath, Bath, United Kingdom, [6]Department of Physical Activity Exercise and Health, University of Wolverhampton, Walsall, United Kingdom, [7]School of Psychology & Speech Pathology, Curtin University, Perth, Australia
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Background/Purpose: Fatigue is a frequently mentioned symptom by people living with rheumatoid arthritis (RA). However, little research has explored the associations between fatigue and other indicators of health and well-being in this population, such as cardiovascular disease (CVD) and quality of life. Therefore, the current study aimed to examine the relationships between fatigue and disease activity, CVD risk, as well as psychological well-being.

Methods: 98 RA patients (66 female, 54 (12) years) completed the Multidimensional Assessment of Fatigue Scale, as well as questionnaires measuring depression, anxiety, subjective vitality, quality of life, and functional ability. CVD risk was assessed with blood pressure, body mass index, cardiorespiratory fitness, as well as serological measures (e.g., lipids, insulin resistance) and Qrisk was used to measure global CVD risk. Disease activity was measured by DAS28 and inflammatory markers. Participants were divided into tertiles based on levels of low (mean [SD] fatigue = 15.5 [4.7]), moderate (mean [SD] fatigue = 27.8 [3.3]) and high (mean [SD] fatigue = 39.9 [4.2]) levels of fatigue. Group differences were analysed by one-way Analyses of Variance, corrections were made for multiple comparisons.

Results: The fatigue groups did not differ with regards to age and sex. Clinical disease activity (p=.03), but not serological markers of inflammation, was different between the three fatigue groups. Those with greater levels of fatigue had lower functional ability, quality of life and subjective vitality, and higher anxiety and depression (p's<.01). Measures of insulin resistance (p's<.02), HDL cholesterol (=.03) and cardiorespiratory fitness (p=.03) were poorer in those with high fatigue (p's<.02), but no other markers of CVD risk (e.g., BMI, lipids, blood pressure) differed between the groups.

Conclusion: These results showed that RA patients with lower levels of fatigue also reported better psychological well-being, functional ability and DAS28 and some CVD risk indicators, but no differences were observed for levels of inflammation. These cross-sectional associations between fatigue and well-being suggest that improving psychological wellbeing, functional ability and cardiorespiratory fitness could also induce improvements in fatigue. However, this will need to be confirmed in longitudinal and intervention studies in which associations between improvements in psychological wellbeing and fatigue can be determined.

Disclosure: J. Veldhuijzen van Zanten, None; **S. Fenton**, None; **P. Rouse**, None; **G. Metsios**, None; **A. Osailan**, None; **C. A. Yu**, None; **N. Ntoumanis**, None; **J. Duda**, None; **G. Kitas**, None.

Abstract Number: 1549

Rheumatoid Arthritis and Periodontal Disease: Salivary ACPA Levels and Clinical Presentation

Zoltan Szekanecz[1], Ildiko Tar[2], Eva Csösz[3], Eva Veiszenbacher[4], Edit Végh[5], Kinga Bágyi[6], Karin Lundberg[7], Nastya Kharlamova[8] and Ildiko Márton[2], [1]Department of Rheumatology, University of Debrecen Faculty of Medicine, Debrecen, HU, [2]Department of Periodontology, University of Debrecen Faculty of Dentistry, Debrecen, Hungary, [3]Center for Molecular Medicine, University of Debrecen Faculty of Medicine, Debrecen, Hungary, [4]Faculty of Dentistry, University of Tirgu Mures, Tirgu Mures, Romania, [5]Department of Rheumatology, University of Debrecen Faculty of Medicine, Debrecen, Hungary, [6]Department of Restorative Dentistry, University of Debrecen Faculty of Dentistry, Debrecen, Hungary, [7]Rheumatology unit, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden, [8]Rheumatology Unit, Department of Medicine, Solna, Karolinska Institute, Stockholm, Sweden
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Background/Purpose: We evaluated the periodontal involvement of rheumatoid arthritis (RA) patients, and we correlated with various laboratory biomarkers including lipids, autoantibodies, serum vitamin D levels, markers of bone metabolism in relation with the periodontal condition and cariological indices; and also correlated them with salivary citrulline and anti citrullinated protein autoantibody levels with the above mentioned clinical and blood test findings.

Methods: Twenty-three RA patients were recruited for the study. Saliva samples were taken following whole scale periodontal and cariological examination. Protein concentration, peptidyl-citrulline and anti-cyclic citrullinated protein (anti-CCP) levels were measured from saliva samples. Blood test results were provided by rheumatologists. Citrullinated enolase protein-1 (CEP-1) level from serum was also measured.

Results: Periodontal diagnoses (scores) seem to have a positive dependency on LDL (R=0.722, p=0.008), PTH1 (R=0.586, p=0.022), D_3 vitamin level (R=0.586, 0.022), the sum of D3/D2 (R=0.634, p=0.011) respectively, in these patients. Anti-CEP-1 positive patients had significantly higher periodontal scores (2.71±0.11 vs 2.50±0.09, $p<0.05$) compared to anti-CEP-1 negative subjects. Interestingly, anti-CEP-1 positive patients had significantly higher triglyceride levels compared to seronegative ones (1.81±0.17 vs 1.42±0.05 mmol/l; $p<0.05$). Salivary citrulline and salivary anti-CCP, (p=0.007, R: 0.583) level has a correlation with the maximum of clinical probing depth.

Conclusion: Our results may add further pieces to the mosaic of RA-periodontitis connection. The possible role of antimicrobial immunity, as well as the possible role of lipids and bone metabolism have also been delineated. Future therapies should aim the disruption of this framework.

Disclosure: Z. Szekanecz, Pfizer Inc, 2,UCB, 2,AbbVie, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Bristol-Myers Squibb, 5,UCB, 5,Amgen, 5,MSD, 5,Pfizer Inc, 8,Bristol-Myers Squibb, 8,Roche Pharmaceuticals, 8,abbvie, 8; **I. Tar**, None; **E. Csösz**, None; **E. Veiszenbacher**, None; **E. Végh**, None; **K. Bágyi**, None; **K. Lundberg**, None; **N. Kharlamova**, None; **I. Márton**, None.

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Abstract Number: 1550

Comorbidities of Rheumatoid Arthritis: Results from the Korean National Health and Nutrition Examination Survey

Hyemin Jeong[1], Young Hee Eun[2], Eun-Jung Park[3], Hyungjin Kim[4], Ji Young Chae[5], Jaejoon Lee[1], Hoon-Suk Cha[2] and Eun-Mi Koh[4], [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Medicine, Samsung Medical Center,

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Background/Purpose: To evaluate the prevalence of comorbidities in patients with rheumatoid arthritis (RA) compared with non-RA population.

Methods: The 2010-2012 Korea National Health and Nutrition Examination Survey (KNHANES), which assesses the general health status of populations in South Korea using interviews and basic health assessment, was analyzed retrospectively. Weighted prevalence and odds ratio (OR) of comorbidities were analyzed in patients with RA compared with non-RA population.

Results: The overall weighted (n = 37,453,158) prevalence RA was 1.5%. Patients with RA were older and more female predominant than subjects without RA. The prevalence of living in urban area, collage graduation, drinking and smoking was lower in patients with RA than non-RA. Patients with RA had more comorbidities including hypertension, dyslipidemia, myocardial infarction (MI) or angina, stoke, osteoarthritis, lung cancer, colon cancer, pulmonary tuberculosis, asthma, diabetes, depression, thyroid disease and chronic kidney disease. After adjusting socioeconomic and lifestyle characteristics, RA was associated with the increased the prevalence of MI or angina (OR 1.86, 95% CI 1.17-2.96, p = 0.009), pulmonary Tb (OR 1.95, 95% CI 1.24 to 3.09, p = 0.004), asthma (OR 1.97, 95% CI 1.05 to 3.71, p = 0.036), thyroid disease (OR 1.71, 95% CI 1.05 to 2.77), depression (OR 2.38, 95% CI 1.47 to 3.85, p < 0.001) and hepatitis B (OR 2.34, 95% CI 1.15 to 4.80, p = 0.020) compared with non-RA population. Prevalence of solid cancer was not significantly associated with RA after adjustment.

Conclusion: RA was associated with increased risk of cardiovascular disease, pulmonary Tb, asthma, thyroid disease, depression and hepatitis B.

Disclosure: H. Jeong, None; **Y. H. Eun**, None; **E. J. Park**, None; **H. Kim**, None; **J. Y. Chae**, None; **J. Lee**, None; **H. S. Cha**, None; **E. M. Koh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comorbidities-of-rheumatoid-arthritis-results-from-the-korean-national-health-and-nutrition-examination-survey

Abstract Number: 1551

Rheumatoid Arthritis Is Associated with Low-/Mid-Frequency Hearing Impairment: Data from the Korean National Health and Nutrition Examination Survey

Hyemin Jeong[1], Young Hee Eun[2], Eun-Jung Park[3], Ji Young Chae[4], Hyungjin Kim[5], Jaejoon Lee[1], Hoon-Suk Cha[2] and Eun-Mi Koh[5], [1]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [2]Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea, [3]Department of Medicine, Division of Rheumatology, Department of Medicine, Jeju National University Hospital, Jeju University School of Medicine, Jeju, South Korea, [4]Departement of Internal Medicine, Bundang Jesaeng General Hospital, Seongnam, Korea, The Republic of, [5]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea
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Background/Purpose: This study aimed to evaluate the association between rheumatoid arthritis (RA) and hearing impairment in the Korean adult population.

Methods: Audiometric and laboratory test data from the 2010–2012 Korean National Health and Nutrition Examination Survey (KNHANES) were used for analysis. The relationship between RA and hearing impairment was analyzed, adjusting various known risk factors associated with hearing impairment. We defined hearing impairment for 2 categories of frequency (low/mid, high): Low/mid frequency, average of 0.5, 1.0, and 2.0 kHz, and high frequency, average of 3.0, 4.0, and 6.0 kHz.

Results: A total of 15,598 subjects completed the audiometric tests. The overall weighted (n = 32,898,665) prevalence of RA was 1.5%. Frequency of hearing impairment was higher in subjects with RA than in those without RA in both low/mid and high frequency (22.0% vs 7.8%, $p < 0.001$ and 43.3% vs. 26.4%, $p < 0.001$, respectively). In multivariable logistic analysis, RA (odds ratios (OR) 1.54, 95% CI 1.07 to 2.22, $p = 0.021$) was an independent risk factor for low/mid frequency hearing impairment along with age (OR 1.12, 95% CI 1.11 to1.13, $p < 0.001$), college graduation (OR 0.51, 95% CI 0.38 to 0.69, $p < 0.001$), and occupational exposure (OR 1.46, 95% CI 1.19 to 1.81, $p < 0.001$). In the multivariable analysis of high-frequency hearing impairment, RA did not show any association with hearing impairment.

Conclusion: This study first demonstrated that RA is associated with low-/mid-frequency hearing impairment after adjustment of various known risk factors.

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Abstract Number: 1552

The Association of Fatigue, Comorbidities and Anti Rheumatic Drugs in Rheumatoid Arthritis: Results from French Cohort Study of Comorbidities

Anne Tournadre[1], Bruno Pereira[2], Laure Gossec[3], Martin Soubrier[4] and Maxime Dougados[5], [1]Rheumatology, UNH-UMR 1019 INRA University of Auvergne and Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [2]Biostatistics unit (DRCI), CHU Gabriel Montpied, Clermont-Ferrand, France, [3]Sorbonne Universités, UPMC University Paris 06, Paris, France, Paris, France, [4]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [5]Paris-Descartes University, Paris, France

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Background/Purpose: The mechanisms of fatigue in rheumatoid arthritis (RA) are still unclear and the effect of antirheumatic drugs on fatigue not fully established. Objectives: To analyse in a large cohort of RA the factors associated with fatigue focusing on social aspects, comorbidities and treatment intake.

Methods: Cross sectional analyses were performed on RA patients from the French cohort study of comorbidities COMEDRA (1). Fatigue was assessed as a quantitative variable (RAID3 0-10 numeric scale) or by class (acceptable <3; moderate 3-4; severe ≥5 out of 10). Relationship with demographic, social, disease characteristics, treatments, comorbidities, physical activity, quality of life was investigated in univariate analyses (Table) and multivariate polynomial regression (Figure).

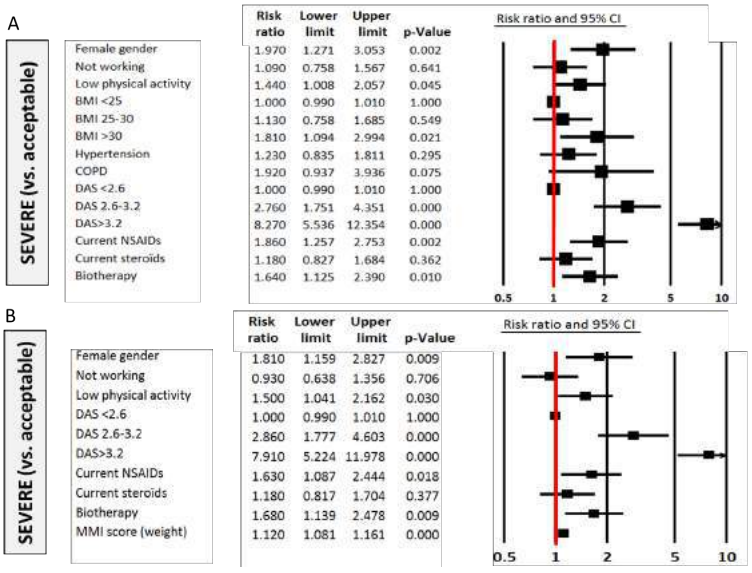
Results: 962 patients were analysed (age 57.7 ± 11.1 years, disease duration 11.1 years [6.2-19.1], mean DAS28 3.1 ± 1.3), 763 (79 %) were female. The mean fatigue score was 3.8± 2.7. Severe fatigue was more frequent in women, in patients not working, with less physical activity and more obesity. Fatigue was correlated with disease duration ($p=0.05$), all disease activity index ($p<0.001$), pain ($p<0.001$), mHAQ ($p<0.001$), sleep ($p<0.001$) and emotional well-being ($p<0.001$). Among comorbidities, hypertension, chronic obstructive pulmonary disease (COPD), fracture history and RA-related surgery were associated with fatigue. Multimorbidity assessed

by the weighted multimorbidity index (MMI.weight) (2) was independently associated with severe fatigue as well as current treatment with NSAID or biotherapy. Methotrexate use and the type of biologic did not impact fatigue score.

Conclusion: Beyond the expected association of fatigue with female gender and disease activity, less physical activity, comorbidities and multimorbidity, treatments could contribute to the persistent fatigue noted in RA. Fatigue was associated with steroids, NSAIDs, biotherapies but not with methotrexate and did not depend of the type of biotherapy. 1. Dougados M et al. Ann Rheum Dis. 2015;74(9):1725-33 2. Radner H et al. Seminars in Arthritis and Rheumatism 2015;45 : 167–173

	RAID3 (0-10) **Beta [95% CI]**	**RAID3 by class, RR [95% CI]** Moderate vs acceptable Severe vs acceptable
Female gender n=763	1.03 [0.6;1.45] ***	1.16 [0.78;1.70] 2.07 [1.43;3.01] ***
Low educational level n=680	0.38 [0.01;0.76] *	0.95 [0.66;1.36] 1.33 [0.94;1.80]
Not working n=628	0.38 [0.02;0.74] *	1.10 [0.78;1.56] 1.43 [1.05;1.94] *
Low physical activity n=353	0.69 [0.33;1.05] ***	1.80[1.26;2.55] *** 1.71 [1.25;2.34]***
BMI 25-30 n=276 ≥30 n=155	0.16 [-0.24;0.55] 1.20 [0.72;1.68] ***	1.20 [0.83;1.75] 1.13 [0.81;1.59] 1.32 [0.78;2.23] 2.39 [1.56;3.67] ***
DAS28 2.6-3.2 >3.2	1.30 [0.86;1.74] *** 2.50 [2.15;2.84] ***	2.20 [1.39;3.48] *** 3.13 [2.04;4.81] *** 3.89 [2.58;5.87] *** 9.35 [6.41;13.64] ***
Hypertension n=281	0.67 [0.29;1.05] ***	1.19 [0.82;1.75] 1.75 [1.26;2.42] ***
COPD n=63	0.72 [0.02;1.41] *	1.53 [0.73;3.20] 2.10 [1.12;3.93] *
Fracture history n=296	0.44 [0.06;0.81] *	1.42 [0.99;2.04] 1.38 [0.99;1.90]
RA-related surgery n=287	0.40 [0.02;0.78] *	0.99 [0.68;1.45] 1.27 [0.92;1.75]
Current NSAIDs n=249	0.75 [0.36;1.14] ***	1.70 [1.14;2.52] ** 1.96 [1.39;2.77] ***
Current steroids n=364	0.75 [0.40;1.1] ***	1.49 [1.05;2.11] ** 1.72 [1.27;2.33] ***
Biotherapy alone or in combination n=672	0.46 [0.07;0.84] *	0.96 [0.67;1.38] 1.45 [1.04;2.01] **

Forest plot showing the overall risk ratio in multiple regression models including comorbidities (A) or weighted multimorbidity index (MMI.weight) (B) between severe fatigue and covariates retained according to univariate results and clinical relevance.



***p<0.001; **p< 0.01; *p< 0.05.

Disclosure: A. Tournadre, None; **B. Pereira**, None; **L. Gossec**, None; **M. Soubrier**, None; **M. Dougados**, AbbVie, Eli Lilly, Merck,

Novartis, Pfizer, UCB Pharma, 2,AbbVie, Eli Lilly, Merck, Novartis, Pfizer, UCB Pharma, 5.

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Abstract Number: 1553

Declining Flare Rates in the First Five Years of RA Disease, but Not after

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Background/Purpose: Flare or episodic worsening of disease activity is an important aspect of the disease experience for patients with rheumatoid arthritis (RA). Improving trends towards lower RA disease activity have been suggested in recent years. However, long-term data on flare rates in RA are lacking. This study aimed to assess trends in the occurrence of flares in RA over disease duration.

Methods: A population-based cohort of patients with RA (age≥18 years; 1987 ACR criteria met in 1988-2007), was used to perform this retrospective medical records review of each clinical visit to estimate flare status. RA flare was defined as any worsening of RA activity leading to initiation/change/increase of therapy (OMERACT 9). All subjects were followed until death, migration or July 1, 2012. Flare rates were calculated as the percentage of visits in flare. Binomial regression models with random effects to account for multiple visits per subject were used to assess the associations between patient characteristics and flare rate. Smoothing splines were used to allow for non-linear effects. Two way interactions between RA disease duration and other patient characteristics were examined.

Results: The study included 650 RA patients (mean age 55.8 years; 69% female) with mean follow up of 10.3 years. Flare status was collected for a total of 17,323 clinical visits. Patients were flaring in 2887 (17%) visits. Figure 1 shows trends in flare rates after RA onset by calendar year of RA diagnosis. There was a statistically significant decline in the RA flare rate across disease duration ($p<0.001$), predominantly in the first 5 years after diagnosis of RA. Patients diagnosed with RA in more recent years experienced fewer flares during the first few years of RA ($p<0.001$). Women tended to have marginally higher flare rates as compared to men, but this did not reach statistical significance ($p=0.16$). There were no differences between the sexes in trends of flare rates over time (interaction $p=0.42$). Flare rates were similar for all ages in the first few years after RA diagnosis, but in subsequent years patients diagnosed with RA at younger ages had higher flare rates than those diagnosed at older ages. Patients with positive rheumatoid factor (RF) had higher flare rates than negative RF ($p<0.001$), and flare rates declined more over disease duration in patients with negative RF than those with positive RF (interaction $p=0.047$; Figure 2).

Conclusion: Patients diagnosed more recently have lower rates of flares than those diagnosed in prior decades. Flare rates declined fastest in the first 5 years of disease and tended to be stable thereafter. These patterns likely reflect improved control of RA activity and possibly milder RA disease course in the recent years. However, flares continue to occur persistently at a constant rate after the five years of RA, reflecting the need for improved long term disease management.

Figure 1. Flare rates by calendar Year of RA diagnosis and RA disease duration

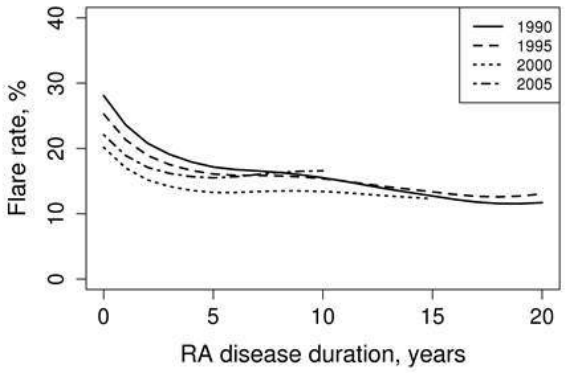
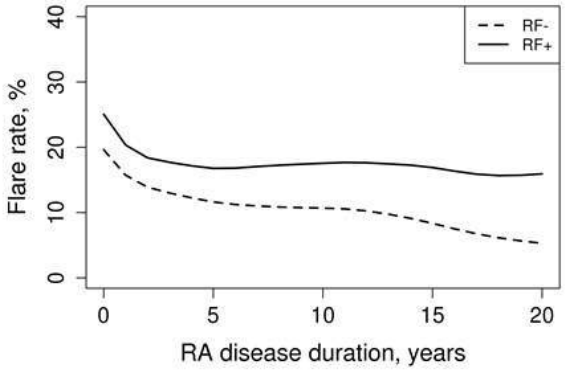


Figure 2. Flare rate According to Rheumatoid Factor



Disclosure: S. Raheel, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **E. Myasoedova**, None.

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Abstract Number: 1554

Longitudinal Trajectories of the Weighted Lansbury Articular Indices and Standard Joint Counts Are Similarly Correlated with Trajectories of Physical Function in Early Inflammatory Arthritis

Siok Hoon Lily Lim[1], Susan J. Bartlett[2], Gilles Boire[3], Boulos Haraoui[4], Edward Keystone[5], J Carter Thorne[6], Janet E. Pope[7], Diane Tin[8], Vivian P. Bykerk[9], **Carol Hitchon**[10] and Canadian Early Arthritis Cohort (CATCH), [1]Pediatrics, University of MAnitoba, Winnipeg, MB, Canada, [2]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheumatology Division, CHUS - Sherbrooke University, Sherbrooke, QC, Canada, [4]Institute de Rheumatologie, Montreal, QC, Canada, [5]Mt. Sinai Hospital, University of Toronto, Toronto, ON, Canada, [6]Southlake Regional Health Centre, Newmarket, ON, Canada, [7]University of Western Ontario, St Joseph's Health Care, London, ON, Canada, [8]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [9]Divison of Rheumatology, Hospital for Special Surgery, New York, NY, [10]University of Manitoba, Winnipeg, MB, Canada

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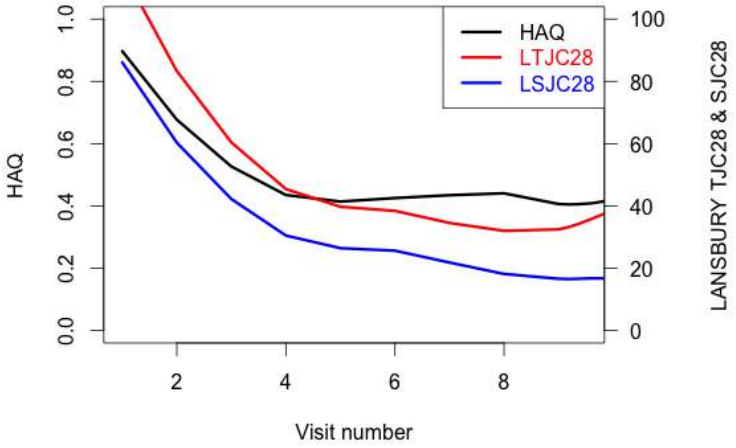
Background/Purpose: Residual disease activity impacts functional status and quality of life (QoL) in patients with early rheumatoid arthritis (ERA). Large weight bearing joints are more likely to impact function such as walking than small non-weight bearing joints although the effect may be task dependent. The Lansbury Articular Index (LAI) weights large joints more than small joints thus may give a better estimate of overall disease burden with respect to large joint function. The Health Assessment Questionnaire (HAQ) seems to weigh upper extremity tasks more than lower extremity or weight bearing tasks. In a large multicenter cohort of ERA patients, we therefore sought to determine associations of LAI with HAQ, QoL and baseline disability status and whether changes in the LAI trajectory more closely reflected the evolution of the HAQ trajectory than the standard joint count measures.

Methods: We used data from subjects with ERA (less than 1 year symptom duration at first visit) followed in a multicentre Early Arthritis Cohort. Arthritis activity measures (DAS28, tender 28 joint count (tjc28), swollen 28 joint count (sjc28), function (Health Assessment questionnaire; HAQ) QoL (SF12 physical (PCS) and mental (MCS) indices) and work status were captured per study protocol. The LAI based on 28 joints was calculated separately for swollen (LS28) and tender (LT28) joint counts. The impact of LS28, LT28 on baseline disability status was modeled using logistic regression. Individuals' trajectories for each measure (HAQ, DAS28, TJC28, SJC28, LT28,LS28) were visualized with LOESS plots and marginal trajectories by variable plotted. Each measure's longitudinal trajectory was fitted using the best fitting fractional polynomials. Each individual disease activity trajectory was then jointly modelled with the HAQ longitudinally (joint modelling). Correlations between each pair of joint trajectories (HAQ with TJC28 or SJC28 or LT28 or LS28) were calculated.

Results: ERA subjects (n=2133, 73% female; baseline mean (SD) Age 53(15) years, DAS 5.1(1.4)) were followed for median (IQR) 24(10,48) months. At last visit 44 % were in remission (DAS28<2.6). Combining all visits, the LS28 strongly correlated with SJC28 (r= 0.9 p<0.0001), PCS (r=-0.4 p<0.0001) and HAQ (r= 0.4 p<0.0001). The LT28 correlated with the TJC28 (0.9 p<0.001), PCS (r=-0.5 p<0.0001) and HAQ (0.5 p<0.0001). Correlations were even stronger with the full LAI (42 joints). Disability or sick leave at baseline (6% of cohort) was associated with higher LT28 (OR 1.003 p=0.001) and higher TJC28 (OR 1.071 p<0.0001) in separate logistic regression models that included age. The HAQ trajectory was highly correlated with the trajectories for DAS28 (r=0.83), LT28 (r=0.83), and TJC28 (r=0.85) and less strongly with trajectories for LS28(r= 0.59) and SJC28 (r=0.61).

Conclusion: The trajectories of function (HAQ) and both Lansbury and standard joint counts are highly correlated over time in ERA. The LAI performed similarly to standard joint counts which are easier to determine. Although type of occupation was not addressed and likely influences the impact of lower extremity involvement, both LT28 and TJ28 associated with baseline work disability.



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Abstract Number: 1555

E-Comorbidity: Evaluation of the Validity of Electronic Comorbidity Assessment in Identifying Comorbid Conditions Among Patients with Rheumatoid and Psoriatic Arthritis

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: 1. to assess the validity of an electronically comorbidity assessment strategy to identify comorbid conditions among RA and PsA patients in standard practice. 2. To evaluate the impact of e-comorbidity assessment on the patients' care and adherence to therapy.

Methods: A cohort of 448 RA and 437 PsA subjects with varying disease duration met the following inclusion criteria: RA diagnosed according to ACR/EULAR criteria and PsA according to CASPAR criteria, started a DMARD/biologic agent, continued therapy >6 months, and followed longitudinally from baseline to follow-up (mean time 24months). Electronic patients reported comorbidities questionnaire according to a RACI [1] and PsACI [2] was implemented as part of electronic patient reported outcome measures tool. The sensitivity, specificity, positive and negative predictive values of the electronic data entry and calculated comorbidity risk were compared to ICD-10 medical record (reference standard) and rheumatology clinic visits outcomes. A control group of 241 RA patients and 252 PsA patients managed according to standard protocols were also assessed and monitored for 2 years. Primary end point: no inferiority of outcomes of the electronic and standard formats. Secondary end point: the patients' adherence to their medications and actions taken to assess and manage the comorbidity risk.

Results: The sensitivity for identifying comorbidities using the electronic approach ranged from a minimum of 94% for atlanto-axial sublaxation to a maximum of 100% for cardiovascular risk (median, 99.2%; interquartile range [IQR]: 96%-100%). Sensitivities for extracting comorbidities using ICD-10 codes ranged from a minimum of 8% for Anxiety to 100% for tumors (median, 66%; IQR: 50%-74%); whereas, sensitivities for extracting comorbidities using clinic outcomes data ranged from a minimum of 4% for falls risk to 100% for diabetes and tumors (median, 38%; IQR: 32%-54%). The median PPV and NPV were 97.7% (IQR: 96-100%) and 99.6% (IQR: 99-100%) for the e-comorbidity tool Vs 61.8% (IQR: 41%-76%) and 97.4% (IQR: 91%-98%) for the ICD-10 codes, respectively. The patients' adherence to anti-rheumatic therapy was significantly ($p<0.1$) higher in the studied group whereas stopping DMARDs for intolerability was significantly ($p<0.01$) higher in the control group. Number of procedure/ screening tests for comorbidity risk assessment was significantly higher in the e-comorbidity group ($P< 0.001$).

Conclusion: e-comorbidity assessment offered a specific and dynamic approach tailored to the patient's needs over the 2-years study period, which is applicable in standard practice. Patient reported e-comorbidity outperformed the standard medical recording systems and can have a role in healthcare management and research. Reclassifying RA patients according to their comorbidity risk would have a positive impact on their adherence to therapy, early assessment of comorbidities with subsequent preventive or treatment decisions.

References:

1. Rheumatoid Arthritis Comorbidity Index. El Miedany et al. Ann Rheum Dis 2016; 75(Suppl2): 154
2. Psoriatic arthritis Comorbidity Index. El Miedany et al. Ann Rheum Dis 2016; 75(Suppl2): 89

Disclosure: Y. M. El Miedany, Speaker Honoraria from Abbvie, Celgene, MSD, Roche, 8; **M. El Gaafary**, None; **S. Youssef**, None;

S. Bahlas, None; **M. Hegazi**, None; **I. Ahmed**, None.

Abstract Number: 1556

Assessment of the Burden of Comorbidities By the Rheumatic Disease Comorbidity Index in Early Rheumatoid Arthritis Patients at Disease Onset

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid Arthritis (RA) is associated with a high prevalence of comorbidities, negatively affecting outcomes like disease activity and physical function. However, not all comorbid conditions have the same impact on the outcomes of interest. The Rheumatic Diseases Comorbidity Index (RDCI) was validated to measure more accurately the burden and prognostic impact of overall comorbidity, based on a weighted preselection of comorbid conditions. We aimed to quantify the total burden of comorbidities, its association with disease outcomes, demographics and Serious Adverse Events (SAE) in early RA.

Methods: The presence of comorbidities was recorded on screening, before treatment initiation in 379 patients with recently diagnosed RA (<1 year) participating in the Care in early RA (CareRA) trial. The RDCI (0-9) was calculated by scoring 11 weighted comorbid conditions. Demographics including gender, age, smoking status, alcohol use and BMI were registered on screening. Disease activity (DAS28-ESR/CRP) was measured at baseline and after 1 year treatment using a treat-to-target approach. All SAE were registered during a 2-year follow-up. The association of RDCI with disease activity, functional disability (HAQ-DI), demographics and SAE was explored by assessing Spearman correlations. Correlations ≤0.29 were considered small, 0.30-0.49 moderate and ≥0.50 strong. Additionally, a multivariate linear regression analysis was performed to control for confounders.

Results: Out of 379 patients, slightly more than half (55.9%) had a RDCI equal to zero. The mean score was 0.8 and the maximum 6. RDCI scores of 1, 2 or ≥3 were obtained in 65 (17.2%), 70 (18.5%) and 32 (8.4%) participants respectively. The most frequent comorbidities were hypertension (22.4%), cardiovascular events (myocardial infarction/stroke or other) (16.6%) and lung diseases (8.4%). A moderately positive correlation was found between RDCI and age ($r = 0.39$, $p<0.001$). RDCI also correlated with disease activity (DAS28-CRP and DAS28-ESR) ($r = 0.19$-0.21, $p<0.001$) and with physical functioning (HAQ-DI) ($r = 0.13$, $p=0.009$) at baseline. After 1 year no more statistically significant correlation was found between the RDCI and DAS28-CRP, DAS28-ESR or HAQ-DI scores. In addition, RDCI correlated positively with the amount of SAE per patient, occurring during this 2-year study ($r = 0.24$, $p<0.001$). Multivariate linear regression confirmed these findings. RDCI was significantly associated with DAS28-CRP at baseline ($\beta=0.127$, $p=0.034$), and amount of SAE per patient ($\beta=0.109$, $p=0.001$) when controlled for gender, age, smoking status, alcohol use, BMI and treatment strategy.

Conclusion: At disease onset, almost half of RA patients in our study population had at least one clinically important comorbidity, as assessed by the RDCI. Scores of this co-morbidity index were positively correlated with age, disease activity and functional ability at baseline, but this correlation disappeared after one year treatment with intensive remission induction strategies. The incidence of SAE was associated with RDCI, reflecting an important impact of comorbidities on patients' overall health evolution.

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Abstract Number: 1557

3-D Explant Method Facilitates the Study of Lymphocytes in Synovium and Reveals a Population of Resident Memory-like T Cells in Rheumatoid Arthritis

Lauren Henderson[1], Deepak Rao[2], Nikola Teslovich[3,4], Sandra King[5], Fumitaka Mizoguchi[6], Sarah Ameri[6], Allyn Morris[7], Christopher Elco[8], James Lederer[9], Scott Martin[10], Barry Simmons[10], John Wright[10], Michael Brenner[2], Soumya Raychaudhuri[11,12,13,14,15], Peter Nigrovic[1,16] and Robert Fuhlbrigge[17,18], [1]Division of Immunology, Boston Children's Hospital, Harvard Medical School, Boston, MA, [2]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Divisions of Genetics and Rheumatology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Brigham and Women's Hospital and Harvard Medical School, Cambridge, MA, [5]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [6]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [7]Division of Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA, [8]Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [9]Department of Surgery, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [10]Department of Orthopedic Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [11]Divisions of Genetics and Rheumatology, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, [12]Program in Medical and Population Genetics, Broad Institute of Massachusetts Technical Institute, Harvard University, Cambridge, MA, [13]Partners Center for Personalized Genetic Medicine, Boston, MA, [14]Rheumatology Unit, Karolinska Institutet, Karolinska University Hospital Solna, Stockholm, Sweden, [15]Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom, [16]Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, Boston, MA, [17]Immunology, Boston Children's Hospital, Boston, MA, [18]Dermatology, Brigham and Women's Hospital, Boston, MA

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Human Etiology and Pathogenesis - Poster II
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Tissue resident memory T (T_{RM}) cells survive indefinitely in barrier tissues and mediate swift immunologic memory responses at sites of microbe entry. T_{RM} cells have been implicated in recurrent site-specific inflammation in skin, intestine, and lung, but little is known about T_{RM} cells in synovium. We employed a highly efficient 3-dimensional (3-D) explant culture technique, developed to recover T_{RM} from skin, to investigate synovial infiltrating T cells.

Methods: Subjects with rheumatoid arthritis (RA) were identified by International Classification of Disease (ICD) codes, supported by medical record review by a board-certified rheumatologist. Synovial tissue samples were obtained from RA patients undergoing medically necessary joint surgery. Collagenase digestion and/or 3-D explant culture was used to isolate synovial T cells. In the 3-D explant culture system, 2mm x 2mm pieces of synovial tissue were placed on Cellfoam matrices, and cultured in T cell media enriched with IL-2 and IL-15 for 3 weeks. Multidimensional analysis of surface markers and cytokine production upon stimulation was performed by mass cytometry (CyTOF).

Results: Synovial samples were obtained from 13 women and 2 men with established RA. Treatment regimens varied (methotrexate, n=9; tumor necrosis factor inhibitors, n=6; prednisone, n=5; non-steroidal anti-inflammatory drugs, n=5). 3-D explant culture of RA synovium samples yielded 5-fold more mononuclear cells, on average, than collagenase digestion (mean number mononuclear cells per mg tissue ± SEM: 25,000 ± 17,000 vs. 5,600 ± 4,700). Approximately, 80% of cells collected by the 3-D explant culture method were $CD3^+$ T cells, with the majority being $CD4^+$ T cells (~80%). The ratio of $CD4^+$ to $CD8^+$ cells was not significantly different between the recovery methods. Multidimensional mass cytometry analyses demonstrated dramatic differences in phenotype between synovial and blood $CD4^+$ memory T cells, with significantly increased CD49d and MHCII and decreased CD27 on synovial T cells. A Th1 phenotype predominated in synovial T cells isolated by explant cultures, with ~35% of $CD4^+$ memory T cells expressing IFNγ and Tbet upon stimulation. Notably, memory $CD4^+$ T cells with a phenotype consistent with T_{RM} cells ($CD62L^-$, $CCR7^-$, $CD69^+$) were identified in all tested synovial samples. While CD69 expression may be induced by recent activation, many of these potential T_{RM} ($CD62L^-$, $CCR7^-$, $CD69^+$) cells did not express two other markers of recent activation, CD25 and MHCII.

Conclusion: 3-D explant culture is a novel tool that can be employed to study lymphocytes that are resident in synovium. Memory T

cells with T_{RM} features were identified in synovial samples from RA patients, supporting the hypothesis that this T cell subset may contribute to the persistence and recurrence of inflammatory arthritis. Further study will be needed to define the functional characteristics and pathophysiologic role of these cells.

Disclosure: L. Henderson, None; **D. Rao**, None; **N. Teslovich**, None; **S. King**, None; **F. Mizoguchi**, None; **S. Ameri**, None; **A. Morris**, None; **C. Elco**, None; **J. Lederer**, None; **S. Martin**, None; **B. Simmons**, None; **J. Wright**, None; **M. Brenner**, None; **S. Raychaudhuri**, None; **P. Nigrovic**, None; **R. Fuhlbrigge**, None.

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Abstract Number: 1558

Lower Expression of a Novel Cytoplasmic Long Noncoding RNA NR_122076 Contributes to Proliferation, Migration and Invasion of Fibroblast-like Synoviocytes from Patients with Rheumatoid Arthritis

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Emerging evidence indicates that long noncoding RNAs (lncRNAs) play critical regulatory roles in various human diseases, especially in cancers and inflammatory disorders. However, the role of lncRNAs in the pathogenesis of rheumatoid arthritis (RA) remains largely unknown.

Methods: Fibroblast-like synoviocytes (FLSs) were separated and cultured from synovial tissues of healthy control (HC) and RA patients. Differentially expressed lncRNAs between HC and RA FLSs were identified by microarray. Expression level and subcellular localization of RNA was validated by quantitative real-time PCR (qRT-PCR) and in situ hybridization (ISH). Transcriptional initiation and termination sites of NR_122076 were identified by rapid amplification of cDNA ends (RACE) analysis. Lentivirus mediated overexpression of NR_122076 were adopted to investigate the function of NR_122076. Proliferation rate was assessed by EdU assay. Migration and invasion of FLSs *in vitro* were measured by the Boyden chamber assay. Cytoskeleton was visualized by immunofluorescence.

Results: We used microarray to establish lncRNA expression profiles in FLSs from HC and RA patients. We found that 94 lncRNAs were upregulated and 195 lncRNAs downregulated by more than 2-fold in RA FLSs compared with HC FLSs. Further qRT-PCR confirmed that, among them, only NR_122076 expression was significantly decreased in the synovial tissues and FLSs from RA patients. Stimulation with PDGF-BB decreased the expression of NR_122076, whereas treatments of methotrexate or dexamethasone increased NR_122076 expression. RNA fluorescent in situ hybridization (FISH) and qRT-PCR of nuclear and cytoplasmic fractions suggested that NR_122076 was mainly located in the cytoplasm. Overexpression of NR_122076 significantly inhibited cell proliferation, migration and invasion in RA FLSs. Furthermore, overexpression of NR_122076 impaired PDGF-BB induced formation of lamillipodia and filopodia.

Conclusion: Decreased expression of NR_122076 contributes to excessive proliferation and aberrant aggressive behaviors of RA FLSs. Our findings suggest NR_122076 might be a possible new therapeutic target against RA.

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Abstract Number: 1559

Shared Genetic Predisposition in Rheumatoid Arthritis–Interstitial Lung Disease and Idiopathic Pulmonary Fibrosis: A Genetic Association Study

Pierre-Antoine Juge[1], Raphaël Borie[2], Caroline Kannengiesser[3], Steven Gazal[3], Patrick Revy[4], Lidwine Wemeau-Stervinou[5], Marie-Pierre Debray[6], Sébastien Ottaviani[7], Sylvain Adam-Marchand[8], Nadia Nathan[9], Gabriel Thabut[10], Christophe Richez[11], Hilario Nunes[12], Isabelle Callebaut[13], Aurélien Justet[2], Nicolas Leulliot[14], Amélie Bonnefond[15], David Salgado[16], Pascal Richette[17], Jean-Pierre Desvignes[16], Huguette Lioté[18], Philippe Froguel[15], Yannick Allanore[19], Olivier Sand[15], Claire Dromer[20], René-Marc Flipo[21], Annick Clément[9], Christophe Béroud[22], Jean Sibilia[23], Baptiste Coustet[1,24], Vincent Cottin[25], Marie-Christophe Boissier[26], Benoit Wallaert[27], Thierry Schaeverbeke[28], Florence Dasto le Moal[29], Aline Frazier[17], Christelle Ménard[30], Martin Soubrier[31], Nathalie Saidenberg[29], Dominique Valeyre[32], Serge Amselem[9], Catherine Boileau[3], Bruno Crestani[2] and Philippe Dieudé[1], [1]Rhumatologie, Hôpital Bichat - Claude Bernard, Paris, France, [2]Pneumologie A, Hôpital Bichat - Claude Bernard, Paris, France, [3]Génétique, Hôpital Bichat - Claude Bernard, Paris, France, [4]Laboratory of Genome Dynamics in the Immune System, Institut Imagine, Paris, France, [5]Pneumologie, CHRU de Lille, Lille, France, [6]Université Paris-Diderot, Paris, France, [7]Rheumatologie, Hôpital Bichat - Claude Bernard, Paris, France, [8]Pneumology, Centre Hospitalier Universitaire de Tours, Tours, France, [9]Pneumologie pédiatrique, Hôpital Trousseau, Paris, France, [10]Pneumologie B, Hôpital Bichat - Claude Bernard, Paris, France, [11]Rhumatologie, Department of Rheumatology, Bordeaux University Hospital, Bordeaux, France, [12]Pneumologie B, Hôpital Avicenne, Paris, France, [13]CNRS UMR_7590, Paris, France, [14]Laboratoire de cristallographie et RMN biologiques, UMR CNRS 8015, Paris, France, [15]CNRS UMR_8199, Lille, France, [16]UMR_S 910, Marseille, France, [17]Rhumatologie, Hôpital Lariboisière, Paris, France, [18]Pneumologie A, Hôpital Tenon, Paris, France, [19]Rhumatologie A, Hôpital Cochin, Paris, France, [20]Imagerie Thoracique et Cardiovasculaire, CHU Bordeaux, Bordeaux, France, [21]Rhumatologie, CHU Lille, Lille, France, [22]INSERM UMR_S 910, Marseille, France, [23]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [24]Rheumatology, Université Paris Descartes, Hopital Cochin, Paris, France, [25]Louis Pradel Hospital, Claude Bernard University Lyon 1, Lyon, France, [26]Li2P, University of Paris 13, Sorbonne Paris Cité, Bobigny, France, [27]Pneumology, CHRU, Lille CEDEX, France, [28]Rheumatology, CHU Bordeaux, Bordeaux, France, [29]Rhumatologie, Hôpital Avicenne, Paris, France, [30]Pneumologie Pédiatrique, Hôpital Trousseau, Paris, France, [31]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [32]Department of Pneumology, Avicenne Hospital (AP-HP), Bobigny, France

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Background/Purpose: Interstitial lung disease (ILD) is one of the leading causes of mortality for rheumatoid arthritis (RA) patients. Despite its high prevalence and mortality, little is known about the pathogenesis of RA–associated ILD (RA-ILD). Given that idiopathic pulmonary fibrosis (IPF) and RA–ILD share the usual interstitial pneumonia pattern and common environmental risk factors such as tobacco smoking, we hypothesized that the two diseases may share additional risk factors including familial pulmonary fibrosis (FPF) susceptibility genes.

Methods: We used whole-exome sequencing (WES) followed by restricted analysis of a discrete number of FPF-linked genes to compare mutations among consecutive RA–ILD patients collected by a French network of pulmonologists and rheumatologists. A burden test was used to assess the excess number of mutations in RA–ILD patients.

Results: Among the 101 RA–ILD patients included, 12 (11.9%) had 13 WES-identified heterozygous mutations in the *TERT*, *RTEL1*, *PARN* or *SFTPC* coding regions. The burden test, based on 81 RA–ILD patients and 1010 controls of European ancestry, revealed an excess of *TERT*, *RTEL1*, *PARN* or *SFTPC* mutations for RA–ILD patients compared to controls ($p=9.45 \times 10^{-4}$, odds ratio [OR] 3.17 95% CI 1.53–6.12). Telomeres were shorter for RA-ILD patients with a *TERT*, *RTEL1* or *PARN* mutation than controls ($p=2.87 \times 10^{-2}$).

Conclusion: Our results support the contribution of FPF-linked genes to RA–ILD susceptibility, linking RA–ILD and IPF pathogeneses. Recent therapeutic advances in IPF may open new avenues for treatment of ILD, the most severe RA manifestation for which effective drugs are lacking.

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Abstract Number: 1560

A Unique Immune Signature in Patients with Active Rheumatoid Arthritis but Normal C-Reactive Protein Levels: Potential for New Therapeutic Targets?

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Background/Purpose: Using musculoskeletal ultrasound (US) to assess joint erosions and disease activity in patients with seropositive rheumatoid arthritis (RA) an atypical subgroup was identified with active disease demonstrated by significant Power Doppler, but normal C-reactive protein (CRP) and erythrocyte sedimentation rate levels. We questioned whether this presentation was associated with delayed diagnosis or relative under treatment, risking worse disease outcome and/or disability. We hypothesized that understanding the underlying immune pathology in this atypical subset could directly influence therapeutic targeting in patients whose needs are not currently met. We aim to stratify patients based on their immune signature to identify new treatment algorithms and therapeutic targets.

Methods: 44 RA patients with active synovitis were recruited, defined by ≥1 joint with Power Doppler detected by US, 29 had normal (n)CRP (≤5mg/L) and 15 had high (h)CRP (>5mg/L) levels. Peripheral blood mononuclear cells (PBMCs), serum and detailed clinical data were collected. 18 age and sex matched healthy donors were also analyzed. Multiple 14-colour flow cytometry panels were used to perform in-depth PBMC immunophenotyping. Serum and intracellular cytokines were assessed using Cytometric Bead Array and flow cytometry. Plasma was subjected to SOMAscan™ (Slow Off-rate Modified Aptamer) Proteomic Assay. Data was analyzed using cluster analysis (partitioning and hierarchical agglomerative algorithms) and correlation analysis (using a shrinkage estimator of the partial correlation matrix).

Results: nCRP patients had increased erosion accrual rate compared to hCRP patients (p=0.022) reflecting more disease-associated joint damage, while other clinical and laboratory parameters were identical. However, nCRP patients were able to mount a CRP response to infection. Serum IL-6 and IL-1β, pro-inflammatory cytokines known to trigger CRP production and support T-cell activation, were significantly elevated in both patient groups compared to healthy donors (p=<0.001) suggesting either defects in downstream IL-6 signaling or the disease mechanism may be IL-6-independent in nCRP patients. In support of this, nCRP patients had an anti-inflammatory phenotype characterized by significantly increased regulatory T-cells (Tregs) (p=0.014) with increased CD161 expression, known to be inversely correlated with CRP levels and associated with increased Treg suppressive capacity. Alternatively, hCRP patients had the expected activated T-cell phenotype including increased central memory T-cells (p=0.024) and Th17 populations. Preliminary proteomic analysis identified significant increases in complement components, serum amyloid P (SAP) and CRP in the hCRP compared to nCRP patients. Strikingly, serum amyloid A, an acute phase protein that has different ligands to CRP and SAP was significantly increased in both patient groups.

Conclusion: This study stratifies distinct patient subgroups using detailed immunophenotyping and proteomic signatures. We have identified altered immunopathological mechanisms in nCRP patients which could translate to improved patient-specific therapies.

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Abstract Number: 1561

Associations of HLA-DRB1 Haplotypes with Disease Characteristics and All-Cause Mortality in Rheumatoid Arthritis

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Background/Purpose : Numerous genetic susceptibility loci have been identified in RA. The HLA-DRB1 shared epitope (SE) sequence is most strongly associated, though there has been increasing interest in amino acids outside the SE region. Recently, investigators have identified 16 HLA haplotypes defined by amino acids at positions 11, 71, and 74. Valine at position 11, particularly the VKA haplotype, has been associated with radiographic progression, mortality, and poor RA treatment response. In this study we examined HLA haplotypes and associations with mortality, presence of subcutaneous nodules, radiographic damage, and RA-associated autoantibodies.

Methods: The study included 1443 U.S veteran participants. Clinical characteristics were recorded at enrolment. Mortality was ascertained via linkage to the National Death Index. DNA was obtained at enrollment and 4-digit HLA-DRB1 genotyping was completed. Amino acids at positions 11, 71, and 74 were determined, and haplotypes assigned based on three amino acid combinations. RF and aCCP were measured from banked serum. Haplotype associations with mortality were examined using age- and sex-adjusted Cox proportional hazards regression, while associations with other disease characteristics were examined using Chi square or Student's t-tests comparing subjects with at least one copy of a given haplotype to those with no copies.

Results: The most frequent haplotype was VKA with 34% of subjects possessing at least one copy. Eight haplotypes were present in frequencies >10% (VKA, VRA, LRA, PAA, GRQ, SRA, SKR, SEA). We found an increased risk of all-cause mortality with SKA (HR 1.38 [95% CI 1.13-1.69]) but not with SE status or other haplotypes, including those with valine at position 11. Radiographic damage was more common in patients with VKA (60% vs 51%, p = 0.002) or VRE (70% vs 53%, p = 0.032) but less common with SRA (44% vs 55%, p = 0.005) and SEA (46% vs 57%, p = 0.023). There were no haplotype associations with subcutaneous nodules. We identified associations between several haplotypes and autoantibody concentration (Table). The VKA haplotype was associated with higher RF and aCCP concentrations. SE positivity based on dual autoantibody status was: RF+/aCCP+ = 77%; RF-/aCCP+ = 79%; RF+/aCCP- = 53%; and RF-/aCCP- = 56%. A similar pattern was observed for VKA haplotype positivity: RF+/aCCP+ = 39%; RF-/aCCP+ = 37%; RF+/aCCP- = 18%; and RF-/aCCP- = 18%.

Conclusion: In contrast to recent reports, we observed little association between HLA haplotype and all cause mortality. However, there were associations of both VKA and VRE haplotypes with presence of radiographic damage and robust associations of VKA with higher RF and aCCP values. Our observations also suggest that associations of both SE and VKA status with seropositivity are driven by associations with aCCP status independent of RF.

RF and aCCP concentrations based on HLA-DRB1 haplotype						
	Rheumatoid Factor Concentration (IU/ml; mean ± SD)			Anti-CCP Concentration (U/ml; mean ± SD)		
Haplotype	Haplotype+	Haplotype-	P	Haplotype+	Haplotype-	P
VKA	347 (639)	321 (676)	**<0.001**	331 (510)	243 (407)	**<0.001**
VRA	317 (520)	334 (709)	**0.048**	303 (449)	261 (445)	0.162
LRA	356 (766)	321 (623)	0.964	311 (485)	259 (431)	0.271
PRA	231 (579)	333 (665)	0.471	291 (295)	272 (450)	0.137
VRE	242 (341)	333 (672)	0.968	267 (488)	273 (445)	0.161
DRE	294 (401)	331 (672)	**0.046**	156 (218)	278 (453)	0.233
VEA	298 (635)	330 (664)	0.502	138 (164)	274 (448)	0.390
SKA	293 (522)	331 (668)	0.969	258 (304)	273 (451)	0.111
PAA	359 (734)	322 (645)	0.655	323 (478)	260 (438)	0.235
GRQ	218 (371)	352 (705)	**0.018**	275 (502)	272 (435)	0.561
SRA	359 (649)	325 (666)	0.450	244 (431)	277 (449)	0.854
SRE	415 (968)	327 (653)	0.411	211 (398)	275 (448)	0.304
LEA	170 (282)	332 (667)	0.092	126 (167)	275 (449)	0.466
SRL	315 (518)	330 (669)	0.495	258 (397)	273 (449)	0.826
SKR	342 (796)	327 (635)	**0.046**	155 (336)	296 (461)	**<0.001**
SEA	309 (607)	334 (673)	0.086	191 (360)	287 (459)	**0.001**

*P-values generated from t-test comparing log-transformed values

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Interaction Between Antibodies to Paraoxonase 1 and PON1 rs662 Polymorphism: New Clues to Understand HDL Dysfunction and Oxidative Stress in Rheumatoid Arthritis

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Background/Purpose: Traditional and non-traditional cardiovascular (CV) risk factors underlie CV disease occurrence in rheumatoid arthritis (RA). Recently, a functional impairment of HDL antioxidant capacity has been observed. Although the actual players are unknown, anti-HDL antibodies have been associated with altered lipid profile, decreased paraoxonase 1 (PON1) activity and CV disease in RA patients. Therefore, we aimed to evaluate whether the presence of antibodies against PON1 may be involved in this scenario.

Methods: IgG anti-PON1 antibodies were quantified by ELISA in serum samples from 175 healthy controls (HC), 54 subjects with traditional CV risk factors and 212 RA patients (all fulfilling 2010 ACR/EULAR classification criteria, 56.1% RF+, 57.0% ACPA+, DAS28 median (IQR) 3.73 (2.24)). A subgroup of 13 RA patients was prospectively followed upon TNFa-blockade for 3 months. PON1 activity and total antioxidant capacity (TAC) were measured in serum. IFNg, IL-8, MCP-1, VEGF, sICAM and TNFa serum levels were assessed by immunoassays. PON1 rs662 (Q>R) status was studied by RT-PCR.

Results: IgG anti-PON1 antibodies are increased in RA patients compared to HC ($p<0.0001$) and CVR groups ($p<0.001$), even after correcting for total IgG levels. Although no associations with lipid profile were found, a positive correlation with HAQ was observed ($r= 0.215$, $p=0.004$). An ANCOVA analysis confirmed an independent effect of both rs662 status ($p<0.0001$) and anti-PON1 levels ($p=0.015$) on PON1 activity, these associations remain after adjusting for disease parameters. Anti-PON1 antibodies were negatively associated with PON1 activity and TAC, a rs662-mediated gene-dosage effect being found. The association between anti-PON1 and TAC mirrored that of found between PON1 and TAC (Table 1) after stratifying by rs662 variants. Similarly, anti-PON1 antibodies were correlated to sICAM serum levels in univariate ($r= 0.226$, $p=0.010$) and multivariate models (B[95% CI], p: 0.159 [0.065, 0.2253], <0.001). Finally, anti-PON1 serum level and TAC were not affected by TNFa-blockade.

Conclusion: Anti-PON1 antibodies can be responsible of PON1 impairment in RA patients, with a potential impact on biomarkers of oxidative status and endothelial activation. A gene-environment interaction of rs662 variants is supported. Overall, anti-PON1 may be the missing link between autoimmunity, oxidative stress and CV disease in RA.

Table 1

	QQ	**QR**	**RR**	
				p-value
	(n=95)	**(n=69)**	**(n=22)**	
Anti-PON1/IgG	11.12 (35.62)	12.60 (35.33)	14.19 (68.39)	0.548
PON1 activity (U)	217.57±86.08	345.96±115.12	418.33±101.17	<0.0001
TAC (mM, T-Eq)	3.99±0.91	3.71±0.86	3.85±0.91	0.106
sICAM-1 (pg/ml)	226.80 (168.92)	273.25 (208.56)	244.31 (278.16)	0.507
Correlations (r, p)				
Anti-PON1 – PON1 activity	r= -0.369 p=0.0002	r= -0.158 p=0.199	r= -0.310 p=0.160	
Anti-PON1 – TAC	r= -0.290 p=0.015	r= -0.259 p=0.056	r= 0.150 p=0.567	
PON1 activity – TAC	r= 0.325 p=0.006	r=0.154 p=0.241	r=0.123 p=0.639	

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Abstract Number: 1563

Enhanced Expression of mRNA for Response Gene to Complement 32 in CD34+ Cells of the Bone Marrow in Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by hyperplasia of synovial lining cells, consisting of macrophage-like type A synoviocytes and fibroblast-like type B synoviocytes. It has been appreciated that type A synoviocytes, which are also called intimal macrophages, are derived from monocyte precursors in the bone marrow (BM). Previous studies showed the accelerated generation of monocyte-lineage cells from BM progenitor cells in RA. Of note, recent studies have demonstrated that response gene to complement 32 (RGC32) is a novel membrane regulator for macrophage phagocytosis. It has been well appreciated that synovial macrophages as well as peripheral blood monocytes have enhanced capacities of phagocytosis. It is thus possible that abnormal expression of RGC32 genes in the BM might be involved in the enhanced phagocytosis of monocytes and macrophages. The current study therefore examined the mRNA expression of RGC32 in BM CD34+ cells from RA patients.

Methods: BM samples were obtained from 48 patients with RA (6 males and 42 females: mean age 58.6 years) and 31 patients with OA (3 males and 28 females: mean age 71.1 years), who gave informed consent, during joint operations via aspiration from iliac crest. CD34+ cells were purified from the BM mononuclear cells by positive selection with magnetic beads. The expression of mRNA for RGC32 was examined by quantitative reverse transcription PCR. The results are shown as the ratio of the copy numbers to those of b-actin mRNA.

Results: The expression of mRNA for RGC32 was significantly higher in RA BM CD34+ cells than OA BM CD34+ cells (Figure). The mRNA expression levels of RGC32 were not correlated with serum C-reactive protein. There were no significant differences in RGC32 mRNA expression between RA patients with MTX and those without MTX (*p=0.4788*) or between RA patients with oral steroids and those without oral steroids (*p=0.0607*). RGC32 mRNA expression was significantly correlated with nuclear factor-kappa B1 (NFkB1) (*p<0.0001,* r=0.5550) gene expression in RA BM CD34+ cells.

Conclusion: These results indicate that the enhanced expression of RGC32 mRNA in BM CD34+ cells plays a pivotal role in the pathogenesis of RA through upregulation of phagocytosis capacities of peripheral blood monocytes and synovial macrophages. Moreover, the data also suggest that the enhanced RGC32 mRNA expression might be closely associated with mRNA expression of NFkB1.

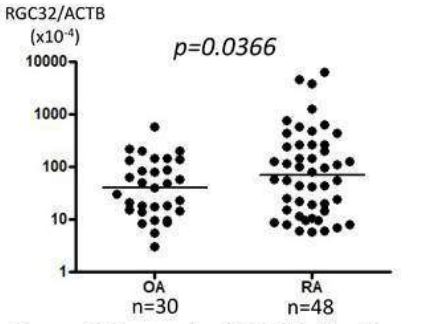

Figure: mRNA expression of RGC32 in Bone Marrow CD34+ cells from OA patients and RA patients

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Abstract Number: 1564

The Comprehensive Analysis for the Transcriptional Organization of Stimuli Responses in Fibroblast-like Synoviocytes from Rheumatoid Arthritis Patients

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Background/Purpose: Fibroblast-like synoviocyte (FLS) is expected to be a novel therapeutic target for rheumatoid arthritis (RA) because of their contribution to pathogenesis. FLS expresses matrix metalloproteinases, chemokines and cytokines in a response to various cytokines in affected joints, which leads bone and cartridge destruction, inflammatory cell recruitment and angiogenesis in pannus. The objective of this study is to investigate the transcriptional organization of stimuli responses and to clarify a character of RA-FLS.

Methods: Synovium were obtained from RA (n = 21) and osteoarthritis (OA) patients (n = 23) who underwent joint replacement surgery with informed consent. Minced synovium were treated with collagenase and cultured in Dulbecco modified Eagle's medium supplemented with 10% fetal bovine serum. At passage 2, FLS were isolated with removal of contaminating CD14 positive cells by magnetic-activated cell sorting. Purified FLS were stimulated with cytokines (TNF-α, IL-1β, IL-6/sIL-6R, IL-17A, IL-18, IFN-γ, IFN-α, TGF-β1 and combination of all 8 cytokines which simulated the mixture of stimuli in the joint) for 10 and 24 hours. Total RNA was extracted and libraries for RNA-sequence were prepared using TruSeq Stranded mRNA Library Prep kit (Illumina), and paired-end sequencing was performed using HiSeq 2500 (Illumina).

Results: The overview of transcriptomes with multi-dimensional scaling plot revealed that there were conserved transcriptome differences between RA and OA-FLS for each stimulatory condition, although the fluctuation vector with each stimuli were similar between RA and OA-FLS. Through the pathway analysis, 12 transcriptional regulators and those downstream genes were supposed to be significantly upregulated in RA-FLS compared to OA-FLS. In particular, E2F transcription factor 6 (E2F6), heat shock factor protein 1 (HSF1), Lysine (K)-specific demethylase 5B (KDM5B), nuclear protein 1 (NUPR1), tumor protein P53 (TP53) were expected to affect the downstream gene expression in stimulatory conditions compared with non-stimulatory condition. Among 1468 downstream genes of these 5 transcriptional regulators, 26 genes related to RA genome-wide association study (GWAS) were detected. Notably, colony stimulating factor 2 (CSF2), cyclin-dependent kinase 2 (CDK2) and flap structure-specific endonuclease 1 (FEN1) were significantly differentially expressed gene not only in RA-FLS compared with OA-FLS, but also in cytokine-stimulated FLS compared with non-stimulatory condition. Furthermore, through the correlation analysis, CSF2 expression which was induced by certain cytokines (IL-1β, TNF-α, all cytokine mixture) was highly correlated with particular transcription factors (i.e. JUN, FOX, JUND).

Conclusion: CSF2 was specifically expressed in RA-FLS and significantly expressed in the presence of stimulation. Although CSF2 locus was raised in RA GWAS, the expression quantitative trait loci (eQTL) effect for CSF2 gene has yet to be determined. Through comprehensive analysis, the mechanism for CSF2 expression and the pathway of RA-FLS specific transcription is expected to be elucidated.

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Abstract Number: 1565

Gene Modules Correlated with Disease Activity and Abatacept Treatment Identified with Weighted Gene Co-Expression Network Analysis of CD4+ T Cell Subsets of RA

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Background/Purpose: Although there are several reports of transcriptome analysis of peripheral blood mononuclear cells (PBMC) in RA, analysis of detailed $CD4^+$ subset and the effect of abatacept on their expression has not been reported so far. We analyzed the transcriptome of detailed $CD4^+$ T cell subsets including them after abatacept treatment, and examined the difference among $CD4^+$T cell subsets and identified gene sets that are closely associated disease activity and abatacept treatment.

Methods: PBMC were taken from RA patients (n = 10) fulfilling 2010 ACR/EULAR criteria, and healthy control (HC) (n = 10). Samples were repeatedly taken from three RA patients 6 months after abatacept treatment. Seven $CD4^+$ T cell subsets (Naive, $CD25^+$ regulatory T cell, follicular helper T cell, helper T cell subsets (Th1, Th17, Th17.1, Th2)) were sorted and total RNA was extracted. Libraries for RNA-sequence were prepared using TruSeq Stranded mRNA Library Prep kit (Illumina), and paired-end sequencing was performed using HiSeq 2500 (Illumina). 149 samples except for 12 outliers were analyzed (4 outliers because of different FACS gating strategy, 8 outliers detected with robust PCA). R version 3.2.3 was used for analysis. Knowledge-based pathway analysis were performed using Ingenuity Pathway Analysis (QIAGEN).

Results: Overview of expression using principal component analysis (PCA) revealed that the samples form RA and HC form distinct groups. Moreover, administration of abatacept exert a large shift toward the expression pattern of HC. Most of differentially expressed gene (DEG) upregulated in RA (n = 1,776) were downregulated with abatacept treatment (n = 1,349). Inversely, most of DEG downregulated in RA (n = 1,860) were upregulated with abatacept treatment (n = 1,294). Knowledge-based network analysis revealed canonical pathway and upstream analysis associated with RA $CD4^+$ subsets and administration of abatacept. While the difference among $CD4^+$ T cell subsets was not remarkable, abatacept treatment largely changed the direction of network including canonical pathway and upstream analysis. Weighted gene co-expression network analysis (WGCNA) revealed the association between gene set (module) and clinical traits. One module was detected that consist of 227 genes and highly correlated with DAS28-CRP (Spearman's rho=0.46, $p=4x10^{-9}$) and abatacept administration (Spearman's rho=-0.91, $p=5x10^{-57}$). Expression of this module differentiate the sample before abatacept treatment and after treatment. Abatacept treatment suppress this module expression and JAK3 and ZAP70 were included in top 30 gene of this module. Pathway analysis of this module revealed that abatacept treatment suppress the network under the TCR signal pathway.

Conclusion: Administration of abatacept exerts a great change on gene expression of general $CD4^+$ subsets. WGCNA identified a gene module that is closely associated with disease activity and abatacept treatment, and the network under the TCR signal pathway was supposed to be suppressed with abatacept administration.

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Abstract Number: 1566

Histone Lysine Methylation and STAT3 Differentially Regulate Constitutive and IL-6-Induced MMPs Gene Activation in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that causes progressive joint destruction. In spite of the modern medications, including biologic reagents, it is still hard to cure RA completely. A line of evidence suggests that synovial fibroblasts (SFs) play an important role in the pathogenesis of RA. RASFs produce matrix metalloproteinases (MMPs) that degrade articular cartilage. Although interleukin-6 (IL-6) is proved to be involved in the pathogenesis of RA, it is unknown whether IL-6 affects MMPs gene transcription in RASFs. Furthermore, recent advances have revealed that epigenetic mechanisms, including histone modifications, are important regulators in gene transcription. Trimethylation of lysine 4 at histone H3 (H3K4me3) is an active histone marker whereas trimethylation of lysine 27 at histone H3 (H3K27me3) is a repressive histone marker. We have hypothesized that epigenetic dysregulation might induce RASF activation. The purpose of this study is to clarify whether histone modifications are associated with MMPs gene activation in RASFs and whether IL-6 regulates MMPs expression in RASFs.

Methods: We compared MMPs gene expression by quantitative RT-PCR and histone lysine methylation in the MMP promoters by chromatin immunoprecipitation (ChIP) assay after stimulation with IL-6 and/or soluble IL-6 receptor α (sIL-6Rα) in RASFs and osteoarthritis (OA) SFs as a control. Chromatin structures in the MMP promoters were evaluated by micrococcal nuclease (MNase) assay in RASFs and OASFs. We investigated the change in the MMPs gene expression after silencing of WDR5 that is required for generating H3K4me3. IL-6 signal induces Signal Transducer and Activator of Transcription 3 (STAT3) activation. To elucidate the mechanisms of IL-6-induced MMPs gene activation in RASFs, we investigated cell surface expression of the IL-6 receptor (gp130 and membrane-bound IL-6Rα) by flow cytometry, phosphorylation of STAT3 by immunoblotting, and binding of STAT3 to the MMP promoters after IL-6 stimulation by ChIP assay in RASFs and OASFs.

Results: MMP-1, 3, 9 and 13 genes were actively transcribed in RASFs. The profiles of histone lysine methylation (H3K4me3 and H3K27me3) and the result of MNase assay indicated that chromatin structures were open in the MMP-1, 3, 9 and 13 promoters in RASFs. The depletion of WDR5 reduced the levels of H3K4me3 as well as the MMP-1, 3, 9 and 13 gene expression. Interestingly, IL-6 and sIL-6Rα significantly increased the expression of MMP-1, 3 and 13, but not MMP-9, in RASFs. Although the expression levels of gp130 as well as IL-6Rα were comparable and STAT3 was similarly phosphorylated after IL-6 stimulation in RASFs and OASFs, STAT3 bound to the MMP-1, 3 and 13 promoters, but not the MMP-9 promoter, after stimulation with IL-6 and sIL-6Rα only in RASFs. It was suggested that binding of STAT3 to the promoters resulted in MMP-1, 3 and 13 gene activation after IL-6 stimulation in RASFs.

Conclusion: Altered profiles of histone lysine methylation and binding of STAT3 to the promoters differentially regulate constitutive and IL-6-induced MMPs gene activation in RASFs and possibly arthritogenic properties of RASFs.

Disclosure: Y. Araki, None; **T. T. Wada**, None; **Y. Aizaki**, None; **K. Yokota**, None; **H. Kajiyama**, None; **Y. F. Asanuma**, None; **K. Sato**, None; **H. Oda**, None; **T. Mimura**, None.

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Abstract Number: 1567

A Functional Genomic Screen of Rheumatoid Arthritis Risk Genes in Primary Human T Cells Reveals DDX6 As a Negative Modulator of Cytokine Expression

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Background/Purpose: In rheumatoid arthritis (RA), genome-wide association studies have identified over 100 risk alleles. A major challenge is identifying causal genes in RA risk loci. As RA risk loci are enriched with many genes expressed in $CD4^+$ memory T cells, our objective was to determine which risk-associated genes regulate T cell cytokine expression and dissect relevant biologic pathways important in RA development.

Methods: A lentiviral small hairpin RNA (shRNA) library targeting ~40 RA risk genes was generated. Each RA risk gene was targeted by 5-8 shRNA clones. The shRNA was used to disrupt expression of RA risk genes in primary human $CD4^+$ memory T cells, which were negatively isolated from healthy donor peripheral blood mononuclear cells. Primary human $CD4^+$ memory T cells underwent infection, selection and then T cell receptor activation to promote cytokine expression. Enzyme-linked immunosorbent assay (ELISA) was used to measure expression of IL-10, IL-13, IL-17A and IFN- γ in culture media. Generation of relative cytokine level per cell number, line of best fit and additional analysis was performed using SAS v9.3. Rank order system was generated to identify genes that modulated cytokine expression in comparison to control shRNA. Genes identified in the primary screen were reassessed in a secondary screen and then further validated.

Results: *DDX6*, a member of the DEAD-box helicase and post-transcriptional regulator family, was identified in our screen as a negative regulator of IL-10, IL-13, IL-17A and IFN-γ expression in activated $CD4^+$ T cells. *DDX6* silencing in $CD4^+$ T cells increased cytokine expression, validating the screen findings. In addition, *DDX6* mRNA levels were elevated in resting $CD4^+$ T cells but decreased when $CD4^+$T cells are functionally activated. Loss of expression inversely correlated with cytokine expression. We then demonstrated that DDX6 (p54/Rck) physically interacts with cytokine mRNA during transcriptionally quiescent states using RNA immunopreciptation.

Conclusion: Our experimental approach provides a systematic strategy to functionally differentiate candidate RA susceptibility genes based on relevant biological pathways. Specifically, we identified *DDX6* as an important regulator of effector function of primary human $CD4^+$ T cells.

Disclosure: R. Ishizawar, EMD Millipore, 3; **C. Lester**, None; **J. Cui**, None; **J. Doench**, None; **R. Plenge**, Merck Pharmaceuticals, 3; **M. Brenner**, Roche Pharmaceuticals, 5.

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Abstract Number: 1568

Microrna-17 Suppresses TNF-α Signaling By Reducing TRAF2 and cIAP2 Association in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: TNF-α is a major cytokine implicated in rheumatoid arthritis (RA) and its expression has shown to be regulated at transcriptional and posttranscriptional levels. However, the impact of changes in microRNA (miRNA) expression on posttranslational processes involved in TNF-α signaling networks is not well-defined in RA. Here we evaluated the effect of miR-17 on TNF-α signaling pathway in human RA synovial fibroblasts (RASFs).

Methods: MiR-17 expression was correlated in SFs/synovial tissue (ST) and serum from RA, osteoarthritis (OA), or healthy (NL) donors using qRT-PCR. Expression of miR-17 was also validated in the rat adjuvant-induced arthritis (AIA) model of RA. RNA sequencing was performed in RASFs transfected with pre-miR-17 or NC-pre-miR using an Ion Proton™ System. Effect of miR-17 on the expression of TNF-α signaling proteins (TRAF2, cIAP1, cIAP2, USP2, and PSMD13) at the basal level and in TNF-α (20ng/ml) stimulated RASFs was determined using Western immunoblotting. Immunoprecipitation (IP) and Western immunoblotting methods were used to determine the effect of miR-17 on the ubiquitination processes in RASFs. Culture supernatants from miR-17 overexpressing and TNF-α-stimulated RASFs were used to study the effect of miR-17 on IL-6, IL-8, production using cytokine array (Ray Biotech). Effect of miR-17 on the nuclear translocation of p-c-Jun and p-STAT3 was studied in TNF-α-stimulated RASFs. Statistical value of $P<0.05$ was considered significant.

Results: We demonstrate that miR-17 expression was significantly low in the serum, SFs, and STs from RA patients as well as in the serum and joints of AIA rats. RNA sequencing analysis showed modulation of 664 genes by pre-miR-17 in human RASFs. Ingenuity pathway analysis of RNA sequencing data identified the ubiquitin proteasome system (UPS) in TNF-α signaling pathway as a primary target of miR-17. Western blot analysis confirmed the reduction of TRAF2, cIAP1, cIAP2, USP2, and PSMD13 expression by miR-17 in TNF-α-stimulated RASFs. IP assays showed that miR-17 restoration increased the K48-linked polyubiquitination of TRAF2, cIAP1, and cIAP2 in TNF-α-stimulated RASFs. Thus, destabilization of TRAF2 by miR-17 reduced the ability of TRAF2 to associate with cIAP2, thereby resulting in the downregulation of TNF-α-induced nuclear translocation of NF-κBp65, p-c-Jun, and p-STAT3 and the production of IL-6, IL-8, MMP-1, and MMP-13 in human RASFs.

Conclusion: This study provides a novel evidence for the role of miR-17 as a negative regulator of TNF-α signaling by modulating the protein ubiquitin processes in human RASFs.

Disclosure: N. Akhtar, None; **A. Singh**, None; **S. Ahmed**, None.

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Abstract Number: 1569

Increased Circulating CD14brightCD16+ Intermediate Monocytes Are Regulated By Interleukin-10 in Patients with Rheumatoid Arthritis

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Background/Purpose: Three different subsets of monocytes, $CD14^{bright}CD16-$ (classical), $CD14^{bright}CD16+$ (intermediate), and $CD14^{dim}CD16+$ (nonclassical) have been recently identified. It has been reported that $CD14^{bright}CD16+$ monocytes are increased in rheumatoid arthritis (RA). However, the role of each monocyte subset in the pathogenesis of RA is still unclear. The purpose of this study was to investigate the association of $CD14^{bright}CD16+$ monocytes with RA.

Methods: The study enrolled 35 untreated RA patients and 14 healthy volunteers. DAS28-ESR was evaluated and peripheral blood samples were obtained at baseline and following 12 weeks after methotrexate treatment. The three subsets of peripheral blood monocytes were analyzed by flow cytometry. Serum levels of cytokines were measured at baseline of the patients. $CD14^{bright}CD16-$

monocytes were isolated and cultured in vitro with indicated cytokines for 14 hours and assessed in CD16 induction.

Results: The proportion of $CD14^{bright}CD16+$ monocytes and serum levels of interleukin-6 (IL-6), IL-8, and IL-10 were increased in RA patients at baseline compared to healthy controls. The degree of disease activity of RA positively correlated with the proportion of $CD14^{bright}CD16+$ monocytes, while proportion of $CD14^{bright}CD16-$ monocytes had negative correlation. When isolated $CD14^{bright}CD16-$ monocytes were stimulated with IL-6, IL-8, and IL-10, IL-10 was the only cytokine that remarkably induced CD16 expression on the cells. Moreover, addition of anti-IL-10 receptor blocking antibody significantly suppressed CD16 expression on $CD14^{bright}CD16-$ monocytes compared with that of control antibody.

Conclusion: The proportion of $CD14^{bright}CD16+$ monocytes positively correlated with RA disease activity and $CD14^{bright}CD16+$ monocytes were induced from $CD14^{bright}CD16-$ monocytes by IL-10 but not by other cytokines upregulated in the sera from RA patients. Our results suggest that $CD14^{bright}CD16+$ monocytes are possibly involved in the pathogenesis of RA and IL-10 may be a key cytokine that regulates $CD14^{bright}CD16+$ monocytes.

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Abstract Number: 1570

Working in Cold Environment Is Associated with Increased Risk of Developing Rheumatoid Arthritis: Results from a Swedish Population-Based Case-Control Study

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Background/Purpose: To investigate whether working in cold environment is associated with an increased risk of developing rheumatoid arthritis (RA) (overall), anti-citrullinated protein antibody (ACPA)-positive RA and ACPA-negative RA.

Methods: Data from the Swedish population-based case-control study (Epidemiological Investigation of Rheumatoid Arthritis (EIRA)) involving 3650 incident cases and 5838 controls were analyzed. Study participants were asked through questionnaires whether they had ever worked in cold indoor or cold outdoor environment. Individuals who were exposed to working in cold environment were also asked to report their exposure duration and frequency. Only exposure up to the year when the first disease symptom appeared was considered. Exposed subjects were compared with unexposed subjects by calculating odds ratios with 95% confidence interval (CI) using logistic regression.

Results: When compared with subjects who had never worked in cold environment, the odds of developing RA (overall), ACPA-positive RA and ACPA-negative RA among those who had ever worked in cold environment were 1.5 (95%CI, 1.4-1.7) ,1.6(95%CI,1.4-1.8) and 1.4(95%CI,1.2-1.6) respectively. These results did not change substantially after adjusting for age, sex, residential area, cigarette smoking, educational level, body mass index, alcohol consumption, occupational class and occupational physical workload. The risk of developing RA increased with increasing cumulative dose of working in cold indoor environment (P for Trend <0.0001) but not working in cold outdoor environment.

Conclusion: Working in cold environment is observed to be associated with increased risk of developing both ACPA-positive and ACPA-negative RA. A dose-response relationship is found between working in cold indoor environment and risk of developing RA.

Disclosure: P. Zeng, None; **L. Klareskog**, None; **C. Bengtsson**, None; **L. Alfredsson**, None.

Abstract Number: 1571

Altered Bioenergetics, Mitochondrial Function and Pro-Inflammatory Pathways in RA Synovium in Response to Tofacitinib

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic joint disease, characterised by synovial inflammation and destruction of articular cartilage/bone. The Janus-Kinase and Signal Transducer and Activator of Transcription (JAK-STAT) signalling pathway is implicated in the pathogenesis of RA. The objective of our research was to examine the effect of tofacitinib, a selective JAK inhibitor, on metabolic activity, mitochondrial function and pro-inflammatory mechanisms in RA.

Methods: Primary RA synovial fibroblasts and *ex-vivo* RA synovial explants were cultured with tofacitinib (1μM). Expression of active phosphoSTAT3 (pSTAT3) was quantified by Western blot. The effect of tofacitinib on RA pro-inflammatory mediators, including cytokines, growth factors and matrix metalloproteinases (MMP) was quantified by ELISA and MSD multiplex assays and on RASFC invasion by Biocoat^{TM} assays. RASFC metabolism was assessed by the XF24-Flux-analyser and RASFC mitochondrial mutagenesis was quantified using a mitochondrial random mutation capture assay (RMCA). Mitochondrial function was assessed for reactive oxygen species (ROS), mitochondrial membrane potential (MMpot) and mitochondrial mass (MM) using the specific cell fluorescent probes and differential gene expression by mitochondrial gene arrays. Mitochondrial morphological structure was assessed by TEM. Lipid peroxidation (4HNE) and serum amyloid A were quantified by ELISA.

Results: IL-6, OSM and IL-17 induce pSTAT3 expression in RASFC. Tofacitinib inhibited basal, OSM- and IL-17-induced secretion of IL-6 and MCP-1 from RASFC ($p<0.05$) with no effect observed for basal and IL-17-induced IL-8 and Rantes. OSM inhibited Rantes secretion from RASFC, an effect that was reversed by Tofacitinib. In RASFC, tofacitinib significantly inhibited ROS ($p<0.05$), MM ($p<0.05$), MMpot ($p<0.05$) and induced glycolytic activity with concomitant attenuation of mitochondrial respiration. This was coupled with altered mitochondrial structural morphology in RASFC and differential regulation of mitochondrial genes, specifically inhibiting BCL2L1, TOMM24, PMAIP1, and inducing UCP-1 and SCS25A ($p<0.05$). This was also associated with changes in hypoxia response genes including HIF1a and PHD2. In RA whole tissue synovial explants, which maintain the architecture and cell-cell contact of the joint thus closely reflecting the *in-vivo* environment, tofacitinib significantly inhibited spontaneous secretion of IL-6, IL-8, IL-1b, ICAM-1, VEGF, Tie2 and MMP1 (all $p<0.05$). While tofacitinib also inhibited TNFa, IFNg and IL-12, this did not reach significance, with no effect on VCAM-1, PIGF, bFGF, 4HNE or A-SAA. Finally conditioned media from tofacitinib treated RA synovial explants inhibited RASFC invasion.

Conclusion: This study further supports JAK-STAT inhibition as a therapeutic target for the treatment of RA

Disclosure: C. Orr, None; **T. McGarry**, None; **M. Biniecka**, None; **J. McCormick**, None; **U. Fearon**, None; **D. J. Veale**, None.

Abstract Number: 1572

Relationship Between KDR (VEGFR2) Gene Polymorphisms and Serum KDR Protein Levels in Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is one of the chronic autoimmune diseases, with genetic and environmental predisposition, and synovial angiogenesis is considered to be a notable stage in its pathogenesis. Angiogenesis or vascular proliferation has been suggested to be a pivotal mechanism involved both inflammation/immune activation and joint invasion and destruction. RA may be considered an „angiogenic| disease" because it is associated with active tissue neovascularization. Vascular endothelial growth factor receptor 2 (VEGFR2; KDR) is the earliest marker for endothelial cell development, it is considered a crucial signal transducer in angiogenesis. And therefore is involved in the development of inflammation. VEGFA is the one of most potent proangiogenic molecule promoting the angiogenic phenotype of RA and is upregulated in RA. The aim of the study was to identify functional KDR variants and their possible association with KDR expression, susceptibility to and severity of RA.

Methods: 641 RA patients and of 340 healthy individuals were examined for +1416A/T KDR gene polymorphisms by PCR-RFLP method and for +889G/A and -604 T/C KDR gene polymorphisms by TaqMan SNP genotyping assay. Serum KDR levels in RA patients and controls were measured by ELISA.

Results: The +1416A/T KDR gene polymorphism under the codominant and recessive (AA+AT vs TT) models were associated with RA (p=0.02; p=0.019, respectively). The +889 G/A KDR gene polymorphism under the dominant (GG vs GA+AA) model was associated with RA (p=0.005). Furthermore, KDR -604 T/C revealed differences in the case-control distribution in codominant and dominant models (all p<0.0001). The genotype-phenotype analysis showed significant association between the KDR+889G/A and Larsen score (p=0.03), VAS score (p=p<000.1), DAS-28 score (p=p<0.0001), HAQ sore (p=0.02), number of swollen joints (p<0.0001), mean value of ESR (p=0.006), mean value of CRP (p<0.0001), and mean value of creatinine (p=0.02). Additionally the number of women with the polymorphic allele +889 A was higher than the number of women with wild type allele -+889 G (p<0.0001). Serum KDR levels were significantly higher in RA patients than in control groups (p=0.002).

Conclusion: Present findings indicated that KDR genetic polymorphism may be associated with the susceptibility to and severity of RA in the Polish population.

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Abstract Number: 1573

Major Histocompatibility Antigen HLA-DQ6.1 (DQA1*0103/DQB1*0601) Increases Rheumatoid Arthritis Risk Independent of Shared Epitope Among Indians

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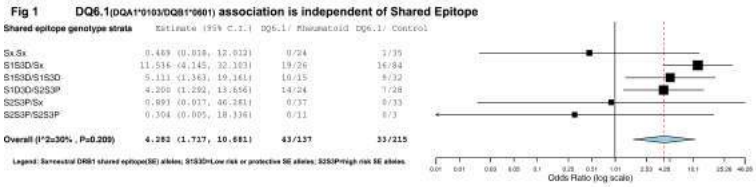
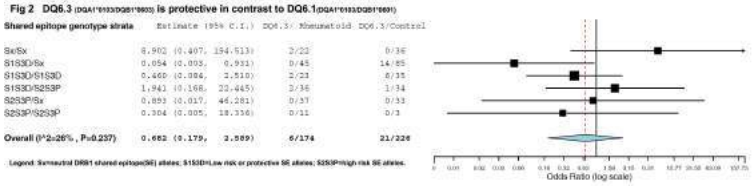
Background/Purpose: The association of HLA-DRB1 shared epitope (SE) with rheumatoid arthritis (RA) does not completely explain MHC association. The HLA-DRB1 alleles are classified into high risk (S2, S3P), low risk (S1, S3D) and neutral (Sx) alleles which increase, decrease or do not affect RA risk respectively. Unlike HLA-DR antigens, HLA-DQ is polymorphic at both alpha and beta chains. DQA1*0103 and DQB1*0601 that form the DQ6.1 heterodimer are autoimmune prone and are associated with achalasia cardia, HashimotoÕs thyroiditis and autoimmune hepatitis). They are common in Japan and India but rare outside Asia. DQ6.3(DQA1*0103/DQB1*0603) was reported to be protective in Finland population. We studied the association of HLA-DQ6 isoforms with RA after controlling for shared epitope.

Methods: 181 patients with RA fulfilling ACR 1987 criteria were recruited from a tertiary referral center in North India along with 250 healthy controls from the same ethnic and regional background. Molecular typing of HLA-DRB1, HLA-DQA1 and HLA-DQB1 alleles were done using PCR and SSOP (sequence specific oligo probe). Subjects were classified into risk strata based on HLA-DRB1 shared epitope genotype. Logistic regression was used to study association. Subjects were risk stratified based on the shared epitope genotype to study the interaction between SE alleles and DQ6.1

Results: The mean age of patients were 37.2(±10.2) years at onset and 74% were female. 76.1% were RF positive and 16.5% had extra-articular manifestations. 43(23.8%) of RA patients had DQ6.1 against 33(13.3%) controls (Odds ratio 2.01, P=0.007). DQ6.3(DQA1*0103/DQB1*0603) was present in 3(1.7%) patients against 16(6.4%) controls (OR 0.37, P=0.037). High risk SE alleles S2 or S3P were present in 84/179 (47%) patients and 73/249 (29%) controls (OR 2.1, P<0.001). Low risk SE alleles S1 or S3P were present in 104/179(58%) of rheumatoid and 178/250 (81%) of controls (OR 0.70, P=0.016). On multivariate analysis, the OR for DQ6.1 increased to 2.76 (P<0.001) while high risk SE alleles S2/S3P had OR 1.99 (P=0.001). After adjustment for SE genotype by stratification and meta-analysis (Fig 1), OR for DQ6.1 further increased to 4.3(1.7-10.7 P=0.002). Both DQ6.1 and DQ6.3 (Fig 2) were in linkage with low risk SE alleles but not high risk alleles.

Conclusion: HLA-DQ6.1 (DQA1*0103/DQB1*0601) is an independent genetic risk factor for Rheumatoid Arthritis in North Indians especially those negative for high risk DRB1 shared epitope alleles. Protective effect of HLA-DQ6.3 (DQA1*0103/DQB1*0603) requires further study.





Disclosure: A. Lawrence, None; **S. Prakash**, None; **U. Bharadwaj**, None; **A. Aggarwal**, None; **R. Misra**, None; **S. Agrawal**, None.

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Abstract Number: 1574

The Role of Shelterin Deficiency in the Senescence in T Cells of Rheumatoid Arthritis

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Background/Purpose: T cells abnormality is an essential part in the pathogenesis of rheumatoid arthritis (RA), which includes a signature of premature immune aging, and restricted proliferative potential of naïve T cells. Shelterin complex is critical for maintaining Telomeres, which are important regulators of aging. We hypothesized that shelterin deficiency may play a key role in the senescence of RA T cells.

Methods: Naïve CD4 T cells were isolated from **29** Newly-onset treatment-naive RA patients and 38 gender-and age- matched healthy controls (HC) . The expression of six shelterin subunits was assessed in naïve and activated CD4 T cells. Critical DNA damage responses and the role of TRF2 in cell apoptosis were tested as well.

Results: The mRNA levels of subunits TRF1, TRF2, Rap1 and TPP1, except POT1 and TIN2, were significantly lower in RA naïve CD4 T cells compare with those from HC. TCR stimulation significantly up-regulated all subunit expression in both group in a time-dependent manner, but the level of healthy controls remained higher than RA patients. Additionally, the deficiency of shelterin subunits were independent of disease activity (measured by DAS28), disease duration or treatment. Consistently, DNA lesions related to apoptosis triggers, including ATM, CHK2, H2AX histone, p53, p21 and GADD45, were up-regulated in RA naïve CD4 T cells compared with HC. Finally, by TRF2-silencing, we showed loss of telomere protection by shelterin ultimately resulted in ATM-p53-dependent DNA damage response in naïve CD4 T cells, which was correlated with caspase-3 activation.

Conclusion: Shelterin deficiency of naïve CD4 T cells in RA patient may be involed in the perturbed T cell homeostasis, and restore T cell competence may be a potential therapeutic target.

Disclosure: W. Zheng, None; **L. Zhang**, None; **H. Chen**, None; **Y. Zhao**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-role-of-shelterin-deficiency-in-the-senescence-in-t-cells-of-rheumatoid-arthritis

Abstract Number: 1575

Transient Circulatory Existence of Multipotential Stromal Cells Is Unlikely to Contribute to the Pathogenesis of Rheumatoid Arthritis

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Session Date: Monday, November 14, 2016
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Session Time: 9:00AM-11:00AM

Background/Purpose: Circulating multipotential stromal cells (MSCs) also termed mesenchymal stem cells have previously been implicated in fibroblast mediated polyarticular joint destruction in rheumatoid arthritis (RA). We hypothesized that skeletal trauma (a biophysical process) rather than a biological basis related to RA may account for any MSC circulation.

Methods: Deep (femoral) and matched peripheral (antecubital) vein blood was collected from 36 patients undergoing lower limb orthopaedic procedures. Peripheral blood was also taken from 15 early and 11 established RA patients as well as 12 healthy controls. Colony-forming unit-fibroblast (CFU-F) assays and cytometric phenotyping of cells were performed. Molecular characterisation of genes related to MSC function was undertaken in comparison to MSCs from iliac crest and femoral marrows, bone, periosteum, adipose tissue and dermal fibroblasts.

Results: 17/36 femoral vein samples contained CFU-Fs, but only 7/74 peripheral vein samples almost exclusively from the orthopaedic cases with only a single peripheral blood colony from one established RA patient. The MSC nature of CFU-Fs was confirmed by expansion and phenotype: CD105/CD73/CD90 positivity and CD19/CD31/CD33/CD34/CD45/CD61 negativity. Their molecular profiles were typical of MSCs with 39/80 genes showing similarity across multiple MSC tissue controls; including osteogenesis-related *ALPL, COL1A1, SPARC,* adipogenic *LPL,* chondrogenic *COL2A1, COL10A1, SOX9* and immature *POU5F, NANOG*, but not fibroblasts.

Conclusion: There is no evidence that MSCs circulate in RA or health. Deep vein MSC numbers may relate to biophysical micro-damage to the trabecular vascular architecture caused by skeletal manipulation. Their numbers are so low that a biological role seems unlikely in early RA or other autoimmune diseases.

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Abstract Number: 1576

Identifying Rheumatoid Arthritis Subtypes Using Synovial Tissue Gene Expression Profiling, Histologic Scoring and Clinical Correlates

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Background/Purpose: The histopathologic features of synovial tissue vary widely among patients with rheumatoid arthritis (RA) undergoing arthroplasty and the clinical significance of this variability is unknown. Improved methods for assessing synovial histopathology could help characterize subtypes of RA and predict clinical outcomes.

Methods: 149 RA patients undergoing total hip or knee arthroplasty were enrolled. 130 synovial tissue samples were stained with hematoxylin and eosin and assessed for 20 histologic features such as lymphocytic infiltrates, neutrophils, mucoid change, vascularity, synovial lining hyperplasia, detritus, fibrin, plasma cell inflammation, binucleate plasma cells, germinal centers, Russell bodies, mast cells, giant cells and synovial giant cells. 19 of the synovial samples were disaggregated and their synovicoytes analyzed by RNA sequencing. We used a standard unsupervised hierarchical clustering approach to group samples and genes with similar expression

profiles. Using the resultant RNAseq sample clusters, we applied a machine learning algorithm (standard Support Vector Machine) using binarized histology features and a leave-one-out cross-validation approach. The model was able to accurately predict which RNAseq cluster a given sample would most likely belong to, suggesting good harmony between the genomic data and the histology. We then used our histology SVM model derived on the 19 samples to cast cluster predictions on the broader set of 130 synovial samples, for which we had complete histology data but no RNAseq.

Results: Unsupervised hierarchical clustering of 19 synoviocyte samples based on genome-wide RNA expression levels identified 2 well-separated subtypes of synovial tissue composition that distinguished samples based on the level of inflammatory cell presence, and a third subgroup within the low-inflammatory cell subset that suggests further subclassification of RA synovial tissue based on non-immune cell types. Confirming the validity of this approach, histology scoring of lymphocytic infiltrates correlated significantly with the RNAseq clusters containing the highest level of hematopoietic lineage transcripts. Furthermore, clinical features such as ESR and obesity correlated with the subsets defined by the RNAseq analyses. Gene set enrichment analysis of differentially expressed genes between the clusters showed variable levels of immune and stromal cell subsets, noting particular differences in IFNg responses. Application of the histology SVM models to the remaining ~100 samples generated predictions of RA synovial gene expression subtypes, which together with ongoing studies connecting clinical parameters to this model suggest an approach to subclassify the disease with greater specificity.

Conclusion: Gene expression clusters derived from RNAseq were used to train a histology scoring system to distinguish between inflammatory and noninflammatory RA synovial tissue. SVM weights indicate that lymphocytic infiltrates, plasma cells, fibrin and synovial lining hyperplasia are predicted to be associated with inflammatory gene expression, while mast cells, vascularity, detritus and mucoid changes are predicted to associate with non-inflammatory samples.

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Abstract Number: 1577

An Investigation of Translocator Protein As a Tissue and Peripheral Blood Biomarker of Inflammation in Rheumatoid Arthritis

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Background/Purpose: Translocator protein (TSPO) is a mitochondrial cholesterol transporter, utilised in diseases as a Positron Emission Tomography (PET) imaging marker of macrophage infiltration. Recent observations support its utility as a PET marker in rheumatoid arthritis (RA), predictive of persistent synovitis and response to treatment. Here, we use synovial tissue taken from areas of known increased TSPO PET tracer uptake *in vivo*, to profile the expression of TSPO within cellular components found within synovium. We further investigated the potential of TSPO as a peripheral blood biomarker of disease activity in RA.

Methods: 10 patients with RA and clinical evidence of knee synovitis were included. Each patient underwent PET-CT of knees with PBR28, a PET tracer targeted to TSPO followed by synovial biopsy within 7 days. Formalin fixed paraffin embedded tissue sections were generated, and stained for macrophage markers CD68, CD163 and the fibroblast activation marker gp38. Peripheral blood mononuclear cells were collected just prior to PET, and lysed for RNA and protein. From surgically obtained synovium in patients with active RA, Fibroblast-like synoviocytes (FLS), monocytes and lymphocytes, were isolated and lysed for RNA and protein analysis. Macrophages were generated by stimulation of synovial monocytes with M-CSF for 7 days. FLS and monocyte-derived macrophages were further stimulated with TNF alpha before being harvested for RNA and protein analysis. Cells from synovium, as well as

monocyte derived macrophages, were also incubated with PBR28 tracer to assess tracer uptake in each cell type.

Results: A positive correlation between PBR28 tracer uptake, clinical synovitis, and semi-quantitative staining scores for TSPO, CD68, CD163, and gp38 was observed (see table). At both RNA and protein level, TSPO was expressed most highly in monocyte derived macrophages, and FLS treated with TNF for 24 hours, being negligible in synovial derived lymphocytes, monocytes and unstimulated FLS; findings that were mirrored by PBR28 uptake radioassay of these cell groups. There was an average 3 fold increase in TSPO expression at mRNA level in peripheral blood mononuclear cells of treatment naïve arthritis patients with clinically active disease, independent of CRP, compared with healthy controls, with TSPO expression correlating with tender and swollen joint count.

Conclusion: Our work demonstrates that TSPO imaging is likely to reflect FLS activation in the synovium as much as it is macrophage infiltration. For treatment-naïve patients, there appears to be a statistically significant, higher expression of TSPO in peripheral blood compared to healthy controls, at both RNA and protein level. Further studies are needed to profile TSPO cell expression in inflammation and ascertain whether TSPO may be a sensitive peripheral blood marker in patients with rheumatoid arthritis.

Table 1: semi-quantitative staining scores of knee synovial biopsy tissue for TSPO, CD68, CD163 and gp38, in relation to clinical synovitis scoring, and PBR28 tracer standardised uptake values (SUV).

Clinical synovitis severity score	PBR28 tracer uptake (SUV) from same knee compartment as biopsy site	TSPO staining score	CD68 staining score	CD163 staining score	gp38 staining score
3 (severe synovitis)	1.3±0.2	3.5±0.4	3.1±0.3	2.5±0.4	2.7±0.3
2 (moderate synovitis)	0.7±0.2	1.7±0.9	1.8±0.5	1.5±0.3	1.6±0.5
1 (minimal synovitis)	0.3±0.1	0.5±0.4	0.4±0.2	0.2±0.1	0.5±0.1

Disclosure: N. Narayan, None; **F. Carlucci**, None; **P. C. Taylor**, None.

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Abstract Number: 1578

Functional Screening of Microrna Using the Inhibitor Library Identified Microrna to Regulate Expression of MMP-3 and IL-6 in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: Synovial fibroblasts play crucial roles in the pathogenesis of rheumatoid arthritis (RA). They secrete proteinases and proinflammatory cytokines to damage the synovial tissues in the RA joints. Their functions are regulated by a number of molecules including microRNAs (miRNAs). MiRNAs are endogenous small noncoding RNAs, and suppress expression of target genes

by binding to 3'- untranslated region (UTR) of the corresponding messenger RNAs. The present study was conducted to identify miRNAs to regulate expression of matrix metalloproteinase-3 (MMP-3) and interleukin-6 (IL-6), which are crucial in the pathogenesis of RA.

Methods: Nine hundred and twenty-four inhibitors of human miRNAs were transfected individually into synovial fibroblast cell lines developed from the RA synovial tissues. The transfected cells were cultured in the presence or absence of 1 ng/ml TNF-α for 24-72 hours. The expression levels of MMP-3 and IL-6 were quantified with enzyme-linked immunosorbent assay. The expression level of ets variant 6 (ETV6) was determined with Western blotting and quantitative polymerase chain reaction analysis. MiRNA array analysis was conducted for evaluation of the miRNA expression levels in the synovial fibroblasts with or without the TNF-α stimulation.

Results: Functional screening of 924 miRNAs using miRNA inhibitor library identified 14 miRNAs to regulate expression of MMP-3 in synovial fibroblasts. Out of these miRNAs, miR-103, miR-129-5p, miR-135a and miR-193b have seed sequence that match with 3' UTR of ETV6, which is a transcriptional repressor of MMP-3. The effects of the four miRNA inhibitors on MMP-3 expression were validated with independent experiments. Inhibitors of miR-103 and miR-129-5p suppressed the expression level of IL-6. The four miRNA inhibitors increased the protein expression of ETV6 without upregulating the mRNA level. MiRNA array analysis revealed that the expression levels of miR-103, miR-129-5p and miR-135a in synovial fibroblasts were increased when they were stimulated with TNF-α.

Conclusion: Functional screening of miRNAs using the inhibitor library identified miR-103, miR-129-5p, miR-135a and miR-193b, which target ETV6, as regulators of MMP-3 and IL-6 expression in RA synovial fibroblasts. These miRNAs could be novel drug targets in RA.

Disclosure: F. Mizoguchi, None; **H. Hasegawa**, None; **H. Kohsaka**, None.

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Abstract Number: 1579

Small Rnaseq Reveals Different Plasma miRNA Signature in Patients with RA and SLE: A Pilot Study

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Background/Purpose: MicroRNAs (miRNAs) are ~22-nt RNAs that post-transcriptionally regulate gene expression and serve as biomarkers of many disease states. Most previous plasma miRNA studies in inflammatory autoimmune diseases have relied on PCR or microarray for candidate miRNAs based on limited information about miRNA function; however, unbiased small RNA sequencing (sRNAseq) could reveal new miRNA disease biomarkers. We hypothesized that plasma miRNAs are altered in inflammatory autoimmune diseases (RA and SLE) compared to control subjects and are differentially altered in RA and in SLE.

Methods: This cross-sectional study included patients with RA, SLE, and age, race and sex matched control subjects (N=12, each). Sequencing was done by Illumina HiSeq3000. High quality reads were mapped to the human genome using Bowtie1. MiRBase21.0 was used to quantify miRNAs. All samples had ≥1 million miRNA reads, and miRNAs having ≥10 reads per sample were analyzed. Reads per mapped read were compared between RA, SLE and control subjects. Significantly altered miRNAs with ≥1.5 fold difference were examined. Putative miRNA targets were generated using TargetScanHuman 7.1 and compared to disease-related pathway genes using the KEGG database.

Results: Significantly elevated plasma miRNAs in patients with RA and SLE compared to control subjects (Table 1) were miR-24-3p and miR-345-5p, which are predicted to target mRNAs encoding interferon gamma or its receptor and HLA-DOA, HLA-DPB1, HLA-

DRB1, and HLA-DRB5. Significantly altered plasma miRNAs in SLE compared to RA and control subjects (Table 2) included miR-194-5p, miR-424-3p, let-7d-5p, miR-652-3p, miR-548o-3p, miR-335-5p, let-7a-3p, miR-369-3p, miR-204-5p, and miR-98-3p, some of which are predicted to target histone and complement proteins, IL10, SSA, and NMDA receptors. Significantly increased plasma miRNAs in RA compared to SLE and control subjects (Table 3) included miR-501-3p, miR-450b-5p and miR-22-3p, some of which are predicted to target TGF beta or its receptor, TLR4, IL6 and IL17.

Conclusion: Several miRNAs in plasma measured by sRNAseq are differentially altered in patients with RA and SLE. Many of the altered miRNAs have predicted targets in disease-related pathways. Further validation is necessary to confirm these findings.

Table 1. Altered miRNAs in both SLE and RA compared to control subjects

	SLE vs Control subjects		RA vs Control subjects	
	Fold diff	P	Fold diff	P
miR-24-3p	3.66	3.70E-02	1.51	1.91E-02
miR-345-5p	1.56	4.61E-02	1.60	1.46E-02

Table 2. Altered miRNAs in SLE compared to both RA and control subjects

	SLE vs Control subjects		SLE vs RA	
	Fold diff	P	Fold diff	P
miR-194-5p	3.74	1.38E-02	3.10	2.04E-02
miR-424-3p	2.14	9.11E-04	1.60	1.88E-03
let-7d-5p	1.77	3.72E-02	1.97	1.04E-02
miR-652-3p	1.59	2.14E-03	1.54	1.66E-03
let-7c-5p	1.53	3.48E-02	1.85	5.34E-04
miR-548o-3p	-1.59	7.34E-03	-1.64	1.20E-02
miR-335-5p	-1.85	4.08E-02	-2.08	3.43E-03
let-7a-3p	-2.04	5.89E-03	-2.22	1.31E-02
miR-369-3p	-2.17	2.28E-02	-1.75	1.89E-02
miR-204-5p	-2.56	2.50E-02	-1.85	2.58E-02
miR-98-3p	-2.63	1.82E-03	-2.08	2.92E-02

Table 3. Altered miRNAs in RA compared to both SLE and control subjects

	RA vs Control subjects		RA vs SLE	
	Fold diff	P	Fold diff	P
miR-501-3p	1.91	4.83E-03	1.67	2.73E-02
miR-450b-5p	1.61	3.44E-02	1.85	1.12E-02
miR-22-3p	1.54	3.59E-02	1.67	1.65E-02

Disclosure: M. J. Ormseth, None; **J. F. Solus**, None; **Y. Guo**, None; **Q. Sheng**, None; **R. Allen**, None; **K. C. Vickers**, None; **C. M. Stein**, None.

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Abstract Number: 1580

Impact of Rituximab on Patient-Reported Outcomes in Patients with Rheumatoid Arthritis from the US Corrona Registry

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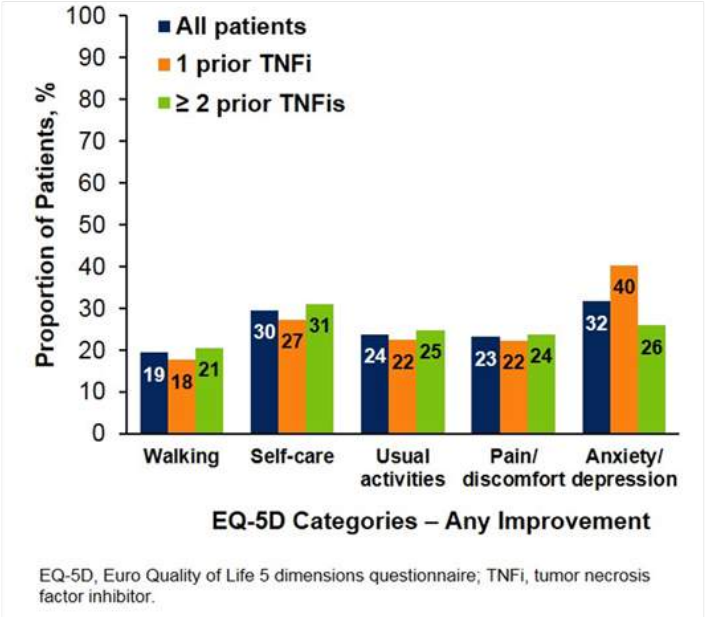
Background/Purpose: Patients with rheumatoid arthritis (RA) experience diminished quality of life and increased disability. Patient-reported outcomes (PROs) are important measures of response to therapy in patients with RA. The objective of this study was to examine the impact of rituximab on PROs in a US observational cohort of patients with RA.

Methods: Between March 1, 2006, and September 1, 2015, patients with RA who had prior exposure to ≥ 1 tumor necrosis factor inhibitor (TNFi) and newly initiated rituximab while not in remission (Clinical Disease Activity Index [CDAI] > 2.8) with a follow-up visit at 1 year (± 3 months) were identified. Changes in PROs, assessed 1 year from baseline and stratified by prior TNFi use, included patient global assessment (PtGA) of disease, pain and fatigue (visual analog score; 0-100); morning stiffness (hours); modified Health Assessment Questionnaire (mHAQ; 0-3) and Euro QoL 5 dimensions questionnaire (EQ-5D). Improvement in EQ-5D domains was defined as patients reporting improvement or resolution of impairment among those who reported impairment at baseline. Outcomes between the 1 and ≥ 2 prior TNFi groups were compared using χ^2 or *t*-tests, as appropriate; only statistically significant differences were noted.

Results: Of the > 40,000 patients in the Corrona RA registry, 667 patients met the study inclusion criteria; 284 (43%) had received 1 prior TNFi and 383 (57%) had received ≥ 2 prior TNFis. Overall, 79% of patients persisted on rituximab through 1 year, 80% of whom received retreatment. The median (IQR) age was 59 (50-66) years; 79% were female. Baseline mean (SD) CDAI was 25.6 (13.9; high disease activity = CDAI > 22). At baseline, patients were substantially impaired by their disease: patients reported median (IQR) PtGA, pain, fatigue and mHAQ scores of 50 (35-73), 60 (31-75), 65 (40-80) and 1 (0.6-1.6), respectively, and a median (IQR) of 1 (0.5-2) hour of morning stiffness. Baseline PROs were mostly similar between the 1 and ≥ 2 prior TNFi groups, although patients with 1 prior TNFi tended to have longer duration of morning stiffness and higher fatigue scores. At 1 year, improvements were reported in all PROs with no significant difference between patients with 1 or ≥ 2 prior TNFis. Overall median (IQR) improvements (baseline value minus the 1-year value) in PtGA, pain and fatigue were 7 (−10 to 25), 7 (−5 to 25) and 9 (−5 to 20), respectively. Improvement in EQ-5D categories is shown (**Figure**). 51.7% of patients reported no improvement in morning stiffness, 28.5% reported improvement of 1-60 minutes and 19.8% reported improvement of > 60 minutes.

Conclusion: Real-world data showed that quality of life in this cohort of patients with long-standing, refractory RA and prior TNFi exposure was substantially impacted by the disease. One year after initiation of rituximab, improvements were reported in all PROs, such as self-care and usual activities, and were similar between patients with exposure to 1 or ≥ 2 prior TNFis.

Figure. Improvement in EQ-5D Categories at 12 Months Among Rituximab Initiators Who Reported Impairment at Baseline



EQ-5D, Euro Quality of Life 5 dimensions questionnaire; TNFi, tumor necrosis factor inhibitor.

Disclosure: L. R. Harrold, Corrona, LLC, 3,Corrona, LLC, 1,Pfizer Inc, 2,Roche Pharmaceuticals, 5; **A. John**, Genentech, Inc., 3; **J. Best**, Genentech, Inc., 3; **S. Zlotnick**, Genentech, Inc., 3; **C. Karki**, Corrona, LLC, 3; **Y. Li**, None; **J. D. Greenberg**, Corroma, LLC, 1,Corrona, LLC, 3,AstraZeneca, Celgene, Genentech, Janssen, Novartis and Pfizer, 5; **J. Kremer**, Corrona, LLC, 1,Corrona, LLC, 3,Abbvie, Amgen, BMS, Genentech, GSK, Lilly, Medimmune, Pfizer and Sanofi, 5.

Abstract Number: 1581

The Combination of IL-6 and IL-6 Receptor Levels As a Biomarker of Response to Tocilizumab in Rheumatoid Arthritis Patients

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Background/Purpose: Several predictors of response to tocilizumab have been described. They include a low HAQ, high baseline CRP or NK levels and certain IL-6R polymorphisms. IL-6 and sIL-6R levels have also been considered as response predictors, but with contradictory results. However, the combination of them has not been studied.

Methods: Heparinized peripheral blood was obtained from 10 healthy donors and 63 RA patients meeting the ACR criteria. In all patients, RA was refractory to treatment with DMARDs, including methotrexate. Tocilizumab treatment was begun following European and Spanish guidelines. Plasma was collected prior to first infusion(baseline), at 4 and at 12w. Laboratory analysis included an haemogram, ESR, CRP, Igs, RF, ACPAs, IL-6 and sIL-6R concentrations. Clinical data collected was DAS28, SDAI, CDAI and EULAR response criteria. *K*-means clustering (SPSSv.18) analysis was applied to identify groups of patients based on IL-6 and sIL-6R concentrations.

Results: Three statistical significant clusters of RA patients were defined by IL-6 and sIL-6R concentrations at baseline: Group 1 with the highest levels of IL-6 and low levels of sIL-6R; Group 2 with low levels of IL-6 and sIL-6R; and Group 3 with the highest levels of sIL-6R (fig. 1). Baseline clinical data of RA patients in each group are presented in Table 1. DAS28 was markedly reduced after 24 weeks of treatment in all groups of patients (group 1: 6.09±0.24 to 3.55±0.46 at t=24w, p=0.001; group 2: 4.68±0.32 to 2.66±0.22 at t=24w, p=0.001;group 3: 6.04±0.30 to 2.89±0.34 at t=24w, p=0.0001). Patients in group 1 achieved the highest rate of remission (60% vs.27% in group 2 and 18% in group 3,p <0.04) and the highest rate of good EULAR response (83,3% vs. 44% and 30.8% in group 3) (fig.2). IL-6 levels, that correlated with RF and IL-15 levels, SDAI and CDAI, did not substantially change after 12w of tocilizumab. On the other hand, sIL-6R levels increased significantly in most patients(93.6%) after 4w of tocilizumab. After 12w, sIL6R levels in all patients of group 1 were still high, and they decreased in 50% of patients of group 3. sIL-6R levels inversely correlated with leukocyte counts/mL and with VSG, PCR and DAS28.

Conclusion: Combination of biomarkers IL-6 and sIL6R is more useful to discriminate those patients with the best response outcome to tocilizumab than both of them separately.

Table 1.

	Group 1 (n=19)	Group 2 (n=30)	Group 3 (n=14)
Age; years mean ± SEM	63.42±2.34	55.77±2.41	64.07±3.20*
Sex % (n)women	84.21 (16)	93.33 (28)	85.71 (12)
Years of evolution mean (range)	11.00 (1-24)	12.00 (2-35)	22.50 (5-33)*
Corticoids % (n)	57.89 (11)	76.67 (13)	78.57 (11)
Monotheraphy % (n)	52.63 (10)	30.00 (9)	71.43 (10)*
MTX % (n)	31.58 (6)	43.33 (13)	21.43 (3)
Others % (n)	15.79 (3)	26.66 (8)	7.14 (1)
Previous DMARDs mean± SEM	2.33±0.33	2.47±0.26	2.86±0.41
Previous biological therapies mean± SEM	1.79±0.30	1.03±0.18	1.43±0.19
HAQ mean± SEM	1.55±0.16	1.37±0.16	1.45±0.12
DAS28 mean± SEM	6.00±0.30	5.50±0.20	5.83±0.31
ESR mm/h mean± SEM	45.61±5.65	44.83±5.15	44.71±8.29
CRP mg/L mean± SEM	20.69±5.13	14.49±4.64	10.51±3.89
CCp + %(n)	73.68 (14)	60.00 (18)	78.57 (11)
CCp (UI/ml)	764.71±252.69	602.75±259.32	390.27±145.62
RF + %(n)	84.21 (16)	53.33 (16)	71.42 (10)
RF (UI/ml)	566.89±133.33	378.08±215.85	768.12±546.61

*p<0.05

Fig. 1

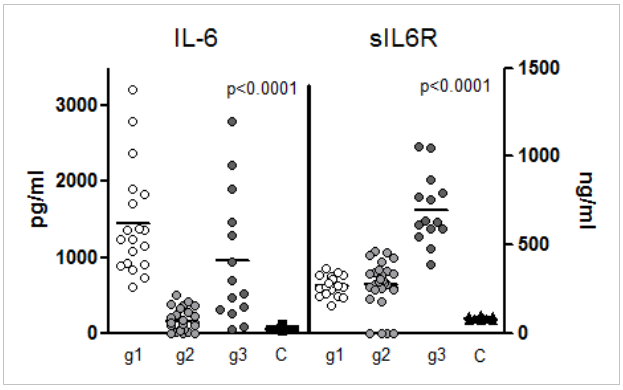
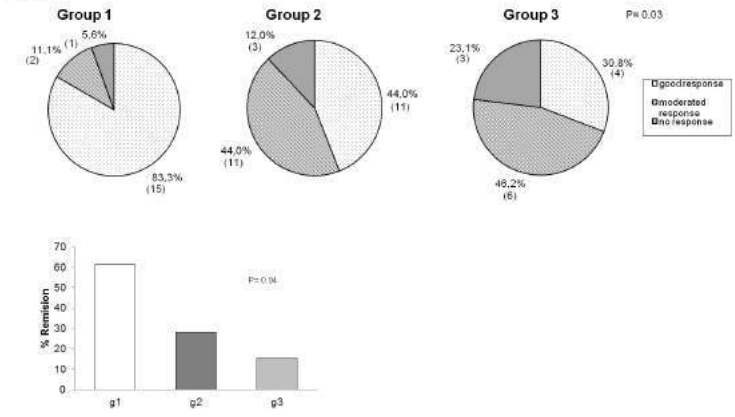


Fig. 2



Disclosure: C. Diaz-Torne, None; **M. A. Ortiz**, None; **P. Moya**, None; **M. V. Hernández**, None; **D. Reina**, None; **I. Castellvi**, None; **J. J. De Agustin**, None; **D. De La Fuente**, None; **H. Corominas**, None; **R. Sanmarti**, None; **J. M. De Llobet Zubiaga**, None; **S. Vidal**, None.

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Abstract Number: 1582

Assessment of Safety, Pharmacokinetics and Pharmacodynamics of a Novel Anti-

CD40 Monoclonal Antibody, CFZ533, in Healthy Volunteers and in Rheumatoid Arthritis Patients

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Aberrant CD40-CD154 pathway signaling has been linked to pathology in autoimmune disease. Blocking the CD40-CD154 pathway prevents T cell-dependent antibody responses, germinal center formation and prolongs renal allograft survival in non-human primates. CFZ533 is a novel, fully human, non-agonistic Fc-silent, anti-CD40 monoclonal antibody being developed for treatment of autoimmune diseases and prevention of rejection in solid-organ transplantation. The objective of present study was to assess the safety, pharmacokinetics (PK) and pharmacodynamics activity (PD) of CFZ533 in humans

Methods: A double-blind, placebo controlled, ascending, single-dose study was conducted in 48 healthy volunteers (HVs) receiving 0.03, 0.1, 0.3, 1.0, 3.0 mg/kg i.v., 3.0 mg/kg s.c. CFZ533 or matching placebo (3:1) as well as in 12 rheumatoid arthritis (RA) patients receiving 10.0 mg/kg i.v. CFZ533 or placebo (1:1). HVs were immunized with a single intramuscular dose of a T-cell dependent neo-antigen, Keyhole Limpet Hemocyanin (KLH) with alum adjuvant on Day 3 and again between Day 29-85 depending on predicted loss of CD40 receptor occupancy (RO) as a function of CFZ533 dose. Blood samples for PK, CD40 RO and anti-KLH IgG and IgM profiling were collected at multiple time points during the study. Anti-KLH antibodies were assessed using a validated human ELISA system with an LOQ of 0.7 (IgG) and 2.1 (IgM) µg/mL. RA patients were evaluated for safety, PK and RO

Results: All doses of CFZ533 and KLH were safe and well tolerated. CFZ533 PK concentrations were quantifiable at all dose levels tested. Complete (≥90%) peripheral CD40 RO by 3.0 mg/kg i.v. CFZ533 in HVs was maintained for 28 days. During this period of full RO, full suppression of the primary humoral response to KLH was evident in all treated subjects (KLH administered 2 days after CFZ533 dosing). After complete CFZ533 washout in 3.0 mg/kg cohort, all subjects mounted a robust anti-KLH response following a re-challenge on Day 85. Full RO in RA patients who received 10.0 mg/kg i.v. CFZ533 was maintained for at least 6 weeks and up to 10 weeks

Conclusion: The favorable safety and tolerability profile of CFZ533 coupled with a predictable concentration-CD40 receptor occupancy relationship and suppression of a primary T cell-dependent antibody response supports future clinical trials of CFZ533 in select autoimmune diseases and transplantation

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Disclosure: A. Slade, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, 3; **P. Koo**, Novartis Pharmaceuticals Corporation, East Hanover, NJ, USA, 3; **Y. He**, Novartis Pharmaceuticals Corporation, Cambridge, MA, USA, 3; **P. Espie**, Novartis Pharmaceuticals Corporation, Basel, Switzerland, 3; **A. Auger-Sarrazin**, Novartis Pharmaceuticals Corporation, Basel, Switzerland, 3; **J. S. Rush**, Novartis Pharmaceuticals Corporation, Basel, Switzerland, 3; **P. Gergely**, Novartis Pharmaceuticals Corporation, Basel, Switzerland, 3.

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Abstract Number: 1583

Body Mass Index Does Not Affect Response to Subcutaneous or Intravenous Abatacept in Patients with Rheumatoid Arthritis

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[6]Excelya, Boulogne-Billancourt, France, [7]Catholic University of the Sacred Heart, Rome, Italy
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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: High BMI is associated with reduced remission rates with anti-TNF agents in RA.[1,2] In ACQUIRE (NCT00559585), SC and IV abatacept (ABA) achieved similar ACR20 responses at 6 months (M)[3] and therapeutic trough concentrations[4] across body weight groups in patients (pts) with RA. This *post hoc* analysis explored clinical outcomes reflecting disease status and pharmacokinetics with SC (fixed dose) or IV (weight-tiered) ABA by BMI.

Methods: In ACQUIRE, pts with RA and MTX inadequate response were randomized (1:1) to SC (125 mg/week) or IV (~10 mg/kg/M) ABA plus MTX. Disease status over 6 M was assessed by DAS28 (CRP) (<2.6), SDAI (≤3.3) and CDAI (≤2.8) remission, mean change in Pt Global Assessment, TJC and SJC, and high-sensitivity CRP (hsCRP). Trough (C_{min}) serum ABA concentrations were measured at 3 and 6 M. Data were analyzed by baseline BMI (underweight/normal, <25 kg/m^2; overweight, 25–<30 kg/m^2; obese, ≥30 kg/m^2) and ABA administration route.

Results: 526 pts (SC 265, IV 261) were underweight/normal; 497 (SC 249, IV 248) overweight; 433 (SC 221, IV 212) obese. Baseline characteristics did not differ by administration route, and for the pooled SC/IV group were similar by BMI (Table 1). Clinical outcomes by BMI at 6 M were similar for SC and IV groups measured by the % of pts in DAS28 (Figure 1), SDAI (underweight/normal, 9.1 vs 10.6%; overweight, 12.0 vs 11.8%; obese, 11.9 vs 9.8%) and CDAI (underweight/normal, 9.0 vs 11.8%; overweight, 13.1 vs 13.7%; obese, 14.3 vs 11.8%) remission; 95% CIs overlapped at all time points. There were no differences in the other outcomes by BMI, except for hsCRP, but this had no impact on remission rates. Results were consistent for the pooled SC/IV group. Although SC ABA C_{min} concentrations decreased with BMI increase, >90% of pts had concentrations >10 µg/mL (efficacy threshold) across BMI groups at 3 and 6 M for both SC and IV ABA (Figure 2).

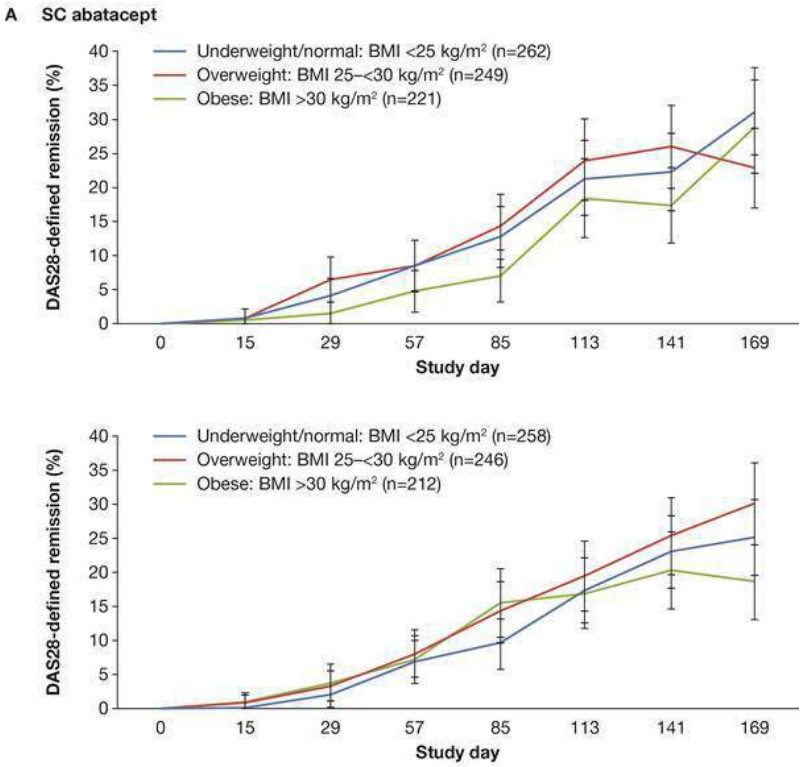
Conclusion: The clinical efficacy of SC and IV abatacept was independent of BMI, even when stringent remission criteria were used. Across BMI groups, >90% pts achieved therapeutic trough concentrations, irrespective of SC or IV administration. 1. Gremese E, et al. *Arthritis Care Res* 2013;**65**:94–100. 2. Iannone F, et al. *Joint Bone Spine* 2015;**82:**187–91. 3. Genovese MC, et al. *Arthritis Rheum* 2011;**63**:2854–64. 4. Murthy B, et al. *Ann Rheum Dis* 2011;**70**(Suppl 3):460 [FRI0347].

Table 1. Baseline Characteristics by BMI Group (pooled SC and IV)

	Underweight/normal, <25 kg/m^2 (n=526)	Overweight, 25–<30 kg/m^2 (n=497)	Obese, ≥30 kg/m^2 (n=433)
BMI, kg/m^2	22.0 (2.1)	27.4 (1.4)	35.2 (5.2)
Age, years	47.5 (14.4)	51.3 (12.2)	51.6 (11.2)
Females, %	83.1	78.9	85.7
Caucasians, %	70.9	76.3	77.1
RA duration, years	8.3 (8.2)	7.7 (7.5)	6.9 (8.2)
TJC/68	28.5 (13.5)	29.3 (13.6)	31.2 (14.1)
SJC/66	19.7 (9.5)	19.6 (8.7)	20.5 (9.2)
hsCRP, mg/dL	3.1 (3.4)	2.5 (2.6)	2.3 (2.5)
DAS28 (CRP)	6.2 (0.9)	6.2 (0.9)	6.3 (0.8)
PGA, 100 mm VAS	66.3 (19.5)	64.9 (20.3)	66.5 (20.9)

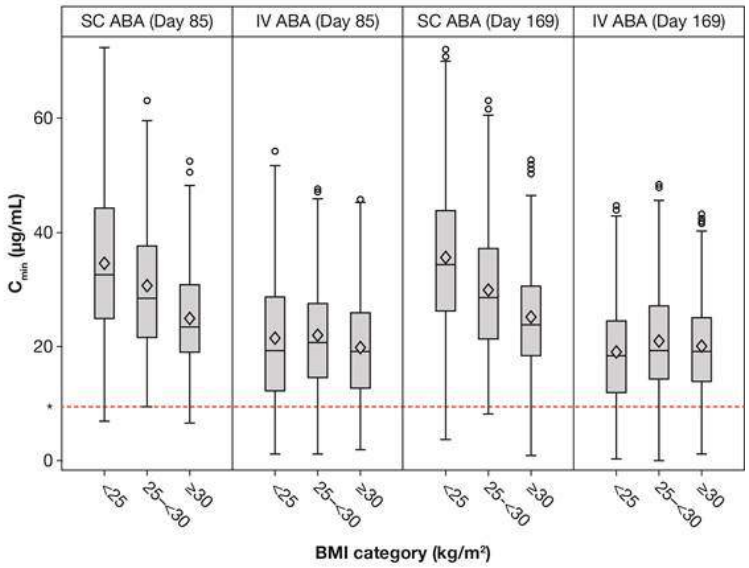
Data are mean (SD) unless indicated otherwise. hsCRP=high-sensitivity CRP; PGA=patient global assessment; VAS=visual analog scale

Figure 1. Percentage of Patients in DAS28 Remission by BMI and SC or IV Administration



As-observed analysis in the intent-to-treat population (>90% of patients reached the final observation at Day 169)

Figure 2. C_{min} Serum Abatacept Concentrations at Month 3 (Day 85) and Month 6 (Day 169) by BMI and SC or IV Administration



*10 µg/mL
Bottom and top of box=first and third quartiles; band inside box=median; ends of whiskers=last observed value within 1.5 times the interquartile range; diamond=mean
C_{min} >10 µg/mL is associated with near-maximal efficacy

Disclosure: M. D'Agostino, Bristol-Myers Squibb, AbbVie, Pfizer, Novartis, MSD, 8,Elsevier, 7; **R. Alten**, Bristol-Myers Squibb, 2,Bristol-Myers Squibb, 8; **E. Mysler**, Bristol-Myers Squibb, Pfizer, AbbVie, Roche, Astra, Sanofi, Biogen, GSK, Lilly, 2,Bristol-Myers Squibb, Pfizer, Roche, Novartis, AbbVie, 8; **M. Le Bars**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. Ye**, Bristol-Myers Squibb, 3; **B. Murthy**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **J. Heitzmann**, Excelya, 3; **R. Vadanici**, Bristol-Myers Squibb, 3; **G. Ferraccioli**, None.

Abstract Number: 1584

Bari-00074565

C. Steven Ernest II, Lisa O'Brien, David Radtke, Michael Heathman, Terence Rooney, William Macias and Xin Zhang, Eli Lilly and Company, Indianapolis, IN

First publication: September 28, 2016

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Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib is an oral selective inhibitor of Janus kinases 1/2 and has demonstrated dose-dependent efficacy in moderate-to-severe RA patients who were DMARD-naïve or with inadequate response to previous conventional or biological disease-modifying anti-rheumatic drugs (cDMARD/bDMARD-IR), in multiple phase 2 and 3 studies. The objective was to characterize the exposure-efficacy relationships and time course of 20, 50, and 70% improvement in the American College of Rheumatology criteria (ACR 20, 50, and 70, respectively) and disease activity score based on 28 joints and high sensitivity C-reactive protein (DAS28-hsCRP), in a combined phase 2/3 analysis.

Methods: The database comprised 7 baricitinib phase 2 and 3 studies in RA patients receiving placebo, 1, 2, 4, 7, 8 and 10 mg QD or 2-mg BID up to 24 weeks. The corresponding pharmacokinetics (PK), ACR 20/50/70 and DAS28-hsCRP response rates were analyzed by both quartile analysis and population pharmacokinetics/pharmacodynamics (PK/PD) modeling. For the quartile analysis, average steady-state concentrations from patients receiving 2- and 4-mg in 4 phase 3 studies were grouped into quartiles and correlated with the percentage of patients achieving ACR 20/50/70 and DAS28-hsCRP $\leq$3.2 and <2.6, at Week 12 and 16. Exposure-response models were also developed to describe the time-course and the exposure-response relationships of ACR 20/50/70 and DAS28-hsCRP following administration of baricitinib or placebo. Patient specific factors affecting the ACR 20/50/70 and DAS28-hsCRP response rates were explored.

Results: Plasma baricitinib concentrations were best characterized by a 2-compartment model with clearance partitioned between renal and non-renal components. Quartile exposure response analysis indicated that clinically relevant higher rates of ACR20/50/70 and DAS28-hsCRP responses were observed in the 3 upper quartiles compared to the lowest quartile. The PK/PD models adequately characterized the time course and exposure-responses of ACR20/50/70 and DAS28-hsCRP. Both baricitinib and placebo exhibited an indirect inhibitory effect on disease progression of ACR and DAS28-hsCRP. The model-estimated maximum response rates for ACR 20, 50, and 70 were 87%, 64%, and 39%, respectively, and 59% and 43% for DAS28-hsCRP $\leq$3.2 and <2.6, respectively. Model-estimated exposure response curves demonstrated that exposures from the 4-mg dose resided on the plateau of the response curves and exposures from 2-mg were lower and closer to the ascending portion of the curves for both ACR responses and DAS28-hsCRP states.

Conclusion: The final models successfully described and predicted the time-dependent changes in ACR20/50/70 and DAS28-hsCRP across the range of doses tested. A 4 mg QD dose was predicted to achieve close to maximal response.

Disclosure: C. S. Ernest II, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **L. O'Brien**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. Radtke**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **M. Heathman**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **W. Macias**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **X. Zhang**, Eli Lilly and Company, 1,Eli Lilly and Company, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/bari-00074565

Abstract Number: 1585

Previous Use of Conventional Disease-Modifying Antirheumatic Drugs and Response to Baricitinib

Arthur F. Kavanaugh[1], Ronald F. van Vollenhoven[2], David Muram[3], Jahangir Alam[3], Vipin Arora[3], Ana Luisa de Macedo Pinto Correia[3], Inmaculada de la Torre[3,4] and James R. O'Dell[5], [1]UC San Diego School of Medicine, La Jolla, CA, [2]Rheumatology Unit, Karolinska University Hospital, Solna, Sweden, [3]Eli Lilly and Company, Indianapolis, IN, [4]Lilly Corporate Center, Eli Lilly and

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First publication: September 28, 2016

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Background/Purpose: Baricitinib (BARI), an oral JAK1/JAK2 inhibitor, is in development for patients (pts) with moderate to severe RA.[1,2] The purpose of this post hoc analysis of 2 completed Phase 3 studies was to determine if previous failure of cDMARDs altered the response to BARI in RA pts and to evaluate the effect of concomitant steroid use and prognostically unfavorable factors on the efficacy of BARI.

Methods: Pts with ≥6 swollen and tender joints and no prior biologic DMARD use were eligible for study inclusion. In RA-BUILD, cDMARD-inadequate responder (IR) pts with hsCRP ≥3.6 mg/L were randomized to placebo (PBO) or BARI (2 or 4 mg) once daily (QD).[1] In RA-BEAM, MTX-IR pts with X-ray erosions and hsCRP ≥6.0 mg/L were randomized to PBO QD, BARI 4 mg QD, or adalimumab 40 mg biweekly.[2] Patients continued background cDMARD (including MTX) therapy. The primary endpoint in both trials was ACR20 at Week 12 for BARI 4 mg vs. PBO.[1,2] This post hoc analysis included the PBO (N=716) and BARI 4 mg (N=714) pts and assessed the number of previous cDMARDS, concurrent corticosteroid use, and effect of poor prognostic factors (high disease activity by Simplified Disease Activity Index [SDAI]>26), RF/ACPA positive, and radiographic erosions).

Results: In PBO pts, 40%, 34%, and 23% previously used MTX alone, MTX + 1 cDMARD, and MTX + ≥2 cDMARDs, respectively; in BARI 4 mg pts the rates were 46%, 29%, and 23%. Oral corticosteroids were used in 56% of PBO and 55% of BARI pts at baseline; pts continued use throughout the studies. Regardless of treatment assignment, the majority of pts had 2 or 3 of the prognostically unfavorable factors (95% in PBO; 96% in BARI pts). The primary objectives were met for both studies.[1,2] The clinical efficacy of BARI 4 mg over PBO at 12 weeks (Table 1) and the percentage of pts with van der Heijde modified Total Sharp Score (mTSS) change from baseline ≤0 at 24 weeks (Table 2) each was similar regardless of the number of cDMARDs previously used, the concomitant use of corticosteroids, or the presence of prognostically unfavorable factors. The rates of serious adverse events and discontinuation due to adverse events were comparable regardless of the number of cDMARDs used, corticosteroid use, or the number of risk factors.

Conclusion: Baricitinib has demonstrated clinical efficacy in a wide range of patients with varying exposure to cDMARDs, concomitant use of corticosteroids, serologic status, and baseline disease activity. **References:** [1]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79. [2]Taylor PC et al. *Arthritis Rheumatol* 2015;67(S10):3927-3928.

Table 1. Efficacy Measures through 12 Weeks Based on Previous cDMARD Usage

	Placebo (N=716)					Baricitinib 4 mg (N=714)				
	MTX Alone N=286	MTX+1 N=246	MTX+≥2 N=164	No Oral Corticosteroids (N=312)	Oral Corticosteroids (N=404)	MTX Alone N=327	MTX+1 N=206	MTX+≥2 N=166	No Oral Corticosteroids (N=324)	Oral Corticosteroids (N=390)
ACR20	116 (40.7)	105 (42.9)	57 (34.8)	122 (39.1)	164 (40.6)	222 (67.9)	138 (67.5)	111 (66.9)	223 (68.8)	256 (65.6)
ACR50	43 (15.1)	41 (16.7)	24 (14.6)	48 (15.4)	63 (15.6)	139 (42.5)	88 (42.9)	65 (39.2)	144 (44.4)	151 (38.7)
ACR70	11 (3.9)	10 (4.1)	8 (4.9)	17 (5.4)	13 (3.2)	70 (21.4)	40 (19.5)	22 (13.3)	63 (19.4)	70 (17.9)
SDAI ≤11	52 (18.2)	45 (18.4)	19 (11.6)	53 (17.0)	69 (17.1)	137 (41.9)	87 (42.4)	58 (34.9)	142 (43.8)	142 (36.4)
SDAI ≤3.3	6 (2.1)	4 (1.6)	1 (0.6)	7 (2.2)	4 (1.0)	37 (11.3)	14 (6.8)	9 (5.4)	27 (8.3)	34 (8.7)
DAS28-ESR ≤3.2	20 (7.0)	18 (7.3)	8 (4.9)	27 (8.7)	23 (5.7)	85 (26.0)	46 (22.4)	34 (20.5)	76 (23.5)	90 (23.1)
DAS28-ESR <2.6	7 (2.5)	4 (1.6)	3 (1.8)	10 (3.2)	5 (1.2)	36 (11.0)	20 (9.8)	16 (9.6)	30 (9.3)	42 (10.8)

Data are n (%).
ACR20/50/70= 20%, 50%, and 70% improvement in American College of Rheumatology criteria; Bari=baricitinib; cDMARD=conventional disease-modifying antirheumatic drugs; DAS28-ESR=Disease Activity Scale 28 erythrocyte sedimentation rate; MTX=methotrexate; SDAI=Simplified Disease Activity Scale

Table 2. Percentage of Patients with mTSS Change from Baseline of ≤0 through 24 Weeks Based on Previous cDMARD and Previous Corticosteroid Usage

	Placebo (N=716)		Baricitinib 4 mg (N=714)	
	Patients with Week 24 mTSS Results (n)	Patients with mTSS Δ from Baseline ≤0 n (%)	Patients with Week 24 mTSS Results (n)	Patients with mTSS Δ from Baseline ≤0 n (%)
MTX previously used	627	455 (72.6)	656	538 (82.0)
No previous MTX use	17	13 (76.5)	12	11 (91.7)
Previous MTX use by group				
MTX alone	254	191 (75.2)	305	255 (83.6)
MTX + 1 cDMARD	221	159 (71.9)	195	158 (81.0)
MTX + ≥2 cDMARDs	152	105 (69.1)	156	125 (80.1)
Corticosteroid use	365	265 (72.6)	364	292 (80.2)
No corticosteroid use	279	203 (72.8)	304	257 (84.5)

Data are n (%).
Δ=change; bari=baricitinib; cDMARD=conventional disease modifying antirheumatic drugs; mTSS=modified Total Sharp Score; MTX=methotrexate

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Disclosure: A. F. Kavanaugh, Eli Lilly and Company, 5; **R. F. van Vollenhoven**, •AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, 5; **D. Muram**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. Alam**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **V. Arora**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **A. L. de Macedo Pinto Correia**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **I. de la Torre**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. R. O'Dell**, Eli Lilly and Company, Medac, Coherus, BMS, GSK, 5.

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Abstract Number: 1586

Efficacy and Safety of Baricitinib in Patients with Rheumatoid Arthritis and an Inadequate Response to Conventional Disease-Modifying Antirheumatic Drugs: A United States Subpopulation Analysis from Two Phase 3 Trials

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SESSION INFORMATION
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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib (bari), an oral selective JAK1 and JAK2 inhibitor, has been shown to be safe and efficacious compared to placebo (PBO) in two Phase 3 trials in patients (pts) with moderate to severe RA and an inadequate response (IR) to conventional DMARDs (cDMARDs).[1,2] The objective of this analysis was to evaluate efficacy and safety of bari 4 mg vs. PBO in the United States (US) vs. the "rest of world" (ROW) subpopulations of these two studies.

Methods: Eligibility requirements included ≥6 swollen and tender joints and no prior biologic DMARD use. In RA-BUILD, cDMARD-IR pts with hsCRP≥3.6 mg/L were randomized to PBO or bari (2 or 4 mg) once daily (QD).[1] In RA-BEAM, MTX-IR pts with x-ray erosions and hsCRP≥6.0 mg/L were randomized to PBO QD, bari 4 mg QD, or adalimumab 40 mg biweekly.[2] Primary endpoint in both trials was ACR20 at Wk 12 for bari 4 mg vs. PBO. This post-hoc analysis combined data from both trials providing overall samples for bari 4 mg (N=714) and PBO (N=716). The geographically-defined subpopulations were US/Puerto Rico [US/PR] and ROW. Descriptive statistics were utilized for efficacy and safety analyses.

Results: There were 188 US/PR and 1,242 ROW pts in this analysis. The proportions of pts who were White or Black/African-American were higher in US/PR; Asians were more represented in ROW. US/PR pts were slightly older, with fewer years of RA, and a lower percentage were RF/ACPA positive or used corticosteroids. More US/PR pts had previously used 1 cDMARD and more ROW had previously used ≥3cDMARDs (Table 1). Bari 4 mg demonstrated better responses vs. PBO across US/PR and ROW for multiple

efficacy outcomes, including ACR20/50/70, LDA, remission, DAS28-CRP, and HAQ-DI (Table 2). Comparing US/PR and ROW efficacy, no systematic differences were observed. No significant safety differences were identified for US/PR or ROW pts at Wk 12 for bari 4 mg vs. PBO in the incidence of ≥1 adverse event (AE), serious AE, or discontinuation due to AE or death (Table 3). There was 1 death in PBO in each subpopulation.

Conclusion: In this post-hoc, pooled analysis from two Phase 3 trials in cDMARD-IR patients, bari 4 mg demonstrated efficacy compared to PBO in US/PR patients. **References:** [1]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79; [2]Taylor P et al. *Arthritis Rheumatol* 2015;67(suppl 10):3928.

Table 1. Demographic & Clinical Characteristics

	Placebo		Bari 4 mg QD	
	US/PR N=92	ROW N=624	US/PR N=96	ROW N=618
Age, years, mean (SD)	55.5 (10.6)	52.4 (12.2)	55.6 (12.5)	52.6 (12.1)
Female, n (%)	74 (80.4)	497 (79.6)	75 (78.1)	487 (78.8)
Race, n (%)				
White	76 (83.5)	379 (60.7)	82 (86.3)	378 (61.2)
Asian	1 (1.1)	207 (33.2)	0	202 (32.7)
Black/African-American	10 (11.0)	4 (0.6)	9 (9.5)	2 (0.3)
Other	4 (4.4)	33 (5.3)	4 (4.2)	36 (5.8)
Tender joint count (28), mean (SD)	15.6 (7.4)	13.6 (6.8)	16.1 (6.8)	13.7 (6.6)
Swollen joint count (28), mean (SD)	10.7 (5.3)	10.7 (5.3)	11.1 (5.0)	10.6 (4.9)
HAQ-DI, mean (SD)	1.6 (0.6)	1.5 (0.7)	1.6 (0.6)	1.6 (0.7)
DAS28-CRP, mean (SD)	5.7 (1.0)	5.6 (0.9)	5.8 (0.8)	5.7 (0.9)
Seropositivity, RF and ACPA positive, n (%)	62 (67.4)	510 (81.7)	53 (55.2)	506 (81.9)
Time from RA diagnosis, years, median	4.6	5.5	3.8	5.5
Current corticosteroid use, n (%)	40 (43.5)	364 (58.3)	34 (35.4)	356 (57.6)
MTX average weekly dose, mg/week (SD)	17.7 (4.9)	14.8 (4.7)	16.9 (4.7)	15.0 (4.7)
No. of cDMARDs previously used, n (%)				
1	62 (67.4)	238 (38.1)	70 (72.9)	271 (43.9)
2	25 (27.2)	225 (36.1)	18 (18.8)	188 (30.4)
≥3	3 (3.3)	161 (25.8)	7 (7.3)	159 (25.7)

DAS28-CRP=Disease Activity Score for the 28 joint count based on high-sensitivity C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index.

Table 2: Efficacy Measures Week 12

	Placebo		Bari 4 mg QD	
	US/PR N=92	ROW N=624	US/PR N=92	ROW N=618
ACR20	28 (30.4)	258 (41.3)	54 (56.3)	425 (68.8)
ACR50	11 (12.0)	100 (16.0)	27 (28.1)	268 (43.4)
ACR70	4(4.3)	26 (4.2)	11 (11.5)	122 (19.7)
CDAI ≤10	17 (18.5)	113 (18.1)	27 (28.1)	248 (40.1)
CDAI ≤2.8	4 (4.3)	11 (1.8)	8 (8.3)	54 (8.7)
SDAI ≤11	17 (18.5)	105 (16.8)	28 (29.2)	256 (41.4)
SDAI ≤3.3	4 (4.3)	7 (1.1)	8 (8.3)	53-(8.6)
ΔDAS28-CRP	-1.1 (0.16)	-1.1 (0.07)	-1.8 (0.15)	-2.2 (0.07)
ΔHAQ-DI	-0.2 (0.06)	-0.4 (0.03)	-0.3 (0.06)	-0.7 (0.03)

Data presented NRI (non-responder imputation), n (%) or least square means (LSM) (SE) change from baseline.
CDAI=Clinical Disease Activity Index; DAS28-CRP=Disease Activity Score for the 28 joint count based on high-sensitivity C-reactive protein; HAQ-DI=Health Assessment Questionnaire-Disability Index; SDAI=Simplified Disease Activity Index.

Table 3: Safety Measures 0-12 Weeks

	Placebo		Bari 4 mg QD	
	US/PR N=92	ROW N=624	US/PR N=92	ROW N=618
≥1 Adverse event (AE)	91 (98.9)	542 (86.9)	94 (97.9)	542 (87.7)
Serious AE	4 (4.3)	18 (2.9)	1 (1.0)	15 (2.4)
Death	1 (1.1)	1 (0.2)	0	0
Study discontinuation due to AE or death	7 (7.6)	14 (2.2)	3 (3.1)	17 (2.8)

Data presented n (%).

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subpopulation-analysis-from-t

Abstract Number: 1587

A Phase 2a, 4-Week Double-Blind, Proof-of-Concept Efficacy and Safety Study of CC-292 Versus Placebo As Co-Therapy with Methotrexate in Active Rheumatoid Arthritis (RA)

Alan J Kivitz[1], Ramesh Gupta[2], Guillermo Valenzuela[3], Edwin Smith[4], Quaiser Rehman[5], Hisham El Kadi[6], Elizabeth Bretton[7], Jacob A. Aelion[8], Anurekh Chadha[9], John Tesser[10], Douglas Hough[11], Shimon Korish[12], Peter H. Schafer[13], Garth Ringheim[14], Donna Sutherland[15] and Li LI[16], [1]Altoona Arthritis & Osteo Ctr, Duncansville, PA, [2]Private Practice, Memphis, TN, [3]Integral Rheumatology & Immunology Specialists, Fort Lauderdale, FL, [4]Rheumatology, Medical University of South Carolina, Charleston, SC, [5]Rheumatology Clinic of Houston, Houston, TX, [6]Arthritis & Osteoporosis Associates, Freehold, NJ, [7]Albuquerque Clinical Trials, Albuquerque, NM, [8]West Tennessee Research Institute, Jackson, TN, [9]Department of Rheumatology, Austin Regional Clinic, Austin, TX, [10]Arizona Arthritis and Rheumatology Research, PLLC, Pheonix, AZ, [11]Clinical Research, Celgene Corporation, Warren, NJ, [12]33 Technology Drive, Celgene Corporation, Warren, NJ, [13]Department of Translational Development, Celgene Corporation, Summit, NJ, [14]Translational Medicine, Celgene Corporation, Summit, NJ, [15]Clinical Research, Celgene Corporation, Summit, NJ, [16]Biostatistics, Celgene Corporation, Summit, NJ

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Background/Purpose: CC-292 is a small molecule inhibitor of Bruton's tyrosine kinase (Btk), which is a component of the B cell receptor signaling complex found in B lymphocytes and myeloid cells. Btk plays a crucial role in B cell development, maturation, and function. CC-292 inhibits Btk activity by irreversible covalent binding with high affinity to the adenosine triphosphate (ATP) binding site of Btk. Inhibition of Btk could regulate inflammation in RA by two different mechanisms; by blocking B cell receptor–dependent B cell proliferation and the reduction of autoantibody levels, and by inhibiting Fc gamma receptor (FcγR)-induced TNFα, IL-1β and IL-6 production in macrophages. CC-292 was evaluated over a 4 week treatment period in female subjects with active RA on background methotrexate (MTX) (NCT01975610).

Methods: 47 adult female RA subjects were randomized 1:1 CC-292 375 mg PO daily or placebo (PBO). Subjects were required to have a diagnosis of sero-positive RA for at least 6 months, meeting the 2010 ACR/EULAR Classification Criteria for RA. The RA must have been active despite at least 3 months of treatment with MTX and on a stable dose (7.5 to 25 mg/week oral or parenteral) for at least 4 weeks prior to randomization. Permitted concomitant RA medications included sulfasalazine, antimalarials, and low dose corticosteroids (prednisone or equivalent ≤ 10 mg/day).

Results: CC-292 showed ACR20 (primary endpoint) improvement in 10 (42%) of 24 RA subjects vs. 5 (22%) of 23 RA subjects on placebo. ACR20 improvement separated from placebo as early as week 1, and progressed through week 4. This positive trend was not considered statistically significant (p=0.25). The magnitude of ACR20 difference of 20% between treatment groups at 4 weeks, although not statistically significant, is on par with the effect seen in RA with other DMARDs. There were numerical trends for ACR50 and ACR70 favoring CC-292. No trends for improvement were observed for the exploratory endpoints of DAS28, HAQ-DI, or swollen and tender joint counts. Pharmacodynamic measurement of Btk occupancy showed no free Btk in the peripheral blood mononuclear cells as early as week 1. CC-292 reduced osteoclast activity, reduced B-cell lymph node trafficking, reduced class switched and activated memory B-cell, and increased mature naive B-cells. Treatment emergent adverse events (TEAEs) were comparable across both treatment arms. The most frequently reported TEAEs (≥ 5% subjects) in the CC-292 arm were nausea, back pain, diarrhea, cough, and migraine. There were no deaths in the study. There were no serious TEAEs and one severe TEAE of stomatitis.

Conclusion: The study did not meet its primary endpoint of improvement in ACR20 at 4 weeks, nor the secondary endpoints of ACR50 and ACR70 at 4 weeks, although there were numerical trends combined with a responder sub-group analysis suggest potential efficacy of CC-292 in this female subject RA population. In this study, CC-292 was well tolerated and had a favorable safety profile over 4 weeks of treatment. CC292 BTK inhibition impacts RA with a different MOA and profile than current therapies.

Disclosure: **A. J. Kivitz**, Celgene, 2,Celgene, 5,Celgene, 8; **R. Gupta**, None; **G. Valenzuela**, None; **E. Smith**, None; **Q. Rehman**, None; **H. El Kadi**, None; **E. Bretton**, None; **J. A. Aelion**, Abbvie, Astra Zeneca, Boehringer, BMS, Celgene, Galapagos, 2,GSK, Janssen, Eli Lilly, Mesoblast, Pfizer, Roche, ISCB, Sanofi-Aventis, Takeda, 2,Abbvie, Boehringer, Celgene, Eli Lilly, 5; **A. Chadha**, None; **J. Tesser**, Celgene, 2; **D. Hough**, Celgene, 3,Celgene, 1; **S. Korish**, Celgene, 1,Celgene, 3; **P. H. Schafer**, Celgene, 1,Celgene, 3; **G. Ringheim**, Celgene, 1,Celgene, 3; **D. Sutherland**, Celgene, 1,Celgene, 3; **L. LI**, Celgene, 1,Celgene, 3.

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Abstract Number: 1588

Treatment with BI 655064 (Antagonistic Anti-CD40 Antibody) Modulates Clinical and Biomarker Parameters Associated with Rheumatoid Arthritis (RA)

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Background/Purpose: Costimulation through the CD40–CD40L axis is implicated in the pathogenesis of RA including T cell-mediated responses, B cell-driven autoantibodies, adhesion molecule expression, synovial hyperplasia and pannus formation, in addition to secretion of proinflammatory cytokines and MMPs. Circulating sCD40L levels are elevated in RA patients versus healthy controls. Studies have shown a significant association between the CD40 rs4810485 T allele and RA. BI 655064 is a humanized antagonistic anti-CD40 monoclonal antibody that blocks the CD40–CD40L interaction in *in vitro* CD40L-induced B cell and APC activation assays with IC50 of <1 nM. In healthy volunteers, BI 655064 was well tolerated in doses up to 240 mg q1w s.c. for 4 wks. Doses ≥120 mg resulted in persistent >90% CD40 receptor occupancy and >90% inhibition of CD40L-induced CD54 upregulation.

Methods: In this double-blind randomized trial (NCT01751776), RA patients (n=67) received either 120 mg BI 655064 or placebo q1w for 12 wks as add-on to MTX. Inclusion criteria were ≥6 swollen and ≥6 tender joints, CRP ≥8 mg/L or ESR ≥28 mm/1h. The primary efficacy endpoint was ACR20 response at wk 12. Select biomarkers were assessed in whole blood and serum pre- and post-treatment with BI 655064. Rs4810485 was genotyped in a subset of patients (25 BI 655064, 18 placebo) by an allelic discrimination assay based on TaqMan PCR. For statistical analysis, patients were grouped into T allele carriers (TT/GT) and non-T allele carriers (GG).

Results: Higher ACR20/50 response rates were observed with BI 655064 (68.2%, 36.4%) vs placebo (45.5%, 18.2%) at wk 12. Baseline variables for the two groups were comparable except mean CRP (BI 655064 9.8 mg/L, placebo 23.6 mg/L; p<0.02). BI 655064 had minimal effects on the median %CD19+ B cell population but larger median decreases in select %CD95+ activated B cell subsets, specifically class switched (CD19+IgD-CD27+CD95+), pre-switched (CD19+IgD+CD27+CD95+) and double-negative (CD19+IgD-CD27-CD95+) cells (p=0.0097) at wk 12. Reductions in median IgG and IgA rheumatoid factor (RF, p=0.0018, p=0.005) and total IgG and IgM levels (p=0.0082, p=0.0002) were observed with BI 655064 vs placebo at 12 wks. Median decreases in IL-6 levels (B cell and monocyte differentiation) and select bone resorption biomarkers (MMP-3 and RANKL p=0.0041) were also observed with BI 655064 vs placebo at 12 wks. In patients who carried at least one T allele, a trend towards better ACR20 responses [72% (TT/GT) vs 50% (GG)] was observed with BI 655064 but not placebo. Two SAEs were reported in each group, but were not considered drug related. The most frequently reported AEs were nasopharyngitis (BI 655064 13.6%, placebo 21.7%) and headache (BI 655064 6.8%, placebo 13.0%).

Conclusion: Treatment of MTX-IR RA patients with BI 655064 resulted in moderate efficacy, which was potentially impacted by the relatively high placebo response rate and the imbalance in baseline CRP, and did not indicate any safety concerns. Treatment with BI 655064 decreased selected activated B cell subsets, inhibited RF production, and reduced levels of select circulating inflammatory and bone resorption biomarkers through 12 wks in RA patients.

Disclosure: S. Visvanathan, Boehringer Ingelheim, 3; **M. Ramanujam**, Boehringer Ingelheim Pharmaceuticals Inc., 3; **C. Schoelch**, Boehringer Ingelheim Pharma GmbH & Co. KG, 3; **P. Baum**, Boehringer Ingelheim Pharma GmbH & Co. KG, 3; **R. Vinisko**, Boehringer Ingelheim Pharmaceuticals Inc., 3; **R. Thiedmann**, Boehringer Ingelheim Pharma GmbH & Co. KG, 3; **U. Müller-Ladner**, Boehringer Ingelheim, 9; **S. Daniluk**, None; **R. Ptaszyński**, None; **S. Padula**, Boehringer Ingelheim, 3; **J. S. Fine**, Boehringer Ingelheim Pharmaceuticals Inc., 3; **J. Steffgen**, Boehringer Ingelheim, 3.

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Abstract Number: 1589

Body Mass Index Does Not Impact Abatacept Retention in Biologic-Naive Patients with Rheumatoid Arthritis Who Have Poor Prognostic Factors: A 12-Month Interim Analysis of an Observational, Prospective Study

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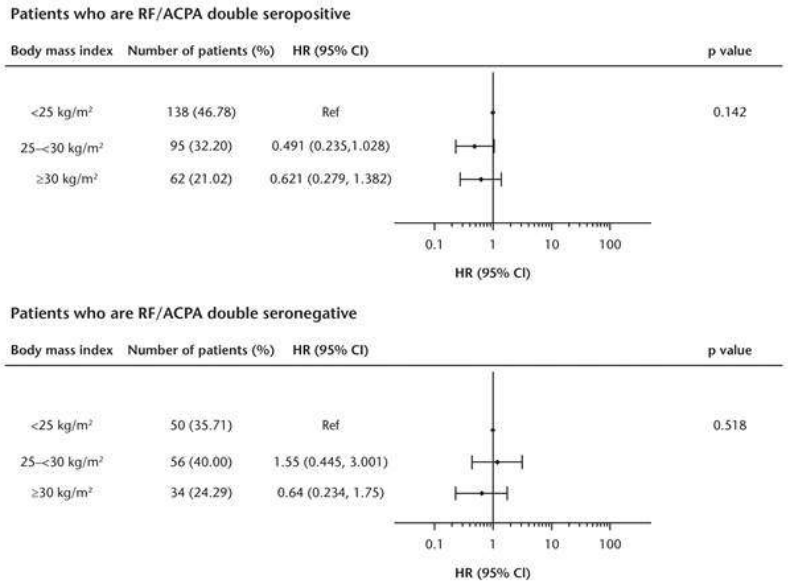
Background/Purpose: In patients with RA, obesity may impair clinical response to anti-TNF agents.[1,2] In contrast, BMI does not appear to impact treatment retention or clinical response to abatacept (ABA);[3] however, data on the effects of BMI are limited for patients with poor prognostic factors (radiographic erosion or RF/anti-citrullinated peptide antibody [ACPA] double seropositivity). Previously, poor prognostic factors were found to positively impact ABA retention, independently of treatment line.[4] The current analysis tested the impact of BMI on ABA retention in biologic-naïve patients with RA who had poor prognostic factors at baseline.

Methods: ACTION is a 2-year, international, observational study of patients with RA who initiated IV ABA in routine clinical practice. Time to ABA discontinuation in biologic-naïve patients was estimated using Kaplan–Meier survival analysis. Clinically relevant variables, known risk factors, and potential predictive factors with significance in univariate models ($p \leq 0.20$) and no collinearity, were entered into multivariate Cox proportional hazards regression models. Prognostic factors of ABA retention were assessed in subgroups of patients with and without radiographic erosion at baseline. As comorbid obesity has previously been linked to a decreased likelihood of joint damage progression in patients with RA who are ACPA positive,[2] BMI status was forced into the multivariate model after stratification for RF/ACPA double-seropositive versus double-seronegative status.

Results: Here we report 1-year results for 677 biologic-naïve patients with ≥1 prior conventional synthetic DMARD failure who enrolled into the ACTION study in two cohorts: 122 from Europe and Canada between May 2008 and December 2010; 555 from across Europe between September 2010 and December 2013. Data from the two enrollment cohorts were pooled owing to similar baseline characteristics. The 12-month ABA crude retention rate (95% CI) in biologic-naïve patients was 78.14% (74.72, 81.16). When forced into the multivariate model, BMI did not significantly impact ABA retention in the subgroups of patients who were RF/ACPA double seropositive (p=0.142) or double seronegative (p=0.518) at baseline (Figure).

Conclusion: Real-world evidence shows that RF/ACPA double seropositivity is predictive of abatacept retention in biologic-naïve patients.[4] BMI does not significantly impact abatacept retention, even in subgroups of patients with poor prognostic factors such as RF/ACPA double seropositivity. 1. Gremese E, et al. *Arthritis Care Res* 2013;**65**:94–100. 2. Iannone F, et al. *Joint Bone Spine* 2015;**82**:187–91. 3. Nüßlein HG, et al. *Clin Exp Rheum* 2016;**34**:489–99. 4. Alten R, et al. *Ann Rheum Dis* 2016;**75** (Suppl 2): 202.



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Abstract Number: 1590

Safety and Efficacy of Baricitinib in Elderly Patients with Moderate to Severe Rheumatoid Arthritis

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Background/Purpose: Baricitinib (bari), an oral JAK1 and JAK2 inhibitor, is in development for patients (pts) with moderate to severe RA. Drug-related problems are common in the elderly; therapies may be less effective and adverse effects more common. The purpose of this post hoc analysis was to evaluate the safety and efficacy of bari in the elderly subpopulation of 2 pooled phase 3 studies.

Methods: Patients with ≥6 swollen and tender joints and no prior biologic DMARD use were eligible for study inclusion. In the RA-BUILD study, csDMARD-IR pts with hsCRP ≥3.6 mg/L were randomized to placebo (PBO) or bari (2 or 4 mg) once daily (QD).[1] In RA-BEAM, methotrexate (MTX)-IR pts with X-ray erosions and hsCRP ≥6.0 mg/L were randomized to PBO QD, bari 4 mg QD, or adalimumab (ADA) 40 mg biweekly.[2] Patients continued background csDMARD (including MTX) therapy. The primary endpoint in both trials was ACR20 at Week (Wk) 12 for bari 4 mg vs. PBO. This post hoc analysis combined data from both trials providing overall samples for PBO (N=716) and bari 4 mg (N=714). Elderly pts were defined as those ≥65 years of age. Summary statistics are presented for demographic, efficacy, and safety data for pts aged <65 and ≥65 years.

Results: In these 2 studies, 249 patients ≥65 years old were randomized and initially treated with PBO (n=113) and bari 4 mg (n=136) (Table 1). The primary endpoints were met for both studies; bari showed significant differences vs. PBO for ACR20 at Wk 12; all key secondary endpoints were also met including mean change in DAS28, SDAI, and HAQ-DI.[1,2] Efficacy measures were similarly improved in pts <65 and ≥65 years of age (Table 1). Adverse events (AEs) occurred more frequently in the elderly population compared to pts aged <65 years; however, the prevalence of serious adverse events (SAEs) and discontinuations due to AEs was not different from PBO (Table 2). At 12 wks there were 2 deaths (both in PBO group <65) and cardiac events were rare, as were serious infections (Table 2); there were 2 herpes zoster events (both in bari 4 mg ≥65). There was 1 SAE of hospitalization due to thrombophlebitis (bari 4 mg <65) and 3 due to fractures, all related to falls (PBO <65, n=1; bari 4 mg <65, n=1; bari 4 mg ≥65, n=1); none of these pts discontinued the study and all events resolved.

Conclusion: In 2 phase 3 studies of bari in RA pts, age did not affect efficacy, but as expected there were more AEs in the elderly in both treatment arms. **References:** [1]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79. [2]Taylor PC et al. *Arthritis Rheumatol* 2015;67(S10):3927-3928.

Table 1. Selected Efficacy Outcomes at Week 12

	PBO		Bari 4 mg QD	
	<65 years (N=603)	**≥65 Years (N=113)**	**<65 years (N=578)**	**≥65 Years (N=136)**
ACR20, n (%)	237 (39.3)	49 (43.4)	387 (67.0)	92 (67.6)
ΔHAQ-DI	-0.3 (0.03)	-0.3 (0.08)	-0.6 (0.03)	-0.6 (0.07)
ΔDAS28-hsCRP	-1.0 (0.06)	-1.2 (0.17)	-2.1 (0.06)	-2.4 (0.17)
ΔSDAI	-13.4 (0.67)	-15.1 (1.79)	-22.7 (0.69)	-25.6 (1.69)

ACR20=American College of Rheumatology 20% improvement criteria; Bari=baricitinib; DAS28=Disease Activity Score 28 joints; hsCRP=high sensitivity C-reactive protein; HAQ-DI=Health Assessment Questionnaire – Disability Index; LSM=least square means; mLOCF=modified last observation carried forward; NRI=nonresponder imputation; PBO=placebo; SE=standard error; SDAI=Simple Disease Activity Index; SE=standard error; Δ=change from baseline

Data presented as NRI, n (%) or mLOCF, LSM (SE) change from baseline.

Table 2. Safety Outcomes at Week 12

	PBO		Bari 4 mg QD	
	<65 years (N=603)	**≥65 Years (N=113)**	**<65 years (N=578)**	**≥65 Years (N=136)**
Patients with ≥1 adverse event	524 (86.9)	109 (96.5)	503 (87.0)	133 (97.8)
Discontinuation from study due to adverse event or death	15 (2.5)	6 (5.3)	13 (2.2)	7 (5.1)
Serious adverse event	15 (2.5)	7 (6.2)	10 (1.7)	6 (4.4)
Serious infections	6 (1.0)	2 (1.8)	3 (0.5)	3 (2.2)
Cardiac disorders*	2 (0.3)	1 (0.9)	1 (0.2)	0

Data presented as n (%). *Any serious adverse event based on the MedDRA dictionary system organ class; Bari=baricitinib; PBO=placebo

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Disclosure: R. Fleischmann, AbbVie, Amgen, Astra Zeneca , Bristol-Myers Squibb, Celgene, Janssen, Eli Lilly, Novartis, Roche, Sanofi-Aventis, Pfizer,UCB, 5; **J. Alam**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **V. Arora**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. D. Bradley**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. E. Schlichting**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. Muram**, Eli Lilly and Company, 1,Eli Lilly and Company, 3.

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Abstract Number: 1591

Efficacy and Safety of Switching from Adalimumab to Baricitinib: Phase 3 Data in Patients with Rheumatoid Arthritis

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Background/Purpose: Baricitinib (bari) is an oral JAK1/JAK2 inhibitor under investigation for the treatment of patients (pts) with moderate to severe RA.[1-2] In the 52-week Phase 3 RA-BEAM study, bari 4 mg once daily (QD) showed clinical improvements compared to placebo (PBO) and to adalimumab (ADA) in MTX-inadequate-responder (IR) pts.[2] The objective of this analysis was to evaluate efficacy and safety in pts from RA-BEAM who changed treatment from ADA to bari either after rescue in RA-BEAM or switch after entering a long-term extension (LTE) study (RA-BEYOND).

Methods: In RA-BEAM (completed September 2015), 1305 pts were randomized 3:3:2 to PBO, bari 4 mg QD, or ADA 40 mg every 2 weeks (wks). At Wk 16 or subsequent visits, IRs (lack of ≥20% reduction in tender and swollen joint count) were rescued to open-label bari 4 mg. At Wk 52, pts could enter the LTE, where all pts received bari 4 mg and remained blinded to their randomized treatment in RA-BEAM. No ADA washout period was applied for rescue or switch from ADA to bari. Efficacy analyses evaluated both rescued and not rescued RA-BEAM pts who entered the LTE ≥24 wks before the present data cutoff. Safety analyses included pts not rescued in RA-BEAM who entered the LTE.

Results: A total of 51 pts were rescued from ADA to bari 4 mg in RA-BEAM; at Wk 52, 67%, 49%, and 24% achieved ACR20, ACR50, and ACR70, respectively. Among pts who completed RA-BEAM without rescue, 381/394 (97%) bari, and 238/241 (99%) ADA pts entered the LTE. Of these, 185 (continued bari) and 108 ADA (switched to bari) pts reached the 24 wk time point and were included in the LTE efficacy analysis and 340 (continued bari) and 211 ADA (switched to bari) pts were included in the LTE safety analysis. Patients who switched from ADA to bari showed improvements in disease control through 12 wks post-switch in the LTE, without evidence of worsening through the following 12 wks (Table 1). Exposure-adjusted incidence rates for total treatment-emergent adverse events (TEAEs) and infections, including serious events, were similar for pts who switched from ADA to bari and those who continued on bari (Table 2).

Conclusion: Switching from ADA to bari without ADA washout was associated with improvements in disease control during the initial 12 wks post-switch, without an increase in overall TEAEs or serious AEs or infections, and without subsequent evidence of worsening. **References**: [1]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79. [2]Taylor PC et al. *Arthritis Rheumatol* 2015;67(S10):3927-3928.

Table 1. Efficacy through 24 Weeks in the LTE RA-BEYOND Study for Patients Not Rescued in RA-BEAM

	Bari to Bari (N=185)			ADA to Bari (N=108)		
	Wk 52	Wk 64	Wk 76	Wk 52	Wk 64	Wk 76
ACR20[a], %	91	84	87	84	93	87
ACR50[a], %	72	68	76	67	67	65
ACR70[a], %	45	46	50	42	48	43
CDAI[b]	7.9	8.2	7.4*	8.7	6.8**	7.3*
SDAI[b]	8.6	8.8	8.2	9.3	7.2**	7.8*
HAQ-DI[b]	0.7	0.8	0.8	0.7	0.7	0.7

ADA=adalimumab; Bari=baricitinib; LTE=long-term extension; Wk=week.
Bari to Bari = patients completing RA-BEAM (Wk 52) without rescue on bari who continued bari in RA-BEYOND. ADA to Bari = patients completing RA-BEAM without rescue on ADA who transitioned to bari (Wk 52) upon entering RA-BEYOND. Weeks are based on time since initial randomization in the 52-week RA-BEAM study. Analyses are based on an August 10, 2015 data cutoff.
[a]Using nonresponder imputation for permanent discontinuation of study drug.
[b]Data are mean values.
*p≤0.05, **p≤0.01; p-values are based on within-group mean change from LTE baseline (Wk 52) using MMRM.

Table 2. Safety through 12 Weeks in the LTE RA-BEYOND Study for Patients Not Rescued in RA-BEAM

	Bari to Bari (n=340; PYE=69.7)	ADA to Bari (n=211; PYE=42.8)
Patients with ≥1 TEAE	112 (32.9) [160.8]	60 (28.4) [140.1]
Infections	46 (13.5) [66.0]	20 (9.5) [46.7]
AEs that led to study drug discontinuation	3 (0.9) [4.3]	3 (1.4) [7.0]
Patients with ≥1 SAE	39 (11.5) [56.0]	18 (8.5) [42.0]
Serious infections	12 (3.5) [17.2]	5 (2.4) [11.7]

ADA=adalimumab; AEs=adverse events; Bari=baricitinib; IR=incidence rate; LTE=long-term extension; PYE=patient-years of exposure; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
Bari to Bari = patients completing RA-BEAM (Wk 52) without rescue on bari who continued bari in RA-BEYOND. ADA to Bari = patients completing RA-BEAM without rescue on ADA who transitioned to bari (Wk 52) upon entering RA-BEYOND. Weeks are based on time since initial randomization in the 52-week RA-BEAM study. Analyses are based on an August 10, 2015 data cutoff.
Data are n (%) [IR].

Disclosure: P. C. Taylor, UCB, Janssen, GSK, Abide therapeutics, 2,Eli Lilly and Company, Pfizer, Galapagos, Abbvie, 5; **E. Keystone**, Abbott, Amgen, AstraZeneca, BMS, Hoffman-LaRoche, Janssen, Eli Lilly and Company, Novartis, Pfizer, Sanofi-Aventis, UCB, 2,Abbott, AstraZeneca, Biotest, BMS, Crescendo, Hoffmann-LaRoche, Genentech, Janssen, Eli Lilly and Company, Merck, Pfizer, UCB, 5,Abbott, AstraZeneca, BMS Canada, Hoffmann-LaRoche, Janssen, Pfizer, UCB, Amgen, 9; **R. Ortmann**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **M. Issa**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **L. Xie**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. Muram**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. D. Bradley**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **S. de Bono**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **Y. Tanaka**, Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, 2,Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Ssanofi, Janssen, Eli Lilly and Company, GSK, 8.

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Abstract Number: 1592

A Randomized, Double-Blind, Parallel-Group, Phase III Study of Shortening the Dosing Interval of Subcutaneous Tocilizumab Monotherapy in RA Patients with an Inadequate Response to Subcutaneous Tocilizumab Every Other Week

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Background/Purpose: The non-inferiority of subcutaneous tocilizumab (TCZ-SC) monotherapy every 2 weeks (q2w) to intravenous TCZ monotherapy every 4 weeks was demonstrated in Japanese patients with rheumatoid arthritis (RA).[1] During the open-label period, patients with an inadequate response to TCZ-SC q2w could shorten the dosing interval to receive TCZ-SC weekly (qw), which resulted in improved efficacy.[2] To confirm this preliminary result, the objective of this study was to determine the efficacy and safety of TCZ-SC qw vs TCZ-SC q2w in patients with RA who had an inadequate response to TCZ-SC q2w.

Methods: Adult RA patients with Disease Activity Index 28-joints based on erythrocyte sedimentation rate (DAS28-ESR) > 3.2, tender joint count (TJC) using 66 joints and swollen joint count (SJC) using 68 joints ≥ 4 each, and C-reactive protein (CRP) ≥ 0.3 mg/dL within 2 weeks of their last TCZ-SC dose, despite ≥ 8 weeks of TCZ-SC q2w therapy, were included. Patients were randomized 1:1 to receive either TCZ-SC 162 mg qw as monotherapy or TCZ-SC 162 mg q2w as monotherapy (double-blind period). After 12 weeks, all patients received TCZ-SC qw for 40 weeks (open-label period). The primary endpoint was the change from baseline in DAS28-ESR at week 12 using analysis of covariance (ANCOVA), adjusted by DAS28-ESR at randomization. The aim of this study was to demonstrate the superiority of TCZ-SC qw to TCZ-SC q2w. Additional efficacy, safety and pharmacokinetic parameters were assessed.

Results: Of the 43 patients enrolled, 21 received TCZ-SC qw and 21 received TCZ-SC q2w. TCZ-SC qw was superior to TCZ-SC q2w for adjusted mean change in DAS28-ESR from baseline to week 12 (−2.10 vs −0.89; $P = 0.0108$ [Table]). The adjusted mean change in Clinical Disease Activity Index from baseline to week 12 was −16.0 in the TCZ-SC qw group and −8.7 in the TCZ-SC q2w group ($P = 0.0979$; as per hierarchical testing). The proportions of patients who achieved DAS28-ESR remission or low disease activity were 42.9% and 25.0% for the TCZ-SC qw and TCZ-SC q2w groups, respectively. Improvements in TJC, SJC, CRP and ESR, and the proportion of patients achieving ACR20/50, were greater in the TCZ-SC qw group than the TCZ-SC q2w group. The proportions of patients who experienced adverse events (AE) were 71.4% and 66.7% in the TCZ-SC qw and TCZ-SC q2w groups, respectively. One patient in each group experienced ≥ 1 serious AE. There was 1 death in the TCZ-SC qw group.

Conclusion: In patients with an inadequate response to TCZ-SC q2w, TCZ-SC qw was superior to TCZ-SC q2w for improving DAS28-ESR at 12 weeks. The safety profile was comparable between patients who received TCZ-SC qw or TCZ-SC q2w, and was consistent with the safety profile of TCZ from previous studies. This study suggests that in patients with an inadequate response to TCZ-

SC q2w, shortening the dosing interval to TCZ-SC qw is an effective treatment option.

1. Ogata A, et al. *Arthritis Care & Res.* 2014;66:344-354.

2. Ogata A, et al. *J Rheumatol.* 2015;42:799-809.

Table. Outcomes at 12 weeks in patients with RA treated with TCZ-SC qw or TCZ-SC q2w (Full Analysis Population, LOCF)[a]

	TCZ-SC 162 mg qw (N = 21)	TCZ-SC 162 mg q2w (N = 20)[b]
DAS28-ESR		
Δ from baseline, adjusted mean	−2.10	−0.89
Remission, % (n)[c]	19.0 (4)	10.0 (2)
LDA, % (n)[c]	23.8 (5)	15.0 (3)
MDA, % (n)[c]	33.3 (7)	45.0 (9)
HDA, % (n)[c]	23.8 (5)	30.0 (6)
CDAI		
Δ from baseline, adjusted mean	−16.0	−8.7
Remission, % (n)[d]	4.8 (1)	0
LDA, % (n)[d]	28.6 (6)	35.0 (7)
MDA, % (n)[d]	42.9 (9)	20.0 (4)
HDA, % (n)[d]	23.8 (5)	45.0 (9)
TJC, Δ from baseline, mean (SD)	−9.1 (11.8)	−4.1 (6.1)
SJC, Δ from baseline, mean (SD)	−6.0 (8.0)	−3.7 (5.8)
ACR20, % (n)	52.4 (11)	20.0 (4)
ACR50, % (n)	38.1 (8)	15.0 (3)
ACR70, % (n)	14.3 (3)	15.0 (3)
CRP, Δ from baseline, mean (SD), mg/dL	−1.2 (4.3)	0.17 (2.2)
ESR, Δ from baseline, mean (SD), mm/hr	−22.5 (22.0)	−2.6 (20.2)

ACR20/50/70, American College of Rheumatology 20/50/70 response; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; DAS28-ESR, Disease Activity Index 28-joint on erythrocyte sedimentation rate; ESR, erythrocyte sedimentation rate; HDA, high disease activity; LDA, low disease activity; LOCF, last observation carried forward; MDA, moderate disease activity; qw, weekly; q2w, every 2 weeks; RA, rheumatoid arthritis; SJC, swollen joint count using 68 joints; TCZ-SC, subcutaneous tocilizumab; TJC, tender joint count using 66 joints.
[a] LOCF imputation was used for missing values.
[b] One patient in the TCZ-SC q2w group was excluded from the analysis population because they had no evaluable measurements after study drug administration.
[c] DAS28-ESR remission was defined as DAS28-ESR < 2.6, LDA as 2.6 ≤ DAS28-ESR ≤ 3.2, MDA as 3.2 < DAS28-ESR ≤ 5.1; HDA as DAS28-ESR > 5.1.
[d] CDAI remission was defined as CDAI ≤ 2.8, LDA as 2.8 < CDAI ≤ 10, MDA as 10 < CDAI ≤ 22; HDA as CDAI > 22.

Disclosure: A. Ogata, Chugai, 5,Chugai, Pfizer, Bristol-Myers Squibb, Astellas, Mitsubishi-Tanabe, Ono, 8; **N. Takagi**, Chugai, 3; **H. Miwa**, Chugai, 3.

Abstract Number: 1593

Baricitinib for Rheumatoid Arthritis: A Systematic Review and Meta-Analysis

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Background/Purpose: Baricitinib is a small molecule inhibitor of the Janus kinase (JAK) pathways that reduce and modulate the production of inflammatory mediators and cytokines. We conducted a systematic review to evaluate the efficacy and safety of baricitinib for the treatment of patients with rheumatoid arthritis.

Methods: A comprehensive search of the literature was conducted in the following electronic databases: Cochrane Library, MEDLINE, EMBASE and Web of Science through April 2016. Also, we searched clinicaltrials.gov. Any randomized controlled trial (RCT) comparing baricitinib alone or in combination with any DMARD versus placebo or other traditional or biologic DMARDs for the treatment of patients with rheumatoid arthritis were included. Two independent reviewers performed study selection, data collection and risk of bias assessment using Covidence.org. Our primary outcome was the percent of patients achieving an American College of Rheumatology (ACR) 50% response. Secondary outcomes included: clinical remission (Disease Activity Score (DAS<2.6)), minimum clinical important difference (MCID) ≥0.22 in the Health Assessment Questionnaire (HAQ), total withdrawals and serious adverse events (SAEs).

Results: Out of 171 citations, 7 RCTs met our inclusion criteria. Most studies were published in abstract format and risk of bias assessment was judged unclear in most domains. Five studies compared more than two doses of baricitinib, however, we only report here results for the dose of 4 mg once daily. Four comparisons were included: i) baricitinib plus methotrexate (MTX) vs MTX, ii) baricitinib alone vs MTX, iii) baricitinib plus MTX vs adalimumab (ADA) plus MTX, and iv) baricitinib plus MTX vs baricitinib alone. For the combination of baricitinib plus MTX, more patients in the baricitinib group achieved an ACR 50 response and clinical remission compared to patients in the MTX group at 12 and 24 weeks (at 12 weeks patients in the control group were re-assigned to baricitinib). The combination group reported lower withdrawal rates at 24 weeks (RR 0.61, (95% CI 0.47-0.81) and similar SAEs at 24 weeks compared to control. For baricitinib alone vs MTX, improvement rates were higher in the baricitinib group at 12 weeks (RR 1.7, 95% CI 1.3-2.1; 1.8, 95% CI 1.2-2.6; 1.3, 95% CI 1.2-1.4; for ACR50, clinical remission, and MCID HAQ rates, respectively). No differences were found in total withdrawals or SAEs. When baricitinib was compared to ADA, greater rates of ACR50 response were observed in the baricitinib group at 12 weeks (RR 1.3; 95% CI 1.1, 1.5); but also higher rates of SAEs compared to the ADA group at 24 weeks were reported (RR 2.5; 95% CI 1.0, 6.1). No significant differences were observed between baricitinib plus MTX compared with baricitinib alone.

Conclusion: Baricitinib alone or combined with MTX had better efficacy responses compared to MTX alone at 12-24 weeks. Total withdrawal rates were lower in the baricitinib combined group when compared to MTX. Baricitinib had similar effects compared to adalimumab, but higher rates of SAEs. Baricitinib can be considered an additional therapeutic option to treat patients with moderate to severe disease who have an inadequate response to other treatment agents.

Disclosure: N. V. Zamora, None; **J. Tayar**, None; **M. A. Lopez-Olivo**, Rheumatology Research Foundation, 2; **R. Christensen**, R. Christensen Consultant for:, 5; **M. Suarez-Almazor**, National Institute for Musculoskeletal and Skin Disorders, 2.

Abstract Number: 1594

First-in-Human Pharmacokinetics and Safety of Escalating Single- and Multiple-Doses of GS-9876, a Novel, Oral SYK Inhibitor, in Healthy Subjects

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Background/Purpose: Spleen Tyrosine Kinase (SYK) mediates immunoreceptor signaling in a range of hematopoietic cells important

for the initiation and progression of inflammatory diseases such as rheumatoid arthritis (RA) and other autoimmune diseases including B lymphocytes, monocytes, macrophages, dendritic cells, and osteoclasts. Cellular data and multiple animal models of disease provide strong preclinical validation for SYK as a therapeutic target in RA. GS-9876 has been identified as a novel, potent and selective SYK inhibitor. Preclinical characterization of GS-9876 utilized in vitro biochemical and cellular assays to assess on-target and off-target pharmacology, and the rat collagen-induced arthritis model to establish in vivo efficacy. Here we describe first-in-human studies of GS-9876 which characterize the pharmacokinetic (PK) profile, safety and tolerability of escalating single- and multiple-doses of GS-9876, as well as the impact of food and acid-reducing agents on GS-9876 PK in healthy subjects.

Methods: Healthy subjects were administered escalating single (2 mg to 50 mg) or multiple (15 mg once daily to 50 mg once daily for 7 days) doses of GS-9876 in the fasted state. PK, safety and tolerability were assessed throughout the study, and reviewed following each dose level, prior to initiation of successive dose escalation cohorts. The impact of food (high-fat breakfast) and a representative acid-reducing agent (omeprazole 20 mg) on GS-9876 PK were assessed using a crossover study design.

Results: Sixty-two subjects received at least one dose of GS-9876. GS-9876 exhibited slightly greater than dose proportional increases in C_{max} but not area under the curve extrapolated to infinity (AUC_{inf}) following single doses (2 mg, 5 mg, 15 mg, 30 mg and 50 mg); dose proportional PK was observed following multiple doses (15 mg and 30 mg once daily). The median terminal elimination half-life was consistent following single or multiple doses and ranged from approximately 21 to 28 hours. Accordingly, GS-9876 exposure accumulated approximately 1.9-fold following multiple once daily doses. Administration of GS-9876 with a high-fat meal slightly reduced GS-9876 C_{max} (13%), but did not affect AUC_{inf}; administration with omeprazole did not affect GS-9876 C_{max} or AUC_{inf}. Intersubject variability in GS-9876 C_{max} and AUC following multiple doses was <25% (coefficient of variation). No clinically significant changes in vital signs, ECGs and safety laboratory tests were observed. No clinically relevant changes in bleeding time were observed. Mild vomiting in one subject was reported as related to GS-9876. All reported AEs were generally mild and self-limiting. No serious AE or discontinuations were reported.

Conclusion: GS-9876 was safe and well tolerated following single doses up to 50 mg and multiple doses up to 30 mg once daily for 7 days. The long terminal elimination half-life of GS-9876 supports a once daily dosing regimen, and GS-9876 may be administered without regard to food or acid-reducing agents. These data support the ongoing development of GS-9876 in inflammatory diseases.

Disclosure: M. Dolton, Gilead Sciences, Inc, 3,Gilead Sciences, Inc, 1; **F. Matzkies**, Gilead Sciences, Inc, 3,Gilead Sciences, Inc, 1; **K. Currie**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 2,Gilead Sciences, Inc, 3; **J. Di Paolo**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **L. Wang**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **H. Zheng**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **S. Ramanathan**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3; **J. Silverman**, Gilead Sciences, Inc, 1,Gilead Sciences, Inc, 3,Merck, 1,Bristol-Myers Squibb, 1,Amgen, 1,Incyte, 1,Celgene, 1,Sunesis, 1,Array, 1,Zimmer, 1.

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Abstract Number: 1595

Magnitude and Duration of Early Response with Tofacitinib: Post-Hoc Analysis of Two Phase 3, Placebo-Controlled Studies

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. ORAL Solo[1] and ORAL Sync[2] are two Phase 3 index studies that demonstrated the efficacy of tofacitinib in adult patients (pts) with RA who were DMARD inadequate

responders (DMARD-IR). Early onset of effect is a clinically meaningful endpoint. This post-hoc analysis examined the magnitude and durability of early response to tofacitinib in ORAL Solo and ORAL Sync.

Methods: ORAL Solo and ORAL Sync were double-blind, placebo (PBO)-controlled, parallel-group studies in pts with active RA and an inadequate response to ≥1 conventional synthetic (cs) or biologic (b) DMARD.[1,2] Pts were randomized to tofacitinib 5 mg BID, tofacitinib 10 mg BID, PBO advanced to tofacitinib 5 mg BID, or PBO advanced to tofacitinib 10 mg BID, either as monotherapy in ORAL Solo or with background csDMARD in ORAL Sync. In ORAL Solo, pts randomized to PBO were advanced to tofacitinib at Month 3; in ORAL Sync, pts randomized to PBO were advanced to tofacitinib at Month 3 (non-responders) or Month 6 (all other pts). In this post-hoc analysis, the following clinical efficacy data for pts on tofacitinib or PBO (prior to advancement to tofacitinib) ± csDMARD, were evaluated at Week 2, Month 3, and Month 6 (ORAL Sync only; no Month 6 PBO comparison in ORAL Solo): change from baseline in Clinical Disease Activity Index (CDAI) >12,[3] HAQ-DI change from baseline ≥0.22, CDAI ≥50% improvement from baseline, CDAI ≥70% improvement from baseline, CDAI ≥85% improvement from baseline, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score improvement from baseline ≥4, Pain visual analog scale (VAS) score change from baseline ≥10. This analysis is post hoc and multiplicity adjustment was done.

Results: Clinical efficacy endpoint data are summarized in Table 1. At Week 2, more patients receiving tofacitinib 5 or 10 mg BID ± csDMARDs (compared to PBO ± csDMARDs) achieved a CDAI change from baseline >12, HAQ-DI improvement from baseline ≥0.22, CDAI ≥50% improvement from baseline and pain VAS change from baseline ≥10. By Month 3, more pts receiving tofacitinib 5 or 10 mg BID ± csDMARDs (compared to PBO ± csDMARDs) achieved the efficacy outcomes measured including improvements from baseline in FACIT-F scores ≥4, CDAI ≥50%, CDAI ≥70%, and CDAI ≥85% improvement from baseline. Responses attained at Month

Table 1. Clinical efficacy endpoints from Week 2 to Month 6 in ORAL Sync and ORAL Solo (FAS[a]; NRI[b])

Improvement from baseline, % pts (95% CI)		ORAL Solo			ORAL Sync		
		Tofacitinib 5 mg BID (N=241)	Tofacitinib 10 mg BID (N=243)	PBO (N=122)	Tofacitinib 5 mg BID + csDMARD (N=312)	Tofacitinib 10 mg BID + csDMARD (N=315)	PBO + csDMARD (N=158)
CDAI >12	Week 2	37.1 (31.0, 43.6)*	43.9 (37.5, 50.5)*	18.5 (12.0, 26.6)	30.4 (25.3, 35.9)*	36.8 (31.3, 42.5)*	17.4 (11.8, 24.3)
	Month 3	71.6 (65.4, 77.2)*	75.5 (69.6, 80.8)*	42.5 (33.5, 51.9)	56.0 (50.3,61.6)*	64.7 (59.1, 70.1)*	32.5 (25.2, 40.4)
	Month 6	79.5 (74.4, 84.6)	78.8 (73.7, 84.0)	NA	53.7 (48.0, 59.4)*	62.1 (56.4, 67.6)*	34.4 (27.0, 42.4)
HAQ-DI ≥0.22	Week 2	49.0 (42.5, 55.5)*	50.6 (44.1, 57.2)*	37.8 (29.1, 47.2)	45.6 (40.0, 51.4)*	53.1 (47.3, 58.8)*	34.2 (26.8, 42.2)
	Month 3	59.6 (53.1, 65.9)*	65.3 (58.9, 71.3)*	39.2 (30.4, 48.5)	49.0 (43.3, 54.7)*	57.1 (51.4, 62.7)*	23.7 (17.3, 31.2)
	Month 6	67.5 (61.6, 73.4)	66.1 (60.1, 72.1)	NA	49.7 (44.0, 55.4)*	55.5 (49.8, 61.2)*	23.7 (17.3, 31.2)
CDAI ≥ 50%	Week 2	19.8 (15.0, 25.5)*	25.1 (19.7, 31.1)*	8.4 (4.1, 14.9)	18.0 (13.8, 22.7)*	20.5 (16.1, 25.5)*	9.0 (5.0, 14.7)
	Month 3	57.3 (50.8, 63.7)*	58.1 (51.6, 64.4)*	25.8 (18.3, 34.6)	45.3 (39.7, 51.0)*	56.5 (50.8, 62.2)*	22.3 (16.1, 29.6)
	Month 6	68.6 (62.7, 74.5)	66.4 (60.4, 72.4)	NA	48.5 (42.9, 54.3)*	58.8 (53.1, 64.4)*	29.3 (22.3, 37.1)
CDAI ≥70%	Week 2	5.1 (2.6, 8.7)	11.3 (7.6, 16.0)*	2.5 (0.5, 7.2)	4.9 (2.8, 8.0)	8.6 (5.7, 12.4)*	3.2 (1.1, 7.4)
	Month 3	33.1 (27.1, 39.4)*	40.7 (34.4, 47.2)*	14.2 (8.5, 21.7)	24.3 (19.6, 29.5)*	31.4 (26.2, 36.9)*	7.6 (4.0, 13.0)
	Month 6	41.8 (35.6,48.1)	49.0 (42.7, 55.3)	NA	31.4 (26.3, 36.9)*	37.9 (32.5, 43.6)*	16.6 (11.1, 23.3)
CDAI ≥ 85%	Week 2	2.1 (0.7, 4.9)	5.0 (2.6, 8.6)	2.5 (0.5, 7.2)	1.0 (0.2, 2.8)	3.3 (1.6, 6.0)*	0.7 (0.0, 3.5)
	Month 3	14.6 (10.4, 19.8)*	17.8 (13.2, 23.3)*	5.8 (2.4, 11.7)	9.4 (6.4, 13.2)*	11.4 (8.1, 15.6)*	1.3 (0.2, 4.5)
	Month 6	22.2 (16.9, 27.4)	27.0 (21.4, 32.6)	NA	10.7 (7.5, 14.7)	18.3 (14.1, 23.1)*	5.7 (2.7, 10.6)
FACIT-F ≥4	Month 1	NA	NA	NA	46.2 (40.4, 52.0)	58.1 (52.3, 63.7)*	39.0 (31.2, 47.1)
	Month 3	61.2 (54.7, 67.4)*	63.4 (56.8, 69.6)*	42.2 (33.1, 51.8)	38.6 (33.1, 44.3)*	51.2 (45.4, 56.9)*	21.8 (15.6, 29.1)
	Month 6	59.2 (53.0, 65.5)	62.4 (56.2, 68.6)	NA	40.9 (35.3, 46.6)*	47.2 (41.5, 53.0)*	21.2 (15.0, 28.4)
PAIN VAS ≥10	Week 2	57.3 (50.8, 63.7)*	61.1 (54.6, 67.3)*	41.2 (32.2, 50.6)	46.3 (40.6, 52.0)*	52.9 (47.2, 58.6)*	36.5 (29.0, 44.6)
	Month 3	69.3 (63.1, 75.1)*	73.9 (67.8, 79.3)*	42.5 (33.5, 51.9)	50.0 (44.3, 55.7)*	57.5 (51.7, 63.1)*	28.7 (21.7, 36.4)
	Month 6	71.0 (65.2, 76.7)	71.0 (65.2, 77.7)	NA	48.4 (42.7, 54.1)*	56.2 (50.4, 61.8)*	30.6 (23.5, 38.4)

*p<0.05 vs placebo. [a]Included all randomized subjects who took ≥1 dose of study medication. [b]Patients who withdrew for any reason before Month 6, or subjects who were advanced to tofacitinib after Month 3 (only for ORAL Sync) have their values on or after withdrawing or advancing set to Non-Response in this analysis. N = total number in each treatment group, number of subjects available for the analysis may vary for individual endpoints. PBO group included only those patients who had not yet advanced to tofacitinib. Comparisons for tofacitinib vs PBO at Month 6 not available for ORAL Solo as all PBO patients advanced to tofacitinib at this time point.

BID, twice daily; CDAI, Clinical Disease Activity Index; csDMARD, conventional synthetic DMARD; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; FAS, full analysis set; NA, not available; NRI, non responder imputation; PBO, placebo; Pts, patients; VAS, visual analog scale.

3 were maintained or increased at Month 6.

Conclusion: DMARD-IR pts with active RA receiving tofacitinib ± csDMARDs appeared to show greater improvements compared to PBO in clinical disease activity, HAQ-DI, and pain as early as Week 2 (first post-baseline assessment), and improvements in fatigue by Month 3. Responses were maintained or improved through Month 3 (monotherapy) or Month 6 (with background DMARD).

References: 1. Fleischmann R et al. N Engl J Med 2012; 367: 495-507. 2. Kremer J et al. Ann Intern Med 2013; 159: 253-261. 3. Curtis JR et al. Arthritis Care Res (Hoboken) 2015; 67: 1345-1353.

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Abstract Number: 1596

Comparative Effectiveness of Tocilizumab Monotherapy with Tumor Necrosis Factor Inhibitors in Combination with Methotrexate in Patients with Rheumatoid Arthritis and Prior Exposure to Tumor Necrosis Factor Inhibitors

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Background/Purpose: Clinical studies have demonstrated the superior efficacy of tocilizumab monotherapy (TCZ mono) to tumor necrosis factor inhibitor (TNFi) monotherapy and the comparable efficacy of TCZ mono with TCZ in combination with methotrexate (MTX). The objective of this study was to compare the effectiveness of TCZ mono vs TNFi in combination with ≤ 10 mg/week MTX (demonstrated effective dose with TNFi[1]) in patients with active rheumatoid arthritis (RA) and prior exposure to TNFis in routine clinical practice.

Methods: Eligible participants were TCZ-naive patients from the Corrona registry who had prior exposure to ≥ 1 TNFi, initiated TCZ mono or a TNFi + ≤ 10 mg MTX between 2010 and 2016 and had a 6-month follow-up visit. The primary outcome was mean change in Clinical Disease Activity Index (CDAI) from baseline at 6 months. Secondary outcomes included change in modified Health Assessment Questionnaire (mHAQ) score, achievement of low disease activity (LDA) or remission (CDAI ≤ 10) and achievement of modified American College of Rheumatology (mACR) 20/50/70 responses at 6 months. The main cohort was a trimmed population excluding patients who fell outside the propensity score (PS) distribution overlap. The PS included age, race, body mass index, smoking status, work status, disease duration, concomitant prednisone use/dose, prior biologic/TNFi use and a baseline disease assessment including ACR functional class, mHAQ, CDAI and patient pain. As a sensitivity analysis, a stratified-matched population was created (stratified by 1 vs ≥ 2 biologics, then matched on PS). Linear and logistic regression models were estimated in the trimmed population adjusting for the same covariates as in the PS.

Results: A total of 312 patients initiated TCZ mono and 119 initiated TNFi + ≤ 10 mg MTX (mean [SD] dose, 8.1 [2.6] mg). Using the PS, there were 416 patients in the trimmed population (TCZ mono, n = 304; TNFi + ≤ 10 mg MTX, n = 112). Both groups included middle-aged patients (mean age, TCZ mono, 59 years; TNFi + ≤ 10 mg MTX, 58 years) with established disease (mean disease duration, TCZ mono, 13 years; TNFi + ≤ 10 mg MTX, 12 years). Those initiating TCZ mono had more severe disease based on mean CDAI (28 vs 25; $P = 0.029$), mean reported pain (61 vs 55, $P = 0.033$) and prior use of ≥ 2 biologics (81% vs 58%; $P < 0.001$) compared with those initiating TNFi + ≤ 10 mg MTX. Both groups had improvement in CDAI and mHAQ and ≈ one-third of patients achieved LDA and a mACR20 response at 6 months. In adjusted models, improvement in disease activity was similar between the treatment groups (**Table**). Similar results were observed in the PS-matched cohort.

Conclusion: Treatment with TCZ mono or TNFi + ≤ 10 mg MTX in patients with prior TNFi exposure was associated with clinical improvement. TCZ mono appears to have similar efficacy as TNFi + MTX and warrants further study in a larger population.

References:

1. Burmester GR, et al. *Ann Rheum Dis*. 2015;74:1037-1044.

Table. Disease activity outcomes at 6 months in patients who initiated TCZ mono compared with those who initiated TNFi + ≤ 10 mg MTX.

	TCZ mono (N = 304)	TNFi + ≤ 10 mg MTX (N = 112)	Unadjusted*	Adjusted†
Primary outcome	**Mean (SD)**	**Mean (SD)**	**β (95% CI)**	**β (95% CI)**
Change in CDAI	−9.6 (14.4)	−7.8 (13.2)	−1.79 (−4.85, 1.28)	−0.15 (−2.88, 2.59)
Secondary outcomes	**Mean (SD)**	**Mean (SD)**	**β (95% CI)**	**β (95% CI)**
Change in mHAQ	−0.1 (0.5)	−0.1 (0.4)	−0.03 (−0.13, 0.06)	−0.03 (−0.13, 0.06)
Achievement of:	**Response rate, n (%)**	**Response rate, n (%)**	**OR (95% CI)**	**OR (95% CI)**
LDA	86 (28.3)	35 (31.3)	0.87 (0.54, 1.39)	1.11 (0.65, 1.89)
mACR20	104 (34.9)	32 (28.6)	1.34 (0.83, 2.15)	1.28 (0.76, 2.17)
mACR50	58 (19.5)	17 (15.2)	1.35 (0.75, 2.44)	1.46 (0.77, 2.79)
mACR70	28 (9.4)	7 (6.3)	1.56 (0.66, 3.67)	1.79 (0.70, 4.57)

CDAI, Clinical Disease Activity Index; LDA, low disease activity; mACR, modified American College of Rheumatology response; mHAQ, modified Health Assessment Questionnaire; MTX, methotrexate; OR, odds ratio; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor.
* TCZ compared with TNFi + ≤ 10 mg MTX.
† Adjusted for gender, age, race (white vs non-white), disabled, retired, baseline CDAI, baseline mHAQ, baseline patient pain, baseline prednisone use/dose, baseline body mass index, prior biologic use, prior TNFi use and ACR functional class.

Disclosure: L. R. Harrold, Pfizer Inc, 2,Roche Pharmaceuticals, 5,Corrona, LLC, 3,Corrona, LLC, 1; **G. W. Reed**, Corrona, LLC, 3,Corrona, LLC, 1; **J. Best**, Genentech, Inc., 3; **S. Zlotnick**, Genentech, Inc., 3; **G. Persuitte**, Corrona, LLC, 3; **J. M. Kremer**, Corrona, LLC, 3,Corrona, LLC, 1,AbbVie, Amgen, BMS, Genentech, GSK, Lilly, Medimmune, Pfizer, and Sanofi, 5.

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Abstract Number: 1597

Dose-Response Modeling Is a Useful Tool to Determine Doses for Phase 3: Experience from Olokizumab

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Background/Purpose: Olokizumab (OKZ) is an anti-interleukin-6 (IL-6) monoclonal antibody in development for the treatment of rheumatoid arthritis (RA). In phase 2 studies, treatment with OKZ+methotrexate (MTX) resulted in significant improvements in disease activity compared to placebo (PBO)+MTX.[1,2] Here, we use dose-response modeling based on phase 2 efficacy and safety data to determine the optimal OKZ doses for phase 3 development. This modeling approach utilizes all available data to reach a scientifically-based decision.

Methods: The nonparametric Jonkheere-Terpstra (JT) test was fitted to DAS28(CRP) data from two phase 2, double-blind, randomized, dose-ranging (60 to 480 mg 4-week [wk] cumulative dose [cd]) studies (RA0056 [NCT01242488] and RA0083 [NCT01463059]) to test for a monotonic dose-response curve with no assumptions on curve shape. The JT test indicated that a dose-response model was statistically significant, allowing the Hill parametric model to be used, with study as a categorical covariate that affected both the ED_{50} and E_{max} parameters. Mean and 95% confidence intervals for response were calculated. The Hill model fitted the data adequately, allowing estimation of the response curves using all available information. To select an appropriate dose, a balance between both safety and efficacy must be achieved. Thus a dose-response model for the incidence of adverse events (AEs) was also required. A logistic regression model was fitted to the 17 most commonly observed preferred terms across pooled phase 2 data.

Results: The JT test indicated a statistically significant monotonic dose-response relationship: $p<0.005$ for all dosing regimens (every 2 wks [Q2W] and every 4 wks [Q4W]) in each study, and across pooled data from the two studies. Categorical DAS28(CRP) endpoints also indicated a monotonic dose-response relationship (Table). A parametric dose-response curve fitted using a Hill model[3] to combined data from the studies (Figure) adequately described the data, with an inflection point of 120 mg 4-wk cd. This is the smallest

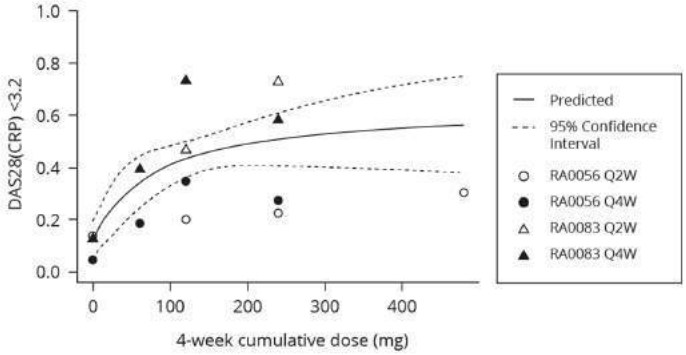
dose that attains a response near the maximum. Dosing frequency had a small, non-statistically significant effect on categorical DAS28(CRP) response. Logistic regression analysis of AEs did not indicate a dose-related increase in AEs vs PBO+MTX, with the exception of injection site reaction.

Conclusion: Efficacy increased with dose without an increase in safety events, and plateaued at approximately 120 mg 4-wk cd. Modeling data were robust, with comparable results for individual studies vs pooled data, and continuous vs categorical responses. Thus a dose at the inflection point (128 mg 4-wk cd, given as 64 mg Q2W) and a dose below the inflection point (64 mg 4-wk cd) were selected for inclusion in the phase 3 program. **References:** 1. Genovese M. Ann Rheum Dis 2014;73(9):1607–15; 2. Takeuchi T. Mod Rheum 2016;26(1):15–23; 3. Reeve R. 2013. J Biopharm Stat 2013;23(3):648–61

Table: Probability of a monotonic dose-response relationship based on the Jonkheere-Terpstra test

Categorical endpoint	Dosing frequency	JT p value
DAS28(CRP) <2.6	Q4W	0.0001
DAS28(CRP) <2.6	Q2W	0.0003
DAS28(CRP) <3.2	Q4W	<0.0001
DAS28(CRP) <3.2	Q2W	0.0020

Figure: Model for proportion of patients with DAS28(CRP) <3.2 at Week 12 as a function of 4-week cumulative dose, based on the Hill model



Disclosure: R. Reeve, Quintiles, Inc., 3; **D. Weilert**, Quintiles, Inc., 3; **E. Korneva**, R-Pharm CJSC, 3; **D. Koloda**, R-Pharm CJSC, 3; **S. Fatenejad**, R-Pharm CJSC, 5.

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Olokizumab Treatment of Both Western and Asian Patients with Rheumatoid Arthritis Who Have Failed Anti-TNF Treatment Results in Sustained Improvements in Patient-Reported Outcomes

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Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) has a high patient (pt) burden with significant impact on health-related quality of life. We report the effect of treatment with olokizumab (OKZ), an interleukin-6 (IL-6)-targeting monoclonal antibody, on pt-reported outcomes (PROs) in both Western and Asian pts with moderate to severe RA who have previously failed anti-TNF therapy.

Methods: Data are reported from two multicenter, double-blind RCTs, RA0056 (NCT01242488) and RA0083 (NCT01463059), and their corresponding open-label extension (OLE) studies, RA0057 (NCT01296711) and RA0089 (NCT01533714). In the RCTs, pts with RA receiving MTX who had previously failed anti-TNF therapy were recruited from Belgium, the US and the UK (RA0056),[1] and Japan, Korea and Taiwan (RA0083).[2] Pts received placebo (PBO), subcutaneous (sc) OKZ 60/120/240 mg every 2 weeks (wks; Q2W) or 4 wks (Q4W) (240 mg Q2W in RA0056 only), or (in RA0056 only) intravenous tocilizumab (TCZ) 8 mg/kg Q4W. Completers were eligible for the OLEs, in which all pts received sc OKZ 120 mg Q2W + MTX (RA0057: 12.5–25.0 mg/wk with dose reductions permitted after Wk 12; RA0089: 6.0–16.0 mg/wk in Japan, 7.5–20.0 mg/wk in Korea and Taiwan). Pts with ongoing serious adverse events were excluded from the OLEs. Clinical efficacy and safety data have been reported previously.[1,2] PROs assessed included health assessment questionnaire-disability index (HAQ-DI), pt's global assessment of disease activity (PtGADA), pt's assessment of arthritis pain (PtAAP), Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire (BRAF-MDQ) and EuroQol 5-Dimensions Questionnaire (EQ-5D). Data are reported for the OL full analysis set (all pts who received ≥1 dose of OKZ with ≥1 efficacy measurement in the OLE). Observed data are reported for Wk 12 of the RCTs and the last time point at which ≥50% of pts reported data in the OLEs; Wk 48 in RA0057 and Wk 40 in RA0089.

Results: 198 pts completed RA0056; 190 (114 OKZ, 40 PBO, 36 TCZ) enrolled in RA0057. 105 pts completed RA0083; 103 (79 OKZ, 24 PBO) enrolled in RA0089. At Wk 12 of the RCTs, both Western (Table A) and Asian (Table B) OKZ-treated pts reported greater improvements in PROs compared to PBO-treated pts, similar to TCZ pts. As expected, PBO-treated pts reported rapid improvements in PROs following switch to OKZ. These changes were maintained to Wk 40/48 of the OLE both in pts receiving OKZ throughout (OKZ→OKZ) and in TCZ-pts switching to OKZ at OLE entry (TCZ→OKZ). Improvements were comparable in magnitude in Western and Asian patients.

Conclusion: OKZ treatment of both Western and Asian pts with moderate to severe RA resulted in sustained improvements across a range of PROs, both in the RCT and OLE, with similar levels of improvement seen in both populations. Changes were maintained to the last time point examined: Wk 40 in Asian pts and Wk 48 in Western pts. **References:** 1. Genovese M. Ann Rheum Dis 2014;73(9):1607–15; 2. Takeuchi T. Mod Rheum 2016;26(1):15–23

Table A: Patient-reported outcomes in Western patients with moderate to severe RA

	Treatment (RA0056 RCT → RA0057 OLE)					
	PBO → OKZ		OKZ → OKZ		TCZ → OKZ	
	RCT Week 12	OLE Week 48	RCT Week 12	OLE Week 48	RCT Week 12	OLE Week 48
Mean change from baseline (SD)						
HAQ-DI	0.07 (0.52) [n=40]	-0.15 (0.66) [n=21]	-0.32 (0.48) [n=114]	-0.45 (0.49) [n=70]	-0.35 (0.28) [n=36]	-0.43 (0.50) [n=23]
PtGADA	-0.1 (29.1) [n=40]	-15.6 (29.8) [n=20]	-18.8 (27.0) [n=111]	-24.0 (28.1) [n=69]	-26.5 (25.5) [n=35]	-30.0 (22.6) [n=22]
PtAAP	-0.4 (29.6) [n=39]	-13.9 (35.6) [n=20]	-20.2 (27.3) [n=113]	-26.8 (30.1) [n=69]	-27.1 (23.4) [n=36]	-35.6 (22.0) [n=23]
BRAF-MDQ	-3.6 (13.5) [n=40]	-8.4 (15.3) [n=20]	-11.4 (12.8) [n=113]	-13.3 (13.2) [n=68]	-13.4 (12.9) [n=35]	-13.3 (12.5) [n=23]
EQ-5D	-6.6 (24.9) [n=40]	5.9 (30.1) [n=21]	10.9 (27.0) [n=113]	17.5 (20.2) [n=69]	18.1 (23.8) [n=36]	24.8 (21.8) [n=23]

Table B: Patient-reported outcomes in Asian patients with moderate to severe RA

	Treatment (RA0083 RCT → RA0089 OLE)			
	PBO → OKZ		OKZ → OKZ	
	RCT Week 12	OLE Week 40	RCT Week 12	OLE Week 40
Mean change from baseline (SD)				
HAQ-DI	0.00 (0.24) [n=24]	-0.28 (0.52) [n=14]	-0.41 (0.42) [n=78]	-0.60 (0.47) [n=42]
PtGADA	-2.9 (20.3) [n=24]	-26.0 (23.5) [n=14]	-26.8 (23.9) [n=78]	-37.5 (24.0) [n=42]
PtAAP	-6.5 (24.7) [n=24]	-31.4 (21.9) [n=14]	-25.3 (25.4) [n=78]	-35.0 (28.9) [n=42]
BRAF-MDQ	-6.0 (10.4) [n=24]	-10.7 (10.8) [n=14]	-11.5 (9.8) [n=78]	-12.4 (11.9) [n=42]
EQ-5D	-6.1 (18.0) [n=24]	18.5 (17.5) [n=14]	13.7 (20.6) [n=78]	21.9 (23.1) [n=42]

BRAF-MDQ: Bristol Rheumatoid Arthritis Fatigue-Multi-Dimensional Questionnaire; EQ-5D: EuroQol-5 Dimensions Questionnaire; HAQ-DI: Health Assessment Questionnaire-Disability Index; PtAAP: patient's assessment of arthritis pain; PtGADA: patient's global assessment of disease activity.

Disclosure: M. C. Genovese, UCB Pharma, R-Pharm CJSC, Sanofi-Aventis, Roche, 2,UCB Pharma, R-Pharm CJSC, Sanofi-Aventis, Roche, GlaxoSmithKline, BirdRock Bio, 5; **P. Durez**, None; **R. Fleischmann**, Genentech Inc, Roche, Abbott, Amgen, UCB Pharma, Pfizer, Bristol-Myers Squibb, Eli Lilly, Sanofi-Aventis, MSD, Novartis, AstraZeneca, Janssen, 2,Roche, Abbott, Amgen, UCB Pharma, Pfizer, Bristol-Myers Squibb, Eli Lilly, Sanofi-Aventis, Novartis, AstraZeneca, Janssen, 5; **Y. Tanaka**, Bristol-Myers Squibb, MSD, Chugai, Mitsubishi- Tanabe, Astellas, AbbVie, Daiichi-Sankyo, 2,Mitsubishi-Tanabe, Abbott, AbbVie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, UCB Pharma, 5; **D. E. Furst**, Abbott, Actelion, Amgen, Bristol-Myers Squibb, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, and UCB Pharma, 2,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen IDEC, Janssen, Gilead, GlaxoSmithKline, NIH, Novartis, Pfizer, Roche/Genentech, and UCB Pharma, 5,Abbott, Actelion, Amgen, Bristol-Myers Squibb, Biogen, IDEC, Janssen, Gilead, NIH, Roche/Genentech, and UCB Pharma, 9; **H. Yamanaka**, Teijin Pharma, Chugai, Astellas, Bristol-Myers Squibb, AbbVie, Daiichi-Sankyo, Mitsubishi-Tanabe, Takeda, UCB Pharma, 2,Teijin Pharma, Bristol-Myers Squibb, AbbVie, 5; **I. Vasyutin**, R-Pharm CJSC, 3; **T. Kaviarasu**, Quintiles Inc, 3; **E. Korneva**, Employee of R-Pharm CJSC, 3; **D. Koloda**, R-Pharm CJSC, 3; **T. Takeuchi**, AstraZeneca, Eli Lilly, Novartis, Mitsubishi-Tanabe, Asahi Kasei, 5,Abott, Astellas, Bristol-Myers Squibb, Chugai, Daiichi-Sankyo, Eisai, Janssen, Mitsubishi-Tanabe, Nippon Shinyaku, Otsuka, Pfizer, Sanofi-Aventis, Santen, Takeda, Teijin, 2.

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Abstract Number: 1599

Speed of Onset of Effect on Patient-Reported Outcomes Assessed through Daily Electronic Patient Diaries in the Baricitinib Phase 3 RA Clinical Program

Peter C. Taylor[1], Grace C. Wright[2], Carol L. Gaich[3], Amy M. DeLozier[3], Stephanie de Bono[3], Douglas E. Schlichting[3], Terence Rooney[3], Jiajun Liu[3], Scott D. Beattie[4] and Maxime Dougados[5], [1]NDORMS, University of Oxford, Oxford, United Kingdom, [2]NYU Langone Medical Center, New York, NM, [3]Eli Lilly and Company, Indianapolis, IN, [4]Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, [5]Dept of Rheumatology, Cochin Hospital, Paris, France

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster II

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Baricitinib (bari), an oral Janus kinase (JAK) 1/JAK2 selective inhibitor, has demonstrated clinical efficacy with a satisfactory safety profile when administered once daily in 4 completed Phase 3 studies in patients with RA[1,2,3,4]. In 2 studies, RA-BEAM (52-week study in patients with inadequate response (IR) to MTX) and RA-BUILD (24-week study in patients with IR to conventional synthetic [cs] DMARDs), patients recorded their worst joint pain, duration and severity of morning joint stiffness (MJS), and worst tiredness each day for 12 weeks using electronic diaries. In previous analyses based on weekly averages of daily scores[3], bari produced significant improvements in patient-reported outcomes (PROs) compared to placebo (pbo) as early as Week 1 and compared to adalimumab (ada) as early as Weeks 2 4. The aim of these analyses was to explore the kinetics of response using daily diary scores without weekly averaging.

Methods: PRO data were analyzed by study day after randomization (Day 1) - Day 28 for all treated patients. Mixed models for repeated measures analysis were applied (with MJS duration by nonparametric methods).

Results: Consistent with the original weekly-averaged data[3], daily diary scores showed significant improvement in patients receiving bari compared to pbo and ada. Improvements relative to pbo were apparent as early as the 3rd day of treatment for MJS severity, worst tiredness, and worst joint pain, and by Day 5 for MJS duration (Figure and Table). Improvements relative to ada were apparent as early as Day 19 for MJS severity, Day 21 for worst tiredness, and Day 17 for worst joint pain. The greatest rapidity and magnitude of benefit was seen with the bari 4-mg daily dose.

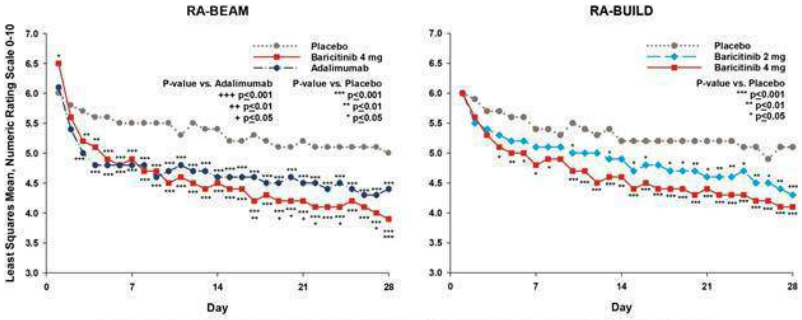

Figure. Worst Joint Pain during the initial 28 days of treatment in Studies RA-BEAM and RA-BUILD.

Table. Patient-Reported Outcomes Collected by Daily Patient Electronic Diaries: First Study Day at which Improvement relative to Placebo or Adalimumab was Observed‡

	RA-BEAM (MTX-IR)			RA-BUILD (csDMARD-IR)	
	Bari 4 mg (N=487) vs Placebo (N=488)	Ada 40 mg (N=330) vs Placebo (N=488)	Bari 4 mg (N=487) vs Ada 40 mg (N=330)	Bari 2 mg (N=229) vs Placebo (N=228)	Bari 4 mg (N=227) vs Placebo (N=228)
MJS Duration	Day 5	Day 3	NS	Day 26	Day 10
MJS Severity NRS	Day 3	Day 2	Day 19	Day 25	Day 4
Worst Tiredness NRS	Day 3	Day 3	Day 21	NS	Day 3
Worst Joint Pain NRS	Day 3	Day 3	Day 17	Day 10	Day 4

‡ First study day demonstrating statistically significant differences in the noted comparisons.
Ada=adalimumab; Bari=baricitinib; csDMARD-IR=inadequate response to conventional synthetic DMARDs; MJS=morning joint stiffness; MTX-IR=inadequate response to methotrexate; NRS=numeric rating scale; NS=no significant differences observed through the first 28 days; RA-BEAM=Study I4V-MC-JADV; RA-BUILD=Study I4V-MC-JADX.

Conclusion: In this post hoc analysis from Phase 3 studies of patients with RA with inadequate response to MTX or other csDMARDs, treatment with bari produced rapid improvements in PROs compared to pbo and ada, with significant differences appearing within the initial days of treatment. **References:** [1]Dougados et al. *Ann Rheum Dis* 2015;74(S2):79; [2]Fleischmann et al. *Arthritis Rheumatol* 2015;67(S10):1360-1361; [3]Taylor et al. presented at ACR 2015; [4]Genovese et al. *N Engl J Med* 2016;374(13):1243-1252.

Disclosure: P. C. Taylor, UCB, Janssen, GSK, Abide therapeutics, 2,Eli Lilly and Company, Pfizer, Galapagos, Abbvie, Janssen, 5; **G. C. Wright**, Abbvie, Amgen, BMS, Crescendo, Genentech, Janssen, Eli Lilly and Company, Medac, Pfizer, Mallinckrodt, UCB, 5,Abbvie, Amgen, BMS, Crescendo, Genentech, Novartis, Mallinckrodt, UCB, 8,Assn of Women in Rheumatology, 9,American Society of Clinical Rheumatology, 9; **C. L. Gaich**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **A. M. DeLozier**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **S. de Bono**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **D. E. Schlichting**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **T. Rooney**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. Liu**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **S. D. Beattie**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **M. Dougados**, AbbVie, Pizer, Eli Lilly

and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 2,AbbVie, Pizer, Eli Lilly and Company, Novartis, UCB, Merck, Roche, BMS, UCB, 5.

Abstract Number: 1600

Evaluation of Disease Activity in Patients with Rheumatoid Arthritis Treated with Tofacitinib By RAPID3: An Analysis of Data from 6 Phase 3 Studies

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The treatment target for RA is remission or low disease activity (LDA). Routine assessment of patient index data 3 (RAPID3) consists of 3 patient-reported ACR RA core data set measures: function, pain, and patient global estimate of status. Here, we use RAPID3 to evaluate disease activity in RA patients treated with tofacitinib in 6 Phase 3 (P3) studies.

Methods: Data were analyzed from 6 P3 studies in which MTX-naïve patients or patients with inadequate response (IR) to MTX, biologic/conventional synthetic DMARDs, or TNF inhibitors (TNFi) received tofacitinib as monotherapy, or with MTX or other csDMARDs. ORAL Standard also included an adalimumab arm. All patients were required to meet the ACR classification criteria for the diagnosis of RA. To calculate RAPID3 scores, each of the 3 individual measures (HAQ-DI, pain visual analog scale [VAS], and patient global assessment VAS) was scored from 0–10 (HAQ-DI was scored from 0–3 × 3.33) for a total of 30, and divided by 3 to give an adjusted 0–10 score. Remission was defined as RAPID3 ≤1 and LDA was defined as RAPID3 ≤2. RAPID3 scores were calculated at the time of the primary endpoint of the index study (either 3 or 6 months) and at the end of each study (either 6, 12, or 24 months). Non-responder imputation was used for all comparisons between treatment and control groups. This analysis was post-hoc. No multiple comparison adjustment was done.

Results: Of the 4,218 patients included in the P3 studies, 3,162 (75.0%) patients were treated with tofacitinib. Across studies, baseline demographics and disease characteristics were similar with the exception of shorter and longer disease duration in ORAL Start and ORAL Step, respectively. Mean RAPID3 score (0–10) at baseline ranged from 5.1 to 6.1 and the proportion of patients with RAPID3 LDA at baseline ranged from 2.8% to 6.3%. At the time of the primary endpoint, significantly ($p<0.05$) higher rates of RAPID3 remission and LDA were observed with tofacitinib 5 mg or 10 mg twice daily (BID) vs the control groups (placebo/MTX) in ORAL Standard, Start and Solo. Adalimumab was not significant vs placebo in ORAL Standard. In ORAL Scan (MTX-IR), ORAL Step (TNFi-IR) and ORAL Sync (DMARD-IR), higher rates of RAPID3 remission and LDA were observed vs placebo, respectively, however these were not consistently significant. At the end of each P3 study, the rates of RAPID3 remission and LDA were sustained or slightly increased vs at the time of the primary endpoint. Higher rates were seen in patients receiving tofacitinib 10 mg BID vs 5 mg BID (Table).

Conclusion: This analysis of the tofacitinib P3 studies demonstrated that patients receiving tofacitinib had improvements in the 3 patient-reported ACR RA core data set measures, and can achieve RAPID3-defined remission and LDA.

Table. RAPID3 rates of remission and LDA in each of the tofacitinib P3 studies

n/N (% response)	Time of primary endpoint[a]		End of study[b]	
	RAPID3 remission (≤1)	RAPID3 LDA (≤2)	RAPID3 remission (≤1)	RAPID3 LDA (≤2)
ORAL Standard (MTX-IR)				
Tofacitinib 5 mg BID	32/193 (16.6)*	65/193 (33.7)*	38/193 (19.7)	75/193 (38.9)
Tofacitinib 10 mg BID	36/194 (18.6)*	78/194 (40.2)*	44/194 (22.7)	81/194 (41.8)
Adalimumab	25/197 (12.7)	55/197 (27.9)	33/197 (16.8)	68/197 (34.5)
Placebo	7/104 (6.7)	21/104 (20.2)	-	-
ORAL Start (MTX-naïve)				
Tofacitinib 5 mg BID	86/363 (23.7)*	153/363 (42.2)*	107/363 (29.5)*	170/363 (46.8)*
Tofacitinib 10 mg BID	123/390 (31.5)*	201/390 (51.5)*	139/390 (35.6)*	198/390 (50.8)*
MTX	22/182 (12.1)	52/182 (28.6)	23/182 (12.6)	53/182 (29.1)
ORAL Scan (MTX-IR)				
Tofacitinib 5 mg BID	39/309 (12.6)	92/309 (29.8)	55/309 (17.8)	108/309 (35.0)
Tofacitinib 10 mg BID	62/308 (20.1)	120/308 (39.0)*	75/308 (24.4)	134/308 (43.5)
Placebo	21/154 (13.6)	41/154 (26.6)	-	-
ORAL Solo (DMARD-IR)				
Tofacitinib 5 mg BID	30/241 (12.5)*	69/241 (28.6)*	41/241 (17.0)	81/241 (33.6)
Tofacitinib 10 mg BID	42/241 (17.4)*	78/241 (32.4)*	58/241 (24.1)	96/241 (39.8)
Placebo	6/120 (5.0)	16/120 (13.3)	-	-
ORAL Sync (DMARD-IR)				
Tofacitinib 5 mg BID	46/311 (14.8)	100/311 (32.2)	54/311 (17.4)	113/311 (36.3)
Tofacitinib 10 mg BID	60/308 (19.5)*	98/308 (31.8)	56/308 (18.2)	120/308 (39.0)
Placebo	19/157 (12.1)	41/157 (26.1)	-	-
ORAL Step (TNFi-IR)				
Tofacitinib 5 mg BID	13/132 (9.9)	30/132 (22.7)*	16/132 (12.1)	34/132 (25.8)
Tofacitinib 10 mg BID	17/133 (12.8)*	36/133 (27.1)*	20/133 (15.0)	42/133 (31.6)
Placebo	5/131 (3.8)	12/131 (9.2)	-	-

Non-responder imputation was used for missing values. *p<0.05 vs placebo/MTX.

[a]3 months (ORAL Step and Solo) or 6 months (ORAL Start, Scan, Sync, and Standard).

[b]6 months (ORAL Step and Solo), 12 months (ORAL Sync and Standard), or 24 months (ORAL Scan and Start).

BID, twice daily; IR, inadequate responder; LDA, low disease activity; P3, Phase 3; RAPID3, routine assessment of patient index data 3; TNFi, tumor necrosis factor inhibitor.

Disclosure: M. J. Bergman, AbbVie, Amgen, BMS, Genentech, Janssen, Pfizer Inc, Novartis, Celgene, 5,AbbVie, Novartis, Celgene, 8,Johnson and Johnson, BMS, Merck, Pfizer Inc, 1; **Y. Yazici**, BMS, Celgene, Genentech, 2,BMS, Celgene, Genentech, 5; **A. Dikranian**, Pfizer Inc, AbbVie, 5,Pfizer Inc, AbbVie, 8; **J. Bourret**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Zang**, Pfizer Inc, 1,Pfizer Inc, 3; **C. F. Mojcik**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 3,Pfizer Inc, 1.

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Abstract Number: 1601

Maintenance Treatment Using Abatacept with Dose Reduction after Achievement of Low Disease Activity in Patients with Rheumatoid Arthritis (MATADOR) – a Prospective, Multicentered, Single Arm Clinical Trial

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Session Time: 9:00AM-11:00AM

Background/Purpose: Aim of this study was to evaluate the feasibility of maintenance therapy with reduced dose of abatacept (ABT) to 250mg/body after achieving low disease activity (LDA).

Methods: RA patients treated with ABT at 13 sites were enrolled to this prospective, interventional study during the period between March 2013 and March 2015. This study was approved by the ethical committee of Hokkaido University or by each clinical center (UMIN-ID：UMIN000010286). Inclusion criteria were as follows: 1) ages at 20 years or older, 2) under treatment with intravenous ABT at approved doses based on weight range, 3) in LDA (DAS28-CRP < 3.2) at least for 6 months, 4) agreed to join this trial with written informed consent, 5) body weight under 125 kg. Recruited patients were maintained with intravenous monthly ABT at a dose of 250 mg/body (MATADOR protocol). The primary end point was the proportion of the patients continued with MATADOR protocol at 1-year. Secondary endpoints included disease activity measured by DAS28CRP, safety and tolerability. Therapy with reduced dose was discontinued when physicians decided upon disease flare or other reasons, when patients requested, or when severe adverse event(s) occurred.

Results: A total of 57 patients were enrolled fulfilling above criteria and received ABT with MATADOR protocol. Data at 1-year was collected from 53 patients. Age of the patients was 60 ± 11 year (mean, SD) and disease duration was 10.5 ± 9.1 years (mean, SD). Methotrexate was used in 60% (32/53) of the patients at dose of 9.0 ± 3.3 mg/wk (mean, SD). MATADOR protocol was continued for 1-year in 81% (43/53) of the evaluated patients. In 5 patients, ABT was re-increased to the original dose. Resting patients discontinued because of severe adverse events in 2, switching to other bDMARDs in 2, and one dropout. DAS28CRP and remission rate (DAS28CRP < 2.6) was 1.59 ± 0.48 (mean, SD) and 88% (46/53) at the beginning of MATADOR protocol and 1.74 ± 0.70 (mean, SD) and 81% (43/53) at 1-year.

Conclusion: In the early phase II study conducted in Japan, placebo or monthly intravenous ABT at 2mg/kg or 10mg/kg was given for active RA patients despite methotrexate treatment. ACR20 response was significantly better both in the 2mg/kg and 10mg/kg group compared with the placebo (Takeuchi T et al, *Mod Rheumatol* 2013). Therefore, it would be

understandable that 250mg/body of ABT exerts its therapeutic effect in patients once reached remission or LDA with approved doses of ABT. Reducing dose of monthly intravenous ABT (250mg/body) is a realistic choice of maintenance therapy for patients with RA after achievement of remission or LDA with approved doses of ABT.

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Abstract Number: 1602

Persistence of Tofacitinib in the Treatment of Rheumatoid Arthritis in Open-Label, Long-Term Extension Studies up to 8 Years

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Background/Purpose: Tofacitinib is an oral JAK inhibitor for the treatment of RA. Open-label, long-term extension (LTE) studies enrolled tofacitinib-treated patients (pts) to evaluate safety and efficacy over time. The time on treatment is considered a composite measure of efficacy and safety, as discontinuation (D/C) is often due to lack of efficacy (LOE) and/or adverse events (AEs) for DMARDs. This analysis estimated drug survival of tofacitinib up to 96 months (mo; 8 years) in LTE studies and describes reasons for D/C.

Methods: Data were pooled from 2 LTE studies (NCT00413699 [ongoing; database unlocked at March 2015 data-cut] and NCT00661661) of pts with RA who had participated in Phase (P) 1/2/3 tofacitinib studies. Of the 6570 pts from P1/2/3 studies, 4867 pts (74.1%) received treatment in LTE studies. Pts received tofacitinib 5 or 10 mg BID as monotherapy or with background DMARDs. Assignment to tofacitinib dose group in this analysis was based on the average daily dose in LTE. Kaplan-Meier analyses estimated drug survival in pts who withdrew for any reason, due to LOE or due to AEs in the LTE, including pts who had previously responded to and tolerated treatment in P1/2/3 studies. Ongoing pts were censored as of March 2015, while pts completing the trial(s) were censored at their completion date. Data are included over 96 mo. Retention data were analyzed by dose, mono vs combination therapy, and baseline characteristics.

Results: 4867 pts were treated for a mean (maximum) duration of 3.0 (7.9) years (yrs) in the LTE. Overall, the median survival for all tofacitinib-treated pts in the LTE was 5.0 yrs [95% CI 4.7, 5.2]; for pts receiving tofacitinib with background DMARDs was 4.9 [4.5, 5.2] yrs and as monotherapy was 5.1 [4.6, 5.9] yrs. Similar survival was observed between doses: median survival was 5.2 [4.8, 5.7] and 4.8 [4.5, 5.2] yrs for 5 and 10 mg BID, respectively. The D/C rate due to LOE was considerably lower than due to AEs (LOE: 3.1%, 3.5%, 3.0%; AEs: 21.6%, 25.2%, 20.0% for all tofacitinib, 5 or 10 mg BID, respectively). The most commonly reported reasons for D/C due to AEs by system organ class were infections/infestations (8.8%, 8.5%, 8.9%), investigations (4.2%, 5.6%, 3.5%) and neoplasms (benign, malignant,

unspecified) (3.2%, 4.4%, 2.8%) for all tofacitinib, 5 or 10 mg BID, respectively. Overall, median survival was generally similar for pts receiving all tofacitinib, 5 and 10 mg BID across selected baseline characteristics (tofacitinib 5 mg BID, Table; tofacitinib all and 10 mg BID, data not shown).

Conclusion: Drug survival in LTE studies provides important information on the long-term safety, efficacy, and tolerability of a therapy. Median survival of tofacitinib was ~5 yrs, with D/C more commonly associated with AEs than LOE. Similar survival was observed for the 5 and 10 mg BID dose groups, for mono vs combination therapy, and across selected baseline characteristics. These data support the use of tofacitinib for long-term RA management.

Table. Median survival by selected baseline characteristics[a] for patients who received tofacitinib 5 mg BID[b]

Baseline characteristic	Total patients	Patients with event (%)[c]	Censored patients (%)[c]	Median survival, yrs (95% CI)
All patients	1,471	48.7	51.3	5.2 (4.8, 5.7)
RF+	930	48.5	51.5	5.5 (5.0, 6.0)
RF-	291	56.7	43.3	4.4 (3.5, 5.2)
Anti-CCP+	333	38.7	61.3	4.4 (3.9, NE)
Anti-CCP-	84	50.0	50.0	3.3 (2.7, NE)
Disease duration				
<1 yr	129	46.5	53.5	4.9 (3.3, NE)
≥1 yr	1,342	48.9	51.1	5.2 (4.8, 5.7)
DAS Q1[d]	289	42.2	57.8	4.9 (4.2, NE)
DAS Q2[d]	271	42.4	57.6	5.0 (4.5, NE)
DAS Q3[d]	240	43.3	56.7	5.5 (4.6, NE)
DAS Q4[d]	213	50.7	49.3	4.2 (3.5, 6.0)

[a]Baseline values were taken from the P1/2/3 index studies
[b]Tofacitinib dose group was based on the average TDD for each patient: TDD <15 mg was considered 5 mg BID; TDD ≥15 mg was considered 10 mg BID
[c]Percentages are based on the total number of patients with available data for each baseline characteristic
[d]DAS quartiles were based on all tofacitinib-treated patients
BID, twice daily; CI, confidence interval; CCP, citric citrullinated peptide; DAS, disease activity score; NE, not evaluable; Q, quartile; RF, rheumatoid factor; TDD, total daily dose; yrs, years

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Abstract Number: 1603

Clinical Responses to Tocilizumab Analyzed By Serologic Status in Rheumatoid Arthritis

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Clinical Responses to Tocilizumab Analyzed by Serologic Status in Rheumatoid Arthritis

Background/Purpose: Biologic medications have improved outcomes for patients with rheumatoid arthritis (RA), but little is known about factors that predict individual response to therapy. One potential factor is the presence or absence of rheumatoid factor (RF) or anti-cyclic citrullinated peptide antibodies (CCP). Rituximab and some csDMARDs show greater efficacy in patients with RF or CCP than in seronegative patients. Recent studies have shown increased expression of genes and activation of IL-6/STAT3 pathways and transcription factors in seronegative RA patients compared with seropositive patients. Tocilizumab (TCZ), a monoclonal antibody to the IL-6 receptor, targets this pathway. We evaluated whether seronegative RA patients differed in their response to TCZ as compared to seropositive patients.

Methods: Data from the US Corrona RA registry were analyzed. Patients with RA starting on TCZ with a follow up visit 4-8 months following initiation of therapy were included. Serological status was analyzed by three methods: seropositivity was defined as RF positive, CCP positive, and either RF or CCP positive. Univariate tests of change scores for measures of disease activity between baseline and follow-up were made for each definition of seropositivity. General linear models were used to adjust for disease duration and baseline disease activity level.

Results: 482 patients initiating TCZ with information on CCP and/or RF status were included. CCP or RF positive patients were less likely to be white and had longer disease duration than seronegative patients; other demographic and clinical features were similar. Univariate analysis showed significant decrease in most measures of clinical disease activity and ESR and CRP with TCZ treatment in both seropositive and seronegative groups (table 1), but no significant differences in responses between groups were observed. Adjusted analyses accounting for disease duration and baseline activity also showed no difference in improvement by serostatus.

Conclusion: In this cohort of patients with RA, the presence of RF or CCP did not influence initial response to TCZ for most measures of disease activity. Both groups had statistically significant improvements in clinical disease activity measures and inflammatory markers. **Table 1:** Differences in disease activity from time of Tocilizumab initiation to follow up, by serologic status at baseline, N=482

Measure of disease activity	CCP and/or RF Seropositive N=343		CCP/RF Seronegative, N=139 (both neg or 1 neg & 1 missing)		Two-sided p values between groups
	Change Score Median, IQR	Visit Change p value+	Change Score Median, IQR	Visit Change p value+	
CDAI	-6.6 -15.6, 0	**<0.01**	-8.5 -17.5, -2.6	**<0.01**	0.12
mHAQ N=336; 139	0 -0.25, 0.13	**0.012**	0 -0.25, 0.13	0.08	0.88
Tender Joint Count (28)	-2 -8, 0	**<0.01**	-3 -9, 0	**<0.01**	0.30
Swollen Joint Count (28)	-2 -5, 0	**<0.01**	-2 -6, 0	**<0.01**	0.06
Patient Disease Activity (VAS)	-7 -25, 7	**<0.01**	-10 -20, 2	**<0.01**	0.74
Patient Pain (VAS)	-5 -25, 10	**<0.01**	-5 -20, 5	**<0.01**	0.77
Patient fatigue (VAS), N=285, 125	-5 -18, 10	**<0.01**	-6 -22, 5	**<0.01**	0.24
MD Disease Activity (VAS)	-14 -30, 0	**<0.01**	-16 -30, 0	**<0.01**	0.27
ESR N=96, 45	-10 -28, 0	**<0.01**	-4 -20, -1	**<0.01**	0.16
CRP (mg/L) N=115; 50	-4.6 -14.9, 0	**<0.01**	-1.8 -7, 0	**<0.01**	0.13
mDAS28 N=336; 139	-0.76 -1.7, 0.07	**<0.01**	-0.88 -1.7, -0.2	**<0.01**	0.19
CDAI: clinical disease activity index; VAS: visual analogue scale; mHAQ: modified health assessment questionnaire; mDAS28: modified disease activity score 28					

+ p values between baseline and follow up are calculated using sign tests (this test ignores ties when computing p values) * p values between groups use two-sided Wilcoxon two-sample tests and ranked difference scores from each group (this test uses the distribution of ranks when computing p values)

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a First-in-Human Study of CR6086, a New Potent EP4 Prostanoid Receptor Antagonist, Demonstrates Good Safety and Tolerability at Therapeutically Relevant Exposures

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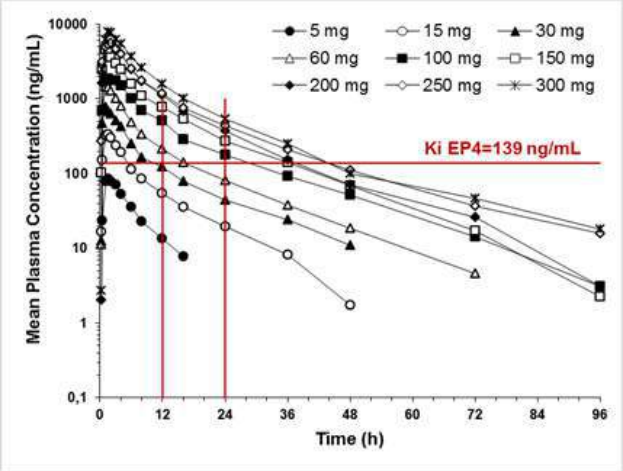
Background/Purpose: CR6086 is a potent and selective antagonist of the prostaglandin EP4 receptor. EP4 receptors have a role in T-cell differentiation and expansion, and thus in the altered immune response in autoimmune diseases such as rheumatoid arthritis. EP4 receptors are then a rational target for novel DMARDs/immunomodulators with added anti-inflammatory properties. Indeed, when oral CR6086 was tested in a series of widely accepted models of arthritis in rodents, it was at least as effective as biological DMARDs in all parameters examined, including edema, clinical arthritis score, and histology. The present first-in-human study evaluated the safety, tolerability, and pharmacokinetics of CR6086 in single ascending doses.

Methods: Oral doses of CR6086 ranging from 5 to 300 mg were administered to healthy men in a randomized, double blind, placebo-controlled fashion. Each of the nine cohorts comprised 6 volunteers on active and 2 on placebo. Food interaction was assessed at 150 mg.

Results: CR6086 was well tolerated up to 300 mg, and the maximum tolerated dose was not reached.The few observed adverse events where mild or moderate in severity, all resolved spontaneously, and their incidence was not dose-related. The pharmacokinetics of CR6086 were dose-independent, with mean peak plasma concentrations (C_{max}) ranging from 90 to 8151 ng/mL and occurring between 1 and 1.75 h after administration. The extent of bioavailability (AUC) ranged from 602 to 68200 ng.h/mL and a high fat meal did not affect CR6086 bioavailability. Plasma protein binding was around 95% (unbound fraction; $f_u = 0.0564$) and CR6086 did not invert into its antipode. CR6086 elimination half-life averaged 13 h and urinary excretion of the unchanged drug was a minor elimination route. Mean peak plasma concentrations of CR6086 (Figure) were above the K_i for the human EP4 receptor (adjusted for plasma protein binding) already at a dose of 15 mg. From the 100 mg dose, the plasma concentrations of CR6086 were higher than the adjusted K_i for a 24-hour period. A comparison with the exposure in rodents indicated that from the single dose of 30 mg, the exposure is pharmacologically relevant in humans.

Conclusion: CR6086 was safe up to the maximum tested dose of 300 mg. The compound is characterized by dose-independent pharmacokinetics producing therapeutically relevant concentrations at well tolerated doses in support for further clinical development as a novel DMARD.



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Abstract Number: 1605

Pooled Safety and Efficacy of Sarilumab in Rheumatoid Arthritis Patients 65 Years of Age and Older

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Background/Purpose: Sarilumab is a human mAb blocking the IL-6Rα. Sarilumab (150 or 200 mg every 2 weeks [q2w] subcutaneously) + MTX demonstrated efficacy vs placebo in patients with RA and inadequate response to MTX (MOBILITY; NCT01061736),[1] and sarilumab (150 or 200 mg q2w) + conventional synthetic DMARDs demonstrated efficacy vs placebo in patients with RA and inadequate response to or intolerance of TNF inhibitors (TARGET; NCT01709578).[2] In both studies, the most common treatment-emergent adverse events (TEAEs) included infections, neutropenia, injection site reactions, and increased transaminases.[1,2] In this pooled exploratory analysis, safety and efficacy of sarilumab were examined in patients <65 and ≥65 years of age from MOBILITY and TARGET.

Methods: Safety and efficacy endpoints (Table) were analyzed in subgroups of patients <65 and ≥65 years. A logistic regression model was used to analyze ACR20 and DAS28-CRP <2.6 responses, and a mixed-effect model for repeated

measures was used for HAQ-Disability Index (HAQ-DI), DAS28-CRP, and clinical disease activity index (CDAI).

Results: In both subgroups, most patients were female (80%-82%). In patients ≥65 years, mean RA duration was longer (13.2 vs 9.5 years) and a higher proportion had prior biologic use (63% vs 48%) vs those <65 years. In both subgroups, incidence of TEAEs and serious AEs (SAEs) was greater in sarilumab-treated patients vs placebo. Infections were the most common TEAEs with sarilumab in both age groups. Incidence of SAEs, including serious infections, was higher in patients ≥65 years vs patients <65 years. In both subgroups, both sarilumab doses vs placebo led to numerically higher ACR20 and DAS28-CRP <2.6 response rates at week 24, improvement from baseline in HAQ-DI at week 12, and improvement from baseline in DAS28-CRP and CDAI at week 24 (Table). In general, efficacy of sarilumab 150 and 200 mg q2w was comparable between patients ≥65 years and <65 years. There was some variability in the proportion of patients >65 years who achieved ACR20 and DAS28-CRP <2.6 responses due to the small number of patients in this subgroup; however, the age-by-treatment interaction was not significant for any of the efficacy endpoints (P>0.2).

Conclusion: Adverse events in both age groups were consistent with the known safety profile of sarilumab. SAEs occurred more frequently in patients ≥65 years compared with patients <65 years, consistent with other studies of biologic agents in the elderly.[3] Both sarilumab doses were superior to placebo in ACR20 and DAS28-CRP <2.6 responses, DAS28-CRP, and CDAI at week 24 and in change from baseline in HAQ-DI at week 12 in both subgroups defined by age. **References:** 1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437. 2. Fleischmann et al. Presented at: ACR; November 7-11, 2015; San Francisco, CA. 3. Ishchenko et al. *Drugs Aging*. 2016;33:387-398.

Table. Pooled Analysis of Safety and Efficacy of Sarilumab in Patients From 2 Phase 3 Studies (MOBILITY and TARGET)

Safety						
	<65 Years of age (N=1716)			**≥65 Years of age (N=266)**		
	Placebo (n=573)	**Sarilumab 150 mg q2w (n=574)**	**Sarilumab 200 mg q2w (n=569)**	**Placebo (n=88)**	**Sarilumab 150 mg q2w (n=86)**	**Sarilumab 200 mg q2w (n=92)**
Any TEAE	326 (56.9)	406 (70.7)	418 (73.5)	52 (59.1)	59 (68.6)	70 (76.1)
Any infection	166 (29.0)	200 (34.8)	194 (34.1)	23 (26.1)	27 (31.4)	39 (42.4)
Serious TEAE	24 (4.2)	35 (6.1)	42 (7.4)	7 (8.0)	7 (8.1)	17 (18.5)
Discontinuations due to TEAE	24 (4.2)	60 (10.5)	66 (11.6)	7 (8.0)	12 (14.0)	17 (18.5)
Serious infections	10 (1.7)	8 (1.4)	15 (2.6)	2 (2.3)	4 (4.7)	4 (4.3)
ALT >3 x ULN	10 (1.7)	46 (8.0)	41 (7.2)	1 (1.1)	3 (3.5)	2 (2.2)
ANC <1.0 Giga/L	0	34 (5.9)	50 (8.8)	1 (1.1)	6 (7.0)	11 (12.0)
Efficacy						
	<65 Years of age (N=1520)			**≥65 Years of age (N=223)**		
	Placebo (n=509)	**Sarilumab 150 mg q2w (n=509)**	**Sarilumab 200 mg q2w (n=502)**	**Placebo (n=70)**	**Sarilumab 150 mg q2w (n=72)**	**Sarilumab 200 mg q2w (n=81)**
ACR20 at week 24[a]						
Number	509	509	502	70	72	81
Response, n (%)	176 (34.6)	292 (57.4)	335 (66.7)	18 (25.7)	41 (56.9)	42 (51.9)
OR (95% CI vs placebo)	-	2.6 (2.0, 3.4)	3.9 (3.0, 5.0)	-	4.0 (1.9, 8.3)	3.0 (1.5, 6.0)
HAQ-DI at week 12[b]						
Number	487	473	473	66	66	76
LS mean change from baseline +/- SE	-0.27 +/- 0.02	-0.47 +/- 0.02	-0.53 +/- 0.02	-0.21 +/- 0.06	-0.43 +/- 0.06	-0.48 +/- 0.06
LS mean difference, 95% CI		-0.20 (-0.27, -0.14)	-0.26 (-0.33, -0.19)		-0.22 (-0.39, -0.04)	-0.26 (-0.43, -0.10)
DAS28-CRP at week 24[b]						
Number	310	386	398	38	48	52
LS mean change from baseline +/- SE	-1.25 +/- 0.07	-2.43 +/- 0.07	-2.81 +/- 0.07	-1.06 +/- 0.20	-2.42 +/- 0.19	-2.87 +/- 0.18
LS mean difference, 95% CI		-1.18 (-1.37, -1.00)	-1.56 (-1.75, -1.38)		-1.35 (-1.88, -0.82)	-1.81 (-2.33, -1.29)
DAS28-CRP <2.6 at week 24[a]						
Number	509	509	502	70	72	81
Yes, n (%)	46 (9.0)	136 (26.7)	169 (33.7)	7 (10.0)	20 (27.8)	20 (24.7)
OR (95% CI vs placebo)	-	3.9 (2.7, 5.6)	5.2 (3.6, 7.4)	-	3.2 (1.2, 8.1)	3.1 (1.2, 8.1)
CDAI at week 24[b]						
Number	311	387	401	39	48	53
LS mean change from baseline +/- SE	-15.4 +/- 0.7	-24.2 +/- 0.7	-26.1 +/- 0.7	-12.8 +/- 1.9	-22.2 +/- 1.8	-25.4 +/- 1.7
LS mean difference, 95% CI		-8.8 (-10.7, -6.9)	-10.6 (-12.6, -8.7)		-9.5 (-14.5, -4.4)	-12.6 (-17.5, -7.7)

ALT, alanine aminotransferase; ANC, absolute neutrophil count; CDAI, clinical disease activity index; CI, confidence interval; HAQ-DI, HAQ-Disability Index; ITT, intent-to-treat; LS, least squares; MMRM, mixed model repeated measures; OR, odds ratio; q2w, every 2 weeks; SE, standard error; TEAE, treatment-emergent adverse event; ULN, upper limit of normal. Patients are considered ACR20 nonresponders from the time they started rescue medication or discontinued study medication. Missing HAQ-DI, DAS28-CRP, and CDAI measurements were not imputed. [a]Mantel-Haenszel estimate stratified by region. [b]MMRM assuming unstructured covariance structure.

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Abstract Number: 1606

Metrotexate Treatment Inmunomodulate the Abnormal Cytokine Expression Present in NaïVe Rheumatoid Arthritis Patients

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster II

Session Type: ACR Poster Session B

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Background/Purpose: Methotrexate (MTX) is the most commonly used DMARD in rheumatoid arthritis (RA) patients. Since the first reports of the efficacy of low-dose MTX in RA, several studies have established its central role in the treatment of RA. Activated T CD4+ lymphocytes play a pivotal role secreting cytokines initiating and perpetuating the chronic inflammation characteristic for this disease. The role of circulating $CD4^+$T lymphocytes in early RA is under discussion and is not well understood. The objective is evaluate the number of IFNγ, IL-4, IL-9 and IL-17 producing $CD4^+$ T lymphocytes and in their $CD4^+$ naïve T cells (T_N), central memory (T_{CM}), non-terminated effector memory (T_{NTEM}) and terminated effector memory (T_{TEM}) T cells activation/differentiation subsets in a population of recently diagnosed DMARD naïve RA patients along the first 6 months of methotrexate (MTX) treatment.

Methods: The number of IFNγ, IL-4, IL-9 and IL-17 producing CD4+ T lymphocytes, and in their T_N, T_{CM}, T_{NTEM} and T_{TEM}subsets in forty untreated patients with RA before MTX treatment and at 3 and 6 months of treatment were assayed using a multiparametric flow cytometry. We have obtained peripheral blood mononuclear cells (PBMC) from AR patients. PBMC were stimulated during six hour with phorbol-myristate-acetate and ionomycin. To study the intracellular cytokine production of CD4+ T lymphocytes we used the next surface antigens: CD3, CD4, CD45RA, CD27, cells were fixed and permed, and simultaneously stained with the next intracellular cytokines: IFNγ, IL-4, IL-9 and IL-17. We acquired in a FacsAria-II flow cytometer and analyzed in Diva and Flow-Jo software. We also studied twenty-five age and sex-matched

healthy subjects as controls.

Results: MTX treatment provoke a significant decrease of the IFNγ CM, NTEM and TEM effector producing T CD4 lymphocytes but not in naïve T CD4+ cells at 3 and 6 months of MTX treatment. However, the IL-17 naïve producing T CD4 lymphocytes were significant expanded along the 6 months of MTX treatment. In other hand, IL-17 CM and NTEM producing T CD4 lymphocytes were significant decreased at 6 months of MTX treatment. The intracellular expression of IL-4 and IL-9 do not shown alterations in RA naïve patients along the MTX treatment.

Conclusion: MTX treatment show immunomodulatory effects on circulating IFNγ and IL-17 producing T CD4 lymphocytes activation/differentiation stage subsets along the first 6 months of MTX treatment. Therefore, MTX are able to reduce the inflammation produce by Th1 effector T CD4 lymphocytes at 6 months. However, MTX are able to reduce Th17 in central memory but not in naive T CD4 lymphocytes, that appear increased, at 6 months of treatment.

Disclosure: J. Monserrat Sanz, None; **A. M. Gómez Lahoz**, None; **M. D. Sosa Reina**, None; **C. Bohórquez Heras**, None; **A. Movasat**, None; **A. Pérez Gómez**, None; **L. Ruiz Gutiérrez**, None; **A. Sánchez Atrio**, None; **E. Cuende Quintana**, None; **M. J. León**, None; **D. Diaz**, None; **F. Albarrán Hernández**, None; **M. Alvarez-Mon**, None.

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Abstract Number: 1607

The Development of a New Anti–Interleukin 6 Blocker for Rheumatoid Arthritis Patients

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Background/Purpose: While interleukin-6 (IL-6) blockade with monoclonal antibodies is an established, clinically validated mechanism for the treatment of rheumatoid arthritis (RA), the need for significant quantities of protein due to the potency and half-life of available agents with resultant high cost has limited patient access to these medications. We have developed gerilimzumab, a highly potent anti-IL6 cytokine antibody with a long half-life, to address this problem. Gerilimzumab is a humanized llama antibody with femtomolar potency and a Fc region mutation engineered to prolong half-life. A 20-24-day half-life in cynomolgus monkeys was observed. We now evaluate the safety of gerilimzumab in healthy volunteers and whether the long half-life seen in monkeys translates to a long half-life in human subjects.

Methods: The primary objective of our multi-ascending dose study was to assess the safety and tolerability of gerilimzumab when administered as three SC doses at 4-weekly intervals to healthy adult participants. Two cohorts were included in the study: a gerilimzumab 5 mg and 20 mg cohort. Each cohort included 6 subjects treated with active drug and 3 subjects treated with placebo.

Results: No SAEs or deaths were observed during the study. All adverse events were mild or moderate in severity. One participant was withdrawn due to a mild urticarial rash. Only injection-site erythema occurred in a dose dependent manner. No laboratory, vital signs or ECG findings of clinical significance were assessed by the investigator. All participants in the placebo and gerilimzumab groups recorded negative ADA test results at all time points. While steady state was not achieved in this study, the estimated half-life of gerilimzumab was approximately 50 days for the 20 mg cohort and

exposure was dose-proportional. No anti-drug antibodies were detected over the course of the study. A numeric decrease from baseline in C-reactive protein, a pharmacodynamic marker of an anti-IL6 effect, was observed in the gerilimzumab groups.

Conclusion: Overall, gerilimzumab (within the dose range 5 mg to 20 mg) appeared safe and well tolerated when administered as three SC injections with an inter-dosing interval of 28 days to healthy volunteers. Gerilimzumab's long half-life and expected potency (based upon preclinical data) differentiate it from other anti-IL6 monoclonal antibodies and provides the potential for a very low cost and conveniently dosed biologic therapy for RA.

Disclosure: A. Glicklich, Bird Rock Bio, Inc, 1,Bird Rock Bio, Inc, 3; **P. Grayson**, Bird Rock Bio, 1,Bird Rock Bio, 3,Bird Rock Bio, 6; **C. Blanchetot**, Argenx, 1,Argenx, 3; **Q. Zhou**, Genor Biopharma Co. Ltd, 3; **A. Kretz-Rommel**, Bird Rock Bio, Inc, 3,Bird Rock Bio, 1.

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Abstract Number: 1608

Lack of Early Change in Disease Activity Score Predicts the Likelihood of Achieving Low Disease Activity at Month 6: Tofacitinib Monotherapy Versus Methotrexate in Methotrexate-Naive Patients with Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral JAK inhibitor for the treatment of rheumatoid arthritis (RA). Treatment guidelines recommend targeting remission or low disease activity (LDA), herein defined as Disease Activity Scores ≤3.2 based on 28 joint counts (DAS28≤3.2) and adjusting therapy after 3–6 months[1] (Mos). Predicting the likelihood of clinical response may help inform early treatment decisions. The aim of this study was to understand the relationship between timing and magnitude of early changes in DAS28, erythrocyte sedimentation rate (DAS28-4[ESR]) and the likelihood of achieving LDA at Mo 6 in RA patients (pts) naïve to methotrexate (MTX).

Methods: In a Phase 3 study (ORAL Start; NCT01039688), MTX-naïve RA pts were randomized 2:2:1 to the following monotherapies: tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID or MTX. Conditional probabilities of pts achieving LDA at Mo 6 were calculated, given failure to achieve DAS28-4(ESR) improvement from baseline (range ≥0.3 to 1.8) at Mo 1 or 3. One-year data with non-responder imputation for missing values was used.

Results: 948 pts received treatment; tofacitinib 5 mg BID (n=370), tofacitinib 10 mg BID (n=394) or MTX (n=184); results previously reported.[2] In this post-hoc analysis, of those patients who failed to achieve DAS28-4(ESR) improvement from baseline ≥1.2 at Mo 3, 6.8% for tofacitinib 5 mg BID, 11.3% for tofacitinib 10 mg BID, and 6.2% for MTX achieved LDA at Mo 6 (Table). A minority of pts (74/353 [20.9%]) receiving tofacitinib 5 mg BID failed to achieve DAS28-4(ESR) improvement ≥1.2 from baseline at Mo 3, while a greater proportion failed for MTX (65/171 [38.0%]). Failure to achieve DAS28-4(ESR) improvement from baseline at Mo 3 (range ≥0.30–1.8) for tofacitinib 5 mg BID and MTX was associated

with a low probability (≤10%) of achieving LDA at Mo 6. For tofacitinib 5 mg BID, failure to achieve lower thresholds of DAS28-4(ESR) improvement (range ≥0.3 to 0.9) at Mo 1 was associated with lower probability of LDA at Mo 6 than higher DAS28-4(ESR) thresholds (≥1.2–1.8) (Table).

Conclusion: Failure to achieve DAS28-4(ESR) improvement ≥1.2 from baseline at Mo 3 was associated with a low probability of achieving LDA at Mo 6 (≤6.8%) for tofacitinib 5 mg BID and MTX. For the minority of MTX-naïve RA pts treated with tofacitinib 5 mg BID or MTX who failed to achieve a minimal clinical response (DAS28-4[ESR] improvement ≥1.2) by Mo 3, another treatment option can be considered at Mo 3, as there is a low probability of reaching LDA at Mo 6.
References: 1. Smolen J et al. Ann Rheum Dis 2016;75(1):3-15. 2. Lee EB et al. N Engl J Med 2014;370:2377-2386.

Given failure to achieve DAS28-4(ESR) improvement at Month 1 or 3		Percentage of patients achieving LDA at Month 6		
DAS28-4(ESR) improvement ≥	Month	Tofacitinib 5 mg BID	Tofacitinib 10 mg BID	MTX*
0.3	1	3.9	14.3	12.7
	3	0.0	15.4	5.0
0.6	1	9.8	18.2	12.8
	3	0.0	8.7	3.0
0.9	1	12.1	15.4	10.9
	3	6.0	11.4	7.8
1.2	1	14.7	19.5	10.0
	3	6.8	11.3	6.2
1.5	1	18.5	21.1	10.6
	3	8.7	11.1	6.5
1.8	1	22.6	23.5	12.8
	3	10.0	10.7	7.5

BID, twice daily; DAS28-4(ESR), disease activity score, erythrocyte sedimentation rate; LDA, low disease activity
*MTX dose – starting dose of 10 mg per week (mg/wk), with increments of 5 mg/wk every 4 weeks to 20 mg/wk by Week 8. Mean dose of MTX was 18.6 mg/wk

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Abstract Number: 1609

Efficacy of Tofacitinib in Patients Who Are Inadequate Responders to

Disease-Modifying Antirheumatic Drugs According to Early Versus Late Duration of Rheumatoid Arthritis: Post-Hoc Analysis of Data from Phase 3 Trials

Stephen Hall[1], Peter Nash[2], Maureen Rischmueller[3], Zirke Wiid[4], David Witcombe[5], David Gruben[6], Ryan DeMasi[7] and Tatjana Lukic[7], [1]Cabrini Medical Centre, Monash University, Melbourne, Australia, [2]University of Queensland, Brisbane, Australia, [3]The Queen Elizabeth Hospital, Adelaide, Australia, [4]Pfizer Australia, Sydney, Australia, [5]Pfizer Australia, Sydney, NSW, Australia, [6]Pfizer Inc, Groton, CT, [7]Pfizer Inc, New York, NY
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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

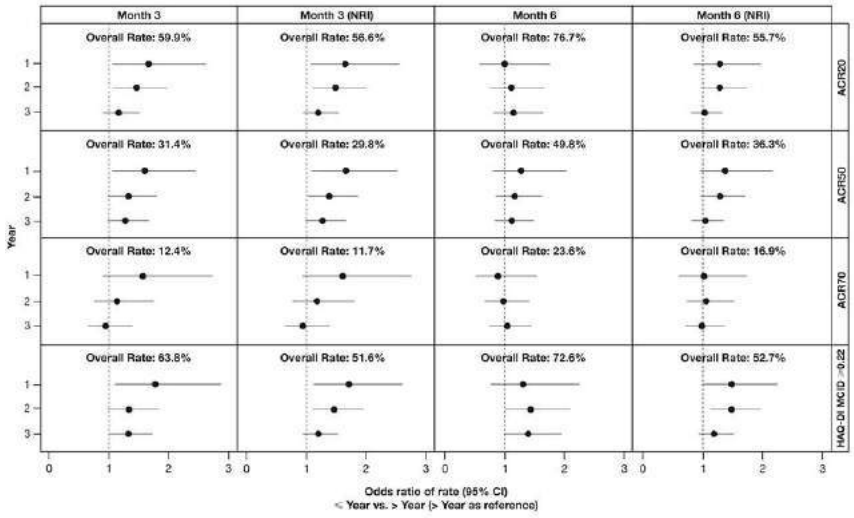
Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This post-hoc analysis of data from Phase 3 studies investigated the efficacy of tofacitinib in patients (pts) according to RA duration (early vs late).

Methods: Pts from 5 placebo-controlled Phase 3 studies (ORAL Step [NCT00960440]; ORAL Scan [NCT00847613]; ORAL Solo [NCT00814307], ORAL Sync [NCT00856544]; ORAL Standard [NCT00853385]) of tofacitinib as monotherapy or with background DMARDs were included. This analysis included pts who were inadequate responders (IR) to ≥1 DMARDs randomized to tofacitinib 5 mg or 10 mg BID, placebo or adalimumab (ORAL Standard); results for tofacitinib 5 mg BID are presented. Pts were evaluated according to RA duration at baseline (years [yr]): ≤1 vs >1; ≤2 vs >2; ≤3 vs >3. For each subset pair, at Month 3 and Month 6 we evaluated proportions of pts achieving ACR20/50/70 response, Disease Activity Score (ESR) (DAS 28-4[ESR]) <2.6 (remission), DAS28-4(ESR) ≤3.2 (low disease activity), HAQ-DI minimal clinically important difference (MCID) ≥0.22, 0.30, 0.50, and 0.80, and mean changes from baseline in DAS28-4(ESR) and HAQ-DI scores. Odds ratios (ORs [for rates]) and mean differences (for change from baseline) were calculated with corresponding 95% CIs, and 2-sided p values (‘>’ category as reference). Non-responder imputation (NRI) was applied for rates. Pts meeting criteria for rescue (failed to achieve ≥20% improvement from baseline at Month 3 in applicable studies) had NRI applied or were excluded from mean change analyses at Month 6.

Results: At Month 3, significantly greater OR for ACR20, ACR50, HAQ-DI MCID ≥0.22, and ≥0.30 were shown for ≤1 vs >1 yr and ≤2 vs >2 yr subsets (Figure). HAQ-DI MCID ≥0.50 and ≥0.80 were significantly greater for ≤1 vs >1 yr, ≤2 vs >2 yr, and ≤3 vs >3 yr subsets. For all other efficacy outcomes, ORs were not statistically significant between subsets at Month 3. Mean changes from baseline in DAS28-4(ESR) were significantly greater for ≤1 vs >1 yr and ≤2 vs >2 yr subsets at Month 3 (Table). Mean changes from baseline in HAQ-DI at Month 3 was significantly greater for ≤1 vs >1 yr, ≤2 vs >2 yr, and ≤3 vs >3 yr subsets. In general, higher responses were seen at Month 3 in pts with early vs late RA disease duration.

Conclusion: In this analysis, a trend was observed indicating that DMARD-IR pts with earlier disease duration at treatment initiation respond better to tofacitinib 5 mg BID than pts with late disease duration. Results suggest that initiating tofacitinib earlier in the disease may yield greater treatment response and thereby reduce the time pts experience active disease.

Figure. Odds ratios of achieving ACR20/50/70 response and HAQ-DI MCID ≥0.22 at Month 3 and Month 6 with tofacitinib 5 mg BID based on disease duration (FAS)



ACR, American College of Rheumatology; BID, twice daily; CI, confidence interval; FAS, full analysis set; HAQ-DI, health assessment questionnaire, disability index; MCID, minimal clinically important difference; NRI, non-responder imputation

Table. Mean change from baseline at Month 3 and Month 6 with tofacitinib 5 mg BID based on disease duration (FAS)

Parameter	Years	Month 3				Month 6			
		Duration ≤ (years)	Duration > (years)	Difference (95% CI)	p value	Duration ≤ (years)	Duration > (years)	Difference (95% CI)	p value
DAS28-4(ESR), mean (SE)	1	-2.11 (0.13) (n=90)	-1.80 (0.04) (n=920)	-0.30 (-0.58, -0.03)	0.0292	-2.42 (0.15) (n=75)	-2.33 (0.04) (n=701)	-0.09 (-0.40, 0.21)	0.5557
	2	-2.00 (0.09) (n=203)	-1.79 (0.04) (n=807)	-0.21 (-0.40, -0.01)	0.0374	-2.47 (0.10) (n=167)	-2.30 (0.05) (n=609)	-0.16 (-0.39, 0.05)	0.1387
	3	-1.88 (0.07) (n=304)	-1.81 (0.04) (n=706)	-0.07 (-0.24, 0.09)	0.3932	-2.42 (0.08) (n=233)	-2.30 (0.05) (n=543)	-0.12 (-0.32, 0.07)	0.2254
HAQ-DI, mean (SE)	1	-0.65 (0.06) (n=96)	-0.43 (0.01) (n=1,019)	-0.22 (-0.34, -0.10)	0.0002	-0.80 (0.08) (n=79)	-0.56 (0.02) (n=775)	-0.23 (-0.37, -0.10)	0.0008
	2	-0.56 (0.04) (n=226)	-0.42 (0.01) (n=889)	-0.13 (-0.22, -0.05)	0.0013	-0.72 (0.04) (n=182)	-0.55 (0.02) (n=672)	-0.17 (-0.27, -0.07)	0.0006
	3	-0.53 (0.03) (n=339)	-0.41 (0.02) (n=776)	-0.11 (-0.18, -0.03)	0.0026	-0.69 (0.04) (n=254)	-0.54 (0.02) (n=600)	-0.15 (-0.24, -0.06)	0.0007

BID, twice daily; CI, confidence interval; DAS28-4(ESR), Disease Activity Score in 28 joints, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire, disability index; FAS, full analysis set; SE, standard error

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Abstract Number: 1610

Safety, Tolerability, and Dose-Dependent Inhibition of T-Cell-Dependent Antibody Response with MEDI4920, a Novel, Engineered CD40L Antagonist: Results of a Single-Ascending Dose Study in Healthy Volunteers

Marius Albulescu[1], Jim Bush[2], Firas Almazedi[2], Ethan Grant[3], Alex Godwood[1], Robert Miday[4], Krista Arbaugh[4], Lisa H. Butler[1], Michele Gunsior[4], Jing Li[5] and David Howe[1], [1]MedImmune, Cambridge, United Kingdom, [2]Covance Clinical Research Unit, Leeds, United Kingdom, [3]Translational Medicine, MedImmune, Gaithersburg, MD, [4]MedImmune, Gaithersburg, MD, [5]MedImmune, Mountain View, CA

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Background/Purpose: The CD40L/CD40 co-stimulatory pathway is important for T-cell-dependent antibody production. Previous clinical programs with intact monoclonal antibodies against CD40L have been discontinued due to thromboembolic events (TE) despite preliminary evidence of clinical efficacy in autoimmune diseases such as systemic lupus erythematosus and idiopathic thrombocytopenic purpura. MEDI4920 is an engineered Fc-deficient CD40L antagonist that is being developed for treatment of numerous autoimmune diseases.

Methods: A Phase 1, randomized, double-blinded, placebo-controlled study was conducted to evaluate the safety and tolerability of single-ascending intravenous doses of MEDI4920 in healthy subjects. Secondary endpoints were T-cell–dependent antibody response (TDAR) inhibition, pharmacokinetic (PK) parameters, and anti-drug antibodies (ADAs) to MEDI4920. To assess TDAR, titers of IgG and IgM antibodies to neoantigen keyhole limpet hemocyanin (KLH) were quantified at Day 43 post-dose. A dose-response model was generated for TDAR inhibition. Fifty-six healthy adult male subjects were randomized and treated in this study: 3 subjects each in a 2:1 ratio in Cohorts 1 and 2 (3 and 10 mg of MEDI4920, respectively, or placebo) and 10 subjects each in a 4:1 ratio in Cohorts 3 through 7 (30, 100, 300, 1,000, and 3,000 mg of MEDI4920, respectively, or placebo).

Results: There were no deaths, no TE events or clinically significant coagulation or platelet function abnormalities, no severe or serious hypersensitivity reactions, no severe or serious infection events, and no infusion-related reactions. Only 1 serious adverse event of fractured tibia was reported in the placebo arm. No safety signals were identified overall. TDAR dose-response analysis at Day 43 demonstrated a statistically significant E_{max} dose response ($P < 0.001$; $ED_{50} = 491$ mg) with the 3,000 mg dose showing 86% inhibition of the TDAR IgG response compared to placebo (95% CI: 68%, 94%; Figure 1). PK parameters (C_{max} and AUC) increased dose proportionally. Most subjects in the lower dose cohorts (3, 10, 30, and 100 mg) developed ADAs to MEDI4920, whereas a decreasing trend was observed for the higher doses (300, 1,000, and 3,000 mg).

Conclusion: MEDI4920 demonstrated an acceptable safety and tolerability profile while showing significant dose-dependent inhibition of TDAR. These encouraging results support further exploration of the safety and efficacy of repeat administration of MEDI4920 in an autoimmune disease in which the CD40/CD40L pathway activation plays a significant role.

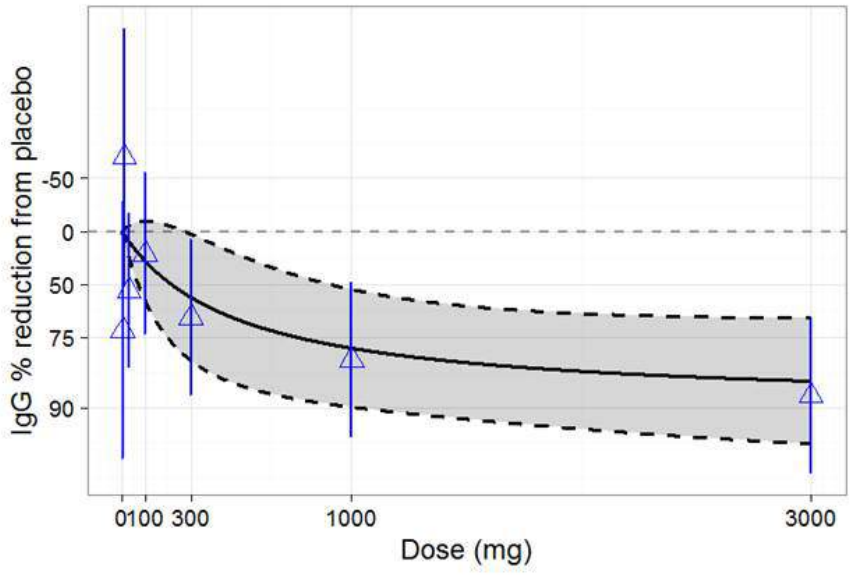

Figure 1: Plot of dose-response model for TDAR inhibition (anti-KLH IgG at Day 43).

Disclosure: M. Albulescu, AstraZeneca, 1,MedImmune, 3; **J. Bush**, Covance, 3,Covance, 1,Covance, 5; **F. Almazedi**, Covance, 3,Covance, 5; **E. Grant**, MedImmune, 3,AstraZeneca, 1; **A. Godwood**, MedImmune, 3,AstraZeneca, 1; **R. Miday**,

MedImmune, 3,AstraZeneca, 1; **K. Arbaugh**, MedImmune, 3,AstraZeneca, 1; **L. H. Butler**, AstraZeneca, 1; **M. Gunsior**, MedImmune, 3,AstraZeneca, 1; **J. Li**, AstraZeneca, 1,Medimmune, 3; **D. Howe**, MedImmune, 3,AstraZeneca, 1.

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Abstract Number: 1611

In Vitro Cellular Profiling of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, Reveals a Distinct Phenotypic Signature Compared to Tocilizumab, an Anti–IL-6 Receptor Monoclonal Antibody

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Background/Purpose: IL-6 plays a central pathogenic role in rheumatoid arthritis (RA). IL-6 signals through a complex of transmembrane IL-6R or soluble IL-6R (sIL-6R) with gp130 to mediate classic or *trans*-signaling, respectively. Sirukumab (CNTO 136) is a human IgG1 k monoclonal antibody (mAb) specific for human IL-6 cytokine and is currently in clinical trials for the treatment of adults with moderately to severely active RA and other diseases. A human primary cell-based phenotypic screening systems (BioMAP®) was used to investigate the effects of sirukumab and to identify discriminating biological activities compared to tocilizumab, an anti-IL-6R mAb. Comparisons were also made with a reference database that includes profiles of drugs used to treat RA.

Methods: BioMAP® systems model disease biology in primary human cells. Sirukumab was profiled across a panel of 12 BioMAP® systems, relevant to inflammatory diseases, at different concentrations in the presence or absence of sIL-6R (50ng/ml). Sirukumab profiles were directly compared to those of tocilizumab and indirectly to compounds already profiled in the BioMAP® reference database including adalimumab, tofacinitib, methotrexate and prednisolone in the presence or absence of sIL-6R. Serum samples from the RA phase 3 sirukumab studies (SIRROUND-M, D, T, & H) were also analyzed at baseline and week 4 post-treatment using the SomaLogic SOMAscan™.

Results: Sirukumab significantly inhibited expression of biomarkers linked to inflammation (P-selectin), immunomodulation (CD69, M-CSF) and tissue remodeling (MMP-9, aSMA, Collagen IV) in the BioMAP® systems. Addition of sIL-6R induced further biomarkers that sirukumab completely blocked. A direct comparison of sirukumab to tocilizumab showed that whilst there was a similar impact on multiple mediators, there were significant differences across all systems assessed. Sirukumab significantly decreased 5 (CD40, Collagen III & IV, TF, PAI-I) and increased 8 (IL-8, ICAM-1, IL-1a, IP-10, IL-2, EGFR, MIG, IL-10) biomarkers under sIL-6R *trans*-signaling; these mediators were not affected by tocilizumab. Conversely, tocilizumab significantly decreased 9 (P-selectin, uPAP, IL-18, MMP3, EGFR, IP-10, MCP-1, MIP-1a E-selectin) and increased 1 (VCAM-1) biomarkers which were not affected by sirukumab. Of note, the serum analysis of RA patients treated with sirukumab confirmed some of the changes seen in the BioMAP® systems, including reduction of PAI-I, increase in IP-10, and lack of decrease in MMP3, MCP-1, MIP-1a, and E-selectin levels. Indirect comparisons of sirukumab to adalimumab, tofacinitib, methotrexate and prednisolone using the BioMAP® algorithm showed that overall the drugs were not similar, reflecting different mechanisms of action.

Conclusion: Sirukumab has a unique BioMAP® phenotypic signature that is further separated from tocilizumab (as well as other reference profiles) with addition of sIL-6R. This signature was confirmed in sera from RA patients treated with sirukumab supporting the hypothesis that the impact of sirukumab on IL-6R signaling is distinct from tocilizumab. The clinical significance of these data requires further experimental exploration.

Disclosure: K. M. Chavele, GSK Medicines Research Centre, 3; **D. Gardner**, Janssen Research & Development, LLC, 3; **M. J. Loza**, Janssen Research & Development, LLC, 3; **B. Dasgupta**, Janssen Research & Development, LLC, 3; **M. Sims**, GSK Medicines Research Centre, 3; **D. Shealy**, Janssen Research & Development, LLC, 3; **J. Reid**, GSK Medicines Research Centre, 3; **R. Rao**, GSK Medicines Research Centre, 3.

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Abstract Number: 1612

Abatacept Targets T Follicular Helper Cells in Patients with Rheumatoid Arthritis

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Background/Purpose: In the pathogenesis of rheumatoid arthritis (RA), T cells can differentiate into functionally distinct subsets, leading to the persistent inflammation and immune abnormality associated with the interactive activation between B cells, monocytes and dendritic cells. However, little is known about pathological immune cell subsets targeted by biologic DMARDs (bDMARD) therapy. The aim of this study was to assess the therapeutic effects of bDMARDs on the diversity of immune cell phenotypes in peripheral blood of patients with RA.

Methods: Peripheral immune cell phenotypes were determined in 108 patients with bio-naïve RA who showed inadequate response to DMARDs and 26 healthy control (HC) subjects by comprehensive 8-color flow cytometric analysis for human immune system termed “the Human Immunology Project” by NIH and FOCIS. We also examined the correlation between the phenotypes and clinical course and assessed the effects of 24-week treatment with bDMARDs.

Results: The proportions of $CD3^+CD4^+CD45RA^-CCR7^-$ effector memory, $CD3^+CD4^+CD45RA^+CCR7^-$ effector T helper cells and $CD4^+CXCR5^+ICOS^+$ T follicular helper cells (Tfh) were higher in patients with active RA than in HC. The

percentages of memory T cells, $CD3^+CD4^+CXCR3^-CCR6^+$ Th17 cells and Tfh cells correlated with serum levels of autoantibodies, whereas that of $CD19^+CD20^-CD27^+CD38^+$ plasmablasts correlated with disease activity scores. All of bDMARDs markedly improved the disease activity scores after 24 week treatment. Treatment with TNF inhibitors reduced the proportion of $CD3^-CD19^-CD14^-CD20^-HLA\text{-}DR^+CD123^+$ plasmacytoid dendritic cells, while tocilizumab reduced the proportion of $CD19^+CD20^+IgD^-CD27^-$ double-negative B cells but increased $CD4^+CCR4^+CD25^+CD127^{low}$Treg cells. Abatacept treatment resulted in marked decrease in the proportion of activated Tfh and the absolute number of Tfh, but slightly reduced Th17 and Treg cells. The proportion of Tfh cells was an independent and significant predictor of the response to abatacept therapy.

Conclusion: These results indicated that the abnormal T cell differentiation correlated with autoantibody production while plasmablast did with disease activity of RA. Molecular targeted therapies induced different changes in different immune cell phenotypes. Among the phenotypes, Tfh cells seem a potential target for abatacept. Immunophenotypic analysis is useful for evaluation of the pathogenesis and prediction of the response to bDMARDs.

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Abstract Number: 1613

Safe and Effective Tocilizumab Therapy in Elderly Patients with Rheumatoid Arthritis

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Background/Purpose: The non-interventional study ICHIBAN was set up in 2010 to evaluate the effectiveness and safety of intravenously administered Tocilizumab (TCZ IV) in patients (pts) with moderate to severe RA in Germany. Clinical data were collected during routine medical consultations including concomitant therapies, co-morbidities, therapeutic responses and adverse events. This interim analysis assessed the effectiveness and safety of long-term TCZ IV treatment

with respect to patients' age.

Methods: The present interim analysis included pts with complete baseline (BL) data before 03rd December 2015 (total; n=2999). 902 pts have completed the maximal 104 week observation period (W104). Subgroups according to age have been defined as <50 years, 50-65 years, >65 years.

Results: At BL the age distribution showed the following proportions: <50 years 28.9%, 50-65 years 48.6%, and >65 years 22.5%. The mean TCZ IV treatment duration was 1.7, 1.8, and 1.7 years, respectively, for the three groups. In comparison to younger pts, the elderly (>65 years) showed longer disease duration, higher inflammatory parameters, higher disease activity, and higher co-morbidity rates at BL. Nevertheless, TCZ IV showed comparable effectiveness in all age groups. At last visit, DAS28 BSG remission (< 2.6) was reached by 55.2%, 51.6%, and 48.8% of pts aged <50, 50-65, and >65 years, respectively. The mean reduction from BL in DAS28-BSG was 2.6, 2.7, and 2.8, respectively. Regarding co-medication, the mean glucocorticosteroid (GC) dose was reduced from 7.1 (BL) to 4.6 mg/d (last visit) and was similar in all subgroups. About 12% of pts stopped GC therapy completely, again similar in all subgroups. At baseline, the rate of TCZ monotherapy (without concomitant sDMARD) was highest in the elderly (53.2%) while combination therapy is more common in younger pts (47.1%). Despite slightly higher incidence rates of adverse events (AE) and serious adverse events (SAE) for the elderly, the rates of infections (27.2; 19.8; 19.2 per 100 patient years [PY]) and serious infections (2.9; 2.9; 3.1 per 100 PY) as well as TCZ discontinuation rates due to an AE (2.9; 2.7; 3.1 per 100 PY) did not increase with age. Gastrointestinal perforation was rarely observed (Figure 1).

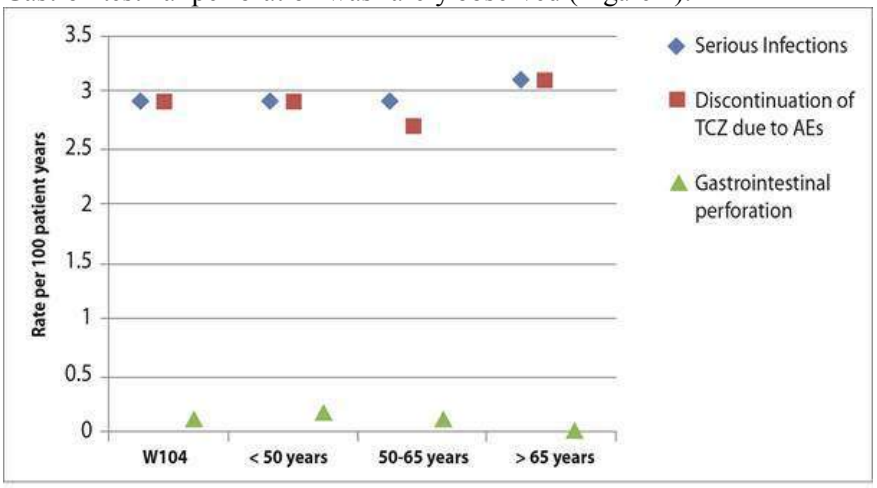

Figure 1

Serious Infections: All SAEs with a MedDRA Preferred Term indicating an infection.

5 patients of the subgroup > 65 years were older than 80 years. No serious infection, no gastrointestinal perforation nor a TCZ discontinuation due to an AE was observed within those 5 patients.

For the two patients with gastrointestinal perforation no history of gastrointestinal disease was documented.

Conclusion: 902 pts were observed for 2 years. TCZ IV treatment resulted in improvements of all disease activity parameters and a reduction in concomitant GC dosing was observed. Despite higher disease burden at baseline, elderly RA pts (> 65 years) benefited to the same extent as younger pts, without increased risk of infections. Considering natural age related risks, the low infection and gastrointestinal perforation rates of elderly pts seem to be attributable to the steroid sparing effect of TCZ therapy. Safety concerns should be no reason to argue against anti IL 6 therapy in elderly pts.

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Abstract Number: 1614

Monotherapy with Abatacept, Rituximab or Tocilizumab Is Not Associated with a Significantly Lower Long Term Retention Than Combination with Synthetic DMARD: Long-Term Registry Data in 4498 Real-Life Patients with Rheumatoid Arthritis

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Background/Purpose: Data are very limited concerning the association between cotreatment with a conventional synthetic DMARD (csDMARD) and long term retention of abatacept (ABA), rituximab (RTX) and tocilizumab (TCZ) in real life.

Methods: This was a pre-specified sub-group analysis of a multicenter open-label observational study of patients with RA according to 1987 ACR criteria who initiated RTX, ABA, or TCZ and were enrolled in 3 French Society of Rheumatology prospective registries (AIR for rituximab, ORA for abatacept, and REGATE for tocilizumab). We used a propensity-score approach to adjust for differences in observed factors that might affect both treatment assignment and outcome.

Results: Data on concomitant treatment were available in 4469 out of 4498 patients (99.6%). 34.9, 34.3 and 40.2% of patients respectively treated with ABA, RTX and TCZ, initiated their biologic in monotherapy. 79.5% of patients with a csDMARD received methotrexate. 3507 patients had a follow-up at 24 months for a total follow-up of 18898 patient-years (RTX: 10545; ABA: 4912; TCZ: 3441). - Effect of concomitant csDMARD on the effectiveness of each drug Drug retention without failure of RTX at 2 years was 67.8[65.2; 70.4]% in patients treated in combination with a csDMARD and 65.1 [61.5;68.8]% in monotherapy, HR of discontinuation 0.89 [0.76;1.05], p= 0.21. Drug retention without failure of RTX at 5 years was 50.1[47.4; 53.0]% in combination and 45.3 [41.5;49.4]% in monotherapy, HR of discontinuation of 0.88 [0.77;1.0], p= 0.08. Drug retention without failure of ABA at 2 years was 42.6[38.9; 46.7]% in patients treated in combination and 36.7 [31.9;42.2]% in monotherapy, HR of discontinuation 0.86 [0.73;1.01], p= 0.08. Drug retention without failure of ABA at 5 years was 22.8[19.7; 26.4]% in combination and 18.7 [15;23.5]% in monotherapy, HR of discontinuation of 0.87 [0.75;1.01], p= 0.07. Drug retention without failure of TCZ at 2 years was 66.1 [62.9; 69.6]% in patients treated in combination and 60.9 [56.8;65.4]% in monotherapy, HR of discontinuation 0.82 [0.66;1.02], p= 0.09. - Effect of concomitant csDMARD on the comparative effectiveness between ABA, RTX and TCZ At 2 years, drug retention without failure among patients treated in combination with a csDMARD was significantly greater with RTX and TCZ than ABA (hazard ratio 1.85 [95% CI: 1.52;2.26], and 1.83 [95% CI: 1.39;2·42], respectively), with no difference between

RTX and TCZ. At 2 years, drug retention without failure among patients treated in monotherapy was significantly greater with RTX and TCZ than ABA (HR 2.29 [95% CI: 1.62;3.25], and 1.84 [95% CI: 1.15;2·96], respectively), with no difference between RTX and TCZ. At 5 years, drug retention without failure among patients treated in combination was significantly greater with RTX than ABA (HR 1.94 [95% CI: 1.64;2·29], and it was the same for patients treated in monotherapy (HR 2.31 [95% CI: 1.22;2·42]).

Conclusion: In real life patients, monotherapy with abatacept, rituximab or tocilizumab is not associated with a lower long term retention than combination with synthetic DMARD.

Disclosure: J. E. Gottenberg, Abbvie, BMS, Gsk, Janssen, Lilly, MSD, Pfizer, Roche, UCB, 5; **J. Morel**, None; **A. Constantin**, None; **T. Bardin**, None; **A. G. Cantagrel**, None; **B. Combe**, None; **M. Dougados**, Pfizer, AbbVie, Celgene, Eli Lilly, Novartis, Roche, and Sanofi-Aventis, 5,Pfizer, AbbVie, UCB, Merck, 8; **R. M. Flipo**, None; **A. Saraux**, None; **T. Schaeverbeke**, None; **J. Sibilia**, None; **M. Soubrier**, None; **O. Vittecoq**, None; **E. Perrodeau**, None; **P. Ravaud**, None; **X. Mariette**, None.

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Abstract Number: 1615

Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, Significantly Improves Physical Function and Reduces Morning Stiffness in Patients with Active Rheumatoid Arthritis Despite Anti-TNF Therapy: Results from a Global, Randomized, Placebo-Controlled, Phase 3 Trial

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Background/Purpose: Improvement in physical function and morning stiffness are key goals of rheumatoid arthritis (RA) treatment. Sirukumab, a selective human anti–IL6 monoclonal antibody, has recently been evaluated in the SIRROUND-T global, Phase 3 study for the treatment of RA in patients (pts) with active disease who were intolerant or refractory to therapies targeting tumor necrosis factor (TNF). This study evaluated the impact of sirukumab on physical function and morning stiffness in pts with active RA despite anti-TNF therapy.

Methods : Eligible pts with active RA who were intolerant or refractory to anti-TNF therapy were randomized (1:1:1) to sirukumab SC 50 mg q4w, sirukumab SC 100 mg q2w, or placebo SC q2w. A significant proportion of pts were also exposed to other non-anti-TNF therapies. At Wk 18, pts in the placebo group were re-randomized to 1 of the 2 sirukumab doses if they had insufficient (<20%) improvement in tender/swollen joints, and at Wk 24, all pts remaining in the placebo group crossed over to 1 of the 2 sirukumab doses. To assess physical function, pts completed the Health Assessment Questionnaire-Disability Index (HAQ-DI) at baseline (BL) and from Wk 2 to 52. A clinically meaningful improvement in

HAQ-DI from BL was defined as a change (reduction) of 0.22 in HAQ-DI, and a normal HAQ-DI score was defined as ≤0.5. The average duration of daily morning stiffness during the previous week in minutes (0–1440 minutes) was evaluated at the same visits as HAQ-DI.

Results: Mean improvement from BL in HAQ-DI score was significantly greater for both sirukumab 50 mg q4w and sirukumab 100 mg q2w compared with placebo at Wk 24 (both P <0.001; **Table**). Improvements from BL were maintained for both sirukumab doses through Wk 52. Improvements from BL in the HAQ-DI score were clinically meaningful (change of −0.22) for a significantly greater proportion of pts with both doses of sirukumab compared with placebo at Wk 24 (both P <0.001); differences between sirukumab and placebo in the proportion of pts achieving a clinically meaningful improvement in HAQ-DI scores were observed as early as Wk 4. A significantly greater proportion of pts receiving sirukumab 100 mg q2w (numerically greater with 50 mg q4w) achieved a HAQ-DI score of ≤0.5 at Wk 24 compared with placebo (P = 0.029). Additionally, there was a significantly greater reduction from BL in the duration of morning stiffness with sirukumab 50 mg q4w (P = 0.011) and a numerically greater reduction from BL with sirukumab 100 mg q2w compared with placebo at Wk 24; for both sirukumab dose groups, these reductions were observed as early as Wk 2 and maintained through Wk 52.

Conclusion: Sirukumab treatment was associated with early, sustained, and clinically meaningful improvements in both physical function and morning stiffness in pts with active RA who were intolerant or refractory to anti-TNF therapy.

Table. HAQ-DI and Morning Stiffness Outcomes at Week 24[a]

		Sirukumab	
Outcome	Placebo (n=294)	50mg q4w (n=292)	100mg q4w (n=292)
HAQ-DI, mean (SD) change from BL	−0.12 (0.49)	−0.31 (0.54)[b]	−0.33 (0.53)[b]
Proportion of pts with clinically meaningful improvement from BL in HAQ-DI, %[c]	37.4	52.2[b]	54.8[b]
HAQ-DI ≤0.5, %	12.6	15.1	19.2[d]
Change from BL in duration of daily morning stiffness (min), mean (SD)	−28.9 (219)	−87.0 (333)[e]	−71.2 (253)

[a]n values are based on initial treatment assignment.
[b]P <0.001 vs placebo.
[c]Minimum clinically meaningful improvement, change of −0.22 from BL.
[d]P = 0.029 vs placebo.
[e]P = 0.011 vs placebo.

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Abstract Number: 1616

Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor-α Monoclonal Antibody: Long-Term Safety and Efficacy for

up to 158 Weeks of Treatment in Patients with Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Inhibition of GM–CSFR-α is a novel approach to treat RA. Mavrilimumab, an investigational human monoclonal antibody targeting GM–CSFR-α, has demonstrated efficacy and an acceptable safety profile in prior 12- and 24 week studies. Here, the long-term (LT) efficacy and safety of mavrilimumab 100 mg every other week (eow) is evaluated for up to 158 (median = 122) weeks treatment in patients (pts) with moderate to severe RA.

Methods: Adult pts were enrolled into this open-label extension (OLE) study (NCT01712399) after completing either EARTH EXPLORER 1 or 2 (NCT01706926; NCT01715896), or transferred from Week 12 onwards because of inadequate response. Pts received subcutaneous mavrilimumab 100 mg eow, consistent with the highest dosage in the Phase IIa study. The LT risk:benefit ratio of mavrilimumab was assessed via evaluation of treatment-emergent adverse events (TEAEs), serious TEAEs (TESAEs), and pulmonary events. Exploratory LT efficacy was measured using clinical (DAS28–CRP and ACR responses) and patient-reported outcomes [PROs: HAQ-DI; Short Form Health Survey (SF)-36; Functional Assessment of Chronic Illness Therapy (FACIT) fatigue]; efficacy duration was assessed via evaluation of major clinical response (maintenance of ACR70 for 24 weeks) and maintenance of DAS28–CRP <2.6. Radiographic progression (modified total Sharp score [mTSS]) was assessed in pts initially enrolled in EARTH EXPLORER 1.

Results: 397 pts were included in the OLE study. Between the Phase IIb and OLE studies, 442 pts received mavrilimumab, with a cumulative safety exposure of approximately 900 pt-years (yrs). Across all time points, the most frequently reported TEAEs for all pts (n [rate/100 pt-yrs]) were nasopharyngitis (69 [7.68]), bronchitis (51 [5.68]), RA (44 [4.90]), urinary tract infection (38 [4.23]), and hypertension (38 [4.23]); the serious infection rate was 1.56/100 pt-yrs. Treatment with mavrilimumab was not associated with substantial effects on pulmonary safety, including function; monocytopenia was not reported and shifts in laboratory values were not clinically significant. At Week 122, ACR20/50/70 responses were achieved in approximately 80%, 50%, and 30% of pts, respectively; 65% of pts achieved DAS28−CRP <3.2 and 41% of pts achieved DAS28−CRP <2.6. In addition, efficacy was demonstrated across PRO endpoints; mean FACIT fatigue and SF-36 components showed improvements from baseline, which were maintained through 122 weeks (Table).

Conclusion: Mavrilimumab demonstrated sustained efficacy and an acceptable safety profile for up to 158 (median = 122) weeks in pts with moderate to severe RA. Mavrilimumab 100 mg eow is suboptimal compared with 150 mg eow in DMARD-IR pts; however, efficacy results remain comparable with previous studies, validating the use of mavrilimumab to

Table. Long-term safety and efficacy data in the as-treated population

Baseline characteristics	**Mavrilimumab eow**			
Mean (SD) age, yrs (N=397)	51.1 (11.2)			
Mean (SD) RA duration, yrs (N=397)	7.87 (6.77)			
Mean (SE) DAS28−CRP (N=442)	5.77 (0.04)			
Long-term safety results (N=442)[a]				
Pts reporting ≥1 TESAE, n (rate/100 pt-yrs)	60 (6.68)			
Pts reporting ≥1 TEAE of special interest, n (rate/100 pt-yrs)	114 (12.7)			
TEAEs of special interest, n (rate/100 pt-yrs)[b]				
Hepatic function abnormalities	2 (0.22)			
Hypersensitivity reactions	13 (1.45)			
Malignancies	5 (0.56)			
Neutropenia	4 (0.45)			
Pulmonary events[c]	83 (9.24)			
Serious infections	14 (1.56)			
Long-term efficacy results	Baseline[d] (n=442[h])	Week 74[e] (n=279[i])	Week 98[f] (n=231[j])	Week 122[g] (n=180[k])
DAS28−CRP <3.2 responders, n (%)	–	158 (56.6)	137 (59.3)	117 (65.0)
DAS28−CRP <2.6 responders, n (%)	–	103 (36.9)	98 (42.4)	73 (40.6)
ACR20 responders, n (%)	–	211 (75.6)	185 (80.1)	145 (79.2)
ACR50 responders, n (%)	–	132 (47.3)	116 (50.2)	92 (50.3)
ACR70 responders, n (%)	–	77 (27.6)	70 (30.3)	49 (26.8)
HAQ-DI				
Mean (SE)	1.58 (0.03)	1.00 (0.04)	0.94 (0.04)	0.97 (0.05)
Responders, n (%)	–	200 (71.7)	167 (72.3)	138 (75.0)
SF-36, mean (SE)				
Mental component	40.1 (0.5)	46.1 (0.6)	46.0 (0.7)	46.6 (0.7)
Physical component	31.4 (0.3)	39.6 (0.5)	39.8 (0.5)	39.7 (0.6)
FACIT fatigue, mean (SE)	27.8 (0.5)	36.0 (0.6)	36.6 (0.6)	36.3 (0.7)
Major clinical response[l], n (%)	75 (17.0)			
Radiographic progression	Baseline[d] (n=324)	Week 74[e] (n=239)	Week 130[m] (n=77)	
mTSS, mean (SE)	35.4 (2.6)	34.4 (3.0)	29.5 (4.6)	

Previous treatment (as-treated OLE population): placebo (n=72); mavrilimumab 30 mg (n=73); mavrilimumab 100 mg (n=128); mavrilimumab 150 mg (n=69); golimumab (n=55)
Data included are observed case
[a]Baseline in 1071 and 1107 through to end of the OLE study. Includes all pts exposed to mavrilimumab in 1071, 1107, or the OLE study
[b]Includes adverse events with onset after the first dose of mavrilimumab
[c]All pulmonary events reviewed by IPEC
[d]Baseline defined as the last assessment prior to the first dose in the 1071 study
[e]Week 48 in OLE study
[f]Week 72 in OLE study
[g]Week 96 in OLE study. This is the last time point where data were available for a substantial number of pts. At Week 158, n=7. For FACIT fatigue and SF-36, data were last recorded at Week 146 (n=17)
[h]At baseline, n=434 (SF-36); n=436 (FACIT fatigue)
[i]At Week 74, n=278 (FACIT fatigue, SF-36)
[j]At Week 98, n=233 (FACIT fatigue, SF-36)
[k]At Week 122, n=183 (ACR20, ACR50, ACR70); n=184 (HAQ-DI, FACIT fatigue, SF-36)
[l]Major clinical response defined as achieving ACR70 and maintaining ACR70 for 24 weeks. Includes pts with ACR70 starting in the randomized phase or the open-label phase
[m]Week 104 in OLE study
eow, every other week; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; IPEC, Independent Pulmonary Expert Committee; mTSS, modified total Sharp score; OLE, open-label extension; pts, patients; SD; standard deviation; SE, standard error; SF-36, Short Form 36 Health Survey; TEAEs, treatment-emergent adverse events; TESAEs, treatment-emergent serious adverse events; yrs, years

target GM–CSFR-α. ^Joint senior authors.

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Abstract Number: 1617

Treatment with Sirukumab, an Anti-IL6 Cytokine Monoclonal Antibody, Improves Fatigue and Health-Related Physical and Emotional Well Being in Patients with Active Rheumatoid Arthritis Refractory to Conventional or Biologic Therapy: Results of 2 Global, Placebo-Controlled, Phase 3 Trials

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SESSION INFORMATION

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Background/Purpose: Patients (pts) with rheumatoid arthritis (RA) often experience both substantial fatigue and a decline in their health-related physical and emotional well-being. Sirukumab is a human anti-IL-6 monoclonal antibody that selectively binds to the cytokine with high affinity, and is under development for RA and a number of other diseases. The effects of sirukumab on health-related physical and emotional well-being and fatigue were evaluated in 2 separate randomized, double-blind, placebo-controlled, multicenter global phase 3 studies in pts with RA refractory to conventional DMARDs (SIRROUND-D) or refractory or intolerant to anti-TNF therapy (SIRROUND-T). Pts may have been taking other biologics prior to both studies.

Methods: In both studies, eligible pts were randomized (1:1:1) to treatment with SC sirukumab 50 mg q4w, 100 mg q2w, or placebo q2w. The placebo-controlled portions of SIRROUND-D and -T were 52 and 24 wks, respectively; thus, results from both studies were examined at Wk 24 and are presented here. The primary objective of both studies was to evaluate

the efficacy of sirukumab in the study-specific RA pt populations. Health-related physical and emotional well-being were evaluated as secondary endpoints using the SF-36 health survey, and fatigue evaluated using the FACIT-Fatigue scale. For SF-36 physical and mental component summary (PCS and MCS) scores, clinically meaningful improvement was defined as a ≥5-point increase from baseline (BL); for FACIT-Fatigue, clinically meaningful improvement was defined as a ≥4-point increase from BL.

Results: A total of 1,670 and 878 pts in SIRROUND-D and -T, respectively, had evaluable data. In both studies, increases (improvements) from BL at Wk 24 in mean SF-36 PCS and MCS scores and all 8 SF-36 domain scores were significantly greater with either sirukumab dose level (50 mg q4w or 100 mg q2w) versus placebo (all $P<0.02$; **Table**). Similarly across both studies, significantly greater mean increases (improvements) from BL at Wk 24 were observed in the FACIT-Fatigue score with sirukumab (either dose) versus placebo (all $P<0.001$ [not adjusted for multiplicity]; **Table**). Improvements in SF-36 and FACIT-Fatigue scores with both sirukumab doses versus placebo were observed at Wk 8 through all time points to Wk 24 in both studies. In addition, across studies, the percentages of pts who achieved clinically meaningful improvements from BL at Wk 24 in SF-36 PCS and MCS scores, and in FACIT-Fatigue score were significantly higher with sirukumab (either dose) versus placebo (all $P<0.02$).

Conclusion: Treatment with sirukumab was associated with significant and clinically meaningful improvements from BL in health-related physical and emotional well-being and fatigue for pts with active RA who had not responded adequately to prior treatment, regardless of whether prior treatment was with conventional DMARDs or TNF inhibitors.

Table. SF-36 and FACIT-Fatigue Outcomes at Week 24[a]

	Placebo		Sirukumab 50 mg q4w		Sirukumab 100 mg q2w	
Outcome	DMARD-refractory (n = 556)	TNF-refractory (n = 294)	DMARD-refractory (n = 557)	TNF-refractory (n = 292)	DMARD-refractory (n = 557)	TNF-refractory (n = 292)
Mean (SD) change from baseline						
SF-36 PCS	2.29 (6.28)	1.68 (6.65)	5.36 (7.33)[b]	4.85 (7.09)[b]	5.85 (7.07)[b]	5.06 (6.88)[b]
SF-36 MCS	2.89 (9.18)	1.08 (8.92)	4.90 (9.65)[b]	3.92 (10.68)[b]	4.22 (9.48)[c]	4.05 (9.28)[b]
SF-36 domain scores						
Bodily pain	3.86 (8.04)	3.12 (7.12)	7.76 (8.55)[b]	7.23 (8.83)[b]	7.71 (9.02)[b]	7.17 (8.49)[b]
General health	1.99 (7.01)	0.74 (7.13)	4.52 (7.75)[b]	3.23 (7.21)[b]	3.87 (7.20)[b]	3.68 (6.66)[b]
Physical function	1.37 (7.98)	0.31 (8.59)	4.29 (8.80)[b]	3.72 (8.35)[b]	5.02 (8.35)[b]	4.25 (8.40)[b]
Role-physical	2.84 (7.95)	1.99 (7.86)	5.33 (8.51)[b]	4.79 (8.53)[b]	5.75 (8.30)[b]	5.04 (8.53)[b]
Vitality	3.17 (8.88)	2.05 (8.37)	5.77 (9.21)[b]	4.89 (9.47)[b]	5.83 (9.23)[b]	4.69 (9.91)[b]
Mental health	2.66 (8.88)	1.24 (8.63)	4.89 (9.76)[b]	3.66 (9.44)[b]	4.21 (9.50)[c]	4.30 (8.84)[b]
Role-emotional	2.58 (10.50)	0.50 (11.67)	5.07 (11.23)[b]	4.20 (12.64)[b]	4.75 (11.31)[b]	4.45 (11.42)[b]
Social function	3.00 (9.23)	1.52 (8.40)	5.35 (9.90)[b]	5.01 (9.74)[b]	5.25 (9.44)[b]	4.76 (9.83)[b]
FACIT-Fatigue score	3.3 (9.3)	1.9 (8.8)	6.5 (9.5)[b]	6.6 (10.8)[b]	6.5 (9.4)[b]	5.6 (9.1)[b]
Number of pts achieving clinically meaningful improvement from baseline, n (%)						
SF-36 PCS[d]	171 (30.8)	86 (29.3)	263 (47.2)[b]	122 (41.8)[c]	283 (50.8)[b]	140 (47.9)[b]
SF-36 MCS[d]	200 (36.0)	80 (27.2)	253 (45.4)[b]	114 (39.0)[c]	243 (43.6)[c]	109 (37.3)[c]
FACIT-Fatigue score[e]	244 (43.9)	119 (40.5)	342 (61.4)[b]	162 (55.7)[b]	331 (59.4)[b]	163 (55.8)[b]

[a]n values are based on initial randomization.
[b]$P \leq 0.001$ vs placebo.
[c]$P < 0.02$ vs placebo.
[d]Increase ≥5 points.
[e]Increase ≥4 points.

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Abstract Number: 1618

Leflunomide, Sulfasalazine and Hydroxychloroquine for Rheumatoid Arthritis: Efficacious but Poorly Tolerated

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SESSION INFORMATION

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Background/Purpose: The combination of methotrexate (MTX), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) (triple therapy) is a highly effective and well-tolerated treatment in rheumatoid arthritis (RA). While MTX is the cornerstone of most successful combination therapies, not all patients are candidates for, or tolerate, MTX. Leflunomide, a disease-modifying anti-rheumatic drug (DMARD) that inhibits DNA synthesis, is a common alternative to MTX. Whether leflunomide can be used as an alternative for MTX in combination with SSZ and HCQ has not previously been studied.

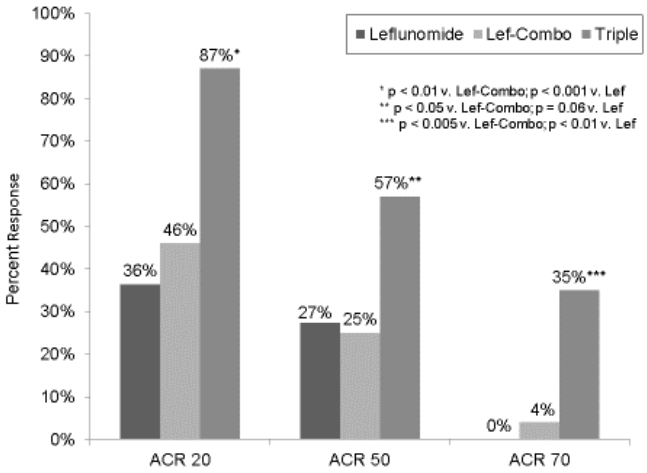
Methods: We performed a 48-week, double-blind, randomized three-armed trial to compare: conventional triple therapy (Triple); the combination of leflunomide, SSZ and HCQ (Lef-Combo); and leflunomide alone (Lef) in RA. Patients were enrolled between 2002 and 2007 and were eligible if they had not previously used leflunomide or combination DMARDs, met 1987 ACR classification criteria for RA, had active disease (≥6 swollen and ≥6 tender joints), and were on stable doses of prednisone ≤ 10 mg/day for at least 4 weeks prior to entry into the study. Patients with intra-articular injections within 4 weeks of entry, functional class IV RA, serum creatinine > 2.0 mg/dL, radiographic evidence of rheumatoid lung disease, significant liver, renal, hematologic, pulmonary, cardiovascular, retinal, or active peptic ulcer disease were excluded from the study. The primary outcome was an ACR-20 response at 48 weeks. Secondary outcomes included ACR-50 and ACR-70 responses. The study was designed to enroll 180 patients in order to achieve a power of 80% for detecting significant differences in the primary outcome.

Results: The study included 69 patients with mean ages ranging from 50-54 years across the three study arms, 77% of whom were RF positive, with median disease duration ranging from 10-24 months, and mean DAS28-ESR scores ranging from 5.7-6.0. Women comprised more of the Lef group (83%) than Triple (52%) ($p<0.05$). In an intent-to-treat analysis, conventional therapy was superior to both Lef-Combo and Lef in the achievement of ACR-20, -50, and -70 responses (Figure 1). The study was terminated prematurely due to the frequency of gastrointestinal (GI) toxicity in the Lef-Combo group (29.2%), which included dyspepsia/nausea and diarrhea in 5 and 2 patients, respectively, all of whom withdrew from

the study. Lef-Combo was efficacious in those that were able to tolerate it with 73% achieving an ACR-20 response.

Conclusion: Although efficacious as combination DMARD therapy in RA, Lef-Combo is poorly tolerated due to GI complications in almost one-third of patients. The loading dose of leflunomide used at enrollment could have contributed to GI toxicity. Providers who employ this combination need to be aware of the potential for GI toxicity and educate patients

Figure 1: ACR Responses by Treatment



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Abstract Number: 1619

EARTH EXPLORER 2, a Phase IIb Exploratory Study Evaluating Efficacy and Safety of Mavrilimumab, a Fully Human Granulocyte-Macrophage Colony-Stimulating Factor Receptor-Alpha Monoclonal Antibody, and the Tumor Necrosis Factor Antagonist Golimumab in Rheumatoid Arthritis

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Background/Purpose: Mavrilimumab, a fully human monoclonal antibody targeting the granulocyte-macrophage colony-stimulating factor receptor-α, has demonstrated efficacy and safety in disease-modifying antirheumatic drug (DMARD)-inadequate responder (IR) patients (pts) with rheumatoid arthritis (RA).[1] Few head-to-head studies in tumor necrosis factor antagonist (aTNF)-IR assess alternative aTNFs vs. other agents; this Phase IIb exploratory study (NCT01715896) evaluates the efficacy and safety of mavrilimumab and golimumab in aTNF-IR and DMARD-IR pts.

Methods: This 24-week study enrolled pts with active RA (28-joint Disease Activity Score [DAS28]–C-reactive protein [CRP]/erythrocyte sedimentation rate [ESR] ≥3.2); ≥4 swollen joints; inadequate response to ≥1 DMARDs and/or 1–2 aTNFs receiving concomitant methotrexate (MTX; 7.5–25.0 mg/week). Pts received subcutaneous mavrilimumab 100 mg every other week (eow), based on data from the Phase IIa study,[2] or golimumab 50 mg alternating with placebo eow. Key endpoints were ACR20/50/70 responses, DAS28–CRP <3.2 and <2.6, Health Assessment Questionnaire Disability Index improvement >0.22 at Week 24 and safety/tolerability. Treatment estimates for mavrilimumab and golimumab are presented with standard errors.

Results: Pts were randomized to mavrilimumab or golimumab (1:1) (Table). Data for pts receiving mavrilimumab 100 mg eow and golimumab 50 mg at Week 24 are shown for the aTNF-IR, DMARD-IR and overall strata (Table). The most common treatment-emergent adverse events (TEAEs) for mavrilimumab 100 mg and golimumab 50 mg were nasopharyngitis (5.7%, 1.5%), headache (4.3%, 2.9%), upper respiratory tract infection (4.3%, 2.9%), viral upper respiratory tract infection (4.3%, 2.9%), and hepatic enzyme increase (4.3%, 2.9%), respectively. Related serious TEAEs were pneumocystis pneumonia (n=1) and lung disorder (n=1) [both in golimumab-treated pts]. No deaths were reported and no significant pulmonary safety signals were identified.

Conclusion: In this exploratory study, mavrilimumab 100 mg eow and golimumab 50 mg demonstrated efficacy and an acceptable safety profile in DMARD-IR and aTNF-IR pts. The study was not powered to demonstrate statistical significance between mavrilimumab and golimumab. As mavrilimumab 100 mg eow has previously been shown to have suboptimal efficacy compared with 150 mg eow in DMARD-IR pts (EARTH EXPLORER 1),[1] additional studies are needed to establish the benefit of a higher dose in pts with moderate to severe RA and inadequate response to aTNF agents.

References: [1]Burmester G, et al. *Arthritis Rheum.* 2014;66:S1231. [2]Burmester G, et al. *Ann Rheum Dis.* 2013;72:1445–1452. ^Joint senior authors. First presented at EULAR 2016.

Table: Patients with TNF-IR disease, DMARD-IR disease and overall patient population

	aTNF-IR	
	Mavrilimumab 100 mg eow (N=31)	**Golimumab 50 mg eow[a] (N=32)**
Patient baseline demographics		
Mean (SD) age, years	50.2 (13.6)	46.9 (10.5)
Mean (SD) RA duration, years	10.09 (7.5)	11.00 (7.1)
Mean (SD) DAS28–CRP	6.05 (0.8)	6.01 (0.6)
Mean (SD) HAQ DI	1.90 (0.5)	1.77 (0.5)
Previous aTNF failures, n (%) One aTNF failure Two aTNF failures	 27 (87.1) 4 (12.9)	 30 (93.8) 2 (6.3)
Key efficacy endpoints at Week 24		
ACR20 responders, % (SE)	72.3 (8.0)	61.2 (8.6)
ACR50 responders, % (SE)	33.5 (8.5)	42.2 (8.7)
ACR70 responders, % (SE)	23.5 (7.6)	24.1 (7.6)
DAS28–CRP adjusted mean change from BL (SE)	–1.99 (0.3)	–2.24 (0.3)
DAS28–CRP low disease activity (DAS28–CRP <3.2), % (SE)	26.8 (8.0)	36.2 (8.5)
DAS28–CRP remission (DAS28–CRP <2.6), % (SE)	20.1 (7.2)	24.1 (7.6)
HAQ DI responders (HAQ DI >0.25), % (SE)	64.5 (8.6)	71.9 (7.9)

	DMARD-IR		Overall population	
	Mavrilimumab 100 mg eow (N=39)	**Golimumab 50 mg eow[a] (N=36)**	**Mavrilimumab 100 mg eow (N=70)**	**Golimumab 50 mg eow[a] (N=68)**
Patient baseline demographics				
Mean (SD) age, years	50.2 (13.3)	52.5 (11.8)	50.2 (13.3)	49.9 (11.4)
Mean (SD) RA duration, years	7.90 (7.0)	9.35 (7.8)	8.87 (7.3)	10.13 (7.5)
Mean (SD) DAS28–CRP	5.63 (1.1)	5.46 (0.9)	5.82 (1.0)	5.72 (0.8)
Mean (SD) HAQ DI	1.36 (0.6)	1.41 (0.5)	1.59 (0.6)	1.58 (0.5)
Key efficacy endpoints at Week 24				
ACR20 responders, % (SE)	53.8 (8.0)	69.4 (7.7)	62.0 (5.8)	65.6 (5.8)_
ACR50 responders, % (SE)	35.9 (7.7)	44.4 (8.3)	34.8 (5.7)	43.4 (6.0)
ACR70 responders, % (SE)	10.3 (4.9)	27.8 (7.5)	16.1 (4.4)	25.9 (5.3)
DAS28–CRP adjusted mean change from BL (SE)	–1.89 (0.2)	–2.27 (0.2)	–1.84 (0.2)	–2.19 (0.2)
DAS28–CRP low disease activity (DAS28–CRP <3.2), % (SE)	30.8 (7.4)	44.4 (8.3)	28.9 (5.4)	40.6 (6.0)
DAS28–CRP remission (DAS28–CRP <2.6), % (SE)	15.4 (5.8)	33.3 (7.9)	17.4 (4.5)	29.0 (5.5)
HAQ DI responders (HAQ DI >0.25), % (SE)	53.8 (8.0)	66.7 (7.9)	58.7 (5.9)	69.0 (5.6)

[a]Alternating with placebo; [b]Percentage difference for mavrilimumab vs. golimumab; [c]Mavrilimumab vs. golimumab
ACR20/50/70, American College of Rheumatology rating scale (20% or more improvement); BL, baseline; CI, confidence intervals; DAS28–CRP, 28-joint Disease Activity Score–C-reactive protein; DMARD-IR, disease-modifying antirheumatic drug inadequate responders; eow, every other week; HAQ DI, Health Assessment Questionnaire Disability Index; RA, rheumatoid arthritis; SD, standard deviation; SE, standard error

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Abstract Number: 1620

Pharmacokinetics, Pharmacodynamics, and Immunogenicity of MEDI4920, a Novel, Engineered CD40 Ligand Antagonist, in Healthy Volunteers

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Background/Purpose: MEDI4920 is a CD40 ligand (CD40L) antagonist under development for the treatment of autoimmune diseases. It is an engineered protein lacking a fragment crystallizable (Fc) moiety to avoid potential thromboembolic events associated with the Fc domain. The safety and tolerability of single ascending intravenous (IV) doses of MEDI4920 in healthy adults were studied in a Phase 1, randomized, blinded, placebo-controlled study. In addition, the pharmacokinetics (PK), immunogenicity, and PK/pharmacodynamic (PD) relationship were assessed and characterized in the study.

Methods: Fifty-six healthy adult male subjects were randomized in the study at a single site and administered either placebo or MEDI4920 (3, 10, 30, 100, 300, 1000, 3000 mg). Blood samples were collected to evaluate the PK, anti-drug antibody (ADA), and PD profiles. MEDI4920 and total soluble CD40L (sCD40L) concentrations were determined using a validated immunoassay and a qualified enzyme-linked immunosorbent assay (ELISA) method, respectively. The presence of ADA to MEDI4920 was determined using a validated ELISA method. PK parameters were obtained using non-compartmental analysis, and a mechanism-based PK/PD model was developed to describe the relationship between MEDI4920 and total sCD40L accumulation in healthy subjects.

Results: Following IV administration, MEDI4920 exposure increased in a dose-proportional manner. The clearance and terminal half-life ranged from 453 to 668 mL/day and 4.41 to 9.68 days, respectively, across the dose cohorts. Administration of MEDI4920 produced a dose-dependent increase in total sCD40L levels that reached a plateau at doses of 1000 mg and higher. A high incidence of ADA was observed in the lower dose cohorts (3, 10, 30, and 100 mg); ADA incidence and titers decreased with increasing dose. In subjects with high ADA titers, MEDI4920 was cleared faster from the circulation at concentrations lower than 1 µg/mL. A rapid decrease in total sCD40L accumulation was observed in subjects with high ADA titers. No association of ADA with clinical adverse events was established.

Conclusion: The PK of MEDI4920 was linear and showed a dose-dependent increase in total sCD40L, consistent with target engagement. The decrease in ADA incidence and titers observed with increasing dose is consistent with the MEDI4920 immunosuppressive mechanism of action. Overall, MEDI4920 demonstrated safety and tolerability in a single ascending dose study in healthy subjects. These data support further investigation of MEDI4920 as a therapy for patients with rheumatoid arthritis. The mechanism-based PK/PD model can be used to explore the effects of various MEDI4920 doses and regimens on target engagement.

Disclosure: J. Li, AstraZeneca, 1,Medimmune, 3; **M. Gunsior**, MedImmune, 3,AstraZeneca, 1; **N. Ly**, AstraZeneca, 1,MedImmune, 3; **A. Godwood**, MedImmune, 3,AstraZeneca, 1; **D. Howe**, MedImmune, 3,AstraZeneca, 1; **M. Albulescu**, AstraZeneca, 1,MedImmune, 3; **L. H. Butler**, AstraZeneca, 1; **K. Arbaugh**, MedImmune, 3,AstraZeneca, 1; **R. Faggioni**, AstraZeneca, 1,MedImmune, 3.

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Abstract Number: 1621

A Phase I, Randomized, Double Blind, Placebo-Controlled, Dose Escalating Study of the Safety, Tolerability and Pharmacokinetics and Pharmacodynamics of Single and Multiple Doses of Hmpl 523 in Australian Male Healthy Subjects

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Background/Purpose: Spleen Tyrosine Kinase (SYK) plays a pivotal role in the regulation of downstream signals in immune receptors, including B cell receptors (BCRs), which play a key role in autoimmune diseases such as rheumatoid arthritis (RA). This abstract reports the results of the first-in-humans study of HMPL 523, a highly selective, potent, and orally available inhibitor of SYK.

Methods: We conducted a 3-part study to investigate the safety, tolerability, and pharmacokinetics (PK) of HMPL-523 as well as its pharmacodynamics (PD) measured by $CD63^+$ as the biomarker, and the effect of food on PK in healthy adult male subjects. The study design is summarized in the table below.

Table Study Design

Endpoints	Part A (Single Ascending Dose) PK							Part B (Multiple Ascending Dose) PK/PD								Part C Effect of Food on PK
general design	A randomized, double- blind, placebo-controlled design															Cross over
Dose	Single dose							Once daily for 14 days								Once on Day 1 and Day 8, respectively
Meal condition	Fasted							Fed					Fed			Fasted on Day 1; wash-out for 7 days; after the consumption of a high-calorie meal on Day 8
Dosage (mg)	5 (N=6)	20 (N=6)	50 (N=6)	100 (N=6)	200 (N=6)	300 (N=6)	Placebo (N=12)	300 (N=6)	400 (N=6)	600 (N=6)	800 (N=6)	Placebo (N=8)	200 (N=12)	300 (N=6)	400 (N=6)	Placebo (N=8)	100 (N=6)

Results: A total of 118 adult male healthy subjects were enrolled at baseline. 114 (96.6%) Subjects completed the study. A total of 83 treatment emergent adverse events (TEAEs) were reported as the following: 38.9% in the HMPL-523 groups, and 32.1% in the placebo groups, respectively. The majority of TEAEs were mild (63/83 or 75.9%) with 18/83 (21.7%) moderate events. Two serious adverse events (SAEs) were reported due to elevated lipase (HMPL-523 200mg) and febrile illness (HMPL-523 400mg) in Part B (multiple ascending doses [MAD]). As a result, HMPL-523 was discontinued in the two subjects. All of the TEAEs and SAEs were resolved. Part A (single ascending dose [SAD]) PK results revealed that HMPL-523 was rapidly absorbed with median time to maximum plasma concentration (T_{max}) between 3 and 6 hours under both fasted and fed conditions. The maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) of HMPL-523 increased proportionally with dose increase up to 800 mg. The terminal half-life ($t_{1/2}$) ranged between 9.808 hours and 13.488 hours across HMPL-523 doses of 100 to 800 mg. Part B (MAD) PK results showed that steady state was achieved within 48 hours of daily administration and accumulation of 1.3 to 1.5 folds was observed over 14 days of dosing. In an *ex vivo* human whole blood PD assay, HMPL-523 inhibited anti-IgE-induced basophil ($CD63^+$) in a concentration-dependent manner with an estimated half maximal effective concentration (EC_{50}) of 47.70 ng/mL. The human PK exposures at 200 mg once daily and above can be expected to provide the target coverage required for clinical efficacy based on the preclinical PK/PD analysis. In Part C, systemic exposure of HMPL-523 was increased up to 1.5 folds when administered in the fed condition compared to the fasted condition, indicating that food consumption increases the relative bioavailability of HMPL-523.

Conclusion: Overall, the safety and laboratory data suggests that the single and multiple doses of HPML-523 were generally well tolerated. A multiple-dose regimen of 300 mg or less of HMPL-523, administered once daily, is

recommended for future Phase II clinical trials for autoimmune diseases.

Disclosure: J. Lickliter, None; **Y. Wu**, Hutchison MediParma Ltd, 3; **Y. Hua**, Hutchison MediPharma Limited, 3; **I. Yuan**, Hutchison MediPharma Limited, 3; **G. Dai**, Hutchison MediPharma Limited, 3; **X. Li**, Hutchison MediPharma Limited, 3; **J. Wang**, Hutchison MediPharma Limited, 3; **Y. Sai**, Hutchison MediPharma Limited, 3; **Z. Sun**, Hutchison MediPharma Limited, 3; **A. Pan**, Hutchison MediPharma Limited, 3; **J. Li**, Hutchison MediPharma Limited, 3; **W. Su**, Hutchison MediPharma Limited, 3.

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Abstract Number: 1622

Safety and Efficacy of Iguratimod in Patients with Active Rheumatoid Arthritis: A Multicenter, Single-Arm, Open-Label, Real World Study

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Background/Purpose: To evaluate the safety and efficacy of iguratimod, a novel DMARD, in active rheumatoid arthritis patients.

Methods: Patients with active rheumatoid arthritis received iguratimod treatment for 24 weeks. During the study, eligible patients could continue to use their anti-rheumatic drugs which were taken in stable dose for at least 3 months before the trial. The investigator could adjust the regimen according to disease activity after 12 weeks treatment. The efficacy and safety of iguratimod were assessed at week 2、4、8、16 and 24. The primary endpoints of efficacy were ACR 20/50/70 response rates at the end of 12^{th} and 24^{th} week; the secondary endpoint of efficacy included changes of DAS28-ESR, HAQ and emotion score from baseline, clinical remission rates at the end of 12^{th} and 24^{th}week. AEs, laboratory/physical examination, and vital signs were investigated to analyze the safety.

Results: The trial was conducted in 48 centers in China. 1759 patients were enrolled in this study, among them 1751 were included in safety analysis, and 1597 patients were evaluated for efficacy. At the end of the 12^{th} week, ACR 20/50/70 response rates were 62.2% (994/1597), 29.5% (471/1597) and 11.0% (176/1597) respectively. At the end of 24^{th} week, ACR20/50/70 response rates were 71.9% (1148/1597), 47.4% (757/1597) and 24.0% (384/1597). DAS28-ESR score was significantly reduced since Week 4 compared to baseline($P<0.001$). The proportions of patients who obtained clinical remission or low disease activity were 22.6% and 34.5% at the end of 12^{th} and 24^{th} week,according to DAS28-ESR score. The disease remission rate by the 2011 ACR/EULAR remissin criteria was 5.7% (79/1379) at the end of 12^{th} week, and 13.3% (187/1403) at the end of 24^{th}week. 38.5% (674/1751) of the patients experienced at least one ADR.Increased ALT 10.8% (189/1751) and AST 9.8% (171/1751), abdominal discomfort 6.3% (111/1751), abdominal pain 4.5% (78/1751), leukopenia 3.9% (69/1751), nausea 2.7% (47/1751), bloating 2.6% (45/1751), dizziness 2.3% (41/1751), diarrhea 2.1% (37/1751).

Conclusion: Iguratimod was effective and well tolerated in active RA patients in this large sample phase IV clinical trial. No unexpected adverse drug reaction was found.

Disclosure: R. Mu, None;

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Abstract Number: 1623

Early Effects of Tofacitinib on Bone Homeostasis in Patients with Rheumatoid Arthritis

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Background/Purpose: The selective Janus kinase (JAK) inhibitor tofacitinib inhibits progression of structural damage in rheumatoid arthritis (RA). These results suggest the possibility that tofacitinib improves osteoclastic bone destruction of RA. However, the detailed mechanism of tofacitinib for bone metabolism in RA is poorly understood. The purpose of this study is to clarify the effect of tofacitinib on bone metabolism, especially osteoclast regulating factor in RA.

Methods: Fourteen patients with active RA who inadequate response to DMARDs (mean age: 54.6 years, mean disease duration: 4.1 years, mean simplified disease activity index: 26.9, ACPA positive: 86%, oral steroid use: 29%, mean oral steroid dose: 10mg/day, MTX use: 93%, mean MTX dose:10.9mg/week, biologic DMARDs naïve: 57%) were started on treatment with tofacitinib 5mg twice daily (BID). Disease activity was assessed using the simplified disease activity index (SDAI). Next, the following soluble biomarkers of bone remodeling were measured by ELISA at the baseline and after 2, 4 and 12 weeks. (i) bone formation marker: osteocalcin (IRMA SRL, corp.); (ii) bone resorption maker: type I collagen cross-linked N-telopeptides (NTx) (ELISA , SLR corp.); (iii) osteoclat regulator: soluble receptor activator of nuclear factor kappa B ligand (sRANKL) (human RANKL ELISA kit, Biomedica) and osteoprotegerin (OPG) (human osteoprotegerin ELISA kit, Biomedica)

Results: After treatment of tofacitinib, SDAI score among all fourteen patients decreased significantly from 26.9±12.4 (mean±SD) at the base line to 14.7±9.9 at week 4 (p<0.0001), to 8.3±6.1 at week 12 (p<0.0001). Average of osteocalcin levels increased significantly from 6.9±4.3 ng/mL at the baseline to 8.8±6.1 at week 12 (p=0.0142), whereas average of NTx levels tend to decrease from 18.2±5.9 nmol BCE/L at the baseline to 16.7±5.8 at week 12. At the baseline, sRANKL levels were significantly correlated with CRP levels (Spearman r^2=0.488, P=0.0054). Average of sRANKL levels decreased significantly from 0.15±0.11 pmol/L at the baseline to 0.09±0.05 at week 2 (p=0.0097), to 0.11±0.10 at week 4 (p=0.0311), to 0.08±0.05 at week 12 (p=0.0014). On the other hand, statistically significant changes in OPG levels were not observed during 12 weeks. Consequently, average of sRANKL/OPG ratio decreased significantly from 4.81±4.82 at the baseline to 2.62±1.84 at week 2 (p=0.0186), to 3.11±2.81 at week 4 (p=0.0191), to 2.11±1.72 at week 12 (p=0.0052). Interestingly, decreasing effects of sRANKL level or sRANKL/OPG ratio were greater in patient with the high sRANKL level (>0.14 pmol/L: mean value of 70 RA patients in previous our study) at the base line.

Conclusion: Here, we show for the first time that tofacitinib has improved inflammatory bone metabolism immediately through the regulation of sRANKL levels and sRANKL/OPG balance in patients with RA. It had been reported that tofacitinib regulated synovitis through inhibition of IL-17 production by CD4+ T cells and IL-6 production by synovial

fibroblasts in RA (Maeshima K. et al. Arthritis Rheum.64:1790-8.2012). Thus, tofacitinib might control of RANKL induction via inhibition of IL-17 and IL-6 production in RA synovium.

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Abstract Number: 1624

Safety of Surgery in Patients Treated with Tocilizumab for Rheumatoid Arthritis : Data from a French Registry

Marie Locci[1], Bernard Combe[2], Cédric Lukas[3], Maxime Dougados[4], Rene-Marc Flipo[5], Christian Marcelli[6], Stephanie Rist Bouillon[7], Jean Sibilia[8] and Jacques Morel[9], [1]rheumatology, CHU Lapeyronie, MONTPELLIER, France, [2]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [3]Rheumatology, CHU Lapeyronie and EA2415, Montpellier University, University of Montpellier, France, [4]Rheumatology, Paris Descartes University, Paris, France, [5]Rheumatology, University Hospital, Lille, France, [6]Rheumatology dept, University Hospital Centre of Caen, Caen, France, [7]Rhumatologie, Hopital La Source, La Source, France, [8]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [9]Rheumatology, Department of Rheumatology, Montpellier University Hospital, Montpellier, France
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Background/Purpose: Rheumatoid Arthritis (RA) patients have a higher risk of post-operative complications compared with the general population, especially considering the risk of infection. It remains unclear whether use of biological DMARDs, including Tocilizumab (TCZ), is an independent risk factor for post-operative complications. The aim of this study was to evaluate safety and predictive factors of complications after surgery in rheumatoid arthritis patients receiving Tocilizumab in routine care.

Methods: Patients treated with TCZ for RA included in the French REGATE registry were included if they underwent surgery. When TCZ was interrupted more than 12 weeks prior to surgery, patients were excluded. Post-operative complications were defined as an adverse event occurring in the 12 weeks after surgery. Frequency of post-surgery complications was collected and compared in patients with and without complications in order to identify factors associated with complications. A second analyze was achieved in patients with post-operative infection (local or general). Qualitative variables were compared by Fisher's test and quantitative variables were compared by the Mann-Whitney test.

Results: Out of 1499 patients from the REGATE registry, a total of 167 patients underwent 175 surgical procedures. These patients were mainly women (84%), the mean age was 58.11 +/- 12.83 years, and the disease duration of 14.96+/- 11.29 years. The mean delay between surgery and the last TCZ infusion was 4.94+/-1.74 weeks (median 4 weeks). Fifteen patients experienced 15 complications (8.9%) with 10 severe infections, 1 intestinal obstruction, 1 RA flare, 1 delayed wound healing, 1 thromboembolic disorder and 1 hemorrhagic complication. Postoperative complications occurred after 7.8% of orthopedic surgeries (8 of 103). The 10 severe infections occurred mostly after orthopedic surgery (7/10). There was 7 surgical site infections (46.7%) and 3 general infections. In 5 patients, TCZ treatment was definitely stopped. On univariate analysis, no risk factor was significantly associated with post-operative complications. However, corticosteroids (p=0.096), previous biological treatment (p=0.096) and previous RTX treatment (p=0.074) almost reached statistically significancy.In multivariate analysis, only previous RTX treatment was close to be significant in multivariate

analysis (OR: 3.27, IC95% 0.92-11.49, p=0.052). Concerning infectious complications, no risk factor was found statistically associated with post-operative complications on univariate analysis. Only diabetes mellitus (p=0.091), foot surgery (p=0.095) and number of TCZ infusions before surgery (p=0.084), were almost statistically significant. In multivariate analysis, only foot surgery (OR: 3.17, IC95% 0.82-12.21 p=0.078) and diabetes mellitus (OR: 3.73, IC95% 0.88-15.79, p=0.057) tended to be associated with infectious post-operative complications.

Conclusion:

In routine practice, the postoperative period in TCZ treated patients seem to be safe when TCZ is stopped 1 month before surgery. Diabetes was significantly associated with an increased risk of post-operative infection in RA patients treated with TCZ.

Disclosure: M. Locci, None; **B. Combe**, None; **C. Lukas**, None; **M. Dougados**, Pfizer, AbbVie, Celgene, Eli Lilly, Novartis, Roche, and Sanofi-Aventis, 5,Pfizer, AbbVie, UCB, Merck, 8; **R. M. Flipo**, None; **C. Marcelli**, None; **S. Rist Bouillon**, None; **J. Sibilia**, None; **J. Morel**, None.

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Abstract Number: 1625

Analysis of a Phase 3 Study Evaluating the Efficacy of Sirukumab, an Anti-IL-6 Cytokine Monoclonal Antibody, Across Subgroups in Patients with Active Rheumatoid Arthritis Despite Treatment with Disease-Modifying Anti-Rheumatic Drugs

Carter Thorne[1], George Karpouzas[2], Tsutomu Takeuchi[3], Shihong Sheng[4], Weichun Xu[4], Ravi Rao[5], Kaiyin Fei[4] and Benjamin Hsu[4], [1]University of Toronto and Southlake Regional Health Centre, Newmarket, ON, Canada, [2]Division of Rheumatology, Harbor-UCLA Medical Center, Torrance, CA, [3]Division of Rheumatology, Keio University School of Medicine, Tokyo, Japan, [4]Janssen Research & Development, LLC, Spring House, PA, [5]GSK Medicines Research Centre, Stevenage, Hertfordshire, United Kingdom

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Session Time: 9:00AM-11:00AM

Background/Purpose: Sirukumab is a human monoclonal antibody that selectively binds to the IL-6 cytokine with high affinity, and is under development for rheumatoid arthritis (RA) and other diseases. Efficacy and safety of sirukumab have recently been evaluated in a global Phase 3 study (SIRROUND-D) in patients (pts) with active RA refractory to conventional, synthetic, disease-modifying antirheumatic drugs (DMARDs). This analysis aimed to compare the efficacy of sirukumab across various subgroups based on demographics, baseline characteristics, and prior/baseline medication use.

Methods: Eligible pts were randomized (1:1:1) to treatment with sirukumab subcutaneous (SC) 50 mg q4w, sirukumab SC 100 mg q2w, or placebo SC q2w. The 2 co-primary efficacy endpoints were ACR20 response at Wk 16 and change from baseline in the modified Sharp/van der Heijde (SHS) radiographic damage score at Wk 52. The first prespecified analysis compared the consistency of ACR20 response at Wk 16 across subgroups, including geographic region, age, weight, rheumatoid factor (RF) positivity, anti-cyclic citrullinated peptide (CCP) positivity, Health Assessment Questionnaire–Disability Index (HAQ-DI), C-reactive protein (CRP) level, disease duration, prior/baseline DMARD use, and baseline

methotrexate (MTX) use. Post-hoc analyses examined ACR50 and DAS (CRP) remission at Wk 24.

Results: Sirukumab 50 mg q4w and 100 mg q2w led to higher rates of ACR20 response at Wk 16 compared with placebo across all parameters analyzed and regardless of disease duration, use of baseline DMARDs, number of prior DMARDs, or baseline MTX dose (**Table**). For most parameters, including age, weight, anti-CCP positivity, combined RF and anti-CCP positivity, and HAQ-DI, sirukumab efficacy, as assessed by rate of ACR20 response at Wk 16 vs placebo, was not significantly associated with a particular subgroup (with the exception of geographic region [$P = 0.032$], RF positivity [$P = 0.012$], and CRP level [$P = 0.005$] when comparing sirukumab 100 mg q2w vs placebo). In all cases, the odds ratios favored sirukumab, but Asia Pacific region, RF-positive status, and CRP level ≥15 mg/dL were associated with the greatest differences in ACR20 response rate at Wk 16 for sirukumab 100 mg q2w vs placebo. In post-hoc analyses of Wk 24 ACR50 and DAS (CRP) remission, greater efficacy was consistently demonstrated with sirukumab compared with placebo across all parameters analyzed, with a few significant associations between sirukumab efficacy and particular subgroups.

Conclusion: Both doses of sirukumab demonstrated greater efficacy than placebo, based on ACR20 response at Wk 16, as well as ACR50 and DAS (CRP) remission at Wk 24, across all subgroups analyzed. These results confirm the consistency of sirukumab efficacy in pts with active RA, regardless of disease duration and prior medication use.

Table. Odds Ratios Comparing ACR20 Response Rates at Wk 16 by Subgroups

	Odds ratio (95% CI) for ACR20 at Wk 16	
Baseline characteristic	**Sirukumab 50 mg q4w, placebo**	**Sirukumab 100 mg q2w, placebo**
Disease duration		
<1 yr	4.154 (1.7, 10.0)	3.846 (1.6, 9.3)
≥1 yr to <3 yrs	3.078 (1.7, 5.7)	3.567 (1.9, 6.6)
≥3 yrs	3.364 (2.5, 4.5)	3.071 (2.3, 4.1)
Baseline DMARDs		
Yes	3.280 (2.5, 4.3)	3.039 (2.3, 3.9)
No	5.020 (1.8, 13.9)	6.389 (2.4, 17.2)
Prior DMARDs		
1	2.682 (1.7, 4.1)	2.348 (1.5, 3.6)
2	4.423 (2.8, 7.1)	4.960 (3.1, 8.0)
≥3	3.323 (2.2, 5.0)	3.000 (2.0, 4.5)
Baseline MTX		
0 mg/wk	5.605 (2.5, 12.7)	5.930 (2.6, 13.4)
>0 to <12.5 mg/wk	3.617 (2.2, 6.0)	3.661 (2.2, 6.0)
≥12.5 mg/wk	3.050 (2.2, 4.2)	2.765 (2.0, 3.8)

CI, confidence interval; q4w, every 4 weeks; q2w, every 2 weeks; DMARD, disease-modifying antirheumatic drug; MTX, methotrexate.

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Abstract Number: 1626

In Real Life Rheumatoid Arthritis Patients, Leflunomide Has Limited

Impact As a Second Line DMARD after Methotrexate

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Background/Purpose: In patients with rheumatoid arthritis (RA), in whom methotrexate (MTX) is not inducing remission or at least low disease activity, or is not tolerated, leflunomide is one conventional synthetic DMARD option that is still commonly used in some countries. We thus investigated whether real life patients with RA benefit from instituting leflunomide after methotrexate.

Methods: The clinical data of all RA patients who had at least once received leflunomide, and who agreed to the pseudonymized analysis of their data (approved by the local ethics committee), were analyzed from the time of leflunomide initiation on to the time of stopping leflunomide or the last visit in 2015, which ever came first.

Results: 144 RA patients treated with leflunomide were identified. Of these, 86 received leflunomide after MTX had failed as a first line DMARD, and 8 received leflunomide as a first line DMARD. 50 patients had another first line therapy. Of the first line leflunomide patients 3 (38%) were still on leflunomide at the last visit, as compared to 6 of the 43 patients (14%) who were switched from MTX to leflunomide, and 0 of the 27 patients in whom leflunomide was added to MTX ($p<0.01$ vs 1^{st} line leflunomide). For leflunomide monotherapy, 29% and 19% were still on the drug after 24 and 48 months, respectively, as compared to 14 and 0% under the combination with MTX. Of all patients who started leflunomide, remission (at least low disease activity) as per CDAI (≤ 2.8 (≤ 10)) was reached by 23% (57%) 3 months, 20% (40%) 6 months, and 16% (34%) one year after initiating leflunomide monotherapy, with corresponding percentages of patients of 39% switched to other approaches at six months and of 60% switched at one year. Under the combination of leflunomide and MTX, remission (at least low disease activity) was seen in 18% (53%) at 3 months, 20% (37%) at 6 months, and 8% (20%) at one year, and 55% and 71% had switched to other modes of action at six months and one year, respectively. Gastrointestinal and mucocutaneous adverse events and hypertension were common, and 4 our patients experienced serious bacterial infections.

Conclusion: While leflunomide may be a longer term option for a subgroup of RA patients with contraindications to MTX or after MTX failure, only a third of patients had acceptable disease control after one year under leflunomide monotherapy, and one in five under leflunomide combined with MTX. These results are supportive of the EULAR recommendations that patients should be switched to a second conventional DMARD in the absence of predictors of bad outcome only. If leflunomide is initiated, the patients need to be followed closely for potential secondary loss of efficacy.

Disclosure: G. Weigt, None; **A. Erler**, None; **M. Aringer**, None.

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Abstract Number: 1627

Network Meta-Analysis to Assess the Relative Efficacy of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, in Combination Therapy for Patients with Active Rheumatoid Arthritis Despite Conventional Dmards

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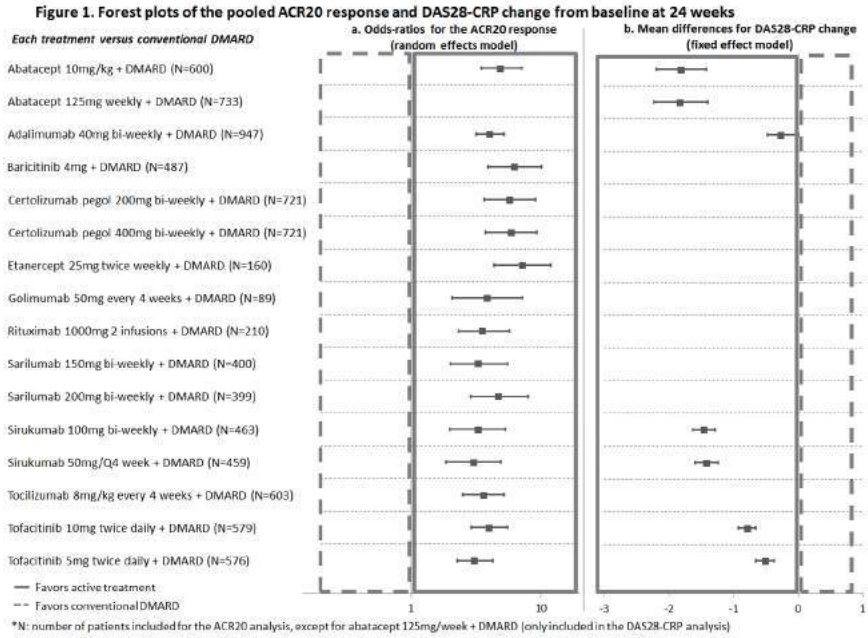
Background/Purpose: Sirukumab is a human anti-interleukin-6 cytokine monoclonal antibody evaluated for the treatment of moderate to severe active rheumatoid arthritis (RA) and other diseases. Our aim is to update previous network meta-analyses (NMAs) comparing biologic (b) disease modifying anti-rheumatic drugs (DMARDs) and targeted synthetic (ts) DMARDs with conventional (c) DMARDs with the inclusion of sirukumab data from the SIRROUND-D trial, a phase 3 pivotal randomized clinical trial in this patient population.

Methods: Bayesian NMA were conducted using randomized controlled trials identified from a systematic literature review. The analysis included only trials assessing a treatment combined with one cDMARD. Studies reporting ACR20 response and change from baseline in disease activity score 28 (DAS28) based on the C-reactive protein (CRP) at 24±4 weeks were included. A Bayesian network meta-regression adjusted for baseline risk (ie, the estimated baseline effect of the common comparator arm in each trial) was conducted for the ACR20 analysis. The baseline risk is used as a proxy to adjust for differences in patients' characteristics that lead to variations across common comparator arms. Evidence networks included treatment and dose-specific nodes except for cDMARDs. Non-informative prior distributions were used. Selection of fixed versus random effects was based on the Deviance Information Criterion (DIC).

Results: The review identified 24 studies reporting results at 24 weeks for abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, rituximab, sarilumab, tocilizumab and tofacitinib, all combined with a cDMARD. ACR20 response rates in the cDMARD arms varied greatly across trials (9% to 46%). The meta-regression adjusting for baseline risk suggested a strong interaction between baseline risk and treatment effect. Based on the DIC, a random effects model was selected for the ACR20 analysis. All bDMARDs (including sirukumab) and tsDMARDS achieved better ACR20 response compared with cDMARDs (**Figure 1a**). Most biologics' credible intervals show significant overlap, suggesting a similar level of efficacy in achieving ACR20. For DAS 28, a fixed effect model was used, and with a small network of available studies. The 4 biologics included in this evidence network performed better than cDMARDs. Sirukumab and abatacept appear to demonstrate improvement over the other agents in the network on this measure (**Figure 1b**).

Conclusion: The NMA suggests that sirukumab has similar ACR20 response, and similar or slightly higher DAS28-CRP improvement, compared with most bDMARDs and tsDMARDs.



Disclosure: S. Peterson, Janssen Research & Development, LLC, 1,Janssen Research & Development, LLC, 3; **M. Pacou**, Amaris, 3; **D. Belhadi**, Amaris, 3; **S. Van Sanden**, Janssen Research & Development, LLC, 3; **T. Webb**, Janssen Research & Development, LLC, 3; **R. Ganguly**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **R. Kurrasch**, GlaxoSmithKline, 1,GlaxoSmithKline, 1; **R. Rao**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **B. Hsu**, Janssen Research & Development, LLC, 1,Janssen Research & Development, LLC, 3; **K. Fei**, Janssen Research and Development, LLC, 1,Janssen Research and Development, LLC, 3; **D. Kielar**, Janssen Research & Development, LLC, 3; **R. Alfonso**, GSK Medicines Research Centre, 3.

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Abstract Number: 1628

Distinct Baseline Serum Molecular Profile and Pharmacodynamic Effects of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, in Asian-Pacific Patients with Active Rheumatoid Arthritis Despite DMARD or Anti-Tnfα Therapy Across Two Global Phase 3 Trials

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Background/Purpose: Baseline differences in rheumatoid arthritis (RA) disease characteristics and molecular profile

across populations may be a reflection of genetic variations and environmental factors such as regional differences in treatment paradigm, access to biologics, diet and lifestyle. These differences may influence response to treatment. The objective of this study was to compare baseline and post treatment molecular profiles of RA patients across geographic regions that were inadequate responders (IR) to conventional DMARDs and anti-TNFs and were treated with sirukumab, a monoclonal antibody that binds IL6.

Methods: Serum samples were taken at baseline, Week 4, and Week 24 in two phase 3 studies of sirukumab in RA: SIRROUND-D (DMARD-IR), and SIRROUND -T (anti-TNF-IR).

Results are reported (from SIRROUND -D|-T) for patients from Asia-Pacific (AP), Europe (EU), and North America(NA), respectively, in the following dose groups: sirukumab 100mg q2w (n=49|33, 98|36, 24|67) and sirukumab 50mg q4w (n=40|21, 103|40, 25|67). Serum was analyzed using the SomaLogic SOMAscan^{TM} platform (376 analytes). Analytes significantly and differentially expressed in baseline RA samples versus independently collected demographically-matched healthy control serum samples were used to derive a serum composite score for each sample set via a log2-transformation of the median of normalized values for the analytes. mRNA from whole blood samples was isolated and profiled using the Affymetrix HT HG-U133+ PM Array. Gene set variation analysis was used to evaluate enrichment of an in vitro derived IL-6 gene signature in each sample and compared across geographic regions. Results: The following analytes, elevated in baseline serum samples from RA patients versus healthy controls, formed the basis of the serum composite score: annexin I, BLC/CXCL13, BPI, CRP, IL6, IP-10/CXCL10, LEAP1/hepcidin, MMP1, MMP3, PBEF, PHI, SAA, SP-D, TIMP-3. At baseline, the serum composite score, as well as individual RA-associated analytes, such as CXCL13, MMP3, and SP-D, were significantly elevated in patients from AP compared with EU or NA. Patients from AP also showed higher enrichment for the in vitro-derived IL-6 gene expression signature at baseline. After 4 and 24 weeks of treatment, the serum composite score and IL-6 gene signature was significantly decreased in all patients from both sirukumab treatment arms compared with placebo. However, stronger pharmacodynamic effects and significantly greater down regulation of both the serum composite score and IL-6 gene signature were observed in AP patients at both 4 and 24 weeks post treatment. These molecular changes were associated with higher baseline RA disease severity and CRP levels observed in patients from the AP region.

Conclusion: RA-related inflammatory proteins and the IL-6 gene signature are significantly elevated at baseline and more extensively down-regulated post sirukumab treatment in both DMARD-IR and TNFi-IR patients from the AP region compared with the rest of world. These differences and their implications with respect to RA disease activity and clinical treatment options will be explored in subsequent analyses.

Disclosure: B. Dasgupta, Janssen Research and Development, LLC, 3; **A. Walsh**, Johnson & Johnson, 1,Johnson & Johnson, 3; **K. Sweet**, Janssen Research and Development, LLC, 3; **N. Peffer**, Johnson & Johnson, 1,Johnson & Johnson, 3; **C. Franks**, 1Janssen Research & Development, LLC, 3; **K. Ma**, None; **M. Sims**, None; **K. Campbell**, Janssen Research and Development, LLC, 3,Janssen Research and Development, LLC, 1; **M. Loza**, Janssen Research and Development, LLC, 3.

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Abstract Number: 1629

Pharmacokinetics of ABT-494 with the Once-Daily Extended-Release Tablet Formulation Being Utilized in the Ongoing Rheumatoid Arthritis Phase 3 Trials

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Background/Purpose: ABT-494 is a selective Janus Kinase 1 inhibitor. In two Phase 2b studies in subjects with rheumatoid arthritis, 6 mg and 12 mg twice-daily (BID) doses of ABT-494 immediate-release formulation achieved optimal benefit-risk profiles. To enhance patients' compliance, an extended-release formulation was developed targeting to achieve comparable exposures with the 6 mg and 12 mg BID of the immediate-release formulation with once-daily (QD) administration. This work characterized the pharmacokinetics of ABT-494 with the extended-release formulation that is currently being utilized in Phase 3.

Methods:

Comparison of ABT-494 pharmacokinetics from the immediate-release and extended-release formulations was conducted following multiple-dose administration in healthy subjects. Two cohorts of subjects were evaluated. In the first cohort, healthy subjects (N = 12) received multiple 15 mg QD doses of the extended-release tablet formulation and multiple 6 mg BID doses of the immediate-release capsule formulation for 7 days. In the second cohort, healthy subjects (N = 12) received multiple 30 mg QD doses of the extended-release tablet formulation and multiple 12 mg BID doses of the immediate-release capsule formulation for 7 days. Both evaluations were conducted following an open-label, randomized, 2-period, 2-sequence, crossover design under fasting conditions. ABT-494 plasma concentrations were measured and pharmacokinetic parameters were calculated using non-compartmental analyses.

Results: At steady-state, ABT-494 AUC_{0-24} ratio [and 90% confidence interval] was 0.94 [0.84 – 1.05], C_{max} ratio was 0.91 [0.74 – 1.12] and C_{min} ratio was 1.09 [0.85 – 1.40] for the 15 mg QD regimen of the extended-release formulation relative to the 6 mg BID regimen of the immediate-release formulation. Similarly, ABT-494 mean AUC_{0-24} ratio was 0.97 [0.87 – 1.09], C_{max} ratio was 0.90 [0.73 – 1.11] and C_{min} ratio was 0.87 [0.75 – 1.02] for the 30 mg QD regimen of the extended-release formulation relative to the 12 mg BID regimen. All evaluated regimens were well-tolerated by healthy subjects.

Conclusion: ABT-494 regimens of 15 mg QD and 30 mg QD of the extended-release formulation, currently being utilized in Phase 3 RA studies, provide similar exposures to 6 mg BID and 12 mg BID, respectively of the immediate-release capsule formulation previously shown to provide optimal benefit-risk profiles in RA Phase 2 trials.

Disclosure: M. E. Mohamed, AbbVie, 1,AbbVie, 3; **J. Zeng**, AbbVie, 1,AbbVie, 3; **I. H. Song**, AbbVie, 1,AbbVie, 3; **A. A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 1630

Consistent Pharmacodynamic Effects of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, on Serum Analytes Across Four Phase 3 Clinical Trials in Rheumatoid Arthritis

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Background/Purpose: The efficacy of sirukumab, an anti-IL-6 cytokine antibody, was evaluated in multiple phase 3 studies in patients with rheumatoid arthritis (RA) (SIRROUND -M, -D, -T, and -H) including the following populations: methotrexate (MTX) inadequate responders (IR), conventional DMARD-IR, and TNF inhibitor (TNFi)-IR. Treatment with sirukumab was hypothesized to normalize expression levels of serum analytes dysregulated at baseline in RA, with a dose response association.

Methods: Serum samples from the 4 studies were analyzed at baseline and Week 4 post-treatment using SomaLogic SOMAscan^{TM} (376 analytes) and validated antibody-based (Meso Scale Discovery, Luminex, and ELISA; 33 analytes) platforms. For the SIRROUND -M, -D, -T, and -H studies, respectively, results are reported for patients given sirukumab 100mg q2w (n=61, 205, 136, 106), sirukumab 50mg q4w (n=61, 203, 128, 115), or placebo (n=0, 122, 56, 0) and demographically-matched healthy controls samples (0, 50, 35, 145). Differences between groups were evaluated by comparing within-subject $\log_2$ ratio of Week 4 over baseline values between treatment groups (adjusted for MTX dose; SIRROUND -D, -T) or versus 0-change (SIRROUND -M, -H), with FDR <0.05 and |fold/reference geometric means|>1.5 considered significant.

Results: At baseline, 24 analytes were significantly elevated and 6 were suppressed in RA patients compared to healthy controls (**Table 1**). Among the elevated analytes, 8 were suppressed by treatment with sirukumab 50mg q4w and 100 mg q2w across all 4 studies, consisting of acute phase proteins, S100A12, MMP-1, and surfactant protein D. Sixteen of the analytes elevated at baseline were not decreased by sirukumab, notably MMP-3 and lymphocyte chemoattractants CXCL10 and CXCL13, the latter 3 known to be decreased by TNF inhibitors. Among analytes suppressed at baseline, none were increased by sirukumab. Among analytes not significantly dysregulated in RA at baseline, 14 were significantly decreased by sirukumab, including complement components, acute phase proteins and neutrophil-associated proteins. Changes in analyte levels were not significantly different between 100mg q2w and 50mg q4w sirukumab dose groups, with the exception of CRP, where decreases were significantly greater with the higher dose only in TNFi-IR patients .

Conclusion: Sirukumab consistently decreased 8 inflammatory proteins which were elevated at baseline across multiple RA populations, with no consistent dose response observed. In addition to expected reductions in acute phase proteins with sirukumab, these included MMP-1 and SP-D. Several markers were not affected, including some lymphocyte chemoattractants that are known to be decreased by TNF inhibitors. The clinical implications of RA-associated analytes not normalized by sirukumab, as well as those decreased below normal levels, remain to be understood.

Table 1. Pharmacodynamic Effects of Sirukumab 50mg q4w on Serum Analytes*

Disease-association	Elevated at baseline			Suppressed at baseline		Not dysregulated at baseline
Change at week 4	Decreased	Not changed		Decreased	Not changed	Decreased
SomaLogic SOMAscan	CRP [CRP]	IP-10 [CXCL10]	*Intracellular:*	C3b [C3]	CCL28 [CCL28]	C4 [C4]
	Hepcidin/LEAP-1 [HAMP]	BLC [CXCL13]	BARK1 [ADRBK1]		LKHA4 [LTA4H]	C5, C5a [C5]
	IL-6 [IL6]	annexin I [ANXA1]	CSK [CSK]		Midkine [MDK]	C5b/C6 [C5, C6]
	MMP-1 [MMP1]	PBEF [NAMPT]	GAPDH, liver [GAPDH]		Glucagon [GCG]	C6 [C6]
	Serum amyloid A [SAA1]	PHI [GPI]	hnRNP A/B [HNRNPAB]		SARP-2 [SFRP1]	C9 [C9]
	Surfactant protein D [SFTPD]†	MMP-3 [MMP3]	hnRNP A2/B1 [HNRNPA2B1]			Factor B [CFB]
			IMDH1 [IMDH1]			Haptoglobin [HP]
			LYNB [LYN]			LPS-binding protein [LBP]
			M2-PK [PKM2]			Serum amyloid P [APCS]
			PKC-B-II [PRKCB]			GRO-beta/gamma [CXCL2,CXCL3]
			SRCN1 [SRC]			FUT5 [FUT5]
MSD/Luminex/ELISA	CRP [CRP]	IP-10 [CXCL10]				Haptoglobin [HP]
	Serum amyloid A [SAA1]	BLC [CXCL13]				Myeloperoxidase [MPO]
	Calgranulin C [S100A12]	MMP-3 [MMP3]†				MMP-9 [MMP9]
	MMP-1 [MMP1]					
	VEGF [VEGFA]					

*Analytes (encoding gene[s]) significant (FDR<0.05, |fold/reference geometric means|>1.5) for disease association (RA at baseline vs. healthy controls) and sirukumab 50mg q4w pharmacodynamic effect (vs. placebo, SIRROUND-D, -T; or no-change, SIRROUND-M, -H) in all studies tested are displayed for SomaLogic SOMAscan and antibody-based (MSD, Luminex, ELISA) platforms.

†Trend for small decrease in all studies (FDR-BH<0.05, |fold/reference geometric means|>1.2 but <1.5).

Disclosure: M. Loza, Janssen Research & Development, LLC, 3; **K. Sweet**, Janssen Research & Development, LLC, 3; **N. Peffer**, Johnson & Johnson, 1,Johnson & Johnson, 3; **C. Franks**, 1Janssen Research & Development, LLC, 3; **K. Ma**, Janssen Research & Development, LLC, 3; **K. Campbell**, Janssen Research and Development, LLC, 3,Janssen Research and Development, LLC, 1; **M. Sims**, GSK, 3; **B. Dasgupta**, Janssen Research & Development, LLC, 3.

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rheumatoid-arthritis

Abstract Number: 1631

Sarilumab Dose Reduction in an Open-Label Extension Study in RA Patients

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Background/Purpose: Sarilumab is a human mAb blocking the IL-6Rα. In the phase 3 MOBILITY (NCT01061736) and TARGET (NCT01709578) studies, sarilumab (150 or 200 mg subcutaneously every 2 weeks [q2w]) demonstrated efficacy in adults with active, moderate-to-severe RA.[1,2] In both studies, infections, neutropenia, injection site reactions, and increased transaminases were among the most common treatment-emergent adverse events. Laboratory changes were consistent with IL-6 signaling blockade. This analysis examined laboratory changes and treatment continuation after sarilumab dose reduction observed through January 2016 in EXTEND (NCT01146652), an open-label, follow-up study evaluating long-term safety and efficacy of sarilumab with or without concomitant conventional synthetic DMARDs.

Methods: Adults with RA who previously participated in sarilumab studies were eligible. Patients who entered into EXTEND initially received sarilumab 150 mg weekly. After dose selection for phase 3 studies, patients were switched to or initiated on sarilumab 200 mg q2w. Per protocol, investigators could reduce the sarilumab dose from 200 mg q2w to 150 mg q2w for absolute neutrophil count (ANC) ≥0.5 to 1.0 Giga/L, platelet count ≥50 to 100 Giga/L, or alanine aminotransferase (ALT) ≥3 to 5 × upper limit of normal. Dose reductions were also performed at the investigator's discretion. Efficacy data from EXTEND were analyzed before and 24 weeks after dose reduction for MOBILITY (n=148) and TARGET (n=47) patients.

Results: As of the January 2016 interim analysis (N=1652), dose reduction from sarilumab 200 mg q2w to 150 mg q2w had occurred in 17.7% of patients (n=292). The most common reasons for dose reduction were decreased ANC (11.3%; n=187) and increased ALT (3.9%; n=65) levels. The most common non-laboratory reason for dose reduction was infection (0.4%; n=7). At the time of analysis, 76.9% of patients (n=247) whose dose was reduced were continuing treatment, with a median treatment duration of 2.3 years after dose reduction. Improvements in ANC and ALT levels were observed over the 6 months after dose reduction (Table). Sarilumab efficacy was maintained in MOBILITY and TARGET patients 24 weeks after dose reduction as assessed by ACR20 response rates (83.1% and 85.1%, respectively) and improvements in HAQ–Disability Index scores (-0.68 and -0.82, respectively).

Conclusion: In patients whose sarilumab dose was reduced from 200 mg q2w to 150 mg q2w, there was an improvement in laboratory abnormalities and continuation of treatment for the majority of patients. Improvements in signs and symptoms of RA and physical function were maintained after dose reduction. **References: 1.** Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437. **2.** Fleischmann et al. Presented at: American College of Rheumatology Annual Meeting; November 7-11, 2015; San Francisco, CA.

Disclosure: M. C. Genovese, Roche, Sanofi, GlaxoSmithKline, R-Pharma, RuiYi, and Bristol-Myers Squibb, 2,Roche, Sanofi, GlaxoSmithKline, R-Pharma, RuiYi, and Bristol-Myers Squibb, 5; **J. Fay**, Regeneron Pharmaceuticals, Inc, 1,Regeneron Pharmaceuticals, Inc, 3; **J. Parrino**, Regeneron Pharmaceuticals, Inc, 1,Regeneron Pharmaceuticals, Inc, 3; **D. Beyer**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **M. Iglesias-Rodriguez**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **N. Graham**, Regeneron Pharmaceuticals, Inc, 1,Regeneron Pharmaceuticals, Inc, 3; **A. Boddy**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **J. A. Simon**, None; **R. Martincova**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **G. R. Burmester**, AbbVie, Bristol-Myers Squibb, MedImmune, Merck, Pfizer, Roche, and UCB, 2,AbbVie, Bristol-Myers Squibb, MedImmune, Merck, Pfizer, Roche, and UCB, 5,AbbVie, Bristol-Myers Squibb, Merck, Pfizer, Roche, and UCB, 8.

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Abstract Number: 1632

Efficacy and Safety of Sarilumab in Subgroups of Patients with Rheumatoid Arthritis from 2 Phase 3 Studies

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Background/Purpose: Sarilumab is a human mAb blocking the IL-6Rα. Efficacy of sarilumab + MTX was demonstrated in patients with RA and inadequate response to MTX (MOBILITY; NCT01061736).[1] Sarilumab + conventional synthetic DMARDs demonstrated efficacy in patients with RA and inadequate response or intolerance to TNF inhibitors (TARGET; NCT01709578).[2] Efficacy and safety of sarilumab across prespecified subpopulations were assessed in a pooled analysis of patients from MOBILITY and TARGET.

Methods: Adult patients from MOBILITY and TARGET were included in this analysis (N=1743). Incidence of ACR20 response at week 24, change from baseline in HAQ–Disability Index (HAQ-DI) at week 12, and change from baseline in DAS28-CRP at week 24 were evaluated for placebo (n=579), sarilumab 150 mg every 2 weeks (q2w) (n=581), and sarilumab 200 mg q2w (n=583) in prespecified subpopulations. Post hoc analysis of clinical disease activity index (CDAI) at week 24 was performed. Treatment-by-subgroup interactions were assessed by a logistic regression model (ACR20: week 24) or mixed-effect model for repeated measures (HAQ-DI: week 12; DAS28-CRP, CDAI: week 24).

Results: Superiority of both sarilumab doses vs placebo was observed across all subgroups except baseline RF status, anti-CCP autoantibody status, and weight (Table; Figure). A smaller treatment effect for sarilumab 150 mg q2w was observed in RF and anti-CCP seronegative patients and those weighing ≥100 kg for ACR20 and DAS28-CRP (Table). Treatment-emergent AEs and serious AEs were more frequent with sarilumab vs placebo. Infections, neutropenia, injection site reactions, and increased transaminases were among the most common TEAEs and occurred more frequently with sarilumab. As previously reported in the individual trials, no serious infections were associated with neutrophil reductions.

Conclusion: Superiority of sarilumab vs placebo, measured by ACR20 response and changes in HAQ-DI, DAS28-CRP, and CDAI, was generally consistent across patient subgroups. The magnitude of the treatment effect was smaller, particularly for sarilumab 150 mg q2w, in patients with baseline seronegativity for RF or anti-CCP autoantibody or with baseline weight ≥100 kg, although there were few patients in these subgroups.

References: 1. Genovese et al. *Arthritis Rheumatol.* 2015;67:1424-1437.

2. Fleischmann et al. Presented at: ACR; November 7-11, 2015; San Francisco, CA.

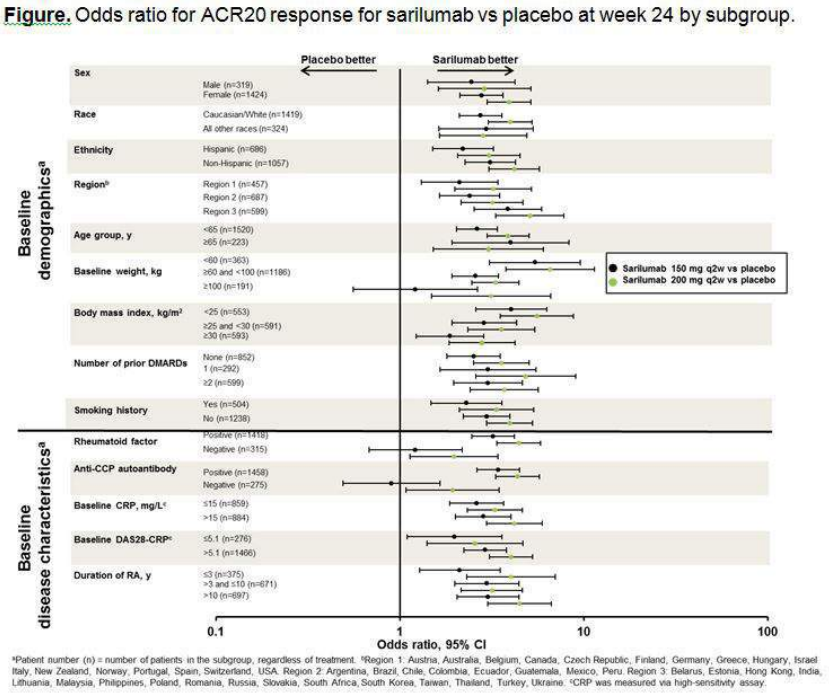
Table. Incidence of ACR20 Response at Week 24, LS Mean Change From Baseline in HAQ-DI at Week 12, LS Mean Change From Baseline in DAS28-CRP at Week 24, and LS Mean Change From Baseline in CDAI at Week 24 in MOBILITY and TARGET Subgroups: Treatment-by-Subgroup Interactions

	***P* value (interaction)**			
Subgroup	**ACR20 at week 24[a]**	**LS mean change from baseline in HAQ-DI at week 12[b]**	**LS mean change from baseline in DAS28-CRP at week 24[b,c]**	**LS mean change from baseline in CDAI at week 24[b]**
Baseline demographics				
Sex (male, female)	0.699	0.190	0.768	0.348
Race (white vs all other races)	0.531	0.770	0.772	0.506
Ethnicity (Hispanic vs non-Hispanic)	0.300	0.322	0.907	0.870
Region (regions 1, 2, 3)[d,e]	0.297	0.308	0.308	0.247
Age group (<65, ≥65 y)	0.269	0.982	0.687	0.800
Baseline weight (<60, ≥60 to <100, ≥100 kg)	0.013	0.189	0.006	0.199
BMI (<25, ≥25 to <30, ≥30 kg/m^2)	0.081	0.463	0.002	0.051
Number of prior DMARDs (none, 1, ≥2)	0.941	0.946	0.435	0.225
Smoking history (yes, no)	0.592	0.320	0.076	0.205
Baseline disease characteristics				
Rheumatoid factor (positive, negative)	0.006	0.001	0.011	0.360
Anti-CCP autoantibody (positive, negative)	0.001	0.010	0.001	0.0002
Baseline CRP (≤15, >15 mg/L)[c]	0.644	0.317	0.142	0.373
Baseline DAS28-CRP (≤5.1, >5.1)[c]	0.379	0.379	0.096	0.074
Duration of RA (≤3, >3 to ≤10, >10 y)	0.495	0.814	0.506	0.387

CDAI, clinical disease activity index; HAQ-DI, HAQ–Disability Index; LS, least squares; MMRM, mixed-effect model for repeated measures. [a]Logistic regression model with terms of treatment, region, subgroup, treatment-by-subgroup, and study indicator. [b]MMRM assuming an unstructured covariance structure with covariate baseline and terms of treatment, region, subgroup, treatment-by-subgroup, visit, treatment-by-visit, treatment-by-visit-by-subgroup, study indicator, and study indicator-by-visit. [c]CRP was measured via high-sensitivity assay. [d]Region 1: Austria, Australia, Belgium, Canada, Czech Republic, Finland, Germany, Greece, Hungary, Israel, Italy, New Zealand, Norway, Portugal, Spain, Switzerland, USA. Region 2: Argentina, Brazil, Chile, Colombia, Ecuador,

Guatemala, Mexico, Peru. Region 3: Belarus, Estonia, Hong Kong, India, Lithuania, Malaysia, Philippines, Poland, Romania, Russia, Slovakia, South Africa, South Korea, Taiwan, Thailand, Turkey, Ukraine. [e]For ACR20 at week 24, a logistic regression model with terms of treatment, region, treatment-by-region, and study indicator was used. For LS mean change from baseline in HAQ-DI at week 12 and DAS28-CRP and CDAI at week 24, MMRM model with terms of treatment, region, treatment-by-region, visit, treatment-by-visit, treatment-by-visit-by-region, study indicator, and study indicator-by-visit was used.

Figure. Odds ratio for ACR20 response for sarilumab vs placebo at week 24 by subgroup.



Disclosure: M. C. Genovese, Bristol-Myers Squibb, GlaxoSmithKline, R-Pharma, Roche, RuiYi, and Sanofi, 2,Bristol-Myers Squibb, GlaxoSmithKline, R-Pharma, Roche, RuiYi, and Sanofi, 5; **R. Fleischmann**, AbbVie, Amgen, Ardea, AstraZeneca, Bristol-Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Pfizer, Roche, Sanofi, and UCB, 2,AbbVie, Akros, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen, Eli Lilly, Pfizer, Roche, and UCB, 5; **E. Mangan**, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **J. van Adelsberg**, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **M. Iglesias-Rodriguez**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **D. Dukovic**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **C. Fan**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **T. W. Huizinga**, Merck, UCB, Bristol Myers Squibb, Biotest AG, Pfizer, GSK, Novartis, Roche, Sanofi-Aventis, Abbott, Crescendo Bioscience, Nycomed, Boeringher, Takeda, Zydus, Epirus and Eli Lilly, 5.

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Abstract Number: 1633

Clinical and Radiographic Outcomes after 3 Years of Sarilumab in Patients with Rheumatoid Arthritis

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Background/Purpose: Sarilumab is a human mAb blocking the IL-6Rα. Sarilumab + MTX demonstrated significant improvements in RA signs and symptoms, physical function, and inhibition of radiographic progression in the 1-year phase 3 MOBILITY study (NCT01061736). This analysis examined 3-year clinical and radiographic outcomes and safety in patients who completed MOBILITY and entered the open-label extension (OLE) study EXTEND (NCT01146652).

Methods: Patients in MOBILITY were initially randomized to placebo or sarilumab 150 or 200 mg every 2 weeks (q2w) subcutaneously for up to 1 year. Early rescue with open-label sarilumab 200 mg q2w was allowed for insufficient response after week 16. After completion of MOBILITY, patients were eligible for enrollment in EXTEND, in which all patients received active treatment (sarilumab 200 mg q2w after final dose selection) + MTX. DAS28-CRP and clinical disease activity index (CDAI) assessed clinical efficacy. Radiographs from patients at baseline and subsequent second and third years were centrally read by 2 readers independently. Linear extrapolation was applied at year 3 for patients who had data at year 2 and from an unscheduled visit between years 2 and 3 but not at year 3. Statistical analysis at year 3 was performed on the basis of patients' original randomized treatment assignment, regardless of whether they were rescued during the double-blind period (MOBILITY).

Results: Of the 1197 randomized patients in MOBILITY, 901 participated in EXTEND (Table). At year 3, after all patients had received open-label sarilumab for 2 years, percentages of patients achieving DAS28-CRP <2.6 or CDAI ≤2.8 were similar in patients originally treated with either dose of sarilumab or placebo, though the initial sarilumab 200 mg group exhibited the most favorable outcomes (Table). Improvements were maintained within each group from year 2 to year 3. Three-year radiographic data were available for 755 patients; linear extrapolation was used in 29. Modified total Sharp scores at year 3 in the initial placebo and sarilumab 150 and 200 mg groups were only slightly increased since year 2 (Table). Treatment-emergent adverse events (TEAEs) occurred in 89.7% of patients over 3 years. The most common TEAEs (≥10%) were neutropenia (19.4%), increased alanine aminotransferase (13.0%), and upper respiratory tract infections (12.7%). Infections were the most frequently reported serious AE (4.2/100 patient-years).

Conclusion: Active treatment with sarilumab 200 mg q2w resulted in durable clinical response and stabilization of radiographic progression at 3 years irrespective of prior treatment, though the initial sarilumab 200 mg group showed the most favorable outcomes. Adverse events were consistent with the anticipated effects of IL-6 inhibition and the known safety profile of sarilumab.

Table. Clinical and Radiographic Data at Baseline, Year 1, Year 2, and Year 3 for Patients With RA Enrolled in the EXTEND Study, in Which All Patients Received Active Treatment (Sarilumab 200 mg q2w After Final Dose Selection) + MTX

Population[a]		**Placebo + MTX -> sarilumab 200 mg q2w + MTX**	**Sarilumab 150 mg q2w + MTX-> sarilumab 200 mg q2w + MTX**	**Sarilumab 200 mg q2w + MTX**
Randomized = original MOBILITY population as denominator[b]				
	Incidence of DAS28-CRP <2.6, yes, n/N (%)[c]			
	Year 1	89/398 (22.4)	136/400 (34.0)	143/399 (35.8)
	Year 2	162/398 (40.7)	159/400 (39.8)	163/399 (40.9)
	Year 3	146/398 (36.7)	148/400 (37.0)	160/399 (40.1)
	Incidence of CDAI remission (CDAI ≤2.8), yes, n/N (%)[c]			
	Year 1	37/398 (9.3)	60/400 (15.0)	75/399 (18.8)
	Year 2	73/398 (18.3)	75/400 (18.8)	81/399 (20.3)
	Year 3	70/398 (17.6)	73/400 (18.3)	87/399 (21.8)
	mTSS change from baseline, mean +/- SEM			
	D Baseline - year 2	3.0 +/- 0.4	1.3 +/- 0.3	0.2 +/- 0.3
	D Baseline - year 3	3.3 +/- 0.5	1.9 +/- 0.4	0.8 +/- 0.3
	D Year 2 - year 3	0.3 +/- 0.1	0.6 +/- 0.2	0.4 +/- 0.1
Completers = patients who completed the OLE for the respective years as denominator[d]				
	DAS28-CRP, mean +/- SEM[c]			
	Baseline (at randomization into MOBILITY)	5.9 +/- 0.0	6.0 +/- 0.0	6.0 +/- 0.0
	Year 1 (randomized population)	3.6 +/- 0.1	2.9 +/- 0.1	2.8 +/- 0.1
	Year 2 (completers)	2.5 +/- 0.1	2.5 +/- 0.1	2.4 +/- 0.1
	Year 3 (completers)	2.5 +/- 0.1	2.4 +/- 0.1	2.3 +/- 0.1
	Incidence of DAS28-CRP <2.6, yes, n/N (%)[c]			
	Year 2	162/270 (60.0)	159/258 (61.6)	163/262 (62.2)
	Year 3	146/249 (58.6)	148/239 (61.9)	160/237 (67.5)
	CDAI, mean +/- SEM[c]			
	Baseline (at randomization into MOBILITY)	40.6 +/- 0.6	40.4 +/- 0.6	40.4 +/- 0.6
	Year 1 (randomized population)	14.7 +/- 0.6	11.0 +/- 0.6	11.0 +/- 0.6
	Year 2 (completers)	8.9 +/- 0.5	8.7 +/- 0.6	8.6 +/- 0.6
	Year 3 (completers)	8.8 +/- 0.6	8.3 +/- 0.6	7.1 +/- 0.5

	Incidence of CDAI remission (CDAI ≤2.8), yes, n/N (%)[c]			
	Year 2	73/271 (26.9)	75/259 (29.0)	81/262 (30.9)
	Year 3	70/249 (28.1)	73/239 (30.5)	87/238 (36.6)
Entered OLE = patients who entered OLE as denominator[e]				
	Incidence of DAS28-CRP <2.6, yes, n/N (%)[c]			
	Year 2	162/307 (52.8)	159/300 (53.0)	163/294 (55.4)
	Year 3	146/307 (47.6)	148/300 (49.3)	160/294 (54.4)
	Incidence of CDAI remission (CDAI ≤2.8), yes, n/N (%)[c]			
	Year 2	73/307 (23.8)	75/300 (25.0)	81/294 (27.6)
	Year 3	70/307 (22.8)	73/300 (24.3)	87/294 (29.6)

D, change; CDAI, clinical disease activity index; mTSS, modified total Sharp score; OLE, open-label extension; q2w, every 2 weeks; SEM, standard error of the mean. [a]Patients were tabulated according to their randomized treatment in MOBILITY. [b]"Randomized population": patients randomized into MOBILITY (ITT population). [c]Clinical endpoints were set to missing after early treatment discontinuation but not after rescue with open-label sarilumab. [d]"Completers": patients who completed 2 and 3 years of EXTEND. [e]"Entered OLE": patients who enrolled in EXTEND after MOBILITY.

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Abstract Number: 1634

Pharmacokinetics and Safety of Three Formulations of Rituximab (CT-P10, US-sourced Innovator Rituximab and EU-sourced Innovator Rituximab) in Patients with Rheumatoid Arthritis: Results from Phase 3 Randomized Controlled Trial over 24 Weeks

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Pharmacokinetics and Safety of Three Formulations of Rituximab (CT-P10, US-sourced Innovator Rituximab and EU-sourced Innovator Rituximab) in Patients with Rheumatoid Arthritis: Result from Phase 3 Randomized Controlled Trial over 24 Weeks

Background/Purpose : CT-P10 is a proposed biosimilar candidate of rituximab, and it has been concluded to be highly similar to the reference product in terms of analytical and functional characteristics and equivalent to EU-sourced innovator rituximab (EU-RTX) in pharmacokinetics (PK) in the patients with RA through phase 1 study.[1] The similarity in terms of PK was tested among CT-P10 and two innovator rituximabs from the different manufacturing sources in RA patients.

Methods : A total of 189 RA patients in PK analysis part from a randomized controlled phase 3 study (NCT02149121) was randomly assigned in 1:1:1 ratio to receive 2 infusions of 1,000 mg CT-P10, US-sourced innovator rituximab (US-RTX) or EU-RTX with a 2-week interval. The following PK parameters were coprimary endpoints: area under the serum concentration-time curve from time zero to the last measurable concentration ($AUC_{0\text{-last}}$), AUC from time zero extrapolated to infinity ($AUC_{0\text{-inf}}$) and maximum concentration after the second infusion (C_{max}) of CT-P10, US-RTX or EU-RTX. Pharmacokinetic similarity is concluded if the 90% confidence interval (CI) for the ratio of geometric means in $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$, and C_{max} are entirely contained within the bounds of 80% and 125% for the following comparisons: CT-P10 vs US-RTX, CT-P10 vs EU-RTX, and US RTX vs EU-RTX.

Results : The PK parameters among 3 treatment groups were highly similar (Table 1). The 90% CIs for the ratio of geometric means for coprimary endpoints fell within the PK equivalence margin of 80-125% indicating that drug exposures from CT-P10 are similar to those from both US-RTX and EU-RTX and also from US-RTX to those of EU-RTX (Table 2). The safety profiles among 3 treatment groups were generally similar. Adverse events (AEs) due to infusion related reaction were reported for 6 (9.4%), 4 (6.2%) and 12 (20.0%) patients in CT P10, US-RTX and EU-RTX, respectively. All these events were mild to moderate (grade 1 or 2) in intensity. Six patients were discontinued due to an AE (2 [3.1%], 3 [4.6%] and 1 [1.7%] patients in CT-P10, US-RTX and EU-RTX, respectively). No malignancy, progressive multifocal leukoencephalopathy, serious infection or death occurred in any of the treatment groups.

Table 1. Pharmacokinetic Secondary Endpoints (Mean ± SD)

Parameter	CT-P10 N=62	US-RTX N=63	EU-RTX N=59
$AUC_{0\text{-last}}$ (h•μg/mL)	188400.03 ± 65341.092	184121.66 ± 65532.728	199754.50 ± 68057.989
$AUC_{0\text{-}\infty}$ (h•μg/mL)	184478.20 ± 56373.724	187138.88 ± 63794.582	206484.59 ± 64727.223
C_{max} (μg/mL)	425.05 ± 95.491	423.07 ± 124.053	474.19 ± 100.494
C_{min} (μg/mL)	0.36 ± 0.583	0.45 ± 0.708	0.47 ± 0.756
$T_{1/2}$ (day)	15.04 ± 3.006	15.19 ± 3.591	15.65 ± 3.198

Table 2. Pharmacokinetic Primary Endpoints

Comparison	Parameter (unit)	Treatment	n	Geometric Least Squares Mean	% Ratio (T /R)	90% CI
CT-P10 (T) vs US-RTX (R)	$AUC_{0\text{-last}}$ (h*µg/mL)	T	62	162414.81	97.07	(88.08, 106.99)
		R	60	167309.07		
	$AUC_{0\text{-}\infty}$ (h*µg/mL)	T	59	162377.28	95.81	(87.39, 105.04)
		R	60	169480.80		
	C_{max} (µg/mL)	T	62	367.03	94.92	(89.61, 100.55)
		R	59	386.65		
CT-P10 (T) vs EU-RTX (R)	$AUC_{0\text{-last}}$ (h*µg/mL)	T	62	162414.81	94.18	(85.40, 103.86)
		R	59	172450.97		
	$AUC_{0\text{-}\infty}$ (h*µg/mL)	T	59	162377.28	89.89	(81.85, 98.72)
		R	56	180637.81		
	C_{max} (µg/mL)	T	62	367.03	89.00	(84.01, 94.28)
		R	59	412.40		
EU-RTX (T) vs US-RTX (R)	$AUC_{0\text{-last}}$ (h*µg/mL)	T	59	172450.97	103.07	(93.32, 113.85)
		R	60	167309.07		
	$AUC_{0\text{-}\infty}$ (h*µg/mL)	T	56	180637.81	106.58	(97.03, 117.08)
		R	60	169480.80		
	C_{max} (µg/mL)	T	59	412.40	106.66	(100.56, 113.13)
		R	59	386.65		

T, test; R, reference

Conclusion : Pharmacokinetic equivalence was demonstrated in terms of $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} in the comparisons of CT-P10 to US-RTX, CT-P10 to EU-RTX, and US-RTX to EU-RTX in RA patients. In addition, comparable safety profiles were observed among the 3 treatment groups. Reference 1. Yoo DH, et al. Arthritis Rheum 2013;65(Suppl 10): S736

Disclosure: C. H. Suh, CELLTRION,Inc., 5; **A. Berrocal Kasay**, CELLTRION,Inc., 2; **E. Chalouhi El-Khouri**, CELLTRION,Inc., 2; **P. Miranda**, CELLTRION,Inc., 2; **L. Bozic Majstorovic**, CELLTRION,Inc., 2; **S. Jeka**, CELLTRION,Inc., 2; **P. Hrycaj**, CELLTRION,Inc., 2; **D. Rekalov**, CELLTRION,Inc., 2; **P. Wiland**, CELLTRION,Inc., 2; **A. Krause**, CELLTRION,Inc., 2; **I. Szombati**, CELLTRION,Inc., 2; **A. Mihailova**, CELLTRION,Inc., 2; **I. Hospodarskyy**, CELLTRION,Inc., 2; **M. Piotrowski**, CELLTRION,Inc., 2; **S. R. Kwon**, CELLTRION,Inc., 2; **E. Y. Lee**, CELLTRION,Inc., 2; **D. H. Yoo**, CELLTRION,Inc., 5; **W. Park**, CELLTRION,Inc., 5; **S. C. Shim**, CELLTRION,Inc., 5; **S. J. Lee**, CELLTRION,Inc., 3; **T. S. Kwon**, CELLTRION,Inc., 3.

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Abstract Number: 1635

Efficacy and Safety of CT-P10, Rituximab Biosimilar Candidate, and Innovator Rituximab in Patients with Rheumatoid Arthritis: Results from Phase 3 Randomized Controlled Trial over 24 Weeks

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Efficacy and Safety of CT-P10, Rituximab Biosimilar Candidate, and Innovator Rituximab in Patients with Rheumatoid Arthritis: Result from Phase 3 Randomized Controlled Trial over 24 Weeks

Background/Purpose: Pharmacokinetic (PK) equivalence was demonstrated, and similar safety profiles of CT-P10 to EU-sourced innovator rituximab (EU-RTX) were shown in the phase 1 studies up to 2 years in RA patients including switching to CT-P10 from EU-RTX.[1,2] The purpose of this study was to demonstrate efficacy equivalence and compare safety profiles of CT-P10 to reference products (combined EU and US-sourced RTX) in RA patients up to 24 weeks.

Methods: In this randomized, controlled phase 3 study, RA patients were randomized to receive CT-P10 or reference products (NCT02149121). The primary efficacy endpoint, change of DAS28-CRP from baseline to week 24, was evaluated and analyzed by using an analysis of covariance (ANCOVA). Therapeutic equivalence is to be concluded if the 95% confidence interval (CI) for the treatment difference in the change of DAS28-CRP from baseline to Week 24 is entirely within the pre-specified equivalence margin of +/-0.60. Additional efficacy, pharmacodynamics (PD) and safety were also evaluated.

Results: A total of 372 RA patients (161 patients and 211 patients in CT-P10 and reference products groups, respectively) were enrolled. Overall efficacy, PD and safety profiles were similar between CT-P10 and reference products groups. The adjusted mean change of DAS28-CRP/ESR from baseline to week 24 was similar between the groups. The 95% CI for the estimate of treatment difference in DAS28-CRP/ESR was entirely within the equivalence margin which indicated therapeutic equivalence between the treatment groups (Table 1). Additional efficacy including ACR and EULAR responses was also shown to be comparable between 2 groups (Table 2). Rapid and complete depletion of B-cell counts were observed immediately after the first infusion, and B-cell kinetics over 24 weeks were similar between the groups. Adverse events (AEs) related to study drug were reported with a similar proportion in each treatment group; 49 (30.4%) and 59 (28.0%) patients in CT-P10 and reference products groups, respectively. Infection related to study drug was reported in 13 (8.1%) and 22 (10.4%) patients in CT-P10 and reference products groups, respectively. No malignancy, progressive multifocal leukoencephalopathy, and serious infusion-related reaction were reported.

Table 1 Improvement of DAS28-CRP and DAS28-ESR

Parameter Treatment	n	Adjusted Mean Change (SE)	Estimate of Treatment Difference	95% CI of Treatment Difference
DAS28-CRP				
CT-P10	139	-2.14 (0.177)	-0.05	(-0.29, 0.20)
Reference products	196	-2.09 (0.176)		
DAS28-ESR				
CT-P10	140	-2.41 (0.182)	-0.06	(-0.31, 0.19)
Reference products	196	-2.35 (0.182)		

Note: Adjusted least squares means and standard error, estimate of treatment difference [CT-P10 – reference products] and 2-sided 95% confidence interval calculated from the ANCOVA model.

Table 2 Proportions of Patients Achieving ACR and EULAR Responses at Week 24

	CT-P10 (N=155)	Reference products (N=203)
Parameter*	**Number (%) of patients**	
ACR20	114 (73.5)	154 (75.9)
ACR50	74 (47.7)	102 (50.2)
ACR70	43 (27.7)	62 (30.5)
EULAR-CRP	129 (83.2)	170 (83.7)
EULAR-ESR	127 (81.9)	170 (83.7)

* For EULAR-CRP/ESR, patients with moderate or good responder were included.

Conclusion: CT-P10 showed highly similar efficacy, PD and safety profiles to reference products up to 24 weeks.

Reference

1. Yoo DH, et al. Arthritis Rheum 2013;65(Suppl 10): S736
2. Yoo DH, et al. Arthritis Rheum 2015;67(Suppl 10): 2449-2452

Disclosure: D. H. Yoo, CELLTRION, Inc., 5; **L. Bozic Majstorovic**, CELLTRION, Inc., 2; **A. Berrocal Kasay**, CELLTRION, Inc., 2; **E. Chalouhi El-Khouri**, CELLTRION, Inc., 2; **F. Irazoque-Palazuelos**, CELLTRION, Inc., 2; **F. Cons Molina**, CELLTRION, Inc., 2; **P. Miranda**, CELLTRION, Inc., 2; **P. Shesternya**, CELLTRION, Inc., 2; **F. G. Medina-Rodriguez**, CELLTRION, Inc., 2; **P. Wiland**, CELLTRION, Inc., 2; **S. Jeka**, CELLTRION, Inc., 2; **O. Garmish**, CELLTRION, Inc., 2; **P. Hrycaj**, CELLTRION, Inc., 2; **D. Rekalov**, CELLTRION, Inc., 2; **N. Fomina**, CELLTRION, Inc., 2; **D. Zisman**, CELLTRION, Inc., 2; **Y. B. Park**, CELLTRION, Inc., 2; **Y. M. Kang**, CELLTRION, Inc., 2; **C. H. Suh**, CELLTRION, Inc., 5; **S. C. Shim**, CELLTRION, Inc., 5; **S. J. Lee**, CELLTRION, Inc., 3; **S. Y. Lee**, CELLTRION, Inc., 3; **W. Park**, CELLTRION, Inc., 5.

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Abstract Number: 1636

Decrease of Tocilizumab in Rheumatoid Arthritis in Remission : A Multicenter Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: The advent of biological therapies in rheumatoid arthritis has significantly reduced the activity of rheumatoid arthritis, leading to obtaining a remission in a significant proportion of patients. However, few data are available to determine the feasibility of decrease of a biological DMARD and define the strategy once remission is achieved.

Methods: This retrospective multicenter study have included patients with rheumatoid arthritis treated with tocilizumab (8mg/kg every 4 weeks) for at least 6 months and who have been a decrease dose for reasons of efficacity. Data were collected in major hospitals in the region Hauts-de-France, 3 months, 6 months and 12 months after reducing tocilizumab (study conducted between 1 January 2010 and 31 December 2015).

Results: 337 patients were included in the analysis. 48 patients had a decrease because of efficacity. All of them were in DAS remission (DAS28 < 2.6) with a mean DAS28 CRP 1.55. 42 patients had a dose reduction to 4mg/kg, when 6 patients had a spacing of the infusions every 6 weeks. At 12 months, the median ΔDAS was 0.49 (p = 0.0002). DAS28 CRP usual dose group was higher than in the Efficacy group (2.99 vs 2.12, p <0.0001). 30 patients (70%) were able to maintain remission (61%) or low dose activity (9%). 4 patients have a DAS28 CRP higher than 3.2 at 12 months. 7 patients (16%) resumed tocilizumab 8mg/kg every 4 weeks before the end of the follow. In case of resumption of tocilizumab in usual dose, there was no significant difference between the initial DAS28 and DAS28 at 3 months (p = 0.1563 and 0.2197) and 6 months of recovery (p = 0.8125 and 0.8984). There was no significant increase of methotrexate or corticosteroids (p <0.0001). The initial weight, a long period of remission before decrease, a low DAS28 CRP appeared predictive of favorable response at 12 months (p = 0.016, 0.012 and 0.0032).

Conclusion: Our study demonstrates the feasibility, safety and efficacy of tocilizumab decrease dose (from 8 to 4mg/kg), to maintain remission or low activity in a majority of patients without concomitant increase in corticosteroids or conventional DMARD.

Disclosure: R. DESBARBIEUX, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/decrease-of-tocilizumab-in-rheumatoid-arthritis-in-remission-a-multicenter-study

Abstract Number: 1637

Real-World Use of Tofacitinib in Rheumatoid Arthritis: Data from the Swiss Clinical Quality Management RA Registry

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Background/Purpose: The oral Janus kinase inhibitor Tofacitinib (Tofa) has been licensed in Switzerland 2013 for the treatment of patients with moderate to severe rheumatoid arthritis (RA), who have failed methotrexate. Besides Tofa, rheumatologists in Switzerland can choose from 5 TNF inhibitors (TNF) and 3 non-TNF-bDMARD (nonTNF) licensed in

the same indication. We aimed at characterizing the patient population starting treatment with Tofa for the first time and at gaining insight into the factors determining the prescription of Tofa vs bMARDs in routine care.

Methods: This is an observational cohort study within the Swiss Clinical Quality Management (SCQM) registry. All therapies with Tofa, TNF, and non-TNF initiated in adult RA patients naïve to Tofa between August 1, 2013 and May 1, 2016 were considered. Exposure of interest was the initiated treatment (Tofa, TNF, non-TNF). Baseline characteristics were described and compared between treatments. Odds for the prescription of Tofa vs TNF and vs non-TNF were assessed with logistic regression after multiple imputation (MI) of missing covariate data assuming a missing at random mechanism. The following covariates at baseline of treatment were included in the model: sex, age, smoking status, seropositivity (rheumatoid factor or ACPA), disease duration, number of previous bDMARDs, BMI, HAQ, and DAS28. A sensitivity analysis with a complete case analysis revealed no concerns with respect to the chosen MI approach.

Results: A total of 1805 therapies were initiated during the study period (328 Tofa, 772 TNF, 705 non-TNF). Tofa therapy was initiated in 25% as second line therapy after conventional DMARDs, in 20% after one bDMARD and in 55% after two or more bDMARDs. Significant differences between Tofa, TNF, and non-TNF were observed for some patient, disease, and treatment characteristics, as well as comorbidities and quality of life measures (Table 1). Tofa as well as non-TNF were used more often as monotherapy than TNF. The multiple regression analysis revealed significantly increased odds for prescribing Tofa as opposed to TNF in patients with two or more previous bDMARDs and with higher age, BMI, and HAQ. Compared to non-TNF, the odds for prescribing Tofa were also significantly higher for patients who had two or more previous bDMARDs and who were seronegative. Of the observed associations, the most relevant was with number of previous bDMARDs.

Conclusion: Taken together our data suggest that in real-life, since being licensed 2013, Tofa was used predominantly as a third+ line therapy.

Table 1 : Baseline characteristics for which significant differences (α = 0.05) between Tofa, TNF, and non-TNF were observed based on univariate tests of available cases (*) using chi-square tests for categorical and Kruskal-Wallis tests for continuous variables or on one of the multiple logistic regression analyses of imputed data (last two columns). Where not indicated otherwise, the sample sizes correspond to the n provided in the first three column headers.

		Tofa (n = 328)	TNF (n = 772)	Non-TNF (n = 705)	OR (95% CI) for Tofa vs. TNF	OR (95% CI) for Tofa vs. Non-TNF
Patient characteristics	Age in yrs*, median (IQR)	58.5 (49 - 68)	56 (45 - 65)	60 (50 - 68)	1.52 (1.02, 1.61) per +20 yrs	0.85 (0.68,1.06) per +20 yrs
	Seropositivity*, # (%)	229 (72) (n = 319)	509 (69) (n = 734)	541 (79.4) (n = 681)	1.10 (0.80,1.52)	0.61 (0.44,0.84)
	BMI in kg/m^2, median (IQR)	25.7 (22.0 - 29.5) (n = 123)	25.1 (22.3 - 29.1) (n = 365)	25.4 (22.0 - 29.4) (n = 274)	1.25 (1.01,1.55) per +7.5 units	0.97 (0.80,1.19) per +7.5 units
Disease characteristics	Disease duration in yrs*, median (IQR)	8.1 (3.6 – 16.7) (n = 316)	4.1 (1.2 – 10.4) (n = 748)	7.2 (2.8 – 14.9) (n = 683)	1.15 (0.97, 1.36) per +10 yrs	1.07 (0.92,1.24) per +10 yrs
	Pain score*, median (IQR)	5.0 (3.0 – 8.0) (n = 100)	4.0 (2.2 – 6.8) (n = 262)	5.0 (3.0 – 7.0) (n = 239)		
	HAQ*, median (IQR)	1.0 (0.6 – 1.6) (n = 101)	0.8 (0.2 – 1.1) (n = 267)	0.8 (0.4 – 1.4) (n = 239)	1.42 (1.06,1.90)	1.25 (0.95,1.64)
Treatment characteristics	Distinct previous bDMARDs*, # (%)					
	0	84 (26)	435 (56)	207 (29)	0.18 (0.13,0.26)	0.68 (0.48,0.96)
	1	65 (20)	199 (26)	227 (32)	0.29 (0.20,0.43)	0.46 (0.33,0.65)
	2+	179 (54)	138 (18)	271 (39)	Reference	Reference
	Reason discontinuation of previous bDMARD*, # (%)					
	AE	56 (24)	70 (21)	95 (20)		
	Ineffectiveness	153 (64)	150 (45)	294 (60)		
	Remission	5 (2)	36 (11)	21 (4)		
	Other	23 (10) (n = 237)	78 (23) (n = 334)	80 (16) (n = 490)		
	csDMARD co-therapy*, # (%)	217 (66)	611 (79)	482 (68)		
	Steroid co-therapy*, # (%)	128 (39)	291 (38)	325 (46)		
Comorbidities	History of heart disease*, # (%)	28 (14) (n = 198)	39 (9) (n = 451)	59 (14) (n = 422)		
	History of cancer*, # (%)	5 (3) (n = 187)	15 (3) (n = 448)	34 (8) (n = 409)		
	History of latent/inactive TB*, # (%)	12 (6) (n = 191)	9 (2) (n = 444)	28 (7) (n = 413)		
	History of serious infections*, # (%)	3 (0.9)	3 (0.4)	13 (1.8)		
Quality of life measures	SF12 physical*, median (IQR)	30.9 (25.8 – 37.9) (n = 63)	39.1 (32.4 – 47.6) (n = 202)	38.5 (30.7 – 46.3) (n = 178)		
	EuroQoL*, median (IQR)	59.8 (43.7 – 75.3) (n = 100)	69.0 (59.8 – 77.9) (n = 264)	69.0 (59.8 – 77.9) (n = 234)		

Disclosure: D. Kyburz, Pfizer Inc, 2,Abbvie, 5,Roche Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,BMS, 5,MSD, 5; **M. Riek**, None; **L. Herzog**, None; **A. Scherer**, None; **C. Gabay**, Roche Pharmaceuticals, 2,Pfizer Inc, 2,Ab2bio, 2,Roche Pharmaceuticals, 5,Pfizer Inc, 5,BMS, 5,MSD, 5,Abbvie, 5,Ab2bio, 5,Debiopharm, 5,Novartis Pharmaceutical Corporation, 5,Celgene, 5; **J. Dudler**, None; **P. Zufferey**, None; **A. Finckh**, None.

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Abstract Number: 1638

Antibody Mediated Immunity Drives Response to Methotrexate Treatment in Rheumatoid Arthritis Patients

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Background/Purpose: Methotrexate (MTX) is the first line treatment for Rheumatoid Arthritis (RA) in Sweden, but one third of patients do not experience satisfying treatment response. Delay in effective treatment cause increased inflammation, handicap and decreased quality of life. The prescription of the most appropriate treatment, in a stratified manner, is thus crucial to provide better and more cost effective health care. MTX is an inhibitor of protein and nucleic acid synthesis that is known to inhibit immune cells. The exact mechanism of MTX is unknown. Here we aimed to:

- Detect the cellular processes elicited by MTX treatment and/or connected to treatment response.
- Predict MTX treatment response using data collected prior to treatment initiation.

Methods: We modeled treatment response based on gene expression and flow cytometry data in a well-characterized routine clinical care cohort. The 57 RA patients underwent clinical evaluation by rheumatologist at the Karolinska Hospital at baseline as well as three months into their treatment. Both times patients contributed blood samples in which broad panels of cell type and activation markers were assayed using flow cytometry and RNA was extracted and sequenced.

Results: We first detected genes whose expression changed upon treatment and/or in connection with a better EULAR treatment response. Treatment had a large effect on gene expression where 132 genes were regulated with a false discovery rate (FDR) < 5%. The gene expression changes that were associated to treatment response (25 genes with FDR < 5%) overlap with the genes regulated by treatment, but in patients that respond well the induced changes were larger. Thus, if MTX is able to elicit stronger effects the patient is more likely to respond well to treatment. Pathway analysis revealed that MTX treatment down-regulated the antibody-driven immune response ($p:1x10^{-26}$). The proportion of plasma cells in peripheral blood was indeed decreased by MTX treatment (p: 0.008). Next we detected genes whose expression in treatment-naïve patients is associated to a later good or moderate EULAR response. We adjusted our analysis for potential confounding factors: percentage of B-cells, ancestry, age, sex and anti-CCP. Our analysis was restricted to genes that we detected as modulated by treatment (50% FDR, 1.3k genes). We observe an enrichment of small p-values, indicating the presence of true associations. Two immunoglobulin genes had a higher expression in those who later respond to treatment (IGLV8-61, IGLV7-46, FDR: 5.4%). Patients who later respond well to treatment indeed had a larger proportion of plasma cells in their peripheral blood (p:0.007). CXCL9 had a lower expression among patients that later respond to treatment ($p: 2x10^{-5}$, FDR: 2.1%). CXCL9 was in fact up-regulated by treatment (p: 0.007), and this up-regulation was stronger in patients who respond well (p: 0.001).

Conclusion: We have detected that MTX treatment is effective in patients with a larger proportion of plasma cells, and that the presence of these cells is significantly diminished by MTX treatment. Patients who respond well express less CXCL9 at baseline, but up-regulates this gene strongly during treatment.

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Abstract Number: 1639

Interchangeability of Innovator Rituximab and Its Biosimilar: Results from International Controlled Comparative 1-Year Study in Patients with Active Rheumatoid Arthritis

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Background/Purpose: Development of biosimilar monoclonal antibodies should not be limited by evaluation of quality, efficacy and safety in comparison with innovator biological product. Interchangeability assessment may have a major impact on biosimilar use in routine practice.

Methods: 160 adults (18-80 y. o.) with active seropositive rheumatoid arthritis (RA) diagnosed by ACR 1987 criteria who did not respond to 1 or more TNF-inhibitors were included in Russia, Ukraine, Belarus and India. After the screening, patients were randomized (1:1) into 2 arms: in the main arm BCD-020 (rituximab biosimilar, JSC BIOCAD, Russia) was dosed at 1000 mg IV on day 1 and 15; in the reference arm innovator rituximab (F.Hoffmann-La Roche, Ltd., Switzerland) was administered using the same regimen. After 6 months patients with active RA were treated repeatedly with partial crossover: half of patients from the main arm received BCD-020, whereas the second half was treated with innovator rituximab (arms BB and BR, respectively). The same was done in patients with active RA from the reference arm (arms RR and RB, respectively). Both periods of treatment (0-24 weeks, 24-48 weeks) were conducted in double-blind manner.

Results: efficacy after the first course of treatment in both arms was equal: at 24 weeks of the treatment ACR20 was reached in 84.14% of patients from the main arm and in 87.01% of patients in the reference arm (95% CI [-13.95%; 8.74%], p=0.773). There were no significant differences after partial crossover at 48 weeks: ACR20 was obtained in 77.78% and 92.31% of patients in RB and RR arms (p=0.250), and in 96.00% and 89.29% in BB and BR arms (p=0.613). Similar data were observed when other efficacy endpoints were compared (remission by DAS28, low activity by DAS28, ACR/EULAR2011 remission etc.). In all arms high rate of ACR70 at week 48 was reached: 40.0% of patients in BB arm, 34,62% in RR arm, 40.74% in RB arm and 39.29% in BR arm. In total, during the first 6 months of treatment AEs were registered in 59.34% and 54.12% of patients in the main and reference arms, respectively, with 2 SAEs in reference arm (myocardial infarction and lung thromboembolism, possibly related). There were no differences in rates of AEs in the switched arms: 44.44% in BB arm, 38.46% in RR arm, 57,14% in RB arm and 62.50% in BR arm, with 1 SAE in BB arm (death due to car accident, unrelated). Incidence of binding antibodies to rituximab was 3.57% and 8.75% in the main and reference arms, respectively (0-24 weeks), and 3.85% in BB arm (24-48 weeks; no binding antibodies in other groups).

Conclusion: BCD-020 is highly similar to innovator rituximab in terms of efficacy, safety and immunogenicity. 1-year data show that switching between products does not affect treatment outcomes.

Disclosure: E. Nasonov, BIOCAD, 8; **V. Mazurov**, BIOCAD, 2; **T. Plaksina**, BIOCAD, 2; **O. Nesmeyanova**, BIOCAD, 2; **L. Knyazeva**, BIOCAD, 2; **A. Eremeeva**, BIOCAD, 3; **E. Chernyaeva**, BIOCAD, 3; **R. Ivanov**, BIOCAD, 3.

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Abstract Number: 1640

Effect of BMI on Baricitinib Efficacy: Pooled Analysis from Two Phase 3 Rheumatoid Arthritis Clinical Trials

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Background/Purpose : The efficacy of some rheumatoid arthritis (RA) therapies is reduced among patients with high BMI. This analysis assessed the effects of baseline BMI on the response to baricitinib treatment in patients with RA and incomplete responses to conventional disease-modifying antirheumatic drugs (cDMARDs).

Methods: This post hoc analysis used pooled data from two phase 3, double-blind, randomized, controlled trials of 6-12 months' duration in patients with RA and an incomplete response to cDMARDs. Efficacy outcomes (e.g., ACR responses, and changes in DAS28-hsCRP, HAQ-DI, SDAI, and CDAI scores) were analyzed by baseline patient BMI tertile (calculated from height and weight measurements at screening).

Results: In all BMI tertiles, patients who received baricitinib 4-mg (n=714) achieved improved clinical outcomes compared to those who received placebo (n=716) in efficacy measures including ACR20, ACR50 and ACR70, mean change in DAS28, SDAI, and CDAI, as well as the proportions of patients who reached low disease activity or remission (Table). No clear pattern emerged to suggest that baseline BMI tertile had a consistent effect on baricitinib efficacy. For some outcomes (e.g., ACR responses), a numeric trend toward reduced efficacy was observed among patients with greater BMI who received baricitinib 4-mg (Table).

Conclusion: Post hoc analysis of these pooled RA trial data suggests that baricitinib therapy is associated with improved clinical outcomes compared to placebo, regardless of baseline patient BMI tertile. As has been shown for other DMARDs, baricitinib treatment effect for patients with higher BMI was numerically smaller than for patients with lower BMI.

Outcome	Lowest BMI Tertile (<22.9)	Middle BMI Tertile (22.9-30.7)	Highest BMI Tertile (>30.7)
ACR20 NRI response, n (%)			
Placebo (N=716)	90 (36.1%)	92 (40.4%)	104 (43.5%)
Baricitinib 4 mg (N=714)	160 (68.4%)	166 (68.0%)	152 (64.7%)
ACR50 NRI response, n (%)			
Placebo (N=716)	36 (14.5%)	38 (16.7%)	37 (15.5%)
Baricitinib 4 mg (N=714)	103 (44.0%)	110 (45.1%)	81 (34.5%)
ACR70 NRI response, n (%)			
Placebo (N=716)	7 (2.8%)	10 (4.4%)	13 (5.4%)
Baricitinib 4 mg (N=714)	44 (18.8%)	51 (20.9%)	37 (15.7%)
DAS28-hsCRP, mLOCF LSM change from baseline (SE)			
Placebo (N=716)	-1.2 (0.12)	-0.9 (0.11)	-1.2 (0.10)
Baricitinib 4 mg (N=714)	-2.5 (0.13)	-2.2 (0.11)	-2.0 (0.10)
HAQ-DI, mLOCF LSM change from baseline (SE)			
Placebo (N=716)	-0.4 (0.06)	-0.3 (0.05)	-0.4 (0.04)
Baricitinib 4 mg (N=714)	-0.7 (0.06)	-0.6 (0.05)	-0.6 (0.04)
CDAI, mLOCF LSM change from baseline (SE)			
Placebo (N=716)	-14.4 (1.25)	-12.2 (1.12)	-15.0 (1.00)
Baricitinib 4 mg (N=714)	-24.0 (1.27)	-21.6 (1.13)	-21.1 (0.99)
SDAI, mLOCF LSM change from baseline (SE)			
Placebo (N=716)	-14.6 (1.29)	-12.2 (1.16)	-14.9 (1.03)
Baricitinib 4 mg (N=714)	-25.6 (1.32)	-22.7 (1.17)	-22.2 (1.02)
mTSS change ≤0 LE (no progression of structural damage), n (%)			
Placebo (N=716)	137 (60.4%)	155 (74.9%)	176 (83.8%)
Baricitinib 4 mg (N=714)	180 (81.1%)	180 (80.0%)	188 (85.5%)

All outcomes are at week 12 except mTSS is at week 24 with data up to rescue.

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Abstract Number: 1641

Survival of Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis

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Background/Purpose: After more than twenty years using Disease Modifying Drugs (DMARDs) is widely known their efficacy in the treatment of Rheumatoid Arthritis (RA) but it is necessary to increase our knowledge on how they work in the long-term in clinical practice. The purpose of this study is to assess the long-term survival of DMARDs (synthetic and biological) and the causes of discontinuation in patients with recent onset of Rheumatoid Arthritis (RA).

Methods: Observational longitudinal study was conducted. Recent onset RA patients diagnosed between April 15th 2007 and 31st December 2010 followed in out-patient clinic at Hospital Clinico San Carlos until December 31st 2015, which used any DMARD treatment were included. Primary outcome: DMARDs discontinuation due to: adverse drug reaction (ADR: moderate or severe), inefficacy, patient decision, improvement, and other causes. Incidence rates of discontinuation (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [CI].

Results: We included 293 courses of DMARDs treatment in 97 patients (815 patient-years). Of these, 78% were women with a mean age at diagnosis of 55.6 ± 15 years. The median time to the start of the first DMARD was 0[0-41] days. 11.5% were taking biological DMARDs, 60.75% were using combined therapy and 86% were taking corticoids. We found 171 discontinuations with an IR of 21 [18-24.4] mainly due to ADR (IR: 13.5[11.2-16.2]) followed by inefficacy (IR: 2.6 [1.6-3.9]). The median survival was 2.6[1.9 to 4] years. The IR of discontinuation related to synthetic and biological DMARDs was 20.4 [17.4-23.9] and 27.2 [17.2-42.3] respectively. The crude IR of discontinuation was higher for Gold (IR: 36.5[22-59]) and Leflunomide (IR: 32.0[21.2-48.1]) being 11.1 [8.2-15] for Methotrexate. Regarding types of regimens, monotherapy had an IR of 17.94[13.9-23.1] whereas combined therapy had an IR of 23.1 [19.2-27.8].

Conclusion: The discontinuation rate is estimated in 21 per 100 patients-year, being ADR the most common cause. Synthetic DMARDs seem to have more survival than biological, being Methotrexate the drug with lowest crude IR of discontinuation rate. Monotherapy seems to have more survival rate than combined therapy. This study contributes to increasing knowledge of the long-term survival of these drugs in real life.

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Abstract Number: 1642

Pharmacokinetic-Pharmacodynamic Analysis of GS-4059-Mediated Bruton's Tyrosine Kinase Inhibition

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Background/Purpose: GS-4059 is a covalent inhibitor of Bruton's Tyrosine Kinase (BTK) under development for the treatment of rheumatoid arthritis (RA) and oncology. This work aimed at characterizing the in vitro and in vivo binding kinetics of GS-4059 and, using pharmacokinetic-pharmacodynamic modeling, to explore the relationship between dose and BTK occupancy to provide a framework for dose selection in clinical studies.

Methods: In vitro, BTK inactivation kinetics of GS-4059 and two other irreversible BTK inhibitors, CC-292 (Cellgene) and ACP-196 (Acerta), was characterized using the Omnia Kinase assay, a highly sensitive fluorescence-based assay that allows for continuous monitoring of BTK activity. Ex vivo BTK binding by GS-4059 was investigated in samples from healthy volunteers who received a single 100 mg or multiple once daily 20 mg oral doses of GS-4059. Free and total (free + drug bound) BTK in peripheral blood mononuclear cells (PBMCs) was measured. A pharmacokinetic-pharmacodynamic (PKPD) model (NONMEM v.7.3) incorporating both BTK inactivation and turnover in PBMCs was developed. BTK occupancy in both PBMCs and splenocytes after multiple ascending daily doses (1.25 - 160 mg) were simulated based on model derived BTK binding kinetics to predict the optimal dose(s) to explore in future studies.

Results: All three compounds exhibited efficient BTK inactivation in vitro with comparable time-dependent inactivation rates over affinity constant ratios (k_{inact}/K_I: 86 - 133 $\mu M^{-1}*h^{-1}$). Significant BTK occupancy was observed after single 100 mg and multiple once daily 20 mg GS-4059 dosing and this occupancy persisted following GS-4059 washout. The PKPD model estimated in vivo population k_{inact}/K_I (69 $\mu M^{-1}*h^{-1}$) was in agreement with the in vitro data. The BTK degradation half-life in PBMCs was estimated to be 64 h (k_{deg} value of 0.011 h^{-1}) providing an explanation for the significant persistence of BTK occupancy following drug washout. Simulations conducted to explore dose (range of 1.25 - 160 mg) suggested that once daily 10 mg GS-4059 provides >80% BTK occupancy in PBMCs over a 24 h period at steady-state; higher doses may be needed to obtain comparable occupancy in the splenocytes.

Conclusion: This analysis provides a mechanistic understanding of in vivo time- and concentration-dependent BTK inactivation and presents a valuable tool in guiding GS-4059 dose selection for RA and oncology patients. The results in this abstract are planned to be presented in part at the American Conference on Pharmacometrics in Bellevue, WA, October 23rd to October 26th, 2016, and published in the conference proceedings (abstract number T.B.D.)

Disclosure: J. D. Lutz, Gilead Sciences, 1,Gilead Sciences, 3; **C. Nelson**, Gilead Sciences, 1,Gilead Sciences, 3; **H. Yu**, Gilead Sciences, 1,Gilead Sciences, 3; **A. Liclican**, Gilead Sciences, 1,Gilead Sciences, 3; **J. Feng**, Gilead Sciences, 1,Gilead Sciences, 3; **A. Billin**, Gilead Sciences, 1,Gilead Sciences, 3; **B. E. Schultz**, Gilead Sciences, 1,Gilead Sciences, 3; **M. Bresnik**, Gilead Sciences, 1,Gilead Sciences, 3; **A. Mathias**, Gilead Sciences, 1,Gilead Sciences, 3.

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Abstract Number: 1643

Tofacitinib: Treatment Outcomes in Seropositive Versus Seronegative Patients in a Phase 3 RA Population

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. This study examined response to treatment with tofacitinib 5 mg or 10 mg twice daily (BID) in seropositive (anti-cyclic citrullinated peptide [CCP]+ and/or RF+) versus seronegative (anti-CCP- and RF-) groups of patients with moderately to severely active RA and an inadequate response to disease-modifying antirheumatic drugs.

Methods: 'Serotype' subgroups were defined at baseline as: anti-CCP+/RF+ (Sero-1); anti-CCP+/RF- (Sero-2); anti-CCP-/RF+ (Sero-3); anti-CCP-/RF- (Sero-4). Subgroup data were pooled from one monotherapy (ORAL Solo) and four combination therapy (ORAL Sync, Standard, Scan, and Step) Phase 3 studies. The proportions of patients achieving ACR20/50/70, disease activity score in 28 joints (4-variable) using erythrocyte sedimentation rate (DAS28-4[ESR])-associated remission and low disease activity, change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI), Short Form (36) (SF-36) physical functioning, and functional assessment of chronic illness therapy (FACIT) were evaluated after 12 weeks. Incidence of adverse events (AEs), discontinuation due to AEs, and serious AEs (SAEs) were compared among subgroups.

Results: In this exploratory analysis, baseline demographics and characteristics were similar between Sero-subgroups 1–4 (n=1551, n=249, n=142, n=449, respectively) for tofacitinib and placebo (PBO; n=670). After 12 weeks of treatment, all Sero-subgroups showed significantly improved ACR20/50/70 response rates with tofacitinib versus PBO (range: $p<0.0001$–$p<0.05$). The same range of significance was obtained for Sero-1 and Sero-2 versus PBO in achieving DAS28-4(ESR)<2.6; the lower treatment differences observed in Sero-3 and Sero-4 subgroups were not significant versus PBO. Tofacitinib showed significant (same range) changes in HAQ-DI and FACIT versus PBO for all Sero-subgroups, and SF-36 physical functioning with the exception of Sero-4 subgroup patients receiving tofacitinib 5 mg BID. Frequencies of AEs and SAEs were similar across all treatment groups and Sero subgroups. Tofacitinib-treated patients showed similar discontinuation incidence rates (per 100 patient-years) due to AEs in all Sero-subgroups (7.7–13.3 versus PBO: 8.6–19.7).

Conclusion: Tofacitinib treatment significantly reduced the signs and symptoms of RA, irrespective of anti-CCP or RF status. In this analysis, DAS28 remission rates and SF-36 physical functioning appeared to be lower in anti-CCP patients. Similar safety endpoints for tofacitinib treatment were observed across all Sero-subgroups.

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Abstract Number: 1644

Dose Selection of Filgotinib, a Selective JAK1 Inhibitor, for Rheumatoid Arthritis Phase 3 Studies: Exposure-DAS28 and ACR Modeling Approach

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Background/Purpose: Filgotinib is an oral, selective Janus kinase 1 (JAK1) inhibitor showing good efficacy and safety in Phase 2B studies in rheumatoid arthritis (RA) patients. The exposure-response modeling and simulation to support the filgotinib dose selection for Phase 3 studies in RA is presented here.

Methods: Population predicted and individual responses to treatment were investigated on the basis of simulated exposures to filgotinib and its active metabolite. Non-linear mixed-effects E-R models using either direct response regression (DAS28) or logistic regression (ACR 20/50/70) models were built to describe improvement in clinical response from baseline in RA patients treated for 24 weeks. The drug effect was modeled using linear or E_{max} model and a composite effective exposure (AUC_{Eff}) defined as sum of individual-predicted exposure for filgotinib and its metabolite taking into account an estimated 10-fold relative potency for filgotinib versus the metabolite. The observed DAS28 change from baseline and ACR responder rates were described as a sum of individual placebo and drug effects. Continuous covariates were evaluated in the models as power functions while binary covariates were tested as factors. The analysis was performed pooling all Phase 2 data available over the doses of 30 to 300 mg as twice or once daily regimen. Simulations of clinical responses (DAS28, ACR and Low Disease Activity [LDA]) were investigated over the 50 to 200 mg daily dose range.

Results: The PK of filgotinib and its metabolite were described by two independent population PK models. Renal function (CLcr) and race were included as statistically significant covariates on the metabolite clearance while no significant covariates were identified in the PK model for filgotinib. Based on the distribution of random effects, filgotinib and its metabolite follow dose-linear PK across the studied dose range. Region was identified as the only significant covariate on the placebo response; placebo effect was predicted to be higher in Western Europe, USA and South America than in the other countries, and included in the exposure-response model for both endpoints. Clinical response at week 12 and week 24 (DAS28 change from baseline and ACR responder rate) increased with dose. A rapid onset in clinical response was also observed during the first 12 weeks followed by continued increase in effect until week 24. Time to reach a given response was shorter at higher doses. Dosing frequency (once or twice daily) did not influence PK of filgotinib and its metabolite as well as clinical response. Simulated clinical response at week 24 following 50 to 200 mg daily dose is reported as mean (95%CI) in the table below:

Parameter (95%CI)	Placebo	50 mg/day	100 mg/day	200 mg/day
Mean DAS28 response	-1.32 (-1.54, -1.10)	-2.19 (-2.33, -2.06)	-2.56 (-2.66, -2.46)	-2.92 (-3.03, -2.80)
LDA (DAS28<3.2)	0.142 (0.109, 0.182)	0.320 (0.287, 0.354)	0.416 (0.387, 0.444)	0.513 (0.482, 0.548)
ACR20 responder rate	0.472 (0.394, 0.533)	0.678 (0.631, 0.720)	0.755 (0.726, 0.785)	0.819 (0.790, 0.848)
ACR50 responder rate	0.204 (0.152, 0.252)	0.385 (0.343, 0.435)	0.476 (0.439, 0.508)	0.563 (0.517, 0.606)
ACR70 responder rate	0.0854 (0.0564, 0.116)	0.201 (0.169, 0.235)	0.273 (0.240, 0.306)	0.353 (0.306, 0.397)

Conclusion: Modeling and simulation on the basis of Phase 2 clinical data show a dose-related response with a maximum efficacy achieved at a daily dose of 200 mg filgotinib, the maximum dose currently being tested in the Phase 3 program.

Disclosure: N. Florence, Galapagos NV, 3; **P. Diderichsen**, None; **E. Cox**, None; **S. Sharma**, Gilead Sciences, 3; **C. Tasset**, Galapagos NV, 3.

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Abstract Number: 1645

Pharmacokinetics (PK), Pharmacodynamics (PD), and Safety of ASP5094, an Anti-Alpha-9-Integrin Monoclonal Antibody, Following Single Intravenous Doses in Healthy Subjects

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SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster II
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: ASP5094 is a recombinant humanized anti-alpha-9 integrin IgG1 monoclonal antibody (mAb) under development for the treatment of rheumatoid arthritis. This first-in-human placebo controlled single ascending dose study was designed to evaluate the safety, tolerability, PK and PD of a single 30 minute intravenous (IV) infusion of ASP5094 at doses ranging from 0.002 to 10 mg/kg in healthy adult subjects.

Methods: 7 sequential cohorts consisting of any race (cohorts A to D) and non-Asian (cohorts E to G) received single increasing doses of IV administered ASP5094 or placebo. Serial Cohorts A and B consisted of 6 subjects each (4 active and 2 placebo) while cohorts C to G consisted of 8 subjects each (6 active and 2 placebo). Serial blood samples were collected for PK (ASP5094 and anti-ASP5094) and PD (alpha-9- integrin receptor occupancy (RO)).

Results: Following a 30-minute infusion of ASP5094 at doses <0.25 mg/kg most serum ASP5094 concentrations fell below the limit of detection (10 ng/mL). At doses that ranged from 0.25-10 mg/kg, mean maximum ASP5094 serum concentrations (C_{max}) increased nonlinearly with dose and ranged from 4742 to 277365 ng/mL. Similarly, mean ASP5094 $AUC_{0\text{-}inf}$ also increased nonlinearly from 165,455 to 77,829,650 ng*h/mL with ASP5094 doses ranging from 0.25 to 10 mg/kg. ASP5094 PK exhibited nonlinear target-mediated drug disposition. Alpha-9 receptor occupancy (RO) on neutrophils remained at 100% for periods of 1, 2, 4 and 8 weeks following a single IV administration at doses of 0.25, 1, 3 and 10 mg/kg ASP5094 respectively. A direct response relationship was observed between serum ASP5094 exposure and RO. One subject dosed at 0.25 mg/kg with ASP5094 tested positive for anti-drug antibodies (ADA) on Day 90 and remained positive throughout study. The last study visit was Day 360. Drug-related adverse events (AE) were reported in 16.7% of the 0.25 mg/kg dose cohort; 33.3% of the 1 mg/kg cohort; 50% of the 3 mg/kg cohort; and 16.7% of the 10 mg/kg cohort, with no dose-dependency. There were no clinically significant abnormal ECG findings in this study.

Conclusion: Single doses of ASP5094 (≤ 10 mg/kg IV) were safe and well tolerated in healthy subjects (any race and non-Asian). ASP5094 PK exhibited nonlinear target-mediated drug disposition. Based on these results, an additional study to explore the PK, PD and safety of multiple doses of ASP5094 in stable RA patients has been initiated.

Disclosure: T. Wang, Astellas Pharma Global Development, Inc., 3; **C. Lademacher**, Astellas Pharma Global Development, Inc., 3; **P. Blahunka**, Astellas Pharma Global Development, Inc., 3; **C. Howieson**, Astellas Pharma Global Development, Inc., 3; **T. Yang**, Astellas Pharma Global Development, Inc., 3; **T. Wojtkowski**, Astellas Pharma Global Development, Inc., 3; **M. Kikuchi**, Astellas Pharma Global Development, Inc., 3; **R. Townsend**, Astellas Pharma Global Development, Inc., 3.

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Abstract Number: 1646

Discontinuation of Methotrexate or Glucocorticoids in Patients with Rheumatoid Arthritis Treated with Tofacitinib: Clinical Efficacy Data from Long-Term Extension Studies

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. In a post-hoc analysis of the tofacitinib RA long-term extension (LTE) studies, we evaluated the effect of discontinuation of MTX or glucocorticoids (GC) on the maintenance of clinical efficacy of tofacitinib.

Methods: Data were analyzed from 2 open-label studies (NCT00413699 [ongoing; March 2015 data-cut] and NCT00661661) of patients (pts) with RA who completed randomized Phase 1/2/3 tofacitinib studies and 3 years of the LTE studies (LTE baseline to Year 3). Pts in this analysis received tofacitinib 5 or 10 mg twice daily (BID) and utilized MTX or GC at LTE baseline. Discontinuation of MTX or GC was defined as no MTX/GC use within the last 30 days prior to the Year 3 visit. Clinical efficacy was evaluated at Year 3 utilizing the Clinical Disease Activity Index (CDAI); further assessment stratified patients by clinical response 3 months after entrance into the LTE studies and was performed for maintenance of response out to Year 3.

Results: Overall, 186/1,608 pts that received MTX at LTE baseline (11.6%; tofacitinib 5 mg BID: n=49; tofacitinib 10 mg BID: n=137) discontinued MTX and 319/1,434 pts that received GC at LTE baseline (22.2%; tofacitinib 5 mg BID: n=114; tofacitinib 10 mg BID: n=205) discontinued GC out to Year 3. Baseline demographics and disease characteristics for pts receiving tofacitinib 5 and 10 mg BID were generally similar irrespective of whether pts discontinued/continued MTX or GC. Most pts who discontinued MTX or discontinued GC achieved CDAI remission (≤2.8) or low disease activity (>2.8–≤10) vs CDAI incomplete response (>10) at Year 3 (Table 1). Mean (standard deviation) time off MTX and GC prior to Year 3, respectively, was 532 (347) and 523 (324) days for tofacitinib 5 mg BID and 593 (338) and 592 (337) days for tofacitinib 10 mg BID. Most pts maintained their 3-month response at Year 3 after the discontinuation of MTX or GC, and response rates were comparable with pts who did not discontinue MTX or GC after Month 3 (Table 2). Furthermore, of those not receiving MTX (1,044 pts) or GC (1,218 pts) at LTE baseline, 65 pts (6.2%; tofacitinib 5 mg BID: n=22; tofacitinib 10 mg BID: n=43) initiated MTX, and 306 pts (25.1%; tofacitinib 5 mg BID: n=82; tofacitinib 10 mg BID: n=224) initiated GC prior to Year 3.

Conclusion: Pts who achieve a high level response with tofacitinib may be able to discontinue MTX or GC and maintain their response. Additional analysis is warranted to understand the reasoning behind why pts initiated MTX or GC in the LTE studies.

Table 1. CDAI response at Year 3 for patients receiving tofacitinib 5 or 10 mg BID stratified by whether patients discontinued MTX or GC

	Discontinued MTX (N=186)		Continued MTX (N=1,422)		Discontinued GC (N=319)		Continued GC (N=1,115)	
CDAI response at Year 3, N (%)	5 mg BID (N=49)	10 mg BID (N=137)	5 mg BID (N=448)	10 mg BID (N=974)	5 mg BID (N=114)	10 mg BID (N=205)	5 mg BID (N=389)	10 mg BID (N=726)
CDAI REM[a]	22 (44.9)	41 (29.9)	112 (25.0)	243 (24.9)	49 (43.0)	60 (29.3)	83 (21.3)	143 (19.7)
CDAI LDA[b]	18 (36.7)	50 (36.5)	210 (46.9)	418 (42.9)	49 (43.0)	74 (36.1)	179 (46.0)	330 (45.5)
CDAI IR[c]	9 (18.4)	45 (32.8)	125 (27.9)	312 (32.0)	16 (14.0)	70 (34.1)	126 (32.4)	252 (34.7)

[a]CDAI score ≤2.8; [b]CDAI >2.8–≤10; [c]CDAI >10

Discontinued MTX/GC: no MTX/GC use within the last 30 days prior to the Year 3 visit

Continued MTX/GC: MTX/GC use for ≥1 day within the last 30 days prior to the Year 3 visit

BID, twice daily; CDAI, Clinical Disease Activity Index; GC, glucocorticoid; IR, incomplete response; LDA, low disease activity; MTX, methotrexate; REM, remission

Table 2. Maintenance of CDAI response at Year 3 for patients receiving tofacitinib 5 or 10 mg BID who discontinued/continued MTX or GC stratified by response at Month 3[a]

CDAI response at Month 3, N (%)		Discontinued MTX Response at Year 3				Continued MTX Response at Year 3				Discontinued GC Response at Year 3				Continued GC Response at Year 3			
		N	CDAI REM[b]	CDAI LDA[c]	CDAI IR[d]	N	CDAI REM[b]	CDAI LDA[c]	CDAI IR[d]	N	CDAI REM[b]	CDAI LDA[c]	CDAI IR[d]	N	CDAI REM[b]	CDAI LDA[c]	CDAI IR[d]
Tofacitinib 5 mg BID	CDAI REM[b]	13	11 (84.6)	1 (7.7)	1 (7.7)	94	54 (57.5)	34 (36.2)	6 (6.4)	29	22 (75.9)	7 (24.1)	0	61	30 (49.2)	26 (42.6)	5 (8.2)
	CDAI LDA[c]	19	7 (36.8)	10 (52.6)	2 (10.5)	195	47 (24.1)	106 (54.4)	41 (21.0)	48	18 (37.5)	25 (52.1)	5 (10.4)	160	37 (23.1)	89 (55.6)	34 (21.3)
	CDAI IR[d]	11	1 (9.1)	6 (54.6)	4 (36.4)	155	9 (5.8)	69 (44.5)	77 (49.7)	26	3 (11.5)	13 (50.0)	10 (38.5)	161	13 (8.1)	61 (37.9)	86 (53.4)
Tofacitinib 10 mg BID	CDAI REM[b]	28	17 (60.7)	7 (25.0)	4 (14.3)	190	117 (61.6)	59 (31.1)	13 (6.8)	25	16 (64.0)	5 (20.0)	4 (16.0)	126	68 (54.0)	47 (37.3)	11 (8.7)
	CDAI LDA[c]	54	17 (31.5)	25 (46.3)	11 (20.4)	430	98 (22.8)	238 (55.4)	94 (21.9)	77	21 (27.3)	41 (53.3)	14 (18.2)	305	56 (18.4)	179 (58.7)	69 (22.6)
	CDAI IR[d]	32	4 (12.5)	6 (18.8)	22 (68.8)	346	25 (7.2)	117 (33.8)	204 (59.0)	61	3 (4.9)	16 (26.2)	42 (68.9)	281	16 (5.7)	95 (33.8)	170 (60.5)

[a]Patients had MTX/GC use at Month 3 visit; [b]CDAI score ≤2.8; [c]CDAI >2.8–≤10; [d]CDAI >10

Discontinued MTX/GC: no MTX/GC use within the last 30 days prior to the Year 3 visit

Continued MTX/GC: MTX/GC use for ≥1 day within the last 30 days prior to the Year 3 visit

BID, twice daily; CDAI, Clinical Disease Activity Index; GC, glucocorticoid; IR, incomplete response; LDA, low disease activity; MTX, methotrexate; REM, remission

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Disclosure: R. Fleischmann, Pfizer Inc, 2,Pfizer Inc, 5; **J. Wollenhaupt**, Pfizer Inc, 8,Pfizer Inc, 1; **S. Cohen**, Pfizer Inc, 2,Pfizer Inc, 5; **M. Weinblatt**, Amgen, BMS, Crescendo Bioscience, UCB, 2,Amgen, AbbVie, BMS, Eli Lilly, Gilead, Pfizer Inc, Roche, 5; **L. Wang**, Pfizer Inc, 1,Pfizer Inc, 3; **H. Fan**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Andrews**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Takiya**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 3,Pfizer Inc, 1.

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Abstract Number: 1647

Tofacitinib, an Oral Janus Kinase Inhibitor, in the Treatment of Rheumatoid Arthritis: Safety and Efficacy in Open-Label, Long-Term Extension Studies over 8 Years

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. The objective of this analysis was to report tofacitinib safety and tolerability and clinical efficacy in long-term extension (LTE) studies over 96 months (Mo).

Methods: Data were pooled from 2 open-label studies (NCT00413699 [ongoing; database unlocked at January 2016 data-cut] and NCT00661661) of patients (pts) with RA who had participated in Phase 1/2/3 tofacitinib studies. Pts received tofacitinib 5 or 10 mg twice daily (BID) as monotherapy or with background DMARDs. Primary endpoints: adverse events (AEs) and confirmed laboratory safety data. Secondary endpoints included clinical efficacy measures (ACR20/50/70

response rates, DAS28-4[ESR], HAQ-DI, and clinical disease activity index). Safety data were included up to Mo 105 and efficacy data up to Mo 90 (n≤100 at Mo 96).

Results: 4,967 pts were treated (mean [max] duration: 1,215 [3,182] days). Total tofacitinib exposure was 16,711 pt-years (py); 77.4% of pts maintained initial dose. In total, 2,370 pts (47.7%) discontinued (AEs: 1,131 [22.8%]; insufficient clinical response: 175 [3.5%]). Most common AE classes: infections and infestations (68.9%) and musculoskeletal/connective tissue disorders (39.0%). Most common AEs: nasopharyngitis (18.7%), upper respiratory tract infection (17.2%), bronchitis and urinary tract infection (12.2% each). Serious AEs occurred in 28.6% of pts, and serious infections (SIEs) in 8.8% of pts. Malignancies, excluding non-melanoma skin cancer, were reported in 3.0% of pts. Incidence rates (IR; pts with events per 100 py) for AEs of interest, with 95% confidence intervals (CIs), are provided in Table 1. IRs for SIEs and malignancies through Mo 105 did not increase vs reported data through Mo 96.[1] Confirmed laboratory data are provided in Table 1. No new safety risks were identified. Clinical responses were sustained from Mo 1 to Mo 90 (Table 2).

Conclusion: In patients with RA who remained in LTEs, tofacitinib (5 or 10 mg BID) with or without background DMARDs was associated with consistent safety through Mo 105, and sustained clinical efficacy through Mo 90.

Reference:

1. Wollenhaupt J et al. Arthritis Rheumatol 2015; 67 (suppl 10): Abstract 1645.

Table 1. Safety data (Mo 105) in LTE studies of tofacitinib in patients with RA

	Tofacitinib (5 and 10 mg BID) ± background DMARDs N=4,967
Incidence rates for AEs of interest, pts with events per 100 py (95% CI)	
SAEs	9.5 (9.0, 10.0)
SIEs	2.6 (2.4, 2.9)
Malignancies (excluding NMSC)	0.9 (0.8, 1.0)
Confirmed laboratory abnormalities, n (%)	
Decreased hemoglobin Decrease from BL in hemoglobin ≥3 g/dL or hemoglobin <7 g/dL	97 (2.0)
Neutropenia <0.5 x 10^3/mm^3	0 (0.0)
Lymphopenia <0.5 x 10^3/mm^3	64 (1.3)
Aminotransferases ALT ≥3 x ULN AST ≥3 x ULN	 292 (5.9) 167 (3.4)
Serum creatinine Increase of ≥50% from BL	 147 (3.0)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, twice daily; CI, confidence interval; BL, baseline; LTE, long-term extension; Mo, Month; N, number of evaluable patients; NMSC, non-melanoma skin cancer; pt, patient; py, pt-years; SAEs, serious adverse events; SE, standard error; SIEs, serious infections; ULN, upper limit of normal

Table 2. Clinical efficacy outcomes (up to Mo 90) in LTE studies of tofacitinib in patients with RA

	Tofacitinib (5 and 10 mg BID) ± background DMARDs		
	BL N=4,782	Mo 1 N=4,776	Mo 90 N=168
ACR response rates, %		N=4,907	N=171
ACR20	–	73.0	83.0
ACR50	–	49.2	56.1
ACR70	–	28.9	32.7
DAS28-4(ESR), mean (SE)	6.29 (0.01)	3.75 (0.02)	3.38 (0.09)
HAQ-DI, mean (SE)*	1.42 (0.01)	0.82 (0.01)	0.76 (0.05)
CDAI, mean change from BL (SE)†	–	-24.0 (0.20)	-28.5 (1.02)

*Number of patients evaluable for HAQ-DI was as follows: BL, N=4,924; Mo 1, N=4,880; Mo 90, N=170.
†Number of patients evaluable for CDAI mean change from BL was as follows: Mo 1, N=4,802; Mo 90, N=169.
BID, twice daily; BL, baseline; CDAI, clinical disease activity index; LTE, long-term extension; Mo, Month; N, number of evaluable patients; SE, standard error

Disclosure: J. Wollenhaupt, Pfizer Inc, 8,Pfizer Inc, 2; **J. Silverfield**, Pfizer Inc, 2; **E. B. Lee**, Pfizer Inc, 5; **K. Terry**, Pfizer Inc, 1,Pfizer Inc, 3; **K. Kwok**, Pfizer Inc, 3,Pfizer Inc, 1; **S. Abramsky**, Pfizer Inc, 1,Pfizer Inc, 3; **M. Wang**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Nduaka**, Pfizer Inc, 1,Pfizer Inc, 3; **R. DeMasi**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 1648

Long-Term Clinical, Radiographic and Patient-Reported Outcomes Based on RAPID3 Responses with Tofacitinib at 6 Months

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. RAPID3 (Routine Assessment of Patient [Pt] Index Data 3) is a pooled index of the three RA core data set pt-reported outcomes (PROs): function, pain, and pt global assessment of disease activity. We compared clinical outcomes, radiographic progression, and PROs at Month 24 in pts achieving remission, low, moderate, and high disease activity (REM, LDA, MDA, and HDA) based on RAPID3 at Month 6.

Methods: ORAL Start (NCT01039688) was a 2-year, Phase 3 randomized controlled trial in which MTX-naïve pts with RA received tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or MTX titrated to 20 mg/week over 8 weeks. RAPID3 scores were calculated at Months 6 and 24 for pts with radiographs at both time points. To calculate RAPID3 scores, each of the 3 individual measures (PtGA visual analog scale [VAS], pain [VAS] and HAQ DI were scored from 0–10 for a total of 30, and divided by 3 to give an adjusted 0–10 score. Outcomes assessed at Month 24 included REM (defined as ≤1), LDA (>1–≤2), MDA (>2–≤4), and HDA (>4) rates based on RAPID3; change from baseline (CFB) in RAPID3, CDAI, and modified Total Sharp Score (mTSS); and proportion of pts with no radiographic progression based on CFB in mTSS ≤0 and HAQ-DI <0.5 (defined as normative).

Results: Pts with RAPID3 HDA at Month 6 had higher baseline RAPID3 scores than those achieving REM/LDA (Table). At Month 6, 24.6%, 32.5%, and 14.1% of pts receiving tofacitinib 5 mg BID, tofacitinib 10 mg BID, and MTX achieved REM, respectively; 19.3%, 20.9%, and 17.9% LDA; 33.2%, 26.2%, and 36.5% MDA; and 22.8%, 20.4%, and 31.4% HDA. A higher proportion of patients were in RAPID3 REM and LDA with tofacitinib vs MTX. Regardless of treatment group, the majority of pts who achieved a specific response at Month 6 maintained or improved their responses at Month 24. CFB in RAPID3 and CDAI at Month 24 was greatest for pts who were in RAPID3 REM/LDA at Month 6. In each treatment group, patients in REM/LDA at Month 6 were more likely to achieve mTSS ≤0 at Month 24 than those with RAPID3 HDA at Month 6. Overall, regardless of RAPID3 category, a higher proportion of pts receiving tofacitinib than MTX had mTSS ≤0. Furthermore, CFB in mTSS at Month 24 with tofacitinib was generally similar across RAPID3 categories; with MTX, it was higher for patients with RAPID3 MDA and HDA. The proportion of pts with normative HAQ-DI scores at Month 24 was highest for pts achieving RAPID3 REM at Month 6, and lowest for those in RAPID3 HDA at Month 6, for each treatment group.

Conclusion: The majority of pts who attained a RAPID3 response at 6 months maintained that response at 24 months. More pts achieving RAPID3 REM or LDA at Month 6 were radiographic non-progressors or had normative HAQ-DI scores at Month 24, compared with those in RAPID3 MDA or HDA.

Table. Clinical, radiographic, and patient-reported outcomes at Month 24 stratified by RAPID3 response at Month 6

	Disease activity based on RAPID3 response at Month 6											
	RAPID3 REM[a]			RAPID3 LDA[b]			RAPID3 MDA[c]			RAPID3 HDA[d]		
	Tofacitinib		MTX	Tofacitinib		MTX	Tofacitinib		MTX	Tofacitinib		MTX
	5 mg BID	10 mg BID		5 mg BID	10 mg BID		5 mg BID	10 mg BID		5 mg BID	10 mg BID	
N (% of all patients in each dose group across all RAPID3 categories)	83 (24.6)	118 (32.5)	22 (14.1)	65 (19.3)	76 (20.9)	28 (17.9)	112 (33.2)	95 (26.2)	57 (36.5)	77 (22.8)	74 (20.4)	49 (31.4)
Baseline RAPID3, mean (SD)	4.9 (2.4)	5.1 (2.2)	5.1 (2.3)	5.8 (2.1)	6.1 (1.9)	4.9 (2.0)	5.6 (1.8)	5.7 (1.6)	5.2 (1.9)	6.5 (1.5)	6.4 (1.7)	6.4 (1.7)
Outcomes at Month 24												
RAPID3 category, n (%)												
REM[a]	47 (72.3)	78 (83.9)	10 (62.5)	26 (48.1)	18 (29.0)	3 (14.3)	13 (14.9)	12 (16.0)	7 (17.9)	4 (7.3)	5 (10.4)	0 (0.0)
LDA[b]	14 (21.5)	7 (7.5)	1 (6.3)	15 (27.8)	16 (25.8)	7 (33.3)	19 (21.8)	13 (17.3)	5 (12.8)	6 (10.9)	7 (14.6)	8 (27.6)
MDA[c]	4 (6.2)	7 (7.5)	4 (25.0)	11 (20.4)	23 (37.1)	6 (28.6)	33 (37.9)	30 (40.0)	22 (56.4)	17 (30.9)	15 (31.3)	10 (34.5)
HDA[d]	0 (0.0)	1 (1.1)	1 (6.3)	2 (3.7)	5 (8.1)	5 (23.8)	22 (25.3)	20 (26.7)	5 (12.8)	28 (50.9)	21 (43.8)	11 (37.9)
RAPID3 mean change from baseline (95% CI)	-4.0 (-4.6, -3.4)	-4.5 (-5.0, -4.1)	-3.6 (-5.2, -2.0)	-4.3 (-4.9, -3.6)	-4.1 (-4.7, -3.5)	-2.7 (-3.8, -1.6)	-2.9 (-3.4, -2.3)	-3.1 (-3.6, -2.6)	-2.7 (-3.4, -2.0)	-2.6 (-3.2, -2.0)	-2.7 (-3.3, -2.1)	-2.9 (-3.7, -2.0)
CDAI mean change from baseline (95% CI)	-32.9 (-36.4, -29.5)	-34.2 (-36.9, -31.4)	-32.8 (-40.5, -25.1)	-31.6 (-36.1, -27.1)	-29.7 (-33.8, -25.6)	-21.4 (-28.0, -14.9)	-28.2 (-31.2, -25.2)	-29.6 (-32.4, -26.7)	-25.6 (-29.7, -21.7)	-27.3 (-31.8, -22.8)	-27.8 (-32.1, -23.5)	-29.2 (-35.4, -23.1)
Radiographic non-progression (change from baseline mTSS ≤0), % (95% CI)	53.0 (41.7, 64.1)	57.6 (48.2, 66.7)	36.4 (17.2, 59.3)	61.5 (48.6, 73.4)	63.2 (51.3, 73.9)	46.4 (27.5, 66.1)	53.6 (43.9, 63.1)	52.6 (42.1, 63.0)	35.1 (22.9, 48.9)	45.5 (34.1, 57.2)	47.3 (35.6, 59.3)	24.5 (13.3, 38.9)
mTSS mean change from baseline (95% CI)	0.6 (0.0, 1.2)	0.2 (0.1, 0.4)	0.7 (-0.2, 1.7)	0.4 (-0.3, 1.2)	0.5 (-0.3, 1.3)	0.5 (-0.1, 1.1)	0.5 (0.2, 0.9)	0.3 (0.0, 0.6)	1.3 (0.2, 2.4)	0.6 (-0.3, 1.6)	-0.4 (-1.8, 1.1)	2.6 (0.9, 4.4)
HAQ-DI <0.5 status, % (95% CI)	72.3 (61.4, 81.6)	72.0 (63.0, 79.9)	50.0 (28.2, 71.8)	50.8 (38.1, 63.4)	43.4 (32.1, 55.3)	28.6 (13.2, 48.7)	28.6 (20.4, 37.9)	33.7 (24.3, 44.1)	19.3 (10.1, 31.9)	13.0 (6.4, 22.6)	14.9 (7.7, 25.0)	18.4 (8.8, 32.0)

Number of evaluable patients varied between parameters; to be included, a patient must have non-missing data for RAPID3 response at Month 6 and efficacy parameter at Month 24

[a]RAPID3 score ≤1; [b]RAPID3 >1–≤2; [c]RAPID3 >2–≤4; [d]RAPID3 >4

BID, twice daily; CDAI, Clinical Disease Activity Index; HAQ-DI, Health Assessment Questionnaire-Disability Index; HDA, high disease activity; LDA, low disease activity; MDA, moderate disease activity; mTSS, modified Total Sharp Score; MTX, methotrexate; REM, remission; SD, standard deviation

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Abstract Number: 1649

Influence of Modifiable Risk Factors on the Response to MTX Alone in Early RA Patients

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Background/Purpose: The aim of early RA treatment is remission. Intensive treatment with MTX and treat-to-target approach achieve remission in 30-50% patients. Modifiable risk factors, as cigarette smoking and alcohol, coffee and tea intake, may affect response to MTX. The objective of this research was to study the influence of tobacco, alcohol, coffee and tea on the response to MTX in RA patients early DMARD-naive

Methods: We conducted a case-control study from 2010 to 2015, where cases were patients who achieved a sustained remission (DAS28PCR<2,6) or low activity (DAS28PCR<3,2) and controls were patients who not reached it. We collected information from a cohort of 182 Caucasian patients with early RA, aged 18-77 years, treated with MTX monotherapy from 1990 to 2015, evaluated quarterly in a specialized unit early RA. Clinical evaluations included DAS28CRP, HAQ, comorbiditIes, cardiovascular risk factors and pharmacovigilance data. All the patients underwent a structured interview about their smoking history and others habits. A descriptive study, comparison of means, univariate and multivariate correlations, logistic regression and survival analysis with SPSS statistics 21 was performed.

Results: Of the 182 patients achieved sutained remission 68 (37,4%) and low activity 99 (54,4%). Almost all patients (95 %) received MTX in rapid escalation (7,5-25mg) in the first 24 months of the onset of symptoms. Younger patients and current smokers responded worse to monotherapy and required higher doses of MTX. The univariate and multivariate analysis of the baseline patient characteristics and relationship of their smoking history with age, RF, ACPA and outcome of MTX monotherapy are shown in table 1 and 2, respectively. The median survival of MTX monotherapy (measure of efficacy, safety and tolerability) was 170 months for non-smokers and 30 months for current smokers (Log Rank 20,21, p 0,000) (see graphic).

Conclusion: The treatment of early RA with MTX alone achieved high rates of remission and low activity, especially in non-smokers. Smoking cessation could significantly improve the response to MTX and therefore should be an integral part of the treatment of early RA patients.

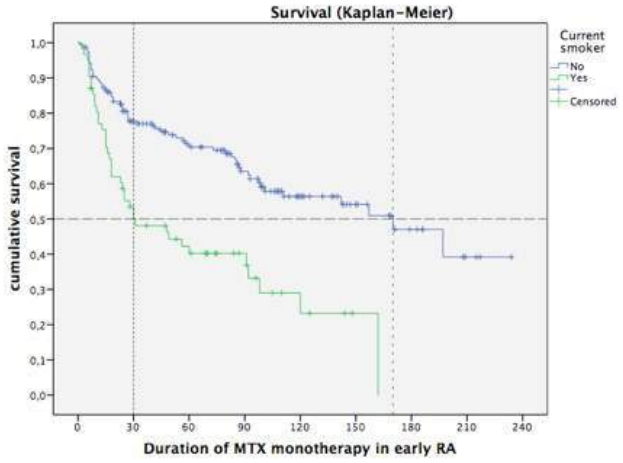
Tabla 1. Analysis of association between baseline characteristics and clinical remission with MTX monotherapy in early RA

		Univariate analysis		Multivariate analysis	
Demographic and clinical characteristics	**DAS remission**	**No remission**	**P**	**OR**	**95% CI**
Age, mean (SD), years	55,28 (13,35)	48,35 (12,43)	0,001		(-10,79 to -3,06)
Female, n(%)	42 (34,1)	81 (65,9)	0,195	0,51	0,26 to 0,97
Low educational level, n (%)	42 (34,2)	80 (65,6)	0,243		
Hard physical job, n (%)	54 (35,5)	98 (64,5)	0,249		
Cigarrette smoking status					
Never smoked n (%)	29 (43,3)	38 (56,7)	0,208		
Former smoker, n (%)	39 (33,9)	76 (66,1)	0,208		
Current smoker, n (%)	21 (21,4)	44 (78,6)	0,003	0,24	0,11 to 0,51
Current alcohol, n (%)	24 (46,2)	28 (53,8)	0,121		
Coffee, n (%)	33 (30,6)	75 (69,4)	0,022		
Tea, n (%)	3 (18,8)	13 (81,3)	0,174		
Obesity, n (%)	16 (38,1)	26 (61,9)	0,911		
Symtom duration to MTX, mean (SD), w	40,6 (28,8)	52,6 (22,78)	0,26		(-9,23 to 33,2)
Status Funtional III, n (%)	4 (15,4)	22 (84,6)	0,015		
Polyarticular initial form, n (%)	38 (32,8)	78 (67,2)	0,089	0,48	0,26 to 0,88
Extra-articular involvement, n (%)	7 (21,2)	26 (78,8)	0,034	0,36	0,15 to 0,89
RF positive, n (%)	51 (35,4)	93 (64,6)	0,291		
ACPA positive, n (%)	38 (33,0)	77 (67,0)	0,108		
DAS 28 PCR basal, unit (SD)	3,89 (0,56)	4,76 (0,75)	0,000		(0,68 to 1,07)
Prednisolone, mean (SD), mg	7,5 (5,7)	8,42 (5,9)	0,306		(-0,85 to 2,69)
MTX dose, mean (SD), mg	15,15 (3,3)	18,07 (3,5)	0,000		(1,87 to 3,97)

Tabla 2. Age, RF and ACPA levels, and doses and outcomes of the MTX monotherapy patients in relation to their smoking history

Smoking history	**RA Age**, mean (SD), y	**RF**,mean (SD), IU	**ACPA**, mean (SD), IU	**Monotherapy duration**, mean (SD), months	**MTX dose**, mean (SD), mg	**Remission**, n (%), OR (95%IC)	**Low activity** n (%), OR (95%IC)	**Need for Biological** n(%), OR (95% IC)
Never Smoked	53,30 (14,78)*	103,88 (190,33)	117,73 (140,34)*	80,13 (57,84)**	16,60 (3,95)	38 (45,2), ns	50 (59,5), ns	22 (26,2), ns
Ex Smoker	52,27 (11,18)	135,21 (184,06)	173,38 (153,57)	69,20 (57,38)	15,60 (3,33)**	34 (45,9), ns	52 (70,3), 2,43 (1,34 to 4,4)**	14 (18,9), 0,42 (0,21 to 0,83)*
Current Smoker	44,98 (10,15)**	158,23 (223,48)	159,3 (149,42)	45,94 (41,93)**	17,74 (3,67)**	13, 0 (21,0), 32 (0,16 to 0,63)**	22 (35,5), 0,30 (0,16 to 0,56)*	30 (48,4), 3,18 (1,71 to 5,91)**

*p<0,05 **p<0,01



Abstract Number: 1650

Treatment with Tofacitinib Inhibits Human Naive B Lymphocyte Development and Function in Vitro

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Background/Purpose: B cells are pivotal to the pathogenesis of many autoimmune diseases including rheumatoid arthritis (RA). Tofacitinib, a JAK inhibitor, is effective and safe in the treatment of RA. Tofacitinib interferes with signal transduction via cytokine receptors using the common γ-chain.Despite of extensive data on T lymphocytes, the impact of tofacitinib on B lymphocytes is poorly understood. In this study we assess the effect of tofacitinib on the differentiation of naive B-lymphocytes and their function.

Methods: Sorted human B cells from cord blood or buffy coat were stimulated in the presence of increasing doses of tofacitinib. B cell phenotypes were determined by flow cytometry. Immunoglobulin concentrations were measured by ELISA. The expression of B cell fate determining genes PRDM1, IRF4, XBP1, and AICDA was analyzed by quantitative RT-PCR.

Results: Tofacitinib treatment strongly impaired plasmablast development, immunoglobulin secretion and induction of PRDM1, IRF-4, and XBP-1 from naive B cells. Interestingly, class switch and AICDA induction from activated naive B cells was only slightly reduced. B cells purified from buffy coats, including naive and memory B cells, stimulated in the presence of tofacitinib, showed only a moderate reduction in plasmablast formation, immunoglobulin secretion and proliferation.

Conclusion: We demonstrated that tofacitinib has a direct impact on human naive B-lymphocytes, independently from its effect on T lymphocytes, by impairing their development into plasmablasts and immunoglobulin secretion. Tofacitinib predominantly affects naive B lymphocytes, while its effect on total peripheral B cells containing naive and memory B cells is less pronounced. Our data are of clinical importance as they suggest that vaccinations should be performed prior to tofacitinib treatment. Furthermore, impairement of B cell function by tofacitimib may directly contribute to its therapeutic effects. This fact has implications for the potential use of tofacitinib in B cell-mediated diseases.

Disclosure: J. Thiel, None; **N. Venhoff**, None; **R. Lorenzetti**, None; **B. Bannert**, None; **R. Voll**, None; **D. Kyburz**, None; **M. Rizzi**, None.

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Abstract Number: 1651

A Case Series on Patients on Tofacitinib in Combination with a Biologic

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Background/Purpose: Although there have been significant advances in the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). patients can experience a lack of or loss of efficacy over time, requiring additions/switching among drugs. Tofacitinib is a highly targeted DMARD but it is not approved for use with biologics. and there has been concern about using tofacitinib in combination with biologics, particularly regarding the toxicity of these combinations. In this small case series, we report 6 patients on tofacitinib and various biologics as an initial documentation of the use tofacitinib and biologics in combination.

Methods: Clinical data of five RA patients and one PsA patient was extracted retrospectively from time prior to starting tofacitinib/biologic combination therapy until completion of 6-28 months of combination treatment. Data extracted included patient demographics, disease characteristics, significant comorbidities, previous and concomitant medications, adverse events (AEs) and serious adverse events (SAEs), laboratory data and clinical disease activity index (CDAI). Data was compared pre and post initiation of combo therapy. Relationship of AEs and SAEs to the combo was assessed based on known potential side effects of tofacitinib and the biologics.

Results: All RA patients fulfilled the 1987 American College of Rheumatology (ACR) classification and the PsA patient fulfilled the ClASsification criteria for Psoriatic ARthritis (CASPAR) All had moderate to severe disease(Table) 3 RA patients on tofacitinib in combination with tocilizumab, 1 with rituximab and 1 with etanercept, and 1 PsA patient on tofacitinib plus tocilizumab experienced no serious AEs and no deaths over 6-28 months (mean: 14 months) infections (67%), GI (67%), and hyperlipidemia (33%) occurred. 2 pts stopped tofacitinib secondary to AE's (table). CDAI at the last report was essentially unchanged (20.9 vs 22.8 table)

Conclusion: In a small case series, there were no deaths nor serious AEs observed when patients used tofacitinib in combination with a biologic for a 6-28 months. This preliminary data indicates that further investigation of such combinations may be justified. Table 1

Demographics			
	RA (n=5)	PsA (n=1)	TOTAL (n=6)
Female (%)	100	100	100
Age (mean years/range)	57.6/41-70	51	56.5/41-70
Seropositivity (%)	100	0	83
Erosive disease (%)	80	100	83
Disease duration (mean years/range)	25.8/6-32	9	18.5/6-32
Patients on background DMARDs (n)	4	1	5
Patients on prednisone (n)	3	1	4
Toxicity			
SAEs	0	0	0
AEs			
Infection	3	1	4
GI	3	1	4
Hematologic	1	0	1
Neurological	1	1	2
Lipids	2	0	2
Muskuloskeletal	1	0	1
Other*	3	1	4
AE resulting in D/C or interruption	3	0	3
SAE	0	0	0
AE	PT #4, #5 (2 AEs)		
D/C due to lack of efficacy (n)	Pt #	1	
Deaths	0	0	0
Efficacy			
Mean months duration on combo (range)	12 (6-28)	4	10.7
Mean CDAI (range)			
At start of combo	21.9 (14-27.5)	16	20.91 (14-27.5)
At end of combo/last visit	23.1 (12.5-41)	21.5	22.8 (12.5-41)

GI = gastroenterological; CNS = central nervous system; D/C = discontinuation; * nocturia, worsening of hyperglycemia, light headedness, nightly cramps, rash, worsening of depression

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Disclosure: N. Barroso, None; **D. E. Furst**, None.

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Abstract Number: 1652

Basement Membrane Remodeling Is Significantly Increased with Rheumatoid Arthritis and Suppressed By IL6 Inhibition: Analysis of Two Phase III Clinical Trial

Natasja Stæhr Gudman[1], Pernille Juhl[2], Christian S. Thudium[3], Anne Sofie Siebuhr[4], Inger Byrjalsen[5], Morten Asser Karsdal[4] and Anne C. Bay-Jensen[4], [1]Nordic Bioscience A/S, Herlev, Denmark, [2]Biomarkers & Research, Nordic Bioscience, Herlev, Denmark, [3]Biomarkers and Research, Nordic Bioscience, Herlev, Denmark, [4]Rheumatology, Nordic Bioscience, Herlev, Denmark, [5]Nordic Bioscience, Clinical Development, Herlev, Denmark
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Background/Purpose: Rheumatoid arthritis (RA) is associated with neovascularization of the synovial membrane and increased risk of cardiovascular disease, consequent to vascular and endothelial dysfunction, which leads to remodeling, and degradation of the basement membrane proteins, such as type IV collagen. The purpose of the study was to investigate the association between basement membrane turnover and disease activity, as well as structural progression in RA.

Methods: Serum samples from patients giving informed consent of the LITHE (n=740) and RADIATE (n=217) studies (two phase III double-blinded placebo controlled studies testing 4- and 8-mg/kg tocilizumab (TCZ) in combination with methotrexate) were included. Basement membrane turnover was measured by the blood-based biomarker C4M reflecting MMP-degraded type IV collagen degradation at baseline, week 4, 16, 24 and 52, and at baseline and week 16 in the LITHE and the RADIATE study. Associations between basement membrane turnovers, treatment response and clinical parameters.

Results: Basement membrane turnover was associated with clinical scores including visual analog scale for pain ($p<0.0001$) and DAS28 DAS28 ($p=<0.0001$) in both studies (table). It was dose-dependently reduced by TCZ (11-40%, figure) and baseline levels were significantly correlated with change in radiographic scores (joint space narrowing ($p=0.001$) and sharp score ($p=0.0002$)).

Conclusion: Basement membrane remodeling was associated with disease activity and radiographic progression at baseline, and was dose-dependently inhibited by TCZ, suggesting a continuous clinical benefit extending past the joint tissue. These data suggest that active RA and disease progression is associated with increased remodeling of basement membrane collagen.

table		LITHE		RADIATE
	r	p	r	P
Age, years		ns		ns
Gender, Male %		ns		ns
BMI		ns		ns
Disease duration, mean years (95%-CI)		ns		ns
Baseline CRP, mg/dl	0.64	<0.0001	0.58	<0.0001
HAQ	0.24	<0.0001	0.30	0.0025
VAS pain	0.21	<0.0001	0.32	<0.0001
DAS28	0.30	<0.0001	0.32	<0.0001
JSN	0.14	0.0002	NA	-
SHP	0.14	0.0002	NA	-
ERN	0.14	0.002	NA	-

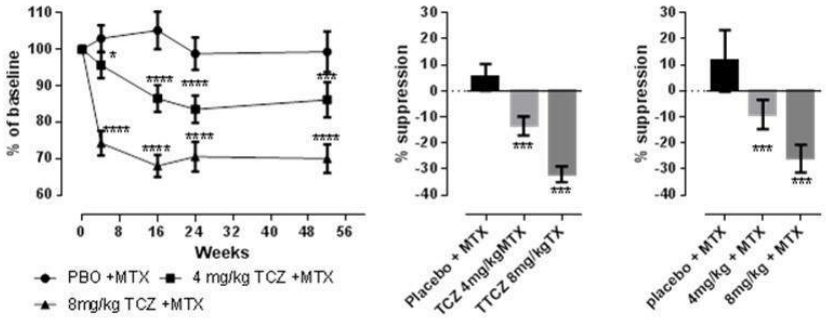

Figure 1. C4M levels were suppressed by IL-6R. A) Showing percentage change from baseline to week 4, 16, 24 and 54 for each of the 3 treatment groups in LITHE. B) Suppression of C4M in LITHE week 16. C) Suppression of C4M in RADIATE week 16. Error bars are shown as SEM. Significant levels are depicted *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Disclosure: N. S. Gudman, Nordic Bioscience A/S, 3; **P. Juhl**, Nordic Bioscience Diagnostic, 3; **C. S. Thudium**, Nordic Bioscience A/S, 3; **A. S. Siebuhr**, Nordic Bioscience Diagnostic, 3; **I. Byrjalsen**, Nordic Bioscience A/S, 3; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3; **A. C. Bay-Jensen**, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2.

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Abstract Number: 1653

Delineating the Effects of Rheumatoid Arthritis Pharmacotherapies on Vascular Inflammation: Rationale and Design of a Clinical Trial

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Background/Purpose: Rheumatoid arthritis is associated with an excess cardiovascular disease (CVD) burden. Fewer CVD events associated with specific DMARD therapies have been reported; however, causal effects on atherosclerosis have never been evaluated rigorously in a randomized trial. Radiolabeled fluorodeoxyglucose (FDG) is taken up by macrophages in atherosclerotic plaques, is detectable with positron emission tomography (PET), and is a surrogate for atherosclerosis. We designed a multi-center randomized controlled clinical trial to: 1) Compare the change (over 24 weeks) in FDG uptake in the aorta and carotid arteries among methotrexate (MTX) inadequate responders who will be

randomized to adding either a TNF inhibitor (i.e. step-up MTX + TNFi) or sulfasalazine + hydroxychloroquine (i.e. step-up triple therapy), and 2) assess whether achieving low RA disease activity or remission (LDAR) is associated with a parallel reduction in arterial FDG uptake. Correlations of change in arterial FDG uptake with change in circulating biomarkers will also be performed.

Methods: The primary hypothesis of the Treatments Against Rheumatoid Arthritis and Effects on FDG-PET (TARGET) Trial is that TNFi +MTX will reduce vascular inflammation to a greater extent than triple therapy after 24 weeks. Secondarily, RA patients with LDAR at 24 weeks will have less vascular inflammation than those with persistent moderate/high disease activity. The primary outcome measure will be the maximal aortic FDG uptake of the most diseased segment (MDSmax) standardized to the blood pool in the superior vena cava [i.e. the target to background ratio (TBR)]. Sample size projections are based on estimates of change in aortic FDG uptake from preliminary sources, 0-15% dropout, 0-15% unintended crossover into the TNFi arm, a conservative 30% LDAR achieved, at least 90% power for the primary and secondary analyses, a two-tailed alpha=0.05, and equal allocation to the treatment arms.

Results: From a published study of 17 RA patients, the mean ± SD baseline aortic MDSmax TBR was 2.51±0.33 units. In the same study, there was a 0.46 unit reduction in this measure after 8 weeks of TNFi. We calculated that the trial would require a pooled sample size of n=170 (n=85 per arm) to detect an absolute difference in the 6-month MDSmax TBR of 0.17 units between the treatment groups with 90% power should the highest projected crossover occur. This same sample size would also have 90% power to detect a 0.19 unit difference in MDSmax TBR between those achieving LDAR vs. moderate or high disease activity, using the same assumptions. The magnitude of these differences is consistent with studies comparing low vs. high dose statin use. Conservatively assuming a 15% drop-out, 100 patients per arm will be enrolled beginning in July 2016.

Conclusion: The TARGET trial, the first to explore the effect of immunomodulation on vascular inflammation in any rheumatic disease, is powered to detect meaningful differences in vascular inflammation between treatments. Further, the minimal detectable difference in arterial inflammation between those achieving LDAR compared with those not responding as may be small, yet clinically meaningful.

Disclosure: J. T. Giles, None; **K. Liao**, None; **N. Paynter**, None; **A. Wohlfahrt**, None; **A. Zartoshti**, None; **R. Broderick**, None; **D. H. Solomon**, None; **J. Bathon**, None.

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Abstract Number: 1654

Differential Serum Protein Expression in Groups of Psoriatic Arthritis Patients Characterised By Specific HLA Genotypes and Clinical Features

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous disease with diverse clinical and radiographic manifestations. A number of human leukocyte antigen (HLA) alleles have been found to be associated with PsA.[1] HLA-C*06:02 is associated with severe skin disease and a late onset, milder musculoskeletal phenotype; HLA-B*27:05 with entheseal-based disease, severe musculoskeletal disease, enthesitis, symmetric sacroiliitis (SI) and mild psoriasis; HLA-B*08:01 with synovial-based disease, asymmetric SI, joint deformity, joint fusion and dactylitis while HLA-B*38:01/39:01 is associated with more axial involvement and joint damage progression.[2] Our hypothesis is that in each of these distinct genetic groups and perhaps as a consequence of the inflammatory events that occur following MHC-peptide interaction, a different pattern of inflammation involving diverse systemic molecules and mediators may be unleashed which in turn determines clinical phenotype and possibly therapeutic response. Our objective is to identify whether there are differences in serum protein expression between groups of patients with specific combinations of HLA genotypes and clinical features.

Methods: Patients with a diagnosis of PsA, fulfilling the CASPAR criteria, aged >18 years were clinically assessed, 10 patients from each of the 4 defined HLA groups. We included a fifth distinct clinical group, Arthritis Mutilans, which as yet has no defined genotype. Serum samples were obtained from all patients. *Proteomics Strategy*: Serum samples from patients in each of the 5 groups were pooled. Serum pools were depleted of high-abundant proteins. The protein concentration of the remaining low abundant protein fractions was measured and subsequently, protein was digested. Finally, samples were purified prior to liquid chromatography-mass spectrometry LC-MS/MS analysis. Data was imported into MaxQuant and Perseus for quantitative and statistical analysis.

Results: Replicate LC-MS/MS analysis of each the 5 pools (n=3) revealed that a total of 437 proteins could be identified. Of these proteins, 219 were found to be significantly differentially expressed between the different groups (False Discovery Rate: 0.01, $p \leq 0.05$). Table 1 describes the number of proteins differentially expressed when comparing one PsA subgroup to the other 4 combined groups.

Comparison	Univariate Analysis (p value ≤0.05)
Arthritis Mutilans vs. Other Genotypes	43 proteins
B*27 vs. Other Genotypes	28 proteins
B*08 vs. Other Genotypes	91 proteins
B*38/39 vs. Other Genotypes	37 proteins
C*06 vs. Other Genotypes	20 proteins

Table1 shows the discovery data analysis summary

Conclusion: In this study, it was possible to identify proteins that were significantly differentially expressed across the 5 PsA phenotypes. Validation strategies are in progress to measure all differentially expressed proteins in individual patient samples using a targeted proteomics approach. This work is an important first step toward the development of a protein biomarker panel that can be used to distinguish between different PsA subgroups. References: 1. Winchester R, et al. A&R64:1134-44, 2012 2. Haroon M, et al. ARD75:155-162, 2016

Disclosure: M. Elmamoun, None; **A. McArdle**, None; **M. Haroon**, None; **R. Winchester**, None; **S. R. Pennington**, None; **O. FitzGerald**, Abbott Immunology Pharmaceuticals, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 2,Abbott Immunology Pharmaceuticals, 5,Pfizer Inc, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,UCB Pharma, 5,Eli Lilly and Company, 5.

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Abstract Number: 1655

Plasma microRNA Expression Profiles in Ankylosing Spondylitis Patients

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SESSION INFORMATION

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Background/Purpose: MicroRNAs (miRNAs) are a group of single-stranded non-coding RNAs of 20-25 nucleotides in length that can potentially regulate every aspect of cellular function. Recent studies have demonstrated that miRNAs can be detected in the circulation and serve as potential biomarkers of various diseases. Our aim was to evaluate whether AS pathogenesis is related to the aberrant expression of plasma miRNAs.

Methods: The expression profile of 800 miRNAs was determined in pooled RNA samples from plasma of AS patients and healthy donors (HDs) (n=3 each) using a nCounter miRNA assay. Next, candidate miRNAs were validated by real time RT-PCR in a validation cohort of 26 AS patients and 26 HDs. To evaluate their relevance in the AS pathogenesis, an analysis was carried out by using the web-based bioinformatics tool IPA. Association studies with the clinical status of the AS patients were also performed. AS activity was defined as BASDAI ≥ 4, CRP > 8 mg/L and ESR > 20 mm/h. Structural damage was evaluated by mSASSS.

Results: In discovery phase, nine miRNAs were differentially expressed (fold change ≥ 2) in the plasma of AS patients *vs.* HDs. After validation, seven of the nine miRNAs clearly distinguished AS plasma samples with high confidence level ($P < 0.05$). Specifically, the circulating levels of miR-146a-5p, miR-125a-5p, and miR22-3p were upregulated, whereas those of miR-320e, miR-151-3p, miR150-5p and miR-451a were downregulated in AS patients *vs.* HDs. The ROC curve analyses of these miRNAs exhibited a moderate distinguishing efficiency, with the AUCs for these miRNA ranging from 0.674 to 0.746. In addition, target gene prediction by IPA analysis showed that these altered miRNAs were involved in affecting various aspect of AS, such as signaling pathways related to inflammatory response and bone turnover. Association studies showed that plasma miR-146a-5p expression was significantly increased in active AS patients as compared with non-active AS patients ($P = 0.037$). In addition, we observed that AS patients with higher structural damage exhibited significantly lower miR-151-3p expression than those with less radiographic severity ($P = 0.045$); the ROC curve analyses showed that relative expression of this miRNA could distinguish AS patients with radiographic severity, with a power AUC of 0.761 ($P= 0.05$).

Conclusion: This study has identified a set of circulating miRNAs which could be attractive candidates as noninvasive biomarkers for the diagnosis of AS patients and may help elucidate the pathogenesis of AS. Funded by PI-0314-2012, SER

Disclosure: P. Font-Ugalde, None; **C. Perez-Sanchez**, None; **C. Lopez-Pedrera**, None; **M. C. Castro-Villegas**, None; **M. C. Abalos-Aguilera**, None; **P. Ruiz-Limon**, None; **N. Barbarroja**, None; **I. Arias de la Rosa**, None; **R. Ortega-Castro**, None; **A. Escudero-Contreras**, None; **E. Collantes-Estévez**, None; **Y. Jiménez-Gómez**, None.

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Abstract Number: 1656

Compare the Potential of Osteoclast Precursors (OCPs) Residing in Bone Marrow and Peripheral Blood As the Surrogates of Psoriasis Pathogenesis

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Session Type: ACR Poster Session B

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Background/Purpose:

Bone marrow (BM) is not only the place where osteoclast precursors (OCPs) are derived from, but also the major reservoirs of OCPs. Current data suggested that the local inflammatory conditions caused by arthritis progression will induce the proliferation of BM-residing OCPs to further mature into multinucleated mature OC with bone erosion activity, which subsequently expedite arthritis progression. No direct evidence is available to support this notion due to the absence of reliable OCP biomarkers and OCP enumeration with high accuracy. It also remains unclear whether the differentiation of OCPs within BM could be affected solely by skin (psoriasis, Ps) but not bone condition (psoriatic arthritis, PsA). We have previously shown that DC-STAMP, a master regulator in osteoclast differentiation, is elevated in patients with psoriatic arthritis (PsA). In addition, we also showed that DC-STAMP has the potential to serve as a diagnostic biomarker to predict the susceptibility of patients with psoriasis to PsA transition. Given that changes in the BM microenvironment might occur at the early stage of Ps to PsA transition, in this study, we investigate whether Ps pathogenesis could affect the microenvironment of bone marrow for OCP differentiation by comparing DC-STAMP expression level and DC-STAMP+ cell frequency in BM and periphery at healthy and disease status.

Methods:

Bone marrow aspirates (BMA) and blood were collected from 13 Ps patients (PASI score between 35-60) and 5 healthy controls (HC). Total cells or enriched CD14+ monocyte were isolated from BMA and blood, analyzed by 12-color flow cytometry *ex vivo*, and enumerated OC by TRAP staining after 8-day *in vitro* culture in OC-promoting media.

Results:

		(a) OC (total)	(b) OC (monocytes)	(c) DC-STAMP MFI	(d) DC-STAMP %	(e) CD14+CD16+ %
HC	blood	21 +/- 22	565 +/- 624	2063 +/-892	10 +/- 12	1.1 +/- 0
	BM	724 +/- 914	1651 +/- 1101	2010 +/-510	22 +/- 8	0.1 +/- 0
Ps	blood	56 +/- 134	992 +/- 813	2478 +/- 591	17 +/- 6	0 +/- 0
	BM	438+/- 625	1800 +/- 1620	1740 +/- 359	27 +/- 12	2.1+/- 0

There are 5 major results: (1) More OCPs were found in BM than blood, which is common for both HC and Ps patients (column b); (2) Ps patients have a slightly higher OCPs in BM than HC (1800 +/- 1620 vs. 1651 +/- 1101); (3) Mean Fluorescence Intensity (MFI) of DCSTAMP: This measure the expression level of DC-STAMP. Comparable MFI were found between blood and BM in HC, whereas DC-STAMP MFI is reduced, although not significant, in BM in Ps patients (column C); (4) OCP (purified monocytes) in Ps's BM is higher than HC (1800 +/- 1620 vs. 1651 +/- 1101, column b). However, the total OCP readouts are lower if monocytes were co-cultured with T & B cells (column a); (5) the inflammatory CD14+CD16+ monocyte subset was elevated in the BM of Ps patients.

Conclusion: (1) Ps pathogenesis induces changes in the BM microenvironment which subsequently affects OCgenesis and OCP frequency within the BM; (2) unidentified cellular factors, such as cell subset & chemokine/cytokines, are present in human bone marrow to suppress OC differentiation (Column A, Ps BM) and DC-STAMP expression (Column C, Ps BM); (3) 3 potential Ps-specific biomarkers are (i) % of CD14+CD16+ cells in BM, (ii) difference between DC-STAMP% in BM and blood (Δ(BM-blood) of DC-STAMP%), and (iii) difference between DC-STAMP MFI in BM and blood (Δ(BM-blood) of DC-STAMP MFI).

Disclosure: Y. G. Chiu, None; **E. Schwarz**, None; **D. Li**, None; **N. Huertas**, None; **C. Bell**, None; **D. Campbell**, None; **C. T. Ritchlin**, Amgen, Janssen Pharmaceutica Product, L.P., and UCB, 2,AbbVie, Amgen, Janssen Pharmaceutica Product, L.P., Regeneron, and UCB, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/compare-the-potential-of-osteoclast-precursors-ocps-residing-in-bone-marrow-and-peripheral-blood-as-the-surrogates-of-psoriasis-pathogenesis

Abstract Number: 1657

Soluble Biomarkers May Differentiate Psoriatic Arthritis from Osteoarthritis

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Session Time: 9:00AM-11:00AM

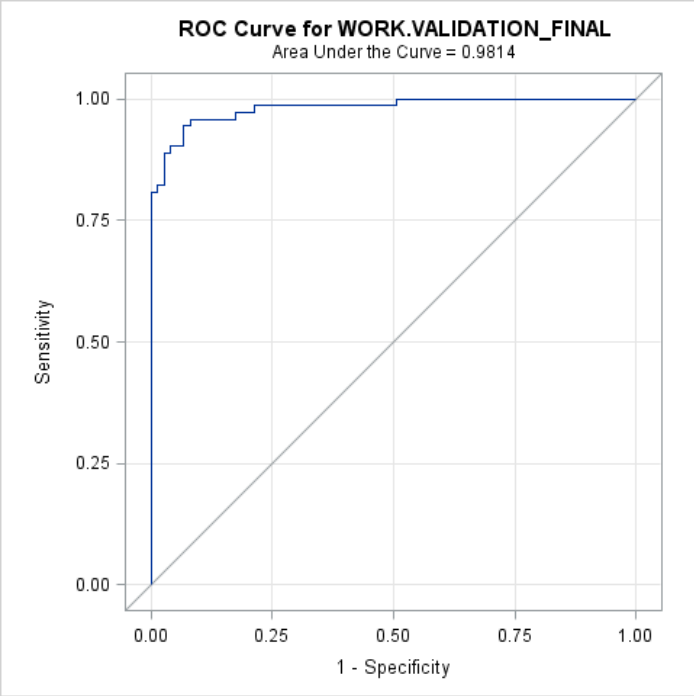
Background/Purpose: It is often difficult to differentiate psoriatic arthritis (PsA) from osteoarthritis (OA) in clinical practice. To aid clinical diagnosis, we aimed to identify soluble biomarkers that differentiate PsA from OA.

Methods: Serum samples from 201 patients with OA (mean age 65 years, 43.3% males, no history of inflammatory disease), 77 patients with PsA satisfying CASPAR criteria (mean age 45 years, 54.5 % males) and 76 healthy controls (mean age 37 years, 50% males) were obtained from the respective biobanks of the Arthritis Program. Samples were obtained at the time of joint replacement surgery (OA) or at the time of clinical assessment (PsA, healthy controls), and stored at -80°C until laboratory assays were conducted. Soluble markers of cartilage metabolism (COMP, hyaluronan), metabolic syndrome (adiponectin, adipsin, resistin, HGF, insulin, leptin) and inflammation/immune response (CRP, IL-1b, -6, -8, TNF-α, MCP-1, NGF) were assayed in the samples using Luminex multiplex assay. Marker levels in serum were compared across the 3 groups using the Kruskal-Wallis test. Pair-wise comparisons were made with Wilcoxon rank sum test. To identify markers that differentiate PsA from OA, multivariate logistic regression analyses with backward elimination, adjusted for age and sex, were constructed using markers determined to be significant at a $p \leq 0.1$ from univariate analyses. Discriminative ability was assessed by way of receiver operating characteristic (ROC) curves based on findings from multivariate models. The final model was further validated in an independent set of 73 PsA and 75 OA samples using predicted probabilities estimated using coefficients from the model developed on the training set.

Results: Univariate analyses revealed the following markers significantly differed across groups ($p<0.001$): COMP, hyaluronan; resistin, HGF, insulin, leptin; CRP, IL -6, -8, TNF-α, MCP-1, NGF. When comparing PsA to OA controlling for age and sex, the following markers significantly differed ($p<0.001$): COMP ; resistin, HGF, insulin; IL-6, -8, TNF-α, MCP-1, NGF; and Adipsin ($p<0.03$). Multivariate analysis demonstrated that COMP (OR 1.24, 95% CI 1.06, 1.46), resistin (OR 1.26, 95% CI 1.07, 1.48), MCP-1 (OR 1.28, 95% CI 1.01, 1.48) and NGF (OR <0.001, 95% CI <0.001, 0.25) were independently associated with PsA vs. OA. The area under the ROC curve (AUROC) for this model was 0.99. Internal cross-validation of the model consistently identified MCP-1 as a PsA marker. Further validation of the model including COMP, resistin, MCP-1 and NGF in an independent sample set showed an AUROC of 0.98 (Figure).

Conclusion: A panel of 4 biomarkers (COMP, resistin, MCP-1, NGF) may distinguish PsA from OA. Clinical utility of these markers will need to be determined in prospective studies.

Figure 1. ROC curve on the validation set (PsA=73 OA=75), with predicted probabilities calculated with coefficients of age, sex, COMP, MCP1, NGF, Resistin from the model developed on the training set.



Disclosure: V. Chandran, None; **A. V. Perruccio**, None; **S. Li**, None; **F. Abji**, None; **R. Gandhi**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/soluble-biomarkers-may-differentiate-psoriatic-arthritis-from-osteoarthritis

Abstract Number: 1658

Regulatory Role of the IL-9/IL-9R System on Pannus Formation in Psoriatic Arthritis

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Background/Purpose: Earlier we have reported that synovial tissues of psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are enriched with the Th9 cells along with its key cytokine IL-9 (1). Here we are reporting new functions of IL-9; its

regulatory role on (i) FLS (fibroblast like synoviocyte) biology and (ii) pannus formation in PsA and RA.

Methods : FLS were isolated from synovial tissue biopsies of PsA, RA and OA (n=5, for each) and cultured (1). IL-9R expression was determined by immunobloting and RT-PCR studies. MTT assay and apoptosis assay (Annexin-V) were performed to determine the pro-growth/survival effect of rIL-9 on FLS. In the cultured FLS IL-6, IL-8, MMP-3 were measured by ELISA.

Results: RT-PCR and immunoblot studies demonstrated presence of IL9-R in FLS of PsA, RA and OA (Fig 1). rIL-9 induced proliferation of FLS and inhibited TNF-a induced apoptosis (Fig 2). rIL-9 induced IL-6 and MMP-3 expression in FLS (Fig 3).

Conclusion: Here we observed that FLS survival/prolifeartion, inflammatory cytokine expression and upregulation of MMP 3 the major components of the inflammatory proliferative cascades for pannus formation are regulated by IL-9. This is the first report to identify the presence of IL-9R on FLS and the functional significance of the IL-9/IL-9R system on FLS biology in PsA and RA. **Figure 1. IL-9R is expressed in FLS -** IL-9R gene was expressed in FLS of PsA and RA patients. Compared to the unactivated T lymphocytes the relative gene expression of IL-9R in FLS of PsA and RA patients was 3.5±0.67, 2.4±0.5, respectively (p<.01, Fig 1). IL-9R expression was confirmed by immunoblotting. The relative intensity (R.I) of IL-9R in FLS of PsA, RA and OA patients was 0.3 ± 0.02, 0.37 ± 0.05, 0.28 ± 0.08 respectively.

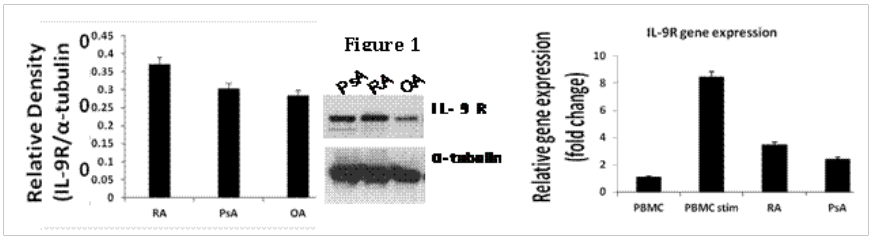


Figure 2. Human rIL-9 promoted survival of FLS- To test the functional significance of the IL9R we investigated whether rIL-9 can promote FLS survival. FLS of PsA, RA and OA were treated with rIL-9 (25 ng/ml) for 48hrs then TNFα (20 ng/ml) for 24 hours to induce apoptosis (1). In the FLS of PsA, TNFα + rIL-9 induced 11.41±3.61% apoptosis compared to 35±5.53% induced apoptosis seen in TNFα alone (p<.01). Similar results were seen in RA and OA FLS.

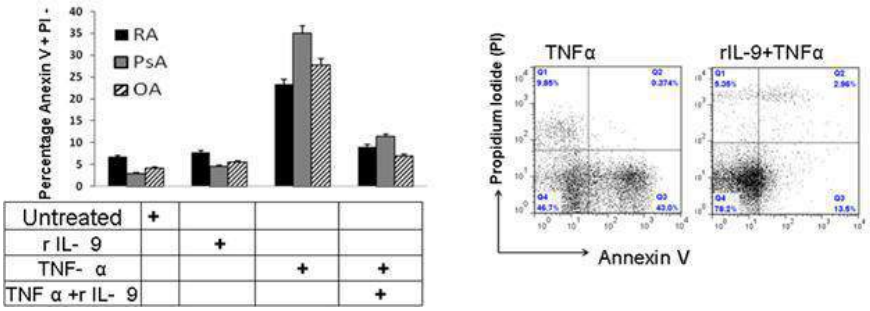
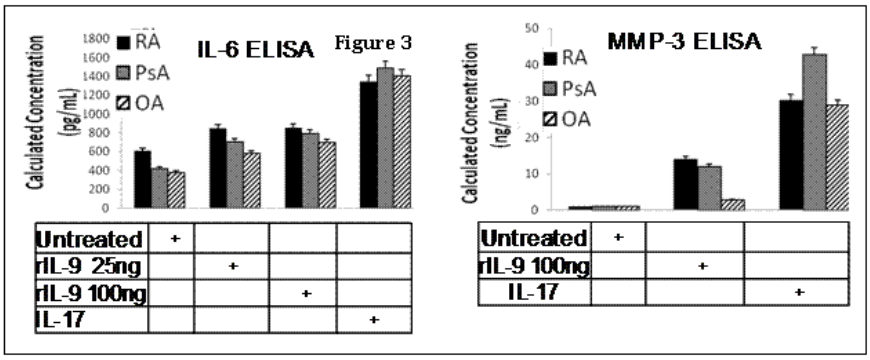


Figure 3. Compared to the untreated FLS, rIL-9 (100 ng/ml) induced upregulation of IL-6 and MMP- 3 (p<.01).



Reference: 1. Raychaudhuri SK, et al. Cytokine 2016; 79:45-51.

Disclosure: S. P. Raychaudhuri, None; **S. K. Raychaudhuri**, None.

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Abstract Number: 1659

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/effect-of-exercise-on-inflammation-and-bone-formation-in-proteoglycan-induced-arthritis-model-microarray-analysis

Abstract Number: 1660

Role of Immune System Cells and Induction of Netosis-Mediated Cell Death in the Development of Atherosclerosis in Ankylosing Spondylitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing Spondylitis (AS) is a chronic inflammatory disease associated with the development of atherosclerosis. Our aims were: 1) To evaluate the involvement of immune system cells and NETosis in the atherosclerosis process in AS patients. 2) To analyze *in vitro* the role of leukocyte subsets in the endothelial function.

Methods: Thirty four AS patients and 34 healthy donors (HDs) were included in the study. Endothelial function was determined by the post occlusive hyperaemia test using Laser-Doppler. The expression of 84 genes related to atherosclerosis was determined in pooled RNA samples from peripheral blood mononuclear cells (PBMCs) of patients and HDs (n=3 each) by PCR array. Validation of several differentially expressed genes in PBMCs and the expression of various markers of oxidative stress and inflammation was quantified in leukocyte subsets. In neutrophils, NETosis markers and cell death by Sytox staining were also analyzed. Plasma DNA was quantified by fluorimetry. *In vitro* co-cultures of endothelial cells (HUVEC) with PBMCs or neutrophils from AS patients were performed.

Results: AS patients showed a prominent endothelial dysfunction, along with a significant alteration (fold change ≥ 2) in the expression of 50 genes related to atherosclerosis in PBMCs. Validation and expression studies showed that lymphocytes of AS patients exhibited an increase of inflammatory markers (STAT3, TNFα, IL1α, IL1β, IL6, IL23, IL2, ERAP1, IL10, IL5 mRNA), nitric oxide synthase (NOS) enzymes (NOS3 mRNA), and genes involved in adhesion (SELL, CDH5, THBS4 mRNA). In turn, monocytes displayed an augmented expression of inflammatory markers (STAT3, IFNγ, IL5, SPP1) and adhesion molecules (VCAM1, SELL), as well as a decrease in mRNA for IL6 and adhesive glycoprotein trombospondin 4 (THBS4). Neutrophils from AS patients showed a significant increase in NETosis and extruded plasma DNA levels, the latter associated with endothelial dysfunction present in AS. In addition, an increase of inflammatory markers (STAT3,

TNFα, IL1β, IL1α, IL5 mRNA), adhesion molecules (ICAM1, SELL mRNA) and NOS3 mRNA was also found in this cell type. Oxidative status-related analyses demonstrated that leukocyte subsets from AS patients displayed an increase in oxidative stress and mitochondrial membrane potential, along with an alteration of TAC and NO at plasma levels. *In vitro* treatment of HUVECs with PBMCs or neutrophils from AS patients promoted an altered activity of the endothelial cells, which displayed altered expression of adhesion molecules, oxidative stress markers, cytokines and NOS enzymes, all of them associated to the pro-atherogenic profile of these patients.

Conclusion: 1) Leukocyte subsets from AS patients display an altered expression profile of key genes involved in the development of atherosclerosis. 2) NETosis is a cellular death mechanism occurring in AS, whose induction may act a key mediator of endothelial dysfunction in these patients. 3) That highly inflammatory PBMCs and neutrophils are responsible, at least partially, for the endothelial alteration displayed by AS patients. Funded by JA PI-0314-2012, SER

Disclosure: Y. Jiménez-Gómez, None; **P. Font-Ugalde**, None; **P. Ruiz-Limon**, None; **M. C. Abalos-Aguilera**, None; **M. C. Castro-Villegas**, None; **N. Barbarroja**, None; **C. Perez-Sanchez**, None; **I. Arias de la Rosa**, None; **I. Arias**, None; **R. Ortega-Castro**, None; **J. Calvo-Gutierrez**, None; **C. Lopez-Pedrera**, None; **A. Escudero-Contreras**, None; **E. Collantes-Estévez**, None.

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Abstract Number: 1661

Toll-like Receptor 4 Induced IL-20 and IL-24 Stimulate Osteoblast Mineralization and Are Increased in Spondyloarthritis

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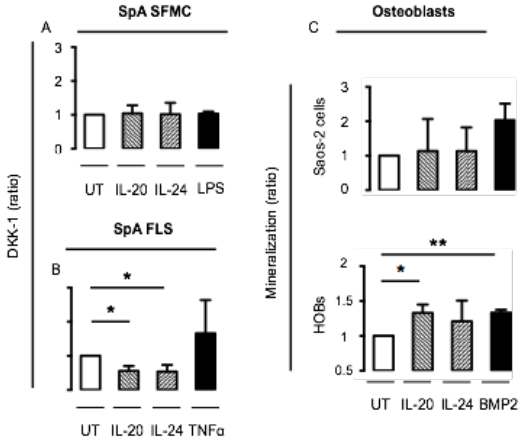
Background/Purpose: The pathogenesis of spondyloarthritis (SpA) involves activation of the innate immune system, inflammation and new bone formation. The innate immune system is activated through pattern recognition receptors including Toll like receptor 4 (TLR4). Inflammation is a result of increased production of pro-inflammatory cytokines and chemokines including tumor necrosis factor alpha (TNFα) and monocyte chemoattractant protein 1 (MCP-1). New bone formation by osteoblasts is determined by a balance between the inhibitory effect of Dickkopf-1 (DKK1) and the stimulatory effect of bone morphogenetic proteins (BMPs). The two cytokines IL-20 and IL-24 have been shown to link innate immune activation and tissue homeostasis.(1) Previously, we have found increased plasma levels of IL-20 and IL-24 in SpA patients. We hypothesized that IL-20 and IL-24 are secreted as part of activation of the innate immune system and affect bone homeostasis. The aim was to describe associations of IL-20 and IL-24 and disease activity and magnetic resonance imaging (MRI) scores and to identify the sources and targets of the two cytokines in SpA.

Methods: Patients with axial SpA (n=83) were included in the study of associations between cytokine levels and disease activity and MRI scores. Patients with peripheral SpA (n=16) were included for studying sources and targets of IL-20 and IL-24 among synovial fluid mononuclear cells (SFMCs), peripheral blood mononuclear cells (PBMCs), and fibroblast-like

synoviocytes (FLSs) using lipopolysaccharide (LPS) and TNFα as positive controls. Healthy human osteoblasts were used for studying the effect of the two cytokines on mineralization using BMP2 as a positive control. The secretion of IL-20, IL-24, MCP-1 and DKK1 were measured by enzyme linked immunosorbant assays and flow cytometry, and mineralization was measured by hydroxyapatite deposition.

Results: The plasma IL-20 and IL-24 levels were increased in SpA patients compared with healthy controls (HCs) by 57% and 83%, respectively (both $p<0.0001$) and there was a trend towards associations with both future switch to biologic therapy ($p=0.031$ and $p=0.11$, respectively), and spine MRI chronicity score ($p=0.10$ and $p=0.15$, respectively). The production of IL-20 and IL-24 was increased by LPS, and this TLR4 induced secretion was greater in SpA PBMCs compared with HC PBMCs. IL-20 and IL-24 increased the production of MCP-1 by SpA SFMCs (but not by SpA FLSs), decreased the production of DKK1 by SpA FLSs (but not by SpA SFMCs) and increased mineralization by human osteoblasts (see Figure). The IL-20 and IL-24 induced production of MCP-1 among the SFMCs was found in activated synovial monocytes only.

Conclusion: Taken together, our findings indicate that IL-20 and IL-24 could be novel links between activation of the innate immune system and new bone formation in SpA. References: 1. Rutz S et al. The IL-20 subfamily of cytokines - from host defence to tissue homeostasis. Nat Rev Immunol. 2014.



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Abstract Number: 1662

The Association Between Radiologic Progression and Serum Levels of Potential Markers of Bone Formation in Ankylosing Spondylitis Patients

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Background/Purpose: The association between inflammation and spinal damage in Ankylosing Spondylitis (AS) remains unclear. Tumor necrosis factor-α (TNF- α) plays pivotal role in inflammatory process of AS. However current cytokine inhibitor strategies in AS fail to halt new bone formation. This condition propounds that the structural damage of AS patients might be affected by noninflammatory processes or non-TNF- α inflammatory pathways. The aim of this study is to investigate the effects of some markers with possible contributions to structural damage in AS and their relationship with radiographic progression.

Methods: The study included 238 AS patients and age and sex-matched 150 healthy controls. All AS patients met Modified New York criteria or ASAS axial spondyloarthritis criteria. When patients applied for their routine follow ups, demographic data (age, gender, disease duration, mediacations), ESR, CRP, and total blood count were recorded. Along with the radiographic evaluation (*mSASSS*), serum levels of DKK-1, BMP-2, BMP-4, Sclerostin (SOST), IL-17, and IL-23 were analyzed.

Results: DKK, SOST, IL17, and IL23 were significantly higher in AS group while bm2 level was significantly lower among AS patients ($p<0.001$). (table-1) When the association between biomarker levels and disease activity parameters was investigated, bm2 concentration was significantly higher and bm4 concentration was lower among patients with higher BASDAI scores (>4) (p:0.046, p:0.033 respectively). No statistically significant difference was found between antiTNF and NSAID groups in terms of marker levels ($p>0.05$). Variance analyses showed that none of the factors solely affected the *mSASSS*. However, if bm2, bm4, and IL 17 levels were greater than median values, the *mSASSS* was affected by 3.3% ($p=0.017$). DKK, SOST, bmp2 and IL17 affected *mSASSS* by 2.6% if they exceeded median values ($p=0.029$). (table-2). These correlations were significant but weak.

Conclusion: The mechanism of new bone formation in AS seem to be complicated and a consequence of inextricable processes. As a manifestation of this confusion, DKK-1 and SOST, with inhibitory effect on bone formation were found to be higher, and BMP-2, a bone formation marker was found to be lower among AS patients. These results propound the importance of local factors (enthesis sites) and possible disease-specific effects of biomarkers.

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Abstract Number: 1663

Assessment of Serum Calprotectin and Osteoprotegerin Levels in a Cohort of Spanish Patients with Axial Spondyloarthritis

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Background/Purpose: Calprotectin is a protein involved in several cellular processes including immunomodulation[1]. Elevated levels of this protein have been observed in inflammatory diseases, since it is secreted into inflamed tissues during monocyte infiltration[2]. Osteoprotegerin (OPG), a member of the tumor necrosis factor receptor superfamily, has been associated with increased risk and severity of atherosclerotic disease[3]. Both molecules have been proposed as potential biomarkers of atherosclerosis[4,5]. In contrast to ankylosing spondylitis (AS), non radiographic axial spondyloarthritis (nr-axSpA) patients do not seem to develop early atherosclerotic disease[6]. Due to this, we aimed to compare calprotectin and OPG levels in AS and nr-axSpA and to assess the potential involvement of both molecules as biomarkers of subclinical atherosclerosis in both types of SpA.

Methods: Serum calprotectin and OPG levels were measured by ELISA in 202 Spanish patients diagnosed with axSpA recruited from Hospital Universitario Marqués de Valdecilla and Hospital de Laredo (Spain). axSpA patients fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria[7]. Of them, 53 fulfilled the definitions for nr-axSpA[7], while 149 also fulfilled definitions for AS according to the 1984 modified New York criteria[8]. Patients with previous history of cardiovascular (CV) disease were excluded. All the patients underwent a carotid ultrasound study to assess the presence of abnormal carotid intima-media thickness (cIMT) and presence of plaques (both surrogate markers of CV disease), as previously described[9]. Differences in calprotectin and OPG levels among the study groups were assessed by Mann-Whitney test. Correlations of these molecules with surrogate markers of CV disease were studied. The association with cIMT values was assessed by linear regression, while the association with plaques was tested by logistic regression. All the results were adjusted by potential confounder factors. Statistical analysis was performed using STATA® v. 11.1.

Results: nr-axSpA and AS patients displayed similar levels of serum calprotectin and OPG. When the potential association between calprotectin and OPG levels and cIMT values or presence of plaques was assessed, no statistically significant results were obtained, neither in the axSpA cohort nor in the two subgroups of AS and nr-axSpA patients ($p>0.05$ for all comparisons).

Conclusion: Our results do not confirm an association between calprotectin and OPG levels with subclinical atherosclerosis in our cohort of Spanish axSpA patients. [1] Arterioscler Thromb Vasc Biol 2015;35(12):2496-2507; [2] Ann Rheum Dis 2014;73:1746–8; [3] J Rheumatol 2014;41(3):429-36; [4] Arthritis Rheumatol 2015;67(10); [5] Clin Exp Rheumatol 2014;32(5):640-6; [6] Clin Exp Rheumatol 2016;34(1):159-60; [7] Ann Rheum Dis 2009;68:777-83; [8] Arthritis Rheum 1984;27:361-368; [9] Clin Exp Rheumatol 2015;33(3):315-320 *FG is a recipient of a Sara Borrell postdoctoral fellowship from the Instituto de Salud Carlos III at the Spanish Ministry of Health (Spain)(CD15/00095). RLM and BU are supported by funds from the RETICS Program (RIER)(RD12/0009/0013) (Spain).*

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Abstract Number: 1664

Protein Fingerprinting Screening Specific Proteins in Serum of Patients with Ankylosing Spondylitis

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Background/Purpose: To study the specific biomarkers by surface-enhanced laser desorption ionization/time of flight mass spectrometry (SELDI-TOF-MS) and protein chip in serum of patients with ankylosing spondylitis (AS).

Methods: The serum samples of 69 AS patients and 12 healthy individuals were detected by SELDI-TOF-MS and weak cation exchange (WCX-2) chip. To find the specific proteins and to set up the diagnostic models by using Biomarker Wizard and Biomarker Pattern software. Then 69 AS patients were divided into several types such as the condition of illness was active or not, HLA-B27 was positive or negative, with or without hip involvement. To study the possible roles of differentially expressed proteins in the pathogenesis of AS.

Results: The first diagnostic model (8085, 2640 and 2932)could be used to diagnose AS in early stage. The sensitivity and specificity were 94.23% and 100% respectively. The second diagnostic model (3677, 3880, 2539, 3159 and 3242) could be used to determine the disease activity of AS. The sensitivity and specificity were 98.11% and 100% respectively. The third diagnostic model (4700, 8687 and 18538) could be used to predict AS whether involve peripheral arthritis or not. The sensitivity and specificity were 80.00% and 82.35% respectively. The serum protein expression were not statistically difference between in the HLA-B27 positive group and HLA-B27 negative group.

Conclusion: The serum protein fingerprinting by SELDI-TOF-MS could identify new biomarkers in AS. The biomarkers may play an important role in pathogenesis of AS. We could diagnose AS in early stage, determine disease activity and predict disease progression by these biomarkers.

Disclosure: D. Ma, None; **G. Z**, None; **K. Xu**, None; **L. Zhang**, None.

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Abstract Number: 1665

Validation of Germ Line Epigenetic Variants Associated with Psoriatic Disease

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Background/Purpose: Heritable epigenetic phenomena may play a role in the parent-of-origin effect observed in psoriasis and psoriatic arthritis (PsA). A previous epigenome-wide association study (EWAS) identified differentially methylated regions (DMRs) in sperm cells of PsA and psoriasis patients without PsA (PsC) compared to controls. This study aimed to assess differential methylation and expression of these regions in somatic tissues.

Methods: Genomic DNA was extracted from whole blood of PsC patients (n=24), PsA patients satisfying the CASPAR criteria (n=13), and controls (n=19). All subjects were males whose semen was previously analyzed by EWAS. DNA was bisulfite converted and the most biologically interesting and statistically significant EWAS hits (oxysterol binding protein like 5 [*OSBPL5*], myelin basic protein [*MBP*], imprinted maternally expressed transcript *H19,* small nucleolar RNA C/D box 115 [*SNORD115*], E74 like ETS transcription factor 5 [*ELF5*], interleukin 22 [*IL22*], protein tyrosine phosphatase receptor type N [*PTPRN2*], junctional adhesion molecule 3 [*JAM3*], and cysteinyl-tRNA synthetase 2 [*CARS2*]) were analyzed by pyrosequencing. Group-wise methylation differences were compared by Student's t test or Wilcoxon rank sum test. Multivariable logistic regression was also performed to adjust for age and psoriasis area and severity index (PASI). Whole blood RNA was collected in Tempus and Paxgene tubes and extracted with their respective kits. Differential expression was analyzed by qRT-PCR using the ΔΔCt method with normalization to glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*).

Results: In whole blood, CpG sites within *JAM3, MBP,* and *PTPRN2* were differentially methylated in PsA vs. controls. *JAM3* and *ELF5* were differentially methylated in PsA vs. PsC. *MBP* was differentially methylated in PsC vs. controls ($p<0.05$). After adjustment for age, *MBP* (OR=0.1, 95% CI 0.1-0.75, p=0.03) and *PTPRN2* (two CpG sites: OR=2.1, 95% CI 1.0-4.3, p=0.04 and OR=2.2, 95% CI 1.0-4.9, p=0.049) remained significantly associated with PsA vs. controls. After adjustment for age and PASI, *JAM3* (OR=26.7, 95% CI 2.6-276, p=0.006) and *ELF5* (OR=31.5, 95% CI 1.6-628, p=0.02) remained significantly associated with PsA vs PsC. No CpG sites were differentially methylated in PsC vs. controls in age-adjusted analyses. All genes except for *ELF5, PTPRN2,* and *IL22* were expressed at detectable levels in whole blood. Preliminary qRT-PCR results showed significantly higher expression of *CARS2* mRNA transcripts in PsA (fold change=1.18, p=0.02) and PsC patients (fold change=1.24, p=0.046) compared to controls, but no significant differences in the levels of *JAM3* and *MBP* between groups.

Conclusion: Several germ line DMRs associated with PsC and PsA were differentially methylated in whole blood. The presence of these DMRs in both the germ line and whole blood suggests they may be heritable epigenetic phenomena associated with PsC and PsA. Investigation of these sites in additional somatic tissues, and in extended patient populations is necessary to strengthen the evidence that they are true heritable epigenetic variations.

Disclosure: R. Pollock, None; **L. Zaman**, None; **V. Chandran**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5.

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Abstract Number: 1666

Microrna s Mir-30b-5p, Mir-34a-5p, and Mir-431-3p Are Highly Expressed in the Plasma of Patients with Ankylosing Spondylitis

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Background/Purpose: The role of miRNAs in immune and inflammatory diseases is increasing exponentially. miRNAs are present in the human plasma in stable form. We proposed to test the hypothesis that patients with ankylosing spondylitis (AS) have an altered miRNA expression profile compared to controls.

Methods: pared to controls. **Methods**: Sixtytwo patients ≥18 years of age with AS based on the modified New York classification criteria (grade 3 and 4 sacroiliitis) and 34 healthy (age, race and sex matched) controls were prospectively recruited. Subjects with active malignancy in last 5 years, rheumatoid arthritis, systemic lupus erythematosus and evidence of HIV or chronic hepatitis B or C infection were excluded. Patients and controls were screened, consented and peripheral blood samples (5 ml) were obtained. The samples were centrifuged at 400 g for seven minutes; plasma transferred to nuclease free tubes and stored at -20°C until analyses. ESR and CRP were measured using routine laboratory methods. Various validated Questionnaires to assess disease, functional activity and patient reported outcomes in AS were administered to the patients. Sixty-eight circulating miRNAs in the plasma of the study subjects were profiled by Firefly Multiplex Circulating miRNA Assay (Abcam, Cambridge, MA) using the Immunology Panel. The assay beads were scanned on BD Accuri C6 flow cytometer (BD Biosciences, San Jose, CA). Data were analyzed using Firefly Analyis Workbench (Abcam). Expression of ten selected miRNAs that were differentially expressed based on the multiplex assay was further validated by qPCR using TaqMan Advanced miRNA assay (ThermoFisher Scientific) following the manufacturer's instructions. Briefly, Total RNA (including miRNA) was isolated from 100 µl of plasma from all the study subjects using the MagMAX mirVana Total RNA Isolation kit. cDNA was generated using 2 µl of purified total RNA with the TaqMan Advanced miRNA cDNA Synthesis kit. qPCR was then performed for each sample using 1 µL of diluted cDNA, TaqMan Advanced miRNA Assays, and Applied Biosystems TaqMan™ Fast Advanced Master Mix under fast cycling conditions. Reactions were run on StepOne Plus real-time PCR system. Data were analyzed on DataAssist v3.01 (ThermoFisher Scientific). Descriptive analyses included continuous variables (the mean ± SD) and the categorical variables(percentage).

Results: Demographics, clinical characteristics and disease activity of the patients are in Table 1. Our data revealed that miR-30b-5p (p=0.005), miR-34a-5p (p=0.007), and miR-431-3p (p=0.014) were highly abundant in the plasma of AS patients compared to the levels prevalent in controls.

Table-1

Patient Demographics

Mean Age in Years ± SD	48.8 ± 12.3
% African American	31.6
% Females	34.4
% HLA B27 Positive	77.4
% TNF-I use	50
BASDAI	5.1 ± 2.5

Conclusion: This study demonstrates that specific miRNAs are differentially expressed between AS patients and healthy subjects and thus can be developed as potential biomarkers. This work was supported in part by USPHS/NIH grants (RO1 AT007373, RO1 AT005520, RO1 AR067056, R21 AR064890) and funds from North East Ohio Medical University to TMH.

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Abstract Number: 1667

Diagnostic Value of Anti-CD74 Antibodies in Axial Spondyloarthritis: Results from a Population with Low HLA-B27 Prevalence Background

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Background/Purpose: Axial spondyloarthritis (axSpA) is still frequently diagnosed late and its pathogenesis is still unclear. Although a strong genetic association of axSpA with HLA-B27 is known, the gene prevalence varies among different world regions, and its value for the identification of patients with axSpA has been questioned. IgG and IgA antibodies against CD74 have shown good sensitivity and specificity and higher positive likelihood ratio (LR+) for axSpA as compared to HLA-B27. In this prospective study, we tested the performance of IgG and IgA anti-CD74 as early diagnostic marker for axSpA as compared to HLA-B27 in Lebanon, which is known as one of the countries with the lowest HLA-B27 prevalence ever reported.

Methods: Sera of axSpA patients and healthy blood donors (HBD) were analyzed for HLA-B27 genes by PCR and for IgG and IgA anti-CD74 by ELISA. The laboratory workers were blinded for clinical data during the analyses. Patients and HBD were recruited after an advertising program among rheumatologists and primary care physicians across Lebanon. Clinical assessment and sera sample collection were performed at a center specialized in axSpA (University center, Hotel-Dieu de France, Beirut). Inclusion criteria were age 18-45 years, Lebanese nationality, symptom duration <3 years, classification to axSpA (ASAS criteria, imaging arm), no prior exposure to biologics. Interpretation of the radiographic images for inclusion in the study was performed centrally and independent of the recruiting rheumatologist. Clinical and laboratory assessments were performed in all axSpA patients. Comparison between groups was performed with the Mann-Whitney U test. For the diagnostic properties of HLA-B27 and anti-CD74 IgGs, ROC curves were calculated.

Results: Sera of 26 axSpA patients and 69 HBD were collected prospectively. AxSpA patients were slightly older than HBD (31.6 and 27.3 years, respectively, p=0.04) with no other demographic differences. Mean symptom duration was 36.4 months (SD 16.5), mean BASDAI 4.2 (SD 2.0) and mean ASDAS 3.2 (SD 1.2). A total of 14 patients (54%) were classified as nr-axSpA. HLA-B27 status was positive in 9/26 axSpA patients (34.6%) but in no HBD (Sensitivity 34.6%, Specificity 100%). In the ROC analysis, IgG4 anti-CD74 showed the best diagnostic value for axSpA (AUC 0.939, cut-off value 0.55). Using this cut-off, positive values of IgG anti-CD74 were found in 24/36 axSpA patients (66.7%) and 5/69 HBD (7.2%) (Sensitivity and Specificity 92.3%, positive predictive value 82.7%, negative predictive value 96.8%, LR+ 12.0, LR- 0.08).

Conclusion: In this first study in a population with low HLA-B27 prevalence, IgG anti-CD74 antibodies showed higher diagnostic value than HLA-B27 for AxSpA. This is of special interest in populations with low HLA-B27 prevalence, especially on the background of diagnosing axSpA when using the clinical arm of the ASAS classification criteria.

Abstract Number: 1668

Selective Inhibition of Tumor Necrosis Factor-α Receptor 2 (TNFR2) Activity Alleviates Psoriasiform Inflammation in Mouse Models

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Background/Purpose: Tumor necrosis factor-α (TNF) activates two receptors globally, TNFR1 and TNFR2. Neutralizing antibodies or soluble TNF receptors can inactivate TNF, blocking activity of both receptors, and have been successful in treating psoriasis (PsO) and psoriatic arthritis (PsA). However, continued use of anti-TNF therapy has been associated with an increase in serious infections, such as reactivation of tuberculosis and malignancies. These side effects are related to TNFR1 blockade. Using mouse models, we showed that activity of both TNFR1 and TNFR2 is critical for TNF-mediated inflammatory responses.[1] Recently, we identified that activation of PRMT5 (protein arginine methyltransferase 5), an enzyme critical for TNF-mediated inflammatory responses, is downstream of TNFR2 but not TNFR1 signaling. This makes PRMT5 a target for treating TNF-dependent inflammatory diseases. Our goal is to demonstrate that selective inactivation of TNFR2 via PRMT5 is effective in treating psoriatic diseases. Our objective is to determine the relative contributions of TNFR1 and TNFR2 to the development of PsO, and to test whether inhibition of PRMT5 activity will alleviate PsO and PsA in animal models.

Methods: To identify the role of TNF receptors in psoriasis we used the imiquimod (IMQ) mouse model. We applied IMQ (4 mg/day/mouse for 4 days) to 10-12 week old wild type (WT), TNFR1-null, TNFR2-null and TNFR1 & 2 double-null mice. To determine the role of PRMT5, we treated a specific PRMT5 small molecule inhibitor EPZ015666 topically 4 hours prior to IMQ application once a day for 4 days. Erythema, scaling and thickness of the IMQ or vehicle treated area was assessed by PASI (Psoriasis Area and Severity Index). Epidermal thickness was measured using ImagePro software on H&E stained skin sections. Immunohistochemistry was used to determine PRMT5 expression. Protein-incorporated SDMA (Symmetrical Dimethyl Arginine), which is the catalytic product of PRMT5 and works as a functional representation of PRMT5 activity, was measured in psoriatic skin using mass spectrometry. Further, we are currently testing whether EPZ015666 can inhibit PsA-like joint disease using a TNF overexpressing mouse strain (ihTNFtg mice[2]).

Results: In WT mice, erythema, scaling, and thickness peaked at day 8 (PASI ~ 8.0). TNFR2-null or double-null mice skin inflammation was undetectable. TNFR1-null mice showed a PASI score of 1 - 2.5. H&E revealed significant keratinocyte hyperplasia and leukocyte infiltration in WT treated with IMQ, which were inhibited in TNFR2-null, TNFR1-null or double-null mice. Further, IMQ-treated mouse skin showed elevated PRMT5 expression. There was a ~ 2-fold increase of SDMA in mouse psoriatic skin compared to the adjacent normal skin. Importantly, topical application of PRMT5 inhibitor, EPZ015666, diminished the IMQ-induced PsO pathogenesis in WT mice (~ 75%).

Conclusion: IMQ-induced psoriasis is critically dependent on TNFR2. An increase in the abundance of PRMT5 was also found in mouse psoriatic skin and the specific PRMT5 inhibitor that can block TNFR2 ameliorates psoriasis in mice.

References

1 Chandrasekharan, U. et al. *Blood* **109**, p1944, 2007

Disclosure: U. Chandrasekharan, None; **C. Braley**, None; **J. Harvey**, None; **Z. Wang**, None; **P. DiCorleto**, None; **M. E. Husni**, Lilly, Novartis, Abbvie, Celgene, Bristol Myers Squibb, Amgen, Janssen, & UCB pharma, 5.

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Abstract Number: 1669

Type 3 Innate Lymphoid Cells Numbers in Peripheral Blood Predict Ustekinumab (Stelara) Therapy Responsiveness in Psoriatic Disease Cases with Subclinical Imaging Enthesopathy

Yasser El-Sherbiny[1], Laura Savage[2], Miriam Wittmann[3], Mark J. D. Goodfield[4] and Dennis McGonagle[1], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]NIHR Musculoskeletal Biomedical Research Unit, University of Leeds, Leeds, United Kingdom, [3]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom, [4]Dermatology, Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom

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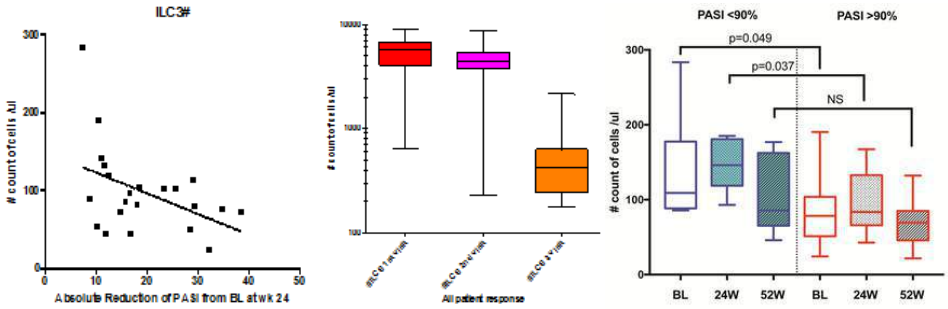
Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Ustekinumab[1] targets the common p40 sub-unit of interleukin-12 (IL-12/interleukin-23 (IL-23). In patients treated with Ustekinumab for psoriasis where patients were selected on the basis of subclinical imaging enthesopathy, we have noted an improvement in subclinical imaging enthesopathy (Savage et al. submitted), raising the possibility that it may be possible to find a biomarker for predicting response to therapy in psoriatic disease. Innate lymphoid cells may be centrally involved in the pathogenesis of psoriatic skin and joints disease[2], since they express IL-23R receptor and are associated with IL-17/IL-22 production. This work tested the hypothesis that peripheral blood ILC perturbations may be useful in defining response in psoriasis cases with imaging confirmed subclinical enthesopathy.

Methods: Peripheral blood collected at baseline (before therapy, 24weeks, 54 weeks) from patients in the MUSTEK trial (Ustekinumab in psoriasis cases who had ultrasound imaging confirmed subclinical enthesopathy) (n=23). Cellular immunophenotyping was performed density gradient separated PBMCs. Innate lymphoid cells were identified as lineage negative (CD3- TCRγδ- TCRαβ- CD19- CD14- CD11c- CD1a- CD303- FcεRI- CD34- CD123-) with positive expression of CD45, CD127. ILC2 cells were identified as Lineage- CD127+ and CRTH2 positive, while ILC3 were identified as Lineage- CD127+, CRTH2 – and CD117 (c-Kit) positive and further subdivided of NKp44+ and NKp44-. ILC1 were identified as lineage- CD127+ CD117-and CRTH2-. For data analysis we separated cases into PASI>90% or PASI <90% responders. The subclinical enthesopathy scores also fell significantly under therapy (Savage et al. submitted)

Results: No correlation was found with total ILCs absolute numbers (ILC1, 2, AND 3) (R= 0.104, p=321, Spearman R) and therapy response.



The absolute numbers of baseline ILC3s was inversely correlated in with the reduction in the PASI score (R= -0.404, p=0308, Spearman R). The ILC3s also fell progressively under therapy. All the patients respond with reduction of PASI score mean 92.6% (range 65.8-100%), Interestingly, those patients with reduction below 90% of PASI score has a significantly higher absolute numbers of ILC3+ cells in peripheral blood at the baseline than PASI (n=6/23) than super-responder group (n=17/23).

Conclusion: Only peripheral blood ILC3s, but not other ILCs changes, correlate with the PASI score (disease activity), Furthermore, excellent responders (PASI reduction > 90%) showed strong correlated with higher ILC3 population at the baseline. This may help to use ILC3 enumeration as predictive parameter for ustekinamab clinical therapeutic response and may be relevant to assessing novel biomarkers for subclincal arthropathy in psoriasis.

Disclosure: Y. El-Sherbiny, None; **L. Savage**, None; **M. Wittmann**, None; **M. J. D. Goodfield**, None; **D. McGonagle**, None.

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Abstract Number: 1670

Cytokine Expression in Groups of Psoriatic Arthritis Patients Characterised By Specific HLA Genotypes and Clinical Features

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Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous disease with diverse clinical and radiographic manifestations. A number of human leukocyte antigen (HLA) alleles have been found to be associated with PsA.[1] HLA-C*06:02 is associated with severe skin disease and a late onset, milder musculoskeletal phenotype; HLA-B*27:05 with entheseal-based disease, severe musculoskeletal disease, enthesitis, symmetric sacroiliitis (SI) and mild psoriasis; HLA-

B*08:01 with synovial-based disease, asymmetric SI, joint deformity, joint fusion and dactylitis while HLA-B*38:01/39:01 is associated with more axial involvement and joint damage progression.[2] Our hypothesis is that in each of these distinct genetic groups and perhaps as a consequence of the inflammatory events that occur following MHC-peptide interaction, a different pattern of inflammation involving diverse systemic molecules and mediators may be unleashed which in turn determines clinical phenotype and possibly therapeutic response. Our objective is to identify whether there are differences in cytokine expression between groups of patients with specific combinations of HLA genotypes and clinical features.

Methods: Patients with a diagnosis of PsA, fulfilling the CASPAR criteria, aged >18 years were clinically assessed, 10 patients from each of the 4 defined HLA groups. We included a fifth distinct clinical group, Arthritis Mutilans (AM), which as yet has no defined genotype. Serum samples were obtained. *Cytokine Strategy*: 50 individual patient samples (10 per group) and 5 reference pools (each pool consists of 50 samples) were subjected to in-house developed and validated multiplexed immunoassays to measure 47 cytokines using the Luminex xMAP. Analysis was performed in the Laboratory for Translational Immunology, UMC, Utrecht, The Netherlands. Data were analysed by 5-parametric curve fitting using BIO-Plex Manager software version 6.1.1.

Results: Forty-seven cytokines were analysed in each individual sample (n=50). Four samples were excluded because of cross reaction. Fourteen cytokines were excluded because they were out of reference range (either above or below). Twelve cytokines were excluded as their coefficient of variation (CV) was > 20%. On analysis of the remaining 21, only 1 cytokines (IL18) was differentially expressed among the 5 groups, Figure1. IL18 was elevated in the HLA-B*27 group, with statistically significant difference between B*27 and AM (P<0.256, CI 135.6 to 9.982) and between B*27 and B*38/39 (P<0.0320, CI 129.3 to 6.524).

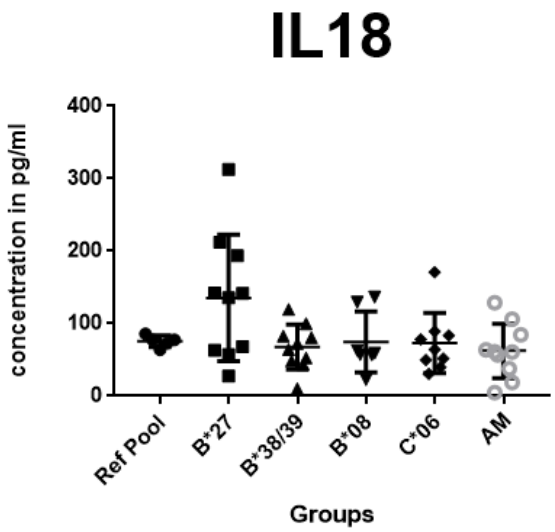

Figure 1 showing result IL18 cytokine in different group

Conclusion: IL18 was found to be elevated in HLA B*27 group. IL18 was significantly different between HLA B*27 group and AM and HLA B*38/39 group. Further analysis with a larger cohort is needed. **References:** 1. Winchester R, et al. A&R64:1134-44, 2012 2. Haroon M, et al. ARD75:155-162, 2016

Disclosure: M. Elmamoun, None; **W. de Jager**, None; **S. de Roock**, None; **M. Haroon**, None; **R. Winchester**, None; **S. R. Pennington**, None; **O. FitzGerald**, Abbott Immunology Pharmaceuticals, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 2,Abbott Immunology Pharmaceuticals, 5,Pfizer Inc, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,UCB Pharma, 5,Eli Lilly and Company, 5.

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Abstract Number: 1671

Pirfenidone Might Inhibit New Bone Formation in Spondyloarthritis: Proof of Concept Study Using Cell Culture Models

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Background/Purpose: The pathogenesis of spondyloarthritis (SpA) involves both inflammation and new bone formation in the spine. In line with this, the disease has been characterized as both inflammatory and fibrotic. Current treatment including inhibitors of tumour necrosis factor alpha (TNFα) seems to dampen inflammation while new bone formation can progress. Therefore, there is an unmet therapeutic need for the treatment of new bone formation in SpA. Fibrosis is mediated by myofibroblasts and new bone formation is the result of increased osteoblast mineralization and decreased osteoclast bone degradation. Here, we evaluate the potential effect of the newly approved anti-fibrotic agent pirfenidone (Esbriet, Pirespa) on fibrosis and new bone formation in cell culture models of SpA. We hypothesized that pirfenidone inhibits SpA myofibroblast formation and activity and osteoblast mineralization.

Methods: Synovial fluid mononuclear cells from patients with SpA (n=6) were included for culturing fibroblast-like synovial cells (FLSs) while osteoblasts were purchased. The cells were cultured with pirfenidone in increasing concentrations (0.25, 0.5, and 1.0 mg/ml) with or without stimulation with tumor necrosis factor alpha (TNFα), transforming growth factor beta (TGFβ), or interferon gamma (INFγ). The proliferation of FLSs was analyzed with light microscopy and flow cytometry using the marker Ki67. The differentiation and activation of FLSs was assessed with flow cytometry, a proteome profiler assay and enzyme-linked immunosorbant assays. The mineralization capacity of the osteoblasts was measured as deposition of hydroxyapatite.

Results: Pirfenidone reduced the Ki67 expression 7.1-fold in untreated FLSs (p=0.001) and 11.0-fold in FLSs stimulated with TGFβ, TNFα, and INFγ (p=0.022). Pirfenidone further inhibited TGFβ induced upregulation of αSMA (Figure 2A) and INFγ induced upregulation of HLA-DR (Figure 2C) in all cultures. There was no difference between the percentage of ICAM-1 positive FLSs in cultures treated with or without pirfenidone. In supernatants from FLSs stimulated with TGFβ, TNFα, and INFγ a total of 12 cytokines or chemokines had values above the detection limit in the membrane-based antibody array. Pirfenidone decreased the secretion of 3 of these 12 cytokines or chemokines more than 2-fold. The changes in secretion of monocyte chemoattractant protein 1 (MCP-1) and chitinase-3-like protein 1 (CHI3L1, also known as YKL-40) were validated with ELISA. Further, pirfenidone decreased the secretion of both DKK1 (p=0.006) and OPG (p=0.02) by SpA FLSs stimulated with TGFβ, TNFα, and INFγ, while the concentration of RANKL was below the detection limit of the ELISA assay in all cultures. Finally, pirfenidone inhibited the deposition of hydroxyapatite by osteoblasts in a dose-dependent manner (p=0.0001). This inhibition was partly reversible when removing pirfenidone after the first week of the mineralization assay.

Conclusion: Taken together, pirfenidone inhibited SpA myofibroblast formation and activity and osteoblast mineralization. This encourages further research in using anti-fibrotics as treatment of new bone formation in SpA.

Disclosure: J. Laustsen, None; **S. Lomholt**, None; **P. Andersen**, None; **J. Kelsen**, None; **T. W. Kragstrup**, None.

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Abstract Number: 1672

Microrna-29a Activation of Canonical Wnt Signaling By Targeting LRP6 in Ankylosing Spondylitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Aberrant regulation of the Wnt pathway is a key element in the pathogenesis of Ankylosing spondylitis (AS). We previously found that miR-29a was significantly upregulated in AS patients.

Methods: We enrolled 45 AS patients and 48 healthy controls. ESR, CRP and HLA-B27 were performed. BASDAI, BASFI, ASDAS and mSASSS were calculated. The levels of miR-29a and mRNA of DKK-1, GSK-3¦Â, ¦Â-catenin, ALP and OC from PBMCs were determined by real-time qPCR. Corresponding protein levels were measured by ELISA. Independent t-test was used to test for the differences between two groups. Correlation analysis was conducted using Spearman¡¯s correlation test. P <0.05 was considered statistically significant. The target prediction of miR-29a was performed. The luciferase activity levels were measured using Promega dual-luciferase reporter assay system. The miR-29a mimic or inhibitor or NC was co-transfected with constructed wt or mut-3¡¯UTR luciferase reporter into HEK293T cells. The miR-29a mimics (50 nmol/L) or inhibitor or NC was co-transfected to hFOB1.19 and MC3T3-E1 cells. The mRNA and protein level of DKK-1, GSK-3¦Â, ¦Â-catenin, OC, ALP, collegen X, Wnt-3a and Runx2 was detected at 48 and 72 hours.

Results: The levels of DKK-1 was significantly higher in AS patients than that in healthy controls, with no correlation with any clinical parameter. No significant difference was observed for other markers.The levels of miR-29a, Dickkopf (DKK)-1, ¦Â-catenin and Runx2 mRNA were significantly higher in AS patients than those in controls ($p<0.05$). In contrast, the levels of Gsk-3¦ÂmRNA was significantly lower in AS patients than that in healthy controls ($p<0.05$). Gsk-3¦ÂmRNA was positively correlated with¦Â-catenin mRNA expression ($p<0.05$) and no other correlation was observed between any other markers ($p>0.05$). Only DKK-1 mRNA expression was negatively correlated with disease course ($p<0.05$) and no other correlation was observed between markers and clinical measurements ($p>0.05$). The luciferase reporter analysis showed that LRP6 was a target of miR-29a. miR29a suppressed LRP6, GSK-3¦Â, DKK-1 expression and facilitated ¦Â-catenin, Wnt-3a, Runx2, OC, ALP, collegen X expression. (Figure 1)

Conclusion: Alteration of bone turnover markers in canonical Wnt pathway was observed in AS which partially explain the complicated mechanism of bone formation. Bioinformatics and ex vivo studies proved that LRP6 is a target gene of miR-29a in AS.

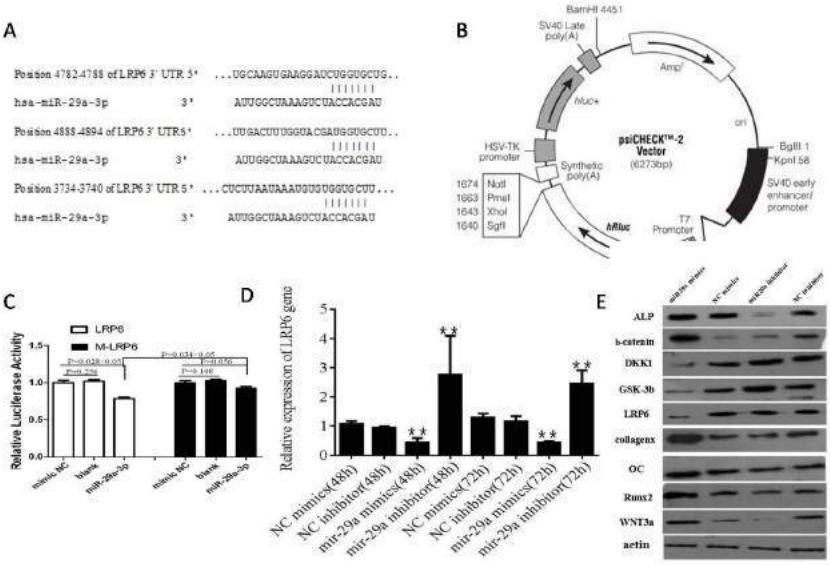

Figure legend: A. The has-miR-29a-3p conserved putative sites of LRP6 3¡¯UTR predicted by TargetScan and miRDB. B. XhoI and Not¢ñ restriction sites of PsicheckTM-2 Vector dual-luciferase miRNA target vector. C. Luciferase reporter result of miR29a mimics or inhibitor transfection to wildtype and mutated LRP6. D. LRP6 was negatively regulated by miR29a at mRNA level by qPCR. E.Wnt signaling markers expression after microRNA transfection by Western blot.

Disclosure: J. Huang, None; **Z. Yin**, None; **Z. Fu**, None; **Z. Ye**, None; **L. Zhang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/microrna-29a-activation-of-canonical-wnt-signaling-by-targeting-lrp6-in-ankylosing-spondylitis

Abstract Number: 1673

Characteristic Phenotypes of Peripheral T Cells and Efficacy of Biological Dmards in Patients with Psoriatic Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Biological DMARDs (bDMARDs) such as adalimumab (ADA), infliximab (IFX), ustekinumab (UST) and secukinumab (SEC) become available and efficacious in patients with psoriatic arthritis (PsA). However, it remains unclear how we can differentially use these bDMARDs to individual patients. We assessed peripheral immune cell

phenotypes in PsA patients treated with bDMARDs and tried to subdivide patients by the lymphocyte phenotypic difference.

Methods: 44 PsA patients with inadequate response to conventional therapy were treated with bDMARDs (IFX 15, ADA 17, certolizumab pegol 1, UST 7, SEC 4 cases) and PASI score, SDAI, DAS28(ESR) were evaluated. Peripheral immune cell phenotypes were assessed by 8-color flow cytometric analysis for human immune system termed by NIH and FOCIS in 20 patients with PsA who showed.

Results: Baseline characteristics of patients with PsA were; mean age 47.7 years, the male/female 27/17, mean disease duration 139.2 months, respectively. All of patients had already been treated with topical therapy, corticosteroid, DMARDs and/or immunosuppressant. Following treatment with bDMARDs, the PASI score, SDAI, DAS28(ESR) were significantly decreased from 8.8/17.7/4.38 at baseline to 3.3/8.6/2.28 at 6 months, respectively, and 29.5 % of patients achieved both SDAI remission and PASI clear at 6 months. No statistical difference in clinical efficacy among bDMARDs was observed. Among $CD4^+$ T cells, although expression of differentiation markers such as CCR7/CD45RA and proportion of Th1 cells were comparable between PsA and HC, activated Th17 cells were significantly higher in patients with PsA than in HC. Contrarily, the proportion of naïve $CD8^+$ T cells were lower, that of central memory $CD8^+$ T cells, effector memory $CD8^+$ T cells, activated $CD8^+$ T cells were significantly higher in patients with PsA than in HC, and the proportion of activated $CD8^+$ T cells correlated with PASI score. In addition, 20 patients with PsA were categorized to 4 different subgroups according to phenotypic difference in $CD4^+CD45RA^-$ T helper subsets: $CXCR3^+CCR6^-CD38^+HLA\text{-}DR^+$ activated Th1 dominant (3 cases), $CXCR3^-CCR6^+$ activated-Th17 dominant (6), $CXCR3^+CCR6^+$ activated-Th1/Th17 high (4), and $CXCR3^-CCR6^-$ activated-Th1/Th17 low (7). After the 6 month-treatment, the proportions of central memory $CD8^+$ T cells, effector memory $CD8^+$ T cells, activated $CD8^+$ T cells, activated Th1 cells and activated Th17 cells were remarkably decreased in patients who showed clinical improvement.

Conclusion: Our study proved that peripheral activated $CD4^+$ helper T cells could divided to 4 patterns; Th1-high, Th17-high, both-high and both-low in patients with PsA. Furthermore, the proportion of activated $CD8^+$ memory T cells and activated Th17 cells was characteristically high, but it was decreased by the treatment with bDMARD, indicating these subsets may contribute to the pathogenesis in PsA. Immunophenotypic analysis is, therefore, useful for evaluation of the therapeutic target and prediction of the response to bDMARDs in patients with PsA.

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Abstract Number: 1674

Do TNF Inhibitors Change the Progression of Sacroiliitis?

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Session Time: 9:00AM-11:00AM

Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory arthritis affecting the sacroiliac (SI) joints and spine causing structural changes seen on clinical radiography. Studies have suggested that NSAID and TNF inhibitor (TNFi) use slow down new bone formation. We evaluated the impact of TNFi treatment on the evolution of radiographic changes in the SI joints in a large and well-characterized long term follow-up cohort and to determine whether TNFi use, over an extended period of time, can have an effect on radiographic change in the SI joints.

Methods: All AS patients satisfying the modified New York criteria prospectively followed, with multiple sets of pelvic radiographs multiple years apart spanning >2 up to >10 years were investigated. Radiographic change and TNFi use in patients with AS and sacroiliitis were assessed. Anteroposterior radiographs of the right and left SI joints were scored by a board certified musculoskeletal radiologist according to the Bath Ankylosing Spondylitis Radiology Index for the spine (BASRI-s). We selected a grade-2 BASRI score change to eliminate concerns associated with reliability for reading a grade-1 score change.

Results: 630 AS patients who met the New York criteria and had at least 2 sets of radiographic SI joint severity data were reviewed. There were 283 patients who initially started with bilateral grade-4 sacroiliitis. Ultimately, 180 patients who initially started either as grade 2 bilaterally or grade-3 on at least 1 side and who could meet these criteria were included in analysis (median follow-up year=3). We conducted multivariable logistic regression model using progression as a dichotomous outcome variable (progressor or non-progressor) to evaluate multivariable associations between TNF-inhibitor use (defined as those who used TNFi for more than 50% of their follow-up period) and SI joint progression after controlling for other factors (including follow-up period, baseline SI joint scores, baseline TNFi use, NSAID index over follow-up period, study sites and clinical/demographic variables such as disease duration, sex, education level, race, current smoking status, subjective disease activity (BASDAI), CRP and comorbidity). Our findings indicate that TNFi use was related to less SI joint progression in AS patients (AOR=0.06, 95% CI 0.004 to 0.99; p=0.0494). In addition, high and low NSAID use, sex, CRP were significantly associated with lesser SI joint progression and could be potential confounders. No significant interaction was found between NSAID and TNFi use.

Conclusion: TNFi use was associated with less radiographic progression utilizing the BASRI scoring system in a large cohort of AS patients who fulfilled NY criteria at entry and were followed, in many cases, for up to and greater than 10 years.

Variable	Adjusted Odds Ratio (AOR) (95% CI)	P
TNFi use (Yes vs. No)	**0.06 (0.004, 0.99)**	**0.0494**
NSAID index (%)		
≤50 & >0 vs. 0 (low vs. no)	0.01 (0.001, 0.43)	0.0169
>50 vs. 0 (high vs. no)	0.001 (0.0001, 0.23)	0.0140
>50 vs. ≤50 & >0 (high vs. low)	0.03 (0.002, 3.50)	0.1924
Baseline SI score (Continuous)	2.44 (.0.21, 28.78)	0.4786
Disease duration (>10 years vs. ≤10 years)	0.21 (.0.02, 1.85)	0.1604
Sex (Male vs. Female)	40.14 (.1.24, 1296)	0.0373
Race (White vs. Others)	10.43 (.0.25, 427.6)	0.2160
Education (college or higher vs. Others)	8.67 (.0.30, 253.1)	0.2095
Current smoking status (Yes vs. No)	2.74 (.0.06, 116.0)	0.5981
# comorbidity (≥1 vs. None)	4.99 (.0.36, 69.46)	0.2312
BASDAI (≥40 vs. <40)	1.11 (.0.14, 8.59)	0.9189
CRP (abnormal vs. normal)	134.3 (.3.74, 4824)	0.0073
Baseline TNFi use (Yes vs. No)	0.52 (.0.04, 7.56)	0.6346
Follow-up years (continuous)	1.32 (.0.81, 2.16)	0.2599

Disclosure: D. Minhas, None; **M. Lee**, None; **M. H. Rahbar**, None; **L. S. Gensler**, AbbVie, Amgen, Janssen, Novartis, UCB, 5; **J. D. Reveille**, Janssen Research & Development, LLC., 9; **M. Weisman**, Bristol-Myers Squibb, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/do-tnf-inhibitors-change-the-progression-of-sacroiliitis

Abstract Number: 1675

Triptolide Inhibits Th17 Differentation By JAK2/STAT3 Signal Pathway in Inflammation of Ankylosing Spondylitis

Hongxiao Liu[1], Junyao Song[1], Ziqi Xu[1], Xinghua Feng[1], Quan Jiang[2] and YaNan Zhao[3], [1]Department of Rheumatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [2]Rheumatology Department, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China, [3]Department of Rheumatology, Guang'anmen Hospital, China Academy of Chinese Medical Sciences, BeiJing, China

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Spondylarthropathies Psoriatic Arthritis – Pathogenesis, Etiology - Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Th17 plays important role in pathogenesis of AS inflammation, and its main effector, IL-17, was the critical effector on mediating it. Activated of Th17 and IL-17 are both depending on JAK/STAT signal pathway. A cluster of recent papers identify Thunder God Vine as a powerful drug in AS treatment in China, in which Triptolide was demonstrated as the key ingredient in anti-inflammatory. This research aims to explore the role of Triptolide played in Th17 differentiation and AS inflammation by interfering the JAK/STAT.

Methods: 30 AS patients (18-50years) in active stage and 15 healthy controls (18-50years) participated in the experiments. All patients were met with the modified New York criteria(Bath Disease Activity Score>4). PBMCs generated from patients were cultivate with different concentrations of Triptolide for 24 hours (High: 50ng/ml; Medium: 25ng/ml; Low: 12.5ng/ml). The supernate level of IL-17 was detected by ELISA, the protein levels of JAK2/STAT3 signal pathway were detected by Western blotting, and the mRNA level of RORc was detected by quantitative PCR (qPCR).

Results: Compared with controls, the protein expression level of pJak2,pSata3,RORc was higher in AS groups than in normal ones(**p<0.001£©. After the intervention of the triptolide, protein expression level of pJak2,pSata3,RORc was lower than in AS groups.(#p<0.05). (Figure1)

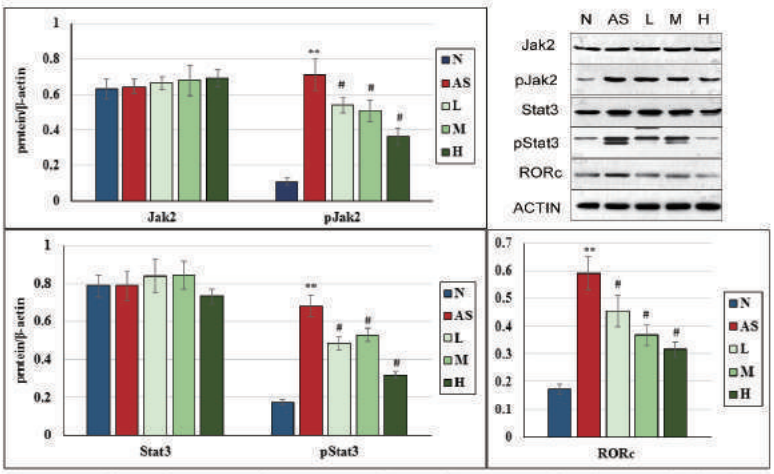

Figure1 Effect of the level of Jak2,pJak2,Stat3,pStat3 and RORc in PBMC of active AS patients after taking triptolide

It showed that protein expression level and phosphorylation level of pJak2,pSata3,RORc was higher in AS groups than in normal ones(**p<0.001). After the intervention of the triptolide,protein expression level and phosphorylation level of pJak2,pSata3,RORc was lower than in AS groups.(#p<0.05).

The transcriptional level of RORc mRNA was higher in AS groups than normal (**p<0.001£©.After the intervention of the triptolide, the transcriptional level of RORc mRNA was lower than in AS groups.(#p<0.05) (Figure2).

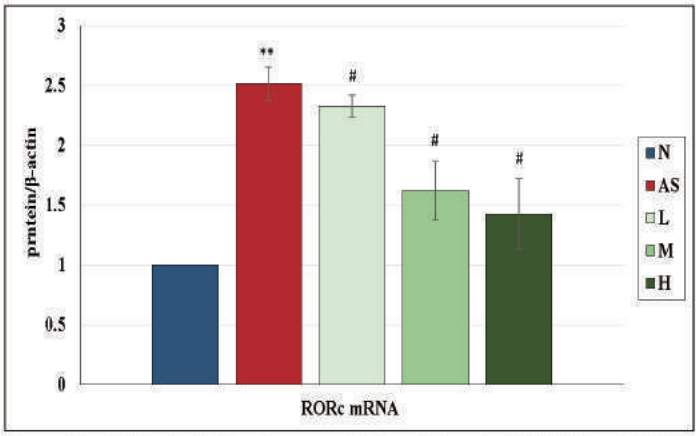

Figure2 Effect of the transcriptional level of RORc mRNA in PBMC of active AS patients after taking triptolide

It showed that the transcriptional level of RORc mRNA was higher in AS groups than in normal ones(**p＜0.001）.After the intervention of the triptolide,the transcriptional level of RORc mRNA was lower than in AS groups.(#p＜0.05).

The level of IL-17 in active AS patients was higher than normal; (**p<0.001);after the intervention of the triptolide,the levels of IL-17 was lower than AS groups .

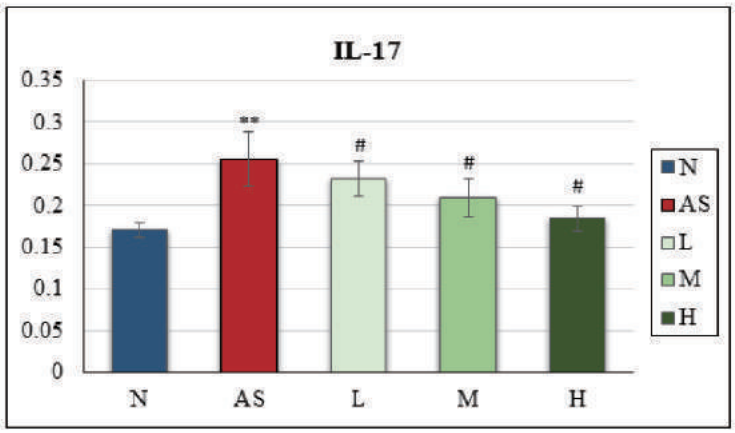

Figure3 Effect of the level of IL-17 in active AS patients after taking triptolide

It showed that the level of IL-17 was higher in AS groups than in normal ones(**p＜0.001）.After the intervention of the triptolide,the level of IL-17 was lower than in AS groups.(#p＜0.05).

(#p<0.05) (Figure3).

Conclusion: Our findings showed the suppression of activated JAK2/STAT3 signal pathway and the depression of pJAK2 and pSTAT3 expression by Triptolide. It might be one of the inhibitive factor modulate RORc transcription on one hand, and could be an depressor in IL-17 secretion directly on another. Which suggesting Triptolide may probably regulates Th17 differentiation through JAK2/STAT3 signal pathway. That¡¯s one of molecular mechanism which it plays in relieving AS inflammation. These exciting findings have broad implications for the inhibitor of JAK/STAT signal pathway in AS targeted therapy.

Disclosure: H. Liu, None; **J. Song**, None; **Z. Xu**, None; **X. Feng**, None; **Q. Jiang**, None; **Y. Zhao**, None.

Abstract Number: 1676

Methotrexate and Anti-Tumor Necrosis Treatment Improve Endothelial Function in Patients with Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis

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Background/Purpose: Inflammatory rheumatic diseases (IRDs) are associated with accelerated atherosclerosis, which progression is related to inflammation (1). One of the first stages in atherogenesis is endothelial dysfunction (ED). Therefore, we aimed to examine the effects of methotrexate (MTX) and anti-tumor necrosis factor (anti-TNF) treatment (with or without MTX co-medication) on endothelial function (EF) in rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

Methods: From the data registry from PSARA (2) (an observational study), we evaluated patients with RA (n=64), PsA (n=30) and AS (n=20) who completed a 6 month follow-up after initiation of anti-rheumatic therapy due to active disease. Only patients with clinical indication of either MTX monotherapy or anti-TNF with or without MTX co-medication (anti-TNF±MTX) were included. Among patients with peripheral arthritis (i.e., all RA and PsA patients), all patients starting on anti-TNF therapy had been previously unsuccessfully treated with MTX, while in patients with axial affection only (i.e., all AS), anti-TNF could be used as the first as well as later disease modifying anti-rheumatic treatment. EF was assessed by finger plethysmography (RH-PAT): Reactive hyperemia index (RHI) <1.67 was considered as ED. In patients with ED at baseline (n=39), we searched for change in EF after 6 weeks and 6 months of anti-rheumatic therapy.

Results: In all IRD patients with ED, RHI improved from baseline to 6 weeks (mean change=0.56, $p<0.005$) and 6 months (mean change=0.46, $p<0.005$). RHI improved at 6 weeks and 6 months in all three diagnoses, but the differences were statistically significant only for RA at 6 weeks and 6 months, and for PsA at 6weeks, with the greatest improvements in RA. The effect of MTX and anti-TNF±MTX at 6 weeks was similar. However, at 6 months, RHI improved more in the MTX group than in the anti-TNF±MTX group (mean change 0.74 vs. 0.24; $p=0.010$), and this difference remained statistically significant after adjustments for potential confounders including traditional cardiovascular risk factors and markers of disease activity.

Conclusion: Treatment with MTX and anti-TNF±MTX appears to relatively fast improve EF in IRD patients with ED, independently of improvement in disease activity. After 6 months, the EF improvement was more pronounced in the MTX users than in the anti TNF±MTX users. Among other factors, this might be due to a better effect of MTX on the vasculature,

or due to different patient populations. For example, RA and SpA patients starting with anti-TNF were more likely to have a longer and therapy resistant disease than patients starting with MTX.

Disclosure: G. Deyab, None; **I. Hokstad**, None; **S. Agewall**, None; **T. Lyberg**, None; **J. E. Whist**, None; **M. Cvancarova Småstuen**, None; **G. Hjeltnes**, None; **I. Hollan**, None.

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Abstract Number: 1677

Serum Complement C3 Component As a Potential Disease Activity Marker in Psoriatic Arthritis

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Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis that occurs in a subgroup of patients suffering from psoriasis. Assessment of PsA disease activity currently mainly rely on clinical examination of the patient, global scales of pain and activity, and the health assessment questionnaire. However, as in other inflammatory arthritides, there is a scarcity of biomarkers for disease activity, with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) being relatively unspecific and within normal limits in many occasions. Serum complement C3 component has recently been suggested as a potential biomarker for disease activity in PsA. **Objective:** To explore the association of complement C3 component with disease activity in PsA.

Methods: We included 36 outpatients fulfilling the CASPAR classification criteria for PsA in our study. Patients were examined at baseline (n = 36), at week 12 (n = 22), and at week 24 (n = 13). Additionally to routine medical examinations, each patient received a full workup including patients and physicians global assessment (VAS), amount of pain (VAS), 66/68 joint count, skin involvement (% of body surface area), enthesitis assessment (Leeds Enthesitis Index), dactylitis count, the SF-36 questionnaire and a blood examination (white blood count, CRP, ESR, Complement C3c, Complement C4). As a surrogate marker for disease activity measurement we calculated the Psoriatic ArthritiS Disease Activity Score (PASDAS). C3c and C4 complement were measured by nephelometry out of heparin-plasma samples of the patient. We performed correlation analysis of the C3c and C4 components with individual markers of disease activity (see above) and then performed unvariable and adjusted regression analysis on the PASDAS. The statistical analysis was conducted using SPSS statistics.

Results: Pearson's correlation showed a significant linear correlation of C3c ($p = 0.001$, $r = 0.372$) and C4 ($p = 0.048$, $r = 0.236$) with the patients PASDAS (see table for individual associations of PsA manifestations). In regression analysis, after correction for age, BMI and duration of disease, the correlation of C3c and PASDAS remained significant ($p = 0.004$, R squared = 0.155), while there was no statistical significance in the correlation of C4 and PASDAS.

Conclusion: In this pilot study in patients with PSA, we observed a significant and independent association of serum C3c with overall disease activity (PASDAS). Looking at individual measures of PsA manifestations, associations for serum C3c were seen for patient global assessment, physicians global assessment, swollen joint count, skin involvement, ESR, CRP and SF-36 physical component score. These findings warrant further investigation of the usefulness of C3c complement component in disease activity monitoring of PsA.

	Serum C3c		Serum C4	
	p	r	p	r
PASDAS	0.001 **	0.372	0.048 *	0.236
Pain (VAS)	0.220	0.065	0.029 *	0.259
Patient Global (VAS)	0.002 **	0.356	0.113	0.190
Physicians Global (VAS)	0.002 **	0.368	0.041 *	0.243
Tender Joints (0-68)	0.488	0.084	0.483	0.085
Swollen Joints (0-66)	0.004 **	0.336	0.319	0.120
Skin involvement (BSA)	0.009 **	0.307	0.767	0.036
ESR	> 0.001 **	0.412	0.346	0.113
CRP	0.002 **	0.370	0.239	0.142
SF-36 PCS ¤	0.033 *	-0.253	0.086	-0.205

Pearson's correlations of C3c and C4 with PASDAS and individual measures of PsA manifestations

¤ Short-Form 36 Questionnaire - Physical Component Score

Disclosure: A. Kerschbaumer, None; **K. Fenzl**, None; **M. Weber**, None; **J. Resch**, None; **M. Kasper**, None; **D. Aletaha**, None; **L. Erlacher**, None.

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Abstract Number: 1678

JAK STAT Kinase Cascade Regulates the IL-23/IL-17 Cytokine Axis in Psoriatic Arthritis

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Background/Purpose: Aberrant activation of IL-23/IL-17 cytokine axis is a dominant pathology in the psoriatic disease. IL-23 regulates expansion/maintenance/functional maturation of Th17 cells. Th17 cells along with their signature cytokines IL-17 and IL-22 is now believed to play a critical role in the pathogenesis of psoriatic arthritis (PsA). Because Tyk2 and JAK2 is recruited to IL-23 receptor it is expected that JAK-STAT mediated signaling system is important in PsA. We hypothesized- (i) JAK STAT signaling system regulates the Th17 cells in PsA and (ii) that Tofacitinib an inhibitor of Jak-1,

Jak-2 and Jak-3 targets the Th17 cells by inhibiting the IL-23 induced JAK STAT signaling system.

Methods: • PBMC and synovial mononuclear cells (SFMC) from PSA patients (n=15) and PBMC from age/sex matched normal individuals (n=15) were collected • All patients had an active disease and were not on DMARDS or biologics • rIL-23 induced activated IL-17+ T cells were generated and evaluated as per our earlier reports (Raychaudhuri SP, et al. Mol Cell Biochem. 2012 ;359:419-29). • Cells were cultured with and without Tofacitinib (50nM) • Western blot studies were done to indentify Jak2/p-Jak2, Tyk2/p-Tyk2, stat3/p-stat3, stat4/p-stat4 in the sorted activated CD3+ T cells. • Hi-D FACS studies were done to identify the activated memory CD4+ CD11a+CD45RO+IL-17+ T cells and CD8+CD11a+CD45RO+IL-17+ T cells in SFMC/PBMC of PsA and PBMC of normal individuals.

Results: In both PsA and controls sorted activated CD3+ T cells in presence of IL-23 demonstrated activation of the following JAK-STAT signaling molecules: Jak2, Tyk2, and stat3 but stat4 activation was substantially weaker. Further we noticed Tofacitinib markedly inhibited phosphorylation of Jak2 and STAT-3 the signaling proteins induced by IL-23. HiD-FACS analysis of the activated CD3+T cells in PsA patients demonstrated that IL-23 induced marked upregulation of IL-17 in the memory T cells (CD11a+CD45RO+) (Fig 1). We noticed that SFMC and PBMC treated with rIL-23 in PsA patients had 30±4.5% and 18±3.8% activated memory CD4+IL-17+ T cells respectively compared to 5± 0.7% in healthy persons ($p<0.001\%$). Further we noticed that CD4+ CD11a+CD45RO+IL-17+ T cells were 5±2% ($p<0.001\%$) (Fig 1) in cells treated with Tofacitinib. Tofacitinib significantly inhibited proliferation of these CD4+CD11a+CD45RO+IL-17+ T cells ($p<0.01\%$) (Fig 1).

Conclusion: · In PsA the key immune response that is the generation of the pathologic CD4+ CD11a+CD45RO+IL-17+ T cells and their proliferation is regulated by the JAK-STAT signaling system. · JAK STAT signaling regulates the Th17 cells in PsA and this may be one of the mechanisms of action of Tofacitinib. These observations provide new insight about the disease process of PsA and its management.

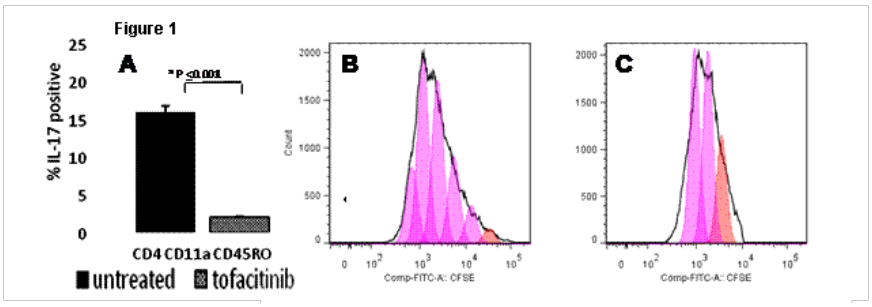

Figure 1. **A.** HiD FACS studies of the PBMC from active ankylosing spondylitis patients demonstrated that- (i) rIL-23 induced marked upregulation of IL-17 in the memory T cells (CD11a+CD45RO+) and that (ii) **rIL-23 induced IL-17 expression could be markedly inhibited by** Tofacitinib ($p<0.001$). **B and C.** CFSE dilution study demonstrated less number of generations and less numbers of CD4+ CD11a+CD45RO+IL-17+ T cells on day 5 in PBMC cultured with tofacitinib (C) compared to cells cultured without Tofacitinib (B).

Disclosure: S. P. Raychaudhuri, None; **S. K. Raychaudhuri**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/jak-stat-kinase-cascade-regulates-the-il-23il-17-cytokine-axis-in-psoriatic-arthritis

Abstract Number: 1679

Predictors of Persistency with TNFi in Biologic-Experienced Versus Biologic-Naive Psa Patients Enrolled in the Corrona Registry

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Economics, Amgen, Thousand Oaks, CA, [6]Wade Outcomes Research and Consulting, Salt Lake City, UT, [7]Corrona, LLC, Southborough, MA, [8]UMass Medical School, Worcester, MA
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Session Time: 9:00AM-11:00AM

Background/Purpose: Little is known about factors associated with persistency of TNFi use among biologic-naïve and biologic-experienced Psoriatic Arthritis (PsA) patients in routine clinical practice in the US. The purpose of this analysis/study is to identify predictors of persistence with TNFi in biologic naïve (bio-naïve) and biologic experienced (bio-experienced) TNFi initiators in the US Corrona registry.

Methods: We identified all PsA patients initiating a TNFi with at least 1 follow-up rheumatology visit from October 2002 to March 2013. Patients were followed until the earliest of: discontinuation of the TNFi, initiation of another biologic/small molecule therapy or last follow-up visit; such that patients who remained on original TNFi were defined as persistent and patients that discontinued or switched TNFi were defined as non-persistent. Patient demographic and clinical characteristics at index date (TNFi initiation) were evaluated. Kaplan-Meier curves evaluated time to discontinuation/switch of TNFi, with censoring for all patients with ≥ 1year gap between visits. The log rank test assessed differences in persistency between bio-naïve versus bio-experienced patients. Cox proportional hazards models (allowing for factors to vary over time [time varying]) were performed to identify predictors of persistency, controlling for potential confounders; models were completed, separately, for the bio-naïve and bio-experienced subgroups.

Results: A total of 1241 patients initiated a TNFi during the study period (at initiation 549 [44%] bio-naïve; 692 [56%] bio-experienced). Median time to discontinuation was 32 months (95% CI 27-37) in bio-naïve patients and 23 (95% CI 18-29) in bio-experienced TNFi initiators which was significantly different based on the log rank test. Moderate or high disease activity based on Clinical Disease Activity Index (CDAI) was associated with being non-persistent within both subgroups, although the level of effect appeared stronger in bio-naïve PsA patients (Table). Bio-naïve patients with higher comorbidity burden had a higher, although not statistically significant, risk of being non-persistent. In contrast, bio-experienced patients with prior treatment with a conventional synthetic disease modifying anti-rheumatic drug (csDMARD) or higher degree of skin disease had higher risks of being non-persistent. Within both groups, patients with shorter disease duration were more likely to be persistent.

Covariates*	**Cox Proportional Hazards Models****	
	Biologic-Naïve **HR (95% CI)**	**Biologic-Experienced** **HR (95% CI)**
Modified Charlson comorbidity index***		
Presence of 1 comorbid condition (vs. none)	1.32 [0.81; 2.15]	0.84 [0.60; 1.19]
Presence of 2 or more comorbid conditions (vs. none)	2.50 [0.99; 6.29]	0.85 [0.47; 1.57]
PsA characteristics		
Disease duration	0.96 [0.92; 0.99]	0.99 [0.97; 1.00]
Prior treatment with a csDMARD	1.18 [0.78; 1.79]	1.40 [1.04; 1.89]
Concomitant prednisone use	1.42 [0.72; 2.83]	1.48 [0.99; 2.23]
Disease activity (time varying)		
Patient reported pain	1.00 [1.00; 1.01]	1.00 [0.99; 1.01]
Moderate disease activity (vs. LDA)	2.50 [1.47; 4.27]	1.62 [1.13; 2.32]
High disease activity (vs. LDA)	2.15 [1.11; 4.13]	1.60 [1.01; 2.53]
Physician global skin assessment	1.18 [0.74; 1.87]	1.38 [1.01; 1.87]

*PsA – psoriatic arthritis, LDA-low disease activity **Adjusted for female gender, race, age, BMI, and smoking status. ***Excludes PsA; dementia, kidney disease, hemiplegia and AIDS not included

Conclusion: Predictors of persistency differed in those who were bio-naïve versus bio-experienced when initiating TNFi.

Disease activity appeared to be a stronger predictor of non-persistence in those who were biologic-naïve as compared to those who were experienced.

Disclosure: C. Etzel, Corrona, LLC, 3,Merck, 9; **B. S. Stolshek**, Amgen, 1,Amgen, 3; **S. Rebello**, Corrona, LLC, 3; **D. Collier**, Amgen, 1,Amgen, 3; **A. Mutebi**, Amgen, 1,Amgen, 3; **S. W. Wade**, Amgen, 5; **W. Malley**, Corrona, LLC, 3; **J. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Janssen, Novartis and Pfizer, Eli Lilly, 5; **L. R. Harrold**, Corrona, LLC, 3,Pfizer Inc, 2,Roche, 5,Corrona, LLC, 1.

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Abstract Number: 1680

Apremilast Monotherapy As the First Systemic Treatment in DMARD-Naive Patients with Active Psoriatic Arthritis: 3-Year Treatment Results

Alvin F. Wells[1], Christopher J. Edwards[2,3], Alan J. Kivitz[4], Paul Bird[5], Dianne Nguyen[6], Kamal Shah[6], Lichen Teng[6] and Jacob A Aelion[7], [1]Rheumatology and Immunotherapy Center, Franklin, WI, [2]University of Southampton, Southampton, United Kingdom, [3]University Hospital Southampton, Southampton, United Kingdom, [4]Altoona Center for Clinical Research, Duncansville, PA, [5]Combined Rheumatology Practice, Kogarah, Australia, [6]Celgene Corporation, Summit, NJ, [7]West Tennessee Research Institute, Jackson, TN

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Session Time: 9:00AM-11:00AM

Background/Purpose: Apremilast (APR) is an oral phosphodiesterase 4 inhibitor that helps regulate the immune response that causes joint inflammation and other manifestations of psoriatic arthritis (PsA), including skin disease. Primary findings from the PALACE 4 study (NCT01307423) demonstrated greater efficacy with APR vs. placebo in disease-modifying antirheumatic drug (DMARD)-naïve patients with active PsA.[1,2] We describe the long-term efficacy and safety of APR monotherapy in DMARD-naïve patients in PALACE 4 for up to 156 weeks.

Methods: Patients were randomized (1:1:1) to placebo, APR 30 mg BID (APR30), or APR 20 mg BID (APR20). Patients whose swollen and tender joint counts (SJC and TJC) had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to APR30 or APR20 if they were initially randomized to placebo, or continued on their initial APR dose. At Week 24, all patients remaining on placebo were re-randomized to APR30 or APR20. Double-blind treatment continued to Week 52 with open-label APR for up to 4 additional years.

Results: A total of 527 patients were randomized and received ≥1 dose of placebo (n=176), APR30 (n=176), or APR20 (n=175). Of the patients entering the third year of therapy, 88.0% (272/309) completed the Week 156 visit. At Week 52, 58.0% (119/205) of patients receiving APR30 and 55.4% (107/193) receiving APR20 achieved a 20% improvement in modified American College of Rheumatology (ACR20) response (Table). At Week 156, rates of improvement in PsA signs and symptoms and physical function were sustained, as shown by modified ACR20/ACR50/ACR70 responses, mean percent change in SJC/TJC, mean change in Health Assessment Questionnaire-Disability Index (HAQ-DI) score, proportion of patients with HAQ-DI exceeding the minimal clinically important difference (MCID) ≥0.30 threshold, achievement of Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) of 0 and dactylitis count of 0, and 75% and 50% reduction from baseline Psoriasis Area and Severity Index (PASI-75 and PASI-50) responses (Table). During Weeks >104 to ≤156, the most common adverse events (AEs) among APR-exposed patients were upper respiratory tract infection (3.2%) and nasopharyngitis (3.9%); serious AEs occurred in 5.2% of APR patients, and no opportunistic infections occurred. In

general, no change in the types of AEs and no increase in the incidence and severity of AEs were seen with longer-term exposure.

Conclusion: Over 156 weeks, APR monotherapy demonstrated sustained response and improvements in PsA signs and symptoms, including SJC, TJC, enthesitis, dactylitis, physical function, and psoriasis. APR continued to demonstrate an acceptable safety profile and was generally well tolerated. **References:** 1. Edwards et al. *Arthritis Rheum.* 2014;66(11 Suppl)S694-5. Abstract 1572. 2. Wells et al. *Arthritis Rheum.* 2014;66(11 Suppl)S264-5. Abstract 602.

	Outcomes at Weeks 52 and 156			
	Week 52		Week 156	
	APR30 n=207*	APR20 n=194*	APR30 n=143*	APR20 n=133*
ACR20, n/m§ (%)	119/205 (58.0)	107/193 (55.4)	84/141 (59.6)	79/131 (60.3)
ACR50, n/m§ (%)	61/205 (29.8)	54/191 (28.3)	50/141 (35.5)	51/131 (38.9)
ACR70, n/m§ (%)	32/206 (15.5)	23/192 (12.0)	33/143 (23.1)	26/130 (20.0)
SJC, mean % change	−76.1	−70.5	−84.3	−78.1
TJC, mean % change	−59.4	−52.4	−65.7	−63.6
HAQ-DI (0-3), mean change	−0.35	−0.28	−0.38	−0.35
HAQ-DI MCID ≥0.30‡, n/m (%)	98/207 (47.3)	89/194 (45.9)	69/143 (48.3)	66/133 (49.6)
MASES of 0, n/m (%)‖	65/127 (51.2)	52/132 (39.4)	50/79 (63.3)	55/91 (60.4)
Dactylitis count of 0, n/m (%)¶	74/102 (72.5)	72/102 (70.6)	60/71 (84.5)	65/73 (89.0)
PASI-75, n/m (%)#	34/119 (28.6)	42/112 (37.5)	32/82 (39.0)	33/77 (42.9)
PASI-50, n/m (%)#	64/119 (53.8)	65/112 (58.0)	46/82 (56.1)	46/77 (59.7)

Data as observed. n/m=number of responders/number of patients with sufficient data for evaluation.
*The n reflects the number of patients treated with APR30 and APR20 regardless of when patients started taking APR (baseline, Week 16, or Week 24) and who had data available at the specific time point; actual number of patients available for each end point may vary. §Denominators vary slightly due to availability of sufficient data for each level of ACR response assessment. ‡Pre-specified MCID threshold, based on the literature (Mease PJ, et al. *Ann Rheum Dis.* 2004;63[Suppl 1]:391) at the time of protocol development and definition of analysis. ‖Examined among patients with enthesitis at baseline and data at the specific time point. Mean MASES at baseline were 3.5 (APR30) and 4.1 (APR20). ¶Examined among patients with dactylitis at baseline and data at the specific time point. Dactylitis mean counts at baseline were 3.6 (APR30) and 3.1 (APR20). #Examined among patients with psoriasis involvement of the body surface area ≥3% at baseline and data at the specific time point.

Disclosure: A. F. Wells, Celgene Corporation, 2; **C. J. Edwards**, Celgene Corporation, Pfizer, Roche, Samsung, 2,Celgene Corporation, Pfizer, Roche, Samsung, 5,Abbott, GSK, Pfizer, Roche, 8; **A. J. Kivitz**, Celgene Corporation, 5,Celgene Corporation, 8; **P. Bird**, Celgene Corporation, 2; **D. Nguyen**, Celgene Corporation, 3; **K. Shah**, Celgene Corporation, 3; **L. Teng**, Celgene Corporation, 3; **J. A. Aelion**, Abbvie, Boehringer, Celgene Corporation, Janssen, 5,Abbvie, Amgen, Boehringer, Celgene Corporation, Janssen, UCB, 2,UCB, 8.

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Abstract Number: 1681

Beneficial Effect of n-3 Polyunsaturated Fatty Acids on Inflammation and Analgesic Use in Psoriatic Arthritis – a Randomised, Double Blind, Placebo-Controlled Trial

Salome Kristensen[1], Erik Berg Schmidt[2], Annette Schlemmer[3], Claus Rasmussen[4], Martin Berg Johansen[5] and Jeppe Hagstrup Christensen[6], [1]The DANBIO registry and the Danish Departments of Rheumatology, Copenhagen, Denmark, [2]Cardiology, Aalborg University Hospital, Aalborg, Denmark, [3]9Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark, [4]Rheumatology, North Denmark Regional Hospital/Aalborg University, Hjoerring, Denmark, [5]5Department of Cardiology and Unit of Clinical Biostatistics and Bioinformatics, Aalborg University Hospital, Aalborg, Denmark, [6]Nephrology, Aalborg University Hospital, Aalborg, Denmark

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster II: Psoriatic Arthritis

Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Marine n-3 polyunsaturated fatty acids (PUFA) have anti-inflammatory effects and may be useful in the treatment of psoriatic arthritis. The effects of n-3 PUFA on inflammatory parameters and use of analgesics were examined in patients with psoriatic arthritis.

Methods: Patients with established psoriatic arthritis were included in this randomized, double blind, placebo-controlled study. Patients received the capsules of 3 g n-3 PUFA/d or 3 g olive oil/d for a 24-week period. Clinical status and use of analgesics were assessed as well as leukotriene formation were quantified at baseline and study end.

Results: One hundred and forty-five patients were randomised and 133 completed the study. After 24 weeks of supplementation participants in the n-3 PUFA group showed a significantly higher formation of leukotriene B_5 ($p < 0.001$) and 5-HEPE ($p < 0.001$) and a significantly lower formation of leukotriene B_4 ($p = 0.004$) compared to controls. Nonsteroidal anti-inflammatory drugs and paracetamol consumption was significantly reduced in the n-3 supplemented group compared to controls (p = 0.04). The n-3 PUFA group also had a significant reduction in disease activity score, tender joint count, enthesitis score and psoriasis area and severity index.

Conclusion: The present study, demonstrated a reduction in the formation of the inflammatory leukotriene B_4, increase in the less inflammatory leukotriene B_5 and reduction in use of nonsteroidal anti-inflammatory drugs and paracetamol after 24 weeks of n-3 PUFA supplementation. The results suggest that n-3 PUFA supplementation is an attractive adjunctive treatment for patients with psoriatic arthritis. Trial registration: NCT01818804

Disclosure: S. Kristensen, The Danish Psoriasis Foundation, 2,The Danish Rheumatism Association, 2,The Aage Bang Foundation, 2,Heinrich Kopps Foundation, 2,Abbvie Foundation, 2,Jacob Madsen and wife Olga Madsen Foundation, 2; **E. B. Schmidt**, None; **A. Schlemmer**, None; **C. Rasmussen**, None; **M. B. Johansen**, None; **J. H. Christensen**, None.

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Abstract Number: 1682

Tnfα Inhibitors Are Associated with Reduced Progression of Carotid Atherosclerotic Plaques By Ultrasound and an Improvement in Aortic Arch Vascular Inflammation By 18-FDG PET/CT in Psoriasis and Psoriatic Arthritis Patients – a Prospective Study from Two Cohorts

Lihi Eder[1], Aditya Joshi[2], Vinod Chandran[3], Amit Dey[4], Richard J. Cook[5], Abhishek Chaturvedi[6], Dafna D. Gladman[7] and Nehal Mehta[8], [1]Medicine, University of Toronto, Women's College Hospital, Toronto, ON, Canada, [2]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, [3]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [4]National Institutes of Health, Bethesda, MD, [5]Department of Statistics and Actuarial Science, University of Waterloo, Waterloo, ON, Canada, [6]National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, MD, [7]Rheumatology, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [8]National Heart, Lung and Blood Institute, National Institutes of Health, Bethesda, MD

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SESSION INFORMATION
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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriasis (PSO) and psoriatic arthritis (PsA) are chronic inflammatory diseases which are associated with increased cardiovascular (CV) diseases. Observational studies have found that TNFα inhibitors (TNFi) are associated with reduced CV events in PSO, however, the impact of TNFi on subclinical indices of CV disease has not been assessed prospectively.

Methods: We performed a two-stage study to understand the effect of TNFi on subclinical CV disease. We first assessed carotid plaque area by ultrasound in PSO and PsA patients (n=319, 66.4% PsA and 33.6% PSO only), who underwent baseline evaluation and follow-ups every 6-12 months, including assessment for CV risk, joint and skin disease and medications. Patients using biologic agents other than TNFi were excluded. Carotid arteries were assessed by ultrasound to measure total plaque area (TPA) at baseline and after 2-3 years. The average annual progression rate (APR) of atherosclerosis [(Follow-up TPA – baseline TPA)/ total years between visits] was the outcome of interest. Due to a statistically significant interaction between sex and TNFi therapy, we assessed APR for men and women separately. The findings from stage 1 led us to create an inception cohort to assess TNFi effect on vascular inflammation in PsA. In stage 2 we studied vascular inflammation using FDG PET/CT in PsA patients on TNFi (n=21) and age and sex matched PsA patients not on any biologics (n=13). This sample underwent clinical phenotyping and FDG PET/CT scans at baseline and 1 year to assess vascular inflammation, measured as target-to-background ratio (TBR). In both studies, statistical analyses included multivariable regression adjusting for CV risk factors and statins, and performing sex-TNFi therapy interaction.

Results: In the first stage, of the 319 patients 56.3% were men and the mean age was 54.5. 61.7% of the patients had at least one carotid plaque at baseline. At follow-up (mean duration 2.9 years), TPA progressed in 46% patients. There was no difference in TPA progression between PsA and PSO (p=0.73). Men had a significantly higher APR compared to women (2.4 vs. 0.6 mm^2, p<0.001). TNFi associated with a reduced APR (β=-2.25, 95% CI -3.45, -1.05, p<0.001) in men, beyond traditional CV risk, statins and DMARDs. However, there was no association between TNFi and APR in women (p=0.71). In the second stage, the mean age was 52 (52% men) with moderate to severe vascular inflammation by FDG PET/CT (average TBR 1.89). At 1 year, patients on TNFi had a reduction in TBR (mean±SEM 1.9±0.06 vs. 1.76±0.05, p=0.03), despite no major change in CV risk factors. However, those not on TNFi had no significant change in their TBR (1.86±0.06 vs. 1.89±0.07, p=0.32) and no difference between men and women was observed by TNFi treatment.

Conclusion: TNFi treatment was associated with reduced progression of carotid plaque and an improvement in vascular inflammation in a large two-stage study of PSO and PsA. This association was stronger in men than women suggesting a role for gender in CV disease progression. Our findings support the importance of TNFi treatment in potentially reducing CV risk; however, large randomized trials are needed to confirm these findings.

Disclosure: L. Eder, None; **A. Joshi**, None; **V. Chandran**, None; **A. Dey**, None; **R. J. Cook**, None; **A. Chaturvedi**, None; **D. D. Gladman**, None; **N. Mehta**, None.

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Abstract Number: 1683

Influence of Axial Involvement on Clinical Characteristics of Psoriatic Arthritis—Descriptive Analysis from the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

Philip J Mease[1], Chitra Karki[2], Mei Liu[2], Arthur Kavanaugh[3], Renganayaki Pandurengan[2], Christopher T. Ritchlin[4], Jacqueline B. Palmer[5] and Jeffrey D. Greenberg[2,6], [1]Swedish Medical Center and University of Washington, Seattle, WA, [2]Corrona, LLC, Southborough, MA, [3]University of California San Diego, La Jolla, CA, [4]Allergy, Immunology and

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster II: Psoriatic Arthritis
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Session Time: 9:00AM-11:00AM

Background/Purpose: Although spinal involvement has been well studied in ankylosing spondylitis,[1] very few studies in psoriatic arthritis (PsA) have characterized patients with axial involvement. The objective of this analysis was to understand the prevalence and describe the baseline characteristics of PsA patients with and without axial involvement in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) registry.

Methods: This cross-sectional descriptive study included all patients with PsA enrolled in the Corrona PsA/SpA registry between March 2013 and March 2016 with non-missing data on axial involvement, defined as having a physician-reported presence of spinal involvement at enrollment, or an MRI or x-ray showing sacroiliitis. Descriptive analyses of patient demographics, clinical measures, patient-reported outcomes and treatment characteristics were reported at the time of enrollment for patients with vs without axial involvement. Statistical comparisons between subgroups were evaluated using *P* values from *t*-tests for continuous variables and chi-squared tests for categorical variables.

Results: As of March 2016, there were a total of 1530 patients with PsA in the Corrona PsA/SpA registry who had non-missing data on physician-reported axial involvement, including 192 patients (12.5%) with axial involvement and 1338 patients (87.5%) without axial involvement. Both subgroups were similar with regards to sex, race, body mass index, disease duration, overall presence of dactylitis and prevalence of most comorbidities (e.g., cardiovascular disease, any cancer, diabetes and serious infection). However, patients with axial involvement were younger (50.4 vs 54.4 years) and significantly more likely to have enthesitis (20.7% vs 19.2%), a history of depression (22.9% vs 12.6%) and biologic use (66.1% vs 54.3%) at enrollment compared to patients without axial involvement. Patients with axial involvement were also more likely to have moderate/severe psoriasis (body surface area > 3%) at enrollment compared with patients without axial involvement, and had worse disease as measured by nail psoriasis, enthesitis counts, achievement of minimal disease activity, AS disease activity and functional index scores, C-reactive protein levels and patient-reported outcomes (**Table**).

Conclusion: Data from the Corrona PsA/SpA registry showed that patients with PsA and axial involvement were more likely to have moderate/severe psoriasis with significantly higher disease activity at the time of registry enrollment compared to those without axial involvement. These findings demonstrate the overall impact of axial involvement on disease activity and highlight the importance of monitoring patients with PsA for signs of axial symptoms or spinal involvement on imaging.

References:

1. Braun A, et al. *Ann Rheum Dis*. 2011;70(10):1782-7.

Disclosure: P. J. Mease, Celgene, Novartis, AbbVie, Amgen, BMS, Lilly, Pfizer and UCB, 2,Celgene, Corrona, Novartis, AbbVie, Amgen, BMS, Crescendo, Genentech, Janssen, Lilly, Merck, Pfizer and UCB, 5,AbbVie, Amgen, BMS, Crescendo, Celgene, Genentech, Janssen, Pfizer and UCB, 8; **C. Karki**, Corrona, LLC, 3; **M. Liu**, Corrona, LLC, 3; **A. Kavanaugh**, Amgen, AbbVie, Janssen, Pfizer and Novartis, 2; **R. Pandurengan**, Corrona, LLC, 3; **C. T. Ritchlin**, Amgen, Janssen Pharmaceutica Product, L.P., and UCB, 2,AbbVie, Amgen, Janssen Pharmaceutica Product, L.P., Regeneron, and UCB, 5; **J. B. Palmer**, Novartis Pharmaceuticals Corporation, 3; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,Eli Lilly, Genentech, Janssen, Novartis and Pfizer, 5.

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Abstract Number: 1684

Updated Results for Serious Infections in Psoriasis Patients with Psoriatic Arthritis in the Psoriasis Longitudinal Assessment and Registry Study

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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: To describe the rates of serious infections (SI) in psoriasis (PsO) pts with psoriatic arthritis (PsA) from PSOLAR, & assess risk with biologic therapy.

Methods: PSOLAR, an international, disease-based, observational study in which pts eligible for, or receiving conventional systemic & biologic agents for PsO are followed prospectively. Characteristics&cumulative incidence rates of SIs occurring within 91 days of biologic administration, for pts who reported PsA, including a subset with PsA confirmed by a joint-specialist are summarized. Cohorts were defined as & attribution was based on treatment exposure in the following order(regardless of sequence & duration):(1) ustekinumab (UST) (2)other sponsor biologic (primarily infliximab [IFX]) (3)non-sponsor biologic (primarily adalimumab/etanercept [ADA/ETN]),&(4)non-biologic therapies(NB) (including immunodulators(IMMs)[eg MTX, cyclosporine], phototherapy,&topical therapy). Exposure to any therapy higher in the order precluded inclusion in the lower cohorts. Multivariate analyses using Cox hazard regression were used to identify factors, including treatments, associated with time to first SI(using exposure within 91 days for biologics vs no biologic use]&for IMMs vs no IMM use]),without use of attribution rules.

Results: As of Aug 23, 2015, PSOLAR was fully enrolled with 12090 pts(48870 total pt-yrs [PY] of follow-up).Number of pts with reported PsA was overall 4315: 1551 UST, 754 IFX, 1650 ADA/ETN, 360 NB; of these pts, 1719 had confirmed PsA(689 UST, 346 IFX, 566 ADA/ETN, 118 NB). Baseline demographics & medical history were generally balanced across cohorts & were comparable to confirmed PsA subset; however, in overall PsA sub-group, more pts in NB cohort were >65yrs of age (UST9.9%, IFX14.2%, ADA/ETN12.4% , NB26.4%) & had a medical history of significant infections(UST29%, IFX35.3%, ADA/ETN28.7%, NB21.7%).In the overall PsA subgroup(18 152 PY of follow-up), rates of SIs/100 PY were:UST1.29, IFX3.13, ADA/ETN2.47,&NB2.29. Among the confirmed PsA subset, rates/100 PY: UST 1.27, IFX 2.64, ADA/ETN 2.42, NB 1.95. In the overall PsA subgroup, age, smoking, history of significant infection, diabetes, & use of biologics other than UST(as a combined group) were associated($p<0.05$) with increased risk for SI, no increased risk was observed with UST or with IMMs.In pts with confirmed PsA, a history of significant infections&use of biologics other than UST(as a combined group) were significantly associated($p<0.05$) with increased infection risk;UST&IMMs were not associated.Inherent bias with respect to observational data may apply. Variability in size&clinical features was noted among treatment groups. Incidence rates are not adjusted for differences. Biologics other than UST were not evaluated individually in statistical analyses.

Conclusion: Unadjusted rates of SIs showed general agreement between the 2 PsA subsets with numerically higher rates for IFX&ADA/ETN. Although some variability was noted in risk factors for 2 PSA groups(overall&confirmed), a history of significant infection & use of biologics other than UST (as a combined group) were found to be associated with increased risk for SIs for both groups. An increased risk was not observed with IMMs in comparison with no IMMs in either PSA group. Similarly, an increased risk was not observed with UST individually or in combination with other biologics in either PsA group.

Disclosure: C. T. Ritchlin, Janssen Scientific Affairs, LLC, 9; **A. Menter**, Janssen Scientific Affairs, LLC, 9; **P. J. Mease**, Janssen Scientific Affairs, LLC, 9; **S. Kalia**, Janssen Scientific Affairs, LLC, 9; **F. Kerdel**, Janssen Scientific Affairs, LLC, 9; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **J. Morgan**, Janssen Scientific Affairs, LLC, 3; **W. Langholff**, JanssenResearch and Development, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **A. Gottlieb**, Janssen Scientific Affairs, LLC, 9.

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Abstract Number: 1685

Updated Results for All-Cause Mortality and Malignancies in Psoriasis Patients with Psoriatic Arthritis in the Psoriasis Longitudinal Assessment and Registry Study

Philip J Mease[1], Alice Gottlieb[2], Alan Menter[3], Christopher T. Ritchlin[4], Sunil Kalia[5], Francisco Kerdel[6], Shelly Kafka[7], Soumya Chakravarty[7], Wayne Langholff[8], Steve Fakharzadeh[7], Kavitha Goyal[7] and Jose U. Scher[9,10], [1]Swedish Medical

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SESSION INFORMATION

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Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: To describe characteristics & potential risk factors(including treatment exposure) for all-cause mortality & malignancies (excluding NMSC) in psoriasis (PsO) patients (pts) with psoriatic arthritis (PsA) from PSOLAR.

Methods: PSOLAR is an international, disease-based, observational study in which pts eligible for or receiving conventional systemic & biologic agents for PsO are followed prospectively. Characteristics & adverse events for pts who reported PsA, including a subset with PsA confirmed by a joint-specialist are summarized. For characteristics & incidence rates, the cohorts were defined as & attribution was based on treatment exposure prior to/during registry in the following order(regardless of sequence & duration):(1)ustekinumab(UST) (2)other sponsor biologic(primarily infliximab[IFX])(3)non-sponsor biologic(primarily adalimumab/etanercept [ADA/ETN]),&(4)non-biologic therapies(NB)(including immunomodulators(IMM)[eg.MTX], phototherapy&topical therapy). Exposure to any therapy higher in the order precluded inclusion in the lower cohorts. Multivariate analyses using Cox hazard regression(without attribution bias)were used to identify factors associated with time to first malignancy&mortality[compared to no biologic use]&for IMM [compared to no IMM use].

Results: As of Aug 23, 2015, PSOLAR is fully enrolled with 12090 pts(48870 total pt-yrs [PY] of follow-up). Overall, 4315 pts reported having PsA:1551 UST, 754 IFX, 1650 ADA/ETN, 360 NB;of these, 1719 had confirmed PsA(689 UST, 346 IFX, 566 ADA/ETN,118 NB). Baseline demographics & medical history were generally balanced across cohorts; however, in overall PsA subgroup, more pts in NB cohort were >65yrs of age&had a medical history of cancer. In overall PsA subgroup, cumulative incidence rates/100PY for all-cause mortality: UST0.34, IFX0.37, ADA/ETN0.57, NB0.75; in statistical analysis: age, history of cardiovascular disease, history of diabetes&smoking were associated with increased risk of mortality($P<0.05$). Cumulative incidence rates/100PY for malignancy:UST0.57, IFX0.71, ADA/ETN0.60,& NB0.96. Statistical analysis identified the following significant($p<0.05$) risk factors for malignancy:severity of PsO, age, smoking,&history of malignancy. For confirmed PsA subset, cumulative incidence rates/100PY for all-cause mortality: UST0.29, IFX0.37, ADA/ETN0.44, NB0.44; age & smoking were associated with increased risk of mortality, Cumulative incidence rates/100PY for malignancy: UST0.53, IFX0.66, ADA/ETN0.96, NB 1.10;age was the only significant factor associated with increased risk of malignancy($p=<0.05$). Inherent bias with observational data may apply. Variability in group size & clinical features was noted.Incidence rates are not adjusted for differences in demographics & disease characteristics (adjustment for such key factors are included in statistical analyses). Statistical analyses interpretation may be limited due to number of deaths in subset of confirmed PSA (24).

Conclusion: Unadjusted rates of all-cause mortality & malignancies for biologics were generally comparable among both PsA subsets with the exception of generally numerically higher rates in pts in NB cohort. The common risk factors associated with mortality for the overall & confirmed PsA subsets were age & smoking; age alone was the common risk factor associated with malignancy. Biologics & IMM use were not associated with increased risk of mortality or malignancy.

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Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **J. U. Scher**, Janssen Scientific Affairs, LLC, 2.

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Abstract Number: 1686

Association of Early Skin Improvement with ACR Responses Among Biologic DMARD-Naive Psoriatic Arthritic Patients Treated with Ixekizumab

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Background/Purpose: Ixekizumab (IXE) is a high-affinity monoclonal antibody that selectively targets interleukin-17A. In a phase 3 study, IXE was superior to placebo (PBO) in achieving ACR20 responses at Week (Wk) 24 in biologic DMARD-naïve (bDMARD-naïve) PsA patients[1]. The objective of this analysis was to explore the association of early skin improvement with ACR responses among IXE-treated patients with both PsA and psoriasis (Ps).

Methods: In a phase 3, multi-center, double-blind randomized trial (SPIRIT-P1; NCT01695239), 417 bDMARD-naïve patients with active PsA were randomized to receive up to 24 wks of treatment of PBO (N=106), adalimumab 40 mg (ADA; active reference arm) once every 2 wks (Q2W; N=101), or IXE 80 mg Q2W (N=103) or Q4W (N=107) following an 160 mg initial dose at Wk 0. In PsA patients with moderate-to-severe Ps (≥3% body surface area [BSA]), ACR and Psoriasis Area and Severity Index (PASI) responses were analyzed up to Wk 24. Patients were demarcated into the following categories based on percent improvement from baseline: PASI:<50, PASI:50 to <75, PASI:75 to <90, and PASI:90 to 100. Missing ACR and PASI responses were imputed using non-responder imputation (NRI) and last observation carried forward (LOCF) methods, respectively. Logistic regression model was utilized to compare ACR response across PASI improvement categories.

Results: Of the 417 PsA patients enrolled, 267 patients (69.5%) had ≥3% BSA at baseline. In IXE treated patients (Q2W and Q4W combined; N=132), patients with skin improvement of PASI≥50 at Wk 4 had greater ACR20/ACR50/ACR70 responses at Wk 24 than patients who had a PASI<50 response at Wk 4 (see Figures). Similar observations were made in patients with ≥10% BSA (data not shown). For IXE- and ADA-treated patients, greater PASI improvement by Wk 24 paralleled greater ACR responses at Wk 24 (See Figures; data not shown).

Conclusion: In PsA patients with moderate-to-severe Ps, greater improvement of psoriatic lesions at Wk 24 of biologic treatment was associated with greater reductions in PsA disease activity as assessed by ACR responses. In IXE treated patients, early PASI responses were predictive of ACR responses at Wk 24. 1. Mease et al. ACR/ARHP Annual Meeting 2015; [abstract 977]

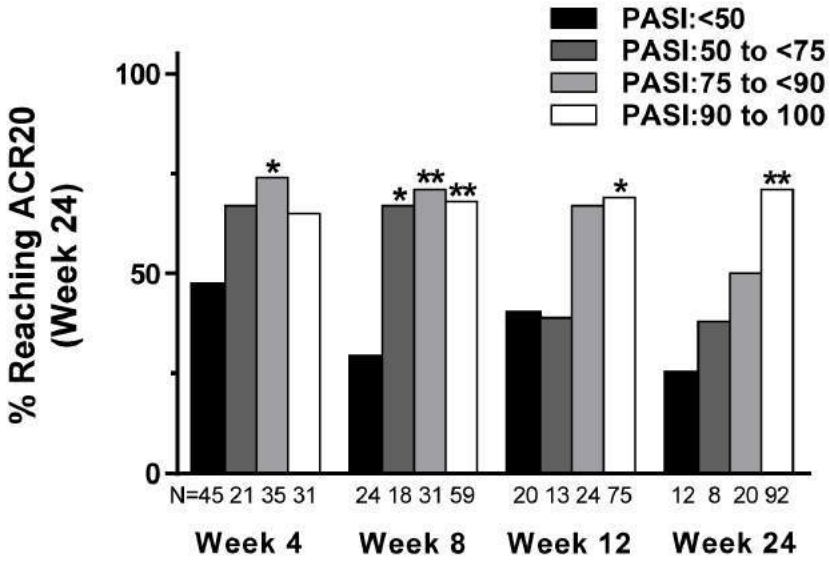

Figure 1. ACR20 response at Week 24 in IXE-treated patients with PsA (N=132) reaching designated PASI responses. ACR and PASI responses were imputed using NRI and LOCF, respectively.
N=Patients (from the ITT population with ≥3% BSA at baseline) reaching designated PASI response category.
*P<.05 versus PASI:<50 ACR response; **P<.01 versus PASI:<50 ACR response

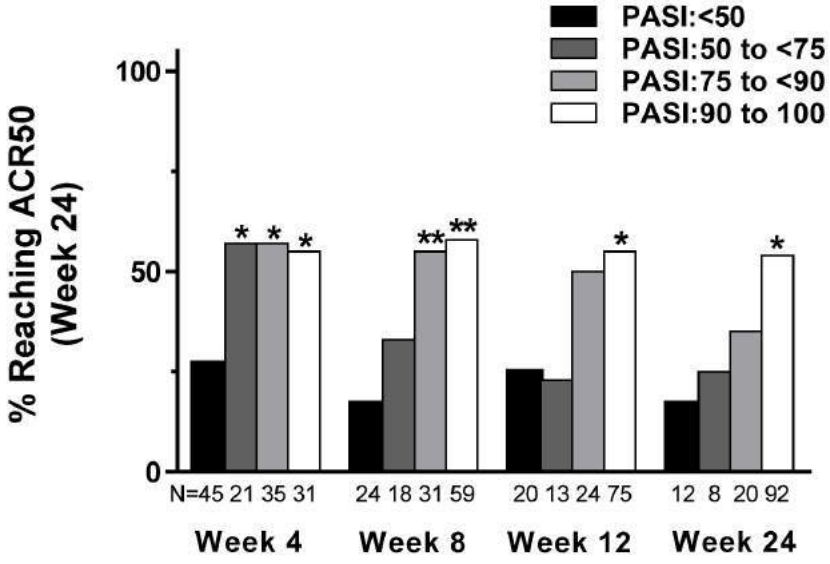

Figure 2. ACR50 response at Week 24 in IXE-treated patients with PsA (N=132) reaching designated PASI responses. ACR and PASI responses were imputed using NRI and LOCF, respectively.
N=Patients (≥3% BSA) reaching designated PASI response category
*P<.05 versus PASI:<50 ACR response; **P<.01 versus PASI:<50 ACR response

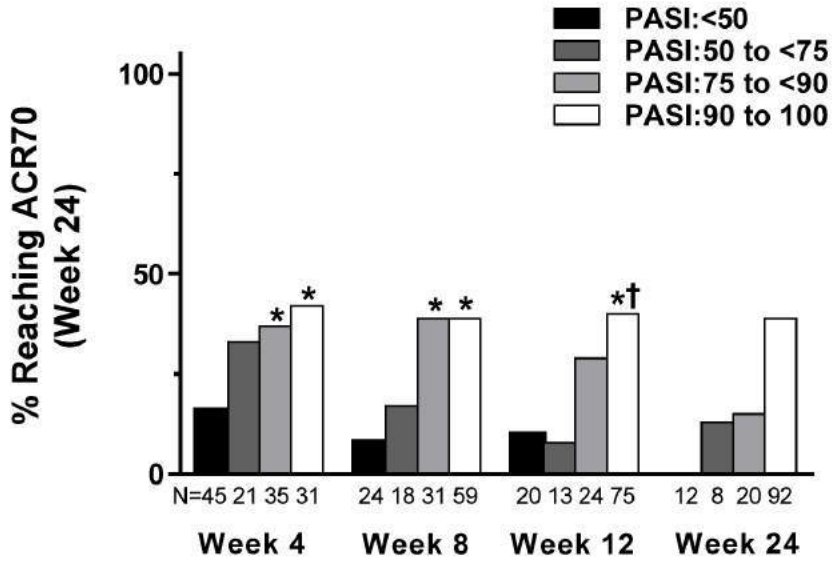

Figure 3. ACR70 response at Week 24 in IXE-treated patients with PsA (N=132) reaching designated PASI responses. ACR and PASI responses were imputed using NRI and LOCF, respectively.
N=Patients (≥3% BSA) reaching designated PASI response category
*P<.05 versus PASI:<50 ACR response; †P<.05 versus PASI:50 to <75 response

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Abstract Number: 1687

Effect of Concomitant Conventional Disease-Modifying Antirheumatic Drugs (DMARDs) on the Efficacy and Safety of Ixekizumab in Biologic DMARD-Naive Patients with Active Psoriatic Arthritis

Alice B. Gottlieb[1], Laura C. Coates[2], Catherine L. Shuler[3], Chen-Yen Lin[3], Susan R. Moriarty[3], Chin H. Lee[3] and Philip J Mease[4], [1]Tufts University School of Medicine, Boston, MA, [2]University of Leeds, Leeds, United Kingdom, [3]Eli Lilly and Company, Indianapolis, IN, [4]Rheumatology Research, Swedish Medical Center and University of Washington, Seattle, WA
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Background/Purpose: PsA is a chronic immune-mediated inflammatory disease associated with psoriasis, peripheral arthritis, enthesitis, dactylitis, and spondylitis. Ixekizumab (IXE) is an IgG4 mAb that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. Data are presented for the phase 3 trial (SPIRIT P1) with IXE treatment of patients (pts) with active PsA. The objective was to evaluate the efficacy and safety of IXE when used alone or in combination with concomitant conventional DMARDs (cDMARDs).

Methods: A total of 417 bDMARD-naive adult pts were randomly assigned 1:1:1:1 to subcutaneous administration of 80-mg IXE every 4 wks (Q4W) or every 2 wks (Q2W), each starting with a 160-mg dose at Wk 0; adalimumab (ADA) 40 mg Q2W (active comparator); or placebo (PBO) during the Double-Blind Treatment Period (DBTP; Wks 0-24). Of these pts, 267 were receiving a concomitant cDMARD at baseline, 149 were not, and 1 did not receive study drug; pts were stratified by cDMARD use, and were to remain on their cDMARD through the DBTP. At Wk 24, efficacy was evaluated by ACR response; and progression of structural damage was assessed by the modified Total Sharp Score (mTSS). Safety assessments included the percentage of pts experiencing treatment emergent adverse events (TEAEs), serious adverse events (SAEs), and discontinuations due to adverse events (AEs). Efficacy analyses were conducted on the Intent to Treat Population, defined as all randomly assigned pts; safety analyses were conducted on the Safety Population, defined as all randomly assigned pts who received at least 1 dose of study drug. Fisher's test was used for treatment comparisons in ACR and AE data, and an analysis of covariance model was used for mTSS data. Missing values were imputed by nonresponder imputation for ACR data and by linear extrapolation for mTSS data.

Results: At Wk 24, compared with pts receiving PBO, significantly more pts receiving IXEQ4W or IXEQ2W (with/without concomitant cDMARD) achieved ACR20/50/70 responses (see Table for ADA results). Pts receiving IXEQ2W (with/without concomitant cDMARD) or IXEQ4W or ADA (with concomitant cDMARD) showed significantly less progression in mTSS from baseline compared with pts receiving PBO (Table). No treatment-by-subgroup effects were observed for ACR20/50/70 or mTSS (Table footnotes). In pts receiving concomitant cDMARDs, significantly more pts receiving IXE or ADA experienced ≥1 TEAE, compared with pts receiving PBO; the percentages of pts with SAEs or discontinuations due to an AE were comparable among treatment groups (Table).

Conclusion: IXE demonstrated efficacy in improvement of PsA signs and symptoms and structural inhibition in bDMARD naive pts with/without concomitant cDMARD use. With concomitant cDMARD use, although significantly more pts receiving IXE or ADA experienced ≥1 TEAE, compared with pts receiving PBO, the frequency of SAEs and discontinuations due to an AE were comparable among all treatment group.

Table: Effect of Concurrent Use of Conventional DMARDs on Efficacy and Safety of Ixekizumab

	Placebo N=106		ADAQ2W N=101		IXEQ4W N=107		IXEQ2W N=103	
Baseline use of cDMARD?	Yes n=69	No n=37	Yes n=67	No n=34	Yes n=68	No n=39	Yes n=63	No n=40
Efficacy Outcomes at Week 24								
ACR20[a], NRI, n (%)	22 (31.9)	10 (27.0)	43 (64.2)***	15 (44.1)	38 (55.9)**	24 (61.5)**	39 (61.9)***	25 (62.5)**
ACR50[a], NRI, n (%)	13 (18.8)	3 (8.1)	28 (41.8)**	11 (32.4)*	26 (38.2)*	17 (43.6)***	30 (47.6)***	18 (45.0)***
ACR70[a], NRI, n (%)	6 (8.7)	0 (0.0)	19 (28.4)**	7 (20.6)**	16 (23.5)*	9 (23.1)**	20 (31.7)***	15 (37.5)***
mTSS[b], change from baseline, LSM (SE)	0.44 (0.101)	0.56 (0.161)	0.11 (0.095)*	0.11 (0.171)	0.13 (0.098)*	0.26 (0.156)	0.11 (0.099)*	0.03 (0.154)*

	Placebo N=106		ADAQ2W N=101		IXEQ4W N=107		IXEQ2W N=102	
Baseline use of cDMARD?	Yes n=69	No n=37	Yes n=67	No n=34	Yes n=68	No n=39	Yes n=63	No n=39
Safety Outcomes at Week 24								
TEAEs[c,d], n (%)	30 (43.5)	20 (54.1)	45 (67.2)**	20 (58.8)	42 (61.8)*	29 (74.4)	40 (63.5)*	27 (69.2)
SAEs[c,d], n (%)	2 (2.9)	0 (0.0)	5 (7.5)	0 (0.0)	3 (4.4)	3 (7.7)	0 (0.0)	3 (7.7)
AEs leading to discontinuation[c,d], n (%)	2 (2.9)	0 (0.0)	1 (1.5)	1 (2.9)	1(1.5)	1 (2.6)	4 (6.3)	0 (0.0)

Abbreviations: ACR=American College of Rheumatology; ACR20=at least 20% improvement in ACR assessments from baseline; ACR50=at least 50% improvement in ACR assessments from baseline; ACR70=at least 70% improvement in ACR assessments from baseline; ADA=adalimumab; AE=adverse events; ANCOVA=analysis of covariance; cDMARD=conventional disease-modifiying antirheumatic drug; IXE=ixekizumab; LSM=least squares mean; N,n=number of patients; NRI=nonresponder imputation; mTSS=modified Total Sharp Score; SAEs=serious adverse events; SE=standard error; TEAEs=treatment-emergent adverse events.

*p<.05; **p≤.01; ***p≤.001; p-values for ACR20/50/70 and AEs are based on Fisher's exact test; p-values for mTSS are from an ANCOVA model with treatment and baseline scores.

[a]Treatment-by-subgroup interaction p-values are .321 (ACR20), .454 (ACR50), and NA (ACR70; because 0 PBO patients without cDMARD achieved ACR70). Treatment-by-subgroup interaction p-values are based on a logistic regression model with effect of treatment, subgroup, and the treatment-by-subgroup interaction, and are tested at the significance level of 0.10.

[b]Treatment-by-subgroup interaction p-value is .727. Treatment-by-subgroup interaction p-value is from an ANCOVA model with treatment, baseline score, subgroup, and interaction of treatment-by-subgroup included as factors.

[c]Patients with ≥1 event.

[d]Statistical analyses presented are for the baseline use of cDMARD – "yes" or "no" subgroup within each treatment group, and the respective baseline use of cDMARD – "yes" or "no" subgroup within the placebo group.

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Mease, AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Eli Lilly and Company, Novartis, Pfizer, Sun, UCB, 2,AbbVie, Amgen, Bristol Myers Squibb, Celgene, Crescendo, Corrona, Dermira, Janssen, Eli Lilly and Company, Merck, Novartis, Pfizer, Sun, UCB, Zynerba, 5,AbbVie, Amgen, Bristol Myers Squibb, Celgene, Crescendo, Janssen, Novartis, Pfizer, UCB, 8.

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Abstract Number: 1688

Ixekizumab Provides Sustained Improvement up to 52 Weeks of Disease Activity As Assessed By Composite Measure Scores in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients with Active Psoriatic Arthritis

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Background/Purpose: PsA, a chronic immune-mediated inflammatory disease, can be progressive and destructive, resulting in physical deformities, impaired function, decreased quality of life, and increased mortality. Ixekizumab (IXE) is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. Data are presented from a phase 3 trial (SPIRIT P1; NCT01695239) with IXE in patients (pts) with active PsA. The objective is to explore the impact of IXE, as assessed by disease activity composite measures, up to 52 weeks (wks).

Methods: 417 bDMARD-naive adult pts with active PSA, were randomly assigned 1:1:1:1 to subcutaneous administration of either 80 mg IXE every 4 wks [Q4W] or every 2 wks [Q2W], each with a 160 mg starting dose at Wk 0; adalimumab (ADA) 40 mg Q2W [active comparator]; or placebo (PBO) in the Double Blind Treatment Period (DBTP; Wks 0-24). Of these pts, 381 continued into the Extension Period (EP; Wks 24-52). PBO- and ADA treated pts were randomly re-assigned (1:1) to 80 mg IXEQ4W or IXEQ2W at Wk 16 (inadequate responders) or Wk 24; ADA-treated pts started IXE, after an 8-wk wash-out period, at Wk 24 (inadequate responders) or Wk 32. Investigators were blinded as to the criteria for inadequate response. Disease activity was measured at Wks 24 and 52 by composite measures including the following: minimum disease activity (MDA) as measured with the Psoriasis Area and Severity Index (MDA_{PASI}) and with the static Physician Global Assessment of psoriasis (MDA_{sPGA}), and modified Composite Psoriatic Disease Activity Indices (CPDAI-12 and CPDAI 14 [see Table 1 footnote]). Analyses for the DBTP were conducted on the Intent-to-Treat Population, defined as all randomly assigned pts; analyses for the EP were conducted on the EP Population, defined as all pts who received at least 1 dose of study drug during the EP. In the DBTP, treatment comparisons were made by a logistic regression model for categorical data with missing values imputed by nonresponder imputation; a mixed model for repeated measures analysis was used for continuous data.

Results: At Wk 24, CPDAI 12 and CPDAI-14 total scores (assesses domains of peripheral arthritis, skin disease, enthesitis, dactylitis [and spinal disease for CPDAI-14 only]) for pts receiving IXEQ4W, IXEQ2W, or ADA, were significantly improved compared with results for pts receiving PBO (Table 1). Similarly, at Wk 24, significantly more pts receiving IXEQ4W, IXEQ2W, or ADA achieved MDA_{sPGA} and MDA_{PASI} compared with pts receiving PBO (Table 1),

and percentages of pts receiving IXEQ4W or IXEQ2W who achieved MDA_{sPGA} and MDA_{PASI} were sustained through Wk 52 (Table 2). Results for MDA_{sPGA} were similar to results for MDA_{PASI} within each treatment group.

Conclusion: IXE provides sustained improvement of disease activity, as measured by various composite measures, for up to 52 wks in bDMARD-naive pts with active PsA.

Table 1: Improvement in Composite Outcome Measures at Week 24 (Double-Blind Treatment Period)

Assessment	PBO N=106	ADA N=101	IXEQ4W N=107	IXEQ2W N=103
NRI:				
MDA_{sPGA}, n (%)	16 (15.1)	35 (34.7)***	31 (29.0)*	39 (37.9)***
MDA_{PASI}, n (%)	16 (15.1)	32 (31.7)**	32 (29.9)**	43 (41.7)***
Change from baseline:				
CPDAI-14[a] Total Score, LSM (SE)	-1.39 (0.29)	-2.59 (0.26)***	-3.49 (0.27)***	-3.59 (0.27)***
CPDAI-12[b] Total Score, LSM (SE)	-1.24 (0.26)	-2.23 (0.23)**	-3.02 (0.23)***	-3.15 (0.24)***

Abbreviations: ADA=adalimumab; ASQol=Ankylosing Spondylitis Quality of Life; CPDAI=Composite Psoriatic Disease Activity Index; IXE=ixekizumab; LSM=least square mean; MDA=minimum disease activity; MDA_{PASI}=MDA measured by Psoriasis Area and Severity Index; MDA_{sPGA}=MDA measured by static Physician Global Assessment of psoriasis; N,n=number of patients; NRI=nonresponder imputation; p=p-value; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error.
[a]CPDAI-14 is modified from CPDAI (Mumtaz A, Gallagher P, Brian K, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis. 2011;70:272-7); this modified index does not include ASQoL questionnaire and has a possible total score of 14.
[b]CPDAI-12 is modified from CPDAI (Mumtaz et al. 2011); this modified index does not include the ASQoL or the BASDAI, and has a possible total score of 12.
*p<.05; **p≤.01; ***p≤.001; MDA p-values for are from a logistic regression model; CPDAI p-values are from a repeated measures mixed model.

Table 2: Improvements in Composite Outcome Measures at Week 52 (Extension Period)

Assessment	PBO/ IXEQ4W N=45	PBO/ IXEQ2W N=46	ADA/ IXEQ4W N=49	ADA/ IXEQ2W N=48	IXEQ4W/ IXEQ4W N=97	IXEQ2W/ IXEQ2W N=96	Total IXEQ4W N=191	Total IXEQ2W N=190
NRI:								
MDA_{sPGA}, n (%)	15 (33.3)	19 (41.3)	20 (40.8)	15 (31.3)	42 (43.3)	38 (39.6)	77 (40.3)	72 (37.9)
MDA_{PASI}, n (%)	15 (33.3)	19 (41.3)	20 (40.8)	15 (31.3)	42 (43.3)	38 (39.6)	77 (40.3)	72 (37.9)

Abbreviations: ADA=adalimumab; IXE=ixekizumab; MDA=minimum disease activity; MDA_{PASI}=MDA measured by Psoriasis Area and Severity Index; MDA_{sPGA}=MDA measured by static Physician Global Assessment of psoriasis; N,n=number of patients; NRI=nonresponder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks.

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Abstract Number: 1689

Ixekizumab Provides Improvements through 52 Weeks in Physical Function, Quality of Life, and Work Productivity in Biologic Disease-Modifying Antirheumatic Drug-Naive Patients with Active Psoriatic Arthritis

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Background/Purpose: PsA has a negative impact on patients' quality of life, physical function, and work productivity. Ixekizumab (IXE) is an IgG4 mAb that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. In this phase 3 trial (SPIRIT P1), previously reported results showed that IXE treatment resulted in significant improvements (compared with placebo [PBO]) at Week [Wk] 24 in the patient reported outcome (PRO) measures of HAQ – Disability Index (HAQ-DI), Short Form-36 Health Survey Physical Component Summary (SF-36 PCS), European Quality of Life 5 Dimensions Visual Analog Scale (EQ-5D VAS), and Work Productivity and Activity Impairment-Specific Health Problem (WPAI-SHP; presenteeism, work productivity, and activity impairment).The objective was to evaluate whether an effect of IXE on improvement of PROs is also observed at Wk 52.

Methods: A total of 417 biologic DMARD (bDMARD)-naive patients (pts) with active PsA were randomly assigned 1:1:1:1 to subcutaneous administration of either 80 mg IXEQ4W or IXEQ2W, each with a 160 mg starting dose at Wk 0; adalimumab [ADA] 40 mg Q2W (active comparator); or PBO in the Double-Blind Treatment Period (DBTP; Wks 0 through 24). Of these pts, 381 continued into the Extension Period (EP; Wks 24-52). PBO- and ADA treated pts were randomly re-assigned (1:1) to 80 mg IXEQ4W or IXEQ2W at Wk 16 (inadequate responders) or Wk 24; ADA-treated pts started IXE after an 8-wk wash-out period at Wk 24 (inadequate responders) or Wk 32. Investigators were blinded as to criteria for inadequate response. Analyses for the EP were conducted on the EP Population, defined as all pts who received at least 1 dose of study drug during the EP. Missing values were imputed by nonresponder imputation for categorical data and modified baseline observation carried forward for continuous data.

Results: Baseline demographics and clinical characteristics were generally similar between treatment groups; population mean baseline (Wk 0) scores for HAQ-DI, SF-36 PCS, and EQ-5D VAS (Table) indicated impaired physical function and quality of life. Physician assessed clinical efficacy was shown by 69% of pts treated with IXE for 52 wks achieving ACR20 response. Pts receiving IXE (Q4W or Q2W) for 52 wks reported similar improvements in HAQ-DI, SF 36, EQ-5D VAS, and WPAI SHP (presenteeism, work productivity, and activity impairment) (Table) as reported at Wk 24, and the percentage of IXE pts with improvement from baseline HAQ-DI score ≥0.35 achieving minimally clinically important difference for HAQ DI was sustained at Wk 52 (Table) compared with Wk 24. At Wk 52, pts receiving ADA/IXE also showed similar improvements in ACR20 response and most PRO measures (Table) to those observed at Wk 24.

Conclusion: IXE provided sustained improvement through 52 wks in physical function, quality of life, and work productivity in bDMARD-naive pts with active PsA.

Table: Summary of Patient-Reported Outcomes at Baseline and Week 52 in Psoriatic Arthritis Patients Treated With Ixekizumab

	Total Population N=381	PBO/ IXEQ4W N=45	PBO/ IXEQ2W N=46	ADAQ2W/ IXEQ4W N=49	ADAQ2W/ IXEQ2W N=48	IXEQ4W/ IXEQ4W N=97	IXEQ2W/ IXEQ2W N=96	Total IXEQ4W N=191	Total IXEQ2W N=190
Assessment, mean (SD)	**Baseline (Week 0) Scores**	**Change from Baseline**		**Change from Baseline**		**Change from Baseline**		**Change from Baseline**	
HAQ-DI[a]	1.16 (0.57)	-0.38 (0.53)	-0.42 (0.60)	-0.47 (0.48)	-0.42 (0.47)	-0.53 (0.56)	-0.55 (0.52)	-0.48 (0.53)	-0.48 (0.53)
SF-36 PCS[b]	33.8 (9.1)	7.3 (9.6)	8.0 (8.5)	7.3 (7.7)	9.0 (8.8)	9.5 (9.5)	9.2 (9.4)	8.4 (9.1)	8.8 (9.0)
EQ-5D VAS[b]	55.6 (20.6)	13.0 (20.3)	15.7 (25.2)	8.2 (25.8)	14.4 (18.9)	14.7 (25.6)	14.4 (21.2)	12.6 (24.5)	14.7 (21.6)
WPAI-SHP: Absenteeism[a]	8.4 (22.1)	-1.9 (17.3)	0.1 (3.9)	-2.7 (36.9)	3.0 (24.2)	-8.3 (21.3)	-0.4 (22.7)	-5.6 (25.1)	0.7 (20.5)
WPAI-SHP: Presenteeism[a]	36.3 (23.7)	-15.7 (20.9)	-17.0 (22.5)	-20.5 (20.1)	-15.8 (18.2)	-23.6 (27.0)	-25.4 (21.3)	-21.2 (24.4)	-20.6 (21.0)
WPAI-SHP: Work Productivity[a]	38.6 (24.7)	-17.9 (23.6)	-16.6 (23.1)	-21.5 (24.7)	-16.8 (23.6)	-25.3 (28.0)	-24.9 (22.9)	-22.9 (26.3)	-20.6 (23.3)
WPAI-SHP: Activity Impairment[a]	47.1 (25.1)	-21.1 (22.2)	-24.8 (25.4)	-21.9 (22.4)	-20.9 (25.6)	-26.2 (26.9)	-29.1 (24.1)	-23.9 (24.7)	-26.0 (24.9)
Assessment, NRI, n (%)									
HAQ-DI MCID[c]	NA	16 (43.2)	16 (40.0)	26 (60.5)	20 (47.6)	52 (57.1)	48 (57.1)	94 (55.0)	84 (50.6)

Abbreviations: ADA=adalimumab; EQ-5D VAS=European Quality of Life 5 Dimensions Visual Analog Scale; HAQ-DI=Health Assessment Questionnaire - Disability Index; IXE=ixekizumab; MCID=minimally clinically important difference; N=number of patients; NA=not applicable; NRI=nonresponder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation; SF-36 PCS=Short Form-36 Health Survey Physical Component Score; WPAI-SHP=Work Productivity and Activity Impairment-Specific Health Problem.

[a]Decrease in score represents improvement.

[b]Increase in score represents improvement.

[c]MCID ≥0.35 improvement from baseline; only patients with a baseline HAQ-DI score ≥0.35 were included in the analysis.

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Burge, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **C. Y. Lin**, Eli Lilly and Company, 3,Eli Lilly and Company, 1; **C. H. Lee**, Eli Lilly and Company, 3,Eli Lilly and Company, 1; **D. Gladman**, AbbVie, Amgen, Celgene, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, UCB, 5.

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Efficacy and Safety of Apremilast and Switch from Etanercept in Patients with Moderate to Severe Psoriasis: 52-Week Results

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Background/Purpose: Psoriasis is a chronic systemic inflammatory disease often treated with conventional systemic and biologic drugs that may variously be ineffective, be inaccessible, or pose significant safety/tolerability risks. The phase 3b LIBERATE (Evaluation in a Placebo-Controlled Study of Oral Apremilast and Etanercept in Plaque Psoriasis) study (NCT01690299) evaluated the efficacy/safety of apremilast (APR) or etanercept (ETN) vs. placebo (PBO) in biologic-naive patients with moderate to severe plaque psoriasis.

Methods: In the double-blind, double-dummy study, patients were randomized (1:1:1) to PBO, APR 30 mg BID, or ETN 50 mg QW through Week 16; thereafter, all patients switched to or continued APR (PBO/APR, ETN/APR, APR/APR). The primary endpoint was achievement of a ≥75% reduction from baseline Psoriasis Area and Severity Index score (PASI-75) at Week 16 with APR vs. PBO; secondary endpoint was PASI-75 achievement at Week 16 with ETN vs. PBO. Additional physician global assessments (PGA) of disease activity were conducted using the static (sPGA), lattice system (LS-PGA), and scalp (ScPGA) instruments; nail disease was evaluated using the Nail Psoriasis Severity Index (NAPSI). Responses were assessed at Weeks 16 and 52 using the last-observation-carried-forward (LOCF) methodology.

Results: 250 patients received ≥1 dose of study drug, had baseline PASI and ≥1 post-treatment PASI evaluations, and were included in the analysis set (PBO n=84; APR n=83; ETN n=83). At baseline, 66.4% (n=166; PBO n=58; APR n=54; ETN n=54) of patients had an ScPGA score ≥3 (moderate to very severe) and 59.2% (n=148; PBO n=46; APR n=52; ETN n=50) had a NAPSI score ≥1. At Week 16, PASI-75 achievement was significantly greater (P<0.0001) with APR (39.8%) or ETN (48.2%) vs. PBO (11.9%). This study was not designed/powered for APR vs. ETN comparisons; Week 16 PASI-75 achievement did not differ significantly between APR and ETN (P=0.2565, post hoc). At Week 16, APR and ETN produced significantly greater achievement of 0/1 ratings (clear/almost clear) vs. PBO in sPGA, LS-PGA, and ScPGA (clear/minimal) (**Table**). Improvements in nail psoriasis were also achieved with APR and ETN at Week 16 (**Table**). At Week 52, PASI-75 response was sustained in APR/APR (50.6%) and ETN/APR (55.4%) patients; 46.4% of PBO/APR patients had a PASI-75 response (**Table**). sPGA, LS-PGA, and ScPGA responses achieved at Week 16 were generally sustained through Week 52 with APR (**Table**). Continued APR treatment over 52 weeks resulted in further improvements in nail psoriasis (**Table**). Overall, adverse events were comparable among the 3 treatment arms. Adverse events with APR and ETN were consistent with their known safety profiles.

Conclusion: APR demonstrated significant efficacy vs. PBO at Week 16; with continued APR treatment, therapeutic responses were generally sustained at Week 52. Efficacy was maintained in ETN patients who switched to APR.

LIBERATE Efficacy Outcomes			
Patients Achieving Response, % (LOCF)			
Week 16	**PBO n=84**	**APR n=83**	**ETN n=83**
PASI-75	11.9	39.8*	48.2*
sPGA 0 or 1§	3.6	21.7‡	28.9*
LS-PGA 0 or 1†	6.0	24.1#	22.9#
ScPGA 0 or 1¶	25.9	44.4**	50.0**
NAPSI-50§§	10.9	25.0##	48.0*
Week 52	**PBO/APR n=84**	**APR/APR n=83**	**ETN/APR n=83**
PASI-75	46.4	50.6	55.4
sPGA 0 or 1§	31.0	24.1	25.3
LS-PGA 0 or 1†	22.6	27.7	24.1
ScPGA 0 or 1¶	46.6	50.0	61.1
NAPSI-50§§	41.3	46.2	68.0

NAPSI-50=≥50% reduction from baseline in NAPSI score.
*$P<0.0001$; ‡$P=0.0005$; #$P\leq0.0021$; **$P\leq0.0458$; ##$P=0.0701$ vs. PBO (LOCF). Italics indicate values are nominally significant due to hierarchical testing of study endpoints.
§With ≥2-point reduction from baseline.
†All patients had LS-PGA ≥4 (moderate to very severe) at baseline.
¶In patients with ScPGA ≥3 (moderate to very severe) at baseline (exploratory): PBO n=58; APR n=54; ETN n=54.
§§In patients with NAPSI ≥1 at baseline: PBO n=46; APR n=52; ETN n=50.

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The Comparative Immunogenicity of Biologic Therapy and Its Clinical Relevance in Psoriatic Arthritis: A Systematic Review of the Literature

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Background/Purpose: Anti-inflammatory biologic agents have been shown to provide significant benefit in controlling disease activity in psoriatic arthritis (PsA) and inhibiting progression of joint damage. Due to their unique protein structures, biologics have varying capacities to generate anti-drug antibodies (ADAbs), which may affect clinical outcomes. A systematic literature review was conducted to explore the immunogenicity of biologics in PsA, with a focus on the frequency of ADAb formation, the potential effects on safety and efficacy, and predictive factors.

Methods: MEDLINE, EMBASE, and Cochrane databases, conference proceedings and review articles were searched for randomized controlled trials (RCTs) and observational studies in PsA published before 4 September 2015 of abatacept (ABA), adalimumab (ADA), certolizumab pegol (CZP), etanercept (ETN), golimumab (GLM), infliximab (INF), rituximab (RTX), secukinumab (SEC), tocilizumab (TCZ), ustekinumab (UST), and CT-P13.

Results: Of 21,889 publications screened, 14 studies in PsA were retained (randomized controlled trials, n=8; prospective cohort studies, n=6). No published studies with immunogenicity data for ABA, CZP, CT-P13, RTX, or TCZ in PsA were identified. ADAb rates varied widely among studies of other biologics in PsA studies, with the highest frequency in studies of ADA (7–54%) and INF (15–33%) and the lowest in studies of ETN (0%) and SEC (0–0.2%) (table).[1-14] Concomitant use of methotrexate was associated with lower rates of ADAbs against ADA,[5] GLM,[7] INF,[5,8] and UST.[13] Patients with ADAbs against ADA,[1-5] INF,[5,8,9] and UST[13] had lower serum drug levels and poorer efficacy outcomes than those without antibodies. ADAbs against ADA[2] and INF[8,9] were also associated with increased rates of adverse events.

Table. Summary of immunogenicity findings in biologic studies in PsA.

Source	ADAbs n/N (%)	ADAb+ correlation with serum level	ADAb+ correlation with MTX	Clinical relevance
ADA				
van Kuijk et al, 2010[1] (OS)	4/22 (18)	↓ serum drug levels	NR	↓ clinical response
Hoxha et al, 2014[2] (OS)	1/15 (7)	NR	NR	↓ clinical response/↑ AEs
Rosas et al, 2014[3] (OS)	4/10 (40)	↓ serum drug levels	NS	↓ clinical response
Vogelzang et al, 2014[4] (OS)	23/103 (22)	↓ serum drug levels	NR	↓ clinical response
Zisapel et al, 2014[5] (OS)	26/48 (54)	↓ serum drug levels	↓ ADAb+ with MTX	↓ clinical response
ETN				
Mease et al, 2014[6] (RCT/LTE)	0/101 (0)	–	–	–
Zisapel et al, 2014[5] (OS)	0/21 (0)	–	–	–
GLM				
Kavanaugh et al, 2014[7*] (RCT/LTE)	20/335 (6)	NR	↓ ADAb+ with MTX	NR
INF				
Kavanaugh et al, 2007[8] (RCT)	26/173 (15)	NR	↓ ADAb+ with MTX	↓ clinical response/↑ AEs
Garces et al, 2013[9] (OS)	3/9 (33)	NR	NR	↓ clinical response/↑ AEs
Zisapel et al, 2014[5] (OS)	5/24 (21)	↓ serum drug levels	↓ ADAb+ with MTX	↓ clinical response
SEC				
McInnes et al, 2014[10] (RCT)	0/28 (0)	–	–	–
Mease et al, 2015[11] (RCT)	1/587 (0.2)	–	–	–
UST				
Gottlieb et al, 2009[12] (RCT)	14/124 (11)	NR	NR	No correlation with ISRs
Zhu et al, 2013[13†] (RCT)	72/927 (8)	↓ serum drug levels	↓ ADAb+ with MTX	↓ clinical response/ no correlation with ISRs

*Report of 5-year long-term extension of GO-REVEAL study †Report of pooled findings of P-SUMMIT 1 and 2
AE, adverse event; ISR, injection site reaction; LTE, long-term extension; OS, observational study; NR, not reported; NS, not significant; RCT, randomized controlled trial.

Conclusion: Based on this literature review, the prevalence of ADAbs was higher with ADA and INF than with other biologics in PsA, with potentially clinically relevant consequences; ADAbs were not reported with etanercept and their prevalence was low with GLM, SEC, and UST. The immunogenicity of these agents is an important (albeit not the only) consideration when selecting therapy, dose and dosing regimen, and use of background anti-proliferative agents.

References: 1. *Ann Rheum Dis* 2010;69:624. **2.** *Ann Rheum Dis* 2014;73:927. **3.** *Arthritis Rheum* 2014b;66:S674. **4.** *Ann Rheum Dis* 2014:73:2178. **5.** *J Rheumatol* 2015;42:73. **6.** *Arthritis Rheum* 2004;50:2264. **7.** *Ann Rheum Dis* 2014;73:1689. **8.** *Ann Rheum Dis* 2007;66:498. **9.** *Ann Rheum Dis* 2013;72(Suppl2):436. **10.** *Ann Rheum Dis* 2014;73:349. **11.** *N Engl J Med* 2015;373:1329. **12.** *Lancet* 2009;373:633. **13.** *Clin Pharmacol Drug Dev* 2013;2:32.

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Inc, 3.

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Validation of a Two-Question Patient Reported Outcome Measure for Psoriasis

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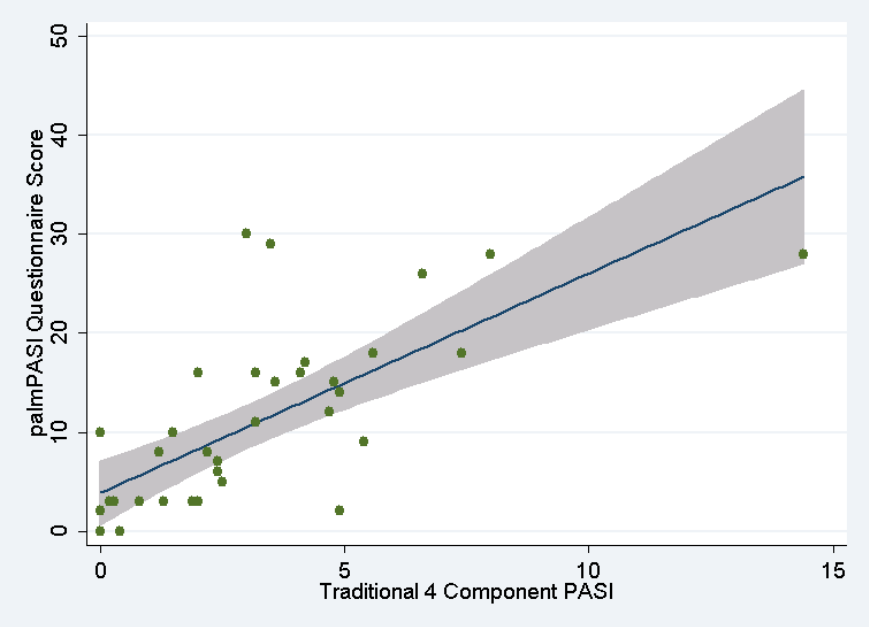
Background/Purpose: While the psoriasis area and severity index (PASI) is the most commonly used assessment tool for psoriasis severity, it has been criticized for its subjectivity and complexity. Expert training is needed to minimize errors, as well as inter-rater and intra-rater variability. It also burdens the provider and does not incorporate the patient's perspective. We validate a simplified two-item palmPASI against previously established standardized measures of psoriasis involvement.

Methods: Adult patients (18 years or older) with psoriasis or psoriatic arthritis (PsA) in the Veterans Affairs Program to Understand the Longterm outcomes in Spondylo-ARthritis (PULSAR) registry participated in this study. Subjects complete a two item "palmPASI" questionnaire, using a 10-point scale to describe how psoriasis affected the patient and the degree of surface area involvement. These palmPASI scores were then compared to formal four-component PASI scores (erythema, induration, scaling, and involved area of lesions), as determined by health care personnel, as well as the Psoriasis Symptom Inventory (PSI) and Dermatology Life Quality Index (DLQI). Correlations were analyzed using Spearman correlations. The relationship between clinical feature and palmPASI scores was analyzed using logistic regression.

Results: A total of 352 subjects completed the palmPASI and a convenience sample of 40 were examined with the formal PASI. Strong correlations exists between palmPASI and PASI (Spearman's rho=0.75, $p<0.001$; see Figure 1), PSI (Spearman's rho=0.73, $p<0.001$), and DLQI (Spearman's rho=0.77, $p<0.001$). Psoriasis area score was highly correlated with the four-component PASI (Spearman's rho=0.75, $p<0.006$). The test-retest reliability of the palmPASI was excellent (rho=0.93, $p<0.001$). African-Americans and those with elevated c-reactive proteins demonstrated higher palmPASI scores.

Conclusion: Assessment of psoriasis and psoriatic arthritis disease activity is crucial when determining treatment efficacy in clinical research. The palmPASI incorporates patient perspectives, requires less than 10 seconds to score, and demonstrates validity when compared against standard psoriasis instruments. This instrument could potentially serve as a reliable and simple standardized tool to guide evidence-based management.



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Chronic Back Pain in Early Psoriatic Arthritis

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Background/Purpose: Axial involvement is less well studied in peripheral spondyloarthritis where chronic back pain is not the predominant symptom, such as in psoriatic arthritis (PsA). Our aim is to describe occurrence of back complaints in newly diagnosed psoriatic arthritis patients and its impact on quality of life for those with chronic back pain (CBP) and inflammatory back pain (IBP).

Methods: Baseline data of incident PsA patients was used from the Dutch south-west Psoriatic Arthritis Registry (DEPAR)

study between August 2013 to March 2016. Trained research nurses took a standardized history and physical examination. Presence of IBP was determined using the Assessment of Spondyloarthritis international Society (ASAS) criteria for IBP. Quality of life was assessed using the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL), and the Short-Form 36 (SF36) subscales.

Results: In total, 323 patients had a baseline assessment. Average age was 50.4 years (SD 13.7) and 50% were male. 212 patients reported having or having had back pain (65%). 103 patients (32%) reported having back pain for more than 3 months at present or in the past twelve months, which is significantly more than in the general population (21%, P<0.0001 (1)). 33 (10%) fulfilled the ASAS-IBP criteria. We compared patients without back pain (n=111) to CBP patients, and within CBP patients we compared the IBP subgroup (n=33) and the non-IBP subgroup (n=70). CBP patients were more often female (60% vs 41%, p<0.001), and had more often at least one tender enthesis on the LEI and/or MASES (64% vs 34%, p<0.001). Quality of life was significantly worse, as reflected in lower median ASQoL scores (6 and 5 vs. 2, p=0.0001) and lower SF36 subscores compared to patients without back pain. IBP patients had significantly worse scores only on the mental health subscale compared to non-IBP patients with CBP.

Conclusion: chronic back pain is common in psoriatic arthritis and occurs more often in female patients. It has a severe impact on quality of life as assessed by both disease-specific and generic questionnaires, while the difference between inflammatory and non-inflammatory back pain groups is less pronounced.

1. Picavet HS, Schouten JS. Musculoskeletal pain in the Netherlands: prevalences, consequences and risk groups, the DMC(3)-study. Pain. 2003;102(1-2):167-78.

Table 1. Characteristics and PROMs at baseline

	chronic back pain, ASAS-IBP+ (n=33)	chronic back pain, ASAS-IBP- (n=70)	no back pain (n=107)	P-values
Age, mean (SD)	44.3 (13.3)	50.6 (15.0)*	51.3 (13.6)	*p=0.04
Female (%)	17 (52)	45 (64)	39 (36)**	**p<0.001
SJC-66, median (IQR)	1 (0-2)	2 (0-5)	2 (1-4)	
TJC-66, median (IQR)	4 (1-8)	4 (2-9)	3 (1-7)	
LEI or MASES >0 (%)	22 (67)	44 (63)	36 (34)**	**p<0.001
PASI, median (IQR)	2.8 (0.6-5.4)	2.5 (0.8-4.6)	2.4 (0.5-4.7)	
Positive modified Schober (%)	25 (76)	80 (76)	71 (66)	
Duration back complaints, median years (IQR)	10.0 (2.3-21.9)	10.1 (3.7-20.0)		
ASQoL, median (IQR)	7 (2-14)	8 (3.1-12)	1 (0-4)**	**p=0.0001
SF36 subscales, median (IQR)				
physical functioning	53 (30-78)	58 (30-70)	75 (55-90)**	**p=0.0001
physical role functioning	50 (28-63)	38 (22-56)	63 (50-88)**	**p=0.0001
bodily pain	41 (31-57)	41 (31-61)	52 (41-62)**	**p=0.0001
general health	44 (30-62)	47 (35-62)	62 (50-77)**	**p=0.0001
vitality	38 (22-56)	50 (38-63)	63 (44-75)**	** p=0.0001
social functioning	63 (38-88)	63 (50-88)	88 (63-100)**	**p=0.0006
emotional role functioning	58 (46-96)	63 (38-100)	92 (58-100)**	**p=0.0009
mental health	58 (45-73)	70 (55-85)*	80 (65-90)**	*p=0.04, **p=0.0001

ASAS-IBP Assessment of SpondyloArthritis international Society classification criteria for Inflammatory Back Pain (+ positive, - negative), SD: Standard Deviation, IQR: interquartile range, SJC: Swollen joint count, TJC: Tender joint count, LEI: Leeds Enthesitis Index, MASES: Maastricht Ankylosing Spondylitis Enthesitis Score, PASI: Psoriasis Area Severity Index, Schober cutoff of ≤5 cm, ASQoL: Ankylosing Spondylitis Quality of Life questionnaire, SF36: Short Form 36.
*significant difference inflammatory vs. non-inflammatory chronic back pain.
**significant difference chronic back pain vs. no back pain

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Does Treat to Target or Achieving Remission Improve Radiographic Outcome in Psa?

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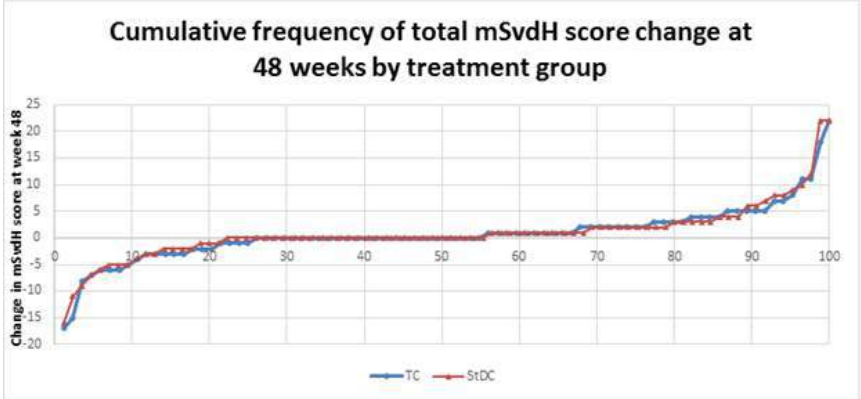
Background/Purpose: The Tight Control of PsA (TICOPA) study was the first to address treat to target in PsA using the minimal disease activity (MDA) criteria, confirming a benefit in terms of disease activity, function and quality of life. Median changes in modified Sharp-van der Heijde radiographic scores were 0 in both groups. Our aim was to investigate further whether treating to target or achieving low disease activity states predicts radiographic change in the TICOPA study.

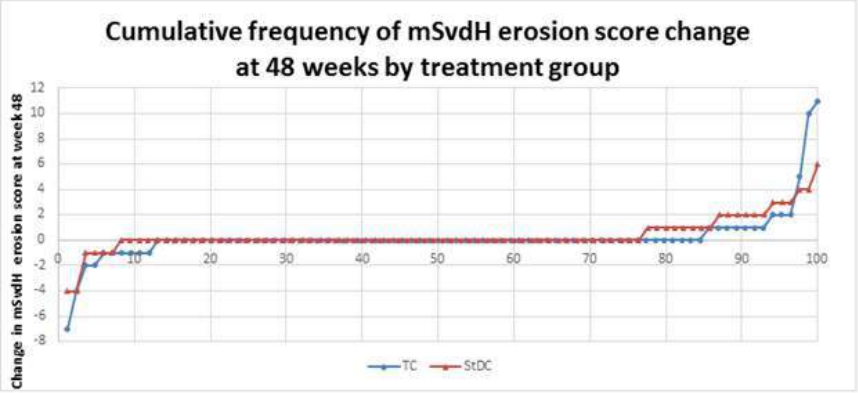
Methods: 206 patients with early PsA (<2 years disease duration) were randomised 1:1 to tight control (4 weekly review, treatment escalated to MDA) or standard care (12 weekly review, no set treatment). Radiographs of the hands and feet were taken at week 0 and 48 and scored by consensus using the modified Sharp-van der Heijde (mSvdH) score. Disease states examined included the MDA criteria, Disease Activity in Psoriatic Arthritis (DAPSA) remission and Very Low Disease Activity (VLDA) defined as meeting all 7 of the MDA cutpoints at any timepoint. Bootstrapped quantile regression, adjusting for baseline values and minimisation factors, was used to compare radiographic scores defined according to treatment or disease states at the 50^{th}, 75^{th} and 90^{th} quantiles.

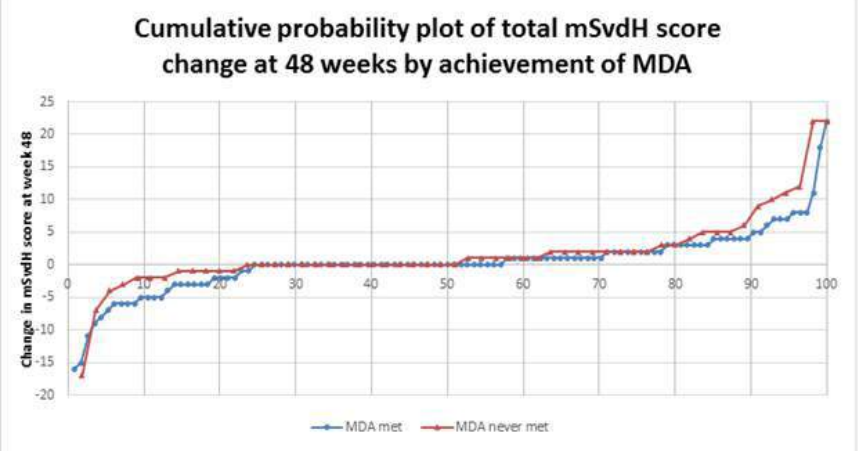
Results: For tight control vs standard therapy, there was no difference in radiographic progression at the median. There was a trend towards reduced progression in total mSvdH score at the 75^{th} & 90^{th} quantiles but this was not significant (see figure and table). For some of the low disease activity states, change in total SvdH score was significantly different at the median for most and at the 75^{th} and 90^{th} quantile (see figure and table). In all cases the trend was towards less progression in the low disease states. Changes in erosion scores were non-significant.

Conclusion: There was no significant difference in radiographic outcome seen with tight control although progression was numerically lower. Achieving MDA, DAPSA remission or VLDA was significantly predictive of total SvdH score for median and some 75/90^{th} quantile scores. Radiographic progression was consistently numerically lower in those achieving the disease states. The lack of effect on erosion scores is likely to reflect the TICOPA study design including a population with early milder disease (30% oligoarthritis), no placebo comparison and a step up treatment protocol. These data suggest a potential impact of tight control and achieving low disease activity states on radiographic outcome but should be interpreted with caution.

SvdH total score	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value	Coefficient (95% CI)	P value
Quantile tested	50		75		90	
Tight control	0.00 (-0.68, 0.68)	1.0	-0.78 (-2.24, 0.68)	0.291	-1.22 (-4.63, 2.18)	0.480
VLDA (7/7)	-1 (-1.77, -0.23)	0.011	-0.78 (-2.14, 0.59)	0.262	-1.5 (-4.73, 1.72)	0.36
MDA 6/7	-1 (-2.04, 0.04)	0.059	-2 (-3.50, -0.50)	0.009	-4.97 (-9.45, -0.49)	0.03
MDA (5/7)	-1 (-1.92, -0.08)	0.03	-0.82 (-2.57, 0.92)	0.35	-4 (-11.4, 3.40)	0.29
DAPSA remission	-1 (-1.92, -0.08)	0.03	-1.48 (-2.87, -0.09)	0.04	-1.35 (-3.85, 1.14)	0.29
SvdH erosion score	Coefficient	P value	Coefficient	P value	Coefficient	P value
Quantile tested	50		75		90	
Tight control	0.00 (0.00, 0.00)	0.722	0.00 (-0.53, 0.53)	1.0	-1 (-2.23, 0.23)	0.11
VLDA (7/7)	0.00 (0.00, 0.00)	0.67	0 (-0.43, 0.43)	1.0	-0.23 (-1.15, 0.69)	0.62
MDA 6/7	0.00 (0.00, 0.00)	0.238	0.00 (-0.79, 0.79)	1.0	-0.9 (-2.12, 0.31)	0.14
MDA (5/7)	0.00 (0.00, 0.00)	0.94	0.00 (-0.47, 0.47)	1.0	-0.3 (-1.62, 1.02)	0.65
DAPSA remission	0.00 (0.00, 0.00)	0.86	0.00 (-0.46, 0.46)	1.0	-0.19 (-1.38, 0.99)	0.75







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Pharmacological Monitoring of Adalimumab and Etanercept-Treated Psoriatic Arthritis Patients in Predicting Future Treatment Response

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Background/Purpose: Up to 40% of patients with inflammatory arthritis on TNF-α inhibitor (TNFi) treatment fail to respond either due to primary inefficacy or loss of response. Based on our previous work (1-2) and others (3), one explanation is immunogenicity leading to the development of anti-drug antibodies (ADAb) and subsequent low drug levels, which has been described in RA. Few data exist on whether such pharmacological tests correlate with treatment response in PsA. Furthermore, the value of measuring such biomarkers may be different between monoclonal antibodies and TNF receptor proteins. Our aim was to (i) evaluate whether the presence of ADAbs/drug levels predict treatment response in patients with PsA treated with TNFi drugs (ii) identify factors that may be associated with drug levels.

Methods: 75 patients were available from the Outcomes of Treatment in PsA Study Syndicate (OUTPASS) (n=49 adalimumab; n=26 etanercept), a national UK prospective observational cohort. Serum samples were collected at 3, 6 and 12 months following initiation of TNFi therapy. ADAbs were measured using radioimmunoassay (RIA) and random (non-trough) drug levels using ELISA assays at 3, 6 and 12 months. Disease activity (DAS28) scores were measured at each visit. Patient self-reported adherence to TNFi was measured at each time-point. Generalised estimating equation (GEE) was used to test the association between ADAbs and drug levels, both biomarkers and treatment response [as assessed by change in DAS28 score between pre-treatment and 12 months post-treatment (ΔDAS28)] and the association between longitudinal/baseline factors with drug levels.

Results: 264 serial samples were suitable for pharmacological testing (n= 174 adalimumab; n=90 etanercept). Mean age was 51±12 years; 61% were female; median BMI 28.9 (IQR 26.0-34.9). 20% (n=10/49) of adalimumab-treated patients were positive for ADAbs, but none were detected in etanercept-treated patients. There was no significant association between etanercept drug levels and ΔDAS over 12 months [β= -0.039 (95% CI -0.31, 0.23), p=0.77]. Using GEE, adalimumab drug levels were significantly associated with ΔDAS28 over 12 months [β= 0.055 (95% CI: 0.011, 0.099) p=0.014], but was not independently associated with ADAb level [β=-0.0015 (95% CI: -0.0031, 0.000047), p=0.057]. Adalimumab concentrations between 4.5-8.5 mg/L were associated with an optimal treatment response at 6 months using concentration-effect curves. Factors that remained significantly associated with adalimumab drug levels were ADAb level [β=-0.0073 (95% CI: -0.0014, 0.18), p<0.0001] and BMI [β=-0.15 (-0.29, -0.00450, p=0.043] in the final GEE model (adjusting for age, gender, adherence, BMI).

Conclusion: TNFi drug-level testing on samples taken at random time-points in the treatment cycle in adalimumab-initiated PsA patients may be clinically useful in determining treatment response over 12 months; interestingly, both the presence of ADAbs and BMI were inversely associated with drug levels. Identification of a drug level threshold for optimal response may help tailor adalimumab therapy for PsA patients in the future. (1) Jani M *et al.* Arthritis Rheumatol. 2015 May;67(8):2011-9. doi: 10.1002/art.39169. (2) Jani M *et al.* Ann Rheum Dis. Published Online First: [31.5.16] doi:10.1136/ annrheumdis-2015-208849 (3) Bartelds GM *et al.* JAMA. 2011;305(14):1460-1468

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Minimal Disease Activity Is a Stable Measure of Therapeutic Response in Psoriatic Arthritis Patients Receiving Treatment with Adalimumab

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Background/Purpose: Minimal disease activity (MDA) is an important goal for patients with rheumatologic disorders, including psoriatic arthritis (PsA). The assessment of MDA could potentially help guide therapeutic modifications as a part of treat-to-target strategies. The availability of data from a large PsA cohort in an observational study of routine clinical care offered a unique possibility to investigate the potential value of MDA as an instrument for guiding treatment decisions during daily clinical practice.

Methods: We analyzed data from a large German multicenter observational study of patients with active PsA who initiated adalimumab (ADA) therapy during routine clinical care. Patients with active disease (Disease Activity Score-28 joints [DAS28] ≥3.2), joint involvement, and adequate MDA data were included in these evaluations. MDA was defined as meeting 5 of 7 criteria as reported by Coates et al. (*Ann Rheum Dis*2010;69:48-53), with slight modifications to criteria for pain, function, and enthesitis to reflect available data. Patients were followed for up to 24 months.

Results: Of 1684 patients with PsA who initiated ADA, the mean age was 50 years, 51% were female, and the disease duration was 9.5 and 18.1 years for arthritis symptoms and psoriasis, respectively. A total of 597/1684 (35.5%) patients achieved MDA at month 6. This proportion increased slightly during the 24-month study (454/1098 [41.3%] at month 12; 348/764 [45.5%] at month 24), likely due to responder bias. Pain was the most difficult criterion to achieve and the absence of enthesitis was the criterion most likely to be fulfilled (Table 1). Correlation analyses for month 6 data found that PGA ≤2 had the highest correlation with the achievement of MDA (Pearson correlation coefficient=0.72), followed by TJC ≤1 (0.61) and pain ≤1 (0.60), while absence of enthesitis (0.21) and BSA ≤3% (0.31) had the lowest correlations with MDA (P<0.001 for all analyses). Among patients with complete data available for all time points from month 6 to month 24 (n=554), 214 (38.6%) achieved an MDA at month 6. Of the patients who achieved MDA at month 6, 118 of 214 (55.1%) also had an MDA at all subsequent time points (months 9, 12, 18, and 24). Of the patients who did not achieve an MDA at month 6 (n=340), 201 (59.1%) failed to achieve an MDA at any subsequent time point.

MDA Criteria	**% of patients (n=1684)**
Tender joint count (TJC) ≤1	46.6%
Swollen joint count (SJC) ≤1	70.1%
Body surface area (BSA) ≤3%	64.8%
Patient pain score ≤1 on a 0-10 point scale*	21.1%
Patient global disease activity (PGA) ≤2	40.1%
Funktionsfragebogen Hannover score ≥83% remaining function†	47.4%
No enthesitis‡	88.8%
*Published criterion is ≤15 points on a 100 point scale †Published criterion is Health Assessment Questionnaire ≤ 0.5 ‡Published criterion is tender entheseal points ≤ 1	

Conclusion: MDA criteria provide a stable assessment of therapeutic response during ADA therapy; most patients who achieved MDA at month 6 experienced sustained MDA, while most patients who did not achieve MDA at month 6 did not reach MDA at any subsequent time point. PGA had the highest correlation with MDA, while enthesitis had the lowest. Our data confirm the relevance of assessing MDA in patients with PsA and indicate that MDA may be useful in guiding therapy in treat-to-target strategies.

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Abstract Number: 1697

Validity of Diagnostic Codes and Point Prevalence of Psoriatic Arthritis in Israel – a Population-Based Study

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Background/Purpose: The information on the population-based prevalence of Psoriatic Arthritis (PsA) is limited. Large population-based databases provide an opportunity to study the epidemiology of PsA, however, strict validation procedures for case ascertainment are required. We aimed to examine the validity of a diagnostic code for PsA in Clalit Health Services (CHS) database in Israel and to estimate its point prevalence in the general population.

Methods: CHS database, Israel's largest public health fund serving 4.3 million enrollees (>50% of Israel's population), has real-time input from pharmaceutical, medical and administrative operating systems. CHS database was searched for all individuals who received their initial diagnostic code of PsA (ICD-9 code 696.0) in 2014. Cases were divided according to the type of specialist (rheumatologists, family physicians, dermatologists, orthopedics) who assigned the diagnostic code of PsA.. Approximately 25% of the cases in each subspecialty group were selected at random for the validation of a diagnostic code of PsA. All medical records of these patients were thoroughly read by two rheumatologists. Based on this information a decision was made whether the PsA diagnosis was 1) definite/probable PsA; 2) not PsA; 3) no data to verify the diagnosis of PsA. We calculated the positive predicted value (PPV) and the 95% confidence interval in each group. Several algorithms were examined to determine the method resulting in the highest PPV. The sensitivity and specificity for the selected algorithm were calculated and the point prevalence of PsA in the general population and its 95% confidence interval (CI) were estimated.

Results: 869 individuals who received a diagnosis of PsA in 2014 were identified. 205 cases were selected for validation based on the specialty of the physician who assigned the diagnosis. The proportion of ICD-9 codes that could be confirmed

by reviewing the medical records was 94%. The PPVs for a diagnostic code assigned by a rheumatologist or given during hospitalization was: 90.5% (95% CI 82.3%, 95.3%), orthopedics 18.2% (95% CI 3.2%, 52.2%) dermatologists 13.3% (95% CI 2.3%, 41.6%) and family physicians 50% (95% CI 29.6%, 70.3%). The selected algorithm comprised the PsA code assigned by a rheumatologist, or a permanent diagnosis code assigned by a family physician combined with use of DMARDs, or PsA code given during hospitalization. This algorithm had sensitivity and specificity of 88.7% and 88.1%, respectively. Using the validated algorithm, 3874 PsA patients were identified among a population of 4,296,000 enrollees in the CHS database, reflecting prevalence of 90 per 100,000 (95% CI 87, 93 per 100,000).

Conclusion: Data within electronic medical records can be used to accurately identify patients with PsA. The estimated prevalence of PsA in the general population in Israel is 0.09%. This figure is consistent with other population-based estimates.

Disclosure: L. Eder, None; **A. D. Cohen**, None; **I. Feldhamer**, None; **S. Greenberg-Dotan**, None; **E. Batat**, None; **D. Zisman**, None.

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Abstract Number: 1698

Late Onset Psoriatic Arthritis in a Longitudinal Cohort: Disease Presentation, Activity over Time and Prognosis

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Background/Purpose: Psoriatic arthritis (PsA) often develops between the 3rd to 5th decades of life. However, little is known about PsA activity and prognosis among patients who develop it at an older age. Hence, our aims were: 1) To evaluate disease activity of late onset PsA (LoPsA) patients at presentation and during follow-up, and 2) To evaluate prognosis after several years of follow-up, compared to younger onset PsA patients (YoPsA).

Methods: The study population included patients from a large longitudinal PsA cohort**.** The patients are followed prospectively according to a standard protocol and all data are stored in a computerized database. Only patients who started their follow up in the PsA clinic within 2 years from diagnosis were included. Patients were divided into two groups: 1) Late onset PsA (LoPsA) – defined as disease onset after the age of 50, 2) Younger onset PsA (YoPsA) – defined as disease onset before age 50. Disease activity over time was calculated according to the adjusted mean active joint count. Patients were compared at presentation, and after 5 years of follow-up. Descriptive statistics are provided and multivariate logistic regression models were developed to compare the two groups.

Results: Five hundred and sixty six patients were included at presentation, 177 above the age of 50 years and 389 below 50 years. The LoPsA group included more women (53% vs 41%, p=0.01). The LoPsA had significantly higher BMI (30.7 ± 7.4 vs 28.2 ± 6.1, p<0.001), more clinically damaged joints at presentation (0.9 ± 2.2 vs 0.3 ± 1.6, p=0.001) and higher modified Steinbrocker score (mSS) (4.3 ± 7.9 vs 1.8 ± 1.4, p=0.0001) (Table 1). Multivariate logistic regression analysis showed that the following variables were independently associated with being in the LoPsA group at presentation: less males (OR 0.4, p=0.001), less HLA-C*06 (OR 0.3, p=0.008), longer psoriasis duration (OR 1.04, p=0.0003), higher BMI

(OR 1.1, p=0.002) and higher mSS (OR 1.1, p=0.009). After 5 years of follow-up, the LoPsA patients showed a non-significant trend for higher adjusted mean active joint count compared to the YoPsA (7.1 ± 7.3 vs 5± 5.2, p=0.07) as well as higher mean mSS compared to the YoPsA (0.7 ± 1.7 vs 0.3 ± 1.3, p=0.02). Multivariate logistic regression analysis revealed higher adjusted mean active joint count (OR 2.04, p=0.049) and higher mean mSS score (OR 2.4, p=0.009) in the LoSpA group compared to the YoPsA group. .

Conclusion: The LoPsA patients at presentation are characterized by female predominance, higher BMI, more damage and less HLA-C*06. After 5 years of follow-up the LoPsA patients are associated with worse prognosis manifested by higher disease activity and more damage.

Table 1: Characteristics of LoPsA and YoPsA at presentation

Variable	YoPsA (n=389)	LoPsA (n=177)	P value
Age at PsA diagnosis, years ± s.d.	34.8 ± 8.5	58.4 ± 7.7	
Age at psoriasis, years ± s.d.	25 ± 10.6	42.4 ± 16.7	<0.001
Females gender, n (%)	159 (41%)	93 (53)	0.01
BMI, mean ± s.d.	28.2 ± 6.1	30.7 ± 7.4	<0.001
Smoking history, n (%)	164 (45)	83 (50)	0.3
Actively inflamed joints count, mean ±s.d.	7.9 ± 8.4	8.7 ± 9.9	0.4
Tenosynovitis, n (%)	85 (22)	34 (19)	0.51
Dactylitis, n (%)	126 (33)	36 (21)	0.003
Damaged joint count, mean ± s.d.	0.3 ± 1.6	0.9 ±2.2	0.001
Modified Steinbrocker score, mean ± s.d.	1.8 ± 4.3	4.3 ± 7.9	0.0001
Sacroiliitis, n (%)	80 (22)	45 (27)	0.3
PASI, mean ± s.d.	5.3 ± 7.8	6 ± 9.8	0.4
Nail involvement, n (%)	150 (39)	67 (38)	0.9
CRP, n (%) positive	56 (46)	24 (34)	0.13
ESR, n (%) positive	142 (43)	71 (46)	0.5
HLA-B*27 (%) positive	44 (14)	16 (12)	0.5
HLA-C*06 (%) positive	79 (26)	24 (18)	0.087

LoPsA – Late onset PsA, YoPsA – Young onset PsA, BMI – Body mass index, PASI – Psoriasis activity severity index, CRP – C reactive protein, ESR – Erythrocyte sedimentation rate

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Abstract Number: 1699

RAPID3 Near Remission Shows Good Agreement with Minimal Disease Activity Criteria in Psoriatic Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: RAPID3 (routine assessment of patient index data) is a patient self-report index which is feasible in busy clinical settings to assess severity and change in clinical status in many rheumatic diseases, including RA, OA, gout, AxSpA. RAPID3 (0-30) includes 3 0-10 measures: a health assessment questionnaire (HAQ) or its multidimensional version (MDHAQ) measuring physical function and two 0-10 visual analogue scales (VAS) for pain and patient global estimate. A score of ≤3 (of 30) identifies near remission (NR) in rheumatoid arthritis. RAPID3 is correlated significantly with other PsA measures; a RAPID3Ps has also been investigated with the addition of a skin VAS for PsA. The Minimal Disease Activity (MDA) criteria for PsA require achievement of 5 of 7 cutpoints in 7 measures: the three RAPID measures; tender joint count (TJC); swollen joint count (SJC); enthesitis count and skin measure. Our aim was to compare patients achieving RAPID3 and RAPID3Ps near remission and MDA criteria in PsA in individual patients in the Tight Control of Psoriatic Arthritis (TICOPA) trial.

Methods: Data from TICOPA were analysed to identify patients achieving RAPID3 and RAPID3Ps NR, and the patients were compared to those achieving the MDA criteria. MDA was achieved if patients achieved 5 of the 7 following cut points: TJC ≤1; SJC ≤1; enthesitis ≤1; PASI ≤1; HAQ function ≤0.5; global VAS ≤20 and pain VAS ≤15. Frequency of residual active disease in the RAPID3 NR states was investigated. A measure of acute phase response is not included in either measure, but CRP levels were assessed to recognize whether an active acute phase response was missed.

Results: The percentage exact agreement (PEA) between RAPID3 NR and MDA was 83.8, 89.8, 87.1, 85.2 at 12, 24, 36, 48 weeks respectively. Adding the skin component to create RAPID3Ps and using the equivalent NR cutpoint (4/40) led to PEA of 85.1, 88.0, 88.5 and 85.1 respectively. Very few patients (2.2-3.8%) were in RAPID3NR but not MDA due to high physician assessed outcomes. For patients in RAPID3NR at the end of the study, residual disease activity is shown in the table. Levels of skin disease in this population were very low with PASI of 0 in 94% of these patients.

Conclusion: RAPID3NR and RAPID3PsNR shows good agreement with the MDA criteria in PsA. The addition of a psoriasis measure did not change the results meaningfully in this population, but may be more infortative in patients with more severe skin disease. The RAPID3 NR definition does allow significant residual disease in a few patients but may be useful as an adjunct to physician examination when monitoring disease activity.

		RAPID3 NR n (%) (n=67)	RAPID3Ps NR n (%)(n=67)
PASDAS	Mean (SD)	1.82 (0.70)	1.79 (0.71)
Tender joint count	0	38 (56.7)	38 (56.7)
	1	11 (16.4)	10 (14.9)
	2	5 (7.5)	6 (9.0)
	3	2 (3.0)	2 (3.0)
	4	5 (7.5)	5 (7.5)
	5	1 (1.5)	1 (1.5)
	7	3 (4.5)	3 (4.5)
	8	2 (3.0)	2 (3.0)
Swollen joint count	0	49 (73.1)	50 (74.6)
	1	9 (13.4)	7 (10.4)
	2	5 (7.5)	5 (7.5)
	3	1 (1.5)	1 (1.5)
	4	2 (3.0)	3 (4.5)
	5	1 (1.5)	1 (1.5)
Enthesitis count	0	48 (71.6)	49 (73.1)
	1	8 (11.9)	7 (10.4)
	2	7 (10.4)	7 (10.4)
	3	3 (4.5)	3 (4.5)
	7	1 (1.5)	1 (1.5)
Dactylitis count	0	62 (92.5)	63 (94)
	1	1 (1.5)	1 (1.5)
	2	3 (4.5)	3 (4.5)
	3	1 (1.5)	0 (0)
PASI	0	63 (94.0)	63 (94.0)
	0.3	1 (1.5)	1 (1.5)
	0.6	1 (1.5)	1 (1.5)
	0.8	0 (0)	1 (1.5)
	3	2 (3.0)	1 (1.5)
CRP	Normal (<5mg/dl)	51 (76.1)	50 (74.6)
	Raised	15 (22.4)	15 (22.4)
	Missing	1 (1.5)	2 (3.0)

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Abstract Number: 1700

Treating Psoriatic Arthritis (PsA) to Target: Defining Psoriatic Arthritis Disease Activity Score (PASDAS) That Reflects Disease Activity in Psa

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Background/Purpose: PASDAS is a composite disease activity measure (range 0–10) for psoriatic arthritis (PsA). Recently, PASDAS disease activity cutoffs were proposed and a minimal disease activity (MDA) state for PsA was also defined as a target for treatment. We aimed to establish a cutoff value of PASDAS that defines MDA state, to validate previously defined PASDAS cutoffs for low and high disease activity (3.2 and 5.4), and to define PASDAS cutoffs reflecting disease activity in our cohort.

Methods: All patients meeting CASPAR criteria were prospectively recruited from a PsA clinic and items necessary to complete the PASDAS and the MDA were evaluated. For aim 1, ROC curve analysis determined the optimal PASDAS cutoff discriminating patients based on MDA state. This analysis was subsequently repeated twice changing the discriminating criteria to meeting 6 of 7 and all 7 of the 7 MDA criteria. For aim 2 sensitivity and specificity of the previously defined PASDAS cutoffs for high and low disease activity were determined. For aim 3 patients were dichotomized based on the decision to escalate treatment by the treating physician (indicator of high disease activity). ROC curve analysis (90% specificity) estimated the PASDAS cutoff for high disease activity. Further, the median value of PASDAS for each treatment change group estimated PASDAS cutoffs for low and high disease. Lastly, ROC curves (90% specificity) estimated PASDAS cutoffs using patient's global assessment of disease activity (PGA) as an external standard (<10 low; ≥10 moderate <60; ≥60 high). The mean values obtained by the 3 methods defined the final PASDAS cutoffs.

Results: 178 patients [53.9% male, mean age 56.8 years, disease duration 17.6 years, mean (SD) PASDAS 3.29 (1.29), 48.9% in MDA] were recruited. See table 1. PASDAS of <3.2 defined MDA (AUC- 0.96, sensitivity 88% [95% CI: 80-93%], specificity 92% [95% CI: 84-96%], Youden index- 0.80). For MDA based on meeting 6 of 7 criteria and all 7 of 7 criteria PASDAS scores of 2.6 and 2.1 maximized sensitivity and specificity, respectively. The published PASDAS cutoffs showed the following sensitivities and specificities (%), respectively: low- 100, 56; high- 12, 99 (PGA as external criterion). ROC curve analysis using treatment escalation as discriminating variable estimated a PASDAS high disease activity cutoff of 4.7 (AUC- 0.76). Median PASDAS of escalation and no-escalation groups were 4.17 and 2.86, respectively. When using PGA, PASDAS cutoffs for low and high disease were 2.08 (AUC- 0.95) and 4.14 (AUC- 0.93), respectively. The final PASDAS cutoffs (mean of 3 methods) for low and high disease activity cutoffs were 2.5 and 4.3, respectively.

Conclusion: A PASDAS score <3.2 reflects MDA. MDA based on stricter criteria may better reflect low disease activity state. Previously defined PASDAS cutoff for low disease activity state has high sensitivity while high disease activity cutoff has high specificity. Our cohort produced lower cutoffs.

Table 1: Cutoff values of PASDAS obtained from various methods.

Cutoff	ROC curve (MDA 5/7)	ROC curve (MDA 6/7)	ROC curve (MDA 7/7)	ROC curve (treatment escalation)	Median Scores	ROC curve (PGA)	Final PASDAS (means)
MDA state	3.2	2.6	2.1	-	-	-	-
Low disease activity state	-	-	-	-	2.86	2.08	2.5
High disease activity state	-	-	-	4.7	4.17	4.14	4.3

Disclosure: M. Got, None; **S. Li**, None; **A. V. Perruccio**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **V. Chandran**, None.

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Abstract Number: 1701

The Presence of Depression Might be an Important Determinant of Achieving Minimal Disease Activity State in Psoriatic Arthritis

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Background/Purpose: Depression and anxiety are well known comorbidities in psoriasis (PsO) and psoriatic arthritis (PsA) with higher prevalence in PsA. Patients with PsA have a worse quality of life than PsO, and the presence of joint pain is associated with higher rates of depression[1]. Previous studies suggested that disease control may reduce symptoms of depression in PsO[2]. Minimal disease activity (MDA) is a desirable state when treating patients with PsA, giving better outcomes as a target overall[3]. To date, no study has evaluated the effect of depression/anxiety on MDA in PsA. The aim of the study was to 1) Compare depression/anxiety scores between patients with MDA to those not in MDA (NMDA) in PsA. 2) Assess the effect of disease related variables, treatment, and depression and anxiety scores on MDA state.

Methods: PsA patients fulfilling the CASPAR criteria were recruited. Patients were assessed for depression/anxiety using the Hospital Anxiety and Depression Scale (HADS-A and HADS-D) and Penn State Worry Questionnaire (PSWQ). Medical history including previous diagnosis or treatment for depression and anxiety, and risk factors of depression was taken. Patients underwent joint and skin assessments and completed questionnaires on health and quality of life. We compared the HADS-D and HADS-A scores and the % of patients with normal (0-7), borderline (8-10) and abnormal (11-21) categories between patients with MDA to those with NMDA, and anxiety by using PSWQ scores and the % of patients in low (16-39), moderate (40-59) and high (60-80) worry categories. Data were analyzed using Mann Whitney, Fisher's exact, Chi-square tests and logistic regression analyses.

Results: 100 PsA patients were recruited, 40 patients were in MDA (age 52±10.6 years, male 55%) and 60 patients in NMDA (age 52±10.6 years, male 55%). TJC68 and SJC66 were lower in MDA compared to NMDA group (P<0.001) with no significant difference in the other 5 items of MDA, the number of patients on DMARD, biological treatment, and depression and anxiety medications. The % of patients with normal, borderline and abnormal HADS-D scores were 95%, 5% and 0 in MDA group vs. 80%, 15% and 5% in NMDA (P=0.084), respectively. Mean HADS-D score was significantly lower in MDA compared to NMDA (2.5±2.4 vs. 4.22±3.4, P=0.009). The % of patients with normal, borderline and abnormal HADS-A scores were 92.5%, 7.5% and 0 in MDA vs. 76%, 17% and 7% in NMDA (P=0.078), respectively. Mean HADS-A score was lower in MDA compared to NMDA. The number of patients in low, moderate and high worry categories and the mean PSWQ scores were similar in both groups. Logistic regression analyses revealed significant relationship between lower TJC (B=0.508 (CI95% 0.37-0.7) P<0.001), lower HADS-D (B=0.841 (CI95% 0.71-0.99) P=0.043) and MDA state.

Conclusion: This is the first study assessing the effect of depression and anxiety on MDA. We found lower depression scores in patients with MDA compared to those in NMDA and significant relationship between depression and MDA state. Our results suggest the importance of recognizing depression in PsA since psychological well-being may contribute to MDA state. **References:**

1. McDonough E. JRheumatol 2014
2. Roubille C. JRheumatol 2015
3. Coates L. Lancet 2015

Disclosure: A. Szentpetery, None; **N. Ikumi**, None; **B. Kirby**, Abbott Immunology Pharmaceuticals, 2; **O. FitzGerald**, Abbott Immunology Pharmaceuticals, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 2,Abbott Immunology Pharmaceuticals, 5,Pfizer Inc, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,UCB Pharma, 5,Eli Lilly and Company, 5.

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Abstract Number: 1702

Baseline Patient Characteristics Associated with Response to Biologic Therapy in Patients with Psoriatic Arthritis Enrolled in the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

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Background/Purpose: The objective of this analysis was to investigate differences in baseline demographic and clinical characteristics of patients with psoriatic arthritis (PsA) who responded to biologics vs those who were non-responders using the US-based Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) registry.

Methods: This analysis included all patients with PsA aged ≥ 18 years enrolled in the Corrona PsA/SpA registry between March 2013 and March 2016 who were receiving biologics at the time of enrollment (baseline) and had ≥ 2 follow-up visits (at 6-month intervals). Responders were defined as those patients who remained on their index biologic and achieved minimal disease activity (MDA) at the second follow-up visit (mean [SD] follow-up, 15.7 [3.7] months) from baseline.[1] Information on demographics, clinical characteristics, patient-reported outcomes and past/current treatments were collected for all patients at baseline enrollment. Statistical comparisons between responders and non-responders were examined by *t*-tests for continuous variables and chi-square tests (or Fisher's exact tests) of independence for categorical variables.

Results: There were 148 patients with PsA in the Corrona PsA/SpA registry that met the inclusion criteria. At the second follow-up visit 34 patients (23.0%) were classified as responders and 114 patients (77.0%) were considered non-responders. The majority of patients were receiving anti–tumor necrosis factor agents at registry enrollment (96.6%). At

baseline, responders and non-responders were similar with regards to age, sex, race, disease duration, prevalence of comorbidities (cardiovascular disease, any cancer, diabetes and serious infection), multiple disease measures (e.g., enthesitis and dactylitis counts, Clinical Disease Activity Index and acute phase reactants) and prior/current treatments. Compared with non-responders, responders to biologics had significantly milder disease at the time of registry enrollment as measured by mean tender joint count (3.4 vs 7.2), patient-reported pain (35.7 vs 51.2), patient-reported fatigue (42.4 vs 54.1), Health Assessment Questionnaire score (0.6 vs 1.0), Bath Ankylosing Spondylitis Disease Activity Index score (3.4 vs 5.0) and Bath Ankylosing Spondylitis Functional Index score (2.0 vs 4.0) (**Table**).

Conclusion: This study from the Corrona PsA/SpA registry found that only 23.0% of patients achieved MDA with their index biologic at the time of the second follow-up visit (mean [SD] follow-up, 15.7 [3.7] months) and were considered responders. Both cohorts were similar with regards to several baseline demographic and clinical characteristics; however, responders generally had less severe disease at enrollment compared with non-responders.

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1. Coates LC, et al. *Ann Rheum Dis*. 2010;69(1):48-53.

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Abstract Number: 1703

Early Onset of Efficacy with Apremilast Monotherapy in Biologic-Naive Patients with Active Psoriatic Arthritis: A Phase IIIb, Randomized, Controlled Trial

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Background/Purpose: ACTIVE is the first apremilast (APR) trial that evaluated time to onset of efficacy beginning at Wk 2 in psoriatic arthritis (PsA) patients (pts) who were biologic-naïve and may have had ≤1 prior conventional disease-modifying antirheumatic drug. We report the study results through Wk 52.

Methods: Pts were randomized (1:1) to APR 30 mg BID or placebo (PBO). At Wk 16, pts whose swollen and tender joint counts (SJC/TJC) had not improved ≥10% were eligible for early escape (investigator discretion): PBO pts received APR, and APR pts continued on APR. At Wk 24, all pts entered the active treatment phase with APR. The primary endpoint was ACR20 response at Wk 16. Other assessments included changes in DAS-28 (CRP), SJC, TJC, and HAQ-DI, morning stiffness duration/severity, and enthesitis, as measured by the Gladman Enthesitis Index (GEI; 0=no enthesitis, 6=all 6 sites active). Along with collection of safety data, tolerability adverse events (AEs) of diarrhea were further characterized.

Results: A total of 219 pts were randomized (APR: n=110; PBO: n=109); 84.5% completed Wk 24 (APR: n=87; PBO: n=98). Separation in the proportion of ACR20 responders to APR vs PBO was noted at Wk 2 (16.4% vs 6.4%; *P*=0.0252), the first post-baseline (BL) visit. Early onset of response to APR was observed across clinical assessments, with improvements in DAS-28 (CRP), SJC, HAQ-DI, enthesitis, and morning stiffness severity (Table). At Wk 16, APR showed significant reduction in PsA disease activity and manifestations vs PBO, with an ACR20 response rate of 38.2% vs 20.2% (*P*=0.0040); DAS-28 (CRP) change of −1.07 vs −0.39 (*P*<0.0001); SJC change of −44.8% vs 1.9%; HAQ-DI change of −0.21 vs −0.06 (*P*=0.0229); improvement in morning stiffness severity in 46.4% vs 26.6% of pts; and GEI change of −1.5 vs −0.4 (*P*=0.0014). With continued APR exposure, the Wk 52 ACR20 response rate was 63.3%, ACR50 and ACR70 response rates were 32.4% and 14.0%, and percent change in SJC was −74.5%. Among APR pts with BL enthesitis, 62.8% reached a GEI of 0. Overall incidence of AEs in the PBO-controlled period was generally similar between APR and PBO. The most commonly reported AEs in ≥5% of pts with APR vs PBO were nasopharyngitis (8.3% vs 6.4%), nausea (8.3% vs 1.8%), headache (7.3% vs 3.7%), hypertension (6.4% vs 6.4%), and diarrhea (14.7% vs 11.0%); using a protocol-defined characterization of diarrhea (≥2 watery/liquid stools/day), overall incidence was lower for APR and PBO (11.0% and 8.3%). Serious AEs were lower with APR vs PBO (2.8% vs 4.6%). In general, no increase was seen in AE incidence/severity with longer-term exposure to APR.

Conclusion: In biologic-naïve pts treated with APR, onset of effect was observed starting with Wk 2, with sustained improvements across PsA manifestations, including morning stiffness and enthesitis through Wk 52. AEs were consistent with those reported for other APR phase III PsA and psoriasis studies.

	Wk 2		Wk 16		Wk 52[a]
	APR n=110	PBO n=109	APR n=110	PBO n=109	APR n=171
ACR20, n/m (%)[b]	18/110 (16.4)*	7/109 (6.4)	42/110 (38.2)§	22/109 (20.2)	107/169 (63.3)
DAS-28 (CRP), mean change[c]	−0.59*	−0.31	−1.07‡	−0.39	−1.58
SJC, mean % change[d]	−28.5	−18.0	−44.8	1.9	−74.5
HAQ-DI score (0-3), mean change[c]	−0.13*	−0.05	−0.21*	−0.06	−0.36
HAQ-DI MCID ≥0.30, n/m (%)[b,e]	24/110 (21.8)	13/109 (11.9)	39/110 (35.5)	30/109 (27.5)	78/171 (45.6)
SF-36v2 PF, mean change[c]	NA	NA	2.43§	−1.04	5.5
Improvement in morning stiffness severity, n/m (%)[b]	47/110 (42.7)	23/109 (21.1)	51/110 (46.4)	29/109 (26.6)	98/171 (57.3)
GEI (0-6), mean change[c,f]	−1.1*	−0.4	−1.5§	−0.4	−1.5

[a]At Wk 52, data are as observed; the n reflects the number of patients treated with APR, regardless of when APR was started (BL, Wk 16, or Wk 24), and who had data available at Wk 52; actual number of patients available for each end point may vary. [b]Full analysis set for Wk 2 and Wk 16; pts with missing data were categorized as non-responders. [c]Full analysis set and least-squares means presented for Wk 2 and Wk 16; arithmetic means presented for Wk 52. [d]SJC mean percent change from BL was calculated based on the last-observation-carried-forward data for Wk 2 and Wk 16. [e]Last-observation-carried-forward data were used prior to non-responder imputation. [f]Evaluated in pts with enthesitis at BL (GEI >0) (Wk 2: APR n=55, PBO n=49; Wk 16: APR n=49, PBO n=48; Wk 52: APR n=86).
*P<0.05; §P<0.005; ‡P<0.0001 vs PBO; based on a mixed-effects model for repeated measures for DAS-28 (CRP), HAQ-DI score, SF-36v2PF, and GEI mean changes from BL, and a Cochran-Mantel-Haenszel test for ACR20 and HAQ-DI MCID ≥0.30.
DAS-28 (CRP)=28-joint count Disease Activity Score (C-reactive protein); ACR20=20% improvement in modified American College of Rheumatology response criteria; HAQ-DI=Health Assessment Questionnaire-Disability Index; MCID=minimal clinically important differences; n/m=number of responders/number of patients with sufficient data for evaluation; SF-36v2 PF=36-item Short-Form Health Survey version 2 Physical Functioning domain score; NA=not available (not assessed at time point).

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Abstract Number: 1704

Consistent Safety and Tolerability of Secukinumab over Long-Term Exposure in Patients with Active Psoriatic Arthritis and Moderate to Severe Plaque Psoriasis: Updated Pooled Safety Analyses

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Background/Purpose: Pooled safety data from the psoriasis (PsO) and psoriatic arthritis (PsA) clinical trial programs of secukinumab (SEC), through approximately 1 year, have been reported previously.[1,2] Specifically, the exposure-adjusted incidence rates (EAIRs) of adverse events (AEs) and serious adverse events (SAEs) for PsO and PsA were 252.9 and 7.8, and 210.3 and 9.0 per 100 patient (pt)-years, respectively. Here we present updated analyses following additional exposure (with a 25 Dec 2015 data cut-off), either from a larger study pool (PsO) and/or an extended follow-up period (PsO, PsA).

Methods: The updated PsO pool consisted of 4 Phase II and 9 Phase III studies in pts with moderate-to-severe plaque PsO, including 2 active comparator studies with etanercept (ETN) and ustekinumab (UST), respectively; the PsA pool consisted of 2 PBO-controlled Phase III studies in pts with active PsA. SEC doses differed in the studies and included intravenous (3–10 mg/kg) or subcutaneous (75–300 mg) loading, followed by subcutaneous maintenance dosing (300, 150, or 75 mg). PBO pts were re-randomized to SEC between 12–24 weeks in the various studies. EAIRs were calculated to minimize the impact of between-group differences in treatment exposure.

Results: In both the PsO and PsA pools, the most frequently reported AEs with SEC were non-serious infections, including nasopharyngitis and upper respiratory tract infection, headache, and arthralgia (Table). The EAIRs of AEs of special interest, including Crohn's disease, *Candida* infections, serious infections, neutropenia, major adverse cardiac events, and malignancy, with SEC (reported in the Table) were similar across PsO and PsA studies, and comparable to those reported previously.[1,2]

Conclusion: Treatment with SEC was well tolerated in PsO and PsA patients. This longer-term safety assessment was consistent with previous reports,[1,2] and did not identify any new safety signals. The long-term safety profile of SEC was comparable across PsO and PsA patients, allowing a broader understanding of the safety of SEC in these two closely related disease populations. **References:** 1. Van de Kerkhof PCM, et al. *J Am Acad Dermatol* 2016;75:83–98; 2. Mease PJ, et al. A*rthritis Rheumatol* 2015; 67 (suppl 10):A2886

Table. Summary of pooled safety across 13 PsO studies and 2 PsA studies (entire safety period)

	PsO			PsA
	Any secukinumab N=3896[a]	Etanercept N=323	Ustekinumab N=336	Any secukinumab N=974[a]
Total exposure, patient-years	7338.8	339.8	320.6	1446.3
Discontinuations due to AEs, n (%)	216 (5.6)[b]	12 (3.7)	8 (2.4)	32 (3.3)
AEs, EAIR per 100 Patient-years (95% CI)				
Any AE	202.2 (195.4–209.1)	233.7 (206.2–263.9)	249.5 (221.1–280.6)	181.5 (169.2–194.5)
Any serious AE	7.4 (6.8–8.1)	6.7 (4.2–10.1)	8.4 (5.5–12.4)	8.3 (6.8–10.0)
Common AEs[c]				
Nasopharyngitis	20.0 (18.8–21.2)	33.8 (27.2–41.4)	30.9 (24.6–38.2)	13.0 (11.1–15.2)
URTI	6.6 (6.0–7.2)	5.5 (3.3–8.7)	9.9 (6.7–14.1)	14.5 (12.4–16.7)
Headache	6.8 (6.2–7.4)	13.5 (9.7–18.3)	14.1 (10.1–19.2)	5.6 (4.4–7.0)
Arthralgia	5.7 (5.2–6.3)	9.0 (6.0–13.0)	9.2 (6.1–13.3)	3.8 (2.8–5.0)
AEs of special interest				
Infections and infestations	71.9 (69.1–74.8)	85.2 (73.1–98.9)	95.5 (82.5–109.9)	70.6 (64.9–76.6)
Candida	1.93 (1.62–2.28)	1.18 (0.32–3.03)	1.57 (0.51–3.67)	1.75 (1.13–2.59)
Serious infections	1.5 (1.2–1.8)	1.2 (0.3–3.0)	1.9 (0.7–4.1)	1.9 (1.2–2.8)
Crohn's disease	0.08 (0.03–0.18)	0.0 (0.00–1.09)	0.0 (0.00–1.15)	0.07 (0.00–0.39)
Ulcerative colitis	0.15 (0.07–0.27)	0.29 (0.01–1.64)	0.0 (0.00–1.15)	0.14 (0.02–0.50)
Neutropenia	0.77 (0.58–1.00)	1.48 (0.48–3.46)	0.0 (0.00–1.15)	1.33 (0.80–2.08)
MACE[d]	0.34 (0.22–0.50)	0.29 (0.01–1.64)	0.31 (0.01–1.74)	0.55 (0.24–1.09)
Malignant or unspecified tumors	0.93 (0.73–1.18)	0.59 (0.07–2.13)	0.94 (0.19–2.74)	0.90 (0.48–1.54)

[a]Includes patients from the placebo groups who were re-randomized to secukinumab treatment. [b]N=3878; disposition data not collected for Study A2102. [c]Most common AEs were events that had an EAIR of ≥5.0 cases per 100 patient-years in the 'any secukinumab' group during the entire safety reporting period. [d]Unadjudicated events.
AE, adverse event; EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiac event; URTI, upper respiratory tract infection.

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Pfizer, Regeneron, Takeda, UCB Pharma, Xenoport, 2,AbbVie, Amgen, Biogen, Boehringer Ingelheim Pharma, Celgene, Centocor, Covagen, Forward Pharma, GlaxoSmithKline, Janssen-Cliag, Leo, Lilly, Medac, Merck Sharp and Dohme Corp., Novartis, Ocean Pharma, Pfizer, Regeneron, Takeda, UCB Pharma, Xenoport, 5; **M. Andersson**, Novartis, 3; **A. Tao**, Novartis, 3; **T. Fox**, Novartis Pharma AG - Switzerland, 1,Novartis Pharma AG - Switzerland, 3; **C. Karyekar**, Novartis Pharmaceuticals, 1,Novartis Pharmaceuticals, 3.

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Abstract Number: 1705

The Risk of Fracture Among Patients with Psoriasis, Psoriatic Arthritis and Rheumatoid Arthritis

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Background/Purpose: While rheumatoid arthritis (RA) has been linked to an increased incidence of osteoporosis (OP) and fracture, few studies have examined the risk of fracture associated with psoriasis and psoriatic arthritis (PsA). In this study, we determined the risk of fracture among patients with PsA, psoriasis and RA compared with the general population.

Methods: A longitudinal cohort study was conducted in The Health Improvement Network (THIN), a primary care medical record database in the United Kingdom, to determine the risk of fracture (all, hip, and vertebral) using data from 1994-2014. Patients aged 18-89 with a diagnosis of PsA, RA, or psoriasis were selected. Diagnosis codes for PsA, RA, and psoriasis have been validated in THIN. Up to 5 unexposed controls matched on practice and start date within the practice were selected for each exposed patient. Cox proportional hazards models were used to calculate the adjusted hazard ratios (aHR) for each outcome. Multivariable models were constructed to include known risk factors and potential confounders (p-value<0.05 and changed the main effects by >10%).

Results: Patients with PsA (N=9,788), RA (N=39,306), psoriasis (N=158,323) and unexposed controls (N=821,834) were identified. Patients with RA had a significantly elevated risk of fracture: all, hip, and vertebral aHR: 1.23 (1.18-1.28), 1.55 (1.40-1.72), 1.53 (1.30-1.80) respectively. Those with mild psoriasis had significantly elevated risk of all fractures and hip fracture: aHR 1.07 (1.05-1.10) and 1.13 (1.04-1.22). Patients with severe psoriasis had significantly elevated risk of all fracture and vertebral fracture: aHR 1.26 (1.15-1.39) and 2.23 (1.03-1.33). Patients with PsA had a significantly elevated risk of all fracture: aHR 1.26 (1.06-1.27). Patients with PsA had an elevated aHR for hip fracture (1.17; 0.86-1.59), however, this was not statistically significant. These results were robust to several sensitivity analyses.

Conclusion: Patients with PsA, severe psoriasis and RA have an elevated risk for fracture. These results underscore the importance of screening for osteoporosis among patients with these inflammatory conditions.

Table: Hazard Ratios for Incident Fracture.

ALL FRACTURES	Number of Events	Incidence*	Unadjusted		Age/Sex Adjusted		Fully Adjusted**	
			HR	CI	HR	CI	HR	CI
Controls	49,168	92.18	REF		REF		REF	
PsA	575	99.23	1.09	1.00-1.18	1.14	1.05-1.24	1.16	1.06-1.27
RA	3,460	148.44	1.63	1.57-1.68	1.32	1.28-1.37	1.23	1.18-1.28
Mild Psoriasis	8,470	92.38	1.01	0.98-1.03	1.09	1.07-1.12	1.07	1.05-1.10
Severe Psoriasis	537	119.91	1.33	1.22-1.45	1.42	1.30-1.55	1.26	1.15-1.39
HIP FRACTURE								
	Number of Events	**Incidence***	**Unadjusted**		**Age/Sex Adjusted**		**Fully Adjusted*****	
			HR	CI	HR	CI	HR	CI
Controls	5,930	10.71	REF		REF		REF	
PsA	54	8.97	0.86	0.66-1.12	1.27	0.97-1.66	1.17	0.86-1.59
RA	730	29.81	2.85	2.64-3.08	1.77	1.64-1.91	1.55	1.40-1.72
Mild Psoriasis	930	9.78	0.92	0.86-0.99	1.16	1.08-1.24	1.13	1.04-1.22
Severe Psoriasis	55	11.77	1.17	0.90-1.53	1.69	1.29-2.20	1.21	0.88-1.66
VERTEBRAL FRACTURE								
	Number of Events	**Incidence***	**Unadjusted**		**Age/Sex Adjusted**		**Fully Adjusted********	
			HR	CI	HR	CI	HR	CI
Controls	2,009	3.62	REF		REF		REF	
PsA	20	3.32	0.94	0.60-1.46	1.06	0.69-1.65	1.07	0.66-1.72
RA	209	8.48	2.40	2.08-2.76	1.70	1.48-1.96	1.53	1.30-1.80
Mild Psoriasis	371	3.89	1.09	0.97-1.21	1.24	1.11-1.39	1.17	1.03-1.33
Severe Psoriasis	32	6.85	2.02	1.42-2.87	2.35	1.66-3.33	2.23	1.54-3.22

*Incidence per 10,000 person-years
The fully adjusted models for each outcome were slightly different after employing a purposeful selection process. The variables contained within each model are specified as below.
**Adjusted for age, sex, cancer, atrial fibrillation, CKD, diabetes, COPD, liver disease, stroke, dementia, SSRI use, TCA use, anti-epileptic use, PPI use, oral steroids, hormone treatment, cyclosporine, smoking, and categorical BMI
***Adjusted for age, sex, cancer, atrial fibrillation, CKD, CVD, diabetes, COPD, stroke, dementia, SSRI use, TCA use, anti-epileptic use, oral steroids, hormone treatment, cyclosporine, smoking, and categorical BMI
****Adjusted for age, sex, atrial fibrillation, diabetes, COPD, stroke, SSRI use, TCA use, PPI use, oral steroids, smoking, and categorical BMI
Abbreviations: PPI = proton pump inhibitor; BMI = Body Mass Index, COPD=chronic obstructive pulmonary disease; CKD=chronic kidney disease; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

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Abstract Number: 1706

Quality of Life at Baseline in Early Psoriatic Arthritis Related to Disease Domains

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Background/Purpose: Psoriatic arthritis (PsA) is a multifaceted disease. Affecting joints, skin, entheses and dactylitis, its impact on health-related quality-of-life (HRQoL) could be substantial. Up to now, the joints have been the main focus of treatment, while other disease facets were expected to improve along with DMARD treatment. Our aim is to describe HRQoL in newly diagnosed PsA patients taking into account swollen joints, tender entheses, dactylitis and the extent of skin involvement.

Methods: Baseline data of incident PsA patients was used from the Dutch south-west Psoriatic Arthritis Registry (DEPAR) study between August 2013 and March 2016. HRQoL was assessed by 8 subscales of the Short-Form 36 (SF-36) questionnaire (0-100, higher score represents a better HRQoL). Patients were classified in arthritis subtypes (i.e. mono-, oligo- or polyarthritis) by their rheumatologist. Entheses were evaluated using the Leeds Enthesitis Index (LEI) and Maastricht Ankylosing Spondylitis Enthesitis Score (MASES; positive if tender entheses >1). Psoriasis was evaluated using the Psoriasis Area Severity Index (PASI; mild: 0-7; moderate/severe: >7) and dactylitis using the Leeds Dactylitis Index (LDI).

Results: 271 patients completed the SF-36 at baseline. Their average age was 50.4 years (SD 13.7) and 50% were male. 256 patients had arthritis: 62 had monoarthritis (M), 125 oligoarthritis (O) and 69 polyarthritis (P). Psoriasis was mild in 74% and moderate/severe in 13%. At least one digit with dactylitis was present in 12% of the patients. A tender enthesis was present in 47% of patients. Mean scores of the subdomains in the SF-36 were similar across the different arthritis-groups, with slightly worse scores for polyarthritis compared to mono- and oligoarthritis. However, when stratifying these groups for the presence of a tender enthesis, HRQoL decreased substantially for all groups across all subdomains of the SF-36, with a median difference of 14.3 points. Irrespective of joint involvement, a tender enthesis (n=127) decreased the mean scores of all subdomains significantly compared to the non-tender enthesis group (n=144, p=0.0001). Severity of psoriasis and presence of dactylitis did not lead to significantly different SF-36 values compared to those not affected.

Conclusion: Having tender entheses impacts HRQoL severly in both its physical and mental dimensions in incident untreated PsA.

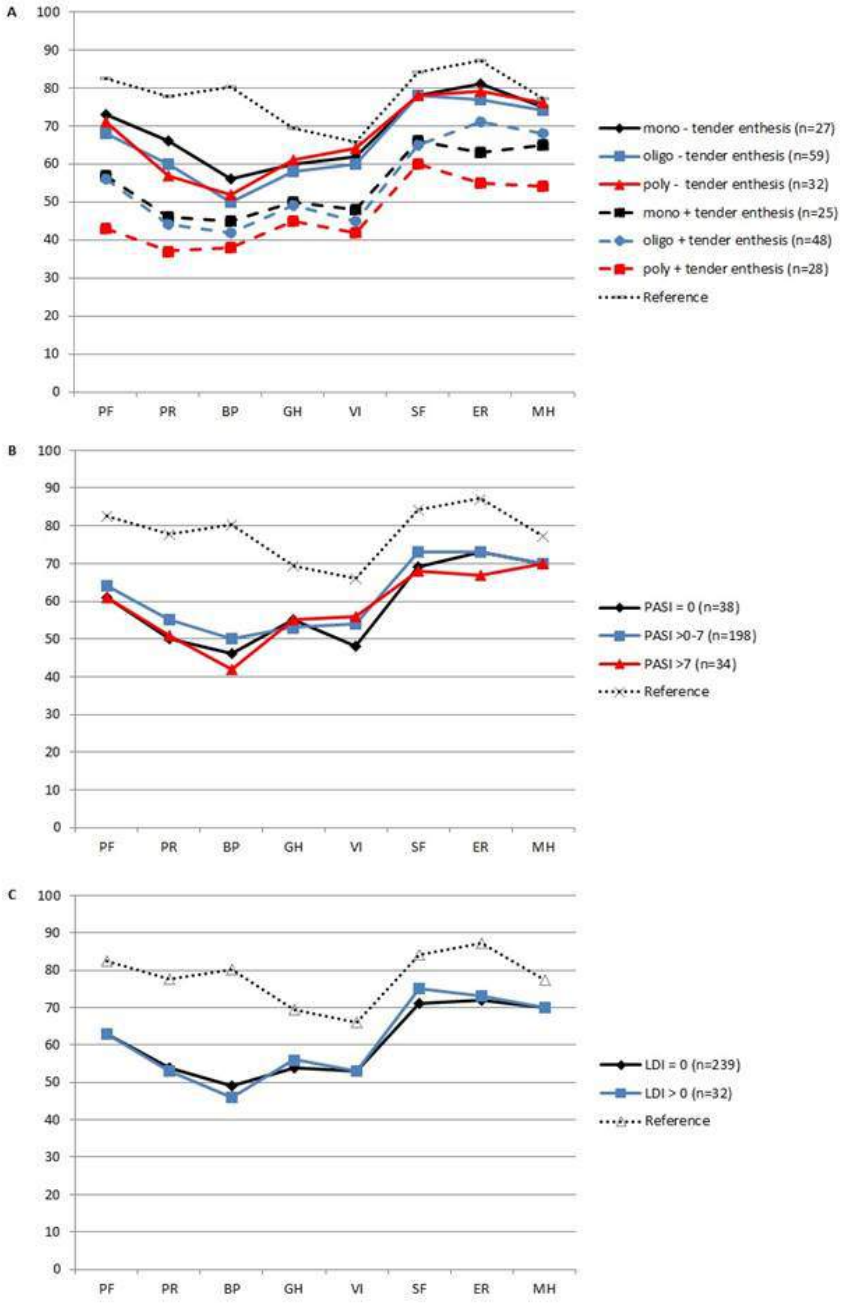

Figure 1. Health related quality of life in patients with monoarthritis (mono), oligoarthritis (oligo), and polyarthritis (poly), with and without presence of a tender enthesis, in different Psoriasis Area Severity Index (PASI) categories and different Leeds Dactylitis Index (LDI) categories. Measured by physical functioning (PF), physical role functioning (PR), bodily pain (BP), general health (GH), vitality (VI), social functioning (SF), emotional role functioning (ER), and mental health (MH) (SF-36)

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Abstract Number: 1707

Ustekinumab and the Comparative Risk for Acute Myocardial Infarction in

Patients with Psoriasis and Psoriatic Arthritis

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Background/Purpose: Ustekinumab (UST), an anti IL12/IL23 monoclonal antibody, is a relatively new biologic used for the treatment of psoriasis (PSO) and psoriatic arthritis (PSA). Its safety profile in real world practice has not been well characterized to date. We assessed the incidence rate (IR) of acute myocardial infarction (AMI) in ustekinumab users and compared it to the corresponding rate for patients treated with tumor necrosis factor inhibitors (TNFi).

Methods: We conducted a retrospective, new user design cohort study of PSO and PSA patients initiating UST or TNFi using 2010-2014 Market scan and 2006-2014 Medicare data. To be included in the cohort, patients have to have at least 12 consecutive months of medical and pharmacy coverage before first prescription date of UST or TNFi (index date). Patients were excluded if they have any of the following: inflammatory disease other than PSO or PSA, prior MI, prior PCI/CABG, malignancy (except non-melanoma skin cancer), HIV, or organ transplant. A sensitivity analysis had more stringent exclusions for patients with past evidence for acute coronary syndrome, angina, or coronary atherosclerosis. Follow up started at index date and ended at earliest of: discontinuation of the index drug (90 days after days of supply), switch to another biologic, the outcome, loss of insurance coverage, death, or end of study (12/31/2014). Patients contributed to only one episode of one specific drug but could contribute to multiple drugs, and standard errors were adjusted to account for this clustering. AMI was identified using diagnosis codes from hospital discharge (Primary or non-primary). Incidence rates (IR) were calculated by dividing number of outcomes by person year exposed. Crude and multi-variable adjusted hazard ratios (HR) were calculated with Cox proportional hazard regression, controlling for potential confounders.

Results: The final cohort included 46,338 initiations of UST or TNFi (17,750 from Medicare, 28,588 from Market scan) representing 39,469 unique patients. Demographic characteristics of the cohort were: age 50.2 (14.9) years, women 54.8%. A total of 181 MIs occurred in 41,302 person years, resulting in an overall IR of 4.38 (3.79, 5.07) per 1000 person years. The crude IRs were 4.62 (2.87, 7.43) for ustekinumab and 4.36(3.74, 5.08) for TNFi (Table). Compared to TNFi, and after multivariable adjustment for potential confounders, the rate of MI for UST-treated patients was not significantly different (HR=1.26, 95% CI 0.76, 2.10) compared to TNFi users (referent). Sensitivity analysis yielded similar results.

Conclusion: In patients with psoriasis and psoriatic arthritis, the rate of myocardial infarction associated with ustekinmab was comparable to the corresponding rate in TNFi users.

Table: Incidence rate and hazard ratios for acute myocardial infarction associated with UST and TNFi

<>	<>Biologic	Event	Person years	IR (95% CI)	Crude HR	Adjusted HR*
<>Cohort 1 **	<>TNFi	164	37620	4.36 (3.74, 5.08)	1.0 (reference)	1.0 (reference)
	<> Adalimumab	58	16620	3.49 (2.70, 4.51)		
	<> Etanercept	72	15330	4.70 (3.73, 5.92)		
	<>Ustekinumab	17	3683	4.62 (2.87, 7.43)	1.10 (0.67, 1.82)	1.28 (0.77, 2.13)
<>Cohort2 ***	<>TNFi	109	34042	3.20 (2.65, 3.86)	1.0 (reference)	1.0 (reference)
	<> Adalimumab	37	15341	2.41 (1.75, 3.33)		
	<> Etanercept	54	13903	3.88 (2.97, 5.07)		
	<>Ustekinumab	10	3404	2.94 (1.58, 5.46)	0.97 (0.51, 1.86)	1.18 (0.61, 2.28)

<>IR: Incidence rate, per 1000 person years. UST: ustekinumab; CI: Confidence interval; HR: Hazard ratio <>*Adjusted for age, gender, diabetes hyperlipidemia, hypertension, obesity, chronic kidney disease, chronic obstructive pulmonary disease, pneumonia, heart failure, sepsis, peptic ulcer disease, fracture, skin ulcer, glucocorticoid use, prior biologic use, smoking status, prostate specific antigen screen, mammography, pap smear, hospitalization in baseline, number physician visit. <>** *Excluded MI, history of MI, malignancy (except non-melanoma skin cancer) or HIV or organ transplant or procedure for percutaneous coronary intervention or coronary artery bypass graft*. <>*** Further excluded *coronary syndrome, angina, and coronary atherosclerosis.*

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Cutaneous Microbiota Features Distinguish Psoriasis from Psoriatic Arthritis

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Background/Purpose: Psoriasis (PsO) is a chronic immune-mediated skin condition affecting ~3% of adults worldwide. Up to a third of PsO patients go on to develop psoriatic arthritis (PsA), a heterogeneous inflammatory arthritis characterized by concomitant bone erosion and osteoproliferation. Although multiple advances have been made in the pathogenesis and therapeutics of these disorders, it is currently not possible to predict which individuals will progress from PsO to PsA. The role of the microbiome as a potential trigger for autoimmunity and rheumatic disease has recently been implicated. The goal

of this study was to characterize the cutaneous microbiota of patients with PsO and PsA (in both psoriatic plaques and unaffected skin) to determine if there are characteristic features related to disease phenotype.

Methods: Skin swabs from subjects with PsO (n=29) and PsA (n=62) were collected from both psoriatic plaque lesions and contralateral unaffected skin. 16S rDNA was extracted per protocol (MoBio, USA) and amplicons targeting the hypervariable V4 region were sequenced using MiSeq (Illumina) to define the microbiota composition. The obtained 16S rRNA sequences were analyzed using the Quantitative Insights into Microbial Ecology (QIIME) pipeline. Taxonomic relative abundance was determined to compare their prevalence among different phenotypes using Kruskal-Wallis statistical analysis. Alpha diversity plots and weighted Unifrac analysis (beta diversity) of cutaneous bacterial communities were generated. False discovery rate analysis was applied to identify unique differentiating taxa.

Results: Baseline characteristics were comparable in both groups. PsO samples had, on average, a similar number of operational taxonomic units as compared to PsA samples. Beta diversity plots did not demonstrate statistically distinct clustering of microbial communities between PsO and PsA subjects, PsO and PsA nonlesional skin, or PsO and PsA lesional skin. Staphylococcus and Corynebacterium were the most abundant genera across all samples. However, several genera were statistically more abundant in PsO compared to PsA lesions, including unclassified Bradyrhizobiaceae ($p<0.0006$), Rahnella ($p<0.0006$), unclassified Prevotellaceae ($p<0.001$), and Parvibaculum ($p<0.002$). Rothia was more abundant in PsA ($p<0.02$).

Conclusion: Our results characterize, for the first time, the cutaneous microbial composition of individuals with PsO compared to those with PsA both in psoriatic lesions and unaffected skin. Although we did not find overall community differences among the various phenotypes, our preliminary observations point towards differences in specific genera, which are characteristically more abundant in PsO. Further in-depth analysis is required to better understand the significance of this dysbiotic process in PsA and whether it contributes to the pathogenesis of the psoriatic disease spectrum. Current efforts are devoted to incorporating healthy controls into our analysis, and analyzing the cutaneous microbiome (and metagenome) across multiple body sites, multiple visits, as well as pre- and post-immunosuppressive/biologic therapy.

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Randomized, Double-Blind Study Comparing Chs-0214 with Etanercept (Enbrel) in Patients with Psoriasis and Psoriatic Arthritis

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Background/Purpose: CHS-0214 is a proposed biosimilar of etanercept, a fusion protein inhibiting tumor necrosis factor. This Phase III multi-center study compared the efficacy and safety of CHS-0214 with commercial, European-sourced etanercept in patients with moderate/severe chronic plaque psoriasis (PsO), including patients with psoriatric arthritis (PsA).

Methods: Patients were randomized to CHS-0214 or etanercept 50 mg SC BIW for 12 weeks (Part 1) and then QW for 36 weeks (Part 2). The percent change in Psoriasis Area and Severity Index (PASI) and the PASI75 at Week 12 were the primary endpoints. The 95% confidence interval (CI) of the treatment difference had to be within the prespecified margin to establish equivalence of CHS-0214 to etanercept. The changes in Health Assessment Questionnaire – Disability Index (HAQ-DI) and hs-CRP were evaluated in patients with PsA.

Results: In 7 countries, 521 patients (102 [19.6%] with PsA) were randomized, and 456 patients (84 [18.4%] with PsA) were evaluable for efficacy at 12 weeks. The PASI75 response rate at 12 weeks was similar for CHS-0214 (64.5%) and etanercept (62.3%). The 95% CI of the treatment difference (-6.36, 11.21) was within the pre-defined equivalence range (-18.0, 18.0). In patients with PsA, the PASI75 response rate was 67.4% for CHS-0214 and 61.0% for etanercept. The mean percent change in PASI at 12 weeks was similar for CHS-0214 (-76.7) and etanercept (-73.4). The 95% CI (-7.63, 0.80) was within the pre-defined equivalence range (-12.5, 12.5). In PsA patients with body surface area (BSA) <2.0 m^2, the mean percent change in PASI was -80.0 for CHS-0214 and -72.0 for etanercept; in PsA patients with BSA ≥ 2.0 m^2, the results were -76.4 for CHS-0214 and -69.9 for etanercept. Mean HAQ-DI scores in patients with PsA were 0.8 and 0.9 at Baseline and decreased to 0.6 and 0.7 at Week 12 for CHS-0214 and etanercept, respectively. Mean hs-CRP scores in patients with PsA were 6.5 and 11.7 at Baseline and decreased to 3.4 and 3.8 at Week 12 for CHS-0214 and etanercept, respectively. Overall, 73.2% of the 261 subjects in the CHS-0214 arm and 76.5% of the 260 subjects in the etanercept arm experienced a treatment emergent adverse event. The majority of the treament emergent adverse events were mild or moderate in severity. No deaths were reported.

Conclusion: This study demonstrated equivalence of CHS-0214 to etanercept with respect to the primary efficacy endpoints. PASI results were similar in patients with PsA as compared with the full study group. Improvement in HAQ-DI and hs-CRP were seen in patients with PsA. Overall both treatments were well tolerated.

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Musculoskeletal Symptoms Preceding the Diagnosis of Psoriatic Arthritis – a Qualitative Exploration of the Patient Journey

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Background/Purpose:

Given the difficulties non-rheumatologists experience to early refer psoriasis patients at risk for Psoriatic Arthritis (PsA) we aim to explore patients experience of musculoskeletal symptoms and understand patients' self-management of symptoms preceding the diagnosis of PsA through a qualitative study to provide a state of the art view on current medical practice eliciting room to improve early detection of PsA.

Methods:

A semi structured interview was developed based on the available literature and informal conversations with patients. The following data was collected from newly diagnosed PsA patients participating in the **D**utch south w**E**st **P**soriatic **AR**thritis cohort (DEPAR): medical history, physical load, previous and current joint and tendon complaints, general complaints, disabilities and emotional status and its influence on their daily life.

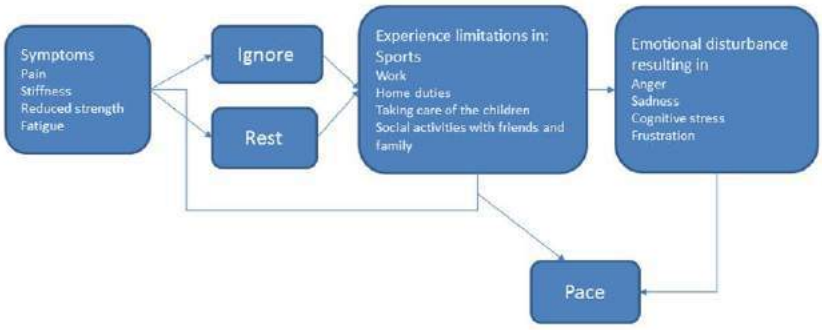
Results:

24 Newly diagnosed PsA patients (median age 52; 54% male; median duration of symptoms four years; 17% mono-, 21% oligo, 29% poly arthritis, 25% dactylitis, 4% axial and 8% enthesitis) participated in this study.

Patient at first did not involve their GP as they attributed their symptoms to physical exertion, obesity or other morbidity. If symptoms continued or worsened they involved their GP. Symptoms of the shoulders, wrists, back, hips and knees were first referred to physiotherapist or other specialists before they were seen by a rheumatologist, often taking years. While patients with hand symptoms were referred to the rheumatologist more quickly, as were patients with rapid accumulation of complaints.

Figure 1 shows the different ways patients dealt with their symptoms before visiting the GP. Patients experience pain, stiffness, loss of strength and fatigue. Some patients decide to proceed with physical activity which often resulted in more pain and inability to perform daily activities. Some choose to avoid all physical activities that causes pain. And others choose to pace their activities. Ultimately, most of our patients ended up choosing for the latter. However, all patients experienced disability which often resulted in stress, frustration, sadness or anger.

Figure 1. Patient journey



Conclusion:

Patients and physicians are not alerted that symptoms of the large joints may be underlying PsA. Patients often first see physiotherapist and other specialist before they finally arrive at the rheumatologist. In the period preceding the diagnosis all patients struggle with pain and other symptoms impacting their daily life. Initially, they choose different coping strategies. While over time they all choose to pace their activities at the cost of losing wellbeing.

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Apremilast Treatment and Long-Term (156-Week) Improvements in Enthesitis and Dactylitis in Patients with Psoriatic Arthritis: Pooled Analysis of a Large Database of 3 Phase III, Randomized, Controlled Trials

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Background/Purpose: Of the multiple manifestations of psoriatic arthritis (PsA), enthesitis and dactylitis are hallmark features that affect many patients (pts), can lead to pain and disability, and may be particularly difficult to manage; the effectiveness of conventional DMARDs for these manifestations is not well documented. Apremilast (APR) is a phosphodiesterase 4 inhibitor that regulates immune responses in PsA; the phase III PALACE trials compared APR efficacy/safety with placebo (PBO) in pts with active PsA despite prior conventional DMARDs and/or biologics. We report the impact of APR treatment over 156 wks on enthesitis and dactylitis in a pooled analysis of the PALACE 1-3 studies.

Methods: Pts were randomized (1:1:1) to PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The PBO-controlled phase continued to Wk 24, with an early escape option at Wk 16. At Wk 24, all remaining PBO pts were re-randomized to APR30 or APR20. Double-blind APR treatment continued to Wk 52; pts could continue APR for up to an additional 4 years during an open-label extension phase. Data for pts entering the study with pre-existing enthesitis or dactylitis were pooled across PALACE 1-3, as pre-specified, to allow for a robust analysis. Enthesitis was evaluated based on the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) (range: 0-13), which indicates the number of painful entheses out of 13 enthesis sites. The dactylitis count (range: 0-20) is the number of digits (hands/feet) with dactylitis present (0=absence, 1=presence). Analyses at Wk 24 used LOCF for missing values and data for early escape pts; Wk 52 and Wk 156 were based on data as observed.

Results: Among pts with enthesitis (n=915) or dactylitis (n=610) at baseline and ≥1 post-baseline value, baseline mean MASES ranged from 4.4 to 4.8 and dactylitis counts ranged from 3.2 to 3.4. At Wk 24, mean change in MASES was −1.3 for APR30 (P=0.0194 vs PBO) and −0.9 for PBO, with 27.5% (APR30) and 22.5% (PBO) of pts achieving a MASES score of 0. Mean change in dactylitis count was −1.8 for APR30 (P=0.0097 vs PBO) and −1.3 for PBO, and a dactylitis count of 0 was achieved by 46.2% of APR30 and 39.0% of PBO pts. Sustained improvement in enthesitis and dactylitis severity was seen in pts who were receiving APR30 at Wk 156, as shown by reductions in MASES and dactylitis counts (Table). Mean % change in MASES with APR30 was −65.2%, and 55.0% of APR30 pts achieved a MASES score of 0. At Wk 156, mean % change in dactylitis count was −83.6% with APR30, and dactylitis counts decreased to 0 in 79.6% of pts. Data for APR20 demonstrated similar results.

Conclusion: The majority of pts (63%) entering the PALACE 1-3 studies had active enthesitis and 42% had dactylitis. APR30 BID demonstrated both early and long-term benefit, up to 156 wks, in treating enthesitis and dactylitis, including resolution of baseline disease in many pts.

Enthesitis and Dactylitis at Wk 24 (LOCF), and Wks 52 and 156 (Data as Observed)

	Wk 24			Wk 52		Wk 156	
MASES*	**PBO n=302**	**APR30 n=315**	**APR20 n=298**	**APR30 n=377**	**APR20 n=326**	**APR30 n=278**	**APR20 n=227**
Baseline, mean	4.8	4.4	4.6	4.4	4.5	4.2	4.4
Mean change from baseline	−0.9	−1.3‡	−1.2	−2.0	−2.2	−2.7	−2.8
Mean % change from baseline	−7.0	−23.6‡	−19.3	−43.5	−42.2	−65.2	−57.6
Median % change from baseline	−21.1	−50.0‡	−40.0	−66.7	−66.7	−100.0	−100.0
Pts achieving score of 0, %	22.5	27.5	27.4	37.7	41.1	55.0	55.1
Dactylitis count§	**PBO n=194**	**APR30 n=214**	**APR20 n=202**	**APR30 n=249**	**APR20 n=225**	**APR30 n=181**	**APR20 n=157**
Baseline, mean	3.3	3.2	3.4	3.4	3.3	3.4	3.0
Mean change from BL	−1.3	−1.8‖	−1.6	−2.5	−2.3	−3.0	−2.4
Mean % change from baseline	−38.2	−48.6	−43.2	−67.9	−70.2	−83.6	−73.4
Median % change from baseline	−66.7	−79.3	−75.0	−100.0	−100.0	−100.0	−100.0
Pts achieving score of 0, %	39.0	46.2	45.9	67.5	66.7	79.6	73.9

The n at Wk 24 represents pts with a baseline value >0 and at least 1 post-baseline value at or before Wk 24. The n at Wk 52 and Wk 156 represents the number of pts taking APR (regardless of when treatment started [baseline, Wk 16, or Wk 24]) with a baseline value >0 and a value at Wk 52 or Wk 156.

*MASES ranges from 0 to 13, with 0 indicating no pain at any assessed enthesis and 13 indicating pain at all assessed entheses. §Dactylitis count is the sum of all scores for each of the 20 digits, with each digit scored as 0=absence or 1=presence of dactylitis. ‡P<0.05 vs PBO. ‖P<0.01 vs PBO.

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Abstract Number: 1712

The Relationship Between Physical Functioning and Work for People with Psoriatic Arthritis: Results from a Large Real-World Study in 16 Countries

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster II: Psoriatic Arthritis

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

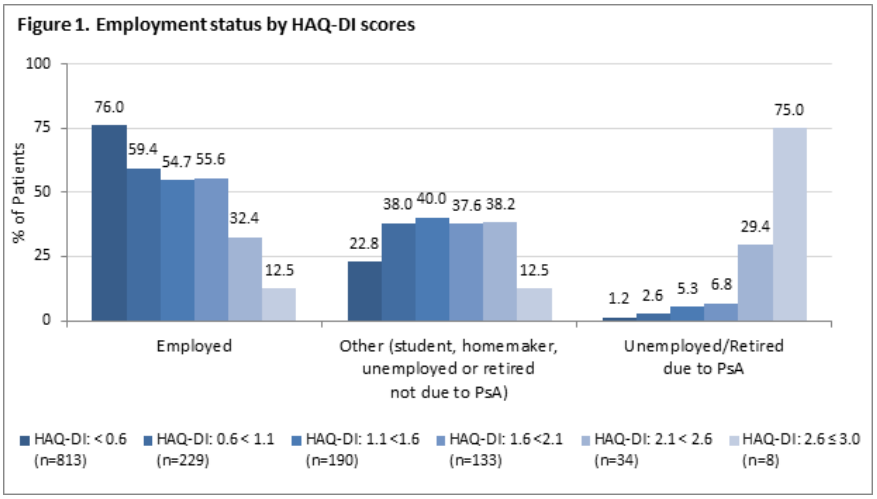
Background/Purpose: Psoriatic arthritis (PsA) has a substantial impact on the physical functioning of affected individuals, though there are limited data on how this relates to impact on valued activities. Our aim was to assess the relationship between physical functioning and work impairment in people with PsA.

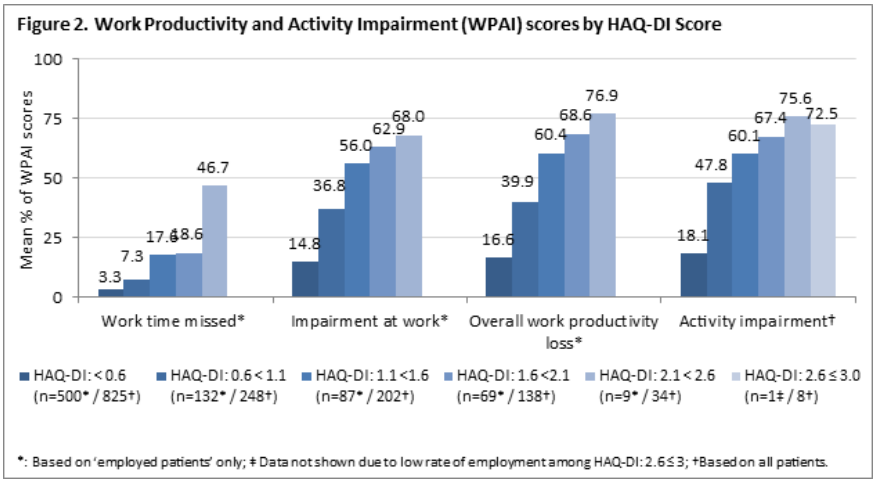
Methods: Data were drawn from an international study of rheumatologists and dermatologists, and their PsA patients across 11 countries (USA, EU, Turkey, Japan, South East Asia, Mexico, Australia and Middle East). Physicians provided diagnosis and patient demographics and their perception of PsA severity, recorded as mild, moderate or severe. Patients reported their employment status, completed the Health Assessment Questionnaire Disability Index (HAQ-DI), and Work Productivity & Activity Impairment questionnaire (WPAI). HAQ-DI scores were compared by physician reported PsA severity. Patients were stratified by their HAQ-DI score into six subgroups (<0.6; 0.6 <1.1; 1.1<1.6; 1.6 <2.1; 2.1 < 2.6; 2.6 <3); employment status and the four WPAI components (work time missed, impairment while working, overall work impairment, and activity impairment) were described by HAQ-DI subgroups.

Results: 1499 patients of working age with a mean age of 44.75yrs (SD 10.15) were analyzed. Patient physical functioning decreased with more severe PsA (HAQ-DI Mean (SD): mild, 0.46 (0.60); moderate, 0.87 (0.69); severe, 1.09 (0.69); *p<0.0001*). HAQ-DI sub-group analysis demonstrated significant differences in employment status with employment

decreasing as HAQ-DI score increased, and the rate of unemployment or retirement due to PsA increasing as HAQ-DI increased *(p<0.0001)* (Figure 1). In employed patients, the percentage of work time missed due to PsA significantly increased as HAQ-DI score increased (Figure 2), as did percentage of impairment while working, and overall work impairment. Among employed and unemployed patients a similar relationship was seen for percentage of activity impairment. All HAQ-DI and WPAI relationships were significant in the overall sample, and on a regional level, categorized as the USA, the 5EU countries, and the rest of world *(p <0.0001)*.

Conclusion: This analysis confirms a strong inverse relationship between physical functioning, employment levels and work productivity in PsA patients. This suggests that strategies to reduce disability in PsA will not only benefit patients but will also have a beneficial societal and economic impact.





Disclosure: P. G. Conaghan, AbbVie, Flexion, Eli Lilly, Novartis, Pfizer Inc, Roche, 5,AbbVie, Novartis, Roche, 8; **R. Alten**, None; **V. Strand**, None; **A. A. Deodhar**, AbbVie, Amgen, Eli Lilly, GlaxoSmithKline, Janssen, Novartis, Pfizer, UCB Pharma, 2,AbbVie, Amgen, Boehringer Ingelheim, Janssen, Novartis, Pfizer, UCB Pharma, 9; **E. Sullivan**, Adelphi Real World, 3; **S. Blackburn**, Adelphi Real World, 3; **H. Tian**, Novartis Pharmaceuticals Corporation, 3,Novartis Pharmaceuticals Corporation, 1; **K. Gandhi**, Novartis Pharmaceuticals Corporation, 1,Novartis Pharmaceuticals Corporation, 3; **S. Jugl**, Shareholder of Novartis Pharma AG, 1,Full-time employee of Novartis Pharma GA, Basel, Switzerland, 3.

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Abstract Number: 1713

Long-Term (156-Week) Safety Profile of Apremilast, an Oral

Phosphodiesterase 4 Inhibitor, in Patients with Psoriatic Arthritis: Pooled Safety Analysis of 3 Phase III, Randomized, Controlled Trials

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SESSION INFORMATION

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Background/Purpose: Apremilast (APR), an oral phosphodiesterase 4 inhibitor, acts to regulate immune activity in psoriatic arthritis (PsA) patients. PALACE 1 (NCT01172938), 2 (NCT01212757), and 3 (NCT01212770) compared the efficacy and safety of APR with placebo (PBO) in patients with active PsA despite prior conventional disease-modifying anti-rheumatic drugs (DMARDs) and/or biologics. This pooled analysis of PALACE 1-3 assessed the long-term safety of APR treatment in patients treated for up to 3 years.

Methods: Patients were randomized (1:1:1) to receive PBO, APR 30 mg BID (APR30), or APR 20 mg BID (APR20) stratified by baseline DMARD use (yes/no). The PBO-controlled phase continued to Week 24; PBO patients were re-randomized to APR30 or APR20 at Week 16 (early escape) or Week 24. Double-blind APR treatment continued to Week 52; patients could continue APR during an open-label, long-term treatment phase. Visits in years 2 and 3 were scheduled at 13-week intervals.

Results: A total of 1,493 patients were randomized and received ≥1 dose of study medication (PBO: n=495; APR30: n=497; APR20: n=501). At the 3-year data cut for PALACE 1-3, 1,441 patients in Weeks 0 to ≤52, 1,028 in Weeks >52 to ≤104, and 865 in Weeks >104 to ≤156 received APR. During the Weeks 0 to ≤52 APR-exposure period, adverse events (AEs) occurring in ≥5% of APR-exposed patients were diarrhea, nausea, headache, upper respiratory tract infection, and nasopharyngitis (Table). Most diarrhea and nausea events were reported within the first 2 weeks of treatment and usually resolved in 4 weeks without medical intervention. The frequency of gastrointestinal AEs decreased with longer exposure (i.e., Weeks >52 to ≤104 or >104 to ≤156; Table); other AEs occurring at ≥5% in the initial period either decreased in frequency or remained stable with prolonged exposure (Table). Most AEs were mild or moderate in severity for up to 156 weeks of APR exposure. Rates of depression remained very low, consistent with earlier findings. The rate of serious AEs (SAEs) was 8.4% during Weeks >104 to ≤156 of APR exposure; most SAEs occurred in 1 patient each. Rates for SAEs of special interest (major cardiac events, malignant neoplasms, serious opportunistic infections) were very low and comparable to those in the first year of treatment. The discontinuation rate due to AEs was 1.8% during Weeks >104 to ≤156 of APR exposure. Marked laboratory abnormalities were infrequent, and most returned to baseline with continued treatment.

Conclusion: APR demonstrated a favorable safety profile and was well tolerated for up to 156 weeks. The incidence of AEs remained stable or decreased with long-term exposure to APR.

Acknowledgment: We thank Adewale O. Adebajo for his work on the original abstract.

	APR-Exposure Period* Weeks 0 to ≤52		APR-Exposure Period* Weeks >52 to ≤104		APR-Exposure Period* Weeks >104 to ≤156	
	APR30 n=721	APR20 n=720	APR30 n=520	APR20 n=508	APR30 n=443	APR20 n=422
Patients, n (%)						
≥1 AE	524 (72.7)	507 (70.4)	316 (60.8)	325 (64.0)	284 (64.1)	272 (64.5)
≥1 SAE	47 (6.5)	40 (5.6)	35 (6.7)	39 (7.7)	40 (9.0)	33 (7.8)
AE leading to drug withdrawal	56 (7.8)	52 (7.2)	13 (2.5)	11 (2.2)	7 (1.6)	9 (2.1)
Death	0 (0.0)	1§ (0.1)	1‡ (0.2)	0 (0.0)	0 (0.0)	0 (0.0)
AEs in ≥5% of patients, any treatment group, n (%)						
Diarrhea	112 (15.5)	88 (12.2)	20 (3.8)	10 (2.0)	12 (2.7)	13 (3.1)
Nausea	108 (15.0)	69 (9.6)	11 (2.1)	8 (1.6)	10 (2.3)	4 (0.9)
Headache	75 (10.4)	61 (8.5)	17 (3.3)	14 (2.8)	12 (2.7)	11 (2.6)
Upper respiratory tract infection	60 (8.3)	71 (9.9)	27 (5.2)	40 (7.9)	24 (5.4)	30 (7.1)
Nasopharyngitis	41 (5.7)	48 (6.7)	31 (6.0)	29 (5.7)	20 (4.5)	30 (7.1)
Select marked abnormalities in clinical laboratory parameters, n/m (%)						
ALT >3× ULN	9/713 (1.3)	8/713 (1.1)	2/518 (0.4)	1/502 (0.2)	2/442 (0.5)	2/419 (0.5)
Creatinine >1.7× ULN	1/713 (0.1)	1/713 (0.1)	0/518 (0.0)	0/502 (0.0)	0/442 (0.0)	1/419 (0.2)
Leukocytes <1.5, 10^9/L	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	0/503 (0.0)	0/442 (0.0)	0/419 (0.0)
Neutrophils <1, 10^9/L	2/713 (0.3)	4/712 (0.6)	3/517 (0.6)	2/502 (0.4)	2/442 (0.5)	1/419 (0.2)
Platelets <75, 10^9/L	0/713 (0.0)	0/712 (0.0)	0/517 (0.0)	1/503 (0.2)	1/441 (0.2)	1/419 (0.2)
Hemoglobin, male <10.5 g/dL, female <8.5 g/dL	5/713 (0.7)	5/712 (0.7)	4/517 (0.8)	0/503 (0.0)	5/442 (1.1)	2/419 (0.5)

*Includes all patients who received APR during the time interval relative to the start of APR. §Multiorgan failure not suspected to be treatment related. ‡Motor vehicle accident on Study Day 489.
n/m=number of patients with ≥1 occurrence of the abnormality at any time point/number of patients with ≥1 post-baseline value; ALT=alanine aminotransferase; ULN=upper limit of normal.

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Abstract Number: 1714

Risk of 10-Year Cardiovascular Disease Assessed By Framingham Risk Score Is Similar in Patients with Psoriatic Arthritis and Psoriasis As Assessed By Atherosclerotic Cardiovascular Disease and Framingham Risk Scores

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Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with psoriatic arthritis (PsA) and psoriasis (PsO) are at increased risk of cardiovascular diseases (CVD) and the risk is higher in patients with severe disease phenotypes[1,2]. A population based study has suggested that PsA, PsO and RA have similar risks for the development of major CV events, therefore CV risk should be addressed in all patients affected by these conditions[3]. The association between psoriatic disease and CV morbidity is poorly understood and studies estimating long-term risk of CVD in PsA and PsO are scarce.The aim of the study was to compare CV risk factors and 10-year CVD risk scores between patients with PsA to those with PsO alone.

Methods: PsA patients fulfilling the CASPAR criteria and PsO with disease duration <10 years were enrolled consecutively from Rheumatology and Dermatology clinics. Fasting bloods were obtained for glucose, insulin, lipids, homocysteine and NT-proBNP. Detailed medical history including items related to comorbidities and known risk factors was taken. Patients underwent thorough physical examination, joint and skin assessments and completed questionnaires on health and quality of life on ipads using a web-based tool. We compared risk factors for CVD between PsA and PSO patients and assessed 10-year CV risk using the Atherosclerotic Cardiovascular Disease (ASCVD) and Framingham Risk Score (FRS). Multiple regression analyses were performed to evaluate the effect of traditional risk factors not included in ASCVD and FRS and disease-related parameters on 10-year CV risk.

Results: 162 patients (100 PsA and 62 PsO) were recruited with mean age 52 (±10.4) for PsA and 40 (±14.7) years for PsO. Mean disease duration for PsA was 17.9 (±10) years. There were significantly more patients with hypertension and metabolic syndrome in the PsA group, and the waist/hip ratio, the number of smokers and patients taking DMARDs and/or biological treatment were also higher compared to PsO. The mean FRS and ASCVD were significantly higher in PsA as compared to PsO (6.04± 6.4% vs. 3.24±5.5%, P=0.007; 6.97±8% vs. 3.98±5%, P=0.008, respectively). Multiple regression analysis revealed that waist/hip ratio had significant effect on FRS and HOMA-R had significant relationship with ASCVD in both diseases. After adjustment for age and sex, we found higher proportion of patients with hyperlipidaemia (P=0.02) and insulin resistance with higher mean HOMA-R in PsO, however FRS and ASCVD scores were similar. We found that HOMA-R and treatment did not show association with 10-year CV risk, and that waist/hip ratio, but not BMI had significant effect on FRS in PsO (β=0.36, P=0.01).

Conclusion: We found similar 10-year risk of CVD in PsA and PsO patients using FRS and ASCVD and that waist/hip ratio had significant effect on FRS. Our results highlight the value of measuring waist/hip ratio and suggest that traditional modifiable risk factors, such as central obesity should be managed appropriately to reduce long-term CVD in psoriatic disease. References:

1. Haroon M. JRheumatol 2014
2. Eder L. Ther Adv Musculoskel Dis 2015
3. Ogdie A. ARD 2015

Disclosure: N. Ikumi, None; **A. Szentpetery**, None; **B. Kirby**, Abbott Immunology Pharmaceuticals, 2; **O. FitzGerald**, Abbott Immunology Pharmaceuticals, 2,Pfizer Inc, 2,Bristol-Myers Squibb, 2,Abbott Immunology Pharmaceuticals, 5,Pfizer Inc, 5,Bristol-Myers Squibb, 5,Celgene, 5,Janssen Pharmaceutica Product, L.P., 5,Novartis Pharmaceutical Corporation, 5,UCB Pharma, 5,Eli Lilly and Company, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-of-10-year-cardiovascular-disease-assessed-by-framingham-risk-score-is-similar-in-patients-with-psoriatic-arthritis-and-psoriasis-as-assessed-by-atherosclerotic-cardiovascular-disease-and-framing

Abstract Number: 1715

ABT-122, an Immunoglobulin Targeting Both TNF-α and IL-17A, Does Not Provide Significantly Greater Efficacy Compared with Adalimumab in Subjects with Psoriatic Arthritis: Results from Exposure-Response Analyses

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Background/Purpose: ABT-122 is a novel dual-variable domain immunoglobulin (DVD-IgTM), which specifically neutralizes both TNF alpha (TNFα) and interleukin-17A (IL-17). Drugs individually neutralizing TNFα or IL-17 have demonstrated efficacy in patients with Psoriatic Arthritis (PsA). The objective of this work was to quantitatively characterize the relationship between ABT-122 or adalimumab serum concentrations and the respective ACR20/50/70, PASI50/75/90 and DAS28 (CRP) responses following treatment in subjects with PsA who have had an inadequate response to methotrexate.

Methods: Subcutaneous (SC) doses of ABT-122 120 mg every week (EW; N=71) and 240 mg EW (N=73) were evaluated in this 12-week randomized, double blind, placebo (N=24) controlled Phase 2 study, with adalimumab 40 mg SC every other week (EOW, N=71) as an active comparator. Serial ABT-122 and adalimumab serum concentrations collected every other week and time course of efficacy data collected at weeks 3, 5, 7, 10, and 12, were analyzed using non-linear mixed-effects modeling. The relationships of ABT-122 and adalimumab average serum concentrations (C_{avg}) during the dosing interval and the ACR20/50/70 and PASI50/75/90 responses as well as dropouts were characterized using Markov models, where active therapies enhanced transition of the status of patients to higher levels of response (e.g. no response to ACR20, ACR20 to ACR50, ACR50 to ACR70). For DAS28 (CRP), indirect response models with ABT-122 and adalimumab suppressing the response were utilized.

Results: The 120 and 240 mg EW doses of ABT-122 provided 2-fold and 4-fold higher molar serum concentrations compared with adalimumab 40 mg EOW dose. There was no evidence of different maximal effects between ABT-122 and adalimumab with available data. The EC_{50} values (the concentrations associated with 50% of maximal effect) on the transition rates between ACR responses for ABT-122 and adalimumab were 6.5 nM (relative standard error [RSE]= 170%) and 13.0 nM (RSE = 61%), respectively. Analyses provided similar results for PASI responses with EC_{50} for the transition rates to higher PASI response (no response to PASI50, PASI50 to PASI75) for ABT-122 and adalimumab as 27 nM (RSE= 91%) and 34 nM (RSE = 58%), respectively. The IC_{50}, concentrations associated with 50% of maximal reduction of DAS28(CRP) responses, for ABT-122 and adalimumab were 60 nM (RSE = 18%) and 32 nM (RSE = 24%), respectively, with maximum inhibition of the baseline DAS28(CRP) level fixed to 45% based on observed data. These analyses indicate that the ACR, PASI and DAS28 (CRP) responses of ABT-122 approximately plateau at an ABT-122 dose of 120 mg EW in PsA patients. Combined analyses across studies in subjects with background MTX and either rheumatoid arthritis or PsA (ABT-122 dose range of 60 mg EOW and 240 mg EW) provided similar results.

Conclusion: The exposure-response relationships of efficacy for ABT-122 and adalimumab were not distinguishably different in subjects with PsA on background MTX. Overall, there was no clear evidence that inhibition of the IL-17 pathway provides significant incremental efficacy benefit in presence of TNF inhibition.

Disclosure: B. Klunder, AbbVie, 1,AbbVie, 3; **A. Khatri**, AbbVie, 1,AbbVie, 3; **M. Minocha**, AbbVie, 1,AbbVie, 3; **P. Peloso**, AbbVie, 1,AbbVie, 3; **A. A. Othman**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 1716

Higher Frequency and Severity of Coronary Plaques on Coronary CT Angiography in Psoriatic Arthritis Patients without Symptoms of Coronary Artery Disease Compared to Controls

Agnes Szentpetery[1], Darragh Brady[2], Gerard Healy[2], Ciaran Redmond[2], Hannah Fleming[2], John Duignan[2], Muhammad Haroon[1], Jonathan Dodd[2] and Oliver FitzGerald[3], [1]St. Vincent's University Hospital, Department of Rheumatology, Dublin, Ireland, [2]St. Vincent's University Hospital, Department of Radiology, Dublin, Ireland, [3]St. Vincent's University Hospital, Department of Rheumatology. UCD Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Dublin, Ireland

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Background/Purpose: Patients with psoriasis (PsO) and psoriatic arthritis (PsA) have an increased prevalence of cardiovascular (CV) risk factors, metabolic syndrome (Metsy), and higher risk for subsequent major CV adverse events[1]. PsA patients have more severe subclinical atherosclerosis compared to those with PsO alone[2]. Previous studies showed higher prevalence of coronary artery plaques in PSO, and in rheumatoid arthritis without diagnosis of coronary artery disease (CAD) compared to controls[3,4]. However, no study to date has compared coronary plaque burden in PsA patients asymptomatic to CAD to controls. The objectives were 1) Study the presence, extent and type of coronary plaques as measured by coronary CT angiography (CCTA) in PsA without symptoms of CAD as compared to controls. 2) Compare plaque measurements between patients with Metsy to those without Metsy (NMetsy) and to controls. 3) Investigate the effect of disease related variables on coronary plaques.

Methods: 50 PsA patients (25 Metsy - 25 NMetsy) and 25 controls without CAD (age and sex-matched) underwent 64-slice CCTA. Plaque localisation, the number of patients with plaque and of affected coronary vessels were assessed. Plaque type was classified into calcified (CP), mixed (MP) and non-calcified plaque (NCP)[5]. Plaque volume was measured for each plaque type and was added to give a total volume (PV) in mm^3. The number of segments with plaque per patient (segment involvement score (SIS 0-15)) and segment stenosis score (SSS 0-60) were calculated. Kruskal-Wallis test, rank correlations and linear regression analyses were used to study the effect of Metsy and PsA related variables on coronary plaques.

Results: Mean age of PsA patients and controls was 58(±8.3) and 57(±5.6) years, the 2 groups were comparable for CV risk factors. 78% of PsA vs 44% of controls had plaques (P=0.007) and the number of patients with affected coronary vessels were higher in PsA (P=0.015). Mean PV, SIS and SSS were higher in PsA (P=0.002, P=0.032, P=0.004; respectively). There were more PsA patients with MP and MP volume was higher compared to controls (P=0.006). Plaque measurements in PsA patients with or without Metsy were similar. Plaque presence, PV and SSS were significantly higher in both Metsy and NMetsy patients compared to controls. Max CRP during the disease correlated significantly with PV, SIS and SSS in PsA. Disease duration, max TJC and max CRP had significant effect on the number of affected coronary vessels (P=0.034, P=0.049, P=0.022, respectively). Linear regression analyses revealed no significant relationship between PV and Metsy, whilst diagnosis of PsA (B=0.324 (CI95% 0.05-0.597) P=0.021) and max CRP (B=0.01 (CI95% 0.004-0.019) P=0.006) were independent predictors of PV.

Conclusion: This pilot study is the first to assess coronary plaques in PsA using CCTA. PsA patients asymptomatic for CAD had a higher presence and extent of plaques, particularly MP, compared to controls. Our results suggest that PsA may result in accelerated coronary plaque formation independent of metabolic disease. **References:**

1. Haroon M. JRheumatol 2014

2. Eder L. ARD 2013
3. Ludwig R. Br JDermatol 2007
4. Karpouzas G. ARD 2014
5. Pflederer T. Atherosclerosis 2010

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Abstract Number: 1717

Progression of Radiographic Axial Damage in Patients with Psoriatic Arthritis. Relation with Clinical and Analytical Factors

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Background/Purpose: Axial involvement in psoriatic arthritis (PsA) is a controversial issue. Lack of unanimity in the definition has led to a wide range of levels of prevalence in the different series published. On the other hand, although radiographic progression in patients with spondylitis is widely known, the different radiographic characteristics of both entities advise against establishing a parallelism between the evolution of the different lesions or the clinical factors which may have an influence on them. Our objectives werw radiographic progression over four years in a group of patients with PsA and axial involvement and relate radiographic damage with clinical and analytical factors.

Methods: Prospective study with patients diagnosed with PsA according to the CASPAR criteria. Axial involvement was defined as the presence of inflammatory back pain along with sacroiliitis and/or syndesmophytes. Patients with less of five years of evolution from the onset of symptoms were included in the study. The radiographic damage was measured with the PASRI method. The difference between both measurements was four years (+ 1 month). The assessment was carried out by two observers (CM et al.). The clinical factors measured were: age, sex, peripheral involvement, smoking , use of NSAIDs (continuous vs. on-demand), biological treatment, measures of activity (BASDAI), function (BASFI) and mobility (BASMI). The following analytical variables were measured: VSG, PCR, B-CrossLaps, P1NP and HLA-B27. From a radiological perspective, the presence of a dorsal or lumbar fracture was also assessed according to the semiquantitative Gennant method.

Results: The study included 45 patients with PsA and axial involvement. The average age of patients was 53.5 years (SD: 12.9), and 31 patients were men. The kappa coefficient between both raters was 0.70. Radiographic progression was higher

in men (3.13 vs. 1.14, p=0.04; in the multivariate analysis: p=0.04, OR: 0.61, 95%CI: 0.39-0.98) and in smokers (active and ex-mokers) (3.81 vs. 1.14, p=0.04; in the multivariate analysis: p=0.04, OR: 0.61, 95%CI: 0.48-0.93). Also, the presence of vertebral fracture was associated to patients with a higher radiographic progression (4.85 vs. 1.82; p=0.001; in the multivariate analysis: p=0.008, OR: 0.59, 95%CI: 0.39-0.87). No differences were found regarding the presence of peripheral manifestations (2.32 vs. 3.57, p=0.3), peripheral joints erosions (2.61 vs. 3.1, p=0.4), continuous use of NSAIDs (1.67 vs. 2.91, p=0.3), biological prescription (2.04 vs. 3.72, p=0.3) or HLA-B27 (2.00 vs. 2.79, p=0.5). A correlation was observed between radiographic progression and the initial PASRI score (p=0.001) and between progression and a lower P1NP concentration (p=0.02). Twelve patients did not show radiographic progression. These patients showed lower initial PASRI scores (5.35 vs. 12.6, p=0,001; in the multivariate analysis: p=0.03; OR: 0.73, 95%CI: 0.55-0.98) and a lower P1NP concentration (38.7 vs. 61.1; p=0.006: in the multivariate analysis: p=0.01; OR: 1.05, 95%CI: 1.008-1.096).

Conclusion: As in patients with spondylitis, male gender, smoking and the presence of initial damage were associated to a higher radiographic progression. Also, these patients were associated to a higher rate of vertebral fracture and lower levels of P1NP. Radiographic progression was not associated to inflammatory parameters, peripheral manifestations or to the treatment used. Approximately 25% of the patients did not show radiographic progression.

Disclosure: A. Quesada-Moreno, None; **M. D. Sanchez-González**, None; **L. Pérez-Garrido**, None; **R. Usategui-Martín**, None; **G. Manzano-Canabal**, None; **C. Hidalgo-Calleja**, None; **O. Martínez-González**, None; **J. Del Pino-Montes**, None; **C. A. Montilla-Morales**, None.

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Abstract Number: 1718

Ustekinumab, Apremilast, TNFi and the Risk for Hospitalized Infection in Patients with Psoriasis and Psoriatic Arthritis

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Background/Purpose: Ustekinumab (UST), an anti IL12/IL23 monoclonal antibody and apremilast, an inhibitor of phosphodiesterase 4 are two relatively new agents used for the treatment of psoriasis (PSO) and psoriatic arthritis (PSA). Potential differences in their risk profiles with respect to serious infection risk compared to tumor necrosis factor inhibitors (TNFi) have been suggested but minimally evaluated in real-world settings.

Methods: We conducted a retrospective, new user design cohort study of PSO or PSA patients initiating apremilast or one of the target biologic DMARDS using 2010-2014 Market scan and 2006-2014 Medicare data. To be included in the cohort, patients have to have at least 12 consecutive months of observable (Enrolled in Medical and pharmacy) before the initiation date (index date). Patients were excluded if they have any diagnosis code for inflammatory disease other than PSO or PSA, malignancy or HIV or organ transplant. Follow up started at index date and ended at earliest of: discontinue of the index drug (90 days after days of supply) or switch to another drug, the outcome, lose of full insurance coverage, death, and end of study. Patients contributed to only one episode of one specific drug but could contribute to multiple drugs. Hospitalized

infection was identified using ICD-9 diagnosis code from hospital discharge (Primary or secondary). Sensitivity analysis was conducted by limiting outcome to primary discharge diagnosis code. Incidence rates (IR) were calculated by dividing number of outcome by person year exposed. Crude and multi-variable adjusted hazard ratios (HR) were calculated with COX proportional hazard regression with robust estimate.

Results: The final cohort included 50,125 initiations of therapies of interest (19,922 from Medicare, 30,203 from Market scan) represented by 40,501 unique PsO/PsA patients. Patient's demographic characteristics were: age 50.4 (14.9) in years, women 54.4%. A total of 2,191 hospital infections occurred in 41,650 person years, resulting in an overall IR of 5.26 (5.04, 5.49) per 100 person years. IRs ranged from 4.36 (3.74, 5.08) for ustekinumab to 8.78 (8.00, 9.64) for infliximab (Table). Compared to adalimumab, the multivariable adjusted HR were 0.77 (0.43, 1.38) for apremilast, and 0.99 (0.83, 1.17) for ustekinumab (Table 1). Infliximab was associated with a significantly increased risk for hospital infection compared to adalimumab.

Conclusion *:* In patients with psoriasis and psoriatic arthritis, the comparative rates of hospitalized infection were generally comparable between TNFi and ustekinmab, although rates were highest for infliximab. Apremilast was associated with a numerically lower risk for serious infection compared to adalimumab. Table: Incidence rate and hazard ratio for hospital infection associated with medications for psoriasis and psoriatic arthritis

<>	<>Biologic	Event	Person years	IR (95% CI)	Crude HR	Adjusted HR*
<>Outcome: Any hospitalized infection	<>Adalimumab	747	16575	4.51 (4.20, 4.84)	1.00 (reference)	1.00 (reference)
	<>Apremilast	26	429	6.06 (4.13, 8.91)	1.19 (0.80, 1.76)	0.77 (0.43, 1.38)
	<>Certolizumab	11	157	7.03 (3.89, 12.69)	1.47 (0.81, 2.64)	1.02 (0.56, 1.84)
	<>Etanercept	785	15314	5.13 (4.78, 5.50)	1.14 (1.04, 1.26)	1.01 (0.91, 1.12)
	<>Golimumab	19	437	4.35 (2.78, 5.50)	0.96 (0.61, 1.52)	1.01 (0.63, 1.61)
	<>Infliximab	441	5022	8.78 (8.00, 9.64)	2.00 (1.78, 2.26)	1.23 (1.08, 1.40)
	<>Ustekinumab	162	3718	4.36 (3.74, 5.08)	0.95 (0.81, 1.13)	0.99 (0.83, 1.17)
<>Outcome: Primary diagnosis of hospitalized infection	<>Adalimumab	477	16800	2.84 (2.60, 3.11)	1.00 (reference)	1.00 (reference)
	<>Apremilast	15	430	3.49 (2.10, 5.78)	1.17 (0.70, 1.96)	0.87 (0.42, 1.78)
	<>Certolizumab	6	158	3.81 (1.71, 8.48)	1.31 (0.60, 2.89)	0.89 (0.41, 1.97)
	<>Etanercept	475	15573	3.05 (2.79, 3.34)	1.08 (0.95, 1.22)	0.95 (0.84, 1.08)
	<>Golimumab	12	442	2.71 (1.54, 4.78)	0.96 (0.54, 1.70)	1.01 (0.57, 1.81)
	<>Infliximab	300	5161	5.81 (5.19, 6.51)	2.07 (1.79, 2.41)	1.26 (1.08, 1.48)
	<>Ustekinumab	91	3761	2.42 (1.97, 2.97)	0.85 (0.68, 1.06)	0.89 (0.71, 1.11)

<>IR: Incidence rate; CI: Confidence interval; HR: Hazard ratio <>*Adjusted for age, gender, diabetes hyperlipidemia, hypertension, obesity, chronic kidney disease, chronic obstructive pulmonary disease, pneumonia, heart failure, sepsis, peptic ulcer disease, fracture, skin ulcer, glucocorticoid use, prior biologic use, smoking status, prostate specific antigen screen, mammography, pap smear, hospitalization in baseline, number physician visit.

Disclosure: F. Xie, None; **L. Chen**, None; **H. Yun**, Amgen, 2; **T. Beukelman**, Novartis Pharmaceutical Corporation, 5,UCB, 5; **J. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

Abstract Number: 1719

Secular Trends in Treatment Patterns for Psoriasis and Psoriatic Arthritis: A Population-Based Cohort Study

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Background/Purpose: Psoriasis (Pso) and psoriatic arthritis (PsA) are complex, multi-system diseases for which an ever-increasing landscape of therapies exists. Little is known about the population level time-trends in use of these agents. We aimed to examine trends in the use of systemic therapy – both conventional and biologic drugs – for psoriasis and psoriatic arthritis.

Methods: Using claims data (2004-2013) from a large nationwide US commercial health plan, we selected patients with 1) Pso without PsA and 2) PsA based on 2 diagnosis codes separated by 7-365 days. In each group, we identified 3 hierarchical treatment groups based on their topical or systemic treatment in a 12-month baseline period prior to the 2nd PsA or Pso diagnosis date (i.e., index date): 1) topical or ultraviolet (UV) therapy only, 2) conventional immunomodulating drugs, and 3) biologics. In the Pso and PsA groups, we calculated the proportion of each treatment groups at baseline and the proportion of a specific conventional or biologic immunomodulating agent over time.

Results: We included 49,950 Pso and 9,706 PsA patients. Mean age (SD) was 46.9 (13.3) years for Pso and 48.2 (11.1) years for PsA. Sixty percent of patients with PsA also had psoriasis. Overall, for baseline treatment of Pso, 82.8% used topical or UV therapy only, 6.8% had conventional immunomodulating drugs and 10.4% used biologic drugs. Baseline treatment of PsA included 18.0% topical or UV therapy only, 32.2% conventional immunomodulating drugs and 49.8% biologic drugs. No substantial time trends were noted in either group. Methotrexate was the most commonly used conventional immunomodulating drug in both Pso (48.7% in 2005 to 61.5% in 2013) and PsA (83.2% in 2005 to 74.2% in 2013) groups. For Pso, etanercept was the most commonly used biologic drug, albeit with a decreasing trend (87.9% to 39.4%), and adalimumab was the 2nd most commonly used drug (2.2% to 28.4%) from 2005 to 2013. Ustekinumab use in Pso has increased from 0.2% in 2009 to 27.7% in 2015 (**Figure 1**). Among biologic drug users for PsA, etanercept, adalimumab and infliximab were the three most commonly used agents across all years. Ustekinumab use in PsA has increased from 0.3% in 2009 to 6.5% in 2013 (**Figure 2**).

Conclusion: Over the past decade, we noted a substantial trend in the patterns of biologic treatment for both Pso and/or PsA. The change in the use of different biologic drugs among patients with Pso has been more pronounced over time compared to PsA, most likely related to the availability of ustekinumab.

Figure 1. Trend in the use of biologic drugs in psoriasis

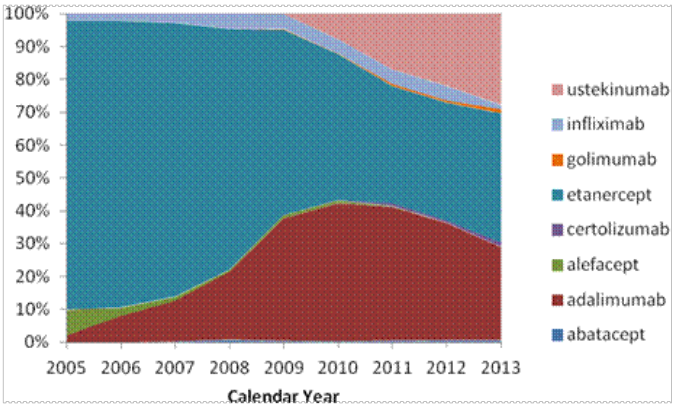
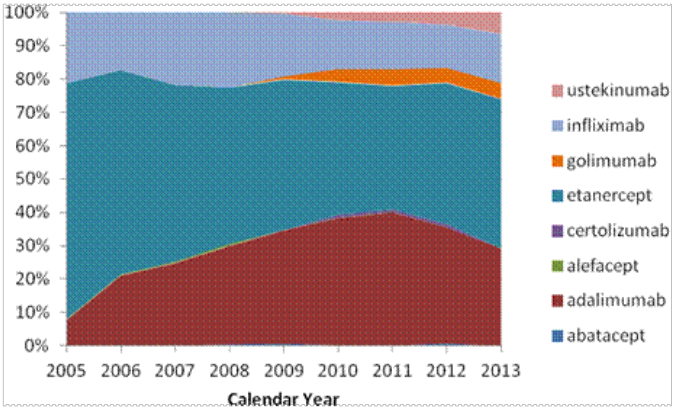


Figure 2. Trend in the use of biologic drugs in psoriatic arthritis



Disclosure: J. F. Merola, Biogen Idec, AbbVie, Amgen, Eli-Lilly, Novartis, Pfizer Inc, Janssen, Momenta, Mallinckrodt, 5,Biogen Idec, 2,AbbVie, Eli-Lilly, 8; **J. Lii**, None; **R. J. Desai**, None; **D. H. Solomon**, Astra Zeneca, Bristol-Myers Squibb, Amgen, 2,Lilly, Pfizer, Genentech, 2; **S. C. Kim**, Pfizer, Lilly, Genentech, AstraZeneca, and Bristol-Myers Squibb, 2.

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Abstract Number: 1720

Predictive Value of Different Tools for Detection of Psoriatic Arthritis in Patients with Psoriasis in Daily Routine Care Using Questionnaires for Diagnosis of Psoriatic Arthritis and Fluorescence-Optical Imaging Technique

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Background/Purpose: Psoriasis (Pso) is one of the most common chronic inflammatory skin disease in Europe. Psoriatic arthritis (PsA) is closely associated to Pso; the skin manifestation appears usually years before PsA-related symptoms emerge. Up to 30% of Pso patients develop PsA; its concrete prevalence is still unclear. Questionnaires for detection of PsA (PASE, PEST, GEPARD) are validated tools for use in dermatology practice with different sensitivity and specificity levels. Fluorescence-optical imaging technique is a new method to detect changes in microvascularisation of the hands as potential early marker for subclinical musculoskeletal inflammation.

Methods: This interims analysis includes 150 Pso patients (diagnosis confirmed by dermatologist) without pre-existing diagnosis of PsA but risk factors for its development (nail psoriasis and/or joint pain or swelling within the last 6 months) from a prospective, multicentre study (XCITING) in Germany. Patients are examined by rheumatologist (clinical examination and ultrasound) to determine PsA-diagnosis. FOI is performed in addition to standard examinations and analysed by an independent experienced reader. The results for PASE, PEST and GEPARD questionnaires as well as for FOI in comparison to the diagnosis of PsA by rheumatologist are compared to survey their sensitivity, specificity and their positive and negative predictive values for detection of PsA.

Results: In 46.4 % of the Pso patients with risk of development of PsA (as defined in inclusion criteria) PsA was diagnosed by rheumatologist using clinical examination and ultrasound. For detection of PsA, PASE questionnaire had a sensitivity of 44.3% and a specificity of 64.2% whereas its positive predictive value was 51.7%, its negative predictive value 57.1%, respectively. Sensitivity of PEST was calculated with a value of 12.9% whereas its specificity was 80.3%; its positive predictive value was 36%, its negative predictive value 51.6%. GEPARD had a sensitivity of 64.3% and a specificity of 38.3% for detection of PsA. Its positive predictive value was 47.4%, its negative predictive value 55.4%. FOI had a specificity of 27.2% and a sensitivity of 51.4%. Its positive predictive value was 37.9%, its negative predictive value 39.3%, respectively.

Conclusion: In this cohort of patients with active Pso and risk of development of PsA, more than 40% of the patients were classified as PsA by rheumatologist using clinical examination and ultrasound. The highest positive and negative predictive values for detection of PsA were detected for use of PASE questionnaire. FOI as new imaging marker had low specificity but marked sensitivity for detection of PsA compared to the questionnaires keeping in mind that only the hands are captured with the device; FOI reached positive and negative predictive values of 37.9 and 39.3%, respectively. For use in clinical routine care, combination of both, FOI and questionnaires might be useful for sufficient PsA diagnosis and exclusion or diagnosis of other types of arthritides of the hands that might be distinguished by use of FOI.

Disclosure: M. Koehm, Pfizer, Janssen, 2; **T. Rossmanith**, Pfizer, Roche Janssen, 2; **H. E. Langer**, Pfizer Inc, 5; **G. Burmester**, UCB, 2,AbbVie, 5,BMS, 5,Hexal, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,MSD, 5,MedImmune, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,AbbVie, 8,BMS, 8,Hexal, 8,MSD, 8,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **S. Wassenberg**, AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 5,AbbVie, Celgene, Janssen, Chugai, Lilly, Pfizer, MSD and UCB, 8; **B. Köhler**, None; **U. Kaesser**, Pfizer Inc, 5; **M. Backhaus**, Roche Pharmaceuticals, 5; **H. Burkhardt**, AbbVie Deutschland, BMS, Chugai, Janssen, Pfizer, UCB, 5,Pfizer Inc, 2; **F. Behrens**, AbbVie Deutschland, Roche, Janssen, 5,Chugai, 8.

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Abstract Number: 1721

Subclinical Atherosclerosis Evolution during 5 Years of Anti-Tnfalpha Treatment in Psoriatic Arthritis Patients: Preliminary Data

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Background/Purpose: Psoriatic Arthritis (PsA) is associated with increased morbility and mortality and an accelerated atherosclerosis. Influence of anti-TNFalpha treatment (a widely used therapy in PsA) in subclinical atherosclerosis is still unclear. The aim of this study was to evaluate subclinical atherosclerosis progression before and after 5 years of anti-TNFalpha treatment.

Methods: Twenty-seven consecutive PsA patients were evaluated before TNF blockers therapy (T0), after 2 years (T1) and after 5 years (T2) of treatment. Subclinical atherosclerosis was evaluated through carotid duplex scanning, analyzing intima-media thickness (IMT) and flow-mediated dilation (FMD). IMT values were expressed as IMT mean (cumulative mean of all the IMT mean in every analyzed carotid segment) and M-MAX (cumulative mean of all the higher IMT in every analyzed carotid segment). Response to therapy was studied by the evaluation of tender and swollen joints (Tj and Sj), DAS 28 (disease activity score), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Metrologic and metabolic data were collected. For the statistical evaluation of parameters over time (T0 vs T1, T1 vs T2) Student's T test for paired data was used.

Results: From T0 to T1 there was a significant deterioration in both IMT-mean and M-MAX (0.72±0.15 vs 0.91±0.37 and 0.89±0.18 vs 1.06±0.39 respectively, $p<0.01$). At T2 IMT-mean did not change significantly (0.91±0.37 vs 0.92± 0,34, p=ns), while M-MAX worsened further (1.06±0.39 vs 1.10±0.35, $p<0.05$). No significant variation in FMD values was observed during the 5 year follow up (T0 vs T1: 5.40±1.93 vs 5.37±1.66, p=ns; T1 vs T0: 5.37±1,66 vs 5.40±1.89, p=ns). Noteworthy, systolic blood pressure and Body Mass Index remained stable from T0 to T2 (132.03± 19.67 vs 132.32± 13.46, p=ns, and 26.33±4.03 vs 25.96±3.41, p=ns), while diastolic blood pressure decreased (79,57±8,73 vs 74.40±6.83, p=0,001). A good response to treatment was evident already at T1, with a significant decrease of: Tj (8.10±5.56 vs 2.09±2.32, $p<0.01$), Sj (3.85±3.84 vs 0.25±0.72, $p<0.01$), DAS 28 (4,16±0.67 vs 2.30±0.82, $p<0.01$) and CRP (11.25±9.16 vs 2.91±1.72, $p<0.01$). The efficacy was preserved from T1 to T2 in terms of Tj (2.09±2.32 vs 1.72± 2.05, p=ns), Sj (0.25±0.72 vs 0.50±0.92, p=ns), DAS 28 (2.30±0.82 vs 2.40±0,9, p=ns), CRP (2.91±1.72 vs 2.73 ±2.51, p=ns).

Conclusion: Our data revealed that in patients with PsA, despite treatment with TNF blockers, there is still a gradual, albeit slight progression of subclinical atherosclerosis assessed by ultrasonography. Other inflammatory mechanisms not related to TNF may be responsible of the progression in atherosclerotic disease.

Disclosure: A. Ortolan, None; **G. Boschetti**, None; **M. Lorenzin**, None; **G. Cherobin**, None; **L. Punzi**, None; **M. Puato**, None; **R. Ramonda**, None.

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Abstract Number: 1722

Predictors of Achieving Remission Among Patients with Psoriatic Arthritis Prescribed TNF Inhibitors

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Background/Purpose: Psoriatic arthritis (PsA) is a heterogeneous disease with varied response to therapy. We examined predictors of remission at one year among patients with PsA initiating a TNF inhibitor (TNFi).

Methods: Patients with PsA enrolled in the Corrona Registry between 2005-2013 with were followed from initiation of a TNFi (etanercept, adalimumab, infliximab, certolizumab, or golimumab) to the visit closest to 12 months from therapy initiation. The outcome of interest was Clinical Disease Activity Index (CDAI) ≤ 2.8 at one year (remission). Given concern about use of the 28-joint count in PsA patients with low joint counts, patients were required to have at least three tender or swollen joints for inclusion. Covariates of interest included baseline demographics (e.g., age, gender, work status), disease manifestations (e.g., enthesitis, dactylitis), patient reported outcomes (e.g., pain, fatigue, function), comorbidities (e.g., hypertension, diabetes), concurrent therapy (methotrexate, NSAIDs, glucocorticoids), and previous biologic use. Univariable associations between covariates and achieving remission at 12 months were tested. Covariates with p-value ≤0.10 and ≤10 missing values were included in a multivariable logistic regression model and removed individually until all remaining variables were significant ($p<0.05$).

Results: Among 1742 TNFi initiations, 725 patients met inclusion/exclusion criteria. Mean age at therapy initiation was 51.5 (SD 12.3) and 56% were female. Mean baseline CDAI was 20 (IQR 14.5-28), median PsA duration was 5 years (IQR 2-11), and 36% had erosions at baseline. The outcome (CDAI≤ 2.8) was achieved by 17% (N=121). Baseline characteristics and differences by outcome are shown in Table 1. In the multivariable model (Table 2), working full time was positively associated with achieving remission (OR 2.30, 95%CI: 1.44-3.68) and baseline pain (OR 0.98 per unit increase in 100 mm VAS), body mass index (OR 0.95 per unit increase, 0.92-0.98), female sex (OR 0.64, 0.41-0.99), previous biologic use (OR 0.58, 0.38-0.90), and baseline CDAI (OR 0.97 per unit increase, 0.95-0.99) were negatively associated with achieving remission.

Conclusion: Among PsA patients initiating a TNFi, ≤25% achieved remission by 12 months. Female gender and higher pain and global scores were previously linked to switching therapies and obesity was associated with lower likelihood of achieving remission; we confirm these findings in this multicenter study representative of care in the US. This is the first study to report that working full time was associated with remission.

Table 1 Demographics and Clinical Characteristics Overall and by Outcome (N=725)				
	All	Follow Up CDAI =2.8 N=121	Follow Up CDAI >2.8 N=604	P value
Female N (%) N=724	403 (56%)	47 (39%)	356 (59%)	<0.0001
Age (Median, IQR) N=724	52 (44-60)	48 (39.5-59)	53 (45-60)	0.06
Duration of PsA (years, IQR) N=721	5 (2-11)	4 (2-11)	5 (1-11)	0.39
Body mass index (median, IQR) N=724	30.9 26.7-36.2	28.7 26-32	31.7 27-37	<0.0001
Baseline CDAI (Median, IQR)	20 14.5-28	16.2 10.4-22	21.0 15.2-28.6	<0.0001
Erosive disease (N, %) N=446	162 (36%)	24 (32%)	138 (27%)	0.45
Joint deformity (N, %) N=273	205 (28.4%)	34 (28%)	171 (28%)	0.99
Tender joint count (Median, IQR)	6 (4-11)	5 (3-7)	7 (4-12)	<0.0001
Swollen joint count (Median, IQR)	4 (2-8)	4 (3-7)	4 (2-8)	0.59
Dactylitis (N, %) N=487	54 (11%)	17 (21%)	37 (9%)	0.002
Enthesitis (N, %) N=487	36 (7%)	7 (9%)	29 (7%)	0.66
Inflammatory Back Pain (N,%) N=487	52 (11%)	5 (6%)	47 (12%)	0.14
Sacroiliitis (N, %) N=487	10 (2%)	0 (0%)	10 (2%)	0.15
Patient Pain (Median, IQR) N=724	52 (27-70)	30 (15-55)	57 (32-75)	<0.0001
Patient Global (Median, IQR)	50 (26-68)	30 (12-50)	50 (30-70)	<0.0001
mHAQ (Median, IQR) N=723	0.375 0.125-0.875	0.125 0-0.5	0.5 0.14-0.88	<0.0001
Patient Fatigue (Median, IQR) N=223	50 (25-75)	23.5 (10-45)	60 (31-75)	<0.0001
Race (N,%) White	669 (92.3%)	109 (90.1%)	560 (92.7%)	0.32*
Education (N,%) N=698 College/University	449 (64%)	92 (79%)	357 (61%)	0.0004**
Marital Status (N,%) N=722 Married/Partnered	523 (72%)	87 (72%)	436 (73%)	0.88#
Work Status (N,%) N=722 Full Time	384 (53%)	87 (72%)	297 (49%)	<0.0001+
Smoker (N,%) N=724 Never Previous Current	 385 (53%) 208 (29%) 131 (18%)	 72 (60%) 31 (26%) 18 (15%)	 313 (52%) 177 (29%) 113 (19%)	0.30
Drinker (N,%) N=707	373 (53%)	77 (65%)	296 (50%)	0.004
Hypertension (N,%)	237 (33%)	25 (21%)	212 (35%)	0.002
Diabetes (N,%)	83 (11%)	7 (6%)	76 (13%)	0.03
Cardiovascular disease (N,%)	52 (7%)	5 (4%)	47 (8%)	0.16
CCP or RF positive (N,%) N=312	68 (22%)	8 (20%)	60 (22%)	0.70
CRP (Median IQR) N=236	4.25 1.75-11.95	4.45 2-20.5	4.25 1.6-10	0.43
ESR (Median, IQR) N=329	15 6-27	8 2-20	17 7-28.5	0.0015
Current prednisone (N,%)	103 (14%)	11 (9%)	92 (15%)	0.08
Current NSAIDs (N,%) N=717	285 (40%)	56 (46%)	229 (38%)	0.11
Current methotrexate (N,%)	391 (54%)	59 (49%)	332 (55%)	0.21
Any previous biologic therapy (N,%)	385 (53%)	46 (38%)	339 (56%)	0.0003

Table 2 Final Multivariable Model: Predictors of CDAI <=2.8 at follow-up visit closest to one year (N=718)		
	Odds Ratio for Achieving CDAI <=2.8	95% Confidence Limits
Work full time	2.30	1.44, 3.68
Patient pain (per 1 mm)	0.98	0.97, 0.99
Body mass index (per 1 unit mg/k^2)	0.95	0.92, 0.98
Baseline CDAI (per 1 unit)	0.97	0.95, 0.99
Previous biologic use	0.58	0.38, 0.90
Female gender	0.64	0.41, 0.99

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Abstract Number: 1723

Composite Psoriatic Disease Activity Index (CPDAI), Defining Remission and Disease Activity States Using Data from Daily Clinical Practice

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Background/Purpose: The Composite Psoriatic Disease Activity Index (CPDAI), a composite disease outcome measure in psoriatic arthritis (PsA) (1),has proved to be a valid and discriminative tool to assess disease activity in PsA. Definitions of disease activity statesare lacking, however therecently developed minimal disease activity state (MDA) as a treatment target has been shown to improve outcome in patients with PsA (2). CPDAI has arbitrary cutoff points to classify disease states into mild, moderate and severe disease but these cutoff points have not been validated. Measuring Outcome in Psoriatic Arthritis (MOPsA) is a new web-based tool which can be used in the assessment of PsA.MOPSA calculates both MDA and CPDAI based on patient reported outcomes and assessment by physicians

Methods: We evaluated consecutive PsA patientsincluded in the MOPSA database.Data collected included joint counts, patientpain and global activity ratings, erythrocyte sedimentation rate, the health assessment questionnaire (HAQ) the psoriasis area severity index (PASI), the Bath ankylosing spondylitis disease activity index (BASDAI), the dermatology life quality index (DLQI), the Psoriatic Arthritis Quality of Life (PsAQoL). TheclinicalDisease Activity Index for Psoriatic Arthritis (cDAPSA) was calculated. Recently published cut off values for DAPSA were used to classify patients into remission (REM), low (LDA), moderate (MoDA) or high (HDA) disease activity. Based on the distributions of CPDAI in each of these clinical DAPSA assigned states, we defined the cut points between groups. Disease activity parameters were compared among the different constituted CPDAI states. Changes of treatment at the index visit was also evaluated

Results: Eighty-sevenPsA patients, 41 (52%) males, mean age 49 years (SD: 12 years) were included. Mean CPDAI differed significantly between patients classified as REM, LDA, MoDA or HDA ($p<0.001$)Cdapsa. Based on the distributions of CPDAI in these groups, we propose cut-off values of <2 for REM, >2 and <4 for LDA, >4 and < 7 for MDA and >7for HDA.With these cut off values 22%, 44%, 14% and 19% of the patients were in REM, LDA, MoDA and HAD, respectively. The table shows results for different disease activity parameters among the four CPDAI states. None of the patients classified as in remission by CPDAI changedDMARDs at the index visit, while 33%, 42% and 53% of patients in LDA, MoDA, and HAD, did undergo a treatment change. **Table:**Disease Activity Parameters according to CPDAI state

Disease Activity Parameter	All Patients (n=87)	Remission (n=20)	Low Disease Activity (n=39)	Moderate Disease Activity (n=12)	High Disease Activity (n=16)
Fulfilling MDA criteria, n (%)	33 (38)	19 (57,6)	14 (42.4)	0 (0)	0 (0)
Mean Tender Joint Count (TJC 68) (SD)	4.2 (6.1)	0.3 (0.9)	2.2 (1.7)	9.75 (10.8)	10.3 (4.7)
Mean Swollen Joint Count (66) (SD)	1 (2.5)	0 (0)	0.72 (1.3)	0.88 (1.7)	3.2 (4.8)
Mean Patient Pain (VAS 0-10) (SD)	3.5 (2.7)	2.45 (2.6)	3.1 (2.6)	4.25 (2.3)	5.4 (2.7)
Mean Patient Global Assessment (VAS 0-10) (SD)	3.5 (2.4)	2.4 (2.3)	3.3 (2.1)	4.3 (2.3)	4.8 (2.6)
Mean HAQ (SD)	0.6 (0.7)	0.175 (0.23)	0.42 (0.5)	0.85 (0.8)	1.5 (0.6)
Mean BASDAI (SD)	1.5 (2.3)	0.22 (0.69)	0.56 (1)	2.1 (2.6)	4.8 (2.2)
Mean PASI (SD)	2.8 (3.4)	0.7 (1.9)	2.6 (2.6)	5.6 (5.5)	3.7 (2.9)
Mean Clinical DAPSA (SD)	12.4 (10.4)	5.15 (4.3)	9.3 (4.2)	19.2 (14.1)	23.6 (11.7)
Mean DLQI (SD)	3.5 (5.6)	1.1 (2.1)	3.1 (4.3)	5.1 (7.2)	6.1 (8.4)
Mean PASQOL (SD)	4.2 (5)	0.85 (1.9)	2.9 (3.7)	6.3 (6)	9.9 (4.8)
Mean erythrocyte sedimentation rate,(SD)	12.2 (9.6)	10.3 (7.6)	11.3 (10.1)	13.9 (11.6)	15.1 (8.2)

Conclusion: CPDAI constitutes a disease-specific,validated and feasible tool for PsA assessment. In thisstudy, we provide criteria for disease activity states that showed good performance in clinical practice

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Abstract Number: 1724

The Effect of Certolizumab Pegol on Skin Manifestations of Psoriatic Arthritis over 4 Years of Treatment

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Background/Purpose: The majority of patients (pts) with psoriatic arthritis (PsA) experience psoriatic skin manifestations, which add to the already high burden of disease. The RAPID-PsA trial (NCT01087788) of certolizumab pegol (CZP) in PsA has shown CZP to be efficacious in improving skin manifestations over 96 weeks (wks) of treatment.[1] Here, we report long-term efficacy data for skin manifestations over 4 years of the RAPID-PsA trial.

Methods: The phase 3 RAPID-PsA trial was double-blind and placebo-controlled to Wk 24, dose-blind to Wk 48 and open-label (OL) to Wk 216. Pts had active PsA and had failed ≥1 DMARD; up to 40% of pts could have received 1 prior anti-TNF. Pts originally randomized to CZP (200 mg Q2W or 400 mg Q4W, following 400 mg loading dose at Wks 0, 2, 4) continued on their assigned dose in the OL period. Here we report outcomes assessing the skin manifestations of PsA in CZP-randomized pts with skin involvement at baseline (≥3% body surface area affected by psoriasis [BSA]). Data are shown as observed case (OC) and with imputation: NRI for categorical measures and LOCF for continuous measures.

Results: Of the 409 pts randomized, 273 received CZP from Wk 0, 166 of whom had baseline skin involvement (≥3% BSA). At baseline, these patients had an average of 24.2% BSA and a mean PASI score of 12.0. Severe skin involvement (≥3% BSA and PASI ≥10) was seen in 71 pts at baseline, with an average of 38.7% BSA affected and a mean PASI score of 22.3 amongst these pts. In pts completing the study, early improvements in PASI responses observed to Wk 24[1] were sustained to Wk 216 following treatment with either dose regimen (Table). Even when conservative imputation methods (NRI) were used, PASI responses were largely maintained, with an increased proportion of pts achieving the most stringent outcome, PASI100 (NRI; Wk 24: 22.3%, Wk 216: 28.3%). Similar sustained improvements were observed in both mean BSA and mean PASI score (Table). At Wk 48, 77.5% of pts with severe skin involvement at baseline (PASI ≥10) achieved a PASI75 response, compared with 54.7% of pts with less severe baseline skin involvement (PASI <10) (NRI). The heightened response in the most severely affected pts remained evident at Wk 216 (PASI75 [NRI]: PASI ≥10: 59.2%, PASI <10: 46.3%).

Conclusion: Improvements in the skin manifestations of PsA, as seen at Wk 24,[1] were maintained over 4 years of CZP treatment with both dose regimens, with additional improvements observed at Wk 216 in the proportion of pts achieving the most stringent measure, the PASI100 response. The increased PASI75 response rate previously observed in pts with severe skin involvement relative to those with less severe skin manifestations was also maintained to Wk 216. **References:** 1.

Table: Skin outcomes for PsA patients treated with CZP over 216 weeks (≥3% BSA at baseline)

	CZP 200 mg Q2W (N=90)			CZP 400 mg Q4W (N=76)			CZP dose-combined (N=166)		
	Wk 24 (NRI)	Wk 216 (NRI)	Wk 216 (OC; n=66)	Wk 24 (NRI)	Wk 216 (NRI)	Wk 216 (OC; n=42)	Wk 24 (NRI)	Wk 216 (NRI)	Wk 216 (OC; n=108)
Outcome, (%)									
PASI75	62.2	60.0	81.8	60.5	42.1	76.2	61.4	51.8	79.6
PASI90	46.7	44.4	60.6	35.5	35.5	64.3	41.6	40.4	62.0
PASI100	30.0	32.2	43.9	13.2	23.7	42.9	22.3	28.3	43.5
	Wk 24 (LOCF)	**Wk 216 (LOCF)**	**Wk 216 (OC; n=67)**	**Wk 24 (LOCF)**	**Wk 216 (LOCF)**	**Wk 216 (OC; n=42)**	**Wk 24 (LOCF)**	**Wk 216 (LOCF)**	**Wk 216 (OC; n=109)**
Mean (SD)									
PASI	2.0 (2.7)	1.8 (2.8)	1.3 (2.1)	3.5 (7.4)	3.5 (9.3)	2.7 (8.7)	2.7 (5.5)	2.6 (6.7)	1.9 (5.6)
CFB	-10.9 (13.6)	-11.0 (13.0)	-11.1 (11.6)	-7.5 (9.2)	-7.5 (9.2)	-9.1 (8.2)	-9.3 (11.9)	-9.4 (11.5)	-10.3 (10.4)
BSA, %	6.8 (12.6)	4.6 (10.5)	2.6 (5.2)	9.6 (17.7)	7.3 (17.7)	3.3 (10.0)	8.1 (15.1)	5.8 (14.2)	2.9 (7.4)
CFB	-17.9 (21.1)	-20.1 (21.8)	-21.6 (20.7)	-13.9 (17.2)	-16.2 (18.5)	-20.0 (17.8)	-16.1 (19.5)	-18.3 (20.4)	-21.0 (19.6)

CFB: change from baseline; LOCF: last observation carried forward; NRI: non-responder imputation; OC: observed case, where n numbers indicate the number of patients reporting data at that time point.

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Combination Therapy of Apremilast and Biologic Agent As a Safe Option of Psoriatic Arthritis and Psoriasis

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Background/Purpose: Psoriasis is a chronic immune-medicated inflammatory condition that affects 2-3% of the population , which is characterized by rash, silver scaling of the skin and can lead to psoriatic arthritis. There are multiple regimens for the treatment of psoriasis including biologic agent, phototherapy and apremilast. Apremilast is an oral phosphodiesterase inhibitor that has been approved as a mono therapy by the FDA in March 2014 for the treatment of psoriatic arthritis and September 2014 for the treatment of moderate to severe plaque psoriasis. While monotherapy with biologic agents is effective for many patients with psoriasis some patients are not satisfied by the outcome and require combination therapy. No data exist on the safety of apremilast as a component of combination therapy with biological therapies. The aim of the study was to determine the safety of apremilast in combination of biologic therapies in the treatment of plaque psoriasis and psoriatic arthritis.

Methods: This was retrospective study, open label study carried out at a single center. Twenty-two patients diagnosed with plaque psoriasis and psoriatic arthritis according to American college of Rheumatology criteria-participated. Apremilast was added to their current biologic agent. Patients were permitted to continue their current biologic treatment.

Results: : 22 patients were treated by biologic agents then added Apremilast with a mean treatment of 8 months (1 Month is the shortest and 24 Months is the longest). Out of these 22 patients, 14 Females (63.6%) and 8 males (36.4%) were in the study. Out of these 22 patients, 5 patients were on ustekinumab and apremilast (27.3%), 3 patients out of the 5 experienced nausea and/or sever diarrhea (50%) and 1 out of the 3 stopped apremilast (33.3%). 6 patients were on adalimumab and apremilast (36.4%), 1 out of the 6 patients experienced nausea (12.5%) but tolerated and 0 patients stopped it. 2 patients were on etanercept and apremilast (9.1%) and 0 patient experienced side effect and was well tolerated. 2 patients were on certolizumab pegol and apremilast (9.1%), 1 patient stopped apremilast due to stomachache (50%). 4 patients were on infliximab and apremilast (18.2%) and 0 patients experienced side effect. 3 patients were on golimumab and apremilast (13.6%) weight loss was observed in 1 patient (33.3%), 1 patient couldn't tolerate and stopped the apremilast (33.3%). 19 patients (86.4%) continued on apremilast with good improvement. 3 patients (13.6%) stopped apremilast due to GIT side effects nausea and/or diarrhea and stomachache. weight loss was observed in 1 patient (4.5%). Nausea and/or Diarrhea were reported by 5 patients (22.7%). No major side effects of cancer or sever infection were reported. There is a mean decrease in the C-reactive protein of 8.68. Patients reported improvement of the rash and pain by more than 50% .

Conclusion: Apremilast can be safely and effectively combined with biologic agents in patients with plaque psoriasis or psoriatic arthritis not responding adequately to these agents alone. No major side effects of cancer or sever infection were reported other than nausea and/or vomiting that were manageable in some patients

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Abstract Number: 1726

An Integrated Safety Data Analysis Across All Phase II and Phase III Clinical Programs for Ustekinumab in Psoriatic Arthritis, Crohn's Disease, and Psoriasis

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Session Time: 9:00AM-11:00AM

Background/Objective: Therapeutic decisions are based on efficacy, but clinicians need to consider medication safety in this process. Here, we report ustekinumab (UST) integrated safety data in patients (pts) with psoriatic arthritis (PsA), Crohn's disease (CD), and psoriasis (PsO). We also compare a subset of PsA pts with & without baseline methotrexate (MTX).

Methods: Integrated safety data from 3 PsA, 5 CD, & 4 PsO trials were analyzed. PsA studies included the Ph2 trial [CNTO743T10] & the 2 Ph3 trials (PSUMMIT 1 & 2) with 222, 615 & 312 pts exposed to UST, respectively. The percentage of pts in the Ph2 study that received MTX was 20.5%. No concomitant DMARDs with the exception of MTX (approximately 50% of pts in each study) were permitted in the 2 Ph3 studies. In the 5 CD trials (Ph2/3Ph3) 1749 pts were exposed to UST. In the 3 Ph3 CD trials, pts received one dose of UST 130mg or ~6mg/kg IV at induction (UNITI-1 & UNITI-2), then 8 weeks later, entered the maintenance phase (IM UNITI) and received UST 90mg SC q8w or q12w for 44 weeks. The percentage of pts on background MTX in UNITI-1 was 9.2% & in UNITI-2, 4.8%. In the PsO studies (1Ph2/3Ph3), a total of 3117 pts received UST 45mg or 90mg SC; *no concomitant DMARD therapy (including MTX) was permitted.* The PsO studies were completed through 5-years of follow-up. All pts who received at least 1 dose of UST are included in this analysis. Safety events are reported in events per 100-pt years. 95% CI for events per 100 PY were estimated.

Results: Through 1 year of follow-up, a total of 1018 PsA pts were treated with UST, of which 465 were co-treated with MTX. Of the 1749 CD pts treated with UST, 139 received MTX. Discontinuation rates of UST due to adverse events (AEs) were comparable across disease states irrespective of MTX use (Table). AE rates (95% CIs for events/100 PY) were noted to be significantly lower in the UST vs PBO groups across the 3 diseases irrespective of MTX use-UST (420.39, 423.45) vs PBO (534.80, 570.44). Serious adverse event rates (SAEs) were also significantly lower in the UST vs PBO across the 3 diseases-UST (14.25, 16.56) vs PBO (24.05, 32.18). Infections and Serious infections (SIs) had numerically lower event rates in UST vs. PBO across the 3 disease states-UST (122.16, 128.72) vs PBO (120.94, 138.27) and UST (2.10, 3.05) vs PBO (2.76, 6.00), respectively (Table). Major adverse cardiovascular events (MACE) did not appear to significantly differ in both PBO & UST pts in PsA, PsO and CD. Event rates of malignancy (excluding non-melanoma skin cancer) were comparable across all disease states. No deaths in PsA or CD were reported.

	Psoriatic Arthritis				Crohn's disease				Psoriasis**	
	PBO		UST		PBO		UST		PBO^	UST^^
	+MTX	-MTX	+MTX	-MTX	+MTX	-MTX	+MTX	-MTX	N/A	N/A
Pts treated	160	219	465	553	76	867	139	1610	733	3117
Pt years of follow-up	64	81	396	454	25	322	89	1017	182	2566
PTs D/C due to AE (%)	5.0	6.4	3.4	2.7	3.9	4.8	6.5	6.1	2.3	2.8
Event rate per 100-pt years										
AEs	381.53	313.34	255.55	253.10	849.48	701.45	646.96	641.16	414.81	390.60
SAEs	20.33	8.64	6.82	11.46	79.76	41.04	40.36	34.91	8.78	8.77
Infections	104.76	101.16	82.32	74.30	139.59	145.51	137.91	133.64	120.71	137.40
Serious infections	1.56	0.00	0.00	1.76	15.95	6.22	13.45	5.80	1.65	1.40
MACE*	0.00	1.23	0.25	1.10	0.00	0.00	0.00	0.10	0.55	0.55
Malignancies (excluding NMSC)	0.00	0.00	0.00	0.22	0.00	0.00	0.00	0.39	0.55	0.43
Deaths	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.19

*MACE adjudicated events includes CV death, non-fatal MI, or non-fatal stroke; **In the psoriasis studies, no concomitant DMARD therapy (including MTX) was permitted. ^includes data from the time of crossover, ^^includes data from the first UST dose onward for patients who crossed over from PBO

Conclusion: UST demonstrates a favorable safety profile in an integrated safety data analysis across the PsA, CD, & PsO phase 2 & 3 clinical trials. The use of UST in PsA appears to be safe & well-tolerated, with fewer event rates of SAEs & SIs noted vs PBO. Despite higher overall rates of SAEs & SIs observed in CD pts, the data do not suggest an influence of UST on either.

Disclosure: L. S. Gensler, Janssen Scientific Affairs, LLC, 2; **E. C. Hsia**, Janssen Research Development, LLC, 3; **C. Gasink**, Janssen Research and Development, LLC, 3; **B. Randazzo**, Janssen Research and Development, LLC, 3; **D. Parenti**, Janssen Scientific Affairs, LLC, 3; **S. Fakharzadeh**, Janssen Scientific Affairs, LLC, 3; **K. L. Tang**, Janssen Research & Development, LLC, 3; **S. Chakravarty**, Janssen Scientific Affairs, LLC, 3.

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Abstract Number: 1727

Association Between Biologic Therapies and Major Adverse Cardiac Events or Cardiac Heart Failure in Psoriatic Arthritis or Psoriasis: A Meta-Analysis

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Association between biologic therapies and major adverse cardiac events or cardiac heart failure in psoriatic arthritis or psoriasis: a meta-analysis. [1]Champs B, [1]Degboe Y, [1]Ruyssen-Witrand A, [2]Barnetche T, [1]Cantagrel A, [1]Constantin A. 1 Centre de Rhumatologie, CHU Purpan & Université Toulouse III - Paul Sabatier, Toulouse, France. 2 Centre de Rhumatologie, CHU Bordeaux & Université Bordeaux, France

Background/Purpose: Patients with psoriatic arthritis (PsA) or psoriasis have an increased risk of cardiovascular morbidity and mortality. The short-term impact of biologic therapies on cardiovascular events is still debated. The objective of this meta-analysis was to investigate the association between biologic therapies and major adverse cardiac events (MACEs) or congestive heart failure (CHF) in PsA or psoriasis patients.

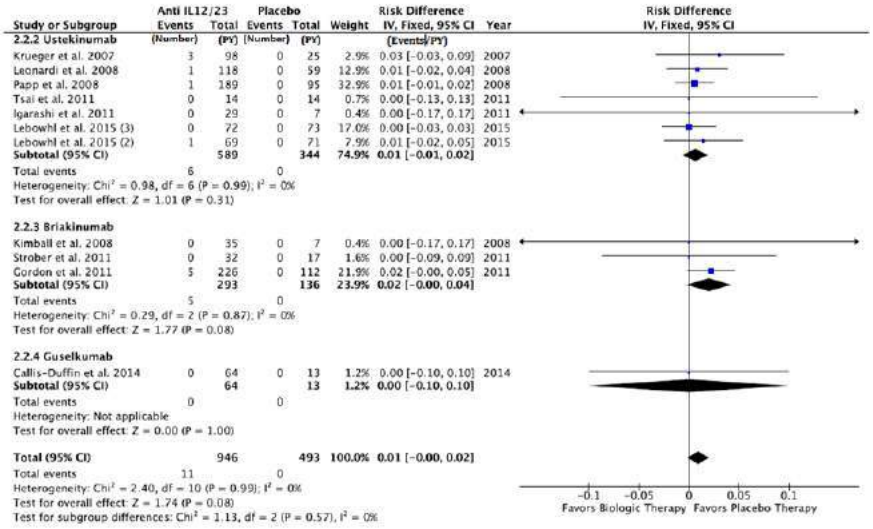
Methods: Study screening was performed using MEDLINE and Cochrane, from database inception to April 2016, including randomized controlled trials (RCTs) of anti-IL12/23 (briakinumab, guselkumab and ustekinumab), anti-IL17 (brodalumab, ixekizumab and secukinumab) or anti-TNF (adalimumab, certolizumab, etanercept, golimumab and infliximab) agents for the treatment of PsA or psoriasis. Two investigators independently performed data extraction of MACEs and CHF events

reported during the placebo-controlled phase of biologic therapies. These outcomes were presented as risk differences with their 95% confidence interval for each selected study. Meta-analyses were carried out independently in PsA or psoriasis, using the inverse variance method. Heterogeneity was tested with the Cochran's Q-test and evaluated by the I^2 statistic. We used RevMan 5.3 for the meta-analysis calculations. P-values less than 0.05 were considered statistically significant.

Results: On 415 studies initially screened, 56 studies were finally selected: 16 in PsA (1339.54 patient-years [P-Y]) and 40 in psoriasis (5128.96 P-Y). Compared with placebo, no significant difference was observed in MACEs in patients receiving anti-IL12/23, anti-IL17 or anti-TNF agents, neither in PsA nor in psoriasis. However, in psoriatic patients, 11 MACEs were observed in the anti-IL12/23 group (946 P-Y) compared to 0 in placebo group (493 P-Y), with 0.01 [-0.00 to 0.02] event / P-Y risk difference, which is not statistically significant (Figure). Similarly, no significant difference was observed in CHF incidence in patients receiving biologic agents, neither in PsA nor in psoriasis.

Conclusion: Even if there was no statistically significant difference in the incidence of MACEs or CHF in patients receiving biologic therapies during the placebo-controlled phase of RCTs, physicians must remain aware of the risk of MACEs or CHF when initiating a biologic therapy in PsA or psoriasis.

Figure: Meta-analysis of MACEs in psoriasis with anti-IL12/23 agent compared to placebo.



Disclosure: B. Champs, None;

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Abstract Number: 1728

Comparison of Adherence to Disease Modifying Antirheumatic Drugs in Psoriatic Arthritis and Other Rheumatic Disease

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Background/Purpose: Psoriatic arthritis (PsA), Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are an inflammatory arthritis causing joint damage and disability. Non-adherence to disease modifying anti-rheumatic drugs (DMARDs) remains a significant barrier to improving clinical outcomes in these diseases. We aimed to compare adherence to DMARDs and associated factors in PsA and other rheumatic diseases.

Methods: This was a cross-sectional study of people with rheumatic disease receiving DMARDs. Patients with PsA (n=108), RA (n=54) and AS (n=54) were recruited from two tertiary rheumatology centers in Turkey (Trakya and Uludag Universities). The patients who met the classification criteria were enrolled in this cross-sectional study. The Beliefs about Medicines Questionnaire (BMQ), Illness Perception Questionnaire-Revised (IPQ-R), Medication Adherence Rating Scale (MARS) were used for the assessment.

Results: Patient characteristics and treatments shown in Table 1. The Specific Necessity was significantly lower in the PsA patients than in AS ($p < 0.001$) and RA ($p < 0.001$) patients. General Overuse and General Harm scores were significantly higher in PsA patients than in AS (p values <0.001) and RA patients (p values, 0.04 and 0.1). These scores were also higher in RA group than in AS group (p values 0.05 and 0.02, respectively). There was no significant difference between groups in the Specific Necessity scores and MARS scores for DMARDs. In PsA patients, illness coherence and timeline cyclical scores were significantly higher than in RA patients (p values, <0.001 and 0.033, respectively). Illness coherence score was significantly lower in RA patients than in AS patients ($p<0.001$). Treatment control score was significantly higher in RA patients than AS ($p=0.029$) patients. In other IPQ subscales there were no significant differences between groups seen in Table 2 and Table 3. In PsA group, the score of BMQ- Specific Necessity negatively correlated with total score of MARS ($r= -0.244$, $p=0.01$). The other correlations between MARS and BMQ scores there were no significant differences.

Conclusion: In conclusions, PsA patients do not have strong belief in personal need for the DMARDs when compared to RA and AS. Also, PsA patients have more concerns about medicines are overused and being harmful.

Table 1: Patient characteristics and treatments

	PsA (n=108)	AS (n=54)	RA (n=54)	All patients (n=216)
Age (years)	46.26±11.09	44.80±7.31	47.70±11.04	46.25±10.27
Gender (male/female)	23/85	33/21	3/51	59/157
Disease duration	7.45±7.17	7.94±5.01	8.83±7.32	7.92±6.73
Nsaii, n%	23 (%21.3)	40 (%74.1)	36 (%66.6)	99 (%45.8)
Steroid, n%	40 (%37)	4 (%7.5)	40 (%75.5)	84 (%39.3)
Methotrexate, n%	63 (%58.3)	2 (%3.8)	42 (%79.2)	107 (%49.5)
Sulfasalazine, n%	24 (%22.2)	24 (%32.9)	25 (%34.2)	77 (%33.8)
Leflunomide, n%	22 (%20.4)	0 (%0)	18 (%33.3)	40 (%18.5)
Anti-TNF	59 (%54.6)	46 (%85.2)	17 (%32.1)	122 (%56.7)
Other treatments*, n%	0 (%0)	0 (%0)	19 (%35.1)	19 (%35.1)

*: abatacept, rituximab, tocilizumab

Table 2: BMQ and MARS questionnaire data for all participants.

Questionnaires	PsA (n=108)	AS (n=54)	RA (n=54)	p
BMQ-Specific Necessity, mean (95%CI)	13.13 (12.18-14.08)	19.16 (18.27-20.05)	17.39 (15.95-18.83)	<0.001
BMQ-Specific Concern, mean (95%CI)	14.49 (13.63-15.35)	14.16 (13.42-14.91)	14.73 (13.67-15.79)	>0.005
BMQ-General Overuse, mean (95%CI)	13.30 (12.70-13.90)	10.86 (10.25-11.47)	12.15 (11.33-12.96)	<0.001
BMQ-General Harm, mean (95%CI)	13.49 (12.83-14.14)	10.27 (9.44-11.10)	11.92 (11.08-12.75)	<0.001
MARS, mean (95%CI)	6.09 (5.79-6.39)	5.85 (5.48-6.22)	5.83 (5.47-6.20)	>0.005

Table 3: IPQ questionnaire data for all participants.

Questionnaires	PsA (n=108)	AS (n=54)	RA (n=54)	p
IPQ-Identity, mean (95%CI)	5.44 (4.48-6.39)	4.52 (3.81-5.23)	5.15 (4.15-6.15)	>0.005
IPQ-Timeline, mean (95%CI)	18.39 (17.84-18.94)	18.90 (18.13-19.67)	18.05 (16.24-19.86)	>0.005
IPQ-Consequences, mean (95%CI)	18.53 (17.44-19.62)	18.40 (17.30-19.51)	18.05 (16.77-19.33)	>0.005
IPQ-Personal control, mean (95%CI)	17.18 (16.43-17.93)	18.24 (17.37-19.10)	17.19 (16.08-18.29)	>0.005
IPQ-Treatment control, mean (95%CI)	15.98 (15.38-16.57)	16.94 (15.40-18.48)	15.05 (14.37-15.74)	0.029
IPQ-Illness coherence, mean (95%CI)	13.88 (13.17-14.60)	14.07 (13.07-15.07)	11.47 (10.92-12.01)	<0.001
IPQ-Timeline cyclical, mean (95%CI)	12.85 (12.24-13.47)	13.75 (12.91-14.60)	14.22 (12.98-13.85)	0.033
IPQ-Emotional representation, mean (95%CI)	18.56 (17.55-19.56)	18.35 (16.83-19.86)	18.88 (17.63-20.63)	>0.005

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Abstract Number: 1729

Secukinumab for the Treatment of Psoriatic Arthritis: Comparative Effectiveness Versus Infliximab Using a Matching-Adjusted Indirect Comparison

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Background/Purpose: Secukinumab (SEC) and infliximab (INF) are approved for the treatment of active PsA in adults with an inadequate response to conventional DMARDs. There are no head-to-head (H2H) randomized controlled trials (RCTs) between SEC and INF. In the absence of a H2H RCT, matching-adjusted indirect comparison (MAIC) can be used to generate comparative effectiveness data in the short and long term. MAIC adjusts for differences in baseline patient characteristics by using individual patient data (IPD) from one or more trials to match the treatment population of another trial. The aim of this MAIC was to assess the relative effectiveness of SEC 150 mg and 300 mg versus INF 5 mg/kg in patients with active PsA using data from the FUTURE 2 and IMPACT 2 RCTs.

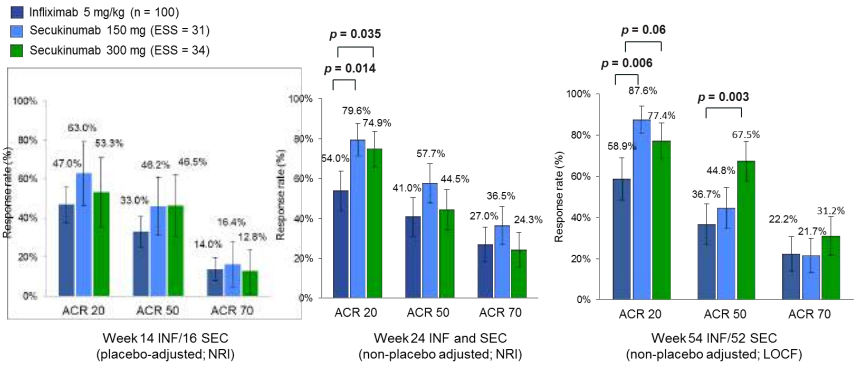
Methods: IPD from the SEC arms of FUTURE 2 (75 mg, n = 99; 150 mg, n = 100; 300 mg, n = 100) were weighted to match baseline characteristics of the INF arm of IMPACT 2 (n = 100); placebo arms were also matched (FUTURE 2, n = 98; IMPACT 2, n = 100). Logistic regression was used to determine weights for age, body weight, sex, race, methotrexate use, presence of psoriasis on ≥ 3% of body surface area, mean PASI score, Health Assessment Questionnaire Disability Index (HAQ-DI) score, dactylitis, enthesitis and previous use of anti-TNFs. Recalculated outcomes from FUTURE 2 (150 mg effective sample size [ESS]: 31; 300 mg ESS: 34; placebo ESS: 15) were compared with published aggregate outcomes

from IMPACT 2 at weeks 14/16, 24 and 54/52 (the closest data points available for comparison). Placebo-adjustment was valid only until week 14/16 because patients could switch to active treatment as early as week 16 in both trials. ACR outcomes are presented as response rates (%) and pairwise comparisons using odds ratios (ORs).

Results: The ACR 20 response at week 14/16 with placebo was 8% in FUTURE and 11% in IMPACT 2, indicating a good match. After placebo-adjustment, at week 14/16 there was no difference in ACR 20 response rate between SEC and INF. At week 24, there was evidence of higher ACR 20 response rates for SEC 150 mg and 300 mg than for INF (OR [95% CI]: 3.33 [1.28–8.69]; $p = 0.014$ and OR: 2.55 [1.07–6.08]; $p = 0.035$, respectively). At week 54/52, there was evidence of a higher ACR 20 response rate for SEC 150 mg (OR [95% CI]: 4.92 [1.56–15.48]; $p = 0.006$) and a higher ACR 50 response rate for SEC 300 mg (OR [95% CI]: 3.59 [1.56–8.29]; $p = 0.003$) than for INF.

Conclusion: This MAIC showed higher ACR 20 response rates for SEC 150 mg and 300 mg than for INF at week 24, and higher ACR 20 (150 mg) and 50 (300 mg) response rates than for INF (non-placebo-adjusted) at week 54/52. There was no evidence of differences in the short-term placebo-adjusted phase. Key limitations of this MAIC are that placebo-adjustments were valid only until week 14/16, week 24 was the only common time point for which outcomes were reported for both RCTs, and the ESS for SEC was low. H2H RCTs remain the gold standard for comparing treatments.

MAIC ACR response rates at weeks 14/16, 24 and 54/52



All *p* values are based on pairwise comparisons using ORs. We avoid strict thresholds when interpreting statistical *p* values, as per the American Statistical Association definition (7 March 2016), but interpret values from 0.1 to 0.001 as weak to moderate evidence and, < 0.001 as strong evidence.
ACR, American College of Rheumatology response criteria; ESS, effective sample size; LOCF, last observation carried forward; NRI, non-responder imputation; OR, odds ratio.

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Abstract Number: 1730

Disease Progression Among Non-Achievers of Minimal Disease Activity in Psa Patients Treated with Infliximab or Golimumab

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Background/Purpose : Early achievement of minimal disease activity (MDA) is recommended as a valid treat-to-target approach in psoriatic arthritis (PsA). The purpose of the current analysis was to evaluate disease progression in PsA patients among non-achievers of MDA treated with anti-TNF agents under Canadian routine practice.

Methods : Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab (IFX) or Golimumab (GLM), or with ustekinumab (UST) for PsA. Eligible people for this analysis included PsA patients treated with IFX who were enrolled since 2005 or with GLM enrolled since 2010 or with UST enrolled since 2014 and with available MDA information at 6 and 12 months of treatment. MDA was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1 or BSA≤3, Pain (VAS)≤15mm, PtGA (VAS)≤20mm, HAQ ≤0.5, tender entheseal points ≤1. Pairwise comparisons in disease parameters were assessed with the non-parametric Wilcoxon test. Variables associated with improved DAS28 and MDA achievement were examined using general linear models and logistic regression, respectively, wherein variables showing a statistical trend (P<0.150) in univariate analysis were considered in multivariate analysis to identify predictors.

Results: A total of 106 patients (55.2% male and 88.7% bio-naïve) were included with a mean (SD) age and disease duration of 49.6 (11.4) and 5.6 (6.9) years, respectively. The proportion of patients who achieved MDA at 6 months was 49.1% (n=52) while 50.9% (n=54) did not achieve MDA. Among patients with MDA at 6 months, 75.0% had sustained MDA at 12 months and among the non-achievers, 14.8% achieved MDA at 12 months of treatment. Disease parameters over time among the non-MDA achievers at 6 months are described in Table 1; overall, no statistical changes were observed between 6 months and 12 months. Multivariate logistic regression analysis showed that lower baseline HAQ (OR=0.459, P=0.071) and MDA achievement at 6 months were associated with higher odds (OR=12.604; P<0.001) of MDA achievement at 12 months of treatment. Multivariate general linear models showed that MDA achievement at 6 months (B=-0.770, P=0.042) and being bio-naïve (B=-2.296, P=0.001) were significant predictors of DAS28 improvement at 12 months of treatment.

Conclusion: The results of the current analysis have shown that achievement of MDA at 6 months is critical for MDA achievement/maintenance at 12 months highlighting the importance of intensive treatment early on. Furthermore, these results highlight the importance of treatment optimization in cases where MDA is not achieved. Table 1: Disease Parameters for MDA Non-Achievers at 6 Months of Treatment

Disease Parameter, mean (SD)	Visit			P-Value
	Baseline	Month 6	Month 12	12 mos vs 6 mos
SJC28	5.57 (5.02)	1.83 (2.63)	2.52 (3.89)	0.243
TJC28	8.92 (6.91)	4.93 (6.11)	4.50 (5.35)	0.968
Pain, mm VAS	55.24 (23.55)	45.30 (19.87)	42.43 (26.71)	0.385
PtGA, mm VAS	59.00 (23.62)	44.61 (22.15)	41.74 (25.49)	0.533
HAQ-DI	1.29 (0.57)	1.15 (0.52)	1.19 (0.56)	0.135
PASI	3.02 (4.43)	1.24 (2.48)	1.27 (1.86)	0.242
Enthesitis Count	1.96 (3.55)	1.67 (3.55)	1.76 (3.11)	0.436
DAS28	4.71 (1.38)	3.62 (1.18)	3.58 (1.40)	0.780

Disclosure: D. Sholter, Janssen Pharmaceutica Product, L.P., 5; **P. Rahman**, Janssen Inc., 5; **M. Sheriff**, Janssen Pharmaceutica Product, L.P., 5; **M. Zummer**, Janssen Pharmaceutica Product, L.P., 5; **S. Kapur**, Janssen Pharmaceutica Product, L.P., 5; **P. Baer**, Janssen Inc., 5; **M. Starr**, Janssen Inc., 5; **J. Kelsall**, Janssen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **B. Osborne**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3.

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Abstract Number: 1731

Disease Burden and Impact of Certolizumab Pegol Treatment on Workplace and Household Productivity Across Working Age Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis Patients

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Background/Purpose: Inflammatory diseases such as rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axSpA), including ankylosing spondylitis (AS) and non-radiographic axSpA (nr-axSpA), can impact significantly on patients' (pts') ability to perform work-related tasks in both paid employment and the household.[1,2] Previous results show improvements in work and household productivity with certolizumab pegol (CZP) in pts with established RA,[3,4] PsA[5] and axSpA.[6] We examined the comparative economic burden of RA, PsA and axSpA and the impact of CZP on productivity after 1 year (yr) in pts of working age.

Methods: Baseline (BL) and 1 yr data from: RA: PREDICT (NCT01255761),[3] RAPID 1 (NCT00152386),[4] RAPID 2 (BL data only, NCT00160602);[4] PsA: RAPID-PsA (NCT01087788);[5] axSpA: RAPID-axSpA (NCT01087762).[6] Pts received CZP loading dose (400 mg at Weeks [Wks] 0, 2, 4), followed by 200 mg Q2W+MTX (RA), or 200 mg Q2W or 400 mg Q4W (PsA/axSpA). The arthritis-specific Work Productivity Survey (WPS),[7] administered Q4W from BL, assessed the impact of disease on workplace and household productivity. Disease burden at BL and WPS responses (LOCF imputation) over 52 wks (RA) and 48 wks (PsA/axSpA), in CZP-treated pts stratified by age and employment status, are summarized descriptively.

Results: At BL, 582/1372 (42%) RA pts, 166/273 (61%) PsA pts, and 157/218 (72%) axSpA pts were employed outside the home. BL demographics were typical of each disease population; mean age of employed pts and pts unemployed due to arthritis/other conditions was similar (Table). Employed pts reported similarly high disease burden at BL across RA, PsA and axSpA (Table); by age, highest absenteeism was in pts aged 35–45 yrs (mean days/month: 3.1 [RA], 2.3 [PsA]) and 25–35 yrs (mean days/month: 2.4 [axSpA]) and presenteeism in pts under 35 yrs (mean days/month: 7.7 [RA], 6.5 [PsA], 7.1 [axSpA]). Compared to employed pts, unemployed pts reported a higher burden on household work and social activities, with highest burden in pts unemployed due to arthritis (Table). Similar improvements were seen in work and household productivity after 1 yr of CZP treatment, regardless of employment status, across all diseases (Table).

Conclusion: RA, PsA and axSpA pts of working age reported comparably high burden of disease on work and household productivity at BL; household burden was greater in disease-disabled pts. CZP treatment leads to comparable improvements in work and household productivity over 1 yr across RA, PsA and axSpA employed and disease-disabled pts. **References:** 1. Mau W. J Rheumatol 2005;32:721-8; 2. Boonen A. Ann Rheum Dis 2010;69:1123-8; 3. Kavanaugh A. Arthritis Rheum 2009;61(11):1592-600; 4. Kavanaugh A. Ann Rheum Dis 2014;73(2):927-8; 5. Kavanaugh A. Arthritis Rheum 2013;65(S10):S140-1; 6. van der Heijde D. Arthritis Rheum 2013;65(S10):S644-55; 7. Osterhaus J. Arth Res Ther

Table: Workplace and household productivity over 1 year in RA (RAPID 1 and 2 [a], PREDICT [b]), PsA (RAPID-PsA [c]) and axSpA (RAPID-axSpA [d]) patients (LOCF)

		RA CZP 200 mg Q2W n=1372	PsA CZP pooled dose n=273	axSpA CZP pooled dose n=218
Age, yrs, mean (SD)	BL [f]	49.5 (10.9)	45.0 (9.8)	39.1 (10.3)
	BL [i]	56.6 (12.1)	51.9 (12.8)	40.5 (14.6)
	BL [j]	51.2 (10.1)	46.8 (13.1)	37.2 (13.3)
Gender, % male	BL [f]	21.5%	53.0%	64.3%
	BL [i]	18.6%	35.5%	55.7%
	BL [j]	21.2%	34.6%	69.2%
WPS responses [e]		Mean, median (n)	Mean, median (n)	Mean, median (n)
Productivity at workplace (employed patients [f])				
Work days missed due to arthritis per month	BL	2.3, 0.0 (582)	1.8, 0.0 (166)	1.8, 0.0 (157)
	1 yr	0.7, 0.0 (476)	0.4, 0.0 (169)	0.3, 0.0 (163)
Days with work productivity reduced by ≥50% due to arthritis per month [g]	BL	6.7, 4.0 (582)	5.1, 0.0 (166)	5.2, 0.0 (157)
	1 yr	1.8, 0.0 (476)	1.3, 0.0 (169)	1.3, 0.0 (163)
Level of arthritis interference with work productivity (0–10 scale) [h]	BL	4.9, 5.0 (581)	4.1, 4.5 (166)	4.5, 5.0 (157)
	1 yr	1.9, 1.0 (476)	1.5, 0.0 (169)	1.4, 0.0 (163)
Household productivity and social participation (employed [f] and unemployed [i] patients)				
Household work days missed due to arthritis per month	BL [f]	6.7, 5.0 (581)	4.1, 0.0 (166)	3.8, 0.0 (157)
	1 yr [f]	2.1, 0.0 (476)	1.3, 0.0 (169)	1.0, 0.0 (163)
	BL [i]	9.2, 6.0 (739)	8.2, 4.0 (107)	9.1, 5.0 (61)
	1 yr [i]	4.2, 0.0 (599)	4.0, 0.0 (104)	3.8, 0.0 (55)
	BL [j]	11.8, 10.0 (319)	11.7, 7.5 (52)	11.6, 10.0 (39)
	1 yr [j]	6.2, 2.0 (252)	7.4, 3.0 (47)	4.9, 0.0 (35)
Household work days with productivity reduced by ≥50% due to arthritis per month [g]	BL [f]	7.9, 6.0 (581)	6.0, 4.0 (166)	6.6, 3.0 (157)
	1 yr [f]	2.4, 0.0 (476)	1.4, 0.0 (169)	1.3, 0.0 (163)
	BL [i]	9.8, 10.0 (738)	8.8, 7.0 (107)	9.6, 6.0 (61)
	1 yr [i]	4.2, 1.0 (599)	5.0, 0.0 (104)	3.3, 0.0 (55)
	BL [j]	10.5, 10.0 (319)	12.2, 10.0 (52)	9.8, 5.0 (39)
	1 yr [j]	5.5, 3.0 (252)	8.4, 5.0 (47)	3.5, 0.0 (35)
Level of arthritis interference with household productivity (0–10 scale) [h]	BL [f]	5.2, 5.0 (581)	4.5, 5.0 (166)	4.3, 5.0 (157)
	1 yr [f]	2.2, 1.0 (476)	1.6, 0.0 (169)	1.4, 0.0 (163)
	BL [i]	6.4, 7.0 (739)	5.9, 6.0 (107)	6.1, 7.0 (61)
	1 yr [i]	3.5, 3.0 (598)	3.1, 2.0 (104)	3.4, 3.0 (55)
	BL [j]	7.2, 7.0 (319)	6.9, 7.0 (52)	6.5, 7.0 (39)
	1 yr [j]	4.5, 5.0 (252)	4.0, 4.0 (47)	3.8, 4.0 (35)
Days missed family/social/leisure activities due to arthritis per month	BL [f]	3.4, 0.0 (581)	3.0, 0.0 (166)	3.6, 0.0 (157)
	1 yr [f]	0.8, 0.0 (476)	0.8, 0.0 (169)	0.7, 0.0 (163)
	BL [i]	5.3, 2.0 (740)	4.8, 0.0 (107)	5.0, 2.0 (61)
	1 yr [i]	1.5, 0.0 (599)	2.2, 0.0 (104)	1.3, 0.0 (55)
	BL [j]	6.5, 3.0 (319)	6.4, 2.5 (52)	6.4, 3.0 (39)
	1 yr [j]	2.2, 0.0 (252)	3.0, 0.0 (47)	1.9, 0.0 (35)

[a] ITT population; [b] FAS (Full Analysis Set): all patients who had a valid efficacy measurement at BL and at least 1 valid efficacy measurement post-BL; [c] RS (Randomized Set): all patients randomized; [d] FAS (Full Analysis Set): all patients who received ≥1 dose of study medication and had a valid BL and post-BL measurement for ASAS20; [e] 1 year responses for RA (RAPID 1+2, PREDICT) analyzed at Wk 52 and for PsA/axSpA at Wk 48 [f] Based only on employed patients at the specified visit; [g] Does not include work days missed counted in the previous question; [h] 0–10 scale, 0=no interference, 10=complete interference; [i] Based on patients not employed at the specified visit; [j] Based on patients unemployed due to arthritis or other conditions, or students at the specified visit (subset of patients not employed); BL: Baseline; yr: year.

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Articular and Axial Involvement Differences in Psoriatic Arthritis Patients Treated with Golimumab in Canadian Real-World Practice

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Session Time: 9:00AM-11:00AM

Background/Purpose: Psoriatic arthritis (PsA) is a complex rheumatic disease with severity that ranges from mild to severe. The mild form of PsA can be referred to as oligoarticular (OLIGO), whereas more severe cases are considered polyarticular (POLY) form. Furthermore, peripheral joint and axial involvement are also recognized in PsA. This analysis examined OLIGO vs. POLY differences and presence of axial involvement at initiation of golimumab (GLM) for the treatment of PsA in a Canadian routine clinical practice setting.

Methods: Biologic Treatment Registry Across Canada (BioTRAC) is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis, ankylosing spondylitis, or PsA with Infliximab, GLM, or ustekinumab for PsA. PsA patients treated with GLM who were enrolled since 2010 were eligible for the analysis. OLIGO involvement was defined as (≤2 SJC) and POLY (>2 SJC), while axial involvement included spinal symptoms or spondylitis with peripheral arthritis. Minimal disease activity (MDA) was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1 or BSA≤3, Pain (VAS)≤15mm, PtGA (VAS)≤20mm, HAQ ≤0.5, tender entheseal points ≤1.

Results: A total of 201 PsA patients were included in this analysis; 30.8% had oligoarthritis, 68.0% had polyarthritis, while 26.0% had axial involvement at baseline. Baseline parameters are described by axial involvement and articular involvement (Table 1). Increased baseline disease activity was observed among patients with axial involvement for MDGA, PtGA, pain, and presence of enthesitis ($p<0.05$). Patients with polyarthritis were older, less likely to have been previously treated with a biologic, and had significantly ($p<0.05$) higher SJC28, TJC28, morning stiffness, MDGA, PtGA, pain, DAS28, HAQ, and enthesitis at GLM initiation. At 6 months, statistically significant between group differences were observed for MDA achievement. There were significantly lower proportions of patients achieving MDA among patients with axial involvement (26.7% vs. 61.8%, $p=0.020$) and polyarthritis (35.9% vs. 80.0%, $p<0.001$). Multivariate logistic regression analysis showed that patients with oligoarticular involvement (OR=3.92; $p=0.035$), younger age (OR=0.96; $p=0.051$), and lower baseline HAQ (OR=0.32; $p=0.007$) were associated with higher odds of MDA achievement at 6 months of treatment while axial involvement did not have a significant impact.

Conclusion: The results of the current analysis highlight that differences exist in the baseline patient profile based on the presence or absence of axial involvement and POLY involvement among PsA patients treated with GLM. Furthermore,

OLIGO disease was identified as a significant independent predictor of MDA achievement with almost a four-fold higher likelihood of achieving target relative to patients with polyarthritis.

Table 1: Patient Characteristics and Disease Parameters at Baseline by Axial and Articular Involvement Axial Involvement Articular Involvement Parameter Mean (SD) / % Yes No p-Value Olgioarthritis Polyarthritis p-value Age: Years 47.8 (13.8) 52.1 (13.3) 0.096 47.4 (11.9) 53.8 (12.7) 0.001 Disease Duration: years 7.0 (8.2) 5.6 (7.4) 0.592 5.2 (7.3) 5.7 (6.9) 0.668 Prior Biologic 5.1% 2.7% 0.605 12.9% 3.0% 0.020 Concomitant DMARDs 76.9% 79.0% 0.821 77.6% 80.8% 0.695 Concomitant MTX 71.8% 57.1% 0.126 63.8% 64.6% >0.999 Concomitant NSAIDS 38.5% 49.5% 0.266 43.5% 48.5% 0.541 ESR: mm/hr 13.7 (10.6) 19.3 (19.0) 0.372 15.1 (15.3) 18.9 (17.5) 0.153 SJC28 6.2(4.4) 5.0(4.5) 0.102 0.9(0.8) 7.3(3.5) <0.001 TJC28 9.1(7.6) 6.9(6.6) 0.142 2.4(2.7) 9.5(6.8) <0.001 Morning stiffness:min 47.9(45.1) 32.3(38.8) 0.064 27.0 (35.4) 42.3(43.2) 0.009 Physician Global (MDGA): NRS 0-10 5.8 (2.0) 4.9(2.0) 0.035 3.9 (1.9) 5.8 (1.8) <0.001 Patient Global (PtGA): VAS mm 61.3(25.7) 51.3(25.1) 0.022 39.6(26.7) 59.4(22.7) <0.001 Pain 59.5(23.5) 48.9(24.4) 0.016 35.3(25.6) 59.6(21.1) <0.001 DAS28 4.5(1.3) 4.3(1.5) 0.490 2.9(1.1) 4.9(1.2) <0.001 PASI 2.3(3.6) 2.5(5.1) 0.424 1.7(2.4) 2.5(5.1) 0.227 HAQ 1.2(0.6) 1.0(0.7) 0.110 0.7 (0.7) 1.2(0.6) <0.001 Dactylitis 41.0% 35.6% 0.565 31.3% 38.3% 0.462 Enthesitis 56.4% 29.7% 0.004 22.6% 37.9% 0.049 Nail Pitting 38.5% 23.8% 0.096 27.1% 25.8% >0.999

Disclosure: M. M. Khraishi, None; **P. Rahman**, Janssen Inc., 5; **A. Tsoukas**, Janssen Inc., 5; **S. Kapur**, Janssen Pharmaceutica Product, L.P., 5; **M. F. Baker**, Janssen Inc., 5; **N. Jones**, Janssen Inc., 5; **M. Starr**, Janseen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **K. Maslova**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3.

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Sustained Efficacy of Ixekizumab in Patients with Moderate-to-Severe Plaque Psoriasis and Concomitant Psoriatic Arthritis

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Background/Purpose: PsA, a chronic immune-mediated inflammatory disease, can be progressive and destructive, resulting in physical deformities, impaired function, decreased quality of life, and increased mortality. Ixekizumab (IXE) is an IgG4 monoclonal antibody that binds with high affinity and specificity to the proinflammatory cytokine IL-17A. Data are presented from a phase 3 trial (SPIRIT P1; NCT01695239) with IXE in patients (pts) with active PsA. The objective is to explore the impact of IXE, as assessed by disease activity composite measures, up to 52 weeks (wks).

Methods: 417 bDMARD-naive adult pts with active PSA, were randomly assigned 1:1:1:1 to subcutaneous administration of either 80 mg IXE every 4 wks [Q4W] or every 2 wks [Q2W], each with a 160 mg starting dose at Wk 0; adalimumab (ADA) 40 mg Q2W [active comparator]; or placebo (PBO) in the Double Blind Treatment Period (DBTP; Wks 0-24). Of these pts, 381 continued into the Extension Period (EP; Wks 24-52). PBO- and ADA treated pts were randomly re-assigned

(1:1) to 80 mg IXEQ4W or IXEQ2W at Wk 16 (inadequate responders) or Wk 24; ADA-treated pts started IXE, after an 8-wk wash-out period, at Wk 24 (inadequate responders) or Wk 32. Investigators were blinded as to the criteria for inadequate response. Disease activity was measured at Wks 24 and 52 by composite measures including the following: minimum disease activity (MDA) as measured with the Psoriasis Area and Severity Index (MDA_{PASI}) and with the static Physician Global Assessment of psoriasis (MDA_{sPGA}), and modified Composite Psoriatic Disease Activity Indices (CPDAI-12 and CPDAI 14 [see Table 1 footnote]). Analyses for the DBTP were conducted on the Intent-to-Treat Population, defined as all randomly assigned pts; analyses for the EP were conducted on the EP Population, defined as all pts who received at least 1 dose of study drug during the EP. In the DBTP, treatment comparisons were made by a logistic regression model for categorical data with missing values imputed by nonresponder imputation; a mixed model for repeated measures analysis was used for continuous data.

Results: At Wk 24, CPDAI 12 and CPDAI-14 total scores (assesses domains of peripheral arthritis, skin disease, enthesitis, dactylitis [and spinal disease for CPDAI-14 only]) for pts receiving IXEQ4W, IXEQ2W, or ADA, were significantly improved compared with results for pts receiving PBO (Table 1). Similarly, at Wk 24, significantly more pts receiving IXEQ4W, IXEQ2W, or ADA achieved MDA_{sPGA} and MDA_{PASI} compared with pts receiving PBO (Table 1), and percentages of pts receiving IXEQ4W or IXEQ2W who achieved MDA_{sPGA} and MDA_{PASI} were sustained through Wk 52 (Table 2). Results for MDA_{sPGA} were similar to results for MDA_{PASI} within each treatment group.

Conclusion: IXE provides sustained improvement of disease activity, as measured by various composite measures, for up to 52 wks in bDMARD-naive pts with active PsA.

Table 1: Improvement in Composite Outcome Measures at Week 24 (Double-Blind Treatment Period)

Assessment	PBO N=106	ADA N=101	IXEQ4W N=107	IXEQ2W N=103
NRI:				
MDA_{sPGA}, n (%)	16 (15.1)	35 (34.7)***	31 (29.0)*	39 (37.9)***
MDA_{PASI}, n (%)	16 (15.1)	32 (31.7)**	32 (29.9)**	43 (41.7)***
Change from baseline:				
CPDAI-14[a] Total Score, LSM (SE)	-1.39 (0.29)	-2.59 (0.26)***	-3.49 (0.27)***	-3.59 (0.27)***
CPDAI-12[b] Total Score, LSM (SE)	-1.24 (0.26)	-2.23 (0.23)**	-3.02 (0.23)***	-3.15 (0.24)***

Abbreviations: ADA=adalimumab; ASQoI=Ankylosing Spondylitis Quality of Life; CPDAI=Composite Psoriatic Disease Activity Index; IXE=ixekizumab; LSM=least square mean; MDA=minimum disease activity; MDA_{PASI}=MDA measured by Psoriasis Area and Severity Index; MDA_{sPGA}=MDA measured by static Physician Global Assessment of psoriasis; N,n=number of patients; NRI=nonresponder imputation; p=p-value; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error.

[a]CPDAI-14 is modified from CPDAI (Mumtaz A, Gallagher P, Brian K, et al. Development of a preliminary composite disease activity index in psoriatic arthritis. Ann Rheum Dis. 2011;70:272-7); this modified index does not include ASQoL questionnaire and has a possible total score of 14.

[b]CPDAI-12 is modified from CPDAI (Mumtaz et al. 2011); this modified index does not include the ASQoL or the BASDAI, and has a possible total score of 12.

*p<.05; **p≤.01; ***p≤.001; MDA p-values for are from a logistic regression model; CPDAI p-values are from a repeated measures mixed model.

Table 2: Improvements in Composite Outcome Measures at Week 52 (Extension Period)

Assessment	PBO/ IXEQ4W N=45	PBO/ IXEQ2W N=46	ADA/ IXEQ4W N=49	ADA/ IXEQ2W N=48	IXEQ4W/ IXEQ4W N=97	IXEQ2W/ IXEQ2W N=96	Total IXEQ4W N=191	Total IXEQ2W N=190
NRI:								
MDA_{sPGA}, n (%)	15 (33.3)	19 (41.3)	20 (40.8)	15 (31.3)	42 (43.3)	38 (39.6)	77 (40.3)	72 (37.9)
MDA_{PASI}, n (%)	15 (33.3)	19 (41.3)	20 (40.8)	15 (31.3)	42 (43.3)	38 (39.6)	77 (40.3)	72 (37.9)

Abbreviations: ADA=adalimumab; IXE=ixekizumab; MDA=minimum disease activity; MDA_{PASI}=MDA measured by Psoriasis Area and Severity Index; MDA_{sPGA}=MDA measured by static Physician Global Assessment of psoriasis; N,n=number of patients; NRI=nonresponder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks.

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Lilly and Company, 1,Eli Lilly and Company, 3; **P. J. Mease**, AbbVie, Amgen, Bristol Myers Squibb, Celgene, Janssen, Eli Lilly and Company, Novartis, Pfizer, Sun, UCB, 2,AbbVie, Amgen, Bristol Myers Squibb, Celgene, Crescendo, Corrona, Dermira, Janssen, Eli Lilly and Company, Merck, Novartis, Pfizer, Sun, UCB, Zynerba, 5,AbbVie, Amgen, Bristol Myers Squibb, Celgene, Crescendo, Janssen, Novartis, Pfizer, UCB, 8.

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Abstract Number: 1734

Apremilast Is Associated with Long-Term DAS-28 (CRP) Remission and Improvements in Skin Disease: Results from a Phase III Study in DMARD/Biologic-Experienced Active Psoriatic Arthritis Patients

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Background/Purpose: Treatment goals for long-term control of skin and joint symptoms in active psoriatic arthritis (PsA) include clinically important changes in DAS-28 (CRP), achievement of remission in DAS-28 (CRP), reduction in swollen joint count (SJC), and decrease in skin disease.[1] PALACE 3 (NCT01212770) included PsA patients (pts) with active joint disease and an active skin lesion at the time of enrollment. We report the impact of apremilast (APR) on PsA manifestations over 4 years.

Methods: Pts were stratified by baseline (BL) DMARD use (yes/no) and psoriasis involvement of the body surface area (<3%/≥3%) and randomized (1:1:1) to placebo (PBO), APR 30 mg BID (APR30), or APR 20 mg BID (APR20). After the 24-week PBO-controlled phase, all pts were treated with APR30 or APR20 and could enroll in the long-term extension. Efficacy assessments were conducted through Week 208.

Results: 505 pts were randomized and received ≥1 dose of study medication (PBO: n=169; APR30: n=167; APR20: n=169). A total of 91% (227/249) of pts starting the fourth year of APR therapy completed the Week 208 visit. Pts treated with APR30 demonstrated sustained decreases in disease activity at Week 208, as shown by mean change from BL in DAS-28 (CRP) of −1.66; 80.3% achieved good/moderate EULAR response and 50.4% achieved DAS-28 (CRP) remission. Sustained effect on inflammation at Week 208 was also demonstrated by mean/median percent changes in SJC, a marker of inflammatory activity, of −77.4%/−100.0% (Table); 64.8% of pts had an SJC 0 or 1. Decreases in disability and maintenance of functionality were shown by sustained improvements in Health Assessment Questionnaire-Disability Index (HAQ-DI) scores (Table). A continued effect on skin disease was shown by decreases in skin involvement, as measured by the Psoriasis Area and Severity Index (PASI); 54.7% of APR30 pts had BL PASI >5 and 27.3% had BL PASI >10; at Week 208, 64.5% had PASI <3 and 77.4% had PASI ≤5. PASI-75 and PASI-50 response rates also signified clinically significant relief (Table). In pts treated with APR20, similar findings were observed at Week 208. No new safety concerns were identified through 208 weeks of APR30 therapy. During Weeks >156 to ≤208 of APR30 exposure, the only AE occurring in ≥5% of pts was nasopharyngitis; most AEs were mild or moderate in severity. Serious AEs occurred in 7.2% of APR30 pts Weeks >156 to ≤208, similar to rates in earlier study periods. Few discontinuations due to AEs (0.7%) occurred over Weeks >156 to ≤208. The APR20 safety profile was similar to that of APR30.

Conclusion: Over 208 weeks, APR demonstrated sustained and clinically important improvements in PsA signs and symptoms, including physical function and associated psoriasis, among pts continuing the study. APR was generally well tolerated with an acceptable safety profile. **Reference:** 1. Gossec et al. *Ann Rheum Dis*. 2015 Dec 7. doi: 10.1136/annrheumdis-2015-208337.

	Outcomes at Week 208
	APR30 n=129*
DAS-28 (CRP), mean change	−1.66
DAS-28 (CRP) <2.6, n/m (%)	64/127 (50.4)
SJC, mean % change	−77.4
TJC, mean % change	−64.4
HAQ-DI (0-3), mean change	−0.42
HAQ-DI MCID ≥0.30, n/m (%)	63/129 (48.8)
HAQ-DI MCID ≥0.35, n/m (%)	63/129 (48.8)
ACR20, n/m§ (%)	85/128 (66.4)
ACR50, n/m§ (%)	51/128 (39.8)
ACR70, n/m§ (%)	31/127 (24.4)
PASI-75, n/m (%)‡	28/62 (45.2)
PASI-50, n/m (%)‡	42/62 (67.7)

Data as observed.
*The n reflects the number of pts treated with APR30, regardless of when APR was started (BL, Week 16, or Week 24) and who had data available at Week 208; actual number of pts available for each end point may vary. §Denominators vary slightly due to availability of sufficient data for each level of ACR response assessment. ‡Examined among pts with psoriasis involvement of the body surface area ≥3% at BL and having data at Week 208.
n/m=number of responders/number of pts with sufficient data for evaluation; TJC=tender joint count; ACR20/50/70=20%/50%/70% improvement in modified American College of Rheumatology response criteria; PASI-75/50=≥75%/≥50% reduction from BL PASI score.

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Abstract Number: 1735

Canadian Humira Post-Marketing Observational Epidemiological Study Assessing Effectiveness in Psoriatic Arthritis (Complete-PsA): Interim Analysis

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Background/Purpose: COMPLETE-PsA is an ongoing observational study planning to enroll 670 psoriatic arthritis (PsA) patients (pts) from ~40 sites across Canada. Main objectives are to compare the real-life effectiveness of adalimumab (ADA) to traditional non-biologic DMARDs and to describe the PsA burden of illness. The goal of this analysis is to describe the demographics and baseline disease parameters of the cohort and to report preliminary Canadian data on the real-life effectiveness of ADA in PsA.

Methods:

This was a pre-specified interim analysis of pts enrolled between 8/2011−8/2015. Eligible pts are adults with active PsA with ≥3 tender and swollen joints, active psoriatic skin lesions or confirmed history of psoriasis, who are anti-TNF naïve and require a change in current treatment. Pts are followed for up to two years as per routine care with suggested assessments at months 3, 6, 9, 12, 18, and 24. Data captured include disease activity (28 tender [TJC28] and swollen [SJC28] joints, HAQ, physician [PGA] and patient [PtGA] global assessment, morning stiffness, psoriasis body surface area [BSA], PASQ, and DLQI), periarticular manifestations, quality of life (SF-36, BDI-II), and work limitations (WLQ).

Results:

Of the 319 pts (ADA n=181, DMARD n=138) included in the analysis, 236 (74%) had available 6-month data. At baseline, mean age was 51.0 yrs (SD 12.3), 51.7% were female, and mean disease duration was 4.2 yrs (SD 6.5). There were no significant differences between treatment groups. Family history of PsA (14.2%) and arthritis subtype (64.2% symmetric polyarthritis) were also comparable.

Within the ADA group, 79.6% were treated with a concomitant DMARD (MTX: 65.7%; HCQ: 18.2%; SSZ: 16%; LEF: 9.4%; AZA: 1.7%; Gold: 1.1%) at baseline, while 63.5% had been previously treated with a DMARD (33.1% with 1 DMARD, 18.8% with 2, 11.6% with ≥3). Within the DMARD group, the following DMARDs were used: MTX (85% of pts), HCQ (18.0%), SSZ (18%), LEF (15.8%), and AZA (1.5%); with 33.8% using ≥1 DMARDs.

At baseline, ADA pts had significantly higher DAS28 (4.9 vs. 4.5; P=0.017), SJC28 (8.5 vs. 6.0; P<0.001), morning stiffness (88.5 vs. 58.7 min; P=0.008), PtGA (56.6 vs. 44.6; P<0.001), HAQ (1.1 vs. 0.9; P<0.001), and lower SF-36 score (26.6 vs. 27.4; P=0.003) but statistically comparable CRP, ESR, TJC28, BSA, PGA, PASQ, and DLQI. Productivity loss was higher in the DMARD group (17.8% vs. 16.4%; P=0.021).

By 6 months, 8% of pts in the DMARD group vs. 2.8% in the ADA group (P=0.035) were discontinued. At 6 months, significant improvements were observed in almost all disease parameters. Adjusting for baseline values, ADA pts had significantly lower DAS28 (2.6 vs. 3.7; P<0.001), TJC28 (3.0 vs. 5.8; P=0.001), SJC28 (1.4 vs. 4.2; P<0.001), PGA (16.9 vs. 34.5; P<0.001), PtGA (29.3 vs. 39.9; P=0.030), HAQ (0.64 vs. 0.93; P<0.001), PASQ (9.5 vs. 10.7; P=0.015) and DLQI (2.2 vs. 4.1; P=0.015) vs. pts in the DMARD group.

Conclusion: PsA pts initiating ADA in Canadian routine clinical care have more severe disease compared with those initiating traditional DMARDs. However, over 6 months, ADA treatment had better retention, and was more effective in reducing symptom severity and improving outcomes.

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Abstract Number: 1736

Efficacy of TNF Inhibitors in Axial Spondyloarthritis According to the Presence of Objective Signs of Inflammation: A Multicentric Retrospective Study

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Background/Purpose: TNF inhibitors (TNFi) are effective treatment in radiographic and non-radiographic axial spondyloarthritis (r-axSpA and nr-axSpA). Nr-axSpA have lower response rate in case of absence of sacroiliitis on magnetic resonance imaging (MRI) or elevated C-reactive protein (CRP) but TNFi efficacy in the absence of clinical, biological or radiological objective signs of axSpA is unknown. The main objective of our study was to compare BASDAI 50 TNFi response rate at 3 months in axSpA depending on the presence or not of objective signs of axSpA.

Methods: Nr-axSpA patients fulfilling ASAS 2009 criteria, without any objective signs defined as the absence at the time of TNFi initiation of radiographic and MRI sacroiliitis, elevated CRP level, dactylitis, anterior uveitis and treated inflammatory bowel disease were included in this retrospective bicentric study between January 2001 and September 2015. They were matched base on a ratio of 1:1, on age, sex and type of TNFi, with axSpA patients having at least one objective sign. Patients had to be treated for at least 3 months with an anti-TNF. The primary outcome of our study was the TNFi efficacy, defined as an achievement of 50% improvement of the initial Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at 3 months. The secondary outcomes were BASDAI 50 achievement over one year and assessment of predictive factors of TNFi response.

Results: We included 84 nr-axSpA patients without any objective sign and 84 axSpA patients with objective signs. Patients were mostly women (76.2%) with a mean ± standard deviation age of 42 ± 11 years. BASDAI 50 achievement rates were significantly higher in patients with objective signs than in patients without, at 3 months (45.1% versus 13.7%, $p<0.0001$) and over one year (61.9% versus 21.4% considering all time point for evaluation, $p<0.0001$). In the total population, positive predictive factors of a BASDAI 50 response achievement at 3 months in univariate analysis were a radiographic sacroiliitis [16/47 (34%) responders versus 22/114 (19.3%) non responders, $p=0.038$], a sacroiliitis on MRI [19/33 (57.6%) responders versus 18/97 (18.6%) non responders, $p < 0.0001$], an elevated CRP [16/48 (33.3%) in responders versus 20/114 (17.5%) in non responders, $p = 0.025$] and a lower mean BASDAI at TNFi initiation [5.4 (1.5) in responders versus 6 (1.5) in non responders, $p = 0.017$]. Overweight or obesity and sacroiliitis on MRI were respectively a negative and positive predictive factors of TNFi efficacy in multivariate analysis in the all population [OR = 0.32, 95%CI (0.11, 0.96), $p = 0.041$ and OR = 6.92, 95%CI (2.41, 19.82), $p < 0.0001$, respectively].

Conclusion: Our study confirms the existence of patients diagnosed with nr-axSpA, according to clinical arm of the ASAS criteria, in whom TNFi have a very low efficacy and should not be used if no objective sign is present at treatment initiation. We also stated high BMI (≥ 25 kg/m^2) as a negative predictive factor of TNFi efficacy.

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spondyloarthritis-according-to-the-presence-of-objective-signs-of-inflammation-a-multicentric-retrospective-study

Abstract Number: 1737

Adherence to Subcutaneous Biological Therapies Among Inflammatory Arthropaty Patients from a University Hospital

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Background/Purpose: Rheumatic inflammatory arthropaties such as Rheumatoid Arthritis (RA), Psoriatic Arthritis (PsA) and Spondyloarthrities (SpA) are chronic diseases that require adequate therapies, sometimes biological drugs, to minimize inflammation and disease progression. The adherence to biologicals is supposed to be better than adherence to synthetic DMARDs, mainly methotrexate. The purpose of this study is to evaluate adherence to subcutaneous biological therapies and to assess the relationship between adherence and different demographic and clinical aspects, and its effect on clinical outcomes.

Methods: Observational retrospective study of 272 clinical records of patients with inflammatory rheumatic diseases on subcutaneous biological treatment, were reviewed. Demographic, clinical characteristics and comorbidities were compiled. Disease activity was classified as low, moderate and high based on DAS 28 in patients with peripheral arthritis and BASDAI in patients with axial SpA. Adherence was obtained for the last year from the Hospital Pharmacy registry (FARHOS). Adherence was randomly rated as good >80% of compliance, medium 60-79% and fair <59%. 11 patients not actually under biological treatment were excluded from analysis. Statistical analyses were performed using SAS for Windows statistical software, version 9.2.

Results: From the 261 patients evaluated, 52% were female, mean aged 54 + 13.9 SD years (range 19-86). 35.6 % had RA diagnosis, 32% PsA, 29.5% axial SpA and, 6% peripheral SpA and 1% non-radiographic axial SpA. Median time of disease progression was 10.7 years. 34% presented more than two comorbidities.39% were under adalimumab, 38 % etanercept, 7.3% golimumab, 5.4% certolizumab, 4.6% tocilizumab, 2,7 % abatacept and 1% ustekinumab. 68 % were on their first biological drug, 25% on the second, and the rest had more than one biologic agent previously prescribed. 46 received concomitant synthetic DMARD. Overall adherence to biological treatment, was good, 93%, and there was no correlation between adherence and diagnose, gender, age, time of disease progression, concurrence of more than two comorbidities, cotreatment with synthetic DMARD, type of biological drug or previous treatment with other biologicals. There has been found correlation between disease activity (DAS, BASDAI) and adherence as shown in the table, P 0.0038 (Chi Square).

Conclusion: The overall adherence to subcutaneous biological therapies is very good and non-compliance has an impact in the disease activity as has been observed in this study. Therefore, it is important to check adherence when clinical response is poor to subcutaneous biological therapies and we must consider the implementation of tools to monitor adherence in order to identify non-compliant patients, quite relevant for clinical decision making.

Adherence / D. Activity	<59%	60-79%	>80%	TOTAL
LOW	2%	4%	61%	67%
MODERATE	0.5%	3.2%	11.3%	15%
HIGH	2%	2%	14%	18%

Disclosure: C. Gómez-Arango, None; **M. L. García-Vivar**, None; **M. Alonso-Diez**, None; **M. M. Alvarez-Lavin**, None; **E. Galindez-Agirregoikoa**, None; **O. Fernández-Berrizbeitia**, None; **E. Ruíz-Lucea**, None; **J. María Blanco-Madrigal**, None; **J. F. Garcia-Llorente**, None; **L. Estopiñán-Fortea**, None; **I. Torre-Salaberri**, None; **E. Guerrero-Basterretxea**, None; **I. Calvo-Zorrilla**, None; **A. Bilbao-González**, None; **N. Rivera-García**, None.

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Abstract Number: 1738

Secukinumab for the Treatment of Psoriatic Arthritis: Comparative Effectiveness Versus Adalimumab Using a Matching-Adjusted Indirect Comparison

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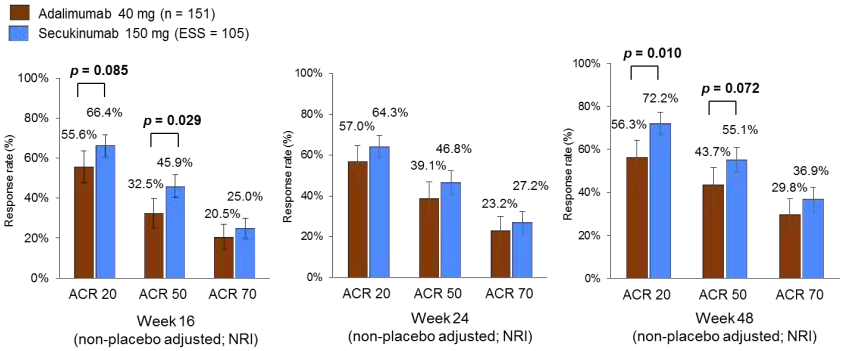
Background/Purpose: Secukinumab (SEC) and adalimumab (ADA) are approved for the treatment of active PsA in adults with an inadequate response to conventional DMARDs. A head-to-head randomized controlled trial (RCT) between SEC and ADA was recently announced (EXCEED 1) but until the results are available, matching-adjusted indirect comparison (MAIC) can be used to estimate short- and long-term comparative effectiveness. MAIC adjusts for differences in baseline patient characteristics by using individual patient data (IPD) from one or more trials to match the population of another trial. The aim of this MAIC was to assess the relative effectiveness of SEC and ADA in active PsA using data from FUTURE 1, FUTURE 2 and ADEPT RCTs.

Methods: IPD from the pooled SEC 150 mg arms of FUTURE 1 (n = 202) and FUTURE 2 (n = 100) were weighted to match the published baseline characteristics of the ADA 40 mg arm of ADEPT (n = 151). SEC 300 mg was not included because it was not used in FUTURE 1. Logistic regression was used to determine weights for age, body weight, sex, race, methotrexate use, presence of psoriasis on ≥ 3% of body surface area, Psoriasis Area Severity Index score, Health Assessment Questionnaire Disability Index (HAQ-DI) score, dactylitis, enthesitis and previous anti-TNF therapy. Recalculated outcomes with SEC 150 mg from the FUTURE RCTs (estimated sample size [ESS]: 105) were compared with published aggregate ADA outcomes from ADEPT at weeks 16, 24 and 48. Placebo-adjustment was not valid because patients in ADEPT could receive rescue therapy from week 12. Comparisons are presented as response rates (%, non-

placebo-adjusted) and as pairwise comparisons using odds ratios (ORs) and change in mean score from baseline for HAQ-DI.

Results: After matching, ACR 20 and 50 response rates at week 16 were higher for SEC than for ADA (OR [95% CI]: 1.57 [0.94, 2.64]; $p = 0.085$ and OR: 1.77 [1.06, 2.96]; $p = 0.029$, respectively). At week 24, there was no evidence of differences in ACR response between SEC and ADA. At week 48, there was evidence of higher ACR 20 and 50 response rates with SEC than with ADA (OR: 2.01 [1.18, 3.43]; $p = 0.010$ and OR: 1.58 [0.96, 2.61]; $p = 0.072$, respectively) and evidence of greater improvements in HAQ-DI score (SEC: −0.50 [−0.56, −0.45] vs ADA: −0.40 [−0.48, −0.32]; $p = 0.0388$). HAQ-DI results were not available at week 16 and there was no evidence of differences at week 24. These findings were consistent with a sensitivity analysis that also matched for PsA disease duration, swollen joint count and CRP (SEC ESS = 62).

Conclusion: This MAIC showed that SEC 150 mg was associated with higher ACR 20 and 50 response rates at weeks 16 and 48, and greater improvements in HAQ-DI scores at week 48, relative to ADA. Key limitations included not being able to placebo-adjust or include the SEC 300 mg dose and the reduced ESS for SEC. The awaited results from EXCEED 1 are needed to substantiate the findings of this analysis.



All *p* values are based on pairwise comparisons using ORs, *p* values were adjusted for multi-comparisons. We avoid strict thresholds when interpreting statistical *p* values, as per the American Statistical Association definition (7 March 2016), but interpret values from 0.1 to 0.001 as weak to moderate evidence and, < 0.001 as strong evidence.
ACR, American College of Rheumatology response criteria; ESS, effective sample size; NRI, non-responder imputation; OR, odds ratio.

MAIC ACR response rates at weeks 16, 24 and 48

Disclosure: P. Nash, Novartis Pharma AG, 2,Novartis Pharma AG, 5,Novartis Pharma AG, 8; **I. B. McInnes**, BMS, Pfizer, Celgene, Astra Zeneca, 2,Novartis, Janssen, Abbvie, Pfizer, UCB, BMS, MSD, 5; **P. J. Mease**, AbbVie, Amgen, BMS, Lily, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Lily, Novartis, Pfizer, UCB, Merck, Sun, Corrona, 5,AbbVie, Amgen, Celgene, Genetech, Novartis, Pfizer, UCB, 8; **E. H. Choy**, None; **H. Thom**, Novartis Pharma AG, F. Hoffmann-La Roche AG, 5; **C. Kalyvas**, Mapi Group, 3,Novartis Pharma AG, 5; **K. Gandhi**, Novartis Pharmaceuticals Corporation, 1,Novartis Pharmaceuticals Corporation, 3; **S. Mpofu**, Novartis Pharma AG, 1,Novartis Pharma AG, 3; **S. Jugl**, Shareholder of Novartis Pharma AG, 1,Full-time employee of Novartis Pharma AG, Basel, Switzerland, 3.

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Abstract Number: 1739

Comparative Effectiveness of Secukinumab and Adalimumab in Ankylosing Spondylitis As Assessed By Matching-Adjusted Indirect Comparison: An Analysis Based on All Pivotal Phase 3 Clinical Trial Data

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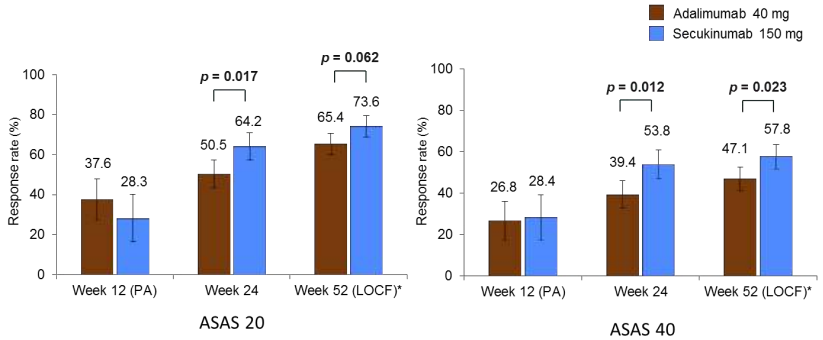
Background/Purpose: Secukinumab (SEC) and adalimumab (ADA) are approved for the treatment of patients with active AS. However, there are no head-to-head randomized controlled trials (RCTs) between SEC and ADA. In the absence of such trials, matching-adjusted indirect comparison (MAIC) can be used to generate comparative effectiveness data. MAIC adjusts for differences in baseline patient characteristics by using individual patient data (IPD) from trials of one treatment to match the population of a different therapy arm of another trial. The aim of this MAIC was to assess the relative effectiveness of SEC 150 mg and ADA 40 mg in patients with active AS.

Methods: IPD from the pooled SEC 150 mg arms of MEASURE 1 (n=125) and MEASURE 2 (n = 72) were weighted to match the published baseline characteristics of the ADA 40 mg arm of ATLAS (n = 208); placebo arms were also matched. Logistic regression was used to determine weights for age, sex, BASFI, CRP and previous anti-TNF therapy. Recalculated SEC 150 mg outcomes (effective sample size [ESS] = 120; placebo ESS = 120) were compared with published aggregated ADA data at weeks 12, 16, 24 and 52. Placebo-adjusted results were valid only until week 12 as patients receiving placebo in ATLAS could switch to open label ADA (69% had switched by week 24). Therefore, all comparisons beyond week 12 were non-placebo adjusted. Imputation methods for missing data were matched between trials. NRI was available for all binary outcome data except for ADA at week 52 which was LOCF only and included placebo switchers. This was matched by including placebo switchers for SEC at week 52. Comparisons are presented as response rate (%) and pairwise comparisons using odds ratios (ORs).

Results: At week 12 there were no differences in placebo-adjusted response rates between SEC and ADA. At week 16, there was a higher ASAS 20 non-placebo adjusted response rate for SEC relative to ADA (OR [95% CI]: 1.60 [1.01–2.54], $p = 0.047$). At week 24, there were higher ASAS 20 and ASAS 40 non-placebo adjusted response rates for SEC relative to ADA (OR [95% CI]: 1.76 [1.11–2.79], $p = 0.017$ and OR [95% CI]: 1.79 [1.14–2.82], $p = 0.012$, respectively). At week 52, there were higher ASAS 20 and ASAS 40 non-placebo adjusted response rates for SEC relative to ADA (OR [95% CI]: 1.48 [0.98–2.22], $p = 0.062$ and OR [95% CI]: 1.54 [1.06–2.23], $p = 0.023$, respectively). A sensitivity analysis that included BASDAI score in the baseline matching showed similar findings.

Conclusion: This MAIC showed that SEC 150 mg was associated with higher (non-placebo-adjusted) ASAS 20 response rates at weeks 16, 24 and 52 and ASAS 40 at weeks 24 and 52 relative to ADA. No differences in placebo-adjusted response rates were evident at week 12. Substantial switching of placebo patients to active therapy in ATLAS precluded analysis of placebo-adjusted data beyond week 12. This exploratory analysis requires confirmation by a head-to-head RCT.

MAIC ASAS 20 and ASAS 40 response rates at weeks 12, 24 and 52



SEC 150 mg ESS (from MEASURE trials): n = 120 (weeks 12 and 24) and n = 177 (week 52).
ADA 40 mg (from ATLAS trial), n = 208 (weeks 12 and 24) and n = 311 (week 52)

*Includes placebo switchers (ATLAS and MEASURE trials).

Week 16 ASAS 20 data not shown as there was no corresponding ASAS 40 outcome. All *p* values are based on pairwise comparisons using ORs. We avoid strict thresholds when interpreting statistical p values, as per the American Statistical Association (7 March 2016), but interpret values between 0.1–0.001 as weak to moderate evidence, and < 0.001 as strong evidence.

ASAS, Assessment of SpondyloArthritis International Society response criteria; ADA, adalimumab; ESS, effective sample size; LOCF, last observation carried forward, PA, placebo-adjusted; SEC, secukinumab.

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Abstract Number: 1740

Long-Term Improvements in Physical Function of DMARD-Naive and DMARD/Biologic-Experienced Psoriatic Arthritis Patients Treated with Apremilast: Data from a Large Database of 4 Phase III Clinical Trials

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Session Time: 9:00AM-11:00AM

Background/Purpose: Improving and preserving patient (pt) physical function is an important goal in managing psoriatic arthritis (PsA). Apremilast (APR) has been shown to improve signs and symptoms, quality of life, and functional disability in DMARD/biologic-experienced (PALACE 1-3 [PAL1-3]) and DMARD-naive (PALACE 4 [PAL4]) pts with active PsA.

We report long-term functional status for pts continuing APR up to 3 yrs.

Methods: Pts were randomized (1:1:1) to placebo (PBO), APR 30 mg BID (APR30), or 20 mg BID (APR20). PBO pts were re-randomized to APR30 or APR20 at Wk 16 (early escape) or Wk 24. HAQ-DI scores were assessed throughout the study for mean change from BL, proportion of pts reaching MCID, and proportion reaching scores ≤1.0 (below clinically significant disability), ≤0.5 (minimal disability), and ≤0.25 (general population). PAL1-3 data were pooled. Wk 16 APR30 data vs PBO were analyzed by LOCF. Wk 156 data are as observed. Mean change and MCID outcomes are for all pts receiving APR30 at any time during the study; disability level data are for pts randomized to APR30 at BL.

Results: PAL1-3 (biologic/DMARD experienced) and PAL4 (DMARD naïve) pts were similar in BL SJC/TJC and DAS-28 (CRP), indicating active PsA. PAL1-3 pts had longer mean duration of PsA and psoriasis, higher PASI scores, and greater corticosteroid use at BL. Despite longer PsA duration in PAL1-3 vs PAL4 (7.4 vs 3.4 yrs), clinically significant BL physical disability was similar: mean HAQ-DI 1.2 (PAL1-3) vs 1.1 (PAL4). At Wk 16, physical function significantly improved with APR30 vs PBO: mean HAQ-DI change −0.23 vs −0.08 (PAL1-3) and −0.21 vs 0.03 (PAL4) (both $P<0.0001$). Significantly more APR30 vs PBO pts reached MCID ≥0.30 and ≥0.35 in both populations. Marked disability at BL was seen in some pts randomized to APR30, with HAQ-DI scores up to 2.63-2.88. More PAL1-3 vs PAL4 APR30 pts had BL HAQ-DI >1.0 (60% vs 54%), >1.5 (31% vs 21%; marked difficulty/need for assistive devices), and >1.75 (19% vs 10%; major disability), highlighting need for early, effective treatment. Few APR30 pts in PAL1-3 or PAL4 had BL scores ≤0.5 (18%-22%) or ≤0.25 (10%-14%). At Wk 16, disability levels shifted; more APR30 vs PBO pts achieved HAQ-DI ≤1.0 (56% vs 48% [PAL1-3]; 60% vs 52% [PAL4]). At Wk 156 in PAL1-3 and PAL4 pts, 62% and 65% achieved HAQ-DI ≤1.0, 38% and 45% achieved ≤0.5, and 28% and 42% reached ≤0.25 (Table). LOCF analyses confirmed Wk 156 results.

Conclusion: With APR30 treatment, physical disability improved early and functionality was maintained over time up to 3 yrs. Most pts achieved HAQ-DI ≤1.0; many attained minimal/mild physical impairment. Over 40% of DMARD-naïve pts randomized to APR30 at BL had functional ability comparable to population norms after 3 yrs; shorter disease duration and no prior DMARD/biologics use in this population suggests that earlier APR treatment may increase the likelihood of maximal functionality for some pts.

Pts Achieving Improvement in Physical Function by HAQ-DI Level at Wk 156*

	PAL1-3	PAL4
Pts Achieving HAQ-DI Disability Threshold, %	**APR30 n=279§**	**APR30 n=94§**
≤1.0[1]	62	65
≤0.5[2]	38	45
≤0.25	28	42
Pts Achieving HAQ-DI MCID Levels, %	**APR30 n=413‡**	**APR30 n=143‡**
≥0.30[3]‖	48	48
≥0.35[4]¶	48	48

HAQ-DI ≤1.0=disability not clinically significant; HAQ-DI ≤0.5=disability remission. HAQ-DI=Health Assessment Questionnaire-Disability Index; MCID=minimal clinically important difference.
*Wk 156 data are based on data as observed. §Analysis in pts randomized to APR30 from BL. ‡Analysis in pts randomized to APR30 at any time (baseline, Wk 16, or Wk 24). ‖Accepted threshold for HAQ-DI MCID in PsA at time of initiation of studies.[3] ¶Currently accepted threshold based on updated research.[4]

1. Sokka T, et al. *Arthritis Rheum.* 2003;48:59-63. 2. Coates LC, et al. *Ann Rheum Dis.* 2010;69:48-53. 3. Mease PJ, et al. *Ann Rheum Dis.* 2004;63(Suppl 1):391. 4. Mease PJ, et al. *J Rheumatol.* 2011;38:2461-2465.

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Abstract Number: 1741

Patients with Active Psoriatic Arthritis Achieving Minimal Disease Activity with Secukinumab Treatment Demonstrate Sustained Improvement of Function and Quality of Life

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Session Time: 9:00AM-11:00AM

Background/Purpose: Secukinumab, a fully human anti–IL-17A monoclonal antibody, previously demonstrated higher minimal disease activity (MDA)[1] response rates and sustained improvements in patient reported outcomes[2] among active psoriatic arthritis (PsA) patients (pts) through Week (Wk) 52 in the FUTURE 2 study. This *post-hoc* analysis is further exploring the impact of secukinumab on individual components of MDA and its relationship with patient-reported outcomes among those who achieved or did not achieve MDA response through Wk 52.

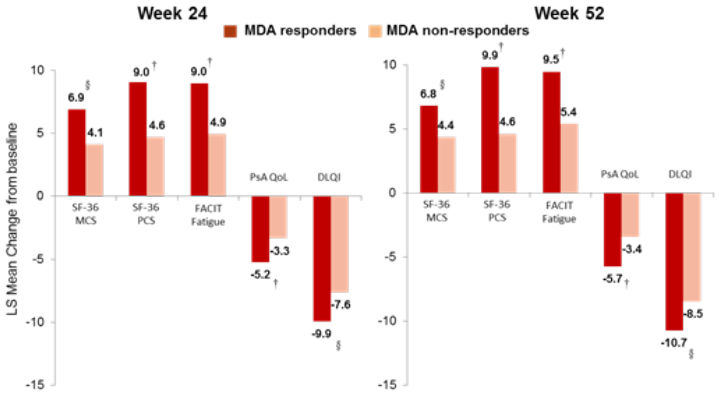
Methods: 397 pts with active PsA were randomized to subcutaneous (s.c) secukinumab (300 mg, 150 mg, or 75 mg) or placebo at baseline, Wks 1, 2, and 3, and every 4 wks (q4w) from Wk 4.[2] Pts were considered in MDA when they met at least 5 of 7 pre-defined criteria.[1] The proportion of pts achieving each individual criterion of MDA and the proportion of pts achieving all seven criteria of MDA were calculated at Wks 24 and 52. Additionally, SF-36 MCS, SF-36 PCS, FACIT-Fatigue, PsAQoL, and DLQI were assessed in MDA responders and non-responders at Wks 24 and 52 using mixed-model for repeated measures (MMRM) analyses.

Results: In the pooled secukinumab (300 mg and 150 mg) MDA responder group, tender entheseal points ≤1 (96%), HAQ-DI ≤0.5 (95%), and PASI ≤1 (91%) were the individual components of MDA that consistently achieved the greatest response rates followed by swollen joint count ≤1 (87%), patient global VAS ≤20 (87%), tender joint count ≤1 (80%), and patient pain VAS ≤15 (78%) at Wk 24. A similar trend for the pooled secukinumab MDA responder group was observed at Wk 52. Among the MDA responders 40% (27/68) and 33% (30/93) met all of the seven components at Wks 24 and 52, respectively in the overall study population. Greater improvements in SF-36 MCS and PCS, PsAQoL, FACIT Fatigue, and DLQI scores were seen among MDA responders compared to non-responders at Wks 24 and 52 (Figure).

Conclusion: In pts treated with secukinumab, the individual components most frequently associated with MDA response were related to enthesitis, skin, and functional status and the arthritis-related components were also achieved by many pts. A high proportion of pts achieved and maintained their MDA response through Wk 52 and amongst those 33 to 40% were able to meet 7/7 MDA criteria. Achieving MDA with secukinumab was associated with greater patient-reported quality of life outcomes indicating MDA may be a patient-relevant outcome References: 1. Coates LC et al. *Ann. Rheum. Dis.* 2016;75 S2:605. 2. Strand V et al. Poster presented at XIX PANLAR Panama 2016, April 10–14, 2016, Panama City,

Panama. 3. McInnes IB, et al. *Lancet* 2015;386:1137–46.

Figure: PROs among MDA responders and non-responders at Wk 24 and 52



†$P < 0.001$; §$P < 0.01$. Data were pooled across treatment arms. Only subjects with baseline and post-baseline assessment were included. LS Means and *P*-values were derived from MMRM with analysis visit, MDA status at analysis visit, and randomization stratum (TNF-a status: naive or inadequate response) as factors; weight and baseline score as continuous covariates; and MDA status by analysis visit and baseline score by analysis visit as interaction terms, as well as an unstructured covariance structure. DLQI analyses performed only on psoriasis subset of patients. FACIT, functional assessment of chronic illness therapy; LS, least squares; MCS, mental component score; MDA, minimal disease activity; PCS, mental component score; PsAQoL, psoriatic arthritis quality of life questionnaire; SF-36, short form-36

Disclosure: L. C. Coates, Abbvie, Janssen, 2,Abbvie, BMS, Celgene, Pfizer, UCB, MSD, Boehringer Ingelheim, Novartis, Lilly, Janssen, 5; **P. J. Mease**, Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 1,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 5,Abbvie, Amgen, BMS, Celgene, Crescendo Bioscience, Genentech, Janssen, Lilly, Merck, Novartis, Pfizer, UCB, 8; **L. Gossec**, UCB, Consultant for AbbVie, BMS, Celgene, Janssen, Novartis, Pfizer and UCB, 2; **B. Kirkham**, Abbvie, Novartis and Roche, 2,Abbott, BMS, Chugai, MSD, Novartis, Pfizer, Roche and UCB,, 5,Abbott, BMS, Chugai, MSD, Novartis, Pfizer, Roche and UCB, 8; **L. Rasouliyan**, Novartis through employment at RTI Health Solutions, 5,RTI Health Solutions, 3; **S. Mpofu**, Novartis, 1,Novartis, 3; **S. Jugl**, Shareholder of Novartis Pharma AG, 1,Full-time employee of Novartis Pharma GA, Basel, Switzerland, 3; **C. Karyekar**, Novartis Pharmaceuticals, 1,Novartis Pharmaceuticals, 3; **K. Gandhi**, Novartis Pharmaceuticals, 1,Novartis Pharmaceuticals, 3.

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Abstract Number: 1742

Effect of DMARD Therapies on NSAID Intake, Quality of Life, and Physical Functioning in Patients with Ankylosing Spondylitis

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Background/Purpose: Conventional treatments include NSAID and physiotherapy remain the mainstay of treatment in Ankylosing Spondylitis (AS). After the failure of conventional therapy, DMARD therapies are recommended for better outcomes in patients with AS. The aim of this study was to compare the effectiveness of DMARD therapies on NSAID intake, quality of life, and physical functioning and to investigate the relation between disease status parameters and functional outcomes.

Methods: A total of 68 patients were assessed using tools to measure disease (the Bath Ankylosing Spondylitis Disease Activity Index [BASDAI], Functional Index [BASFI], and Metrology Index [BASMI]), physical functioning (Health Assessment Questionnaire for the Spondylarthropathies [HAQ-S]), fear of movement (Tampa Scale for Kinesiophobia [TSK]), and quality of life (Ankylosing Spondylitis Quality of Life Scale [ASQoL]) status from the patient's perspective. To calculate NSAID intake, the type of NSAID, dose, percentage of days with intake were recorded, along with DMARD therapy, age, body mass index (BMI), and disease duration. The NSAID equivalent scoring was calculated according to recommendations from longitudinal clinical studies. The drug therapy groups were compared using the Kruskal-Wallis test and the Chi-square test. Correlation between the scales was evaluated by Spearman's correlation coefficient.

Results: A total of 68 patients (36 women, 32 men; mean age:44.37±10.06 years; mean disease duration:9.63±8.63 years) treated with 4 different DMARDs (Adalimumab+Golimumab=17; Infliximab =17; Etanercept =14; Sulphasalazine =20) were included. NSAID intake was significantly lower in the Infliximab therapy (INFX) (mean:29.34±86.13) compared to the Adalimumab+Golimumab therapy (ADA+GO) (mean:33.25±76.04;p=0.011); the Etanercept therapy (ETA) (mean:33.47±58.23;p=0.041) and the Sulphasalazine therapy (ST) (mean: 74.54±83.30;p=0.002). ASQoL scores were significantly lower in the INFX (mean:3.65±6.17;p=0.011), the ADA+GO therapy (mean:4.35±6.99;p=0.048) and the ETA therapy (mean:4.00±6.13;p=0.013) compared to the ST (mean:10.00±7.07). HAQ-S scores were significantly lower in the ETA therapy (mean:0.34±0.50; p=0.013) and the ADA therapy (mean:0.35±0.44;p=0.024). BMI (p=0.475), disease duration (p=0.551), TSK (p=0.132), BASDAI (p=0.069), BASFI (p=0.271), and BASMI (p=0.769) were similar between DMARD therapies. Age (r=0.400; p=0.001) and disease duration (r=0.255;p=0.037) were correlated with BASMI. There were significant positive correlations between BMI and HAQ-S (r=0.268; p=0.027), BASFI (r=0.245;p=0.044), and ASQoL (r=0.283;p=0.019). TSK was correlated with ASQoL (r=-0.261;p=0.031).

Conclusion: The results suggest that the ability of specific DMARDs to decrease NSAID intake might be considered clinically relevant. The INFX therapy had superior results on NSAID intake and quality of life while the ETA and the ADA+GO therapy were more effective on physical functioning independent of BMI, disease duration, fear of movement, and disease activity. In addition, patients with AS had fear of movement that affect health-related quality of life in spite of the positive results of drug therapies.

Disclosure: G. KINIKLI, None; **G. I. KINIKLI**, None; **S. KARAHAN**, None; **A. YUKSEK**, None; **A. ATES**, None; **M. TURGAY**, None.

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Abstract Number: 1743

Prevalence of Inflammatory Neck Pain in a Cohort of Patients with Psoriatic Arthritis and Its Association with Clinical and Radiographic Features

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Session Time: 9:00AM-11:00AM

Background/Purpose: Cervical inflammatory pain is very common and rarely studied in patients with Psoriatic Arthritis (PsA). The purpose of our study was to evaluate the prevalence of Inflammatory Neck Pain (INP) in patients with PsA and its association with clinical features.

Methods: Patients with PsA according to CASPAR criteria ≥ 18 years, belonging to RAPSODIA cohort were included. Sociodemographic data, clinical features and treatment received were recorded. Peripheral joints assessment was performed by counting 66/68 swollen/tender joints and the following indexes were calculated DAS28, DAPSA, CPDAI and MDA. Cutaneous involvement was evaluated by PASI and BSA, and nail by PNSS. The presence of dactilitis and enthesitis (MASES) was assessed. Spinal disease activity (BASDAI), functional capacity (HAQ and BASFI) and quality of life (PsAQol and ASQoL) were evaluated with appropriate self- administered questionnaires. The presence of INP was defined as pain in the cervical region with classical inflammatory characteristics and was evaluated as a dichotomous variable (yes/no). Radiographs of the spine and pelvic region were performed and read by a single blinded physician according to BASRI and mSASSS indexes.

Results: 110 patients were included, 56 men (50.9%) with a median age of 55 years (IQR 44.7-63.2). Inflammatory neck pain was reported by 32 patients (29.1%), and it was significantly more frequent in those with mixed involvement (axial and peripheral) (68.8%) vs those with only peripheral involvement (31.3%), p = 0.01. Patients with INP had poorer quality of life for ASQoL (6.1 ± 3.6 vs 6 ± 5.3, p = 0.04) and PsAQoL (8.9 ± 6 vs 6 ± 6, p = 0.02), worse functional capacity (BASFI 4.6 ± 2.5 vs 3.3 ± 2.8, p = 0.03), and higher disease activity [(BASDAI 5.4 ± 2.7 vs 3.8 ± 2.7, p = 0.007) and CPDAI (8.2 ± 3.5 vs 6.3 ± 3.7, p = 0.03)]. MDA was less frequently met by patients with INP (7.1% vs 29.3%, p=0.02). In the logistic regression analysis, fulfillment of ASAS criteria for axSpA was the only variable associated with INP (OR = 7.96, 95%CI: 1.6-40.4, p = 0.01).

Conclusion: A third of patients in this cohort had INP, and it was significantly more common in those fulfilling ASAS criteria for axSpA.

Disclosure: O. L. Cerda, None; **M. Landi**, None; **C. Zaffarana**, None; **J. Gallino Yanzi**, None; **E. Schneeberger**, None; **G. Citera**, None.

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Abstract Number: 1744

Expression of C1q By Podocytes at Late Stages of Proliferative Lupus Glomerulonephritis

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Background/Purpose: In NZM2328 (NZM), a mouse model of proliferative lupus glomerulonephritis (GN), lupus GN can be categorized to four stages, i.e. normal, acute GN (aGN), early chronic or transitional GN (tGN) and chronic GN (cGN). There is a high incidence of lupus GN in homozygous C1q deficiency and a marked incidence of severe lupus GN in presence of anti-C1q Ab in man. Interrogation of the microarray data from dissected NZM glomeruli indicates the C1q transcripts are increased in all stages of GN. At aGN this increase may be accountable by infiltrating macrophages. The reason for the increase in C1q transcripts at both tGN and cGN is not clear.

Methods: Podocytes, mesangial and endothelial cells were sorted from anti-GBM treated NZM mice and normal controls by flow cytometry with Abs specific for these populations. Q-PCR (C1qa, C1qb and C1qc) was performed on sorted cells. Similarly Q-PCR for C1q was performed on tubular cells isolated by laser microdissection from C57BL/6, NZM and NZM.Lc1R27 (R27), a NZM congenic line resistant to the progression of aGN to cGN despite the presence of immune complexes and complement activation. In situ hybridization (ISH) was performed with C1qc riboprobe. Immunofluorescence (IF) was done on kidneys with cell-specific and anti-C1q Abs tagged with different flourochromes and analyzed by confocal microscopy. Similarly IF was done on human renal biopsies and on urinary cells from normal and lupus patients. IF staining was also done on podocyte lines derived from NZM transformed by a temperature sensitive virus containing the SV40 large T Ag.

Results: C1q mRNA was detected in podocytes isolated from the kidneys of NZM treated with anti-GBM Abs. ISH collaborated this finding. At the protein level, C1q expression was shown by confocal microscopy with Abs to C1q and synaptopodin, a podocyte-specific protein. Similarly the presence of C1q was shown in podocytes of NZM kidneys with tGN and cGN but not in NZM or R27 kidneys with aGN. The presence of C1q was shown in one of four NZM podocyte cell lines. With "normal" renal tissue from patients with renal cell carcinoma and lupus GN renal biopsies (Classes II-IV), C1q expression by podocytes was limited to biopsies with Class III or IV lupus GN. The presence of C1q positive podocytes in the urine of five lupus patients with severe proteinuria and telescopic cellular elements (presumably class IV) was demonstrated. Similarly increased expression of C1q by tubular cells in severe GN was documented.

Conclusion: *C1q is shown for the first time to be made by podocytes.* Its expression is detected in two models of immune complex mediated GN. Its expression is detected in podocytes from kidney biopsies and in patients' urine. The expression of C3 in podocytes and in tubular cells in diseased kidneys was also found. The function of these expressed complement components in lupus GN remains to be determined in view of the recent documented role of C1q and C3 in CNS. Our findings suggest locally produced complements may have more profound effects on the kidney. The presence of C1q positive podocytes suggests that this can be useful as a biomarker for diagnostic purpose and for monitoring the effectiveness of therapy.

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Abstract Number: 1745

Disturbance of Renal Circadian Rhythm in Lupus Nephritis

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Background/Purpose: Circadian rhythm is a universal phenomenon that allows organisms to anticipate and respond to changes in their environment by regulating sleep and feeding patterns, blood pressure, metabolism, detoxification and response to pathogens. In the kidney intrinsic circadian rhythm of a subset of genes is associated with circadian regulation of GFR, blood pressure, urine pH, Na and K excretion and detoxification of drugs. We found a disturbance of expression of key clock transcriptional regulators in the kidneys of mice with SLE nephritis. The purpose of these experiments was to determine how this abnormality affected transcriptional regulation of renally expressed genes and immune cell homeostasis.

Methods: We studied NZB/W mice at the age of 12 weeks (without proteinuria) and 30 weeks (with 300mg/dl proteinuria). Kidneys and blood were harvested at 4 hour intervals. Kidneys were perfused with PBS and used to generate RNA, protein lysates and single cells for flow cytometry analysis. Whole blood counts were performed in a BD analyzer and white blood cell subtypes were analyzed using flow cytometry. RNA was analyzed using RNASeq and real-time PCR. Lysates were analyzed for expression of BMAL1 and Per2.

Results: Young NZB/W mice have normal circadian oscillation of peripheral WBCs. Circadian oscillation of peripheral blood RBCs, lymphocytes and neutrophils was likewise normal in the nephritic mice. There was a marked increase of circulating renal macrophages in the nephritic mice but circadian rhythm of $Ly6C^{hi}$ vs $Ly6C^{lo}$ cells followed a normal pattern. Kidneys of young NZB/W mice displayed a normal circadian pattern of expression of the master transcriptional regulators of circadian rhythm including Bmal1, Clock, Per and Cry genes. By contrast, kidneys from the nephritic mice had attenuated rhythm of these genes with inversion of the normal pattern. This abnormality was confirmed in two different sets of mice using qPCR. To determine how this affected general gene expression in the kidneys we performed mRNASeq of whole perfused kidneys. Of the 18952 genes detected by RNASeq, 2442 genes (12.9%) were regulated in a circadian fashion in young mice and 2074 (10.9%) in nephritic mice. There was little overlap in the two genesets, confirming a marked dysregulation of normal circadian patterns of renal gene expression. Although many of the genes that were upregulated in nephritic compared with young mice at any time of the day were associated with immune and inflammatory processes, analysis of the genes whose circadian rhythm was dysregulated in nephritic mice indicated that most are involved in metabolic rather than immune processes.

Conclusion: Circadian dysfunction in the setting of lupus nephritis may have important implications for the delivery and metabolism of therapeutics. Because circadian transcriptional regulators can influence the severity of inflammation and fibrosis, dysfunction of the renal circadian clock might also contribute to the progression of renal injury and may therefore be a potentially druggable target for therapeutic intervention.

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Abstract Number: 1746

Immune Complex-Induced IL-6 Production By Lupus Prone Mesangial Cells Is Mediated By Neuraminidase Activity

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Background/Purpose: We made the novel observation that glycosphingolipid (GSL) levels and neuraminidase (NEU) (an enzyme that mediates GSL catabolism) activity/expression are altered in the kidneys and/or urine of lupus mice and human patients with proliferative nephritis compared to their non-nephritic counterparts and healthy controls. Specifically, elevated GSL levels were observed in the mesangial region of glomeruli. We hypothesize that activation of mesangial cells (MCs) in the progression of lupus nephritis is mediated in part by NEU1-mediated LacCer elevation, contributing to renal inflammation in lupus nephritis.

Methods: NEU1 expression and the GSL Lactosylceramide (LacCer) levels in kidney sections were analyzed by immunohistochemistry and immunofluorescence. MES13 mouse MCs were: 1) incubated with the GSLs LacCer and glucosylceramide (GlcCer) over time and cytokine gene expression measured by real-time RTPCR; and 2) transfected with increasing amounts of an expression vector for NEU1, and IL-6 production was measured in the media by ELISA, while cellular LacCer levels were measured by Supercritical Fluid Chromatography coupled with tandem mass spectrometry. Primary MCs were grown from glomeruli isolated from kidneys of pre-nephritic MRL/lpr mice. Once established and verified to be MCs, the primary MCs were analyzed between passages 6 and 10 following activation with heat aggregated IgG (HA-IgG, a mimic of immune complex deposition) for IL-6 and MCP-1 production by ELISA, Neu1 message levels by real-time RTPCR, and NEU1 expression and cellular localization by immunofluorescence.

Results: NEU1 and LacCer were observed to be highly expressed in MCs on renal sections of nephritic MRL/lpr mice by immunohistochemistry. Using the mouse MES13 MC line, we demonstrate that exogenous addition of LacCer and GlcCer increases the expression of several cytokines, including IL-6. Over-expression of NEU1 increases LacCer levels and IL-6 production. In primary MCs from pre-nephritic lupus mice, Neu1 expression, IL-6 production and MCP-1 production are significantly increased following addition of HA-IgG in a dose-dependent manner. IL-6 production is significantly increased within 6 hours following addition of HA-IgG stimulation. Importantly, addition of an FDA-approved inhibitor of NEU activity significantly and dose-dependently inhibited HA-IgG-induced IL-6, but not MCP-1 production. NEU1, typically located in the lysosomes, is translocated to the plasma membrane in some cell types upon activation. Analyses of changes in cellular localiation of NEU1 in HA-IgG-activated lupus prone MCs is pending.

Conclusion: Together these results suggest that immune complex activated IL-6 production of MRL/lpr lupus prone MCs is mediated by NEU-mediated GSL catabolism. Targeting NEU activity, or NEU1 specifically, may reduce MC cytokine production and thus renal inflammation in lupus nephritis.

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Abstract Number: 1747

Dissecting the Role of Single Complement Deficiencies in a Novel Model for Apoptotic Cell-Induced Lupus

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Background/Purpose: The role of complement in Systemic Lupus Erythematosus (SLE) is complex as complement deficiencies in early components of the classical pathway cause lupus with high penetrance, yet terminal complement activation at the level of the glomeruli causes kidney inflammation and damage in SLE. Aberrant accumulation or processing of dying cells that expose nucleosomes is thought to stimulate the production of lupus autoantibodies. To determine the relative contributions of excess dying cells, complement and autoantibodies, we created novel genetic models of lupus that contained one or more of these abnormalities, all on the C57BL/6 background.

Methods: Bicongenic mice were created by crossing mice deficient in the apoptotic cell (AC) opsonin, MFG-E8 (that accumulates AC in the germinal centers of the spleen), to *sle1* mice (that produce autoantibodies to chromatin). These mice were then backcrossed to either C1q or C3 KO mice to create triple mutants. Anti-chromatin and anti-ds-DNA autoantibodies were measured by ELISA assay (n=20-30 per group). Autoantibodies specificities were determined on pooled sera (n=15-20 per strain) with the Autoantigen Microarray Super Panel (UT Southwestern Microarray Core). AC accumulation in the spleen and kidneys was detected by TUNEL staining (Roche). Kidney damage was evaluated by blood urea nitrogen (Amplite, AAT Bioquest), immuno-fluorescence for complement C3 (MP Biomedicals) and IgG2c (Jackson Immunoresearch), PAS staining and electron microscopy (E/M) (University of Washington Histology and Specialized Pathology Services).

Results: *sle1*.MFG-E8 double mutant mice had significantly higher anti-DNA autoantibodies compared to sle1 mice alone ($P<0.001$). When *sle1*.MFG-E8 mice were crossed to C1q or C3 KO to create triple mutant mice, anti-chromatin and anti-DNA autoantibodies increased further (triple mutants compared to double mutants; $p<0.05$). In addition, when these strains were compared on an autoantigen array, the triple mutants demonstrated a significant broadening in antigenic specificity to include aggrecan, collagens, alpha-actinin, and others. Both triple mutant mouse strains showed AC accumulation in the kidneys and developed severe glomerulonephritis as determined by PAS staining. E/M analysis confirmed leukocyte infiltration and electron dense deposits near podocytes with podocyte destruction, as well as extensive tubular damage. Immunofluorescence analysis C1q triple mutants had abundant C3 deposition in the glomeruli, likely via activation of the alternative pathway, F4/80+ cell infiltrates in the interstitial and periglomerular space, and very prominent IgG2c deposits.

Conclusion: These studies reveal a stepwise contribution of all three elements studied here to lupus-like disease, and indicate that defective clearance of dying cells coupled with autoantibody production and impaired early complement function leads to a severe glomerulonephritis. Whereas it is likely that C3 activation contributed to nephritis in triple mutants lacking C1q, triple mutants lacking C3 also showed broadening of the autoantibody repertoire and developed intense nephritis suggesting that IgG FcgR engagement is sufficient to result in severe kidney damage.

Disclosure: L. Colonna, None; **C. J. Sontheimer**, None; **L. M. Tanaka**, None; **K. L. Hudkins**, None; **C. E. Alpers**, None; **K. B. Elkon**, None; **Y. Peng**, None.

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Abstract Number: 1748

Effects of Anti-High Mobility Group Box 1 Antibody for MRL/Lpr lupus-Prone Mice

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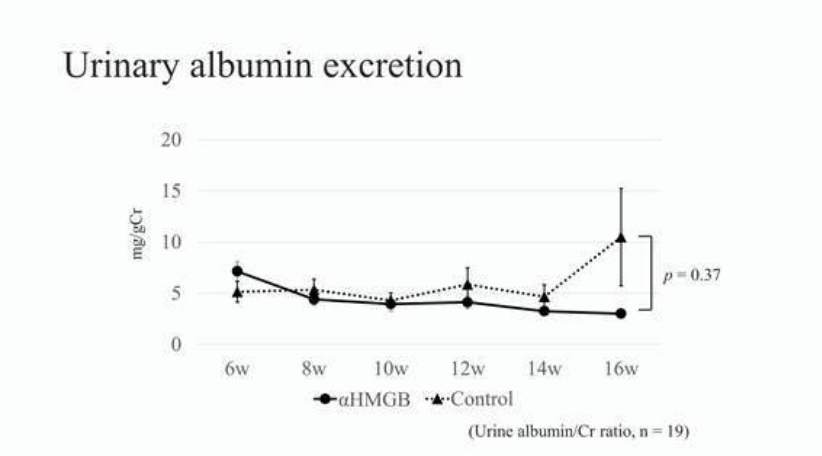
Background/Purpose: High mobility group box 1 (HMGB1) is a ubiquitous non-histone nuclear protein that exerts proinflammatory functions in the extracellular milieu. Here we evaluate the efficacy of neutralizing anti-HMGB1 monoclonal antibody (mAb) whether it ameliorates lupus activities including nephritis and serological abnormalities in MRL/lpr lupus-prone mice.

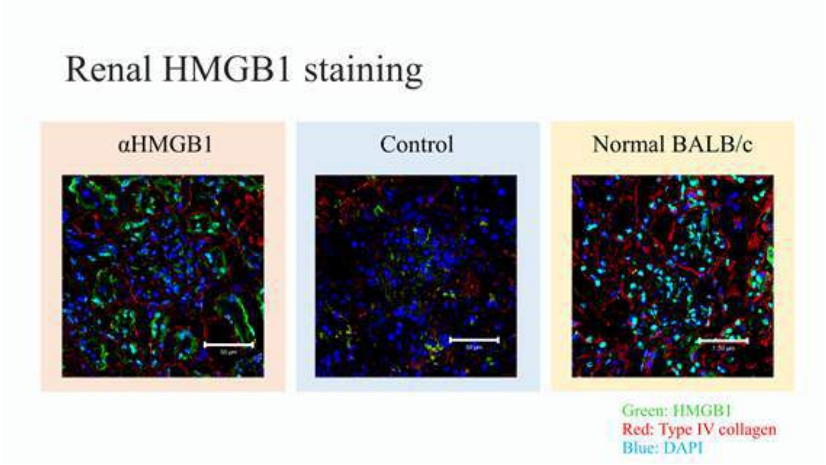
Methods: We administered the anti-HMGB1 mAb (5 mg/kg weight) neutralizing ICAM-1-inducing activity of HMGB1 *in vitro* or class-matched control IgG2a intravenously twice a week from 4 to 15 weeks. Urine albumin was monitored every 2 weeks and histological evaluation of kidneys was conducted at 16 weeks. Anti-ds DNA antibody titers, cytokines and chemokines were also evaluated.

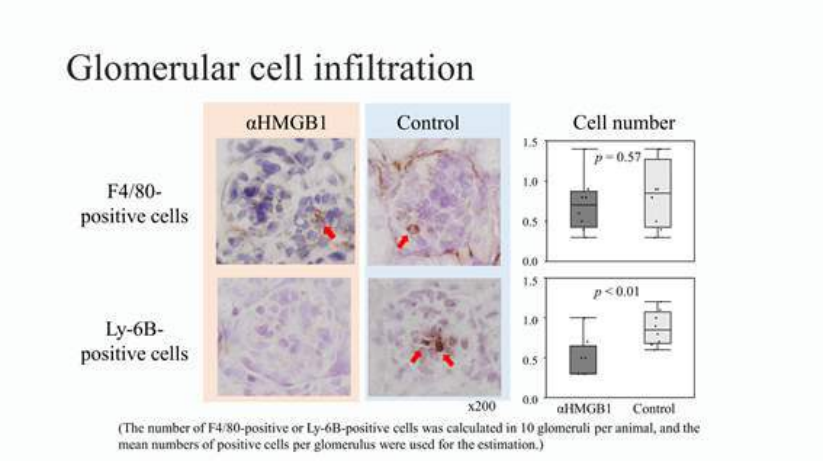
Lymphadenopathies were also evaluated by 1-(2'-deoxy-2'-[18F]fluoroarabinofuranosyl)cytosine ([^{18}F]FAC) PET/CT at 12 weeks.

Results: Anti-HMGB1 mAb tended to reduce the albuminuria compared to an isotype control at 16 weeks. Consistent with the urinary albumin excretion, the glomerular complement deposition was improved. However therefre no significant differences in the IgG depositions and renal pathological scores between the two groups. Regarding serological abnormalities, the anti-dsDNA antibody titers, cytokine and chemokine levels were not altered. Moreover, antagonizing HMGB1 treatment failed to show significant reduction of plasma HMGB1 level and was insufficient to suppress the translocations of HMGB1 in the kidney. The plasma HMGB1 level in this model mouse tended to be high compared to C57BL/6 mice. Although therefre no significant differences in the glomerular infiltrations of F4/80 positive cells, the infiltrations of Ly-6B positive cells and Ly-6G positive area were significantly decreased by anti-HMGB1 mAb. Renal mRNA expressions of cytokine and chemokine, such as IFN-alpha, TNF-alpha and IL-6, were unaltered by the treatment with anti-HMGB1 mAb. The weights of lymphoid tissues were almost similar and [^{18}F]FAC PET/CT revealed the similar accumulations in cervical and axilla lymph nodes in the two groups.

Conclusion: Anti-HMGB1 mAb demonstrated therapeutic potential against lupus nephritis through inhibiting neutrophil recruitments, but the abundance of HMGB1 release in this model mouse might blunt the effectiveness.







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Abstract Number: 1749

The Role of Mucosal-Associated Invariant T (MAIT) Cells in Lupus Dermatitis

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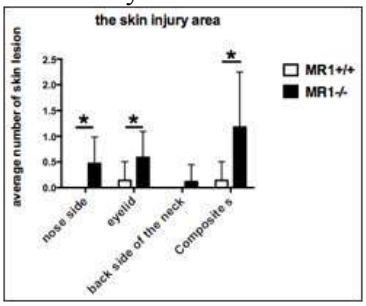
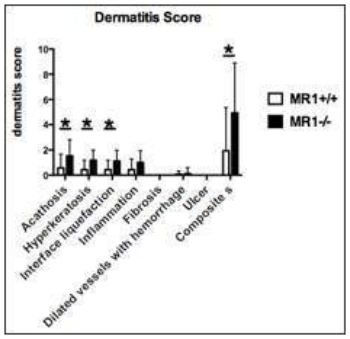
Background/Purpose: Mucosal-associated invariant T (MAIT) cells are innate T cells that are restricted by MHC-related molecule-1 (MR1) and express a semi-invariant TCRa chain: Va7.2-Ja33 in humans and Va19-Ja33 in mice. Previously, we have demonstrated that MAIT cells played a protective role against experimental autoimmune encephalomyelitis, an animal model of human multiple sclerosis. We have found that MAIT cells are activated in patients with systemic lupus erythematosus (SLE) and that the activation state of MAIT cells correlated with SLE disease activity index (SLEDAI) score. Therefore, we conducted this study to clarify functions of MAIT cells in a lupus model by using FcgRIIB$^{-/-}$ Yaa mice.

Methods: FcgRIIB$^{-/-}$ Yaa mice were crossed to MR1 deficient mice lacking MAIT cells, and disease progression was compared between MR1-/- FcgRIIB$^{-/-}$ Yaa and FcgRIIB$^{-/-}$ Yaa mice. Serum anti-dsDNA antibody levels were measured by anti-dsDNA- ELISA Kit (Libis) and urinary microalbumin were evaluated by SIEMENS DCA 2000. At the time of sacrifice, the severity of nephritis and dermatitis were assessed by histologically. Haematoxylin-eosin staining of skin sections were graded on a scale of 1 to 3 for acanthosis; 1 to 2 for hyperkeratosis, interface liquefaction, inflammation, dermal cellularity, presence of dilated vessels with hemorrhage; 0 to 1 for ulcer or erosion. For statistical analysis, all data were analyzed using GraphPad Prism (GraphPad), and differences between the groups were assessed using the Mann-Whitney U test. The significance level was set at $p < 0.05$. Associations between 2 variables were analyzed using Spearman correlation.

Results: MR1-/- FcgRIIB$^{-/-}$ Yaa mice showed exacerbated inflammation in the skin lesions. There was a high degree of inflammatory cells infiltration into the skin and a significant worsening of dermatitis score in MR1-/- FcgRIIB$^{-/-}$ Yaa mice compared to FcgRIIB$^{-/-}$ Yaa mice. There were no differences in serum levels of anti-dsDNA antibody, proteinuria, and kidney histopathology.

Conclusion: The present study demonstrates that dermatitis was exacerbated in MR1-/- FcgRIIB$^{-/-}$ Yaa mice, indicating that MAIT cells may have a suppressive effect on skin inflammation. Because MAIT cells have recently been found in human skin, MAIT cells may be useful therapeutic targets for the treatment of lupus dermatitis.





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Abstract Number: 1750

Down-Regulation of microRNA-200a-3p, Targeting C-Terminal Binding Protein-2 (CtBP2), Is Involved in Hypoproduction of IL-2 in SLE-Derived T Cells

Eri Katsuyama[1], Yan Minglu[1], Katsue Sunahori-Watanabe[1], Sonia Zeggar[1], Sumie Hiramatsu[1], Keiji Ohashi[1], Haruki Watanabe[1], Takayuki Katsuyama[1], Noriko Toyota-Tatebe[2], Ken-ei Sada[1] and Jun Wada[1], [1]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan, [2]Department of Nephrology, Rheumatology, Endocrinology and Metabolism, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Science, Okayama, Japan

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease caused by genetic and epigenetic mechanisms. MicroRNAs (miRNAs) are small non-coding RNAs, post-transcriptionally regulate the stability of target genes via base-pairing with mRNA 3'-untranslated regions (3'-UTRs), and have been reported to be implicated in the development of autoimmune diseases. To identify candidate miRNA and its target in unbiased fashion, we conducted the RNA sequencing using CD4+ T cells from spleen of MRL/lpr (MRL) lupus model mice and C57BL/6J (B6) mice as a control. Here we newly determined candidate disease-related miRNA, miR-200a-3p, which was significantly downregulated in MRL mice. Since its target genes, CtBP and ZEB were also upregulated in MRL mice and play an important role to suppress IL-2 as a transcriptional co-suppressor complex, we examined the role of miR200-3p in increased expression of CtBP2/ZEB and subsequent defects of IL-2 production in lupus T cells.

Methods: Functional analyses were performed by transfection of miR-200a-3p mimics in EL4 mouse T cell line. The expression levels of miR-200a-3p and its target gene were examined using TaqMan Quantitative PCR (qPCR). The transcript and protein level of IL-2 under the stimulation with phorbol 12-myristate 13-acetate (PMA) (10ng/ml) and ionomycin (1uM) was examined by qPCR and ELISA respectively. Promoter activity was evaluated with luciferase plasmid containing IL-2 promoter region. Specific binding of CtBP/ZEB to IL-2 sequence that negatively regulates IL-2 expression was evaluated by electrophoretic mobility shift assay (EMSA) and chromatin immunoprecipitation (ChIP) assay.

Results: We confirmed the lower expression of miR-200a-3p ($p<0.0001$) as well as the higher expression of CtBP2 ($p<0.05$) in MRL mice compared with B6 mice using qPCR. The expression level of ZEB2 was also tended to decreased ($p=0.56$) while ZEB1 ($p<0.01$) was downregulated in MRL mice by qPCR. In EL4 cells with miR-200a-3p overexpression, the expression level of ZEB and CtBP2 mRNA was significantly downregulated, while IL-2 mRNA level was upregulated by q-PCR. IL-2 concentration in the supernatant from stimulated EL4 cells was also higher under the treatment of miR-200a-3p by ELISA. IL-2 promoter activity was elevated by miR-200a-3p overexpression by luciferase assay. EMSA demonstrated that specific binding of ZEB1, ZEB2 and CtBP2 to IL-2 gene was decreased after miR-200a-3p overexpression. Finally, ChIP assay revealed that the complex of CtBP2 in regulatory sequence of IL-2 was augmented in MRL mice compared with B6 mice, while the complex was downregulated in EL4 with miR-200a-3p overexpression.

Conclusion: Collectively, IL-2 production was elevated after miR-200a-3p overexpression by targeting ZEB1, ZEB2 and CtBP2. Our data suggest that downregulation of miR-200a-3p causes IL-2 suppression through ZEB1, ZEB2 and CtBP2 in SLE T cells, which could involve the lupus pathogenesis by dysregulation of T cells.

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Abstract Number: 1751

Coagulation Pathway Function in Ischemia/Reperfusion Tissue Injury in Autoimmune Prone Mice

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SESSION INFORMATION
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Background/Purpose: Impaired fibrinolysis in systemic lupus erythematosus (SLE) contributes to disease magnifications including increased risk of thrombosis and tissue ischemia. Aberrant complement activation is a major factor in tissue injury in SLE. Previous work has focused on the role of complement activation in tissue injury due to ischemia in the MRL/*lpr*mice, an autoimmune prone mouse strain with a propensity to develop lymphadenopathy, glomerulonephritis, and polyarthritis. Complement inhibition at varying points in the cascade resulted in differing efficacies in tissue injury attenuation of tissue injury. A potential role for thrombin, a coagulation component was identified. The current work elucidates the mechanism by which the two pathways interact to contribute to hypercoagulability and increased risk of thrombosis in SLE.

Methods: Complement C1q inhibitor and coagulation inhibitors targeting the intrinsic and extrinsic pathways (Tissue Factor Pathway Inhibitor (TFPI) and Anti-thrombin III) were used to evaluate and compare resulting tissue pathology, generation of secondary inflammatory mediators involved ischemic/reperfusion injury. Using a superior mesenteric artery ischemia model, we compared the pathology of mesenteric ischemia/reperfusion (IR) induced tissue injury between immune competent (C57BL/6) and autoimmune prone (B6.MRL/*lpr*) mice after administration of complement or specific coagulation pathway inhibitors. The pathology was assessed by immunohistochemistry/ immunofluorescence analysis and western blot analysis of complement and coagulation components.

Results: Tissue Factor Pathway Inhibitor (TFPI) and Anti-thrombin III (ATIII) resulted in reduction of tissue injury, as determined by histopathology scoring. However, TFPI was significantly more effective in attenuating tissue injury in the MRL/*lpr* mice with less edema and villous destruction in the intestine. Western blot analysis was used to determine if there reductions in thrombin levels and if this corresponded with decreased levels of activated complement components. As expected if C5 was the interaction point between the pathways, there were no differences in C3 activation between the groups. The level of C5 activation and thrombin levels are being analyzed. Immunofluorescent analysis of tissue sections confirm these results and assess changes in the molecular components such as C3/Ig deposition, membrane attack complex formation, glycoprotein Ia/IIa exposure, and thrombin localization.

Conclusion: The interaction between thrombin and the complement pathway in SLE has significant clinical implications. The results from this study indicate inhibition of the coagulation cascade, prior to prothrombin activation is the most effective point to inhibit tissue injury. Inhibiting with TFPI does not affect C3 activation but reduces edema and disruption of the vascular and lamina propria structure, suggesting a positive feedback loop between the complement and coagulation cascades downstream of C3. CIP/Protocol number: MED-09-349

Disclosure: R. C. Robbins, None; **C. Tracy**, None; **J. Edison**, None; **S. Peng**, None; **C. Moratz**, None.

Abstract Number: 1752

IL-23 Promotes the Generation of DNT Cells and Shifts the Balance Between IL-2 and IL-17 Production in Murine and Human SLE

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Background/Purpose: MRL/lpr mice develop a chronic inflammatory disease characterized by accumulation of $CD4^-CD8^-B220^+$T cells mimicking human lupus; IL-23 driven IL-17 producing cell contribute to lupus severity in B6/lpr mice, an autoimmune model that is characterized by deficient Fas-mediated apoptosis but without the autoimmune genetic background of MRL/lpr. We previously reported that in MRL.lpr mice, administration of neutralizing IL-23Ab ameliorates lupus severity. The studies presented below sought to explain the profound effect IL-23 has on murine lupus pathogenesis.

Methods: T cells were extracted from the blood of patients who fulfilled at least 4 out of 11 ACR criteria for SLE. We generated MRL/lpr mice that lack the IL-23 receptor by backcrossing the MRL/lpr mouse with a B6.IL-23 receptor (IL23R) deficient mouse for 11 generations. Proteinuria was monitored at regular intervals. Spleens, kidneys and lymph nodes were harvested and used for flow cytometry and histology at different time points. ELISA was used for measurement of cytokines and dsDNA antibody levels in the serum.

Results: Genetic deletion of IL-23R in MRL/lpr mice attenuated lupus nephritis strikingly decreasing the accumulation of double negative T (DNT) cells in the kidneys ($IL23R^{+/+}$MRL/lpr vs. $IL23R^{-/-}$MRL/lpr: 8.38+/-1.76 $x10^4$ cells vs. 2.00+/-0.37 $x10^4$ cells, $p<0.05$). We observed a similar decrease of DNT accumulation in secondary lymphoid organs in IL23R deficient vs the IL23R sufficient mice. Using in vivo BrDU staining and in vitro proliferation experiments, we found that the decrease in the DNT cell population in the spleen and lymph nodes of $IL23R^{-/-}$MRL/lpr vs the $IL23R^{+/+}$ MRL/lpr mice was through 1. Decreased DNT proliferation ($IL23R^{+/+}$MRL/lpr vs. $IL23R^{-/-}$MRL/lpr: 4.61+/-0.83% vs. 1.26+/-0.33%). 2. Increased DNT cell death ($IL23R^{+/+}$MRL/lpr vs. $IL23R^{-/-}$MRL/lpr: 37.13+/- 2.21 % vs. 46.11+/-0.21%), and 3. Decreased conversion of $CD4^+$ T cells into DNT upon stimulation ($IL23R^{+/+}$MRL/lpr vs. $IL23R^{-/-}$MRL/lpr vs. MRL/MPJ: 11.95+/-0.07% vs. 4.90+/- 0.42% ($p<0.05$) vs. 3.19+/-0.07% ($p<0.05$ compared to wild type). Moreover, T cells from IL-23R deficient animals had significantly increased IL-2, and reduced IL-17 production compared to wild type animals. In vitro incubation of MRL/lpr splenocytes with IL-23 not only promoted IL-17 production, as expected, but also downregulated IL-2 production (IL-2 in non-IL23 vs IL-23 treated: 281.67+/-16.26 vs. 151+/-47.03 pg/mL). Conversely, exogenous IL-2 reversed IL-23-induced IL-17 secretion from $IL-23R^{+/+}$ MRL/lpr lymphocytes indicating that IL-23 critically regulates the balance between IL-2 and IL-17 in lupus prone mice. Finally, ex vivo treatment of T cells from SLE patients with IL-23 increased the proportions of IL-17-producing T cells and DN T cells (non-IL23 vs IL-23 treated: 27.72+/- 14.41% vs. 47.85+/- 16.47%) while downregulating the production of IL-2 (non-IL23 vs IL-23 treated: 314+/-198 vs. 220+/-131 pg/mL).

Conclusion: Our results show that IL-23 regulates the production of two pivotal cytokines in murine and human SLE while promoting the production of pro-inflammatory DNT cells, critically influencing the balance between pro and anti-inflammatory cytokines in lupus.

Disclosure: H. Dai, None; **F. He**, None; **G. C. Tsokos**, None; **V. C. Kyttaris**, None.

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Abstract Number: 1753

Signal Transducer and Activator of Transcription (STAT) 3 Regulates Tcrαβ +CD4-CD8- T Cells in Systemic Lupus Erythematosus (SLE)

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Background/Purpose: TCRαβ+CD4-CD8-T cells (double negative T cells, DNT) have been reported to produce inflammatory cytokines such as IL-17, and infiltrate the kidneys of patients with lupus nephritis. We previously reported that inhibition of the transcription regulator STAT3 ameliorates systemic lupus erythematosus (SLE) by reducing DNT accumulation in MRL/lpr lupus –prone mice. However, the underlying mechanism remains unclear.

Methods: MRL/lpr mice were treated with Stattic, a STAT3 inhibitor, or placebo starting at 8 weeks of age for 4-8 weeks. B6/lpr T cell STAT3 knockout (TCKO) mice were bred by crossing B6-CD4 ^{Cre} Stat3$^{fl/fl}$mice with B6/lpr mice and followed until disease development. Proteinuria and serum dsDNA antibody levels were monitored. Spleens, kidneys and lymph nodes were collected for flow cytometry and histology at different time points. Peripheral blood T cells from SLE patients and healthy controls were used to evaluate the proportion of DNT, as well as PD-1 and IL-17 expression. DNT cells were sorted from B6/lpr STAT3 TCKO and Stattic-treated MRL/lpr mice, and were used to assay glycolysis stress by Seahorse XFp analyzer. Glycolysis associated genes expressions were analyzed by q-PCR.

Results: Stattic significantly attenuated disease activity in MRL/lpr mice, with decreased serum dsDNA antibody levels (Stattic treated vs placebo: 1,634±211 vs. 18,365±2,132U/ml, $p<0.0001$), suppressed crescentic glomerulonephritis, reduced spleen size, and diminished skin lesions. Similar results were found in B6/lpr STAT3 TCKO mice. The number of DNT cells were reduced significantly in B6/lpr STAT3 TCKO mice in both kidneys (wild type vs STAT3 TCKO: 31.3±9.6% vs 17.6±6.5%, $p=0.0005$) and peripheral lymphoid organs (wild type vs STAT3 TCKO: Spleen: 35.4±7.8% vs 26.5±6.1%, $p=0.0051$; Lymph node: 73.1±11.8 vs. 61.5±10.1, p=0.0168). Moreover, IL-17 production and PD-1 expression were significant decreased in DNT cells from B6/lpr STAT3 TCKO mice. Moreover, p-STAT3 was increased in DNT cells from SLE patients compared with healthy control (17.6±2.1% vs. 6.5±1.3%, $p<0.0001$). Accordingly, PD-1, as well as IL-17 expression was upregulated in p-STAT3+ DNT as compared to p-STAT3- DNT from SLE patients. XF glycolysis stress assay revealed that DNT from B6/lpr STAT3 TCKO (or Stattic treated MRL/lpr) mice showed lower extracellular acidification rate and glycolysis capacity than matched controls. In vitro treatment with 2-DG could significantly reduced generation and IL-17 production in DNT from B6/lpr STAT3$^{fl/fl}$ mice, but has less effect on B6/lpr STAT3 TCKO mice. Gene expression analysis shown that HIF1α, GLUT-1, PDK1 mRNA levels were increased in DNT from B6/Lpr STAT3$^{fl/fl}$mice as compared to B6/lpr STAT3 TCKO mice (4.5 ±2.1 fold, 3.1 ±1.0 fold, and 2.5 ±0.7 fold, respectively). Similar increase was seen in SLE patients derived DNT cells as compared to healthy control DNT.

Conclusion: This is the first study to provide evidence that STAT3 regulates the generation, function and pathogenicity of DNT in systemic lupus erythematosus. Specific targeting of STAT3 in SLE T cells may help restore the balance between pro-inflammatory and regulatory T cells, an imbalance that underlies SLE pathophysiology.

Disclosure: F. He, None; **H. Li**, None; **G. C. Tsokos**, None; **V. C. Kyttaris**, None.

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Abstract Number: 1754

Double-Negative T (DNT) Cell over-Expressing PD-1 and Helios Is Responsible for Lupus Tissue Injury in Systemic Lupus Erythematosus (SLE): Direct Proof That Increased Interferon Alpha (IFNα) Expression Is Sufficient to Induce SLE in Ifnα-Transgenic Mice

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Session Date: Monday, November 14, 2016

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Background/Purpose: Previous studies strongly suggest that interferon α (IFNα) may be the principal driver of SLE, where increased IFNα and IFNα-regulated gene transcripts explain many of the immune alterations seen in SLE patients. However, the causal relationship between IFNα and SLE remains speculative and direct evidence for this causal link is required for more effective intervention of the disease. To directly prove the role of IFNα in inducing SLE, we generated transgenic (Tg) mice that express IFNα under the control of the inducible doxycycline (Dox) promoter.

Methods: The mouse *IFNα a1* (mIFNα) cDNA inserted downstream of the TetOp promoter of pTet Splice vector to generate TetOp-mIFNα. TetOp-mIFNα was microinjected into fertilized eggs of C57BL/6 mice to obtain TetOp-mIFNα Tg mice. The mice were mated with EμSR-tTA Tg mice (FVB/N background), expressing the Tet-transactivator (*tTA*) gene downstream of the Ig heavy chain enhancer and SRα promoter (Felsher and Bishop, Mol Cell 4:199, 1999), resulting in lymphoid cell-specific gene expression (EμSR-tTA) to produce double transgenic TetOp-mIFNα/EμSR-tTA mice of a C57BL6/FVBN background (IFNα Tg C57BL6/FVBN mice). These mice produced IFNα 4 weeks after cessation of 50 μg/mL of Dox. This IFNα Tg mice were also back-crossed to make IFNα Tg mice of C57BL/6 background to guarantee the universality of the result.

Results: IFNα expression alone was sufficient to induce disease with characteristics identical to SLE, i.e., serum anti-double stranded DNA (dsDNA) antibody, immune complexes (IC) and tissue injury including glomerulonephritis accompanied by IC deposition, alopecia, epidermal liquefaction, positive lupus-band skin test and classical splenic onion-skin lesions. In these mice, activated $CD3^+CD4^-CD8^-$ double-negative T (DNT) cells, which were also $TCR\alpha\beta^+B220^+CD1d\text{-teteramer}^-$, expanded significantly. When transferred into naïve recipients, these DNT cells infiltrated to the glomeruli of transgenic mice and induced *de novo* glomerulonephritis and alopecia. These DNT cells had halted differentiation and massively accumulated at the DN1 stage in the thymus. The DNT cell was characterized by the over-expression of PD-1 and Helios, an indicator of autoreactive DNT cell of CD8 T cell origin as shown by Rodriguez-Rodriguez N et al (J Immunol 194:4207, 2015).

Conclusion: The results show that increased expression of IFNα is sufficient to induce SLE, and that DNT cell expressing PD-1 and Helios may play important roles in lupus tissue injury. The study is in collaboration with Dr. Dean W Felsher (Stanford University, Division of Oncology, Department of Medicine and Pathology).

Disclosure: K. Tsumiyama, None; **C. Akiyama**, None; **Y. Miyazaki**, None; **Y. Miura**, None; **A. Hashiramoto**, None; **S. Shiozawa**, None.

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Abstract Number: 1755

Dendritic Cell-Specific Loss of Caspase 8 Incites Symptoms of Neuropsychiatric Systemic Lupus Erythematosus

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Background/Purpose: Previous studies implicate dendritic cells (DCs) in the initiation and persistence of systemic lupus erythematosus (SLE), and although DCs from SLE patients exhibit elevated activation, the factors responsible remain largely unknown. Neuropsychiatric symptoms of SLE (NP-SLE), which affect roughly 40-70% of SLE patients, include headaches, cognitive dysfunction and psychiatric disorders, and may be among the earliest symptoms of SLE. Mice with an underlying defect in Fas (MRL/lpr) display cognitive and affective dysfunction characteristic of NP-SLE. We have shown that DC-specific loss of caspase 8, an enzyme in the Fas pathway classically linked to apoptosis initiation and necroptosis suppression, induces a SLE-like disease that originates from heightened DC activation. However, whether there exists a link between caspase 8 signaling, heightened DC activation and NP-SLE is a mystery. To this end, we examined the neurological consequences of DC-specific caspase 8 deletion.

Methods: Mice with caspase 8 flanked by *loxP* sites ($Casp8^{fl/fl}$, WT) were bred to mice expressing Cre under control of the CD11c gene promoter (Cre^{CD11c}) to generate $Cre^{CD11c}Casp8^{flox/flox}$mice. Neurological deficiency was assessed via 8 tests (exit circle, startle reflex, seeking behavior, beam balancing, round stick balancing, beam walk: 3 cm, beam walk: 2 cm, beam walk:1 cm) with each test providing 0, 0.5 or 1 points depending on the severity of the behavioral deficit and, when combined, provide a neurological severity score (NSS). Cellular infiltration into the brain was assessed using 10-color flow cytometric analysis.

Results: With age, $Cre^{CD11c}Casp8^{flox/flox}$ mice develop an inflammatory disease reminiscent of both classic murine models of SLE and human SLE that is characterized by splenomegaly, lymphadenopathy, autoantibodies, elevated serum cytokines, glomerulonephritis, immune complex deposition in the kidney and proteinuria. Strikingly, $Cre^{CD11c}Casp8^{flox/flox}$mice develop neurological deficiencies, with a 4-fold higher NSS than WT mice. These observed behavioral consequences correlate with increased numbers of microglia, as well as cellular infiltration of not only DCs, but also macrophages, lymphocytes and neutrophils. The cellular infiltration is reminiscent of an acute model of traumatic brain injury, wherein physical damage to the brain promotes leakage of the blood-brain barrier. However, in our case, this breach of the blood-brain barrier is the direct result of DC-specific caspase 8 deletion and chronic systemic inflammation.

Conclusion: Our previous studies showed that DC-specific loss of caspase 8 induced a SLE-like disease that originated from heightened DC activation. We now reveal that deletion of caspase 8 in DCs is sufficient to incite symptoms of NP-SLE that correspond with a breach in the blood-brain barrier and leukocyte infiltration. These data substantiate a novel DC-

specific mechanism whereby caspase 8 controls DC activation to prevent not only end-organ failure and peripheral pathology associated with SLE-like disease, but also NP-SLE manifestations, thereby highlighting a potentially useful target for therapy.

Disclosure: H. Makinde, None; **H. R. Perlman**, None; **C. Cuda**, None.

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Abstract Number: 1756

Novel Role of Rho Kinase in Neutrophil Netosis during UVB Induced-Skin Inflammation

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Background/Purpose: Skin inflammation appears in cutaneous or systemic lupus erythematosus. Ultraviolet B (UVB) is an important environmental trigger of skin inflammation in lupus. Mechanisms linking UVB to autoimmune inflammation in lupus are not well understood. Neutrophils, the most abundant circulating leukocytes, are the first group of cells to be recruited to the site of photodamage, prior to monocytes and lymphocytes, in response to UVB-irradiation. Studies have suggested that neutrophils may pave the way for the subsequent recruitment of monocytes and lymphocytes. All of these cell types orchestrate and together contribute to the local inflammation at the site of photodamage, and the systemic consequences. However, little is known about the role of neutrophils in UVB-induced skin inflammation. Neutrophil NETosis is a newly characterized neutrophil cell death that releases neutrophil extracellular traps (NETs), which have been shown to be important in autoimmune inflammation, including lupus pathogenesis. NETs develop as release of the decondensed nuclear chromatin from a ruptured nuclear envelope. Recent studies from our and other groups indicate the importance of the actin cytoskeleton in neutrophil NETosis. Rho kinase (ROCK) is known to regulate actin-myosin (actomyosin) networks. Whether ROCK regulates neutrophil NETosis and contributes to UVB-induced skin inflammation has not been investigated.

Methods: To explore the role of ROCK in neutrophil NETosis, we investigated the effects of ROCK inhibition on neutrophil NETosis in vitro in human neutrophils and neutrophil NETosis in UVB-induced skin inflammation in mice.

Results: In vitro, we found that PMA stimulation induced F-actin polymerization and ROCK activation in human neutrophils. In addition, inhibition of ROCK activation attenuated F-actin polymerization. Importantly, inhibition of ROCK by different ROCK inhibitors, or interfering F-actin polymerization with cytochalasin D, significantly alleviated PMA-induced NET formation in human neutrophils. To explore the effects of ROCK in vivo in UVB-induced skin inflammation, we found that exposure of female C57BL/6J WT mice to UVB with a dose of 250 mJ/cm^2/day for 5 consecutive days induces neutrophil recruitment and NET formation which display IL-17 in the dermis of mouse skin. Importantly, application of the dual ROCK1/2 inhibitor HA1077 intraperitoneally (i.p.) attenuated neutrophil recruitment and NET formation in UVB-irradiated mouse skin *in vivo*. Most importantly, ROCK inhibition attenuated neutrophil NETosis among the infiltrated neutrophils in the UVB-exposed mouse skin.

Conclusion: Our preliminary studies therefore elucidated a novel mechanism that ROCK regulates neutrophil NET release, and confirmed the protective role of ROCK inhibition in neutrophil NETosis both in vitro and in vivo. Our findings may provide insights into a novel therapeutic target for treatment of UVB-induced skin inflammation, including lupus.

Disclosure: M. L. Liu, None; **M. Sharma**, None; **V. P. Werth**, None.

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Abstract Number: 1757

Association of the Lupus Low Disease Activity State (LLDAS) with Health-Related Quality of Life

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SESSION INFORMATION

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Background/Purpose: Systemic lupus erythematosus (SLE) is associated with significant impairment of health-related quality of life (HR-QoL). Recently, meeting a definition of a Lupus Low Disease Activity State (LLDAS), analogous to low disease activity in rheumatoid arthritis, was preliminarily validated as associated with protection from damage accrual. The LLDAS definition has not been previously evaluated for association with patient reported outcomes. The objective of this study was to determine whether LLDAS was associated with better HR-QoL, and examine predictors of HR-QoL, in a large multiethnic, multinational cohort of SLE patients.

Methods: Data were collected prospectively from 1422 patients at a single visit and analysed cross-sectionally. Disease status was measured using the SLE disease activity index (SLEDAI-2K), physician global assessment (PGA) and SLICC-ACR damage index. HR-QoL was measured using the Medical Outcomes Study 36-item Short Form Health Survey (SF-36v2).

Results: Significant differences in SF-36 domain scores were found between patients stratified by ethnic group, education

level, damage score, or by the presence of active musculoskeletal or cutaneous manifestations. In multiple linear regression analysis, Asian ethnicity ($p<0.001$), higher education level ($p<0.001$), younger age ($p<0.001$) and shorter disease duration ($p<0.01$) were significantly associated with better physical component scores (PCS). Musculoskeletal disease activity ($p<0.001$) was negatively associated with PCS, and cutaneous activity ($p=0.04$) was negatively associated with mental component scores (MCS). Disease damage was associated with worse PCS ($p<0.001$), but not MCS scores. Compared to patients not meeting criteria for LLDAS, patients in LLDAS had higher HR-QoL as measured by better PCS ($p<0.001$) and MCS ($p<0.001$) scores; this remained significant after adjustment for other variables.

Conclusion: Ethnicity, education, and disease damage affect HR-QoL. Musculoskeletal activity is associated with poor physical components of HR-QoL, and cutaneous activity is associated with poor mental components of HR-QoL. Patients in LLDAS have better HR-QoL than those who are not in LLDAS.

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Abstract Number: 1758

Physical Activity and Sedentary Behaviour in Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are at increased risk for premature cardiovascular disease. As sedentary behaviour and lack of physical activity (PA) are known cardiovascular risk factors, we studied PA levels in SLE and RA patients, in comparison to healthy controls, using accelerometry.

Methods: For this cross-sectional study, RA and SLE patients were recruited from rheumatology clinics at an academic medical center. Age- and gender-matched healthy controls were recruited through local advertising. RA and SLE patients met the respective ACR classification criteria and disease activity was assessed by the SLEDAI-2K and DAS28-CRP, respectively. PA was assessed by self-report patient questionnaires and measured by triaxial accelerometer worn during waking hours for seven consecutive days. Minutes per day of sedentary, light, and moderate-vigorous physical activity (MVPA) were recorded and compared between SLE, RA, and healthy control participants using ANOVA.

Results: There were 59 participants: 20 SLE patients, 19 RA patients, and 20 healthy controls. Disease activity was quiescent in both patient groups with mean (SD) SLEDAI-2K and DAS28-CRP scores of 2.9 (2.1) and 2.3 (1.4), respectively. All three groups demonstrated high levels of sedentary behaviour, with mean (SD) sedentary time of 10.1 (1.3) hours/day, or 76.4% of total accelerometer wear time. Total MVPA (mean ± SD, minutes/day) was significantly

lower in SLE (34.5 ± 22.7) and RA (41.5 ± 21.3) patients compared to controls (64.9 ± 22.4) (p<0.001). Physical activity guidelines[1] for MVPA (≥ 150 minutes/week) were less frequently met by SLE (2/20, 10.0%) and RA (3/19, 15.8%) patients compared to healthy controls (9/20, 45.0%) (p=0.02). There was no significant difference between SLE, RA and control participants in the amount of time spent in sedentary behaviour (p=0.80) or light activity (p=0.17). Self-reported PA data by patients and controls correlated poorly with accelerometry data, with all participants over-reporting time spent performing MVPA, and underestimating sedentary time.

Conclusion: Given the increased cardiovascular risk, low MVPA and high sedentary behaviour identified by accelerometry among RA and SLE patients with inactive disease is concerning. Investigation of factors impacting PA and sedentary behaviour in RA and SLE patients is necessary, in order to design effective interventions to target this modifiable cardiovascular risk factor in these vulnerable patient populations.

[1] Tremblay MS, Warburton DER, Janssen I, Paterson DH, Latimer AE, Rhodes RE, Kho ME, Hicks A, Leblanc AG, Zehr L, Murumets K, Duggan M. New Canadian physical activity guidelines. *Appl Physiol Nutr Metab* 2011;36:36–46.

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Abstract Number: 1759

Sleep Disturbance Is Associated with Worsening Patient-Reported Outcomes over Two Years in Systemic Lupus Erythematosus (SLE)

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Background/Purpose: Although studies to date have suggested sleep disturbance among individuals with SLE, prior studies have been small and have examined a limited number of outcomes. We examined the relationship between sleep disturbance and a range of patient-reported outcomes (PROs), both concurrently and longitudinally, in a large cohort of individuals with SLE.

Methods: Data from the Lupus Outcomes Study (2010-2012; n = 711), obtained through annual structured telephone interviews, were used. All participants had physician-confirmed SLE. The Medical Outcomes Study Sleep Scale was administered in 2010 and used to calculate the 9-item Sleep Problems Index (SPI) score. SPI scores range from 0 – 100; higher scores indicate greater sleep problems. The following PROs were examined: self-reported disease activity (Systemic Lupus Activity Questionnaire; SLAQ); modified SLAQ (mSLAQ) excluding symptoms of depression, fatigue, and forgetfulness; disability (Valued Life Activities, 0 – 3 scale); single item rating of SLE activity (0 – 10 scale); Fatigue (0 – 100 scale); SF36 Bodily Pain scale score (0 – 100 scale); and depressive symptoms (Centers for Epidemiological Studies Depression scale; CESD). Relationships between SPI and PROs were examined concurrently and longitudinally after 2 years using multiple linear regression controlling for age, sex, race, income, education, lupus duration, baseline self-reported disease damage (Brief Index of Lupus Damage; BILD), oral steroid use, smoking, depression, obesity, and physical inactivity. Analyses of all PROs except SLAQ and mSLAQ also included mSLAQ as a covariate. Longitudinal

models added the baseline value of the dependent variable.

Results: The sample was 93% female, 61% white non-Hispanic, mean age 53 ±13 years, and mean SLE duration 20 ±9 years. Mean SLAQ in 2010 was 10.9 ± 7.4. The mean SPI in this sample was 44.9 ± 13.7, > one standard deviation higher than the population mean of 25.8 ± 18.6[1]. In cross-sectional analysis, sleep problems were significantly associated with poor outcomes for each PRO (Table 1). Additionally, sleep disturbance was associated with worsening of each PRO over a 2-year period.

Conclusion: Sleep problems appear to be linked to a variety of poor patient-reported outcomes concurrently and to worsening of these outcomes over time. Mechanism for this relationship are not known, but sleep problems have been linked to higher levels of systemic inflammation, greater pain sensitivity, and greater fatigue in the general population. Future studies are needed to characterize sleep problems in SLE objectively, and to identify relationships with clinical outcomes. [1] http://gim.med.ucla.edu/FacultyPages/Hays/surveys/SLEEP/

Table 1. Association of Medical Outcomes Study Sleep Scale Sleep Problems Index with Patient-reported outcomes, Concurrently and Longitudinally, Adjusted Models[1, 2, 3]

	Concurrent	2 years later[3]
SLAQ	2.50 (<.0001)*	0.68 (<.0001)
SLAQ, modified†	1.92 (<.0001)	0.50 (.0002)
SLE activity (0-10)[2]	0.13 (.04)	0.19 (0.01)
VLA[2]	0.10 (<.0001)	0.02 (.05)
Fatigue [2]	6.42 (<.0001)	1.35 (0.02)
SF36 Bodily Pain[2]§	1.03 (.0002)	0.87 (.004)
CESD[2]	3.84 (<.0001)	1.31 (<.0001)

* Tabled values are beta per 10-point change in SPI (p-value) from multiple regression analysis. † items querying depressed mood, fatigue, and forgetfulness are excluded from scoring § Score reversed so that higher score reflects greater pain. [1] All analyses control for age, sex, disease duration, income, education, race/ethnicity, oral steroid use (0.5 – 9.5 mg, ≥10 mg), disease organ damage (BILD), obesity, smoking, and physical inactivity [2] Analyses add modified SLAQ as covariate [3] Analyses add baseline value of PRO as covariate Note: Higher scores on all scales reflect worse outcomes. Note: Sleep Problems Index consists of 9 items queries trouble falling asleep, sleep was not quiet, not getting enough sleep, awakening short of breath or with headache, feeling drowsy or sleepy during the day, and trouble staying awake during the day

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Systemic Lupus Erythematosus in Immigrants: Results from the 1000 Canadian Faces of Lupus Study

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Background/Purpose: Ethnic differences in SLE are well known, but little is known about SLE in patients who have immigrated to North America from elsewhere in the world. Increasing rates of migration of individuals at high risk for SLE to Canada raise the potential for increased SLE specific healthcare needs. We aimed to describe immigrant patients within the 1000 Canadian Faces of Lupus Study.

Methods: The 1000 Faces of Lupus cohort is a multi-centre Canadian cohort of >2000 incident and prevalent SLE patients. Sociodemographic variables, ACR classification criteria, SLEDAI scores, SLICC/ACR damage index (SDI) scores, and treatment history are collected using standardized tools. Ethnicity was self-reported. Cross-sectional baseline analyses included t tests and logistic regression.

Results: 1243/ 2048 patients provided information on country of birth and were included. Immigrants made up 20% of participants (254/1243), similar to the percent (20.6%) in the general Canadian population. Immigrants arrived in Canada at a mean age of 16±10 years, and had been in Canada an average of 16±14 years at time of SLE diagnosis. Among immigrants, only 32% were Caucasian versus 73% of the Canadian born patients; OR 0.2, 95%CI 0.13-0.23); while 35% of immigrants were Asian versus 13% of Canadian-born patients; OR 3.5, 95%CI 2.6-4.9). Disease duration (10 vs 9 years) and age at diagnosis (31 vs. 28 years) were similar across groups, but 32% of Canadian-born had disease onset in childhood versus 25% of immigrants; OR 1.5 95%CI 1.0-2.1). Mean ACR criteria (5.3 vs. 5.2) were similar, but immigrants were more likely to have lupus nephritis (42% vs. 27%; OR 2.0, 95% CI 1.5-2.7). Exposure to lupus drugs and self-reported access to care were similar between groups. SLEDAI scores were similar between the groups, but patient-reported disease activity scores (SLAQ) were significantly lower in immigrants (8.5 vs 10.7, mean difference (MD) -2.2; 95%CI -3.0- -1.4), while damage was higher in immigrants (SDI scores 1.4 vs 1.0; MD 0.4, 95%CI 0.1-0.6). Immigrants had higher physical health-associated quality of life (PCS) (41 vs. 37; MD 3.7, 95%CI 0.4-6.9) but mental health-

associated quality of life (MCS) was similar. Comparing immigrant Asians (N=86) to Canadian born Asians (N=118); disease duration was similar, but immigrants were older at diagnosis (25 vs. 15 years), with only 20% having childhood-onset versus 58% of Canadian-born, OR 0.2, 95% CI 0.1-0.3. Number of ACR criteria, frequency of nephritis (50 vs 52%), medications, SLEDAI and SLAQ scores were similar. Immigrant and Canadian-born Asians had similar PCS and MCS scores and self-reported access to care, but immigrants had lower incomes (32% vs 17% low income, OR 2.2, 95% CI 1.1-4.6). SDI scores were higher in immigrants (0.9 vs 0.5; MD 0.4, 95%CI 0.04-0.80).

Conclusion: Our data suggest relatively severe disease with high frequencies of nephritis and damage in immigrant SLE patients. The low proportion of immigrants with childhood onset SLE also suggests barriers to immigration in children with SLE. Statistics Canada predicts that the proportion of immigrants will increase by 50%by 2031; monitoring information about the characteristics of lupus in immigrants is timely and relevant.

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Abstract Number: 1761

Fatigue in Patients with Systemic Lupus Erythematosus Is Independent of Their Disease Activity but Dependent on Their Damage Accrual and Body Mass Index

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Background/Purpose: Fatigue is omnipresent in patients with SLE. According to one study 80-90 % of the subjects report some degree of fatigue. This has huge impact on the patient's activities of daily living and overall quality of life. The fatigue associated with SLE was traditionally considered to be a consequence of SLE disease activity and difficult to measure and quantify in clinical practice. Recent recommendations from several international rheumatology societies and patient advocacy groups have focused on improving quality of life by focusing on issues such as fatigue during clinical encounters with SLE patients. The goal of this study is to measure severity of fatigue in our SLE cohort and to identify any predictors of fatigue.

Methods: We administered a well validated tool of fatigue measure Fatigue Severity Scale (FSS) to consecutive, consenting SLE subjects during their routine outpatient visits at a tertiary care center. Their demographic data, lab values, comorbidities and current medications were recorded at the time of visit. A rheumatologist blinded to the patient FSS scores calculated the SELENA-SLEDAI and SLICC/ACR damage index scores. Statistical analysis using SAS Software (SAS Institute Inc. Cary, NC) was done to identify any predictive variables using multiple regression models and a

stepwise multiple regression models.

Results: FSS was collected from 100 unique patients over a period of 9 months (Table 1). The majority of patients reported significant fatigue with minimal or no disease activity. FSS scores were unrelated to SLEDAI, disease duration, and plasma hemoglobin concentration (Table 2). FSS correlated significantly with SLICC/ACR (p=0.0123) and BMI (p=0.0337). Ethnicity, type of medications, comorbidities, and especially fibromyalgia, were found not to be predictive of fatigue in this cohort.

Conclusion: Results of this study suggest that organ damage accrual may be associated with the severity of fatigue in patients with SLE, independently of their disease activity or duration. Overall the results may implicate, in addition to aggressive early treatment to minimize damage accrual, lifestyle modification such as diet and increased physical activity to lower BMI as a potential therapeutic adjunct to improve fatigue in SLE.

Table-1-Details of patients enrolled in Fatigue Severity scale

Variables	***N=100***
Age (Years)	
n	100
Mean ±SD	45.5±13.1
Range	17--78
Disease Duration (years)	
n	100
Mean ±SD	15.4±11.2
Range	1--50
Race/Ethnicity, N (%)	
African American	26 (26.0 %)
Asian	19 (19.0 %)
Caucasian	25 (25.0%)
Hispanic	30 (30.0 %)
Gender, N (%)	
Female	93 (93.0%)
Male	7 (7.0 %)
FSS	
n	100
Mean ±SD	4.0 ±1.7
Range	1--7
SLEDAI Score	
n	100
Mean ±SD	3.3±2.8
Range	0--12
SLICC/ACR	
n	100
Mean ±SD	1.7±1.8
Range	0--8
BMI	
n	99
Mean ±SD	27.4±6.1
Range	16.8--48.9

Table-2. Multiple Regression model Results predicting fatigue adjusted for key confounders.

Variable	β, beta estimate	Std. Error	95% confidence Interval		*P*-Value(*)
			Lower	Upper	
SLEDAI	0.058	0.062	-0.065	0.181	0.3493
SLICC/ACR	0.271	0.106	0.060	0.481	0.0123
Disease Duration	-0.014	0.017	-0.048	0.019	0.3914
BMI	0.060	0.028	0.005	0.115	0.0337
Hemoglobin	0.165	0.124	-0.082	0.412	0.1875

P Value (*) were obtained using Multiple Regression model

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Abstract Number: 1762

Systemic Lupus Erythematosus and the Evaluation of Poor Sleep

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Background/Purpose: Poor sleep quality is an underappreciated complaint commonly observed in patients with SLE. We hypothesize that poor sleep quality contributes to worsening lupus disease activity. The aims of this study are to evaluate the relationship between: 1) subjective sleep measures and active SLE, 2) objective sleep actigraphy and active SLE, and 3) confounding variables that influence sleep quality and active SLE.

Methods: A prospective, longitudinal, observational study was designed to evaluate the relationship between sleep quality and SLE disease activity. Analysis was restricted to the first study visit. 127 subjects from the Lupus Clinic at Washington University who met ACR or SLICC criteria for SLE were enrolled. Patients with hepatitis B/C, HIV, cirrhosis, ESRD, or pregnancy were excluded. Pittsburgh Sleep Quality Index (PSQI), Epworth Sleepiness Scale (ESS), Patient Reported Outcomes Measurement Instrument System (PROMIS)-Sleep Related Impairment (SRI), and PROMIS-Sleep Disturbance (SD) survey instruments were administered to measure patient reported subjective sleep quality. 39 actigraphy watches recorded objective sleep data (sleep efficiency) over 7 days. SLEDAI 2K Responder Index-50 (S2K RI-50) assessed SLE disease activity (S2K RI-50 >4 = active SLE). Pearson Correlation measured the correlation between individual measures of sleep quality and SLE activity. Univariate and multivariate regression analyses explored predictors of active SLE and

poor sleep.

Results: Of the sleep surveys, SRI (Pearson coefficient 0.20, p=0.026) and SD (Pearson 0.20, p=0.031) both correlated with active SLE, whereas ESS (p=0.66) and PSQI (p=0.74) did not. Univariate linear regression of SRI showed that active SLE predicted an increase in SRI that was significant but with modest effect (r^2=0.042, p=0.026) whereas PROMIS-Fatigue (r^2=0.69, p<0.0001) and PROMIS-Anxiety (r^2=0.34, p<0.0001) comorbidities had a stronger effect on predicting SRI. In multivariate linear regression, only the effect of fatigue remained significant (p<0.0001). Univariate and multivariate analyses of predictors of SD showed similar results. Sleep efficiency measured by actigraphy was nearly significant with active SLE (Pearson coefficient -0.30, p=0.064) due to underpowered sample size (n=39). However, sleep efficiency poorly correlated with the subjective sleep surveys: SRI (Pearson -0.18, p=0.28), SD (Pearson -0.19, p=0.26), ESS (Pearson -0.16, p=0.33), PSQI (Pearson -0.33, p=0.09).

Conclusion: Our study reinforces that poor sleep quality remains a problem in SLE patients. We found that the SRI and SD surveys correlated with active SLE, but when considering confounding variables, fatigue best explained the relationship between poor sleep. Interestingly, despite the low sample size, we nearly achieved statistical significance when examining sleep efficiency via actigraphy to active SLE. Furthermore, sleep efficiency poorly correlated with the patient-reported sleep surveys. Thus, these data suggest that sleep quality is an unappreciated need in patients with SLE, and that current, validated sleep surveys may not best represent poor sleep quality for these patients.

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Abstract Number: 1763

Long-Term Impact of Belimumab on Health-Related Quality of Life and Fatigue in Patients with Systemic Lupus Erythematosus Following 7 Years of Treatment Exposure: Impact of Clinical Characteristics over Time

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Background/Purpose: Despite improvements in medical care leading to improved survival, systemic lupus erythematosus (SLE) adversely affects patients' health related quality of life (HRQoL). To explore the impact of clinical characteristics on reported HRQoL and fatigue, we performed a post hoc analysis (HO-16-17189) based on the long-term continuation study (GSK study 112233; NCT00724867) of the BLISS-76 randomized controlled trial (RCT) in the US.

Methods: In the continuation study, patients who received active drug in the RCT continued to receive the same doses of belimumab (1 or 10 mg/kg IV, every 28 days; all 10 mg/kg post-Mar 2011) plus standard of care (SoC) (belimumab/belimumab group). Patients previously receiving placebo received belimumab 10 mg/kg IV (placebo/belimumab group). HRQoL and fatigue assessments included Short Form-36v2 (SF-36) Medical Outcomes Survey and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue. In the post hoc analyses, subgroup

assessments were based on treatment (placebo/belimumab or belimumab/belimumab); responders (SLE Responder Index [SRI]-4 response within 1 year); high disease activity (high anti-dsDNA, low C3/C4); flare (SLE Flare Index); steroid dose (0 to 7.5 mg/d, ≥7.5 mg/d); damage (Systemic Lupus International Collaborating Clinics/American College of Rheumatology [SLICC] Damage Index [SDI]; 0, 1, and ≥2) at baseline (BL). Mixed-effect models were used to obtain means over time, with adjustments for disease duration and activity, BL HRQoL scores, age, gender, and race.

Results: The modified intent-to-treat population comprised 268 patients; 140 completed the continuation study. Statistically significant associations were observed between treatment groups and change from BL in SF-36 Physical (PCS) and Mental component (MCS), and FACIT scores (all $p<0.01$; **Table**). Responders and those with high disease activity reported numerically larger improvements from BL in HRQoL scores. Reported HRQoL scores were similar between all other subgroups at BL.

Table: Impact of key clinical characteristics on HRQoL from BL to Year 6 Week 48 (adjusted means)

	Treatment group Change from BL to Year 6 Week 48		Responder[1] (SRI-4 responder at Year 1) Change from BL to Year 6 Week 48		High disease activity at BL (high anti-dsDNA, low C3/C4) Change from BL to Year 6 Week 48	
	Placebo/belimumab (N=58)	Belimumab/belimumab (N=127)	No (N=70)	Yes (N=89)	No (N=119)	Yes (N=66)
Mean (SD)						
SF-36v2 PCS	1.98	5.77*	4.30	5.21	3.92	5.81
SF-36v2 MCS	-1.10	3.51†	0.90	2.77	1.18	3.57
FACIT-Fatigue score	-0.53	5.75‡	3.02	4.98	2.85	5.31

[1]Patients with a BL Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index (SELENA-SLEDAI) score <4 were excluded from the responder subgroup analysis;
*p=0.0019; †p=0.0027; ‡p=0.0002 (p values vs placebo/belimumab). All other p values were not statistically significant.

Conclusion: Differences in SF-36 and FACIT outcomes between treatment subgroups must be considered in light of differing BL scores: those for the placebo/belimumab arm were at time of entry into the extension study, following successful SoC treatment; whereas the belimumab/belimumab arm BL scores were at entry into the RCT. Further analyses, using comparable BL scores (at RCT entry) for all treatment groups will better characterize this patient subgroup. The lack of significant associations based on response status could partly be explained by the definition of 'responders', which was based on clinician assessments and may not have fully captured the patient experience. For all other subgroup analyses, sample sizes were small and not powered to show significant associations. Study funded by GSK/Human Genome Sciences, Inc. Nicole Cash, MRes PhD, Fishawack Indicia Ltd, UK, provided editorial assistance, funded by GSK.

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Abstract Number: 1764

Effect of Disease Remission on Organ Damage and Quality of Life in Chinese Patients with Systemic Lupus Erythematosus

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Background/Purpose: To study the effect of disease remission on quality of life and organ damage in patients with systemic lupus erythematosus.

Methods: Consecutive patients who fulfilled the ACR classification for SLE were recruited from our lupus out-patient clinics. Their remission status was determined according to the European consensus (DORIS definition): (1) Complete remission (clinical SLEDAI=0, serology inactive); and (2) Clinical remission (clinical SLEDAI=0, serology active). These two categories were further divided into those who required ongoing immunosuppressive treatment (prednisone ≤5mg/d or other immunosuppressive agents) and who did not. The duration of the remission status was also verified by medical record review. The increase in SLE organ damage (SDI) score since 5 years prior to recruitment was compared between patients who were and were not in clinical remission for at least 5 years. Participants were randomly selected for assessment of quality of life by using both the validated version of SF36 and the LupusPRO (version 1.8) and comparison was made between those who did and did not achieve clinical remission for ≥5 years by the independent Students' t-test.

Results: A total of 618 SLE patients were studied (92% women; age 45.5±8.1 years, SLE duration 11.8±8.1 years). All were ethnic Chinese. At the last clinic visit, clinical remission (serology active) was present in 227 (37%) patients (median duration 28 months) and complete remission (clinical and serology inactive) was present in 232 (38%) patients (median duration 48 months). Clinical and complete remission for ≥5years was achieved in 55 (9%) and 98 (16%) of the patients, respectively. 40 (26%) patients with remission ≥5 years were taken off all medications. No significant differences in the cumulative frequencies of organ manifestations since SLE diagnosis were observed between patients with clinical/complete remission for ≥5years and <5 years. However, patients with remission ≥5 years were significantly older (48.6±13.5 vs 44.5±14.7 years; p=0.002) and had a longer SLE duration (16.8±7.8 vs 10.3±7.5 years; p<0.001). In patients with remission for ≥5years, the increase in SDI score over the preceding 5 years was significantly lower than those with remission for <5 years (0.18±0.47 vs 0.50±0.90; p<0.001). 88 patients with remission ≥5 years and 283 patients with remission <5 years were assessed for quality of life at random. The physical component (61.7±21.6 vs 53.6±21.1; p=0.03) and mental component (61.0±21.8 vs 54.6±20.9; p=0.02) scores of the SF36 were significantly higher in patients with remission ≥5 years. On the other hand, scores of the health related domains (81.1±15.7 vs 73.1±16.1; p<0.001) but not the non-health related domains (57.6±18.4 vs 58.6±14.8; p=0.64) of the Chinese LupusPRO were significantly higher in patients with remission ≥5 years compared to those with remission <5 years.

Conclusion: In this cross-sectional study of Chinese patients with SLE, long-lasting clinical remission was present in a quarter of patients, the majority of whom were on maintenance immunosuppressive medications. Those with clinical remission for more than 5 years had less organ damage accrual over time and better health related quality of life.

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Abstract Number: 1765

Minimal Clinically Important Differences for Generic Patient Reported Outcomes Tools in SLE

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Background/Purpose: Patients with Systemic lupus erythematosus (SLE) have significant impairment in quality of life (QOL). Health related QOL (HRQOL) is one of the four established core outcomes in SLE. Generic PRO instruments such as Short Form 36(SF-36), SF-6D, EuroQOL (EQ-5D) and the Functional Assessment of Chronic Illness Therapy (FACIT-Fatigue)) have been shown to be valid and reliable in SLE. The purpose of this study is to determine minimal clinically important difference (MCID) of SF-36 and FACIT-fatigue against varied physician assessed DA indices, using data sharing resource from Glaxo-Smith-Kline (GSK), collected during Belimumab clinical trial – BLISS 52.

Methods: Longitudinal data from BLISS 52 clinical trial from 867 SLE patients was acquired from GSK for purpose of these analyses. DA measures (SLEDAI, BILAG) were used as anchors. MCID estimates were obtained against all possible predefined DA and composite DA endpoints used in SLE clinical trials. Mixed model analysis was utilized for the first 4 visits, one month apart for these analyses for individual DA anchors. For SELENA-SLEDAI Flare Index (SFI) and composite measures, 6,069 observation data from 7 visits were used.

Results: 867 SLE patient data consisting of 95% women, with mean (SD) age 35.5 (11.1) yrs., were available. Nearly 65% were Asian or White ethnicity. Median (IQR) SLEDAI, BILAG were 10.0 (4.0) and 17 (11.0) respectively. Median (IQR) MCS, PCS, FACIT-Fatigue were 40.3 (14.3), 41.7 (12.9) and 34.0 (14.0) respectively. MCID against SLEDAI and SRI are shown in table 1 and table 2 respectively. Results for MCID against BILAG are not included in the table but will be available for presentation. SF36 domains and FACIT-fatigue were responsive to improvement in DA endpoints – SELENA-SLEDAI, SFI, BILAG and composite measures. SF36 domains and FACIT-Fatigue were not consistently responsive to worsening in DA.

Conclusion: Our study provides SLE specific MCIDs against commonly used DA measures and further reinforce the need for use of disease specific MCID over "generic" values of improvement/worsening by 2.5 and 5.0 in domain and composite scores of SF36.

Table 2

	SRI4 N=851		SRI6 N=658		SRI8 N=453	
PF	6.4	(5.0;7.9)	8.4	(6.6;10.1)	9.3	(7.1;11.4)
RP	8.4	(6.6;10.1)	8.4	(6.6;10.1)	10.7	(8.0;13.3)
BP	11.7	(9.9;13.4)	11.7	(9.9;13.4)	12.7	(9.9;15.5)
GH	7	(5.7;8.2)	7	(5.7;8.2)	8.2	(6.2;10.1)
VT	7.9	(6.5;9.3)	7.9	(6.5;9.3)	10	(7.9;12)
SF	7.8	(6.1;9.5)	7.8	(6.1;9.5)	8	(5.4;10.6)
RE	6.5	(4.7;8.2)	6.5	(4.7;8.2)	9.2	(6.7;11.8)
MH	6.5	(5.2;7.8)	6.5	(5.2;7.8)	7.7	(5.8;9.6)
MCS	3.4	(2.7;4.2)	3.4	(2.7;4.2)	4.2	(3.2;5.2)
PCS	3.4	(2.9;4)	3.4	(2.9;4)	4.4	(3.5;5.3)
FACIT-Fatigue	4.3	(3.6;4.9)	4.3	(3.6;4.9)	4.9	(3.9;5.9)

Table 1

PGA	Improving: ↓ PGA <-0.3 N=1022 mean (95% CI)	Stable: Δ PGA -0.3 to +0.3 N=2521 mean (95% CI)	Worsening: ↑PGA >+0.3 N=25 mean (95% CI)
PF	4.0 (3;5.1)	1.5 (1;2)	-1.8 (-3.5;0)
RP	5.8 (4.5;7)	1.9 (1.2;2.5)	-1.2 (-3.3;0.9)
BP	7.3 (5.9;8.6)	2.3 (1.6;2.9)	-3.1 (-5.4;-0.9)
GH	5.0 (4.1;6)	1.6 (1.1;2)	-2.2 (-3.8;-0.7)
VT	6.0 (4.9;7)	1.5 (1;2)	-1.9 (-3.6;-0.2)
SF	5.2 (3.8;6.5)	1.6 (0.9;2.3)	-3.8 (-6.1;-1.6)
RE	4.7 (3.4;6)	1.4 (0.8;2.1)	-1.8 (-3.9;0.4)
MH	3.9 (2.9;4.9)	1.3 (0.8;1.8)	-1.2 (-2.9;0.4)
MCS	2.3 (1.8;2.9)	0.7 (0.4;1)	-1.0 (-1.9;-0.1)
PCS	2.3 (1.9;2.7)	0.7 (0.5;0.9)	-0.8 (-1.4;-0.2)
FACIT-Fatigue	2.8 (2.3;3.3)	0.7 (0.4;0.9)	-1.3 (-2.1;-0.5)
SLEDAI	**Improving: ↓ SLEDAI <-4 N=583 mean (95% CI)**	**Stable: delta SLEDAI -3 to +3 N=1860 mean (95% CI)**	**Worsening: ↑ SLEDAI >+4 n=158 mean (95% CI)**
PF	3.6 (2.5;4.8)	1.4 (0.9;1.9)	-0.1 (-2.1;2)
RP	5.4 (3.9;6.8)	2.0 (1.4;2.6)	-0.9 (-3.4;1.7)
BP	6.8 (5.3;8.4)	2.3 (1.6;2.9)	-1.9 (-4.6;0.9)
GH	3.9 (2.9;5)	1.6 (1.2;2.1)	0.7 (-1.1;2.6)
VT	4.7 (3.5;5.8)	1.9 (1.3;2.4)	-1.4 (-3.5;0.7)
SF	3.4 (1.9;4.9)	1.8 (1.1;2.4)	-1.0 (-3.7;1.7)
RE	4.9 (3.4;6.4)	1.3 (0.7;2)	-1.3 (-3.9;1.3)
MH	3.9 (2.7;5)	1.3 (0.8;1.8)	-0.8 (-2.8;1.2)
MCS	2.0 (1.4;2.6)	0.7 (0.5;1)	-0.6 (-1.7;0.5)
PCS	1.9 (1.4;2.3)	0.7 (0.6;0.9)	0.0 (-0.8;0.8)
FACIT-Fatigue	2.3 (1.8;2.9)	0.8 (0.6;1)	-0.6 (-1.6;0.4)
SFI	**Have Resolved N=358 mean (95% CI)**	**Same N=1810 mean (95% CI)**	**New Flare N=535 mean (95% CI)**
PF	3.9 (2.5;5.3)	1.7 (1.2;2.2)	0.2 (-1.3;1.6)
RP	4.9 (3.1;6.6)	2.5 (1.8;3.1)	0.5 (-1.2;2.3)
BP	8.8 (6.9;10.8)	2.8 (2.1;3.4)	-1.6 (-3.5;0.2)
GH	4.4 (3.1;5.7)	1.8 (1.4;2.3)	1.0 (-0.3;2.2)
VT	6.2 (4.8;7.6)	2.0 (1.5;2.5)	-0.3 (-1.7;1.2)
SF	4.7 (2.9;6.6)	2.0 (1.4;2.7)	-1.2 (-3;0.7)
RE	3.8 (2;5.6)	1.9 (1.3;2.6)	0.4 (-1.4;2.2)
MH	5.3 (4;6.6)	1.6 (1.1;2.1)	-1.2 (-2.5;0.2)
MCS	2.5 (1.7;3.2)	0.9 (0.6;1.1)	-0.3 (-1.1;0.4)
PCS	2.1 (1.6;2.7)	0.9 (0.7;1.1)	0.2 (-0.4;0.7)
FACIT-Fatigue	2.9 (2.2;3.6)	1.0 (0.7;1.2)	-0.4 (-1.1;0.3)

Disclosure: H. Devilliers, None; **N. Annapureddy**, None; **M. Jolly**, Pfizer Inc, 9.

Abstract Number: 1766

Impact of Depression on SLE Flares

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Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE) involves a wide range of peripheral and central neuropsychiatric manifestations. Depression is one of those and is very common in patients with SLE. The aim of this study was to determine if depression increases the risk of lupus flare in our patient population at Temple University Hospital, which is predominantly African American, and also to determine if therapy for Depression impacts SLE flares.

Methods: Data were collected from patients with SLE who fulfilled at least 4 SLICC criteria, at each clinic encounter from January 2013 to December 2015. Patients' demographics, medical, surgical and social history, medication list and laboratory results were included. Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) and Systemic Lupus International Collaborating Clinic (SLICC) Damage Index (SDI) were also extracted and analyzed as they were incorporated into our Epic Care EHR and routinely extracted to facilitate disease monitoring.

Results: Out of 209 patients present in the lupus cohort, 38 patients had a diagnosis of depression in their medical history. On review of these patient charts, 32 patients were included (6 excluded for having only 2 visits). 34 patients with diagnoses of lupus randomly selected from our cohort and without depression acted as control. The majority of our patients with concurrent lupus and depression were in the 40^{th} and 50^{th} decade of life. Only 62.5% (20/32) of patients were on antidepressants. SLEDAI analysis revealed that 62.5% (20/32) patients had at least a lupus flare and 75% (9/12) of these patients were not on any antidepressants, whereas those on antidepressants 55%(11/20) had lupus flare. The two groups were not statistically different (chi-square, p= 0.083). Interestingly lupus patients with depression compared to patients without depression, had statistically more flares (chi-square, p= 0.027). On our analysis though higher SLICC scores were common in lupus patients with depression, it did not reach significance (chi-square, p= 0.392). Also on comparing other comorbidities including HTN, diabetes, infections and social factors such as smoking, these were more common in lupus with depression (chi-square, p=0.041).

Conclusion: Prevalence of depression is high in SLE patients. We confirmed that Lupus patients with depression have significantly more flare compared to those without depression. Although it has been shown that the risk of lupus flare is high in those untreated for depression, in our cohort there was no statistical significance compared to those not on antidepressants. Other factors besides treatment that played a significant role in our cohort was presence of comorbid illnesses. Depression might be considered an independent risk factor for Lupus flares.

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Abstract Number: 1767

Poor Body Image in Lupus: Is It Disease Activity, Damage, Sleep, Pain, Fatigue, Stress, Function, Medications, Depression or Fibromyalgia?

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) have poorer body image (BI) than age matched

controls. Few studies have been done looking at the effect of disease activity, damage, sleep, stress, pain, fatigue, function, medications, depression and fibromyalgia (FM) in SLE patients. These 10 variables are frequently correlated, and their individual effect on BI is difficult to tease out. To improve BI in SLE, we need to better understand where we need to focus our attention among these 10 variables to guide development of specific interventions. We aimed to evaluate the relative role of disease activity, damage, sleep, stress, pain, fatigue, function, medications, depression and FM on BI in SLE patients.

Methods: 115 SLE patients receiving rheumatology care at two academic medical centers were recruited. Each patient completed the following: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT), Perceived Stress Scale (PSS), Patient Health Questionnaire (PHQ-9 for depression), Insomnia Severity Index (ISI), pain inventory and LupusPro. Body image and physical function was measured using the BI (BILS) and Physical health (PH) domains of LupusPRO. Disease activity and damage were assessed using SELENA-SLEDAI (SS) and SLICC/ACR Damage Index (SDI). Charts were reviewed to evaluate if the patient had been diagnosed with FM by a rheumatologist. Multivariate regression analyses (including stepwise modelling) were conducted with BI as the dependent variable for (a) all patients, and for patients (b) without and (c) with FM.

Results: 115 SLE patients with mean (SD) age of 40 (14) yrs. Ninety percent were women, and 15% had concomitant FM. Over 60% were currently on prednisone. Mean (SD) SS and BILS score were 4.8 (4.1) and 74.5 (27.7) respectively. For all patients, with all 10 variables in the regression analysis, PSS remained the single independent inverse predictor of BI after adjusting for other 9 variables. On stepwise regression, PSS and Pain were predictors of BI (Table 1). Among SLE patients without FM, the SS, PSS, PHQ were independent predictors of poor BI, after adjusting for the other 6 variables. On stepwise modeling, only PSS, PHQ, and SS were predictors of BI among non-FM SLE patients. When SS was replaced by SS arthritis, rash, alopecia items in this model, PSS, PHQ and active rash were found to be independent predictors. Among SLE patients with FM, none of the 9 variables independently predicted poor BI. On stepwise modelling PH was a predictor of BI in SLE patients with FM.

Conclusion: PSS (and not FM or steroid use) is an important and independent predictor of BI for all SLE patients. Among SLE patients without FM, besides PSS, active disease (rash specially) and depression are also important drivers of poor BI.

	All patients (n=94)						(-) FM (n=81)						(+) FM (n=12)					
	Full model			Stepwise			Full model			Stepwise			Full model			Stepwise		
	β	95%CI	p	β	95%CI	p	β	95%CI	p	β	95%CI	p	β	95%CI	p	β	95%CI	p
Sleep	-0.11	-1.31-0.49	0.37				0.03	-0.99-1.19	0.85				0.08	-2.15-2.57	0.80			
FACIT	-0.03	-0.38-0.28	0.77				0.03	-0.30-0.40	0.78				1.28	-0.01-3.82	0.05			
PHQ	-0.12	-0.69-0.22	0.30				-0.42	-3.24--0.62	**0.004**	-0.45	-2.92--1.16	**<0.001**	0.23	-0.70-1.02	0.59			
Pain	-0.11	-0.82-0.35	0.42	-0.34	-1.12--0.34	**<0.001**	-0.13	-0.91-0.31	0.34				-0.83	-5.59-2.67	0.34			
PSS	-0.27	-3.63--0.49	**0.01**	-0.36	-4.16--1.39	**<0.001**	-0.22	-3.52--0.03	**0.046**	-0.20	-3.23--0.03	**0.046**	-0.51	-10.6-4.84	0.32			
PH	0.14	-0.12-0.41	0.27				-0.03	-0.32-0.25	0.82				0.43	-0.97-1.61	0.49	0.75	0.22-0.87	**0.003**
FM	0.09	-8.26-21.49	0.38															
Steroid	-0.05	-14.1-8.24	0.60				0.01	-11.4-12.5	0.93				-0.49	-44.4-0.004	0.05			
SS	-0.17	-2.35-0.23	0.11				-0.23	-2.76--0.16	**0.03**	-0.26	-2.70--0.54	**0.004**	1.10	-2.77-20.5	0.09			
SDI	0.11	-1.78-7.44	0.22				0.07	-2.81-6.58	0.43				0.42	-5.18-26.8	0.12			

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activity-damage-sleep-pain-fatigue-stress-function-medications-depression-or-fibromyalgia

Abstract Number: 1768

Fatigue in SLE Is Associated with Neuropsychiatric Involvement, Pain, Impaired Sleep and a Reduced Quality of Life

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Background/Purpose: Fatigue is a major patient complaint in SLE, often severely impacting quality of life and activities including work. In this study, we analyze neuropsychiatric (NP) symptoms in relation to fatigue in SLE together with measures of disease activity, organ damage and potential contributing factors such as pain, psychiatric co-morbidities and sleep quality.

Methods: Measurements of fatigue were performed using the Fatigue Severity Scale (FSS) and the Visual Analogue Scale (100mm) (VAS). NP manifestations were defined according to NPACR case definitions. Disease activity, organ damage, health related quality of life and co-morbid conditions were recorded. Pain was recorded using the VAS (100mm). Depression and anxiety were evaluated with the Hospital Anxiety and Depression scale (HAD). Sleep disturbances were assessed using the Karolinska Sleep Questionnaire (KSQ). Cerebrospinal fluid was obtained in 33 patients who consented to lumbar puncture. Linear regression analyses were performed with VAS fatigue and FSS as outcome variables.

Results: 72 SLE patients and 26 matched healthy controls were included in this cross-sectional study. VAS fatigue and FSS were closely correlated ($r=0.63$, $p<0.001$). An increased VAS fatigue in the SLE group was associated with the following NP manifestations; cerebrovascular disease ($p=0.047$), headache ($p<0.01$), cognitive dysfunction ($p=0.008$) and depression ($p=0.006$). Furthermore, higher VAS fatigue scores correlated with increased HAD anxiety and HAD depression scores ($p<0.001$), lower EQ5D scores ($p<0.001$) and higher pain scores ($p<0.001$). However, there were no correlations between VAS fatigue score and age, disease duration, organ damage, co-morbidity or disease activity. Detection of CSF oligoclonal bands did not correlate with fatigue scores. Although most correlations were similar when using the FSS as outcome we found small differences compared to VAS fatigue; presence of autonomic neuropathy correlated with increased FSS ($p=0.049$) and there was no significant correlation between FSS and headache ($p=0.163$). In addition, a reduced overall sleep quality was seen comparing SLE patients and healthy controls using the KSQ ($p<0.001$). An increased FSS and VAS fatigue score in the SLE group correlated with scores in 3 sub-indices of the KSQ; insomnia ($p<0.001$), repeated awakenings ($p<0.001$) and daytime sleepiness ($p<0.001$). Finally, lower EQ5D scores was associated with increased both FSS and VAS fatigue scores ($p<0.001$ for both).

Conclusion: NP involvement in SLE may contribute to fatigue development in these patients, hypothetically mediated in part by a reduced sleep quality. Other factors, such as pain and concomitant psychiatric disease are also implicated, while disease activity may be of less importance.

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Abstract Number: 1769

Fatigue in Anti-Nuclear Antibody Positive Individuals with Insufficient Criteria to Diagnose a Systemic Autoimmune Rheumatic Disease

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Background/Purpose: Fatigue is a common symptom of Systemic Autoimmune Rheumatic Disease (SARD) and has been proposed to result from the elaboration of pro-inflammatory factors in these conditions. Patients with SARD have a protracted pre-clinical phase during which progressive immunologic derangements occur culminating in disease, however it is unknown at what point during this progression that fatigue develops and whether it is associated with any specific immunologic changes. The objective of the current study was to determine whether ANA^+ individuals who lack sufficient symptoms for a SARD diagnosis suffer from fatigue and assess the correlation between fatigue, autoantibody profile, and the presence of an interferon signature.

Methods: Healthy ANA^- controls and ANA^+ (≥1:160 by immunofluorescence) participants with no (ANA No Symptoms, ANS), at least one symptom (Undifferentiated Connective Tissue Disease, UCTD), or meeting SARD classification criteria were recruited. Fatigue was assessed using a modified version of the FACIT-F questionnaire and the presence of fibromyalgia determined using the modified 2010 ACR criteria questionnaire (score ≥ 13). Peripheral blood IFN-induced gene expression was quantified by NanoString and the normalized levels of 5 ubiquitously expressed IFN-induced genes summed to produce an IFN5 score. ANAs and levels of specific autoantibodies were measured by the hospital laboratory.

Results: Fatigue and fibromyalgia were assessed in 117 individuals (22 healthy controls (HC), 30 ANS, 25 UCTD, 40 SARD). All ANA^+ subjects were significantly more fatigued than HC (FACIT-F score (mean ± SD): HC = 49.45 ± 5.54, ANA^+ subjects = 28.78 ± 14.52, $p < 0.0001$) and this was true for each of the subsets examined independently. None of the HC and 35.8% of the ANA^+ subjects had fibromyalgia ($p = 0.0004$), with similar proportions in all ANA^+ subsets. As many of the ANA^+ subjects with low fatigue scores also had fibromyalgia, we assessed whether fatigue was present in ANA^+ subjects without fibromyalgia. Even in the absence of fibromyalgia, all ANA^+ subsets were significantly more fatigued than HC (HC = 49.45 ± 5.54, ANS = 40.61 ± 11.31, UCTD = 34.62 ± 12.62, SARD = 33.24 ± 11.66, all $p < 0.05$), with no significant differences between subsets. There was no association between the FACIT-F score in ANA^+ subjects (as a group or the individual subsets) and the titre of ANA, number of different autoantibody specificities, or IFN5 score, either in the presence or absence of fibromyalgia.

Conclusion: Fatigue is common in ANA^+ individuals who lack sufficient criteria for a SARD diagnosis and cannot be solely attributed to fibromylagia or the extent of the immunologic derangement.

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Abstract Number: 1770

The Impact of Comorbidities on Quality of Life in Systemic Lupus Erythematosus in the First 10 Years

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The Impact of Comorbidities on Quality of Life in Systemic Lupus Erythematosus in the first 10 years

Background/Purpose: The Medical Outcome Survey Short Form 36 (SF-36) is one of the most widely used tools for measuring patient reported outcomes. Our previous studies have shown that SF-36 improves in the first 2 years of an inception cohort and stabilizes in years 2-5 However the accrual of comorbidities in SLE increases over 8 years. The aim of this study is to assess quality of life(QoL) in a multinational multicenter cohort over years 4-10 of disease and assess the impact of comorbidities on QoL.

Methods: An international research network comprised of 33 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2016. Clinical and laboratory features of SLE, comorbidities, and SF-36 are gathered in a standardized protocol annually. Comorbidities including atherosclerotic vascular events (AVEs), osteoporosis, osteonecrosis and diabetes are assessed using the SLICC/ACR Damage Index (SLICC/DI). Attribution of a vascular event to atherosclerosis (AS) is made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical AS changes on imaging or pathology and/or evidence of AS elsewhere. Diagnosis of osteoporosis is based on abnormal bone mineral density and osteonecrosis was confirmed using joint symptoms associated with abnormal imaging consistent with osteonecrosis. Diabetes diagnosis is based on therapy, regardless of treatment type. The outcomes assessed include all 8 domains, physical component scores (PSC) and mental component scores (MCS) of SF-36. In order to test for change in SF-36 over the 10-year period, linear mixed models were run separately for the composite scores. Each model adjusted for repeated measures by patients and by centre. The impact of AVEs, osteoporosis, osteonecrosis and diabetes. on component scores was assessed using univariate and multivariate regression models

Results: 416 patients constitute the study population, of which 88.9% female, the mean disease duration at enrolment was 5.4 ± 4.3 months and the mean age at diagnosis was 34.6 ± 13.4 years. The race/ethnicity distribution was as follows: 55.3% Caucasian, 13.9% Black, 18.3% Asian, 9.4% Hispanic and 3.1% other. No significant change in SF-36 domains or component scores over years 4-10 were seen (Table 1). However, in a multivariable linear regression the presence of osteonecrosis (PE; 95% CI) (-8.6; -16.0, -1.3) (p=0.021) and osteoporosis (-15.0; -26.0, -4.3) (p=0.006) significantly impact the mean PCS. The comorbidities did not impact the MCS

Table 1. SF-36 domains and component scores over years 4-10

Years since Baseline Visit	4	6	8	10
Physical Component Summary	42.78	43.01	42.61	42.51
Bodily Pain	64.83	65.40	64.80	64.09
General Health	53.18	52.85	52.48	52.66
Physical Function	71.46	72.69	71.93	70.58
Role Physical	60.20	61.98	62.24	61.58
Mental Component Summary	47.51	48.02	48.23	47.84
Role Emotion	71.47	72.16	73.96	70.23
Social Function	72.57	73.68	72.57	73.23
Vitality	51.97	52.82	51.90	52.00
Mental Health	69.22	70.71	71.14	70.48

Conclusion: In an inception cohort SF-36 QoL measures do not change significantly over years 4-10 of their disease. However the comorbidities osteonecrosis and osteoporosis significantly impact the PCS.

Disclosure: M. Urowitz, None; **D. D. Gladman**, None; **N. Anderson**, None; **J. Su**, None.

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Abstract Number: 1771

Depression Is Associated with a Poorer with Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with frequent involvement of the central nervous system. Among the items included in the nomenclature for neuropsychiatric SLE, mood disorders have been identified. Despite the fact that depression is prevalent in SLE, its importance and impact may be underestimated. There are previous reports from Asia and North America about the association of depression with poor Health-Related Quality of Life (HRQoL) in SLE patients. However, there are few reports about this matter from Latin-American patients. The aim of the study was to evaluate whether depression is associated with poor HRQoL in Latin-American SLE patients.

Methods: In a cross-sectional single center study, we evaluated 94 SLE patients, who were seen in our Rheumatology Department between March 2015 and June 2016. SLE was defined by the 1997 revised and updated ACR criteria.

Demographic and clinical data were obtained from interview, physical exam and chart review. Disease activity was ascertained with the systemic lupus erythematosus disease activity index (SLEDAI), and disease damage was ascertained with the SLICC/ACR damage index (SDI). Depression was measured with the Beck's test, which determined its severity varying from minimal (0-13) to severe (29-63) and HRQoL with the SF-36. Univariable and multivariable linear regression models were performed in order to evaluate the association between depression and HRQoL Multivariable analyses were adjusted for age, disease duration, socioeconomic status, SLEDAI, SDI, use of prednisone, antimalarials and immunosuppressive drugs.

Results: Ninety-four SLE patients with a mean age of 45.50 (SD: 12.24) years. Almost all of them were mestizo, only one was African Latin-American. The mean SLEDAI was 4.97 (SD 4.15), the mean SDI was 0.91 (SD 1.21), the mean physical component of the SF36 was 46.43 (SD 18.97) and the mean mental component of the SF36 was 48.65 (SD: 17.71), mean Beck's test was 6.44 (SD 7.25). Univariable and multivariable associations between Beck's test and components of SF-36 are depicted in Table 1. Table1: Association of depression with HRQoL

	Univariable		Multivariable*	
	B (95% CI)	p value	B (95% CI)	p value
Physical Component Score	-1.07 (-1.55; -0.59)	<0.001	-1.02 (-1.47; -0.57)	<0.001
Mental Component Score	-1.12 (-1.56; -0.68)	<0.001	-1.14 (-1.54; -0.74)	<0.001
Physical Functioning	-1.24 (-1.87;-0.61)	<0.001	-1.18 (-1.72; -0.63)	<0.001
Physical Role	-1.14 (-2.2; -0.02)	0.046	-1.04(-2.09; -0.004)	0.049
General health	-0.84 (-1.3; -0.37)	<0.001	-0.84 (-1.28; -0.40)	<0.001
Bodily pain	-1.12 (-1.71; -0.53)	<0.001	-1.02 (-1.59; -0.44)	<0.001
Vitality	-0.94 (-1.37; -0.51)	<0.001	-0.96 (-1.38; -0.55)	<0.001
Social Role	-1,36 (-1.9; -0.80)	<0.001	-1.42 (-1.96; -0.88)	<0.001
Emotional Role	-1.53 (-2.6; -0.43)	0.006	-1.50 (0.50; -2.49)	0.003
Mental Health	-0.88 (-1.34; -0.42)	<0.001	-0.92 (-1.37; -0.48)	<0.001

CI: Confidence Interval*Adjusted by age, disease duration, socioeconomic status, SLEDAI, SDI, use of prednisone, antimalarials and immunosuppressive drugs.

Conclusion: In SLE patients, the presence of depression is associated with a worse HRQoL, independently of other risk factors.

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WITHDRAWN

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Abstract Number: 1773

Risk Factors for Cerebrovascular Events in Systemic Lupus Erythematosus: Results from an International, Inception Cohort Study

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Background/Purpose: Neuropsychiatric (NP) disease in patients with SLE includes cerebrovascular events (CerVE). We determined the frequency, attribution and risk factors for CerVE in a large, multi-ethnic/racial, inception cohort of SLE patients with long-term followup.

Methods: A prospective study of new onset SLE patients was performed by an international network of 32 academic centers in 11 countries. Patients were evaluated at enrollment and annually for up to 17 years. Data were collected at each assessment on demographic and clinical manifestations, medications, SLE disease activity index-2000 (SLEDAI-2K) and Systemic Lupus International Collaborating Clinics (SLICC)/ACR damage index (SDI). Nervous system events were recorded using the ACR case definitions for 19 NP syndromes. These included the following CerVE: (i) Stroke; (ii) Transient ischemia; (iii) Chronic multifocal ischemia; (iv) Subarachnoid and intracranial hemorrhage; (v) Sinus thrombosis. Pre-defined rules determined the attribution of NP events to SLE and non-SLE causes. Demographic variables, clinical variables, medications and NP related lupus autoantibodies were examined as potential predictors of the risk of SLE CerVE by univariate and multivariate Cox regression analyses.

Results: Of 1,826 SLE patients, 88.8% were female, 48.8% Caucasian, 16.8% African, 15.4% Hispanic, 15% Asian and 4% other. At enrollment the mean±SD age was 35.1±13.3 years, SLE duration was 5.6±4.2 months, SLEDAI-2K was 5.3±5.4 and SDI was 0.31±0.73. The mean follow-up was 6.5±4.1 years. Over the study 929 (50.9%) patients had 1,844 NP events of which 573 (31.1%) in 378/1826 (20.7%) patients were attributed to SLE. CerVE were the fourth most frequent NP event: 82/1,826 (4.5%) patients had 109 events of which 103/109 (94.5%) were attributed to SLE and 44 (40.4%) were identified at the enrollment visit. The incidence of first and recurrent CerVE was 5.8/1000 and 32.7/1000 person years respectively. The predominant events were stroke [60/109 (55.0%)] and transient ischemia [28/109 (25.7%)] followed by subarachnoid and intracranial hemorrhage [9/109 (8.3%)], chronic multifocal ischemia [9/109 (8.3%)] and sinus thrombosis [3/109 (2.8%)]. Multivariate analysis identified significant associations between CerVE and concurrent NP events attributed to SLE (HR (95% CI): (3.18; 1.72-5.88), concurrent non-SLE NP events (2.75; 1.55-4.89) ($p<0.001$), patients of African ancestry at US SLICC sites (2.95; 1.44-6.06) ($p=0.003$) and increased cumulative organ damage score (excluding NP variables) ($p=0.04$). There was a significant association between lupus anticoagulant at enrolment and the risk of first CerVE (4.4; 1.8-10.9) but not with recurrent events (0.87; 0.34-2.24) ($p=0.012$) likely due to the greater use of anticoagulants following the initial CerVE event (94%) compared to at the time of the initial events (37%).

Conclusion: CerVE are the fourth most frequent NP event in SLE, are usually attributable to lupus and occur frequently around the time of SLE diagnosis. Risk factors include other concurrent NP events, African ancestry and lupus anticoagulant.

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Chronological Analysis of Damage Accrual in Patientes with Systemic Lupus Erythematosus: Results from the Spanish Registry of Patients with SLE of the Spanish Society of Rheumatology (RELESSER)

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Background/Purpose: Mortality in systemic lupus erythematosus (SLE) has improved over the last decades. Outcome measures as damage became more important. **Objectives:** To study the manifestations of damage from the point of view of the timing of its appearance.

Methods: In the first transverse phase of RELESSER, accumulated information on 400 variables per patient at the time of the last evaluation was collected. Among these SLICC/ACR Damage Index (SDI) items were included. We evaluated damage manifestations in each system and the temporal relationship of their appearance with the time of diagnosis of SLE. Cumulative incidence function for damage by the Aalen-Johansen method was estimated. Bootstrap technique was used to calculate the p-values to compare rates os accumulation of damage over time.The impact on mortality was studied controlling for sex, race, age at diagnosis and delay of diagnosis of SLE, with a model of multivariate Cox regression. The rate of increase or accumulation of damage is significantly higher ($p<0.001$) higher short time after SLE diagnosis. The

proportion of patients with damage in at least 1 system at 5 and 10 years was 18.9% (17.3-20.4) and 29.2% (27.3-31.1). That is while in the 1st year 7.4% of patients present damage in any system, only 2.9% per year do so since the 1st to the 5th year after diagnosis and, between the 5th and 10th year there was only an annual increase of damage of 2.1%. The risk of death is multiplied by 2.04 (1.7-2.3) at the time that a new system is damaged. When entering into a multivariate model the damage in each systems a statistically significant impact on neuropsychiatric, renal, pulmonary, CV systems and malignancy was found, with multiplicative risk factors of 2.0, 1.8, 2.8, 1.7 and 2.7, respectively.

Results: 2,662 SLE patients had the dates of presentation of each event of damage: 2,417 (91.0%) women, 2,402 (92.8%) Caucasian, mean age (±SD) 34.0 (±13.6) years at the time of diagnosis. The mean follow-up duration was 115.6 (±50.8) months and 112 (4.2%) patients died. At the time of the study 917 (34.4%) patients had at least 1 manifestation of damage, the average number systems per patient with at least 1 manifestation of damage was 0.54 (±0.92) and the average score was 0.65 SDI (±1.2). The systems more frequently damaged were musculoskeletal (MS) (11.9%), ophtalmic (7.8%) and cardiovascular (CV) (5.9%). In the 1st year after SLE diagnosis, the cumulative incidence (CI 95%) of damage in at least 1 system was estimated in 7.4% (6.4-8.4), at 5 years 18.9% (17.3-20.4) and after more than 10 years 29.2% (27.3-31.1).The systems damaged at earlier stages, 1 year after SLE diagnosis, were: MS 1.7% (1.2-2.2), neuropsychiatric 1.3% (0.8-1.7) and renal 1.2% (0.8-1.6). The CV and cutaneous systems also had relatively early damage, 0.9% (0.6-1.3) and 0.8% (0.5-1.2) respectively.

Conclusion:

Damage occurs already in early stages of the disease. It appears early in MS, neuropsychiatric and kidneys. The increase or accumulation of damage is greater in the 1st year after the diagnosis of SLE. The accumulation of visceral damage increases the mortality rate.

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Abstract Number: 1775

Smoking As a Predictor of Cutaneous Activity in Systemic Lupus Erythematosus

Shawn Kwatra[1], Michelle Petri[2] and Wei Fu[3], [1]Dermatology, Johns Hopkins University School of Medicine, Baltimore, MD, [2]Rheumatology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [3]Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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ACR Abstract Authors: Shawn G. Kwatra[1], Wei Fu[2], Michelle Petri[2] [1]Department of Dermatology, [2]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD **Title:** Smoking as a Predictor of Cutaneous

Activity in Systemic Lupus Erythematosus

Background/Purpose: Smoking is associated with increased disease activity in patients with systemic lupus erythematosus (SLE) and cutaneous lupus erythematosus (CLE) in cross-sectional analyses. We sought to determine the associations between smoking status, presence of cutaneous activity, and SLE disease activity among patients enrolled in a US-based SLE Cohort featuring a large African-American population.

Methods: The Hopkins Lupus Cohort was queried for demographic information, clinical information, and laboratory parameters between current smokers and never smokers. SLE patients that developed rash vs. those that did not (according to the validated SLEDAI criteria for rash) were compared with smoking status and the following co-variables: age, ethnicity, sex, ESR, urine protein/creatinine ratio, anti-Ro, anti-La, anti-DNA, Low C3, and Low C4.

Results: Current smokers vs. never smokers Current smokers were significantly more likely than never smokers to have an active rash (49.58% vs. 36.31%, p <0.0001) and ESR > 20 (p < 0.0006). Non-smokers were significantly more likely to have anti-Ro antibodies as compared to current smokers with no significant differences found in additional co-variables. SLE Patients who developed new rash during the course of follow-up vs. patients without rash SLE patients who developed a new rash were significantly more likely than SLE patients without a rash to have a younger age of SLE diagnosis (p < 0.0015), higher SLEDAI continuous score (5.53 vs. 2.26, p < 0.0001) and SLEDAI score ≥ 2 (100% vs. 57.04%, p < 0.0001), Urine protein creatinine ratio > 0.5 (p 0.0256), anti-dsDNA ≥ 10 (36.12% vs. 23.78%, p<0.0001), low C3 < 79 and low C4 < 12 with no significant differences in percentage of patients positive for anti-Ro and anti-La antibodies. Association between Smoking and New Rash Smoking was significantly associated with new rash in SLE patients after adjusting for sex, ethnicity, and hydroxychloroquine use (p < 0.0001). Duration from SLE diagnosis to new rash were compared between current smokers and never smokers. Both non-parametric Kaplan-Meier curve and a parametric Weibull curve demonstrated current smokers developed rash significantly earlier than never smokers. The hazard of developing a rash is 40% higher among current smokers than never smokers, with the effect persisting after adjusting for sex and ethnicity.

Conclusion: Current smokers with SLE are significantly more likely than non-smokers to have an active rash. The hazard of developing a rash is 40% higher among current smokers than never smokers. SLE patients who developed rash as compared to patients that did not develop a rash had significantly increased SLE disease activity and several laboratory abnormalities including increased urine protein creatinine ratio > 0.5, anti-dsDNA ≥ 10, low C3 < 79 and low C4.

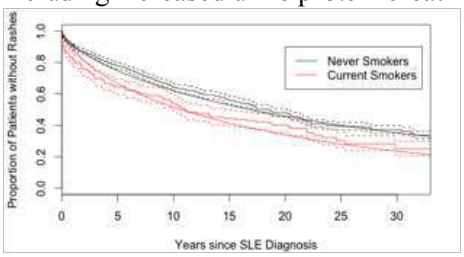

Figure 1: Kaplan-Meier Plot & Weibull Curve examining risk of developing rash among never smokers vs. current smokers

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Abstract Number: 1776

Analysis of Progressive Brain and Corpus Callosum Atrophy and Association with Th1 and Th2 Cytokines in Systemic Lupus Erythematosus

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Background/Purpose: The pathophysiology of brain damage SLE is complex. The aim of this study was to determine brain atrophy progression and the association with Th1 and Th2 in systemic lupus erythemathosus (SLE) patients.

Methods: Consecutive SLE patients followed at the Rheumatology unit of the State University of Campinas were enrolled in this follow-up study. Healthy volunteers, matched by age and sex, were included as control group. A complete clinical, laboratory and neurological evaluation was performed in all subjects. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and current therapy. MRIs were repeated in all individuals after a mean follow-up time of a minimum of 12 months. Sagittal T1-weighted images were used for volumetric measurements (Neuroline®). Volumes smaller 2 standard deviation from the means of controls were considered abnormal. Sera cytokines Th1 (TNF-α, IFN-γ, IL-12) and Th2 (IL-4, IL-6, IL-10) were performed by enzyme linked immunosorbent assay (ELISA) at the end of the study. Total dose of corticosteroids and other immunosuppressant medications used since the onset of disease were calculated by data obtained by careful review of the medical charts. Data were compared by non-parametric tests.

Results: Eighty-five SLE patients (81 women; mean age of 41.14±11.08 years; range 24-73) and 59 (52 women; mean age of 40.14±13.42 years; range 18-69) healthy controls were included. At the first MRI, 38 patients had active disease (mean SLEDAI scores of 3.71± 4.24; range 0-16). 60 (70.5%) had SDI≥1. Neuropsychiatric manifestations were observed in 31 (36.4%). aCL were positive in 35.5%. Mean total dose of corticosteroid dose was 41.95± 34.09g (0-13.58). Mean cerebral (1056.45± 86.75cm^3 and corpus callosum volume 11.57±2.1cm^3) were significant smaller at baseline when compared to controls (cerebral 1086.37± 165.77cm^3; corpus callosum 14.67±14.33 cm^3 volume; $p<0.01$). We observed a significant greater progressive loss of cerebral (2.3±1.08%), and corpus callosum volume (5.83%±4.97%) in SLE patients when compared to controls (cerebral volume change=0.32±1.73%; p=0.028 and corpus callosum volume change=0.03±0.19%; $p<0.001$). There was an association between IL-12 and progressive brain atrophy (p=0.008) and a direct correlation between sera IL-12 levels and percentage loss of brain volume (rs=0.3; p=0.015). We did not observe an association between brain or corpus callosum atrophy and aCL (p=0.688; p=0.094), total dose of corticosteroids (p=0.479; p=0.647, respectively), or other cytokines, clinical, laboratory manifestations and treatment.

Conclusion: IL-12 was associated with progressive loss of brain volume in SLE, suggesting immunological basis for global atrophy in SLE. Cytokines act as crucial mediators in the bidirectional signaling between the immune system and the brain and may be considered biomarkers for brain damage in SLE.

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Abstract Number: 1777

The Accumulation of Organ Damage, Public Insurance Enrollment and Youth Are Associated with Increased Hospitalizations in a Population-Based

Cohort of Lupus Patient

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Background/Purpose: Individuals with systemic lupus erythematosus (SLE) are frequently hospitalized. Determining factors associated with hospitalization rates may help to identify patients at highest risk for poor outcomes and improve healthcare resource utilization.

Methods: The Georgians Organized Against Lupus (GOAL) is a cohort of validated patients with SLE living in Atlanta, predominantly derived from the population-based Georgia Lupus Registry. Since 2011, participants are surveyed annually on sociodemographics, health insurance, the Self-Administered Brief Index of Lupus Damage (SA-BILD), and the Systemic Lupus Activity Questionnaire (SLAQ). Those with accumulation of any organ damage during the study period were deemed a Damage Progressor (DP). Patients were matched to the Georgia Hospital Discharge Database to capture all hospitalizations throughout the state from 2011 through 2013. Multivariable Poisson regression analyses were performed to explore the independent effect of demographic and disease-related factors on the hospitalization rate (HR), defined as the number of hospital admissions per 1000 person-years, and on the incidence rate ratio of hospitalizations.

Results: 731 individuals were surveyed. 94% were female, 79% black, 35% had a high school education or less, and 45% lived below the Federal poverty level. Mean ages at SLE diagnosis and survey completion were 32.8 and 46.6 years, respectively, with mean disease duration of 13.8 years (±9.3) at the time of survey completion. 35% had private insurance, 47% public insurance (Medicare and/or Medicaid), and 17% were uninsured. Baseline self-reported disease activity was mild, moderate, and severe in 26%, 23%, and 50% of participants, respectively. While 25% had no organ damage at baseline, 38% had mild and 37% had severe damage. 345 individuals were hospitalized during the 3-year study period. The overall unadjusted HR per 1000 person-years was 668 and the HRs were 806 and 559 for those who were and were not a DP, respectively (p=0.01). The ratio of HRs for those who were DPs relative to those who were not DPs was 1.33 (95% CI: 1.02-1.73, P=0.04) after adjusting for confounders. Ages 18-34 at baseline, public insurance enrollment, severe disease activity, severe organ damage, and being a DP were independent predictors of increased HRs.

Conclusion: In this population-based cohort, nearly half were hospitalized over the 3-year study period. Notably, gender, race, education and poverty were not associated with increased hospitalizations. Our data suggest organ damage may increase the risk of hospitalizations with a 33% increased rate in DPs. Individuals enrolled in Medicare and/or Medicaid had over double the rate of hospitalizations compared to those with private insurance. The reasons for increased hospitalization with public insurance are unclear and should be explored further.

Multivariable Analysis of Potential Factors Associated with Rate of Hospital Admission					
		Hospital Admission Rate (per 1000 person-years)		Incident Rate Ratio (IRR)	
Effect	Category	Mean HA Rate (95% CI)	P value	IRR (95% CI)	p value
Gender	Male	390 (207-733)	0.67	(Ref)	
	Female	439 (326-593)		1.13 (0.64-1.98)	0.68
Race	Non-Black	377 (219-648)	0.35	(Ref)	
	Black	455 (320-645)		1.21 (0.80-1.83)	0.38
Baseline Age	18-34	516 (336-792)	0.085	(Ref)	
	35-54	383 (247-594)		0.74 (0.56-0.98)	0.033
	>55	359 (224-575)		0.70 (0.49-1.00)	0.049
Disease Duration[1]	0-5 Years	467 (310-703)	0.54	(Ref)	
	6-10 years	397 (231-680)		0.85 (0.56-1.28)	0.44
	>=11 years	383 (254-576)		0.82 (0.58-1.15)	0.25
Education Level	High School	481 (327-709)	0.27	(Ref)	
	Some College	417 (281-619)		0.87 (0.64-1.17)	0.35
	College+	353 (202-618)		0.73 (0.50-1.07)	0.11
Poverty	No	440 (303-638)	0.46	(Ref)	
	Yes	389 (238-636)		0.89 (0.65-1.21)	0.45
Insurance Source	Private	277 (184-417)	0.0002	(Ref)	
	Public	577 (384-867)		2.08 (1.43-3.04)	0.0001
	Uninsured	443 (242-813)		1.60 (0.91-2.80)	0.1
Disease Activity	Mild (0-10)	297 (196-452)	0.0022	(Ref)	
	Moderate(11-16)	421 (242-732)		1.41 (0.88-2.27)	0.15
	Severe (>=17)	566 (372-861)		1.90 (1.32-2.74)	0.0006
Organ Damage	None	335 (187-603)	0.0016	(Ref)	
	Mild (SA-BILD=1-2)	360 (230-563)		1.07 (0.67-1.73)	0.77
	Severe (SA-BILD≥3)	588 (414-833)		1.75 (1.16-2.64)	0.0071
Damage Progressor	No	359 (240-537)	0.041	(Ref)	
	Yes	477 (304-749)		1.33 (1.02-1.73)	0.035

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Abstract Number: 1778

Differences Between Early and Late Cardiovascular Disease in a Population-Based Cohort of Systemic Lupus Erythematosus Patients

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Background/Purpose: It has long been known that mortality after years of systemic lupus erythematosus (SLE) is often associated with cardiovascular disease (CVD). Recent studies have also observed excess early CVD, even before SLE diagnosis. This is the first population-based study with large numbers of blacks to evaluate early vs. late CVD.

Methods: The Georgia Lupus Registry (GLR) is a population-based registry of SLE patients living in Atlanta, GA from 2002-04. Patients were validated by meeting ≥4 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by a board certified rheumatologist and were matched to the Georgia Hospital Discharge Database, capturing all hospitalizations throughout the state from 2000 through 2013. CVD related hospitalizations (CVD-H) were identified based on the first 3 admission codes, which included ischemic heart, cerebrovascular, and peripheral vascular diseases. 2 periods were

evaluated. The “Early Period” was defined as the period prior to and within the first 2 years after diagnosis. The “Late Period” was defined as the period afterwards. Multivariable logistic regression analyses were performed to explore the independent effect of demographic and disease-related factors on CVD-H.

Results: 336 incident SLE patients had 34 CVD-H’s during the surveillance period 2000-2013, 16 as Early CVD (6 ischemic heart, 7 cerebrovascular, 3 peripheral vascular) and 18 as Late CVD (4 ischemic heart, 13 cerebrovascular, 1 other vascular). Characteristics of the Early Period were a mean age at SLE and CVD-H of 52.5 and 52.2, respectively. 81.3% were female and 81.3% black. There were less photosensitivity and more serositis, renal disorder, and neurologic disorder in CVD-H compared to other incident patients (data not shown). Multivariable regression analysis showed 30% increased odds of a CVD-H for every 5-year increase in age at SLE diagnosis and over 6-fold increase in odds with neurologic disorder. Characteristics of the Late Period were a mean age at SLE and CVD-H of 40.1 and 45.8, respectively. 100% were female and 94.4% black. There was more renal disorder in CVD-H compared to other incident patients (data not shown). Multivariable regression analysis showed reduced odds (0.22) of a CVD-H with serositis and a nearly 6-fold (5.71) increase in odds with renal disorder. Race was not a factor in either period.

Conclusion: In this population-based cohort, there were significant numbers of CVD events, with nearly equal numbers of CVD-H’s in the Early Period compared to the Late Period. Consistent with previous findings, the Early Period is marked by higher risk in those with late onset of disease. The Late Period had more cerebrovascular events. Other manifestations may help identify those at higher risk for CVD-H’s.

Multivariable logistic regression for the outcome of cardiovascular disease related hospitalizations

	Factor*	OR (95%CI)	P value
Early Period	Age at SLE diagnosis, per 5 years ↑	1.30 (1.11-1.52)	**0.0011**
	Gender (female)	0.47 (0.12-1.85)	0.28
	Race (black)	2.00 (0.52-7.68)	0.31
	Arthritis	0.50 (0.17-1.49)	0.22
	Neurologic disorder	6.14 (1.79-21.09)	**0.0039**
Late Period	Age at SLE diagnosis, per 5 years ↑	1.05 (0.90-1.22)	0.52
	Race (black)	5.67 (0.72-44.39)	0.098
	Serositis	0.22 (0.06-0.83)	**0.025**
	Renal Disorder	5.71 (1.98-16.43)	**0.0012**
	*ACR Criteria with p<0.2 in the univariable analysis were included in the multivariable regression analysis		

Disclosure: S. Garg, None; **G. Bao**, None; **M. Niyibizi**, None; **C. Drenkard**, None; **S. S. Lim**, None.

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Abstract Number: 1779

Remission and Low Lupus Disease Activity Status (LLDAS) Protect Lupus Patients from Damage Occurrence: Data from a Multi-Ethnic, Multinational Latin American Lupus Cohort

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Background/Purpose: Recently, definitions of both Remission and LLDAS have been proposed which include disease activity status and medication intake [immunosuppressive (IS) drugs and corticosteroids]. The aim of this study was to evaluate both on the outcome of SLE patients from a multinational, multi-ethnic Latin American cohort.

Methods: Interval was defined as the period between two SLEDAIs or between one SLEDAI and the end of the follow-up. Four disease activity statuses were defined: Remission off-therapy=SLEDAI=0 without prednisone or IS drugs; Remission on-therapy= SLEDAI=0 and a prednisone dose≤5mg/d and/or IS drugs in maintenance dose; LLDAS=SLEDAI≤4, a prednisone dose≤7.5mg/d and/or IS drugs in maintenance dose; and non-optimally controlled status= SLEDAI>4 and/or prednisone dose>7.5mg/d and/or IS drugs in induction dose. Antimalarials were allowed in all groups. Predefined outcomes were mortality, new damage [defined as an increase of at least 1 point in the SLICC/ACR damage index (SDI)] and severe new damage (defined as an increase of at least 3 points in the SDI). Univariable and multivariable Cox regression models adjusted for possible confounders were performed in order to define the impact of disease activity status, as time-dependent variable, on these outcomes.

Results: One thousand three hundred and fifty patients from this cohort, with at least two intervals, accounted for the 5672 intervals examined. Median length of the intervals was 7.1 months (interquartile rank 5.1-11.7). Median number of intervals per patients was 4 (2-7). The most frequent interval was non-optimally controlled (4446; 78.4%), followed by LLDAS (566; 10.0%), remission on-therapy (553; 9.7%) and remission off-therapy (107; 1.9%). Seventy-nine patients died during the follow-up, 606 presented new damage and 177 severe new damage. Because of the limited number of intervals in the off-therapy group, this group was combined with the on-therapy group. The impact of these disease activity statuses on the pre-specified outcomes is depicted in table 1. Of importance, in multivariable analyses, remission on/off therapy was associated with both, a lower risk of new damage (HR:0.52; 95%CI:0.37-0.72), and of severe new damage (HR:0.32; 95%CI:0.15-0.65); LLDAS was associated with a lower risk of severe new damage (HR:0.46; 95%CI:0.23-0.91). Although the HR were in the right direction for the mortality outcome, the confidence intervals were too wide, probably because of the relative low number of events in this category.

Conclusion: Remission on/off therapy diminished the risk of new and severe new damage, and LLDAS diminished the risk of severe new damage after adjusting for other well-known risk factors of damage.

Table 1: Impact of disease activity statuses on mortality, new damage and severe new damage. Univariable and multivariable analyses

Group	Mortality		New damage**		Severe new damage***	
	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)	Unadjusted Hazard Ratio (95% CI)	Adjusted* Hazard Ratio (95% CI)
Remission (On/Off Therapy)	0.46 (0.17–1.27)	0.56 (0.20–1.55)	**0.47 (0.34–0.65)**	**0.52 (0.37–0.72)**	**0.30 (0.16–0.60)**	**0.32 (0.15–0.65)**
p-value	0.1330	0.2623	**< 0.0001**	**< 0.0001**	**0.0006**	**0.0017**
LLDAS	0.65 (0.26–1.60)	0.81 (0.32–2.02)	**0.69 (0.50–0.93)**	0.74 (0.54–1.01)	**0.41 (0.21–0.81)**	**0.46 (0.23–0.91)**
p-value	0.3454	0.6476	**0.0164**	0.0610	**0.0100**	**0.0247**
Non-Optimally Controlled	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.

LLDAS: Lupus low disease activity status; CI: Confidence Interval; Ref: Reference group. *Adjusted by age at baseline, gender, ethnicity, socioeconomic status, years of instruction, medical coverage and first SDI. **One-point increment in the SDI. ***Three-point increment in the SDI.

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Abstract Number: 1780

Pulmonary Disease in Late Versus Early Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

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Background/Purpose: Phenotypes often differ in late-onset systemic lupus erythematosus (SLE) compared to SLE features in early-onset patients. Prior studies have suggested that there may be more pulmonary disease in the older onset population. This systematic review and meta-analysis evaluates the differences in pulmonary manifestations between late and early-onset SLE.

Methods: We searched the literature using PubMed, CINAHL, Web of Science and Cochrane Library. We excluded studies that did not include ACR SLE classification criteria, lacked early-onset controls, defined late-onset SLE as <50 years of age, or were not written in English. Two authors rated study quality using the Newcastle Ottawa Quality Scale. We used

random effects models to create Forest plots to compare odds ratios and 95% confidence intervals of pulmonary manifestations by onset age. We specifically assessed interstitial lung disease, serositis, pleuritis, pulmonary embolism, pulmonary hypertension, or a composite of any lung disease. We assessed heterogeneity using I^2.

Results: Thirty six studies, representing 10,504 early-onset and 1,529 late-onset patients with SLE, met eligibility criteria. The prevalence of pulmonary manifestations was higher in the late-onset group as shown in **Table 1**. Interstitial lung disease (ILD) was nearly three times as common (OR 2.56 (1.27, 5.16)) with low study heterogeneity (I^2 23%, p=0.23). Pleuritis (OR 1.53 (1.19, 1.96)) and serositis (OR 1.24 (1.03, 1.51)) were also more common in the late-onset group for which there was low to moderate heterogeneity (I^2 36%, p=0.07 and I^2 43%, p=0.005). The mean Newcastle Ottawa Quality Scale score for study quality was 6.9 ±0.7 (scale 0-9).

Conclusion: Pulmonary manifestations of SLE appear to be more common in late-onset SLE patients compared to their younger peers, particularly ILD. Age-related changes of the immune system, tobacco and antigen exposure history, race, and possible association with Sjogren's syndrome are possible contributors that should be examined in future studies.

Table 1: Meta-analysis summary statistics for pulmonary findings in late vs early-onset SLE

Pulmonary Manifestation	Total cases	Late-onset n=1529	Early-onset n=10504	OR (95% CI)	Heterogeneity I^2 (%), p
ILD	82	29/294	53/1267	2.56 (1.27, 5.16)	26, 0.23
Pleuritis	1212	223/939	989/6415	1.53 (1.19, 1.96)	36, 0.07
Serositis	3151	462/1529	2689/9892	1.24 (1.03, 1.51)	43, 0.01
PE	10	5/64	5/166	2.73 (0.78, 9.60)	0, 0.50
Pulm HTN	5	1/36	4/160	1.72 (0.22, 13.49)	0, 0.40
Any	2987	486/1529	2501/10504	1.57 (1.30, 1.91)	42, 0.01

I^2 interpretation: low heterogeneity ≤25%, moderate 50%, and high >75%

Disclosure: J. Medlin, None; **K. Hansen**, None; **S. McCoy**, None; **C. M. Bartels**, None.

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Abstract Number: 1781

Analysis of Influences of Various Factors on the Prognosis of Acute Confusional State of Diffuse Psychiatric/Neuropsychological Syndromes in Systemic Lupus Erythematosus

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Background/Purpose: Neuropsychiatric systemic lupus erythematosus (NPSLE), especially diffuse psychiatric/neuropsychological syndromes (diffuse NPSLE), is one of the most difficult complications of the disease. For the evaluation and the diagnosis of central nervous system manifestations, including NPSLE, MRI is a very useful tool to detect the various abnormalities. We previously disclosed that patients with diffuse NPSLE and MRI abnormalities have

more severe inflammation in the central nervous system compared with those without MRI abnormalities, as evidenced by poorer prognosis. Of note, acute confusional state (ACS) is the most recalcitrant manifestation in diffuse NPSLE. However, it remains unclear whether abnormalities in brain MRI still have any influences in patients with ACS. The aim of this study is to explore the influences of various factors, including brain MRI abnormalities, on the prognosis of patients with ACS.

Methods: Thirty-six patients with ACS admitted to our University Hospitals from 1992 to 2015 were exhaustively enrolled in this study. Their medical charts and brain MRI scans were reviewed. The influences of various factors on the mortality of the patients were analyzed.

Results: During the observation periods (33.7}85.4months, mean}SD), 8 of the 36 patients (22.2%) died. The causes of death were related with the disease activity of SLE, mainly NPSLE, in the 8 patients. All the fatal patients died within 8 months from the onset of ACS (3.00}2.97 months, mean}SD). Notably, all these 8 patients presented brain MRI abnormalities, whereas none of the 18 patients without MRI abnormalities died. Accordingly, the presence of brain MRI abnormalities significantly increased the mortality rate in patients with ACS. To explore in detail the effects of various factors, including MRI abnormalities, on the mortality of patients with ACS, further analysis was carried out using Cox proportional hazards model. As shown in Table, the presence of brain MRI abnormalities, the presence of serum anti-Sm antibodies and serum IL-6 levels significantly increased the risk for mortality in multivariate analysis.

Conclusion: These results demonstrate that patients with ACS of diffuse NPSLE with MRI abnormalities have more severe diseases, resulting in poorer prognoses. The data also indicate that serum anti-Sm antibodies and serum IL-6 are critical factors influencing the prognosis of patients with ACS. **Table**

Effects of various factors on the survival in patients with acute confusional state

	Univariate HR (95% CI)*	p	Multivariate HR (95% CI)*	p
Age	2.767 (0.205-35.957)	0.4328		
Male gender	$1.812e^{-7}$ (0.722-0.722)	0.0238	$1.303e^{-8}$ ($2.11e^{-136}$-0.851)	0.0367
Abnormalities on MRI scan	$1.350e^{+7}$ (4.479-4.479)	0.0004	$1.904e^{+9}$ (8.172-$9.669e^{+24}$)	0.0013
Serum anti-Sm	2.486 (0.573-16.963)	0.2349	$6.565e^{+16}$ (7.027-$4.787e^{+55}$)	0.0167
Serum IL-6	1.001 (0.9998-1.002)	0.0742	$6.01e^{+17}$ (30.039-$9.42e^{+56}$))	0.0070
CSF IL-6	0.193 ($8.44e^{-15}$-9.409)	0.6127	$1.732e^{-9}$ ($3.54e^{-42}$-$1.32e^{+16}$)	0.1749

Disclosure: G. Abe, None; **Y. Arinuma**, None; **H. Kikuchi**, None; **S. Hirohata**, None.

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Abstract Number: 1782

Subclinical Myocarditis in Systemic Lupus Erythematosus Patients without Cardiovascular Disease

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Background/Purpose : Cardiovascular disease (CVD) remains a leading cause of death in SLE. Lupus patients have a 2-3 fold increased risk to develop heart failure compared with matched controls. Both traditional CVD risk factors and SLE itself play an important role in its development and associated excess deaths. Interest has emerged to study potential underlying mechanisms such as the presence of myocardial inflammation in attempts for early intervention when warranted. This study was initiated to evaluate the prevalence of myocardial inflammation in SLE using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), and the association of FDG uptake with disease characteristics in SLE patients without clinical CVD.

Methods: Patients <45 years old in the Columbia University Lupus Cohort without clinical evidence of CVD, history of antiphospholipid antibody syndrome, or cardiac related symptoms were invited to participate. All patients met the 1997 ACR SLE Classification criteria. Ten SLE patients underwent cardiac FDG-PET/CT imaging for evaluation of myocarditis by standardized methods. Demographics, SLE-specific characteristics, and CVD risk factors were ascertained. Coronary artery disease was evaluated by the Agatston coronary artery calcium score. The prevalence of myocarditis and its association with SLE-disease characteristics and conventional CVD risk factors was evaluated.

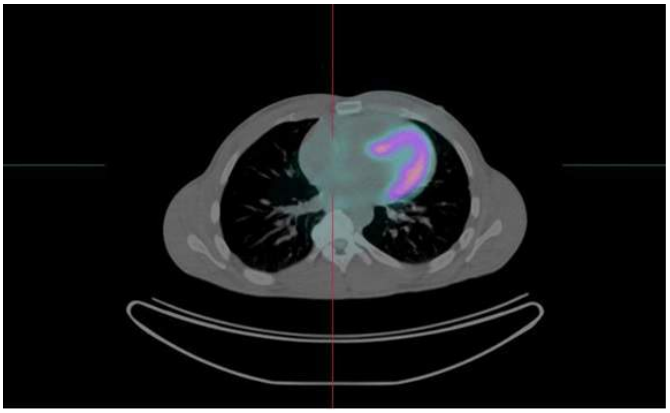
Results: Table 1 depicts the patient characteristics. The mean age was 33±7 years, 80% were female, 80% Hispanic and 20% were non-Hispanic Black. The median SLEDAI-2K and SLICC SDI scores were 2 (1-4) and 0 (0-0), respectively. Median SLE disease duration was 11 years (7-15). None of the patients had hypertension, diabetes, or smoked. Non-specific ST-T abnormalities were seen in 50% of the patients. The mean ejection fraction was 64±4%. Three of the ten patients (30%) had increased FDG myocardial uptake, with a diffuse pattern noted in all (Figure 1). No SLE-specific characteristics were associated with this outcome (Table 1).

Conclusion: This pilot study shows that myocarditis, identified by myocardial FDG-PET uptake, is prevalent in SLE patients without clinical CVD despite low disease activity. This supports the use of FDG-PET/CT imaging in the diagnosis of myocarditis in SLE and to further evaluate the prevalence of myocardial involvement in lupus. **Table 1.** Patient Characteristics and Cardiovascular diagnostic tests (n=10).

	Total (n=10)	Myocarditis (n= 3)	No Myocarditis (n= 7)	p-value
Age, years, mean ± SD	33 ± 7	33 ± 2	33 ± 8	0.97
Female, n (%)	8 (80%)	2 (66%)	6 (86%)	1.0
Race/Ethnicity				
Non-Hispanic White, n (%)	0	0	0	1.0
Non-Hispanic Black, n (%)	2 (20%)	0	2 (28%)	1.0
Hispanic, n (%)	8 (80%)	3 (100%)	5 (62%)	0.47
SLE duration, years, median (IQR)	11 (7-15)	10 (2-15)	12 (7-16)	0.58
ANA, n (%)	10 (100%)	3 (100%)	7(100%)	1.0
Anti-ds-DNA, n (%)	6 (60%)	1 (33%)	5 (71%)	0.5
Anti-ds-DNA titer, median (IQR)	56 (17-116)	21 (7-193)	77 (17-116)	0.66
SSA, n (%)	5 (50%)	2 (67%)	3 (43%)	1.0
SSB, n (%)	3 (30%)	0	3 (43%)	0.47
Lupus anticoagulant, n (%)	1 (10%)	0	1 (14%)	1.0
Anti-cardiolipin IgG/M, n (%)	0	0	0	1.0
Anti-b2-glycoprotein-1, n (%)	0	0	0	1.0
C3, mean ± SD	97 ± 32	101 ± 57	96 ± 21	0.89
C4, median (IQR)	14 (11-26)	15 (8-32)	14 (11-36)	1.0
SLEDAI-2K, median (IQR)	2 (1-4)	2 (2-4)	2 (0-5)	0.91
SLICC, median (IQR)	0 (0-0)	0 (0-0)	0 (0-2)	0.41
CRP, median (IQR)	0.9 (0.7-3.1)	2 (0.7-3.1)	0.9 (0.5-3.9)	0.82
ESR, median (IQR)	24 (11-36)	22 (8-36)	24 (11-57)	0.88
Current prednisone, n (%)	4 (40%)	1 (33%)	3 (43%)	1.0
Antimalarials, n (%)	8 (80%)	2 (67%)	6 (86%)	1.0
Azathioprine, n (%)	1 (10%)	0	1 (17%)	1.0
Mycophenolate mofetil, n (%)	4 (40%)	1 (33%)	3 (43%)	1.0
Current smoking, n (%)	0	0	0	1.0
Hypertension, n (%)	0	0	0	1.0
SBP, mean ± SD	114 ± 10	111 ± 13	115 ± 9	0.57
DBP, mean ± SD	73 ±11	72 ± 15	74 ± 10	0.85
Diabetes, n (%)	0	0	0	1.0
Total Cholesterol, mean ± SD	167 ± 44	184 ± 82	159 ± 20	0.65
LDL, mean ± SD	99 ± 39	112 ± 77	93 ± 14	0.70
HDL, mean ± SD	53 ± 11	57 ± 12	51 ± 12	0.49
Triglycerides, median (IQR)	67 (48-78)	74 (64-86)	52 (48-78)	0.38
Elevated Troponins, n (%)	0	0	0	1.0
Statin use, n (%)	1 (10%)	1 (33%)	0	0.3
EKG Non-specific ST-T changes, n (%)	5 (50%)	2 (67%)	3 (43%)	1.0
EKG QTc duration (ms), mean ± SD	420 ±25	423 ± 11	419 ± 31	0.83
Heart Rate, mean ± SD	76 ± 7	72 ± 12	77 ±4	0.55

CAC score, median (IQR)	0 (0-0)	0 (0-17)	0 (0-0)	0.22
EF (%), mean ± SD	64 ± 4	64 ± 7	65 ± 2	0.90
Diffuse Myocarditis, n (%)	3 (30%)	3 (100%)	-	-
Focal Myocarditis, n (%)	0	0	-	-

Figure 1. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography showing diffuse myocardial FDG uptake.



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Abstract Number: 1783

Phenome-Wide Association Study Identifies a New Association of Atrial Fibrillation in Males with Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) has a female to male ratio of 9:1. While SLE is more prevalent in females, males with SLE may have increased disease severity and mortality. Mechanisms for these outcomes are not known, as males are often understudied. We assessed differences in comorbidities in males vs. females by performing the first electronic health record (EHR)-based phenome-wide association study (PheWAS) in SLE. Similar to genome-wide

association studies, PheWAS compare two groups using ICD-9 codes in place of single nucleotide polymorphisms.

Methods: We used our validated algorithm of ≥ 4 counts of the SLE ICD-9 code (710.0) and ANA positive ≥ 1:160 while excluding dermatomyositis and systemic sclerosis ICD-9 codes to identify SLE cases in a de-identified EHR called the Synthetic Derivative (SD). The SD contains over 2.5 million subjects with clinical data collected longitudinally over several decades. Our algorithm has an internally validated positive predictive value of 94% and a sensitivity of 86%. PheWAS was performed in males vs. females adjusting for race and current age in logistic regression models and correcting for multiple testing using Bonferroni.

Results: We identified 986 females and 111 males with SLE. Males and females had similar mean current age, age at first SLE ICD-9 code, race breakdown, mean years of follow-up, and number of SLE code counts (Table 1). Adjusting for race and current age, males were more likely to have cardiac codes vs. females including atrial fibrillation odds ratio (OR) = 4.50 (95% CI 2.32 – 8.72), $p = 8.6 \times 10^{-6}$, other chronic ischemic heart disease OR = 4.40 (2.24 – 8.64), $p = 1.7 \times 10^{-5}$, atrial fibrillation and flutter OR = 4.08 (2.12 – 7.83), $p = 2.4 \times 10^{-5}$, and coronary atherosclerosis OR = 3.34 (95% CI 1.87 – 5.97), $p = 4.56 \times 10^{-5}$ (Figure 1). These four codes met the Bonferroni threshold for significance ($p < 1.26 \times 10^{-4}$). There were 51 SLE patients with the atrial fibrillation code, who were all confirmed on chart review. Males and females with atrial fibrillation had similar race breakdown, mean current age, and age at first SLE and atrial fibrillation codes.

Conclusion : These findings demonstrate the ability of PheWAS to uncover novel phenotype associations within a disease. While there is a 5-fold increased risk of cardiovascular disease overall in SLE, the increased relative risk of atrial fibrillation in males vs. females with SLE has not been identified. The odds of atrial fibrillation are two times higher in males in the general population; however, our data show a more pronounced sex difference in SLE patients.

Table 1.

Demographics	Males (n = 111)	Females (n = 986)	p value*
Current age, mean ± SD	52 ± 18	50 ± 17	p = 0.42
Age at first SLE ICD-9 code, mean ± SD	43 ± 18	40 ± 17	p = 0.08
Race/ethnicity (%)			
Caucasian	69%	69%	p = 0.32
African American	27%	26%	
Asian	4%	3%	
Hispanic	0%	2%	
Years of follow-up in the EHR, mean ± SD	8 ± 5	9 ± 5	p = 0.23
Number of counts of the SLE ICD-9 code (710.0), mean ± SD	17 ± 15	19 ± 22	p = 0.73

*Mann-Whitney U for continuous variables, Fisher's exact test for categorical variables.

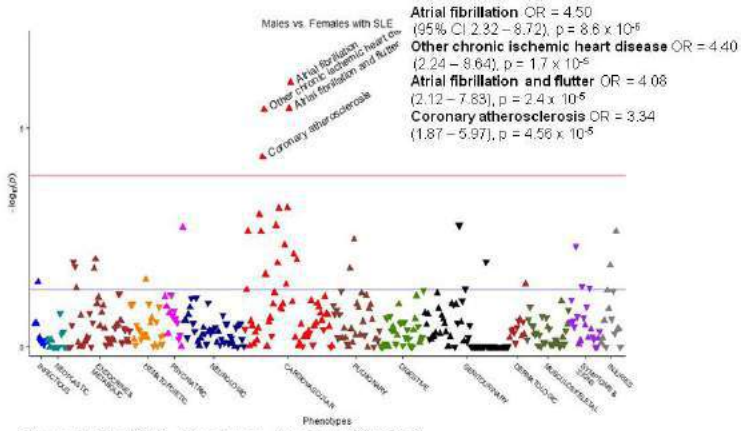

Figure 1. PheWAS of males vs. females with SLE.
The x axis represents the PheWAS codes that are mapped to ICD-9 codes organized by organ system. The y axis represents the level of significance. Females are the reference group. The lower horizontal line represents the $p < 0.05$ significance threshold. The upper horizontal line represents the Bonferroni threshold ($p < 1.26 \times 10^{-4}$). The four codes that met the Bonferroni threshold are shown above with adjusted odds ratio and 95% confidence intervals.

Disclosure: A. Barnado, None; **R. Carroll**, None; **C. Casey**, None; **J. C. Denny**, None; **L. J. Crofford**, None.

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Abstract Number: 1784

The Risk of Pulmonary Embolism and Deep Venous Thrombosis in Systemic Lupus Erythematosus: A Population-Based Study

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Background/Purpose: Prior population-based studies have shown an increased risk for cardiovascular complications in patients with SLE. However, the magnitude of the risk for venous thromboembolism (VTE) has not been well quantified in this patient group, particularly within the general population context. Our objective was to determine the risk of venous thromboembolism (VTE), pulmonary embolism (PE), and deep vein thrombosis (DVT) in individuals with incident systemic lupus erythematosus (SLE) in the general population.

Methods: Using the Health Information Network (THIN) database, a population database that includes 11.1 million patients, 6.2% of the population of the United Kingdom, we conducted a cohort study of all patients with incident SLE and up to 10 age-, sex-, and entry time-matched individuals from the general population. SLE patients were identified by read codes for systemic involvement of lupus, excluding cutaneous-only disease. We compared incidence rates of PE, DVT, and VTE between the two groups and within the SLE group according to SLE disease duration. We calculated hazard ratios (HRs), adjusting for potential confounders including the comorbidities stroke, myocardial infarction, kidney disease, and

malignancy, the use of NSAIDs, aspirin, and glucocorticoids, and for smoking status.

Results: Among 1494 individuals with SLE (87.1% female, mean age 50 years), there were 13 cases of DVT and 14 of PE. Among the 10,473 individuals without SLE, there were 38 cases of DVT and 33 of PE. The incidence rates of PE, DVT, and VTE were 1.6, 1.4, and 2.9 per 1000 person-years in the SLE group, whereas the corresponding rates were 0.5, 0.6, and 1.1 per 1000 person-years among individuals without SLE. Compared with non-SLE individuals, the multivariable HRs among patients with SLE were 3.17 (95% CI, 1.65-6.10), 3.42 (95% CI, 1.72-6.81), and 3.14 (95% CI, 1.94-5.07) for PE, DVT and VTE, respectively. The age-, sex-, BMI-, and entry time-matched HRs for PE, DVT, and VTE were highest during the first year after SLE diagnosis: 14.30 (95% CI, 4.02-50.82), 8.70 (95% CI, 1.74-43.40), and 10.82 (95% CI, 3.91-29.90), respectively.

Conclusion: These findings provide population-based evidence that patients with SLE are at an increased risk of VTE, especially within the first year after SLE diagnosis. Increased monitoring for this potentially fatal outcome and its modifiable risk factors is warranted in this patient population, particularly early after disease onset.

Table 1. Age and sex adjusted risk for PE, DVT, or both (VTE) in SLE according to follow-up period.

Time after diagnosis	PE HR (95% CI)	DVT HR (95% CI)	VTE HR (95% CI)
1 year	11.24 (3.47-36.97)	11.48 (2.56-51.59)	10.44 (4.02-27.12)
3 years	6.03 (2.97-12.25)	4.65 (1.93011.17)	5.21 (2.97-9.11)
5 years	3.74 (1.92-7.28)	3.48 (1.62-7.46)	2.56 (2.13-5.93)
Total follow up	2.40 (1.33-4.33)	3.31 (1.84-5.94)	2.76 (1.82-4.21)

HR= Age-, Sex-, BMI-, and Entry Time-Matched Hazard Ratio

Disclosure: A. Jorge, None; **N. Lu**, None; **H. Choi**, None.

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Abstract Number: 1785

Prevalence and Associated Factors of Low Bone Mass in Adults with Systemic Lupus Erythmatosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, multisystem autoimmune disease characterized by recurrent flares. SLE patients are often treated with glucocorticoids, which place this population at risk of significant bone loss. Low bone mineral density (BMD) predisposes patients to fragility fractures, which may result in severe pain, disability and mortality. The aims of this study are: 1) To determine the prevalence of low bone density and symptomatic fragility fractures in inception patients of the Toronto Lupus Cohort (TLC). 2) To determine the factors associated with low BMD in SLE inception patients.

Methods: Prospectively collected data from the TLC (1996-2015) of inception patients' first BMD were analyzed. For pre-menopausal women/males <50 years, BMD 'below expected range for age' was defined by a Z-score ≤2.0 S.D. For post-menopausal women/males age 50 or older, osteoporosis was defined by a T-score ≤-2.5 S.D and low bone mass by a T-score between -1.0 and -2.5 S.D. Patients' BMDs were defined as abnormal if their Z-score was ≤-2.0 or T-score was <-1.0 S.D, and the remainder as normal. Descriptive analysis and logistic regression were employed to determine factors associated with abnormal BMD.

Results: Of 1807 patients in the TLC, 286 are inception patients with BMD results (mean age 37.9 years ± 13.7); 88.8% are female. The mean duration from SLE diagnosis to time of first BMD is 2.20 ± 2.57 years. The overall prevalence of abnormal BMD is 31.5%. In pre-menopausal women (n=173), the prevalence of BMD below expected range is 17.3%. In post-menopausal women (n=81), the prevalence of osteoporosis and low BMD are 12.3% and 43.2%, respectively. In males <50 years (n=22), the prevalence of BMD below expected range was 27.3%. In males age 50 or older, (n=10), the prevalence of osteoporosis and low BMD were 10% and 80%, respectively. In multivariate analysis, age at first BMD remained statistically significantly associated with abnormal BMD (44.72 ± 17.14 years), with an OR of 1.06 (p<0.0001). Cumulative dose of glucocorticoids up to the date of BMD was also significantly associated with abnormal BMD (11.55 grams/day ± 10.99), with an OR of 1.04 (p=0.009) (Table 1). Of 769 inception patients, 85 (11.1%) experienced symptomatic fragility fractures over the course of their disease.

Conclusion: The prevalence of low BMD is high in SLE patients. Abnormal BMD is associated with older age and higher cumulative glucocorticoid dose. Identifying factors associated with low BMD is important in the development of preventative measures.

Table 1: Variables Associated with Abnormal BMD in 286 SLE Patients

Variables	Abnormal BMD n=90	Normal BMD n=196	Univariate OR* | p value	Multivariate OR* | p value
Age**	44.72 ± 17.14	34.89 ± 10.55	1.06 (1.03, 1.08) | <.0001	1.06 (1.04, 1.08) | <.0001
Female sex	75 (83.3%)	179 (91.3%)	0.47(0.23, 1.00) | 0.05	
Cumulative ACR criteria**	4.49 ± 1.02	4.73 ± 1.10	0.80 (0.63, 1.02) | 0.08	
SDI excluding osteoporosis**	0.85 ± 1.23	0.46 ± 0.88	1.43 (1.12, 1.82) | 0.004	
Treatment with vitamin D**	58 (64.4%)	103 (52.6%)	1.63 (0.94, 2.80) | 0.08	
Treatment with calcium**	58 (64.4%)	103 (52.6%)	1.63 (0.94, 2.80) | 0.08	
Treatment with bisphosphonates**	16 (17.8%)	22 (11.2%)	1.72 (0.85, 3.47) | 0.13	
Treatment with immunosuppressives***	58 (64.4%)	107 (54.6%)	1.51 (0.90, 2.52) | 0.12	
Cumulative dose of glucocorticoids**	11.55 ± 10.99	10.14 ± 8.40	1.03 (1.00, 1.05) | 0.06	1.04(1.01, 1.07) | 0.009

*95% CI in parentheses **Up to time of first BMD ***Immunosuppressives include: azathioprine, methotrexate, cyclophosphamide, mycophenolate mofetil, cyclosporine

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Disclosure: G. Cramarossa, None; **M. Urowitz**, None; **J. Su**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene

Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **Z. Touma**, None.

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Abstract Number: 1786

Long-Term Evolution of Risk Factors for Atherosclerotic Cardiovascular Events in Systemic Lupus Erythematosus in a Large Case Control Cohort Study

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Background/Purpose: Certain traditional and disease-related factors have been identified to accelerate atherosclerosis in systemic lupus erythematosus (SLE). Due to the lack of long-term prospective studies, the evolution over time and relative importance of these variables in the development of atherosclerotic cardiovascular events (CVEs) is not known. We aimed to determine the evolution of CVE risk factors over 15 years,

Methods: 250 female lupus patients (mean age at enrollment 44.5±12 years, mean disease duration 13.7±9.7 years) and 250 age-matched healthy women (mean age 44.1±14 years) were recruited between 1998 and 2000. All subjects had similarly low (3.2%) 10-year Framingham Risk Score (FRS) Variables assessed at study entry included family history of premature for coronary artery disease (CAD). CAD, hypertension, diabetes, dyslipidemia (total cholesterol, triglycerides, LDL, VLDL, HDL, lipoprotein a), smoking, physical activity, body mass index (BMI), menstrual status, use of oral contraceptives or hormone replacement therapy, serum creatinine, homocysteine and C-reactive protein. For lupus patients, SLEDAI-2K and the 3-year adjusted mean SLEDAI (AMS) (1998-2000 and 2005-2007) were calculated to quantify global disease activity. Additional parameters included antiphospholipid antibodies; information on antimalarials, prednisone and immunosuppressants were also collected. Subjects were followed for 15 years for the development of CVEs [angina, myocardial infarction (fatal, non-fatal), transient ischemic attack, stroke (fatal, non-fatal)]. Analysis was performed with SAS 9.3 software for 2000-2007 and 2008-2015; $p<0.05$ was considered significant.

Results: SLE patients had consistently higher rates of CVEs, the difference becoming greater with longer follow up ($p=0.0001$). CVEs occurred in 41/210 patients (19.5%) and 8/138 controls (5.8%), mostly in the second part (2008-2015) (24/41, 58.5% vs. 17/41, 41.5% in patients, 4 CVEs in each part in controls). Coronary artery disease was more common in SLE (32/210, 15.2% vs. 5/138, 3.6%, $p=0.0041$). There was no significant difference for cerebrovascular disease (10/210, 4.8% vs. 3/138, 2.2%, $p=0.213$). SLE [HR=2.8, 95% CI 1.3-6.3], older age and triglycerides>2.8mmol/L were predictive of CAD in the early phase. In the late phase, hypertension, diabetes, dyslipidemia and high BMI were more prominent in patients who suffered a CVE. Time-adjusted disease activity (AMS) was lower in those late phase patients; however their cumulative prednisone dose between 2000-2007 was significantly higher. Of note, 60% of the new hypertension and all new diabetes cases were attributed to glucocoricoids. Thirty-one deaths occurred in patients (10 due to CVEs) and 6 in controls (none due to CVEs); all CVE-related deaths occurred between 2008 and 2015.

Conclusion: SLE patients had a 4-fold increased risk for CVEs and all-cause mortality as compared to healthy controls after 15 years. Disease-related factors dominate cardiovascular risk during the early stages while traditional factors, partially related to corticosteroid treatment, play a significant role later in disease course.

Disclosure: K. Tselios, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **J. Su**, None; **O. Ace**, None; **M. Urowitz**, None.

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Abstract Number: 1787

Increased Heart Rate Variability Reflects Improvement in Clinical Status of Patients with Systemic Lupus Erythematosus

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Background/Purpose: Decreased heart rate variability (HRV) is a sign of potentially serious cardiac morbidity and is known to reflect autonomic dysfunction and inflammatory dysregulation (1). We have previously reported a cross-sectional association as well as association of changes between disease activity and HRV in patients with systemic lupus erythematosus (SLE) (2). We have not however yet demonstrated a predictable temporal relationship over time between SLE disease activity and HRV in individual patients.

Methods: To prospectively test the hypothesis that clinical improvement is reflected by increased HRV, we designed an ongoing clinical trial to include HRV measurements using a 5 min ECG and HRV parameters calculated in the time domain (RMSSD and pNN50) and frequency domain [high frequency (HF) and the low frequency to high frequency (LF/HF) ratio]. Here we report findings from 32 SLE patients (31 female, age 46.2 +/- 10.9) who have completed a minimum of 2 visits to date. A mixed effects linear model was used to compare the change in HRV parameters between 83 paired visits. Two groups were compared, those with clinical improvement between visits (group 1) and those with same or worse disease activity (group 2). Clinical improvement was defined as >/= 1 letter grade improvement in BILAG between visits with no new BILAG A or B scores.

Results: There was improvement in 14 (17%) of the paired, consecutive visits and no improvement or worsening in 69 (83%) visits. An inverse relationship was observed between clinical improvement and change in RMSSD, change in pNN50 and % change in HF (Table 1). The LF/HF ratio increased significantly between visits of patients in group 1 and decreased between visits in group 2 (4.51±1.95% vs. -0.14±0.83%, respectively; p=0.031).

Conclusion: HRV changes reflect changes in clinical status over time in patients with SLE. These data suggest that HRV may be a simple non-invasive tool for tracking clinical improvement and underscore the role of the autonomic nervous

system in inflammatory pathways. **Table 1.**

Variable	Group 1 visits (n=14)	Group 2 visits (n=69)	P-value
Delta RMSSD (ms)	-87.6±39.4	7.1±17.7	0.027
Delta pNN50 (ms)	-3.18±2.03	0.02±0.92	0.15
Delta HF (%)	-27.0±8.4	-5.7±3.6	0.022
Delta LF/HF (%)	4.51±1.95	-0.14±0.83	0.031

References:

1. Tracey KJ. The inflammatory reflex. Nature. 2002;4206917:853-9.
2. Thanou A, Stavrakis S, Dyer J, Kamp S, Munroe ME, Albert D, James JA, Merrill JT. Heart Rate Variability Is Associated with SLE Flare and with TNF- and IFN-Mediated Signaling. American College of Rheumatology Annual Scientific Meeting. San Francisco, CA. November 7-11, 2015.

Disclosure: A. Thanou, None; **S. Stavrakis**, None; **J. W. Dyer**, None; **S. Kamp**, None; **J. A. James**, None; **J. T. Merrill**, Lilly, Anthera, GSK, UCB, BMS, EMD Serono, Celgene, Biogen, Takeda, Seattle Genetics Abbvie, Questcor, 5,BMS, GSK, Pfizer, 2.

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Abstract Number: 1788

Alterations in Sense of Smell and Limbic Structures in Patients with Systemic Lupus Erythematosus during 3-Years Follow-up

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Background/Purpose: Many neurologic and neurodegenerative abnormalities are first demonstrable in the olfactory system with loss of smell up to 10 years before the onset of cognitive or motor dysfunction. The aim of this follow-up study was to assess the prevalence and progression of olfactory disorder in SLE compared with healthy controls, to correlate with presence of neuropsychiatric manifestations, disease activity, presence of Anti-P and limbic structure volume reduction during 3 years follow-up.

Methods: Consecutive SLE patients were enrolled in this study. The control group was consisted by age and sex matched healthy individuals. Neurological manifestations were analyzed according to the ACR criteria. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity (SLEDAI), and damage (SDI). Anti-P was performed by ELISA. Olfactory functions were evaluated using the Sniffin' Sticks test, in 3 stages (TDI). We measure the

volumes of the amygdala and hippocampus by MRI scans 3T Phillips scanner. Volumes were processed using FreeSurfer® software. Clinical, laboratory evaluation, the volumes of the amygdala (AG) and hippocampus (HC), olfactory functions and Anti-P was performed every year for 3 year for each patients. $p<0.05$ was considered significant.

Results: We included 83 SLE patients (91.5% female; mean age 39.6 years; SD±11.1 years) and 60 healthy volunteers (90.1% female; mean age 38.6 years; SD±13.3 years) ($p>0.05$). Olfactory changes were observed in 44 (53.0%) SLE patients and in 18 (30.0%) controls ($p=0.001$). SLE patients had significantly lower mean in all three phases (TDI) of the olfactory assessment [mean of 29.04 (SD ± 5.13)] when compared with healthy volunteers [mean of 31.35 (SD ± 4.24)] ($p=0.004$) and decrease in the sense of smell was correlated with age ($p=0.002$; $r= -0.331$), anxiety ($p=0.008$; $r= -0.291$), depression ($p= 0.005$; $r= -0.308$) and index damage ($p= 0.018$; $r= -0.268$). We also observed an association between olfactory changes and SDI ($p=0.049$), photosensitivity ($p=0.038$) and leukopenia ($p=0.002$). Not significant decrease of smell was observed in the follow-up ($p>0.05$). Limbic structure volume reduction were not associated with olfactory changes ($p>0.05$).We did not observed significant decrease in the limbic structures volume between patients [median mm^3: AG 3500.61; HC 7831.64] and controls [AG 3350.62 ($p=0.272$); HC 7391.65 ($p=0.234$)]. The decrease of the limbic volumes in patients was not significant in the follow-up [median AG volume mm^3: T_1 3500.61 ($p=0.16$); T_2 3508.94 ($p=0.12$); and T_3 3461.01 ($p=0.19$)] [median HC volume mm^3: T_1 7831.64 ($p=0.32$); T_2 7680.85 ($p=0.23$); and $T_3$7911.19 ($p=0.27$)]. Anti-P were identified exclusively in SLE patients and were present in 14 (10.8%) of them in the first assessment and remained positive in the two following annual assessments ($p<0.001$). Anti-P was associated with decrease left amygdala volume in the second assessment (T_2) ($p=0.016$) and not associated with decrease of smell ($p=0.390$), CNS involvement ($p= 0.713$) or psychosis ($p= 0.076$).

Conclusion: Smell deficiency has been suggested to be an early and predictive sign in several CNS diseases, and therefore, might be a useful and easy tool for the physician in early diagnosis of CNS involvement in autoimmune disease.

Disclosure: F. A. Peres, None; **K. de Oliveira Peliçari**, None; **M. Postal**, None; **N. A. Sinicato**, None; **L. Rittner**, None; **L. T. Costallat**, None; **S. Appenzeller**, None.

Abstract Number: 1789

Herpetic Viruses in Lupus

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Background/Purpose: The risk of Herpes Virus infections, both Varicella Zoster virus (VZV) and Herpes simplex virus (HSV), is not known in Systemic Lupus Erythematosus (SLE). This study was initiated to establish the prevalence of HSV

& VZV infections in hospitalized SLE patients.

Methods: This is a retrospective cohort study evaluating the prevalence of VZV and HSV in SLE patients hospitalized at Columbia University Medical Center-New York Presbyterian Hospital. Data from electronic medical records (EMR) were obtained from the Columbia University Medical Center (CUMC) Clinical Data Warehouse between January 2000 and September 2014. A total of 2,013 hospitalized patients were identified in the Data Warehouse as having SLE using a validated method. Patients were classified as having SLE based on the International Classification of Diseases, Ninth Revision (ICD-9) codes, using 2 or more SLE ICD-9 code (710.0 and/or 695.4) or at least 1 SLE ICD-9 code and a nephritis (582 or 583 and subtypes); this method has a positive predictive value for SLE of 0.88. Herpetic zoster infections were identified using ICD-9 code 053 (and subtypes) on discharge diagnosis. Herpes simplex infections were identified using ICD-9 code 054 (and subtypes) on discharge diagnosis.

Results: Of the 2,013 hospitalized SLE patients; there were 59 cases of varicella zoster and 129 cases of herpes simplex. Of the 59 patients with VZV, 28 had complicated zoster infection. Of these cases, 12 patients had CNS zoster, 6 patients had ophthalmic zoster, and 10 patients had disseminated zoster. There was one death from disseminated zoster. Of the 129 HSV cases, one patient had HSV meningitis, 5 patients had ophthalmic HSV infection, 56 patients with oral and/or genital ulcers, and 67 patients had unspecified HSV infections as a discharge diagnosis. Based on these data the prevalence of varicella zoster in SLE was 2.93% and HSV was 6.41%; with a 9.34% overall prevalence of herpetic infections.

Conclusion: The risk of herpetic infections in SLE is 9.34% in a cohort of hospitalized SLE patients with one death from disseminated zoster. Our data suggest that HSV/VZV is not uncommon in SLE and mortality from complicated VZV is high. SLE patients admitted with a vesicular rash or meningeal symptoms should be evaluated for VZV and have a low threshold for initiating anti-viral treatment. The data is insufficient to substantiate the recommendation for prophylactic use of antiviral treatment in SLE except for high-risk patients with recurrent infections. However, we believe the data presented here further substantiates the need for VZV vaccination in SLE patients.

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Accrual of Disease Comorbidities over 8 Years in a Multicentre Inception SLE Cohort

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Background/Purpose: The annual accrual of comorbidities in patients with SLE is not well described. We report the annual occurrence of these features in an inception cohort of patients with SLE.

Methods: An international research network comprised of 33 centres from 11 countries has followed an inception cohort of SLE patients yearly according to a standardized protocol between 2000 and 2016. Of these, 717 patients followed for a minimum of 8 years constitute the study population. Comorbidities including atherosclerotic vascular events (AVEs), osteoporosis, osteonecrosis and diabetes are assessed using the SLICC/ACR Damage Index (SLICC/DI). AVEs are described and attributed on a specialized form. Diagnosis of an event is confirmed using standard clinical criteria, relevant laboratory data and imaging where appropriate. Attribution to atherosclerosis is made on the basis of lupus disease being inactive at the time of the event, and/or the presence of typical atherosclerosis (AS) changes on imaging or pathology and/or evidence of AS elsewhere. Diagnosis of osteoporosis is based on abnormal bone mineral density and osteonecrosis was based on joint symptoms associated with abnormal imaging consistent with osteonecrosis. Diabetes diagnosis is based on therapy, regardless of treatment type. Descriptive statistics were used.

Results: Of the 717 patients followed for at least 8 years, 90.2% were female, 47.3% were Caucasian, 13.8% were Black, 19.4% were Asian, 16.3% Hispanic and 3.2% other. Their mean age at enrolment was 34.2±13.1 years and SLEDAI-2K at enrolment was 4.17±4.49. The duration from diagnosis to enrolment was 5.9±4.4 months. Table 1. Cumulative SDI, AVEs, Osteoporosis, Osteonecrosis and Diabetes in the first 8 Years of Follow-up (n=717)

Follow-up	SDI (mean±std)	AVE	Osteoporosis	Osteonecrosis	Diabetes
1	0.3±0.7	4 (0.5%)	3 (0.4)	3 (0.4%)	13 (1.8%)
2	0.5±1.0	5 (0.7%)	5 (0.7%)	10 (1.4%)	17 (2.4%)
3	0.6±1.2	10 (1.4%)	7 (1.0%)	15 (2.1%)	17 (2.4%)
4	0.7±1.2	13 (1.8%)	10 (1.4%)	18 (2.5%)	19 (2.7%)
5	0.8±1.3	18 (2.5%)	11 (1.5%)	21 (2.9%)	19 (2.7%)
6	1.0 ±1.4	20 (2.8%)	15 (2.1%)	25 (3.5%)	21 (2.9%)
7	1.0±1.4	21 (2.9%)	17 (2.4%)	27 (3.8%)	22 (3.1%)
8	1.1±1.5	25 (3.5%)	19 (2.7%)	31 (4.3%)	25 (3.5%)

Table 2. Cumulative Comorbidities by Year in Caucasians Compared to All Other Ethnicities

	Follow up years since SLE diagnosis							
Comorbidity	1	2	3	4	5	6	7	8
AVE Caucasian (%)	0.59	0.88	2.06	2.95	3.54	4.13	4.42	5.60
AVE Other (%)	0.53	0.53	0.79	0.79	1.59	1.59	1.59	1.59
Osteoporosis Caucasians (%)	0.00	0.59	1.18	1.77	2.06	3.25	3.55	4.14
Osteoporosis Others (%)	0.79	0.79	0.79	1.06	1.06	1.06	1.32	1.32
Osteonecrosis Caucasians (%)	0.59	1.18	1.18	1.47	1.47	2.07	2.07	2.66
Osteonecrosis Others (%)	0.26	1.59	2.91	3.44	4.23	4.76	5.29	5.82
Diabetes Caucasian (%)	1.77	2.65	2.65	2.95	2.95	2.96	2.96	3.25
Diabetes Other (%)	1.85	2.12	2.12	2.38	2.38	2.91	3.17	3.70

Mean SDI gradually increases over 8 years. The accumulation of AVEs, osteoporosis, osteonecrosis and diabetes all increase progressively over an 8-year period. Caucasians accumulate AVEs and osteoporosis more frequently than all "other" ethnicities. In contrast, all "other" ethnicities accumulate osteonecrosis more frequently than Caucasians. All ethnicities accumulate diabetes at the same frequency.

Conclusion: As expected disease damage and comorbidities in newly diagnosed patients increase over their first 8 years. Different ethnicities accumulate comorbidities at different rates

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Disclosure: M. Urowitz, None; **D. D. Gladman**, None; **N. Anderson**, None; **J. Su**, None.

Abstract Number: 1791

Loss of Elbow Hyperextension in Females with Early Rheumatologic Disease Was Common in Systemic Lupus Erythematosus and Rheumatoid Arthritis but Rare in Fibromyalgia

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Background/Purpose: The elbow extension angle (ELB) is commonly given as 180o although most healthy females exhibit hyperextension(1). The loss of hyperextension (LOH) in a female is the earliest sign of elbow arthritis(2) and can be regarded as evidence of organic disease. Therefore, diseases commonly involving the elbow, such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) might be associated with LOH whilst diseases such as osteoarthritis (OA), which does not alone affect the elbow, or fibromyalgia (FM), a non-organic disorder, would be expected to maintain normal ELB. A trained clinician can estimate the ELB accurately(3). One of us (Case) has been recording the ELB as neutral, hyperextended, or contracted in female patients at the time of 1st rheumatologic contact. To test the hypothesis that ELB may be used as a diagnostic tool in early arthritis we reviewed the scanned electronic medical record at our institution for the period January 1, 2003 – December 31, 2007.

Methods: All outpatient female patients were eligible. The primary rheumatologic diagnosis at the time of last follow-up was used. The ACR disease criteria available during the study period were observed. All study patients with RA and SLE met criteria; FM patients were included if they exhibited diffuse pain with multiple diffuse tender points (not necessarily 11 of 18). The Mann-Whitney U test was used to distinguish disease subgroups, and Spearman's correlation to compare age and duration of disease with LOH. Statistics were done with SPSS.

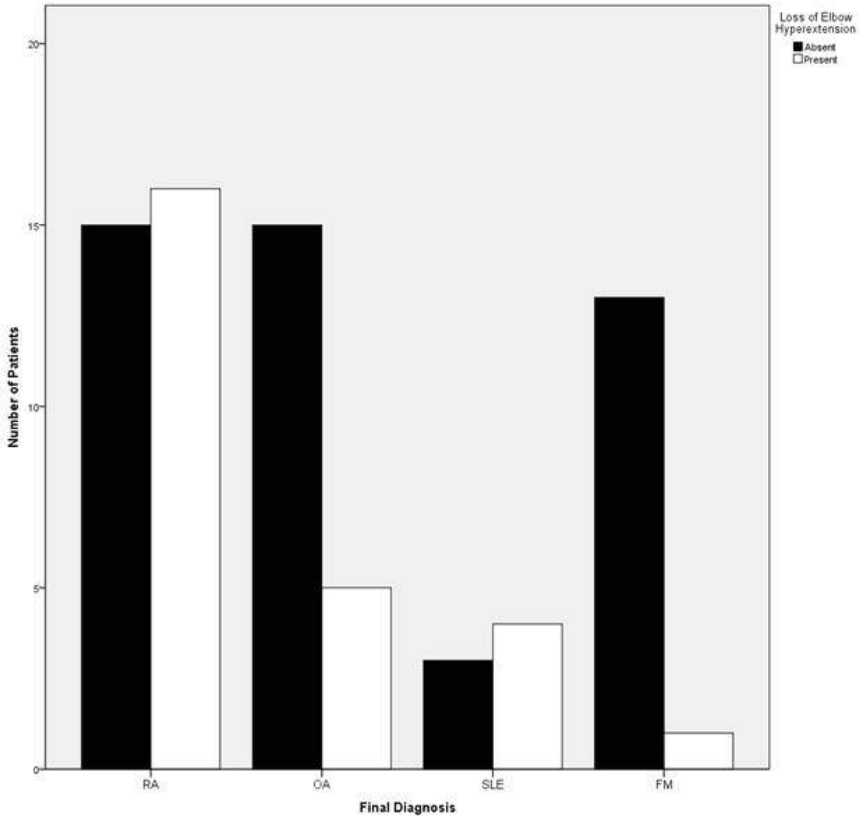
Results: The charts from 717 patients were available. Of these, 396 had the initial ELB recorded (55%). (Most of the remainder had exclusively lower extremity-directed exams; data not shown.) 106 of these had disease onset of less than one year. They had a mean age of 51.0 (SD 14.1) years and were followed for a mean of 2.1 (SD 3.0) years. The final diagnoses were RA in 31 (29.2%), OA in 20 (18.9%), SLE in 7 (6.6%), FM in 14 (13.2%), other in 34 (32.1%). FM could be distinguished from RA ($p=0.005$) and SLE ($p=0.04$) but not from OA ($p=0.062$). RA could not be distinguished from SLE ($p=0.874$). Only one in 14 FM patients evidenced LOH. These findings are expressed in the Figure. Among the 396 patients with disease of any duration, RA could be distinguished from OA ($p<0.0001$) and FM ($p<0.0001$); FM, however, could not be distinguished from SLE ($p=0.316$). An observed LOH in FM was correlated with duration of disease ($p<0.0001$) but not with age ($p=0.280$).

Conclusion: The hypothesis that early LOH was associated with RA and SLE but not with FM was confirmed. Early FM rarely had LOH whereas RA and SLE commonly did. Measurement of the ELB is potentially a new diagnostic sign in the rheumatologic exam. References:

(1) Amis et al, Clinics Rheum Dis (1982) 571-591

(2) Lockie, Arthritis and Allied Conditions (1982) p. 22

(3) Blonna et al, Knee Surg Sports Traumatol Arthrosc (2012) 20:1378-1285



Disclosure: J. P. Case, None; **H. Tucker**, None; **C. Wang**, None.

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Abstract Number: 1792

Cardiac Surgery in Systemic Lupus Erythematosus Patients: Clinical Characteristics and Outcomes

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Background/Purpose: To study the clinical characteristics and outcomes of Systemic Lupus Erythematosus (SLE) patients that underwent cardiac surgery.

Methods: Retrospective analysis of 30 SLE patients (ACR classification criteria), who underwent cardiac surgery at a single center. Demographics, comorbidities, clinical, serologic characteristics, cardiovascular risk scores and treatment were recorded. Type of surgery, postoperative complications, mortality and histology were analyzed. **Statistics:** Differences between groups were evaluated with the Student t test or Mann-Whitney U test (continuous variables); chi-square or FisherÕs exact test (categorical variables). Odds ratios (OR) and 95% confidence intervals are presented.

Results: Disease duration at surgery was 2 years. Valve replacement was the most frequent procedure in 16 (53%), followed by pericardial window in 11 (37%). Indications for pericardial window were cardiac tamponade and recurrent pericarditis. **Tables 1** and **2** summarize characteristics of SLE at cardiac surgery. At least one postoperative complication was present in 63% (mainly infections). An aortic cross-clamp time > 76 minutes was associated with at least one postoperative complication (OR 6.4, 95% CI 1.1-35.4, p=0.03). Main valvular histopathological findings in the patients that underwent valve replacement were: myxoid degeneration (n=5), fibrosis (n=5), Libman-Sacks endocarditis (n=3), endocarditis (n=3). Early death occurred in 5 patients (17%) and late in 3 (10%); main causes were sepsis and heart failure. Patients with active disease were associated with pericardial window (OR 12.6, 95% CI 1.9-79, p=0.007); lymphopenia < 1200 (OR 10.1, 95% CI 1.05-97, p=0.04); age < 30 years (OR 7.7, 95% CI 1.2-46.3, p=0.02), NYHA class III (OR 7.0, 95% CI 1.1-42, p=0.03). Patients with postoperative infections were associated with length of hospital stay > 2 weeks (OR 54.9, 95% CI 5.0-602.1, p=0.001); days in ICU > 10 (OR 20, 95% CI 1.6-171.7, p=0.01); duration of mechanical ventilation > 5 days (OR 16.9, 95% CI 1.6-171.7, p=0.01), pulmonary artery systolic pressure > 50 mmHg (OR 7.8, 95% CI 1.4-41.2, p=0.01).

Conclusion: Cardiac surgery in SLE confers high morbidity and mortality. SLE-specific preoperative risk scores should be designed to identify prognostic factors. **Table 1**

Variable	
Age—years	27 (18-59)
Disease duration—months	48 (0-241)
Prednisone—n (%)	23 (77)
Current dose of prednisone—mg	6.2 (0-240)
Azathioprine—n (%)	13 (43)
Current dose of azathioprine—mg	0 (0-200)
Mycophenolate mofetil—n (%)	2 (7)
Current dose of mycophenolate mofetil—mg	0 (0-2500)
Antimalarials—n (%)	8 (27)
Aspirin—n (%)	3 (10)
Oral anticoagulants—n (%)	4 (13)
SLEDAI-2K score	2 (0-27)
SLICC/ACR Damage Index	2 (0-6)
Anti-dsDNA	22.2 (1.7-2743)
Anti-dsDNA +—n +/n tested (%)	20/23 (87)
Low C3—n (%)	12 (43)
Low C4—n (%)	13 (46)

Table 2

Variable	N (%)
Echocardiographic findings	
LVEF—%[a]	61 (12)
Pulmonary artery systolic pressure—mmHg[a]	42 (23)
Right ventricular dysfunction—n (%)	8 (27)
Valvular vegetations—n (%)	6 (21)
Affected valve—n (%) None Aortic Mitral Aortic+Mitral Aortic+Pulmonary Mitral+Pulmonary Mitral+Tricuspid 4 valves	11 (37) 6 (20) 4 (13) 1 (3) 1 (3) 1 (3) 4 (13) 1 (3)
Valvular insufficiency—n (%) Mild Moderate Severe	7 (24) 8 (28) 8 (28)
Valvular stenosis—n (%) Mild Moderate Severe	1 (3) 2 (7) 6 (21)
NYHA class—n (%) I II III IV	7 (23) 9 (30) 9 (30) 5 (17)
EuroSCORE II—%	2 (0.3-11.2)
Laboratory parameters Hemoglobin—g/dl Leukocytes $x10^3/mm^3$ Neutrophils $x10^3/mm^3$ Lymphocytes $x10^3/mm^3$ Platelets—K/ul Serum creatinine—mg/dl Albumin—g/dl ESR—mm/h CRP—mg/dl	10 (6.6-15.2) 6.6 (2.2-24.4) 4.8 (1.8-21.5) 0.7 (0.1-2.8) 215 (13-657) 0.9 (0.3-8.0) 2.8 (1.6-4.4) 24 (2-67) 2.8 (0.4-6.5)
Type of surgery—n (%) Valve replacement Pericardial window Revascularization Pericardiectomy Auricular thrombectomy	16 (53) 11 (37) 1 (3) 1 (3) 1 (3)
Emergency surgery—n (%)	2 (7)
Urgent surgery—n (%)	18 (60)
Elective surgery—n (%)	10 (33)
Surgical time—hours	3 (1-7)
Extracorporeal circulation time—minutes	97.5 (45-265)
Aortic cross-clamp time—minutes	76 (30-195)
Blood transfusion—units	2 (0-4)
Bleeding—ml	450 (10-2400)
Type of prosthetic heart valve—n (%) Biological Mechanical	1 (6) 15 (94)
Days in ICU	4 (0-96)
Mechanical ventilation—days	1 (0-96)

Hospital stay—days	13 (0-96)

Disclosure: L. Quintanilla-González, None; **J. Tejeda-Maldonado**, None; **J. Galindo-Uribe**, None; **A. Hinojosa-Azaola**, None.

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Abstract Number: 1793

Visceral Adiposity Assessed By DXA in Juvenile-Onset Systemic Lupus Erythematosus: A Correlation with Damage Index and Disease Duration

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Background/Purpose: Young woman with lupus (SLE) are at increased risk of early atherosclerosis leading to cardiovascular disease in adult life and consequently higher morbidity and mortality. Recently, it has been demonstrated that visceral adipose tissue (VAT) is associated with increased incidence of metabolic risk in subclinical atherosclerosis beyond its contribution to overall adiposity. Nowadays, a new application of dual-energy X-ray absorptiometry (DXA) is to measure VAT in the android region of a whole body site with high accuracy and strong correlation with computed tomography (CT) to quantify visceral fat. Thus, the objective of this study was assess alterations of visceral adipose tissue (VAT) measured by DXA in juvenile female SLE (JoSLE) patients compared with age-matched healthy controls and evaluate its correlation with disease parameters and treatment.

Methods: Fifty-six JoSLE female patients were evaluated and compared with age-matched female healthy controls. Demographic and anthropometric, disease duration, disease activity score (SLEDAI), cumulative organ damage (SLICC-DI/ACR), glucocorticoid (GC) use and hydroxychloroquine use were recorded by interview and eletronic chart review. Visceral adipose tissue (VAT) was analyzed by dual-energy X-ray absortiometry (DXA, Hologic - using a specific software - APEX 4.0).

Results: SLE patients had mean disease duration of 5.71 ± 3.98 years, mean current prednisone dose of 15.99 ± 18.62 mg/day and cumulative glucocorticoid dose of 6.79 ± 7.13 g, mean SLEDAI of 4.60 ± 5.54 in the last year and eleven (19.6%) patients had SLICC-DI/ACR higher than one. SLE patients and controls were similar regarding age (18.4 ± 3.2 vs. 18.6 ± 3.8 yrs, p=0.808), weight (57.4 ± 10.8 vs. 56.8 ± 9.3 kg, p=0.752), BMI (23.1 ± 3.6 vs. 22.3 ± 3.2 kg/m², p=0.205) and lean mass (36.19 ± 6.60 vs. 36.81 ± 4.24 kg, p=0.420). JoSLE patients presented higher levels of fat mass compared to healthy controls (19.26 ± 6.60 vs. 17.86 ± 6.22 kg, p=0.017), as well as % fat (32.93 ± 6.35 vs. 30.82 ± 5.72 %, p=0.004). Furthermore, SLE patients had higher values of VAT parameters than controls, namely VAT mass (280.55 ± 132.42 vs. 199.60 ± 98.67 g, p<0.001), VAT area (58.19 ± 27.47 vs. 41.41 ± 20.50 cm², p<0.001) and VAT volume (303.36 ± 143.19 vs. 215.78 ± 106.66 cm^3, p<0.001). In SLE patients, VAT volume correlated with disease duration (r=0.313; p=0.019) and SLICC-DI/ACR (r=0.300; p=0.025) but not with SLEDAI (p=0.907), current use of GC (p=0.449), cumulative use of GC

(p=0.346) or hydroxychloroquine use (p=0.385).

Conclusion: JoSLE patients showed higher levels of VAT parameters compared to healthy controls. Its correlation with higher cumulative organ damage index and disease duration could suggest that VAT can be useful to evaluate cardiovascular risk in this group of patients.

Disclosure: J. Paupitz, None; **G. Lima**, None; **N. E. Aikawa**, None; **L. Takayama**, None; **L. Seguro**, None; **E. Bonfa**, None; **R. M. R. Pereira**, None.

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Abstract Number: 1794

The High Disease Activity State Is an Adverse Prognostic Indicator in SLE and Defines a Clinically Distinct Population

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Background/Purpose: The heterogeneity of SLE in terms of disease characteristics is an issue not only for the diagnostic process but also for disease management. Previously, a SLEDAI score ≥10, herein termed the High Disease Activity State (HDAS), has been shown to predict treatment response to belimumab. Whether HDAS could provide other prognostic information on outcomes is less well understood.

Methods: Using data collected prospectively between 2007 and 2015 from 211 SLE patients, who fulfilled either ACR (97.2%) or only SLICC (2.8%) classification criteria and were seen at a tertiary SLE clinic for ≥1 year, we examined the association of sociodemographic and disease characteristics with ever experiencing HDAS during the observed period. We also investigated the association of ever experiencing HDAS with longitudinal SLE outcomes, including adjusted mean SLEDAI (AMS), flare incidence according to SLE Flare Index, and damage accrual according to the SLICC/ACR Damage Index for SLE. For multivariable analyses of longitudinal outcomes, associations were adjusted for observation time, and the association with AMS was also adjusted for cumulative prednisolone dose.

Results: Patients were observed for a median of 4.5 years (range: 1 – 7.9 years); 42.7% experienced HDAS at least once during the observation period. Among those who experienced HDAS, 31.1% experienced a single episode of HDAS, 33.3% experienced 2 – 3 episodes and the remainder experienced between 4 – 30 episodes of HDAS. The median time to first HDAS was 9 months after enrolment (range 0 – 6.7 years). Females patients diagnosed at ≥45 years had substantially lower odds of ever experiencing HDAS (Odds Ratio, OR: 0.3, 95% Confidence Interval, 95% CI: 0.1 – 0.5; p=0.003). When compared to patients never experiencing HDAS, patients experiencing at least 1 episode of HDAS were more likely to have anti-dsDNA autoantibodies (OR: 5.6, 95%CI: 2.8 – 11.3; p<0.001), have a positive direct antiglobulin test (OR: 2.7, 95%CI: 1.3 – 5.3; p = 0.006) or present with hypocomplementemia (OR: 2.3, 95% CI: 1.3 – 4.0; p=0.005). Patients who experienced at least one episode of HDAS had significantly greater odds of having AMS in the highest quartile (AMS ≥4.3: OR: 10.8, 95%CI: 4.3 - 27.2; p<0.001). Similarly, they were also more likely to experience a greater number of mild/moderate and severe flares during the observation period (number of mild/moderate flares ≥5: OR: 8.0, 95% CI: 3.1 –

21.1; p<0.001; number of severe flares ≥3: OR: 16.7, 95%CI: 4.8 - 57.6; p<0.001). HDAS was associated with substantially greater odds of experiencing neuropsychiatric, renal and vasculitis disease activity (OR>10, p≤0.001 for all) and of accruing new damage (OR: 2.6, 95% CI: 1.4 - 4.7; p=0.002) during the observation period.

Conclusion: Patients who ever experience HDAS represent a distinct clinical cohort with worse longitudinal disease outcomes. The occurrence of HDAS can serve as a prognostic indicator applicable to a heterogeneous lupus population.

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Abstract Number: 1795

Four Years Follow-up of Subclinical Atherosclerosis in Systemic Lupus Erythematosus Patients

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Background/Purpose: Systemic lupus erythematosus (SLE) patients have increased risk of advanced atherosclerosis and cardiovascular disease. The mechanism of premature atherosclerosis in SLE is not completely understood, and systemic inflammation representing disease activity and traditional risk factors such as overweight and dyslipidemia have been regarded to contribute. Many SLE patients have low disease activity or sporadic occurrence of mild symptoms after a period of vigorous manifestations derived from autoimmune activation. It has not been evaluated whether SLE patients with mild activity have a risk of atherosclerosis progression, while it's a common situation which many SLE patients are undergoing. Previously we evaluated subclinical atherosclerosis of SLE patients with mild disease activity by Doppler ultrasound 4 years ago. This time we checked them again and assessed which features affects their changes.

Methods: We assessed carotid artery intima-media thickness (cIMT) and carotid plaque by Doppler ultrasonography among sixty-one female SLE patients who were enrolled in the previous work 4 years ago, and analyzed the changes with clinical characteristics.

Results: The SLE disease activity index of the participants was 4.2 ± 3.9, and $25(OH)D_3$ level was elevated than previous study (25.7 ± 6.9 vs 12.7 ± 8.6 ng/mL, $p < 0.001$), while other features were similar. The mean cIMT of SLE patients was 0.39 ± 0.09 mm and 11 patients had carotid plaques, which were not significantly different with previous study. Twenty one patients had the increased cIMT, while 35 patients had decreased cIMT. And new carotid plaque was developed in 7 SLE patients, while the carotid plaque of 10 SLE patients was resolved. The patients with increased cIMT had lower body mass index (BMI) (19.8 ± 1.8 vs 21.7 ± 3.1 kg/m^2, $p = 0.007$), longer disease duration (102.0 ± 42.2 vs 74.8 ± 55.2 months, $p = 0.006$) and higher total steroid dose (18.5 ± 21.6 vs 10.5 ± 22.9 g, $p < 0.001$) compared with those not. The patients having new carotid plaque had lower high-density lipoprotein (HDL) cholesterol levels (41.6 ± 10.2 vs 55.6 ± 15.5 mg/dL, $p = 0.024$) and were taking higher doses of current steroid (8.9 ± 9.5 vs 3.6 ± 4.5mg, $p = 0.008$). On multiple regression analysis, BMI (0.62 [0.42 – 0.91], $p = 0.01$) and HDL cholesterol (0.94 [0.89 – 1.0], $p = 0.02$) were revealed to affect

cIMT increment, and current steroid dose (1.14 [1.01 – 1.28], p = 0.04) were revealed to affect plaque development.

Conclusion: BMI have been known to affect atherosclerosis and vitamin D deficiency has been known to associate with cardiovascular disease. In contrast of other studies, our data showed BMI contributed negatively cIMT increment. The result about BMI was regarded that very low BMI might have a harmful effect to atherosclerosis, considered that mean BMI was much lower (21.0 ± 2.8 kg/m^2) than other studies.[4] The follow up study for SLE patients with low disease activity showed low BMI and HDL cholesterol might be a risk factor for subclinical atherosclerosis and current steroid dose could be associated with plaque development.

Disclosure: J. Y. Jung, None; **H. A. Kim**, None; **C. H. Suh**, None.

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Abstract Number: 1796

Osteoporosis and Vertebral Fractures in Patients with Systemic Lupus Erythematosus: A Systematic Review and Meta-Analysis

Mario García-Carrasco[1,2], Pamela Soto-Santillan[3], Samanda Adriana Rojas villarraga[4], Nicolás Molano-González[5] and **Claudia Mendoza Pinto**[6], [1]Systemic Autoimmune Diseases Research Unit, HGR 36-CIBIOR Instituto Mexicano del Seguro Social, Puebla, Mexico, [2]Inmunología y Reumatología, Universidad Autónoma de Puebla, Puebla, Mexico, [3]Internal Medicine, Systemic Autoimmune Diseases Research Unit, IMSS, Puebla, México, Puebla, Mexico, [4]Novartis de Colombia, Bogota, Colombia, [5]Center for Autoimmune Diseases Research (CREA). School of Medicine and Health Sciences, Universidad del Rosario, Bogotá, Colombia., Bogota, Colombia, [6]Systemic Autoimmune Diseases Research Unit, HGR 36-CIBIOR, IMSS, Puebla, Mexico

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Background/Purpose: Observational studies have indicated a high but heterogeneous prevalence of low bone mineral density (BMD) and vertebral fractures (FV) in patients with systemic lupus erythematosus (SLE). The aim of this meta-analysis was to evaluate the relationship of SLE and BMD, osteoporosis and vertebral fracture risk.

Methods: A systematic review and meta-regression analysis were performed following the Preferred Reporting Items for Systematic Meta- Analyses (PRISMA) guidelines. Articles were identified from electronic databases (PubMed, Embase, VHL, SciELO and the Cochrane Library). The search was conducted using MesH terms, Boolean operators and keywords, which included "systemic lupus erythematosus", "osteoporosis", "bone mineral density" and "vertebral fractures". Prospective longitudinal and cross-sectional studies were considered for review without language restrictions. Articles were screened for suitability and those selected were evaluated by two investigators who extracted information on study characteristics, outcomes of interest, risk of bias and summarized strength of evidence. Data was extracted where studies met inclusion criteria and were of sufficient quality. BMD reported as the mean ± standard deviation evaluated by dual-energy X-ray absorptiometry (DXA) was analyzed including information of SLE cases and controls, treatment, menopausal status and fractures through a meta-regression analysis adjusted by anatomical region. Data were analyzed using the Metafor package in R (3.0.2 version).

Results: In total 54 articles were identified and analyzed (12593 SLE cases/six anatomical regions and 14235 controls/six

anatomical regions). SLE women had less BMD than healthy controls (p< 0,0001), however, in SLE men this difference was absent when they were compared to controls. When only SLE patients were analyzed, the BMD measurements were not statistically different between those with a background of corticosteroid (CTS) therapy and those without CTS therapy. Not surprisingly, postmenopausal SLE patients had lower BMD (lumbar spine and total hip) compared to premenopausal patients (p< 0,0001). The BMD was not different between patients with and without fractures.

Conclusion: This systematic review and meta-regression depicts that women with SLE had higher risk of low BMD than healthy controls. These data did not show that CTS therapy had an impact on BMD.

Disclosure: M. García-Carrasco, None; **P. Soto-Santillan**, None; **S. A. Rojas villarraga**, None; **N. Molano-González**, None; **C. Mendoza Pinto**, None.

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Abstract Number: 1797

Seasonal Differences in the Disease Onset and the Exacerbation of Systemic Lupus Erythematosus

Takehisa Ogura[1], Ayako Hirata[1], Sayaka Takenaka[2], Hideki Ito[2], Yuki Fujisawa[1], Norihide Hayashi[2], Rie Kujime[1], Munetugu Imamura[2], Kennosuke Mizushina[1], Takaharu Katagiri[2] and Hideto Kameda[1], [1]Department of Rheumatology, Toho University Ohashi Medical Center, Tokyo, Japan, [2]Toho University Ohashi Medical Center, Tokyo, Japan

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Background/Purpose: It has been well acknowledged that both genetic and environmental factors are important in the pathogenesis of systemic lupus erythematosus (SLE). To elucidate the environmental factors associated with SLE pathogenesis, we investigated the seasonal differences in the disease onset and the exacerbation of SLE.

Methods: In the present study, we retrospectively reviewed the medical records of 122 patients with SLE (88.5% female and the average age of 43 years) fulfilling the 1997 revised ACR classification criteria. The mean observation period was 7.2 years. The disease exacerbation was defined as either a new appearance of clinical manifestations of SLE or the clinical condition requiring the start or dose increment of glucocorticoids by at least 50%.

Results: The disease onset was the most frequently observed in Spring (31.0%) and the least in Fall (16.1%). A total of 167 disease exacerbations were observed among 879 patient-years, and more interestingly, the disease exacerbation was significantly more frequently observed in Spring (38.3%) and significantly less frequently observed in Fall (10.8%) as compared with other seasons. It should be noted that the both disease onset (0.0%) and exacerbation (2.4%) of SLE were the least in September. Disease manifestation at the exacerbation was similar throughout the seasons, and 60.0% of the disease exacerbation did not accompany serological activity defined by the increase in anti-DNA antibody or the decrease in complement activity.

Conclusion: Concordant seasonal differences between the disease onset and the exacerbation implicated the crucial role of environmental factors in the pathogenesis of SLE, possibly through the activation of innate immune systems.

Disclosure: T. Ogura, None; **A. Hirata**, None; **S. Takenaka**, None; **H. Ito**, None; **Y. Fujisawa**, None; **N. Hayashi**, None; **R. Kujime**, None; **M. Imamura**, None; **K. Mizushina**, None; **T. Katagiri**, None; **H. Kameda**, None.

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Abstract Number: 1798

Risk Factors for Osteonecrosis in Systemic Lupus Erythematosus: A Systematic Review

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster II: Damage Accrual and Quality of Life

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Non-traumatic osteonecrosis (ON) is a well-recognized complication in systemic lupus erythematosus (SLE). The reported symptomatic ON prevalence is 10-15% and as high as 44% when including asymptomatic lesions. ON causes disability and affects quality of life (QoL). Bones collapse from ON has serious clinical implications and may lead to severe joint damage requiring total joint arthroplasty (TJA). The aim of this study was to identify specific risk factors for ON in SLE patients, in order to better guide monitoring of this debilitating complication.

Methods:

A systematic review was conducted using MEDLINE, PUBMED and EMBASE, searching to February 2015 using the MeSH terms “Osteonecrosis”, “Systemic lupus erythematosus” and synonymous text words. Randomized controlled trials (RCT), case control, cohort and cross sectional studies reporting at least one risk factor for ON were included. Risk factors for ON in SLE patients were compiled. The quality of evidence of each risk factor was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method. The quality of each study was assessed using the Newcastle-Ottawa scale (NOS).

Results:

Of the 536 references yielded, 28 met inclusion criteria. In the literature, the major risk factor associated with ON remains

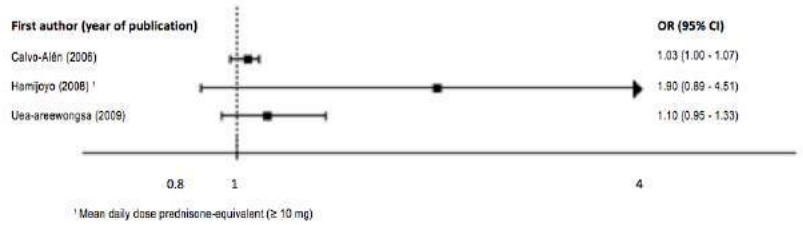
the use of corticosteroids (CS). ON is much more prevalent in SLE than in other systemic conditions requiring the use of CS, suggesting that the use of CS is not the only factor. Multiple other clinical variables were evaluated in studies, including disease activity, arthritis, neuropsychiatric SLE, Raynaud's phenomenon, vasculitis, serositis, gastrointestinal involvement, hypertension, oral ulcers, renal disease, alopecia, antiphospholipid antibodies, antimalarials and immunosuppressive agents. However, for those other risk factors, the research evidence was weak and the association between these variables and the development of ON was controversial (see forest plots).

Conclusion:

Based on the best evidence available, CS use is the only modifiable risk factor clearly associated with ON in SLE patients. Physicians should maintain a high index of suspicion for ON in SLE patients, especially with any history of CS exposure. We suggest adopting a preventive strategy with a judicious use of CS.

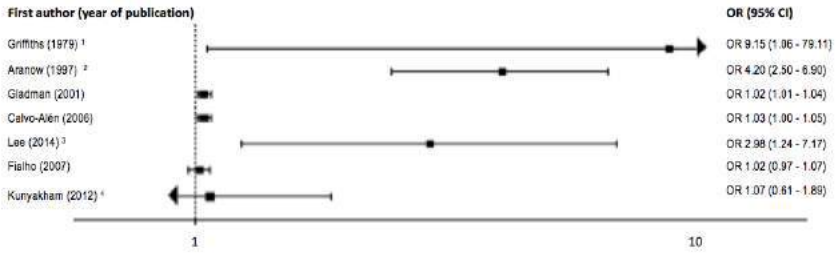
A. Corticosteroids

Mean daily dose of CS



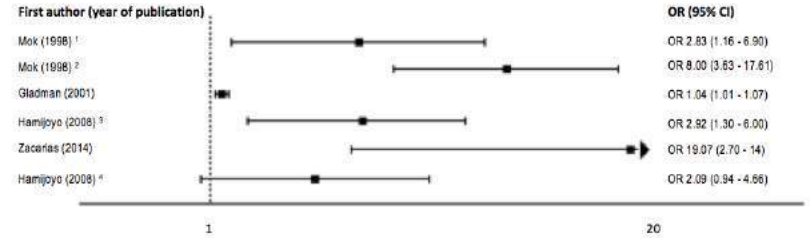
[1] Mean daily dose prednisone-equivalent (≥ 10 mg)

Highest dose of CS



[1] Prednisolone >10 mg/day
[2] Dose over the preceding 5 years of at least 30mg/day
[3] High-dose steroid therapy:>30 mg, but<100 mg of prednisone equivalent per day
[4] High-dose steroid therapy was defined as a steroid dosage equivalent to prednisolone > 30 mg/day at any time during follow-up

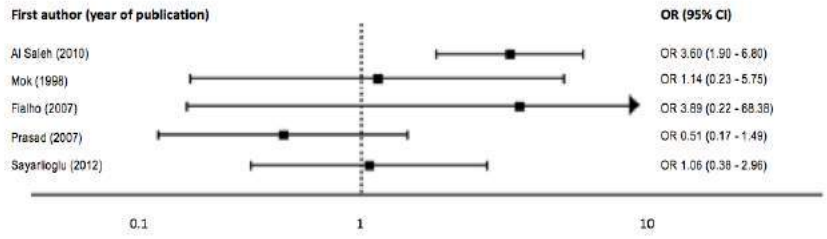
Total cumulative CS dose



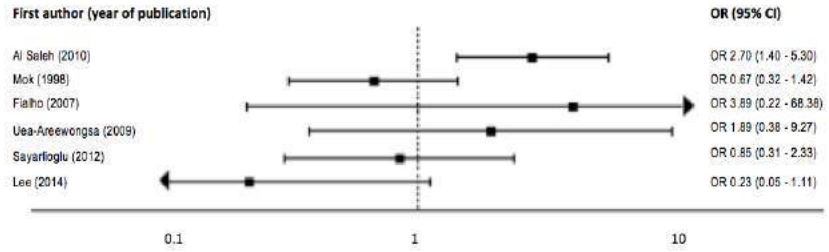
[1]Total cumulative prednisone dose in 1 month > 1.8g
[2]Total cumulative prednisone dose in 4 months > 4g
[3] Mean total cumulative prednisone-equivalent dose ≥ 23.4 g
[4] Mean cumulative prednisone-equivalent dose in first month ≥ 1.37 g

B. Antiphospholipid antibodies

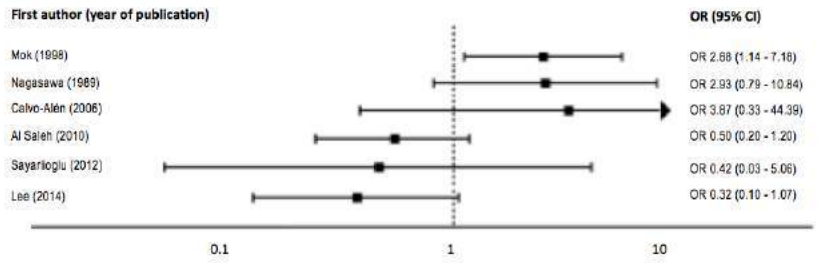
Anti-cardiolipin antibodies IgM



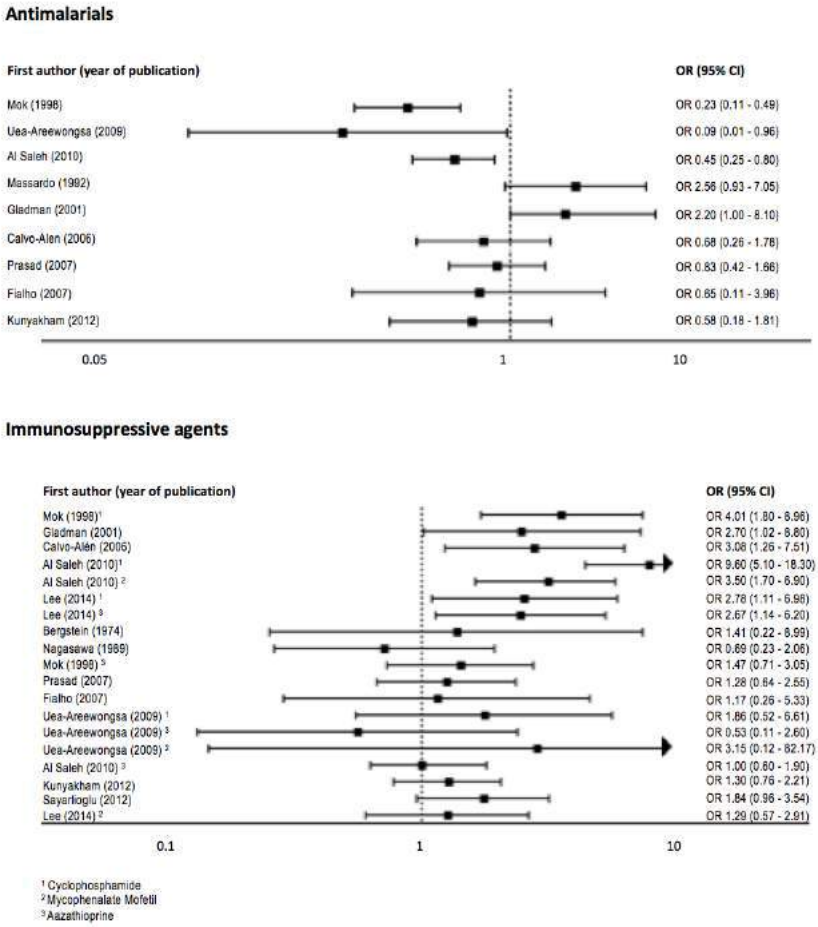
Anti-cardiolipin antibodies IgG



Lupus anticoagulant



C. Medication



Disclosure: S. Hussein, None; **M. Suitner**, None; **A. Baril-Dionne**, None; **M. L. Popescu**, None; **N. Santesso**, None; **S. O. Keeling**, None; **J. E. Pope**, None; **A. Fifi-Mah**, None; **J. Bourré-Tessier**, None.

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Abstract Number: 1799

Smoking, Antiphospholipid Antibodies and Thrombosis in SLE

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Background/Purpose: Smoking is a risk factor for systemic lupus erythematosus and in particular for discoid lupus. A recent study, suggested that history of smoking was associated with antiphospholipid antibodies. We investigated the association between smoking and antiphospholipid antibodies in systemic lupus erythematosus as well as the relationship between smoking, antiphospholipid antibodies, and vascular events.

Methods: 2406 patients in a prospective SLE cohort had smoking assessed at baseline (ever, current, never). The lupus anticoagulant was assessed by dRVVT with mixing studies and confirmatory tests. Anticardiolipin and anti-beta2 glycoprotein 1 were measured by ELISA (INOVA). Vascular events were defined as stroke, myocardial infarction, digital gangrene, and deep vein thrombosis.

Results: Table 1 shows the frequency of each antiphospholipid antibody by smoking status. Table 2 shows the association of smoking with thrombotic events among patients with antiphospholipid antibodies. Unadjusted p-values and p-values adjusted for ethnicity are given. Table 1: Association between Smoking and Antiphospholipid Antibodies

	LAC (RVVT)	Anticardiolipin	Anti-beta2 glycoprotein
Ever smoking	245 (28.7%)	411 (48.1%)	149 (30%)
Past smoking	145 (29.3%)	246 (49.8%)	103 (32.4%)
Current smoking	97 (27.6%)	165 (46.6%)	46 (26.3%)
Never smoking	373 (25.3%)	721 (48.9%)	271 (28.6%)
P Value (Ever vs. Never)	0.0734	0.6943	0.5635
P Value (Past vs. Never)	0.0802	0.734	0.1986
P Value (Current vs. Never)	0.3818	0.4361	0.5346
adj. P Value (Ever vs. Never)	0.0933	0.6434	0.6169
adj. P Value (Past vs. Never)	0.1146	0.8189	0.2484
adj. P Value (Current vs. Never)	0.3893	0.4017	0.5779

Table 2: Association between smoking and thrombosis in SLE patients with antiphospholipid antibodies

	Stroke	Myocardial Infarction	Digital Gangrene	DVT
Ever smoking	29 (3.3%)	60 (6.8%)	19 (2.2%)	121 (13.7%)
Past smoking	19 (3.8%)	34 (6.7%)	13 (2.6%)	72 (14.2%)
Current smoking	10 (2.8%)	26 (7.1%)	6 (1.6%)	47 (12.8%)
Never smoking	55 (3.7%)	49 (3.2%)	26 (1.7%)	200 (13.2%)
P Value (Ever vs.Never)	0.6901	0.0001	0.4359	0.6891
P Value (Past vs.Never)	0.9033	0.0008	0.2288	0.5611
P Value (Current vs.Never)	0.4239	0.0009	0.9246	0.8721
adj. P Value (Ever vs.Never)	0.5787	0.0001	0.5037	0.8909
adj. P Value (Past vs.Never)	0.9203	0.0010	0.2349	0.6928
adj. P Value (Current vs.Never)	0.3944	0.0012	0.8303	0.6906

Conclusion: There was no statistically significant association between past or current smoking and antiphospholipid

antibodies in our lupus cohort. Current smokers had a slightly lower frequency of lupus anticoagulant and anti-beta2 glycoprotein 1 than past smokers. Among SLE patients with antiphospholipid antibodies, smoking was associated with myocardial infarction ($p<0.01$), but not with stroke, digital gangrene or venous thrombosis.

Disclosure: M. Petri, None; **G. Stojan**, None; **W. Fu**, None.

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Abstract Number: 1800

Prevalence of ECG Cardiovascular Abnormalities in Lupus Patients: A Novel Approach Using 5 ECG Elements

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Background/Purpose: Lupus patients are at increased risk for cardiovascular disease (CVD). Chou et al. (Ann Inter Med 2011) found that resting ECG abnormalities, in particular ECG 4-elements (ECG-4), were associated with subsequent CVD events in the general population.

ECG-4 included the following elements: **1)** ST-segment and/or T-wave abnormalities; **2)** left ventricular hypertrophy (LVH); **3)** left axis deviation (LAD) and left anterior fascicular block (LAFB); and **4)** left bundle branch block (LBBB) and right bundle branch block (RBBB). However, ECG-4 did not include Q-wave and we have established **ECG-5** elements which included Q-wave in addition to the elements of ECG-4.

We aimed to determine the prevalence of ECG-4 and ECG-5 in an SLE cohort and to examine the factors associated with ECG-4 and -5.

Methods: A standard digitally recorded 12-lead resting supine ECG was performed on consecutive patients attending the Lupus Clinic between 2012- 2015. A senior cardiologist interpreted coded ECGs using the Minnesota code classification system. Patients with ECG-4 and -5 were compared to those with normal ECG by t-test and chi-squared test Univariate and multivariate Cox regression models and time-dependent multivariate cox regression models were built to assess the associations between the covariates and ECG-4 and -5.

Descriptive analyses of patients' demographics, disease activity and damage, and antibodies abnormalities were studied in ECG-4 and -5. For the analysis we used the clinical/laboratory data available at the date of ECG.

Results: Of 487 patients, 104 (21.4%) and 118 (24.2%) patients had one or more of the ECG-4 and ECG-5 elements respectively**.** A higher prevalence ECG-4 and -5 was identified among older SLE patients and patients with longer SLE disease duration (Table1). The burden of ECG-4 and ECG-5 elements increased with age. In the univariate analyses, patients with ECG-4 and -5 were older, had a longer lupus disease duration, more active SLE disease (Adjusted Mean SLEDAI-2K 2 years prior to ECG), higher SDI and higher cumulative dose of glucocorticoids compared to patients with normal ECG. The multivariate analyses showed that ECG-4 and -5 were associated with older age and higher SLE disease

activity while treatment of hyperlipidemia was protective (Table 2).

Conclusion: We described a novel approach using 5 ECG elements to identify SLE patients at increased risk for CVD events. A high prevalence of ECG-5 (24.2%) was found in this SLE cohort. Controlling SLE disease activity is important since it was associated with ECG-5. Early identification of ECG-5 in SLE patients might allow for better stratification and risk management.

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Table 1. Demographic and clinical characteristics of SLE patients with normal ECG, ECG-4 and ECG-5 at first visit

Variables		ECG Normal n=314	ECG-4 n=104	P	ECG-5 n=118	P
Sex	F	286 (91.1%)	92(88.5)	0.43	104 (88.1%)	0.357
	M	28 (8.9%)	12 (11.5%)		14 (11.9%)	
Ethnicities	Caucasian	181 (58.2%)	59 (57.8%)	0.09	69 (59.5%)	0.146
	Black	51 (16.4%)	26 (25.5%)		27 (23.3%)	
	Asian	38 (12.2%)	10 (9.8%)		12 (10.3%)	
	Others	41 (13.2%)	7 (6.4)		8 (6.9%)	
Age at SLE diagnosis	Mean ± SD	29.6 ± 11.3	30.66±11.01	0.42	30.46 ± 11.86	0.50
Age at ECG	Mean ± SD	44.87± 12.9	50.14±14.1	<0.001	49.95± 15.01	<0.001
Disease duration at ECG	Mean ± SD	15.23± 10.2	19.48±11.03	<0.001	19.49± 11.44	<0.001
Follow up duration at ECG	Mean ± SD	10.57 ± 9.4	13.69±11.29	0.006	13.41± 11.24	0.008
SLEDAI-2K at the first visit	Mean ± SD	9.24 ± 8.3	10.2±7.78	0.30	9.82± 7.67	0.52
SDI	Mean ± SD	0.27 ± 0.7	0.44±0.92	0.07	0.44± 0.90	0.06
Cumulative prednisone (gm)	Mean ± SD	5.24± 16.5	9.16±31.25	0.10	8.96± 29.85	0.10
Treated with antimalarial		147 (46.8%)	51 (49.0%)	0.69	59 (50.0%)	0.55
Treated with immunosuppressive		93 (29.6%)	33 (31.7%)	0.68	37 (31.4%)	0.73
Hypertension		153 (48.7%)	65 (62.5%)	0.015	74 (63.6%)	0.006
Hyperlipidemia on statin ever before ECG		87 (27.7%)	40 (38.5%)	0.039	44(37.3%)	0.05
DM 3 years prior to ECG		16 (5.1%)	4 (3.8%)	0.60	4 (3.4%)	0.45
Smoking ever prior to ECG		91 (29%)	30 (28.8%)	0.97	34 (28.8%)	0.91

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Table 2. Multivariate Cox Regression analysis for ECG-4-and ECG-5

Variables	ECG-4		ECG-5	
	HR (95% CI)	P	HR (95% CI)	P
Age at each visit	1.05 (1.01-1.07)	0.002	1.04 (1.007-1.06)	0.01
AMS (2 years prior to ECG)	1.08 (1.02-1.16)	0.009	1.07 (1.002-1.14)	0.04
SDI	1.29 (1.10-1.53)	0.002	1.28 (1.08-1.51)	0.004
Hyperlipidemia on statin ever before ECG	0.44 (0.21-0.89)	0.02	0.44 (0.22-0.87)	0.02
Hypertension	0.66 (0.34-1.26)	0.21	0.75 (0.4-1.39)	0.36
Ever smoked before ECG	1.13 (0.59-2.16)	0.71	1.09 (0.58-2.06)	0.77
Immunosuppressive treatment at each visit	1.88 (1.01-3.51)	0.05	1.67 (0.93-3.04)	0.09
Antimalarial treatment at each visit	1.76 (0.87-3.58)	0.12	1.81 (0.92-3.56)	0.12

AMS Adjusted Mean SLEDAI-2
HR Hazard ratio

Disclosure: H. Al Rayes, None; **P. Harvey**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **A. Sabapathy**, None; **M. Urowitz**, None; **Z. Touma**, None.

Abstract Number: 1801

Clinical Implications of Persistent Sinus Tachycardia in Systemic Lupus Erythematous: A Retrospective Study

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Background/Purpose: Resting Sinus Tachycardia (ST) is found in approximately 50 % of patients with SLE. Unexplained episodes of intermittent ST could be a manifestation of disease activity. Approximately 13-15 % of patients, however, continue to have unexplained ST that persists beyond the duration of disease flare. The significance of this finding is still under investigation, but may be associated with physical deconditioning, higher SLEDAI scores or occult serositis. We conducted a retrospective study to further elucidate its clinical significance.

Methods: SLE was defined as patients fulfilling SLICC 2012 criteria. Persistent ST was defined as unexplained resting heart rate > 90 bpm in > 50 % of all outpatient visits; a minimum of 8 outpatient visits were required such that transient episodes of tachycardia were excluded. Also excluded were tachycardia episodes with potential explanation e.g. acute illness, severe pain, fever, acute anemia, hyperthyroidism, pregnancy and history of cardiac arrhythmias. A retrospective chart review was performed in patients with a diagnosis of SLE between January 2000 and December 2015. Patients meeting SLICC 2012 criteria and > 8 outpatient visits were dichotomized into groups with or without persistent ST. Multiple variables were compared: demographics; individual components of SLICC 2012 criteria at the first and the latest follow-up; laboratory tests including ENA, APL, ESR/CRP, anemia and nephritis class; pulmonary, cardiac and renal components of SLICC damage index; comorbidities including APS, hypertension, hyperlipidemia and history of deep vein thrombosis; and, hydroxychloroquine, angiotensin converting enzyme inhibitor and beta blocker use. Fisher's exact test was used and two sided p value < 0.05 considered significant.

Results: Charts of 375 patients were reviewed. 106 met inclusion criteria. 17 (16%) had persistent ST. At the time of statistical analysis, complete data was available in 16 patients with persistent ST and 61 patients without. The mean duration of follow up was 6.4 and 7.3 years respectively. Persistent ST was found to be associated with the following in univariate analysis: serositis at presentation (44% vs 14% P 0.017), proteinuria > 500 mg/24 hour at the latest follow up (63% vs 33% P 0.044) and anti-histone antibodies (75% vs 42% P 0.026). Quantitative analysis of maximal proteinuria revealed an association of persistent ST with any proteinuria > 500 mg/24 hr (63% vs 31% P 0.02) as well as nephrotic proteinuria > 3 gm/24 hr (44% vs 18% P 0.045). In addition, class 5 nephritis was more common (25% vs 5% P 0.031) in this group. Other variables trending towards significance include: active urinary sediment/> 5 RBCs/hpf at latest follow up (50% vs 23% P 0.059), anti-DNA antibodies (75% vs 46% P 0.0504) and APS (25% vs 8% P 0.08).

Conclusion: Unexplained persistent ST could be a meaningful clinical sign in SLE. Early in natural history, this may imply the presence of incipient serositis while later on, of an ongoing proteinuric renal disease. A novel finding of high prevalence of anti-histone antibodies in this subgroup needs further scrutiny to discern its significance.

Disclosure: S. Bhusal, None; **B. Alhaddad**, None; **D. Einstadter**, None; **S. Ballou**, None.

Abstract Number: 1802

Prevalence of CMV in the Ohio State University Lupus Population

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Background/Purpose: Systemic Lupus Erythematous (SLE) is a clinically variable autoimmune disease occurring predominantly in women of childbearing age. SLE treatment can range from close clinical monitoring to potent systemic immunosuppressive therapy. CMV is a common, endemic virus endemic that half of the United States population has been exposed to. Patients on immunosuppressive medications are at higher risk for complications from CMV, and published case reports describe significant morbidity and mortality SLE patients with active CMV infections.. Despite the potential for increased risk of CMV infection while immunosuppressed, no studies to date have examined CMV seropositivity and positive viral load prevalence in SLE patients and it is not the standard of care to test for CMV. Robust exist data from the transplant population, a group exposed to similar immunosuppression but not in SLE.

Methods: We recruited participants from The Ohio State University's Lupus Clinic who were. >18 years with confirmed SLE diagnosis. We collected demographic information, laboratory data, SLE history, current medications, and serum CMV immunoglobulin G (IgG) antibody titer. If CMV IgG antibody titer was positive, a CMV polymerase chain reaction (PCR) viral load was measured.

Results: Baseline characteristics of the 75 SLE patients are summarized in **Table 1**. Of the enrolled subjects, 66% had a positive CMV IgG titer, but the viral CMV load has been undetectable for all tested participants (**Table 2)**.

Conclusion: Among the 75 SLE patients tested, CMV IgG seropositivity is 66%, which is comparable to the general population. Among the SLE patients with positive CMV IgG antibodies, none had evidence of active CMV infection by CMV viral load, including patients on immunosuppressive medications. These results differ greatly from the similarly immunosuppressed post-transplant population where 20-60% of patients have acquired acute CMV infections defined by positive viral load. These results suggest that CMV status does not need to be routinely checked in the SLE population unless specifically clinically indicated. **Table 1: Participant Characteristics**

	% (n)or Mean (n)
Age, mean (no.)	39.5 (75)
African American, % (no.)	38.7 %(75)
Caucasian, % (no.)	57.3% (75)
Female, % (no.)	88.0%(75)
Duration disease (years), mean (no.)	10.1 (75)
SLEDAI, mean (no.),	2.8 (75)
Lupus nephritis, % (no.)	47.4% (75)
WBC (K/uL), mean (no.)	5.6 (75)

Table 2: Proportion of Participants CMV IgG and Positive CMV PCR Viral Load

	CMV IgG positive % (no.)	Positive CMV viral load
Total Number patients	66% (60)	0
On cyclophosphamide	100% (2)	0
On mycophenolic acid/ mycophenolate mofetil	55.3% (38)	0

Disclosure: B. LaMoreaux, None; **A. Meara**, None; **H. Steigelman**, None; **J. Yedimenko**, None; **W. N. Jarjour**, None; **S. P. Ardoin**, None.

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Abstract Number: 1803

General Features of SLE Patients Presenting with Autoimmune Hemolytic Anemia

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster II: Damage Accrual and Quality of Life

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Anemia in systemic lupus erythematosus (SLE) might have various etiologies; however, autoimmune hemolytic anemia (AIHA) is the characteristic hematologic feature. AIHA might be primary or have other etiologies as well. We evaluated the demographic, clinical features and prognosis of SLE patients with AIHA. In addition, their features and prognosis were compared to AIHA patients who were admitted to the Hematology Department of our institution.

Methods: Data about SLE patients with AIHA were obtained from patients' medical records. The diagnosis of SLE was based on 1997 revised ACR criteria. SLE patients with and without AIHA were compared to each other. In addition, medical records of patients with AIHA being followed up at the Hematology Department were screened for their clinical features and outcome.

Results: We included 333 SLE patients (307 females, 26 males, mean age: 37.7±12.4 years). AIHA was diagnosed in 20 patients (6%). Male SLE patients had more frequent AIHA than females (15.4% vs. 4.6%, p=0.04). Coombs test positivity was present in 60 patients (18%). Coombs positivity tended to be more frequent in male SLE patients (30.8% vs. 16.9%, p=0.1). SLE patients with AIHA had more frequent active disease (SLEDAI>4) (75% vs. 42.2%, p=0.006), accompanying thrombocytopenia (45% vs. 14.4%, p=0.003), renal involvement (50% vs. 28.5%, p=0.05), anti-dsDNA positivity (65% vs. 47.6%, p=0.12) and hypocomplementemia (70% vs. 33%, p=0.002). Contrarily, photosensitivity (40% vs. 69.5%, p=0.01) and arthritis (40% vs. 78.7%, p=0.001) were significantly less frequent in SLE patients with AIHA. Fortytwo patients (11.5%) had Coombs positivity without AIHA. Coombs (+) SLE patients had less frequent photosensitivity (53.3% vs. 71.1%, p=0.01); however, more frequent pleural involvement (25% vs. 14.3%, p=0.04), leucopenia (55% vs. 37.3%, p=0.01), lymphopenia (75% vs. 59.8%, p=0.03), anti-dsDNA positivity (70% vs. 44%, p=0.001), anti-ribozomal P positivity (11.9% vs. 4.5%, p=0.05), renal involvement (51.7% vs. 24.7%, p=0.001) and hypocomplementemia (67.3% vs. 27.7%,p=0.001). Two patients presented with AIHA during pregnancy. Survival of SLE patients with and without AIHA were not found to be different. When clinical features of fortyone AIHA patients (27 female, 14 male, mean age: 61.1±18 vs 35.4±10.5) diagnosed at the Hematology Department were compared to SLE patients with AIHA, the former group was significantly older (p<0.001). Being female (85% vs. 65.9%, p=0.1) and relapses (20% vs. 9.8%, p=0.2) tended to be more frequent in the SLE group. SLE patients with AIHA and other AIHAs had similar survival.

Conclusion: AIHA was diagnosed in 6% of our SLE patients. AIHA was more frequent in males and seemed to be associated with active disease, renal involvement, and anti-dsDNA positivity. SLE patients with AIHA were significantly younger than AIHA patients being follwed up at the Hematology Department.

Disclosure: R. Elezi, None; **G. E. Pamuk**, None; **M. Maden**, None; **M. A. Balci**, None; **O. N. Pamuk**, None.

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Abstract Number: 1804

Pulmonary Arterial Hypertension in Systemic Lupus Erythematosus: a Single Centre Experience

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Background/Purpose: Pulmonary arterial hypertension (PAH) is detected in 0.5-17.5% of patients with systemic lupus erythematosus (SLE). Systemic inflammation may play a dominant role in its development, particularly in the early phases of PAH. Aim of this study was to describe the characteristics of PAH in a defined lupus cohort.

Methods: We identified patients who had been diagnosed with PAH, defined as right ventricular systolic pressure

(RVSP)>40mmHg on at least two separate transthoracic echocardiograms (TTE) using our database of a long term longitudinal prospective cohort study of SLE patients. Patients' charts were hand-searched based on a pre-established protocol to derive PAH cause and symptoms at presentation. Variables including demographics, associated clinical and immunological features, PAH-targeted and systemic treatment as well as survival were retrieved from the database.

Results: Fifty-one patients (47 females) were diagnosed with PAH since clinic inception. SLE was the sole cause (SLE-PAH) in 42 (82.4%) whereas other causes were identified in 9 (17.6%). Mean age of the SLE-PAH patients was 31.2±11.2 years at lupus onset and 38.7±12.3 years at PAH diagnosis. PAH was diagnosed within the first year of SLE in 13 (31%) cases. Main indications for TTE were unexplained dyspnea in 33 patients (78.6%), chest pain in 15 (35.7%), dry cough in 17 (40.5%) and syncope in 3 (7.1%). Mean initial RVSP was 59.2±17mmHg. Right heart catheterization (RHC) was performed in 15 patients [mean systolic pulmonary artery pressure (PAP)=62.7±24.7mmHg, diastolic PAP=25.4±9.4mmHg, mean PAP=39.4±14.8mmHg, pulmonary capillary wedge pressure=9.1±4.7mmHg, pulmonary vascular resistance=901±508 dynes-sec-cm^{-5}]. Upon PAH diagnosis, there was no other lupus clinical manifestation in 11 patients (26.2%, 8/11 had active serology which was concordant with PAH over time). Thirty-one (73.8%) had active involvement of other organs (4 central nervous system, 8 kidneys, 4 heart, 3 lung, 7 vasculitis, 8 musculoskeletal, 17 mucocutaneous and 1 catastrophic antiphospholipid syndrome). Active serology (low complement and/or increased anti-dsDNA titers) was detected in 28 (66.7%) patients, while 29 (69%) had positive anti-RNP, 10 (23.8%) lupus anticoagulant and 13 (31%) anticardiolipin antibodies. Immunosuppressive therapy was administered in 28 patients and was succesful in 24 (85.7%) with a mean RVSP reduction of 17.7±7.3mmHg (from 63.7±19.1 to 44.1±14mmHg) in 6.1±3.1 months. Induction treatment consisted of prednisone (mean initial dose 41.6±16mg/d) in all patients, methylprednisolone pulses in 8, cyclophosphamide pulses in 4 and other immunosuppressants in 12 (8 mycophenolate, 4 azathioprine). PAH-targeted therapy was administered to 5/28 patients (11 in total, 6 phosphodiesterase-5 inhibitors, 7 bosentan, 1 epoprostenol) and was discontinued in two due to PAP normalization. Two-year and 5-year survival was 95.2% and 90.5% respectively.

Conclusion: SLE-PAH was usually diagnosed early in disease course and accompanied by other clinical and serological lupus manifestations. Aggressive immunosuppressive therapy was succesful in the majority of cases.

Disclosure: K. Tselios, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **M. Urowitz**, None.

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Abstract Number: 1805

Factors Associated with Complete Remission in Patients with Systemic Lupus Erythematosus: A Retrospective Cohort Study in One Center

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by disease flares, alternated with periods of clinical remission. In the past years, the "treat-to-target" strategy in SLE patients has been proposed, in order to reach complete remission and prevent long-term damage accrual and mortality. Data regarding demographic, clinical and serological factors associated with complete remission have been discordant and not fully addressed, which represents the aim of the present study.

Methods: A retrospective cohort study was performed. We included patients with SLE according to the ACR classification criteria who entered to our institution between January 2003 and December 2007, with a follow-up of at least 8 years from the time of severe activity (SLE Disease Activity Index-2000 [SLEDAI-2K] ≥ 6). Moreover, severe SLE manifestations not included in the SLEDAI-2K (hemolytic anemia, myelitis, mononeuritis multiplex, myocarditis and diffuse alveolar hemorrhage) were recorded. We studied relevant demographic, clinical and serologic factors at the beginning, at the 3rd, 6th and 12th month, and at the end of the follow-up. We defined "complete remission" as SLEDAI-2K = 0 during at least one year without any immunosuppressive treatment; prednisone 1-5 mg/day and antimalarials were allowed. Flares were defined according to the Safety of Estrogens in Lupus Erythematosus National Assessment (SELENA)-SLEDAI criteria. Differences between groups were assessed by Student's T test. Chi square test was used and RR was calculated along with 95% CI. Multivariate analysis was performed.

Results: 114 patients fulfilled our inclusion criteria: 107 (93.85%) were women with a mean age of 30.21±8.3 years and a follow-up period of 117.9±3.14 months. 24 patients (21.05%) achieved complete remission and 5 (4.38%) achieved prolonged remission (≥ 5 years in complete remission). After univariate analysis, the following variables were associated with complete remission: SLEDAI-2K at 3rd month of follow-up (3.09 vs 8.27, p<0.001), total number of disease flares (2.20 vs 4.48, p<0.001), initial urine protein/creatinine ratio (0.47 vs 2.26, p<0.001), proliferative nephritis (RR=0.116 CI 95% 0.016-0.826, p=0.004), lymphopenia at the end (RR=0.440 CI 95% 0.221-0.873, p=0.031) and low C3 at the beginning of the follow-up (RR=0.36 CI 95% 0.167-0.772, p=0.01), treatment with azathioprine (RR=0.353 CI 95% 0.175-0.714, p=0.018) and mycophenolic acid (RR=0.072 CI 95% 0.010-0.513, p<0.001), and articular activity (RR=2.471 CI 95% 1.151-5.305, p=0.021). The variables that remained associated with complete remission after multivariate analysis were SLEDAI-2K at 3rd month of follow-up (RR=0.851 CI 95% 0.737-0.984, p=0.029) and total number of disease flares (RR=0.735, CI 95% 0.563-0.959, p=0.024).

Conclusion: Twenty-one percent of our patients achieved a complete remission. SLEDAI-2K at 3rd month of follow-up and total number of disease flares over the patients' disease course were independently associated with complete remission. Our findings are clinically relevant to encourage an aggressive immunosuppressive treatment and close monitoring at early stages of the disease.

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Abstract Number: 1806

Adherence to Treatment and Social, Educational Levels in Patients with Systemic Lupus Erythematosus

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Background/Purpose: To assess adherence to treatment in patients with Systemic Lupus Erythematosus (SLE) and to determine its relationship with social, educational levels and disease activity.

Methods: Prospective cross-sectional study. We included consecutive SLE patients (ACR 1997 criteria), over 18 years old , between April and July 2014, receiving at least one specific drug for the disease. Socioeconomic and educational status (education level, years of effective education, social coverage, and socioeconomic status according Graffar scale) - demographic variables (age and sex), related to the disease (time of evolution, current medication and polypharmacy), were studied. To assess adherence to oral medication CQR self-questionnaire was used, and Morisky Green for hydroxychloroquine, steroids and other immunosuppressants (methotrexate, azathioprine, mycophenolate mofetil, cyclophosphamide). Adherence to parenteral medication (cyclophosphamide, methotrexate, rituximab and belimumab) it was made through direct observation. We excluded patients with severe visual impairment and / or previous neurocognitive impairment that could not complete those self-questionnaires. Statistical analysis: Descriptive statistics. Chi-square test and Fisher test, Pearson/Spearman correlation coefficient test and logistic regression model was used.

Results: One hundred and ten patients were includes, 91% female, mean age 37 (± 12.5) years, mean duration of disease of 9.9 (± 7.8) years, mean SLEDAI and SLICC was 2.07 (± 3.3) and 0.9 (± 1.5) respectively. Effective education years were 11.4 (± 4.1) and only one patient was unlearned. Fourty percent of patients were unemployed at the time of the study; 55% had public social coverage but providing medication to 100%; 57% of patients had lower socioeconomic level (50% mid to lower and 7% lower), and certificate of disability from their disease. Eighty percent of patients were receiving hydroxychloroquine, 65% steroids and 20% MMF as immunosuppressant oral more used; 86% of patients were polymedicated. Adherence to treatment, assessed by MG was good for most patients (57% to hydroxychloroquine, 63% to steroids and 56% to other immunosuppressants, respectively). The main cause of lack of adherence to medication was forgetfulness of taking them (24%); 63% of patients had good overall adherence assessed by CQR. Patients with less education level had lower adherence to receive hydroxychloroquine ($p \leq 0.0001$). Polypharmacy patients had lower adherence to oral steroids ($p \leq 0.02$). Adherence to treatment was not associated with age, duration of disease, SELENA SLEDAI, SLICC DI, socioeconomic status or occupation.

Conclusion: Global adherence to treatment in lupus patients was good, evaluated by MG and CQR. Lower educational level was associated with lower adherence to treatment with hydroxychloroquine. Polypharmacy patients had lower adherence to use of oral steroids. Lack of adherence to treatment was not associated with age, duration of SLE, SELENA SLEDAI, SLICC DI, socioeconomic status, or occupation.

Disclosure: R. Sueldo, None; **M. C. Bertolaccini**, None; **R. Maldonado**, None; **J. Romero**, None; **L. Gonzalez Lucero**, None; **M. Machado Escobar**, None; **L. Galindo**, None; **M. Santana**, None; **E. Lucero**, None.

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Abstract Number: 1807

Prevalence of Progressive Multifocal Leukoencephalopathy in Adults and Children with Systemic Lupus Erythematosus

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Background/Purpose: In the era of powerful immunosuppression, opportunistic infections are an increasing concern in Systemic Lupus Erythematosus (SLE). A potentially fatal opportunistic demyelinating disease of the central nervous system, progressive multifocal leukoencephalopathy (PML), results from infection of oligodendrocytes by John Cunningham Virus (JC virus). Reactivation of the latent JC virus was recently described in SLE patients; the incidence of PML was estimated at 4/100,000 SLE discharges. This study was initiated to evaluate the prevalence of PML in adult and pediatric SLE patients at two large academic centers, with a focus on validating PML and SLE diagnoses with clinical information obtained from corresponding medical records, in order to better define the risk of PML in SLE.

Methods: This is a retrospective cohort study evaluating the prevalence of PML in two large academic centers. Patients with SLE were identified using the validated method of either an International Classification of Diseases, Ninth Revision (ICD-9) code of 710.0 or 695.4. All patients with SLE admitted to Columbia University Medical Center (CUMC) between 1986 and 2013 using electronic medical record data (EMR) from the Clinical Data Warehouse, or at Northwell Health (NWH) between 2013 and 2016, were included. Patients with Rheumatoid Arthritis (RA), identified by ICD-9 code 714, were evaluated as the disease control group. Among the case and control groups, cases of PML were identified using ICD-9 code of 046.3. Medication exposure was evaluated in the SLE patients.

Results: A total of 5409 individual SLE patients admitted to CUMC from 1983 to 2013 and 1788 SLE patients admitted to NWH from 2013 to 2016 were identified. Of these 6847 SLE patients, 3 patients also had an ICD-9 diagnosis code of 046.3 for PML. Upon review of the EMR, the diagnosis of PML was substantiated for one patient; the second patient was evaluated for PML but had CSF negative for JC virus and was treated for CNS lupus. EMR admission data could not be retrieved for the third patient and the diagnosis could not be confirmed. None of the 10,776 patients admitted for RA at CUMC had PML. Out of the 5409 SLE patients at CUMC, 212 were also renal transplant recipients and 83 had concomitant HIV/AIDS. Based on inpatient pharmacy records of the 5409 hospitalized SLE patients at CUMC, 59.2% were treated with steroids and 16.09% with immunosuppressants (7.76% mycophenolate, 3.42% cyclophosphamide, 2.88% azathioprine and 2.03% rituximab). Of note, none of the patients with PML had juvenile SLE (jSLE). At CUMC, the prevalence of PML in hospitalized patients is between 1.8-3.7 per 10,000 discharges and 0 at NWH. Based on these data, the combined prevalence of PML in hospitalized SLE patients at the two hospitals is between 1 and 2 per 7,197 admitted patients=1.4-2.8/10,000.

Conclusion: The prevalence of PML in adult SLE patients is less than 3/10,000 patients; PML has not yet been documented in jSLE. These data do not substantiate the need for JC virus screening in SLE patients prior to initiation of immunosuppression. Additionally, our experience emphasizes the need for thorough review of the data obtained from EMR.

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Abstract Number: 1808

Frequency and Factors Associated with Thirty Day Hospital Readmissions Among Systemic Lupus Erythematosus Patients in a Community Hospital in

the California Central Valley

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune condition which has one of the highest rates of hospital readmissions in the United States. There is scant data on the factors affecting early readmissions of SLE patients. One study on SLE patients found a 30-day readmission rate of 17%. Our study was undertaken to identify factors and predictors associated with early (thirty-day) hospital readmissions in patients with SLE in our hospital Community Regional Medical Center (CRMC) in Fresno, California.

Methods: Our study was a retrospective cohort study, which was approved by the IRB. Using hospital discharge database from CRMC, we identified SLE patients by ICD-9-CM diagnosis code 710.0 who had a hospitalization during timeframe January 2010 to May 2015. We evaluated each hospitalization as a possible index event leading up to a readmission. Early readmission was defined as readmission to the hospital within 30 days of previous hospital discharge date. SLE patients who had met criteria for early readmission comprised the Study Group, while SLE patients without early readmission formed the Control Group. Collected variables include patient demographics, type of insurance, laboratory values, use of immunosuppressive medications, teaching service status, rheumatology consultation and diagnoses upon admission and readmission. Diagnoses data collected were classified and analyzed as either Infection or Non-infection. Descriptive analysis was done, and Chi-square test of association (SPSS software) was used to find significant relationships among several variables.

Results: Of the 968 SLE patients identified between Jan. 2010 and May 2015, 539 of them (56%) were hospitalized at least once. Of the 539 patients, 100 (18%) met criteria for the study group with early readmission; 97 closely matched hospitalized patients without early readmission were the control group. All these patients included in the study and control groups met the 1997 Update of the 1982 American College of Rheumatology Revised Criteria for Classification of SLE. Regarding immunosuppressive medications, we found that SLE patients who were on steroids during index hospitalization were less likely to be readmitted within 30 days, $p = 0.027$. We also found that patients who had ever received Cellcept were likely to have early readmission, $p = 0.033$. Patients with diagnosis of infection at the index visit did not have a higher likelihood of early readmission, $p = 0.298$. There was a significant difference in the mean creatinine values between the study group (2.26) and the control group (1.45) $p = 0.044$. No other significant differences were observed for age, gender, length of stay, platelet count, hemoglobin, or lymphocyte counts. Insurance type was not significantly associated to likelihood of readmission, $p = 0.535$. However, it is important to note that the large majority of the insurances for both study and control groups were Medicare/Medical. Early readmission was not significantly associated with the other following variables: use of Imuran, Methotrexate, Plaquenil, disposition at discharge (home/nursing home), Rheumatology consultation, or type of service (teaching or nonteaching). Likelihood of early readmission and the use of cyclophosphamide, cyclosporine, tacrolimus, rituximab, belimumab, IVIG and leflunomide could not be analyzed because there were too few data points in some categories.

Conclusion: Among SLE patients in our hospital, treatment with steroid therapy was associated with less likelihood of early hospital readmission within 30 days of discharge. Cellcept use was related to higher likelihood of early readmission, possibly as an indicator of severity of SLE in the patient population studied. Although infections are known complications of immunosuppression or immune disease, no significant association was found between infection at index hospitalization and early readmission in our patient population. The significant association found between higher mean values of creatinine in the study group compared to the control group may support the possibility of renal disease as a predictor of early readmission. As infections were not found to be significantly associated with early readmissions, this may imply that it

could be lupus-related factors or other comorbidities that may be related to this finding of a high readmission rate (18%) of SLE patients in CRMC. Further studies into the specific factors affecting early readmissions of SLE patients are warranted, which would be avenues for further improvement of quality and transitions of care of lupus patients in the Central Valley.
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Abstract Number: 1809

Influence of Solar Radiation in Cutaneous Manifestations of Lupus: Data from the Gladel Cohort

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Background/Purpose: Classically, it has been thought that sun exposure is a risk factor for developing cutaneous manifestations in Systemic Lupus Erythematosus. On the other hand, in experimental studies UV radiation has a number of immunomodulatory effects and stimulates vitamin D synthesis. Our objective was to examine the mucocutaneous

manifestations of SLE patients from the GLADEL cohort in relation to solar radiation of the place where they lived along Latin America by performing an ecological study.

Methods: GLADEL patients were categorized according to solar radiation (insolation on horizontal surface) of the Rheumatology Center where they were recruited, ascertained between the period of cohort follow up (1995-2004); this was obtained using NASA Surface meteorology and Solar Energy estimator (https://eosweb.larc.nasa.gov/cgi-bin/sse/interann.cgi?email=skip@larc.nasa.gov). Alopecia, photosensitivity, malar rash, discoid lesions, oral ulcers and subacute cutaneous lupus at cohort entry and during follow up were examined in multivariate models in relation to the average daily solar radiation of the city of residence (as a continuous variable) and other possible confounders.

Results: GLADEL cohort included 1480 lupus patients, with a disease duration < 2 years at entry, 89.9 % female (CI 88-91), mean age 29.5 years (SD 12.3), median follow up 52 months (IQR 24-70), from 34 centers of 22 cities of 9 countries in Latin America. Latitudes of these centers varied between -38° S (Mar del Plata, Argentina) and 25.7° N (Monterrey, Mexico) and mean daily solar radiation varied between 4.44 Kwh/m^2/day (Porto Alegre, Brazil) and 6.08 Kwh/m^2/day (Recife, Brazil) (Table 1). When entering the cohort, 1191 patients (80.47 %) had one or more of the cutaneous manifestations mentioned above and 434 patients (29.31%) developed new skin involvement during follow up. In logistic regression analysis after adjusting for age, gender, ethnic group, urban residence, latitude, antimalarial use and antibodies (anti DNA, anti Sm, anti Ro, antiphospholipid, low C3), living in a city with higher daily solar radiation (examined at 1 Kwh/m^2/day increments) was not associated to any of the cutaneous manifestations at disease onset or during follow up (Table 2).

Conclusion: In the GLADEL cohort, the average solar radiation of the city of residence was not associated with an increased risk of developing cutaneous manifestations. Table 1. Latitude and solar radiation of GLADEL patients' cities of residence.

City	Latitude	Mean daily solar radiation (1995-2004) (Kwh/m^2/day)	Lupus patients in GLADEL, N (%)
Monterrey, Mexico	25.68 N	5.28	32 (2.2)
La Habana, Cuba	23.13 N	5.80	27 (1.8)
Aguas Calientes, Mexico	21.88 N	6.00	20 (1.3)
Guadalajara, Mexico	20.67 N	5.88	55 (3.7)
Mexico DF, Mexico	19.43 N	5.59	184 (12.4)
Guatemala, Guatemala	14.64 N	5.32	29 (1.9)
Caracas, Venezuela	10.49 N	5.64	72 (4.9)
San Cristobal, Venezuela	7.77 N	4.93	22 (1.5)
Medellin, Colombia	6.25 N	4.53	98 (6.6)
Bogota, Colombia	4.61 N	4.81	80 (5.4)
Recife, Brazil	-8.05 S	6.08	20 (1.3)
Lima, Peru	-12.05 S	5.53	100 (6.8)
Goiana, Brazil	-16.64 S	5.46	55 (3.7)
Campinas, Brazil	-22.90 S	5.11	40 (2.7)
Sao Pablo, Brazil	-23.63 S	4.67	102 (6.9)
Porto Alegre, Brazil	-30.03 S	4.44	32 (2.2)
Cordoba, Argentina	-31.40 S	5.16	92 (6.2)
Rosario, Argentina	-32.95 S	4.82	119 (8.0)
Santiago, Chile	-33.46 S	5.53	117 (7.9)
Buenos Aires, Argentina	-34.60 S	4.69	92 (6.2)
La Plata, Argentina	-34.92 S	4.67	44 (2.9)
Mar del Plata, Argentina	-38.00 S	4.50	48 (3.2)

Table 2. Associations of average daily solar radiation of city of residence (examined at increments of 1 Kwh/m^2/day) by multivariable logistic regression analysis

Clinical manifestation	OR (manifestation before/at cohort inclusion)	OR (new manifestation)	OR (manifestation during follow up)
Alopecia	0.79 (0.61-1.02)	1.35 (0.92-1.98)	1.08 (0.83-1.42)
Oral/nasal ulcers	0.81 (0.62-1.04)	1.05 (0.66-1.69)	0.74 (0.53-1.03)
Photosensitivity	0.79 (0.62-1.03)	0.63 (0.39-1.04)	0.81 (0.60-1.09)
Subacute cutaneous lupus	1.21 (0.57-2.54)	0.81 (0.31-2.13)	0.7 (0.30- 1.62)
Malar rash	0.92 (0.71-1.18)	1.41 (0.91-2.16)	1.17 (0.89-1.52)
Discoid lesions	1.24 (0.82-1.88)	1.83 (0.81-4.11)	1.29 (0.77-2.18)
Any of the previous	0.88 (0.64-1.23)	1.32 (1.00-1.75)	1.23 (0.95-1.59)

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Abstract Number: 1810

Health Care Utilization Preceding Diagnosis of Systemic Lupus Erythematosus in Youth

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Background/Purpose: Early diagnosis and treatment of youth with SLE are crucial to prevent organ damage and reduce mortality. Understanding health care utilization prior to diagnosis may inform interventions to minimize diagnostic delay. We determined the frequency and associated factors for health care visits among youth with SLE in the year prior to diagnosis.

Methods: We used national administrative claims data (Optum Labs Data Warehouse) for privately insured U.S. enrollees from May 2000 to December 2013 to identify an incident cohort of youth ages 10-24 years with SLE. Incident cases were defined by ≥ 3 outpatient or inpatient visit claims with an ICD-9 primary diagnosis code for SLE (710.0) > 30 days apart, with ≥ 1 year of preceding continuous enrollment without a code for SLE. The mean number of ambulatory (AMB), emergency (ED), and inpatient (IP) visits in the year prior to the first SLE diagnosis code were compared to visits per year for healthy controls matched 2:1 by age and sex. For each SLE visit type, we also calculated the mean number of visits in

the 3 and 6 months prior to diagnosis, and determined the most frequent primary diagnosis codes in the year prior. We used multivariable negative binomial regression models to examine associations between demographic or disease-related factors and AMB, ED, and IP utilization in the year prior to SLE diagnosis.

Results: We included 724 SLE subjects and 1448 controls comprised of 88% females, with a mean age of 18.6 years (standard deviation, SD 3.7). Compared to controls, fewer youth with SLE were white or from the Midwest; 24% had subsequent diagnoses for nephritis. Youth with SLE had significantly higher mean visits of all types in the year pre-diagnosis compared to controls: 9.5 (SD 10.0) vs 3.0 (4.5) for AMB ($p<0.001$), 3.6 (6.0) vs 0.9 (2.0) for ED ($p<0.001$), and 1.4 (4.4) vs 0.2 (1.5) for IP ($p<0.001$) (Figure). The most common primary diagnosis codes for pre-diagnosis AMB, ED and IP visits were: Other acne [706.1], Primary thrombocytopenia unspecified [287.3], and Fever unspecified [780.6], respectively. Subsequent nephritis was associated with decreased AMB, but increased IP visits. Preceding psychiatric diagnosis was associated with increased AMB and ED visits (Table). Female sex, Asian and Black race were associated with decreased AMB visits.

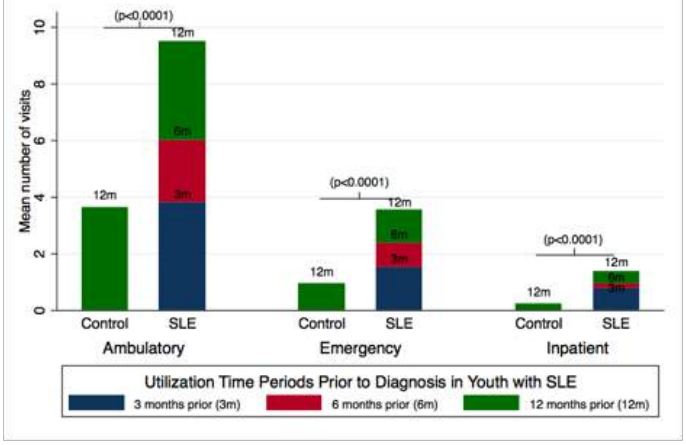
Conclusion: Youth with SLE have higher rates of health care utilization in the year preceding diagnosis compared to healthy peers. Strategies to improve early identification of youth with SLE, especially those presenting with psychiatric or renal manifestations, may allow earlier treatment and improve outcomes.

Table. Factors Associated with Pre-diagnosis Health Care Utilization in Youth with SLE

Predictors	Ambulatory	Emergency	Inpatient
	Multivariate Incidence Rate Ratio (95% CI)		
Race/Ethnicity			
White	-	-	-
Black	0.8 (0.7-0.98)*	1.2 (0.9-1.6)	1.9 (0.8-4.1)
Hispanic	1.2 (1.0-1.4)	1.1 (0.9-1.5)	1.5 (0.6-3.7)
Asian	0.7 (0.6-0.9)*	0.6 (0.4-0.8)**	0.7 (0.2-2.2)
Age, years			
10-15	-	-	-
16-18	1.1 (1.0-1.4)	1.1 (0.8-1.5)	0.9 (0.4-2.2)
19-21	1.2 (1.0-1.5)*	1.1 (0.8-1.4)	1.8 (0.8-4.2)
22-24	1.2 (1.0-1.4)	1.2 (0.9-1.6)	1.4 (0.6-3.3)
Female	0.7 (0.6-0.8)***	0.9 (0.6-1.2)	0.8 (0.3-2.1)
Region			
Northeast	-	-	-
Midwest	1.0 (0.8-1.2)	1.1 (0.7-1.5)	0.9 (0.3-2.7)
South	1.0 (0.8-1.2)	0.9 (0.67-1.3)	1.2 (0.4-3.5)
West	1.0 (0.7-1.2)	1.1 (0.8-1.7)	0.4 (0.1-1.8)
Highest education (household)			
Less than 12th grade	-	-	-
High school diploma	1.1 (0.6-2.0)	2.7 (0.99-7.2)	0.6 (0.04-8.0)
Less than bachelor degree	1.2 (0.7-2.2)	2.6 (0.96-6.9)	1.0 (0.1-13.7)
Bachelor degree or higher	1.5 (0.9-2.7)	2.6 (0.95-7.0)	0.6 (0.04-9.0
SLE nephritis	0.8 (0.7-0.9)**	1.2 (0.9-1.5)	2.9 (1.4-5.9)**
Seizures or Stroke	1.3 (1.1-1.7)*	1.5 (1.0-2.1)	2.4 (0.8-7.3)
Preceding psychiatric diagnosis	1.4 (1.2-1.7)***	1.8 (1.4-2.3)***	2.1 (0.9-4.9)

Shown are results from multivariable negative binomial regression models examining associations between demographic or disease factors and health care utilization. Separate models (n = 666) were used for ambulatory, emergency, and inpatient visits. * = p <0.05; ** = p < 0.01; *** = p < 0.001

Figure: Health Care Utilization 1 Year Prior to Diagnosis in Youth with SLE Compared to Healthy Peers



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Abstract Number: 1811

Systemic Lupus Erythematosus: Detailed Anatomy of a Cohort (follow-up for more than 35 years).

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Background/Purpose: Very long-term follow-up has rarely been reported in lupus patients. We report on the follow up of (up to 37 years) of our lupus cohort from January 1978 to December 2015.

Methods: We have undertaken an exhaustive case review of our entire cohort of lupus patients at University College London Hospital. Electronic and paper records were reviewed for demographic, clinical and pathological outcomes of our patients. For those patients no longer under active follow up, information was retrieved through telephone consults and discussions with primary care physicians and other rheumatologists.

Results: 673 patients (M 55 F 618) with lupus were included. Patients were predominately Caucasian (58.4%) Afro-caribbean (14.9%) and South Asian (8.8%). Average age at diagnosis was 28.9 years (SD +/- 12.5). Major lupus manifestations were arthralgia/arthritis (90.9.2%), rash (66.2%), photosensitivity (41.5%), serositis (37.8%), oral ulcers (27.3%) and alopecia (23.7%). Over a third of patients had renal involvement (34.6%). 90% confirmed on biopsy. 46% class IV, 22.3% class III and 17.2% class V. 20.8% patients had major CNS involvement at some point in their disease. 93.6% of patients were ANA positive (titre>1:80) . 62.9% were double stranded DNA antibody positive, 48.6% had low C3. Other autoimmune conditions diagnosed in our cohort include hypothyroidism (7.7%), Sjogrens (7%) and anti-phospholipid syndrome (6.8%). 2.5% of patients were also diagnosed with idiopathic thrombocytopenic purpura and 4.6% developed haemolytic anaemia. A large majority of patients were treated with Prednisolone during their disease. Disease modifying drugs including Hydroxychloroquine (85.4%), Azathioprine (39.8%), Mycophenolate (36.8%), Cyclophosphamide (23%), Methotrexate (11.8%) were also used in combination. 19.9% of our patients received Rituximab. The majority of patients remain in active follow up (68.1%). The mean follow up is 15.1 years. 14.7% have died, 8.1% moved away (known location), 5% have moved away (unknown location). Cancer was a major cause of death (31.8%), notably of the breast (16.1%) and lung (14.3%) and Non-Hodgkin's lymphoma (10.7%). The second leading cause of death was infection (30.7%) followed by cardiovascular disease including stroke and myocardial infarction (8%).

Conclusion: Although the outlook for SLE has improved in the past 50 years, it remains a condition with significant morbidity and mortality. The introduction of Rituximab has provided an additional therapeutic strategy beyond conventional immunosuppression but it is not a cure. We await the introduction of more successful biologic therapies to improve the outcome for our patients.

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Abstract Number: 1812

Impact of Severe Organic CNS Involvement in Cognitive Function in a Cohort of Systemic Lupus Erythematosus Patients

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Background/Purpose: Our purpose was to investigate cognitive dysfunction (CD) in a cohort of Neuropsychiatric Systemic Lupus Erythematosus (NPSLE) patients (n=16) with severe central nervous system (CNS) involvement that had been previously evaluated prospectively in our department.

Methods: Of a 16 patient cohort with a well documented history of CNS involvement (NPSLE), 11 patients participated in the study. Eleven non-NPSLE patients and 28 healthy controls, all female, with mean age 41.2 (±11.4) years were included. Healthy controls were age, sex and education matched. Participants were administered a 1-hour neuropsychological battery as proposed by the American College of Rheumatology (ACR-SLE battery). Data on depression using the Center of Epidemiological Studies of Depression (CESD) questionnaire, cognitive failures as reported from participants using the Cognitive Failures Questionnaire (CFQ) and levels of fatigue using the Facit Fatigue (FF) questionnaire were also collected. A Visual Analogue Scale (VAS) was used for pain assessment. Patients were evaluated for the presence of anti-dsDNA, Neuromyelitis Optica (NMO)-IgG, anti-ribosomal P and anticardiolipin antibodies (aCL). Presence of concurrent Antiphospholipid Antibody Syndrome (APS) was documented. Disease activity was assessed using the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), and permanent damage due to SLE using the SLICC/ACR Damage Index. Analysis of variance was performed in order to assess the statistical significance of the observed differences. Pairwise comparisons were made using the Tukey's HSD test. All analyses were done using the STATISTICA 10.0 software for Windows.

Results: Analysis of variance revealed significant differences between groups in three domains of neuropsychiatric tests: Stroop color, Greek verbal learning test (GVLT) 1,2, Rey osterrieth complex figure (ROCF) copy trial, and in the FF questionnaire. When post-hoc analysis was performed those differences were weakened, however a tendency maintained for the ROCF copy trial (p=0.06). In the patients sample, aCL positive subjects had lower values in the immediate recall trial of the GVLT, (p=0.01) and in the immediate ROCF trial (p=0.02) as compared to the non aCL ones. Also, APS patients had lower digit symbol test and lower CESD results compared to the non APS patients (p=0.01 and 0.04, respectively). Finally higher SDI scores were positively correlated to CESD scores (p=0.0) and SLEDAI scores were moderately negatively correlated to Word Reading Efficiency (WRE) and Stroop color-words scores.

Conclusion: Severe neurological involvement does not produce severe cognitive dysfunction. NPSLE patients showed a tendency to deficient visual-spatial processing. However, in the patient's sample, those with aCL antibodies showed deficits in memory processes. APS patients showed worse psychomotor speed. Both patients with APS and patients with higher SDI scores showed more depression.

Abstract Number: 1813

Prevalence and Incidence of Systemic Lupus Erythematosus in Tucuman - Argentina

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is the paradigm of the autoimmune diseases that primarily affects women in a ratio of 9: 1. In England and America the prevalence varies from 12 to 42 cases / 100,000 inhabitants and the incidence of 1-3 cases / 100,000 inhabitants. No data on incidence and prevalence of SLE in Argentina is available. The aim of this study is to determine the prevalence and incidence of SLE in the province of Tucuman, Argentina.

Methods: A cross-sectional study was conducted. Medical records of outpatient and inpatient of 4 hospitals in the province and attended by all doctors of Rheumatology Society of Tucuman (n = 28) except for a center, were reviewed retrospectively. We included patients over 16 years with diagnosis of SLE (4 ACR criteria 1982/1997) residents in the province of Tucuman and with at least two clinic visits between January 2005 and December 2012. We excluded patients with other concomitant diagnosis of autoimmune disease. Demographic variables related to the disease (diagnosis date, age, mortality, cause of death and clinical) were analyzed. The population data were taken from the National Census of 2010. The province of Tucuman has 17 departments with a population of 1,448,716 inhabitants, 45% are in the center area and the remaining 65% distributed in the areas west and south. The population over 16 years is 1,011,188 inhabitants. The prevalence was calculated as the number of cases per 100,000 inhabitants in the period 2005 - 2012 and the annual incidence in the same period.

Results: 353 patients were identified. The mean age at diagnosis was 30.5 ± 11.7 years, 93.5% were women. The prevalence was 25.6 cases / 100,000 inhabitants (95% CI 22.6-28.8) and adjusted for age (≥ 16 years) of 36.7 cases / 100,000 inhabitants (95% CI 32.8-41.1). The annual incidence in 2005: was 1.8 cases / 100,000 inhabitants (95% CI 1-2.9) 2006: of 2 cases / 100,000 inhabitants (95% CI 1.2-3.2), 2007: 1.4 cases / 100,000 inhabitants (95% ; 0.7-2.4), 2008: 2.1 cases / 100,000 inhabitants (95% CI 1.2-2.9), 2009: 2.2 cases / 100,000 inhabitants (95% CI 1.3-3.3), 2010: 2.2 cases / 100,000 population (95 % 1.2-3.3), 2011: of 2.8 cases / 100,000 inhabitants (95% CI, 1.9-4) and 2012: of 4.2 cases / 100,000 inhabitants (95% CI 2.9-5.8). A significant increase of incidence was found comparing the periods 2005 and 2012 (p = 0.0019). Mortality was 9.1%, the most common cause were infections (14/32) .The change rate of deaths corrected by year follow-up is similar to the change in the incidence rate corrected by year of follow up through periods.

Conclusion: The prevalence of SLE in the province of Tucuman was of 36.7 cases / 100,000 inhabitants. The annual incidence in 2005 was 1.8 and in 2012 4.2casos / 100,000 inhabitants. This is the first study of prevalence and incidence of SLE in a population of Argentina.

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Abstract Number: 1814

Epidemiology and Microbiology of Pneumonia in Systemic Lupus Erythematosus (SLE)

Gabriela García-Guevara[1], Ricardo Ríos-Corzo[2], Hilda Fragoso-Loyo[3], Juan Jakez-Ocampo[4], John Hernandez-Flores[2], Mariana Lopez-Lopez[5], Eduardo Carrillo-Maravilla[6], Jose Sifuentes-Osornio[2] and **Yemil Atisha-Fregoso**[7], [1]Internal Medicine, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico, Mexico, [2]Internal Medicine, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [3]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [4]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, México, Mexico, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico, [6]Medicina Interna, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [7]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Mexico City, Mexico

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Background/Purpose: Pneumonia, remains as a main cause of mortality in patients with SLE. There are not specific guidelines for the empiric treatment in these patients. The aim of this study was to establish the epidemiological characteristics, the microbiological isolations and the rate of complications of patients with SLE and pneumonia.

Methods: We retrospectively reviewed medical records of patients with SLE (ACR criteria) and Pneumonia who attended the emergency room in a single tertiary care center, (January 2010 - March 2015). We collected laboratory and clinical data: demographics, treatment and disease activity (SLEDAI-2K). We collected isolation data from the microbiology department and from the medical record to ascertain that the isolation was considered responsible of pneumonia. Patients were followed for 30 days after discharge. A negative outcome was defined as need of mechanical ventilation (MV), septic shock or death during follow-up. Statistics. Descriptive statistics were used.

Results: We included 163 patients (121 women, 74%), who presented 194 episodes of pneumonia. At evaluation the mean ± SD age was 34.6 ± 12.4 years, time since diagnosis of SLE 7.1 ± 8.2 years and SLEDAI 2K was 8 ± 5.6. Duration of hospitalization was 10.7 ± 7.2 days. In 154 of the episodes patients were taken prednisone (mean dose 18 mg). In fifty eight of the episodes (29.8%) was possible to obtain a positive microbiology report. The isolated microorganisms are depicted in table 1. Fifty seven (29%) patients presented a negative outcome: 13 (7%) septic shock, 50 (26%) needed MV and 12 (6%) patients died.

Table 1. Isolated microorganisms in 58 pneumonia episodes in SLE patients

	n	%
Streptococccus pneumoniae	**4**	**6.8**
Pseudomonas aeruginosa	8	13.7
Aspergillus	7	12
Klebsiella pneumoniae	5	8.6
Methicillin-sensitive Staphylococcus aureus	5	8.6
Methicillin-resistant Staphylococcus aureus	4	6.8
E. coli	4	6.8
Strepnotrophomonas	3	5.1
Enterococcus	2	3.4
Moraxella	2	3.4
S. epidermidis	2	3.4
H.parainfluenza	2	3.4
Enterobacter cloacae	2	3.4
Acinetobacter	2	3.4
Mycobacterium tuberculosis	1	1.7
Streptococcus agalactiae	1	1.7
Candida albicans	1	1.7
H. influenza	1	1.7
P. jirovecci	1	1.7
Serratia	1	1.7
TOTAL	58	100

Conclusion: In this study, a high proportion of patients with SLE and pneumonia presented a negative outcome. With an acceptable percentage of episodes with microbiological isolation, we identified a very high incidence of atypical microorganisms, this must be taken into account for empirical antibiotic selection in these patients.

Disclosure: G. García-Guevara, None; **R. Ríos-Corzo**, None; **H. Fragoso-Loyo**, None; **J. Jakez-Ocampo**, None; **J. Hernandez-Flores**, None; **M. Lopez-Lopez**, None; **E. Carrillo-Maravilla**, None; **J. Sifuentes-Osornio**, None; **Y. Atisha-Fregoso**, None.

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Abstract Number: 1815

Frequency and Predictors of Attaining the Lupus Low Disease Activity State (LLDAS) in a Multinational SLE Cohort from the Asia Pacific

Vera Golder[1], Rangi Kandane-Rathnayake[2], Alberta Y. Hoi[3], Molla Huq[4], Worawit Louthrenoo[5], Yuan An[6], Zhanguo Li[6], Shue Fen Luo[7], Sargunan Sockalingam[8], Chak Sing Lau[9], Alfred Lee[10], Mo Yin Mok[10], Aisha Lateef[11], Kate Franklyn[3], Susan Morton[12], Sandra V. Navarra[13], Leonid Zamora[13], Yeong-Jian Wu[7], Laniyati Hamijoyo[14], Madelynn Chan[15], Sean O'Neill[16], Fiona Goldblatt[17], Eric F Morand[3], **Mandana Nikpour**[18] and Asia Pacific Lupus Collaboration, [1]Southern Clinical School, Centre for Inflammatory Diseases, Monash University, Melbourne, Australia, [2]Rheumatology, Monash University, Melbourne, Australia, [3]Centre for Inflammatory Diseases, Monash University, Melbourne, Australia, [4]Department of Medicine (Rheumatology), Melbourne University, Melbourne, Australia, [5]Division of Rheumatology, Department of Internal Medicine, Chiang Mai University, Chiang Mai, Thailand, [6]Peking University People's Hospital, Beijing, China, [7]Chang Gung University, Taoyuan County, Taiwan, [8]University of Malaya, Kuala Lumpur, Malaysia, [9]Univ Dept of Medicine, Queen Mary Hospital, Hong Kong, Hong Kong, [10]Queen Mary Hospital, Hong Kong, Hong Kong,

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster II: Damage Accrual and Quality of Life

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic heterogeneous disease with considerable burden from disease activity and damage. A novel clinical treatment target in the form of the Lupus Low Disease Activity State (LLDAS) has been recently reported (Franklyn et al, Ann Rheum Dis, 2015), with retrospective validation showing that time spent in LLDAS translated to reduced damage accrual. The objectives of this study were to describe the frequency and identify the predictors of attaining LLDAS in a large multinational cohort of patients with SLE.

Methods: Data were collected at the baseline visit of SLE patients enrolled in a longitudinal study in 12 centres across the Asia Pacific. Data were analysed cross-sectionally against the recently published definition of LLDAS, and the frequency and characteristics associated with LLDAS attainment were determined. Stepwise multivariable logistic regression was used to determine predictors of LLDAS.

Results: Of the 1846 patients assessed, criteria for LLDAS were met by 44%. Data revealed that patients with shorter disease duration were less likely to be in LLDAS (OR 0.31, 95% CI 0.19-0.49, p<0.001). Likewise, patients with a history of discoid rash (OR 0.66, 95% CI 0.49-0.89, p=0.006), renal disease (OR 0.60, 95% CI 0.48-0.75, p<0.001), or who had elevated double stranded DNA (OR 0.65, 95% CI 0.53-0.81, p<0.001) or hypocomplementaemia (OR 0.52, 95% CI 0.40-0.67, p<0.001) were less likely to be in LLDAS. When countries were compared, higher national social wealth (OR 1.57, 95% CI 1.25-1.98, p<0.001) as measured by the Gross Domestic Product per capita was positively associated with LLDAS.

Conclusion: In a large multinational SLE cohort, the lupus low disease activity state is observed in less than half of patients at a single point in time. Disease duration and phenotype, as well as national social wealth, are predictive of LLDAS.

Abstract Number: 1816

SLE and Uctd in the Rheumatology Informatics System for Effectiveness (RISE) Registry

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Session Time: 9:00AM-11:00AM

Background/Purpose: The ACR-sponsored RISE (Rheumatology Informatics System for Effectiveness) Registry is an electronic health record (EHR)-based national database of rheumatology clinical visits. De-identified patient data are currently extracted and tabulated from the EHRs of over 50 clinics, representing 250 clinicians. At this time, the majority contributing clinicians are in community-based practices (98.7%). We identified and characterized patients with prevalent systemic lupus erythematosus (SLE) and undifferentiated connective tissue disease (UCTD) in RISE and studied the ICD9 and ICD10 coding.

Methods: We included each patient's last visit in the RISE Registry between April 1 2015 and March 31 2016. For ICD9, SLE and UCTD were defined using 710.0 and 710.9. For ICD10, SLE and UCTD were defined using codes M32.0-M32.9 and M35.9, respectively. Patient characteristics, ICD9 and ICD10 classification from the last visit for each individual patient during this time were included in the analysis. We examined the primary ICD10 rheumatology diagnosis for all patients with an ICD9 code of 710.9 for UCTD.

Results: Patients with prevalent SLE and UCTD in RISE were, on average, in their early fifties and approximately one third were on Medicare. Both groups were around 90% female. Although patients with these diagnoses were predominantly white, those with SLE were more likely to be black than those with UCTD. According to ICD9 codes, 13,416 patients had SLE, and 10,698 had UCTD. Fewer patients had ICD10 codes, likely due to the more recent introduction of ICD10. By ICD10 coding, 10,813 SLE patients and 3,624 UCTD patients were identified. Of SLE patients, 90% of patients were identified using a general SLE ICD10 code: 4,173 had code M32.19 (SLE, other organ), 3,146 had code M32.9 (SLE unspecified), 1,797 had code M32.10 (SLE organ unspecified), and 667 had code M32.8 (other forms of SLE). Smaller numbers of patients were given more specific lupus diagnoses, including 689 with SLE glomerular (M32.14), 174 with SLE lung involvement (M32.13), 81 with SLE pericarditis (M32.12), and 6 with SLE endocarditis (M32.11). Some patients had multiple SLE codes. The ICD10 coding varied for those with an ICD9 code of 710.9 for UCTD. The most common codes were for unspecified systemic connective tissue disease or overlap syndrome (3,624 had M35.9, 816 had M36.8, 516 had M35.8, and 391 had M35.1). Of those identified as UCTD by ICD9 coding, 15.7% had M32 codes for SLE, 14.7% had M35 codes for Sjogren's syndrome, 2.9% had M34 codes for scleroderma, and 2.1% had M33 codes for myositis.

Conclusion: The population within the RISE Registry provides a unique cohort of lupus patients followed, up to this point in the registry, entirely by community clinicians. The transition from ICD9 to ICD10 may result in some changed diagnoses, particularly with some movement from UCTD to more specific diagnoses. RISE includes data on prescribed medications, labs, and patient-reported or physician-reported disease activity measures. Studying this patient group will provide unique insight into the day-to-day community management, prognosis and complications of patients living with SLE throughout the United States. **Table. Characteristics of patients with SLE or UCTD in the RISE Registry between April 1, 2015**

and March 31, 2016, presented as % unless otherwise noted

	SLE (ICD-10) (n=9470)	**UCTD (ICD-10)** (n=3624)
Age in yrs**	52 (15.32)	53 (14.80)
Female	91.2	91.0
Race		
White	46.3	62.0
Black	22.1	9.8
Asian	2.5	1.5
American Indian	0.2	0.1
Native Hawaiian	0.2	0.03
Other	16.4	13.9
Missing	13.6	13.7
Health Insurance		
Medicare	32.5	30.0
Medicaid*	0	0
Commercial	71.9	70.3
Other	16.4	13.9
Missing	13.6	13.7
Region		
Mid-west	14.6	17.3
Northeast	9.1	17.4
Southeast	39.2	34.1
Southwest	23.1	18.3
West	6.1	4.3
Missing	13.6	13.7
Rheumatology visits**	4 (3.55)	4 (6.6)

* Medicaid insurance status is not currently accurately reported in the RISE registry. ** presented as mean (sd)

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Abstract Number: 1817

A Longitudinal Analysis of Change in Lupus Disease Activity Pattern in Hopkins Lupus Cohort Using a Multistate Markov Model Approach

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster II: Damage Accrual and Quality of Life

Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a multi-systemic inflammatory disease with extreme variability of its activity over time. We have described three main patterns: long quiescence (or remission), chronic activity and relapsing-remitting (or flare). Patients may move through a series of these activity states over time. To capture these complex fluctuations, we used a Multistate Markov model to describe and evaluate SLE disease activity patterns over time in a longitudinal lupus cohort.

Methods: SLE patients were followed up quarterly in Hopkins Lupus Cohort for 1- 28 years. Medication, disease activity (by, Physician Global Assessment (PGA) and SLE Disease Activity Index (SLEDAI), C3, C4, anti-dsDNA, antiphospholipid antibodies and urine protein/ creatinine ratio were recorded at each visit. For each patient, visits were divided into 1-year blocks. Any 1-year block with only one visit or patients followed for only 1 year were excluded. SLE disease activity patterns were defined using PGA and SLEDAI: Long Quiescent (LQ), SLEDAI/PGA=0 for all visits within 1-year blocks; Relapsing-Remitting (RR), periods of disease activity (SLEDAI/PGA>0) interspersed with periods of disease inactivity (SLEDAI/PGA=0) within 1-year block; Chronic Active (CA), SLEDAI/PGA scores >0 for all visits within 1-year block. Multistate Markov models were used to provide estimates of relative transition rates and identified predictors of change in disease activity patterns.

Results: 1735 SLE patients were included in this analysis. 92.3% were females, Mean+/-SD Age 32.8 +/- 13.1 years at diagnosis. 52.9% were Caucasian and 40.3% African American, the remainder had other ethnicity, mostly Asian. 127 patients died during follow up. Likelihood of deterioration (from LQ to RR; from RR to CA; from LQ to CA) was greater than improvement (from RR to LQ; from CA to RR; from CA to LQ). At year one, 63.6% remained in LQ, while at year two and year five, 58.2% and 84.1% had deteriorated from LQ pattern to either RR or CA pattern. From the RR pattern, the estimated probability for deterioration (to CA pattern) was higher than improvement (to LQ pattern), regardless of years since SLE diagnosis. Multivariate analysis (see table 1) identified that race/ethnicity (African American), low C3, low C4, ESR >20, taking prednisone or anti-hypertension drug were predictors for deterioration. Plaquenil improved survival.

Table 1 Hazard Ratio and 95% confidence interval of Predictors of Transitions using Multivariate Analysis

	LQ -> RR	LQ -> CA	RR -> CA	RR -> LQ	CA -> LQ	CA -> RR	LQ -> Death	RR -> Death	CA -> Death
RACE									
African American	1.15 (0.9,1.46)	2.2 (0.78,6.26)	**1.81 (1.59,2.06)***	0.72 (0.58,0.89)	0.42 (0.15,1.2)	0.8 (0.7,0.91)	2.28 (0.54,9.59)	1.57 (0.93,2.64)	0.59 (0.31,1.12)
Other	0.89 (0.57,1.39)	0.86 (0.11,6.77)	1.41 (1.09,1.83)	1.31 (0.91,1.87)	1.89 (0.39,9.19)	0.97 (0.75,1.26)	/	0.4 (0.05,2.94)	/
Caucasian	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref
Current Smoking	1.15 (0.86,1.53)	1.09 (0.34,3.48)	1.03 (0.88,1.21)	1.18 (0.92,1.53)	0.58 (0.13,2.56)	0.83 (0.71,0.98)	/	2.06 (1.25,3.4)	2.5 (1.31,4.77)
Urine Protein Creatine Ratio	1.23 (0.68,2.24)	/	1.11 (0.96,1.28)	**0.48 (0.34,0.68)***	0.75 (0.21,2.76)	1.03 (0.9,1.19)	2.89 (0.32,25.73)	1.79 (1.11,2.89)	2.15 (1.1,4.19)
Low C3	2.49 (0.92,6.75)	/	**1.75 (1.51,2.03)***	**0.38 (0.24,0.59)***	/	0.93 (0.8,1.08)	/	1.46 (0.82,2.59)	1.86 (0.9,3.84)
Low C4	0.89 (0.1,8.09)	/	**1.56 (1.32,1.83)***	**0.2 (0.1,0.4)***	/	0.96 (0.82,1.13)	/	1.69 (0.88,3.26)	1.13 (0.52,2.46)
ESR.c	0.93 (0.75,1.14)	1.26 (0.5,3.18)	**1.28 (1.13,1.45)***	**0.68 (0.56,0.81)***	1.38 (0.49,3.92)	0.99 (0.87,1.12)	3.44 (0.64,18.43)	2.4 (1.34,4.29)	1.37 (0.64,2.92)
Prednisone	1.21 (0.97,1.51)	1.06 (0.38,2.94)	1.06 (0.94,1.19)	**0.65 (0.54,0.78)***	1.19 (0.44,3.24)	1.02 (0.9,1.16)	3.96 (0.92,17.08)	**3.83 (1.99,7.38)***	2.34 (1,5.44)
Plaquenil	1.4 (1.13,1.74)	1.55 (0.59,4.08)	**1.28 (1.12,1.45)***	0.98 (0.81,1.18)	3.48 (0.77,15.67)	1.06 (0.93,1.21)	0.94 (0.23,3.81)	**0.37 (0.23,0.59)***	0.7 (0.37,1.33)
Anti Hypertension Drug	1.05 (0.86,1.28)	0.36 (0.13,0.99)	1.08 (0.96,1.21)	1.1 (0.92,1.31)	0.74 (0.28,1.96)	0.96 (0.85,1.08)	1.45 (0.35,5.97)	**2.99 (1.7,5.26)***	2.02 (1.03,3.97)

*** P value < 0.0006, accounting for multiple comparison**

Conclusion: 1 year after SLE diagnosis, more than half of patient with LQ deteriorated. Patients in RR were more likely to deteriorate than improve. Plaquenil showed great promise in improving survival.

Disclosure: W. Fu, None; **M. Petri**, None.

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Abstract Number: 1818

Predictors for Mortality in Hospitalized Patients with Systemic Lupus Erythematosus from 1999 to 2009: A Follow-up Multicenter Study in China

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Session Time: 9:00AM-11:00AM

Background/Purpose: To find out prognostic factors predicting the outcome of Chinese patients with systemic lupus erythematosus (SLE) at the time of their first admission.

Methods: A database (http://sys.91sqs.com/sle) has been built to collect the medical records of SLE patients by the Lupus Collaborative Group under the supervisor of Jiangsu Rheumatology Association since 2010 (Feng X et al, J Rheumatol 2011; 38:1289-1295). Up to 2015, the hospitalization data of nearly 2,500 SLE patients who first admitted during the 1999-2009 decade in Jiangsu Province, China, were documented. Those with known survival status were extracted for the assessment of potential factors associated with mortality. The independency of factors significantly related was established by multivariate Cox regression analysis.

Results: Totally 1,372 patients from 26 centers were enrolled (Figure 1), in which 92.3% were female and 17.2% were deceased after following-up for a median time of 7.8 years. The main causes of death were infection (30.1%), neuropsychiatric impairment (14.8%), renal failure (14.4%) and cardiopulmonary involvement (8.5%). Ill-defined causes of death, most recorded as cardiopulmonary failure or multiple organ failure, represented 25.4% of the total deaths. Compared with those dead within one year after the hospitalization, patients died later had less neuropsychiatric impairments (7.6% vs. 23.8%) but more cardiopulmonary involvements (12.2% vs. 3.8%). Independent predictors for mortality at the time of first admission were age more than 45 years old [hazard ratio (HR) 1.38], disease duration more than 2 years (HR 1.54), neuropsychiatric involvement (HR 1.93), cardiopulmonary involvement (HR 1.85), anemia (HR 1.53), thrombocytopenia (HR 1.51), hypoalbuminemia (HR 1.47), increased blood urea nitrogen (HR 1.74) and serum creatinine (HR 1.66), whereas the positivity of anti-Sm antibody (HR 0.60), the use of anti-malarial drugs (HR 0.49) and cyclophosphamide (HR 0.60) were protective factors. SLEDAI score, proteinuria or hypocomplementemia was not independently associated with the outcome in this cohort.

Conclusion: Old age, long disease duration and vital organ involvement predict a poor outcome in Chinese SLE patients, while early intervention with cyclophosphamide and anti-malarial drugs is beneficial for long-term prognosis.

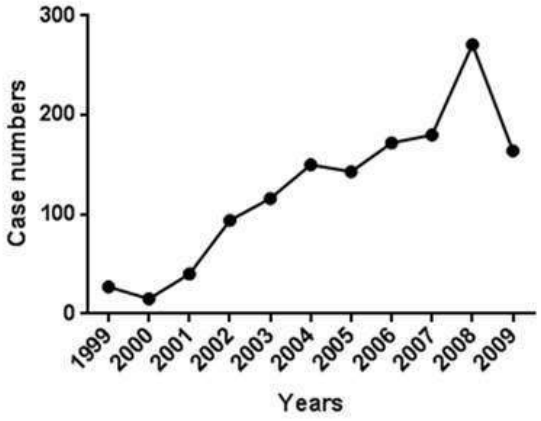

Figure 1 number of cases enrolled each year

Disclosure: X. Feng, None; **W. Pan**, None; **L. Liu**, None; **M. Wu**, None; **L. Sun**, None.

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Abstract Number: 1819

Myocarditis in Systemic Lupus Erythematosus

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Background/Purpose : Cardiovascular disease (CVD) is a leading cause of death in patients with SLE. Lupus patients have a 2-3 fold increased risk of heart failure compared to age matched controls. Although the mechanisms remain unclear, lupus myocarditis (LM) has been proposed as a contributor. ^{18}F-Fluoro-Deoxyglucose Positron Emission Computed Tomography (FDG-PET/CT) imaging has emerged as a novel modality to visualize myocardial inflammation in rheumatic diseases. The current study discusses our experience with FDG-PET/CT scanning in LM.

Methods: A total of eight SLE patients diagnosed with LM by FDG-PET/CT are described in this series. Demographics, SLE-specific characteristics, and CVD risk factors were ascertained. Coronary artery disease was evaluated by the Agatston coronary calcium score and/or coronary catheterization.

Results: Eight SLE patients (mean age 43±12 years) seen at the Lupus Center for complaints of chest pain 4 (50%), intermittent shortness of breath 2 (25%) or palpitations 2 (25%) followed from November 2015 to February 2016, underwent cardiac FDG-PET/CT for evaluation of LM. Six patients were female, 4/8 were Hispanic and 4/8 were non-Hispanic Black. The median SLEDAI-2K and SLICC SDI scores were 5 (2-11) and 1.5 (0-2), respectively. Mean SLE disease duration prior to the diagnosis of LM was 11±6 years. One patient had hypertension and diabetes, and 3 patients

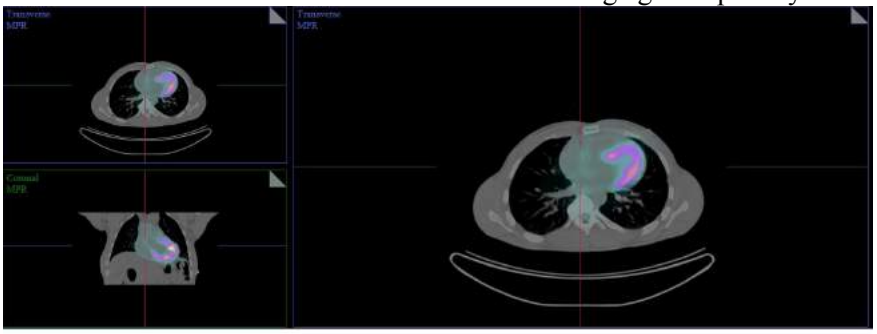
were former or current smokers. Of the 8 patients, 1 had a history of pericarditis and 5 had prior severe lupus activity and organ involvement: 4 had lupus nephritis and 1 had CNS lupus. All patients were ANA positive, 7 ds-DNA+ and 5 were anti-SSA antibody positive. None of the patients had anti-phospholipid antibody syndrome or APL antibodies. One patient had elevated troponins and elevated pro-BNP. Electrocardiographic abnormalities were noted in all patients with 5 having non-specific ST-T changes and sinus tachycardia. Interestingly, only 5 patients had echocardiographic abnormalities: pericardial effusion in 3 (38%), global hypokinesis in 2 (25%) and valvular abnormalities 2 (25%). The mean ejection fraction was 41±16% (Table 1). On cardiac FDG-PET/CT imaging, all patients had diffuse myocardial uptake (Figure 1).

Conclusion: These data propose that cardiac FDG-PET/CT imaging has higher sensitivity than 2-D echocardiography in detecting myocardial inflammation in SLE and support the use of FDG-PET/CT in the diagnosis of myocarditis in SLE.

Table 1. Diagnostic Findings of SLE patients with FDG-PET/CT diagnosed myocarditis (n=8).

Laboratory Data	
C3, *mean (±SD)*	84.5 ± 26.5
C4, *mean (±SD)*	16.8 ± 11.1
Ds-DNA Antibody titer, *mean (±SD)*	113.4 ±99.7
ESR, *mean (±SD)*	45.4 ± 26.6
CRP, *mean (±SD)*	5.5 ± 28.9
Elevated Troponin, *n (%)*	1 (12%)
Elevated Pro-BNP, *n* (%)	1 (12%)
EKG abnormalities	
Non-specific ST-T-wave abnormalities, *n(%)*	5 (63%)
Sinus Tachycardia, *n(%)*	5 (63%)
Right Bundle Branch Block, *n(%)*	2 (25%)
Left Atrial Dilatation, *n(%)*	1 (12%)
No abnormalities n *(%)*	0 (0%)
Transthoracic Echocardiogram	
Ejection Fraction (EF) , mean % *(±SD)*	41(16.3)
Abnormal EF, n *(%)*	4 (50%)
Other Echocardiographic Abnormalities	
Global hypokinesis, *n(%)*	2 (25%)
Pericardial effusion, *n(%)*	3 (38%)
Wall Motion abnormalities, *n (%)*	1 (12%)
Valvular abnormalities, *n(%)*	2 (25%)
Left atrial dilatation, *n(%)*	1 (12%)
Left Ventricular Dilatation, *n(%)*	1 (12%)
No abnormalities, n*(%)*	3 (38%)
Abnormal Coronary Angiogram (n=4)	1 (12%)
Coronary Calcium Score >0 (n=4)	1 (12%)
^{18}F-FDG-PET/CT	
Diffuse myocardial uptake, *n(%)*	8 (100%)
Focal on diffuse myocardial uptake, *n(%)*	1 (12%)

Figure 1. Transverse and Coronal views of ^{18}F-FDG-PET/CT imaging of Lupus Myocarditis showing septal, lateral and inferior uptake.



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Abstract Number: 1820

Dectin-1 on Monocytic Cells Mediates Aberrant Innate and Adaptive Immune Responses in Patients with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis - Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Dectin-1 is a c-type lectin like receptor that signals via syk and is involved in anti-fungal immunity. Dectin-1 was found to trigger experimental inflammatory arthritis, and likely play a role in the pathogenesis of some autoimmune diseases. This study aimed to examine (1) dectin-1 expression on circulating CD14+ monocytes in patients with systemic lupus erythematosus (SLE), (2) the effects of dectin-1 stimulation in ROS production by lupus monocytes and (3) Syk signaling and cytokine profile of dectin-1 stimulated lupus monocyte-derived dendritic cells (MDDCs).

Methods: SLE patients with active and inactive diseases and healthy subjects were recruited. MDDCs were derived from peripheral monocytes in the presence of IL-4 and GM-CSF. Dectin-1 agonists including curdlan, zymosan and toll-like receptor agonists Pam3CSK4 (TLR2) and LPS (TLR4) were used to stimulate monocytes and/or MDDCs. Dectin-1, ROS and phosphorylated-syk (p-Syk) were measured by flow cytometry. Cytokine profile was measured by and multi-bead immunoassay.

Results: The percentage of dectin-1 expressing monocytes was significantly lower in active SLE patients (64.5+24.3%) compared to inactive patients (89.6+7.2%) and healthy controls (91.7+9.5%) (both $p<0.001$). The absolute count of dectin-1 expressing monocytes correlated significantly and inversely with SLEDAI ($r=-0.40$, $p<0.001$), anti-dsDNA antibody level ($r=-0.29$, $p=0.004$), C3 ($r=0.35$, $p=0.001$) and C4 ($r=0.24$, $p=0.02$). Despite this, ROS production upon stimulation by dectin-1 agonists was comparable between these 3 groups. Stimulation of dectin-1 led to activation and maturation of MDDCs with upregulation of HLA-DR and CD86 (all $p<0.001$). SLE MDDCs showed higher p-Syk activation compared to normal MDDCs upon dectin-1 stimulation (6.0+2.0 vs 2.8+1.0%, $p<0.001$). Curdlan-stimulated MDDCs produced higher levels of IL-1β, IL-23 and TNF-α. Adding TLR2 agonist to curdlan, SLE MDDCs produced significantly higher level of IL-1β (327.1+51.5 vs 125.3+88.5, $p=0.009$) and IL-6 (median 39.8 vs 21.7, $p=0.03$) compared to normal MDDCs. Combination of TLR4 agonist and curdlan induced IL-12 and TNF-α in normal MDDCs whereas lupus MDDCs produced predominant IL-6 and TNF-α.

Conclusion: Active SLE patients had significantly lower circulating dectin-1 expressing CD14+ monocytes which produced comparable level of ROS upon stimulation compared to inactive patients and healthy subjects. Dectin-1 agonists led to activation, maturation and higher p-Syk activation in SLE MDDCs. Concomitant dectin-1 and TLR2 stimulation induced production of Th17 promoting cytokines, among which IL-1β and IL-6 were significantly higher in SLE compared to normal MDDCs.

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Abstract Number: 1821

Demethylated CD4+CD28+KIR+CD11ahi T Cells Are Characterized By a Pro-Inflammatory Transcriptome and Interact with Genetic Risk to Predict Disease Activity in Lupus

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Background/Purpose: T cell DNA methylation defects play an important role in the pathogenesis of systemic lupus erythematosus. A CD4+CD28+ T cell subset characterized by overexpression of methylation sensitive genes, including CD11a and the KIR gene cluster, has been recently described in autoimmunity. The goal of this study was to characterize this T cell subset *in vitro* and in patients with SLE.

Methods: The size of the CD4+CD28+KIR+CD11a^{hi} T cell subset was determined by flow cytometry in 49 female lupus patients of European descent. SLEDAI scores were calculated at the time of blood draw, and all patients were genotyped across 43 confirmed lupus susceptibility loci and a total genetic risk score for lupus was calculated. CD4+CD28+KIR+CD11a^{hi} and CD4+CD28+KIR-CD11a^{low} T cells were isolated from peripheral blood samples of normal healthy individuals after *in vitro* treatment with 5-azacytidine, and genome-wide DNA methylation and RNA sequencing was performed in both subsets. RNA sequences in the CDR3 region were used to assess the TCR repertoire.

Results: The CD4+CD28+KIR+CD11a^{hi} T cell subset size correlated with disease activity in lupus patients as measured by SLEDAI score (r=0.36, P= 0.012). Linear regression models suggest that the subset size is a better predictor of disease activity when normalized for total genetic risk in each individual (r=0.42, P=0.003), suggesting that the relationship between KIR+CD11a^{hi} T cell subset size and disease activity in lupus is influenced by genetic risk. Genome-wide DNA methylation analysis identified a total of 31,019 differentially methylated sites in KIR+CD11a^{hi} compared to autologous KIR-CD11a^{low} T cells, with 30,736 methylation sites (99.1%) being hypomethylated. RNA sequencing analysis identified 1,620 overexpressed genes in the KIR+CD11a^{hi} T cell subset, including key pro-inflammatory cytokine genes, adhesion molecules, Fc-gamma receptor genes, Toll-like receptor genes, HLA molecules, and metalloproteinases. Of particular interest, and similar to what is known in lupus T cells, the experimentally derived demethylated KIR+CD11a^{hi} T cell subset demonstrates reduced IL-2 mRNA expression (3.3-fold). Bioinformatics analysis of 718 genes that are hypomethylated and overexpressed in KIR+CD11a^{hi} T cells revealed significant enrichment in pro-inflammatory gene ontologies, pathways, and gene meta-groups. Analysis of the TCR repertoire suggests that the KIR+CD11a^{hi} T cell subset is polyclonal, but with less diverse clonality compared to autologous KIR-CD11a^{low} T cells (mean number of TCR clones 673±72 versus 837±39; P= 0.001).

Conclusion: CD4+CD28+KIR+CD11a^{hi} T cells are polyclonal and demethylated, and characterized by a pro-inflammatory transcriptional profile. These cells are expanded in lupus patients, and interact with total genetic risk to predict and possibly contribute to disease activity.

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Abstract Number: 1822

CD4+ T Cell Lymphopenia Is Associated with Deficient Ubiquitination of the Cell Cycle Inhibibitor p27kip1 By the E3 Ligase Casitas B-Lineage Lymphoma-b in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Lymphopenia has been associated with the development of autoimmune diseases. Particularly, in patients with Systemic Lupus Erythematosus (SLE) is a common clinical feature. However, the molecular mechanisms related to lymphopenia in SLE have not been fully addressed. Besides, the E3 ligase Cbl-b has been shown to regulate T cell responsiveness and its deficiency has been documented in SLE. The aim of this study was to assess $CD4^+$ T cell number and proliferation regulated by cell cycle inhibitors ubiquitination by the E3 ligase Cbl-b in SLE patients.

Methods: We included 20 patients with SLE (8 in remission and 12 with active untreated disease) according to the classification criteria of the American College of Rheumatology and 20 age and gender-matched healthy controls. Absolute peripheral lymphocyte count was obtained for each subject. PBMCs were isolated by density gradient and effector ($CD4^+CD25^-$) T cells were purified by magnetic selection and stimulated with anti-CD3+anti-CD28 beads. The expression of total ubiquitin, Cbl-b, $p27^{kip1}$ and $p21^{cip1}$ was analyzed by Western blotting. Interaction between Cbl-b, $p27^{kip}$ and $p21^{cip1}$ was addressed by immunoprecipitation (IP). Proliferative responses were assessed by CFSE. Differences were assessed by t Student test and Spearman correlation coefficient was also used. $p<0.05$ was considered as statistically significant.

Results: We found decreased Cbl-b expression in effector T cells from SLE patients in comparison to healthy controls (1.6±0.2 vs 3.8±1.3, p=0.003), which was associated with lower proliferation upon TCR stimulation vs healthy controls (p=0.022). Decreased proliferation and absolute number of effector T cells correlated with Cbl-b expression (r=0.553, p=0.020; r=0.680, p=0.003, respectively). Moreover, this phenomenon was associated with diminished ubiquitination of the cell cycle inhibitor $p27^{kip1}$ in effector T cells from SLE patients when compared to healthy controls. We did not find differences in ubiquitination and expression of another cell cycle inhibitor, $p21^{cip1}$ in comparison to healthy controls. Interestingly, we also found by IP assays, that $p27^{kip1}$ and $p21^{cip1}$ interact with Cbl-b. We found no significant differences regarding to disease activity.

Conclusion: Our data suggest that the deficiency of the E3 ligase Cbl-b is associated with the presence of lymphopenia in SLE patients. This phenomenon is related to decreased ubiquitination of the cell cycle inhibitor $p27^{kip1}$ in effector T cells from SLE patients, which triggers its sustained expression as well as decreased proliferation of lupus lymphocytes. Furthermore, this effect is specific to $p27^{kip1}$, since even though, $p21^{cip1}$ also interacts with Cbl-b, its ubiquitination and

expression was not related to this E3 ligase in SLE patients. To our knowledge, this is the first evidence that suggest deficient ubiquitination as a molecular mechanism of lymphopenia in SLE patients.

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Abstract Number: 1823

African American and European American SLE Patients with Variable Disease Activity Reveal Distinct Differences in CD4+ T Cell and Monocyte Pathways

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disorder with both genetic and environmental contributions to disease etiology. Patients with different ancestral backgrounds have different clinical presentation and severity, which likely result from variation in immune cell composition or response. Understanding the functional biology of the immune system in SLE patients with variable disease activity is critical to understanding the mechanisms behind disease activity.

Methods: European American (EA) SLE patients (n=20) and African American (AA) SLE patients (n=14) with elevated (SLEDAI >4) and suppressed (SLEDAI≤4) disease activity were matched to healthy controls. Using single cell proteomics by CyTOF, PBMCs were clustered using 33 markers and cell heterogeneity was visualized using viSNE in Cytobank. PBMCs were stimulated with either T cell receptor (anti-CD3/CD28) or B cell receptor (anti-IgG/IgM (Fab')2) stimulation and assessed for pERK, pPLCγ2, and p38 in cell subsets by flow cytometry. Plasma cytokine levels were assessed by 51-plex xMAP assays and ELISAs. FlowJo was used for flow cytometry analysis and Mann-Whitney test was used to compare non-normally distributed data. Analyses were performed using GraphPad Prism and TIBCO SpotFire. All SLE patients met at least 4 SLE ACR classification criteria.

Results: SLE patients were differentiated from healthy controls by elevated frequencies of HLA-DR+CD11c+ monocytes and dendritic cells (p=0.0248) and CD38-CD24-IgD+CD27- naïve B cells (p=0.0326). Compared to SLE-low patients, EA SLE-high disease activity patients had a higher frequency of CD4+ T cells (p=0.0433) and fewer CD56+ NK cells (p=0.0402), which correlated significantly with disease activity (p=0.0305 and p=0.0281, respectively). EA SLE-high disease activity patients also had decreased expression of the inhibitory receptor CD85j on monocytes and B cells (p<0.05), which correlated with elevated Th1, Th2 and Th17-type plasma cytokines (p<0.05). In contrast, AA SLE-high disease activity patients had no differences in NK cell frequencies or CD85j expression, but did have increased frequencies of effector memory CD4+ T cells (p=0.035). Further, CD4+ T cells in AA SLE-high disease activity patients had an

activated phenotype with higher frequencies of CCR6+ (p=0.0127), CD25+ (p=0.0181), CD127+(p=0.0253) and CXCR3+ (p=0.0350) CD4+ T cells compared to SLE-low patients. This activated CD4+ T cell phenotype in AA SLE-high disease activity patients correlated with elevated ICAM-1 (p=0.004) and diminished TGF-b (p=0.035) plasma levels compared to AA SLE-low patients. No significant differences in TCR or BCR signaling were observed between patients with high and low disease activity, but pro-inflammatory cytokines were significantly elevated in both EA and AA SLE-hi patients.

Conclusion: Our results support a model where differences in the regulation of monocytes and/or B cells are associated with SLE disease, but elevated cytokine production through activated CD4+ T helper cell pathways may contribute to heightened autoimmune disease activity in both European American and African American SLE patients.

Disclosure: S. Slight-Webb, None; **R. Lu**, None; **K. M. Bean**, None; **H. T. Maecker**, None; **P. J. Utz**, None; **J. M. Guthridge**, None; **J. A. James**, None.

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Abstract Number: 1824

Mycophenolate Mofetil Use Associates with Unique Biologic Changes in B Cell and T Regulatory Cell Pathways in SLE Patients

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Background/Purpose: The management of systemic lupus erythematosus (SLE) is complicated by a heterogeneous clinical presentation. Currently, mycophenolate mofetil (MMF) is a commonly used medication to treat major organ involvement in SLE, specifically in patients with lupus nephritis. The effectiveness of therapy is determined by clinical response, but the associated modulations of the lupus immune system in MMF responders are not known. This study assesses the systemic immunological changes that occur in SLE patients on MMF.

Methods: SLE patients currently receiving MMF (n=5) or not receiving MMF (n=15) were assessed in a cross-sectional design. Median disease activity and corticosteroid use was not significantly different between treatment groups. All SLE patients meet ACR criteria for classification of disease. Single-cell analysis of cell surface markers were completed by mass cytometry on PBMCs and cellular heterogeneity was visualized using viSNE in Cytobank. Further, phospho-specific flow cytometry was used to measure basal levels of pERK, pPLCγ2, pSTAT5 and p38 and expression following CD3/CD28 (TCR) and anti-IgG and IgM (BCR) stimulation. Soluble mediator levels in plasma were assessed using a 51-plex (Affymetrix) and by ELISA (eBioscience).

Results: Patients on MMF had significant reductions in transitional B cells (IgD+CD24+CD38+CD27-)(p=0.0143) and naïve B cells (IgD+CD38±CD24-CD27-)(p=0.0139) compared to SLE patients not taking this medication. In addition, activation of both monocytes (CD86+HLA-DR+)(p=0.0373) and B cells (CD86+CD19+CD20+) (p=0.05) were reduced in

patients on MMF compared to non-MMF patients. MMF patients also had elevated levels of T cells that expressed CD161 (p=0.0488), a marker known to identify a subset of T regulatory cells, which significantly correlated with increased IL-2 levels in plasma. MMF patients also had reductions in a number of plasma cytokines and soluble mediators including chemokines (MIG, RANTES), growth factors (VEGF-A, SDF-1α, PDGF-BB) and the adhesion molecule VCAM-1 compared to non-MMF patients (p<0,05). Following BCR stimulation, patients on MMF had reduced levels of pSTAT5 (p=0.0367).

Conclusion: Our results indicate that SLE patients on MMF have reductions in both the frequency and activation status of antigen presenting cells and pro-inflammatory soluble mediator pathways, which is accompanied by an increase in T regulatory populations. Together these data provide potential insights to MMF mechanisms of action in SLE patients, define changes in MMF treated patients with suppressed disease activity and suggest immunologic changes that may be found in patients on this background medication.

Disclosure: S. Slight-Webb, None; **R. Lu**, None; **K. M. Bean**, None; **H. T. Maecker**, None; **P. J. Utz**, None; **J. M. Guthridge**, None; **J. A. James**, None.

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Abstract Number: 1825

the Non-Coding Genome and the Genetics of Systemic Lupus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a multi-system, complex disease believed to be triggered by gene-environment interactions. While we have made considerable progress in investigation of genetic risk for SLE, there remains much to learn about how the environment and genetic variation interact to create that genetic risk. Over 80% of the human genome is believed to express non-coding sequences. Of 46 single nucleotide polymorphisms (SNPs) shown to confer genetic risk for SLE in recent genome-wide association studies, 30 lie within non-coding regions of the human genome. We therefore sought to identify and describe the functional elements (aside from genes) located within these regions of interest.

Methods: We used a next-generation sequencing approach (chromatin immunoprecipitation (ChIP) followed by sequencing) to identify epigenetic marks associated with enhancer function (H3K4me1/H3K4me3/H3K27ac) in adult neutrophils to determine whether enhancer-associated histone marks were enriched within the linkage disequilibrium (LD) blocks encompassing the 46 SNPs of interest. We also interrogated available data in Roadmap Epigenomics for CD4+ T cells and CD19+ B cells to identify these same elements in lymphoid cells.

Results: All three cell types demonstrated enrichment of enhancer-associated histone marks compared to genomic background within LD blocks encoded by SLE-associated SNPs. In addition, within the promoter regions of these LD blocks, all three cell types demonstrated enrichment for transcription factor binding sites above genomic background. In CD19+ B cells, all but one of the LD blocks of interest were also enriched for enhancer-associated histone marks.

Conclusion: Regions of genetic risk for SLE contain functional genomic elements that are involved in the regulation and coordination of transcription on a genome-wide basis. These regions specifically are enriched for epigenetic marks associated with enhancer function, and appear to be correlated with active, dynamic regions of the genome as evidenced by the abundance of transcription factor binding in these regions of interest. Elucidating the specific roles of these non-coding elements within these cell-type-specific genomes will be crucial to our understanding of SLE pathogenesis.

Disclosure: J. Hui-Yuen, None; **L. Zhu**, None; **L. P. Wong**, None; **K. Jiang**, None; **Y. Chen**, None; **T. Liu**, None; **J. Jarvis**, None.

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Abstract Number: 1826

STAT3 Phosphorylation Mediates the Stimulatory Effects of Interferon Alpha on B Cell Differentiation and Activation in SLE

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Background/Purpose: In our previous work, we reported a link between interferon alpha inhibition and decreased expression of B cell activation genes in ex vivo whole blood samples from interferon kinoid-treated SLE patients. Here, we investigated the mechanisms underlying the effects of interferon alpha on B cell activation and differentiation.

Methods: PBMC and purified total (CD20+) or naïve (CD19+ CD20+ IgD+ CD27-) B cells were obtained from healthy controls and SLE patients. The effects of interferon alpha on B cell differentiation were studied by flow cytometry. STAT1 and STAT3 phosphorylation in CD20+ B cells (9 SLE and 5 control individuals) was evaluated by Western Blot. The role of STAT3 on B cell responses to interferon alpha was studied using pharmacological inhibitors (STA21 and S31201) and PBMC from STAT3-deficient individuals (n=5).

Results: Spontaneous levels of STAT3, but not STAT1, phosphorylation were significantly higher in total B cells from SLE patients compared to controls. In purified naïve B cells from controls, interferon alpha induced STAT1 and STAT3 phosphorylation. Interferon alpha also displayed direct stimulatory effects on purified naïve B cells from healthy individuals, as evidenced by a significant induction of cell surface CD38 and CD95 in the presence of the cytokine. Incubation of normal PBMC with interferon alpha induced a B cell differentiation pattern as observed spontaneously in SLE PBMC: decreased naïve, decreased unswitched memory, increased switched memory cells and increased plasmablasts. In addition, expression of cell surface CD95 was significantly induced by interferon alpha in all these B cell sub-populations, except in plasmablasts (unstimulated plasmablasts highly express CD95). Interferon alpha-induced B cell differentiation in total PBMC was significantly inhibited in the presence of STAT3 inhibitors, or in PBMC from STAT3-deficient patients.

Conclusion: Interferon alpha displays direct stimulatory effects on B cell differentiation and activation in SLE. STAT3

phosphorylation mediates the effects of interferon alpha stimulation in naïve B cells, an observation that opens new therapeutic perspectives in SLE.

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Abstract Number: 1827

Type I IFN Signature Low and High SLE Subjects with Moderate to Severe Disease Activity Have Distinct Gene Expression Signatures of Immunologic Pathways and Cell Types

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Background/Purpose: Type I interferon (IFN) has been implicated in SLE pathogenesis, and the majority of subjects with SLE have elevated expression of type I IFN-inducible genes in their blood. Anifrolumab, a fully human, IgG_1 κ monoclonal antibody against the type I IFN receptor, is in Phase III clinical trials for the treatment of moderate to severe SLE (NCT02446912 and NCT02446899). Understanding other molecular pathways, either dependent on or independent of type I IFN signaling, is critical to elucidating heterogeneous mechanisms in SLE and to identifying subject subsets for personalized disease management.

Methods: Baseline blood samples from adult subjects with moderate to severe SLE from two Phase IIb clinical studies (NCT01438489; N=265, NCT01283139; N=416) were profiled with whole genome array analyses. Type I IFN gene signature status (high or low) was determined by a central laboratory utilizing an analytically validated four gene (*IFI27, IFI44, IFI44L, RSAD2*) qPCR-based test from subjects' whole blood. A predetermined, delta Ct-based cut-off point, in the trough of the bimodal distribution, was utilized to segregate IFN-high from IFN-low subjects at baseline. Blood from healthy controls was stimulated *ex vivo* with IFN-β, IFN-γ, IFN-λ, IFN-ω, or a pool of all IFN-α subtypes, with or without blocking antibodies for each IFN type, to develop IFN-type-specific signatures. Ninety additional cell type and cytokine pathway specific gene signatures derived from the literature were also evaluated with the Phase IIb sample data. A Fisher's exact test was used for enrichment calculations (signatures cut at median), and comparisons were adjusted for multiplicity through false discovery rate.

Results: 79% of SLE subjects in the combined study population were determined to have an elevated type I IFN gene signature. From the type I IFN signature high subjects, 29/95 signatures evaluated had significant enrichment, including those for B cells (q=1.17E-17, OR=6.4), plasma cells (q=6.96E-11, OR=3.9), and CD40L signaling (q=1.07E-08, OR=3.3), relative to type I IFN-low subjects. In stark contrast, type I IFN signature low subjects had enrichment for eosinophils (q=5.4E-6, OR=0.39), and type II IFN (IFN-γ) specifically inducible gene signatures (q=4.6E-3, OR=0.47). These findings were significant in the combined study population, as well as the NCT01438489 study population, and were either significant or similarly trending for the NCT01283139 population (q<0.05).

Conclusion: SLE subjects who are type I IFN high, had elevated concentrations of B cell, plasma cell, and other inflammatory cytokine pathways. Type I IFN-low subjects, by contrast, were enriched for eosinophil and type II IFN pathways. These observations provide new insights into the molecular heterogeneity underlying SLE and suggest new therapeutic approaches, particularly for type I IFN signature low subjects.

Disclosure: H. Liu, Medimmune, 3; **B. Higgs**, Medimmune, LLC, 3; **W. Rees**, medimmune, LLC, 3; **C. Morehouse**, Medimmune, LLC, 3; **K. Streicher**, Medimmune, LLC, 3; **P. Brohawn**, Medimmune, LLC, 3; **G. Illei**, AstraZeneca, 1,Medimmune, 3; **K. Ranade**, Medimmune, LLC, 3.

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Abstract Number: 1828

Metabolic Reprogramming in CD4+CD28-CXCR3intt-bethi cells and Its Relevance to Pathogenesis in Patients with SLE

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Background/Purpose: $CD4^+$ T cells play a crucial role in pathological process of Systemic Lupus Erythematosus (SLE). Recently, importance of metabolic reprograming in immunocompetent cells was highlighted. We found that preferential induction of T-bet by IFN-γ is an important factor for shift to glycolysis in activated $CD4^+$ T cells in vitro. In this study, we examine the mechanism by which IFN-γ and T-bet in $CD4^+$T cells involved in pathogenesis of SLE.

Methods: Peripheral blood mononuclear cells were obtained from 19 healthy controls (HCs), 30 patients with bio-naïve active RA and 60 patients with active SLE. The expression of CXCR3, T-bet, mTORC1 phosphorylation and IFN-γ production in $CD4^+$T cells were measured by flow cytometry, and assessed the correlation with clinical characteristics.

Results: We found that $CD4^+$ T cells consisted of 3 subsets of $CD28^+CXCR3^{lo}$ T-bet^{lo} cells (R1), $CD28^+CXCR3^{hi}$T-bet^{int} cells (R2), $CD28^-CXCR3^{int}$T-bet^{hi} cells (R3). The percentage of R3 in SLE patients was significantly higher compared to HCs (HCs; 1.1±0.2%, RA; 5.5±1.8%, p=0.06, SLE; 5.6±1.1%, p=0.02). $CD4^+CD28^-CXCR3^{int}$T-bet^{hi} cells mainly consisted of $CD45RA^-CCR7^-$ effector memory cells and were significantly activated compared to other subsets ($HLA\text{-}DR^+CD38^+$ cells; R1: 2.8±0.6%, R2: 11.2±1.5%, R3: 27.6±2.3%, p<0.0001, ANOVA). $CD4^+CD28^-CXCR3^{int}$T-

bet^{hi} cells from SLE patients showed pronounced IFN-γ production compared to HCs (T-bet^{hi} IFN-γ^{+} cells; HCs: 1.1±0.4%, RA: 1.7±0.6%, p=0.50, SLE: 5.6±1.3%, p=0.04). Interestingly, the ratio of CD4^{+}CD28^{-}CXCR3^{int}T-bet^{hi} cells was significantly correlated with the number of immunosuppressants previously used for the SLE patients, that is treatment-resistant (p=0.03, logistic regression analysis). Phosphorylation of mTORC1, which is important for shift to glycolysis, in CD4^{+} T cells from patients with RA and SLE was significantly increased compared to HCs (ΔMFI of p-mTORC1; HCs: 284.9, RA: 563, p=0.01, SLE: 511.7, p=0.03). T-bet expression was significantly correlated with mTOC1 phosphorylation and IFN-γ production in CD4^{+}T cells from patients with SLE (p-mTORC1: r=0.4718, p<0.01, IFN-γ production: r=0.4915, p=0.01, Pearson).

Conclusion: These results indicated that CD4^{+}CD28^{-}CXCR3^{int}T-bet^{hi} cells might be related to refractory to established therapies in patients with SLE. In addition, these cells are constitutively activated accompanied with shift to glycolysis through IFN-γ-mTORC1-T-bet pathway. We highlight CD4^{+}CD28^{-}CXCR3^{int}T-bet^{hi} cells and their metabolic reprogramming as a potential target for pathological process in SLE.

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Abstract Number: 1829

Hyper-Responsiveness to TLR-4 Stimulation in SLE: Association with High Levels of Serum IFN-Alpha and a Distinct Inflammatory Cytokine Profile

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Background/Purpose: IFN-alpha is a pathogenic factor in SLE. High serum interferon activity (IFN-high) marks a subgroup of SLE patients strongly associated with double-stranded DNA (dsDNA) antibodies. However, the pathologic differences between IFN-high patients remain largely unknown. It is likely that IFN-high versus IFN-low patients will have differences in basic disease biology and will exhibit different responses to treatment. In this study, we sought to better characterize the IFN-high and IFN-low subgroups in human SLE by studying the stimulated cytokine responses post whole blood stimulation by Toll-like receptor (TLR) agonists.

Methods: SLE patients (n= 32) meeting ACR criteria for SLE and healthy controls (n=10) were recruited. Serum IFN-activity scores were calculated using the WISH assay and used to bin patients as IFN-high and IFN-low. Whole blood was dispensed into tubes coated with the TLR agonists LPS, CpG and R848 (Tru-Culture.) The stimulated IFN-alpha production was measured by WISH. Cytokine production in patient sera and after whole blood TLR stimulation was measured by bead-based multiplex assay.

Results: Of the 32 patients studied, 9 were IFN-high and 23 were IFN-low. Compared to IFN-low, IFN-high tended to be younger (27.3 versus 54.3 years), more associated elevated dsDNA titers (62.5% vs. 47.6%) and low C4 levels (62.5% vs. 13.0%). Usage of hydroxycholorquine and prednisone was similar between groups. Principal component analysis on cytokine levels in SLE patient sera identified distinct clusters according to serum IFN activity. IFN-high patients responded more dramatically to the TLR-4 agonist LPS than IFN-low ($p<0.05$), and controls ($p=0.05$). Post TLR-4 stimulation, IFN-high patients produced more CXCL9 ($p=0.025$), and less IL-12 ($p=0.015$) and VEGF ($p=0.015$) than IFN-low patients. In addition, post TLR-4 stimulation, VEGF and IL-1beta ($p=0.0003$) and VEGF/IL-12($p=0.002$) were positively correlated in the IFN-high group, but not in the IFN-low group. In the IFN-low group, very different cytokine clusters emerged featuring IL-17, for example; IL-17/IL-4 ($p<0.0001$) and IL-17/IL-5 ($p<0.0001$).

Conclusion: We have observed clinical and novel biologic differences between IFN-high and low SLE subgroups. High-IFN SLE patients tend to be younger and more serologically active than their low-IFN counterparts. We demonstrate that IFN-high patients are significantly more responsive to TLR4 stimulation and produce a distinct inflammatory cytokine profile post TLR4 stimulation compared to IFN-low SLE. A recent study demonstrated that anti-dsDNA antibodies bind to TLR4 to activate the NLRP3 inflammasome in monocytes from SLE patients, and this interaction was associated with elevated IL1b and IL-17 secretion (Zhang et al. J Transl Med,2016, 14:156). Taken together with our preliminary findings, this suggests the novel possibility that the NLRP3 inflammasome is aberrantly or differentially activated in IFN-high compared to IFN-low SLE, and may offer novel insight into SLE pathogenesis and targeted treatment. Further studies directed at inflammasome activation in the context of IFN-high and IFN-low SLE are underway.

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Abstract Number: 1830

The Role of Tripartite Motif-Containing 21 in Interferon Signature of Systemic Lupus Erythematosus

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Background/Purpose: Although the increased expression of type I interferon (IFN)-inducible genes, called “IFN signature”, has been suggested to have important roles in the pathogenesis of systemic lupus erythematosus (SLE), its mechanism still remains unclear. Recent studies in vitro or with mice suggest that tripartite motif-containing 21 (TRIM21), an autoantigen also called Ro52 or SSA1, is involved in the regulation of type I IFN production as an E3 ubiquitin ligase for IFN regulatory factors (IRF). Here, we investigated the pathological role of TRIM21 in SLE.

Methods: We collected peripheral blood mononuclear cells (PBMC) from 20 patients who met the 1997 ACR SLE

classification criteria and 24 healthy controls (HC), and analyzed the mRNA expression of TRIM21, type I IFNs, type I IFN-inducible genes by qPCR. We also quantified protein levels of TRIM21 and IRF proteins in the PBMC from SLE patients and HC by Western blot analysis. To evaluate the degree of ubiquitylation of IRF proteins, PBMC were incubated with a proteasome inhibitor MG-132.

Results: There were no significant differences in age and sex ratio between patients with SLE and HC (41.2 ± 13.9 vs 34.1 ± 10.4 years, $p = 0.09$, and 67% vs 75% (female), $p = 0.73$, respectively). Seven patients (35%) with SLE had anti-TRIM21 autoantibody while all of HC were negative for anti-TRIM21 antibody. The mRNA and protein levels of TRIM21 were significantly higher in PBMC from patients with SLE as compared to HC. Although transcript levels of multiple genes including *MX1*, *IFI27*, *IFI44* and *SIGLEC1*, known as type IFN-inducible genes, were significantly higher in patients with SLE as compared to HC, there was no significant difference in mRNA levels of type I IFNs themselves between SLE and HC. In HC, IFN-α and IFN-β mRNA levels were negatively correlated with the level of TRIM21 transcript ($r = -0.52$, $p = 0.0087$, and $r = -0.48$, $p = 0.018$, respectively). On the other hand, there was no significant correlation between TRIM21 transcript level and IFN-α mRNA ($r = 0.21$, $p = 0.37$) or IFN-β mRNA level ($r = 0.24$, $p = 0.30$) in SLE. To investigate the degrees of ubiquitylation of IRF proteins, PBMC from patients with SLE and HC were incubated with MG-132. Although the protein expression levels of IRF3 and IRF5 were significantly increased by MG-132 in PBMC from HC, the effect of MG-132 was not observed in PBMC from SLE patients.

Conclusion: This study suggests that dysregulation of E3 ubiquitin ligase activity of TRIM21 for IRF proteins may be associated with the increased expression of type I IFN-inducible genes in SLE.

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A Novel Graph Theoretic Approach Applied to Modular Repertoire Analysis Identifies a Dual Molecular Progression in Adult SLE Patients, with Distinct Interferon and Neutrophil Transcription Patterns

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Background/Purpose: Gene expression studies support a pivotal role for type I interferon (IFN) in SLE. Previous work using a modular repertoire analysis based on co-clustered gene sets, has demonstrated that the SLE IFN signature is not restricted to a type I IFN signature, but involves the gradual activation of 3 distinct IFN modules (M1.2, M3.4 and M5.12) driven by various IFN types. The aim of this study was to refine and discover novel modular interactions in adult SLE

patients.

Methods: Consecutive SLE patients fulfilling the ACR criteria were enrolled (n=157 samples). Disease activity (DA) was measured according to the SELENA-SLEDAI score. Microarray data were generated using Illumina beadchips. Modular repertoire analyses were performed using the second generation of a blood modular framework comprising 260 modules. Modules with 20% transcripts differentially expressed compared to healthy matched controls were considered active. A novel graph theoretic approach, previously applied to the analysis of somatic evolution in cancer (unpublished), was used to generate an ordered, branching progression model of modular activation in which upstream module activity predisposes the activation of downstream modules. An SLE-specific graph based on module activation in our dataset was built in order to generate hypotheses regarding disease progression in SLE. Trajectories of a focused subgraph were enumerated and samples were clustered to their most likely trajectory group. Significance to clinical characteristics was evaluated using Fisher's exact test and ANOVA, for categorical and continuous characteristics, respectively.

Results: The graph theoretic analysis revealed two distinct patterns involving IFN and neutrophil related modules. Both patterns involved the upregulation of M1.2 followed by M3.4. At this point, the patterns split into the activation of either M5.12 or the M5.15 neutrophil module. Along the shared trajectory, we observed a monotonic increase in DA, dsDNA titers, and corticosteroid dosage. The subjects on the neutrophil (M5.15) trajectory had a marked increase in DA and corticosteroid dosage, although dsDNA levels were unchanged. Moreover, the neutrophil trajectory also had a larger ($p=0.04$) enrichment for renal involvement (80%) than the M5.12 IFN trajectory (40%).

Conclusion: Our analysis revealed a refinement within the hierarchical structure of the peripheral blood IFN modules previously described. Two subgroups, defined by progression along disjoint paths bolstered by their association to overall DA, active nephritis, dsDNA levels, and corticosteroid dosage, are identified. This suggests a dual mode of disease progression in SLE, with either the completion of IFN signature (to include IFNγ) or the activation of neutrophil path associated with renal involvement. ACR2016_Graph theory figure

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Abstract Number: 1832

Increased Interferon b Expression in Bone Marrow Mediates a Senescent Phenotype and Impaired Production of Immunomodulatory Factors By SLE Mesenchymal Stromal Cells

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Background/Purpose: Bone marrow mesenchymal stromal cells (MSCs) are multipotent stem cells that create a special microenvironment for hematopoiesis and immunity. MSCs display robust immunomodulatory properties and transplantation

of human MSC significantly improves nephritis in murine models of lupus. Immunomodulation by MSCs from lupus patients appears to be impaired, but the mechanisms underlying this defect is unknown. Our previous studies identified an IFN-I signature in SLE bone marrow (BM) and peripheral blood. In fibroblasts, prolonged treatment with IFNb, but not IFNα, has been shown to induce senescence through activation of reactive oxygen species (ROS), ATM and p53 DNA damage and repair (DDR) pathways. Here we investigate whether human SLE MSCs undergo senescence, the potential role of IFNb as a mediator in the SLE BM, and the implications for SLE pathogenesis.

Methods: SLE patients fulfilling ACR classification criteria and healthy controls were recruited under an IRB approved protocol (n=6 each). BM MSCs were isolated with low density Ficoll/Hypaque (1.073 g/ml) and grown in tissue culture. MSC phenotype was verified by flow cytometry. MSCs were studied using immunocytochemistry, real-time PCR, western blotting, comet assay for DNA damage, beta-galactosidase assay and RNA interference.

Results: The expression of IFNb was increased 5 folds ($p<0.05$) and IFNβ specific genes were significantly elevated in SLE MSCs. In addition, SLE MSCs displayed significantly reduced proliferation rate, increased production of ROS, increased DDR, and senescence associate secretory phenotype (SASP) as evidenced by increased cytokine production (all $p<0.05$): IL6 (4x), IL8 (8x), GRO1(9x), MCP2 (7x), RANTE1 (5x), GM-CSF (7x). The expression of immunomodulatory factors was significantly reduced (all $p < 0.05$): TGFβ (4x), IDO1 (3x) and LIF (10x). To begin to explore the signalling pathways that may mediate IFNB activation and DNA damage, we examined the level of Mitochondrial Antiviral Signaling Protein (MAVS), an intracytoplasmic nucleic acid sensor (also known as Interferon Beta Promoter Stimulator Protein 1). MAVS was positively correlated with the level of IFNb ($r > 0.9$, $p< 0.01$)， and strikingly, silencing MAVs inhibited IFNb expression and reversed the SASP in SLE MSCs.

Conclusion: The relative contribution of IFNα vs. IFNb to SLE disease pathogenesis remains unclear. IFNb has distinct features as compared to IFNα with higher affinity binding to IFN-I receptors, distinct gene transcripts and induction of senescence in fibroblasts. Our current data suggest that SLE BM MSCs produce IFNb, have increased ROS, DDR and SASP, decreased production of immunomodulatory factors, and elevated levels of MAVS. As a key regulator of IFNb expression, the expression of MAVS is highly correlated with the expression of IFNb. In addition, silencing MAVS disrupts IFNb production and rescues SASP in SLE MSCs. Our novel findings of an IFNb positive feedback loop and related SASP in SLE BM MSCs highlight a novel role for IFNb activation in SLE pathogenesis. Moreover, the essential role of MAVS in the IFNb positive feedback loop suggests dysregulated intracytoplasmic nucleic acid sensing and potential novel therapeutic targets for SLE treatment.

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Abstract Number: 1833

Autoantibody Response to TROVE2 in Systemic LUPUS Erythematosus Patients

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Background/Purpose: Ro60/TROVE2 is a clinically important member of the nuclear antigen family. It binds synergistically YRNAs, allowing the formation of a stable complex with exoribonuclease polynucleotide phosphorylase. The main known function of TROVE2 is so to perform a quality control of misfolded ncRNA (such as Alu RNAs and pre-5S rRNAs), enhancing the cell survival. For that, anti-TROVE2 antibodies are major targets of the immune system in SLE patients and can be identified years before the disease manifestation, providing advantage of an early diagnosis. Epitope mapping studies showed that TROVE2 has an immunodominant epitope between 169-190 a.a. These amino acids reside in a loop involved in binding single-stranded RNA, so anti-TROVE2 antibodies target a key part for its functional mechanism. Hence, although the underlying cause of the disease is not fully defined, SLE is related to the cellular function of the TROVE2 protein. In this work, we analyze the host-guest binding of the TROVE2-autoantibody system in SLE patients and healthy subjects.

Methods: Cross-sectional prospective study of 20 SLE patients diagnosed according to the SLICC-ACR2012 criteria, from the Rheumatology Department of La Fe Hospital. All patients showed high anti-Ro Ab (SSA) concentrations (>200,0 U/mL). We have also taken 8 healthy individuals as negative controls, who had anti-Ro Ab concentrations <15 U/mL. A sensitive TROVE2-based QCM-D biosensor was developed.

Results: Pre–steady–state analysis revealed an antibody bipolar bridging mechanism for the host-guest binding of the TROVE2-autoantibody system, for the first time. Although Fc receptors (such as Fc-gamma receptors) do not exist on the protein surface, its MIDAS motif is the Fc receptor exposed when the epitope-paratope binding takes place initially. In this molecular recognition, the protein hydration shell dynamics plays also an important role. Furthermore, we demonstrate that the TRIM21a:TROVE2 association is a calcium-dependent adhesion system. Thus, the 'bridging' role in the TROVE2 bound, a feature of pathogenic superantigens, leads to the inhibition of the biological function of the Ro/SSA ribonucleoprotein. The MIDAS motif acts as a YES logic gate, having a key role in the intracellular antibody signaling, activating, or deactivating, the innate immune system.

Conclusion: Our results suggest a distinct pathway of induction of anti–TROVE2 autoimmunity in SLE patients. The different interaction mechanism of autoantibodies in SLE patients would suggest a majority necrosis-induced specificity, and not apoptosis as in healthy subjects. Anti-TROVE2 cell-penetrating autoantibodies will so induce the inhibition of degradative activity of the TROVE2 autoantigen in SLE disease. This one would imply the accumulation of the Alu RNAs, stimulating intracellular RNA sensors to induce inflammatory responses. The originated increase of calcium intracellular level favors the TRIM21a-TROVE2 binding through the PRYSPRY domain and therefore, an inhibitory effect on the TRIM21 physiological function. Financial support by GVA (PROMETEO II 2014/040 and GV15/83 project) and from MINECO and FEDER (CTQ2013-42914-R project) is acknowledged

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Abstract Number: 1834

Commensal Ro60 Autoantigen Ortholog Cross-Reactivity in Human Lupus and Gnotobiotic Models

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Background/Purpose: The earliest autoantibodies in lupus are directed against the autoantigen Ro60, an RNA binding protein with orthologs that we identified in a subset of skin, oral, and gut commensal species. Thus we hypothesized that commensal Ro60 orthologs may trigger autoimmunity via epitope cross-reactivity in genetically susceptible individuals.

Methods: V4 16S rDNA samples from SLE and control subjects were sequenced using 2x250bp paired-end reads on the Illumina MiSeq platform and also tested for species-specific enrichment for Ro60 bacteria by real-time PCR. Co-immuniprecipitation was performed using human SLE serum and Ro60 ortholog-containing *Propionibacterium propionicum* and *Bacteroides thetaiotaomicron* lysates. A northern blot of the resulting RNA was probed for bacterial Y RNA. Memory CD4 T cells from SLE patients were sorted into CCR6+ and CCR6- populations. Ro60-specific T cell clones were isolated and stimulated with heat-killed bacteria. Germ-free mice in gnotobiotic isolators were monocolonized by oral gavage with *B. thetaiotaomicron*. Serum was tested for anti-Ro60 antibodies by ELISA. Lymphocytes from mesenteric lymph node and spleen were stimulated with recombinant Ro60 and proliferation was assessed using a luminescent cell viability assay.

Results: Ro60-producing oral and gut commensals were prevalent in healthy controls and lupus patients. However, when human serum was used to co-immmunoprecipitate Ro60 and its bound Y RNA from a skin commensal, *P. propionicum*, only antibodies from human Ro60-positive lupus patients bound commensal Ro60. Lack of reactivity in Ro60-negative patients or healthy controls suggested antibody cross-reactivity between human and commensal Ro60. Next, Ro60 autoantigen-specific CCR6+ and CCR6- CD4 memory T cells clones from lupus patients were isolated and expanded using a T cell library assay. Ro60 T cell clones positive for the tissue-homing marker CCR6 proliferated in response to *P. propionicum*, demonstrating T cell cross-reactivity with commensal Ro60. Finally, germ-free mice were monocolonized with *B. thetaiotaomicron*. Mesenteric lymph node and spleen cells from monocolonized mice proliferated in response to bacterial Ro60 and sera contained anti-human Ro60 IgG antibodies.

Conclusion: Ro60 autoimmune T and B cells from human lupus patients reacted with commensal Ro60 *in vitro*, and commensal Ro60 triggered anti-human Ro60 responses *in vivo*. Taken together, these data support that colonization with autoantigen ortholog-producing species may induce and sustain chronic autoimmunity in lupus. This concept may apply more broadly to human autoimmune diseases and could lead to development of novel microbiota-targeted approaches to treat autoimmunity.

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Study on the Expression of NOD2 in Lupus Nephritis and Its Potential Signaling Pathway

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Session Title: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis - Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Nucleotide-binding oligomerization domain (NOD) - containing 2 (NOD2) is a NOD - like receptors (NLRs) which plays important role in immune regulation and inflammatory response. There are increasing evidences to show that NOD2 may contribute to the development of numerous auto inflammatory and autoimmune disorders. However, their role in lupus nephritis (LN) is not known. Here, we explored the role of NOD2 in LN.

Methods: Immunohistochemistry was applied to observe the expression of NOD2 in renal biopsies. Real-time quantitative polymerase chain reaction (RT-qPCR) was used to detect the level of NOD2 mRNA in the biopsies. In vitro studies, HK-2 cells (renal tubular epithelial cell-line) were cultured with different inflammatory stimulation, western blot was used to investigate their expression of NOD2 and the following activation of MAPK pathway signals (ERK1/2, p38 and JNK), real-time qPCR was applied to observe the mRNA levels of downstream pro-inflammatory mediators (IL-1b, IL-8, MCP-1, TGF-b1, IL-6) .

Results: (1) Immunohistochemistry staining demonstrated that the expression of NOD2 in LN is higher than that of normal control ($P=0.002$), and the mRNA level of NOD2 in renal tissue of LN patients was higher than that of normal control ($P=0.001$). (2) In vitro studies, the urine and serum from onset LN patients can significantly promote higher NOD2 expression in HK2 cells than that from healthy control ($P<0.001$). In addition, TGF-b1, LPS and muramyl dipeptide (MDP) can also induce higher NOD2 expression in HK2 cells ($P<0.001$, respectively). (3) The activation of NOD2 increased phosphorylation of ERK1/2, p38 and JNK. Moreover, the activation of NOD2 induced the release of pro-inflammatory mediators including IL-1b, IL-8, MCP-1, TGF-b1, IL-6.

Conclusion: Our study showed NOD2 expression was increased in LN patients. The activation of NOD2 can promote the activation of MAPK signaling pathway and release of downstream pro-inflammatory mediators. NOD2 may participate in the pathogenesis of LN.

Disclosure: O. Jin, None; **C. Hou**, None; **Q. Li**, None; **X. Zhang**, None; **Q. Wei**, None; **H. Huang**, None; **M. Qiu**, None; **J. Gu**, None.

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Abstract Number: 1836

SLE Bone Marrow Contains Factors That Promote Type I Interferon Activation

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Background/Purpose: SLE is characterized by the inappropriate activation of type I Interferon (IFN) and increases in apoptosis and NETosis by neutrophils, which in combination with defective apoptotic cell and NET clearance provides an ongoing source of self-antigen. IFN further propagates the disease process by promoting B cell activation, survival, and differentiation into plasma cells (PC). PC produces autoantibodies that form immune complexes (IC) to further stimulate IFN production creating a vicious cycle. Important questions that remain unclear are the site and mechanisms of IFN activation. We have recently demonstrated a prominent IFN signature in the bone marrow (BM) of SLE patients that is more pronounced than paired peripheral blood and correlated with higher serum autoantibodies and disease activity. We hypothesize that BM is a key site of IFN activation in SLE.

Methods: BM supernatant (BMS) and serum were obtained from SLE patients (n=11) and healthy controls (HC, n=4). Plasmacytoid dendritic cells (pDC) were purified from healthy donor blood. To determine if BMS and serum induce IFN production, pDC was cultured with 5% BMS or serum with and without necrotic cell material. Necrotic cell material was generated by repeat freeze-thawed U937 cells. Culture supernatants were collected and IFNα was measured by ELISA. Blocking experiment was performed using 10ug/ml Hydroxychloroquine and 5ug/ml anti-CD32.

Results: We found that BMS from 27% of SLE patients was able to induce pDC to produce IFNα even without adding necrotic cell material (BM: 7.9±2.5, BM + necrotic: 7.7±2.1 ng/ml, n=3). The serum from the same patients also induced pDC to produce IFNα, but this effect was greatly enhanced by necrotic cell material (serum: 5.0±2.3, serum + necrotic: 256.46±153.54 ng/ml, n=3). BMS from 36% of SLE patients did not induce IFN production even with necrotic cell material (BM+necrotic: 0.014±0.007 ng/ml, n=4) although paired serum was able to do so with added necrotic cell material (serum+necrotic: 19.25±9.24 ng/ml, n=4). In contrast, neither BMS nor serum from 36% of SLE was able to induce IFNα production by pDC (serum+necrotic: 0.003±0.001, BM+necrotic: 0.0028±0.0018 ng/ml, n=4). BMS and serum from HC did not induce pDC to produce IFN (serum+necrotic: 0.0007±0.0007, BM+necrotic: 0.0045±0.0042 ng/ml, n=4). Serum autoantibodies were higher in the IFN inducer SLE subjects (average number of autoantibodies present for non-IFN inducer= 1 vs. 3.57 for IFN inducers, p=0.01). The ability of SLE BMS and serum to induce IFN was dependent on endosomal toll-like receptors as treating pDC with hydroxychloroquine inhibited IFN production. The induction was also blocked by anti-CD32 suggesting dependency on FcγRIIa. The relationship to the IFN signature and NETosis is under evaluation. Additionally, we are examining ICs as interferogenic factors in the BM.

Conclusion: These data suggest that the SLE BM contains factor(s) that promote type I IFN production by pDC that correlates with the presence of serum autoantibodies. The mechanisms of IFN induction in the BM appear to be dependent on TLR and FCR signalling and may relate to the presence of immune complexes generated in situ.

Disclosure: N. Meednu, None; **A. Bird**, None; **J. Barnard**, None; **M. Kaplan**, None; **J. H. Anolik**, None.

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Abstract Number: 1837

Genetic Susceptibility Loci for Systemic Lupus Erythematosus in the Dominican Republic Population

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease with marked disparities in prevalence and disease characteristics among different populations. Those disparities are believed to result from both genetic and environmental factors. The purpose of this study is to identify genetic susceptibility alleles for SLE in the Dominican Republic (DR) population which has a high prevalence for SLE.

Methods: SLE patients (n = 208) who fulfilled the 1997 revised American College of Rheumatology criteria for the classification of SLE and age/sex-matched healthy controls (n = 205) from the DR were recruited for this case-control study. Genomic DNA was prepared from whole blood and subjected to Sequenom MassARRAY iPLEX genotyping analyses for 42 selected single nucleotide polymorphisms (SNPs). The allele frequencies in SLE patients and healthy controls were compared using Pearson Chi-Square or Fisher's Exact test.

Results: Among the 19 human leukocyte antigen (HLA) gene alleles analyzed, HLA-DQA1 (rs 9271366) shows the strongest association with SLE (OR = 5.48, $p = 0.0001$, Pearson Chi-Square test). SNPs at HLA-DRA (rs6903608, rs9268880, and rs9268979) and HLA-DRB2 (rs9271055) also contribute to SLE susceptibility in the DR population ($p = 0.0086$, OR = 2.09; $p = 0.0061$, OR = 2.21; $p = 0.0012$, OR = 2.86; and $p = 0.0059$, OR = 3.27, respectively). Among the 23 non-HLA gene alleles analyzed, SNP1858C/T (rs2476601) in the tyrosine phosphatase, non-receptor type 22 (PTPN22) gene shows the highest odds ratio for SLE (OR = 6.54, $p = 0.038$, Pearson Chi-Square test). SNPs in the STAT4 gene (rs11889341), PMS2 gene (rs1860460), and TNFSF4 gene (rs2205960) also contribute to SLE susceptibility in the DR population ($p = 0.025$, OR = 2.2; $p = 0.032$, OR = 1.7; and $p = 0.035$, OR = 2.39, respectively). However, SNPs in the IRF5 (rs12537284 and rs2070197), BLK (rs13277113), and TNFAIP3 (rs 5029939) genes that have been frequently identified as SLE susceptibility alleles in other populations do not show association with SLE in the DR population ($p = 0.824$, 0.4, 0.468, and 0.896, respectively).

Conclusion: SNPs in the HLA-DQA1, HLA-DRA, and HLA-DRB2 alleles and non-HLA genes PTPN22, STAT4, PMS2, and TNFSF4 contribute to SLE susceptibility in the DR population. However, SNPs in the IRF5, BLK, and TNFAIP3 genes may not contribute to SLE susceptibility in the DR population. This is the first study focusing on SLE patients from the DR who may have unique genetic risk factors for the development of SLE.

Disclosure: E. Loyo, None; **Z. Liu**, None; **C. Tineo**, None; **P. Gottschalk**, None; **G. Paulino**, None; **Y. Yu**, None; **Y. Yue**, None; **M. Hearth-Holmes**, None; **Z. Zhang**, None; **K. Su**, None.

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Abstract Number: 1838

Antibodies Against Bacterial Products Curli/DNA Are Found in Lupus Patients and Are Associated with Disease Flares

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Background/Purpose: Bacterial infections are a major contributor to morbidity and mortality in SLE, a known trigger of flares and they are often difficult to distinguish from lupus flares as a definitive biomarker is still lacking. Urinary tract infections (UTIs) such as those due to uropathogenic *E. coli* (UPEC), are characterized by the generation of a unique form of amyloid called curli. We have previously demonstrated that curli amyloid can induce or accelerate disease in mouse models of SLE. Curli can strengthen the structure of biofilms and integrate extracellular DNA, which in turn can be both adjuvant and a self-antigen in lupus patients. Curli can elicit a humoral response against themselves. Based on our previous results, we hypothesize that SLE patients can generate anti-Curli/DNA antibodies and that they correlate with flares

Methods: We investigated 34 lupus patients who met at least 4 SLICC criteria, 29 women and 5 men. 17 sex matched healthy controls were used. We developed a novel ELISA to detect anti-curli antibodies by using the curli/DNA complex as antigen. We tested IgG and IgA subclasses. We also performed competitive ELISAs to determine if curli/DNA antibodies cross reacted with classic lupus autoantibodies. Finally, we correlated the levels of anti-curli/DNA antibodies with several clinical parameters including anti-dsDNA antibodies, bacteriuria and disease flares (SLEDAI). Flares were calculated as an increase of at least 3 points in the SLEDAI from the prior visit.

Results: We found that Lupus patients and healthy controls generated anti-curli antibodies of both IgG and IgA subclasses. We also found that anti-curli antibodies recognized human chromatin but not dsDNA. Interestingly, female lupus patients had significant higher levels of anti-curli antibodies than female controls and males with lupus ($p=0.047$ and $p=0.026$ respectively). Remarkably, higher levels of anti-curli antibodies significantly correlated with the levels of anti-dsDNA antibodies ($p=0.029$), persistent bacteriuria ($p=0.035$) and lupus flares ($p=0.024$).

Conclusion: Taken together these results demonstrate that both healthy controls and lupus patients are exposed to curli-forming bacteria and generate systemic and mucosal immune responses (IgG and IgA subclasses) against curli. Moreover, women with SLE have much higher levels of anti-curli antibodies than men possibly due to higher rate of urinary tract infection, especially by *E. coli*. Since many female patients had persistent bacteriuria, bacterial colonization could be a significant pathogenic mechanism in lupus. Finally, the levels of anti-curli antibodies in lupus patients are a promising biomarker of flares.

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Abstract Number: 1839

Elevated Plasma Cell-Free Mitochondrial DNA Defines a Subgroup of Lupus Patients with Membranous Lupus Nephritis

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with protean manifestations,

characterized by production of antibodies against nucleic acids and upregulation of type I interferon-inducible genes in a majority of SLE patients. The principal drivers of this interferon signature are still not well understood. Recent work has shown that oxidized mitochondrial DNA released by neutrophils can stimulate plasmacytoid dendritic cells to produce interferon-α. (1) We hypothesized that cell-free mitochondrial DNA might contribute to type I interferon production in SLE, and we sought to examine whether cell-free mtDNA levels were increased in SLE patients relative to controls, or during disease flares.

Methods: A retrospective analysis was performed using banked plasma samples from 164 patients in the FLARE SLE cohort along with 57 banked plasma samples from healthy donors. All patients in the FLARE cohort meet 4/11 ACR SLE classification criteria. DNA was isolated from the plasma samples and real-time quantitative PCR was performed, amplifying a target sequence in the mitochondrially-encoded gene NADH dehydrogenase I, as previously published. (2) In-depth clinical phenotyping of SLE patients in the cohort was performed and used to define subgroups of SLE patients, as well as the specific disease manifestations present during flares.

Results: No significant difference was seen in cell-free mtDNA in plasma from SLE patients versus healthy donors (HD - 3060.3 copies/uL, N=57, SLE - 3845.5 copies/uL, N=164, p=0.22). However, cell-free mtDNA levels were elevated in a subset of SLE patients with a history of membranous lupus nephritis, including those with a component of proliferative nephritis (WHO class V/III+V/IV+V), relative to patients with proliferative nephritis alone (WHO class III or class IV) (5313.9 copies/uL, N=34 vs. 2062.5 copies/uL, N=17, p=0.02). A subset of 70 patients had multiple samples collected at visits before, during, and after flares of disease activity. Cell-free mtDNA levels rose at the peak of disease activity as assessed by SLEDAI score in 11/16 flares of class V/III+V/IV+V nephritis (p=0.04), while it only did so in 4/11 of the remaining nephritis flares. In contrast, cell-free mtDNA rose at the peak of disease activity in only 4/20 flares where alopecia was present (p=0.02).

Conclusion: Cell-free mtDNA levels are elevated in a subset of SLE patients with a history of membranous nephritis, and were more likely to rise during flares of membranous nephritis versus other types of disease flares. References 1. Lood, C. et al. Neutrophil extracellular traps enriched in oxidized mitochondrial DNA are interferogenic and contribute to lupus-like disease. Nat. Med. advance on, (2016). 2. Nakahira, K. et al. Circulating mitochondrial DNA in patients in the ICU as a marker of mortality: derivation and validation. PLoS Med. 10, e1001577; discussion e1001577 (2013).

Disclosure: D. Fernandez, None; **M. A. Pabon**, None; **M. Olferiev**, None; **A. C. Hernandez**, None; **F. Malick**, None; **L. Khalili**, None; **A. M. K. Choi**, None; **K. Nakahira**, None; **M. K. Crow**, Medimmune, 5.

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Abstract Number: 1840

A Dichotomy of Regulatory Immunome Is Related to Disease Activity in Juvenile Systemic Lupus Erythematosus

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Background/Purpose: The pathogenesis of SLE involves disturbances to the homeostatic balance between the immune effector and regulatory system. The conventional mono-dimensional mechanistic interrogation of one cell type or molecule at a time is inadequate for a multifactorial disease such as lupus where multiple derangements contribute to disease causation and progression. The ability to scrutinise multiple components and both arms of the immune balance simultaneously is a critical unmet need. We hypothesise that abnormalities of different components within the immune-regulatory mechanism contributes to lupus pathogenesis. To address such unmet needs and hypotheses, we employed a multi-dimensional approach to study the immunome of jSLE patients. This approach may have immediate translational value of identifying immune cell subsets relevant for clinical prognostication and elucidation of mechanism to single out therapeutic targets.

Methods: Peripheral blood mononuclear cells from 14 jSLE patients out of a cohort of 58, stratified by clinical scoring (SLEDAI and SLE activity score) into active and inactive disease, were interrogated with multi-dimensional mass cytometry (Cytometry by time-of-flight). Active disease is defined as persistent activity/refractory to treatment, flare or new diagnosis of lupus. Analysis was performed using a machine learning custom software through an unbiased, unsupervised approach based on dimensional reductions followed by automated cell classification, clustering and visualisation.

Results: Significant immunome differences stratified by disease activity were found. In active disease, enrichment of a CD45RA+ (naive) CD38+ CD4+ cell population was observed; indicative of a potential novel T cell involvement in lupus flare. Concurrently, a counterintuitive increase in the natural regulatory T cell (CD25+ CD152+ Foxp3+) population in active disease was found. This observation likely underscores an ineffective attempt of the T regulatory system to overcompensate the inflammatory response. This is in contrast to a greater degree of B regulatory cells (CD19+ IL10+) expansion with inactive disease after CpG oligodeoxynucleotides challenge (inactive: 3.56%, interquartile range (IQR): 3.18% to 6.84%; active: 2.12%, IQR: 2.02% to 2.20%) (not significant, Mann Whitney u test). Significance of these changes will be determined with increasing sample size.

Conclusion:

Our holistic analysis of the adaptive immune system underscores 2 critical points. 1) The presence of naive T cells expansion in association with disease flare underlines a plausible pathologic role that demands further functional analysis. 2) Dichotomy of the adaptive regulatory immunome at the level of the T and B cell suggests a potential ineffectiveness of the T cell based regulatory mechanism in active lupus in contrast to the expansion of the regulatory B cell population observed with quiescent disease. These findings highlighted the importance of further studies required to fulfil the dual translational goals of identifying therapeutic targets by distilling cellular subset for mechanistic study and providing predictive immunome signatures of clinical fate.

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Abstract Number: 1841

Dysregulation of the Splicing Machinery Components in Leukocytes from Patients with Systemic Lupus Erythematosus: Influence on Autoimmune and Atherothrombotic Mechanisms

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Background/Purpose: The aim of this study was to evaluate whether alterations in the splicing-machinery could influence the development and activity of the disease and the atherothrombotic profile of SLE patients.

Methods: An array of selected components of the major- (n=12) and minor-spliceosome (n=4) and associated splicing factors (n=28) was developed, and their expression levels were evaluated using a Fluidigm methodology, in purified leukocytes (monocytes, lymphocytes and neutrophils) from 14 SLE patients and 14 healthy donors. In parallel, an extensive clinical/serological evaluation was performed. Carotid intimate media thickness (CIMT) was used as atherosclerosis marker. Endothelial activity was monitored by laser-doppler flowmetry, netosis was analyzed by fluorescence microscopy, and pro-inflammatory and oxidative stress markers were quantified by flow cytometry and RT-PCR. Then, association of these splicing components with clinical and analytical features were investigated.

Results: As a general feature, a significant reduction in relevant splicing factors and spliceosome components was found in all the leukocyte subtypes of SLE patients. Interestingly, we found a specific altered profile of splicing factors and spliceosome components when compared monocytes (i.e. U2AF1, FBP11, SRSF6), lymphocytes (i. e. RBM22, RB17, SRSF6) and neutrophils (i. e. SRSF10, SND1). Association studies showed that the reduced levels of some components of spliceosome in both monocytes and neutrophils were linked to the occurrence of thrombotic events. In lymphocytes those reduced levels were strongly related to the positivity for anti-dsDNA antibodies in SLE patients, thus suggesting that reduced spliceosome machinery would contribute to increase in altered autoantigen assembly, to which autorreactive T helper cells might react, inducing increased autoantibody production. In addition, reduced spliceosome machinery might derive of the described over-expression of specific anti-spliceosomal autoantibodies in SLE patients. Correlation studies demonstrated an inverse relationship among reduced levels of spliceosome components/splicing factors and high activity of the disease (measured as SLEDAI), endothelial dysfunction, netosis, and increased expression levels of peroxides and peroxynitrites, as well as of altered mitochondrial membrane potential in monocytes and neutrophils. Concomitantly, a direct relationship among reduced levels of spliceosome components/splicing factors in monocytes and neutrophils and low levels of serum complement factors C3 and C4 was established.

Conclusion: These results reveal the existence of SLE-associated spliceosome alterations, which could be related to the development and activity of this autoimmune condition and have influence on the induction of mechanisms that drive atherothrombosis in this disorder.Ongoing studies would clarify the potential physiological implications of these findings, which may provide novel diagnostic-biomarkers and therapeutic-tools to treat SLE. Funded by CTS7940, PI15/01333.

Disclosure: C. Lopez-Pedrera, None; **S. Pedraza-Arévalo**, None; **M. del Río-Moreno**, None; **M. Á. Aguirre Zamorano**, None; **P. Ruiz-Limon**, None; **N. Barbarroja**, None; **Y. Jiménez-Gómez**, None; **I. Arias de la Rosa**, None; **E. Collantes-Estévez**, None; **P. Segui**, None; **M. J. Cuadrado**, None; **J. P. Castaño**, None; **R. M. Luque**, None; **C. Perez-Sanchez**, None.

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Abstract Number: 1842

Pentraxin 3 Level Positively Correlated with Pulmonary Arterial

Hypertension in Systemic Lupus Erythematosus Patients

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Background/Purpose: Systemic lupus erythematosus (SLE) is a kind of chronic and autoimmune disease with variable multi-system involvement of unknown causes, which is characterized by periods of relapsing-remitting course. Inflammation and vascular abnormalities are the main pathological changes. Part of the SLE patients may present with pulmonary artery hypertension (PAH), which can seriously affect the quality of life and eventually lead to death. The etiology and pathogenesis of PAH is affected by many factors which have not yet been fully elucidated. Till now, there is no highly sensitive and specific biomarker for early diagnosis and prognosis for SLE patients with PAH. The aim of this study is to investigate the plasma level of pentraxin 3 (PTX3) and its clinical significance as a potential biomarker in SLE patients.

Methods: 1) In this study, 46 patients with SLE were enrolled. The diagnostic criteria for SLE were based on the American College of Rheumatology (ACR) revised criteria in 1997 or ACR revised SLE classification standards in 2009. All subjects retained serum and plasma samples, and recorded contemporary clinical manifestations and laboratory data, including duration, clinical symptoms and signs, blood-urine- defecate-test, liver and kidney function, blood lipids, erythrocyte sedimentation rate, C-reactive protein, complement series, antinuclear antibodies (ANAs), anti-ds-DNA antibodies, antiphospholipid antibodies and immunoglobulin, SLEDAI and other data. SLE patients were divided into two groups, activity group and no activity group according to the SLEDAI; further, the activity group was divided into three subgroups, mild, moderate and severe group; all patients were measured by the UCG, PASP≥40mmHg was determined SLE-PAH (add up to 26 cases), while PASP <25 mmHg was the SLE-NPAH (20 cases). 2) 21 healthy subjects were selected as controls. All subjects were collected serum and plasma, stored at -80℃. 3) Enzyme-linked immunosorbent assay (ELISA) and electrochemiluminescence immunoassay (ECLIA) were used to detect plasma PTX3 level and serum NT-proBNP level, respectively.

Results: 1) The levels of PTX3 and NT-proBNP of SLE group were significantly higher than healthy control group (P=0.007 and 0.013, respectively). 2) Among SLE patients, PTX3 and NT-proBNP levels increased significantly of SLE-PAH group than those of SLE-NPAH (P=0.001 and 0.022, respectively). 3) The expression of PTX3 in activity group was higher than non-active group (P=0.029). There was no significant difference among mild, moderate and severe activity SLE group in the expression of PTX3 (P=0.14). 4) There was no significant correlation between the levels of PTX3 and NT-proBNP in patients with SLE-PAH (r=0.098, P=0.655). 5) In SLE-PAH group, the expression of PTX3 was positively correlated with SLEDAI scores (r=0.350, P=0.017), while negatively correlated with serum albumin (r=-0.327, P=0.018) ；PTX3 has no correlation with CRP (r=0.097, P=0.651), but was positively correlated with CRP by adjusting age and sex (r=0.178, P<0.001). 6) Multiple linear regression analysis showed that SLEDAI sores were independent predictors of PTX3 level. 7) Receiver operating characteristic (ROC) curve demonstrated the plasma PTX3 level more accurately than NT-proBNP in distinguishing SLE-PAH from SLE-NPAH .

Conclusion: The circulating levels of PTX3 in SLE-PAH were significantly higher, and positively correlated with CRP level, indicating that PTX3 may be involved in SLE-PAH development. PTX3 may be a sensitive biomarker for SLE-PAH diagnosis.

Abstract Number: 1843

Single Cell Expression Quantitative Trait Loci (eQTL) Analysis of Established SLE-Risk Loci in Lupus Patient Monocytes

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis - Poster I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: While most of the confirmed SLE-risk loci are in or near genes with immune system function, a major unanswered question is how these loci influence diverse immune cell subsets. In this study we performed a single cell eQTL analysis in human monocytes to determine impact of some well-established SLE-risk loci in single human monocytes.

Methods: CD14++CD16- classical monocytes (CL) and CD14dimCD16+ non classical (NCL) monocytes from SLE patients were purified by magnetic separation. The Fluidigm C1 System was used for single cell capture and target gene pre-amplification and equal numbers of classical and non-classical monocytes were studied. Real time PCR was used to quantify expression of 90 monocyte-related genes, and the same SLE patients were genotyped for 7 SLE-risk SNPs to enable eQTL analysis. Non-parametric analyses were used with the single cell data in CL and NCL populations separately.

Results:

We observed a large number of significant eQTL associations that surpassed the 5% FDR, supporting the idea that single cell gene expression data allows for robust eQTL discovery. The SLE-associated SNPs demonstrated more eQTLs in NCLs as compared to CLs ($p=2.5x10^{-8}$). For a given SNP, the eQTL associated transcripts differed between cell types ($p<0.001$ for all 7 SNPs for discordance), suggesting that the same SNP resulted in different cellular events between the two monocyte subsets. When comparing eQTL lists between the different SLE-associated SNPs, there was a greater degree of sharing observed in NCLs as compared to CLs. Loci which shared a significant proportion of eQTL associations with each other in NCLs included TNFAIP3, IRF5, IRF7, PTPN22, and SPP1. In CLs, TNFAIP3 shared a large number of eQTLs with SPP1 and ITGAM, although SPP1 and ITGAM showed more limited overlap with each other. Thus, SLE-associated risk loci exert coordinated effects on gene expression within individual human monocytes, and the risk loci interact in different ways in different cell types.

Conclusion: This study emphasizes the strength of single cell gene expression strategy for eQTL discovery. Our study revealed striking differences in the occurrence and interaction between of SLE risk associated eQTLs within different but closely related cell types. This suggests pleiotropic effects from each locus across various immune cell types, and a high degree of complexity when considering how these loci impact the immune system.

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Abstract Number: 1844

Mesenchymal Stem Cells Ameliorate the Deficiencies in Immunomodulatory and Phagocytic Capacities of Lupus Macrophages

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Background/Purpose: Evidence has accumulated that umbilical cord (UC)-derived mesenchymal stem cells (MSCs) show therapeutic effects on systemic lupus erythematosus (SLE). Deficiency in SLE macrophages exhibits excessive activation and inefficient clearance of self nuclear antigens. In this study, we aim to investigate whether UC-MSCs could increase the immunomodulatory function and phagocytic activity of lupus macrophages.

Methods: Blood samples were collected from 9 SLE patients, who fulfilled the SLE diagnostic criteria of American College of Rheumatology in 1999. All patients' Systemic Lupus Erythematosus Disease Activity Indexes (SLEDAI) were above 8. $CD14^+$ monocytes were isolated from peripheral blood of healthy donors (HCs) and SLE patients. We cultured human monocytes for 7 days with macrophage colony-stimulating factor (M-CSF) to generate macrophages, and then co-cultured them for 2 more days with/without UC-MSCs in transwell culture systems. $CD4^+$ T cells isolated from HCs were co-cultured with/without prepared macrophages. After 4 days, the proliferation levels of T cells were detected by flow cytometry. To determine the phagocytic activity of macrophages, apoptotic neutrophils were added into the cultures for 2 hours. The uptake of apoptotic cells were determined by flow cytometry.

Results: Compared with HC macrophages, the immunomodulatory function of SLE macrophages was impaired. SLE macrophages were incapable of suppressing the proliferation of $CD4^+$ T cells effectively. The phagocytic activity of SLE macrophages was also deficient in engulfment of apoptotic cells. Next, we determined the capacities of immunomodulatory and phagocytosis of SLE macrophages co-cultured with UC-MSCs in a transwell system. Flow cytometric analysis showed that SLE macrophages co-cultured with UC-MSCs significantly increased the abilities to suppress the $CD4^+$ T cells proliferation and phagocytic activities to engulf apoptotic neutrophils compared with macrophages cultured alone.

Conclusion: Our results indicate that UC-MSCs promoted the immunomodulatory function and phagocytic activity of macrophages in SLE, providing a novel mechanism for MSC-therapeutic function for SLE.

Disclosure: W. Deng, None; **W. Chen**, None; **Z. Zhang**, None; **S. Huang**, None; **W. Kong**, None; **X. Feng**, None; **L. Sun**, None.

Abstract Number: 1845

TGF-β-Induced Tissue Fibrosis Is Abrogated in Mice Containing a Constitutive Genetic Deletion of Nox4 (Nox4 knockout)

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Background/Purpose: Excessive deposition of collagen and other connective tissue components in the skin and multiple internal organs is characteristic of Systemic Sclerosis (SSc). Besides the well characterized profibrotic effects of TGF-β, oxidative stress and other factors have been implicated in SSc pathogenesis. NADPH oxidase 4 (NOX4) is one of seven NADPH oxidases responsible for the production of reactive oxygen species (ROS) which are critical mediators of oxidative stress. TGF-β potently stimulates NOX4 expression, making NOX4 a critical downstream regulator of TGF-β profibrotic effects. Unlike other NOX proteins, NOX4 does not require cofactors to mediate its effects and therefore alterations in its effects are due to changes in its expression and production. The purpose of the studies described here was to evaluate the effect of the genetic deletion of *Nox4* in a murine model of TGF-β-induced tissue fibrosis.

Methods: Male and female C57BL6/J control mice and *Nox4* knockout mice in which *Nox4* expression has been eliminated by replacement of exon 4 of the *Nox4* gene with a neomycin cassette were implanted subcutaneously in the right intrascapular region at 4 weeks of age with osmotic pumps containing either saline or 2.5 µg TGF-β1. C57BL6/J mice with normal *Nox4*were similarly implanted with osmotic pumps. These pumps deliver a daily dose of 150 ng TGF-β/day for 28 days. Mice were sacrificed 28 days after the pumps had dispersed their contents. Skin adjacent to the pump implantation site and both lungs were isolated for analysis. A portion of each tissue was fixed in formalin and processed for histopathologic analysis (hematoxyllin/eosin and Masson's trichrome stains). Another sample of each tissue was hydrolyzed for measurement of hydroxyproline content.

Results: Histopathology studies in samples from control C57BL6/J TGF-β-treated mice showed peribronchial fibrosis and diffuse interstitial lung fibrosis. In contrast, *Nox4* knockout mice showed normal lung histology. Similarly, profound dermal fibrosis was evident in skin from C56BL6/J mice implanted with TGF-β pumps but not in skin isolated from *Nox4* knockout mice. Hydroxyproline levels in C57BL6/ control mice skin demonstrated a 104% increase in female control mice and a 59% increase in male control mice in response to TGF-β however TGF-β failed to increase the hydroxyproline content of *Nox4* knockout mice tissues of either sex. In the lung, TGF-β caused increased hydroxyproline levels in female control mice by 83% and by 116% in male control mice whereas no significant changes were observed in *Nox4*knockout mice of either sex.

Conclusion: Genetic deletion of *Nox4* in mice abrogated the ability of TGF-β delivered by subcutaneously implanted osmotic pumps to induce skin or lung tissue fibrosis. This result confirms several recent *in vitro* studies demonstrating a role for *Nox4* as an important mediator of the profibrotic effects of TGF-β-induced tissue fibrosis. Since *Nox4* is constitutively active, increased levels of its expression induced by TGF-β are likely to contribute to the pathogenesis of fibrotic diseases. The results of this study highlight the potential of *Nox4* inhibition as a potential therapeutic target in the treatment of SSc and other fibroproliferative disorders.

Disclosure: P. J. Wermuth, None; **S. A. Jimenez**, None.

Abstract Number: 1846

Cutaneous and Visceral Fibrosis Induced By Endothelial Cell-Specific Constitutive Activation of TGF-β1 Signaling in Mice

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Background/Purpose: Microvascular damage is an early event in Systemic Sclerosis (SSc) pathogenesis and may represent the initiating stimulus for the subsequent establishment and progression of the fibrotic process. Extensive experimental evidence shows the increased expression and production of the pleiotropic growth factor transforming growth factor-β (TGF-β) and of TGF-β-regulated genes in SSc patient tissues however, the effects of cell-specific TGF-β expression in endothelial cells have not been studied. The purpose of these studies was to generate a transgenic mouse strain characterized by the inducible expression of TGF-β signaling specifically in cells of endothelial lineage. The novel transgenic mouse strain (TGFβ^{ca}-Cdh5 Cre) would be utilized for the evaluation of the effect of upregulated TGF-β expression specifically in the microvasculature and to examine directly the role of endothelial cell activation in the development of tissue fibrosis.

Methods: A transgenic mouse strain carrying an inducible constitutively active TGF-β receptor I (TBRI^{ca}) allele was intercrossed with a second mouse strain (B6.Cg-Tg(Cdh5-cre/ERT2)Mlia/J) carrying a Cre-ER^{T2} expression cassette controlled by the endothelial cell-specific Cdh5 promoter. A functional TBRI^{ca}allele is generated by intraperitoneal injection of 4-OH tamoxifen, yielding constitutive and unrestricted TGF-β signaling in all cells of endothelial lineage. The results of the intercross were evaluated by histopathologic staining of skin and visceral tissues, by immunhistochemical staining of lung for α-smooth muscle actin and von Willebrand factor, measurement of tissue hydroxyproline content, and by evaluation of the expression of genes associated with tissue fibrosis, myofibroblast differentiation and TGF-β signaling.

Results: Constitutive TGFβ-1 signaling in endothelial lineage cells resulted in severe and progressive cutaneous and visceral tissue fibrosis compared to saline-injected control mice. Increased collagen deposition and microvascular fibroproliferative changes in the dermis, lungs, myocardium, liver, and kidney were observed by histopathological analysis of these tissues. A 2.2 fold increase in hydroxyproline content of the skin and a 2.8 fold increase in the lung was observed. Increased expression of several profibrotic genes associated with tissue fibrosis and the transdifferentiation and activation of myofibroblasts was demonstrated in total RNA isolated from skin and lungs of these animals.

Conclusion: A remarkable observation was the development of extensive fibrosis in the skin, lungs and other organs in mice with constitutive endothelial cell-specific activation of TGF-β-signaling. Alterations resembling the microvascular pathology characteristic of human SSc were also observed. These results render this transgenic mouse strain a valuable model for SSc as they reproduce the typical cutaneous and visceral tissue fibrosis and severe fibroproliferative microvascular alterations found in SSc. These results also provide new information about the pathogenesis of tissue fibrosis in response to the effect of increased TGF-β expression specifically in cells of endothelial origin.

Abstract Number: 1847

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-11

Abstract Number: 1848

Adenosine A2A Receptor (A2AR) Stimulates Collagen Type III Synthesis Via β-Catenin Activation in Vitro and in Vivo

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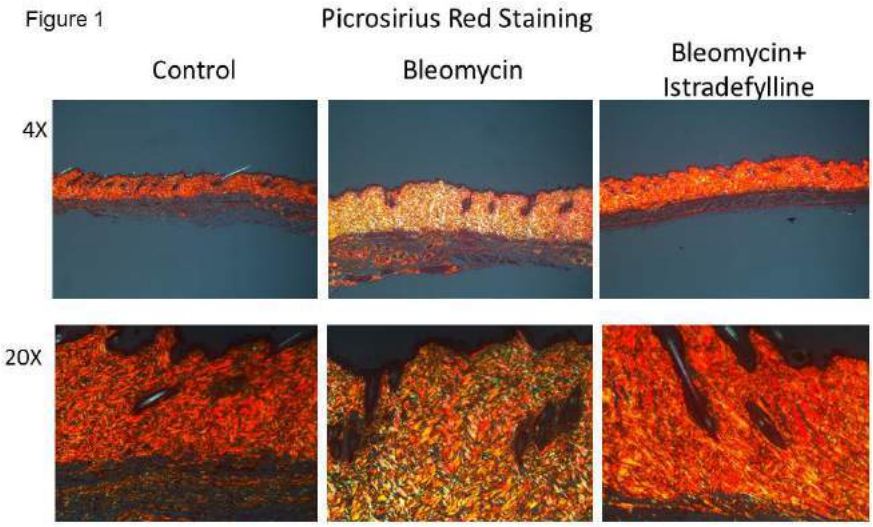
Background/Purpose: Fibrosis of skin and other organs is a hallmark of Scleroderma. We and others have previously reported that A2AR plays a role in skin and organ fibrosis in murine models of scleroderma. A2AR stimulation induces collagen type I and type III (Col1 and Col3) synthesis, mediators of fibrosis and scarring, via a mechanism involving cAMP/PKA/p38-MAPK/AKT. Wnt signaling is important in fibrosis and cAMP and Wnt signaling pathways converge. We therefore asked whether A2AR stimulates Wnt signaling pathways to promote collagen synthesis.

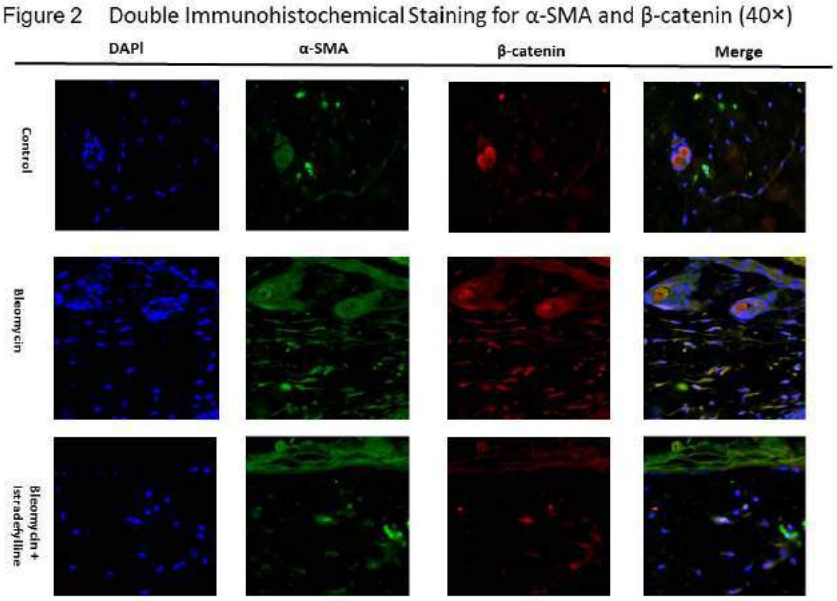
Methods: Total β-catenin, de-phosphorylated β-catenin (canonical activation, de-phospho β-catenin), and phosphorylated β-catenin at Ser552 (non-canonical activation, p-Ser552 β-catenin) levels were determined in primary human dermal fibroblast cytosol and nucleus by western blot and fluorescence microscopy after stimulation by A2AR-selective agonist CGS21680, with / without A2AR-selective antagonist (SCH582611) pretreatment. β-catenin was knocked down by lentiviral transfection with scrambled-siRNA or specific-siRNA, and Col1 and Col3 levels determined by western blot. In vivo effects were studied in a bleomycin-induced dermal fibrosis model using Wnt signaling reporter mice, Tcf/lef1-GFP homogenous mice, and mice were treated with A2AR antagonist (Istradefylline). Morphometric features and levels of hydroxyproline were determined as measures of dermal fibrosis. Fibrosis was confirmed by Picrosirius red stain. Immunohistochemistry for GFP and β-catenin were determined as measures of β-catenin translocation.

Results: CGS21680 stimulation rapidly (15min) increased cellular β-catenin to 176 ± 16 % of control ($n = 6$, $P < 0.05$); Both de-phospho β-catenin (168 ± 30% of control, $n = 6$, $P > 0.05$) and p-Ser552 β-catenin (220 ± 22 % of control, $n = 6$, $P < 0.05$) were increased. CGS21680 stimulated translocation of total, de-phospho, and p-Ser552 β-catenin to the nucleus. A2AR-stimulation increased Col1 synthesis similarly in β-catenin knockdown and scrambled cells. However, β-catenin knockdown abrogated the A2AR-stimulated increments in Col3 synthesis by 73% (66 ± 14% vs. 18 ± 16% increase of Col3, $n = 8$, $P < 0.05$). A2AR antagonist–treated mice were protected from developing bleomycin-induced dermal fibrosis (Figure 1) and there was diminished nuclear translocation of β-catenin in the affected skin (Figure 2).

Conclusion: A2AR stimulation promotes Col3 synthesis via canonical and non-canonical β-catenin activation, leading to dermal fibrosis and scarring. Selectively modifying this pathway represents an attractive therapeutic target in fibrotic



diseases such as scleroderma.



Disclosure: J. Zhang, None; **G. Shaikh**, None; **C. Corciulo**, None; **T. Wilder**, None; **M. Perez-Aso**, None; **A. Mediero**, CP15/0053, 2, 9,Patent for the use of adenosine A2AR agonists to prevent prosthesis loosening. Patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **B. Cronstein**, Canfite Pharma, 1,Celgene, AstraZeneca, Takeda, 2,Revive Therapeutics, 5,Always hopeful, 9.

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Abstract Number: 1849

Fibroblast Growth Factor 9/ Fibroblast Growth Factor Receptor 3 Signaling Is Upstream of Several Profibrotic Pathways and Induces Fibroblast Activation and Tissue Fibrosis in SSc

Tatjana Mallano[1], Alfiya Distler[1], Clara Dees[1], Jingang Huang[2], Debomita Chakraborty[3], Oliver Distler[4,5], Georg Schett[6] and Joerg H.W Distler[7], [1]Department of Internal Medicine III, Institute for Clinical Immunology, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany, [2]Department of Internal Medicine 3 and Institute for Clinical Immunology, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany, [3]Department of Internal Medicine III, Institute of Clinical Immunology, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany, [4]Center of Exper Rheumatology, University Hospital Zurich, Zurich, Switzerland, [5]Research of Systemic Autoimmune Diseases, Division of Rheumatology, University Hospital Zurich, 8952 Schlieren, Switzerland, [6]Department of Internal Medicine III, Institute for Clinical Immunology,, Friedrich-Alexander-University Erlangen-Nuremberg (FAU), Erlangen, Germany, [7]Department of Internal Medicine 3, Rheumatology and Immunology, Friedrich-Alexander University Erlangen-Nuremberg, Erlangen, Germany

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FGF9 / FGFR3 signaling is upstream of several profibrotic pathways and induces fibroblast activation and tissue fibrosis in SSc

Background/Purpose: Systemic sclerosis (SSc) is a chronic fibrotic connective disease of unknown etiology that affects the skin and internal organs. Fibroblast growth factor receptor 3 (FGFR3) belongs to a family of 4 different FGF receptors. Alterations of FGF signaling receptors have been linked to a variety of skeletal dysformations and are also found in some forms of cancer. An FGFR3 isoform binds FGF-1 (acidic FGF) and FGF-9 and binding of one of these FGFs to FGFR3 induces homodimerization and activates the receptor tyrosine kinase function. The purpose of this study was to elucidate the role of FGF9/FGFR3 signaling in Systemic Sclerosis.

Methods: The expression of FGF9 and FGFR3 in skin tissue and in human dermal fibroblasts was determined by real-time PCR, Western blot and immunohistochemistry. Knock-down and overexpression strategies were used to evaluate the effect of both on fibroblast activation. The outcome of mice with fibroblast-specific knockout of FGF9 or non-conditional knockout of FGFR3 was evaluated in bleomycin-induced skin fibrosis; fibrosis induced by overexpression of a constitutively active TGF-β receptor I (TBRIact) and in the Tsk model. FGFR3 pharmacological inhibition with PD 173074 was evaluated in vitro as well as in murine models of fibrosis.

Results: Our results show an upregulation of FGFR3 and in particular of its ligand FGF-9 in the skin of SSc patients. The upregulation of FGF9 was induced by TGFβ in vitro and in vivo and inhibition of TGFβ signaling blocked the upregulation of FGF9 in experimental fibrosis. SSc fibroblasts were more responsive to FGF-9 stimulation with enhanced activation of downstream mediators such as ERK and p38. Stimulation of fibroblasts with recombinant FGF9 or overexpression of a constitutively active FGFR3 induced myofibroblast-differentiation of resting fibroblasts, stimulated the collagen release and induced the expression of profibrotic mediators such as CTGF, ET-1 and IL4R. Inactivation of FGFR3, FGF9 or of the downstream mediators ERK and p38 reduced fibroblast activation and prevented the upregulation of pro-fibrotic target genes. Consistent with the induction of FGF9 by TGFβ and the profibrotic effects of FGF9, fibroblasts lacking FGF9 or FGFR3 were less sensitive to TGFβ stimulation. Inactivation of FGF9 or of its receptor FGFR3 exerted potent antifibrotic effects in several preclinical models. Knockout of FGF9 or FGFR3 ameliorated experimental fibrosis in bleomycin, TBRIact and Tsk animal model. Moreover, pharmacological inhibition of FGFR3 by the selective inhibitor prevented not only progression of fibrosis in experimental fibrosis, but also induced regression of pre-established fibrosis.

Conclusion: We demonstrate a novel role of FGF9/FGFR3 signaling in fibroblast activation and tissue fibrosis. FGF9/FGFR3 signaling is activated in SSc in a TGF-β dependent manner and induces several well-known profibrotic pathways to promote fibroblast-to-myofibroblast transition and collagen release. Pharmacologic or genetic inactivation of FGF9 or FGFR3 ameliorated fibroblast activation and fibrosis in several murine models.

Disclosure: T. Mallano, None; **A. Distler**, None; **C. Dees**, None; **J. Huang**, None; **D. Chakraborty**, None; **O. Distler**, None; **G. Schett**, None; **J. H. W. Distler**, None.

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Abstract Number: 1850

Optimization of a Murine Model to Recapitulate Dermal and Pulmonary Features of SSc

Tomoya Watanabe[1], Tetsuya Nishimoto[2], Jonathan Heywood[3], Stanley Hoffman[4], Logan Mlakar[4] and Carol A. Feghali-Bostwick[5], [1]Rheumatology, Medical University of South Carolina, Charleston, SC, [2]Department of Medicine, Medical University of South Carolina, Charleston, SC, [3]Rheumataology, Medical University of South Carolina, Chareston, SC, [4]Medical University of South Carolina, Charleston, SC, [5]Medicine, Medical University of South Carolina, Charleston, SC

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Session Time: 9:00AM-11:00AM

Background/Purpose: The murine bleomycin (BLM)-induced fibrosis model is the most widely used in systemic sclerosis (SSc) studies. Traditionally, daily subcutaneous injections of BLM for 4-6 weeks are commonly used to induce local dermal inflammation and fibrosis. However, this model has disadvantages such as localized cutaneous fibrosis, rare involvement of the lung, and a requirement for repeated local injections. It was recently reported that systemic delivery of BLM via continuous diffusion from subcutaneously implanted osmotic minipumps can cause fibrosis of the skin, lungs, and other internal organs. However, the mouse strain, dosage of BLM, administration period, and additional important features differ from one report to the next. In this study, we have investigated the dosage of BLM, extent of fibrosis, and time-dependent changes in dermal and pulmonary fibrosis in C57BL/6J mice using the pump model.

Methods: BLM was administered to 8 week-old, male C57BL/6J mice using osmotic minipumps implanted subcutaneously and containing either 100µl saline as vehicle or BLM for 7 days. BLM was administered at 1.0 U/kg, 10 U/kg, 60 U/kg, or 110 U/kg. Pumps were implanted for 7 days. Lung and skin tissues were harvested on days 10, 14, 21, and 28 post-implantation. The extent of pulmonary fibrosis was measured using hydroxyproline assay. The extent of dermal fibrosis was quantified using both hydroxyproline assay and measurement of dermal thickness. Furthermore, the mRNA levels of fibrosis-related genes were measured using real-time PCR.

Results: Mice treated with different concentrations of BLM showed a dose-dependent increase in lung fibrosis by day 28. The levels of collagen in lungs from mice treated with high dose BLM were significantly greater than levels in lungs from mice treated with vehicle or lower doses of BLM. On the other hand, dermal fibrosis was not increased in a dose- or time-dependent manner. Interestingly, marked dermal thickness was induced by low dose BLM while no significant changes were noted with high-dose BLM by day 28. However, dermal thickness was significantly increased 10 days post BLM. Hydroxyproline assay also revealed that the amount of collagen in skin on day 10 was significantly higher than in skin treated with vehicle. However, by day 21 there were no significant differences in dermal thickness or collagen content between the treatment groups.

Conclusion: Our findings show that dermal fibrosis in C57BL/6J mice using the pump model differs with mouse strains, dose of BLM, and duration of the model. The BLM pump model is a powerful tool for the functional analysis of systemic fibrosis and the testing of potential therapies. However, the choice of mouse strains, duration of BLM administration and

dose must be carefully considered when using this model.

Disclosure: T. Watanabe, None; **T. Nishimoto**, None; **J. Heywood**, None; **S. Hoffman**, None; **L. Mlakar**, None; **C. A. Feghali-Bostwick**, None.

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Abstract Number: 1851

The Effect of Narrow Band Ultraviolet A1 Light on Bleomycin-Induced Mouse Model of Scleroderma

Diana Karpec[1,2], Romualdas Rudys[2], Laima Leonaviciene[2], Zygmunt Mackiewicz[2], Ruta Bradunaite[2], Gailute Kirdaite[2], Rita Rugiene[2] and Algirdas Venalis[2,3], [1]Clinics of Rheumatology, Traumatology-Orthopedics and Reconstructive Surgery, Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania, [2]State Research Institute Centre for Innovative Medicine, Vilnius, Lithuania, [3]Vilnius University Hospital Santariskiu Klinikos, Vilnius, Lithuania

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Session Time: 9:00AM-11:00AM

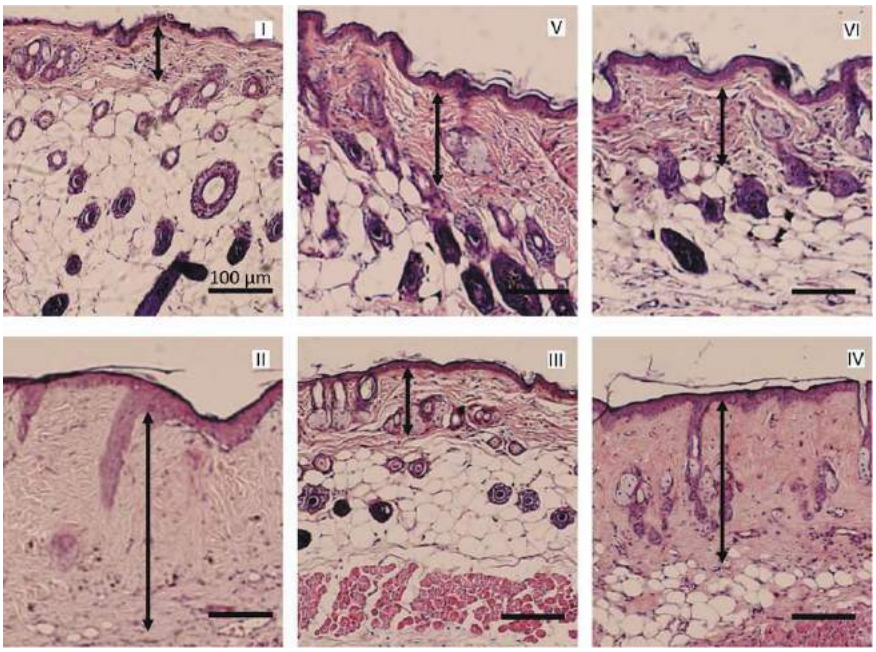
Background/Purpose: Ultraviolet A1 (UVA1) phototherapy implications for systemic sclerosis still remain the area of research. The aim of the study was to evaluate narrow band 365 nm ± 5 nm light effectiveness and safety for the treatment of dermal fibrosis in bleomycin-induced mouse model of scleroderma using light emitting diodes device.

Methods: DBA/2 strain mice were randomly divided to 6 groups: I – healthy animals; II – control group with bleomycin-induced scleroderma, III and IV – mice with established scleroderma, treated with high- and medium-dose of UVA1 light; V and VI – healthy mice treated with high- and medium-dose of UVA1 light. Light source emitting a narrow band UVA1 light of 365±5 nm and 21 mW/cm² power density was used in the study. Phototherapy was performed 3 times weekly for 5 weeks. The average cumulative doses were 600 J/cm² for medium- and 1200 J/cm² for high-dose treatment. Histological analysis with hematoxylin – eosin staining for dermal thickness measurement was performed. The immunohistochemical staining for p53 and Ki-67 proteins was performed using specific antibodies. Statistical significance was expressed by a P-value < 0.05.

Results: Phototherapy course was well tolerated by the animals. The dermal thickness of mice treated with high- and medium dose of UVA1 was significantly reduced to 272.9 ± 113.2 and 394 ± 125.9 μm, respectively, in comparison to control group II (599 ± 55.7 μm) ($p<0.05$). Parallel data were analyzed of UVA1- treated healthy mice skin: there was no dermal thickness change in both medium- and high-dose groups. The progression of dermal thickness is summarized in Figure 1. In the healthy mice group (I) the percentage of Ki-67-positive cells was 50.4 ± 2.6% and the number of these positive cells were reduced to 36.1 ± 3% in control group (II) after bleomycin injections ($p < 0.05$). The percentage of Ki-67 positive cells after medium- and high-dose UVA1 treatment of scleroderma skin (group IV and III) was 37.2 ± 2.8% and 35.4 ± 3.2%, respectively, and did not differ from the control group (II). The expression of p53 was significantly higher in the skin of control group (II) compared to healthy mice skin (I). After UVA1 treatment of mice with scleroderma, the expression of p53 did not differ in comparison to the control group without phototherapy (II). There was no statistically significant change of both p53 and Ki-67 expression between healthy (I) and UVA1-treated healthy mice skin (groups V and VI).

Conclusion: Medium- and high-dose 365 nm UVA1 effect on reducing dermal thickness is dose-dependent. This irradiation

does not affect dermal thickness in healthy skin. Cell apoptosis (p53) and proliferation (Ki-67) changes in the dermal and subcutaneous layers suggest a favorable narrow light effect in the experimental sclerosis and healthy mice groups. Narrow band UVA1 phototherapy using light emitting diodes device might be the new era of dermal fibrosis phototherapy.



Disclosure: D. Karpec, None; **R. Rudys**, None; **L. Leonaviciene**, None; **Z. Mackiewicz**, None; **R. Bradunaite**, None; **G. Kirdaite**, None; **R. Rugiene**, None; **A. Venalis**, None.

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Abstract Number: 1852

Decreased Expression of Sirtuin 7 By Lung Fibroblasts from Patients with Scleroderma Contributes to Elevated Collagen Production

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SESSION INFORMATION

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Background/Purpose: Pulmonary fibrosis is a severe complication of systemic sclerosis (SSc). Changes in the expression levels of sirtuins (SIRTs), a family of NAD^+-dependent histone deacetylases, have been reported recently in patients with SSc and other fibrotic diseases, implying a possible pathophysiologic role. Out of 7 known human SIRTs, SIRT1 has received the most attention. We have comparatively assessed the mRNA and protein expression of all SIRTs in primary lung fibroblasts from scleroderma patients with pulmonary fibrosis, idiopathic pulmonary fibrosis (IPF), and from healthy controls, and begun addressing mechanistic implications of the observed differences.

Methods: mRNA levels of SIRT1-7 were measured by RT-qPCR in lung tissue and fibroblasts from scleroderma patients with lung fibrosis and patients with IPF, as well as from healthy controls; protein levels were measured by western blotting. Intracellular delivery of SIRT7-encoding plasmid constructs and SIRT7-inhibiting siRNA to cultured adult normal human lung fibroblasts was performed by electroporation. The effects of SIRT7 on mRNA of collagen chains COL1A1, COL1A2, and COL3A1 and on protein levels of type I collagen, with and without stimulation with recombinant TGF-β, were assessed.

Results: mRNA and protein levels of all SIRTs tended to be lower in lung tissues and fibroblasts from patients with fibrosis compared to controls, but the levels of SIRT7 mRNA and protein in pulmonary fibroblasts were significantly lower, particularly in scleroderma ($p<0.001$ for SIRT7 mRNA and $p=0.019$ for SIRT7 protein). SIRT7 overexpression in fibroblast cultures inhibited basal and TGF-β-induced levels of collagen, reducing COL1A1 mRNA levels by 5 to 10 fold, COL1A2 mRNA by 2 to 3 fold, and COL3A1 by 3 to 5 fold; the levels of collagen protein were reduced by ~3 fold. SIRT7 silencing increased collagen protein by ~2 fold.

Conclusion: Pulmonary fibrosis is characterized by lower levels of sirtuins, with a particularly notable decrease in SIRT7 in scleroderma. Overexpression of SIRT7 decreases collagen mRNA and protein levels in cultured lung fibroblasts and attenuates TGF-β-induced increases in collagen. These findings identify SIRT7 as a pathophysiologic contributor to lung fibrosis.

Disclosure: A. E. Wyman, None; **Z. Noor**, None; **N. W. Todd**, None; **I. G. Luzina**, None; **S. P. Atamas**, None.

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Abstract Number: 1853

Klf5+/-;Fli1+/- Mice Recapitulate Protracted Wound Healing and Cardiac and Intestinal Involvement Associated with Systemic Sclerosis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease characterized by vasculopathy and tissue fibrosis. Although the most recognizable manifestation is skin disease, SSc can affect the lungs, heart, gastrointestinal tract and kidney resulting in significant morbidity and mortality. Digital ulcers and gangrene caused by progressive vasculopathy are also critical complications of SSc, strongly affecting physical function. Although animal models mimicking its entire pathology were previously unavailable, we have recently established mice with double heterozygous deficiency of the *Klf5* and *Fli1* genes, both of which are epigenetically suppressed in SSc dermal fibroblasts, spontaneously developing features of SSc, including fibrosis and vasculopathy of the skin and lung, B cell activation, and autoantibody production. In this study, we further investigated if $Klf5^{+/-}$;$Fli1^{+/-}$ mice recapitulate delayed wound healing and cardiac and intestinal involvement characteristic of SSc.

Methods: Four full-thickness excisional wounds per mouse were generated by an 8-mm biopsy punch on the back skin. The process of wound healing was assessed macroscopically and histologically. Angiogenesis and vasculogenesis were assayed by *ex vivo* retinal explant culture assay and *in vivo* matrigel plug assay, respectively. Myocardium, small intestine, and colon samples were analyzed by quantitative reverse transcription PCR, immunoblotting, and immunohistochemistry.

Results: Wound healing was markedly delayed in *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice compared with wild type (WT) mice. In scar tissue, vascular network was poorly developed in *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice compared with WT mice. However, at day 5 after wounding the number and the diameter of newly formed vessels in granulation tissue were significantly increased in *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice compared with WT mice. In *ex vivo* retinal explants culture assay, angiogenesis was markedly accelerated in *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice. In contrast, vasculogenesis was impaired in *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice when evaluated by *in vivo* matrigel plug assay. Importantly, the stimulation of angiogenesis- and vasculogenesis-related factors suppressed the expression of both KLF5 and Fli1 in human dermal microvascular endothelial cells and murine mesenchymal stem cells, respectively. With respect to visceral organ involvement, apoptotic vascular endothelial cells were evident together with interstitial fibrosis in heart and dysfunction of intestine due to a switch from a contractile to synthetic phenotype of intestinal smooth muscle cells was suspected.

Conclusion: *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice mimic delayed wound healing and cardiac and intestinal involvement of SSc. Delayed wound healing seems to be associated with accelerated angiogenesis and suppressed vasculogenesis together with impaired anastomosis of newly formed vessels with pre-existing ones. Cardiac fibrosis and intestinal dysfunction were due to endothelial apoptosis and a phenotypical alteration of intestinal smooth muscle cells, respectively. These results indicate that *Klf5*$^{+/-}$;*Fli1*$^{+/-}$ mice could serve as a reliable tool to investigate the details of disease process underlying SSc.

Disclosure: K. Nakamura, None; **Y. Asano**, None; **T. Miyagawa**, None; **M. Hirabayashi**, None; **T. Yamashita**, None; **R. Saigusa**, None; **S. Miura**, None; **T. Toyama**, None; **T. Takahashi**, None; **Y. Ichimura**, None; **T. Taniguchi**, None; **A. Yoshizaki**, None; **M. Trojanowska**, None; **S. Sato**, None.

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Abstract Number: 1854

Increased Percentage of CD204/CD206 Double Positive Monocytes Correlates with Specific Lung and Skin Involvement Parameters and an “Active” Capillaroscopic Pattern of Microangiopathy in Systemic Sclerosis Patients

Stefano Soldano[1], Paola Contini[2], Amelia Chiara Trombetta[3], Barbara Ruaro[4], Sabrina Paolino[4], Carmen Pizzorni[4], Renata Brizzolara[4], Paola Montagna[4], Alberto Sulli[4] and **Maurizio Cutolo**[4], [1]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genoa, Italy, [2]Division of Clinical Immunology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genova, Italy, [3]Department of Internal Medicine, University of Genova,, Research Laboratory and Academic Division of Clinical Rheumatology, Genova, Italy, [4]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genova, Italy

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Background/Purpose: Immune cell activation plays a crucial role in the pathogenesis of systemic sclerosis (SSc), and macrophages may be important mediators in this complex pathway (1,2). In SSc patients (pts), alternatively activated macrophages (M2) are present in the skin infiltrate, contributing to dermal fibrosis (2). M2 may differentiate from peripheral blood monocytes (PBMs), and are characterized by the expression of specific phenotype markers, such as CD206 (mannose receptor-1), and CD204 (macrophage scavenger receptor) (1). The study investigated the percentages of circulating $CD206^+/CD204^+$PBMs in SSc pts and possible correlations with specific clinical parameters.

Methods: Sera from forty-one SSc pts (36 females/5 males, mean age 62±15 years), who fulfilled the new EULAR/ACR criteria (3), and twenty voluntary healthy subjects (HS - 16 females/4 males, 61±10 years) were collected after EC approval and Informed Consent signed. Lung involvement (DLCO) and specific SSc autoantibodies (anti-centromere/CENP; anti-topoisomerase/Scl70; RNApoly3; fibrillarin; Th/Th0; PM-Scl75) were analysed. Nailfold videocapillaroscopy (NVC) was performed to define the pattern of microangiopathy. PBMs from SSc pts and HS were evaluated by flow cytometry (FC) by investigating cell positive for CD14 (monocyte/macrophage marker), CD206 and CD204. The statistical analysis was carried out using Mann-Whitney non-parametric U-test and correlation test.

Results: Among the 41 SSc pts, 27 showed a "limited" cutaneous involvement (lSSc) and 14 a "diffuse" cutaneous involvement (dSSc). The analysis of specific auto-antibodies yielded 13 pts positive for CENP, 16 pts positive for Scl70, 6 pts positive for the other investigated autoantibodies. Six pts were found Ab negative and excluded from the study. The evaluation by FC of circulating $CD14^+$cells did not show any significant difference between SSc patients and HS. However, in the $CD14^+$cell subset the percentage of $CD206^+CD204^+$cells was significantly increased in SSc pts compared to HS ($p=0.02$). The percentage of these cells was increased in lSSc pts ($p=0.06$), but significantly increased in dSSc pts ($p=0.03$) and inversely correlated with DLCO ($p=0.032$, $R=0.13$). In addition, $CD206^+CD204^+$cells were increased in Scl70-positive pts and significantly increased in CENP positive pts ($p=0.011$). NVC analysis identified 12 SSc pts with an "early" pattern, 14 pts with an "active" pattern and 16 pts with a "late" pattern. The percentage of $CD206^+CD204^+$cells was increased in pts with "early" or "late" NVC pattern ($p=0.09$, $p=0.06$) but significantly increased in those with the "active" pattern compared to HS ($p=0.04$).

Conclusion: The results confirmed the presence of an increased percentage of cells with an M2 phenotype in the peripheral blood of SSc pts. M2 cells seem to correlate with specific lung and skin involvement, autoantibody positivity and an "active" NVC pattern of microangiopathy. **References:** 1 Higashi-Kuwata N et al. Arthritis Res Ther 2010:12:R128. 2 Nakayama W et al. Rheumatol Int 2012;32:403–7. 3 van der Hoogen F et al. Arthrit Rheum 2013;65:2737-47.

Disclosure: S. Soldano, None; **P. Contini**, None; **A. C. Trombetta**, None; **B. Ruaro**, None; **S. Paolino**, None; **C. Pizzorni**, None; **R. Brizzolara**, None; **P. Montagna**, None; **A. Sulli**, None; **M. Cutolo**, Actelion, BMS, Sanofi-Aventis, 2,Actelion, BMS, Sanofi-Aventis, 5.

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Abstract Number: 1855

Phosphodiesterase-5 Inhibitors Attenuate Fibrotic Phenotype and Restore Anti-Fibrotic Resopnses of Cutaneous Fibroblasts in Patients with Scleroderma

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Background/Purpose: Scleroderma (SSc) is a chronic autoimmune disease, characterized by excessive fibrosis of skin and internal organs due to uncontrolled proliferation of fibroblasts and deposition of extracellular matrix protein. Till date there is no promising therapy available for treatment of fibrosis in Scleroderma. Herein, we hypothesize that Phosphodiesterase5 inhibitors (PDE5i) attenuate fibrotic phenotype of cutaneous fibroblasts in patients with scleroderma.

Methods: Primary fibroblast cultures from midforearm skin of 13 Patients with scleroderma (as per ACR/LeRoy criteria) and 5 healthy individuals were established. To mimic disease condition fibroblasts were pre-stimulated with Transforming growth factor-beta1 (TGF-β1) (10 ng/ml) for 1 hour followed by further incubation with TGF-β1 and PDE5i; Sildenafil (10μM) and Zaprinast (10μM), for 24 hours (Strategy 1). In another strategy fibroblast were pre-treated with Sildenafil (10μM) and Zaprinast (10μM) for 1 hour followed by incubation with TGF-β1 (10 ng/ml) for 24 hours (Strategy 2). Expression of profibrotic genes; collagen 1 alpha 1 (COL1A1), collagen 1 alpha 2 (COL1A2), Fibronectin, alpha smooth muscle actin-1(ASMA1), connective tissue growth factor (CTGF), and antifibrotic gene; Matrix metalloproteinases 2/Tissue inhibitor of metalloproteinases (MMP2/TIMP) was analyzed with real time PCR and later their protein expressions were confirmed by Western Blot. Further, effect of PDE5i on TGF-β1 downstream signaling; canonical and non-canonical pathways, were analyzed with western blot. ANOVA and Student's t-Test were used for statistical analysis in SPSS 13 software.

Results: TGF-β1 significantly increased the expression of COL1A1, COL1A2, ASMA1, fibronectin, and CTGF at mRNA and protein levels compared to untreated fibroblasts. TGF-β1 induced fibrotic genes expression were significantly higher in SSc fibroblasts compared to healthy fibroblasts. In both Healthy and SSc fibroblasts, Sildenafil and Zaprinast treatment in both the strategies, significantly reduced the mRNA and protein expression of type 1 collagen, ASMA-1, fibronectin and CTGF compared to treatment with TGF-β1. Moreover, Sildenafil and Zaprinast treatment restored the levels of MMP2/TIMP1 in fibroblasts which were suppressed by TGF-β1 treatment. MMP2 level was significantly increased in culture supernatant of Healthy and SSc fibroblasts treated with PDE5i. Sildenafil and Zaprinast both reduced the phosphorylation of Smad3 (canonical) and Erk1/2 (non-canonical) in SSc fibroblasts.

Conclusion: PDE5i, Sildenafil and Zaprinast, not only attenuate the pro-fibrotic phenotype but also increase anti-fibrotic response in TGF-β1 treated cutaneous fibroblasts in SSc patients. Antifibrotic effect of PDE5i is mediated by affecting both canonical as well non-canonical TGF-β1 mediated downstream signaling pathways.

Disclosure: V. Agarwal, None; **M. K. Rai**, None; **V. Agrawal**, None; **H. Singh**, None; **S. Chaturvedi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/phosphodiesterase-5-inhibitors-attenuate-fibrotic-phenotype-and-restore-anti-fibrotic-resopnses-of-cutaneous-fibroblasts-in-patients-with-scleroderma

Abstract Number: 1856

Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) As a Potential Topical Treatment for Scleroderma

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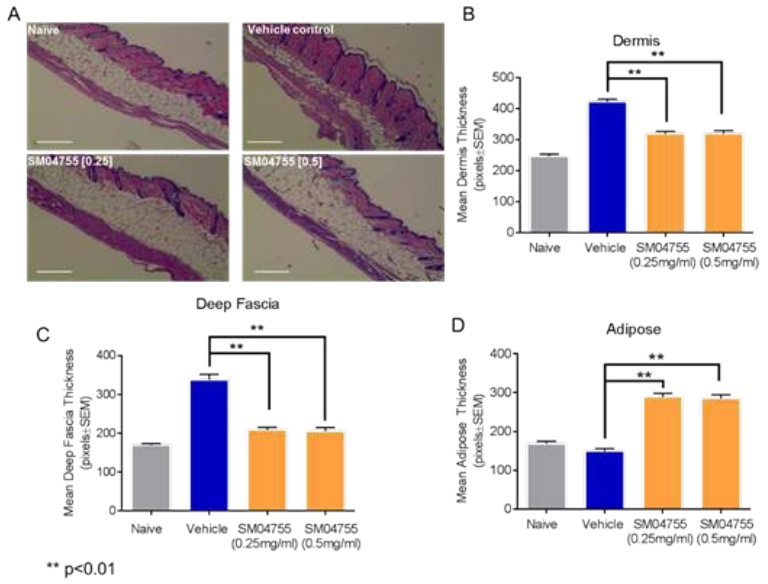
Background/Purpose: Scleroderma is an autoimmune fibrotic disease, which presents skin manifestations among others. The Wnt pathway plays an important role in inflammation, skin fibrosis, and vasculopathy, and is upregulated in scleroderma. SM04755, a novel, topical, small-molecule Wnt pathway inhibitor was evaluated in a series of preclinical studies to determine its potential to reduce inflammation, dermal fibrosis, and vasculopathy, thereby improving skin health in scleroderma.

Methods: Wnt pathway inhibition of SM04755 was measured using a cell-based reporter assay. Anti-inflammatory activity was evaluated by measuring TNF-α and IL-6 secretion using ELISA in THP-1 monocytes stimulated with Lipopolysaccharides (LPS), and PBMCs stimulated with anti-CD3/anti-CD28. The effect on fibrosis was assessed in TGF-β stimulated human dermal fibroblasts by measuring smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF), and collagen expression by qPCR. The effect on myofibroblast differentiation and reversion was measured by immunocytochemistry for αSMA. Pharmacokinetics were evaluated following topical application in rats and mini-pigs by analysis of compound concentrations in skin and plasma. *In vivo* efficacy was evaluated in a subcutaneous bleomycin-induced mouse model of scleroderma by histological measurements of the thickness of various layers of the skin, and CD31 immunohistochemistry for vasculopathy.

Results: SM04755 demonstrated potent (EC_{50}=152nM) and selective inhibition of Wnt signaling. SM04755 inhibited LPS and anti-CD3/anti-CD28 induced TNF-α and IL-6 secretion (EC_{50}=500nM) in THP-1 cells and PBMCs. SM04755 treatment significantly ($p<0.05$) inhibited dermal fibrosis measured by a decrease in TGF-β stimulated αSMA, PAI-1, CTGF, and collagen gene expression in human dermal fibroblasts. SM04755 reduced αSMA stained stress fibers in myofibroblasts (EC_{50}=400nM) thus reversing fibrosis. Single topical application of SM04755 showed skin concentrations >EC_{50} for >24hrs, with minimal systemic exposure or toxicity. In a bleomycin-induced mouse scleroderma model, topical SM04755 treatment after induction of fibrosis significantly ($p<0.01$) reduced thickness of dermis and deep fascia, and increased thickness of the adipose layer, as compared to vehicle, thereby reversing bleomycin-induced dermal fibrosis. SM04755 treatment also reduced vasculopathy measured as a decrease in the endothelial marker CD31 staining in the skin.

Conclusion: SM04755 inhibited inflammation and reversed dermal fibrosis *in vitro*. In a bleomycin-induced mouse scleroderma model, topically applied SM04755 reversed dermal fibrosis, increased adipose tissue, and reduced vasculopathy compared to vehicle, with minimal exposure in the plasma or systemic toxicity. SM04755 has potential as a topical therapy for scleroderma.

Figure. SM04755 reduced the thickness of the dermis and deep fascia relative to control in a bleomycin-induced scleroderma model in mice



Disclosure: V. Deshmukh, Samumed, LLC, 3; **A. Hood**, Samumed, LLC, 3; **M. Ibanez**, Samumed, LLC, 3; **L. Dellamary**, Samumed, LLC, 3; **J. Stewart**, Samumed, LLC, 3; **T. Seo**, Samumed, LLC, 3; **J. Hood**, Samumed, LLC, 9; **Y. Yazici**, Samumed, LLC, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/discovery-of-a-small-molecule-inhibitor-of-the-wnt-pathway-sm04755-as-a-potential-topical-treatment-for-scleroderma

Abstract Number: 1857

A Novel Highly Selective 5-Hydroxytryptamine 2B (5-HT2B) Receptor Antagonist Ameliorating Fibrosis in Preclinical Models of Systemic Sclerosis

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Background/Purpose: Microvascular injury is one of the first pathological events in systemic sclerosis, and precedes the fibrosis. A consequence of vascular damage is the exposure of subendothelial connective tissue that causes activation of platelets and local serotonin (5-hydroxytryptamine, 5-HT) release. Binding of 5-HT to 5-HT_{2B} receptors on fibroblasts results in increased myofibroblast differentiation and release of excessive amounts of matrix proteins subsequently leading to fibrosis. Thus, pharmacologic inhibition of 5-HT_{2B} receptors may represent a new treatment opportunity for systemic sclerosis. In this study a novel highly selective 5-HT_{2B} receptor antagonist was evaluated for its ability to reduce the

production of matrix proteins in human dermal fibroblasts and to ameliorate fibrosis in the tight-skin-1 model of systemic sclerosis.

Methods: Dermal fibroblasts isolated from patients with systemic sclerosis were cultured with different concentrations of the 5-HT_{2B} receptor antagonist AM1125 with or without 1 μM 5-HT. Anti-fibrotic effects were evaluated by measuring matrix production, myofibroblast differentiation and TGF-β production. The tight-skin-1 model was used to evaluate anti-fibrotic effects *in vivo* using a therapeutic treatment approach. AM1125 was administered at 10 and 50 mg/kg orally, b.i.d. from week 5 to week 10. Hypodermal thickening, myofibroblast counts and collagen production (hydroxyproline) were evaluated at the end of the treatment period.

Results: *In vitro* AM1125 dose-dependently reduced TGF-β, PAI, nuclear SMAD2/3 and collagens in human dermal fibroblasts. In addition, stress fiber formation and α-SMA mRNA were reduced indicating decreased myofibroblast differentiation. Therapeutic treatment with the 5-HT_{2B} receptor antagonist AM1125 at 50 mg/kg reduced hypodermal thickness ($p<0.001$), myofibroblast counts ($p<0.05$) and hydroxyproline content ($p<0.01$) in the tight-skin-1 model. In addition, the lower dose (10 mg/kg) reduced hypodermal thickness ($p<0.001$).

Conclusion: The results demonstrate that the 5-HT_{2B} receptor antagonist AM1125 prevents pro-fibrotic events in human dermal fibroblasts and attenuates dermal fibrosis using a therapeutic treatment approach in the tight-skin-1 model. Thus, 5-HT_{2B} receptor antagonists, exemplified by the novel compound AM1125, could represent a new treatment opportunity for systemic sclerosis.

Disclosure: C. Wenglén, AnaMar AB, 3; **L. Pettersson**, Anamar AB, 3; **H. Arozenius**, AnaMar AB, 3; **G. Ekström**, AnaMar AB, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-novel-highly-selective-5-hydroxytryptamine-2b-5-ht2b-receptor-antagonist-ameliorating-fibrosis-in-preclinical-models-of-systemic-sclerosis

Abstract Number: 1858

Phenotypical and Functional Characteristics of in Vitro Expanded Adipose-Derived Mesenchymal Stem Cells from Patients with Systemic Sclerosis

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Background/Purpose: Adult stem cells, namely those of mesenchymal origin (MSCs), have received attention as an ideal source of regenerative cells because of their multi-potential ability to replicate. Adipose tissue (AT) is an alternative

attractive source of MSCs, due to its abundance and surgical accessibility. Recent studies have shown that autologous fat grafting may be effective in the treatment of specific skin lesions in systemic sclerosis (SSc), but no specific study exists aimed at investigating whether AT-MSCs in patients with SSc maintain normal phenotypic and functional characteristics. Aim of the study was to investigate whether AT-MSCs from patients with SSc (SSc-AT-MSCs) are phenotypically and functionally identical to those from healthy controls (HCs)

Methods: AT samples were obtained from 8 patients with the diffuse cutaneous variant of SSc (dcSSc) and from 5 HCs. Key parameters of AT-MSC phenotype and function were assessed in both MSC populations, including the capacity (a) to express specific MSC surface antigens (CD105, CD73, CD29, CD90, CD44) by FACS analysis, (b) to proliferate (growth kinetics assay), (c) to differentiate along the adipogenic and osteogenic lineages, (d) to suppress in vitro lymphocyte proliferation induced by the mixed lymphocyte reaction (MLR), and (e) to support endothelial cell (EC) tube formation.

Results: AT-MSCs from SSc patients and HC showed similar cell surface phenotype and multilineage differentiation capabilities. Phenotypically, SSc- and HC-AT-MSCs highly expressed CD105, CD73, CD90, HLA-ABC and were mostly negative for HLA-DR expression. When cultured in standard induction medium, both SSc- and HC-AT-MSCs similarly differentiated toward the osteogenic and adipogenic lineages. In MLR assays, no significant differences in AT-MSC-mediated inhibition of proliferation were observed between SSc- and HC-AT-MSCs. Using AT-MSC/EC co-cultures, we observed that both SSc- and HC-AT-MSCs improve tube formation by both HC- and SSc-ECs. This effect was enhanced under hypoxic conditions in all of the co-cultures.

Conclusion: Our study shows that AT-MSCs from patients with SSc exhibit the same phenotypic pattern, proliferative and differentiation potentials, as well as the same immune-suppressive properties than those from HC. The SSc-AT-MSC activity we observed as pro-angiogenic effectors, namely under hypoxic conditions, may suggest that autologous AT-MSCs grafting may represent a future possible therapeutic option in patients with this disorder.

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Abstract Number: 1859

Fucosyltransferase-1 Mediated Fucosylation of TGF-βR1 Is Critical to TGF-β Signaling in Scleroderma and in Bleomycin-Induced Fibrosis

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Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease characterized by systemic fibrosis. The

dysregulation of transforming growth factor-β (TGF-β) signaling causes proliferation of myofibroblasts and results in the uncontrolled release of extracellular matrix. We have published that fucosyltransferase-1 (Fut1), an α-1,2 fucosyltransferase, plays an important role in rheumatoid arthritis synovial fibroblast proliferation. In this study, we examine the role of Fut1 in TGF-β receptor (TGF-βR) fucosylation, downstream signaling pathways, and target genes involved in scleroderma pathogenesis.

Methods: qPCR and ELISA were performed to assess the levels of Fut1 in SSc dermal fibroblasts and patient sera, respectively. To determine fucosylation of TGF-βR1, TGF-βR1 was immunoprecipitated from wild type (WT) dermal fibroblasts and immunoblotted with ulex europaeus agglutinin 1, which detects α-1,2 fucosylated protein. To confirm TGF-bR1 fucosylation, Fut1 was knocked down in SSc dermal fibroblasts using Fut1 shRNA. We evaluated Fut1 involvement in TGF-β signaling, myofibroblast differentiation, and TGF-b-associated target genes in WT and Fut1$^{-/-}$ dermal fibroblasts via immunofluorescence (IF), qPCR, and Western blotting. An *in vivo* wound healing model was performed with Fut1$^{-/-}$ and WT mice and wound healing was assessed over 8 days. To elucidate the role of Fut1 in an animal model of scleroderma, bleomycin was injected intradermally into Fut1$^{-/-}$ and WT mice for 9 days. Mice were euthanized and skin harvested for Masson's trichrome staining and hydroxyproline assay, a quantitative measure of collagen.

Results: Fut1 mRNA and protein were significantly elevated in SSc compared to NL dermal fibroblasts and patient sera, respectively. We found via immunoprecipitation that TGF-βR1 is fucosylated by Fut1. We found less TGF-bR1 in SSc dermal fibroblasts when transduced with Fut1 shRNA, confirming the role of Fut1 in TGF-bR1 fucosylation. TGF-β-induced phosphorylation of Smad2, Erk1/2, and Jnk was markedly reduced in Fut1$^{-/-}$ dermal fibroblasts compared to WT, indicating that Fut1 is essential to TGF-βR1-mediated signaling pathways. Impaired transcription of myofibroblast differentiation inducing genes, Twist2 and Snail, was observed in Fut1$^{-/-}$ dermal fibroblasts. We found a significant decrease in α-smooth muscle actin in Fut1$^{-/-}$ compared to WT dermal fibroblasts as determined by IF and Western blotting, indicating a critical role for Fut1 in myofibroblast differentiation. In the wound repair model, Fut1$^{-/-}$ mouse wounds healed more slowly than WT mouse wounds. Fut1$^{-/-}$ mice developed significantly less bleomycin-induced skin fibrosis and collagen deposition compared to WT mice as determined by Masson's trichrome staining and hydroxyproline assay, respectively.

Conclusion: Fut1 expression is elevated in SSc dermal fibroblasts and patient sera. Fucosylation of TGF-βR1 is critical to myofibroblast differentiation and TGF-β signaling. In addition, Fut1$^{-/-}$ mice exhibit delayed wound repair and diminished bleomycin-induced skin fibrosis, indicating an essential role for Fut1 in SSc pathology. Fut1 may be a novel therapeutic target for SSc.

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Abstract Number: 1860

Activating Transcription Factor 3 – a New Linkage Between Vasculopathy and Organ Fibrosis in Systemic Sclerosis

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Background/Purpose: Since vascular manifestations such as Raynaud's phenomenon and morphological changes on nailfold capillaroscopy often precede the onset of other clinical manifestations of systemic sclerosis (SSc), the identification of pathways linking vasculopathy to organ fibrosis might thus provide important insights into early disease mechanisms and allow early targeted intervention for both fibrotic and vascular events. Recently, activating transcription factor 3 (ATF3), a member of the ATF/cAMP-responsive element binding (CREB) family of transcription factors, which regulates cellular response to stress, was characterized as a downstream mediator of canonical TGF-β signaling in fibroblast activation and tissue fibrosis. In this study we aimed to investigate the role of ATF3 linking vasculopathy to organ fibrosis.

Methods: ATF3 expression in vessels of either human skin samples of SSc patients and healthy volunteers, or murine skin and lung tissue of Fra2 transgenic (tg) mice was analyzed by multi-chanel immunofluorescence (IF) and confocal laser scanning microscopy. Human umbilical vein (HUVEC), human microvascular endothelial cells (HMEC) and smooth muscle cells (SMC) as well as immortalized blood (BEC-TI) and lymphatic (LEC-TI) endothelial cells were transfected with pCMV-ATF3 and pCMV plasmid constructs and cell proliferation and survival were measured by microtiter tetrazolium (MTT) and apoptosis assays, migration by chemotaxis-induced migration assay, and tube formation in a matrigel basement membrane matrix. Additionally, *ex vivo* mouse fetal metatarsal assays were performed using ATF3 knockout and wildtype littermates to study the angiogenetic process.

Results: ATF3 was significantly upregulated in fibroblasts of skin biopsies of SSc patients and of various organs of fibrosis models. ATF3 deficiency ameliorated fibrosis in various mouse models including Fra2 tg mice, a genetic model resembling both fibrosis and vasculopathy. Notably, ATF3 was significantly upregulated in vascular cells of fibrotic tissues of SSc patients and Fra2 tg mice. Multi-color IF and confocal laser scanning microscopy of skin and lung biopsies of SSc patients and Fra2 tg mice revealed an increased expression of ATF3 especially in microvascular endothelial cells and smooth muscle cells. ATF3 overexpression in smooth muscle cells led to an extensively enhanced proliferation and increased migratory capacity whereas endothelial cells showed a SSc-like phenotype with reduced proliferation and migration. After ATF3 overexpression, tube formation capacity was completely altered as assessed by cumulative tube length, tube numbers and capillary sprouting. To investigate vessel outgrowth from a different perspective, we used the *ex vivo* fetal mouse metatarsal assay. ATF3 knockout mice showed a completely altered angiogenic response as assessed by tube length, number of branches and number junctions compared to wildtype controls.

Conclusion: We identified ATF3 as a new profibrotic factor in endogenous activated fibroblasts as wells as in disturbed vasculature suggesting ATF3 as a potential therapeutic target intervening both fibrotic and vascular manifestations.

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Abstract Number: 1861

Modelling the Interaction Between Disease Microenvironment and Mesenchymal Cells in Systemic Sclerosis

Zeinab Taki[1], Bahja Ahmed Abdi[2], Henrique Rosario[3], Sara Zafar[4], Amy Hart[3], Shiwen Xu[5], Christopher Denton[6], David Abraham[6] and Richard J. Stratton[7], [1]Department of Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [2]Division of Medicine, Centre for Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [3]Centre of Rheumatology and Connective Tissue disease, University College London, London, United Kingdom, [4]Centre of Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [5]Division of Medicine, Centre for Rheumatology and Connective tissue disease, University College London, London, United Kingdom, [6]Division of Medicine, Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [7]Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom
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Background/Purpose: Systemic Sclerosis (SSc) has complex aetiology with many potential driving forces, one of which is the microenvironment in lesional skin, in which resident mesenchymal stem cells (MSCs), are exposed to aberrantly expressed growth factors and cytokines, and excessively stiffened and abundant extracellular matrix. We hypothesise that MScs are persistently activated within this microenvironment contributing to chronic aberrant tissue repair and fibrosis. The effects of skin blister fluid (BF) and IL-31, the maximally induced cytokine in SSc BF, were studied in models of interaction between the disease microenvironment and MSCs. MSCs were studied *in situ* using amitotic nuclear division as a marker of their activation.

Methods: Staining of tissue spreads for metakaryotic nuclear divisions was used as a method to identify MSCs in SSc tissues. SSc BF sampled from forearm skin, as well as control BF (each diluted 1:125 in 0.2% DMEM) and IL-31, were studied as possible agonists in scratch wound assays and Western blots for SSc associated proteins. MSCs derived from both adipose and skin biopsy tissue were induced to differentiate into osteoblasts on soft and stiff extracellular matrix representations. Levels of pro-fibrotic factors were measured by qPCR in MSCs exposed to microenvironment representations.

Results: Metakaryotic nuclear divisions were observed in cells associated with fibrillar collagen in the deep dermal layer of SSc skin. SSc BF enhanced migration of MSCs compared with control BF, (~1 and ~0.7 mm^2 respectively p=0.231) and induced αSMA expression in MSCs ~ 3 times more than media only and ~ 1.5 times more than control BF. Collagen I and CTGF expression were also induced in MSCs by SSc BF. In addition, IL-31 enhanced migration of SSc and control dermal fibroblasts in the scratch wound assay (1.3mm^2 SEM=0.08 and 0.45mm^2 SEM= 0.07 in 0.2% DMEM and 50ng/ml IL-31 respectively at 20 hours, p=0.0001), inhibited by Wortmannin and U0126 (1.4mm^2 and 1.3mm^2 respectively, p=0.0001). The same was seen with MSCs, by 24 hours the area of the scratch in IL-31 treated wells was 0.9mm^2 compared to 1.5mm^2 for Wortmannin treatment (p=0.027). IL-31 did not fully reproduce the protein and migratory effects of blister fluid on MSCs. IL-31 had no effect on Collagen I expression (relative density of 0.7 vs 1.0 and 2.4 for 0.2% DMEM and SSc BF respectively). Matrix stiffness enhanced osteogenic differentiation of MSCs, this effect was enhanced further with IL-31 and TGFβ but abolished when treated with CCG1423 (an inhibitor of the matrix sensing protein MRTFA). Stiff matrices also elevated expression of a-SMA and Collagen I mRNA.

Conclusion: Proliferating metakaryotic cells were found to be present in the deep dermis of SSc patients and they may represent activated stem cells. SSc patients BF and SSc associated cytokine IL-31 enhanced pro-fibrotic differentiation of MSCs. Our findings suggest that MSCs may be important in SSc pathogenesis and that factors within the dermal interstitial fluid generate a microenvironment inducing them to create or induce excessive pro-fibrotic cells.

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Abstract Number: 1862

Modelling Healthy and Scleroderma Fibrotic Skin in Vitro: Mechanical Stress Alters Macrophage Cytokine Expression and Triggers Signalling Via the Mechano-Sensing Transcription Factor Myocardin-Related Transcription Factor-a

Angela Tam[1], Shiwen Xu[1], Henry Lopez[1], Korsa Khan[2], Bahja Ahmed Abdi[3], Henrique Rosario[4], Nikita Arumalla[2], Mark Gibson[2], Christopher Denton[2], David Abraham[2], Barbara D Smith[5] and Richard J Stratton[2], [1]Division of Medicine, Centre for Rheumatology and Connective tissue disease, University College London, London, United Kingdom, [2]Division of Medicine, Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [3]Division of Medicine, Centre for Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [4]Division of Medicine, Centre of Rheumatology and Connective Tissue Diseases, University College London, London, United Kingdom, [5]Boston University School of Medicine, Boston, MA

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Background/Purpose: Skin involvement is one of the most prominent clinical features in scleroderma. There is a marked contrast in mechanical stiffness between healthy forearm skin which has a Young's modulus of 4-12kPa, and scleroderma fibrotic skin at 50-80kPa. We have shown that mechano-sensing properties of fibroblasts in scleroderma are mediated by myocardin-related transcription factor A (MRTF-A). This study is to investigate if a mechanically-stressed microenvironment promotes macrophages towards a pathogenic phenotype, and whether MRTF-A mediates this process.

Methods: Control and scleroderma skin sections were immunostained with anti-CD68 and anti-MRTF-A antibodies (n=3). Human PBMC-derived macrophages were cultured in RPMI/M-CSF on 4kPa and 50kPa collagen-fibronectin-coated plates to mimic "soft"/healthy and "stiff"/fibrotic skin, and unpolarised, or activated with LPS(10ng/ml) or IL-10(10ng/ml) for macrophages designated M(0), M(LPS) and M(IL-10) (n=4). MRTF-A expression was assessed by qPCR and Western blot. Conditioned media was profiled by Luminex array for inflammatory cytokines. Mouse bone marrow-derived macrophages (BMDMs) of wildtype (WT) and MRTF-A-null mice were maintained in RPMI/M-CSF on soft and stiff substrates.

Results: We observed increased accumulation of $CD68^+$ macrophages and MRTF-A^+CD68^+macrophages in perivascular areas of scleroderma skin compared to control skin. No significant differences were detected in MRTF-A expression by qPCR between control and scleroderma macrophages, although stiff substrate increased expression of MRTF-A protein. M(LPS) expressed TNF-α and IL-12 mRNA (10-fold lower in expression or undetectable in M(0), respectively), on soft substrate. Macrophages on stiff substrate showed a trend towards decreased LPS-induced TNF-α and IL-12 mRNA. M(LPS) on soft substrate expressed IFN-γ, which was undetectable with M(LPS) on stiff substrate (mean difference (Δ) 0.2075±0.1576pg/ml, $p<0.01$). M(IL-10) on stiff substrate showed increased MCP-1 expression compared to soft (Δ 2590±2233pg/ml, $p<0.05$). M(LPS) on stiff compared to soft substrate showed increased MCP-3 expression (Δ 57.01±49.22pg/ml, $p<0.05$). M(IL-10) on stiff substrate showed a trend towards increased MCP-3 compared to soft

substrate. M(IL-10) on stiff substrate showed increased fractalkine compared to soft substrate (Δ 51.22±36.28pg/ml, $p<0.01$). WT BMDMs displayed a more elongated morphology on stiff compared to soft substrate while MRTF-A-null BMDMs remained rounded on stiff substrate.

Conclusion: MRTF-A is a mechanical stress-responsive transcription factor which regulates cytoskeletal and ECM-related genes. MRTF-A may mediate mechanical stress and macrophage activation in scleroderma. A stiff microenvironment promoted macrophages to change from a pro-inflammatory phenotype towards a pro-healing phenotype marked by the loss or reduced expression of inflammatory markers IFN-γ, TNF-a and IL-12 alongside increased expression of monocyte chemoattractants MCP-1, MCP-3 and the pro-healing macrophage marker fractalkine.

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Abstract Number: 1863

Non-Invasive Investigation of Perfusion, Microvascular Structure, Erythema, Oxidative Stress and Oxygenation in Healthy Controls and in Patients with Primary and Secondary Raynaud's Phenomenon

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Background/Purpose: It is well established that measurements of cutaneous microvascular dysfunction (measured with laser Doppler imaging [LDI]) and structural abnormality (measured with nailfold capillaroscopy [NC]) differentiate between primary Raynaud's phenomenon (PRP) and systemic sclerosis (SSc). Spectroscopy to measure free radical induced oxidative stress (OS) and oxygenation (OX) has been less well studied despite both being implicated in SSc pathogenesis. The aim of this study was to evaluate all of these parameters and to determine how the additional information provided by spectroscopy compares to established techniques in a population of patients with SSc (subtyped as limited or diffuse cutaneous (lcSSc, dcSSc) depending upon skin involvement), PRP and undifferentiated connective tissue disease (UCTD) and in healthy controls (HC).

Methods: Perfusion images (dual wavelength [superficial capillary and deeper thermoregulatory microcirculation layers, LDI]) were taken of the hand pre and post local heating. Distal dorsal difference (DDD, digit-dorsum) was calculated at baseline and perfusion increase (POST/PRE) calculated at the digit and dorsum. Nailfold capillaroscopy (NC) was carried

out at 200x magnification over the whole nailbed on the non-dominant ring finger. Capillary density and width were calculated from images using automated software. Spectroscopy (light shone onto the skin with a fibre and collected by spectrometer) was carried out at 9 sites of the body. Oxidative stress (OS) measurements were taken with UV light and erythema (E, pseudo-measure of blood flow) and oxygenation (OX) with white light. Comparisons were made between groups with an ANOVA (STATA).

Results: 92 patients with lcSSc, 47 with dcSSc, 31 with PRP, 35 with UCTD, 61 HC were assessed. Data is presented in table 1. LDI showed smaller values for DDD (thermoregulatory layer) and POST/PRE digit and dorsum (thermoregulatory and capillary layers) for SSc vs HC. NC density was significantly lower and width significantly higher in the SSc vs HC group. OS was significantly increased in 7/9 sites in SSc vs HC groups. E was significantly lower at 8/9 sites for the SSc vs HC group. OX was lower at the digit in SSc vs HC group but overall showed no trend for increase or decrease.

Conclusion: The data confirms microvascular dysfunction and structural changes in SSc in a large data set. In addition these changes are matched by increased free radical stress (OS). These changes now need to be measured prospectively and these studies are underway.

Table 1. LDI, spectroscopy (E, OX, OS) and NC data [Median (IQR)] at the digit and dorsum.

Technique	Parameter	HC n=61	PRP n=31	UCTD n=35	LcSSc n=92	DcSSc n=47	P value (one-way ANOVA)
LDI	Red DDD (Arb PU)	197 (89 to 261)	118 (36 to 255)	175 (61 to 285)	162 (39 to 258)	42 (-9 to 159)	0.0019**
	Red POST/PRE digit	2.23 (1.68 to 2.98)	2.16 (1.12 to 2.71)	2.74 (2.00 to 3.57)	2.00 (1.41 to 2.53)	1.54 (1.28 to 2.46)	0.0093**
	Red POST/PRE dorsum	1.99 (1.59 to 2.88)	2.72 (2.12 to 3.30)	2.51 (1.81 to 4.13)	1.98 (1.47 to 2.95)	1.87 (1.26 to 3.00)	0.0064**
	Green DDD (Arb PU)	5.5 (-7 to 25.5)	1.0 (-9.2 to 23.3)	0.0 (-7.5 to 16)	0.0 (-9 to 23)	1.1 (-16 to 14.5)	0.4302
	Green POST/PRE heating finger	1.3 (1.2 to 1.7)	1.3 (1.0 to 1.8)	1.4 (1.2 to 2.4)	1.3 (1.2 to 1.8)	1.2 (1.0 to 1.5)	0.0330*
	Green POST/PRE dorsum	1.4 (1.2 to 1.5)	1.5 (1.3 to 1.9)	1.6 (1.3 to 2.3)	1.4 (1.2 to 1.8)	1.4 (1.2 to 1.6)	0.0136**
NC	Vessel density	13.21 (10.99 to 15.79)	13.50 (10.05 to 14.60)	11.45 (8.81 to 14.10)	9.07 (6.84 to 11.49)	8.98 (6.73 to 11.19)	<0.0001***
	Mean width (mm)	13.37 (12.25 to 15.54)	14.03 (12.91 to 15.59)	14.78 (12.76 to 16.64)	16.60 (14.14 to 21.27)	17.38 (13.85 to 20.95)	<0.0001***
Spectroscopy (Arbitrary units)	OS digit	3.86 (3.27 to 4.64)	3.51 (2.80 to 3.95)	3.61 (3.21 to 4.72)	4.67 (3.7 to 5.40)	4.32 (3.78 to 5.06)	0.1706
	OS dorsum	3.56 (3.17 to 4.27)	3.62 (2.60 to 4.21)	3.61 (3.00 to 4.01)	4.32 (3.84 to 5.25)	4.20 (3.34 to 4.78)	<0.0001***
	E digit	222.9 (218.6 to 224.9)	218.1 (213.0 to 223.5)	218.6 (208.8 to 222.4)	220.4 (214.0 to 225.7)	220.5 (207.9 to 225.3)	0.0229*
	E dorsum	213.8 (208.3 to 219.0)	206.4 (197.4 to 216.0)	210.2 (200.1 to 218.9)	207.0 (198.9 to 214.3)	203.4 (192.8 to 209.7)	0.0003**
	OX digit	0.15 (0.08 to 0.21)	0.17 (0.12 to 0.23)	0.22 (0.13 to 0.30)	0.10 (0.02 to 0.23)	0.13 (0.35 to 0.18)	0.0021**
	OX dorsum	0.09 (0.01 to 0.14)	0.12 (-0.00 to 0.21)	0.07 (0.03 to 0.18)	0.11 (0.05 to 0.16)	0.12 (0.06 to 0.18)	0.7213
* Significant at the p<0.05 level, ** Significant at the p<0.01 level, *** Significant at the p<0.0001 level							

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Abstract Number: 1864

No Evidence of Association of ATP8B4 F436L missense Variant in a Large Systemic Sclerosis Cohort

Elena Lopez-Isac[1], Lara Bossini-Castillo[2], Ana B Palma[2], Shervin Assassi[3], Carmen Pilar Simeón[4], Norberto Ortego Centeno[5], Esther Vicente-Rabaneda[6], Carlos Tolosa[7], Manuel Rubio-Rivas[8], Jose Andres Roman Ivorra[9], Lorenzo Beretta[10], Gianluca Moroncini[11], Nicolas Hunzelmann[12], Joerg HW Distler[13], Gabriela Riekemasten[14], Jeska K. de Vries-Bouwstra[15], Alexandre E. Voskuyl[16], Timothy R.D.J. Radstake[17], Ariane L. Herrick[18], Christopher Denton[19], Carmen Fonseca[20], Maureen D Mayes[3] and Javier Martín[1], [1]Institute of Parasitology and Biomedicine López-Neyra, IPBLN-CSIC, Granada, Spain, [2]Cellular Biology and Immunology, Institute of Parasitology and Biomedicine López-Neyra (CSIC), Granada, Spain, [3]Department of Internal Medicine - Rheumatology, University of Texas-McGovern Medical School, Houston, TX, [4]Internal Medicine, Hospital Universitari Vall d'Hebron, Barcelona, Spain, [5]Internal Medicine, Hospital Clínico San Cecilio, Granada, Spain, [6]Rheumatology, H.U. La Princesa, Madrid, Spain, [7]Department of Internal Medicine, Corporación Sanitaria Universitaria Parc Taulí, Barcelona, Spain, [8]Department of Internal Medicine, Hospital Universitario de Bellvitge, Barcelona, Spain, [9]Department of Rheumatology, Hospital Universitario y Politecnico La Fe, Valencia, Spain, [10]Referral Center for Systemic Autoimmune Diseases, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milan, Italy, [11]Dipartimento di Scienze mediche e Chirurgiche, Università politecnica delle Marche and Ospedali Riuniti, Ancona, Italy, [12]Department of Dermatology, University of Cologne, Cologne, Germany, [13]Internal Medicine 3, University of Erlangen, Erlangen, Germany, [14]Department of Rheumatology, University of Lübeck, Luebeck, Germany, [15]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [16]Department of Rheumatology, VU University medical center, Amsterdam, Netherlands, [17]Laboratory of Translational Immunology, UMC Utrecht, Utrecht, Netherlands, [18]Centre for Musculoskeletal Research, University of Manchester, MAHSC, Salford Royal Hospital, Manchester, United Kingdom, [19]Division of Medicine, Centre for Rheumatology and Connective Tissue Disease, University College London, London, United Kingdom, [20]Centre for Rheumatology, Royal Free and University College Medical School, London, United Kingdom

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Background/Purpose: Systemic sclerosis (SSc) is a complex autoimmune disease with heterogeneous clinical manifestations. Over the past seven years our knowledge of the SSc genetic component has greatly increased, mainly thanks to large genetic studies including genome wide association studies (GWASs). However, there is still a large proportion of the SSc heritability that remains unexplained. One of the hypotheses proposed to explain the missing heritability for complex diseases involves rare and low-frequency variants, which are not usually analyzed in GWASs. Next-generation sequencing (NGS) technologies, like whole exome sequencing (WES), have provided a useful strategy for the study of non-common variants. In this regard, Gao *et al*. performed WES on SSc and reported a novel gene, *ATP8B4*, as a risk factor for the disease. Their results pointed out F436L (rs55687265) missense variant as the potential causal variant for the association signal. The aim of the present study was to further evaluate the reported signal of association in a large SSc cohort.

Methods: The complete set of individuals enrolled for this study comprised a total of 7,426 SSc patients and 13,087 healthy controls of European ancestry. F436L (rs55687265) rare variant was genotyped using TaqMan SNP genotyping technology. First, association tests were performed in each of the six different case-control cohorts. An inverse variance meta-analysis under a fixed effect model was performed to combine the results in the different cohorts.

Results: A trend towards association was observed for one of the case-control set (P_{value} = 0.071, OR = 1.58) (Table 1). However, we did not observe any suggestive or significant association signal for the remaining cohorts. Interestingly, we also observed opposite-direction allelic effects across the different populations for the same allele. The meta-analysis combining all the sample sets showed no significant association with the disease (P_{meta} = 0.484, OR = 1.07). Although we did not find statistically significant associations, a possible role of this locus in SSc susceptibility cannot be ruled out, since we did not assess whether other *ATP8B4*variants were associated with SSc susceptibility.

Conclusion: This study could not replicate the association of *ATP8B4* rs55687265 with SSc. Our results highlight the importance of validation of WES results with other sequencing methods as well as replication of the new associations in independent studies in order to identify true disease-causing mutations.

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Abstract Number: 1865

Urinary Cell Adhesion Molecules As Markers of Renal Involvement in Systemic Sclerosis

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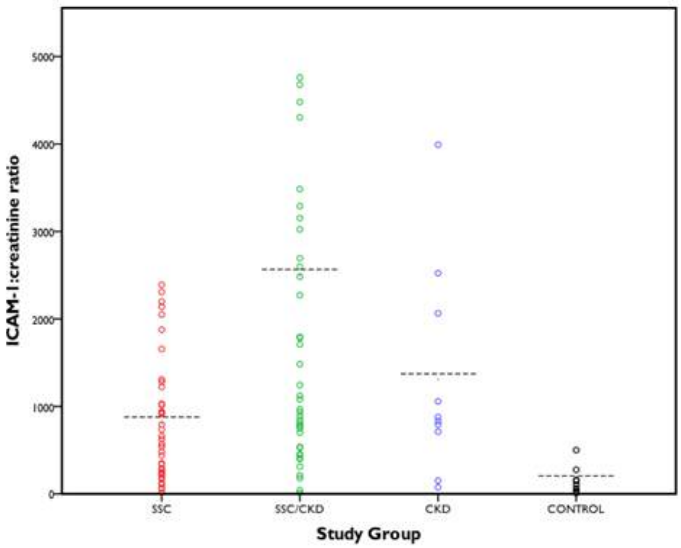
Background/Purpose: Renal involvement in systemic sclerosis (SSc) includes scleroderma renal crisis as well as progressive organ fibrosis. Detection and management of these disease complications is challenging and there is a clinical need for biomarkers that reflect renal involvement. The immunoglobulin superfamily adhesion molecules ICAM-1 and VCAM-1 are upregulated in affected tissues in SSc and other connective tissue diseases. Serum levels of ICAM-1 and VCAM-1 have been elevated in previous studies, but in some instances this reflects the multi-organ burden of disease and organ-specific analysis may to be more robust.

Methods: We collected urine and serum from 80 SSc patients, with or without renal disease, and compared them with patients with CKD of other causes (n=10) and healthy controls (n=12). We used bead-based multiplex analysis to measure cell adhesion molecule concentrations.

Results were compared between groups by Kruskal-Wallis test. **Results:** 40 SSc patients had CKD defined by eGFR and urinalysis. Risk factors for renal involvement (SSc-CKD) included diffuse skin involvement and anti-RNA polymerase III antibodies. Serum concentrations of ICAM-1 or VCAM-1 did not differ significantly between SSc-CKD and the three control groups. Urine VCAM-1 concentrations were increased in SSc patients with renal involvement (mean VCAM-1:creatinine ratio 922, SD 953 versus 654, SD 708 for those without renal involvement) but this did not reach significance. Urine ICAM-1 was markedly upregulated in SSc-CKD (mean ICAM-1:creatinine ratio 1601, SD 1394 versus 806, SD 701 for SSc without renal involvement and 1307, SD 1211 for CKD of other causes, $p<0.001$)



Conclusion: This is the first study to examine urinary cell adhesion molecule concentrations in SSc. Our results confirm the potential utility of urine soluble ICAM-1 as a marker of renal involvement in SSc. Together with previous work by our group on urinary chemokines, the finding of raised urine cell adhesion molecules in the absence of raised serum concentrations supports the utility of urine biomarkers in defining localized SSc disease activity.

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Abstract Number: 1866

Human and Experimental Tracheal Stenosis Is Characterized By a TGF-β-Dependent Fibrotic Component

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Background/Purpose: Acquired tracheal stenosis (ATS) is an unusual disease secondary to inflammatory diseases or to prolonged mechanical trauma. Tracheal mucosa undergoes inflammation and granulation tissue formation with subsequent narrowing of the tracheal lumen. The aim of this study was to analyse the potential role of TGF-β pro-fibrotic pathway in the development of tracheal stenosis.

Methods: Human tissues were obtained by excision of tracheobronchial granulation tissues from patients with benign airway stenosis (n=7) and healthy controls (n=9). We developed a model of tracheal stenosis in adult NZ rabbits, where after a previous incomplete transverse incision the trachea, a circumferential thermal injury to the mucosa with electrocautery was made. To assess the involvement and potential as therapeutic target of pro-fibrotic factor TGF-β1 in this model, rabbits were postoperatively treated with either a peri-tracheal collagen sponge containing a peptide antagonist of TGF-β1 p17 (2mg/ml) or control vehicle. Animals were sacrificed and tracheas excised at 4 weeks for histomorphometric and immunohistochemical (IHC) analysis. Collagen accumulation was analyzed by Masson's trichrome staining and expression of TGF-β pathway surrogate markers (α-SMA myofibroblasts, CTGF and p-Smad2/3) by immunohistochemistry. Quantitative data were compared by Mann-Whitney U-test and correlation analysis by Spearman's rank test. p-value less than 0.05 was considered significant.

Results: Histological examination of human and rabbit stenotic tracheas showed an extensive submucosal fibrotic, collagen stained area, as well as inflammatory cell infiltration and epithelial hyperplasia. We observed a significant increase in the density of $\alpha\text{-SMA}^+$ myofibroblasts and $CTGF^+$ cells in both cases compared to control tracheas. In human stenotic tracheal tissues, this was accompanied by increased nuclear p-Smad2/3 expression compared to healthy tissues. In rabbit stenotic lesions, p17 treatment significantly reduced the fibrotic thickness ($p=0.0006$) and the densities of $\alpha\text{-SMA}^+$ myofibroblasts and $CTGF^+$ cells per mm^2 ($p=0.0084$ and $p=0.001$ respectively). However, we did not observe a significant increase in the luminal stenotic area in p17 compared to saline-treated group. Correlation between the tracheal luminal area and collagen thickness was non-significant ($r=0.29$, $p=0.17$).

Conclusion: Tracheal stenosis is characterized by an important fibrotic component and by the activation of the TGF-β pro-fibrotic pathway. The animal model reproduces similar features and therefore, it provides a valid preclinical model. Local treatment with TGF-β1 antagonist demonstrates its ability to reduce the fibrotic but not the stenotic component, suggesting that fibrosis is only a partial contributor to the reduction of the tracheal lumen in ATS

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An Abnormal Nailfold Capillaroscopy Pattern Is Common in Patients with Connective Tissue Disease and Is Associated with Pulmonary and Oesophageal Involvement, Even in the Absence of Systemic Sclerosis

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Background/Purpose: RP is a common symptom of CTD. Nailfold capillary microscopy (NCM) has previously been shown to be associated with disease severity and internal organ involvement in relatively small non-consecutive cohorts. NCM may help in early recognition and awareness of (SSc like) internal organ involvement. It is unclear to which extent NCM abnormalities occur in several CTDs and whether these are associated with organ involvement. We evaluated consecutive patients visiting the vascular lab for NCM.

Methods: NCM was retrospectively assessed in consecutive patients with suspected RP (n=961) between 2008 and 2013 according to standardized procedures at our center. In 25 patients NCM was not assessable, in 177 RP was not present after careful chart review. Patients were classified as primary RP (normal NCM and ANA <1:80, n=235) or secondary RP, comprising very early diagnosis of SSc (VEDOSS, n=203), SSc according to ACR/EULAR criteria (n=39), SS according to American European Consensus Group criteria (n=37), *SLE* according to SLICC criteria (n=22), MCTD based on criteria defined by Kasuwaka (n=7) or when not meeting criteria as no classifiable disease (n=216). NCM was classified as normal, non-specific (≥3 dilated capillaries per finger) or SSc pattern: early, active or late. Giant capillaries were abnormal per definition, capillary loss was defined <20 capillaries per 3 mm. Pulmonary involvement was defined as forced vital capacity or diffusion capacity <70%, interstitial lung disease on HRCT and/or pulmonary arterial hypertension. Gastro-intestinal involvement was defined as scintigraphically (Tc-99M colloid) abnormal oesophagus motility.

Results: SSc pattern was observed in 32% of patients with SS , 31% SLE and 85% MCTD (table 1). Organ involvement was more frequent in secondary RP patients with a SSc pattern (figure 1). When analyzing patients fulfilling criteria for CTD separately this relation still existed (pulmonary 21 versus 8%; oesophageal 17 versus 9%), even after exclusion of VEDOSS and SSc patients. Also, in patients with giant capillaries pulmonary and oesophageal involvement was more frequent, while no relation was found for dilated capillaries. Capillary loss was associated with oesophageal involvement only.

Conclusion: SSc-like NCM pattern is common in CTD patients and appears to be associated with a greater prevalence of organ involvement, even in the absence of VEDOSS and SSc. Although this was a retrospective cohort, these data underline the importance of assessing NCM in RP patients to evaluate the risk for organ involvement in CTD other than SSc, already in early stages of the disease.

Table 1. Nailfold capillaroscopic pattern per patient diagnosis group in patients with Raynaud's phenomenon

Nailfold capillaroscopic pattern	Diagnosis group						
	PRP n=235	No class. n=216	VEDOSS n=203	SSc n=39	Sjögren n=37	SLE n=22	MCTD n=7
Normal	235 (100)	58 (27)	9 (4)	2 (5)	13 (35)	7 (32)	1 (14)
Non-specific	0 (0)	158 (73)	4 (2)	3 (8)	12 (32)	8 (36)	0 (0)
Early	0 (0)	0 (0)	90 (44)	7 (2)	6 (16)	2 (9)	1 (14)
Active	0 (0)	0 (0)	96 (47)	27 (69)	6 (16)	4 (18)	4 (57)
Late	0 (0)	0 (0)	4 (2)	0 (0)	0 (0)	1 (4)	1 (14)

Number (percentage)

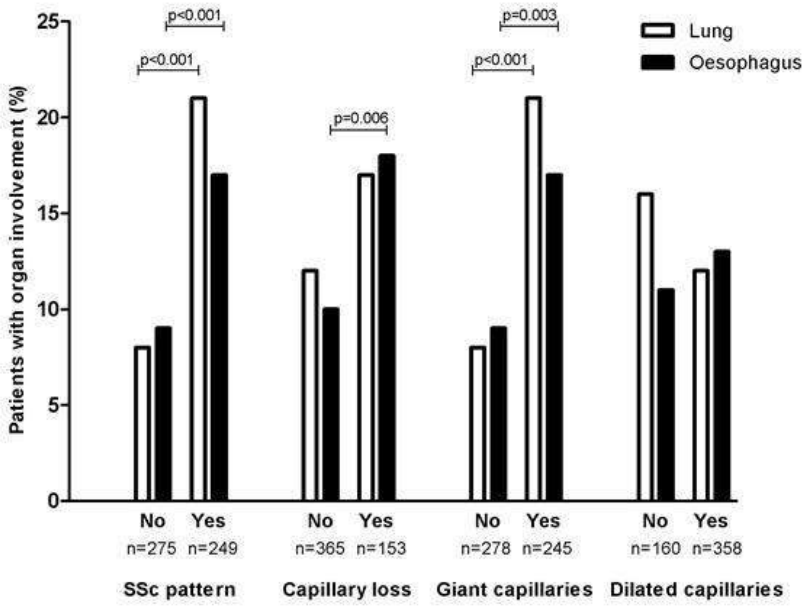

Figure 1. Organ involvement and nailfold capillaries in patients with secondary Raynaud's phenomenon

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Abstract Number: 1868

Rates and Predictors of Physical Therapy and Occupational Therapy Utilization in Systemic Sclerosis: A Scleroderma Patient-Centered Intervention Network Cohort Study

Karima Becetti[1], Jessica K. Gordon[1], Joseph Nguyen[2], Carol Mancuso[3], Linda Kwakkenbos[4,5], Marie-Eve Carrier[5], Brett D. Thombs[4,5], Robert F. Spiera[1] and SPIN Investigators, [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [3]Medicine, Hospital for Special Surgery, New York, NY, [4]McGill University, Montreal, QC, Canada, [5]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada

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Background/Purpose: Systemic sclerosis (SSc) is characterized by significant disability due to musculoskeletal involvement. Physical and occupational therapy (PT/OT) have been suggested to improve hand function, speaking and eating ability. However, the rate of PT/OT use has been shown to be low amongst SSc patients. We aim to identify

demographic, disease-specific and psychological variables associated with PT/OT use in SSc.

Methods: Subjects were adult patients with SSc enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort, recruited from Canada, the USA and Europe. Medical variables were provided by enrolling physicians. Subjects completed demographic variables, including information on PT/OT use in the 3 months prior to enrollment, and questionnaires to evaluate disability, hand dysfunction, pain, fatigue, symptoms of anxiety and depression, body image distress, and self-efficacy. Demographic, medical, and psychological variables were compared between patients who had used PT/OT services and those who did not using chi-square and independent samples t-tests (or non-parametric equivalents) as appropriate. Multivariable binary logistic regression was then used to identify factors associated with PT/OT use in the 3 months prior to enrollment.

Results: Analysis included 993 subjects with mean age of 55.2 ± 12.1 years and mean disease duration of 11.6 ± 8.8 years. 87% were females and 57% had limited SSc. 19% of subjects used PT/OT in the 3 months prior to enrollment, with hands being the most common indication (54%). PT/OT users had shorter disease duration, higher skin scores, and were more likely to have tendon friction rubs and joint contractures compared to non-users (Table 1). They had higher disability, lower rates of employment and self-efficacy, more pain, fatigue, and symptoms of depression, anxiety, and body image distress. Adjusting for other factors, PT/OT use was associated with being on disability (odds ratio [OR] 3.22, 95% confidence interval [CI] 1.81-5.71), more education (OR 1.10, 95% CI 1.04-1.17), early (≤ 3 years) SSc (OR 1.71, 95% CI 1.01-2.87), moderately severe small joint contractures (OR 1.78, 95% CI 1.11-2.86), and severe large joint contractures (OR 4.51, 95% CI 1.69-12.03) (Table 2).

Conclusion: Fewer than 20% of SSc patients in a large international cohort use PT/OT services. These patients had earlier disease, more severe musculoskeletal manifestations and higher disability. Additional studies are needed to further explore the impact of psychological distress and other factors including health insurance on PT/OT use.

Table 1. Differences in demographic, medical and psychological variables between subjects who used PT/OT in the 3 months prior to enrollment in the SPIN Cohort and those who did not*				
Variable		**Used PT/OT (n = 188)**	**Did Not Use PT/OT (n = 805)**	***p-value***
Age (years)		56.0 (11.9)	55.1 (12.1)	0.33
Sex (Female)		165 (88%)	699 (87%)	0.73
Race/Ethnicity**	White	162 (86%)	668 (83%)	Reference
	Black	10 (5%)	53 (7%)	0.48
	Other	16 (9%)	83 (10%)	0.43
Education (years)		**15.8 (3.2)**	**15.0 (3.1)**	**< 0.01**
Current Occupation	Full time/Part time employed	57 (30%)	346 (43%)	Reference
	Unemployed	**28 (15%)**	**104 (13%)**	**0.05**
	Retired	**51 (27%)**	**191 (24%)**	**0.02**
	On disability	**31 (17%)**	**58 (7%)**	**< 0.01**
	Other	21 (11%)	106 (13%)	0.51
Housing location - City/Urban (vs. Non City/Urban)		71 (38%)	264 (33%)	0.19
Diffuse disease subset (vs. Limited)		**91 (50%)**	**314 (40%)**	**0.01**
Disease duration since first non-Raynaud's manifestation (years)		**10.1 (8.4)**	**12.0 (8.9)**	**0.01**
Early onset disease, ≤ 3 years		**40 (23%)**	**101 (14%)**	**< 0.01**
Modified Rodnan Skin Score (0-51)		**10.7 (11.1)**	**7.4 (7.9)**	**< 0.01**
Any digital ulcerations		73 (40%)	318 (40%)	0.92
Tendon friction rubs	Never	114 (61%)	576 (72%)	Reference
	Currently	**24 (13%)**	**68 (8%)**	**0.02**
	In the past	24 (13%)	87 (11%)	0.19
Small joints contractures	No-mild (0-25%)	114 (61%)	594 (74%)	Reference
	Moderate (25-50%)	**48 (26%)**	**131 (16%)**	**< 0.01**
	Severe (>50%)	**4.2 (9%)**	**34 (4%)**	**< 0.01**
Large joints contractures	No-mild (0-25%)	143 (76%)	675 (84%)	Reference
	Moderate (25-50%)	**22 (12%)**	**63 (8%)**	**0.06**
	Severe (>50%)	**14 (7%)**	**14 (2%)**	**< 0.01**
Cochin Hand Function Scale		**20.9 (20.2)**	**12.1**	**< 0.01**

(CHFS-II)		**20.9 (20.2)**	**(14.8)**	**< 0.01**
Scleroderma Health Assessment Questionnaire (SHAQ)		**1.1 (0.7)**	**0.7 (0.7)**	**< 0.01**
Patient Health Questionnaire Depression Scale (PHQ-8)		**7.4 (5.9)**	**5.8 (5.2)**	**< 0.01**
Patient Reported Outcomes Measurement Information System (PROMIS-29)	Anxiety domain	**53.1 (10.2)**	**51.1 (9.9)**	**0.01**
	Fatigue domain	**58.4 (10.2)**	**55.1 (11.3)**	**< 0.01**
	Pain domain	**59.1 (9.3)**	**54.9 (9.7)**	**< 0.01**
Satisfaction with Appearance Scale (SWAP)		**33.6 (19.1)**	**30.0 (19.0)**	**0.02**
Social Interaction Anxiety Scale-6 (SIAS-6)		2.7 (4.4)	2.3 (3.6)	0.32
Self-Efficacy for Managing Chronic Disease (SEMCD)		**5.8 (2.2)**	**6.6 (2.3)**	**< 0.01**
*Values are presented as number (%) for categorical variables and mean (standard deviation) for categorical variables				
**Consolidated variable accounting for the different understanding of race and ethnicity in different parts of the world				

Table 2. Results from multivariable logistic regression analysis reporting factors predictive for PT/OT utilization in the 3 months prior to enrollment in the SPIN cohort

Variable		**Adjusted Odds Ratio (95% Confidence Interval)**	***p-value***
Age		1.02 (1.00 – 1.04)	0.04
Sex (male)		0.87 (0.51 – 1.50)	0.61
Education		**1.10 (1.04 – 1.17)**	**< 0.01**
Employment status	Full time/Part time employed	Reference	
	Unemployed	1.69 (0.96 – 2.96)	0.07
	Retired	1.13 (0.65 – 1.95)	0.67
	On disability	**3.22 (1.81 – 5.71)**	**< 0.01**
	Other	1.38 (0.76 – 2.52)	0.29
Early SSc (disease duration ≤ 3 years)		**1.71 (1.01 – 2.87)**	**0.04**
Small joints contractures	No-mild (0-25%)	Reference	
	Moderate (25-50%)	**1.78 (1.11 – 2.86)**	**0.02**
	Severe (>50%)	1.61 (0.76 – 3.43)	0.22
Large joint contractures	No-mild (0-25%)	Reference	
	Moderate (25-50%)	1.25 (0.66 – 2.33)	0.49
	Severe (>50%)	**4.51 (1.69 – 12.03)**	**<0.01**

Disclosure: K. Becetti, None; **J. K. Gordon**, None; **J. Nguyen**, None; **C. Mancuso**, None; **L. Kwakkenbos**, None; **M. E. Carrier**, None; **B. D. Thombs**, None; **R. F. Spiera**, None.

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Abstract Number: 1869

Mental Health Care in Systemic Sclerosis; Rates of Utilization and Associated Factors in the Scleroderma Patient-Centered Intervention Network Cohort

Karima Becetti[1], Jessica K. Gordon[1], Joseph Nguyen[2], Carol Mancuso[3], Linda Kwakkenbos[4,5], Marie-Eve Carrier[4,5], Brett D. Thombs[4,5], Robert F. Spiera[1] and SPIN Investigators, [1]Rheumatology, Hospital for Special Surgery, New York, NY, [2]Epidemiology and Biostatistics, Hospital for Special Surgery, New York, NY, [3]Medicine, Hospital for Special Surgery, New York, NY, [4]McGill University, Montreal, QC, Canada, [5]Lady Davis Institute for Medical Research, Jewish General Hospital, Montreal, QC, Canada

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is characterized by high disfigurement, morbidity, and mortality. It carries significant psychosocial impact including depression, anxiety and body image distress. However, no previous studies evaluated mental health services (MHS) utilization in SSc. Our aim was to determine the rate and source of mental healthcare for patients with SSc, and explore factors associated with MHS use.

Methods: Subjects were adult patients with SSc enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort, recruited from Canada, the USA and Europe. Medical variables were provided by enrolling physicians. Subjects completed demographic variables, including questions on MHS use in the 3 months prior to enrollment, and questionnaires evaluating symptoms of depression, anxiety, fatigue, sleep disturbance, body image distress, and pain. Demographic, medical, and psychological variables were compared between patients who had used MHS and those who did not using chi-square and independent samples t-tests (or non-parametric equivalents) as appropriate. Multivariable logistic regression was then used to identify potential factors predictive of MHS use in the last 3 months.

Results: Of the included 1000 subjects, 87% were females and 57% had limited SSc. Mean age was 55.2 ± 12.1 years and mean disease duration was 11.6 ± 8.9 years. 20% used MHS in the 3 months prior to enrollment. General practitioners were the most common providers of MHS (59%), followed by psychologists (21%) and psychiatrists (13%). MHS users had shorter disease duration, more pain and were more likely to report gastrointestinal (GI) symptoms compared to non-users (Table 1). They were more likely to smoke, live in the city, be divorced and disabled, and have more symptoms of depression, anxiety, fatigue, and body image distress. Adjusting for all other factors, MHS use was associated with being on disability (odds ratio [OR] 2.50, 95% confidence interval [CI] 1.33-4.69), having shorter disease duration (OR 0.97, 95% CI 0.95-0.99), esophageal symptoms (OR 2.40, 95% CI 1.14-5.06), and higher depression (OR 1.05, 95% CI 1.00-1.10) and anxiety (OR 1.05, 95% CI 1.02-1.08) symptom scores (Table 2).

Conclusion: 20% of patients in the SPIN Cohort received mental health care in the 3 months prior to enrollment, of whom only 34% received care from a mental health specialist. Patients receiving MHS had earlier disease, more GI symptoms, higher disability, and more psychological distress. Additional studies are needed to evaluate the mental health needs of SSc patients and determine barriers to MHS use including cultural and health insurance factors.

Table 1. Differences in demographic, medical and psychological variables between subjects who used MHS in the 3 months prior to enrollment in the SPIN Cohort and those who did not*

Variable		Used MHS (n = 195)	Did Not Use MHS (n = 805)	*p-value*
Age (years)		54.1 (12.3)	55.5 (12.1)	0.14
Sex (female)		169 (87%)	701 (87%)	0.88
Race/Ethnicity**	White	166 (85%)	664 (83%)	Reference
	Black	16 (8%)	47 (6%)	0.31
	Other	13 (7%)	86 (11%)	0.10
Marital status	Married	113 (58%)	536 (67%)	Reference
	Single	23 (12%)	97 (12%)	0.64
	Widowed	7 (4%)	32 (4%)	0.93
	Divorced	**36 (18%)**	**81 (10%)**	**< 0.01**
	Common Law	16 (8%)	52 (7%)	0.21
Education (years)		15.4 (3.2)	15.1 (3.1)	0.25
Current Occupation	Full time/part time employed	65 (33%)	338 (42%)	Reference
	Unemployed	29 (15%)	103 (13%)	0.13
	Retired	35 (18%)	207 (26%)	0.57
	On disability	**34 (17%)**	**55 (7%)**	**< 0.01**
	Other	32 (16%)	102 (13%)	0.04
Housing location - City/urban (vs. non-city/urban)		**79 (41%)**	**256 (32%)**	**0.02**
Smoking		**19 (10%)**	**39 (5%)**	**0.01**
Alcohol		99 (51%)	394 (49%)	0.73
Diffuse disease subset (vs. limited)		114 (61%)	455 (58%)	0.36
Disease duration since first non-Raynaud's manifestation (years)		**9.9 (8.5)**	**12.0 (8.9)**	**< 0.01**
Modified Rodnan Skin Score		8.1 (9.4)	8.0 (8.6)	0.89
Gastrointestinal symptoms	Esophageal	**182 (93%)**	**686 (85%)**	**0.01**
	Stomach	**75 (39%)**	**229 (29%)**	**0.02**
	Intestinal	88 (45%)	298 (37%)	0.06
Interstitial lung disease		76 (39%)	279 (35%)	0.41
Pulmonary arterial hypertension		18 (9%)	72 (9%)	0.93
Scleroderma renal crisis		7 (4%)	38 (5%)	0.48
Patient Health Questionnaire Depression Scale (PHQ-8)		**8.8 (6.0)**	**5.4 (5.0)**	**< 0.01**
Patient Reported Outcomes Measurement Information System (PROMIS-29)	Anxiety domain	**56.7 (10.1)**	**50.2 (9.5)**	**< 0.01**
	Fatigue domain	**60.0 (9.6)**	**54.6 (11.3)**	**< 0.01**
	Sleep disturbance domain	**55.3 (7.8)**	**51.9 (8.7)**	**< 0.01**

Pain domain	**57.8 (9.4)**	**55.2 (9.8)**	**< 0.01**
Satisfaction with Appearance Scale (SWAP)	**34.8 (19.5)**	**29.7 (18.8)**	**< 0.01**
Social Interaction Anxiety Scale-6 (SIAS-6)	**3.5 (4.8)**	**2.1 (3.4)**	**< 0.01**
Cochin Hand Function Scale (CHFS-II)	**16.0 (17.6)**	**13.2 (15.9)**	**0.04**
Scleroderma Health Assessment Questionnaire (SHAQ)	**0.9 (0.7)**	**0.7 (0.7)**	**< 0.01**

*Values are presented as number (%) for categorical variables and mean (standard deviation) for categorical variables

**Consolidated variable accounting for the different understanding of race and ethnicity in different parts of the world

Table 2. Results from multivariable logistic regression analysis reporting factors predictive for mental health services utilization in the 3 months prior to enrollment in the SPIN cohort

Variable		**Adjusted Odds Ratio (95% Confidence Interval)**	***p-value***
Age		1.01 (0.99 - 1.03)	0.58
Male sex (vs. female)		0.86 (0.48 - 1.54)	0.62
Education		1.03 (0.97 - 1.09)	0.35
Marital status	Married	Reference	
	Single	0.72 (0.36 - 1.43)	0.35
	Widowed	2.07 (0.81 - 5.31)	0.13
	Divorced	1.68 (0.97 - 2.89)	0.06
	Common Law	0.97 (0.46 - 2.03)	0.93
Current Occupation	Full time/part time employed	Reference	
	Unemployed	1.22 (0.67 - 2.24)	0.51
	Retired	0.90 (0.50 - 1.62)	0.72
	On Disability	**2.50 (1.33 - 4.69)**	**< 0.01**
	Other	1.69 (0.96 - 3.00)	0.07
Diffuse disease (vs. limited)		0.76 (0.50 - 1.15)	0.19
Disease duration		**0.97 (0.95 - 0.99)**	**0.01**
Gastrointestinal symptoms	Esophageal	**2.40 (1.14 - 5.06)**	**0.02**
	Stomach	1.21 (0.79 - 1.86)	0.38
	Intestinal	0.83 (0.54 - 1.27)	0.39
PHQ-8		**1.05 (1.00 - 1.10)**	**0.04**
PROMIS-29 – Anxiety domain		**1.05 (1.02 - 1.08)**	**< 0.01**
SWAP		1.00 (0.98 - 1.01)	0.69
SHAQ		0.86 (0.62 - 1.20)	0.38

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Abstract Number: 1870

First Pilot Study of an Implantable Loop Recorder (ILR) in Systemic Sclerosis Detects Significant Cardiac Arrhythmias with CMR Abnormalities

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Background/Purpose: SSc-cardiomyopathy associated conduction abnormalities carry a poor prognosis, but their pathogenesis is unclear. Early detection to prevent complications is essential. ILRs are well-established in cardiology practice. In patients (pts) with SSc and no known cardiac disease, we aimed to test feasibility of the REVEAL® ILR, the spectrum of cardiac conduction abnormalities (CCA) detected & association with CMR abnormality.

Methods: 20 pts with (ACR/EULAR criteria) SSc, with no diabetes &/or more than 1 cardiovascular (CV) risk factor, were assessed for SSc/CV profile & comprehensive CV assessment performed, inc. 3T delayed enhancement-CMR (reported by CMR-cardiologists) & ILR insertion. ILR data was downloaded 3 monthly +/- at pt request if symptomatic. Baseline CMR compared to 30 healthy controls (HC) and 1-year ILR data is reported with CMR. CK/troponin data available by time of ACR.

Results: ILR data was available for 19 pts; 63% female, 84% Caucasian; mean (SD) age 53 (12)years, median (IQR) time from 1st non-RP symptom 7.5(1.8, 19.5)years; 32% dcSSc, 32% ACA+ve, 21% Scl70+ve, 47% palpitations hx, 42% known ILD, 11% DU hx, 0% pulmonary hypertension. CMR data was available for 15 SSc pts (DE in 14; 1 pt claustrophobic, no IV access in 2, 1 CMR abandoned due to PPM insertion for CHB). Extracellular volume (ECV) was higher in SSc pts vs. HC; mean difference (diff.) 4.9 (3.2, 6.6)% p<0.001 $R^2$0.568, adj. for age/sex; with greater late gadolinium enhancement detection in SSc (36% vs. 3% in HC, p=0.009) (both markers of fibrosis), with lower LVmass/EDV (p=0.006) & trend for lower LV mass in SSc. Eleven (58%) patients had ILR findings: 7 (37%) supraventricular ectopics (SVE), 2 (11%) ventricular ectopics (VE), 3 (16%) bigeminy, 1 (5%) couplet, 1 (5%) salvo, & 5 (26%) arrhythmias of which 1 atrial flutter, 1 atrial flutter leading to atrial fibrillation, 1 SVT and 2 serious arrhythmias of 1 VT & 1 complete heart block (CHB). Of the 5 pts with arrhythmias, 4 were asymptomatic at time of arrhythmia (pt with VT had palpitations), 3 had dcSSc (inc. both serious arrhythmias), 2 ACA+ve, 1 Scl70, 2 known ILD, 2 DU hx. Trend towards greater ECV & distensibility (ie lower arterial stiffness) seen in pts with arrhythmias. Trend for higher ECV in those with SVE [unadj. mean diff. (95%CI) 1.1 (-2.5, 4.7)% p0.513], VE [0.7 (-4.9, 6.3)% p0.789] & arrhythmias [1.8 (-3.7, 7.3)%]. Table 1: CMR measures in SSc pts with/without arrhythmias (values=mean(SD) *n(%))

CMR variable	No arrhythmia N (%)=12 (80)	Arrhythmia N (%)=3 (20)	Unadjusted mean difference (95% CI), p value	Mean difference (95% CI), p value adjusted for age & sex
LVEF, %	60.11 (4.97)	60.12 (2.16)	0.01 (-6.48, 6.50), 0.997	0.30 (-5.52, 6.12), 0.912
LVmass/BSA, g/m^2	44.90 (11.66)	44.33 (5.80)	-0.57 (-15.86, 14.71), 0.937	-0.12 (-13.43, 13.18), 0.984
LV mass/EDV, g/ml	0.54 (0.08)	0.52 (0.05)	-0.03 (-0.13, 0.08), 0.592	-0.03 (-0.15, 0.09), 0.612
RVEF, %	57.30 (19.18)	59.23 (5.35)	1.94 (-22.84, 26.71), 0.869	0.18 (-18.28, 18.65), 0.983
Torsion, degrees	12.57 (5.78) (n=10)	14.36 (0.98)	1.79 (-2.45, 6.03), 0.615	1.64 (-6.31, 9.58), 0.652
ECV, %	29.55 (3.31) (n=11)	32.32 (2.0)	2.77 (-1.67, 7.20), 0.199	2.82 (-1.99, 7.63), 0.220
Presence of LGE	5 (41.7)*	0 (0.0)*	p=0.258	-
Distensibility, $10^{-3}mmHg^{-1}$	3.69 (2.25) (n=11)	5.73 (4.46)	2.04 (-8.17, 12.24), 0.277	1.96 (-1.84, 5.75), 0.277

Conclusion: This first ILR in SSc study demonstrates its feasibility and utility in the incidental detection of CCA, including serious cardiac arrhythmias & suggests associated CMR abnormalities. These data support the need for identification of pts at risk that would benefit from ILR & provide insights into the pathogenesis of SSc-cardiomyopathy.

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Abstract Number: 1871

Predicting Vascular Complications in Systemic Sclerosis: A Prospective Cohort Study

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Background/Purpose: Vascular disease is of fundamental importance in the pathogenesis of scleroderma. Two major vascular complications in scleroderma patients that cause substantial morbidity and mortality are digital ulcerations (DU) and pulmonary hypertension (PH). The ability to predict which patients will develop these complications is poor in current clinical practice.

Methods: We conducted a prospective observational cohort study of 300 patients who were subsequently followed for at least a five-year period. Adult patients were included that met American College of Rheumatology criteria for scleroderma

or have at least 3 of 5 features of the CREST syndrome. At baseline patients lacked evidence of pulmonary hypertension (PH) and were without current DU. At each visit the patient was examined for signs and symptoms of development of PH and DU. The primary outcomes were (1) pulmonary hypertension defined as a mean pulmonary artery pressure greater than or equal to 25 mm Hg obtained by right heart cardiac catheterization and (2) DU were defined as new onset of severe vascular compromise as evidenced by development of ischemic digital ulcerations, gangrene or digital loss. All classes of PH were modeled together in the primary analysis (pulmonary arterial hypertension (PAH), interstitial lung disease-associated PH) as these classes are not pathogenically mutually exclusive.

Results: The majority of the patients in the cohort (N=300) were middle-aged Caucasian females, with 13% of patients being male and 14% being African American. 58% of the patients had limited disease with an average disease duration of 10 ± 8.4 years from 1st non-RP symptom at study entry. Tables 1 & 2 show demographic data and baseline values for clinical tests by each of the individual outcomes. Patients who developed PH were more likely to have diffuse disease compared to patients without PH. Interestingly, baseline DLCO was lower in patients who develop both DU and PH. There was no difference in DU incidence in PH compared to non-PH groups (Fisher exact p=0.38).

Conclusion: We hypothesized that baseline echocardiographic and pulmonary function study parameters would be predictive of vascular outcomes. Our study demonstrates that the diffuse subtype and the distance walked at the baseline 6-minute walk test are predictive of developing PH, but not DU. We speculate that there may be unique pathophysiology that contributes to developing different vascular outcomes.

	PH	No PH	P-value
Demographics	**N=31**	**N=269**	
Sex	80% Female	87% Female	0.274
Race	64% Caucasian	81% Caucasian	0.109
	29% African Americans	12% African Americans	
	7% Other	7% Other	
Disease Characteristics			
Type	35% Limited	60% Limited	**0.014**
Age at diagnosis	46±12.9	44±12.2	0.405
Age of first non-RP sx (yr)	45.2±13.2	41.8±12.3	0.199
Age of RP (yr)	42.9±13.7	39.4±13.6	0.185
Age at enrollment in cohort (yr)	54.9±11.7	51.9±11.8	0.192
Studies			
Baseline 6 Minute Walk distance (ft)	553±19.6	598±9.9	**0.04**
Baseline DLCO	62.2±4.1	80.8±1.4	**<0.0001**
Baseline FEV1	66.7±3.1	81.3±1	**<0.0001**
Baseline FVC	66.5±3.1	81.7±1	**<0.0001**
Baseline RVSP	35.9±6.5	32.3±5.8	**0.0049**

Table 1. Differences in Patient Characteristics by Pulmonary Hypertension Status

	DU since cohort entry	No DU	P-value
Demographics	**N=69**	**N=231**	
Sex	78% Female	89% Female	**0.026**
Race	79% Caucasian	79% Caucasian	0.937
	16% African American	14% African American	
	5% Other	7% Other	
Disease Characteristics			
Type	65% Limited	56% Limited	0.34
Age at diagnosis	41.5±12.9	45.1±11.9	**0.042**
Age at first non-RP sx (yr)	39.5±13.5	43.1±11.9	0.051
Age of RP onset (yr)	36.8±13.8	40.6±13.5	**0.048**
Age at enrollment in cohort (yr)	50.6±11.3	52±12	0.196
History of digital ulcers	56 (81%)	44 (19%)	**<0.001**
Studies			
Baseline 6 Minute Walk distance (ft)	587±147	595±159	0.684
Baseline DLCO	71.8±19	81.2±22.7	**0.0009**
Baseline FEV1	79.5±17.6	79.9±16.7	0.871
Baseline FVC	79.2±17	80.5±17.2	0.596
Baseline RVSP	33.2±5.6	32.5±6.1	0.412

Table 2. Differences in Patient Characteristics by Digital Ulcerations

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Abstract Number: 1872

The Effect of Cyclophosphamide on Pulmonary Function and Dependence on Disease Activity of Interstitial Lung Disease Associated with Systemic Sclerosis

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THE EFFECT OF CYCLOPHOSPHAMIDE ON PULMONARY FUNCTION AND DEPENDENCE ON DISEASE ACTIVITY OF INTERSTITIAL LUNG DISEASE ASSOCIATED WITH SYSTEMIC SCLEROSIS

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Background/Purpose: The pathogenesis of interstitial lung disease associated with systemic sclerosis (SSc-ILD) is not completely elucidated, although it is believed that chronic alveolar inflammation leads to increasing fibrosis. Treatment strategies using cyclophosphamide (CYC) have been focusing on the inflammatory pathway of SSc-ILD. We hypothesized that CYC is more effective in patients that are in the early, inflammatory phase. The objectives of this study are analyze the effects of intravenously CYC pulses (750mg/m^2) on pulmonary function (FVC, DLCO) in SSc-ILD after 12, 24 and 36 months, and whether this effect is dependent on the extent of ILD, the proportion of ground glass compared to fibrosis, SSc disease duration or baseline DLCO <60%.

Methods: Patients with SSc-ILD receiving CYC pulses between 2003 and 2015 were classified by the Goh (2008) criteria in either limited or extensive ILD, using HRCT at baseline independently judged by two raters. Pulmonary function tests were performed at 0, 6, 12, 24 and 36 months. Missing outcome data due to drop-out were replaced by last observation carried forward, except in case of death.

Results: Seventy-five patients were included, 33 with limited ILD, 42 with extensive ILD. There were no baseline differences in age, gender, SSc subtype classification, disease duration or autoantibody status. FVC and DLCO were stable after 12, 24 and 36 months of follow-up (table 1).

Table 1. Pulmonary function test during follow-up

		Baseline	Follow-up	Mean difference with 95%-CI	P-value
Δ baseline vs. 12 months	FVC	85 (72 – 97)	87 (77 – 101)	2.5 (0.3 - 5.3)	0.08
	DLCO	43 (33 – 57)	46 (36 – 59)	-0.3 (-2.7 - 2.2)	0.83
Δ baseline vs. 24 months	FVC	85 (72 – 97)	91 (71 – 104)	2.8 (-1.3 - 7.0)	0.18
	DLCO	43 (33 – 57)	43 (35 – 59)	0.8 (-2.6 - 4.1)	0.66
Δ baseline vs. 36 months	FVC	85 (72 – 97)	90 (73 – 103)	2.2 (-4.3 - 8.7)	0.49
	DLCO	43 (33 – 57)	43 (36 – 62)	2.5 (-1.7 - 6.7)	0.25

Analysis with last observation carried forward and per protocol analysis showed similar results
FVC and DLCO baseline and follow-up values are % of predicted

There was no effect in the degree of change in FVC and DLCO for the different effect modifiers (table 2): the extent of ILD, proportion of ground glass compared to fibrosis, short SSc disease duration or baseline DLCO <60%.

Table 2. Linear regression analysis				
		Δ 0-12 months		
		B	SE (B)	p-value
FVC	Constant	0.3	4.9	0.95
	Limited vs. extensive	1.3	3.3	0.69
	Constant	1.6	5.8	0.79
	GGO > fibrosis	0.4	3.4	0.91
	Constant	8.2	4.8	0.1
	Disease duration <3 yr	-4.8	3.6	0.2
	Constant	1.0	5.1	0.84
	Baseline DLCO <60%	1.3	4.0	0.76
DLCO	Constant	0.1	4.3	0.99
	Limited vs. extensive	0.6	2.8	0.83
	Constant	-0.4	5.1	0.9
	GGO > fibrosis	0.8	2.9	0.78
	Constant	-0.3	4.3	0.94
	Disease duration <3 yr	1.0	3.2	0.75
	Constant	2.6	4.4	0.56
	Baseline DLCO <60%	-1.1	3.4	0.76

FVC and DLCO values are % of predicted

Conclusion: Pulmonary function in SSc-related ILD was stable during 36 months of follow-up after cyclophosphamide pulse therapy. The extent of ILD, proportion of ground glass, SSc disease duration and baseline DLCO <60% did not influence the effect of CYC on pulmonary function. It could not be shown that CYC is more effective in the early phase of SSc-ILD.

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Abstract Number: 1873

Longitudinal Analysis of Modified Rodnan Skin Score in Systemic Sclerosis Using Group-Based Trajectory Modelling

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Background/Purpose: The modified Rodnan skin score (mRSS) is a clinical evaluation score of the extent of cutaneous fibrosis in systemic sclerosis (SSc). mRSS has been associated with morbi-mortality in several studies. This study aimed to delineate different trajectories of mRSS changes overtime in a large database of patients and to compare patients' characteristics in clusters of patients identified. In this report, the results for non-treated patients are presented.

Methods: From a large French multi-center database of 2098 SSc patients, we included patients fulfilling the 1980 ACR criteria with at least two available records of mRSS. Treatment status was defined as steroids or immunosuppressive intake. Group-based modelling was used to cluster similar mRSS patterns into trajectories. Then variables of clusters obtained were compared using the SAS software.

Results: 818 patients were included: 306 had never received treatment, 403 had been treated and treatment status was unavailable for 109. Treated patients were more severe than non-treated patients with a higher frequency of diffuse cutaneous (dc) SSc, anti-topoisomerase I antibodies, muscular and joint involvements, interstitial lung disease ($p<0.0001$), and mortality ($p=0.003$). Two subgroups of similar trajectory among untreated patients were identified ($p<0.001$, figure 1). The analysis of tendencies showed that patients in cluster 1 had a low baseline mRSS (mean mRSS: 4.15±3.66) that did not change significantly during the follow-up (mean mRSS: 4.11±4.00, mean follow-up: 3.50±2.78 years; $p=0.78$). Patients in cluster 2 had a higher mRSS at baseline (mean mRSS: 21.23±6.96) with a significant decrease during the follow-up (mean mRSS: 17.62±8.5, mean follow-up: 2.98±3.04 years; $p<0.0001$). Patients in cluster 2 had a higher frequency of dcSSc (77% vs. 7%, $p<0.0001$), anti-topoisomerase I antibodies (52% vs. 17%, $p<0.0001$), muscle involvements (23% vs. 6%, $p=0.008$), digital ulcers (56% vs. 34%, $p=0.026$), gastrointestinal tract involvements (42% vs. 20%, $p=0.0079$) and interstitial lung disease (25% vs. 1%, $p<0.0001$). There was no significant difference between the two clusters concerning heart involvement, pulmonary arterial hypertension and mortality.

Conclusion: This work led to the identification of two different clusters among non-treated patients from a French multicenter database, based on similar mRSS trajectories. Interestingly, mRSS of cluster 2 significantly decreased overtime whereas the patients received no immunosuppressive treatment. Nevertheless, they remained exposed to more severe complications than cluster 1. The analysis of the entire database and comparisons between treated and untreated patients might provide new insights into the natural history of this disease. *EL and VS have contributed equally to this work.*

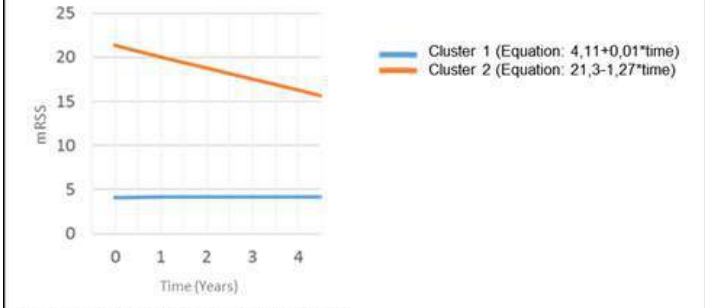

Figure 1: Main results of group-based modelling.

Cluster 1: First subgroup with low mRSS at baseline (mean mRSS: 4.15±3.66) unchanged during the follow-up (mean mRSS: 4.11±4.00, mean follow-up: 3.50±2.78 years, p=0.78). N=278.

Cluster 2: Second subgroup with high mRSS at baseline (mean mRSS : 21.23±6.96) decreasing during the follow-up (mean mRSS: 17.62±8.5, mean follow-up: 2.98±3.04 years; p<0.0001). N=26.

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Abstract Number: 1874

Low Rate of Progression in Cases of Isolated Raynaud's Phenomenon Screened By Nailfold Videocapillaroscopy and Antinuclear Antibody Status Supports Negative Predictive Value of These Tests

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Background/Purpose: Raynaud's phenomenon is common but can progress to definite connective tissue disease. We have observed long term follow up of an unselected consecutive cohort of isolated RP to define frequency of progression and negative predictive value of nailfold capillaroscopy (NC) and ANA testing. Cases attending a dedicated Raynaud's clinic were stratified according to baseline assessment and observed serially. Frequency of SSc or connective tissue diagnosis at presentation and progression of nailfold capillary abnormality or development of positive ANA was determined during routine follow up.

Methods: Cases of suspected RP were referred from primary care to a dedicated Raynaud's clinic. In addition to clinical management of Raynaud's symptoms all cases had baseline ANA testing and nailfold capillaroscopy (NC) for stratification and diagnosis. There were also clinically evaluated for presence of connective tissue disease (CTD). Those with a SSc specific ANA were referred for evaluation comprehensive assessment in a specialized CTD clinic. In cases of isolated RP without evidence of CTD but considered at risk of progression annual review was performed. The number of cases with significant evolution was determined.

Results: Patients with definite symptoms of RP were assessed by clinical examination, autoantibody testing and capillaroscopy (n=457). Of these, 119 cases were assessed as potential secondary RP and were reviewed at least once. Mean (SD) follow up of RP cases was 2.0 (1.8) years with a range of 1 to 12 years. A total of 350/457 (76.7%) had negative ANA, an additional 3/119 (2.5%) became ANA positive during follow-up. NC confirmed 335/457 (73.3%) had normal capillaries and 7/119 (5.9%) developed abnormal NVC during follow up, none with ANA evolution. At first assessment 23/457 (5%) had SSc specific ANA positivity (centromere, Scl-70, RNApol3, U3-RNP reactivity) and these were referred to the CTD clinic for evaluation and review. Of these, 12/23 (52.2%) had abnormal NVC and 8/23 (34.8%) had clinical evidence of connective tissue disease. 4 fulfilled classification criteria for SSc (2 limited and 2 diffuse SSc). No SSc pattern ANA was observed in other patients during follow up. No cases developed defined CTD within the follow up period (ANA+/NC+). 28 ANA positive cases were reviewed and none developed NC progression to abnormal. Thus, overall the rate of significant change in these tests was low and no patients with negative ANA and normal NC progressed.

Conclusion: Feasibility and utility of systematic baseline assessment of cases presenting with isolated RP is confirmed. Routine assessment of ANA and NC is known to be useful in identifying cases of RP with SSc specific ANA, including new SSc diagnosis, and those at risk of long term progression. However, these tests are often normal and then the rate of progression is very low. In this cohort cases with negative tests did not show any clinical progression confirming that these tests have a robust negative predictive value.

Disclosure: L. Parker, None; **K. Howell**, None; **V. H. Ong**, None; **C. P.Denton**, GSK, Celgene, Actelion, Bayer, Sanofi, Roche, Inventiva, 5,GSK, Actelion, Roche, Inventiva, 2.

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Abstract Number: 1875

Physical Activity in Patients with Systemic Sclerosis

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Physical Activity in Patients with Systemic Sclerosis Liem SIE, Meessen JMTA, Wolterbeek R, Ajmone Marsan N, Ninaber MK, Vliet Vlieland TPM, de Vries-Bouwstra JK

Background/Purpose **:** Systemic sclerosis (SSc) is a condition with major consequences on many aspects of patient's functioning. Whereas its impact on exercise capabilities and daily activities has been well described, the association between the disease and its severity and physical activity (PA) is largely unknown. The aim of this study was to compare PA levels of Dutch SSc patients to the Dutch population and study factors associated with PA levels and determine needs and preferences of SSc patients regarding PA.

Methods: 59 SSc patients referred to a multidisciplinary care pathway and fulfilling the ACR 1980[1] or LeRoy criteria[2] for SSc completed the Short QUestionnaire to ASess Health-Enhancing PA[3]. The proportion of patients meeting the Dutch recommendation for PA (=moderate intensity PA for 30 minutes on > or = 5 days/week) and the total minutes of PA per week were calculated. Data were compared with aggregated data of the Dutch population (Central Bureau of Statistics; N=5789) and compared by means of t-tests. The following characteristics were extracted from the medical record: Body Mass Index, disease duration, modified Rodnan skin score, current or past immunosuppressive therapy, left ventricular ejection fraction, six minute walking distance, diffuse capacity for carbon monoxide, presence of anti-Scl-70-/ anti-centromere-antibodies, interstitial lung disease, proximal muscular weakness, synovitis, joint contractures or atrophy. The needs and preferences of SSc patients regarding PA were assessed by means of a self-developed questionnaire. Patients' characteristics and needs and preferences were multivariately compared between patients with low and patients with high levels of PA (less or more than the average minutes/week of the Dutch population).

Results: Of the 59 included patients 52 (88%) were women. The median age was 65 years and 14 (24%) SSc patients were aged 55 years and below. Stratified for age (<55 or ≥55 years) and gender, the proportion of SSc patients meeting the Dutch recommendation for PA was not significantly different from the Dutch population. However, the total minutes of PA per week was significantly lower among SSc patients as compared with the Dutch population (1729 vs. 2614, Table 1). Multivariable analyses showed that male gender and joint/muscle involvement were associated with lower PA levels (p=0.044; p=0.013). Patients not meeting the Dutch recommendations more often reported pain during exercise and a lack of energy interfering with exercise (p=0.049; p=0.002). 39 (67%) patients stated to need more information about PA.

Conclusion: In SSc patients, the total number of minutes of physical activity per week is significantly lower as compared to the general population. Pain, lack of energy, male gender and joint/muscle involvement seem to interfere with exercise, underlining the need for proper guidance of systemic sclerosis patients by health care providers. ***References:*** [1]Arthritis Rheum 1980 May;23(5):581–90. [2]LeRoy E et al. J Rheumatol. 2001;28(7):1573–6. [3]Wendel-Vos G et al. J Clin Epidemiol. 2003 56(12):1163–9.

Table 1. Minutes per week; mean (SD)		Total	Women		Men
			< 55	≥ 55	≥ 55
All activities	SSc	1729 (1003)	1944 (1176)	1819 (916)	818 (637)
	DP	2614 (1422)	2951 (1280)	2015 (1423)	2065 (1460)
	P-value	*<0.001*	*0.001*	0.202	*<0.001*
Working or school activities	SSc	363 (711)	827 (931)	258 (608)	1 (4)
	DP	1162 (1097)	1312 (919)	376 (720)	672 (1023)
	P-value	*<0.001*	0.052	0.241	*<0.001*
Commuting	SSc	48 (132)	57 (78)	54 (157)	0 (0)
	DP	93 (257)	123 (258)	47 (198)	76 (278)
	P-value	*0.010*	*0.002*	0.788	*<0.001*
Household activities	SSc	785 (609)	620 (508)	945 (596)	244 (516)
	DP	745 (799)	1027 (928)	1012 (858)	474 (592)
	P-value	0.617	*0.003*	0.501	0.240
Leisure time activities	SSc	516 (423)	440 (355)	534 (464)	572 (345)
	DP	617 (639)	493 (487)	590 (647)	848 (812)
	P-value	0.072	0.579	0.475	*0.037*
Sport	SSc	89 (115)	108 (74)	88 (135)	56 (50)
	DP	141 (257)	123 (193)	82 (182)	131 (294)
	P-value	*<0.001*	0.460	0.791	*<0.001*
SSc = Systemic Sclerosis patients DP = Dutch population (Number of male participants = 2687; Number of female participants = 3102)					

Abstract Number: 1876

Prevalence of Anti-RNA Polymerase III IgG Antibody in a Cohort of Patients with Delayed Wound Healing

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Prevalence of Anti-RNA Polymerase III IgG Antibody in a Cohort of Patients with Delayed Wound Healing

Background/Purpose: Anti-RNA polymerase III IgG antibody (Pol3) is associated with diffuse cutaneous scleroderma. Depending on the population studied, Pol3 prevalence in scleroderma patients ranges from 9-20% whereas its reported prevalence is less than 1% in healthy individuals. Pol3 is therefore considered highly specific for scleroderma. Emerging

data suggests that this antibody is also associated with co-temporal development of malignancy in the scleroderma population. The purpose of this study was to determine the prevalence of Pol3 in patients with delayed wound healing.

Methods: The Wound Etiology and Healing (WE-HEAL) Study is an IRB approved biospecimen and data repository designed to investigate the immunologic features of delayed wound healing. A proportion of WE-HEAL patients undergo autoimmune serologic profiling (including Pol3) as part of their ongoing clinical care due to either skin graft failure, planned surgical intervention or prior to initiation of immunosuppressants. Testing for Pol3 was performed by RDL Reference Laboratory (Los Angeles, CA) with a result of >20 units considered positive. In patients with positive Pol3 results we investigated the percentage of scleroderma and other autoimmune diseases.

Results: Of the 568 patients enrolled in the WE-HEAL study at the time of data lock, Pol3 was positive in 9 out of 167 patients (5.4%) who had the test performed. There was no significant difference in baseline characteristics or wound outcome between Pol3 positive patients and Pol3 negative patients. (Table 1). Only 1 of the 9 patients with positive Pol3 had scleroderma (11.1%). This patient had longstanding diffuse scleroderma and was also diagnosed with metastatic breast cancer at the same time that her wounds developed. Of the other 8 patients one patient had a history of cervical cancer but 7 had no active or prior malignancy. In this cohort Pol3 was associated with other immune mediated skin disorders with a prevalence of 4.7% in Hidradenitis Suppurativa, 20% in patients with Sjogren's Syndrome and 11.7% in patients with Rheumatoid Arthritis.

Conclusion: In this longitudinal cohort of patients with delayed wound healing Pol3 antibody was positive in 5% of patients tested which is higher than expected based on prevalence of this autoantibody in the general population. We postulate that Pol3 may not be unique to scleroderma and that other autoimmune mediated skin conditions such as vasculitic leg ulcers and hidradenitis may also be associated with Pol3 positivity. The findings suggest that patients with immune mediated wound issues have a higher than expected Pol3 positivity rate, a finding which further investigation in this ongoing longitudinal study.

	Pol3 Negative (n = 158)	Pol3 Positive (n = 9)	p-value	Prevalence of Pol3
Age, years ± sd	**57.43 ± 17.33**	**59.56 ± 20.76**	**0.72**	
Gender				
Female (%)	104 (65.8)	6 (66.7)	1	5.50%
Male (%)	54 (34.2)	3 (33.3)		5.30%
Race				
African American (%)	69 (43.7)	6 (66.7)		8.00%
Asian (%)	1 (0.6)	0 (0.0)	**0.4**	0.00%
Caucasian (%)	88 (55.7)	3 (33.3)		3.30%
Smoking status				
Current Smoker (%)	27 (17.1)	2 (22.2)		6.90%
Never Smoked (%)	79 (50.0)	6 (66.7)	**0.39**	7.10%
Past Smoker (%)	52 (32.9)	1 (11.1)		1.90%
History of malignancy (%)	**20 (12.7)**	**2 (22.2)**	**0.75**	**8.30%**
Breast (%)	4 (2.5)	1 (11.1)		20.00%
Colon (%)	6 (3.8)	0 (0.0)		0.00%
Lymphoma (%)	2 (1.3)	0 (0.0)		0.00%
Cervix (%)	0 (0.0)	1 (11.1)		100.00%
Multiple Myeloma (%)	1 (0.6)	0 (0.0)		0.00%
Stomach (%)	1 (0.6)	0 (0.0)		0.00%
Skin (%)	6 (3.8)	0 (0.0)		0.00%
Type 2 Diabetes (%)	**33 (20.9)**	**3 (33.3)**	**0.64**	**8.30%**
Any immune disease	**120 (75.9)**	**6 (66.7)**	**0.99**	**4.80%**
Systemic lupus erythematosus (%)	8 (5.1)	0 (0.0)	1	0.00%
Sjogren's Syndrome (%)	4 (2.5)	1 (11.1)	0.64	20.00%
Rheumatoid Arthritis (%)	15 (9.5)	2 (22.2)	0.51	11.80%
Scleroderma (%)	17 (10.8)	1 (11.1)	0.28	5.60%
Diffuse (%)	3 (1.9)	1 (11.1)		25.00%
Limited (%)	11 (7.0)	0 (0.0)		0.00%
Localized (%)	3 (1.9)	0 (0.0)		0.00%
Hidradenitis suppurativa, n (%)	40 (25.3)	2 (22.2)	1	4.80%
Wound data (n = 125)	118 (74.7)	7 (77.8)	**1**	5.60%
Surface area at presentation, cm^2 ± sd	37.75 ± 76.05	27.86 ± 48.91	0.74	
Wound Duration, years ± sd	1.52 ± 2.62	0.79 ± 0.81	0.46	
Final outcome, Healed (%)	62 (52.5)	4 (57.1)		
Final outcome, Never healed (%)	41 (34.7)	3 (42.9)	0.6	
Final outcome, Once healed (%)	15 (12.7)	0 (0.0)		
Hidradenitis Suppurativa Data (n=42)	40 (25.3)	2 (22.2)	1	4.80%
HS Sartorius score at presentation ± sd	63.24 ± 48.36	38.50 ± 40.31	0.48	
HS duration at presentation, years ± sd	10.94 ±10.67	2.50 ± 0.71	0.28	

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Abstract Number: 1877

Confirmatory Factor Analysis and Assessment of Differential Item Functioning of the Satisfaction with Appearance Scale in Systemic Sclerosis: A Comparison Across Sex, Race/Ethnicity and Disease Subtype

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Session Time: 9:00AM-11:00AM

Background/Purpose: The Satisfaction with Appearance Scale (SWAP) has been used to assess dissatisfaction with appearance and social discomfort relative to disfigurement in systemic sclerosis (scleroderma, SSc); however, it has not been validated across sexes, different racial/ethnic groups, and varying disease subtypes. The study objectives were to evaluate the established two-factor structure of the SWAP; and examine the metric equivalences of the SWAP among male and female patients, Black and White patients, and patients with diffuse and limited SSc subtypes.

Methods: SSc patients were sampled from 21 centers within the international Scleroderma Patient-centered Intervention Network (SPIN) Cohort. Confirmatory factor analysis (CFA) was used to evaluate the established SWAP two-factor structure (Dissatisfaction with Appearance and Social Discomfort). The Multiple-Indicator Multiple-Cause (MIMIC) model was utilized to assess differential item functioning (DIF).

Results: The SWAP was completed by 748 SSc patients, including 651 female patients, 700 White patients, and 455 with limited SSc. Results from the CFA revealed that the two-factor model (Dissatisfaction with Appearance and Social Discomfort) demonstrated good fit based on the CFI and TLI indices, and slightly less than acceptable fit based on the RMSEA, $x^2(75)=742.33$, $p<.001$, CFI=0.98, TLI=0.97, RMSEA=0.11. Statistically significant, but small-magnitude DIF was found for six SWAP items across socio-demographic or disease characteristics; however, the overall estimates in SWAP scores were not influenced substantively by DIF.

Conclusion: SWAP scores from male and female SSc patients, Black and White patients, and patients with diffuse and limited SSc can be compared and pooled without concern that measurement differences may substantially influence results. Replications of the current study with larger samples of male patients as well as Black and other/racial ethnic minority groups are needed.

Abstract Number: 1878

Speckle Tracking Echocardiography: A Sensitive Technique for Detecting Early Left Ventricular Dysfunction in Patients with Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular damage and excessive fibrosis in the skin and internal organs. Myocardial fibrosis which contributes to either right or left ventricular diastolic dysfunction by reducing the ventricular compliance, is associated with poor prognosis. The aim of this study was to evaluate left ventricular (LV) dysfunction in patients with subclinical cardiac involvement by 2-dimensional speckle tracking echocardiography (2D STE)

Methods: Forty-seven patients (52±12 years, 89.4% women) and 36 gender and age-matched healthy subjects underwent transthoracic 2D STE. We evaluated global LV and RV strains, diastolic variables, cardiac biomarkers, inflammatory and metabolic parameters.

Results: The longitudinal peak systolic strains (PSS)—2CH, longitudinal PSS—APLAX , longitudinal PSS—4CH and global longitudinal PSS of the left ventricle were significantly lower in the SSc group compared with controls (-18,2±3,2% vs. -20± 2,7% p=0.02; -17,8±3,5 vs. -20,3±3,3% p=0,001; -23±3 vs.-21,8±3% p=0,000; -17,5±5,7% vs. -20,6±2,7 % p=0,000 respectively). Although early (E) and late (A) diastolic peak velocity were decreased in SSc group, E/A ratio was similar in both groups. No differences in right ventricle (RV) strain and tricuspid annular plane systolic excursion (TAPSE) were found. B-type natriuretic peptide (BNP), CRP and ESR were significantly higher in patients with SSc (198±250 mg/dl vs.122,5±161 mg/dl p=0,01; 0,5±0,4mg/dl vs. 0,3±0,3 mg/dl p=0,012; 21,7±15 mm/h vs. 11±8,5 mm/h p=0,000 respectively). Although there was no difference between the weights, patients with SSc were shorter than healthy subjects and BMI was significantly higher (28,5±5 vs 25,9±2 kg/m²). The homeostatic model assessment (HOMA) and fasting insulin were also higher in SSc group 1,9±1,3 vs 1,3±0,6 p=0,02; 8±4,9 vs 5,6 ±2,4 IU/mL p=0,008) (Table).

Conclusion: The use of 2D STE can be a sensitive method for detecting subclinic LV dysfunction in SSc patients with preserved left ventricular ejection fraction (LVEF) and pulmonary arterial pressure (PAP). Metabolic and inflammatory parameters should be considered as risk factors for development of overt cardiac disease.

	SSc	Healthy Control	p
Age (years)	51,9±12,4	49,4±6	0,292
Female [n (%)]	42/47 (89,4%)	33/36 (91,7%)	0,724
BMI (kg/m²)	28,5±5,3	25,9±2,2	0,011
Current smoking [n (%)]	11/47 (23,4%)	12/36 (33,3%)	o,317
Leukocyte (/µL)	7602±1844	6380±1245	0,001
Hemoglobin (g/dl)	12,8±1,7	12,8±1,2	0,963
Neutrophil (/µL)	4634±1584	3453±808	0,00
Lymphocyte (/µL)	2144±823	2256±587	0,181
CRP (mg/dl)	0,5±0,4	0,3±0,3	0,012
ESR (mm/h)	21,7±14,9	11±8,6	0,00
Fasting plasma glucose (mg/dl)	93,5±18	92,5±9	0,368
Insulin (IU/ml)	8,06±4,9	5,6±2,4	0,008
HbA1C (%)	5,1±1,6	5,7±3,4	0,225
HOMA	1,9±1,3	1,3±0,6	0,015
LDL (mg/dl)	120±36,8	154,7±63,3	0,015
Total cholesterol (mg/dl)	196,5±45	230,4±33,6	0,007
HDL (mg/dl)	52,4±15	52,7±13	0,936
Uric acid (mg/dl)	4,3±1,3	3,9±0,9	0,089
E (m/s)	0,20±0,21	0,25±0,27	0,049
A (m/s)	0,18±0,10	0,19±0,05	0,049
E/A (rate)	1,33±1,8	1,5±2	0,794
Longitudinal PSS—APLAX (%)	-18,2±3,2	-20±2,7	0,02
Longitudinal PSS—4CH(%)	-17,8±3,5	-20,3±3,3	0,001
Longitudinal PSS—2CH(%)	-23±3	-21,8±3	0,00
Global longitudinal PSS (%)	-17,5±5,7	-20,6±2,7	0,00
RV PSS (%)	-17,5±4,2	-18,9±3,9	0,121
TAPSE	21±4	21,4±4,6	0,71
PAP (mmHg)	14,5±14	11,1±13,2	0,311
LVEF (%)	72,3±6	75,4±4,3	0,01
Homosistein (mmol/L)	13,6±5,7	11,7±2,6	0,22
BNP (pg/ml)	198±250 (111)	122,5±16 (70)	0,01
Galectin 3 (pg/ml)	7,5±3,2	8,1±2,4	0,096

Disclosure: D. Temiz Karadag, None; **T. Sahin**, None; **S. Tekeoglu**, None; **O. Ozdemir Işik**, None; **A. Yazici**, None; **F. C. Eraldemir**, None; **A. Cefle**, None.

Abstract Number: 1879

The Correlation Between Oxidized Low-Density Lipoprotein and Clinical Manifestations in Patients with Systemic Sclerosis

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Background/Purpose: Oxidized low-density lipoprotein (LDL), especially malondialdehyde modified LDL (MDA-LDL) has attracted attention as a predictive serum marker for the secondary development of atherosclerotic lesions. Although increased levels of MDA-LDL have been found in patients with rheumatoid arthritis and systemic lupus erythematosus, few studies have described MDA-LDL levels in patients with systemic sclerosis (SSc). The aim of this study was to investigate the correlation between MDA-LDL and clinical symptoms in patients with SSc.

Methods: The study involved 58 patients with SSc consisting of 10 male and 48 female patients with a mean age of 63.1 ± 14.0 years. The serum of 10 patients with SLE was used as controls. Of 58 patients, 16 patients had diffuse cutaneous systemic sclerosis (dcSSc) and 42 had limited cutaneous systemic sclerosis (lcSSc). The oxidized LDL levels were measured using the oxidized-LDL ELISA kit (Sekisui Medical Co., Ltd., Japan) according to the manufacturer's protocol.

Results: Increased levels of oxidized LDL were found in patients with dcSSc when compared with patients with SLE. The MDA-LDL/LDL-C ratio was higher in patients with dcSSc and lcSSc than in those with SLE. A significant negative correlation was observed between the %DLco and MDA-LDL levels as well as between %DLco and MDA-LDL/LDL-C. The MDA-LDL/LDL-C ratio strongly correlated with %DLco, more so than did the MDA-LDL levels. Right ventricular systolic pressure measured by echocardiography, immunoglobulin G (IgG), KL-6, and surfactant protein D showed positive correlations to oxidized LDL/LDL-C. When we defined patients with increased MDA-LDL levels by using the standard values mentioned above, and analyzed associations with clinical signs, significantly more patients in the increased MDA-LDL group had complications with lung pulmonary hypertension, and the positivity rate for anti-centromere antibodies was higher in the increased MDA-LDL group.

Conclusion: Many patients with SSc had increased levels of oxidized LDL, which may be a reflection of increased atherosclerosis lesions in patients with SSc. A positive correlation between decreased levels of %DLco, KL-6, and SP-D and oxidized LDL/LDL-C was observed and this may indicate that oxidized LDL is involved in the progression of interstitial pulmonary lesions in patients with SSc. Little is known about abnormal lipid metabolism in patients with SSc when compared with that of patients with RA and SLE. However, the frequency of complications in lipid metabolism is high in patients with SSc and the pathology of SSc remains unclear.

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Abstract Number: 1880

A Large Proportion of Patients in an Early Systemic Sclerosis-Associated Interstitial Lung Disease Cohort Have Coexisting Pulmonary Hypertension

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Background/Purpose: Systemic Sclerosis (SSc) is a multi-organ system disease manifested by fibrosis, vascular damage and dysregulation of the immune system. The leading causes of death are interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). ILD is present in up to 80% of patients with SSc and clinically significant ILD affects approximately 25% of patients with SSc. Our objective was to evaluate the presence of pulmonary hypertension (PH) in a cohort of patients with early onset SSc-associated ILD (SSc-ILD).

Methods: Subjects with a diagnosis of SSc based on 2013 ACR/EULAR classification criteria and ILD based on high-resolution computed tomography were included in our prospective observational cohort. Subjects with disease duration of ≤ 7 years, based on inclusion criteria for ongoing controlled trials in SSc-ILD, were also identified. Subjects with PH were identified based on right heart catheterization (RHC) and were classified into PH groups 1, 2, and 3 (Table 1).

Results: Ninety-four subjects with SSc-ILD were included in this analysis. Seventy-seven percent of patients were female, the mean age was approximately 52 years old, the mean disease duration was 2.8 years after initial non-Raynaud's Phenomenon (RP) symptom, approximately 61% had diffuse cutaneous SSc, ANA was positive in 91%, anti-Scl-70 antibody was positive in 28%, and anti-centromere antibody was positive in 8% of subjects. Of those 94 subjects, 25 subjects had a diagnosis of PH based on RHC and 20 of those subjects had early onset SSc (Table 1).

Conclusion: In a large SSc-ILD cohort, with many subjects of earlier disease duration, a significant proportion of patients have co-existing PH. These are novel findings that should be entertained when designing trials for SSc-ILD and should be validated in other cohorts of SSc-ILD.

Table 1. PH in SSc-ILD

	Any Length of Disease Duration After Initial Non-RP Symptom (n=94)	Disease Duration ≤7 Years After Initial Non-RP Symptom (n=81)
FVC (% Predicted) Mean± SD (n=)	75.6 ± 16.0 (93)	74.9 ± 15.3 (81)
DLco (% Predicted) Mean± SD (n=)	54.1 ± 22.7 (83)	53.5 ± 20.6 (73)
No PH* % (n =)	73.4% (69)	75.3% (61)
PH* (Group 1, 2 and 3 PH) % (n =)	26.6 % (25)	24.7% (20)
Group 1 PH* % (n =)	6.4 % (6)	7.4% (6)
Group 2 PH* % (n =)	4.3% (4)	2.5% (2)
Group 3 PH* % (n =)	15.9% (15)	14.8% (12)

*PH Classification
Non-PH: mPAP < 25.
Group 1 PH (PAH): mPAP ≥ 25; PCWP ≤ 15.
Group 2 PH (left heart disease): mPAP≥25 ; PCWP>15.
Group 3 PH (lung disease/ hypoxia): mPAP≥25; PCWP≤15 ; FVC < 60% or moderate/severe ILD.

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Abstract Number: 1881

Targeting Oncostatin M in the Target Tissue: Assessment of in-Vivo Affinity and Target Engagement of an Anti-OSM Monoclonal Antibody By Combining Blood and Skin Blister Fluid Data

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Background/Purpose: Oncostatin M (OSM) is a pleiotropic member of the gp130/IL-6 cytokine family involved in pathological processes of fibrosis, inflammation and vasculopathy. Diffuse cutaneous systemic sclerosis (DcSSc) subjects have increased OSM serum levels and OSM/OSM-related genes are upregulated in DcSSc skin biopsies (Feeney 2016). A previous monoclonal antibody developed for the treatment of RA was discontinued due to lack of efficacy likely associated to poor binding affinity (Choy 2013). A novel IgG1 Mab (GSK2330811), with approximately (~) >10 fold increased binding affinity in-vitro, is being developed for the treatment of DcSSc. We aimed to assess target engagement in the target tissue (skin) and to determine the antibody in-vivo affinity using physiology-based pharmacokinetic modelling (PBPK) in a first time in human study (Study 201246).

Methods: Healthy males and females of non-child bearing potential aged 18 to 65 received single ascending subcutaneous doses of GSK2330811 (0.1-6mg/kg) or placebo. Skin suction blisters were raised on the volar surface of the forearm by applying suction for 4 hours followed by collection of the blister fluid. Validated immunoassays were used to measure target engagement (free and total OSM) and GSK2330811 concentrations in blood and skin. A combined PBPK and target mediated drug disposition model (TMDD) was developed to assess in-vivo affinity of GSK2330811 (Cao, 2014).

Results: 30 Subjects received GSK2330811 and 10 placebo. GSK2330811 showed a favourable safety and tolerability profile compared to placebo. Skin suction blisters were well tolerated. The PK of GSK2330811 was consistent with IgG1 Mab against a soluble target. The typical apparent distribution volume was 11.5 l (95% CI: 10.2-13.1) and the typical apparent systemic clearance was 14.1 ml/hr (95% CI: 12.7-15.6). The mean terminal half-life was ~3 weeks. GSK2330811 ratio between skin and plasma concentration was ~ 20-30%. Estimated in-vivo affinity was ~ 0.6 nM. A rapid (~ 30 min) OSM target turnover was estimated based on total OSM data. Free OSM levels were below the limit of quantitation after drug administration in both serum and blister fluid indicating substantial OSM inhibition. At the top dose level ~ 90% of target engagement is predicted in serum, while slightly lower values (~70-80%) are predicted in the skin blister fluid.

Conclusion: This study demonstrates that GSK2330811 has sufficient affinity to achieve high target engagement in systemic circulation and target tissue. Skin blister analysis provided valuable data to inform the mechanistic target engagement model. These data support progression of GSK2330811. A proof of mechanism study in subjects with DcSSc is being developed. **References**: Feeney M, et al. Arthritis Rheumatol 2015;67(suppl 10) Choy EH, et al. Arthritis Res Ther 2013 Sep 24;15 (5):R132 Cao Y & Jusko WJ. J Pharmacokinet Pharmacodyn 2014;41(4):375-387

Disclosure: J. Reid, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **S. Zamuner**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **K. Edwards**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **S. Rumley**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **K. Sully**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **M. Feeney**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **S. Kumar**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **D. Fernando**, GlaxoSmithKline, 3,GlaxoSmithKline, 1; **N. Wisniacki**, GlaxoSmithKline, 3,GlaxoSmithKline, 1.

Abstract Number: 1882

Predictors of Response to Methotrexate in Patients with Eosinophilic Fasciitis (Shulman's Disease)

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Background/Purpose: Eosinophilic fasciitis (EF) is a rare scleroderma-like disorder described in 1974 by Shulman. It is characterized by the acute onset of edema and induration of the skin and the subcutaneous tissue associated with peripheral blood eosinophilia. Deep skin biopsy shows characteristic alterations in the muscle fascia. There is no consensus regarding the treatment of the EF. Oral or intravenous glucocorticoids (GC) are usually the initial treatment with significant improvement in most cases. Immunosuppressive drugs may be associated when the response is insufficient and the most used is methotrexate (MTX). The response to MTX is usually favorable, especially in cases with concomitant morphea lesions[1]. In this study we investigated which demographic, clinical and laboratory baseline features are associated with remission during MTX treatment in patients with EF.

Methods: We performed an observational, retrospective (1983–2014) and multicentric study of patients with EF from 5 Spanish university hospitals. Inclusion criteria: 1) characteristic cutaneous manifestations; 2) deep biopsy with consistent changes in muscle fascia, and 3) treatment with MTX. Response to treatment was divided into: 1) complete remission (absence of symptoms and disappearance of lesions); 2) partial response (patients who develop limitation despite treatment); and 3) lack of response (persistence of symptoms and findings on examination)[1]. Statistical non-parametric tests were used for the data analysis, Kruskal Wallis for continuous variables and χ^2 for categorical variables.

Results: 33 patients were included, 18 women (54.5%), with a mean age of 54.6 years (range 22–81) and median duration of disease until diagnosis of 4 months (range: 1–25). Most of these patients (97%) had previously been treated with GC with insufficient response, 8 (24.2%) had previously received other immunomodulatory drugs (hydroxychloroquine, azathioprine, cyclosporine) and 5 (15.2%) photochemotherapy (PUVA). MTX median dose was 15 mg/week (range: 10–25); 16 cases (48.5%) achieved complete remission, 15 (45.5%) partial response and 2 (6%) lack of response. Patients who achieved complete remission had a mean age at diagnosis slightly higher (64), presented more frequently induration ≥ 50% of body surface, myalgia and associated malignancies but C-reactive protein (CRP) levels were lower. Of all the variables analyzed, only low CRP level was significantly associated with complete remission (P=0.004). Two patients in remission relapsed after discontinuation of MTX, with a favourable response to re-treatment with GC.

Conclusion: The only variable that seems to be associated with remission during treatment with MTX in our series is the absence of elevated CRP. All other variables showed no significant differences, although the statistical power may be small due to the limited sample size.

	Complete remission (N=16)	Partial response (N=15)	Lack of response (n=2)	P value
Age at diagnosis	64 (40-73)	49,5 (42-57)	54 (42-69)	0.640
Female gender	8 (44%)	8 (44%)	2 (11%)	0.405
Smoking	3 (25%)	8 (67%)	1 (8.3%)	0.204
Time to diagnosis (months)	4,0 (2-7)	4,0 (2.5-7.5)	6,5 (3-10)	0.867
Induration ≥ 50%	10 (56%)	7 (39%)	1 (5%)	0.437
Erythema	4 (40%)	5(50%) 1	1 (10%)	0.79
Pruritus	3 (50%)	2 (33%)	1 (17%)	0.419
Edema of extremities	8 (35%)	13 (56%)	2 (9%)	0.151
“Orange peel”	3 (37%)	5 (62%)	-	0.545
Hyperpigmentation	4 (40%)	5 (50%)	1 (10%)	0.791
Other morphea lesions	6 (50%)	5 (42%)	1 (8%)	0.808
Arthritis	3 (43%)	4 (57%)	-	0.709
Joint contractures	3 (43%)	4 (57%)	-	0.709
Muscle weakness	6 (75%)	2 (25%)	-	0.144
Myalgia	10 (53%)	8 (42%)	1 (5%)	0.628
Carpal tunnel syndrome	3 (50%)	3 (50%)	-	-
Raised ESR	8 (50%)	7 (44%)	1 (6%)	0.926
Raised CRP	7 (39%)	11 (61%)	-	0.004*
Eosinophilia	10 (42%)	13 (54%)	1 (4.2%)	0.500
Hipergammaglolinemia	5 (45%)	6 (54%)	-	0.570
ANA	4 (36%)	6 (54%)	1 (9%)	0.714
Glucocorticoids	14 (44%)	16 (50%)	2 (6%)	0.539
Other previous treatments	3 (37%)	4 (50%)	1 (12%)	0.646
PUVA	3 (60%)	1 (20%)	1 (20%)	0.207
Neoplasm	4 (80%)	1 (20%)	-	0.236

References: 1. Lebeaux D, et al. Rheumatology (Oxford). 2012;51:557-61

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Abstract Number: 1883

Exercise Habits and Factors Associated with Exercise in Systemic Sclerosis: A Scleroderma Patient-Centered Intervention Network (SPIN) Cohort Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: Exercise is associated with improved health in many medical conditions. Little is known about the exercise habits of people with systemic sclerosis (SSc, or scleroderma). This study assessed the proportion of individuals with SSc who exercise and associations of demographic and disease variables with exercise. Additionally, the weekly amount of time spent exercising and the types of exercise performed were assessed among patients exercising.

Methods: The sample consisted of adult participants with SSc enrolled in the Scleroderma Patient-centered Intervention Network (SPIN) Cohort who completed baseline questionnaires from March 2014 through August 2015. Baseline questionnaires included questions on exercise habits, physician-reported medical characteristics, self-report demographic characteristics, the Health Assessment Questionnaire – Disability Index (HAQ-DI), Patient Health Questionnaire-9, and PROMIS-29.

Results: Of 752 patients, 389 (51.7%) reported presently engaging in exercise, and these patients exercised on average 4.7 hours (SD=2.8) per week. Among patients who reported exercising, walking was most commonly reported (n=295, 75.8%). In bivariate analyses, present exercise was associated with more education, lower body mass index, some (versus no) alcohol consumption, non-smoking, limited/sine disease subtype, absence of skin thickening, lower disability, higher physical function, lower symptoms of anxiety and depression, less fatigue, lower sleep disturbance, higher ability to participate in social roles and activities, and less pain.

Conclusion: Approximately half of SSc patients reported that they are currently exercising with walking being the most common form of exercise. Understanding exercise patterns and factors associated with exercise will help better inform intervention programs to support exercise for patients with SSc.

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Abstract Number: 1884

Esophageal Dilation and Interstitial Lung Disease Incidence and Progression in Systemic Sclerosis

Kimberly Showalter[1], Aileen Hoffmann[2], Carrie Richardson[3,4], Julia (Jungwha) Lee[5], David Aaby[6], Rishi Agrawal[7], Jane Dematte[8], Rowland W. Chang[9] and Monique Hinchcliff[10], [1]Internal Medicine, McGaw Medical Center of Northwestern University, Chicago, IL, [2]Department of Medicine, Division of Rheumatology, Northwestern University Feinberg School of Medicine, Northwestern University, Chicago, IL, [3]Department of Medicine, McGaw Medical Center of Northwestern University, Chicago, IL, [4]Department of Rheumatology, Johns Hopkins University, Baltimore, MD, [5]Preventive Medicine/Biostatistics, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Northwestern University Feinberg School of Medicine, Chicago, IL, [7]Radiology, Northwestern University Feinberg School of Medicine, Chicago, IL, [8]Pulmonology, Northwestern University Feinberg School of Medicine, Chicago, IL, [9]Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [10]Northwestern University, Feinberg School of Medicine Scleroderma Program, Chicago, IL

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Background/Purpose: Interstitial lung disease (ILD) is the leading cause of death in systemic sclerosis (SSc). Esophageal dysfunction and aspiration may play a role in SSc-ILD. We showed that esophageal dilation on high-resolution computed tomography (HRCT) scans correlated positively with radiographic ILD and negatively with forced vital capacity (FVC)[1]. We also showed that a widest esophageal diameter (WED) >=19mm on HRCT had the highest combined sensitivity and specificity for associated ILD[2]. The purpose of this retrospective, longitudinal study was to determine if a larger WED is a risk factor for SSc-ILD incidence and progression.

Methods: Subjects that fulfilled American College of Rheumatology 2013 SSc criteria with >= one HRCT and two pulmonary function tests were included. The first available HRCT was defined as the baseline exam. WED was measured. ILD was quantified by published methods[3]. In subjects without radiographic ILD and with baseline FVC >=70% predicted, incident restrictive lung disease was defined as new FVC <70% predicted. Change in FVC % predicted was used as a surrogate for ILD progression.

Results: In total, 249 subjects were included with a median follow up of 2.9 years (0.02-13.4y). Twenty-five subjects died. At baseline, 88 (82%) with a WED >=19mm had radiographic ILD compared with 94 (66%) with a WED <19mm (p=0.005; Table 1). Three of 55 without baseline ILD developed incident restrictive lung disease. At baseline, those with WED >=19mm had an 8.38 lower FVC % predicted than those with WED<19mm. In total, there was no clinically significant decline (i.e. >5% change) in FVC % predicted (Fig. 1). There was no significant difference in change in FVC % predicted between those with WED >=19 vs. <19mm (beta=0.2663; 95% CI -0.2256, 0.7583).

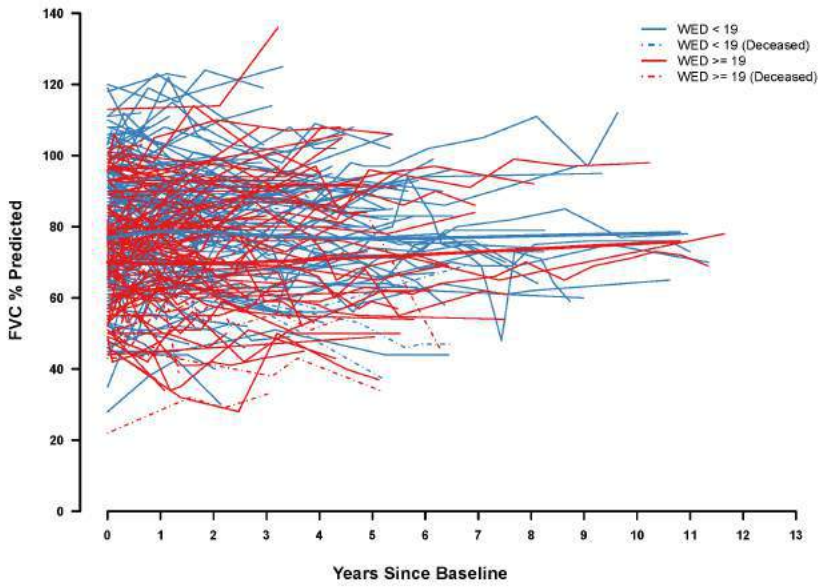
Conclusion: SSc-ILD often occurs before referral to a tertiary center. Those with a larger WED had an FVC % predicted at baseline that was clinically and statistically significantly lower than those with a smaller WED. Despite this, a larger WED at baseline was not associated with more rapid decline in FVC % predicted. References: 1. Richardson et al. Esophageal dilatation and interstitial lung disease in systemic sclerosis: a cross-sectional study. Semin Arthritis Rheum 2016 2. Hoffmann et al. Comment on: Esophageal dilatation and interstitial lung disease in systemic sclerosis: a cross-sectional study. Semin Arthritis Rheum 2016 3. Kazerooni et al. Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring. AJR Am J Roentgenol

Table 1. Baseline Characteristics (n=249)				
Mean (SD) or n (%)	Total (N=249)	WED <19 (N=142)	WED≥19 (N=107)	p-value
Age at time of HRCT, years	50.9 (11.4)	49.8 (11.4)	52.3 (11.2)	0.084
Sex, women	206 (83%)	130 (92%)	76 (71%)	**<0.001**
Body mass index, kg/m^2	26.2 (5.8)	26.3 (5.9)	26.2 (5.8)	0.933
Ethnicity, white	190 (79%)	111 (80%)	79 (76%)	0.428
Smoker, current or former	93 (38%)	51 (36%)	42 (40%)	0.609
Proton Pump Inhibitor use, baseline	145 (60%)	70 (51%)	75 (73%)	**0.001**
Alcohol, current	103 (52%)	61 (57%)	42 (45%)	0.094
SSc disease subtype, diffuse cutaneous	100 (40%)	52 (37%)	48 (45%)	0.402
Years since first non-Raynaud Symptom	6.6 (10.5)	5.6 (7.4)	7.8 (13.4)	0.129
SSc-specific antibodies, positive	156 (78%)	92 (81%)	64 (75%)	0.359
Anti-topoisomerase I (Scl-70)	72 (34%)	40 (34%)	32 (34%)	0.982
Anti-centromere (ACA)	46 (21%)	25 (20%)	21 (23%)	0.658
RNA polymerase III	43 (25%)	30 (31%)	13 (18%)	0.063
Modified Rodnan skin score	11.4 (10.5)	10.4 (9.9)	12.7 (11.2)	0.107
Baseline radiographic ILD present	182 (73%)	94 (66%)	88 (82%)	**0.005**

Abbreviations: HRCT, high-resolution computed tomography; WED, widest esophageal diameter (median=17mm, range 0-44mm); SSc, systemic sclerosis

1997;169:977-83

Figure 1. Change in Forced Vital Capacity (FVC % Predicted) Over Time in 249 Patients with Systemic Sclerosis



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Abstract Number: 1885

Can Nailfold Videocapillaroscopy Images be Interpreted Reliably By Different Observers? Results of an Inter-Reader and Intra-Reader Exercise Among Rheumatologists with Different Experience in This Field

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Hernandez-Molina[5], Marcelo Audisio[6], Susana Roverano[7], Margarita González de Urizar[8], José Francisco Díaz Coto[9], Blanca Herrera Velasco[10], Mijahil Cornejo Ortega[11], Ana María Sapag Durán[12], Janeth Villegas Guzmán[13], Luìs Fernando Medina Quintero[14], Mirtha Sabelli[15], Carlos Velasquez[16], Sandy Sapag Durán[17], Oscar Sedano[18], Martín Zapata Zúñiga[19], Maria Fonseca[20], Maurizio Cutolo[21] and PANLAR Capillaroscopy Group, [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Rheumatology, Instituto Nacional de Rehabilitación, Mexico City, Mexico, [3]Rheumatology, Instituto Nacional de Cardiologia Ignacio Chavez, Mexico City, Mexico, [4]Instituto Nacional de Rehabilitación, Mexico, Mexico, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico City, Mexico, [6]Servicio de Reumatología del Hospital Nacional de Clínicas, Córdoba, Argentina, [7]Rheumatology, Hospital Jose Maria Cullen, Santa Fe, Argentina, [8]Rheumatology, Hospital San Ramón, Ciudad del Este, Paraguay, [9]Rheumatology, Hospital Clínica Bíblica, San José, Costa Rica, [10]Rheumatology, Universidad de San Fancisco Xavier de Chuquisaca, Sucre, Bolivia (Plurinational State of), [11]Rheumatology, Hospital Nacional Arzobispo Loayza, Lima, Peru, [12]Rheumatology, Hospital Universitario Japonés, Santa Cruz, Bolivia (Plurinational State of), [13]Rheumatology, Hospital Nacional Dos de Mayo, Lima, Peru, [14]Internal Medicine, Universidad del Valle, Cali, Colombia, [15]Rheumatology Unit, Internal Medicine Service, Hospital Italiano de Buenos Aires, Instituto Universitario Hospital Italiano de Buenos Aires, and Fundacion PM Catoggio, Buenos Aires, Argentina, [16]Clínica Universitaria Bolivariana, Universidad Pontificia Bolivariana, Medellín, Colombia, [17]Reumatología, Instituto de Investigación en Reumatología Sapag & Sapag, Santa Cruz de la Sierra, Bolivia (Plurinational State of), [18]Rheumatology, Hospital Marino Molina Scippa ESSALUD, Lima, Peru, [19]Rheumatology, Hospitl General Jerez, Jerez, Mexico, [20]Rheumatology, Hospital Bernardino Rivadavia, Buenos Aires, Argentina, [21]Research Laboratory and Academic Division of Clinical Rheumatology, Department of Internal Medicine, University of Genova, Genoa, Italy, Genova, Italy
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Background/Purpose: Nailfold videocapillaroscopy (VCP) has become an established method to assess the microcirculation in patients with Raynaud's phenomenon and connective tissue diseases. The 2013 Systemic Sclerosis (SSc) criteria included capillaroscopy as a necessary tool for SSc classification. Adequate training for identification of Systemic Sclerosis capillaroscopic patterns is relevant for all Rheumatologists. To date, there is little evidence of the reliability of VCP findings amongst different readers. We evaluated inter- and intra-reader agreement of 13 Rheumatologists to identify SSc capillaroscopy patterns ("early", "active" and "late") proposed by Cutolo et al (ref 1).

Methods: Thirteen rheumatologists (7 without experience and 6 with more than 2 years of experience in the routine performance and reading of capillaroscopic images) received a 20 min training regarding the identification of SSc capillarosocpy patterns to standardize reading criteria. Then, they individually rated 60 videocapillaroscopy images (12 from healthy subjects, 48 from SSc patients) at baseline, and 4 weeks after the first reading using an electronic platform in order to perform the intra-reader exercise. The reading of an expert with more than 15 years of experience in capillaroscopy was considered the gold standard. Data was analyzed using Cohen´s kappa for concordance, Student´s t test and ANOVA were used to compare kappa means for inter-reader, intra-reader and inter-pattern readings.

Results: Mean inter-reader and intra-reader kappa were 0.45 and 0.49, respectively, reflecting moderate agreement. Mean kappa scores were significantly higher among experienced readers when compared with unexperienced readers (inter-reader kappa: 0.58 vs 0.34, p=0.001, intra-reader kappa: 0.65 vs 0.37, p=0.01). Agreement was substantial (kappa =0.61) for the identification of normal vs abnormal capillaroscopy, and higher than the overall agreement (p=0.009). Agreement was higher for the identification of "active" (0.48, p=0.009) and "late" SSc patterns (0.56, p=0.008) than for the identification of "early" SSc pattern (0.35, p=0.003) when compared to overall agreement in all participants. Agreement for "early" and "active" patterns was higher in experienced vs not experienced readers ("early" pattern kappa=0.45 vs 0.26, p=0.01, "active" pattern kappa= 0.62 vs 0.35, p=0.006, "late" pattern kappa=0.66 vs 0.48, p=0.12).

Conclusion: There is moderate agreement among rheumatologists for the identification of SSc videocapillaroscopy patterns, while there is substantial agreement among rheumatologists regardless their experience in videocapillaroscopy, in the identification of normal and abnormal capillaroscopic images. Agreement for the identification of "active" and "late" patterns is higher than for "early" capillaroscopic pattern. The identification of "early" capillaroscopic changes may require more experience in the performance and interpretation of this technique. Ref 1. Cutolo M et al. J Rheumatol 2000;27:155-60.

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Abstract Number: 1886

Right Ventricular Load-Adaptability and Response to Therapy in Scleroderma Versus Idiopathic Pulmonary Arterial Hypertension

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Background/Purpose: Recent studies have suggested that right ventricular (RV) adaptation in patients with scleroderma-associated pulmonary arterial hypertension (SSc-PAH) is worse than in patients with idiopathic pulmonary arterial hypertension (IPAH). This has been proposed as one of the explanations for increased mortality in SSc-PAH. However, few studies have compared incident groups of treatment naive SSc-PAH and IPAH patients. The objective of this study is to compare RV remodeling and load-adaptability metrics in patients with SSc-PAH versus IPAH at the time of diagnostic right heart catheterization (RHC) at our institution and at 1 year follow up.

Methods: A retrospective review of adults with SSc-PAH and IPAH who underwent RHC at Stanford Medical Center between 2002-2016 was performed. Inclusion criteria were as follows: mean pulmonary artery pressure (mPAP) greater than or equal to 25 mmHg, baseline echocardiogram within 3 months of RHC, absence of left heart disease (pulmonary capillary wedge pressure less than or equal to 15 mmHg), and absence of severe ILD (FVC and/or TLC < 70%). Baseline characteristics, RHC parameters, and standard echocardiographic measurements including right ventricular fractional area change (RVFAC), tricuspid annular plane systolic excursion (TAPSE), and RV global longitudinal strain (RV GLS) were obtained. Load-adaptability metrics, including the ratio of cardiac index to mean pulmonary artery pressure (CI/mPAP), right atrial pressure to pulmonary pulse pressure (RAP/PP), and RV global longitudinal strain to pulmonary vascular resistance (RV GLS/PVR) were compared between the SSc-PAH and IPAH groups. We used non-parametric Mann Whitney U-test for continuous variables and Fischers Exact Test for categorical variables. Change in RV function was examined by follow up echo (1 year post-RHC) in a subset of patients matched on PH-directed therapy.

Results: Twenty-four PVR matched SSc-PAH and IPAH subjects with newly diagnosed PAH were included in the study. Average duration of SSc was 3 years and median PVR was 12 (3-25 Wood units). There was no significant difference between the two groups in age, sex, baseline NT-proBNP, or degree of treatment at 1 year. At baseline there was no difference in resting right ventricular metrics, including RV FAC, RV GLS, TAPSE, or right atrial size (Table 1). With regards to load-adaptability, there was no difference in RAP/PP, CI/MPAP, or the RV load-adaptability metrics allometrically adjusted for PVR in each group. Overall there was improvement in RVFAC, RV GLS, and TAPSE at 1 year in both groups, though notably we did not observe a significant difference in the degree of response in RV function to therapy between Ssc-PAH and IPAH.

Conclusion: In well-matched SSc-PAH and IPAH patients without ILD or left heart disease, we did not observe a difference in baseline RV function or response to treatment.

Table 1. Results

	Ssc-PAH (n=24)	IPAH (n=24)	P
Sex			
Female, n	23	18	0.1
Male, n	1	6	
Age at PAH diagnosis, median (IQR)	62 (53-68)	52 (45-66)	0.17
Baseline Therapy (oral), n	4*	3	0.66
Therapy at 1 year			
None, n	0	1	0.21
Single oral, n	7	13	
Dual oral, n	11	7	
IV prostacyclin, n	4	3	
IV pros + oral, n	2	0	
NT-proBNP baseline, median (IQR)	1836 (428 - 2583)	420 (203 - 1674)	0.43
NT-proBNP 1 yr, median (IQR)	363 (136 - 1590)	103 (51-314)	0.11
Serologies (for Ssc)			
ANA, n (%)	21 (88%)	N/A	
anti-centromere, n (%)	11 (46%)	N/A	
Scl-70, n (%)	1 (4%)	N/A	
Right ventricular metrics			
RV FAC, % (CI)	25 (22-27)	22 (21-28)	0.41
RV GLS, % (CI)	14 (11-17)	13 (10-17)	0.97
TAPSE, mm (CI)	16 (12-21)	17 (14-18)	0.59
RA area, cm2 (CI)	21 (18-26)	21 (17-24)	0.85
RAP/PP, (CI)	0.15 (0.09-0.22)	0.13 (0.09 - 0.20)	0.66
CI/MPAP, (L/min/m2)/mmHg (CI)	0.04 (0.04-0.05)	0.04 (0.03 - 0.05)	0.56
Change in RV function			
% change in RV FAC (CI)	22% (-8 - 42)	29% (-12 - 40)	0.79
% change in RV GLS (CI)	26% (-13 - 50)	35% (-13 - 55)	1
% change in TAPSE (CI)	20% (-24 - 46)	15% (0 - 36)	0.81

Baseline characteristics, baseline RV metrics, and change in RV function from baseline to 1 year in Ssc-PAH and IPAH groups. Differences in continuous variables were measured using Wilcoxon rank-sum test and categorical variables using Fischer's exact test. Median values for RV metrics and change in RV function are reported. RV FAC = right ventricular fractional area change, RV GLS = right ventricular global longitudinal strain, TAPSE = tricuspid annular plane systolic excursion, RAP = right atrial pressure, PP = pulmonary pulse pressure, CI= cardiac index, MPAP = mean pulmonary artery pressure. Oral therapies include endothelin receptor antagonist, phosphodiesterase-5 inhibitor, and calcium-channel blocker. *All 4 SSc patients on baseline therapy were on PDE-5 inhibitor for Raynaud's phenomenon.

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Abstract Number: 1887

Olfactory Impairment Is Associate with Cognitive Dysfunction and Regional Brain Atrophy in Systemic Sclerosis

Mariana Freschi Bombini[1], Fernando A. Peres[2], Nailu A. Sinicato[3], Aline Tamires Lapa[2], Leticia Rittner[4], Roberto Souza[5], Ana Paula del Rio[1], João Francisco Marques-Neto[1] and Simone Appenzeller[1], [1]State University of Campinas, Campinas, Brazil, [2]Medicine, State University of Campinas, Campinas, Brazil, [3]Pediatrics, State University of Campinas, Campinas, Brazil, [4]Electrical Engineering, State University of Campinas, Campinas, Brazil, [5]State University of Campinas, campinas, Brazil

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Background/Purpose: Several factors has been described as responsible for the association between olfactory impairment and brain regions. In systemic sclerosis (SSc) the olfactory interaction has been little explored. To evaluate the interaction between olfactory impairment, neuropychiatric manifestations, clinical, laboratorial and treatment features in SSc**.**

Methods: We screened consecutive SSc patients followed in a longitudinal cohort from 2011 to 2015 and age and sex matched controls. We excluded patients with overlapping rheumatic diseases. Cognitive evaluation was performed using the Montreal Cognitive Assessment (MoCA). Individual with scores≤26 were considered impaired. Mood disorders were determined through Beck´s Depression and Beck´s Anxiety Inventories. SSc patients were further assessed for clinical and laboratory SSc manifestations, disease activity (Valentini Activity Index), severity activity (Medsger Severity Index). Total dose of corticosteroids and other immunosuppressant medications used since the onset of the disease were calculated. MRI scans were performed in a 3T Phillips® scanner. Sagittal T1 weighted images were used for FreeSurfer automatic volumetric measurements. Olfactory functions was evaluated through Sniffin' Sticks kit (Burghart Medizintechnik, Wedel, Germany). Sniffin' Sticks kit consists of three stages: odor threshold, discrimination, and identification. The maximum score in each stage was 16 points, with a total score of 48 points. Subjects with a score < 30 were considered impaired [hyposmia (score between 15–30) and anosmia (scores of <15). Data were compared by non-parametric tests.

Results: We included 63 SSc patients [55 (87.3%) women; mean age of 51.01 ±11.32 years; range 20 – 82] with mean disease duration of 10.56 ±4.55 years. The control group consisted of 65 healthy volunteers [52 (80%) women p=0.418 with a mean age of 49.05±7.24; p=0.317]. Olfactory impairment were significantly higher in SSc patients [38 (60.3%)] when compared to controls [29 (44.6%)] (p=0.048). Regarding the three different stage SSc patients had significant abnormalities in the threshold [score media 6.3 vs 7.9 (p=0.016)], discrimination [score media 10.17 vs 11.5 (p=0.008)], score total [media 27.4 vs 31.24 (p=0.001)] when compared to controls. Comparing SSc patients with and without olfactory functions we observed in SSc with olfactory impairment had significant decrease in right and left hippocampus (9.5 cm^3 vs 11.3 cm^3; p=0.010) and right and left thalamic (6.05 cm^3 vs 7.2 cm^3; p=0.025) volume. Cognitive impairment was observed in 10 patients (24%) SSc and associated with decreased in discrimination (p=0.023) and identification scores (p=0.002). Significantly decreased of identification scores was associated with increase depression symptoms (p=0.032). We did not observe association between olfactory impairment and clinical, laboratory and treatment manifestations.

Conclusion: Olfactory impairment was frequently observed in SSc and associated with decreased volumes of hippocampus and thalamus. Cognitive impairment and mood disorders were the only clinical manifestations associated with olfactory function.

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Abstract Number: 1888

Reliability, Validity, and Sensitivity to Change of the Simplified Duruoz Hand Index in Systemic Sclerosis

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Background/Purpose: Hand involvement is observed in almost all patients with Systemic Sclerosis (SSc), and is due in various proportions to skin and tendon fibrosis, arthritis and microvascular impairment, sometimes complicated with digital ulcers (DUs). The Duruoz's Hand Index (DHI) (or Cochin hand functional disability scale), is a reliable tool for hand function assessment in diseases like rheumatoid arthritis and SSc. A short form of the DHI comprising of 6 items (DHI-6) has been recently developed and validated. The purpose of this study was to assess the reliability, validity and sensitivity to change of the new DHI-6 in a cohort of patients with SSc.

Methods: 70 consecutive patients with SSc, examined in our EUSTAR center, satisfying the 2013 ACR/EULAR classification criteria, were included. Patients completed the DHI, the Scleroderma Health Assessment Questionnaire (SHAQ) questionnaires and the Hand Mobility in Scleroderma (HAMIS) test. Three anthropometric measures to assess finger range of motion were also measured: the finger extension (FE), finger-to-palm distance (FTP) and Δ FTP (FE - FTP). **Step 1**: In 38 patients the test-retest reliability, using intra-class correlation coefficients (ICC), and the internal consistency (Cronbach's alpha test) were examined. **Step 2**: In all 70 patients, the criterion validity by correlation coefficients with SHAQ, HAMIS and the anthropometric measures, and the discriminative capacity between different subsets of patients by Mann-Whitney U-test were examined. Moreover, the DHI-6 was correlated with DHI. **Step 3**: 35 consecutive patients had a second evaluation at an interval of (mean± SD) 8.1±30. months; among them, 8 patients had progressive early diffuse SSc. Sensitivity to change was assessed in these patients using the effect size (ES) (Cohen's d) and the standardized response mean (SRM).

Results: The study included 63 females/7 males with SSc, age 50.9±13.0 years, disease duration 5.8±5.6 years; 27 with diffuse cutaneous SSc (dcSSc) and 43 with limited cutaneous SSc (lcSSc). The DHI-6 had a score of 6.7±6.5, range 0-25 (possible range 0-30) at baseline, and 8.3±7.0, range 0-24 at follow-up. The DHI-6 presented an excellent test-retest reliability (ICC 0.98), and a good internal consistency (Cronbach's alpha 0.89). Criterion validity of the DHI-6 was proved by moderate to strong correlations with HAMIS, FE, FTP, Δ FTP and the SHAQ disability index (Spearman's rho 0.48-0.82, $p<001$). Correlation of the DHI-6 with the DHI was excellent, with a Spearman's rho of 0.96, $p<0.001$. The discriminative capacity of the DHI-6 was proven by statistically significant differences between patients with and without: synovitis, flexion contractures of the fingers, and history of DUs. The sensitivity to change (ES of 0.57 and SRM of 1.11) was very good for detecting a minimally important difference.

Conclusion: The simplified DHI is a brief, valid and reliable instrument for measuring hand disability in SSc. These results suggest that the DHI-6 could be used both in day-to-day practice and in clinical trials, reducing patient burden and increasing research capacity. However, more studies are needed to confirm these results.

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Predictors of Acro-Osteolysis in Systemic Sclerosis

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SESSION INFORMATION

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Background/Purpose: Acro-osteolysis (AO) is the bony resorption on the distal tufts of the digits, a characteristic radiological finding in Systemic Sclerosis (SSc) with estimated prevalence of 20-25% [1][2]. Some studies have suggested an association of digital ischemia and SSc specific auto-antibodies with AO [1][3][4], but the pathogenesis of AO remains poorly understood. Our goal is to better understand the factors associated with development of AO in SSc.

Methods: We evaluated 168 outpatients who met criteria for SSc [5] and were seen between 2010 and 2015. We collected relevant clinical information, including laboratory and hand x-ray assessments, obtained within 5 years of this analysis. Patients were grouped by presence or absence of AO based on hand x-rays. Associations between potential risk factors and AO were assessed with unconditional logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for presence of AO.

Results: Of the 168 SSc patients studied, a total of 43 (26%) had AO. In univariate analysis, anti-topoisomerase I antibody (anti-topo I) and digital tip ulcers (DTUs) had the strongest association with AO (Table-1). In multivariate model, after adjusting for Anti-Topo I and DTUs (prior and current DTUs), AO was positively associated with Anti-Topo I (OR=4.3, 95% CI: 1.8-9.9), prior DTUs (OR=5.6, 95% CI: 2.2-14.2), current DTUs (OR=4.2, 95% CI: 1.9-9.4), and hand contractures (OR=3.3, 95% CI: 1.4-7.8), whereas AO was inversely associated with age of disease onset (OR=0.97, 95% CI: 0.94-0.99). Although not statistically significant, the Anti-centromere antibody was also inversely associated with AO (OR=0.4, 95% CI: 0.14-1.08). We found no associations of AO with current skin score, synovitis, tendon friction rubs, or RNA polymerase III antibody.

Conclusion: Our findings suggest that both digital ischemia and anti-topo I are strongly and independently associated with AO. Additionally, AO was strongly associated with hand contractures and younger age of disease onset. Prospective studies are needed to confirm if more aggressive treatment of digital ischemia in this subset of patients will lead to lower risk of AO and hand contractures. **References:**

1- Avouac et al. Ann Rheum Dis. 2006; 65:1088

2- Arslan Tas et al. Rheumatol Int. 2012; 32:3581

3- Johnstone et al. Rheumatol. 2012; 51:2234

4- Steen et al. Semin Arthritis Rheum. 2005; 35:35

5- Hoogen et al. Ann Rheum Dis. 2013; 72:1747 & Arthritis Rheum. 2013; 65:2737

	Table-1: PatientsÕ demographics and Systemic Sclerosis clinical features in relation to acro-osteolysis						
		Acro-osteolysis* n=43 (25.6%)	No Acro-osteolysis* n=125 (74.4%)	Univariable Analysis	Multivariable Analysis Adjusting for anti-topo I	Multivariable Analysis Adjusting for prior and current DTUs
		Mean(SD) or Col%	Mean(SD) or Col%	OR, (95%CI), p value	OR, (95%CI), p value	OR, (95%CI), p value
Age (year)		57.6(13.2)	59.4(12.6)	0.99, (0.96-1.01), p=0.7		
Sex	**Female**	37(26%)	104(74%)	1.2, (0.5-3.3) p=0.66		
	Male	6(22%)	21(78%)			
Race	**Caucasian**	28(25%)	84(75%)	0.9, (0.5-2.0), p=0.9		
	AA	5(29%)	12(71%)			
	Other	9(31%)	29(69%)			
Ethnicity	**Hispanic**	4(29%)	10(71%)	1.2, (0.3-4.0), p=0.5		
	Non-Hispanic	39(25%)	115(75%)			
SSc-type	**Limited**	12(16%)	63(84%)	0.37, (0.17-0.8), p=0.0082	0.53, (0.2-1.2), p=0.14	0.35, (0.15-0.8), p=0.014
	Diffuse	31(34%)	60(66%)			
Disease Duration(year)		16.6(9.0)	13.9(9.5)	1.0, (0.99-1.06), p=0.1		
RaynaudÕs Duration(year)		16.7(10.5)	14.4(10.5)	1.0, (0.99-1.05), p=0.2		
Age at Disease Onset(year)		41(14.6)	45.8(12.3)	0.97, (0.94-0.99), p=0.039	0.96, (0.93-0.99), p=0.01	0.97, (0.94-0.99), p=0.046
Age at RaynaudÕs Onset(year)		40.9(14.9)	45.3(13.7)	0.98, (0.95-1.002), p=0.08		
Overlap with RA	**Yes**	9(21%)	33(79%)	0.8, (0.3-1.8), p=0.52		
	No	33(26%)	92(74%)			
Prior DTUs**	**Yes**	35(40%)	53(60%)	6.6, (2.76-16.24), p<0.0001	5.6, (2.2-14.2), p<0.0001	/
	No	7(9%)	71(91%)			
Current DTUs**	**Yes**	23(49%)	24(51%)	5.3, (2.49-11.39), p<0.0001	4.2, (1.9-9.4), p=0.001	/
	No	18(15%)	100(85%)			
Prior TFRs**	**Yes**	11(29%)	27(71%)	1.6, (0.7-3.8), p=0.26		
	No	20(20%)	80(80%)			
Current TFRs**	**Yes**	5(31%)	11(69%)	1.3, (0.5-4.3), p=0.4		
	No	37(25%)	113(75%)			
Prior synovitis**	**Yes**	10(21%)	38(79%)	0.8, (0.4-1.9), p=0.6		
	No	25(24.5%)	77(75.5%)			
Current Synovitis**	**Yes**	5(25%)	15(75%)	0.99, (0.3-2.9), p=1.0		
	No	37(25%)	110(75%)			

Anti-topo I	**Positive**	24(52%)	22(48%)	6.5, (2.99-14.04), p<0.0001	/	4.3, (1.8-9.9), p=0.001
	Negative	17(16%)	101(84%)			
RNA pol III	**Positive**	5(21%)	19(79%)	0.8, (0.3-2.4), p=0.7		
	Negative	29(24%)	90(76%)			
ACA	**Positive**	5(14%)	31(86%)	0.4, (0.14-1.08), p=0.06		
	Negative	38(29%)	92(71%)			
OA*	**Yes**	28(30%)	64(70%)	1.8, (0.9-3.6), p=0.1		
	No	15(20%)	61(80%)			
Osteopenia*	**Yes**	14(29%)	34(71%)	1.5, (0.7-3.2), p=0.3		
	No	24(22%)	87(78%)			
Calcinosis*	**Yes**	27(35%)	51(65%)	2.32, (1.13-4.74), p=0.02	2.4, (1.1-5.4), p=0.026	1.6, (0.7-3.5), p=0.25
	No	16(18.6%)	70(81.4%)			
Erosions*	**Yes**	10(38%)	16(62%)	2.0, (0.8-4.9), p=0.1		
	No	33(23%)	108(77%)			
Hand Contractures**	**Yes**	23(41%)	33(59%)	4.23, (1.95-9.2), p=0.0002	3.3, (1.5-7.5), p=0.004	3.3, (1.4-7.8), p=0.006
	No	14(14%)	85(86%)			
ILD***	**Yes**	34(33%)	69(67%)	3.12, (1.2-8.1), p=0.016	2.0, (0.8-5.7), p=0.16	2.8, (0.99-7.6), p=0.052
	No	6(13.6%)	38(86.4%)			
Current mRSS		3.8(2.9)	3.3(5.6)	1.0, (0.95-1.08), p=0.58		

*Documented by hand x-rays **Documented on physical exam ***Documented by high resolution CT scan of the chest
SSc: systemic sclerosis; DTU: digital tip ulcer; RA: rheumatoid arthritis; TFRs: tendon friction rubs; Anti-topo I: anti-topoisomerase I or Scl70; RNA pol III: anti-RNA polymerase III antibody; ACA: anti-centromere antibody; OA: osteoarthritis; ILD: interstitial lung disease; mRSS: modified Rodnan skin score

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Abstract Number: 1890

Functional Disability and Its Predictors in Systemic Sclerosis: A Study from the Desscipher Project within the European Scleroderma Trials and Research Group

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SESSION INFORMATION

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Background/Purpose: Systemic sclerosis (SSc) can greatly impact the patients' quality of life due to its multisystem manifestations. The health assessment questionnaire (HAQ) is one of the most commonly used measures of disability in musculoskeletal disorders and was extended to form the scleroderma HAQ (SHAQ), a more disease-specific disability scale that incorporates the HAQ and 5 visual analogue scales (VAS) into one score. This cross-sectional study aims to identify contributors of disability in SSc by means of the SHAQ.

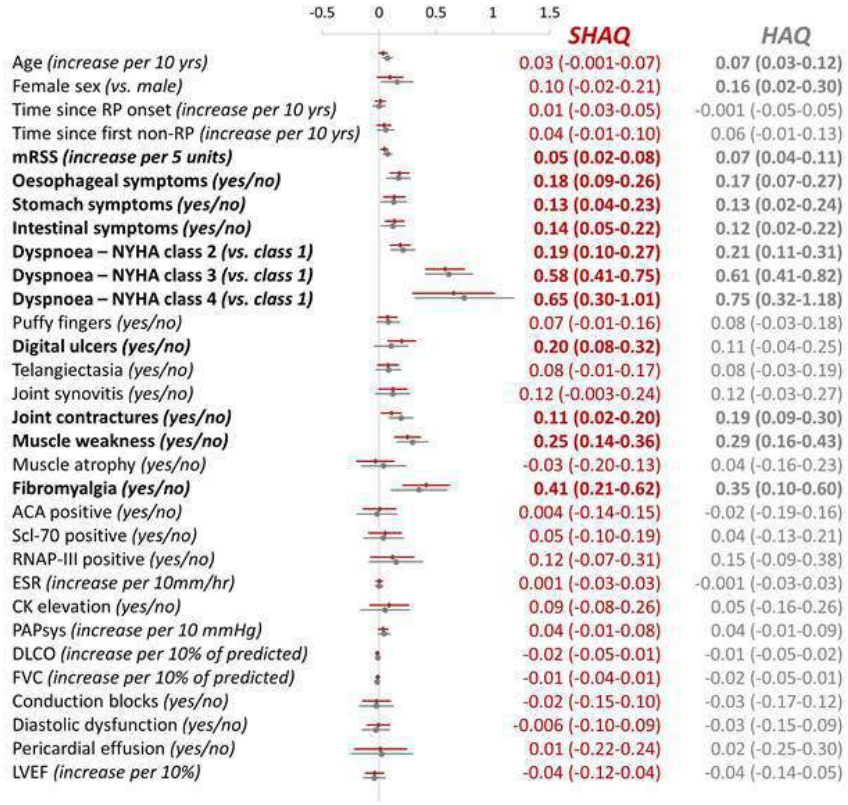
Methods: Adult patients from the prospective DeSScipher cohort were included in the analysis if they had one complete SHAQ recorded (range 0-3) and fulfilled either the 1980 ACR or the 2013 ACR/EULAR criteria for SSc. Multiple linear regression analysis was used to assess the combined effect of factors defined *a priori* and possibly associated with a lower SHAQ.

Results: Between June 2013 and January 2016, 813 patients had one complete SHAQ recorded (34% of all patients followed in the DeSScipher cohort). The mean SHAQ score was 0.86 (standard deviation [SD] 0.65) and the mean HAQ score was 0.92 (SD 0.77). 60% of patients were in the "mild to moderate difficulty" SHAQ category (score of 0-1), 34% in the "moderate to severe disability" category (score of 1-2) and 6% in the "severe to very severe disability" category (score of 2-3). In order of magnitude, the means of the five VASs included in the SHAQ were: Overall disease severity (30, IQR 10-51), Raynaud's phenomenon (21, IQR 3-50), pulmonary symptoms (10, IQR 1-40), gastrointestinal symptoms (6, IQR 1-31) and digital ulcers (2, IQR 1-30). In multiple linear regression, the main contributor to functional disability was dyspnea. The SHAQ scores reported by patients with NYHA class 4, 3 or 2 were on average 0.65 units (95% confidence interval

[CI] 0.30-1.01), 0.58 units (95%CI 0.41-0.75) and 0.19 units (95%CI 0.10-0.27) higher than that of patients with NYHA class 1. The presence of fibromyalgia (0.41 units, 95%CI 0.21-0.62) as well as muscle weakness (0.25 units, 95%CI 0.14-0.36) were also associated with higher levels of disability (Figure). Patients reporting esophageal, gastric and intestinal symptoms simultaneously had, on average, a SHAQ score of 0.45 units (95% CI 0.33-0.58) higher than patients reporting no gastrointestinal symptoms. Patients with symptoms in two gastrointestinal regions had a SHAQ score of 0.28 units (95%CI 0.17-0.39) and in one region of 0.13 units (95% CI 0.04-0.23) higher than patients with no symptoms. The contributing factors to an impaired functional ability were similar in patients with diffuse SSc and patients with limited SSc.

Conclusion: Patients perceive dyspnea, pain, muscle weakness and gastrointestinal symptoms as the main factors driving their level of disability. **Acknowledgement:** The DeSScipher project was funded by the European Community's Framework Programme 7 under grant agreement N° 305495.

Figure Multivariable regression coefficients with 95% CI for the **SHAQ** and HAQ scores (both ranging from 0 to 3).



ACA, anticentromere autoantibodies; CI, confidence interval; DLCO, single breath diffusing capacity for monoxide; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mRSS, modified Rodnan skin score; NYHA, New York Heart Association; PAPsys systolic, pulmonary artery pressure as estimated by echocardiography; RP, Raynaud's phenomenon; Scl-70, anti-topoisomerase autoantibodies; yrs, years.

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Abstract Number: 1891

Excellent Reliability of Semiquantitative Nailfold Capillaroscopy Assessment in a Systemic Sclerosis Cohort – a Pilot Study

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Background/Purpose: Nailfold capillaroscopy (NFC) is essential in the evaluation and classification of systemic sclerosis (SSc). Semiquantitative capillaroscopy scoring is a promising tool for assessing disease activity, severity and change in SSc, however there is no consensus yet over which capillaroscopy abnormalities should be analyzed and how. We aimed to investigate the reliability of the qualitative and semiquantitative scoring of NFC assessment between two raters and test-retest for each rater in a SSc cohort.

Methods: This is a pilot study from one EUSTAR centre, where 2 raters assessed the NFC images of 48 consecutive patients with SSc. Data were analyzed in 3 ways: step **1.** qualitatively by 'normal' / 'abnormal' category, step **2.** 'early', 'active', 'late' scleroderma patterns and unclassifiable in any pattern, and step **3.**semiquantitatively by calculating the mean score for capillary loss, disorganization of the microvasculat array, giant capillaries, microhaemorrhages and capillary ramifications; combinations of giant capillaries and microhaemorrhages (as a surrogate for vascular activity) and disorganization and ramifications (surrogate for vascular damage) were also assessed. Variables for all steps were calculated for all fingers and for each finger. Inter-rater/intrarater agreement was assessed by Cohen's kappa coefficients for qualitative variables and by intraclass correlation coefficients (ICC) for mean score values of abnormalities. Differences in scores between patients with digital ulcers (DUs) history and Bosentan treatment were analyzed by logistic regression.

Results: Interrater reliability ranged from good to excellent agreement for mean score values of abnormalities in all fingers (ICC coefficients 0.745 to 0.897) and was excellent for activity (ICC coefficient of 0.923) and damage combinations (ICC coefficient of 0.918). Assessment of abnormalities in a qualitative manner (normal/abnormal or with capillaroscopy patterns) showed weaker interrater agreement than the semiquantitative assessment (k coefficient <0.7). When scores were assessed in each finger, interrater reliability was good to excellent for mean scores of abnormalities and activity and damage combinations (ICC coefficients 0.781 to 0.867 for mean abnormalities scores and 0.713 to 0.856 for combinations), whereas for qualitative assessments interrater reliability was much weaker (k coefficients <0.7). Intrarater variability was good to excellent for mean score values of abnormalities and activity and damage combinations in all fingers and separate fingers for both raters; for qualitative assessment only one of the raters had good test-retest reliability. There was no difference in scores between patients with/without DUs history or Bosentan treatment.

Conclusion: Reliability of NFC assessment is essential in SSc trials/clinical practice to ensure quality of data. This pilot study demonstrates very good reliability between raters of the semiquantitative NFC assessment in a SSc cohort. Combinations of capillaroscopy abnormalities had very good reliability and might be preferred because they are less time consuming. A longitudinal assessment and confirmation of our results in other cohorts is needed.

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semiquantitative-nailfold-capillaroscopy-assessment-in-a-systemic-sclerosis-cohort-a-pilot-study

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Immunosignature Technology Differentiates Patients with Systemic Sclerosis and Internal Organ Involvement

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic sclerosis (SSc) is a connective tissue disease (CTD) characterized by fibrosis, vascular complications, and inflammation affecting both skin and internal organs. Diagnosis of SSc is difficult due to the complexity of manifestations and overlap with other autoimmune (AI) diseases. Clinical classification criteria including SSc-specific autoantibodies have been developed, but disease manifestations are often advanced once patients fulfill these criteria. In addition, heterogeneity in clinical presentation, internal organ involvement, and rate of disease progression make counseling and management of each individual patient challenging. The Immuno*Signature*(IMS) Technology has shown promise as a new diagnostic platform for both chronic and infectious diseases. The goal of this study was to identify specific antibody signatures that differentiate SSc patients from healthy individuals and those with other AI, as well as those SSc patients with and without particular internal organ complications.

Methods: Plasma samples from a study population of 876 subjects were evaluated; the cohort was comprised of SSc (n=301), dermatomyositis (DM) (396), mixed and undifferentiated CTD (31), polymyositis (14), systemic lupus erythematosus (8), other AI (42), and healthy controls (84). All met validated classification criteria for each specific disease. An IMS assay was used to detect plasma antibodies bound to an array of ~126,000 unique peptides. Peptide sequences were designed to broadly sample chemical space thus providing a library of diverse epitope mimetics for antibodies to selectively bind. Features most discriminating SSc contrasts were identified using a t-test. Support vector machine classifiers were trained and assessed by 100 iterations of 5-fold cross validation.

Results: Cross-validated estimates of classification performance are provided in Table 1. One classifier distinguished SSc patients from healthy donors. Additional classifiers differentiated SSc from other AI diseases or from DM in particular. Finally, SSc patients that suffered from interstitial lung disease (ILD), renal crisis, or gastric antral vascular ectasia (GAVE) within a year of their blood draw could be distinguished from those SSc patients who did not. Up to 10,000 peptides whose antibody-binding characteristics differentiated health status groups were used as inputs to these classifiers.

Conclusion: Reproducible binding patterns produced by peripheral-blood antibody repertoires on a mimetic-peptide microarray can differentiate SSc from healthy donors and from other AI diseases. In addition, distinctive signatures were established for SSc patients with internal organ complications including ILD, renal crisis, and GAVE. This suggests that the IMS technology may be instrumental in the development of both new diagnostic and prognostic tests for SSc.

Table 1. Classification Performance Estimates of IMS for SSc Diagnosis and Prognosis				
Contrast	**AUC**	**Sens. @ 90% Spec.**	**Spec. @ 90% Sens.**	**Accuracy @ Sens. = Spec.**
SSc vs Healthy	0.96 (0.95-0.97)	90% (86-94%)	91% (86-93%)	90% (88-92%)
SSc vs Other AI	0.77 (0.75-0.79)	42% (35-47%)	40% (32-47%)	70% (68-73%)
SSc vs DM	0.77 (0.74-0.8)	40% (33-48%)	41% (33-48%)	70% (67-73%)
ILD+ vs ILD-	0.68 (0.64-0.72)	23% (13-33%)	31% (21-41%)	63% (59-68%)
Renal Crisis+ vs Crisis-	0.72 (0.60-0.82)	27% (3-53%)	42% (12-62%)	65% (55-76%)
GAVE+ vs GAVE-	0.77 (0.64-0.84)	28% (8-46%)	49% (10-67%)	69% (62-77%)

Disclosure: L. Chung, None; **D. Fiorentino**, None; **R. Gerwien**, HealthTell, Inc., 1,HealthTell, Inc., 3; **K. Jia**, None; **J. B. Legutki**, HealthTell, Inc., 1,HealthTell, Inc., 3; **A. V. Vergara**, None; **L. Zhu**, None; **T. M. Tarasow**, Healthtell, Inc., 3,HealthTell, Inc., 1; **K. Sykes**, HealthTell, Inc., 1,HealthTell, Inc., 3.

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Abstract Number: 1893

Prevalence of Antiphospholipid Antibodies in Systemic Sclerosis: A Systematic Review and Meta-Analysis

Angélique Lemaire[1,2], **Vincent Sobanski**[2,3,4,5], Luc Dauchet[6], Eric Hachulla[1,2,3,5], Sylvain Dubucquoi[3,5,7], Marc Lambert[1,2,3,5], Pierre-Yves Hatron[1,2,8] and David Launay[1,2,3,5], [1]CHU Lille, Département de Médecine Interne et Immunologie Clinique, F-59000 Lille, France, Lille, France, [2]CHU Lille, Centre national de référence maladies systémiques et auto-immunes rares (sclérodermie systémique), F-59000 Lille, France, Lille, France, [3]Inserm, U995, F-59000 Lille, France, Lille, France, [4]CHU Lille, Département de Médecine Interne et Immunologie Clinique, F-59000 Lille, France, [5]Univ. Lille, U995, Lille Inflammation Research International Center (LIRIC), F-59000 Lille, France, Lille, France, [6]CHU Lille, Service d'Epidémiologie, économie de la santé et prevention, F-59000 Lille, France, Lille, France, [7]CHU Lille, Laboratoire d'Immunologie, F-59000 Lille, France, Lille, France, [8]Univ Lille, CHU Lille, F-59000 Lille, France, Lille, France

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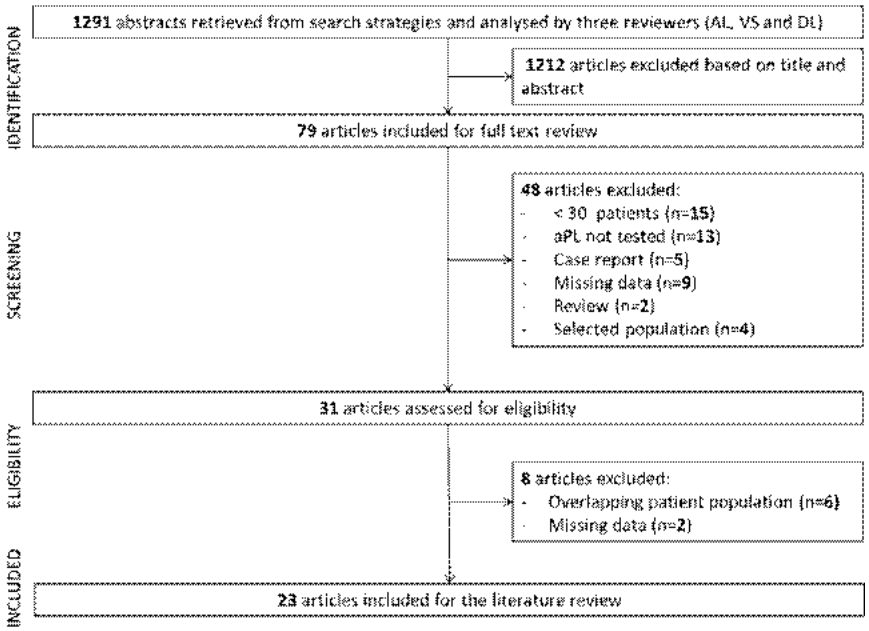
Background/Purpose: Antiphospholipid antibodies (aPL) can be present in the sera of systemic sclerosis (SSc) patients. Important variations of their prevalence are observed in the literature. Their clinical associations remain largely unknown. The aim of this study was to perform a systematic review of published reports and a meta-analysis to estimate the prevalence of aPL in SSc.

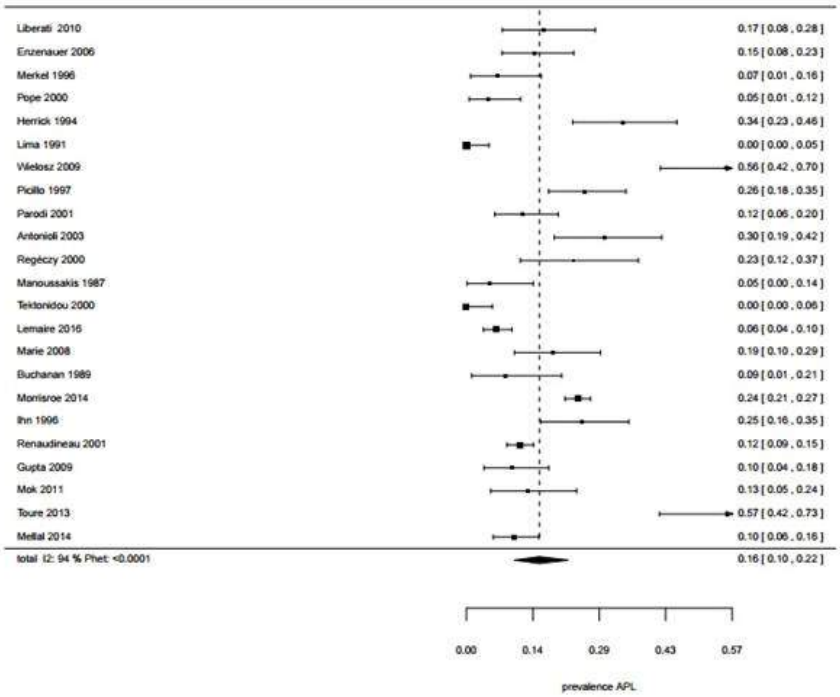
Methods: A systematic review of the literature was carried out in PubMed and Embase between May 1975 and November 2015 by 3 of the authors (AL, VS and DL). We used combinations of the terms "systemic sclerosis", "antiphospholipid

antibodies", "antiphospholipid syndrome", "anticardiolipin antibodies", "lupus anticoagulant", "anti-β2GP1", "anti-phosphatidylethanolamine", "thrombosis", "pulmonary embolism", "deep vein thrombosis", "stroke", "myocardial infarct", "pregnancy". We adapted the search strategy to the specificities of each database. After screening the titles and abstracts, studies were selected after a full-length review. Inclusion criteria were: French or English-language publication, adult patients with SSc, and at least 30 patients with SSc tested for lupus anticoagulant (LA), or/and anticardiolipin (aCL) or/and anti- β2Glycoprotein 1 (anti-β2GP1) antibodies. Meta-analysis was performed using number of aPL positive (at least one of the three antibodies positive) and negative patients.

Results: 1291 references were retrieved as result of search, 79 articles were included for full text review after reading the titles and abstracts. Of these articles, 31 were assessed for eligibility. Finally, 23 studies were included in the meta-analysis, representing a total population of 2937 SSc patients. Prevalence of aPL positivity (one or more) in SSc in literature ranged from 0 to 58%. The overall pooled prevalence of aPL in SSc was 16% (95%CI [10-22]). LA was found in 0 to 16% of patients; aCL in 0 to 34% and anti-β2GpI in 0 to 50%. The prevalence of aCL was 11% (95%CI [7-15]), and prevalence of anti-β2GP1 was 9% (95%CI [3-19]). Clinical manifestations associated with aPL positivity were more frequently pulmonary arterial hypertension (PAH) or digital ulcer (DU). Six studies out of 11 found an association between aPL and PAH (aCL in 5, one or more aPL in 1). Two studies out of 8 found an association between aPL (aCL) and DU and 2 studies found a trend.

Conclusion: The prevalence of aPL in SSc was highly variable (range 0-58%). The overall pooled prevalence was 16% (95%CI [10-22]). The most frequent clinical manifestation associated with aPL positivity was PAH. AL and VS have contributed equally to this work.





Disclosure: A. Lemaire, None; **V. Sobanski**, None; **L. Dauchet**, None; **E. Hachulla**, None; **S. Dubucquoi**, None; **M. Lambert**, None; **P. Y. Hatron**, None; **D. Launay**, None.

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Abstract Number: 1894

Increased Mortality in Systemic Sclerosis Patients with Fibrosing Myopathy

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Background/Purpose: Skeletal myopathy in systemic sclerosis (SSc) is associated with poor outcomes such as disability. The spectrum of muscle histopathology of weak SSc patients is heterogeneous. The purpose of this study was to determine the clinical phenotype and outcome of those with predominant fibrosis on muscle biopsy and compare them to those with inflammatory and/or necrotizing muscle biopsies.

Methods: This retrospective, cross-sectional study included SSc patients with muscle weakness and muscle biopsies available for review. Biopsies were assessed for individual pathologic features including inflammation, necrosis, and fibrosis as previously described (1). Biopsies were assigned a histopathologic category of “inflammatory myopathy” if they

had inflammation and/or necrosis with or without fibrosis. Biopsies with predominant fibrosis and no inflammation or necrosis were designated as "fibrosing myopathy". Clinical data including SSc subtype, disease duration, serum creatine kinase (CK) levels, electromyography (EMG), autoantibody profile, and survival (including Kaplan Meier curves) were compared between the two groups.

Results: 47 biopsies from weak SSc patients were available for review; 8 had fibrosing myopathy, 28 had inflammatory myopathy, and 11 could not be classified as either of these. Survival analyses demonstrated that patients with fibrosing myopathy had a statistically significant higher death rate (5 of 8; 62.5%) compared to those with inflammatory myopathy (4 of 28; 14.3%; p=0.01) (Figure 1). The mean time to death from muscle biopsy was 0.28 ± 0.19 years in those with fibrosing myopathy compared to 2.50 ± 1.6 years with inflammatory myopathy (p=0.01). Although not reaching statistical significance, compared to those with inflammatory myopathy, SSc patients with fibrosing myopathy were more likely to have the diffuse SSc subtype (87% vs. 64%, p=0.21), African-American race (62.5% vs. 35.7%; p=0.17), shorter disease duration since first non-Raynaud's symptoms (2.31 + 1.97 years vs. 2.86 ± 3.4 years; p=0.58), and lower FVC (55.5 ± 31.9 vs. 66.4 ± 17.6; p=0.23). There was also a trend for patients with fibrosing myopathy to have lower CK values (516 ± 391 vs. 2477 ± 3511, p=0.13) and more frequent non-irritable myopathy on EMG (57.1% vs. 34.7%, p=0.27). Anti-Scl-70 antibodies were found in 25% (2 of 8) of patients with fibrosing myopathy and only 4% (1 of 28) of those with inflammatory myopathy (p=0.14).

Conclusion: SSc patients with muscle weakness and a fibrosing myopathy have markedly increased mortality compared to those with inflammatory myopathy.

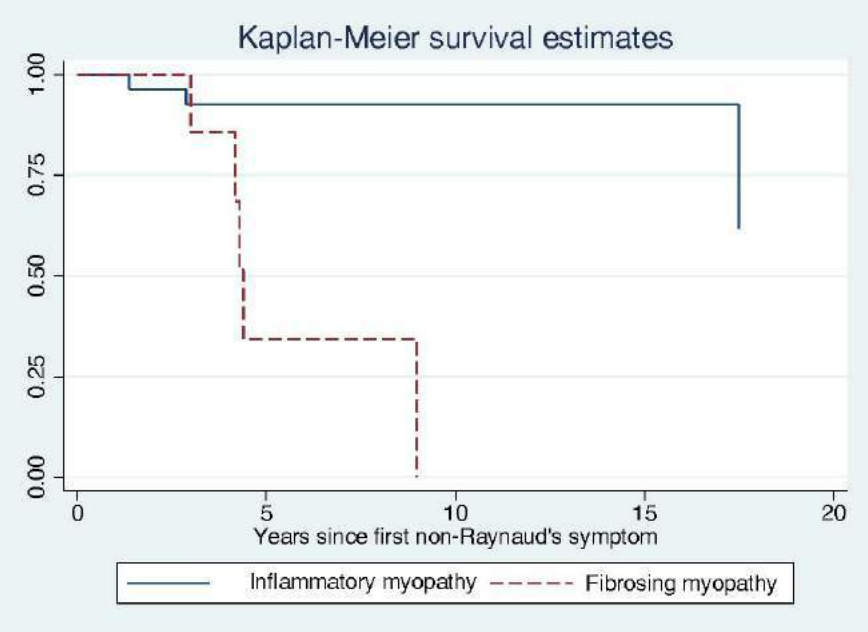

Figure 1: Kaplan-Meier survival estimates comparing SSc patients with fibrosing myopathy vs. inflammatory myopathy
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ADDIN ZOTERO_BIBL {"custom":[]} CSL_BIBLIOGRAPHY 1. Paik JJ, Wigley FM, Lloyd TE, Corse AM, Casciola-Rosen L, Shah AA, et al. Spectrum of Muscle Histopathologic Findings in Forty-Two Scleroderma Patients With Weakness. *Arthritis Care Res* 2015;67:1416–1425.

Disclosure: J. J. Paik, None; **F. M. Wigley**, CSL Behring, 2,Allergan, Inc., 2,Cytori, 2,Corbus, 2,Boehringer Ingelheim, 2; **A. A. Shah**, None; **A. Corse**, None; **L. K. Hummers**, None; **A. Mammen**, None.

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Abstract Number: 1895

Increased CXCL4/PF4 Presence in Systemic Sclerosis and Absence of

Heparin Directed Autoantibodies

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Session Time: 9:00AM-11:00AM

Background/Purpose: Platelet factor 4 (PF4), also called CXLC4 is a chemokine that is found in higher levels in systemic sclerosis (SSc) patients and is in particular associated with lung involvement and early diffuse disease, conditions which are correlated with certain SSc auto antibody types. PF4 is also the antigenic target, when combined with heparin complexes, involved in heparin induced thrombocytopenia (HIT). Anti-PF4 antibodies, both heparin dependant and independent, are more prevalent in systemic lupus erythematous (SLE) patients and murine models suggest increased anti heparin antibodies in SSc(1). Our aim was to examine whether certain SSc patients then also had an associated increase in heparin dependant anti PF4-heparin antibodies.

Methods: 102 patients' sera from our SSc patient bank, recruited from consenting adult patients with a diagnosis of SSc established between 1988 and 1995, were randomly selected, each with a particular SSc related antibody (anti centromere (ACA), anti topoisomerase I antibody (ATA), RNA polymerase III (RNAP), anti Th/To). Each patient serum was tested for the presence of anti PF4-heparin antibodies using ELISA technique. A second group of SLE patients were also tested and acted as controls. Patient files were reviewed for comorbidities, type of SSc, and the presence of interstitial lung disease.

Results: A total of 102 SSc patients, split as follows: 20 with ATA antibodies, 20 with anti Th/To, 31 with ACA and 31 with RNAP. There was no significant differences in the presence of anti PF4-heparin between each SSc antibody subgroup, at 5%, 5%, 6.4% and 0% respectively. 26 patients (25.5%) had ILD, in particular 65% of ATA patients. 3.8% compared to 3.9% (p=1) of patients with and without ILD had anti PF4-heparin antibodies respectively. No patient with diffuse cutaneous SSc had anti PF4-heparin antibodies compared to 4.9% of patients with limited cutaneous disease (p=0.58). Of the 21 lupus patients, 14% of patients had anti PF4-heparin compared to 3.9% of 102 of SSc patients (p=0.095). None of these patients had any documented HIT.

Conclusion: Despite previously demonstrated increased PF4 or CXCL4 levels, there does not seem to be an associated increase in anti PF4-heparin antibodies in SSc patients, either with or without ILD. There is no indication that these patients will accrue false positives on HIT screening, which are based on anti PF4-heparin detection, and there are no direct antigenic arguments for an increased risk of HIT itself. This may provide insight into the antigenicity of CXCL4, although it may be interesting to examine the presence of heparin independent PF4 antibodies.

1. Matic M, Shibata S, Fillit HM. Monoclonal antibody to heparan sulfate from autoimmune tight skin (TSK) mice binds to the endothelial cell surface. Immunol Invest 1997;26:371-81.

Disclosure: B. Zheng, None; **N. Blais**, None; **J. L. Senécal**, None; **G. Perez**, None; **M. Koenig**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-cxcl4pf4-presence-in-systemic-sclerosis-and-absence-of-heparin-directed-autoantibodies

Abstract Number: 1896

Efficacy of Pulmonary Arterial Hypertension-Specific Drugs Combination

Therapy in Survival of Patients with Pulmonary Arterial Hypertension Associated with Systemic Sclerosis and Other Connective Tissue Diseases

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Background/Purpose: Survival of patients with pulmonary arterial hypertension (PAH) associated with connective tissue disease (CTD), especially systemic sclerosis (SSc), is poorer than that of patients with idiopathic PAH. Notably, combination therapy using PAH-specific drugs has been recently shown to improve survival of patients with idiopathic PAH, In the present study, we evaluated survival of patients with PAH associated with SSc and other CTDs under PAH-specific drugs combination therapy.

Methods: We performed a retrospective-cohort study of 117 patients with PAH associated with CTD, including 54 SSc, 29 MCTD, 24 SLE and 10 other CTD patients, who were followed up between January 1980 and March 2016 in our hospital. PAH was diagnosed based on heart catheterization. Our combination therapy strategy for PAH intended to achieve the following goals: 1) improvement in WHO-functional class and 2) reduction of serum BNP level of less than 100 pg/ml, based on our previous study as well as on the results demonstrated by Hoeper et. al, (Eur Respir J 2005; 26: 858–863). The PAH-specific drugs, including bosentan, ambrisentan, macitentan, sildenafil, tadalafil, riociguat, epoprostenol, and beraprost (an oral prostacyclin analog that is only available in Japan), were switched from drug to drug or adopted in combination so as to achieve these predetermined therapeutic goals once a month. We performed Cox's proportional hazard analysis for survival measured from the date of the diagnosis of PAH using propensity score (PS) methods. PS for combination therapy was estimated from a variety of factors and condition at the initial treatment for PAH using logistic regression.

Results: Sixty patients, including in 26 patients with SSc, were treated under our combination therapy strategy. The PAH-specific medications in this group at the last observation are shown in Table 1. Multivariate study demonstrated that combination therapy significantly reduced the risk for death (HR 0.316, 95%CI: 0.161-0.593) in patients with PAH associated with CTD. As shown in Table 2, stratified analysis revealed that combination therapy appeared to improve survival in PAH patients with SSc, although the efficacy was inferior to that in PAH patients with other CTDs.

Conclusion: The results demonstrate that combination therapy using PAH-specific drugs improved survival of PAH patients with ~~both~~ SSc and other CTDs. The data also confirm that the prognosis of PAH associated with SSc is worse than that of PAH associated with other CTDs. Further efforts are required for treatment of PAH associated with SSc.

Table1. Use of PAH-specific drugs in combination therapy

Combination					Number of Patients (%)			
					SSc		ALL CTD	
• *Single*				5	*(19.2)*	*19*	*(31.7)*	
- BPS					3	(11.5)	15	(25.0)
- AMB					0	(0.0)	1	(1.7)
- TAD					1	(3.8)	1	(1.7)
- RIO					1	(3.8)	1	(1.7)
- EPO					0	(0.0)	1	(1.7)
• *Combination (2 drugs)*					*12*	*(46.2)*	*25*	*(41.7)*
- BPS	+	BOS			2	(7.7)	6	(10.0)
- BPS	+	AMB			1	(3.8)	1	(1.7)
- BPS			+	SIL	4	(15.4)	7	(11.7)
- BPS			+	TAD	2	(7.7)	2	(3.3)
-		BOS	+	TAD	2	(7.7)	3	(5.0)
-		BOS	+	SIL	1	(3.8)	1	(1.7)
-		AMB	+	TAD	0	(0.0)	1	(1.7)
-		MAC	+	TAD	0	(0.0)	1	(1.7)
- EPO			+	SIL	0	(0.0)	3	(5.0)
• *Combination (3 drugs)*					*8*	*(30.8)*	*14*	*(23.3)*
- BPS	+	BOS	+	SIL	4	(15.4)	4	(6.7)
- BPS	+	BOS	+	TAD	3	(11.2)	3	(5.0)
- BPS	+	AMB	+	SIL	0	(0.0)	1	(1.7)
- BPS	+	AMB	+	TAD	0	(0.0)	4	(6.7)
- EPO	+	AMB	+	RIO	1	(3.8)	1	(1.7)
- EPO	+	MAC	+	TAD	0	(0.0)	1	(1.7)
• *Non*					*1*	*(3.8)*	*2*	*(3.3)*
Total					*26*	*(100%)*	*60*	*(100%)*

BPS :beraprost, BOS: bosentan, SIL: sildenafil, TAD: tadalafil, EPO: epoprostenol, AMB: ambrisentan, MAC: macitentan, RIO: riociguat

Table 2. Hazard Ratio for Death in PAH Patients with CTDs

Factor	HR for death	95%CI	*P*
holistic analysis (N=117)			
Age at diagnosis of PAH	1.101	0.994-1.031	*0.1920*
WHO-FC(4,3 vs 2,1)	2.258	1.340-3.839	*0.0022*
Combination therapy	0.316	0.161-0.593	*0.0002*
stratified analysis			
SSc (N=54)			
Combination therapy	0.556	0.227-1.265	*0.1053*
Other CTDs (N=63)			
Combination therapy	0.218	0.077-0.531	*0.0005*

Combination therapy: combination therapy using PAH-specific drugs

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Disclosure: S. Tanaka, None; **Y. Matsueda**, None; **G. Abe**, None; **J. Okada**, None; **S. Hirohata**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/efficacy-of-pulmonary-arterial-hypertension-specific-drugs-combination-therapy-in-survival-of-patients-with-pulmonary-arterial-hypertension-associated-with-systemic-sclerosis-and-other-connective-tiss

Abstract Number: 1897

Vitamin-D Levels and Gastrointestinal (GI) Manifestations in Systemic Sclerosis (SSc)

Suzanne Kafaja[1], Aly Aly[2], Yossra A Suliman[3], Mohamed Alemam[4], Philip J. Clements[5] and Daniel E. Furst[6], [1]Medicine/Rheumatology, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Chamblion St,, Alexandria Faculty of Medicine, Alexandria, Egypt, [3]Rheumatology and Rehabilitation dept., Rheumatology and Rehabilitation dept. Assiut university hospital, Assiut Egypt, Assiut, Egypt, [4]Clinical Pathology and Laboratory Medicine Department, Assistant Lecturer, Qena, Egypt, [5]Medicine, University of California, Los Angeles,

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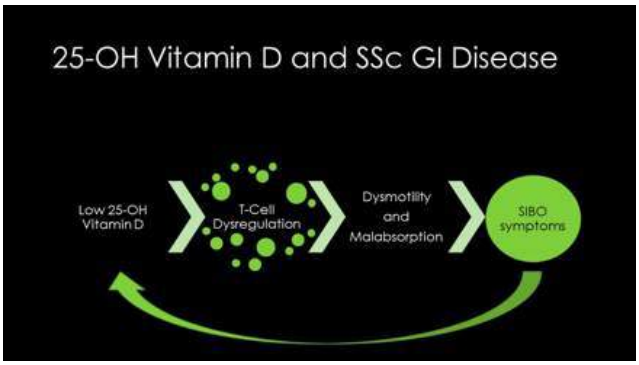
Background/Purpose: The GI tract is one of the most commonly affected systems in SSc patients. GI disease in SSc patients is thought to be multifactorial and its pathogenesis remains elusive. Researchers suggest that malabsorption of vitamin D might impair enteric T-cell mediated immune response and affect the myenteric plexus leading to gastroparesis. Also, delayed GI motility has been associated with the development of bacterial overgrowth in SSc. Taken together, one can envision a system in which low levels of vitamin D, through its effect on cell dysregulation, may lead to decreased GI motility and small intestinal bacterial overgrowth (SIBO). This has been the basis of our hypothesis associating low levels of Vitamin D with GI manifestations and disease in SSc patients. Our objective in this study is to evaluate the methodology for assessing SIBO by means of Lactulose vs. Hydrogen Breath testing (LBT vs. HBT). To investigate SIBO and 25-OH Vitamin D levels in relation to other clinical markers of SSc activity. Finally, to examine the relationship between SIBO (by means of LBT) and 25-OH Vitamin D levels in SSc patients.



Methods: Retrospective analysis of all SSc patients from the *UCLA SSc program* and the UCLA- database. Those meeting the 2013 ACR/EULAR SSc classification criteria, and having 25- OH Vit. D with or without LBT and/or SIBO clinical diagnosis were included in this evaluation. All patients with non-SSc diagnoses and those lacking Vitamin D levels were excluded. Logistic regression comparing LBT and hydrogen breath tests was used. A Chi-square test was used to test for difference in proportion of patients with low vitamin D among subjects who had a positive LBT compared to subjects who had a negative LBT.

Results: Of 2700 patients in the database, 608 met our inclusion criteria of having either Vitamin D levels or LBT. 163 did not have 25-OH Vitamin D, leaving 445 who were analyzed in this study. Subjects were between the ages of 48-69, with comparable female representation in both groups at 89 vs. 90% in LBT+ vs. LBT negative groups , respectively. We found a *statistically significant difference* in proportion of subjects who had low vitamin D in patients with positive LBT compared to those with negative LBT ($p<0.001$). We found a statistically significant difference in the false negative rate of the hydrogen test and the false negative rate of the methane test ($p<0.001$) indicating that *Hydrogen Breath Testing* is an adequate mode of testing for detecting SIBO in SSc. Analysis of normal/high vitamin D, with LBT positivity, by means of logistic regression model, showed no association between both factors and either SSc type, or the presence of ILD or PAH.

Conclusion: Our preliminary data suggest a ***strong association between LBT positivity and low vitamin D level.*** Decreased gut motility may be at the core of the pathogenic pathways bridging hypovitaminosis D and SIBO.

Disclosure: S. Kafaja, None; **A. Aly**, None; **Y. A. Suliman**, None; **M. Alemam**, None; **P. J. Clements**, None; **D. E. Furst**, None.

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Abstract Number: 1898

The Lack of Association of Osteoporosis with Proton Pump Inhibitor in Scleroderma: A UK Single Centre Cohort Experience

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics - Poster II

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Background/Purpose: Recent studies suggest that proton pump inhibitor (PPI) use is variably associated with risk of osteoporosis. The aim of this study was to investigate the relationship between PPI use and development of osteoporosis in Scleroderma (SSc) patients. This association however has not been well characterized in a large cohort of patients.

Methods: We reviewed the records of patients followed up in our centre over a period of 10 years. Those who have had at least one bone densitometry (DEXA) performed were included in the study. Demographic and basic clinical characteristics were recorded for all patients, including results of the DEXA scans and PPI treatment prior to DEXA (none, standard dose PPIs or high dose PPIs). In addition, data on potential confounding factors, such as smoking history, steroid or bisphosphonate treatment, were also collected. Ordinal logistic regression was used to assess the effects of these factors on the DEXA results.

Results: In this study 199 SSc patients were included. Of those 91% (n=182) were female, 31% (n=61) had diffuse disease. Mean age at first DEXA scan was 57 years (range 18 to 84 years). Mean disease duration at first DEXA was 12.7 years (interquartile range 5.8 to 18.5). Bone density was normal in 21% (n=41), 40% (n=80) had osteopenia and 39% (n=78) had osteoporosis. By univariable analysis there was no significant association between prior PPI treatment and DEXA scan results (p=0.205). Among those who had normal DEXA 22% have not had treatment with PPIs, 49% have had standard dose and 29% have had high doses of PPIs. Among those with osteopenia, 12.5% had not been treated with PPIs, while 47.5% and 40% had received standard or high doses of PPIs respectively. Among subjects with osteoporosis, 27% had not had PPI treatment, while 41% and 32% have had standard and higher than standard doses of PPIs. We found no association between gender, disease subset or antibody specificity and bone density. Body mass index (BMI) was negatively associated with development of osteoporosis (OR 0.89; 95% CI 0.84, 0.94; p<0.001), while age showed a strong positive association (OR 1.07; 95% CI 1.04, 1.1; p<0.001). Presence of calcinosis showed a mild, borderline significant association with development of osteoporosis (OR 1.67, 95% CI 0.91, 3.06; p=0.096). Interestingly, there was a strong association between calcinosis and PPI use; among patients who had not received PPIs, calcinosis was present in 12.5%, among those on standard dose PPIs, 20% had calcinosis and among those on high doses of PPIs, calcinosis was present in 39%, p=0.003. Multivariable analysis of the effect of PPIs on bone density was fitted. After adjusting for age, BMI, steroid and bisphosphonate treatment, there was no association between PPI treatment and development of osteopenia or osteoporosis.

Conclusion: Our data do not support an association between prior PPI treatment and development of osteoporosis. However, the association of calcinosis with prior PPI treatment and trend of association of calcinosis with osteoporosis is noteworthy and warrants further study in other cohorts. Our results suggest that addressing coexisting risk factors for osteoporosis is required for SSc patients on PPI.

Disclosure: A. Afonso, None; **S. Nihtyanova**, None; **C. Denton**, GSK, Celgene, Actelion, Bayer, Sanofi, Roche-Genentech, Inventiva, 5,CSL Behring, GSK, Actelion, Roche-Genentech, Inventiva, 2; **V. H. Ong**, None.

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Abstract Number: 1899

The Intestinal Involvement in Systemic Sclerosis Is Characterized By a Peculiar Gut Microbiota

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Background/Purpose: Gastrointestinal involvement is recognized as a major cause of morbidity and mortality in systemic sclerosis (SSc). The pathophysiology is still unclear and includes impairment of motility, digestion, absorption and excretion. Few data on composition and function of gut micro-environment in SSc are reported in literature but there is a growing body of evidences supporting the hypothesis of a relation between gut microbiota, the host immune system and metabolic/nutritional status. The goal of this study was to characterize the gut microbiota in SSc patients compared to healthy subjects to investigate whether specific microbial species may be responsible of dysbiosis in SSc patients with gastrointestinal involvement. Furthermore, we investigated the composition of microbiota in different subsets of SSc according to patient's nutritional status to verify if microbiota characteristics may be used as a biomarker for malnutrition and poor prognosis in patients with SSc.

Methods: A total of 66 SSc patients were enrolled: 66.7% presented a normal BMI, 15.1% were underweight, while 18.2% were overweight. Gastrointestinal involvement was evaluated through UCLA-GIT 2.0 questionnaire while nutritional status was assessed through the MUST and selected blood biomarkers (albumin, Vitamin D, Vitamin B12, folate, Ferritin, cholesterol). Faecal samples were obtained from SSc patients and healthy controls. The composition of microbiota was determined through 16S-rRNA pirosequencing performed using the GS Titanium technology (Roche 454). Dedicated statistic (LEfSe) was used to identify taxa that showed differential expression between the groups; α- and β-diversity and Firmicutes/Bacteroidetes ratio were determined.

Results: In our cohort of patients the mean total UCLA GIT 2.0 score was 0.4±0.3. The values representing species richness were significantly different in the SSc group compared to controls (p=0.009 for Shannon index mean values). Noticeably, this difference was mostly accountable to BMI>25 subgroup. Firmicutes/Bacteroidetes ratio was inverted (>1) in the SSc group compared to controls, as already reported in literature for obese patients. At genus level SSc patients showed a differential expression in 21 taxa compared to controls with higher levels of genera such as Ruminococcus, Roseburia, Lactobacillus and Faecalibacterium and a decrease of genera such as Clostridium, Odoribacter, Veillonella and Prevotella. The differences in microbiota composition between SSc patients and controls were supported also by principal coordinate analysis (PCoA) of the values representing phylogenetic distance of microbial communities between specimens. Conversely, there were no substantial differences among subgroups of SSc patients according to BMI and according with the any specific gastrointestinal tract symptoms reported in the questionnaires.

Conclusion: Our analysis demonstrates an altered and distinct composition of gut microbiota in SSc patients compared to healthy controls. This may be the result of the complex pathophysiology of the disease and, at the same time, it may perpetuate immunologic aberrations and contribute to its clinical features. Though in the overweight SSc patients there seems to exist an overlap with the distinctive microbiota of obese patients, no definitive data are available to explain the relation between the nutritional status and gut microbiota in SSc patients.

Disclosure: S. Bosello, None; **F. Paroni Sterbini**, None; **G. Natalello**, None; **G. Canestrari**, None; **F. Parisi**, None; **M. Sanguinetti**, None; **G. Ferraccioli**, Roche, Pfizer, Abbott, 5.

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Abstract Number: 1900

Anti-Topoisomerase Positive Systemic Sclerosis – Prognosis Infaust?

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Background/Purpose: Anti-topoisomerase antibodies (ATA) in systemic sclerosis have been associated with poorer prognosis including diffuse skin involvement, pulmonary fibrosis, cardiac involvement and increased mortality. However, 30-60% of ATA-positive SSc patients demonstrate only limited skin involvement and some have only mild disease course. In SSc, optimal risk stratification is of utmost importance for tailored clinical management at the patient level. Therefore, we aimed to determine the prevalence of mild disease among ATA positive patients and to investigate which readily available clinical parameters best identify patients with highest disease severity.

Methods: Data from baseline visits of all subjects in the Leiden Systemic Sclerosis cohort were extracted. Patients fulfilling ACR 2013 criteria and ATA positive were included. Descriptive statistics were used to summarize sociodemographic, clinical and serological features. Patients with grade 3 or 4 disease on general, peripheral vascular, skin, lung or kidney Medsger severity scale were considered to be severely diseased. We compared presence of diffuse cutaneous involvement, Raynaud's, pitting scars, calcinosis, proximal muscle weakness, >10% weight loss, interstitial lung disease and pro-BNP between the severity groups and corrected for confounding by disease duration (time since non-Raynaud) by stratifying into quartiles.

Results: Of 422 SSc patients in the database, 344 patients had SSc meeting ACR criteria. 89 patients were exclusively ATA-positive, of which n=42 with mild disease and n=47 with severe disease. Patients with severe disease appeared to be younger, more often non-caucasian, with a longer time-since non-Raynaud and more often had diffuse skin involvement (dcSSc), calcinosis and weight loss (Table 1). Stratification by disease duration, however, showed that age and skin involvement were similar between patients with mild and severe disease. Only age at onset of first non-Raynaud, percentage of non-caucasians and percentage of patients with >10% weight loss was consistently different for patients with severe disease (Table 2).

Conclusion: In our cohort, 47% of ATA-positive patients presented with mild systemic sclerosis, which could not be explained by disease duration. This suggests that solely the presence of ATA is of limited clinical relevance. Readily available sociodemographic and clinical parameters including type of skin involvement seem to have only limited value in

identifying ATA patients with more severe SSc. More complex serological findings as antibody titers and fine-specifity of ATA should be defined for optimal serological subsetting.

Table 1. Characteristics of mild disease versus severe disease in anti-topoisomerase I positive SSc patients

	mild disease (n=42)	severe disease (n=47)	p-value
DEMOGRAPHIC			
mean age, years (SD)	55.3 (15.6)	49.5 (14.6)	**0.073**[a]
female, % (n)	73.8 (31)	66 (31)	0.421[b]
caucasian, % (n)	87.5 (35)	51.4 (19)	**0.001**[b]
median time since Raynaud (IQR)	9.2 (1.3-14.7)	6.0 (2.4-12.8)	0.749[c]
median time since non-Raynaud (IQR)	1.5 (0.5-4.3)	4.1 (1.4-11.2)	**0.010**[c]
CLINICAL FINDINGS			
dcSSc, % (n)	40.5 (17)	61.7 (29)	**0.045**
Raynaud's, % (n)	95.2 (40)	97.9 (46)	0.600[d]
calcinosis, % (n)	0 (0)	6 (13)	**0.027**[d]
friction rubs, % (n)	11.9 (5)	13.0 (6)	1.000[d]
synovitis, % (n)	12.2 (5)	23.4 (11)	0.174[b]
proximal muscle weakness, % (n)	9.8 (4)	6.4 (3)	0.700[d]
>10% weight loss, % (n)	7.1 (3)	23.4 (11)	**0.035**[b]
interstitial lung disease, % (n)	35.7 (15)	48.9 (23)	0.208[b]
proBNP, median (IQR)	92.7 (49.5-321.4)	84.7 (44.0-399.6)	0.944[c]

SSc systemic sclerosis; dcSSc diffuse cutaneous systemic sclerosis

[a] Independent sample t-test; [b] Chi-square test; [c] Mann-Whitney; [d] Fisher's exact

Table 2. Characteristics of mild disease versus severe disease in anti-topoisomerase I positive SSc patients stratified by time of non-Raynaud

	DISEASE DURATION 1ST QUARTILE (0.0-0.8 YRS)			DISEASE DURATION 2ND QUARTILE (0.8-2.5 YRS)			DISEASE DURATION 3TH QUARTILE (2.5-8.2 YRS)			DISEASE DURATION 4TH QUARTILE (8.2- 44.1 YRS)		
	mild disease (n= 12)	sever disease (n= 10)	p-value	mild disease (n=13)	sever disease (n=9)	p-value	mild disease (n=11)	sever disease (n=12)	p-value	mild disease (n=6)	sever disease (n=16)	p-value
DEMOGRAPHIC												
age at onset Raynaud, mean (SD)	54.0 (14.6)	45.0 (9.6)	0.135[a]	41.2 (15.3)	41.3 (16.4)	0.935[a]	40.5 (13.1)	35.0 (14.6)	0.336[a]	47.1 (8.8)	36.2 (10.6)	0.105[a]
age at onset non-Raynaud, mean (SD)	57.9 (11.1)	50.3 (9.5)	0.056[a]	49.5 (25.5)	44.8 (16.9)	0.664[a]	45.3 (10.1)	38.1 (18.5)	0.056[a]	48.5 (9.9)	38.7 (14.4)	0.065[a]
female, % (n)	75.0 (9)	20 (2)	**0.030**[b]	76.9 (10)	77.8 (7)	1.000[b]	72.7 (8)	83.3 (10)	0.640[b]	66.7 (4)	75.0 (12)	1.000[b]
caucasian, % (n)	100 (12)	60.5 (6)	**0.049**[b]	75.0 (9)	33.3 (2)	0.141[b]	90.9 (10)	46.4 (6)	0.050[b]	60.0 (4)	57.17 (8)	0.603[b]
CLINICAL FINDINGS												
dcSSc, % (n)	50.0 (6)	70.0 (7)	0.415[b]	30.8 (4)	66.7 (6)	0.192[b]	54.5 (6)	41.7 (5)	0.537[b]	16.7 (1)	68.8 (11)	0.056[b]
mRSS, median (IQR)	5.5 (2.0-11.0)	19.0 (6.5-28.3)	0.055[a]	4.0 (2.0-13.0)	16.0 (5.0-21.0)	0.140[a]	5.0 (2.0-7.0)	5.5 (4.0-10.0)	0.336[a]	5 (0.0-6.8)	8.0 (2.3-12.5)	0.206[a]
calcinosis, % (n)	0 (0)	10.0 (1)	0.455[b]	0 (0)	25 (2)	0.133[b]	0 (0)	0 (0)	-	0 (0)	18.8 (3)	0.532[b]
friction rubs, % (n)	8.3 (1)	30.0 (3)	0.293[b]	23.1 (3)	25.0 (2)	1.000[b]	9.1 (1)	0 (0)	0.478[b]	0 (0)	6.3 (1)	1.000[b]
synovitis, % (n)	16.2 (2)	0 (0)	0.476[b]	23.1 (3)	44.4 (4)	0.376[b]	0 (0)	41.7 (5)	0.037[b]	0 (0)	12.5 (2)	1.000[b]
proximal muscle weakness, % (n)	16.7 (2)	20.0 (2)	1.000[b]	15.4 (2)	11.1 (1)	1.000[b]	0 (0)	0(0)	-	0 (0)	0 (0)	-
>10% weight loss, % (n)	16.7 (2)	30.0 (3)	0.624[b]	7.7 (1)	33.3 (3)	0.264[b]	0 (0)	25.0 (3)	0.217[b]	0 (0)	12.5 (2)	1.000[b]
interstitial lung disease, % (n)	25.0 (3)	30.0 (3)	1.000[b]	30.8 (4)	22.2 (2)	1.000[b]	45.5 (5)	50.0 (6)	0.827[b]	50.0 (3)	75.0 (12)	0.334[b]
proBNP, median (IQR)	101.6 (50.7-398.5)	233.8 (62.2-609.9)	0.391[a]	160.3 (66.1-452.5)	175.2 (60.9-808.0)	0.815[a]	89.7 (47.7-128.1)	58.3 (26.0-112.8)	0.442[a]	65.1 (28.0-141.0)	59.8 (46.0-181.8)	0.461[a]

SSc systemic sclerosis; dcSSc diffuse cutaneous systemic sclerosis

[a] Chi-square test; [b] Mann-Whitney; [c] Fisher's exact

Disclosure: M. Boonstra, None; **G. A. Beerends**, None; **H. U. Scherer**, None; **T. W. J. Huizinga**, None; **J. K. de Vries-Bouwstra**, None.

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Abstract Number: 1901

Screening for Pulmonary Arterial Hypertension in an Unselected Prospective Systemic Sclerosis Cohort

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Background/Purpose: Screening for pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc) improves outcome. The DETECT screening algorithm (DETECT-algorithm) is recommended in a high-risk SSc subgroup. The aim of this study is to compare the positive predictive value (PPV) of screening using the 2009 European Society of Cardiology/European Respiratory Society guidelines (ESC/ERS-guidelines) and the DETECT-algorithm and comparing their cost-effectiveness in an unselected day-to-day SSc population.

Methods: 195 consecutive SSc patients, included in the Ghent University hospital systemic sclerosis unit, having their yearly SSc-specific visit between February 2015 and February 2016 were prospectively screened using both algorithms and the cost-effectiveness was calculated.

Results: In 63 (32%) of the 195 included patients (11%/71%/18% limited/limited cutaneous/diffuse cutaneous SSc), a right heart catheterization (RHC) was recommended (46/4/13 using DETECT-algorithm alone/ESC/ERS-guidelines alone/both algorithms). A RHC was performed in 53 patients: (36 [78%]/4 [100%]/13 [100%] where recommended by DETECT-algorithm alone/ESC/ERS-guidelines alone/both). PAH was diagnosed in 3 patients (incidence 1.5%/year, 95%CI:0.5-4.4%), in whom both algorithms recommended a RHC. The PPV was 23%,95%CI:8-50% (3/13) for both algorithms, 18%,95%CI:6-41% (3/17) for the ESC/ERS-guidelines and 6%,95%CI:2-17% (3/49) for the DETECT-algorithm. The average cost for screening was 80 and 227 euro using the ESC/ERS-guidelines and the DETECT-algorithm respectively.

Conclusion: In an unselected SSc population, the PPV is 23% when both algorithms recommend RHC. Interestingly, with only one algorithm used, the PPV drops to 18% for the ESC/ERS-guidelines and 6% for the DETECT-algorithm. Based upon this comparison and on cost-effectiveness, echocardiography may remain an important first step screening tool for PAH in SSc.

Disclosure: E. Vandecasteele, None; **B. Drieghe**, None; **K. Melsens**, None; **K. Thevissen**, None; **M. De Pauw**, None; **E. Deschepper**, None; **S. Decuman**, None; **K. Bonroy**, None; **Y. Piette**, None; **F. De Keyser**, None; **G. Brusselle**, None; **V. Smith**, None.

Abstract Number: 1902

Detecting the Pulmonary Vascular Involvement and the Changes in Gene Activation Profiles at Early Stage of Systemic Sclerosis in Patients with Raynaud Phenomenon

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Background/Purpose: Raynaud phenomenon (RP) is known to precede other disease manifestations of systemic sclerosis (SSc), and classically viewed as reversible vasospasm due to functional changes in the digital arteries of the hands. However, progressive structural changes were found in the small blood vessels in many patients with SSc. Pulmonary arterial hypertension (PAH) is also prominent as a vascular involvement in SSc, which remains a leading cause of death in spite of current best treatments. As the pulmonary vascular disease (PVD) can be well compensated for, more than a half of the pulmonary circulation is impaired before early PAH is detected. Recently, it has been reported that stress testing with exercise Doppler echocardiography (DE) may facilitate early diagnosis of PVD. In this study, we tried to detect the specific changes at the stage of subclinical PVD of SSc in patients with RP

Methods: Total of 46 cases without PAH symptoms (NYHA I) with RP were investigated. To detect the involvement of pulmonary vessels, mean pulmonary artery pressure-cardiac output (mPpa-Q) response was estimated by exercise DE with Master's two-step stress, which reflects the elasticity of pulmonary artery. Then, the expressed genes in peripheral blood were explored with using next-generation sequencing. The differences between SSc-related autoantibody negative (R group=19) and positive group (S group) consisting of with (S1 group; n=22) and without (S2 group; n=7) scleroderma were investigated. The SSc-related autoantibodies include anti-RNP (n=4), topoisomerase-1 (n=1), centromere (n=23) and RNA polymerase III antibodies (n=0).

Results: The estimated mPpa-Q (mmHg•min/L) by exercise DE was significantly elevated in S group as compared with R group (6.54±5.31 vs. 4.49±2.39, $p<0.05$). In the S group, the average of estimated mPpa-Q in S1 group was higher than that in S2 group (6.70±5.97 vs. 6.01±2.60). Based on the differences in gene expression between S group and R group by ANOVA, 30 differentially expressed genes (DEGs) were selected, and then subjected to a hierarchical clustering with assessment of the statistical robustness. The hierarchical clustering showed major 2 clusters, and one of them consisted of only cases in S group, which included one case in S2 group. When we focused on 117 genes reported to be directly implicated in the development of PAH

(Parikh VN et al., Circulation. 2012;125:1520-1532.), it is noteworthy that 11 of them were differentially expressed in S2 group ($p<0.05$ by Student's t-test) as compared with R group.

Conclusion: Although detection of early PVD in SSc patients remains a major challenge, we have shown that estimated mPpa-Q which reflects elasticity of pulmonary arteries were significantly increased in S group. As S2 group is considered as very early SSc, it is notable that the average of mPpa-Q in S2 group was located between established SSc (S1) and Raynaud only (R) group. Moreover, some of genes involved in PAH development were differentially expressed in S2 group as compared with R group. It means that the changes toward PVD had already started at the very early stage of SSc. In order to detect crucial factors for PAH development, it is very important to follow up the clinical courses of these cases.

Disclosure: Y. Koyama, None; **S. Fuke**, None; **Y. Sato**, None; **T. Higuchi**, None.

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Abstract Number: 1903

Determining Disease Course in Localized Scleroderma: A Prospective Cohort Study

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Background/Purpose: Localized scleroderma (LS) is characterized by skin sclerosis, producing devastating impairment in those affected. It was previously thought to "burn out" within 5 years, but recent studies have challenged this notion. However, no studies have prospectively examined LS disease activity over time. Understanding the course of LS is necessary to determine how to counsel and evaluate patients and to plan outcome and interventional studies. The aim of the present study was to determine the disease course of LS using a validated clinical outcome measures in a prospective cohort of patients.

Methods: Prospective cohort study of 131 participants from the Morphea in Adults and Children (MAC) cohort with at least two years of follow-up and modified LS skin severity scores (mLoSSI) scores recorded. Study visits were conducted at six to twelve month intervals. Disease activity was defined as mLoSSI score greater than 0. Time to recurrence of disease activity from the first visit with inactive disease was compared between the linear and generalized subtype using survival analysis with the log-rank (Mantel-Cox) test. All statistical analysis was performed using GraphPad Prism 6.0.

Results: 131 participants (670 study visits) were included. Fifty had at least 5 years of follow-up. Mean total follow-up was 4.3±1.7 years. The majority of participants were Caucasian (72%), female (77%), and had either a linear (55%) or generalized (31%) subtype. Median baseline mLoSSI score was 5. The mean time to first recurrence of disease activity after initial resolution of activity was 1.1 years for generalized LS and 2.3 years for linear LS. Overall, 44% of those with generalized LS had a recurrence of disease activity compared to 21% of those with the linear subtype (Hazard ratio 2.79, 95% CI 1.48-7.94). Of the 50 participants with at least five years of follow-up, 56% had a recurrence of disease activity. All but three subjects had similar or milder disease activity than the initial presentation.

Conclusion: Disease activity improves in the majority of LS patients over time. Some patients with LS have a monophasic disease course in which activity resolves. However, a substantial number of patients have a relapsing remitting course over many years. Specifically, those with the generalized subtype appear to be at a higher risk for future disease flares. Patients with LS warrant monitoring for disease flares for extended periods of time.

Disclosure: J. O'Brien, None; **H. Jacobe**, Merck Co., 5.

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Abstract Number: 1904

Elevated GITRL Is Associated with Multi-Organ Involvement and Increased Disease Activity of Primarty Sjogren's Syndrome and Promotes Pathogenic Th1/17 Differentiation

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SESSION INFORMATION

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Session Title: T Cell Biology and Targets in Autoimmune Disease - Poster Session I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Accumulating data showed that Glucocorticoid-induced Tumor Necrosis Factor Receptor Family-related Protein (GITR), with its ligand (GITRL), plays an important role in promoting T-cell-mediated immunity and exacerbating autoimmunity in animal models. But its pathogenesis role in primary sjögren syndrome (pSS) remains unclear. Our study aimed to evaluate whether GITRL is related to disease severity and organ involvement in pSS patients and explore the possible mechanisms.

Methods: 78 pSS patients and 44 healthy controls were recruited, and the serum level of GITRL was measured by ELISA, and the serum levels of interleukin (IL) -17A, IL-17E, IL-17F, IL-6, IL-22 and IL-23 were determined by multiplex cytokine assays. $CD4^+$ T lymphocytes were isolated from PBMCs of 5 healthy donors by $CD4^+$ T Cell isolation kit and cultured in TexMACS™ GMP medium with anti-CD3 monoantibody (mAb), anti-CD28

mAb and rhIL-2. For Th1/Th17 cell differentiation and the pathway exploration of pS6 and pSTAT5, $CD4^+$T cells were treated either with recombinant human GITRL protein or with the medium control for 5 days. Surface marker, intracellular cytokine and phosphorylated signal protein were evaluated by flow cytometry. Clinical and laboratory data were collected and the clinical relevance of GITRL in pSS was analyzed

Results: *S*erum levels of GITRL were significantly higher in pSS patients than those in HC. There is a negative correlation between elevated levels of serum GITRL and WBC, Neutrophils, PLT, C_3 and C_4, and a positive correlation with Lymphocytes, IgG and RF. Interestingly, pSS patients with overt hypothyroidism showed higher level of serum GITRL comparing to pSS patients with subclinical hypothyroidism and normal thyroid function. Patients with pulmonary involvement had higher serum GITRL level, and pSS patients of moderate to high disease activity (ESSDAI≥5) showed higher serum level of GITRL. Moreover, *S*erum GITRL level was positively correlated with the Th17 related cytokine profile including IL-17A, IL-17E, IL-17F, IL-1β, IL-22 and IL-23, some of which had been shown to be the causal agents increasing autoimmunity and organ involvement in pSS. After GITRL treatment, we found the expansion of Th1, Th17 and Th1/17cells in vitro and there was a dose-dependent effect. We also found that the increased activaton of mTOR (S6 and STAT3) signaling in Th cells after GITRL ligation.

Conclusion: Our results identified the clinical significance of GITRL in exacerbating disease activity in pSS patients, and its pathogenic roles in enhancing the differentiation of Th1, Th17 and Th1/17 cells and the possible involved signaling pathways.

Disclosure: X. Sun, None; **Y. Gan Sr.**, None; **J. He**, None; **Z. Li**, None.

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Abstract Number: 1905

Therapeutic Targeting of JAK/STAT Pathway Inhibits Follicular Helper T Cell Maturation and Function

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Background/Purpose: T follicular helper (Tfh) cells represent a $CD4^+$T cell subset specialized to provide help to B cells and to induce memory B cell and plasma cell differentiation. Proportion of blood Tfh cells are increased in patients with systemic lupus erythematosus, Sjogren's syndrome and rheumatoid arthritis (RA)[1]. The study of STAT3-deficient patients showed that JAK/STAT pathway play a crucial role in human Tfh development and function[2]. Tofacitinib is a pan JAK inhibitor with potent inhibition of JAK3 and 1 and to a

minor degree JAK2. The main reported mechanism of action of this drug, already approved for RA in many countries is the inhibition of numerous proinflammatory cytokines. JAK/STAT inhibitors are known to induce a decrease in $CD4^+$T cells but their effect on T-cell subpopulations is not known. We therefore investigated whether therapeutic targeting of JAK/STAT pathway could also result in the inhibition of Tfh differentiation and function.

Methods: Mononuclear cells were isolated from peripheral blood of healthy human donors. After selection, naive $CD4^+$T cells were cultured in the presence of cytokines known to induce Tfh differentiation. Tofacitinib, was added at 2 different times: first concomitantly to IL12 and anti-human CD3/CD28 beads required to promote Tfh differentiation in order to evaluate the effect of tofacitinib (at concentrations from 0 to 3 µM) on Tfh differentiation; second after 3 days of in vitro Tfh cell-differentiation to assess the effect of tofacitinib on Tfh function after 14, 24, 48 and 72 hours of tofacitinib exposure. The differentiation of naive $CD4^+$T cells into Tfh was analyzed using flow cytometry (positive staining for CXCR5, ICOS, PD1). Differentiation into Th1 and Th17 cells was analyzed using flow cytometry. The function of Tfh was assessed by intracellular staining of IL21 using flow cytometry. Cell viability was assessed using flow cytometry.

Results: Induction of Tfh differentiation in vitro. We first confirmed that the protocol used to differentiate naive $CD4^+$T cells into Tfh was efficacious: IL12 and anti-CD3/CD28 allowed to induce the differentiation of 33% (from 6 to 53%, n=6) of Tfh. Expression of Bcl-6, the specific transcription factor of Tfh, was significantly higher in Tfh than in non Tfh cells. Inhibition of Tfh differentiation. First, adding tofacitinib concomitantly to IL12 and beads dramatically decreased Tfh differentiation in a dose dependent manner (52% without tofacitinib vs 5% with tofacitinib, maximal inhibition of 90%). JAK/STAT inhibition also demonstrated an inhibition of Th1 and Th17. Tofactinib did not induce T-cell mortality, as demonstrated by viability test. Inhibition of Tfh function. Second, the addition of tofacitinib after Tfh-cell commitment induced a reduction of IL21. Maximal reduction was obtained after an exposure to tofacitinib during 48hours.

Conclusion: We demonstrate that JAK/STAT pathway inhibition impairs Tfh differentiation and function in vitro in healthy controls. We are currently extending our analyses to blood samples from patients with RA and other autoimmune diseases. These results highlight an additional mechanism of action of JAK/STAT inhibitors in autoimmune diseases. [1] Ueno. J Clin Immunol, 2016; [2] Ma et al. Blood, 2012

Disclosure: F. Sagez, French Society of Rheumatology Grant, 2; **J. E. Gottenberg**, None.

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Abstract Number: 1906

Impact of Environmental Factors and Inflammation on Alterations of the Total Peripheral T-Cell Compartment in Granulomatosis with Polyangiitis

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Background/Purpose: Autoimmune diseases are driven by a combination of predisposing genetic and environmental factors resulting in self-perpetuating chronic inflammation and tissue damage. In granulomatosis with polyangiitis (GPA), impaired regulatory T-cell function and an expansion of circulating effector memory T-cell subsets has been reported. While expansion of circulating effector memory T-cells has been linked to disease pathogenesis and progression, the causes driving alterations of the peripheral T-cell compartment have remained poorly understood so far. To investigate mechanisms driving alterations of the peripheral T-cell compartment in GPA, we performed combined approach using phenotyping, transcriptome and functional analyses of T-cell populations.

Methods: Sorted CD4+ and CD8+ single-positive and CD4+CD8+ double-positive T-cells were subject to transcriptomic profiling in GPA and healthy controls (each n=3). To characterize functional consequences of transcriptional alterations in T cell subpopulation from GPA-patients, differentially expressed genes from GPA-patients were investigated by gene ontology (GO) analysis. The frequency of circulating antigen-specific T-cells and phenotype of T-cells from 20 HLA-A2-positive patients with GPA and 20 healthy controls was assessed by flow cytometry. Antigen-specificity was detected using peptide/MHC class I dextramers in HLA-A2-positive subjects.

Results: Transcriptome signatures from GPA-patients presented significantly GO enriched signaling pathways for nuclear factor-kB (NF-kB), toll-like receptors (TLR), cytokine/cytokine receptor interaction (interleukins IL-1b and IL-18), and chemokine cell signaling pathways. Notably, significant enrichment of pathways consistent with immune responses triggered by various pathogens and infections was found including *Staphylococcus aureus* and Epstein Barr virus (EBV). Grouping of patients according to presence or absence of T-cell specificity for cytomegalovirus (CMV) and EBV showed that concomitant cellular CMV- and EBV-positivity was associated with a significant increase in the percentage of CD28- T-cells in GPA whereas sole or absent CMV- or EBV-positivity was not. T-cell specificity for other viruses (influenza A virus, metapneumovirus, respiratory syncytial virus) and PR3 was infrequently detected in GPA. Notably, antigen-specific T-cells were not specifically enriched within any of the T-cell subsets.

Conclusion: On genetic and cellular basis, here we show that , environmental factors including concomitant CMV- and EBV-infection and inflammation impact on alterations of the T-cell compartment in autoimmune disease. We identified cellular cytokine signatures (IL-1b, IL-18) on the transcriptomic level, which could represent novel targets for anti-cytokine-based induction therapies. Our data support antiviral therapy as another supplemental disease-modifying approach to be further evaluated in autoimmune disease such as GPA. Thus, our study provides novel insights into mechanisms driving autoimmune disease and on potential therapeutic targets.

Abstract Number: 1907

T-Bet Regulates Ahr-Mediated Th-17 Differentiation Independently of IFNγ

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Background/Purpose: Our previous reports showed that the development of collagen-induced arthritis was suppressed in T-bet transgenic (T-bet Tg) mice. The regulatory mechanism might relate to dysfunction of Th-17 cell differentiation by the overexpression of T-bet gene. The purpose of this study is to clarify the effect of T-bet overexpression on Th-17 cell differentiation.

Methods: T-bet overexpressing IFNγ deficient (T-bet Tg/IFNγ$^{-/-}$) mice were generated by crossing T-bet Tg mice under the promoter of CD2 gene with IFNγ deficient (IFNγ$^{-/-}$) mice. CD4^{+} T cells from C57BL/6 (WT), T-bet Tg, or T-bet Tg/IFNγ$^{-/-}$ mice were cultured for Th-17 differentiation, and the cytokine production (IFNγ, IL-17) and the expression of transcription factors (T-bet, RORγt) was analyzed. We examined the expression of IL-6 receptor (IL-6R) constituted by CD126 and CD130 and the phosphorylation of STAT3 by IL-6 stimulation of CD4^{+} T cells. The mRNA expression of transcription factors (*tbx21, rorc, stat3, stat1, runx1, irf4, nfkbiz, and ahr*) associated with the Th-17 differentiation were examined in the Th-17 condition. We transduced retrovirus expressing T-bet gene into naïve CD4^{+} T cells of WT or IFNγ$^{-/-}$ mice, and investigated cytokines and transcription factors expression. Moreover, we examined the expression of aryl hydrocarbon receptor (AHR) in Th-17 condition by flow cytometry in both T-bet Tg mice and retroviral transduction of T-bet gene. We investigated the facilitation of Th-17 differentiation by the addition of AHR ligand, 6-formylindolo [3,2-b] carbazole (FICZ), and analyzed the mRNA expression of *cyp1a1*, which was the AHR target gene.

Results: In both T-bet Tg and T-bet Tg/IFNγ$^{-/-}$ mice, RORγt expression and IL-17 production were inhibited in Th-17 condition, and IL-6R expression and STAT3 phosphorylation of CD4^{+} T cells were decreased. We also observed the inhibition of IL-17 production in CD4^{+} T cells of WT and IFNγ$^{-/-}$ mice transduced with T-bet, whereas T-bet transduction in vitro had no effects on IL-6 receptor expression and STAT3 phosphorylation. The mRNA expression of *nfkbiz* was up-regulated, but *rorc* and *ahr* were down-regulated with T-bet overexpression in both T-bet Tg mice and T-bet gene transduction under the Th-17 condition. FACS analyses revealed that the expression of AHR was significantly decreased not only in T-bet Tg and T-bet Tg/IFNγ$^{-/-}$ mice but also in T-bet gene transduced cells from both WT and IFNγ$^{-/-}$ mice. IL-17 production and the expression of *cyp1a1* by T-bet overexpression were not promoted by the addition of FICZ.

Conclusion: T-bet overexpression in CD4+ T cells repressed Th-17 differentiation by suppression of IL-17 production, RORgt expression, and AHR expression. Our findings support the possibility that regulatory mechanisms of Th-17 differentiation by T-bet overexpression might be due to the IFNγ-independent suppression of AHR.

Disclosure: M. Yokosawa, None; **Y. Kondo**, None; **S. Kaneko**, None; **S. Segawa**, None; **H. Tsuboi**, None; **I. Matsumoto**, None; **T. Sumida**, None.

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Abstract Number: 1908

Identification of a Novel Pro-Inflammatory T Cell Epitope from His-tRNA-Synthetase Associated with Interstitial Lung Disease in Anti-Jo-1 Positive Patients

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Background/Purpose: Previous studies have demonstrated that $CD4^+$ T cells from peripheral blood of anti-histidyl-tRNA synthetase (anti-His-tRNA) also known as anti-Jo-1 positive patients proliferate in response to stimulation with full-length His-tRNA and a N-terminal fragment comprising residues 1-60. Our group has already characterized a specific $CD4^+$T cell response towards the full length His-tRNA-synthetase and a peptide in the N-terminal fragment in blood and broncho-alveolar lavage of myositis patients. In this study we are presenting a novel epitope that identifies patients with moderate-severe interstitial lung disease (ILD).

Methods: Sixteen anti-Jo-1 positive patients with antisynthetase syndrome followed at the Karolinska University Hospital were enrolled. As controls we included HLA-DRB1*03-positive healthy individual (HCs, n=8). Peripheral blood mononuclear cells were isolated by Ficoll-Hypaque density centrifugation and *in vitro*stimulated with: a) full length His-tRNA protein; b) a novel HLA-DR*03:01 binding peptide from native

His-tRNA; c) an altered peptide ligand (APL) variant of His-tRNA, designed to prevent recognition by HLA-DR3/His-tRNA-specific TCRs. T cell activation was assessed by CD40L up-regulation and expression of pro-inflammatory cytokines (IFN-g, IL-2 and IL-17A) by flow cytometry. Clinical and laboratory data were documented: myositis-specific and associated autoantibodies, manual muscle test (MMT-8), health assessment questionnaire (HAQ) and interstitial lung disease (ILD). Descriptive statistics are shown with mean and standard deviation or median and IQR. Student's T test or Mann-Withney U-test were used to analyze differences between groups.

Results: At the time of blood sampling the patients had a mean age of 58 years (48-83 years), with a median disease duration of 50 months (11-70 months), MMT8 score 80 (79-80), HAQ 0.25 (0-13-0.75). Eighty-four percent were female, 13/16 patients had ILD and 13/16 had muscle weakness. T cell activation towards the novel His-tRNA peptide was observed in two of the 16 anti-Jo-1 positive patients. When stimulating with the APL version of His-tRNA, no T cell activation was observed in one of the patients that was reactive for the peptide. For evaluation of pro-inflammatory features, the His-tRNA-specific T cells displayed significant up-regulated levels of IFN-g ($p<0.05$) compared to HC ($p<0.05$). Additionally one out of eight healthy donors displayed a modest response to both the novel His-tRNA peptide and the full length His-tRNA protein. In this context only IL-2, and no other pro-inflammatory cytokine production was observed. The patients that showed an upregulation of CD40L in $CD4^+$T cells to the novel His-tRNA peptide had a moderate-severe clinical progression of ILD that required aggressive immunosuppressive treatment.

Conclusion: In this study, we demonstrate the presence of His-tRNA-reactive $CD4^+$ T cells in peripheral blood from anti-Jo-1 positive patients and a novel His-tRNA peptide, characterized by the expression of IFN-g. This phenotype seemed to correlate to a moderate-severe clinical progression of ILD.

Disclosure: A. S. Galindo-Feria, None; **I. Albrecht**, Sanofi Genzyme, 3; **A. Notarnicola**, None; **M. Dastmalchi**, None; **A. Dubnovitsky**, None; **T. Sandalova**, None; **G. Kozhukh**, None; **L. Rönnblom**, Astra Zeneca, 2; **A. Achour**, None; **V. Malmström**, None; **I. E. Lundberg**, Astra Zeneca, Bristol Myers Squibb, 2,Scientific advisor: Bristol Myers Squibb, aTyr and IDERA, 5.

Abstract Number: 1909

The Transcription Factor Fra2 Is Playing a Key Role in Treg Development and Autoimmunity

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Background/Purpose: Decreased numbers or altered functions of regulatory T cells (Tregs) have been reported in many inflammatory rheumatic diseases, and Tregs are considered promising therapeutic targets for autoimmune diseases. It is thus of high importance to delineate the pathways controlling Tregs biology and the onset of autoimmunity. Fos-related antigen 2 (Fra2) is a transcription factor belonging to the Fos family proteins which is part of the AP-1 transcription complex. Our aim is to characterize the potential role of Fra2 in controlling Tregs and autoimmunity.

Methods: Fra2 transgenic (tg) mice were generated, in which the Fra2 transcription factor is ubiquitously overexpressed. T lymphocyte populations were analyzed by flow cytometry, and pathological manifestations in multiple organs by histology. Bone marrow cells were transferred into lethally irradiated recipients to create Fra2-wt chimeric mice. Purified CD4 T cells were transferred into $Rag2^{-/-}$mice lacking T and B cells.

Results: At 3 weeks of age, Fra2 mice showed a striking decrease of the Treg population ($CD4^+CD25^+FoxP3^+$ in wt and Fra2 littermates spleens: 11.35 and 5.75% of $CD4^+$, respectively, p=0.0005, n=6). The strong decrease in Tregs was stable over time and also observed in $CD4^+$ single positive thymocytes, indicating that Fra2 mice have a defect in natural Treg development. Interestingly, from 7 weeks on, we could also detect the appearance of activated T cells ($CD4^+$ and $CD8^+$, with $CD62L^{high}CD44^{high}CD127^{low}$profile) which represented up to 60% of total T cells by 16 weeks of age. While the phenotype of young mice was limited to decreased Tregs, macroscopic and histological observations in 16 week-old mice showed the presence of an extensive multi-organ autoimmune phenotype: Perivascular inflammatory infiltrates, containing T cells, B cells and numerous granulocytes were observed in the lung and liver with fibrosis and vasculopthy. Extensive inflammation and fibrosis were observed in the thymus. Spleens were also enlarged with pronounced extramedullary haematopoiesis. Fra2 tg mice also developed dermatitis on eyelids and back-skin, with an increase in dermal and epidermal thickness. Finally, duodenum was enlarged due to acute inflammation and reactive hyperplasia. To understand whether the effect of Fra2 is T cell intrinsic or extrinsic, we also performed bone marrow transfer experiments in which irradiated wt recipient mice received Fra2 tg bone marrow. Interestingly, chimera mice displayed a decreased percentage of Tregs confirming an intrinsic role of Fra2 in Treg development. Finally we could show that transfer of purified CD4 T cells from Fra2 tg mice into lymphopenic host ($Rag2^{-/-}$) was sufficient to transfer the phenotype, demonstrating the ability of CD4 T cells to induce the phenotype.

Conclusion: These data suggest that Fra2 overexpression inhibits natural Treg development, resulting in **1:** diminished Tregs, **2:** activation of effector T cells and **3:**development of inflammation in multiple organs. This is the first evidence for a role of Fra2 in controlling Treg development and autoimmunity. This murine model also provides a unique opportunity to delineate the function of the Fra2 pathway in T cells and Tregs and its impact on autoimmunity.

Disclosure: F. Renoux, Swisslife, 2; **M. Stellato**, None; **D. Impellizzieri**, None; **R. Huang**, Sanofi-Genzyme, 3; **A. Subramaniam**, Sanofi-Genzyme, 3; **C. Dees**, None; **J. H. Distler**, None; **G. Kania**, Bayer, 2; **O. Boyman**, None; **O. Distler**, Bayer, Sanofi, Ergonex, Boehringer Ingelheim, Actelion, Pfizer, 2,4 D Science, Actelion, Active Biotec, Bayer, BiogenIdec, BMS, Boehringer Ingelheim, EpiPharm, Ergonex, espeRare foundation, Genentech/Roche, GSK, Inventiva, Lilly, medac, MedImmune, Pharmacyclics, Pfizer, Serodapharm, Sinoxa, 5.

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Abstract Number: 1910

IL-21 Inhibits Treg Differentiation and Function in SLE By Modulating GATA-3 and CTLA-4

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Background/Purpose: Studies indicate quantitative and qualitative Treg insufficiencies underlying the dysregulated immune response in SLE. However, it is unknown what mechanisms drive the Treg dysfunction in SLE. GATA-3 is critical in differentiation and functions of murine Treg. IL-21 is upregulated in SLE and tips the balance from Treg to Th17 differentiation in mice. We sought to identify a mechanism that would link IL-21 and GATA-3 to understand the altered differentiation and function of SLE Tregs.

Methods: $CD3^+$ T cells were isolated from matched SLE and healthy control (HC) subjects. The cells were cultured in the presence of anti-CD3/CD28 with or without rapamycin, after which IL-21 was measured in the supernatant by LUMINEX assay. Naïve $CD4^+$ T cells from matched SLE and HC subjects were cultured for 3 days in the presence of anti-CD3/CD28, TGF-β, and IL-2 with or without IL-21. Frequency of $CD4^+CD25^+FOXP3^+$ Tregs and expression of GATA-3 and CTLA-4 in the Treg were determined by flow cytometry. Total STAT3 and its phosphorylation at tyrosine 705 ($pSTAT3^{Y705}$) were examined by immunoblotting. Next, $CD4^+CD25^-$ responder T cells (Tresp cells) and autologous $CD4^+CD25^+$ Tregs were magnetically isolated. Treg function was determined in the presence or absence of IL-21 by assessing the % suppression of proliferation of CFSE-stained Tresp cells cultured for 5 days in the presence of anti-CD3 and irradiated autologous PBMCs. FOXP3, GATA-3, and CTLA-4 expression in the Treg were determined upon coculture. In some experiments, Tregs were expanded *in vitro* for 4 weeks with or without rapamycin before coculture. Statistical analyses were done using Student's t-test.

Results: IL-21 inhibited SLE Treg differentiation (% $CD4^+CD25^+FOXP3^+$ cells with and without IL-21: 40.78±3.26%, 64.75±3.16%; p=0.0002). Suppressive function of SLE Tregs was diminished (SLE: 30.25±4.48%, HC: 46.63±4.90%, p=0.03) and further inhibited by IL-21 (18.99±4.95%, p=0.042), while IL-21 did not promote the Tresp cell proliferation. pSTAT3 was upregulated in SLE $CD4^+$ T cells, which was further promoted by IL-21 under Treg-polarizing conditions. GATA-3 (Relative MFI: 0.81±0.09, p=0.032) and CTLA-4 were downregulated in freshly isolated $CD4^+CD25^+FOXP3^+$ cells in SLE (% $CTLA\text{-}4^+$ cells, SLE: 5.11±0.75%, HC: 6.96±0.79%; p=0.034). IL-21 inhibited GATA-3 expression in $CD4^+CD25^+FOXP3^+$ cells in SLE (% $GATA\text{-}3^+$ cells with and without IL-21: 35.29±5.87%, 67.72±7.37%; p=0.0002). IL-21 suppressed CTLA-4 expression in SLE Tregs (% $FOXP3^+CTLA\text{-}4^+$cells with and without IL-21: 8.62±1.35%, 29.46±5.31%; p=0.001). In turn, rapamycin blocked T-cell IL-21 secretion, while it promoted FOXP3, GATA-3, and CTLA-4 expression and suppressive function of SLE Tregs.

Conclusion: IL-21inhibits Treg differentiation and function in SLE potentially by downregulating GATA-3 and

CTLA-4, whereas rapamycin promotes Treg differentiation and function in part by suppressing IL-21.

Disclosure: H. Kato, None; **A. Perl**, None.

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Abstract Number: 1911

Potent and Selective Tyk2 Inhibitor Highly Efficacious in Rodent Models of Inflammatory Bowel Disease and Psoriasis

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Background/Purpose: Tyk2 is a member of the JAK family kinases and is a key mediator of IL-12, IL-23, and type I interferon signaling. These cytokines have been implicated in the pathogenesis of multiple inflammatory and autoimmune diseases such as lupus, psoriasis and inflammatory bowel diseases (IBD). Supported by compelling data from human genetic association studies, Tyk2 inhibition is an attractive therapeutic strategy for autoimmune diseases.

Methods: We utilized cutting edge proprietary structure-based drug design tools to identify highly selective Tyk2 inhibitors. These inhibitors were characterized for their potency and selectivity in enzyme and cell-based assays, and in mouse models of IBD and psoriasis.

Results: We have identified NDI-031407, a small molecule inhibitor of Tyk2, with potent enzyme and cellular activity, and excellent selectivity against other JAK family kinases and panels of receptors, transporters, ion channels, CYP enzymes and the hERG channel. This compound inhibits Tyk2 in a biochemical assay with a Ki of 0.2 nM, and is 218-, 148-, and 20-fold selective against JAK1, JAK2, and JAK3, respectively. Cell-based potency and selectivity of NDI-031407 was demonstrated in human PBMC assays by blockade of IL-12 induced phospho-STAT4, GM-CSF induced phospho-STAT5, and IL-2 induced phospho-STAT5, with IC_{50} of 0.10 μM, 3.9 μM and 0.24 μM, respectively. In addition, NDI-031407 inhibited IL-12 induced IFNγ with IC_{50} of 0.7 μM and 3.8 μM in human and mouse whole blood, respectively. We investigated the *in vivo* efficacy of NDI-031407 in mouse models of psoriasis and IBD. In an IL-23-induced mouse psoriasis model, NDI-031407 dose-dependently reduced disease with up to 74% inhibition of ear swelling and 96% inhibition of tissue levels of IL-17A at 100 mg/kg, highlighting the crucial role of Tyk2 inhibition in Th17 pathogenesis mediated by IL-23. In addition, NDI-031407 was highly efficacious in an imiquimod-induced mouse psoriasis model. NDI-031407 at 100 mg/kg achieved the same efficacy as dexamethasone in reduction of psoriasis score without body weight reduction. NDI-031407 treated mice had improved skin histology and dose-dependent reduction of spleen weight. To investigate the role of Tyk2 inhibition in Th1-driven pathogenesis, we tested NDI-031407 in a

$CD4^+CD45RA^+$ adoptive transfer model that resembles the pathology of human Crohn's disease. NDI-031407 treatment improved disease outcomes by reduction of body weight loss and colonic weight/length ratio, and improved colon histology. 100 mg/kg of NDI-031407 treatment also reduced colon myeloperoxidase levels to those of disease-free control mice, demonstrating the remarkable anti-inflammatory efficacy of Tyk2 inhibitors in this disease model.

Conclusion: Utilizing unique and innovative structure-based drug design technologies, we rapidly designed highly selective and potent Tyk2 inhibitors with suitable pharmaceutical properties as potential therapeutics in inflammatory disorders. We validated the vital role of Tyk2 in disease pathogenesis of psoriasis and IBD in preclinical mouse models.

Disclosure: W. Miao, Nimbus Therapeutics, 3; **C. Masse**, NImbus Therapeutics, 3; **J. Greenwood**, Schrodinger, 3; **R. Kapeller**, Nimbus Therapeutics, 3; **W. Westlin**, Nimbus Therapeutics, 3.

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Abstract Number: 1912

A New Avenue of Immune Regulation Conferred By Self-Glycerophospholipids Via Mobilization and Migration of Myeloid-Derived Suppressor Cells

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SESSION INFORMATION

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Session Title: T Cell Biology and Targets in Autoimmune Disease - Poster Session I

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Session Time: 9:00AM-11:00AM

Background/Purpose: Lipids function as essential components of biological membranes, as signaling molecules, and as energy storage molecules. Glycerol-based phospholipids, called glycerophospholipids (GPL), are the most abundant membrane lipids. Their glycerol backbone is esterified to phosphoric acid, resulting in the formation of phosphatidic acid (PA), from which all other GPLs are formed by the addition of a polar headgroup like choline, ethanolamine, glycerol, inositol, and serine, producing the main phospholipids in the cell, namely phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylglycerol (PG), phosphatidylinositol (PI) and phosphatidylserine (PS), respectively. GPLs such as PA, PC, PE, PI, and PS, have been eluted and identified by mass spectrometry as natural human CD1d ligands, and PC and PE have been eluted from murine CD1d. However, the functions of T cells that recognize abundant self GPLs are not known. Here, we identified these T cells in various lymphoid organs in normal and autoimmune-prone mice, investigated cell-cell interactions, and determined their role in animal models of autoimmune disease.

Methods: CD1d tetramers were loaded with various GPL antigens, and cells analyzed by flow cytometry. Cell-

cell interactions between GPL-reactive T cells and other immune cells were analyzed using *in vivo* and *in vitro* assays. *In vivo*effects of GPLs were tested in autoimmune animal models.

Results: CD1d tetramers loaded with GPLs, namely PA, PC, PE, PI, PS and BMP, identify 0.4–4% T cells in the lymphoid organs of normal and autoimmune-prone NZB/NZW and NZM.2328 mice. GPL-reactive T cells don't recognize glycolipid-loaded tetramers and don't respond to glycolipid αGalCer, suggesting that GPL-reactive T cells are distinct from other CD1d-restricted, invariant natural killer T cells. GPL-reactive T-cells expand, express CD69, and produce cytokines upon *in vivo* priming. However, all self-GPL antigens tested potently inhibited the proliferation and cytokine production by invariant natural killer T-cells via mobilization and migration of monocytic myeloid-derived suppressor cells into peripheral organs. These myeloid-derived suppressor cells inhibited invariant natural killer T-cells via interleukin-10. Treatment with a GPL antigen ameliorated autoimmune hepatitis, reduced pro-inflammatory cytokines and granulocyte accumulation, but recruited interleukin-10 producing myeloid derived suppressor cells that upon adoptive transfer protected against autoimmune disease in an animal model.

Conclusion: Normal immune repertoire contains T cells reactive to self GPLs, which ameliorate autoimmune disease via mobilization and migration of a subset of myeloid-derived suppressor cells. These novel observations have important implications for conditions with altered lipid metabolism and inflammation such as atherosclerosis and autoimmune disease. Acknowledgement: Supported in part by NICHD R03 to RCH, NICHD R21 and NIAID R01 to RRS.

Disclosure: R. Halder, None; **R. R. Singh**, None.

Abstract Number: 1913

B Cell Depletion Therapy Impact CD8 T Cells in ANCA-Associated Vasculitis

Antoine Néel[1,2], Marie Bucchia[3], Aurelie Caristan[1], Mélanie Néel[2], Marie Rimbert[4], Christian Agard[1], Maryvonne Hourmant[5], Gaelle Tilly[2], Michelle Yap[2], François Perrin[1], Pascal Godmer[6], Julie Graveleau[1], Sophie Brouard[2], Celine Bressollette[7], Fadi Fakhouri[8], Mohamed Hamidou[9] and Nicolas Degauque[2], [1]Internal Medicine Department, Nantes University Hospital, Nantes, France, [2]INSERM U1064, Nantes, France, [3]Pediatrics, Nantes University Hospital, Nantes, France, [4]Immunology Laboratory, Nantes University Hospital, Nantes, France, [5]Nephrology, Nantes University Hospital, Nantes, France, [6]CH Vannes, Vannes, France, [7]Virology Laboratory, Nantes University Hospital, Nantes, France, [8]Nephrology Department, Nantes University Hospital, Nantes, France, [9]Internal Medicine Department, Internal Medicine Department, Nantes University Hospital, Nantes, France

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Background/Purpose: In anti-neutrophil cytoplasmic antibodies associated vasculitis (AAV), several clues suggest that the efficacy of B cell depletion therapy lies beyond the suppression of ANCA-producing cells and may involve the suppression of B-T cell crosstalk. However, little if any data are available regarding the impact of rituximab on CD4, regulatory T and CD8 T cells in this setting.

Methods: Using polychromatic flow cytometry we performed a thorough immunophenotypic analysis of CD4, regulatory T and CD8 cells of 53 patients with AAV in order to compare the effect of conventional immunosuppressants (CIS) and rituximab (RTX) on these 3 T cells compartments. Cytokine/chemokine production of *in vitro* stimulated CD8 T cells was assessed using a multiplex Luminex immunoassay

Results: Among CD4 T cells, we found that frequency of naïve and memory subsets and the expression of CCR5, CCR4 and CD161 were not influenced by maintenance treatment type. Similarly, total Treg frequency and Treg subsets including $CD161^{+}$, $Helios^{+}$, resting ($CD45RA^{+}$) and memory ($CD45RA^{-}FoxP3^{hi}$) Tregs were comparable among RTX and CIS treated patients. By contrast, the type of maintenance treatment markedly influenced the CD8+ T cell compartment. Indeed, RTX inhibited late differentiated effector memory (TEMRA; $CD45RA^{+}CCR7^{-}$) CD8 cell expansion whereas CIS had the opposite effect, particularly in CMV positive individuals. Furthermore, we found that unlike CIS, B cell depletion therapy effectively inhibited the pro-inflammatory cytokine/chemokine production of *in vitro* stimulated CD8 T cells.

Conclusion: B cell depletion therapy has a profound impact on the CD8 T cell compartment. This observation raises the question whether the disruption of B cell help to CD8 T cells could contribute to the dramatic efficacy of RTX. Whether B cell depletion therapy promotes CD8 T cell exhaustion and/or inhibits immunosenescence deserves further investigations.

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Abstract Number: 1914

Immune Recognition of a Novel Citrullinated Epitope of Cartilage Proteoglycan Aggrecan in Mice with Proteoglycan-Induced Arthritis and in Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease leading to the inflammatory destruction of synovial joints. Anti-citrullinated protein antibodies (ACPA) are frequently detected in the serum of RA patients and may contribute to the pathogenesis of RA. Citrullination, which may involve several endogenous (self) proteins, is a post-translational modification of arginine residues in the protein backbone. Previous studies identified a citrullinated epitope in cartilage proteoglycan (PG) aggrecan, which elicited pro-inflammatory cytokine production by RA T cells in vitro. Moreover, we have recently reported the presence of ACPA-reactive (citrullinated) PG in RA cartilage. The purpose of the present study was to identify novel citrullinated epitopes in human PG that are recognized by T cells and/or antibodies from RA patients.

Methods: We used spleen cells from mice with PG-induced arthritis (PGIA) as screening tools to select citrulline (Cit)-containing PG peptides that were more immunogenic than their arginine (R)-containing counterparts. The Cit-R pairs of selected peptides were then tested for induction of pro-inflammatory T-cell cytokine production in RA and healthy control peripheral blood mononuclear cell (PBMC) cultures using cytokine ELISA and flow cytometry methods. Anti-Cit and anti-R peptide antibodies in mouse serum or human plasma were detected by ELISA.

Results: Spleen cells from mice with PGIA exhibited greater T-cell cytokine secretion in response to the Cit than the R version of PG peptide 49 (P49) and anti-P49 antibodies were detected in PGIA serum. PBMC from RA patients, but not PBMC from healthy controls responded to the citrullinated form of P49 (designated Cit49) with robust cytokine production in vitro. Importantly, high levels of anti-Cit49 antibodies were found in the plasma of ACPA-positive RA patients (n = 32). However, there was no correlation between the levels of Cit49-induced T-cell cytokines and anti-Cit49 antibodies in ACPA-positive RA. Another PG peptide (Cit13) similar to the previously described T-cell epitope induced greater cytokine responses than R13 by healthy control (but not RA) PBMC, however, anti-Cit13 antibodies were rarely detected in human plasma.

Conclusion: We have identified a novel citrullinated human PG epitope (Cit49), which is highly immunogenic both in mice with PGIA and patients with RA. The lack of correlation between T-cell and antibody reactivity with Cit49 in the ACPA-positive RA group suggests that this peptide is recognized as either a strong T-cell epitope or a strong B-cell epitope in different subsets of ACPA-positive patients. As citrullinated PG may be present in RA articular cartilage, Cit PG epitope-induced T-cell activation or deposition of Cit PG epitope-specific antibodies can occur in the joints of ACPA-positive RA patients, potentially contributing to cartilage destruction.

Disclosure: A. Markovics, None; **T. Ocsko**, None; **R. S. Katz**, None; **E. I. Buzas**, None; **T. T. Glant**, None; **K. Mikecz**, None.

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Abstract Number: 1915

Partial Elimination of Intestinal Microbiota Dampens T Helper 17 Cell Differentiation and Established Collagen-Induced Arthritis in Mice

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Background/Purpose: High-throughput sequencing of intestinal microbiota recently revealed that the composition of intestinal microbiota is perturbed in patients with new onset untreated rheumatoid arthritis (RA). In mice, both germ-free condition and administration of oral antibiotics before the onset of arthritis modulate T cell differentiation and attenuate the disease. However, it is not known whether and how modulation of intestinal microbiota after the onset of arthritis may influence the disease. Here, we investigated the involvement of commensal intestinal microbiota in the progression of established arthritis in both T cell-dependent and -independent mouse models.

Methods: Mice with established collagen-induced arthritis (CIA) as the most widely-used T cell-dependent model of RA, as well as mice with K/BxN serum-transfer arthritis as a T cell-independent model were treated orally with a cocktail of metronidazole, neomycin, ampicillin (1 g/l each) and vancomycin (0.5 g/l) for one week to partially eliminate intestinal microbiota. Arthritis was assessed macroscopically and by histologic analysis. Differentiation of Th1, Th17 and regulatory T (Treg) cells and production of their prototypic cytokines in intestinal lamina propria and joint-draining lymph nodes were assessed by flow cytometry and Luminex array. Development of anti-collagen type II antibodies was assessed in serum of CIA mice using ELISA. Intestinal and synovial expression of cytokines and serum amyloid A (SAA) isotypes was measured by qPCR.

Results: Elimination of intestinal microbiota in mice with ongoing CIA specifically suppressed intestinal Th17 cell differentiation without affecting Th1 and Treg cells. Accordingly, production of interleukin-17 (IL-17), but not interferon γ, IL-4 and IL-10, by lamina propria lymphocytes was significantly diminished in antibiotic-treated mice. Furthermore, intestinal expression of SAA isoforms and IL-22, known to promote lamina propria Th17 cell differentiation, was suppressed in antibiotic-treated CIA mice. Importantly, elimination of intestinal microbiota resulted in suppressed Th17 cell differentiation and IL-17 production in joint-draining lymph nodes and reduced the severity of established CIA. In contrast, antibiotic treatment did not influence disease severity in the T cell-independent K/BxN serum-transfer arthritis. Intriguingly, the abundance of intestinal Th17 cells strongly correlated with the severity of arthritis in the CIA mice. However, elimination of intestinal microbiota after disease onset did not affect the development of anti-collagen type II autoantibodies.

Conclusion : These observations suggest that modulation of commensal intestinal microbiota during established arthritis specifically suppress Th17 differentiation and dampen T cell-mediated arthritic processes. While our study does not advocate the use of antibiotics as a treatment for RA, it supports the notion that inflammatory signals provided by the gut microbiota continue to promote arthritis after its onset. Understanding the exact mechanisms linking the intestinal T cell response with arthritis may help identifying novel therapeutic strategies for RA.

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Abstract Number: 1916

Heightened MAIT Cell Sensitivity to MR1 Ligands Could Impact Control of Dysbiosis in Patients with Rheumatoid Arthritis and Ankylosing Spondylitis

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Background/Purpose: Mucosal associated invariant T (MAIT) cells are an innate-like lymphocyte population predominant at mucosal sites, which express a semi-invariant T cell receptor restricted to the MHC class I-like molecule, MR1. MR1 presents ligands derived from the riboflavin synthesis pathway, common to a range of bacteria and yeast. There is evidence in rheumatoid arthritis (RA) and ankylosing spondylitis (AS) for oral and/or gastrointestinal microbial dysbiosis. However the mechanisms underlying these disease associations are unclear. We analyzed how the response of MAIT cells to MR1 ligand might influence the development of dysbiosis.

Methods: We compared the frequency of $CD3^{+}CD4^{-}CD161^{hi}TRAV1\text{-}2^{+}$ PB MAIT cells in 45 RA, 10 AS patients, and 38 healthy controls (HC). We investigated the frequency of 5-OP-RU-specific MAIT cells using

MR1-tetramers and analyzed cellular activation of MAIT cells in arthritis patients and HC after stimulation with 5-OP-RU ligand. We identified compositional variations in the oral microbiome of RA patients, and assessed whether these variations are reflected in riboflavin biosynthesis pathways

Results: Bacterial species capable of riboflavin synthesis and thus MAIT cell ligand production, including *Streptococcus infantilis*, *Rothia dentocarisosa*, *Rothia mucilaginosa* and *Prevotella melaninogenica* were more abundant in the oral microbiome of RA patients than HC. We observed no difference in MAIT cell frequencies when comparing HC, RA and AS patient groups matched for age and sex. However, the proportion of PB MAIT cells declined with age in all groups and accordingly, was significantly lower in patients with late- rather than early-onset RA. PB MAIT cells were constitutively more activated than conventional T cells. The frequency of 5-OP-RU-specific PB MAIT cells ranged from 0.8-8%. When stimulated ex vivo with the riboflavin metabolite 5-OP-RU, PB MAIT cells upregulated CD69. In response to 5-OP-RU, approximately 50% of MAIT cells secreted TNF and 10% secreted IFN-g, while less than 1% secreted IL-17. The ligand was highly specific, as conventional T cells in the same culture were not activated. When compared to HC MAIT cells, MAIT cells from arthritis patients were more susceptible to apoptosis in response to 5-OP-RU, and residual live cells expressed lower levels of CD69 or TNF than HC.

Conclusion: PB MAIT cells decline with age in arthritis patients similar to HC. MAIT cells of arthritis patients have greater susceptibility to MR1 ligand-induced cell death in vitro and the surviving cells have lower capacity for cytokine production. Certain bacterial species enriched at the RA mucosal sites are capable of riboflavin biosynthesis, and presumptively, the formation and release of MR1 ligands, which could impact control of dysbiosis by MAIT cells.

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Abstract Number: 1917

Rheumatoid Arthritis Cells Produce Extracellular Vesicles That Incorporate PD-1 and microRNAs Targeting the PD-1 Pathway in Surrounding Cells

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Background/Purpose: Programmed death-1 (PD-1) is a central marker of T cell exhaustion. Exhausted T cells are present in inflammatory conditions, where they fail to eliminate the disease, and contribute to development of chronicity. They are suggested associated with a favorable prognosis in rheumatoid arthritis (RA), yet this is not fully elucidated [1]. Extracellular vesicles (EVs) carrying proteins and microRNAs (miRNAs), among other constituents have been recognized as an important route of communication in the microenvironment.

Methods: Plasma and synovial fluid from RA patients were examined for the presence of EVs by capturing EVs on CD63 coated beads. EVs were furthermore isolated from supernatants from synovial fluid mononuclear cell (SFMC) and peripheral blood mononuclear cell (PBMC) cultures and characterized. The presence of PD-1 in EVs was examined by immuno-gold electron microscopy (EM), ELISA and western blotting. EVs purified from RA and healthy control (HC) PBMC cultures were co-cultured with lymphocytes and U937 cells (a cell line negative for PD-1), and EVs from WT mice were co-cultured with cells from PD-$1^{-/-}$ mice. PD-1 expression and cell proliferation of the exposed cells were analyzed. Finally, miRNA expression in EVs from cultured RA and HC cells was investigated by sequencing.

Results: PD-1 was detected in EVs in plasma and synovial fluid from RA patients. The presence of PD-1^{+} EVs in RA and HC cell culture supernatants was confirmed with immuno-gold EM and western blotting. Co-culturing these EVs with other cells induced PD-1 on the surface of lymphocytes and U937 cells. PD-1 was furthermore induced on PD-$1^{-/-}$ cells, when these were co-cultured with EVs from WT mice. EVs from RA PBMCs increased recipient cell proliferation, compared with both EVs from HC PBMCs and cells without EVs. This was not changed by addition of recombinant PD-L1. MicroRNAs repressing expression of the co-inhibitory receptors PD-1, TIM-3 and CTLA-4, all associated with an exhausted T cell profile, were up-regulated in EVs from stimulated PBMC cultures, however not in EVs from RA SFMCs. In EVs from non-stimulated RA PBMC cultures, miRNAs repressing the exhausted T cell pathway were down-regulated compared to EVs from HC cultures, suggesting that RA PBMCs in a steady-state aim to transfer information maintaining an exhausted T cell profile.

Conclusion: EVs from RA PBMCs carry and transfer PD-1 and incorporate less miRNAs repressing the PD-1 pathway and other markers of T cell exhaustion. Despite this, EVs from RA PBMCs increase proliferation of recipient cells *in vitro*. In addition, EVs from RA synovial cells express low levels of miRNA that regulate PD-1, TIM-3 and CTLA-4, facilitating continuous T-cell exhaustion. In conclusion this suggests that EVs are pro-inflammatory in RA, and contribute substantially to the development of chronicity. 1. McKinney, E. F., et al. *Nature* **523,** 612–616 (2015).

Disclosure: S. Greisen, None; **Y. Yan**, None; **A. Hansen**, None; **M. Venø**, None; **J. R. Nyengaard**, None; **M. Hvid**, None; **A. Sharpe**, None; **J. Kjems**, None; **B. Deleuran**, None.

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Abstract Number: 1918

Characterising the Specificity, Function and Behavior of CD4+ T Cells

Initiating Inflammation in a Murine Model of Rheumatoid Arthritis

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Background/Purpose: $CD4^+$ T cells are important contributors to the pathogenesis of Rheumatoid Arthritis (RA). The presence of activated T cells in the inflamed synovium, strong associations with HLA-DR4, ptpn22, ctla4 and cd28 implicate their contribution, while the success of T cell targeted CTLA-4-Ig therapeutic provide more direct evidence. Yet it remains unclear when and where $CD4^+$ T cells mediate this pathogenic effect and whether the specificity of the cells is important.

Methods: A variation of antigen-induced arthritis using ovalbumin (OVA) as the inciting challenge was used to model articular inflammation. Th1 polarised OVA specific fluorescent (DsRed) OT-II TcR transgenic T cells were adoptively transferred and expanded *in vivo* by challenge with OVA/CFA. This allowed subsequent analysis and tracking of antigen-specific T cells as they were recruited to the ankle joint following periarticular injection of heat aggregated OVA (HAO). Flow cytometry allowed phenotyping of cells recruited to the inflamed articular environment. The T cell receptor (TcR) diversity of infiltrating endogenous T cells was assessed by PCR of Vβ genes. Dynamic interactions of responding DsRed T cell populations with joint residing CD11c YFP dendritic cells were visualized using intravital multiphoton laser scanning microscopy.

Results: Low numbers of the inciting OVA specific $CD4^+$ T cells could be found in the joint tissue. However, a large influx of endogenous $CD4^+$ T cells of unknown antigen specificity was also found. In comparison with the $CD4^+$ T cells in the draining lymph node, this recruited T cell population expressed surface activation markers, produced TNFa and IFNg upon *ex vivo* restimulation and exhibited a narrower range of T cell receptor Vb usage. In addition, intravital imaging of the inflamed joint revealed that a sub-population of this infiltrate demonstrated slower motility speeds and longer periods of contact with articular dendritic cells, while others rapidly migrated throughout the tissue.

Conclusion: We present data demonstrating that while the numbers of inciting antigen-specific T cells to the joint tissue is small, it is associated with a subsequent influx of a large endogenous population of unknown antigen specificity that had acquired the ability to secrete pro-inflammtory cytokines. Oligoclonal TcR Vβ gene expression by the $CD4^+$ T cells in the inflamed joint suggests some degree of antigen-specificity in recruitment while intravital imaging reveals that some of this infiltrate exhibits behaviour consistent with recognition of cognate peptide-MHCII.

Disclosure: R. Benson, None; **C. Prendergast**, None; **I. B. McInnes**, BMS, Pfizer, Celgene, Astra Zeneca, 2; **J. Brewer**, None; **P. Garside**, None.

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Abstract Number: 1919

Analysis of T Cell Repertoire Diversity of CD4+ Memory and NaïVe T Cells By Next Generation Sequencing and Its Association with Rheumatoid Arthritis Disease Parameters

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: T Cell Biology and Targets in Autoimmune Disease - Poster Session I

Session Type: ACR Poster Session B

Session Time: 9:00AM-11:00AM

Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by peripheral polyarthritis. The importance of CD4+ T cell in the pathophysiology of RA is well-known and it has been reported that the diversity of T cell receptor (TCR) of CD4+ T cells is decreased in rheumatoid arthritis. However, the relationship between the decrease of TCR repertoire diversity of CD4+ T cells and RA pathophysiology remains unclear. To investigate the significance of this phenomenon in RA pathophysiology, we analyzed TCR repertoire and its association with disease activity and other parameters related to RA.

Methods: Peripheral blood CD4+ memory (CD3+CD4+CD45RA-) and naïve (CD3+CD4+CD45RA+) T cells from 18 RA patients and 21 age and sex-matched healthy donors were obtained. All RA patients satisfied the 2010 ACR/EULAR classification criteria for RA. cDNAs of TCR-beta were synthesized and amplified by 5'-race method. Sequencing was performed by Miseq. Concentrations of serum cytokines were assessed with Multiplex ELAISA. Renyi entropy was used to comprehensively assess TCR repertoire diversity, and correlation with disease activity, concentrations of serum cytokines, the number of shared epitope alleles and other clinical parameters was examined.

Results: TCR repertoire diversity of both memory and naïve CD4+ T cells was significantly reduced in RA patients with high disease activity compared to healthy donors. It is generally thought that the reduction of TCR diversity of CD4+ T cells reflects the existence of antigen specific immune responses in RA, and this immune response may be associated with antigens presented on HLA class II. Our results showed a positive correlation between the dosage of shared epitope and reduction of TCR repertoire diversity in CD4+ T cells. Also, there was a negative correlation between TCR repertoire diversity of CD4+ T cells and disease activity indices, such as Disease Activity Score (DAS) 28-CRP, DAS28-ESR, and Clinical Disease Activity Index (CDAI). On the other hand, concentrations of serum cytokines, including pro-inflammatory cytokines, did not show significant correlation with TCR repertoire diversity of CD4+ T cells. These phenomenon were found not only in CD4+ memory T cells but also in CD4+ naïve T cells.

Conclusion: Our results suggest that antigen specific immune responses of CD4+ T cells to self-antigens

presented on HLA class II with shared epitope may contribute to the pathophysiology of rheumatoid arthritis in a different manner from inflammatory cytokines. These antigen specific responses, not only in CD4+ memory T cells subset, but also in CD4+ naïve T cells subset, may be related to RA pathophysiology and may suggest the importance of homeostatic expansion in RA.

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Abstract Number: 1920

Vitamin D Induces a Type 1 Regulatory T Cell (Tr1)-like Phenotype in Human C-C Chemokine Receptor Type 6 (Ccr6)+ th Cells and Promotes Their Migration to an Inflammatory Environment

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Background/Purpose: The active vitamin D metabolite $1,25(OH)_2D_3$ suppresses various experimental autoimmune diseases. In addition, serum vitamin D levels, vitamin D intake and polymorphisms in the vitamin D receptor (VDR) are associated with disease incidence and severity in human autoimmune diseases such as rheumatoid arthritis (RA). However, the mechanism behind these immunosuppressive effects is currently unknown. Previously we have demonstrated that $1,25(OH)_2D_3$ directly inhibits pathogenicity of $CCR6^+$ T helper (Th) cells. These cells, which include Th17 and Th17.1 cells, are thought to play an important role in the pathogenesis of autoimmune diseases such as rheumatoid arthritis (RA). They produce cytokines like IL-17A and TNFα and activate synovial fibroblasts to induce a pro-inflammatory feedback loop. This interaction may underlie the chronic joint inflammation in RA. Therefore $CCR6^+$ Th cells are an interesting therapeutic target in this disease. Here we further investigated the effect of $1,25(OH)_2D_3$ on $CCR6^+$ Th cells to understand how

$1,25(OH)_2D_3$ suppresses the inflammatory responses in autoimmune diseases.

Methods: We cultured $CCR6^+$ Th cells from treatment-naïve early RA patients with or without $1,25(OH)_2D_3$ and generated gene-expression profiles. These profiles were validated using RT-PCR, ELISA and flow cytometry. Functional effects were evaluated via co-culture with RA synovial fibroblasts (RASF) and Boyden chamber-based migration assays.

Results: Gene-expression profiles from $CCR6^+$ Th cells confirmed that $1,25(OH)_2D_3$ treatment downregulated pro-inflammatory cytokines like IL-17A, IL-17F and IL-22, but also genes important for the pathogenic Th17 phenotype like RORC and IL-23R. In contrast, $1,25(OH)_2D_3$ induced the anti-inflammatory cytokine IL-10, but not the classical Treg transcription factor FoxP3. Instead, upregulation of genes like LAG3, c-MAF, CTLA4, and IRF8 suggests the induction of a Tr1-like phenotype. Interestingly, these $CCR6^+$ Th cells cultured with $1,25(OH)_2D_3$ were less capable of inducing the pro-inflammatory loop upon interaction with RASF. This suggests that the modulated $CCR6^+$ Th cells could contribute to regulating synovial inflammation. However, for this they need to be capable of migration towards inflammatory sites. Therefore we investigated the migration of $CCR6^+$ Th cells treated with $1,25(OH)_2D_3$ towards synovial inflammation as modeled by the $CCR6^+$ Th – RASF co-culture. Indeed, the $1,25(OH)_2D_3$-treated $CCR6^+$ Th cells migrate faster towards the site of inflammation than untreated cells.

Conclusion: $1,25(OH)_2D_3$ inhibits the pathogenic Th17 phenotype in $CCR6^+$ Th cells, while inducing a regulatory Tr1-like phenotype. These cells will then migrate towards the site of inflammation, where they are less potent activators of RASF. This effect of $1,25(OH)_2D_3$ on $CCR6^+$ Th cells may underlie the suppression of RA by vitamin D.

Disclosure: W. Dankers, None; **J. P. van Hamburg**, None; **N. Davelaar**, None; **P. Asmawidjaja**, None; **H. Wen**, None; **J. van Leeuwen**, None; **E. Colin**, None; **E. Lubberts**, None.

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Abstract Number: 1921

Evidence for Prevotella Copri As an Immune-Relevant Bacterium in Rheumatoid Arthritis

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Background/Purpose: *Prevotella copri*, an intestinal commensal microbe, may be prominent in stool samples of patients with new-onset rheumatoid arthritis (NORA). However, it has been unclear whether the organism is immune-relevant in RA pathogenesis.

Methods: HLA-DR-presented peptides were identified directly from RA patients' synovial tissue or peripheral blood mononuclear cells (PBMC) by tandem mass spectrometry. *P. copri* peptides or source proteins were then tested for T cell reactivity by IFN-γ ELISpot assay and for antibody responses by ELISA using cells and sera from DMARD-naive NORA patients, chronic RA (CRA) patients, and controls. For comparison, humoral responses to *P. gingivalis*, *B. fragilis,*and *E. coli* were also tested. Serum samples were analyzed for innate, Th1, and Th17 mediators by Luminex. Moreover, available serum and synovial fluid (SF) samples were tested for the presence of *P. copri* 16S rDNA by nested PCR. All RA patients met the 2010 ACR/EULAR criteria for RA.

Results: We identified an HLA-DR-presented peptide from a 27-kD protein of *P. copri* (*Pc*-p27), which stimulated Th1 responses in 17 of 40 NORA patients (42%), but not in Lyme arthritis patients (P=0.0007) or healthy controls (P<0.0001). We then found that 17 of 78 NORA patients (22%) and 16 of 49 CRA patients (33%) had IgG or IgA antibody responses to *Pc*-p27, but rarely to both. Similar results were obtained when testing was done with the whole *P. copri* organism. Three types of comparison groups suggested that *P. copri* antibody responses are specific for RA. First, *P. copri* antibodies were rarely found in patients with other rheumatic diseases or in healthy controls. Second, antibody levels to 2 other gut commensals, *B. fragilis* and *E. coli*, were similar or less in RA patients than those in patients with other type of arthritis or in healthy controls. Third, although IgG and often IgA antibodies to the oral periodontal pathogen, *P. gingivalis*, were detected in 25% of the 127 RA patients, there was little overlap between this group and those with *P. copri* antibodies. In patients with *P. copri* IgA antibodies, these responses correlated with Th17 cytokines and most had anti-citrullinated protein antibodies (ACPA). In contrast, serum *P. copri* IgG levels correlated with the Th1 cytokine CXCL10, and with significantly less frequent ACPA (P=0.01). Of 18 patients in whom both serum and SF were available, 3 of 5 patients with IgG *P. copri* antibodies had 16S DNA for *Prevotella* detected in SF compared with none of the patients with IgA *P. copri* antibodies or no *P. copri*antibodies (P=0.01).

Conclusion: Subgroups of RA patients have differential immune responses to *P. copri*. IgA antibody responses to *P. copri* correlated with Th17 cytokine responses and frequent ACPA, which may signify localized interactions between microbes and host immune cells in the gut mucosa. In contrast, IgG *P. copri* antibody responses were associated with *Prevotella* 16S DNA in SF, Th1 immune responses, and infrequent ACPA, which may result from systemic spread of the organism, presumably carried to joints within cells. These observations suggest that *P. copri* is an immune-relevant bacterium in subgroups of patients with RA, supporting a new paradigm in RA pathogenesis.

Disclosure: A. Pianta, None; **S. Arvikar**, None; **K. Strle**, None; **E. E. Drouin**, None; **Q. Wang**, None; **C. E. Costello**, NIH, 2; **A. C. Steere**, NIH, 2.

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Abstract Number: 1922

TNF-α and IL-6 Induced Upregulation of CCR5 and CXCR3 Participate in Vδ2 Chemotaxis in RA

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Background/Purpose: Vδ2T cells, a subpopulation of γδ T cells with inflammatory features, play a vital role in inflammation, tumor immunology, infectious disease and autoimmunity. However, the role of Vδ2 T cells in the pathogenesis of rheumatoid arthritis remains elusive.

Methods: 68 patients with rheumatoid arthritis, 21 patients with osteoarthritis and 21 healthy controls were enrolled in the study. All RA patients fulfilling the 2010 ACR/EULAR criteria for RA. Peripheral Vδ2T population, apoptosis, proliferation, chemokine receptor expression and pro-inflammatory cytokine secretion were quantified by flow cytometry. The infiltration of Vδ2 T cells within synovium was examined by immunohistochemistry and flow cytometry. The effect of TNF-α and IL-6 on Vδ2 T migration was determined by flow cytometry and transwell migration assay.

Results: The percentage of peripheral Vδ2T cells of active RA were significantly decreased compared with healthy controls (1.80±1.76% vs 5.68±2.72%), which were negatively correlated with the disease activity indexes including DAS28($r=-0.6341$, $p<0.01$), CRP($r=-0.4352$, $p<0.01$) and ESR($r=-0.4364$, $p<0.01$). However, the Vδ2T cells infiltrated in the synovium of RA were increased compared with OA ($p<0.05$). Comparing with OA Vδ2T cells, both peripheral and synovium Vδ2T cells of RA produced higher level of IFN-γ and IL-17 ($p<0.05$). The chemokine receptor CCR5 and CXCR3 expressed on Vδ2T cells in RA were significantly higher than HC and OA patients ($p<0.05$), which were induced by TNF-α and IL-6. TNF-α antagonist therapy restored the peripheral Vδ2 T cell in RA.

Conclusion: Elevated TNF-α and IL-6 in RA patients induced high expression of CCR5 and CXCR3 on Vδ2T cells, which subsequently promote Vδ2 T cells infiltrate into synovium and play an important role in the pathogenesis of RA. Vδ2 T cell is a promising potential biomarker and therapeutic target of RA.

Disclosure: W. MO, None; **S. YIN**, None; **C. ZHOU**, None; **X. Zhang**, None.

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Abstract Number: 1923

Activated Partial Thromboplastin Time Reflects Disease Activity in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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Background/Purpose: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of systemic vasculitides associated with ANCA specific for myeloperoxidase (MPO) or proteinase-3 (PR3), and includes microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), and eosinophilic granulomatosis with polyangiitis (EGPA). A high prevalence of venous thromboembolism has been reported in several cohort studies of patients with AAV, not only during active disease but also when patients are in remission. Recently, it has also been suggested that patients with AAV in the active stage are in a hypercoagulable state. However, the clinical significance of the increased incidence of venous thromboembolism among patients with AAV has not been fully recognized. Here we examined the relationship between markers for hypercoagulability and disease activity including inflammatory markers and kidney functions, and assessed the implication of abnormal coagulation status in patients with AAV.

Methods: Fifty-five patients who had been referred to Niigata University Hospital and diagnosed as having AAV (MPA (n=29), GPA (n=23), EGPA (n=3)) between 2009 and 2015 were recruited. Plasma fibrin degradation products (FDP), D-dimer, and activated thromboplastin time (APTT) were measured, and the APTT ratio was calculated and standardized using data from control plasma. Disease activity was assessed at the same time in accordance with the Birmingham Vasculitis Activity Score (BVAS). Other laboratory data including kidney function parameters and serum C-reactive protein (CRP) were also examined, and analyzed using Spearman's rank correlation coefficient and stepwise multiple regression analysis to determine their relationship with coagulation parameters. A P value of <0.05 was taken to denote statistical significance.

Results: The mean value of FDP was elevated at 11.4 μg/ml (normal <9μg/ml), the mean D-dimer value was also elevated at 4.5 μg/ml (normal <1 μg/ml), and the mean APTT ratio was 1.15. In 44 patients, the APTT ratio was >1.01. Spearman's rank correlation coefficient analysis showed that FDP and D-dimer were positively associated with CRP, daily urinary protein excretion, and BVAS, and negatively correlated with the estimated glomerular filtration rate (eGFR), whereas the APTT ratio was positively associated with BVAS. Although stepwise multiple regression analysis revealed no factor that significantly affected FDP or D-dimer, BVAS was selected as a positive independent variable affecting the APTT ratio (rho=0.3401, p=0.01186). In addition, the mean BVAS was significantly higher in patients with an APTT ratio of ≥1.01 (n=44), compared to patients with an APTT ratio of ≤1.0 (n=11) (16.1 ± 5.4 versus 11.2±5.9, p=0.0114).

Conclusion: Prolongation of APTT reflects AAV disease activity and is considered to be a possible biomarker in affected patients.

Disclosure: Y. Wada, None; **T. Kuroda**, None; **M. Nakano**, None; **I. Narita**, None.

vasculitis

Abstract Number: 1924

Clinical Features and Outcome in Patients with Elderly Onset ANCA Associated Vasculitis

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Background/Purpose: ANCA-associated vasculitis (AAV) usually occurs in elderly patients, but only a few studies regarding clinical features in elderly onset AAV have been reported. So far, there was no report describing clinical features of elderly onset AAV patients in Japan. The purpose of this study is to compare clinical features and outcome between elderly onset (≥75 years old) and younger Japanese AAV patients (<75 years old).

Methods: AAV patients who met the criteria for granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomaosis with polyangiitis (EGPA) were included in this study. AAV patients initially treated at Fukushima Medical University Hospital (Fukushima, Japan) from April 2004 to March 2016 were retrospectively reviewed. These patients were divided into 2 groups: elderly, age ≥ 75 (N = 10) and younger, age < 75 (N = 26). We compared the following clinical features between the 2 groups: age at diagnosis, sex, Birmingham Vasculitis Activity Score (BVAS), clinical symptoms, laboratory data, therapy and outcome.

Results: Thirty six AAV patients (9 GPA, 24 MPA and 3 EGPA) were included in this study. General clinical features showed similar between the two groups except for female rates and body weight in the elderly, compared to younger patients (80% vs. 42.3% and 43.6 vs. 58.9kg, respectively). In clinical symptoms, elderly AAV patients showed significantly higher rates of kidney involvement than younger AAV (90% vs. 50%, p = 0.03). Laboratory data showed significantly lower RBC and ferritin levels in the elderly than younger AAV (241 vs. 438 ng/mL, p = 0.021). As to therapy, significantly lower PSL doses were administered in elderly AAV patients (34 vs. 45.3 mg/day, p = 0.038). Overall survival analysis (Kaplan-Meier curve) showed significantly lower survival in elderly AAV (58.3% vs. 96.2%, p = 0.008). Five MPA patients died; the number of patients and causes of death were as follows: 4 in elderly AAV (alveolar hemorrhage, renal failure, bacterial pneumonia and pneumocystis pneumonia), and 1 in younger AAV (alveolar hemorrhage). We further analyzed correlation between serum ferritin levels and clinical items. Serum ferritin levels positively correlated with serum ALT (rs 0.47, p = 0.013) and C3 levels (rs 0.4, p = 0.045) but not with Hb, RBC, Cr, age at diagnosis, and BVAS scores.

Conclusion: Elderly AAV patients showed similar clinical features except for increased rate of females, kidney manifestations and lighter body weight. Lower serum ferritin levels in the elderly may show milder inflammatory state than younger AAV at initial manifestation. Serum ferritin, an acute phase protein, are produced in inflammatory state (macrophage activation) and considered as a biomarker of disease activity in several

autoimmune diseases. Serum ferritin levels in this study positively correlated with ALT and C3 levels, which can be considered as a possible biomarker of disease activity in AAV patients. The causes of death in elderly AAV can be explained with vasculitis progression itself (especially MPA patients), infection, and treatment using lower PSL doses. Proper management and monitoring of adverse events should be performed in patients with elderly AAV.

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Abstract Number: 1925

Interest of Procalcitonin for the Follow-up of ANCA-Associated Vasculitis: Data from a Cohort of 99 Patients

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Background/Purpose: The prognosis of the ANCA associated vasculitis (AAV) has improved with the new immunosuppressive treatments but infectious complications remain frequent. Procalcitonin (PCT) is used for a quick diagnosis of bacterial infection. The aim of this study was to assess the diagnostic accuracy of PCT for the differential diagnoses of a bacterial infection from a vasculitis flare.

Methods: All patients with a granulomatosis with polyangiitis (GPA), a eosinophilic granulomatosis with polyangiitis (EGPA) or a microscopic polyangiitis (MPA) followed in our internal medicine department were included. PCT was determined by KRYPTOR assay (Thermo Fisher BRAHMS). All bacterial infections or flares up of the vasculitis were recorded. The diagnosis of flare up was based on increase of the BVAS or the BVAS WEG. Infections were confirmed by a positive microbial test or an evidence of infection on imaging. For the cases without evidence of positive microbial test, the diagnosis was established when two out of three practitioners of the unit gave the same opinion.

Results: The cohort consisted of 99 AAV (GPA = 73; EGPA = 21; MPA = 5). The follow up was of 5 years [1,8 ; 9,2]. 53 patients experienced 96 flare ups. Those were GPA in 70% of cases. 57 patients developed 74 bacterial infections. 11 were excluded because of a lack of proof. 27 had a positive microbial test. The value of

PCT was found for 55,4% of the registered events. PCT was higher in cases of bacterial infection than flare up (0,3 µg/l [0,11 ; 1,9] vs 0,08 µg/l [0,05 ; 0,13], p<0,0001). The same results were found for the bacterial infection with a proof by positive microbial test (0,55 µg/l [0,13 ; 3] vs 0,08 [0,05 ; 0,13], p=0,0021). For a threshold in 0,11µg/l, the sensibility and the specificity of the PCT were of 75% and 73,5% respectively. For a threshold of 48mg/l, the sensibility of the CRP was 71,4% and the specificity was 62,8%.

Conclusion: Five retrospective studies were carried on this subject. For two studies, the result seems to show an increase of procalcitonin during active vasculitis. But this result is inconstant and uncertain. Three studies found results similar to ours; during bacterial infections, the PCT increase more than during flares. Therefore, a modification of the discriminant threshold could allow the using of this marker to distinguish a flare up of infection. One study that used the same assay to determine the PCT, showed that a threshold of 0,1 µg/l was effective. The accuracy of PCT for the diagnosis of bacterial infection in patients with AAV is better than CRP. PCT seems to be useful to distinguish a flare up from a bacterial infection although PCT rises too in flare up.

Disclosure: A. Lemaire, None; **R. Outh**, None; **A. Mania**, None; **G. Marceau**, None; **P. Berland**, None; **M. Andre**, None; **O. Aumaître**, None.

Abstract Number: 1926

Indications for Testing and Diagnostic Outcome in Patients with Positive ANCA at a Canadian Tertiary Care Centre

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Background/Purpose: Anti-neutrophil cytoplasmic antibodies (ANCA) are a hallmark of a subset of small vasculitides collectively termed ANCA-associated vasculitis (AAV). With widespread availability of ANCA testing, interpreting positive results has become increasingly challenging. Here, we conducted a retrospective study to evaluate indications for testing and diagnosis of patients with positive ANCA.

Methods: We searched The Ottawa Hospital biochemistry database and reviewed the records of patients with positive ANCA (defined as elevated myeloperoxidase [MPO] or proteinase 3 [PR3] titers) tested between April 1, 2014 and March 31, 2015. Indications for ordering ANCA and final diagnosis were determined.

Results: 1889 ANCA tests were performed in the study year. 112 patients had at least 1 positive ANCA in the

study year and 169 total tests were positive. *Indications and diagnosis of patients with first-time positive ANCA testing:* 69 patients had first-time positive ANCA in the study year, with 35 (51%) anti-MPO positive, 31 (45%) anti-PR3 positive, and 3 (4%) doubly positive. The indications for testing were suspicion for AAV in 20 patients (29%), suspicion for unspecified vasculitis in 20 (29%), suspicion for an inflammatory condition in 25 (36%), and unknown in 4 (6%). Overall, 27 patients (39% of first time positives) were diagnosed with AAV corresponding to 80%, 40%, 12%, and 0% of patients tested for these indications, respectively. Thirty-one (45%) patients had other inflammatory or infectious etiologies (most commonly inflammatory bowel disease (n=5), lupus (n=4), and inflammatory eye diseases (n=3)), and non-inflammatory diagnoses accounted for the remaining 11 (16%). Patients with AAV had significantly higher mean maximum PR3 and MPO titers than those with non-AAV diagnoses (1138 vs. 145 and 323 vs. 119 respectively, $p<0.05$ by Student's t-test). *Indications and outcomes of repeat ANCA testing:* 68 patients had repeat ANCA testing in the study year, 43 of which were first tested prior to the study year. In total, 120 repeat ANCAs were performed; 84 of these were done on 44 patients with AAV and 36 on 24 patients with other diagnoses. Altogether, 80% of patients with AAV were re-tested in the study year (between 1 and 6 times, median 2 tests) vs. 42% of those with non-AAV conditions (between 1 and 5 times, median 1 test). Routine monitoring (as opposed to testing for changed clinical status) accounted for 72% of all repeat tests (n=86). Management was changed in response to serial ANCA testing in 11 AAV patients, 10 of whom were tested at time of changed clinical status. Overall, management was changed in 9% of all patients with repeat ANCA, 34% of all re-tests performed for changed clinical status and 1% of re-tests conducted routinely.

Conclusion: Despite widespread ANCA testing, few patients who start with low clinical suspicion for AAV and have positive ANCA are subsequently diagnosed with AAV. Serial ANCA testing is a common practice but is not supported by clear evidence, and few ANCA re-tests subsequently lead to change in management. Clarification of guidelines on effective ANCA ordering may limit unnecessary hospital laboratory costs and patient bother.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/indications-for-testing-and-diagnostic-outcome-in-patients-with-positive-anca-at-a-canadian-tertiary-care-centre

Abstract Number: 1927

Relapses in Patients with ANCA-Associated Vasculitis: A Retrospective Study on Severity and Organ Involvement Compared to Initial Onset

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SESSION INFORMATION

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Session Title: Vasculitis - Poster II: ANCA-Associated Vasculitis

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Background/Purpose: Despite progress in induction and maintenance therapy in ANCA-associated vasculitis (AAV), relapses remain the main challenge in this disease with a rate above 50%. Few data exist on the clinical features of those relapses. Our goal was to investigate the severity of relapse events (RE) and their mode of presentation in patients with AAV.

Methods: Patients from a single center diagnosed with AAV – granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA) and microscopic polyangiitis (MPA) – between 1990 and 2014, and experiencing at least one relapse according to Hellmich and al (Ann Rheum Dis 2007; 66: 605-17), were retrospectively investigated. The different organ involvements were registered during each relapse. Presentation at onset and RE were compared for each patient. The BVAS was used to assess the activity of each relapse. Statistical analysis was performed using SAS v9.4. Chi-square test of McNemar and Student test were used on paired time series to compare the proportions, and to compare mean values between initial onset and relapses respectively.

Results: Ninety-nine patients with AAV were followed in our centre: 53 patients (30 male/23 female, mean age at diagnosis 58,2 years old [49-70]) experiencing at least one relapse during their follow-up were included – 38 GPA patients (72%), 3 MPA (6%), 12 EGPA (22%) – with a total of 96 RE. The rate of RE in our series was 53% with a median time of follow-up of 81.5 months (36-130). The mean time to first RE after initial onset was 25 months. The distribution of patients was as followed: thirty patients experienced one single RE, 14 had 2, 5 had 3, 2 had 4 and 2 had respectively 7 and 8. Fifty-five percent of relapse events had the same initial organ as initial onset. Compared to initial onset, some clinical manifestations were less present: general symptoms (30% vs 69%, $p<0.0001$) including fever and weight loss; ear-throat-nose (ETN) (53% vs 81%, $p<0.0001$) including sinusitis, chondritis and conductive hearing loss; lung involvement (59% vs 74%, $p=0.0071$), with nodules (28% vs 44%, $p=0.00071$), interstitial infiltrates (13% vs 32%, $p=0.004$), pleural effusion (3% vs 12%, $p=0.014$) and alveolar hemorrhage (7% vs 27%, p=0,0002); peripheral neuropathies (7% vs 18%) and cranial nerves involvement (5% vs 20%) (p=0,0007); joints with arthritis or arthralgia alone. Moreover, some organs involvement known as being associated with a worse prognosis at initial onset were significantly less present: kidney with hematuria, proteinuria and acute kidney injury; heart but mostly related to pericarditis (1% vs 22%, $p<0.0001$), myocarditis being rare (2% vs 3%). Skin, eye and bowel manifestations were not significantly less involved during relapse events, as well as nasal crusting and ulcers, and bloody nasal discharge. The mean BVAS at initial onset was 9,47 (6-11) and 5,09 (3-6) at relapse ($p<0,0001$). Among the 96 relapse events, 44 (45.8%) had a new organ involvement compared to initial onset. None of these new manifestations were life-threatening.

Conclusion: Our study suggests that global activity of RE in AAV patients is significantly lower than on initial onset. Fewer organs seem to be involved in relapses, as shown by the decrease of the BVAS between diagnosis of the AAV and the RE. This probably reflects the effect of the follow-up visits. RE turn out to begin with the same manifestations as initial onset in most of cases which could facilitate early recognition of relapses.

Disclosure: R. Outh, None; **A. Lemaire**, None; **A. Mania**, None; **P. Berland**, None; **M. Andre**, None; **O. Aumaître**, None.

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Abstract Number: 1928

Treatment of ANCA Associated Vasculitis in the Very Elderly

Omer Ali[1], Kelly Ameneshoa[2], Maire Condon[1], Sanjeev Patel[3], Bhrigu Sood[2], David Makanjuola[1] and Fiona Harris[2], [1]Renal, St Helier hospital, London, United Kingdom, [2]St Helier hospital, London, United Kingdom, [3]Rheumatology, St Helier University Hospital, London, United Kingdom

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Background/Purpose: Anti-neutrophil cytoplasmic antibody associated vasculitis (AAV) are a group of disorders predominantly affecting older patients and frequently presenting with acute kidney injury. Despite the improvements made in treating these disorders, appropriate treatment strategies in the very elderly (above the age of 80) remain undefined, as the majority of clinical trials have excluded this age group and therefore it is still unclear whether the benefits of immunosuppression outweigh the risks.

Methods: We retrospectively examined 31 cases who presented with AAV and acute kidney injury in individuals aged >80 between 2006 to 2015 with a mean follow up of 39 months

Results: 32% were PR3 positive, 58% MPO positive and 10% negative. Mean creatinine at presentation was 367 mmol/L and 48% required acute dialysis on presentation. 68% of patients were treated with Cyclophosphamide as induction therapy while 16% received Azathioprine and steroids. Infection was documented in 33% of patients. Survival rate at one year was 76% and the incidence of end-stage kidney disease was 52%.

Number	31
Age	83 ± 2.7
Female	66.7%
Ethnicity: White Asians	94% 6%
Mean creatinine at presentation (µmol/l)	367
Dialysis at presentation	48%
Plasma exchange	22%
Induction Cyclophosphamide and steroids Azathioprine and steroids None	68% 16% 16%
Maintenance: Azathioprine and Steroids Mycophenolate Mofetil and steroids Steroids only None	32% 12% 26% 30%
Patient survival 1 year	76%
Renal Survival 1 year	52%

Conclusion: The results of this study show that a significant percentage of the very elderly patients can benefit from immunosuppresion therapy for AAV, despite the higher risks of adverse effects from these medications. However the precise details of what to give and for how long remains unclear.

Disclosure: O. Ali, None; **K. Ameneshoa**, None; **M. Condon**, None; **S. Patel**, None; **B. Sood**, None; **D. Makanjuola**, None; **F. Harris**, None.

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Abstract Number: 1929

Comparison of Two Different ANCA Iif Methods with EIA and Disease Phenotype

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Background/Purpose: ANCAs are used as diagnostic markers in patients with autoimmune vasculitis such as Granulomatosis with polyangitis (GPA), Microscopic polyangitis (MPA), and Eosinophilic granulomatosis with polyangitis (EGPA). Technique in laboratory testing for ANCAs differs among different centers. The purpose of this study is to compare two different techniques of IIF with enzyme immunoassay (EIA) and disease phenotype, specifically GPA.

Methods: Patient charts from a single tertiary medical center between August 2014 to August 2015 were retrospectively reviewed to identify occurrences in which two different methods of ANCA's by IIF (method A and B) were completed as well as ANCA by EIA on the same day. Method A: IIF first screens samples on two slides, one with ethanol-fixed human neutrophils, and one with formalin-fixed human neutrophils, before determining the titer by ethanol fixation. Method B first performs automated EIA testing for MPO and PR3 antibodies (Abs) with a reflex to IIF if the MPO or PR3 Abs is equivocal or positive (> 0.4 U). Detection of ANCA is performed by IIF using slides coated with ethanol-fixed human neutrophils. Disease phenotype correlations were limited to GPA since c-ANCA and PR3 Abs are relatively specific for this disease. Correlations were determined by phi coefficient (Φ) and measures of significance determined by Fisher's Exact Test.

Results: Fifty two patients had ANCA IIF testing done by two different established methods, A and B, on the same day. The correlation of c-ANCA by Method A IIF to PR3 Abs by EIA resulted in Φ of 0.609 ($p = <0.0001$) compared to Φ of 0.7025 ($p<0.0001$) when comparing Method B. The correlation of p-ANCA by method A IIF to MPO Abs by EIA resulted in Φ of 0.3578 ($p=0.0166$) compared to Φ of 0.4548 ($p=0.0019$) when comparing Method B. Correlation of c-ANCA by method A IIF to GPA disease phenotype resulted in a Φ of 0.2807 ($p= 0.0945$) compared with Φ of 0.3933 ($p= 0.0101$) when comparing Method B.

Conclusion: When comparing two different ANCA testing methods, Method B, in which IIF is done only after a positive EIA and only with ethanol fixation, appears to have a stronger concordance with PR3 and MPO Abs as determined by EIA as well as disease phenotype. Limitations of this study included the small number of patients, and the technician dependent nature of IIF technique. A follow up study may consider using a larger number of patients.

Disclosure: P. Bhadbhade, None; **M. Maz**, None; **L. Tilzer**, None; **F. Plapp**, None; **J. Springer**, Vasculitis Foundation, 9,Genentech and Biogen IDEC Inc., 9.

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Abstract Number: 1930

Factors Associated with Glucocorticoid Exposure in ANCA-Associated Vasculitis

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Background/Purpose: Factors associated with cumulative glucocorticoid exposure in granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) have not previously been described. We examined the association between baseline characteristics and cumulative glucocorticoid dose in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial comparing rituximab (RTX) with cyclophosphamide (CYC) followed by azathioprine for severe ANCA-associated vasculitis.

Methods: All patients received at least one 1000 mg dose of intravenous methylprednisolone prior to the initiation of prednisone at 1 mg/kg. Prednisone was reduced to 40 mg/day by 1 month and tapered off by month 6 but could be restarted or increased in response to persistent or increased disease activity. For this analysis, cumulative glucocorticoid doses were calculated monthly during induction (months 0-6) and maintenance (months 7-18). Prednisone and intravenous methylprednisolone were considered separately and when combined. The associations between baseline characteristics and cumulative dose were examined using generalized estimating equations to estimate mean differences and 95% confidence intervals (CI) over time after adjusting for potential confounders. Logistic regression was used to estimate odds ratios for achievement of glucocorticoid-free maintenance, defined as the absence of any glucocorticoid received from month 6 until study discontinuation.

Results: Mean ± SD cumulative prednisone dose was 3458 ± 806 mg at month 6 and 3771 ± 1044 mg at month 18. 89 patients (45%) achieved glucocorticoid-free maintenance. During the maintenance phase, relapsing disease (adjusted mean difference +324 mg over 12 months versus new diagnosis, 95% CI 56 to 592) and overweight or obese body mass index (BMI) (+397 mg, 95% CI 137 to 659) were associated with increased cumulative prednisone dose. In multivariate logistic regression, anti-proteinase 3 (PR3) antibody positivity (OR 0.50, 95% CI 0.26 to 0.97) was associated with decreased odds for achievement of glucocorticoid-free maintenance. Treatment with RTX was associated with decreased cumulative prednisone dose in comparison with CYC during induction (adjusted mean difference -251 mg over 6 months, 95% CI -411 to -91) but not during maintenance (+107 mg over 12 months, 95% CI -189 to +402).

Conclusion: In this clinical trial of GPA or MPA with protocol-defined glucocorticoid tapering, relapsing disease and increased BMI were associated with increased glucocorticoid exposure following induction of remission. PR3 positivity was associated with decreased likelihood of achieving glucocorticoid-free remission. Induction treatment with RTX was associated with a minimal mean decrease in prednisone exposure during induction only. These findings may allow for the prospective identification of patients with GPA or MPA at increased risk for chronic glucocorticoid exposure and toxicity.

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Abstract Number: 1931

MRI Findings in Granulomatosis with Polyangiitis: Pachymeningitis and Implications in Quality of Life

Violeta Higuera-Ortiz[1], Natllely Ruiz[1], Daniel Carrillo[2], Abraham Reynoso[2], Rosa Delia Delgado-Hernández[2] and **Luis F. Flores-Suarez**[1], [1]Primary Systemic Vasculitides Clinic, Instituto Nacional de Enfermedades Respiratorias, Mexico City, Mexico, [2]Radiology and Molecular Imaging, Instituto Nacional de Ciencias Médicas y Nutrición, Mexico City, Mexico

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Background/Purpose: The frequency of CNS involvement in granulomatosis with polyangiitis (GPA) is uncommon (4-18%). Among them, pachymeningitis (PM) has been reported in 0.6-8%. Improvement of these complications has been reported with conventional therapy (CS + CYC), and recently with rituximab, but many patients have recurrences. Data on related factors, outcome and quality of life is scarce. We preliminarily describe CNS involvement as investigated with MRI, PM presence in symptomatic and asymptomatic patients with GPA, and its implications for quality of life.

Methods: Forty consecutive GPA patients fullfiling the ACR criteria and/or the 2012 Chapel Hill Consensus Conference definition were studied. After informed consent, gadolinium-enhanced brain MRI in search of PM, irrespective of CNS symptoms, was done. The presence of diffuse or focal meningeal enhancement was necessary for PM diagnosis. Main subgroups for analysis were formed according to two main criteria: PM on MRI, and CNS symptoms presence or absence. They were compared regarding clinical, serological, neuroimaging and treatment-related findings. Functional status was assessed with the Short Form 36 (SF-36) health survey and Karnofsky Performance Scale Index. Univariate analysis was used to establish proportions with means ± SD and medians calculated; bivariate analysis was used to compare groups, Student's t test for continuous variables and X^2 test with Yates correction for categorical variables. Significance was established when $p<0.05$.

Results: Ten patients had generalised disease, the rest localised. Age range was 8-72 years old. Main differences regarding PM and CNS symptomatology as related to MRI findings are shown in the table.

Significant differences according to presence of CNS symptoms			
Variable	Symptomatic (n-20)	Asymptomatic (n-20)	p value
Cranial nerve palsy	5/20	0/20	<0.009
PM	13/20	6/20	0.05
Severely active disease *	9/20	0/20	0.001
Remission (at time of MRI)	3/20	17/20	0.001
Visual analogue scale (VAS) ♯	3.61 ± 2.3	0.6 ± 1.2	<0.009
Significant differences according to PM in MRI			
Variable	PM present (n-19)	PM absent (n-21)	p value
Cranial nerve palsy	5/19	0/21	0.02
Myalgias	4/19	0/21	0.04
Severely active disease	9/19	0/21	<0.009
Remission	4/19	15/21	0.003
BVAS-WG ♯	2.7 ± 2.7	0.1 ± 0.5	0.002
SF-36 §	21.5 (0-65)	50 (43-60)	0.001
Subglottic stenosis (SGS)	3/19	14/21	0.002

* Defined as that compromising life or vital organ function; ♯ mean values ± SD; § median values (intervals)

Conclusion: We found PM in 19/40 cases (47.5%) and irrespective of symptoms it was present in 1/3 of cases. Its cause (active disease or chronic inflammation, possibly due to fibrosis) is difficult to discern. Therefore, optimal therapeutic measures are unknown. Although the majority of patients had localised -predominant upper airway and ocular- disease, SGS had developed in a minority of patients with PM. This may suggest that operative mechanisms differ in both locations, and although scarring has been considered to play a role in PM in GPA, it might not be exclusive. Certain features relate straightforwardly to better health status, but in those asymptomatic PM patients, we found lower SF-36 scores, implying impaired quality of life. That PM occurs frequently in localised disease does not mean less severity than generalised malady. Although limited by the small sample size, CNS involvement detection in GPA, even in absence of symptoms, could be useful as impairment in quality of life may occur. Further research on this issue is warranted, with proper placement of early neuroimaging.

Disclosure: V. Higuera-Ortiz, None; **N. Ruiz**, None; **D. Carrillo**, None; **A. Reynoso**, None; **R. D. Delgado-Hernández**, None; **L. F. Flores-Suarez**, None.

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Abstract Number: 1932

Precapillary Pulmonary Hypertension in Granulomatosis with Polyangiitis: A Case Series with Long-Term Follow-up

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Background/Purpose: A few isolated case reports of precapillary pulmonary hypertension (PH) in ANCA-associated vasculitides, mostly granulomatosis with polyangiitis (GPA), have been published. The characteristics and outcomes of PH–GPA patients entered in the FVSG database were analyzed.

Methods: GPA patients with precapillary PH were included from this series. GPA diagnosis was based on ACR classification criteria or the revised Chapel Hill Conference Consensus (CHCC) nomenclature. Patients with connective tissue disease or undergoing hemodialysis were excluded. Chronic thromboembolic pulmonary hypertension required appropriate investigations to be excluded. Precapillary PH was defined as mean pulmonary arterial pressure (mPAP) ≥25 mm Hg at rest, with mean pulmonary capillary wedge pressure (PCWP) ≤15 mm Hg, measured during right heart catheterization (RHC).

Results: Among the 1065 GPA patients entered in the database, 3 male (0.3%) had precapillary PH; mean age, 43.1 years. All had systemic GPA according to the revised CHCC nomenclature and ACR criteria. Precapillary PH was diagnosed 4 years before GPA in 1 patient and after an average of 1.8 years for the others. All patients had NYHA III dyspnea and confirmed precapillary PH at RHC. In 1 patient, lung biopsy showed histological evidence of granulomatous vasculitis, and arteriolar and venous involvement; a ventilation–perfusion scan detected multiple perfusion defects consistent with thromboembolic disease that was ruled out by pulmonary angiography showing poor peripheral perfusion with a typical “dead tree” aspect, likely due to small-vessel vasculitis. At PH diagnosis, in combination with high-dose glucocorticoids, cyclophosphamide or rituximab was continued in 1 patient each. PH treatment was prescribed only in the patient with preexisting PH who received continuous epoprostenol infusions. Repeat RHC showed significant clinical and hemodynamic improvement in the 3 patients; their mean mPAP decreased from 51.6 (range, 41–70) to 33.0 mm Hg (range, 29–42). The patient with preexisting PH died of sepsis during GPA induction therapy. After treatment, in the patient with multiple ventilation–perfusion-scan defects, no change was observed. With median follow-up post-PH diagnosis of 4.2 years, the 2 other patients are alive, with NYHA class II dyspnea and in complete GPA remission, with median daily prednisone dose at 2.5 mg.

Conclusion: The data from this first series indicated that GPA can be a rare cause of precapillary PH. Lung small-vessel vasculitis is likely to be causative. GPA-caused precapillary PH may respond to combined high dose glucocorticoids and cyclophosphamide or rituximab.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/precapillary-pulmonary-hypertension-in-granulomatosis-with-polyangiitis-a-case-series-with-long-term-follow-up

Abstract Number: 1933

M2 Macrophage Is the Predominant Phenotype in Airways Inflammatory Lesions in Patients with Granulomatosis with Polyangiitis

Alexandre W.S. Souza[1], Mirjan van Timmeren[2], Jan-Stephan Sanders[3], Coen A. Stegeman[4], Peter Heeringa[5], Cees G.M. Kallenberg[6] and Johanna Westra[6], [1]Universidade Federal de São Paulo, São Paulo, Brazil, [2]University of Groningen, Groningen, Netherlands, [3]University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [4]Nephrology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [5]Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [6]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands

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Background/Purpose: Macrophages may present two main phenotypes indicated as M1 and M2 under different stimuli. M1- and M2-macrophages have divergent functions that range from enhancement of inflammation for M1- to tissue repair and remodeling for M2-macrophages. The balance between tissue M1- or M2-macrophages is variable in different diseases, depending on the pathophysiological process. Granulamatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis that mainly affects the respiratory tract and kidneys. Necrotizing granulomatous inflammation is the hallmark of airways involvement in GPA. The objective of this study is to evaluate the distribution of M1- and M2-macrophage phenotypes in biopsies from the airways of patients with active GPA and to analyze their associations with T- and B cells in those biopsies as well as with nasal carriage of *Staphylococcus aureus*, disease parameters and therapy.

Methods: Thirty-five consecutive patients with GPA and active disease involving the airways who underwent a biopsy from the respiratory tract were included in this cross-sectional study. Immunohistochemistry was performed to assess the distribution of macrophages, T- and B cells using the markers CD68, CD3 and CD20, respectively. CD86 was used as M1 marker and CD163 as M2 marker. All slides were scanned and the expression of all markers was quantified in percentage by the positive pixel count algorithm.

Results are expressed as median percentage and interquartile range or as mean percentage and standard deviation. At the time of the biopsy, GPA patients were assessed for nasal carriage of *Staphylococcus aureus* and treatment. Results: Percentages of macrophages and T cells were significantly higher than that of B cells in the respiratory tract from GPA patients [8.9% (6.4-17.4) vs. 7.4% (5.2-12.4) vs. 4.3 (2.4-8.4); $p < 0.0001$]. M2 macrophages were more frequent than M1 macrophages [18.2% (9.2-30.5) vs. 32.4 (21.3-41.9); $p = 0.0007$]. Percentages of T cells were higher in nose biopsies than in biopsies from other sites [8.3% (6.0-15.1) vs. 5.2 (3.0-6.5); $p = 0.021$] whereas macrophages were more predominant in biopsy sites other than the nose [20.7% (7.2-29.6) vs. 8.4% (6.3-13.6) $p = 0.039$]. Carriage of *Staphylococcus aureus* was associated with higher T cell scores [10.5% (6.6-15.4) vs. 5.9% (4.8-7.4) $p = 0.014$]. The frequency of macrophages, especially M2 macrophages, was higher in GPA patients treated with immunosuppressive agents [44.4% ± 18.3 vs. 29.8% ± 13.2; $p = 0.010$), whereas daily prednisolone dose was positively correlated with all macrophage markers as follows: CD68 (rho = 0.858; $p = 0.001$), CD86 (rho = 0.753; $p = 0.012$) and CD163 (rho = 0.759; $p = 0.011$). However, in multivariate analysis no independent associations were found between disease parameters or

therapy and macrophages or T cells.

Conclusion: In GPA patients, M2 is the predominant macrophage phenotype in the respiratory tract. Although some associations were observed between macrophages and T cells with therapy and nasal carriage of *Staphylococcus aureus*, they were not independent from other factors in multivariate analysis.

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Abstract Number: 1934

Cutaneous Manifestations of ANCA-Associated Vasculitis

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Background/Purpose: The cutaneous manifestations of anti-neutrophil cytoplasmic antibody-associated vasculitis (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA), are varied and have not been well characterized. This study aimed to describe the spectrum and extent of dermatologic features of AAV.

Methods: A large, cross-sectional study describing, comparing, and contrasting the cutaneous manifestations of GPA, MPA, and EGPA was performed using data from the Diagnostic and Classification Criteria in Vasculitis (DCVAS) study. The DCVAS study is a large, international, collaborative effort to collect comprehensive clinical data on a large cohort of patients with vasculitis with a goal of developing new classification and diagnostic criteria.

Results: Data from 1274 patients with AAV from 130 centers worldwide were available for this study: 702 (55%) with GPA, 331 (26%) with MPA, and 241 (19%) with EGPA. Cutaneous findings were common in patients with AAV (Table 1), affecting 239 (34%) patients with GPA, 97 (29%) patients with MPA, and 113 (47%) patients with EGPA. The most frequent cutaneous manifestations in each type of AAV were as follows: GPA: petechiae or purpura (N=113; 16%), painful skin lesions of any type (N=66; 9.4%), and maculopapular rash (N=47; 6.7%); MPA: petechiae or purpura (N=33; 10%), livedo reticularis or racemosa (N=25; 7.6%), and maculopapular rash (N=20; 6.0%); and EGPA: petechiae or purpura (N=50; 21%), maculopapular rash (N=36;

15%), pruritus (N=30; 13%), and urticaria (N=19; 7.9%).

Conclusion: This is the largest study of cutaneous manifestations of AAV ever conducted. Utilizing data collected comprehensively via a standard protocol, it demonstrates that skin lesions are quite common and varied in GPA, MPA, and EGPA. Future analyses will focus on examining the association of specific cutaneous manifestations of AAV with other organ system involvement and laboratory findings. Table 1. Cutaneous findings among patients with ANCA-associated vasculitis

GPA N = 702 MPA N = 331 EGPA N = 241 p-value Male, N (%) 352 (50%) 144 (44%) 124 (51%) 0.09 Age, mean (SD) 53 (16) 64 (14) 54 (15) <0.001 PR3-ANCA, N (%) 515 (74%) 22 (6.7%) 10 (4.2%) <0.001 MPO-ANCA, N (%) 66 (9.4%) 286 (86%) 89 (37%) <0.001 Cutaneous Findings, N (%) 239 (34%) 97 (29%) 113 (47%) <0.001 Pruritus 26 (3.7%) 10 (3.0%) 30 (13%) <0.001 Painful skin lesions 66 (9.4%) 16 (4.8%) 24 (10%) 0.03 Cutaneous infarct 12 (1.7%) 1 (0.3%) 5 (2.1%) 0.10 Petechiae / purpura 113 (16%) 33 (10%) 50 (21%) <0.001 Maculopapular rash 47 (6.7%) 20 (6.0%) 36 (15%) <0.001 Livedo reticularis 4 (0.6%) 19 (5.7%) 4 (1.7%) <0.001 Livedo racemosa 2 (0.3%) 6 (1.8%) 1 (0.4%) 0.03 Non-tender nodules 8 (1.1%) 5 (1.5%) 5 (2.1%) 0.56 Tender nodules 21 (3.0%) 6 (1.8%) 4 (1.7%) 0.36 Gangrene 11 (1.6%) 4 (1.2%) 4 (1.7%) 0.91 Splinter hemorrhage 11 (1.6%) 1 (0.3%) 6 (2.5%) 0.06 Ulcer 30 (4.3%) 5 (1.5%) 10 (4.2%) 0.07 Urticaria 5 (0.7%) 2 (0.6%) 19 (7.9%) <0.001 Other 33 (4.7%) 15 (4.5%) 14 (5.8%) 0.75

ANCA: anti-neutrophil cytoplasmic antibody-associated vasculitis; SD: standard deviation; PR3: proteinase 3; MPO: myeloperoxidase; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosis with polyangiitis.

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Hypertrophic Pachymeningitis in a Population with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Retrospective Study in a Single Japanese Institution

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Background/Purpose: Hypertrophic pachymeningitis (HP) is an inflammatory disorder causing focal and diffuse thickening of the dura mater. It is realized that anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) contributes to the development of HP, whereas the epidemiologic and clinical characteristics of patients with HP in the whole population of AAV are still uncertain. In this study, we demonstrated the characteristics of patients with HP compared with those of patients without HP in AAV.

Methods: We retrospectively investigated the clinical records of 39 Japanese patients with AAV (18 men and 21 women). Among them, patients with associated HP were detected. To determine the characteristics of HP in AAV, the epidemiological and clinical data from patients with HP were statistically compared with those from patients without HP.

Results: Of 39 patients with AAV, 7 (17.9%) had associated HP. All patients with HP were classified as having granulomatosis with polyangiitis (GPA), whereas only 5 of 32 patients without HP were diagnosed as having GPA ($P < 0.0001$) (Table 1). The frequencies of myeloperoxidase (MPO)-ANCA and proteinase 3-ANCA positivity in patients with HP were equivalent, while MPO-ANCA positivity was obviously dominant in patients without HP. HP occurred as the initial clinical episode of AAV in 3 patients (7.7% of all AAV). Frequent significant characteristics of patients with HP were headache, cranial neuropathy, and paranasal involvement ($P < 0.05$), and histopathological findings from paranasal involvement were useful for the diagnosis of GPA in some patients with HP. Combination therapy of corticosteroid and an immunosuppressant, such as methotrexate, cyclophosphamide, or rituximab, was effective for achieving remission and improving radiographic findings of HP.

Conclusion: To our knowledge, this is the first study that has described the epidemiological analyses of HP in the whole population of AAV. We conclude that the epidemiological features of AAV patients with HP are different from those of patients without HP. The geographical studies of AAV indicated that the predominance of microscopic polyangiitis and MPO-ANCA positivity as epidemiologically specific to Japan, whereas GPA and PR3-ANCA positivity are dominant in European countries. However, the epidemiology of patients with HP is similar to that of patients in European countries. In addition, HP impacts the diagnosis of AAV because it could be an initial clinical sign of disease as well as associated with frequent existence of granulomatous lesions in the respiratory tract.

Table 1. Characteristics of AAV patients with and without HP

	With HP (n = 7)	Without HP (n = 32)	*P* value※
Male : female	3 : 4	15 : 17	0.591
Age, year	67 ± 10	60 ± 13	0.180
Classification of AAV			
MPA (%)	0	24 (75.0)	**< 0.0001**
GPA (%)	7 (100)	5 (15.6)	**< 0.0001**
EGPA (%)	0	3 (9.4)	0.502
MPO-ANCA positive (%)	3 (42.9)	24 (75.0)	0.114
PR3-ANCA positive (%)	3 (42.9)	4 (12.5)	0.094
CRP, mg/dL	6.8 ± 6.6	7.6 ± 6.2	0.884
BVAS	13.7 ± 6.0	19.9 ± 9.1	0.081
Symptoms			
General symptoms (%)	4 (57.1)	23 (71.9)	0.917
Cutaneous (%)	1 (14.3)	11 (34.4)	0.289
Mucous membrane and eyes (%)	2 (28.6)	4 (12.5)	0.290
ENT (%)	6 (85.7)	9 (28.1)	**0.008**
Chest (%)	4 (57.1)	18 (56.3)	0.952
Cardiovascular (%)	0	3 (9.4)	0.543
Abdominal (%)	0	4 (12.5)	0.437
Renal (%)	3 (42.9)	17 (53.1)	0.225
Nervous system (%)	7 (100)	17 (53.1)	0.060
Headache (%)	6 (85.7)	2 (6.3)	**< 0.0001**
Seizure (%)	2 (28.6)	1 (3.1)	0.077
Consciousness disturbance (%)	1 (14.3)	2 (6.3)	0.467
Cerebrovascular event (%)	0	4 (12.5)	0.764
Cranial neuropathy, total (%)	5 (71.4)	5 (15.6)	**0.007**
Sensory peripheral neuropathy (%)	1 (14.3)	13 (39.4)	0.237
Mononeuritis multiplex (%)	0	13 (39.4)	**0.043**

AAV, ANCA associated vasculitis; MPA, microscopic polyangiitis; GPA, granulomatosis with polyangiitis; EGPA, eosinophilic granulomatosis with polyangiitis; BVAS, the Birmingham Vasculitis Activity Score; ENT, ear, nose, and throat; The variable data are shown as mean ± SD (standard deviation).
※Data between two groups were compared by using Mann-Whitney U-test and Chi square for independent test.

Disclosure: Y. Shimojima, None; **D. Kishida**, None; **A. Hineno**, None; **M. Yazaki**, None; **Y. Sekijima**, None; **S. I. Ikeda**, None.

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Clinical Characteristics of Inflammatory Eye Disease in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Retrospective Cohort Study

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Clinical Characteristics of Inflammatory Eye Disease in Patients with Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis: A Retrospective Cohort Study

Background/Purpose: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a systemic small vessel vasculitis characterized by presence of cytoplasmic-ANCA or perinuclear-ANCA, that can virtually affect any organ system. Inflammatory eye disease (IED) is a well-recognized manifestation of AAV though the data on its clinical characteristics and outcome are limited.

Methods: Medical records of 501 patients with AAV seen at our institution were reviewed. Data on demographics, ophthalmologic manifestation, laboratory investigations, treatment (ocular and systemic), disease activity, systemic organ involvement, and outcomes were abstracted. Descriptive statistics were used to summarize the data.

Results: 77 patients (mean age 50.1 years; 52% female; 96% Caucasian) with median follow-up of 6.1 years had IED. Proteinase-3 (PR-3) serology was positive in 39 patients (51%); myeloperoxidase (MPO) serology was positive in 24 patients (31%) and ANCA serology was negative in 14 patients (28%). IED was one of the initial manifestations leading to diagnosis of AAV in the majority of patients (68%) with median time from IED to diagnosis of AAV of 1.6 months. IED occurred after the diagnosis of AAV in about one-third of patients with median time from diagnosis of AAV to IED of 41.2 months. Mean Birmingham Vasculitis Activity Score (BVAS) during active IED was 6.0. Mean erythrocyte sedimentation rate during active IED was 41.8 mm/hr. Episcleritis was the most common type of IED (17%) followed by scleritis (14%), orbital inflammation (orbital pseudotumor/orbital myositis) (12%), cranial nerve III, IV or VI palsy (12%), conjunctivitis (9%), optic neuritis

(8%), amaurosis fugax (8%), uveitis (5%), lacrimal duct stenosis (5%), peripheral ulcerative keratitis (4%), retinal vasculitis (4%) and dacryoadenitis (4%). The most common manifestation of IED was redness (49%) followed by eye pain (35%), visual acuity loss (27%; gradual visual acuity loss 17% and sudden visual acuity loss 10%), diplopia (19%), and photophobia (13%). IED occurred bilaterally in 52% of patients. Oral glucocorticoids were used to treat IED in the majority of patients (91%) while topical glucocorticoids were used in 31%. Cyclophosphamide was the most frequently used immunosuppressive agent (53%) followed by methotrexate (34%), rituximab (26%), azathioprine (26%), mycophenolate (9%) and intra-orbital glucocorticoid injection (6%) in patients with orbital pseudotumor/orbital myositis. Complete remission was achieved in 94% of patients. However, relapse was common (18%). The median number of relapses was 1 during the period of observation.

Conclusion: IED occurs in about 15% of patients with AAV. Episcleritis, scleritis, orbital inflammation and cranial nerve palsy were the most common subtypes of IED. Inflammation from IED responded well to treatment although relapse was common.

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Abstract Number: 1937

Analysis of Innate and Adaptive Immune Responses in Eosinophilic Granulomatosis with Polyangiitis (Churg-Strauss)

Jeremie Dion[1,2], Jonathan London[2,3], Benjamin Chaigne[2,4], Nicolas Dumoitier[2], Bertrand Dunogué[5], Pascal Cohen[3], Matthieu Groh[4], Claire Le Jeunne[4], Luc Mouthon[2,5] and Benjamin Terrier[2,5], [1]Internal medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [2]INSERM U1016, Institut Cochin, Equipe Neutrophiles et Vascularites, Paris, France, [3]Internal Medecine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [4]National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [5]Internal Medicine, National Referral Center for Rare Systemic Autoimmune Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France

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Background/Purpose: Eosinophilic granulomatosis with polyangiitis (EGPA, formerly called Churg-Strauss syndrome) belongs to ANCA-associated vasculitis and is characterized by late onset asthma, blood and tissue eosinophilia and systemic symptoms. Studies on pathophysiology of EGPA are scarce, explaining the lack of specific targeted therapy. In the present study, we analyzed the implication of innate and adaptive immunity in

EGPA through a systematic phenotyping of T and B cells, type 2 innate lymphoid cell (ILC2) as well as cytokine profile in active and remission EGPA.

Methods: We included 15 patients with active EGPA, 8 patients in remission and 20 healthy controls (HC). B and T cells and type 2 innate lymphoid cells (ILC2) in peripheral blood were studied using flow cytometry. Cytokines and chemokines were assessed in sera from active EGPA (n=20), remission EGPA (n=25) and healthy controls (n=35), using Luminex® and ELISA.

Results: Compared to HC, overall EGPA patients had a significant increase of Th2 polarized (IL-4^+) $CD4^+$ T cells (3.6±3.8% *vs.* 1.1±1.3%, p=0.002) and a trend for increase of Th9 (IL-9^+) cells (0.81±0.86% *vs.* 0.40±0.52%, p=0.1) and Th17 (IL-17^+) $CD4^+$ T cells (1.5±1.1% *vs.*0.9±0.5%, p=0.056), no differences were observed between active and remission patients in these groups. T follicular helpers (TFH) were increased in patients (7.3±3.1% vs 4.5±1.5%, p=0.001) whereas regulatory CD4 T cells were decreased (0.75±0.4% vs 1.5±0.8%, p=0.02). B cells from EGPA patients displayed an activated profile compared to HC with a significant increase of CD95 expression (56±13% vs 27±2%, p<0.0001), CD86 (28±14% vs 12±12%, p<0.001) and CD69 (11±11% vs 1.9±1.8%, p<0.0001). B cells inhibition markers expression, i.e. CD72 and CD22, was lower in EGPA than in controls (60±23% vs 81±8% for CD72, p<0.01, and 74±22% vs 87±9% for CD22, p<0.01). Circulating ILC2 were significantly decreased in EGPA patients compared to controls (317±336 vs 563±284 cells/ml, p<0.05) and in active EGPA compared to remission (143±53 vs 491±415 cells/ml, p<0.05). Regarding serum cytokine profile, levels of soluble ST2 (469 ± 268 vs 288±102 pg/ml, p=0.002), IL-25 (302±405 vs 107±99 pg/ml, p=0.04), TSLP (5.6±5.9 vs 1.4±1.3 pg/ml, p=0.001) and TARC/CCL17 (1143±710 vs 709±287 pg/ml, p=0.05) were increased in EGPA compared to controls. Th2 cytokines were also more elevated in EGPA than in HC, including IL-5 (2.8±6 vs 0.53±0.11 pg/ml, p<0.0001) and IL-9 (1.6±2 vs 0.58±0.2 pg/ml, p=0.03). Th1-related cytokine IFN-γ was also elevated (2.1±0.8 vs 1.6±0.2 pg/ml, p=0.02) as well as Th17-related cytokine IL-17 (10.2±22 vs 1.3±0.4 pg/ml, p=0.03). In contrast, no differences were noted for serum IL-33.

Conclusion: EGPA patients are characterized by a Th2 polarization of T cell response and a trend for Th9 and Th17 polarization in peripheral blood, an activation of B cells and a dramatic decrease of blood ILC2 during active disease. This decrease could be explained by a recruitment of these cells within involved tissues. Increase of IL-25, TSLP and TARC as well as Th2-related cytokines in serum could illustrate the cross-talk between innate and adaptive immunity in this disease, in which ILC2 could play a central role.

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Bronchiectasis Are Highly Prevalent in Anti-MPO ANCA-Associated Vasculitis and Associate with a Distinct Disease Phenotype

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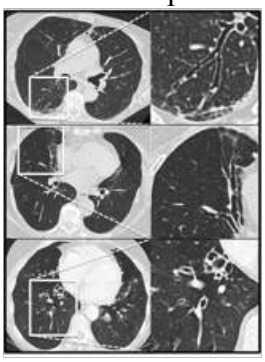
Background/Purpose: To assess the prevalence of bronchiectasis in a western cohort of ANCA positive GPA or MPA and its correlations with disease phenotype and outcome.

Methods: Retrospective study of AAV patients followed at Nantes University Hospital (2005-2015). Clinical, biological and follow-up data were collected through chart review. Chest High-Resolution CTs were interpreted by 2 experienced radiologists blinded to the clinical data, using Feischner Society criteria.

Results: Fifty eight patients were included, 30 patients had MPA (51,7%) and 28 patients had GPA (48,3%). Anti-MPO-ANCA and anti-PR3-ANCA were present in 39 (67,2%) had 19 (32,8%) patients, respectively. Overall, bronchiectasis were found in 22 patients (37,9%), all of whom had anti-MPO ANCA. Representative images from 3 patients are shown in Figure 1. In multivariate analysis, bronchiectasis were independently associated with anti-MPO-ANCA, female gender and age at AAV diagnosis. Further, anti-MPO ANCA patients with bronchiectasis had more frequent peripheral nerve involvement (54,5 vs 17,6%, p=0.019) and less frequent renal involvement than those without bronchiectasis (40,9% vs 82,3%, p=0,009). Disease course, survival and risk of severe pulmonary infection was similar in patients with/without bronchiectasis on chest CT.



Conclusion: Bronchiectasis is an underestimated pre-existing respiratory condition in Caucasian patients with anti-MPO AAV. This subset of patients exhibits a distinct phenotype but similar outcomes. Further studies are needed to confirm our findings and enlighten the clinical implications of this association. Whether the respiratory tract could be the site of initiation of anti-MPO auto-immunity remains to be investigated.

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Abstract Number: 1939

Immunologic, Clinical and Demographic Correlates in 51 Cocaine Users with Serum Anti-Neutrophil Cytoplasmic Antibodies

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Background/Purpose: Exposure to illicit cocaine and its frequent adulterant, levamisole, is associated with the development of serum anti-neutrophil cytoplasmic autoantibodies (ANCA) and a variety of hematologic, renal and skin abnormalities (e.g., thrombotic purpura). The mechanisms of cocaine/levamisole-associated autoimmunity (CLAA) are unknown but may involve drug-induced neutrophil activation. Most reports of CLAA have examined small cohorts (< 20 subjects) or have focused on select clinical abnormalities. In order to gain a fuller picture of CLAA and generate new hypotheses regarding pathogenesis, we analyzed a cohort of 51 CLAA subjects identified in a large, academic healthcare system between 2000 and 2015.

Methods: We queried an electronic database and rheumatology referral records for individuals with positive ANCA testing results (ANCA+) and evidence of cocaine exposure by urine toxicology (cocaine+). Individuals were excluded if they had biopsy-proven ANCA-associated vasculitis. Clinical and immunologic parameters were extracted from the electronic medical record. We compared rates of certain parameters with rates within the cocaine+ (n = 6,233) or ANCA+ (n = 310) populations in a de-identified clinical data repository (DCDR) using univariate (Chi square, Fisher's exact) and multivariate (logistic regression) analyses.

Results: Hematologic abnormalities were almost universal (94.1%), with anemia (84.3%), leukopenia (64.7%) and neutropenia (47.1%) the most frequently reported. Renal (74.5%), skin (58.8%) and musculoskeletal (37.3%) abnormalities were also common. When compared to the cocaine+ population, the CLAA group showed similar estimated age at first positive cocaine result (46.6 vs. 47.7 years), but it was more female (56.9% vs. 38.8%, $p = 0.0016$) and less African-American (19.6% vs. 37.5%, $p = 0.0130$). Among those tested, the CLAA group showed higher rates of anti-phospholipid Abs (ACLAs) (69% vs. 29.1%, $p < 0.0001$) and lupus inhibitor (LI) (80% vs. 34.9%, $p = 0.0002$) but not ANA (22.4% vs. 19.4%) or active HCV infection (46% vs. 52.7%). ANCA in CLAA subjects were generally high titer (often > 1:2048) and of P-ANCA pattern (60.8%). Compared to the ANCA+ population, the CLAA population had significantly higher rates of MPO/PR3 double-positivity (31.4% vs. 2.6%, $p < 0.0001$). Finally, multivariate logistic regression analysis identified a significant association in the CLAA population between anti-phospholipid Abs and skin abnormalities (OR 7.1, 95%CI 1.3 – 49.2).

Conclusion: CLAA subjects showed a variety of previously reported hematologic, skin and MSK abnormalities. However, results from our demographic analysis suggest that, in cocaine users, the development of ANCA and/or clinical abnormalities prompting ANCA testing are influenced by sex and race. Moreover, exposure to cocaine in this population may also lead to development of LI and APLAs, which could contribute to skin abnormalities such as thrombotic purpura. Finally, high-titer P-ANCA with double-positivity may help clinicians differentiate CLAA from other forms of ANCA-associated disease.

Abstract Number: 1940

High Prevalence of Inflammatory Heart Disease in Eosinophillic Granulomatosis with Polyangiitis (Churg Strauss) Patients

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Background/Purpose: To establish EGPA/Churg Strauss inflammatory heart disease prevalence and develop an algorithm for heart disease screening in EGPA patients.

Methods: An audit of all EGPA patients attending Addenbrooke's was performed. Clinical presentation, cardiac studies, disease outcome measures and clinical course was noted. Values are given as percentages and median (IQR). Mann Whitney U was used.

Results: 131 EGPA patients (47% men) were followed of whom 96 (73%) underwent cardiac evaluation. Median age was 50 years (38 - 58), 37% were ANCA +ve and asthma preceded diagnosis in most by a median of 97 months (36 - 240). 41 of those screened (43%) were symptomatic for heart disease with: dyspnoea (47%), chest pain (29%), limb oedema (24%), palpitations (13%), syncope (4%), abdominal discomfort (2%) and shock (2%). 27/96 (28%) patients had EGPA-related heart disease in 20 of whom this was present at EGPA diagnosis, 5 developed it at time of EGPA flare and it preceeded EGPA diagnosis in two,. 59% (24) of those who were symptomatic and 5% (3) of those who did not have cardiac symptoms had EGPA heart disease. 15% patients had myocarditis, 6% pericarditis, 5% myopericarditis and 1 coronary vasospasm. One patient with pericarditis also had periaortitis. Cardiac abnormalities of any sort were found in 52% patients. Patients who had EGPA heart disease were younger (46 [28 - 52] V 50 [41 - 59]; p = 0.04), more frequently ANCA-negative (85% V 69%; NS), had higher BVAS scores (3 [1 - 4] V 1 [0.75 - 2]; p = 0.005), had higher eosinophil counts (5.60 [1.44 - 11,57] V 1.60 [0.75 - 4.00] x10^9/L; p = 0.029) and higher CRP levels (52 [30 - 100] V 15 [5 - 81] mg/L; p = 0.017). Troponin I was determined in 33 patients and was elevated in 75% patients with EGPA inflammatory heart disease V 14% without (p = 0.001). Table 1 shows the percentage of cardiac abnormalities.

Conclusion: Twenty seven percent of EGPA patients have heart disease with 60% of those symptomatic for heart disease and 5% of those asymptomatic for it being affected. Our multiple comparisons suggest that EGPA patients with inflammatory heart disease have more aggressive systemic disease associated with higher markers of inflammation. All EGPA patients should have ECG, troponin and echocardiography as screening investigations with progression to cMRI for patients with heightened suspicion for cardiac disease. Table 1: Incidence of heart abnormalities in EGPA patients symptomatic and asymptomatic for heart disease. (n=100; 4 patients originally screened in the asymptomatic group later became symptomatic and were again tested)

	Evaluated patients (n=100)	Asymptomatic patients (n=55)	Symptomatic patients (n=45)	p
Detected abnormalities	52/100 (52%)	25/55 (45%)	27/45 (60%)	0.09
ECG	70/100 (70%)	40/55 (73%)	30/45 (67%)	
Minor	16/70 (23%)	6/40 (15%)	10/30 (33%)	0.17
Major	9/70 (13%)	0/40	9/30 (30%)	**<0.01**
Holter	11/100 (11%)	0/55	11/41 (24%)	
TTE	82/100 (82%)	49/55 (89%)	33/45 (73%)	
Pericardial effusion	9/82 (10%)	3/49 (6%)	7/33 (21%)	0.09
Diastolic dysfunction	23/82 (28%)	12/49 (25%)	11/33 (33%)	0.63
LVEF < 55%	10/82 (12%)	2/49 (4%)	8/33 (24%)	**0.02**
Wall motion abnormality	10/82 (12%)	3/49 (6%)	7/33 (21%)	
Global	6/82 (7%)	1/49 (2%)	5/33 (16%)	0.08
Regional	4/82 (5%)	2/49 (4%)	2/33 (6%)	1
Dilated cardiomyopathy	4/82 (5%)	1/49 (2%)	3/33 (9%)	0.31
Cardiomyopathy	5/82 (6%)	1/49 (2%)	4/33 (12%)	0.16
MRI	37/100 (37%)	12/55 (22%)	25/45 (56%)	
Pericardial effusion	6/37 (16%)	2/12 (17%)	4/25 (16%)	0.51
Diastolic dysfunction	3/37 (8%)	2/12 (17%)	1/25 (4%)	0.28
LVEF < 55%	10/37 (27%)	2/12 (17%)	8/25 (32%)	0.15
Wall motion abnormality	11/37 (30%)	3/12 (25%)	9/25 (36%)	0.64
Global	3/37 (8%)	0/12	3/25 (12%)	0.27
Regional	8/37 (29%)	2/12 (17%)	6/25 (24%)	0.45
Dilated cardiomyopathy	4/37 (11%)	1/12 (8%)	3/25 (12%)	0.64
Cardiomyopathy	10/37 (27%)	2/12 (17%)	8/25 (32%)	0.41
LGE	12/37 (32%)	2/12 (17%)	10/25 (40%)	0.09
Endocardium	8/37 (22%)	2/12 (17%)	6/25 (24%)	0.27
Myocardium	3/37 (8%)	2/12 (17%)	1/25 (4%)	0.58
Epicardium	0/37	0/12	0/25	

BVAS = Birmingham Vasculitis Activity Score, ECG = Electrocardiogram, cMRI = Cardiac Magnetic Resonance Imaging, LGE = Late gadolinium enhancement, LVEF= Left ventricle ejective fraction, TTE = Transthoracic Echocardiography. $p<0.05$ was considered significant difference between those symptomatic and asymptomatic for heart disease.

Disclosure: E. G. Vives, None; **L. Harty**, None; **D. Jayne**, None.

Abstract Number: 1941

Retrospective Survey of Concomitant Autoimmune Diseases and Autoantibodies in a Cohort of Patients with ANCA-Associated Vasculitis (AAV)

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Background/Purpose: Anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) - granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) have heterogenous clinic and biologic phenotypes. Sporadic reports indicate that some AAV patients may have other autoimmune diseases but the frequency of the association is unknown. Our purpose was to assess the frequency of other autoimmune diseases or autoantibodies in a well-defined cohort of AAV patients.

Methods: Retrospective survey of a cohort of patients regularly controlled at outpatient facility of an Autoimmune Disease Department in a 5-year period (2011-2016). Clinical and immunologic data were retrieved from electronic records. All patients were diagnosed and treated by the authors.

Results: We included 110 AAV patients – 36 (32.7%) GPA, 45 (40.9%) MPA and 29 (26.4%) EGPA. Manifestations with higher prevalence were: chest, ear-nose-throat (ENT), mucous membranes/eyes in GPA; renal in MPA, and chest, ENT, abdominal in EGPA. Regarding to ANCA specificity – 23 (20.9%) against proteinase 3 (PR3)-ANCA, 68 (61.8%) against myeloperoxidase (MPO)-ANCA and 19 (17.3%) were ANCA negative. An additional autoimmune disease (usually organ-specific) was identified in 52 patients (47.3%), 17 (32.7%) had more than one. Associated autoimmune diseases included hypothyroidism (19,17.3%), vitamin B12 deficiency (16,13.8%), Sjögren syndrome (8,7.3%), interstitial lung disease (4,3.6%), hyperthyroidism (3,2.7%), primary biliar cholangitis (3,2.7%), celiac disease (3,2.7%), autoimmune hepatitis (2,1.8%), autoimmune thrombocytopenia (2,1.8%), myositis (2,1.8%), cryoglobulinemia (2,1.8%), anti-GBM disease (1,0.9%), and vitiligo (1,0.9%). Autoantibodies detected with higher prevalence were: ASMA (65,59.1%), ANAs (54,49.1%), anti-parietal cells (26,23.6%), anti-peroxidase (14,12.8%), anti-thyroglobulin (7,6.4%), anti-SSa/Ro (5,4.5%), anti-SSb/La (3,2.7%) and anti-dsDNA (2,1.8%). Prevalence of organ-specific autoimmune disease was higher in MPA (29,64.4%,p=0.001). Vitamin B12 deficiency was also more prevalent in MPA (25.6%,p=0.008) and in MPO-ANCA (19.1%,p=0.005). Sjögren syndrome was more prevalent in MPA (11.1%,p=0.022). Some autoantibodies were detected with higher prevalence in MPA – ANAs (68.9%,p<0.001), anti-parietal cells (31.1%,p=0.005), anti-thyroglobulin (13.3%,p=0.044), anti-SSa/Ro (8.9%,p=0.015), anti-SSb/La (4.4%,p=0.044), anti-DNAds (4.4%,p=0.003); and in anti MPO carriers - ANAs (55.9%,p=0.039), anti-SSa/Ro

(7.4%,p=0.010), anti-SSb/La (4.4%,p=0.020), anti-DNAds (2.9%,p=0.046).

Conclusion: A substantial percentage of AAV patients, particularly MPA and anti MPO carriers, have associated autoimmune diseases and autoantibodies. The limitations of our study (retrospective assessment and lack of comparator) do not allow accurate estimation of prevalence. The severity of AAV and difficulties in management, may lead to overlooking of associated autoimmune diseases which appear to be frequent. Associated autoimmune disease may contribute to additional burden in AAV patients. (Supported by SAF 2014 57708-R).

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Abstract Number: 1942

Presentation and Clinical Features of ANCA-Associated Vasculitis in US African Americans: Experience from a Single Center

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Title: Presentation and Clinical Features of ANCA-associated Vasculitis in US African Americans: Experience From a Single Center

Background/Purpose: Little is known about the presentation, clinical features, and prognosis of ANCA-associated vasculitis (AAV)in non-Caucasian populations. More specifically, there is a paucity of studies in US African-Americans (AAs). Some studies have described that AA race as a predictor of resistance to treatment and relapse. Little else is known about how AAs present when affected by AAV. The objective of this study is to describe the clinical characteristics of AAV in AAs in comparison to Caucasians.

Methods: Retrospective cohort analysis of patients with AAV diagnosis vasculitis per ICD-9 codes (446.0, 446.4, 447.6) during a 12-year period (2003-2015). Variables analyzed included: sex, age, duration of symptoms, time to diagnosis, ANCA antibodies, serum creatinine and organ involvement based on BVAS score. Disease severity was assessed European Vasculitis Study Group definitions. Treatment agents (steroids, DMARDs, biologics) and requirement of renal replacement therapy were recorded. Caucasians controls were chosen randomly with a 2:1 ratio with AA individuals. Fisher's exact and Wilcoxon two-sample test were used

for the analysis categorical and continuous variables, respectively.

Results: 29 cases of AAV in AAs were confirmed. AAs were younger at the time of diagnosis (44.3 [31.0-55.0] vs 56.0 [50.0-68.0], p= 0.002). There were no differences in frequencies of AAV disease subsets, ANCA antibodies, disease severity, or most organ involvements between AAs and Caucasians (Tables 1-3). AAs with GPA had less disease severity as measured by the BVAS score (9.5 ±6.3 vs 14.5 ±7.5 p=0.03)

Conclusion: Few differences were found between US AAs and Caucasians with AAV. These included younger age at presentation and less disease severity in AAs with GPA. Even though generalizability of these results is limited by the small size and retrospective nature of this cohort, this is the first study that describes differences in AAV in AA individuals.

Table 1. Descriptive data of African-American vs Caucasian individuals at time of diagnosis of ANCA-associated vasculitis

	AA n = 29	*C n = 58*	*p*
Age (average)*	44.3 (31.0-55.0)	56.0 (50.0-68.0)	**0.002**
Sex			
Female	20 (69)	25 (43)	0.493
Duration of symptoms (median and range in months)**	8 (0.5 – 120)	5 (0.3 – 169)	
Time to diagnosis (median and range in weeks)**	2.5 (0.5 – 52)	2 (0.14 – 416)	
Diagnosis			0.174
GPA	15 (51.7)	40 (69)	
EGPA	1 (3.5)	3 (5.2)	
MPA	13 (44.8)	15 (25.8)	
Renal limited***	3 (23)	3 (20)	
ANCA			0.449
pANCA	11 (38)	19 (33)	
cANCA	10 (34)	28 (48)	
Negative	8 (28)	11 (19)	
Biopsy	14 (48)	31 (53)	0.233
Treatment			
Steroids	28 (100)	58 (100)	
DMARDS	25 (89.3)	38 (65.5)	**0.021**
Biologics	8 (28.5)	11 (19.0)	0.406
Dialysis	7 (26.9/0	6 (10.3)	0.099

GPA = Granulomatosis with Polyangiits. EGPA = Eosinophilic Granulomatosis with Polyangiitis. MPA = Microscopic with Polyangiitis
*Values expressed as median (lower quartile-upper quartile) **Values expressed as median (range) ***MPA renal limited disease compared to all patients with diagnosis of MPA.

Table 2. Demographics and disease states of African American and Caucasian individuals with diagnosis of ANCA vasculitis

	GPA			EGPA			MPA		
	AA n = 15	*C n = 40*	*p*	*AA n = 1*	*C n = 3*	*p*	*AA n=13*	*C n = 15*	*p*
Age (median)*	37.0 (25.0-47.0)	57.5 (48.5-67.5)	**0.002**	53	60 (59.0-61.0)	0.437	54 (45.0-63.0)	64 (51.0-72.0)	0.113
Sex									
Female	12 (80)	21 (52.5)	0.074	0 (0)	1 (33.3)	1.000	7 (53.9)	11 (73.3)	0.433
ANCA			1.000			1.000			0.340
cANCA	10 (67)	26 (65)		0 (0)	0 (0)		0 (0)	2 (13.3)	
pANCA	1 (7)	5 (13)		0 (0)	2 (66.7)		10 (77)	12 (80)	
Negative	4 (26)	9 (22)		1 (100)	1 (33.3)		3 (23)	1 (6.7)	
Anti-MPO	0 (0)	4 (10.0)	0.561	0 (0)	1 (33.3)	1.000	9 (81.8)	12 (80.0)	1.000
Anti-PR3	7 (50)	21 (51)	0.749	0 (0)	0 (0)		0 (0)	0 (0)	
Serum Creatinine (mg/dl)	1.6 ± 1.6	2.0 ± 2.3	0.163	0.8	2.5 ± 2.9	1.000	3.2 ± 4.2	2.2 ± 1.9	0.579
Disease severity**			0.641			1.000			0.331
Localized	5 (33.3)	7 (17.5)		0 (0)	0 (0)		0 (0)	0 (0)	
Early systemic	3 (20)	12 (30)		1 (100)	1 (33.3)		3 (23.0)	2 (13.3)	
Generalized	3 (20)	11 (27.5)		0 (0)	1 (33.3)		4 (30.8)	9 (60.0)	
Severe	4 (26.7)	10 (25)		0 (0)	1 (33.3)		6 (46.2)	4 (26.7)	

GPA = Granulomatosis with Polyangiitis. EGPA = Eosinophilic Granulomatosis with Polyangiitis. MPA = Microscopic with Polyangiitis
Values expressed as mean ± standard deviation or number (percentage). *Values expressed as median (lower quartile-upper quartile) **Disease Severity based on EUVAS Study Group Criteria.

Table 3. Disease activity and organ involvement in African American and Caucasian individuals with diagnosis of ANCA vasculitis

	GPA			EGPA			MPA		
	AA n = 15	*C n = 40*	*p*	*AA n = 1*	*C n = 3*	*p*	*AA n = 13*	*C n = 15*	*p*
BVAS	9.5 ±6.3	14.5 ±7.5	**0.025**	13	18.7 ± 5.7	0.437	13.9 ±5.5	15.6 ± 4.9	0.411
General	13 (86.7)	38 (95)	0.298	1 (100)	3 (100)	1.000	13 (100)	15 (100)	1.000
Cutaneous	1 (6.7)	8 (20)	0.418	1 (100)	0 (0)	0.250	1 (7.69)	2 (13.3)	1.000
Mucous membranes/eyes	1 (6.7)	8 (20)	0.418	0 (0)	0 (0)		0 (0)	2 (13.3)	0.484
Ear, nose and throat	5 (33.3)	27 (67.5)	**0.032**	0 (0)	3 (100)	0.250	0 (0)	0 (0)	
Pulmonary	8 (53.3)	21 (52.5)	1.000	1 (100)	2 (66.7)	1.000	9 (69.2)	7 (46.7)	0.276
Cardiovascular	0 (0)	0 (0)		0 (0)	0 (0)		1 (7.7)	0 (0)	0.464
Abdominal	0 (0)	1 (2.5)	1.000	0 (0)	0 (0)		0 (0)	3 (20)	0.226
Renal	6 (40.0)	21 (52.5)	0.547	0 (0)	3 (100)	1.000	10 (76.9)	10 (66.7)	0.686
Nervous System	2 (13.3)	4 (10.0)	0.660	1 (100)	3 (100)	1.000	1 (7.7)	3 (20)	0.600

GPA = Granulomatosis with Polyangiitis. EGPA = Eosinophilic Granulomatosis with Polyangiitis. MPA = Microscopic with Polyangiitis.
Values expressed as mean ± standard deviation or number (percentage).

Disclosure: S. Sattui, None; **A. Westfall**, None; **A. L. Gaffo**, None.

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Abstract Number: 1943

Factors Predictive of ANCA-Associated Vasculitis Relapse

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Background/Purpose: To identify associations between patients' clinical and biological characteristics at diagnosis of antineutrophil cytoplasmic antibody-associated vasculitides (AAVs), and their relapse during follow-up.

Methods: Long-term follow-up data from 5 FVSG prospective trials (CHUSPAN I, CHUSPAN II, CORTAGE, MAINRITSAN and WEGENT) were pooled. Relapses were defined as the recurrence and/or appearance of ≥1 new vasculitis manifestation(s) after remission lasting ≥3 months. For eosinophilic granulomatosis with polyangiitis (EGPA), relapses were defined as new appearance, recurrence or worsening of clinical EGPA manifestation(s) (excluding asthma and/or ENT), requiring the addition, change or dose increase of glucocorticoids and/or other immunosuppressants. Patient and disease characteristics at enrollment were entered into a competing-risks model (1), with relapse as the event of interest and death the competing event. Times to relapse and/or death were calculated from treatment onset and analyses were stratified for the randomization group in each trial. Univariate and multivariate analyses were computed.

Results: Patients with PAN (n=108) and those included during a relapse of a formerly diagnosed AAV (n=23) were excluded. Finally, the characteristics of 610 patients (183 EGPA, 203 granulomatosis with polyangiitis [GPA] and 224 microscopic polyangiitis [MPA]) were included in the analyses. Mean±SD follow-up was 74.6±50.5 months. At diagnosis, mean±SD age was 59.6±15.2 years and mean creatinine 154±164 µmol/L. Anti-proteinase–3 (PR3) and anti-myeloperoxidase (MPO) ANCA were detected in 170 (28%) and 244 (40%) patients, respectively; ANCA or ELISA were negative for 195 (32%) patients and unavailable for 1 MPA patient. During follow-up, 267 (43.8%) patients relapsed and 106 (17.3%) died, 67 of them without prior relapse. A higher relapse risk was independently associated with arthralgias/myalgias (subhazard ratio [sHR]=1.41; *P*=0.017), anti-PR3 ANCA (sHR=1.91; *P*=0.010) or anti-MPO (sHR=1.49; *P*=0.022) ANCA, but the relapse risk was lower for age >70 years (sHR=0.68; *P*=0.025) or creatinine >200 µmol/L (sHR=0.60; *P*=0.010) at disease diagnosis.

Conclusion: For GPA, MPA and EGPA patients, relapse risk was lower for age >70 years or creatinine >200 µmol/L at disease onset, but higher for arthralgias/myalgias, anti-MPO ANCA or especially anti-PR3 ANCA. These results should enable us to develop a score predictive of AAV relapse that could help clinicians determine the best adapted maintenance treatment for each patient. **Reference** 1. Fine JP *et al*. J Am Stat Assoc 1999;94:496–509

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Abstract Number: 1944

Disease Activity, Glucocorticoid Exposure, and Rituximab Determine Body Composition Changes during Induction Treatment of ANCA-Associated Vasculitis

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SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Vasculitis - Poster II: ANCA-Associated Vasculitis
Session Type: ACR Poster Session B
Session Time: 9:00AM-11:00AM

Background/Purpose: ANCA-associated vasculitis (AAV) treatment includes high dose glucocorticoids (GCs), which are associated with increased body-mass index (BMI), a complication abhorred by patients and associated with increased risk of metabolic and cardiovascular complications. A prior study found increased BMI to be independent of GC exposure for AAV (Arthritis Care Res 2008;59:746). The ability to classify BMI change as an adverse event related to GC exposure or a positive outcome reflecting improved disease activity is critical in studies investigating steroid-sparing strategies. We evaluated this further by investigating the complex relationship between BMI, GC exposure, and disease activity.

Methods: We analyzed patients enrolled in the Rituximab in ANCA-Associated Vasculitis (RAVE) trial. First, we replicated the methods used by the prior study by performing a multivariate linear regression to investigate the relationship between GC exposure (prednisone equivalent) and BMI changes while adjusting for age, sex, baseline BMI and creatinine, GC exposure prior to baseline, disease status (new diagnosis versus flaring), ANCA subtype (PR3- or MPO-ANCA+), randomization arm, and flare during the study. Second, we used mixed effects regression models to determine the time-varying relationship between the cumulative moving average of disease activity and BMI as well as cumulative GC exposure during induction treatment (the first 6 months of the trial) when accounting for confounders. Third, we used the same methods to assess the relationship between BMI and quality of life (QOL), as measured by SF36 scores.

Results: In RAVE (N=197), 99 (50%) patients were male, the mean age was 52.8 (±15.5) years, and the mean

baseline BVAS/WG was 8.0 (±3.1). The majority were PR3-ANCA+ (67%). The baseline BMI was 28.8 (±6.3) and the largest BMI change occurred during induction (+1.1 (±2.2) kg/m^2, P<0.0001). During RAVE, the mean cumulative GC dose was 5,038mg (±2,638), most administered in the first 6 months. In fully adjusted multivariate linear regression models, there was no association between GC exposure and change in BMI at 6, 12, and 18 months (P>0.3 for all analyses). However, in fully adjusted mixed-effects models, both cumulative GC exposure and moving averages of BVAS/WG were associated with BMI change in opposing directions [+0.2kg/m^2 per 1gm GC (±0.04) and -0.1 per BVAS/WG point (±0.02), both P<0.001]; randomization to rituximab was associated with increased BMI [+0.7 (±0.2) P<0.0001]. Increasing BMI was associated with worse QOL in every SF 36 domain (P<0.03 for all analyses).

Conclusion: During AAV induction, increased BMI was associated with increased GC exposure but also improved disease control and randomization to rituximab. These observations raises important questions regarding whether increased BMI should be classified as an adverse event related to GC therapy as BMI increases may actually indicate effective disease control whereas decreased BMI may augur poorly for long-term disease control. The observed association between rituximab and increased BMI deserves additional evaluation.

Disclosure: Z. Wallace, None; **E. Miloslavsky**, None; **S. H. Unizony**, None; **N. Lu**, None; **G. S. Hoffman**, None; **C. G. M. Kallenberg**, None; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Bristol-Myers Squibb, 2; **P. A. Merkel**, Chemocentryx, 5,Chemocentryx, 9; **P. A. Monach**, Genentech and Biogen IDEC Inc., 2,Bristol-Myers Squibb, 2,MedScape, 5,GlaxoSmithKline, 2,Vasculitis Foundation Board of Directors, 6,Editorial Board of Arthritis and Rheumatology, 6; **P. Seo**, None; **R. F. Spiera**, Chemocentryx, 9; **E. W. St.Clair**, Eli Lilly and Company, 2,Bristol-Myers Squibb, 5,Biogen Idec, 2; **P. Bruntetta**, Genentech, Inc., 3; **M. Cascino**, Roche Pharmaceuticals/Genentech, 2; **H. K. Choi**, None; **J. H. Stone**, Genentech/Roche, 2,Xencor, 2,Xencor, 5,Genentech/Roche, 5.

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Abstract Number: 1945

Development and Validation of Case-Finding Algorithms for the Identification of Patients with ANCA-Associated Vasculitis and Large-Vessel Vasculitis in Healthcare Administrative Databases

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Background/Purpose: ANCA-associated vasculitis (AAV) is a group of vasculitides that consists of granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (Churg-Strauss; EGPA), and microscopic polyangiitis (MPA). Large-vessel vasculitis (LVV) includes Takayasu's arteritis (TAK) and giant cell arteritis (GCA). Validated algorithms are needed to accurately identify patients with AAV and LVV in administrative databases. This study sought to evaluate and validate case-finding algorithms for AAV and LVV in 3 large health administrative databases.

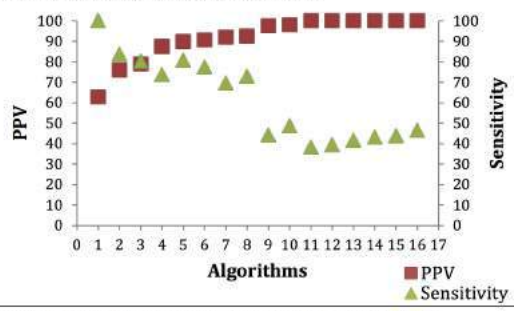
Methods: To develop the algorithms, 125 patients per disease and per healthcare system (System 1 and System 2) were randomly selected using the International Classification of Diseases version 9 (ICD9) codes for GPA: 446.4, EGPA: 446.4, MPA: 446.0, TAK: 446.7, and GCA: 446.5. 16 case-finding algorithms were constructed using a combination of ICD9 code, encounter type (1 inpatient ICD9 code on 3 consecutive days or 2 outpatient ICD9 codes 3 months apart), physician specialty, use of immunosuppressive medications, ANCA pattern (for AAV), and age (< 50 and ≥ 50 years) for LVV algorithms. The diagnosis was confirmed by chart review using the modified ACR classification criteria or the Chapel Hill Consensus Conference definitions for each disease. The positive predictive value (PPV) of each algorithm was calculated. For validation, algorithms with the highest average PPV from both Systems 1 and 2 with at least sensitivity > 50% were validated in the third healthcare system (System 3).

Results: A total of 1,250 patients were included in the study. Figures 1 and 2 show the average PPV and sensitivity of the 16 algorithms for AAV and LVV tested in Systems 1 and 2. The ICD9 code alone had a low PPV. Most algorithms with the highest average PPV had the encounter and/or specialty variables as part of the algorithm. Adding the ANCA pattern increased PPV in AAV algorithms. Table 1 shows the PPV of algorithms with the highest average PPV validated in System 3.

Conclusion: Case-finding algorithms can accurately identify patients with AAV and LVV. These algorithms can be used to assemble population-based cohorts of patients with AAV and LVV and facilitate future research in healthcare use, outcomes, and comparative effectiveness.

Figure 1. Average positive predictive (PPV) and sensitivity of algorithms for AAV

Granulomatosis with polyangiitis



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2. ICD9+Medications
3. ICD9+Encounter
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5. ICD9+Specialty
6. ICD9+Specialty+Medications
7. ICD9+Encounter+Specialty+Medication
8. ICD9+Encounter+Specialty
9. ICD9+Medications+cANCA
10. ICD9+cANCA
11.ICD9+Encounter+Specialty+Medications+cANCA
12. ICD9+Encounter+Medications+cANCA
13. ICD9+Encounter+Specialty+cANCA
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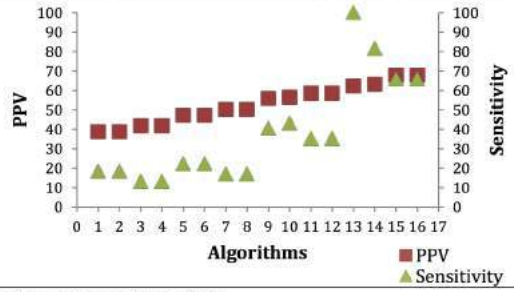
15. ICD9+Encounter+cANCA
16. ICD9+Specialty+cANCA

Eosinophilic granulomatosis with polyangiitis



1. ICD9+Encounter+pANCA
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6. ICD9+Medications+pANCA
7. ICD9+Specialty+pANCA
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9. ICD9+Encounter+Medications
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11. ICD9+Encounter+Specialty
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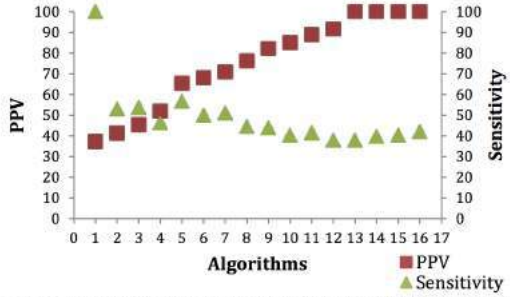
16. ICD9+Specialty+Medications

Microscopic polyangiitis



1. ICD9
2. ICD9+Medications
3. ICD9+Encounter
4. ICD9+Encounter+Medications
5. ICD9+Specialty
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8. ICD9+Encounter+Specialty+Medications
9. ICD9+pANCA
10. ICD9+Medications+pANCA
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12. ICD9+Encounter+Medications+pANCA
13. ICD9+Encounter+Specialty+Medications+pANCA
14. ICD9+Encounter+Specialty+pANCA
15. ICD9+Specialty+Medications+pANCA
16. ICD9+Specialty+pANCA

Average positive predictive (PPV) and sensitivity of algorithms for granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), and microscopic polyangiitis (MPA) at healthcare systems 1 and 2. Algorithms are arranged by the lowest to the highest PPV. Highlighted on the right is the algorithm with the highest average PPV not including the ANCA pattern.

PPV: Positive predictive value.

ICD9: ICD9: 446.4 for GPA/EGPA and 446.0 for MPA. Given that GPA and EGPA share the same ICD9 code, patients who ever had ICD9 codes 283.3 (eosinophilia) *or* 493.X (asthma) were excluded when testing algorithms for GPA and those who ever had ICD9 codes 283.3 (eosinophilia) *and* 493.X (asthma) were included when testing for EGPA.

Encounter: 1 inpatient ICD9 code on 3 consecutive days or 2 ICD9 codes 3 months apart.

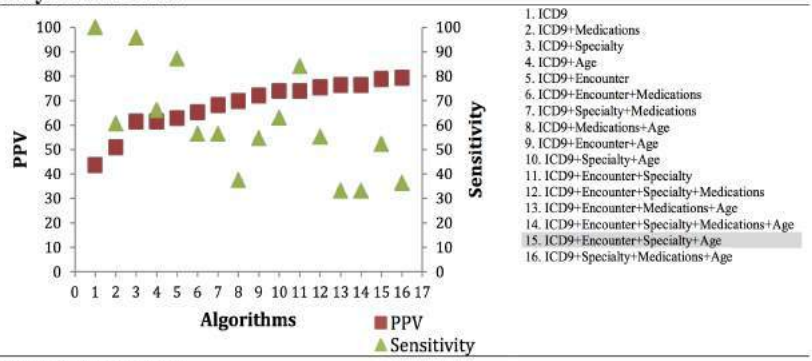
Specialty: Rheumatologist, Allergist/Immunologist, Nephrologist, Pulmonologist, or Otorhinolaryngologist involved in the care of the patient.

Medications: Glucocorticoids, disease-modifying anti-rheumatic drugs, and biologics.

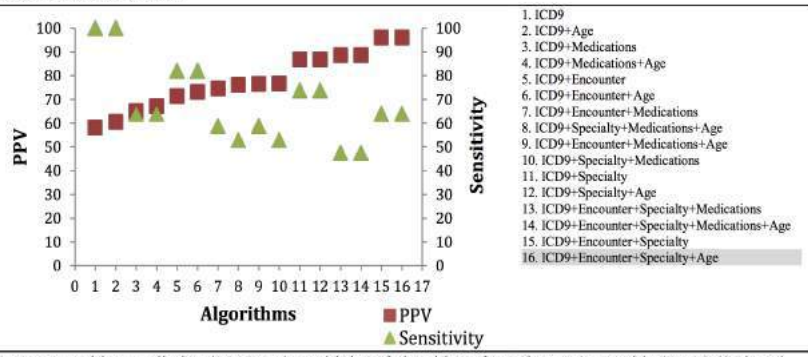
ANCA: Positive test for cytoplasmic pattern (cANCA) or perinuclear pattern (pANCA) of anti-neutrophil cytoplasmic antibody.

Figure 2. Average positive predictive (PPV) and sensitivity of algorithms for Takayasu's arteritis and giant cell arteritis

Takayasu's arteritis



Giant cell arteritis



Average positive predictive (PPV) and sensitivity of algorithms for Takayasu's arteritis (TAK) (**2A**) and giant cell arteritis (GCA) (**2B**) at healthcare systems 1 and 2. Algorithms are arranged by the lowest to the highest PPV. Highlighted on the right is the algorithm with the highest average PPV.

PPV: Positive predictive value.

ICD9: ICD9 code 446.5 for TAK and 446.7 for GCA.

Encounter: 1 inpatient ICD9 code on 3 consecutive days or 2 ICD9 codes 3 months apart.

Specialty: Rheumatologist, Cardiologist, or Vascular Surgeon involved in the care of the patient.

Medications: Glucocorticoids, disease-modifying anti-rheumatic drugs, and biologics.

Age: Current age less than 50 years for TAK and more or equal than 50 years for GCA.

Table 1. Positive predictive value of the algorithms with the highest average positive predictive value developed from Systems 1 and 2, and validated in System 3			
	Algorithm	PPV %	95% CI
GPA	**ICD9+Encounter+Specialty**	92.5	87.0 - 97.9
	ICD9+Encounter+Specialty+cANCA*	100.0	99.1 - 100.0
EGPA	**ICD9+Specialty**	100.0	73.5 - 100.0
	ICD9+Specialty+ pANCA*	100.0	47.8 - 100.0
MPA	**ICD9+Encounter+Specialty+Medications**	76.2	60.4 - 91.9
	ICD9+Encounter+Specialty+Medications+pANCA*	100.0	82.5 - 100.0
TAK	**ICD9+Encounter+Specialty+Age**	78.8	68.1 - 89.4
GCA	**ICD9+Encounter+Specialty+Age**	95.9	91.7 - 100.0

***Given that the anti-neutrophil cytoplasmic antibody (ANCA) test is not readily searchable in many healthcare systems we sought to validate algorithms with and without the ANCA pattern. PPV: Positive predictive value; CI: Confidence interval. GPA: Granulomatosis with polyangiitis; EGPA: Eosinophilic granulomatosis with polyangiitis; MPA: Microscopic polyangiitis; TAK: Takayasu's arteritis; GCA: Giant cell arteritis. ICD9: 446.4 for GPA/EGPA; 446.0 for MPA; 446.5 for TAK; 446.7 for GCA. Encounter: 1 inpatient ICD9 code on 3 consecutive days or 2 ICD9 codes 3 months apart. Specialty: Rheumatologist, Allergist/Immunologist, Nephrologist, Pulmonologist, or Otorhinolaryngologist involved in the care of the patients with GPA, EGPA, or MPA. Rheumatologist, Cardiologist, or Vascular Surgeon involved in the care of the patients with TAK or GCA. ANCA: Positive test for cytoplasmic pattern (cANCA) and perinuclear pattern (pANCA) of anti-neutrophil cytoplasmic antibody. Medications: Glucocorticoids, disease-modifying anti-rheumatic drugs, and biologics. Age: Current age less than 50 years for TAK and more or equal than 50 years for GCA.**

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Abstract Number: 1946

Antineutrophil Cytoplasmic Antibody (ANCA) Type and Body Mass Index in ANCA-Associated Vasculitis (AAV)

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Antineutrophil Cytoplasmic Antibody (ANCA) Type and Body Mass Index in ANCA-Associated Vasculitis (AAV)

Background/Purpose: Phenotypic, genetic, and treatment differences distinguish PR3- and MPO-ANCA+ ANCA-associated vasculitis (AAV) patients and suggest that these serotypes represent distinct conditions which might have different risk factors. Being overweight or obese is a risk factor in some autoimmune conditions (e.g., rheumatoid arthritis) but differences in body mass index (BMI) between the PR3- and MPO-ANCA+ AAV subtypes have not been investigated. Such differences could suggest novel genetic or environmental risk factors and have implications for treatment response, as in psoriatic arthritis, and the risk of cardiovascular disease which is a common cause of death in AAV. We evaluated whether BMI differences exist between patients with PR3-ANCA+ and MPO-ANCA+ AAV.

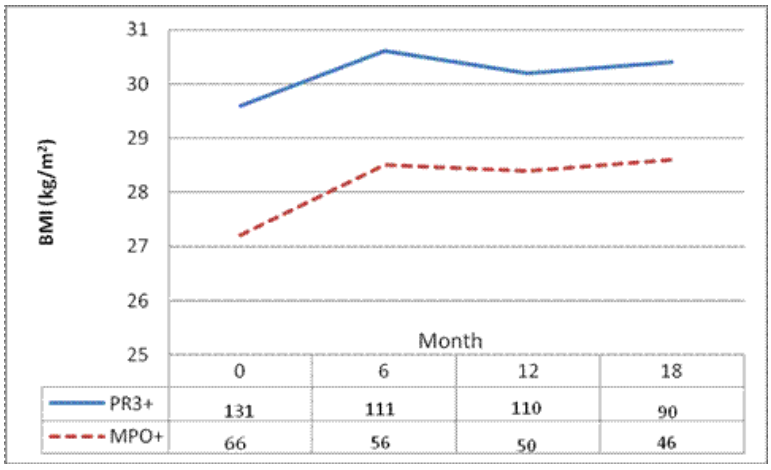
Methods: We analyzed AAV patients from the Rituximab in ANCA-Associated Vasculitis (RAVE) trial. In univariate analyses, we compared the BMI of PR3- and MPO-ANCA+ AAV patients at enrollment; in a multivariate linear regression, we adjusted for age, gender, glucocorticoids prior to enrollment, relapsing disease at baseline, and baseline disease activity. We used an analysis of response profile to evaluate trends in BMI, adjusted for the above confounders as well as glucocorticoid exposure and flares during the trial.

Results: The majority of patients in RAVE (N=197, Table 1) were PR3+ (131, 67%). PR3-ANCA+ patients had a higher baseline BMI (29.6±6.6 vs. 27.2 ± 5.3; P=0.01) and were more often obese (42% vs. 24%, P=0.04). When analyzing only those with a new diagnosis at enrollment (N=96), PR3-ANCA+ patients still had a significantly higher BMI (29.2 ± 6.2 vs. 26.8 ± 4.9, P=0.04). In multivariate regression analyses, these differences (PR3-ANCA+ BMI 2.1 kg/m^2 (±1.1) higher than MPO-ANCA+ patients) remained (P=0.047). To address the potential impact of disease duration on BMI, we investigated the temporal trend in BMI between AAV subtypes over the course of the trial (18 months) and found a constant difference in BMI (Figure 1; P=0.3).

Conclusion: PR3-ANCA+ patients have a significantly higher BMI than MPO-ANCA+ patients, even after adjustment for important potential confounders. Several possibilities may explain findings. First, an elevated BMI may predispose to PR3-ANCA+ AAV. Second, the activity of hormones associated with metabolism (e.g., leptin) may differ in AAV subtypes. Third, BMI differences could be related to variations in shared genetic risk factors. **Table 1: RAVE Trial Cohort**

Variable	**PR3-ANCA+**	**MPO-ANCA+**	**P-Value**
Number (N, %)	131 (66.5%)	66 (33.5%)	
Age	49.6 (±14.8)	59 (±15)	<0.001
Male (N, %)	75 (57.3%)	24 (36.4%)	0.007
Baseline BVAS-WG	8.3 (±3.2)	8.5 (±3.1)	0.8
New Diagnosis at Enrollment	50 (38.2%)	46 (70%)	<0.0001
Disease Category			
Granulomatosis with polyangiitis (N, %)	127 (97%)	20 (30%)	<0.0001
Microscopic polyangiitis (N, %)	4 (3%)	44 (66.7%)	
Indeterminant (N, %)	0 (0%)	2 (3%)	
Weight and BMI			
Baseline weight (kg)	89.3 (±22.0)	77.2 (±16.0)	<0.0001
Baseline BMI (kg/m^2)	29.6 (±6.6)	27.2 (± 5.3)	<0.0001
Obese (N, %)	55 (42%)	16 (24%)	0.04
Glucocorticoid Dosing			
GC prior to baseline (mg)	1263 (±1492)	1130 (±1408)	0.6
GC over the course of study (mg)	4838.2 (±2001)	4817.7 (±3433.1)	0.96

Figure 1: Change in BMI During the RAVE Trial, Analysis of Response Profile



Disclosure: Z. Wallace, None; **N. Lu**, None; **E. Miloslavsky**, None; **U. Specks**, Genentech, 5; **G. S. Hoffman**, None; **C. G. M. Kallenberg**, None; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Bristol-Myers Squibb, 2; **P. A. Merkel**, Chemocentryx, 5,Chemocentryx, 9; **P. A. Monach**, Genentech and Biogen IDEC Inc., 2,Bristol-Myers Squibb, 2,MedScape, 5,GlaxoSmithKline, 2,Vasculitis Foundation Board of

Directors, 6,Editorial Board of Arthritis and Rheumatology, 6; **P. Seo**, None; **R. F. Spiera**, Chemocentryx, 9; **E. W. St.Clair**, Eli Lilly and Company, 2,Bristol-Myers Squibb, 5,Biogen Idec, 2; **P. Bruntetta**, Genentech, Inc., 3; **H. K. Choi**, None; **J. H. Stone**, Genentech/Roche, 2,Xencor, 2,Xencor, 5,Genentech/Roche, 5.

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Abstract Number: 1947

Ocular Manifestations of ANCA-Associated Vasculitis

Sophie Cai[1,2], George Papaliodis[2,3], Leo Lu[4], Hyon K. Choi[5], Ulrich Specks[6], Peter A. Merkel[7], Philip Seo[8], Robert F. Spiera[9], Carol A. Langford[10], Gary S. Hoffman[11], Cees G.M. Kallenberg[12], William St Clair[13], Nadia Tchao[14], Fernando Fervenza[6], Paul A. Monach[15], W Joseph McCune[16], John H. Stone[17], **Eli Miloslavsky**[18] and RAVE-ITN and WGET Research Groups, [1]Ophthalmology, Johns Hopkins Wilmer Eye Institute, Baltimore, MD, [2]Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Uveitis and Immunology, Massachusetts Eye and Ear, Boston, MA, [4]Allergy, Immunology, and Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [6]Mayo Clinic, Rochester, MN, [7]Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [8]Medicine, Johns Hopkins University, Baltimore, MD, [9]Hospital for Special Surgery, Cornell, New York, NY, [10]Rheumatic and Immunologic Diseases, Cleveland Clinic, Cleveland, OH, [11]Rheumatology, Cleveland Clinic, Cleveland, OH, [12]Rheumatology and Clinical Immunology, University of Groningen, University Medical Center Groningen, Groningen, Netherlands, [13]Rheumatology, Duke University Medical Center, Durham, NC, [14]Immune Tolerance Network, San Francisco, CA, [15]Rheumatology, Boston University School of Medicine, Boston, MA, [16]Int Med/ Rheum, University of Michigan, Ann Arbor, MI, [17]Massachusetts General Hospital Rheumatology Unit, Harvard Medical School, Boston, MA, [18]Division of Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

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Background/Purpose: Ocular involvement in ANCA-associated vasculitis (AAV) can cause substantial morbidity. We aimed to characterize patterns of ocular involvement in AAV and their response to treatment.

Methods: We analyzed data from two large randomized controlled trials of AAV – the Rituximab in ANCA-Associated Vasculitis (RAVE) trial and Wegener's Granulomatosis Etanercept Trial (WGET). Ocular involvement was assessed at baseline and patients were followed until the common close-out dates. Pooled post-hoc analysis was performed of initial and overall prevalences of ocular involvement. Clinical features associated with ocular involvement, time to remission, and relapse were assessed by Cox proportional hazards and logistic regression models.

Results: 377 patients were included (Table 1). 64 patients (17.0%) had ocular involvement at study entry; conjunctivitis/episcleritis was the most common subtype, while uveitis and retinal involvement were the rarest (Table 2). Over a median follow-up time of 35.4 months, 24 patients (6.4%) developed new ocular involvement. Non-white race was associated with higher odds of having retroorbital mass/proptosis (OR 4.51; P = 0.014). Female sex (OR 2.70; P = 0.032) and PR3 ANCA positive status (OR 4.48; P = 0.048) were associated with higher odds of having scleritis. Among patients with ocular disease at study entry, median times to remission were 1.3 months for conjunctivitis/episcleritis, 1.4 months for retroorbital mass/proptosis, 0.2 months for scleritis, and 0.3 months for retinal exudates/hemorrhage. Treatment with rituximab trended toward association with decreased time to remission of retroorbital mass/proptosis (HR 10.0; P = 0.060). Relapses of ocular disease occurred in 5 patients (12.5%) with conjunctivitis/episcleritis, 3 patients (25.0%) with retroorbital mass/proptosis, and 6 patients (37.5%) with scleritis. No patient treated with rituximab developed a relapse of conjunctivitis/episcleritis or proptosis.

Conclusion: Conjunctivitis/episcleritis, scleritis, and retroorbital mass/proptosis were the most common ocular manifestations of AAV. Race and sex may be associated with certain subtypes of ocular involvement. The relative efficacies of cyclophosphamide and rituximab in the treatment of retroorbital mass/proptosis deserve further study.

Table 1. Study population baseline characteristics (N=377)

Age (years), mean (SD)	51.4 (15.5)
Sex, male, n (%)	208 (55.2)
Race, white, n (%)	350 (92.8)
New diagnosis, n (%)	176 (46.7)
Limited disease, n (%)	52 (13.8)
WG diagnosis, n (%)	327 (87.0)
PR3 ANCA positive, n (%)	277 (74.5)
MPO ANCA positive, n (%)	70 (18.8)
RAVE trial participant, n (%)	197 (52.3)
Treatment with rituximab, n (%)	99 (26.3)
WGET trial participant, n (%)	180 (47.7)
Treatment with etanercept, n (%)	89 (23.6)

Table 2. Prevalence of AAV ocular involvement

	Baseline prevalence	Overall prevalence
Conjunctivitis/episcleritis, n (%)	41 (10.9)	62 (16.4)
Retroorbital mass/proptosis, n (%)	12 (3.2)	17 (4.5)
Uveitis, n (%)	0 (0.0)	2 (0.5)
Scleritis, n (%)	16 (4.2)	22 (5.8)
Retinal exudates/hemorrhage, n (%)	1 (0.3)	1 (0.3)

References: 1. Etanercept plus standard therapy for Wegener's granulomatosis. *N Engl J Med.* Jan 27 2005;352(4):351-361. 2. Specks U, Merkel PA, Seo P, et al. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *N Engl J Med.* Aug 1 2013;369(5):417-427.

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Abstract Number: 1948

Evaluation of Body Composition Parameters in Granulomatosis with Polyangiitis: Association of Fat Mass Parameters with Disease Activity and Inflammatory Markers

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SESSION INFORMATION

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Background/Purpose: Granulomatosis with polyangiitis (GPA, Wegener´s) patients are more exposed to traditional cardiovascular risk factor, including obesity. In rheumatic diseases, inflammation has been associated with abnormal body composition (BC). Visceral adipose tissue (VAT) is a metabolically active tissue and is a source of humoral and cellular inflammation. It has been demonstrated that VAT is associated with incidence metabolic risk beyond its contribution to overall adiposity. Therefore, the objective of this study is to compare BC parameters, with emphasis in body fat and VAT, in GPA patients versus healthy controls and to explore the association of these parameters with disease activity and inflammatory markers.

Methods: This cross-sectional study was conducted in 32 GPA patients and 32 healthy controls matched by sex, age and body mass index (BMI). Disease activity was assessed by Birmingham Vasculitis Activity Score (BVAS) and ANCA. Damage was assessed by Vasculitis Damage Index (VDI). C-reactive protein (CRP, normal: < 5mg/L) and Erythrocyte sedimentation rate (ESR, normal < 15mm/1st hour for men and < 20mm/1st hour for women) were measured. BC was analyzed using dual-energy X-ray absorptiometry (DXA). Fat mass parameters evaluated were: total fat mass (FM), adiposity (percentage of body fat), fat mass index (FMI: fat mass/ht^2) and VAT (g, cm^3, cm^2).

Results: Compared GPA patients with healthy controls, a significantly greater VAT (696.00 ± 284.96 *vs.* 574.34 ± 243.82 g, p=0.03; 752.34 ± 313.01 *vs.* 621 ± 263.60 cm^3, p=0.03 and 144.34 ± 60.02 *vs.* 119.11 ± 50.54 cm^2, p=0.03) were observed in patients. GPA patients with BVAS > 1 demonstrated higher adiposity (38.71 ± 12.16 *vs.* 31.47 ± 9.29%, p=0.04) and FMI (13.78 ± 6.43 *vs.* 9.66 ± 4.39 Kg/m^2, p=0.02), compared to patients with BVAS ≤ 1. ANCA and VDI were not associated with any fat mass parameters. Elevated CRP and ESR were observed in GPA patients with higher FMI (13.54 ± 6.45 vs. 9.72 ± 4.45 Kg/m^2 p=0.04 and 13.68 ±

6.81 vs. 9.68 ± 4.27 Kg/m^2 p=0.03, respectively). No correlation was observed between fat mass parameters (FM, adiposity, FMI and VAT) and prednisone cumulative dose (p>0.05).

Conclusion: Our data suggest that GPA patients have abnormal BC, mainly in fat mass parameters and these variables are associated with inflammation and disease activity suggesting that BC should be evaluated in GPA patients to understand and prevent comorbidities in these subjects.

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Abstract Number: 1949

Presentation, Prognosis and Clinical-Pathological Correlations of Cutaneous Manifestations in ANCA-Associated Vasculitides

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Background/Purpose: Cutaneous involvement is frequent during ANCA-associated vasculitis (AAV) and can reveal the disease. However, no large study on presentation and clinical-pathological correlations is available. In the present study, we aimed to analyze the spectrum and impact of cutaneous manifestations (CM) during AAV, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA), and to perform clinical-pathological correlations.

Methods: We conducted a French multicenter retrospective study on patients with AAV included in the French Vasculitis Study Group database. Clinical and biological presentation, and relapse-free and overall survival

have been analyzed in patients with and without CM. Clinical-pathological correlations of 38 biopsies from 32 patients were performed by 3 pathologists in a blind manner.

Results: 1553 patients were included: GPA (n=743), EGPA (n=436) and MPA (n=374). Cutaneous manifestations were more frequent in EGPA (53%) and MPA (52%) compared to GPA (35%) ($p<0.0001$), and palpable purpura was the most frequent reported CM (21%). Oral ulcers were more frequent in GPA than in MPA and EGPA (4.6% vs. 0.3% and 2.5%, $p<0.001$). Pitting edema and livedo were more frequent in MPA than in GPA and EGPA (19.5% vs. 4.3% and 13%, $p<0.001$, and 12.4% vs. 2.6% and 0.5%, $p<0.001$, respectively). Urticarial lesions were more frequent in EGPA than in GPA and MPA (11.5% vs. 2% and 3.5%, $p<0.001$), such as nodules ($p<0.0001$) and purpura ($p=0.0004$). Pyoderma gangrenosum (1.1%) and gingival hyperplasia (0.9%) were only observed in GPA. GPA patients with CM had more frequent vasculitis manifestations (i.e., alveolar hemorrhage, renal and gastrointestinal involvement) than granulomatosis manifestations (pulmonary nodules, pachymeningitis). Finally, relapse-free survival [HR 1.29, $p=0.03$] and overall survival [HR 1.89, $p=0.005$] were poorer in GPA patients with CM, but not in MPA and EGPA. For clinical-pathological correlations, CM biopsy specimen included purpura (n=13), nodules (n=10), papules (n=5), urticaria (n=4) and unspecified lesions (n=6). Pathological analysis showed vasculitis (68%), granulomatous infiltrates (72%), and both (50%). Vasculitis was mainly observed in purpura and nodules (86 and 80%). Granulomatous infiltrates were variable and observed regardless of the type of AAV: granulomatous vasculitis was noted in half of purpura and nodules, whereas interstitial granulomatous dermatitis was mainly noted in urticaria and papules in 75 and 60%, respectively. Neutrophils were predominant in 63%, and eosinophils seemed to be more frequent in EGPA than GPA.

Conclusion: Cutaneous manifestations are common in AAV, and more frequently observed in EGPA and MPA than GPA. Some CM are quite specific to the type of AAV. Cutaneous involvement is associated with more severe disease and poorer outcome in GPA. Clinical-pathological correlations revealed that no histological feature was specific to the type of AAV, but granulomatous infiltrates differs according to the type of lesions.

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Abstract Number: 1950

ANCA-Associated Vasculitides and IgG4-Related Disease: An Overlapping Syndrome? a European Observational Study of 18 Patients

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Background/Purpose: Atypical manifestations have been described in patients with antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV), such as periaortic fibrosis, pachymeningitis and orbital mass. Because these manifestations have been frequently described in the spectrum of IgG4-related disease (IgG4-RD), we hypothesized that both diseases could overlap.

Methods: We conducted a European retrospective multicenter observational study, including patients with AAV fulfilling 1990 ACR criteria and/or EMA algorithm and/or the definitions from the 2012 Chapel Hill Consensus Conference, and IgG4-RD fulfilling Umehara criteria. Such criteria defined IgG4-RD as possible, probable or definite. Data were collected using a standardized form by physicians in charge of patients.

Results: Eighteen patients were included (mean age 56.8 years, 13 men and 5 women). AAV and IgG4-RD diagnoses were made concomitantly in 12/18 patients (67%). AAV diagnosis preceded IgG4-RD diagnosis in 4/18 (22%) with a mean interval of 90 months (24-156), and IgG4-RD preceded AAV in 2/18 (11%). AAV diagnosis included granulomatosis with polyangiitis (GPA) in 14 (78%), microscopic polyangiitis (MPA) in 2 (12%), eosinophilic granulomatosis and polyangiitis (EGPA) in 1 (5%) and renal-limited AAV in 1 (5%). ANCA were positive in 15 patients (83%), including PR3-ANCA in 9 cases and MPO-ANCA in 5 cases. At diagnosis, mean BVAS was 16 (4-36). IgG4-RD diagnosis included definite IgG4-RD in 5 cases (28%), probable IgG4-RD in 5 (28%) and possible IgG4-RD in 8 (44%). IgG4-RD involvement were chronic periaortitis (i.e., retroperitoneal fibrosis, periaortitis and/or aortic aneurysm) in 9/18 patients (50%), orbital mass and tubulointerstitial nephritis in 4 cases each (22%), prevertebral fibrosis in 3 (16,7%), pachymeningitis and autoimmune pancreatitis in 2 cases each (11%), and salivary gland involvement, dacryoadenitis, mesenteric fibrosis, interstitial lung disease and myocardial involvement in 1 case each (5%). Medium serum IgG4 level was 2.3 g/L (range <0.07-4.85). Nineteen biopsies were performed and were contributive in 16/18 (84%) patients. Overall, 9/18 had histological evidence of vasculitis and 10/18 evidence of IgG4-RD. Histological features of IgG4-RD included dense lymphoplasmacytic infiltrate in 100% and dense fibrosis in 80%, but no obliterative phlebitis. IgG4/IgG ratio >40% was obtained in 50% and a number of IgG4-positive plasma cells >10 per high-power field in 80%. Patients required a median number of 2 (range 0-4) lines of immunosuppressants in association with corticosteroids. During a mean follow-up was 65.6 months (range 4-156), AAV relapsed in 9/18 (50%) whereas IgG4-RD relapsed in 3/18 (17%). One patient died because of diverticular peritonitis.

Conclusion: This study illustrates that AAV and IgG4-RD may overlap, suggesting that they could represent

various expressions of similar Th2 dominant imbalance of T cell responses. Identification of manifestations suggesting IgG4-RD in AAV patients could be useful, in particular in case of IgG4-RD manifestations mimicking refractory granulomatous lesions.

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Abstract Number: 1951

Phenotypic and Functional Perturbations of Peripheral B and T Lymphocytes in Granulomatosis with Polyangiitis and Microscopic Polyangiitis

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Background/Purpose: Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) are both anti-neutrophil cytoplasm antibodies (ANCA)-associated vasculitides (AAV), but differ in clinical presentation. Anti-myeloperoxydase (MPO)-ANCA were demonstrated to be pathogenic in mice, whereas proteinase 3 (PR3) itself is responsible for disruption of immune silencing in GPA rather than anti-PR3-ANCA. Perturbations in lymphocyte homeostasis associated with these abnormalities could differ between both conditions.

Methods: We analyzed the phenotypic characteristics of lymphocyte subsets in peripheral blood of 32 consecutive GPA patients and 8 MPA patients with active disease and 22 healthy controls (HC). Using flow cytometry we studied the expression of activation and inhibitory markers, cytokine receptors and inflammatory

cytokines in B cells, and main effector (i.e. Th1, Th2, Th9 and Th17 cells) and regulatory T cell (Tregs) subsets.

Results: B cell analyses revealed that B cell subsets were similar between GPA and HC. In contrast, MPA patients had significantly more $IgD^{+}/CD27^{-}$ naive B cells (69.1% vs. 50.7%, P=0.04) and less $IgD^{-}/CD27^{+}$ class-switched memory B cells (3.8% vs. 8.7%, P=0.05) than HC. No difference between GPA and MPA patients vs. HC was noted for the expression of the activation markers (CD86 and CD95) or for the inhibitory receptors (CD22, CD32, CD72 and FCRL5) within B cells. Percentage of B-cell expressing CD69 was significantly higher in GPA (3.0% vs. 1.5%, P=0.02) and MPA (5.2% vs. 1.5%, P=0.019) compared to HC, respectively, as well as CD40 expression in GPA compared to HC (MFI ratio 20.57 vs 48.59, P=0.038). Expression of BAFF-R was strikingly lower in GPA and MPA compared to HC (MFI ratio 11.5 vs. 45.2, P<0.001 for GPA, and 14.0 vs. 45.2, P=0.003 for MPA). Finally, we found significantly more IL-6-producing B cells in GPA than in HC (25.7% vs. 14.9%, P<0.001), whereas IL-6-producing B cells were decreased in MPA compared to HC (4.6% vs. 14.9%, P=0.0049). In contrast, the frequency of TNFα-producing B cells were lower in GPA and MPA patients than in HC (15.9% and 8.4% vs. 30.0%, P=0.008 and P=0.006, respectively). T cell analyses found more Th2 (1.76% vs. 1.0%, P=0.028), Th9 (1.0% vs. 0.2%, P<0.001) and Th17 (1.44% vs 0.90%, P=0.03) cells in GPA compared to HC, whereas no difference was noted between MPA and HC. The percentage of Tregs was similar between GPA and MPA vs. HC. However, the $FoxP3^{low}/CD25^{+}$ T cell subset, that includes both naive Tregs and non-regulatory effector T cells, was significantly higher in GPA (6.4% vs. 4.1%, P=0.016) than in HC. No difference between groups was noted regarding the proportion of follicular helper T cells.

Conclusion: Main phenotypic characteristics of lymphocytes in GPA and MPA patients are an increased expression CD69 and CD40 activation markers and decreased expression of BAFF-R on B cells, suggesting a role of this cytokine. In addition, IL-6-producing B cells were increased in GPA whereas TNF-α-producing B cells were decreased, raising the question of the potential benefit of anti-IL-6. GPA patients differed from MPA patient by a skewed distribution of Th2, Th9 and Th17 cells.

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Abstract Number: 1952

Kv1.3 Channel Blockade Modulates the Effector Function of B Cells in Granulomatosis with Polyangiitis

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Background/Purpose: Granulomatosis with polyangiitis (GPA) patients are often treated with immunesuppressives or B cell depleting therapy. While B cells are involved in GPA pathogenesis as precursors of anti-neutrophil cytoplasmic antibody (ANCA) producing plasma cells, they can also exert cytokine dependent pro-inflammatory and regulatory functions. In GPA, treatment strategies could be improved by selective targeting of the effector function of B cells. Here, we investigated the effect of the Kv1.3 channel blocker dalazatide (formerly ShK-186) on effector and regulatory B cell function.

Methods: The distribution of B cell subsets was determined in peripheral blood samples of 33 GPA patients and 17 matched healthy controls (HC). Peripheral blood mononuclear cells (PBMC) from GPA patients and HC were stimulated *in vitro* with CpG-ODN or a combination of CpG, B cell activating factor (BAFF) and interleukin(IL)-21 in the presence and absence of dalazatide. The production levels of total IgG and PR3-ANCA IgG in culture supernatants were analysed by ELISA and Phadia EliA, respectively. In addition, the effect of dalazatide on B cell proliferation and cytokine production was determined by flow cytometry.

Results: Circulating switched and unswitched memory B cells were relatively decreased in GPA patients as compared to HC. Treating stimulated PBMCs with dalazatide resulted in decreased production of both total and PR3-ANCA IgG. Proliferation of B cells was not affected by dalazatide. A strong decrease in production of the pro-inflammatory cytokines TNFα, IL2 and IFNγ was observed with dalazatide treatment. While IL10 production was also decreased with dalazatide treatment in GPA patient samples, this effect was less pronounced. As such, dalazatide modulated the TNFα/IL10 ratio among the B cells, resulting in a relative increase in the regulatory B cell pool.

Conclusion: Dalazatide clearly modulates the effector function of B cells *in vitro,* by decreasing autoantibody production and the release of pro-inflammatory cytokines. Kv1.3 channel blockade may hold promise as a novel therapeutic strategy in GPA and other B cell mediated autoimmune disorders.

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Abstract Number: 1953

Management and Outcomes of ANCA-Associated Vasculitis in Unselected Cases within a Large Health Region of England

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SESSION INFORMATION

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Session Title: Vasculitis - Poster II: ANCA-Associated Vasculitis

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Background/Purpose: Most data on management and outcomes of ANCA-associated vasculitis (AAV) come from highly selected populations in tertiary referral centres, or clinical trials. These results may not be generalizable to clinical practice across all hospitals.

Methods: Rheumatology and Renal units in all hospitals within one of four health regions in England were invited to undertake a retrospective case note audit of all patients newly diagnosed with AAV during April 2013-December 2014. Data were collected on specialty of attending physician, patient demographics, place of diagnosis, date of symptom onset, admission or first clinic appointment, and diagnosis, BVAS organ systems involved, details of remission induction, and outcomes including hospitalisation for infection and death. The odds ratio (OR) for infection was estimated using logistic regression, and the hazard ratio (HR) for death was estimated using cox regression; both were adjusted for confounders age and renal involvement.

Results: Cases were contributed by 19 (56%) of 34 invited units. 126 newly diagnosed cases were included, 59% from Rheumatology and 41% from Renal units. 69 (54.8%) were diagnosed as inpatients, and 57 (45.2%) as outpatients. Cyclophosphamide (CYC) was the most common remission agent used in 95 (75%), Rituximab in 6 (5%), and other agents in 25 (20%). Frequency of organ involvement at diagnosis is shown in table 1. Diagnostic delay from first symptoms to diagnosis was median 2.6 (interquartile range 1.2-6.1) months. It was shorter in the sicker patients (defined as inpatients) 1.8(0.9-3.7) compared to outpatients, 4.1(2.0-12.6). Among inpatients, delay from admission to diagnosis ranged from 0-53 days (median 6, IQR 3-10.5). Of the 95 newly diagnosed patients treated with CYC, 70 (74%) received IV and 25 (26%) oral. 22 (23%) had infections requiring hospitalisation during or within 6 months of CYC treatment, and 14 (15%) died during follow up (table 1). Compared to IV, the crude OR for infection with oral CYC was 2.9 (1.1-7.7) and HR for death was 2.1 (0.7-6.4). Once adjusted for age and renal involvement, OR for infection remained elevated at 2.3 (0.8-6.9) and HR for death was 1.8(0.5-5.9).

Conclusion: There are potential opportunities to reduce the delay between admission and diagnosis amongst hospitalised patients. The need to improve care is highlighted by the significant mortality and infection rate in this unselected group. Although this analysis is limited by lack of power, and like all observational comparison of treatments at risk of confounding by indication, it raises the hypothesis that in contrast to the more selected CYCLOPS trial population, the routine use of oral CYC may be associated with an increased risk of death and infection requiring hospitalization.

Table 1: Frequency of organ systems affected at diagnosis, and infection & mortality after cyclophosphamide.

BVAS organ system affected		% affected		
	General	72%		
	Renal	64%		
	Chest	50%		
	ENT	46%		
	Cutaneous	24%		
	Nervous system	24%		
	Mucous membranes / Eyes	18%		
	Abdominal	10%		
	Cardiovascular	7%		
Mortality		**N (%)**	**Crude HR**	**Adjusted HR†**
	IV	8/70 (11%)	1	1
	PO	6/25 (24%)	2.1 (0.7-6.4)	1,8 (0.5-5.9)
Infection		**N (%)**	**Crude OR**	**Adjusted OR†**
	IV	13/70 (19%)	1	1
	PO	9/25 (36%)	2.9 (1.1-7.7)	2.3 (0.8-6.9)

† adjusted for patient age and renal involvement

Abstract Number: 1954

Clinical Features and Long Term Outcome of 105 Patients of Granulomatosis with Polyangiitis: A Single Centre Experience from North India

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Background/Purpose: The published Indian data on Granulomatosis with Polyangiitis (GPA) is sparse and only in the form of few small case series. The purpose of this study was to describe the clinical features, treatment and long term outcome of 105 patients with GPA from a tertiary care centre in north India and compare them with

published single center experiences from Europe and America.

Methods: Clinical data of all patients diagnosed to have GPA between April 2005 and April 2016 were retrieved. Clinical details including the clinical presentation, laboratory data, treatment received and outcomes of 105 patients of GPA were obtained. The disease activity at presentation was assessed with Briminghams Vasculitis Activity Score (BVAS v3) and the patients were classified according to EUVAS categories into localized, early systemic, generalized, severe and refractory categories. Our results were compared with published single center experiences from Europe and USA.

Results: A total of 105 patients (60 females and 45 males) were diagnosed to have GPA at a mean age of 40.31 years. The duration of follow up ranged from 0 months to 136 months with a mean duration of follow up of 37.21 months. Ninety four (89.52%) patients had ANCA positivity by either IIF or ELISA and 11 (10.48%) were ANCA negative. Upper respiratory tract involvement was seen in 76.19% of patients. Renal and lung involvement was seen in 51.43% and 67.62% of patients respectively. Cavitating lung lesions were seen in 21.9% of patients and subglottic stenosis was noted in 3 patients. Ocular, ear, CNS, peripheral nervous system, heart, gastrointestinal and skin involvement was seen in 40.95%, 18.1%, 28.57%, 11.43%, 5.71%, 12.38% and 29.52% respectively. Constitutional symptoms were noted in 62.86% of patients and joint symptoms were present in 43.81% of patients. The mean BVAS v3 score was 17.78. Among the EUVAS categories, localized disease was seen in 3 patients, early systemic disease in 44 patients, generalized disease in 38 patients. Seventeen patients had severe disease and one patient had refractory disease. All the patients were treated with steroids at presentation and cyclophosphamide (either oral or intravenous) was used in 90 patients. Rituximab was used as primary remission induction in 6 patients while 25 patients received it as secondary remission induction agent. Plasma exchange was performed in 6 patients and 3 patients received intravenous immunoglobulins. Total 17 patients expired out of which 9 patients expired at first admission and 4 patients expired within 1 year of diagnosis. The cause of death was attributed to disease activity in 11 patients, disease activity plus sepsis in 3 patients and sepsis alone in 3 patients. Twenty six patients experienced relapses during the follow up period which were managed appropriately. Comparison of our findings with single center experiences from Europe and USA is shown in table 1.

Conclusion: Indian population seems to get effected by GPA at an earlier age compared to the western population and also has a lesser renal involvement. The other organ involvement, response to therapy, relapse rates and mortality appear to be similar between the Indian and western population. Table 1: Comparison of clinical features of GPA among European, American and Indian patients

	Mahr et al. 2012, Europe	Holle et al. 2011, Germany	Reinhold-Keller et al. 2000, Germany	Stone et al. 2002, USA	Hoffman et al. 1992, USA	Kumar et al. 2015, India	Our study 2016, India
Total no. of patients	396	445	155	180	158	45	105
Male / female (%)	54/46	50/50	49/51	60/40	50/50	42/58	43/57
Mean age at diagnosis (range)	55	51 (12-85)	48 (13-74)	47	41	46	40 (15-70)
Study period	1995-2003	1966-2002	1966-1993	2000-2002	1968-1992	2009-2014	2005-2016
Mean duration of follow up (yrs)	4.75	6	7	NA	8	-	3.1
c-ANCA / PR3 positivity (%)	-/79	81/80	84	76/73	88	62/ 38	82/62
p-ANCA/ MPO positivity (%)	-/11	4	3/-	11/12	-	11/ 7	9/7
Organ involvement (%)							
ENT	84	98	93	90	92	80	79
Joints	-	73	61	81	67	42	44
Lung	67	60	55	75	85	49	68
Kidney	77	60	54	68	77	33	51
Eye	39	40	40	31	52	31	41
Peripheral nervous system	28	23	21	14	15	7	11
Skin	30	26	21	39	46	9	30
Heart	10	11	13	4	8	7	6
Central nervous system	-	10	-	5	8	13	27
GIT	7	3	3	7	0	9	12
Relapses during FU (%)	47	50	64	-	-	53	31
Expired (%)	14	10	14	-	-		17

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Abstract Number: 1955

Rituximab Versus Azathioprine to Maintain Remission of ANCA-Associated Vasculitides (MAINRITSAN): Follow-up at 60 Months

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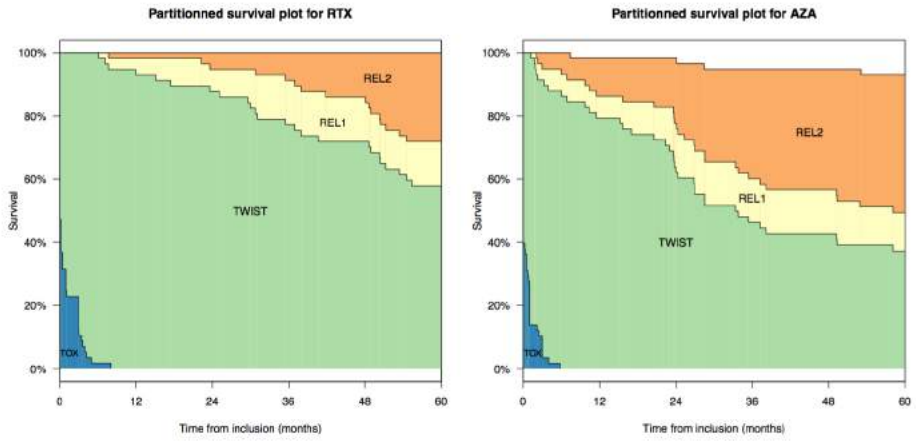
Background/Purpose: The previously reported prospective, randomizedÐcontrolled MAINRITSAN trial compared rituximab (RTX) to azathioprine (AZA) for maintenance of ANCA-associated vasculitis (AAV) remissions obtained with a combined cyclophosphamide and glucocorticoid (GC) induction regimen. Patients were randomly assigned to receive 500-mg RTX infusions on D1, D15 and 5.5 months later, then every 6 months until 18 months, or AZA for 22 months (initial dose: 2 mg/kg/d). Trial results demonstrated that RTX was superior to AZA at maintaining AAV remission during the planned 28 months of follow-up. We now report the pre-specified long-term outcomes at 60 months of MAINRITSAN trial patients.

Methods: SurvivorsÕ outcomes were ascertained prospectively. Data on survival, relapse, cancers, cardiovascular morbidity and other adverse events were collected from physicians. All patients were analyzed according to randomization group. Quality-adjusted time-without-symptoms-and-toxicity (Q-TWiST) analysis was computed, with the aim of better discerning the therapeutic impact and tradeoffs between treatment toxicity (severe adverse events, SAEs) and disease activity (relapse).

Results: Data from 60 months of follow-up were available for 110 (96%) of the 115 randomized participants. For the RTX- and AZA-treated groups, respectively: 0 and 4 died; 60-month overall survival rates were 100% and 93.0% [95% CI 86.7Ð99.9%] (P=0.045); all-relapseÐfree survival rates were 57.9% [95% CI 46.4Ð72.2%] and 37.2% [95% CI 26.5Ð52.2%] (P=0.012); and major relapse-free survival rates were 71.9% [95% CI 61.2Ð84.6%)] and 49.4% [95% CI 38.0Ð64.3%] (P=0.003). In contrast, no between-group differences were observed for survival without SAEs (P=0.95) and the cumulative GC dose (P=0.11) at 60 months.

For RTX-treated patients, PR3-ANCA positivity or ANCA persistence 12 months after starting maintenance therapy were associated with higher major relapse rates. During the 60-month follow-up, RTX- and AZA-arm patients had similar amounts of time spent with SAEs (P=0.21), whereas the former, compared to the latter, spent 9.7 months less with major relapses (P<0.001) and 12.6 months more without relapse or toxicity (P<0.001). The threshold utility analysis at 60 months showed that the Q-TWiST period was significantly longer for RTX- than AZA-arm patients (55.2 vs. 47.95 months, respectively, P<0.001) (Figure).

Conclusion: This long-term analysis showed that, despite late relapses after the 28-month initial follow-up period, maintenance therapy with RTX remained significantly superior to AZA to maintain remission at 60 months and was associated with better survival. ANCA monitoring seems to be relevant to guide treatment duration.



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Abstract Number: 1956

High Dose Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Tumor Necrosis Factor Inhibitor Use Results in Less Radiographic Progression in Ankylosing Spondylitis – a Longitudinal Analysis

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Background/Purpose: Over the last decade, the disease modifying effects of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Tumor Necrosis Factor inhibitors (TNFi) have resulted in conflicting studies. No study has examined their relationship longitudinally addressing both NSAID and TNFi use. The objective of this study was to explore the direct and interactive effects of NSAIDs and TNFi on radiographic progression in Ankylosing Spondylitis (AS).

Methods: We included 527 patients meeting the modified New York criteria in a prospective cohort with at least 2 years of clinical and radiologic follow up. Progression was defined longitudinally, with >=2 modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) unit increase in 24 months. To avoid ceiling effects, patients with high mSASSS scores were censored when they could not meet the definition of progression over the next follow up period. We used a longitudinal mixed-effects multivariable logistic regression model to determine the associations of TNFi use and NSAID use with radiographic progression.

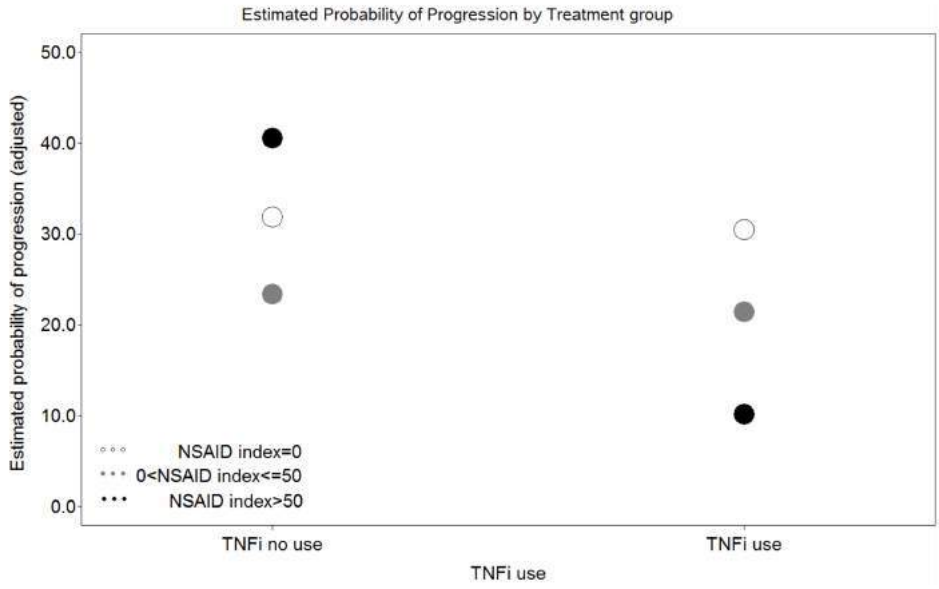
Results: Of the 527 patients, 75.7% were male with a baseline mean (SD) age and disease duration of 42.5(13.28) and 18.45(13.13) years respectively. The baseline median mSASSS was 5.36 [IQR 0.00, 28.00] and patients were followed for a mean of 4.29(2.5) years. NSAIDs and TNFi were used in 78.0% and 58.4% of patients respectively. Of 1413 visits included in this analysis, 38%, 29% and 23% had an NSAID index of 0, >0 & =<50, and >50 respectively. Multivariable results showed significant interaction between TNFi and NSAIDs (p=0.034) indicating lower progression for only those using TNFi and high dose NSAIDs [index >50]; (OR=0.17, 95%CI 0.05, 0.55, p=0.003).

Conclusion: Use of NSAIDs and TNFi in AS patients has a synergic effect in slowing radiographic progression with the greatest effect in those using both high-dose NSAIDs and TNFi.

Table 1. Longitudinal association of NSAID and TNFi use with radiographic progression, taking into account interaction, and controlling for potential confounding

Covariate	Adjusted Odds Ratio (95% CI)	p-value
TNFi use * NSAID use interaction effect		***0. 0340***
TNFi use vs. no TNFi use *for NSAID index>50*	**0.17 (0.05, 0.55)**	**0.0033**
TNFi use vs. no TNFi use *for 0< NSAID index*	**0.89 (0.32, 2.51)**	**0.8278**
TNFi use vs. no TNFi use *for no NSAID use≤50*	**0.94 (0.38, 2.33)**	**0.8867**
Baseline mSASSS ≥4	7.00 (3.68, 13.3)	<0.0001
Disease duration>10 years	2.65 (1.41, 4.96)	0.0026
Male gender	2.26 (1.14, 4.47)	0.0195
White race	1.04 (0.50, 2.16)	0.9175
Education ≥ than college	0.90 (0.39, 2.07)	0.7952
current smoking	2.16 (1.01, 4.66)	0.0481
# comorbidity≥1	0.72 (0.38, 1.39)	0.3304
BASDAI ≥40	0.84 (0.48, 1.47)	0.5311
Abnormal CRP	1.18 (0.66, 2.10)	0.5820
Baseline TNFi use	1.31 (0.67, 2.52)	0.4264

Figure 1. Estimated probability of progression based on NSAID index and TNFi use



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Abstract Number: 1957

No Increased Risk of Chronic Kidney Disease with Allopurinol Use

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Background/Purpose: Chronic kidney disease (CKD) is a cause and consequence of hyperuricemia. While clinicians are often cautious about using allopurinol in patients with CKD, there is emerging evidence that urate-lowering therapy (ULT) may be beneficial in subjects with renal dysfunction. Whether patients with gout may experience less CKD with allopurinol is not clear.

Methods: We conducted a cohort study in The Health Improvement Network (THIN), which is a general practitioner electronic medical records database representative of the UK general population. We included subjects aged 18-89 with incident gout between 01/01/2000-12/31/2014 who had had at least 1 GP contact in the year prior to study entry. We excluded individuals with CKD stage ≥3 prior to gout diagnosis. We identified allopurinol initiators after their incident gout diagnosis. We computed propensity scores (PS) to minimize effects of confounding by indication using logistic regression, with incident allopurinol use as the dependent variable and potential confounders that reflect indication for allopurinol use and/or risk of CKD (table) as the independent variables. Each incident allopurinol user was matched 1:1 with an unexposed subject with greedy matching using the PS within 1-year cohort accrual blocks. Follow-up started from the index date (date of 1stallopurinol prescription for the exposed, and randomly assigned date for the unexposed within the one-year accrual block), and continued until CKD stage ≥3, death, or end of study. The relation of incident allopurinol use among subjects with incident gout to development of CKD ≥3 was assessed using Cox proportional hazard models. Since allopurinol initiators may stop using allopurinol or non-users may start using allopurinol during the follow-up period, we performed a sensitivity analysis in which subjects were censored if their exposure status changed.

Results: There were 13,727 allopurinol initiators who were PS-matched with 13,727 non-users, among whom 1401 and 1319, respectively, developed CKD stage ≥3, with mean follow-up time of 4 years for both groups. Overall, covariates were well-balanced in the two groups, with mean age of 58 years and mean BMI of 30 kg/m^2. Allopurinol use was not associated with an increased risk of developing CKD ≥3 compared with non-users, with a hazards ratio (HR) of 1.05 (95% CI 0.97-1.13). When additionally adjusted for the potential confounders included in the original PS model, the effect estimate remained unchanged (table). In the sensitivity analysis the adjusted HR did not change materially (HR=1.04, 95% CI 0.96-1.14).

Table. Risk of progression to CKD 3-5 among subjects with incident gout and incident allopurinol use.		
	Incident allopurinol user (N=13,727)	**Non-allopurinol user (N=13,727)**
Incident CKD ≥3, N	1401	1319
Mean follow-up time, years	4.04	3.96
Crude incidence rate (CKD ≥3) per 1000 person-years	25.26	24.28
Crude HR (95% CI)	1.05 (0.97-1.13)	
Adjusted* HR (95% CI)	1.05 (0.98,1.14)	
Sensitivity analysis Adjusted* HR (95% CI)	1.04 (0.96-1.14)	
* Variables included in the propensity-score model and included in the adjusted HR model: 1) gout duration; 2) baseline serum urate; 3) baseline kidney function and albuminuria; 4) general (age, gender, body mass index); 5) comorbidities (cardiovascular disease, diabetes mellitus, heart failure, hypertension); 6) hospitalization; 7) medication use (angiotensin-converting-enzyme inhibitor, aspirin, colchicine, diuretics, insulin, other drugs for diabetes mellitus, losartan, other angiotensin II receptor blockers, nonsteroidal anti-inflammatory drugs). CKD: chronic kidney disease; HR: hazard ratio; CI: confidence interval.		

Conclusion: In this large cohort, the prescription of allopurinol was not associated with increased risk of renal function deterioration. This is an important message for health care providers, highlighting that therapy for gout with allopurinol should not have a harmful effect on renal function.

Disclosure: A. B. Vargas-Santos, None; **C. Peloquin**, None; **Y. Zhang**, None; **T. Neogi**, None.

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Abstract Number: 1958

Effect of Poverty Status in 2009, % of Years in Poverty Between 2003 and 2009, and Exiting Poverty Permanently By 2009 on SLE Damage in 2015

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Background/Purpose : The relationship between poverty and SLE damage has been observed in several cross-sectional studies. The aim of the present study was to use longitudinal data to examine the effects of poverty status, dose of poverty, and exiting poverty on subsequent disease damage.

Methods: Data are from the UCSF Lupus Outcomes Study. Study participants were recruited from diverse sources in 2003 and followed through 2015 through annual structured surveys. SLE diagnoses were confirmed by medical record review. In each year we characterized the respondents' poverty status in the surveys based on household income and family size. Beginning in 2009, the survey included a validated measure of disease damage, the Brief Index of Lupus Damage. We used ordinary least squares regression to estimate the impact of 1) poverty in 2009, 2) the dose of poverty defined as the percentage of years in poverty between 2003 and 2009, and 3) the effect of permanently leaving poverty by 2009 on change in damage between 2009 and 2015, with and without adjustment for potential confounding variables (demographics, education, SLE duration, characteristics of health care, and health behaviors). To account for attrition and missing variables, multiple imputation was used.

Results: In 2009, there were 783 respondents to the Lupus Outcomes Study annual survey, of whom 94% were female, 35% non-white, and 15% were in poverty. They were 49.8(SD12.3) years of age and had had SLE for 16.9(SD8.3) years. Damage scores averaged 1.9(SD2.0, range 0-12). Table 1 shows the effect of poverty in 2009, dose of poverty between 2003 and 2009, and exiting poverty permanently by 2009 on change in damage, with and without adjustment. Those in poverty had greater increases in damage as did those continuously poor vs. poor some years vs. never poor. Exiting poverty was associated with change in damage scores closer to that among those who were never poor with the passage of as little as a year and smaller than those who remained poor. In all analyses, adjustment had minimal effect on results, indicating that the effect of confounding variables was minimal.

Conclusion: Persons with SLE who were poor in all years experience greater accrual of damage than those who were poor only some years and those who were never poor, but exiting poverty is associated with a decreased accrual of damage. Income support policies may be critical to reducing damage in SLE.

Table 1. Effect of Poverty, Percent of Years in Poverty, and Exiting Poverty on Change in BILD Damage Scores, 2009-2015

	Poverty Status in 2009		Percent of Years in Poverty, 2003-2009			
	Poor	Not Poor	All Years	≥50% of Yrs.	<50% of Yrs.	Never Poor
Unadjusted	2.02	1.33	2.52	159	1.54	1.32
Adjusted	1.97	1.34	2.45	1.45	1.49	1.34
		Exited Poverty Permanently by 2009				
	Stayed Poor	**1 Yr. Ago**	**2-3 Yrs. Ago**	**5-11 Yrs. Ago**	**Total**	**Never Poor**
Unadjusted	2.08	1.47	1.43	1.17	1.40	1.33
Adjusted	1.98	1.24	1.44	1.08	1.30	1.36

Cells are change in damage scores. Adjusted models include demographics, duration, health care characteristics and health behaviors. Change in damage scores differs significantly by poverty status, percent of years in poverty, and exiting poverty, with and without adjustment ($p < .05$).

Disclosure: E. H. Yelin, None; **J. Yazdany**, None; **L. Trupin**, None.

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Abstract Number: 1959

How Do Bone Marrow Lesions Cause Osteoarthritis Pain? a Structural and Functional Tissue-Based Study

Nidhi Sofat[1], Lena Assi[2], Anasuya Kuttapitiya[3], Alan Boyde[4], Vivian Ejindu[5] and Christine Heron[5], [1]Basic Medical Sciences, St. George's, University of London, London, United Kingdom, [2]St George's University of London, Institute for Infection & Immunity, London, United Kingdom, [3]St George's, University of London, Institute for Infection & Immunity, London, United Kingdom, [4]Queen Mary University of London, London, United Kingdom, [5]Department of Radiology, St George's Hospital, London, United Kingdom
First publication: September 28, 2016

SESSION INFORMATION
Session Date: Monday, November 14, 2016
Session Title: Plenary Session II: Discovery 2016
Session Type: ACR Plenary Session
Session Time: 11:00AM-12:30PM

Background/Purpose: Bone marrow lesions (BML) are well described in osteoarthritis (OA) and associate with pain, but little is known about histological and functional features of BMLs. We evaluated BMLs using novel tissue analysis tools to understand how they mediate pain.

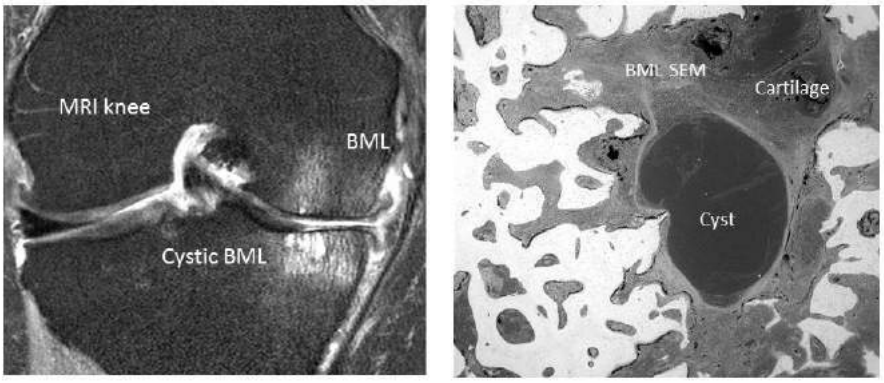
Methods: Subjects fulfilling ACR criteria for knee OA were recruited with early and advanced OA with matched controls (n=96). Advanced OA subjects had a total knee replacement (TKR)(n=72). Early knee OA subjects had pain but did not require surgery (n=12). Controls (n=12) were recruited for pain measures and tissue comparisons from non-OA knee surgery. All subjects were assessed by Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC). Participants had knee MRI to define BML characteristics and tissue damage. Tissue was harvested at TKR for BML analysis using scanning electron microscopy (SEM) and tissue microarray using Illumina. For SEM, tissue blocks were embedded in poly (methylmethacrylate) to give intact tissue and analysed to obtain 3 Dimensional SEM. For microarray, RNA was isolated and reverse transcribed using the Qiagen system and subjected to microarray.

Results: The mean (SD) total WOMAC scores in the groups were: advanced OA 1436.2 (471.6), early OA 797.4 (549.6) and controls 10.5 (12.6), demonstrating that the advanced OA group had severe pain ($p<0.0001$). MRI scoring in the advanced OA group showed all had tibial and femoral BMLs. SEM found most normal bone marrow was adipocytic with adipocytes the major bone lining cells, making and moulding trabecular excrescences. Bone volume fraction was starkly reduced in BMLs, with marrow replaced by dense fibrous connective tissue, hyaline cartilage and fibrocartilage. Aggressive resorption was found at the periphery of BML patches and areas of calcified cartilage deep in the bone, arising by mineralisation of cartilage formed within the bone organ (Figure 1). Microarray of 24 samples from the knee OA BMLs and controls showed 218 genes were differentially regulated compared with control samples ($p<0.05$). Gene groups demonstrating highest levels of regulation included extracellular matrix proteins, thrombospondin 4, chondrocyte-expressed matrix metalloproteinases (MMP-13), neuro-epithelial and axonal development proteins, pro-inflammatory cytokines and catenin signalling.

Conclusion: Our work is the first to employ SEM and microarray in one study to interrogate OA BMLs. We have

found that BMLs demonstrate areas of high metabolic activity, expressing cartilage proteins and enzymes in addition to neuronal differentiation proteins which could explain why they are strongly associated with pain.

Figure 1.



Disclosure: **N. Sofat**, None; **L. Assi**, None; **A. Kuttapitiya**, None; **A. Boyde**, None; **V. Ejindu**, None; **C. Heron**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/how-do-bone-marrow-lesions-cause-osteoarthritis-pain-a-structural-and-functional-tissue-based-study

Abstract Number: 1960

2015 ACR/ARHP Workforce Study in the U.S.: The Role of Graduate Medical Education (GME) in Adult Rheumatology

Marcy Bolster[1], Anne R. Bass[2], Jonathan S. Hausmann[3], Marcia Ditmyer[4], Seetha Monrad[5] and Daniel Battafarano[6], [1]Rheumatology, Allergy and Immunology, Massachusetts General Hospital, Boston, MA, [2]Rheumatology, Hospital for Special Surgery Weill Cornell Medical College, New York, NY, [3]Rheumatology, Beth Israel Deaconess Medical Center, Boston, MA, [4]Academy for Academic Research, Las Vegas, NV, [5]Internal Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [6]Medicine, San Antonio Military Medical Center, San Antonio, TX

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Plenary Session II: Discovery 2016

Session Type: ACR Plenary Session

Session Time: 11:00AM-12:30PM

2015 ACR/ARHP Workforce Study in the U.S.: The Role of Graduate Medical Education (GME) in Adult Rheumatology

Background/Purpose: The 2015 ACR/ARHP Workforce Study provides a projection of the supply and demand for rheumatology care 2015-2030. GME plays a critical role, through training, to provide the flow of new rheumatologists into our field and is thus essential for addressing the gap of excess demand for adult rheumatology services.

Methods: ACR member data, state licensure registries, ABIM certificates, AAMC, ACGME, and National Resident Matching Program data, and an online survey of ACR members, were used to provide practitioner demographics, work settings, full/part-time status, retirement planning and numbers of fellows in training (FIT). Projections were made of the future supply of adult rheumatologists based on the current workforce, fellowship graduation rates, succession planning, workload, practice settings and generational changes. Factors used in demand projections included patient demographics, healthcare usage, practice trends, disease prevalence, U.S. population growth, and per capita income. We assumed one clinical practice full time equivalent (FTE) to be 1.0 FTE for private practitioners and 0.5 FTE for academic practitioners.

Results: The current supply of rheumatologists is 4,497 FTE but by 2030 is projected to fall by 31% to 3,455. The current demand for rheumatologists is 5615 FTE, 1,118 (36%) more than the supply. By 2030, excess demand will be 4,729 (138%) more than supply. There are 113 adult rheumatology programs with 431 available positions. If all positions fill, 215 fellows are expected to graduate each year (42 more fellows/year than the 2005 workforce study). Assuming a 100% position fill rate/year and no changes in the number of fellow positions offered, the average number of Clinical FTE of adult fellows projected to enter the workforce yearly is less than 215, at 107, based on the projected number of female millennials who plan to work part-time and the almost 20% of international medical graduates (IMG) who plan to practice outside the U.S. Adding to the workforce deficit, about 50% of the rheumatology workforce is projected to retire over the next 15 years with over 80% of those retiring planning to reduce their patient load by > 25% in the near term (Figure 1).

Conclusion: The current U.S. adult rheumatology workforce is in jeopardy of an accelerated decline due to decreased productivity and accelerated attrition. While it remains critical to recruit medical students and residents to pursue training in rheumatology, this will not provide ample numbers of rheumatologists to meet the

deficit in supply. Efforts to close this gap are essential and should include incentives for pursuing rheumatology training such as loan repayment, innovative mechanisms for GME funding, enhanced use of nurse practitioners and physician assistants in clinical practice, and novel strategies to improve patient access to care.

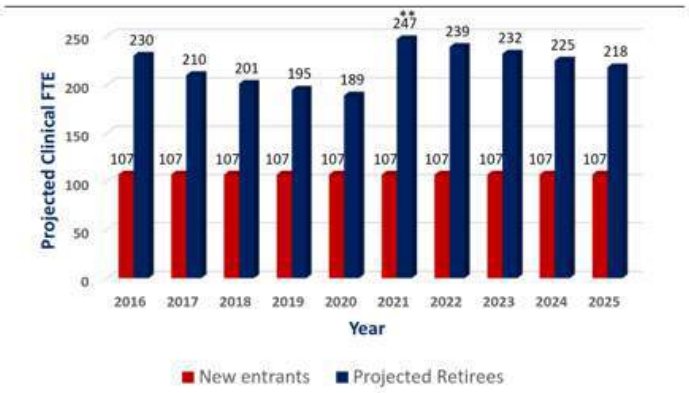


Figure 1. Comparison of Clinical FTE of New Entrants vs. Projected Retirees of Adult Rheumatologists 2016 to 2025; **Workforce modeling saw a jump in 2021 due to increased retirement projections coupled with increased projected patient load reduction in 2020.

Disclosure: M. Bolster, Johnson and Johnson, 1,Eli Lilly and Company, 2,RRF Amgen Fellowship Award, 9; **A. R. Bass**, None; **J. S. Hausmann**, None; **M. Ditmyer**, None; **S. Monrad**, None; **D. Battafarano**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/2015-acrarhp-workforce-study-in-the-u-s-the-role-of-graduate-medical-education-gme-in-adult-rheumatology

Abstract Number: 1961

Identification of Novel Genetic Susceptibility Loci in Primary Antiphospholipid Syndrome

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SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Antiphospholipid Syndrome
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Antiphospholipid syndrome (APS) is an autoimmune disease with incompletely understood etiology, characterized by recurrent thrombosis and pregnancy complications. We conducted this study to understand the genetic basis of primary APS.

Methods: We studied two independent cohorts of primary APS patients of European descent, consisting of 89 patients and 3072 healthy controls from Spain, and 133 patients and 1560 healthy controls from Italy. Genotyping of ~200,000 variants was performed using the HumanImmuno v1 BeadChip. Genetic association analysis was performed following rigorous quality control measures. A meta-analysis between the two cohorts was performed to identify susceptibility loci for primary APS. Additional genetic variants within loci of suggestive genetic association were imputed up to the 1000 Genomes Project density and then included in the analysis.

Results: We identified a novel genetic susceptibility locus for primary APS in *PLEK*, encoding pleckstrin, which plays an important role in hemostasis and platelet function (odds ratio= 1.71, P=7.89 x 10-6). Importantly, expression quantitative trait loci (eQTL) analysis revealed that the disease risk allele in *PLEK* is associated with significant reduction in *PLEK* mRNA expression (P=2.6 x 10-6), and is located within an active enhancer region identified by histone H3K27 acetylation and DNase hypersensitivity. Our data also confirmed the genetic association between APS and *STAT4* (odds ratio= 1.66, P=4.67 x 10-6). The association within the HLA was the most significant genetic association detected for APS in our study, with the most robust effect within HLA class II upstream of *HLA-DQA1* (OR 1.87, P=2.45 x 10-8).

Conclusion: This is the first genome-wide association study in primary APS. Our findings suggest a novel putative functional genetic susceptibility locus for primary APS in *PLEK*, and identify genetic susceptibility loci within the HLA class II locus and the common autoimmunity locus in *STAT4*. *MAR and AS equally contributed to this work

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Disclosure: E. Gensterblum, None; **T. Hughes**, None; **M. Martínez-Bueno**, None; **M. O. Borghi**, None; **G. J. Pons-Estel**, None; **G. Espinosa**, None; **A. Zhernakova**, None; **C. Wijmenga**, None; **R. Cervera**, None; **P. L. Meroni**, None; **M. Alarcón-Riquelme**, None; **A. Sawalha**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identification-of-novel-genetic-susceptibility-loci-in-primary-antiphospholipid-syndrome

Abstract Number: 1962

Antiphospholipid Syndrome Neutrophils Are Characterized By Overexpression of P-Selectin Glycoprotein Ligand 1, a Potential Therapeutic Target

Jason S Knight[1], Patrick S. Coit[1], He Meng[1], Srilakshmi Yalavarthi[1], Paul Renauer[1], Robert C Grenn[1], Levi F Mazza[1], Hui Wang[2], Daniel T Eitzman[2] and Amr H Sawalha[1], [1]Division of Rheumatology, University of Michigan, Ann Arbor, MI, [2]Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI
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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Treatment of the thrombotic manifestations of antiphospholipid syndrome (APS) primarily focuses on inhibiting clotting pathways. In an effort to identify upstream inflammatory targets that might launch these pathways, we investigated APS patient neutrophils.

Methods: We isolated neutrophils from the peripheral blood of 9 primary APS patients (as defined by Sydney criteria) and 9 healthy controls matched for age, sex, and ethnicity. A comprehensive transcriptome analysis was performed using paired-end 100bp mRNA sequencing reads generated on an Illumina HiSeq 2000 instrument. RNA sequencing data were normalized and analyzed using the EdgeR software package in the R programming environment. Differential gene expression between patients and controls was defined using a fold difference of >2 and a false discovery rate <0.01. Gene ontology, pathway, and functional enrichment analyses were performed. To model APS-associated venous thrombosis in mice, IgG fractions were prepared from either healthy volunteers or patients with primary APS, who had high-titer IgG anti-β_2GPI. C57BL/6 wild-type mice were treated with control or APS IgG by intraperitoneal injection. A laparotomy was then performed, and a ligature was fastened around the inferior vena cava (IVC) to cause an 80-90% reduction in IVC blood flow. Thrombus formation in the IVC was assessed 6 hours after the procedure. Mechanistic details were further elucidated using P-selectin glycoprotein ligand 1 (PSGL-1) knockout mice, adoptive transfer of neutrophils, and an inhibitory anti-PSGL-1 antibody.

Results: RNA sequencing analysis identified 593 overexpressed and 769 underexpressed genes in neutrophils from primary APS patients compared to age, sex, and ethnicity matched healthy controls. APS neutrophils demonstrate a pro-inflammatory phenotype with prominent transcriptional overexpression of interferon-regulated genes, the Toll-like receptor signaling pathway, Fc-gamma receptors, and adhesion molecules, including the leukocyte selectin ligand PSGL-1. The expression of neutrophil PSGL-1 was further characterized in an independent cohort of 15 primary APS patients, again revealing upregulation as compared to matched controls. In a flow-restriction model of IVC thrombosis, the introduction of APS IgG (as compared to control IgG) increases both thrombus size and thrombosis frequency in wild-type mice. While APS IgG does *not* accelerate thrombosis in PSGL-1 knockout mice, the phenotype can be rescued with infusion of wild-type neutrophils into PSGL-1 knockout mice. As proof of therapeutic potential, an anti-PSGL-1 monoclonal antibody inhibits APS IgG-mediated thrombosis in wild-type mice.

Conclusion: APS neutrophils demonstrate a baseline activated phenotype, which includes the upregulation of adhesion molecules. In a model of venous thrombosis, neutrophil PSGL-1 is required for APS IgG-mediated acceleration of thrombosis. PSGL-1 represents a potential therapeutic target in APS.

Disclosure: J. S. Knight, None; **P. S. Coit**, None; **H. Meng**, None; **S. Yalavarthi**, None; **P. Renauer**, None; **R. C. Grenn**, None; **L. F. Mazza**, None; **H. Wang**, None; **D. T. Eitzman**, None; **A. H. Sawalha**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/antiphospholipid-syndrome-neutrophils-are-characterized-by-overexpression-of-p-selectin-glycoprotein-ligand-1-a-potential-therapeutic-target

Abstract Number: 1963

Thrombospondin-1 Is Elevated in the Plasma of Patients with

Antiphospholipid Syndrome and Is Correlated with Free Active TGF-b1 Levels, IL-1b and IL-17A

Markos Patsouras, Athanasios G. Tzioufas and Panayiotis G Vlachoyiannopoulos, School of Medicine, Pathophysiology Department, National and Kapodistrian University of Athens, Athens, Greece

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Antiphospholipid Syndrome

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Antiphospholipid syndrome (APS) is an acquired thombophillia characterized by recurrent thromboembolism and pregnancy morbidity. Thrombospondin (TSP-1) is a matricellular glycoprotein secreted by platelets upon activation with proinflammatory, antiangiogenic and pro-apoptotic properties. TSP-1 activates TGF-β_1 and has been shown to be involved in TH-17 response. We aimed to investigate the role of Thrombospondin-1 in APS.

Methods: The study involved 90 patients with APS, 46 healthy controls (HC) and 26 SLE patients. Plasma, serum, and total IgG were isolated from all groups. Monocytes and CD4+ T-cells were isolated from 4 HC. Human Umbilical Vein Endothelial Cells were isolated from 2 APS patients and 5 HC and cultured with plasma or total IgG from HC or APS patients. Monocytes were stimulated with total IgG and these supernatants were used to stimulate CD4+ T-cells. Plasma and cell culture supernatant were analyzed for the presence of: TSP-1, IL-1b, IL-17A and free active TGF-b_1 levels using an ELISA.

Results: APS patients had higher plasma levels of TSP-1 than HCs and SLE patients (APS: mean 390ng/ml vs HC: 144.3 vs SLE: 153.0 $p<0.0001$) Patient plasma free active TGF-b1 levels were higher and strongly correlated with TSP-1 ($r =0.827$ and $p<0.0001$). Among the APS patients those with TSP-1 levels >600ng/ml had detectable IL-1b and IL-17A in their plasma. APS HUVECs cultured under standard conditions and HC HUVECs cultured with APS plasma expressed higher levels of TSP-1 than HC HUVECs cultured with HC plasma. (APS=139.4ng/ml vs HC=22.8ng/ml $p=0.0009$). Monocytes stimulated with APS total IgG produced higher levels of IL-1b and TSP-1 compared to the ones stimulated with HC IgG (700pg/ml vs 50pg/ml and 500ng/ml vs 200ng/ml respectively). APS stimulated supernatants induced the expression of IL-17A from healthy donor T-cells (250pg/ml) whereas the HC had no effect. Patients with APS and pregnancy morbidity alone expressed lower TSP-1 levels (130.1ng/ml) than APS patients with miscarriages and thrombosis (403.2ng\ml).

Conclusion: Preliminary results suggest that APS patients have higher TSP-1 plasma levels which correlate with free active TGF-b1. Monocytes and HUVECs treated with APS plasma and APS IgG produce higher levels of TSP-1 and IL-1b and these supernatants induce the expression of IL-17A from naïve T-cells. All these suggest a possible involvement of TSP-1 in thrombus formation, inflammation and inhibition of angiogenesis that needs further study.

Disclosure: M. Patsouras, None; **A. G. Tzioufas**, None; **P. G. Vlachoyiannopoulos**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/thrombospondin-1-is-elevated-in-the-plasma-of-patients-with-antiphospholipid-syndrome-and-is-correlated-with-free-active-tgf-b1-levels-il-1b-and-il-17a

Abstract Number: 1964

The Frequency and Clinical Significance of IgA Anticardiolipin and Anti-β2-Glycoprotein-I Antibodies in Antiphospholipid Antibody Patients with and without Lupus

Ayten Yazici[1,2], OZAN UNLU[3], Cecilia B. Chighizola[4], Doruk Erkan[5], Michelle Petri[6] and On Behalf of APS ACTION .[7], [1]Hospital for Special Surgery, Cornell Weill Cornell Medicine, NEW YORK CITY, NY, Turkey, [2]Rheumatology, Kocaeli University School of Medicine, Kocaeli, Turkey, [3]Rheumatology Department, Hospital for Special Surgery, Weill Cornell Medicine, New York, NY, [4]Department of Clinical Sciences and Community Health, University of Milan, IRCCS Istituto Auxologico Italiano, Milano, Italy, [5]Rheumatology, Hospital for Special Surgery- Weill Cornell Medicine, New York, NY, [6]Rheumatology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [7]., New York, NY
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Session Title: Antiphospholipid Syndrome
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: APS ACTION International Clinical Database and Repository was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL)-positive patients with/without other systemic autoimmune diseases (SAIDx). Although, IgA aCL and IgA aβ_2GPI were included in the new SLICC systemic lupus erythematosus (SLE) classification criteria, the prevalence and clinical significance of IgA isotype have been controversial. Thus our objective was to better define the prevalence and clinical significance of IgA aCL and aβ_2GPI in aPL-positive patients with/without SLE.

Methods: A web-based data capture system is used to store patient demographics, aPL-related history, and medications. The inclusion criteria are positive aPL based on the Updated Sapporo classification criteria at least twice within one year prior to enrolment. Patients are followed every 12±3 months with clinical data and blood collection. The baseline samples are analysed in the APS ACTION core laboratories to confirm aPL-positivity. For this cross sectional study, using chi square test, we compared the demographic and clinical characteristics of aPL-positive patients with/without SLE based on different aCL/aβ_2GPI isotypes.

Results: As of April 2016, 638 aPL-positive patients recruited from 24 centers; 489 (77%) had core laboratory assessments of IgG/M/A aCL/aβ_2GPI. Forty-two patients were excluded due to the diagnosis of a SAIDx other than aPL/APS and/or SLE. Thus, 320 (72%) aPL-positive patients without SLE (258 [81%] with APS) and 127 (28%) with SLE (96 [76%] with APS) were analyzed. The frequency of aCL and aβ_2GPI IgG/M/A positivity (defined as > 20U) was not different between the two groups except the IgG isotype, which was more common in aPL-positive patients without SLE (53% vs 42% [p: 0.03] for aCL and 38% vs 21% [p: 0.03] for aβ_2GPI). However, the frequency of IgA aβ_2GPI positivity was 3-fold higher than IgA aCL positivity (33% vs 11% [p<0.001] in those with SLE, and 32% vs 12% in those without SLE [p<0.001]). The demographics and aPL-related clinical manifestations were not different among aCL/aβ_2GPI IgG, IgM, and IgA isotypes (Table). The results were similar when the aCL/aβ_2GPI ELISA cut-off was set to 40U. Of note, the frequency (%) of isolated aCL IgG/M/A- and aβ_2GPI IgG/M/A-positive patients (independent of the LA status) were 22/19/1 and 11/11/8,

respectively (when the ELISA cut-off was set to 20U); isolated aβ_2GPI IgA positivity was significantly higher in aPL-positive patients with SLE, compared to those without SLE (p: 0.006).

Conclusion: Although IgA aβ_2GPI positivity is more common than IgA aCL positivity, especially in SLE, the aCL/aβ_2GPI IgA isotype does not distinguish between aPL-positive patients: a) with/without SLE; and b) with different aPL-related clinical events.

Table: Clinical features of All IgG, IgM and IgA aPL positive patients, cut-off aPL ELISA ≥20u.

n (%)	aCL IgG n=224	aCL IgM n=200	aCL IgA n=54	aB_2GPI IgG n=149	aB_2GPI IgM n=135	aB_2GPI IgA n=143	p
Gender (F)	158(70.5)	146 (73)	36 (66.7)	103 (69.1)	94 (69.6)	99 (69.2)	0.986
Caucasian	143 (63.8)	135 (67.5)	34 (63)	94 (63.1)	91 (67.4)	91 (63.6)	0.905
Black	3 (1.4)	6 (3)	4 (7.4)	2 (1.3)	3 (2.2)	8 (5.6)	
Others	78 (34.8)	59 (29,5)	16 (29,6)	53 (35,6)	41 (30,4)	44 (30,8)	
Mean Age	46.9±12.1 (18-81)	48.3±12.4 (18-83)	49.1±13.4 (26-81)	46.6±12.1 (18-81)	48.8±13 (18-83)	48.9±12.3 (23-81)	N/A
SLE	53 (23.7)	50 (25)	14 (25.9)	26 (17.4)	32 (23.7)	42 (29.4)	0.305
Thrombosis	133 (57.4)	104 (52)	33 (61.1)	95 (63.7)	71 (52.6)	81 (56.6)	0.237
Obstetric	17 (7.6)	22 (11)	7 (13)	12 (8.1)	11 (8.1)	10 (7)	0.615
Thrombosis + Obstetric	35 (15.6)	27 (13.5)	8 (14.8)	19 (12.8)	19 (14.1)	24 (16.8)	0.927
Non-criteria*	39 (17.4)	47 (23.5)	6 (11.1)	23 (15.4)	34 (25.2)	28 (19.6)	0.093

***Sapporo Classification Criteria not met**

Disclosure: A. Yazici, None; **O. UNLU**, None; **C. B. Chighizola**, None; **D. Erkan**, None; **M. Petri**, None; **O. B. O. A. A. .**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-frequency-and-clinical-significance-of-iga-anticardiolipin-and-anti-%ce%b22-glycoprotein-i-antibodies-in-antiphospholipid-antibody-patients-with-and-without-lupus

Abstract Number: 1965

Antiphospholipid Syndrome Alliance for Clinical Trials & International Networking Registry Analysis: First and Recurrent Thrombosis Risk after 720 Patient-Years of Follow-up

Ozan Unlu[1], W. David Branch[2], Paul R. Fortin[3], Maria Gerosa[4], Guillermo J. Pons-Estel[5], Maria Tektonidou[6], Amaia Ugarte[7], Doruk Erkan[8] and On Behalf of APS ACTION .[9], [1]Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, Weill Cornell Medicine, New York, NY, [2]Obstetrics and Gynecology, University of Utah and Intermountain Healthcare, Salt Lake City, UT, [3]Medicine, CHU de Québec -

Université Laval, Québec, QC, Canada, [4]University of Milan, Istituto Ortopedico Gaetano Pini, Milano, Italy, [5]Department of Autoimmune Diseases, Institut Clínic de Medicina i Dermatologia, Hospital Clínic de Barcelona, Barcelona, Spain, [6]First Department of Internal Medicine, School of Medicine, National University of Athens, Athens, Greece, [7]Hospital Universitario Cruces, Biscay, Spain, [8]Rheumatology, Hospital for Special Surgery-Weill Cornell Medicine, New York, NY, [9]., New York, NY
First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Antiphospholipid Syndrome
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: APS ACTION Registry was created to study the natural course of disease over 10 years in persistently antiphospholipid antibody (aPL)-positive patients. Previously, based on five new thrombotic events, we reported the one-year first and recurrent thrombosis risk in persistently aPL-positive patients as 0% and 1.7%, respectively (Erkan et al. *Arthritis Rheumatol*. 2015; 67 [suppl 10]). The objective was to report additional thrombotic events based on one-, two-, and three-year follow-up visits.

Methods: A web-based data capture system is used to store patient demographics, aPL-related history, and medications. The inclusion criteria are positive aPL based on the Updated Sapporo Classification Criteria at least twice within one year prior to enrollment. Patients are followed every 12±3 months; they also receive advice on cardiovascular disease and thrombosis prevention at each visit. We report the new events in a descriptive fashion.

Results: As of April 2016, 627 patients included in the APS ACTION Registry (aPL/APS without any other autoimmune disease: 410, and aPL/APS associated with another autoimmune disease: 217). Of 627 patients, 432 (67.7%), 244 (38.2%), and 43 (6.7%) completed their one-, two-, and three-year follow-up visits, respectively. Mean follow up times were 1.67 years (505 patient-years) and 1.65 years (215 patient-years) for those with and without a history of thrombosis, respectively. Based on a total of 12 recurrent (7 events during the 1st year; 3 during the 2nd year; and 2 during the 3rd year) and four initial (2 events during the 1st year; 1 during the 2nd year; and 1 during the 3rd year) events since the inception of the registry (Table), the incident thrombosis risk was 2.37 and 1.86 per 100 patient-years in patients with and without history of thrombosis, respectively. The annual thrombosis risk was 2.38% and 1.86% in patients with and without history of thrombosis, respectively.

Conclusion: The incident thrombosis risk is relatively low and commonly associated with lupus anticoagulant and/or triple aPL-positivity as well as non-aPL thrombosis risk factors in our multi-center international cohort. Annual and risk stratified analysis of APS ACTION registry will better determine the risk of thrombosis in persistently aPL-positive patients based on different risk profiles.

Baseline Data^				Follow-Up Data^		
Age*/Sex/ Race	**Other AIDx**	**aPL Profile**	**Thrombotic Event**	**New Event****	**aPL-related Medications***	**Concomitant Thrombosis Risk Factors**
34/F/W	SLE	aCL	No	PE (N/A)	HCQ x 180m	Obesity, Sedentary Lifestyle, Smoking
46/M/W	SLE	Triple aPL	DVT	MI (38m)	Warfarin x11 y (INR: 2.5) HCQ x 38m	Sedentary Lifestyle, HL, HTN
57/M/W	No	aCL, aB2GPI	VT x 4***	MI (13y)	Warfarin x12y (INR: 2.3) HCQ x12y	Sedentary Lifestyle, Smoking
58/F/W	No	aCL, aB2GPI	DVT/PE. Peripheral Artery***	Peripheral Artery (14y)	Statin Warfarin x 14y (INR: 1.8) HCQ x 11m	HTN, DM, HL, RF, Sedentary Lifestyle
26/F/W	No	Triple aPL	DVT x2 +PE***	MI (26m)	Acenocoumarol x 26m (INR unknown)	Protein S Deficiency
30/F/W	SLE	LA	No	Hepatic Artery (N/A)	ASA x6y	Sedentary Lifestyle, Previous Smoking
57/F/W	SLE	LA, aCL	CAPS	MI(14 y)	Statin ASA x41m Warfarin x14y (INR: 1.6) HCQ x 24 y Clopidogrel x 41m	HL, Sedentary Lifestyle
43/M/W	No	LA	Hepatic Microthrombosis	Stroke (20m)	Warfarin x 11y (INR: 2.19)	PFO
23/M/W	SLE	LA, aCL	DVT x2***	PE (57m)	Patient stopped medication several months prior to event (Normally on	Factor V Leiden Heterozygous, Protein S Deficiency,

					Rivaroxaban)	Sedentary Lifestyle, Obesity
25/F/W	No	LA	No	DVT Arm (N/A)	None	Sedentary Lifestyle, Obesity
64/F/W	No	Triple aPL	No	Adrenal hemorrhage (Microthrombosis)(N/A)	Statin ASA x 12y	Hospitalization

* At the time of recurrence ** Duration between the last thrombosis and recurrence in parenthesis *** History of recurrent thromboses ^ Patient with new events since the last analysis **AIDx:** autoimmune disease**; ASA:** aspirin; **CVD:** cardiovascular disease; **DM:** diabetes mellitus; **DVT:** deep vein thrombosis; **F:** female; **HL:** Hyperlipidemia; **HTN;** hypertension; **Immob/Sx**: immobilization & postsurgical; **INR:** international randomization ratio: **M:** male; **MI:** Myocardial Infarction; **PE:** pulmonary embolism; **PFO:** patent foremen ovale; **RF:** renal failure defined as GFR < 60 ml/min; **SLE:** systemic lupus erythematosus., **VT:** Venous Thrombosis

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Abstract Number: 1966

Antibodies Against Domain 1 and Domain 4/5 of β2 Glycoprotein I: Clinical Relevance in Obstetric Anti-Phospholipid Syndrome

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SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Antiphospholipid Syndrome
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: The domain reactivity of antibodies against b2 glycoprotein I (anti-b2GPI) has been investigated in patients with thrombotic anti-phospholipid syndrome (APS), leading to the identification of antibodies targeting domain 1 of the molecule (anti-D1) as the most relevant autoantibody subpopulation. Scarce attention has been paid to the domain profiling of patients with pregnancy morbidity (PM). The aim of this study was to characterize the relevance of the fine epitope reactivity of anti-b2GPI antibodies in anti-phospholipid antibody (aPL)-associated PM.

Methods: Women with persistent positivity for anti-b2GPI IgG antibodies at medium-high titers, with at least one pregnancy and without systemic autoimmune disease were included. Anti-D1 and anti-D4/5 antibodies were tested using a chemiluminescent immunoassay and a research ELISA assay, respectively (QUANTA Flash b2GPI IgG and QUANTA Lite, Inova Diagnostics). Statistical analysis was performed using R package.

Results: 138 women fulfilling the inclusion criteria were retrospectively recruited at 3 referral centres. 49 patients (35%) had obstetric APS, 18 (13%) thrombotic APS, 37 (27%) thrombotic and obstetric APS while 34 women (25%) were asymptomatic aPL carriers. 81 women (60%) displayed triple aPL positivity, 32 (23%) had two positive aPL test and 23 (17%) carried a single aPL positivity. 110 patients had at least one untreated pregnancy, culminating in a live birth in 31 cases (28%). 89 women underwent a pregnancy course while receiving treatment, with 71 women (80%) having a live birth. A significant difference in the distribution of positive anti-D1 antibodies emerged between women with or without PM and with or without thrombosis ($p=0.05$, $c^2=2.710$ and $p<0.001$, $c^2=12.174$, respectively); no significant difference was observed for anti-D4/5 antibodies (**Table 1**). In a multivariate logistic regression model also encompassing treatment, positive anti-D1 antibodies, but not anti-D4/5, were significantly associated with obstetric complications, conferring an odds ratio (OR) of 2.32 ($p=0.040$ and $p=0.724$, respectively). Triple aPL positivity corrected by treatment significantly predicted PM ($p=0.015$, OR=2.78).

Conclusion: Our data suggest that anti-D1 antibodies are significantly associated not only with thrombosis but also with obstetric morbidity while positive anti-D4/5 antibodies are not predictive of PM. **Table 1. Different combinations of reactivity against D1 and D4/5 in women with or without pregnancy morbidity (PM) according to the updated classification Criteria for APS and in women with or without thrombosis.**

	No PM (%)	PM (%)	No thrombosis (%)	Thrombosis (%)
Anti-D1+/anti-D4/5-	15 (29%)	43 (50%)	27 (33%)	31 (56%)
Anti-D1-/anti-D4/5+	9 (17%)	9 (11%)	16 (19%)	2 (4%)
Anti-D1+/anti-D4/5+	11 (21%)	14 (16%)	15 (18%)	13 (24%)
Anti-D1-/anti-D4/5-	17 (33%)	20 (23%)	25 (30%)	9 (16%)
Total	52	86	83	55

Disclosure: C. B. Chighizola, None; **L. Andreoli**, None; **M. Tonello**, None; **M. G. Raimondo**, None; **F. Pregnolato**, None; **C. Nalli**, None; **E. Mattia**, None; **L. Cesana**, None; **R. Kumar**, None; **C. Comerio**, None; **C. Grossi**, None; **F. Mombelli**, None; **M. Gerosa**, None; **M. O. Borghi**, None; **A. Ruffatti**, None; **A. Tincani**, None; **P. L. Meroni**, None.

Abstract Number: 1967

Depression Is a Risk Factor for Low Treatment Adherence in African American People with Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Title: Healthcare Disparities in Rheumatology

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Session Time: 2:30PM-4:00PM

Background/Purpose: African American (AA) people with Systemic Lupus Erythematosus (SLE) are at high risk for severe disease and depression, and often require complex medication regimes. Prior data suggest that AA patients with SLE have poor medication adherence; however little is known about the leading patient-centered factors. We sought to examine the effect of depression, medication satisfaction, and self-confidence to manage lupus on treatment adherence in an AA population with SLE.

Methods: The Georgians Organized Against Lupus (GOAL) is a longitudinal cohort of patients with SLE living in Atlanta, predominantly derived from the population-based Georgia Lupus Registry. Since 2011, participants are surveyed annually on multiple exposures and outcomes. For this study, we selected all AA participants who completed the Morisky Medication Adherence Scale (MMAS-8) in 2015. MMAS-8 scores range from 0-8 and a cutpoint <6 has been validated as indicator of low adherence. Depressive symptoms were assessed with the Patient Health Questionnaire (PHQ-9) and categorized as minimal, mild/moderate, and moderately severe/severe depressive symptoms using clinically validated cutpoints. Self-confidence was assessed with the Stanford Self-efficacy 6-item Scale, and medication satisfaction with an ad-hoc 4-point Likert scale question (How satisfied are you with your current lupus medication options?). The association between patient centered-factors and low adherence (MMAS-8 <6) were examined with multiple logistic regression. Self-reported disease activity, organ damage, and demographic factors were tested as covariates.

Results: We examined 632 AA participants (93% females; 44% living below the poverty level; 43% under- or uninsured). Mean age, disease duration and education at survey were 48, 15 and 14 years, respectively. Mild to severe depressive symptoms were endorsed by 392 (63%) and low adherence by 329 (54%) participants. Multivariate analysis revealed that the odds of low adherence were significantly higher in those with mild/moderate (OR= 2.3) and moderately severe/severe (OR= 2.4) depressive symptoms, compared to those with none/minimal symptoms. While women and younger participants were more likely to be low-adherent, disease activity, organ damage and other patient-centered factors were not associated with treatment adherence.

Table 1. Factors associated with Low Treatment Adherence* in AA patients with SLE

Factor	OR (95% CI)	P value
Depressive symptoms (ref: none/minimal)		
Mild/Moderate	2.28 (1.45-3.58)	0.0003
Moderately severe/Severe	2.41 (1.25-4.66)	0.0007
Female gender	2.83 (1.35-5.96)	0.0061
Age at Survey (per 5 years ↓)	1.10 (1.02-1.18)	0.017
Education (per 3 years ↑)	1.16 (0.95-1.43)	0.15
Disease activity score (per 1 unit ↑ SLAQ score)	1.02 (0.99-1.05)	0.11
Confidence of manage lupus (per 1 point ↑)	0.96 (0.88-1.05)	0.35
Severe organ damage (SA-BILD score ≥3; ref: 0-2)	0.92 (0.63-1.34)	0.66
Under or uninsured	1.02 (0.69-1.51)	0.93
Unsatisfied/Somewhat unsatisfied with medications	1.35 (0.74-2.46)	0.33

*Low adherence defined as MMAS-8 <6; SLAQ: Systemic Lupus Activity Questionnaire; SA-BILD: self-administered Brief Index Lupus Damage.

Conclusion: Over half of AA patients with SLE are low adherent to their medications, and over 60% have depressive symptoms ranging from mild to severe. Women, those of younger age, and those with depressive symptoms are at high risk of low adherence. Notably, satisfaction with treatment and self-confidence were not associated with adherence. Our findings point to the need for wide-scale depression screening and effective depression management interventions as means to potentially improve treatment adherence in AA populations with SLE.

Disclosure: C. Drenkard, None; **S. Mathew**, None; **G. Bao**, None; **S. S. Lim**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/depression-is-a-risk-factor-for-low-treatment-adherence-in-african-american-people-with-systemic-lupus-erythematosus

Abstract Number: 1968

Adverse Childhood Experiences and Outcomes of Systemic Lupus Erythematosus

Laura Trupin[1], Patricia P. Katz[1], Cristina Lanata[1], Edward H. Yelin[1], Lindsey A. Criswell[1], Charles G. Helmick[2], Jinoos Yazdany[1] and Maria Dall'Era[1], [1]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [2]National Center for Chronic Disease Prevention and Health Promotion, Centers for Disease Control and Prevention, Atlanta, GA

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Session Title: Healthcare Disparities in Rheumatology

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Background/Purpose: Adverse childhood experiences such as extreme deprivation, neglect, abuse, parental separation or incarceration, have been associated with adult health status, including onset of rheumatic diseases.

It has been hypothesized that cumulative trauma may have long term effects on immune regulation, putting children at greater risk for autoimmune disease as adults. However, there has been no research on the association of adverse experiences in childhood with outcomes of rheumatic diseases. In this analysis, we examine the association of adverse experiences in childhood with disease activity and damage, depression, and quality of life among adults with systemic lupus erythematosus (SLE).

Methods: Data were derived from the California Lupus Epidemiology Study (CLUES), a population based, multi-ethnic cohort of patients with SLE begun in 2015. Participants completed an extensive interview including validated self-report measures of SLE activity (Systemic Lupus Activity Questionnaire; SLAQ) and damage (Brief Index of Lupus Damage; BILD), quality of life (SF-36), depression (Patient Health Questionnaire; PHQ-8) and sociodemographic measures. They also completed the Adverse Childhood Experiences (ACE) questionnaire, a validated 8-item scale included in the Behavioral Risk Factor Surveillance System, covering parental separation, mental illness or suicide, incarceration, dysfunction due to drugs or alcohol, and verbal, physical or sexual abuse prior to age 18. Each endorsed item is given one point, and the scores were categorized as 0, 1, 2-3, and ≥4. We compared SLE outcomes by ACE score categories using ANOVA.

Results: To date, 126 CLUES participants have completed the ACE questionnaire. Participants were mostly women (88%) and racially diverse (30% white, 23% Hispanic, 15% African American, 30% Asian American). Mean age was 44±14; mean age at diagnosis 27±12. Among the individual ACE items, parental separation or divorce was most commonly reported (34%), but nearly all the items were endorsed by at least 10% of participants. Median ACE score was 1, and 20 (16%) had a score of 4 or higher. ACE scores ≥4 were more common in Hispanic (24%) and African American (37%) participants, and in participants with poverty level income (50%). Scores did not differ by age at study entry or diagnosis. Higher ACE scores were associated with greater SLE activity and damage, poorer quality of life, and higher levels of depressive symptoms (Table).

Conclusion: Adverse childhood experiences are reported frequently among individuals with SLE and appear to be associated with poor SLE outcomes. As the cohort expands, we will compare ACE scores in the cohort to the general population and examine the associations between childhood experiences and SLE outcomes in a multivariable context that takes into account sociodemographic differences.

ACE Score categories					
Outcomes	0 (n=52)	1 (n=26)	2-3 (n=28)	≥4 (n=20)	p-value
SLE activity (SLAQ)	5.4 (5.3)	6.3 (5.4)	12.9 (7.5)	12.6 (8.8)	<0.001
SLE damage (BILD)	1.9 (2.1)	1.5 (1.6)	1.9 (2.3)	3.3 (3.1)	0.05
Quality of life (SF36 PCS)	45.6 (10.6)	44.8 (9.0)	38.8 (11.0)	27.4 (8.9)	<0.001
Depressive symptoms (PHQ-8)	4.4 (4.1)	4.1 (3.7)	8.5 (5.2)	8.3 (4.2)	<0.001
Table values are mean (sd) of outcome measure.					

Disclosure: L. Trupin, None; **P. P. Katz**, None; **C. Lanata**, None; **E. H. Yelin**, None; **L. A. Criswell**, None; **C. G. Helmick**, None; **J. Yazdany**, None; **M. Dall'Era**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/adverse-childhood-experiences-and-outcomes-of-systemic-lupus-erythematosus

Abstract Number: 1969

Peer Approaches to Lupus Self-Management (PALS): A Novel Lupus Peer Mentorship Intervention

Edith M. Williams[1], Leonard Egede[2], Jim Oates[3], Delia Voronca[2] and Mulugeta Gebregziabher[2], [1]Public Health Sciences, Medical University of South Carolina, Charleston, SC, [2]Medical University of South Carolina, Charleston, SC, [3]Medicine/Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC
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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease that is associated with increased morbidity, mortality, health care costs and decreased quality of life. In the United States, African Americans have three to four times greater burden of lupus compared with Caucasians, with the highest rates experienced by African American women. While evidence-based self-management interventions that incorporate social support and health education have reduced pain, improved function, and delayed disability among lupus patients, persistent disparities may be due to the non-responsiveness of existing programs to the unique needs of African Americans and/or women with lupus. Peer mentoring interventions are effective in other chronic conditions that disproportionately affect minorities, such as diabetes, HIV, and kidney disease, but there is currently no empirically tested peer mentoring intervention developed for SLE patients.

Methods: A literature review, needs assessment, and patient interviews guided the development of a peer mentoring training manual and intervention. The intervention was piloted with African American women with lupus participating in the SLE database at the Medical University of South Carolina. Seven mentors were trained and paired with 21 mentees to encourage mentees to engage in activities that promote the learning of disease self-management skills and to support the mentees' practice of these learned skills by telephone for at least 60 minutes every week for 12 weeks. Mentee outcomes of self-management, disease progression (including disease activity, damage, and cytokine balance) were obtained at baseline, mid-intervention (6 weeks from baseline), and immediately post-intervention (12 weeks from baseline), using validated tools. All participants met at least four components of the 1997 ACR revised criteria for SLE. Descriptive statistics and effect sizes will be calculated to determine clinically important (>0.3) changes.

Results: Preliminary data from the PALS pilot study suggest that the peer mentoring intervention is credible, acceptable and likely to be effective at improving self-management, decreasing disease activity and improving quality of life in women with SLE. Between baseline and 6 weeks (mid-intervention), mentees (n=20) reported increased social support; improved physical functioning, general health, social functioning, vitality, and patient activation; and decreased physical limitation, bodily pain, and emotional limitation. Observed changes exceeded the clinically meaningful level of 0.3, suggesting that the intervention will likely be effective at 12 weeks. At 6 weeks, both mentees (n=20) and mentors (n=7) gave high ratings for perception and credibility of the intervention. Post-intervention (12 week) data is currently being analyzed and will be shared.

Conclusion: Given the success of the peer mentoring approach, and its responsiveness to the needs of this unique population, this intervention could result in health improvements that have not been attainable with other interventions. This could lead to significant reductions in disparities and have considerable public health impact.

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self-management-pals-a-novel-lupus-peer-mentorship-intervention

Abstract Number: 1970

Disparities in Access to Specialist Care at the Time of Diagnosis of Systemic Lupus Erythematosus

Lisa Gaynon[1], Patricia P. Katz[2], Maria Dall'Era[3], Laura Trupin[2], Lindsey A. Criswell[4], Cristina Lanata[4], Charles Hemlick[5] and Jinoos Yazdany[2], [1]Internal Medicine, California Pacific Medical Center, San Francisco, CA, [2]Medicine/Rheumatology, University of California, San Francisco, San Francisco, CA, [3]Division of Rheumatology, University of California, San Francisco, San Francisco, CA, [4]Division of Rheumatology, UCSF, San Francisco, CA, [5]Centers for Disease Control and Prevention, Atlanta, GA
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SESSION INFORMATION
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Session Time: 2:30PM-4:00PM

Background/Purpose: Disparities in outcomes among racial/ethnic minorities and individuals with low socioeconomic status with systemic lupus erythematosus (SLE) have been well reported. The degree to which these populations have delayed access to specialists, particularly at the time of diagnosis, is less well described and was the focus of this study.

Methods: Data were derived from the California Lupus Epidemiology Study (CLUES), a population-based, longitudinal, multi-ethnic cohort of patients with SLE. Data were collected via annual telephone interviews as well as in-person clinical visits. Questions on access to care included time from onset of symptoms to diagnosis of SLE, the specialty of the diagnosing physician, the time until first visit with a specialist (rheumatologist or nephrologist) if not diagnosed by one, and the specialty of the physician currently managing SLE. The significance of the relationships between these variables and race, poverty level, education level and health literacy was determined through chi-squared tests.

Results: This study included 196 patients, with a mean age of 45 (SD 15) years. Thirteen percent had an education level ≤ high school, 34% had limited health literacy and 13% were below 125% of the federal poverty level. The racial/ethnic distribution was 30% Caucasian, 22% Hispanic, 14% African-American and 33% Asian. The time from symptom onset to receiving a diagnosis of SLE varied, with 32% diagnosed in ≤3 months, 22% in 3-6 months, 15% in 6-12 months and 32% in >12 months. There were no significant differences for this outcome by race, education, literacy or poverty level. Of the 84 (43%) patients who received their initial diagnosis from a physician other than a rheumatologist or nephrologist, 64 (76%) were referred to a rheumatologist or nephrologist within 3 months but 20 (24%) experienced a delay >3 months. There was a significant difference in the time to referral to a specialist by race and education level: 64% of African-Americans and 66% of Asians saw a specialist within 3 months of diagnosis, compared with 92% and 85% for Caucasians and Hispanics respectively ($p=0.02$). For those with an education level ≤ high school, 45% were referred within the first 3 months compared with 81% of those with a higher level of education ($p=0.01$).

Conclusion: The time from symptom onset to diagnosis of SLE varied greatly within this population, with up to 32% waiting over 1 year for a diagnosis. Roughly a quarter of SLE patients not initially diagnosed by a

rheumatologist or nephrologist experienced a delay in access to specialty care at the time of diagnosis. Of these patients, African-Americans and Asians, as well as those with a lower level of education had the longest delays in accessing specialists.

Disclosure: L. Gaynon, None; **P. P. Katz**, None; **M. Dall'Era**, None; **L. Trupin**, None; **L. A. Criswell**, None; **C. Lanata**, None; **C. Hemlick**, None; **J. Yazdany**, None.

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Abstract Number: 1971

Predictors of Delays to Care and Associated Outcomes in Pediatric Lupus Patients from the Childhood Arthritis and Rheumatology Research Alliance Registry

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Background/Purpose: Disparities in access to care to pediatric rheumatologists have been described in JIA, but little has been published in regards to pediatric lupus. We aimed to examine demographic and clinical features of pediatric lupus patients in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) registry with delays to first encounter with a pediatric rheumatologist and to investigate associations between delays and disease outcomes.

Methods: CARRA registry data for participants meeting ACR classification criteria for lupus were analyzed. Delays of one month, 3 months, and one year from symptom onset to first encounter with a pediatric rheumatologist were examined. Predictors of delay, associations between levels of delay, and associations between delays and disease outcomes, including patient reported outcomes of pain and health-related quality of life, were investigated.

Results: Data from 598 participants were analyzed. The median time to first encounter with a pediatric rheumatologist was 1.4 months; 24% of participants had delays between 1-3 months, 23% between 3 months to one year, and 9% had delays of one year or more. The percentage of participants with a family history of SLE (p-trend=0.004) and percentage of participants from a low income household (p-trend=0.01) increased significantly with each level of delay, while younger ages of onset were observed with increasing delays (p-trend=0.001). In

multivariate regression models, presence of neurologic disease, absence of discoid rash, and location in a state with a low density of pediatric rheumatologists predicted delays of one month or greater. Younger age of onset, absence of proliferative lupus nephritis, and low density of pediatric rheumatologists predicted delays of 3 months or greater. Predictors for one year or greater were younger age of onset and low household income. Poor and very poor quality of life, disability by ACR functional class, moderate to severe pain, and worse patient/parent global wellness scores were associated with delays of 3 months or more when assessed on follow up. All of these effects were significant after controlling for baseline outcome status, age of onset, sex, and race/ethnicity except disability by ACR functional class. When accounting for low income in these models, delays of 3 months remained a significant predictor for only health related quality of life with OR 5.00 (CI 1.46, 17.18).

Conclusion: Severe delays of one year or more from symptom onset to first encounter with a pediatric rheumatologist exist in a notable minority of CARRA registry participants. Increasing delays in care are seen disproportionately in those who are younger, have a family history of SLE, and are from low income households. While location in an area with a low density of pediatric rheumatologists predicted delays of 1 month or greater and delays of 3 months or greater, no differences in the proportion of participants from these areas were seen between levels of delay. Delays of 3 months or more are associated with poorer outcomes, and worse health related quality of life even after accounting for confounding socio-demographic features.

Disclosure: T. Rubinstein, Lupus Foundation of America, 2; **N. Ilowite**, None; **D. Wahezi**, None.

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Abstract Number: 1972

Creatine Kinase in the United States Population: Impact of Demographics, Comorbidities and Body Composition on the Normal Range

Neilia-Kay McGill, Joshua F. Baker and Michael D. George, Rheumatology, University of Pennsylvania, Philadelphia, PA

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Healthcare Disparities in Rheumatology

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The accurate interpretation of creatine kinase (CK) values is critical as this laboratory measure guides the workup of suspected myopathies. Incidentally discovered CK elevation is a common reason for rheumatology referral. This study comprehensively evaluated clinical factors associated with CK levels among a nationally representative sample and determined the distribution of CK levels in race-ethnicity subgroups.

Methods: Data was analyzed from the cross-sectional National Health and Nutrition Examination Survey (NHANES) 2011-2014, which interviews and examines a representative sample of the U.S. population. Included

subjects were non-pregnant adults ≥ 20 years old. Race-ethnicity was based on self-report. In analyses stratified by sex, linear and logistic regression was used to identified clinical variables associated with CK levels and the likelihood of an individual being outside of sex-specific reference ranges. To assess the role of muscle mass on race-ethnicity differences in CK, linear models were adjusted for body mass index (BMI), arm circumference, and waist circumference. In order to inform the appropriate upper limit of normal reference range, 95th percentiles of CK in sex/race-ethnicity subgroups were calculated, excluding patients with strenuous exercise in the past 3 days.

Results: A total of 10,096 subjects were included: 4119 non-Hispanic white, 2256 non-Hispanic black, 2159 Hispanic and 1270 Asian subjects. In linear and logistic regression, race-ethnicity was most strongly associated with CK among men and women. Compared to white subjects, CK was more likely to be abnormal in black men (OR 8.39, 95% CI 6.11 to 11.52) and in black women (OR 5.08, 95% CI 3.65 to 7.08). Greater BMI, chronic kidney disease, recent exercise, and physical activity were modestly associated with elevated CK, while men ≥ 70 were less likely to have an elevated CK (Table). Race-ethnicity differences in CK remained after adjustment for BMI, waist circumference, and arm circumference. The 95th percentile of CK was 312 (95% CI 268 to 356) in white men, 712 (95% CI 530 to 894) in black men, 188 (95% CI 122 to 254) in white women, and 323 (95% CI 218 to 428) in black women (Figure).

Conclusion: Creatine kinase values in the general population are substantially higher in black patients particularly among men. These racial differences are not explained by differences in body composition. Proposed reference ranges for race-specific subgroups in this study are markedly higher than current reference ranges and provide a practical guide for clinicians when interpreting CK values.

Table: Multivariable logistic regression of odds of having creatine kinase above the upper limit of normal (334 IU/L in males, 199 IU/L in females)

	Male	Female
	OR (95% CI) abnormal CK	**OR (95% CI) abnormal CK**
Race-ethnicity (vs. White)		
Black	8.39 (6.11,11.52)***	5.08 (3.65,7.08)***
Hispanic	1.72 (1.26,2.34)**	1.20 (0.83,1.73)
Asian	2.41 (1.58,3.66)***	1.18 (0.68,2.03)
Other	1.78 (0.82,3.85)	1.59 (0.65,3.87)
Age (vs. 20-29 years old)		
30-49	0.97 (0.70,1.34)	0.69 (0.41,1.15)
50-69	0.52 (0.30,0.90)*	0.66 (0.36,1.23)
≥ 70	0.26 (0.11,0.60)**	0.55 (0.25,1.20)
BMI (vs. 20-25 kg/m^2)		
< 18.5	0.55 (0.23,1.48)	0.20 (0.05,0.75)*
25-30	2.29 (1.67,3.13)***	1.16 (0.75,1.79)
≥ 30	2.52 (1.80,3.54)***	1.11 (0.72,1.70)
GFR (vs. ≥ 90 ml/min/1.73m^2)		
60-89	1.56 (1.22,1.99)**	1.60 (1.10,2.32)*
30-59	2.21 (0.99,4.92)	2.06 (1.18,3.60)*
<30	0.44 (0.07,2.88)	1.00 (0.30,3.34)
Exercise in past 3 days	1.78 (1.27,2.50)**	1.55 (0.89,2.68)
Vigorous recreation	1.49 (1.13,1.95)**	1.47 (0.97,2.23)

Heavy alcohol use, thyroid disease, hypertension, smoking, diabetes, cholesterol medication use, vigorous work included but not shown with $p > 0.05$ in men and women. BMI = body mass index. GFR = glomerular filtration rate. * < 0.05, ** < 0.01, *** < 0.001

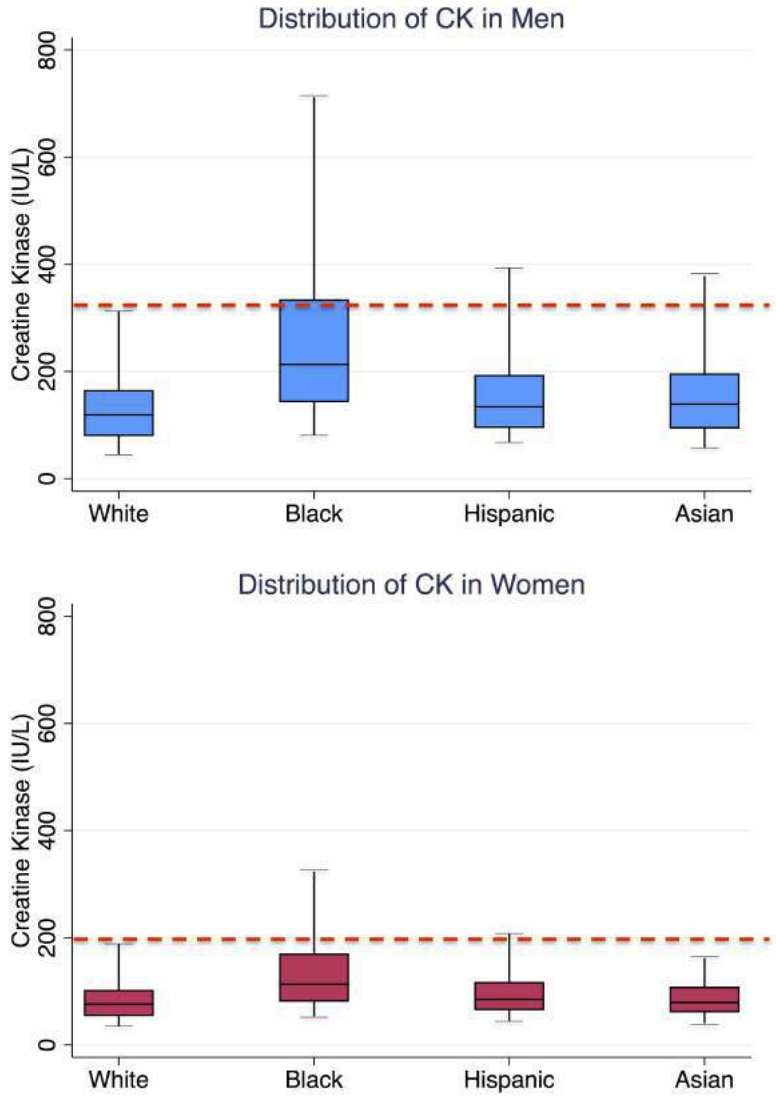

Figure: Box plots showing distribution of creatine kinase (CK) values in non-pregnant subjects ≥ 20 years old with no strenuous exercise in the past 3 days, NHANES 2011-2012 (n= 3,156). Dotted line indicates current reference range (334 IU/L in men, 199 IU/L in women). Bars indicate 5th and 95th percentile.

Disclosure: N. K. McGill, None; **J. F. Baker**, None; **M. D. George**, None.

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Abstract Number: 1973

Intramuscular Versus Ultrasound Guided Peritendinous Glucocorticoid Injection for Tenosynovitis in Patients with Rheumatoid Arthritis – a Randomised, Double-Blind, Controlled Study

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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases II: Ultrasound in Rheumatoid Arthritis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

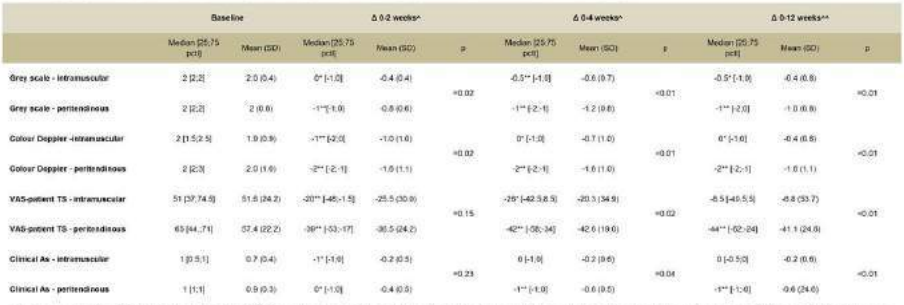
Background/Purpose: The aim of this study was to compare the efficacy of intramuscular versus ultrasound (US)-guided peritendinous glucocorticoid injection in providing disease control after 2, 4 and 12 weeks in rheumatoid arthritis(RA) patients with tenosynovitis.

Methods: Fifty RA patients with tenosynovitis were randomised into two double-blind groups: A. “intramuscular group”, receiving intramuscular injection of betamethasone and US-guided peritendinous isotonic saline injection and B. “peritendinous group” receiving saline intramuscularly and US-guided peritendinous betamethasone injection. All patients were in stable disease-modifying anti-rheumatic drug treatment prior to and during the study. Patients were excluded, and considered non-responders, if any treatments were altered during the follow-up period. “US tenosynovitis remission”, defined as US tenosynovitis grey-scale score ≤1 and colour Doppler score=0, was assessed at week 4 (primary outcome), and weeks 2 and 12, using non-responder imputation for missing data. The tenosynovitis was assessed at baseline, 2, 4 and 12 weeks using the semi-quantitative scoring system for GS (0-3) and CD(0-3) as proposed by the OMERACT US group, clinical assessment and a patient reported pain tenosynovitis visual analogue scale (VAS tenosynovitis) from 0-100

Results: US tenosynovitis remission at week 4 was achieved in 25% (6/24) [95% confidence limits: 8%; 42%] in the “intramuscular group”, versus 64% (16/25) [45%; 83%] in the “peritendinous group” (Fisher exact test; $p<0.01$). Corresponding values for the “intramuscular group” versus the “peritendinous group” at 2 and 12 weeks were 21% [5%; 37%] versus 48% [28%; 68%] ($p=0.07$) and 8% (0%; 19%) versus 44% (24%; 63%) ($p<0.01$). Most US and clinical/patient-reported scores improved more in the “peritendinous group” at all follow up visits (see table 1).

Conclusion: In this randomised double-blind clinical trial, RA patients with tenosynovitis responded significantly better to US guided peritendinous glucocorticoid injection than to intramuscular glucocorticoid injection, both at 4 and 12 weeks follow up.

Table 1 Tenosynovitis outcome values: At baseline,changes within patients receiving the intramuscular BM injection group ("im group") and patients receiving US-guided peritendinous BM injection ("peritendinous group"), and differences between groups.



	Baseline		Δ 0-2 weeks^			Δ 0-4 weeks^			Δ 0-12 weeks^^		
	Median [25;75 pctl]	Mean (SD)	Median [25;75 pctl]	Mean (SD)	p	Median [25;75 pctl]	Mean (SD)	p	Median [25;75 pctl]	Mean (SD)	p
Grey scale - intramuscular	2 [2;2]	2.0 (0.4)	0* [-1;0]	-0.4 (0.4)	<0.02	-0.5** [-1;0]	-0.6 (0.7)	<0.01	-0.5* [-1;0]	-0.4 (0.8)	<0.01
Grey scale - peritendinous	2 [2;2]	2 (0.0)	-1** [-1;0]	-0.8 (0.6)		-1** [-2;-1]	-1.2 (0.8)		-1** [-2;0]	-1.0 (0.8)	
Colour Doppler -intramuscular	2 [1.5;2.5]	1.9 (0.9)	-1** [-2;0]	-1.0 (1.0)	<0.02	0* [-1;0]	-0.7 (1.0)	<0.01	0* [-1;0]	-0.4 (0.8)	<0.01
Colour Doppler - peritendinous	2 [2;3]	2.0 (1.0)	-2** [-2;-1]	-1.6 (1.1)		-2** [-2;-1]	-1.6 (1.0)		-2** [-2;-1]	-1.6 (1.1)	
VAS-patient TS - intramuscular	51 [37;74.5]	51.8 (24.2)	-20** [-45;-1.5]	-25.5 (30.8)	<0.15	-29* [-42.5;-8.5]	-20.3 (34.9)	<0.02	-8.5 [-40.5;5]	-8.8 (33.7)	<0.01
VAS-patient TS - peritendinous	65 [44;71]	57.4 (22.2)	-39** [-53;-17]	-36.5 (24.2)		-42** [-58;-34]	-42.6 (19.6)		-44** [-62;-24]	-41.1 (24.9)	
Clinical As - intramuscular	1 [0.5;1]	0.7 (0.4)	-1* [-1;0]	-0.2 (0.5)	<0.23	0 [-1;0]	-0.2 (0.6)	<0.04	0 [-0.5;0]	-0.2 (0.6)	<0.01
Clinical As - peritendinous	1 [1;1]	0.9 (0.3)	0* [-1;0]	-0.4 (0.5)		-1** [-1;0]	-0.6 (0.5)		-1** [-1;-0]	-0.6 (24.6)	

*Note: p,p-value for Mann Whitney U test of difference between changes from baseline between "im group" and "peritendinous" group; *p<0.05,**p<0.01, Wilcoxon Signed Rank testof changes within groups; ^1 missing value calculated as last observation carried forward; ^^ 16 missing values calculated as last observation carried forward; BM, betamethasone; US, ultrasound; TS, tenosynovitis; VAS TS, patient reported visual analogue scale (0-100 mm) for pain tenosynovitis; As, assessments*

Disclosure: M. Ammitzbøll-Danielsen, None; **M. Ostergaard**, Abbvie, BMS, Boehringer-Ingelheim, Eli Lilly, Janssen, Merck, Pfizer, Roche, UCB, Celgene, Sanofi, Regeneron, Novartis, 2; **V. Fana**, None; **D. Glinatsi**, None; **U. M. Døhn**, None; **L. M. Ørnbjerg**, None; **E. Naredo**, None; **L. Terslev**, None.

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Abstract Number: 1974

Is Ultrasound of the Hands Enough to Reveal Ongoing Subclinical Inflammation in Rheumatoid Arthritis Patients in Clinical Remission According to Composite Scores?

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Imaging of Rheumatic Diseases II: Ultrasound in Rheumatoid Arthritis

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Several studies have shown the presence of subclinical inflammation by ultrasound (US) in rheumatoid arthritis (RA) patients despite clinical remission according to clinical composite scores. However, no agreement exists on which joints to assess when monitoring RA patients in remission to reveal potential subclinical inflammation. The present objective was to evaluate if US examination of the hands is sufficient for this purpose.

Methods: A total of 209 patients with RA (mean (SD) age 53 (13) years, disease duration 10 (9) years, 81% women, 79% anti-CCP positive) were included when initiating bDMARDs, with 182 patients continuing at 6

months and 152 patients at 12 months. The patients were assessed at baseline and after 6 and 12 months with patient's global disease activity VAS, clinical examination (assessor's disease activity VAS, tender and swollen joint counts performed by a study nurse) and ESR. DAS28(ESR), CDAI, SDAI and ACR/EULAR Boolean remission were calculated. All US examinations (semi-quantitative scoring (0-3)) of GS and PD (PIP 2-3, MCP 1-5, wrist (RC, IC, RU), elbow, knee, tibiotalar, MTP 1-5 and extensor carpi ulnaris (ECU)/tibialis posterior (TP) tendons bilaterally) were performed by one rheumatologist (HBH) with high intra-reader reliability (using Siemens Acuson Antares, excellence version, 5-13 MHz probe, optimized for PD with no upgrading during the study). In all the calculations only GS ≥2 and PD≥1 were regarded as US pathology. To explore if bilateral examinations of the hands (wrist, MCP/PIP joints, ECU tendon) could represent overall US pathology, the percentages of patients with US pathology present only in other sites than the hands (i.e. elbow, knee, ankle, MTP joints, TP tendons) at 6 and 12 months were calculated.

Results: At 6 months, depending on the different composite scores, 20.7%-40.8% were in clinical remission, but in these patients, US pathology was commonly present (75.7% - 86.1% for GS and 67.6% - 77.2% for PD). At 12 months, 23.0%-38.8% of the patients were in clinical remission, still having GS and PD pathology in 60.0% - 78.0% and 57.1% - 72.5%, respectively (table 1 shows the percentage US pathology depending on joint regions). In patients in remission, there was a low frequency of patients with US pathology only in joints other than the hands (GS found in 13.2 - 17.1% and PD in 2.4- 8.1 % at 6 months and 12 months) (table 2).

Conclusion: A majority of patients in remission according to clinical composite scores still had US pathology (especially in wrist, finger and MTP joints). PD activity has been shown to be associated to radiologic damage, and presently a very low percentage of patients had PD activity not detected by examination only of the hands. Thus, a feasible US examination including only the hands seems to reveal most of the patients with subclinical inflammation.

	Percentages of GS/PD pathology in spite of clinical remission according to composite scores							
	6 months				12 months			
Joints assessed bilaterally	DAS28 (n=74)	CDAI (n=37)	SDAI (n=42)	Boolean (n=38)	DAS28 (n=58)	CDAI (n=38)	SDAI (n=42)	Boolean (n=35)
Wrist (RU, MC, RU)	30/38	35/46	36/50	37/47	40/45	26/39	24/38	29/31
Finger joints (MCP1-5, PIP2-3)	41/40	43/24	43/24	47/24	41/36	26/26	31/29	23/26
Large joints (elbow, knee, ankle)	12/5	11/3	12/5	11/3	10/7	5/5	5/5	3/3
MTP 1-5	62/33	58/31	63/32	66/26	60/30	47/24	50/23	54/23
ECU and TP	20/28	13/24	14/26	11/21	17/19	21/18	19/17	20/17

Percentages of patients with no US pathology present in hands (wrist, MCP1-5, PIP 2-3, ECU bilaterally), but in at least one other joint/tendon (elbow, knee, ankle, MTP1-5, TP) in patients in clinical remission according to composite scores								
	6 months				12 months			
	DAS28 remission	CDAI remission	SDAI remission	Boolean remission	DAS28 remission	CDAI remission	SDAI remission	Boolean remission
Grey Scale	10.8	13.5	16.7	15.8	15.3	13.2	14.3	17.1
Power Doppler	8.1	5.4	7.1	5.3	5.1	2.6	2.4	2.9

Disclosure: H. B. Hammer, None; **T. K. Kvien**, None; **L. Terslev**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/is-ultrasound-of-the-hands-enough-to-reveal-ongoing-subclinical-inflammation-in-rheumatoid-arthritis-patients-in-clinical-remission-according-to-composite-scores

Abstract Number: 1975

Severity and Improvement of Morning Stiffness Independently Associate with Tenosynovitis in Patients with Rheumatoid Arthritis

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Japan, [2]Chiba Aoba Municipal Hospital, Chiba, Japan, [3]Matudo City Hospital, Matudo, Japan, [4]Asahi General Hospital, Asahi, Japan, [5]National Hospital Organization Shimoshizu National Hospital, Yotsukaido, Japan, [6]National Hospital Organization Chiba-East Hospital, Chiba, Japan
First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016
Session Title: Imaging of Rheumatic Diseases II: Ultrasound in Rheumatoid Arthritis
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

Morning stiffness has long been recognized by both patients and rheumatologists as a characteristic feature of rheumatoid arthritis (RA). However, morning stiffness is no more included in 2010 ACR/EULAR Classification Criteria for RA or in major instruments for evaluating disease activity of RA such as Disease Activity Score (DAS), ACR Core Set, Simplified Disease Activity Index (SDAI), and 2011 ACR/EULAR Provisional Definition of Remission for the lack of solid evidence for its independent value. In this study, we aimed to clarify the associations between morning stiffness and synovial inflammation and determine the independent value and the optimal measurement of morning stiffness in patients with RA.

Methods: We enrolled 76 consecutive RA patients who underwent musculoskeletal ultrasound and agreed to participate in the study. In addition to asking the duration of morning stiffness, we asked patients to complete a diagram which represents the time course of their morning stiffness in the dominant hand. We also determined the activity of synovitis in 11 joints and tenosynovitis in 8 tendons/tendon compartments in the same hand by using power Doppler (PD) ultrasound with a semiquantitative score (0-3).

Results: Study patients were predominated by women (78.9%) with a mean age of 58.4 (SD 14.6) years and a median disease duration of 24 (IQR 8-63.75) months. Rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) had been positive in 84.2% and 77.6%, respectively. For synovitis, swollen/tender joint counts more strongly correlated with total PD scores ($r = 0.379$-0.561, $p \leq 0.001$) than did any parameters of morning stiffness ($r = 0.217$-0.314, $p = 0.006$-0.021) (Table 1). For tenosynovitis, however, the severity on awakening and the improvement of morning stiffness more strongly correlated with total PD scores ($r = 0.503$-0.561, $p < 0.001$) than did swollen/tender joint counts ($r = 0.276$-0.388, $p = 0.001$-0.016) (Table 1). Multivariate analyses identified the severity on awakening and the improvement but not the duration of morning stiffness as factors that independently associate with the total tenosynovial PD score.

Table 1. Correlations between clinical manifestations and ultrasound scores in dominant hand

	Joint count		Morning stiffness				
	Swollen joint	Tender joint	Duration	Severity VAS on awakening	Improvement of VAS at 1/4	Improvement of VAS at 1/2	Improvement of VAS at bedtime
Intra-articular synovial power Doppler score							
ρ *	0.561	0.379	0.265	0.314	0.217	0.266	0.306
p value *	< 0.001	0.001	0.021	0.006	0.060	0.020	0.007
Tenosynovial power Doppler score							
ρ *	0.388	0.276	0.280	0.503	0.505	0.561	0.538
p value *	0.001	0.016	0.014	< 0.001	< 0.001	< 0.001	< 0.001

* Spearman's correlation coefficient

VAS, visual analogue scale

Conclusion: Our data demonstrate a pathophysiological link between morning stiffness and tenosynovitis and also give an insight into the optimal measurement of morning stiffness. Our data support an independent value of evaluating morning stiffness in the management of RA.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/severity-and-improvement-of-morning-stiffness-independently-associate-with-tenosynovitis-in-patients-with-rheumatoid-arthritis

Abstract Number: 1976

Ultrasound Inflammation in Patients Presenting with Arthralgia Is Associated with Developing Arthritis

Myrthe van der Ven[1], Marjolein Van der Veer-Meerkerk[1], David F. Ten Cate[2], Nigara Rasappu[3], Marc R. Kok[4], Dora Csakvari[5], **Johanna M.W. Hazes**[2], Andreas H. Gerards[6] and Jolanda J. Luime[3], [1]Rheumatology, Erasmus University Medical Centre, Rotterdam, Netherlands, [2]Department of Rheumatology, Erasmus University Medical Centre, Rotterdam, Netherlands, [3]Rheumatology, Erasmus Medical Centre, Rotterdam, Netherlands, [4]Rheumatology, Maasstad Hospital, Rotterdam, Netherlands, [5]Rheumatology, Erasmus University Medical Centre, ROTTERDAM, Netherlands, [6]Rheumatology, Vlietland Hospital, Schiedam, Netherlands
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Session Time: 2:30PM-4:00PM

Background/Purpose: To further decrease the burden of RA we need to identify patients early, preferably in absence of clinical apparent synovitis. Recent studies in US suggest that earlier detection is possible. We aim to identify arthralgia patients developing clinical apparent inflammatory arthritis (IA) within a year using US to detect subclinical synovitis at first consultation.

Methods: We followed arthralgia patients with at least two painful joints of hands, feet or shoulders without clinical apparent synovitis over one year in a multi-centre cohort study. Their symptoms needed to be present <1 year and were not explained by other conditions (e.g. fibromyalgia). We collected data at baseline, 6 months and 12 months follow-up including physical examination, laboratory variables (ESR, CRP, auto-antibodies), diagnosis and medication. At baseline we also examined 26 joints (bilateral MCP2-5, PIP2-5, wrist, MTP2-5) by US and images were scored semi-quantitatively on greyscale (GS; 0-3) and power Doppler (PD; 0-3). US synovitis was defined as GS grade 2 or 3 and/or presence of PD. One-year incident IA was defined as clinical soft tissue swelling. Univariate logistic regression was used to analyse the association between demographic characteristics, clinical characteristics, and US findings and the incidence of IA for all patients. This was then further explored selecting the strongest variables ($p<0.157$) in a multivariate logistic regression. Missing values in independent variables were imputed using STATA (multiple imputation by chained equations (m=5)).

Results: In total, 196 patients were included of whom 160 completed the 12 months follow-up. At baseline 71 (37%) arthralgia patients had US synovitis and in 29 (15%) patients PD signal was detected. Incident IA was present in 37 (19%) patients (Table 1: baseline characteristics) of whom 22 patients initiated DMARD treatment during the one-year follow-up. Strongest associations in the univariate analysis were found for RF (OR 2.4), morning stiffness >30 minutes (OR 2.9), ACPA (OR 3.8), US synovitis (OR 2.1) and PD signal (OR 4.8). In the

multivariate logistic regression the presence of morning stiffness >30 minutes (OR 3.7: 95%CI 1.4-9.5), ACPA (OR 4.0: 95%CI 1.5-10.6) and PD signal (OR 4.3: 95%CI 1.7-10.9) were associated with incident IA (Table 2).

Conclusion: One-year incident IA was present in 19% of the early arthralgia patients of which 53% showed US synovitis at baseline. The presence of PD signal, morning stiffness >30 minutes and ACPA were significantly associated with the development of IA after one year.

Table 1 Baseline characteristics (n=194)

	IA patients (n=37)	Non-IA patients (n=157)	p-value*
Women, n (%)	30 (81)	127 (80)	0.923
Age, years, mean (sd)	44 (11)	45 (12)	0.742
BMI, mean (sd)	26.7 (4.6)	27.3 (5.1)	0.476
SJC44, median (IQR)	0 (0-0)	0 (0-0)	-
TJC44, median (IQR)	4 (3-8)	5 (3-7)	0.979
RF positive, n (%)	14 (40)	34 (22)	0.031
ACPA positive, n (%)	12 (34)	18 (12)	0.001
ESR, median (IQR)	11 (6-24)	10 (5-19)	0.298
CRP, median (IQR)	2 (1-14)	3 (1-8)	0.917
Morning stiffness, minutes, median (IQR)	60 (30-90)	30 (15-60)	0.033
DAS28, mean (sd)	3.5 (1.1)	3.2 (1.0)	0.171
US synovitis, n (%)	20 (54)	52 (34)	0.039
PD score >0, n (%)	14 (38)	16 (11)	<0.001

IA: inflammatory arthritis; BMI: body mass index; SJC44: swollen joint count in 44 joints; TJC44: tender joint count in 44 joints; RF: rheumatoid factor; ACPA: anti-citrullinated protein antibody; DAS44: disease activity score in 44 joints; US: ultrasound; PD: power Doppler; IQR: interquartile range; sd: standard deviation; *Depending on the distribution of the data, we used the independent *t* test or the Wilcoxon-Mann-Whitney test, frequencies were compared using a Chi2 test, p-value≤0.05

Table 2 Univariate logistic regression analyses and multivariate logistic regression analysis after multiple imputation (n=194)

	Univariate model		Multivariate model 1		Multivariate model 2	
			US synovitis		Presence of PD	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
Demographics						
Age, years	0.99 (0.96-1.03)	0.732				
Sex	1.05 (0.42-2.62)	0.909				
BMI	0.97 (0.89-1.04)	0.384				
Clinical variables						
Tender joints, range 0-44	1.00 (0.92-1.08)	0.959				
DAS28	1.39 (0.97-1.99)	0.077				
Morning stiffness >30 minutes	2.85 (1.21-6.70)	0.016	3.64 (1.41-9.39)	0.007	3.67 (1.42-9.50)	0.007
Rheumatoid factor positive	2.35 (1.08-5.12)	0.032				
ACPA positive	3.79 (1.61-8.90)	0.002	4.89 (1.90-12.55)	0.001	3.98 (1.50-10.56)	0.006
CRP	1.00 (0.98-1.03)	0.754				
ESR	1.02 (0.99-1.04)	0.180				
Ultrasound						
US positive	2.13 (1.02-4.44)	0.044	2.23 (1.41-4.90)	0.045		
PD positive	4.80 (2.05-11.28)	<0.001			4.26 (1.67-10.86)	0.002

BMI: body mass index; ACPA: anti-citrullinated protein antibody; US: ultrasound; PD: power Doppler; OR: odds ratio

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Abstract Number: 1977

Impact of Ultrasound in Treatment Decision of Rheumatoid Arthritis Assessed in Routine Clinical Practice

César Sifuentes-Cantú[1], Lina Saldarriaga-Rivera[2], Ana Cecilia Lozada[2], Irazu Contreras-Yañez[3], Marwin Gutierrez[4] and Virginia Pascual-Ramos[5], [1]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Division of musculoskeletal and rheumatic diseases, Instituto Nacional de Rehabilitación, Mexico City, Mexico, [3]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico, Mexico, [4]Instituto Nacional de Rehabilitación, Mexico, Mexico, [5]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico
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SESSION INFORMATION

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Session Title: Imaging of Rheumatic Diseases II: Ultrasound in Rheumatoid Arthritis
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Background/Purpose: Remission or low disease activity is the therapeutic target for rheumatoid arthritis (RA). There is a consistent body of evidence supporting the value of ultrasound in the diagnosis, disease activity and treatment monitoring of RA patients. In spite of these pieces of information, the impact of ultrasound in treatment decisions in RA patients from real clinical setting has not yet sufficiently studied. Purpose: To explore the impact of ultrasound findings, in terms of the proportion of patients in whom treatment recommendation differed after the ultrasound examination in RA outpatients. We also tested the variations of ultrasound impact according to the level of patient´s disease activity or the physician´s experience.

Methods: 85 consecutive RA outpatients were included. In the 1st step a senior rheumatologist (SR) and a trainee in rheumatology (TR), blinded to each other evaluation performed a clinical assesment that included DAS28; then, they independently proposed a treatment recommendation. In a 2nd step, all patients underwent an ultrasound examination using the 7-joints score (US-7,[2]) by an experienced rheumatologist blinded to clinical evaluation; US-7 assessed gray scale sinovitis (GS), power doppler sinovitis (PD) and accordingly determined disease activity. In the final step, all the patients returned to both, the SR and the TR, who integrated the US-7 findings to their previous evaluation and reviewed their prescription. TR and SR changes of treatment (pre- and post-US-7) were recorded on standardized formats. Patients received final recommendation only from the SR. US-7 usefulness was separately evaluated by the SR and the TR according to a Likert scale (0= not useful at all, 10= very useful). Patients signed informed consent.

Results: Patients were mainly female (91.4%), with (mean±SD) 45.13 ± 12.4 years of age and disease duration of 7.45±3.9 years. Sixty one (71.8%) patients were in DAS28-remission (<2.6), meanwhile 24 (28.2%) had some level of disease activity according to DAS28. US-7 evaluations showed that 98.8% of the patients had at least some degree of GS sinovitis and 22.6% had PD. In 34 (20%) out of the 170 clinical evaluations (85 patients concomitantly evaluated by SR and TR), US-7 modified treatment and it was most frequently increased. Interestingly, 24 out of these 34 evaluations were performed by TR vs. 10 performed by the SR: 70.5% vs. 29.5%, p=0.01. Also, US-7 usefulness was scored higher by TR than by the SR, 4.9±2.5 mm vs. 4.1±1.8, p= 0.02. Disease activity did not affect the impact of US-7 on treatment recomendation.

Conclusion: US-7 findings impacted treatment in up to 20% of RA patients assessed in routine clinical practice; this impact was greater in TR than in SR. References: 1. Naredo E, Collado P, Cruz A, Palop MJ, et al. Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression. Arthritis Rheum. 2007 Feb 15;57(1):116-24. 2. Backhaus et al. Evaluation of a novel 7-joint ultrasound score in daily rheumatologic practice: a pilot project. Arthritis Rheum. 2009;61: 1194-201

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Abstract Number: 1978

Differential Pattern of Doppler Signals at Lower Extremity Entheses of Healthy Children

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Background/Purpose: Musculoskeletal ultrasound (MSUS) can enhance the clinical assessment of the pediatric enthesis. Doppler signals in particular are considered a sign of pathology but may not be specific for enthesitis. The normal pediatric enthesis can exhibit Doppler. The aim was to obtain data of knee and ankle entheses in healthy children at the peak of linear growth as a reference for patients.

Methods: 42 males and females, 11-14 years old, free of musculoskeletal (MSK) symptoms, conditions or medication affecting the MSK system, no MSK injuries in the past 3 months and no participation in sports more than 3 times per week took part. The Quadriceps insertion, proximal and distal patella tendon insertion and Achilles enthesis were examined in Power and Colour Doppler using an Esaote Mylab 70 XVG Gold with a linear probe 6 to 18 MHz. Doppler settings were optimized individually to obtain maximum sensitivity. Extremities were assessed in neutral and 30 degrees flexion. Images were acquired by one examiner and read by two. 10 volunteers were reassessed 2 days later. Presence of Doppler signals was assessed directly at the bone/cartilage interface as well as within 2mm, 5mm and 10mm using a scoring system 0=no Doppler signals via 1a=single signal, 1b=single confluent signal up to 3 b=3 and more confluent signals. Signals at the enthesis were differentiated from peri-tendinous and intra-cartilage signals. A marginal logistic regression model with generalized estimating equation for associations between ultrasound signal detection and distance, Doppler mode, position, location, and side of measurement was used. Agreement between observers and scan days was determined using prevalence- and bias-adjusted Kappa.

Results: Doppler signals were hardly ever present directly at the tendon bone junction but did show the highest prevalence within 2 mm of the enthesis with an Odds ratio (OR) of 4.58 (95 % CI 2.71-7.72), $p<0.001$, and 5 mm, OR 4.24 (95 % CI 2.18-8.25), $p<0.001$. Doppler signals were significantly less likely to be present in the proximal patella and Achilles tendon insertion compared with the Quadriceps and distal patella tendon insertion ($p<0.001$ each). There was no significant difference between right and left as well as the two degrees of flexion in the logistic regression model. The mean(range) for kappas between the first and second assessment at the various distances and entheses was 0.82 (0.45-1). The mean(range) for kappas regarding agreement between the

two readers at the various distances and entheses was 0.87 (0.46-1).

Conclusion: We found Doppler signals especially within 2 and 5 mm of the enthesis of the Quadriceps and distal Patella tendon. Contrary to results in adults with Spondylarthritis, Doppler signals were not consistently more prevalent in the flexed or extended position. Results showed good agreement between the right and the left extremity and were stable over time. Our results indicate the need to differentiate various entheses in MSUS. Doppler signals may be more specific for pathology in the proximal Patella tendon and Achilles tendon than in the Quadriceps or distal Patella tendon insertion. The exam should be performed in various positions of the joint.

Disclosure: J. Roth, Abbvie, 2,Abbvie, 5; **S. Stinson**, None; **L. Di Geso**, None.

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Abstract Number: 1979

Post-Arthroplasty Pain Trajectories after Total Knee Arthroplasty and Their Association with 6- and 12-Month Pain

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Background/Purpose: Total knee arthroplasty (TKA) is a common elective surgery to treat pain and functional limitation due to refractory arthritis. Post-operative pain is commonly underestimated and undertreated, which can prolong hospital stay, and interfere with engagement in rehabilitation exercises and lead to poorer health-related quality of life (HRQOL). Our **objective**was to examine if immediate post-arthroplasty pain trajectory (pain scores plotted from pre-operative to all time-points post-operative) is associated with long-term pain outcome after total knee arthroplasty (TKA), and assess important correlates of pain trajectories.

Methods: We used the data from the pain sub-study of the FORCE-TJR study, a nationally representative cohort of U.S. patients (n =28,000) undergoing TKA (or hip arthroplasty) from more than 150 surgeons in 22 states. In a sub-study, patients evaluated pain severity at 2- and 8-weeks after index TKA using a validated survey; pain was assessed on a 0-10 numeric rating scale (NRS). We used group-based trajectory models to determine the number and shape of short-term pain (baseline, 2 weeks, and 8 weeks post-op) trajectories. We then examined the predictive ability of these short-term pain trajectory for longer-term pain outcomes at 6 and 12 months, using

multiple linear regression analyses with logit function. Outcomes were Knee injury and Osteoarthritis Outcome Score (KOOS) pain at 6 and 12-months (higher score, worse pain). Multivariable logistic regression adjusted for age, gender, body mass index (BMI), race, Charlson Comorbidity count, and pre-operative health-related quality of life as measured by the SF-36 physical health (PCS) and mental health (MCS) scores.

Results: 659 TKA patients provided 2-week and 8-week pain survey data. The majority of respondents were female (64.5%) and at least 65 years old (66.5%). Among respondents two pain trajectories were evident, with majority being pain responders (72%); i.e. pain decreased in a meaningful way after TKA compared to pre-operative pain) and a smaller proportion were pain non-responders (28%). Early pain trajectory was highly significantly associated with 6- and 12-month pain outcome on KOOS. Additional factors significantly associated at 6 and 12 months were, Charlson Comorbidity count 3, and pre-operative PCS and MCS. African American/other race was significantly associated with pain outcome at 6 months, but not 12 months. Gender, age, and BMI were not significantly associated with pain trajectory at either 6- or 12-months.

Conclusion: We found that pain trajectory up to 8-weeks post-TKA surgery independently predicted longer-term pain outcome. Interventions to modify early post-operative pain experience may lead to better pain outcome (and other patient-reported outcomes) after TKA. Table 1. Predictors of 6- and 12-month KOOSpain scale after TKA among members of FORCE-TJR

	6-month		12-month	
	Coefficient	95% CI; p-value	Coefficient	95% CI; p-value
Non-responder Pain Trajectory	**-11.83**	**-14.48, 9.17; p<0.001**	-10.22	-13.98, -6.46; **p<0.001**
Age	0.06	-0.08,0.21;p=0.42	0.05	-0.16, 0.27; p=0.63
Gender (Female)	1.82	-0.71, 4.35; p=0.42	1.48	-1.94, 4.91; p=0.40
BMI				
25<30	0.30	-3.45, 4.06; p=0.87	-1.75	-7.02, 3.51; p=0.51
30<35	1.52	-2.30,5.33;p=0.44	-1.17	-6.45, 4.12; p=0.67
≥35	1.16	-3.00, 5.32; p=0.59	0.96	-4.79, 6.71; p=0.74
Race				
African American/Others	**-5.73**	**-10.88, -0.57; p=0.03**	1.66	-6.64, 9.95; p=0.69
Charlson Comorbidity Count				
1	-1.42	-4.28, 1.44; p=0.33	-2.94	-6.73, 0.86; p=0.13
2	-1.89	-6.13, 2.35; p=0.38	3.72	-2.17, 9.62; p=0.22
>= 3	**-7.63**	**-12.84, -2.42; p<0.001**	1.16	-5.99, 8.31; p=0.75
Pre-op SF-36 MCS	**0.30**	**0.15, 0.45; p<0.001**	**0.39**	**0.19, 0.60; p<0.001**
Pre-op SF-36 PCS	**0.31**	**0.21, 0.42; p<0.001**	**0.32**	**0.18, 0.47; p<0.001**

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Abstract Number: 1980

Relation of Pain Sensitization to the Evolution from Intermittent to Chronic, Persistent Pain in Knee Osteoarthritis: The Multicenter Osteoarthritis Study

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Background/Purpose: Patients with knee osteoarthritis (OA) often start with acute intermittent, activity-related pain, which evolves to additionally experiencing chronic, persistent pain; why this transition happens is not known. It is possible that peripheral and central sensitization, which is associated with knee pain severity in knee OA, contributes to the transition from solely acute intermittent pain to chronic, persistent pain. We assessed whether a marker of sensitization, pressure pain threshold (PPT), was associated with change from intermittent to chronic, persistent pain over time in a large cohort of older adults with or at risk of knee OA.

Methods: The Multicenter Osteoarthritis (MOST) Study is a NIH-funded cohort longitudinal cohort of persons with or at high risk of knee OA. Subjects had a standardized somatosensory evaluation of mechanical pressure pain thresholds (PPT) at the wrist and patella and completed pain questionnaires at baseline and two years later. PPT was assessed with an algometer ($1cm^2$ tip, 0.5 Kg/sec) as the point at which the subject felt the pressure change to slight pain. The average of 3 PPT trials was categorized into sex-specific tertiles. Lower PPT indicates more sensitization/pain sensitivity; at a site of disease (e.g., knee), it indicates peripheral sensitization, while at a site without disease (e.g., wrist), it indicates central sensitization. The Intermittent and Constant OA Pain (ICOAP) instrument assesses presence and severity of intermittent and constant pain, and for intermittent pain, its frequency (5-point Likert scale for each). Using the knee-specific ICOAP, pain patterns were defined as: 1) no intermittent or constant pain; 2) intermittent pain only (of at least mild severity occurring at least sometimes); and 3) constant pain (of at least mild severity) with or without intermittent pain. Among subjects with either no pain or intermittent pain only at baseline, we evaluated the relation of baseline PPT to incidence of constant pain using logistic regression. We compared the two highest PPT tertiles with the lowest tertile as there appeared to be a threshold effect. All analyses were adjusted for age, sex, BMI, depressive symptoms, catastrophizing, and clinic site.

Results: There were 1951 subjects included (mean age 68, 60% female, mean BMI 31), of whom ~8% developed constant pain over two years. A low level of peripheral sensitization, as reflected by medium and high knee PPT tertiles, was associated with a lower risk of developing incident constant pain [OR: 0.64 (0.40-1.00, p= 0.05)]. Similarly, a low level of central sensitization as measured by wrist PPT was also associated with a lower risk of incident constant pain [OR: 0.52 (0.32-0.86, p=0.01)].

Conclusion: Lower levels of peripheral and central pain sensitization are associated with lower rates of evolution or progression of the pain pattern from intermittent or no pain to constant pain over time. These

findings support the hypothesis that sensitization plays an important role in changing a patient's pattern and severity of OA-related pain. These findings have implications for understanding the transition from acute to chronic pain.

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Abstract Number: 1981

A Pilot Pulsed Arterial Spin Labeling Study of Regional Cerebral Blood Flow in Response to Pain in RA, before and after DMARD Treatment

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Background/Purpose: Although significant advances have been made in treating inflammation in RA, little is known about central nervous system (CNS) pain pathways in inflammatory arthritis. Recognizing this gap in knowledge, the ACR Pain Management Task Force emphasized the need for quantitative, non-invasive biomarkers of pain and the application of these measures to the study of pain. Our objective was to use pulsed arterial spin labeling (pASL), a type of functional MRI, to evaluate the neural correlates of clinical pain in RA and to characterize changes in CNS pain pathways in response to DMARD treatment.

Methods: This pilot study included 2 stages: 1) a cross-sectional analysis of 15 RA patients with active disease compared to 16 age- and sex-matched controls, and 2) a prospective analysis of 10 RA patients followed for 12-weeks after starting DMARD treatment. To be included, RA patients had to have chronic pain with an average of at least 3/10 in intensity at the MCPs and be starting a DMARD for active disease. Controls could not have current pain or have a history of chronic pain conditions or systemic inflammatory disease. All subjects underwent 6-min pulsed arterial spin labeling scans (voxel size = 3.515*3.515*6.25 mm, number of slices = 16) to assess regional cerebral blood flow (rCBF) using a 3T Siemens MAGNETOM Skyra, with a 32-channel head

coil. Scans were obtained under the following conditions: resting state and pressure at the left MCP joints. The experimental stimulus was applied using a blood pressure cuff inflated to achieve 40/100 pain in the patients and using the same pressure for the matched controls. RA patients were followed for 12-weeks after starting a DMARD and scanned again at the end of the treatment using the same parameters.

Results: The pressure stimulus was more painful in RA patients (median 50.0; interquartile range (IQR) 36.5-65.0) than in controls (median 3.5; IQR 0-11.3; p = 0.0001). Accordingly, a significant stimulus-induced increase in rCBF in the middle anterior and pregenual anterior cingulate cortices (aMCC/pgACC) was observed only in RA patients (Figure).The group x condition interaction trended for significance in a region-of-interest analysis (p = 0.065). After 12-weeks of treatment with a DMARD, normalized rCBF in the aMCC/pgACC decreased from a mean ± SD of 0.92 ± 0.08 to 0.87 ± 0.10 (one-sided p = 0.10), becoming similar to control values (0.87 ± 0.10).

Conclusion: These preliminary results suggest that: a) pASL may be able to identify CNS pathways involved in the regulation of pain in RA, and b) activity in these pathways may change in response to DMARD treatment. The aMCC and pgACC are brain regions that have been implicated in the cognitive modulation of pain affect in chronic, non-inflammatory pain states. Larger studies are needed to determine if rCBF in these regions will be useful as as an objective biomarker of pain in future studies evaluating the efficacy of pain interventions in RA.

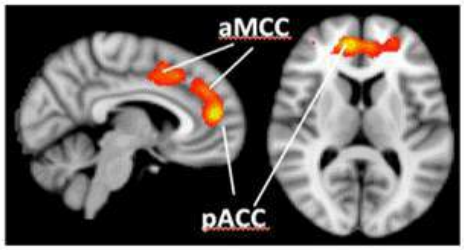

Figure. Pain-induced differences in regional cerebral blood flow in the middle anterior cingulate cortex (aMCC) and pregenual anterior cingulate cortex (pACC) in RA patients (N = 15) compared to controls (N = 16).

Disclosure: Y. C. Lee, None; **A. Fine**, None; **E. Protsenko**, None; **E. Massarotti**, None; **R. R. Edwards**, None; **V. Napadow**, None; **M. Loggia**, None.

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Abstract Number: 1982

Comparative Safety of Long-Acting Opioids for Non-Cancer Pain

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Background/Purpose: The use of opioid analgesics for non-cancer, primarily musculoskeletal pain, in the U.S. has increased markedly and has been accompanied by an increase in deaths and hospitalizations due to opioid toxicity. Opioids likely vary with regard to these risks. There are particular concerns about transdermal fentanyl and long-acting oxycodone. Transdermal fentanyl has variable absorption and prolonged effects. There was an increase in opioid-related mortality after the addition of long-acting oxycodone to formularies and reports that oxycodone was involved in approximately one in three cases of opioid-related deaths. Thus, it is important to define the comparative safety of long-acting opioids, particularly transdermal fentanyl and oxycodone. We aimed to compare the risk of death in patients with chronic non-cancer pain receiving transdermal fentanyl, oxycodone slow release (SR), and morphine SR.

Methods: We conducted a retrospective cohort study in 50,658 patients enrolled in Tennessee Medicaid who filled prescriptions for: transdermal fentanyl (n=8,717), oxycodone SR (n=14,118), or morphine SR (n=27,823) between 1/1/1999 through 12/31/2011. Individuals with cancer or other serious diagnoses were excluded. The primary outcome was out-of-hospital mortality. Relative risk was estimated with the use of Cox proportional hazard models; propensity scores were used to adjust for multiple potential confounders, using a time-dependent analysis.

Results: Long-acting opioids were used primarily for musculoskeletal pain, which accounted for more than 90% of the prescriptions. There were 689 deaths during 44,385 person-years of follow-up; the all-cause mortality rate was 155/10,000 patient-years. All-cause mortality was not significantly different in patients using transdermal fentanyl compared to morphine SR (adjusted HR=0.96, 95% C.I.: 0.77-1.21). However, patients taking oxycodone SR had 21% lower mortality risk (adjusted HR=0.79, 95% C.I. 0.66-0.95) than those receiving morphine SR. Sensitivity analyses, including propensity score–matched cohorts and follow-up restricted to the first year of evaluation yielded similar results.

Conclusion: Patients taking long-acting opioids for non-cancer pain, primarily musculoskeletal pain, have a high mortality risk. Our findings suggest that there is a significant decreased risk of death in patients taking oxycodone SR compared to those taking morphine SR.

Disclosure: C. P. Chung, None; **W. Dupont**, None; **K. Murray**, None; **K. Hall**, None; **C. M. Stein**, None; **W. Ray**, None.

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Abstract Number: 1983

Pain and Sensitization in Women with Aromatase Inhibitor-Associated Arthralgias

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Background/Purpose: Aromatase inhibitors (AIs) are the preferred treatment for estrogen receptor positive breast cancer in postmenopausal women, but are frequently associated with arthralgias, which can decrease adherence. While the syndrome of AI-associated arthralgias has been well-recognized, the mechanism by which AIs induce arthralgias is not clear. Estrogen may be anti-nociceptive, and therefore with estrogen deprivation, it is possible pain sensitization develops. Further, whether exercise, which decreases AI-associated arthralgia pain, mediates its effects through improving pain sensitization is not known. Pressure pain threshold (PPT) provides one means of assessing pain sensitization. We therefore examined the relation of PPT to pain in AI-associated arthralgias, and also evaluated the effect of exercise on pain and PPT.

Methods: The HOPE (Hormones and Physical Exercise) study randomized 121 postmenopausal women with history of breast cancer treated with AIs for at least 6 months and also had arthralgias to an exercise intervention versus usual care. Exclusion criteria included pre-existing rheumatologic conditions. The exercise group had supervised resistance training twice a week and 150 minutes of aerobic exercise weekly. The usual care group did not have any specific exercise support. Self-reported pain severity (WOMAC for lower extremity symptoms; QuickDash for upper extremity symptoms), pain location and an assessment of pain sensitization measured by PPT evaluations at the knee and wrist using a hand-held algometer were obtained. We evaluated the relationship between pain severity, number of painful sites and PPT using linear regression.

Results: Of the 121 subjects enrolled in the trial, 99 subjects had pain and PPT data available at 6-months. Their mean age was 62 and mean BMI was 30. Higher number of joints with pain were associated with higher baseline pain severity scores on WOMAC (42.6±5.2 for 7-10 sites vs. 9.4±3.7 with 0-3 sites, $p<.0001$) and on QuickDash (29.2±3.4 for 7-10 sites vs. 12.0±2.3 with 0-3 sites, $p<.0001$), and with lower PPT at baseline (PPT 1.94±0.47 for 7-10 sites and 3.31±0.32 with 0-3 sites, p 0.02) (**Table 1**). While pain severity improved more in the exercise arm than the usual care arm, there was no significant change in PPT over time (**Table 2**).

Conclusion: The severity of AI-associated arthralgias by WOMAC and QuickDash were associated with number of painful joints and PPT. While pain severity improved with exercise, this improvement was unrelated to improvement in PPT, suggesting that pain improvement through exercise must occur through mechanisms other than improvements in pain sensitization.

Table 1: Relation of Number of Painful Sites to Pain Severity (WOMAC, QuickDash) and to PPT

	# of Patients	Pain sites	Baseline Mean ± SE	Overall p-value	p-value
QuickDash	26	0-3	12.0 ± 2.3	0.0001	
	26	4-6	22.4 ± 2.3		0.002
	12	7-10	29.2 ± 3.5		<.0001
WOMAC	26	0-3	9.4 ± 3.7	<.0001	
	26	4-6	17.6 ± 3.6		0.1
	12	7-10	42.6 ± 5.2		<.0001
PPT wrist	26	0-3	3.3 ± 0.3	0.06	
	26	4-6	3.1 ± 0.3		0.6
	12	7-10	1.9 ± 0.5		0.02
PPT knee	26	0-3	3.3 ± 0.3	0.07	
	26	4-6	2.6 ± 0.3		0.1
	12	7-10	1.9 ± 0.5		0.03

Table 2: Change in Pain Severity and PPT over 12 months by Intervention Group

	Exercise		Usual Care		
Change over 12 months	Mean	95% CI	Mean	95% CI	p-value
WOMAC	-9.4	-14.2 to -4.6	9.9	2.8 to 16.9	<.001
QuickDash	-6.7	-10.0 to -3.4	1.3	-2.3 to 4.9	0.002
PPT wrist	-0.4	-1.2 to 0.5	0.1	-0.7 to 0.9	0.4
PPT knee	-0.4	-1.3 to 0.5	0.7	-0.1 to 1.5	0.08

Disclosure: M. Crespo-Bosque, None; **C. Brown**, None; **B. Cartmel**, None; **M. Harrigan**, None; **M. Irwin**, None; **T. Neogi**, None.

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Abstract Number: 1984

Which Factors Associate with Localized Knee Pain and Generalized Pain: A 10-Year Longitudinal Study?

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Background/Purpose: The correlates of localized knee pain (KP) and multi-site pain (MSP) have been clearly

demonstrated; however, whether these factors also contribute to intermittent or persistent knee pain or MSP remains unclear. Furthermore, which peripheral structural pathology leads to persistent knee pain or MSP is yet available, there may be different mechanisms underlying their pathogenesis. Therefore, this study aimed to describe the risk factors for persistent knee pain and persistent MSP, and to investigate the associations of MRI-defined knee structural pathology with these different types of pain.

Methods: 1099 participants (mean age 63 years; range 51-81 years) from the population-based Tasmanian Older Adult Cohort study were recruited at baseline. 875, 768 and 563 participants attended years 2.6, 5.1 and 10.7 follow-up, respectively. Demographic, psychological, lifestyle and comorbidities data were obtained at baseline. T1-weighted or T2-weighted fat saturated MRI of the right knee was performed to measure knee structural pathology--cartilage defects, bone marrow lesions (BMLs) and effusion-synovitis at baseline. Presence of pain (yes/no) at the neck, back, hands, shoulders, hips, knees and feet was assessed by questionnaire at each time-point. Participants were classified as never (N), persistent (P) and intermittent (I) pain, respectively, if they had knee pain or MSP (≥2 sites) at: no assessment, four consecutive assessments from baseline with all others considered intermittent pain. Multi-nominal logistic regression was used to analyse the data with adjustment for potential confounders.

Results: A total of 563 patients (50% female, mean BMI 27.6 kg/m^2) were included. Of these, 33%, 50% and 17% were NKP, IKP and PKP, and 11%, 41% and 48% were NMSP, IMSP and PMSP, respectively. In multivariable analyses, IKP and PKP were significantly associated with baseline BMI, emotional problems, and musculoskeletal diseases. Female gender was also associated with increased odds of IMSP and PMSP. There were no associations of age, physical activity, education level, occupation and other comorbidities with either KP or MSP. Furthermore, PKP but not IKP was associated with cartilage defects (OR 2.55, 95% CI 1.38 to 4.72), BMLs (OR 1.93, 95% CI 1.07 to 3.47) and effusion-synovitis (OR 1.89, 95% CI 1.08 to 3.31) after adjustment for age, sex, BMI, other potential confounders. However, no significant associations of these lesions with IMSP or PMSP were observed.

Conclusion: Higher BMI, psychological problems and musculoskeletal diseases are associated with both intermittent and persistent KP and MSP, suggesting that factors contributing to pain may be shared in the pathogenesis of regional and generalised pain, but gender may have a different role in regional pain and generalized pain. Knee structural lesions predict PKP but not IKP, IMSP and PMSP, indicating that peripheral pathology is most important for ongoing localized pain, but it might be a trigger in contributing to generalised pain. Further research is needed to understand the underlying mechanisms of structural pathology differences in regional pain and generalised pain.

Disclosure: F. Pan, None; **D. Aitken**, None; **J. Tian**, None; **F. M. Cicuttini**, None; **C. Ding**, None; **G. Jones**, None.

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Abstract Number: 1985

IL-18 Elevation in Macrophage Activation Syndrome: Human Evidence for a Chronic Set-Point and Murine Evidence for a Non-Hematopoietic Source

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Background/Purpose: Macrophage Activation Syndrome (MAS) is a life-threatening sepsis-like condition complicating many systemic JIA (sJIA) and Adult-Onset Stills Disease (AOSD) patients. We recently identified that gain-of-function mutations in inflammasome component *NLRC4* cause an inflammasomopathy of early-onset enterocolitis, life-threatening MAS, and extraordinary serum IL-18. Similar serum IL-18 levels are also present in sJIA/AOSD patients with a history of MAS.

Methods: We used plate-bound ELISA and custom bead-based multiplex cytokine arrays to characterize IL-18 and related cytokines in a uniquely broad cohort of autoinflammatory patients with and without a history of MAS. We genome-edited a gain-of-function mutation in *Nlrc4* into the mouse germline and assessed IL-18 levels in *Nlrc4*/wildtype bone marrow chimeras.

Results: Extraordinary elevations of serum IL-18, but not its endogenous antagonist IL-18 Binding Protein (IL-18BP) or other related cytokines, uniquely marked patients with a history of MAS but not other inflammasomopathies or IL-1-mediated diseases. Patients with monophasic disease show a slow normalization of serum IL-18 long after normalization of other cytokines and acute phase proteins while patients with early-onset or relapsing disease, including those bearing *NLRC4* mutations, showed persistence of extraordinary IL-18. IL-18 in some patients measured serially over several years showed persistence of an abnormally high "set point" even with completely inactive disease (Fig.1). Mice bearing an *Nlrc4*-T337S point mutation displayed no spontaneous inflammation, but demonstrated chronic elevation of serum IL-18. Elevated IL-18 was present as early as 3 weeks of age and was unaffected by administration of broad-spectrum antibiotics. Elevated IL-18 was dependent on the inflammasome adaptor ASC, suggesting canonical inflammasome activation and cleavage of IL-18. Surprisingly, bone marrow chimeras made from Nlrc4-T337S mice demonstrated that IL-18 hyperproduction derived from non-hematopoietic cells (Fig.2).

Conclusion: Extraordinary high serum IL-18 levels are uniquely associated with the clinical presentation of recurrent MAS and may be a promising diagnostic biomarker and therapeutic target. The main source of IL-18 in Nlrc4-T337S mice is non-hematopoietic and suggests that the serum IL-18 "set point" observed in MAS patients, particularly those with *NLRC4* mutations, would be resistant to bone marrow transplantation. This research was supported by the Intramural Research Programs of NIAMS and NIAID of the NIH.

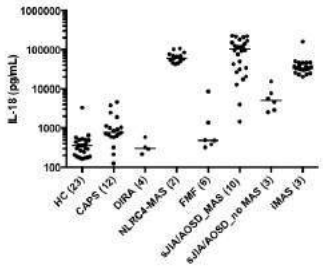

Figure 1: Serum IL-18 in patients with inflammmasomopathies (CAPS-Cryopyrin-Associated Periodic Syndromes and FMF- Familial Mediterranean Fever) and the IL-1 mediated disease DIRA-Deficiency of IL-1 Receptor Antagonist. Diagnosis (number of pts) HC-healthy controls; iMAS-Idiopathic MAS.

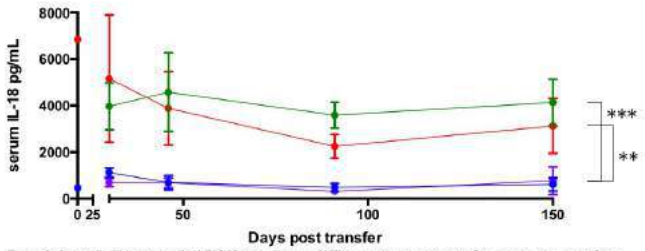

Figure 2: Serum IL-18 levels in *Nlrc4*-T337S and wild-type (WT) bone marrow chimeras. Day 0 indicates serum from donor mice. Blue = WT immune cells, WT host; Purple = *Nlrc4*-T337S immune cells, WT host; Green = WT immune cells, *Nlrc4*-T337S host; Red = *Nlrc4*-T337S immune cells, *Nlrc4*-T337S host. **p<0.01, ***p<0.005, Repeated Measures ANOVA with Tukey's post-test.

Disclosure: Z. Tariq, None; **E. Weiss**, None; **W. Goodspeed**, None; **R. Goldbach-Mansky**, None; **S. Canna**, AB2Bio, 6.

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Abstract Number: 1986

Murine Model of Arthritis Flare Identifies Tissue Resident Memory T Cells in Recurrent Synovitis

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Background/Purpose: There are 75,000 children affected by JIA in the United States. Despite recent therapeutic advances, treatment often requires chronic therapy and is associated with considerable cost and morbidity, yet is still not curative as episodic flares are common. However, the pathophysiology of these flares is not well understood. There is a common observation that arthritis flares exhibit a strong tendency to recur in the same joints. This fixed pattern of joint involvement is highly individualized and persists for decades. To study this phenomenon, we established a murine model of recurrent, joint-specific inflammation.

Methods: Methylated bovine serum albumin (meBSA) or ovalbumin (OVA) is injected into the wrist, knee and ankle joints of B6 mice. The contralateral side was injected with vehicle as a negative control. For the OVA conditions, 5x10^6 CD3+ cells collected from peripheral lymph nodes of OT-I mice were transferred IV into the mice 1 day prior to intra-articular OVA injection. Interleukin-1 was concurrently injected into the footpad of the mice to stimulate the immune response. Arthritis flare was triggered by i.p. meBSA or OVA re-stimulation. At days 7 (acute inflammation), 28 (remission) and 31 (flare), the joints were analyzed for inflammation by measuring joint thickness, histological evaluation, and flow cytometry analysis of disaggregated synovium.

Results: 7 days after injection, there is measureable swelling and histological evidence of synovitis, specifically in the joints exposed to the antigen. In the synovium, there is a corresponding increase in CD4 and CD8 T cell populations. At 28 days after injection, inflammation subsides with normalization of both joint size and resolution of synovitis. During this post-inflammatory remission, we found a persistent population of antigen-specific cells with resident memory T cell (TRM) phenotype (CD45.2+CD3+CD8+CD44+CD62L-CD69hi). These TRM cells are preferentially increased in the synovium of the joint exposed to antigen. Upon intraperitoneal challenge with antigen, there is a recurrent inflammation specifically in the joints previously exposed to antigen, and a corresponding expansion of antigen-specific CD8+ TRM cells in the synovium is also seen.

Conclusion: Here, we created an inducible model of recurrent, joint-specific inflammation. Our data suggests synovial resident memory T cells may represent the basis for joint-specific memory in inflammatory arthritis.

Abstract Number: 1987

Recessive Coding and Regulatory Mutations in FBLIM1 Underlie the Pathogenesis of Sterile Osteomyelitis

Allison Cox[1], Benjamin W Darbro[2], Ronald Laxer[3], Xinyu Bing[4], Alexis Finer[5], Albert Erives[6], Vinit Mahajan[7], Alexander G Bassuk[1] and Polly Ferguson[8], [1]Pediatrics and Interdisciplinary Graduate Program in Genetics, University of Iowa Carver College of Medicine, Iowa City, IA, [2]Department of Pediatrics and Interdisciplinary Graduate Program in Genetics, University of Iowa Carver College of Medicine, Iowa City, IA, [3]Div of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [4]Department of Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA, [5]Pediatrics, University of Iowa Carver College of Medicine, Iowa City, IA, [6]Biology and Interdisciplinary Graduate Program in Genetics, University of Iowa Carver College of Medicine, Iowa City, IA, [7]Department of Ophthalmology and Visual Sciences,, University of Iowa Carver College of Medicine, Iowa City, IA, [8]Department of Pediatrics--Rheumatology, University of Iowa Carver College of Medicine, Iowa City, IA

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Background/Purpose: Chronic recurrent multifocal osteomyelitis (CRMO) is a rare, pediatric, autoinflammatory disease characterized by bone pain due to sterile osteomyelitis, and is often accompanied by psoriasis or inflammatory bowel disease. There is evidence for a genetic basis in several syndromic forms of the disease including the Deficiency of the Interleukin-1 Receptor Antagonist (DIRA; due to mutations in *IL1RN*), Majeed syndrome (due to mutations in *LPIN2*) and murine chronic multifocal osteomyelitis (due to mutations in *Pstpip2*). However, for the majority of cases of CRMO, the genetic basis remains unknown.

Methods: We used whole exome and Sanger sequencing, gene expression microarray and Luciferease assays to identify additional CRMO susceptibility genes.

Results: Via whole-exome sequencing, we detected a homozygous mutation in the filamin-binding domain of *FBLIM1* in an affected child with consanguineous parents. Microarray analysis of bone marrow macrophages from the CRMO murine model (cmo mouse) determined that the *Fblim1* ortholog is the most differentially expressed gene, further implicating it in disease pathogenesis. In addition, studies suggest FBLIM1/FBLP1 is an anti-inflammatory molecule regulated by STAT3, and one involved in bone remodeling via ERK1/2 phosphorylation and the subsequent regulation of RANKL activation. We sequenced *FBLIM1* in 96 CRMO subjects and found a second proband with compound heterozygous mutations in *FBLIM1* composed of a novel frameshift mutation in exon 6 and a rare regulatory variant. The enhancer contains binding sites for STAT3 and NR4A2. Enhancer activity of a 1-kb region around the mutation was validated by luciferase assays in fluoride-treated SaOS2 cells, as was the effect of the mutation on regulatory activity. In SaOS2 cells, overexpressing the regulatory mutation showed the flanking region acts as an enhancer, and the mutation ablates enhancer activity.

Conclusion: Our data implicate *FBLIM1* in the pathogenesis of CRMO and autoinflammatory disease.

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Abstract Number: 1988

Oral Health and Anti-Citrullinated Peptide Antibodies in Juvenile Idiopathic Arthritis

Sriharsha Grevich[1,2], Peggy Lee[3], Sarah Ringold[1,4,5], Brian Leroux[3], Hannah Leahey[5], Megan Yuasa[5], Jessica Foster[5], Jeremy Sokolove[6], Lauren Lahey[7], William Robinson[7], Joshua Newson[8] and Anne Stevens[2,5,8], [1]Pediatrics, University of Washington, Seattle, WA, [2]Seattle Children's Hospital, Seattle, WA, [3]School of Dentistry, University of Washington, Seattle, WA, [4]Seattle Children's Hospital, seattle, WA, [5]Seattle Children's Research Institute, Seattle, WA, [6]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [7]Stanford University, Stanford, CA, [8]University of Washington, Seattle, WA

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Background/Purpose: Oral pathogens that cause periodontitis have been implicated as triggers for rheumatoid arthritis (RA), via antibodies to citrullinated proteins. Gingivitis is common in children and is a chronic inflammatory precursor to periodontitis. Patients with juvenile idiopathic arthritis (JIA) rarely produce anti-citrullinated peptide antibodies (ACPA). The children with polyarticular JIA who carry ACPA tend to have more aggressive arthritis, similar to adult RA patients. We hypothesized that gingival inflammation is associated with JIA, and that ACPA may represent a link between JIA and oral health. Our objectives were to: (a) Test for increased frequency of gingivitis in children with JIA compared to controls and (b) Test for correlations between ACPA and dental clinical outcomes.

Methods: This was a cross-sectional study of 85 patients with JIA and 62 dental clinic patients at a children's hospital. A second control group was derived from 11 healthy child volunteers. Serum from an additional historic cohort of 30 healthy children was used to study ACPA. Dental indices were compared between groups using linear regression adjusting for demographic characteristics. ACPA were detected with a commercial CCP3 assay and also to 29 citrullinated full-length peptides using a custom multiplex autoantibody assay. Elevated levels for antibodies to each peptide were defined as values larger than the maximum value for the historical controls. Positive ACPA was defined as elevated levels of antibodies specific for more than 4 of the citrullinated proteins. The prevalence of positive ACPA was compared across groups using the Fisher's exact test.

Results: Although JIA patients overall had better oral health than dental controls they had significantly more bleeding on probing of the gingiva, the most specific sign of active inflammation ($p = 0.007$). There was no correlation between JIA disease activity or immunosuppression with dental indices. TMJ arthritis was

associated with a higher gingival index. Patient smoking (only present in dental group) and household smoking exposure in JIA group correlated with a worse 'decay, missing, filling teeth' index (DMFT) score. By commercial CCP3 assay ACPA were detected in only four JIA patients (all poly-JIA), but elevated levels were detected by the custom array in 15/41 (37%) of poly JIA, 14/36 (39%) of oligo JIA, and 19/58 (33%) of dental controls. Antibodies to more than 4 citrullinated peptides were most common in poly JIA 9/41 (22%) compared with 1/36 (3%) for oligo JIA, and 2/58 (3.4%) for dental controls, (p=0.002). We found no associations between ACPA status and any dental index.

Conclusion: Gingival inflammation was associated with JIA, suggesting that a systemic immune response could be triggered by oral bacteria involved in both oral and synovial inflammation, and cannot be attributed to poor dental hygiene secondary to JIA disability. Microbial analysis of plaque will help understand this relationship further. No association was found between ACPA and gingival inflammation; however more sensitive and specific tests for ACPA may lead to improved prognosis and understanding of the triggers for arthritis in children.

Disclosure: S. Grevich, None; **P. Lee**, None; **S. Ringold**, None; **B. Leroux**, None; **H. Leahey**, None; **M. Yuasa**, None; **J. Foster**, None; **J. Sokolove**, None; **L. Lahey**, None; **W. Robinson**, None; **J. Newson**, None; **A. Stevens**, None.

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Abstract Number: 1989

Mechanism of STAT3 Gain-of-Function in a Patient with JIA

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Background/Purpose: The transcription factor signal transducer and activator of transcription 3 (STAT3) mediates cytokine-induced changes in gene expression. STAT3 is classically activated by phosphorylation followed by homodimerization, nuclear translocation and DNA binding. STAT3 is downstream of numerous cytokines, including interleukin-6 (IL-6). IL-6 is a pro-inflammatory cytokine and therapeutic blockade of the IL-6 receptor using tocilizumab is approved for the treatment of rheumatoid arthritis and juvenile idiopathic arthritis. Germline, gain-of-function (GOF) mutations in STAT3 have been shown to cause multi-organ autoimmunity, including juvenile-onset polyarthritis. Patients with STAT3 GOF also have short stature and decreased T regulatory cells. Specific mechanisms by which STAT3 GOF mutations impact the roles of STAT3 have not been determined.

Methods: We investigated STAT3 activation using flow cytometry and Western blot in STAT3-deficient cells and cells engineered with heterozygous (het) and homozygous (homo) mutations in the STAT3 DNA binding domain (G421R), modeling a variant discovered in a GOF patient with polyarthritis, autoimmune hemolytic anemia, autoimmune hepatitis and scleroderma-like skin. Constructs containing STAT3 cDNA were modified and used in transfection experiments with a luciferase reporter. DNA binding was determined using an ELISA based assay. G421R STAT3 GOF mice were created using genetic engineering. Phenotypic characteristics were noted and the T cell compartments were analyzed by flow cytometry *ex vivo*and after polarization.

Results: De-phosphorylation of G421R is delayed in a dose-dependent manner (homo>het>WT) in response to multiple cytokines, similar to primary patient cells. However, co-transfection of WT with G421R results in reduced transcriptional activity compared to G421R alone, suggesting G421R is not dominant. Cellular fractionation experiments reveal the prolonged phospho-G421R is retained in the nucleus. This was consistent with the finding that G421R displayed stronger DNA binding. After IL-6 stimulation, un-phosphorylated G421R increases compared to WT. Unlike WT, un-phosphorylated G421R is also found in the nucleus in the resting state. Further, un-phosphorylated G421R retains transcriptional activity, unlike un-phosphorylated WT. Interestingly, STAT3 GOF mice recapitulate the small size noted in STAT3 GOF patients, and in a dose-dependent fashion. After polarizing conditions, CD4 T cells from STAT3 GOF were less likely to develop into CD25+Foxp3+ regulatory cells, but produced increased IL-17 expressing cells.

Conclusion: Our data suggests that G421R enhances STAT3 activity through increased DNA binding and enhanced transcriptional capacity of un-phosphorylated molecules. Initial characterization of STAT3 GOF mice suggests this model recapitulates the human disease. Future work will further characterize these mice, as well as investigate the mechanisms of other STAT3 GOF mutations. These studies will provide valuable information on the role of STAT3 in autoimmunity and arthritis, particularly given the potential impact of therapeutic inhibition of STAT3 in human disease.

Disclosure: T. P. Vogel, Mallinckrodt Pharmaceuticals, 2; **N. Saucier**, None; **M. P. Keppel**, None; **M. A. Cooper**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mechanism-of-stat3-gain-of-function-in-a-patient-with-jia

Abstract Number: 1990

Increased Risk of Cardiovascular Events in Patients with Rheumatoid Arthritis over a 15 Year Time Period That Is Comparable to Type 2 Diabetes

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Center, Location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands
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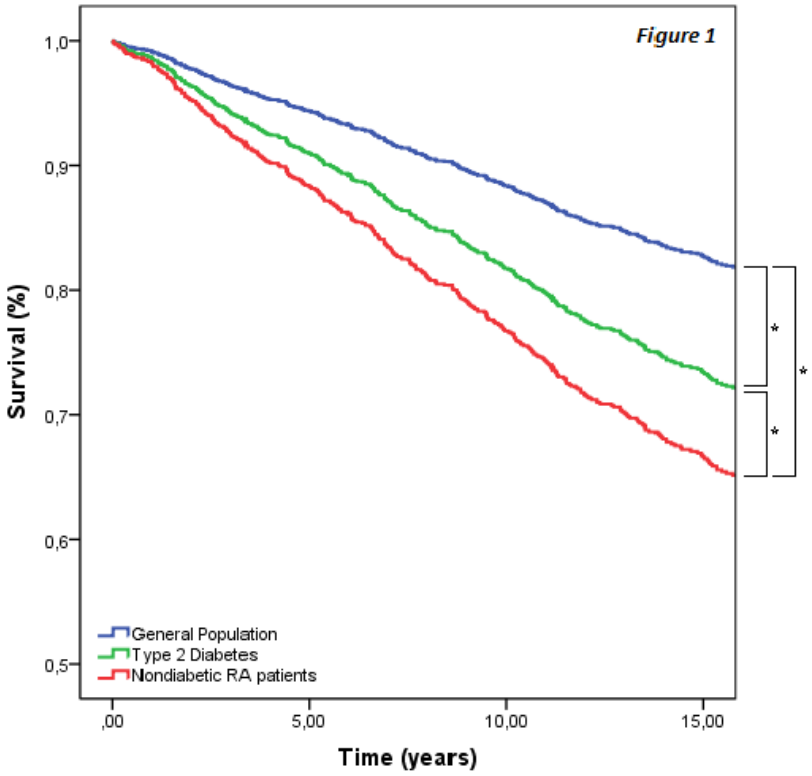
Session Date: Monday, November 14, 2016
Session Title: Rheumatoid Arthritis – Clinical Aspects II: Risk and Impact of Comorbidity
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

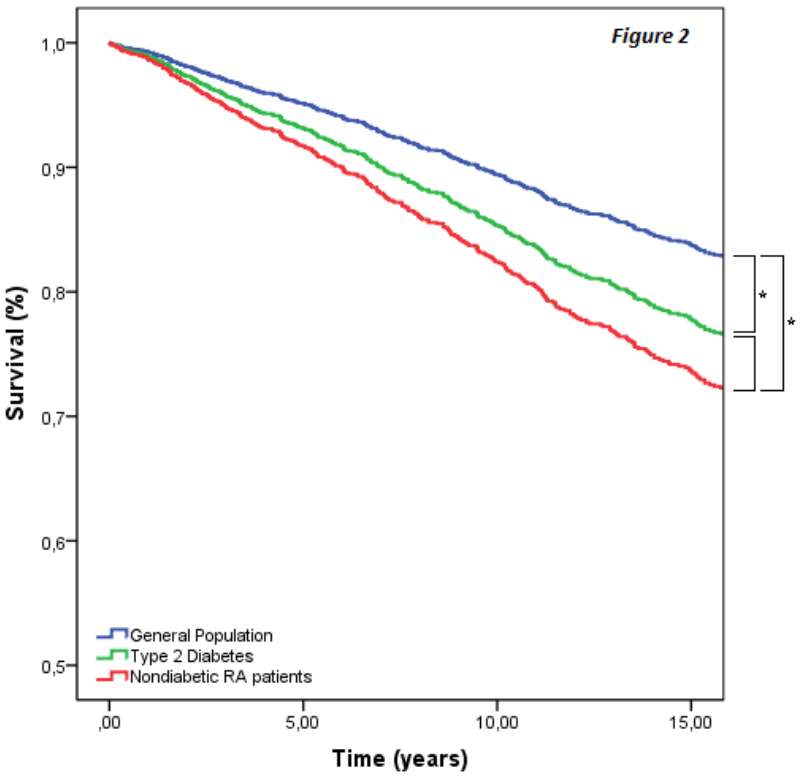
Background/Purpose: Cardiovascular (CV) disease is a prevalent comorbidity in patients with rheumatoid arthritis (RA). However, recent cohort studies with long term follow up studying this risk are scarce. We report the results of a 15 year observational cohort study comparing the risk of CV events in patients with RA to the general population and participants with type 2 diabetes (DM).

Methods: The CARRÉ study is a prospective cohort study with the purpose of investigating CV disease and its risk factors in a random sample of 353 patients with longstanding RA. CV endpoints were assessed at baseline, 3, 10 and 15 years of follow up and compared to the Hoorn Study population (n=2540), a cohort representative of the general population designed to analyze glucose metabolism and CV risk factors over 15 years. Incidence rates per 100 person-years were calculated and Cox regression analyses were performed to investigate CV risk in these persons.

Results: 96 patients with RA developed a CV event during 2703 person-years of follow up resulting in an incidence rate of 3.6 per 100 person-years. In the Hoorn Study population, 298 individuals developed a CV event, of which 41 had DM, during a follow up of 25335 person-years, resulting in an incidence rate of 1.4 per 100 person-years in the general population. Age and sex adjusted hazard rates (HR) for CV events were increased for RA (2.14 [95% CI 1.65-2.78, P<0.01]) and DM (1.63 [95% CI 1.17 – 2.27, P<0.01]) compared to the general population (figure 1). HR was significantly increased in RA (1.73 [95% CI 1.27 – 2.35, P<0.01]) and reached borderline significance in DM (1.42 [95% CI 1.00 – 2.00, P=0.047]) after additional adjustment for traditional CV risk factors (figure 2). Exclusion of prevalent CV disease resulted in increased HR for RA (2.16 [95% CI 1.53 – 3.04, P<0.01]) and not for DM (1.28 [95% CI 0.83 – 1.98, P=0.27]) compared to the general population after adjustment for traditional CV risk factors.

Conclusion: The incidence rate of CV events was 3.6 per 100 person-years in patients with established RA which is more than double that of the general population. RA patients have an increased risk of CV endpoints comparable to type 2 DM. This increased risk remains for RA patients even after adjustment for traditional CV risk factors, indicating that the (ongoing) systemic inflammation of RA is an independent contributor to CV risk.





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Abstract Number: 1991

Risk of Incident Diabetes Mellitus and Its Association with Disease-Modifying Antirheumatic Drugs and Statins in Rheumatoid Arthritis

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Background/Purpose: Diabetes mellitus (DM) is an important cardiovascular risk factor in RA. Although a few prior studies reported DM risk reduction with hydroxychloroquine (HCQ) and TNF inhibitors in RA, at present the impact of newer biologics and statins, the timing, dosing and the sustainability of the HCQ effect are unknown. In this study, we examined the incident DM rate and the impact of DMARDs and statins in RA patients.

Methods: We studied patients with RA and ≥1 year participation in the National Data Bank for Rheumatic Diseases without baseline DM from 2000 through 2015. DM was determined by self-report or initiating DM medication. DMARDs were categorized into 4 mutually exclusive groups: (1) MTX monotherapy (reference) (2) any abatacept (ABA) with or without MTX (3) any other DMARD with MTX (4) all other DMARDs without MTX; along with separate statin, glucocorticoids (GC), and HCQ (yes/no) variables. Time-varying Cox proportional hazard models were used to adjust for sociodemographics, comorbidities, BMI, and RA severity measures.

Results: A total of 1,139 incident DM cases were observed during median (IQR) 4.6 (2.5-8.8) years of followup in 13,669 RA patients. The incidence rate in RA patients found to be increased (age and sex-adjusted SIR 1.37 [1.29-1.45]) compared to that of in US adult population (*Table 1*). Adjusted HR (95% CI) for DM were 0.67 (0.57, 0.80) for HCQ, 0.52 (0.31, 0.89) for ABA, 1.31 (1.15, 1.49) for GC, and 1.56 (1.36, 1.78) for statins. Other synthetic/biologic DMARDs were not associated with any risk change (*Table 2*). DM risk reduction started after 2 years of HCQ treatment, HR 0.76 (0.58-1.00), and continued to decrease with longer duration, >4 years HR 0.69 (0.59-0.81). HCQ doses of <400mg/day (HR 0.71, 0.52-0.96) and ≥400mg/day (HR 0.66, 0.55-0.81) were both associated with DM risk reduction. Patients who initiated and then discontinued HCQ (N=342) had a nonsignificant risk reduction up to 6 months compared to HCQ never-used patients: HR 0.65 (0.21-2.0) for ≥ 3 months, 0.88 (0.28-2.75) for ≥ 6 months, and 1.27 (0.31-5.10) for ≥ 1 year off-HCQ. Concomitant use of HCQ either with GC (HR 0.69, 0.51-0.93) or statins (HR 0.92, 0.68-1.25) abolished risk increase associated with both drugs.

Conclusion: Incidence of DM in RA patients is increased. HCQ and ABA were associated with decreased risk of DM, and GC and statins with increased risk. HCQ confers a sustainable, dose and treatment duration-dependent DM risk reduction, and also attenuates the increased risk associated with GC or statins. Careful monitoring for DM should be considered in RA patients especially who were on GC or statins.

Table 1. Crude incidence rates (95% CI) and standardized incidence ratios (95% CI) of diabetes in rheumatoid arthritis by treatment compared with US population

	No. of DM	Person-years	Incidence rate (95% CI) per 100 person-years	SIR* (95% CI)
All patients	1,139	71,668	1.59 (1.50-1.68)	1.37 (1.29-1.45)
Any statins	369	14,851	2.48 (2.24-2.75)	2.10 (1.89-2.34)
Any glucocorticoids	407	20,369	1.99 (1.81-2.20)	1.72 (1.56-1.91)
Any HCQ	161	15,603	1.03 (0.88-1.20)	0.91 (0.78-1.07)
DMARD Category				
MTX monotherapy	186	12,761	1.46 (1.26-1.68)	1.21 (1.04-1.42)
Any abatacept	17	1,490	1.14 (0.71-1.83)	0.96 (0.58-1.59)
Any other DMARD with MTX	224	15,270	1.47 (1.29-1.67)	1.27 (1.10-1.45)
Other or no DMARDs	551	26,541	2.08 (1.91-2.26)	1.82 (1.67-1.99)

**All participants included were age <80 years.*

Table 2. Association of different treatments with incident diabetes in RA patients				
Time-dependent treatment variables	**Unadjusted Hazard Ratio (95% CI)**	***P* value**	**Adjusted Hazard Ratio* (95% CI)**	***P* value**
Statins	1.73 (1.52-1.97)	<0.001	1.56 (1.36-1.78)	<0.001
Glucocorticoids	1.43 (1.26-1.61)	<0.001	1.31 (1.15-1.49)	<0.001
HCQ	0.66 (0.55-0.78)	<0.001	0.67 (0.57-0.80)	<0.001
DMARD groups				
MTX monotherapy (referent)	1.0	-	1.0	-
Any abatacept	0.82 (0.52-1.29)	0.390	0.52 (0.31-0.89)	0.017
Any other DMARD with MTX	0.98 (0.82-1.18)	0.881	0.87 (0.72-1.05)	0.152
Other or no DMARDs	1.36 (1.17-1.58)	<0.001	1.11 (1.36-1.78)	0.190
**Adjusted for age, age square, sex, disease duration, socioeconomic status (employment and income), ethnicity, smoking, hypertension, comorbidity index, BMI, HAQ, NSAID usage and year of entry*				

Disclosure: G. Ozen, None; **S. Pedro**, None; **M. Holmqvist**, None; **F. Wolfe**, None; **K. Michaud**, None.

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Abstract Number: 1992

Rheumatoid Arthritis Is an Independent Risk Factor for Increased Insulin Resistance and Impaired Beta-Cell Function: Impact of Disease Activity

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Background/Purpose: Increased insulin resistance and impaired β-cell function have been demonstrated in pts with rheumatoid arthritis (RA). The aim of our study was to investigate these metabolic disturbances in RA pts compared to controls and analyze its association with disease activity.

Methods: The study population included 127 non-diabetic subjects: 90 RA pts (mean age 52.4±9.9 yrs, disease duration 9 yrs, range 4-13) and 37 matched controls (mean age 49.0±7.5 yrs). All pts were on disease modifying anti-rheumatic drugs (methotrexate 93.3%, steroids 65.6% (5 mg/day, range 5-10, none on steroids >10 mg/day), biologic therapy 27.8%). Clinical work-up included determination of the body mass index (BMI), waist circumference (WC), blood pressure (BP), disease activity (mDAS28-SE), inflammation markers, lipids, glucose, specific insulin, and C peptide. The updated-computer Homeostasis Model Assessment was used to calculate insulin resistance (HOMA2-IR) and β-cell function (HOMA2-%B). HOMA2-IR>1 was defined as increased insulin resistance. Lack of compensatory rise of HOMA2-%B implied impaired β-cell function.

Results: Increased insulin resistance (logHOMA2-IR>1) was detected in 74.4% of RA pts and in 54.2% controls, p=0.025. RA pts also had higher values of logHOMA2-IR than controls 1.4 (range 1.0-2.3) vs. 1.2 (range 0.8-1.4); p=0.008; followed with impaired β cell function: HOMA2-%B 148 (116-190) vs.141 (114-158) p=0.186. Univariate regression revealed association of logHOMA2-IR with all insulin resistance risk factors: age, BMI, WC, BP, and triglycerides, while multivariate analysis demonstrated that beside BMI and triglycerides, RA itself was an independent risk factors for logHOMA2-IR (β 0.065, 95% CI 0.019-0.112, p=0.006). Increased insulin resistance was more frequent in pts with DAS28-SE≥5.1 than DAS28-SE<5.1 (84.0% vs. 63.6%, p=0.021). Importantly, these groups were comparable regarding all insulin resistance risk factors and anti-inflammatory treatment including glycocorticoids. Pts with high disease activity also had higher levels of logHOMA2-IR (1.7 (1.2-2.5) vs. 1.3 (0.9-1.9) (p=0.003) while HOMA2-%B was not different 150 (118-195) vs.133 (115-184) p=0.446. In comparison with controls, both RA groups were not different regarding insulin resistance risk factors (Table 1). Parameters of glucose metabolism were comparable between controls and pts with DAS28-SE<5.1. Significant difference of logHOMA2-IR and logHOMA2-IR>1 was found between controls and pts with DAS-SE≥5.1. This was not followed with increase of HOMA2-%B.

Conclusion: RA pts had higher logHOMA2-IR than controls which was followed with impaired β cell function. More significant difference was demonstrated in pts with high disease activity compared to controls. RA itself was an independent risk factor for increased insulin resistance

Table 1. Parameters of Insulin Resistance in RA pts with Different Levels of Disease Activity and Controls					
Laboratory	**RA pts with DAS28≥5.1 (N=46)**	**RA pts with DAS28<5.1 (N=44)**	**Controls (N=37)**	**Controls vs. RA pts with DAS-SE≥5.1**	**Controls vs. RA pts with DAS-SE<5.1**
Age (years)	52.8±10.7	52.2±9.2	49.0±7.5	ns	ns
BMI (kg/m^2)	25.6±4.7	25.7±3.8	26.2±4.3	ns	ns
Hypertension (%)	12/46 (26.1)	16/44 (36.4)	8/37 (21.6)	ns	ns
Triglycerides (mmol/L)	1.2 (0.8-1.6)	1.2 (0.8-1.5)	1.0 (0.8-1.4)	ns	ns
Blood glucose (mmol/L)	5.0±0.6	4.7±0.6	4.7±0.8	ns	ns
Insulin (pmol/L)	79 (58-120)	57 (39-91)	55.3 (36-69)	0.000	ns
C-peptide (pmol/L)	960 (680-1130)	700 (465-860)	600 (450-880)	0.005	ns
logHOMA2-IR	1.7 (1.2-2.5)	1.3 (0.9-1.9)	1.2 (0.8-1.4)	**0.000**	ns
HOMA2-IR>1 (%)	39/46 (84.8)	28/44 (63.6)	20/37 (54.16)	**0.002**	ns
HOMA2-%B	150 (118-195)	143 (115-184)	141 (114-158)	**ns**	ns

Disclosure: G. Ristic, None; **V. Subota**, None; **D. Stanisavljevic**, None; **B. Glisic**, None; **M. Petronijevic**, None; **D. Stefanovic**, None.

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Abstract Number: 1993

The Risk of Stroke in Patients with Rheumatoid Arthritis and the Association with Competing Adverse Events

Yvette Meißner[1], Adrian Richter[2], Joern Kekow[3], Hans Peter Tony[4], Elke Wilden[5], Angela Zink[6,7], Joachim Listing[2] and Anja Strangfeld[7], [1]Programme Area Epidemiology, German Rheumatism Research Center, Berlin, Germany, [2]German Rheumatism Research Center, Berlin, Germany, [3]University of Magdeburg, Clinic of Rheumatology, Magdeburg, Germany, [4]Rheumatology / Clinical Immunology, University Hospital Würzburg, Würzburg, Germany, [5]Rheumatologist, Köln, Germany, [6]Rheumatology and Clinical Immunology, Charité - University Medicine Berlin, Berlin, Germany, [7]Epidemiology, German Rheumatism Research Center, Berlin, Germany

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk for infections, hospitalizations and cardiovascular (CV) events. The association of serious adverse events (SAE) with the risk of developing a stroke is unclear. We aimed to examine the cumulative incidence of strokes depending on precedent SAEs and the effect of CV treatment.

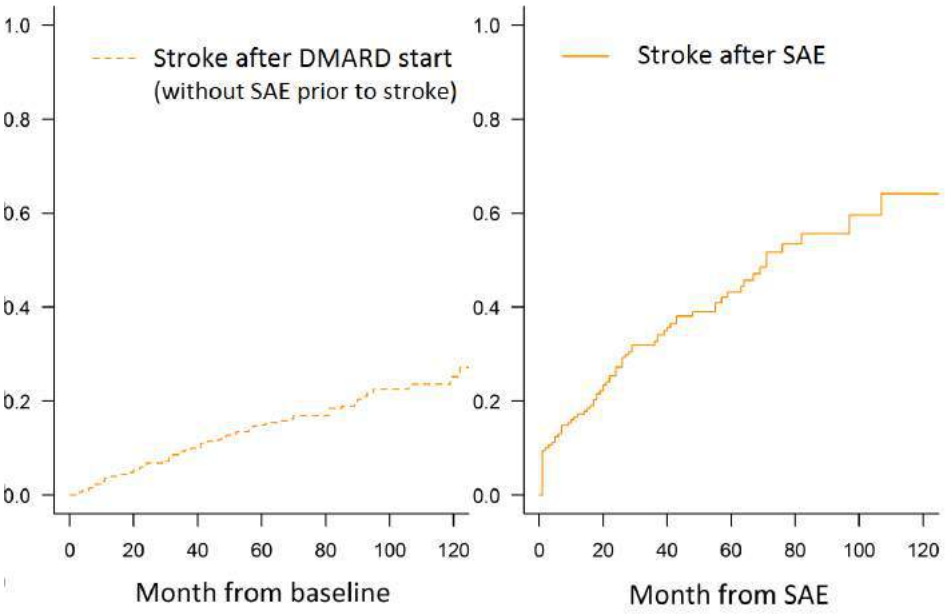
Methods: We performed a nested case-control study within the German biologics register RABBIT. Since May 2001, RA patients have been enrolled at start of a conventional synthetic (cs) or biologic (b) DMARD after ≥1 csDMARD failure. Rheumatologists report patient characteristics, comorbidities and their therapy at baseline as well as clinical status, disease activity, RA treatment and SAEs every 6 months. We considered all incident non-haemorrhagic strokes reported until October 2015 as cases. Two controls were matched to each case (Table); all but three cases could be matched. In addition, we considered all hospitalized SAEs reported before the event of stroke (index date in matched controls). We calculated the cumulative incidence of stroke depending on precedent SAEs and applied multi-state proportional hazard models.

Results: Compared to the remaining cohort, cases and controls were older and had more CV risk factors. Cases and controls were similar in treatment of RA, comorbid osteoporosis, and diabetes but CV diseases were significantly less frequently treated in cases (Table). In an adjusted model, patients with treated CV diseases had a moderately elevated risk for stroke (hazard ratio (HR): 1.41 [95% CI: 0.66, 3.01]) (Ref: patients with no CV disease). In contrast, patients with untreated CV disease had a highly increased risk (HR: 3.10 [1.41, 6.79]). Treatment with TNF inhibitors or other bDMARDs was not associated with the stroke risk (HR: 0.9 [0.6, 1.4] and 0.7 [0.4, 1.2], Ref: csDMARDs). The cumulative incidence of stroke was 2.5-fold higher in patients with precedent hospitalized SAEs than in patients without (Figure). Immediately after SAEs the risk was most pronounced.

Conclusion: The risk of stroke in RA patients may be driven by precedent SAEs requiring hospitalization. In addition, untreated CV disease was a significant risk factor for a future stroke. These results strengthen the need for a better CV management in RA patients. Table: Baseline characteristics of the cohort, controls and cases.

Parameter	Cohort	Controls	Cases	Matching
N	12,598	316	158	2:1
Age, years, mean (SD)	55.8 (12.6)*	62.7 (10.2)	63.4 (10.8)	X
Female gender	9648 (76.6)	236 (74.7)	118 (74.7)	X
Hypertension	4638 (36.8)*	176 (55.7)	88 (55.7)	X
Coronary heart disease	727 (5.8)	26 (8.2)	13 (8.2)	X
Heart failure	283 (2.2)	6 (1.9)	3 (1.9)	X
Diabetes	1229 (9.8)*	52 (16.5)	26 (16.5)	X
Smoking, never	5381 (42.7)	128 (40.5)	64 (40.5)	X
Enrolment prior to 2007	4916 (39.0)*	172 (54.4)	86 (54.4)	X
DAS28, mean (SD)	5.1 (1.3)*	5.4 (1.4)	5.5 (1.3)	
CRP in mg/l, mean (SD)	18.2 (25.9)*	21.8 (40.1)	23.8 (30.6)	
TNFi at baseline	6281 (49.9)	155 (49.1)	79 (50.0)	
Other bDMARDs at baseline	2048 (16.3)	54 (17.1)	31 (19.6)	
Hyperlipoproteinemia	980 (7.8)*	37 (11.7)	26 (16.5)	
Osteoporosis	2195 (17.4)*	76 (24.1)	47 (29.7)	
Osteoporosis w/o treatment	332/2195 (15.1)*	13/76 (17.1)	6/47 (12.8)	
Diabetes w/o treatment	239/1229 (19.4)*	15/52 (28.8)	3/26 (11.5)	
CVD w/o treatment	1102/5162 (21.3)*	38/187 (20.3)	33/100 (33.0)	

Values are given as numbers (%) or otherwise specified. *Statistically significant difference ($p<0.05$) vs. cases. Abbreviations: SD, standard deviation; w/o, without. Figure: Cumulative incidence of stroke in a case-control study: stroke without prior SAE (left), stroke after SAE (right).



Disclosure: Y. Meißner, None; **A. Richter**, None; **J. Kekow**, None; **H. P. Tony**, None; **E. Wilden**, None; **A. Zink**, None; **J. Listing**, None; **A. Strangfeld**, None.

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Abstract Number: 1994

Associations of Chronic Lung Comorbidity with Medications, Disease Activity, and All-Cause Mortality in Rheumatoid Arthritis

Bryant R. England[1,2], Harlan Sayles[3], Kaleb Michaud[3,4], Liron Caplan[5], Lisa A. Davis[6,7], Grant W. Cannon[8], Brian Sauer[9], E. Blair Solow[10], Andreas Reimold[11], Gail S. Kerr[12], Pascale Schwab[13], Joshua F. Baker[14], Namrata Singh[15] and Ted R. Mikuls[16], [1]VA Nebraska-Western Iowa, Omaha, NE, [2]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]National Data Bank for Rheumatic Diseases, Wichita, KS, [5]Div of Rheumatology, Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, [6]Denver VAMC and Univ of Colorado School of Medicine, Aurora, CO, [7]Medicine, Division of Rheumatology, Denver Health and Hospital Authority, Denver, CO, [8]Internal Medicine, Veterans Affairs Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT, [9]IDEAS Center and Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [10]Rheumatology, UT Southwestern Medical Center, Dallas, TX, [11]Dallas VA Medical Center and University of Texas Southwestern Medical Center, Dallas, TX, [12]Washington DC VAMC, Georgetown University Hospital, Howard University Hospital, Washington, DC, [13]Div Arth & Rheum Dis, Portland VA and Oregon Health & Science University, Portland, OR, [14]Medicine/Rheumatology, University of Pennsylvania and Philadelphia VAMC, Philadelphia, PA, [15]Internal Medicine, University of Iowa Hospitals and Clinics and Iowa City VA, Iowa City, IA, [16]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE

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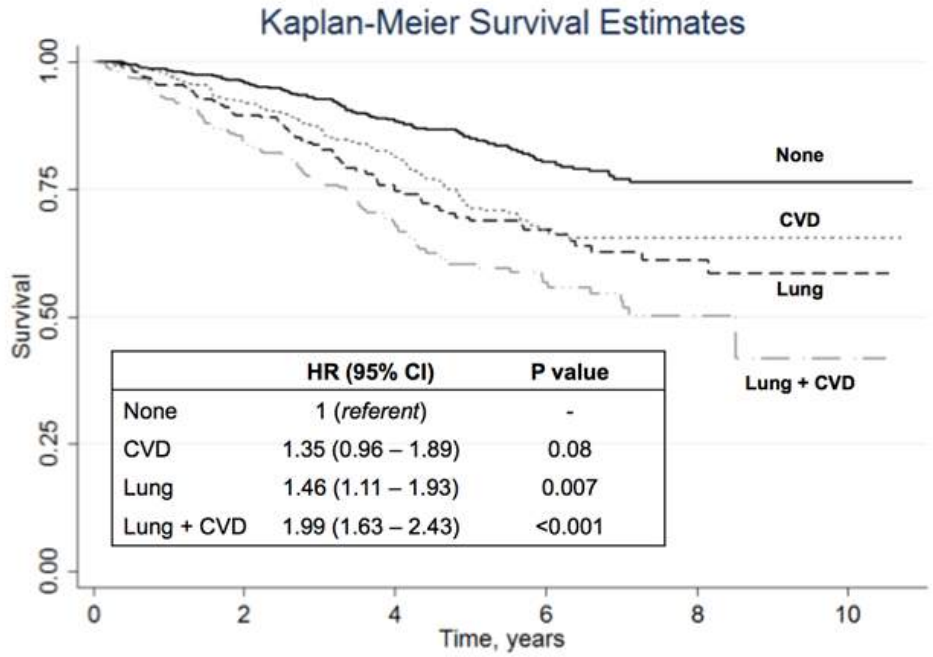
Background/Purpose: While the impact of interstitial lung disease (ILD) on mortality in RA has been demonstrated, less is known about the influence of other lung diseases either in isolation or in the context of other comorbidity. Thus, we assessed the associations of chronic lung disease (CLD) comorbidity with RA disease characteristics, DMARD use, all-cause mortality, and compared the impact of CLD and cardiovascular disease (CVD) comorbidity on survival.

Methods: Participants were enrollees in a longitudinal observational cohort of US veterans with RA. We characterized comorbidity using the Healthcare Cost and Utilization Project Clinical Classification Software (CLD: categories 127, 128, 130-133; CVD: categories 96-117) from national administrative data over the 12 months preceding enrollment. Analyses were also conducted using ICD-9 codes for ILD and chronic obstructive pulmonary disease (COPD) documented by treating physicians at enrollment. Vital status was determined by the National Death Index. We constructed multivariable logistic and linear regression models to assess associations of CLD comorbidity with RA disease characteristics and medications; multivariable Cox proportional hazards regression models were used to assess the associations with all-cause mortality. Finally, we compared the relative and combined impact of CLD and CVD comorbidity on survival with Kaplan-Meier (KM) curves and Cox regression models.

Results: A total of 2,053 participants were included with mean age of 64 (SD 11) years, RA duration 12 (11) years, 90% male, 87% RF or CCP positive, and 80% current or former smokers. CLD comorbidity was present in 34% (18% COPD, 4% asthma, 2% pleural, 1% external agent/chronic failure, 23% other lung [includes ILD]). CLD comorbidity was associated with higher ESR, CRP, and DAS28 and lower odds of obtaining DAS28 remission (OR 0.76, 95% CI 0.62-0.92). CLD comorbidity was associated with lower odds of ever methotrexate use (OR 0.67, 95% CI 0.55-0.82) and higher odds of ever azathioprine (OR 1.67, 95% CI 1.04-2.67), leflunomide (OR 1.50, 95% CI 1.20-1.87), and prednisone (OR 1.44, 95% CI 1.19-1.76) use. No association was observed with ever biologic use (OR 1.10, 95% CI 0.91-1.34). CLD was associated with 50% increased mortality (95% CI 1.28-1.75), driven by COPD (HR 1.59, 95% CI 1.30-1.94) and other lung disease (HR 1.33, 95% CI 1.24-1.44). Physician classification performed similarly for COPD (HR 1.49, 95% CI 1.18-1.88) but demonstrated increased mortality risk specifically for ILD (HR 1.92, 95% CI 1.26-2.94). KM curves and HRs for CLD and CVD comorbidity are shown in Figure 1.

Conclusion: Chronic lung comorbidity is associated with higher RA disease activity, altered DMARD selection, and increased mortality. Reduced survival is similar, and additive, to that of CVD. Identification and aggressive treatment of chronic lung disease in RA should not be limited to ILD.



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Abstract Number: 1995

Smoking Is Associated with Unfavorable Flare/ Remission Pattern in Patients with Rheumatoid Arthritis

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Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Smoking is well recognized as a risk factor for rheumatoid arthritis (RA), and determinant of RA disease activity, severity, response to therapy, and possibly mortality. However, long-term data on flare rates in RA among patients with smoking history are lacking. The purpose of this study was to assess trends in the occurrence of flares and remissions in RA among smokers and non-smokers.

Methods: A population-based cohort of patients with RA (age≥18 years; 1987 ACR criteria met in 1988-2007) was used to perform this retrospective medical records review of each clinical visit to estimate flare and remission status. RA flare was defined as any worsening of RA activity leading to initiation/change/increase of therapy (OMERACT 9). Remission was defined as the absence of disease activity (i.e. tender joint count [TJC] = 0 + swollen joint count [SJC] = 0 + ESR ≤ 10 mm/hr) (OMERACT 7). All subjects were followed until death, migration or July 1, 2012. Binomial regression models with random effects to account for multiple visits per subject were used to assess the association between smoking status and flare/remission rates adjusting for age, sex, and calendar year. Smoothing splines were used to allow for non-linear effects. Two way interactions between RA disease duration and smoking status were examined.

Results: The study included 650 RA patients (mean age 55.8 years; 69% female) with mean follow up of 10.3 years. Flare/ remission status was collected for a total of 17,323 clinical visits. Patients were flaring in 2887 (17%) visits and were in remission in 1747 (10%) visits. Current smokers had higher flare rates than non-smokers (p=0.047) and former smokers were not different from non-smokers (p=0.87; Figure 1). A borderline interaction between smoking status and RA disease duration indicated there were no differences in flare rates by smoking status during the first few years of RA disease duration, but subsequently current smokers had higher flare rates as compared to non-smokers (p=0.072). The pattern of RA disease flares over the follow up time was similar among former smokers and non-smokers (p=0.16). The overall rate of remission by baseline smoking status was significantly lower in current smokers than non-smokers (p=0.034; Figure 2). There was no difference in remission rates for former smokers compared to non-smokers (p=0.24), and no indication that remission rates differed over the disease course for current smokers (interaction p=0.42) or former smokers (interaction p=0.93) compared to non-smokers.

Conclusion: In this long term followup study, current smokers have higher rates of flares compared to non-smokers. Concordantly, remission rates were lower in smokers compared to the non-smokers. Smoking adversely affects RA flare/ remission. These findings should be helpful in counseling patients with RA who smoke.

Figure 1. Flare Occurrence According to Smoking Status at RA diagnosis

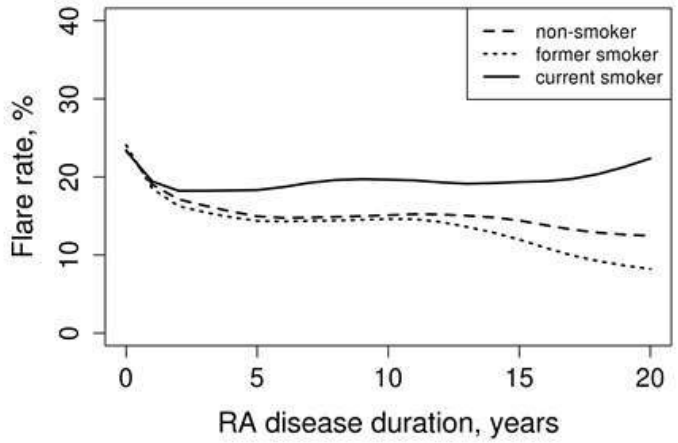
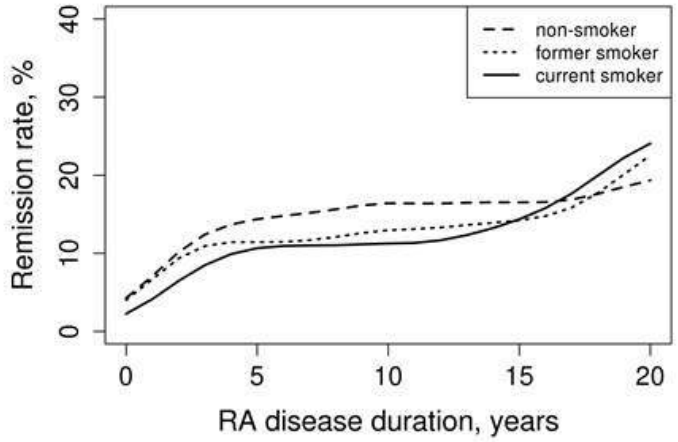


Figure 2. Remission Rates According to Smoking Status at RA diagnosis



Disclosure: S. Raheel, None; **C. S. Crowson**, None; **E. L. Matteson**, None; **E. Myasoedova**, None.

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Abstract Number: 1996

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/withdrawn-12

Abstract Number: 1997

Non-Medical Switch from Originator to Biosimilar Infliximab in Patients with Inflammatory Arthritis – Impact on s-Infliximab and Antidrug-Antibodies. Results from the Danish Rheumatologic Biobank and the Danbio Registry

Bente Glintborg[1], Tina Marie Kringelbach[1], Estrid Høgdall[1], Inge Juul Sørensen[2], Dorte Vendelbo Jensen[2], Anne Gitte Loft[3], Oliver Hendricks[4], Inger Marie Jensen Hansen[2], Asta Linauskas[2], Salome Kristensen[2], Hanne Lindegaard[5], Henrik Nordin[2], Nils Bolstad[6], David Warren[6], Johanna Gehin[6], Guro Løvik Goll[6], Kathrine Lederballe Grøn[2], Grith Eng[2], Christian Enevold[1], Claus Henrik Nielsen[1], Julia Sidenius Johansen[1] and **Merete Lund Hetland**[1], [1]Danish Rheumatologic Biobank and DANBIO registry, Rigshospitalet, Glostrup, Gentofte and Herlev University Hospital, Copenhagen, Denmark, [2]The DANBIO registry and the Danish Departments of Rheumatology, Copenhagen, Denmark, [3]Departments of Rheumatology at Vejle and Aarhus Hospitals, Vejle and Aarhus, Denmark, [4]Dep. of Rheumatology, King Christians Hospital for Rheumatic Diseases, Copenhagen, Denmark, [5]The DANBIO registry and the Danish Departments of Rheumatology, Odense, Denmark, [6]Department of Medical Biochemistry, OUS-Radiumhospitalet and Diakonhjemmet Sykehus, Oslo, Norway
First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy II: Safety and Cost Effectiveness

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: According to national guidelines issued in 2015, a non-medical switch from originator infliximab (IFX) (Remicade) to biosimilar Remsima was conducted in all Danish patients with inflammatory rheumatic diseases treated in routine care. We aimed to investigate 1) effects of the switch on serum (s) IFX and presence of anti-drug antibodies (ADA) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (axial SpA), 2) association between sIFX and ADA at the time of switch and adherence to Remsima treatment.

Methods: We included Remicade-treated patients, who switched to and were treated with Remsima. Blood samples were drawn at baseline (immediately before switching) and during follow-up (after ~3, 6, 12 months, immediately before IFX infusion to ensure trough levels). sIFX and ADA were analyzed using automated in-house assays at OUS-Radiumhospitalet. Trough sIFX<3mg/l was considered low and ≤1mg/l very low. If sIFX<5mg/l, ADA was measured. ADA≤30AU/l was considered low and ADA>30AU/l median-high. Clinical characteristics and outcomes were registered in the DANBIO registry. Remission was defined by disease activity composite scores (DAS28<2.6 (RA, PsA) and ASDAS<1.3 (axial SpA)). Medians (IQR) or percentages are shown. Comparisons were performed using Mann Whitney U test (unpaired) and Wilcoxon signed rank test (paired). The impact of baseline sIFX and ADA on treatment adherence was studied by Kaplan-Meier drug survival curves and Cox regression analyses.

Results: 231 pts with available baseline samples from 9 departments were included (age 52 (46-65) years, 51% women). Previous IFX treatment duration was 7.1 (4.5-9.7) years. Observation time after switch was 345 (275-361) days. Trough sIFX levels increased from 2.5 mg/L at switch to 2.9 mg/L 3 months after (Table). 18 of 108 pts (17%) with low baseline sIFX had high sIFX at 3 months, and 6 of 82 pts (7%) with high baseline sIFX had low sIFX at 3 months. Presence of medium-high ADA was unchanged over time (Table) and 94% of patients had similar ADA levels at baseline and at 3 months. Concomitant methotrexate (yes/no) was not associated with baseline sIFX or ADA (both p>0.05, Mann Whitney). Patients with low sIFX (<3mg/L) received lower IFX doses than pts with sIFX≥3mg/l (i.e. 260 (200-320)mg vs. 300 (252-400)mg, p=0.005) and with longer intervals (8 (8-9)weeks vs. 7 (6-8)weeks, p<0.001). Being in remission at baseline (61%/58%/18% of RA/PsA/axial SpA patients) or at 3 months (56%/68%/19%) was not associated with sIFX (all p>0.05). A total of 37 pts (16%) stopped Remsima treatment during follow-up (lack of effect (17 pts), adverse events (11 pts), other reasons (9 pts)), median treatment duration was 126 (85-210) days. In these patients, 13/37 (35%) had low

baseline s-IFX and 5 pts had ADA at baseline. ADA levels in individual patients were unchanged at the time of withdrawal of Remsima treatment. Treatment adherence was higher in patients with low baseline sIFX (<3mg/L) vs. ≥3 mg/L (Figure), also when stratified by diagnosis (RA, PsA, axial SpA. Data not shown). Presence of ADA had no impact on treatment adherence (Log rank, P=0.8).

Conclusion: In this highly selected group of patients treated with Remicade for >5 years, a non-medical switch to biosimilar Remsima had no negative impact on drug concentration or presence of ADA at 3 and 6 months following switch. At baseline, 53% of patients had low sIFX, but few patients had ADA, perhaps indicating low immunogenicity of IFX in these patients. The poorer treatment adherence among patients with high sIFX at the time of switch warrants further investigation.

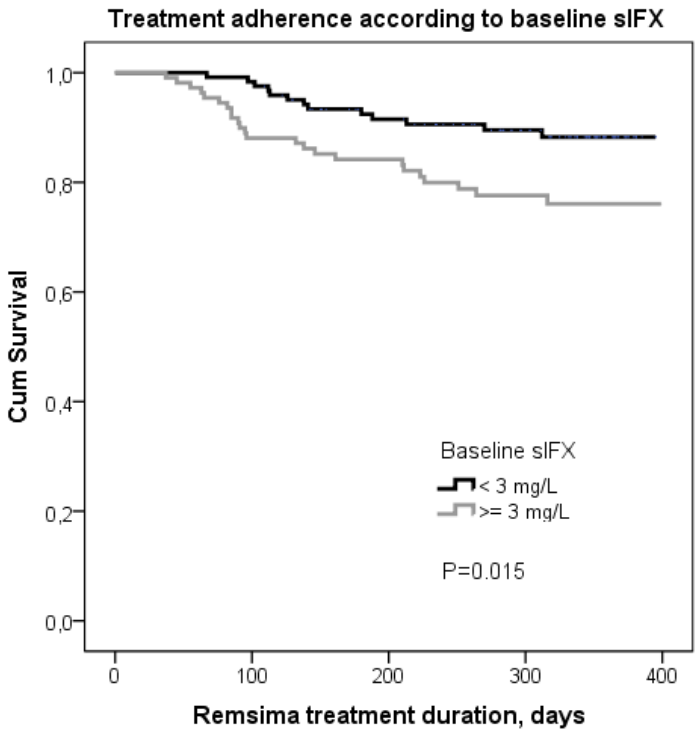
BASELINE DEMOGRAPHICS ACCORDING TO DIAGNOSIS

	Rheumatoid arthritis, RA	**Psoriatic arthritis, PsA**	**Axial SpA**	**Other polyarthritis**
Number of patients, n	115	33	73	10
Remsima dose, mg/kg	3.2 (3.0-4.6)	4.8 (3.5-5.1)	4.8 (3.2-5.1)	4.2 (3.1-5.4)
Remsima dose interval, weeks	8 (6-8)	7 (6-8)	8 (6-8)	8 (6-8)
Concomitant methotrexate, n (%)	89 (77%)	14 (42%)	13 (18%)	3 (30%)

S-IFX AND ADA AT BASELINE AND FOLLOW-UP. ALL DIAGNOSES

	Baseline (0-45 days)	**3 months (46-135 days)**	**6 months (136-286 days)**	**P-values**	
Patients with available samples, n	231	190	125*	P1	P2
Remsima dose, mg	300 (220-400)	300 (220-380)	270 (210-380)	0.03	0.06
Trough s-Infliximab, n (%)	61 (26%)	45 (23%)	29 (23%)	0.001	0.5
0-1 mg/L (very low)	61 (26%)	51 (27%)	32 (24%)		
1-3 mg/L (low)	42 (18%)	28 (15%)	19 (15%)		
3-5 mg/L (high)	67 (29%)	66 (35%)	45 (36%)		
≥5 mg/L (high)					
Trough s-Infliximab, mg/L	2.5 (0.9-5.9)	2.9 (1.2-6.0)	3.1 (1.1-6.4)	<0.0001	0.3
ADA, n (%)	131 (56%)	96 (51%)	65 (52%)	1.0	1.0
≤30 AU/L (low)	33 (14%)	28 (15%)	15 (12%)		
>30 AU/L (median-high)	67 (29%)	66 (35%)	45 (36%)		
Not measured (i.e. sIFX ≥ 5 mg/L)					

* 10 patients who stopped treatment >14 days before blood-sampling are excluded
Numbers are medians (ranges) unless otherwise stated P1: Baseline vs. 3 months, P2: 3 months vs. 6 months



Disclosure: B. Glintborg, None; **T. M. Kringelbach**, None; **E. Høgdall**, None; **I. Juul Sørensen**, None; **D. V. Jensen**, None; **A. G. Loft**, MSD, UCB, AbbVie, Pfizer., 8; **O. Hendricks**, None; **I. M. Jensen Hansen**, None; **A. Linauskas**, None; **S. Kristensen**, None; **H. Lindegaard**, Novartis, Eli Lilly DK, Boehringer Ingelheim Danmark, MSD Denmark, 5; **H. Nordin**, None; **N. Bolstad**, None; **D. Warren**, None; **J. Gehin**, None; **G. L. Goll**, Pfizer, Abbvie, Orion, Roche, 2; **K. Lederballe Grøn**, None; **G. Eng**, None; **C. Enevold**, None; **C. H. Nielsen**, None; **J. S. Johansen**, None; **M. Lund Hetland**, AbbVie, BMS, MSD, Roche, Pfizer, UCB, Crescendo, 2.

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Abstract Number: 1998

Long-Term Registry Data in 4498 Patients with Rheumatoid Arthritis Indicate a Similar Safety but a Different Drug Retention Between Abatacept, Rituximab and Tocilizumab

Jacques-Eric Gottenberg[1], Jacques Morel[2], Arnaud Constantin[3], Thomas Bardin[4], Alain G. Cantagrel[5], Bernard Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Alain Saraux[9], Thierry Schaeverbeke[10], Jean Sibilia[11], Martin Soubrier[12], Olivier Vittecoq[13,14], Elodie Perrodeau[15], Philippe Ravaud[16], Xavier Mariette[17] and on behalf of the French Society of Rheumatology and of all the investigators participating to the AIR, ORA and REGATE registries, [1]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [2]Rheumatology, Department of Rheumatology, Montpellier University Hospital, Montpellier, France, [3]Rheumatology, CHU Purpan - Hopital Pierre-Paul Riquet, Toulouse, France, [4]Clinique de Rhumatologie, Hopital Lariboisiere, Paris Cedex 10, France, [5]Rheumatology, Centre Hospitalier Universitaire, Toulouse

Purpan, Toulouse, France, [6]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [7]Rheumatology, Paris Descartes University, Paris, France, [8]Rheumatology, University Hospital, Lille, France, [9]Rheumatology, Brest University Hospital, Brest, France, [10]Rheumatology, CHU Bordeaux, Bordeaux, France, [11]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [12]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [13]Rheumatology, Rouen University Hospital &INSERM U905, Rouen, France, [14]Rheumatology, Rouen University Hospital, Rouen, France, [15]Epidemiology, Hopital Hotel Dieu, Paris Descartes University, Paris, France, [16]Epidemiologist, PARIS, France, [17]Rheumatology, Rheumatology department, Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France

First publication: September 28, 2016

SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy II: Safety and Cost Effectiveness

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Three non-TNF targeted biologics – rituximab, abatacept, and tocilizumab – are widely used, notably in TNF-IR patients. We aimed to compare the efficacy and safety of the drugs in common practice.

Methods:

This was a multicenter open-label observational study of patients with RA according to 1987 American College of Rheumatology criteria who were initiating rituximab, abatacept, or tocilizumab treatment and enrolled in three French Society of Rheumatology prospective registries (AIR for rituximab, ORA for abatacept, and REGATE for tocilizumab). Severe adverse events (death, serious infection, major adverse cardiovascular events, and cancer) were validated by chart review by three experts. The primary outcome was drug retention without failure at month 24. Failure was defined as all-cause death; rituximab, abatacept, or tocilizumab discontinuation; initiation of a new biologic or a combination of conventional DMARDs; or increase in corticosteroid dose greater than 10 mg/day compared to baseline at two successive visits. We used a propensity-score approach to adjust for differences in observed factors that might affect both treatment assignment and outcome.

Results:

In total, 4,498 patients (abatacept: 1,016, rituximab: 1,984, and tocilizumab: 1,498) were enrolled in the registries, with a follow-up of 18,898 patient-years (abatacept: 4,912, rituximab: 10,545, and tocilizumab: 3,441). Among the 4498 enrolled patients (median disease duration: 11 [5-18] years, 83.3% of patients previously treated with a biologic, median number of prior of anti-TNF 2 [1; 3]), 3,507 patients had a follow-up at month 24. At month 24, 64.6% of patients [95% confidence interval (95% CI): 61.1; 68·5] were still receiving rituximab without failure, 40.0% [95% CI: 36·0; 45·0] abatacept, and 61.3% [95% CI; 54·9; 68·8] tocilizumab (Figure 1). Drug retention without failure was significantly greater with rituximab and tocilizumab than abatacept (hazard ratio 2·00 [95% CI: 1·65; 2·43]; p<0·001, and 1·82 [95% CI: 1·37; 2·41], p<0·001, respectively), with no difference between rituximab and tocilizumab. Concordant results were observed in six sensitivity analyses. At month 60, drug retention without failure was significantly greater with rituximab than abatacept (48.1% [95% CI: 44.3; 52.5] and 21.0% [95% CI: 18.1; 24.6], respectively, HR 2.06 [95% CI: 1.78; 2.39]; p<0·001).

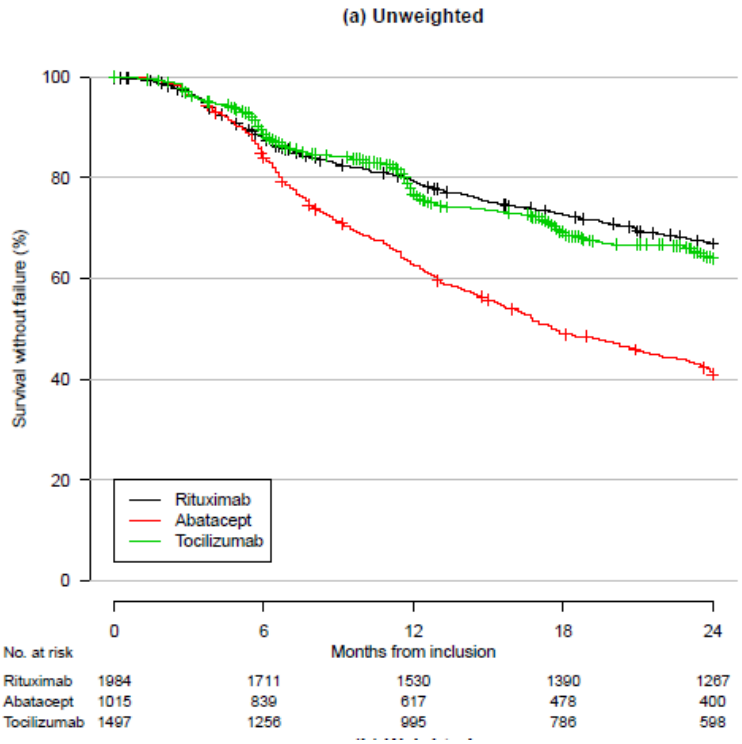
At month 24, 513 patients (6.7/100 patient-years) had experienced at least one of the adverse events of specific

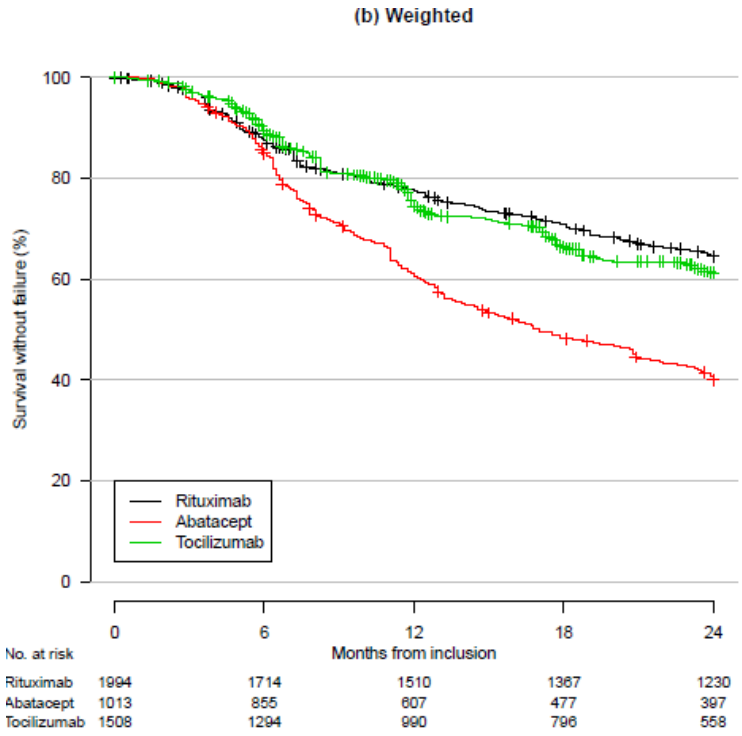
interest including serious infection, MACE, cancer, or death: 255 in the rituximab registry (7.3/100 patient-years), 116 in the abatacept registry (6.4/100 patient-years), and 142 in the tocilizumab registry (6.0/100 patient/years) (IRR abatacept versus rituximab: 0.79 [0.56;1.12], p=0.19; IRR tocilizumab versus rituximab: 0.87 [0.58;1.32], p=0.52; IRR abatacept versus tocilizumab 0.91 [0.57;1.47], p=0.71).

Conclusion:

Among patients followed up in common practice with long-standing RA, mostly refractory to at least one previous biologic, the effectiveness at two years seems lower for abatacept than rituximab and tocilizumab. Safety of the three drugs seems similar.

Figure 1. Drug survival without failure in RA patients treated with abatacept, rituximab and tocilizumab





Disclosure: J. E. Gottenberg, None; **J. Morel**, None; **A. Constantin**, None; **T. Bardin**, None; **A. G. Cantagrel**, None; **B. Combe**, None; **M. Dougados**, Pfizer, AbbVie, Celgene, Eli Lilly, Novartis, Roche, and Sanofi-Aventis, 5,Pfizer, AbbVie, UCB, Merck, 8; **R. M. Flipo**, None; **A. Saraux**, None; **T. Schaeverbeke**, None; **J. Sibilia**, None; **M. Soubrier**, None; **O. Vittecoq**, None; **E. Perrodeau**, None; **P. Ravaud**, None; **X. Mariette**, None.

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Abstract Number: 1999

Claims-Based Analysis of Cost-Effectiveness Among Patients with Rheumatoid Arthritis Who Switched from a Tumor Necrosis Factor Inhibitor to Another Targeted Disease-Modifying Antirheumatic Drug

Machaon Bonafede[1], Wenhui Wei[2], Chieh-I Chen[3], Donna McMorrow[1], Stefano Fiore[4], Jonathan Fay[3], Toshio Kimura[3] and Jeffrey R. Curtis[5], [1]Truven Health Analytics, Cambridge, MA, [2]Sanofi US, Inc., Bridgewater, NJ, [3]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, [4]Sanofi Genzyme, Bridgwater, NJ, [5]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy II: Safety and Cost Effectiveness

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with rheumatoid arthritis (RA) who have an inadequate response to a tumor necrosis factor inhibitor (TNFi) can switch to another targeted disease-modifying antirheumatic drug (DMARD), either by changing to another TNFi ("cycling") or by switching to a new mechanism of action ("new MOA switching"). Given potential differences in outcomes conditional on choosing either of these strategies, this study examined the cost per effectively treated patient in the first year after TNFi cycling or new MOA switching.

Methods: This claims-based analysis included a cohort of patients with RA in the Truven Health Analytics MarketScan Commercial database who either cycled from a TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) to another TNFi or switched to a new MOA biologic (abatacept or tocilizumab) or targeted oral DMARD (tofacitinib) between January 2010 and December 2014. A validated claims-based algorithm was applied to estimate treatment effectiveness for the 12-month post-switch period based on six criteria: 1) adherence ≥80%; 2) no dose increase; 3) no addition of a synthetic DMARD (leflunomide, methotrexate, sulfasalazine, or hydroxychloroquine); 4) no switch to another targeted DMARD; 5) no new/increased oral glucocorticoid; and 6) intra-articular injections on <2 days. Costs were calculated from healthcare claims based on the paid amount for targeted DMARDs, adjusted for inflation according to price changes for the individual medications during the study period. Cost per effectively treated patient was defined as the average 12-month post-switching cost per patient for targeted DMARDs divided by the proportion of patients categorized by the algorithm as effectively treated. Bivariate analysis was conducted to compare treatment effectiveness and costs between TNFi cyclers and new MOA switchers.

Results: A total of 8,517 patients were analyzed (5,997 TNFi cyclers and 2,520 new MOA switchers). TNFi cyclers and new MOA switchers had similar age (mean±SD, 49.7±9.6 vs 51.0±9.3 years), sex (female, 81.2% vs 83.9%), and comorbidity (mean±SD Deyo-Charlson index score, 1.4±0.8 vs 1.5±1.0). Costs and treatment effectiveness favored new MOA switchers over TNFi cyclers, resulting in higher cost per effectively treated patient for TNFi cycling vs new MOA switching. Differences in adherence, subsequent treatment switches, and dose increases were major drivers of cost effectiveness (Table).

Outcomes in 12-Month Post-Switch Period	TNFi Cyclers (N=5,997)	New MOA Switchers (N=2,520)	Difference*	*P**
Average targeted DMARD costs	$38,456	$33,008	-$5,448	<0.001
Effectiveness, per claims-based algorithm				
Overall (all six criteria)	23.3%	26.0%	2.7%	0.008
Adherence	39.1%	39.8%	0.7%	0.560
No dose increase	88.0%	93.9%	5.9%	<0.001
No new conventional synthetic DMARD	85.0%	85.7%	0.8%	0.371
No switch to another targeted DMARD	64.2%	69.6%	5.4%	<0.001
No increased/new glucocorticoids	85.9%	85.3%	-0.6%	0.451
Intra-articular injections on <2 days	90.6%	90.6%	0.0%	0.973
Drug cost per effectively treated patient				
Overall (all six criteria)	$165,200	$126,991	–$38,208	
Adherence	$98,387	$83,013	–$15,373	
No dose increase	$43,694	$35,156	–$8,538	
No new conventional synthetic DMARD	$45,264	$38,509	–$6,755	
No switch to another targeted DMARD	$59,917	$47,423	–$12,494	
No increased/new glucocorticoids	$44,746	$38,688	–$6,058	
Intra-articular injections on <2 days	$42,456	$36,450	–$6,005	
* New MOA switchers vs TNFi cyclers; *P*-value from Chi-square test for categorical variables and t-test for continuous variables.				

Conclusion: After prior exposure to TNFi, switching to a new MOA rather than cycling to another TNFi was associated with better treatment effectiveness and lower drug costs, resulting in lower cost per effectively treated patient.

Disclosure: M. Bonafede, Truven Health Analytics, 3; **W. Wei**, Sanofi, 1,Sanofi, 3; **C. I. Chen**, Regeneron, 1,Regeneron, 3; **D. McMorrow**, Truven Health Analytics, 3; **S. Fiore**, Sanofi Genzyme, 1,Sanofi Genzyme, 3; **J. Fay**, Regeneron, 1,Regeneron, 3; **T. Kimura**, Regeneron, 1,Regeneron, 3; **J. R. Curtis**, Regeneron, 5.

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Abstract Number: 2000

Incidence of Cancer in Patients with Rheumatoid Arthritis and a

History of Cancer Treated with Rituximab or Abatacept

Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Thomas Bardin[3], Alain Cantagrel[4], Bernard Combe[5], Maxime Dougados[6], RENE MARC FLIPO[7], Olivier Vittecoq[8], Thierry Schaeverbeke[9], Isabelle Pane[10], Jean Sibilia[11], Xavier Mariette[12] and on behaf of all of the investigators of the AIR registry and of the French Society of Rheumatology , [1]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [2]Epidemiology, Hotel Dieu, PARIS, France, [3]Clinique de Rhumatologie, Hopital Lariboisiere, Paris Cedex 10, France, [4]Rheumatology, INSERM CNRS UMR 1043, Paul Sabatier University Toulouse, Purpan Teaching Hospital, Toulouse, France, [5]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [6]Rheumatology, Paris Descartes University, Paris, France, [7]Rheumatology, Department of Rheumatology, CHU Teaching Hospital Lille, France., Lille, France, [8]INSERM U905 & Normandy University, Institute for Research and Innovation in Biomedicine, Rouen, France, [9]Rheumatology, CHU Bordeaux, Bordeaux, France, [10]Epidemiology, Hotel Dieu, Paris, France, [11]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [12]Institut National de la Santé et de la Recherche Médicale, Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy II: Safety and Cost Effectiveness

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with a history of cancer were excluded from pivotal clinical trials evaluating biologics. Therefore, only registries can inform us on the incidence of cancers in such patients treated with a biologic.

Methods: Registries of the French Society of Rheumatology AIR and ORA included 1986 and 1024 patients to study tolerance and efficacy of rituximab (RTX) and abatacept (ABA) in common practice, respectively. Cancers and serious infections were validated by analysis of the charts of patients.

Results: Treatment with rituximab 270 patients had a history of cancer and 1656 patients did not have a history of cancer before RTX (60 missing data). The 1656 patients without a history of cancer had a mean follow-up of 5.4 years (8942 patient-years) and 83 cancers occurred (*0.9 cancers/100 patient-years*). Among the 270 patients with a history of cancer, mean follow-up was 5.2 years (1404 patient-years) and 48 incident cancers (*3.4 cancers/100 patient-years*), including 19 new cancers (1.3 cancers/100 patient-years) and 29 relapses of past cancers (2.1 cancers/100 patient-years). Cancers occurred after a median period of 32.2 (18.5 ; 53.9) months and 37.7 (21.7 ; 57.8) months after RTX initiation in patients with and without a history of cancer, respectively. Cancers occurred after a median number of 2 (1 ; 4) and 2 (1 ; 4) cycles, in patients with and without a history of cancer, respectively. Treatment with abatacept 55 patients had a history of cancer and 961 patients did not have a history of cancer before abatacept (8 missing data). The 961 patients had a mean follow-up of 4.8 years (4613 patient-years) and 61 cancers occurred (*1.3 cancers/100 patient-years*). The 55 patients with a history of cancer had a mean follow-up of 4.6 years (253 patient-years). Five incident cancers occurred (*2.0 cancers/100 patient-years*) including 3 new cancers (1.2 cancers/100 patient-years) and 2 relapses of past cancers (0.8 cancers/100 patient-years). Cancers occurred after a median period of 8.0 (6.4 ; 24.3) months and 34.8 (19.4 ; 46.1) months after ABA initiation in patients with and without a history of cancer, respectively.

Conclusion: The incidence of cancers in patients with a history of cancer treated with abatacept and rituximab, approximately two to three-fold that of patients without a history of cancer, is in the range of what is expected in these patients at higher risk of cancer.

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Abstract Number: 2001

Perioperative Use of Synthetic Disease-Modifying Anti-Rheumatic Drugs or Tumor Necrosis Factor α Inhibitors Does Not Associate with Increased Rates of Post-Operative Infections

Hsin-Hsuan Juo[1,2], Anders Peck[3,4], Nancy Gove[5] and Bernard Ng[1,2], [1]Division of Rheumatology, Department of Medicine, University of Washington, Seattle, WA, [2]Rheumatology, VA Puget Sound Healthcare System, Seattle, WA, [3]Medicine / Rheumatology, University of Washington, Seattle, WA, [4]The Seattle Arthritis Clinic, Seattle, WA, [5]Biostatistics, Seattle Children's Research Institute, Seattle, WA

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy II: Safety and Cost Effectiveness

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The aim of the study is to assess whether the risk of post-operative infectious complications in rheumatoid arthritis (RA) patients undergoing surgical procedures is greater in patients continuing therapy with different disease-modifying anti-rheumatic drugs (DMARDs) and/or biologic agents (BA) compared with patients who stop their medications prior to surgery.

Methods: Using the United States Department of Veterans Affairs (VA) administrative databases & surgical quality registry, we identified surgical procedures in RA patients, who were on at least one DMARD or one BA in the perioperative period, between October 1, 1999 and September 30, 2009. We used the VA pharmacy database and a previously validated method to determine whether the medication had been stopped prior to or continued through surgery. Surgeries among RA patients were divided into the following treatment groups: methotrexate (MTX) alone, hydroxychloroquine (HCQ) alone, leflunomide (LEF) alone, and MTX plus TNFα - inhibitor (TNFi). Primary endpoints were total infectious complications and wound infection. Unconditional multivariable logistic regression models were used to calculate odds ratios and compare infection risk of infection between groups. Statistical significance is defined with $p<0.05$.

Results: We identified a total of 9362 surgeries among 5544 RA patients during this period. In the MTX monotherapy group, a total of 2601 surgeries were identified. MTX was continued in 1961 surgeries. Continuing MTX during surgeries was not associated with post-operative infection (OR=0.79, *p*=0.11) and post- operative wound infection (OR=0.77, *p*=0.10). In the HCQ monotherapy group, a total of 2012 surgeries were identified. HCQ was continued in 1496 surgeries. Continuing HCQ during surgeries was not associated with post- operative infections (OR= 0.93, *p*=0.67) or wound infection (OR 0.86, *p*=0.42). In the LEF monotherapy group, a total of 652 surgeries were identified. LEF was continued in 508 surgeries. Continuing LEF during surgeries was not associated with post- operative infections (OR=0.78, *p*=0.34) or wound infections (OR 0.87, *p*=0.63). In the MTX plus TNFi group, a total of 386 surgeries were identified. Both drugs were continued in 196 surgeries. MTX was stopped and TNFi continued in 59 surgeries. MTX was continued and TNFi was stopped in 72 surgeries. Both MTX and TNFi were stopped in 59 surgeries. With stopping both MTX and TNFi before surgery as reference, continuing [i] only MTX (OR=0.80, *p*=0.77) or [ii] only TNFi (OR=0.15, *p*=0.12) or [iii] both drugs (OR=0.35, *p*=0.15) were not associated with post- operative infections. Continuing [i] only MTX (OR=1.18, *p*=0.86) or [ii] only TNFi (OR=0.19, *p*=0.23) or [iii] both drugs (OR=0.38, *p*=0.32) were not associated with post- operative wound infections, either.

Conclusion: Our results suggest that the continuation of DMARD monotherapy such as MTX, HCQ, LEF, or the combination of MTX and TNFi therapy for RA in the perioperative setting is not associated with increased rates of overall post- operative infectious complications and wound infections. This is a retrospective study evaluating all surgeries. Further sub-group analyses for specific surgeries will be analyzed in our future studies.

Disclosure: H. H. Juo, None; **A. Peck**, None; **N. Gove**, None; **B. Ng**, None.

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Abstract Number: 2002

Differences in Features of Chronic Back Pain in First Degree Relatives of Patients with Ankylosing Spondylitis (AS) Compared to the U.S. Population

David Kung[1], Michael Weisman[2], MinJae Lee[3], Lianne S. Gensler[4], Michael Ward[5], Amirali Tahanan[3], Laura A. Diekman[1], Shervin Assassi[6], Mohammad H. Rahbar[3] and John D. Reveille[1], [1]Rheumatology, University of Texas-McGovern Medical School, Houston, TX, [2]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]Biostatistics/Epidemiology/Research Design (BERD) Core | Center for Clinical and Translational Sciences, University of Texas-McGovern Medical School, Houston, TX, [4]Medicine/Rheumatology, UCSF, San Francisco, CA, [5]NIH/NIAMS, Bethesda, MD, [6]Department of Internal Medicine - Rheumatology, University of Texas-McGovern Medical School, Houston, TX

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment III: Axial Spondyloarthritis – Clinical

Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: To compare the clinical features of spondyloarthritis in first degree relatives (FDRs) of patients with ankylosing spondylitis (AS) with chronic back pain (CBP) with those participants in a nationally representative sample of US adults examined in 2009-2010 US National Health and Nutrition Examination Survey (NHANES) who also had CBP.

Methods: Non-Hispanic White FDRs of AS patients, without a prior diagnosis of AS, between the ages of 20-69 were included in a prospective cohort study. A questionnaire was used to obtain demographic and clinical data focusing on features of spondyloarthritis. We compared demographic and clinical features between FDR and NHANES cohorts using both univariable and multivariable regression analyses, controlling for age and gender. We focused on non-Hispanic whites because of the limited number of nonwhite FDRs available from the family study. Excluded from the analysis were 20 FDRs and 12 participants in the 2009-2010 NHANES study with CBP who carried a diagnosis of AS.

Results: This study of non-Hispanic White FDRs with chronic back pain without a prior AS diagnosis between 20-69 years of age, including 67 FDRs from 60 families from a total of 499 FDRs examined and 722 with chronic back pain of the 2244 white participants in the 2009-2010 NHANES cohort. Significant results are shown in Table 1. FDRs of AS patients were more likely to have neck, buttock and hip pain. They were also more likely to have alternating buttock pain, pain that improves with activity and worsens with rest as well as pain that awakens them at night and morning stiffness of >30 minutes. Of particular interest was a higher frequency of heel pain and ulcerative colitis and marginal increases in uveitis and psoriasis. Of note, there were no significant differences in the frequencies of upper, mid or low back pain (data not shown). Also, although FDRs of AS patients were more likely to use non-steroidal anti-inflammatory drugs (NSAIDs) for their back pain, there were no differences in response to NSAIDs compared to the US population (data not shown).

Table 1. Comparison of AS-FDR and NHANES Non-Hispanic Whites Aged 20-69 Years with Chronic Back Pain Based on Univariable/Multivariable Regression Models

Variable	FDR's n=67	NHANES n=772	Univariable P value	Multivariable P value
Male, %	43.3	45.9	0.685	0.683
Age (±SD in years)	45.2 (± 13.5)	45.1 (± 13.6)	0.933	0.934
Age Onset (±SD in years)	26.1 (± 12.3)	32.6 (± 14.1)	<0.0001	<0.0001
Neck pain, %	52.2	36.1	0.009	0.011
buttock pain, %	49.3	30.7	0.001	0.002
hip pain, %	43.3	15.9	0.0006	0.001
Alternating buttock pain, %	57.4	32.5	<0.0001	<0.0001
Pain improves with activity,%	86.9	65.4	0.002	0.003
Pain worsens with rest,%	31.8	23.6	<0.0001	0.0002
Pain awakens from sleep,%	61.9	48.1	0.036	0.046
Morning stiffness >30 minutes,%	74.6	48.6	0.0003	0.001
Heel pain not due to trauma,%	49.2	19.6	<0.0001	<0.0001
Uveitis, %	3.1	0.65	0.039	0.068
Ulcerative colitis,%	4.6	1.0	0.015	0.030
Crohn's disease,%	0	0.4	0.615	0.989
Psoriasis,%	11.1	5.3	0.057	0.065

Conclusion: Chronic back pain in FDRs of non-Hispanic White AS patients not carrying a diagnosis of AS shares significantly more features of axial spondyloarthritis than chronic back pain in the general population. The

clinician should have a high index of suspicion of axial spondyloarthritis in the clinical evaluation and treatment of chronic back pain in this group.

Disclosure: D. Kung, None; **M. Weisman**, None; **M. Lee**, None; **L. S. Gensler**, AbbVie, Amgen, Janssen, Novartis, UCB, 5; **M. Ward**, None; **A. Tahanan**, None; **L. A. Diekman**, None; **S. Assassi**, Boehringer Ingelheim, 5,Genentech and Biogen IDEC Inc., 2,Bayer HealthCare, 2; **M. H. Rahbar**, None; **J. D. Reveille**, None.

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Abstract Number: 2003

Validation of the ASAS Health Index: Results of a Multicenter International Study in 23 Countries

Uta Kiltz[1], Désirée van der Heijde[2], Annelies Boonen[3], Jürgen Braun[1] and ASAS HI international validation study, [1]Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Internal Medicine, Division of Rheumatology, Maastricht University Medical Center, Maastricht, Netherlands

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment III: Axial Spondyloarthritis – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The ASAS Health Index (ASAS HI) was developed to measure functioning and health in patients with spondyloarthritis (SpA) aiming to better define the impact of disease in these patients. The 17 questions of the questionnaire (range 0-17, with a lower score indicating a better health status) have now been translated into 18 languages worldwide. Face validity and feasibility (time of completion) have already been assessed in a field test. The objective of the present study was test construct validity, discrimination across relevant health states, reliability and responsiveness of the original English version and the 16 translations of the ASAS HI in 23 countries

Methods: A convenient sample of SpA patients fullfilling the ASAS classification criteria for either axial (axSpA) or peripheral SpA (pSpA) were included into the study from 33 centers of 22 countries worldwide. Data were collected by the local rheumatologist. Construct validity against other health outcomes was evaluated by Spearman correlation. Discrimination across patient reported health states was decribed. Test-retest reliability was assessed by intraclass correlation coefficient (ICC) in patients without treatment changes (stable disease state, interval 4-7 days). In those patients who required a therapeutic change because of high disease activity, responsiveness was tested (standardized response mean (SRM)) after 2-24 weeks depending on the type of medication.

Results: 1548 patients were included: 64.9% male, mean (SD) age 42.0 (13.4) years, mean (SD) BASDAI 4.1

(2.5). There were 1299 patients with axSpA (375 nr-axSpA and 924 AS patients) and 256 patients with pSpA. The total score of the ASAS HI was 6.7 ± 4.3 (mean ± SD). Floor or ceiling effects were limited (0.8 and 6.9%, respectively). Convergent validity ranged as hypothesized with Spearman correlations from low (age: 0.10) to good (BASDAI: 0.70). ASAS HI scores showed<span" roman"="Roman"" new="New"> a high internal consistency with a Cronbachs-α of 0.93. The ASAS HI discriminated well between patients with different stages of disease activity and function irrespective of the tool applied (ASDAS, BASDAI and BASFI) (table). The groups with greater disease activity and more impaired functioning had higher mean ASAS HI scores (indicating impaired functioning) than those with lower disease activity. Reliability (tested in 578 patients) was good (ICC: 0.87 (95%CI 0.84 to 0.89), p<0.01) and comparable across all disease subtypes. Sensitivity to change (tested in 246 patients) showed a moderate SRM of -0.44 for NSAIDs (n= 75 patients), 0.69 for DMARDs (n=41) and -0.85 for TNFi (n=127). The smallest detectable change in this cohort was 3.0.

Conclusion: The ASAS HI is a valid, reliable and responsive measure of disease severity in people affected by SpA. It should be used in clinical trials to evaluate the impact of SpA and its treatment on overall functioning and health. Table: Discriminative ability of the ASAS HI stratified by disease activity

ASDAS status groups				
	inactive (n=245)	moderate (n=283)	high (n=500)	very high (n=289
ASAS HI	2.9 ± 3.1	5.1 ± 3.5	7.3 ± 3.6	10.4 ± 35
BASFI	0.9 ± 1.4	2.1 ± 1.9	3.7 ± 2.5	5.9 ± 2.5
BASDAI	1.2 ± 0.9	2.7 ± 1.3	4.7 ± 1.7	7.0 ± 1.6

Disclosure: U. Kiltz, None; **D. van der Heijde**, None; **A. Boonen**, None; **J. Braun**, None.

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Abstract Number: 2004

Is Disease Activity Associated with Work Productivity Loss, Presenteeism and Absenteeism in Patients with Early Axial Spondyloarthritis? Results from the Spondyloarthritis Caught Early (SPACE)-Cohort

Miranda van Lunteren[1], Pauline Bakker[1], Zineb Ez-Zaitouni[1], Camilla Fongen[2], Robert Landewé[3], Maikel van Oosterhout[4], Roberta Ramonda[5], Floris van Gaalen[1] and Désirée van der Heijde[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [3]Rheumatology, Academic Medical Center, Amsterdam, Netherlands, [4]Rheumatology, Groene Hart Hospital, Gouda, Netherlands, [5]Rheumatology Unit, University of Padova, Padova, Italy

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Session Time: 2:30PM-4:00PM

Background/Purpose: Disease activity has an important impact on work productivity in patients with Ankylosing Spondylitis (AS). However, if and to what extent this is the case in early axial Spondyloarthritis (axSpA) and if it is similar in subgroups of patients e.g. male vs. female patients. The aim is to investigate if the impact of disease activity, assessed by ASDAS (AS Disease Activity Score, CRP based), on work productivity is similar according to gender, age, medication use, profession, HLA-B27 status and duration of back pain at baseline in early axSpA patients.

Methods: The SPACE-cohort includes patients (chronic back pain ≥3 months, ≤2 years, onset <45 years) from 5 European centers. Patients who fulfilled the ASAS criteria for axSpA were included in the analysis. Work Productivity and Activity Impairment questionnaire (WPAI) was completed by patients at baseline to assess Work Productivity Loss (WPL; i.e. total work impairment due to disease), presenteeism (i.e. decreased work functionality due to disease) and absenteeism (i.e. absence at work due to disease) in the past 7 days. Higher scores indicate greater impairment (range 0-100). ASDAS was used to assess disease activity. Gender, age, medication use, profession and duration of back pain were tested for effect modification ($p<0.20$) one by one in a linear regression model. Continuous variables were split by the median.

Results: 124 axSpA patients working at baseline were included; 73 fulfilled the clinical arm, 51 patients the imaging arm of the ASAS axSpA criteria. Patients were on average 31.1 years old (SD 7.7), 50.8% were male and had a mean duration of back pain of 13.7 months (SD 7.8). They worked on average 28.0 (SD 15.7) hours and missed 3.3 (SD 8.8) hours per week at work due to axSpA. Mean WPL, presenteeism, and absenteeism (SD) were 35.7% (29.4), 33.2% (27.0) and 9.3% (22.6) respectively. Patients had a mean ASDAS of 2.4 (SD 0.9). In the univariable model (Table 1), 1 point increase in ASDAS resulted in an increase of 18.5%, 16.9%, 9.6% in WPL, presenteeism and absenteeism, respectively. Fulfilment of the clinical or imaging arm was not an effect modifier (WPL $p=0.69$; presenteeism $p=0.66$; absenteeism $p=0.58$). Gender was an effect modifier in the associations between ASDAS and WPL ($p=0.22$, borderline significant) and presenteeism ($p=0.15$). The use of NSAIDs ($p=0.16$), age, and gender (two-way interaction $p=0.06$) were effect modifiers of absenteeism. The associations remained statistically significant in all stratified models, except in several models of absenteeism.

Conclusion: In early axSpA, higher disease activity is associated with increased work productivity loss including presenteeism and absenteeism. The same level of disease activity appears to have more adverse impact on work productivity in women than in men. Disease activity was associated with higher absenteeism in patients using NSAIDs, younger men and older women.

Table 1: Association between ASDAS and Work Productivity Loss, presenteeism, absenteeism and stratified for its related effect modifiers at baseline among axial Spondyloarthritis patients who performed paid work in the SPACE cohort (n=124)

	n	WPL Coefficient (SE)	p-value	Presenteeism Coefficient (SE)	p-value	Absenteeism Coefficient (SE)	p-value
Univariable model							
ASDAS	124	18.5 (2.4)	<0.001	16.9 (2.2)	<0.001	9.6 (2.0)	<0.001
Model for gender							
Men							
ASDAS	63	15.2 (3.5)	<0.001	13.3 (3.2)	<0.001	6.8 (2.9)	0.021
Women							
ASDAS	61	20.9 (3.1)	<0.001	19.4 (2.8)	<0.001	12.6 (2.9)	<0.001
Model for use of NSAIDs							
No NSAIDs							
ASDAS	29	12.8 (4.7)	0.011	11.4 (4.0)	0.009	2.3 (2.5)	0.376
NSAIDs							
ASDAS	95	17.3 (2.8)	<0.001	15.8 (2.6)	<0.001	10.7 (2.6)	<0.001
Model for age and gender							
Men <30.6 years							
ASDAS	35	18.8 (5.2)	0.001	16.5 (4.6)	0.001	8.9 (4.4)	0.050
Men ≥30.6 years							
ASDAS	28	11.5 (4.5)	0.015	10.0 (4.5)	0.034	5.1 (3.4)	0.144
Women <30.6 years							
ASDAS	28	16.8 (6.7)	0.019	16.6 (6.3)	0.014	4.5 (5.2)	0.401
Women ≥30.6 years							
ASDAS	27	23.1 (3.0)	<0.001	20.9 (2.6)	<0.001	16.7 (3.3)	<0.001

Abbreviations: Work Productivity Loss, WPL; Standard Error, SE; Ankylosing Spondylitis Disease Activity Score, CRP based, ASDAS

Disclosure: M. van Lunteren, None; **P. Bakker**, None; **Z. Ez-Zaitouni**, None; **C. Fongen**, None; **R. Landewé**, None; **M. van Oosterhout**, None; **R. Ramonda**, None; **F. van Gaalen**, None; **D. van der Heijde**, None.

Abstract Number: 2005

Exploring the Window of Opportunity for Drug-Free Clinical Remission in Patients with Active, Very Early Peripheral Spondyloarthritis

Philippe Carron[1], Gaëlle Varkas[2], Heleen Cypers[2], Liesbet Van Praet[1], Dirk Elewaut[2] and Filip van Den Bosch[1], [1]Department of Rheumatology, Ghent University Hospital, Ghent, Belgium, [2]Laboratory for Molecular Immunology and Inflammation, Department of Rheumatology, VIB, Ghent University and Ghent University Hospital, Ghent, Belgium

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: To evaluate drug-free sustained clinical remission and clinical relapse after induction therapy with golimumab in patients with active peripheral Spondyloarthritis (pSpA) in a very early stage of the disease. The hypothesis would be that treatment with a TNF-blocker at this early ("immature") stage of the disease would result in a significant higher number of patients in clinical remission compared to placebo.

Methods: CRESPA (Clinical REmission in peripheral SPondyloArthritis) is an ongoing monocentric study of golimumab treatment in pSpA patients. Eligible patients were ≥18 years and fulfilled the Assessment of SpondyloArthritis international Society (ASAS) classification criteria for pSpA. All patients had a symptom duration of less than 3 months. Patients were randomized 2:1 to receive golimumab 50 mg every 4 weeks or matching placebo for 24 weeks. The primary endpoint was the percentage of patients achieving clinical remission at week 24. Clinical remission was defined as the absence of arthritis, enthesitis and dactylitis on clinical examination. If patient were in clinical remission at two major consecutive visits planned at week 12 and 24, treatment was stopped. These patients were prospectively followed to assess the percentage of patients in drug-free sustained clinical remission or having a clinical relapse of arthritis, dactylitis and enthesitis. In case of clinical relapse patients were retreated with open-label golimumab in the extension part of this trial.

Results: In total 60 patients were randomized of whom 20 received placebo and 40 golimumab. Baseline demographics and disease characteristics were generally similar between the 2 groups. At week 24 a significantly higher percentage of patients receiving golimumab achieved clinical remission compared to patients receiving placebo (75% (30/40) versus 20% (4/20); P<0.001). At week 12 similar results were observed (70% (28/40) versus 15% (3/20) ; P<0.001). Sustained clinical remission (both at week 12 and 24) was observed in 67.5% (27/40) of golimumab treated patients, compared to only 15% (3/20) in the placebo group; in these patients treatment was stopped. All patients had at least a follow up of 6 months after discontinuation of treatment with a maximum of 52 months. 60% (18/30) of these patients are still in drug-free sustained clinical remission and 40% (12/30) had a clinical relapse. In the 12 patients with relapse after withdrawal of treatment, 10 patients (83.3%) already experienced this flare within 6 months of discontinuation.

Conclusion: In patients with active, very early peripheral spondyloarthritis, treatment with golimumab led to high percentages of clinical remission at week 12 and 24. A high percentage of patients stayed in sustained drug-free clinical remission after induction therapy with golimumab the first 24 weeks.

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Abstract Number: 2006

Tuberculosis Incidence in Ankylosing Spondylitis, Psoriatic Arthritis, and Other Spondyloarthropathies in Sweden: A Population-Based Cohort Study

Mirjam K. de Vries[1], Elizabeth V. Arkema[1], Jerker Jonsson[2], Judith Bruchfeld[3], Lennart TH Jacobsson[4] and Johan Askling[1,5], [1]Clinical Epidemiology Unit, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, Stockholm, Sweden, [2]Infectious Diseases Unit, Karolinska University Hospital, The Public Health Agency of Sweden, Stockholm, Sweden, [3]Department of Medicine, Infectious Diseases Unit, Karolinska

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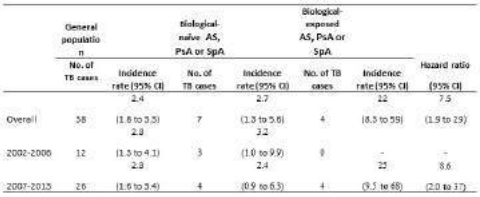
Session Time: 2:30PM-4:00PM

Background/Purpose: Patients with rheumatoid arthritis (RA) are at a well-documented increased risk of tuberculosis (TB) compared to the general population, both with and without treatment with tumor necrosis factor inhibitors (TNFi). Whether or to what extent these increased risks apply also to patients with ankylosing spondylitis (AS), psoriatic arthritis (PsA), or other types of spondyloarthropathies (SpA), whose age, gender and disease characteristics differ from RA, is much less known. We therefore investigated TB risks in these conditions, in relation to biological treatment and risks in the general population.

Methods: Through linkages including the Swedish national Patient, Population, TB and Rheumatology registers, we identified all individuals in Sweden registered with AS, PsA or SpA, and matched general population comparators, who were followed for TB from 2002 through 2013. Incidence rates were estimated for biological-naïve and biological-exposed patients and their comparators. We calculated hazard ratios (HR) and 95% confidence intervals (CI) for the whole period and stratified by calendar period. HRs were adjusted for age, sex and country of birth.

Results: 38,702 patients with AS, PsA or SpA, and 200,417 population comparators were included. Thirteen percent of patients used a biological drug during the study period, of which 99% was a TNFi. The average age of patients was approximately 10 years lower than the RA patients of the previous study. During the study period, 11 TB cases were identified among the patients, corresponding to an incidence rate (per 100,000) of 2.7 (95% CI 1.3 to 5.6) for biological-naïve patients, 22 (95%CI 8.3 to 59.2) for biological-exposed patients, and 2.4 (95% CI 1.8 to 3.3) for the general population. The HR comparing biological-naïve to biological-exposed patients was 7.5 (95% CI 1.9 to 29), and 1.2 (95% CI 0.5 to 2.7) comparing biological-naïve patients compared to the general population.

Conclusion: Biological-naïve AS, PsA and SpA patients have a similar risk of TB as the general population, and hence lower incidences than those previously reported in RA. However, these patients had a 7.5-fold higher risk of TB when treated with TNFi. Although the absolute risk of TB is low, and the most cases occurred in the biological-naïve group, the risk of TB increased after treatment with TNFi. **Table:** Incidence rates and 95% confidence intervals of tuberculosis (TB) in the general population and patients with AS, PsA or SpA with and without biologic therapy. Hazard ratios for TB comparing biological-naïve to biological-exposed, overall and stratified by calendar time of follow-up.



	General population		Biological-naïve AS, PsA or SpA		Biological-exposed AS, PsA or SpA		
	No. of TB cases	Incidence rate (95% CI)	No. of TB cases	Incidence rate (95% CI)	No. of TB cases	Incidence rate (95% CI)	Hazard ratio (95% CI)
Overall	58	2.4 (1.8 to 3.3)	7	2.7 (1.3 to 5.6)	4	22 (8.3 to 59)	7.5 (1.9 to 29)
2002-2006	12	2.8 (1.5 to 4.1)	3	3.2 (1.0 to 9.9)	0	-	-
2007-2015	26	2.4 (1.6 to 3.4)	4	2.4 (0.9 to 6.3)	4	25 (9.5 to 66)	8.6 (2.0 to 37)

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Abstract Number: 2007

Sensitivity and Specificity of Autoantibodies Against CD74 in Early Axial Spondyloarthritis

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment III: Axial Spondyloarthritis – Clinical

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Making the diagnosis of axial spondyloarthritis (axSpA) may be difficult. Antibodies against CD74 have been shown to be present in 2/3 of patients with long established axial SpA. InterSpA is an international multicenter study, conducted to compare the sensitivity and specificity of anti-CD74 and HLA-B27 in patients with axSpA of recent onset.

Methods: Patients between 18 and 45 years suffering from inflammatory back pain (IBP) for maximally 2 years were recruited. The presence of ankylosing spondylitis, additional inflammatory rheumatic disorders and biologic therapy were exclusion criteria. MRI of the sacroiliac joint was performed in all patients; HLA-B27 was detected by genotyping and anti-CD74 using a CE certified kit of Aesku Diagnostics (Wendelsheim, Germany). The sensitivity of anti-CD74 and HLA-B27 were calculated in patients fulfilling the imaging arm of ASAS criteria, in all patients fulfilling ASAS criteria and in 100 blood donors. Both the MRI reading as well as the laboratory procedures were performed blinded.

Results: 205 patients suffering from IBP were recruited. There were 40 recruiting failures, and complete data sets are currently available of 122 patients (mean age 29 years, mean duration of IBP 13 months, 56% male). Sacroiliitis was diagnosed by the expert reader in 67 % and HLA-B27 was positive in 69 % of the patients. 23 patients fulfilled the ASAS criteria of axSpA by the imaging arm only, 59 by both the imaging and clinical arm and 22 by the clinical arm only. The sensitivities of IgA anti-CD74, IgG anti-CD74 and HLA-B27 were 64.6%, 24.4% and 75% in the axSpA patients fulfilling the imaging arm, 65.4%, 23.1% and 80.7% in the patients fulfilling ASAS criteria, and 3%, 5% and 8% in the blood donors. The likelihood ratios are 21.5 (IgA anti-CD74), 4.9 (IgG anti-CD74) and 9.4 (HLA-B27) when considering the patients fulfilling the imaging arm, and 21.8 (IgA anti-CD74), 4.6 (IgG anti-CD74) and 10.1 (HLA-B27) when considering all patients fulfilling ASAS criteria.

Conclusion: In view of the high likelihood ratio, IgA anti-CD74 is a useful addition to our diagnostic tools for axSpA.

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None; **J. Sieper**, Abbott, Eli Lilly, Janssen, Merck, Novartis, Pfizer, UCB Pharma, 8,Abbott, Eli Lilly, Janssen, Merck, Novartis, Pfizer, UCB Pharma, 5; **C. Stille**, None; **U. von Hinüber**, None; **P. Wagener**, None; **H. Weidemann**, None; **S. Zinke**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/sensitivity-and-specificity-of-autoantibodies-against-cd74-in-early-axial-spondyloarthritis

Abstract Number: 2008

Rapamycin Elicits Rapid and Lasting Improvement of Disease Activity through Blocking Pro-Inflammatory T Cell Lineage Specification in Patients with Active SLE

Zhi-Wei Lai[1], Ivan Marchena[2], Hajra Tily[2], Ricardo Garcia[1], Julie Yu[2], Lisa Francis[2], Maha Dawood[2], Ryan Kelly[2], Stephen Faraone[2], Paul E. Phillips[3] and Andras Perl[4], [1]Medicine, SUNY, Syracuse, NY, [2]SUNY, Syracuse, NY, [3]Dept of Medicine/Div of Rheum, SUNY-Upstate Medical Univ, Syracuse, NY, [4]Department of Medicine, Upstate Medical University, Syracuse, NY

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The rationale for this prospective, biomarker-driven, open-label clinical trial of rapamycin (ClinicalTrials.gov Identifier: NCT00779194) has been based on growing evidence for involvement of the mechanistic target of rapamycin (mTOR) in abnormal T-cell activation and preliminary results of clinical efficacy in mice (Arthritis Rheum. 37:289-97) and patients with SLE (Arthritis Rheum. 54:2983-8; J Immunol.191:2236-46).

Methods: 40 SLE patients meeting eligibility criteria were started on 2 mg of rapamycin (sirolimus) with the dose adjusted to tolerance and trough levels of 6-15 ng/ml. British Isles Lupus Assessment Group (BILAG; Rheumatology 44:902-6) scores, SLE disease activity index (SLEDAI; Arthritis Rheum. 35:630-40), and routine laboratory and immunological assessments were performed before 1st rapamycin dose and 1 month, 3 months, 6 months, 9 months, and 12 months after initiation of treatment. At each study visit, blood samples were obtained from healthy controls matched for patients' age, gender, and ethnicity for parallel analyses 665 flow cytometry biomarkers. Patients having active disease with SLEDAI of 10.2±0.8 (mean±SEM), prednisone dose of 23.7±4.9 mg/day, and proteinuria <0.5 g/day, who were unresponsive or intolerant to conventional immunosuppressants, were enrolled. Prednisone dose was titrated to control disease activity during the study.

Results: Therapeutic rapamycin plasma levels were achieved between months 1 (6.9 ng/ml) through 12 (7.8 ng/ml). 11 patients dropped out due to non-compliance. Among safety outcomes, fasting lipid profile, liver function, platelet and lymphocyte counts were unchanged, while neutrophil counts (from 5,100/µl to 3,900/µl) and haemoglobin (from 13.5 to 12.9 g/dl) were moderately reduced in 12 months. As primary clinical efficacy endpoint, reduction of SLEDAI (≥4) and BILAG disease activity scores (≥2) over 12 months was met in 16 of 29 patients (55%). Among 29 patients, 19 achieved ≥4-point drop of SLEDAI, no BILAG A flare and only one BILAG B flare, indicating a 65.5% SLE Responder Index (Arthritis Care Res. 61:1143-51). SLEDAI was

reduced from baseline of 10.2±0.8 to 7.5±0.9 at 1 month (p=0.04) and 4.8±0.8 at 12 months (p=0.00002). Within the SLEDAI components, arthritis, rash, and hypocomplementemia were significantly improved after 12 months. BILAG was reduced from baseline of 28.9±1.9 to 23.8±2.2 at 1 month (p=0.005) and 17.4±1.9 at 12 months (p=0.00003).Within BILAG components, fatigue, cardiopulmonary, musculoskeletal and mucocutaneous organ-domain scores were significantly reduced after 12 months. Daily prednisone use was reduced from 23.7±4.9 mg to 7.2±2.3 mg after 12 months (p=0.02). Rapamycin blocked the activity of mTOR complex 1 in all T cells, expanded $CD4^+CD25^+FoxP3^+$ regulatory, $CD4^+$ central-memory ($CD62L^+CD197^+$), and $CD8^+$ effector-memory ($CD62L^-CD197^-$) T cells and inhibited the pro-inflammatory necrosis and IL-4 production of $CD4^-CD8^-$ double-negative T cells after 12 months.

Conclusion: Rapamycin elicits rapid, progressive, and sustained improvement of disease activity via correcting abnormal T-cell lineage specification in patients with active SLE.

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Abstract Number: 2009

The Effect of Anifrolumab on Cutaneous Manifestations and Arthritis in Moderate to Severe Systemic Lupus Erythematosus (SLE) Using Categorical SLEDAI–2K Responses and Continuous Measures of Activity As Outcome Measures

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The Phase IIb MUSE study (NCT01438489) of intravenous anifrolumab in 305 patients with moderate to severely active SLE (300 or 1,000 mg vs. placebo, every 4 weeks for 48 weeks) demonstrated efficacy in multiple composite endpoints, with many favoring the 300 mg dose at Day 365.

Methods: This exploratory analysis compares the impact of anifrolumab on common individual manifestations of SLE including: rash, alopecia, and arthritis using the categorical descriptors of SLEDAI–2K and continuous outcome measures of cutaneous activity (rates of ≥50% improvement in the Cutaneous Lupus Erythematosus

Disease Area and Severity Index [CLASI] activity score) and arthritis (change from baseline in swollen and tender joint counts).

Results: At Day 365, placebo response was minimal for SLEDAI–2K rash (Table), distinguishing a substantial treatment effect of anifrolumab, with 300 mg response rates markedly greater than 1,000 mg. More patients treated with anifrolumab compared with placebo also achieved ≥50% improvement in CLASI, but with minimal distinction between doses. The placebo group demonstrated response rates to alopecia and arthritis on SLEDAI–2K of 26% and 42%, respectively. A significantly greater response in alopecia and arthritis manifestations was achieved with 300 mg anifrolumab, with only modest drop-off in efficacy rates with 1,000 mg. Compared with placebo, decreased tender and swollen joint counts were greater in patients treated with anifrolumab, with no difference between doses. Anifrolumab effects on SLEDAI–2K improvement for each manifestation, were primarily seen in patients with a high type I interferon gene signature at baseline (IFN high), driven by lower placebo response rates in this subpopulation.

Conclusion: Anifrolumab demonstrated greater rates of improvement than placebo in rash, alopecia and joint manifestations, with greatest effects achieved by 300 mg anifrolumab in IFN-high patients. An apparent inverse dose response favoring the 300 mg (lower) dose, previously reported for several composite outcomes, characterized the SLEDAI–2K rash response which requires complete resolution of the rash, but was less pronounced in arthritis and alopecia categories or when using quantitative measures. These data contribute understanding of the impact of anifrolumab on individual lupus features, and suggests benefits of continuous variables, as demonstrated by the CLASI and joint counts, in outcome measures to inform interpretable trial designs.

Table: Improvement in individual manifestations of SLE at Day 365

	Placebo	Anifrolumab 300 mg*	*P*-Value	Anifrolumab 1,000 mg*	*P*-Value
Improvement at Day 365					
Skin, n (%)					
Rash (SLEDAI–2K)	13/88 (14.8)	39/88 (44.3)	<0.001	23/82 (28.0)	0.033
Alopecia (SLEDAI–2K)	19/74 (25.7)	32/75 (42.7)	0.026	33/82 (40.2)	0.064
≥50% improvement in CLASI#	34/101 (33.7)	58/99 (58.6)	<0.001	51/102 (50.0)	0.018
Arthritis, n (%)					
Arthritis (SLEDAI–2K)	42/99 (42.4)	55/97 (56.7)	0.032	49/98 (50.0)	0.249
Tender and swollen joint					
Baseline, mean (SD)	7.8 (6.5)	8.2 (6.0)		8.1 (6.4)	
Change from baseline, mean (SD)	-3.4 (5.9)	-5.5 (6.3)	0.004	-5.4 (6.8)	0.005

*Every 28 days from Day 1 to Day 337

#Patients with CLASI>0 at baseline

CLASI, Cutaneous Lupus Erythematosus Disease Area and Severity Index; SD, standard deviation

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Abstract Number: 2010

Predictive Factors of Adherence to Treatment in an International Prospective Study of Blood Hydroxychloroquine Levels in SLE Patients with Flares

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies

Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose:

Non-adherence to treatment, a major cause of continued lupus activity and flares, may be difficult to recognize. In this international prospective study, we evaluated adherence to hydroxychloroquine (HCQ) in systemic lupus erythematosus (SLE) patients with flares (ClinicalTrials.gov: NCT01509989).

Methods:

This study included 305 SLE patients (who all met the SLICC criteria) from 19 centers in 10 countries, all of whom had been prescribed HCQ for at least 2 months and were having a disease flare according to the SELENA-SLEDAI Flare Index. Adherence to HCQ was assessed by (1) blood concentrations of HCQ and its main metabolite desethylchloroquine ([HCQ] <200ng/ml and/or undetectable [DCQ] defining severe non-adherence by dosage), (2) self-questionnaires (MASRI<80% and/or Morisky<6 defining non-adherence by questionnaires), and (3) physician's assessments (on a VAS 0-100).

Results:

305 patients (288 women; mean age 38±12ys) met the inclusion criteria. Fifty-six patients (18.4%) were severely non-adherent by dosage (1 missing data point): 44 patients (14.5%) had [HCQ] <200ng/ml and 12 additional patients (3.9%) had an undetectable concentration of DCQ indicating a very recent resumption of treatment. Comparison between non adherent and adherent patients is summarized in table 1. These 56 non-adherent patients by dosage were younger at SLE diagnosis (28±11 vs 23±9; p=0.0025), more likely to be unemployed (46.3% vs 30.9%; p=0.03), and less likely treated with steroids (60.7% vs 79.8%; p=0.0050), whereas their exposure to immunosuppressive drugs was not different. Drug level assessment at inclusion was most often their first drug measurement (84% vs 71%, p=0.046). Their anxiety and depression scores (on the HADS questionnaire) were not different from those of the other patients. Even if their median MASRI and Morisky scores were statistically significantly lower, 24 non adherent patients (43%) would still have been defined as adherent by at least one questionnaire. Moreover, even if the median [Q1-Q3] physician's adherence rating was statistically significantly lower in these 56 patients (75 [43-90] vs 87 [70-95], p<0.0001), their expert physicians considered that 42 patients (75%) took at least half of their treatment and even that 24 (43%) took at least 80% of their treatment.

Among the 305 patients, 121 (39.9%) were non adherent by self-questionnaires. The total non-adherence (dosage + self-questionnaires) was 47%, with only 7% of the patients being classified as non-adherent by both methods.

Conclusion:

These data show that blood HCQ and DCQ measurements objectively identify significant non-adherence in nearly 20% of SLE patients who are flaring. Non-adherence can be missed by the physician and underreported by the patient strongly suggesting the usefulness of blood assays in this setting and the value of using different methods to increase the likelihood of diagnose of non adherence.

Table 1: Characteristics of 304 patients according to their adherence defined by blood drug levels.

	Non-adherent patients by dosage (n=56)	Other patients (n = 248)*	p
Mean Age (± SD) (yr)	35.4 (10.8)	38.2 (11.7)	0.09
Sex, female (%)	55 (98.2)	232 (93.5)	0.09
Ethnicity - White - Black - Asian - Other	 23 (41.1) 21 (37.5) 4 (7.1) 8 (14.3)	 129 (52.0) 62 (25.0) 32 (12.9) 25 (10.1)	0.13
Highest educational level (n=295) - Before high school - High school level - After high school	 8 (14.8) 14 (25.9) 32 (59.3)	 38 (15.8) 64 (26.6) 139 (57.7)	0.97
Employment status (n=297) - Unemployed - Employed - In formation	 25 (46.3) 24 (44.4) 5 (9.3)	 75 (30.9) 154 (63.4) 14 (5.8)	0.03
Active smokers (%) (n=302)	10 (18.2)	34 (13.8)	0.64
Mean age at diagnosis (± SD) (yr)	23.1 (8.9)	28.0 (11.3)	0.0025
Median disease duration [Q1-Q3] (yr)	11 [7 - 17]	9 [5 - 14]	0.06
Median duration of HCQ use [Q1-Q3] (yr) (n=303)	6.1 [3.9 - 11.0]	7.9 [3.3 - 12.3]	0.50
Previous blood HCQ level determination (%) (n=303)	9 (16.1)	72 (29.1)	0.046
Median BMI [Q1-Q3] (n=294)	24 [22 - 30]	23 [21 - 28]	0.06
Median Serum Creatinine (µmol/L) (n=296)	60 [53 - 70]	64 [54 - 79]	0.94
Current use of steroids (%)	34 (60.7)	198 (79.8)	0.005
Current use of immunosuppressive drug or biotherapy (%)	23 (41.1)	117 (47.2)	0.46
Median PGA [Q1-Q3]	1.6 [1.0 - 2.0]	1.5 [1.1 - 2.0]	0.61
Median SELENA-SLEDAI score [Q1-Q3]	8.0 [6.0 - 10.0]	8.0 [6.0 - 10.0]	0.60
Severe Lupus flare (%)	20 (35.7)	112 (45.2)	0.20
Median HADS anxiety score on a 0-21 scale [Q1-Q3] (n=298)	8.0 [3.0 - 10.5]	8.0 [5.0 - 11.0]	0.30
Median HADS depression score on a 0-21scale [Q1-Q3](n=292)	5.5 [4.0 - 9.0]	6.0 [3.0 - 8.0]	0.38
Median MASRI HCQ score on a 0-100 scale [Q1-Q3] (n=298)	74.0 [50.0 - 90.0]	98.0 [90.0 - 100.0]	<0.0001
Median Morisky HCQ score on a 0-8 scale [Q1-Q3] (n=300)	4.6 [2.5 - 6.0]	7.0 [5.8 - 8.0]	<0.0001
Median HCQ adherence by physician on a 0-100 scale [Q1-Q3]	75 [43 - 90]	87 [70 - 95]	< 0.0001

Legends: HCQ Hydroxychloroquine; DCQ: desetylhydroxychloroquine; SD: standard deviation; Q1: quartile 1; SELENA-SLEDAI: SLE Disease Activity Index; PGA: physician's global-assessment visual-analogue scale.
MASRI is a self-questionnaire assessing adherence from the patient's point of view.
Non-adherence was defined by [HCQ] <200ng/ml and/or undetectable concentration of DCQ.
"Others" included patients perfectly adherent as well as less adherent patients with a blood level of HCQ >200 ng/ml and a measurable DCQ.
*: 1 missing data regarding [HCQ] and [DCQ].
PS: The multivariate analysis of the predictive factors is ongoing.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/predictive-factors-of-adherence-to-treatment-in-an-international-prospective-study-of-blood-hydroxychloroquine-levels-in-sle-patients-with-flares

Abstract Number: 2011

Enteric-Coated Mycophenolate Sodium Versus Azathioprine for Patients with Moderate/Severe Active Systemic Lupus Erythematosus: Results from a Phase 3, Randomized, Parallel, Multicentre Study

Josefina Cortés-Hernández[1], luis Sáez-Comet[2], Mercedes Pérez-Conesa[2], M Rubio Rivas[3], Francesca Mitjavila[4], A. Castro Salomó[5], Sandra Parra[6], J. Cuquet Pedragosa[7], Vera Ortiz-Santamaría[8], M. Mauri Plana[9], Segundo Bujan-Rivas[10], P Suñé Martin[11], Xavier Vidal[12] and Josep Ordi-Ros[13], [1]Internal Medicine Department, Vall d´Hebron Hospital, Barcelona, Spain, [2]Internal Medicine, Miguel Servet University Hospital, Zaragoza, Spain, [3]Internal Medicine, hopital Universitario Bellvitge, Barcelona, Spain, [4]Internal Medicine, Bellvitge University Hospital, Barcelona, Spain, [5]Hospital Universitari de Reus, Spain, Reus, Spain, [6]Internal Medicine, Sant Joan de Reus University Hospital, Reus, Spain, [7]Internal Medicine, Granollers University Hospital, Granollers, Spain, [8]Rheumatology, Hospital General. Granollers., Granollers, Spain, [9]Internal Medicine, Mataró Hospital, Mataró, Spain, [10]Vall d'Hebron Hospital, Barcelona, Barcelona, Spain, [11]Pharmacy Department, Vall d'Hebron Hospital, Barcelona, Spain, [12]Statistical Department, Vall d'Hebron Hospital, Barcelona, Spain, [13]Internal Medicine, Systemic Autoimmune disease Research Unit. Hospital Vall d'Hebron., Barcelona, Spain

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Treatment of non-renal manifestations in systemic lupus erythematosus (SLE) remains challenging. To date, available data on the efficacy, safety and steroid-sparing effects of non-biological therapies is limited and provided mainly by small open-label studies and few randomized controlled trials (RCTs). The aim of the study is to assess the efficacy and safety of enteric-coated mycophenolate sodium (EC-MPs) compared with azathioprine (AZA) for active non-renal SLE.

Methods: This is a 24-month randomized, superiority, open-label, multicenter study (ClinicalTrials.gov: NCT01112215). Adults age ≥18 years with moderate-to-severe active SLE disease were recruited from 13 Hospitals in Spain. Patients were stratified by centre and SLEDAI-2k score (6-9 *vs.* ≥10) and randomized (1:1) to receive oral EC-MPs (target dose: 1440 mg/day) or azathioprine (target dose: 2 mg/Kg, according to TPMT levels when available), in addition to background therapy with oral prednisone and antimalarial agents. To have a ≥80% statistical power to detect a ~20% difference in clinical response between the 2 study groups, assuming a clinical response in the AZA group at 2 years of 40-50% we calculated we needed 120 patients in each group with a two-sided significance level of 0.05. Statistical analysis was by intention-to-treat. Rates of complete remission (CR) at 3 and 24 months were the primary endpoints. Secondary endpoints included time to CR, rate and time to BILAG A/B or BILAG A flares, reduction of corticosteroids and adverse events.

Results: A total of 240 patients were included. More patients in the EC-MPs group than in the azathioprine group achieved CR at 3 (32.5% vs. 19.2%, p=0.027) and 24 months (71.2% vs. 48.3%, p=0.0005). Time to CR was shorter in the EC-MPs group (hazard ratio, 1.43; 95% CI, 1.07 to 1.91; P=0.017). BILAG A/B flares were observed in 86 (71.7%) AZA-treated and 60 (50%) EC-MPs-treated patients (p=0.001). Time to first flare was longer with EC-MFs (hazard ratio, 1.81; 95% CI, 1.3 to 2.56; p=0.0004). New BILAG A flares occurred in 26 (21.7%) AZA-treated and 10 (8.3%) EC-MPs-treated patients (p=0.004). Time to severe flare was longer in the

EC-MPs group (hazard ratio, 2.84; 95% CI, 1.37 to 5.89; p=0.0029). Steroid reduction was superior in the EC-MPS group (p=0.024). Adverse events did not differ between groups except for leukopenia in the AZA group.

Conclusion: EC-MPs was superior to AZA for treating active disease and preventing relapse in non-renal SLE patients.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/enteric-coated-mycophenolate-sodium-versus-azathioprine-for-patients-with-moderatesevere-active-systemic-lupus-erythematosus-results-from-a-phase-3-randomized-parallel-multicentre-study

Abstract Number: 2012

Utility of the Lupus Low Disease Activity State Definition in Discriminating Responders in the Phase IIb Muse Trial of Anifrolumab in Systemic Lupus Erythematosus

E. Morand[1], A. Berglind[2], T. Sheytanova[2], R. Tummala[3] and G. Illei[3], [1]Monash University, Melbourne, Australia, [2]AstraZeneca, Mölndal, Sweden, [3]MedImmune, Gaithersburg, MD

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

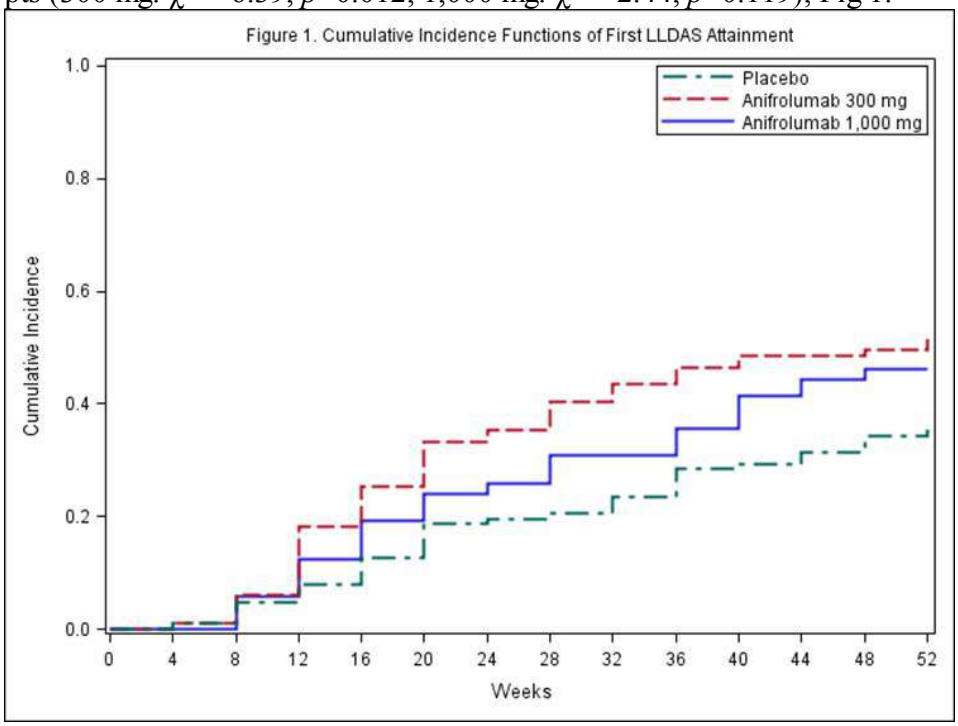
Background/Purpose: Preliminary validation of a Lupus Low Disease Activity State (LLDAS) definition has demonstrated that LLDAS attainment is associated with reduced damage accrual in patients (pts) with SLE.[1] However, it has not been evaluated in randomized controlled trials (RCTs). We present a *post-hoc* analysis evaluating LLDAS in the MUSE trial of anifrolumab in pts with moderate to severe SLE.[2]

Methods: LLDAS requires all of the following: SLEDAI–2K <4 without major organ activity, no new disease activity, Physician's Global Assessment (0–3) <1, prednisolone <7.5 mg/day, and tolerance of standard immunosuppressant dosages.[1] LLDAS criteria were assessed at each study visit. The utility of LLDAS, its association with other endpoints, and the difference in attaining LLDAS between pts treated with anifrolumab and placebo, were explored using descriptive statistics, logistic regression, and Gray's test.

Results: During the 52-week study period of MUSE, pts received intravenous placebo (n=102), anifrolumab 300 mg (n=99), or anifrolumab 1,000 mg (n=104), in addition to standard of care, every 4 weeks for 48 weeks. LLDAS criteria were met, at least once, by 35%, 52%, and 46% of pts, respectively (odds ratio [OR] vs. placebo; 300 mg: 1.97, 90% CI 1.19, 3.25; *p*=0.027; 1,000 mg: 1.63, 90% CI 1.00, 2.68; *p*=0.103). Positive associations were observed between LLDAS and both the SLE Responder Index (SRI[4]) and BILAG-based

Composite Lupus Assessment (BICLA) at 52 weeks, irrespective of treatment; 87% and 74% of pts meeting LLDAS criteria at 52 weeks also fulfilled the SRI(4) and BICLA criteria, respectively (χ^2 = 57.61 and 55.18; p<0.0001 in each case). However, LLDAS was more stringent, with 47% of SRI(4) and 51% of BICLA responders reaching LLDAS.

Compared with placebo, anifrolumab 300 mg and 1,000 mg treatments were associated with increases in LLDAS attainment from Week 12 and Week 28, respectively, with ORs ranging between 1.7 and 3.6 (300 mg), and 1.7 and 2.5 (1,000 mg) at subsequent visits. At Week 52, LLDAS was achieved more frequently in the anifrolumab groups (OR vs. placebo; 300 mg: 3.41, 90% CI 1.93, 6.06, p=0.001; 1,000 mg: 2.03, 90% CI 1.13, 3.64, p=0.046). ORs for spending ≥50% of observed time in LLDAS were 3.04 (90% CI 1.53, 6.06; p=0.008) and 2.17 (90% CI 1.07, 4.39; p=0.072), respectively. Anifrolumab-treated pts reached LLDAS earlier than placebo pts (300 mg: χ^2 = 6.39, p=0.012; 1,000 mg: χ^2 = 2.44, p=0.119), Fig 1.



Conclusion: In the MUSE study, LLDAS correlated with clinically relevant definitions of treatment response and discriminated responders from non-responders. Treatment with anifrolumab 300 mg was associated with up to 3.6-fold increase in odds of LLDAS attainment. LLDAS should be considered as an outcome measure in SLE RCTs.

[1]Franklyn K, et al. *Ann Rheum Dis* 2015;doi:10.1136/annrheumdis-2015-207726.
[2]Furie R, et al. Arthritis Rheumtol 2015;67(Suppl 10):Abs 3223.

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Abstract Number: 2013

BIIB059, a Monoclonal Antibody Targeting BDCA2, Shows Evidence

of Biological Activity and Early Clinical Proof of Concept in Subjects with Active Cutaneous SLE

Richard Furie[1], Victoria P. Werth[2], Joseph Merola[3], Wenting Wang[4], Dania Rabah[4], Catherine Barbey[4], Cynthia Carrillo-Infante[4], Taylor Reynolds[4], Lauren Stevenson[4], David Martin[4] and Nathalie Franchimont[4], [1]Division of Rheumatology, Northwell Health, Great Neck, NY, [2]Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, PA, [3]Harvard Medical School, Boston, MA, [4]Biogen, Cambridge, MA

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment III: Novel and Current Therapies

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Type I interferons (IFN-I) are implicated in the pathogenesis of systemic lupus erythematosus (SLE). BDCA2 is a plasmacytoid dendritic cell (pDC)-specific receptor that, upon engagement, inhibits the production of IFN-I and other inflammatory mediators produced by human pDCs. Targeting BDCA2, therefore, represents an attractive therapeutic strategy for inhibiting pDC-driven inflammation that is such a prominent feature of SLE. BIIB059 is an investigational humanized anti-BDCA2 monoclonal antibody. This first-in-patient study aimed to assess the safety, tolerability, pharmacokinetics (PK), pharmacodynamic (PD) effects and clinical activity of BIIB059 in adult SLE patients with active cutaneous disease following administration of a single BIIB059 dose.

Methods: A phase 1b randomized, double-blinded, placebo-controlled, multicenter clinical trial was conducted in 12 adult SLE subjects (meeting 1997 ACR criteria) with active cutaneous manifestations [including acute, sub-acute and/or chronic cutaneous forms of cutaneous lupus erythematosus (CLE)]. Subjects received a single IV administration of either BIIB059 20 mg/kg (n=8) or placebo (n=4). A panel of IFN-responsive genes (IRG) was assessed from whole blood by qPCR at baseline and several post-dose time points. Skin biopsies from active lesions were obtained and evaluated at baseline and week 4 for IFN-regulated proteins, including MxA using quantitative immunohistochemistry. CLE disease activity was determined using the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI™), and safety data, including adverse events (AEs) and laboratory tests, were also collected.

Results: Most SLE subjects had high IRG signatures in the blood and/or skin biopsies demonstrating features of inflammation consistent with active CLE, including elevated expression of MxA and other IFN-regulated proteins. A single dose of BIIB059 led to reversible inhibition of IRG in the blood. A marked decrease in skin expression of MxA at week 4 was observed in 5 of the 6 subjects treated with BIIB059 who had elevated MxA at baseline compared to less pronounced effects in the 4 placebo subjects (all with elevated baseline MxA). In addition, CLASI-activity at week 12 was also notably decreased in 6 of 8 BIIB059-treated subjects compared to the 4 placebo subjects (2/4 non-responders, 1/4 lost to follow-up and 1/4 treated with IV steroids for SLE flare). BIIB059 was generally well tolerated; the incidence of AEs was similar between BIIB059- and placebo-treated SLE subjects, and most AEs were mild or moderate in severity. There were no withdrawals due to AEs.

Conclusion: A single dose of BIIB059 resulted in inhibition of the IRG in peripheral blood and MxA expression in lesional skin of SLE subjects, consistent with BIIB059's proposed mechanism of action. The clinical and biomarker data together confirm the role of human pDCs in SLE skin pathology, and support further development of BIIB059 in SLE.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/biib059-a-monoclonal-antibody-targeting-bdca2-shows-evidence-of-biological-activity-and-early-clinical-proof-of-concept-in-subjects-with-active-cutaneous-sle

Abstract Number: 2014

A Deep Insight into Causes and Predictors of Death in Systemic Sclerosis

Muriel Elhai[1], Christophe Meune[2], Jerome Avouac[1], Fazia Amrouche[3], Eric Hachulla[4], Alexandra Balbir-Gurman[5], Gabriela Riemekasten[6], Paolo Airò[7], Patricia E. Carreira[8], **Yannick Allanore**[9] and on behalf of EUSTAR co-authors, [1]Rheumatology A department and INSERM U1016, Paris Descartes University, Cochin Hospital, Paris, France, [2]Paris XIII University, Bobigny, France, [3]Paris Descartes University, Cochin Hospital, Paris, France, [4]CHU Lille, Lille, France, [5]B Shine Department of Rheumatology, Rambam Health Care Campus,. Rappaport Faculty of Medicine, Technion, Haifa, Israel, [6]Department of Rheumatology, University of Luebeck, Lübeck, Germany, [7]Rheumatology and Clinical immunology Unit, Spedali Civili of Brescia, Brescia, Italy, [8]Multidisciplinary Pulmonary Hypertension Unit. Hospital Universitario 12 de Octubre, Madrid, Spain, [9]Immunogenetics, Cochin Institute, Paris, France

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics II

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose : Systemic sclerosis (SSc), a connective tissue disease, is associated with high mortality rates. The main causes and risk factors for death are only poorly known. Our aim was to better determine causes and predictors for mortality by using two complementary strategies.

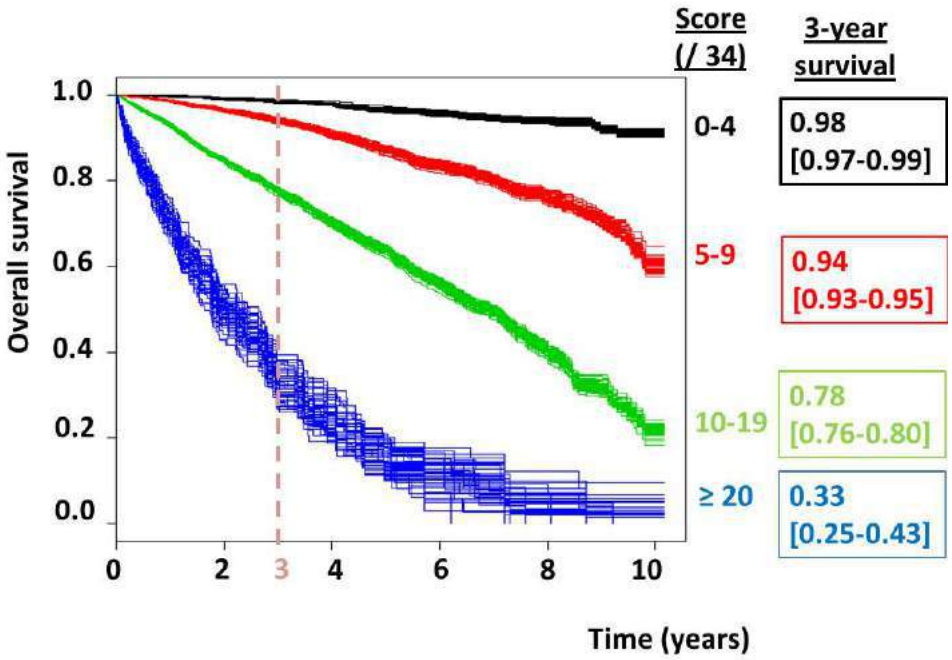
Methods : We first studied causes and predictors of death among the international multicenter EUSTAR cohort; overall survival was estimated by the Kaplan-Meier method, prognostic factors were identified by multivariate cox analysis with imputations for missing data. A risk score for 3-years mortality was established and internally validated by bootstrapping. We then examined standardized mortality rates, its trends over time and the causes of death in SSc-patients from the exhaustive analysis of all death certificates in France from 2000 to 2011.

Results : In Eustar cohort, a total of 11,193 SSc-patients were included: 86% of women, 31% of diffuse cutaneous forms, and mean disease duration: 8.1 years. During a median follow-up of 2.3 years, 1072 (9.6%) patients died. Multivariate analysis identified 14 independent predictors for death (age, male sex, CRP elevation, dyspnea, lung fibrosis and decrease in DLCO and FVC, proteinuria, and scleroderma renal crisis, heart failure,

Rodnan skin score, digital ulcers, and joint involvement) leading to establishment of a prognostic score. This score had better discrimination to predict survival at 3-years than previous mortality score ($p<0.0001$). Furthermore, it allowed accurate stratification of patients in four distinct groups of disease severity (Fig. 1). Death certificates identified 2719 deaths related to SSc: the causes of death strengthened those observed using the EUSTAR cohort highlighting the major contribution of the cardiovascular system (Fig. 2). The overall O:E ratio demonstrated an increased risk of death by infection (5.61), respiratory (2.99) and cardiovascular diseases (1.39) (particularly before 60 years (3.14)) in SSc-patients. Death certificates also revealed a decrease in standardized mortality rates during the time (1 per 10^5 patients in 2000 to 0.6 per 10^5 patients in 2011).

Conclusion : Using two complementary sources of information, which allowed working on the unreached number of 3700 deaths, we provide insight into the causes of deaths and emphasis on the contribution of the cardiopulmonary system. In addition, we have established a robust mortality score to estimate the 3-year survival of SSc-patients. The Scope score allows risk-stratification and will support future studies to improve the management in the perspective of extending survival in SSc.

Figure 1 Overall survival



according to simplified score categories. Curves are plotted for each of the 50 imputed dataset.

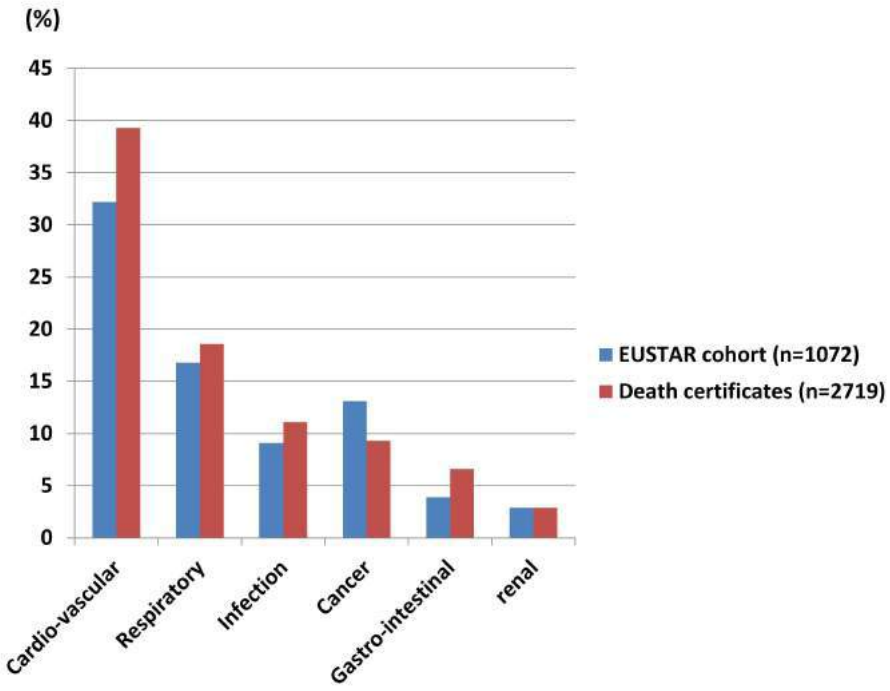


Figure 2: Causes of death in EUSTAR cohort and in French death certificates

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Disclosure: M. Elhai, None; **C. Meune**, None; **J. Avouac**, INVENTIVA, 9; **F. Amrouche**, None; **E. Hachulla**, None; **A. Balbir-Gurman**, None; **G. Riemekasten**, None; **P. Airò**, None; **P. E. Carreira**, None; **Y. Allanore**, None.

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Abstract Number: 2015

The Systemic Sclerosis Disease State Is Associated with Specific Alterations in Gastrointestinal Microbiota in Two Independent Cohorts

Elizabeth R. Volkmann[1], Anna-Maria Hoffmann-Vold[2], Yu-Ling Chang[3], Jonathan Jacobs[4], Philip J. Clements[4], Martin Kummen[2], Johannes R. Hov[2], Kirsten Tillisch[1], Venu Lagishetty[1], Oyvind Midtvedt[5], Øyvind Molberg[5] and Jonathan Braun[3], [1]University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [2]Oslo University Hospital, Oslo, Norway, [3]Pathology and Laboratory Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [4]Medicine, University of California, Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [5]Rheumatology, Oslo University Hospital, Oslo, Norway

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Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics II

Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

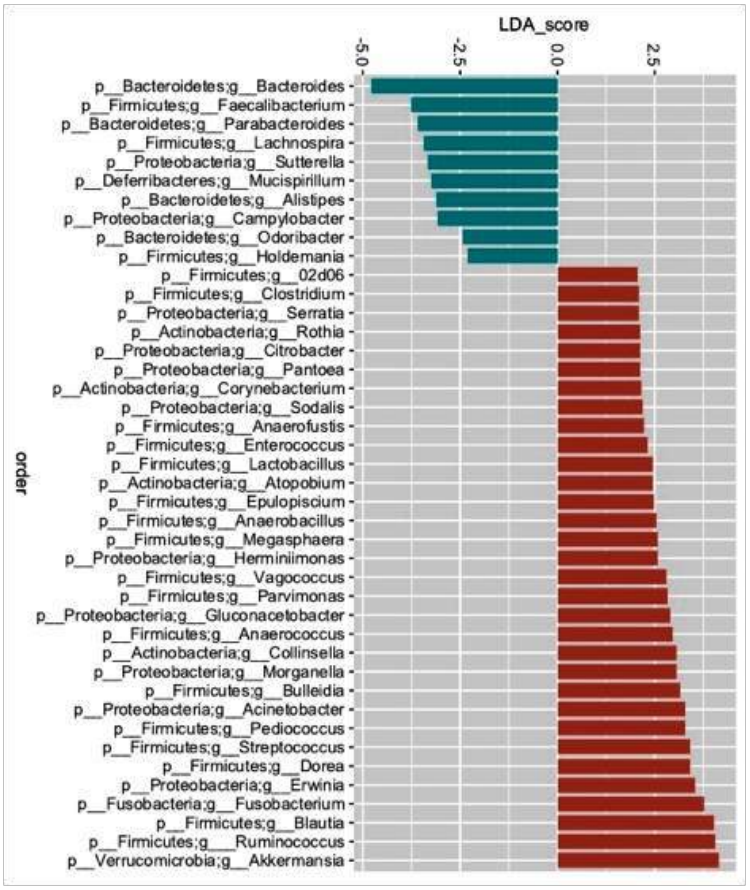
Background/Purpose: A single center study demonstrated that systemic sclerosis (SSc) patients have a distinct colonic microbial consortium (based on lavage specimens) compared with healthy controls and that these ecological changes are associated with SSc-gastrointestinal tract (GIT) symptoms.[1] The purpose of the present study was to compare the fecal microbial composition in SSc patients from 2 independent cohorts and to determine whether certain microbial genera are associated with SSc-GIT symptoms.

Methods: Adults SSc patients from UCLA and Oslo University Hospital were eligible to participate. Healthy controls were also recruited (1:1). SSc patients completed the GIT 2.0 questionnaire to assess GIT symptom severity at the time of the stool collection. The microbiota from these samples were determined by Illumina HiSeq 2500 16S rRNA sequencing at UCLA, and operational taxonomic units were selected using the Greengenes database at 97% identity. Linear discriminant analysis effect size was used to identify the genera that showed differential expression in the two cohorts. Differential expression analysis for sequence count data was used to identify specific genera associated with GIT symptoms.

Results: 17 UCLA SSc patients (88% Female; Median age 52.1 years), 17 Oslo SSc patients (71% Female; Median age 60.5 years), and 17 healthy controls (60% Female; Median age 29.0 years) were enrolled. The mean (SD) total GIT 2.0 score was 0.7 (0.6) and 0.6 (0.5), and the median (IR) disease duration was 6.6 (2.5, 16.4) and 7.0 (1.0, 19.2) for the UCLA and Oslo cohorts, respectively. Principal coordinate analysis illustrated significant microbial community differences between the UCLA SSc and control cohorts (p=0.001) and between the Oslo SSc and control cohorts (p=0.002). At the genus level, SSc patients had significantly lower levels of protective commensal genera, such as *Bacteroides* (UCLA and Oslo), *Faecalibacterium* (UCLA), *Clostridium* (Oslo); and significantly higher levels of pathobiont genera, such as *Fusobacterium* (UCLA), compared with controls (Figure 1). SSc patients with none/mild GIT symptoms had higher levels of commensal genera, such as *Clostridium*, compared with patients with moderate/severe GIT symptoms.

Conclusion: Consistent with the results of our prior study[1], the present analysis detected specific aberrations in the lower GIT microbiota of patients with SSc from two geographically and ethnically distinct cohorts. These findings suggest that GIT dysbiosis may be a pathological feature of the SSc disease state. **References**:

[1]Volkmann et al. Arthritis Rheum 2016;68:1483-92. **Figure 1. Genus level taxa associated with UCLA SSc patients versus healthy controls.** Linear Discriminant Analysis (LDA) was used to calculate the effect size for these associations. Positive and negative effect sizes denote genera increased (red) or decreased (green) in SSc

patients, respectively. 

Disclosure: E. R. Volkmann, None; **A. M. Hoffmann-Vold**, None; **Y. L. Chang**, None; **J. Jacobs**, None; **P. J. Clements**, None; **M. Kummen**, None; **J. R. Hov**, None; **K. Tillisch**, None; **V. Lagishetty**, None; **O. Midtvedt**, None; **Ø. Molberg**, None; **J. Braun**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-systemic-sclerosis-disease-state-is-associated-with-specific-alterations-in-gastrointestinal-microbiota-in-two-independent-cohorts

Abstract Number: 2016

Esophageal Disease in Systemic Sclerosis: Does Heritability Play a Role?

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Background/Purpose: Systemic sclerosis (SSc) associated gastroesophageal reflux disease (GERD) can cause symptoms of dysphagia and heartburn, and is associated with esophagitis, stricture, Barrett's esophagus, and esophageal adenocarcinoma. A genealogic resource, the Utah Population Database (UPDB) has successfully identified systemic sclerosis (SSc) pedigrees and comparable hereditable risk for this disease. We hypothesized that these pedigrees could be used to assess for the hereditability of esophageal disease in order to risk stratify SSc patients with esophageal symptoms and inform their monitoring needs.

Methods: SSc (ICD-9 710.1 and ICD-10 M34.0, M34.1, and M34.9), GERD (ICD-9 530.1 and ICD-10 K21.9), dysphagia (ICD-9 787.20), esophageal stricture (ICD9 530.3 and ICD10 K 22.2), Barrett's esophagus (ICD-9 530.85 and ICD-10 K22.7), and esophageal adenocarcinoma (ICD-9 150.9 and ICD-10 C15.9) was identified from statewide discharge data, the University of Utah Health Science Center Enterprise Data Warehouse, and death certificates and were linked to the UPDB for analysis. SSc probands that had pedigree information for first, second, and third degree relatives were analyzed for the presence of each of the aforementioned diagnostic codes. Inheritance was evaluated by familial standardized incidence ratio and relative risks (RR) to first, second, third, fourth degree relatives and spouses for cases of SSc. Five matched controls were selected from the statewide UPDB population file without replacement in a Monte Carlo method to simulate random sampling in this low penetrate disease. The controls were matched on gender, birth year, and whether they were born in Utah.

Results: A software kinship analysis tool analyzed 2227 unique SSc patients and 11136 controls. In this study, 15% of the SSc from the Utah population is familial based on calculated population attributable risk. The SSc proband had a significant presence of esophageal symptoms and disease: GERD (RR: 3.28), dysphagia (RR 5.58), esophageal stricture (RR: 5.16), esophagitis (RR: 4.86), and Barrett's (RR: 4.52 (all $p<2e-16$) as expected. In a first-degree relative of a SSc proband GERD (RR: 1.14, $p=6.85e-05$), dysphagia (RR: 1.22 $p=0.002$), and esophagitis (RR: 1.37, $p=2.10e-06$) were significantly seen in SSc first degree relatives (parents and children). Esophagitis and dysphagia was significantly seen in first cousins (RR: 1.09, $p=0.03$) and spouses (RR; 1.37, $p=0.02$), suggesting that both genetics and similar exposures (ie, diet) may play a role in pathogenesis. Esophageal stricture and Barrett's esophagus do not appear to be hereditable and were also not seen in spouses. None of the SSc cases had esophageal adenocarcinoma.

Conclusion: The UPDB is a resource that allows for meaningful inheritance analysis. These data suggest that independent of GERD, esophagitis in SSc patients and their relatives may have both a hereditable and environmental etiology. Importantly, there does not seem to be a heritable component to Barrett's esophagus in this population suggesting that modulation of reflux may play an important role in prevention.

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Abstract Number: 2017

Performance of Modified Rodnan Skin Score in Early Diffuse Cutaneous Scleroderma-Analysis from 4 International Cohorts

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Background/Purpose: The modified Rodnan skin score (mRSS) is used as a primary outcome measure in clinical trials of dcSSc. EUSTAR analysis has proposed that a lower mRSS and earlier disease duration are associated with progressive disease, as defined by worsening mRSS [1]. Our objective was to find an optimal cut off for worsening mRSS in 4 cohorts of dcSSc.

Methods: We used 4 cohorts with early dcSSc (defined as ≤60 months from 1st non-RP sign or symptom) – 2 US cohorts [Combined Response Index in Systemic Sclerosis [CRISS] and Prospective Registry in Early Systemic Sclerosis [PRESS]], the UK Royal Free Hospital [RFH] cohort, and the Australian Scleroderma Interest Group [ASIG] cohort. Inclusion criteria included dcSSc diagnosed by a scleroderma physician, mRSS data at 2 time points (12±3 months apart), and availability of disease duration (defined as 1st non Raynaud phenomenon sign or symptom). Worsening of skin fibrosis was defined as increase in mRSS >5 points and ≥25% from baseline to 2nd visit. To identify the optimal cut point of baseline MRSS that yields the highest sensitivity for worsening disease, we developed the ROC curves. For worsening of mRSS, we fitted logistic regression model with worsening as outcome variable and a binary variable of baseline mRSS cut point as predictor.

Results: There were 231 patients with early dcSSc included in the analysis. Mean (SD) disease duration was 26.7 (14.6) months, median=23.67 months. We evaluated 3 cut points for disease duration based on inclusion criterion from recent clinical trials: ≤24, 36, and 60 months. For all disease durations, approximately 10% of patients had mRSS worsening at 1-year period. A mRSS cut off of ≤28 had the highest probability of worsening (Table). mRSS of ≤28 was able to enrich worsening mRSS from 10% to approximately 14% for different cut points but excluded 26-27% of patients with early dcSSc. **Worsening in mRSS for the Whole Cohort vs. Cut Point of ≤28**

	N	Disease duration ≤ 24 mos.	N	Disease duration ≤ 36 mos.	N	Disease duration ≤ 60 mos.
All subjects who worsened	122	12 (9.84%)	175	18 (10.29%)	231	24 (10.39%)
Proportion who worsen with mRSS ≤28 (worsen*/ total cohort with mRSS ≤28	89	12/89=13.48%	129	18/129=13.95%	169	24/169=14.20%
Probability of worsening for mRSS ≤28 (worsen* with mRSS ≤28/all patients who worsened*)	12	12/12=100%	18	18/18=100%	24	24/24=100%
Probability of improvement with mRSS ≤28 (improved**/ total cohort with mRSS ≤28	34	34/89=38.20%	51	51/129=39.53%	68	68/169=40.24%

*increase in mRSS>5 points and ≥25% from baseline to second visit

*decrease in mRSS>5 points and ≥25% from baseline to second visit

Conclusion: In this preliminary analysis, a mRSS≤28 was the optimal cut point for worsening disease in 4 cohorts with dcSSc. This threshold gained an additional 4% of patients who worsened but excluded 26-27% of patients with early dcSSc. Further criteria are needed for enrichment of patients with dcSSc so large proportion of patients are not excluded from participating in RCTs . **References:** Maurer B Ann Rheum Dis 2015

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Abstract Number: 2018

A Clinical Risk Prediction Model for Skin Thickness Progression in Early Diffuse Scleroderma

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Background/Purpose: Systemic sclerosis (SSc) is a rapidly evolving field with multiple potential therapeutic agents under development and several active clinical trials focused on treating diffuse cutaneous SSc. When weighing management decisions for therapy and considering clinical trial involvement, estimating the likelihood of skin thickness progression over the next year will be helpful. **Objectives:** To derive a clinical risk prediction tool to predict skin thickness progression over one year.

Methods: We used a US single-center cohort of prospectively followed early diffuse SSc patients seen for an initial visit from Jan. 1, 1980 to Dec. 31, 2014. To reflect current early diffuse SSc clinical trial design, early was defined as <3 years after the first non-Raynaud symptoms and diffuse skin as proximal to the elbows or knees. Eligible patients had ≥ 2 modified Rodnan skin scores (mRSS) within one year of the first SSc center visit, for ≥ 3 mRSS over one year. The outcome was mRSS progression at any time over one year of follow-up, defined as an increase of ≥5 points and a 25% increase in the mRSS from baseline. SSc autoantibodies were confirmed by the gold standard methods of immunodiffusion or immunoprecipitation. Skin change was assessed in multiple ways, including Receiver Operating Curve (ROC) analysis to determine a risk cut-off point for mRSS. Multivariable logistic regression modeling was used. Beta-estimates were rounded to the nearest 0.5, summed and ROC analysis performed.

Results: Among 317 eligible patients the mean age was 50.8 ± 13.5 years, 74% female and 92% Caucasian. The median disease duration from first SSc symptom was 0.90 years (IQR 0.63, 1.46). The mean first visit mRSS was 23±11. 25% (n=79) were scl-70 positive, 56% (n=178) RNA-polymerase III positive (RNAP) positive, 54 (17%) other SSc-associated antibody and 2% (n=6) missing. In total, 163 patients (51%) developed skin progression over one year. The mean time to peak mRSS among progressors was 0.51±0.23 years from the first visit. ROC analysis showed mRSS ≤27 to best predict skin progression. A 4-variable model was developed to predict skin progression over one year (Table 1) with a AUC = 0.81 (95% CI 0.75, 0.88). When β-estimates were rounded and summed as in Table 1, a 3-level risk stratification model was created with rate of skin progression depicted in Table 2. The AUC for this model remained excellent at 0.80 (0.75, 0.85).

Conclusion: We have derived an accurate 3-level clinical risk stratification tool for skin thickness progression over one year of follow-up in early diffuse SSc patients.

Table 1: Multivariable Logistic Regression Model

	β	**Odds Ratio (95% Confidence Interval)**	**p-value**	**Points Assigned**
Disease duration< 1 year	1.33	3.79 (1.74, 8.23)	0.0008	1.5
Pulmonary fibrosis on chest imaging	-1.35	0.26 (0.11, 0.62)	0.002	-1.5
SSc antibody **RNAP** **Scl-70** **Other SSc antibody**	-1.53	0.22 (0.08, 0.60)	0.003	0 0 -1.5
Baseline mRSS ≤27	2.39	10.96 (4.31. 27.84)	<0.0001	2.5
				Sum Score

Table 2: 3-level risk stratification tool for predicting skin progression		
	Sum Score	**% of diffuse SSc patients with skin thickness progression**
Low risk	-0.5 and below	10%
Moderate risk	0 to 1.5	28%
High risk	2.5 and above	72%
AUC = 0.80 (0.64, 0.73)		

Disclosure: R. T. Domsic, Bayer Healthcare, 2,Biogen-Idec, 2; **M. Lucas**, None; **V. D. Steen**, None; **T. A. Medsger Jr.**, None.

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Abstract Number: 2019

Faces in Motion: Clinical Subtyping in Scleroderma Using Changes in Forced Vital Capacity

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Background/Purpose: Prognostication in scleroderma has historically depended on using static measures such as antibody status and extent of skin involvement to stratify risk of mortality and major organ complications. These static measures are intrinsically unable to inform the difference between disease activity and disease damage in scleroderma, which is a critical for clinicians considering the timing of potentially toxic treatment. We hypothesized that serial changes in a clinical outcome of interest--in this case the forced vital capacity (FVC)Ñcould itself be used to classify patients with a common disease course and comparable mortality.

Methods: We retrospectively applied a form of latent subtype analysis called probabilistic subtype modeling (PSM) to serial lung function data from patients followed at an academic scleroderma referral center, to identify shared trajectories of FVC among individuals over time. We then examined mortality across each of these shared trajectories using Kaplan Meier curves and adjustment for demographics with Cox proportional hazards models.

Results: Serial FVC from 1615 patients defined 10 trajectories by PSM, which were collapsed by the authors into 5 clinically similar patterns of FVC change over time (Figure 1). Mortality separated largely into 3 groups (Figure 2), with a protective hazard in subgroups with intact lung function (HR of 0.36 [95%CI=0.30Ñ0.44] and 0.60 [0.44Ñ0.82]) in Groups A and B, respectively, an intermediate mortality in the subgroup with variable FVC (Group C HR 0.98 [0.80Ñ1.21]), and a high mortality among patients with depressed and declining FVC (HR 2.14 [1.77Ñ2.59] and 2.81 [2.33Ñ3.41] in Groups D and E, respectively). Major antibody, skin extent, race, gender, disease onset after age 55, and the presence of calcinosis most frequently helped distinguish among the FVC trajectory subtypes. However, the highest prevalence of any single characteristic within a subtypeÑfor example, diffuse skin (68%) or centromere antibody (37%)Ñwere not sufficiently associated with an FVC trajectory to serve as the only distinguishing feature among subtypes.

Conclusion: Grouping patients by longitudinal change in FVC identifies patients with similar risk of mortality, illustrating the potential utility of incorporating serial clinical metrics into the risk assessment of patients with scleroderma. If identifiable early within an individualÕs course, clinical trajectories may be powerful tool to inform treatment decisions.

Figure 1: FVC Trajectories Defined by Probabilistic Subtype Modeling, Collapsed into Five Groups (A-E)

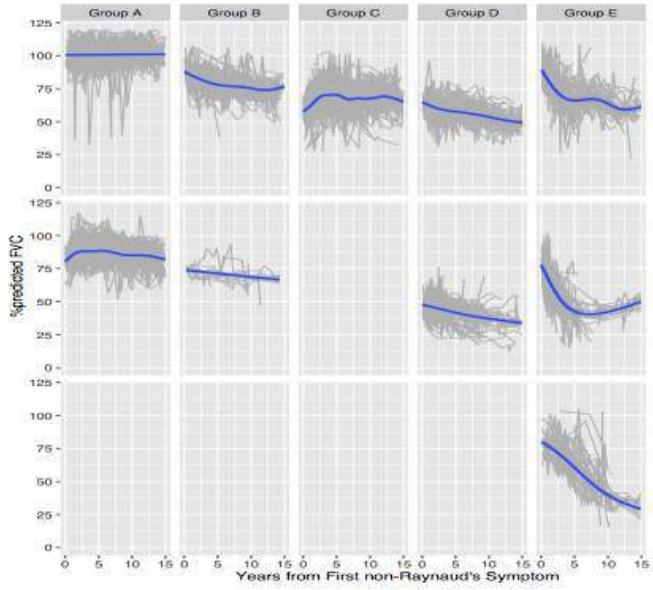
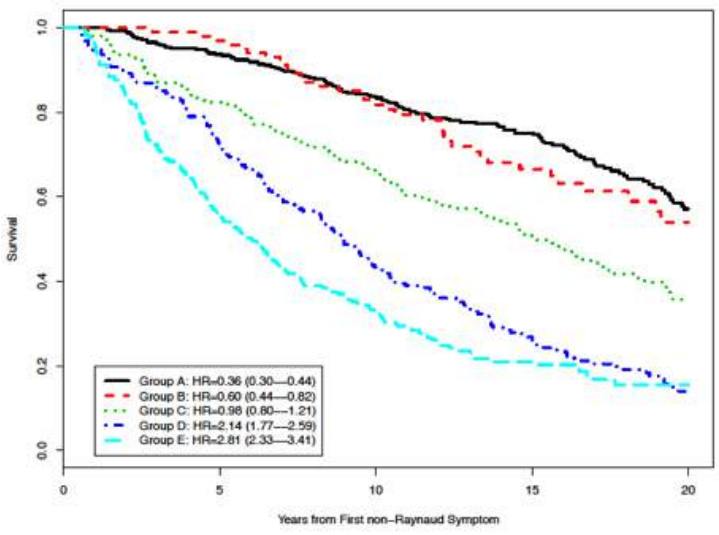


Figure 2: Kaplan–Meier Curves for Outcome of Mortality by pFVC Trajectory Type



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Abstract Number: 2020

Making the Case for Self-Management Education: Marketing Lessons Learned from Qualitative Research

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Background/Purpose: Self-management education (SME) uses educational and behavioral strategies to help people with arthritis (PWA) and other chronic conditions (CC) develop healthy behaviors and gain confidence in their ability to manage their condition. Approximately 11% of PWA report attending a SME program. Past audience research suggested that a primary reason PWA do not attend SME programs is that they do not know the programs exist. Past research also suggested that arthritis frequently is a lower priority if a PWA also has another CC, and approximately 47% of PWA also have another condition. PWA can learn key self-management skills (i.e. problem-solving, goal-setting, and self-monitoring) by attending generic SME programs, or programs for their higher priority CC even if they are not motivated to attend for arthritis. This research developed and tested messages and creative executions to motivate people with CC, including PWA, to learn more about SME programs.

Methods: 20 focus groups were conducted (6 for feasibility testing, 6 for concept testing, 8 for materials testing) in 8 cities in the East, Midwest, West and South United States in 2013-2015. Gender-stratified groups were held with people aged 45–75 years old who had one or more CC. All groups were conducted using a structured moderator's guide, and results were summarized across groups using thematic analysis. Participants discussed their views and preferences about SME-related terminology, messages, and ad concepts and executions.

Results: A total of 156 people participated. The sample was 51% male; 49% white, 30% black, and 22% Hispanic; 69% had less than college degree, 56% had incomes <$40,000; and 23% were age 65-75.Over half of the sample had arthritis (56%) and more than one CC (57%).Although unfamiliar with SME terminology, most participants grasped and valued the concept. Messages that explained benefits (e.g., increased energy, reduced stress, feel better) and program components (goal-setting, self-monitoring) were the most important factors in motivating this audience to seek additional information about SME. Although most referred to themselves as having a chronic disease, "ongoing health problem" was preferred to "chronic disease" or "chronic illness" terminology. The terms "strategies and techniques" were favored over "skills and tools." Other important message characteristics included having a personal and positive tone, using empowering language, and

describing benefits without overpromising. Participants preferred a website rather than phone number for more information.

Conclusion: Consumers, including PWA, are receptive to SME although they were not previously aware of the term. Lack of familiarity with SME necessitates informational messages and outreach tools. Concepts seen as personal, believable, and credible which also provided information about processes and benefits of SME were preferred. It is possible to craft messages that appeal to people with a variety of CC, including arthritis. The findings from this research are being used to develop the *Learn More. Feel Better.*broad SME awareness campaign designed to motivate people with CC, including PWA, to seek out SME.

Disclosure: T. J. Brady, None; **B. Lafontant**, None; **T. Baker**, None; **R. Ledsky**, None.

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Abstract Number: 2021

Development of an Item Bank on Disease and Treatment Associated Knowledge of Rheumatoid Arthritis to Improve Patient Engagement in Care

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Background/Purpose: Patient involvement and personalization of healthcare have become increasingly important in managing chronic diseases. Knowledge about their disease and its treatment is an important precondition for patients to be able to be involved in their own care. Therefore many healthcare professionals offer patients with Rheumatoid Arthritis (RA) education about RA and its treatment. An instrument to assess patients' knowledge about their disease and its treatment provides health professionals as well as researchers with a tool to identify and target patients' information needs. Also, it can be used to evaluate the effect if educational efforts and to monitor progress. Currently available patient knowledge questionnaires were developed before the introduction of biologicals as well as treat to target strategies in rheumatoid arthritis (RA). In fact a general limitation of static questionnaires is that their content may become outdated over time. Therefore we developed the Disease and treatment Associated Knowledge in RA item bank (DataK-RA). This Item Response Theory (IRT) based item bank can be kept up to date by adding or removing items, without changing the common scale. Moreover, the scoring procedure also provides the flexibility to use any subset of items, while retaining comparability with other applications of the item bank.

Methods: An initial item pool was developed from a systematic review of existing knowledge questionnaires, supplemented by an elaborate qualitative approach in cooperation with health professionals and patients. Consensus was reached on relevant content through a RAND modified Delphi scoring procedure by rheumatology nurses (n=6) and rheumatologists (n=6), and a consensus meeting with rheumatology nurses (n=6) and rheumatologists (n=4). Subsequently, a focus group among RA patients (n=9) was organized to identify additional content areas. Patients and health professionals also rated readability, feasibility and comprehensiveness of the resulting items. Item pool reduction and initial validation of the item pool (n=62) were performed using a cross-sectional sample of 473 patients with RA.

Results: Twenty items were discarded based on a corrected item-total point biserial correlation <0.30. Confirmatory factor analysis with weighted least squares estimation on the polychoric correlation matrix suggested acceptable fit for a unidimensional model for the remaining 42 items (CFI .97 TLI=.97, RMSEA=0.02, WRMR=0.97), supporting the proposed scoring procedure for the item bank. Scores were highly reliable and normally distributed with minimal ceiling (1.8%) and no floor effects (0.0%).

Conclusion: The DataK-RA item bank of 42 items was developed to comprehensively measure knowledge on all relevant aspects of RA and its treatment. The results of this study suggest it is a promising measure of factual disease related knowledge in RA. Work directed at developing tailored short-forms and a computerized adaptive testing algorithm is currently ongoing. Acknowledgements*:* We thank all rheumatology nurses, rheumatologists and patients who have helped in the development or validation of the item bank.

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Abstract Number: 2022

Developing a Gout Needs Assessment Incorporating Patient Perspective on Self-Management, Self-Efficacy and Disease Specific Knowledge, to Inform a Patient Education Initiative

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Background/Purpose: Gout is the most common inflammatory arthritis in adults, with great impact on quality of life. Despite excellent therapeutic options, outcomes remain suboptimal. Research supports the need for patient-centered education interventions as an integral part of effective gout management. While studies have

demonstrated that provider-created knowledge assessments can be a first-step in designing patient education interventions, they have not typically included patient identified needs. This is especially important since gout patients need assistance in diet and lifestyle change in addition to urate management. We developed a needs assessment which inquired about patient perspective and self-efficacy re: gout self-management. Our purpose was to identify disease–specific knowledge gaps and patient-identified concerns, to ensure their inclusion in a patient education initiative for gout patients.

Methods: We developed a 26-item needs assessment, including Likert & open-ended questions to assess patient self-efficacy around essential gout-related knowledge and patient-identified needs to enhance self-management. Knowledge-based questions were derived from evidence-based clinical guidelines re: gout treatment and lifestyle changes and data from our concurrent gout patient education study. Potential participants (357) were treated for gout by rheumatologists in an ambulatory clinic or private office and approached either in person or by mail.

Results: One hundred questionnaires were completed, with a return rate of 42/294 (14%) by mail and 58/63 (92%) in-person. Mean yrs since diagnosis: 10.8; M74%, F26%; mean age: 64 yrs; Race/Ethnicity: White 78% Asian 12% African American 7% Latino 2%. Completed college or above: 79%. In the preceding 6 months 13.4% had >3 flares; of these, 33% felt their gout was “under control.” Fifty-four % of respondents did not know “how often to have uric acid checked”; in patients with >3 flares in past 6 months , 77% did not know; 29% did not know their uric acid goal; 51% of all respondents did not know “how to manage side-effects of medications.” When asked about purpose of bridge therapy, 60% were unsure or did not answer; 55% did not answer or didn’t know when they should discontinue bridge therapy. When asked about “information of most interest [to them]”, most frequent response was diet guidelines; 83% wanted to hear from an MD; 61% from a nutritionist.

Conclusion: Even in a highly educated sample of rheumatologist-treated gout patients with a mean diagnosis of 10.8y, we found major patient knowledge gaps in essential gout-related self-management skills. Core findings include gaps related to: uric acid goals, frequency of testing, bridge therapy and outcome expectations. In open-ended questions, patients stated a desire for more information about diet guidelines, and input from a nutritionist. Our results are consistent with prior studies showing large gaps in critical gout patient knowledge, which are likely associated with widely reported poor gout patient outcomes. Our data informed the content of an educational symposium for gout patients and may be of use to others involved in enhancing self-management and improving outcomes for gout patients.

Disclosure: A. Rifaat, None; **A. Batterman**, None; **R. Horton**, None; **T. R. Fields**, Advisory Board, speaker's bureua: Takeda Pharmaceuticals, 9,Advisory board: Astrazenica Pharmaceuticals, 5.

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Abstract Number: 2023

Patient Barriers to Osteoporosis Screening in a Medical Clinic: Why Underserved Patients Who Follow Recommendations for Colonoscopy and Mammography Fail to Get Their DXA Scans

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Background/Purpose: Osteoporosis is a silent disease until it is complicated by fractures. Fractures are common; they place an enormous medical and personal burden on the elderly and take a major economic toll on the nation. Despite this fact, screening for osteoporosis by DXA scan remains inadequate mainly because most patients are unaware of its importance. We found that the rate of DXA scan completion by patients who visited our hospital's outpatient medical clinic was only 23.6% of all eligible women ≥65 years. The objective of this study was to identify specific patient barriers that prevent patients from completing a DXA test ordered during a clinic visit.

Methods: Between December 2014 and March 2015 DXA scans were appropriately ordered for 133 women ≥65 years who had visited the Rochester General Hospital medicine clinic; 75 completed the recommended DXA scan and 58 patients did not. A retrospective chart review of the 58 non-compliers showed that 13 of them had completed DXA at a much later date, 3 had died, 4 switched PCP to outside practice; these patients were excluded. We conducted a structured telephonic interview of the remaining 38 patients with the help of a barrier related questionnaire: • Are you aware you have DXA scan ordered? • If yes, did you schedule the appointment? • Do you use wheelchair, cane or walker for ambulation? • Do you have transportation issues? • Do you have problems with child care / elder care? • Are you working / retired? All patients were counseled on the importance of osteoporosis screening at the end of the interview Of the 38 patients we attempted to call, 3 refused to continue the conversation, 2 were hospitalized for critical illness, 3 Nepali speakers could not answer the questions, even with the help of an interpreter, 3 did not answer despite >2 phone calls. That left us with 25 effective calls. Of the 25 patients with completed surveys (none of whom had completed a recommended DXA scan), 72% (18/25) were up to date with mammography and 68% (17/25) had completed colonoscopy testing. 80%(20/25) were insured by medicare/medicaid and 84%(21/25) were retired

Results: Based on the structured questionnaire we were able to identify several patient barriers to osteoporosis screening: • 72% (18/25) of patients reported lack of awareness that a DXA test was ordered. • 24% (6/25) reported lack of transportation to go for the test • 20%(5/25) cited health issues • 4%(1/25) had to care for an elderly family member • 36%(9/25) used a cane/wheelchair/walker for ambulation.

Conclusion: The main patient related barrier to osteoporosis screening is patients' lack of awareness about osteoporosis, the reason for screening and the consequences of osteoporosis if left untreated. Patients are usually asymptomatic and believe that weak bones are a part of ageing naturally. There is also lack of effective physician patient communication and counseling on osteoporosis. The fact that most patients who failed to complete their DXA scan are up to date with other screening tests such as colonoscopy and mammography suggest that non-compliance is not the only reason for poor rates of osteoporosis screening

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Disclosure: S. John, None; **S. Kiwalkar**, None; **H. M. A. Ahmed**, None; **W. Polashenski**, None.

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Abstract Number: 2024

Effect of a Revised Counselor Training on Skills Development and Knowledge of Volunteers with Systemic Lupus Erythematosus

Melissa T. Flores[1], Jillian A. Rose[2], Priscilla Toral[1], Roberta Horton[1] and Janice Karbachinskiy[3], [1]Social Work Programs, Hospital for Special Surgery, New York, NY, [2]Hospital for Special Surgery, New York, NY, [3]New York-Presbyterian Hospital Weill Cornell, New York, NY
First publication: September 28, 2016

SESSION INFORMATION
Session Date: Monday, November 14, 2016
Session Title: ARHP III: Education and Community Programs
Session Type: ARHP Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: A needs assessment was conducted on an evidenced-based, national lupus telephone peer counseling service, ongoing since 1988, with 30,000+ client contacts to date. We have reported on the evolution of this hospital-based program at previous ACR/ARHP annual meetings. Trained peer volunteers have proven to be skilled providers of psychosocial support for SLE & other chronic illnesses. Findings from staff & veteran peer counselors trained in 1988 & 1994 using an 8-week, 20-hour curriculum on peer counseling skills & impacts of lupus, pointed to the need to update the training program. Recommendations included more hands-on learning opportunities, increased preparation for the initial call, integration of new technology to enhance communication & shortening the length of training.

Methods: The training was revised to a 6-week, 18-hour program. The core curriculum components were maintained & included updated materials, a culture/diversity module, counseling tools, enhanced resource guide & a workbook-style trainee manual. After a comprehensive recruitment process, 8 women from diverse backgrounds, mean age 47, were selected & participated in the new training. Two instruments were utilized pre & post training to assess trainees: the Applied Knowledge Assessment (AKA), a validated 30-item multiple choice test that measures knowledge of SLE & counseling skills, & the Communications Exercise (CE), a 21-item test with rating scale & open-ended questions to assess communication skills. Paired t-tests (α=.05) were conducted to examine differences in mean scores.

Results: AKA results indicated that most trainees (75%) showed an increase in overall scores. The mean pre & post test scores (59 & 68 respectively) were significantly different, $t(7) = 3.457$, p=011. The relative change from pre to post was 16%. Types of questions were categorized into two groups: peer counseling skills & medical impacts of SLE. Stratified results showed that most trainees (88%) showed an improvement in counseling skills, with one trainee improving by 50%. Similarly, 75% trainees showed an increase in medical knowledge, with one trainee improving by 75%. For the CE, most trainees (88%) showed improvement in overall scores after the training. The mean pre & post test scores (60 & 83 respectively) were significantly different, $t(7) = 2.808$, p=026. The relative change from pre to post was 38%, with one trainee improving by 200%. Open-ended responses assessing trainee's ability to respond to hypothetical callers underscore improved effective communication, including increases in empathy, reflecting feelings, summarizing & utilization of open-ended questions. Decreases in premature problem-solving, advice-giving & closed-ended questions were also noted.

Conclusion: Despite limitations due to a small sample size, our results highlight overall improvement in counseling skills, medical knowledge of SLE & communication skills. Results indicate that we were able to successfully enhance the training while retaining the core elements of the original curriculum. Furthermore, this training program continues to be a relevant model to effectively prepare peers to support patients with chronic

illness, supporting previous findings.

Disclosure: M. T. Flores, None; **J. A. Rose**, None; **P. Toral**, None; **R. Horton**, None; **J. Karbachinskiy**, None.

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Abstract Number: 2025

Lupus Education Advancement Project (LEAP): Rheumatology Fellows Serving As Educators Increased Knowledge and Efficiency in Lupus Recognition and Referral By Providers in Primary and Emergency Care

Diane Gross[1], Amy Caron[2], Irene Blanco[3], Alfred Denio[4], Sheetal Desai[5], Amanda Sammut[6] and Zoon Naqvi[7], [1]S.L.E. Lupus Foundation/Lupus Research Institute, New York, NY, [2]Lupus Research Institute, Ny, NY, [3]Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, [4]Rheumatology, Geisinger Medical Center, Danville, PA, [5]Medicine/Rheumatology, Unviersity of California, Irvine, Orange, CA, [6]NYC Health and Hospitals/Harlem Hospital Center and Columbia University Medical Center, New York, NY, [7]Albert Einstein College of Medicine, Bronx, NY

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: Primary and emergency care providers may have received 45 minutes of lupus education in medical school. Providers may fail in recognizing lupus because symptoms are often vague, delaying referrals and diagnosis for 2-6 years. Delay can lead to accrual of organ damage and death, which is more prevalent in minority populations. Many patients are referred to rheumatology not meeting assessment criteria for lupus, creating barriers to rheumatology care for urgent patients. The goal of LEAP is to increase lupus knowledge and improve lupus assessment and referral procedures among primary and emergency providers within the healthcare system.

Methods : LEAP enlisted rheumatology fellows to serve as educators to deliver a 1 Continuing Medical Education credit seminar. Four sites were selected based on commitment from Rheumatology Fellowship Program Directors or previous experience with the Teaching Fellows in Lupus Project, after which LEAP was modeled. Sites identified a problem in lupus referrals and included ways to address the problem in the seminar. Examples of problems in referrals that were addressed in the seminar include 1) ANA titer not included in the referral; 2) patients referred with only a positive ANA and no relevant clinical symptoms included; 3) consults with rheumatology conducted prior to issuing a formal referral. Rates will be analyzed to assess if the seminar changed behavior. Voluntary, anonymous pre/post assessments were used to evaluate changes in knowledge and behavior and collect qualitative data. A t-test was used to analyze independent group means.

Results: Preliminary data from 427 assessments were analyzed on a 9-point scale. Total mean score increased 2.10 immediately post seminar and 2.88 points at 4-6 weeks post seminar ($p<.01$). Over 85% reported the 1) activity improved medical or practice knowledge and 2) they would make changes that will benefit patient care. Respondents are considering lupus more at 4-6 weeks post seminar.

Conclusion: Rheumatology fellows can increase knowledge and promote behavior change in lupus assessment and referral among primary and emergency providers. LEAP may be an effective strategy to reduce health disparities in lupus.

Table 1. Knowledge Change Pre/Post/4-6 Weeks Post Seminar

Assessment (Group Data)	N	Mean Score (SD)	Mean Score Change from Pre Assessment	P-Value
Pre Seminar	208	5.07 (2.38)	n/a	<.01
Post Seminar	199	7.17 (1.45)	2.10	<.01
4-6 Weeks Post Seminar	20	7.95 (1.90)	2.88	<.01

Table 2. Sustained Behavior Changes Matched Assessments Pre to 4-6 Weeks Post **N=15**

Question	Pre %	4-6 Weeks Post %
1) You consider lupus in your differential diagnosis during an exam?		
Very Often	0 (0.0)	11 (73.3)
Somewhat Often	3 (20.0)	3 (20.0)
Not Very Often	1 (6.7)	1 (6.7)
Not At All	11 (73.3)	0 (0.0)
2) You refer patients to the rheumatologist for suspected lupus?		
Extensively	1 (6.7)	12 (80.0)
Significantly	0 (0.0)	1 (6.7)
Occasionally	3 (20.0)	1 (6.7)
Seldom	0 (0.0)	1 (6.7)
Never	11 (73.3)	0 (0.0)
3) You refer patients to lupus educational material or other educational resources?		
Always	0 (0.0)	11 (73.3)
Often	0 (0.0)	1 (6.7)
Occasionally	0 (0.0)	1 (6.7)
Rarely	3 (20.0)	2 (13.3)
Never	12 (80.0)	0 (0.0)

Disclosure: D. Gross, None; **A. Caron**, None; **I. Blanco**, None; **A. Denio**, None; **S. Desai**, None; **A. Sammut**, None; **Z. Naqvi**, None.

Abstract Number: 2026

Are Adult Trajectories of Weight over a Lifetime Linked to Foot Problems Years Later?

Alyssa B. Dufour[1], Elena Losina[2], Hylton B. Menz[3], Michael P. Lavalley[4] and Marian T. Hannan[5], [1]Institute for Aging Research, Hebrew SeniorLife, Harvard Medical School & Beth Israel Deaconess Medical Center, Boston, MA, [2]Orthopaedics, Brigham & Women's Hospital, Boston, MA, [3]Musculoskeletal Research Centre, La Trobe University, Bundoora, VIC, Australia, [4]Biostatistics, Boston University School of Public Health, Boston, MA, [5]Institute for Aging Research, Hebrew SL & Harvard Med School, Boston, MA

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Session Time: 4:30PM-6:00PM

Background/Purpose: Obesity and foot problems are common in older adults and associated with many negative health outcomes. Better understanding of the consequences of patterns of weight change may lead to better prediction and dealing with foot pain and foot disorders. This study identified longitudinal trajectories of weight in a population-based study and examined the association of these groups with current foot problems.

Methods: We used 28 measures of weight over 57 years to identify trajectories of weight in 2445 members of the Framingham Foot Study using k-means longitudinal cluster analysis. Foot examinations (2002-2008) recorded presence of foot pain, hallux valgus, claw toes, hammer toes and overlapping toes on each foot. Associations between weight group membership and foot problems at time of foot exam, adjusted for age and sex, were examined using logistic regression with generalized estimating equation correction for two feet per subject. The reference group used for analysis was the group with the lowest weight trajectory ("E").

Results: We found 5 trajectories of weight, representing relatively constant patterns over time, with weight increasing from groups E to A. Those in group "E" were more likely to be older, while the youngest were in group "A" group (Table 1). "E" had the lowest prevalence of foot pain (14%) while group "A" had the highest (22%). Similarly, group "A" had the lowest prevalence of hallux valgus, while group "E" had the highest (36%). Compared to group "E", other groups were more likely to have foot pain (ORs 1.57-3.50, Table 2) and less likely to have hallux valgus (ORs 0.73-0.99). For claw toes, all but one group were more likely to have claw toes compared to group "E". Groups "A" and "D" were more likely to have hammer toes (ORs 2.40 and 1.35, respectively) compared to group "E". We found no associations between overlapping toes and group membership.

Conclusion: Trajectories with higher weight over a lifetime had increased odds of foot pain and claw toes, and decreased odds of hallux valgus later in life. These results provide evidence that having lower weight over one's lifetime can reduce the likelihood of foot problems later in life.

Table 1. Participant characteristics by weight trajectory group in members of the Framingham Foot Stud (2002-2008).					
	A N=201/ 402 feet	B N=644/ 1288 feet	C N=617/ 1233 feet	D N=506/ 1011 feet	E N=477/ 954 feet
Age (years)	63 ± 9.0	69 ± 11.2	68 ± 10.5	66 ± 9.7	71 ± 11.9
Body mass index (kg/m^2)	37 ± 6.3	27 ± 3.3	29 ± 4.0	31 ± 4.3	23 ± 2.9
Female	76 (19%)	1036 (80%)	478 (39%)	230 (23%)	918 (96%)
Foot pain	88 (22%)	240 (19%)	222 (18%)	186 (18%)	135 (14%)
Hallux Valgus	57 (14%)	408 (32%)	267 (22%)	169 (17%)	341 (36%)
Claw Toes	9 (2%)	29 (2%)	29 (2%)	24 (2%)	18 (2%)
Hammer toes	89 (22%)	246 (19%)	197 (16%)	165 (16%)	174 (18%)
Overlapping toes	14 (3%)	99 (8%)	73 (6%)	48 (5%)	90 (9%)

Table 2. Association between weight trajectory group membership and foot problems in members of the Framingham Foot Study (2002-2008), adjusted for age and sex. *p<0.05				
	A vs. E	B vs. E	C vs. E	D vs. E
Foot pain	3.5 (2.49, 4.9)*	1.57 (1.25, 1.98)*	2.16 (1.68, 2.77)*	2.63 (2.00, 3.47)*
Hallux Valgus	0.72 (0.51, 1.02)	0.99 (0.82, 1.18)	0.86 (0.7, 1.06)	0.77 (0.61, 0.99)*
Claw toes	3.97 (1.57, 10)*	1.52 (0.83, 2.79)	2.24 (1.17, 4.29)*	3.1 (1.51, 6.38)*
Hammer toes	2.4 (1.71, 3.38)*	1.2 (0.96, 1.5)	1.12 (0.87, 1.45)	1.35 (1.02, 1.79)*
Overlapping toes	0.78 (0.41, 1.48)	0.93 (0.68, 1.27)	0.87 (0.6, 1.25)	0.85 (0.55, 1.32)

Disclosure: A. B. Dufour, None; **E. Losina**, None; **H. B. Menz**, None; **M. P. Lavalley**, None; **M. T. Hannan**, None.

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Abstract Number: 2027

The Association of Light and Moderate-to-Vigorous Walking with Incident Poor Health Outcomes over Two Years in People with or at High Risk of Knee Osteoarthritis

Sally Fenton[1,2], Joan Duda[3], Rainer Klocke[4], Abishek Abishek[5], Alison Rushton[3], Michael Doherty[6], Weiya Zhang[7], George D. Kitas[2], Tuhina Neogi[8], Michael Nevitt[9], Cora E Lewis[10], James Torner[11], Dorothy D. Dunlop[12] and Daniel White[13], [1]School of Sport, Exercise and Rehabilitation, University of Birmingham, Birmingham, United Kingdom, [2]Department of Rheumatology, Russells Hall Hospital, Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [3]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, UK, Birmingham, United Kingdom, [4]Rheumatology Department, The Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [5]Faculty of Medicine and Health Sciences, University of Nottingham, Nottingham, United Kingdom, [6]University of Nottingham, Nottingham, United Kingdom, [7]Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, United Kingdom, [8]Clinical Epidemiology, Boston University School of Medicine, Boston, MA, [9]Department of Epidemiology & Biostatistics, University of California San Francisco School of Medicine, San Francisco, CA, [10]Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, [11]University of Iowa, UIowa, Iowa City, IA, [12]Center for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL, [13]Department of Physical Therapy, University of Delaware, Newark, DE
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Background/Purpose: Regular engagement in physical activity reduces the risk adverse health outcomes such as cardiovascular diseases, functional limitation, and depression in people with knee osteoarthritis (OA). While walking is the most common form of physical activity for older adults, the relative health benefits of walking at a light intensity and at a moderate-to-vigorous intensity are unclear. The primary purpose of this study was to investigate the association of replacing 'no-walking' with different intensities of walking, with risk of developing adverse health outcomes over two years among people with or at high risk of knee OA.

Methods: The Multicenter Osteoarthritis Study (MOST) is a NIH-funded longitudinal cohort of older adults who have or are at high risk of knee OA. Steps/day over 7 days were objectively measured with a StepWatch monitor at the 60-month MOST study visit. Walking was classified in minutes per day (min/day) of no-walking (<1 step/minute), very-light walking (1 – 50 steps/min), moderately-light walking (51 – 100 steps/min) and moderate-to-vigorous walking (>100 steps/min). Incident outcomes were slow gait speed during a 20-meter walk (<1 metre/second), comorbidity (Charlson index ≥1), depressive symptoms (CES-D ≥16) and low balance confidence (Activities-specific Balance Confidence scale <67) assessed 2 years post 60-month MOST study visit (i.e., 84-month MOST study visit). Isotemporal substitution analysis was conducted to evaluate the effect of replacing 10 minutes of 'no-walking' with 10 minutes of walking at very-light, moderately-light and moderate-to-vigorous intensities, with study outcomes. All models were adjusted for age, sex, BMI, study site, race, education, marital status and lower limb pain.

Results: Of the 1782 subjects who wore the StepWatch for ≥3 days (Age 67.3 ± 7.7, 60% women, BMI 30.7 ± 5.9), incidence of poor health outcomes ranged from 5.6% for depressive symptoms (82/1460) to 16.6% for slow gait speed (251/1514). Replacing 10 minutes of no-walking with 10 minutes of moderate-to-vigorous walking per/day was associated with modest reductions in the risk of slow gate speed and low balance confidence (RR = 0.75 and 0.81, respectively), though low balance confidence bordered on significance (p =.05) (Table 1). Replacing 10 minutes of no-walking with 10 minutes of very-light walking per/day was associated with a small reduction in risk of comorbidity (RR = 0.97).

Conclusion: Findings indicate the presence of a dose-response relationship with regards to walking intensity and pertinent health outcomes in people with, or at high risk of OA. Specifcally, replacing no-walking with just 10 minutes of walking at increasing intensities each day may hold positive consequences for preserving functional gate speed, sustaining confidence with regards to functional capacity (i.e., balance confidence), and reducing risk of comorbidity. *Table 1.*Adjusted risk ratios

	Risk of Incident Slow Gait Speed at 2 years (< 1.0 m/s) *N = 1514*		*Risk of Depressive symptoms at 2 years (CES-D > 16)* *N = 1460*		*Risk of Comorbidity at 2 years (Charlson > 1)* *N = 1238*		Risk of Low Balance Confidence (ABC < 67) N = 1578	
	Adjusted* Risk Ratio	95% CI	Adjusted* Risk Ratio	95% CI	Adjusted* Risk Ratio	95% CI	Adjusted* Risk Ratio	95% CI
Replace 10 minutes of no-walking with 10 minutes of very-light walking *(1 - 50 steps/min)*	0.99	0.97, 1.01	1.00	0.97, 1.04	0.97	0.95, 1.00	0.99	0.97, 1.01
Replace 10 minutes of no-walking with 10 minutes of moderately-light walking *(50 - 100 steps/min)*	0.94	0.87, 1.01	1.10	0.98, 1.25	1.00	0.91, 1.11	0.94	0.86, 1.02
Replace 10 minutes of no-walking with 10 minutes moderate-to-vigorous walking *(> 100 steps/min)*	0.75	0.61, 0.92	0.82	0.60, 1.11	0.77	0.58, 1.02	0.81	0.65, 1.00

Disclosure: S. Fenton, None; **J. Duda**, None; **R. Klocke**, None; **A. Abishek**, None; **A. Rushton**, None; **M. Doherty**, None; **W. Zhang**, None; **G. D. Kitas**, None; **T. Neogi**, None; **M. Nevitt**, None; **C. E. Lewis**, None; **J. Torner**, None; **D. D. Dunlop**, None; **D. White**, None.

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moderate-to-vigorous-walking-with-incident-poor-health-outcomes-over-two-years-in-people-with-or-at-high-risk-of-knee-osteoarthritis

Abstract Number: 2028

Relationship of Limb Length Inequality and Incident and Progressive Knee and Hip Radiographic Osteoarthritis and Symptoms

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Background/Purpose: Limb length inequality (LLI) is a condition in which one limb is longer than the other. Previous reports of a link between LLI and knee radiographic osteoarthritis (rOA) are limited by short follow-up durations. This longitudinal analysis examined the hazard of incident and progressive rOA and symptoms of the knee and hip by LLI in a large community-based cohort over a median 10-year follow-up period.

Methods: Participants were African American and Caucasian men and women 45+ years old enrolled from 1991-1997 (original cohort) or 2003-2004 (enrichment cohort), and follow up data were collected during 1999-2004, 2006-2010, or 2012-2015 (median follow-up time = 10 years, range= 4-22 years). Lower extremity lengths were measured with a tape measure from anterior superior iliac spine to distal medial malleolus with the participant supine; LLI was defined as ≥ 2 cm difference between limbs. Radiographs (anteroposterior [AP] standing knee and AP supine pelvic) were read for Kellgren-Lawrence grade (KLG). Incident rOA was defined as KLG <2 at baseline that becomes KLG ≥2 at follow-up. Progressive OA was defined as ≥ 1 KLG increase with baseline KL=1. Incident symptoms were defined as new symptoms (pain, aching, or stiffness on most days) at follow-up among joints without symptoms at baseline. Progressive symptoms were defined as joints with mild or moderate baseline symptoms that increased ≥1 level of severity (to moderate or severe) at follow-up. Separate parametric Weibull time-to-event models estimated hazard ratios of the association of LLI and knee and hip outcomes, adjusting for cohort (original or enrichment), time of LLI assessment (1991-1997 or 1999-2004), age, sex, race, and body mass index (BMI). In models where symptoms were the outcome, rOA was included as a covariate. Interactions between LLI and covariates were examined ($p<0.10$ considered statistically significant).

Results: At baseline, complete LLI with knee and hip radiograph data were available for 2872 and 2669 participants with at least one follow-up, respectively. Characteristics of the pooled sample were: mean ± standard deviation (SD) baseline age 61 ± 9.8 years; 2/3 women; 1/3 African American; mean ± SD baseline BMI 30 ± 6.4 kg/m^2, and 7% with a LLI. The hazards of incident or progressive knee or hip rOA and symptoms by LLI were not statistically different (Table). There was a statistically significant interaction between LLI and

BMI for progressive knee rOA; thus, results were stratified by BMI (<30 and ≥30 kg/m^2). Among participants with BMI≥30, the adjusted hazard for progressive knee rOA was 76% higher among those with LLI vs. no LLI (adjusted hazard ratio 1.76, 95% confidence interval 1.12, 2.75).

Conclusion : Among obese participants, LLI was associated with progressive knee rOA. These results suggest that obese individuals with knee rOA and LLI may benefit from interventions to limit rOA progression.

Table. Adjusted* Hazard Ratio (aHR) and 95% Confidence Interval (CI) of Baseline Limb Length Inequality (LLI) and Knee and Hip Incident and Progressive Radiographic Osteoarthritis (rOA) and Joint Symptoms Outcomes.

Joint	Outcome	n	aHR (95% CI)
Knee	Incident rOA	1783	0.88 (0.61, 1.29)
	Progressive rOA	976	1.16 (0.81, 1.67)
	Incident symptoms**	1332	1.12 (0.77, 1.64)
	Progressive symptoms**	874	1.19 (0.78, 1.81)
Hip	Incident rOA	1519	0.92 (0.59, 1.44)
	Progressive rOA	1608	1.28 (0.88, 1.88)
	Incident symptoms**	1419	1.08 (0.73, 1.62)
	Progressive symptoms**	649	1.00 (0.58, 1.74)

*Adjusted for cohort (original vs. enrichment), time of baseline LLI assessment, age, sex, race, body mass index.

**Knee symptoms outcomes adjusted for variables listed above + knee rOA; hip symptoms outcomes adjusted for variables listed above + hip rOA.

Disclosure: Y. M. Golightly, None; **C. Alvarez**, None; **K. Allen**, None; **J. B. Renner**, None; **J. M. Jordan**, None.

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Abstract Number: 2029

Risk of Knee Pain, Radiographic Osteoarthritis and Knee Arthroplasty in Retired Professional Footballers Compared to the General Population

Gwen Fernandes[1,2,3], Sanjay M Parekh[1,2], Jonathan P Moses[1,2], Colin Fuller[4], Brigitte Scammell[1,2,3], Mark Batt[1,2,3], Weiya Zhang[1,2,3] and Michael Doherty[1,2,3], [1]Division of Rheumatology, Orthopaedics and Dermatology, School of Medicine, University of Nottingham, Nottingham, United Kingdom, [2]Arthritis Research UK Centre for Sports, Exercise and Osteoarthritis, Nottingham, United Kingdom, [3]Arthritis Research UK Pain Centre, Nottingham, United Kingdom, [4]Colin Fuller Consultancy Ltd, Nottingham, United Kingdom

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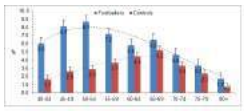
Background/Purpose: To determine the prevalence of knee pain (KP), radiographic knee osteoarthritis (RKOA) and total knee replacements (TKR) in ex-professional footballers compared to general population controls and to determine the associated risk factors.

Methods: 1207 ex-footballers and 4085 controls were recruited in the United Kingdom from professional football associations and the general population in East Midlands respectively. Current KP was defined as pain in or around the knees or most days of the last month. RKOA was examined in a subset of 470 ex-footballers and 491 controls, irrespective of pain status. RKOA was assessed using the Nottingham Line Drawing Atlas (NLDA) scores and the Kellgren Lawrence (KL) grading with a cutoff for OA of ≥3. All known risk factors such as age, body mass index (BMI), knee injury, high risk occupation, 2D4D digit ratio, self-reported constitutional knee alignment and nodal OA were assessed and included in a univariate analysis to identify their significance to knee pain/OA. Values were adjusted for use in a generalised linear model (GLM) with Poisson distribution to determine the relative risk (RR) and 95% confidence interval (CI) of KP and KOA in ex-footballers compared to controls.

Results : The mean age of ex-footballers was 59 years (SD ± 11.7) and that of the controls 62.8 years (SD +10.4) ($p<0.01$). They were gender matched (all men) with no difference on BMI ($p=0.135$). However, ex-footballers had more nodal OA, type 3 finger ratio (2D<4D), pain elsewhere and knee malalignment, knee injuries (65.7% v 24%) but less comorbidities than controls ($p<0.001$). Ex-footballers are almost twice as likely to present with KP [RR 1.84, 95%CI 1.71-2.00, $P<0.001$] and RKOA compared to the controls once adjusting for risk factors [RR 1.69, 95%CI 1.44-1.98 (r/knee) RR 1.69, 95% CI 1.44-1.97 (l/knee), $p<0.001$]. Ex-footballers report more KP across all age-groups and report onset of KP almost 15-20 years earlier (aged 50-54 years) compared to controls (aged 60-69 years; Figure 1). Ex-footballers reported RKOA (20 years) and TKR (5 years) earlier than controls. They were also almost three times more likely to have a TKR (either unilateral or bilateral) [RR 2.79, 95%CI 2.42-3.23, $p<0.001$] and a physician diagnosis of OA [RR 2.62, 95% CI 2.32-2.96, $p<0.001$) and twice as likely to have radiographic chondrocalcinosis [RR 1.78, 95%CI 1.56-2.02, $p<0.001$].

Figure 1 ***Prevalence of KP by age in the football and control population***

Conclusion: The prevalence of KP, RKOA and TKR are 2-3 times higher and the peak ages of onset are 5-20 earlier in ex-footballers compared to the general population in the UK. The higher prevalence of knee injuries and presumed repetive microtrauma of professional football are likely to be the major attributable factors. Employers and the Industrial Injuries Advisory Council should consider this risk and whether KOA is an



industrial compensatable disease.

Disclosure: G. Fernandes, Arthritis Research UK, 2; **S. M. Parekh**, Arthritis Research UK, 2; **J. P. Moses**, Arthritis Research UK, 2; **C. Fuller**, Arthritis Research UK, 2; **B. Scammell**, Arthritis Research UK, 2; **M. Batt**, Arthritis Research UK, 2; **W. Zhang**, Arthritis Research UK, 2; **M. Doherty**, Arthritis Research UK, 2.

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Abstract Number: 2030

Difference in Risk Factor Profile Between Medial and Lateral Compartment Involvement in Tibiofemoral Knee Osteoarthritis

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Background/Purpose: Tibiofemoral radiographic osteoarthritis (TFROA) can occur in medial, lateral, or both compartments. While several risk factors have been found to be associated with the risk of TFROA, no study has formally examined if the risk factor profile (or magnitude of association) differs among the subtype of TFROA (i.e., medial and lateral TFROA). Elucidation of the relationship between the putative risk factors and the occurrence of each subtype of TFROA can improve our understanding of its causality, thereby guiding the development of precision medicine and strategies.

Methods: Among participants in the Osteoarthritis Initiative, we identified subjects without compartment-specific ROA in either knee at baseline (i.e., joint space narrowing =0 in both medial and lateral tibiofemoral compartments). Subjects were followed for up to 72 months with annual bilateral knee X-rays. Medial or lateral TFROA was defined by Kellgren and Lawrence grade ≥2 and joint space narrowing ≥1 in the respective compartments. We examined traditional risk factors (i.e., sex, age, body mass index [BMI], race, knee injury) on the risk of TFROA subtypes (i.e., medial vs. lateral TFROA) and tested the heterogeneity of TFROA subtypes using the duplication method for nominal polytomous logistic regression.

Results: Of 2874 subjects (5748 knees) without TFROA in either compartment at baseline (mean age=59.9, 58.9% women, mean BMI=27.8 kg/m^2, 29.0% with a history of knee injury), 306 knees (5.3%) developed medial, 84 (1.5%) developed lateral, and 5 (0.1%) developed bilateral compartment TFROA. Women had a 3.7 times higher risk of developing lateral compartment TFROA than men (RR=3.70, 95% CI: 2.08-6.57), whereas no such association existed on the risk of medial compartment TFROA, suggesting a different impact of sex on the risk of TFROA between the two subtypes (P for heterogeneity < 0.001) **(Table)**. A higher BMI tended to have a larger association with the risk of medial compartment TFROA than with lateral compartment TFROA (P for heterogeneity=0.06). Furthermore, non-Whites appeared to be at a higher risk for lateral compartment TFROA than Whites, but not for medical compartment TFROA (P for heterogeneity=0.09). Associations with age and a history of knee injury did not differ between medial and lateral compartment involvement **(Table)**.

Conclusion: The risk factor profile for medial compartment TFROA may differ from that for lateral disease. Wide hips among women might explain high risk of lateral compartment TFROA whereas weight gravity falling more on the medial side might explain high risk of medial compartment TFROA. These findings suggest that personalized preventive and treatment strategies may be feasible for individuals with differential susceptibility to a specific subtype of TFROA.

Table. Risk factors in relation to risk of compartment-specific TFROA and subtype heterogeneity						
Risk Factor	No. knees	Medial TFROA		Lateral TFROA		P value for heterogeneity
		Risk (%)	RR (95% CI)	Risk (%)	RR (95% CI)	
Age(years)*	5748	5.32	1.16 (1.10 to 1.27)	1.46	1.27 (1.10 to 1.40)	0.19
Sex						
Men	2362	5.25	1.00 (ref)	0.59	1.00 (ref)	<0.001
Women	3386	5.38	1.14 (0.90 to 1.43)	2.07	3.56 (2.00 to 6.34)	
Race						
White	4766	5.41	1.00 (ref)	1.30	1.00 (ref)	0.09
Non-White	976	5.12	0.88 (0.64 to 1.21)	2.05	1.59 (0.94 to 2.68)	
BMI (kg/m^2)*	5748	5.32	1.23 (1.18 to 1.30)	1.46	1.14 (1.04 to 1.22)	0.06
Injury						
No	4081	4.19	1.00 (ref)	1.20	1.00 (ref)	0.98
Yes	1667	8.10	1.88 (1.49 to 2.37)	2.10	1.87 (1.18 to 2.94)	
* RR for age in 5 years difference; RR for BMI in 2 unit difference.						

Disclosure: **N. Lu**, None; **J. Niu**, None; **H. Choi**, None; **Y. Zhang**, None.

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Dietary Patterns and Radiographic Progression of Knee Osteoarthritis: Data from the Osteoarthritis Initiative

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Background/Purpose: Although some individual foods and nutrients have been associated with knee osteoarthritis (OA) progression, the association between overall diet and OA progression is unknown. We aimed to examine the prospective association of major dietary patterns characterized by principal component analysis (PCA) with radiographic progression of knee OA.

Methods: In the Osteoarthritis Initiative (OAI), 2741 participants (4302 knees) with modest to moderate radiographic knee OA in at least one knee (Kellgren and Lawrence [KL] grade of 1, 2 or 3) who had dietary data at baseline were followed 12, 24, 36 and 48 months. We defined radiographic knee OA progression for a specific knee as at least one full score increase of KL grade characterized by joint space narrowing and/or osteophytes from baseline to 48 months. Dietary intake was assessed with a Block Brief Food Frequency Questionnaire completed at baseline. Two dietary patterns were identified by PCA: the Prudent pattern characterized by high intakes of fruit/vegetables, legumes, whole grains, and fish; the Western pattern characterized by high intakes of red / processed meats, refined grains, and French fries. The Cox proportional hazards models using a discrete likelihood method were developed to calculate hazard ratios (HR) after adjusting for age, sex, race, body mass index (BMI), baseline KL, injury/surgery, NSAIDs use, physical activity, and total calorie intake. We also used quantitative loss in joint space width (JSW) over time between the medial femur and tibia of the knee based on plain radiographs as the secondary measure of knee OA progression. Linear mixed models for repeated measures were used to assess the association between dietary patterns and JSW loss over time.

Results: Among 2741 participants (4302 knees) with OA at baseline, 721 knees had structural progression over 48 months. In multivariable adjusted models, a higher score for the Prudent dietary pattern was associated with a reduced risk of knee OA progression (p trend <0.01), while a higher score for the Western pattern was associated with an increased risk of progression (p trend <0.01) (Table). In addition, we observed a significant dose-response relationship between each dietary pattern score and adjusted mean JSW loss (Table). The observed associations attenuated after additionally adjusting for BMI.

Conclusion: Following the Prudent dietary pattern may reduce the risk of knee OA progression, whereas following the Western pattern may be associated with an increased risk of progression. The associations were partially mediated by BMI. Replication of these novel findings in other prospective studies demonstrating that improvement of dietary quality leads to delay in knee OA progression are needed. **Key words: Dietary pattern, osteoarthritis progression, joint space width.**

Risk of knee OA progression

Table. Dietary patterns and knee OA progression measured by the increase of Kellgren and Lawrence (KL) grade and Joint Space Width (JSW) loss (n=2741)											
			JSW Loss (mm)								
	Quartiles	HR (95% CI) *	*P* trend	HR (95% CI) ‡	*P* trend	ΔJSW (SE) ┼	*P*	*P* trend	ΔJSW (SE) ‡	*P*	*P* trend
Western pattern	Q1	1.00 (Ref)	**<0.01**	1.00 (Ref)	**0.02**	0.27(0.02)	Ref	**0.04**	0.27(0.02)	Ref	0.20
	Q2	**1.26(1.00,1.60)**		1.19(0.94,1.51)		0.28(0.02)	0.67		0.27(0.02)	0.89	
	Q3	**1.39(1.07,1.80)**		1.28(0.98,1.66)		0.31(0.02)	0.22		0.28(0.02)	0.63	
	Q4	**1.60(1.17,2.17)**		**1.44(1.05,1.97)**		**0.34(0.03)**	**0.04**		0.32(0.03)	0.19	
Prudent pattern	Q1	1.00 (Ref)	**<0.01**	1.00 (Ref)	**0.03**	0.32(0.02)	Ref	**<0.01**	0.30(0.02)	Ref	**0.01**
	Q2	0.84(0.67,1.05)		0.87(0.70,1.09)		0.34(0.02)	0.52		0.33(0.02)	0.30	
	Q3	**0.78(0.62,0.99)**		0.80(0.64,1.01)		0.29(0.02)	0.25		0.28(0.02)	0.39	
	Q4	**0.72(0.56,0.93)**		**0.77(0.60,0.98)**		**0.25(0.02)**	**<0.01**		**0.24(0.02)**	**0.03**	

* Adjusting for age, sex, race, physical activity, injury/surgery, NSAIDs use, baseline KL grade, and total energy intake. ┼ Adjusting for age, sex, race, physical activity, injury/surgery, NSAIDs use, baseline JSW, the changes of rim distance and beam angle, total energy intake. ‡ Additionally adjusting for BMI.

Disclosure: B. Lu, None; **J. Driban**, None; **C. Xu**, None; **T. E. McAlindon**, None; **C. B. Eaton**, None.

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Abstract Number: 2032

Genome-Wide Association Analysis Reveals Novel Juvenile Idiopathic Arthritis Susceptibility Loci

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Background/Purpose: Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease, affecting approximately 1 in 1,000 children. JIA is a complex genetic trait and encompasses a wide spectrum of clinical heterogeneity. To date, genetic association studies in JIA had limited sample sizes, used heterogeneous patient populations containing all disease subtypes, or included only candidate regions (e.g. Immunochip). In this study, we focused on oligoarticular and rheumatoid factor negative (RF^-) polyarticular subtypes of JIA because they are clinically similar and the most prevalent forms of disease. This study employed large cohorts and imputed SNP data in a genome-wide association study (GWAS) to catalog novel genetic risk factors.

Methods: Three cohorts totaling 2,751 oligoarticular or RF^- polyarticular JIA cases and 15,864 controls, all of European ancestry, were genotyped using two platforms. Cohort 1 (814 cases and 3,055 controls) and cohort 2 (1,057 cases and 11,824 controls) were genotyped on the Affymetrix Genome-Wide Human SNP 6.0 Array, while cohort 3 (880 cases and 985 controls) was genotyped on the Illumina HumanCoreExome-12+ Array. Imputation was performed using 1000 Genomes Project data, followed by a meta-analysis of all 3 cohorts.

Results: Meta-analysis resulted in suggestive evidence of association ($P<1x10^{-6}$) at 10 regions along the genome: JAK1 (rs10889504: OR=0.78, $P=4.18x10^{-7}$), PRR9_LOR (rs873234: OR=1.43, $P=5.12x10^{-8}$), PTH1R (rs1138518: OR=1.23, $P=1.87x10^{-7}$), ILDR1_CD86 (rs1138518: OR=1.45, $P=6.73x10^{-8}$), FLJ41649 (rs10807228: OR=1.42, $P=5.80x10^{-7}$), AHI1_LINC00271 (rs9321502: OR=1.18, $P=3.48x10^{-7}$), HBP1 (rs111865019: OR=0.84, $P=7.29x10^{-7}$), ASAP1 (rs34962169: OR=1.43, $P=6.36x10^{-7}$), WDFY4 (rs1904603: OR=1.27, $P=1.79x10^{-7}$), and RNF215 (rs5753109: OR=1.19, $P=3.09x10^{-7}$). Among these regions, association studies in other autoimmune diseases provided additional evidence of support for JAK1 (Celiac Disease: rs12409333 - $r^2=0.898$, $P=3.80x10^{-5}$, Multiple Sclerosis: rs12409333 - $r^2=0.898$, $P=2.70x10^{-4}$), ILDR1_CD86 (Celiac Disease: rs2061197 - $r^2=0.407$, $P=8.55x10^{-6}$), AHI1_LINC00271 (Autoimmune Thyroid Disease: rs2179781 - $r^2=0.757$, $P=4.84x10^{-4}$, Celiac Disease: rs12206850 - $r^2=0.701$, $P=6.89x10^{-4}$, Multiple Sclerosis: rs11154801 - $r^2=0.740$, $P=1.00x10^{-13}$, Type 1 Diabetes: rs11154801 -$r^2=0.740$, $P=2.55x10^{-5}$) and WDFY4 (Systemic Lupus Erythematosus: rs877819 - $r^2=0.473$, $P=8.00x10^{-9}$). Furthermore, *cis* expression quantitative trait loci were shown for PTH1R (rs2242116), AHI1 (rs2614276), HBP1 (rs7790080, rs2301801, and rs2237659), WDFY4 (rs2940707), and RNF215 (rs2242116). Histone modifications of JAK1 (rs6588107: H3K4Me1, H3K27Ac and rs72922282: H3K4Me3, H3K27Ac), AHI_LINC00271 (rs6935146: H3K4Me1), and ASAP1 (rs67434056: H3K4Me1) showed additional regulation of gene expression.

Conclusion: These genome-wide genetic association results are supported by findings in other autoimmune diseases and/or relate to gene expression levels. Thus, they are likely to represent novel regions potentially contributing to the disease pathology of oligoarticular and RF^- polyarticular JIA.

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Abstract Number: 2033

A Multi-Dimensional Genomic Map for Polyarticular Juvenile Idiopathic Arthritis

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Background/Purpose: Polyarticular juvenile idiopathic arthritis (JIA) is a complex trait characterized by gene-environment interactions. While we are beginning to identify multiple genomic regions associated with disease risk in JIA, most of that risk is located within non-coding regions of the genome. Thus, to develop a mechanistic understanding of how genetic variance contributes to JIA, we require a detailed understanding of the non-coding genome and the functional elements located within these regions.

Methods: We created a multidimensional genomic map in JIA. Using genome-wide methylation sequencing, RNA sequencing, and chromatin immunoprecipitation-sequencing for informative histone marks (H3K4me1 and H3K27ac) in neutrophils, as well as whole genome sequencing on the Illumina 10x platform, we provide new insights into the interaction between genetic variation, the epigenome, and gene expression in the context of a common human disease.

Results: The epigenomes of JIA neutrophils display numerous differences from those from healthy children. DNA methylation changes, however, had only a weak effect on gene expression. In contrast, H3K4me and H3K27ac marks, commonly associated with enhancer functions, strongly correlated with gene expression. Furthermore, although some unique/novel enhancer marks were associated with insertion-deletion events (indels) identified on whole genome sequencing, genetic variation could account for no more than 30% of the JIA-specific epigenome. Treatment with methotrexate was associated with a re-ordering of transcription associated with changes in both methylation and histone marks, including histone and methylation marks located within indels. This finding demonstrates the plasticity of the epigenome in this setting. Alterations in histone marks most strongly associated with the transcriptional changes that accompanied the initiation of therapy.

Conclusion: JIA represents a complex genetic-epigenetic trait characterized by aberrant transcription in pathologically relevant cells. Initiation of effective therapy is associated with significant re-ordering of the epigenome, even in genomic regions where there is underlying genetic variance.

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Abstract Number: 2034

Novel Susceptible Genes for Behçet's Disease Identified By Dense Genotyping of Immune-Related Loci Implicate Host Responses to Microbial Exposure

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Background/Purpose: Recent genetic studies have identified multiple susceptibility loci for Behçet's disease. However, these genetic factors do not fully explain the apparent disease heritability.The purpose of this study was to densely genotype loci associated with immune-related diseases to identify novel susceptibility loci for Behçet's disease.

Methods: 1900 Turkish Behçet's disease patients and 1779 controls were genotyped using the Immunochip. For novel loci with association test $P<5\times10^{-5}$, additional SNPs in the region were genotyped or imputed using 1000 Genomes Project data as a reference. For replication, the lead genotyped SNP in each novel locus with $P<5\times10^{-5}$ in the Turkish population was genotyped in 982 cases and 826 controls from Iran. We also replicated disease associations with imputed previous GWAS data from 608 Japanese cases and 737 controls. $P<5\times10^{-8}$was considered the threshold for genome-wide significance.

Results: *HLA-B*51* was the strongest associated marker and rs1050502 the strongest associated SNP. rs1050502 is located in exon 2 of *HLA-B* and the risk allele T is a tag SNP for *HLA-B*51*. Outside of the MHC region, we identified 4 novel loci, *IL1A-IL1B*, *ADO-EGR2*, *IRF8,* and *CEBPB-PTPN1*, which exceeded genome-wide significance in Turks. Genotyping Iranian samples and meta-analysis with Turkish data replicated associations of three loci, *ADO-EGR2*, *IRF8* and *CEBPB-PTPN1*. Comprehensive meta-analysis of the regional imputed genotype data of Turks and Japanese replicated two loci, *ADO-EGR2* and *IRF8*, and revealed two additional novel loci, *RIPK2* and *LACC1*. The disease associated allele of rs4402765, the lead marker of the *IL1A-IL1B* locus, was associated with both decreased interleukin-1α and increased interleukin-1β protein production. Ancestry specific *FUT2*non-secretor genotypes, homozygous rs601338 (p.Trp143Ter) in Turks and Iranians and rs1047781 (p.Ile129Phe) in Japanese, showed strong disease association. The non-secretor genotype has been associated with Crohn's disease and gut microbiome composition.

Conclusion: Here, we conducted an Immunochip study in the largest Behçet's disease discovery cohort ever with multiple populations for replication. This study identified 6 novel loci (*IL1A-IL1B*, *RIPK2*, *ADO-EGR2*, *LACC1*, *IRF8*, and *CEBPB-PTPN1*) with genome-wide significance for Behçet's disease. Our findings that the disease-associated allele of *IL1A* is associated with dysregulated IL-1 biology, with less IL-1alpha and more IL-1beta production, and that functionally defective structural *FUT2* variants are associated with disease risk suggest that an impaired host response to microbes, including those of the microbiome, may contribute to Behçet's disease susceptibility.

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Abstract Number: 2035

Dosage Contribution of a Non-Classical HLA Gene, HLA-Doa, to the Risk of Rheumatoid Arthritis

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Background/Purpose: Despite the progress in human leukocyte antigen (HLA) causal variant mapping, independent localization of major histocompatibility complex (MHC) risk from classical HLA genes is challenging.

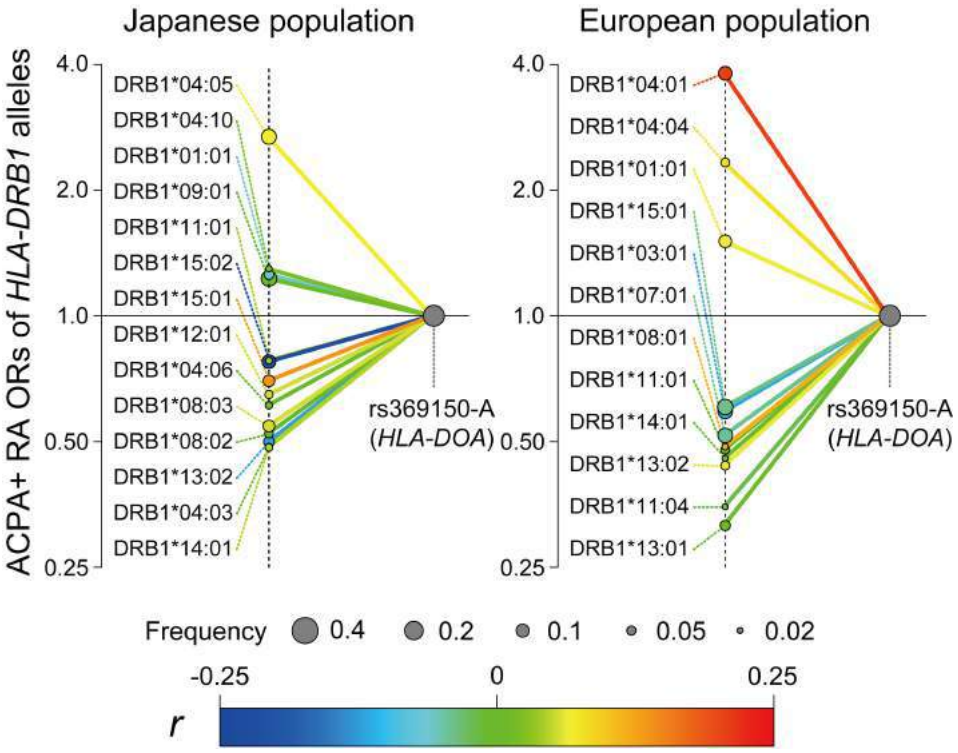
Methods: We conducted a large-scale MHC fine-mapping analysis of rheumatoid arthritis (RA), an autoimmune disease with chronic destruction of synovial joints in Japanese (6,244 RA cases and 23,731 controls). We applied the HLA imputation method using the reference panel of the Japanese population (n = 908). We further conducted a multi-ethnic validation study by assessing the MHC fine-mapping analyses of RA in east Asians and Europeans (n = 7,097 and 23,149, respectively).

Results: Our study identified a risk of a synonymous mutation at *HLA-DOA*, a non-classical HLA gene, on anti-citrullinated-protein-autoantibody (ACPA)-positive RA risk (rs378352, odds ratio [OR] = 1.20, $P = 1.4 \times 10^{-9}$), independently from the risk classical HLA genes (*HLA-DRB1*, *HLA-DPB1*, and *HLA-B*). The *HLA-DOA* risk variant demonstrated a cis-expression quantitative trait loci (cis-eQTL) effect on *HLA-DOA* expression levels, demonstrating its dosage expression effect on RA risk. Independent risk of the *HLA-DOA* variant was further validated in east Asians (OR = 1.15, $P = 0.0040$) and Europeans (OR = 1.06, $P = 0.031$). Trans-ethnic comparison revealed different linkage disequilibrium (LD) patterns between *HLA-DOA* and *HLA-DRB1*, which explains the observed *HLA-DOA* variant risk heterogeneity among ethnicities; which was most evident in Japanese but not in Europeans.

Conclusion: Whilst the previous HLA fine-mapping studies have identified amino acid polymorphisms of the classical HLA genes as driving genetic susceptibility of the diseases, our study additionally identifies the dosage contribution of a non-classical HLA gene to disease etiology. Our study contributes to understanding of HLA

immunology in human diseases, and suggests the value of incorporating additional ancestry in MHC fine-mapping.

SNP	Gene	Ref /Alt	Population	Cohort	No. subjects	Ref allele freq in controls	ACPA+ RA OR (95%CI)	*P*
rs378352 (rs369150)	*HLA-DOA*	A/G	Japanese	BBJ1	16,029	0.26	1.24 (1.13-1.36)	4.6×10^{-6}
				BBJ2	3,815	0.26	1.13 (0.96-1.33)	0.15
				IORRA	7,207	0.26	1.16 (1.04-1.29)	0.0053
				Kyoto	1,799	0.25	1.27 (1.03-1.58)	0.027
				Meta	28,850	0.26	1.20 (1.13-1.28)	1.4×10^{-9}
			east Asian	-	7,097	0.31	1.15 (1.05-1.27)	0.0040
			European	-	23,149	0.26	1.06 (1.01-1.12)	0.031



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Whole Exome Sequencing in Early Onset Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) is a multisystemic autoimmune disorder with different genetic and environmental factors playing role in its pathogenesis. Early onset SLE, familial SLE, and syndromic SLE are rare situations which may lead to identification of monogenic defects responsible for the disease. Identification of monogenic causes through these cases can help us to understand the pathogenic mechanisms in SLE. We aimed to discover monogenic defects causing SLE by performing whole exome sequencing (WES) in familial or early-onset SLE cases.

Methods: We enrolled 12 pediatric SLE cases (from 7 different families) who had disease onset before 5 years of age and a family history consistent with an autosomal recessive inheritance (affected siblings or parenteral consanguinity). Whole exome sequencing and bioinformatic analyses were performed in six index cases and the suspected mutations were confirmed by Sanger sequencing. Only *C1Q* gene was analyzed by Sanger sequencing in patient 4 since he had similar features with the first three cases.

Results: There was consanguinity in all families. The characteristics of index SLE cases are presented in Table 1. We have demonstrated a homozygous nonsense mutation (c.622C>T/p.Gln208Ter) in *C1QA* gene in 2 patients; homozygous nonsense mutation (c.79C>T/p.Gln27Ter) in *C1QC* gene in 1; homozygous missense mutation (c.100G>A/p.Gly34Arg) in *C1QC* gene in 1; homozygous stop codon mutation (c.1945G>C/p.Ala649Pro) in *C1S* gene in 1; homozygous frameshift mutation (c.290_291delCA/p.Thr97Ilefs*2) in *DNASE1L3* gene in 1 patient. There was a candidate novel gene in 1 patient and functional studies on this gene are ongoing.

Conclusion: Five of our patients had homozygous mutations in the genes coding for early complement proteins. The risk to develop pediatric SLE is estimated to be 93% for C1q and 66% for C1s/r defects. There are around 100 published cases with homozygous C1q deficiency. The clinical presentations are variable; however, they usually had cutaneous involvement, normal C3, C4 levels and negative anti-dsDNA which was the case in our patients. C1s deficiency is much rarer. The nonsense mutation in C1S gene of our patients was novel. *DNASE1L3*

gene encodes for DNase1 enzyme which functions as an endonuclease cleaving DNA. Deletion in *DNASE1L3* gene has been previously reported to be associated with SLE in the study on 7 SLE families where it was shown that protein encoded by the mutant *DNASE1L3* completely lacked DNase activity. We suggest that monogenic causes/associations should be sought for an early-onset SLE.

Table1. Characteristics of pediatric patients with early-onset systemic lupus erythematosus

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7
Lupus in sibling	+	+	-	-	+	-	+
Mutant genes	C1QA	C1QC	C1QC	C1QA	C1S	DNASE1L3	Candidate novel gene
Malar/discoid rash/photosensitivity	+	+	+	+	+	+	-
Oral ulcers	+	+	+	-	+	-	-
Arthritis	+	+	-	-	+	+	-
Nephritis	-	-	-	-	+	+	-
Hematologic involvement	+	+	+	-	+	+	-
Decrease in C3, C4	-	-	-	-	+	+	+
Other positive utoantibodies (all patients were positive for ANA)	Anti-SM	Rheumatoid factor	Anti-SM, SSA, lupus antivoagulant	Anti-SM, U1 RNP	AntidsDNA, SSA, U1 RNP, anti-histon	Anti-dsDNA, Anti-cardiolipin	Anti-dsDNA, direct Coombs

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Proteostasis Dysregulation and Autoinflammation in Patients with TRNT1 Deficiency

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Background/Purpose: Hypomorphic mutations in the *TRNT1* gene result in a syndrome of sideroblastic anemia, immunodeficiency, periodic fevers and developmental delay (SIFD). The TRNT1 enzyme is essential for tRNA maturation and regulation, aminoacylation and protein synthesis. Complete deficiency is incompatible with life.

Methods: Genetic studies included whole exome sequencing and candidate gene screening. Patient cells were used for deep RNA and tRNA sequencing, cytokine profiling, immunophenotyping, immunoblotting and electron microscopy (EM).

Results: We have identified 9 patients with biallelic missense mutations in *TRNT1*. 5 out of 9 mutations have not been reported. Patients suffered from recurrent fevers, variable degrees of immunodeficiency and a combination of inflammatory and degenerative disease. Inflammatory cytokines, mainly IL-6, IFN-g and IFN-induced cytokines were found elevated in the serum and in stimulated cells ex vivo. Deep tRNA sequencing of patients' fibroblasts showed that more than two third of patient's mature tRNAs were decreased compared to controls. EM microscopy of bone marrow and skin biopsy tissues showed striking abnormalities across all cell types, including pyknotic nuclei, disorganized cytoskeleton, extranuclear DNA, and abnormal mitochondria. We observed a mix of necroptotic and normal appearing cells in all tissues. Autophagosomal vesicles were observed intracellularly and in the serum. Intriguingly, the patient with the most severe inflammatory phenotype had evidence by EM of different, coexisting, types of cell death, proteinaceous substance and cellular debris in the bone marrow stroma. In agreement, gene expression profiling from patients' fibroblasts and whole blood, showed that the top differentially expressed genes belonged to pathways involving DNA damage control, protein trafficking, acute phase response, and extracellular tissue homeostasis. By immunoprecipitation, we further determined that patients' fibroblasts have malfunction in the maintenance of proteostasis as evidenced by dysregulation in proteasome and autophagy function, and accumulation of ubiquitinated proteins. No effective treatment has been described for this syndrome so far. Preliminary experience in our cohort suggests that treatment with a TNF-a inhibitor is beneficial for suppressing inflammation, stabilizing anemia and improving growth.

Conclusion: Mutations of TRNT1 enzyme lead to a severe and often fatal syndrome, linking protein homeostasis and autoinflammation. Future study of this disease will likely give new insights at cellular level about the role of protein homeostasis in immune cell development and susceptibility to inflammation in general. It might also provide more insights for targeted therapies of inflammatory diseases linked to protein degradation.

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Pediatric Rheumatology Care and Outcomes Improvement Network Demonstrates Improvement on Quality Measures for Children with Juvenile Idiopathic Arthritis

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Background/Purpose: Pediatric Rheumatology Care and Outcomes Improvement Network (PR-COIN) is a growing multi-center network organized on a learning health system model designed to improve outcomes of care for children with juvenile idiopathic arthritis (JIA). Since 2011, data from JIA clinical encounters have been entered into a shared registry to track performance on process and outcome quality measures (QMs) to drive improved outcomes. Currently, 17 centers learn established quality improvement methodology to conduct quality improvement work and share best practices at biannual face-to-face learning sessions and monthly webinars.

Methods: Statistical process control methods are used to determine if there are changes in performance on the

QMs. A centerline (the mean of the first 12 months of data) and control limits (±3 SD) are calculated, and control charts are monitored for special causes. Site specific and aggregate control charts are displayed monthly. If it is determined that a sustainable change has occurred, a new centerline and new control limits are calculated. Process QMs include measurement of: arthritis-related pain, physician global assessment of disease activity (PGA), joint counts, health related quality of life, physical function, medication counseling, as well as adherence to guidelines for uveitis screening, medication toxicity monitoring, and tuberculosis screening. Outcome QMs include: proportion of patients with clinical inactive disease (CID), mild to no pain, and optimal physical function; mean clinical Juvenile Arthritis Disease Activity Score 10 (cJADAS10); and percent of polyarthritis or oligoarthritis patients with inactive or low disease activity by cJADAS10.

Results: As of May 2016, 3716 JIA patients are enrolled, with over 20,000 visits recorded in the registry. Performance improvements have been achieved in process QMs, including percent of patients on Disease Modifying Anti Rheumatic Drug (DMARD) who had appropriate toxicity lab monitoring (from 56 to 82%) and documented medication counseling with DMARD initiation (from 59 to 93%). In addition, PR-COIN sites reliably perform complete joint counts (99%), PGA (96%), measurement of arthritis-related pain (94%), and tuberculosis screening for patients newly prescribed biologic drugs (99%). Forty-two percent of all PR-COIN patients have CID, with marked center-to-center variability (range 25% to 59%) and statistical improvement in a subset of centers. Seventy-five percent of patients have mild to no pain, and 60% have optimal physical function. PR-COIN has shown improved outcomes in mean cJADAS10 scores (from 4.4 to 3.8) and percentage of patients with inactive or low disease activity by cJADAS10 (from 49 to 54%) from 2011 to present.

Conclusion: PR-COIN has demonstrated success in improving processes of care for management of JIA. There is, however, variability in performance across centers. The dichotomous outcome measure “clinical inactive disease” has been slow to show statistical improvement in aggregate. By adopting a continuous outcome measure, the cJADAS10, PR-COIN has been able to demonstrate incremental improvements in outcomes for patients with JIA.

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Abstract Number: 2039

Assessing Barriers to Uveitis Screening in Patients with JIA: A Qualitative Study

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Background/Purpose: Uveitis is a major complication in patients with juvenile idiopathic arthritis (JIA) can be completely asymptomatic until vision loss develops. In order to prevent ocular complications, it is important to adhere to the recommended screening guidelines which range from every 3 to 12 months depending on JIA subtype, age of onset, duration of diagnosis and ANA status. However, this schedule may be difficulty for patients to adhere to. Little literature exists regarding compliance with uveitis screening in patients with JIA and we do not fully understand the barriers to obtaining screening eye exams. The specific aim of this quality improvement study as to assess barriers to obtaining screening eye exams in patients with JIA.

Methods: Patients with JIA were identified by ICD-9 code in our electronic medical record (EMR) prior to scheduled follow up appointments. They were then identified a adherent or non-adherent with established uveitis screening guidelines based on documentation of eye exams in the EMR. The guardians of those patients that were non-adherent were called the week prior to their scheduled appointments and a semi-structured interview was conducted. The interview included questions regarding the patient's most recent eye exam, knowledge about the screening frequency, and barriers to completing the eye exams. The results were then analyzed qualitatively to determine any categorical variables present and the relative importance of each variable.

Results: 92 patients, ages 3-22 years, were identified as non-adherent to screening exam guidelines out of a possible 246 total patients with JIA with upcoming appointments. 45 guardians of these patients or patients older than 18 years were interviewed by phone. Responses were categorized into system problems, access to care, and knowledge. System problems (57.8%) represented the largest category. These problems included the most recent eye exam not being in the EMR, the wrong provider was identified in the EMR, or difficulty with scheduling an appointment. 48.9% of patients who were identified by review of EMR record as non-adherent with screening exams had parent/guardian reports of more recent eye exams. Lack of appropriate parent knowledge regarding uveitis screening was also identified as a key barrier with 26.7% unaware of how often screening exams should be performed. Access to care was the least cited category with 20% of those interviewed identifying a barrier such as transportation or insurance.

Conclusion: This qualitative study identified system problems as the greatest barrier to obtaining screening eye exams in this patient population. The most common system problem was the most recent eye exam not being in the EMR. Lack of knowledge also appears to contribute. These results will be helpful in planning the next steps in improving compliance with uveitis screening.

Disclosure: L. Ballenger, None; **K. Driest**, None; **S. P. Ardoin**, None.

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Abstract Number: 2040

Responsiveness of Patient Reported Outcomes Measurement Information System Measures in RA Patients Starting or Switching a DMARD

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Background/Purpose: The Patient Reported Outcome Measurement Information System (PROMIS) is an NIH-developed metric for assessing multidimensional aspects of health across different conditions. Prior RA studies have reported cross-sectional results from PROMIS measures but were limited by small numbers of patients with active inflammatory disease. The purpose of this study was to evaluate the performance of multiple PROMIS measures in active RA patients initiating DMARDs.

Methods: Subjects were the first 148 RA patients enrolled in an ongoing multi-site, prospective observational study. Inclusion required active disease necessitating a start/switch to a new DMARD based on physician assessment. Subjects were evaluated before and 12-24 weeks after DMARD initiation. Subjects completed the PROMIS Global Health v1.1 short form and the following PROMIS computer adapted tests (CATs): Pain Interference, Pain Behavior, Sleep Disturbance, Sleep Related Impairment, Fatigue, Anxiety, and Depression. Scores were T-scores standardized to a general population mean of 50 ± 10. Higher scores indicate more of the concept measured. We performed linear regression models to identify cross-sectional associations between baseline PROMIS measures and disease activity measured using the CDAI; paired t-tests to evaluate responsiveness in subjects with follow-up data; and Pearson correlations to identify associations between changes in PROMIS measures and changes in CDAI.

Results: 85% of the cohort was female. Mean RA duration was 10.1 ± 12.8 years. At baseline, the mean CDAI was 25.3 ± 14.4. In multivariable linear regression models adjusted for age, sex, race, disease duration, and seropositive status, higher CDAI categories were significantly associated with higher PROMIS scores of pain, sleep, fatigue, and anxiety and lower PROMIS scores of physical and mental health ($P \leq 0.05$). Among 89 patients with pre/post data, paired t-tests showed statistically significant decreases in PROMIS domain measures ($P \leq 0.01$), ranging from -3.3 ± 8.2 to -5.5 ± 7.5 (Table). PROMIS Global Profile physical scores increased by 4.6 ± 7.3 ($P < 0.0001$), and PROMIS Global Profile mental scores increased by 2.0 ± 7.4 ($P = 0.01$). Changes were significantly correlated with changes in CDAI for all measures (absolute rho's = 0.21-0.33) except for the Global Profiles and Depression.

Conclusion: These data confirm the ability of PROMIS measures to distinguish RA patient groups based on levels of disease activity. Although minimal clinically important improvements have not been defined, our data suggest that PROMIS instruments are responsive to changes in therapy. We conclude that PROMIS measures may be useful tools for assessing RA symptoms in research studies and in routine clinical care, before and after starting a new DMARD.

Table. Mean (±SD) PROMIS Scores for RA patients before and 12-24 weeks after starting a DMARD (N = 89).				
	Mean Baseline Score	**Mean Follow-Up Score**	**Mean Change**	**P Value***
Physical Global Health Profile	41.7 (±7.5)	46.3 (±8.3)	4.6 (±7.3)	<0.0001
Mental Global Health Profile	48.3 (±8.6)	50.3 (±9.1)	2.0 (±7.4)	0.01
Pain Interference CAT	59.8 (±8.4)	54.5 (±8.0)	-5.5 (±7.5)	<0.0001
Pain Behavior CAT	58.9 (±5.1)	54.3 (±8.1)	-4.6 (±8.9)	<0.0001
Sleep Disturbance CAT	55.6 (±8.6)	50.96 (±9.4)	-4.7 (±9.7)	<0.0001
Sleep Related Impairment CAT	55.8 (±10.3)	51.4 (±10.8)	-4.1 (±10.0)	0.0003
Fatigue CAT	56.7 (±8.6)	51.9 (±8.9)	-4.7 (±8.7)	<0.0001
Anxiety CAT	54.4 (±8.7)	51.2 (±9.4)	-3.3 (±8.0)	0.0003
Depression CAT	50.9 (±9.1)	47.7 (±9.1)	-3.3 (±8.2)	0.0004

* P-values from paired t-tests

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Validity and Reliability of Patient Reported Outcomes Measurement Information System (PROMIS®) Global Health Short Form in Patients with SLE

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Background/Purpose: The measurement of patient reported outcomes (PROs) is a growing priority for performance improvement in clinical care of chronic conditions such as SLE. Measuring PROs at the point of care requires validated instruments with minimal responder burden. PROMIS¨ Global Health Short Form (GHSF) is a 10 question generic PRO instrument measuring global physical and mental health domains with T-scores normalized to the general population (mean score = 50). The validity and reliability of the PROMIS GHSF have not been demonstrated in SLE. The aims of this study were to evaluate: 1) validity and 2) test-retest reliability of PROMIS GHSF in adults with SLE.

Methods: Adult outpatients meeting 1997 ACR SLE classification criteria were recruited from a SLE Center of Excellence. Subjects completed the SF-36, LupusQoL-US, selected PROMIS CATs, and PROMIS GHSF. PROMIS GHSF global physical and mental health scores were compared with PROMIS CATs and legacy instruments using Spearman correlations. Test-retest reliability was evaluated among subjects reporting stable SLE activity at two assessments a week apart using intraclass correlation coefficients (ICC).

Results: PROMIS GHSF demonstrated face validity with SLE patients scoring worse than the general population in global physical health (mean T-score 41.6 +/- SD 8.8; range 19.9 - 67.7) and global mental health (mean T-score 43.7 +/- SD 8.7; range 25.1 - 67.6). PROMIS GHSF physical health scores correlated strongly with physical function, pain, and social health domains in the PROMIS CATs, SF-36, and LupusQoL, while PROMIS GHSF mental health scores correlated strongly with the PROMIS depression CAT and the LupusQoL emotional health domain (table 1). Correlation between PROMIS GHSF physical health and the SF-36 physical component scores (PCS) was weak, while correlation between PROMIS GHSF mental health and the SF-36 mental component scores (MCS) was moderate (table 1). Test-retest reliability for both PROMIS GHSF physical and mental health scores was high with ICCs of 0.89 and 0.85 respectively. Median time to complete the short form was less than 2 minutes.

Conclusion: This study is the first to demonstrate the validity and reliability of PROMIS GHSF in adults with SLE. PROMIS GHSF can be used to quickly, accurately, and reliably screen for impaired physical function, pain, and depression and could be an important tool in the measurement of patient centered outcomes and improvement of quality of care in SLE.

Table 1. Spearman Correlations of PROMIS GHSF with PROMIS CATs, SF-36, and LupusQoL		
	PROMIS Global Physical Health (n = 199)	**PROMIS Global Mental Health** (n = 187)
PROMIS CATs		
Physical Function	**0.77**	0.54
Mobility	**0.75**	0.49
Pain Behavior	**-0.71**	-0.59
Pain Interference	**-0.80**	-0.59
Fatigue	-0.65	-0.60
Anger	-0.42	-0.57
Anxiety	-0.41	-0.61
Depression	-0.48	**-0.73**
Ability to Participate in Social Roles	**0.74**	0.65
Satisfaction with Participation in Social Roles	0.61	0.59
Sleep-Related Interference	-0.51	-0.52
Sleep Disturbance	-0.53	-0.52
Applied Cognition-Abilities	0.52	0.59
Applied Cognition-Concerns	-0.55	-0.63
SF-36		
Physical Function	**0.75**	0.46
Role Physical	0.61	0.46
PCS	0.34	0.08* (p = 0.25)
Mental Health	0.17* (p = 0.014)	0.23* (p = 0.002)
Role Emotional	0.50	0.61
MCS	0.52	0.68
Bodily Pain	**-0.80**	-0.55

Social Function	**0.70**	0.66
Vitality	0.53	0.54
Global Health	-0.38	-0.27
LupusQoL		
Physical Health	**0.77**	0.59
Emotional Health	0.52	**0.70**
Pain	**0.74**	0.56
Fatigue	0.62	0.62
Planning	0.69	0.62
Intimate Relations	0.53	0.46
Burden to Others	0.52	0.53
Body Image	0.35	0.46
Correlations > 0.7 are considered strong. All p-values are < 0.0001, except where indicated by *.		

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Abstract Number: 2042

Improving the Overall Pneumococcal Vaccination Rate in Lupus Patients at the Rheumatology Clinic

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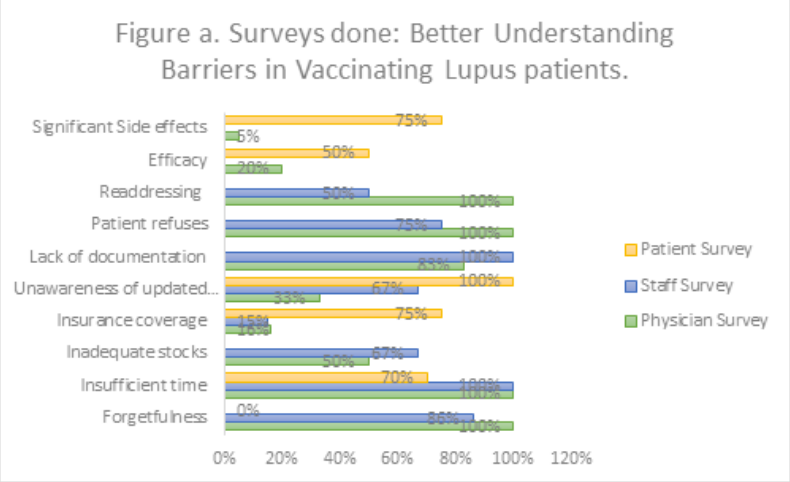
Background/Purpose: The risk of developing invasive pneumococcal pneumonia is 13 times higher in Lupus patients in comparison with general population. CDC anticipates 7.6 Million-Dollar medical cost reduction by providing pneumococcal vaccination per guidelines. Improving overall pneumococcal vaccination rate in lupus patients at our clinic through a multifaceted quality improvement initiative.

Methods: Eligibility: All lupus patients should receive pneumococcal vaccination. With help of quality improvement tools (interview with stakeholders {fig a}, process mapping) we analyzed the underlying barriers in providing vaccination and prepared a cause & effect diagram {fig b}. Following interventions were implemented, based on above analysis: **Staff** was responsible to confirm previous Pneumococcal vaccination, administer vaccines and update immunization history. **Physicians** were responsible to review daily reminders and place correct vaccination orders. **Patients** were given information handouts and education regarding Pneumococcal vaccines. After implementation of project, we calculated following rates (per week): Pneumococcal Vaccination (PCV 13, PCV 23 & vaccination complete) rates (percentage of pneumococcal vaccination given), documentation error rate (percentage of charts with immunization schedule not updated), historical error rate (percentage of patients not given pneumococcal vaccination due to unknown previous vaccination history) and vaccination refusal rate (percentage of patients refusing pneumococcal vaccination). Weekly progress was plotted on graph and discussed with the team members which helped us in modifying the interventions iteratively for achieving better rates.

Results: In 2 months {fig c}, overall vaccination improved from 8% to 28.2%, PCV 13 vaccination rate improved from 5% to 27.8%, PCV 23 vaccination rate improved from 8% to 50% and pneumococcal vaccination complete rate increased from 2% to 50%. Patient refusal rate decreased from 25% to 14%. 40% of patients are still not receiving immunization because of other reasons (forgetfulness, insufficient time).

Conclusion: Integrated workflow and performance data sharing helped in improving vaccination rates. Ongoing efforts are focused to overcome remaining barriers and achieve better rates.



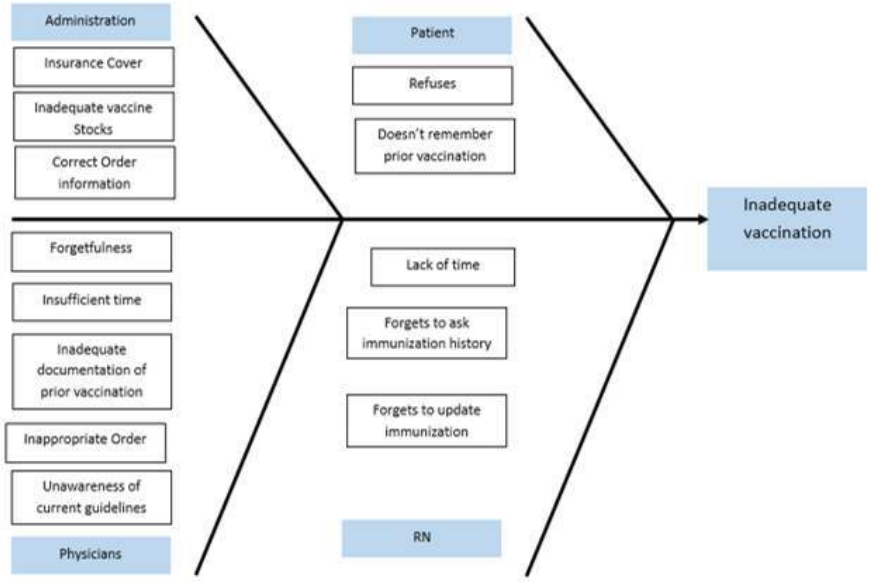
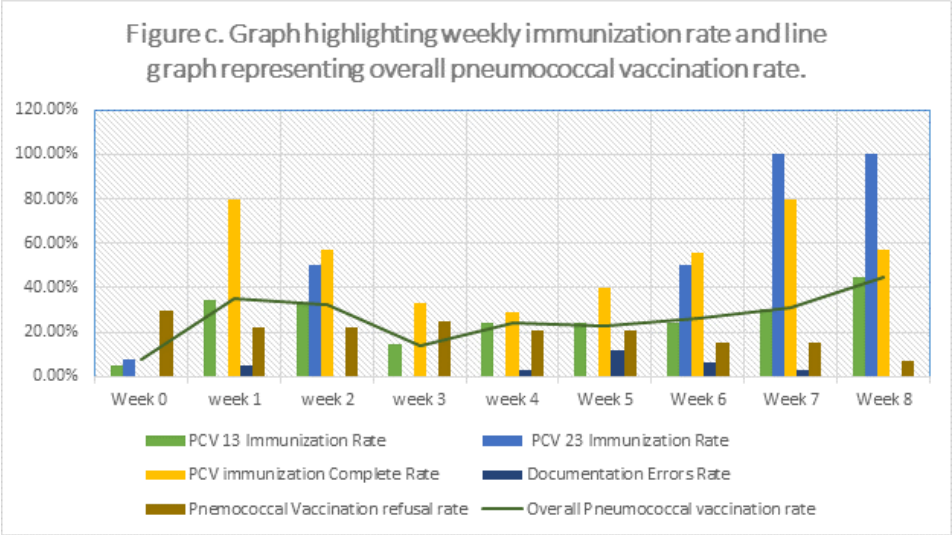


Figure b. Cause & Effect Diagram



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Abstract Number: 2043

Feasibility and Accuracy of Translating a Patient Safety Quality Measure into an Automated e-Measure

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Background/Purpose: Physician payments in the U.S. are shifting from fee-for-service to a value-based system, which will require quality measures to be extracted automatically from the electronic health record (EHR). However, the feasibility and accuracy of such "e-specification" of quality measures has not been widely reported. In this study, we compared the accuracy of automated electronic vs. manual chart review abstraction for a sample patient safety quality measure.

Methods: We developed electronic specifications for the following measure – "If a patient receives rituximab, then s/he should be screened for prior Hepatitis B infection with Hepatitis B surface antigen and Hepatitis B core antibody tests prior to rituximab initiation, because Hepatitis B reactivation is a potentially fatal (and preventable) adverse event in this population." We used EHR data derived from a tertiary care university center that has almost one million outpatient visits per year. Patients were included if they had at least 2 encounters during the 12 months before and at least one encounter 30 days after their first rituximab dose during the study period (June 2012-January 2016). We queried EHR structured data to define a denominator population of rituximab users and to classify the receipt of adequate Hepatitis B screening at any time prior to starting rituximab treatment. Two physicians performed chart reviews, including reviewing all clinical notes and scanned documents, to validate these data.

Results: The EHR query of structured data identified 1,167 users of rituximab in the denominator for this measure. Physician chart review found that this was an overestimate (321 patients did not receive the medication or had a historical reference to the medication). The automated query identified 618 (out of 1,167) patients in the numerator for this measure. Physician chart review found that this was an underestimate of actual testing, as 11% of the 926 patients in the denominator had additional lab results described in clinical narratives. The use of chart review in addition to electronic queries of EHR data increased the performance on this patient safety measure from 53% to 61%, representing a 15% increase.

Conclusion: Relying solely on the extraction of structured data from the EHR resulted in an overestimate of the denominator population and an underestimate of the numerator of Hepatitis B screening for this patient safety quality measure. Such misclassifications may threaten the validity of e-measurement and potentially undermine physicians' incentives to participate in a value-based payment system. As the number of e-Measures expands, accurate reporting will need to rely on additional strategies, including natural language processing for extraction of unstructured data from clinical notes, as well as changes to provider workflows to collect critical data elements in structured fields.

Table: Performance of patient safety measure using automated and manual data extraction.			
	EHR Query Using Structured Data N	Chart Review Findings N	EHR Query Using Structured Data & Chart Review Findings N
Denominator			
Patients taking rituximab after EMR go-live date	1,167	Of the 1,167 • 179 where rituximab was not completed or discontinued • 142 where rituximab was historical use	926
Numerator			
Receipt of Hepatitis B surface antigen (HepBsAg) and core (HepBCab) antibody labs prior to starting rituximab	Of the 1,167: • 618 had HepBsAg and HepBCab test results in a structured EHR table	Of the 926: • 561 received HepBsAg and HepBCab tests per structured EHR data table • 13 also had a lab value of "see text" where text was valid • 44 had no Hepatitis B test data but did have a test result mentioned in a clinical note, of which 4 received HepBsAg and HepBCab tests	565
Proportion of patients at risk receiving adequate testing	53%		61%

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Abstract Number: 2044

Effect of Pregnancy on Disease Flares in Patients with Systemic Lupus Erythematosus

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Background/Purpose: There are conflicting results about the effect pregnancy has on the health of systemic lupus erythematosus (SLE) women. The objective of the current analysis was to estimate the effect of pregnancy on disease flares in SLE using a stratified Cox model.

Methods: Data were prospectively collected in a university-based cohort from 1987-2015. Patients met ACR or SLICC criteria for SLE. All women aged 14-45 years with >1 measurement of disease activity were included, regardless of pregnancy status. Visits were classified into one of three exposure categories: pregnant, 1-year postpartum period, or non-pregnant/non-postpartum period (unexposed). Patients were allowed to switch from

one category of exposure to another between any two clinic visits based on pregnancy status. At each visit, disease activity was measured by Physician Global Assessment (PGA) and SELENA-SLEDAI. Flares during follow-up were defined as: 1) change in PGA ≥1 from previous visit and 2) change in SELENA-SLEDAI ≥4 from previous visit. Patients with a >1-year gap in study visits were considered lost to follow-up, but were allowed to re-enter the cohort. Hazard ratios (HR) between 1) pregnant and unexposed periods and 2) postpartum and unexposed periods were estimated with a stratified Cox model, a model that adjusts baseline hazards based on the number of previous flares. Hydroxychloroquine (HCQ) was explored as a time-varying covariate, with effect measure modification defined by likelihood ratio test (α=0.20).

Results: There were 1349 patients, including 398 pregnancies in 304 patients. Median age at cohort entry was 31 years, and median follow-up was 4 years. The crude incidence of flares based on the PGA definition was 60.7 per 100 person-years (PY) during pregnancy compared to 40.2 per 100 PY during non-pregnant/non-postpartum periods (Table 1). Stratified Cox models estimated an increased rate of flare during pregnancy (HR: 1.59; 95% CI: 1.27, 1.96), with no evidence of an increased rate during the postpartum period. There was effect modification by HCQ use. Among periods of no HCQ use, the HR of flares in pregnancy compared to non-pregnant/non-postpartum periods was estimated to be 1.83 (95% CI: 1.34, 2.45) compared to 1.26 (95% CI: 0.88, 1.69) among periods with HCQ use (likelihood ratio p-value: 0.04). When flares were defined by SELENA-SLEDAI, results were similar, with an increased rate of flare during pregnancy but no observed increased rate of flare postpartum compared to non-pregnant/non-postpartum periods. No evidence of effect modification by HCQ use was found when flares were defined by SELENA-SLEDAI.

Conclusion: Our study supports and extends previous findings that the incidence of flare is increased during pregnancy. Continuing HCQ in pregnancy, however, appeared to mitigate the risk of flare during pregnancy. We did not find evidence of an increased rate of flare postpartum.

Table 1. Crude incidence, crude incidence rate ratio, and hazard ratio of flares during pregnancy and postpartum periods compared to non-pregnant/non-postpartum periods (n=1349)

	Crude incidence per 100 person-years	Hazard Ratio (95% CI)
PGA[A]		
All patients		
Not pregnant/postpartum	40.2	1.0 (ref)
Pregnancy	60.7	1.59 (1.27, 1.96)
Postpartum	39.9	1.02 (0.83, 1.25)
Patients exposed to hydroxychloroquine[B]		
Not pregnant/postpartum	38.0	1.0 (ref)
Pregnancy	42.1	1.26 (0.88, 1.69)
Postpartum	35.3	1.02 (0.72, 1.32)
Patients unexposed to hydroxychloroquine[C]		
Not pregnant/postpartum	45.3	1.0 (ref)
Pregnancy	84.3	1.83 (1.34, 2.45)
Postpartum	46.0	0.98 (0.67, 1.31)
SELENA-SLEDAI[D]		
All patients		
Not pregnant/postpartum	47.3	1.0 (ref)
Pregnancy	63.4	1.57 (1.25, 1.92)
Postpartum	45.8	1.09 (0.89, 1.32)
Patients exposed to hydroxychloroquine[B]		
Not pregnant/postpartum	45.9	1.0 (ref)
Pregnancy	51.8	1.35 (0.92, 1.81)
Postpartum	47.1	1.13 (0.88, 1.44)
Patients unexposed to hydroxychloroquine[C]		
Not pregnant/postpartum	50.3	1.0 (ref)
Pregnancy	78.1	1.59 (1.17, 2.09)
Postpartum	44.1	0.91 (0.64, 1.20)

[A]flare defined as change in ≥1 from PGA score at previous visit
[B]all of the person-time included (during pregnancy, the postpartum period, and non-pregnant/postpartum period) was exposed to hydroxychloroquine
[C]all of the person-time included (during pregnancy, the postpartum period, and non-pregnant/postpartum period) was unexposed to hydroxychloroquine
[D]flare defined as change in ≥4 from SELENA-SLEDAI score at previous visit
CI: confidence interval; PGA: Physician Global Assessment of disease activity; SLE: systemic lupus erythematosus; SLEDAI: SLE Disease Activity Index

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Abstract Number: 2045

Early Preeclampsia Risk in Lupus Pregnancy: A Swedish Population-Based Register Investigation

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Background/Purpose: Early preeclampsia is a serious pregnancy complication characterized by abnormal placentation and diffuse maternal endothelial cell dysfunction, and requires emergent delivery which may be very premature. SLE has been shown to increase the risk of preeclampsia, but little is known about the risks of early onset preeclampsia – a pregnancy morbidity associated with stroke, placental abruptions, and perinatal death.

Methods: Using national population-based Swedish registers we identified women with SLE (≥2 visits with corresponding ICD codes) and without SLE who gave birth to singleton infants 2001-2012 in the Swedish Medical Birth Register. Comparators without SLE were drawn from the general population. Preeclampsia was defined using date of first corresponding diagnosis during pregnancy to define early onset (<34 weeks). The association between early preeclampsia and maternal SLE was estimated by multivariable-adjusted modified Poisson models for first, subsequent, and all births. BMI, age, smoking, and pregestational hypertension and diabetes were included as potential confounders. We used ICD-10- coded visit and heparin dispensing during pregnancy from the Prescribed Drug Register (2006-2012) as a proxy for antiphospholipid syndrome (APS).Preeclampsia history was adjusted for in analyses of subsequent and all births. We investigated effect modification by pregestational hypertension, examined residual confounding by APS and misclassification of preeclampsia due to lupus nephritis.

Results: There were 742 births to women with SLE (343 first births) and 10484 births to women from the general population (4443 first births). Compared to the general population, SLE was associated with a significantly increased risk of early preeclampsia for all, first, and subsequent births [RR=7.3, (95% CI=4.5, 11.9), mvar-adj, all births]. Adjustment for APS proxy attenuated the association (RR=3.7, 95% CI=1.7, 7.9), but SLE remained significantly associated with early preeclampsia. Findings were similar among women without pregestational hypertension, a strong risk factor for early preeclampsia, as well as in the absence of recent nephrology care. RRs for early preeclampsia were smaller, but significant, for subsequent births compared to first and all births [RR=2.8, (95% CI=1.2, 6.4) subsequent].

Conclusion: Women with SLE are at increased risk of preeclampsia before 34 weeks gestation, and importantly, this increased risk may be independent of pregestational hypertension, APS, BMI, or smoking. Traditional risk factors alone may not explain the increased risk of early preeclampsia among women with SLE for first, subsequent, or any birth. Women with SLE during pregnancy should continue to be monitored carefully for early preeclampsia and future research is needed to identify what non-traditional preeclampsia factors might be causing this serious outcome.

Disclosure: J. F. Simard, None; **E. V. Arkema**, None; **C. Nguyen**, None; **E. Svenungsson**, None; **A. K. Wikstrom**, None; **K. Palmsten**, None; **J. E. Salmon**, None.

Abstract Number: 2046

The Low-Dose Intravenous Cyclophosphamide Euro-Lupus Regimen Does Not Impact the Ovarian Reserve of Lupus Patients, As Measured By Serum Anti-Mullerian Hormone Levels

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SESSION INFORMATION

Session Date: Monday, November 14, 2016

Session Title: Reproductive Issues in Rheumatic Disorders

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The low-dose intravenous (IV) cyclophosphamide (CY) Euro-Lupus (EL) regimen (cumulative dose 3g) has been developped to reduce gonadal toxicity. Although no case of premature menopause has been reported, uncertainty persists regarding a marginal effect on the ovarian reserve. To address this issue, we measured serum titers of anti-Mullerian hormone (AMH) in patients suffering from systemic lupus erythematosus (SLE) treated with the EL regimen and compared them to those measured in SLE patients treated with higher doses of IVCY and in those never treated with IVCY.

Methods: Serum anti-Mullerian hormone (AMH) levels were measured by ELISA (Ansh Laboratories, TX, USA) in a cohort of 169 consecutive premenopausal female SLE patients fulfilling the SLICC/ACR criteria. Demographic and clinical data were collected, as well as the cumulative dose of IVCY. Patient's consent was obtained, as appropriate.

Results: Median serum AMH titers of patients given the 3g EL IVCY regimen (1.15 ng/ml ; n=31) did not differ from those measured in patients never treated with IVCY (1.42 ng/ml ; n=112). By contrast, and as anticipated, serum AMH titers were statistically lower in patients treated with >3g IVCY (median : 0.71 ng/ml; n=26 ; mean ± SD IVCY dose of 8.1 ± 3.7g ; p=0.036 by Mann-Whitney test). These results were confirmed when serum AMH values were adjusted for age (based on titers measured in the cohort of SLE patients who never received IVCY). Patients given >6g IVCY (n=15 ; mean ± SD IVCY dose : 10 ± 3.9g) have much lower median age-adjusted serum AMH values (0.09 ng/ml) compared to patients never given IVCY (p=0.008 by Mann-Whitney test). In 10 patients, paired serum samples were tested before and after EL IVCY. Median AMH values did not differ (1.54 ng/ml before and 1.39 ng/ml after : p=0.49 by Wilcoxon matched-pairs signed rank test).

Conclusion: Based on cross-sectional and longitudinal data, the EL IVCY regimen does not impact the ovarian reserve of SLE patients and can therefore be proposed as induction immunosuppressive therapy in severe patients without risk of compromising fertility.

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Abstract Number: 2047

Impact of in Utero Hydroxychloroquine Exposure on the Risk of Cutaneous Neonatal Lupus Erythematosus

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Background/Purpose: Histopathologic studies of cutaneous neonatal lupus erythematosus (cNLE) lesions usually show interface dermatitis. Hydroxychloroquine (HCQ) is an effective treatment for interface dermatitis seen in connective tissue diseases. It may also be effective for cNLE. Due to the transplacental passage of HCQ, fetuses of treated mothers are exposed to HCQ. The aim of this study was to asses if in utero exposure to HCQ would lower the risk of cNLE.

Methods: A multicenter case control study was performed. Inclusion criteria were: (1) infant born to a woman positive for anti-Ro ± anti-La antibodies and with a diagnosis of either systemic lupus erythematosus, Sjogren's syndrome, dermatomyositis or rheumatoid arthritis, (2) infant cNLE status documented, and (3) documentation of maternal medications during pregnancy. Children with cardiac NLE were excluded from this study. Generalized estimating equation (GEE) was used to account for within-family correlation of data. A subgroup analysis was performed including only cases with cNLE onset ≤ 4 weeks of life, as neonates are not continued on HCQ after delivery therefore HCQ levels are expected to decline after birth.

Results: A total of 545 children (10 twin pairs) were included. Cases (N=112) and controls (N=433) differed with respect to maternal characteristics (Table 1). 169 (31%) infants were exposed to HCQ. Univariable GEE

models showed that maternal diagnosis, anti-La antibody, maternal intake of HCQ and maternal intake of non-fluorinated steroids ± azathioprine were associated with cNLE (Table 2). In multivariable GEE, maternal intake of HCQ remained associated with a significant decrease in cNLE (Table 3). 41/112 infants with cNLE had onset of rash within 4 weeks after birth. When analyses were restricted to these early onset cNLE cases, results were similar to that of the entire study population (multivariable GEE, maternal intake of HCQ OR 0.2 (95% CI 0.1-0.7); p=0.009).

Conclusion: In this large multicenter study of 545 children born to women with anti-Ro ± anti-La antibodies and a connective tissue disease and/or RA, in utero HCQ exposure was associated with a decreased risk of cNLE.

Table 1. Baseline characteristics

	Patients (N)	Cases (N=112)	Controls (N=433)	p value
Maternal characteristics[1]	535			
Age at child birth, years (median (IQR))	522	31 (29-35)	32 (29-35)	0.446
Diagnosis, N (%)	535			<0.001
Sjogren's syndrome		31 (27.7)	116 (27.4)	
SLE		52 (46.4)	261 (61.7)	
Dermatomyositis		0	1 (0.2)	
RA or juvenile idiopathic arthritis		3 (2.7)	15 (3.6)	
Sjogren's syndrome and SLE		26 (23.2)	29 (6.9)	
Sjogren's syndrome and RA		0	1 (0.2)	
Anti-Ro antibody positive, N (%)	535	112 (100)	418 (99)	0.589
Anti-La antibody positive, N (%)	507	79 (72)	191 (48)	<0.001
Medication intake, N (%)				
Hydroxychloroquine	535	19 (17)	145 (34)	<0.001
Fluorinated steroids ± IVIG ± plasmapheresis	535	7 (6)	17 (4)	0.310
Non-fluorinated steroids ± azathioprine	532	31 (28)	185 (44)	0.002
Children characteristics	545			
Gender, female:male, N	543	65:47	207:224	0.059
Born ≥ year 2000, N (%)	545	64 (57)	277 (64)	0.183
Age of onset of cNLE, weeks (median (IQR))	108	6 (3-10)	N/A	N/A

[1] N=535 due to 10 twin pregnancies

Table 2. Variables associated with cNLE in univariable GEE		
Maternal characteristics	OR (95% CI)	p value
Age at child birth	1.0 (0.9-1.03)	0.517
SS diagnosis	2.0 (1.3-3.1)	0.002
Anti-La antibody positive	2.8 (1.7-4.4)	<0.001
Intake of HCQ	0.4 (0.2-0.7)	0.001
Intake of fluorinated steroids ± IVIG ± plasmapheresis	1.5 (0.6-3.8)	0.387
Intake of non-fluorinated steroids ± azathioprine	0.5 (0.3-0.8)	0.002
Children characteristics		
Female gender	1.5 (1.0-2.2)	0.054
Born ≥ year 2000	1.4 (0.9-2.1)	0.158

Table 3. Variables associated with cNLE in multivariable GEE		
Maternal characteristics	OR (95% CI)	p value
Anti-La antibody positive	2.5 (1.6-4.1)	<0.001
Intake of HCQ	0.4 (0.2-0.8)	0.008
Children characteristics		
Female gender	1.7 (1.1-2.7)	0.012

Disclosure: J. Barsalou, None; **N. Costedoat-Chalumeau**, None; **A. Berhanu**, None; **C. Fors-Nieves**, None; **U. Shah**, None; **P. Brown**, None; **C. Laskin**, None; **N. Morel**, None; **K. Levesque**, None; **J. P. Buyon**, None; **E. Silverman**, None; **P. M. Izmirly**, None.

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Abstract Number: 2048

Evaluating Transfer of Certolizumab Pegol into Breast Milk: Results from a Prospective, Postmarketing, Multicenter Pharmacokinetic Study

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Background/Purpose: Women with chronic inflammatory diseases, including rheumatic diseases and Crohn's disease (CD), face uncertainty regarding the safety of the use of biologics during breastfeeding. For women with RA, postpartum flare is common.[1] Currently, limited and non-validated data exist on potential transfer of anti-TNFs into breast milk. CRADLE was the first sponsored study designed to evaluate certolizumab pegol (CZP) concentrations in breast milk, and to estimate average daily infant dose of maternal CZP (the daily amount of CZP potentially ingested by infants).

Methods: CRADLE (NCT02154425) was a safety and pharmacokinetic study of lactating mothers (≥6 weeks postpartum) receiving commercial CZP for an approved indication. Decision to treat with CZP and to breastfeed was made independently of study participation. At steady-state (≥3 CZP doses), breast milk samples were collected at days 0, 2, 4, 6, 8, 10, 12, 14 (±28) from each mother across 1 dosing period (14 days for 200 mg Q2W; 28 days for 400 mg Q4W). Maternal burden was minimized through in-home visits with nurses. A highly sensitive CZP-specific ELISA was developed (validated in milk; LLQ=0.032 μg/mL, 10-fold lower than assay used in CZP pharmacokinetic studies[2]). CZP stability in milk was confirmed.

Results: 18 CZP-treated mothers were screened and 17 entered the sampling period; 16 on 200 mg Q2W; 1 on 400 mg Q4W (7 RA; 5 SpA; 5 CD; Table A). Samples from 4/17 mothers had no measurable CZP in breast milk; 13/17 had quantifiable levels at any time point (highest concentration: 0.076 μg/mL; Table B). Estimated average daily infant dose ranged 0–0.0104 mg/kg/day; median relative infant dose (calculated[3] *post hoc* by Dr Hale): 0.15%. The infants of mothers exposed to CZP had a safety profile consisting of events occurring in unexposed infants of similar age (Table C).

Conclusion: Using the highly sensitive assay, CZP was undetectable in 56% of milk samples collected. When detectable, CZP concentrations were less than 3 times LLQ (<1% of expected plasma concentration of a therapeutic dose),[2] indicating no to minimal transfer of CZP from plasma to breast milk. Relative infant dose was below 0.5% of maternal dose; <10% is considered unlikely to be of clinical concern.[3] In addition, CZP absorption by infants via breast milk is unlikely due to its Fc-free molecular structure[4] and the low bioavailability of biologics after oral administration. These findings are reassuring and imply that continuation of CZP treatment is compatible with breastfeeding. **References:** 1. de Man Y. Arthritis Rheum 2008;59:1241–8; 2. Lacroix B. Gastroenterol 2010;138:S163–4; 3. Bennett P. Drugs and Human Lactation. 1996; 4. Israel E. Immunology 1997;92:69–74. *[Resubmission from ACG 2016]* Funding: UCB Pharma. We are indebted to the mothers and their infants for their altruistic participation. We thank the nurses, investigator teams, and Nicole Hurst (PPD) and acknowledge Amanda Golembesky and Gerry Parker, UCB Pharma.

Table A: Baseline characteristics of mothers and infants

	All mothers (n=18) [a]
Mean (SD), unless otherwise stated	
Age, years	33.7 (4.2)
Weight, kg	68.9 (9.6) [b]
BMI, kg/m²	23.6 (3.0) [b]
Mother's indication for CZP treatment, n [b]	
Rheumatoid arthritis	7
Crohn's disease	5
Psoriatic arthritis	3
Axial spondyloarthritis/ankylosing spondylitis	2
	All infants (n=17)
Mean (SD), unless otherwise stated	
Female, n (%)	11 (64.7)
Gestational age at birth, weeks	39.9 (0.8)
Weight at birth, kg	3.4 (0.5)

[a] Includes 1 screen failure; [b] n=17.

Table B: Concentrations of CZP (µg/mL) in breast milk after administration of CZP dose in mothers

Patient	Relative time (days)								
	0	2	4	6	8	10	12	14	28
1	0.057	0.051	0.066	0.065	0.062	0.056	0.052	0.041	-
2	BLQ	BLQ	0.035	0.037	0.041	BLQ	0.043	BLQ	-
3	BLQ	0.032	0.049	0.053	0.037	0.037	0.033	0.033	-
4	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
5	0.056	0.069	0.074	0.076	0.076	0.069	0.069	0.060	-
6	BLQ	BLQ	0.044	0.048	BLQ	BLQ	BLQ	BLQ	-
7	BLQ	BLQ	BLQ	BLQ	BLQ	0.035	BLQ	BLQ	-
8	BLQ	BLQ	0.035	0.034	0.043	BLQ	BLQ	BLQ	-
9	0.039	0.040	0.047	0.045	0.042	0.043	0.038	0.035	-
10	BLQ	BLQ	BLQ	0.033	0.042	0.042	BLQ	BLQ	-
11	BLQ	BLQ	0.051	0.038	0.042	BLQ	0.033	BLQ	-
12	BLQ	BLQ	0.034	0.037	0.033	BLQ	BLQ	BLQ	-
13	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
14	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	-
15	BLQ	BLQ	0.041	0.034	0.033	BLQ	0.037	BLQ	-
16	0.040	0.033	0.036	0.037	0.043	BLQ	BLQ	BLQ	-
17	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ

Key: BLQ (<0.032 µg/mL); Less than 2×LLQ (<0.064 µg/mL); Less than 3×LLQ (<0.096 µg/mL)

Days 0 and 14 are pre-dose for mothers on CZP 200 mg Q2W dosing regimen;
Days 0 and 28 are pre-dose for the mother on CZP 400 mg Q4W dosing regimen.

BLQ: below the limit of quantification, <0.032 µg/mL; LLQ: lower limit of quantification.

For reference, the mean 12-week CZP plasma C_{trough} value, ie. the trough concentration at steady-state, reported from patients with rheumatoid arthritis receiving CZP 200 mg Q2W in the RAPID2 trial was 15.7 µg/mL (95% CI: 14.0, 17.7).[2]

Table C: Summary of adverse events from the Safety Set during the CRADLE study (from screening to safety follow-up)

	Mothers (n=18) n (%)	Infants (n=17) n (%)
Any adverse event	10 (55.6)	8 (47.1)
Intensity		
Mild	3 (16.7)	6 (35.3)
Moderate	6 (33.3)	2 (11.8)
Severe	1 (5.6) [a]	0

Severe	1 (5.6) [a]	0
Serious adverse events	1 (5.6) [a]	0
Discontinuations due to adverse events	1 (5.6) [b]	0
Drug-related adverse events	4 (22.2)	1 (5.9)
Herpes zoster	1 (5.6)	-
Crohn's disease flare	1 (5.6)	-
Upper respiratory tract infection	2 (11.1)	-
Pneumonia	1 (5.6)	-
Nasopharyngitis	-	1 (5.9)
Adverse events of interest [c]	0	0
Deaths	0	0

Adverse events are reported from the Safety Set, which included all mothers who received at least 1 dose of CZP, and the infants of all mothers who participated in the study. The safety follow-up period extended up to 5 weeks (±5 days) after the final sample was obtained. [a] Breast abscess during screening period, which resolved prior to sampling; [b] Herpes zoster during screening period resulting in screen failure; [c] Includes any opportunistic infections, any malignancies (including unspecified), any major adverse cardiac events, any hematopoietic cytopenias, any serious bleeding events, any hepatic events, and any injection or injection site reactions in mothers.

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Abstract Number: 2049

Serious Infections in RA Offspring Exposed to Tumor Necrosis Factor Inhibitors

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Background/Purpose: Tumor Necrosis Factor inhibitors (TNFi) are increasingly used during RA pregnancy.

Most of these are actively transported across the placenta, reaching higher fetal than maternal blood levels. Despite concerns that these drugs cause immunosuppression, there are no data on the risk of serious infections in exposed offspring. Thus, we evaluated serious infections in RA offspring exposed to TNFi in the preconception and/or gestational period compared to unexposed RA offspring, as well as to children from the general population.

Methods: The "PregnAncies in RA mothers and Outcomes in offspring in the United States cohort (PAROUS)" includes all women with ≥1 hospitalization for delivery after RA diagnosis, identified through MarketScan commercial databases (2011-2014). PAROUS also includes a randomly selected control group of women, matched ≥4:1 for age, year of delivery, and state of residence, without an RA diagnosis prior to or at the time of delivery. Only women continuously enrolled within MarketScan for ≥12 months prior to delivery and with available child linkage were included in PAROUS. We identified children born live to RA mothers and their matched controls, and defined TNFi exposure based on ≥1 filled prescription of adalimumab, certolizumab, etanercept, golimumab, or infliximab during pregnancy and/or the preconception period (ie 12 weeks prior to conception). We ascertained serious infections based on ≥1 hospitalization with infection as a primary diagnosis, ≤12 months of life. We performed multivariate analyses with generalized estimating equations to adjust for maternal demographics, co-morbidities, pregnancy complications, and drugs.

Results: We identified 2455 RA offspring and 11 018 matched controls. Among children born to RA women, 290 (11.8%) were exposed to TNFi during pregnancy (ie TNFi pregnancy) (including 109 in the third trimester), 109 (4.4%) were unexposed during pregnancy but exposed in the preconception period (ie TNFi preconception), and 2056 (83.7%) were unexposed both during the pregnancy and preconception periods (ie RA with no TNFi). Each group of RA offspring experienced more serious infections vs general population controls [TNFi pregnancy 3.1% (95%CI 1.5,6.0), TNFi third trimester 2.8% (95%CI 0.7,8.4), TNFi preconception 1.8% (95%CI 0.5,6.4), RA with no TNFi 2.1% (95%CI 1.6,2.9), vs controls 0.2% (95%CI 0.1,0.2)]. In multivariate analyses, children born to RA women had a substantially increased risk of serious infections vs controls [OR for TNFi pregnancy 15.4 (95%CI 6.2,38.6), OR for TNFi preconception 9.6 (95%CI 2.1,43.8), OR for RA with no TNFi 12.8 (95%CI 6.9,23.8)]. We were unable to establish an increased risk of serious infections in RA offspring exposed to TNFi during pregnancy compared to unexposed RA offspring (OR 1.2; 95%CI 0.6,2.6); results were similar when we restricted TNFi exposure to the third trimester (OR 1.0; 95%CI 0.3,3.4).

Conclusion: Compared to children from the general population, children born to RA women have a substantially increased risk of serious infections. We were unable to establish a marked excess risk for serious infections in RA offspring exposed to TNFi during pregnancy, including the third trimester, vs unexposed RA offspring.

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Abstract Number: 2050

Screening for and Management of Comorbidities after a Nurse-Led Program: Results of a 3 Year Longitudinal Study in 776 Established RA Patients

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Dernis Labous[12], Isabelle Chary-Valckenaere[13], Liana Euller-Ziegler[14], Rene-Marc Flipo[15], Philippe Gaudin[16], Melanie Gilson[17], Sandrine Guis[18], Xavier Mariette[19], Gaël Mouterde[20], Sophie Pouplin[21], Pascal Richette[22], Alain Saraux[23], Thierry Schaeverbeke[24], Jean Sibilia[25] and Maxime Dougados[26], [1]Rheumatology, Pitié Salpêtrière Hospital, Paris, France, [2]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [3]COMEDRA working group, Paris, France, [4]Hopital Cochin, Paris Descartes University, Paris, France, [5]Rheumatology, CHU Gabriel-Montpied, Clermont-Ferrand, France, [6]Hôpital Lariboisière, Paris, France, [7]Rheumatology dept, APHP St-Antoine hospital, Univ Paris 06, Paris, France, Paris, France, [8]Purpan Hospital, Toulouse, France, [9]University Hospital, Toulouse, France, [10]CHU RENNES, Rennes, France, [11]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [12]Le Mans Hospital, Le Mans, France, [13]University Hospital, Nancy, France, [14]Rheumatology, Nice, France, [15]Rheumatology, University Hospital, Lille, France, [16]Rheumatology, Grenoble University Hospital, France, Grenoble, France, [17]Hopital Sud, Grenoble, France, [18]Rheumatology 1, CRMBM-CEMEREM 7339, Aix-Marseille Université, AP-HM, CNRS, Marseilles, France, [19]Rheumatology, Rheumatology department, Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France, [20]Rheumatology Department, Hopital Lapeyronie, Montpellier, France, [21]Rheumatology Department & Inserm 905, Department of Rheumatology, Rouen University Hospital & Inserm 905, Institute for Biomedical Research, University of Rouen, Rouen, France, [22]Rhumatologie, Hôpital Lariboisière, Paris, France, [23]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [24]Rheumatology, CHU Bordeaux, Bordeaux, France, [25]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [26]Paris Descartes University, Paris, France
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Background/Purpose: Patients with RA are either more at risk of, or less well screened for, several comorbidities including cardiovascular (CV) risk, cancer, infections and osteoporosis.[1] In 2012, patients with established RA participated in a trial including a nurse visit for comorbidity counselling [2]. In the present follow-up study, we aimed to quantify both at study entry and 3 years after the trial ended, comorbidity screening and management in this population.

Methods: *Study design*:This was an open long term (3 years) extension of the COMEDRA 6 month randomized controlled trial in which patients with definite, stable RA were visiting a nurse for comorbidity counselling.[2] Comorbidity status was assessed and nurses provided advice on screening and management, at baseline and 3 years later. *Outcome measure:* A score was developed to quantify comorbidity screening and management: this score gives 50 points to CV risk (ie hypertension, diabetes, lipids, renal insufficiency), 20 points to cancer, 20 points to vaccination and 10 points to osteoporosis screening. Lower scores indicate better screening and management. *Statistical analysis*: The score was compared between baseline and 3-year assessment using a Wilcoxon test for paired data. For each comorbidity, the percentage of patients in conformity with screening and/or management recommendations was also assessed at both timepoints and compared using a MacNemar test for paired data.

Results: Of the 970 recruited patients, 776 (80%) were followed up at 2-4 years and 769 (79%) had available data for comorbidities at both timepoints: mean (±SD) age 58 (±11) years, mean disease duration 14 (±10) years; 614 (80%) were women and 538 (70%) were receiving a biologic with a mean DAS28 of 3.0±1.3. At baseline,

the mean comorbidity screening score was 36.6(±19.9) (range, 0-100) and it improved at 3 years to 24.3(±17.8) (p<0.0001) thus with a relative improvement of 33%. Patients in conformity with management recommendations improved most remarkably for CV risk screening, vaccination status and bone densitometry performance, whereas cancer screening improved less (Table).

Conclusion: Comorbidity screening is suboptimal but has improved notably in this study over 3 years, after a nurse-led program aiming at checking systematically for comorbidity screening and giving patient advice. Improvements were particularly important for CV screening and vaccinations. This long-term efficacy pleads in favour of nurse-led interventions to better address comorbidities in RA.

Ref 1. Baillet A, Gossec L et al. Ann Rheum Dis. 2016;75(6):965-73.

Ref 2. Dougados M, Soubrier M, et al. Ann Rheum Dis. 2015;74(9):1725-33.

Table % of patients in conformity with screening and management recommendations, for each comorbidity

Comorbidity	COMEDRA study baseline (month 0 for group I and month 6 for group II)	Follow-up at 3 years	*p* value between baseline and follow up date
CV risk			
Hypertension	75.2	96.2	<0.0001
Diabetes	55.9	69.6	<0.0001
Hyperlipidemia	59.6	74.5	<0.0001
Renal insufficiency	77.8	94.5	<0.0001
Cancer screening			
Colon	59.3	56.8	0.19
Skin	60.2	81.1	<0.0001
Prostate	96.5	96.0	0.34
Breast	81.8	83.6	0.29
Cervix	71.4	71.1	0.94
Vaccination			
Influenza	44.1	54.7	p<0.0001
Pneumococcus	59.9	65.3	<0.01
Osteoporosis screening			
Bone densitometry	74.4	88.0	<0.0001

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/screening-for-and-management-of-comorbidities-after-a-nurse-led-program-results-of-a-3-year-longitudinal-study-in-776-established-ra-patients

Abstract Number: 2051

Risk Factors for Cardiovascular Disease Predate the Onset of Symptoms of Rheumatoid Arthritis

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SESSION INFORMATION
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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of developing cardiovascular (CV) comorbidity compared with the general population. Contradictory results concerning CV disease prior to onset of RA have been reported. Of the known CVD risk factors, a more atherogenic lipid profile and smoking have been presented prior to RA onset. In this study, lifestyle factors, lipid levels, presence of hypertension and diabetes were evaluated in individuals prior to onset of symptoms of RA and matched population controls from northern Sweden.

Methods: A nested case-control study was based on population surveys from The Västerbotten Intervention Programme (VIP) and the WHO Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA). Data were collected by a questionnaire (socioeconomic and lifestyle factors), assessments by a nurse (body mass index; BMI, waist and blood pressure), and blood sampling. The registers of patients with RA (ARA criteria) attending the Department of Rheumatology, Umeå was co-analysed with the registers from VIP and MONICA. This study included 547 pre-symptomatic individuals (median age 50.2 years; 372f/175m, median (IQR) predating time 5.0 (7.0) years), and 1641 controls (median age 50.3 years; 1116f/525m). CVD risk factors were defined as: hypertension (systolic ≥140 mmHg and/or diastolic ≥90 mmHg including hypertensive treatment), elevated ApoB/ApoA1 ratio (females ≥0.7, males ≥0.8, including lipid lowering treatment), BMI ≥25, diabetes, and ever smoker.

Results: In conditional logistic regression models elevated ApoB/ApoA1 ratio (OR 1.3 (95% CI 1.0,1.6)), smoking (OR 2.0 (95% CI 1.6,2.5)), BMI≥ 25 (OR 1.3 (95% CI 1.1,1.6)) and diabetes (OR 2.0 (95% CI 1.1,3.7)) were associated with individuals who subsequently developed RA. In women elevated ApoB/ApoA1 (OR 1.4 (95% CI 1.1-1.8)), smoking (OR 1.9 (95% CI 1.1-1.8)), and BMI ≥25 (OR 1.3 (95% CI 1.1-1.7)) were significant for being pre-symptomatic for RA, in men the risk factors were smoking (OR 2.2 (95% CI 1.5-2.5), and diabetes (OR 4.7 (95% CI 1.71-13.1)). Stratifying on the median age, the factor remaining significant for the future RA group in older individuals was smoking (OR 1.7 (95% CI 1.2,2.5)), whereas in the individuals ≤50.2 years the factors were: elevated ApoB/ApoA1 ratio (OR 1.4 (95% CI 1.0,1.9)), BMI ≥25.0 (OR 1.5 (95% CI 1.0-2.0)), and smoking (OR 2.1 (95% CI 1.5,3.0). The pre-symptomatic individuals had significantly higher frequency of risk factors, 42% had ≥3 of these compared with 30% of the matched controls (OR 2.8 (95% CI 1.8, 4.5)). Especially, ACPA positive pre-symptomatic individuals had a high OR for future RA when having ≥3 of the CV risk factors (OR 5.7 (95% CI 2.1-15.3)).

Conclusion: Several of the CV risk factors were present in individuals already years before onset of symptoms of RA. One third of the pre-symptomatic individuals had at least 3 of these factors present. The risk factors for CVD associated with future RA differ between women and men. In younger individuals as well as ACPA

positive individuals the CVD risk factors have a greater impact. These results urge an early CV prevention in patients with RA.

Disclosure: H. Kokkonen, None; **L. Ärlestig**, None; **S. Rantapää-Dahlqvist**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/risk-factors-for-cardiovascular-disease-predate-the-onset-of-symptoms-of-rheumatoid-arthritis

Abstract Number: 2052

Preoperative Timing of Infliximab and Risk of Post-Operative Infection in a Medicare Cohort

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Background/Purpose: Patients taking biologic DMARDs often undergo elective surgery, but data to guide if and when to hold biologics before surgery is limited. This study evaluated whether the timing of infliximab before elective hip or knee arthroplasty was associated with an increased risk of serious infection.

Methods: A retrospective cohort study using U.S. Medicare data evaluated adults with rheumatoid arthritis, inflammatory bowel disease, psoriasis, psoriatic arthritis, or ankylosing spondylitis who received infliximab within 6 months of elective inpatient primary or revision total knee or hip arthroplasty from 2007-2013. Multivariable logistic or Cox regression evaluated associations of infliximab stop time (time between most recent infusion and surgery) with 1) hospitalized infection within 30 days of surgery (excluding urinary infections given relative lack of specificity) using a validated set of discharge diagnoses and 2) rate of prosthetic joint infection (PJI, ICD9 996.66) within 1 year (including within 30 days), adjusting for confounders. Analyses considering the propensity of being in each stop time category were also performed using inverse probability weighting.

Results: Among 4288 surgeries in 3867 patients, the 30 day cumulative incidence of infection was 6.3% (n = 270), with bacteremia, skin/soft tissue infection, and pneumonia the most common infections. In adjusted analyses, infliximab stop time < 4 weeks vs 8-12 weeks was not associated with an increase in infection within 30 days [OR 0.85, 95% CI 0.58,1.25] [Table]. Risk factors for infection included oral glucocorticoid dose > 10mg, age > 80, higher Charlson comorbidity, previous hospitalized infection, more outpatient visits, and year 2007-2009 (vs 2010-2013) [Table]. Over 12 months, the rate of PJI was 2.9 per 100 person-years (n = 105

infections) and was similar for patients who stopped infliximab < 4 weeks vs ≥ 4 weeks before surgery [Figure]. After adjustment, infliximab stop time of < 4 weeks vs 8-12 weeks was not associated with increased rate of PJI [HR 1.01, 95% CI 0.56, 1.82]. Risk factors for PJI included glucocorticoid use, revision surgery, previous hospitalized infection, extra-articular RA, and year 2007-2009. Results were similar in propensity-adjusted analyses.

Conclusion: Administering infliximab within 4 weeks of elective total knee or hip arthroplasty was not associated with a higher risk of short or long-term serious infection compared to withholding infliximab for longer periods of time. In contrast, glucocorticoid use, especially > 10mg per day, was associated with an increased risk of infection. **Table:** Results of multivariable logistic regression analysis for serious infection within 30 days, based on 4283 observations among 3863 patients

	30 day infection	p-value
	OR (95% CI)	
Infliximab pre-operative stop time		
< 4 weeks	0.85 (0.58, 1.25)	0.40
4-8 weeks	0.90 (0.64, 1.26)	0.53
8-12 weeks	Reference	-
12-16 weeks	0.88 (0.47, 1.64)	0.68
≥ 16 weeks	1.01 (0.56, 1.83)	0.98
Glucocorticoid dose		
None	Reference	-
≤ 5mg/day	1.00 (0.68, 1.47)	0.99
5-10mg/day	1.15 (0.78, 1.69)	0.49
> 10mg/day	2.07 (1.29, 3.34)	< 0.01
Non-biologic DMARD use	1.08 (0.83, 1.42)	0.56
Age ≥ 80 years old	1.74 (1.22, 2.48)	< 0.01
Female	1.10 (.080, 1.51)	0.57
Autoimmune Disease		
Rheumatoid Arthritis	Reference	-
Inflammatory Bowel Disease	1.07 (0.70, 1.64)	0.76
Psoriatic arthritis/psoriasis/ankylosing spondylitis	0.98 (0.65, 1.47)	0.93
Charlson score, per 1 point increase	1.08 (1.03, 1.12)	< 0.001
Hospitalizations in the past year		
None	Reference	-
Hospitalization without infection	0.70 (0.48, 1.00)	0.05
Hospitalization with infection	1.88 (1.27, 2.79)	< 0.01
Outpatient visits in the past year, per visit	1.02 (1.01, 1.03)	< 0.01
Calendar year		
2007-2009	Reference	-
2010-2013	0.68 (0.52, 0.87)	< 0.01

Region included in the model but not significant with p > 0.05 and not shown. Tested but not included in the final model after step-wise backward selection with p

> 0.2 (forcing in age, sex, disease type, glucocorticoid use, traditional DMARD use): race, urban, zip code based median household income quintiles, dual eligibility status, skilled nursing facility stay past year, surgery type, osteonecrosis, extra-articular RA, diabetes, COPD/asthma, kidney disease, obesity, previous biologic therapy, infliximab infusion interval, infliximab dose, antibiotic prescription in the past year

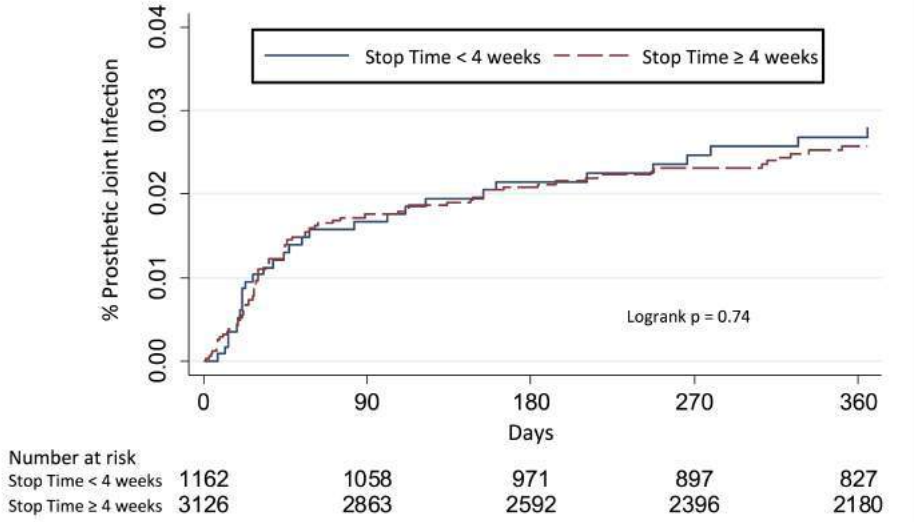

Figure: Kaplan-Meier curves showing prosthetic joint infection within 1 year of surgery by pre-operative infliximab stop time, censoring at death, end of enrollment, subsequent hip or knee arthroplasty, or 1 year

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Abstract Number: 2053

Prosthetic Joint Infection with Staphylococcus Aureus: Recurrence after Surgical Treatment in U.S. Veterans with and without Rheumatoid Arthritis

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Background/Purpose: Studies have shown rheumatoid arthritis (RA) to be a risk factor for development of prosthetic joint infections (PJI) and for worse outcome from PJI compared to non-RA patients, but these findings may not be generalizable to the U.S. veterans. Thus, we aimed to evaluate the risk for recurrence of PJI in RA patients compared with non-RA patients among the veteran population.

Methods: We conducted a retrospective cohort study of all patients admitted for a *S. aureus* PJI and undergoing surgical intervention between 2003 and 2010 at 123 Veterans Affairs Medical Centers (VAMCs). RA was the exposure of interest, identified using the ICD9 code 714.0, and the outcome was recurrent PJI. Co-variates studied were age, sex, methicillin resistance status of *staphylococcal aureus*, site of PJI, time to recurrence of PJI, co-morbidities (i.e., hypertension, diabetes, renal disease, Charlson comorbidity score), steroid use and the type of surgical intervention done for the index PJI. T-test was used to compare continuous variables; Chi-square or Fisher exact test was used to compare dichotomous variables among the RA and non-RA groups. Cox proportional hazards regression model was used to compare the time to recurrent PJI for the RA versus non-RA group.

Results: Of the 731 veterans in our cohort who had a revision surgery for their first *S.aureus* PJI, 91 (12.4%) had RA. PJI patients with RA tended to be older than PJI patients without RA (mean years: 67.6 vs. 65.1, p=0.03). The two groups did not differ based on the time to their first PJI after arthroplasty. The RA patients had a significantly higher prevalence of hypertension. The prevalence of diabetes and renal disease and the Charlson Comorbidity score were similar among the two groups. RA patients tended to have a lower risk for recurrence of PJI compared with non-RA patients; however, this association was not statistically significant (HR=0.78, 95% CI 0.5-1.2, p=0.27). Infection with methicillin-resistant *S.aureus* (MRSA) carried an increased risk of recurrent PJI (HR=1.36, 95% CI 1.03-1.80) compared with MSSA. Two-stage exchange surgery was associated with a lower recurrence rate compared with debridement, antibiotics and implant retention (HR=0.35, 95% CI 0.23-0.53, p<0.001).

Conclusion: : MRSA PJI and the type of surgical intervention were the main predictors of recurrent PJI in a national cohort of veterans with *S. aureus* PJI treated with surgical modality. Our study results are in keeping with reports that two-stage prosthesis revision offers the best chance for recurrence-free 2-year outcomes following PJI. In contrast, our results did not find RA to be a risk factor for worse disease outcome or increased PJI. The strength of our study is the identification of a large cohort of veterans with *S. aureus* PJI with a validated outcome of recurrence. The small number of female patients and the possible higher co-morbidity inherent in our cohort are limitations that affect the generalizability of our findings to non-veteran populations. To summarize, prior RA diagnosis was not associated with recurrence of *S. aureus* PJI compared with non-RA patients in the veteran population.

Disclosure: N. Singh, None; **R. Nair**, None; **M. Goto**, None; **E. Field**, None; **P. Lenert**, None; **R. Carnahan**, None; **M. Schweizer**, None; **E. Perencevich**, None.

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Abstract Number: 2054

Effect of Temporary Methotrexate Discontinuation on Efficacy of Seasonal Influenza Vaccination in Patients with Rheumatoid Arthritis: A Randomized Clinical Trial

Jin Kyun Park[1], Min Ah Lee Lee[2], Kyung Hee Lee[2], Eun Young Lee[1], Yeong Wook Song[3], Yunhee Choi[4], Kevin L. Winthrop[5] and **Eun Bong Lee**[6], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University, Seoul, South Korea, [2]Internal Medicine, Seoul National University College of Medicine, Seoul, Korea, The Republic of, [3]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, South Korea, [4]Division of Medical Statistics, Medical Research Collaborating Center, Seoul National University College of Medicine, Seoul, Korea, The Republic of, [5]Oregon Health and Sciences University, Portland, OR, [6]Seoul National University, Seoul, Korea, Republic of

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at a higher risk of infection due to the underlying immune dysfunction and immune suppression associated with treatment. Thus, vaccination against preventable diseases including influenza is recommended for all RA patients. Methotrexate (MTX), the mainstay of treatment in RA, has been associated with decreased response to influenza vaccination. This study was aimed to investigate whether a temporary discontinuation of MTX improves the vaccine efficacy to seasonal influenza.

Methods: In this single center, randomized, single-blind, open-label, prospective, parallel group intervention study, RA patients with stable MTX dose were randomly assigned to continue MTX (Group 1), to hold MTX for 4 weeks before vaccination (Group 2), to hold MTX for 2 weeks before and for 2 weeks after vaccination (Group 3) and to hold MTX for 4 weeks after vaccination (Group 4). We measured HI antibody titers against each antigen at baseline prior to vaccination with tri-valent seasonal influenza vaccination containing A/California/72009 (H1N1), A/Switzerland/9715293/2013 (H3N2) and B/Phuket/3073/2013 (B-Yamagata), and then again 4 weeks post-vaccination. Satisfactory vaccine response was defined as ¡Ã 4-fold increase in post-vaccination antibody titer relative to baseline. Protective antibody titer was defined as ¡Ã1:40.

Results: The per-protocol population comprised 219 patients (54, 44, 49 and 52 patients for Group 1, 2, 3 and 4, respectively). Prevaccination titer did not differ between the 4 groups. Four weeks after vaccination, Group 3 and Group 4 showed higher increase in antibody titers against H1N1 and H3N2 and B-Yamagata antigens than Group 1. The percentage of the satisfactory vaccine response against H3N2 and B-Yamagata were statistically higher in Group 3 and Group 4 than Group 1. By contrast, Group 2 were comparable to Group 1 in regard to increase in antibody titers and satisfactory vaccine response (Figure). The percentage of patients who showed protective titers for H1N1 and B-Yamagata was prominently increased in Group 3 and 4 as compared with group 1 (Figure). All groups showed high percentage of protective titers for H3N2. The influenza vaccine was well tolerated. RA flares were observed in 4 (7.4%), 6 (13.6%), 9 (18.4%) and 6 (11.5%) patients in Group 1, 2, 3 and 4, respectively, after vaccination.

Conclusion: Temporary discontinuation of MTX improves the immunogenicity of seasonal influenza vaccination

in RA patients. Further studies are needed to determine the duration of MTX discontinuation. **Trial registration:** [www.clinicaltrials.gov, protocol number NCT02748785]

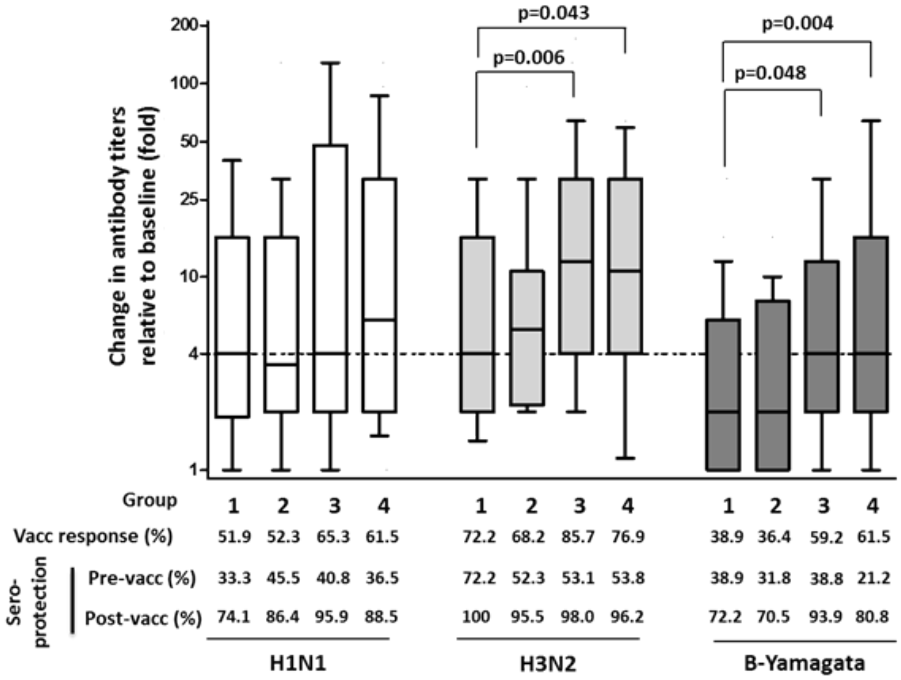

Figure. Fold change in antibody titers relative to baseline and proportion of satisfactory vaccine response. Box represents the interquartile range, the median is represented by the horizontal line. Whiskers represent 10 and 90th percentiles. Horizontal line marks 4 fold increase in antibody titers. Mann-Whitney test used to compare treatment groups. Vacc, vaccination.

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Abstract Number: 2055

Myocardial Abnormalities Are Associated with Corrected QT Interval in Patients with Rheumatoid Arthritis without Cardiac Symptoms Assessed Using Cardiac Magnetic Resonance Imaging

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Background/Purpose: Individuals with rheumatoid arthritis (RA) have two-fold higher risk of sudden death than age- and sex-matched controls without RA. We hypothesized that myocardial abnormalities are associated with corrected QT (QTc) interval in RA. This study aimed to prospectively investigate the association of myocardial abnormalities assessed using cardiac magnetic resonance imaging (CMR) with QTc interval in patients with RA without cardiac symptoms.

Methods: Consecutive patients with RA and control subjects without cardiac symptoms were enrolled. Patients with RA and control subjects with no history and/or clinical findings of systemic hypertension, coronary artery disease, valvular heart disease, atrial fibrillation, diabetes mellitus, and dyslipidemia underwent CMR. Patients with RA were administered non-biologic disease-modifying antirheumatic drugs (nbDMARDs) or biologic DMARDs (bDMARDs). Images were assessed for myocardial late gadolinium enhancement (LGE: an indicator of myocardial fibrosis or myocarditis) and T2-weighted imaging (T2WI: indicator of active inflammation). The 440-ms QTc interval was considered prolonged in this study. We investigated the association of MR-assessed myocardial abnormalities with QTc interval.

Results: We enrolled 70 patients (mean age, 55.2±6.7 years; 88% female). nbDMARDs (26, methotrexate [MTX, 9.7±2.1 mg]; 7, other drugs) and bDMARDs (15, infliximab; 15, tocilizumab; 7, abatacept plus MTX [9.8±1.4 mg]) were administered to 33 and 37 patients with RA, respectively. Myocardial and T2WI abnormalities were seen in 27 (38%) and 7 (10%) patients with RA, respectively. A total of 20 (28%) patients with RA were LGE positive, wherein 7 showed T2WI abnormalities. Simplified disease activity index scores in the LGE-positive group were significantly higher than that in the LGE-negative group (p=0.011). All patients with RA showed normal QTc interval (412.0±20.5 ms). However, the QTc interval in the LGE-positive group was significant higher than that in the LGE-negative group (431.1±20.1 vs 408.2±10.5 ms; p=0.001). Myocardial abnormalities were associated with QTc interval (ρ=0.356, p=0.014). The QTc interval in the bDMARDs group was significantly lower than that in the nbDMARDs group (p=0.001). Other RA characteristics such as disease duration, autoantibody status, and cardiovascular risk factors were not associated with myocardial abnormalities and QTc interval. Receiver operating characteristic analysis showed that the QTc interval reliably detected myocardial abnormalities (area under the curve 0.898; 95% confidence interval, 0.830–0.900). Considering patients with RA and normal QTc interval and using 420-ms cut-off value, the sensitivity and specificity for detecting myocardial abnormalities were 91% and 70%, respectively.

Conclusion: Myocardial abnormalities may contribute to the QTc interval. We should consider the possibility of subclinical cardiac involvements in RA cases even in those with normal QTc interval.

Abstract Number: 2056

Choroid Plexus Infiltrates in Lupus Model (MRL/lpr) Mice Represent Tertiary Lymphoid Structures, Shedding Light on the Immunological Mechanisms of Neuropsychiatric Lupus

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Background/Purpose: MRL/lpr mice develop an overt neuropsychiatric phenotype including depression and cognitive dysfunction, similar to diffuse neuropsychiatric manifestations of human lupus. Additionally, MRL/lpr mice display a robust infiltration of predominately lymphocytes through the choroid plexus (CP) of the central nervous system. Radiological studies and evaluation of pathological tissue has provided evidence to suggest CP involvement in human lupus as well. There has been, however, little evaluation of the functional features of these infiltrating cells, or their potential contribution to neuropsychiatric disease. Localized tertiary lymphoid structures have been described in various neoplastic and autoimmune models, including the kidneys and peritoneum of spontaneous and inducible lupus models. Given the immunoprivileged nature of the central nervous system and recent studies describing the critical role of the CP in immune surveillance, we evaluated 3D reconstructions of cellular infiltrates, and now hypothesize that the CP infiltrates in MRL/lpr mice consist of tertiary lymphoid structures (including ectopic germinal centers), induced in response to local inflammatory signals.

Methods: We evaluated MRL/lpr and control MRL/+ mice at several time points, beginning at 5 weeks of age. Expression of lymphotoxin-β and CXCL13 were evaluated by RT-qPCR at 8, 12 and 16 weeks of age. Brain tissue was immunofluorescently stained at 5, 8, 12 and 16 weeks of age to determine the phenotypical characteristics of infiltrating cells, as well as the kinetics of their infiltration. High resolution three dimensional reconstructions were generated by confocal microscopy, and both scanning and transmission electron microscopy were used to study regional compartmentalization and local intercellular interactions of infiltrating cells.

Results: We found dramatically increased lymphotoxin-β and CXCL13, key molecules in lymphoid follicle organization, in the CP of MRL/lpr mice. Lymphotoxin-β and CXCL13 were upregulated by 8 weeks of age, well before any significant cellular infiltration was present. Upon detailed examination, we found organizational and phenotypic features of lymphoid follicles, including structural reticular fibers and type I collagen cords, as well as clusters of proliferating (PCNA+) T and B cells, organized according to local chemokine gradients. Furthermore, we identified phenotypically distinct groups of B-Cells (e.g. IgM^+, $GL7^+$, $BCL6^+$) and T-Cells (e.g. $FoxP3^+$, $BCL6^+$, GL7+), as well as follicular dendritic cells. Finally, we found aggregates of $CD138^+$plasma cells, in localized regions sharply demarcated from naïve B-cells.

Conclusion: Based on the structural, organizational and phenotypical characteristics of the MRL/lpr CP

infiltrate, we conclude that the CP of MRL/lpr mice contain tertiary lymphoid structures with germinal center activity, the pathogenicity of which, including production of neuropathic autoantibodies, remains to be determined.

Disclosure: A. Stock, None; **S. Gelb**, None; **A. Ben-Zvi**, None; **C. Putterman**, None.

Abstract Number: 2057

TLR-7-Mediated Lupus Nephritis Flares Are Independent of Type I Interferon Signaling

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Animal Models

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by the formation of autoantibodies, immune complex deposition, elevated production of type I interferons (IFNs), and inflammatory-mediated multi-organ damage. Lupus nephritis (LN) flares contribute to high mortality and morbidity among patients. Activation of endosomal toll-like receptor (TLR) 7 is an important trigger of LN activity. Stimulation of TLR7 leads to type I interferon (IFN) production and nuclear factor kappaB (NFkB) activation. Type I IFNs are important for TLR7-mediated immunoproliferation, but their role in TLR7-mediated nephritis has not been examined. This study explores the novel hypothesis that TLR7 promotion of lupus nephritis is independent of type I IFNs.

Methods: To address this hypothesis, we use the lupus prone NZM 2328 and iNZM (NZM2328 lacking a functional type I IFN receptor) murine models. In order to induce LN flares, we administered 100µg of R848 (TLR 7 agonist) epicutaneously to the right ear or intraperitoneally (IP) to 10-week old female NZM2328 and iNZM mice thrice weekly. Serum was collected from mice every 2 weeks and urine collected every week. Mice were harvested at 14 days or at LN onset. Double stranded DNA antibodies were quantified via ELISA. Immunofluorescence for C3 and IgG was performed on kidney tissue to examine the extent of immune complex deposition. Flow cytometry was used to characterize the immune cell populations in the kidney for both strains. Real-time qPCR was performed to examine gene expression in the kidney following R848 treatment.

Results: Lymphoproliferative response to R848 was absent in iNZM mice, consistent with previous reports. Notably, both NZM2328 and iNZM mice exhibit a decline in survival after 3 to 4 weeks of R848 treatment. This

decline was significantly more robust with epicutaneous vs. IP injection of R848. Both NZM and iNZM mice demonstrated equivalent acceleration of lupus characteristics including: rise in dsDNA antibodies, increased kidney immune complex deposition, and development of proteinuria. They also demonstrated infiltration of the kidney by macrophages and dendritic cells 2 weeks into treatment. Transcriptional changes within the kidney identified upregulation of inflammasome-associated genes as a shared response in both NZM2328 and iNZM mice after R848 treatment.

Conclusion: The development of TLR7-mediated lupus nephritis flares occurs independent of type I IFN signaling. Further investigation into the role of the inflammasome in mediating TLR7-driven lupus is key to development of novel therapies which may prevent lupus nephritis flare induction.

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Abstract Number: 2058

Ectonucleotidase-Mediated Protection of Lupus Mice from Exaggerated Immune Responses and Arterial Vasculopathy

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Background/Purpose: CD39 and CD73 are so-called ectonucleotidases, surface enzymes expressed by leukocytes and endothelial cells that jut into the extracellular space. There, they mediate the step-wise conversion of the autocrine and paracrine danger signal ATP into anti-inflammatory adenosine. Given the established role of a cell's "purinergic halo" in maintenance of immune and vascular homeostasis, we hypothesized that ectonucleotidases might play a protective role in lupus.

Methods: Lupus can be modeled by intraperitoneal administration of pristane to mice. Cardinal features of lupus develop over 6-9 months, including anti-ribonucleoprotein (RNP) antibody production and immune-complex nephritis. In this study, we administered either pristane or saline to three groups of female C57BL/6 mice: wild-type (WT), $CD39^{-/-}$, and $CD73^{-/-}$. After 36 weeks, we characterized serum autoantibodies, splenocyte activation/polarization, neutrophil responses, proteinuria, and endothelial function.

Results: As both CD39 and CD73 have well-recognized roles in regulatory T cell function, we first assessed adaptive immune responses. In the T-cell compartment, deficiency of either ectonucleotidase led to a 3-fold expansion of autoimmune-promoting T_H17 (but not T_H1) cells. $CD39^{-/-}$ mice developed marked spenomegaly in

response to pristane. Activated B cells and plasma cells were expanded in CD73$^{-/-}$ mice. Regarding serum autoantibodies, the CD73$^{-/-}$ mice in particular showed exaggerated anti-RNP production in response to pristane (a 10-fold increase) as compared to WT. As purinergic signaling may also regulate innate immune cells, we assessed an effector function of emerging importance in lupus, neutrophil extracellular trap (NET) release. NETs are pro-inflammatory webs of chromatin extruded from neutrophils. CD73 deficiency resulted in relative neutrophilia in response to pristane, while deficiency of either ectonucleotidase led to exaggerated NET release (a 2-fold increase) as compared to WT. Further, CD73$^{-/-}$ mice demonstrated heightened levels of plasma cell-free DNA, a surrogate for circulating NETs. Both nephritis and accelerated arterial disease are major causes of morbidity in lupus. Urine protein was elevated in both pristane-treated CD39$^{-/-}$ and CD73$^{-/-}$ mice as compared to pristane-treated WT. The administration of pristane to WT mice triggered only subtle dysfunction of the arterial endothelium. In contrast, both CD39$^{-/-}$ and CD73$^{-/-}$ mice demonstrated striking dysfunction in response to pristane. This endothelial dysfunction could be rescued by treatment with superoxide dismutase, suggesting a role for oxidative stress in driving the vasculopathy.

Conclusion: These data are the first to link ectonucleotidases with lupus autoimmunity and vascular disease. In particular, they newly implicate purinergic signaling in the regulation of lupus T-cell responses and NET release, and demonstrate that ectonucleotidases protect against endothelial dysfunction in lupus by suppressing oxidative stress. New therapeutic strategies may harness purinergic signaling to limit the damage inflicted by lupus upon organs and blood vessels.

Disclosure: J. S. Knight, None; **L. F. Mazza**, None; **S. Yalavarthi**, None; **Y. Kanthi**, None; **D. J. Pinsky**, None.

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Abstract Number: 2059

Serine/Arginine-Rich Splicing Factor 1 (SRSF1) Is a Novel Factor in T Cell Homeostasis and Its Selective Loss in T Cells Causes Autoimmunity and Lupus-like Nephritis

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Background/Purpose: T cells from patients with systemic lupus erythematosus (SLE) express reduced amounts of the critical CD3 zeta signaling chain, and produce low levels of the vital cytokine interleukin (IL)-2. We used

a discovery approach namely mass spectrometry analysis of proteins “pulled-down” by a CD3 zeta mRNA-defined oligonucleotide, and identified the splicing regulator serine arginine-rich splicing factor 1 (SRSF1). We showed that SRSF1 promotes generation of a full-length CD3 zeta transcript over a short spliced unstable isoform to promote normal expression of CD3 zeta chain in human T cells. We found that SRSF1 expression levels are decreased in SLE T cells, more so in patients with worse disease. We further showed that force expression of SRSF1 into SLE T cells rescues IL-2 production. While these findings suggest that SRSF1 deficiency is important in SLE T cell dysfunction, it remains unknown whether SRSF1 contributes to immune-mediated disease. To this end, in this study, we generated mice with a T cell-restricted deletion of SRSF1 to evaluate the mechanistic role of SRSF1 in T cell dysfunction and the development of immune-mediated disease *in vivo*.

Methods: *Srsf1* “floxed” mice were crossed with *Lck.Cre* (*distal promoter)* transgenic mice to delete SRSF1 specifically in mature T cells and generate the T cell *Srsf1* conditional knockout (*Srsf1*-cko) mice. Mice were euthanized at 10-16 weeks of age, or aged to >1 year. Central (thymus) and peripheral (spleen, lymph nodes) lymphoid organs were analyzed for immune cell phenotype and function by flow cytometry, enzyme-linked immunosorbent assay (ELISA) and intracellular staining. Serum and urine were collected at monthly intervals to assess autoantibody levels and proteinuria respectively. Non-lymphoid (lung, liver, kidney) tissues were fixed, sectioned and stained with hematoxylin and eosin to evaluate histopathology.

Results: *Srsf1*-cko mice develop peripheral T cell lymphopenia, with a striking reduction in the CD8 compartment. T cells exhibit an activated phenotype and produce increased amounts of IFN-γ and IL-17 but lower amounts of IL-2 upon e*x vivo* stimulation. The *Srsf1*-cko mice develop increased levels of autoantibodies, and exhibit increased proteinuria compared to control mice. Kidney histopathology shows evidence of glomerular damage with glomerular hyperproliferation, glomerular capillary hyperplasia, and interstitial infiltration of mononuclear cells. These results indicate that lack of SRSF1 leads to an aberrant T cell homeostasis, aberrant T cell activation, with increased inflammatory cytokine production, autoantibody development and kidney damage.

Conclusion: SRSF1 is a novel regulator of T cell homeostasis and function, and its deficiency leads to autoimmunity and lupus-like nephritis. Therefore, deficiency of SRSF1 in T cells may represent a molecular defect that contributes to the pathogenesis of systemic autoimmune disease.

Disclosure: V. R. Moulton, None; **H. Li**, None; **M. W. Mosho**, None; **A. R. Gillooly**, None; **M. L. Keane**, None; **G. C. Tsokos**, None.

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Abstract Number: 2060

Bim Suppresses the Development of SLE By Limiting Macrophage Inflammatory Responses

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Background/Purpose: The Bcl-2 family guards the mitochondrial apoptotic pathway. Among numerous Bcl-2 antagonists, only the loss of Bim in mice leads to the development of SLE-like disease, suggesting Bim's unique status that exerts dominance in several pathways that are vital for the development of SLE. However, the role that Bim plays in macrophage functions and relevance to SLE is unknown.

Methods: We generated mice lacking Bim specifically in macrophages ($Cre^{LysM}Bim^{fl/fl}$) and assessed mice at 8 months of age for characterization of SLE-like disease. Macrophage turnover/proliferation and activation were examined *in vivo* using flow cytometric analyses. To better understand the role of Bim in regulating transcriptional profile in kidney macrophages, RNA-seq analysis was performed on sorted macrophages from $Cre^{LysM}Bim^{fl/fl}$ and $Bim^{fl/fl}$ mice.

Results: $Cre^{LysM}Bim^{fl/fl}$ mice displayed splenomegaly, lymphadenopathy, hyperglobulinemia, IC deposition in the kidney, proteinuria, GN, and early mortality as compared to $Bim^{fl/fl}$ and mice lacking Bim in either lymphocyte compartments. $Cre^{LysM}Bim^{fl/fl}$ mice were lack of splenic marginal zone macrophages (MZMs) and marginal zone B cells (MZ-B cells), which is also evident in lupus patients. Bim functions in macrophages are independent of its role in apoptosis as there were no differences in the rate of EdU incorporation in macrophages from $Bim^{fl/fl}$ and $Cre^{LysM}Bim^{fl/fl}$ mice. TLRs, the well-known initiators of autoimmune disease, are not required for the break in tolerance, as mice lacking MyD88 or TRIF in $Cre^{LysM}Bim^{fl/fl}$ mice ($MyD88^{fl/fl}$ $Cre^{LysM}Bim^{fl/fl}$ and $TRIF^{-/-}$ $Cre^{LysM}Bim^{fl/fl}$) developed systemic autoimmunity similar to $Cre^{LysM}Bim^{fl/fl}$ mice. However, $TRIF^{-/-}Cre^{LysM}Bim^{fl/fl}$ mice did not develop end-stage GN. Consistent with these data, $Cre^{LysM}Bim^{fl/fl}$ mice showed increased numbers of kidney macrophages, while $TRIF^{-/-}$ $Cre^{LysM}Bim^{fl/fl}$ mice exhibited significantly reduced numbers as identified by multi-parameter flow cytometry. To better understand the effect of Bim deletion in kidney macrophages *in vivo*, we utilized RNA-seq for FACSorted kidney macrophages from young and old mice. Exploratory analysis via principal component analysis (PCA) revealed that Bim deletion affected the transcriptional profile of kidney macrophages. We were able to identify unique cellular processes up-regulated in $Cre^{LysM}Bim^{fl/fl}$ kidney macrophages using pairwise GO processes analyses. We also identified that kidney macrophages from $Cre^{LysM}Bim^{fl/fl}$ mice significantly up-regulate *ifnar1*, the receptor for IFNα and IFNβ.

Conclusion: The expression of Bim in macrophages is sufficient to inhibit SLE-like pathogenesis. Bim controls macrophage functions independent of its role in apoptosis which challenges the conventional dogma that Bim's role in autoimmunity is to prevent the escape of autoreactive lymphocytes from apoptosis. We provide data to identify the role of kidney macrophages throughout SLE-like disease development in the context of Bim deficiency. The discovery of Bim-regulated transcriptome in kidney macrophages are crucial for translational studies leading to the development of new targets for SLE.

Disclosure: F. Tsai, None; **C. Cuda**, None; **H. R. Perlman**, None; **P. J. Homan**, None; **S. Dominguez**, None; **A. Shaffer**, None; **G. K. Haines III**, None; **J. Hutcheson**, None.

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Abstract Number: 2061

Successful Treatment of Murine Lupus Nephritis with Helminths Related Tuftsin-Phosphorylcholine Compound and Its Effect on the Microbiota

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Background/Purpose: , In areas where helminths infections are common, autoimmune diseases are rare. Treatment with helminthes and their ova, improved clinical findings of inflammatory bowel disease, multiple sclerosis and rheumatoid-arthritis. The immunomodulatory functions of some helminths were attributed to the phosphorylcholine (PC) moiety. We aimed to decipher the tolerogenic potential of Tuftsin-PC (TPC) compound in mice genetically prone to develop lupus when the disease was already established. In addition we analyzed the microbiota, assuming that it may be affected by TPC treatment on lupus development.

Methods: , Lupus prone NZBXW/F1 mice received subcutaneously TPC (5 mg/1 ml), 3 times a week starting at 24 weeks of age, when proteinuria showed 10 mg/dl. At this point feces were collected weekly. Autoantibodies were tested by ELISA, cytokines secretion by splenocytes in-vitro using DuoSet ELISA, T-regulatory-cells by FACS. Glomerulonephritis was addressed by detection of proteinuria, and immunoglobulin complex deposition in the mesangium of the kidneys of the mice by immunofluorescence. Stools from the mice were collected every 3 days for microbiome analyses. DNA was extracted from the stools and then sequenced using Illumina Miseq platform. Data analysis was performed using QIIME.

Results: Our results show that TPC treatment attenuated the development of glomerulonephritis in lupus prone mice, manifested by reduced proteinuria and immunoglobulin deposition in the kidney mesangium. TPC also increased the expression of IL-10 ($p < 0.001$), and inhibited the production of IFNg , IL-1b and IL-17 ($p < 0.03$). TPC significantly expanded $CD4^+CD25^+FOXP3^+$ T-regulatory cells (Tregs) phenotype in the treated mice. The microbiota analyses showed that TPC exhibited a marked depletion of *Akkermansia* (specifically muciniphila species) and higher abundance of *Odoribacter* compared to PBS treated mice, which correlated to proteinuria

levels. Generally, high protein secretions correlated with an increased abundance of four bacteria genera; *Akkermansia* AF12, S24-7, *Bacteroides*, and one bacteria order *Clostridiales*. High protein levels were correlated also with decreased levels of thirty three additional otus, with the *Odoribacter* genus among them.

Conclusion: Our data indicate that TPC treatment inhibits lupus nephritis development in genetically lupus prone mice, attenuates pro-inflammatory cytokines and enhance anti-inflammatory IL-10 expression, as well as Tregs expansion. The results propose harnessing novel natural therapy for lupus patients. In addition our results show that TPC significantly alters the microbiota composition which correlated with decreased protein levels in the urine.

Disclosure: Y. Shoenfeld, None; **T. Bashi**, None; **H. Gershon**, None; **O. Givol**, None; **A. Volkov**, None; **I. Barshack**, None; **M. Fridkin**, None; **M. Blank**, None; **O. Koren**, None.

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Abstract Number: 2062

Increased Expression of Response Gene to Complement-32 in Kidney Biopsies from Patients with Lupus Nephritis

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Background/Purpose: RGC (Response Gene to Complement)-32 is a cell cycle regulator widely expressed in normal tissues including brain, kidney, spleen, thymus, multiple tumors and in a variety of cell lines. RGC-32 is localized in the cytoplasm and translocates to the nucleus upon upregulation by complement activation, growth factors and cytokines. Depending on the cell type, physiological or pathological conditions, RGC-32 can stimulate cell growth through increased p34CDC2 kinase activity and Akt phosphorylation or suppress it via arrest in mitotic progression. Previous studies by our group have shown that RGC-32 is critical for murine Th17 cell differentiation in vitro and in vivo. Initially identified in rat oligodendrocytes in response to sublytic C5b-9 complex, RGC-32 is induced by TGFβ in fibroblasts and human proximal tubular epithelial cells (PTEC) and mediates TGFβ dependent profibrotic pathways that contribute to renal fibrosis. RGC-32 expression has been

described in tubules of normal human kidneys and its upregulation was reported in tubules from patients with IgA nephropathy. The expression patterns and function of RGC-32 in lupus nephritis (LN) have not yet been investigated.

Methods: In situ expression and localization of RGC-32 was assessed by immunohistochemistry in kidney biopsies from 25 lupus patients with proliferative lupus nephritis and 11 patients with other nephropathies (IgA nephropathy, minimal change disease, ANCA-associated glomerulonephritis, nephrosclerosis, acute tubular necrosis). In vitro, the expression of RGC-32 in human PTEC cells was assessed by Flow cytometry, Western blot and RT-PCR in the presence or absence of cytokines with known nephritogenic potential such as IL-1, TNFα, IFNγ and TGFβ.

Results: Consistent with the staining distribution reported in normal kidneys, RGC-32 immunostaining was predominant in proximal and distal tubules and was detected in a focal or diffuse pattern. Tubular mean staining intensity was significantly higher in SLE than in non-SLE specimens (2.0±0.23 vs 1.30±0.49; p=0.04) and was noted both in areas of normal appearing as well as damaged tubules. RGC-32 expression was also detected in glomeruli and in inflammatory cells in the interstitium of LN biopsies and colocalized with CD4+ T cells and CD68+ macrophages, respectively. Staining intensity was significantly higher in glomeruli and interstitium of LN specimens compared to disease controls (2.4±1.4 vs.1.6±0.8 and 1.8± 0.9 vs. 0.96±0.4 respectively) and correlated with the activity (r=0.4), chronicity (r=0.5) and interstitial fibrosis scores (r=0.5). In vitro, RGC- 32 mRNA and protein expression was upregulated in PTEC by nephritogenic cytokines including IL-1 (7.8 fold), TNFα (5 fold), TGFβ (3.1 fold) and to a lesser extent by IFNγ (2.1 fold).

Conclusion: RGC-32 expression is increased in glomeruli and tubulointerstitium from patients with lupus nephritis. Upregulation of RGC-32 is mediated by proinflammatory cytokines and may play pathogenetic role in organ damage in SLE by promoting manifestations of progressive renal disease such as interstitial fibrosis.

Disclosure: J. Yip, None; **V. Nguyen**, None; **A. Tatomir**, None; **A. Mekala**, None; **D. Boodhou**, None; **H. Rus**, None; **C. Drachenberg**, None; **V. Rus**, None.

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Abstract Number: 2063

Identification of Microrna Predictive of Outcome in Lupus Nephritis

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Background/Purpose: High dose corticosteroids such as cyclophosphamide are commonly used to treat lupus nephritis (LN). Although effective in preventing end stage renal disease (ESRD) in most cases, significant long-term side effects such as infections, increased risk of malignancy, and infertility are common and are related to the duration of therapy or the cumulative dose of medications. These side effects could be mitigated via a personalized medicine approach, if an individual's response to treatment could be predicted. However there are currently no markers that can reliably determine response or refractoriness to treatment at an individual level. MicroRNAs (miRNAs), a class of small, non-coding RNAs responsible for post-transcriptional regulation, have been shown to have altered expression levels in a variety of diseases suggesting their potential use as diagnostic, prognostic, and treatment response biomarkers. We propose miRNAs can be appropriate predictive markers for response to cyclophosphamide treatment.

Methods: <span">RNA was isolated and analyzed via TaqMan® Array MicroRNA 384-well Cards, from formalin-fixed paraffin embedded (FFPE) renal biopsies of two unique cohorts of patients with LN who were subsequently treated with cyclophosphamide and had at least 2 years of follow up history. Patients who responded to cyclophosphamide based on urinalysis criteria of no active urinary sediments, no RBCs and/or WBCs in urine, and proteinuria less than 1 gram were classified as responders while those that did not fit the criteria were classified as non-responders. The first cohort was composed of 32 patients with 17 responders and 15 non-responders, while the second cohort (the validation cohort) contained 39 patients with 22 responders and 17 non-responders. Significantly differentially expressed miRNAs, determined via $2^{-\Delta\Delta Ct}$method, from the first cohort were validated by the second cohort. Potential target mRNAs for candidate miRNAs were determined through miRDB, TarBase, RNA22, and Ingenuity Pathway Analysis (IPA) databases. Predicted targets were further analyzed for disease activity and nephrotoxicity through IPA.

Results: Six significantly up-regulated miRNAs, hsa-miR-30c-2-3p, hsa-miR-29b-1-5p, hsa-miR-195-3p, hsa-miR-424-3p, hsa-miR-1260a, and hsa-miR-1248 were found in responders. Analysis of miRNA targets generated by four prediction algorithms revealed immunological disease specificity and renal involvement.

Conclusion: These miRNAs may act as prognostic markers of renal outcomes and treatment response, which can establish a more personalized treatment of lupus nephritis in the future. As our next step we will attempt further validation of these miRNAs in serum and urine of patients with lupus nephritis.

Disclosure: M. Hadavand, None; **N. Binmadi**, None; **H. Zhou**, None; **M. Tandon**, None; **S. Hasni**, None; **I. Alevizos**, None.

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Abstract Number: 2064

Blood and Kidney Molecular Profiles Distinguish Subjects with Lupus Nephritis from Other Kidney Disorders

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Background/Purpose: Kidney biopsy remains the gold standard for diagnosis and staging of Lupus Nephritis (LN). Although kidney biopsies are commonly performed in the clinical setting, they carry morbidity. Identification of reliable biomarkers in the blood that correlate with pathological changes in the kidney of LN patients may allow LN diagnosis and staging with only a minimally-invasive drawing of blood.. To that end, we performed a comparative transcriptomic and proteomic biomarker analysis of blood samples and kidney biopsies from LN patients compared to samples from healthy controls and non-lupus kidney disorders. We evaluated whether a molecular signature could identify LN patients versus the comparator disease states and if that signature was similar between the kidney and blood.

Methods: Paired-end strand specific RNASeq was used for gene expression profiling of blood and kidney biopsies from healthy subjects (n=12 and 5 respectively), Lupus Nephritis (10,7) and other kidney diseases such as Diabetic Nephropathy (DN) (10,5), Hypertension (HT) (11,4), Minimal Change (MC) (6,3), and Membranous (MB) (4,4) collected under informed consent. For each sample, approximately 100 million reads were sequenced for a total of ~50 million fragments. Serum collected from these subjects was profiled for autoantibody specificities using ProtoArray®.

Results: RNA-Seq analysis from blood samples revealed a signature enriched in IFN-inducible transcripts unique in the LN patients when compared to the blood transcriptomes from healthy controls or patients with DN, HT, MC, or MB. Remarkably, signatures of "kidney damage" pathways were also identifiable in the blood of LN subjects. Increased expression of the "Complement System" pathway was observed in blood across 3 of the 5 diseases tested (LN,DN,HT). RNASeq analysis of kidney biopsies showed a more homogeneous landscape across the different diseases, with a core of 50 common genes related to kidney injury pathways. Most of the LN kidney biopsy samples exhibited an upregulation of IFN signature genes, that also correlated with blood IFN signatures in the same patients. Broad autoantibody analysis of serum samples indicated that LN patients exhibited vast upregulation of autoantibodies versus healthy controls, in stark contrast to the other kidney diseases examined where autoantibodies were found to be down-modulated (DN, MC, MB).

Conclusion: In this study, we performed blood and kidney transcriptomics and broad serum autoantibody profiling comparing LN patients to patients with other kidney diseases. Pathway analysis of differentially expressed transcripts indicated a unique profile in the blood and kidney biopsies of LN patients in comparison with other kidney diseases. We were able to identify an interferon signature in both the blood and kidney biopsies from LN patients, which correlated between the two tissues. We also identified a kidney damage signature in the blood of LN patients. Further validation studies are needed to determine the utility of using whole blood biomarker testing analysis to replace conventional kidney biopsies in subjects with LN.

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T. Parker, None; **D. Levine**, None; **S. V. Seshan**, None; **A. Gong**, None; **T. Sato**, Janssen Research and Development, LLC, 3; **J. Benson**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1.

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Abstract Number: 2065

Platelet FcγRIIa Polymorphism H131R Associates with Subclinical Atherosclerosis and Increased Platelet Activity in SLE

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Background/Purpose: Systemic lupus erythematosus (SLE) is a complex autoimmune disease characterized by heterogeneity of presentation, an undulating course, and elevated risk for premature cardiovascular disease. Platelets have been understudied as a relevant contributor. Yet, these cells, which contain transcripts and the necessary molecular machinery to conduct translation, are intercellular regulators of inflammation and immune activation and play a key role in atherothrombosis. Platelets express low affinity type 2 receptors (FcγRIIA) whose ligand is the Fc portion of IgG. A single amino acid substitution, H131R, in the extracellular ligand binding domain increases the affinity for IgG and may account for individual variation in platelet activation, specifically an increase of function. Accordingly, this study addressed the hypothesis that FcγRIIA genotype associates with preclinical atherosclerosis and platelet hyperreactivity.

Methods: Genotyping at rs1801274 (allelic discrimination, HWE P=NS) was performed in 71 SLE patients and 30 healthy controls. In 49 of the SLE patients and 30 healthy controls, carotid ultrasound for plaque (≥50% increase over background IMT in any arterial segment); levels of soluble E-selectin as a proxy of endothelial cell activation; and C3, C4 to reflect complement activation were assessed. In 22 SLE patients, monocyte-platelet (MPA) and leukocyte-platelet aggregates (LPA), and light transmission aggregometry (LTA) in response to submaximal concentrations of collagen and arachidonic acid were evaluated.

Results: Overall genotyping for FcγRIIA revealed 43 SLE patients carrying at least one copy of the variant allele and 28 patients who were homozygous for the ancestral allele. For the 49 with IMT, carotid plaque was reported in 22. A significant enrichment of carotid plaque was identified in patients with a variant compared to those who were homozygous ancestral (58% vs 25%, p=0.039). In contrast, among 30 healthy controls, the presence of carotid plaque was not associated with the variant or ancestral genotype (15% vs 15%). Soluble E-selectin (mean + 2SD, shown as dichotomous being above normal controls) was significantly increased in those

patients with the variant vs ancestral (64% vs 23%, p=0.013). Complement levels, a proxy of circulating immune complexes, were lower in patients with the variant vs ancestral (64% vs 40%). With regard to platelet reactivity, among 22 SLE subjects evaluated, there was a significant increase in MPA and LPA (above controls, mean + 2SD) in those carrying at least one variant compared to the ancestral group (86% vs 37%, p=0.02 and 46% vs 12%, p=0.05, respectively). Platelet aggregation was more robust for those patients with the variant vs ancestral in response to 160 uM arachidonic acid and 1 ug/mL collagen (47% vs 19% and 47% vs 14%, respectively).

Conclusion: These data suggest a model in which an FcγRIIA polymorphism associates with preclinical atherosclerosis and confers increased platelet activity in the setting of SLE, a disease characterized by circulating immune complexes.

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Anti-Ds-DNA Antibodies Regulate Atherothrombosis in Systemic Lupus Erythematosus through the Induction of Netosis, the Prothrombotic and Proinflammatory Activities of Monocytes and the Endothelial Activation

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Background/Purpose: The role of anti-dsDNA in the pathogenesis of the systemic lupus erythematosus (SLE) has been clearly established. However, the influence of these autoantibodies in the atherothrombotic status of SLE patients has not yet been evaluated. Aim: 1. To analyse in vivo the involvement of anti-dsDNA antibodies in the development of CVD in SLE patients. 2. To evaluate in vitro the mechanisms underlying the effects of anti-dsDNA antibodies in these processes.

Methods: The study was conducted in 50 SLE patients and 38 healthy donors. Endothelial function was assessed by measuring the post-occlusive hyperaemia using Laser-Doppler. Various markers of oxidative stress,

inflammatory cytokines, prothrombotic mediators and NETosis, were quantified in purified leukocytes and plasma from SLE patients and controls. Activation of intracellular pathways was analyzed in monocytes using pathscan intracellular signaling array. In vitro, purified neutrophils, monocytes and lymphocytes from healthy donors and endothelial cells (HUVEC) were treated separately and in a trans-well co-culture system with anti-dsDNA antibodies isolated from the serum of SLE patients. Then, markers of inflammation, thrombosis, oxidative stress and NETosis were evaluated by flow cytometry (protein) and RT-PCR (mRNA).

Results: SLE patients showed impaired micro-vascular endothelial function (reduction of hyperaemia post occlusion area) and altered expression levels of pro-inflammatory proteins (IL6, IL8, MCP-1 and PCR), prothrombotic molecules (TF), oxidative stress markers (peroxides and mitochondrial membrane potential) and netosis-related molecules (elastase, myeloperoxidase and free-DNA). Monocytes from anti-dsDNA-positive SLE patients showed activation of various intracellular pathways (ErK, STAT-3, p38, JNK and GSK). Association studies demonstrated that molecules related to inflammation and thrombosis, endothelial dysfunction, oxidative status and netosis were linked to the occurrence of thrombotic events, as well as to the presence of anti-dsDNA antibodies. In vitro treatment of purified leukocytes with anti-dsDNA antibodies promoted an increase in the production of NETosis, levels of peroxides and percentage of cells with altered mitochondrial membrane potential, as well as enlarged expression of a number of proinflammatory and prothrombotic molecules. In vitro treatment of HUVEC with anti-dsDNA antibodies promoted an increase in endothelial activation molecules (ICAM-1, VCAM-1 and E-selectin). All those effects on leukocyte subtypes and endothelial cells were even more pronounced when they were cocultured.

Conclusion: 1. Positivity for anti-dsDNA antibodies is linked to an increased pro-atherothrombotic status in SLE patients. 2. Anti-dsDNA antibodies, in vitro, promote NETosis, modulate the expression of molecules related to inflammation and thrombosis, and induce endothelial activation. Together, that data suggest the involvement of such autoantibodies on atherothrombosis development in SLE. Acknowledgements: Supported by CTS-7940, PI15/01333 Disclosure of Interest: None declared

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Abstract Number: 2067

Dermal Fibroblasts from Patients with Lupus Nephritis Express an Anti-Fibrotic Transcriptome

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Background/Purpose: The premise of this study is that the impact of renal injury in lupus nephritis is widespread with consequences to resident cells in other tissue beds, such as non-sun exposed non-lesional skin. Reflection of a relevant pathway in renal tissue by a more readily accessible compartment would be an advance. Single-cell transcriptional states may provide a framework for understanding how in vivo biological function emerges from complex cell ensembles.

Methods: As an approved nested study within the SLE Accelerated Medicines Partnership (AMP), single cell RNAseq was performed on cell suspensions prepared from ~2 mm punch biopsies of non-lesional non-sun exposed skin from the buttocks of 3 SLE patients with proteinuria and known ISN/RPS Class and 3 healthy controls. Libraries were prepared on the Fluidigm C1 platform followed by sequencing on an Illumina HiSeq 2500. Differential expression was used to assign in vivo cell-type compositions through unsupervised sampling and modeling of transcriptional states in single cells. We generated 36 single-cell data sets with on average 852 genes/cell and 37% of reads mapping to the reference genome. Data are expressed as log2 transcripts per million.

Results: Based on expression of COL1A1, COL1A2, COL3A1, MFAP5 and MFAP4, assignments yielded 12 fibroblasts from 3 patients. From the one Class II subject there were 5 single cell transcriptomes. The other 2 subjects (1 Class IV,V; 1 Class III,V) yielded 7 single cell transcriptomes. From the 3 controls, there were 22 transcriptomes. In the aggregate data for controls, the top one thousand genes were used for a cluster analysis of categories in the DAVID annotation. In the controls, a prominent cluster with an enrichment score of 5.60, in the extracellular matrix category, was significantly represented in the set (P=3.77E-12). The DAVID annotation of skin transcriptomes from subjects with proliferative nephritis resembled the healthy controls; however, closer scrutiny showed differences as highlighted in Table 1 which focuses on the expression of an annotated gene set of transcripts in the extracellular matrix category (11 are shown) comparing case vs control. In dermal fibroblasts from subjects with proliferative disease the expression of anti-fibrotic genes was increased while pro-fibrotic genes were attenuated. This result suggests that an event involving localized fibrosis of renal tissue yields at distant sites (such as the skin), a fibroblast transcriptome which exerts a countermeasure to forestall fibrosis. The profile of transcripts of subjects with class II resembled controls.

Conclusion: Single-cell RNAseq is feasible and informative in cell specific transcriptome analysis of fresh non-lesional skin biopsies from SLE patients with a spectrum of active renal disease. The expression of fibroblasts and genes reflective of anti-fibrotic pathways support application of this novel approach to study readily accessible tissue.

Table 1		
	Case	Control
Anti-fibrotic		
TIMP1	8.78**	6.04
TIMP3	9.03	7.82
CTHRC1	8.24	6.56
Pro-fibrotic		
COL1A2*	9.65	13.25
MFAP4	7.08	8.51
FBLN1*	6.61	10.31
FN1	8.83	9.32
ELN	7.15	8.52
SPARC*	5.22	10.88
CCDC80*	5.13	10.98
TGFBR2	8.13	9.69
*P<0.05, case vs control, **Units, log((average of transcripts),2)		

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Abstract Number: 2068

Type 2 Innate Lymphoid Cells – Cellular Source of Profibrotic Mediators Rapidly and Persistently Recruited in Experimental Fibrosis and Systemic Sclerosis

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Background/Purpose: Type 2 innate lymphoid cells (ILC2s) are identified as population of cells with lymphoid morphology lacking re-arranged antigen-specific receptors. Recently, emerging data show that ILC2s might play a key role in the pathogenic process of fibrotic diseases. However, the potential benefit of applying ILC2s as therapeutic target remains to be elucidated. We aimed to profile ILC2s in fibrotic tissues and to evaluate the functional impact of IC2s in the pathogenesis of systemic sclerosis (SSc).

Methods: Human blood samples and skin sections (sixty-nine patients with SSc and 47 healthy controls) as well as skin and lung tissue of various fibrotic mouse models were analyzed by flow cytometry and multi-color immunohistochemistry using several complementary panels of markers each. Kinetics of ILC2 accumulation during the course of fibrosis was studied and ILC2s were further profiled by transcriptome as well as secretome analysis.

Results: Significantly elevated numbers of ILC2s were detected in the skin (10-fold increase) and blood (4-fold increase) of SSc patients by two independent established sets of ILC2 markers compared to healthy controls. In contrast to circulating ILC2s, skin-resident ILC2s express various activation markers and stained positive for skin homing markers. Furthermore, our data suggest that ILC2s might be involved in the pathogenesis of fibrosis in SSc by showing multiple associations of ILC2 counts with fibrotic manifestations in SSc patients. Significantly higher frequencies were observed in diffuse cutaneous (dc)SSc patients compared to limited cutaneous SSc (lcSSc). The modified Rodnan Skin Score (mRSS) positively correlated with ILC2 counts and pulmonary involvement. In parallel, we detected significantly elevated numbers of ILC2s in the fibrotic skin of bleomycin-induced and DNA topoisomerase I-induced mice compared to control mice. Moreover, in the tight-skin (Tsk)-1model of fibrosis resembling less inflammatory stages of SSc significantly increased ILC2 counts were detected compared to control mice. Kinetic analyses revealed an early upregulation of ILC2s in experimental models of fibrosis. In contrast to lineage positive lymphocytes that peak at early inflammatory stages of fibrosis, however disappear over time, ILC2s persist also in later stages of established fibrosis. Profiling of ILC2s in the fibrotic tissue revealed exaggerated production of pro-fibrotic cytokines that in turn activate fibroblasts to produce extracellular matrix proteins.

Conclusion: Here, we provide first evidence for a role of ILC2s in the pathogenesis of SSc by demonstrating increased ILC2 counts in the skin and blood of human SSc patients. These findings were indirectly supported by elevated numbers of ILC2s in the fibrotic skin and lung sections of various mouse models for SSc, reflecting different pathophysiological aspects of the disease. The pro-fibrotic phenotype of ILC2s and their persistant upregulation in early as well as in late stages of fibrosis suggest a central role of ILC2s in the pathogenesis of fibrosis.

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Abstract Number: 2069

Dipeptidyl-Peptidase-4 (DPP4) Positive Fibroblast Subpopulation Promotes Fibrosis and Are a Molecular Target for Treatment of

Fibrosis

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Background/Purpose: Dipeptidyl-peptidase-4 (DPP4) has been recently shown to identify a distinct dermal lineage with intrinsic fibrogenic potential and its targeted inhibition leads to reduced scar formation (1). Fibrotic disease may be considered as a consequence of persistent, exaggerated and uncontrolled tissue repair processes. Systemic sclerosis is the prototype of fibrotic diseases and effective antifibrotic therapies are still lacking. DPP4 inhibitors are already used in treatment of diabetes. The aim of the study was to characterize the DPP4 positive cells, investigate the expression of DPP4 in SSc skin and to evaluate the antifibrotic effect of DPP4 inhibitors in preclinical models of systemic sclerosis.

Methods: Mouse fibroblasts were isolated and DPP4 positive cells properties were assessed after cell sorting. Expression of DPP4 in human and murine skin was analyzed by immunofluorescence. DPP4 inhibitors were tested in two different concentrations administered orally (Sitagliptin 3mg/kg/d and 10mg/kg/d, Vildagliptin 1,5mg/kg/d and 15mg/kg/d) in bleomycin induced skin fibrosis and in sclerodermatous chronic graft-versus-host disease mouse model (cGvHD). The antifibrotic effect on skin was assessed by hydroxyproline assay, alpha smooth muscle cells quantification and measuring the dermal thickness. Inflammatory infiltrate was asses by CD45 immunofluorescence staining.

Results: We have demonstrated that DPP4 positive cells are a unique population of cells implicated in fibrosis. DPP4 positive fibroblasts count is increased not only in experimental fibrosis, but also in skin biopsies from SSc patients as compared to healthy volunteers. Treatment with DPP4 inhibitor reduced dermal thickness in both mouse models ($p<0.05$). The differentiation of resting myofibroblast into fibroblast was also significantly decreased ($p<0.05$) in all treatment groups. Collagen content of the skin diminished by 40% in comparison with NaCl injected mice or syngeneic transplanted mice. Moreover, DDP4 inhibitors reduced the inflammatory infiltrates in two different pathophysiological settings of fibrosis.

Conclusion: DPP4 identifies a subpopulation of fibrosis-promoting fibroblasts that plays a key role in the pathogenesis of fibrosis in SSc. Moreover, inhibitors of DPP4 show a significant antifibrotic effect in several

mouse models of established fibrosis in well tolerated doses. These results may have direct clinical implications as DPP4 inhibitors are already in clinical use for diabetes.

Reference: 1. Rinkevich Y, Walmsley GG, Hu MS, Maan ZN, Newman AM, Drukker M, et al. Skin fibrosis. Identification and isolation of a dermal lineage with intrinsic fibrogenic potential. Science. 2015;348(6232):aaa2151.

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Abstract Number: 2070

Long Noncoding RNA H19X Is a Master Regulator of Extracellular Matrix Production in Systemic Sclerosis and Other Fibrotic Disease

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Background/Purpose: Long noncoding RNAs (lncRNAs) are an emerging class of large noncoding transcripts involved in the regulation of gene expression in health and disease. We have recently identified a novel lncRNA, H19X, which is strictly regulated by TGFβ in a dose and time dependent manner. Here we aim to characterize the expression of H19X in Systemic Sclerosis (SSc) and other fibrotic diseases as well as its function in fibrotic events.

Methods: Skin and lung biopsies from patients with SSc, idiopathic pulmonary fibrosis (IPF), and healthy controls (HC) were obtained from cohorts at four different expert centers. Expression of H19X was analyzed by RNA Sequencing Ilumina HiSeq2000 and quantitative (q)PCR respectively. The function of H19X was investigated in skin fibroblasts transfected with locked nucleic acid oligonucleotides (LNA GapmeRs) by using the following methods: microarray analysis, qPCR, immunofluorescence, sircol, contraction assay, ELISA and

Western blot (WB). In situ hybridization of H19X in SSc dermal fibroblast was performed using Stellaris FISH probes.

Results: H19X expression was consistently upregulated across all the four cohorts (SSc n=34, HC= 26), using different techniques. The upregulation was also consistent across different subsets of patients and between patients with different disease durations. H19X showed a similar expression profile in clinically non-fibrotic and clinically fibrotic skin biopsies indicating a role in early disease development. Moreover, H19X expression was also significantly increased in SSc interstitial lung disease patients versus HC (n=11 each, $p<0.05$). A significant H19X overexpression was also detected in IPF samples suggesting a broader role of H19X in fibrotic diseases (n=11 each, $p<0.05$). Microarray analysis after H19X silencing revealed a strong involvement in extracellular matrix production with collagens being the most downregulated genes. Accordingly, collagen catabolic process, extracellular matrix organization and extracellular matrix disassembly were among the pathways with highest number of enriched genes. Downregulation of collagen Iα1, fibronectin and α-smooth muscle actin (αSMA) after H19X knockdown was confirmed by qPCR (n=5, $p<0.05$). Sircol assay for pan-collagen production, ELISA for pro-collagen Iα1 and WB analysis for fibronectin confirmed the importance of H19X in the regulation of extracellular matrix components. Additionally, silencing of H19X significantly impaired αSMA fiber formation, stress fiber formation as well as cell contractility strongly suggesting an important role of H19X in the development of the myofibroblast phenotype (n=5-6, $p<0.05$). Cell fractionation showed that TGFβ induced expression of H19X is localized mainly into the nucleus. In situ hybridization confirmed H19X localization as mainly nuclear and within a defined spot indicating that H19X could influence gene expression by interacting directly with the chromatin (n=4).

Conclusion: This is the first study reporting a significant upregulation of H19X expression in SSc and across fibrotic organs. By focusing on this novel class of regulatory, noncoding RNAs new perspectives in the pathogenesis of fibrotic diseases are opened.

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Abstract Number: 2071

Expression of Neuraminidase 1 (NEU1) Is Upregulated in the Lungs of Scleroderma Patients with Pulmonary Fibrosis, and Gene Delivery of NEU1 to Mouse Lungs Elicits Accumulation of CD8+ Lymphocytes and Collagen

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics I

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Session Time: 4:30PM-6:00PM

Background/Purpose: We and others have previously reported that pulmonary fibrosis in patients with scleroderma is accompanied by pulmonary accumulation of predominantly CD8+ T lymphocytes. Earlier reports also suggested that NEU1, a sialidase that removes terminal sialic acid from glycoproteins, is associated with and may contribute to both fibrotic changes and immune disturbances in the lungs, but the mechanistic details of such contributions remain unclear.

Methods: Immunohistochemical analyses were used to analyze NEU1 expression in the lung of patients with scleroderma and healthy controls. Cell culture studies were performed in normal adult primary pulmonary fibroblasts (PF). Overexpression of human NEU1 in mouse lungs in vivo and in cultured human lung fibroblasts was performed utilizing a replication-deficient recombinant adenovirus. In PF cell cultures, the effect of NEU1 overexpression on the levels of type I collagen protein were assessed utilizing western blotting. In the in vivo experiments, total and differential bronchoalveolar lavage (BAL) cells counts, flow cytometry of BAL cells, immunohistochemistry of lung tissues, trichrome staining for collagen, and total lung collagen measurements were utilized to characterize NEU1 overexpression-induced changes.

Results: NEU1 was expressed in airway epithelial cells, endothelial cells, and parenchymal cells in all tested lung tissue samples, but the expression was more pronounced in the lungs of scleroderma patients with pulmonary fibrosis. Western blot analyses revealed a strong increase in NEU1 expression in cultured PF from patients with scleroderma compared to healthy controls. NEU1 overexpression in normal fibroblast cultures led to a significant elevation in collagen levels, without increasing TGF-β mRNA or total or active TGF-β protein. Simultaneously, overexpression of NEU1 caused autocatalytic proteolysis of MMP14, a collagen-degrading enzyme, whose desialylation state is known to accelerate self-proteolysis. Intratracheal instillation of a NEU1-encoding but not a control adenovirus in mice in vivo caused accumulation of lymphocytes in BAL and lung tissue, elevation in total pulmonary TGF-β, and increases in pulmonary collagen. The accumulating lymphocytes were predominantly T cells, with CD8+ cells exceeding CD4+ cells by nearly 2 fold.

Conclusion: NEU1 expression is elevated in the lungs of scleroderma patients with pulmonary fibrosis, contributing to collagen protein accumulation by activating autocatalytic proteolysis of the collagen-degrading enzyme MMP14. In vivo, NEU1 gene delivery causes pulmonary fibrosis and lymphocytosis with predominant accumulation of CD8+ T cells, which are also seen in patients with scleroderma lung disease. Together, these data suggest an important pathophysiological role for NEU1 in pulmonary abnormalities observed in patients with scleroderma.

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Abstract Number: 2072

Fli1-Haploinsufficient Dermal Fibroblasts Promote Skin-Localized Transdifferentiation of Th2- and Th17-like Regulatory T Cells

Ryosuke Saigusa[1], Yoshihide Asano[2], Takuya Miyagawa[2], Megumi Hirabayashi[2], Kouki Nakamura[1], Shunsuke Miura[3], Takashi Yamashita[2], Yohei Ichimura[1], Takehiro Takahashi[1], Tetsuo Toyama[2], Takashi Taniguchi[1], Ayumi Yoshizaki[2], Maria Trojanowska[4] and Shinichi Sato[1], [1]Dermatology, The University of Tokyo Graduate School of Medicine, Tokyo, Japan, [2]Dermatology, University of Tokyo Graduate School of Medicine, Tokyo, Japan, [3]University of Tokyo Graduate School of Medicine, Tokyo, Japan, [4]Arthritis Center, Boston University, Arthritis Center, Boston, MA

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Background/Purpose: Systemic sclerosis (SSc) is a multisystem connective tissue disease characterized by autoimmunity/inflammation, vasculopathy, and tissue fibrosis. Fli1 is a member of Ets family transcription factor, the deficiency of which is a potential predisposing factor of SSc. Although the detailed mechanism explaining Fli1 downregulation still remains unknown, an epigenetic mechanism is reported at least in dermal fibroblasts, and Fli1 deficiency contributes to the induction of an SSc-like phenotype in those cells. A recent study has demonstrated that activated dermal fibroblasts regulate skin-localized transdifferentiation of regulatory T cells (Tregs) into T helper (Th) 2-like cells through the production of IL-33 in SSc, suggesting that activated dermal fibroblasts induce and/or amplify aberrant immune response characteristic of SSc. Based on these backgrounds, we conducted experiments with *Fli1*$^{+/-}$mice to elucidate the potential role of Fli1 deficiency in dermal fibroblast-dependent modification of Tregs.

Methods: The cytokine expression profile of skin-homing Tregs was assessed by Flow cytometry. Cytokine expression was examined in the skin and cultivated cells by immunostaining and/or quantitative reverse transcription PCR. Fli1 binding to the target gene promoters was assessed by chromatin immunoprecipitation. Co-culture of *Fli1*$^{+/-}$ fibroblasts and wild type Tregs was performed with or without blocking antibodies against target cytokines.

Results: The proportions of Th2- and Th17-like Tregs were increased in the lesional skin of BLM-treated *Fli1*$^{+/-}$ mice. *Fli1*$^{+/-}$ fibroblasts abundantly expressed IL-33 and IL-6, in particular IL-33, and Fli1 occupied the promoters of the *IL33* and *IL6* genes in human dermal fibroblasts. More importantly, the proportions of IL-4- and IL-17A-producing cells were higher in wild type Tregs co-cultured with *Fli1*$^{+/-}$ fibroblasts than in those co-cultured with wild type fibroblasts. To investigate the impact of IL-33 and IL-6 overexpression in *Fli1*$^{+/-}$ fibroblasts on Tregs, we next co-cultured them in the presence of neutralizing antibodies against these cytokines, which revealed that the increased proportions of IL-4- and IL-17A-producing Tregs co-cultured with *Fli1*$^{+/-}$ fibroblasts were decreased by neutralizing IL-33 and IL-6, respectively.

Conclusion: IL-33 and IL-6 overexpression in dermal fibroblasts due to Fli1 deficiency may contribute to the induction of Th2- and Th17-like Tregs in the skin, respectively, leading to the development of skin fibrosis in SSc. These data indicate a pivotal contribution of Fli1-deficienct dermal fibroblasts to the aberrant immune response in SSc.

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Abstract Number: 2073

Jumonji Domain Containing Protein 3 (JMJD3) As a Novel Epigenetic Mechanism of Fibroblast Activation By Regulation of Fra-2

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Background/Purpose: Prolonged endogenous activation of fibroblasts is a major hallmark of fibrosing disorders such as Systemic Sclerosis (SSc). It results in tissue fibrosis, organ failure and a high morbidity and mortality. Trimethylation of H3 at lysine residue K27 (H3K27me3) is an epigenetic mark that mediates gene repression. H3K27me3 was recently identified as an important negative regulator of fibroblast activation [1]. Demethylation of H3K27me3 is mediated by JMJD3. JMJD3 inhibitors are currently being tested as therapeutic strategies in malignant diseases. The aim of this study is to characterize the role of JMJD3 in fibroblast activation and to explore JMJD3 as a potential drug target in SSc.

Methods: The expression of JMJD3 was analyzed by qPCR, IF and Western blot in patients with SSc, healthy controls and in experimental fibrosis. siRNA mediated knockdown and pharmacologic inhibition by GSKJ4 were used to target JMJD3. *In vivo,* the effects of JMJD3-inhibiton were analyzed in the mouse model of bleomycin-induced dermal fibrosis, in the model of Topoisomerase-I-induced (TopoI) fibrosis and in a mouse model with adenoviral overexpression of a constitutively active transforming growth factor beta (TGF-β) receptor type 1 (TBR^{act}). Signaling pathways regulated by JMJD3 were analyzed *in vitro* and *in vivo* using qPCR, Western Blot and reporter assays.

Results: The expression of JMJD3 was increased in the skin of SSc patients as compared to healthy volunteers. Accumulation of JMJD3 was also observed in experimental models of SSc. TGF-β potently induced the expression of JMJD3 *in vitro* and *in vivo*. Pharmacologic inhibition and siRNA mediated knockdown of JMJD3 strongly upregulated the levels of H3K27me3 *in vitro* and *in vivo*. Inhibition of JMJD3 reverted the activated fibroblast phenotype in SSc fibroblasts and persistently decreased the expression of contractile fibers and of α-smooth muscle actin. Secretion of collagen was reduced upon inhibition of JMJD3. JMJD3- inhibition also resulted in a significant down-regulation of the profibrotic transcription factor Fra-2 *in vitro* and *in vivo*. Overexpression of Fra-2 in JMJD3-knockdown fibroblasts restored the profibrotic effect of JMJD3. *In vivo*, inhibition of JMJD3 ameliorated fibrosis in bleomycin-, TopoI- and TBR^{act}-induced experimental fibrosiswith reduced dermal thickening, hydroxyproline content and myofibroblast differentiation.

Conclusion: We present first evidence that histone methylation by JMJD3 contributes to the activated phenotype of SSc fibroblasts. JMJD3 is upregulated by TGF-β in SSc. Inhibition of JMJD3 prevents the aberrant collagen release and ameliorates the activated fibroblast phenotype in SSc fibroblasts. *In vivo* inhibition of JMJD3 has potent anti-fibrotic effects in several preclinical models of SSc. Reference: 1. Kramer, M., et al., *Inhibition of H3K27 histone trimethylation activates fibroblasts and induces fibrosis.* Ann Rheum Dis, 2013. **72**(4): p. 614-20.

Disclosure: C. Bergmann, None; **A. Brandt**, None; **C. Dees**, None; **Y. Zhang**, None; **N. Y. Lin**, None; **C. W. Chen**, None; **T. Mallano**, None; **R. Liang**, None; **P. S. Kam**, None; **O. Distler**, None; **G. Schett**, None; **J. H. Distler**, None.

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Abstract Number: 2074

Herpes Zoster and the Risk of Incident Giant Cell Arteritis

Bryant R. England[1], Ted R. Mikuls[2], Fenglong Xie[3], Shuo Yang[3], Lang Chen[3] and Jeffrey Curtis[4], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [3]Division of Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [4]Division Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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Background/Purpose: Antigenic triggers initiating granulomatous inflammation in giant cell arteritis (GCA) have yet to be elucidated. Recently, histopathological studies of temporal arteries from GCA patients have identified varicella zoster virus (VZV) antigen, implicating VZV as a potential causative organism. Given the cross-sectional design of past studies, the temporal relationship between herpes zoster (HZ) infection and GCA has not been established. Furthermore, if VZV is pathogenic, it is possible that HZ vaccination or antiviral

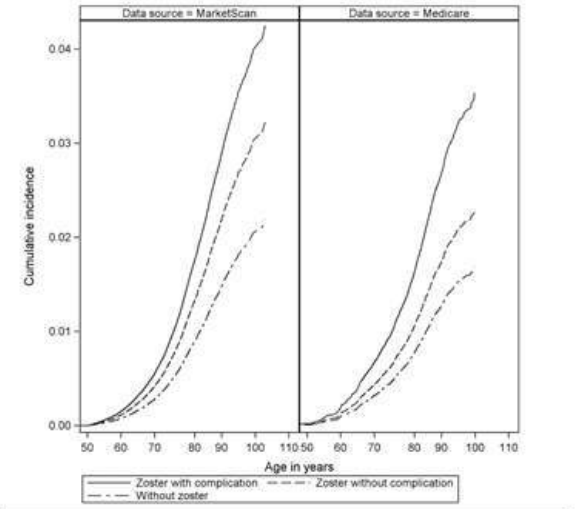
treatments could prevent GCA. We assessed the associations of HZ, HZ treatment, and HZ vaccination with new onset GCA using two large administrative databases.

Methods: We utilized a random 5% sample of Medicare data (2006-2013) and the MarketScan Commercial Claims and Encounters database (2010-2014). Enrollees age >50 years with 365 days of continuous enrollment and without prior GCA or polymyalgia rheumatica were eligible for analysis. HZ events were identified by ICD-9 codes from hospital discharge or physician visits and classified as complicated (053.X, excluding 053.9) or uncomplicated (053.9). Antiviral treatments within 7 days of a HZ diagnosis were collected from pharmacy claims. HZ vaccination was identified through current procedural terminology and national drug codes. Incident GCA was defined by ICD-9 codes for GCA (446.5) from one hospital discharge or two physician visits 7 to 365 days apart. Using Poisson regression, we calculated GCA incidence stratified by HZ exposure. Cox proportional hazards regression was used to examine time-varying multivariable-adjusted associations of HZ, HZ treatment, and HZ vaccination with incident GCA.

Results: A total of 16,664,161 persons were included (1,250,931 Medicare; 15,413,230 MarketScan) with 8,962 GCA cases (1,777 Medicare; 7,185 MarketScan) occurring over 37,993,079 pt-yrs of follow-up. GCA incidence was highest in those with complicated HZ in both datasets. Adjusting for age and sex, complicated HZ was associated with an ~2-fold increased risk while uncomplicated HZ was associated with a ~50% increased risk of GCA (Figure 1 table). The cumulative incidence of GCA stratified by HZ and adjusted hazard ratios (HR) are shown in Figure 1. Neither antiviral therapy (Medicare HR 0.70 [95% CI 0.48-1.03], MarketScan HR 1.15 [0.86-1.53]) nor HZ vaccination (HR 0.97, 95% CI 0.89-1.04) was associated with GCA.

Conclusion: HZ events are associated with an increased risk of GCA, with the highest risk amongst those with complicated HZ (e.g. cranial nerve involvement). These findings are among the first to establish a temporal relationship of prior HZ with subsequent GCA and provide further support for a potential causal association. We did not find evidence that either HZ vaccination or antiviral treatment is protective for GCA but additional study is warranted.

Figure 1. Cumulative incidence of GCA by herpes zoster.



	MarketScan HR (95% CI)	Medicare HR (95% CI)
No Zoster	*Referent*	*Referent*
Uncomplicated Zoster	1.47 (1.25-1.73)	1.37 (1.10-1.72)
Complicated Zoster	1.93 (1.41-2.63)	2.12 (1.45-3.11)

Disclosure: B. R. England, None; **T. R. Mikuls**, Pfizer Inc, 5,Roche Pharmaceuticals, 2; **F. Xie**, None; **S. Yang**, None; **L. Chen**, None; **J. Curtis**, None.

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Abstract Number: 2075

No Detection of Varicella-Zoster Virus in Temporal Arteries of Patients with Giant Cell Arteritis

Francesco Muratore[1], Stefania Croci[2], Ione Tamagnini[3], Alessandro Zerbini[2], Salvatore Bellafiore[4], Lucia Belloni[5], Luigi Boiardi[6], Alessandra Bisagni[7], Maria Parmeggiani[8], Alberto Cavazza[9] and Carlo Salvarani[1], [1]Rheumatology Unit, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [2]Clinical Immunology, Allergy and Advanced Biotechnologies Unit,, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [3]Pathology Unit, Department of Oncology, Arsicpedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [4]Pathology Unit, Department of Oncology, Arcispedale S Maria Nuova, Reggio Emilia, Italy, [5]Clinical Immunology, Allergy and Advanced Biotechnologies Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [6]Rheumatology Unit, Arcispedale S.Maria Nuova, IRCCS, Reggio Emilia, Italy, [7]Pathology Unit, Department of Oncology, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [8]. Clinical Immunology, Allergy and Advanced Biotechnologies Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy, [9]Pathology Unit, Arcispedale S Maria Nuova-IRCCS, Reggio Emilia, Italy

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SESSION INFORMATION

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Background/Purpose: Recent studies found an high prevalence of varicella-zoster virus (VZV) infection in temporal arteries (TAs) from both temporal artery biopsy (TAB)-positive and TAB-negative giant cell arteritis (GCA) patients compared to controls, suggesting that VZV infection may trigger the inflammatory cascade that characterizes GCA (1,2). The aim of our study was to analyze VZV infection in TAs from patients with TAB-positive GCA (biopsy-proven GCA), TAB-negative GCA (patients with negative TAB and a final diagnosis of GCA) and controls (patients with negative TAB and a final diagnosis different from GCA).

Methods: 79 formalin-fixed, paraffin-embedded (FFPE) TABs performed between 2009 and 2012 from 34 TAB-positive GCA patients, 15 TAB-negative GCA patients and 30 controls were retrieved. Six 5-µm sections of all FFPE TABs were cut. The first section was analyzed by immunohistochemistry using a mouse monoclonal antiVZV glycoprotein E (gE) IgG1 antibody (Santa CruzBiotechnology, Dallas, TX) and UltraView DAB Detection Kit (Ventana, Roche, Tucson, Az.). DNA was extracted from the remaining 5 sections with the QIAamp DNA FFPE tissue kit (Qiagen) and analyzed by real-time polymerase chain reaction (PCR) for the presence of VZV with primers for the major DNA binding protein of VZV (ORF 29) using both the VZV ELITe MGB kit (CE-IVD assay) and the primers designed by Gilden et al (1,2). For 10 of the 34 TAB-positive GCA patients, a specimen of temporal artery longer than 2 mm obtained at the time of TAB and immediately stored frozen at -80°C was available. DNA was extracted from these 10 frozen specimens with the RNA/DNA/Protein purification kit (Norgen Biotek) and analyzed by PCR for the presence of VZV DNA. 30 additional 5-µm sections were cut from each of these 10 FFPE TABs for which the frozen specimens were available and analyzed by immunohistochemistry. A FFPE skin lesion from a patient with active infection with VZV was used as

positive control.

Results: Immunohistochemical analysis detected VZV antigen in 1/34 (3%) TAB-positive GCA, 0/15 TAB-negative GCA and 0/30 controls, and in none of the 300 sections cut from the 10 FFPE TABs positive for GCA for which the frozen specimens were available. Instead VZV antigen was clearly detected in the skin lesion from a patient with active infection used as positive control. DNA obtained from all TABs was amplifiable. DNA obtained from frozen TABs was more concentrated than that obtained from FFPE TABs which allowed to load a higher quantity of DNA per reaction increasing assay sensitivity. VZV DNA was not detected in any of the FFPE TABs nor in frozen TABs, but was clearly detected in the FFPE skin lesion used as positive control. The histopathologic analysis showed transmural inflammation in all sections and no skip areas were found.

Conclusion: Our data do not support a role for VZV infection in the etiopathogenesis of GCA in Italian patients.
References: 1. Gilden D, et al. Prevalence and distribution of VZV in temporal arteries of patients with giant cell arteritis. Neurology. 2015 May 12;84(19):1948-55. 2. Nagel MA, et al. Analysis of Varicella-Zoster Virus in Temporal Arteries Biopsy Positive and Negative for Giant Cell Arteritis. JAMA Neurol. 2015 Nov 1;72(11):1281-7.

Disclosure: F. Muratore, None; **S. Croci**, None; **I. Tamagnini**, None; **A. Zerbini**, None; **S. Bellafiore**, None; **L. Belloni**, None; **L. Boiardi**, None; **A. Bisagni**, None; **M. Parmeggiani**, None; **A. Cavazza**, None; **C. Salvarani**, None.

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Abstract Number: 2076

Impact of Vasculitis on Employment and Income: An Online Survey of Participants in the Rare Diseases Clinical Research Network – Vasculitis Clinical Research Consortium Patient Contact Registry

Lillian Barra[1], Renee Borchin[2], Cristina Burroughs[3], Simon Carette[4], George Casey[5], Carol A McAlear[6], Antoine Sreih[7], Kalen Young[5], Peter A. Merkel[8], **Christian Pagnoux**[9] and Vasculitis Clinical Research Consortium and the Vasculitis Patient-Powered Research Network , [1]Medicine, Division of Rheumatology, Schulich School of Medicine and Dentistry, Western University, London, ON, Canada, [2]University of South Florida, Tampa, FL, [3]Vasculitis center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [4]Division of Rheumatology, Mount Sinai Hospital, University of Toronto, Toronto, ON, Canada, [5]Vasculitis Foundation, Kansas city, MN, [6]Penn Vasculitis Center, Division of Rheumatology, University of Pennsylvania, Philadelphia, PA, [7]Department of Rheumatology, University of Pennsylvania, Philadelphia, PA, [8]Division of Rheumatology, Univ of Pennsylvania; Perelman School of Med, Philadelphia, PA, [9]Division of Rheumatology, Mount Sinai Hospital, University Health Network, University of Toronto, Toronto, Canada, Toronto, ON, Canada

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Background/Purpose: Work disability associated with rheumatic diseases accounts for an important part of the costs of these conditions. Few studies have investigated disability among patients with vasculitis and most such research was conducted before 2005 and focused on granulomatosis with polyangiitis (GPA). The purpose of this study (VascWork) was to learn about the impact of vasculitis on employment and income in patients with systemic vasculitides.

Methods: Patients enrolled in the Vasculitis Clinical Research Consortium Patient Contact Registry, living in the USA or Canada, and followed for more than 1 year since their vasculitis was diagnosed were invited via email to participate in an on-line survey-based study. Participants were asked about their disease, their employment and work status, and the financial impact of their vasculitis on their lives.

Results: Between June and December, 2015, 421 patients completed the survey: 205 with GPA, 67 with eosinophilic granulomatosis with polyangiitis, 33 with microscopic polyangiitis, 27 with Takayasu arteritis, 27 with Behçet's disease and 62 with other forms of vasculitis. 125 (30%) patients were male; mean age 54.5±13 years; 92% Caucasian; 354 (84%) living in USA. Compared to patients who continued to work after a diagnosis of vasculitis, patients who stopped working or retired early because of their vasculitis (N=111) were older (56±11 vs. 53±11 years, p=0.036) and, accounting for sex and age, were less likely to have health insurance (OR=0.36; 95% CI: 0.15–0.9) and less likely to have attained education beyond high school (OR=0.51; 95% CI: 0.26–0.99). Figure 1 summarizes the work status of patients at time of diagnosis and at last follow-up (mean of 9±6.5 years).

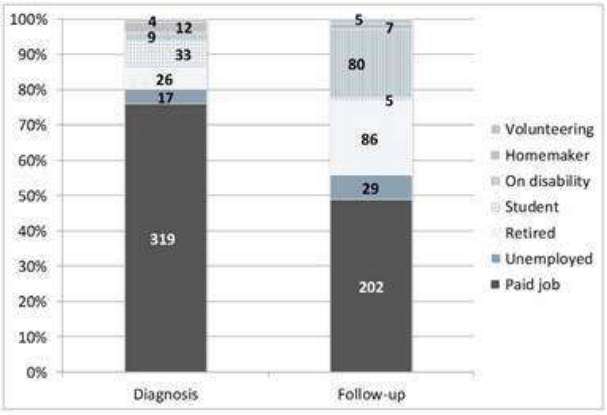

Figure 1. Work status of patients at time of diagnosis and at last follow-up. 76 patients reported income loss with an average (range) loss of 45% (2-95%). 253 patients (61%) reported having paid for some of their medications or investigations for vasculitis, leading 32 patients to not receive some prescribed treatment or testing because they could not afford the costs. Patients who were unable to pay for treatments had more often become unable to work (OR=3.12; 95% CI: 1.14–8.52).

Conclusion: This study using patient self-reported data demonstrates substantial limitations in work, productivity, and net personal income loss that patients accrue due to vasculitis. These burdens of disease are additive to the effects of vasculitis on physical functioning and directly negatively impact patients' healthcare and overall quality of life.

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Abstract Number: 2077

Impact of Diabetes, Angiotensin Converting Enzyme Inhibitor or Angiotensin II Receptor Blocker Use, and Statin Use on Presentation and Outcomes in Patients with Giant Cell Arteritis

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Background/Purpose: Few retrospective studies in giant cell arteritis (GCA) previously reported, separately, that 1) patients with diabetes had less positive temporal artery biopsies (TAB), 2) patients on angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin II receptor blockers (ARB) experienced fewer relapses and 3) patients on statins experienced the same frequency of clinical complications and relapses as non-exposed patients. This retrospective chart review study simultaneously investigated the impact of these 3 factors on a cohort of patients followed in 2 large North American centers.

Methods: Patient who were diagnosed with GCA were included in this study if they met the American College of Rheumatology's (ACR) modified classification criteria (age >50 and ≥2 of the following: new onset headache, TA abnormality, ESR >40mm, abnormal TAB and large vessel vasculitis by angiogram or biopsy). Their demographics, presenting symptoms, TAB results, disease complications and outcomes (relapses, duration of glucocorticoid use) were compared between exposed (diabetes/ACE/ARB/statin) and non-exposed patients.

Results: Of 175 charts reviewed of consecutive patients with a diagnosis of GCA (between 1993-2015) seen in the 2 study centers, 137 met the ACR modified classification criteria. 70% were female and the mean (SD) age at diagnosis was 71 (8.9) years. 17 patients had preexisting diabetes (11 developed diabetes after diagnosis), 36 were using ACE-Is (14 more after), 26 were using ARBs (6 more after) and 52 were on statins (15 more after). TAB was less often positive in patients with diabetes (RR 0.24 [95% CI: 0.069-0.81], $p < 0.02$). The cumulative probability of flaring over time was higher in both patients with pre- and post-diagnosis diabetes when compared to non-diabetic patients (log-rank, $p < 0.03$), with adjusted HRs of 0.25 [0.10-0.62] and 0.28 [0.095-0.84], respectively. There was a significant difference in the probability of successful discontinuation of prednisone for ACE-I therapy (log-rank, $p < 0.03$), but a nonsignificant trend for ARB therapy when compared to non-exposed patients, with adjusted HRs of 0.44 [0.22-0.87] and 0.60 [0.30-1.2] respectively. Clinical complications (Table 1) and relapse rates (log-rank test, $p > 0.80$, adjusted HR 0.54 (0.24-1.2)) did not significantly differ between patients on statin therapy or not.

	Diabetes	Statin therapy	ACE-I therapy	ARB therapy
Positive temporal artery biopsy	0.24* 95% CI (0.069-0.81)	0.69	0.95	0.50
Headache	1.77	1.77* 95% CI (0.96-3.26)	1.2	1.09
Temporal artery tenderness	1.0	1.5	0.79	1.3
Jaw claudication	0.80	1.03	1.5	1.1
Upper limb claudication	0.48	0.30* 95% CI (0.081-1.1)	0.67	0.88
Lower limb claudication	0.00	0.22	0.79	0.11
Anterior ischemic optic neuropathy	2.3	1.16	1.4	0.88
Visual loss	1.6	0.95	1.2	0.49
Other large vessel manifestation	0.48	0.48* 95% CI (0.23-1.0)	1.06	0.69

Table 1. Relative risk ratios of the presenting features of giant cell arteritis * $p < 0.05$

Conclusion: In this study, patients with GCA and diabetes appeared more likely to have a negative TAB, and to relapse. ACE-I therapy showed an independent association with success at discontinuing prednisone. Statin therapy did not alter the clinical presentation or course of GCA. These observed findings confirm most (but not all) of those from similar, yet separate studies which explored this topic.

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Abstract Number: 2078

Global Ethnic and Geographic Differences in the Clinical Features of ANCA-Associated Vasculitis

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Background/Purpose: There are few data on clinical profiles of ANCA-associated vasculitis (AAV) and or ANCA specificity in different ethnic populations. This study examined differences in the clinical features of AAV between populations using the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) dataset.

Methods: DCVAS is an international, multi-center observational study recruiting in 128 sites worldwide. Rheumatology, renal, immunology, neurology, respiratory and dermatology specialties contributed to recruitment. Ethnic groups were categorized into 8 groups: Chinese, Northern & Southern European, Indian subcontinent, Japanese, Middle Eastern, White American. Other ethnic groups of <50 people were excluded. ANCA type was categorized as MPO, PR3, and ANCA-negative. The extent of organ involvement was classified by the presence of constitutional, musculoskeletal, skin, ophthalmic, ENT, respiratory, cardiovascular, gastroenterological, genitourinary, and neurological symptoms. Differences were analyzed by chi-squared test using a Bonferroni correction, and logistic regression (adjusting for age, sex, specialty of recruiting center). Northern European was the reference group.

Results: Data from 1,069 patients were included (Table 1). Recruiting specialties were not evenly distributed among ethnic groups. There were differences in ANCA type between ethnic categories ($p<0.001$). MPO was more common than PR3 in Southern European, Chinese, & Japanese; and PR3 was more common in the other ethnic categories. ANCA-negative AAV was more common in White Americans than in Northern Europeans. These effects remained after adjustment for age, sex, and recruiting specialty. There were differences in organ involvement in the crude analysis: systemic involvement was less common in Southern Europeans, renal involvement more common in Chinese and Japanese, musculoskeletal less common in Southern European, Chinese and Japanese, ophthalmic more common in Indian and less common in Japanese. Adjustment for age and sex did not alter the associations. However, recruiting specialty confounded the association between ethnicity and system involvement for all organ systems. Due to interaction, the analysis was stratified by recruiting specialty. The majority (83.7%) of patients were recruited by rheumatology. Within this group, there were no significant differences, except ophthalmic and ENT involvement were less common in Japanese people compared to Northern Europeans. The numbers in the other specialties were too small to draw conclusions.

Conclusion: This study confirms the previously-observed differential occurrence of MPO-AAV and PR3-AAV. Organ system involvement in AAV does not appear to be different among various ethnic groups, after accounting for the different likelihood of seeing and recording symptoms in different specialties.

Table 1: Demographic data, recruiting specialties, diagnoses, and ANCA type of patients with ANCA-associated vasculitis in the cohort

		n	%
Sex	Male	532	49.8%
	Female	537	50.2%
Age (years)	Median, IQR	58.6	(46.3-69.1)
Ethnic category	Chinese	81	7.6%
	European North	486	45.5%
	European South	100	9.4%
	Indian subcontinent	60	5.6%
	Japanese	64	6.0%
	Middle Eastern/ Turkish	92	8.6%
	White American	186	17.4%
Recruiting Specialty	Rheumatology	895	83.7%
	Nephrology	142	13.3%
	Immunology	22	2.1%
	Neurology	5	0.5%
	Respiratory	3	0.3%
	Dermatology	2	0.2%
Diagnosis	GPA	592	55.4%
	MPA	284	26.6%
	EGPA	193	18.0%
ANCA-type	MPO	372	34.8%
	PR3	446	41.7%
	Negative	160	15.0%
	Other*	91	8.5%

n: number, IQR: interquartile range, GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis, EGPA: eosinophilic granulomatosis with polyangiitis, ANCA: anti-neutrophil cytoplasmic antibody, MPO: myeloperoxidase, PR3: proteinase-3.
* ANCA-type Other category either had not had their ANCA tested (n=13), were both MPO&PR3+ve (n=7) or only had ANCA on immunofluorescence (n=71); ELISA

Disclosure: F. Pearce, None; **A. Craven**, None; **P. A. Merkel**, None; **R. Luqmani**, None; **R. A. Watts**, None.

Abstract Number: 2079

Incidence and Risk of Pneumocystis Jirovecii Pneumonia Following Rituximab Treatment in Granulomatosis with Polyangiitis in the United States: An Analysis from a National Database

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Background/Purpose: Pneumocystis Jirovecii pneumonia (PJP) is a life-threatening complication in granulomatosis with polyangiitis (GPA). Guidelines from EULAR for ANCA-associated vasculitis (AAV) recommend institution of PJP chemoprophylaxis during cyclophosphamide therapy. Rituximab has been increasingly used in AAV, however the necessity for PJP chemoprophylaxis in this group of patients is unclear. The objective of this study was to determine the incidence and risk of PJP in GPA patients who received Rituximab.

Methods: We conducted a retrospective cohort study using the 2006 to 2013 Truven Health Analytics MarketScan Commercial Claims database which contains inpatient, outpatient, and pharmacy claims from the privately-insured US population. We selected patients aged 2-60 years old and identified GPA and PJP cases using ICD-9-CM codes 466.4 and 136.3, respectively. As GPA shares the same ICD-9-CM code with eosinophilic granulomatosis with polyangiitis, patients with eosinophilia (ICD-9-CM 288.3) were excluded. From these patient records, we collected demographic data, dates of first coding for GPA, presence of PJP and dates of PJP onset, dates of Rituximab use, presence and dates of PJP chemoprophylaxis, and use of immunosuppressive drugs within 90 days of PJP onset. We performed all statistical analyses using STATA (STATA Corp, College Station, TX).

Results: We identified 4,606 patients with GPA. Only 7% of GPA cases (n=322) were children under 21 years of age. The mean age at the time of first coding for GPA was 44.5 ± 12.6 years and 54.5% were female. Less than a quarter of GPA patients received Rituximab chemotherapy during the study period (n=636 patients, 13.8 %). During the study period, 23 GPA patients (0.5%) were diagnosed with PJP. The mean age at PJP onset was 47± 13 years with slight female preponderance (65%). The annual incidence rate of PJP in GPA patients across all ages, regardless of treatment, was 2 cases per 1,000 person-years. Two of the PJP patients were diagnosed with PJP within 2 months of Rituximab initiation, resulting in an annual incidence rate of PJP in Rituximab-

treated GPA patients of 1 case per 1,000 person-years. The relative risk of PJP in Rituximab-treated patients was 0.6 (95% CI 0.14-2.53, p=0.48) compared to non-Rituximab-treated patients. Among the 636 patients who received Rituximab, 339 patients (53%) had claims for PJP chemoprophylaxis within 90 days prior to the PJP onset; only one of these developed PJP while on the PJP prophylaxis. The relative risk of developing PJP on prophylaxis medication was 1.0 (95% CI 0.99-1.01, p=0.9).

Conclusion: The overall incidence of PJP in GPA patients and in Rituximab-treated GPA patients in particular, was low. Rituximab does not appear to be associated with an increased risk of PJP in GPA patients. Chemoprophylaxis for PJP may not be indicated in the Rituximab-treated GPA patients. Further study is warranted to evaluate cost-effectiveness of PJP chemoprophylaxis in Rituximab-treated GPA population.

Disclosure: S. Panupattanapong, None; **A. R. French**, None; **A. J. White**, None; **M. A. Olsen**, None; **M. Rendulic**, None; **M. E. Hartman**, None.

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Abstract Number: 2080

Three Simple Tests to Raise the Index of Suspicion for Fibromyalgia in Primary Care

Amanda W. St. John[1], Jonathan H. Aebischer[2], Robert M. Bennett[3], Madeleine J. Sanford[2], Kaitlin Z. Haws[4] and Kim D. Jones[3], [1]Anesthesiology and Pain Medicine, Oregon Health & Science University, Portland, OR, [2]Department of Family Medicine, Oregon Health & Science University, Portland, OR, [3]Schools of Nursing and Medicine, Oregon Health & Science University, Portland, OR, [4]Department of Internal Medicine and Geriatrics, Oregon Health & Science University, Portland, OR

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Background/Purpose: Fibromyalgia (FM) is a multi-symptomatic pain disorder that affects 10-15 million US adults, including 1 in 20 patients seen in primary care. As such, primary care providers are increasingly expected to recognize and diagnose these patients rather than rely on specialists such as rheumatologists. The purpose of this study was to evaluate the usefulness of 3 simple measures, that when routinely used, will alert the clinician to consider a diagnosis of FM.

Methods: A descriptive cross sectional study assessed adults being seen in 2 academic primary care clinics. Data sources included chart review, history, physical exam and patient-completed surveys.

Results: 356 patients were studied (mean age 50 ± 16.3 years, 70% female). Chart review revealed that 53 (15%) of these patients carried a diagnosis of FM in their medical record. On survey, 159 had pain of which 122 (77%) stated that their pain was present greater than three months. On physical exam, those who had FM were

tender at a lower level of sphygmomanometery-evoked pain than those without FM (128 mmHg ± 5.4 vs 181 mmHg ± 6.1, p< 0.0001). Similarly, those with FM exhibited more bilateral skin roll tenderness (upper trapezii, radii, interphalangeal joints, anterior thighs) compared to those without FM (p < 0.0001). Pinching the Achilles tendon with 4 kg over 4 seconds was the most commonly endorsed tender area in FM patients. Similarly, those with FM endorsed the question "I have a persistent deep aching pain over most of my body" more commonly than those without FM (p < 0.0001).

Conclusion: Primary care providers should schedule a visit to fully evaluate a patient for FM if the patient has any of the following: 1) sphygmomanometry-evoked allodynia, 2) pain on the Achilles tendon pinch, or 3) endorses the statement "I have a persistent deep aching over most of my body." By raising providers' index of suspicion for FM, patients may be spared years cycling through the medical system before receiving a diagnosis and beginning treatment.

Disclosure: A. W. St. John, None; **J. H. Aebischer**, None; **R. M. Bennett**, None; **M. J. Sanford**, None; **K. Z. Haws**, None; **K. D. Jones**, None.

Abstract Number: 2081

Dermal Temperature Is an Excelent Prognostic Indicator to Guide RA Therapy

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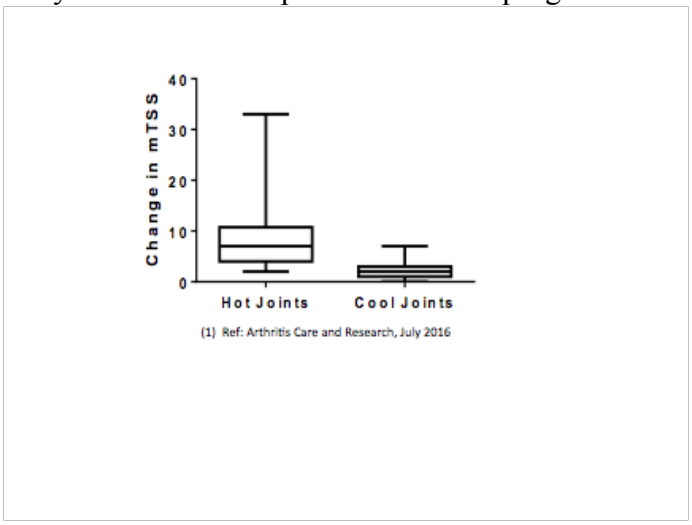
Background/Purpose: Nurses and rheumatology extenders can rapidly identify rheumatoid arthritis (RA) patients who flare, with high predictive value for which individual is at high risk for crippling deformity. Published literature has shown that an elevated dermal temperature Òwarm jointÓ can identify RA patients who most need disease modifying therapy (DMARD).(1) Nurses or rheumatologic extenders in clinic can assess in less than a minute which specific patient will develop radiographic damage by documenting a single dermal temperature of 97 F or greater over the left wrist.

Methods: All 297 sero-positive RA patients were on DMARD therapy in good control or remission at least 6 months. Hand/wrist xrays were obtained annually. In each case where there was a significant worsening of skeletal damage, the clinic visit record showed a dermal temperature over 97 F in the left wrist (used as the default joint for dermal assessment). None of the 297 RA patients were permitted prednisone or narcotics; stable doses of anti-inflammatory medications were permitted. Annual xray analysis was performed by a single reader, blinded and in random sequence. The minimal meaningful change in mean total Sharp score (mTSS) was ≥ 5 U.

Results: Over a three year period, there was demonstrable radiographic damage in 15 RA patients (5%) of the 297 RA patients in this trial. All 297 remained on stable DMARD therapy for the three years with control of RA disease, except for the 15 RA patients with a dermal temperature over 97F; 12 women and 3 men. There were no differences in baseline characteristics between the stable RA patients and the 15 who flared. The 15 patients flared while on stable DMARDs. Subsequent to recording a dermal temperature at least 97 F or over in the left wrist, the damage was clear on the following annual xray. The DMARD therapy in the 297 patients included methotrexate(MTX) alone (32%), MTX / TNF (35%), MTX/ abatacept (10%), MTX/ rituximab (15%), MTX/ JAK (5%), or any biologic alone without MTX (3%). The flares with subsequent xray damage occurred randomly on each of the DMARD treatment regimens.

Conclusion: Triage performed by a nurse or rheumatology extender may rapidly identify which patients most need a change in DMARD therapy. If the dermal temperature is 97F or higher, this predicts that a specific RA patient will have radiologic damage in the next years. Dermal temperature can be a prognostic indicator to guide therapy and avoid permanent joint damage.



Dermal Temperature predicts flare and radiographic damage in RA patients previously well controlled on DMARD therapy

	Less than 97F (n=282)	97F or higher (n=15)
Erosions	1.2 (0.16), no change	9.7 (6.7), 38% worse after 3 yrs
Joint space loss	1.6 (0.9), no change	12.1 (8.8), 34% worse after 3 yrs
mTSS	2.8 (1.2), no change	21.8 (14.5), 36% worse after 3 yrs

Results are presented as absolute unit change over 3 years with standard deviation (sd) and as the % change compared to baseline in these patients.

Disclosure: J. Ball, None; **M. Greenwald**, None.

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Abstract Number: 2082

Identification of Major Clinical Characteristics and Linear Correlations Among DAS28, HAQ and Morning Stiffness Time Using Smart System of Disease Management (SSDM)

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Background/Purpose: There are more than 5 million rheumatoid arthritis (RA) patients in China, but only 5,000 rheumatologists. Treat-to-target (T2T) is a widely accepted cretria as management strategy for rheumatoid arthritis (RA) to achieve defined outcomes (remission or low disease activity), but the Chinese rheumatologists can hardly provide patients with a complete assessment in the clinic due to limited time. Our previous study shows that patients in China can master the application of Smart System of Disease Management (SSDM) for accurately evaluating disease activity score in 28 joints (DAS28) and health assessment questionnaire (HAQ) after training. The purpose of this study is to describe major clinical characteristics of Chinese RA patients using SSDM and analyze the potential association among DAS28, HAQ and morning stiffness time in real world.

Methods: SSDM includes physicians' and patients' application system. The patient application system includes self-assessment (DAS28, HAQ), morning stiffness time and medication management. After data entry, patients can synchronize data to the mobile terminal of authorized rheumatologist. All patients fulfilling the 1987 ACR criteria for RA were recruited. The mean of each variable was analyzed using t-test, assuming normality for DAS28 distribution and the level of disease activity was analyzed using Pearson's statistics. One-way analysis of variance was employed to explore for difference between sub-groups.

Results: From August 2014 to May 2016, data were extracted online from the mobile terminals of 741 rheumatologists in 295 rheumatology centers across China. A total of 5,756 RA patients participated in the study. The mean age was 46.37 ±13.32 (18 to 99) years and the median disease duration was 2.58 (0 to 51.83) years. All patients performed self-assessment of DAS28, HAQ and morning stiffness time for 8,533 times. At baseline, the mean DAS28, HAQ scores and morning stiffness time were 3.75 ± 2.52 (0.21 to 9.71), 2.75 ± 4.30 (0 to 24) and 19.02 ± 30.01 (0 to 240) minutes respectively. DAS28 was positively correlated with HAQ and stiffness time independently. Both HAQ and morning stiffness time showed linear regression association with DAS28

score, the regression equation as “DAS28 = 3.40 + 0.019*morning stiffness time” and ““DAS28 = 3.41 + 0.0145*HAQ” respectively, p<0.01. According to the T2T criteria, 19.29% of patients achieved remission (Rem), 12.78% with low disease activity (LDA), 42.50% with moderate disease activity (MDA) and 25.43% with high disease activity (HDA). The most commonly used medication were small molecule DMARDs (92.7%) include leflunomide (65.33%), methotrexate (45.99%) and hdroxychloroquine (44.19%). Etanercept (2.40%) was the most common being used biological DMARDs (6.07%). The number of DMARDs being taken by patients who reach target was significantly less than who fail to reach target (2.78 ± 1.64 vs 3.05 ± 1.74), p = 0.019.

Conclusion: SSDM is an effective mobile interface to serve for RA patients performing self-management as well as to supply physicians with valuable data. DAS28 was positively correlated with HAQ and morning stiffness time independently. HAQ and morning stiffness time could surrogate reflect disease activity.

Disclosure: J. Huang, None; **H. Wang**, None; **J. Yang**, None; **W. Fan**, None; **H. Wei**, None; **R. Mu**, None; **X. Duan**, None; **X. Liu**, None; **F. He**, None; **Z. Zhang**, None; **F. Xiao**, None; **H. Xiao**, None; **Y. Jia**, None; **Y. Liu**, None; **L. Zhang**, None; **B. Wu**, None; **X. Li**, None.

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Abstract Number: 2083

Comparing the Electronic Patient Reported Outcome (ePro) Tool Versus the Paper Reported Outcome (pPro) Tool in Rheumatoid Arthritis Patients Treated with Certolizumab Pegol

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Background/Purpose: Clinical disease activity for patients with rheumatoid arthritis requires frequent monitoring for optimal management. Patient reported outcome (PRO) tools provide information that complements physician’s assessment of changes in disease activity and response to treatment. The use of electronic data capturing (ePRO) is potentially advantageous over paper based (pPRO) in terms of reducing missing data, reducing ambiguous responses and allowing time-stamped records and analysis.

Methods: Patients were assigned randomly to either ePRO or pPRO at visit one. At visit 2, patients crossed over into the other PRO modality (both pre-treatment) and remained in that arm for subsequent visits at week 6,

12 and 36. Patient assessments included 28 swollen (SJC) and tender joint counts (TJC), Patient assessment of pain (PAAP), Patient assessment of global disease activity (PtGADA) and Bristol Arthritis Fatigue Multidimensional Questionnaire (BRAF-MDQ).

Results: 52 patients with mean RA duration 11.7 years were enrolled and. Mean age was 55.7 (SD 14.3) years and 67% were female.

There was moderate to high correlation (Table 1) and agreement (Figure 1) between Nurse-Patient-Physician PRO assessments. There was no significant difference in PtGADA, PAAP and BRAF-MDQ between ePRO and pPRO assessments.

Patients reported high levels of satisfaction with both PRO arms with only 2 patients (8.3%) reporting dissatisfaction. 88-92% reported that they were either satisfied or very satisfied with either tool. 58% of those who transitioned from ePRO to pPRO had no preference for one over the other format whereas 67% of those who transitioned from pPRO to ePRO preferred the electronic tablet.

Conclusion: Both ePRO and pPRO provided consistent results and demonstrated equivalence in PRO assessment. ePRO was well embraced by patients with only a minority reporting dissatisfaction. It may be a desirable inclusion in routine RA and potentially other disease assessments for its added reliability, consistency and increased patient involvement.

Acknowledgements

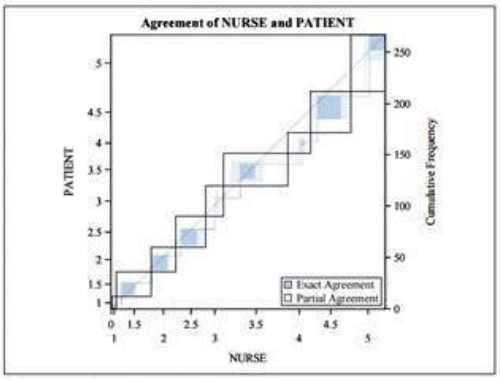
1. UCB Australia for financial support

2. Australian Rheumatologists for supplying patient data.

Table 1: PRO Spearman Correlation coefficients scores (p values) for Swollen Joint Count(SJC) and Tender Joint Count(TJC) between Nurse, Physician and Patient

Joint Assess	Assessor	Nurse	Patient	Physician
PRO- TJC	Nurse	1.00	0.83(<.0001)	0.85(<.0001)
	Patient	0.83(<.0001)	1.00	0.59(0.005)
	Physician	0.85(<.0001)	0.59(0.005)	1.00
PRO- SJC	Nurse	1.00	0.69(<.0001)	0.66(<.0001)
	Patient	0.69(<.0001)	1.00	0.42(0.058)
	Physician	0.66(<.0001)	0.42(0.058)	1.00

Figure 1: Agreement scores for Tender Joint Count (Overall) between all Nurse and Patient



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Abstract Number: 2084

Effects of a Web-Based Patient Decision Aid on Biologics for Rheumatoid Arthritis: A Proof-of-Concept Study

Linda Li[1], Chris Shaw[2], Diane Lacaille[1], Elaine Yacyshyn[3], C. Allyson Jones[4], Paul Adam[5], Cheryl Koehn[6], Alison Hoens[7], Jasmina Geldman[8], Charles Goldsmith[9], Eric C. Sayre[8] and Nick Bansback[10], [1]Rheumatology, Arthritis Research Canada, Richmond, BC, Canada, [2]School of Interactive Arts and Technology, Simon Fraser University, Surrey, BC, Canada, [3]University of Alberta, Edmonton, AB, Canada, [4]Physical Therapy, University of Alberta, Edmonton, AB, Canada, [5]Mary Pack Arthritis Program, Vancouver, BC, Canada, [6]Arthritis Consumer Experts, Vancouver, BC, Canada, [7]Dept of Physical Therapy, University of British Columbia, Vancouver, BC, Canada, [8]Arthritis Research Canada, Richmond, BC, Canada, [9]Faculty of Health Sciences, Simon Fraser University, Vancouver, BC, Canada, [10]School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose : Under the treat-to-target approach for patients with rheumatoid arthritis (RA), a biologic agent is considered when the target is not met despite trying disease-modifying anti-rheumatic drugs. However,

patients sometimes struggle with the decision to use these medications due to the potential side effects. We have developed a user-friendly decision aid, *ANSWER-2*, for patients who are considering biologic and small molecule agents. Patient decision aids are designed to present the potential benefits and harm of treatment options and clarify individuals' preferences. A main feature of *ANSWER-2* is the trade-off exercise designed to help patients consider value-sensitive options (e.g., the mode and frequency of medication administration). We aimed to assess the extent to which *ANSWER-2*reduces patient's decisional conflict, and improves their medication-related knowledge and self-management capacity.

Methods: We used a pre-post study design. Participants were recruited from rheumatologists' clinics, patient groups and social networking sites (e.g., Facebook). Individuals were eligible if they: 1) had a physician diagnosis of RA, 2) had been recommended to start/switch to a new biologic or small molecule agent, and 3) had internet access. Access to *ANSWER-2* was provided immediately after enrollment. Participants completed outcome measures before and within 2 days after using *ANSWER-2*. They included: 1) Decisional Conflict Scale (DCS; 0-100, scores < 25 are associated with follow-through with decisions), 2) Partners in Health Scale (PIHS; 0-88, lower = better), and 3) Medication Education Impact Questionnaire (MeiQ; 6 subscales, higher score = better). Paired t-test or Wilcoxon signed-rank test was used to assess differences pre and post intervention.

Results: 50 participants were enrolled in November 2014 – December 2015. The majority were women (n = 40) with a mean age of 49.6 years (SD: 12.2). 64% (n = 32) attended/completed university. The median disease duration was 5 years (Q1; Q3: 2; 10). The mean DCS was 45.9 (SD: 25.1) pre-intervention and 25.1 (SD: 21.8) post-intervention (change: -21.2, 95% CI: -28.1, -14.4; $p < 0.001$). Before using *ANSWER-2*, 20% of participants scored < 25, compared to 52% after the intervention. Similar results were observed in the PIHS (pre: 25.3, SD: 14.8; post: 20.4, SD: 13.0; change: -3.7, 95% CI: -6.3, -1.0; $p= 0.009$). Findings from the MeiQ were mixed, with statistically significant differences found in the self-management sub-scales (Table 1).

Table 1: Results of MeiQ Subscales

MeiQ subscale (maximum possible score)	Before (SD)	After (SD)	Difference (95% CI)	*p*
Information Quality (30)	21.9 (5.5)	22.4 (5.0)	0.3 (-0.6, 1.3)	0.490
Active Communication (24)	18.8 (4.6)	19.5 (3.7)	0.7 (-0.1, 1.4)	0.086
Coming to Terms with Diagnosis & Treatment (24)	19.4 (3.0)	19.7 (2.9)	0.3 (-0.3, 1.0)	0.299
Self-management Ability (36)	26.7 (5.3)	28.0 (4.9)	1.3 (0.0, 2.5)	0.048
Self-management Role & Responsibility (36)	31.8 (3.3)	32.6 (2.8)	0.9 (0.2, 1.6)	0.012
Self-management Support (24)	17.5 (4.4)	18.9 (3.2)	1.1 (0.2, 2.0)	0.019

Conclusion: Patients' decisional conflict and self-management capacity improved after using *ANSWER-2*. Our results show similar changes to other studies evaluating patient decision aids in chronic diseases, including RA[1]. Future research comparing *ANSWER-2*with education material on biologics will provide further insight into the value of patient decision aids in RA management. (1) Li et al. *Arthritis Care Res* 66:1472-81, 2014.

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Abstract Number: 2085

Minding the Gap: the Use of Nurse Practitioners and Physician Assistants in U.S. Rheumatology Practice to Affect Rheumatology Workforce Shortages

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Title: Minding the Gap: The Use of Nurse Practitioners and Physician Assistants in U.S. Rheumatology Practice to Affect Rheumatology Workforce Shortages Authors: Smith BJ[1], Bolster MB[2], Ditmyer M[3], Jones KB[4], Monrad S[5], Battafarano DF[6] [1] McIntosh Clinic, P.C. **[2]** Massachusetts General Hospital **[3]University of Nevada, Las Vegas, [4]Nationwide Children's Hospital, [5]University of Michigan, [6]San Antonio Military Medical Center**

Background/Purpose: The United States (U.S.) is facing a significant deficit of physicians and **rheumatology is subject to workforce challenges. Currently, in many areas in the U.S., persons with rheumatic disease face prolonged wait times and experience significant travel distances to a rheumatologist. Nurse Practitioners (NPs) and Physician Assistants (PAs), valuable members of the healthcare team, are utilized by about 25% of rheumatology practices.** The 2015 ACR Workforce Study sought to expand current knowledge of the rheumatology workforce which included NP/PAs.

Methods: The 2015 ACR/ARHP Workforce Study was completed using several primary and secondary data sources, including ACR member data, state licensure registries, the 2005 ACR workforce study, professional organizations, and other medical literature. These data were augmented by a web-based survey to collect information on demographics, work settings, practice patterns, and retirement planning.

Results: Thirty-two completed survey responses were received (30% response rate; 32/110 NP/PA members), of which 23% were NPs (19/82) and 46% were PAs (13/28). Self reported as female were 54% (n=26) and 12.5% (n=6) as male, representative of the gender breakdown in the NP/PA professions. On average, NPs reported working 43 hours/week, while PAs reported working 39 hours/week. Of these hours, most were in clinical care (NP Mean=30 hours; PA Mean=27) with NPs reporting an average 31 patients and PAs an average 47 patients seen/week. A small percentage (<18% combined NP/PA) reported performing and billing for ultrasounds, DXA scans, and office based infusions. Although the majority of new patient visits seen by NP/PAs are shared visits with a rheumatologist, follow-up patients are mostly managed as independent visits (Figure 1). About 27% NPs/PAs plan to retire in the next 10 years. Of those, all plan to reduce their patient load before that time by 25-50%.

Conclusion: NP/PAs have been identified as a potential means of increasing the rheumatology workforce. While NP/PAs have different formal educational training, they function similarly within a rheumatology office and are able to accomplish unique needs of the practice, within the scope of state legal requirements. NPs and PAs offer one potential solution to meet rheumatology workforce needs particularly if use of this valuable resource is expanded and optimized. As the majority of NP/PA clinical encounters are follow-up visits accomplished "independently", an opportunity to maximize the rheumatology workforce occurs when physicians, NPs and PAs function to the highest level of their licensure. Our data is limited only to NP/PA ARHP members and does not fully reflect NP/PAs in the rheumatology workforce. Recruitment and training strategies to increase the number of rheumatology NP/PAs to augment the workforce and improve access-to-care should be explored.

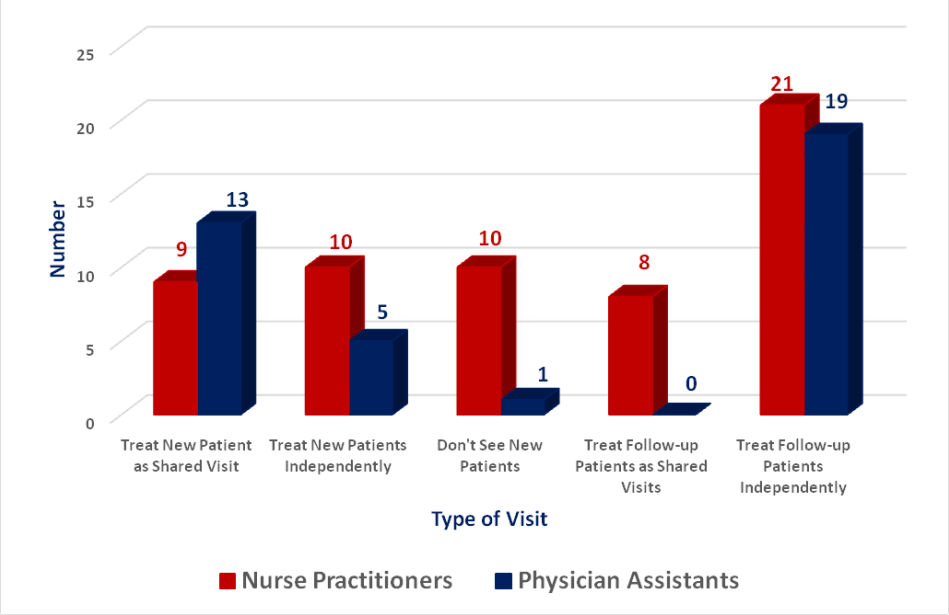

Figure 1. Comparison of Shared vs. Independent Visits NPs vs. PAs.

Disclosure: B. J. Smith, ARHP, 9; **M. B. Bolster**, ARHP, 9; **M. Ditmyer**, None; **K. B. Jones**, None; **S. Monrad**, None; **D. Battafarano**, None.

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Abstract Number: 2086

Hexagonal Phase Phospholipid Neutralization Assay Is the Most Sensitive but Least Specific Among Nine Tests for Detecting APS in SLE or Non-SLE Patients

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SESSION INFORMATION

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Session Title: Antiphospholipid Syndrome - Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Antiphospholipid antibody syndrome (APS) is an autoimmune, hypercoagulable state which may elicit thrombosis and pregnancy loss. Although several tests exist to guide diagnosis of APS and SLE, their utilization has been highly variable among laboratories. Therefore, we have introduced a panel of nine tests and examined their sensitivity and specificity for supporting the diagnosis of APS in SLE and non-SLE patients at our Institution between 2010 and 2015.

Methods: 356 SLE and 288 non-SLE patients were evaluated for the presence of APS, as earlier defined (*J. Thromb. Haemost.* 4:295-306). SLE patients satisfied the ACR criteria for a definitive diagnosis (*Arthritis Rheum.* 25:1271-1277; *Arthritis Rheum.* 40:1725). Lupus anticoagulants were assessed in house on fresh samples within 24 h of acquisition by hexagonal phase phospholipid neutralization assay (HPPNA; delta <10 seconds; Stago, Parsippany, NJ), diluted Russell viper venom test (DRVVT; <1.2 normalized ratio; Stago), and platelet neutralization procedure (PNP; delta < 1 second) using a STA-R Evolution instrument (Stago). IgG, IgM, and IgA antibodies against β2-glycoprotein 1 (aβ2-IgG, aβ2-IgM, aβ2-IgA) and cardiolipin (aCL-IgG, aCL-IgM, aCL-IgA) were measured by Quest Diagnostics (Madison, NJ). Sensitivity and specificity for detection of APS was calculated in both SLE and non-SLE patients and compared amongst these assays by χ^2 test using GraphPad software (San Diego, CA).

Results: 77/356 SLE patients had APS when using a combination of nine tests. Table 1 shows the frequency of positive and negative test results and p value for each assay in the SLE cohort. HPPNA has provided by far the greatest sensitivity at 73% for detecting APS in SLE patients relative to all other tests. In contrast, HPPNA has lower specificity at 85% as compared to all other test. While not shown, HPPNA also exhibited the greatest sensitivity at 78% for detecting APS in 61/78 non-SLE patients. Importantly, the 2nd most sensitive test for detection of APS in non-SLE patients was DRVVT at 14.3%; which was lower than that of HPPNA (chi-square $p<0.0001$). However, DRVVT had greater specificity at 96% for detection on APS in non-SLE subjects ($p<0.0001$).

Conclusion: This study indicates that HPPNA is the most sensitive but least specific assay for detecting APS both in SLE and non-SLE subjects. While it has been underutilized in a survey of 53 North-American Coagulation Laboratories (*Am. J. Clin. Pathol.* 134:764-773), these data clearly indicate the relevance of HPPNA for the clinical diagnosis of APS in patients who need long-term anticoagulation to prevent life-threatening thrombotic events.

Table 1. Sensitivity and specificity of nine test for detection of APS in SLE patients									
TEST	HPPNA	PNP	DRVVT	aβ2-IgG	aβ2-IgM	aβ2-IgA	aCL-IgG	aCL-IgM	aCL-IgA
APS+TEST+	54	15	16	11	5	8	21	18	8
APS+TEST-	20	22	51	55	61	58	52	54	61
APS-TEST+	40	4	5	0	8	9	5	23	3
APS-TEST-	226	141	234	262	258	257	262	247	245
p value	<0.0001	<0.0001	<0.0001	<0.0001	0.23	0.0039	<0.0001	<0.0001	<0.0001
Sensitivity (%)	73	41	24	17	8	12	29	25	12
p value vs HPPNA	-	0.0009	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Specificity (%)	85	97	98	100	97	97	98	91	99
p value vs HPPNA	-	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Disclosure: K. Banki, None; **P. Aleksiejuk**, None; **J. Patel**, None; **A. Perl**, Pfizer Inc, 2.

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Abstract Number: 2087

A Type I Interferon Signature in Monocytes and Decreased Levels of Circulating Plasmacytoid Dendritic Cells in Patients with Primary Antiphospholipid Syndrome

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In several autoimmune diseases, most notably in systemic lupus erythematosus (SLE), a type I interferon (IFN) signature has been described. This signature is thought to be related to the activation of plasmacytoid dendritic cells (pDCs) and their subsequent production of type I IFN. Whether a type I IFN

signature is also present in patients with (primary) antiphospholipid syndrome ((P)APS) and its contribution to its pathophysiology is as of yet unknown. Therefore, we assessed the presence of a type I IFN signature in monocytes of SLE, SLE+APS and PAPS patients and determined the frequency of pDCs as key producers of type I IFN.

Methods: The expression of four type I IFN inducible genes Ly6E, IFITM1, IFI44L and Serping-1 was determined by RT-qPCR in monocytes isolated from peripheral blood of healthy controls (HC, n=24), patients with SLE (n=52), SLE+APS (n=30) and PAPS (n=24). Expression levels were used to calculate a type I IFN signature score. The frequency of pDCs was determined by flow cytometry by double positive staining for BDCA2 and BDCA4. The percentage of classical, intermediate and non-classical monocyte subsets was determined by CD14 and CD16 expression using flow cytometry on isolated monocytes.

Results: The mean (±95% confidence interval) type I IFN score was 1.91 (1.52 – 2.30, $p<0.001$) in SLE patients, 1.74 (1.27 – 2.20, $p<0.001$) in SLE+APS patients and 0.97 (0.41 – 1.54, $p=0.03$) in PAPS patients as compared with 0.00 (-0.36 – 0.36) in HC. SLE patients had a statistically significant higher type I IFN score as compared with PAPS patients ($p=0.014$). The median frequency (interquartile range) of pDCs in SLE, SLE+APS and PAPS was respectively 0.22% (0.15 – 0.38, $p=0.005$), 0.24% (0.20 – 0.30, $p=0.003$) and 0.18% (0.14 – 0.35, $p=0.004$) as compared with 0.40% (0.25 – 0.49) in HC. In patients with SLE, the type I IFN score correlated with disease activity. Although not related to a clinical or serological APS phenotype or the expression of tissue factor, the type I IFN score correlated with the proportion of monocytes subsets in APS patients.

Conclusion: We confirm the presence of a type I IFN signature in monocytes of SLE patients but show for the first time the presence of this in PAPS patients as well. In line what has been reported in SLE, pDCs frequencies are reduced in the circulation of PAPS patients as well. Altogether, these observations justify further research into the role of pDCs in the pathogenesis of PAPS aside to that in SLE.

Disclosure: L. L. van den Hoogen, None; **R. D. E. Fritsch-Stork**, None; **M. A. Versnel**, None; **R. H. W. M. Derksen**, None; **J. A. G. van Roon**, None; **T. R. D. J. Radstake**, None.

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Abstract Number: 2088

Rituximab Use in Pediatric Lupus Anticoagulant Hypoprothrombinemia Syndrome – Report of Three Cases and Review of the Literature

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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

Lupus anticoagulant hypoprothrombinemia syndrome (LA-HPS) is a rare condition that may predispose to both thrombosis and bleeding due to positive lupus anticoagulant (LA) and factor II (FII) deficiency. It can be seen in association with infections or systemic lupus erythematosus (SLE) and may require glucocorticoids (GC) and/or immunosuppressive medications. The purpose of this report is to describe the novel use of rituximab (RTX) as a steroid-sparing agent in three pediatric SLE cases and to systematically review the literature on pediatric cases of LA-HPS.

Methods:

Pediatric LA-HPS cases that received only RTX for LA-HPS (in addition to GC) at two institutions between January 2010 and June 2016 were analyzed descriptively. PubMed was queried for "pediatric" or "children" and "lupus anticoagulant hypoprothrombinemia", "acquired hypoprothrombinemia", "lupus anticoagulant" or "hypoprothrombinemia", retrieving all articles in English. Relevant articles and their references were checked. Pediatric LA-HPS cases (≤18 years) with bleeding or thrombotic events were included in the systematic analysis. Information obtained included demographics, presenting symptoms, diagnoses, treatments, pre/post-treatment prothrombin time (PT)/partial thromboplastin time (PTT)/LA/FII levels and outcomes.

Results:

In addition to three LA-HPS cases identified at our institutions (Table 1), as of June 2016, 35 articles reported 52 pediatric LA-HPS cases [mean age: 7.9y (10m – 17y); Female/Male: (2:1); viral illness 27 (52%), SLE 20 (38%), and other 5 (10%)]. All cases had a positive LA and FII deficiency (range: 0-40%). All cases presented with bleeding diathesis and were treated with various regimens, but there was no reported use of RTX. Of cases with viral illness, 23/27 (85%) received no or supportive treatment alone with 4/27 (15%) receiving GC and/or immunosuppressive medications. Of SLE cases, the majority 18/20 (90%) received GC [7/18 (39%) combined with immunosuppressive medications] with only 1/20 (5%) receiving supportive treatment alone. Post-treatment LA and FII were checked in 29/52 (56%) and 34/52 (65%) cases respectively. Patients had complete resolution: 25 (48%), partial/clinical resolution: 23 (44%), or no response/not available: 4 (8%) based on further bleeding diathesis/thrombotic events and post-treatment FII levels.

-

Conclusion:

Based on our experience with three pediatric SLE LA-HPS patients, RTX: a) is an effective steroid sparing agent; b) improves or normalizes FII levels; and c) does not affect LA positivity. Our systematic literature review of pediatric LA-HPS cases demonstrates that: a) viral illness-associated LA-HPS is mostly transient; b) steroid is the mainstay in the acute management of SLE-associated LA-HPS; c) there are no standardized maintenance treatments for SLE-associated LA-HPS; and d) there is no reported use of RTX in the literature.

Table 1: Rituximab and Glucocorticoid Combination Therapy in three pediatric SLE cases with LA-HPS

	Case 1	Case 2	Case 3
Demographics	11 yo Hispanic female	16 yo Hispanic male	13 yo Hispanic male
Presenting symptoms	Mucosal (gum) bleeding	Deep vein thrombosis Recurrent epistaxis*	Persistent epistaxis
Pre-treatment LA	+	+	+
Pre-treatment average Factor II level**	9.9%	10.6%	5.0 %
Treatment	IV pulse (30mg/kg) MPD x 5d, PO GC RTX 750mg/m^2 x 2, 2 wk apart	IV pulse (30mg/kg) MPD x 3d, PO GC RTX 750mg/m^2 x 2, 2 wk apart^	IV high dose (2mg/kg) MPD, PO GC RTX 750mg/m^2 x 2, 2 wk apart (mo 0,6)
Post-treatment LA	+ (8 mo)	+ (6 mo)	- (9 mo)
Post-treatment Factor II level	40% (5mo)	45% (3 mo)	100% (31 mo)
Outcome°	Partial resolution	Partial resolution	Complete resolution
GC dose (1 year)	0.5 mg/kg	0.3 mg/kg	0.1 mg/kg

LA-HPS: lupus anticoagulant hypoprothrombinemia syndrome, SLE: systemic lupus erythematosus, yo: years old, mo: months, wk: week, d: day, IV: intravenous, PO: oral, MPD: methylprednisolone, GC: glucocorticoid, RTX: rituximab
*Two years after deep vein thrombosis
**Factor II level normal range 79-135%
^Treated with RTX two years after initial presentation
°Complete resolution: no further bleeding diathesis/thrombotic events and normal FII level; Partial resolution: improved or resolved bleeding diathesis/thrombotic events and improved FII level (not normal); Clinical resolution: no further bleeding diathesis/thrombotic events and FII level not available or not improved; No response: persistent or new bleeding diathesis/thrombotic events (regardless of FII level)

Disclosure: K. Cetin Gedik, None; **S. Siddique**, None; **C. L. Aguiar**, None; **D. Erkan**, None.

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Abstract Number: 2089

Deviation of T and B Cell Subset and Its Association with Single Nucleotide Polymorphisms in Patients with Antiphospholipid Syndrome

Ryo Hisada[1], Masaru Kato[1], Hisako Nakagawa[2], Eri Sugawara[1], Masatoshi Kanda[1], Kazumasa Ohmura[1], Ikuma Nakagawa[1], Kenji Oku[1], Toshiyuki Bohgaki[1], Olga Amengual[1], Tetsuya Horita[1], Shinsuke Yasuda[1] and Tatsuya Atsumi[1], [1]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [2]Department of Probiotics Immunology, Institute for Genetic Medicine, Hokkaido University, Sapporo, Japan

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Session Type: ACR Poster Session C

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Background/Purpose: Antiphospholipid syndrome (APS) is a well-characterized autoimmune and thrombotic disorder but its pathogenesis remains to be elucidated. Genomic studies have revealed the association of signal transducer and activator of transcription 4 (STAT4) and B lymphoid kinase (BLK) with APS, suggesting the involvement of T cell differentiation and B cell maturation in the development of APS. However, little information has been available on the role of T and B cells in the pathogenesis of APS. We aimed to identify the deviation of lymphocyte subset and its association with single nucleotide polymorphisms (SNPs) in APS patients.

Methods: This cross-sectional study included patients with primary APS (PAPS), APS associated with systemic lupus erythematosus (SLE/APS) and healthy controls. Peripheral blood mononuclear cells and genomic DNA were obtained from these subjects. T cells were analyzed into 12 subsets with markers as follows; CD3, CD4, CD25, CD45RA, CD127, CD45RA, CCR6, CCR7, CXCR3, CXCR5. B cells were analyzed into 6 subsets with markers as follows; CD3, CD4, CD24, CD27, CD38, IgD. In addition, a total of 28 SNPs, which had been shown to associate either with SLE or with thrombotic diseases, were analyzed by TaqMan genotyping assay.

Results: Seventeen PAPS, eight SLE/APS patients and eight healthy controls were included in this study. In T cell analysis, Th2 cells ($CD3^{+}CD4^{+}CD45RA^{-}CCR6^{-}CXCR3^{-}CXCR5^{-}$) were increased in PAPS ($p = 0.016$, Dunnett's test) and SLE/APS ($p = 0.013$) patients compared to healthy controls. Resting regulatory T cells ($CD4^{+}CD25^{int/high}CD45RA^{+}CD127^{low}$) were decreased in PAPS patients compared to healthy controls ($p = 0.017$). In B cell analysis, pre-switched memory B cells ($CD3^{-}CD19^{+}$ $CD27^{+}IgD^{+}$) and post-switched memory B cells ($CD3^{-}CD19^{+}CD27^{+}IgD^{-}$) were simultaneously decreased in PAPS patients compared to healthy controls ($p = 0.022$ and $p = 0.016$, respectively). In SNPs analysis, one of Toll-like receptor 7 gene polymorphisms (rs3853839) was associated with the decrease of post-switched memory B cells observed in PAPS patients ($p = 0.038$).

Conclusion: In APS patients, Th2 cells were increased while resting regulatory T cells, pre- and post-switched memory B cells were decreased. Furthermore, association between Toll-like receptor 7 and a decrease of memory B cells was found in APS patients. The deviation in lymphocyte subsets in patients with APS could be, in part, immunogenetically regulated, presumably contributing to the development of this syndrome.

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Abstract Number: 2090

Investigating the Genetic Variations of Antiphospholipid Syndrome By High-Throughput Exome Sequencing

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Background/Purpose: The antiphospholipid syndrome (APS) is an autoimmune disease characterized by the presence of antiphospholipid antibodies in serum together with clinical manifestations such as thrombosis, fetal loss, hemolytic anemia, and thrombocytopenia. Along with a crucial role of antiphospholipid antibody, proofs of the genetic predisposition of APS are not fully elucidated. The purpose of this study is to identify the novel genetic variations of primary and secondary Korean APS patient group.

Methods: Genomic DNA was isolated from 6 patients of established APS and 6 age/gender-matched healthy control's blood sample and whole-exome sequencing was performed using the Illumina HiSeq-2500 platform. Samples were submitted through analysis software where sequencing reads were mapped to the human reference genome (GRCh37, UCSC hg19 from NCBI, Feb 2009) using the Burrows-Wheeler Aligner algorithm, with removal of PCR duplicates using Picard. Local re-alignment, base quality recalibration and variant calling were performed using the Genome Analysis Toolkit. The potential effect of rare coding-sequence single nucleotide variants were predicted using predictive tools that included Polyphen-2, SIFT, and combined annotation-dependent depletion (CADD) Phred. To sort novel variation in patients group, <span">all variants observed in HapMap, dbSNP, 1000 Genome, and NHLBI ESP6500 databases w<span">ere filtered to be eliminated. Demographic, Clincal (cerebral infarction, pulmonary thromboembolism or recurrent pregnancy loss) and laboratory (lupus anticoagulant, anti-cardiolipin antibody, anti-beta2-glycoprotein1antibody) parameters were reviewed from the medical record of APS group.

Results: Overall mean target exon coverage was 96.4% of targets with at least one read at a mean depth of 185–223× in patients group. A total of 43 potentially disease-associated variants observed in APS group that were absent from the reference databases were identified. 30 of them were missense variants (*MST1L, TUBA3E, IDUA, HGC6.3, C7ORF26, MUC3A, METTL2B, RP1L1, ADAMTSL2, SUFU, TPBGL, CCDC168* etc), 11 frameshift (*HLA-DR5, CD36, ATXN3, HS3ST6, LILRB3, FAM47C* etc), and 2 stop variants (*PABPC3, CCDC154*). Notably, *CD36*gene on chromosome 7 (NM_000072.3) encodes the major glycoprotein of the platelet surface, which serves as a receptor for thrombospondin and is involved in cell adhesion /blood coagulation, shows frameshift variant in 5/12 alleles of APS group.

Conclusion: We demonstrated high-throughput profiling of the genomic and transcriptomic data in APS patient group. Several novel, potentially disease-associated variants were identified. Further investigation regarding functional relationship with APS pathogenensis, and comparison between primary and secondary APS is needed.

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Abstract Number: 2091

Antiphospholipid Syndrome Patients' Time within Therapeutic Range

of International Normalized Ratio (INR)

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Background/Purpose: Antiphospholipid Syndrome (APS) is a systemic autoimmune disease characterized by recurrent arterial or venous thrombosis and/or recurrent pregnancy morbidities, with persistently positive antiphospholipid antibodies. Patients with APS who have had a thrombosis require anticoagulation with a vitamin K antagonist (VKA), mainly warfarin, to a target international normalized ratio (INR) indefinitely. The purpose of this study was to investigate whether patients with APS are spending more or less time within therapeutic range (TTR) of INR compared to non-APS controls.

Methods: All patients within a large, multi-center university hospital system with possible APS who were also prescribed warfarin between July 2012 and July 2015 were first identified, and then chart reviewed for accuracy. True diagnosis was based on an APS diagnosis identified as the reason for anticoagulation in chart notes, or fulfillment of Sapporo criteria for diagnosis of APS while being prescribed warfarin therapy. These patients were then age- and sex-matched with controls, consisting of all non-APS patients who were on warfarin. The TTR for each patient was calculated using the percent of days in range (Roosendaal method). The APS and control patients' TTR values were compared overall, as well as in subcategories such as the type of thrombotic event, presence of lupus anticoagulant, and enrollment in a pharmacy monitoring program.

Results: Of 149 patients surveyed, there were 45 APS patients who met all inclusion criteria. These were matched with 45 control patients. There were no differences seen for any of the analyzed variables, including mean INR, when comparing controls with APS patients. As determined by logistic regression analysis, using the 50th percentile as a cut-off, an increase in 10 years of age was associated with having higher TTR [p=0.01, OR=1.91 (1.17-3.12)], though this association was only seen in APS patients, and not in the controls. Positivity for the lupus anticoagulant did not affect TTR. Patients who were enrolled in a pharmacy monitoring program had increased TTR for both controls [p=0.011, OR=5.77 (1.50-22.15)] and APS patients [p=0.011, OR=9.02 (1.64-49.58)]. When comparing TTR values for patients with the same thrombotic event type, most TTR values were similar, however, APS patients with deep vein thrombosis had a higher TTR as compared to the controls (p=0.016).

Conclusion: APS patients and controls have no significant difference in TTR values, even when analyzing specific manifestations, with the exception of venous thrombosis, which was slightly better managed in APS patients. Young APS patients, but not controls, had markedly decreased TTR, independent of disease duration. Individuals enrolled in a pharmacy monitoring program had, in general, more visits, longer duration of treatment and reached their TTR to a higher degree. Surprisingly, the presence of certain antiphospholipid antibodies also did not impact TTR. This study indicates that there is no evidence that anticoagulation with a VKA (most often warfarin) is particularly difficult, or that TTRs in patients with antiphospholipid syndrome are different in this regard than a control population.

Disclosure: M. Greenfield, None; **L. Durcan**, None; **G. Del Zoppo**, None.

Abstract Number: 2092

Plasma Soluble Triggering Receptor Expressed on Myeloid Cells-1 Is Elevated in Patients with Thrombotic Primary Antiphospholipid Syndrome.

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Background/Purpose : Primary antiphospholipid syndrome (PAPS) is characterized by thrombotic and/or obstetrical morbidity in the presence of persistent antiphospholipid antibodies (APLA) and in the absence of other autoimmune disease. APLA are necessary, but not sufficient for the clinical manifestations of APS. Triggering receptor expressed on myeloid cells-1 (TREM-1) is an innate-immune cell-surface receptor involved in amplification of TLR-4-mediated inflammatory response. Soluble TREM-1 (sTREM-1) reflects membrane TREM-1 upregulation and exerts an anti-inflammatory effect. **Aim**: To determine plasma level of sTREM-1 in .patients with PAPS

Methods: A cross-sectional, case-control study. Plasma level of sTREM-1 was analyzed by ELISA in a cohort of consecutively recruited patients diagnosed with PAPS (defined by Sapporo criteria), asymptomatic patients with persistently positive APLA, and healthy controls (HC). Patients diagnosed with other inflammatory disease, .and/or with concurrent infection, and/or malignancy as well as during pregnancy or puerperium were excluded

Results: The study groups comprised of 36 patients with PAPS (age 50.25±16.4 yrs.), 10 asymptomatic APLA-53.5±18.4 yrs.) and 21 HC (30.19±6.3 yrs.). Of the PAPS group, 30 patients (83.3%) had) positive patients thrombotic and/or obstetrical features prior to the study encounter (past PAPS), while 6 patients (16.7%) were evaluated at the time of PAPS-related thrombotic event (current thrombotic PAPS). The mean plasma sTREM-1 level was significantly greater in the PAPS group compared to HC (98.1±95.0 pg/ml, vs. 45.5±10.46 pg/ml, p=0.0013), between current thrombotic PAPS and HC (p=0.0002) and asymptomatic APLA (64.3±28.7 pg/ml, p=0.03), as well as between past PAPS and HC (p=0.02). Plasma sTREM-1 was positively correlated with older age (r=0.59, p<0.0001), higher ferritin level (r=0.44, p=0.005), higher ESR (r=0.43, p=0.003) as well as with elevated serum creatinine (r=0.64, p<0.0001) and lower eGFR (r=-0.63, p<0.0001). Plasma level of

sTREM-1 was not different in the asymptomatic APLA group compared to HC. Plasma sTREM-1 level was significantly higher in the PAPS patients who ever had MI ($p<0.001$), stroke ($p=0.02$), venous thrombophlebitis ($p=0.02$), pulmonary embolism ($p=0.001$), and arterial thrombosis ($p<0.0001$). Plasma sTREM-1 level was neither associated with anti-cardiolipin, anti-β_2 glycoprotein I (IgG/IgM/IgA) Abs' titers and/or lupus anticoagulant positivity, nor with single-, double- or triple- APLA positivity. A multivariate regression model was used to predict the sTREM-1 level by thrombotic PAPS ever, age, diabetes mellitus, hypertension and dyslipidemia found that sTREM-1 level is independently associated with thrombotic PAPS ($p = 0.001$).

Conclusion: Our data show for the first time that plasma sTREM-1 level is significantly elevated in patients with PAPS as well as during a thrombotic PAPS event. Soluble TREM-1 might be used as a biomarker for thrombosis .in patients with PAPS

Disclosure: Y. Molad, None; **Y. Edel**, None; **Y. Pri-Paz Basson**, None; **E. Pokroy-Shapira**, None; **S. Oren**, None; **A. Dortort**, None; **V. Kliminski**, None.

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Abstract Number: 2093

Association of Conventional Risk Factors and Antiphospholipid Antibodies to Thrombosis in Patients with Autoimmune Diseases: Lessons Learned from a Year-Long Systematic Assessment

Polona Žigon[1], Anuška Podovšovnik[2], Ales Ambrozic[3], Matija Tomsic[1], Alojzija Hocevar[1], Natasa Gaspersic[3], Ziga Rotar[1], Sonja Praprotnik[4], Snezna Sodin Semrl[1,5] and Saša Čučnik[1,6], [1]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [2]Divison of Internal Medicine, General Hospital Izola, Izola, Slovenia, [3]Department of Rheumatology, University Medical Centre Ljubljana, 1000 Ljubljana, Slovenia, [4]Department of Rheumatology, University Medical Centre Ljubljana, Slovenia, Ljubljana, Slovenia, [5]Faculty of Mathematics, Natural Science and Information Technology, University of Primorska, Koper, Slovenia, [6]Faculty of Pharmacy, University of Ljubljana, Ljubljana, Slovenia
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Background/Purpose: Patients with autoimmune disorders are at risk for thrombotic events and antiphospholipid antibodies (aPL) are one of known markers of increased thrombotic risk. The aims of our cross-sectional retrospective study were a) to evaluate association of different risk factors with thrombosis and b) to calculate the risk score of individual patients for experiencing thrombosis on a large cohort of unselected patients

with autoimmune diseases, treated at our secondary/tertiary medical center.

Methods: Lupus anticoagulant (LA)[1], IgG, IgM, and IgA isotypes of anti-cardiolipin antibodies (aCL)[1], anti-β2glycoprotein I (anti-β2GPI)[1] and anti-phosphatidylserine/prothrombin antibodies (aPS/PT)[1] were determined in sera of 585 consecutive patients with inflammatory rheumatic diseases and different conditions (Table 1) between January 1 and November 30, 2014. Medical records were analyzed, looking at patient age, gender, body mass index (BMI), thrombocytopenia, arterial hypertension, hyperlipidemia, diabetes, smoking, history of thrombotic or obstetric complications and current therapy including oral contraception. **Table 1: Patients' clinical characteristics**

No. of patients with	Venous Thrombosis	Arterial Thrombosis	Obstetric Complicaitons
APS (107)	52	40	39
Cerebrovascular insult (18)	3	15	1
Systemic lupus erythematosus (54)	2	0	4
Rheumatoid arthritis (14)	1	1	0
Sjogren's syndrome (34)	1	0	2
Systemic sclerosis (7)	0	0	0
Spondylo-arthritis (34)	0	0	5
Polymyalgia rheumatica (6)	2	0	0
Giant-cell arteritis (26)	1	3	1
Other Vasculitis (26)	2	2	0
Patients with different conditions (259)*	25	19	78

*Raynaud's phenomenon, migraine, depression, fibromyalgia, ischemic lesions.

Results: A univariate logistic regression revealed that BMI, hiperlipidemia, arterial hypertension, use of oral contraceptive pill and thrombocytopenia were significantly associated with thrombosis (Table 2). Among tested aPL only IgM isotype of aCL and anti-β2GPI showed no association to thrombosis. A thrombotic risk score calculation (TRS) was constructed by assigning to each of the 13 variables showing significant correlation to thrombosis, a number of points proportional to its β-regression coefficient divided by the value of the lowest β-coefficient (βx/βmin). TRS values were significantly higher in patients with thrombosis than non-thrombotic patients (median (IQR) 2 (0-7)) vs. 8 (2-13), p<0.001), showing area under ROC curve of 0.703. **Table 2: Association of risk factors to thrombosis**

Conventional risk factor for thrombosis	n	OR (95% CI)	p	β-coefficient	βx/βmin
Smoking	539	0.903 (0.589-1.383)	0.638		
Bosy mass index	488	1.561 (1.025-2.378)	0.037	0.61	1
Hiperlipidaemia	500	2.795 (1.836-4.256)	<0.001	1.51	2
Arterial hypertension	582	2.321 (1.575-3.419)	<0.001	3.85	6
Oral contraceptive pill	431	5.407 (2.039-14.340)	<0.001	13.00	21
Thrombocitopenia	569	1.907 (0.995-3.654)	0.049	2.36	4
Diabetes	529	1.471 (0.701-3.087)	0.305		
aPL association to thrombosis	**n**	**OR (95% CI)**	**p**	**β-coefficient**	**βx/βmin**
LA	358	2.8 (1.7-4.7)	<0.001	2.686	5
aCL IgG	582	2.4 (1.6-3.9)	<0.001	1.361	3
aCL IgM	582	1.4 (0.7-3.1)	0.341		
aCL IgA	582	5.3 (1.0-28.9)	0.034	0.917	2
anti-beta IgG	582	2.5 (1.5 -4.2)	<0.001	0.881	2
anti-beta IgGM	582	1.4 (0.7-2.9)	0.409		
anti-beta IgGA	582	2.6 (1.4 -5.07)	0.003	1.163	2
aPS/PT IgG	582	3.3 (1.7-5.9)	<0.001	1.686	3
aPS/PT IgM	582	2.0 (1.1 -3.5)	0.022	1.154	2
aPS/PT IgA	582	2.6 (1.2-5.3)	0.009	0.500	1

Conclusion: Our results show that, in addition to various conventional risk factors, aPS/PT (all isotypes), aCL (IgG and IgA) and anti-β2GPI (IgG and IgA) associate with thrombotic risk in patients with autoimmune diseases. Calculation of a TRS accounting for significant conventional risk factors and aPL, better assesses thrombotic risk in different patients with autoimmune diseases compared to evaluating individual or just conventional factors alone.

1. Zigon et al, Thrombosis, Atherosclerosis and Atherothrombosis - New Insights and Experimental Protocols, Chapter 6, InTech 2015

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Abstract Number: 2094

Complement Activation in Antiphospholipid Syndrome Due to the Multi-Activated Pathways of the Complement System

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Background/Purpose: Complement activation is proposed as one of the major thrombophilic mechanisms in antiphospholipid syndrome (APS). Among three complement pathways (classical, alternative and lectin), activation of classical pathway triggered by the immune complexes (IC) composed of antiphospholipid antibodies (aPL) has been considered as the mainstream of the phenomenon. However, we have reported that in APS patients, the serum IC levels were relatively low, and antibodies against C1q, the first component of the classical pathway that boost the complement activation immunologically are highly present. Recently, in vitro reports revealed that beta-2 glycoprotein I, a major target of aPL, interacts with the factor H (FH), one of the complement regulatory factors (CRF). CRF are the group of proteins that suppress the excessive activation of complement pathway mainly in the alternative pathway, of which activation spontaneously cleaves C3 and spreads activation to the late complement components thus contributes to the acceleration of inflammation. Membrane cofactor protein (MCP) and FH are the two major CRF that inhibit the C3 cleavage. The former inhibits the cleavage on cell surfaces, and the latter soluble components. We evaluated them in APS patients.

Methods: The patients with connective tissue diseases including APS that visited the Hokkaido University Hospital rheumatology clinic during 2000 and 2013 were enrolled. The solid-phase enzyme-linked immunosorbent assays (ELISA) were performed as to detect the excessive activations of different complement pathways qualitatively (Wieslab® Complement system Screen, Euro Diagnostic). Serum MCP levels (MCP ELISA kit, Cloud-Clone) and FH levels (factor H human ELISA kit, Human Innovative Research) were also tested. Autoantibodies against FH were determined by western-blotting which detects the antibodies in 10% of patients with atypical hemolytic uremic syndrome, according to the previous reports (Moore et al, Blood, 2010 etc.).

Results: Twenty-six patients with primary APS (PAPS), 45 systemic lupus erythematosus (SLE), and 56 other autoimmune diseases (control) were enrolled. Serum complement levels of PAPS as well as SLE were low compared with control (C3: 85.9±35.6, 73.0±51.5 vs 109.4±42.8 mg/dl). In PAPS, 22/26 (84.6%) showed normal serum IC levels. Excessive complement activations over 99 percentile of normal healthy controls were observed in 5/26 for the classical pathway and 4/26 for the alternative pathway. The serum levels of MCP were in normal range in all the groups. On the contrary, serum FH levels were significantly depleted in PAPS as well as SLE compared with control (median 180.1, 146.1 vs 368.5 μg/ml, $p < 0.0001$). In PAPS, serum FH levels were positively correlated with serum C3 levels ($p = 0.015$, $R^2 = 0.502$), however no significant correlation with the presence of any aPL was confirmed. Autoantibodies against FH were not detected in any of the patients.

Conclusion: Complement activation in APS patients were multifactorial partly due to activation of classical pathway with less contribution of the circulating IC and the activation of alternative pathways mainly due to depletion of FH.

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Abstract Number: 2095

Autoantibodies Against High Density Lipoprotein-Associated Proteins Are Related to Elevated Oxidized Low Density Lipoprotein Levels in Antiphospholipid Syndrome

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Background/Purpose:

Oxidized low-density lipoprotein (oxLDL), a key molecule in atherogenesis, serves as the source of anionic charged particles that bind to beta2glycoprotein I (B_2GPI) and reinforces procoagulant activity or concomitant atherosclerosis in the presence of antiphospholipid antibodies(aPL). High density lipoprotein (HDL) is the major molecule not only blocks arteriosclerotic/procoagulant function of oxLDL but helps prevent LDL from oxidation with the assistance of HDL-associated proteins such as paraoxonase type 1 (PON-1) and apolipoprotein A-1 (ApoA-1).In antiphospholipid syndrome(APS), as well as in systemic lupus erythematosus (SLE), autoantibodies against HDL are prevalent and inversely correlate with serum HDL levels which may in turn, be associated with the production of oxLDL. In this study, we identified autoantibodies against HDL(aHDL), PON-1(aPON-1) or ApoA-1(aApoA-1) and explored their correlations with oxLDL in patients with APS.

Methods:

This study was designed as a retrospective and cross-sectional study and comprised a total of consecutive patients with primary APS (PAPS) (n=24),SLE (n= 47) and non-lupus connective tissue diseases (others)(n=19) who visited Hokkaido University Hospital Rheumatology clinic during 2009 and 2012. Blood samples of 52 healthy controls (healthy) were also investigated. Lupus anticoagulant assays and aPL ELISAs (IgG/M of anticardiolipin antibodies, anti-B_2GPI antibodies and phosphatidylserine dependent antiprothrombin antibodies) were performed in all patients.In-hose ELISA was used to detect aHDL, aApo-A1 and aPON-1 according to the previous report (Batuca *et al*, Rheumatology(Oxford), 2009). Serum oxLDL levels were measured with a commercial ELISA (MDA-oxLDL, Human, ELISA Kit,Biomedica, UK). Kruskal-Wallis test was employed to analyze the data of three or more groups

Results:

Among the patient groups, serum levels of lipoproteins (LDL, HDL) and the prevalence of statin treatment were comparable, while serum levels of oxLDL were significantly elevated in PAPS (PAPS vs. SLE vs. others (mean+/-2SD): 3.27+/-6.89 vs. 1.69+/- 4.35 vs. 0.8 +/- 3.72 mg/ml, $p<0.05$). Titers of aHDL were similar among the patient groups, while the titers of aApo-A1 and aPON-1 were significantly elevated in PAPS (aAPO-A1vs. PAPS vs. SLE vs. others vs. healthy (means +/-2SD) 0.93+/-0.63 vs. 0.63+/-0.94 vs. 0.45+/-0.50 vs. 0.42+/-0.96 mg/ml $p<0.002$) (aPON-1: PAPS vs. SLE vs. others vs. healthy(mean+/-2SD) 148+/-182 vs. 116 +/- 196 vs. 72.6 +/- 156 %positive control, $p<0.005$). In PAPS, patients with positive (over healthy control 99 percentile) aAPO-A1 and aPON-1 were significantly prevalent. Either antibody was positive in 14/24 of PAPS, whilst in SLE and others were 14/47 and 7/19, respectively ($p<0.01$). Double positivity (aApo-A1 and aPON-1) was found in 5/24 PAPS, 5/47 SLE and 1/19 in others($p<0.01$). None of the aPL or total aPL titers (aPL scores) correlated with autoantibodies related to HDL nor with oxLDL levels.

Conclusion:

Elevated oxLDL in PAPS may be one of the causal mechanisms of the disease and might be consequence of the impairment of the antioxidant function of HDL induced by the presence of aApoA-I and aPON .

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Venous Antiphospholipid Syndrome: Is the Unprovoked Nature of the 1st Thrombosis Associated with Clinical or Biological Features?

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Background/Purpose: Risk of recurrence after a first episode of venous thrombo-embolism (VTE) is strongly correlated to VTE characteristics. Indefinite anticoagulation is recommended for patients with unprovoked VTE. VTE is the most frequent manifestation of antiphospholipid syndrome (APS). However a search for antiphospholipid antibodies (aPL) is not systematically performed after a provoked thrombosis. And although long-term anticoagulation is usually advised in APS, some authors have suggested stopping anticoagulation in provoked VTE. We aimed to determine the features of venous APS, according to the provoked or unprovoked nature of the first thrombotic event.

Methods: We performed a retrospective study of patients who met Sidney criteria of APS, revealed by VTE. Provoked event was defined as major if VTE occurred < 12 weeks after surgery, after ≥ 3 days strict immobilization, or after lower-limb fracture and as minor if VTE occurred during travel, immobilisation, sepsis, oestrogen treatment or pregnancy. Other VTE were considered unprovoked.

Results: The files of 57 women and 30 men, with a mean age of 36.2 +/- 16.1 years were reviewed. VTE presented as: deep vein thrombosis (DVT) n= 46/87, pulmonary embolism +/- DVT n= 41/87. Laboratory exams revealed: lupus anticoagulant n = 67/87, triple positivity n = 38/87. VTE was provoked by major factors in 9 and minor factors in 36/87 patients. Pregnancy and oestrogens were involved in 29 cases. Mean follow-up was 121.7 +/- 73.1 months: 27 patients presented with one or more further thrombosis; the 1st recurrence was venous in 22 and arterial in 5/27 patients; 11/27 occured under anticoagulation. We found no correlation between clinical features and 1st recurrence. We observed one death related to catastrophic APS, and six major haemorrhages. In bivariate analysis, the unprovoked nature of VTE was associated with a higher age, male sex, dyslipidemia and past history of VTE. In multivariate analysis, we found no correlation between the nature of VTE and clinical or biological features at diagnosis or during follow-up.

Conclusion: Provoking factors are frequent in venous APS. In this venous APS cohort with numerous high risk-profile patients, provoked nature of VTE was not correlated to clinical or biological features. A search for aPL should be advised in young patients with VTE even if thrombosis is provoked. This study does not support the

hypothesis of a lower risk-profile of APS patients with provoked VTE.

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Abstract Number: 2097

Cardiolipin-Producing Candidate Commensals in the Gut Microbiome of Antiphospholipid Syndrome Patients

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Background/Purpose: Pathogen-associated transient antiphospholipid antibodies suggest a microbial trigger for antiphospholipid syndrome (APS). We hypothesized that the gut microbiota could represent a chronic stimulus in APS patients and defined the fecal microbiome and IgA-coated microbiota in APS patients over time and correlated them with autoantigen-related responses.

Methods: Anti-β_2-glycoprotein I (β_2GPI)-positive APS patients, patients with non-autoimmune thrombophilic states, and healthy donors were sampled at 3 time points (0, 4 and 8 weeks). Sixty stool samples of 22 APS patients, 13 samples of 6 controls, and 49 samples of 19 healthy donors were collected to date including dietary and medication history as well as HLA-DR53 genotype. PBMC proliferation to β_2GPI was determined by [^{3}H]-thymidine incorporation and autoantibodies against β_2GPIdomain I using a standardized kit (Inova). Stool DNA was PCR-amplified using barcoded primers targeting the V4 region of the 16S rRNA gene. Samples were sequenced using 2x250bp paired-end reads on an Illumina MiSeq instrument and analyzed using Quantitative Insights Into Microbial Ecology (QIIME) and Linear Discriminant Analysis Effect Size (LEfSe) methods.

Results: PBMCs from HLA-DR53+ APS patients responded preferentially to β_2GPI compared to controls. APS versus control fecal microbiomes showed a significant decrease in the genus *Bilophila* and an increase in the genus *Slackia* within the family of *Coriobacteriaceae* across multiple time points. 59% of APS patients but none of the control subjects were persistently positive for anti-domain I (DI) antibodies. Anti-DI IgG positivity correlated significantly with increased abundances of *Slackia* and a decrease in the butyrate-producing genus

Butyricimonas ($p<0.01$ for each taxon).

Conclusion: High-throughput sequencing of APS gut microbiomes revealed a persistent enrichment of the genus *Slackia* over time, particularly among the anti-DI IgG+ APS patients. *Slackia* is capable of producing phospholipids including cardiolipin. We speculate that gut commensal-derived cardiolipin contributes to a conformational change of β_2GPI exposing DI, thereby promoting autoreactivity against the major B cell epitope. Reduction of the butyrate producer *Butyricimonas* might associate with less regulatory T cells allowing for stronger proliferation towards β_2GPI as butyrate is known to directly induce this cell type. In summary, this ongoing microbiome study represents the first 16S rRNA community profiling in APS patients and uncovered an altered microbial community with potential implications for the pathogenesis of APS that will be tested in follow-up studies.

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Abstract Number: 2098

Non-Criteria Anti-Phospholipid Antibodies in SLE Patients

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Background/Purpose: Current classification criteria for definite antiphospholipid syndrome (APS) recommend the use of one or more of three positive standardized laboratory assays, including anticardiolipin antibodies, lupus anticoagulant, and antibodies directed to β(2)glycoprotein I. Several other autoantibodies have been proposed to be relevant to APS. The aim of the study was to assess the prevalence of non-criteria anti-phospholipid antibodies (APL) in patients diagnosed with systemic lupus erythematosus (SLE) and their association with APS diagnosis and its clinical manifestations.

Methods: The 449 subjects meeting SLE ACR classification criteria were evaluated. The following non-criteria APL were assessed by ELISA using standardized techniques: anti-phosphatidyl ethanolamine (aPE), anti-prothromin (aPTR), anti-phosphatidyl serine (aPS), anti-annexin V (AnV).

Results:

Non-criteria APL included aPTR in 28.1% patients, aPS in 19.7% patients , AnV in 24.2% patients, aPE in 21.1% SLE patients. In 127 patients with SLE APS was diagnosed. The diagnosis of APS was associated with the presence of aPE (OR:5.69) and aPTR (OR: 2.51). The risk of developing thrombosis occurred in patients

with presence of AnV IgG (OR 4.06), aPTR (OR 2.61) and aPS (OR 2,10).The presence of aPE IgM (OR 4.41), aPS (OR 2.27) and aPTR (OR 2.04) were risk factors for pregnancy failures. Epilepsy was significantly more common in patients with presence of aPE IgM (OR 4.75) and aPE IgG (OR 4.30).

Conclusion: Non-criteria APL are relatively common in patients with SLE and demonstrate a significant association with the diagnosis of APS, as well as its most important clinical symptoms.

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Microrna As Potential Modulators of Atherothrombosis in Antiphospholipid Syndrome

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Background/Purpose: 1) To identify and characterize microRNAs linked to thrombosis and atherosclerosis development in APS; 2) To assess the effects of antiphospholipid antibodies in that epigenetic process.

Methods: Six microRNAs proven to be involved in atherothrombosis development (miR-124-a, -125a, -125b, -146a, -155, and -222), were quantified in purified leukocytes from 23 APS and 56 healthy donors. In parallel, pro-inflammatory and prothrombotic proteins and oxidative stress markers were evaluated at both, plasma and cellular levels. Proteins related to the biogenesis of miRNAs (Drosha, Dicer, Ago-1, Ago-2 and Xpo-5) were quantified by RT-PCR and Western blot. The clinical cardiovascular disease (CVD) profile was further recorded in APS patients. In vitro experiments were performed in endothelial cells (ECs), monocytes, and neutrophils, which were treated with anti-phospholipid antibodies of IgG isotype (aPL-IgG) purified from APS patients' serum, or with IgG from healthy donors (IgG-NHS).

Results: Levels of microRNAs in neutrophils were lower in APS than in healthy donors. Accordingly, gene and protein expression of miRNA biogenesis-related molecules were reduced. In monocytes, miR124a and -125a

were low, while miR-146a and miR-155 appeared elevated. The expression levels of some miRNAs differentially expressed in neutrophils and monocytes significantly correlated with parameters related to autoimmunity, thrombosis, inflammation and oxidative stress. Association studies showed that the occurrence of thrombotic events and the presence of a pathological increase in the CIMT were linked to altered levels of a number of miRNAs in neutrophils and monocytes, as well as with low levels of proteins related to miRNA biogenesis. An additional control group, including 20 patients with thrombosis but without aPL was evaluated. Thrombotic patients displayed a specific profile of miRNA expression that differed from that of APS patients, thus indicating a differential mode of regulation and activity. In vitro treatment of neutrophils, monocytes, and ECs with aPL-IgG antibodies deregulated microRNAs expression, and decreased miRNA biogenesis-related proteins. Accordingly, aPL-IgG antibodies induced upregulation of MCP-1, TF and VCAM-1, and downregulation of eNOS, relevant markers of endothelial dysfunction, and potential targets of the miRNAs evaluated. Monocyte transfections with pre-miR-124a and/or -125a validated the data obtained, causing reduction in atherothrombosis-related target molecules.

Conclusion: 1. Specific miRNAs might act as modulators of atherothrombosis in APS patients. 2. Antiphospholipid antibodies regulate CVD in APS, at least partially, by regulating the biogenesis and the expression of miRNAs. Funded by CTS7940, PI15/01333.

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Abstract Number: 2100

Pharmaceutical Disruption of B2GPI CXCL4 Complex Using Computationally Designed Oligopeptides

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Background/Purpose: Antiphospholipid syndrome (APS) is an autoimmune thrombophilia characterized by recurrent thromboembolism and or pregnancy morbidity in the presence of antiphospholid antibodies (aPL). Major auto antigen is B2 Glycoprotein I (B2GPI). APL form immunocomplexes with B2GPI and activate platelets leading to thrombus formation. Previous studies have shown that APS patients have higher circulating levels of platelet derived chemokines. Among them CXCL4, a proinflammatory chemokine with antiangiogenic properties, has already been proven to bind and dimerize B2GPI leading to the formation of a triple complex,

aPl-B2GPI-CXCL4, which strongly activates platelets. Therefore, we aimed to investigate the pharmaceutical disruption of the B2GPI-CXCL4 interaction.

Methods: An in vitro binding assay was developed for the study of B2GPI-CXCL4 interaction. Briefly, 1 μg/ml B2GPI was coated overnight on high binding polystyrene plates and CXCL4 was incubated in various concentrations for 2 hours. Detection of CXCL4 was performed using a biotinylated polyclonal goat anti-human antibody against CXCL4 followed by Streptavidin-HRP incubation with TMB as substrate. Next in silico molecular docking experiments using the MAESTRO and GLIDE (Schrodinger Inc.) software determined the exact interaction residues of CXCL4 and B2GPI. A number of oligopeptide CXCL4 fragments was screened according to their capacity to bind on B2GPI on the interaction interface with CXCL4. The amino acid sequence of the most promising was further modified in order to achieve high binding strength and optimal solubility properties. Finally, four oligopeptides were designed and synthesized. These oligopeptides were tested using the aforementioned assay for their ability to bind on B2GPI and consequently to inhibit B2GPI-CXCL4 interaction. B2GPI was incubated with the oligopeptides prior to the addition of 10ng/ml of CXCL4.

Results: Preincubation of B2GPI with the peptides resulted in partial inhibition of B2GPI-CXCL4 interaction in all cases. Among them one presented the highest inhibiting properties which resulted in 40% inhibition of CXCL4 binding on B2GPI.

Conclusion: Preliminary results show that the designed peptides exhibit inhibiting properties. Further experiments and possibly amino acid alterations are required to determine their exact efficiency. Once desirable inhibition and solubility properties are achieved these oligopeptides could be tested as lead compounds for potential therapeutic agents.

Disclosure: M. Patsouras, None; **E. Papakonstantinou**, None; **E. Eliopoulos**, None; **P. G. Vlachoyiannopoulos**, None.

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Abstract Number: 2101

the Association Between ABO Blood Types and Venous Thromboembolism in Individuals with a Positive Antiphospholipid Antibody Profile Is Varied By Sex

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Background/Purpose: Venous thrombotic events (VTE) are the most common complications in patients with persistently positive aPL antibodies (aPL+)[1] · The pathogenesis of VTE is multifactorial, and not all aPL+ individuals develop thrombosis[2]. ABO blood type, a determinant of plasma levels of von Willebrand factor (vWF), is an established VTE risk factor in the general population, but not in aPL+ patients. In the general population, non-type O blood type is associated with a higher risk of VTE. The objective of this study was to investigate the association between ABO blood type and VTE in aPL+ patients.

Methods: We included patients >18 years old followed at an urban tertiary care center between 2000 and 2015 with the serologic criteria for aPL positivity by the revised Sapporo Criteria (anticardiolipin IgG or IgM >40 IU, and/or anti-beta-2- glycoprotein1 IgG or IgM >40 IU or positive lupus anticoagulant measured twice at least 12 weeks apart)[3] and a type and screen. VTE were verified by radiological criteria and historical records. Data including age, sex, race, body mass index, smoking status (ever smoker), blood type, hypertension, diabetes, and ever use of aspirin or warfarin were ascertained from chart review. Odds ratios of VTE were estimated with logistic regression models for O vs. non-O blood type. Because there was a significant statistical interaction between sex and ABO, the results were stratified by sex. Logistic regression models were adjusted for age, sex, race, DM, HTN, and smoking status.

Results: Of the 226 study patients, 47 (21%) were men. The rates of VTE were 33% overall, 38% among men, and 32% among women. Overall, men were slightly older, more likely to smoke and to receive anticoagulation (Table 1). There was no association between blood type and VTE in the overall sample (Table 2). However, the frequency of non-O blood type was significantly higher in men with VTE than in men without VTE, 72% and 35%, respectively. The odds of VTE were significantly higher among men with non-O blood type compared to men with O blood type, adjusted OR 4.7 (1.2, 18.7), p=0.03. The association between ABO and VTE was not significant among women. There was no association between ABO blood type and arterial thrombosis.

Conclusion: The association between ABO and VTE varies by sex in aPL+ individuals. Non-O blood type is associated with a higher risk of VTE in men, but not in women. The effects of ABO blood types on vWF in aPL+ individuals may be attenuated by genetic and environmental factors that differ by sex. Understanding the relationship between sex, ABO, and aPL may elucidate thrombosis mechanisms of VTE in aPL+ individuals.

Table 1. Baseline Characteristics of aPL positive Patients by Sex

Patient Characteristics	aPL positive women n=179	aPL positive men n=47	p-value
Age at aPL measurement, median (IQR), years	43 (29, 53)	47 (38, 63)	0.02
Black race, n (%)	57 (36)	16 (36)	0.92
Hispanic ethnicity, n (%)	61 (23)	11 (43)	0.22
History of diabetes, n (%)	63 (35)	22 (46)	0.15
History of hypertension, n (%)	112 (62)	36 (75)	0.08
Ever smoked, n (%)	56 (33)	23 (49)	0.04
Low Density Lipoprotein> 100 mg/dl, n (%)*	60 (53)	9 (27)	0.01
Body Mass Index, median (IQR), kg/m2	28 (23, 34)	28 (25, 36)	0.55
Aspirin use	88 (48)	26 (54)	0.48
Anticoagulant use	72 (40)	27 (56)	0.04
Prednisone use	88 (48)	26 (54)	0.47
SLE by ACR/SLICC Criteria	61 (36)	9 (21)	0.06
Non-type O blood type	91 (48)	23 (50)	0.80

References 1. Cervera R, et al. Arthritis Rheum. 46:1019–1027 2. Erkan D, et al. Rheumatology. 2002;41(8):924-9 3. Miyakis S, et al. J Thromb Haemost. 2006;4(2):295-306

Table 2. Rates and Odds Ratios of VTE for Non-O Blood Type

VTE	Non-O Blood Type n (%)	Unadjusted OR for VTE for Non-O Blood Type (95% CI)	p-value	OR for VTE Adjusted for Age, Race, DM, HTN (95% CI)	p-value
Overall Sample (n=75)	44 (59)	1.6 (0.94, 2.8)	0.08	1.7 (0.9, 3.1)	0.1
Men (n=18)	13 (72)	4.9 (1.4, 17.8)	0.01	4.7(1.2, 18.7)	0.03
Women (n=57)	31 (54)	1.2 (0.66, 2.3)	0.52	1.2 (0.58, 2.4)	0.65

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Abstract Number: 2102

the Prevalence and Associations of IgG/a/M ANTI-β2GPI and ANTI-Domain I Antibodies in an Antiphospholipid Syndrome (APS) Cohort of Patients from Turkey

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Background/Purpose: Domain(D)I is the immunodominant epitope of antiβ2-glycoproteinI(aβ2GPI) and in several studies antibodies to DI were shown to be associated with clinical manifestations of APS. Herein, we aimed to describe the prevalence, correlations and clinical associations of IgG/IgA/IgM aβ2GPI and aDI in an APS cohort of patients from Turkey.

Methods: Serum was obtained from 75 patients with: primary APS, n=31; systemic lupus erythematosus (SLE) and APS, n=44. IgG/IgA/IgM aβ2GPI, aDI and IgG anticardiolipin (aCL) were measured by ELISA. Positivity was defined as titres > 99th percentile of the mean activity of healthy control cohort. Cut-offs for positivity were: 17GPLU; 9GBU; 14GDIU for IgG aCL/aβ2GPI and aDI, 18MBU; 21MDIU for IgM aβ2 GPI and aDI, and 9ABU; 8ADIU for IgA aβ2 GPI and aDI respectively. Lupus anticoagulant (LA) was measured in the clinical laboratory of Istanbul Faculty of Medicine. Triple positivity was defined as IgG aβ2GPI/aCL and LA; double positivity as LA/IgG aCL, LA/IgG aβ2GPI or IgG aCL/aβ2GPI and single positivity as LA or IgG aCL or IgG β2GPI.

Results: 76% of the patients were female. The mean age and duration of disease were 40±11 years and 114±92 months respectively. 17 patients suffered arterial thrombosis (AT) only, 23 venous thrombosis (VT) only, 5 AT + VT, 15 pregnancy morbidity (PM) only, 13 thrombosis and PM and 2 catastrophic antiphospholipid syndrome. The prevalence and the titers of the tested antiphospholipid antibodies(aPL) are shown in tables 1 and 2. There were patients with single positivity for IgA aDI (n=2) and aβ2GP1 (n=1) and they all suffered vascular thrombosis. Comparison of the vascular thrombosis only and PM only groups revealed a significantly higher IgM aDI positivity (table1) and titer in the PM only group (mean, interquartile range; 14, 8 vs 22,15 respectively; p=0.04) There were 10 triple positives, 19 double and 49 single positives. 80% of patients with triple positivity had vascular thrombosis and all had IgG aDI antibodies. There was a positive correlation between IgG aβ2GP1 and DI ($p<0.05$). 58 % of double and 27 % of single positives had IgG aDI antibodies.

Conclusion: We found a high prevalence of IgA aβ2GP1 and aDI in this cohort. Given that some patients with thrombosis had single positivity for IgA aβ2GP1 and aDI, these tests may help to recognize a small group of patients with APS. Significantly more patients with PM only were positive for IgM aDI. Whether testing IgM aDI

may be of value in relation to PM needs to be validated. Despite lacking significance, the positivity for IgG aDI was higher in the vascular thrombosis group. IgG aDI was more frequent in triple-positives most of whom had thrombotic events. There was a positive correlation between IgG aDI and aβ2GPI which may show that DI is the major antigenic target in β2GPI and that IgG aDI antibodies can be used to identify APS patients with a high thrombotic risk. **TABLE** THE PREVALENCE OF THE TESTED aPL

	All patients (n=75)	Vascular Thrombosis only (n=45)	PM only (n=15)	P
IgG anti-β2GPI	17%	19%	14%	NS
IgA anti-β2GPI	36%	38%	43%	NS
IgM anti-β2GPI	36%	34%	36%	NS
IgG anti-DI	20%	26%	7%	NS
IgA anti-DI	36%	45%	29%	NS
IgM anti-DI	29%	21%	57%	**<0.05**
IgG aCL	29%	28%	29%	NS
LA	58%	57%	54%	NS

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Abstract Number: 2103

Peripheral Blood B Cells Are Expanded and Their Cytokine Expression Is Dysregulated in Juvenile Dermatomyositis

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Background/Purpose: Juvenile dermatomyositis (JDM) is a rare form of childhood autoimmune myositis that presents with proximal muscle weakness and heliotrope rash. B cells are strongly implicated in the pathogenesis of the disease and can generate myositis specific antibodies, that are associated with clinical subgroups. We propose that B cells may also contribute to the disease by producing pro-inflammatory cytokines, triggered by type I interferons.

Methods: Samples and data were collected from children with JDM recruited to the UK JDM Cohort and Biomarker Study. Peripheral blood mononuclear cells (PBMC) samples from JDM patients before treatment and on treatment were selected for analysis. PBMC from child healthy controls (CHC) (n=25) and JDM patients (n=61) were incubated in the presence of phorbol 12-myristate 13-acetate (PMA), Ionomycin and Golgi Plug for 4hrs and cytokine expression was analysed by flow cytometry. PBMC and sorted B cells were also stimulated for 48hr with R848 (TLR7/8) and assessed for intracellular IL-6 and IL-10 by flow cytometry and protein levels were measured by ELISA. PBMC were stained *ex-vivo* to look at B cell subset frequency and Ki67 expression. Differences between groups were analysed using paired/unpaired t tests or one-way ANOVA (Prism 6 software).

Results: B cell frequency was significantly higher in pre-treatment JDM patients compared to CHC samples (mean frequency of total PBMC 25.72% Vs. 22.69% (ns) (£6 months treatment) or 16.26% in CHC; $p<0.01$). This difference was most marked in the immature B cell subset (mean frequency of total B cells 36.05% Vs. 3.66% (£6 months on treatment) or 12.4% in CHC; $p<0.01$). The immature B cell subset was more proliferative before treatment (mean Ki-67% of 17.63% Vs. 8.86% (>6 months on treatment) or 7.18% in CHC; $p<0.01$). Whole transcriptome RNA sequencing of B cells from paired pre and on treatment patient samples showed an upregulation of the type I interferon signature. Of particular interest Toll-like receptor 7 (TLR7) was up-regulated in B cells from patients' pre-treatment. When B cells were stimulated with TLR7 agonist (R848) there was reduced expression of IL-10 detected by ELISA from JDM compared to CHC samples (10.61pg/ml Vs. 75.01pg/ml (mean values)). However, IL-6 expression responded the same in JDM compared to CHC (486.18pg/ml Vs. 414.29pg/ml (mean values)).

Conclusion: We have identified a subset of immature B cells that are expanded, more proliferative and express both IL-6 and IL-10 in pre-treatment patients. The up-regulated type I interferon signature in JDM could contribute to the expansion of immature B cells with an imbalance of IL-6 and IL-10 production.

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Abstract Number: 2104

Treatment with Tocilizumab Decreases CXCL13 Expression in Cultured Temporal Arteries from Patients with Giant Cell Arteritis

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Background/Purpose: IL-6 has been considered a biomarker of disease activity in GCA and a potential therapeutic target. However, the functional role of IL-6 in GCA has not been explored. IL-6 has important roles in B cell homeostasis and Th17 differentiation as well as in driving the acute–phase response which underlines systemic symptoms in GCA. Blocking IL-6 receptor with tocilizumab (TCZ) has shown efficacy in maintaining remission in case series of refractory patients with GCA and in a recently published randomized clinical trial (Villiger PM *et al* Lancet 2016). We hypothesized that TCZ may disturb B cell homeostasis and interfere with tertiary lymphoid organ (TLO) formation. To explore TLO formation in GCA arteries and to investigate the impact of IL-6R blockade with TCZ on TLO markers in ex-vivo cultured arteries from patients with GCA.

Methods: Formation of TLO was explored in temporal artery biopsies from patients with GCA by immunofluorescence using CD20 (B cell marker) and CD21 (follicular dendritic cell marker). Expression of TLO markers CXCL13, LTα and LTβ was assessed by quantitative real-time PCR in temporal artery biopsies from 13 patients with GCA and 13 control individuals. To investigate the effect of TCZ, temporal arteries from 13 GCA patients and 8 controls were cultured on 3D matrix (Matrigel) with or without TCZ (purchased from Roche) at 10mg/ml or IgG isotype control at the same concentration. After 5-day culture, expression of CXCL13, LTα and LTβ was assessed by quantitative RT-PCR. Other pro-inflammatory (IL-1b) survival (BCL-6, BAFF) or remodeling (TGFb) molecules relevant to GCA pathogenesis were also assessed.

Results: B cell clusters intermingled with follicular dendritic cells were identified in temporal artery biopsies from patients with GCA, particularly in the adventitial layer. mRNA expression of CXCL13 (16.93 vs 7.10 relative units, p=0.001), LTα (16,82 vs 6.18, p=0.0001) and LTβ (16.75 vs 9.54, p=0.014) was significantly higher in temporal arteries from GCA patients compared to healthy controls. After 5-day culture, TCZ selectively induced a significantly decrease in CXCL13 mRNA expression in cultured arteries (p=0.023). No significant changes in LTα , LTβ, IL-1β, BCL-6, BAFF or TGFβ expression were observed upon TCZ treatment.

Conclusion: Treatment with TCZ elicits a significant and selective reduction of CXCL13 expression in temporal artery lesions from patients with GCA. Disruption of B cell homeostasis may partially account for the therapeutic effects of TCZ in patients with GCA. Supported by SAF 2014/57708-R

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Abstract Number: 2105

Autoimmune Pancreatitis-Associated Autoantigens Among 100 IgG4-Related Diseases Patients

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Background/Purpose: IgG4-related disease (IgG4-RD) is a fibroinflammatory disorder of uncertain etiology. Recognition of this disease as a distinct entity stemmed from investigation into autoimmune pancreatitis (AIP), which was ultimately found to be part of a larger, systemic process. Prior studies on AIP have revealed 8 associated autoantigens including carbonic anhydrase (CA) isoforms 1, 2 and 4, lactoferrin (LAF), trypsin (PRSS2), trypsin inhibitor (SPINK1), E3 ubiquitin protein ligase (UBR2) and amylase-2A (AMY). While many AIP patients have IgG4-RD, these studies did not exclude type 2 AIP (non-IgG4 related), did not include patients with other manifestations of IgG4-RD and did not fully explore the B cell response. Our aim was to examine these autoantigens among a large and diverse cohort of systemic IgG4-RD patients.

Methods: Six of these autoantigens were commercially available in a recombinant form (CA-1, CA-2, CA-4, LAF, PRSS2, SPINK1). IgG4-RD patients (n = 100) were recruited between January 2012 and June 2016 and plasma samples frozen at -20°C until use. All samples had active disease at the time of collection. Disease controls (n = 25) included ANCA-associated vasculitis, rheumatoid arthritis and systemic lupus erythematosus. Healthy donors (n = 40) were used as negative controls. All proteins were studied by ELISA using a series of secondary antibodies (IgG, IgG1, IgG2, IgG3, and IgG4). Our cohort was powered to evaluate the correlation between autoantibody positivity and the presence of salivary gland, lymph node, pancreatic, lacrimal gland, lung, and retroperitoneal involvement.

Results: Our IgG4-RD cohort consisted of over 26 different organ manifestations including 47% with salivary gland, 28% lymph node, 21% pancreatic, 20% lacrimal gland, 20% lung and 20% retroperitoneal involvement. 77% had biopsy-proven disease while the remaining 22% had compelling clinical phenotypes with elevated serum IgG4 concentrations. 72% of the cohort had elevated serum IgG4 concentrations and 35%, elevated IgG1 concentrations. Overall, we observed a positive B cell autoantibody response in 26% of our IgG4-RD cohort. Each autoantigen was individually seen at a lower frequency, in the range of 5-10% of the cohort. 60% of the disease control cohort (15 of 25) showed a response to at least 1 of the 6 autoantigens. The predominant autoantibody subclass was of IgG1 (61%) closely followed by IgG4 (58%). IgG2 and IgG3 were also seen but at

a much lower frequencies (8% and 33%, respectively). Autoantibodies of each subclass correlated to serum elevations of that subclass. Taken as a group, the presence of one or more of these autoantibodies did not correlate to salivary gland, lymph node, pancreatic, lacrimal gland, lung, or retroperitoneal involvement.

Conclusion: Autoantibodies previously reported in association with AIP were observed among a large cohort of systemic IgG4-RD patients. The presence of these autoantibodies did not correlate to pancreatic involvement nor were they specific for IgG4-RD. This finding of promiscuous autoreactivity likely represents a breach in tolerance in IgG4-RD providing support for an autoimmune etiology to this disease.

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Abstract Number: 2106

Regulation of Marginal Zone B Cell Differentiation By microRNA-146a

Jennifer K. King[1], May Paing[2], Nolan Ung[2], Jorge Contreras[2], Michael Alberti[2], Thilini Fernando[2], Kelvin Zhang[2], Matteo Pellegrini[2] and Dinesh Rao[2], [1]Medicine, Rheumatology, UCLA, Los Angeles, CA, [2]UCLA, Los Angeles, CA

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Background/Purpose: B cell development in the bone marrow is followed by specification into several functional subsets in the spleen, including marginal zone B (MZB) cells or follicular cells (FO). Both subsets have been shown to contribute to autoimmune phenotypes by secretion of autoantibodies, such as dsDNA in systemic lupus erythematosus (SLE). Recently, microRNAs, short non-coding RNAs, have been shown to influence a myriad of aspects in immune cell development, including B cell development. Recent work has demonstrated that deficiency of the NFkB feedback regulator, miR-146a, led to a range of hematopoietic phenotypes, but B cell phenotypes have not been extensively characterized. Here, we have found that autoimmune lupus-prone miR-146a deficient mice demonstrate a reduction in MZB cells that likely represents a developmental block, while displaying a corresponding increase in FO cells.

Methods: We use high-throughput sequencing and comparative analysis of developmental stage-specific transcriptomes to characterize this defect.

Results: We determined that the differentiation of MZB cells was impaired due to a miR-146a-dependent decrease in Notch signaling. Further, we discovered that the cell-fate regulator protein, Numb, is a direct target of miR-146a, and that its derepression in miR-146a-deficent B-cells likely underlies the decrease in Notch

signaling.

Conclusion: Collectively, we describe a new role for the function of miR-146a in regulating marginal zone B cell development, which may ultimately contribute to autoimmune and/or inflammatory phenotypes.

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Abstract Number: 2107

Targeting Mir-155 in Rheumatoid Arthritis B Cells Reduces Antibody Production

Mariola Kurowska-Stolarska[1], Iain B McInnes[2], Stefano Alivernini[3], Aziza Elmesmari[4], Gianfranco Ferraccioli[5], James Reilly[2] and David W. McCarey[6,7], [1]Institute of Infection,Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom, [2]Institute of Infection, Immunity and Inflammation, College of Medicine, Veterinary Medicine and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]Division of Rheumatology, Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [4]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, United Kingdom, [5]Division of Rheumatology - Institute of Rheumatology and Affine Sciences, Catholic University of the Sacred Heart, Rome, Italy, [6]Glasgow Royal Infirmary, Glasgow, United Kingdom, [7]Centre for Rheumatic Diseases, Centre for Rheumatic Diseases, Glasgow, United Kingdom

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Background/Purpose: Better understanding of epigenetic regulatory mechanisms in RA pathogenesis will facilitate the development of new biomarkers or therapeutic strategies. MicroRNAs are post-transcriptional regulators that co-ordinate cell activation by fine-tuning multiple intracellular pathways. We recently observed that microRNA-155 is up-regulated in RA B cells, particularly in anti-citrullinated protein antibodies (ACPA) positive RA patients. Herein, we examined the role of endogenous miR-155 in RA B cell function. **Materials and**

Methods: Peripheral blood (PB) was obtained from healthy controls (HC) and RA patients (2010 ACR/EULAR classification criteria). To asses endogenous levels of miR-155 in B cells subsets; $CD19^{+}$ B cell from both groups (n=6 each) were stained with antibodies against na•ve and memory subsets specific markers (CD27, CD38, IgD and IgM) and sorted with FACSAriaIII followed by quantitative RT-PCR with miR-155 and U6 (housekeeping) specific primers. miR-155 *in situ* hybridisation combined with CD20 staining was performed on

RA synovial tissues (n=5). $CD19^+$ B cells of ACPA positive RA patients (n=5-6) were transfected with miR-155 inhibitors (miR-155I) or control inhibitor (CI). 48h later, quantitative RT-PCR was performed to identify transcription factors that regulate the B cell transcriptome and are under control of miR-155 (*PAX5*, *PRDM1*, *PU.1* and *IRF4)*. To evaluate antibody production (IgG and IgG-ACPA), $CD19^+$ cells of $ACPA^+$ RA patients (n=5) were transfected with miR-155 inhibitor or a control; and cultured in the presence of BAFF (20 ng/ml) and IL-6 (30 ng/ml) or were stimulated with a plate bound CD40 ligand (2 µg/ml), BAFF (100 ng/ml), IL-21 (50 ng/ml) and anti-IgM (5µg/ml). Each condition was performed in 14 replicates. Supernatants were assessed for the presence of total IgG and IgG-ACPA using standard or immune scan ELISA, respectively.

Results: Analysis of the expression of miR-155 in B cell subsets: na•ve, $CD27^-IgD^+$; pre-switched memory, $CD27^+IgD^+$; post-switched memory, $CD27^+IgD^-$; and double negative memory cells ($CD27^-IgD^-$) revealed that the double negative memory B cell population expressed the highest levels of miR-155, which was significantly higher in $ACPA^+$RA compared to HC B cells (Figure 1). Furthermore, CD20 cells in ectopic follicular structures in RA synovium expressed high levels of miR-155. Functional studies revealed that inhibition of endogenous miR-155 in RA B cells led to the de-repression of *PU.1* but did not impact *PAX5*, *PRDM1* and *IRF4* levels (Figure 2A). This was associated with the substantial reduction in BCR crosslinking induced antibody production by RA B cells (Figure 2B).

Conclusion: Our study demonstrates that antibody production by RA B cells is controlled by the miR-155-PU1 pathway. We propose that an inhibitor of miR-155 could be used to simultaneously treat both myeloid and lymphoid synovial phenotypes increasing the current response rate of RA patients.

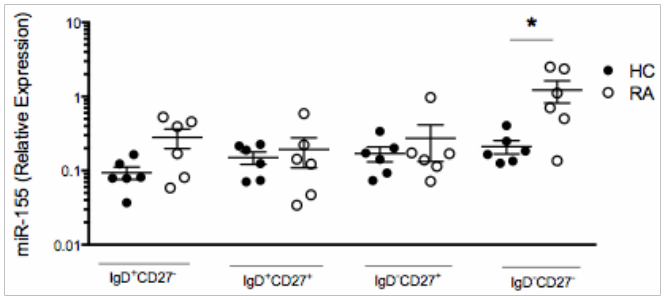
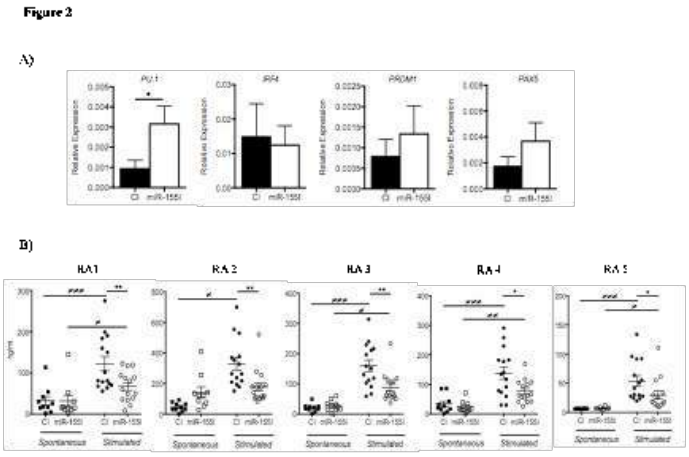


Figure 1



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Abstract Number: 2108

DNA Hypomethylation in Promoter Region of Zbtb38 Gene Ultimately Leads to Downregulated Expression of Anti-Inflammatory IL1r2 in Experiential Model of Rheumatoid Arthritis

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Background/Purpose: Interleukin 1 beta (IL1B) is a multifunctional cytokine that is highly expressed in rheumatoid arthritis (RA) and drives pro-inflammatory pathways via interleukin 1 receptor 1 (IL1R1)-mediated signaling. IL1B-specific receptor, IL1r2 is a decoy receptor that can sequester IL1B and acts as an anti-inflammatory factor. We investigated how an arthritis-specific epigenetic event is connected with the suppressed expression of anti-inflammatory IL1r2. The main goal of the current study is to explore gene regulatory pathways are involved in arthritis.

Methods: Disease-associated DNA methylation profiles analyses were conducted by methylated CpG island recovery assay (MIRA-chip) in arthritic B cells. Gene expression changes were investigated by microarray platforms and quantitative real-time polymerase chain reaction (RT-qPCR). Targeted gene silencing was carried out by electroporation of gene-specific shRNA expressing plasmids, and gene expression changes were monitored using RT–qPCR and Western blotting. Transient transfection studies were used for functional characterization of IL1r2 promoter.

Results: The promoter region of Zbtb38 transcription factor encoding gene was differentially methylated in B cells isolated from arthritic mice, which hypomethylation resulted in high expression of Zbtb38. Zbtb38 directly regulates IL1r2 gene expression and initiates its silencing in arthritic B cells. AhR transcription factor is also intimately involved in transcriptional regulation of IL1r2 and acts against Zbtb38. The fine balance of these two transcription factors can define the actual expression status of IL1r2 gene.

Conclusion: Zbtb38 forms a molecular bridge between an arthritis-associated epigenetic alteration (i.e., de novo DNA hypomethylation in Zbtb38 promoter) and transcriptional silencing of IL1r2 gene in arthritic B cells. In this context, Zbtb38 works as a potent repressor that turns off an anti-inflammatory pathway and significantly contributes to pathogenesis of arthritis.

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experiential-model-of-rheumatoid-arthritis

Abstract Number: 2109

Immunoprofiling of Bruton's Tyrosine Kinase (Btk)/Tec Family Kinase Inhibitors Indicate Activities Beyond Btk in Immunocyte Function

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Background/Purpose: CC-292, CC-90008, and ibrutinib are covalent Btk/Tec family kinase inhibitors that block Btk activity by binding with high affinity to the adenosine triphosphate (ATP) binding site of Btk and forming a covalent bond with cysteine 384 in the target Btk protein, providing rapid, complete, and prolonged inhibition of Btk activity. The objective of this study is to provide an immunoprofile of covalent modifiers of Btk that may impact the therapeutic opportunities of this class of compounds by assessing their impact on B-cells, T-cells, NK cells, monocytes, osteoclasts, dendritic cells, and basophils.

Methods: B cell function was measured by BCR signaling and induced proliferation, plasmablast differentiation, IgG and IL-6 production, and surface expression of activation markers (CD86, CD40, CD54, and CD69). T cell function was measured by proliferation, cytokine production and CD8 T cell degranulation after TCR stimulation. NK function was measured by degranulation after exposure to K562 cells. Monocyte/macrophage activity was assessed by Fcγ Receptor-mediated TNFα production and basophil activity was measured by FcεR-mediated degranulation. Effects on osteoclastogenesis and TLR9 activation were measured in osteoclasts and dendritic cells, respectively.

Results: The three Btk inhibitors tested here had both similarities and differences in the net activities observed on immunocyte function. All three inhibitors blocked Btk-mediated PLCγ2 phosphorylation in B-cells, FCεR-mediated degranulation in basophils, and osteoclastogenesis and bone degrading activity in myeloid-derived osteoclasts. Differences were observed in B-cell function depending on the stimulus. BCR-induced proliferation was inhibited by CC-292 and ibrutinib, but only weakly for CC-90008. Similarly, CC-292 and ibrutinib blocked BCR-induced ERK1/2 phosphorylation, but CC-90008 had no effect. Conversely ibrutinib was not active in assays where CC-292 and CC-9008 were active, including IL-6 production, plasmablast differentiation, and IgG secretion. CC-90008 and ibrutinib, but not CC-292 were potent inhibitors of T-cell proliferation. Yet, all three inhibited T-cell cytokine production and degranulation. In monocyte FCγR-mediated TNFα production, TLR9-mediated mDC activation, and NK degranulation, CC292 and ibrutinib showed inhibitory activity, but none was observed for CC-90008.

Conclusion: The data gathered from the immunophenotyping of CC-292, CC-90008 and ibrutinib identified

differential functional impact on various immunocyte functions, within and beyond the original identification of B-cell activities regulated by Btk. Clinical inflammatory disease indications for these Btk inhibitors would therefore need to be differentially assessed to match the relative importance of particular disease mechanisms to the differential activities beyond Btk. B-cell antibody production, T-cell proliferation and cytokine production, NK cell function, and myeloid and osteoclast function vary significantly among the three inhibitors with the only common features being basophil degranulation and osteoclast function.

Disclosure: J. Kosek, Celgene, 1,Celgene, 3; **L. Capone**, Celgene, 1,Celgene, 3; **M. Adams**, Celgene, 1,Celgene, 3; **E. M. Hur**, Celgene, 1,Celgene, 3; **P. H. Schafer**, Celgene, 1,Celgene, 3; **G. Ringheim**, Celgene, 3,Celgene, 1.

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Abstract Number: 2110

Synovial Fibroblasts Regulate B Cell Survival Via B Cell Activating Factor of the TNF Family (BAFF)

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Background/Purpose: In rheumatoid arthritis (RA), synovial fibroblasts (SF) are one main contributor of joint destruction since they resist apoptosis and secrete pro-inflammatory cytokines and matrix degrading enzymes. Therefore, they are key players in directing immune responses in direct interaction with other cell types, like B cells. TNF superfamily members, like B cell activating factor of the TNF family (BAFF) are important B cell function modulators and survival factors and are produced by synovial fibroblasts under certain conditions. Since better understanding of B cell – fibroblast interaction will lead to potential new treatment targets, we started to characterize this interplay.

Methods: Osteoarthritis (OA, n=5) and RA (n=5) synovial fibroblasts (SF) were co-cultured in passage 3-6 with B cells. Following a preincubation period of 48h with different inflammatory mediators (TNF, IL-1, IFN-γ) or B cell stimulating factors (BAFF, CpG), B cells were added to SF cultures and incubated for another 48h period. To determine B cell survival, we used AnnexinV/PI costain in FACS. AnnexinV/PI double negative B cells (living) are given as percentage of total B cells. To specifically block the action of BAFF, we used Belimumab.

Results: The presence of SF increased B cell survival from 5.2% to 55.3% ($p<0.001$). RA SF as compared to

OA SF showed similar capacity to increase B cell survival as compared to OA SF. However, conditioned media from RA SF showed increased capacity to enhance B cell survival as compared to OA SF supernatants (RA: 15.7% vs. OA: 11.1%, p=0.04). SF preincubation with INF-γ (survival 70.8%, p=0.015), IL-1 (survival 71.5%, p=0.018), or CpG (survival 87.7%, p=0.0002) further increased survival of B cells as compared to unstimulated SF. IFN-γ (0.1-50 ng/ml) induced BAFF from SF in a concentration dependent manner (ANOVA p<0.01). RA and OA SF showed the same response to INF-γ. Blocking BAFF by adding Belimumab (10µg/ml) decreased IFN induced survival to control values (survival 52.03%, p=0.58). Belimumab, INF-γ, or IL-1 in B cell only cultures had no effect on survival, respectively. After preincubation of SF with BAFF (0.1-10ng/ml), B cell survival was increased in a concentration dependent manner (ANOVA p<0.01, max. survival 78.7% with BAFF 10ng/ml) and inhibited in the presence of Belimumab (survival 64.9%, p=0.08).

Conclusion: B cell survival is increased in the presence of RA an OA SF in a similar manner, although RA SF spontaneously produce more soluble B cell survival factors as compared to OA SF. Preincubating fibroblasts with BAFF, IFN-γ, IL-1, or CpG affects fibroblast function to further increase B cell survival. INF-γ- and BAFF-induced SF mediated increase in B cell survival can be blocked by Belimumab. Therefore, strategies to interfere with BAFF directly in the joint might lead to decreased B cell survival and reduced inflammation.

Disclosure: T. Lowin, None; **M. Schneider**, None; **G. Pongratz**, None.

Abstract Number: 2111

Generation and Characterization of Anti-Citrullinated Protein Antibody-Producing B-Cell Clones

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Background/Purpose: Rheumatoid arthritis (RA) is the most frequent form of autoimmune arthritis with a prevalence of almost 1% worldwide. Anti-citrullinated protein antibodies (ACPA) are the most specific biomarker for rheumatoid arthritis (RA)(1). Although therapies designed to deplete B cells, which are the precursor to antibody-secreting cells, are effective in the treatment of RA(2), they only modestly affect ACPA and having no effect on antibodies to recall antigens in serum of treated patients(3). This suggests that autoreactive B cells may contribute to RA pathophysiology by additional mechanisms independent of terminal differentiation toward ACPA-producing plasma cells. Unfortunately, the lack of tools has prevented reliable identification of citrullinated protein (CP)-reactive B cells. Our objective was to develop a novel tool to characterize and model the function of (low-frequency) autoreactive B cells in RA.

Methods: B-cell clones from either blood or synovial fluid of CCP2+ RA patients were immortalized by a technique previously described for obtaining clones for recall antigens(4). ELISA and FACS were used to identify CCP2-reactive clones and to further characterize surface marker and cytokine expression. BCR-signaling competence was tested by calcium flux, and antigen internalization was visualized on Amnis Imagestream. Global gene expression profiles were interrogated by RNA sequencing.

Results: We have identified three unique B-cell clones from two RA patients that can secrete antibodies with specific binding to CCP2 yet show no reactivity to the control arginine variant. While clones generated through this method can secrete soluble antibody, they retain surface immunoglobulin expression, mobilize calcium in response to citrullinated protein antigen and can internalize their antigen. Finally, these clones have a unique surface profile of costimulatory molecules and can secrete both pro- and anti-inflammatory cytokines.

Conclusion: We present here the application of a unique cloning method to establish autoreactive human B-cell clones in RA. We propose that this technique can also be used for other autoimmune diseases with described autoantigen reactivity and that these B cells can be in turn utilized for the identification of autoreactive T cells recognizing novel autoantigen epitopes.

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Abstract Number: 2112

Disease-Activity Associated Autoantibodies to Malondialdehyde-Modified Proteins Can be Isolated from Synovial B Cells in RA

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Background/Purpose: Malondialdehyde (MDA) is a naturally occurring reactive aldehyde that arises during apoptosis or as a consequence of elevated reactive oxygen species and lipid peroxidation. Free MDA can post-translationally modify lysine residues in a protein carbonylation process that generates neo-epitopes that can be recognized by autoantibodies.

Methods: Serum IgG anti-MDA levels were compared in 71 healthy controls, 30 OA, and 283 SLE and 162 RA patients, identified by ACR criteria. IgG anti-MDA was measured by sandwich ELISA using MDA-modified BSA. After flow cytometry sorting of RA synovial memory B cells, and single cell Ab-gene PCR, 114 mAbs were expressed and tested for MDA-reactivity. Analyses used the 2-sided Mann-Whitney test or Spearman correlation.

Results: In sera, IgG anti-MDA was significantly increased in SLE (17±21 RU/ml, $p<0.0001$) and RA patients (13±11 RU/ml, $p<0.0001$), compared to controls (5±3 RU/ml). In SLE, IgG anti-MDA correlated with disease activity by SELENA-SLEDAI ($p<0.0001$, $R=0.34$, $n=219$). Levels were also significantly higher in SLE patients with active disease (SLEDAI≥6, 18.9±17.3 RU/ml, $p=0.001$) than with low disease activity (SLEDAI<6, 11.5±16.6). In RA patients, IgG anti-MDA correlated with DAS28-ESR ($p<0.0001$, $R=0.35$, $n=157$). Compared to RA patients with low disease activity (DAS28<3.2, 6±3), levels were significantly increased in RA with moderate activity (DAS28 3.2-5.1, 12±11 RU/ml, $p=0.005$) and high activity (DAS28>5.1, 15±12 RU/ml, $p=0.001$). In DMARD naïve RA ($n=62$), IgG anti-MDA also correlated with serum TNFα ($p=0.002$, $R=0.39$), IL-6 ($p=0.03$, $R=0.27$), and CRP levels ($p=0.003$, $R=0.37$). In RA synovial mAbs, we identified four clones (3.5%) that recognized MDA-modified epitopes. The most reactive clone, 1276:01F04, showed high specific binding to MDA but was non-reactive with carbamylated or 4-HNE-modifications. Specificity was confirmed in antigen-competition studies with MDA or MDA acetaldehyde (MAA) protein adducts. This mAb also bound MDA-modified human fibrinogen and albumin. No cross-reactivity with citrullinated epitopes was detected, and mAbs with ACPA or RF reactivity did not bind MDA. Notably, 1276:01F04 originated from an IgG1-bearing B cell that was encoded by near germline variable genes (VH4-39, 1 R-mutation in HCDR3; VL1-51, 2 S-mutations in FR1).

Conclusion: IgM binding to MDA-adducts may be common in health from birth and are part of the natural

antibody pool. Yet, IgG anti-MDA are associated with inflammatory conditions including increased disease activity in autoimmune patients. Importantly, MDA-autoreactive B cells could also be isolated from RA synovium, the site of disease. Further studies are merited to investigate the potential pathogenic properties of IgG anti-MDA B-cells/autoantibodies.

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Abstract Number: 2113

Anti-Carbamylated Protein Antibody (cross)-Reactivity Against Multiple Carbamylated Protein Antigens

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Background/Purpose: Antibodies that target carbamylated proteins (anti-CarP) have been implicated in rheumatoid arthritis and are known to associate with joint damage. Furthermore, these autoantibodies can be found years before the onset of RA and the presence of anti-CarP antibodies in arthralgia patients associates with RA development. Although a large amount of clinical data is now available in relation to the occurrence of anti-CarP antibodies, little is known about their characteristics, such as their ability to react against multiple antigens and their capacities to be cross-reactive.

Methods: We investigated the reactivity of anti-CarP antibodies in serum samples from 160 RA patients (according to the ACR 1987 criteria) and 40 healthy controls using ELISA (enzyme-linked immunosorbent assay).Five different antigens, foetal calf serum, human serum albumin, bovine myelin basic protein, H1 histones and human prothrombin were selected and used in carbamylated and non-modified form. Cross-reactivity within serum samples was investigated using inhibition studies.

Results: The sera of RA samples are able to recognize a large diversity of carbamylated proteins, with positivity ranging between 39% and 58%. The recognition pattern that is observed is quite diverse, but 24% of the RA patients were able to recognize all 5 carbamylated antigens, while this occurred in none of the control samples. Furthermore, the amount of antigens that can be recognized correlates with the anti-CarP antibody levels. As for cross-reactivity, we observe that antibody binding to one carbamylated protein can often be inhibited by any of the other carbamylated proteins, but not by its non-carbamylated counterpart, indicating the cross-reactive nature of anti-CarP antibodies towards several carbamylated proteins. Interestingly, while anti-

CarP antibodies seem to be highly cross-reactive towards different carbamylated antigens, the cross-reactivity towards citrullinated proteins is limited.

Conclusion: These data suggest that anti-CarP antibodies areable to recognize many different carbamylated proteins. An anti-CarP antibody response initiated by one carbamylated protein may therefore result in recognition of several carbamylated proteins in RA patients.

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Abstract Number: 2114

Exposure to Carbamylated Self- and Non-Self-Proteins Can Lead to a Break-of -Tolerance and the Induction of Autoimmunity

Jacqueline Dekkers[1], Marije K. Verheul[2], Jeroen Stoop[3], Bisheng Liu[4], Peter A. van Veelen[5], Martin Hegen[6], Stephen Rapecki[7], Tom WJ Huizinga[2], Leendert A. Trouw[4] and René Toes[4], [1]Rheumatology, Department of Rheumatology, Leiden University Medical Center (LUMC), Leiden, Netherlands, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Leiden University Medical Center (LUMC), Leiden, Netherlands, [4]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Immunohematology and Bloodbank, Leiden University Medical Center, Leiden, Netherlands, [6]Inflammation, Wyeth Pharmaceuticals, Cambridge, MA, [7]UCB Pharma, Slough, United Kingdom

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Background/Purpose: Autoantibodies are an important hallmark of Rheumatoid Arthritis (RA). Approximately 50% of RA patients harbor anti-carbamylated protein (CarP) antibodies. These autoantibodies target proteins that are modified through a posttranslational modification named carbamylation or homocitrullination. It has been postulated that posttranslational modifications can play a role in the breach of tolerance towards self-antigens. These anti-carbamylated protein (CarP) antibodies can recognize both carbamylated foreign- and self-proteins. It is currently unknown whether carbamylated foreign-proteins can evoke an anti-CarP autoimmune response or whether this can only be facilitated through carbamylation of self-proteins. Therefore we studied whether carbamylation of self- and foreign-proteins can drive loss of B-cell tolerance to carbamylated proteins.

Methods: Mice were immunized with carbamylated- or non-modified (auto)antigens and analyzed for autoantibody responses. Anti-CarP hybridomas were sequenced using single cell PCR-based antibody cloning technology. Mass spectrometry was used to identify carbamylated self-proteins in rheumatic joint tissue. Serum reactivity towards Ca-human serum albumin and Ca-FCS was determined for 100 RA-patients of the Leiden

Early Arthritis Cohort and 40 healthy subjects.

Results: Immunization with carbamylated self-proteins (Albumin) resulted in a potent anti-CarP antibody response against both carbamylated foreign- and self-proteins. Likewise, immunization with carbamylated foreign-proteins (OVA) induced a strong anti-CarP response against both carbamylated foreign- and self-proteins. Similar to serum anti-CarP antibodies, murine monoclonal anti-CarP antibodies were highly specific and cross-reactive to multiple carbamylated (auto)antigens. Although citrulline greatly resembles homocitrulline residues in structure, anti-CarP antibodies differ in antigen recognition profile from ACPA as they are able to discriminate between citrullinated and homocitrullinated forms of the same protein. Interestingly, we were able to identify carbamylated-albumin, in RA synovial tissue, indicating that albumin is present in carbamylated form locally in the inflamed joint. Moreover, we detected antibody responses against carbamylated-human albumin were observed in 38% of early RA patients from the Leiden Early Arthritis Clinic.

Conclusion: These results show that not only carbamylated self-, but also carbamylated non-self-proteins can lead to a breach of B-cell tolerance leading to B-cell responses against carbamylated self-proteins. These results indicate that auto-reactive B-cells to carbamylated proteins as well as it is underlying T-cell response could find its origin in the exposure to carbamylated foreign-proteins.

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Abstract Number: 2115

Rheumatoid Factors May Potentiate Immune Complex Formation of Anti-Citrullinated Protein Antibodies

Willem J.J. Falkenburg[1,2], Dirkjan van Schaardenburg[3,4], Jana Koers[5], Pleuni Ooijevaar-de Heer[5], Gertjan Wolbink[6,7], Arthur E.H. Bentlage[8], Gestur Vidarsson[8] and Theo Rispens[5], [1]Rheumatology, Amsterdam Rheumatology and immunology Center | Reade, Amsterdam, Netherlands, [2]Department of Immunopathology, Sanquin Research, Amsterdam, Netherlands, [3]Rheumatology, Amsterdam Rheumatology and immunology Center, location Academic Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [4]Rheumatology, Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [5]Immunopathology, Sanquin Research, Amsterdam, Netherlands, [6]Immunopathology, Sanquin Research and Landsteiner Laboratory Academic Medical Center, Amsterdam, Netherlands, [7]Rheumatology, Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands, [8]Experimental Immunohematology, Sanquin Research, Amsterdam, Netherlands

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Background/Purpose: Rheumatoid arthritis (RA) is a complex inflammatory disorder in which autoantibodies play a prominent role. Several types of autoantibodies, including rheumatoid factors (RFs) - primarily IgM antibodies binding to the Fc-domain of IgG- and anti-citrullinated protein antibodies (ACPAs) have predictive value for RA onset and severity. Interestingly, the combined presence of both types of antibodies is a better marker for a more severe disease than the presence of only RFs or only ACPAs. While pathogenic properties of both RF and ACPA in isolation have been studied in detail, few studies have investigated the combination.

Methods: In this study, we investigated the interactions between RFs and ACPAs using well-defined recombinant monoclonal RFs and ACPAs in a biosensor system (IBIS). Monoclonal ACPAs (100nM) with or without 25nM monoclonal IgM-RFs were flowed over sensor-spots to which six different citrullinated peptides or their arginine controls were coupled. Changes in refractive index caused by binding of molecules were measured and plotted as response units against flowing time in sensorgrams.

Results: We observed that interactions between ACPAs and citrullinated peptide targets were substantially enhanced by the presence of hexameric RF (Figure 1A). The observed increase in RU was mathematically greater than could be explained by a 1:1 or even a 1:2 interaction between ACPAs and RF. This suggests that the RFs enhance the binding of ACPAs to their targets by crosslinking them (Figure 1B). These results could be replicated using RF and ACPA from RA patients' serum. RF+ ACPA+ sera treated with Dithiothreitol (DTT) to reduce the IgM-RF showed a decreased binding of ACPAs to the citrullinated peptide targets.

Conclusion: We hypothesize that RFs may contribute to pathogenesis in RA by potentiating immune complex formation of ACPAs.

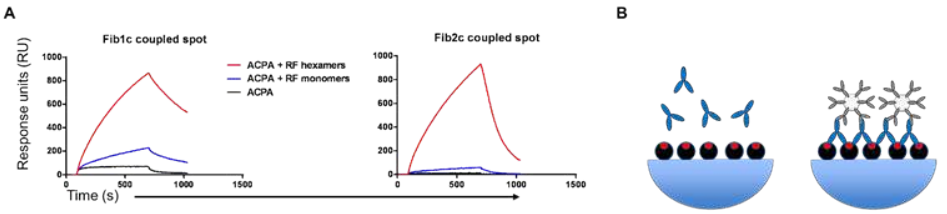

Fig. 1: (A) Interactions between ACPAs and citrullinated peptide targets (Fib1c, Fib2c) spotted on the sensor were substantially enhanced by the presence of hexameric RF. Conditions with only RF showed no binding. (B) Interpretation of A: ACPAs alone have a low affinity interaction with their targets. Hexameric RFs binding to ACPAs form higher avidity immune complexes, crosslinking ACPAs onto their citrullinated targets.

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Abstract Number: 2116

Cytokines Inhibition Modulates Activation and Homing Receptor of Different Peripheral Memory B Cell Subsets in RA

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Background/Purpose: With the advent of B cell targeted therapies the modulation of memory B cells seems to be a prime target. Human peripheral memory B cells can be distinguished by the phenotypic expression of CD27 and IgD defining three major B cell subpopulations: CD27+IgD+ pre-switch, CD27+IgD- post-switch and CD27-IgD- double negative memory B cells. We analyzed these different memory populations in RA and under IL6-R blockade.

Methods: B cells were phenotypically analyzed from RA patients at baseline, week 12 and week 24 under tocilizumab (TCZ) treatment. Memory B cell subsets were defined by CD27 and IgD and were further analyzed by color flow cytometry for surface staining of CD95, intracellular ki-67 and CXCR3 expression.

Results: The phenotypically analyzed profile in RA patients (n=60) and healthy donors (n=20) revealed that the memory B cells are activated and have higher expression of CXCR3. Surface and intracellular staining of B cells showed a significantly higher percentage of CD95 (p=0.01), ki-67 (p=0.04) and CXCR3 (p= 0.03) expression in RA. CD95 & ki-67 expressions were highest in post-switch memory B cells while CXCR3 expression was highest in pre-switch. The expressions of ki-67, CD95 and CXCR3 were significantly reduced during IL-6R blockade (Tocilizumab) therapy at week 12 & 24 in all B cell subsets.

Conclusion: Our data suggests that the three major peripheral memory B cell populations, pre-, post-switch and double negative B cells are activated in RA with enhanced CD95, Ki-67 and CXCR3 expressions compared to healthy individuals. These higher expressions in all memory B cell subsets can be reduced by IL-6R inhibition in vivo.

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Abstract Number: 2117

B Cell Phenotype and in Vitro Function in Patients with Rheumatoid Arthritis Developing Low Serum Immunoglobulins after Multiple Cycles of Rituximab

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Background/Purpose: Repeat treatment with rituximab (RTX) predisposes some patients with rheumatoid arthritis (RA) to develop low levels of serum immunoglobulins (Igs). Understanding B cell function in relation to preserving immunity and a sustained clinical response is thus essential. We have investigated the relationships between B cell phenotype and *in vitro* function in patients RTX-naïve and in those maintaining normal serum Igs (IgM>0.4g/L and IgG>7g/L) or developing low Igs after RTX.

Methods: Serum and peripheral blood mononuclear cells (PBMC) were collected from 56 RA patients (12 pre- and 34 post-RTX). Flow cytometry (% and Mean Fluorescence intensity–MFI) was used to determine naïve and memory B cell subsets (IgD/CD27) and additionally BAFFR, CD32, CD5 and IgM. Post-RTX all patients had evidence of IgD+CD27- naïve B cell reconstitution (>25%) after a period of sustained depletion (<5 CD19+B cells/ml). Serum Igs were analysed in relation to phenotypes, BAFF and soluble CD23 (sCD23; released on differentiation to CD27+ status; normal range 1024-5025pg/ml). PBMC were cultured for 7 days with T cell dependent (TD) (anti-IgM+anti-CD40+IL4+IL21) and T cell independent (TI) (CpG+IL2) stimuli. Classes of Igs, sCD23 and anti-cyclic citrullinated peptides (anti-CCP) were measured in supernatants.

Results: After a median 5 cycles of RTX, 17 patients had normal serum Igs and 17 had developed either low IgM (n=11) or IgG (n=9) or both (n=3). Significant differences between low and normal Igs groups were noted in disease duration (median 25 vs 15 years, p=0.005) and sCD23 levels (median 908 vs 3702pg/ml, p=0.002). Median number and % CD19+B cells, RTX cycles, time from last cycle and serum BAFF were similar. Patients with low Igs also had lower %BAFFR+ pre-switch B cells (IgD+CD27+;p=0.008), higher %CD32B+ switched B cells (IgD-CD27+;p=0.02) and a negative correlation of serum IgM levels and %CD32B+ switched B cells (R^2=0.44;p=0.004). *In vitro,* IgM, IgG or IgA and sCD23 production (normalized for B cell count) was similar between groups. IgM-CCP was only produced after TD and TI stimulus but IgG-CCP was produced spontaneously in all cultures. Significantly higher levels of both IgM- and IgG-CCP antibodies were detected in supernatants from low Ig group.

Conclusion: In patients developing low serum Igs, defective B cell maturation to memory phenotype was suggested by significantly lower levels of serum sCD23. Low serum Igs were also associated with possible reduced BAFFR-mediated anti-apoptotic signaling in IgD+CD27+ B cells and a greater %CD32B+ on memory B cells, resulting in higher thresholds for differentiation to Ig production. In *vitro,* however, similar amounts of Ig were present in cultures from those with normal or low serum Igs, suggesting a lack of underlying, intrinsic B cell defects. The lack of efficient B cell differentiation in individual patients with low Igs may relate to B cell interactions with immune complexes or with different T cell subsets, possibly resulting from disturbances in RTX-induced germinal centre structure. Our results further suggest increased selection and/or survival properties of autoreactive B cells in patients with low serum total Igs evident in a more robust production of anti-CCP antibodies.

Disclosure: G. Cambridge, None; **R. A. Moura**, None; **V. Reddy**, None; **M. J. Leandro**, None.

Abstract Number: 2118

Rituximab Treated Non Responder Rheumatoid Arthritis Patients Are Generating a New Autoantibody Repertoire

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Rituximab (RTX) has shown clinical efficacy but up to 40 % of RTX treated rheumatoid arthritis (RA) patients are poor responders (Ann Rheum Dis. 2005 Feb;64(2):246-52) and the commonly used RA biomarkers (*RF/ACPA)* are poor predictors for therapy response. Others reported associations between BAFF/BLyS levels, Fcg RIII and IL-6 genotype, interferon type I signatures and Epstein-Barr virus genome in bone marrow and clinical outcome (Arthritis Res Ther. 2012 Apr 27;14(2)). In this study the autoantibody repertoire analysed on protein macorarrays from RA patients under RTX treatment was correlation to clinical DAS28 response.

Methods: Screening of RA sera was conducted on 37.830 unique human proteins on protein marcoarrays (http://www.engine-gmbh.de) with sera taken before and 24 weeks after treatment. The autoantibody response of different immunoglobulin classes IgD, IgA, and IgG was recorded and bioinformatically evaluated. Response was determined according to DAS28 criteria. DAS 28 scores in the responder group before treatment was from 5.4 – 7.8 and in the non-responder group 5,6 – 6,8. We analyzed 26 RA patient sera (9 responder, 7 non-responder and 10 patients with blinded response classification) investigated the data of found autoantigens *in silico*and by hierarchical clustering.

Results: : In the cohort of 26 patients 1292 different autoantigens (IgD,IgA,IgG) were detected. Using protein array we investigated clusters of autoantigen responses that disappeared or developed during RTX treatment of RA patients. Post treatment developing responses against new autoantigens can be correlated to mRNA tissue expression data and were interestingly found organ-specifically expressed. RA autoantigenic patterns before and 6 month after RTX treatment were patient-specific and no relevant autoantigenic cluster was found that was shared between patients or associated with response. However, RTX reduced the repertoire of autoantibodies after 24 weeks of treatment in the tested RA patient cohort on average by 60%. RA patients which do not respond

are generating on average 63% new autoantibodies. In good responders to RTX only 5,5% (+/-3%) new autoantibodies can be detected. The IgA and IgG autoantibody repertoire in the serum after 24 weeks of RTX treatment is reduced (IgA: 41%, IgG :31%) in good responders whereas it is increased (IgA: 1,3%, IgG: 24%) in non responders to RTX

Conclusion: RA patients present highly individual autoantibody profiles before and after RTX treatment, which do not reveal antigen-specific patterns for outcome prediction. However, after 6 month of RTX treatment the autoantibody repertoire in all good responding RA patients is reduced and non responders to RTX change their autoantibody repertoire directed against new but patient specific antigens. The fast rebuilding of functional B cells might be a underlying mechanistic difference between responders and non-responders to rituximab.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/rituximab-treated-non-responder-rheumatoid-arthritis-patients-are-generating-a-new-autoantibody-repertoire

Abstract Number: 2119

Wogonin, a Plant-Derived Flavonoid, Exert Anti-Inflammatory and Chondroprotective Effects through the Activation Nrf2/HO-1 Signaling in Human OA Chondrocytes

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Session Time: 9:00AM-11:00AM

Background/Purpose: Osteoarthritis (OA), characterized by progressive destruction of articular cartilage, is the most common form of human arthritis. Wogonin is a naturally occurring flavonoid found in root extract of *Scutellaria baicalensis,* and it has been shown to exhibit diverse biological activities. Here, we evaluated the potential anti-inflammatory and chondroprotective effects of Wogonin in IL-1β stimulated human OA chondrocytes.

Methods: Primary human OA chondrocytes were isolated by enzymatic digestion of the cartilage obtained from OA patients who underwent total knee arthroplasty at Crystal Clinic, Akron, Ohio. Effect of Wogonin on IL-1β-induced mRNA and protein expression of iNOS, COX2, IL-6, MMP-3, MMP-9, MMP-13, ADAMTS4, ACAN and COL2A1 was examined by Taqman Gene expression assays and immunoblotting, respectively. Estimation of NO in culture supernatant was done using Griess assay. PGE_2 in culture supernatant was quantified by ELISA. Protein levels of nuclear factor (erythroid-derived 2)-like 2 (Nrf2), heme-oxygenase-1 (HO-1), and the total protein levels and phosphorylation of MAPKs were assayed by immunoblotting. siRNA mediated knockdown

was used to deplete target protein. Cellular uptake of Wogonin in OA chondrocytes was quantified by MRM analysis using mass-spectrometry.

Results: Wogonin completely suppressed the IL-1β-induced mRNA and protein expression of COX2, IL-6, iNOS, MMP-3, MMP-9, MMP-13, and ADAMTS-4 in human OA chondrocytes. Further, Wogonin significantly inhibited the NO and PGE_2 production in IL-1β-stimulated human OA chondrocytes. Interestingly, Wogonin treatment increased the expression of type II collagen (COL2A1) and aggrecan (ACAN) in IL-1β-treated OA chondrocytes. Wogonin modulated the expression of IL-1β-induced phosphorylation of MAPKs (ERK1/2, JNK, and P38) in OA chondrocytes. Additionally, Wogonin activated redox sensitive transcription factor Nrf2, which has been shown to possess major chondroprotective role. Further, Wogonin upregulated the expression of Nrf2-dependent cytoprotective gene HO-1 in human OA chondrocytes. Inhibition of activity or knockdown of HO-1 expression abrogated the chondroprotective effect of Wogonin in IL-1β-stimulated human OA chondrocytes. Cellular uptake studies showed that Wogonin levels increased in a time dependent manner indicating the absence of metabolism of Wogonin in human OA chondrocytes. These data indicate that increased intracellular accumulation in due course of time activate Nrf2/HO-1 axis that may be responsible for the observed anti-inflammatory and chondroprotective activity of Wogonin under pathological conditions.

Conclusion: The present study suggests that Wogonin could be an effective chondroprotective and anti-inflammatory agent as it switched the chondrocyte gene expression from catabolic towards anabolic response and this effect was mediated, at least in part by the activation of Nrf2 and upregulation of HO-1 expression in OA chondrocytes.

Disclosure: M. N. Khan, None; **A. Haseeb**, None; **S. Haynie**, None; **T. M. Haqqi**, None.

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Abstract Number: 2120

Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04690) As a Potential Treatment for Degenerative Disc Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: Degenerative Disc Disease (DDD), one of the main causes of low back pain, is characterized by degeneration of intervertebral disc, nucleus pulposus (NP), and cartilage matrix, resulting in decreased disc height and function. Treatment of DDD is limited to analgesics or surgery aimed at relieving symptoms, and no current therapy can reverse disc degeneration. Wnt signaling plays an important role in DDD by regulating the proliferation and differentiation of resident NP cells. SM04690, a novel, small-molecule, Wnt

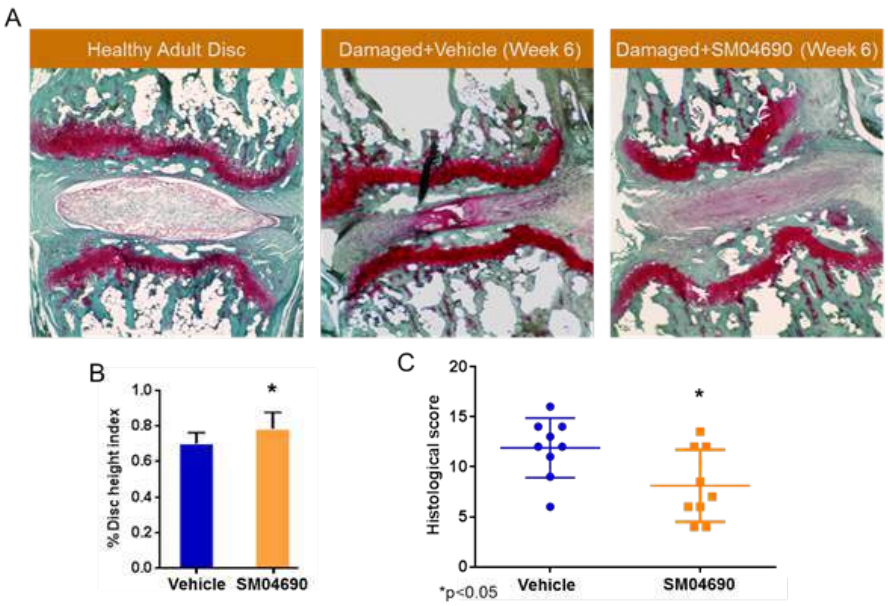
pathway inhibitor was evaluated in a series of preclinical studies to determine its potential to induce proliferation and differentiation of primary NP cells, thereby promoting disc healing.

Methods: Wnt pathway inhibition was measured using a cell-based reporter assay. *In vitro* proliferation of NP cells from rat coccygeal discs, treated with vehicle or various concentrations of SM04690 for 5 days was measured by cell doubling index (CDI= cell number/initial cell number/days). Differentiation of NP cells into "chondrocyte-like" NP cells with vehicle or SM04690 treatment for 12 days was measured by Alcian blue staining and absorbance based quantification. Pharmacokinetics were evaluated by intradiscal injection in rats and rabbits, followed by analysis of compound concentrations in the disc and plasma. *In vivo* efficacy was evaluated in a rat coccygeal intervertebral disc "needle puncture" model using radiographic measurement of disk height index (DHI = disk height/vertebral height), and histological scoring (total 4-16) of Safranin O-stained sections for integrity of annulus fibrosus (AF), border between AF and NP, cellularity, and matrix of NP.

Results: SM04690 demonstrated potent (EC_{50} =11nM) and selective inhibition of Wnt signaling. *In vitro* proliferation measured as CDI was ~2-fold higher in cells treated with SM04690 compared to vehicle ($P<0.05$). Cells treated with SM4690 also showed significantly increased Alcian blue absorbance, indicating differentiation to "chondrocyte-like" cells ($P<0.01$). Single intradiscal injection of SM04690 resulted in disc concentrations >EC50 for >180 days, with minimal systemic exposure or toxicity, measured as behavioral, health, gross morphology, and microscopic adverse changes. In the rat DDD model, SM04690 treatment increased Safranin O-stained cartilage matrix (Figure A), thereby resulting in significantly increased radiographically measured % DHI ($P<0.05$; Figure B), and decreased histology scores ($P<0.05$; Figure C) vs. vehicle control.

Conclusion: SM04690, a small molecule Wnt pathway inhibitor promoted proliferation and differentiation of NP cells *in vitro*. In a rat model of DDD, SM04690 regenerated NP cells and cartilage matrix, and improved disc height, health, and shape compared to vehicle, with minimal plasma exposure or systemic toxicity. These results suggested that SM04690 has potential as a treatment for DDD.

Figure 1. SM04690 stimulated differentiation of NP cells and improved disc height and health in a rat model of DDD.



Disclosure: C. Barroga, Samumed, LLC, 3; **V. Deshmukh**, Samumed, LLC, 3; **L. Dellamary**, Samumed, LLC, 3; **J. Stewart**, Samumed, LLC, 3; **H. Hu**, Samumed, LLC, 3; **J. Hood**, Samumed, LLC, 9; **Y. Yazici**, Samumed, LLC, 3.

Abstract Number: 2121

Identification of microRNA-181a-5p and microRNA-4454 As Mediators of Facet Cartilage Degeneration

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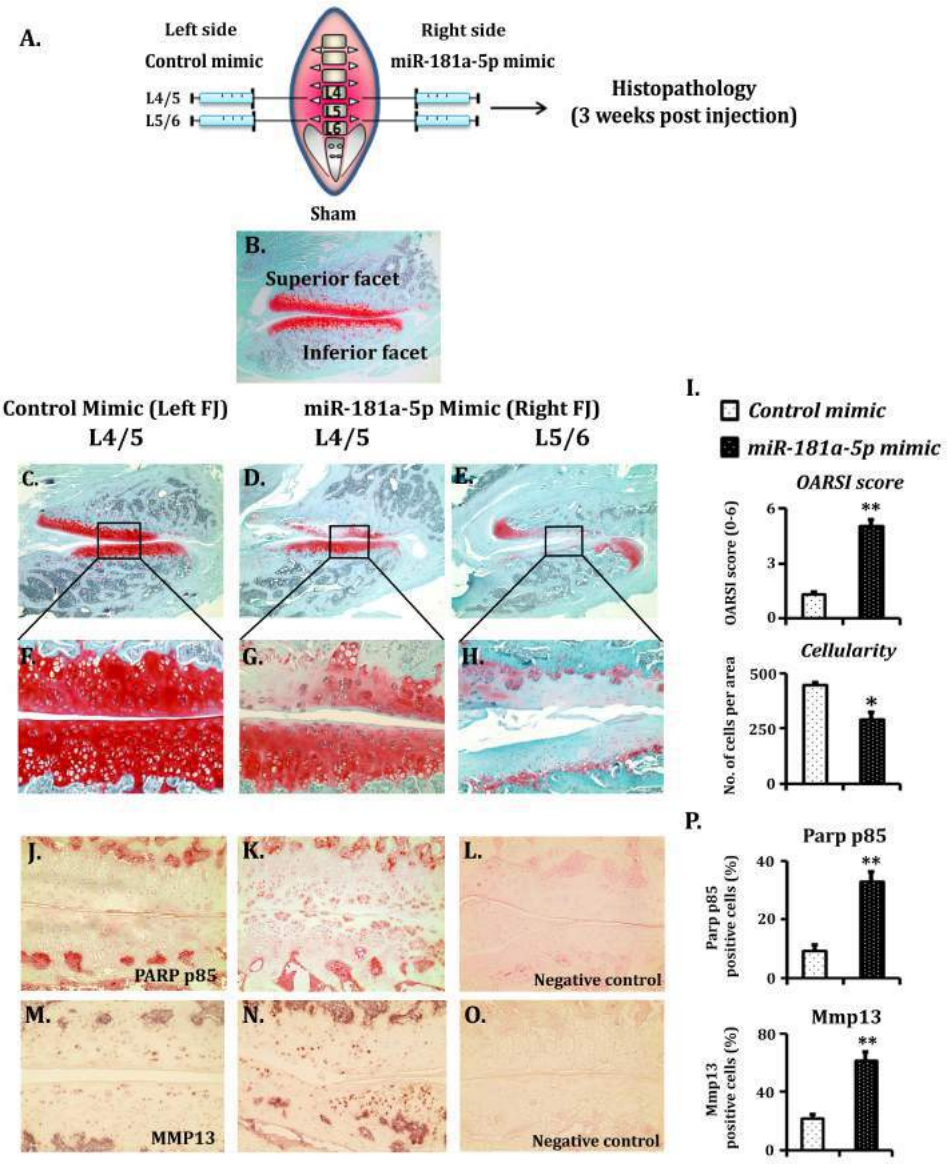
Background/Purpose: Osteoarthritis (OA) of spine (facet joints, FJ) is one of the major causes of severe low back pain and disability worldwide. However, specific mechanisms associated with facet cartilage degeneration during FJ OA are largely unknown. For the first time, in this study we investigated the role of microRNAs (miRNAs) in the pathophysiology of facet cartilage degeneration during FJ OA.

Methods: Based on MRI and histopathology, we first established and validated a patient cohort (Group 1 patients [control group]: normal or mild facet cartilage degeneration and Group 2 patients [FJ OA group]: moderate to severe facet cartilage degeneration). Using this cohort, we screened 2,100 miRNAs using miRNA-array analysis and differentially regulated miRNAs were further tested by qPCR analysis. Human FJ OA chondrocytes were cultured and transfected with miRNA mimics/inhibitors (or control mimic/inhibitor) to determine the effect of miRNA enhancement/inhibition on the expression of catabolic/inflammatory/anabolic/apoptosis markers. Signaling pathways modulated by miRNAs were also identified using mirDIP/pathDIP. Furthermore, we injected the miR-181a-5p mimic into FJs of rats to see the effect *in vivo*.

Results: Out of 2,100 miRNAs, we specifically identified 2 miRNAs (miR-181a-5p and miR-4454) that were significantly up-regulated in FJ OA cartilage compared to control facet cartilage and exhibited significant correlation with MRI grading. Further, we treated FJ OA chondrocytes with miR-181a-5p or miR-4454 or control mimic/inhibitor and showed that treatment with both miR-181a-5p or miR-4454 mimic significantly elevated the expression of inflammatory/catabolic/apoptosis markers and reduced expression of type II collagen;

inhibition of these two miRNAs was able to reverse these destructive effects in IL-1β treated cells. Our study further identified that IL-1β mediated activation of NF-κB signaling upregulated miR-181a-5p and miR-4454 expression to sustain NF-κB activation in part through zinc finger protein 440 siRNA (si*ZNF440*)-mediated phosphorylation of Ser536 NF-κB-p65 and reduction of IκB expression, resulting in a positive feedback loop that can sustain NF-κB-p65 activity. Finally, by injecting miR-181a-5p mimic in rat FJs, we observed a FJ OA phenotype in facet cartilage associated with enhanced catabolic activity and chondrocyte apoptosis *in vivo*.

Conclusion: Using clinical, *in vitro* functional and *in vivo* studies, we for the first time have identified miR-181a-5p and miR-4454 as mediators of facet cartilage degeneration.



Disclosure: A. Nakamura, None; **Y. R. Rampersaud**, None; **A. Sharma**, None; **S. J. Lewis**, None; **B. Wu**, None; **P. Datta**, None; **K. Sundararajan**, None; **H. Endisha**, None; **E. Rossomacha**, None; **J. S. Rockel**, None; **I. Jurisica**, None; **M. kapoor**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/identification-of-microrna-181a-5p-and-microrna-4454-as-mediators-of-facet-cartilage-degeneration

Abstract Number: 2122

KiSS1 Is a Regulator of ADAMTS4 and ADAMTS5 Expression and Is Post-Transcriptionally Regulated By Micro-RNA N105 in Human OA Chondrocytes

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Background/Purpose: Osteoarthritis (OA) is a chronic and debilitating disease of the articulating joints in every population. Micro-RNAs are ~22 nucleotides long non-coding single stranded RNAs that mostly regulate post-transcriptional gene expression. In order to dissect the role of novel miRNAs in OA pathogenesis we exploited the next generation sequencing technology and comprehensively profiled the miRNAs expression in OA chondrocytes.

Methods: Chondrocytes were prepared by the enzymatic digestion of discarded human cartilage from donors who underwent total knee arthroplasty due to OA. Total RNA directly from the cartilage or from chondrocytes was prepared using Trizol and miRNeasy Mini kit respectively. RNA purity, integrity and NGS library integrity was verified using Agilent 2100 Bioanalyzer. The small RNA library was prepared using a kit (Illumina). Cluster generation and sequencing was performed on MiSeq system. The small RNA sequencing reads were aligned to genomic reference (hg19) and novel miRNA sequences were extracted from NGS data using Strand NGS software. miRNA targets were identified using open web bioinformatics program Diana Tools. Expression of mature miRNAs was quantified using individual miScript Primer Assay. Expression of KiSS1 and other OA related catabolic and anabolic genes was quantified using TaqMan Assays and of proteins by Western blotting. Chondrocytes were transfected with siRNAs, control miRNA, miR-N105 mimic or inhibitor using Amaxa Nucleofactor System.

Results: We analyzed the 95% of the ~20 million reads from the miRNA-Seq which passed the quality filter using the Strand NGS Software and identified 15 miRNAs as potential novel miRNAs. Based on differential expression and abundance novel miRNA miR-N105 was selected for further analysis. Expression of miR-N105 was downregulated upon IL-1β treatment in chondrocytes in a time dependent manner. Interestingly expression of miR-N105 was significantly low in damaged cartilage compared to the expression levels detected in the smooth cartilage of the same patients (n=8). Diana Tool predicted KiSS1 (KiSS-1 metastasis-suppressor) as a potential target of miR-N105. Expression of KiSS1 was 4 fold induced in OA chondrocytes upon IL-1β treatment. In the damaged cartilage expression of KiSS1 was significantly higher compared to the smooth cartilage. Overexpression of miR-N105 inhibited the IL-1β induced expression of KiSS1 which was rescued upon transfection of miR-N105 inhibitor suggesting KiSS1 is a bona fide target of miR-N105. siRNA-mediated knockdown of KiSS1 or its inhibition by overexpression of miR-N105 enhanced the expression of ACAN and reduced the expression levels of ADAMTS4 and ADAMTS5 in IL-1β-stimulated OA chondrocytes. Importantly,

overexpression of KiSS1 inhibited the ACAN expression but significantly enhanced the expression of ADAMTS4 and ADAMTS5 in IL-1β-stimulated OA chondrocytes.

Conclusion: We identified a novel miRNA-N105 that was differentially expressed in smooth and damaged OA cartilage, and validated KiSS1 mRNA as its target in OA chondrocytes. Our data also identifies for the first time KiSS1 as an important regulator of genes associated with the pathogenesis of OA.

Disclosure: M. Shahidul Makki, None; **T. Haqqi**, None.

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Abstract Number: 2123

Follistatin-like Protein 1 Is a Potent Regulator of Articular Chondrocytes in Osteoarthritis

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Background/Purpose: Osteoarthritis (OA) is the most common degenerative disease of the joints, affecting nearly 30 million Americans. It is characterized by a change in chondrocyte phenotype. The default route of chondrocyte differentiation is terminal differentiation, hypertrophy, apoptosis, and bone formation. In healthy articular cartilage, this default route is somehow blocked to obtain permanent cartilage. In OA, this block is lifted resulting in chondrocyte terminal differentiation characterized by a decrease in production of extracellular matrix proteins (type 2 collagen and aggrecan) and an increase in production of type 10 collagen, matrix metalloproteinase 13 (MMP13), and the transcription factor Runx2. Follistatin-like protein 1 (FSTL-1) is a protein produced by articular chondrocytes. Its expression is decreased in OA. Homozygous FSTL1 knockout (KO) mice display hypocellular cartilage as well as extensive skeletal defects. We therefore sought to determine whether loss of FSTL-1 in OA contributes to disease and whether increasing FSTL-1 expression will slow or reverse OA.

Methods: FSTL-1 expression in OA and healthy human cartilage was evaluated by immunofluorescence. Cartilage was evaluated in sectioned knee joints from FSTL-1 KO mice by staining with safranin-O. In vitro experiments were performed with human articular chondrocytes immortalized with the human telomerase gene and HPV oncogenes E6 and E7. The cells were transduced with a lentivirus encoding human FSTL-1 shRNA, or with an adenovirus encoding FSTL-1. Quantitative gene expression analysis was performed using real-time PCR for MMP13, aggrecan, collagens type 2 (COL2A) and type 10 (COL10A). Protein extracts from chondrocyte pellets were analyzed for Sox9 and phospho (p)-Smad3 by Western blotting.

Results: FSTL-1 expression was reduced in the OA chondrocytes. In FSTL-1 KO mice, a marked reduction in

articular cartilage cellularity, cartilage thickness, and matrix proteoglycan content was observed at 12 months of age. Downregulation of FSTL-1 expression in TGFβ-stimulated human chondrocyte pellet cultures led to abnormally small pellets with reduced proteoglycan content. The chondrocytes displayed an OA-like phenotype characterized by increased MMP13, COL10A, Runx2, and reduced Sox9, COL2A, aggrecan, and p-Smad3 expression. Transduction of chondrocytes with an FSTL-1 transgene led to a substantial increase in expression of COL2A.

Conclusion: These studies demonstrate that FSTL-1 plays a critical role in maintaining healthy cartilage by blocking the default route of chondrocyte terminal differentiation. Furthermore, we have shown that restoring FSTL-1 expression in chondrocytes can reverse changes observed in OA.

Disclosure: Y. Chaly, None; **B. Hostager**, None; **S. Smith**, None; **R. Hirsch**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/follistatin-like-protein-1-is-a-potent-regulator-of-articular-chondrocytes-in-osteoarthritis

Abstract Number: 2124

Maintenance of Chondrocyte Phenotypic Stability By TRPC6 Calcium Channel Activity

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Session Type: ACR Poster Session C

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Background/Purpose: The ELR+ CXC chemokine CXCL6 is produced by healthy articular chondrocytes and retained within the cartilage matrix via interactions with heparan sulphate proteoglycans. There, it signals via CXCR2 to promote maintenance of articular cartilage homeostasis, particularly during conditions of physiological challenge, which was indicated by increased cartilage degradation in $CXCR2^{-/-}$mice following destabilization of the medial meniscus. The transient receptor potential channel 6 (TRPC6) mechanosensitive ion channel was demonstrated to be a specific mediator of CXCR2 driven cell migration. This project aims to investigate whether TRPC6 activity is required for CXCR2-mediated cartilage homeostasis.

Methods: Costal chondrocytes were isolated from $CXCR2^{-/-}$ mice, $TRPC6^{-/-}$mice and their wild type (WT) littermates and expanded under standard conditions. Chondrocyte TRPC channel and phenotypic gene expression was assessed using real time RT-PCR, Western blot and immunohistochemistry. Sulfated proteoglycan content of chondrocyte micromasses was measured using Alcian blue staining and spectrophotometric quantification. CXCR2 was activated using murine CXCL6 whilst TRPC6 was specifically activated using hyp9, a stabilized

derivative of the TRPC6-selective activator hyperforin. Calcium mobilization in chondrocytes was measured using a fura-2 calcium influx assay. AKT phosphorylation was analyzed by Western blot.

Results: TRPC6 mRNA and protein was detected in WT murine chondrocytes. $TRPC6^{-/-}$ and $CXCR2^{-/-}$ chondrocytes expressed lower levels of the chondrocyte differentiation markers SOX9 and type II collagen in comparison to WT controls, accompanied by less AKT phosphorylation. $TRPC6^{-/-}$ chondrocyte micromass cultures produced significantly less sulfated proteoglycans in comparison to WT. CXCL6 treatment of WT chondrocytes resulted in increased intracellular calcium mobilization and AKT phosphorylation, which was not observed in CXCL6 treated $TRPC6^{-/-}$cells. In vitro activation of TRPC6 using hyp9 led to increased AKT phosphorylation and resulted in a significant increase in SOX9 and type II collagen mRNA expression, together with a decrease in type X collagen mRNA expression.

Conclusion: TRPC6 is required for chondrocyte phenotypic stability and for CXCL6-induced calcium influx and AKT phosphorylation. In vitro TRPC6 activation is sufficient to increase the key chondrocyte phenotypic marker gene expression in murine chondrocytes, indicating that TRPC6 may be an ideal pharmacological target for reducing the loss of chondrocyte phenotypic stability and cartilage degradation during osteoarthritis.

Disclosure: J. Sherwood, None; **J. Bertrand**, None; **F. Dell'Accio**, None; **T. Pap**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/maintenance-of-chondrocyte-phenotypic-stability-by-trpc6-calcium-channel-activity

Abstract Number: 2125

Aggrecan Degradation Is Not Just Aggrecan Degradation:a Study of the Neo-Epitopes Tege and Args Released from Cartilage upon Aggrecanase Activity

Anne Sofie Siebuhr[1], Yi He[2], Yunyun Lou[2], Sabine Hoielt[3], Morten Asser Karsdal[1] and **Anne C. Bay-Jensen**[1], [1]Rheumatology, Nordic Bioscience, Herlev, Denmark, [2]Rheumatology, Nordic Bioscience, Biomarkers and Research, Herlev, Denmark, [3]Rheumatology, Nordic Bioscience, Biomarkers and Research, 2730, Denmark
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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

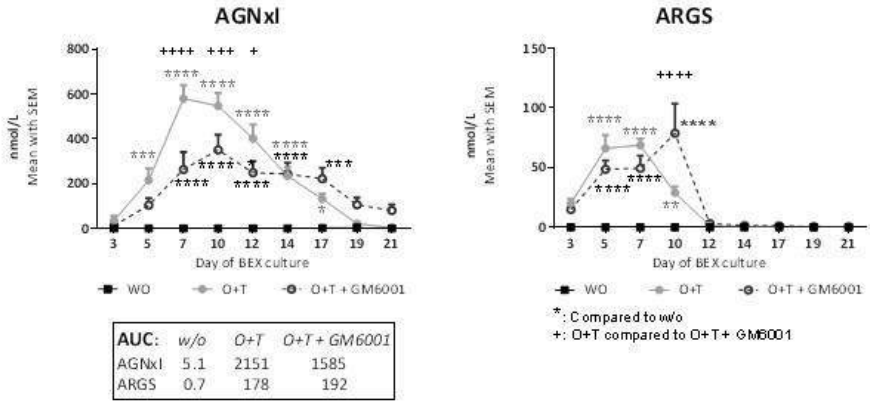
Background/Purpose: Cartilage degradation is a hallmark of arthritic disease. The main constituents of cartilage is aggrecan and type II collagen. Previous studies have shown that aggrecan degradation is prior to type II collagen degradation and that only aggrecanase degradation but not matrix metalloproteinases (MMP) degradation of aggrecan was reversible. It is therefore essential to have biomarkers that can detect reversible and irreversible aggrecan degradation to identify the condition of the cartilage. Of the well-known aggrecanase degradation site at NITEGE(373)-(374)ARGS, ARGS is released by only aggrecanse, but NITEGE is retained in the aggrecan molecule and in theory needs additional aggrecan degradation to be released. The numbers indicate the aggrecanase cleavage site. The aim was to investigate the profile of two neo-epitope biomarkers of

aggrecanase degraded aggrecan at NITEGE(373)-(374)ARGS in a bovine cartilage explants model.

Methods: Catabolic stimulated (oncostatin M and TNF-a; O+T) bovine cartilage explants were treated with or without the generic MMP inhibitor, GM6001. Explants without catabolic stimulation was used as negative control. In the culture supernatant two biomarkers investigating aggrecanase degraded aggrecan was measured. The AGNxI competitive ELISA detects the NITEGE^{373} neo-epitope and the ARGS sandwich ELISA detects the ^{374}ARGSVI neo-epitope. Statistical differences between groups were tested by two-way ANOVA.

Results: The AGNxI level was significantly increased compared to w/o from day 5 to day 17. GM6001 significantly lowered the release of AGNxI compared to O+T alone at day 7 ($p<0.0001$), day 10 ($p=0.0007$) and 12 ($p=0.01$). In addition, GM6001 shifted the release to 2days later in the culture period, as the AGNxI level was first significantly increased compared to w/o at day 7 to day 17, where the level was higher than O+T, but non-significant. The ARGS level was significantly increased at day 5, 10 and 12 for both O+T and O+T + GM6001 compared to w/o. At day 10 the ARGS level was higher in O+T + GM6001 than O+T ($p<0.0001$).

Conclusion: The prolonged release of AGNxI and the significantly lowered level of AGNxI with the MMP-inhibitor, suggest that the AGNxI release is somewhat dependent of MMP activity. In contrast, the ARGS release seems not to be MMP-dependent as there was a significant increase in O+T with the MMP-inhibitor compared to w/o and the peak was pronounced. In summary, aggrecan degradation is not just aggrecan degradation and different neo-epitopes have different importance in cartilage degradation.



AUC:	w/o	O+T	O+T + GM6001
AGNxI	5.1	2151	1585
ARGS	0.7	178	192

Disclosure: A. S. Siebuhr, Nordic Bioscience Diagnostic, 3; **Y. He**, Nordic Bioscience A/S, 3; **Y. Lou**, None; **S. Hoielt**, Nordic Bioscience A/S, 3; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3; **A. C. Bay-Jensen**, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/aggrecan-degradation-is-not-just-aggrecan-degradationa-study-of-the-neo-epitopes-tege-and-args-released-from-cartilage-upon-aggrecanase-activity

Abstract Number: 2126

Cytokine Dependent Effects of Anti-Inflammatory Inhibitors Targeting JAK and p38 on Cartilage Turnover

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SESSION INFORMATION

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Background/Purpose:

Rheumatoid arthritis (RA) and inflammatory subtypes of osteoarthritis (iOA) are degenerative joint diseases with an inflammatory component allowing for potential anti-inflammatory treatment benefit. A number of different signaling pathways have been associated with the inflammation-driven degradation of the extracellular matrix (ECM), and targeted in drug development with varying clinical results.

A better understanding of the signaling pathways and how their modulation affect ECM remodeling may therefore help in selecting novel anti-inflammatory treatments for iOA and RA.

The aim of this study was to investigate the differential effect of the anti-inflammatory inhibitors SB203580 (p38 inhibitor) and Tofacitinib (Jak inhibitor) on cartilage turnover driven by two different cytokines, IL-1α and TNF-α.

Methods:

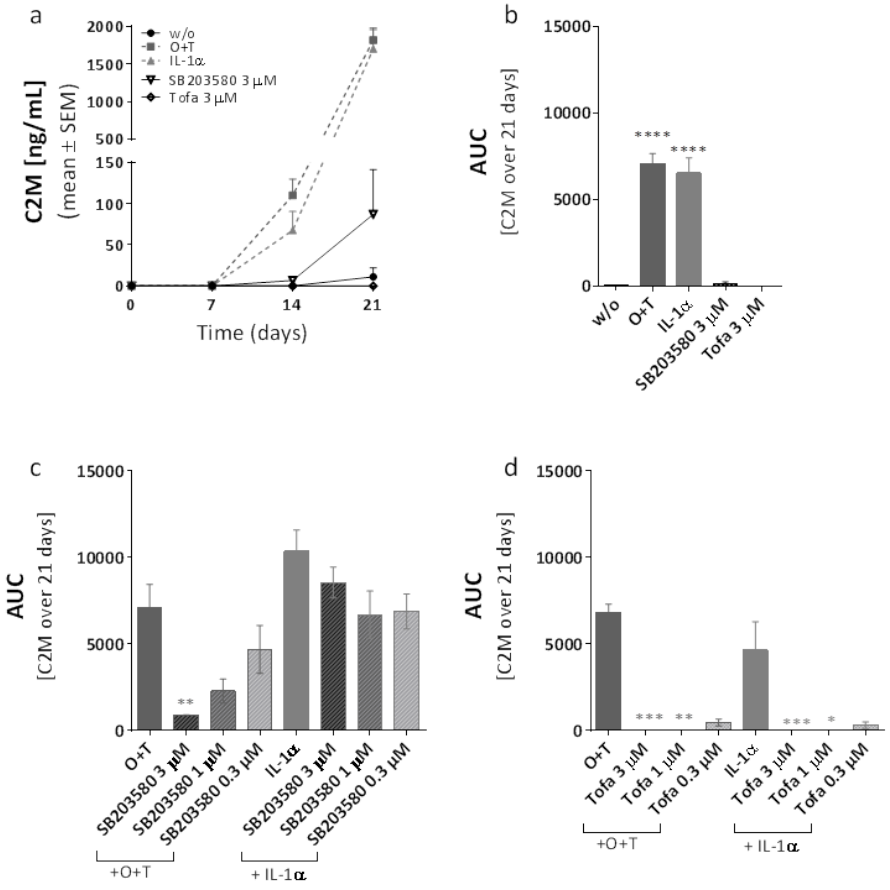
Full depth cartilage ex vivo cultures were cultured for 3 weeks stimulated with either OSM [10 ng/ml] and TNF-α[2 ng/ml] [O+T] or IL-1α [10 ng/mL] alone, together with SB203580 or Tofacitinib at 3 μM, 1 μM and 0.3 μM. Untreated explants (w/o) were included as negative control. The cartilage ECM turnover was assessed by measuring the tissue fingerprint biomarkers C2M and AGNx1 in the conditioned medium with ELISA.

Results:

Aggrecanase mediated degradation of aggrecan was measured by AGNx1. The JAK inhibitor Tofacitinib significantly inhibited the release of AGNx1 in a dose dependent manner in both O+T and IL-1α stimulated cartilage, while the p38 inhibitor SB203580 had no effect. The degradation of type II collagen was measured by the MMP-mediated degradation of type II collagen (C2M) (Fig 1). Tofacitinib significantly inhibited C2M release in O+T and IL-1α stimulated cultures (Fig. 1d). SB203580 significantly inhibited C2M in O+T stimulated conditions in a dose dependent manner (Fig 1c). In contrast, SB203580 failed to inhibit C2M release in IL-1α stimulated conditions (Fig. 1c).

Conclusion:

The two inhibitors tested here had a positive effect on the degradation of type II collagen; however, for the p38 inhibitor only in a TNF-α driven setting. Furthermore, only the JAK inhibitor was able to inhibit aggrecan degradation, while the p38 inhibitor failed to do so in both TNF-α and IL-1α stimulated conditions. These findings suggest that anti-inflammatory effects tested ex vivo are dependent on type of cytokine activation, and, thus, indicate that signaling pathways driving inflammatory joint diseases needs to be given consideration when assessing the effect of potential anti-inflammatory treatments.



Disclosure: C. S. Thudium, Nordic Bioscience A/S, 3; **C. F. Kjelgaard-Petersen**, None; **B. Christensen**, Nordic Bioscience A/S, 3; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3; **A. C. Bay-Jensen**, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cytokine-dependent-effects-of-anti-inflammatory-inhibitors-targeting-jak-and-p38-on-cartilage-turnover

Abstract Number: 2127

Dicam Promotes Proliferation and Hypertrophic Differentiation of Chondrocyte through Indian Hedgehog Signaling of Primary Cilia

Seungwoo Han[1,2], Hye-Ri Park[2], Min-Su Han[2], Eun-Ju Lee[2], Ji-Ae Jang[2], Ji-Min Kim[3], Gun-Woo Kim[2,4] and Younkwan Jung[2], [1]Internal Medicine, Daegu Fatima hospital, Daegu, Korea, The Republic of, [2]Fatima Research Institute, Daegu, Korea, The Republic of, [3]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, Korea, The Republic of, [4]Rheumatology, Daegu Fatima hospital, Daegu, Korea, The Republic of

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Background/Purpose: Chondrocytes in growth plate is known to respond to hydrostatic loading by increasing Indian hedgehog (Ihh) signaling, and that the primary cilium is required for this mechano-biological signal transduction to occur. Dicam (dual Ig domain containing cell adhesion molecule) was originally cloned from human chondrocyte cell-line, HCS-2/8 cells, but the role during endochondral bone formation and osteoarthritis has not been elucidated. This study reveals that Dicam has a novel function as a modulator of primary cilia-mediated Ihh signaling in chondrocytes.

Methods: Primary chondrocytes and tibia were isolated from limbs of C57BL/6 embryo (E15.5) and used in vitro study. Cartilage-specific Dicam transgenic (Col2-DICAM-Tg) mice were constructed and the phenotype of E15.5 long bone was compared with their wild type-littermates.

Results: Dicam mainly expressed in resting and proliferating chondrocytes in growth plate and it was increased by Pthrp and BMP2 in primary chondrocytes. Gain-of function study with Col2-Dicam-Tg revealed that Dicam increased length of long bones. Col2-Dicam-Tg showed an increased expression of chondrogenic, Col2a1 and proliferating marker, PCNA in immunostaining analysis. In addition, early and late hypertrophic chondrocyte marker, Col10a1 and MMP13, respectively, also increased in Col2-Dicam-Tg compared to wild-type. To elucidate a molecular mechanism of Dicam, we checked the major signaling targets in chondrogenesis, which showed an increased expression of Hhip and Zfp521, the target molecule of Ihh and Pthrp signaling, respectively. Other Ihh signaling molecules such as Ptch1, Gli2, and Gli3 and Ihh itself were also increased by Dicam overexpression in primary chondrocytes. Mechanistically, Dicam was localized to primary cilia of chondrocytes and increased a number of primary cilia and their assembly molecule, IFT88/polaris. Both knock-down of IFT88/polaris and hedgehog signaling antagonist, cyclopamine, attenuated the Dicam-mediated increase of length in primary tibia organ culture.

Conclusion: Dicam was localized to primary cilia and increased proliferation and hypertrophic differentiation of chondrocytes through Ihh signaling resulting in an increase of bone length In Vivo.

Disclosure: **S. Han**, None; **H. R. Park**, None; **M. S. Han**, None; **E. J. Lee**, None; **J. A. Jang**, None; **J. M. Kim**, None; **G. W. Kim**, None; **Y. Jung**, None.

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Abstract Number: 2128

Autophagic Clearance of Dysfunctional Mitochondria Requires Parkin in Human Chondrocytes

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Background/Purpose: Due to exogenous stresses chondrocytes mitochondrial dysfunction is known to occur in osteoarthritis (OA) and amplifies the inflammatory cytokine induced cartilage degradation. Autophagy is an evolutionarily conserved mechanism that plays a central role in mitochondrial quality control. Here we investigated (a) whether IL-1β induce mitochondrial damage; and (b) whether the damaged mitochondria are cleared by autophagy in human OA chondrocytes under pathological conditions.

Methods: Primary human OA chondrocytes were isolated by enzymatic digestion of the undamaged cartilage obtained from OA patients who underwent total knee arthroplasty at Crystal Clinic, Akron, Ohio. Chondrocytes were treated with IL-1β (5ng/ml) followed by total RNA isolation for qPCR or lysate preparation for Western blotting. Mitochondrial damage and dysfunction was determined by JC-1 staining of chondrocytes followed by flow cytometry. Mitochondrial ROS levels as an indicator of mitochondrial damage and dysfunction were determined by MitoSOX red dye assay. Rapamycin was used to activate autophagy in OA chondrocytes and autophagic flux was confirmed by immunoblotting and immunofluorescence staining of LC3 protein. siRNA mediated knockdown of ATG5 or small inhibitors 3MA, Bafilomycin A1, chloroquine and ammonium chloride were used to inhibit autophagy in OA chondrocytes. Targeting of mitochondria by mitophagy was assessed by colocalization of mitochondria with parkin or p62 or LC3 protein or lysosomes. siRNA mediated knockdown of PARK2 was used to block mitophagy. Activation of Parkin and ubiquitination of Mfn1 and Mfn2 was assessed by immunoblotting.

Results: OA chondrocytes treated with IL-1β showed increased expression of COX-2, iNOS, IL6 and MMPs and decreased expression of COL2A1 and aggrecan. IL-1β treated OA chondrocytes also had decreased mitochondrial potential and several fold higher mitochondrial ROS production compared to controls and concomitant enhanced autophagic flux evidenced by increased LC3-II formation. Immunofluorescence staining of endogenous LC3 as well as of transiently overexpressed LC3-GFP protein also demonstrated increased autophagic flux in OA chondrocytes with damaged mitochondria. Autophagy inhibition augmented the IL-1β induced mitochondrial dysfunction, ROS production and OA like gene expression and apoptosis in OA chondrocytes while autophagy activation by rapamycin blocked the mitochondrial dysfunction and OA like gene expression. Immunofluorescence staining of mitochondria (using Mitotracker red) and of parkin or p62 protein or LC3 protein and lysosomes showed increased colocalization in IL-1β treated OA chondrocytes indicating active mitophagy. siRNA mediated knockdown of PARK2 blocked mitophagy and clearance of mitofusins and damaged mitochondria resulting in enhanced mitochondrial dysfunction and OA like gene expression in IL-1b-stimulated OA chondrocytes.

Conclusion: Our data directly demonstrate a link between the diminished autophagy and sustenance of mitochondrial dysfunction in OA and highlight the importance of the development of strategies to activate autophagy for better management of OA.

Disclosure: M. Y. Ansari, None; **T. M. Haqqi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/autophagic-clearance-of-dysfunctional-mitochondria-requires-parkin-in-human-chondrocytes

Abstract Number: 2129

Extracellular Adenosine Deficiency Plays a Role in the Pathogenesis of

Osteoarthritis (OA) and Adenosine Replacement Prevents Post-Traumatic Osteoarthritis

Carmen Corciulo[1], Matin Lendhey[2], Tuere Wilder[1], Oran Kennedy[2] and Bruce Cronstein[3], [1]Department of Medicine, Division of Rheumatology, NYU School of Medicine, New York, NY, [2]Department of Orthopaedic Surgery, NYU-School of Medicine, New York, NY, [3]Medicine, Division of Rheumatology, NYU School of Medicine, New York, NY

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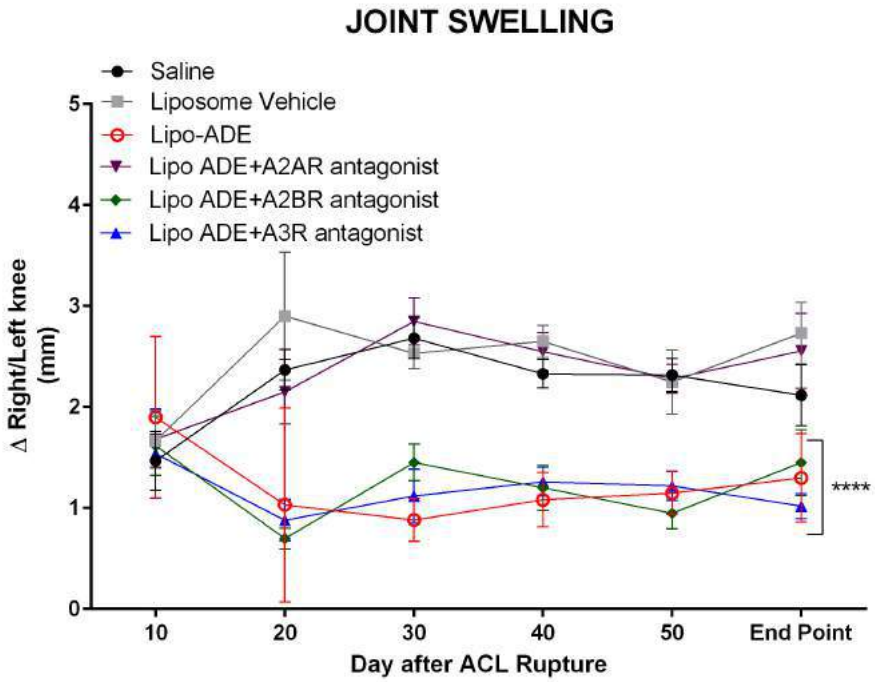
Background/Purpose: Extracellular adenosine is highly regulated and plays an important homeostatic role via occupancy of cell surface receptors (A1R, A2AR, A2BR, A3R). Mice lacking A2AR develop spontaneous OA and A2AR-deficient chondrocytes express MMPs and Col10, suggesting a homeostatic role for adenosine/A2AR in cartilage. We tested whether diminished extracellular adenosine (generated from ATP by CD73 and/or CD39) contributes to OA and whether adenosine replacement ameliorates OA.

Methods: Chondrocytes were harvested from neonatal mice. ATP in chondrocytes and supernates was measured by luciferase-mediated bioluminescence, adenosine by HPLC and mRNA by RT-PCR. Modified OARSI scoring was carried out on safranin O-stained sections of knees from 1 yr old CD73KO mice. Post-traumatic OA was induced by application of mechanical load on rat tibia (14 wk old). Liposomal suspensions (100µl) +/- adenosine (10mg/Kg) +/- A2A, A2B or A3 receptor antagonists (1 mg/Kg, 5-6 rats/group) were injected every 10d for 56d.

Results: Treatment of rat tibial explants with IL-1β (5 ng/ml) markedly reduced ATP and adenosine release (38±17% of control, $p<0.05$, n=3; 76±7% of control, $p<0.01$; n=5, respectively). Moreover, applying a physiologic load increased adenosine release from untreated (199±27% of control, $p<0.001$, n=5) but not IL-1β treated explants (77±6%, $p<0.01$ vs control, n= 5). IL-1β–treated chondrocytes have reduced expression of ATP transporters pannexin-1 and ankh as well as CD73 (45±15%, 13±5%, 37±17%, $p<0.05$ of control, n=3, respectively). Mice lacking CD73 have mild OA (modified OARSI 1.5±0.4, $p<0.05$ vs. WT, n=5), consistent with findings in CD73-deficient patients (Arthritis Rheumatol. 2015; 67 (10)). Replacing adenosine by intraarticular injection of adenosine-liposomes reduced knee swelling and prevented OA changes in a rat model (Fig. 1 and 2) compared to saline or empty liposomes. An A2AR antagonist, but not A2BR or A3R antagonists, reversed these effects (Fig. 2).

Conclusion: Endogenous adenosine production from ATP maintains cartilage homeostasis; inflammation/injury reduces ATP release and adenosine production contributing to cartilage destruction. Adenosine replacement prevents OA development and may be useful to treat OA. Fig. 1



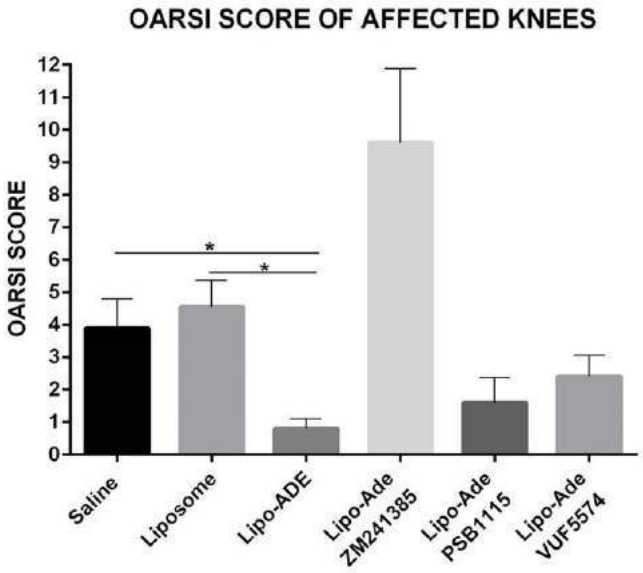


Fig. 2

Disclosure: C. Corciulo, None; **M. Lendhey**, None; **T. Wilder**, None; **O. Kennedy**, None; **B. Cronstein**, Canfite Pharma, 1,Celgene, AstraZeneca, Takeda, 2,Revive Therapeutics, 5,Always hopeful, 9.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/extracellular-adenosine-deficiency-plays-a-role-in-the-pathogenesis-of-osteoarthritis-oa-and-adenosine-replacement-prevents-post-traumatic-osteoarthritis

Abstract Number: 2130

Unloading Results in Rapid Loss of TGFβ Signaling in Cartilage: Role of Loading-Induced TGF-B Signaling in Maintenance of Articular Chondrocyte Phenotype?

Arjan van Caam[1], Wojciech Madej[2], Esmeralda Blaney Davidson[1], Pieter Buma[2] and Peter M. van der Kraan[1], [1]Experimental Rheumatology, Radboud university medical center, Nijmegen, Netherlands, [2]Orthopaedic Research Lab, Radboud university medical center, Nijmegen, Netherlands

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SESSION INFORMATION

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Session Type: ACR Poster Session C

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Background/Purpose: Absence of joint loading leads to cartilage atrophy and degeneration for unknown reason. We hypothesized that *in vivo* chondrocytes are exposed to permanent, loading mediated, TGFβ signaling and that loss of loading will result in rapid loss of protective TGFβ signalling. Additionally, we investigated the effects of inflammation on this loading mediated TGFβ signalling.

Methods : Bovine metacarpophalangeal joints were obtained from a local abattoir. TGFβ/Smad2/3P signaling was monitored by immunohistochemistry for phosphorylated-Smad2 (Smad2P) and by gene expression analysis using qPCR. A physiological load of 3 MPa (1 Hz) for 30 min was used for loading experiments. Sulfated glycosaminoglycan (GAG) levels were measured using DMB. Conditioned medium (OAS-CM), obtained from synovial biopsies of OA patients, was used to study inflammation.

Results: Active TGFβ signaling was abundantly present throughout all layers of freshly loaded cartilage. However, after unloading this signalling diminished rapidly and showed significant reduction after 2 hours. Compressive loading of articular cartilage resulted in swift restoration of Smad2P levels as well as potent up-regulation of Smad2/3P dependent gene expression including *Tgfb1*, and its receptor *ALK5*. Importantly, this process was repeatable, but could be inhibited by the ALK4/5/7 inhibitor SB-505124, indicating TGFβ or Activin signaling as the driver. However, loading effects could be mimicked by exogenous rhTGFβ1(1 or 10 ng/ml), but not by exogenous rhActivin A (1or 10 ng/ml). Unloading of explants for 2 weeks resulted in profound GAG loss and increased chondrocyte hypertrophy (*Col10a1*). Remarkably, neither repeated loading nor exogenous TGFβ1 counteracted GAG loss, but repeated loading did inhibit the elevation of *Col10a1* expression as effective as exogenous TGF-β. Strikingly, OAS-CM inhibited loading-induced expression of *ALK5* and down regulated expression of *Tgfbr2*, the essential type II receptor for TGFβ signaling, and this was reflected in reduced expression of loading-induced Smad2/3P dependent genes

Conclusion: Our data strongly indicate that, *in vivo*, articular cartilage has enduring TGFβ signalling when regularly loaded, but which is inhibited in inflammatory conditions. This loading- induced TGFβ signalling has an important role in maintenance of chondrocyte phenotype but not of cartilage GAG content. Based on these results and our earlier findings we suggest that loading-induced TGF-β signalling is crucial to maintain articular cartilage functioning and that this protective system can be impaired under inflammatory conditions.

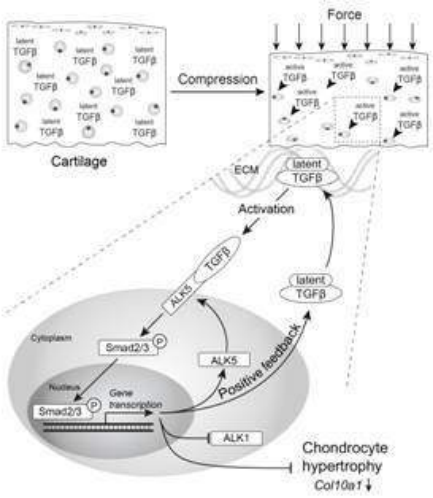

Figure 1: Loading induced Smad2/3P activates a positive feedback loop by inducing expression of its own activating receptor: ALK5, and (inactive) TGFβ1, which after production will bind to the ECM and return the system to its original stage.

Disclosure: A. van Caam, None; **W. Madej**, None; **E. Blaney Davidson**, None; **P. Buma**, None; **P. M. van der Kraan**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/unloading-results-in-rapid-loss-of-tgf%ce%b2-signaling-in-cartilage-role-of-loading-induced-tgf-%ce%b2-signaling-in-maintenance-of-articular-chondrocyte-phenotype

Abstract Number: 2131

Transient Receptor Potential Ankyrin 1 (TRPA1) Is Functionally Expressed in Primary Human Osteoarthritic Chondrocytes and Mediates Cartilage Destruction and Joint Pain in the Mia-Model of Osteoarthritis

Elina Nummenmaa[1], Lauri J Moilanen[1], Mari Hämäläinen[1], Erja-Leena Paukkeri[1], Riina Nieminen[1], Teemu Moilanen[2], Katriina Vuolteenaho[1] and **Eeva Moilanen**[1], [1]The Immunopharmacology Research Group, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland, [2]Coxa Hospital for Joint Replacement, Tampere, Finland

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Background/Purpose: Transient receptor potential ankyrin 1 (TRPA1) is a membrane associated cation channel, which is widely expressed in neuronal cells and known to be involved in nociception and neurogenic inflammation. More recently, TRPA1 has also been found to be expressed in some non-neuronal cells, such as

keratinocytes and synoviocytes, but the functional roles of non-neuronal expression remain to be studied. TRPA1 has previously been shown to be up-regulated and activated by agents formed endogenously in inflammatory and hypoxic conditions characteristic to human and MIA-model of osteoarthritis (OA). We hypothesized that TRPA1 is expressed and functional in human OA chondrocytes and mediates cartilage destruction and joint pain in MIA-induced experimental OA.

Methods: Expression of TRPA1 in primary human OA chondrocytes was assessed by quantitative RT-PCR and Western Blot analysis. The functionality of the TRPA1 channel was assessed by Ca^{2+}-influx measurements. Production of MMP-1, MMP-3, MMP-13, IL-6 and PGE_2 subsequent to TRPA1 activation were measured by immunoassay. Wild type and TRPA1 knock-out mice were used in mouse cartilage culture experiments. To induce experimental OA, MIA was injected into mouse knee joint either at lower (37.5ug) or higher (500 ug) dose, and contralateral knee was injected with the vehicle. Joint pain was estimated by weight-bearing test at baseline and thereafter weekly. The animals were sacrificed four weeks after the MIA injections and histological changes in the knee joints were assessed according to the OARSI guidelines. The responses between wild type (WT) and TRPA1 deficient (knock-out, KO) mice were compared.

Results: Remarkably, TRPA1 was found to be expressed and inducible by IL-1β in primary human OA chondrocytes. The TRPA1 channel was found to be functional, as stimulation with the TRPA1 agonist AITC caused an increase in Ca^{2+}-influx, which was attenuated by the TRPA1 antagonist HC-030031. Pharmacological inhibition of TRPA1 with the selective antagonist HC-030031 downregulated the production of MMP-1, MMP-3, MMP-13, IL-6 and PGE_2 in primary human OA chondrocytes. Furthermore, genetic depletion of TRPA1 downregulated the production of MMP-3, IL-6 and PGE_2 in murine cartilage explants. Both doses of MIA caused spontaneous joint pain in WT mice as shown in weight-bearing test. However, in TRPA1 deficient mice no response was seen following the lower dose of MIA, and the response after the higher dose of MIA was clearly attenuated. Also, the higher dose of MIA caused cartilage changes typical for OA in the WT mice. Interestingly, the TRPA1 deficient mice did not develop such destructive joint changes following MIA injections.

Conclusion: The TRPA1 cation channel was found to be functionally expressed in primary human OA chondrocytes and to mediate inflammatory and catabolic effects, which are both original findings. Further, in MIA-induced experimental OA TRPA1 was found to contribute to the development of cartilage changes and joint pain. The inflammatory and hypoxic environment in the OA joint is conducive to enhance the expression and activation of TRPA1. The results reveal TRPA1 as a potential mediator and drug target in osteoarthritis.

Disclosure: E. Nummenmaa, None; **L. J. Moilanen**, None; **M. Hämäläinen**, None; **E. L. Paukkeri**, None; **R. Nieminen**, None; **T. Moilanen**, None; **K. Vuolteenaho**, None; **E. Moilanen**, the Competitive Research Funding of the Pirkanmaa Hospital District, Finland, 2,Tampere Tuberculosis Foundation, Finland, 2.

Abstract Number: 2132

Deficient Autophagy Induces Premature Senescence in Aging and Osteoarthritis

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Associated Node to ProteoRed, Rheumatology Division, Proteomics Group-ProteoRed/ISCIII, INIBIC-CHUAC, A Coruña, Spain, [3]Degradome Lab, Universidad de Oviedo, Oviedo, Spain, [4]Rheumatology Division, INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), La Coruña, Spain
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Background/Purpose: Previous findings indicated that autophagy is defective in Aging and Osteoarthritis (OA). Autophagy is essential to maintain chondrocyte homeostasis by regulating the intracellular macromolecule and organelle turnover. However, the specific targets that regulate this homeostatic mechanism are still unknown. *The objective of study is to identify relevant targets regulating autophagy in Aging and OA.*

Methods: Human chondrocytes were transfected with siRNA for Atg5 (100 nM, 72 hours), an important autophagy marker, to block the autophagy pathway. To identify the key proteins associated to defective autophagy, we performed quantitative proteomics analysis using iTRAQ labeling coupled with on-line 2D LC/MS/MS. Protein identification and quantification were performed using Protein Pilot Software v 4.0. Each MS/MS spectrum was searched in the Uniprot/Swissprot database for *Homo sapiens*. Human chondrocytes, human cartilage from healthy, aged and OA human patients and mouse knee joints from young and old mice were employed. To evaluate the role of Lamin A/C overexpression on autophagy pathway in human chondrocytes, CRISPR-Cas9 technology was used.

Results: 487 different proteins were identified in response to defective autophagy in human chondrocytes. 24 targets were significantly altered ($p<0.05$) between siCtrl and siAtg5 (11 were decreased and 13 increased). Cytoskeleton organization, collagen catabolism, oxidative stress, and aging pathways are associated with chondrocytes with deficient autophagy. Taking into account the key role of autophagy in the regulation of aging and OA, we focused on Prelamin A/C. Prelamin A/C is a nuclear protein implicated in premature cell senescence that was found upregulated ($p < 0.05$). Autophagy proteins Atg5 and LC3, as well as Lamin A/C were evaluated in human chondrocytes. The results indicated a reduction in autophagy expression, accompanied with an increase in Lamin A/C. Furthermore, in aging and OA human cartilage, autophagy markers were reduced while Lamin A/C expression was increased. Histological analysis of mouse knee joints from young and old mice revealed a reduction in LC3 expression, as well as an increase in Lamin A/C expression. Importantly, *in vitro* premature aging model by genetic deletion of Zinc Metalloproteinase 24 (Zmpste24) via CRISPR-Cas9, showed a Lamin A/C overexpression, accompanied by a reduction of LC3 in human chondrocytes, suggesting that autophagy loss-of-function is intimately correlated with increased premature senescence in human chondrocytes.

Conclusion: Proteomic analysis has revealed features of premature senescence when autophagy is disrupted in chondrocytes. Lamin A/C, a nuclear protein contributing to structural integrity to the nucleus and matrix was identified as candidate target for regulating cartilage function under defective autophagy, such as aging and OA. These results support the hypothesis that autophagy is decreased with aging. Therefore, targeting Lamin A/C a promising strategy to find novel therapeutics for cartilage aging and OA.

Abstract Number: 2133

Simulation of Cartilage Damage in Osteoarthritis Using Patient-Derived Induced Pluripotent Stem Cells

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Background/Purpose: Osteoarthritis (OA) is a degenerative joint disease, leading to pain and functional limitation. Although OA is a most common form of musculoskeletal disease, the pathogenesis still remains to be determined. This study was aimed to investigate the characteristics of cartilage derived from OA-iPSCs.

Methods: Dermal fibroblasts were obtained from one patient with early onset OA (age=31) and a healthy sibling without OA under informed consent. OA-iPSCs and control-iPSCs were reprogrammed from dermal fibroblasts, and differentiated into chondrocytes using outgrowth cells extending from embryoid bodies. The expression of cartilage specific markers was determined by immunohistochemical staining and reverse transcription-polymerase chain reaction (RT-PCR). To simulate the inflammatory condition of OA, chondrocytes differentiated from iPSCs were cultured in the presence of interleukin-1α.

Results: Dermal fibroblasts of OA patient and a healthy sibling were successfully reprogrammed into iPSCs. Pluripotency of OA-iPSCs and control-iPSCs was confirmed by immunohistochemical staining and RT-PCR for Nanog, Oct4, Fox2, and other pluripotent markers. All iPSCs were efficiently differentiated into cartilaginous pellet, which exhibit the chondrocyte-specific markers. Cartilage from OA-iPSCs showed an impaired mechanical integrity with porous structures. The expression of collagen type II were significantly decreased in OA-iPSC-cartilage, compared to control-iPSC-cartilage. Treatment of IL-1α enhanced the loss of cartilage, and the expression of matrix metalloproteinases and inflammatory molecules, in OA-iPSC-cartilage.

Conclusion: This study presented the impaired function of cartilage differentiated from OA patient derived iPSCs, and the simulation of cartilage damage in inflammatory condition of OA. Disease modeling of OA using patient-derived iPSCs would provide the better understanding for OA pathogenesis.

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Abstract Number: 2134

Bone Replaces Cartilage in Non-Weight Bearing Regions of Immobilized Knees

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Bone Replaces Cartilage In Non-Weight Bearing Regions Of Immobilized Knees

Background/Purpose:

Osteoarthritis causes pain, restricts joint range of motion, reduces function, is highly prevalent worldwide and contributes to an ever-increasing burden on global health care costs[1]. Joint immobility damages articular tissues including cartilage, and has been used as an experimental model for OA[2, 3]. Various immobilization models in animals have been used including use of straps/slings, splints/casts, or rigid external fixation with or without weight-bearing on the immobilized joint, a crucial factor in articular homeostasis[4]. Therefore, the pathophysiology of immobility-related cartilage alterations and hence directions for treatment would still benefit from new data. This study examined the effect of knee joint immobilization in flexion on tibial epiphysis articular cartilage, comparing weight-bearing and non-weight-bearing regions.

Methods:

Eleven rat knees were rigidly immobilized for 32 weeks at 135° of flexion. Contralateral limbs served as controls. The medial tibial epiphysis on histological sagittal sections was divided into non-weight-bearing (anterior) and weight-bearing (middle, posterior) regions on digital images. We quantified cartilage thickness and glycosaminoglycan (GAG) staining intensity using safranin O, as well as the distribution of collagen I and II using picrosirius red under polarized light. We evaluated osteoblast activity and the presence of mesenchymal stem cells (MSCs) using immunohistochemistry to osteocalcin and overlapping CD90 and CD73 staining on serial sections, respectively.

Results:

Immobilized mean cartilage thickness was reduced in the anterior region but increased in the posterior region (92±68µm, 235±56µm respectively, Figure 1A top) compared to contralateral (154±49µm, $p=0.022$; 186±48µm, $p<0.001$, respectively, Figure 1A bottom). GAG cartilage staining area was 2±4% in the anterior region of

immobilized knees compared to 28±12% contralaterally (p=0.003). Immobilized knees had decreased collagen II staining area (11±9% vs 36±12%, p=0.006) and increased collagen I staining area (61±20% vs 43±12%, p=0.033) in the anterior cartilage region (Figure 1B top). Osteocalcin (Figure 1C) and MSC staining (Figure 1D) were decreased in immobilized knees (p=0.003 and p=0.036 for CD90 only, respectively) with no significant inter-regional differences.

Conclusion:

After 32 weeks of knee immobilization, the non-weight-bearing region of the tibia articular cartilage was thinner, lost GAG, and was replaced by bone. Long-duration immobility may share pathophysiologic features with OA and should be intervened upon in earlier stages.

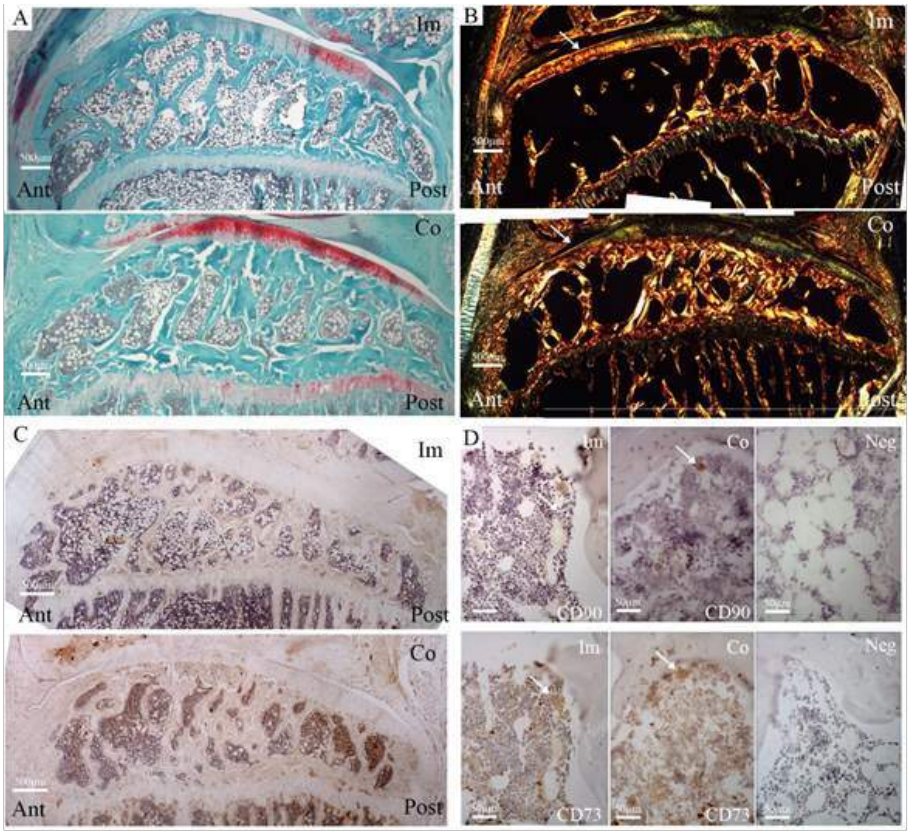

Figure 1. Cartilage changes following immobilization. (A) Digital reconstruction of tibial epiphysis and articular surface from immobilized (top) and contralateral (bottom) rat knee sections. Staining is with safranin-O. (B) Tibial epiphysis and articular surface from immobilized (top) and contralateral (bottom) rat knee sections. Staining is with picro sirius red under polarized light where collagen I appears red or yellow and collagen II appears green. Arrows identify different collagen colouration in the anterior region of the joint between the immobilized knee joint and the contralateral. (C) Immunohistochemistry: osteocalcin distribution. (D) Immunohistochemistry: CD90 (above) and CD73 (below) staining in adjacent serial sections of immobilized and contralateral rat knees as well as corresponding negative control. Background staining is with hematoxylin. Ant = anterior region; Co = contralateral; Im = immobilized; Neg = negative control; Post = posterior region.

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Abstract Number: 2135

Knee Osteoarthritis Pain Is Differentially Associated with Tissue Degradation and Joint Inflammation

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Background/Purpose: Osteoarthritis (OA) is a disease characterized by pain and tissue destruction, in some cases concomitant with inflammation. The link between pain and tissue destruction is yet unknown, and there is a lack objective quantifiable parameters. Collagens are the main structural proteins of the joint extracellular matrix. The degradation of especially type I (connective tissue), II (cartilage), III (synovium) and IV (basement membrane) collagens have been shown to be elevated in OA. So we investigated whether biomarkers reflecting collagen degradation were associated with knee OA representing with different pain and inflammatory phenotypes.

Methods: 111 knee OA patients, 62% women, from NYUHJD progression cohort study with varying degree of OA were included: mean (SD) age, 62 (10); mean(SD) BMI, 27(4); NSAID users, 23%; radiographic OA (KL≥2) 68%; and bilateral knee OA; 87%. Pain was assessed by VAS_{pain} and WOMAC at baseline (BL) at a 2-year follow-up (FU) visit. Median (IQR) were 39 (13-69) and 37 (13-52) for BL VAS_{pain} and $WOMAC_{pain}$. 4 BL serum biomarkers of type I, II, III and IV collagen degradation (C1M, C2M, C3M, C4M), and the 2 inflammatory biomarkers CRPM and hsCRP, were assessed. Data were log2 transformed. Associations between BL biomarkers, BL pain and change (CHG) pain scores were assessed by multivariate linear model including gender, age, BMI, $KL_{signal\ knee}$, bilateral knee OA and NSAID use. Patients with cont. mild/moderate pain had a BL VASpain<54 and FU VASpain<30, cont. moderate/severe pain had VASpain>30 at baseline and FU, and transitional severe pain had either VASpain_BL<30 and VASpain_FU>54 or VASpain_BL>54 and VASpain_FU<30 (ref). Patients with; low biochemical disease activity index (bDAI) low in CRPM (<12nM) moderate bDAI were high in CRPM but low in hsCRP (<5), and high bDAI (flare) were high in CRPM and hsCRP.

Results: ***BL association between pain and biomarkers*** C2M (β -17.9, p<0.0001) and $KL_{signal\ knee}$ (β -5.4, p=0.0031) were significantly associated with WOMAC pain. C2M (β -12.4, p=0.0033), C3M (β -19.9, p=0.059), age (β -0.84, p<0.0018), $KL_{signal\ knee}$ (β 8.9, p=0.0021) and bilateral knee OA (β -12.2, p=0.087) were associated with VAS_{pain}. ***Association between BL biomarkers and CHG pain*** C2M (β 13.3, p=0.0016), age (β 0.5, p=0.029) and bilateral OA (β -12.0, p=0.043) were significantly associated with delta $WOMAC_{pain}$. Only age, BMI and NSAID use was associated with CHG VAS_{pain}. ***Association between pain phenotypes and BL biomarkers*** Patients with cont. mild/moderate pain had significantly higher C2M compared patients with transitional severe pain (p=0.0014) and cont. moderate/severe pain (p=0.04). ***Biomarker, BL pain and CHG pain in patients w. inflammatory OA*** Patient with low bDAI had lower $WOMAC_{pain}$ (p<0.05) and VAS_{pain}(p<0.1). C1M was higher (p<0.05) in the flare group compared to the low and moderate bDAI groups. C3M was higher (p<0.05) in the moderate bDAI group than the low DAI group.

Conclusion: Different collagen degradation products are linked differentially to different phenotypes. Cartilage degradation (C2M) was consistently linked to CHG pain phenotypes, whereas it was not associated with an inflammatory phenotype. In contrast, C1M and C3M were linked to inflammatory and flared OA.

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Abstract Number: 2136

CD14 Deficiency Delays Progression of Cartilage Degeneration and Protects Against Early Deficits in Functional Outcomes in a Murine Osteoarthritis Model

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Background/Purpose: CD14, though expressed by multiple cell types, is highly expressed by monocytes and macrophages. It forms a complex with Toll-like receptors (TLRs), particularly TLR-2 and TLR-4, thereby facilitating innate inflammatory responses. Elevated expression of CD14 has been associated with joint space narrowing and symptoms in patients with OA (Daghestani et al. 2015). Previous work from our lab has shown that soluble CD14 is present in synovial fluid from patients with knee OA, and sensitizes fibroblast like synoviocytes (FLS) to respond to TLR ligands. The purpose of the current study was to test whether deficiency of CD14 modulates development of structural and functional features of disease using a murine knee OA model

Methods: CD14 deficient mice ($CD14^{-/-}$) and C57BL/6J congenic controls (WT) were obtained through Jackson Laboratory. 10-12 week old male mice from both strains were subjected to de-stabilization of medial meniscus (DMM), sham surgery or left unoperated. Six and nineteen weeks post-surgery were chosen as early and advanced time points in this model. Groups of 5-9 mice at each timepoint were sacrificed and knee joint histopathology evaluated using the modified OARSI score (Miller RE et al. 2016). As a surrogate for joint pain, changes in spontaneous activity were investigated longitudinally (every 4 weeks, up to 16 weeks) after DMM surgery in the two strains, using the LABORAS® Laboratory animal behavior observation registration and analysis system (Metris B.V., Hoofdorp, The Netherlands).

Results: $CD14^{-/-}$ mice showed similar degrees of cartilage erosion (Mean score ±SEM, 4.667±1.38) as WT controls (4.6±0.6, $p>0.9999$) at 6 weeks post-DMM. However, by 19 weeks post-DMM, cartilage erosion was significantly reduced in the CD14 knockouts (6.0±0.46) in contrast to their WT counterparts (13.44±2.5, $p<0.0001$). By contrast at 19 weeks post-DMM, both strains displayed similar osteophytosis (WT: 104.4±23.16; $CD14^{-/-}$: 138.8±22.48, $p=0.15$). Analysis of spontaneous activity indicated significant decreases in climbing activity by WT mice at 4 and 8 weeks post-DMM (~84% lesser than baseline). The CD14 deficient mice in contrast maintained climbing activity through the course of 16 weeks after DMM surgery. Furthermore, $CD14^{-/-}$ mice initiated significantly greater number of climbs each hour at 8, 12 and 16 weeks post-DMM as compared to baseline ($p\leq0.004$), and their WT counterparts ($p\geq0.11$).

Conclusion: Deficiency of CD14 expression significantly diminished progression of cartilage erosion observed

in the advanced phase, and protected the mice from early climbing deficits described in this model. No significant protection from osteophytosis was observed. These findings indicate that CD14-mediated mechanisms may be targets to ameliorate symptoms and prevent progression of structural disease. Loss of CD14 appears to affect structural and functional outcomes in this model through different mechanisms over different timelines. Further studies are needed to characterize the cell types involved and the specific mechanisms of action for suitable therapeutic targeting of OA progression.

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Abstract Number: 2137

Subchondral Bone Structure and Pain Behaviors in Collagenase Induced Noninflammatory Monoarthritis in Mice

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Background/Purpose: Bone histomorphometry can define OA changes in rodents and in Antigen-Induced arthritis in rats. We previously found that pain from inflammatory monoarthritis in mouse knees correlated with bone histomorphometry measures. In order to determine whether these changes were due to pain or due to inflammation, we used micro CT to correlate pain behaviors with histomorphometric bone changes in knees from mice with collagenase induced non-inflammatory monoarthritis with and without analgesia with intra-articular (IA) vanilloids and botulinum toxin.

Methods: Chronic non-inflammatory arthritis was produced by IA injection of 10 µl collagenase (COL) (10IU) into the left knee of C57BL6 male mice 4 weeks prior to pain behavior testing using evoked pain scores (EPS) and an automated dynamic weight bearing (ADWB) device. EPS was a tally of fights and vocalizations/min with knee palpation at 15.6 psi. Percent weight and time on each limb was measured with ADWB apparatus (Bioseb, Vitrolles, France). IA vanilloids resiniferatoxin (RTX) and capsaicin (CAP) (10µl each of 0.001%RTX, or 0.01% CAP) were given 7 days prior to pain testing. IA botulinum toxin A (BTX) (10µl 0.02 IU) was injected 3 days before testing. Knees were imaged on a micro-CT scanner (micro-CT40; ScanCo Medical AG, Bassersdorf, Switzerland). Subchondral trabecular bone volume fraction (BV/TV), trabecular thickness (Tb.Th in µm), trabecular spacing (Tb.S in µm), and number (Th.N/mm) were calculated from coronal slices using the ScanCo bone trabecular morphometry program.<span">

Results: Arthritis pain behavior was low in naïve mice - EPS (0.57) and ADWB proportions for weight (40.9%) and time (97.4%) were normal. IA COL arthritis significantly increased EPS (4.0) but had very little effect on ADWB for weight (39.7%) and time (98.0%). Forepaw compensatory weight bearing increased only from 9.3% in naïve mice to 10.9% in COL arthritic mice. In selected mice with COL arthritis in contrast to inflammatory monoarthritis, there was no significant correlation between pain as measured by EPS or ADWB and any measure of bone histomorphometry. There was no significant difference in bone volume, trabecular number, thickness or spacing between naïve and arthritic mice. IA neurotoxin treatment of COL arthritis with either BTX or Vanilloids (RTX or CAP) did not have a consistent effect on bone histomorphometry.

Conclusion: IA COL induced monoarthritis increased EPS in mice but had little effect on spontaneous pain as measured by ADWB. MicroCT did not find significant changes in BV/TV proportion, Tb.Th or Tb.Sp in COL non-inflammatory arthritis. IA neurotoxin treatments with BTX, RTX and CAP did not affect subchondral bone. These findings are not consistent with other findings in OA rodent models or our previous results with chronic inflammatory arthritis. These results suggest that pain alone is not sufficient to produce changes in bone histomorphometry. It may be that offloading is more important and that 4 weeks is not long enough to cause gait offloading in this model. We have noted increased offloading in this model after 6 weeks. It will be important to study whether offloading with additional chronicity will change bone morphometry.

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Abstract Number: 2138

Transcriptional Analysis of Synovial Tissue Reveals Sustained Inflammatory Chemokine Expression Despite Minimal Histopathologic Change in the Destabilization of Medial Meniscus Model of Murine Knee Osteoarthritis

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Background/Purpose: The destabilization of medial meniscus (DMM) model of instability-induced OA replicates disease-related tissue pathology (including cartilage erosion, osteophytosis) and pain-related joint dysfunction, making it a useful model to investigate OA pathogenesis. Synovial inflammation characterized histopathologically, although common in OA, is not a prominent feature in this model leading some to suggest lack of significant synovial involvement. The aim of the current study was to determine if molecular analysis of synovium post-DMM could identify changes in synovial activity not otherwise revealed by histopathology.

Methods: 10-12 week old male C56BL/6J (WT) mice were subjected to DMM surgery of the right knee. Six weeks (early OA) and nineteen weeks (advanced OA) after surgery, groups of 5 mice were sacrificed and joints evaluated by histopathology for synovial hyperplasia. Hyperplasia was scored on a scale of 0-3 based on lining cell layers in three anatomic locations: superior to the medial meniscus (S.M.M), inferior to the medial meniscus (I.M.M) and in the medial peri-patellar (M.P.P) region. For molecular analysis, anterior synovial tissues were harvested at 1, 2, 4, 8 and 16 weeks post-DMM, and tissues from 3-5 mice were pooled per sample, RNA was isolated, and mRNA quantified using QX200^{TM} Droplet Digital^{TM} PCR System (BioRad, Hercules, CA). Expression of CD68 (monocytes/ macrophages), CD3δ, (T lymphocytes), and specific chemokines (CCL19 and CCL21, upregulated in OA patients) were expressed relative to TATA box binding protein (TBP)

Results: Evaluation of synovial hyperplasia showed mild or no hyperplasia (score≤1) at 6 weeks (Mean±SEM at S.M.M: 1±0.32, I.M.M: 0.33±0.33, M.P.P: 0.8±0.2) and 19 weeks (S.M.M: 0.5±0.29, I.M.M: 0.5±0.29, M.P.P.: 0.4±0.25) post-DMM. Furthermore, synovial hyperplasia post-DMM was not increased significantly compared to un-operated or sham-operated controls. In contrast, CD68 mRNA expression significantly increased early and peaked at 4 weeks post DMM surgery (21.61±3.03, $p<0.0001$) as compared to unoperated controls (2.72±1.47). No significant variation in expression of CD3d or CCL19 was detected over the time course. However, analysis of CCL21 expression indicated significantly elevated and sustained expression starting 2 weeks post-DMM (17.82±1.55), which continued to increase up to 16 weeks (34.1±3.79) post-DMM.

Conclusion: The current study suggests that molecular changes indicative of synovial inflammation are detectable in the DMM model of OA, despite minimal changes in synovial hyperplasia. Increased CD68 expression suggests an early increase in macrophages, along with a progressive increase in chemokine (CCL21) expression up to 16 weeks. The significance of these expression patterns to disease development has yet to be determined. A more comprehensive evaluation of synovial activation and its relationship with disease features, will be the focus of future studies to better understand how molecular and cellular activation within the synovial microenvironment may promote disease.

Disclosure: N. Sambamurthy, None; **V. Nguyen**, None; **J. G. Lieberthal**, None; **G. R. Dodge**, None; **C. R. Scanzello**, None.

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Abstract Number: 2139

High Fat Diet Induced Longitudinal Metabolic Changes Contribute to Acceleration of Osteoarthritis in Mice

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Background/Purpose: The contribution of metabolic changes induced by high fat diet (HFD) to OA is poorly understood. We sought to determine if diet regulates longitudinal changes to metabolic factors that contribute to OA.

Methods: Mice were fed normal chow diet until 9 weeks of age and then placed onto HFD or lean diet (LD) for 18 weeks, followed by resumption of normal chow, and evaluated longitudinally up to 12 months of age. Some mice were subjected to surgically-induced OA at the end of special diet. Plasma and knee joints were collected at each time points.

Results: We determined that HFD significantly increased fasting blood glucose levels, body weight, BMI and leptin levels as compared to LD fed mice. Histopathological analysis using OARSI scoring clearly showed that HFD fed mice exhibited accelerated spontaneous OA at 9 months of age as well as acceleration in the surgically induced OA at 10 and 20 wks post surgery in comparison to LD fed mice. Of the 170 metabolites analysed in blood plasma at each time point, lysophosphatidyl choline analogues (lysoPCaC20:4, lysoPCaC17:0, lysoPCaC18:0) and one phosphatidyl choline analogue (PCaaC36:2) were increased longitudinally in the HFD fed mice. Our ongoing studies are now evaluating if these LysoPC metabolomics signatures are responsible for initiating and accelerating cartilage degradative process observed in HFD fed mice and if we may predict the osteoarthritis severity by using some biomarkers as well as the involvement of the leptin-driven pathway.

Conclusion: We identified that high fat diet induces and maintains selective metabolic changes and increases OA progression in both spontaneous and surgically induced OA. We anticipate that these identified metabolomics signatures are involved in OA pathogenesis during obesity and therapeutic modulation of leptin pathway may help to attenuate or reverse OA pathologies.

***PD & YZ has equal first author contribution**

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Abstract Number: 2140

Phenotypic and Functional Characteristics of Exosomes Isolated from Human Osteoarthritis (OA) Synovial Fluid

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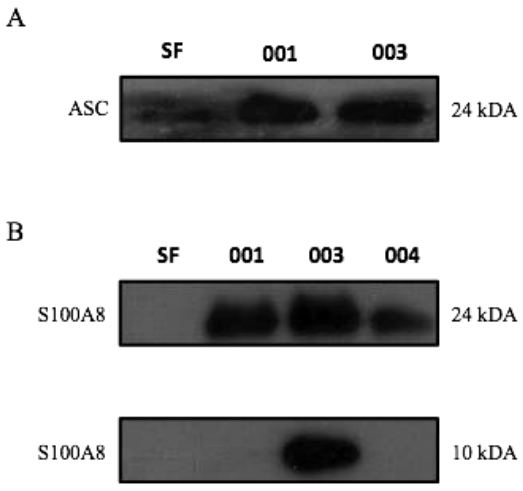
Background/Purpose: Exosomes are biologically active microvesicles derived from the endosomal membrane system understood to play a significant role in a wide range of inflammatory diseases. Exosomes both initiate and propagate inflammation through a number of mechanisms including antigen presentation and by serving as cargo vessels for damage-associated molecular patterns (DAMPs) and cytokines. In RA, synovial fluid (SF)-derived microparticles modulate chemokine and cytokine release in cultured synoviocytes. However, SF-derived microvesicles in osteoarthritis (OA) remain largely unexplored. Tumour-derived exosomes express a number of proteins known to contribute to metastasis and tissue remodelling which are conserved across OA pathogenesis including matrix metalloproteinases (MMP) and the damage-associated molecular pattern molecule (DAMP), S100A8. These proteins contribute to synovial inflammation, cartilage degradation and subchondral bone turnover in OA, We therefore sought to **1)** isolate exosomes from the SF of patients with OA **2)** determine whether these exosomes expressed any factors known to potentiate OA, including MMPs and S100 proteins and **3)** assess the functional effects of isolated SF-derived exosomes on primary human macrophages.

Methods: Exosomes were isolated from SF using an Exo-Spin isolation kit. Western immunoblotting was carried out on both exosomes and neat SF isolated from patients with OA. Primary human macrophages were treated with exosomes for 24 hours and expression of S100A8, S100A12 and RANK was analyzed by quantitative PCR (qPCR). Cytokine production by macrophages in response to exosomes was assessed by ELISA. $CD14^+$ monocytes were treated with M-CSF and exosomes or neat synovial fluid in the presence or absence of RANKL for 14 days and then stained for TRAP to analyse the ability of exosomes to drive osteoclast differentiation.

Results: Western blot analysis revealed robust expression of MMP-1 and S100A8 in exosomes from OA SF (N=3 donors) (Fig). The inflammasome adaptor protein, ASC, was also similarly detected in both exosomes and neat SF. SF-derived exosomes (25 μg/ml) upregulated S100A8 and S100A12 in human macrophages by approximately 16 to 20-fold by qPCR, while a 50-fold increase in RANK expression was observed. SF-derived exosomes were also shown to induce a 7-fold increase in IL-6 release from primary macrophages. Finally, both SF-exosomes and neat SF from OA patients promoted the differentiation of osteoclast precursor cells.

Conclusion: Based on these studies we propose that synovial fluid-derived exosomes could aggravate OA via 1) synovial inflammation through up-regulation of DAMPs, MMP and cytokines and 2) subchondral bone remodelling through promotion of osteoclastogenesis and increased expression of RANK in haematopoeitic



cells.

Disclosure: G. M. McCarthy, None; **D. McGagh**, None; **C. C. Cunningham**, None; **E. M. Corr**, None; **L. Sullivan**, None; **F. Haji**, None; **A. Dunne**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/phenotypic-and-functional-characteristics-of-exosomes-isolated-from-human-osteoarthritis-oa-synovial-fluid

Abstract Number: 2141

Terminal Uridylyl Transferase ZCCHC6-Dependent Generation of miRNA Diversity in Primary Human Chondrocytes

Abdul Haseeb[1], Mohammad Shahidul Makki[2], Mohammad Ansari[3], Helen Piontkivska[4] and Tariq M. Haqqi[1], [1]Anatomy & Neurobiology, Northeast Ohio Medical University, Rootstown, OH, [2]4209 St Rt 44 PO Box 95, Northeast Ohio Medical University, Rootstown, OH, [3]Anatomy & Neurobiology, Northeast Ohio Medical University, Roostown, OH, [4]Kent State University, Kent, OH

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Terminal Uridylyl Transferase ZCCHC6-dependent Generation Of miRNA Diversity In Primary Human Chondrocytes

Background/Purpose: MicroRNAs (miRNAs) are a group of small, noncoding RNAs that post-transcriptionally regulate gene expression. miRNAs play important roles in chondrocyte function and in the development of osteoarthritis. We characterized the dynamic repertoire of the chondrocyte miRNAs and isomiRs by deep sequencing analysis in chondrocytes isolated from normal subjects as well as OA patients in response to the treatment with inflammatory cytokine IL-1b. We also tested the role of TUT7/ZCCHC6 in non-template addition of nucleotides at the ends of specific miRNAs in human chondrocytes.

Methods: Joint cartilage samples were obtained from normal subjects at autopsy and OA patients who underwent joint arthroplasty at the Crystal Clinic, Akron, OH. Primary human chondrocytes were prepared by sequential digestion of the cartilage pieces by pronase (1 mg/ml) for 2 hrs and collagenase A (1 mg/ml) for 16 hrs. Cells were serum starved overnight followed by treatment with IL-1b (2 ng/ml) for different durations (2 hrs, 12 hrs and 24 hrs). Expression of TUT7/ZCCHC6 was knocked down using ON-TARGETplus SMARTpool (GE Dharmacon). Total RNA was prepared using miRNeasy kit (Qiagen) and libraries for sequencing were prepared using True seq small RNA library preparation kit (Illumina). Next generation sequencing was performed on Illumina MiSeq sequencer. Data were analyzed using CLC genomics suite version 8 (Qiagen).

Results: There was a modest difference in the expression of miRNAs in normal and OA chondrocytes in the presence or absence of IL-1b. We found a number of miRNAs that showed a wide range of sequence modifications including nucleotide additions and deletions at 5' and 3' ends; and nucleotide substitutions. Some modifications resulted in seed shifts. Interestingly, miR-140-3p, an important miRNA involved in chondrocyte function, was found to have the highest number of modifications (Figure 1). Many of these modifications have been shown to impart a change in the miRNAs' ability to regulate gene expression. Knockdown of TUT7/ZCCHC6 resulted in a significant change in the isomiR profile in human chondrocytes demonstrating that TUT7/ZCCHC6 contributes to the miRNA complexity in human chondrocytes.

Conclusion: Together, these results reveal a complex repertoire of miRNAs and isomiRs in primary human chondrocytes and their dynamic changes in response to IL-1b treatment. Here we also show the role of TUT7/ZCCHC6 in generating the miRNA diversity in human chondrocytes. These findings will help us better understand miRNA-mediated control of gene expression in the pathogenesis of OA. This work was supported in part by USPHS/NIH grants (RO1 AT007373, RO1 AT005520, RO1 AR067056, R21 AR064890) and funds from North East Ohio Medical University to TMH.

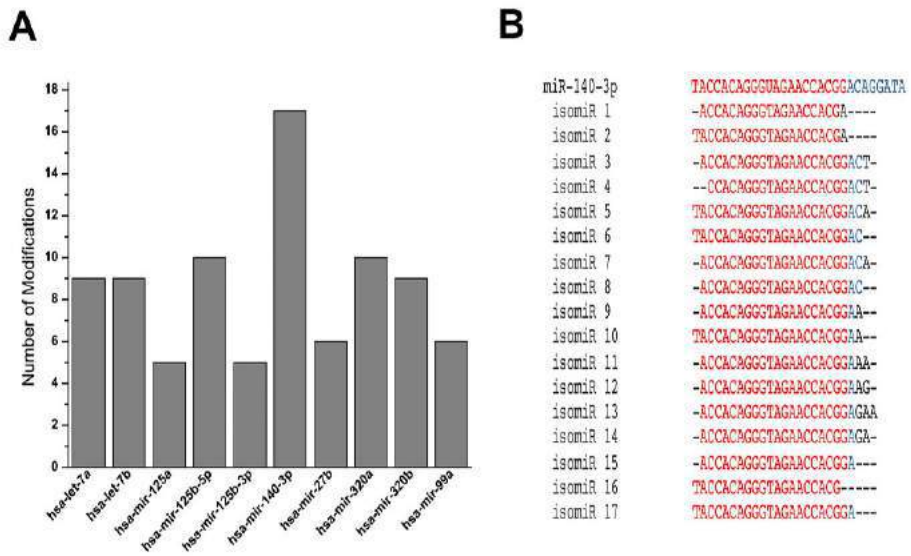

Figure 1. A. Number of modifications in 10 most modified miRNAs with ³100 reads**. B.** Individual modifications with ³100 read counts in miR-140-3p aligned with the archetype miRBase sequence.

Disclosure: A. Haseeb, None; **M. Shahidul Makki**, None; **M. Ansari**, None; **H. Piontkivska**, None; **T. M. Haqqi**, None.

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Abstract Number: 2142

Identification of Novel Molecules Targeting Cartilage Aging As Osteoarthritis Therapeutics

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Background/Purpose: Effective treatments for Osteoarthritis (OA) are not available. In aging-related diseases, including OA, failure of cellular homeostasis mechanisms, such as autophagy can cause extracellular matrix destruction and cell death. Chondrocytes are essential for the maintenance of cartilage integrity. With aging, chondrocyte function is diminished, contributing to a cellular senescence phenotype often observed in OA chondrocytes. In addition, a defect in autophagy is observed in both aging and cartilage degeneration. *The objective of this study was to identify anti-senescence and pro-autophagy molecules by a cell-based high-throughput screening (HTS) in human chondrocytes.*

Methods: To induce cellular senescence or reduced autophagy, immortalized human chondrocytes (TC28a2) were seeded (3000 cells/well) in 384 well plates, and treated with IL-6 (10 ng/ml) for 72 or 18 hours, respectively. Then, chondrocytes were incubated with Prestwick Chemical Library (1120 approved drugs with chemical and pharmacological diversity, as well as bioavailability and safety in humans) at 10 μM for 48 hours. To identify anti-senescence hits, nuclei was stained with Hoechst 33342 (10 μM), while β–galactosidase subcellular structures was stained by using Imagene Green C12FDG substrate (10 μM). To evaluate autophagic flux, a reporter cell line was generated by lentiviral transfection of pBABE-mCherry-EGFP-LC3 plasmid in TC28a2 chondrocytes. Plates were imaged by using Operetta® High Content Screening (HCS) system in non-confocal mode using the 20x WD objective. For each well, 4 fields and 4 planes of bright field, Hoechst and fluorescein channels were obtained. Relative intensity of C12FDG in cytoplasm and number of autophagosomes/autolysosomes per area of cytoplasm were determined to quantitate β–galactosidase activity and autophagy flux respectively. For compound validation, senescence markers, autophagic flux and apoptosis were evaluated.

Results: A primary screening was performed to identify anti-senescence compounds by measurement of senescence-associated β-galactosidase activity. 308 compounds with anti-senescence effects were identified. The anti-senescence hits were analyzed by monitorizing autophagic flux. 42 compounds with both anti-senescence and pro-autophagy effects were selected. Then, 2 compounds were selected for further validation. These compounds significantly reduced senescence ($p < 0.01$) and increased autophagic flux ($p < 0.01$) in response to IL-6. Furthermore, they conferred protection against cell death by apoptosis in human chondrocytes.

Conclusion: These observations provide a unique opportunity to study cartilage aging with the objective to explore the therapeutic potential of pharmacological prevention of chondrocyte senescence and autophagy as a

strategy to slow or reverse aging-associated changes, prevent the onset of OA and provide benefits for its clinical management.

Disclosure: B. Carames, None; **U. Nogueira-Recalde**, None; **E. Dominguez**, None; **M. I. Loza**, None; **F. J. Blanco**, None.

Abstract Number: 2143

A Small Molecule, SM04690, Has Inhibitory Effects on the Wnt Pathway and Inflammation in Vitro, with Potential Implications for the Treatment of Osteoarthritis

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Background/Purpose: Osteoarthritis (OA) involves thinning cartilage and increased subchondral bone. Amongst many cellular processes, inflammation has been associated with OA. Wnt signaling plays a role in mediating inflammation. SM04690, a novel, small-molecule Wnt pathway inhibitor that has previously been shown to regenerate and protect cartilage in an animal model of OA, was evaluated in a series of preclinical studies to determine its potential to inhibit inflammation.

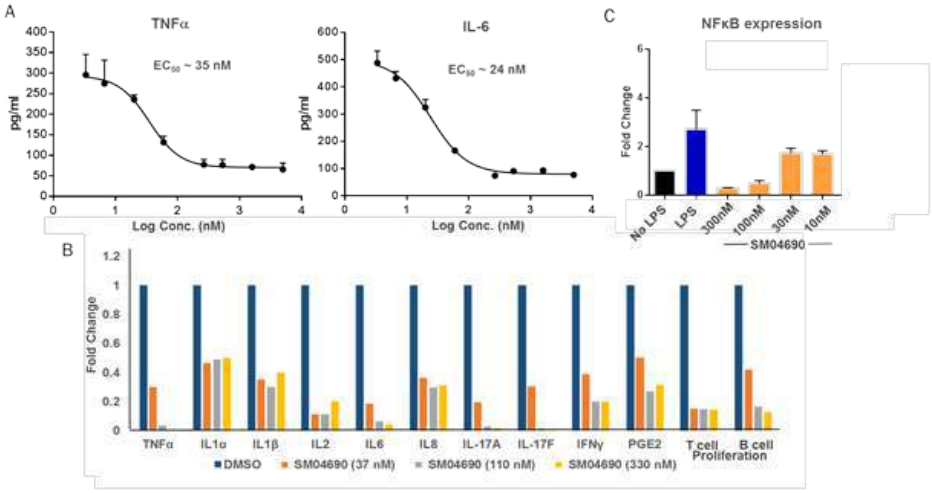
Methods: Wnt pathway inhibition was measured using a cell-based reporter assay. Anti-inflammatory activity was evaluated by measuring TNF-α and IL-6 secretion using ELISA in synovial fibroblasts stimulated with IL1b, THP-1 monocyte cells stimulated with lipopolysaccharides (LPS), and peripheral blood mononuclear cells (PBMCs) stimulated with anti-CD3/anti-CD28. A panel of pro- and anti-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFNγ, and PGE2) was evaluated by ELISA, T and B cell proliferation by flow cytometry in PBMCs, and T and B cell co-cultures stimulated with super-antigen or LPS, compared to vehicle or benchmark steroids (Cyclosporin A and Prednisolone). The effect of SM04690 on the LPS-induced expression and phosphorylation of NFkB in THP-1 cells was evaluated by qPCR and Western Blot.

Results: SM04690 demonstrated potent (EC_{50} =11nM) and selective inhibition of Wnt signaling. SM04690 inhibited IL-1b-induced TNF-α and IL-6 secretion in synovial fibroblasts (EC_{50} =30nM; Figure A). SM04690 also inhibited LPS and anti-CD3/anti-CD28-induced TNF-α and IL-6 secretion in THP-1 cells (EC_{50} =10nM), and PBMCs. SM04690 significantly inhibited ($p<0.01$, effect size >40%, no toxicity) super-antigen- and LPS-stimulated production of various pro-inflammatory cytokines (TNF-α, IL-1α, IL-1β, IL-2, IL-6, IL-8, IL-17A, IL-17F, IFNγ, PGE2), and T and B cell proliferation in PBMCs and T and B cell co-cultures (Figure B). The anti-inflammatory activity of SM04690 in these assays was comparable to or better than the activities of Cyclosporin

A and Prednisolone. Additionally, SM4690 treatment decreased LPS-induced gene expression (3-fold, $p<0.01$) and phosphorylation of NFkB in THP-1 cells (Figure C).

Conclusion: SM04690, a small molecule Wnt pathway inhibitor was a potent anti-inflammatory agent in various cell types, with inhibition of NFkB signaling *in vitro*. This anti-inflammatory activity of SM4690 may provide beneficial effects in the treatment of various diseases, including OA.

Figure. SM04690 inhibited cytokine production and NFkB expression.



Disclosure: V. Deshmukh, Samumed, LLC, 3; **M. Ibanez**, Samumed, LLC, 3; **C. Barroga**, Samumed, LLC, 3; **J. Hood**, Samumed, LLC, 9; **Y. Yazici**, Samumed, LLC, 3.

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Abstract Number: 2144

Functional Analysis of Macrophages in BehçEt's Disease: C-C Chemokine Receptor Type 1 (CCR1) and IL-10 Are Implicated in Pathogenesis of the Disease

Hiroto Nakano[1], Yohei Kirino[1], Momoko Ohno[1], Kana Higashitani[1], Mitsuhiro Takeno[2], Ryusuke Yoshimi[1] and Hideaki Nakajima[3], [1]Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Tokyo, Japan, [3]Department of Hematology and Clinical Immunology, Yokohama City University School of Medicine, Yokohama, Japan

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Session Date: Tuesday, November 15, 2016

Session Title: Cytokines, Mediators, Cell-Cell Adhesion, Cell Trafficking and Angiogenesis - Poster II
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

The recent GWAS and subsequent studies have identified susceptible genes such as CCR1 and IL10 genes, suggesting pathological roles of macrophages in Behçet's disease (BD). The purpose of this study is to compare features of in vitro differentiated M1 and M2 macrophages from peripheral blood between BD and healthy controls (HC).

Methods:

Differentiations into M1 or M2 macrophages were induced in vitro from peripheral monocytes in presence of GM-CSF or M-CSF, respectively. Expressions of CD68, CD163, and CCR1 were determined by realtime PCR and flow cytometric analyses. For the macrophages that were treated with LPS for 24 hours, the supernatants were analyzed for cytokine profiles using beads assay.

Results:

Differentiated M1 macrophage produced higher amounts of IL-6 whereas, M2 macrophage secreted higher volume of IL-10. M2 macrophage has increased expression of CD163 protein and mRNA compared to M1 macrophage. CCR1 expression was increased in M2 macrophage compared to M1 macrophage (Figure 1). Cell surface CCR1 protein expression in M1 macrophage was significantly higher in BD patients compared to HC (Figure 2, t test). BD associated SNP (rs1518111) allele T is risk for decreased expression of IL10 mRNA in HC M2 macrophage.

Conclusion:

The data suggest that both susceptible CCR1 and IL10 genes are implicated in pathogenesis of BD. Further experiments including functional analyses are required to elucidate mechanisms how M1 or M2 macrophages are involved in pathogenesis of BD.

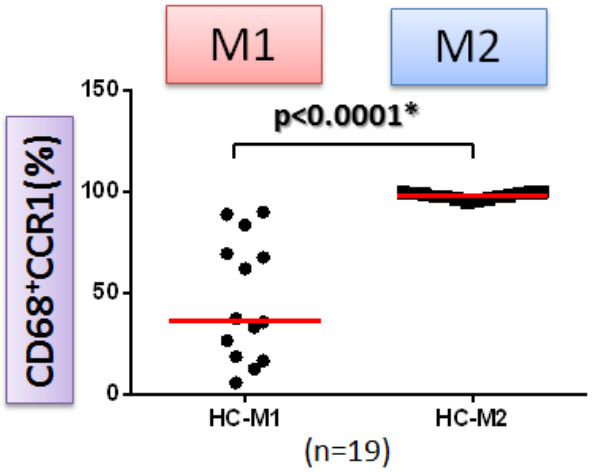

Figure 1: Difference of CCR1 expression between M1 and M2 Mϕ. Flow cytometry result showing elevated expression of CCR1 mRNA in M2 Mϕ.

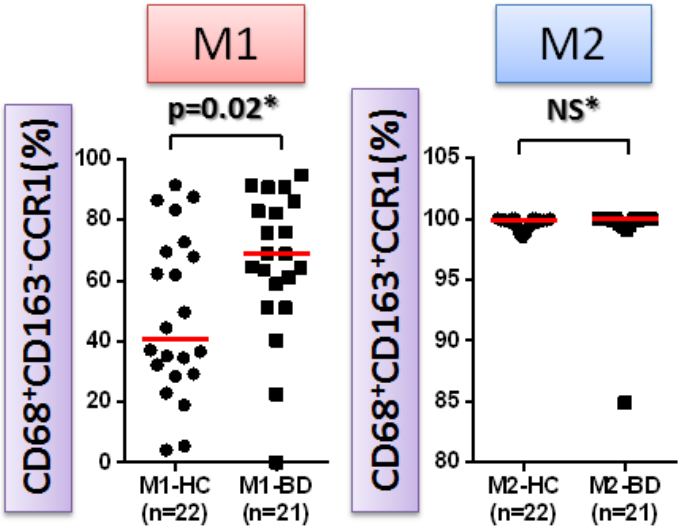

Figure 2: Difference of CCR1 expression between BD and HC. CCR1 expression in M1 Mϕ was significantly higher in flow cytometry analysis.

Disclosure: H. Nakano, None; **Y. Kirino**, None; **M. Ohno**, None; **K. Higashitani**, None; **M. Takeno**, None; **R. Yoshimi**, None; **H. Nakajima**, None.

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Abstract Number: 2145

The Modulation of Macrophage Polarization By SIRT1 Maybe New Target Therapy in Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

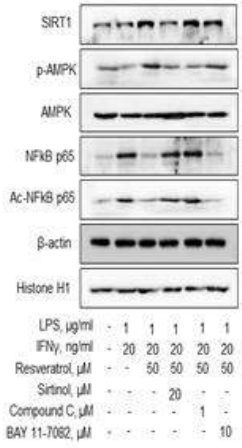
Background/Purpose: The polarization of macrophages was the expressed to M1/M2 phenotype by various

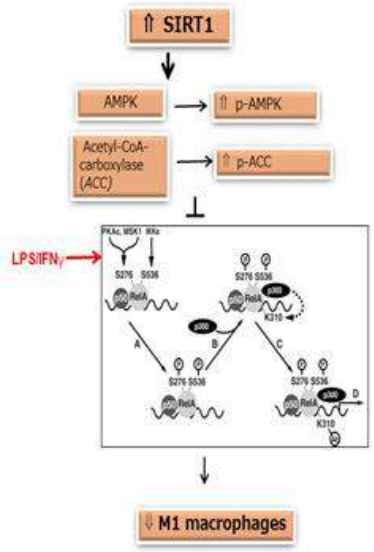
stimuli or environment signals. The M1 macrophage was pro-inflammatory phenotype and was key effector cells in the immune response of rheumatoid arthritis (RA). So, M1 macrophage influenced the inflammation of RA synovial membrane and joint destruction in RA, whereas M2 macrophage was anti-inflammatory phenotype and could down-regulate the production of proinflammatory cytokines in RA. The SIRT1 attenuated the RA inflammation via dawn-regulation of NF-¥êB signaling. However, the effect of SIRT1 on macrophages polarization remained unclear. So we aimed to check out that activated SIRT1 modulated macrophages polarization into M1 phenotype and controlled the inflammation of RA.

Methods: Monocytes from synovial fluid of RA patients, bone marrow–derived monocytes (BMDCs) from mice were studied. monocytes were cultured with M-CSF for 7days to differentiate into M0 macrophages (monocyte-derived mature macrophages M0 phenotype). M0 macrophages were incubated with LPS and IFN-gamma in order to obtain M1 macrophages. M1 macrophage markers were detected by real-time PCR.

Results: Activation of SIRT1 was achieved by Resveratrol, activated SIRT1 attenuated M1 macrophage phenotypes and pro-inflammatory cytokine expression. macrophages obtained from SIRT1-tg mice, which were overexpression of SIRT1, exhibited decreased M1 markers in association with enhanced activation of AMPK/ACC compared with macrophage from control C57BL/6 mice. In addition to SIRT1 activation, M1 polarizing signal, acetylation of NF-¥êB p65, was suppressed. In SIRT1-deficient macrophages, resveratrol fail to increase AMPK activity and to decrease the expression M1 markers owing to enhanced acetylation of NF-¥êB p65.

Conclusion:





SIRT1 maybe an important modulator of M1 macrophages polarization and increased AMPK activity, that suppressed acetylation of NF-¥êB p65 during inflammation of RA. so, modulation of SIRT1 maybe a new target in RA treatment.

Disclosure: S. Y. Lee, None; **W. T. Chung**, None; **S. W. Lee**, None; **S. Y. Park**, None; **B. Jae Ho**, None.

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Abstract Number: 2146

Clinical Characterization of Itch in Dermatomyositis and the Role of Increased Skin Interleukin-31

Hee Joo Kim[1,2,3], Diletta Bonciani[1,2,4], Sandra M. Pena[2], Janice Tiao[2], Padma Sahu[1,2], Muhammad M. Bashir[1,2] and Victoria P. Werth[1,2], [1]Department of Dermatology, Corporal Michael J. Crescenz VAMC, Philadelphia, PA, [2]Department of Dermatology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, [3]Department of Dermatology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea, The Republic of, [4]Department of Surgery and Translational Medicine, Section of Dermatology, University of Florence, Florence, Italy

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Background/Purpose: Interleukin-31 (IL-31) has been implicated in pruritus associated with various itchy skin diseases, including atopic dermatitis and cutaneous T cell lymphoma. While pruritus is a prominent feature in dermatomyositis (DM), there are few studies to evaluate clinical characteristics and pathogenesis of itch in DM. We examined the prevalence and severity of pruritus in patients with DM, and investigated the presence of IL-31 and IL-31 receptor in skin tissue to explain the pathomechanism of itch in DM patients.

Methods: Pruritus and disease activity of DM were evaluated by a visual analog scale (VAS) and the Cutaneous Disease and Activity Severity Index (CDASI), respectively. Gene expression of IL-31 and IL-31 receptor alpha (IL-31RA) in lesional DM skin was evaluated by qRT-PCR, and was compared with that of non-lesional DM skin, and skin tissue of cutaneous lupus erythematosus (CLE) patients and healthy controls (HC). Immunohistochemical analysis assessed IL-31 expression in skin tissue. The Spearman rank test was used to evaluate the relationship between itch intensity and disease activity, as well as itch intensity and lesional gene expression of IL-31 and IL-31RA. The Kruskal-Wallis test with Dunn's post hoc test was used to compare the difference of IL-31 and IL-31RA mRNA expression, and immunohistochemical analysis of skin IL-31 expression in DM and HC.

Results: About half of 164 patients with DM (25 male, 139 female; 61 classic DM and 103 clinically amyopathic DM; mean age ± SD 52.5 ± 14 years) had moderate to severe itch (28.66% moderate, 20.73% severe itch). Pruritus in DM was positively correlated with disease activity, with a correlation coefficient of 0.337 between VAS itch score and CDASI activity score ($p<0.01$). Skin IL-31 and IL-31RA gene expression was significantly up-regulated in DM compared to HC and CLE ($p<0.05$). IL-31 mRNA expression was positively correlated with VAS itch score ($r= 0.7619$, $p=0.03$). Immunoreactivity for IL-31 was also stronger in lesional skin of DM ($p=0.0001$).

Conclusion: In conclusion, we confirmed that itch is a prevalent symptom in many patients with DM involving the skin, and that skin IL-31 is significantly higher in DM than CLE and HC. This is the first study to suggest IL-31's crucial role in the skin for pruritus in DM.

Disclosure: H. J. Kim, None; **D. Bonciani**, None; **S. M. Pena**, None; **J. Tiao**, None; **P. Sahu**, None; **M. M. Bashir**, None; **V. P. Werth**, None.

Abstract Number: 2147

Lack of Pro-Inflammatory Cyto/Chemokines in ANA+ Individuals with Insufficient Criteria for a Diagnosis of Systemic Autoimmune Rheumatic Disease

Waleed Hafiz[1], Nan-Hua Chang[2], Babak Noamani[3], Dennisse Bonilla[3], Larissa Lisnevskaia[4], Earl Silverman[5], Arthur Bookman[6], Sindhu R. Johnson[7], Carolina Landolt-Marticorena[3] and Joan Wither[3], [1]Rheumatology, University of Toronto, Toronto, ON, Canada, [2]Genetics and Development, Krembil Research Institute, University Health Network, Toronto, ON, Canada, [3]Krembil Research Institute, University Health Network, Toronto, ON, Canada, [4]Lakeridge Health Services, Oshawa, ON, Canada, [5]Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [6]Rheumatology, University Health Network, Toronto, ON, Canada, [7]Rheumatology, Mount Sinai Hospital and University Health Network, Toronto, ON, Canada

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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Systemic Autoimmune Rheumatic Disease (SARD) often have a prolonged pre-clinical phase during which they are anti-nuclear antibody (ANA) positive but lack clinical symptoms. It has been proposed that progression from asymptomatic autoimmunity to clinical disease is accompanied by immunologic changes that could be used as predictors of disease development. Our objective was to identify cyto/chemokine abnormalities in ANA^+individuals who lack sufficient criteria for a diagnosis of SARD.

Methods: ANA^+ individuals who: 1) lacked clinical symptoms of SARD (ANA No Symptoms, ANS); 2) had a least one clinical symptom of SARD (Undifferentiated Connective Tissue Disease, UCTD); or 3) had a recently diagnosed steroid and immunosuppressive naïve SARD were recruited, and compared with ANA^- healthy controls (HC). The levels of 30 cyto/chemokines were measured, 29 by Luminex and one (BAFF) by ELISA. Peripheral blood interferon (IFN)-induced and BAFF gene expression was quantified by NanoString. The normalized levels of 5 ubiquitously expressed IFN-induced genes were summed to produce an IFN5 score.

Results: Cyto/chemokines were measured in plasma samples for 145 individuals (21 HC, 37 ANS, 28 UCTD, and 59 early SARD (6 SLE, 25 SjD, 25 SSc, and 3 MCTD/DM)). The plasma levels of four cyto/chemokines, IP-10, eotaxin, BAFF, and TNF-α, were significantly elevated in early SARD patients when compared to HC (Bonferroni corrected $p = 0.0001, 0.0006, 0.003, 0.033$, respectively). The levels of IP-10, eotaxin, and TNF-α were not significantly elevated in ANS and UCTD individuals as compared to HC. Although there was a trend to elevated serum BAFF levels in UCTD and ANS individuals, this only achieved statistical significance in UCTD patients ($p = 0.037$ and 0.065, respectively). However, ANS individuals had significant elevations of *BAFF* RNA in their peripheral blood ($p = 0.009$). We have previously reported that all ANA^+ subgroups (ANS, UCTD and early SARD) have significantly elevated IFN5 scores. The levels of IP-10, serum BAFF, and *BAFF* RNA

were positively correlated with IFN5 scores in ANA^+individuals, suggesting that these pro-inflammatory factors are induced by type I IFN.

Conclusion: Although elevated levels of several pro-inflammatory factors are seen in early SARD patients, these factors are not elevated in ANA^+ individuals who lack sufficient criteria for a diagnosis of SARD. Thus, elevations of pro-inflammatory factors appear to parallel progression to clinical disease.

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Abstract Number: 2148

Recruitment of Circulating Monocytes By TNF/IL-6-Induced Expression of Vascular Cell Adhesion Molecule 1 (VCAM-1) Drives Valvular Inflammation in K/B/g7 Mice

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Background/Purpose: Cardiovascular (CV) comorbidity is common in rheumatic diseases and includes accelerated atherosclerosis and inflammatory valvular heart disease (iVHD). KRN T cell receptor (TCR) transgenic mice congenically expressing the H-2^{g7}MHC class II molecule (K/B/g7) develop spontaneous autoimmune arthritis and provide a powerful tool for understanding the effects of chronic inflammation on the cardiovascular system. In particular, K/B/g7 mice develop iVHD with many features mirroring human pathology. By 3 weeks of age their mitral valves (MVs) uniformly demonstrate histological evidence of inflammatory infiltration. By 8 weeks, drastic MV leaflet thickening with increased collagen content and accumulation of inflammatory monocytes is apparent. Here we explored the molecular mechanisms driving iVHD in K/B/g7 mice.

Methods: Serum TNFα and IL-6 are elevated in K/B/g7 mice. Due to the established roles for these cytokines in the pathogenesis of rheumatoid arthritis and iVHD in humans, we hypothesized that they are critical mediators of iVHD in the K/B/g7 model. We used neutralizing monoclonal antibodies to test this hypothesis, treating one

cohort of K/B/g7 mice at the time of iVHD onset (4 weeks of age, initiation) and another after iVHD had been established (6 weeks of age, maintenance). The mice were given twice weekly injections of 200 μg mAb blocking TNFα, IL-6, VCAM-1, or α4β1 integrin (very late antigen 4, VLA-4) for 4 weeks. We assessed arthritis severity during the treatment period. The effect of these blocking antibodies on iVHD was determined using histological assessment and immunofluorescent staining and compared to animals that received injections of isotype control mAb.

Results: Neutralization of TNFα or IL-6 prevented iVHD progression. In both cases, this was correlated with significantly reduced expression of VCAM-1 at the blood-endothelial interface and also with significant reductions in arthritis severity. Neutralization of VCAM-1 or α4β1 did not reduce the severity of joint inflammation, but completely prevented induction of iVHD. Interestingly, when used as a treatment for established iVHD, only TNFα and VCAM-1 neutralization reduced iVHD severity, but neither significantly reduced the severity of established arthritis.

Conclusion: These studies identify a TNFα/IL-6-VCAM1-α4β1 axis as a critical driver of iVHD initiation and maintenance in K/B/g7 mice. Ongoing studies utilizing conditional gene knockouts aim to confirm the dominant inflammatory cellular element(s) recruited to the valve tissue via surface expression of α4β1. These results may inform treatment strategies for repurposing existing therapeutics (e.g. natalizumab) to treat iVHD in the setting of systemic rheumatic diseases.

Disclosure: L. Meier, None; **J. L. Auger**, None; **B. J. Engelson**, None; **E. Breed**, None; **J. Boyer**, None; **B. A. Binstadt**, None.

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Abstract Number: 2149

Adipokines Alter the Interaction Between Rheumatoid Arthritis Synovial Fibroblasts Adhesion and Endothelial Cells

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Background/Purpose: Synovial fibroblast plays a key role in rheumatoid arthritis (RA), which is a chronic polyarticular inflammatory disease. SF are able to migrate long distances *in vivo* via the vasculature as previously shown in our SCID mouse migration model. In inflammatory processes, adipose tissue plays an important role as an endocrine organ. Some of its effects may be mediated by immunomodulating adipokines. RASF and endothelial cells (EC) are affected by adipokines in RA. The interaction between RASF and EC may be a crucial process in the migration of RASF through the vasculature.

Methods:

The expression of selected adhesion molecules from RASF and EC was analyzed by real-time PCR. For this purpose, primary RASF and EC were stimulated with adiponectin (10 µg/ml), visfatin (100 ng/ml) and resistin (20 ng/ml), and "therapeutically" with methotrexate (1.5 µM) and the glucocorticoids prednisolone (1 µM) and dexamethasone (1 µM).

RASF adhesion to EC was studied under flow conditions (flow rates: 18.4/30.5/60.5 ml/h) in a dynamic adhesion assay as flow conditions are required for selectins to obtain their active conformation.

Results:

Under dynamic flow condition, which simulate the blood flow *in vivo*, the adhesion of RASF to EC was increased after stimulation with visfatin (+156%/+87%/+89%) and TNF-α (+61%/+18%/+19%). On the other hand, reduced adhesion was observed after stimulation with dexamethasone (-9%/-39%/-53%) and prednisolone (-31%/-64%/-53%). In EC, TNF-α upregulated the expression of ICAM-1 (47-fold; n=9), while adiponectin decreased it (-2.9-fold; n=5). The expression of VCAM-1 was slightly decreased after stimulation with adiponectin (-1.3-fold; n=5) in EC, whereas TNF-α led to a strong upregulation (235-fold; n=7). P- Selectin was down-regulated after stimulation with TNF-α (-8.6-fold; n=7) in EC. The expression of integrin α2 was upregulated after stimulation with resistin (2.8-fold; n=7) and TNF-α (13-fold; n=6). Only TNF-α increased the expression of ICAM-1 (40-fold; n=5) in RASF, while both visfatin (2.9-fold; n=10) and TNF-α (59-fold; n=9) increased the expression of VCAM-1 in RASF.

Conclusion:

During migration of RAFS *in vivo,* the adhesion of RASF to EC most likely plays a key role. Adipokines increase the adhesion of RASF to EC under dynamic flow conditions. Migration of RASF and spreading of RA to different joint could therefore be enhanced by the influence of adipokines on adhesion molecules and their effect strengthening the adhesion of RASF to EC. Glucocorticoids caused the opposite effect, which could explain some of the protective effects observed in patients. Adipokines alter the expression of adhesion molecules and the RASF/EC interaction with the effects differing between adipokines.

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Abstract Number: 2150

Autoimmune Uveitis : Potential Role of Interleukin-22 (IL-22) in Pathogenesis

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Background/Purpose: : IL-22 is a member of IL-10 family, with both anti- inflammatory and pro- inflammatory functions, orchestrating the immune and inflammatory response.IL-22 is secreted by dendritic cells and T lymphocytes and act on non hematopoietic cells. Co-expressed IL-17A regulates the pro-inflammatory versus tissue-protective functions of IL-22. Behçet's disease (BD) is a chronic systemic inflammatory disorder at the crossroad between autoimmune and auto inflammatory syndromes. Uveitis is a sight threatening condition affects 60-80 % of the BD patients (pts).We aimed at this study to investigate the potential role of IL - 22 in uveitis associated with BD.

Methods: Serum IL-22 was detected by ELISA in 35 uveitis pts and 10 healthy controls enrolled in 4 groups ; Group 1: pts with active uveitis associated with BD(n=11),Group 2: pts with inactive uveitis associated with BD (n=12), Group 3 : pts with uveitis without apparent auto immune and /or rheumatic manifestations (n=12) and Group 4 :healthy controls (n=10).

Results: The mean serum level of IL- 22 of BD pts with active uveitis was significantly very high compared to the control (p=0.001),the mean serum level of IL – 22 of BD pts with inactive uveitis was significantly high compared to those of healthy controls (p=0.001), the mean serum levels of IL-22of BD pts with active uveits was significantly higer than those of BD pts with inactive uveitis (p=0.01), the mean serum levels of IL-22 of non Behçet's uveitis was not significantly different compared to healthy controls .Although comparing the mean serum levels of IL-22 based on site of ocular inflammation there was no statistical significance, it seems that pts of non Behçet's with posterior uveitis had higher levels of IL-22 compared to those with anterior uveitis in the same group denoting the potential role of IL 22 in vasculopathy involving the choroid plexus.

Conclusion: We could suggest that IL - 22 play an important potential role in the pathogenesis of uveitis associated with BD vasculopathy and may serve as a biomarker of disease activity.

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Abstract Number: 2151

Fractalkine (CX3CL1) Is Expressed By Arterial Endothelium and Vascular Smooth Muscle Cells (VSMC) in GCA

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Background/Purpose: The development of giant-cell arteritis (GCA) lesions requires amplification cascades resulting in continuous recruitment of lymphocytes and monocytes. Interferon-gamma (IFNg)- induced or up-regulated chemokines CCL-2, CXCL9, CXCL10, and CXCL11 play an important role in inflammatory cell recruitment, a process in which not only endothelial cells but also vascular smooth muscle cells (VSMC) seem to be involved (Corbera-Bellalta M et al Ann Rheum Dis 2016). CX3CL1, also known as fractalkine, and along with its unique receptor CX3CR1, are the only members of CX3C chemokine/ chemokine receptor family. CX3CL1 has two isoforms mediating different functions. The transmembrane protein form regulates cell adhesion, while the soluble one (generated by proteolytic cleavage) has chemotactic function. Soluble fractalkine is elevated in serum from patients with small-vessel vasculitis. However, expression of fractalkine and its receptor have not been explored in GCA. To explore CXCL1/CXCR1 expression in GCA lesions and in temporal artery- derived VSMC.

Methods: RNA was extracted from fresh temporal arteries of 12 GCA patients and 8 healthy controls using chloroform-isopropanol classic method. CX3CL1 mRNA expression was assessed by quantitative real-time PCR (Applied Biosystems). Fresh arteries from 1 GCA patient and 1 control were subjected to immunofluorescence using specific antibodies (Cell Signaling). VSMC obtained from cultured temporal arteries were treated with IFNg and/or TNFa for 3 days, and CX3CL1 expression by VSMC was detected by realtime PCR.

Results: CX3CL1 mRNA expression was constitutively expressed by control arteries and downregulated in GCA lesions compared with controls, probably due to VSMCs loss in the media of inflamed arteries. Consistently, immunofluorescence studies disclosed that CX3CL1 protein expression was intensively expressed by the endothelium of the GCA-involved artery and by VSMC remaining in the media. CX3CR1 was expressed by infiltrating leukocytes in GCA. As with other chemokines, CX3CL1 expression was significantly up regulated in VSMC cultured in the presence of inflammatory mediators (IFNg and TNFa). VSMC did not express CX3CR1.

Conclusion: Fractalkine and its receptor are expressed in GCA lesions. VSMCs react to the presence of inflammatory cytokines by expressing CX3CL1, highlighting a possible role of this chemokine not only in leukocyte recruitment by endothelial cells but also in leukocyte progression through the VSMC in the medial layer. Functional chemotaxis studies are ongoing to confirm this point. Supported by SAF 2014/57708-R and PIE13/00033

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Abstract Number: 2152

S100A11 Protein Is Increased in Rheumatoid Arthritis and Is Associated with Disease Activity and Inflammation

Lucie Andres Cerezo[1], **Barbora Šumová**[1], Klára Prajzlerová[1], David Veigl[2], Karel Pavelka[1], Jiří Vencovský[3] and Ladislav Senolt[3], [1]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [2]1st Orthopaedic Clinic, 1st Faculty of Medicine, Charles University, Prague, Czech Republic, Prague, Czech Republic, [3]Institute of Rheumatology, Department of Rheumatology, 1st Faculty of Medicine, Charles University, Prague, Czech Republic

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Background/Purpose: Calgizzarin (S100A11) is a member of the S100 protein family that acts in different tumors via regulating number of biologic functions. Recent data suggest its association with low grade inflammation in OA. The aim of the study was to analyze the expression of S100A11 in synovial tissue, synovial fluid and serum of patients with rheumatoid arthritis (RA) and osteoarthritis (OA) and to characterize its potential association with disease activity.

Methods: S100A11 expression was analyzed in synovial tissues from patients with RA (n=6) and OA (n=6) by immunohistochemistry. Immunofluorescence staining was used to co-localize S100A11 within RA synovial tissue (n=4). Serum and synovial fluid S100A11 levels were measured by ELISA (Biovendor) in 40 patients fulfilling the American College of Rheumatology criteria for the classification of RA and in 39 subjects with OA. Disease activity score based on 28 joints (DAS28-CRP) was used to assess disease activity. For in vitro experiments, peripheral blood mononuclear cells (PBMCs) and synovial fibroblasts (SFs) were obtained from patients with RA and OA (n=6-9). Expression and protein synthesis of S100A11 and cytokines were analyzed by RT-PCR, ELISA and Western Blot.

Results: The expression of S100A11 was significantly up-regulated in the synovial lining and sublining layers ($p<0.01$) and vessels ($p<0.05$) in patients with RA compared to OA and its expression was associated with fibroblasts, T lymphocytes and macrophages. Serum (14.13 [4.26-119.8] vs. 9.50 [4.95-30.16] ng/ml; $p=0.004$) and particularly synovial fluid (195.8 [20.22-974.2] vs. 28.40 [8.20-259.80] ng/ml; $p<0.0001$) S100A11 levels were significantly increased in patients with RA compared to OA. Moreover, the levels of S100A11 were higher in synovial fluid compared to serum in both RA and OA patients ($p<0.0001$). In patients with RA, synovial fluid S100A11 correlated significantly with DAS28 ($r=0.350$, $p=0.027$), CRP ($r=0.463$, $p=0.003$), synovial fluid leukocyte count ($r=0.677$, $p<0.001$), ACPA ($r=0.424$, $p=0.006$), but not with IgM-RF ($r=0.059$, $p=0.719$). No such associations were observed in serum. In addition, S100A11 is synthetized and spontaneously secreted in higher concentrations by PBMCs ($p=0.01$) and SFs ($p=0.03$) isolated from patients with RA in comparison with OA. Extracellular S100A11 protein stimulates the production of pro-inflammatory cytokines IL-6 and TNFα in PBMCs ($p<0.05$) and SFs ($p<0.01$).

Conclusion: Our data provide the first evidence of S100A11 up-regulation and its association with inflammation and disease activity in patients with RA. Acknowledgement**:** Supported by grant 15-34065A of the Agency for Healthcare Research of the Czech Republic and MHCR 023728.

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Abstract Number: 2153

Syndecans Mediate Rantes/CCL5 Induced MMP-1 and MMP-13 Expression in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: RANTES/CCL5 (RANTES) is a C-C chemokine that binds to its receptor (CCR5) and initiates inflammatory processes in rheumatoid arthritis (RA) by facilitating leukocyte infiltration. Syndecans (also known as heparin sulfate proteoglycans, HSPGs) modulate chemokine interaction with the endothelium thereby facilitating leukocyte infiltration. However, the role of RANTES/CCL5 beyond its chemotactic activity and the role of syndecans in RANTES/CCL5 induced matrix metalloproteinase (MMP)-1 and MMP-13 expression is not yet studied. The present study was carried out to determine the role of syndecans on the RANTES/CCL5 induced MMP-1 and MMP-13 expression in human rheumatoid arthritis synovial fibroblasts (RASFs).

Methods: Human RASFs and normal SFs (NLSFs) were isolated from de-identified RA synovial tissues and healthy synovial tissues, respectively, under the IRB approved protocol. Basal cell lysates were prepared to study the expression of syndecan-1, -2, -3, and -4) was studied using qRT-PCR and Western immunoblotting methods. RASFs were treated with RANTES/CCL5 (20-100 ng/ml), IL-1β (10 ng/ml), or TNF-α (20 ng/ml) for 24 h alone or in presence of a known HSPG inhibitor, Heparinase III (0.5 U/ml). Effect of RANTES/CCL5 on MMP-1 and MMP-13 expression was evaluated using qRT-PCR and ELISA methods. Conditioned media was collected and concentrated for to determine MMP-1 and MMP-13 expression using Western immunoblotting. $p<0.05$ was considered significant.

Results: Our results showed that RANTES/CCL5 significantly induced MMP-1 and MMP-13 mRNA and protein expression ($p<0.05$). Since syndecans influence inflammatory processes by interacting with chemokines, we compared the basal expression levels of syndecans in NLSFs and RASFs. Our qRT-PCR results showed that the expression of syndecan-2 (~320%) and syndecan-4 (~80%) was significantly higher in RASFs when compared to NLSFs ($p<0.05$). No significant changes were observed in syndecan-1 and syndecan-3 expression

in RASFs compared to NLSFs. Furthermore, Western immunoblotting results confirmed that RASFs showed an increase in expression of syndecan-2 (~300 %) and syndecan-4 (~290 %) with ($p<0.05$) with no significant change in syndecan-1 and syndecan-3 expression compared to NLSFs. In addition, further stimulation of RASFs with RANTES/CCL5, IL-1β, or TNF-α for 24 h resulted in a selective induction in syndecan-2 and syndecan-4 expression ($p<0.01$) compared to the non-stimulated control. RANTES/CCL5, IL-1β, or TNF-α stimulation did not alter syndecan-1 and syndecan-3 expression in RASFs. To study whether RANTES/CCL5 induced MMP-1 and MMP-13 expression is modulated by syndecans in RASFs, we evaluated the effect of Heparinase III (HSPG inhibitor) on the ability of RANTES/CCL5 to induce MMP-1 and MMP-13 expression in RASFs. Analysis of the conditioned media showed that pretreatment with Heparinase III significantly reduced the ability of RANTES/CCL5 to induce MMP-1 and MMP-13 protein expression in RASFs ($p<0.05$).

Conclusion: Human RASFs express higher levels of syndecan-2 and syndecan-4 compared to NLSFs. In general, syndecans may also contribute to the process of tissue destruction in RA by mediating RANTES/CCL5-induced MMP-1 and MMP-13 expression in RASFs.

Disclosure: S. Agere, None; **N. Akhtar**, None; **S. Ahmed**, None.

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Abstract Number: 2154

Novel Pathogenic Functions of IL-11 on RA Joint Fibroblasts and Endothelial Cells

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease affecting 2.5 millions of Americans. Several cytokines are involved in RA pathogenesis and may serve as potential therapeutic targets. IL-11, a member of the IL-6 family of cytokines, plays important roles in a number of physiological functions. However, pathological overexpression of IL-11 in autoimmune diseases, including RA, has also been described. Despite its overexpression in RA joint, data from studies describing the role of IL-11 in RA are controversial. In phase I/II studies, treatment with IL-11 did not affect disease activity, while others established that patients in remission had lower serum IL-11 levels that correlated with disease activity score (DAS)28 improvement. To address these controversies, we sought to elucidate the expression pattern, and functional role of IL-11 and IL-11R in RA synovitis.

Methods:

IL-11 and IL-11Ra expressions were determined in RA tissues and cells (RA subjects meet the 1987 Revised Criteria for RA Classification) using immunohistochemistry and ELISA. IL-11 effector functions on RA fibroblasts and endothelial cells were studied using scratch assay and endothelial cell migration and tube formation.

Results: We found that IL-11 levels were significantly higher in RA synovial fluid (SF) compared to osteoarthritis (OA) SF (47 fold) and plasma from RA (19 fold), OA (75 fold) and normal (NL) (18 fold) volunteers. The expression of IL-11 was significantly elevated (2 fold) in the sublining endothelial cells of RA relative to NL synovial tissues (STs). In addition, the expression of IL-11 was higher (2.5 fold) in the lining fibroblasts of RA compared to OA STs. Both histology and Western blot analysis demonstrated that IL-11Ra is expressed in RA ST fibroblasts and endothelial cells but not in NL or RA macrophages. IL-11 expression was enhanced in RA ST fibroblasts primarily by IL-1b; however, expression in endothelial and RA monocytes and macrophages was only promoted by RA SF. Employing RA fibroblasts based scratch assay, we observed that IL-11 could dose dependently promote RA fibroblast proliferation through IL-11Ra starting at 100 ng/ml, as the proliferative effect was abrogated in the presence of IL-11Ra-Fc chimeric protein. In addition, IL-11 induced synovial fibroblasts to release IL-8 and VEGF which contributed to endothelial cell transmigration and tube formation. Furthermore, IL-11, starting at a dose of 1 ng/ml, induced endothelial cell migration (13-75 fold) and tube formation (19 fold) indicating that IL-11 can contribute to angiogenesis at a physiologically relevant concentration (up to 3.7 ng/ml is expressed in RA SF). The addition of the soluble IL-11Ra-Fc chimeric protein reduced the IL-11 induced endothelial cell migration by 50% and abrogated the tube formation driven by RA SF suggesting that the IL-11 pro-angiogenic effect is mediated through IL-11Ra.

Conclusion: The binding of IL-11 to IL-11Ra on RA fibroblasts and endothelial cells promoted cell proliferation and angiogenesis respectively. Therefore, our study suggests that IL-11 may be responsible for synovial fibroblast hyperplasia and it further potentiates disease severity by increasing the invasion of blood vessels into the RA pannus.

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Abstract Number: 2155

Crosstalk Between IL-6 and TNF-Alpha Signaling Pathway in Rheumatoid Arthritis Synovial Fibroblasts

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Background/Purpose: Although elevated IL-6 and its soluble receptor (sIL6R) have been found in the serum and synovium of arthritic patients, the molecular mechanisms by which it contributes to the pathogenesis of rheumatoid arthritis (RA) is not fully understood. Fibroblast-like synoviocytes (FLS) are one of the key players in the chronic inflammation of RA. Despite the knowledge provided by different studies, it is not fully resolved how cytokines present in the inflammatory environment of the RA synovium and particularly IL-6, synergize and contribute to the establishment of the rheumatoid arthritis synovial fibroblast (RASF) inflammatory phenotype.

Methods: Total RNA was extracted from 8 HSF lines and 5 RASF stimulated with either TNF-α (20ng/ml), IL-6 and sIL-6R (20ng/ml each) or in combination for 24h were used for this study. The cRNA from 4 HSF lines stimulated with either TNF-α or IL-6 and sIL-6R was hybridized in Affymetrix GeneChip® PrimeView™ Human Gene Expression Array platform containing a total of 49,395 probe sets. The microarray data analysis was performed by using Expression Console and Transcriptome Analysis Console (TAC) software (Affymetrix). Additionally, differentially expressed genes were analyzed to identify potential functional pathways using the Database for Annotation, Visualization and Integrated Discovery (DAVID). Validation of microarray data as well as synergy and priming experiments were performed by quantitative RT-PCR using specific primers.

Results: Using microarray analysis we identified genes differentially regulated (≥2 folds vs control) by the trans-signal activation of IL-6 (522 genes) and TNF-α (2640 genes) in FLS cells in culture. Interestingly, we found a significant overlap between TNF-a and IL-6/sIL-6R regulated genes. Almost 55% (287 genes) of total IL-6/sIL-6R regulated genes are common to those of TNF-a. Simultaneous induction of FLS cells with both factors synergistically stimulated the expression of selected common genes as MCP-1 and IL-6 genes, in contrast to CCL5 or IL-8 which are only activated by TNF-a in our cellular system. These data suggest that the crosstalk between TNF-a and IL-6/sIL-6R controls specific group of genes. Furthermore, stimulation of RASF cells with both inflammatory factors further enhanced the expression of these genes up to 10 fold compared to non-pathological FLS. In addition, priming experiments stimulating FLS cells with either TNF-a or IL-6/sIL-6R, followed by induction with the counterpart factor at different time-points, demonstrated that the synergistic effect requires the constant presence of both factors. These data suggest that the mechanism of crosstalk between TNF-a and IL-6/sIL-6R more likely occurs through regulation of signaling and/or transcriptional mediators rather than at a post-transcriptional level.

Conclusion: Our study suggests that despite the differential IL-6 and TNF-a intracellular signaling, there is significant overlap between the transcriptional response induced by both factors. In addition, a potent synergistic effect was confirmed for some target genes, pointing to a relevant interaction of both cytokines in the RASF pro-inflammatory effector response.

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Abstract Number: 2156

IL-6 and TNF-α Modulate Expressions of Cell Cycle Regulators of Rheumatoid Arthritis Fibroblast-like Synoviocytes

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Background/Purpose: Iinterleukin(IL)-6 and tumor necrosis factor(TNF)-α play important roles in the pathogenesis of RA, however, it remains unclear how they affect or modulate the cell cycle of Rheumatoid Arthritis Fibroblast-Like Synoviocyte (RA-FLS). Cyclins, Cyclin-Dependent Kinases (CDKs) and CDK inhibitors (CDKIs) co-operate to regulate the cell cycle, and several conditions such as replicative senescence, irradiation, low serum culture and high cellular density culture are reported to induce the expression of CDKIs, including INK4 family and Cip/Kip family, resulting in inhibiting the growth of RA-FLS (Rheumatoid Arthritis Fibroblast-Like Synoviocyte) (1). In this study, we investigated the expression of Cell Cycle regulators under stimulations of IL-6 and TNF-α.

Methods: Under stimulations of IL-6/ soluble IL-6 receptor (100 ng/ml) or TNF-α (10ng/ml), total RNA and protein were extracted from RA-FLS to analyze expressions of CDK inhibitors($p16^{INK4a}$, $p21^{Cip1}$ and $p27^{Kip1}$) by real-time PCR, and Cyclin D1 by Western Blot, respectively.

Results: Expressions of $p16^{INK4a}$ was decreased by IL-6 stimulation and $p27^{Kip1}$ was increased by TNF-α, whereas $p21^{Cip1}$ was not changed. The expression of Cyclin D1 was increased by both of IL-6 and TNF-α.

Conclusion: In RA-FLS, IL-6 and TNF-α modulate the expression of $p16^{INK4a}$, $p27^{Kip1}$ genes, and induce the expression of Cyclin D1. Our results suggest IL-6 and TNF-α co-operate to drive the G1 to S phase transition in the cell cycle of RA-FLS. **Reference:** 1. Ken Taniguchi et al. *nature medicine* 1999 Jul;5(7):760-7.

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Abstract Number: 2157

Share the Fate: Fibroblast-like Synoviocyte Cell-to-Cell Organelle Transfer Is Directed By the Inflammatory Microenvironment

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Background/Purpose: Fibroblast-like synoviocytes (FLS) form a complex tissue network via long-distance intercellular connections with wide intercellular matrix spaces. The adaptive synovial tissue response to inflammation likely depends upon the concerted activity of FLS. Using an in-vitro synovial organ culture system, we explore mechanisms of FLS directional cell-cell cooperation.

Methods: Human FLS were prepared from synovial tissues obtained as discarded specimens following joint arthroplasty. Cells were labeled with cell tracker dyes or specific organelle dyes and cultured in spherical matrigel micromasses. For selected experiments, micromasses were challenged with TNF or IFN-gamma. Data was acquired by confocal live cell imaging. Analysis of the resulting 4D movies was done using Imaris® software.

Results: To examine whether FLS transfer cytoplasmic cargo, we labeled 50% of FLS with green cell tracker dye and the other 50 % with Mitotracker. Over time, red labeled organelles accumulated in green labeled cells with a transfer rate of 10 % of newly affected cells/day. Confocal live cell imaging revealed that FLS indeed use their long-distance intercellular connections for transfer of organelles. When micromasses were stimulated with TNF (10 ng/ml) the transfer rate increased by 2-fold when compared to control. By contrast, IFN-gamma-stimulation (100 U/ml) resulted in decreased organelle transfer. The combined treatment of micromasses with TNF and IFN-gamma, however, increased the transfer rate to a level beyond stimulation with TNF alone.

Conclusion: Our experiments suggest transfer of cytoplasmic cargo, including organelles such as mitochondria between FLS. As transfer is distinctly regulated by the cytokine milieu, organelle transfer seems to be part of the adaptive synovial response to inflammation. These studies may provide insight into how synoviocytes orchestrate their activity. Further studies will demonstrate the significance of directional cytoplasmic cargo exchange for the function of the normal as well as the diseased synovium.

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Abstract Number: 2158

Serum Uric Acid Is Positively Associated with Pulmonary Function in Korean Health Screening Examinees: A Cross-Sectional Study

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Background/Purpose: Serum uric acid (SUA) has been shown to be a powerful endogenous antioxidant in the body. The double-edged characteristics of serum uric acid (SUA) and mixed results from previous studies have complicated determination of whether SUA plays a pulmonary-protective or pulmonary-destructive role. We hypothesized that SUA could have an important role in protecting the lung from oxidant damage and preventing a decline in pulmonary function. Therefore, we performed this study to investigate the association between SUA and spirometric values in a large sample drawn from a healthy population without overt clinical disease.

Methods: The Kangbuk Samsung Health Study was a cohort study of subjects who underwent a comprehensive annual or biennial examination at Kangbuk Samsung Hospital in Seoul, South Korea. We performed a cross-sectional study on 69,928 Koreans (30,572 men) without overt medical conditions who underwent a health examination in 2010.

Results: : The overall prevalence of hyperuricemia among Korean health screening examinees was 25.5% in males and 8.5% in females. Overall serum urate level was 5.1 ± 1.4 mg/dL in men and 5.0 ± 1.4 mg/dL in women. In sex-stratified analyses of SUA level, mean SUA level was positively associated with a quartile increase in Percent predicted forced vital capacity (FVC%) and forced expiratory volume in 1 s (FEV1%) in both genders ($P < 0.001$). FVC% and FEV1% were positively correlated with SUA in both genders (FVC %: $r = 0.361$; FEV1 %: $r = 0.314$ in males and FVC%: $r = 0.413$; FEV1%: $r = 0.382$ in females, all $P < 0.001$). Increasing levels of FEV1% and FVC% were associated with an increasing incidence of hyperuricemia in both genders, indicating that FVC% and FEV1% are predictive of hyperuricemia independently of other confounding factors. The adjusted ORs for hyperuricemia comparing quartiles 2, 3, and 4 to quartile 1 of FVC% in men were 0.876 (95% CI, 0.809-0.949), 0.631 (0.574-0.695), and 0.311 (0.278-0.349), respectively. The adjusted ORs for hyperuricemia comparing quartiles 2, 3, and 4 to quartile 1 of FEV1% in men were 0.791 (95% CI, 0.729-0.859), 0.565 (0.513-0.623), and 0.302 (0.270-0.337), respectively (P for trend <0.001). Similarly,

the adjusted ORs of hyperuricemia in women decreased significantly across quartiles 2 to 4 of FEV1% and FVC % compared with the highest quartile as the reference group (*P*for trend <0.001).

Conclusion: To the best of our knowledge, this is the first cohort study to show a significant positive association between hyperuricemia and good pulmonary function in a healthy Korean population, supporting the hypothesis that hyperuricemia might have a favorable effect on lung function. Longitudinal follow-up studies are required to confirm this positive association between SUA and lung function.

Disclosure: J. K. Ahn, None; **J. Hwang**, None; **J. U. Song**, None; **H. Jeong**, None; **J. Y. Chae**, None; **H. Kim**, None; **H. S. Cha**, None; **E. M. Koh**, None.

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Abstract Number: 2159

Allopurinol Use Is Associated with Lower Risk of Peripheral Vascular Disease in the US Elderly

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Background/Purpose: Gout is associated with higher cardiovascular disease risk. Based on our previous work, there is evidence that allopurinol use reduces the risk of myocardial infarction and cardiovascular disease in the elderly. This work attempts to assess whether allopurinol use reduces the risk of peripheral vascular disease.

Methods: We used the 2006-2012 5% random sample of Medicare beneficiaries to study the association of new allopurinol initiation and the risk of incident peripheral vascular disease, in a cohort study. Multivariable-adjusted Cox regression models adjusted for age, gender, race, and Charlson index, in addition to various cardio-protective medications (beta-blockers, ACE inhibitors, diuretics, statins). We calculated hazards ratio (HR) with 95% confidence intervals (CI).

Results: 3,167 of the 26,985 episodes of incident allopurinol use were associated with incident peripheral vascular disease (11.74% episodes). Allopurinol use was associated with reduced hazards of peripheral vascular disease, with unadjusted HR of 0.91 (95% CI, 0.84 to 0.98); multivariable-adjusted HR 0.89 (95% CI, 0.82 to 0.96) (Table 1). Compared to no allopurinol use, only the longest allopurinol use duration was associated with lower HR of peripheral vascular disease: >2 years, 0.77 (95% CI, 0.65 to 0.91). Other factors associated with higher hazard of peripheral vascular disease were: age 75-<85 and ≥85, male gender, higher Charlson index score, and the use of beta-blockers. Allopurinol dose was also significant in univariate analysis but not in the multivariate analysis (Table 2).

Conclusion: Incident allopurinol use was associated with a reduction in the risk of incident peripheral vascular disease; allopurinol dose was not. Only allopurinol use durations greater than 2 years reduced the risk of incident peripheral vascular disease. Future studies need to assess underlying mechanisms of this association and to assess risk-benefit ratio of allopurinol use for peripheral vascular disease prevention. Table 1: Univariate and multivariate adjusted hazard ratios for peripheral vascular disease based on allopurinol use.

	Unadjusted HR (95% CI) [pvalue]	Multivariable-adjusted HR (95% CI) [pvalue]
Allopurinol use- ref, no		
Yes	0.91 (0.84, 0.98) [0.01]	0.89 (0.82, 0.96) [0.002]

Table 2: Univariate and multivariate adjusted hazard ratios for peripheral vascular disease based on allopurinol dose and duration.

	Unadjusted HR (95% CI) [pvalue]	Multivariable-adjusted M6 HR (95% CI) [pvalue]
Allopurinol dose use1		
<200 mg/day	ref	ref
200-299 mg/day	0.87 (0.77, 0.99) [0.03]	0.91 (0.81, 1.04) [0.17]
>300 mg/day	0.83 (0.75, 0.92) [0.0003]	0.96 (0.87, 1.06) [0.42]
Allopurinol use duration dur2		
0 days	ref	ref
1-180 days	0.97 (0.88, 1.08) [0.64]	0.99 (0.88, 1.11) [0.83]
181 days -2 years	0.91 (0.82, 1.00) [0.56]	0.90 (0.81, 1.00) [0.54]
> 2 years	0.77 (0.65, 0.91) [0.01]	0.77 (0.65, 0.92) [0.003]

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **J. Cleveland**, None.

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Abstract Number: 2160

Allopurinol Use and the Risk of Acute Cardiovascular Events in Patients with Gout and Diabetes

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Background/Purpose: To examine the effect of allopurinol on the risk of incident myocardial infarction (MI) or stroke in patients with gout and diabetes

Methods: We used the 2007-2010 Multi-Payer Claims Database (MPCD) that linked health plan data from national commercial and governmental insurances, representing beneficiaries with United Healthcare, Medicare, or Medicaid coverage. In patients with gout and diabetes, we assessed whether current allopurinol use, defined as a new filled prescription for allopurinol, was associated with the risk of first Incident hospitalized MI or stroke (composite acute cardiovascular event), after which observations were censored. Multivariable-adjusted Cox proportional hazards models included demographics, cardiovascular risk factors and comorbidities; hazard ratios [HR] (95% confidence intervals [CI]) were calculated. Sensitivity analyses included additional adjustment for immune diseases and colchicine use.

Results: There were 2,053,185 person days of current allopurinol use and 1,671,583 person days of prior allopurinol use. There were 158 incident MIs or strokes in current and 151 in prior allopurinol users, respectively. Compared to previous allopurinol users, current allopurinol users had significantly lower adjusted hazard of incident stroke or MI, HR=0.67 (95% CI, 0.53, 0.84). Compared to previous allopurinol use for 0-6 months, current allopurinol use for 0-6 months was associated with significantly lower risk of incident MI or stroke, 0.61 (95% CI, 0.46, 0.81). Sensitivity analyses confirmed these findings.

Conclusion: Allopurinol use was protective against the occurence of acute cardiovascular events in patients with gout and diabetes. Future studies should explore the key mechanisms of allopurinol's potential cardio-protective effect.

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **R. Ramachandaran**, None; **J. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 2161

Association Between Inflammation and Systolic Blood Pressure at Normal and High C-Reactive Protein Levels

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Background/Purpose: While inflammation is linked with higher blood pressure (BP) in the general population, few studies have examined this relationship in patients with elevated levels of inflammation. Previous studies suggest that elevated levels of inflammation may modify the relationship between traditional cardiovascular (CV) risk factors and CV risk. The objective of this study was to examine the relationship between inflammation and systolic BP (SBP) across a broad range of high sensitivity C-reactive protein (hsCRP) levels, in a large outpatient cohort including but not limited to patients with rheumatic conditions.

Methods : We studied all outpatients at two large tertiary care centers (Outpatient cohort), between January 1, 2009 and December 31, 2010, using data from the electronic medical records (EMR). The National Health and Nutrition Examination Survey (NHANES), a general population cohort, was studied using the same time period. Inclusion criteria for both cohorts were age>=18 years with hsCRP and BP measured on the same day. Since graphical assessment of hsCRP (common log transformed) and SBP in the outpatient cohort showed a non-linear association, we constructed a generalized additive model with penalized splines to examine the association between hsCRP and SBP. All models were adjusted for age, gender, race and use of anti-hypertensive therapy. The same method was applied to the NHANES cohort**.** We reviewed the medical records of 50 random patients in the highest hsCRP decile to determine the most frequent diagnosis.

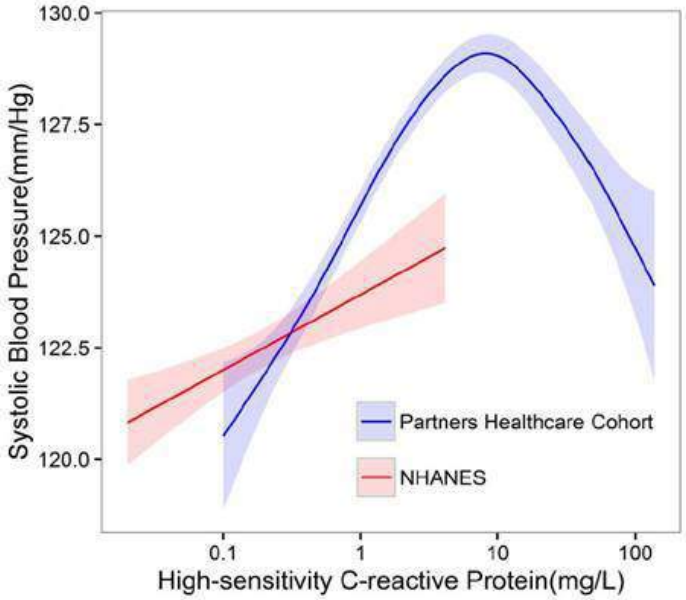
Results : We studied 24,203 subjects from the outpatient cohort and 5,332 from NHANES (**Table**). In the outpatient cohort, we observed al non-linear relationship between hsCRP and SBP. Higher hsCRP was associated with higher SBP at hsCRP levels <7.8mg/L. At levels above 7.8 mg/L, hsCRP was inversely associated with SBP. In NHANES, we observed a linear relationship where an increase in hsCRP was associated with an increase in SBP (**Figure**). In the outpatient cohort, the most frequent diagnosis for patients in the highest decile hsCRP was inflammatory arthritis (50%), of which rheumatoid arthritis was the most common.

Conclusion : In a large outpatient cohort, we observed a positive linear relationship between hsCRP and SBP when hsCRP <7.8 mg/L. This relationship is consistent with previously published studies, and replicated in our NHANES analysis. However, at levels above hsCRP of 7.8 mg/L, there was an inverse relationship between hsCRP and SBP. These findings suggest the need for careful consideration of BP as a CV risk factor in patients with active inflammation.

Table. Characteristics of participants in the outpatient cohort and the National Health and Nutrition Examination Survey (NHANES)

Characteristic	Outpatient Cohort N=24203	NHANES N=5332
Age at measurement, years, mean (SD)	54.45 (15.52)	48.40 (18.37)
Female (%)	62.51	50.68
Ethinicity (%)		
Non-Hispanic White	80.42	48.61
Non-Hispanic Black	5.47	16.64
Others	14.21	34.75
Anti-hypertensive medication use (%)	25.36	31.08
C-reactive Protein, mg/L, median (25th, 75th)	2.20 (0.90, 6.00)	0.19 (0.08, 0.44)
Systolic Blood Pressure, mm/Hg, mean (SD)	126.76 (16.85)	122.48 (18.34)
Diastolic Blood Pressure, mm/Hg, mean (SD)	76.07 (15.40)	69.47 (11.95)

Figure. The relationship between high sensitivity C-reactive protein levels (hsCRP) and mean systolic blood pressure (SBP) with 95% confidence intervals, in the outpatient cohort and NHANES*.



(*Outpatient cohort hsCRP range: 0.10 to 138.60 mg/L; NHANES: 0.02 to 4.22 mg/L)

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Abstract Number: 2162

Frequent Discussion of Insomnia and Weight Gain with Glucocorticoid Therapy: An Analysis of Twitter Posts

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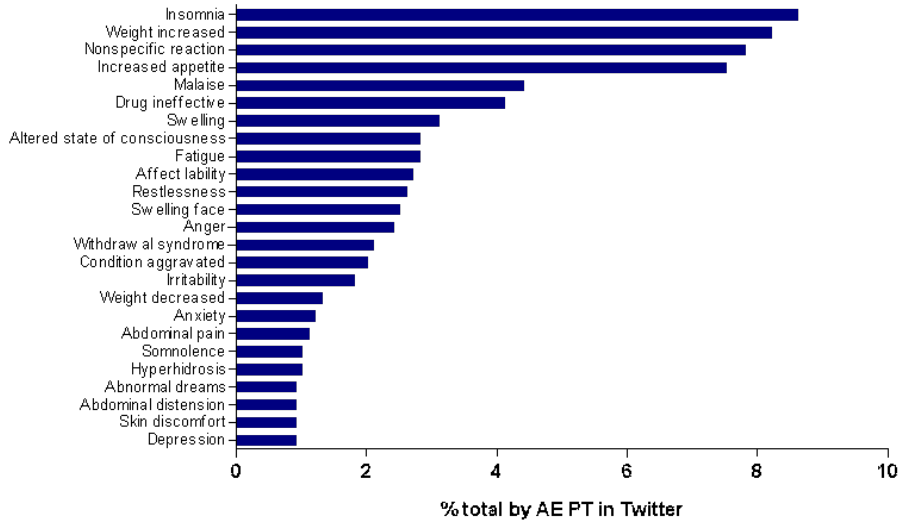
Background/Purpose: Glucocorticoid (GC) therapy is used widely in patients with inflammatory diseases. However their effectiveness is offset by a range of potential harms. Clinicians and patients have differing views on the importance of certain side effects with GC therapy, which can lead to misunderstanding and a breakdown in doctor-patient relationships. People now readily share their thoughts and experiences of health related matters on social media such as Twitter, including information about medications and their side effects. There are now vast amounts of information within this domain that could return useful knowledge about patient reported adverse events (AEs) with their medications. The aim of this study was to detect and quantify GC-related AEs using a computerised system for automated suspected adverse drug reaction (ADR) detection from narrative text in Twitter.

Methods: All Tweets mentioning prednisolone or prednisone between 1st October 2012 and 30th June 2015 were acquired and anonymised before being processed through automated natural language processing software which mapped possible symptoms (e.g. can't sleep) to preferred terms (PTs) in the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary (e.g. insomnia). Tweets were automatically categorised using a Bayesian probabilistic model based on their likelihood of containing text relating to a GC related adverse drug reaction (ADR). Tweets with high probability of containing an ADR, defined as proto-AE tweets, were further analysed to determine which AE symptoms appeared most commonly.

Results: There were 81,524 distinct tweets mentioning prednisolone or prednisone between the specified dates. 20,206 were identified as proto-AEs i.e. had a high probability of representing an ADR. Within proto-AE tweets, 26,894 unique PTs were captured. The 5 most commonly reported PTs in proto-AE tweets were 'insomnia' (8.6%), 'weight increased' (8.2%), 'non-specific reaction' (7.8%), 'increased appetite' (7.5%) and 'malaise' (4.4%) (Figure 1). The top 5 and 25 PTs accounted for 25.0% and 74.6% of all AE PTs respectively.

Conclusion: Insomnia and weight gain were the most frequently reported GC-related AEs posted on Twitter. There remains a disconnect between the frequency of these patient reported AEs and our collective knowledge about these events. Pharmacovigilance in Twitter has the potential to be a valuable, supplementary source of data for determining which drug side effects patients most commonly find troublesome

Figure 1: Glucocorticoid related AE PTs reported in Twitter



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Depressive Symptoms in Patients Consulting for the First Time at the Division of Rheumatology

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Background/Purpose: Depression can easily go unnoticed in routine clinical care. The delay in the diagnosis

may increase the risk of chronicity, the number of visits, health care costs and deteriorates the quality of life. . The aims of our study was to estimate the prevalence of depressive symptoms in patients consulting for the first time and determine if patients with depression had different reasons for consultation and highest score in the visual analog scale (VAS) of pain than patients without depression.

Methods: A observational, prospective study was performed. We included patients who consulted for the first time in Rheumatology Service, excluding these with psychiatric treatments and rheumatic diseases. The PHQ-9 (Patient Health Questionnaire) evaluated the presence of depressive symptoms in the last two weeks. According to the score, they were classified in 4 categories: (1) major depressive syndrome, (2) other depressive disorders, (3) positive depressive symptoms and (4) negative depressive symptoms. To perform the analysis the patients were divided into those with a depressive disorder (1 and 2) and those who did not have it (3 and 4). T-test or Mann Whitney test was used as sample size distribution for continuous variables. Chi square or Fisher exact test was used as expected frequency distribution table for categorical variables. Multivariate logistic regression analysis taking depression as the dependent variable was performed.

Results: 121 patients were included in the study. 86% were women, mean age of 49±15 years. The most frequent reasons for consultations were polyarthralgia (35.5%) and back pain (13%). According PHQ-9, 37% of patients were classified in major depressive syndrome and 19% in other depressive disorders. No statistically significant differences between patients with and without a depressive disorder in terms of different reasons were found. However, patients with depressive disorders were more VAS pain (7, IQR 5-8) than patients without depression (5, IQR 4-6) and more days with pain in the week (7, IQR 5-7 vs 5, IQR 3-7), both with $p < 0.01$. Increased frequency of self-medication (61% vs 39%) and sleep disorders (63% vs 37%) among patients with depressive disorders was observed, although these differences were not statistically significant. In the multivariate analysis, the only variable that was found associated with depression was independently VAS pain (OR 1.33, CI 1.13-1.56).

Conclusion: High percentage of patients had a depressive disorder with higher frequency and pain perception. So rheumatologists should be aware of this problem in order to make a proper diagnosis, optimize the application of complementary studies, and perform a multidisciplinary approach to the patient.

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Depression and the Risk of Psoriatic Arthritis Among Patients with Psoriasis: A Population-Based Cohort Study

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Depression and the Risk of Psoriatic Arthritis among Patients with Psoriasis: A Population-based Cohort Study

Background/Purpose: The factors that contribute to the development of psoriatic arthritis (PsA) among patients with psoriasis are not well known. Individuals with psoriasis are at increased risk of developing major depressive disorder (MDD), and it has been suggested that systemic inflammation associated with immune activation to external stressors/exposures may be a possible mechanism for PsA. Our objective was to determine if MDD confers an independent risk towards the development of PsA among patients with psoriasis.

Methods: Newly diagnosed cases of psoriasis were identified in adults from The Health Improvement Network (THIN) database between 1987 and 2012. The exposure was incident diagnosis of MDD among those with psoriasis. The primary outcome was development of PsA. Cox proportional-hazards models were used to estimate the hazard ratio for the development of PsA. Age, sex, medical comorbidities, socioeconomic status, obesity status, smoking status, alcohol use and psoriasis severity (defined by use of therapies intended for moderate-severe psoriasis) were assessed as effect modifiers and confounders.

Results: In total, 73,447 cases of incident psoriasis were identified, of which 5216 (7.1%) developed MDD. Those that developed MDD were more likely to be younger, female, current smokers, with at least one comorbidity, socially deprived and with moderate-severe psoriasis, and less likely to be obese or alcohol users, (all p-values <0.0001). Among all psoriasis patients, 1466 (2.0%) developed PsA during the observation period. There was no evidence for effect modification by any of the covariates (p=0.368). Individuals with psoriasis who developed MDD were at significantly greater risk of subsequently developing PsA (HR 1.55, 95%CI 1.27–1.90, p<0.0001) compared to those who did not develop MDD, when adjustments were made for age and sex. This association remained significant after adjusting for all covariates (HR 1.34, 95%CI 1.02–1.75, p=0.034) (Table 1, Figure 1).

Conclusion: MDD significantly increased the risk of developing PsA among individuals with psoriasis. Heightened attention to screening for and managing MDD in patients with psoriasis may reduce PsA incidence.

Financial and Commercial Disclosures: This study was supported by a CIHR-Leo Pharma Studentship in Psoriatic Disease through the Canadian Association of Psoriasis Patients. Funding sources played no role in study design, analysis or abstract preparation.

Conflicts of Interest: None of the authors have any conflicts of interest.

Table 1. Hazard ratios for the risk of psoriatic arthritis associated with depression among patients with psoriasis are shown in unadjusted and adjusted models.

Model	**Hazard Ratio (95% CI)**	***P*-value**
Unadjusted Model		
Depression	1.56 (1.28 to 1.90)	<0.0001
Age and Sex Adjusted Model		
Depression	1.55 (1.27 to 1.90)	<0.0001
Age	0.81 (0.73 to 0.90)	<0.0001
Sex	1.15 (1.04 to 1.28)	0.006
Multivariable Adjusted Model		
Depression	1.34 (1.02 to 1.75)	0.034
Age	0.66 (0.58 to 0.76)	<0.0001
Sex	1.23 (1.08 to 1.40)	0.002
Obesity Status	1.63 (1.42 to 1.88)	<0.0001
Smoking Status	0.90 (0.82 to 0.99)	0.028
Alcohol Use	0.98 (0.82 to 1.16)	0.788
Charlson Comorbidity Index	0.90 (0.82 to 0.99)	0.034
Townsend Deprivation Index	0.99 (0.94 to 1.04)	0.648
Psoriasis Severity	1.86 (1.62 to 2.14)	<0.0001

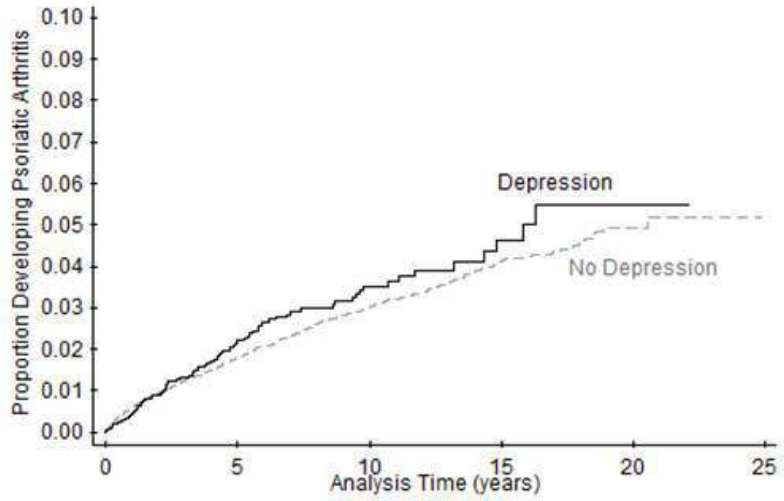

Figure 1. Kaplan-Meier failure curves are shown to estimate the proportion of psoriasis patients who developed psoriatic arthritis based on exposure to depression (black) or no exposure to depression (dotted grey).

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Abstract Number: 2165

Natural Language Processing to Rapidly Identify Potential Signals for Adverse Events Using Electronic Medical Record Data: Example of Arthralgias and Vedolizumab

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Natural language processing to rapidly identify potential signals for adverse events using electronic medical record data: example of arthralgias and vedolizumab

Background/Purpose:

In our rheumatology practice, we noted an increased number of referrals for debilitating joint pain in inflammatory bowel disease (IBD) patients who received vedolizumab. Vedolizumab is a humanized monoclonal antibody targeting a4b7 integrin in the intestinal mucosa, FDA approved in 2014. The objective of this study was to assess for a potential link between arthralgias and subjects who received vedolizumab. Since joint symptoms are uncommonly coded by gastroenterologists, we hypothesized that applying natural language processing (NLP) to extract information from narrative notes, would detect an association that would not be observed using ICD9 codes alone.

Methods: We studied 10,742 IBD patients from a published and validated electronic medical record cohort from 2 large tertiary care centers. Vedolizumab users were identified by electronic prescriptions for infusions. Information on arthralgia was obtained using ³1 ICD9 codes for 'arthralgia' (719.4x), at any point during follow-up. We also processed notes for the concept arthralgia + subconcepts, e.g. ankle pain, with NLP arthralgia defined as ³1 mention of the concept 'arthralgia'. To determine the performance characteristics of ICD9 and NLP for arthralgia, we randomly selected 100 subjects to establish gold standard cases of arthralgia. We tested the association between vedolizumab use and arthralgia by constructing logistic regression models adjusted by the potential confounders age, sex, IBD follow-up time and IBD treatments (**Table 1**).

Results: We studied 10,742 subjects of which 3.5% received vedolizumab; clinical characteristics in **Table 1**. Compared to medical record review, NLP had a higher accuracy for arthralgia: PPV 0.90 vs 0.78 using ICD9 codes (**Table 2**). Using NLP, the prevalence of arthralgia was higher among IBD patients who received vedolizumab (77.1%) compared to those who did not (49.1%). After adjusting for potential confounders, there was no association between vedolizumab and the ICD9 code for arthralgia (OR 0.96, 95%CI 0.73-1.25). In contrast, we observed a significant association between vedolizumab and NLP for arthralgia after adjustment (OR 1.72, 95% CI 1.32-2.29).

Conclusion: Using NLP, we confirmed the clinical observation of an increased prevalence of arthralgias among patients who received vedolizumab. This signal would not have been detected using ICD9 codes alone. This study provided preliminary data for a potential association and future studies are needed to determine the exact timing of joint symptoms in relation to vedolizumab.

Table 1. Characteristics of IBD patients who did and did not receive vedolizumab.

	IBD cohort (no vedolizumab) N=10,366	Vedolizumab N=376
Age, mean (SD)	47.1(18.8)	41.7(14.8)
IBD follow-up time in months, mean (SD)	53.7(56.9)	84.6(69.3)
Female (%)	53.4%	58.5%
IBD treatments, ever/never use (%)		
TNFi use	11.7%	72.1%
Immunomodulator*	13.7%	76.6%
5-Aminosalicylic acid**	4.0%	44.7%

*Immunomodulator= azathioprine, methotrexate, 6-mercaptopurine

**5-Aminosalicylic acid= basalazide, mesalamine, olsalazine, sulfasalazine

Table 2. Performance characteristics of classifying arthralgia in patients using ICD9 codes compared to NLP.

	ICD9 for arthralgia		NLP for arthralgia	
		95% CI		95% CI
Positive predictive value (PPV)	0.79	0.59-0.92	0.9	0.76-0.97
Negative predictive value (NPV)	0.71	0.59-0.81	0.88	0.77-0.95
Sensitivity	0.52	0.36-0.68	0.83	0.69-0.93
Specificity	0.89	0.78-0.96	0.93	0.82-0.98

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Abstract Number: 2166

Inflammatory Arthropathy and Hashimoto's Thyroiditis: Prevalence and Associated Factors

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Background/Purpose: Patients with Hashimoto´s thyroiditis (HT) are frequently seen by rheumatologists due to rheumatic complain that do not fit into diagnostic criteria for a definite arthropathy. The purpose of this study was to establish the prevalence and associated factors of undifferentiated inflammatory arthropathy (UIA) in a sample of Hispanic patients with Hashimoto's thyroiditis (HT).

Methods: Cross-sectional study in consecutive patients with HT from the outpatient clinic of the Endocrinology Division of the University Hospital. Diagnosis was based on the presence of anti-thyroid peroxidase antibodies (N=76) or typical ultrasonographic findings (N=25).

Results: One hundred one patients were evaluated by two rheumatologists (EJGC, LMVH). Ninety six percent

were female and the median age was 50.01 years. We excluded six patients from the study (five who met the American College of Rheumatology 1987 criteria for RA and one who met the Assessment of SpondyloArthritis international Society criteria for SpA). Overall, 73.27% referred arthralgias and 36.30% axial inflammatory pain. ANA were positive in 54.46%, RF in 12.87%, and ACPA in 2.97% of patients. Twenty five percent of patients met criteria for undifferentiated inflammatory arthropathy (UIA). The following features distinguished HT patients with UIA versus HT patients without UIA: peripheral arthralgias (100.00% vs. 58.60, $p < 0.0001$), xerostomy (64.00% vs. 34.30%, $p = 0.0200$), xerophtalmy (64.00% vs. 40.00%, $p = 0.0330$), myalgia (96.00% vs. 50.00%, $p < 0.0001$), Raynaud phenomenon (32.00% vs. 8.60%, $p = 0.0100$) and axial inflammatory manifestations (68.00% vs. 24,30%, $p = 0,0001$). The independent risk factors for UIA were the presence of myalgia (OR = 15.04; 95% CI: 1.83 – 123.41) and axial inflammatory manifestations (OR = 4.20; 95% CI: 1.37 – 12.87). RF and ACPA were positive in 3 and 1 patients with UIA; and in 7 and 1 patients without UIA, respectively (NS). There was no correlation between thyroid function levels and UIA, and no laboratory tests showed clinical utility as predictors of UIA in patients with HT.

Conclusion: One out of four patients with HT of our sample had UIA. Risk factors for the development of UIA were the presence of myalgia and axial inflammatory manifestations. UIA is a common manifestation in patients with HT. Therefore, HT should be considered in the differential diagnosis of patients with inflammatory joint symptoms.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/inflammatory-arthropathy-and-hashimotos-thyroiditis-prevalence-and-associated-factors

Abstract Number: 2167

Validation of the Earp Questionnaire: Detection of Psoriatic Arthritis in the Spanish Population

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Background/Purpose: Psoriatic arthritis (PsA) is a progressive, debilitating condition. It is estimated that

between 25 and 35% of patients with psoriasis may develop psoriatic arthritis during the course of the disease. In these patients the psoriasis precedes the onset of PsA by an average of 10 years, so it is very important that dermatologists should be able to recognise the signs and symptoms of this in order to start the diagnostic process. The EARP (Early ARthritis for Psoriatic patients) questionnaire is a detection tool for PsA in psoriatic patients, which has good psychometric properties in its original Italian version that had not yet been validated for the Spanish population.

Methods: Observational, cross-sectional, multicentre study. A dermatologist and a rheumatologist participated at each centre. The dermatologist included patients between 18 and 85 years of age who had been diagnosed with psoriasis and who were not seeing a rheumatologist and did not have any other dermatological conditions. Basic sociodemographic and clinical variables were recorded. The patients answered the EARP questionnaire and a question about their health status. The rheumatologist then performed a physical examination of the same patients with additional analytical/radiological tests, if deemed necessary according to clinical practice, to conclude whether PsA was present/absent. The study was approved by the Independent Ethics Committee of Hospital de la Santa Creu i Sant Pau de Barcelona.

Results: 377 patients were included with a mean age (SD) of 48.1 (14.3) years, 56% male. 35.4% had completed secondary education and 42.5% were employed. A cut-off point of ≥4 points in the EARP questionnaire indicated a diagnosis of PsA. The EARP questionnaire was feasible (1.6% non-response) with good internal consistency (Cronbach's α=0.776) and good construct validity, as there was a statistically significant correlation between the CASPAR criteria (p=0.01) and the rheumatologist's diagnosis (p<0.01). The EARP questionnaire presented a sensitivity of 84.4% and a specificity of 62.9%, with a higher percentage of false positives than false negatives (37.1%;15.6%) (Table 2). No statistically significant sociodemographic differences were found between the patients who were and were not diagnosed with PsA by the rheumatologist.

Conclusion: The Spanish version of the EARP questionnaire is a valid tool for the early detection of PsA symptoms by dermatologists when assessing patients who are susceptible to this condition.

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Abstract Number: 2168

Metabolic Syndrome, All Cause Mortality and Atherosclerotic Cardiovascular Disease in Rheumatic Diseases

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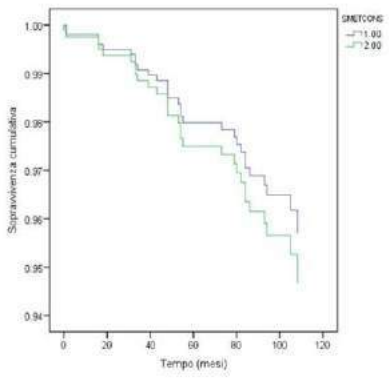
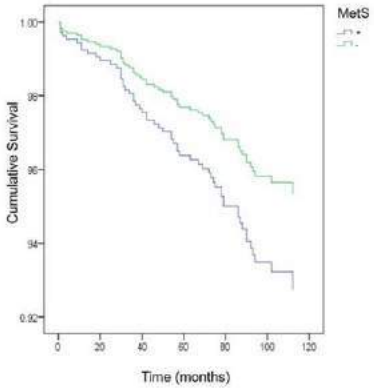
Session Time: 9:00AM-11:00AM

Background/Purpose: all-cause and cardiovascular mortality and cardiovascular morbidity are reportedly increased in rheumatic diseases, both inflammatory and non-inflammatory. Few studies, however have addressed the impact of metabolic syndrome (MetS) on mortality and cardiovascular morbidity (ASCVD, death, stroke, Myocardial infarction, peripheral arterial disease) in rheumatic diseases.

Methods: MetS was defined according the 2009 Consensus criteria (1), as the presence of at least among 3 among increased abdominal circumference (AC: M ≥ 94 cm; F ≥ 80 cm) , elevated blood pressure (BP: ≥130/85), triglycerides (TG ≥150 mg/dL), glucose (GLU: ≥100 mg/dL), or reduced HDL-Cholesterol (HDL M<40 F<50 mg/dL). The original population consisted of 1234 non-selected rheumatic patients without a history of major cardiovascular. 259 patients were eventually excluded from data analysis, because of lack of follow-up (N=252) or evidence of cardiovascular events before inclusion in the study (N=7). Of the remaining 975 patients (M 217; F 758), complete data were available for 849 patients; Mets variables were missing in < 5% of patient (AC 2.15%; BP 2.36%; GLU 3.79%; HDL 4.52%; TG 3.90%). According to current practice (2), missing data were imputed by multiple imputation, using the multivariate imputation by chained equation algorithm (3). Survival and ASCVD event risk were evaluated by Kaplan-Meier and Cox proportional hazard models. Statistical computations were performed with SPSS and R softwares.

Results: The mean duration of follow-up was 7.38 years (0-1 – 11.67), totalling 7195 patient-year. 219 (22.5%) were affected by non inflammatory diseases, 260 (26.7%) by RA, 152 (15.6%) by psoriatic arthritis/SpA, and 344 (35.3%) by CTD or vasculitis. In the whole population, 63 deaths and 115 ASCVD events in 58 patients were observed, with no significant differences between MetS + (N=330) and MetS- (N=645) patients. In the Cox Model, Mets was not correlated with the risk of death (HR 0.996 95% CI 0.577-1.721, p = 0.989), or ASCVD (HR 1.514, 95% CI 0.876-2.617, p = 0.138). For both all-cause mortality and ASCVD, age (HR 1.103, 95% CI 1.073-1.134, and HR 1.983 95% CI 1.095-3.591 respectively) and male sex (HR 1.943, 95% CI 1.066-3.541 and HR 1.046 95% CI 1.021-1.072 respectively) were correlated with the outcome.





Conclusion: In our population patients affected by non-selected rheumatic diseases, metabolic syndrome did not influence all-cause deaths and atherosclerotic cardiovascular events. These data seem to confirm previous observations showing that factors other than traditional risk factors have a major impact on cardiovascular mortality and morbidity in rheumatic diseases. **References**

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(3) van Buuren, S. Stat Methods Med Res , 2007. 16: 219-242.

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Abstract Number: 2169

Presence of Cardiovascular Risk Factors Across Different Inflammatory Joint Disease Entities: Results from a Norwegian, Multi-Centre Project

Grunde Wibetoe[1], Eirik Ikdahl[2], Silvia Rollefstad[2], Anne Salberg[3], Dag Magnar Soldal[4], Tore K Kvien[5], Glenn Haugeberg[6] and Anne Grete Semb[7], [1]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Diakonhjemmet Hospital, Oslo, Norway, [3]Hospital for Rheumatic Diseases, Lillehammer, Norway, [4]Rheumatology, Hospital of Southern Norway, Kristiansand, Norway, [5]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [6]Martina Hansens Hospital, Bærum, Norway, [7]Preventive Cardio-Rheuma clinic, Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway

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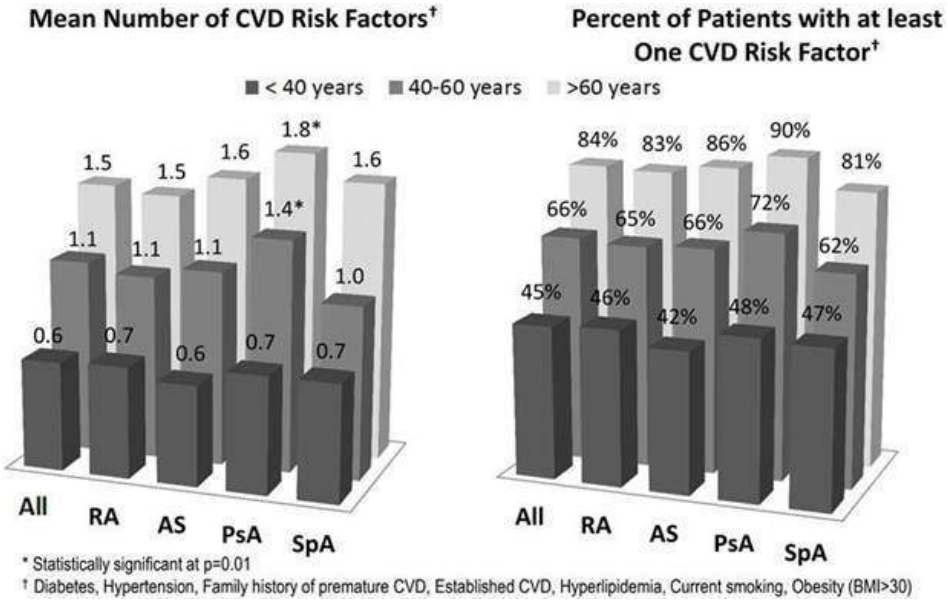
Background/Purpose: EULAR recommendations for cardiovascular disease (CVD) risk management in inflammatory joint diseases (IJD) advocates annual CVD risk assessments to reduce the increased CVD risk. Knowledge of the prevalent CVD risk factors in different diagnoses may enable tailoring of efficient CVD preventive strategies. Our aims were: I) Evaluate prevalence of CVD risk factors in IJD patients and 10-year risk for fatal CVD according to the systemic coronary risk evaluation (SCORE). II) Investigate CVD risk factor distribution across IJD entities and age groups.

Methods: In the nationwide NOrwegian Collaboration on Atherosclerosis in patients with Rheumatic joint diseases (NOCAR) project, annual CVD risk assessment is implemented. IJD patients ≥30 years of age are eligible for inclusion. Recorded CVD risk factors include non-fasting lipids, blood pressure (BP), self-reported CVD risk variables and established CVD. SCORE estimates were compared across IJD diagnoses for males and females individually, using analysis of variance, stratified by decennial age. Number of CVD risk factors, determined by presence of diabetes, hypertension, family history of premature CVD, hyperlipidemia (total cholesterol >8 mmol/L and/or low-density lipoprotein cholesterol> 6 mmol/L), current smoking or obesity (body mass index>30kg/m^2), was counted for each patient. Frequency of CVD risk factors for was estimated and compared across the four major entities, using logistic regression (age and sex adjusted).

Results: Of 2647 patients included (rheumatoid arthritis [RA]: n=1696, ankylosing spondylitis [AS]: n=445, psoriatic arthritis [PsA]: n=376 and other spondyloarthritides [SpA]: n=130), 58% were females and the median (inter-quartile range [IQR]) age and disease duration were 57.4 (46.8-66.8) and 8.0 (3.8-15.9) years, respectively. Median (IQR) crude SCORE estimate was 2.2% (0.5-4.3) and comparable across diagnoses, apart from male AS patients having lower SCORE estimates (p=0.01). CVD risk factor prevalence were comparable across individual IJD diagnoses, except PsA patients who had significantly (p=0.01) more CVD risk factors in the oldest age groups.The percentage with at least one CVD risk factor and mean number of risk factors was 45 % and 0.6 in individuals < 40 years, increasing to 66% and 1.1 and 84% and 1.5 in age groups 40-60 and >60 years, respectively (Figure). In detail, CVD risk factor rates were: family history of premature CVD: 18%, established CVD: 10%, current smoking: 20%, hypertension: 53%, obesity: 18%, diabetes: 7%, hyperlipidemia: 1%. PsA patients were significantly more likely to be obese (p=0.001), hyperlipidemics (p<0.05), diabetics (p<0.001), hypertensive (p<0.0001), and were less frequently smokers (p=0.04).

Conclusion: A high rate of CVD risk factors was present even in young patients. Apart from PsA, the prevalence of CVD risk factors was uniformly distributed across all IJD entities.



Disclosure: G. Wibetoe, None; **E. Ikdahl**, None; **S. Rollefstad**, None; **A. Salberg**, None; **D. M. Soldal**, None; **T. K. Kvien**, None; **G. Haugeberg**, Go Treat IT, 4; **A. G. Semb**, None.

Abstract Number: 2170

Cardiovascular Risk in Patients with Psoriasis, Psoriatic and Rheumatoid Arthritis: A Prospective Study Using Secured Anonymised Information Technology Databank in Wales, United Kingdom

Ernest H. Choy[1], Roxanne Cooksey[2], Sinead Brophy[2], Jonathan Kennedy[2], Fabiola Fernandez-Gutierrez[3], Ruth Davies[4], Timothy Pickles[5] and Vincent Piguet[6], [1]CREATE Center, Division of Infection and Immunity,, Cardiff University, Cardiff, United Kingdom, [2]College of Medicine, Swansea University, Swansea, United Kingdom, [3]Cancer Research UK Manchester Institute, Manchester, United Kingdom, [4]CREATE Centre, Division of Infection and Immunity, Cardiff University, Cardiff, United Kingdom, [5]CREATE Center, Division of Infection and Immunity, Cardiff University, Cardiff, United Kingdom, [6]Division of Infection and Immunity, Cardiff University, Cardiff, United Kingdom

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Background/Purpose: Compared with cardiovascular (CV) risk in rheumatoid arthritis (RA), precise CV risk in psoriatic arthritis (PsA) and psoriasis is less established, particularly the relative contribution of traditional CV risk factors versus systemic inflammation. The objective of this study is to compare the incidence of Major Adverse Cardiac Events (MACE) among patients with RA, PsA and psoriasis with population controls adjusting for traditional CV risk factors, systemic inflammation, and Disease Modifying Anti-Rheumatic Drug s(DMARDs).

Methods: Using linked, routinely collected health data from 1999 to 2013 in Wales UK, available from the Secure Anonymised Information Linkage (SAIL) databank, which includes general practitioner, and hospital datasets, the incidence of a MACE was investigated in individuals with RA (n=8,650), PsA (n=2,128), psoriasis (n=24,630) and population controls (n= 1,187,706), while controlling for traditional CV risk factors, systemic inflammation (measured by erythrocyte sedimentation rate (ESR)), and DMARDs.

Results: Demographic details and incidence of MACE are listed in Table 1. After controlling for traditional risk factors, CV risk was significantly increased for individuals with RA (HR: 1.2, 95% CI: 1.0-1.3, p=0.038) and psoriasis (HR: 1.1, 95% CI: 1.0-1.3, p=0.025) but not for PsA (HR: 1.0, 95% CI: 0.7-1.5, p=0.887). ESR was significantly higher in patients with RA compared with patients with psoriasis, PsA and controls. ESR was associated with increased in CV risk in RA but not psoriasis or PsA. No interaction between DMARDs and MACE occurrence was observed. **Table 1: Baseline Characteristics AND INCIDENCE OF MACE** ControlRAPsAPsoriasis(n=1187706)(n=8650)(n=2128)(n=24630)Age at diagnosis (SD)50 (17.2)59.6 (14.6)50.3 (13.1)51.4 (16.2)Male49%32%47%49%Baseline BMI (SD)25.5 (5.1)26.8 (5.5)27.8 (5.9)26.5 (5.4) Hyperlipidemia 7.30% 13.90% 12.60% 11.40% Diabetes 7.80% 14.10% 13.10% 11.90% Hypertension21.60% 39.70% 33.30% 29.90% Smoker21.20% 24.60% 21.90% 27.90% MACE Incidence rate per 1000PY (95% CI)4.5 (4.5 to 4.6)9.6 (8.8 to 10.5)2.9 (2.2 to 3.9)5.3 (5.0 to 5.7)

Conclusion: In addition to traditional CV risk factors, there is an increased incidence of CV disease for RA and psoriasis, but not for PsA. This demonstrates the varying mediators of CV risk across the conditions and highlights the need for different CV risk reduction strategies for specific diseases.

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Abstract Number: 2171

Increased Rates of Hypertension in Patients with Psoriatic Arthritis Compared to Psoriasis Alone: Results from the UK Biobank

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Background/Purpose:

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with the presence of psoriasis. Both conditions are influenced by lifestyle factors such as alcohol consumption, smoking and obesity. Furthermore, there is evidence that PsA is associated with an increased risk of cardiovascular disease (CVD) compared to the general population. The aim of this study was i) to compare lifestyle factors between individuals with PsA, psoriasis and a control group and ii) to assess the relationship between these inflammatory diseases and CVD outcomes.

Methods:

UK Biobank recruited 502,664 people aged 40-70 years in the UK between 2006 and 2010. Cross-sectional data on lifestyle, sociodemographics, and health and medical history were collected at the assessment visit by questionnaire and interview by a research nurse. Participants were asked if they have ever been diagnosed by a physician with PsA, psoriasis or any other disease. Lifestyle factors including alcohol (current or past intake) and smoking status (ever or never) were recorded and height and weight measured to calculate BMI. In this cross-sectional study, the frequency of these factors was compared between PsA, psoriasis and healthy controls using logistic or linear regression analyses depending on the outcome, adjusting for age and gender. Comparison between disease groups was performed by linear combinations of coefficients post estimation. Three CVD outcomes: heart attack, angina and hypertension, were tested for association with disease group using logistic regression including BMI, smoking, alcohol, age and gender as covariates. Odds ratios (OR) and β coefficients are reported with 95% confidence intervals (CI).

Results:

A total of 476,626 participants were included; 862 participants with PsA, 4,761 participants with psoriasis and 471,003 control participants (Table). Compared with the control group; both the PsA and psoriasis groups had higher BMI (β 1.43 (95% CI 1.11-1.75) and 0.72 (0.58-0.85) respectively), the psoriasis group smoked more (OR 1.63 (1.54-1.72)) and the PsA group had a lower rate of current drinkers (OR 0.68 (0.55-0.85)). Comparing between disease groups; the PsA group had a higher BMI (β 0.69 (0.32-1.06)) and lower rates of both ever smoking and current alcohol consumption (OR 0.70 (0.61-0.81) and 0.65 (0.51-0.83) respectively). Finally, hypertension was more prevalent in PsA compared to the control and psoriasis cohorts (OR 1.71 (1.48-1.97) and 1.55 (1.33-1.82) respectively).

Conclusion: Using a large population based cohort we have shown that self-reported rates of hypertension are significantly higher in patients with PsA compared with psoriasis independently of known CVD risk factors. The results contribute to our understanding of the lower quality of life reported by patients with PsA.

	Control (n=471,003)	Psoriasis (n=4,761)	PsA (n=862)
Age, mean (sd)	56.4 (8.1)	56.3 (8.1)	56.1 (7.4)
Males (%)	45.1	52.9	47.9
BMI, mean (sd)	27.4 (4.8)	28.3 (5.5)	28.8 (5.3)
Current drinkers (%)	92.1	92.6	88.9
Ever smokers (%)	44.6	57.3	47.8
Hypertension (%)	26.9	29.2	37.7
Heart attack (%)	2.2	2.9	2.8
Angina (%)	3.1	4.0	4.3

Disclosure: E. Bellou, None; **S. M. M. Verstappen**, None; **M. Cook**, None; **J. C. Sergeant**, None; **R. B. Warren**, None; **A. Barton**, None; **J. Bowes**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/increased-rates-of-hypertension-in-patients-with-psoriatic-arthritis-compared-to-psoriasis-alone-results-from-the-uk-biobank

Abstract Number: 2172

Impact of Biologic and Non-Biologic Treatment on the Incidence of Traditional Cardiovascular Risk Factors Among Patients with Rheumatoid Arthritis, Psoriatic Arthritis, or Psoriasis

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Background/Purpose: Studies have suggested that the chronic inflammatory nature of rheumatic conditions (rheumatoid arthritis (RA) and psoriatic arthritis (PsA)) as well as psoriasis (PsO) may predispose patients to cardiovascular (CV) disease and metabolic disorders. However, the individual impact of RA, PsA, PsO, and their treatments, on traditional CV risk factors - hypertension, diabetes mellitus (DM), hyperlipidemia, and obesity - is not well understood.

Methods: Patients with RA, PsA, and PsO with visits between January 1, 2002 and June 30, 2014 were identified (and included in three separate cohorts) in MarketScan, a large US employer-based claims database. The index date was defined as the date of RA, PsA or PsO diagnosis, and patients were required to be continuously enrolled for 12 months prior to the index date. Four cohorts were defined for each of the three diagnoses based on treatment (or lack thereof) during follow-up. The four cohorts were 1) TNF inhibitor (TNFi) monotherapy, 2) non-biologic (nb)DMARD monotherapy, 3) TNFi + any other nbDMARD combination therapy, and 4) No DMARD treatment. The treatment cohorts were followed from the date treatment was initiated after the index date until disenrollment, end of study period, switching medications to qualify for a different treatment

cohort, or until the last available day supply of any medication in the designated treatment cohort. The primary outcome was the first occurrence of the CV risk factors during the follow-up period. Incidence rates (IR) per 1,000 patient-years (PY) with 95% confidence intervals (CI) were calculated. Incidence outcomes were age- and sex-standardized to the MarketScan general population.

Results: We identified 126,820 patients with RA, 18,924 with PsA, and 28,788 with PsO. Mean age at index date was similar for both PsO and PsA patients (50 yrs), but RA patients were older (56 yrs). Mean follow-up time ranged from 2.4 years to 3.0 years. Among RA patients, incidence rates of the 4 CV outcomes were fairly consistent between DMARD treated and non-treated patients, with numerically lower rates for hyperlipidemia and obesity. In PsO patients, monotherapy cohorts had higher rates of all outcomes than those not receiving any DMARDs. In PsA patients, rates of hypertension, diabetes and obesity were similar among all treatment groups, whereas hyperlipidemia displayed numerically higher rates among the DMARD treated cohorts (Table 1).

Conclusion: Impact of treatment on CV risk factors is not consistent across disease states or the CV risk factors. When treating patients there needs to be consideration for both the underlying disease states, and the CV risk factor of interest. The results highlight the importance of close monitoring and careful management of CV risk factors in patients with RA, PsA and PsO.

Table 1. Age- and sex-standardized incidence of cardiovascular risk factors during follow-up for patients with rheumatoid arthritis, psoriasis, and psoriatic arthritis treated with TNFi medications and/or nbDMARDs or no DMARDs

	Rheumatoid Arthritis (N = 126,820)			Psoriasis (N = 28,788)			Psoriatic Arthritis (N = 18,924)		
	Events	Patient Years	IR [95% CI]	Events	Patient Years	IR [95% CI]	Events	Patient Years	IR [95% CI]
Hypertension									
No DMARD	298	2,378	81.0 [67.3-94.8]	1,446	19,305	61.2 [58.0-64.5]	90	831	98.2 [74.2-122.1]
TNFi monotherapy	564	4,576	86.8 [75.7-97.9]	310	3,504	82.7 [71.6-93.8]	478	4,563	89.4 [79.9-98.9]
nbDMARD monotherapy	9,631	69,389	86.1 [83.2-88.9]	418	2,936	102.2 [90.8-113.6]	593	4,346	100.8 [91.0-110.5]
TNFi + nbDMARD	529	3,226	94.7 [80.2-109.3]	10	47	180.1 [60.5-299.7]	66	396	132.2 [93.1-171.4]
Diabetes mellitus									
No DMARD	78	4,059	12.1 [7.75-16.5]	385	26,475	10.7 [9.6-11.9]	27	1,173	18.5 [9.0-28.0]
TNFi monotherapy	105	6,023	11.1 [8.2-13.9]	110	4,268	21.5 [17.0-25.9]	124	5,937	16.9 [13.2-20.6]
nbDMARD monotherapy	1,856	105,328	12.6 [11.4-13.7]	113	3,893	21.0 [16.0-26.0]	155	5,859	19.3 [14.6-23.9]
TNFi + nbDMARD	102	4,658	18.9 [10.7-27.1]	2	54	30.2 [11.7-72.1]	18	514	25.8 [12.5-39.0]
Hyperlipidemia									
No DMARD	258	3,370	51.0 [41.0-61.0]	1,258	22,345	41.6 [39.3-44.0]	70	1,029	48.0 [36.2-59.7]
TNFi monotherapy	344	5,505	44.0 [36.0-51.9]	296	3,768	61.6 [54.0-69.2]	443	5,136	66.4 [59.2-73.5]
nbDMARD monotherapy	6,630	90,636	44.9 [43.1-46.8]	358	3,377	70.1 [61.6-78.5]	478	5,132	65.6 [57.8-73.4]
TNFi + nbDMARD	307	4,289	39.8 [33.8-45.8]	9	51	119.7 [34.0-205.3]	47	480	71.5 [44.1-98.9]
Obesity									
No DMARD	148	4,294	33.0 [25.2-40.7]	715	27,885	22.8 [20.8-24.7]	48	1,254	32.2 [20.7-43.8]
TNFi monotherapy	111	6,390	18.2 [13.5-23.0]	148	4,423	32.8 [26.2-39.3]	254	6,160	41.0 [34.0-48.0]
nbDMARD monotherapy	2,856	111,231	26.1 [24.0-28.2]	165	4,173	36.7 [28.9-44.5]	215	6,198	32.6 [25.6-39.6]
TNFi + nbDMARD	83	5,006	22.7 [12.6-32.8]	2	64	15.1 [6.1-36.2]	31	529	58.4 [24.9-91.9]

IR, incidence rate; CI, 95% confidence interval; nbDMARD, nonbiologic disease-modifying antirheumatic drug; TNFi, tumor necrosis factor inhibitor.

Disclosure: H. Radner, Amgen, 9; **T. Lesperance**, Amgen, 9; **N. A. Accortt**, Amgen, 3,Amgen, 1; **D. H. Solomon**, Amgen, 9.

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Abstract Number: 2173

Patient Reported Disease Activity and Efficacy of Biologic Therapy in Patients with Psoriatic Arthritis. an Observational Study of 107 Patients of the Estonian Society for Rheumatology Biologic Therapy Register during 2008-2014

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Background/Purpose: Psoriatic arthritis is a heterogenous disease that can effectively be treated with biologic therapy. The treatment outcome is affected by difference in disease expression and patients population. The aim of this study was to evaluate the patient reported outcome of the therapy and the disease activity in the perspective of gender differences.

Methods: Data on patients with psoriatic arthritis were extracted from the Estonian Society for Rheumatology Biologic Therapy Register from 2008 to 2014. Demographic, clinical and disease activity measurements were evaluated at the initiation of the biologic therapy and at patients last recorded registry entry during the observational period. The association of gender and patient reported outcome measures and objective disease acitivity measures were assessed with Wilcoxon rank-sum test, linear regression was used to adapt for potential confounders.

Results: Among 107 patients (mean age 44.8 (standard deviation, ±12.4) years, mean stay in register 32.3 (±24.8) months, mean number of registry entries 5.4 (±2.8)) 53.3% were females. At the initiation of biologic therapy, female patients had more active disease by both subjective (visual analogue scale (VAS) value of pain, female vs male means 60.2 vs 47.7, p=0.0365; HAQ-DI 1.65 vs 0.70, p=0.0023) and objective disease activity measures (DAS28 5.2 vs 4.0, p=0.0071; BASDAI 6.8 vs 5.4, p=0.0423). Female patients had more active disease also at the last recorded visit (VAS pain 30.8 vs 17.6, p=0.0022; VAS global assessment 30.5 vs 16.2, p=0.0007; HAQ-DI 1.0573 vs 0.44, p=0.0085; DAS28 3.1 vs 1.8, p=0.0001; BASDAI 3.5 vs 2.2, p=0.0084). The differences persisted after adjustment for age, time in the register and change in the biologic therapy. During the treatment period all the objective and subjective disease activity measures improved without a gender difference with an exeption of HAQ-DI which showed bigger change in female patients (-1.00 vs -0.24, p= 0.0148).

Conclusion: Previous studies have shown that men have higher objective disease activity and are more likely to develop structural damage whereas women have higher activity in patient reported outcomes (1). In this study female patients were susceptible to more active disease regarding most aspects of psoriatic arthritis. However further studies are needed to evaluate the relationship to the disease expression or other manifestations of the disease and female gender. In this population there was no gender difference in treatment efficacy by objective measures. 1. Eder et al. Ann Rheum Dis 2013;72:578-582

Disclosure: S. Tälli, None; **M. Tammaru**, None; **K. Otsa**, None.

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Abstract Number: 2174

Effect of Anti-Rheumatic Treatment on Selenium Levels in Rheumatoid Arthritis, Psoriatic Arthritis and Ankylosing Spondylitis

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Background/Purpose: The cause of the increased cardiovascular risk in inflammatory rheumatic diseases (IRDs) is still unclear. Intriguingly, selenium-deficiency, which might be caused by poor diet or inflammation, has been proposed to contribute to development of cardiovascular disease (CVD), and selenium supplementation has been reported to decrease CV risk. Moreover, decreased selenium-levels are likely to promote inflammation.

The aim of this study was to compare serum selenium (s-Se) levels in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), and to evaluate if these levels are influenced by methotrexate (MTX) and/or anti-tumor necrosis factor treatment (anti-TNF). Furthermore, to assess if s-Se levels are associated with markers of disease activity and endothelial function (EF).

Methods:

From the biobank of PSARA study, we examined samples from 131 IRD patients starting with either MTX or anti-TNF with or without MTX (anti-TNF±MTX) due to high active disease. s-Se (atomic absorption spectroscopy), EF (finger plethysmography) and serologic inflammatory biomarkers were evaluated at baseline and after 6 weeks and 6 months of therapy.

Results: The baseline median s-Se levels in the total IRD group (72µg/L) were within the reference range 50-120 µg/L. The s-Se levels increased in all groups after 6 weeks and 6 months of therapy, but the differences from baseline were not statistically significant. Changes in s-Se were significantly related to changes in CRP and ESR (both p=0.001 at 6 weeks and p=0.033 and p=0.035 at 6 months, respectively), but not to changes in EF. There were no statistically significant differences neither in s-Se baseline levels nor in changes in s-Se between baseline and follow up between RA , AS and PsA . In patients treated with MTX, s-Se levels increased after 6 weeks (p=0.012) and 6 months of therapy (p=0.038). In patients treated with anti-TNF±MTX, there were no changes in s-Se levels during the follow-up.

Conclusion: IRD patients had s-Se levels within the normal range. The s-Se levels increased after 6 weeks and 6 months of anti-rheumatic therapy, but the differences were statistically significant only in patients treated with MTX monotherapy (not in those treated with anti-TNF). Thus, larger and longer studies are needed to determine if anti-rheumatic treatment, in particular MTX, might influence CV risk through increasing s-Se levels (either due to its anti-inflammatory effect or other effects).

Disclosure: G. Deyab, None; **I. Hokstad**, None; **M. Cvancarova Småstuen**, None; **S. Agewall**, None; **J. E. Whist**, None; **I. Hollan**, South-Eastern Norway Regional Health Authority, 2,the Norwegian Society for Rheumatology, 2,the Norwegian Rheumatism Association of the Norwegian Women's Public Health Association, 2.

Abstract Number: 2175

Comparisons of Patients Prescribed Biosimilars or BIO-Originators for Autoimmune Diseases in Germany

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Background/Purpose: To compare the characteristics of patients who receive biosimilars against patients receiving bio-originators.

Methods: The Adelphi Biosimilars Programme 2016 is a cross-sectional survey of German rheumatologists who prescribe biosimilars. For a sample of their RA, AxSpA and PsA first line biosimilar or bio-originator patients, initiated since 2015 (the introduction of biosimilars in Germany), rheumatologists reported patient characteristics including: demographics, insurance coverage, clinical status and treatment history. Physicians were asked to describe a typical biosimilar patient in comparison to a bio-originator patient.

Results: No differences were observed in age, gender, ethnicity, BMI and employment status between biosimilar patients (n=100) and bio-originator patients (n=52). Patients initiated on bio-originators were more likely to have private health coverage (13%) than biosimilar patients (8%). 8% of biosimilar patients were 'deteriorating rapidly' at therapy initiation but this was 21% in bio-originator patients. Biosimilar patients were using non-advanced therapies (e.g. DMARD) for 11.6 months longer than bio-originator patients. Rheumatologist responses suggested there is no 'typical' biosimilar patient from a clinical/demographic perspective, though 28% stated it was cost difference that motivates them to prescribe to a specific patient.

Conclusion: The data shows that biosimilars are initiated in patients who are clinically less severe than bio-originator patients and that they also spend more time on alternative non-biologic therapies before biologic initiation. This suggests that when a more severe patient is being treated physician are more likely to choose are more well-known bio-originator. Physicians did not describe a 'typical' patient in terms of clinical characteristics and stated that it was cost reasons that would drive them to prescribe biosimilars in most patients, suggesting that payer pressure is influencing prescribing decisions.

Disclosure: S. Kachroo, Merck and Co Inc, 3; **C. Black**, Merck and Co Inc, 3; **E. Sullivan**, Adelphi Real World, 3; **J. Waller**, Adelphi Real World, 3; **J. Piercy**, Adelphi Real World, 3.

Abstract Number: 2176

Comorbidities and DMARD, NSAID and Steroid Use in a Real Life Cohort of 8,981 Patients with Psoriatic Arthritis

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Background/Purpose: Psoriatic arthritis (PsA) treatment options are based on the use of DMARDs and NSAID but their use may vary widely, despite international recommendations and guidelines. We aimed at determining the prevalence of comorbidities and prescription patterns of synthetic DMARDs, NSAIDs, and other drugs in a real-life cohort of patients and to determine if sex influences the use and retention rates of therapeutic options.

Methods: We performed a retrospective cohort analysis of administrative health databases of Lombardia region (>10 million population) through the RECORD study of the Italian Society of Rheumatology. PsA and comorbidities were identified using specific copayment exemptions (045.696.0 for PsA) from January 1st 2005 to December 31st 2015 and then linked to DMARD, NSAID, steroid, and other prescriptions. The influence of sex on prescriptions and retention rates was evaluated using Cox regression analyses and the results presented as hazard ratios (HR) and 95% confidence intervals (95%CI).

Results: We identified 8,981 PsA cases (**Table 1**) and the prescribed DMARDs, NSAIDs and steroids are reported in **Table 2**. Among clinical features, most comorbidities were found in significantly different proportions in men and women. Of note, 0.8% of patients had a diagnosis of depression while 20.5% received anti-depressants (both being more frequent in women). Methotrexate (MTX) was used in 59% of patients, almost equally in its oral and parenteral formulation, with the latter most commonly prescribed at 10 mg weekly dose. MTX was most frequently prescribed to men, while sulfasalazine and hydroxychloroquine (HCQ) to women. Of note, women received more steroids while men received more NSAIDs. A higher risk for MTX discontinuation was found in women (HR1.06,95%CI1-1.1,p-value0.047), who retained HCQ more commonly (HR0.83,95%CI0.72-0.96, p-value0.012); no differences were observed for other DMARDs retention rates.

Conclusion: In our real-life cohort of patients with PsA anti-depressants are largely used, especially in women. Among DMARDs, MTX is most frequently prescribed but appears to be largely used in its oral formulation and at low dose. Off-label treatments for PsA such as HCQ and steroids are used more frequently in women. In general terms, women and men with PsA have different comorbidities and may underlie different treatment choices. **Table 1.**

	Total n 8,981	Men n 4,478 (49.9%)	Women n 4,503 (50.1%)	*p* value
Age, years median (IQR)	51.9 (42-61)	51.2 (41.5-61.1)	52.6 (42.6-61)	0.0158
Disease duration, years median (IQR)	4.7 (2.2-7.6)	4.9 (2.3-7.7)	4.6 (2.1-7.6)	0.0012
Crohn, n	26 (0.3%)	14 (0.3%)	12 (0.3%)	0.684
Hypertension, n	1,428 (15.9%)	704 (15.7%)	724 (16.1%)	0.644
Dyslipidemia, n	256 (2.9%)	127 (2.8%)	129 (2.9%)	0.935
Diabetes, n	730 (8.1%)	397 (8.9%)	333 (7.4%)	0.011
Liver disease, n	132 (1.5%)	77 (1.7%)	55 (1.2%)	0.050
Liver cirrhosis, n	41 (0.5%)	30 (0.7%)	11 (0.2%)	0.003
Chronic kidney disease, n	89 (1%)	54 (1.2%)	35 (0.8%)	0.040
Depression, n	73 (0.8%)	23 (0.5%)	50 (1.1%)	0.002
Prescription of anti-depressants, n	1,840 (20.5%)	648 (14.5%)	1,192 (26.5%)	<0.001

Table 2.

	Total n 8,981	Men n 4,478 (49.9%)	Women n 4,503 (50.1%)	*p* value
Methotrexate, n	5,301 (59%)	2,740 (61.2%)	2,561 (56.9%)	<0.001
Oral methotrexate, n	2,164 (24.1%)	1,151 (25.7%)	1,013 (22.5%)	<0.001
Parenteral methotrexate, n				
7.5 mg/week, n	433 (4.8%)	199 (4.4%)	234 (5.2%)	NS
10 mg/week, n	1,510 (16.8%)	730 (16.3%)	780 (17.3%)	NS
15 mg/week, n	1,035 (11.5%)	561 (12.5%)	474 (10.5%)	0.003
20 mg/week, n	142 (1.6%)	90 (2%)	52 (1.2%)	0.001
25 mg/week, n	17 (0.2%)	9 (0.2%)	8 (0.2%)	NS
Cyclosporine, n	1,238 (13.8%)	653 (14.6%)	585 (13%)	0.029
Leflunomide, n	600 (6.7%)	275 (6.1%)	325 (7.22%)	0.041
Sulfasalazine, n	2,192 (24.4%)	982 (21.9%)	1,210 (26.9%)	<0.001
Hydroxychloroquine, n	1,117 (12,4%)	340 (7.6%)	777 (17.3%)	<0.001
Oral steroids, n	5,196 (57.9%)	2,519 (56.3%)	2,677 (59.5%)	0.002
NSAIDs, n	4,034 (44.9%)	2,127 (47.5%)	1,907 (42.4%)	<0.001

Disclosure: E. Generali, None; **G. Carrara**, None; **C. A. Scirè**, None; **C. Selmi**, None.

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Specificity of Spinal Pain Features in Assessment and Classification of Spondyloarthritis

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Background/Purpose: Classification criteria lacking specificity cause inclusion of many false positives in settings with low prevalence of disease. The ASAS axial spondyloarthritis (axSpA) criteria have 84% specificity. If the prevalence of axSpA among chronic back pain (CBP) patients is 5% one expects 3.6 false positively labeled persons for each true axSpA patient. Back pain is a key issue in the classification of axSpA. Our aim is to assess the specificity of spinal pain features to obtain better performance of the ASAS criteria.

Methods: We assessed (1) low back pain or stiffness; (2) thoracic inter-scapular back pain or stiffness; (3) frontal chest pain or discomfort by analyzing data from two earlier studies.[1,2] *Inflammatory* back pain (IBP) is defined as 4 or 5 Calin criteria: onset of back discomfort ≤ age 40; insidious onset; persistence for ≥ 3 months; morning stiffness; improvement with exercises. In the *first* study[1], 739 apparently healthy leisure time sportsmen (orienteers) completed a detailed questionnaire on spinal and chest pain features. AxSpA is assumed to be absent in this group. The *seco*nd study[2] (a Swiss family study on AS) enabled assessing specificity of chest and back pain features in B27- first degree relatives of 275 B27+ AS patients. All (both B27+ and B27-) participants underwent clinical exam, full HLA-typing, radiography of SI joints and completed questionnaires, including chest and spinal pain features. Pelvic x-rays were blindly read, twice by each of 2 investigators. They agreed in 95.6% (kappa 66.4).

Results: The table shows the specificities for the sportsmen. The 3 pain syndromes were highly associated ($p<0.001$). Low back pain *ever* is age related. The specificity in the age groups 10-19, 20-29, 30-39, 40-49, 50-59 year are 70.1%, 46.3%, 52.1%, 42.8%, and 37.1% respectively. Altogether 24.1% of back pain *ever* can be classified as chronic IBP. The specificity of diagnostic spinal x-rays is 67.5%. Radiographs were done in 25% (6/24) in people with IBP < 3 months duration, but in 67 % (40/60) of people with ≥ 3 months IBP. Specificity was 99.1% for not using analgesics because of back pain ≤ last 6 months. The likelihood ratio for having had a diagnostic spinal radiograph is 2.2 (46/84:67/264) if chronic IBP is present compared to absent. Specificity was very high (99.1%) for not using analgesics because of back pain ≤ last 6 months. AS or sacroiliitis was found in 20/274 (7.3%) B27+ relatives. Sacroiliitis was never observed in B27- relatives with IBP. Of note B27+ relatives *without sacroiliitis* have more often chest pain and IBP than B27- relatives suggesting axSpA or spondylitic disease in B27+ relatives.[2] The specificities for the B27- relatives are shown in the table.

Conclusion: Better knowledge of specificity of spinal pain syndromes may help improving performance of classification criteria for axSpA. Chest pain and use of analgesics seem promising candidate variables.

Spinal Pain Syndrome	Orienteers[1] % specificity (n=739)	B27- Relatives % specificity (n=248)	B27- Relatives % positive (n=248)	B27+ SI-Relatives % positive (n=248)
mean age (yr)	32.7	28.7	28.7	28.0
males (%)	64.4	48.0	48.0	41.5
Low back pain *ever*	52.9	41.1	58.9	62.5
Inflammatory back pain	89.1	89.5	10.5^	16.1^
Onset < 40 yr	21.6	48.0	52.0	57.7
Insidious onset	44.5	69.0	31.0	27.8
Duration > 3 months	69.5	87.3	12.7	15.0
Morning stiffness	62.6	79.8	20.2	27.0
Improvement	41.7	81.3	18.7	18.6
with exercises				
Chest pain or discomfort[2]	91.5	93.4	6.6*	14.9*
Thoracic pain or discomfort	85.4	89.4	10.6#	13.5#

[1]Scan J Rheumatol 1988;17:475-81 ^ $0.10 < p < 0.05$ * $p < 0.01$ # $p > 0.05$

[2]J Rheumatol 1988;15;836-9

Disclosure: S. Van Der Linden, None; **H. Baumberger**, None; **M. A. Khan**, None.

Abstract Number: 2178

Statin Use and Increased Risk of Musculoskeletal Conditions: A Retrospective Cohort Study with Propensity Score-Matching

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Background/Purpose: Given conflicting evidence regarding statin use and the relationship with musculoskeletal

conditions, and the rising disability and societal/personal repercussions associated with both osteoarthritis (OA) and back pain, understanding predisposing exposures (including medication related) deserve further attention. The objective of this study was to examine the association between statin use and the risk of being diagnosed with non-traumatic arthropathies, back disorders, and use-related injury in a propensity score-matched cohort with long-term follow-up.

Methods: This was a retrospective cohort study using clinical, administrative, and pharmacy data from 10/2003-3/2012 from patients enrolled in the military health care system in the San Antonio Multimarket region. Two treatment groups were defined: statin-users (those who newly received statins for ≥120 days) and non-users (included patients before initiating statins or never used statins). We excluded prevalent statin users, patients who had < 2 years of baseline period, or <1 medical encounter at followup period. A propensity score-matched cohort was generated to match statin-users and non-users using 115 variables (including personal history, social history, family history, healthcare utilization, baseline period start date, followup duration, comorbidities, Charlson comorbidity index, use of various classes of medications, and undergoing invasive and noninvasive cardiovascular procedures during the baseline period). Outcomes assessed included ICD-9 diagnoses codes for validated AHRQ disease categories of: non-traumatic arthropathies (ex. OA), back disorders (ex. intervertebral disc disorders), and use-related injury (ex. sprains and strains). As primary analysis (for space consideration we do not include the secondary and sensitivity analyses), we examined odds ratios of outcomes in statin-users and nonusers in the propensity score-matched cohort using conditional logistic regression analysis.

Results: A total of 60,455 patients were identified. We propensity score-matched 6728 non-users with 6728 statin-users (52 years of age, ~47% women). Statin users had a higher odds of non-traumatic arthropathies (odds ratio (OR) 1.17; 95%CI 1.09-1.25), back disorders (OR 1.27; 95%CI 1.19-1.36), and use related injury (OR 1.11; 95%CI 1.03-1.19).

Conclusion: Statin use was associated with a significant increase risk of non-traumatic arthropathies, back disorders, and use-related injury. These data challenge several existing studies implicating a protective effect of statins on musculoskeletal conditions. Our results provide additional motivation to further investigate the overall impact of statin therapy on musculoskeletal health, specifically if prescribed for primary prevention in physically active individuals.

Disclosure: U. E. Makris, VA health services grant, 2; **C. A. Alvarez**, None; **E. M. Mortensen**, None; **I. Mansi**, None.

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What Are the Risk Factors for Knee Pain, Radiographic Knee Osteoarthritis and Total Knee Replacement in Professional Footballers?

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Background/Purpose: Football is the world's most popular team sport. However, whether professional footballers have a higher prevalence of knee injury and subsequently, knee pain (KP), radiographic knee osteoarthritis (RKOA) and total knee replacement (TKR) than the general population remains largely unknown. We therefore undertook a population-based study comparing ex-professional footballers and the general population to (1) determine the prevalence of KP, RKOA and TKR; and (2) investigate the specific risk factors associated with these three conditions. This is the second part of the project, aiming to determine the specific risk factors that are associated with KP, RKOA and TKR within footballers.

Methods: A case control study was undertaken in footballers, where cases were defined as footballers with KP, RKOA or TKR and controls were those without these outcomes. A questionnaire survey was undertaken in 4775 retired professional footballers in the UK, via Football Clubs and organisations (including the Professional Footballers Association). 1207 footballers (25.3%) responded to the survey and 472 additionally agreed to undergo standardised bilateral knee radiographs. Potential risk factors were collected through the questionnaire. KP was defined as pain in or around the knees for most days of the last month. RKOA was assessed via weight-bearing semi-flexed posterior-anterior and 30° flexion skyline views and graded using the Kellgren-Lawrence (KL) system (RKOA defined as KL$\geq$3) and the Nottingham Line Drawing Atlas (NLDA). TKR was a self-reported measure, confirmed in some by x-ray. Significant risk factors for each outcome were determined using multivariate logistic regression and reported as odds ratio (OR) with 95% confidence interval (CI).

Results: The prevalence of KP in footballers was 52.2%, which is twice as common as the general population (25.2% reported in Study Part 1 abstract). Knee injury and its subsequent investigations/interventions (exploratory and/or corrective surgery) and management (intra-articular knee injections) were associated with KP. While a number of other significant risk factors were identified for KP, very few were identified for RKOA and none for TKR (Table 1).

Risk Factors	**Odds Ratio**, OR (95% Confidence Interval, CI)		
	KP	RKOA	TKR
BMI (≥25kg)	1.07 (1.04 – 1.10) ‡	0.95 (0.50 – 1.82)	0.92 (0.60 – 1.41)
Digit (2D:4D) Ratio	1.34 (1.05 – 1.72) *	1.00 (1.00 – 1.00)	1.02 (0.70 – 1.50)
Familial Knee OA	1.85 (1.37 – 2.51) ‡	0.74 (0.39 – 1.40)	0.80 (0.49 – 1.29)
Familial Hip OA	1.50 (1.06 – 2.11) *	0.68 (0.31 – 1.51)	1.04 (0.62 – 1.75)
Familial Hand OA	1.63 (1.18 – 2.25) †	0.48 (0.22 – 1.06)	1.04 (0.64 – 1.69)
Familial Knee Replacement	1.21 (0.87 – 1.71)	0.87 (0.43 – 1.77)	0.66 (0.62 – 1.20)
Constitutional Malalignment	1.28 (0.93 – 1.76)	0.87 (0.39 – 1.96)	1.13 (0.69 – 1.82)
Joint Injury	4.22 (3.26 – 5.48) ‡	1.71 (0.91 – 3.20)	1.14 (0.78 – 1.68)
Surgical Intervention #	4.19 (3.23 – 5.43) ‡	3.08 (1.50 – 6.31) †	0.97 (0.66 – 1.41)
Injections	2.55 (2.01 – 3.25) ‡	1.81 (1.06 – 3.07) *	0.87 (0.60 – 1.25)

Table 1 #surgical intervention, which includes exploratory, corrective and/or lesser surgery. OR adjusted for age and BMI; *p<0.05, †p<0.01, ‡p<0.001

Conclusion: Knee injuries, together with subsequent investigations (specifically exploratory and interventional arthroscopy) and management (specifically intra-articular knee injections), were strongly associated with risk of later KP and RKOA. Football organisations need to be mindful of these data and apply strategies to minimise the risk of knee injury (and subsequent investigation and management) in professional football players.

Disclosure: S. M. Parekh, Arthritis Research UK, 2; **G. S. Fernandes**, Arthritis Research UK, 2; **J. P. Moses**, Arthritis Research UK, 2; **C. Fuller**, Arthritis Research UK, 2; **B. Scammell**, Arthritis Research UK, 2; **M. Batt**, Arthritis Research UK, 2; **W. Zhang**, Arthritis Research UK, 2; **M. Doherty**, Arthritis Research UK, 2.

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Abstract Number: 2180

Association of Anterior Cruciate Ligament/Meniscal Injury with Knee Function, Knee Pain, and Knee Osteoarthritis in Military Officers

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Background/Purpose: Traumatic knee injuries, such as injuries to the anterior cruciate ligament (ACL) and menisci, are associated with early onset osteoarthritis (OA). Our understanding of the pathobiology underlying this association is limited, and detailed studies of knee injury populations are needed. This longitudinal study examined the association between knee injury and function, pain, and OA in a cohort of military officers. The precipitating effect of injury on OA has not previously been studied in this population, which has a high rate of knee injury.

Methods: We assessed pain, function, and OA in military officers with a prior history of ACL/meniscal injuries (knee injury subcohort) and compared them to a group of injury-free participants (injury-free subcohort). Both subcohorts were drawn from an existing cohort of 6452 military officers enrolled between 2004 and 2008, when participants were matriculating cadets at the U.S. Air Force Academy, U.S. Military Academy, or U.S. Naval Academy. The knee injury subcohort had ACL or meniscal injuries prior to, or during, their 4-year academy career (n=106). The injury-free subcohort was site-matched from the same source cohort and had no history of ACL/meniscal injuries (n=108). Injury status was verified via re-administration of injury history questionnaire (all injuries) and clinical record review (post-matriculation injuries). Both groups completed a questionnaire between 08/11/15 and 05/10/16 that assessed physician-diagnosed OA, patient-reported knee outcomes (Knee injury and OA Outcome Score, or KOOS), and a single-item measure for knee pain, aching, or stiffness (5-point Likert scale) in the past 30 days. Data were analyzed using descriptive statistics and log-binomial regression models. KOOS scores were scaled (0=extreme deficit, 100=no deficit).

Results: Mean age was 27.7 years (injured: 27.7 years; non-injured 27.7 years) and 38% were women (injured: 34%; non-injured: 42%). Mean weight was 77.4 kg and body mass index was 25.1 kg/m^2. Mean time from first ACL/meniscal injury to follow-up assessment was 8.5 years. Among the subjects with a history of ACL/meniscal injuries, nearly one in ten (10/108) had been diagnosed with knee OA. In comparison, none of the non-injured (0/106) had been diagnosed with knee OA (p=0.0357). ACL/meniscal injury subjects had clinically-relevant deficits on KOOS symptoms, sports/recreation (SR) and quality of life (QOL) scales (mean differences: -7.1, -7.6 and -10.5 respectively, all p<0.0001). Deficits on KOOS pain and activities of daily living scales were smaller and not clinically-relevant (mean differences: -4.3 and -2.6 respectively, both p<0.01). Over one-third of ACL/meniscal injury subjects endorsed (moderate/severe) the single-item question about knee pain, aching, or stiffness in the past 30 days (39/108), compared to 11% of non-injured (12/106, p=0.0001).

Conclusion: By the midpoint of their military careers, officers with a history of ACL/meniscal injury have deficits in knee-related QOL and physically-vigorous knee function (KOOS SR). Their OA prevalence (10% by age 28) is concerning given their youth and the physically-demanding nature of their profession.

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Abstract Number: 2181

High Dietary Fiber Intake Is Associated with Lower Likelihood of Severe Knee Pain Trajectory

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High Dietary Fiber Intake is Associated with a Lower Likelihood of Severe Knee Pain Trajectory

Background/Purpose: Dietary fiber has been found to reduce systemic inflammation and body weight, both of which are linked with joint pain in knee osteoarthritis (OA). In this study, we assessed the association between fiber intake and knee pain trajectories over time.

Methods: In the Osteoarthritis Initiative of 4,796 participants with or at risk of knee OA, dietary fiber intake was estimated using a validated food frequency questionnaire at baseline and sex-specific quartiles of dietary fiber were created. Knee pain score was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline and annually for 8 years, and ranged from 0 (no pain) to 20 (worst pain). Group-based trajectory modeling was used to identify distinct WOMAC pain patterns with knee replacement (KR) cases censored at time of surgery. We used multivariable polytomous regression to assess dietary fiber and pain trajectories.

Results: Of the 4,075 participants (8,150 knees) remaining at year 8, baseline age [mean (SD)] was 61.3 (9.1) years and BMI was 28.6 (4.8) kg/m^2. During the 8-year course, 4.9% of the subjects underwent KR. We identified four distinct pain trajectories with the mean posterior probabilities ≥0.87 (**Figure**). None of the trajectories suggested substantial worsening of pain over time. Compared with the group of no pain, participants who had higher dietary total fiber had a lower likelihood of being in the severe pain group (p-trend<0.08) with those at the highest quartile having a statistically significant 29% lower likelihood of being in this group (**Table**).

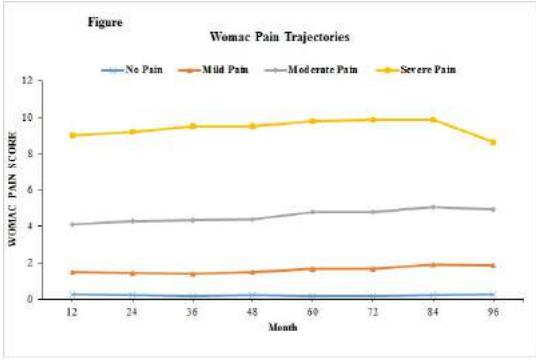
Similar results were found for grain fiber with severe pain trajectory (p-trend<0.01). Results were similar among those with radiographic OA defined by Kellgren-Lawrence grade ≥2 at baseline or when selecting the more painful knee based on WOMAC score. Because improvement in pain was noted between baseline and month 12 for all trajectories, we examined the relation of fiber intake and WOMAC trajectories starting at month 12, and the results did not change materially.

Conclusion: Our study suggests that higher dietary total or grain fiber was inversely related to a pain trajectory characterized by severe pain over 8 years.

Table

	Dietary total fiber			
	Quartile (Q)1 [Lowest]	Q2 vs. Q1	Q3 vs. Q1	Q4 [Highest] vs. Q1
Median (IQR) (g/day)	8.6 (6.4,11.3)	12.5 (9.9, 15.5)	15.1 (12.4, 18.9)	20.6 (16.2, 26.3)
Pain trajectory groups				
No pain (n=2,848)	% 22.4	24.3	25.9	27.3
	Reference (1.00)			
Mild pain (n=3,102)	% 23.9	26.1	24.3	25.8
	Model 1*	1.15 (0.97,1.37)	0.90 (0.76,1.07)	1.04 (0.87,1.23)
	Model 2	1.18 (0.99,1.42)	0.93 (0.78,1.12)	1.11 (0.92,1.33)
Moderate pain (n=1,697)	% 27.9	25.1	25.5	23.5
	Model 1	0.91 (0.75,1.10)	0.81 (0.67,0.97)	0.73 (0.60,0.89)
	Model 2	0.98 (0.80,1.21)	0.91 (0.74,1.11)	0.86 (0.70,1.07)
Severe pain (n=503)	% 36.7	25.8	21.5	19.2
	Model 1	0.62 (0.46,0.83)	0.69 (0.51,0.92)	0.54 (0.39,0.74)
	Model 2	0.72 (0.52,0.996)	0.91 (0.66,1.24)	0.71 (0.50,0.995)

IQR: Interquartile range;* Model 1: Adjusted for age (years), sex (men vs. women), race (white vs. non-white), BMI (baseline, kg/m^2), total calorie intake (kcal); Model 2: further adjusted for education level (below vs. college or above), tobacco use (never, former, current smokers), physical activity (PASE, continuous), depression scale (CES-D: <16 vs. ≥16), baseline radiographic OA status (yes vs. no), and NSAID use (yes vs. no).



Disclosure: Z. Dai, None; **N. Lu**, None; **J. Niu**, None; **D. T. Felson**, None; **Y. Zhang**, None.

Abstract Number: 2182

Levels of Severity of Hip and Knee OA – Validation of Lay Descriptions

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Background/Purpose: Estimating the proportion of the population with severe OA is useful for health service planning. To calculate the proportion of the population with mild, moderate or severe OA, the Global Burden of Disease 2010 Study (GBD2010) used published WOMAC scores. From this, the proportion of the population in high income countries with mild OA was estimated as 71%, moderate 27% and severe 2%. Lay descriptions of levels of severity of OA were developed for GBD2010. If these are accurate measures of disease severity, these descriptions would be useful additions to population-based health questionnaires or brief assessments in clinical practice. The aim of this study is to validate lay descriptions of mild, moderate and severe OA and determine the proportion of a cohort within each category.

Methods: The descriptions were presented to the KHOALA cohort comprising OA knee and hip prevalent cases recruited as a representative sample of French patients with clinical and radiographic OA. Participants indicated which description they felt best described their condition. An additional level of "No pain or disability" was added for this cohort. Mild OA was described as "Has pain in the leg, which causes some difficulty running, walking long distances, and getting up and down" Moderate OA: "Has moderate pain in the leg, which makes the person limp, and causes some difficulty walking, standing, lifting and carrying heavy things, getting up and down and sleeping" Severe OA: "Has severe pain in the leg, which makes the person limp and causes a lot of difficulty walking, standing, lifting and carrying heavy things, getting up and down, and sleeping" Participants also completed WOMAC, EQ5D, EUROQOL VAS and walking times.

Results: Currently, 307 participants have completed the questionnaire with results shown in the table below. There was a significant trend for the WOMAC, EQ5D, EUROQOL and Maximal walking time to decline as the self-reported level of severity moved from none through mild and moderate to severe. The lay descriptions show significant convergent and divergent validity with the standardized measures used.

Conclusion: These preliminary results suggest that the lay descriptions are understandable by participants in this cohort. Those who rated their condition as consistent with the severe description also scored worse on the measures of pain and function. 14% classified themselves as having severe OA, in contrast to GBD2010, where

only 2% were classified as severe OA. The burden of OA may in fact be greater than reported in GBD2010 as the proportion of the population living with more severe disease may have been underestimated. Further assessment is being undertaken with a larger sample of the KHOALA cohort. These lay descriptions may be useful as a brief starting point for discussions in clinical care, or a contribution to the assessment of severity of OA.

	No pain/ Difficulty Mean (sd)	Mild Mean (sd)	Moderate Mean (sd)	Severe Mean (sd)	P value
n	49	135	80	43	
% of total	16.0	44.0	26.1	14.0	
Age	63.3 (7.1)	60.5 (8.1)	62.1 (8.7)	61.3 (8.0)	
WOMAC Pain [0-20]	3.0 (2.3)	5.2 (2.6)	7.5 (2.9)	11.0 (2.9)	<0.0001
WOMAC Function [0-68]	11.4 (8.8)	16.8 (9.4)	25.1 (12.3)	36.9 (9.3)	<0.0001
EQ5D [0,1]	0.9 (0.1)	0.8 (0.2)	0.7 (0.2)	0.4 (0.3)	<0.0001
EUROQOL VAS [0,100]	76.2 (12.1)	72.8 (15.1)	63.8 (15.0)	52.7 (14.9)	<0.0001
Maximal walking time	90.9 (53.3)	95.7 (84.9)	55.5 (47.7)	19.1 (12.1)	<0.0001

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Abstract Number: 2183

The Electronic Osteoarthritis Knee and Hip Quality of Life (OAKHQOL) Questionnaire: A Useful and Valid Alternative to Measure Health-Related Quality of Life in Knee Osteoarthritis

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Background/Purpose: With the growing development of new technologies in clinical research, an electronic version of the OsteoArthritis Knee and Hip Quality Of Life (OAKHQOL), the e-OAKHQOL, has been formulated. This study aims to assess the validity of the e-OAKHQOL questionnaire and analyze whether the answers were affected by the form of administration (electronic versus paper).

Methods:

Two samples of patients with knee osteoarthritis (ACR criteria) were constituted. The first was composed of subjects, recruited by their general practitioner and who could choose to respond to the electronic or paper version. The second included subjects who responded to the paper version and were matched with respondents to the electronic version in the first sample. The OAKHQOL questionnaire contains 43 items, 3 of them are independent, and describes health-related quality of life (HRQoL) in 5 dimensions: physical activity, mental health, pain, social functioning and social support. A total score is normalized to a score from 0 (worst HRQoL) to 100 (best HRQoL). Two complementary analytical methods were used, the classical test theory (CTT) and a Rasch measurement model for item response theory (partial credit model).

Results: The electronic form was preferred by 471 (89.7%) patients. Among them, 345 were matched to the respondents of the paper version. The percentage of missing responses was lower in electronic than paper form (1.6% versus 2.0%, p = 0.01). The confirmatory factor analysis showed that the 4 or 5-factor models best fit with the data, although the CFI value was slightly below 0.9 (RMSEA value was below 0.08 as expected for model with good fit). Discrimination was good for the physical activity, mental health and pain dimensions. Rasch analysis revealed four items with underfitting. Internal consistency was excellent for dimensions Physical Activities (PSI = 0.96) and mental health (PSI = 0.93) but were slightly less than 0.85 for the other dimensions. No meaningful differential item functioning was detected for the mode of instrument administration, gender, age, educational level, low-back pain and BMI.

Conclusion:

Analysis with CTT and Rasch measurement of the e-OAKHQOL questionnaire revealed the good measurement properties of the five dimensions, so it may be a valuable alternative to the paper form. The instrument may offer many advantages in research and routine clinical practice such as immediate availability of the patient's score and better collection of data.

Disclosure: M. Wieczorek, None; **C. Rotonda**, None; **F. Guillemin**, None; **A. C. Rat**, None.

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Abstract Number: 2184

Evidence Based Physical Activity Threshold to Predict Improved/High Function in Older Adults with Lower Extremity Conditions: The Osteoarthritis Initiative

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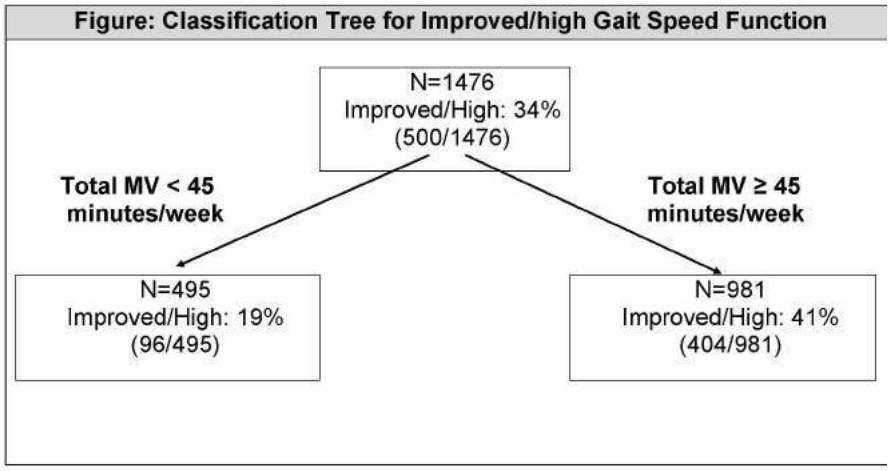
Background/Purpose: Physical activity guidelines for adults stipulate at least 150 minutes/week moderate-to-vigorous (MV) intensity physical activity acquired in bouts lasting 10 minutes or more (MV-bout). But, 2 in 5 adults with lower-extremity conditions not only fail to meet guidelines, they are physically inactive, not performing a single 10 minute MV-bout session of MV activity in a week. The objective of this study is to identify evidence-based thresholds related to improved low function or sustained high function (improved/high) among adults with lower limb joint symptoms.

Methods: Adults with symptomatic (pain/aching/stiffness) lower extremity joints from an Osteoarthritis Initiative accelerometer substudy had gait speed (n=1476) and self-reported SF-12 physical component score (PCS) function (n=1629) assessed two years apart. Year2 function compared to baseline assessed as improving to a better or remaining in the best (i.e., maintaining high) 2-year function quintile. Alternative physical activity metrics (sedentary, light intensity activity, total MV activity, and non-sedentary minutes/week) were evaluated against the legacy MV-bout metric to predict improved/high function using the area under the receiver operating curve (AUC). Classification tree analysis identified minimum threshold levels.

Results: Two years later 34% of adults (aged 40-83) had improved/high gait speed and 38% had improved/high SF-12 PCS function. Only total weekly MV activity was a stronger significant predictor of improved/high function (greater AUC) than the legacy MV-bout metric for both gait speed and SF-12 function and the only predictor selected by classification tree analyses (Figure 1). Meeting the 45 total MV minute/week threshold increased the relative risk (RR) for improved/high function (gait speed RR 1.8, 95% CI: 1.6 to 2.1; self-reported physical function RR 1.4, 95% CI: 1.3 to 1.6) compared to less active adults. Thresholds were consistent across sex, BMI, knee OA status and age.

Conclusion: Meeting an evidence-based threshold of 45 total MV minutes/week increased the likelihood of function preservation in high functioning persons and improvement in those with functional limitations among adults having lower limb joint symptoms. This threshold is a less demanding goal than the current guidelines in two ways. First, all time spent in MV activities contributes to attaining the 45 minute goal in contrast to the legacy MV-bout threshold which is only met through activity acquired in bouts lasting at least 10 minutes. Second, 45 minutes/week may be a more feasible goal than the current 150 minutes/week minimum. This evidence-based threshold represents an intermediate goal towards achieving the current physical activity guideline for adults with lower limb symptoms.



Disclosure: **J. Song**, NIH, 2; **J. Lee**, NIH, 2; **P. Semanik**, NIH, 2; **A. Gilbert**, NIH, 2; **L. S. Ehrlich-Jones**, NIH, 2; **C. Pellegrini**, NIH, 2; **D. Pinto**, NIH, 2; **R. W. Chang**, NIH, 2; **B. Ainsworth**, None; **D. D. Dunlop**, NIH, 2.

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Abstract Number: 2185

Prevalence and Trends in Prescribed Opioid Use Among US Adults with Arthritis, 2008-2013, Medical Expenditure Panel Survey

Jennifer M. Hootman[1], Miriam Cisternas[2], Louise Murphy[3] and Jan Losby[4], [1]Centers for Disease Control and Prevention, Kennesaw, GA, [2]MCG Data Services, Carlsbad, CA, [3]Division of Population Health, Centers for Disease and Control, Atlanta, GA, [4]Division of Unintential Injury Prevention, Centers for Disease Control and Prevention, Atlanta, GA

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Background/Purpose: <span">Since 1999, overuse deaths from opioids in the US has quadrupled with

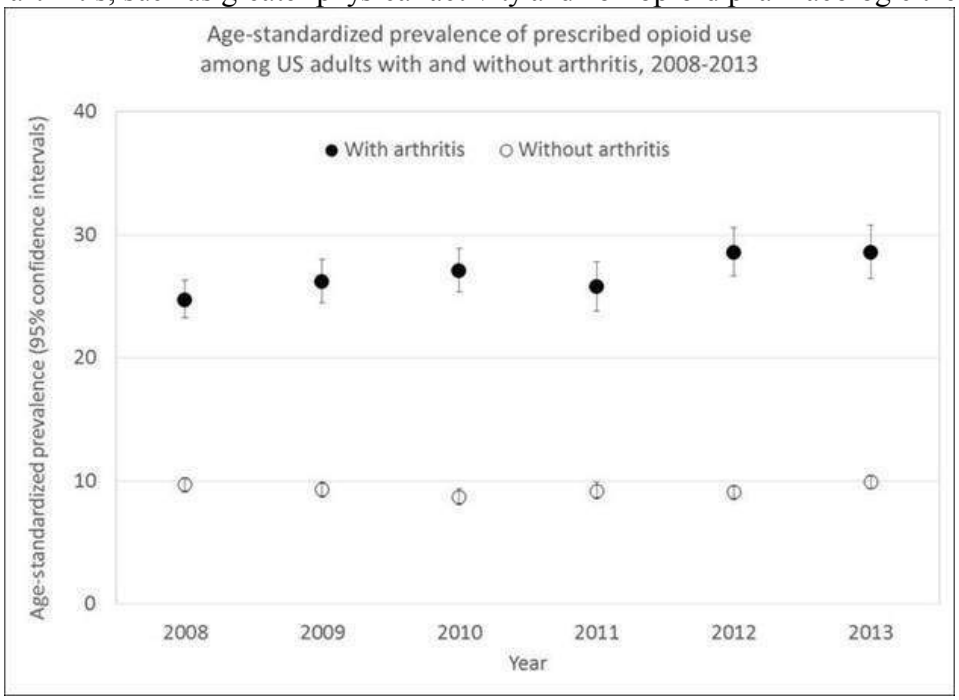
prescription use driving the epidemic. From 1999 to 2014, more than 165,000 persons died from overdose related to opioid pain medication in the United States. The 2012 American College of Rheumatology Osteoarthritis treatment guidelines provide limited guidance, using the GRADE evidence rating system, on opioid prescribing: opioids are conditionally not recommended for hand OA and there is no recommendation for knee and hip OA. National US population-based estimates of prescribed opioid use among adults with arthritis are unknown; therefore, we examined prevalence of and trends in use (2008-2013) among adults with and without arthritis; among those with arthritis, we estimated prevalence of use across selected socio-demographic characteristics.

Methods: <span">We analyzed 2008 to 2013 Medical Expenditure Panel Survey (MEPS) data. MEPS is annual survey designed to represent the US civilian non-institutionalized population. For each year, we categorized respondents as using prescribed opioids if they reported filling ≥ 1 narcotic analgesics prescription during that year. We categorized respondents as having arthritis if they reported ≥ 1 of ICD-9-CM 274, 710, 712 – 716, 719, and 729.

Results: <span">In 2013, 36.6 million (15.4%) US adults filled an opioid prescription and US adults with arthritis comprised approximately half (53%) of all US adults taking prescribed opioids. Prevalence among those with and without arthritis was 29.3% (95% confidence interval [CI] =27.4-31.1) and 9.9% (95% CI=9.3-10.4), respectively. From 2008 to 2013, prescribed opioid use prevalence (age-standardized) rose by 4 percentage points (4.4 million) among adults with arthritis (2008=24.7%; 95% CI=23.3-26.3; 2013=28.6%; 95% CI=26.5-30.8) but remained constant among adults without arthritis (Figure). Adults with arthritis with the highest prescribed opioid prevalence were those who were publicly insured only (37.8%), had < high school education (33.7%), some college/associate degree (32.2%), high school graduate (31.9%), or were non-Hispanic Blacks (31.8%). <span">

Conclusion: <span"><span">In 2013, US adults with arthritis represented more than half of prescribed opioid users in the general population of US adults with nearly 1 in 3 US adults with arthritis filling an opioid prescription. Using the US Centers for Disease Control and Prevention March 2016 opioid prescribing guideline for managing chronic pain may reduce high prescribing for this population and optimize pain management care while improving patient safety. The arthritis population may also benefit from attention to strategies outlined in the recent National Pain Strategy and greater use of evidence-based, non-pharmaceutical methods of reducing joint pain for arthritis, such as greater physical activity and non-opioid pharmacologic therapies. <span">

Conclusion:



Disclosure: J. M. Hootman, None; **M. Cisternas**, None; **L. Murphy**, None; **J. Losby**, None.

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Abstract Number: 2186

Analgesic Use and Subsequent Risk of Falls in Participants with or at Risk of Knee Osteoarthritis

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Background/Purpose: Analgesics including opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), antidepressants, and nutraceuticals are commonly used for pain relief in osteoarthritis (OA). Although it has been reported that opioids and some antidepressants may increase the risk of falls, results from studies assessing the association between analgesic use and falls are mixed. Prior studies were limited by focusing on a single fall as the outcome, and lack of adjusting for pain severity, concurrent use of other medications associated with falls (e.g., anticholinergics), and other potential confounders. Our objective was to assess the association between type of analgesic use and subsequent risk of falls among participants with or at risk of knee OA.

Methods: We performed a longitudinal analysis with 4 years of follow-up (n=4,511) from the Osteoarthritis Initiative (OAI) cohort study. Analgesic use was identified through medication inventory and/or questionnaires. We grouped patients into 6 exclusive subgroups based on annually assessed analgesic use in the following hierarchical order of potency: (1) opioids, (2) antidepressants, (3) prescription NSAIDs, (4) over-the counter (OTC) NSAIDs/aspirin and other pain medications, (5) nutraceuticals, and (6) no analgesic use. We used multivariate logistic regression with generalized estimating equations to estimate the effect of analgesic use on the subsequent risk of any fall and recurrent falls in the following year, adjusted for sociodemographics, health status/behavior (e.g., pain severity, concurrent use of other medications related to falls), and access-to-care factors.

Results: Overall analgesic use decreased from 64.8% at baseline to 52.8% at the 4-year follow-up visit. In contrast, opioid use increased from 2.9% to 3.5% over this same time period. In each annual follow-up period, approximately 33% of participants self-reported at least one occurrence of a fall and 15% reported recurrent falls (i.e.≥ 2). Compared to those without any analgesic use, participants in the opioid and antidepressant groups had modest increased odds of both any fall (opioids: adjusted OR [aOR]: 1.37, 95% CI 1.08-1.74; antidepressants: aOR=1.27, 95% CI: 1.09-1.48) and recurrent falls (opioids: aOR: 1.34, 95% CI 1.00-1.80; antidepressants: aOR=1.34, 95% CI: 1.10-1.64; **Table 1**). Participants in the OTC NSAIDs/other pain medications group had a 24% higher odds of recurrent falls.

Conclusion: Opioids and antidepressants were associated with a modest increased risk of both any fall and recurrent falls after adjustment for pain severity and other potential confounders, among participants with or at risk of knee OA. Clinical management of pain with opioids and antidepressants among those at risk of falling warrants caution. Future research is needed to exmine and better understand the association between risk of falls and the use of OTC NSAIDs/other pain medications.

Table 1. Multivariate models of analgesic use and subsequent risk of falls

	aOR*	(95% CI)
Any falls		
No pain medications	1.00	reference
Opioids	1.37	(1.08, 1.74)
Antidepressants	1.27	(1.09, 1.48)
Prescription NSAIDs	1.08	(0.93, 1.25)
Over-the-counter NSAIDs and other pain medications	1.13	(0.99, 1.28)
Nutraceuticals	1.08	(0.95, 1.24)
Recurrent falls		
No pain medications	1.00	reference
Opioids	1.34	(1.00, 1.80)
Antidepressants	1.34	(1.10, 1.64)
Prescription NSAIDs	1.10	(0.89, 1.35)
Over-the-counter NSAIDs and other pain medications	1.24	(1.05, 1.47)
Nutraceuticals	1.19	(0.99, 1.42)

Abbreviations: NSAIDs: non-steroidal anti-inflammatory drugs; OR: odds ratio, CI: Confidence Interval *Multivariate models were adjusted for sociodemographics (age, sex, race, marital status, education), time-varying health status/behavior (Charlson's comorbidity index, history of knee surgery, depression, BMI, K/L grade, WOMAC total scores, KOOS symptom subscale, pain severity, Short Form-12 health survey, anticholinergic, diuretic, and muscle relaxant use), and access to health care factors (i.e., health insurance coverage, annual household income).

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Abstract Number: 2187

Vitamin D Levels and Fragility Fractures in Postmenopausal Portuguese Women- Results from Epireumapt

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Background/Purpose: Vitamin D is implicated in bone homeostasis and its deficiency is associated with a progressive bone loss and fragility fractures. Our aim was to characterize vitamin D levels in Portuguese post-menopausal woman and evaluate its association with prevalent osteoporotic vertebral fractures (VF) and vertebral bone mineral density (BMD).

Methods: The present study was conducted under the scope of EpiReumaPt cross-sectional, population-based study. The study population was women ≥ 65years-old from EpiReumaPt (882 participants representative of Portuguese postmenopausal women). 25- hydroxyvitamin D serum levels were determined and Vitamin D insufficiency was defined as <30ng/ml and Vitamin D deficiency as <10ng/ml. Clinical Risk factors for fractures and OP treatment were assessed. Ten-year risk of fractures was calculated using FRAX tool. VF were evaluated by CT Scan and classified using the Genant method. Vertebral BMD was performed and osteoporosis was defined using the t-score cut-offs of the World Health Organization. Prevalence estimates were computed as weighted proportions for take into account the sampling design. Multivariate regression models were used to assess the association of vitamin D levels and VF and BMD. Age, body mass index, NUTS II, seasons and glomerular filtration rate were considered as possible confounders.

Results: Vitamin D insufficiency was present in 38.4% of Portuguese postmenopausal women and 14.2% had vitamin D deficiency. The prevalence of osteoporosis was 15% and of VF was 11.7% among Portuguese postmenopausal women. Regarding clinical risk factors 49.1% of postmenopausal women reported having at least one previous fragility fracture independently of the localization. The mean10-year risk for a major fracture was 9.9 ± 9.5 % and for hip fracture was 4.4 ± 7.2%. A significant number of postmenopausal women had ≥10% of 10- year risk for major fracture (38.2 %) and of postmenopausal women had ≥3 % of 10-year risk for hip fracture (7.9 %). Only, 53% of the OP postmenopausal women were under treatment. Vitamin D deficiency was independently associated with prevalent VF (OR=15.9; 95%CI 1.93,130.55; p= 0.010) but not with vertebral BMD (β= -0.016; 95%IC -0.178, 0.146; p=0.848). Vitamin D insufficiency was not significantly associated with VF or with BMD.

Conclusion: Portugal is a sunny country of Southern Europe**,** levels of vitamin D are below the recommended levels for a large proportion of post-menopausal Portuguese women and this fact is associated with vertebral fragility fractures. Vitamin D supplementation recommendations should be reviewed and public health policies should address this issue.

Disclosure: A. M. Rodrigues, None; **A. C. Rodrigues**, None; **M. Eusebio**, None; **P. S. Coelho**, None; **J. M. Mendes**, None; **J. C. Branco**, None; **H. Canhão**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/vitamin-d-levels-and-fragility-fractures-in-postmenopausal-portuguese-women-results-from-epireumapt

Abstract Number: 2188

Association Between Extent of Symptomatic Joint Involvement in Osteoarthritis and Comorbid Lung Disease in Patients Scheduled for Joint-Replacement Surgery

Anthony V. Perruccio[1,2,3], Rajiv Gandhi[4], J. Denise Power[5,6] and Elizabeth M. Badley[7], [1]The Arthritis Program, University Health Network, Toronto, ON, Canada, [2]Dalla Lana School of Public Health, University of Toronto, Toronto, ON, Canada, [3]Health Care & Outcomes Research, Krembil Research Institute, University Health Network, Toronto, ON, Canada, [4]University Health Network, Arthritis Program, Toronto, ON, Canada, [5]Arthritis Program, Toronto Western Hospital, University Health Network, Toronto, ON, Canada, [6]Dalla Lana School of Public Health, Toronto, ON, Canada, [7]Toronto Western Research Institute, Toronto, ON, Canada
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Background/Purpose: Comorbidity is highly prevalent in osteoarthritis (OA), although the origin of this is not well understood. The presence of multi-joint symptoms in OA, and noted associations between obesity and OA in non-weight bearing joints, suggests a likely systemic component. Lung disease has also has been associated with obesity and other systemic factors. Our purpose is to investigate the association between the extent of symptomatic joint involvement in patients with OA and prevalent lung disease.

Methods: Patients with end-stage hip and knee OA were recruited from an orthopaedic clinic in 2010-2012. Patient questionnaires captured symptomatic joints, comorbidities (lung disease, heart disease, diabetes, and high blood pressure), BMI (calculated from reported height and weight), smoking status, functional limitations (Western Ontario McMaster University OA Index physical function subscale) and demographic characteristics. Bivariate analysis tested trends in lung disease prevalence by symptomatic joint count categories (1; 2-4; and 5+). Logistic regression analyses evaluated the association between symptomatic joint count (continuous) and lung disease, adjusting for other assessed study measures.

Results: Study sample: 913 individuals scheduled for joint replacement surgery (469 knees and 444 hips). Mean age was 64 years, 44% male. Lung disease was reported by 9.5%. Mean symptomatic joint count was 4.4 (range: 1-20); almost 40% reported ≥5 symptomatic joints. Comparing individuals reporting lung disease with those who did not, those reporting lung disease had significantly higher mean BMI (mean ± SD: 33.2 ± 8.0 vs 29.4 ± 6.2); more previous/current smokers 41.4% vs 23.6%, greater comorbidity (significantly more with heart disease, diabetes, and high blood pressure), and greater symptomatic joint count (mean ± SD: 6.2 ± 4.4 vs 4.2 ± 3.2). A statistically significant increasing trend in lung disease prevalence was observed with joint count categories (1; 2-4; 5+). Logistic regression showed, adjusted for study covariates, each numerical increase in symptomatic joint count was associated with a 7% (OR: 1.07, 95% CI: 1.01, 1.14) increased odds of reporting lung disease. Other independent predictors of lung disease were previous/current smoker (OR: 2.64, 95% CI: 1.32, 4, 5.26), reporting diabetes (OR: 2.37, 95% CI: 1.28, 4.40) and having functional limitations (OR: 1.03, 95% CI: 1.01, 1.06). Females were significantly more likely to report lung disease (OR: 2.40, 95% CI: 1.34, 4.28). There were no significant associations with BMI, high blood pressure or surgical hip or knee group.

Conclusion: Findings suggest that having multi-joint symptoms in OA may increase the probability of concurrent lung disease. This raises questions for OA research including the nature of possible underlying mechanisms.

Disclosure: A. V. Perruccio, None; **R. Gandhi**, None; **J. D. Power**, None; **E. M. Badley**, None.

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Abstract Number: 2189

The Association of Arthritis and Lung Diseases: A Population-Based Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: While rheumatoid arthritis is associated with a number of different lung conditions, the relationship with osteoarthritis, overwhelmingly the most frequent type of arthritis in the population, has been less well studied. Objective: to examine whether arthritis is associated with an increased likelihood of reporting asthma and/or COPD.

Methods: Data from the 2011- 2012 Canadian Community Health Survey, a representative survey of the household population, restricting analyses to the population age >= 35 years (n=88,734). Participants were asked about specific long term health conditions diagnosed by a health professional, including arthritis (excluding fibromyalgia), asthma, and COPD (specifically chronic bronchitis, emphysema or chronic obstructive pulmonary disease). Multinominal logistic regression was used to examine associations between lung conditions (none, asthma only, COPD only, both asthma and COPD) and arthritis, controlling for covariates: age, sex, education, household income, smoking status (never, former, current), body mass index (BMI: underweight, normal, overweight, obese), and mean number of other chronic conditions (out of 9). Sensitivity analysis: a) analyses were restricted to those reporting OA; b) analyses were stratified by BMI categories given the strong association of obesity and arthritis and the possibility of metabolic/inflammatory pathways.

Results: People with arthritis (23 % of the population) more frequently reported lung conditions than those without, respectively asthma only 8.2% vs 5.5%, COPD only 5.4% vs 2.0%, and asthma+COPD 3.4% vs 0.8%. Compared to those without, people with arthritis, were more likely to be current or former smokers (70.3% vs 57.0%), to be obese (26.8% vs 16.7%) and have more other chronic conditions (mean 1.5 vs 0.5). In regression analyses arthritis was significantly associated with all lung conditions: OR (95%CI): asthma only 1.48 (1.26, 1.73); COPD only 1.60 (1.34, 1.91); asthma+COPD 1.98 (1.65, 2.37). The odds of all lung conditions were significantly higher for females. Being a current or former smoker was significantly associated with COPD, but not with asthma. Obesity and the number of other chronic conditions were significant risk factors for reporting all

lung conditions. Sensitivity analyses: results were unchanged when restricted to OA. Analyses stratified by BMI categories gave similar results.

Conclusion: This population-based study confirms a relationship between arthritis and lung diseases, and adds to the scant previous literature. The increased odds of reporting lung diseases by people with arthritis raises questions as to the mechanism. The consistency of the association over BMI categories suggests pathways other than those mediated by metabolic/inflammatory factors. The findings also suggest that recommendations for the management of arthritis should consider the potential implications of having lung disease, for example, for physical activity.

Disclosure: E. M. Badley, None; **M. Maguire**, None; **A. V. Perruccio**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-association-of-arthritis-and-lung-diseases-a-population-based-study

Abstract Number: 2190

Prevalence of Severe Joint Pain Among Adults with Doctor-Diagnosed Arthritis— United States, 2002–2014

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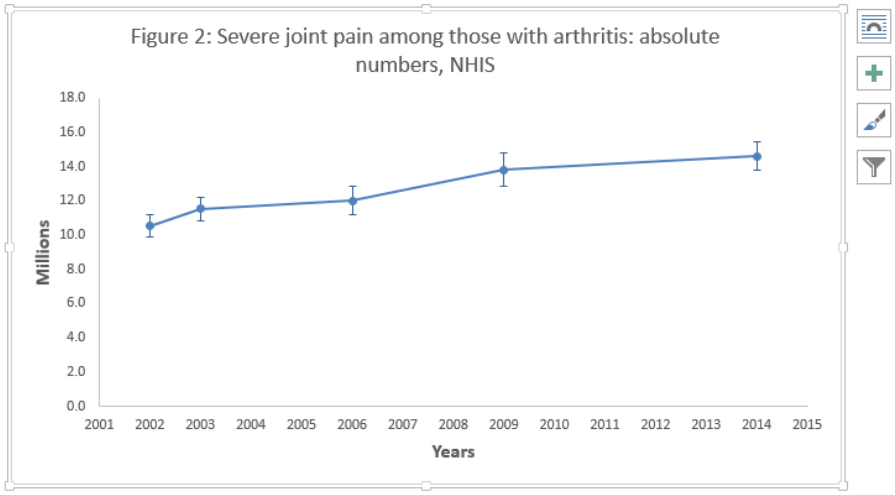
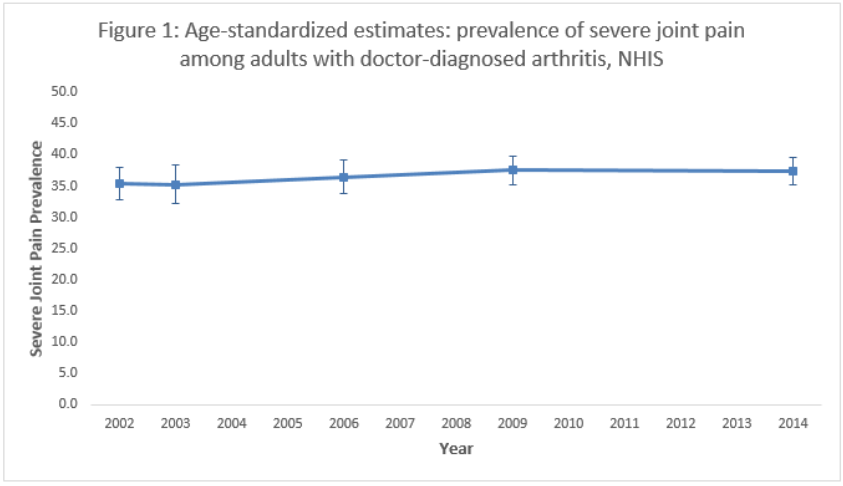
Background/Purpose: Severe joint pain (SJP) from arthritis may reflect insufficiently managed pain, and SJP can limit an individual's ability to perform basic functions. We determined the prevalence of SJP among adults with doctor-diagnosed arthritis, overall and by various sociodemographic and health characteristics in 2014, and examined whether the absolute number and age-standardized prevalence of SJP changed for the years 2002, 2003, 2006, 2009, and 2014.

Methods: We used data from the National Health Interview Survey, an annual, nationally representative, in-person interview survey of health status and behaviors of the noninstitutionalized civilian U.S. population. Unweighted sample sizes and final response rates were 31,044 (74.3%) in 2002; 30,852 (74.2%) in 2003; 24,275 (70.8%) in 2006; 27,731 (65.4%) in 2009; and 36,697 (58.9%) in 2014. Adults were defined as having doctor-diagnosed arthritis if they answered "yes" to "Have you ever been told by a doctor or other health professional that you have some form of arthritis, rheumatoid arthritis, gout, lupus, or fibromyalgia?" Respondents assessed their joint pain on a scale of 0 to 10 in the past 30 days, "where 0 is no pain or aching and 10 is pain and aching as bad as it can be." Severe joint pain was defined as a 7 to 10. Prevalence estimates were age-standardized to the projected U.S. 2000 population (the US public health standard): differences were statistically significant if 95% confidence intervals (CIs) did not overlap.

Results: The age-standardized prevalence of SJP did not differ significantly by year (Figure 1). In 2014, over one third of adults with arthritis had SJP (37.4%) with the highest age-standardized prevalence of SJP among those who had serious psychological distress (66.7%), were unable to work or disabled (61.5%), or identified as non-Hispanic blacks (58.1%). The estimated number of adults with arthritis and SJP increased significantly from 2002 (10.5 million, 95% CI: 9.9-11.1 million) to 2014 (14.6 million, 95% CI: 13.8-15.4 million) (Figure 2).

Conclusion: The prevalence of SJP in the past 30 days remained high (range: 35.3-37.5%) and stable from 2002-2014, but absolute numbers continue to grow and in 2014, was almost 15 million. This is likely due to the aging of the population. Increased dissemination of evidence-based physical activity interventions shown to reduce joint pain in adults with arthritis is needed. National efforts to improve generic pain management (e.g., the 2016 National Pain Strategy) may also help.





Disclosure: K. E. Barbour, None; **M. Boring**, None; **C. Hemlick**, None; **L. Murphy**, None; **J. Qin**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-severe-joint-

Abstract Number: 2191

Arthritis As a Potential Barrier to Physical Activity Among Adults with Depression – United States, Behavioral Risk Factor Surveillance System, 2013

Jennifer M. Hootman[1], Louise Murphy[2], Kamil E. Barbour[3] and Michael Boring[3], [1]Division of Population Health, Centers for Disease Control and Prevention, Kennesaw, GA, [2]Division of Populatio Health, Centers for Disease Control and Prevention, Atlanta, GA, [3]Arthritis Program, Centers for Disease Control and Prevention, Atlanta, GA

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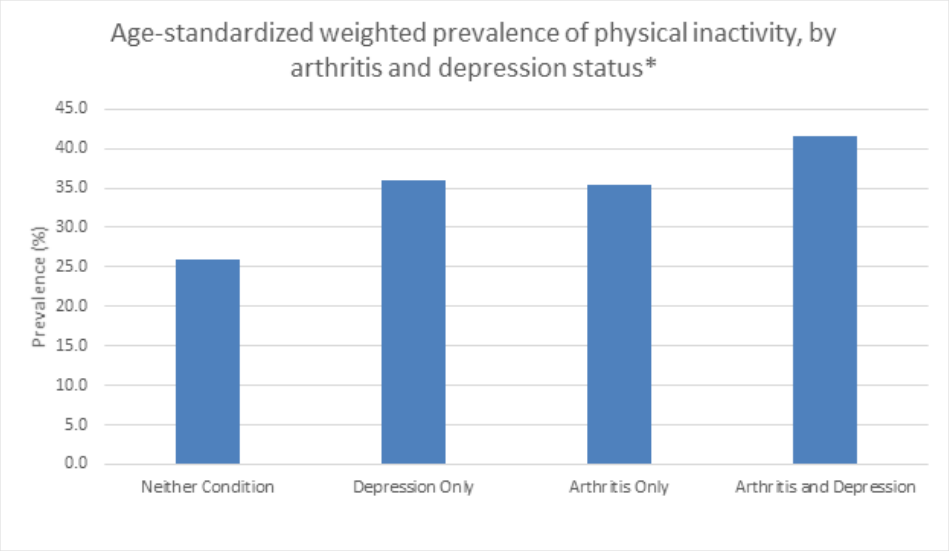
Background/Purpose: Depression is one of the most common mental disorders in the United States, affecting 15.7 million adults. It frequently co-occurs with other chronic conditions (e.g., arthritis), particularly in middle age and older adults. Despite the considerable evidence that physical activity reduces symptoms and adverse effects of arthritis and depression, physical inactivity is highly prevalent among those with these conditions. The study purpose was to estimate the 2013 prevalence of: 1) arthritis among adults with self-reported depression; 2) physical inactivity among adults with depression by arthritis status.

Methods: The Behavioral Risk Factor Surveillance System (BRFSS) is an annual state-based random-digit dialed telephone survey of the civilian, noninstitutionalized US population aged >18 years. Doctor-diagnosed arthritis was defined as a 'yes' to: "Have you ever been told by a doctor or other health care professional that you have arthritis, rheumatoid arthritis, gout, lupus or fibromyalgia?" Self-reported depression was defined as a 'yes' to: "Ever told you have a depressive disorder, including depression, major depression, dysthymia, or minor depression?" Physical activity level was assessed using 6 questions on frequency and duration of participation in activities of moderate and vigorous intensity. Persons reporting no participation in either moderate or vigorous physical activity were classified as physically inactive. The 2013 BRFSS (n= 491,773) weighted median response and cooperation rates were 45.9% and 65.7%, respectively. Calculation of percentages and 95% confidence intervals (CI) accounted for the NHIS' multistage, complex sample design. Percentages were age-standardized using the 2000 US projected adult population provided by the US National Center for Health Statistics.

Results: In 2013, 42.8% (95% CI=42.2-43.5; 18.5 million) of US adults with self-reported depression also had arthritis. Compared to adults with neither condition (25.9%; CI=25.6-26.3), adults with depression only (35.9%; CI=35.2-36.5), arthritis only (35.3%; CI=34.5-36.2), and both depression and arthritis (41.6%; CI=40.3-42.9) had significantly higher prevalence of physical inactivity (Figure).

Conclusion: Depression and arthritis frequently co-occur and the combination is associated with high prevalence of physical inactivity, a missed opportunity to engage in a proven non-pharmaceutical self-management strategy for both conditions. Through universal screening of patients with arthritis for depression,

health care providers may identify a treatable barrier to increasing physical activity.



Disclosure: J. M. Hootman, None; **L. Murphy**, None; **K. E. Barbour**, None; **M. Boring**, None.

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Abstract Number: 2192

Association Between Quality of Sleep and Quality of Life Among Japanese Systemic Lupus Erythematosus Outpatients

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Background/Purpose: Systemic Lupus Erythematosus (SLE) patients are known to have sleep disturbances. Quality of sleep may affect quality of life, but this association has not been systematically evaluated. The aim of this study was to examine the distribution and association of quality of sleep and quality of life among patients diagnosed with SLE.

Methods: SLE outpatients at three rheumatology centers in Western Japan were included in this cross-sectional study. The consented participants completed Japanese versions of the following questionnaires: the Pittsburgh Sleep Quality Index (PSQI), the 12 item Short Form Health Survey (SF-12), and the Lupus Patient-Reported Outcome tool (LupusPRO). Clinical information, including the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI), was obtained from medical records. Correlation coefficients (r) were used to measure the associations between the PSQI and the other factors. Stability of quality of sleep was examined by administering the PSQI at baseline (T1) and 2 weeks later (T2).

Results: The study included 205 SLE patients. The mean age was 47.8±13.6 years (mean SLE duration: 15.0±8.8 years) and >90% were female. The mean SLEDAI score was 3.9±3.7. The majority of the participants (62.9%) had sleep disturbances (PSQI<6.0). Neither the overall PSQI, nor the subcategories were associated with duration of SLE, prednisolone dosage, or SLEDAI. Total PSQI score was weakly associated with all of the SF-12 subcategories (range of r: −0.26–0.39) and showed weak to moderate associations with the LupusPRO subcategories (r: −0.51–0.22), except for “medication”, “procreation”, and “satisfaction with care” (all r<0.20). Analysis of the seven PSQI subcategories revealed that “daytime dysfunction” was weakly to moderately associated with all of the SF-12 subcategories (r: −0.27–0.47) and all of the LupusPRO subcategories (r: −0.59–0.20), except for “procreation” and “satisfaction with care”. However, “sleep duration” was not associated with any of the SF-12 or LupusPRO subcategories. “Sleep efficiency” was weakly associated with “physical health”, “physical function”, and “pain“ in the SF-12 and LupusPRO. “Sleep quality” and “sleep disturbances” were weakly associated with “pain” and the “emotional” and “mental” subcategories in the SF-12 and LupusPRO. The analysis of the stability of sleep quality, revealed a correlation coefficient of 0.79 for the total PSQI scores at T1 and T2. Among the seven PSQI subcategories, the T1 and T2 measurements of “sleep efficiency” and “sleep disturbance” were moderately associated (0.54 and 0.61, respectively), and those for “use of sleep medication” and “sleep latency” were strongly associated (>0.8).

Conclusion: We found that quality of sleep, especially “sleep efficiency”, was poor for the majority of patients in the sample. Quality of sleep was associated with various aspects of quality of life, especially pain, vitality, and emotional health. Management of pain and emotional health may be important for improving quality of sleep in SLE patients.

Disclosure: M. Inoue, None; **K. Makimoto**, None; **K. Shiozawa**, None; **R. Yoshihara**, None; **T. Yamane**, None; **Y. Shima**, None; **T. Hirano**, None.

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Abstract Number: 2193

The Frequency of and Patient Characteristics Associated with Fear of Movement in Adults with Symptomatic Knee Osteoarthritis

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Background/Purpose: Fear of movement is associated with increased pain, decreased physical function, decreased activity, and negative psychological symptoms. Little is known about fear of movement in the context of osteoarthritis. This study examined the frequency of and factors associated with fear of movement among patients with symptomatic knee osteoarthritis (sxKOA), using the new Brief Fear of Movement (BFOM) measure.

Methods: This cross-sectional study is a secondary analysis of data from a randomized exercise trial among patients with sxKOA. Participants (n=350) were recruited from an academic medical center, the community, and an ongoing cohort study. Participants (mean age = 65.3 ± 10.9; 71.7% female; 26.3% nonwhite) had sxKOA based on a physician diagnosis and/or a prior radiograph. The BFOM scale contains 6 items using a 4-point scale ranging from "strongly agree" to "strongly disagree." We examined relationships of BFOM with: age, sex, race (white vs. nonwhite), education (bachelor's degree or higher vs. up to a bachelor's degree), Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and activities of daily living (ADL) subscales, knee symptom duration, depressive symptoms (PHQ-8), falls in the prior 12 months, history of knee injury, family history of knee problems, self-efficacy for exercise (SEE), and unilateral balance test. We created a 3-level ordinal variable, which grouped participants based on agreement ("agree" or "strongly agree') with 0, 1-2, or 3+ items on the BFOM scale. General linear models with trend tests were used to compare participant characteristics across the 3 BFOM categories. A proportional odds logistic regression model with backward selection was used to examine multivariable associations of participant characteristics with the ordinal BFOM variable.

Results: The majority of participants (76%) agreed with at least 1 item on the BFOM scale, and 36% endorsed 3+ items, suggesting high fear of movement. In bivariate analyses, the following were significantly associated ($p<0.05$) with the ordinal BFOM variable: age, KOOS pain, KOOS ADL, PHQ-8, and SEE (Table). In the multivariable model (for which the proportional odds assumption was met), the following remained after backward selection: age (odds ratio (OR) = 0.74 per 10-point increase, 95% confidence interval (CI) = 0.60 – 0.97), KOOS ADL (OR = 0.66 per 10-point increase, 95% CI = 0.54 - 0.90), PHQ-8 (OR = 1.11, 95%CI = 1.04 – 1.20), and SEE (OR = 0.99, 95%CI = 0.97 – 1.00).

Conclusion: Among patients with sxKOA, there was a high frequency of fear of movement, which can negatively impact physical activity, an important component of osteoarthritis management. Psychological variables were significantly associated with BFOM, suggesting that behavioral and psychological interventions may decrease fear of movement and improve clinical outcomes in individuals with sxKOA.

Table. Bivariate Associations of Participant Characteristics with Fear of Movement, N=350.				
	Agree with none (n=81, 23.1%)	Agree with 1 to 2 (n=142, 40.6%)	Agree with 3 to 6 (n=127, 36.3%)	Trend p-value
Age (mean years ± SD)	68.7 ± 8.0	65.1 ± 11.6	63.3 ± 11.8	<0.01
Female (%)	72.8	69.0	74.0	0.64
Nonwhite (%)	21.5	23.7	32.5	0.15
Bachelor's degree or post graduate work (%)	66.7	61.3	52.8	0.12
KOOS Pain (mean ± SD)	67.2 ± 16.9	64.1 ± 16.6	56.2 ± 18.7	<0.01
KOOS ADL (mean ± SD)	73.7 ± 8.1	68.7± 17.3	60.3 ± 19.9	<0.01
Symptom Duration (mean years ± SD)	13.4 ± 10.9	13.8± 12.4	12.1±11.3	0.49
PHQ-8 (mean ± SD)	2.1 ± 2.2	3.1 ± 3.4	5.6 ± 5.1	<0.01
≥1 fall in the previous 12 months (%)	33.3	32.4	36.5	0.77
History of knee injury (%)	45.7	50.0	52.8	0.61
Family history of knee problems (%)	75.4	79.1	79.8	0.77
SEE (mean ± SD)	61.9 ± 8.3	58.1 ± 18.7	50.8 ± 22.0	<0.01
Unilateral balance test (mean seconds ± SD)	7.48 ± 3.39	7.26 ± 3.61	7.12 ± 3.59	0.78

Disclosure: A. Gunn, None; **T. A. Schwartz**, None; **L. F. Callahan**, None; **Y. M. Golightly**, None; **A. P. Goode**, None; **C. Hill**, None; **K. Huffman**, None; **M. D. Iversen**, None; **A. Pathak**, None; **S. Taylor**, None; **K. Allen**, None.

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Abstract Number: 2194

The Association Between Arthritis and Carpal Tunnel Syndrome:

National Health Interview Survey, 2010

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Background/Purpose: Carpal tunnel syndrome (CTS) is associated with high-repetition, forceful jobs. Additionally, non-occupational factors, such as arthritis, have been associated with CTS. There is conflicting evidence about the association between arthritis and CTS[1], probably due to studies with small samples, obtained from medical clinics rather than the general population, and "work-related" CTS populations. We used data from the 2010 National Health Information Survey (NHIS), representative of the U.S. civilian non-institutionalized population, to determine the risk for CTS for people with arthritis after controlling for occupational and non-occupational factors.

Methods: We analyzed adults (age 18-65). CTS cases were defined as "Have you EVER been told by a doctor or other health professional that you have a condition affecting the wrist and hand called carpal tunnel syndrome?" Arthritis and diabetes were self-reported in a similar fashion. Obesity was those with Body Mass Index (BMI) ≥30, and smoking as those who never or ever smoked. To identify occupational type, respondents were categorized in five major Standard Occupational Classification System categories (SOC): 1) Management, professional, and related; 2) Sales and office; 3) Service; 4) Natural resources, construction and maintenance; and 5) Production, transportation, and material moving, each of which represent progressively greater exposure to high-repetition, forceful jobs. We completed a logistical regression using appropriate NHIS weights: Step 1 included age, sex, race/ethnicity, education, and employment status; Step 2 the SOC; Step 3 arthritis and other co-morbidities. NHIS weights were applied to all analyses.

Results: Of our sample of 22,012 adults, 7.5% (95%CI: 7.0, 7.9) had CTS. Older adults and females were more likely to report CTS, while Hispanic/Non-Hispanic Other were less likely than Non-Hispanic Whites (See Table 1). Only respondents working in Production were significantly more likely to report CTS than those in Management (OR 1.4: (95% CI 1.1, 1.8) (Table 1). Diabetes, obesity, and smoking were all independent risk factors for CTS, with odds ratios ranging from 1.3 to 1.5. The arthritis odds ratio was 3.1 (95%CI 2.7, 3.5).

Table 1: Multivariable adjusted odds ratios (OR) with 95% confidence intervals (95% CI) for adults with and without CTS: NHIS 2010

Variable	OR (95% CI)
Age: 35-65 (referent: 18-34)	3.2 (2.6, 3.9)
Sex: Female (referent: Male)	2.6 (2.2, 3.0)
Race/ethnicity (referent: Non-Hispanic White)	
Hispanic	0.7 (0.6, 0.9)
Non-Hispanic Black	1.0 (0.8, 1.2)
Non-Hispanic Other	0.6 (0.4, 0.9)
Education: > College (referent: <College)	1.0 (0.9, 1.2)
Employment: Employed (referent: Not employed)	0.9 (0.8, 1.0)
SOC category: (referent: Management)	
Sales and office	1.2 (1.0, 1.4)
Service	1.1 (0.9, 1.4)
Natural resources, construction and maintenance	1.2 (0.9, 1.6)
Production, transportation, and material moving	1.4 (1.1, 1.8)
Arthritis: arthritis (referent: no arthritis)	3.1 (2.7, 3.5)
Diabetes: diabetes (referent: no diabetes)	1.5 (1.2, 1.8)
Obesity: BMI >30 (referent: BMI ≤30)	1.3 (1.2, 1.5)
Smoke: ever smoked (referent: never smoked)	1.4 (1.2, 1.6)

Conclusion: Respondents with arthritis were 3 times more likely to report CTS than those without arthritis, and were at similar risk as older adults. Non-occupational factors such as diabetes, obesity and smoking are as likely to be risk factors for CTS as jobs that require high repetition and forceful hand exertions. While both occupation and non-occupational factors are important risk factors for CTS, arthritis is one of the prime risk factor for CTS in the general population. References: 1. Burger MC, et al. Non-Occupational Risk Factors for Carpal Tunnel Syndrome: A Review. Women's Health Bull. 2016;3(2):e34820.

Disclosure: N. A. Baker, None;

Abstract Number: 2195

Conceptualizing the Life Course in the Employment Experiences of Working-Aged Adults with Arthritis: A Qualitative Study

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Background/Purpose: Research consistently finds that arthritis contributes to work disability. Yet, few studies have examined how employment experiences differ across the life course. This study examines the concept of the life course and its impact on the employment experiences of young, middle-aged and older adults with arthritis.

Methods: A series of focus groups and interviews with young (ages 18 to 34 years, n = 7), middle-aged (ages 35 to 54 years, n = 13) and older adults (>55 years, n = 25) living with arthritis were conducted. Participants were asked about aging with arthritis and ways in which their life circumstances, disease characteristics and career progress changed over time and affected their involvement in paid work. Two investigators independently coded data and incongruences were discussed. A modified grounded theory approach was used to inductively build a conceptual framework of the life course.

Results: The life course was made up of three interconnected domains that included life phase (i.e., changing social roles and responsibilities), career stage/job tenure (i.e., duration of employment and seniority in a job) and disease course (i.e., short- and long-term changes to arthritis symptoms). Life course domains and their impact on work experiences tended to differ based on the calendar age of the participant. Young adults described having to spend more energy transitioning into stable employment and a fear of worsening symptoms. Attributed to an early career phase, young adults were more reluctant to request workplace accommodations. Middle-aged adults discussed how their arthritis disrupted roles outside of work (e.g., parenting and marriage). Being in the mid-career stage and having greater job tenure offered more opportunities to access accommodations and benefits. For both young and middle-aged adults, having arthritis at a non-normative time of life created a barrier to disclosing the details of their condition and asking for help. In contrast, older adults talked about their life phase as being a time where they weighed the decision to retire against continuing to work. Related to a longer disease duration and greater job tenure, older adults discussed a toolbox of strategies they used to manage their arthritis and employment. When compared to the younger age groups, older adults were more likely to acknowledge that an arthritis diagnosis was part of aging and they were more comfortable talking to others about their limitations and requesting support.

Conclusion: Life course differences existed when comparing the employment experiences of young, middle-aged and older adults with arthritis, and should be considered in the development of work disability prevention policies and programs. Future research should also be conducted to identify opportunities for measuring life course domains in population health studies.

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Abstract Number: 2196

Trajectories and Predictors of Fear-Avoidance in Persons with Rheumatoid Arthritis. a Longitudinal Observational Study

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Trajectories and Predictors of Fear-Avoidance in Persons With Rheumatoid Arthritis. A Longitudinal Observational Study

Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease with symptoms such as pain, severe fatigue, depression and activity limitation. Pain and activity limitation are known to increase the risk of developing fear-avoidance behavior but their associations with physical activity are not fully verified. RA is a chronic disease that people have to live with for many years but knowledge on how fear-avoidance develops over time is still scarce. The aim of the study was to identify and describe groups with different trajectories of fear-avoidance beliefs over 2 years and to identify predictors for each trajectory in people with RA.

Methods: A sample of 2569 people with RA (mean age 58, 77% women) was identified via the Swedish Rheumatology Quality Registers. They responded, at baseline and at 1-year and 2-year follow-ups, to a valid questionnaire on demographics (age, gender, number of children and adults in household, education, income) health-enhancing physical activity (HEPA, current and maintained), disease-related factors (co-morbidity, perceived health, pain, fatigue, activity limitation) and psychosocial matters (fear-avoidance beliefs, anxiety/depression and self-efficacy for exercise). Data were analyzed with k-means longitudinal cluster analysis to identify trajectories of fear-avoidance beliefs and multinomial logistic regression to identify predictors of each trajectory.

Results: Three stable trajectories of fear-avoidance beliefs were identified from the cluster analysis; one with low (n = 1060) fear-avoidance beliefs, one with moderate (n = 1043) and one with high (n = 466). Predictors of stable high fear-avoidance beliefs, compared to low or moderate levels, were male gender, below average

income, current physical activity below HEPA levels and high activity limitation. Additional predictors of high fear-avoidance beliefs compared to low were below-university education, high pain, moderate activity limitation and low self-efficacy for exercise (Table 1).

Conclusion: There are 3 stable trajectories of fear-avoidance behavior in people with RA. The strongest modifiable predictors of persistently high fear-avoidance beliefs are more pronounced activity limitation, pain, below HEPA levels and low self-efficacy for exercise. These factors are important to identify at an early stage in people with RA in order to develop strategies to prevent high fear-avoidance behavior. Table 1. Baseline predictors of trajectories with high (n = 466) vs low (n = 1060) and moderate (n = 1043) fear/avoidance beliefs. Odds ratios (OR) and 95% confidence intervals (CI). Bold figures indicate significant predictors ($p < 0.01$).

Baseline predictors		**High vs low**	**High vs moderate**
		OR (95% CI)	**OR (95% CI)**
Gender	Women vs men	**0.30 (0.22-0.41)**	**0.51 (0.39-0.67)**
Education	High school vs university	**1.84 (1.29-2.62)**	1.33 (0.96-1.85)
	Elementary school vs university	**1.99 (1.38-2.86)**	1.34 (0.96-1.87)
Income	Above vs below average	**0.42 (0.31-0.57)**	**0.50 (0.38-0.65)**
Current HEPA	Yes vs no	**0.54 (0.41-0.72)**	**0.70 (0.55-0.89)**
Pain (VAS, 0-100)[a]	≥55 vs <30	**2.58 (1.58-4.22)**	1.22 (0.79-1.87)
Activity limitation[a] (HAQ, 0-3)	>1.0 vs 0	**7.14 (4.19-12.19)**	**2.11 (1.28-3.47)**
	0.1-1.0 vs 0	**3.10 (2.01-4.78)**	1.60 (1.04-2.48)
Anxiety/depression (EuroQoL, yes/some/no)	Some vs no	**1.50 (1.13-2.01)**	1.31 (1.01-1.69)
Self-efficacy for exercise (ESES, 6-60)[a]	Highest tertile vs lowest tertile	**0.53 (0.38-0.76)**	0.87 (0.63-1.19)

[a]High values indicate worse health HEPA = Health-enhancing physical activity VAS = Visual analogue scale HAQ = Stanford Health Assessment Questionnaire EuroQoL = Euro quality of life ESES = Exercise self-efficacy scale

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Comparison of Objectively Measured Physical Activity Among People with Symptomatic Knee Osteoarthritis with the General US Population

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Background/Purpose: People with knee osteoarthritis (OA) are thought to be less physically active than those without OA. This includes time in moderate-to-vigorous physical activity (MVPA), a critical level of intensity associated with numerous health benefits, and walking, the most common type of physical activity in older adults. However, little empirical data exists to support these trends. The purpose of this study was to compare objectively measured physical activity and walking among people with symptomatic knee OA (SxOA) with people from the US population of the same sex and similar age. We hypothesized that those with SxOA will be less active than the US population.

Methods: We used data from the Osteoarthritis Initiative (OAI), a large prospective cohort study of knee OA (n=486), and the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample from the United States (n=1455). Physical activity was measured in both cohorts with an accelerometer-enabled monitor worn for ≥ 10 hours/day for ≥ 4 days (NHANES – Actigraph 7124; OAI – Actigraph GT1M). Data were collected in OAI from 2008-2010, and in NHANES from 2005-2006. SxOA was defined as those with Kellgren–Lawrence grade ≥ 2 and knee pain on most of the last 30 days. MVPA was defined as ≥ 2020 activity counts/min. We also classified those who walked ≥10 minutes/week at ≥80 steps/min to reflect purposeful walking. Within age- and sex-specific strata, we compared mean time in MVPA between cohorts with independent t-tests and calculated the likelihood that people with SxOA walked purposefully ≥10 min/day compared with the US population using odds ratios (OR).

Results: Within age- and sex-specific strata, physical activity levels were generally similar ($p>0.05$) among people with SxOA and the general US population. People with SxOA spend on average 4-29 minutes in MVPA, while the US population spent 2-26 minutes in MVPA (Figure 1)**.** The proportion of people who walked at least 10 min/day was 8-60% for those with SxOA and 10-54% in the US population (Table 1). The odds of walking at least 10 minutes/day was similar for individuals with SxOA relative to the US population.

Conclusion: Strikingly low levels of physical activity were observed in both people with SxOA and people in the general US population. The presence of pain and OA is not likely a primary reason for low levels of physical activity among people with SxOA. **Figure 1.** Mean minutes per day (± 95% CI) in MVPA for the US population (NHANES) and people with SxOA (OAI SxOA).

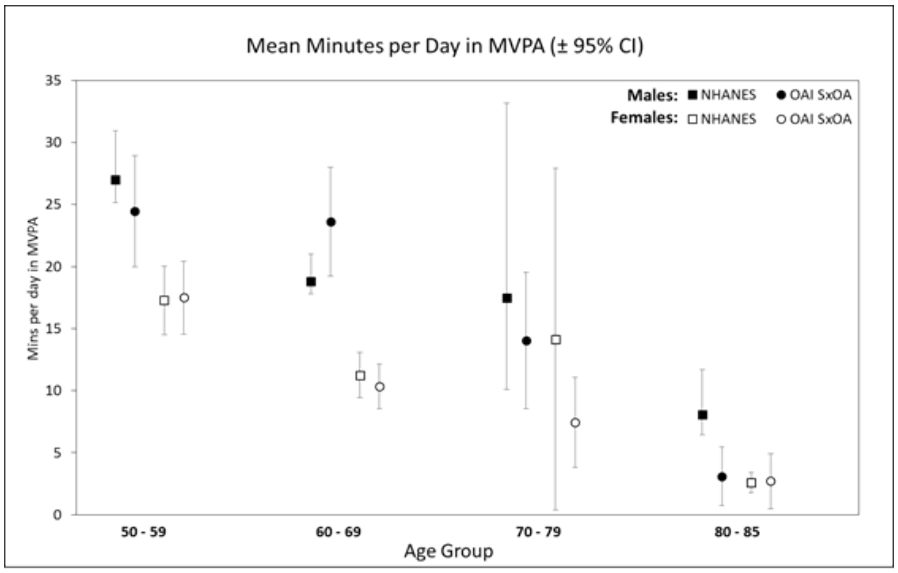

Table 1. Proportions and odds ratio (± 95% CI) for walking purposefully at least 10 minutes/day for people with SxOA (OAI) relative to the US population (NHANES).

		Sample	n	Percentage walking ≥10 mins at 80 steps/min	OR (95%CI)
Male	**50-59**	NHANES	229	53.7	Reference
		OAI SxOA	67	59.7	1.3 (0.7 - 2.2)
	60-69	NHANES	249	50.1	Reference
		OAI SxOA	75	60.0	1.5 (0.9 - 2.5)
	70-79	NHANES	189	29.7	Reference
		OAI SxOA	68	35.3	1.3 (0.7 - 2.3)
	80-85	NHANES	86	13.4	Reference
		OAI SxOA	12	8.3	0.6 (0.1 - 5.3)
Female	**50-59**	NHANES	227	51.1	Reference
		OAI SxOA	71	42.3	0.7 (0.1 - 1.2)
	60-69	NHANES	253	35.2	Reference
		OAI SxOA	67	35.6	1.0 (0.6 - 1.6)
	70-79	NHANES	152	24.7	Reference
		OAI SxOA	75	18.7	0.7 (0.4 - 1.4)
	80-85	NHANES	70	10.8	Reference
		OAI SxOA	14	14.3	1.3 (0.2 - 6.9)

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Is Joint Hypermobility Related to Foot Osteoarthritis and Symptoms?

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Background/Purpose: Reports of associations of hypermobility and osteoarthritis (OA) vary widely**.** One possible cause for this lack of agreement may be different impacts of hypermobility by joint site. No prior cohort study has examined this association at the foot. This cross-sectional analysis assessed joint hypermobility with foot OA and symptoms in a large community-based cohort.

Methods: Of the 863 community-based participants with complete foot radiographs (2012-15), 848 had Beighton data (joint hypermobility; 2003-2010). Beighton criteria assessed the ability to do: passive dorsiflexion fifth finger ≥ 90 degrees, passive apposition thumb to forearm, elbow hyperextension ≥10 degrees, knee hyperextension ≥10 degrees, and palms on floor during forward trunk flexion with knees extended. One point was given for each completed maneuver (total score: 0 [unable to do any maneuver] to 9 [all maneuvers done]). Joint hypermobility was defined as Beighton score ≥4; the knee maneuver alone also was examined specifically due to the biomechanical connection of the knee and foot/ankle. Standing anteroposterior and lateral foot x-rays were read with the LaTrobe atlas to measure osteophytes (OST, 0-3) and joint space narrowing (JSN, 0-3) at five joint sites: first metatarsophalangeal, first cuneo-metatarsal, second cuneo-metatarsal, navicular-first cuneiform, and talonavicular. A joint with a score ≥2 OST or JSN was considered to have radiographic OA (rOA). Foot rOA was defined as ≥1 joint with rOA within the same foot. Foot symptoms (yes/no) was based on response to: "On most days of any one month in the last 12 months did you have pain, aching or stiffness in your left/right foot?" Separate logistic regression person-based models were used to estimate associations of foot rOA, site rOA, and symptoms with hypermobility, adjusting for covariates of age, sex, race (Caucasian vs. African American), body mass index (BMI), and history of foot injury. Pairwise interactions between hypermobility and each covariate were examined (<0.10 considered significant).

Results: This sample was 68% women and 33% African American (mean age=71 years, mean BMI=31 kg/m^2). Joint hypermobility was present in 59 participants (7%); 189 (22%) participants had foot rOA, and 176 (21%) had foot symptoms. The adjusted odds of talonavicular rOA and foot symptoms were 3.0 and 2.4 times higher, respectively, among participants able vs. unable to perform the knee maneuver but based on small numbers. While no association was seen for foot rOA and hypermobility, non-significant increased estimates suggested possible relationships with specific foot joints and with foot symptoms (Table). No statistical interactions of hypermobility by covariates were observed.

Conclusion: Joint hypermobility may be related to rOA of specific foot joints and with foot symptoms. Future longitudinal studies will clarify the influence of hypermobility on the incidence and progression of foot OA and

symptoms.

Table. Adjusted* odds ratios (OR) and 95% confidence intervals (CI) for association of foot outcomes with Beighton Criteria.

Foot Outcome	Overall	Beighton Score ≥4	Beighton Score <4	Adjusted OR	Knee Maneuver	No Knee Maneuver	Adjusted OR
	N=848	n=59	n=789	(95% CI)	n=34	n=811	(95% CI)
Foot rOA, n (%)	189 (22.3)	12 (20.3)	177 (22.4)	1.08 (0.55, 2.12)	7 (20.6)	181 (22.3)	0.91 (0.38, 2.15)
1st metatarsophalangeal rOA, n (%)	88 (10.4)	7 (11.9)	81(10.3)	1.36 (0.59, 3.14)	3 (8.8)	85 (10.5)	0.82 (0.25, 2.77)
1st cuneo-metatarsal rOA, n (%)	21 (2.5)	0 (0)	21 (2.7)	†	0 (0)	21 (2.6)	†
2nd cuneo-metatarsal rOA, n (%)	59 (7.0)	5 (8.5)	54 (6.8)	1.55 (0.57, 4.22)	3 (8.8)	56 (6.9)	1.32 (0.38, 4.65)
Navicular-1st cuneiform rOA, n (%)	41 (4.8)	4 (6.8)	37 (4.7)	2.16 (0.70, 6.67)	2 (5.9)	39 (4.8)	1.23 (0.27, 5.59)
Talonavicular rOA, n (%)	49 (5.8)	4 (6.8)	45 (5.7)	1.65 (0.55, 4.95)	5 (14.7)	43 (5.3)	**3.05 (1.10, 8.51)**
Foot symptoms, n (%)	176 (20.8)	17 (28.8)	159 (20.2)	1.54 (0.84, 2.83)	12 (35.3)	163 (20.1)	**2.40 (1.15, 5.04)**

*Adjusted for age, sex, race, body mass index, and history of foot injury

†Participants with hypermobility (Beighton score ≥4 or able to complete knee maneuver) did not have1st cuneo-metatarsal rOA.

Abbreviations: OR = odds ratio, CI = confidence interval, rOA = radiographic osteoarthritis

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Abstract Number: 2199

Peri-Aortic Adipose Tissue Volume Is Directly Associated with Fat Accumulation in Adjacent Trunk Muscles Independent of Other Fat Depots: The Framingham Study

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Background/Purpose: Age-related accumulation of muscular fat and loss of muscle mass contribute to impaired

muscle function and consequent mobility impairment in older adults. These muscle changes may result from excess ectopic fat accumulation, which produces inflammatory cytokines that promote differentiation of muscle satellite cells into adipocytes versus myoblasts. It is unknown whether this muscle-fat cross-talk occurs primarily via systemic effects of circulating cytokines, or through paracrine effects between adjacent compartments. Our objective was to determine the association of peri-aortic adipose tissue (PAAT) volume with size and fat content of adjacent trunk muscles among 948 participants (56% women) in the community-based Framingham Study.

Methods: Multidetector CT abdominal imaging measured PAAT volume (cm^3), as well as cross-sectional area (mm^2) and attenuation (HU), a marker of fat content, of the erector spinae, transversospinalis, and trapezius muscles at the T7 and T8 levels. Cross-sectional area and attenuation of each muscle was averaged for the left and right sides, and across vertebral levels. Linear regression was used to calculate coefficients (β) estimating the associations of PAAT volume with muscle cross-sectional area and attenuation, adjusting for sex, age, height, body mass index (BMI) and self-reported physical activity (Framingham Physical Activity Index). Models were further adjusted for abdominal visceral (VAT) and subcutaneous adipose tissue (SAT) volumes (cm^3), measured from the same CT images, to determine if PAAT associations were independent of abdominal fat depots.

Results: Mean age was 58 years (range 45-81), mean BMI was 28 kg/m^2 (range 18-53). While there was no association with muscle cross sectional area (β=-0.96, P=0.37), PAAT was inversely associated with muscle attenuation (β=-0.31, P<0.0001), indicating greater muscle fat content with increasing PAAT. The association remained after further adjustment for VAT (β for PAAT=-0.21, P<0.0001) and SAT (β for PAAT=-0.33, P<0.0001). Results were similar when stratified by sex and categorizing PAAT as quartiles.

Conclusion: We found that increased fat surrounding the aorta was associated with greater fat content in nearby trunk muscles, independent of overall obesity and specific abdominal fat depot volumes. PAAT was not, however, associated with trunk muscle size. Our findings suggest that age-related fat accumulation in skeletal muscle may result mainly from local paracrine effects of adjacent fat depots. Cross-talk between neighboring fat and muscle is a potential novel target for therapies aiming to prevent or restore loss of muscle function.

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Abstract Number: 2200

Association of Active Commuting and Physical Activity in Women with Fibromyalgia

Manuel Herrador-Colmenero[1], **Fernando Estévez-López**[1], Víctor Segura-Jiménez[1], Inmaculada C Álvarez-Gallardo[1], Alberto Soriano-Maldonado[1], Daniel Camiletti-Moirón[1,2], Virginia A Aparicio[1], Manuel Delgado-Fernández[1] and Palma Chillón[1], [1]University of Granada, Granada, Spain, [2]University of Cádiz, Cádiz, Spain

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Epidemiology and Public Health - ARHP Poster

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Background/Purpose: Fibromyalgia symptomatology results in a low functional capacity[1], limiting the daily activities and the quality of life of the patients[2]. Walking for commuting is a healthy behaviour which might be one of the sources for increasing the physical activity in women[3,4]. We aimed to examine the association between active commuting and objectively measured physical activity in women with fibromyalgia.

Methods: A total of 486 fibromyalgia women who meet the 1990 American College of Rheumatology Fibromyalgia criteria were enrolled in this cross-sectional study. Mode of commuting was assessed with a mode of commuting questionnaire[5]. Physical activity was measured by accelerometry during 7 complete days. One way analysis of covariance was performed between active (i.e. walk or cycling) and passive commuters (i.e. users of cars, motorbikes and bus). Linear regression analyses were conducted to further examine the relationships between mode of commuting and physical activity in separates models. All analyses were conducted separately in two age groups, i.e.: <51 (young group) and ≥51 (older group)[6]. Age, algometer score and accelerometry wear time were used as confounders.

Results: Active commuters from both age groups spent less time in sedentary activities (all $p<0.001$), greater time in all physical activity intensities (all $p\leq0.001$; except vigorous, $p<0.05$), and registered a higher amount of steps ($p\leq0.001$) than passive commuters. The results of the linear regression analysis showed, in the younger group, a positive and significant association between active commuting and moderate, moderate to vigorous physical activity, total physical activity and steps count (all $p\leq0.01$). Active commuting was negatively and significantly associated with sedentary time ($p=0.008$). No association between active commuting and accelerometry outcomes were observed in the older group.

Conclusion: Findings of the current study suggest that, in fibromyalgia women, commuting actively is associated with less time in sedentary activities, greater levels of physical activity and a higher amount step counts. A public health strategy for increasing the physical activity levels in this population might be to promote walking to reach the daily destinations (i.e., work, supermarket…). References: [1]Carbonell-Baeza A et al., *Pain Med.* 2011;12:1667–75. [2] Mas AJ et al., *Clin Exp Rheumatol.* 2008;26:519–26. [3] Yang L et al., *Prev Med.* 2012;55:453–7. [4] Yang X et al., *Prev Med.* 2014;59:5–11. [5] Herrador-Colmenero M et al., *J Sports Sci* 2015;33:850–62. [6] Herrador-Colmenero M et al., *Clin Exp Rheumatol.*2016;34:S67–73. Funding: The Spanish Ministry of Economy and Competitiveness (I+D+i DEP2010-15639, I+D+i DEP2013-40908-R, BES-2014-067612, FPU12/00963 and FPU13/01088).

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Abstract Number: 2201

Self-Reported Breathlessness on Exertion Is Associated with Poor Outcomes Among Women with Systemic Lupus Erythematosus (SLE)

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Background/Purpose: Breathlessness is often considered as a predictor of functional outcomes in pulmonary disease, but has not been examined in SLE.

Methods: Data were from the National Data Bank for Rheumatic Diseases (NDB), for which participants complete questionnaires every 6 months. Only women with SLE who completed one of the most recent completed questionnaires were included (n = 278). Breathlessness was assessed with the Medical Research Council questionnaire (Table 1). Outcomes examined were self-reported lupus status (Systemic Lupus Activity Questionnaire, SLAQ[1]), assessment of lupus activity (rating from 0 [not active] – 100 [very active]), global assessment of health status (rating from 0 [doing very well] – 10 [doing very poorly]), and self-reported assessments of pain, fatigue, and sleep problems, each rated 0 – 10 with higher ratings reflecting worse symptoms. ANOVAs and multivariate linear regression analyses estimated the relationship of breathlessness on outcomes. Multivariate analyses controlled for age, low education, low income, body mass index (BMI), duration of SLE, self-reported disease damage (Brief Inventory of Lupus Damage, BILD[2]), Rheumatic Disease Comorbidity Index (RDCI)[3], current or former smoking, and self-reported chronic obstructive pulmonary disease (COPD) or asthma.

Results: Mean age was 58 ± 13 years, 22% had education ≤ high school, and 47% had low income. Mean disease duration was 21 ± 12 years, mean BMI was 29 ± 8, and mean score on the RDCI was 2.7 ± 1.8. 5% were current smokers, 41% were former smokers, and 7% had self-reported COPD. In both unadjusted and unadjusted analyses, breathlessness ratings were associated with worse outcomes on each measure (Table 2).

Conclusion: Breathlessness was associated with worse patient-reported outcomes among this group of women with SLE, even after controlling for disease status, smoking, and self-reported COPD. While self-reports of breathlessness are often used to assess pulmonary functioning, these items may also indicate poor cardiorespiratory fitness. [1] Karlson EW, et al. *Lupus* 2003; 12:280. [2] Yazdany J, et al. *Arthritis Care Res* 2011; 63:1170 [3] England BR, et al. *Arthritis Care Res* 2015; 6: 865

Table 1. MRC categories and frequencies	
	% (n)
Group 0: Only get breathless with strenuous exercise	39.8 (98)
Group 1: Get short of breath when hurrying on a level or up a slight hill	25.6 (63)
Group 2: Walk slower than people of the same age on the level because of breathlessness or have to stop for breath when walking at my own pace on the level	14.2 (35)
Group 3: Have to stop for breath after walking 100 yards or after a few minutes on the level	20.2 (50)
Group 4: Too breathless to leave the house	0.8 (2)
• Groups 3 and 4 were combined for analysis. • Respondents were instructed not to answer items if activity problems were due to other physical problems	

Table 2. Association of breathlessness ratings with outcomes					
	Group 0	Group 1	Group 2	Group 3/4	p-value*
SLAQ	8.3 ± 6.1	10.4 ± 6.3	13.5 ± 6.8	14.9 ± 7.8	.05
Lupus activity rating	21.1 ± 24.0	28.0 ± 22.9	38.1 ± 29.4	45.1 ± 30.6	.009
Global health status rating	2.5 ± 2.3	3.6 ± 2.3	4.9 ± 2.3	5.7 ± 2.7	<.0001
Pain	2.5 ± 2.6	4.0 ± 2.5	5.2 ± 2.8	5.5 ± 2.7	.005
Fatigue	3.5 ± 2.9	4.4 ± 2.7	6.4 ± 2.7	6.8 ± 2.5	<.0001
Sleep	3.1 ± 2.9	4.1 ± 3.0	5.3 ± 3.4	5.8 ± 3.0	.008
* p-value from multiple linear regression controlling for age, education, income, BMI, smoking (current or former), SLE duration, SLE damage (BILD score), comorbidity index (RDCI), and self-reported COPD (chronic obstructive pulmonary disease, emphysema, or chronic bronchitis) or asthma					

Disclosure: P. P. Katz, None; **S. Pedro**, None; **R. S. Katz**, None; **F. Wolfe**, None; **K. Michaud**, Rheumatology Research Foundation, Pfizer, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/self-reported-breathlessness-on-exertion-is-associated-with-poor-outcomes-among-women-with-systemic-lupus-erythematosus-sle

Abstract Number: 2202

Comparison of New and Old American College of Rheumatology Classification Criterion for Diagnosis of Fibromyalgia

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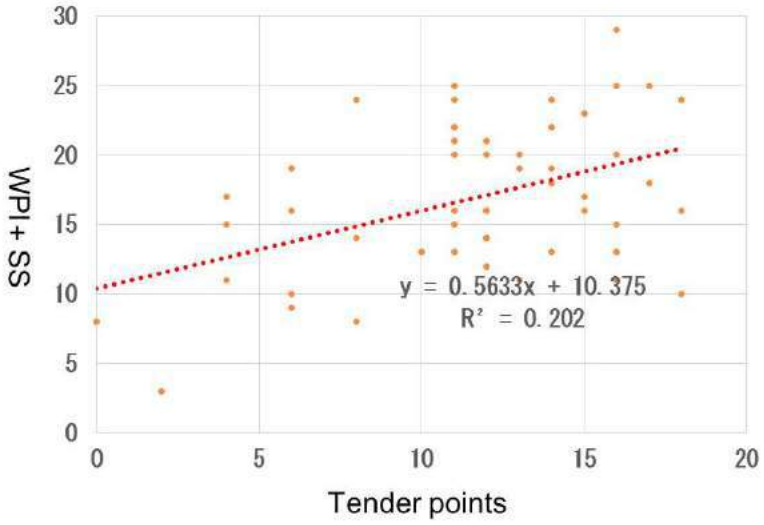
Session Time: 9:00AM-11:00AM

Background/Purpose: Fibromyalgia (FM) is a chronic disease characterized by severe, long lasting pain that spreads widely in almost whole body. The cause of the disease is still unknown, and no efficient treatment has yet been established. It is well known that the severity of pain as well as accompanying symptoms can often be influenced either by psychological or by social factors, which support the recognition of the disease as one of functional somatic disorders.

Methods: American College of Rheumatology (ACR) revised the classification criteria for diagnosis of FM in 2010, after 20 years of clinical use of the old one that had been published in 1990. Old criteria simply classifies patients as FM by number of tender points (11 or more, out of 18 in total), whereas new one considers not only the extent of widespread pain but also the severity of pain and many accompanying symptoms. In this study, comparison between the new and old criterion was performed in total 61 patients with FM or doubtful FM (male 11, female 50, average age 54.0 years, average duration from onset 4.5 years).

Results: Tender points by 1990 criteria was 12.0 in average (min 0, max 18), with 42 patients out of 56 presenting 11 or more, who were diagnosed as FM. Average Widespread Pain Index (WPI) and Symptom Severity (SS) by 2010 criteria scored 10.9 (min 2, max 18) and 6.1 (min 1, max 12), respectively, resulting 38 out of 59 were diagnosed as FM (WPI>7, SS>5 or 3<WPI<6, SS>9). Sum of the two scores in new criteria, WPI and SS, was 16.8 in average (min 3, max 29), and demonstrated positive correlation with tender points in old criteria (r=0.45). However, diagnoses by the two criterion did not always coincide.

Conclusion: Despite of overall accordance between two criterions, the diagnosis did not always coincide. Interestingly, the positivity of tender points in old criteria as well as that of widespread pain in new one demonstrated significant differences by the locus. Moreover, the positivity of accompanying symptoms in new criteria (41 in total) demonstrated significant differences from each other. All these differences may suggest that pain and tender locus as well as accompanying symptoms could be weighed either more or less, not equally as they are, depending the influence in diagnosis. Physicians should apply these criterion flexibly.



Correlation of two ACR classification criterion for diagnosis of fibromyalgia.
Tender points in old criteria (1990) and WPI+SS in new criteria (2010) demonstrated positive correlation. WPI, widespread pain index; SS, symptom severity.

Disclosure: K. Shi, None; **K. Miki**, None; **M. Yukioka**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-of-new-and-old-american-college-of-rheumatology-classification-criterion-for-diagnosis-of-fibromyalgia

Abstract Number: 2203

Self-Reported Childhood Maltreatment and Traumatic Events Among Israeli Patients Suffering from Fibromyalgia and Rheumatoid Arthritis

Raneen Hellou[1], Winfried Häuser[2], Inbal Brenner[3], Dan Buskila[4], Giris Jacob[5], Ori Elkayam[6], Valerie Aloush[7] and Jacob N. Ablin[8], [1]Internal medicine F, Tel Aviv Sourasky Medical center, Tel Aviv, Israel, [2]Department of Psychosomatic Medicine and Psychotherapy, Technische Universität München, Munich, Germany, [3]Shalvata Mental Health Center, Hod Hasharon, Israel, [4]Internal Medicine, Soroka Medical Center, Beer Sheva, Israel, [5]Internal medicine F, Tel Aviv Sourasky medical center, Zichron Yakov, Israel, [6]Rheumatology, Tel Aviv Sourasky Medical Center and the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, [7]Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, [8]Institute of Rheumatology, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

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Session Time: 9:00AM-11:00AM

Abstract:

Background/Purpose: the association between Fibromyalgia Syndrome (FMS) and childhood maltreatment and adversity has frequently been proposed but limited data exists regarding the trans-cultural nature of this association, based on retrospective self-report analysis. Moreover, the differences between FMS and other chronic rheumatic disorders such as rheumatoid arthritis have not been extensively analyzed.

Methods: 75 Israeli FMS patients and 23 Rheumatoid Arthritis (RA) patients were compared. Childhood maltreatment was assessed by the Childhood Maltreatment Questionnaire (CTQ) and potential depressive and anxiety disorder were assessed by the Patient Health Questionnaire PHQ-4. FMS severity was assessed by use of the Widespread Pain Index (WPI), the Symptom Severity Score (SSS) and the Fibromyalgia Impact Questionnaire (FIQ). Potential posttraumatic stress disorder (PTSD) was diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders IV-TR symptom criteria by the Posttraumatic Diagnostic Scale (PDS). RA severity was assessed by the RA Disease Activity Index (RADAI). Health status was assessed by the Short Form 36 health survey (SF-36).

Results: Similar to previous reports in other countries, high levels of self-reported childhood adversity were reported by Israeli FMS patients. PTSD was significantly more common among FMS patients compared with RA patients, as well as reports of childhood emotional abuse, physical and emotional neglect. The OR for PTSD among FMS patients compared with RA patients, when controlling for anxiety and depression, was 4.9 with 95% CI 1.02-23.6. ($p<0.05$). Reports of physical and sexual abuse did not significantly differ between FMS and RA patients and no significant difference was found regarding rates of "severe" and "very severe" childhood trauma between the groups. Levels of depression and anxiety were significantly higher among FMS patients compared with RA patients. FMS patients demonstrated significantly lower scores regarding energy/fatigue, emotional wellbeing, and social functioning compared with RA patients.

Conclusion: The study demonstrated the cross cultural association between FMS and childhood maltreatment, including neglect and emotional abuse as well as PTSD. Significant differences were demonstrated between FMS patients and patients suffering from RA, a model of an inflammatory chronic rheumatic disease.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/self-reported-childhood-maltreatment-and-traumatic-events-among-israeli-patients-suffering-from-fibromyalgia-and-rheumatoid-arthritis

Abstract Number: 2204

Distinctive Personality Profiles of Fibromyalgia and Chronic Fatigue Syndrome Patients

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Background/Purpose: The current study is an innovative exploratory investigation, aiming at identifying differences in personality profiles within FMS and CFS patients.

Methods: 344 participants (309 female, 35 male) reported suffering from FMS and/or CFS and consented to participate in the study. Participants were recruited at an Israeli FM/CFS patient meeting held in May 2013, and through an announcement posted on several social networks. Participants were asked to complete a research questionnaire, which included FMS criteria and severity scales, and measures of personality, emotional functioning, positivity, social support and subjective assessment of general health. 204 participants completed the research questionnaire (40.7% attrition rate).

Results: A cluster analysis produced two distinct clusters, which differed significantly on psychological variables, but did not differ on demographic variables or illness severity. As compared to cluster number 2 (N=107), participants classified into cluster number 1 (N=97) showed a less adaptive pattern, with higher levels of Harm Avoidance and Alexithymia; higher prevalence of Type D personality; and lower levels of Persistence, Reward Dependence, Cooperation, Self-Directedness, social support and positivity.

Conclusion: The significant pattern of results indicates at least two distinct personality profiles of FM and CFS patients. Findings from this research may help improve the evaluation and treatment of FM and CFS patients, based on each patient's unique needs, psychological resources and weaknesses, as proposed by the current trend of personalized medicine.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/distinctive-personality-profiles-of-fibromyalgia-and-chronic-fatigue-syndrome-patients

Abstract Number: 2205

Cognitive Functioning in Fibromyalgia: The Central Role of Effort

Jacob Ablin[1], Tamar Bar On –Kalfon[2], Gilad Gal[3] and Ran Shorer[2], [1]Rheumatology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel, [2]Rheumatology, Tel Aviv Sourasky medical center, Tel Aviv, Israel, [3]School of Behavioral Sciences, Tel Aviv-Jaffa Academic College, Tel Aviv, Israel

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Background/Purpose: Fibromyalgia syndrome (FMS) patients demonstrate deficits in tests of attention, executive functioning and verbal memory. We assessed the role of effort in the cognitive impairment in FMS patients, alongside common symptoms of pain, fatigue and depression.

Methods: 50 FMS patients underwent a computerized cognitive assessment battery including memory, executive function, attention and information processing speed (NeuroTrax Corp.). Age and education standardized scores

were computed. Effort was assessed by the Test of Memory Malingering (TOMM). FMS symptoms were assessed by the Fibromyalgia Impact Questionnaire (FIQ), Widespread Pain Index (WPI) and Symptom Severity Scale (SSS), a Visual Analogue Scale (VAS) of clinical pain and the Beck depression inventory (BDI-2).

Results: FMS patients showed impaired performance on the memory, attention and information processing speed domains. According to the TOMM, sub-optimal effort was shown by 16% of patients. TOMM scores were not associated with pain, fatigue or depression. After controlling for effort, no significant impairment was found in memory scores; however attention and information processing speed scores remained significantly low. Multiple regressions analysis, performed in order to evaluate the contribution of effort, pain, fatigue and depression, found effort to be the only significant variable accounting for variance of cognitive scores on all domains.

Conclusion: The findings confirm impaired attention and processing speed in FMS patients, independent of effort level. Nonetheless, the findings point to a general and strong effect of effort on neuropsychological performance in FMS patients, especially in the domain of memory, emphasizes the importance of effort testing in this population.

Disclosure: J. Ablin, None; **T. Bar On –Kalfon**, None; **G. Gal**, None; **R. Shorer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cognitive-functioning-in-fibromyalgia-the-central-role-of-effort

Abstract Number: 2206

Data on Treatment from Brazilian Fibromyalgia Patients Registry (EpiFibro)

José E. Martinez[1,2], Marcelo C. Rezende[1,3], Eduardo Paiva[1,4], Daniel Pollak[1,5], Milton Helfenstein Jr[1,6], Jose Roberto Provenza[1,7], Aline Ranzolin[1,8], Luiz Severiano Ribeiro[1,9], Eduardo J. R. Souza[1,10], Roberto E Heymann[1,11] and Marcos Renato Assis[1,12], [1]Brazilian Society of Rheumatology, São Paulo, Brazil, [2]Rheumatology, Pontificia Universidade Católica de São Paulo, Sorocaba, Brazil, [3]Santa Casa de Campo Grande, Campo Grande, Brazil, [4]Rheumatology, Universidade Federal do Parana, Curitiba Parana, Brazil, [5]Rheumatology, Universidade Federal de São Paulo, São Paulo, Brazil, [6]RUA JOAO DE LACERDA SOARES, 90, Universidade Federal de São Paulo, Sao Paulo, Brazil, [7]Rheumatology, Pontifícia Universidade Católica de Campinas, Campinas, Brazil, [8]Hospital das Clínicas - Universidade Federal de Pernambuco, Recife, Brazil, [9]Instituto de Previdência dos Servidores do Estado de Minas Gerais, Belo Horizonte, Brazil, [10]Santa Casa de Belo Horizonte, Belo Horizonte, Brazil, [11]Universidade Federal de São Paulo, São Paulo, Brazil, [12]Rheumatology, Faculdade de Medicina de Marilia, Marilia, Brazil

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Background/Purpose: The Brazilian registry on fibromyalgia syndrome (EpiFibro) included 810 patients who satisfied the American College of Rheumatology Classification Criteria for Fibromyalgia (ACR1990) at the time

of diagnosis. Objectives – 1. Describe treatment modalities for Brazilian Patients; 2. Describe treatment measures in each of the modalities.

Methods: – A transversal study on a multicenter cohort of Brazilian Fibromyalgia patients. All patients fulfilled at the data entry the American College of Rheumatology Classification Criteria for Fibromyalgia. The analysis was made through descriptive statistical technique (frequency and standard deviation).

Results: Three hundred and forty two (342) entries were excluded for having incomplete forms at the treatment modalities. In relation of the therapeutic modalities, it was observed: sixty-six (66) patients are taking only medications and no non-pharmacological therapy; four hundred and fifty five (455) patients are taking some medicines; three hundred and three (303) patients are receiving some kind of health education; two hundred and six (206) patients are practicing exercises and ninety seven (97) are getting some kind of other non-pharmacological measures. The most frequent combination of modalities is medicine, health education and exercises (89). The only 2 drugs approved for fibromyalgia in Brazil are duloxetine (57 patients in use) and pregabalin (11 patients in use). Other medications with proved efficacy by literature have also being prescribed off label, such as amitriptyline (115), venlafaxine (17), fluoxetine (49), cyclobenzaprine (77), tramadol (30) and gabapentin (11). The most used medication associations are: fluoxetine and amitriptyline (88), fluoxetine and cyclobenzaprine (14), amitriptyline and cyclobenzaprine (7), tramadol and paracetamol (23). Other associations were also reported: pregabalin and duloxetine (2), pregabalin and amitriptyline (3), pregabalin and fluoxetine (5), gabapentin and duloxetine (1), gabapentin and amitriptyline (1). There were also prescribed triple associations. In relation to exercises, 108 patients practice aerobics, 26 stretching exercises and 2 strengthening exercises. The most frequent combination is aerobics and stretching exercises (48). The non-pharmacological measures most used are heated swimming pool exercises (17), relaxing techniques (10), acupuncture (10), psychotherapy (9), massage (6) and tender point infiltration (6). It has been also mentioned hypnosis, homeopathy and biofeedback.

Conclusion: The majority of Brazilian fibromyalgia patients are treated by a combination of pharmacological and non-pharmacological measures. It is prescribed approved medications for fibromyalgia, but the most prescribed drug is amitriptyline off label, probably for economic reasons. The most prescribed medicine combination is fluoxetine and amitriptyline. The most practiced exercises are the aerobics modalities and the most non-pharmacological measures are health education and exercises in heated swimming pool.

Disclosure: J. E. Martinez, None; **M. C. Rezende**, None; **E. Paiva**, None; **D. Pollak**, None; **M. Helfenstein Jr**, None; **J. R. Provenza**, None; **A. Ranzolin**, None; **L. S. Ribeiro**, None; **E. J. R. Souza**, None; **R. E. Heymann**, None; **M. R. Assis**, None.

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Abstract Number: 2207

WITHDRAWN

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/what-percentage-of-fibromyalgia-patients-are-challenging-to-treat

Abstract Number: 2208

Mediators of the Relationship Between Pain and Disability in the Distal Upper Limb

Daniel Whibley[1,2,3], Kathryn Remmes Martin[1,2,3], Karina Lovell[4], Gareth T. Jones[1,2,3] and Arm Pain Trial Investigators, [1]Arthritis Research UK / MRC Centre for Musculoskeletal Health and Work, University of Aberdeen, Aberdeen, United Kingdom, [2]Aberdeen Centre for Arthritis and Musculoskeletal Health, University of Aberdeen, Aberdeen, United Kingdom, [3]Epidemiology Group, School of Medicine, Medical Sciences and Nutrition, University of Aberdeen, Aberdeen, United Kingdom, [4]School of Nursing, Midwifery and Social Work, University of Manchester, Manchester, United Kingdom

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Background/Purpose: Disabling distal upper limb pain is common but relatively understudied. Fear avoidance (FA) models of disability have been empirically tested for back and lower limb pain. There is a lack of research investigating their tenability for disabling distal upper limb pain. Given the region's distinct functional demands, it is important to understand the role of psychosocial and behavioural factors in the pain-disability relationship. The aim of this study was to investigate whether any of five psychosocial or behavioural factors implicated in FA models mediated the distal upper limb pain-disability relationship: kinesiophobia, psychological distress, multiple somatic symptoms, beliefs about prognosis, change in physical activity, and change in leisure time arm use.

Methods: This observational study used data from a UK multi-centre randomized controlled trial to investigate mediators of the relationship between: 1.) Pain and disability at the time of referral; 2.) Baseline pain, and disability 26wks later. Patients referred to physiotherapy with distal upper limb pain/disability completed self-report questionnaires at baseline, 6, 13 and 26wks. Information was collected on pain intensity (11-point Numeric Rating Scale), disability (modified Disabilities of the Arm, Shoulder and Hand questionnaire), kinesiophobia (Tampa Scale for Kinesiophobia), quality of life (EQ-5D), somatic symptoms (Modified Somatic Perception questionnaire), beliefs about prognosis, physical activity and leisure time arm use. Mediation analysis included use of Baron and Kenny criteria, Sobel tests, and, for longitudinal models, analysis of covariance using data collected at three follow-up time points (baseline, 26 weeks and either 6 or 13 weeks). Models were adjusted for age, gender, diagnostic category, pain duration and history, and trial treatment group: (a) immediate physiotherapy; or normally timed physiotherapy, with (b) advice to rest; or (c) advice to remain active during a six-to-seven week waiting period. Sensitivity analyses used multiple imputation by chained equations to assess for bias due to missing data.

Results: 538 participants (54% female; mean age 49yrs, SD 14) provided data. The relationship between pain and disability at time of physiotherapy referral was partially mediated by kinesiophobia, which explained 12.6% of the total effect of pain on disability (95%CI 5.3-16.8%). Longitudinally, there was evidence that development of prognostic pessimism over the initial treatment period partially mediated the relationship between pain at time of referral and disability 26wks later (14.2% of the total effect, 95%CI 0.04%-23.4%). Sensitivity analyses using multiple imputation made only minor differences to the results, and no difference to their interpretation.

Conclusion: We have demonstrated that kinesiophobia and prognostic pessimism partially mediated the distal upper limb pain-disability relationship. While psychological distress and activity avoidance have been found to mediate the relationship in back and lower limb pain, they were not identified in this population. This would suggest that cognitive constructs may be more important treatment targets for distal upper limb pain.

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WITHDRAWN

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Abstract Number: 2210

WITHDRAWN

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WITHDRAWN

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Abstract Number: 2213

The Four Stages of Fibromyalgia: Potential for More Precise Treatment Approaches

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Background/Purpose: Fibromyalgia (FM) is characterized by chronic widespread pain and tenderness making it difficult to manage. Accounting for FM heterogeneity might elicit an improvement in patient treatment. Chronic diseases are a dynamic process with increasing and decreasing symptomology and clinical manifestations. Several diseases similar to FM have known chronicity trends; rheumatoid arthritis has stages indicated by disease progression, and according to the Centers for Disease Control and Prevention, three different disease courses exist. The objective of this study was to cluster patients into stages, or similar disease profiles, based on severity of FM (i.e., patient co-morbidities, regions of pain, and procedures), as well as time.

Methods: We identified 2,529 FM patients with a total of 79,570 clinical visits between January 1999 and February 2014 from an administrative claims data. Patients were clustered based on similarity of co-morbidities (symptom severity), region of pain (widespread pain), and procedures (treatment intensity) by implementing a sequence of unsupervised and supervised learning techniques. Text analysis and a review of physician notes were conducted to obtain secondary conditions and diseases to assist in the understanding of stage classification.

Results: There were four parent stages of FM identified and labeled: 1) regional FM with classic symptoms; 2) generalized FM with increasing widespread pain and some additional symptoms; 3) FM with advanced and associated conditions, increasing widespread pain, increased sleep disturbances, and chemical sensitivity; and 4) secondary FM reactive to disease. Approximately 45% of patient observations were reclassified when the constraints of time were lifted. Most notably, the rate of stage misclassification dramatically reduced from 11.2% to 4.4% when patients were reclassified based on exponential increases in disease severity as opposed to time. These findings lend support that FM stages are more characterized by disease severity and are less time-dependent.

Conclusion: Generally, patients increase in their symptom severity and region of pain by stage. Parallels are beginning to emerge between the different stages and presentations of underlying conditions. General clustering seems to be occurring but requires more research. Nonetheless, this work makes a case for the presence of FM stages in which important clinical ramifications exist that may lead to a more precise treatment approach for FM patients.

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Abstract Number: 2215

WITHDRAWN

Abstract Number: 2216

WITHDRAWN

Abstract Number: 2217

Adherence to Drug Therapy in Patients with Fibromyalgia

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Background/Purpose: As in other chronic diseases, adherence to the treatment regimen of patients with fibromyalgia (FM) is low (between 30 and 80%), depending on the definition of adherence and the methodology used to measure it. This study aims to determine the level of adherence to drug therapy in patients with FM and identify factors associated with non-compliance to therapy.

Methods: an analytical and cross-sectional study was conducted. Patients with FM were included considering the classification criteria (ACR 1990) for both those who were receiving drugs for the treatment for their disease and those who attended the outpatient clinic. For the assessment of adherence, the questionnaires CQR (Compliance Questionnaire on Rheumatology) were used, to assess anxiety GAD-7 (Generalized Anxiety Disorder), to assess depression PHQ-9 (Patient Helth Questionnaire) and to assess the impact disease of the S-FIQ (Spanish Fibromyalgia Impact Questionnaire) were used.

Results: 78 patients were surveyed (70 women). The mean age was 47,3 years. 41% (32 patients) were adherent (CQR> 80). 41% (19) of the nonadherent had severe depression according to the PHQ-9 vs 6% (2) of those which if adhered. 67% (31) of the nonadherent had severe anxiety by questionnaire GAD-7 vs the 16% (5) of which adhered. It was also observed that 87% (40) of nonadherent had low quality of life measured by the S-FIQ (S-FIQ >50%) questionnaire vs. a 50% (16) of the adherent members who had good quality of life. The three cases showed a statistically significant association with non-adherence to drug treatment.

Conclusion: it was observed that less than half of FM patients were adherent to drug treatment. Factors associated with nonadherence were depression, anxiety and reduced quality of life.

Disclosure: G. Bennasar Sr., None; **A. Secco**, None; **M. Mamani**, None.

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Abstract Number: 2218

Do Some Patients with Distal Upper Limb Pain Benefit More Than Others from Advice to Remain Active?

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Background/Purpose: We have previously shown that, among patients awaiting physiotherapy for distal upper limb pain/disability, advice to remain active is associated with greater functional recovery compared to advice to rest. In low back pain, studies of stratified care have shown that matching patients to optimal interventions reduces costs of treatment, and can help individuals return to work. In contrast, few studies have examined whether patients benefit from a stratified approach to distal upper limb pain management. Thus, the aim of the current study was to investigate whether pre-specified patient characteristics (baseline pain intensity, pain duration, gender, employment status, pain history, and diagnostic category) modified the effect of advice, among patients referred for physiotherapy with distal upper limb pain.

Methods: This observational study used data from a UK multi-centre randomized controlled trial. Participants underwent a clinical examination and completed questionnaires before trial randomisation to either (a) advice to rest; or (b) advice to remain active, at the start of the six-to-seven week waiting time for physiotherapy. Follow-up questionnaires were mailed 6, 13 and 26 weeks later. Questionnaire items asked about pain intensity (11-point Numeric Rating Scale), employment status, pain duration and pain-related disability, using the modified

Disabilities of the Arm, Shoulder and Hand questionnaire (mDASH). A difference of 1 unit on the mDASH equates to 1 additional functional limitation and was therefore interpreted as clinically meaningful change. The interaction between advice group and the 6 pre-defined factors on change in disability at 6, 13 and 26 weeks was quantified using linear regression, controlling for the level of disability at the time of referral.

Results: 282 participants with complete follow-up data were included in this analysis (57% female; mean age 50yrs, SD 14). There was a significant interaction between gender and treatment effect at 26 weeks (p=0.011). Males who received advice to remain active had greater functional improvement than males advised to rest, a difference that was both statistically significant and clinically meaningful (mDASH improvement 1.47, p=0.003). In contrast, among females, active advice was not associated with an improvement in outcome (mDASH improvement -0.17, p=0.68). This sex-treatment interaction was evident from 6-week follow-up (mDASH improvement in men, compared to women, among those advised to remain active: 1.11, p=0.05). No other factors were identified as effect modifiers.

Conclusion: Of six patient characteristics investigated as possible effect modifiers of advice for distal upper limb pain, only gender was identified to be of statistical significance and clinical importance. Active advice, previously found to be more effective overall, was particularly effective in males. It should be noted that the trial was not powered specifically to look at interactions and that this secondary data analysis was hypothesis-generating. The mechanisms driving the gender effect require further study before the introduction of stratified management approaches in distal upper limb pain can be supported.

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Abstract Number: 2219

Clinical and Radiological Characteristics of Patients with Adhesive Capsulitis and Shoulder Impingement Syndrome

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Background/Purpose: Idiopathic adhesive capsulitis is described as a frozen shoulder with severe and global

range-of-motion loss of unknown etiology. On the other hand, the most common cause of shoulder pain is impingement syndrome. The aim of our study was to investigate of clinical and radiological features of adhesive capsulitis and shoulder impingement syndrome according to functional outcomes.

Methods: One hundred and fifty patients with adhesive capsulitis and shoulder impingement syndrome enrolled. The demographic characteristics of the patients were examined. Magnetic resonance imaging (MRI) and routine blood test results were recorded. Constant Shoulder Score (CSS), Shoulder Disability Questionnaire (SDQ) and Visual Analog Scale (VAS) were used to measure pain and functional status. Statistical analysis was made using NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA).

Results were evaluated considering the significance level $p< 0.05$. **Results:** The mean age of the patients was 54.57±6.20 years (min:36; max: 66; median: 55) out of 150 patients, 96 were women and 54 were men. Seventy-five patients had adhesive capsulitis and Seventy-five patients had shoulder impingement syndrome. There was no statistically significant difference between the two groups with respect to descriptive characteristics of the patients ($p>0.05$). Hypertension (HT), diabetes mellitus (DM) and hyperlipidemia were significantly higher were detected in patients with adhesive capsulitis ($p <0.05$). No significant was noted difference in terms of thyroid disease, and cardiac disease between the groups ($p> 0.05$). The functional disturbance and disability evaluated by CSS and SDQ were significantly higher in patients with adhesive capsulitis ($p<0.05$). According to the radiological findings, partial rupture and effusion were significantly higher in patients with shoulder impingement syndrome ($p<0.05$). No significant difference was determined between the groups according to the presence of labral tear or total rupture in MRI results ($p>0.05$). No difference was noted CSS and SDQ scores according to presence of partial rupture in both groups ($p>0.05$).

Conclusion: In present study, the radiological findings may not be associated with severe pain or poor functional status. DM, HT and accompanying hyperlipidemia were risk factors for adhesive capsulitis. Comorbid diseases should be kept in mind. It is important to identify high-risk patients to prevent and to arrange the treatment strategies.

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Abstract Number: 2220

Impact of Fibromyalgia on DAS28 in Patients with Rheumatoid Arthritis

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Background/Purpose: To estimate the prevalence of secondary fibromyalgia (FM) in patients with RA and its effect on the disease activity score (DAS28) in a tertiary care teaching hospital.

Methods: Patients aged above 18 years who had been diagnosed with rheumatoid arthritis (RA) as per the ACR/EULAR criteria 2010 were included in the study. Fibromyalgia (FM) was diagnosed using the ACR 1990 criteria. Patients with incomplete clinical data and above 75 years were excluded. Laboratory and clinical findings were entered in a structured format. DAS28 was assessed using ESR and supplemented with CRP, only if ESR was not available. Statistical analyses were performed using SPSS v16 software. The study was approved by the Institutional Ethics Committee of PGIMER, Chandigarh.

Results: A total of 371 subjects were recruited with a mean age of 46 (±12.3) years. The study population followed normal distribution in age with a median of 46 years and mode of 45 years. The male to female ratio was 1:5.4. The prevalence of FM was 18.1% amongst RA patients (67/372). In patients with secondary FM 92.5% were female compared to 82.6% without FM. 65.7% patients with FM had a disease duration of greater than 5 years compared to 46.9% patients without FM. 71.6% of patients with FM had high disease severity compared with only 43.9% patients without FM. The average DAS28 score was significantly higher [($p<0.001$); 95% CI: 1.2 - 3.7] in patients with secondary FM (5.68±1.49) compared to those without FM (4.92±1.62). In sub-analyses of independent variables of DAS28, tender joint counts were significantly higher [($p<0.001$); 95% CI: 3 – 8.8] in patients with FM (17.90) as compared to RA patients without FM (11.98). Also, the patients' global health scores were worse [$p<0.001$; 95% CI: 5.5 - 21.6] in RA patients with FM. Swollen joint count and ESR values were comparable in both the groups.

Conclusion: The present study reports that 18.1% of the RA patients had associated FM. TJC and GH of patients are affected by the co-existing FM. The study advocates the development of new outcome measures that are more objective and depend upon reliable laboratory biomarkers/ultrasound evidence of synovitis for assessing the disease activity of RA patients.

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Abstract Number: 2221

Recognition of Secondary Fibromyalgia Using an Index of 3 Components of the Multi-Dimensional Health Assessment Questionnaire: 90% Agreement with ACR Criteria for Fibromyalgia

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Background/Purpose: Secondary fibromyalgia (FM) is seen 15-20% of patients with rheumatoid arthritis (RA) (1), systemic lupus erythematosus (SLE) (2), osteoarthritis (OA), and other rheumatic diseases. New formal ACR criteria for FM are available (3), but not used in most routine care, largely because it is not feasible for patients with different diagnoses to complete different questionnaires in busy clinical settings. Scores on a Multidimensional Health Assessment Questionnaire/routine assessment of patient index data (MDHAQ /RAPID3) may provide clues to FM (4, 5). We analyzed MDHAQ/RAPID3 scores in patients with RA or OA, who had or did not have secondary FM, to develop a simple index to identify patients with secondary FM comparable to ACR FM Criteria.

Methods: All patients with all diagnoses at one academic center complete an MDHAQ/RAPID3 at all visits before seeing the rheumatologist. Nine MDHAQ measures were studied: 1. a 0-10 physical function (FN) scale; 2. pain (PN) and 3. patient global estimate (PATGL) on 0-10 visual analog scales (VAS) (compiled into a 0-30 RAPID3); 4. sleep quality; 5. anxiety; 6. depression; 7. 0-10 fatigue VAS; 8. 0-48 RADAI self-report of painful joints; 9. 60 item symptom checklist. Patients in this study also completed a widespread pain questionnaire to assess ACR FM Criteria (6), and the rheumatologist assigned a diagnosis of FM independent of any questionnaire results. The 9 MDHAQ measures were analyzed in patients with primary RA or OA for frequencies and area under receiver-operating-characteristic (ROC) curves for secondary FM according to ACR FM Criteria or clinical criteria, to develop a simple FM index for optimal discrimination of secondary FM vs no secondary FM.

Results: 84 patients with OA or RA were studied; 58 did not have secondary FM by ACR criteria or clinical diagnosis, 16 had FM by both criteria, 6 had FM only by clinical criteria, and 4 only by ACR criteria. Agreement between clinical and ACR Criteria was substantial (kappa 0.68, $p<0.001$) (6), and only data for ACR Criteria are presented. Patients who had secondary FM had higher mean scores on all 9 MDHAQ scales studied and ROC areas>0.80. A simple MDHAQ 0-3 FM index involves allocating one point each for pain≥6/10, RADAI≥16/48, and symptom checklist≥16/60. A score of 2/3 on the MDHAQ FM index classified identically 90% of patients with FM by ACR Criteria.

Conclusion: A simple 0-3 MDHAQ-FM index based on pain, RADAI self-report joint count, and symptom checklist provides 90% agreement with the new ACR FM criteria. The MDHAQ is feasible in busy clinical settings, as the same questionnaire can provide important clinical information in all patients with all diagnoses, and appears useful to identify secondary FM.

	Cut-off point, sensitivity, and specificity for MDHAQ item and the composite FM in the Liverpool Hospital Australia dataset (N = 84). FM diagnosis by ACR criteria				
	Cut-off point	**ROC Area**	**Sensitivity**	**Specificity**	**Correctly classified**
Symptom checklist (0-60)	≥ 16	0.98	77.3%	83.9%	82.1%
RADAI (0-48)	≥ 16	0.90	84.2%	80.8%	81.7%
MDHAQ-PAIN (0-10)	≥ 6	0.88	86.4%	75.8%	78.6%
Composite FM	≥ 1		94.7%	57.7%	67.6%
	≥ 2		94.7%	88.5%	90.1%
	≥ 3		63.2%	96.1%	87.3%

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Tai Chi Is More Effective Than Aerobic Exercise in Treating Fibromyalgia: A Randomized Controlled Trial

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Background/Purpose: Fibromyalgia is a complex disorder with strong psychological and pain components and is best managed with multidisciplinary therapies. Previous studies have suggested that Tai Chi is an integrated mind-body approach that enhances both physical and mental health and may be an effective treatment for fibromyalgia. It is unknown however whether Tai Chi is better than aerobic exercise, a common treatment for this population, and if so whether the effectiveness of Tai Chi depends on its duration and intensity.

Methods: We conducted a 52-week, single-blind, randomized trial of Tai Chi vs. aerobic exercise for fibromyalgia (ACR 1990 and 2010 diagnostic criteria). Participants were randomized to 1 of 4 Tai Chi intervention groups: 12 or 24 weeks of Tai Chi once or twice per week, or an aerobic exercise intervention held twice per week for 24 weeks. The primary endpoint was change in the Revised Fibromyalgia Impact Questionnaire (FIQR) score at 24 weeks. Secondary endpoints included change in patient global assessments, the Hospital Anxiety and Depression scale (HADS), depression (Beck II), sleep quality (PSQI), arthritis self-efficacy scale (ASES-8), and 6-minute walk tests and health-related quality of life (SF-36 PCS and SF-36 MCS). The comparative efficacy of the five treatments was determined using longitudinal regression based on the intent-to-treat principal using evaluations made at 0, 12, 24 and 52 weeks. We report treatment contrasts at 24 weeks focusing on comparisons of: 1) Aerobic Exercise vs. average of four Tai Chi groups; 2) average of 12 week Tai Chi vs 24 week Tai Chi; and 3) average of once per week Tai Chi vs. twice per week Tai Chi.

Results: The mean age of subjects was 51.8y (SD 12.4), mean disease duration 8.8y (7.5), mean BMI 30.0 kg/m^2 (SD 6.7), 93% were female, and 61% were white. Treatment groups did not differ in baseline outcome expectation. All Tai Chi groups (averaged across the 4 groups), compared to aerobic exercise showed statistically significant improvements in FIQR ($p=0.03$), patient global assessment ($p=0.005$), anxiety and depression ($p=0.006$), and self-efficacy ($p=0.0004$). Significant improvements for most but not all outcomes favor 24 week vs. 12 weeks, compared to aerobic exercise **(Table 1).** Participants in Tai Chi groups had significantly higher class attendance than the Aerobic Exercise group (54-63% vs 35%), $p<0.0001$). No serious adverse events were observed.

Conclusion: Tai Chi significantly reduced the symptom severity of fibromyalgia and was more effective than aerobic exercise for a variety of physical and mental health outcomes among a general population of individuals with fibromyalgia. The higher attendance rate in Tai Chi could also indicate that it is a preferable intervention in this patient population, though further study is warranted. Tai Chi should be considered as an important non-pharmacologic treatment option in patients with Fibromyalgia.

Table 1: Change in Outcomes from baseline to 24 weeks by groups (4 Tai Chi groups vs. Aerobic Exercise)						
Outcome	**Aerobic Exercise**	**Tai Chi 1x12 weeks**	**Tai Chi 2x12 weeks**	**Tai Chi 1x24 weeks**	**Tai Chi 2x24 weeks**	**P-value (Tai Chi vs Aerobic Exercise at 24 weeks**
FIQR*	-9.2 (-14.3, -4.1)	-11.4 (-18.7, -4.1)	-11.4 (-18.4, -4.4)	-16.7 (-23.4, -10.1)	-25.4 (-32.3, -18.4)	**0.03**
Sleep Quality*	-1.1 (-2.1, -0.1)	-0.8 (-2.2, 0.6)	-1.3 (-2.7, 0.1)	-1.9 (-3.2, -0.6)	-2.1 (-3.5, -0.7)	0.48
Patient Global*	-0.4 (-1, 0.2)	-1 (-1.8, -0.1)	-1.3 (-2.2, -0.5)	-1.6 (-2.4, -0.8)	-2.0 (-2.8, -1.2)	**0.005**
Beck Depression*	-5.2 (-7.7, -2.7)	-3.8 (-7.5, -0.2)	-4.3 (-7.8, -0.8)	-7.5 (-10.8, -4.1)	-9.5 (-13.0, -6.0)	0.49
HADS_Anxiety*	0.0 (-0.9, 0.9)	-1.9 (-3.2, -0.7)	-0.8 (-2.0, 0.4)	-1.4 (-2.5, -0.2)	-2.1 (-3.4, -0.8)	**0.006**
Self-efficacy^	-0.1 (-0.7, 0.5)	0.8 (0, 1.7)	1.1 (0.3, 1.9)	1.5 (0.7, 2.2)	1.5 (0.6, 2.3)	**0.0004**
SF-36 PCS^	4.0 (2.0, 6.0)	2.4 (-0.4, 5.2)	3.9 (1.2, 6.6)	5.0 (2.5, 7.6)	5.9 (3.1, 8.8)	0.79
SF-36 MCS^	0.9 (-1.8, 3.6)	3.2 (-0.4, 6.9)	0.3 (-3.2, 3.9)	5.3 (1.9, 8.7)	7.4 (3.6, 11.2)	0.06
6 min walk test (meters)^	17.7 (1.5, 33.9)	29 (7.4, 50.7)	31.6 (9.8, 53.3)	23.1 (2.6, 43.7)	17.6 (-5.2, 40.4)	0.43

*higher values indicate worse function, negative change value indicates improvement. ^higher values indicate better function, positive change value indicates improvement

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tai-chi-is-more-effective-than-aerobic-exercise-in-treating-fibromyalgia-a-randomized-controlled-trial

Abstract Number: 2223

Can Fibromyalgia be Empirically Defined By the Number of Pain

Locations Plus Symptoms?

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes - Poster II: Clinical Focus

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Both the revised 2010 FM criteria (Wolfe et al.) and the 2013 FM criteria (Bennett et al.), rely on counting the number of pain locations plus a certain number of symptoms as presumptive evidence for the patient having widespread pain. However, little is known about how these criteria operate in the primary setting.

Methods: A descriptive cross sectional study assessed adults being seen in2 primary care clinics. Data sources included chart review, history, physical exam and patient-completed surveys.

Results: Altogether 357 patients were studied (all female, age 50 ± 16.3 years). Chart review revealed that 50 patients carried a diagnosis of FM in their medical record. However, only 17 patients fulfilled the 2013 FM diagnostic criteria. A comparison of the 2 diagnostic groups is shown in the following table:

Test	Clinician diagnosed FM (n=50)	Criteria diagnosed FM (n=17)	P Value
Number of pain locations	12.7±7.86	15 ± 4.1± 4.09	<0.001
SIQR symptom score	32.7±9.4	36.1± 8.6	0.17
BP pain threshold	132.3±51.5	122.1±18.4	0.47
Total SIQR score	66.7±18.4	62.5 ± 18.4	0.41
SIQR function	50.2±20.10	52.7±20.10	0.67
SIQR pain	6.5± 1.97	7.1 ± 2.01	0.26
SIQR tenderness	6.8±32.86	7.9±2.49	0.13
SIQR sleep	6.5±3.67	8.1 ± 2.35	0.99
Environmental sensitivity	6.8±3.21	7.5±3.06	0.42
“I have a persistent deep aching pain over most of my body.”	7.9±2.59	9.1 ± 1.13	<0.01

Conclusion: These results show that clinician diagnosed and criteria diagnosed patients were very similar in most descriptive variables. The 2013 criteria are based on a pain locations score >16 and a SIQR symptom score of>21. It is seen that the symptoms score does not account for the difference in diagnosis, but the number of pain locations was significantly less in the clinician diagnosed FM. Thus it appears that there is a group of “fibromyalgia like” patients that differ from 2013 criteria patients only in the number of pain locations. This raises 3 questions: 1. What should we call the clinic diagnosed patients who are symptomatically similar but differ from criteria diagnosed patients only in the number of pain locations? 2. Is the number of pain locations representative of the concept of widespread pain? 3. Would the concept of widespread pain be better defined by a question, such as seen in the last row?

Disclosure: R. M. Bennett, None; **K. D. Jones**, None; **J. H. Aebischer**, None; **A. W. St. John**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/can-fibromyalgia-be-empirically-defined-by-the-number-of-pain-locations-plus-symptoms

Abstract Number: 2224

Influence of Caffeine on Opioid Analgesics in Fibromyalgia

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Caffeine's action as an NSAID adjuvant are well understood, yet little clinical research has explored its effects on opioid analgesia. We present data from a large sample of fibromyalgia patients assessing the effect of caffeine use in the presence and absence of opioid analgesics.

Methods: 962 patients (67% female) presenting to a tertiary pain clinic and meeting the 2011 American College of Rheumatology (ACR) survey criteria for fibromyalgia were included. Patients completed the Brief Pain Inventory (BPI), Hospital Anxiety and Depression Survey (HADS), PROMIS fatigue measure, pain catastrophizing scale, and Oswestry Disability Index (ODI). Consumption of caffeinated beverages and opioid analgesics was assessed using a dichotomous item: patients indicated "yes" or "no" to daily consumption. General linear models were used to determine effect of caffeine use on independent measures. Gender and smoking status differed in univariate analysis and were controlled for as covariates. Adjusted mean differences (x) (standard error) are reported. Analyses were performed with SPSS 22.

Results: 568 (59%) patients were on current opioid therapy (66% female) and 394 (41%) were not (67% female). In patients on opioid therapy, caffeine consumers had significantly lower pain severity [$F= 4.3$, $p= .04$, $x= .33(.16)$], pain interference [$F= 8.1$, $p< .001$, $x= 0.5(0.2)$], fatigue [$F= 14.2$, $p< .001$, $x= 2.5(0.7)$], depression [$F= 5.2$, $p= .01$, $x= 1.0(0.4)$], catastrophizing [$F= 11.0$, $p< .001$, $x= 3.8(1.2)$] and disability [$F= 12.9$, $p< .001$, $x= 3.3(0.9)$] compared to non-caffeine consumers. Anxiety did not differ between caffeine groups. In the opioid negative group, caffeine consumers reported significantly less fatigue than non-consumers [$F= 5.3$, $p= .02$, $x= 2.0(0.9)$]. No other measures differed significantly between caffeine consumers and non-consumers in patients not on opioid therapy.

Conclusion: Fibromyalgia patients on opioid therapy that also use caffeine reported significantly lower symptoms compared to patients that do not consume caffeine. However, in patients not on opioid therapy, caffeine consumers don't share the same benefits seen in subjects on opioid therapy. These results suggest that consumption of caffeine in conjunction with opioid analgesics could possibly provide therapeutic benefits not seen with opioids or caffeine alone. Further research is needed to assess caffeine's adjuvant effects on opioid analgesics in chronic pain.

Disclosure: J. R. Scott, None; **D. J. Clauw**, None; **C. M. Brummett**, None; **R. E. Harris**, None; **A. L. Hassett**, None; **S. E. Harte**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/influence-of-caffeine-on-opioid-analgesics-in-fibromyalgia

Abstract Number: 2225

Treatment Outcomes of Newly and Formerly Diagnosed Patients with Fibromyalgia after Fibromyalgia Treatment Program

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Fibromyalgia, Soft Tissue Disorders, Regional and Specific Clinical Pain Syndromes - Poster II: Clinical Focus

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: We compared treatment outcomes between newly diagnosed versus formerly diagnosed patients seen in the brief interdisciplinary fibromyalgia treatment program (FTP). The FTP includes diagnostic evaluation as well as treatment, focused on cognitive behavioral therapy.

Methods: We studied 978 fibromyalgia who underwent the FTP and met the 1990 ACR clinical criteria for fibromyalgia. We abstracted the patients' diagnosis information from electronic medical record. All the 978 patients completed the Fibromyalgia Impact Questionnaire (FIQ) and the Short Form-36 Health Status Questionnaire (SF-36) at baseline.

Results: Five hundreds thirty-five patients (55%) received diagnosis of fibromyalgia when seen in FTP and were defined as newly diagnosed group. The rest, 443 patients (45%), were previously diagnosed with fibromyalgia and were confirmed to have fibromyalgia at the FTP, were defined as formerly diagnosed group. It had been 3.6 (9.2 SD) years for those formerly diagnosed patients had their fibromylgia diagnosed before they seen in FTP. Those formerly diagnosed patients were more likely to be older, and to have higher BMI and longer duration of fibromyalgia symptoms compared to early diagnosed patients. After adjusting for these differences, no differences were found in the FIQ total score, FIQ subscales, and all the SF-36 subscores between newly and formerly diagnosed patients. After treatment, 313 patients (58.5%) in newly diagnosed group and 224 patients (50.3%) in formerly diagnosed group completed the 6-12 month follow-up questionnaires, and both groups tended to improve excepted for the FIQ depression subscale and SF-36 general health perceptions and role emotional subscores; however, the formerly diagnosed patients had significantly less improvement in the FIQ subscales in work missed days (P=0.04).

Conclusion: In our clinic sample, included both newly and formerly diagnosed patient with over ½ being newly diagnosed, there was no differences on symptom severity and quality of live between newly and formerly

diagnosed fibromyalgia patients. Both groups benefited from the FTP similarly. Brief, interdisciplinary FTP could both benefit incident and prevalent fibromyalgia patients; moreover, these newly diagnosed patients might miss less work days after treatment. Further studies are needed to verify our results and to demonstrate the mechanisms underneath this phenomenon.

Disclosure: J. Jiao, None; **C. A. Luedtke**, None; **A. Vincent**, None; **T. H. Oh**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/treatment-outcomes-of-newly-and-formerly-diagnosed-patients-with-fibromyalgia-after-fibromyalgia-treatment-program

Abstract Number: 2226

Independent and Combined Association of Overall Physical Fitness and Subjective Well-Being Components with Fatigue in Fibromyalgia

Fernando Estévez-López[1,2], Alberto Soriano-Maldonado[1], Inmaculada C Álvarez-Gallardo[1], Víctor Segura-Jiménez[1,3], Maria Rodriguez-Ayllon[1], Manuel Herrador-Colmenero[1], Manuel Pulido-Martos[4], Rinie Geenen[2], Ana Carbonell-Baeza[3] and Manuel Delgado-Fernández[1], [1]University of Granada, Granada, Spain, [2]Utrecht University, Utrecht, Netherlands, [3]University of Cádiz, Cádiz, Spain, [4]University of Jaén, Jaén, Spain
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Session Date: Tuesday, November 15, 2016

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The highest prevalence of severe fatigue in rheumatic diseases is observed in FM[1]. Physical fitness and subjective well-being have been suggested as resilience resources that can help to deal with FM symptomatology[2,3]. The present study aimed to examine: (i) the independent association of overall physical fitness and subjective well-being with fatigue, and (ii) the combined association of overall physical fitness and subjective well-being components with fatigue in FM.

Methods: We used data from the al-Ándalus project, which is a population-based cross-sectional study. A total of 420 women with FM, who met the 1990 ACR FM criteria, were included in the present study. Fatigue was assessed with Multidimentional Fatigue Inventory. Physical fitness was measured with the Senior Fitness Test battery. The scores of each physical fitness test were transformed to standardized *z*-scores ([value-mean]/standard deviation) to compute an overall physical fitness score. Subjective well-being was assessed with two questionnaires: the Positive and Negative Affect Schedule (for positive affect and negative affect) and Satisfaction with Life Scale (for satisfaction with life).

Results: Based on preliminary analyses to identify potential confounders, all analyses of the present study were adjusted by age and body fat percentage. All partial correlations between overall physical fitness, positive affect, negative affect, and satisfaction with life and fatigue dimensions were significant (all, $p \leq .004$). Linear regression models showed that: (i) overall physical fitness was independently associated with general fatigue and physical fatigue (both, $p < .001$), (ii) positive affect was independently associated with lower scores at all fatigue dimensions (all, $p < .001$), (iii) negative affect was independently associated with reduced motivation and mental

fatigue (p<.001 and p=.01, respectively), and (iv) satisfaction with life was independently associated with mental fatigue (p=.046). Analyses of covariance showed statistically significant combined associations of overall physical fitness and positive affect with general and physical fatigue (all, p<.001).

Conclusion: Findings of the present study highlight the significance of the association of physical fitness and positive affect with fatigue of women with FM. Further research, using longitudinal data, testing the causality of the present findings is required. **References**: [1]Overman, CL et al., *Clin Rheumatol*. 2016;35(2):409-15. [2]Estévez-López, F et al., *Qual Life Res*. 2015;24(8):1865-73. [3]Sturgeon, JA and Zautra AJ. *Curr Pain Headache Rep*. 2013 Mar;17(3):317. **Funding**: The Spanish Ministry of Economy and Competitiveness (I+D+i DEP2010-15639, I+D+i DEP2013-40908-R, BES-2014-067612, and BES-2011-047133) and of Education (FPU12/00963 and FPU13/01088).

Abstract Number: 2227

Sustained Remission and Relapse Rate after Non-Conventional DMARD Withdrawal in Patients with Rheumatoid Arthritis

Andrea Ramirez-Gomez[1], Aldo Barajas-Ochoa[1], Jose Juan Castaneda-Sanchez[1], Jose Dionisio Castillo-Ortiz[1], Jorge M. Sanchez-Gonzalez[2] and **Cesar Ramos-Remus**[2], [1]Unidad de Investigacion en Enfermedades Cronico-Degenerativas, Guadalajara, Mexico, [2]Vicerrectoria Academica, Universidad Autonoma de Guadalajara, Guadalajara, Mexico

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Health Services Research - Poster III

Session Type: ACR Poster Session C

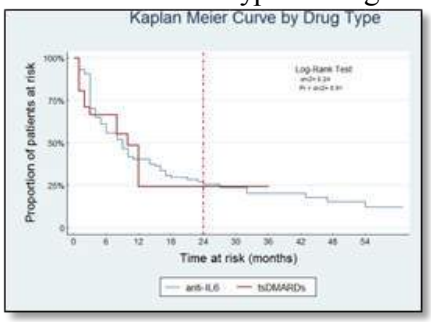
Session Time: 9:00AM-11:00AM

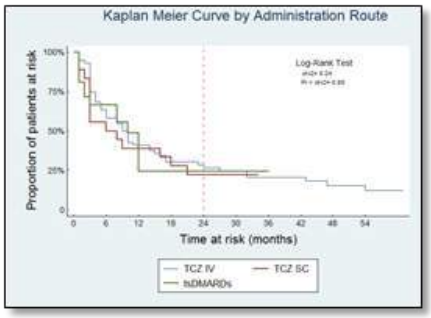
Background/Purpose: The treatment of rheumatoid arthritis (RA) has evolved continuously. The introduction of non-conventional DMARDs, which include biologic and targeted synthetic DMARDs (tsDMARDs), has been a breakthrough. Although there is plenty information on when to initiate these drugs, data on when to stop them is scant. The objective of this study was to assess the length of remission and relapse rate in patients with RA who had to discontinue tocilizumab (TCZ) or tsDMARDs (tofacitinib or baricitinib) due to the completion of extended long-term clinical trials, and to compare the survival curves of disease remission.

Methods: A prospective cohort study of RA patients in remission (DAS28 < 2.6, 0 swollen joints) assembled at the time of their last dose of either tocilizumab (subcutaneous [SC] or intravenous [IV]), tofacitinib or baricitinib. Patients were followed every 8 weeks through a COPCORD questionnaire and every 4 months by an in-office assessment. Doses of methotrexate were not changed. Patients were instructed to contact our center should any RA-related symptoms occur. The primary endpoint was relapse, defined as the presence of ≥1 swollen joints. Kaplan-

Meier curves were calculated per type of drug (TCZ and tsDMARDs) and per route of administration (PO, SC and IV). A log-rank test was used to assess differences among survival curves and Cox regression was used to evaluate variables as predictors of relapse. Significance was set at $p<0.05$.

Results: Ninety-nine patients were analyzed, 88% female, with a mean age of 47±13 years. Sixty patients were treated with TCZ-IV, 18 with TCZ-SC and 21 with tsDMARDs. During the follow-up of 165 person-years, 27 patients (27%) maintained remission. The median time until relapse was 9 months. No significant differences were found between the type of drug or the administration route. No variables were identified as relapse predictors.





Conclusion: Long-term remission is possible in a proportion of patients after suspending a non-conventional DMARD. This effect has been previously reported with multiple biologic agents but not with tsDMARDs. Further studies are required to establish algorithms on the discontinuation of non-conventional DMARDs after achieving remission.

Disclosure: A. Ramirez-Gomez, None; **A. Barajas-Ochoa**, None; **J. J. Castaneda-Sanchez**, None; **J. D. Castillo-Ortiz**, None; **J. M. Sanchez-Gonzalez**, None; **C. Ramos-Remus**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/sustained-remission-and-relapse-rate-after-non-conventional-dmard-withdrawal-in-patients-with-rheumatoid-arthritis

Abstract Number: 2228

Real-World Cost of Treating Inadequate Responders to Anti-Tumor Necrosis Factor Therapy

A Nadkarni[1] and M Brouillette[2], [1]Bristol-Myers Squibb, Princeton, NJ, [2]Truven Health Analytics, Bethesda, MD
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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: RA patients (pts) receiving anti-TNF therapy may have an inadequate response (IR) to 1st-line treatment. Among pts for whom treatment fails, little is known about associated treatment costs or the proportion with an IR to a 2nd-line anti-TNF. We quantified the RA-related healthcare cost of treating pts with an IR to an anti-TNF using an adaptation of a published administrative claims-based algorithm to identify IR. We examined the probability of IR to 1st- and 2nd-line anti-TNF biologics, and assessed RA-related healthcare costs among pts with an IR to 1st- or 2nd-line treatments.

Methods: This was a retrospective, observational cohort study based on administrative claims data. Adults (aged ≥18 yrs) with RA initiating an anti-TNF between 1-1-2009 and 12-31-2013 were included. Pts were required to have continuous insurance enrollment for 12 mths before initiating an anti-TNF, and no treatment with any biologics during this period. Pts who experienced an IR to 1st-line anti-TNF and were treated with a 2nd-line anti-TNF were analyzed as a sub-sample. Variable-length follow-up was measured for both the 1st- and 2nd-line treatments, beginning with initiation of an anti-TNF and continuing until one of the following: use of a biologic other than the initiated anti-TNF, disenrollment from health insurance or reaching the study end date of 12-31-2013. IR was defined as a composite of discontinuation or switch of the initiated anti-TNF, anti-TNF dose escalation, initiation of a new non-biologic DMARD, new/increased oral glucocorticoid (OGC) use/dose or receiving ≥2 injections of glucocorticoid (IGC). Kaplan–Meier analysis was used to calculate probability of IR over time. RA-related healthcare utilization and costs were expressed in per-pt per-month (PPPM) units and corresponded to medical claims with an International Classification of Diseases, Ninth Revision, Clinical Modification diagnosis code for RA, the initiated anti-TNF and non-biologic DMARDs.

Results: A total of 26,785 pts met our inclusion criteria for the 1st-line analysis; 4638 for the 2nd-line analysis. Mean follow-up time was 525 days for 1st line and 383 days for 2nd line; Kaplan–Meier-estimated probabilities of IR were 67% at 6 mths, 82% at 12 mths and 91% at 24 mths for 1st line; 77%, 89% and 95% at 6, 12 and 24 mths for 2nd line. In both lines, the primary reason for IR was discontinuation of initiated anti-TNF (52–61% of pts), followed by: 2+ IGC (30–33%); switch of initiated anti-TNF (23–34%); initiation of a new non-biologic DMARD (14–27%); anti-TNF dose escalation (15–19%); new/increased OGC use/dose (13–15%). Average RA-related PPPM costs were $3883 (SD $10,697) for pts with an IR to 1st-line therapy and $6831 (SD $32,849) for pts with an IR to 2nd-line therapy.

Conclusion: In this retrospective study using real-world data, a high proportion of pts with RA experienced an event indicative of IR to 1st- or 2nd-line anti-TNF treatment. The RA-related healthcare costs of treating pts with IR were substantial.[1]

Disclosure: A. Nadkarni, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **M. Brouillette**, Janssen Scientific Affairs, 2,Truven Health Analytics, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/real-world-cost-of-treating-inadequate-responders-to-anti-tumor-necrosis-factor-therapy

Abstract Number: 2229

Economic Burden of Rheumatoid Arthritis Is Higher for ACPA-Positive Patients

J Shafrin[1], N Hou[1], MG Tebeka[1], L Rosenblatt[2], K Price[2], C Patel[3] and K Michaud[4], [1]Precision Health Economics, Los Angeles, CA, [2]Bristol-Myers Squibb, Princeton, NJ, [3]Bristol-Myers Squibb, Princeton, NY, [4]University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Anti-citrullinated protein antibodies (ACPA) have emerged as promising serological biomarkers of rapidly progressing RA and are associated with more severe disease and joint damage. ACPA testing has been increasingly used as a routine tool for RA diagnosis. Furthermore, treatment efficacy has been shown to vary by ACPA-positive (+) status.[1] However, little is known about the economic burden of patients with RA who are ACPA+.

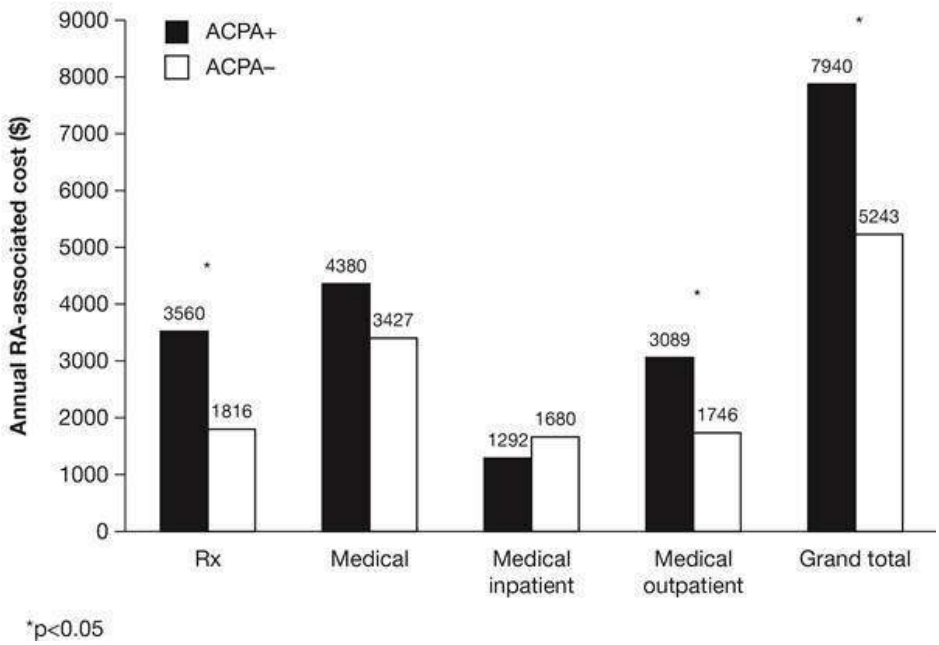
Methods: IMS PharMetrics Plus health insurance claims and electronic medical record (EMR) data from 2010 to 2015 were used to identify patients with incident RA. Patients were ≥18 years of age, had ≥1 inpatient or ≥2 outpatient claims reporting an RA diagnosis code (International Classification of Disease, Ninth Revision, code 714.0), and had an anti-cyclic citrullinated peptide (anti-CCP, a surrogate of ACPA) antibody test within 6 months of diagnosis. Incident patients were defined as those who had no claims with an RA diagnosis code in the 6 months before the first observed RA diagnosis. The primary outcome of interest was RA-related medical expenditure, defined as the sum of payer- and patient-paid amounts for all claims with an RA diagnosis code. Secondary outcomes included healthcare utilization metrics such as treatment with a DMARD and physician visits. Generalized linear regression models were used for each outcome, with ACPA+ status (anti-CCP ≥20 U/mL), age, sex and Charlson co-morbidity index as explanatory variables.

Results: Of 647,171 patients diagnosed with RA, 89,296 were incident cases meeting inclusion criteria and 47% (n=42,285) had an anti-CCP test. Restricting the sample to 9747 patients with a linked EMR, 859 reported an ACPA test result. Of these, 25% (n=212) were ACPA+ and 26% (n=219) were male. Compared with ACPA-negative (–) patients, adjusted results showed that ACPA+ patients were more likely to use either conventional (71.2 vs 49.6%, $p<0.001$) or biologic (20.3 vs 11.8%, $p<0.001$) DMARDs during the first year after diagnosis, and had more physician visits (5.57 vs 3.91 times/year, $p<0.001$). The annual RA-associated total expenditure was $7940 for ACPA+ and $5243 for ACPA– patients (Δ=$2697, p=0.002; Figure 1). Medical expenditure (i.e. excluding prescription drug costs) was $4380 for ACPA+ and $3427 for ACPA– patients (Δ=$954, p=0.168).

Conclusion: Patients with RA who are ACPA+ have a higher RA-related economic burden than patients who are ACPA–. Providers may consider utilizing the results of anti-CCP testing to inform treatment decisions in this higher-cost population of patients with RA.

1. Sokolove JS, et al. *Ann Rheum Dis* 2016;**75**:709–14.

Figure 1. Economic Burden of RA by ACPA Status



Disclosure: J. Shafrin, Precision Health Economics, 3; **N. Hou**, Precision Health Economics, 3; **M. Tebeka**, Precision Health Economics, 3; **L. Rosenblatt**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **K. Price**, Bristol-Myers Squibb, 3; **C. Patel**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **K. Michaud**, Rheumatology Research Foundation, Pfizer, 2.

Abstract Number: 2230

Models Using Claims-Based Administrative Data Are Poor Predictors of Rheumatoid Arthritis Disease Activity in VA Rheumatoid Arthritis (VARA) Patients

Brian Sauer[1], Chia-Chen Teng[2], Neil Accortt[3], Zachary Burningham[4], David Collier[5], Mona Trivedi[6] and Grant W. Cannon[7], [1]IDEAS Center and Division of Epidemiology, HSR&D SLC VA Medical Center and University of Utah, Salt Lake City, UT, [2]Salt Lake City VA Medical Center and University of Utah, Salt Lake City, UT, [3]Center for Observational Research, Amgen, Inc., C, CA, [4]SLC Veterans Affairs Medical Center, SLC IDEAS Center, Salt Lake City, UT, [5]Amgen Inc., Thousand Oaks, CA, [6]Amgen, Thousand Oaks, CA, [7]Internal Medicine, Veterans Affairs Salt Lake City Health Care System and University of Utah School of Medicine, Salt Lake City, UT

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Session Time: 9:00AM-11:00AM

Background/Purpose: The goal of this study was to validate a claims-based statistical model to predict disease activity measured by the 28-joint count Disease Activity Score (DAS28) in a population of Veteran patients enrolled in the VARA registry.

Methods: VARA enrolled Veterans were included in the study if they had a healthcare encounter during the 365-days prior to their DAS28 score and were without diagnoses of cancer, organ transplantation, or other autoimmune diseases. Models using claims data were developed to predict the first DAS28 fulfilling these criteria. Three models were developed based on initial selection of variables for analyses. All variables included in the model were required to have a prevalence in the population ³1%. The 1st model started with 253 variables believed to be associated with disease activity (all clinical predictors). The 2nd model leveraged hierarchical classification systems for pharmacy, procedure and diagnostic codes along with the clinically derived variables for high-dimensional variable selection of 1,275 possible predictors (all predictors). The 3rd approach pre-screened all predictors with a significant bivariate association with the DAS28 resulting in 279 predictors (pre-screening). Models were also compared for patients with <5 years of RA disease to those ³5 years of RA disease. The least absolute shrinkage and selection operator (LASSO) with 5-fold cross-validation was used for variable selection and model development. The classification accuracy was examined for 4 disease activity categories: remission (<2.6), low (2.6-3.1), moderate (3.2-5.1) and high (>5.1) activity.

Results: There were 1,582 Veterans who fulfilled inclusion criteria. The adjusted r-square for the 3 models tested ranged from 0.221-0.223 (Table 1). The number of predictors in the final models were 32 for the clinical predictors, 45 for all predictors and 46 among pre-screened. The adjusted r-square for models based on patients with <5 years (n=429) of RA disease were slightly better than for patients with ³5 years (n=1056) of RA disease. Correct Classification ranged from 40% to 41% for the three models.

Conclusion: The multiple models tested found many predictors with significant unique correlation with the DAS28. Nevertheless, the overall model performance revealed similar results and showed relatively weak overall predictive accuracy in measuring disease activity when using DAS28 as the dependent variables. The models performed poorly at predicting patients with remission and high disease activity making the overall correct classification rate <50% for all models. Duration of disease did not have a large impact on model performance. Future research should investigate additional strategies to collect disease activity measures directly from medical records and allow inclusion of additional laboratory and other clinical data.

Table 1: Model Validation by Initial Set of Predictor Variables

Variable Sets			All Clinical Predictors	All Predictors	Pre-screening
Potential Predictors			253	1275	279
Potential Predictors with ≥ 1% prevalence (i.e., predictors put in model)			175	567	230
Predictors in final model			32	45	46
5-fold cross-validated R-Square (test)			0.237	0.243	0.246
5-fold cross-validated Adj. R-Square (test)			0.221	0.221	0.223
<5 years of RA disease Adj. R-Square (test)			0.218	0.190	0.196
≥5 years of RA disease Adj. R-Square (test)			0.186	0.185	0.185
Classification Accuracy					
4 Categories	High	TPR	11%	10%	11%
	(>5.1)	PPV	58%	62%	63%
	Moderate	TPR	85%	88%	87%
	(3.2-5.1)	PPV	43%	43%	43%
	Low	TPR	20%	18%	18%
	(2.6-3.1)	PPV	22%	21%	21%
	Remission	TPR	0.3%	0%	0%
	(<2.6)	PPV	100%	0%	0%
	CCR (95% C.I.)		40% (38%-42%)	41% (38%-43%)	41 % (38%-43%)

CCR = Correct Classification Rate
TPR = True Positive Rate
PPV = Positive Predictive Value

Disclosure: B. Sauer, Amgen, 2; **C. C. Teng**, Amgen, 2; **N. Accortt**, Amgen, 3,Amgen, 1; **Z. Burningham**, Amgen, 2; **D. Collier**, Amgen, 3,Amgen, 1; **M. Trivedi**, Amgen, 3,Amgen, 1; **G. W. Cannon**, Amgen, 2.

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Abstract Number: 2231

Change in Health Care Utilization after Etanercept Initiation in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) have higher healthcare utilization (HCU) and costs than patients without RA[1]. Evidence is mixed as to the impact of biologic treatment on HCU. The purpose of this study was to evaluate HCU before and after etanercept (ETN) initiation.

Methods: We conducted a retrospective cohort study using claims data. Adult RA patients newly exposed to ETN from January 1, 2010 through December 31, 2013 were included. Patients were required to have at least 1 inpatient or outpatient claim for RA (ICD-9-CM 714.0) in the primary position, and at least 1 ETN medication claim; the earliest ETN claim served as index date. Patients were excluded if they had exposure to a biologic DMARD or had a claim for psoriasis, psoriatic arthritis, ankylosing spondylitis, or juvenile idiopathic arthritis. The proportion of days covered (PDC) was calculated and used as a measure of ETN compliance. The primary outcome was the change in HCU (both overall and RA-related) in the year before and after ETN initiation. McNemar's test and paired t-test were used to determine statistical significance for dichotomous and continuous variables, respectively. To compare the HCU across ETN compliance groups, F-test and Chi-square test were used for categorical and continuous variables, respectively.

Results: We identified 6,737 ETN initiators. The mean age was 49.8 years and 77.3% were female. Frequency of medication use for oral corticosteroids, opioid analgesics, NSAIDS and NB-DMARDS decreased significantly from the pre-index to post-index period (Table 1). There was a significant decrease in overall outpatient services, ED visits and hospitalizations from the pre-index to post-index period (data not shown). In the post-index period, there was a statistically significant decrease in HCU factors with increasing ETN compliance (Table 2).

Conclusion: Health care utilization, including medication use, outpatient services and inpatient admissions decreased after ETN initiation. Patients who were the most compliant with their medication experienced significantly lower utilization than non-compliant patients. The reduction in HCU is consistent with a reduction in disease activity as shown in clinical trials of ETN.[2]

1. Michet CJ, et al. Hospitalization Rates and Utilization Among Patients With Rheumatoid Arthritis: A Population-Based Study From 1987 to 2012 in Olmsted County, Minnesota. Mayo Clinic Proceedings. 2015;90:176–183.

2. Moreland LW, et al. Etanercept therapy in rheumatoid arthritis: a randomized, controlled trial. Annals of internal medicine. 1999 Mar 16;130(6):478-86.

Table 1. Pre- and Post-Index Comparison of the use Pharmacologic Treatments for RA

	Pre-index	Post-index	*P-Value*
Medication Use			
NB DMARDs use (n, %)	5,865 (87.1)	5,330 (79.1)	<.001
No. of NB DMARDs use (mean ± SD)	1.3 ± 0.8	1.1 ± 0.7	<.001
Oral corticosteroids (n, %)	4,756 (70.6)	3,817 (56.7)	<.001
Oral opioid analgesics (n, %)	3,695 (54.8)	3,515 (52.2)	<.001
Oral NSAIDs (n, %)	3,421 (50.8)	2,654 (39.4)	<.001

Table 2. Overall and RA-Related Health Service Utilization by Etanercept Compliance

	Pre-index	Post-Index			
		ETN Proportion Days of Covered			
		0-39%	40-79%	80-100%	*P*-Value[a]
	N=6,737	N = 1,899; 28.2%	N = 1,826; 27.1%	N = 3,012; 44.7%	
Overall Utilization					
No. of outpatient services (mean ± SD)	22.0 ± 17.0	24.4 ± 18.8	22.3 ± 17.7	18.9 ± 14.5	<.001
No. of office visits (mean ± SD)	17.1 ± 14.0	17.7 ± 13.9	17.1 ± 13.7	14.7 ± 12.1	<.001
No. of outpatient hospital services (mean ± SD)	4.5 ± 6.4	5.1 ± 7.8	4.1 ± 5.6	3.5 ± 5.5	<.001
No. of lab visits (mean ± SD)	2.5 ± 3.4	2.6 ± 3.6	2.4 ± 3.2	2.2 ± 3.0	<.001
Any ED visits (n, %)	1,439 (21.4)	492(25.9)	390 (21.4)	425 (14.1)	<.001
Any inpatient admissions (n, %)	674 (10.0)	257 (13.5)	217 (11.9)	193 (6.4)	<.001
RA-related utilization					
No. of RA-related outpatient services[b] (mean ± SD)	5.9 ± 4.9	7.4 ± 6.3	6.8 ± 5.3	6.4 ± 4.8	<.001
No. of RA-related office visits[b] (mean ± SD)	4.8 ± 4.3	5.5 ± 4.5	5.5 ± 4.3	5.1 ± 4.0	0.002
No. of diagnostic lab tests[c] (mean ± SD)	4.3 ± 2.9	4.1 ± 3.3	4.1 ± 3.0	4.0 ± 2.6	0.398
No. of diagnostic imaging studies[d] (mean ± SD)	2.6 ± 2.5	2.4 ± 3.0	2.1 ± 2.5	1.6 ± 2.0	<.001
Total joint arthroplasty[b], joint reconstruction, or soft tissue procedures (n, %)	264 (3.9)	81 (4.3)	91 (5.0)	98 (3.3)	0.010

[a] For comparisons among categories of Etanercept Compliance
[b] Claims with RA diagnosis in any diagnosis field
[c] Including complete blood cell (CBC), erythrocyte sedimentation rate test (ESR), C-reactive protein (CRP), rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP), anti-MCV antibodies, and multi-biomarker disease activity (MDBA) test
[d] Including plain film X-rays, CT scans, MRI, and ultrasonography

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Disclosure: **N. Accortt**, Amgen, 3,Amgen, 1; **J. Schenfeld**, Docs Global, Inc., 3,Amgen, Inc., 5; **E. Chang**, Amgen, 3; **E. Papoyan**, None; **M. S. Broder**, Amgen, 3.

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Abstract Number: 2232

Above-Label Dosing with Biologics in Treatment-NaïVe and Treatment-Experienced Patients with Moderate-to-Severe Psoriatic Arthritis

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Title: Above-Label Dosing with Biologics in Treatment-Naïve and Treatment-Experienced Patients with Moderate-to-Severe Psoriatic Arthritis **Authors:** S. Schwartzman*[1], Y. Li[2], H. Zhou[3], V. Herrera[2], J. Palmer[2]
Affiliations: [1]Hospital for Special Surgery, New York, NY, US; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, US; [3]KMK Consulting Inc., Morristown, NJ, US

Background/Purpose: Moderate-to-severe psoriatic arthritis (PsA) patients may be treated with biologics. Limited evidence is available about biologic utilization patterns outside approved doses. This study described the extent of dosing for etanercept (ETA), adalimumab (ADA), certolizumab (CER), golimumab (GOL), and ustekinumab (UST) among moderate-to-severe PsA patients who were biologic naïve versus (vs) previously treated with biologics.

Methods: Adult PsA patients in the MarketScan® claims database were identified between 01/01/2011–12/31/2013 (identification period), with a 1-year follow-up and 3-month look-forward period (post-index period) ending 3/31/2015. Patients included had ≥1 PsA diagnosis using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 696.0 and ≥1 pharmacy claim for ETA, ADA, CER, GOL, or UST during the identification period. Patients were considered treatment-naive if they had no prior biologic use or treatment-experienced if they had previous use of any biologic in the 6 months before the index date. Excluded patients had any other autoimmune disease indicated for treatment with biologics of interest. Intravenous biologic therapy was not evaluated due to lack of available data in MarketScan databases. Mean days of above-label use (daily maintenance dose ≥10% higher than indication), below-label use (daily maintenance dose ≤10% less than indication), and on-label use (daily maintenance dose ±10% than indication) per patient were described and stratified by treatment-naïve vs treatment-experienced patients.

Results: This study identified 4245 PsA patients receiving biologic therapy: ETA (n=2342), ADA (n=1788), and GOL (n=115), respectively. Patients on CER (n=0) or UST (n=14) were not included due to small sample size and because both agents were only approved for PsA in late 2013. The majority of patients were male (~50-60%), with a mean age of ~50 years of age, and from the South of the United States. Across all three biologic patient cohorts examined, the majority of PsA patients were treatment-experienced, with ETA showing the highest proportion of patients with prior biologic use (67%), followed by GOL (57%) and ADA (56%) (Table 1). Treatment-experienced patients on ADA had greater mean days of above-label use compared to those naive to treatment (47 vs 19 days); however, treatment-experienced patients on ETA and GOL had fewer days of above-label use on average compared to naïve counterparts (ETA: 16 vs 20 days; GOL: 9 vs 16 days). **Table 1. Mean days of above-label, on-label, and below-label use per patient per year**

	ETA (n=2342)	ADA (n=1788)	GOL (n=115)
Total number of patients, n (%)			
Naïve	783 (33.4)	791 (44.2)	49 (42.6)
Experienced	1559 (66.6)	997 (55.8)	66 (57.4)
Total days on treatment, n			
Naïve	299	306	304
Experienced	291	299	309
Average days of above-label use, mean (SD)			
Naïve	20 (61)	19 (54)	16 (67)
Experienced	16 (60)	47 (107)	9 (49)
Average days of on-label use, mean (SD)			
Naïve	277 (99)	286 (86)	288 (77)
Experienced	271 (101)	251 (123)	300 (77)
Average days of below-label use, mean (SD)			
Naïve	3 (24)	1 (14)	0 (0)
Experienced	4 (33)	0 (9)	0 (0)

Conclusion: Above-label use was observed in PsA patients treated with ETA, ADA, and GOL; Prior biologic use seems to be a factor in above-label use of ADA versus other biologic cohorts.

Disclosure: S. Schwartzman, Speaker for: Genentech, Janssen, AbbVie, Crescendo, Pfizer, Hospira, and Novartis, 8,National Psoriasis Foundation: Board Member, 6,Consultant for: Genentech, Janssen, AbbVie, Pfizer, Epirus, Hospira, Novartis, Regeneron, and Crescendo, 5,Scientific Advisory Board: Crescendo - Bioscience, 9; **Y. Li**, Novartis Pharmaceuticals Corporation, 3; **H. Zhou**, KMK Consulting Inc., 3; **V. Herrera**, Novartis Pharmaceuticals Corporation, 3,Novartis Pharmaceuticals Corporation, 1; **J. B. Palmer**, Novartis Pharmaceuticals Corporation, 3.

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Abstract Number: 2233

Predictors of Adherence and Costs in First and Second Years after Biologic Initiation in Patients with Rheumatoid Arthritis (RA)

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic disease requiring continuous therapy to reach low disease activity targets and to delay its long-term health effects. We investigated predictors of adherence with biologic therapy and healthcare costs among patients with RA in the first and second year after first biologic initiation.

Methods: <span">Patients with RA initiating a first (index) biologic between January 1, 2009 and December 31, 2012 and with 2 years of continuous enrollment were identified in the IMS PharMetrics Plus commercial claims database.Based on Year 1 data, we classified patients as 'effectively' or 'non-effectively' treated using a validated algorithm that considers six criteria of adherence, treatment changes, or steroid use. Adherence on index agent was defined by proportion of days covered (PDC) >80%. Logistic regression models assessed predictors of adherence at Years 1 and 2 using demographic, clinical and pre-index cost characteristics that were statistically significant in univariate analysis. Inverse probability of treatment weighted structural models were used to estimate total and RA-related healthcare costs in Year 2, controlling for baseline characteristics and effective/non-effective treatment in Year 1.

Results: <span">Of the 10,374 eligible patients, 76.1% were female, median age was 51 years, and 77.9% used a non-biologic disease-modifying antirheumatic drug (DMARD) in 12 months pre-index. In Year 1, 29.7% were considered effectively treated.Among all patients, 46.0% and 33.6% were adherent over the entire one and two year periods, respectively. Patients using the infused agents, infliximab and abatacept, had the highest adherence (63.7%, 48.0) in Year 1, with infliximab users more adherent (47.0%) over 2 years. Adherence across the four subcutaneous agents was highest for adalimumab and etanercept. Adherence was more likely in older patients, males, and those with prior DMARD use over both time periods (Table). Additional predictors of adherence in both years were index drug, region and payer type. Higher total healthcare costs during Year 2 were predicted by effective treatment in Year 1, choice of index drug, greater patient age at index, prior use of glucocorticoids, and greater comorbidity burden ($p<0.05$). Effective treatment in Year 1, patient age at index, geographic region, and index year were significant predictors ($p<0.05$) of RA-related healthcare costs in Year 2.

Conclusion: <span">Adherence in both time periods varied by drug, prior DMARD use, and demographic factors with several of these being significant predictors in Year 1 and 2.Year 2 total and RA-related health care costs were predicted by common variables of older age and effective treatment in Year 1. <span">

Table. Predictors of 1- and 2-Year Adherence (PDC > 80%) With Biologic Therapy		
Independent Variable	**1 Year Adherence OR (95% CI)**	**2 Year Adherence OR (95% CI)**
Index Biologic (reference etanercept, n = 4,426))		
Abatacept (n = 487)	1.3 (1.1, 1.6)	1.0 (0.8, 1.2)
Adalimumab (n = 3,926)	1.1 (1.0, 1.2)	1.0 (0.9, 1.1)
Certolizumab (n = 255)	0.9 (0.7, 1.2)	1.0 (0.7, 1.3)
Golimumab (n = 369)	0.7 (0.6, 0.9)	0.8 (0.6, 1.0)
Infliximab (n = 911)	2.4 (2.0, 2.7)	1.9 (1.6, 2.2)
Age Group (reference 18-34 years)		
35-44 years	1.1 (0.9, 1.3)	1.1 (1.0, 1.4)
45-54 years	1.3 (1.1, 1.5)	1.6 (1.3, 1.9)
55-64 years	1.6 (1.4, 1.9)	2.0 (1.7, 2.3)
Male (reference female)	1.3 (1.2, 1.5)	1.4 (1.2, 1.5)
Region (versus Northeast)		
Midwest	1.0 (0.9, 1.1)	1.0 (0.9, 1.1)
South	0.8 (0.7, 0.8)	0.8 (0.7, 0.9)
West	0.9 (0.7, 1.0)	0.9 (0.7, 1.1)
Payer Type (reference Commercial)		
Self-insured	0.9 (0.9, 1.0)	0.9 (0.9, 1.0)
Other/Unknown	0.5 (0.4, 0.8)	0.5 (0.3, 0.8)
Prior DMARD Use (reference no use)	1.5 (1.4, 1.7)	1.5 (1.3, 1.6)
Index Year (reference 2009)[1]		
2010	1.2 (1.1, 1.3)	--
2011	1.1 (1.0, 1.3)	--
2012	1.1 (1.0, 1.2)	--
Log (Pre-index Total Healthcare Costs)	0.9 (0.9, 1.0)	0.9 (0.9, 0.9)

[1]Index year did not meet selection criteria for inclusion in 2-year model. OR=odds ratio

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Disclosure: B. S. Stolshek, Amgen, 1,Amgen, 3; **S. W. Wade**, Amgen, 5; **A. De**, Amgen, Inc., 5; **R. L. Wade**, Amgen, Inc., 5; **J. Yeaw**, Amgen, Inc., 5.

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Abstract Number: 2234

Economic Impact of Above-Label Dosing with Biologics in Patients with Moderate-to-Severe Psoriatic Arthritis

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Authors: S. Schwartzman*[1], Y. Li[2], H. Zhou[3], V. Herrera[2], J. Palmer[2] **Affiliations:** [1]Hospital for Special Surgery, New York, NY, US; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, US; [3]KMK Consulting Inc., Morristown, NJ, US

Background/Purpose: Disease control among patients with moderate-to-severe psoriatic arthritis (PsA) may involve above-label dosing of biologic drugs; limited information is available about the economic impact of above-label dosing. We examined the costs associated with above-label dosing among patients with moderate-to-severe PsA receiving etanercept (ETA), adalimumab (ADA), certolizumab (CER), golimumab (GOL), and ustekinumab (UST).

Methods: Adult PsA patients in the MarketScan® Commercial Claims databases were identified between 01/01/2011–03/31/2013 (identification period) and followed-up for 1 year, with a 3-month look-forward period (post-index period) ending in 3/31/2015. Patients had ≥1 PsA diagnosis using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code 696.0, ≥1 pharmacy claim for ETA, ADA, CER, GOL, or UST during the identification period. Intravenous therapy was not evaluated due to lack of available data in MarketScan databases. Patients who switched to a different biologic following the use of their initial biologic or had any autoimmune disease for which one of the studied biologics of interest could potentially be used were excluded. Above-label use was defined as a daily maintenance dose ≥10% higher than indicated in the label. Each cohort and its total healthcare costs associated with above-label use were divided into 3 categorizes: <30, 30-179 and ≥180 days, respectively.

Results: This study identified 4245 PsA patients on ETA (n=2342), ADA (n=1788), and GOL (n=115). Patients on CER (n=0) or UST (n=14) were not included due to small sample size and because both agents were approved for PsA in late 2013. Ninety percent of the ETA, 85% of the ADA, and 96% of the GOL patient cohorts had at least 30 days of above-label use. Five and a half percent (5.5%) of the ETA, 5.4% of the ADA, and 1.7% of the GOL patient cohorts had at least 30-179 days of above-label use whereas 4% of the ETA, 9.6% of the ADA, and 2.6% of the GOL patient cohorts had ≥180 days above-label use. In the post-index period, the mean total all-cause healthcare costs (medical and pharmacy) were increased in the biologic patient cohorts with more above-label use (ETA cohort: $30,625 <30 days vs. $55,359 ≥180 days; ADA cohort: $31,620 <30 days vs. $54,176 ≥180 days; GOL cohort: $37,224 <30 days vs. $47,993 ≥180 days, respectively). Within the above-label use categories, ETA and ADA showed increased costs associated with increased duration of above-label dosing in annual mean total all-cause healthcare costs per patient (ETA: $10,561 <30 days; $16,213 30-179 days; $25,167 ≥180 days; ADA: $13,446 <30 days; $17,623 30-179 days; $16,251 ≥180 days); The observations for patients treated with GOL are limited by the small sample size.

Table 1. Patient Demographic and Total Healthcare Costs Associated with Above-label Use of ETA, ADA and GOL

	<30 days Above-label Use			30-179 days Above-label Us			≥180 days Above-label Use		
	ETA (n=2118)	ADA (n=1520)	GOL (n=110)	ETA (n=129)	ADA (n=97)	GOL (n=2)	ETA (n=95)	ADA (n=171)	GOL (n=3)
Age (years), mean (SD)	50.7 (10.9)	49.3 (11.3)	48.7 (12.4)	49.2 (10.9)	49.5 (12.3)	53.0 (0.0)	51.4 (11.0)	51.0 (9.9)	48.3 (26.8)
Gender, n (%)									
Female	849 (40.1)	613 (40.3)	54 (49.1)	61 (47.3)	50 (51.5)	1 (50)	50 (52.6)	77 (45.0)	0 (0.0)
Geographic region, n (%)									
Northeast	383 (18.1)	215 (14.1)	19 (17.3)	24 (18.6)	9 (9.3)	0 (0)	9 (9.5)	19 (11.1)	0 (0)
North central	561 (26.5)	353 (23.2)	27 (24.5)	28 (21.7)	21 (21.6)	1 (50)	23 (24.2)	56 (32.7)	0 (0)
South	703 (33.2)	628 (41.3)	45 (40.9)	48 (37.2)	41 (42.3)	1 (50)	45 (47.4)	61 (35.7)	1 (33.3)
West	455 (21.5)	309 (20.3)	16 (14.5)	28 (21.7)	25 (25.8)	0 (0)	17 (17.9)	33 (19.3)	2 (66.7)
Unknown	16 (0.8)	15 (1.0)	3 (2.7)	1 (0.8)	1 (1.0)	0 (0)	1 (1.1)	2 (1.2)	0 (0)
Total healthcare costs in post-index period, mean (SD)[a,b]									
All-cause	$30,625 ($17,928)	$31,620 ($13,782)	$37,224 ($29,411)	$35,602 ($16,600)	$38,915 ($30,454)	$64,349 ($7927)	$55,359 ($17,718)	$54,176 ($15,841)	$47,993 ($8845)
PsA-specific	$23,246 ($6558)	$24,411 ($6300)	$26,155 ($6975)	$27,533 ($8424)	$26,911 ($8899)	$46,607 ($985)	$44,827 ($9,006)	$45,289 ($10,532)	$44,533 ($7896)
Biologic	$22,812 ($6390)	$23,919 ($6178)	$25,381 ($6325)	$27,104 ($8467)	$26,331 ($8564)	$46,019 ($1109)	$44,282 ($8941)	$44,854 ($10,526)	$44,334 ($7710)
Non-biologic	$7814 ($16, 667)	$7701 ($12,760)	$11,843 ($30,631)	$8498 ($14,802)	$12,584 ($28,389)	$18,330 ($6,818)	$11,076 ($15,918)	$9323 ($11,511)	$3658 ($3335)
Difference in total healthcare costs per patient (post –/pre- index period dose escalation), mean (SD)[a,b]									
All-cause	$10,561 ($19,757)	$13,446 ($21,321)	$15,299 ($30,310)	$16,213 ($20,624)	$17,623 ($35,969)	$33,481 ($28,679)	$25,167 ($21,120)	$16,251 ($19,983)	$30,201 ($17,553)
PsA-specific	$10,726 ($11,501)	$14,412 ($12,192)	$14,921 ($12,242)	$16,549 ($16,862)	$16,481 ($14,642)	$34,494 ($17,802)	$23,730 ($20,097)	$18,327 ($15,647)	$34,606 ($19,327)
Biologic	$10,818 ($11,099)	$14,480 ($12,115)	$14,803 ($12,087)	$17,240 ($15,376)	$16,593 ($14,407)	$35,030 ($16,650)	$23,562 ($20,049)	$18,464 ($15,459)	$34,789 ($19,142)
Non-biologic	$-257 ($16,690)	$-1,035 ($18,038)	$496 ($31,392)	$-1027 ($15,202)	$1030 ($32,444)	$-1549 ($12,029)	$1606 ($15,199)	$-2213 ($14,192)	$-4587 ($4482)

[a] Adjusted to 2014 US dollars
[b] All-cause and PsA-related healthcare costs=medical and prescription drug costs
ETA, etanercept; ADA, adalimumab; GOL, golimumab

Conclusion: Even a short duration of above-label dosing was associated with increased total healthcare costs among PsA patients treated with ETA and ADA.

Disclosure: S. Schwartzman, Speaker for: Genentech, Janssen, AbbVie, Crescendo, Pfizer, Hospira, and Novartis, 8,National Psoriasis Foundation: Board Member, 6,Consultant for: Genentech, Janssen, AbbVie, Pfizer, Epirus, Hospira, Novartis, Regeneron, and Crescendo, 5,Scientific Advisory Board: Crescendo - Bioscience, 9; **Y. Li**, Novartis Pharmaceuticals Corporation, 3; **H. Zhou**, KMK Consulting Inc., 3; **V. Herrera**, Novartis Pharmaceuticals Corporation, 3,Novartis Pharmaceuticals Corporation, 1; **J. B. Palmer**, Novartis Pharmaceuticals Corporation, 3.

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Abstract Number: 2235

Utilization of Ambulatory Physician Encounters, Emergency Room Visits and Hospitalizations By RA Patients: A 13 Year Population Health Study

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Background/Purpose: To determine total and subspecialty physician encounters, emergency room (ER) visits and hospitalizations in an incident cohort of rheumatoid arthritis (RA) cases and matched control patients over 13 years.

Methods: A retrospective cohort study was performed utilizing administrative health care data from approximately 1 million people with access to universal healthcare. Using ICD-9 and ICD-10 diagnostic codes, 7 RA case definitions were used. Each case was matched by age and gender to 4 randomly selected controls. Data included physician billings, ER visits and hospital discharges over 13 years.

Results: The number of incident RA cases varied from 3,460 to 27,657 depending upon the case definition. The mean (SD) age was 56.0 (17.8) years and the proportion of females was 68%. Using a single representative case definition for RA, the utilization of different services in the index year and after 13 years of follow-up is summarized in Table 1. All encounters with physicians and services by RA patients were significantly higher than controls ($p<0.0001$ for all) and were highest in the index year, declining thereafter. Over 13 years the reduction in utilization varied by service from 78% (Rheumatologists; $p<0.0001$), 54.7% (Internal medicine; $p<0.0001$), 17.1% (primary care physicians; $p<0.0001$), 9.2% (other physicians; $p<0.0001$), 30.2% (ER visits; $p<0.01$) and 63% (hospitalizations; $p<0.0001$). **Table 1: Utilization of physician and clinical services by RA patients and controls**

Clinical service	Encounters/year in index year		Encounters/year after 13 years	
	RA cases	Controls	RA cases	Controls
All physicians	17.26	6.35	12.88	7.82
Rheumatologists	2.40	0.01	0.53	0.02
General internists	0.74	0.19	0.33	0.16
Other physicians	3.98	1.52	3.61	2.21
Primary care physicians	10.14	4.64	8.41	5.43
Emergency room visits	0.58	0.27	0.40	0.25
Hospitalizations	1.40	0.30	0.52	0.35

Conclusion: In RA patients, health care utilization is highest in the first year following the diagnosis which is also the time of maximal involvement by rheumatologists. Utilization declines over time and encounters with patient's primary care and other physician groups predominate.

Disclosure: J. G. Hanly, None; **K. Thompson**, None; **C. Skedgel**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/utilization-of-ambulatory-physician-encounters-emergency-room-visits-and-hospitalizations-by-ra-patients-a-13-year-population-health-study

Abstract Number: 2236

Effects of Repository Corticotropin Injection on Medication Use in Patients with Rheumatologic Conditions: A Claims Data Study

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Background/Purpose: Repository corticotropin injection (RCI) may produce anti-inflammatory and immune-modulatory effects. This study examined the demographics of those who used RCI and the trends in medication use, specifically prednisone, after RCI initiation.

Methods: This retrospective analysis of the Symphony Health Solutions Patient Transactional Dataset from 2008 to 2015 included patients with at least 1 claim for RA, SLE, or DM/PM, and any use of RCI. Patients with claims for non-rheumatologic conditions that may also be treated by RCI, namely, multiple sclerosis and proteinuria, were excluded. Demographics, patterns of RCI use, and concomitant medications (corticosteroids [CS], biologics, NSAIDs, and DMARDs) were reported. Patients were followed for concomitant medication use from 2 years prior to and 1 year after RCI initiation. Paired two-tailed t-test was used to calculate the *p* values for the use of each drug class before/after RCI initiation**.**

Results: Out of 2.7 million rheumatologic patients in the database over 6 years, there were 2,749 patients who used RCI - 1269 RA patients, 874 SLE patients, and 606 with DM/PM (**Table 1**). SLE patients were younger than RA and DM/PM patients, and most of the patients were female for all 3 conditions. Majority of patients received 80U of RCI twice weekly. The study identified 504 RA, 322 SLE, and 222 DM/PM patients with sufficient follow up time to evaluate concomitant medication use. For all 3 conditions, the proportions of patients who used any CS were significantly lower after RCI initiation: reduced from 67% pre-index to 54% post-index for RA, from 73% to 58% for SLE, and from 76% to 58% for DM/PM ($p < 0.05$ for all comparisons, **Figure 1**). Proportions of patients on biologics and DMARDs were also significantly lowered after RCI initiation. In **Figure 2**, among patients who had taken CS consistently 24 weeks before RCI initiation, dose reductions were statistically significant for RA (28%), and trended lower without statistical significance for SLE (25%) and DM/PM (25%). Limitation of the retrospective analysis include uncertainties in diagnosis, medication use, and factors influencing medication changes.

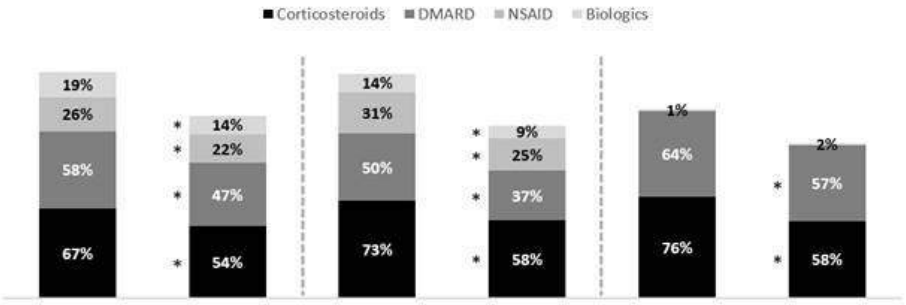
Conclusion: This claims-based study of patients with RA, SLE, and DM/PM indicated that RCI use may be associated with significant reductions in CS requirements.

Table 1. Patient Characteristics

Patient Characteristics	RA	SLE	DM/PM
Number of patients on RCI	1269	874	606
Age, Mean (Years)	59.1	48.1	55.5
Female	78%	89%	70%
RCI dose of 80U twice weekly	58%	57%	68%
RCI dose of 200U weekly	12%	15%	16%
RCI duration, Mean (Days)	115.7	129.2	157.1

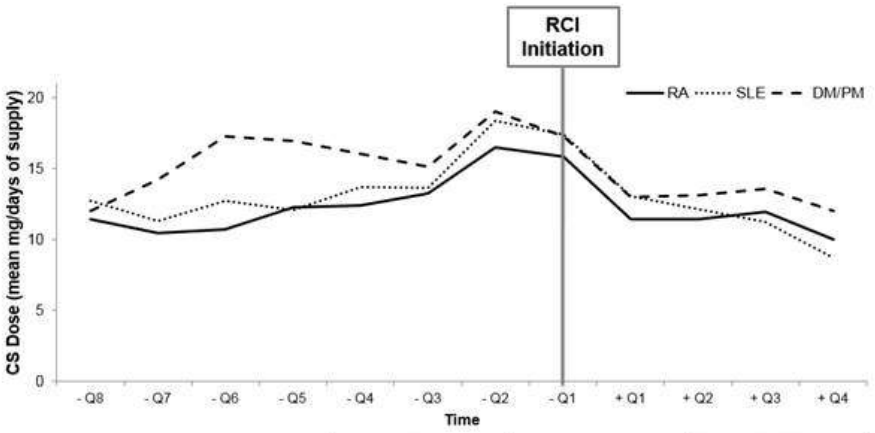
RCI=Repository Corticotropin Injection

Figure 1. Change in Medication Use Before and After RCI Initiation



* denotes p <0.05
RCI = repository corticotropin injection; Sum of column >100% because patients received multiple medications concomitantly

Figure 2. Corticosteroid (CS) Dose Trend, in Patients who had 24 Weeks of Consistent Use before RCI Initiation



	RA	SLE	DM/PM
Number of Patients	201	131	121
CS Dose 1Q Pre-RCI, Mean ± 95% CI	15.86 ± 1.71	17.39 ± 2.27	17.31 ± 2.18
CS Dose 1Q Post-RCI, Mean ± 95% CI	11.47 ± 1.63	13.05 ± 2.27	12.98 ± 2.34

RCI=Repository Corticotropin Injection; CI = Confidence Interval

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Disclosure: G. Myung, None; **W. Nelson**, Mallinckrodt Pharmaceuticals, 3,Mallinckrodt Pharmaceuticals, 1; **M. A. McMahon**, None.

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Abstract Number: 2237

Biologic DMARD Use Among U.S. Patients in an Online Rheumatoid Arthritis Community

Lawrence Chang[1], Yoko Tanaka[2], Cynthia J Larmore[1], Leilei Qian[1], Baojin Zhu[1] and Andre B. Araujo[1], [1]Eli

Lilly and Company, Indianapolis, IN, [2]Eli Lilly and Company, Indianapolis, KS
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Background/Purpose: Multiple biologic DMARDs (bDMARDs) are approved in the US for the treatment of RA. Previous studies have indicated significant clinical inertia in moving patients who have failed conventional DMARDs (cDMARDs) to bDMARDs. We sought to identify factors associated with bDMARD use.

Methods : The data for this analysis were obtained from the 2015 online RA community survey "Rheumatoid Arthritis in America". The survey was administered by Health Union between August 6, 2015 and Sep. 12, 2015. Subjects self-identified as having RA and were recruited from RheumatoidArthritis.net subscribers, email and social media (N=3149). Patients aged 18 years or older at RA diagnosis, living in the US, and naïve to clinical trials (N=2735) were included in this analysis. Survey variables included demographics; financial status; disease onset and disease status; patient reported outcomes; RA therapy; provider/practice characteristics; patient knowledge, attitudes, perceptions of RA (disease, therapy, and care), patient behaviors; and medication history. A regression tree partitioning algorithm was used as the primary analysis to systematically identify subgroups of patients where bDMARD use was substantially different from the overall population. As a secondary analysis, logistic regression with stepwise selection was also performed.

Results : Patients were mostly women (96%), Caucasian (87.9%), mean age was 51.5 years, and mean time since diagnosis of 7.3 years. Overall, 72.6% of patients had signs and symptoms that suggested their RA disease was not controlled and 38.2% were naïve to bDMARDs. Ever use of a bDMARD was higher in uncontrolled patients (vs. patients who had evidence of disease control); this observation was consistent across disease duration (Figure). Of 47 subgroup variables used in the regression tree algorithm, three variables were associated with bDMARD use and met the stringent selection criteria (consistency, internal/external validity): (1) time since RA diagnosis (≥2 years); (2) expected annual out of pocket spending (≥$2000); and (3) preferred medication route of administration (prefer injection/infusion). The stepwise logistic regression retained 18 variables including the three variables identified by regression tree analysis. Of the remaining 15 variables, odds ratios for ever use of bDMARDs greater than 2.0 were observed among patients who were uninsured, were treated by a rheumatologist, had moderate/severe disease at symptom onset or currently, and prior use of cDMARDs.

Conclusion : In this online community of RA patients, 72.6% did not have disease in control and 38.2% had never used a biologic. bDMARD use varied considerably among patient subgroups, particularly by time since RA diagnosis, expected annual out-of-pocket spending, and preferred medication route of administration.

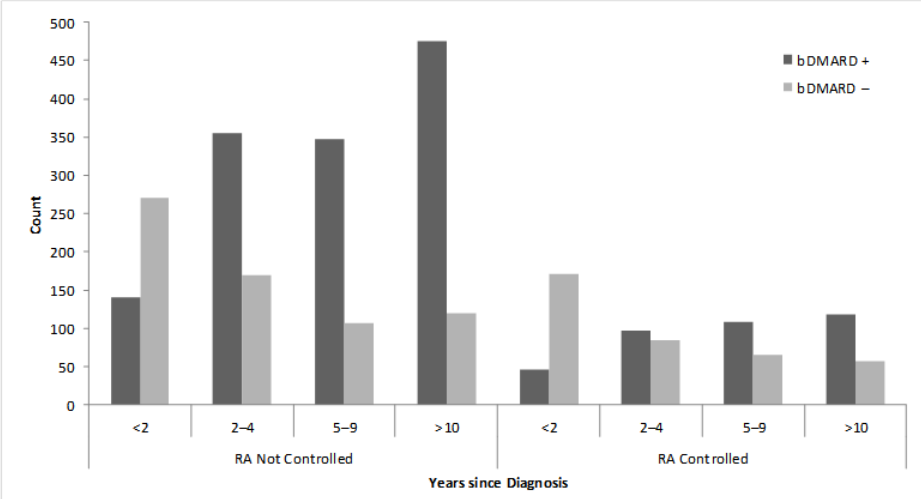

Figure. Ever use of bDMARDs by disease status and years since diagnosis (n=2735).

Disclosure: L. Chang, Eli Lilly and Company, 1; **Y. Tanaka**, Eli Lilly and Company, 1; **C. J. Larmore**, Eli Lilly and Company, 1; **L. Qian**, Eli Lilly and Company, 1; **B. Zhu**, Eli Lilly and Company, 1; **A. B. Araujo**, Eli Lilly and Company, 1.

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Abstract Number: 2238

RA Medication Preferences Among U.S. Patients in an Online Rheumatoid Arthritis Community

Baojin Zhu[1], Lawrence Chang[1], Leilei Qian[1], Cynthia J Larmore[1], Yoko Tanaka[2] and Andre B. Araujo[1], [1]Eli Lilly and Company, Indianapolis, IN, [2]Eli Lilly and Company, Indianapolis, KS
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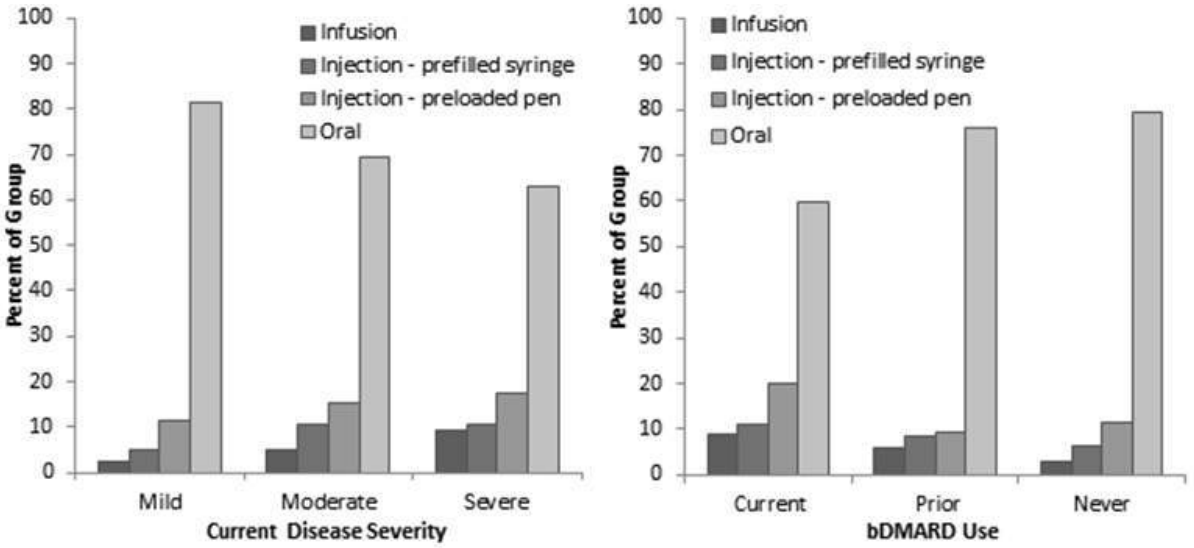
Background/Purpose: Medications used to manage RA vary in efficacy, safety, and convenience of use. A better understanding of patient preferences of these attributes is key to understanding patient barriers to effective therapeutic management. The objective of this study was to evaluate US patient views of RA medication attributes.

Methods: The data for this analysis were obtained from the 2015 online RA community survey "Rheumatoid Arthritis in America". The survey was administered by Health Union between August 6, 2015 and Sep. 12, 2015. Subjects self-identified as having RA and were recruited from RheumatoidArthritis.net subscribers, email and

social media (N=3149). Patients aged 18 years or older at RA diagnosis, living in the US, and naïve to clinical trials (N=2735) were included in this analysis. Within the survey, patients ranked eight attributes—reduce the severity of flares, injection, infusion, proven safety record, reduce the number of flares, minimal side effects, pill, and rapid reduction of RA symptoms—assuming equal insurance and cost-effectiveness from 1 (most important) to 8 (least important). This ranking and patient preference for drug administration route were analyzed for all subjects and by age (<45, 45–64, ≥65 years old), gender, race (Caucasian, yes/no), RA disease severity (mild, moderate, and severe), and use of bDMARDs using ANOVA for continuous variables and Chi-square tests for categorical variables.

Results: Patients ranked "rapid reduction of RA symptoms" at mean (SD): 3.0 (1.8) over "minimal side effects" 3.4 (1.8); "proven safety record" 3.5 (2.0); "reduces the severity of flares" 3.5 (1.6); number of flares 3.6 (1.6); and taken as a pill 5.5 (1.9), injection 6.5 (1.7), or infusion 7.0 (1.7). For drug formulation, the majority (70%) of RA patients surveyed preferred oral medication to injection with preloaded pen (15%), injection with syringe (9%), or infusion (6%), with difference in preference by disease severity and history of bDMARD use (Figure).

Conclusion: Rapid reduction of symptoms was rated the most important attribute of RA medications, assuming equal insurance and cost-effectiveness. Oral was the preferred route of administration, with more severe (vs. less severe) and bDMARD-current (vs. bDMARD-prior/never) patients having a greater preference for non-oral. A better understanding of patient medication preference should help identify patient barriers to effective management of RA. **Figure 1**. Subgroup analysis of drug formulation preference by current disease severity (n=2100) and history of bDMARD use (n=2735).



Disclosure: B. Zhu, Eli Lilly and Company, 1; **L. Chang**, Eli Lilly and Company, 1; **L. Qian**, Eli Lilly and Company, 1; **C. J. Larmore**, Eli Lilly and Company, 1; **Y. Tanaka**, Eli Lilly and Company, 1; **A. B. Araujo**, Eli Lilly and Company, 1.

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Abstract Number: 2239

Patterns of Abatacept Utilization in Patients with Rheumatoid Arthritis. Have the Baseline Characteristics of These Patients Changed over Time?

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Background/Purpose: Abatacept (ABA), a T cell co-stimulation inhibitor, was initially approved by the European Medicine Agency (EMA) for patients with rheumatoid arthritis (RA) who had failed ≥ 1 tumor necrosis factor inhibitor (TNFi), and was available in Europe in 2008. Thereafter EMA also approved ABA for patients failing methotrexate (biologic-naïve patients): this was available in Europe after 2011.These different RA target populations might lead to a change in the RA population treated with ABA over time. Our objective is to analyze differences in the baseline characteristics of RA patients treated with ABA according to calendar year

Methods: All patients from the BIOBADASER 2.0 register with a diagnosis of RA and treated with ABA from January 2008 to December 2014 were selected and divided according to calendar year: 2008-2011 and 2012-2014. Variables analyzed: age; gender; disease duration; number of previous biological agents; disease activity at initiation of biological drug, measured by the DAS-28 score; concomitant treatment with glucocorticoids and synthetic DMARDs; baseline comorbidities (ischemic heart disease, malignancy, diabetes, chronic obstructive pulmonary disease, heart failure and hepatitis B infection); and ABA treatment duration

Results: From January 2008 to December 2014, 252 RA patients treated with ABA were included in the BIOBADASER 2.0 register. Baseline characteristics and distribution by calendar year are shown in Table 1. At baseline, patients treated with abatacept between 2008-2011 had significantly higher basal activity [DAS28 (5.18 (1.46) vs 4.74 (1.57); p 0.037], longer time on ABA [13.44 (12.1) m vs 7.59 (9.1) m; p= 0.039], and fewer patients with ischemic heart disease [1 (0.6%) vs 4 (4.6%), p=0.031], compared with patients treated between 2012-2014. No differences in other parameters were found

Conclusion: Abatacept treatment pattern has not been changed over the time and is being used in patients who failed ≥ 1 biological agent. Initially, patients treated with abatacept had significantly higher baseline DAS28, and a longer time on biological treatment, probably reflecting disease management in Spain **Table 1. Differences in basal characteristics and presence of comorbidities of patients treated with abatacept according to calendar year**

Years		2008-2011	2012-2014	p
Number of abatacept patients		165	87	
Age at initiation of first biologic agent (years), mean (SD)		55.9 (12.5)	58.2 (12.8)	0.171
Women, n (%)		137 (83.0)	71 (81.6)	0.778
Disease duration (years), mean (SD)		12.1 (7.9)	11.9 (8.6)	0.580
Number of previous biologic agents	0	19 (11.5)	8 (9.2)	0.809
	1	45 (27.3)	26 (29.9)	
	≥ 2	101 (61.2)	53 (60.9)	
Basal DAS28, m (SD)		5.18 (1.46)	4.74 (1.57)	**0.037**
Concomitant sDMARD (%)	0	65 (39.4)	34 (39.1)	0.587
	1	92 (55.8)	46 (52.9)	
Concomitant corticosteroids (%)		87 (52.7)	47 (54.0)	0.845
Basal comorbidity (%)				
Ischemic heart disease		1 (0.6)	4 (4.6)	**0.031**
Malignancy		3 (1.8)	2 (2.3)	0.795
Diabetes		14 (8.5)	9 (10.3)	0.626
CPOD		9 (5.4)	3 (3.4)	0.477
Heart failure		2 (1.2)	4 (4.6)	0.094
Hepatitis B virus infection		5 (3.0)	5 (5.7)	0.294
Duration of abatacept (months)*		13.4 (12.1)	7.6 (9.1)	**0.039**

*from abatacept initiation to switch to other biologic

Disclosure: M. V. Hernández, None; **C. Sánchez-Piedra**, None; **J. Inciarte-Mundo**, None; **F. Sanchez-Alonso**, None; **J. Manero**, None; **R. Roselló**, None; **E. Pérez-Pampin**, None; **R. Morla**, None; **C. Rodriguez-Lozano**, None; **D. Ruiz-Montesinos**, None; **R. Sanmarti**, None; **J. J. Gómez-Reino**, None.

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Abstract Number: 2240

A Descriptive Analysis of Real-World Treatment Patterns in a Turkish Rheumatology Population That Continued Innovator Infliximab

(Remicade) Therapy or Switched to Biosimilar Infliximab

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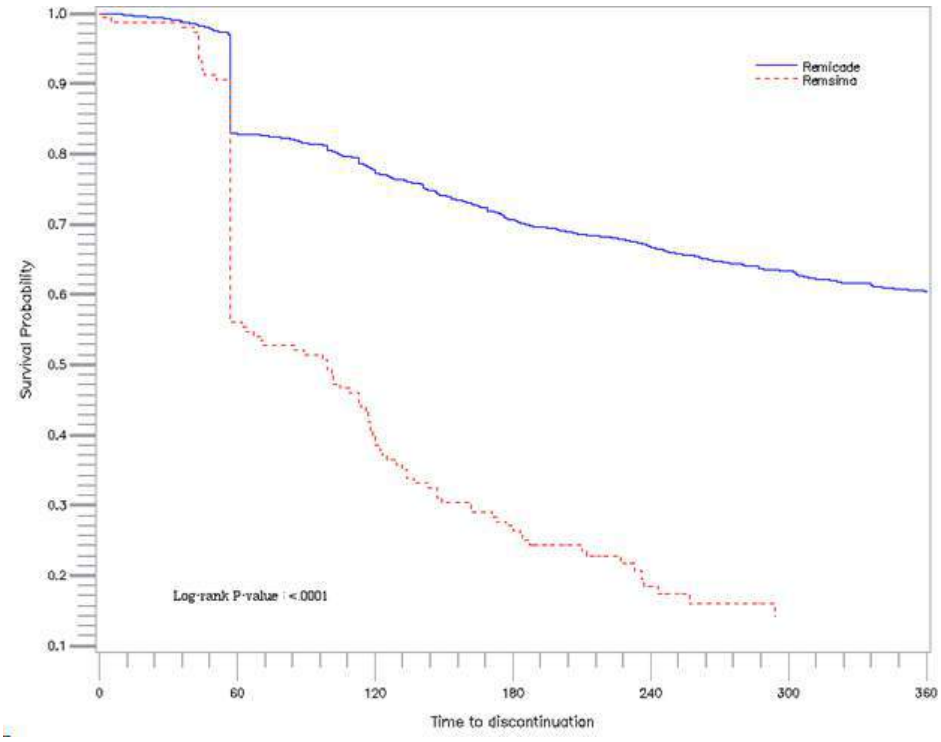
Background/Purpose: This study examined treatment patterns in a rheumatology patient (pt) population initially prescribed innovator infliximab (IFX) that either switched to biosimilar infliximab (CT-P13) or continued on IFX following availability of CT-P13 in the Turkish healthcare system.

Methods: Adult pts with ≥1 diagnosis code (ICD-10-CM M05.X; M06.X) for rheumatoid arthritis (RA) and a prescription for IFX were identified in a national Turkish health care database during the study period (01DEC2010-01DEC2015). Eligible pts were those who continued on IFX (Continuers cohort; CC) or switched from IFX to CT-P13 (Switchers cohort; SC) during the identification period; had continuous medical/pharmacy benefit enrollment ≥12 months before and ≥6 months after the index date (date of switch for SC and a random IFX prescription date for CC); had a prescription claim for IFX within 16 weeks of the index date during the baseline period. Demographics, concomitant disease, medications, and treatment patterns (dose, refill interval, discontinuation, and switch) were summarized. A confirmed discontinuation was defined as a switch to another biologic medication or the absence of an index biologic claim for ≥120 days without censoring. Patient weight was unavailable in the dataset.

Results: Key results are shown in the Table and Figure. A total of 3018 pts met study criteria. The majority (95%; n=2870; CC) continued on IFX and had a mean age of 44 years; 46% were female and mean follow up of 12 months. A total of 148 pts (5%) switched to CT-P13 (SC) and had mean age of 44 years; 51% female and mean follow up of 9 months. Approximately 40% of pts in each cohort had a concomitant diagnosis for ankylosing spondylitis (AS; Table). Other concomitant diseases and medications appeared balanced between cohorts. In the CC, pts had an average of 4.7 infusions at a mean dose of 4.4 vials approximately every 10 weeks. In the SC, pts had an average of 2.6 infusions at a mean dose of 3.6 vials approximately every 10 weeks. Therapy discontinuation occurred in 38% in the CC; average time to any discontinuation or censoring of IFX was 256 days (Table). In the SC, CT-P13 discontinuation was observed in 82%; average time to any discontinuation or censoring of CT-P13 was 124 days; 74% of SC switched to another biologic with 94% of these returning to IFX.

Conclusion: This study shows switching from IFX to CT-P13 was infrequent. However, in those switching to CT-P13, a high percentage (82%) of CT-P13 discontinuation was observed and the majority returned to IFX. Further studies are needed to understand the reasons for these observations.

	Switchers Cohort (N=148)		Continuers Cohort (N=2870)	
	N/Mean	%/SD	N/Mean	%/SD
Age (Mean) (years)	44	13	44	12
Gender				
Female	75	51%	1,332	46 %
Average Length of Follow up Period (in Months)	9	2	12	3
Concomitant Disease During Baseline Period				
Ankylosing Spondylitis	73	49%	1,214	42%
Psoriatic Arthritis or Psoriasis	19	13%	582	20%
Crohn's Disease	6	4%	191	7%
Ulcerative Colitis	8	5%	157	5%
Concomitant RA-Medications During Follow-Up Period				
Methotrexate	31	21%	652	23%
Sulfasalazine	21	14%	340	12%
Dosing Characteristics				
Average # of doses within follow up period	2.6	1.6	4.7	2.4
Mean # of weeks between doses	10.1	5.1	9.9	3.8
Mean # of days between 1st and 2nd dose	75	48	70	34
Mean # of days between 2nd and 3rd dose	72	38	70	29
Mean # of days between 3rd and 4th dose	65	31	67	26
Mean # of vials per Infusion	3.6	1.6	4.4	1.9
Switching				
# and % of patients with ≥1 switch	110	74%	471	16%
% of Primary Switches from CT-P13 to IFX	103	94%	NA	NA
Discontinuation				
# of Patients Confirmed to Have Discontinued	121	82%	1,089	38%
Time to confirmed discontinuation (days)	94	58	126	91
Time to any discontinuation or censoring (days):	124	87	256	138



Disclosure: Y. Yazici, Janssen Scientific Affairs, LLC, 2; **L. Xie**, Janssen Scientific Affairs, LLC, 5; **A. Ogbomo**, Janssen Scientific Affairs, LLC, 5; **D. Parenti**, Janssen Scientific Affairs, LLC, 3; **K. Goyal**, Janssen Scientific Affairs, LLC, 3; **A. Teeple**, Janssen Scientific Affairs, LLC, 3; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **I. Simsek**, Janssen Scientific Affairs, LLC, 2.

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Abstract Number: 2241

Health Economics of Uncontrolled Gout in the United States: A Systematic Literature Review

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Background/Purpose: Gout is a crystal deposition disease and the most prevalent inflammatory arthritis in the United States (US). Maintaining gout control has been associated with reduced healthcare resource utilization and healthcare costs, with uncontrolled gout (serum uric acid [sUA] >6 mg/dl or ≥1 flare in past year) incurring >1.3 times the costs compared to controlled gout (sUA <6 mg/dl and no flares in past year).[1] The long-term impacts of uncontrolled gout, including economic consequences, have not been well summarized. A systematic literature review was conducted to clarify the economic value of controlling gout with treatment in the US.

Methods: A search of published literature from Jan 2006 to Jan 2016 was conducted in PubMed, EMBASE, MEDLINE In-Process, the Cochrane Collaboration, and other non-indexed citations. Three independent researchers reviewed the results using predetermined inclusion and exclusion criteria. Preliminary inclusion criteria were: 1) gout disease focus; 2) reported disease burden or treatment outcomes; 3) English language. Non-human studies, opinion-based reviews, and case-reports were excluded.

Results: We identified 178 studies meeting eligibility criteria. All studies reporting longitudinal epidemiology data indicated an increased prevalence of gout over time, ranging from 1.1% in 1959–1962 to 3.7% in 2009–2010. Of the 178 studies, 13 were found in which primary analyses of healthcare costs in patients with gout were conducted (**Table**). Classification of gout in US-focused retrospective claims database analyses were largely based on an incident population, which underestimates the true economic burden. Cost estimates for gout treatment in the US range from $7.7 billion for gout-specific costs to ≥$20 billion for total costs. Overall, the data show a substantial cost of care associated with uncontrolled gout that increases with disease severity and comorbidities, such as end-stage renal disease.

Conclusion: In the US, uncontrolled gout results in a significant economic burden that is higher in patients with more severe disease. Uncontrolled gout is associated with higher economic costs than controlled gout; furthermore, controlled gout has been associated with lower healthcare costs and protection against comorbidities. This study

was sponsored by AstraZeneca.

1. Morlock R, et al. *Value Health.* 2015;18:A640-641.

Table. Summary of Studies Reporting Healthcare Costs Associated with Gout

Reference	Sample Size	Main Findings
Retrospective Database Analyses		
Jackson et al. *BMJ Open* 2015	Total: 102,703 0–1 flares: 89,201 2 flares: 9714 3+ flares: 3788	Total costs, mean (SD) (USD) all-cause: Total: $11,974 (30,349) 0–1 flares: $11,839 (30,866) 2 flares: $12,101 (26,957) 3+ flares: $14,824 (25,819) Similar trends were seen for medical and pharmacy costs
Park et al. *Clin Ther* 2012	Total: 352 sUA <6: 35 sUA 6-8.99: 231 sUA≥9: 83	Total costs, mean (SD) (2010 USD) all cause: sUA <6: $10,417 (12,868) sUA 6–8.99: $11,155 (16,428) sUA ≥9: $16,408 (22,857) Similar trends seen for medical, hospitalization, and pharmacy costs
Wu et al. *Am J Ther* 2012	Patients with refractory gout, tophi and ≥3 flares: 679 Gout-free matched controls: 679	Total costs, mean (SD) (2008 USD): Refractory ≥3 flares: $17,603 (33,119) Matched gout-free: $6891 (25,413) Refractory ≥6 flares: $25,778 (38,212) Matched gout-free: $4312 (13,841): Similar trends seen for medical and pharmacy costs
Saseen et al. *Rheumatology (Oxford)* 2012	Total: 204,449 Infrequent gout: 199,225 Frequent gout: 5224 Matched: 15,669 (10,446 infrequent gout, 5223 frequent gout)	Medical costs, mean (USD) all cause: Infrequent gout: $8209 Frequent gout: $8505
Rascati et al. *J Manag Care Pharm* 2011	Total: 449 sUA <6 mg/dl: 75 sUA 6-8.99 mg/dl: 305 sUA ≥9 mg/dl: 69	Medical costs, mean (USD) all cause: sUA <6 mg/dl: $8521 sUA 6-8.99 mg/dl: $9352 sUA ≥9 mg/dl: $13,444
Rascati et al. *Arthritis Rheum* 2011	Total: 352 sUA <6 mg/dl: 38 sUA 6-8.99 mg/dl: 231 sUA ≥9 mg/dl: 83	Total costs, mean (USD) all cause: sUA <6 mg/dl: $11,365 sUA 6-8.99 mg/dl: $11,551 sUA ≥9 mg/dl: $14,474
Halpern et al. *J Clin Rheumatol* 2009	Main findings apply to 3070 patients	Cost of flares, mean (SD) (USD) sUA < 6.0: $259 (592) sUA ≥6.0-<9.0: $477 (2792) sUA ≥9.0: $562 (1845)
Wu et al. *J Rheumatol* 2009	Total: 2237	Total costs, mean (SD) (2005 USD) per flare: $3,096 (9575) Total direct costs per flare, mean: sUA <6.0: $2389 (95% CI $2291–$2487) sUA 6-8.99: $2523 (95% CI $2419–$2626) SUA ≥9: $4944 (95% CI $4742–$5147)
Wu et al. *Arthritis Rheum* 2009	Total: 679 Subgroup with ≥6 flares: 195	Total incremental costs (2008 USD): Total: $10,222 ≥6 flares: $22,237
Wu et al. *J Manag Care Pharm* 2008	Total: 2237 sUA <6.0: 633 sUA 6-8.99: 1173 sUA ≥9.0: 431	Total costs, mean (SD) (2005 USD) all-cause: Gout patients: $14,734 (24,401) Matched gout-free: $9219 (20,186)
Brook et al. *Curr Med Res Opin* 2006	Gout: 1171 No gout: 247,867	Total costs, mean (SD) (USD): Gout: $6870 No gout: $3705 Similar trends seen for direct medical and ED costs
Estimation of costs		
Cisternas et al. ACR/ARHP 2014	2.7 million patients with gout	Total costs, mean per person (2011 USD): With gout: $11,663 Without gout: $4643 Total medical costs, all-cause: $31.8 billion Pharmacy costs, mean per person: With gout: $2497
Logistic regression of cost data		
Li et al. *Am J Pharm Benefits* 2013	50.1 million ambulatory visits (sample size NR)	Gout-related costs, annually (USD): $286 million 61% of total costs are drug costs Total direct annual ambulatory costs: Gout-associated: $933 million Gouty arthritis attack-attributed: $297 million (32%)

Abbreviations: ED, emergency department; NR, not reported; SD, standard deviation; sUA, serum uric acid; USD, United States dollars

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Disclosure: S. Kabadi, AstraZeneca, 3; **J. Myers**, Medical Decision Modeling Inc. - AstraZeneca, 5; **C. Bly**, Medical Decision Modeling Inc. - AstraZeneca, 5; **R. Wielage**, Medical Decision Modeling Inc. - AstraZeneca, 5;

R. Morlock, Former employee of: Ardea Biosciences, 3.

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Abstract Number: 2242

Comparison of Assessment and Management of RA and Other Rheumatic Diseases By Rheumatologists in Private Practices or an Academic Medical Center

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Background/Purpose: Since 80% of rheumatologists practice outside the university setting, training projects for rheumatoid arthritis (RA) may benefit from an improved understanding of RA management and care in private practice (PP). The aim of this study was to determine whether similarities and differences exist in the delivery of care and treatment of RA and other rheumatic diseases in PP and academic settings.

Methods: 18 rheumatology clinicians were observed by a second year medical student: 9 in PP and 9 at an academic medical center (UNV). Observational data (without chart review) were collected, including patient demographics, rheumatologic diagnoses, general physical exam, joint exam, and therapy. Clinicians were interviewed to survey therapeutic approaches to RA.

Results: Of 195 total patient visits, 83 (43%) were at UNV and 112 (57%) at PP. New patients represented 25% of UNV visits and 18% of PP visits. Visit length for new patients averaged 44 minutes at UNV and 29 minutes at PP. Established RA patients represented 38% of UNV visits and 22% of PP visits. Visit length for established RA patients averaged 33 minutes at UNV and 17 minutes at PP (Figure 1). For inspection, auscultation and joint palpation of established RA patients, the weighted point value averaged 2.4 points at UNV and 2.7 points at PP. UNV physicians were found to use Biologics 17% more frequently compared to PP physicians (Figure 2). Rank order of the top five diagnoses for UNV was RA, OA, fibromyalgia, Sjogrens, and gout. For PP the rank order was RA, OA, gout, psoriatic arthritis, and fibromyalgia.

Conclusion: Average visit length for established RA patients differed between UNV and PP groups, with visits being 48% shorter in PP settings. Patient populations also differed, with new patient visits representing a greater proportion of UNV visits. The elevated frequency of biologic prescription in the UNV group suggests a difference in treatment approaches. In contrast, complexity of established RA patient physical exams (detail points) was similar between the two groups. Diagnostic frequency of common rheumatologic diseases was also similar.

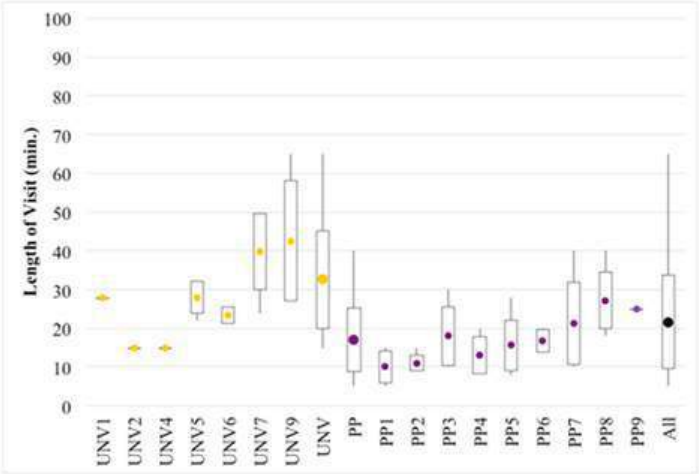

Figure 1. Established RA Visit Length, By Physician Group. Data are mean values ± 1 SD.

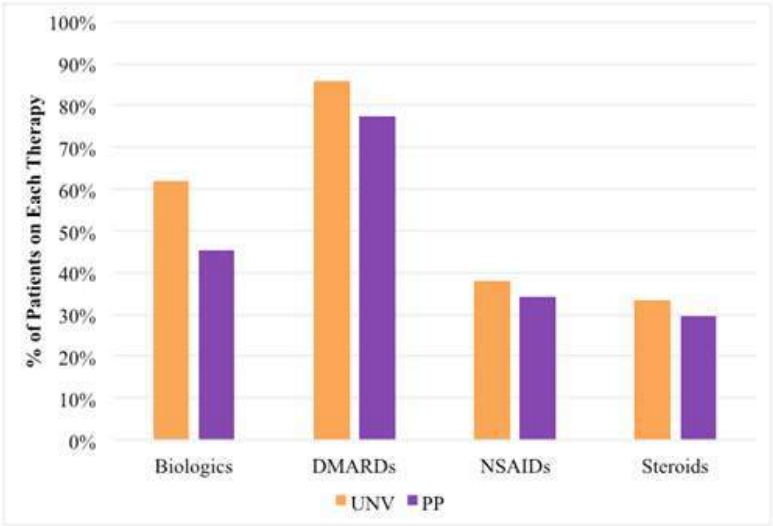

Figure 2. RA Therapy Choices, By Physician Group

Disclosure: A. Coleman, None; **H. Lindsley**, None; **J. Wick**, None.

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Abstract Number: 2243

The Paucity of the Evidence Base for American College of Rheumatology Practice Guidelines

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Background/Purpose: The American College of Rheumatology (ACR) practice guidelines establish U.S. and international treatment recommendations and hence performance measures and research priorities, so we sought to characterize the quality of evidence, the strength of recommendations and their relationship in the ACR guidelines.

Methods: For consistency (because ACR guidelines as of March 2016 used 3 different evidence grading systems), two independent reviewers applied the American College of Cardiology (ACC)/ American Heart Association (AHA) grading system to evaluate the quality (level) of evidence and class (benefit to harm or strength) of ACR treatment recommendations. To give each guideline equal weight, we reported results as medians and interquartile ranges (IQR) of the percentages of recommendations by level and class within each guideline.

Results: In the 8 guidelines (Glucocorticoid Induced Osteoporosis (GIOP); Juvenile Idiopathic Arthritis (JIA); Gout; Lupus Nephritis (LN); Osteoarthritis (OA); Spondyloarthritis (SpA); Polymyalgia Rheumatica (PMR); Rheumatoid Arthritis (RA)) involving 403 (range 10-102) recommendations, 23% (IQR 12-30%) were supported by level A (high) quality evidence; 18% (IQR 15-20%) level B (moderate); and 50% level C (IQR 46-70%) (low) (Table 1). In the 4 guidelines that reported the strength of 143 recommendations, 26% (IQR 21-31%) were class I (high benefit to harm ratio); 62% (IQR 58-64%) class II (moderate to low benefit to harm); and 16% (IQR 13-19%) class III (harm exceeds benefit) (Table 2). Overall, only 10% (IQR 7-12%) of recommendations (mean 9% of 143 recommendations) had both level A evidence and class I strength of recommendation. Of the level A and class I recommendations, the majority involved OA. Similarly, only 6% (IQR 2-12%) of recommendations (mean 9% of 143 recommendations) had both level B evidence and class I strength of recommendation. Most recommendations were level C and class II (median 30%, IQR 21-41%%, mean 32%). At the extremes, OA (58%) and GIOP (35%) had the most level A recommendations, and JIA (2%) and PMR (10%) had the least. Conversely, level C evidence comprised 86% of JIA recommendations, 70% of RA and 70% of LN.

Conclusion: The ACR clinical practice guidelines consist primarily of low-level evidence with moderate to low strength of recommendation. Few recommendations are both strong and supported by high-level evidence, emphasizing the need to expand the evidence base. _

Table 1. Guideline recommendations by Level (Quality) of evidence

Guideline	A	B	C
GIOP	35% (13/37)	19% (7/37)	46% (17/37)
JIA	2% (2/102)	12% (12/102)	86% (88/102)
Gout	21% (18.5/88)	31% (27/88)	48% (42/88)
LN	24% (8/33)	6% (2/33)	70% (23/33)
OA	58% (35/60)	17% (10/60)	25% (15/60)
SpA	29% (11/38)	20% (7.5/38)	51% (19.5/38)
PMR	10% 1/10	45% (4.5/10)	45% (4.5/10)
RA	13% 4.5/35	17% (6/35)	69% (24/35)
Mean	24%	21%	55%
Median (IQR)	23% (12-30%)	18% (15-23%)	50% (46-70%)

Table 2. Guideline Recommendations by Class (Strength) of recommendations

Guideline	I	II	III
OA	22% (13/60)	62% (37/60)	17% (10/60)
SpA	18% (7/38)	66% (25/38)	16% (6/38)
PMR	10% (3/10)	45% (4.5/10)	25% (2.5/10)
RA	34% (12/35)	63% (22/35)	3% (1/35)
Mean	26%	59%	15%
Median (IQR)	26% (21-31%)	62% (58-64%)	16% (13-19%)

Disclosure: **A. Duarte-Garcia**, None; **R. Zamore**, None; **J. B. Wong**, None.

Abstract Number: 2244

Utilization Patterns of Subcutaneously Administered Biologic Medications within a Sample of Rheumatoid Arthritis Patients

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Background/Purpose: Adherence to medication is crucial to the maximum therapeutic benefit of biologic treatment. The plethora of currently approved biologic agents makes comparison of the various medications more difficult, particularly when drug dosing and administration schedules vary. This study used administrative claims to investigate real world utilization and adherence patterns of subcutaneous (subQ) biologic treatment in a population of patients with RA.

Methods: The earliest incident adalimumab (ADA), certolizumab (CER), etanercept (ETA), and golimumab (GLM) biologic cycles of treatment were identified in the Truven MarketScan® and Optum Clinformatics™ research databases for adult patients with an RA diagnosis (ICD-9: 714.xx) between 2009 – 2013. Members were required to have ≥ two index biologic fills, and continuous eligibility for at least 6 months prior to biologic initiation. Members were followed until the end of their treatment, eligibility was lost, or the end of the data was reached. Utilization measures included biologic placement, treatment gaps measured as the number of days between expected refill dates, dose escalation, defined as any appearance of a twofold increase in dose from the starting dose, and medication adherence assessed by the proportion of days' covered (PDC). Members with 80% of the days in their treatment period covered by the index medication were categorized as adherent. One-way ANOVA and chi-square tests of equality of proportions were conducted to assess group differences.

Results: Modal monthly calculated dosages were in line with recommended prescribing guidelines for all four treatments (Table 1). GLM and CER were significantly less likely to be administered as a first line biologic compared to ADA and ETA; however GLM members were more likely to be adherent (*p*s < 0.05). ADA and GLM members displayed the greatest refill consistency within the Truven database as evidenced by lower gaps between refills (*p*s < 0.05). Consistent with the label, ADA cycles were more likely to show a dose escalation (*ps* < 0.001). Nearly two-thirds of all treatment cycles persisted for ≥ 6 months, with the greatest proportion from the ETA group across both databases. ($p < 0.001$).

Conclusion: Significant differences in biologic utilization patterns were observed among the four treatment

groups. ADA and ETA were the most common first line biologics, though GLM cycles were associated with greater refill consistency and levels of adherence. These findings have implications for healthcare decision makers interested in quality improvement or optimization of adherence in patients treated with subcutaneous biologic therapies.

Table 1. Biologic Utilization Descriptive Statistics: Results from Multiple Data Sources

	ADA		CER		ETA		GLM			
Truven Database										
Sample Size	11,425		1,471		12,965		2,043			
Recommended Mo. Dose	80 mg[1]		400 mg		200 mg		50 mg			
Modal Calculated Dose	80 mg		400 mg		196 mg		47 mg			
	f	%	*f*	%	*f*	%	*f*	%	*p*	*post hoc*[2]
% Adherent (PDC ≥ 0.80)	8,614	75.4%	980	66.6%	9,318	71.9%	1,619	79.2%	**<0.001**	a,b,c,d,e,f
% as 1st Line Therapy	8,678	76.0%	694	47.2%	10,686	82.4%	994	48.7%	**<0.001**	a,b,c,d
% Continuing for ≥ 6 Months	7,909	69.2%	960	65.3%	9,171	70.7%	1,393	68.2%	**<0.001**	a,b,d,f
% with a Dose Escalation	1,356	11.9%	76	5.2%	432	3.3%	78	3.8%	**<0.001**	a,b,c,d,f
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Refill Interval Gap (days)	9.2	13.5	10.3	11.1	10.4	15.1	8.4	9.9	**<0.001**	a,b,e,f
Optum Database	**ADA**		**CER**		**ETA**		**GLM**			
Sample Size	3,202		731		4,811		956			
Recommended Mo. Dose	80 mg[1]		400 mg		200 mg		50 mg			
Modal Calculated Dose	80 mg		400 mg		196 mg		47 mg			
	f	%	*f*	%	*f*	%	*f*	%	*p*	*post hoc*
% Adherent (PDC ≥ 0.80)	2,275	71.0%	485	66.3%	3,329	69.2%	721	75.4%	**<0.001**	a,c,e,f
% as 1st Line Therapy	2,342	73.1%	377	51.6%	3,974	82.6%	516	54.0%	**<0.001**	a,b,c,d,f
% Surviving for 6 Months	2,104	65.7%	460	62.9%	3,312	68.8%	637	66.6%	**<0.01**	b,d
% with a Dose Escalation	358	11.2%	42	5.7%	91	1.9%	64	6.7%	**<0.001**	a,b,c,d,f
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Refill Interval Gap (days)	9.1	12.6	8.4	8.4	9.6	13.2	8.3	10.9	**<0.05**	f

1 Dose may be adjusted to 40 mg weekly in patients not taking methotrexate.
2 post hoc comparisons: A: ADA ≠ CER; B: ADA ≠ ETA; C: ADA ≠ GLM; D: CER ≠ ETA; E: CER ≠ GLM; F: ETA ≠ GLM.

Disclosure: J. Tkacz, Janssen Scientific Affairs, LLC, 5; **B. Brady**, Janssen Scientific Affairs, LLC, 5; **L. A. Ellis**, Janssen Scientific Affairs, LLC, 3; **R. Meyer**, Janssen Scientific Affairs, LLC, 3.

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Abstract Number: 2245

Injectable Corticosteroid Use in Musculoskeletal Care Specialties

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Background/Purpose: Injectable corticosteroids (IC) are widely used for joint and soft tissue injections. Although four main types of preparations are available, there is sparse evidence and consensus for the selection and utilization of ICs. Using national outpatient Medicare data, we studied the utilization of IC preparations amongst musculoskeletal (MSK) care specialists.

Methods: A retrospective secondary analysis of Medicare physician and other supplier Public Use Files from 2014 were used for assessing injectable corticosteroids' utilization. Non-duplicative billing claims for ten preparations of IC were calculated by MSK provider specialty and by State. MSK provider specialties were grouped into six groups that billed the majority of the services as shown in Table 1. Number of services submitted were standardized with Prednisone 5 mg to reflect unique doses. Cost per standardized service was then calculated. For national trends, injectable corticosteroids were aggregated to five main classes. Descriptive analysis was conducted using R-Studio (Version 0.98.1102) and Tableau (Version 9.3).

Results: Amongst the most commonly used ICs, methylprednisolone 40mg and 80mg preparations were cheapest and most commonly used preparations (Table 1). Triamcinolone 10mg and betamethasone preparations were the next most commonly utilized. Amongst these, betamethasone was more expensive and least used by Radiology and Rheumatology. Triamcinolone 1mg was the most expensive and was utilized mainly by the Pain Management. Moreover, Dexamethasone being the least expensive was also heavily utilized by the Pain Management. Hydrocortisone and triamcinolone diacetate were least utilized. Among MSK providers, Orthopedists had the highest utilization of IC, and Radiologists the least (Figure 1). In other words, Orthopedists showed the highest service counts as well as payments for IC use. When compared with other MSK specialties in the Top 10 states for national trends (Figure 2), Orthopedists were the dominant providers for total billing in these states, but Pain Management followed by Rheumatology had the most number of services per provider. In contrast to number of standardized service units, the highest payments were for betamethasone, methylprednisolone, and triamcinolone injectable corticosteroids.

Conclusion: This study highlights the disproportionate spending on certain types of injectable corticosteroids by MSK providers with no clear guidelines on their use. Variations between MSK providers in injectable corticosteroids types and dosage bespeak the need for additional research aimed at establishing uniform injectable corticosteroid use guidelines. There is a need for further trials investigating the comparative efficacy of different injectable corticosteroids with specific outcome measures to facilitate a more evidence-based practice.

Table 1A: 2014 Raw Service Counts for Injectable Corticosteroid Preparations

Provider Type	Betamethasone 3mg	Dexamethasone 1mg	Hydrocortisone 100mg	Methylprednisolone 20mg	Methylprednisolone 40mg	Methylprednisolone 80mg	Triamcinolone Acetonide 1mg	Triamcinolone Acetonide 10mg	Triamcinolone Diacetate 5mg	Triamcinolone Hexacetonide 5mg
Orthopedics	1,131,457	562,997	1,494	84,525	1,081,771	502,753	21,693	3,629,868	88,905	90,158
Pain_Mx	204,436	703,559	99	27,580	211,363	140,320	364,192	745,740	16,529	6,260
PMR	194,302	447,516	68	17,091	136,045	88,455	44,737	719,343	35,940	3,823
Podiatry	141,876	289,807		17,819	71,374	8,805	1,541	245,814	2,803	3,891
Radiology	23,086	29,528	17	361	13,429	12,873	7,458	59,314	726	
Rheumatology	59,998	81,331	7,808	73,068	215,733	128,490	91	860,776	16,777	78,025

Table 1B: 2014 Payments of Injectable Corticosteroid Preparations

Provider Type	Betamethasone 3mg	Dexamethasone 1mg	Hydrocortisone 100mg	Methylprednisolone 20mg	Methylprednisolone 40mg	Methylprednisolone 80mg	Triamcinolone Acetonide 1mg	Triamcinolone Acetonide 10mg	Triamcinolone Diacetate 5mg	Triamcinolone Hexacetonide 5mg
Orthopedics	$4,858,483	$56,784	$6,165	$211,405	$2,443,684	$2,158,916	$61,253	$4,814,311	$47,806	$110,596
Pain_Mx	$886,419	$73,094	$421	$69,142	$483,851	$616,529	$810,405	$1,015,772	$22,868	$5,901
PMR	$843,155	$46,291	$293	$43,169	$310,243	$386,835	$105,905	$976,356	$21,661	$4,662
Podiatry	$661,748	$29,324		$43,844	$161,827	$37,469	$4,125	$325,319	$853	$5,100
Radiology	$100,629	$3,075	$68	$925	$31,107	$57,259	$21,212	$80,361	$156	
Rheumatology	$253,529	$8,285	$31,762	$181,568	$486,464	$552,820	$141	$1,150,522	$7,786	$97,311

Table 1C: 2014 Standardized Service Counts[a]

Provider Type	Betamethasone 3mg	Dexamethasone 1mg	Hydrocortisone 100mg	Methylprednisolone 20mg	Methylprednisolone 40mg	Methylprednisolone 80mg	Triamcinolone Acetonide 1mg	Triamcinolone Acetonide 10mg	Triamcinolone Diacetate 5mg	Triamcinolone Hexacetonide 5mg
Orthopedics	5,657,285	748,785	7,470	422,624	10,817,712	10,855,056	5,423	9,024,648	111,131	112,698
Pain_Mx	1,022,180	935,734	495	137,898	2,113,632	2,806,390	91,048	1,864,361	28,661	7,825
PMR	971,508	595,197	340	85,455	1,360,448	1,769,098	11,184	1,798,357	44,924	4,779
Podiatry	709,378	385,443		89,093	713,735	176,100	385	614,536	2,504	4,864
Radiology	115,430	39,272	85	1,805	134,296	257,450	1,865	148,284	900	
Rheumatology	299,992	108,170	39,038	365,341	2,157,331	2,569,800	23	2,151,940	20,971	97,531

Table 1D: 2014 Payment per Standardized Service ($)[b]

Provider Type	Betamethasone 3mg	Dexamethasone 1mg	Hydrocortisone 100mg	Methylprednisolone 20mg	Methylprednisolone 40mg	Methylprednisolone 80mg	Triamcinolone Acetonide 1mg	Triamcinolone Acetonide 10mg	Triamcinolone Diacetate 5mg	Triamcinolone Hexacetonide 5mg
Pain_Mx	0.87	0.08	0.84	0.49	0.23	0.22	9.91	0.54	0.69	1.04
Radiology	0.87	0.08	0.80	0.51	0.23	0.22	7.55	0.54	0.17	
PMR	0.86	0.08	0.86	0.50	0.23	0.22	9.81	0.54	0.79	0.97
Podiatry	0.84	0.08		0.49	0.23	0.21	10.50	0.53	0.25	1.07
Orthopedics	0.85	0.08	0.83	0.49	0.23	0.21	11.40	0.53	0.38	0.99
Rheumatology	0.85	0.08	0.82	0.50	0.22	0.21	7.01	0.53	0.34	0.99

a: Service counts were standardized to prednisone 5mg units using standard conversion units eg Depromedrol 4mg is equivalent to Prednisone 5mg, and Depomedrol 40mg one service unit is equal to 10 Prednisone 5mg units.
b: Payment for Standardized Service was calculated by dividing sum standardized services by sum payments for the respective fields.
PM-R – Physical Medicine and Rehabilitation (includes Sports Medicine), Pain_Mx -Pain Management includes Interventional Pain Management, Orthopedics includes Hand Surgery, Radiology includes Interventional Radiology.

Figure 1. 2014 Payments and Standardized Services by Specialty and Injectable Corticosteroid Preparation

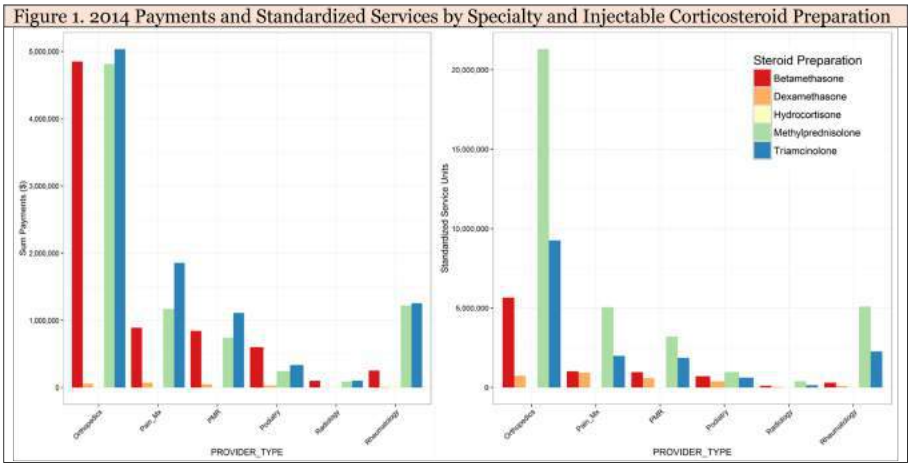
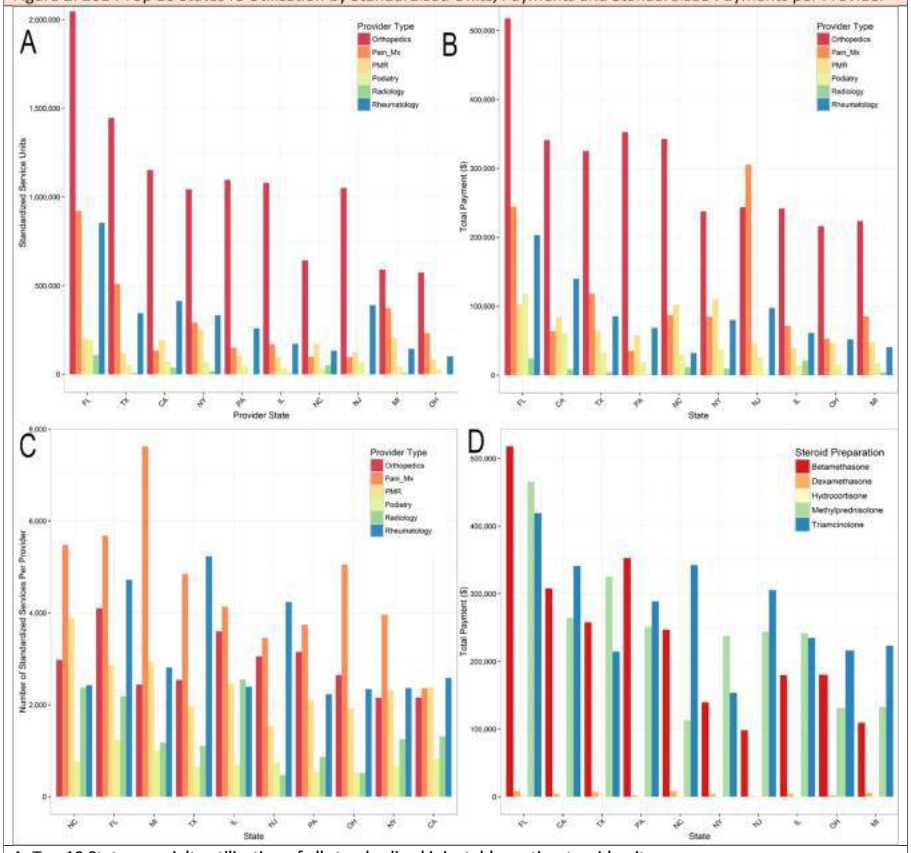


Figure 2. 2014 Top 10 States IC Utilization by Standardized Units, Payments and Standardized Payments per Provider



A: Top 10 States specialty utilization of all standardized injectable corticosteroid units.
B: Specialty payment of all injectable corticosteroid units in the top 10 States.
C: Top 10 States standardized services per provider by specialty.
D: Payment of injectable corticosteroids in Top 10 States ordered by total payment.

Disclosure: G. S. Kaeley, None; **M. Thway**, None; **S. Dodani**, None.

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Abstract Number: 2246

Glucocorticoids in Early Rheumatoid Arthritis Management, Friend or Foe?

Diederik Decock[1], Rene Westhovens[1,2], Veerle Stouten[1], Kristien Van der Elst[2,3], Johan Joly[2], Patrick Verschueren[1,2] and CareRA Study Group, [1]KU Leuven Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium, [2]Rheumatology, University Hospitals Leuven, Leuven, Belgium, [3]KU Leuven, Department of Public Health and Primary Care, Skeletal Biology and Engineering Research Center, Leuven, Belgium

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SESSION INFORMATION

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Background/Purpose: The Care in early Rheumatoid Arthritis (CareRA) trial compares different combinations of csDMARDs with remission induction glucocorticoid (GC) schemes starting at high or moderate dosages in a treat to target approach. Efficacy results after 52 weeks showed high rates of DAS28(CRP) remission reaching >60%. However, many physicians are still reluctant to use such regimens in practice for fear of side effects. This study explores the risk-benefit balance of GC-based intensive treatment strategies.

Methods: DMARD unexperienced Early Rheumatoid Arthritis (ERA) patients were stratified into a high- or low-risk arm based on classical prognostic markers. High risk patients were randomized to COBRA Classic (Methotrexate (MTX) + Sulphasalazine + prednisone stepdown from 60mg), COBRA Slim (MTX + prednisone stepdown from 30mg) or COBRA Avant-Garde (MTX + Leflunomide + prednisone stepdown from 30mg). Low risk patients were randomized to MTX Tight Step Up (MTX-TSU) without oral GCs or COBRA Slim. Prednisone was tapered down over 6 weeks to 7.5mg in Classic and 5mg in the other COBRA arms. Oral GCs were stopped at week 34. DMARD monotherapy was aimed for in all strategies. Demographics and disease parameters were routinely registered. All patients attending the week 52 visit in CareRA were analyzed. Remission, low disease activity, obesity and arterial hypertension were defined as DAS28(CRP)<2.6, DAS28(CRP)≤3.2, BMI ≥30 kg/m² and systolic/diastolic blood pressure ≥140/90 mmHg. This analysis describes trial effectiveness, effects of treatment on BMI and blood pressure, and safety events of interest.

Results: Of the 379 patients included in our trial, 349 (91.3%) attended week 52. Remission and low disease activity were achieved in 227/349 (65.6%) and 278 (80.3%) patients respectively, with 236 (68.2%) patients on MTX monotherapy. The therapeutic strategy could be followed per protocol by 263 (75.4%) patients. Of patients not able to follow the protocol 26 (7.4%) were using biologicals and 18 (5.2%) GCs. Table 1 gives detailed information per treatment strategy. BMI changed 0.0 ±3.2 kg/m^2 after 52 treatment weeks. The proportion of obese patients did not rise between baseline and week 52 (20.1% vs 20.3%). Systolic and diastolic blood pressure changed -0.9 ±15.8 mmHg and -0.4 ±10.6 mmHg respectively, without a significant change in the proportion of hypertensive patients (10.7% vs 6.1%). The only difference between treatments arms in either risk groups was a BMI decrease in Avant-Garde compared to Classic and Slim between baseline and week 52 (p=0.01). Diabetes and glucose intolerance were reported only once, in Cobra Slim and Classic respectively. Hyperglycaemia was reported once in Classic, Avant-Garde and MTX-TSU. Glycosuria was reported in 1 Avant-Garde patient. No differences between groups were observed in infection rate. Most common were respiratory infections.

Conclusion: Intensive treatment strategies using short-term glucocorticoids for remission induction show a favourable risk-benefit ratio after 1 year, with only a small proportion of patients requiring biologics and no need for prolonged GC use in ERA.

Disclosure: D. Decock, None; **R. Westhovens**, None; **V. Stouten**, None; **K. Van der Elst**, None; **J. Joly**, None; **P. Verschueren**, IWT grant, 2,Pfizer chair for early RA research, 2.

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Abstract Number: 2247

REAL-Life Cost of UK Healthcare Resource for Patients with Rheumatoid Arthritis, Comparing High and Low/Remission Disease States

Bruce Kirkham[1], Estee Chan[2], Alexandra Vincent[2] and Alison Elliott[3], [1]Rheumatology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom, [2]Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom, [3]Market Access Directorate, Roche Products LTD UK, Welwyn Garden City, United Kingdom
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Background/Purpose: Rheumatoid Arthritis (RA) has differing therapeutic outcomes, with resulting differences in function and quality of life. Little is known about the effects of disease activity states on costs of routine care of people with RA. We quantified the real medical costs of treating patients with RA who were in a high DAS28 state (HDAS) versus low DAS28 or remission (LDAS), in a Guys & St Thomas' NHS Foundation Trust (GSTT) and Roche Products Ltd collaborative project.

Methods: The GSTT RA Centre database of 1,700 patients with RA, was used to generate two groups of 60 patients with high DAS28 (DAS28>5.1) scores and low DAS/remission, matched in terms of age, sex and duration of disease. Patients with co-morbidities such as significant chronic medical conditions, cancer and fibromyalgia were excluded to ensure comparable groups. Health Assessment Questionnaire (HAQ-DI) and EQ-5D values were compared. All medical costs incurred at GSTT from August 2013 to September 2015 were collated, including drug costs, inpatient and outpatient procedures and investigations.

Results: The mean and range for average HAQ-DI and EQ-5D respectively was 1.78 (0.15-2.92) and 0.286 (0.691 – [-0.239]) for the HDAS group and 0.70 (0-2.31) and 0.714 (1-0.258) for the LDAS group, both significantly different. Total GSTT pharmaceutical costs were £390,904, with biologic drug costs of £377,507 for HDAS patients and £324,805, with biologic drug costs of £321,401, for LDAS patients. 17 people in the HDAS group took concomitant prednisolone compared to 5 in the LDAS group. Total costs for the HDAS group were £733.984.02 ($1,078,957) vs £483,755.97 ($711,121) for the LDAS group, a difference of £250,228.05 ($367,835). Costs for patients living near our centre to those living at a distance did not differ significantly indicating that much of their hospital care took place at GSTT. The annual GSTT cost per patient increment of HDAS RA vs LDAS RA was £2085 ($3,066). These costs do not capture non-GSTT healthcare costs.

Conclusion: This study describes 'real world' hospital costs of treating patients with rheumatoid arthritis who have different disease activity, with minimal co-morbidity differences, treated by the same team. Poor function and quality of life for those people in high disease activity despite higher use of concomitant steroids and similar biologic drug use, shows the challenging nature of their RA. The data further support strategies to treat early and effectively by demonstrating that patients with low disease activity has a lower cost impact on the Trust and improved function and quality of life scores.

Disclosure: B. Kirkham, None; **E. Chan**, None; **A. Vincent**, None; **A. Elliott**, Roche Products LTD, 3.

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Abstract Number: 2248

The "Financial Toxicity" of Therapy in Patients with Rheumatoid

Arthritis

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Background/Purpose: In the pre-biologic era, major costs faced by patients with RA included hospitalization and joint replacement. Biologic agent development has led to increasing outpatient costs. The effects of this from a patient's perspective have not been thoroughly explored although modeling exists in the oncology literature[1]. The purpose is to present patients' perspective of how medical costs impact their view of financial burden in rheumatologic care.

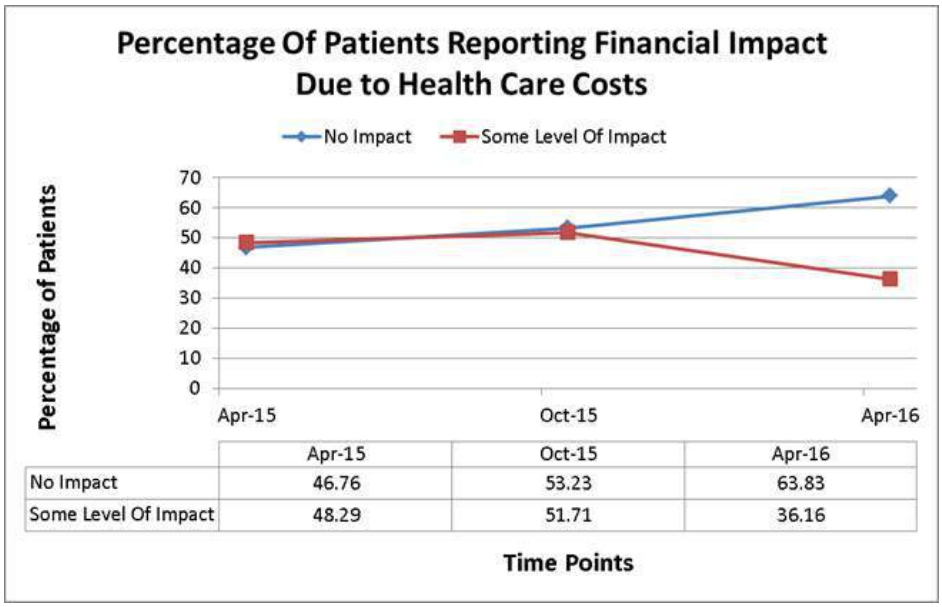
Methods: In this retrospective cross-sectional study, the US Rheumatology database JointMan® was utilized. Patients complete a financial impact form at every visit. Patients respond on a Likkert scale to the question, "How much of an impact does the cost of your medical care received from our office have on your life financially?" Response options: intolerable, severe, moderate, mild or none. Percentages of each response category were calculated for the time periods: 4/20/15–6/15/15, 10/20/2015–12/15/20, and 4/20/15–6/15/2016. Patients were also asked whether their financial situation would cause them to skip visits, postpone a visit, have difficulty paying for a visit or medication, cut dosage of medications, skip doses of medications, or fail to fill a medication.

Results: Of the 12554 responses, the mean patient age was 58, 73.11% female; 90.94% Caucasian. All patients had Medicare or private insurance; none were uninsured.

Response	Response Count	Percentage
Intolerable	31	0.25%
Severe	384	3.06%
Moderate	1997	15.91%
Mild	3132	24.95%
None	7010	55.84%

Global distribution of all responses

A two-sided T-Test comparing the "none" category for the April 2016 time point to all other categories combined revealed a statistically significant relationship $t=21.87$ ($p<0.0001$).



	Apr-15	Oct-15	Apr-16
No Impact	46.76	53.23	63.83
Some Level Of Impact	48.29	51.71	36.16

Conclusion: Surprisingly, there was an increasing trend in the "none" category indicating no perceived financial impact. Potential explanations include that this analysis was mostly from one large rheumatology practice where all patients surveyed were insured. In this population health insurers recognize the importance of biologics and were more likely to approve therapy. Competitive financial strategies are employed by pharmaceutical companies offering multiple or substantial co-pay assistance. ACR guidelines for treatment pathways are published including recommendations for biologic therapy which may aid insurance coverage.

1. Khera, N. J. Clin. Onc, 2014. 32(29)3337

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Abstract Number: 2249

Comparison of Discontinuation Rates Among Patients with RA Initiating Biologics

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Background/Purpose: While difficult to directly compare effectiveness of biologics in observational settings, drug discontinuation can be a useful substitute. We compared the discontinuation rates of individual and groups of biologics, by mechanism of action, mode of delivery, previous biologic use, line of treatment, and concomitant MTX and/or prednisone.

Methods: Using a large US-wide observational cohort, the National Data Bank for Rheumatic Diseases (NDB), we characterized patients with RA who initiated a biologic from 2005 through 2015. For simplicity, we included tofacitinib as a non-TNF (NTNF) biologic. Baseline characteristics were assessed by each biologic and by grouped mechanism of action. Discontinuation, described using Kaplan-Meier survival curves, was defined as either stopping the drug or adding another DMARD. Sensitivity analyses defined discontinuation only as stopping the drug. Discontinuation rates were further analyzed by stratifying several factors: route of administration (SC *vs* PO *vs* IV), line of treatment (1st, 2nd, 3rd+), prior use of biologics (TNF or NTNF) and concomitant use of MTX and/or prednisone.

Results: A total of 2458 patients initiated a TNF and 1349 a NTNF, representing 6326.5 and 2987.5 patients-years of follow-up, respectively. Overall, median survival (IQR) was 1.5 (0.5-3.0) for TNFs and 2 (1- 3.5) for NTNFs, or 4 (2-9) and 4 (2-7.5) in sensitivity analysis. Figure illustrates individual biologic survival curves by mechanism of action. Grouping by route of administration, the median survival was for PO of 3.0 (2-6) years and did not differ between IV and SC (1.5 (0.5 – 2.5) years). When considering later lines of treatment, the rates of discontinuation were similar with median survival (IQR) of TNF *vs* NTNF: 1st line 3.5 (1-9.5) *vs* 2.5 (1-5.5), 2nd line 4 (1.5 -9.5) *vs* . (5.5-.) and 3rd+ line of treatment 3.5 (2-8) *vs* 3 (1-5). Stratifying by prior use of TNF, the survival was longer for TNF vs. NTNF 1.5 (1-3.5) *vs* 0.5 (0.5 -0.5) years, but the reverse occurred with prior use of NTNF, 1 (0.5 -1.5) vs. 2 (1.-3.5) years. For both groups, discontinuation rates were lower with no concomitant MTX, TNF 8.5 (3.5-.) vs. NTNF 6 (3.5 -.).

Conclusion: As more medication options became available over the past decade, discontinuation rates of biologics for patients with RA have increased and have become more similar. Surprisingly we found rates to decrease when biologics were taken without MTX, an area for further investigation.

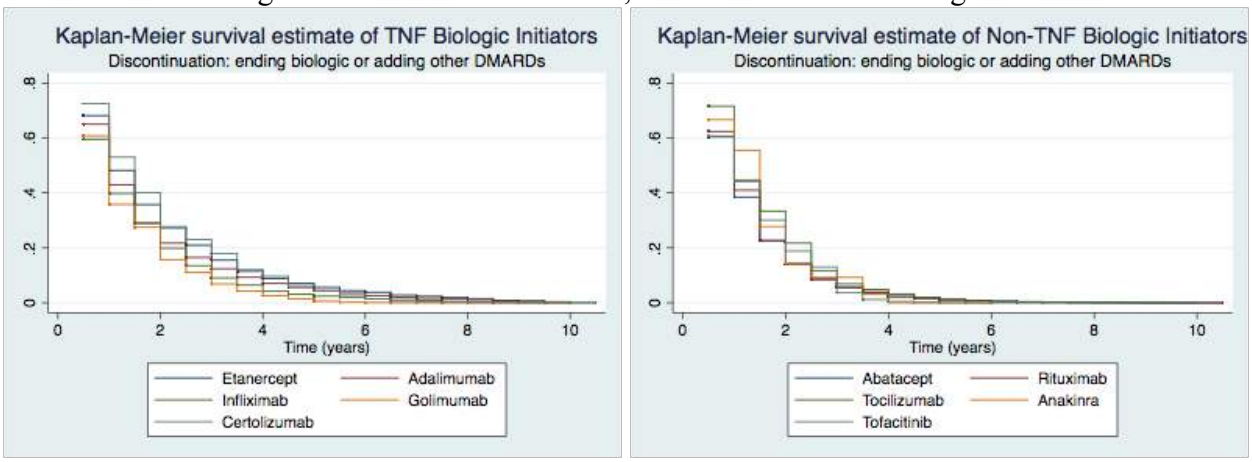

Figure – Discontinuation curves of TNF and NTNF biologic initiators.

Disclosure: S. Pedro, None; **K. Michaud**, Rheumatology Research Foundation, Pfizer, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-of-discontinuation-rates-among-patients-with-ra-initiating-biologics

Abstract Number: 2250

A Real World View of Rheumatoid Arthritis Patients Treated with Advanced Therapies: Comparing Patient Profiles and Outcomes

Laurent Chanroux and Fara Mboge, Therapy Watch, Research Partnership, London, United Kingdom
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Background/Purpose: Advanced therapies including bDMARDs and tofacitinib have been shown to help control disease progression in rheumatoid arthritis (RA) and reduce joint damage. The aim of our research is to better understand if certain patient types may be more suitable for specific treatment options and assess if any of these achieve significantly different outcomes in RA patients.

Methods: We used data collected as part of an online treatment survey conducted among a panel of rheumatologists between June 2014 and January 2016 in the USA. We reviewed and analysed a total of 4,044 patient forms reported by 206 physicians. Physicians were sampled to provide a mix of practice types and regions that would be representative of the universe of treaters. The record forms collected were split into 3 patient groups, group 1 = those treated with an TNF-inhibitor biologic (etanercept, adalimumab, infliximab, certolizumab pegol, golimumab), group 2 = those treated with a non-TNF biologic (abatacept, rituximab, tocilizumab) and group 3 = those treated with the JAK-inhibitor, tofacitinib. We analysed demographic data for these patients along with their current DAS, joint count, HAQ score and perceived disease severity to assess their response to therapy over time.

Results: On average, non-TNF biologic patients are older than TNF-inhibitor (TNFi) and tofacitinib patients (53.9 years old vs. 50.0 and 51.2, respectively) and more likely to be female (75%, $p < 0.05$). In addition, they more commonly suffer from comorbid conditions (83%) particularly when compared with TNFi patients (73%). TNFi patients are significantly more likely to be on their 1st ever biologic (86%) compared to non-TNF and tofacitinib patients (41% and 53%, respectively) and have been on their current treatment for longer on average (32 months vs. 23 for non-TNF and 11 for tofacitinib patients). TNFi patients have on average been diagnosed for the shortest amount of time (64 months vs. 72 and 84 for tofacitinib and non-TNF patients) and experienced the shortest delay between diagnosis and 1st biologic initiation (28 months vs. 46 and 40 for tofacitinib and non-TNF patients). A significantly larger proportion of TNFi patients is considered to have mild RA (69%) vs. non-TNF and tofacitinib patients which are more likely to suffer from moderate to severe disease. TNFi patients are more frequently deemed to be in full remission (34%) and are more likely to have a DAS28 < 2.6 (54%) while non-TNF and tofacitinib are significantly more likely to have a DAS28 between 3.2 and 5.1. However, there were no significant differences in the mean DAS28 and HAQ scores reported for patients in all 3 groups and limited differences in their mean joint counts. There were significant differences in the proportion of patients that were deemed to have severe RA at diagnosis in each group (35% for non-TNF patients, 29 for tofacitinib patients and 23% for TNFi patients) and accounting for these differences in severity at diagnosis we saw reduced differences in the proportion of patients currently in remission in each treatment group. Nevertheless, TNFi and tofacitinib patients are significantly more likely to be employed full time (51% and 48%, respectively) vs. non-TNF patients (40%) while a smaller percentage of TNFi patients are unable to work due to their RA (5%) when compared to non-TNF and tofacitinib patients (both 9%).

Conclusion: While there are significant differences in the demographics and treatment flow of patients treated with TNFi, non-TNF biologic and tofacitinib, it is unclear whether treatment choices are based on specific patient profiles or treatment guidelines and non-clinical factors. In addition, while each drug group achieved a reduction in the proportion of patients with severe disease and a considerable proportion of patients with low disease activity or remission, it is unclear whether better outcomes are consistently achieved with one treatment option vs. another. Additional research is needed to better ascertain if differences in perceived outcomes are real and what factors are truly driving them.

Disclosure: L. Chanroux, None; **F. Mboge**, None.

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Abstract Number: 2251

Secukinumab Vs Adalimumab for the Treatment of Ankylosing Spondylitis: A Cost per Responder Analysis at 52 Weeks from the US Perspective

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Secukinumab vs adalimumab for the treatment of ankylosing spondylitis: A cost per responder analysis at 52 weeks from the US perspective

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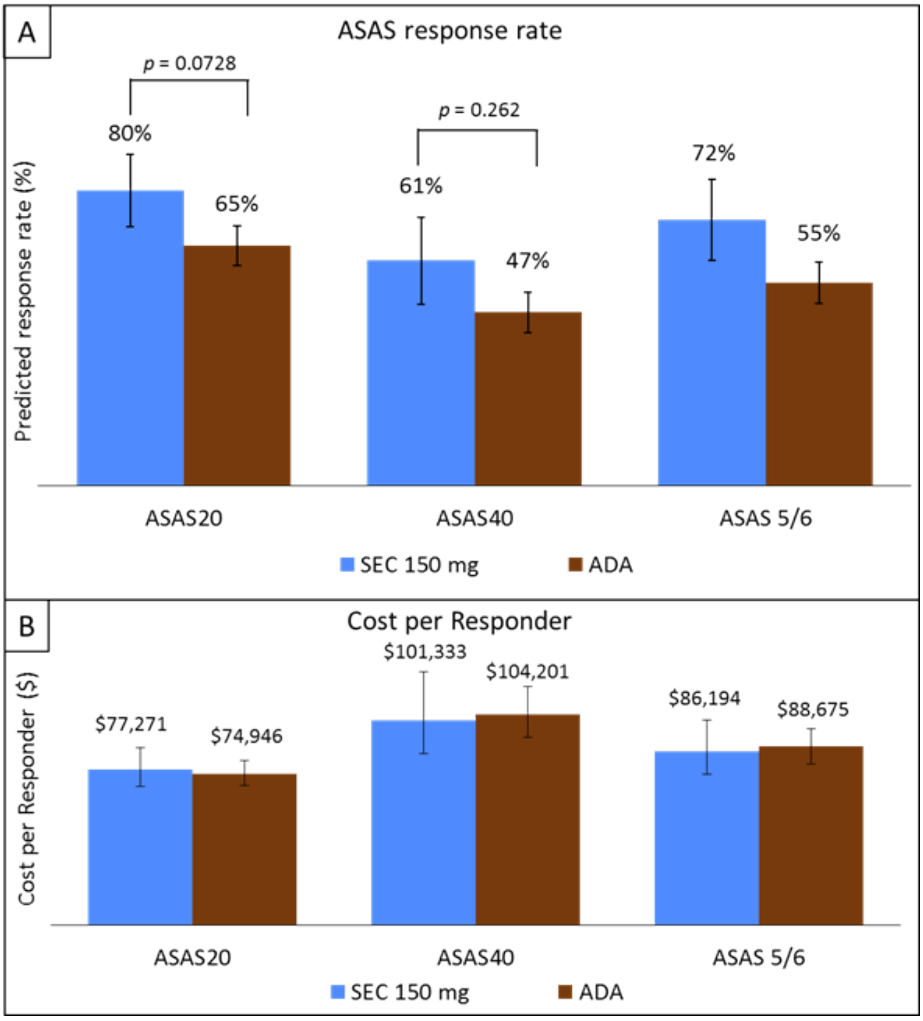
Background/Purpose: The cost per responder analysis attempts to quantify the relative value of the two comparator drugs by assessing how the two agents compare in terms of cost per treatment outcome. The objective of this analysis was to estimate and compare the long-term cost per responder based on the Assessment of Spondyloarthritis International Society (ASAS) outcomes following 52 weeks of treatment of ankylosing spondylitis (AS) with the anti-IL-17A antibody Secukinumab relative to the anti-TNF antibody Adalimumab.

Methods: The cost per responder for each treatment namely Secukinumab and Adalimumab was estimated by dividing the drug acquisition cost for the course of treatment with its response rate. Drug costs were estimated on the basis of the official US drug acquisition costs and the number of doses required for 52 weeks. Long-term response rates were estimated using a matching-adjusted indirect comparison (MAIC) technique based on the data from MEASURE 2 and ATLAS clinical trials of Secukinumab and Adalimumab, respectively. MAIC analysis matched the age, gender distribution, Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), C-reactive protein (CRP) and TNF-naive proportion at the baseline. A sensitivity analyses was also conducted by varying the choice of baseline characteristics (all above except BASDAI) used in MAIC analysis.

Results: MAIC analysis showed that ASAS (20, 40 and 5/6) response rates were significantly higher for Secukinumab compared to Adalimumab at 52 weeks. ASAS 20, ASAS 40 and ASAS 5/6 response rates were 80% vs 65%, 61% vs 47%, 72% vs 55% for Secukinumab vs Adalimumab, respectively (**Figure 1A**). The cost per ASAS 20 responder was $77,271 vs $74,946, cost per ASAS40 responder was $101,333 vs $104,202, whereas, costs per ASAS 5/6 responder was $86,194 vs $88,675 for Secukinumab vs Adalimumab, respectively (**Figure 1B**). While the costs per ASAS (40 and 5/6) responders were about 3% lower for Secukinumab compared to Adalimumab, the cost per ASAS 20 responders for Secukinumab was about 3% higher than that of Adalimumab at 52 weeks. Sensitivity analyses for ASAS response rates and cost per responder showed similar results, confirming the robustness of our main analysis.

Conclusion: The long-term cost per responder for ASAS (40 and 5/6) outcomes over 52-week treatment period were lower for Secukinumab compared to Adalimumab in AS patients. These findings indicate that Secukinumab represents a cost-efficient treatment choice for the treatment of AS patients in the US. **Keywords:** Adalimumab, Ankylosing spondylitis, Cost per responder, Matching-adjusted indirect comparison, Secukinumab

Figure 1: Predicted response rate (A) and cost per responder (B) analysis of ASAS (20, 40 and 5/6) for Secukinumab vs Adalimumab for the treatment of ankylosing spondylitis at 52 weeks in principal analysis



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Abstract Number: 2252

Estimated Cost of SLE Hospitalizations

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SESSION INFORMATION

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Background/Purpose: Systemic lupus erythematosus (SLE) treatment comes at a high price, with both direct costs related to healthcare resource utilization and indirect ones related to decreased work productivity. Previous studies have attempted to estimate the annual medical costs of SLE patients in the United States using available Medicare datasets. This study was initiated to estimate health care costs to payers for SLE treatment at a major U.S. academic institution.

Methods: This is a retrospective cohort study evaluating healthcare utilization for patients with SLE treated at Columbia University Medical Center/NewYork-Presbyterian Hospital between January 2000 and September 2014, using electronic medical record (EMR) data from the Clinical Data Warehouse. The control groups are represented by patients with rheumatoid arthritis (RA) and patients with renal transplants. Patients with SLE, RA, or renal transplant were identified using diagnostic codes from the International Classification of Diseases, Ninth Revision (ICD-9). Data on diagnosis-related group (DRG) weighting was obtained from www.cms.gov; base rates for emergency and hospital visits were obtained from www.health.ny.gov.

Results: 4,800 hospitalized patients with SLE were identified based on one ICD-9 code for lupus. The diagnosis of SLE using these criteria was validated based on review of 134 charts; this method of identifying SLE cases in the Data Warehouse had a positive predictive value (PPV) of 0.66 for diagnosing SLE. A total of 5,642 patients with renal transplant, and 7,273 with RA were also identified. Reimbursement from payers for hospital admissions and ER visits were estimated from the DRG weights and base rates. The DRG provides a weighting system based on the severity of the average patient. For SLE and RA alone, the respective weight is 0.7882 and 0.7337; with a comorbid condition, it is 1.1645 and 1.2287. For SLE with a major comorbid condition, it is 2.4409, while the renal transplant weight is 3.154 regardless of comorbidities or severity.

	SLE	Renal Transplant	RA
Unique Patients (N)	4,800	5,642	7,273
ED Visit (N)	20,178	18,426	31,718
Average ED Visits/patient	4.20	3.27	4.36
Reimbursement for ED visit ($)	155.57	622.54	144.82
Total Reimbursement for ED Visits ($ x 10^6)	3.14	11.47	4.59
Hospital Admissions (N)	10,464	23,518	16,255
Hospital Admissions/patient	2.18	4.17	2.23
Reimbursement per Hospital Admission ($)	23,830	30,800	10,960
Total Reimbursement Hospital Admissions ($ x 10^6)	249.39	724.25	178.21

Conclusion: These data suggest that the cost to payers, health insurance companies, for hospital-based care for SLE (252.53 mil $) is higher than that for RA (182.8 mil $) despite the much higher prevalence of RA. However, the true cost of a lupus patient to the admitting hospital—especially a hospital that provides tertiary and quaternary care—can be much higher than what is reimbursed; it is likely closer to the cost of a transplant patient, as patients with moderate/severe SLE are treated with the same immunosuppressants as transplant recipients and are at risk for the same co-morbidities. In sum, these data suggest that SLE care in hospitals is expensive for health insurers. Further efforts should be made to improve outpatient management in order to reduce excessive use of emergency room resources, as has been done with the renal transplant population. Additionally, hospitals and providers should lobby for a revision of the DRG weights for SLE.

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Abstract Number: 2253

Treatment Persistence with Subcutaneous TNF-Alpha Inhibitors in France

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Background/Purpose: Immune-mediated rheumatic disease (IMRD) including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS), are severe and disabling chronic diseases in rheumatology. Biotherapies such as subcutaneous tumor necrosis factor-alpha inhibitors (SC-TNFis) have transformed the management of rheumatoïd diseases. Very few studies have assessed the persistence to all four SC- TNFis for IMRD in a European setting. The objective of this study was to describe treatment persistence in a real-world setting, among patients diagnosed with IRMD, initiating treatment with an SC-TNFi in France and who were naïve of biotherapies (subcutaneous and intravenous) in the last 18 months.

Methods: The *Système National d'Information Inter-régime* [French national health insurance scheme information-sharing system] (SNIIR-AM) database lists all outpatient and inpatient healthcare consumption for individuals covered by the general health insurance scheme. Using French claims data, patients were included through Long Term Disease (LTD) status and hospital admission, based on ICD-10 codes. Identification of RA was based on M05, M06, M08.0, M08.2, M08.4 and M13 ICD-10 codes. For AS, identification was based on M08.1, M08.8, M08.9, M45 and M46 to M14 ICD-10 codes, and identification of PsA was based on M07 and M09 ICD-10 codes. Patients were then identified through filled prescription for adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab (GLM) between 06/01/2012 and 12/31/2013. Persistence was estimated using Kaplan Meier analysis.

Results: A total of 4,750 patients with RA were identified, 5,735 with AS and 1,244 with PsA. For the overall cohort of IMRD naïves patients, comparisons over 12 months showed that persistence was different between the four SC-TNFis, with persistence rates of 59.1% for CZP, 56.4% for ETA, 57.2% for ADA and 60.2% for GLM ($p=0.0004$). For RA cohort ($p<0.0983$) persistence rates were 60.3% for CMZ, 60.9% for ETA, 62.2 % for ADA

and 63.8% for GLM. For AS ($p<0.0001$) persistence rates were 52.7% for ETA, 54.6% for ADA and 58.9 % for GLM. For PsA, persistence rates were 52.5% for ETA, 57.8% for ADA and 55.9 % for GLM ($p=0.2014$). For AS and PsA analysis sample size of CMZ cohort were too small to estimate Kaplan-Meier curves.

Conclusion: Persistence rates observed in naïves patients varied according to SC-TNFis with significant difference for the overall and the AS cohorts. Those results seem correspond with others results published recently in the literature

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Abstract Number: 2254

Patient Adherence with Biologic Therapy in Rheumatoid Arthritis: A Real-World Review of Compliance

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Background/Purpose: Biologic agents (bDMARDs) have been shown to help control disease progression in rheumatoid arthritis (RA) and reduce joint damage. The aim of our research is to better understand patient compliance to guide the development of strategies to combat poor adherence.

Methods: We used data collected as part of an online patient survey conducted among 500 Rheumatoid Arthritis (RA) patients in December 2015 in 5 EU countries (France, Germany, Italy, Spain, UK). We focused our research on 197 patients treated with a biologic, 111 of which missed a dose in treatment within the previous 6 months. We analysed the route of administration of their treatment to assess the influence of intravenous infusions (IV) versus subcutaneous injections (SC). We also explored whether any correlation existed between patients' adherence to therapy and their relationship with the doctor they would normally see for their RA.

Results: 56.3% of our patients reported missing a dose of their biologic in the previous 6 months and on average these patients missed 2.8 doses during this period. Reasons cited for missing their dose include: "I felt better and didn't think I needed it" (29%), "I felt worse and didn't want it" (22%), "I didn't think it was helping" (17%) and other less common reasons such as infection, other types of sickness or surgery. Patients treated with SC biologics account for 55.3% of our sample and 54.1% of these patients reported being non-compliant with treatment in the period analysed, missing on average 2.8 doses. Although we had previously hypothesized that adherence may be higher among patients receiving an IV biologic, 58.0% of IV patients reported being non-compliant with treatment with a mean of 2.7 missed doses. Interestingly 38% of IV patients cited feeling better and thinking they did not need treatment, whereas 20% of SC patients reported feeling worse and not wanting to take their injection treatment. We

then looked at assessing whether the route of administration had an effect on patient's compliance to treatment using Pearson correlation analysis however, our findings deduced no significant relationship between both data sets. Further analysis looked at whether the relationship with the primary health care professional (HCP) had any possible influence on the outcome of compliance, however once again a Pearson correlation analysis found no significant link when non-compliant patients scored their relationship based on specific statements describing their relationship with the doctor they normally see for their RA.

Conclusion: Our research shows that a significant proportion of biologic patients miss one or more doses of their prescribed biologic over a 6 month period despite the benefits and cost of these therapies. Additional research is needed to optimise patient engagement with their disease and the healthcare providers they interact with to ensure improved long-term compliance with therapy.

Disclosure: L. Chanroux, None; **F. Mboge**, None; **D. Baldock**, None.

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Abstract Number: 2255

Characterization of Low-Density Granulocytes in Autoinflammatory Disorders

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Background/Purpose: Autoinflammatory disorders (AD) are characterized by recurrent fevers associated with systemic symptoms involving joints, skin, muscles, and eyes in the absence of adaptive immune responses. Profound dysregulations in various innate immune pathways including the inflammasome-mediated IL-1 signaling are characteristic of these syndromes. While previous studies have revealed that neutrophils may play critical roles in driving the inflammatory process in AD, whether specific neutrophil subsets and neutrophil processes play distinct pathogenic roles in these diseases remains to be characterized.

Methods: We examined the presence of distinct proinflammatory neutrophil subsets in AD and assessed their pathogenic potential. Blood was obtained from healthy controls and from patients with Familial Mediterranean Fever (FMF), Pyogenic Arthritis, Pyoderma gangrenosum, and Acne (PAPA) syndrome, Cryopyrin Associated Periodic Syndromes (CAPS), Tumor necrosis factor receptor-associated periodic syndrome (TRAPS), Autoinflammation-PLCG2-associated antibody deficiency-immune dysregulation (APLAID), and mutation negative AD. Normal density granulocytes (NDGs) were isolated by dextran sedimentation and PBMCs were isolated by Ficoll gradient. Presence of low-density granulocytes (LDGs) was assessed by a negative selection magnetic bead procedure from the PBMC fraction. The capacity of NDGs and LDGs to synthesize neutrophil extracellular traps (NETs) spontaneously was assessed by fluorescence microscopy.

Results: LDGs were classified as $CD15^{+}/CD14^{lo}$ or $CD10^{+}/CD14^{lo}$ and were detected, to varying extents, in all auto-inflammatory samples tested. Compared to healthy control NDGs and autologous NDGs, LDGs from AD patients displayed an enhanced ability to spontaneously form NETs. The proinflammatory cytokine IL-1β was externalized in NETs from NDGs and LDGs from AD patients. NDGs and LDGs from AD patients displayed distinct mRNA expression profile for inflammasome-related proteins and nucleic acid-sensing TLRs.

Conclusion: Collectively, these preliminary results suggest that LDGs are present in AD, may represent a potential source for IL-1β production and contribute to tissue damage and disease manifestations.

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Abstract Number: 2256

Histopathologic Features and Tissue Interferon-Response Gene Scoring of Lesional Skin Samples for Diagnosis in Autoinflammatory Disorders

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Background/Purpose: Many genetically defined autoinflammatory diseases (AID) are caused by innate immune dysregulation and present with “neutrophilic dermatoses”. This study systematically assesses immune-cell infiltrates, and interferon (IFN) scores in skin biopsies of 2 IFN-mediated AID: STING-Associated Vasculopathy with onset in Infancy (SAVI) and Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) and 2 IL-1-mediated AID, Neonatal-onset Multisystem Inflammatory Disease (NOMID) and Deficiency of IL-1 Receptor Antagonist (DIRA). We hypothesize that histopathologic and immunologic

features present in skin lesions can distinguish IFN- from IL-1-mediated disorders.

Methods: Tissue from skin lesions of patients with NOMID (n=4), DIRA (n=4), SAVI (n=3), CANDLE (n=5) and other interferonopathies (UIFN) (n=7) were stained with H&E. Immunohistochemistry with antibodies to Myeloperoxidase (MPO/Neutrophil), CD163 (macrophage), CD123 (plasmacytoid dendritic cell (pDC)), CD3 (T cell), CD19 (B cells) was performed. The presence of Neutrophil extracellular traps (NETs, citrullinated histone H4) and IFN-inducible protein (Mx1) were assessed by immunofluorescence. An RNA IFN score was obtained. Inflammatory cells in skin regions were semi-quantitatively scored: 0=absent, 1=scant, 2=moderate or 3=abundant.

Results:

Clinically, NOMID patients present with urticaria, DIRA with pustulosis, CANDLE with nodular rashes and SAVI with acral violaceous vasculitic plaques. Histochemically, dense MPO+ cells within intraepidermal microabscesses were seen only in DIRA. In CANDLE, MPO+ and CD163+ cells were noted predominantly in the deep dermis and sucutis. SAVI had intravascular thrombi, fibrinoid necrosis of vascular wall with abundant perivascular MPO+ and CD163+ cells. Nuclear debris was seen in SAVI and CANDLE. Mild CD123+ cells were seen in dermis and perivascular areas in SAVI and CANDLE; but not in DIRA and rarely in one NOMID sample. CD3+ cells were seen predominantly in dermis and perivascular areas in SAVI, and in periadnexal areas in CANDLE. Dermal CD19+ cells were noted only in a patient with long-standing SAVI. The presence of NETs was evident in NOMID, DIRA and CANDLE, but not in SAVI. SAVI and CANDLE samples have positive Mx-1 staining and high IFN-response gene scores, but not in NOMID and DIRA.

Conclusion: A distinct histologic pattern of neutrophil and macrophage infiltration characterizes SAVI, CANDLE, NOMID and DIRA skin biopsies, while Mx-1 staining and the IFN score distinguish IFN- and IL-1 mediated AID. Thus, the histologic and immunologic assessment of skin biopsies may guide the diagnosis and identify dysregulated immune pathways in AID. Furthermore the skin can serve as a tissue model to evaluate molecular pathways that lead to the skin manifestations in genetically defined and undefined inflammatory diseases.

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Abstract Number: 2257

Regulation of Mitochondrial Proton Gradient Is Critical for NLRP3 Inflammasome Activation

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Background/Purpose: Self-activating mutations in NLRP3 cause a spectrum of autoinflammatory diseases known

as cryopyrin-associated periodic syndromes (CAPS). NLRP3 is a key component of a multiprotein complex known as the inflammasome that mediates the maturation of the proinflammatory cytokine IL-1β, and can induce rapid cell death in a process known as pyronecrosis. Although several models for inflammasome activation have been proposed the precise molecular mechanism, as well as the role of NRLP3 mutations, remains to be elucidated. Emerging evidence suggests that mitochondria are involved in inflammasome activation. ATP is produced from ADP in the presence of a proton gradient across the mitochondrial membrane by ATP synthase (F(1)F(0) ATP synthase). F-type ATPases consist of two structural domains, F(1) - containing the extramembraneous catalytic core, and F(0) - containing the membrane proton channel. ATP5O appears to be part of the connector linking these two components and it confers sensitivity to oligomycin induced increase in the proton gradient. Here we asked whether regulation of mitochondrial membrane potential by ATP50 and oligomycin plays a role in NLRP3 inflammasome activation.

Methods: ATP5O expression was knocked down in THP-1 cells. Cells were stimulated with LPS followed by oligomycin and ATP. IL-1β release and intracellular IL-1β were measured with a flow-based assay. Supernatants were incubated with IL-1β-capture beads, added back to fixed and permeabilized cells, and both were stained with antibodies against IL-1β, then evaluated by flow cytometry. Viability of non-fixed cells was evaluated with 7AAD staining. LPS stimulated cells were also evaluated by immunofluorescence and western blot analysis.

Results: By flow analysis we provide evidence that an increase in the proton gradient induced by oligomycin results in a significant increase in ATP induced inflammasome activation, while knockdown of ATP5O, results in a significant reduction in inflammasome activation. Decreasing the proton gradient with FCCP and 2DG significantly inhibits inflammasome activation, suggesting a requirement for an increased proton gradient across the mitochondrial membrane. Using confocal microscopy of BMDM from NLRP3 knockout mice to visualize pyronecrosis, we provide evidence that this process is NLRP3 dependent.

Conclusion: These data suggest a previously unrecognized role for ATP5O in regulating mitochondrial membrane potential, which can regulate NLRP3 inflammasome activation. These results point toward mitochondrial membrane potential as a novel therapeutic target for NLRP3-mediated inflammatory diseases.

Disclosure: J. H. Edwan, None; **R. Goldbach-Mansky**, None; **R. A. Colbert**, None.

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Abstract Number: 2258

Role of NLRP12 on Disease Severity in Autoimmune Arthritis

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Background/Purpose: Nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) are cytoplasmic sensors that response to danger signals released by invading pathogen or self-damaged

tissues. NLRP12 is a member of the NLR protein family and classified as a negative regulator of inflammation and autoimmune response. However, the role of NLRP12 for autoimmune arthritis has not been explored. To investigate the NLRP12 effect on rheumatoid arthritis (RA), we decided to study whether NLRP12 deficiency would have an impact on disease outcome using the RA model of collagen-induced arthritis (CIA).

Methods: C57BL/6 *Nlrp12*$^{-/-}$ mice were obtained from Dr. Jenny Ting's laboratory and backcrossed onto DBA/1J background for eleven generations. These mice and wild type (WT) mice were induced with CIA. Arthritis development was monitored for 45 days, and joint samples were harvested for histological analysis and RT-PCR detection of cytokine production in the joints.

Results: We found that *Nlrp12*$^{-/-}$ mice show reduced clinical scores and diminished paw swelling compared to WT mice throughout disease development. Histological joint sections of *Nlrp12*$^{-/-}$ mice show a decrease in immune cell infiltration to the synovial membrane and space, reduced cartilage damage, and less bone erosion. Then we examined the cytokine expression in the joints of *Nlrp12*$^{-/-}$ mice and found that the proinflammatory cytokines IL-1beta and IL-6 were substantially reduced compared to WT mice, whereas TNFalpha and IL-17 expressions remain similar between *Nlrp12*$^{-/-}$ mice and WT mice.

Conclusion: Our results indicate that NLRP12 deficiency reduces autoimmune arthritis in the CIA model by decreased inflammation and proinflammatory cytokines in the joints. Further studies are needed to identify the innate immune cells and the molecular pathways in which NLRP12 functions in autoimmune arthritis as they could lead to potential therapeutic targets for patients with RA.

Disclosure: R. Lupo, None; **P. Liu**, None.

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Abstract Number: 2259

Suppression of Monosodium Urate Crystal-Induced Cytokine Production Via Inhibition of Histone Deacetylases 1/2

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Background/Purpose: Acute gout is a highly common and painful form of inflammatory arthritis, occurring mainly in men above the age of 50. The recurring flares of arthritis are elicited by monosodium urate (MSU) crystal deposits in the joints that, in the presence of a secondary stimulus, can induce synergistic cytokine production. Sodium butyrate can inhibit MSU-induced cytokine production via broad inhibition of class I histone deacetylases

(HDACs)[1], which includes HDAC1, -2, -3, and -8. HDACs could therefore be an important target for new therapies against gout. Our aim is to further pinpoint the HDAC(s) involved in MSU-induced cytokine production.

Methods: Primary peripheral blood mononuclear cells were isolated from healthy donors. The cells were pre-incubated with a highly specific HDAC1/2 inhibitor, Romidepsin, or other metabolic inhibitors and stimulated with a combination of palmitic acid (C16.0) and MSU crystals. Cytokine levels were measured by ELISA, transcription was measured with qPCR. *In vivo* effects of Romidepsin were assessed in C57Bl/6 mice. The mice received 2 intraperitoneal doses of Romidepsin, after which we injected them intra-articularly with a MSU crystals and a TLR2 ligand. Joint swelling was assessed macroscopically, IL-6 and KC were measured in the synovium, and total joints were sent for histology.

Results: Romidepsin potently inhibited C16.0+MSU-induced inflammatory cytokines in healthy volunteers. It furthermore induced transcription of PTEN, a negative regulator of PI3K/Akt signaling, and CPT1A, a β-oxidation enzyme that is down-regulated by Akt. Additionally, inhibiting glycolysis with 2-deoxy-D-glucose decreased C16.0+MSU-induced cytokine production, and inhibition of β-oxidation with etomoxir increased it. *In vivo*, Romidepsin potently inhibits macroscopic joint swelling already at a dose of 0.03 mg/kg. IL-6 and KC were not significantly reduced in the synovium. We are still awaiting the histology results.

Conclusion: These results suggest that Romidepsin inhibits MSU-induced cytokine production by restoring cellular energy homeostasis, possibly by inhibiting Akt signaling. In a relevant mouse model for gout, Romidepsin significantly inhibits macroscopic joint swelling. With these results, we provide a rationale for HDAC1/2 inhibition as a potent anti-inflammatory treatment which may have beneficial effects in acute gout.

References 1. Cleophas MC, Crisan TO, Lemmers H, et al. Suppression of monosodium urate crystal-induced cytokine production by butyrate is mediated by the inhibition of class I histone deacetylases. *Ann Rheum Dis* 2015.

Disclosure: M. Cleophas, None; **T. Crisan**, None; **C. Dinarello**, None; **M. G. Netea**, European Research Council, 9; **L. A. B. Joosten**, None.

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Abstract Number: 2260

Anti-Inflammatory Role of Lubricin/Proteoglycan 4 (PRG4) in Monosodium Urate (MSU)-Crystal Induced Arthritis.

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Background/Purpose: Lubricin/proteoglycan-4 (PRG4) is a mucinous glycoprotein secreted by synovial fibroblast and superficial zone chondrocyte. PRG4 has a homeostatic multifaceted role in the joint including boundary lubrication, friction lowering of apposed cartilage surfaces and prevention of synovial overgrowth. PRG4 is abundant in the synovial fluid (SF) and its levels are reduced in SF from patients with inflammatory arthropathies[3]. In animal models of post-traumatic osteoarthritis (OA) and inflammatory arthritis, PRG4 expression is reduced in cartilage and synovium. PRG4 intra-articular treatment retards progression of cartilage degeneration in preclinical post-traumatic osteoarthritis. Recent studies have suggested that PRG4 may have anti-inflammatory properties. Musculoskeletal ultrasound studies have highlighted the deposition of MSU-crystals onto the superficial margin of cartilage defined by US OMERACT definition as the Òdouble contourÓ sign and its deposition contributes to abnormal joint homeostasis. The objective of this study was to evaluate the anti-inflammatory properties of PRG4 in MSU in acute gout inflammation

Methods: Synovial fluid (SF) aspirates from normal and patients with acute gout flares were used to evaluate the activation TLR2 and TLR4 on HEK cells. Activation of TLR2 and TLR4 on HEK cells was assessed by immunoprecipitation of PRG4 from gout SF. We evaluated the impact of recombinant human PRG4 (rhPRG4) on MSU-induced release of interleukin-1 beta (IL-1b), tumor necrosis factor alpha (TNF-a), interleukin-8 (IL-8) by human monocytic cell line, THP-1 using ELISA, immunohistochemistry, and western-blot analysis. We also evaluated the role rhPRG4 in inhibiting the NLRP3 inflammasome in THP-1 cells.

Results: Using TLR-HEK cells systems, we found that synovial fluid from acute gout (n=5) activated primarily through TLR2 rather than TLR4. Normal synovial fluid did not result in either TLR2 and TLR4 activation. Gout SF treatment resulted in a significant higher TLR2 activation compared to normal SF ($p<0.001$). Removal of PRG4 from gout SF by immunoprecipitation with a monoclonal anti-PRG4 antibody resulted in higher TLR2-HEK activation compared to gout SF and untreated controls. In a dose dependent manner, rhPRG4 significantly inhibited IL-1b, TNF-a and IL-8 production by human monocytic cell line, THP-1 in response to MSU using ELISA, western blot analysis and immunohistochemistry. Immunohistochemistry of NLRP3 showed a dose dependent inhibition by rhPRG4 comparable to its inhibition by colchicine.

Conclusion: PRG4 is a mucinous glycoprotein secreted by synovial fibroblasts and superficial zone chondrocytes which retards progression MSU-crystal induced arthritis by binding to TLR2 and this binding mediates a novel anti-inflammatory role for PRG4 in joint homeostasis. Our findings provide a better understanding of the molecular mechanism(s) of PRG4 in MSU-crystal induced arthritis with important implications in the development of novel biological strategies in gout.

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Abstract Number: 2261

Methotrexate Inhibits Intracellular Redox Signaling Induced By the Reactive Oxygen Species; Malondialdehyde and Acetaldehyde

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Klassen[5], James R. O'Dell[5], Daniel R. Anderson[3], Geoffrey M. Thiele[3] and Ted R Mikuls[6], [1]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [2]Research Services, Omaha VA Medical Center, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]Cell Biology and Physiology, University of Nebraska Medical Center, Omaha, NE, [5]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [6]Internal Medicine, Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE

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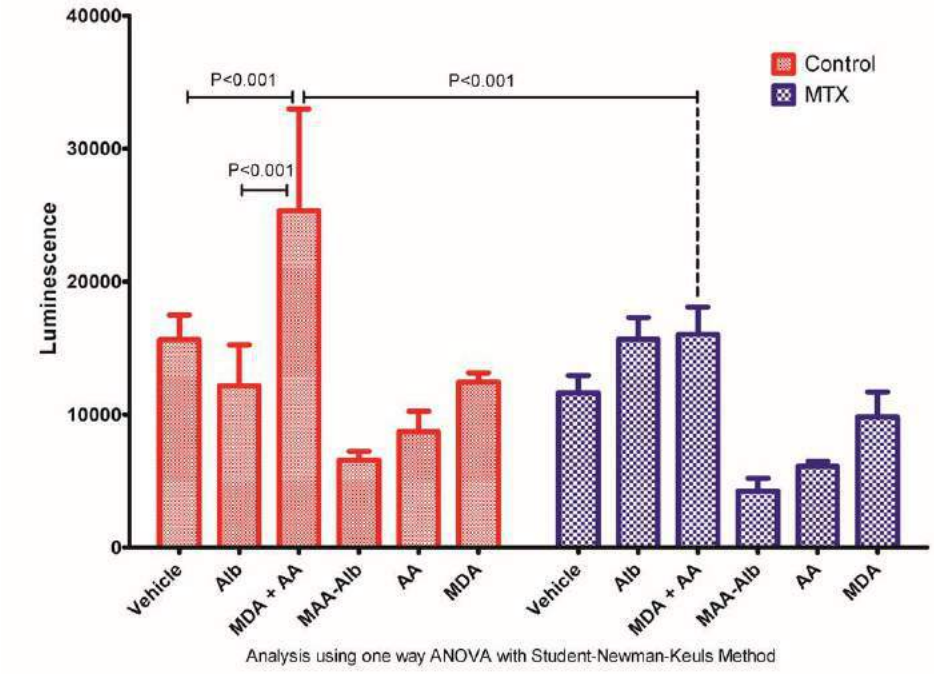
Background/Purpose: Inflammatory diseases such as rheumatoid arthritis (RA) are associated with oxidative stress as a result of elevated levels of reactive oxygen species (ROS). Oxidative stress leads to the formation of malondialdehyde (MDA) and acetaldehyde (AA), both of which react to form malondialdehyde-acetaldehyde (MAA) protein adducts. Our previous *in vitro* experiments have demonstrated that methotrexate (MTX) significantly decreases MAA-adduction of proteins (human albumin). Furthermore, the ROS generated by the reaction of MDA+AA to form MAA-adducted proteins are directly scavenged by MTX. However, the biological relevance of MTX's ability to scavenge ROS and inhibit the generation of MAA-adducted proteins remains unclear. Therefore, we tested the hypothesis that MTX inhibits intracellular redox signaling as well as the formation of MAA-adducted proteins.

Methods: To test our hypothesis, we examined the activation of a well-described redox-sensitive intracellular signaling pathway in which nuclear factor erythroid 2-related factor (NRF2), a redox-sensitive transcription factor, is stabilized and translocates to the nucleus. In the nucleus, NRF2 binds to antioxidant response elements (ARE) by utilizing a NRF2/ARE Luciferase reporter cell line in which luciferase expression is under control NRF2. Cells were incubated with vehicle, Human Serum Albumin (ALB), AA, MDA, MDA+AA (unbound), MAA-Alb for 24 hours at 37^{o}C in the absence or presence of MTX (2μM). In addition, to further evaluate the scavenging of ROS by MTX, tert-butylhydroquinone (TBHQ, 5 mM), a known inducer of NRF2, in the presence of MTX was added to NRF2/ARE cells and incubated for 24 hours. NRF2 activation was quantified by measuring the amount of luciferase via luminescence the cell line produced in response to various stimuli.

Results: As shown in Figure 1. MDA+AA significantly ($p<0.001$) increased NRF2 activation compared to cells treated with vehicle or Alb controls and MTX significantly attenuated ($p<0.001$) this redox-sensitive response. NRF2 activation with AA, MDA, or MAA-Alb in isolation demonstrated no increase in NRF activation. Furthermore, as a positive control MTX significantly ($p<0.001$) inhibited the well-characterized TBHQ-dependent activation of NRF2 by almost 3-fold.

Conclusion: This study demonstrates that when MDA+AA are mixed in the culture, a biologically relevant redox-sensitive signaling pathway is induced, that activates NRF2. Interestingly, the MAA-adduct (MAA-Alb) is unable to activate NRF2, indicating the response is activated through the metabolites of ROS. Furthermore, the ability of MTX to inhibit this redox-dependent cellular response corroborates our previous observation that MTX scavenges ROS. Together, these data strongly indicate a novel mechanism of MTX and suggest a new therapeutic benefit of MTX, which is its antioxidant potential.

Figure 1



Disclosure: **A. Chiou**, None; **M. J. Duryee**, None; **C. Sarmiento**, None; **M. Zimmerman**, None; **C. D. Hunter**, None; **L. W. Klassen**, None; **J. R. O'Dell**, Eli Lilly and Company, Medac, Coherus, BMS, GSK, 5; **D. R. Anderson**, None; **G. M. Thiele**, None; **T. R. Mikuls**, None.

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Abstract Number: 2262

CR6086 a New Potent EP4 Receptor Antagonist with Immunomodulatory Activities

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Background/Purpose: In the early phase of rheumatoid arthritis (RA), PGE_2 recruits different immune cells from the blood stream into target tissues. Via the EP4 receptor, PGE_2 acts as a cytokine amplifier (e.g. triggers IL-6 expression in macrophages) and induces the expansion of inflammatory T helper 17 (Th17) cells by increasing the activity of IL-23/IL-17 axis. These mechanisms play a pivotal role in the development of autoimmunity. [2]

Interestingly, in a mouse model of collagen antibody-induced arthritis (CAIA), EP4 knockout mice were resistant to the development of experimental arthritis.[3] These findings strongly suggest that EP4 receptor antagonists may potentially act as novel early DMARDs. CR6086, a selective antagonist of EP4 receptor, was previously found to improve or resolve disease features in the rat and mouse CIA model of RA.[4,5] In this study we present a pharmacological characterization of CR6086, and provide evidence for its immunomodulatory effects on *in vitro* models of IL-23 and IL-17 release from human cells.

Methods: We assessed first the functional effect of CR6086 on the human EP4 receptor by measuring the levels of PGE2-stimulated cyclic adenosine monophosphate (cAMP) production in stably transfected HEK293 cells, and on human THP1 cells differentiated with PMA to macrophages. Different models of immune cell differentiation and expansion were used, and the effect of CR6086 was evaluated by ELISA on IL-23 release from human dendritic cells, and on IL-17 release from human Th17 cells.

Results: CR6086 showed high affinity for the human EP4 receptor with a Ki = 16.6 nM, and strong inhibitory effect on PGE2-stimulated cAMP levels, with an IC_{50} of 22nM and 58nM in stably transfected HEK293 cells, and in THP1 differentiated macrophages, respectively. The analysis of the immunomodulatory potential for CR6086 was made by analyzing the release of selected cytokines (i.e. IL-23 and IL-17, Table 1) related with the activation and progression of the immune response in the RA pathology. We found that CR6086 dose-dependently reduced IL-23 release in activated human dendritic cells, and inhibited IL-17 release in activated human Th17 cells. In both the cell models CR6086 appeared more effective than naproxen.

Conclusion: CR6086 is a new potent EP4 receptor antagonist with immunomodulatory potential. In fact, it significantly reduced the release of IL-23 and IL-17, two cytokines important for the activation of the immune response during the early phases of RA. References: <>[1] Aoki T, Narumiya S. Trends Pharmacol Sci. 2012 Jun;33(6):304-11. <>[2] Lubberts E. Nat Rev Rheumatol. 2015 Jul;11(7):415-29. <>[3]McCoy JM et al J Clin Invest. 2002 Sep;110(5):651-8. <>[4]Chiusaroli R et al. (abs) Ann Rheum Dis 2015;74:215. <>[5]Chiusaroli R et al. (abs) Ann Rheum Dis 2015;74: 216.

Table 1. Immunomodulatory potential for CR6086 in comparison with naproxen in human cells

Concentration (μM)	Dendritic cells IL-23 release (% inhibition, mean ± sem)		Th17 cells IL-17 release (% inhibition, mean ± sem)	
	CR6086	naproxen	CR6086	naproxen
0,01	18 ± 7 (n=9)	-	-	-
0,03	-	-	54 ± 33 (n=6)	-
0,1	32 ± 8 (n=18)	-	67 ± 16 (n=20)	-
1	65 ± 13 (n=25)	2 ± 11 (n=15)	103 ± 32 (n=28)	26 ± 18 (n=28)
10	65 ± 9 (n=24)	49 ± 11 (n=24)	152 ± 21 (n=28)	40 ± 22 (n=27)
30	81 ± 11 (n=6)	37 ± 7 (n=6)	-	-

Disclosure: T. Piepoli, Rottapharm Biotech, 3; **D. Maggioni**, None; **S. Zerbi**, Rottapharm Biotech, 3; **A. Stucchi**, Rottapharm Biotech, 3; **L. Mennuni**, Rottapharm Biotech, 3; **M. Lanza**, Rottapharm Biotech, 3; **G. Caselli**, Rottapharm Biotech, 3; **L. C. Rovati**, Rottapharm Biotech, 3.

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Abstract Number: 2263

Apolipoprotein E Regulates Inflammation and Joint Destruction during Antigen-Induced Arthritis (AIA)

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic inflammatory disease largely driven by immune complexes and their interaction with FcγRs present on macrophages within the synovium. In RA joint destruction has been associated with an increased lipid oxidation and an altered lipid profile. Apolipoprotein E (Apo E) is an important regulator of LDL levels and its absence strongly elevates LDL in the serum. In the present study we investigated the role of Apo E in inflammation and joint destruction during antigen-induced arthritis (AIA).

Methods: Experimental arthritis (AIA) was induced by injection of 60 µg mBSA into the right knee joint of and wild type (WT) control mice previously immunized with mBSA/CFA. Joint swelling was measured by uptake of ^{99m} Technecium (^{99m}Tc) and expressed as a ratio of the uptake in the right (injected) and left (non injected) knee joint. Humoral immunity (mBSA antibody titer) was measured by ELISA. WT BM-MΦ were stimulated for 24 hours *in vitro* with or without 50µg/ml oxLDL and the mRNA expression of the FcγRs was measured by qPCR. Joint inflammation and bone erosion were measured by histological analysis using an arbitrary scale from 0 to 3. TRAP$^+$cells were determined using immunohistochemistry.

Results: Apo E$^{-/-}$ mice showed significantly less joint swelling at day 1, 3 and 7 after AIA induction compared to WT controls (21%, 17%, 18% lower, respectively). Serum mBSA antibody levels (total IgG, IgG1, IgG2a and IgG2b) are comparable between the two immunized mouse strains. LDL serum levels were significantly higher in arthritic Apo E$^{-/-}$ mice and LDL/oxLDL was found within synovial macrophages. At day 21, histology of the knee joints showed less infiltration of inflammatory cells within synovium and joint cavity (22 % and 44% lower, respectively) in the ApoE$^{-/-}$ mice compared to WT controls. WT BM-MΦ stimulated with oxLDL displayed a significant down-regulation of mRNA levels of FcγR I and FcγR II when compared to their non stimulated controls (1,7 and 2,3 fold change, respectively). Joint destruction was significantly reduced in the Apo E$^{-/-}$ mice, as indicated by the reduction of chondrocyte death (32% reduction) and bone erosion (25% reduction from 1.5±0.2 to 1.1 ±0.1). In line with that, ApoE$^{-/-}$ mice showed a reduction of the number of osteoclasts present at the area of resorption within the arthritic knee joints (36% lower from 20±4 osteoclasts/section in WT mice to 12±5 in ApoE$^{-/-}$mice), as measured by image analysis of TRAP staining.

Conclusion: Apo E regulates inflammation and joint destruction during AIA by regulating LDL(oxLDL) levels and macrophage FcγRs expression within the synovium.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/apolipoprotein-e-regulates-inflammation-and-joint-destruction-during-antigen-induced-arthritis-aia

Abstract Number: 2264

Lack of Obesity-Related Changes in Adipocytes and Inflammatory Cells in the Infrapatellar Fat Pad (IFP): A Different Type of Fat?

Anja de Jong[1], I.R. klein-Wieringa[1], Stefan Andersen[2], Joanneke Kwekkeboom[1], Linda van Toorn[1], Badelog de Lange[1], Danny van Delft[3], John Garcia[4], Wu Wei[5], Huub van der Heide[3], Yvonne Bastiaansen-Jenniskens[4], Gerjo van Osch[4], Anne-Marie Zuurmond[6], Vedrana Stojanovic-Susulic[7], Rob Nelissen[3], René Toes[1], Margreet Kloppenburg[1] and Andreea Ioan-Facsinay[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Charles River Nederland B.V., Leiden, Netherlands, [3]Orthopaedics, Leiden University Medical Center, Leiden, Netherlands, [4]Orthopaedics, Erasmus MC, Rotterdam, Netherlands, [5]Orthopaedics, Erasmus MC, rotterdam, Netherlands, [6]TNO, Leiden, Netherlands, [7]Janssen, Pharmaceutical Companies Johnson & Johnson, Springhouse, PA

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Background/Purpose: Obesity is associated with the development and progression of osteoarthritis (OA). Although the mechanisms involved in this association are poorly understood, it is well appreciated that obesity-induced changes in adipose tissue could affect whole body metabolism and inflammatory responses through secreted mediators. The infrapatellar fat pad (IFP) is an adipose tissue depot in the knee joint. Due to its intracapsular and extrasynovial localization, it is conceivable that the IFP could contribute to the pathophysiology of OA through release of soluble mediators. However, it is still unclear whether and how the IFP is affected by obesity. Therefore, we set-out to investigate whether obesity-related changes described in other adipose tissue depots can also be found in IFP.

Methods: IFP volume was determined in 83 knee OA patients with MRI using sagittal T1 and T2-weighted images. IFP and subcutaneous adipose tissue (SCAT) were obtained from 76 knee OA patients, all undergoing joint replacement surgery (total N=129: 69% women, mean age 65 years, mean (SD) body mass index (BMI) 29.7 kg/m^2 (5.31)). IFP volume was measured by manual segmentation of the IFP boundaries on section-by-section sagittal T1-weighted images, using the software program OsiriX. Sagittal T2-weighted images were used to distinguish and compare between IFP and non-IFP structures. The software program OsiriX measured the IFP volume by making a 3D-model of the drawn contours. Crown-like structures (CLS) were determined using immunohistochemistry. Adipocyte size was determined by light microscopy and histology. Stromal vascular fraction (SVF) cells were characterized by flow cytometry.

Results: The IFP volume determined by MRI associated with gender ($B = 0.610$, $p < 0.001$) and height ($B = 0.692$, $p < 0.001$), but not with BMI. The mean volume of IFP adipocytes was 271 pL and was not correlated with BMI; in contrast, SCAT adipocytes were larger (551 pL) and did correlate with BMI ($r = 0.38$, $p = 0.004$). Few CLS were observed in IFP, with no differences between overweight/obese and lean individuals. Moreover, obesity was not associated with higher infiltrating immune cell numbers in IFP. Likewise, the percentage of CD3, CD4, CD8 or CD14 positive cells did not correlate with obesity. Extensive characterization of IFP macrophages revealed that CD206 and CD163, usually associated with an anti-inflammatory phenotype, were the most abundantly expressed surface markers on macrophages (81% and 41 % respectively), but macrophages produced predominantly IL-6 and TNFα, and little IL-10. Interestingly, $CD163^+$ macrophages had an activated and pro-inflammatory phenotype.

Conclusion: In conclusion, we did not find obesity-related changes in IFP regarding IFP volume, adipocyte size and volume, CLS, number and phenotype of infiltrating cells, although we did found obesity-related changes in SCAT. This indicates that IFP is affected differently by obesity than other fat depots such as SCAT and visceral adipose tissue, suggesting that IFP might have a different function than the standard fat depots.

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Abstract Number: 2265

NET-Inducing Capacity Is a Biomarker in ANCA-Associated Vasculitis Independent of ANCA Antibodies

Tineke Kraaij[1], Sylvia Kamerling[1], Jaap Bakker[2], Francesca Brunini[3], Charles Pusey[3], Hans Ulrich Scherer[4], René E.M. Toes[5], Ton Rabelink[1], Cees van Kooten[1] and Onno Teng[1], [1]Nephrology, Leiden University Medical Center, Leiden, Netherlands, [2]Clinical Chemistry, Leiden University Medical Center, Leiden, Netherlands, [3]Imperial College, London, United Kingdom, [4]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [5]Rheumatology, Leiden University Medical Center, Leiden, Netherlands

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Background/Purpose: Neutrophil extracellular traps (NETs) play an important role in the pathogenesis of ANCA-associated vasculitis (AAV). Sera of MPO-ANCA or PR3-ANCA positive patients can induce NETs In vitro. The present study aimed to investigate whether NET induction could serve as a biomarker in MPO- and PR3-positive AAV patients.

Methods: Healthy neutrophils were stimulated with 10% serum from 62 GPA patients, 37 MPA patients and 18 healthy subjects. NETs were stained with Sytox and imaged by automated 3D confocal laser scanning microscopy and quantified with digital image analysis. NET-inducing capacity was defined as the fold increase of quantified NETs relative to healthy control. To investigate NET induction by ANCA autoantibodies, IgG was isolated from sera using protein G agarose beads after which depletion of IgG in the flow through was confirmed with ELISA.

Results: Both GPA and MPA samples showed significantly higher NET-inducing capacity (fold change mean ±SEM for GPA 40±7.4, $p<0.0001$ and for MPA 153.2±44.9, $p<0.01$). MPA sera had a significantly higher NET-inducing capacity than GPA ($p<0.0001$). In 14 AAV patients who had seroconverted, we observed that the NET-

inducing capacity returned to levels of healthy controls (1.40±0.42, p=0.37). However, we found no correlation of NET-inducing capacity with titers of MPO and PR3 antibodies (r=0.17, p=0.35 for MPO and r=-0.04, p=0.79 for PR3). To further determine whether NET release was mediated by ANCA autoantibodies, we isolated MPO-ANCA IgG and PR3-ANCA IgG from 5 different sera. These purified IgG antibodies did not show NET-inducing capacity (1.40±0.33, p=0.45). In contrast, corresponding IgG-depleted sera had similar NET-inducing capacity as whole sera (12.91±4.5 for IgG-depleted sera and 18.88±7.26 for whole sera, p=0.51).

Conclusion: These data show that NET release in AAV patients is independent of MPO-ANCA or PR3-ANCA. Therefore, these data indicate that NET release might be a novel biomarker of AAV that is independent of ANCA autoantibodies. Our data supports the hypothesis that NETs are a source of autoantigens for the production of ANCA.

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Abstract Number: 2266

A Melanocortin Fusion Peptide (AQB-565) Optimized for Melanocortin Receptor Engagement Significantly Reduces Inflammation in an In Vivo model of Acute Gout

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Background/Purpose: The melanocortins (MCs) are endogenous peptides (including ACTH, α-MSH and γ-MSH), which bind 5 G protein-coupled receptors (MCRs 1 through 5) with varying affinity. They exert anti-inflammatory effects primarily via MCR3, and also MCR1 and possibly other MCRs. ACTH is unique among MCs in stimulating adrenal corticosteroid production via MCR2. It is rapidly effective and has been used to treat acute gout and several other inflammatory conditions, but can be associated with some corticosteroid-related toxicities. Our objective was to generate novel ACTH-containing MC fusion peptides that maximize anti-inflammatory activity in part through MCR3 while reducing corticosteroid induction.

Methods: A series of peptides containing ACTH linked to other MCs were chemically synthesized, and selectivity for each MCR was evaluated using CHO cells transfected with individual MCRs. Anti-inflammatory activity was

evaluated in the mouse air pouch model of acute gout. Peptides were administered via sc injection (doses: 3, 10, 30 nmoles [nm]) at 1 hr before (pre-Rx) or 1 hr after (post-Rx) urate crystal injection into the pouch. The pouch was lavaged 4 hrs after crystal injection, and neutrophils and other inflammatory mediators were quantified. Plasma corticosterone levels were measured at 60 min in healthy mice.

Results: AQB-565, a 47aa peptide containing $ACTH_{1-24}$ and NDP-MSH (a more potent analog of α-MSH) fused with a 10aa linker, showed an 11-fold more potent agonist of MCR3 than ACTH (Table). It also showed ~20-fold greater activity on MCR4 and MCR5 relative to ACTH.

Selectivity and Potency of AQB-565 and ACTH on Individual Melanocortin Receptors

MCR	MCR1	MCR2	MCR3	MCR4	MCR5
AQB-565 EC_{50} (nM)	0.39	0.21	0.80	1.8	9.6
$ACTH_{1-24}$ EC_{50} (nM)	0.34	0.13	7.3	34	190
Relative Potency (AQB-565 *vs.* ACTH)	Similar	Similar	9x	19x	20x

Serial dilutions of peptide were incubated with CHO-MCR cells for 30 minutes, cyclic AMP levels were determined by LANCE assay. Eleven concentrations of each peptide were tested in triplicate, data were fit to a 4-paramater curve, and receptor activation was expressed as half-maximal effective concentration (EC_{50}). Relative potency is expressed as: ACTH EC50/AQB-565 EC50.

AQB-565 was more potent than ACTH (all data expressed as percent relative to control). Pre-Rx with AQB-565 significantly reduced neutrophil influx compared to ACTH at 3 nm (78±23% *vs.* 5±42%, p<.001) with no significant difference at 10 nm (92±7% *vs.* 82±18%) or 30 nm (92±4% *vs.* 89±11%). Pre-Rx with AQB-565 significantly reduced IL-1β levels compared to ACTH at 3 nm (39±21% *vs.* 10±19%, p<0.0001) and 10 nm (60±13% *vs.* 46±16%, p<.05) with no significant difference at 30 nm (76±7% *vs.* 61±9%). AQB-565 (3 nm) reduced accumulation of cytokines and chemokines in the air pouch exudate: TNFα (-55%), IL-6 (-84%), IL-17 (-60%), GM-CSF (-37%), MCP-1 (-46%), MIP-1β (-53%), and KC (-84%). Treatment with AQB-565 decreased mouse corticosterone levels by 40% (p=0.05) at similarly effective doses to ACTH. AQB-565 was also effective when given post-Rx with decreases of 85±15% and 46±26% of neutrophils and IL-1β levels, respectively.

Conclusion: The fusion of the MCs NDP-MSH and ACTH creates a molecule (AQB-565) reflecting a strategy of targeted MCR modulation with greater anti-inflammatory effects in an *in vivo* model of acute gout and decreased adrenal steroidogenesis. This novel compound has promise as a potential therapeutic for acute gout and possibly multiple additional inflammatory conditions.

Disclosure: R. Berenson, None; **M. A. Matthews**, None; **W. Wallis**, None; **R. Dua**, None; **M. Moore**, None; **R. Terkeltaub**, Aequus BioPharma, 5,Ardea/Astra-Zeneca, 5,Revive, 5,SOBI, 5,Selecta, 5,Relburn, 5,ProThera, 5,Horizon, 5; **C. Clegg**, None.

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Abstract Number: 2267

AMP-Activated Protein Kinase: A Target for Methotrexate in Macrophages

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Background/Purpose: Methotrexate (MTX) remains a cornerstone of treatment in multiple forms of inflammatory arthritis, lupus and vasculitis. The anti-inflammatory effects of MTX are more likely to result from an increase in intracellular and extracellular adenosine concentration, which are produced after inhibition of the enzyme AICAR transformylase by MTX, which converts the nucleotide analog AICAR (5-aminoimidazole-4-carboxamide ribonucleotide), also known as ZMP to formyl-AICAR, resulting in the accumulation of this metabolite. Another function of AICAR is the activation of the AMP-dependent kinase (AMPK). AMPK is a highly conserved trimeric protein kinase complex that exists in essentially all eukaryotic cells and is a crucial cellular energy sensor. In mammals, AMPK is activated by an increasing cellular ADP/ATP ratio secondary to metabolic stress (glucose deprivation, hypoxia, and ischemia) or accelerate ATP consumption. Once activated by decreased intracellular energy status, AMPK will promote ATP production by switching on catabolic and turning off anabolic biosynthetic pathways. We hypothesize that AMPK activation mediates a major portion of the anti-inflammatory effects of MTX and that this may account for the efficacy of MTX in rheumatic diseases. A better understanding of the molecular targets of methotrexate may allow the development of novel anti-inflammatory drugs.

Methods: We investigated the role of the anti-inflammatory effect of methotrexate via AMPK in human monocytes-derived macrophages (MDM) and mouse bone marrow-derived macrophages (BMDM) along with AICAR and A769662 (well knows as AMPK activators) and compound C, a selective ATP-competitive inhibitor of AMPK**.** AMPK phosphorylation and total AMPK were measured by Western blotting. Cells were then stimulated with LPS or TNF-α, and *production of* pro-inflammatory cytokines were measured in the supernatant using a Luminex multiplex assay technique. We also generated AMPKα1 deficient macrophages in order to test if these are resistant to the anti-inflammatory effects of MTX.

Results: MTX induced AMPK phosphorylation in a time and dose-dependent manner, with effects comparable to the synthetic AMPK activator A769662 and AICAR both in hMDM and BMDM. MTX-induced AMPK activation was associated with a reduction in the production of pro-inflammatory cytokines (IL-6, IL-1 β, and TNF-α) in response to LPS and TNF stimulation. Compound C is able to partially reverse the effects of MTX on LPS and TNF -induced cytokine production, suggesting that AMPK activation is responsible for these anti-inflammatory effects. Folic acid is not able to revert the MTX activation of AMPK in hMDM and BMDM.

Conclusion: Methotrexate is able to induce AMPK activation in both human and mouse macrophages, and suppress pro-inflammatory cytokines in a manner dependent on AMPK activity. These results have been confirmed genetically in macrophages deficient in AMPK subunits and models of chronic inflammation and diseases such as serum transfer arthritis. Our findings raise the possibility that some anti-inflammatory effects of MTX are mediated by AMPK, suggest that AMPK may be a target for the action of current ‘antimetabolite’ anti-inflammatory agents and a target for the development of new anti-inflammatory drugs.

Disclosure: C. Cudrici, None; **M. Pelletier**, None; **R. M. Siegel**, None.

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Abstract Number: 2268

Fructose Amplifies Inflammatory Potential in Human Monocytic Cells Via Reduction of AMP-Activated Protein Kinase Activity

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Background/Purpose: High dietary content of fructose (in table sugar, sweetened sodas, energy beverages, and fruit juices) is a substantial risk factor for both hyperuricemia and developing gout. Fructose is well recognized to elevate serum uric acid via increased hepatic uric acid production through ATP consumption needed to metabolize fructose. Specifically, fructose metabolism in multiple cell types can lead to ATP depletion, and generation of AMP, and also of uric acid through xanthine oxidase (XO). The objective of this study was to test the hypothesis that fructose is pro-inflammatory *in vitro* in human monocyte-macrophage lineage cells, which play a major role in initiating and regulating the gout inflammation cascade. In doing so, we examined the roles of fructose stimulated uric acid generation. Soluble uric acid decreases hepatocyte activity of AMP-activated protein kinase (AMPK), a constitutive master inhibitor of inflammatory responses to urate crystals. AMPK tissue activity is decreased in obesity and diabetes.

Methods: Human monocytic THP-1 cells were cultured in RPMI media (1% FCS) containing 5 mM glucose for 24 hours. Fructose (5 or 15 mM) was then added to the media, and cells were cultured for additional 48 hours. For controls, glucose (2, 5 or 15 mM) was used instead of fructose. In some cases, febuxostat (xanthine oxidease inhibitor, 1 μM)) was added 30 min before addition of fructose. To determine the effect on fructose on inflammatory potential of THP-1 cells, twenty-four hours after addition of fructose, the cells were treated with LPS (1μg/ml) for another 24 hours. Expression of total AMPKα, Thr172 phosphorylated AMPKα indicative of AMPK activation, and expression of AMP deaminase 1 (AMPD1) were examined by Western blot analysis. Inflammatory cytokine and chemokine IL-1β and CXCL8, respectively, were measured by ELISA.

Results: Decreased phosphorylation of AMPKα, correlated with increased expression of AMPD1, were observed in THP-1 cells in response to fructose, but not glucose, at 5 and 15 mM concentrations. In addition, these effects were inhibited by febuxostat, suggesting dependence of endogenous uric acid generation. In comparison, fructose at 2 mM concentration had no effect on phosphorylation of AMPKa and expression of AMPD1. Moreover, inflammatory potential of THP-1 cells was enhanced by fructose, evidenced by significantly increased LPS-induced expression of IL-1β and CXCL8 (by ~30% and 20%, respectively).

Conclusion: Excessive dietary fructose can increase peripheral monocyte inflammatory potential by reducing AMPK activity, in association with endogenously cell-generated uric acid. These observations may contribute to the marked increase in risk of developing gouty arthritis in those with high dietary fructose.

Disclosure: X. Cao, None; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3; **R. Terkeltaub**, Aequus BioPharma, 5,Ardea/Astra-Zeneca, 5,Revive, 5,SOBI, 5,Selecta, 5,Relburn, 5,ProThera, 5,Horizon, 5; **R. Liu-Bryan**, AstraZeneca, 2.

Abstract Number: 2269

Proteinaceous Amorphous Calcium Carbonates As a Novel Family of Crystals in Synovial Fluid from Symptomatic Joints

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Background/Purpose: There are many types of particulate matter in synovial fluid, and specific identification of these particles are challenging. We assessed synovial fluid samples from arthropathic joints and identified that crystals displaying Maltese-cross pattern under polarized light microscopy. We are first to report that such crystals are actually proteinaceous amorphous calcium carbonate crystals (PACC).

Methods: 174 symptomatic synovial fluid (SF) samples were included in this study, which were collected as discarded SF for joints aspirated for clinical care. Polarized light microscopy and alizarin red S staining were used to screen SF samples. Chemically specific techniques including Raman microspectroscopy (μRS) and scanning electron microscopy (SEM) coupled with energy dispersive x-ray (EDX) analyses were used to characterize crystals with Maltese-cross patterned birefringence.

Results: Maltese-cross birefringent crystals were present in 5.7% (10 of 174 SF) of symptomatic joints and positively stained with alizarin red S. Raman spectrum of these crystals was similar to those of sodium carbonate and calcium carbonate in bands 700 – 750 cm^{-1} and 1070 – 1090 cm^{-1}. Raman microspectroscopy (μRS) and SEM/EDX analyses showed absence of phosphate groups, excluding the possible crystals' association with basic calcium phosphates. The molar ratio (1:3.68) between calcium and oxygen in these crystals was close to the ratio in calcium carbonate ($CaCO_3$, 1:3). These crystals dissolved with protein digesting enzymes. As a result, we term these crystals "proteinaceous calcium carbonate crystals (PCCD)".

Conclusion: Theses data provide chemically specific evidence that birefringent particles displaying Maltese-cross birefringence patterns are an amorphous form of calcium carbonate that also include a proteinaceous phase. Our findings counter the prior notion that such crystals are lipids (based on birefringence) or basic calcium phosphates (based on alizarin red S staining). These crystals were observed in symptomatic joints, occurred at a frequency comparable to that observed for calcium pyrophosphate (CPPD) crystals, and their presence was initially overlooked by clinical microscopic observation. This study should elevate the consciousness of clinical microscopists in considering PACC as a crystal species involved in joint arthropathy.

Disclosure: B. Li, None; **N. Singer**, None; **O. Akkus**, CWRU, 9.

Abstract Number: 2270

Inflammasome/IL-1β Activation Induced By Calcium Pyrophosphate Dihydrate Crystals Is Mainly Driven By a P2X7 Receptor-Independent Potassium Efflux

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Background/Purpose: Calcium pyrophosphate crystals including monoclinic and triclinic dihydrate phases (m- and t-CPPD) are found in 40% of end-stage osteoarthritis (OA) patients. Frequently asymptomatic, it can give rise to synovitis contributing to OA lesion worsening. Microcrystal inflammation is orchestrated by macrophage interleukin (IL)-1β secretion which required a 2-step process: synthesis of precursor form proIL-1β and its cleavage to mature IL-1β by active caspase 1 depending on the NLRP3 (*NOD-like receptor family, pyrin domain containing 3*) inflammasome activation. Several pathways can be entailed in inflammasome activation in response to danger signals: ATP-dependent potassium (K^+) efflux, reactive oxygen species (ROS) production, or mitochondrial disruption. We have previously demonstrated that m- and t-CPPD differentially induced NLRP3 protein expression and IL-1β production but intracellular mechanism leading to NLRP3 inflammasome activation is not clearly defined.

Methods: Human THP-1 or THP-1 ρ° cells (treated with ethidium bromide), and bone marrow-derived macrophages (BMDM) from wild type (wt) or P2X7 receptor knock-out (*p2x7r*$^{-/-}$) mice were primed before stimulation with synthetic m- and t-CPPD crystals in presence or absence of K^+-enriched media (KCl 50mM – to block K^+ efflux), N-acetyl-L-cystein (NAC 50mM – an intracellular ROS scavenger) or oxidized ATP (oxATP 200µM – an antagonist of ATP receptor). IL-1β and extracellular ATP (ATP_e) concentrations were measured in cell culture supernatants whereas intracellular ROS production and mitochondrial membrane potential were evaluated using fluorescent probes (DFDA and JC-1, respectively).

Results: First, we observed that CPPD stimulation induced a *de novo*ROS production combined with a stronger mitochondrial membrane depolarization following m-CPPD than t-CPPD crystal stimulation. This latter effect and IL-1β production were inhibited in presence of NAC. Moreover, we showed a drastic inhibition of IL-1β maturation process in THP-1 ρ° cells which have a mitochondrial ROS production deficiency. Second, K^+-enriched media on one hand inhibited CPPD-mediated IL-1β production by THP-1 cells and on the other hand

restored basal levels of ROS and mitochondrial membrane potential. Finally, we found that m- and t-CPPD crystals differentially brought on an ATP release and that IL-1β production was partially inhibited by oxATP. However, although ATP_e can trigger K^+ efflux through P2X7 receptor opening, we observed a similar or only a weak decreased IL-1β production between wt and *p2x7r*$^{-/-}$ BMDM after t-CPPD and m-CPPD stimulation respectively. In contrast, IL-1β production is completely abrogated in presence of KCl as well wt as *p2x7r*$^{-/-}$ BMDM.

Conclusion: We demonstrated that K^+ efflux triggered by CPPD crystals is the first signal leading to mitochondrial ROS production and disruption which are considered as intracellular danger signal required for NLRP3 activation and IL-1β production. Interestingly, K^+ efflux is partially dependent on P2X7 receptor through ATP release but the main K^+ channel has to be defined.

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Abstract Number: 2271

Mutation in Osteoprotegerin Gene: Early-Onset Osteoarthritis and Chondrocalcinosis in a US Family of Italian/German Ancestry

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Background/Purpose: Chondrocalcinosis is characterized by calcium pyrophosphate dihydrate (CPPD) deposition in articular cartilage. It can occur as a rare autosomal dominant disorder with florid early-onset osteoarthritis (OA). Two observed gene mutations are: ANKH [1] (progressive ankylosis; on chromosome 5p) and TNFRSF11B [2] (coding for osteoprotegerin (OPG), on chromosome 8q). ANKH mutations apparently affect extracellular pyrophosphate (PPi) levels by altering its transporter function. OPG, a decoy receptor, regulates bone remodeling by binding receptor activator nuclear factor Kappa beta ligand (RANKL), preventing osteoclast bone resorption. Any alteration in the bone remodeling process, may alter bone mineral density. We report a US family with gain-of-function mutation in TNFRSF11B coding for OPG that is potentially related to this family's severe

OPG-CPPD phenotype. Previously, only 1 family with the same OPG gene mutation has been described in the literature (Ramos et al, 2015). The purpose of this study is to screen 3 generations of affected members of a US family of Italian/German ancestry with early-onset autosomal dominant OA and radiographic chondrocalcinosis for mutations in ANKH or TNFRSF11B.

Methods: Subjects were identified by proband's rheumatologist. Clinical presentations, similar to the proband were noted in 6 out of 10 male family members over 3 consecutive generations. Genetic testing was performed on peripheral blood and buccal swab samples from proband and 2 other affected family members, in accordance with institutional guidelines for human subjects with written informed consent and IRB approval. DNA isolated from samples was amplified for ANKH and TNRSF11B by PCR using gene-specific primers and subjected to dideoxy sequencing of PCR products. Patient sequences were compared to control samples and sequence anomalies were confirmed by antisense sequencing of the PCR products.

Results: The proband, a 43 year old male patient, presented at age 31, with progressive polyarticular crippling arthritis resulting in pain and disability. His knee X-rays showed advanced loss of joint space. X-rays of his wrists, elbows and ankles also revealed severe arthropathy and extensive chondrocalcinosis, strongly suggestive of CPPD disease. Arthrocentesis and synovial fluid analysis was deferred due to absence of significant joint effusions. Diagnostic work up for primary metabolic disorders associated with CPPD was negative. Genetic testing of proband and 2 affected family members identified a read-through mutation of the termination codon (A=>T; Stop402Leu) in TNFRSF11B. Studies performed by Ramos et al show that the mutant-OPG has enhanced capacity to inhibit osteoclastogenesis. Hence, this mutation is potentially linked to this family's severe OA-CPPD phenotype.

Conclusion: We have identified a second family with a read-through, gain of function mutation (Stop402Leu) in TNFRSF11B gene coding for OPG that is likely related to their OA/CPPD phenotype. While it is not yet clear how mutations in OPG may give rise to the CPPD phenotype, targeted inhibition of OPG binding to RANKL may become a therapeutic approach to prevent and/or treat pathological joint chondrocalcinosis.

Disclosure: U. Qazi, None; **C. J. Williams**, None; **M. L. Bernstein**, None; **A. Charniak**, None; **A. Ortiz**, None; **A. K. Rosenthal**, None; **L. Cardinal**, None; **A. T. Kaell**, None.

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Abstract Number: 2272

The Influence of Genetic Variants on Renal Uric Acid Excretion in Response to Frusemide

Nicola Dalbeth[1], Jordyn de Kwant[1], Gregory Gamble[2], Amanda Phipps-Green[3], Anne Horne[2], Robert Doughty[1], Lisa K. Stamp[4] and Tony R. Merriman[5], [1]University of Auckland, Auckland, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]University of Otago, Dunedin, New Zealand, [4]University of Otago, Christchurch, New Zealand, [5]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand

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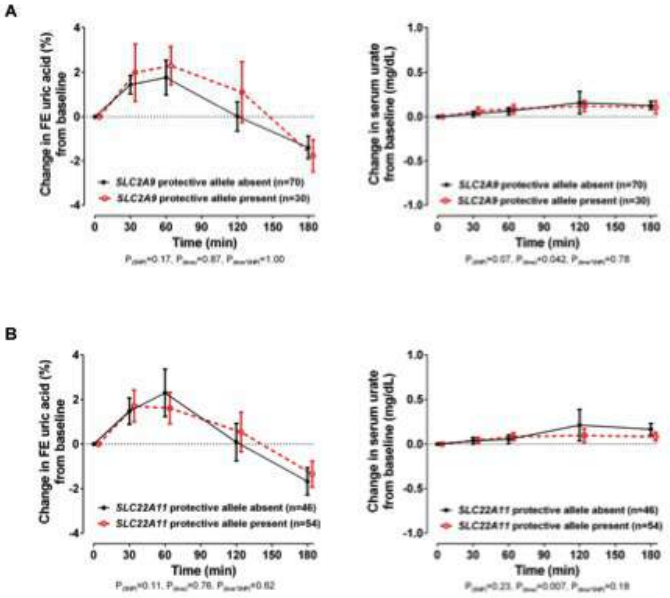
Background/Purpose: Diuretic use is strongly associated with development of hyperuricaemia and gout. Genetic variation in the renal uric acid transporters *SLC2A9* (encoding GLUT9) and *SLC22A11* (encoding OAT4) has been reported to interact with diuretic use to increase the risk of developing gout at a population level. The aim of this study was to determine whether variation in *SLC2A9* or *SLC22A11* influences renal handling of uric acid in response to frusemide.

Methods: Following an overnight fast and one week of a low salt diet, healthy participants (n=100) aged 18-50 years attended a study visit with intake of a single oral 40mg tablet of frusemide. Blood and urine samples were obtained for urate, sodium, potassium, creatinine, prior to frusemide and then 30, 60, 120, and 180 minutes after frusemide. The *SLC2A9* SNP *rs11942223* and *SLC22A11* SNP *rs2078267* were genotyped and data were analysed based on the presence or absence of the gout-protective allele. The primary endpoint was change in fractional excretion of uric acid (FEUA) and secondary endpoint was change in serum urate.

Results: Oral intake of 40 mg frusemide led to a marked diuresis (mean (SD) urine volume 2162 (717) ml over 180 minutes) and increase in fractional excretion of both sodium (FENa) and potassium (FEK) over the 180 minute study period (P<0.001 for all). Following intake of frusemide, FEUA initially increased (mean (SD) change from baseline +1.9 (3.0) % at 60 minutes, P<0.001) and then decreased (mean (SD) change from baseline -1.5 (2.1) % at 180 minutes, P<0.001). A very small increase in serum urate was observed over the study period (mean (SD) change from baseline +0.12 (0.17) mg/dL at 180 minutes, P<0.001). At both 60 and 180 minute time-points, change in FENa predicted change in FEUA, independent of urine volume (standardized β for both time-points >0.46, P<0.001). The presence of the protective alleles for *SLC2A9* and *SLC22A11* did not significantly alter the FEUA or serum urate responses to the frusemide load (Figure).

Conclusion: Intake of frusemide leads to a biphasic FEUA response, with initial increase and subsequent reduction in FEUA. Our data do not support the hypothesis that genetic variation in *SLC2A9* or *SLC22A11* influences acute changes in renal handling of uric acid in response to frusemide intake. **Figure:** Mean (95% CI) change from baseline in FEUA and serum urate based on presence of A. *SLC2A9* protective allele and B. *SLC22A11* protective allele. Sex, ethnicity and age adjusted P values are shown.



Disclosure: **N. Dalbeth**, None; **J. de Kwant**, None; **G. Gamble**, None; **A. Phipps-Green**, None; **A. Horne**, None; **R. Doughty**, None; **L. K. Stamp**, None; **T. R. Merriman**, None.

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variants-on-renal-uric-acid-excretion-in-response-to-frusemide

Abstract Number: 2273

Trans-Ancestral Meta-Analysis Identifies Nine New Loci Associated with Serum Uric Acid Concentrations

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Background/Purpose: Serum uric acid is an important biomarker for gout disease and kidney function. Genome-wide association study (GWAS) meta-analyses have identified 28 loci in European and Japanese population samples. Combined analysis of these summary data across populations offers the opportunity to discover new serum uric acid (SUA) associations through greater sample size and power, and trans-ancestral analyses provide the opportunity for fine-mapping associations with greater resolution given differing linkage disequilibrium patterns between populations.

Methods: Summary statistics from European (N=110,238) (PMID 23263486) and East Asian (N=21,268) (PMID 22797727) meta-analyses were obtained. We used ImpG v1.0 (PMID 24990607) to impute the results into 1000 Genomes phase 3 variants, and performed sample-size weighted z-score meta-analysis. LD-independent variants with $P_{META} < 5x10\text{-}8$, not in LD ($r2<0.1$) with previously identified regions, were considered novel SUA loci. We used functional partitioned LD score regression (PMID 26414678) on all associated loci in the European GWAS to identify SNP-heritability enriched tissue-specific regulatory regions, for use as functional priors in PAINTOR (PMID 26189819) fine mapping analyses to identify putative causal variants.

Results: Trans-ancestral meta-analysis of European and East Asian GWAS revealed nine new SUA-associated loci ($P_{META} < 5x10^{-8}$). Three of the new loci are located in the 11q12.3-13.2 region near the established SLC22A11/12 association. Additional novel loci are located near the FGF5, LNC00603, HLA-DQB1, B4GALT1, BICC1 and USP2 genes. Tissue-focused functional partitioning of SNP-heritability indicated the strongest enrichments of kidney, GI and liver tissues ($P<10^{-7}$), among other significant tissues (Figure 1). Trans-ancestral meta-analysis and functional fine-mapping decreases the numbers of SNPs in causal variant credible sets, and for example pinpoints the rs17632159 SNP as likely causal (posterior $P>0.9$) at the TMEM171/174 locus.

Conclusion: Meta-analysis of existing GWAS increases power and leads to the identification of nine new loci associated with serum uric acid levels. Increased resolution in trans-ancestral GWAS, with functional annotation

enrichments, improves fine-mapping of serum urate GWAS loci.

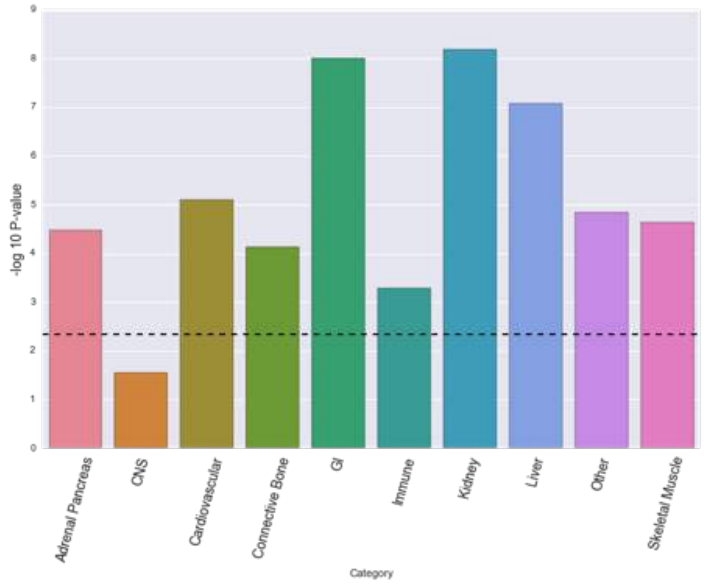

Figure 1: Tissue-type SNP heritability enrichment P-values in serum uric acid GWAS.

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Abstract Number: 2274

Evidence of Phospho-Degron Regulating Expression of Urate Secretory Transporter ABCG2

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Background/Purpose: ABCG2 is a high capacity urate secretory transporter of the renal proximal tubule. The common Q141K ABCG2 mutation causes gout in humans through an increased instability of the nucleotide-binding domain leading to enhanced degradation and reduced function.

Methods: Typical biochemical and cell biological techniques

Results: Here, we found ABCG2 protein rescued from degradation with the proteasome inhibitor MG-132 is

phosphorylated; raising the possibility that a phospho-degron regulates ABCG2 trafficking and expression. An *in silico*analysis of ABCG2 revealed a limited number of predicted phosphorylation sites, including S195, a serine conserved in the mammalian lineage. The upstream RXRXS represents a target motif for AKT1 and PKA, which both co-immunoprecipitated with ABCG2. Specifically, endogenous AKT1 pulled down both over expressed ABCG2 in HEK293 cells as well as endogenous ABCG2 in mouse kidney lysate. AKT1 and ABCG2 transcript co-localize in the proximal S2 segment of the mammalian nephron and inhibiting the AKT1 kinase cascade with PI3K inhibitor LY294002, or with growth factor receptor (RTK) inhibitor Vandetanib, dramatically up-regulated ABCG2 expression. Conversely, activating the AKT1 cascade with FBS down-regulated ABCG2 expression. Replacement of the S195 residue with a phosphomimetic aspartic acid resulted in significant reduction in ABCG2 expression, localization of ABCG2 to peri-nuclear compartments, and significant sensitivity to MG-132; confirming the S195 residue as a phospho-degron. Finally, a non-phosphorylatable S195A substitution led to the complete rescue of the Q141K gout mutant protein expression and trafficking.

Conclusion: Modeled ABCG2 structure indicates phosphorylation of the S195 residue may only be possible when the nucleotide-binding domains are separated, suggesting the S195 phospho-degron may be part of a novel regulatory mechanism for function and trafficking in ABC transporters. Funded by: American Heart Association 14SDG18060004 & Ardea BioSciences.

Disclosure: A. Hofherr, None; **M. Li**, None; **M. Kottgen**, None; **O. M. Woodward**, Ardea BioSciences, 2,AstraZeneca, 1.

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Abstract Number: 2275

Genome-Wide Association Study of Gout in New Zealand Polynesian People

Tanya Flynn[1], Ruth Topless[1], Murray Cadzow[1], Amanda Phipps-Green[1], Nick Burns[1], Nicola Dalbeth[2], Lisa K. Stamp[3], Jennie Harre Hindmarsh[4] and Tony R. Merriman[5], [1]University of Otago, Dunedin, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]University of Otago, Christchurch, New Zealand, [4]Ngati Porou Hauora Charitable Trust, Te Puia Springs, New Zealand, [5]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand

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Background/Purpose: The prevalence of gout in New Zealand Polynesian (Māori and Pacific) populations is approximately twice that of the New Zealand European population, with a younger average age of onset and more severe symptoms. We aimed to undertake a genome-wide association study of gout in Polynesian people. Additionally, we assessed the differences in genetic susceptibility to gout between Eastern and Western Polynesian individuals to further identify regions involved in gout risk.

Methods: Polynesian individuals with clinically-ascertained gout (n_{gout} = 929) or with no history of gout ($n_{control}$ = 861) were recruited. This cohort was divided into Eastern (New Zealand and Cook Island Māori; n_{gout} = 566, $n_{control}$ = 605) and Western Polynesian (Samoan, Tongan, Tokelauan and Niuean; n_{gout} = 363, $n_{control}$ = 256) based on self-reported ancestry and principal component clusters. Genotyping across the Infinium CoreExome chip and logistic regression analyses adjusted for sex and age were conducted. Differential effect of each variant in the two cohorts was compared using Cochran's Q-test during meta-analysis, in order to identify heterogeneous effects. Genome-wide significant association was set at $P < 5.0x10^{-8}$ and suggestive association at $P < 1.0x10^{-5}$.

Results: The only genome-wide significant result in the combined Polynesian cohort was at *ABCG2* (*rs2231142*: OR = 2.31, $P = 9.7x10^{-14}$). The Western Polynesian cohort showed a genome-wide significant effect for *rs2231142* (OR = 2.65, $P = 1.4x10^{-11}$), but the Eastern Polynesian cohort did not (OR = 1.87, $P = 5.2x10^{-4}$). These results were not significantly different ($P_Q = 0.13$). Two other variants in the *ABCG2* locus (*rs6857847* and *rs3737488*) had significant Q-test p-values ($P_Q = 5.1x10^{-8}$ and $2.8x10^{-8}$), with strong protective effects in Western Polynesian (OR = 0.47, $P = 2.0x10^{-7}$; and OR = 0.47, $P = 1.36x10^{-7}$), but weak susceptibility effects in Eastern Polynesian people (OR = 1.22, $P = 4.3x10^{-2}$; and OR = 1.23, $P = 3.5x10^{-2}$). A variant on Chromosome 18 (*rs4939827*) also produced a genome-wide significant Q-test p-value ($P_Q = 1.5x10^{-8}$). This variant had a suggestively significant protective effect in Western Polynesian (OR = 0.53, $P = 7.4x10^{-6}$) and a non-significant susceptibility effect in Eastern Polynesian individuals (OR = 1.38, $P = 5.0x10^{-4}$).

Conclusion: Genome-wide association analysis of Polynesian cohorts revealed a significant effect at *ABCG2* in the Western Polynesian, but not Eastern Polynesian, cohort. There was a genome-wide significant difference in effect at *rs4939827*, within an intron of *SMAD7*, a gene that has been associated with inflammatory bowel disease, colorectal cancer, and chronic kidney disease and that is involved in the regulation of TGF-beta signalling.

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Abstract Number: 2276

Pleiotropic Effect of ABCG2 in Gout

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Background/Purpose: The ABCG2 Q141K (*rs2231142*) variant is an established cause of hyperuricaemia in Europeans. Although the effect size of *ABCG2 rs2231142* on serum urate levels is ~60% that of *SLC2A9,* the effect size of *ABCG2* on gout is consistently greater than that of *SLC2A9*[1,2]. We tested the hypothesis that *ABCG2* plays a role in gout additional to causing hyperuricemia by testing for association of *rs2231142* with gout using asymptomatic hyperuricemic controls. *SLC2A9 rs11942223* was included for comparison.

Methods: There were 1,672 European gout cases and 15,367 controls and 1,197 New Zealand Polynesian (Māori and Pacific Island) gout cases and 1,371 controls. The Polynesian sample set was divided into Eastern (EP) and Western Polynesian (WP). Association testing was done using logistic regression with multivariate adjusting for confounding variables, including highest recorded serum urate in analyses with gout cases.

Results: In the European sample set, the 141K allele was strongly associated with asymptomatic hyperuricemia compared with normouricemic controls (OR=1.55, P=4.3x10^{-18}) and with gout compared with asymptomatic hyperuricemia controls (OR=1.83, P=2.6x10^{-14}). In the Polynesian sample sets, the 141K variant was not associated with asymptomatic hyperuricemia compared with normouricemic controls (WP: OR=1.22, P=0.35; EP: OR=0.99, P=0.97) whereas there was a strong risk effect for gout compared with asymptomatic hyperuricemia (WP: OR=2.35, P=3.9x10^{-5}; EP: OR=2.15, P=0.010). For *SLC2A9 rs11942223,* there was no positive association with gout compared with asymptomatic hyperuricemia controls in any of the ancestral sample sets (Europeans: OR=0.82, P=0.022; WP: OR=0.81, P=0.69 and EP: OR=1.39, P=0.41).

Conclusion: These data are consistent with a role for *ABCG2* 141K in gout pathogenesis when hyperuricemia is established, potentially through formation of monosodium urate crystals and/or regulation of the inflammatory response to deposited crystals. In Polynesian people *ABCG2* 141K does not play a role in determining hyperuricemia. 1. Kottgen et al. *Nat Genet* 2013;45:145-54. 2. Phipps-Green et al. *Ann Rheum Dis* 2016;75:124-30.

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Abstract Number: 2277

Exon Sequencing Reveals a Significant Burden of Non-Synonymous Variants in Both SLC22A11 (OAT4) and SLC22A12 (URAT1) in European Hyperuricemic Individuals

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Background/Purpose: Common variants within the uric acid transporter genes *SLC22A11* (OAT4) and *SLC22A12* (URAT1) have been associated with hyperuricaemia and gout in multiple populations, but these associations have been with intronic or intergenic variants with no obvious causal role in protein function. This research aimed to characterise the exonic sequences of *SLC22A11* and *SLC22A12* in European and Polynesian individuals and assess whether rare non-synonymous variants in these genes are causal of hyperuricemia.

Methods: The exonic regions of *SLC22A11* and *SLC22A12* were sequenced in 422 individuals with hyperuricemia or gout (Polynesian = 227, European = 195) and 386 individuals without hyperuricemia or gout (Polynesian = 213, European = 173). All non-synonymous variants were identified and analysed using burden testing methods. SIFT, Polyphen-2, and PROVEAN were used to predict the effect of these non-synonymous variants on protein function.

Results: Eighteen non-synonymous variants were identified in *SLC22A11* and *SLC22A12*, of these sixteen were missense (*SLC22A11* = 9, *SLC22A12* = 7) and two were nonsense (*SLC22A11* = 1, *SLC22A12* = 1). The nonsense variant in *SLC22A11* was found in one Māori woman and three European men, all with high serum urate levels (average = 8.55 mg/dL), whilst the *SLC22A12* nonsense variant was found in a Tongan man with a normal serum urate level of 5.04 mg/dL. Burden analyses of all non-synonymous variants in the European cohort produced a significant burden of risk variants ($P = 0.02$) in *SLC22A11*, and a significant burden of protective variants in *SLC22A12* ($P = 0.01$). The same effect was not seen in the Polynesian cohort ($P = 0.29$ and 0.73, respectively). Prediction of the functional effects of each of the missense variants suggests only three of the nine *SLC22A11* variants, but six of the seven *SLC22A12* variants, modify protein function.

Conclusion: Rare non-synonymous variants in both *SLC22A12* and *SLC22A11* significantly associate with hyperuricemia in European individuals. Our data confirm the protective effect of rare genetic variants in *SLC22A12*, encoding the uric acid transporter URAT1. This is the first time rare genetic variants in *SLC22A11* have been implicated in causing hyperuricemia, and our findings challenge current understanding of OAT4 (SLC22A11) as a transporter that mediates renal uric acid reabsorption. Notably, the vast majority of missense variants in other solute transporters are neutral or loss-of-function[1]. 1. Leabman et al. *Proc Natl Acad Sci U S A* 2003;100:5896-901.

Disclosure: T. Flynn, None; **J. Boocock**, None; **M. Cadzow**, None; **R. Topless**, None; **A. Phipps-Green**, None; **N. Dalbeth**, None; **L. K. Stamp**, None; **D. B. Mount**, None; **A. Mandal**, None; **H. K. Choi**, None; **E. A. Stahl**, None; **T. R. Merriman**, None.

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hyperuricemic-individuals

Abstract Number: 2278

Precision of Gout Definitions for Population-Based Genetic Studies: Analysis of the UK Biobank

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Background/Purpose : Accurate case-definition is important for epidemiological studies of gout. However, in multipurpose cohort studies frequently used for genome wide association studies, limited information is usually available for gout case-definition. Many different combinations of available data have been used to identify gout cases in large genetic epidemiological studies. The aim of this study was to determine the most precise case-definition of gout from the limited items available in multipurpose cohorts for use in for population-based genetic studies.

Methods: Data from the UK Biobank were analysed. Data (including genome-wide genotypes) were available for 105,421 European participants aged 40 to 69 years without kidney disease. Gout definitions and combinations of these definitions were identified from previous epidemiological studies. Self-report of gout was defined by reporting of gout diagnosis by the participant at the time of study interview. Hospital diagnosis of gout was defined by either primary or secondary hospital discharge coding for gout (ICD10 M10 including subcodes). Urate lowering therapy (ULT) use was defined by self-report of allopurinol, febuxostat, or sulphinpyrazone use, without leukemia or lymphoma (ICD10 C81-C96). Winnard-defined gout was defined by hospital diagnosis or gout specific medication (ULT or colchicine)[1]. Logistic regression was performed genome-wide using plink2 adjusted for age, sex, waist circumference, and waist circumference to height ratio.

Results : There were 2066 (2.0%) gout cases defined by self-report of gout, 1652 (1.6%) defined by ULT use, 382 (0.4%) defined by hospital diagnosis, 2295 (2.2%) defined by self-report of gout or ULT use, and 1861 (1.8%) gout cases defined by Winnard-definition. For the originally reported 10 hyperuricaemia SNPs[2], association with gout at genome-wide significance (P<5x10-8) was observed for 5 SNPs (*ABCG2, SLC2A9, GCKR, SLC17A3* and *SLC22A12*) using the definition of self-report of gout and the definition of self-report of gout or ULT use, 4 SNPs (*ABCG2, SLC2A9, GCKR,* and *SLC17A3*) using the Winnard definition, 3 SNPs (*ABCG2, SLC2A9,* and *GCKR*) using the ULT use definition, and 2 SNPs (*ABCG2* and *SLC2A9)* using the hospital diagnosis definition (Table). The definitions of self-report of gout or ULT use, and self-report of gout alone had greatest precision for all analyses.

Conclusion: Of existing definitions that use routinely collected data, case definitions that include self-report of gout have the greatest precision for detecting genome wide significant associations in epidemiological studies of gout. **References:** 1. Winnard et al Rheumatology 2012, 2. Kottgen et al Nature Genetics 2013.

Table: Odds ratios [95% CI] and P values for originally reported 10 hyperuricaemia SNPs (Kottgen et al. 2013) using different gout definitions. Data are adjusted by age, sex, waist circumference and waist to height ratio.

	Self-report (n=2066)	ULT use (n=1652)	Hospital diagnosis (n=382)	Self-Report or ULT use (n=2295)	Winnard (n=1861)
Rs2231142 (ABCG2)	2.10 [2.10 – 2.45], 2.38x10-92	2.29 [2.10 – 2.50], 4.22x10-77	2.10 [1.76 – 2.52], 3.57x10-16	2.22 [2.06 – 2.40], 1.93x10-95	2.18 [2.00 – 2.37], 4.47x10-74
Rs12498742 (SLC2A9)	0.56 [0.51 – 0.61], 6.14x10-39	0.55 [0.50 – 0.61], 4.75x10-32	0.57 [0.47 – 0.70], 4.12x10-8	0.55 [0.51 – 0.60], 1.00x10-43	0.56 [0.51 – 0.61], 8.22x10-35
Rs1260326 (GCKR)	1.31 [1.23 – 1.40], 2.22x10-17	1.26 [1.18 – 1.36], 9.30x10-11	1.33 [1.15 – 1.53], 0.00010	1.28 [1.21 – 1.36], 4.63x10-16	1.26 [1.18 – 1.35], 6.47x10-12
Rs1165151 (SLC17A3)	0.83 [0.78 – 0.88], 5.36x10-9	0.83 [0.77 – 0.89], 1.47x10-7	0.94 [0.81 – 1.08], 0.38	0.82 [0.77 – 0.87], 7.87x10-11	0.83 [0.77 – 0.89], 4.43x10-8
Rs478607 (SLC22A12)	1.27 [1.17 – 1.37], 2.32x10-8	1.29 [1.18 – 1.42], 5.42x10-8	1.16 [0.95 – 1.40], 0.14	1.27 [1.18 – 1.38], 2.00x10-9	1.26 [1.15 – 1.37], 2.18x10-7
Rs1471633 (PDZK1)	1.18 [1.11 – 1.26], 2.60x10-7	1.19 [1.10 – 1.28], 2.25x10-6	1.05 [0.91 – 1.21], 0.50	1.17 [1.11 – 1.25], 1.86x10-7	1.18 [1.10 – 1.26], 1.54x10-6
Rs3741414 (INHBE)	0.83 [0.76 – 0.89], 9.86x10-7	0.83 [0.76 – 0.91], 2.38x10-5	0.80 [0.67 – 0.95], 0.013	0.84 [0.78 – 0.90], 2.81x10-6	0.844 [0.78 – 0.92], 3.96x10-5
Rs1171614 (SLC16A9)	0.82 [0.76 – 0.89], 1.11x10-6	0.86 [0.79 – 0.94], 0.00053	0.88 [0.74 – 1.05], 0.15	0.84 [0.78 – 0.91], 4.78x10-6	0.87 [0.81 – 0.95], 0.0012
Rs2078267 (SLC22A11)	1.15 [1.08 – 1.22], 1.61x10-5	1.17 [1.09 – 1.25], 1.86x10-5	1.18 [1.02 – 1.36], 0.026	1.17 [1.10 – 1.24], 5.18x10-7	1.16 [1.08 – 1.23], 1.97x10-5
Rs675209 (RREB1)	1.10 [1.03 – 1.18], 0.0056	1.10 [1.02 – 1.19], 0.017	0.98 [0.83 – 1.15], 0.80	1.09 [1.02 – 1.17], 0.0078	1.09 [1.01 – 1.17], 0.024

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Abstract Number: 2279

Soluble Urate: A Direct Mediator of Bone Turnover?

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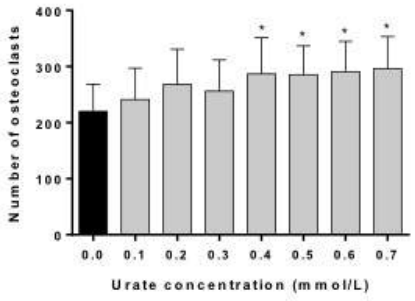
Background/Purpose: Observational studies have reported that hyperuricemia may be protective in the development of osteoporosis. Serum urate concentrations positively correlate with bone density, and higher serum urate concentrations are associated with reduced risk of fragility fractures. The mechanisms of this bone-urate relationship are currently unexplained. The aim of this laboratory study was to examine whether soluble urate directly influences function of bone cells to promote bone formation.

Methods: For all assays, we examined the effects of soluble urate at physiological temperature and pH, at a range of urate concentrations consistent with those observed in humans (0 (control), 0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70 mmol/L). The effects of soluble urate on osteoclast development and function were examined using the RAW264.7 cell line osteoclastogenesis assay, a murine bone marrow osteoclastogenesis assay, a human peripheral blood osteoclastogenesis assay and a rat mature osteoclast assay. The early osteoblast-like MC3T3 cell line was used to examine the effects of soluble urate on cell viability (using MTT and alamarBlue assays), mineralisation, and gene expression for osteoblast differentiation markers. The MLO-Y4 osteocyte line was used to determine the effects of soluble urate on osteocyte viability and expression of genes implicated in osteocyte function.

Results: Addition of soluble urate in the RAW264.7 osteoclastogenesis assay led to small increases in osteoclast

formation (ANOVA p=0.018, Figure). However, no significant effects on osteoclast number or activity were observed in the murine bone marrow assay, human peripheral blood osteoclastogenesis assay or rat mature osteoclast assay. In the MC3T3 osteoblast assays, soluble urate did not alter cell viability, mineralisation, or gene expression of markers including type 1 collagen, osteocalcin or osteoprotegerin. Similarly, in MLO-Y4 osteocyte assays, soluble urate did not alter cell viability or gene expression of RANKL, E11 or connexin-43.

Conclusion: Soluble urate at physiological concentrations does not promote anabolic bone formation pathways in *in vitro* bone cell assays. These data do not support the concept that the observed positive association between serum urate and bone density is due to direct effects of urate on bone. **Figure:** RAW264.7 osteoclastogenesis assays (showing pooled data from six biological repeats), demonstrating that higher concentrations of soluble urate leads to small increases in osteoclast formation. Dunnett multiple comparison test compared with control (no added urate) *p<0.05.



Disclosure: **N. Dalbeth**, None; **B. Pool**, None; **A. Chhana**, None; **J. M. Lin**, None; **M. L. Tay**, None; **P. Tan**, None; **K. E. Callon**, None; **D. Naot**, None; **J. Cornish**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/soluble-urate-a-direct-mediator-of-bone-turnover

Abstract Number: 2280

Monosodium Urate Crystal-Induced Inflammation Promotes Osteocyte Expression of Pro-Resorptive and Inflammatory Mediators: Implications for Erosive Gout

Ashika Chhana[1], Mei-Lin Tay[2], Bregina Pool[3], Karen E. Callon[2], David Musson[2], Dorit Naot[1], Gregory Gamble[3], Jillian Cornish[3] and **Nicola Dalbeth**[2], [1]Medicine, University of Auckland, Auckland, New Zealand, [2]University of Auckland, Auckland, New Zealand, [3]Department of Medicine, University of Auckland, Auckland, New Zealand

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Background/Purpose: Bone erosion in gout is strongly associated with tophi; lesions comprising of inflammatory cells surrounding collections of monosodium urate (MSU) crystals. Osteocytes are the most abundant cell population within bone and are important regulators of bone remodeling. The aim of this study was

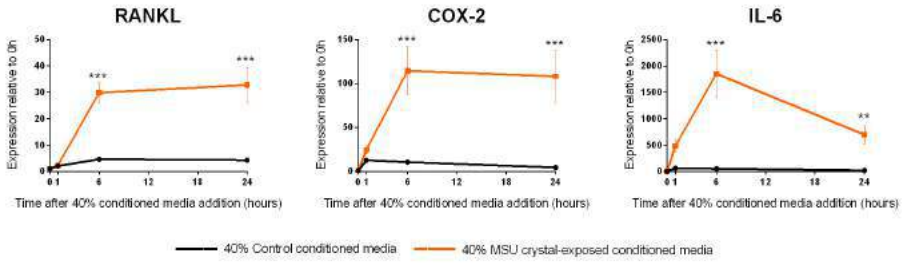
to investigate the direct effects of MSU crystals and indirect effects of MSU crystal-induced inflammation on osteocyte function.

Methods: For direct *in vitro* assays, MSU crystals were added to MLO-Y4 osteocyte-like cells cultured in type I collagen gels (3D) for 1h, 6h and 24h. For indirect *in vitro* assays, RAW264.7 macrophage-like cells were cultured with or without MSU crystals (0.5mg/mL) for 24h and supernatants were harvested and filtered for conditioned media preparation. The conditioned media (40%) was then added to the 3D MLO-Y4 cultures for 1h, 6h and 24h. All changes in MLO-Y4 gene expression were examined using real-time PCR and analyzed using two-way ANOVA with *post hoc* Sidak's tests. The relationship between osteocytes, MSU crystals and macrophages in erosive gout was examined by polarizing light microscopy and CD68 immunohistochemistry in joint samples obtained from cadaveric donors with crystal-proven gout.

Results: In the direct *in vitro* assays, culture with MSU crystals alone did not alter the expression of osteocyte-related genes or inflammatory mediator gene expression ($P>0.1$ for all). In contrast, addition of conditioned media from MSU crystal-exposed RAW264.7 cells to MLO-Y4 cultures led to a ~2-4-fold increase in expression of E11 and connexin43 at the 6h and 24h time-points compared to control conditioned media ($P<0.0001$). RANKL expression was also increased at 6h and 24h ($P<0001$, Figure) and OPG expression was reduced at the 6h time-point by ~2-fold ($P=0.007$). In addition, expression of inflammatory genes was upregulated, including TNF-a (~4-fold at 1h), IL-1b (~5-fold at 6h and 24h), IL-8 (>500-fold at all time-points), IL-11 (>200-fold at 6h and 24h), IL-6 and cyclooxygenase-2 (Figure) ($P\leq0.001$ for all)**.** In histological analysis of cadaveric joint samples affected by gout, numerous CD68+ macrophages and MSU crystals were identified in proximity to osteocytes within bone.

Conclusion: MSU crystals do not directly influence osteocyte-related gene expression. However, interactions between MSU crystals and immune cells in the joint may promote osteocyte expression of pro-resorptive and inflammatory mediators, which can have important consequences for local bone remodeling. These indirect effects on osteocyte function may contribute to bone erosion in gout.

Figure: Mean (SEM) changes in relative expression levels of RANKL, COX-2 and IL-6 in MLO-Y4 cells cultured with 40% conditioned media from MSU crystal-exposed RAW264.7 cells or control RAW264.7 cells (no MSU). *Post hoc* Sidak's test, *p<0.05, **p<0.01 and ***p<0.001 vs control conditioned media.



Disclosure: A. Chhana, None; **M. L. Tay**, None; **B. Pool**, None; **K. E. Callon**, None; **D. Musson**, None; **D. Naot**, None; **G. Gamble**, None; **J. Cornish**, None; **N. Dalbeth**, None.

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Abstract Number: 2281

Monosodium Urate Monohydrate (MSU) Crystals Induces Cartilage Degeneration By Accelerating Hypertrophy and Mineralization.

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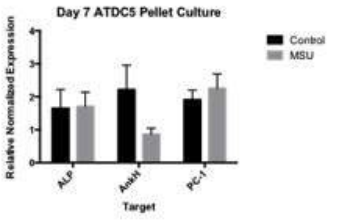
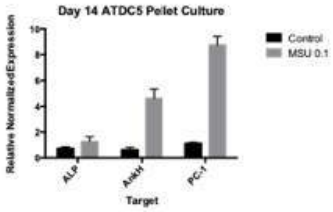
Background/Purpose: Previous studies have shown that abnormal loads induce meniscus cell damage and matrix degradation both in-vivo and in-vitro[1,2]. Monosodium urate (MSU) crystal is considered a Òdanger signalÓ as it activates the innate immunity[3]. Presence of MSU in synovial fluid is associated with the worst osteoarthritis (OA) pathology and disease progression[4]. Mineralization is dependent on the ratio of Phosphate/Pyrophosphate (Pi/PPi) that is influenced by manifold factors including Ank, Enpp1 and Alp respectively[5]. The objective of this study was to investigate the effect of increasing concentrations of MSU crystals on chondrocyte function, differentiation, and mineralization.

Methods: Primary chondrogenic cell line (ATDC5) was cultured in a 1:1 mixture of DMEM/F12 medium containing 10% FBS, Insulin-Transferrin-Selenium and incubated with increasing concentrations of endotoxin-free MSU crystals at increasing concentrations (0.01, 0.025, 0.05 and 0.1 mg/ml) for 4, 7, and 14 days respectively. Purification of total cellular RNA for real time PCR was prepared from ATDC5 cells at different time points. Real-time quantitative PCR and immunohistochemistry were performed on specific extracellular matrix genes, metalloproteinases, and specific mineralization genes such as Ankh, Enpp1 and Alp. Alcian-blue and Alizarin red S staining was performed at selected time point of ATDC5 cells exposed to different MSU concentrations.

Results: MSU crystals have a negative effect in the function and differentiation of ATDC5 chondrogenic cell lines. The ability of chondrocyte to produce matrix protein assessed by relative mRNA expression of aggrecan and type II collagen was reduced in chondrocytes following culture with MSU crystals and correlated with Alcian-blue staining. The expression of Type X collagen and MMP-13 in monolayer and pellet cultures was increased following culture with MSU crystals and correlated with Alizarin red staining. The expression of genes involved in extracellular PPi metabolism such as Ankh and Epp1 were increased after prolonged exposure to MSU crystals (1-way ANOVA $p<0.05$) while Alp remained unchanged (Figure 1). The expression of Ankh, Enpp1 and Alkp was confirmed by western blotting ($p<0.05$) and was associated with changes in the extracellular Pi/PPi ratio.

Conclusion: Long-term culture of MSU crystals with chondrogenic cell line ATDC5 impairs the function and differentiation of chondrocytes with increased hypertrophy and mineralization. Our findings lend additional support to the potential involvement of the innate immune system in OA pathology and progression by accelerating chondrocyte hypertrophy. **Figure 1.** Increase in Ankh, PC-1 gene expression compared to Alp in ATDC5 14 day pellet cultures exposed to 0.1 mg/ml MSU.





Disclosure: **N. Yang**, None; **A. M. Reginato**, None; **C. Sun**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/monosodium-urate-monohydrate-msu-crystals-induces-cartilage-degeneration-by-accelerating-hypertrophy-and-mineralization

Abstract Number: 2282

Ferritin Levels Are Associated with Urate and Gout – a Role for Iron Metabolism in Gout ?

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Background/Purpose: Transferrin and its cell-surface receptor regulate iron uptake and ferritin sequesters free iron and acts as a store for excess iron. Ferritin has been positively associated with serum urate in the National Health and Nutrition Examination Survey III [1]. There have been observational and interventional studies suggesting a role for iron as a trigger for gout flares, which may be due to pro-inflammatory activities associated with iron [2]. Consistent with this, genetic variation in the transferrin receptor has been associated with gout and with an increased likelihood of self-report of an iron-rich food as a trigger of flares [3]. This observational study aimed to replicate the association of serum ferritin with serum urate (SU) and to test for association of serum ferritin with gout.

Methods: Association with gout was assessed in European (100 cases, 60 controls) and Polynesian (100 cases, 60 controls) male individuals from New Zealand (NZ) and a mixture of Latino, African American and European (33

cases, 60 controls) individuals from the United States (US). People with liver damage/ disease were excluded. For the SU association analysis, 180 participants without gout from NZ and the US and an additional 1,260 participants from the Jackson Heart Study (JHS) were used. Participants taking diuretic medication, or who had kidney disease or gout or first-degree relatives with gout were excluded from the SU analysis. Multiple regression analyses adjusted for age, sex (where relevant) and body mass index were done using R v3.3.0. Self-reported grandparental ancestry (for Polynesian) and C-reactive protein level (for JHS and US) were also included as covariates in the various analyses. Beta and OR statistics are expressed per 10 ng/mL increase in ferritin.

Results: Serum ferritin was positively associated with gout in NZ Polynesian [OR=1.031, *P*=4.4E-03] and US [OR=1.214, *P*=6.9E-05] participants but not NZ Europeans [OR=0.997, *P*=0.84] (Table). A positive association of ferritin with urate was observed in both NZ Polynesian [ß=0.081 µmol/L, *P*=1.1E-03] and US [ß=0.29 µmol/L, *P*=4.3E-06] individuals but not in NZ Europeans [ß=0.052 µmol/L, *P*=0.33]. A positive association of serum ferritin with SU was found in both males (ß=0.046 µmol/L, *P*=9.3E-03) and females (ß=0.081 µmol/L, *P*=1.6E-03) in the JHS.

Conclusion: The association of ferritin with SU and gout was independent of C-reactive protein level, suggesting that the relationship is not due to the elevation of ferritin in inflammation [4] and consistent with a direct role for iron metabolism in the control of SU and gout. This is supported by the previous report of association of the transferrin receptor with gout. 1. Ghio et al. *Free Radic Res*. 2005;39:337-42. 2. Facchini. *Rheumatology*. 2003;42:1550-55. 3. Merriman et al. *Arthritis Rheumatol*.2015;S67(10). 4. Kell et al. *Metallomics*, 2014. 6:748-73.

Population	Serum Urate [µmol /L]		Gout [case/control]		NU/HU	
	Beta [95% CI]	*P*	OR [95% CI]	*P*	OR [95% CI]	*P*
JHS (males)	0.046 [0.011 - 0.080]	9.3E-03	-	-	1.012 [1.010 - 1.023]	1.4E-02
JHS (females)	0.081 [0.030 - 0.131]	1.6E-03	-	-	1.040 [1.011 - 1.067]	3.3E-03
JHS (combined)	0.059 [0.031 - 0.087]	3.2E-05	-	-	1.016 [1.010 - 1.026]	1.1E-03
NZ European	0.052 [-0.055 - 0.159]	0.33	0.997 [0.973 - 1.023]	0.84	1.010 [0.984 - 1.024]	0.65
NZ Polynesian	0.081 [0.033 - 0.129]	1.1E-03	1.031 [1.011 - 1.046]	4.4E-03	1.021 [1.011 - 1.031]	8.6E-04
US	0.296 [0.176 - 0.417]	4.3E-06	1.214 [1.120 - 1.358]	6.9E-05	1.056 [1.021 - 1.101]	3.7E-03

Disclosure: T. Fatima, None; **T. R. Merriman**, None; **L. K. Stamp**, None; **N. Dalbeth**, None; **C. Iverson**, AstraZeneca, 3,AstraZeneca, 1; **J. N. Miner**, Ardea Biosciences, Inc., a member of the AstraZeneca Group, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/ferritin-levels-are-associated-with-urate-and-gout-a-role-for-iron-metabolism-in-gout

Abstract Number: 2283

Suppression of Monosodium Urate (MSU) Crystals-Induced Inflammatory Response By Inhibiting TGF-β Activated Kinase 1

(TAK1)

Anil Singh[1], Kayla O'Sullivan[2], Mukesh Chourasia[3], Sadiq Umar[4], Mahamudul Haque[2], Bhanupriya Madarampalli[2] and Salahuddin Ahmed[2], [1]Washington State University, College of Pharmacy, Spokane, WA, [2]Department of Pharmaceutical Sciences, Washington State University, College of Pharmacy, Spokane, WA, [3]Department of Pharmacoinformatics,, National lnstitute of Pharmaceutical Education and Research, Hajipur,, India, [4]Department of Pharmaceutical Science, Washington State University, College of Pharmacy, Spokane, WA
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Background/Purpose: Monosodium urate (MSU) crystals are known to activate inflammatory pathways that overlap with interleukin-1β (IL-1β) signaling. The present study was carried out to determine if MSU utilizes IL-1β signaling proteins to elicit inflammatory responses.

Methods: THP-1 monocytes were converted to macrophages with phorbol myristate acetate (PMA) for 3 hours followed by stimulation with MSU crystals (25-200 μg/ml) for 0-24 hours. Whole cell extracts were prepared for the detection of cellular proteins by Western blotting method, while the conditioned media was collected for the quantitation of secreted IL-1β and TNF-α by ELISA. Molecular dynamics (MD) simulation was performed using protein preparation wizard of Schrodinger suit 2014.3 on TAK1-TAB1 protein with a tautomeric form of MSU as a ligand. Recombinant human TAK1 protein was used for *in vitro* kinase assay. For *in vivo* evaluation, C57BL/6J mice were administered (5Z)-7-Oxozeaenol (an inhibitor of TAK1; 5 mg/kg, p.o.) or febuxostat (5 mg/kg. p.o.) 2 hours prior to MSU injection (0.5 mg/20 μl) in the footpad. Changes in the paw circumferences were measured up to 48 hours of MSU injection.

Results: Stimulation of THP-1 macrophages with MSU (25-200 μg/ml) resulted in a dose- and time-dependent increase in IL-1β and TNF-α production ($p<0.05$). At the cellular level, MSU selectively inhibited the global expression pattern of K^{63}-linked ubiquitination without affecting K^{48}-linked ubiquitination in activated THP-1 cells. Interestingly, a rapid phosphorylation of IRAK-4 (Thr^{345}/Ser^{346}), IRAK-1 (Thr^{387}), IRAK-1 (Thr^{209}), and TAK1 ($Thr^{184/187}$) in THP-1 macrophages was observed within 5 to 15 minutes of MSU stimulation. Blockade of IL-1β secretion by Brefeldin A in THP1 macrophages had no effect on MSU-induced TAK1 activation, suggesting TAK1 as a direct target of MSU. To evaluate the importance of IL-1β signaling proteins using chemical inhibitors, we found that the inhibition of TAK1, but not IRAK-1/4 or TRAF6, completely abrogated MSU-induced IL-1β and TNF-α production in THP-1 macrophages ($p<0.01$). Furthermore, *in silico* simulation of TAK1 revealed that MSU is capable of activating TAK1 and arresting its conformational position in active state, thereby, causing sustained TAK1 kinase activation. Furthermore, *in vitro* kinase assay results also showed that MSU (100-500 μg/ml) induces autophosphorylation of TAK1 protein in a dose-dependent manner ($p<0.05$). Findings from *in vivo* studies suggest that the pretreatment of mice with (5Z)-7-Oxozeaenol significantly inhibited MSU-induced paw circumferences in mice ($p<0.01$), which was comparable to febuxostat treatment.

Conclusion: Our study shows that MSU is capable of inducing TAK1 activation in THP-1 macrophages independent of endogenous IL-1β, suggesting TAK1 as a potential therapeutic target for the treatment of gout.

Disclosure: A. Singh, None; **K. O'Sullivan**, None; **M. Chourasia**, None; **S. Umar**, None; **M. Haque**, None; **B. Madarampalli**, None; **S. Ahmed**, None.

Abstract Number: 2284

Differential Effect of MSU-Crystal Induced Inflammation on Macrophage Polarization

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Background/Purpose: Gouty arthritis is a common inflammatory joint disease that arises in response to the deposition of monosodium urate (MSU) crystals in soft joints, periarticular and articular joints of individuals with hyperuricemia[1]. Studies have shown that the inflammatory response occurs when macrophages within the joint space phagocytose MSU crystals[2]. Macrophages (THP-1 monocytes or Mφ) are a functionally heterogeneous cell population that have two different phenotypes related to different stimuli: M1 (classically activated) and M2 (alternatively activated)[3]. Based on their activation status, macrophages can influence a response cascade in gout. The objective of this study was to investigate MSU-induced responses on macrophages, and M1 and M2 polarized macrophages by using cytokine array, immunohistochemistry, and Western blot analysis.

Methods: The human monocytic cell line THP-1 differentiated into macrophages using 10 ng/ml PMA. Once differentiated, macrophages were incubated with LPS and IFN-γ for classical macrophage activation (M1) or IL-4 and IL-13 for alternative activation (M2). MSU-crystals were induced 48 hours later to both M1 and M2 polarized macrophages and re-incubated. After the incubation, the impact of MSU-crystals on macrophage polarization was studied and assessed by performing cytokine array, immunohistochemistry, and Western blotting.

Results: Immunohistochemistry shows that there is a differential effect produced by MSU crystals as seen by either having a pro-stimulatory effect or an anti-inflammatory effect based on the cytokine or chemokine. Macrophages show a 2-fold increase in IL-1β, IL-8, TNF-α, IL-6, GRO, and GRO-α compared to M1 and M2. IL-10, an anti-inflammatory cytokine, increased on M2 compared to macrophages and M1. Additionally, TGF-β2 did not differ between THP-1 monocytes, M1 and M2. Osteopontin, an anionic phosphoprotein, mediates biomineralization. There was a 2 fold increase in osteopontin in M1 and M2 compared to macrophages.

Conclusion: Our results from immunohistochemistry and Western blot analysis confirm that there are significant differences between crystal activation in macrophages, M1, and M2 due to their inherent functions. Upon MSU-crystal induction, a more robust effect is seen on the macrophages compared to M1 and M2 polarized macrophages. This area of research warrants further investigation. **References** 1. Roddy E, Choi HK. Epidemiology of Gout. Rheum Dis Clin North Am. 2014;40:155-75. 2. Liu-Bryan R, Scott P, Sydlaske A, Rose DM, Terkeltaub R (2005) Innate immunity conferred by Toll-like receptors 2 and 4 and myeloid differentiation

factor 88 expression is pivotal to monosodium urate monohydrate crystal-induced inflammation. Arthritis Rheum. 52(9):2936–46

3. Laria, Antonella et al. “The Macrophages in Rheumatic Diseases.” Journal of Inflammation Research 9 (2016): 1–11. PMC. Web. 19 June 2016.

Disclosure: R. Ahmed, None; **N. Yang**, None; **C. Sun**, None; **A. M. Reginato**, None.

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Abstract Number: 2285

12/15-Lipoxygenase Inhibition By ML351 Protects Against Uric Acid Crystal-Induced Acute Arthritis in Mice

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Background/Purpose: Treatment of acute gout involves the use of NSAIDs, colchicine or corticosteroids. Unfortunately, co-morbid conditions such as chronic kidney disease, peptic ulcer disease and congestive heart failure make the use of these agents dangerous or contraindicated. Therefore, there is an unmet need for new therapies in acute gout. Eicosanoids have been implicated in a vast number of inflammatory conditions, such as gout. Currently, over a hundred different eicosanoids have been identified, with many having potent bioactive signaling capacity. Monosodium uric (MSU) crystals are known to induce eicosanoid inflammatory mediators. We hypothesized that a complete study of these eicosanoid mediators might identify new therapeutic targets in acute gout.

Methods: Complete eicosanoid profiling was determined by ultra-performance liquid chromatography-electrospray ionization triple quadrupole mass spectrometric (UPLC-QTRAP/MS/MS) method, and was conducted in peritoneal lavage 7 hours after MSU (3mg) intraperitoneal injection, and in bone marrow derived macrophages (BMDM) supernatants after either MSU (0.25mg/ml) stimulation for 4 hours, or LPS (100ng/ml) for one hour plus MSU (0.25mg/ml) stimulation for 4 hrs. To test the hypothesis that selective 12/15-lipoxygenase (LOX) inhibition by intraperitoneal ML351 (50mg/kg) protects against MSU inflammation, we used two MSU crystals-induced inflammation murine models: subcutaneous air-pouch model to measure MSU crystal-induced cytokine production by ELISA and inflammatory cell accumulation 7hrs after MSU (3mg) injection; and intraarticular injection of MSU (100µg) crystals. Histopathological studies from the injected joints were carried after 7hrs.

Results: Complete eicosanoid profiling identified COX and 15 LOX eicosanoids as the mediators more abundant in BMDM after LPS/MSU stimulation. Of note, only 15 LOX eicosanoids were released after just MSU stimulation in BMDM. Interestingly, 12/15 LOX eicosanoids were highly represented in the peritoneal lavages after MSU

intraperitoneal injection. In the *in vivo*models, intra-articularly injected MSU crystals provoked a neutrophilic infiltration that was significantly reduced in joints from mice treated with ML351 inhibitor. MSU crystal-induced inflammatory cell infiltration was also significantly attenuated in mice treated with the 12/15 LOX inhibitor. Of interest, amount of IL-6 and IL-1β in the pouch were not decreased in the 12/15 LOX inhibitor group suggesting an IL-1β independent effect.

Conclusion: 12/15 LOX eicosanoids are abundant after MSU crystal stimulation, and their inhibition by ML351 decreased cellular infiltration in two models of MSU crystal induced inflammation. Therefore, selective 12/15 LOX inhibition might be an attractive potential target in acute gout flares safer than the current treatments.

Disclosure: R. Coras, None; **A. Stubelius**, None; **O. Quehenberger**, None; **M. Guma**, None.

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Abstract Number: 2286

Bioresponsive Glucocorticoid-Loaded Microparticles to Prevent Acute Gout Flares

Alex Stubelius[1], Wangzhong Sheng[2], Sangeun Lee[1], Adah Almutairi[3] and Monica Guma[4], [1]Skaggs School of Pharmacy and Pharmaceutical Sciences, UCSD, La Jolla, CA, [2]1Skaggs School of Pharmacy and Pharmaceutical Sciences, UCSD, La Jolla, CA, [3]Skaggs School of Pharmacy and Pharmaceutical Sciences., UCSD, La Jolla, CA, [4]Medicine, UCSD, La Jolla, CA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Gout is a common and very painful form of arthritis triggered by deposits of monosodium urate (MSU) crystals in the joints. Lifestyle factors such as dietary intake trigger gout flares, but trauma and surgery also induce gout attacks. Systemic non-steroidal or steroidal anti-inflammatory therapies are unsuitable to treat postsurgical gout flares due to their side effects. Postsurgical gout flares typically involve previously affected joints and develop within 8 days after surgery. These features make it ideal for a local, safe prophylactic therapeutic option. Thus, we developed a prophylactic therapeutic system of activatable particles, which would release the drug of interest only under inflammation exposure, minimizing the amount of drug required to control inflammation and circumventing collateral damage to healthy tissues (Fig. 1). This pH sensitive release system of glucocorticoid-loaded microparticles could be prophylactically injected in the joint at risk.

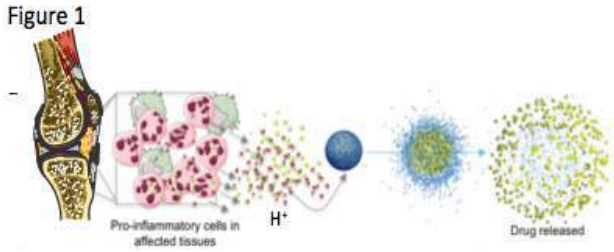
Methods: Acetalation of dextran (AcDex, 10kDa) was determined by NMR (64%), and 3-5mM particles were formulated by electrospray. The signal of these particles is Òturned onÓ upon exposure to acidic pH, which reveals hydroxyl groups and thus increases the materialÕs hydrophilicity. After the hydrophobicity switch, drug diffuses out the polymer matrix. Dexamethasone palmitate (DXM-P) release was analyzed by LC-MS under different pH. Bone-marrow derived macrophages (BMDM) were treated prophylactically for up to 48hrs. with either free DXM-P, DXM-P loaded into AcDex particles, or DXM-P loaded into the slow-release FDA-approved

poly(lactic-co-glycolic acid; PLGA) particles and then stimulated with LPS (100ng/ml) and MSU (0.25mg/ml) overnight. Cytokine amounts were determined by ELISA in BMDM supernatants. We also used an air-pouch model of MSU-induced inflammation to test the particles. We administered either free DXM-P or DXM-P-loaded AcDex particles 24 hrs. before MSU (3mg) injection in the pouch. Cell count was determined after pouch lavage.

Results: The release of DXM-P from AcDex particles increased in lower pH, confirming their responsiveness. Prophylactic treatment *in vitro* of BMDM with DXM-P-loaded AcDex particles up to 48 hrs. before MSU stimulation, significantly reduced IL-1b, TNFα and IL-6 cytokine production compared to both free drug and slow release PLGA-particles. *In vivo*, DXM-P loaded particles significantly reduced cell infiltration in the air pouch when prophylactically injected 24 hrs. before MSU injection.

Conclusion: We have successfully developed a prophylactic option to prevent acute gout flares in post-surgical patients.

Figure 1



Disclosure: **A. Stubelius**, None; **W. Sheng**, None; **S. Lee**, None; **A. Almutairi**, None; **M. Guma**, None.

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Abstract Number: 2287

Serum Urate and Its Association with Endothelial Dysfunction in Young Adults

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Background/Purpose: Both serum urate (sUA) and endothelial dysfunction have been associated with hypertension and cardiovascular disease. Increasing sUA level has been associated with endothelial dysfunction

and higher inflammatory markers (e.g., high sensitivity c –reactive protein [hsCRP]). To date, however, few studies have examined the relationship between sUA, endothelial dysfunction, and blood pressure (BP) including young and largely healthy individuals. **Objectives**: To determine whether there is an association between higher sUA, endothelial dysfunction as measured by flow-mediated dilation (FMD), and BP in young adults.

Methods: We conducted a cross-sectional analysis of baseline data for consecutively enrolled individuals (age 18 – 40 years). Inclusion criteria were: baseline systolic BP (SBP) ≥ 120 and <160 mmHg or diastolic BP (DBP) ≥ 80 and < 100 mmHg, and sUA ≥ 5.0 mg/dL for men or ≥ 4.0 mg/dL for women. Clinic SBP and DBP, 24- hours ambulatory BP monitoring (ABPM), hsCRP, and sUA level were obtained. Associations between sUA, endothelial dysfunction measured by FMD, and ABPM variables were evaluated using a general linear model. Adjustments for age, gender, race, and BMI were applied after significant univariate results. Data reported are mean +standard deviation (SD).

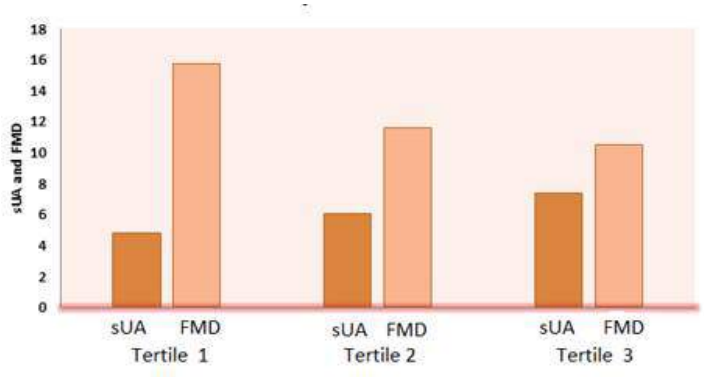
Results: There were 69 participants included in the analysis. Participants recruited had a mean age of 29.0 ± 6.9 years, 30 % were female, 43 % African-Americans, mean BMI was 29.0 ± 6.0 kg/m², and mean sUA was 5.9 ± 1.1 mg/dL (range from 3.9 to 8.5 mg/dL). We found no significant cross-sectional associations between sUA, FMD, and BP variables assessed by ABPM (Table). Participants in the upper tertile of sUA had significantly more endothelial dysfunction as measured by FMD than those in the lower tertiles (Figure). However, this difference was no longer significant after multivariable adjustment age, gender, race, and BMI.

Conclusion: In this cross-sectional analysis of young adults, there was no evidence to support an association between sUA levels and endothelial dysfunction or BP. Endothelial dysfunction or BP might be associated with changes in sUA when measured longitudinally in individuals, but not when measured cross-sectionally in populations. Larger studies will be needed to confirm these results. **Table. Cross-sectional correlation between sUA, FMD, and Ambulatory Blood Pressure parameters**

Parameters	r	p-value
sUA and FMD	**-0.19**	**0.15**
sUA and SBP	**-0.02**	**0.85**
sUA and DBP	**-0.07**	**0.61**
sUA and MAP	**-0.02**	**0.86**

sUA: serum uric acid, SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial blood pressure, FMD: flow-mediated dilation

Figure. Tertiles of sUA and FMD unadjusted correlation



The p for trend for FMD across SUA tertiles is p = 0.006

Disclosure: M. B. Saddekni, None; **K. G. Saag**, Ardea/AstraZeneca, 5,Crealta, 5,Takeda, 5,Ardea/AstraZeneca, 2,Crealta, 2,Takeda, 2; **T. Dudenbostel**, None; **S. Oparil**, Actelion Pharmaceuticals US, 2,AstraZeneca, 2,Bayer Healthcare Pharmaceuticals, 2,Merck and Co., 2,NIH/NHLBI, 2,NHLBI, 2,Novartis Pharmaceutical Corporation, 2,Amgen, 5,AstraZeneca, 5,Bayer, 5,Boehringer Ingelheim, 5,Forest Labs Inc., 5,GlaxoSmithKline, 5,Medtronic, 5; **D. A. Calhoun**, None; **D. I. Feig**, None; **P. M. Muntner**, None; **D. T. Redden**, None; **P. J. Foster**, None; **E. J. Rahn**, None; **S. R. Biggers**, None; **P. Li**, None; **A. L. Gaffo**, US Government, 3,Cymabay, 5,Ardea, 5,Amgen, 2,AstraZeneca, 2.

Abstract Number: 2288

Inflammatory Status and Serum Uric Acid Determine High-Density Lipoprotein Cholesterol Levels in a Non-Rheumatic Population

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Background/Purpose: In inflammatory disorders, highest incidence of cardiovascular (CV) events paradoxically occurs at lower lipid levels [ARD.70:482], especially for high-density lipoprotein cholesterol (HDLc). Current data in general, non-inflammatory population suggest a similar but milder phenomenon [Circulation.107:391]. Serum uric acid (SUA) levels appear to determine the inflammatory status of the subjects, even in normouricemia [EHJ.27:1174]. The aim of this work was to assess whether inflammatory status and SUA associate with HDLc levels in a hypertensive population aged 65 years or older.

Methods: Analysis of the FAPRES study (cross-sectional study aimed that assessed the prevalence of atrial fibrillation in hypertensive patients aged 65 years or older). Inflammatory status was considered based on serum leukocytes. A comparison between serum lipids levels (HDLc, low-density lipoprotein-cholesterol [LDLc], total cholesterol [TCh], triglycerides [TG]) and different tertiles of leukocytes and SUA was performed using ANOVA. Correlation between leukocytes and SUA was analyzed by Pearson's coefficient. In case of significant differences, a multivariate linear regression model was built for each lipid parameter to adjust for potential confounders (age, gender, CV risk factors, renal failure, BMI, use of diuretics or statins, prior coronary disease, sinus rhythm at EKG).

Results: 860 patients were analyzed, mean aged 72.9 years (SD±5.8), 52.5% females. Leukocytes and SUA levels mildly correlated (r=0.127, p=0.001). Lower HDLc and higher TG levels were found in upper tertiles of both leukocytes and SUA, with no differences on TCh and LDLc (Table). Multivariate analysis confirmed an independent, inverse association of HDLc with both leukocytes (β=-0.001, p=0.025) and SUA (β=-1.054, p=0.037); and for TG levels, an independent, direct association was found with both leukocytes (β=+0.004, p=0.049) and SUA levels (β=+8.411, p=0.003).

Conclusion: In a hypertensive population aged 65 years or older, both inflammatory status and SUA levels showed an inverse, independent association with HDLc, following current data on patients with inflammatory disorders. Interestingly, SUA and leukocytes mildly correlated. This phenomenon might help to define a pro-atherogenic

profile on the general population.

Mean (±SD)	TCh	p	HDLc	p	LDLc	p	TG	p
- Leukocytes <5900	197.8 (±41.3)	0.15	54.3 (±13.2)	0.006	121.1 (±35.9)	0.20	115.2 (±48.6)	0.03
- Leukocytes 5900-7200	195.6 (±35.0)		53.1 (±12.7)		118.7 (±29.9)		132.7 (±88.3)	
- Leukocytes >7200	191.7 (±41.7)		50.8 (±12.6)		116.1 (±34.7)		129.0 (±54.8)	
- SUA<4.7	198.1 (±40.5)	0.32	56.6 (±13.8)	<0.001	119.6 (±36.6)	0.60	111.6 (±47.9)	0.001
- SUA 4.7-5.8	194.3 (±36.3)		54.8 (±12.9)		117.5 (±32.5)		117.5 (±47.0)	
- SUA>5.8	191.7 (±37.1)		49.7 (±10.8)		116.6 (±31.3)		135.6 (±90.7)	

Disclosure: **M. Andrés**, None; **M. A. Quintanilla**, None; **E. Pascual**, None; **P. Morillas**, None.

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Abstract Number: 2289

Obesity and Echocardiographic Changes in the Different Stages of Gout

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Background/Purpose: Studies on gout and its stages as a cardiovascular (CV) risk factor are few and with contradictory results. We compared echocardiographic parameters, known as independently associated with CV risk, and the scores obtained by using the Framingham Risk Score (FRS) in order to establish the differences in CV risk between obese and non-obese patients (pts) in the individual stages of gout.

Methods: A total of 201 pts were examined cross-sectionally, divided into three groups: asymptomatic hyperuricemia (n=52), 29 males and 23 females aged 55.23±15.94 years; gouty arthritis without tophi (n=86), 71 males and 15 females aged 56.36±12.29 years and gouty tophi (n=63), 60 males and 3 females aged 58.89±11.03 years. Obesity was defined as body mass index (BMI)>30 kg/m². FRS was calculated. Pts underwent echocardiography performed by one investigator, unaware of the cases clinical data, with 2.5MHz transducer. The following parameters were measured: left atrium (LA) size, thickness of the interventricular septum (IVS) and of posterior wall (PW) of the left ventricle in end-diastolic phase, fractional shortening (FS), Sm - reflecting systolic function of the left ventricle, Em - a sensitive indicator of diastolic dysfunction and E/Em ratio - an indicator of left ventricular filling pressure. Data were analyzed by Kolmogorov-Smirnov, t-test, Mann-Whitney, ANOVA test and

multiple linear regression.

Results: In asymptomatic hyperuricemia 22 (42.3%) of the pts were obese. In this group no difference was estimated in FRS (p=0.187), FS (p=0.885), Sm (p=0.400), Em (p=0.459) and E/Em (p=0.422) between obese and non-obese pts. However, obese pts had larger LA (mean±SD; 40.68±5.22 vs 36.50±5.37 mm, p=0.007), thicker IVS (mean±SD; 12.71±1.46 vs 11.18±2.18 mm, p=0.006) and thicker PW (mean±SD; 12.41±1.66 vs 10.48±2.03 mm, p=0.002). In gouty arthritis without tophi 41 (47.7%) of the pts had obesity. FRS (p=0.238), FS (p=0.110), Sm (p=0.341), Em (p=0.430) and E/Em (p=0.887) were equal between obese and non-obese pts, but obese pts had larger LA (mean±SD; 39.66±4.36 vs 36.60±5.12 mm, p=0.004), thicker PW (mean±SD; 12.71±1.67 vs 12.05±1.89 mm, p=0.037) and tended to have thicker IVS (mean±SD; 12.74±1.50 vs 12.02±1.87 mm, p=0.054). Twenty six (41.3%) of gouty tophi were obese. Comparison between obese and non-obese gouty tophi pts showed no difference in FRS (p=0.990), FS (p=0.157), Sm (p=0.830), Em (p=0.059) and E/Em (p=0.138). Likewise, pts with obesity had larger LA (mean±SD; 42.45±5.96 vs 39.25±5.84 mm, p=0.039), thicker PW (mean±SD; 13.50±2.46 vs 12.13±1.77 mm, p=0.007) and a tendency of thicker IVS (mean±SD; 13.17±1.42 vs 12.26±2.05 mm, p=0.056). Multiple linear regression, adjusted for age, revealed that the increase of BMI was a factor for thickening of the PW in asymptomatic hyperuricemia (r^2=0.565), gouty arthritis without tophi (r^2=0.305) and gouty tophi (r^2=0.261).

Conclusion: In the three stages of gout obese subjects had more pronounced alterations in the heart morphology, although the lack of differences in the left ventricular function and in the FRS. The simultaneous use of FRS and echocardiography contribute for a more complete assessment of CV risk in gout.

Disclosure: R. Gancheva, None; **A. Kundurdjiev**, None; **M. Ivanova**, None; **T. Kundurzhiev**, None; **Z. Kolarov**, None.

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Abstract Number: 2290

Crystal-Proven Gout and Disease Severity Factors Influencing the Prevalence of Cardiovascular Diseases

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Background/Purpose: Gout is a health disorder affecting many patients worldwide. Clinical gout studies showed

a high prevalence of cardiovascular diseases (CVD), raising the question whether gout is a risk factor for CVD. Our aim was to examine the prevalence of CVD in patients with crystal-proven gout compared to non-gout arthritis controls and to analyze whether disease severity is associated with CVD in gout.

Methods: From July 2011 until May 2016 patients with arthritis referred for diagnosis were consecutively included in the **Go**ut **A**rnhem-**L**iemers (GOAL) cohort. Joint fluid analysis was performed in all patients for crystal-proof of gout, controls were negative for crystals. Patients' characteristics and CVD (angina pectoris, myocardial infarction, heart failure, transient ischemic attack, cerebrovascular accident, peripheral vascular disease, heart valve abnormality, arrhythmia) were collected. In gout patients, gout disease severity factors (disease duration, attack frequency, tophi, affected joints, serum urate acid level, joint damage) were also collected. A 'case-control' analysis was performed to compare gout patients with controls for the prevalence of CVD, correcting for confounders. Within gout patients, the association between gout disease severity factors and CVD was analyzed.

Results: In total 700 crystal-proven gout patients and 276 non-gout arthritis controls were enrolled in the 'case-control' analysis. Forty-seven percent of 700 gout patients and 24% of 276 controls had one or more prevalent CVD (Table 1). Gout was strongly associated with an increased prevalence of CVD compared to controls, corrected for confounders in a multivariate regression (OR: 3.39; 95% CI, 2.37-4.84). In gout patients, disease duration ≥2 years, tophaceous gout, oligo- or polyarthritis, serum urate acid >0.55 mmol/L and joint damage were univariate risk factors for CVD (Table 2). After adding the cardiovascular risk factors in the multivariate logistic regression model, disease duration ≥2 years (OR: 2.01; 95% CI, 1.31-3.09), oligo- or polyarthritis (OR: 1.66; 95% CI, 1.03-2.66), serum urate acid >0.55mmol/L (OR: 1.73; 95% CI, 1.12-2.68) and joint damage (OR: 2.26; 95% CI, 1.38-3.69) were still independently associated with prevalent CVD.

Conclusion: After adjustment for cardiovascular risk factors, crystal-proven gout was strongly associated with an increased prevalence of CVD compared to controls. Within gout patients, disease severity (disease duration ≥2 years, oligo- or polyarthritis, serum urate acid >0.55 mmol/L and joint damage) were independently associated with prevalent CVD.

Table 1

Patients' clinical characteristics, cardiovascular risk factors and the prevalence of CVD in patients with crystal-proven gout and non-gout arthritis controls.

Patients' characteristics	Gout (n= 700)	Non-gout (n= 276)	P value[a]	Odds ratio (95% CI)
Age, years, mean (SD)	62.0 (13.4)	58.4 (14.8)	0.000	1.02 (1.01-1.03)
Male sex, No. (%)	573 (81.9%)	140 (50.7%)	0.000	4.38 (3.23-5.94)
Body mass index, kg/m^2, mean (SD)	29.4 (5.6)	26.9 (5.1)	0.000	1.10 (1.07-1.13)
Family history of CVD, No. (%)	166 (23.7%)	47 (17.0%)	0.023	1.52 (1.068-2.17)
Smoking, No. (%)				
No	370 (52.9%)	149 (54%)	0.000	
Stopped	211 (30.1%)	43 (15.6%)	0.000	1.98 (1.35-2.89)
Yes	119 (17.0%)	84 (30.4%)	0.001	0.57 (0.41-0.80)
Alcohol consumption, No. (%)				
>21 units per week	190 (27.2%)	51 (18.5%)	0.004	1.65 (1.17-2.33)
Creatinine level, µmol/L, mean (SD)	102.5 (40.6)[c]	77.2 (34.5)[d]	0.000	1.04 (1.03-1.05)
Glomerular filtration rate, mL/min/1.73m^2, mean (SD)	64.7 (21.5)[e]	78.32 (16.3)[f]	0.000	0.96 (0.95-0.97)
Diabetes mellitus, No. (%)	123 (17.6%)	33 (12.0%)	0.031	1.57 (1.04-2.37)
Hypertension, No. (%)	431 (61.6%)	92 (33.3%)	0.000	3.20 (2.39-4.30)
Hypercholesterolaemia, No. (%)	203 (29.0%)	44 (15.9%)	0.000	2.15 (1.50-3.09)
Cardiovascular diseases, No.(%)				
≥1[b]	331 (47.3%)	66 (23.9%)	0.000	2.85 (2.09-3.91)
Angina pectoris, No. (%)	86 (12.3%)	10 (3.6%)	0.000	3.73 (1.91-7.28)
Myocardial infarction, No. (%)	102 (14.6%)	11 (4.0%)	0.000	4.11 (2.17-7.78)
Heart failure, No. (%)	98 (14.0%)	8 (2.9%)	0.000	5.45 (2.62-11.37)
Transient ischemic attack, No. (%)	47 (6.7%)	10 (3.6%)	0.064	1.92 (0.95-3.85)
Cerebrovascular accident, No. (%)	47 (6.7%)	7 (2.5%)	0.010	2.77 (1.24-6.20)
Peripheral vascular disease, No. (%)	54 (7.7%)	6 (2.2%)	0.001	3.76 (1.60-8.85)
Heart valve abnormality, No. (%)	51 (7.3%)	8 (2.9%)	0.010	2.63 (1.23-5.62)
Arrhythmia, No. (%)	117 (16.7%)	21 (7.6%)	0.000	2.44 (1.50-3.97)

SD: standard deviation; CI: confidence interval; CVD: cardiovascular diseases.

[a] Based on the differences in both groups after univariate logistic regression analysis.

[b] Angina pectoris, myocardial infarction, heart failure, transient ischemic attack, cerebrovascular accident, peripheral vascular disease, heart valve abnormality, or arrhythmia.

[c] n= 684.

[d] n= 258.

[e] n= 452.

[f] n= 132.

Table 2
Patients' clinical characteristics, cardiovascular risk factors and gout disease severity factors of crystal-proven gout patients (n=700) with and without prevalent CVD.

Patients' characteristics	CVD: Yes (n= 331)	CVD: No (n= 369)	P value[a]	Odds ratio (95% CI)
Age, years, mean (SD)	67.8 (11.4)	56.8 (12.9)	0.000	1.08 (1.06-1.09)
Male sex, No. (%)	253 (76.4%)	320 (86.7%)	0.000	0.50 (0.34-0.74)
Body mass index, kg/m^2, mean (SD)	29.0 (5.6)	29.8 (5.6)	0.078	0.98 (0.95-1.01)
Family history of CVD, No. (%)	80 (24.2%)	86 (23.3%)	0.789	1.05 (0.74-1.49)
Smoking, No. (%)				
No	155 (46.8%)	215 (58.3%)	0.000	
Stopped	126 (38.1%)	85 (23.0%)	0.000	2.06 (1.46-2.90)
Yes	50 (15.1%)	69 (18.7%)	0.981	1.01 (0.66-1.53)
Alcohol consumption, No. (%)				
>21 units per week	77 (23.3%)	113 (30.8%)	0.026	0.68 (0.49-0.96)
Creatinine level, µmol/L, mean (SD)	110.6 (43.5)[b]	95.1 (36.4)[c]	0.000	1.01 (1.01-1.02)
Glomerular filtration rate, mL/min/1.73m^2, mean (SD)	58.1 (21.7)[d]	71.1 (19.1)[e]	0.000	0.97 (0.96-0.98)
Diabetes mellitus, No. (%)	90 (27.2%)	33 (8.9%)	0.000	3.80 (2.47-5.86)
Hypertension, No. (%)	223 (67.4%)	208 (56.4%)	0.003	1.60 (1.17-2.18)
Hypercholesterolaemia, No. (%)	119 (36.0%)	84 (22.8%)	0.000	1.90 (1.37-2.65)
Disease duration, No. (%)				
≥ 2 years	201 (67.9%)[f]	182 (57.2%)[g]	0.006	1.58 (1.14-2.20)
Attack frequency, No. (%)				
≥ 4 attacks per year	110 (33.3%)[h]	99 (27.0%)[i]	0.067	1.35 (0.98-1.87)
Tophaceous gout, No. (%)	125 (37.8%)	92 (24.9%)	0.000	1.83 (1.32-2.53)
Oligo- or polyarthritis, No. (%)	85 (25.7%)	56 (15.2%)	0.001	1.93 (1.33-2.81)
Serum urate acid, mmol/L, No. (%)				
> 0.55	124 (37.6%)[j]	76 (20.6%)	0.000	2.32 (1.66-3.25)
Joint damage, No. (%)	85 (32.4%)[k]	41 (11.7%)[l]	0.000	3.63 (2.40-5.50)

SD: standard deviation; CI: confidence interval; CVD: cardiovascular diseases.
[a] Based on the differences in both groups after univariate logistic regression analysis.
[b] n= 324.
[c] n= 360.
[d] n= 239.
[e] n= 213.
[f] n= 297.
[g] n= 320.
[h] n= 330.
[i] n= 367.
[j] n= 330.
[k] n= 262.
[l] n= 351.

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Abstract Number: 2291

Impact of Plasma Urate and Tophaceous Burden on Inflammatory Biomarkers of Cardiovascular Disease

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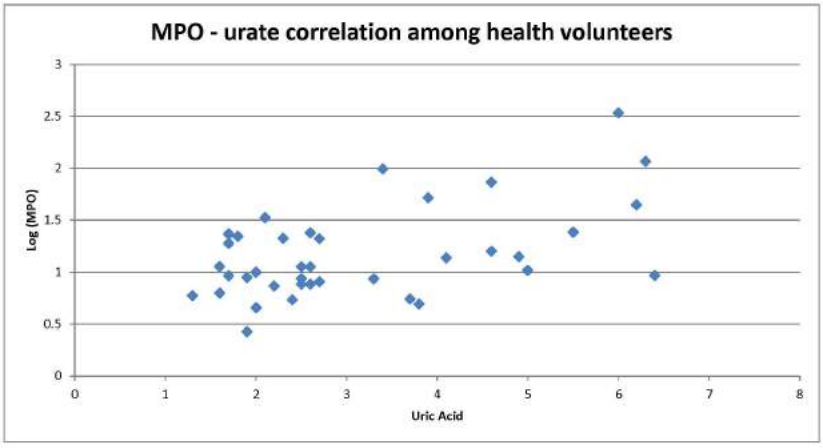
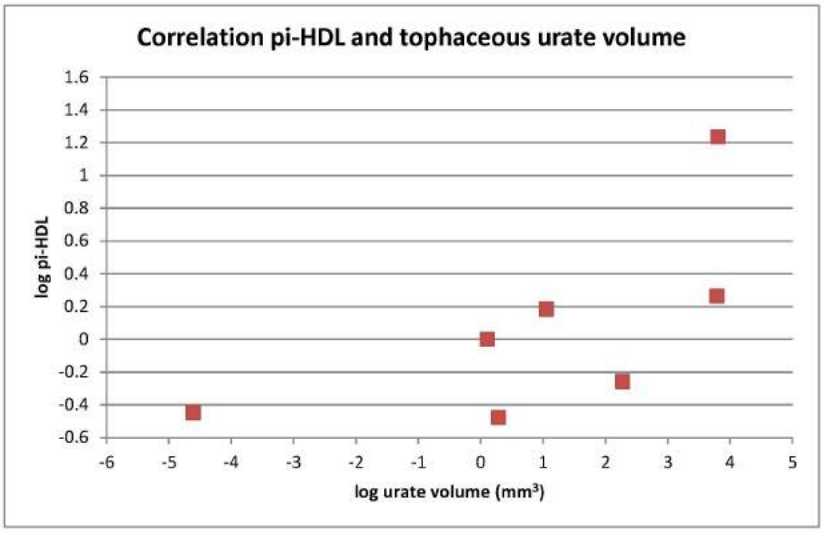
Background/Purpose: Gout and hyperuricemia have been associated with cardiovascular disease. Studies have documented the impact of serum urate levels on hypertension and that increased urate levels lead to release of myeloperoxidase from neutrophils in gout patients. Our group has described that HDL can function as anti-inflammatory HDL (protective) or pro-inflammatory HDL (piHDL –which exacerbates progression of cardiovascular disease) in RA, SLE and SSc patients. We sought to evaluate association between hyperuricemia and tophaceous urate load on biomarkers of cardiovascular disease.

Methods: Using plasma from healthy normal controls (from established SLE – piHDL comparator group) we compared plasma urate with myeloperoxidase (MPO), piHDL, and traditional cardiovascular measures (BMI, Total Cholesterol, HDL, LDL). Pro-inflammatory HDL function was determined by measuring the change in fluorescence intensity caused by oxidation of DCFH by oxidized LDL in the presence or absence of test HDL**.** Fluorescence intensity in the absence of HDL was normalized to 1.0. Values greater than 1.0 after the addition of HDL indicated piHDL. MPO levels were measured using ELISA (R&D Biosystems). In this pilot study, we also investigated the relationship between urate burden and pro-inflammatory biomarkers by estimating total body urate burden in 7 patients. Urate volume was summed across all 4 extremities using dual energy CT. Pro-inflammatory HDL was measured as described above. (At time of abstract submission, MPO not evaluated.)

Results: Among the sample of normal controls, plasma urate was correlated with MPO ($r=0.51$, $p< 0.001$). Urate levels were not correlated with piHDL, age, ethnicity or BMI. Urate levels were correlated with total cholesterol ($r= 0.30$, $p = 0.05$) and LDL ($r = 0.03$, $p < 0.05$) but not HDL or TG. Among the pilot sample of gout patients, though small sample size, piHDL was well correlated with measured urate burden, $r = 0.75$, $p = 0.05$ (and $r = 0.66$, $p = 0.10$ for log transformed variables shown below). piHDL was not associated with urate, total cholesterol, HDL or LDL.

Conclusion: Increased plasma urate levels are associated with increased MPO levels in healthy normals but not piHDL. Increased urate deposits in gout patients are associated with increased piHDL activity. These findings may represent separate intermediary pathways between hyperuricemia and urate burden and cardiovascular disease.





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Abstract Number: 2292

Decreased Endothelial and Smooth Muscle Responsiveness in the Vasculature of Gout Patients Compared with Healthy Controls: Relationship Between Flow- and Nitrate-Mediated Dilation, Serum Urate and CRP

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Background/Purpose: Gout is an independent risk factor for cardiovascular disease (CVD). Investigators studying the relationship between gout and CVD have focused on acute coronary outcomes, with limited evidence available regarding peripheral arterial function. Using high-resolution ultrasound imaging of the brachial artery, we examined endothelial and smooth muscle arterial function in gout subjects versus healthy controls.

Methods: 34 untreated male gout subjects and 64 healthy control males were included. By enrollment criteria some gout subjects, but no healthy controls, had coronary artery disease (CAD) or diabetes, or were current smokers. Demographics and medical history were recorded. Participants underwent brachial artery flow-mediated dilation (FMD; arterial response to blood flow after transient interruption using a distal blood pressure cuff) and nitroglycerine-mediated dilation (NMD) to assess endothelium-dependent and independent arterial smooth muscle responsiveness, respectively. Dynamic ultrasound images were assessed by two independent observers, with results reported as percentage change in arterial diameter from baseline.

Results: Compared with healthy controls, gout subjects had a higher prevalence of CAD (21% vs 0%, $p<0.05$), chronic kidney disease (76% vs 0, $p<0.05$), hypertension (71% vs 22%, $p<0.05$) and hyperlipidemia (50% vs 18%, $p<0.05$), but a similar low prevalence of diabetes (6% vs 0%, $p=0.12$). 29% of gout patients were current smokers (p vs control<0.05). Gout subjects were slightly older (58.9 vs 53.2 years, $p<0.05$), and significantly more gout patients were African American (44% vs 8%). Both FMD (2.20±3.12 vs 3.56±2.50, $p=0.021$) and NMD (16.69±9.01 vs 24.51±7.18, $p=0.00002$) were significantly reduced in the gout group vs controls. Gout non-smokers, white gout patients, and gout patients lacking specific co-morbidities persisted in having decreased FMD and NMD compared with controls. Gout patients with versus without specific co-morbidities had similar degrees of impaired FMD and NMD. Analysis of the gout group showed an inverse Pearson correlation between FMD and CRP ($R=-0.42$, $p=0.017$), a trend for inverse Pearson correlation between FMD and serum urate ($R=-0.31$, $p=0.08$); but no correlation between NMD and CRP or serum urate.

Conclusion: Compared with healthy controls, patients with gout have reduced arterial function as measured by FMD and NMD. While the increased prevalence of comorbidities among gout patients may contribute to diminished arterial function, it appears to be insufficient to explain the endothelial and smooth muscle dysfunction observed. Hyperuricemia and chronic inflammation may contribute to endothelial dysfunction among gout patients, but do not appear to contribute to smooth muscle dysfunction. Whether appropriate gout therapy may improve FMD and NMD in gout patients remains to be determined.

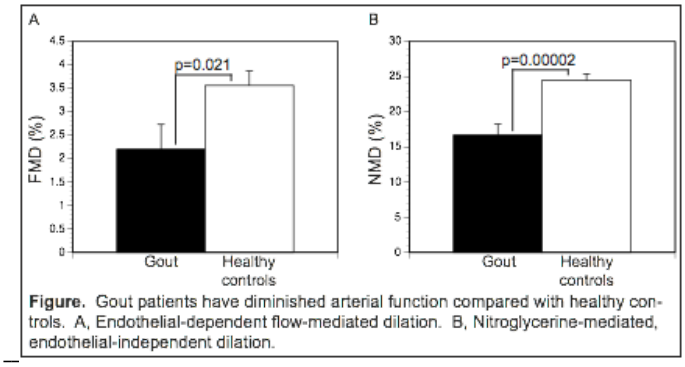

Figure. Gout patients have diminished arterial function compared with healthy controls. A, Endothelial-dependent flow-mediated dilation. B, Nitroglycerine-mediated, endothelial-independent dilation.

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Abstract Number: 2293

Cardiometabolic Risk and Subclinical Urate Deposits in Patients with Symptomatic Hyperuricemia and Metabolic Syndrome

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Background/Purpose: Elevated serum uric acid (sUA) levels, with and without gout, are associated with systemic inflammation, coronary artery disease (CAD), chronic kidney disease, and diabetes. Patients with asymptomatic hyperuricemia may have subclinical urate deposits in joints and arteries. Positron emission tomography (PET)-measured coronary flow reserve (CFR) is a senstive marker of myocardial perfusion and a quantitative predictor of clinical CAD risk. Patients with CFR <2.0 are at increased risk for major adverse cardiac events and cardiac death. We aimed to determine the association between sUA levels and CFR, insulin resistance, renal function, systemic inflammation, and subclinical urate deposits in patients with asymptomatic hyperuricemia and metabolic syndrome.

Methods: Adults aged ≥40 years with sUA levels ≥6.5 mg/dl and metabolic syndrome according to the National Cholesterol Education Program –Adult Treatment Panel III criteria were eligible. Patients with gout, nephrolithiasis, symptomatic CAD or pulmonary disease and those using xanthine oxidase inhibitors or probenecid were excluded. We assessed resting and stress induced (after adenosine infusion) myocardial blood flow (MBF) using a cardiac PET and calculated CFR from these data. We also measured sUA, IL-6, high-sensitivity c-reactive protein (hs-CRP), serum creatinine, insulin resistance by homeostatic model assessment (HOMA-IR) method, and urate deposits using dual-energy CT (DECT) of the foot and carotid arteries.

Results: We conducted an interim analysis including 18 subjects (**Table**) with the mean (SD) age of 66.0 (7.4) years and mean (SD) sUA level of 8.1 mg/dl (1.1). The mean (SD) CFR was abnormaly low at 1.9 (0.4) and the mean (SD) stress MBF was 1.5 (0.4) ml/min/g. On univariate regression analyses, sUA had no signficant association with CFR (β=-0.05, p=0.9), stress MBF (β=0.17, p=0.7), IL-6 (β=-1.14, p=0.5), serum creatinine (β=0.31, p=0.5) HOMA-IR (β=0.95, p=0.5), hs-CRP(β=-5.45, p=0.06), and eGFR (β=-0.76, p=0.15). Four patients (22.2%) were found to have urate deposits in the foot by DECT with urate volume ranging between 0.01 to 0.39 cm^3. None had urate deposits in the carotid arteries.

Conclusion: In this interim analysis of the pilot study involving patients with asymptomatic hyperuricemia, no relationship was noted between sUA and CFR and other cardiometabolic markers. However, we found urate deposits in the foot in over one-fifth of the patients. Final analyis that further determines the link bewteen sUA and cardiometabolic risk in patients with asymptomatic hyperuricemia and metabolic syndrome is underway.

Table: Summary of the study cohort (n=18)		
Demographics	Age, years	66.0 ± 7.4
	Male	4 (22.2%)
Clinical characteristics	BMI, kg/m2	35.3 ± 6.3
	Waist circumference, inches	49.2 ± 20.2
	SBP, mmHg	139.1 ± 15.6
	DBP, mmHg	71.4 ± 8.3
Laboratory characteristics	Uric acid, mg/dl	8.1 ± 1.1
	IL-6, pg/ml (ref: 0.0-15.5)	7.5 ± 8.6
	Serum creatinine, mg/dl	1.0 ± 0.2
	GFR, mL/min/1.73m^2	44.7 ± 11.9
	Fasting glucose, mg/dl (ref: 65-99)	104.9 ± 19.9
	HOMA-IR (ref <2.0)	5.9 ± 4.6
	Hs-CRP, mg/L (ref: 0.0-3.0)	12.2 ± 20.7
Cardiac PET findings	Coronary flow reserve (ref >2.0)	1.9 ± 0.4
	Myocardial blood flow at stress, mL/min/g	1.5 ± 0.4
	LV EF at rest, %	61.4 ± 10.1
DECT of the foot	Urate deposits	4 (22.2%)
DECT of the neck	Urate deposits	0 (0%)
Data are presented as Mean ± SD or N (%). BMI= body mass index, SBP=systolic blood pressure, DBP=diastolic blood pressure, IL= interleukin, GFR= glomerular filtration rate, HOMA-IR=homeostatic model assessment – insulin resistance, LV EF=left ventricular ejection fraction, PET=Positron emission tomography, DECT=dual energy CT		

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Abstract Number: 2294

Uric Acid Production and Blood Pressure: The Role of Uric Acid Concentration As Well As Uric Acid Production

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Background/Purpose: Blood pressure and hypertension are associated with uric acid, the end product of purine catabolism, but the underlying mechanism remainds unclear. During the final stage of purine metabolism, xanthine oxidase (XO) breaks down hypoxanthine to xanthine, and xanthine to uric acid, while reactive oxygen species (ROS) are formed. Accumulation of ROS by increased uric acid production has been suggested as a possible underlying mechanism for the association between uric acid and high blood pressure. We therefore investigated whether (i) serum uric acid concentration and/or (ii) 24h urinary uric acid excretion, as proxy for uric acid production, are associated with ambulatory blood pressure and hypertension.

Methods: Cross-sectional analyses were conducted among 2660 individuals (52% men, mean age 60.0±8.2 years; 26.7% type 2 diabetes [by design]) from The Maastricht Study. Multivariable linear and logistic regression analyses were performed to investigate the association of serum uric acid concentration and 24h urinary uric acid excretion with 24h pulse pressure (PP), 24h mean arterial pressure (MAP) and hypertension. Hypertension was defined as mean 24h systolic BP of ≥ 135 mmHg, 24h DBP ≥ 85 mmHg, and/or the use of anti-hypertensive medication. Analyses were adjusted for sex, age, glucose metabolism status, and further for treatment of diabetes and hypertension, body mass index, smoking behavior, alcohol consumption, education, and eGFR (in the logistic analyses, no adjustment for anti-hypertensive medication). Analyses exploring the role of serum uric acid were additionally adjusted for 24h urine uric acid excretion, whereas analyses exploring the role of 24h urine uric acid excretion were additionally adjusted for serum uric acid concentration and fractional excretion of uric acid (FE_{UA}).

Results: In fully adjusted analyses, serum uric acid concentration (per standard deviation [SD] of 330 μmol/L) was associated with higher MAP (β 0.50 mmHg (95% confidence [CI], 0.14 to 0.88; *P*=0.01) and positively associated with hypertension (odds ratio 1.29; CI, 1.14 to 1.46; *P*-value <0.001). Twenty-four-hour urinary uric acid excretion (per SD 141 mg/day/1.73m^2) was associated with higher MAP (β 0.85 mmHg; CI, 0.30 to 1.40; *P*--value <0.001). There was no significant association between serum and 24h urinary uric acid excretion with PP. There was no interaction for the aforementioned associations with sex or age.

Conclusion: We found evidence of associations between serum uric acid concentration with MAP and hypertension. Additionally, 24h uric acid excretion was associated with MAP. This indicates that both serum uric acid concentration and uric acid production are, independent of each other, associated with blood pressure.

Disclosure: L. E. J. M. Scheepers, None; **A. Boonen**, None; **P. C. Dagnelie**, None; **M. T. Schram**, None; **C. J. H. van der Kallen**, None; **R. M. A. Henry**, None; **A. A. Kroon**, None; **C. D. A. Stehouwer**, None; **I. C. W. Arts**, None.

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Abstract Number: 2295

A Non-Linear Relationship Between Physical Activity and Serum Uric Acid Concentrations: Nhanes 2003-2004

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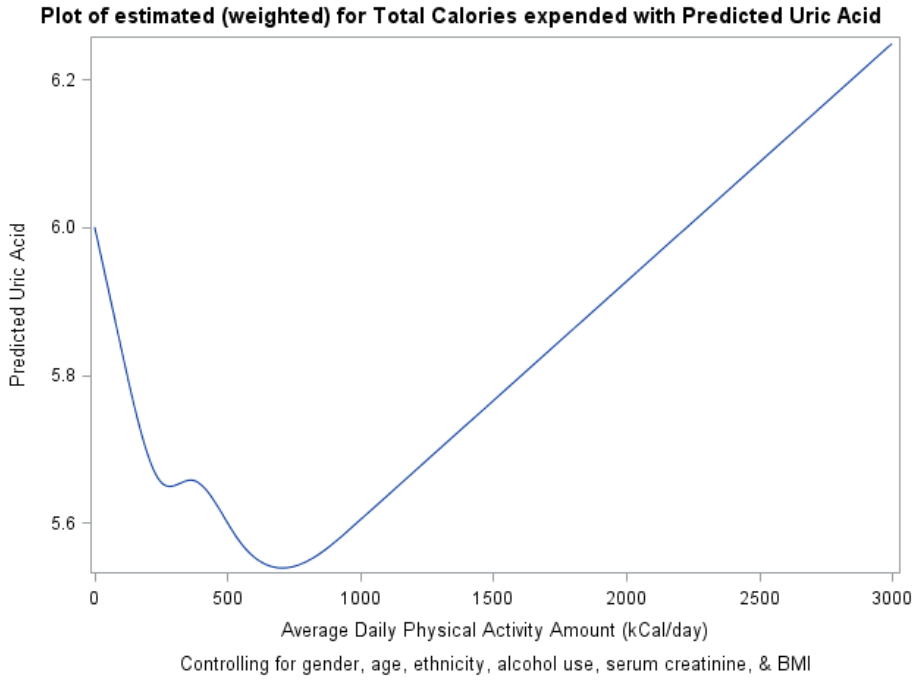
Background/Purpose: Hyperuricemia is a known cardio-metabolic risk factor as well as risk factor for gout. Physical activity has been found to improve many other cardio-metabolic risk factors; however, the relationship between physical activity and serum uric acid levels is not well understood. It has been shown that physical activity improves insulin sensitivity, lowering fasting serum insulin levels, and that lower insulin levels improve uric acid excretion. It would follow that physical activity may be beneficial in lowering serum uric acid levels. We aimed to evaluate how objectively measured physical activity related with serum uric acid concentrations in the 2003-2004 National Health and Nutrition Examination Survey (NHANES).

Methods: As part of the 2003-2004 NHANES serum uric acid was measured via a colorimetric enzymatic assay. Physical activity was assessed with seven days of ActiGraph accelerometry (n=3475). Here we used restricted cubic splines to parametrically estimate the relationship of physical activity amounts and serum uric acid levels, while controlling for age, gender, ethnicity, alcohol use, body mass index (BMI), and renal function.

Results: We found a borderline overall relationship of physical activity amounts and serum uric acid (df=4, p=0.519) and a significant effect of the non-linear portion over and above the additional impact of linear effect (df=3, p=0.0331). This non-linear relationship between physical activity and uric acid was U-shaped: below 760 kCal/day, uric acid was inversely related to physical activity amount; above 760 kCal/day, uric acid was positively related to physical activity amount. The median physical activity amount was 403 kCal/day, with 75% of the study population averaging less than 604 kCal/day and 90% of the study population averaging less than 849 kCal/day. The mean serum uric acid of the study population was 5.36mg/dL with a standard deviation of 1.36 mg/dL. Based on this relationship, the effects of physical activity on predicted serum uric acid ranged over 0.7 mg/dL (5.5-6.2 mg/dL).

Conclusion: In a nationally representative sample of US adults, a non-linear, U-shaped, relationship between

objectively measured physical activity and serum uric acid was found. This suggests possible competing mechanisms by which physical activity influences serum uric acid at lower and higher amounts and intensities of physical activity.



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Abstract Number: 2296

The Influence of Androgen Deprivation Therapy on Serum Uric Acid Level

Jae Hyun Lee[1], Eun Hye Park[2], Sang Wan Chung[3], Jaehyung Hur[3], You Jung Ha[3], Yeong Wook Song[1,4] and Yun Jong Lee[5,6], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [2]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, The Republic of, [3]Division of Rheumatology, Department of Internal Medicine, Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [4]Department of Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [5]Internal Medicine, Seoul National University College of Medicine, Seoul, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea

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Background/Purpose: The prevalence of hyperuricemia and gout suggests that sex hormones play a role in the gender difference with gout. Estrogen has been thought to reduce serum uric acid levels by increasing renal urate elimination. However, studies on the relationship between testosterone and uric acid levels showed conflicting results. We performed this study to define whether anti-androgen treatment affects serum uric acid levels in men.

Methods: This retrospective study reviewed the medical records of 178 patients who underwent anti-androgen treatment for advanced prostate cancer from January 2004 to December 2013 at Seoul National University Bundang Hospital. We enrolled 92 patients with available pre- and post-treatment (3 or 6-month) uric acid levels among them. An age-matched control included 46 prostate cancer patients who underwent surgical treatment only and had available pre- and post-treatment uric acid levels. The change of serum uric acid levels was compared by generalized estimation equation (GEE) model between patients with and without anti-androgen treatment.

Results: Compared to the control group, patients with anti-androgen treatment showed a more pronounced reduction of uric acid levels at both 3 and 6 months (estimation = -0.765 at 3-month and -0.739 at 6-month after anti-androgen treatment, both p-value < 0.001, Figure 1A). After further adjusting with hemoglobin, blood urea nitrogen, serum creatinine and serum protein levels, the difference was still significant (estimation = -0.831 at 3-month and -0.766 at 6-month, both p-value < 0.001, Figure 1B). When patients were stratified according to pre-treatment uric acid level (uric acid > 7 mg/dL versus <= 7 mg/dL), patients with hyperuricemia showed a more decrease in uric acid levels at 3-month compared to those with normouricemia (estimation = -1.072, p < 0.001, Figure 2).

Conclusion: These results showed that serum uric acid levels significantly decreased after anti-androgen therapy and suggest that male sex hormone could partially explain the gender difference in gout and hyperuricemia prevalence.

Keywords: Uric acid, hyperuricemia, gout, anti-androgen treatment

Table 1. Baseline characteristics

Characteristics	Anti-androgen treatment (n = 92)	No anti-androgen treatment (n = 46)	p-value
Age at treatment, years	71.62 ± 6.75	71.59 ± 6.17	0.978
Body mass index (n=122)	24.07 ± 2.66	24.16 ± 2.58	0.861
Comorbidities, n (%)			
Hypertension	50 (54.3)	25 (54.3)	1.000
Diabetes mellitus	24 (26.1)	15 (32.6)	0.643
Coronary artery disease	7 (7.6)	3 (6.5)	1.000
Dyslipidemia	5 (5.4)	2 (4.3)	1.000
Chronic kidney disease	1 (1.1)	1 (2.2)	1.000
Nephrolithiasis	3 (3.3)	0 (0)	0.551
Malignancy	8 (8.7)	4 (8.7)	1.000
Medication			
Hydrochlorothiazide	6 (6.5)	6 (13.0)	0.200
Aspirin	16 (17.4)	13 (28.3)	0.140
Clopidogrel	2 (2.2)	0 (0)	0.552
CCB	23 (25.0)	12 (26.1)	0.890
ARB	19 (20.7)	17 (37.0)	0.040
Statins	12 (13.0)	10 (21.7)	0.188
Anti-androgen treatment			
Bicalutamide + Goserelin	88 (95.7)		
Biclutamide + Leuprorelin	2 (2.2)		
Cyproterone + Goserelin	1 (1.1)		
Bicalutmide alone	1 (1.1)		
Baseline laboratory findings			
Uric acid	5.66 ± 1.46	5.30 ± 1.59	0.185
WBC	6.83 ± 1.80	6.55 ± 2.01	0.400
Hemoglobin	14.39 ± 3.72	14.24 ± 1.32	0.799
Platelet	219.24 ± 61.24	210.74 ± 50.60	0.389
BUN	16.68 ± 5.28	17.04 ± 5.04	0.703
Creatinine	1.08 ± 0.32	1.09 ± 0.24	0.845
GFR	73.25 ± 22.86	69.70 ± 15.22	0.343
Cholesterol	177.59 ± 39.95	167.72 ± 27.50	0.092
Protein	7.06 ± 0.60	7.05 ± 0.58	0.959
Albumin	4.22 ± 0.42	4.30 ± 0.36	0.253

CCB, calcium channel blocker; *ARB,* angiotensin II receptor blocker; *WBC,* white blood cell; *BUN,* blood urea nitrogen; GFR, glomerular filtration rate

Figure 1. Estimated uric acid levels of two groups (A) by unadjusted generalized estimation equation model and (B) adjusted generalized estimation equation model. The continuous line indicates uric acid levels of the patients with anti-androgen treatment, and the dashed line indicates uric acid level of those without anti-androgen treatment.

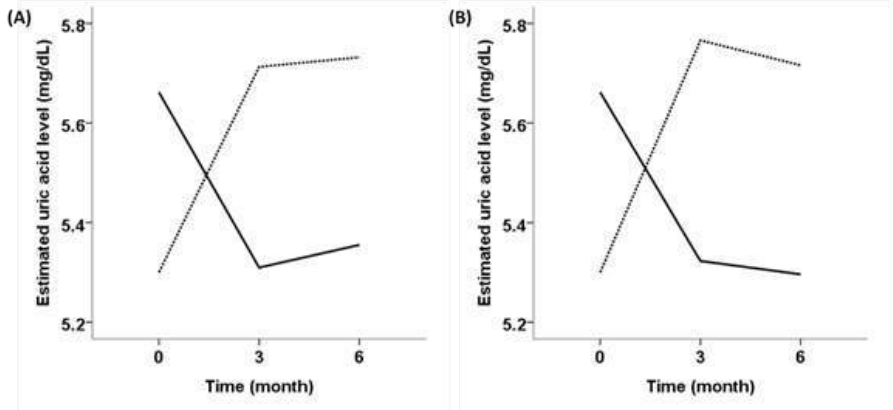
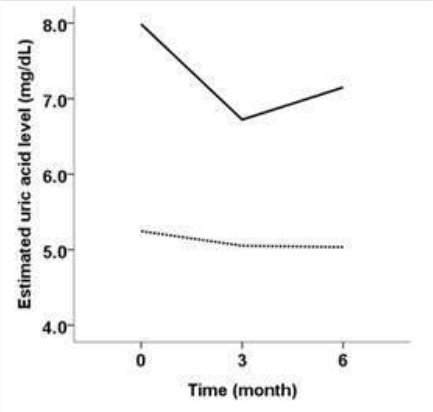


Figure 2. Estimated uric acid levels of patients with pre-treatment uric acid > 7.0 mg/dL (continuous line) and ≤ 7.0 mg/dL (dashed line).



Disclosure: J. H. Lee, None; **E. H. Park**, None; **S. W. Chung**, None; **J. Hur**, None; **Y. J. Ha**, None; **Y. W. Song**, None; **Y. J. Lee**, None.

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Abstract Number: 2297

Serum Urate and Its Association with Race in Young Adults: Baseline Analysis from a Randomized Clinical Trial

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Background/Purpose: Increased levels of serum urate (sUA) have been reported in association with hypertension, chronic kidney disease, and obesity. All these conditions are over-represented in US African Americans, who also have greater environmental risk factors for developing hyperuricemia including elevated fructose intake. Our group has previously reported that young African Americans have lower sUA concentrations than Caucasians after adjustment for clinical and demographic factors. **Objectives:** To determine whether there is a differential association between sUA and race in young adults.

Methods: We examined baseline data on consecutively enrolled individuals (age 18 – 40 years) in an interventional study aimed at lowering blood pressure (BP) through the administration of a urate-lowering therapy. African Americans were over-represented in the sample by study design. Enrollment criteria included a sUA of ≥

5.0 mg/dL for men or ≥ 4.0 mg/dL for women. After sUA means comparisons between African Americans and other races using t-test, we performed multivariable adjustments for age, sex, serum creatinine, and body mass index (BMI) in a multiple linear regression model.

Results: Sixty-nine participants recruited from Birmingham, AL were included in the analysis. Participants had a mean age (±standard deviation) of 29.0 ± 6.9 years, 30% were female, 43% were African Americans (AAs), and the mean BMI was 29.0 ± 6.0 kg/m². The mean sUA was 5.9 ± 1.1 mg/dL (range: 3.9 to 8.5 mg/dL). We found a significantly lower sUA for African Americans compared to persons of other races (5.5 ± 1.2 mg/dL vs 6.3 ± 1.0 mg/dL, p= 0.009). After multivariable analysis the difference in sUA between African Americans and other races was attenuated to non-significance (p= 0.33) due to the effects of BMI and sex. As expected, the association between sUA and sex was significant (Table).

Conclusion: In this cross-sectional analysis of young adults, African Americans had lower sUA concentrations than other races. However, in our model this difference is explained by the effect of sex differences in sUA and BMI. A potential limitation is that participants were enrolled after they met a sUA threshold so not all the ranges of sUA in a normal population are represented in this analysis. Larger studies will be needed to fully address this question. **Table. Multivariable regression model on the association between serum urate and race among young adults (n=69)**

Variable	Estimate (95% confidence interval)	p
Race (African-Americans versus other races)	-0.32 (-0.88 – 0.24)	0.3
Age (per year)	0.009 (-0.03 – 0.04)	0.6
Sex (men versus women)	1.44 (0.75 – 2.14)	<0.001
BMI (per unit of kg/m^2)	0.04 (0.01-0.08)	0.02
Serum creatinine (per milligram per deciliter)	0.42 (-1.17 - 2.03)	0.6

BMI= Body-mass index

Disclosure: M. B. Saddekni, None; **A. L. Gaffo**, US Government, 3,Cymabay, 5,Ardea, 5,Amgen, 2,AstraZeneca, 2; **P. J. Foster**, None; **E. J. Rahn**, None; **S. R. Biggers**, None; **P. Li**, None; **K. G. Saag**, Ardea/AstraZeneca, 5,Crealta, 5,Takeda, 5,Ardea/AstraZeneca, 2,Crealta, 2,Takeda, 2.

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Abstract Number: 2298

Incident Risk of Acute Gout Among Active Smokers: Data from Nationwide Inpatient Sample

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Background/Purpose: Smoking has been found to be negatively correlated with serum uric acid levels by virtue of reduced production and increased consumption of endogenous anti-oxidant uric acid among smokers and has been reported to decrease incidence of gout. We looked at the question of association between active smoking and acute gout by examining this association using a large inpatient US database.

Methods: We used the Nationwide Inpatient Sample (NIS) database (largest publicly available all-payer inpatient care database in the United States) from the years 2009-2011 to identify patients aged ³ 18 years without missing information for gender and age. Current smokers among them were selected using previously validated ICD-9 code 305.1. Hospitalizations with history of smoking but not active smoker were. Patients who developed acute gout during hospitalization were identified based on ICD-9 code 274.01 marked as a secondary diagnosis. Patients with acute gout as a primary diagnosis were excluded to prevent confounding from a group that may still have been actively smoking at the time of their flare. Univariate logistic regression was used to examine the previously reported confounding factors including age, sex, diabetes, hyperlipidemia, hypertension, chronic kidney disease (CKD), early menopause/post menopause, major organ transplant, obesity and alcohol. We then constructed a multivariable logistic regression using all factors with significant associations during univariate analysis (defined as $p<0.10$). STATA version 13.0 (College Station, TX) was used for analysis to accommodate for the complex design of survey sample data (NIS).

Results: A total of 17,847,045 discharge records were used in the analysis. Both univariate (OR 0.59, CI 0.54-0.63, $p<0.0001$) and multivariate (OR 0.64, CI 0.59-0.68, $p<0.0001$) regressions showed statistically significant reduction of acute gout incidence among hospitalized patients who were current smokers but were assumed to have ceased smoking during hospital stay.

Conclusion: Active tobacco use was associated with a lower risk of acute inpatient gouty arthritis, even when controlling for conventional risk factors. More study is needed to correlate this finding with uric acid levels, and a better understanding of the mechanisms that explain this finding are necessary. Figure 1: Selection process for discharges included in analysis

Incident acute gout	Odds Ratio	Standard Error	*p* value	95% Confidence Interval
Current smoking	0.59	0.02	**<0.0001**	0.54-0.63
Age	1.03	0.00	**<0.0001**	1.03-1.03
Male	3.14	0.07	**<0.0001**	3.01-3.27
CKD	6.32	0.14	**<0.0001**	6.04-6.61
Major Transplant	3.13	0.21	**<0.0001**	2.75-3.56
HTN	3.83	0.10	**<0.0001**	3.64-4.03
HLD	2.00	0.05	**<0.0001**	1.91-2.10
Alcohol use	1.47	0.07	**<0.0001**	1.34-1.61
Obesity	2.19	0.06	**<0.0001**	2.07-2.30
DM	2.39	0.05	**<0.0001**	2.29-2.49

Table 1: Univariate analysis (logistic regression) of incident acute gout in current smokers among hospitalized patients.

Incident acute gout	Odds Ratio	Standard Error	*p* value	95% Confidence Interval
Current smoking	**0.64**	0.02	**<0.0001**	0.59-0.68
Age	1.02	0.00	**<0.0001**	1.02-1.02
Male	2.62	0.05	**<0.0001**	2.52-2.73
CKD	3.55	0.09	**<0.0001**	3.38-3.73
Major Transplant	1.48	0.10	**<0.0001**	1.31-1.69
HTN	1.66	0.05	**<0.0001**	1.57-1.75
HLD	1.10	0.02	**<0.0001**	1.05-1.15
Alcohol use	2.27	0.10	**<0.0001**	2.08-2.48
Obesity	2.22	0.06	**<0.0001**	2.11-2.34
DM	1.18	0.03	**<0.0001**	1.13-1.23

Table 2: Multivariate logistic regression of incident acute gout among hospitalized patients.

Disclosure: D. Poudel, None; **P. Karmacharya**, None; **A. Donato**, None.

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Abstract Number: 2299

Predictors of Mortality in People with Recent Onset of Gout: A Prospective Observational Study

Zoe Vincent[1], Gregory Gamble[2], Meaghan House[2], Julie Knight[1], Anne Horne[2], William J. Taylor[3] and **Nicola Dalbeth**[1], [1]University of Auckland, Auckland, New Zealand, [2]Department of Medicine, University of Auckland, Auckland, New Zealand, [3]University of Otago, Wellington, New Zealand

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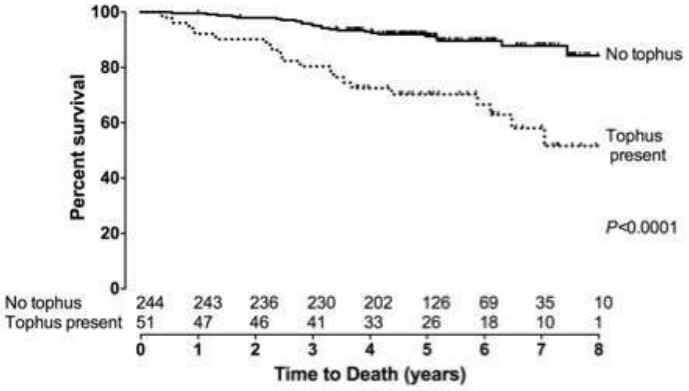
Background/Purpose: Many studies have reported that gout is associated with increased risk of cardiovascular events and mortality. However, information regarding gout disease severity is limited in these studies and it is unclear how gout impacts on mortality risk. The aim of this study was to determine mortality rates and predictors of mortality in people with recent onset of gout.

Methods: People with gout disease duration <10 years were recruited into a prospective observational study from primary and secondary care settings. Comprehensive clinical assessment was completed at baseline. Participants were prospectively followed for at least one year. Information about death was systematically collected from primary and secondary health records. Standardised mortality ratios (SMR) were calculated and risk factors for

mortality were analysed using Cox proportional hazard regression models.

Results: The mean (SD) follow-up duration was 5.1 (1.6) years (a total 1,511 patient years accrued). Of the 295 participants, 43 (14.6%) had died at the time of censorship (SMR 1.96 (95% CI 1.44, 2.62)). Of the 43 participants who died, 26 deaths (60.5%) were due to a cardiovascular cause and 17 (39.5%) were due to a non-cardiovascular cause. In Cox proportional hazards analysis, older age (70-80 years hazard ratio (HR) 5.71, 95% CI 2.02 to 16.19, *P*=0.001; 80-91 years HR 5.45, 95% CI 1.68 to 17.71, *P*=0.005), diuretic use (HR 3.09, 95% CI 1.63 to 5.87, *P*<0.001) and presence of subcutaneous tophi (HR 3.08, 95% CI 1.62 to 5.83, *P*<0.001, Figure) were independently associated with an increased risk of all-cause mortality. The presence of subcutaneous tophi was the only baseline variable independently associated with both cardiovascular cause of death (HR 2.90, 95% CI 1.29 to 6.51, *P*=0.01) and non-cardiovascular cause of death (HR 3.86, 95% CI 1.41 to 10.56, *P*=0.01).

Conclusion: People with gout disease duration <10 years have an increased risk of age/sex/ethnicity standardized death. The presence of subcutaneous tophi at baseline is an independent predictor of both cardiovascular and non-cardiovascular mortality. **Figure: Effect of tophi on all-cause mortality**. Kaplan–Meier survival plot comparing participants with tophi present at baseline with participants with no tophi at baseline for all-cause mortality. Time axis in years, unadjusted *P* value is shown.



Disclosure: Z. Vincent, None; **G. Gamble**, None; **M. House**, None; **J. Knight**, None; **A. Horne**, None; **W. J. Taylor**, None; **N. Dalbeth**, None.

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Abstract Number: 2300

Tophaceous Gout and the Risk of Mortality: A General Population-Based Study

Hyon K. Choi[1], Leo Lu[2], Sharan K. Rai[3,4] and Yuqing Zhang[5], [1]Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [2]Allergy, Immunology, and Rheumatology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [3]Arthritis Research Canada, Vancouver, BC, Canada, [4]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [5]Clinical Epidemiology and Training Unit, Boston University School of Medicine, Boston, MA

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Tophaceous Gout and the Risk of Mortality: A General Population-Based Study

Background/Purpose: A recent study based on data from a gout specialty clinic (N=706) found that patients with tophi (N=215) had a two-fold increased risk of mortality compared to those without tophi. However, no population-based data are available on the topic. We evaluated the mortality impact of tophaceous gout in a general population context.

Methods: Using an electronic medical record database representative of the UK general population, we identified tophaceous gout cases (based on physician diagnosis) and up to 5 non-tophaceous gout controls matched on sex, age, gout duration, and entry time between January 1, 1995 and December 31, 2015. We calculated mortality rates and hazard ratios (HRs) using a Cox proportional hazard model to adjust for demographics, lifestyle factors, comorbidities, medications, and healthcare use. We conducted subgroup analyses based on age (≤70 and >70) and sex.

Results: Among 618 patients with tophaceous gout (55% men, mean age=73 years), the mortality rate was 64.7 deaths/1000 person-years, whereas among 2850 matched gout patients (56% men, mean age=73 years), the corresponding mortality rate was 45.5 deaths/1000 person-years. Tophaceous gout was associated with a 60% increased risk of mortality (HR=1.60; 95% CI, 1.29-1.97) compared to those without tophi. After adjusting for covariates, these estimates remained similar (HR=1.60; 95% CI, 1.28-1.99). Those in the younger age group (≤70 years) and who were male tended to have a larger HR (**Table 1**).

Conclusion: This general population-based cohort study indicates that tophaceous gout is associated with an increased risk of death among gout patients, particularly among those who are younger (≤70) or male. Total urate burden as well as morbidity and functional decline associated with chronic tophaceous gout may explain the increased mortality.

Table 1. Mortality Rates and Hazard Ratios among Gout Patients according to Tophi Status

	Tophi status	N	Deaths	Follow-up time (PY)	Mean follow-up (PY)	Mortality rate/1000 PY (95%CI)	Unadjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)
Total	Yes	618	168	2598	4.20	64.67 (55.26 to 75.23)	1.60 (1.29 to 1.97)	1.60 (1.28 to 1.99)
	No	2850	590	12957	4.55	45.53 (41.93 to 49.36)	1.0 (reference)	1.0 (reference)
Male	Yes	342	86	1537	4.50	55.94 (44.74 to 69.08)	1.74 (1.30 to 2.32)	1.75 (1.28 to 2.39)
	No	1597	261	7875	4.93	33.14 (29.25 to 37.42)	1.0 (reference)	1.0 (reference)
Female	Yes	276	82	1060	3.84	77.34 (61.51 to 96.01)	1.48 (1.09 to 2.00)	1.40 (1.02 to 1.93)
	No	1253	329	5083	4.06	64.73 (57.92 to 72.11)	1.0 (reference)	1.0 (reference)
≤70	Yes	205	30	1210	5.90	24.79 (16.72 to 35.38)	1.81 (1.09 to 3.02)	2.35 (1.25 to 4.40)
	No	872	84	5358	6.14	15.68 (12.50 to 19.41)	1.0 (reference)	1.0 (reference)
>70	Yes	413	138	1387	3.36	99.47 (83.57 to 117.52)	1.55 (1.23 to 1.95)	1.58 (1.24 to 2.02)
	No	1978	506	7599	3.84	66.58 (60.91 to 72.65)	1.0 (reference)	1.0 (reference)
Abbreviations: PY—person-years; CI—confidence interval; HR—hazard ratio.								

Disclosure: H. K. Choi, None; **L. Lu**, None; **S. K. Rai**, None; **Y. Zhang**, None.

Abstract Number: 2301

Gout and Subsequent Risk of Incident Erectile Dysfunction: A Population-Based Cohort Study from the United Kingdom

Alyshah Abdul Sultan[1], Christian Mallen[2], Richard Hayward[1], Sara Muller[2], Rebecca Whittle[3], Matthew Hotston[4] and **Edward Roddy**[2], [1]Research Institute of Primary Care & Health Sciences, Keele University, Keele, United Kingdom, [2]Research Institute for Primary Care and Health Sciences, Keele University, Keele, United Kingdom, [3]Research Institute for Primary Care and Health Sciences, Keele University, Stoke-on-Trent, United Kingdom, [4]Urology, Royal Cornwall Hospital, Truro, United Kingdom

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Background/Purpose: Gout is the most prevalent inflammatory arthritis, affecting 2.4% of adults in the UK. Recently, a link has been suggested between gout and erectile dysfunction (ED), however studies quantifying ED reporting by gout patients are lacking. The aim of this study was to determine the population level absolute and relative rates of ED reporting by patients with gout over a decade in England.

Methods: Utilising data from one of the largest English primary care consultation databases (Clinical Practice Research Datalink), we identified 9,653 men with incident gout and matched them to 38,218 controls (ratio 1:4) by age and practice. Absolute and relative rate of incident ED was calculated using Cox regression models. Absolute rates within specific time periods before and after gout diagnosis were compared to controls using Poisson regression models.

Results: Overall, the absolute rate of ED post-gout diagnosis was 193 (95% Confidence interval (CI): 184-202) per 10,000 person-years. This corresponded to a 31% (Hazard Ratio (HR) = 1.31 95%CI: 1.24-1.40) increased relative risk and 0.6% excess absolute risk compared to those without gout (Table 1). Among those prescribed urate-lowering therapy, the risk of ED was similar for cases and controls (HR=1.10 95CI: 1.01-1.19). Compared to controls, the risk of ED was also high in the year before gout diagnosis (incidence rate ratio= 1.63 95%CI 1.27-2.08). Our relative risk estimates remained broadly similar when we restricted our analyses to those with ED treated with medication.

Conclusion: We have shown a statistically significant increased risk of ED among men with gout, however, the absolute risk difference is small indicating limited influence of disease on ED. Clinicians should be aware that higher reporting of ED before gout diagnosis suggests a possible influence of hyperuricemia on arterial vasculature warranting further investigations. Overall our finding are reassuring to patients and clinicians.

Table 1: Absolute and relative rate of Erectile Dysfunction after gout diagnosis

Variable	Cases Rate[1] (95% CI)	Controls Rate (95% CI)	Hazard Ratio[2] (95% CI)	Absolute risk difference[1]
Overall Erectile Dysfunction				
All ages	192.8 (184.0-202.1)	136.2 (132.1-140.4)	1.31 (1.24-1.40)	56.6
≤34	61.4 (45.4-127.4)	34.6 (27.3-43.9)	1.20 (0.79-1.83)	26.8
35 – 44	112.4 (99.5-127.4)	76.2 (70.1-82.8)	1.18 (1.01-1.39)	36.4
45 – 54	211.7 (196.1-228.6)	146.0 (138.6-153.5)	1.28 (1.16-1.41)	65.7
55 – 64	262.8 (245.1-281.4)	186.3 (178.3-194.8)	1.37 (1.25-1.49)	76.5
Medication treated Erectile Dysfunction				
All ages	80.2 (77.1-83.5)	113.7 (107.0-120.9)	1.36 (1.26-1.47)	33.5
≤34	16.3 (11.5-23.0)	33.6 (22.4-50.9)	1.24 (0.67-2.29)	17.3
35 – 44	45.7 (41.1-51.0)	62.4 (52.8-73.6)	1.11 (0.89-1.37)	16.6
45 – 54	87.1 (81.6-92.9)	126.8 (114.8-140.0)	1.30 (1.15-1.47)	39.7
55 – 64	108.8 (102.7-115.3)	156.7 (143.2-171.5)	1.46 (1.30-1.64)	47.9

[1]Per 10,000 person-years [2]Adjusted for smoking status, Alcohol consumption, Body Mass Index, age, Ischemic heart disease, chronic diseases, hypertension, diabetes and depression.

Disclosure: A. Abdul Sultan, None; **C. Mallen**, None; **R. Hayward**, None; **S. Muller**, None; **R. Whittle**, None; **M. Hotston**, None; **E. Roddy**, None.

Abstract Number: 2303

Trends in Gout and Rheumatoid Arthritis Hospitalizations in Canada from 2000-2011

Sharan K. Rai[1,2], J. Antonio Avina-Zubieta[2,3], Natalie McCormick[2,4], Mary A. De Vera[2,5], Diane Lacaille[2,6], Eric C. Sayre[2] and Hyon K. Choi[7,8], [1]Experimental Medicine, University of British Columbia, Vancouver, BC, Canada, [2]Arthritis Research Canada, Richmond, BC, Canada, [3]Division of Rheumatology, Department of Medicine, University of British Columbia, Vancouver, BC, Canada, [4]Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [5]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada, [6]Medicine, University of British Columbia, Vancouver, BC, Canada, [7]Division of Rheumatology, Allergy, and Immunology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, [8]Arthritis Research Canada, Vancouver, BC, Canada

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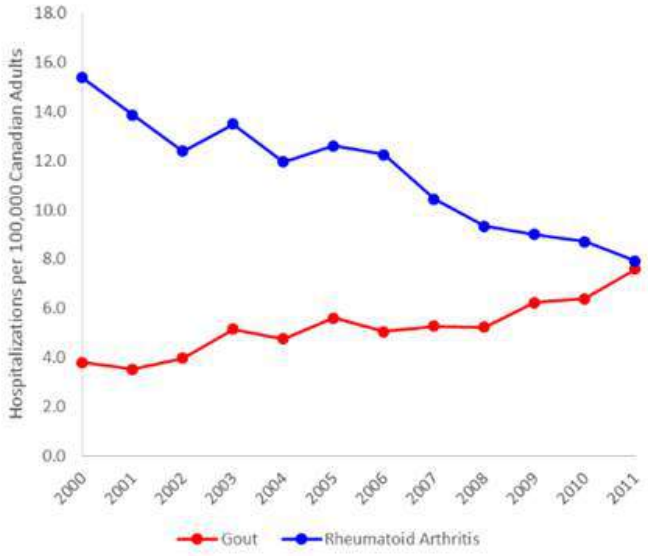
Background/Purpose: Gout and rheumatoid arthritis (RA) are the two most common forms of inflammatory arthritis worldwide. As hospitalizations for both conditions lead to substantial health resource use, contemporary inpatient trends and associated costs may provide important benchmarks of disease burden. However, relevant data are limited. We evaluated contemporary hospitalization trends for gout and RA in a Canadian general population context.

Methods: We used PopulationData BC, a population-based dataset spanning the entire Canadian province of British Columbia. We included patients at least 18 years of age who were hospitalized from 2000-2011 with a principal diagnosis of either gout (ICD-9-CM 274 or ICD-10-CA M10) or RA (ICD-9-CM 714 or ICD-10-CA M05 or M06). We calculated annual rates of hospitalizations (expressed per 100,000 Canadian adults) for gout and RA. We assessed the trend of total hip and knee replacements among study patients. We evaluated the inpatient economic burden for both conditions. Costs were inflation-adjusted to 2011 Canadian dollars. We assessed all annual trends using Poisson and linear regression models.

Results: From 2000 to 2011, the annual hospitalization rate for those with a principal diagnosis of RA declined by 49% from 15.4 to 7.9 per 100,000 Canadian adults ($p<0.001$), whereas that for gout increased by 100% (i.e., doubled) from 3.8 to 7.6 per 100,000 Canadian adults ($p<0.001$) **(Figure)**. Thus, at the beginning of the study period, hospitalizations for RA were approximately 4 times more frequent than those for gout; however, these opposing trends of the two conditions led to similar hospitalization rates by 2011 (i.e., 7.9 and 7.6 per 100,000 Canadian adults for RA and gout, respectively). Approximately 31% of hospitalizations with a principal diagnosis of RA were associated with total hip or knee replacement. From 2000 to 2011, the rate of these surgeries in patients with a principal diagnosis of RA decreased from 3.8 to 2.9 per 100,000 Canadian adults ($p=0.0097$). In contrast, less than 1% of hospitalizations with a principal diagnosis of gout were associated with total hip or knee replacement. The inflation-adjusted inpatient costs associated with a principal diagnosis of gout more than doubled

over the study period from $19,426 to $43,783 (2011 CAD) per 100,000 Canadian adults (p<0.001), whereas those for RA decreased by 40% from $103,314 to $62,348 per 100,000 Canadian adults (p=0.0023) over the same period.

Conclusion: Our findings indicate that hospitalization rates for gout have doubled over the past decade, while those for RA have decreased considerably. While these data provide an encouraging benchmark for RA care, they also highlight the critical need to improve gout management and prevention to mitigate its rising disease burden in



Canada and beyond.

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Abstract Number: 2304

Decreased Occurrence of Colon Cancer Among Gout Patients: Assessment By Physician Diagnosis and Colonoscopy

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Background/Purpose: The relationship between gout and cancer remains unclear. Whereas some studies have reported possible anti-cancer benefits of uric acid and monosodium urate crystals, others have found an increased risk of cancer in gout patients. Our study aimed to clarify the relationship between gout and colon metaplasia, including cancer and polyps.

Methods: We conducted a retrospective study of patients in a VA hospital system using two distinct approaches. To obtain a historical, cross-sectional view of colon cancer prevalence, we assessed the presence of physician-coded diagnoses of colon cancer and/or polyps in gout patients, versus patients with osteoarthritis (OA) but no gout, with active records in our computerized patient record system (CPRS) between 2007 and 2008. Lung and prostate cancer prevalence were recorded for comparison. In the second approach, we included only patients with documented colonoscopy reports in CPRS, and performed a retrospective cohort study of colon cancer and polyp incidences in gout versus OA patients over a ten-year period (2001-2010). In addition, colon cancer and polyp incidences were compared between patients who had undergone screening versus diagnostic colonoscopy, those who used aspirin or NSAIDs and those who did not, and between gout patients who used allopurinol and/or colchicine and those who did not.

Results: 1287 gout patients and 1287 OA patients were included. Gout and OA patients were similar in age, ethnicity, BMI and smoking history. Gout patients had a lower physician-coded prevalence of all colonic lesions (cancer or polyp: 1.8 versus 9.6%, $p<0.001$), and a lower prevalence of colon cancer (1.0 versus 1.9%, $p<0.001$), than OA patients (Figure A). Lung and prostate cancer were similar between the two groups. Among 581 gout patients and 598 OA subjects with documented colonoscopies, the ten-year incidence of colon cancer was lower in gout patients than in patients with OA (0.8 versus 3.7%, $p=0.0008$) (Figure B). This difference in colon cancer incidence remained significant after accounting for NSAID and/or aspirin use. Among gout patients, the use of colchicine and/or allopurinol, as well as the presence or absence of concomitant of OA, did not appear to influence colon cancer prevalence. Differences in colon cancer incidence were significant between gout and OA patients undergoing diagnostic colonoscopy (0.5% in gout patients versus 4.6% in OA patients, $p<0.001$) but not those undergoing screening colonoscopy (0.9% in gout patients versus 1% in OA patients, $p=1.0$). No protective effect of gout was observed for prostate or lung cancer.

Conclusion: Patients with gout had decreased physician-reported prevalence, and colonoscopy-documented incidence of colon cancer compared to patients with OA, suggesting a possible protective effect of gout or a gout-associated clinical, epidemiological or genetic factor.

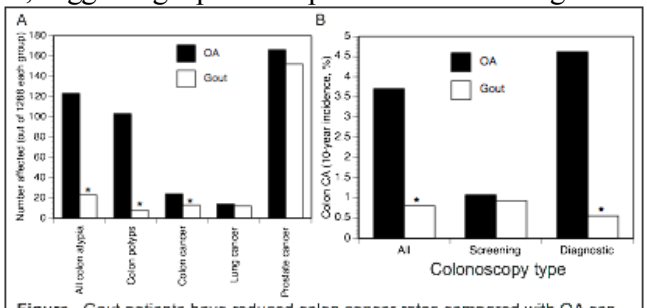

Figure. Gout patients have reduced colon cancer rates compared with OA controls. A, Prevalence based on physician documentation. B, Incidence based on colonoscopy results. *=p<0.01 compared with OA.

Disclosure: A. Slobodnick, None; **S. Krasnokutsky Samuels**, None; **A. Lehmann**, None; **R. Keenan**, None; **F. Francois**, None; **M. H. Pillinger**, None.

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Abstract Number: 2305

Mapping the Topography of Gout Flares: Solutions for Flare Reporting in Gout Clinical Trials

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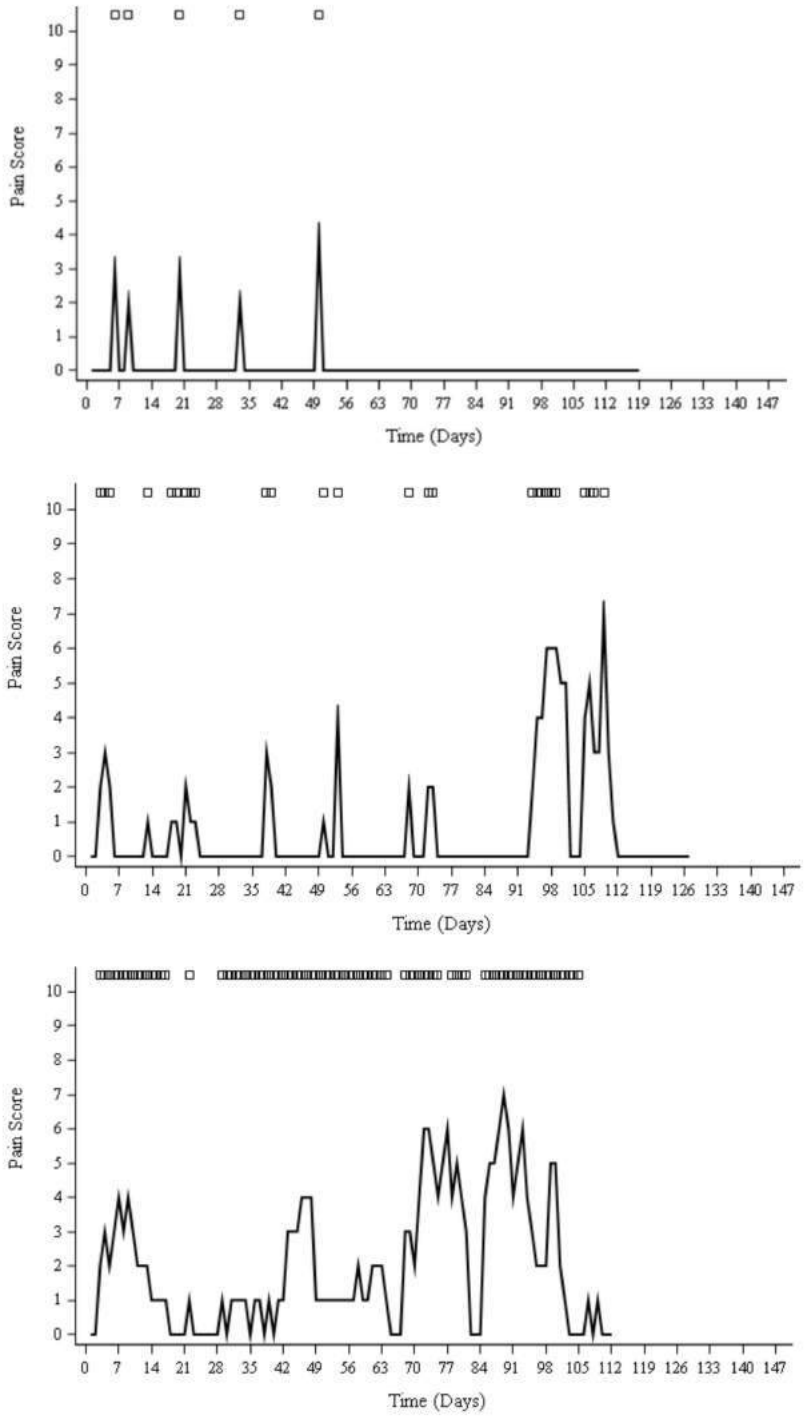
Background/Purpose : Recurrent flares of inflammatory arthritis are the central clinical feature of gout. However, methods of gout flare reporting in research settings are inconsistent and poorly defined. The aim of this study was to map patterns of gout flare and assess the concurrent validity of different methods of flare reporting by comparison with other methods of gout disease activity.

Methods: Flare diary entries from a randomised controlled trial of patients with gout were analysed. Over a four-month period, participants (n=120) completed daily flare diary entries with recording of self-report of flare, pain score (Likert scale 0-10) and medications taken for flare. The time-course domain in the 2015 ACR/EULAR gout classification criteria was used to define the time elements of a typical flare (time to maximal pain <24 hours, resolution of symptoms in ≤14 days, complete resolution between symptomatic episodes). Pain x time plots for each individual participant were inspected and analysed for six methods of flare reporting including flare count, time to first flare, number of days with self-reported flare, number of days with self-reported flares requiring medication, number of days with Gaffo-defined flare (CART approach: pain score >3 and self-report)[1], and area under the pain-time curve (AUC pain). Concurrent validity assessment included correlation analysis of these methods of reporting with other measures of gout activity measured monthly over the same time period (area under the curve (AUC) variable-time plot analysis); patient and physician global assessments, joint counts, and C-reactive protein (CRP).

Results: Inspection of individual plots showed wide variation in the severity, frequency and duration of flare (Figure), with only 55/120 (45.8%) experiencing predominantly typical flares over the four-month study period. Flare counts over time could not be reliably calculated due to difficulty determining the boundaries of individual flares for some participants. Time to first flare correlated poorly with other measures of gout activity. In contrast, all other tested methods of flare reporting significantly correlated with other measures of gout activity; AUC pain correlated most strongly with AUC CRP ($r=0.43$, $P<0.001$), and number of days of self-reported flare correlated most strongly with other measures of disease severity (AUC patient global 0.62, AUC physician global 0.62, AUC tender joint count 0.53, AUC swollen joint count 0.44, $P<0.001$ for all).

Conclusion: There is wide variation in the patterns of flare over time in individuals with gout, leading to challenges for flare reporting in clinical trials. Time-dependent reporting strategies such as the number of days in self-reported flare correlate well with other measures of gout disease severity and may provide a more accurate measure of severity of flare burden over time. **Reference:** Gaffo et al A&R 2012

Figure. Pain-time plots from three separate individuals showing the variation in patterns of flare. Dots represent days with self-report of flare.



Disclosure: **N. Teoh**, None; **G. Gamble**, None; **A. Horne**, None; **W. J. Taylor**, None; **K. Palmano**, Fonterra Co-operative Group Ltd, 3; **N. Dalbeth**, None.

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Abstract Number: 2306

Improving Predictive Value of Gout Case Definitions in Electric Medical Records Utilizing Natural Language Processing: a Novel Informatics Approach

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Background/Purpose: To date, most of the models used to identify gout cases within large administrative databases have relied solely only on administrative billing codes. The positive predictive value (PPV) of these models ranged from 33-86%. Natural language processing (NLP) is a range of computational techniques for analyzing and representing naturally occurring written or oral text for the purpose of achieving human-like language processing for a range of tasks or applications. In this study we aimed to develop and validate an algorithm that accurately identifies gout patients within the Partners biobank database using both codified data and information from clinical text notes using NLP.

Methods: To create a gold-standard training set, a training set of 200 patients was created. Two rheumatologists reviewed the electric medical records of the 200 patients and classified them as having the disease (Y), probably having the disease (P), not having the disease (N) or unable to make a classification (U). We used the clinician-reviewed classifications to train models to predict the probability of a gout diagnosis or no gout on the basis of a logistic regression classifier with the adaptive least absolute shrinkage and selection operator (LASSO) procedure to select informative variables. We constructed three separate models to predict a diagnosis of gout in our partners biobank cohort- (1) model utilizing number of gout ICD-9 codes alone (ICD-9 model), (2) model comprising all codified variables including disease complications (codified model) (3) a combined model including both codified and NLP variables (combined model).

Results: The area under the curve (AUC) for the combined model was 0.901 (95% CI 0.830-0.972), with a sensitivity of 0.936 at a positive predictive value cut-off of 0.902. The AUC of the ICD-9 model was 0.721 (95% CI 0.617-0.825), while that of the codified model was 0.879 (95% CI 0.806-0.952). Addition of NLP narrative terms to our final model resulted in improving the sensitivity to 0.936 from 0.89, at the same PPV level of 0.902, thus resulting in improved identification of gout cases by 4.12%, compared to the codified model. On review of medical records from an additional random set of 50 patients each predicted to have gout by the combined model, 44 were correctly identified as having this diagnosis through chart review resulting in a positive predictive value of 88%.

Conclusion: Including narrative concepts from natural language processing improves the accuracy of EMR case-definition for gout while simultaneously identifying more subjects compared to models using codified data alone.

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Abstract Number: 2307

Influence of Season and Residential Environment on Development of Anti-Melanoma Differentiation-Associated Gene 5 Antibody-Positive Dermatomyositis with Interstitial Lung Disease

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Background/Purpose: Environmental triggers such as infection are considered to be involved in pathogenesis of polymyositis (PM) and dermatomyositis (DM). This study was aimed to investigate influence of season and residential environment on development of PM/DM-associated interstitial lung disease (ILD), in association with myositis-specific autoantibodies.

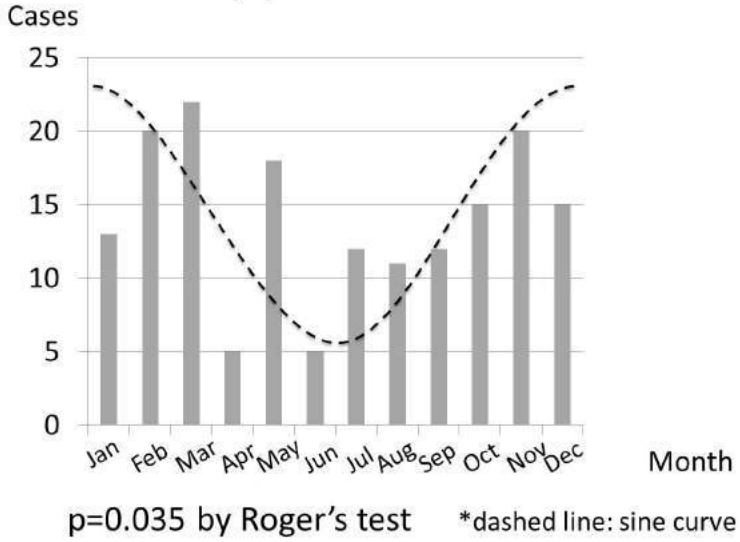
Methods: This study used data recorded in a multicenter retrospective cohort of Japanese patients with PM/DM-associated ILD (JAMI cohort), which involved 44 institutions across Japan. Inclusion criteria of the JAMI cohort were adult-onset, definite or probable PM/DM including clinically amyopathic DM (CADM), ILD confirmed by imaging, and availability of serum samples at diagnosis. Demographic and clinical information was retrospectively collected by chart review, and sera were subjected to autoantibody assays; ELISA for anti-melanoma

differentiation-associated gene 5 (MDA5) and RNA immunoprecipitation for anti-aminoacyl-tRNA synthetase (ARS), including Jo-1, PL-7, PL-12, EJ, OJ, and KS. Seasonality was assessed by Roger's test in patients who developed the disease in the past 5 years. As for residential environment, we evaluated if patients' residence at disease onset was close to the major freshwater sites. The waterfront was defined as area within 1.75 km from large river, lake, or pond calculated on the Google map.

Results: Of 498 patients enrolled, anti-MDA5 and anti-ARS antibodies were detected in 212 (42%) and 165 (33%), respectively. Since one had both antibodies, 122 (24%) were regarded as the anti-MDA5/ARS-negative group. Anti-MDA5-positive patients represented a higher frequency of CADM (76% versus 24% or 30%; P <0.01 for both comparisons), and a lower cumulative survival rate at 6 months (67% versus 97% or 96%; P <0.01 for both comparisons), compared to anti-ARS-positive or anti-MDA5/ARS-negative group. Interestingly, seasonality of the disease onset was found in anti-MDA5-positive patients (P = 0.035, Figure1): more cases developed the disease in autumn/winter than in spring/summer, but not in anti-ARS-positive or anti-MDA5/ARS-negative group (P = 0.73 and 0.59, respectively). Clinical features were comparable between anti-MDA5-positive patients who developed the disease in autumn/winter and those who developed in spring/summer. The proportion of patients who resided in freshwater waterfront at disease onset was significantly higher in anti-MDA5-positive group than in anti-ARS-positive or anti-MDA5/ARS-negative group (65% versus 50% or 50%; P <0.01 for both comparisons).

Conclusion: Anti-MDA5 antibody-positive DM-associated ILD developed predominantly in autumn/winter and clustered around freshwater waterfront, suggesting roles of environmental triggers in development of the disease.

Figure 1. Month of onset of anti-MDA5 antibody positive cases



Disclosure: **N. Nishina**, None; **S. Sato**, anti- MDA5 antibody-measuring kit, 9; **Y. Kawaguchi**, None; **A. Kawakami**, None; **M. Tamura**, None; **K. Ikeda**, None; **T. Nunokawa**, None; **Y. Tanino**, None; **K. Asakawa**, None; **Y. Kaneko**, None; **T. Gono**, None; **K. Masui**, None; **M. Kuwana**, anti- MDA5 antibody-measuring kit, 9.

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Abstract Number: 2308

Thigh Muscle MRI Reveals Extensive Muscle Edema and Early Fatty Replacement in Patients with Immune-Mediated Necrotizing Myopathy

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Background/Purpose: The aim of this study was to define the pattern of muscle involvement in patients with immune-mediated necrotizing myopathy (IMNM).

Methods: All Johns Hopkins Myositis Longitudinal Cohort subjects with an available thigh magnetic resonance imaging (tMRI) who fulfilled criteria for IMNM, dermatomyositis (DM), polymyositis (PM), clinically amyopathic DM (CADM) or inclusion body myositis (IBM) were included in the study. Fifteen muscles were assessed by tMRI for the presence or absence of edema, atrophy, fatty replacement, and fascial edema. Disease subgroups were compared using univariate and multivariate analysis. Within IMNM, patients with anti-SRP and anti-HMGCR were also compared.

Results: The study included 666 subjects (101 IMNM, 176 PM, 219 DM, 17 CADM and 153 IBM). Compared to patients with DM or PM, IMNM was characterized by a higher proportion of thigh muscles with edema, atrophy, and fatty replacement ($p<0.01$), independent of other confounding variables. Compared with anti-SRP, anti-HMGCR patients showed a lesser proportion of muscles with atrophy (-9%, $p=0.04$). In IMNM, muscle abnormalities were especially common in the lateral rotator and gluteal groups. Fascial involvement was more widespread in DM. Interestingly, fatty replacement of muscle tissue began early during the course of IMNM as well as the other muscle diseases. Although it had a negative predictive value of 93%, an optimal combination of tMRI features had only a 55% positive predictive value for diagnosing IMNM.

Conclusion: Compared to patients with DM or PM, IMNM is characterized by more widespread muscle involvement. Compared with anti-HMGCR, anti-SRP patients seem to have more severe muscle involvement.

Abstract Number: 2309

Focal Myositis: New Insights on Diagnosis and Pathology

Laure Gallay[1], Philippe Petiot[2], Arnaud Hot[3], Francoise Thivolet-Bejui[4] and Nathalie Streichenberger[4], [1]Department of Internal Medicine, Edouard Heriot University Hospital, Hoscpices Civils de Lyon, Lyon cedex 03, France, [2]Department of Neurology, Croix-Rousse Hospital, Hospices Civils de Lyon, Lyon, France, [3]Department of Internal Medicine, Edouard Herriot University Hospital, Hospices Civils de Lyon, Lyon cedex 03, France, [4]Department of Pathology, Neurology and Neurosurgery Pierre Wertheimer University Hospital, Hospices Civils de Lyon, Bron, France

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Background/Purpose: Due to the rarity of the entity, the literature on focal myositis (FM) fails to address important questions on its nosology, associated disorders, clinical presentation and therapeutic management. We sought to shed light on clinical, pathological, and therapeutic features of FM through the analysis of data from a large patient cohort.

Methods: We searched for confirmed cases of FM in the Lyon University Hospital's database of patients diagnosed with myositis since year 2000. FM was diagnosed as per the usual clinicopathological definition. Clinical, serological, imaging, pathological and therapeutic data were collected. When missing from the original pathological analysis, complementary immunohistochemistry was redone when possible.

Results: Of the 810 patients included in the myositis database, 36 (4.4%) had confirmed FM (22 males, 14 females, mean age=45) (Figure 1.A). The main clinical signs were focal muscular pain (78%), fever (28%) and local erythema (36%). Serum creatine kinase was usually normal (81%); conversely, serum immunological abnormalities (mild to marked inflammation as determined by ESR or CRP, autoantibodies such as anti nuclear or anti-extractable nuclear antigen, and dysglobulinemia) were found in the sera of 58% of the patients. Beyond confirming previously-reported findings, the pathological analyses also illustrated significant rates of vascularitis within the muscle (73%) and fasciitis (75%). While FM's etiopathogeny remains enigmatic, this study highlighted frequent association with immune-mediated inflammatory disease (IMID) (39%), neoplasia (19%), radiculopathy (14%) and trauma (8%) (Figure 1.B). IMID included Behcet's disease (n=5), various inflammatory rheumatic diseases (n= 5) and others. Neoplasms were solid cancers in six cases (bladder n=2, thyroid n=1, skin n=1, prostate n=1, and adenocarcinoma of unknown primary site n=1), and hemopathies in two (one had both). Contrasting with the usual perception, two-thirds of the cohort required immunosuppressive therapy. As first line, all patients received steroids. The recurrence rate was 36%. In case of refractory disease, or frequent relapses, a second line was considered with azathioprine, methotrexate, intravenous immunoglobulin or cyclophosphamide. Interestingly, when underlying disease was present, the FM clinical course was often correlated with the associated pathology evolution.

Conclusion: This study provides new clinic-pathological features to define FM. Despite of the classic view of a seldom painful and spontaneously resolving disorder, this work suggests that FM can be a serious disease and require active treatment. Moreover, these results suggest that FM patients should receive IMID and neoplasia screening.

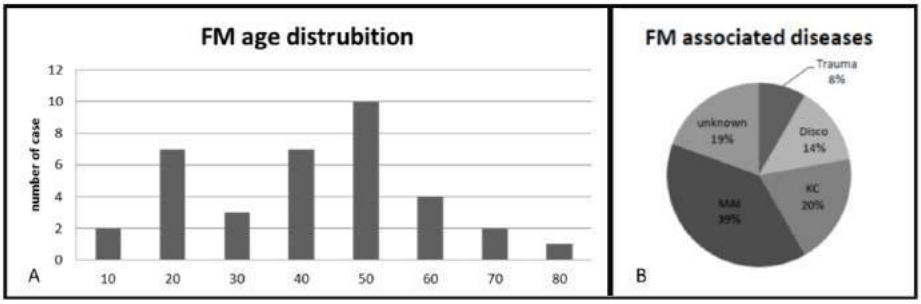

Figure 1. A. Age distribution in FM cohort. B. Associated disease distribution in the cohort.

Disclosure: L. Gallay, None; **P. Petiot**, None; **A. Hot**, None; **F. Thivolet-Bejui**, None; **N. Streichenberger**, None.

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Abstract Number: 2310

The Predictive Risk Factors for Complication of Infection during the Treatment for Inflammatory Myopathies Complicated with Interstitial Lung Disease

Yumiko SUGIYAMA[1,2], Maasa Tamura[1,2,3], Ryusuke Yoshimi[1,2], Naoki Hamada[1,2], Hideto Nagai[1,2], Yuko Tatekabe[1,2], Naomi Tsuchida[2,4], Yutaro Soejima[1,2], Yosuke Kunishita[2,4], Daiga Kishimoto[1,2], Hiroto Nakano[1,2], Reikou Kamiyama[1,2], Kaoru Minegishi[2,5], Yukiko Asami[1,2], Yohei Kirino[2,4], Shigeru Ohno[2,5] and Hideaki Nakajima[1], [1]Department of Stem Cell and Immune Regulation, Yokohama City University Graduate School of Medicine, Yokohama, Japan, [2]Y-CURD Study Group, Yokohama, Japan, [3]Nagaoka Red Cross Hospital, Nagaoka, Japan, [4]Department of Hematology and Clinical Immunology, Yokohama City University School of Medicine, Yokohama, Japan, [5]Center for Rheumatic Disease, Yokohama City University Medical Center, Yokohama, Japan
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Background/Purpose: Interstitial lung disease (ILD) is one of the predominant causes of death in polymyositis/dermatomyositis (PM/DM). We have already reported that low P_aCO_2 and interstitial lesions in more cranial zone of lungs are independent prognostic factors for ILD associated with PM/DM (PM/DM-ILD), and the most common causes of death in early stage are respiratory failure and infection. Here we investigated the predictive factors for complication of infection during treatment for PM/DM-ILD.

Methods: We retrospectively analyzed clinical features, laboratory and high-resolution computed tomography (HRCT) findings at baseline, initial therapeutic regimens, clinical outcomes, and episode of serious infection of patients with PM/DM-ILD who had received initial treatment at the two hospitals belonging

to Yokohama City University from 1993 to 2015. The lungs were horizontally divided into 4 zones (Zone A to D from more cranial area) in HRCT, and severity of ILD lesions were evaluated in each zone.
We conducted univariate and multivariate analyses to extract risk factors for death and infection.

Results: One hundred six patients (PM 19, DM 49, clinically amyopathic DM (CADM) 38) were recruited. The mean age was 55 +/- 14 years, and 77 (73%) were female. As initial therapies, oral prednisolone (PSL) was prescribed in all patients. Methylprednisolone (mPSL) pulse, intravenous cyclophosphamide (IVCY), and oral calcineurin inhibitor therapies were performed in 77 (73%), 43 (41%) and 73 (69%), respectively. Thirty-seven (35%) received combination therapy with IVCY and a calcineurin inhibitor. Forty patients (38%) had a total of 54 events of serious infection at 40 +/- 26 days from initiation of immunosuppressants. The foci of infection were seen most commonly in lung
(bacterial pneumonia 19, pulmonary suppuration 2, pneumocystis pneumonia 9, CMV infection 15, and the others 9). Lower serum albumin level ($p = 0.01$), higher serum CRP, LDH, KL-6 levels ($p = 0.01$, $p = 0.001$, $p = 0.01$, respectively), high initial dose of PSL ($p = 0.01$), mPSL pulse ($p = 0.02$), IVCY ($p <$
0.001), and combined immunosuppressants ($p = 0.04$) were extracted as risk factors for infection by univariate analyses (Table 1). There was no significant relation between severity of ILD and infection. A multivariate logistic regression analyses revealed that the high initial dosage of PSL ($p = 0.003$, hazard ratio 6.21) and higher serum LDH level ($p = 0.017$, hazard ratio 4.08) were independent risk factors for infection. Of 11 patients, who died within 6 months, four (36%) were died of infection.

Conclusion: Although rapid and intensive therapies are required for PM/DM-associated ILD, appropriate monitoring, prophylaxis and early treatment for infection are important, especially in patients who received high-dose of initial glucocorticoid and showed higher serum LDH level.

Table 1. Demographic, clinical, and laboratory features of 106 patients with PM/DM-ILD

Variable	Infection (+) ($n = 40$)	Infection (-) ($n = 66$)	P
Woman	26 (65%)	52 (79%)	0.09
Age (year)	58 ± 13[c]	53 ± 13[c]	0.11
Disease type	PM: 4, DM: 26, CADM: 10	PM: 14, DM: 23, CADM: 28	0.01*
Death	13 (33%)	9 (14%)	0.02*
Laboratory data			
CK (U/L)	324 [120 - 923][f]	195 [76 - 1622][f]	0.55
LDH (U/L)	520 [329 - 676][f]	313 [252 - 454][f]	0.001*
KL-6 (U/mL)	851 [613 - 1242][f]	628 [416 - 867][f]	0.01*
Albumin (g/dL)	3.3 ± 0.6[c]	3.6 ± 0.5[c]	0.01*
CRP (mg/dL)	0.9 [0.26 - 2.64][f]	0.29 [0.1 - 1.2][f]	0.01*
Lymphocyte (/μL)	807 [570 - 1279][f]	961 [647 - 1373][f]	0.43
P_aCO_2 (mmHg)	37.5 [33.2 - 39.5][f]	38.3 [35.6 - 41.6][f]	0.12
Treatment			
PSL dose > 0.5 mg/kg	31 (78%)	33 (50%)	0.01*
mPSL pulse	34 (85%)	43 (65%)	0.02*
IVCY	20 (50%)	23 (35%)	<0.001*
Calcineurin inhibitor[a]	38 (95%)	35 (53%)	0.12
Combination[b]	19 (48%)	18 (27%)	0.04*
IVIg[c]	4 (10%)	4 (6%)	0.48
ST[d]	23 (58%)	28 (42%)	0.29
HRCT (ILD lesion expanded until each zones)			
Zone A	20 (50%)	34 (52%)	0.76
Zone B	25 (63%)	12 (18%)	0.81
Zone C	35 (88%)	57 (86%)	0.87
Zone D	36 (90%)	61 (92%)	0.20
All zone	7 [4-11][f]	6 [4-9][f]	0.46

[a] Calcineurin inhibitor includes cyclosporine and tacrolimus.
[b] Combination regimen includes PSL, calcineurin inhibitor and IVCY.
[c] Intravenous immunoglobulin.
[d] Sulfamethoxazole' trimethoprim for prophyraxis against *Pneumocystis jiroveci* pneumonia.
[e] Mean ± SD.
[f] Median [interquartile range].
*$p < 0.05$.

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disease

Abstract Number: 2311

Initial Predictors of Short-Term Poor Survival Rates in Patients with Polymyositis/Dermatomyositis-Associated Interstitial Lung Disease

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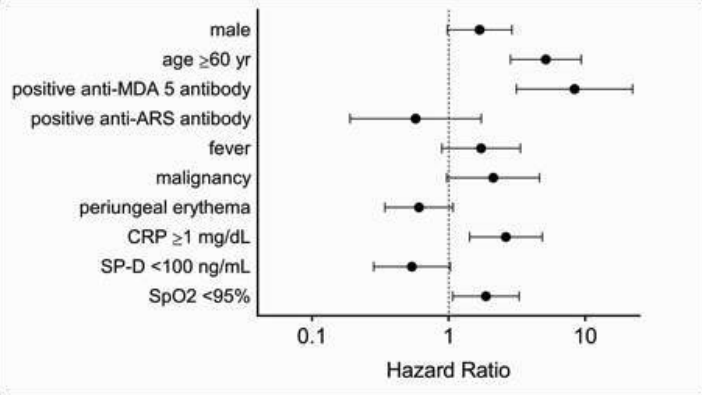
Background/Purpose: Polymyositis (PM)/dermatomyositis (DM) is a chronic inflammatory disorder that affects muscle, skin and lung in various degree, and interstitial lung disease (ILD) is a major cause of death. In clinical setting, it is necessary to predict future clinical manifestations and outcomes accurately before initiation of treatment. In this study, we examined initial predictors of poor survival in patients with PM/DM-associated ILD.

Methods: This study used a database of a multicenter retrospective cohort of Japanese patients with PM/DM-associated ILD (JAMI cohort), which involved 44 institutions across Japan. Inclusion criteria of the JAMI cohort were adult-onset, definite or probable PM/DM including clinically amyopathic DM (CADM), ILD confirmed by imaging study, and availability of sera at diagnosis. Demographic features, diagnosis, clinical features, laboratory findings, high-resolution CT patterns and treatment regimens used were retrospectively collected. Serum samples were subjected to autoantibody assays; enzyme-linked immunosorbent assay for anti-melanoma differentiation-associated gene 5 (MDA5) and RNA immunoprecipitation for anti-aminoacyl-tRNA synthetase (ARS). Cumulative survival rates were calculated using the Kaplan-Meier method and equality of survival curves was tested by the Breslow test. The best model for predicting survival was searched using multivariate analysis using step-wise selection of parameters and the Cox proportional hazards regression model.

Results: This study enrolled 497 patients, including 76 (15%) with PM, 158 (32%) with classic DM, 263 (53%) with CADM (median observation period: 20 months, IQR 5-43). Autoantibody analysis revealed 209 (42%) positive for anti-MDA5 and 166 (34%) positive for anti-ARS antibodies. By univariate analysis, age at onset (>60 years), male, CADM, fever, Raynaud phenomenon, absence of muscle weakness, skin ulceration, CRP (>1 mg/dL), CK (<750 IU/L), aldolase (<17.5 IU/L), SP-D (<100 ng/mL), ferritin (>500 ng/mL), random GGA pattern on CT, SpO_2 (<95%), positive anti-MDA5, and negative anti-ARS were identified as initial parameters associated with subsequent mortality. By testing various combinations of parameters selected by univariate analysis, we propose a model consisting of independent predictors of poor survival rates (**Figure**). In terms of treatment regimens introduced, use of calcineurin inhibitors was associated with better survival rates while corticosteroid pulse therapy and intravenous immunoglobulin were associated with poor outcomes.

Conclusion: Using a large cohort of well-defined patient population, we have successfully identified independent predictors of short-term mortality in patients with PM/DM-associated ILD.

Figure: Multivariate analysis for predictors of poor prognosis: Estimated hazard ratios for mortality with the 95% confidence intervals



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Abstract Number: 2312

Anti-TIF1-Gamma Antibodies Are Not Associated with Other Paraneoplastic Rheumatic Syndromes Than Dermatomyositis

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Background/Purpose: An association between cancer and dermatomyositis (DM), referred to as cancer-associated myositis, is well recognized and clinically important. The overall cancer risk is up to 25-30% among DM patients. The high frequency of malignancies detected close to DM diagnosis suggests that DM can be a paraneoplastic syndrome, and cancer within three years of DM diagnosis is often defined as cancer associated myositis (CAM). The absence of a biomarker for CAM leads to a thorough screening for cancer in patients diagnosed with DM. Recently anti-TIF1-gamma has been discovered to be associated with cancer and DM. A meta-analysis claimed pooled sensitivity of anti-TIF1-gamma for diagnosing cancer-associated DM to be 78% (95% CI 45–94%), and specificity to be 89% (95% CI 82–93%). Thus anti-TIF1-gamma has shown promising results as a marker for CAM. However, none of the studies evaluated anti-TIF1-gamma association with cancer with or without other paraneoplastic rheumatic syndrome than DM. To clarify the specificity of anti-TIF1-gamma antibodies as a biomarker for CAM we analyzed the frequency of anti-TIF1-gamma antibodies in other cancer associated inflammatory rheumatic syndromes as well as in cancer patients and healthy controls.

Methods: Sera from patients with paraneoplastic rheumatic syndrome (n=91) (arthritis n=39, Raynaud´s n=23, other n=29) , patients with solid cancer (n=95) and healthy controls (n=80) were analyzed for the frequency of anti-TIF1-gamma IgG by ELISA using a commercially available recombinant TIF1-gamma protein as coating antigen. The cut-off value was calculated by adding 2SD to the mean OD value of 80 healthy controls.

Results: Positivity for anti-TIF1-gamma IgG was 3,3% (n=3) in patients with paraneoplastic rheumatic syndrome, 3,1% (n=3) in cancer patients and 1,3% (n=1) in healthy controls. There was no significant difference in positivity between the groups (p>0,05). Sensitivity and specificity for diagnosing cancer were 3,2% and 98,7%, and for paraneoplastic rheumatic syndromes, 3,3% and 96,84% respectively.

Conclusion: AntiTIF1-gamma antibodies are rarely present in patients with solid cancers or paraneoplastic rheumatic syndromes. This finding strengthens the approach to use anti-TIF1-gamma IgG as marker for cancer-associated DM.

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Abstract Number: 2313

Profile of Cardiovascular Burden in Myositis: A Case-Control Study

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Background/Purpose: Research has indicated that cardiovascular disease is the leading cause of death in the Idiopathic Inflammatory Myopathies (IIM). Only a small number of studies have investigated the burden of cardiovascular morbidity in patients with myositis in comparison to a healthy population. Arterial stiffness, a strong predictor of cardiovascular risk, can be non-invasively quantified via the Reactive Hyperaemia Index (RHI) and the Augmentation Index (AI), unadjusted and adjusted to 75 beats per minute. A reduced RHI and a raised AI is indicative of endothelial dysfunction and increased arterial stiffness. The aim of this study was to characterise the presence of cardiovascular risk factors in an IIM population in comparison to a healthy population.

Methods: Adults with a verified IIM diagnosis were recruited. A healthy matched control cohort was also recruited. The following investigations were carried out on each patient on the same day: tobacco use assessment, brain natriuretic peptide (BNP) measurement, body composition analysis, blood pressure measurement, measurement of fasting cholesterol, triglyceride, C-reactive protein (CRP), insulin and glucose concentrations, carotid artery intima-medial thickness (CIMT) and plaque identification via ultrasound, ejection fraction measurement and valve dysfunction identification via echocardiography. Radial artery stiffness (RHI and AI) was quantified non-invasively using the endoPAT system. Ten year cardiovascular disease (CVD) risk was calculated for each patient via QRISK2. Continuous variables were compared between the two groups with the Mann-Whitney U test and categorical variables were compared with the Chi-squared test.

Results: Nineteen IIM patients with confirmed disease according to the Bohan and Peter criteria and 20 healthy controls were recruited (Table 1). A higher proportion of the IIM cases were female and were slightly younger. AI (unadjusted and adjusted to 75 bpm) was higher for the IIM cases and RHI did not differ. Previous tobacco use was similar between the two groups. Median lean fat mass and total body water was lower in the IIM cases and body mass index (BMI) was raised. Cholesterol, insulin, CRP, glucose and triglyceride measurements did not vary between the two groups. Median haemodynamic measurements (BNP, SBP, DBP, ejection fraction), CIMT and the number of identified carotid plaques and heart valve abnormalities were similar in each group. Ten year CVD risk was similar between each group.

Conclusion: This study indicates that arterial stiffness (measured as AI), a strong indicator of cardiovascular risk, is increased in IIM patients. Further, IIM is associated with increased BMI and variations in body composition. Cardiac function, atherosclerosis burden, 10 year CVD risk, cholesterol profile and insulin resistance is similar in IIM cases and controls. A further study of the cardiovascular manifestations in a larger IIM cohort is warranted.

Table 1 - Comparison of demographic and cardiovascular variables between IIM cases and controls			
	Cases n = 19	**Controls n = 20**	**p-value**
No. female (%)	15 (79)	9 (45)	0.09
Median age/years (IQR)	39 (34, 49)	42 (33, 47)	0.92
Median alcohol intake/units per week (IQR)	0 (0, 2)	3 (1, 16)	<0.01
No. current smokers (%)	5 (26)	6 (30)	1.00
Median smoking pack years (IQR)	1 (0, 7)	1 (0, 7)	0.94
Median BNP/pg/ml (IQR)	67 (50, 90)	53 (23, 91)	0.19
Median EF percentage (IQR)	58 (55, 64)	61 (59, 66)	0.17
No. with a valvular abnormality (%)	9 (47)	7 (35)	0.63
Median systolic blood pressure/mmHg (IQR)	135 (113, 144)	120 (112, 133)	0.16
Median diastolic blood pressure/mmHg (IQR)	77 (69, 83)	74 (69, 78)	0.50
Median CIMT/mm (IQR)	0.06 (0.05, 0.06)	0.06 (0.05, 0.06)	0.93
No. with plaque present (%)	1 (5)	2 (10)	1.00
Median RHI (IQR)	2.1 (1.7, 2.6)	2.1 (1.9, 2.6)	0.63
Median AI (IQR)	16.0 (-4.8, 24.0)	6 (-5.5, 14.0)	0.22
Median AI @ 75bpm (IQR)	6.5 (-10.8, 20.5)	-1.0 (-8.5, 9.5)	0.14
Median body fat % (IQR)	36.2 (27.6, 44.6)	32.4 (26.0, 36.6)	0.29
Median lean fat mass/Kg (IQR)	44.8 (42.4, 51.9)	55.4 (46.2, 61.6)	0.06
Median total body water/Kg (IQR)	33.8 (31.8, 38.6)	40.6 (33.8, 45.1)	0.13
Median body water % (IQR)	46.7 (40.5, 53.1)	49.4 (46.0, 54.1)	0.18
Median BMR/Kcal (IQR)	1432 (1330, 1690)	1707 (1440, 1871)	0.11
Median whole body impedance/Ω (IQR)	637 (584, 746)	611 (551, 678)	0.37
Median BMI/Kg/m^2 (IQR)	29.6 (23.3, 33.1)	25.8 (25.1, 31.4)	0.64
Median fasting insulin/mU/L (IQR)	6.4 (4.2, 11.3)	7.5 (5.2, 11)	0.88
Median fasting glucose/mmol/L (IQR)	4.7 (4.2, 5)	4.8 (4.5, 5)	0.62
Median total cholesterol/mmol/L (IQR)	5.1 (4.3, 5.4)	4.9 (4.3, 5.5)	0.78
Median triglyceride/mmol/L	1.2 (0.9, 1.8)	1 (0.7, 1.8)	0.37
Median HDL/mmol/L (IQR)	1.5 (1.1, 1.8)	1.4 (1.2, 1.6)	0.88
Median LDL/mmol/L	2.9 (2.4, 3.3)	2.8 (2.5, 3.3)	0.94
Median cholesterol:HDL ratio (IQR)	3.4 (3.0, 4.8)	3.3 (2.7, 4.1)	0.65
No. raised cholesterol:HDL ratio (%)	7 (37)	7 (35)	0.73
Median CRP/mg/L (IQR)	1.4 (0.5, 4.5)	1.2 (0.8, 2.2)	0.12
Mean 10 Year CVD risk percentage (SD)	4.7 (5.4)	4.2 (4.5)	0.76

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Anti-Mi2 Dermatomyositis Revisited: Pure DM Phenotype with Muscle Fiber Necrosis and High Risk of Malignancy

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Background/Purpose: Anti-Mi2 autoantibodies (Aabs) have been proposed to be highly specific for dermatomyositis (DM) and to be associated with a DM classical phenotype consisting of typical skin rashes and low extra-muscular features. Cancer has been estimated in about 30% of all DM patients. Patients with anti-Mi2 DM are considered having a good prognosis, possibly related to a markedly lower risk of malignancy reported in this subset. Nonetheless, there has been only a few and small cohort descriptions of this DM subgroup. Our objective was therefore to describe the phenotype of anti-Mi-2 DM in a large French cohort.

Methods: A national multicenter retrospective cohort study was performed (15 medical centers) including all patients with a clinical phenotype suggestive of DM (cutaneous manifestations and/or muscle involvement) and a positive anti-Mi2 Aabs. Medical records were retrospectively reviewed. Muscle strength was assessed using the Medical Research Council (MRC) scale and cancer-associated myositis (CAM) was defined as a cancer occurring ± 3 years of diagnosing myositis.

Results: A total of 65 patients were identified, 62% were female and mean age at diagnosis was 54 years old (yo) (±17 yo). DM skin rash was reported in 88% of patients, most frequently Gottron papules and/or sign (68%), periungueal erythema (51%) and heliotrope rash (40%). Peripheral muscle weakness was reported in 92% of patients and dysphagia was reported in 34% of patients. At diagnosis, patients displayed severe muscle weakness

(MRC 3/5, ±1/5*)* with mean CK level of 5085 UI/L (±5535 UI/L). Systematic review of muscle biopsies (n=11) showed marked inflammatory infiltrates. Strikingly, necrosis and regeneration were identified in all patients (n=11/11). C5b-9 deposition was found in all patients mainly on non-necrotic fibers but only sparsely on capillaries and without prominent capillary loss. Arthritis, Raynaud phenomenon and interstitial lung disease were reported in less than 20 % of patients**.** CAM was identified in 20% of patients and detected within one year and a half of DM diagnosis in most patients (n=11/12). All CAM patients, but one (38 yo), were diagnosed over 50 yo. There was no predominant histological subtype of malignancy (gastro-intestinal, urological, gynecological and pulmonary) and cancer was metastatic in a third of patients. Survival rate was 83% after a mean follow-up of 4.9 years from cancer diagnosis. Ninety-eight percent of patients were initially treated with corticosteroids (CS), in combination with immunosuppressant (IS) in 60% of cases. Patients treated with CS monotherapy (n=14), needed second-line agents upon follow-up in 60% of cases. In all, 53% of patients relapsed upon CS and/or IS tapering.

Conclusion: In this large French cohort, patients with anti-Mi2 DM displayed a phenotype with 3 main characteristics (i) pure DM phenotype (low overlap features) (ii) necrotizing myositis (severe weakness, high CK level and muscle fiber necrosis) and (iii) higher than expected malignancy rate.

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Abstract Number: 2315

The Effectiveness of Social Media in Recruiting for Rare Rheumatic Diseases

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Background/Purpose: Clinical research is dependent on being able to recruit and enroll appropriate patients in sufficient numbers to make robust conclusions. For many diseases it can be difficult to obtain satisfactory numbers of participants, which can impact the quality of research performed. Investigators have used a variety of

advertising methods to reach potential participants for research studies. Advertising through new technology platforms offers many advantages over other types of study advertising, particularly for rare diseases. By using these platforms, very specific groups of individuals can be targeted, thus increasing the probability that a person who sees a notice for a study has the disease being investigated. The idiopathic inflammatory myopathies are a group of rare muscle disorders and we performed advertising campaigns using Facebook and Google advertising platforms for these diseases in an attempt to evaluate their relative characteristics and effectiveness.

Methods: IRB approval was obtained to use Facebook and Google advertising platforms for four NIH non-interventional studies attempting to enroll patients with juvenile or adult dermatomyositis, polymyositis, or inclusion body myositis. Targeted words and ad criteria were developed in conjunction with experts from each platform. Similar terms and criteria were picked for each platform. The advertising ran on Google from October 9th to November 18th 2015 and on Facebook from September 30th 2015 to February 17th 2016.

Results: Google ads had 1,285,733 views and Facebook ads had 335,941 views. In total, 0.54% of impressions on Google and 2.29% of impressions on Facebook led to a click of the advertisement. Google averaged about 80 cents a click and Facebook averaged 30 cents a click. Each site also collected additional advertising data about the population reached. On the Google platform 17 search terms led to 10 or more individuals clicking the advertisement and they were not the 17 terms with the highest number of impressions. With a list of 49 keywords there were 1110 distinct search terms used by end users that led to our advertisement being displayed. Facebook ads reached 191,098 individual people. The majority of individuals reached were female (175,914 female, 336 male, 127 unknown) and between the ages of 45-64 years (63% of the clicks and 55% of views). The vast majority of individuals seeing the Facebook ad did so on a mobile news feed (98% of all clicks and 97% of all views) with the rest viewing the ad on their desktop feed, third party mobile application or website, or desktop right hand column in order of frequency for views and clicks. Of the mobile devices used to access the content, 40% of clicks were on an android smartphone, 36% on an iPhone, 15% on an iPad, and 4% on an Android tablet.

Conclusion: Both Google and Facebook advertising platforms were able to reach a large audience of potential study participants for a rare disease. Each platform collects its own type of user data and differs in how ads can be targeted. Overall, Facebook was cheaper per a click, led to more absolute clicks, and had a higher percentage of individuals who saw the ad click it.

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Abstract Number: 2316

Successful Treatment of Statin-Induced Autoimmune Myopathy without Corticosteroids

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Background/Purpose: Statin-induced autoimmune myopathy (SI-AIM) is often difficult to treat. While corticosteroids (CSs) are the mainstay induction therapy used by most clinicians for autoimmune myopathies, SI-AIM seems corticosteroid resistant. Intravenous immune globulin (IVIG) on the other hand has been used with success as part of an induction regimen or even as monotherapy (Mammen AL, NEJM, 2015). Our objective was to describe the clinical phenotype and successful treatment regimens of patients with SI-AIM but not treated with CSs.

Methods: Our study included all patients from the Université de Montréal AIM cohort (comprising four academic hospitals) with a documented anti-3-hydroxy-3-methylglutaryl-CoA reductase (anti-HMGCR) autoantibody. We selected statin-exposed patients who did not receive any CSs during the course of their treatment and performed a retrospective review of medical records. Remission was defined as a serum creatine kinase (CK) level <500 U/L whereas maintenance of remission corresponded to a CK level <500 U/L sustained for at least 6 months.

Results: From a cohort of 45 anti-HMGCR positive AIM patients, 42 were previously exposed to statins, of whom 8 patients (4 men, 4 women, mean age 59 years) were not treated with CSs and therefore selected for study. Three clinical stages of myopathy were recognized: stage 1 (serum CK elevation, normal muscle strength, normal EMG), stage 2 (CK elevation, normal strength, myopathic EMG) and stage 3 myopathy (CK elevation, proximal muscle weakness, myopathic EMG). Three out of 8 patients presented and were treated in stage 1 myopathy after a mean statin discontinuation time of 23 months (range 5-74 months). The remaining 5/8 patients presented in stage 3 myopathy. The mean time between statin cessation and treatment initiation was 5 months (range 0-10 months), with one patient improving to stage 2 myopathy upon statin discontinuation. MTX monotherapy induced remission in all 3 patients presenting in stage 1 myopathy and in 1 patient in stage 2 myopathy. The mean time to remission was 7 months (range 4-13 months). In the remaining 4 patients with stage 3 myopathy, IVIG was successfully used in 3 patients to induce remission with either MTX or MTX+AZA, whereas 1 patient responded to a MTX+AZA combination alone. The mean time to remission for stage 3 myopathy was 10 months (range 1-21 months). MTX monotherapy (n=5/6) or a MTX+AZA combination (n=1) were able to maintain remission in the 6 patients available for analysis. Thus, all 8 patients did not require CSs to achieve remission.

Conclusion: Eight patients with SI-AIM were successfully treated with immunosuppressive and/or immunomodulating agents but not with CSs. Four patients with normal strength (i.e. in stage 1 or 2) responded to MTX monotherapy. In patients with proximal muscle weakness, combination therapies with MTX+IVIG, MTX+AZA or MTX+AZA+IVIG were successfully used and thus, these approaches appear reasonable induction strategies in stage 3. Early recognition of stage 1 SI-AIM and timely treatment initiation could minimize the use of IVIG and CS therapies and consequently lead to better outcomes in these patients.

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Preliminary Validation of a Magnetic Resonance Imaging-Based Inflammatory Scoring System in Adult Myositis

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Background/Purpose: in patients with active myositis, magnetic resonance imaging (MRI) often demonstrates muscle edema thought to represent active inflammation. An MRI-based muscle inflammatory scoring system has been validated for juvenile myositis (Rheumatology 2011; 50:2237), but to the best of our knowledge there is no such a scoring system for adult myositis. We aimed to validate an MRI-based edema score for patients with adult myositis.

Methods: twenty-one patients (9 polymyositis [PM], 12 dermatomyositis diagnosed according to Bohan and Peter criteria) were included in the study. In 8/9 patients with PM the diagnosis was confirmed by consistent histology. MRI of the thigh and pelvic floor muscles was performed on a 1.0 or 1.5T scanner using a surface coil. Edema (1= present, 0= absent) was assessed by fat-suppressed sequences in 17 thigh and pelvic floor muscles and a score (0-17) was calculated by adding the separate muscle scores by three blinded independent observers. Sensitivity to change was assessed by sign test. Muscle strength was evaluated in 12 muscle groups by manual muscle test (MMT) and graded according to the extended Medical Research Council scale (0-5). Serum creatine kinase (CK) levels were measured (U/l) and MMT performed simultaneously or within a week from the MRI study in each patient.

Results: 38 MRI scans were available from 21 patients. 10 patients had new onset of myositis. Two patients had 4 scans, 1 had 3 scans, 9 had 2 scans, and 9 had 1 scan each. The median MRI edema score was 2.7 and the interquartile range (IQR) 8.96. Inter-rater Cronbach's alpha was 0.984, while single-measure intraclass correlation coefficient (ICC) was 0.954 (95% confidence interval [CI] 0.922-0.974). Bland-Altman's plot showed no significant differences between raters. Two raters evaluated the same MRI exams on 2 different time points to determine intra-rater variability. Cronbach's alpha was 0.903 and 0.921, while single-measure ICC was 0.815 (95% CI 0.667-0.901) and 0.851 (95% CI 0.729-0.921) for rater 1 and 2, respectively. In 7 patients for whom a repeat MRI after treatment onset was available median edema score decreased from a median of 8.83 (IQR 9.18) to 0.71 (IQR 12.3) (p 0.07). MRI edema score did not correlate with serum CK levels (median 384, IQR 1317) or MMT (median 4.39, IQR 0.45) ($p>0.05$ Spearman's rho).

Conclusion: the MRI edema score presented herein is highly reproducible with good inter- and intra-rater variability and appears to be sensitive to change. The significant lack of correlation of MRI edema score with serum CK levels and MMT suggests that these measures of myositis activity may be at least partially uncoupled, suggesting that MRI score adds information on disease activity above the CK and MMT, although the small sample size hampers a confident conclusion in this regard.

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Abstract Number: 2318

Real World Use of the Myositis Autoantibody Panel

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Background/Purpose: The identification of myositis specific and associated autoantibodies occurring in idiopathic inflammatory myopathies (IIMs) has improved classification and prognosis determinations. With commercial availability, these autoantibodies are being ordered outside of the research setting in routine clinical practice. While these autoantibodies are reported to occur in approximately 30% of IIMs, real world positivity rates and ordering patterns have not been described. We aimed to determine the positivity rate within our tertiary health system, and the proportional ordering of the myositis panel between specialists.

Methods: We included all Duke University Health System patients who had a myositis autoantibody panel (including anti-Jo-1, PL-7, PL-12, EJ, OJ, Mi-2, SRP, PM/Scl, Ku and U2-snRNP) ordered between October 2014 and December 2015. We recorded specific autoantibody positivity for the institution and by ordering specialty. Ordering provider was classified as either adult or pediatric and grouped by provider specialty. Specialty groups included pulmonary, rheumatology, neurology, dermatology, cardiovascular, emergency medicine and general medicine.

Results: Out of 378 myositis antibody panels ordered, 79 (20.9%) returned positive (Table). Overall, 59% of positive tests were myositis specific autoantibodies. Among positive tests, anti-synthetase antibodies were the most common (29.1%) followed by anti-Mi-2 (27.8%). Of the 5 assayed, only 3 anti-synthetase antibodies were detected in this population, anti-Jo-1, anti-PL-7, and anti-PL-12. Combined, adult pulmonary, rheumatology and neurology ordered 85.7% of the antibody panels; adult pulmonary ordered the most tests (242; 64%). Positivity rates were 50% for adult cardiovascular and general pediatrics (4 panels ordered), followed by adult

rheumatology (31.7%; 13 tests). Six patients were positive for two different antibodies; anti-Mi-2 occurred in 4 of the 6. The panel was performed twice in 4 patients; in 1 patient, an initially negative panel later found anti-U2-snRNP.

Conclusion: This is the first study to determine the positivity rate of the myositis antibody panel in real-world use in a tertiary referral center. Within our multi-specialty practice, the majority of testing was performed by adult pulmonary, followed by rheumatology and neurology. Our results may reflect the presence of an active interstitial lung disease clinic. Of interest, anti-Jo-1 had a nearly equal prevalence to the other anti-synthetase antibodies in this population. Both anti-Mi-2 and anti-Ku antibodies were seen across the majority of ordering specialties, while the anti-PM/Scl antibody was primarily found by pulmonology. Overall, our test positivity rates were similar to prior reports in disease-specific populations. Further characterization of this cohort will help guide future use of this testing.

Table. Positive myositis antibody tests by provider group and autoantibody. In total, 47 MSAs were positive and 32 MAAs were positive. *Anti-synthetase antibodies.

Specialty	Tests Ordered	Positive Tests	Myositis Specific Autoantibodies					Myositis Associated Autoantibodies		
			Jo1*	PL-7*	PL-12*	Mi-2	SRP	Pm/Scl	Ku	U2-snRNP
Adult Pulmonology	242	45	5	6	4	11	1	7	6	5
Adult Rheumatology	41	13	2	2	-	2	-	1	2	4
Adult Neurology	41	10	1	-	-	4	1	1	2	1
Adult Dermatology	2	-	-	-	-	-	-	-	-	-
Adult Cardiovascular	4	2	1	-	1	-	-	-	-	-
Emergency Medicine	1	-	-	-	-	-	-	-	-	-
Adult General Medicine	24	3	-	-	1	1	-	-	1	-
Pediatric Rheumatology	18	4	-	-	-	3	-	-	1	-
Pediatric Neurology	1	-	-	-	-	-	-	-	-	-
General Pediatrics	4	2	-	-	-	1	-	1	-	-
Totals	378	79	9	8	6	22	2	10	12	10

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Abstract Number: 2319

High Prevalence of Asymptomatic Vertebral Fractures in Inflammatory Myositis

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Background/Purpose: Patients with inflammatory myositis have increased prevalence of symptomatic fractures. Early detection of asymptomatic vertebral fractures may help in their prevention. We studied the frequency of asymptomatic vertebral fracture and its risk factors in inflammatory myositis.

Methods: Adults with inflammatory myositis were included and dorsal and lumbar spine lateral radiographs were taken. The scoring was done using Genant's semi-quantitative method. Besides demographic data, weight, height, postmenopausal status, duration of corticosteroid use, anticonvulsants, calcium supplements, and other co-morbidities like diabetes or hypothyroidism and past history of non-vertebral fracture were recorded. Bone mineral density was done using DEXA. Myositis Damage Index (MDI) was also assessed. All results are expressed in median and IQR.

Results: 100 patients (82 females) with myositis of age 35.5 (28.5-46) years and disease duration 3 (1.81-8.0) years were studied. Twenty patients were postmenopausal women. 35 patients had adult dermatomyositis (DM), 26 each had polymyositis and 26 connective tissue disease associated myositis and 13 had juvenile onset myositis. Forty-six patients had asymptomatic vertebral fractures. 19 patients had more than one fracture. Half the fractures occurred in those with disease <5 years. Of the 69 fractures, 47 (68.1%) were mild, 16 (23.2%) were moderate and 6 (8.7%) were severe. 11^{th} and 12^{th} thoracic vertebrae were most commonly affected. Of the 67 patients who underwent BMD assessment, 62.7% were osteopenic and 26.9% were osteoporotic. T scores of DEXA scan at the lower third of the radius correlated negatively with fracture number (r=-0.27 (-0.50 to -0.005), p=0.04). Gender, age, duration of disease, intake of corticosteroid or calcium, BMI, menopausal status, or MDI had no correlation with number of fractures.

Conclusion: Patients with inflammatory myositis have high prevalance of asymptomatic vertebral fractures.

Disclosure: L. Gupta, None; **S. Edavalath**, None; **R. Misra**, None; **A. Lawrence**, None.

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Abstract Number: 2320

Oropharyngeal Dysphagia in Autoimmune Myositis

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Background/Purpose: Oropharyngeal dysphagia (OPD) is an ominous finding in autoimmune myositis (AIM), yet few studies have evaluated the disease subsets at higher risk for this life-threatening complication. Recent AIM classifications have identified three dominant entities: pure dermatomyositis (DM), necrotizing autoimmune myositis (NAM), and overlap myositis (OM). Pure polymyositis (PM) is uncommon and is an exclusion diagnosis. The aim of the present study was to describe, in relation to DM, NAM and OM, the clinical and laboratory characteristics associated with OPD.

Methods: A retrospective cohort of patients diagnosed with AIM between January 2001 and January 2016 was identified in two academic hospitals affiliated with the University of Montreal. All patients with objective OPD, defined by an abnormal videofluoroscopy swallow study (VFSS) and/or the need for percutaneous gastrojejunostomy (PGJ), were included. Severe dysphagia was defined as aspiration visualized on VFSS and/or the need for PGJ and/or aspiration pneumonia. The associations between OPD and various characteristics, including diagnostic subsets of AIM, clinical and laboratory features, and the presence of cancer within 3 years of AIM diagnosis, were examined.

Results: Within the total cohort of 180 patients with a diagnosis of AIM, the main subset was OM (n=94, 52.2%) and the other subsets were distributed as follows: 46 pure DM, 37 NAM, and 3 PM. Objective OPD was present in 26 patients (14.4%). An abnormal VFSS was documented in 25 patients and 9 patients had a PGJ. For this dysphagic cohort, the mean age (+/-SD) was 62.9 (+/- 10.7) years and 61.5% were women. The main diagnostic subset was pure DM (n=12, 44.4%), while 6 patients had NAM, and 8 had OM. Among the 8 OM patients, 6 had concomitant distal oesophageal dilatation on chest CT, 5 of which had scleroderma features. Each of the DM-specific autoantibodies (aAbs) (TIF, NXP2, Mi-2 and SAE) was represented among the pure DM patients, while HMGCR and SRP aAbs were only found in NAM. In OM, only one patient had Jo-1 aAbs, while RNA polymerase III, PM-Scl and U1RNP aAbs were also seen. Cancer was found in 24/180 patients and was more prevalent among the dysphagic (n=10/26, 38.5%) compared to the non-dysphagic patients (n=14/154, 9.1%) (p=0.0005). Dysphagic patients in the DM subset showed the highest rate of cancer (n=8, 66.7%). Severe OPD was identified in 11/26 patients. Six of them had DM, all with an associated cancer. Severe dysphagia was also present in 3 NAM and 3 OM. OPD was treated with methylprednisolone pulses as induction therapy in 15 patients, and IVIG in 21. Evolution of OPD was generally favorable, and complete remission was seen in 17 patients (65.4%). However, in the subset of cancer-associated pure DM, only 2 patients (25%) had resolution of OPD. Overall, 6 patients with

OPD died, of which 3 had pure DM associated with cancer.

Conclusion: Our study demonstrates that pure DM is the dominant AIM subset associated with objective OPD. Cancer is significantly more prevalent among the dysphagic patients, specifically in the pure DM subset. Based on this evidence, clinicians are urged to aggressively investigate pure DM patients with OPD for evidence of cancer.

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Early Damage and Mortality in a Cohort of Patients with Myositis Followed up to 20 Years

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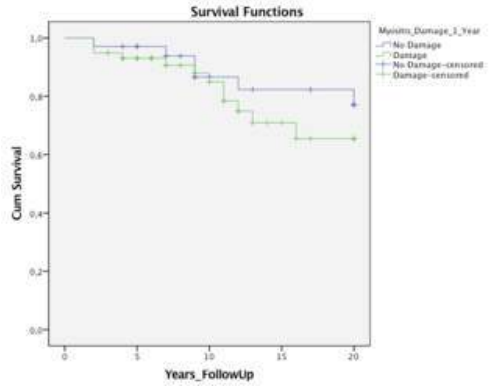
Background/Purpose: Idiopathic inflammatory myopathies (IIM) are a group of rare diseases, including dermatomyositis (DM), polymyositis (PM) and juvenile dermatomyositis (JDM). Patients often need long-term treatment with corticosteroids and immunosupressive drugs, as full remission is uncommon. A method to evaluate damage accrual in these patients has been previously developed[1] and our aim was to determine if early damage in the course of the disease is predictive of mortality.

Methods : We reviewed the clinical records of 92 patients with IIM (Bohan and Peter criteria) with at least 2 years of follow up. JDM patients diagnosed before the age of 16 were excluded. The patients were evaluated according to gender, ethnicity, age at diagnosis, use of corticosteroids and immunosupressive therapy and time of follow-up. Damage captured by the Myositis Damage Index (MDI) was assessed 1 year post-diagnosis and for those who died within 20 years of diagnosis, the year and cause of death were also determined. Time to death was analysed using Cox regression and Kaplan-Meier, and patients who were lost to follow up were censored at the time of the last observation.

Results : Sixty-seven patients were female (72.8%), the mean age at diagnosis was 41.6 years (95% CI 38.5-43.81) and the mean time of follow up was 13.54 years (95% CI 11.65-15.43). Sixty-three per cent of patients were White, 22.8% Afro-Caribbean, 13% South Asian and 1.1% Black. Thirty-eight per cent had DM, 32.6% PM,

26.1% overlap syndrome and 3.3% JDM. For every 1 point increase in the MDI score at 1 year post-diagnosis, the patient was 1.486 time more likely to die; HR 1.486 (95% CI 1.096-2.016; $P = 0.011$). A Kaplan-Meier survival curve between patients with no damage (MDI score = 0) and with damage (MDI score >/= 1) also showed a difference between the 2 groups, but it was not statistically significant (graph 1).

Graph 1: Kaplan-Meier Curve with Time to Death in Damage vs No Damage at 1 Year Post-Diagnosis



The type of damage in each group is described in table 1.

Table 1 – Damage by Assessed Group

MDI Manifestations (%)	Alive (n = 74)	Dead (n = 18)
Muscular	45.9	50
Skeletal	1.4	5.6
Cutaneous	9.5	11.1
Gastrointestinal	1.4	5.6
Pulmonary	17.6	44.4
Cardiovascular	6.8	11.1
Peripheral Vascular	0	11.1
Endocrine	5.4	11.1
Ocular	0	0
Malignancy	0	5.6

Conclusion : Early damage in the course of IIM is associated with increased mortality up to 20 years after diagnosis. Further studies are necessary to establish the factors which contribute the most to this early damage.
References: 1- Sultan SM et al. *Ann Rheum Dis.* 2011;70(7):1272-1276.

Disclosure: S. Guerreiro Castro, None; **P. Mota**, None; **D. A. Isenberg**, None.

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Abstract Number: 2322

The Clinical Significance of Curvilinear Bodies on Ultrastructural Examination of Muscle

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Background/Purpose: Hydroxychloroquine (HCQ) therapy for autoimmune disease may be associated with detection of curvilinear bodies (CB) on ultrastructural examination of muscle. Whilst ocular toxicity is related to cumulative HCQ dose, the clinical significance of CB is uncertain and whether their detection reflects dose-dependent toxicity is not known.

Methods: The electronic database of muscle biopsies reported in the Anatomical Pathology Laboratory, SA Pathology was searched from 2006 to the present, to identify biopsies with CB. The clinical features of these patients, including body mass index and cumulative HCQ dose were recorded. A control group of 16 patients with biopsy-proven idiopathic inflammatory myositis (IIM) who were on HCQ at the time of biopsy but who did not have histopathological evidence of CB was identified from the South Australian Myositis Database.

Results: 19 patients with CB on ultrastructural examination of muscle were identified; details were available for 18. Among patients with CB, 7/18 also had IIM. 7/10 of patients with CB who did not have IIM or MHC1/11 expression had documented proximal weakness, 7/11 had raised serum creatinine kinase (CK) levels. There was no difference in body weight (p=0.47), body mass index (p=0.93), cumulative HCQ dose (p=0.52) or cumulative dose adjusted for body weight (p=0.39) or body-mass index (p=0.32) between patients with CB and controls. Patients with CB had lower median CK levels than controls (p=0.034). Weakness was present in 12/17 patients and 12/16 controls (p=1.0). Concurrent proton-pump inhibitors were co-prescribed in 12/18 (67%) patients with CB and in 6/16 (38%) controls (p=0.17).

Conclusion: In contrast with HCQ-induced ocular toxicity, the development of CB does not appear to be related to cumulative HCQ dose or body weight. Patients with CB frequently have muscle weakness even in the absence of MHC1 expression suggesting a role for non-immune mechanisms of muscle injury. A high proportion of patients with CB are co-prescribed proton pump inhibitors raising the possibility that co-prescription of both agents may disrupt lysosomal function and adversely affect muscle function.

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Evaluation of Case-Finding Algorithms for Identification of Patients with Dermatomyositis

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Background/Purpose: In order to enable meaningful clinical care and research, accurate algorithms are needed to identify patients with dermatomyositis (DM). In this study, we aimed to evaluate DM case-finding algorithms in a large health administrative database.

Methods: 100 patients were randomly selected from the Vanderbilt Synthetic Derivative, a de-identified version of the medical record, using the International Classification of Diseases version 9 (ICD9) code for DM: 710.3. We developed 13 algorithms using combinations of frequency of ICD9 code, clinic encounter (defined as two ICD9 codes at least three months apart in one year), provider specialty (Rheumatology, Neurology, or Dermatology), use of immunosuppressant medications (prednisone alone or other immunosuppressants), Current Procedural Terminology code (for electromyogram or skin or muscle biopsy), and creatine kinase level over 600 IU/L. Diagnosis was confirmed by manual review of the de-identified chart using documented diagnosis of DM or DM sine myositis by rheumatologist, dermatologist, or neurologist as the gold standard. Age, ANA status, chart length, and number and type of Bohan and Peter (B&P) criteria were extracted from each chart. Patients with DM sine myositis or incomplete medical records were excluded from analysis of test characteristics with B&P criteria.

Results: Of the 100 patients reviewed, sixty-four were diagnosed as having DM by provider documentation and forty met threshold for diagnosis of as least "possible" DM by B&P criteria. Table 1 shows the algorithm characteristics, including positive predictive value (PPV), cohort sensitivity, and specificity in both subsets of patients. Table 2 shows characteristics of DM patients found with the algorithms. An algorithm of clinic encounter and prednisone dose of at least 20mg daily had the highest PPV and specificity in each group (PPV: 95.3, 96.8; specificity: 94.4, 97). Provider specialty and immunosuppressant medications separately had high sensitivity in each group (sensitivity > 95%).

Conclusion: An algorithm of clinic encounter with prednisone dosage of at least 20mg daily had the highest PPV. An algorithm of 3 or more instances of ICD9 code 710.3had well performing test characteristics as well, with cohort sensitivity and positive predictive value. These algorithms can be used to identify cohorts of patients with rare disease in electronic medical records or administrative database and enable further study of outcomes and

Table 1. Algorithm Characteristics in Vanderbilt Synthetic Derivative

Algorithm	PPV (%)	Cohort Sensitivity (%)	Specificity (%)
Provider verified			
Encounter	91.5	84.4	86.1
Provider**	76.8	98.4	47.2
Prednisone	75.7	78.1	55.5
Medications**	68.9	96.9	28.6
CK, >600IU/L	86.7	20.3	94.4
CPT	59.1	20.3	75
Encounter + Provider	91.4	82.8	86.1
Encounter + Medications	93	82.8	88.9
Encounter + Prednisone*	95.3	64.1	94.4
Encounter + Prednisone + Medications	95.2	62.5	94.4
ICD9, 1 instances**	66.0	100	8.3
ICD9, 2 instances	84.5	93.7	69.4
ICD9, 3 instances	84.3	92.2	69.4
B&P Diagnosis			
Encounter	89.7	87.5	88.2
Provider**	68.4	97.5	47
Prednisone	76.1	87.5	58.8
Medications**	60	97.5	23.5
CK, >600 IU/L	80	30	91.2
CPT	52.6	25	73.5
Encounter + Provider	89.5	85	88.2
Encounter + Medications	92.1	87.5	91.2
Encounter + Prednisone*	96.8	75	97
Encounter + Prednisone + Medications	96.8	75	97
ICD9, 1 instances**	56.3	100	8.8
ICD9, 2 instances **	79.6	97.5	70.6
ICD9, 3 instances**	79.2	95	70.6

* Algorithm with the highest average PPV
** Algorithms with cohort sensitivity >95%
PPV: positive predictive value. **PROVIDER VERIFIED**: Rheumatologist, Neurologist, or Dermatologist confirmation of diagnosis in documentation. **ENCOUNTER**: 2 outpatient ICD9 codes 3 months apart. **PROVIDER**: a Rheumatologist, Dermatologist, or Neurologist coding the ICD9 code. **PREDNISONE**: >20mg (or equivalent) per day. **MEDICATIONS**: an immunosuppressive medication used. **CK**: Creatine Kinase. **CPT**: for muscle biopsy, skin biopsy, or electromyogram. **ICD9**: ICD9 code 710.3 **B&P DIAGNOSIS**: Meeting possible, probable, or definite criteria for Bohan and Peter criteria for dermatomyositis.

quality improvement.

Table 2. Characteristics of Patients with Dermatomyositis in a Random Cohort of from Vanderbilt Synthetic Derivative.

Provider Verified, n = 64	
Age, years	53.3 ± 18.7
Chart length, years	12.7 ± 4.9
ANA positivity (%)	52
B&P Criteria, n = 40	
Age, years	49.2 ± 18.9
Chart length, years	13.8 ± 4.8
ANA positivity (%)	55

Plus-minus values are means ± SD
PROVIDER VERIFIED: Rheumatologist, Neurologist, or Dermatologist confirmation of diagnosis in documentation. **B&P DIAGNOSIS**: Meeting possible, probable, or definite criteria for Bohan and Peter criteria for dermatomyositis.

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Effects of 12 Weeks Low-Intensity Blood-Flow Restricted Resistance Training on Knee Extensor Strength in Patients with Sporadic Inclusion Body Myositis

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Background/Purpose: Sporadic inclusion body myositis (sIBM) represents a progressive inflammatory muscle disease, which causes severe loss in skeletal muscle mass and strength, especially in the quadriceps muscles. Loss in muscle strength has been reported as high as 15% per year in sIBM patients[1]. The impairment in muscle performance causes reductions in physical function and quality of life, eventually leading to loss of independency. Only few studies have investigated the effects of exercise training in sIBM patients and none have employed a non-exercising control group for reference. Therefore the objective of the present study was to investigate the effect of 12 wks low-intensity blood-flow restricted (BFR) training vs. the natural time course of disease progression on maximal knee extensor muscle strength in sIBM patients.

Methods: The present data are part of a larger randomized controlled trial reported in clinicaltrials.gov database (NCT02317094). Twenty-two patients diagnosed with sIBM (4 females, 18 males, 69.0±5.6 years) were tested for maximal unilateral isometric knee extensor muscle strength in both legs (mean of right and left leg is presented), using an isokinetic dynamometer (KinCom; Chattecx Corp., Chattanooga, TN, USA). Following baseline testing participants were randomized to a BFR-training group (BFR, n=11) or to a non-exercising control group (CON, n=11). The BFR group performed unilateral BFR-training for both legs (leg press, knee extension, knee flexion, dorsal flexion & plantar flexion, 3-4 sets per exercise) two times per week for 12 wks. Exercise intensity (training loads) was ~25RM and blood-flow restriction was achieved using an inflatable pneumatic cuff applied at the proximal part of the shank/thigh. Cuff pressure (110 mmHg) was maintained throughout all sets and pauses while released by the cessation of the final set of each exercise, before continuing with the next exercise.

Results: At 12 wks follow-up CON showed a significant reduction in isometric knee extensor strength compared to baseline (-9.1%, p=0.051). In comparison, analyzing patients with satisfactory training compliance (>60%, n=8) BFR showed no change in knee extensor strength (+5.7%, N.S.). Further, a group x time interaction in maximal knee extensor strength was observed from baseline to 12 wks follow-up (p=0.021).

Conclusion: By extrapolating the present data the disease-related rate of loss in knee extensor muscle function in the present sIBM patients (~30% per year) appeared to be much greater than previously reported in old healthy adults (2-4% per year). Notably, maximal knee extensor muscle strength was preserved in response to 12 wks of BFR training, although on the other hand no specific improvements were observed. These findings indicate that BFR-training may have a protective effect on skeletal muscle function in sIBM patients, preventing or delaying the loss in contractile capacity seen with progression of the disease in the present non-exercising control group.

Disclosure: A. N. Jørgensen, None; **P. Aagaard**, None; **M. Christiansen**, None; **U. Frandsen**, None; **L. P. Diederichsen**, None.

Abstract Number: 2325

ANTI-Hmgcr Antibodies Demonstrate High Diagnostic VALUE in the Diagnosis of Immune Mediated Necrotizing Myopathy Following Statin Exposure

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Background/Purpose: Anti-HMGCR antibodies represent a characteristic serological feature of statin-exposed and statin-unexposed patients with immune mediated necrotizing myopathy (IMNM). We assessed anti-HMGCR antibodies in patients with suspected IMNM following statin exposure and patients with other autoimmune inflammatory diseases.

Methods: We evaluated the presence of anti-HMGCR autoantibodies in sera samples from 13 statin-exposed patients who were suspected of having IMNM, 38 patients with different inflammatory and autoimmune rheumatic diseases (systemic lupus erythematous, rheumatoid arthritis, ankylosing spondylitis, systemic sclerosis, polymyositis and anti-phospholipid syndrome) and 29 healthy subjects. The autoantibodies were detected by two assays: a new chemiluminescence QUANTA Flash HMGCR kit utilizing BIO-FLASH system, and QUANTA Lite®HMGCR ELISA kit.

Results: Twelve samples from patients with suspicion for IMNM were found positive for anti-HMGCR antibodies by both assays. Only one of the 13 samples that were found positive by QUANTA Flash HMGCR was negative by QUANTA Lite® HMGCR. A very good qualitative agreement was found between these two assays (kappa=0.949; P value < 0.0001; 95% CI, 0.918 - 1.0). A quantitative comparison between QUANTA Flash HMGCR and QUANTA Lite® HMGCR based on the levels of anti-HMGCR antibodies also revealed a strong correlation (Spearman's coefficient 0.846; 95% CI, 0.686 -0.928). In statin-exposed patients, the diagnosis of necrotizing myopathy was proven by muscle biopsy (10 patients underwent biopsy before and 3 patients after the detection of anti HMGCR antibodies). All samples from healthy subjects and from the disease-controlled patient cohort were negative for anti-HMGCR antibodies. Receiver operating characteristic (ROC) analysis for QUANTA Flash and QUANTA Lite® yielded area under the curve values of 0.997 and 1.0 respectively. The sensitivity and

specificity for IMNM were 100% and 100% for ELISA and 100% and 96.3% for CIA resulting in odds ratios of 1593 and 491.2 correspondingly.

Conclusion: The presence of anti-HMGCR antibodies is a useful biomarker of IMNM in statin-exposed patients. There is a good correlation between the two anti-HMGCR antibody assays evaluated in the present study.

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Abstract Number: 2326

Intravenous Cyclophosphamide Followed By Oral Immunosuppressive Treatment Versus Rituximab in Inflammatory Myopathy-Related Interstitial Lung Disease

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Background/Purpose: Interstitial lung disease (ILD) associated with inflammatory myopathy (IM) has a poor prognosis and requires specific treatments. Intravenous Cyclophosphamide (CYC) is one of the main treatments for moderate to severe ILD in Europe. Recent data suggested that Rituximab (RTX) could also be effective in this context. We thus retrospectively compared the efficacy of CYC followed by classical immunosuppressive treatment (IST) *vs*. RTX in inflammatory myopathy-related ILD.

Methods: Between 2003-15, 43 patients with IM-related ILD were included either at diagnosis or during a relapse. Pulmonary progression was defined in accordance with the American Thoracic Society (ATS), including NYHA stage progression, any severe event related to the ILD, CT-scan worsening and/or pulmonary function test aggravation (FVC > 10% and DLCO > 15% decrease). Serious adverse events were recorded in both groups. Uni- and multivariate statistical analyses were performed using appropriate tests.

Results: Steroids were given to all patients and cumulative doses were similar in both groups. Twenty-eight patients received intravenous CYC (6 monthly pulses [2-12], 700mg/m2), always followed by classical IST, including azathioprine (n = 14) or mycophenolate mofetil (n = 5). Fifteen patients were included in the RTX group and received two pulses initially (1g, D1-D15); infusions were repeated every 6 months (1g, median = 2 times [1-3]). Only six patients (40%) received concomitant classical IST. Median FCV at enrolment was 55% [29-113] in CYC group *vs*. 71% [45-96] in the RTX group (p = 0.01) and median DLCO was 30% [15-66] in CYC group *vs*. 42% [21-88] in RTX group (p = 0.03). After two year, median FVC increased by 38% (p = 0.02) and median DLCO increased by 32% (p = 0.08) in the CYC group as compared to 31% (p = 0.002) and 0% (p = 0.84) in the RTX group, respectively. However, ILD progression occurred in 11 patients (39%) after two years as compared to 2 patients (13%) in the RTX group. Whereas it was similar after 6 months in both groups, the survival without pulmonary progression showed a significant advantage for RTX group at two years (p = 0.023). Multivariate analysis showed that a ≥15% DLCO decrease at six months was the only criterion predicting the pulmonary progression at two years (p = 0.03). Nine patients (32%) had serious adverse events (mostly infectious complications) in CYC group, as compared to one (7%) in the RXT group (p = 0.07).

Conclusion: Patients receiving RTX for IM-related ILD showed a better survival without pulmonary progression than those treated with CYC followed by conventional IST. The difference was more significant during the "maintenance therapy period". RTX seemed also better tolerated than CYC. The place of RTX in this context should thus be reconsidered and validated prospectively.

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Abstract Number: 2327

Cardiac Involvement in Inflammatory Myopathies: A Report from the Remicam Registry

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Background/Purpose: diverse forms of cardiac involvement (CI) have been described in inflammatory myopathies (IM), and is a frequent cause of death in these diseases

Methods: A multicenter retrospective study from the REMICAM registry was performed. All patients were diagnosed with IM according to Bohan and Peter criteria, followed between Jan 1980 and Dec 2014 and classified into 7 different clinical subgroups: primary dermatomyositis (DM), primary polymyositis (PM), juvenile dermatomyositis (JuvM), cancer associated myositis (CAM), overlap myositis (OM), inclusion body myositis (IBM) and necrotizing myositis (NM). CI was defined as the presence of cardiac arrhythmia (EKG +/-Holter), myocarditis and/or pericarditis (echocardiography). Descriptive statistics, univariate and multivariate analysis were performed. Kaplan Meyer curves with long-rank analysis were used for survival.

Results: : From 478 patients (74% w, 44±23 y at diagnosis, 10±8 y of follow-up, 28% PM, 22% DM, 19,9% OM, 19,2% JuvM, 8,4% CAM, 1,3% IBM, 1,3% NM), 98 (21%) presented cardiac involvement: 53 arrhythmia, 25 myocarditis and 30 pericarditis. Patients with CI were older at diagnosis (55 vs 40 y, p<.0001), and presented more frequently DM (p=.003). CI as a whole was associated with older age (p=.003), cardiovascular disease (CVD) (p<.0001), pulmonary hypertension (PH) (p=.005), and dysphagia (p=.016), less presence of calcinosis (p=.004), higher erythrocyte sedimentation rate (ESR) (p=.003). Arrhythmia was associated with older age (p=.008), CVD (p<.0001) and less calcinosis. Myocarditis was associated with pulmonary hypertension (p=.03), arterial hypertension (p=.008) and dysphagia (.001). Pericarditis was associated with CVD (p=.002), Raynaud (p=.008) and cancer (p=.03). Median survival was 16±3 and 35±10 years for patients with or without CI (p<.0001). Seven patients were lost to follow up and 47 (52%) died, mainly from CV event (32%), infection (28%), cancer (17%) and interstitial lung disease (4%).

Conclusion: Cardiac involvement appears in 20% patients with inflammatory myopathies and confers bad prognosis, with elevated mortality. Arrhythmia is associated with older age and cardiovascular disease, suggesting that other factors could influence survival, but myocarditis is associated with dysphagia, with could suggest the presence of a more severe disease.

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Serum Ferritin Levels, Distribution of Ground Glass Opacities and New Development of Lung Infiltration during Therapy Predict Prognosis of

Interstitial Lung Disease in Anti-MDA5 Ab Positive Dermatomyositis

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Background/Purpose: Anti-MDA5 Ab positive dermatomyositis (DM) is a unique subset of inflammatory myopathy characterized by non- or mild muscle weakness, skin manifestation such as palmar pustles, and high prevalence of rapidly progressive interstitial lung disease (RP-ILD) with resistance to therapies. RP-ILD determines prognosis of DM patients with anti-MDA5 Ab, and intensive immunosuppressive therapy, a combination therapy with high dose glucocorticoid (GC), cyclophosphamide (CY) and calcineurin inhibitors such as cyclosporine (CsA) is required for ILD. However, there are patients who fail to response the treatment and it is not clear what patients are resistant to intensive immunosuppressive therapy. The aim of the present study is to identify poor prognostic factors in RP-ILD in DM positive for anti-MDA5 Ab.

Methods: Retrospective analysis was performed on consecutive 15 anti-MDA5 + patients with RP-ILD among 63 inflammatory myositis who admitted our department from 2007 to 2015. RP-ILD was defined by ILD with worsening of respiratory condition and chest infiltration within 1 month. Anti-MDA Ab was measured by ELISA in our lab. All patients were treated with combination of high dose GC (pulse therapy followed by 60mg/day of predonisolone), IVCY (500-750mg every 2-4 week) and CsA (12h intravenous administration adjusted to Cmax above 1000ng/ml during infusion and Cmin 200-250 ng/ml. Imaging analysis was conducted by 3 independent investigators.

Results: Subjects were 15 patients of 8 males and 7 female with age of 57.9±10.4 year; 14 of them were amyopathic DM (DM). Eight of them died within 6 month (7 died of respiratory failure), and 7 survived by immunosuppressive therapy. Comparison of clinical features of poor and good prognosis was shown in Table 1. Serum ferritin levels before immunosuppressive therapy and increase in ferritin levels during the treatment was high in patients with poor prognosis. The numbers of lung fields with ground glass opacities (GGO) was large in the dead. New infiltrate during the therapy was frequently found in the dead. Based on these findings, we made a score to predict the prognosis; add points of 3 factors:1) if serum ferritin levels before treatment >1000ng/ml or increase in ferritin levels during therapy >2000 ng/ml: point 1, if no: 0; 2) if numbers of lung fields (rt/lt upper, middle and lower, total 6 fields) with GGO > 4: point 1, or if <3: point 0; and if lung infiltrate was improved within 2 week starting therapy: point -1, no change: 0, and worsened or new infiltrate: 1. When the score was 3 and2, 3/3 (100%) and 5/7(71%) died, respectively while all of score <2 survived.

	Survive	Death	p
number	7	8	
ADM/DM	7/0	7/1	0.33
M/F	3/4	5/3	0.44
Age	52.4+3.4	63.0+3.2	0.04
Ferritin before Treatment(ng/ml)	851+481(498)	1697+450 (1385)	
(A) Ferritin before Treatment>1000	1 (14%)	6(75%)	o.o4
Increase in Ferritin after Treatment	1125+3461(711)	6934+3238(2206)	0.31
(B) Increase in ferritin >2000	1(14%)	5(62%)	0.05
Ferritin (A) or (B)	1(14%)	6 (75%)	0.04
AaD02 (mmHg)	24.2+54.2 (21.6)	94.9+50.7(34.5)	0.35
Number of lung fields with GGO	4.0+1.6 (3)	5.8+0.3 (6)	0.03
Number of lung fields with GGO>4	3(42%)	8 (100%)	0.01
Change in lung infiltrate in 2 weeks after treatment	Improved : 4 No Change:2 Worsened :1	Improved : 6 No Change:2 Worsened :0	0.02

Conclusion: When serum ferritin levels are elevated before treatment , ferritin levels are ibncrased during therapy, many lung fields are affected by GGO and new lung infiltrate emerged during the therapy, the prognosis of ILD of DM patients with anti-MDA5 Ab is poor in spite of intensive immunosuppressive therapy.

Abstract Number: 2329

Intravenous Immunoglobulins in the Treatment of Idiophatic Inflammatory Myopathies: Where Do We Stand?

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Session Title: Muscle Biology, Myositis and Myopathies - Poster II: Clinical

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Background/Purpose: several data are available about the use of IvIg in the treatment of idiopathic inflammatory myopathies (IIM), but the results derive from small cohorts. The aim of our study is to evaluate the efficacy of IvIg in a monocentric cohort of patients with IIMs.

Methods: retrospective study of IIM pts treated in our unit with IvIg in the last 5 years (2gr/kg/month). We evaluated ESR, CRP, creatine kinase CK; muscle strength (manual muscle test 8 - MMT8), clinical symptoms (dysphagia, dyspnea, loss of strength) at the baseline, after 6 months and at the last follow-up. We analyzed indications to treatment, major organ involvement, previous therapies, adverse events (AE).

Results: 50 pts were enrolled (17 M, 33 F), 25 PM, 24 DM, 1 IBM; 9 (3 PM, 6 DM) were affected by paraneoplastic disease. Mean disease duration was 23.7±47 months. Indications to the treatment were: loss of strenght (all patients), dysphagia (19), lung involvement (6), DM rash (18), arthritis (2) and fever (1). IvIg were chosen for refractory disease (32 pts), neoplasia (9), recurrent infections (8), pregnancy (1). Previous treatment included corticosteroids in all patients (mean cumulative dose 5.4±7.0 grams), MTX in 17, CSA in 6, rituximab in 3, CYC in 5, AZA in 4, MMF in 5. After 6 months muscular strength improved in 26/41 patients and no patient worsen. Mean CK levels were significantly reduced from 1647±2140UI/ml to 368±662UI/ml ($p=0.023$). Mean MMT8 values increased from 56.0 to 61.6 ($p<0.001$). DM skin rash improved in 12/18 patients, dysphagia in 16/19, dyspnea in 7/10, arthritis in 2/2. At last observation 21 patients were still in IvIg treatment; patients received a mean of 29 infusions (min 1, max 164). 41 patients are still in follow up (9 died for myositis related causes); the mean follow-up duration is 66 months. Seven patients presented AE but only 2 pts stopped the treatment (1 arrhythmia, 1 heart failure). 47 patients maintained improvement of the muscular strength, 1 pt presented DM skin rash, dysphagia was still present in 12 pts but less severe compared to the baseline. MMT8 globally improved ($p<0.001$) and CK reduced ($p<0.001$).

Conclusion: IvIg is an expensive treatment, but our data confirmed their efficacy and safety particularly in refractory IIM patients. Muscular strength, dysphagia, arthritis and DM skin rash are the most responsive manifestations, particularly during the first 6 months of the therapy. On the light of these data, new perspective trials on the therapeutic approach of IIM are needed, to evaluate the best timing of IvIg treatment in IIM.

Disclosure: S. Barsotti, None; **E. Cioffi**, None; **A. Tripoli**, None; **E. Calabresi**, None; **A. G. Tavoni**, None; **A. d'Ascanio**, None; **R. Neri**, None; **M. Mosca**, None.

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Abstract Number: 2330

Ultrasound Imaging in Inclusion Body Myositis

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Background/Purpose: Inclusion body myositis (IBM) is the most common idiopathic inflammatory myopathy in patients over the age of 50. For atypical or early cases where classic histopathologic changes are lacking, imaging can play a role in identifying subclinical muscle involvement. Muscle sonography has shown an increased muscle echointensity (EI) seen in various disease states. This study was undertaken to assess the pattern of muscle involvement in IBM patients with the use of ultrasound and identify potential imaging features of the disease.

Methods: Patients seen from November 2015 to May 2016 with clinicopathologically or clinically defined IBM by European Neuromuscular center were included in the study. Seven muscle groups were imaged bilaterally for each patient (deltoids, biceps, flexor carpi ulnaris, flexor digitorum profundus, rectus femoris, tibialis anterior and gastrocnemius) using a standardized protocol. Images were coded for muscle severity qualitatively using the Heckmatt score (1 normal, 2 slightly increased muscle EI, 3 marked increase in EI with decreased bone echo, and 4 severely increased EI with no bone echo). Quantitative values for muscle echointensity were calculated for each muscle by manually segmenting each muscle through ITK-Snap and calculating average pixel intensity through MATLAB. Mean values were calculated for each muscle group.

Results: Sixteen patients were included in the study, 8 male and 8 female, all Caucasian. Average duration of disease was 11.8 years. Of the 7 muscle groups studied, the muscles showing the most severe abnormalities with a Heckmatt score of 3 or more were the gastrocnemius and flexor digitorum profundus. Quantitative assessment of echointensities similarly showed the highest values for the gastrocnemius, flexor digitorum profundus and the biceps. There was also asymmetry often seen between muscle groups of the same patient, particularly in the gastrocnemius, with a heterogeneously increased EI, often in a "popcorn pattern".

Conclusion: Muscle sonography can be a useful adjunct evaluation in patients suspected to have inclusions body myositis. Findings are a heterogenously increased echogenicity in affected muscles. Most severely affected muscle groups tended to be the gastrocnemius and flexor digitorum profundus. The presence of asymmetry between sides may also be an additional indicator of the disease.

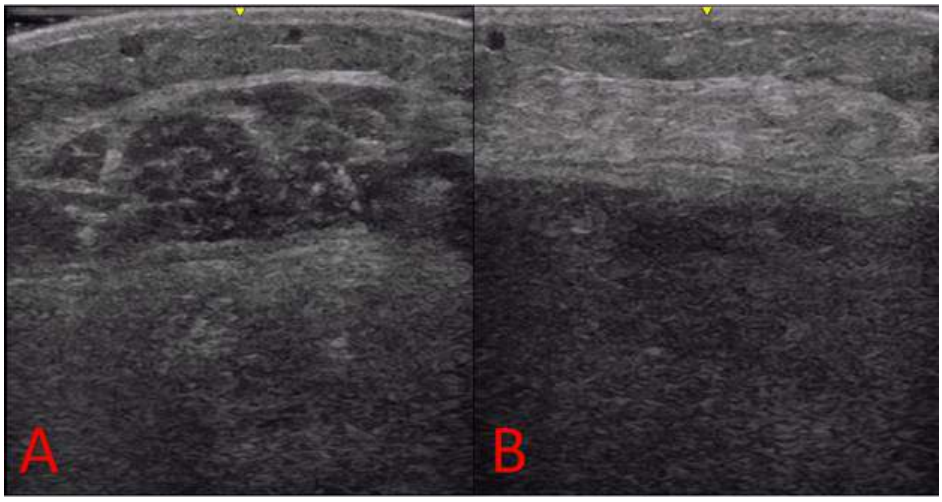

Figure 1. Asymmetry of appearance of gastrocnemius in same patient: A left, B right

Figure 2. Heterogenous increase in EI of gastrocnemius muscle ("popcorn pattern")

Muscle	Heckmatt score, mean	Echointensity, mean
Deltoids	2.58	80.2
Biceps	2.84	90.72
Flexor carpi ulnaris	2.84	78.54
Flexor Digitorum Profundus	3.37	90.73
Rectus femoris	2.93	80.35
Tibialis anterior	2.9	89.2
Gastrocnemius	3.37	91.28

Table 1. Averaged echointensities per muscle group by quantitative and qualitative assessments

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Abstract Number: 2331

Trends in Joint Replacement Surgery in Patients with Rheumatoid Arthritis

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Background/Purpose: The purpose of this study was to analyze time-trends in various types of total joint arthroplasty (TJA) and assess if the proportion of the procedures performed on patients with RA has changed over time.

Methods: The Nationwide Inpatient Sample (NIS) database was queried from 2002 to 2012 to identify the number of patients per year undergoing TJA of the shoulder (TSA), elbow (TEA), knee (TKA), hip (THA), and ankle (TAA). We determined the proportion of these patients with a diagnosis of RA. Consistent with the design of the NIS, sampling weights were applied to obtain national estimates. Population-based rates of TJA were calculated using population estimates from the U.S. Census Bureau.

Results: During the study period, the overall utilization of TJA increased by 64.7% while the prevalence of comorbid RA in all TJA increased 0.1%. However, when stratified by specific joint, the prevalence of RA in patients undergoing TJA significantly decreased ($p < 0.05$) by 12% for TEA and 0.9% for TSA, decreased 4.6% ($p = 0.06$) for TAA, while there were increases of 0.2% for THA and 0.1% for TKA.

Conclusion: While the incidence of TJA is increasing nationally, the epidemiological landscape of TSA, TEA, and TAA performed in the RA population has varied. Such findings may be evidence of the successful early implementation of biological DMARD therapy and/or adoption of aggressive treatment strategies using combinations of traditional and biological DMARDs.

Disclosure: J. A. Singh, TAP, Savient, 2,Savient, Takeda, Regeneron, Merz, Iroko, Bioiberica, Crealta and Allergan pharmaceuticals, WebMD, UBM LLC and the American College of Rheumatology, 5; **B. Young**, None; **S. Watson**, None; **J. perez**, None; **G. McGwin**, None; **B. Ponce**, None.

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Abstract Number: 2332

Midterm Outcome of Modular Metal-on-Metal Total Hip Arthroplasty

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Background/Purpose: Wear, osteolysis, and late aseptic loosening associated with ultrahigh-molecular-weight polyethylene components used in total hip arthroplasties (THA) have led to increased interest in metal-on-metal (MOM) prostheses. The availability of large-diameter metal femoral heads results in increased range of motion, reduced potential for femoral neck impingement on the acetabular rim. Despite the potential advantages, however, a continuing concern with MOM articulation is the release of metal ion debris locally and systemically in patients' blood and urine. These metal-metal wear-related complications include formation of pseudotumors, metalosis, and soft tissue necrosis. This study reports midterm outcome of THA with a Pinnacle (DePuy, Japan) modular MOM acetabular prosthesis.

Methods: From 2006 to 2008, primary THA, 86 primary THA (80 patients) were performed using a Pinnacle (DePuy, Japan) modular MOM acetabular prosthesis. There were 14 men and 72women with the mean age of 62.4 years. The preoperative diagnosis of most patients was osteoarthritis. Clinical hip function outcomes were evaluated using the Japanese Orthopaedic Association (JOA) hip score at preoperative and final follow-up. A perfect JOA hip score is 100 and the worst score is 0. Radiological analysis was performed at final follow-up. And the potential of MRI was examined for screening of pseudotumors following MOM THA. MRI was conducted in all hips postoperatively.

Results: Eight patients (9 hips) were lost before their 6-year follow-up. So, 77 THA (72 patients) were evaluated at mean 7.2-year follow-up (range 6-9.1 years). The mean (± SD) preoperative JOA hip score of 45.2 (± 12.2)

improved significantly to 86.5 (± 10.7) postoperatively at final follow-up. Four patients (4 hips) experienced problems with dislocation but no recurrent instability. An additional 1 patient (1 hip) was infected at 3.5-year after primary arthroplasty. The infected THA eventually led to removal of the stem and liner, and was performed one stage revision THA. Fifteen patients (17 hips) were observed in pseudotumor attributable to the MOM articulation by MRI from 2-year to 5-year after arthroplasty. Four patient (4 hips) was switched to a metal-on-polyethylene articulation from 5.1-year to 8.1-year postoperatively due to development with pain and swelling. In the 4 patients, 3 patients were observed pseudotumor and 1 patient were not observed, but all patients were diagnosed as ARMD (adverse reactions to metal debris). In 18 patients with pseudotumor and/or revision surgery, we evaluated between 14 patients with not revision surgery and 4 patients with revision surgery. At radiological analysis the mean cup angle of inclination was significant higher in the patients with revision surgery. Kaplan-Meier survivorship for the THA construct in this group was constant at 96.1% at 6 years after arthroplasty.

Conclusion: Clinical scores such as JOA score revealed excellent outcomes at mean 7.2-year follow-up. However, prevalence of pseudotumors per hip was 22.1%. The current cohort of patients will continue to be followed with special attention being paid to any potential local tissue reaction or other complications resulting from metal wear debris.

Disclosure: H. Wakabayashi, None; **M. Hasegawa**, None; **T. Yamaguchi**, None; **Y. Naito**, None; **A. Sudo**, None.

Abstract Number: 2333

Comparison of Clinical Outcomes of Total Ankle Arthroplasty Between Biologics and NON-Biologics Treatment Groups in Patients with Rheumatoid Arthritis

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Background/Purpose: In progress of medical treatment against rheumatoid arthritis (RA) disease activity using methotrexate (MTX) and/or biologics, we often see cases that require surgical intervention for progressive ankle joint destruction and disorder. Total ankle arthroplasty (TAA) had been one of the procedures for destructive ankle joint in RA cases. In this situation, whether biologics treatment could contribute to improve the outcomes after TAA is not elucidated.

Methods: A retrospective observational study was completed for 21 cases receiving a mobile-bearing ankle prosthesis design for treatment of rheumatoid ankle from October 2010 to May 2014. Duration of the postoperative observation was between 2 and 6 years. The FINE mobile-bearing prosthesis (Teijin-Nakashima Medical Co., Ltd., Okayama, Japan) was used. Within 21 cases, 10 cases were treated with biologics (infliximab, etanercept, tocilizumab, abatacept), and 11 cases were treated with NON-biologics drugs (MTX, tacrolimus, salazosulfapyridine, bucilamine). Preoperative and postoperative score for Japanese Society of surgery of Foot (JSSF) RA foot ankle scale was evaluated. A postoperative self-administered foot evaluation questionnaire (SAFE-Q) was also administered at the final follow-up. Prosthesis sinking, appearance of radiolucent area, tilting angle between tibial and talar compornent were investigated as radiographic evaluation. These parameters were compared between bio group and NON-bio group.

Results: There was no significant difference between the two groups in disease duration (bio: 20.1±11.2 years, NON-bio: 18.2±7.7 years), age (bio: 62.9±3.0 years old, NON-bio: 67.2±1.5 years old), DAS28-CRP score (bio: 2.53±0.48, NON-bio: 2.86±0.83), and doze of administered prednisolone (bio: 1.2±2.1 mg/day, NON-bio: 2.2±2.2 mg/day). On the other hand, the proportion of cases without prednisolone administration was significantly high in bio group (bio :7/10 [70%], NON-bio: 3/11 [27%]). In both groups, JSSF score was significantly improved after surgery, and there was no significant difference in postoperative score between the two groups. In SAFE-Q score at the final follow-up, there was no significant difference between the two groups, pain and pain related index (bio: 77.9±15.3, NON-bio: 82.4±10.9), physical functioning and daily living index (bio: 53.2±25.7, NON-bio: 52.7±17.3), social functioning (bio: 57.5±35.0, NON-bio: 45.4±32.7), shoe related index (bio: 46.7±48.2, NON-bio: 59.2±29.8), general health and well-being index (bio: 60.0±34.1, NON-bio: 76.8±22.6). In radiographic findings, appearance of radiolucent area in posterior tibial component was seen in 4 cases of biologics group. Talar prosthesis sinking was seen in 3 cases of biologics group. Tilting angle between components showed no significant difference between the two groups (bio: 0.3±0.2 degrees, NON-bio: 0.2±0.25 degrees).

Conclusion: No significant difference in postoperative clinical outcomes after TAA was found between biologics treatment group and NON-biologics treatment group within 2-6 years follow-up. Control of the disease activity is firstly important, and when tight control of RA was achieved even in NON-biologics treatment cases, TAA seems to be appropriate for RA patients. However, because biologics has the ability to stop the administration of prednisolone, biologics treatment cases has theoretically an advantage for prosthesis durability from the perspective of the strength of bone mineral structure. Long term follow-up is required.

Disclosure: M. Hirao, None; **K. Ebina**, Daiichi Sankyo, 8; **T. Noguchi**, None; **H. Tsuboi**, None; **J. Hashimoto**, None; **H. Yoshikawa**, None.

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Abstract Number: 2334

Ultrasound-Guided Facet Joint Injections through a Longitudinal Approach

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Background/Purpose: Facet joint-mediated pain has been identified as a common cause of lumbar pain. Steroid injections are currently made to treat them, usually performed under fluoroscopy or Computed Tomography-guidance. Ultrasound (US) is also appropriate to locate facet joints and some authors showed efficacy of US-guided injections through a transversal approach. On a longitudinal view, facet joints are easy-to-identify as a series of lumps with the joint capsule appearing as a thin hypoechoic line covering the joint. Each lump corresponds to the inferior articular process of the superior vertebra overlying the superior articular process of the vertebra below it. Considering the good visibility of these joints and their capsule on the longitudinal view, we studied the feasibility of US-guided facet joint injections using a longitudinal inline approach.

Methods: Patients referred to our Rheumatology department to receive facet joint injections under fluoroscopy have been included. To realize the injection, we first located the accurate lumbar level on a longitudinal median view and facet joints have been identified placing the probe 2-3 cm away from the median line. The needle was inserted in the axis of the probe to reach the hypoechoic line corresponding to the capsule or, if not visible, the top of the lump. When we obtained the bone contact, iodinated contrast medium followed by cortivazol has been injected. Finally, we made a lumbar X-ray. The first objective was to assess the number of injections realized in front of the joint. For secondary objectives, we assessed the number of accurate arthrography, the duration of the procedure and the occurrence of adverse events. During the US examination, the visibility of the capsule and the presence of osteophytes have been collected.

Results: Thirty-eight patients have been included by two operators. We excluded four patients because of a poor visibility of the spinal structures. Mean age was 58.4 years (range, 30-82) and mean BMI was 25.2 kg/m^2 (range, 18-34). US showed osteophytes in 42% and the articular capsule was inconstantly visible (25%). One-hundred and forty-four injections have been performed and 141 X-ray analyzed. One-hundred and twenty-three injections (87%) have been correctly realized in front of the joint. However, a proper arthrography has been obtained in only 35 cases (25%). Mean procedure duration was 8.5 minutes for four injections. No complication occurred, six patients (18%) reported a transient pain exacerbation.

Conclusion: With a longitudinal inline approach, 87% of US-guided facet joint injections were realized in front of the joint. However, we obtained a correct arthrography in only 25%. The depth of the target-point, the inconstant visualization of the capsule and the obliquity of the needle probably explain this result.

Disclosure: C. Darrieutort-Laffite, None; **A. Colombey**, None; **J. Glemarec**, None; **Y. Maugars**, None; **B. Le Goff**, None.

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Abstract Number: 2335

Recent Changes of Radiological Findings and Patients' Background of Rheumatoid Hip and Knee

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Background/Purpose: Treatment of rheumatoid arthritis (RA) has been dramatically changed by methotrexate (MTX) and biologics. According to introduction of these effective drugs for the control of disease activity, several changes in RA have been reported, especially in large joints. For the surgical numbers of total hip arthroplasty (THA) and total knee arthroplasty (TKA) in RA, most of studies showed decreased numbers of THA and TKA. The aim of this study was to investigate recent changes of number of surgery in the cases of THA and TKA, radiological findings, laboratory data, and patients' background such as dose changes of drugs in the regional center for RA.

Methods: Between 2000 and 2015, 81 primary cases of THA and 239 primary cases of TKA were performed for RA. We analyzed the changes of the number of surgery. The age at the time of surgery, pre- and peri-operative laboratory data, such as white blood cell count (WBC), hemoglobin (Hb), and C-reactive protein (CRP) were reviewed. Also, medication with methotrexate (MTX) and corticosteroids (CS) were also carefully reviewed. In radiographic analyses of the hip, presence of acetabular protrusion and bone spur formation were evaluated. For femoral side, canal width ratio and cortical index were analyzed. For the cases of TKA, Larsen grades, preoperative femoral-tibial angle (FTA), and the appearance of bone spur were analyzed. Statistical analysis was performed using Cochran-Armitage test and linear regression analysis. The p-values less than 0.05 were considered statistically significant.

Results: The numbers of THA and TKA were significantly decreased with time ($p<0.01$, respectively). The average age at surgery showed continual increase (THA; $p<0.05$, TKA; $p<0.01$). The administration rate and averaged dose of CS were decreased with year (THA; $p<0.05$, TKA; $p<0.01$). On the other hand, although the average dose of MTX was increased with year (THA $p<0.05$, TKA $p<0.01$), the administration rate of MTX did not show any changes. The pre- and peri-surgical WBC and Hb did not show any changes with year. The averaged pre-surgical CRP decreased for THA （$p<0.05$）, but no significant difference was observed in TKA cases. Peri-surgical change of CRP did not show any changes for both group. In radiographic analyses, TKA cases did not show proportional changes in the Larsen grades. Although cases with a severe varus deformity were decreased, the mean FTA showed no changes during the period. Interestingly, we found the continual increase of the case number of RA knee with the spur formation ($p<0.01$). For THA cases, the presence of acetabular protrusion was decreased and the presence of bone spur formation around the acetabulum was increased. Although the canal width ratio did not show any changes, the cortical index were significantly increased with year ($p<0.01$).

Conclusion: In our registry, the numbers of primary THA and TKA for RA were significantly decreased during the time period. Our results may reflect increased cases of OA changes of hips and knees in RA. Tight control of the disease by effective drugs may influenced improved disease activity and prevention of joint destruction.

Disclosure: Y. Mochida, None; **K. Ishii**, None; **H. Miyamae**, None; **N. Mitsugi**, None; **T. Saito**, None.

Abstract Number: 2336

Splinting for Trigger Finger. Short Term Effects

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Background/Purpose: Inflammatory processes of flexor tendons of fingers can produce pain and less (impaired) functionality. Trigger finger (stenosing tenosynovitis) is frequently seen in clinical practice. It is characterized by pain, snapping or locking when flexing the finger. The European consensus guideline for managing trigger finger suggests different interventions according to severity and duration of symptoms (orthoses/splints, corticosteroid injections, and surgical treatment.) Splinting is often indicated in order to prevent tendon friction. Among the different types of splinting, the experts recommend those that provide 0° metacarpophalangeal (MCF) blocking to avoid movement and load of the tendon through the A1 pulley. The aim of this study is to determine the short term effectiveness of splinting for trigger finger according to severity and duration of symptoms.

Methods: We included patients with Trigger finger diagnosis, type 1 to 3 according to Quinnell grading classification (mild, moderate, severe symptoms) who was under stable medication. Patients that received physiotherapy treatment and corticosteroid injections within 2 months before entry were excluded. Subjects were evaluated at admission and 30 days after using the splint with pain VAS, hand strength (jamar dynamometer), ability and dexterity (Picking up test) and global impact of hand disorders in daily activities (DASH disabilities of the arm, shoulder and hand). They were equipped with trigger finger splint providing 0° blocking of MCF to prevent sliding and tendon load through the A1 pulley. Patients used the splint for four weeks to perform daily activities.

Results: 15 patients were included (13 women and 2 men), 90% with trigger finger type 2/3 of Quinnell classification and 1 to 5 months of symptoms duration. 100% improved performance of daily activities according to DASH questionnaire. In 80% a decrease in frequency of locking, stiffness of the hand and fingers flexion were observed. We could not find changes in pain and strength parameters.

Conclusion: All the patients included improved the ability to perform daily activities after a month of splinting; and in most of the patients a decrease in the frequency of locking during finger flexion was noted. Even when these results are encouraging, it would be useful to increase the sample size and compare the splinting with other therapeutic modalities for the conservative treatment of trigger finger.

Abstract Number: 2337

Sleep Quality, Disturbances and Physical Activity: A Nationwide Survey Among Health Professionals on Their Engagement with Irish People Who Have Rheumatic Disease

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Background/Purpose: Sleep disturbance is common in people who have inflammatory arthritis and can contribute to disability, symptomatology, and use of increased healthcare. Disturbed sleep is a common complaint among people with inflammatory arthritis and this consequently has an effect on their overall quality of life, in addition to their mental and physical health. Little is known regarding the current practice of Health Professionals in Rheumatology on their engagement with patients in discussing their sleep quality and disturbances therefore, it is important to investigate if there are any educational needs in this important area of practice

Methods: Objectives were to investigate the awareness of Irish Health Professionals in Rheumatology on their patients' engagement when discussing sleep quality, sleep disturbances and physical activity, among Irish people who have inflammatory arthritis. Members from the Irish Rheumatology Health Professionals Society (n=43) were invited to participate in a cross-sectional survey hosted on SurveyMonkey$^{(R)TM}$. Ethical approval was received. Descriptive statistics, Chi-square tests/Fisher's exact tests were used to analyse the data using SPSS v22

Results: Twenty eight (65%) Health Professional's responded. Results found the mean number of years qualified to be 16.93 (SD 6.82), mean number of years working in Rheumatology to be 10.07 (SD 4.04) and 40% of respondents reporting half of their patient workload coming from people who have inflammatory arthritis. Just 52% discuss sleep with their patients with 46% mentioning fatigue as their main reason when enquiring. Of those who do discuss sleep, 100% of their patients mentioned 'pain' and 'waking up in the middle of the night or early morning' as disturbances when discussing their sleep, while 67% reported 'taken prescribed or over the counter medication' to help with their sleep. There was no statistically significant association between longer years qualified, more years working with people with inflammatory arthritis or health profession, when discussing sleep. When using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), Health Professional's were active 2,248 minutes per week. This exceeds the American College of Sports Medicines' physical activity guidelines however, is low compared to other physical activity Health Professional surveys from European countries, even-though 100% of respondents believe it is important to measure physical activity

Conclusion: Only half of Health Professional's discuss sleep with their patients with fatigue as the main reason when enquiring. Health Professional's meet the physical activity guidelines however, are less active than their European peers. There is a need to develop education and training for physiotherapists in the importance of enquiring about their patients sleep quality and disturbances and the potential impact it has on their physical activity levels. In addition, the effects of physical activity and exercise interventions on poor sleep quality and

disturbances needs to be examined so that Health Professional's are in a better position to promote health and well-being in people with Inflammatory Arthritis, in this important area of practice

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Disclosure: S. McKenna, None; **A. Donnelly**, None; **S. Fraser**, None; **N. Kennedy**, None.

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Abstract Number: 2338

The Relationship Between Anxiety and Physical Activity Participation in Adults with Persistent Knee Pain and the Moderating Effect of Neighborhood Social Cohesion

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Background/Purpose : Behavioral theories suggest psychological distress reduces physical activity (PA) engagement via behavioral inhibition. Community factors such as neighborhood cohesion are also associated with PA. This study examined the association between emotional distress and PA in adults with persistent knee pain and identified whether neighborhood social cohesion moderates this relationship.

Methods : Data from 601 African American and White adults > 45 years with persistent knee pain (defined as pain, aching, stiffness on most days) enrolled in the Johnston Osteoarthritis Project (2006-2011) were analyzed. Moderate/vigorous intensity PA (MVPA), measured using the Behavioral Risk Factor Surveillance Survey (BRFSS) PA scale, was categorized into a 3-level variable according to 2008 US PA Guidelines (0-9, 10-<150, ³150 MVPA minutes/week). The Arthritis Impact Measurement Scales (AIMS 2) – Anxiety scale measured anxiety (higher scores indicate more anxiety) and SampsonÕs Neighborhood Cohesion Scale assessed social cohesion (higher scores indicate greater cohesion). Covariates included: demographics (age, gender, race, education, body mass index (BMI), employment), medical history (comorbidities, symptomatic KOA), depression (CES-D), community factors (poverty level, neighborhood walkability, safety, aesthetics), perceived helplessness, and WOMAC physical function, stiffness and pain. A generalized logit model examined associations between MVPA levels and anxiety and the interaction between perceived social cohesion and anxiety, adjusting for covariates (**Table**).

Results : ParticipantsÕ mean age was 68.9 years (SD=9), 407(67%) were Caucasian, 431 (72%) were female. 403 (67%) adults had knee pain for ³ 5 years and mean AIMS-2 anxiety score was 3.36 (SD=1.9). 222 (37%) adults engaged in < 10 minutes of MVPA/week, 138 (23%) in 10-149 minutes/week and 241 (40%) met DHHS requirements of ³ 150 min of MVPA/week. Three hundred fourteen individuals (52%) reported positive neighborhood social cohesion. Factors associated with engagement in some MVPA and meeting recommended MVPA levels were: younger age, female gender, better knee function, fewer comorbidities, less depression, longer duration of knee pain, and positive neighborhood social cohesion and aesthetics. A two-unit increase in the AIMS anxiety subscale, among individuals who perceived positive cohesion, was associated with increased odds of engaging in MVPA.

Conclusion : Neighborhood social cohesion appears to moderate the relationship between anxiety and participation in weekly MVPA. Specifically, social cohesion did not affect those engaged in high PA levels but did promote more PA among those who were anxious/tense. Recognizing the positive affect of social cohesion on anxiety and MVPA may inform counseling strategies for adults with persistent knee pain to adopt PA to manage their pain.

Table: Correlates of Weekly Physical Activity Participation in Adults with Persistent Knee Pain From Multivariate Generalized Logit Model

Explanatory Variable	10 - <150 min MVPA/week	>= 150 min MVPA/week	Type III p-value
Anxiety (AIMS-2)			0.71
Cohesion			**0.02**
2-point increase Anxiety/Tension with no neighborhood social cohesion	OR = 0.87 95%CI = 0.58-1.3	OR = 1.01 95%CI = 0.69-1.48	
			0.06
2- point increase Anxiety/Tension with neighborhood social cohesion	OR = 1.49 95%CI = 0.98-2.27	OR = 1.01 95%CI = 0.70-1.47	
Race	OR = 0.77 95%CI = 0.46-1.32	OR = 0.65 95%CI = 0.41-1.05	0.29
Duration of Knee Pain (years)	OR = 1.85 95%CI = 1.04-3.27	OR = 1.28 95%CI = 0.77-2.13	**0.07**
Has > 2 Comorbidities	OR = 0.45 95%CI = 0.26-0.78	OR = 0.69 95%CI = 0.43-1.12	**0.015**
Female	OR = 2.11 95%CI = 1.18-3.78	OR = 1.07 95%CI = 0.67-1.73	**0.025**
Age (years)	OR = 0.95 95%CI = 0.92-0.98	OR = 0.98 95%CI = 0.95-1.00	**0.003**
Depressed (CES-D)	OR = 0.68 95%CI = 0.32-1.40	OR = 0.35 95%CI = 0.16-0.73	**0.02**
Aesthetically Nice Neighborhood	OR = 0.64 95%CI = 0.36-1.12	OR = 0.56 95%CI = 0.34-0.94	**0.07**
Knee Function (WOMAC)	OR = 0.98 95%CI = 0.96-0.99	OR = 0.97 95%CI = 0.95-0.98	**0.0006**
Diagnosed with knee osteoarthritis (KOA)	OR = 0.61 95%CI = 0.34-1.05	OR = 0.66 95%CI = 0.41-1.06	0.13

* reference category for MVPA is 0-9 minutes of MVPA per week

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Disclosure: M. D. Iversen, None; **C. Alvarez**, None; **R. J. Cleveland**, None; **J. M. Jordan**, None; **L. F. Callahan**, None.

Abstract Number: 2339

Does Physical Activity Change after Total Hip or Knee Arthroplasty: A Systematic Review and Meta-Analysis

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Background/Purpose: Total joint replacement surgery has become one of the most common elective surgical procedures. Improvements in pain and physical function following total hip arthroplasty (THA) and total knee arthroplasty (TKA) are known however less is known about changes in physical activity (PA). A recent systematic review qualitatively described changes in PA following THA and TKA but did not examine changes in pain, quality of life, and physical function. As such, the purpose of this study is to conduct a systematic review of the literature, with meta-analysis, on the change in PA after THA or TKA surgery and evaluate other factors such as changes in pain levels, physical function and quality of life that may contribute to participation in PA.

Methods: We searched three databases (Pubmed, CINAHL and Embase) for peer-reviewed, English-language cohort studies that tracked change in accelerometer measured PA in the same population from pre- to-post surgery. Two reviewers independently screened titles, abstracts, and full-texts with a third reviewer settling disagreements. Two reviewers independently abstracted demographic and outcome data relating to PA, pain, physical function and quality of life. Random-effects models were used to produce standardized mean differences (SMD) for physical activity, quality of life, pain, and physical function outcomes. Effect sizes were gauged as small (SMD=0.2), moderate (SMD=0.5) and large (SMD=0.8). Heterogeneity was measured with I^2.

Results: Eleven studies (531 total patients) published between 2002-2014 met eligibility criteria. Subjects mean ages ranged from 42.1 to 69.0 years of age, mean body mass index ranged from 23.0 to 32.6, and a majority of participants were women. Surgical area (TKA or THA) varied with THA alone (n=4 studies), TKA alone (n=5 studies), and combined either THA and TKA patients (n=2 studies). At 6 months post-surgery no significant increase in accelerometer measured PA was found when compared to pre-surgery PA (SMD=0.09; 95% CI -0.08 to 0.25; I^2=0%). A small-to-moderate significant effect was found for accelerometer measured PA at 12 months post-surgery when compared to pre-surgery PA (SMD=0.43; 95% CI 0.22 to 0.64; I^2=0%). At 6-monts post surgery large and significant effects were found for reduction in pain (SMD= -1.25 ((95% CI -1.89, -0.61)), improved quality of life (SMD=0.71 ((95% CI 0.08, 1.34)), and improved physical function (SMD=0.84 ((95% CI 0.21, 1.47)).

Conclusion: Despite large improvements in pain, physical function and quality of life, participants PA levels remained the same at 6 months and showed modest improvement at 12 months post TKA or THA. Reasons for the decreased levels of PA are unknown but may be behavioral in nature. Considering the consistency of effect demonstrated across these eleven studies future studies should seek to understand the barriers for decreased PA following TKA or THA so that future intervention studies may improve PA among this subgroup of patients.

Disclosure: T. Hammett, None; **M. Austin**, None; **A. Simonian**, None; **R. Butler**, None; **A. P. Goode**, None.

Abstract Number: 2340

Relation Between Range of Motion and Physical Activity While Recovering after Total Knee Replacement

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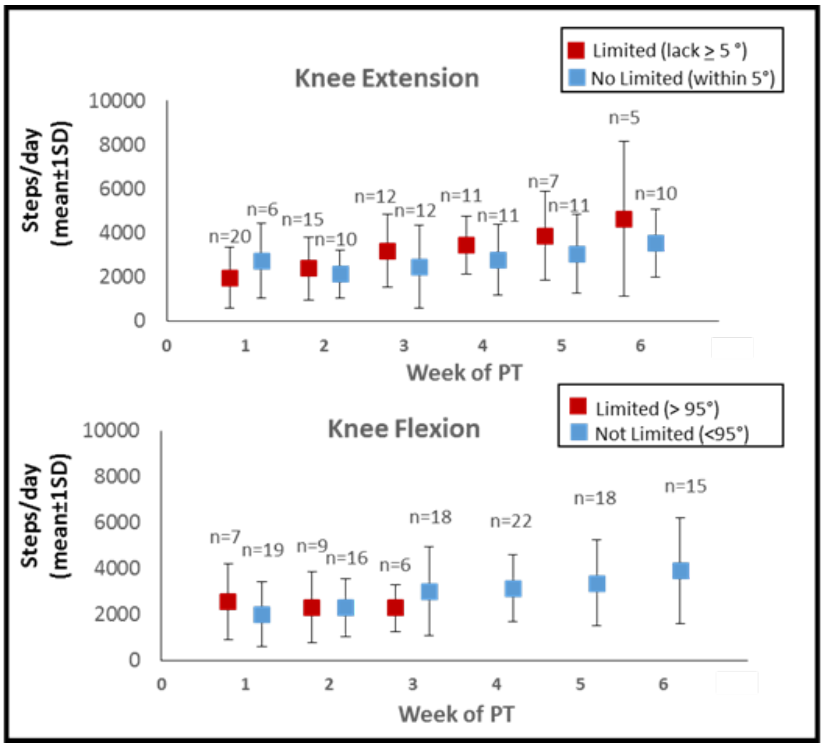
Background/Purpose: Standard post-operative physical therapy (PT) for total knee replacement (TKR) aims to increase knee range of motion (ROM), which is important for walking and adopting an active lifestyle, e.g., taking more steps/day, after TKR. However, it is unclear to what extent limited ROM may be a barrier to physical activity after TKR. This is important to study since ROM is a modifiable impairment that can be prioritized in PT after TKR. The purpose of this study was to evaluate the association of ROM with physical activity over the first 6 weeks of PT after TKR.

Methods: We recruited patients with a first time unilateral TKR from a local PT clinic. We excluded people with comorbidity that affected physical function other than arthritis. We quantified physical activity as steps/day using an accelerometer enabled monitor (Actigraph GT3X) worn for at least 3 days during waking hours. Knee ROM was measured by a physical therapist using a standardized approach. We classified lacking $\geq 5°$ of full knee extension as limited extension, and knee flexion $\leq 95°$ as limited flexion. We examined the difference in steps/day between those with and without limited knee ROM with physical activity each week of PT (weeks 1 to 6) using difference tests and 95% Confidence Intervals (CI).

Results: We included 26 people after TKR (age [mean± sd] 64.9 ± 9.1 years, BMI 34.5 ± 7.5 kg/m^2, 56% female) at baseline. Participants walked 1889 ± 1467 steps/day at week 1, and 3474 ± 2277 step/day at week 6. In general, there was little difference in steps/day between those with and without limited ROM. For instance, there was a non-statistically significant difference in steps/day between those with limited extension (n=20) compared with those without (n=6) (776 steps/day, 95% CI [-2185, 633.26]). In a similar fashion, there was little difference among those with limited flexion (n=7) compared with those without (538 steps/day, 95% CI[-818, 1894]). A small difference was observed at week 6 for extension. No participants had limited flexion after week 3. (Figure)

Conclusion: Our preliminary findings show little difference in physical activity among people with and without ROM limitations after TKR. Limited ROM, even at clinically significant levels, may not be a major barrier to physical activity after TKR. **Figure:** Weekly steps/day for people after TKR with and without limited knee extension/flexion during outpatient PT [sample size (n) provided above each data point].



Abstract Number: 2341

Prediction of Triaxial Accelerometer Counts from Unaxial Acceleromenter Counts Among Adults with or at Risk for Knee Osteoarthritis: Data from the Osteoarthritis Initiative

Julia (Jungwha) Lee[1], Jing Song[2], Rowland W. Chang[3], Pamela Semanik[4], Christine Pellegrini[5], Linda S. Ehrlich-Jones[6], Daniel Pinto[7], Rebecca D. Jackson[8] and Dorothy D. Dunlop[2], [1]Preventive Medicine/Biostatistics, Northwestern University Feinberg School of Medicine, Chicago, IL, [2]Center for Healthcare Studies, Northwestern University Feinberg School of Medicine, Chicago, IL, [3]Institute for Public Health and Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [4]College of Nursing, Rush University, Chicago, IL, [5]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL, [6]Research CROR, Rehabilitation Institute Chicago, Chicago, IL, [7]Department of Physical Therapy & Human Movement Sciences, Northwestern University, Chicago, IL, [8]Ohio State University, Columbus, OH
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Background/Purpose: Physical activity monitoring studies in rheumatology initially used uniaxial accelerometers. But advanced triaxial accelerometry technology replaced uniaxial accelerometers. Uniaxial devices measure accelerations in one dimension while triaxial devices measure body accelerations in three planes of movement planes. The aim of this study is to create a crosswalk table between uniaxial and triaxial physical activity measures to facilitate comparing work from previous studies based on uniaxial devices with new studies using triaxial devices.

Methods: An Osteoarthritis Initiative subset of 185 community dwelling adults aged 45 years or older having knee osteoarthritis or knee osteoarthritis risk factors simultaneously monitored physical activity using both a uniaxial accelerometer (ActiGraph GT1M) and a triaxial accelerometer (ActiGraph GT3X) worn on the waist for 7 days. Relationship of minute-by-minute output data from the two accelerometers (uniaxial activity counts; triaxial vector magnitude counts) was evaluated using classification tree analysis (Salford Systems CART® v8.0). Data were split into learning (835,221 matched minutes/130 persons) and test (361,941 matched minutes/55 persons) sets. The learning set was used to get uniaxial cutpoints and the test set was used to test the cutpoints. Optimal classification trees (i.e., minimizing misclassification error) identified best-performing cutpoints for uniaxial activity counts to predict triaxial vector magnitude counts using least absolute deviation (LAD) splitting methods. Medians of triaxial vector magnitude counts in each terminal node were used as predicted values for that node. Mean absolute deviation (MAD), a measure of model error, was independently estimated in the test set. Data included only waking hours and excluded sleep periods at night.

Results: 185 participants included 55% with radiographic knee OA (Kellgren-Lawrence grade score ≥ 2), 10% with high pain (SF-12 bodily pain ≥ 3), and 43% with obese weight (body mass index ≥ 30 kg/m^2). Classification tree analyses identified 26 best-performing (i.e., minimum misclassification error) cutpoints for uniaxial activity counts to predict triaxial vector magnitude counts in the learning set (Table 1). MAD estimate was 302.33 in the test set using 26 optimal cutpoints from the learning set.

Conclusion: This crosswalk table between uniaxial and triaxial physical activity measures will facilitate comparisons of previous uniaxial data with future studies using newer triaxial technology in knee osteoarthritis populations.

Table 1. Uniaxial Activity Count Cutpoints and Predicted Triaxial Vector Magnitude Counts for Each Node Number

Node Number	Number of Observations	Uniaxial Activity Count Cutpoints	Predicted Triaxial Vector Magnitude Counts
1	416,933	0	0
2	80,580	1 – 23	75.85
3	37,416	24 – 45	141.16
4	32,577	46 – 75	236.51
. . .	. . .	. . .	. . .
23	732	4239 - 4742	5107.15
24	449	4743 - 5168	5580.56
25	626	5169 - 6626	6122.38
26	194	6627 or above	7756.02

Disclosure: J. Lee, NIH, 2; **J. Song**, NIH, 2; **R. W. Chang**, NIH, 2; **P. Semanik**, NIH, 2; **C. Pellegrini**, NIH, 2; **L. S. Ehrlich-Jones**, NIH, 2; **D. Pinto**, NIH, 2; **R. D. Jackson**, None; **D. D. Dunlop**, NIH, 2.

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Abstract Number: 2342

Understanding Patient Barriers and Facilitators to Healthy Eating and Physical Activity before and after Knee Replacement

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Background/Purpose: Knee replacement typically results in reduced pain and improved physical function, yet post-operative physical activity levels often remain unchanged. Many patients also gain weight following surgery, yet no weight management programs exist for this population. We sought to identify patient-reported barriers and facilitators to healthy eating and physical activity among patients before or after knee replacement.

Methods: Twenty patients with knee osteoarthritis between 40-79 years who had a knee replacement surgery scheduled or completed within 3 months were interviewed. Interview topics included perceived barriers and facilitators to healthy eating and physical activity, both before or after knee replacement. Interviews were coded and analyzed using constant comparative analysis.

Results: Interviews were completed by 11 pre-operative and 9 post-operative patients (overall mean 64.7±9.8 years, 45% female, 90% White, BMI 30.8±5.5 kg/m^2). The most common barriers to healthy eating identified were desire for high fat/calorie foods, overconsumption, and mood. Time-related factors (i.e., planning meals, making time to grocery shop) and portion control were identified as facilitators to healthy eating. Barriers for activity included pain, physical limitations, and lack of motivation, whereas facilitators included having motivation to improve knee symptoms/outcomes, building activity habits, and monitoring activity levels.

Conclusion: Identifying the specific barriers and facilitators influencing eating and activity behaviors provides critical insight from the patient perspective which will aid in developing a patient-centered weight loss program for knee replacement patients. Understanding these factors could guide clinician discussions encouraging weight loss pre- or post-operatively in overweight and obese knee replacement patients.

Disclosure: C. Pellegrini, NIH, 2; **G. Ledford**, None; **R. W. Chang**, NIH, 2; **K. Cameron**, None.

Abstract Number: 2343

A Phase 2, Multi-Center, Randomized, Double-Blind, Active-Controlled, Parallel Group Study to Evaluate the Safety and Dose Effectiveness of Intradermal Injections of Purified Apis Mellifera Toxin to Improve Pain and Physical Function in Patients with Osteoarthritis of the Knee

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Background/Purpose: This Phase 2a/b trial evaluated the safety and dose effectiveness of honeybee toxin (purified *Apis mellifera*toxin) injections to improve pain and physical function in patients with osteoarthritis (OA) of the knee.

Methods: Eligible patients were ≥35 years (men and women), with OA in one or both knees (Grade 1-3) and with pain symptoms ≥4 on a visual analog scale (VAS) after medication washout. Eligible patients were randomized to histamine controls: 2.75 µg (n=4), 8.25 µg (n=3), or 27.5 µg (n=4); or to honeybee toxin: 100 µg (n=9), 300 µg (n=10) or 1000 µg (n=10). Patients received 10 intradermal injections (5 in each knee) with syringes randomly filled with control, toxin or saline depending on treatment assignment. Injection sites were randomly targeted to the OA knee because honeybee toxin has systemic effectiveness as well as local activity. Safety evaluated any significant adverse events (AEs) including immediate hypersensitivity reactions from treatment after a negative honeybee toxin skin test (50 µg). Efficacy endpoints were assessed at Predose (Day 1), and Follow-Up Visits (Day 7 and 14) for pain and physical function using subscores from the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Version LK 3.1, as well as for patient global assessment (PGA) and physician global assessment (PhGA).

Results: The majority of patients (33/40, 82.5%) reported at least one treatment-emergent adverse event (TEAE) that were primarily mild to moderate injection site reactions (discomfort, edema, induration, pain, pruritus, urticaria and warmth). All injection site reactions resolved by Day 14. There were no discontinuations or SAEs associated with the honeybee toxin doses, and there were no changes in laboratory parameters, vital signs, or electrocardiograms. At Day 7, WOMAC pain subscores showed an improvement in pain relative to control for all three honeybee toxin doses but not significantly; i.e., least square mean (LSM) difference from control: -2.23, -2.27 and 2.11, respectively, for the 100 µg, 300 µg and 1000 µg doses; p=0.2880. Physical function subscores, however, showed significant improvement versus control at Day 7: -11.27 (p=0.0374), -11.38 (p=0.0308) and -10.35 (p=0.0541), respectively, for the honeybee toxin doses. Further, at Day 7, a significant majority of all patients treated with honeybee toxin (66.5%; p=0.0177) assessed their condition (PGA) as being “very good or good” whereas 90% of patients in the control group perceived their condition as being “fair or poor.” The PhGA was generally consistent with the PGA. Regarding Day 14 efficacy assessments, most were consistent with Day 7, however, the improvements among the doses were not as significant.

Conclusion: The honeybee toxin regimens resulted in consistent improvement in pain, physical function, and global health perceptions in patients with knee OA. The safety profile raised no concerns or issues related to treatment. The results of this Phase 2 trial provide sufficient clinical evidence to justify investigating the safety and efficacy of honeybee toxin (purified *Apis mellifera* toxin) for treating patients with OA pain and inflammation in a Phase 3 trial.

Disclosure: D. R. Schumacher, honeybee toxin (purified Apis mellifera toxin), 2; **A. Jakubowska**, honeybee toxin (purified Apis mellifera toxin), 3; **C. M. H. Kim**, honeybee toxin (purified Apis mellifera toxin), 4.

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Abstract Number: 2344

Inflammation and Glucose Homeostasis Are Associated with Specific Structural Features Among Adults without Knee Osteoarthritis

Alina Stout[1], Mary Barbe[2], Charles B. Eaton[3], Mamta Amin[4], Fatimah Al Eid[1], Lori Lyn Price[5], Bing Lu[6], Grace H. Lo[7], Ming Zhang[8], Timothy E. McAlindon[9] and Jeffrey Driban[8], [1]Rheumatology, Tufts Medical Center, Boston, MA, [2]Temple University School of Medicine, Philadelphia, PA, [3]Family Medicine and Community Health(Epidemiology), Alpert Medical School of Brown University, Pawtucket, RI, [4]Department of Anatomy and Cell Biology, Temple University School of Medicine, Philadelphia, PA, [5]Clinical Care Research, Tufts Medical Center, Boston, MA, [6]Brigham & Women's Hospital and Harvard Medical School, Boston, MA, [7]Immunology, Allergy, Rheumatology, Baylor College of Medicine, Houston, TX, [8]Tufts Medical Center, Boston, MA, [9]Division of Rheumatology, Tufts Medical Center, Boston, MA

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Background/Purpose: Adults with osteoarthritis (OA) have greater glucose concentrations and inflammation. It remains unclear if inflammation and glucose homeostasis are related to specific features of early stage OA. Bone marrow lesions (BMLs) and effusion are early features of OA that can change size in < 12 weeks and are associated with knee pain and OA progression. We explored if serum concentrations of impaired glucose homeostasis (glucose, glycated serum protein [GSP]) or inflammation (C-reactive protein; CRP) were associated with the prevalence of knee BMLs or effusion.

Methods: We conducted a cross-sectional study with baseline data from the Osteoarthritis Initiative. We selected participants who had no radiographic knee OA, were at high risk for knee OA, and had sagittal fat-suppressed knee magnetic resonance images and fasting serum. Blinded staff conducted assays for CRP, GSP, and glucose. One reader segmented BML volume using a semi-automated program (intra-tester ICC > 0.86). Two readers used a semi-automated program to segment effusion volume (intra-tester ICC > 0.84). We defined BML prevalence as a knee with a BML volume ≥ 1 cc and effusion prevalence as a knee with an effusion volume ≥ 7.5 cc. We performed separate logistic regression models for these 2 outcomes with each biomarker as a predictor, adjusting

for age, sex, body mass index (BMI), and Physical Activity Scale for the Elderly (PASE) scores. We explored interactions between the biomarkers and BMI. When a nonlinear relationship was present we performed piece-wise logistic regressions.

Results: We included 343 participants with a mean age of 59 ± 9 years, BMI of 27.9 ± 4.5 kg/m^2, PASE score of 171 ± 82, and 64% female. CRP was associated with BML prevalence (odds ratio [OR] = 1.43, 95% confidence interval [CI] = 1.09 to 1.87; Table 1). For effusion, we found an interaction between BMI and CRP: among adults with a BMI < 25 kg/m^2 there was a trend towards a positive association between CRP and effusion (OR = 1.40, 95% CI = 1.00 to 1.97), while no significant association was observed among people with a BMI ≥ 25 kg/m^2. We detected a nonlinear relationship between GSP and effusion prevalence: for GSP levels ≥ 5.5cc people with greater concentrations were more likely to have effusion, while for GSP levels < 5.5cc people with lower concentrations were more likely to have effusion (Table 2).

Conclusion: Among individuals without knee OA, CRP is related to the presence of BMLs and effusion among normal weight individuals. Abnormal GSP is associated with effusion. It will be valuable to explore if inflammation and glucose homeostasis are predictive of symptomatic knee OA.

Table 1. C-Reactive Protein (CRP) is Associated with the Prevalence of Bone Marrow Lesions (BMLs)

Predictor (continuous)	**No BML (n = 287) Mean (SD) (Reference)**	**Prevalent BML (n = 56) Mean (SD)**	**Prevalent BML Crude OR (per unit of biomarker concentration)**	**Prevalent BML Adjusted OR (per unit of biomarker concentration)**
CRP (mg/L)	3.24 (1.22)	3.67 (1.12)	**1.36 (1.05, 1.75)**	**1.43 (1.09, 1.87)**
lnGSP	5.50 (0.70)	5.43 (0.82)	0.87 (0.58, 1.32)	0.97 (0.65, 1.46)
Glucose (mg/dL)	109.3 (27.2)	114.6 (22.2)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)

OR = odds ratio, lnGSP = glycated serum protein (log). Adjusted analyses included age, body mass index, sex, and PASE score.

Table 2. Glycated Serum Protein (GSP) is Associated with the Prevalence of Effusion

Predictor (continuous)	No-Little Effusion (n = 173) Mean (SD) (Reference)	Effusion (≥ 7.5 cc) (n = 170) Mean (SD)	Prevalent Effusion Crude OR (per unit of biomarker concentration	Prevalent Effusion Adjusted OR (per unit of biomarker concentration)
CRP (mg/L)	3.29 (1.27)	3.34 (1.16)	1.04 (0.87, 1.24)	1.01 (0.83, 1.22)
lnGSP < 5.5	5.10 (0.29)	4.99 (0.40)	**0.36 (0.18, 0.73)**	**0.39 (0.18, 0.83)**
lnGSP ≥ 5.5	6.01 (0.49)	6.29 (0.71)	**2.01 (1.22, 3.32)**	**2.02 (1.22, 3.34)**
Glucose (mg/dL)	108.7 (27.9)	111.7 (25.1)	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)

OR = odds ratio, CRP = C-reactive protein. Adjusted analyses included age, body mass index, sex, and PASE score.

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Abstract Number: 2345

Relation of Varus Knee Thrust during Walking to Two-Year Incidence of Frequent Ankle, Hip, and Lower Back Pain

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Background/Purpose: Varus knee thrust is an abrupt change in frontal plane alignment of the tibiofemoral joint observed during gait. Thrust has been previously linked to radiographic knee OA progression, worsening cartilage and bone marrow lesions, and knee pain. Knee thrust is a dynamic event that likely influences the entire kinematic chain of the lower limb and causes trunk lean yet the effects of thrust on the hip and ankle and the lower back are not known. As low back, hip, and ankle pain are impactful problems among older adults, and as varus thrust is potentially modifiable through gait retraining interventions, determining a relation of thrust to pain at these regions is of interest. *Our objective was to determine the effects of knee thrust on the two-year incidence of frequent ankle, hip, and low back pain in older adults with or at risk for OA.*

Methods: The Multicenter Osteoarthritis Study (MOST) is a prospective cohort study of older Americans that have or are at risk for knee OA. At the 60-month clinic exam, 60 Hz frontal plane video recordings were acquired as participants completed two self-paced walking trials over a 4.9 meter walkway. A trained reader, blinded to disease status, assessed the presence of varus thrust on a majority of steps (intra-rater $\kappa = 0.73$). Frequent ankle, hip, and low back pain was self-reported by MOST participants using a homunculus. Among participants with no pain at the 60-month exam, incident frequent pain in these regions was defined at the 84-month exam as "pain, aching, or stiffness on most days in the past 30 days." To assess the relation of thrust to incident pain, we used logistic regression adjusting for age, sex, race, BMI, and gait speed. In limb-based analyses (hip and ankle pain), generalized estimating equations accounted for two limbs from the same subject.

Results: 1375 subjects (mean age 67.3 ± 7.7; mean BMI 30.3 ± 5.7; 89.3% White; 58.7% female) contributed to the person-based analysis. 2158 knees from 1087 subjects comprised the sample for the limb-based analyses. Varus thrust was observed in 31.3% of knees. Nonsignificant results suggested that knees with thrust may have 1.30 times the odds (95% CI: 0.97, 1.73) of incident hip pain ($p = 0.08$), and that persons with thrust in at least one knee have 1.47 times the odds (95% CI: 0.96, 2.24) of incident low back pain ($p = 0.08$) compared to knees without thrust. No association was found between knee thrust and risk of incident ankle pain ($p = 0.22$) (see Table).

Conclusion: While small numbers of incident pain cases may have restricted our ability to detect significant relationships, nonsignificant findings suggest a possible association between varus thrust and two-year risk of developing frequent hip and low back pain. Further investigation into the relationship between aberrant movement at the knee and painful injury at these regions may help explain these findings.

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Abstract Number: 2346

The Improving Motivation for Physical Activity in Arthritis Clinical Trial for Adults with Knee Osteoarthritis and Rheumatoid Arthritis

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Abstract:

Background/Purpose: Insufficiently active adults experience reduced quality of life. Because half of adults with arthritis are physically inactive, we evaluated the additional effect of a motivational-interviewing based lifestyle physical activity intervention when added to physician-advice-only control group on pain and physical function in adults with knee osteoarthritis or rheumatoid arthritis (RA).

Methods: Participants meeting American College of Rheumatology criteria for knee osteoarthritis or RA were randomized to physician-advise-only control or motivational-interviewing-based physical activity intervention group. For the motivational-interviewing intervention, participants met with a physical activity advocate who facilitated individualized physical activity goal setting and behavior change using motivational interviewing. Primary outcomes were pain and function evaluated by Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for knee osteoarthritis and Health Assessment Questionnaire (HAQ) for RA at baseline, 3 months, and 6 months. Secondary outcome was accelerometer-measured moderate-to-vigorous physical activity (MVPA). Linear regression with generalized estimating equations (GEE) was used to evaluate the average intervention effect on changes in outcomes from baseline to 3 months and/or 6 months.

Results: Participants included 155 adults with knee osteoarthritis (76 intervention, 79 control) and 185 adults with RA (93 intervention, 92 control). The knee osteoarthritis participants who received the motivational-interviewing physical activity intervention had WOMAC pain score improve by 0.91 points (95% CI 0.05, 1.77), WOMAC function improve by 1.91 points (95% CI -0.66, 4.47), and their average daily physical activity increased by 22.79 minutes/day (95% CI -18.45, 64.04) more than control. For the RA intervention group, HAQ function score improved by 0.11 (95% CI -0.01, 0.22) compared to controls.

Conclusion: Motivational-interviewing-based physical activity intervention participants with knee osteoarthritis experienced significant improvement in pain compared to physician-advice-only controls. Both knee osteoarthritis and RA intervention participants demonstrated a trend towards improved physical function.

Table 1. Outcomes at baseline, 3 and 6 month follow-up for participants with Knee Osteoarthritis

	Intervention		Control		Difference between intervention and control groups
WOMAC Pain					
Baseline (n=76/79)	5.95	(5.14, 6.76)	5.41	(4.68, 6.15)	
3 month (n=65/60)	5.27	(4.45, 6.09)	6.03	(5.20, 6.86)	
6 month (n=57/66)	5.24	(4.43, 6.05)	5.21	(4.43, 6.00)	
Overall improvement from baseline[1]	0.70	(0.02, 1.37)*	-0.22	(-0.74, 0.31)	0.91 (0.05, 1.77)*
WOMAC Physical Function					
Baseline (n=76/79)	18.22	(15.45, 20.99)	16.97	(14.49, 19.45)	
3 month (n=65/60)	16.89	(14.07, 19.70)	17.36	(14.76, 19.95)	
6 month (n=57/66)	15.29	(12.62, 17.96)	16.15	(13.65, 18.60)	
Overall improvement from baseline[1]	2.13	(0.15, 4.11)*	0.23	(-1.40, 1.85)	1.91 (-0.66, 4.47)
Average daily physical activity minutes					
Baseline (n =74/70)	22.63	(18.50, 26.75)	16.67	(11.97, 21.36)	
3 month (n=57/54)	24.69	(19.62, 29.76)	18.11	(13.58, 22.66)	
6 month (n=42/52)	26.70	(20.74, 32.65)	16.56	(12.04, 21.09)	
Overall improvement from baseline[1]	3.07	(-0.20, 6.33)	0.67	(-2.07, 3.41)	2.40 (-1.86, 6.66)

n:treatment/control
Mean or mean change (95% confidence limits)
WOMAC Western Ontario and McMaster Universities Osteoarthritis Index. Pain scale 0 (no pain) to 20. Physical Function scale 0 (best function) to 68.
* P<0.05
1. Overall improvement was calculated where positive change is better and negative change is worse.

Table 2. Outcomes at baseline, 3 and 6 month follow-up for participants with Rheumatoid Arthritis

	Intervention		Control		Difference between intervention and control groups
HAQ-Pain					
Baseline (n=93/92)	3.87	(2.88, 3.85)	3.29	(2.86, 3.73)	
3 month (n=84/81)	3.44	(2.92, 3.96)	3.04	(2.58, 3.51)	
6 month (n=76/76)	3.46	(2.91, 4.00)	3.72	(3.13, 4.32)	
Overall improvement from baseline[1]	-0.08	(-0.50, 0.35)	-0.09	(-0.48, 0.30)	0.01 (-0.56, 0.58)
HAQ-Function					
Baseline (n=93/92)	0.72	(0.57, 0.87)	0.66	(0.52, 0.80)	
3 month (n=84/81)	0.54	(0.40, 0.68)	0.57	(0.44, 0.70)	
6 month (n=76/76)	0.60	(0.44, 0.76)	0.65	(0.50, 0.80)	
Overall improvement from baseline[1]	0.15	(0.06, 0.25)*	0.05	(-0.02, 0.12)	0.11 (-0.01, 0.22)
Average daily physical activity minutes					
Baseline (n =86/86)	18.08	(14.42, 21.74)	21.58	(17.48, 25.74)	
3 month (n=73/74)	19.48	(15.50, 23.46)	19.49	(14.72, 24.27)	
6 month (n=62/63)	19.98	(15.87, 24.08)	21.42	(16.75, 26.08)	
Overall improvement from baseline[1]	1.64	(-0.38, 3.67)	-1.13	(-0.80, 0.48)	2.77 (-0.53, 6.08)

n:treatment/control
Mean or mean change (95% confidence interval)
HAQ Health Assessment Questionnaire. Pain scale 0 (no pain) to 10. Function scale 0 (best function) to 3.
* P<0.05
1. Overall improvement was calculated where positive change is better and negative change is worse.

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Abstract Number: 2347

Serum Levels of Resistin Are Associated with Synovial Inflammation and Knee Structural Changes in Patients with Symptomatic Knee Osteoarthritis

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Background/Purpose: Due to these sparse and inconsistent clinical data, our current study aims to describe the associations between serum levels of resistin, knee synovial inflammation and structural changes in patients with knee osteoarthritis (OA).

Methods: Patients (n = 200) with symptomatic knee OA (assessed according to American College of Rheumatology criteria) (mean 63.1 years, range 49-79, female 46.5%) participated in this study and all measures were performed at baseline and two years later. Serum levels of resistin were measured using enzyme-linked immunosorbent assay. Infrapatellar fat pad (IPFP) high signal intensity alteration and effusion-synovitis were measured from magnetic resonance imaging (MRI) to represent synovial inflammation. Knee structural changes such as cartilage volume, cartilage defects and bone marrow lesions (BMLs) were assessed in MRI semi-quantitatively or quantitatively. Multilevel mixed-effects liner regression or logistic regression was used in the data analyses.

Results: Serum level of resistin was not significantly associated with age, sex and BMI. It was significantly and positively associated with high signal intensity alteration within IPFP and effusion-synovitis score and volume in univariable and multivariable analyses (Table 1). Additionally, it was significantly and positively associated with total scores of tibiofemoral cartilage defects and BMLs before and after adjustment for co-variables (Table 1). The association between serum levels of resistin and tibial cartilage volume was negative but not significant in multivariable analyses. There were no significant interactions between serum resistin, sex and BMI on synovial inflammation and knee structural change.

Conclusion: Serum levels of resistin were significantly and positively associated with synovial inflammation and knee structural abnormalities, suggesting a potential role of resistin in knee OA. Table 1. The association between resistin and knee structural changes

	Multivariable* β (95% CI)
IPFP signal intensity alteration	
Volume (H) (mm^3 per ng/ml)	**5.18 (2.24, 8.13)**
Percentage (H) (percent per µg/ml)	**0.16 (0.06, 0.26)**
Clustering factor (H) (unit per µg/ml)	**7.15 (2.30, 12.00)**
Effusion-synovitis	
Volume (mm^3 per ng/ml)	**77.31 (1.17, 153.45)**
Presence	**1.06 (1.02, 1.10)**
Tibiofemoral cartilage defects (grade per µg/ml)	**19.15 (3.09, 35.22)**
Lateral	9.31 (-1.42, 20.05)
Medial	10.21 (-0.71, 21.13)
Tibiofemoral BMLs (grade per µg/ml)	**29.69 (7.87, 51.51)**
Lateral	**14.56 (4.20, 24.92)**
Medial	11.33 (-3.78, 26.45)

*Adjustment for age, sex, BMI, treatment allocation and randomization.

Disclosure: W. HAN, None; **F. M. Cicuttini**, None; **G. Jones**, None; **C. Ding**, None.

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Does Arthritis in Other Joints and Spine Influence the 1-Year Outcome of Total Hip Replacement? a Prospective European Multicenter Cohort Study Measuring the Influence of Musculoskeletal Morbidity

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Background/Purpose: Whilst arthritis in other affected joints and back pain is known to lead to worse outcomes following total hip replacement surgery, these risk factors have not previously been operationalized as a musculoskeletal morbidity profile. The aim of this study was to measure the influence of other joints and spine (in four musculoskeletal morbidity grades) on the 1-year outcome of primary hip replacement.

Methods: The European Collaborative Database of Cost and Practice Patterns of Total Hip Replacement study (EUROHIP) consists of 1,327 patients receiving primary THR for osteoarthritis (OA) across 20 European orthopedic centers. The primary outcome was whether or not a patient responded to THR at 12-months as measured by the relative effect per patient (REPP score), calculated for each patient using the total WOMAC score. The primary predictor of interest was the grade of musculoskeletal morbidity (MSM). The cohort was grouped into four combinations of arthritis based on the index joint, other large joints and spine respectively: MSM grade 1 (single-joint), 2 (multi-joints), 3 (single-joint and spine), 4 (multi-joints and spine) (Table 1). Confounders adjusted for were: age, sex, body mass index, living alone, years of hip pain, ASA grade, anxiety/depression, pre-operative WOMAC subscales.

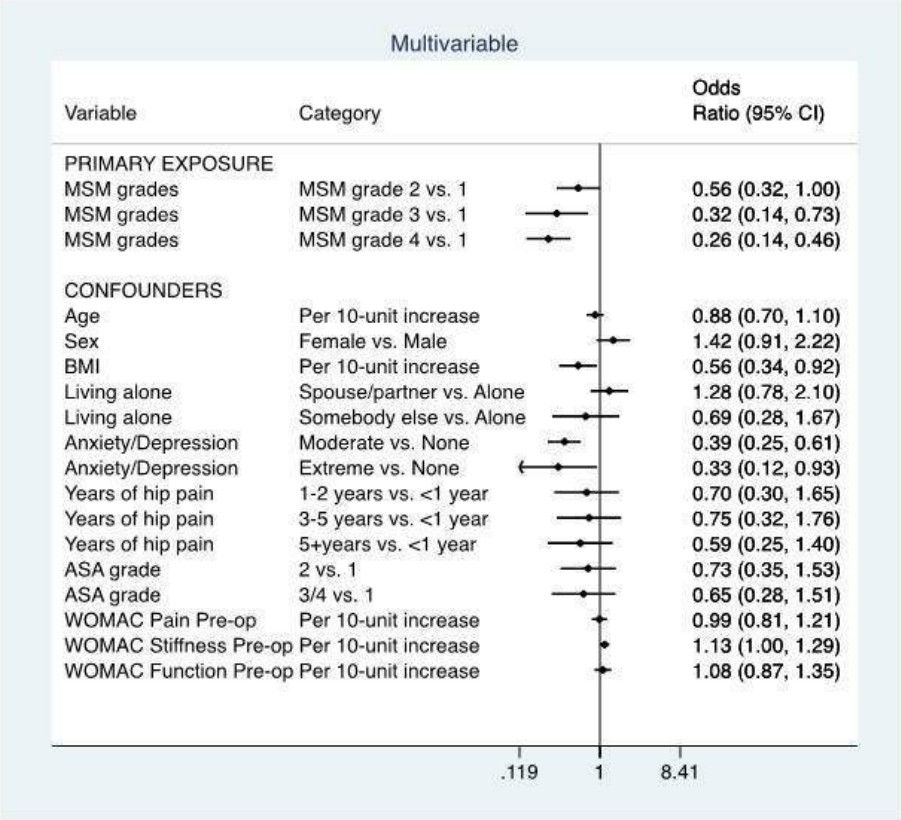
Results: 845 patients were included for this analysis with complete 12-month follow-up WOMAC scores. The mean age was 65.7 years and 55.2% were female. Increasing MSM grade was associated with worse outcomes of surgery, where the responder rates for THR were: 254 (92.4%) MSM grade 1, 272 (87.2%) MSM grade 2, 46 (80.7%) MSM grade 3, 142 (74.4%) MSM grade 4. This was confirmed in adjusted logistic regression models: MSM grade 4 vs. 1 odds ratio (OR) 0.26 95% confidence interval (CI) (0.14, 0.46); MSM grade 3 vs. 1 OR 0.32 95%CI (0.14, 0.73); MSM grade 2 vs. 1 OR 0.56 95%CI (0.32, 1.00) (Fig.1).

Conclusion: Other joints and spine measured as musculoskeletal morbidity have a strong influence on the 1-year outcome after THR. The effect size was large in comparison to other risk factors. Even so, the majority of patients in MSM grade 4 can still profit from surgery (>75% responder rate).

Table 1. Description of Musculoskeletal morbidity (MSM) grades

	Without Spine	With Spine
Index Joint	**Grade 1**	**Grade 3**
	416 (32.1%)	112 (8.6%)
Index & Other large joints	**Grade 2**	**Grade 4**
	479 (36.9%)	291 (22.4%)

Figure 1. Forest plot describing results of multivariable logistic regression models



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Longitudinal Construct Validity for Four Patient-Reported Outcomes Measurement Information System (PROMIS) Short Forms: Physical Function, Pain Interference, Depression, and Anxiety Among Adults with Knee Osteoarthritis

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Background/Purpose: Patient-Reported Outcomes Measurement Information System (PROMIS) provides clinicians and researchers access to reliable, valid measures of health status to resolve many challenges associated with the comparability and interpretability in OA. However, for adults with OA, longitudinal construct validity, i.e. ability of a measurement instrument to detect changes over time, of PROMIS instruments is unknown. Our purpose is to evaluate the longitudinal construct validity for 4 PROMIS Short Forms: Physical Function, Pain Interference, Depression, and Anxiety among those with knee OA following the recommended guidelines of the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN).

Methods: We performed a longitudinal analysis using the pooled, similar treatment effects that resulted from a randomized trial comparing Tai Chi with physical therapy in adults with symptomatic knee OA (ACR criteria). Participants completed questionnaires at baseline and after 12-week intervention. Longitudinal construct validity was investigated according to the COSMIN standard by testing 6 *a priori* hypotheses regarding expected Spearman's correlations between changes in PROMIS scores and changes in legacy measures (Short Form-36 subscales, WOMAC, Beck Depression, Perceived Stress, 6-minute and 20-Meter Walk Tests). After an item-by-item comparison of PROMIS short forms and legacy measures, an expert group formulated each hypothesis by including direction, strength, and rationale for expected correlation. Each PROMIS short form was assigned an overall rating of longitudinal construct validity based on its total number of confirmed hypotheses: High, 5-6 of 6 ($\geq$75%); Moderate, 3-4 of 6 (50%$\leq$ x <75%); or Poor, 0-2 of 6 (<50%).

Results: We examined 165 participants (mean age 61 years, 70% female, 53% white, 92% Kellgren/Lawrence Grade $\geq$ 2). We confirmed 5 of 6 *a priori* hypotheses (83%) for PROMIS Physical Function. For Pain Interference, Depression, and Anxiety, respectively 4 of 6 (67%), 3 of 6 (50%) and 4 of 6 (67%) hypotheses were confirmed. Therefore, PROMIS Physical Function has high longitudinal construct validity, and PROMIS Depression, Anxiety, and Pain Interference have moderate longitudinal construct validity.

Conclusion: Our results support that these 4 PROMIS short forms: Physical Function, Pain Interference, Depression, and Anxiety have the ability to detect changes over time for their intended construct among people with symptomatic knee OA. In addition, we provide an important standard of reference for clinicians and researchers to better apply or interpret these instruments in future clinical trials. Additional studies using PROMIS instruments of different domains or among cross-cultural OA populations are warranted.

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Radiographic Outcomes from a Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee

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Background/Purpose: Knee osteoarthritis (OA) is characterized by pain, functional impairment, disability, and joint space narrowing due to degradation of articular cartilage and bone remodeling. The Wnt signaling pathway is known to play a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[1] SM04690 is a small molecule inhibitor of the Wnt pathway in development as a potential OA therapeutic to be administered as an intra-articular (IA) injection into the affected joint. A phase 1, first-in-human, multicenter, 24-week, single-dose-escalation, randomized controlled trial (RCT) of SM04690 was completed in subjects with moderate to severe knee OA. This report provides exploratory radiographic outcomes.

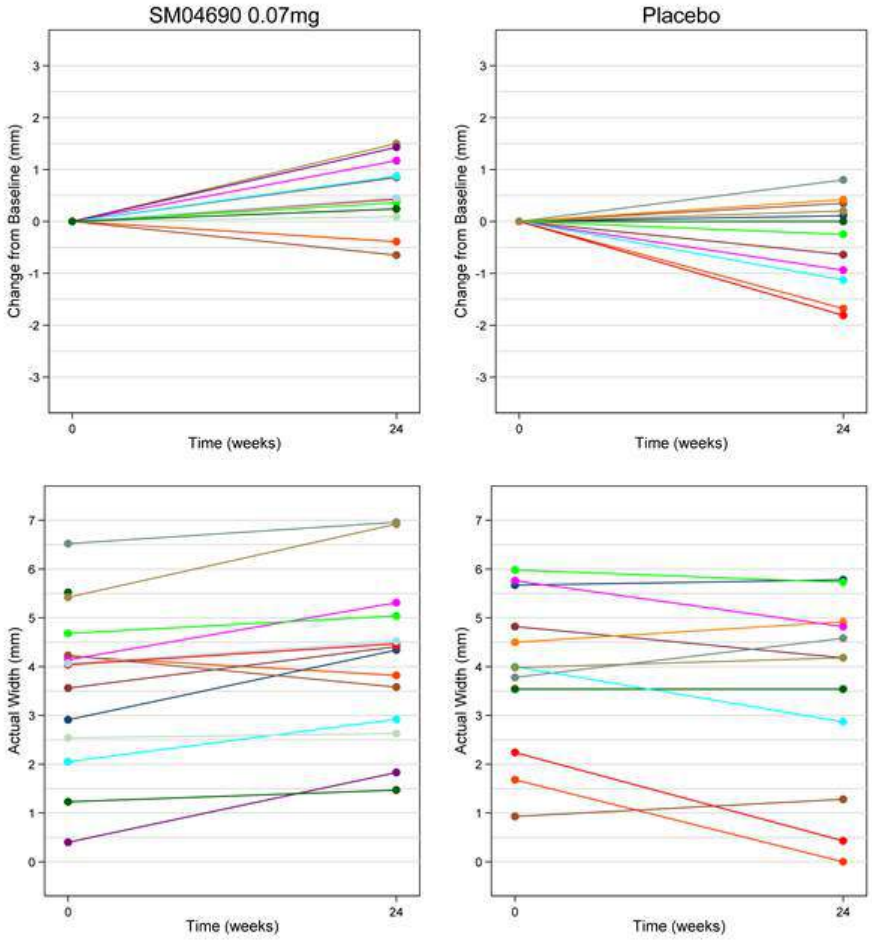
Methods: In the completed phase 1 RCT, escalation cohorts were dosed at 0.03 mg, 0.07 mg, and 0.23 mg SM04690 per 2 mL injection. A sample size of 20 subjects (randomized, 16 active: 4 placebo) per dosing cohort was selected. Subjects were administered a single IA injection into the target knee on Treatment Day 1, and participated in a follow-up period of 24 weeks. Safety, pharmacokinetics (PK), biomarker, and preliminary efficacy data were collected. To evaluate change from baseline in joint space width (JSW), X-rays of the target knee joint were taken at baseline and week 24. An exploratory analysis of change in JSW was conducted using repeated measures analysis of covariance (ANCOVA) adjusting for baseline JSW in the modified Intention-to-treat (mITT) population.

Results: Sixty-one subjects (average age 62.6 [±5.7] years, female n=41 [67%], average BMI 30.4 [±4.7] kg/m^2) were enrolled. In the mITT population at 24 weeks, the 0.07 mg cohort displayed a statistically significant change from baseline in medial JSW (0.49 mm [0.75]) as compared to placebo (-0.33 mm [0.87]) (P=0.02). No change or improvement in medial JSW was observed in 9 of 15 subjects (60%) in the 0.03 mg cohort, 12 of 15 subjects (80%) in the 0.07 mg cohort, and 6 of 11 (55%) subjects in the placebo cohort. In the 0.23 mg cohort, 9 of 16 (56%) subjects demonstrated worsening of JSW. Individual radiographic responses for the 0.07mg cohort and placebo group are presented in the Figure.

Conclusion: Exploratory radiographic outcomes from this completed phase 1 study suggested that treatment with SM04690 may have maintained or increased joint space width compared to placebo, providing proof of concept data of efficacy in the treatment of knee OA. Further evaluation studies are ongoing. References:

1. Gelse K. Osteoarthr Cartil. 2012; 20(2):16271

Figure. Individual Medial Joint Space Width over Time in 0.07 mg and Placebo Cohorts [Modified ITT]



Disclosure: C. J. Swearingen, Samumed, LLC, 3; **S. Majumdar**, Samumed, LLC, 5,GE Healthcare, 2; **I. Simsek**, Samumed, LLC, 3; **A. DiFrancesco**, Samumed, LLC, 3; **J. Tambiah**, Samumed, LLC, 3; **Y. Yazici**, Samumed, LLC, 3.

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Abstract Number: 2351

Racial Differences in Magnetic Resonance Image-Based Three-Dimensional Bone Shape of the Knee: Data from the Osteoarthritis Initiative (OAI)

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Background/Purpose: African Americans have higher prevalence and greater severity of knee osteoarthritis (OA) on radiographs compared with Caucasians. Magnetic resonance imaging (MRI)-based quantification of 3-dimensional (3D) anatomical changes of the knees may offer superior insights into potential racial differences in joint morphology compared with radiographs. Therefore, we applied this method to examine anatomical differences between African Americans and Caucasians.

Methods: We used data from the OAI, a longitudinal cohort study designed to investigate the natural history of and risk factors for knee OA. Active appearance modelling, which has excellent reliability, was used to automatically segment the knee MRI (MAGNETOM Trio, Siemens) sagittal 3D DESS-we sequence from each femur as principal components from a shape model. The OA bone shape vector is a line through the mean shape of a training set of OA and non-OA femurs, also expressed as principal components. Individual bone shapes are projected orthogonally onto the OA bone shape vector. Zero is defined as the mean non-OA shape, 1 unit is 1 SD of the non-OA shape distribution. Positive values indicate more of an OA shape. Separate vectors were prepared for males and females. We quantified the difference in 3D femur bone shape between African Americans and Caucasians, stratified by sex, using linear regression, adjusting for KL grade, age, and body mass index (BMI), using generalized estimating equations to account for the correlation between knees within the same subject.

Results: We included 1534 African American and 7319 Caucasian knees that had 3D bone shape measured at baseline. Of African Americans, 481 male and 1053 female knees were assessed. Of Caucasians, 3165 male and 1053 female knees were included. In male and female knees, the crude mean 3D bone shape vectors for the distal femur were higher for African Americans compared with Caucasians, even at KL grade 0 (**Table 1**). Significant differences in 3D bone shape were found between in African Americans and Caucasians, stratified by sex, controlling for age and BMI (**Table 2**).

Conclusion: African Americans had more overall anatomical changes of OA than Caucasians in MRI-based 3D femur bone shape, which were not due to differences in KL grade, age, or BMI. Further, African Americans had higher OA vector values, even at KL grade 0, than Caucasians, and this may explain the higher prevalence of OA in African Americans. Of note, age and BMI had only minimal effect on 3D femur bone shape change. This finding of racial differences in 3D bone shape warrants further investigation to understand the underlying mechanisms causing these differences to gain further insight into factors influencing the pathogenesis of OA.

Table 1. Baseline demographics and crude mean 3D OA bone shape vectors.				
	Male (N=3646)		**Female** (N=5027)	
	African American Mean (SD) (n = 481)	**Caucasians**Mean (SD) (n=3165)	**African American** Mean (SD) (n=1053)	**Caucasians** Mean (SD) (n=3974)
Overall 3D OA bone shape vectors	1.1 (1.5)	0.6 (1.4)	1.9 (1.8)	0.8 (1.5)
Bone shape at KL 0	0.3 (1.5)	0.0 (1.0)	0.6 (1.3)	0.0 (1.0)
Age, years	58.9 (9.2)	61.2 (9.5)	59.0 (8.2)	62.0 (9.1)
BMI, kg/m^2	30.2 (5.1)	28.6 (4.0)	31.5(5.0)	27.6 (5.1)

Table 2. Sex-specific adjusted mean differences in 3D femur bone shape between African American and Caucasian knees, adjusted for age, BML, and KL grade.				
	Male		**Female**	
	β (95% CI)	P value	β (95% CI)	P value
Adjusted mean differences in 3D OA bone shape vectors: African American vs. Caucasian	0.42 (0.27-0.57)	<.0001	0.81 (0.67-0.95)	<.0001
Age (per year increase)	0.0071 (0.0018-0.0124)	0.0083	0.0114 (0.0057-0.0170)	<.0001
BMI (per kg/m^2 increase)	0.0271 (0.0151-0.0390)	<.0001	0.0413 (0.0311-0.0515)	<.0001

Disclosure: J. S. Li, None; **M. A. Bowes**, Imorphics Ltd, 3; **D. T. Felson**, zimmer knee creations, 5; **P. G. Conaghan**, AbbVie, Flexion, Eli Lilly, Novartis, Pfizer Inc, Roche, 5,AbbVie, Novartis, Roche, 8; **C. Brown**, None; **T. Neogi**, None.

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Abstract Number: 2352

Obesity-Related Systemic Inflammation and Knee Synovitis

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Background/Purpose: Obesity, a major risk factor for knee osteoarthritis (OA), is a state of systemic inflammation through elaboration of adipokines (pro and anti-inflammatory cytokines) from adipose tissue. Whether degree of adiposity or systemic level of pro-inflammatory adipokines is associated with presence of local inflammation (synovitis) in knee OA is not known. Thus, in this study, we evaluated the cross-sectional association between total body fat mass and serum leptin (a proinflammatory adipokine) level to the presence of synovitis of the knee on MRI in community-dwelling older adults, with and without knee OA.

Methods: We included participants from the Multicenter Osteoarthritis (MOST) study, which has whole body Dual Energy X-ray (DXA) for assessment of fat mass, serum leptin assay and knee MRI (fat-suppressed (FS) fast spin-echo intermediate-weighted (IW) sequences) for evaluation of synovitis available. Sex-specific tertiles were created for total body fat mass and serum leptin from baseline visit. Person-level synovitis was defined by WORMS score >=1 on knee MRI from the same visit separately at 3 specific sites: 1) Infrapatellar fat pad; 2) Intercondylar; and 3) whole knee Effusion. A sum score of synovitis was calculated by adding the scores at the above sites. To assess the relation of fat mass tertiles and serum leptin tertiles to knee synovitis, we performed logistic regression for the site specific synovitis and linear regression for sum of synovitis score, adjusting for age, sex, education, physical activity, smoking status and body weight (proxy for loading effect). Analyses were repeated, stratified by the presence of radiographic knee OA (Kellegren-Lawrence grade ≥2) status.

Results: Among 2871 subjects, 1015 subjects developed synovitis (162 infrapatellar, 419 intercondylar and 462 effusion). We did not find an association between tertiles of fat mass or serum leptin with site specific synovitis or sum of synovitis scores (**Table 1**). Results did not change when stratified by radiographic knee OA.

Conclusion: Our results suggest that presence of knee synovitis may not be associated with obesity-related systemic inflammation. However, as our study is limited by power, larger studies are needed to comprehensively study this relation between obesity-related systemic inflammation and synovitis in knee OA as it may provide insight into the pathogenesis of knee OA.

Table 1 : Association of tertiles of absolute body fat mass and serum leptin with site specific synovitis			
Sex-specific total body fat mass tertiles	**n/N**	**Crude OR**	**Adjusted* OR (95% CI)**
	Infrapatellar fat pad synovitis		
Tertile 1 (lowest)	61/957	1.50	0.64 (0.32-1.27)
Tertile 2	59/949	1.46	0.92 (0.56-1.54)
Tertile 3 (ref)	42/965	1.0	1.0
	Intercondylar synovitis		
Tertile 1 (lowest)	155/887	1.61	1.01 (0.64-1.60)
Tertile 2	158/903	1.61	1.26 (0.89-1.77)
Tertile 3 (ref)	106/910	1.0	1.0
	Effusion synovitis		
Tertile 1 (lowest)	137/853	1.10	0.66 (0.43-1.04)
Tertile 2	155/851	1.26	0.99 (0.71-1.38)
Tertile 3 (ref)	134/881	1.0	1.0
Sex-specific serum leptin tertiles			
	Infrapatellar fat pad synovitis		
Tertile 1 (lowest)	10/220	0.66	0.74 (0.27-2.00)
Tertile 2	13/221	0.87	1.97 (0.43-2.22)
Tertile 3 (ref)	15/224	1.0	1.0
	Intercondylar synovitis		
Tertile 1 (lowest)	43/194	1.54	1.67 (0.89-3.12)
Tertile 2	31/210	0.93	1.01 (0.57-1.80)
Tertile 3 (ref)	33/211	1.0	1.0
	Effusion synovitis		
Tertile 1 (lowest)	24/187	0.49	0.73 (0.38-1.42)
Tertile 2	28/163	0.57	0.75 (0.46-1.33)
Tertile 3 (ref)	46/199	1.0	1.0
*Age, sex, education, smoking, physical activity (physical activity scale for elders) and body weight			

Disclosure: D. Misra, None; **T. Neogi**, None; **M. C. Nevitt**, None; **J. Torner**, None; **C. E. Lewis**, None; **D. T. Felson**, zimmer knee creations, 5.

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Abstract Number: 2353

Radiographic Variations in Hip Morphology Are Associated with Hip Symptoms: A Cross-Sectional Analysis of a Large Community-Based Cohort

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Background/Purpose: Preliminary investigation in this cohort supported an association between hip morphology and symptoms, however, the influence of race, gender, age, BMI and radiographic hip OA (rHOA) remains unclear.

Methods: Data are from the baseline visit of the Johnston County OA Project. Hip symptoms were assessed by: 1) patient-reported groin pain (yes/no) and 2) hip pain on internal rotation (yes/no). RHOA was defined as a Kellgren Lawrence grade of 2 or more. Standardized software (OxMorf, Oxford, UK) was used to assess hip morphology. We focused on 5 key hip morphologies (Table). Joint-based logistic regression models, stratified by sex, and employing generalized estimating equations to account for intra-person correlation, were used to estimate Odds Ratios (OR) associations between morphologic measures and symptomatic outcomes, adjusting for race, age, BMI, and side (labeled OR^1), while a second model considered the influence of baseline rHOA (labeled OR^2); interactions between rHOA and morphologic measures were considered significant at a p value of <0.1, in which case stratified analyses were performed.

Results: The analysis sample included 4530 hips from 2274 individuals, mean age 64 years, mean BMI 29kg/m^2, 30% Black, 39% male. Approximately 20% of hips had rHOA. Among women, significant associations were identified between hip symptom outcomes and increasing alpha angle, Gosvig ratio, triangular index height, and protrusio acetabula independent of race, age, and BMI. However, after adjusting for rHOA, the associations with pain on internal rotation were no longer statistically significant, and those with groin pain were seen only for hips with rHOA. Additionally, protrusio acetabula was protective for groin pain in this model (Table, left). For men, a similar statistically significant association between hip symptom outcomes and increasing alpha angle, Gosvig ratio, triangular index height, and lateral center edge angle (CEA) was noted. After adjustment for rHOA, these associations were attenuated, although significant associations remained between pain on internal rotation and increasing Gosvig ratio, triangular index height, and for CEA <=25 degrees (versus referent 25-40 degrees). For the groin pain outcome, a statistically significant association with alpha angle was present only in those with rHOA. In this model, a low CEA (<=25 degrees) was associated with greater odds of groin pain, while a high CEA (>40 degrees) was protective (Table, right).

Conclusion: Hip pain on internal rotation and groin pain were more likely with certain hip morphologies in men and women, however this association was highly dependent on baseline rHOA status. Pincer-type morphologies

(CEA>40 degrees and protrusio) appeared protective for groin pain when coupled with rHOA. One hypothesis is that the added depth and acetabular coverage could increase stability and reduce extreme range of motion, resulting in reduced symptoms.

TABLE. Associations (and corresponding 95% confidence intervals) between morphologic measures and hip symptom outcomes by sex, before (OR[1]) and after (OR[2]) adjustment for rHOA

MORPHOLOGIC MEASURES	WOMEN (n=2755 hips)				MEN (n=1775 hips)			
	PAIN ON INTERNAL ROTATION (n=1618)		GROIN PAIN (n=215)		PAIN ON INTERNAL ROTATION (n=858)		GROIN PAIN (n=166)	
	OR[1]	OR[2]	OR[1]	OR[2]	OR[1]	OR[2]	OR[1]	OR[2]
Cam-type morphology								
Alpha angle (°)	**1.14 (1.07, 1.20)**	1.04 (0.98, 1.11)	**1.23 (1.14, 1.33)**	1.01 (0.92, 1.11)	1.11 (**1.04, 1.18**)	1.05 (0.98, 1.13)	**1.49 (1.35, 1.65)**	(-)rHOA: 0.84 (0.62, 1.14)* (+)rHOA: **1.34 (1.16, 1.55)**
Gosvig ratio (mm)	**1.32 (1.13,1.53)**	1.17 (0.99, 1.39)	**1.73 (1.35, 2.23)**	(-)rHOA: 0.43 (0.20, 0.92)* (+)rHOA: **1.43 (1.10, 1.87)**	**1.41 (1.17, 1.70)**	**1.25 (1.02, 1.53)**	**3.04 (1.97,4.71)**	1.56 (0.97, 2.52)
Triangular Index Height (mm)	1.02 (0.98, 1.06)	1.00 (0.96, 1.05)	**1.12 (1.05, 1.19)**	(-)rHOA: 0.86 (0.69, 1.07)* (+)rHOA: **1.12 (1.04, 1.21)**	**1.04 (1.00-1.10)**	**1.04 (1.00, 1.09)**	**1.19 (1.09, 1.29)**	1.11 (0.99, 1.24)
Dysplasia morphology								
CEA (≤25 vs 25-40°)	1.13 (0.94, 1.36)	1.18 (0.97, 1.43)	0.87 (0.60, 1.25)	1.11 (0.74, 1.66)	**1.31 (1.07, 1.59)**	**1.39 (1.12, 1.71)**	1.39 (0.95, 2.05)	**1.87 (1.17, 3.01)**
Pincer-type morphology								
CEA (>40 vs 25-40°)	1.20 (0.93, 1.56)	0.98 (0.73, 1.33)	1.34 (0.85, 2.11)	0.85 (0.50, 1.45)	1.22 (0.83, 1.79)	1.09 (0.68, 1.73)	0.84 (0.42, 1.66)	**0.31 (0.14, 0.73)**
Protrusio (yes/no)	**1.51 (1.13, 2.02)**	1.28 (0.94, 1.75)	0.99 (0.59, 1.68)	**0.55 (0.31, 0.99)**	ND	ND	ND	ND

*Where there was a significant interaction between the morphologic measure and KLG, results were stratified by KLG and two ORs are given
OR: Odds ratio; rHOA: radiographic hip osteoarthritis; (-)rHOA=no rHOA; (+)rHOA=with rHOA; CEA: center edge angle; ND: Protrusio for males not calculated due to low number (n=9 hips)

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Abstract Number: 2354

Pharmaceutical Grade Chondroitin Sulfate Improves Knee Osteoarthritis Symptoms More Than Placebo and As Much As Celecoxib: Results of the Chondroitin Vs Celecoxib Vs Placebo Trial (CONCEPT)

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Background/Purpose: For the assessment of Symptomatic Slow Acting Drugs in Osteoarthritis (SYSADOAs), regulatory Agencies request the assessment of two co-primary endpoints: pain and function. They also recommend the design of three-arm studies including the investigational drug, a placebo and an active comparator.

Methods: The CONCEPT study investigated the symptomatic effects of pharmaceutical grade Chondroitin Sulfate (CS) (800 mg/day), Celecoxib (CE) (200 mg/day) and a placebo (PL) in a double-blind, double-dummy Phase III clinical trial.

Results: 604 patients recruited in 5 European countries, with knee osteoarthritis (OA) in accordance with the ACR criteria, were followed for 182 days. In the intention to treat analysis, pain (VAS) was significantly reduced, at D182, in the CS (-52%) and in the CE (-52%) compared to PL (-42%) ($P < 0.05$ for both). No differences were observed between CS and CE. The Lequesne index, measuring pain and function, showed similar results with CS (-37%) and CE (-36%) being significantly different from PL (-28%) ($P < 0,05$ for both) and no difference between CS and CE. Similar results were observed for the Minimum Clinically Important Improvement (MCII)

and Patient Acceptable Symptoms State (PASS) at D182 for the intention to-treat and per-protocol populations. Safety analyses showed no significant differences between the three groups.

Conclusion: Pharmaceutical grade Chondroitin Sulfate, at the dose of 800 mg/day, reduced pain and improved function to the same extent as Celecoxib and significantly more than placebo, in patients with knee osteoarthritis.

Disclosure: J. Y. Reginster, Servier, Novartis, Negma, Lilly, Wyeth, Amgen, GlaxoSmithKline, Roche, Merckle, Nycomed-Takeda, NPS, IBSA-Genevrier, Theramex, UCB, Asahi Kasei, Endocyte, Radius Health, 5,Merck Sharp and Dohme, Lilly, Rottapharm, IBSA, Genevrier, Novartis, Servier, Roche, GlaxoSmithKline, Merckle, Teijin, Teva, Analis, Theramex, Nycomed, NovoNordisk, Ebewee Pharma, Zodiac, Danone, Will Pharma, Amgen, 9,Bristol Myers Squibb, Merck Sharp and Dohme, Rottapharm, Teva, Roche, Amgen, Lilly, Novartis, GlaxoSmithKline, Servier, Pfizer, Theramex, Danone, Organon, Therabel, Boehringer, Chiltern, Galapagos, 2;

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Abstract Number: 2355

Histology of Bone Marrow Lesions in Osteoarthritis: A Systematic Literature Review

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Background/Purpose: Bone marrow lesions (BMLs) are of high interest in osteoarthritis for their association with pain and structural progression. They are characterized on magnetic resonance (MR) images as ill-defined areas of hyper intensity on fat-suppressed, T2 weighted, and short tau inversion recovery (STIR) sequences and of intermediate or low intensity on T1 weighted sequences in comparison with normal subchondral bone. Our understanding of the underlying mechanism of action of BMLs will be increased by histopathological studies of the subchondral bone. Therefore, we performed a systematic literature review.

Methods: We searched relevant databases up to May 2016 without language restrictions for articles describing the histology of BMLs in patients with primary osteoarthritis. We identified 503 unique records that were screened independently by two authors. Based on title and abstract we excluded 463 records (agreement 96.0%, k=0.65), and for the remaining 40 records we retrieved full-text papers to assess eligibility. Finally, we included 11 articles in this review by mutual agreement. Due to heterogeneity between studies meta-analysis was not possible.

Results: All studies used specimens from total joint replacement surgery (knee n=7; hip n=4). Study size ranged from 6 to 60 patients (median 15). Studies differed in histological and radiological methods (e.g. in vivo (n=8)

versus ex vivo (n=3) imaging and imaging sequences). Most reported histological findings in BMLs were fibrosis (knee n=7; hip n=3), necrosis (knee n=4; hip n=3) and trabecular abnormalities (knee n=5; hip n=2). Bone marrow edema (n=5) was predominantly reported in hip studies (n=3), and less in knee studies (n=2). Other reported findings were: hyper vascularity or blood vessel hyperplasia (n=5), bone remodelling (n=3) and increased bone volume fraction (n=4). Two knee studies correlating topography of MR imaging with histology, compared subchondral bone with and without BMLs. Both studies demonstrated fibrosis, necrosis and trabecular abnormalities were increased in BMLs compared to control subchondral bone. In three knee studies micro-computed tomography was used showing that trabeculae of BMLs were thicker and more plate-like shaped than trabeculae in control specimens.

Conclusion: Published data summarized in this systematic review indicated that several histological features are reported in BMLs; consistently reported are fibrosis, necrosis and trabecular abnormalities. How and whether these histological features are related is not clear. However, to think of BMLs as merely reflecting increased water content within the bone marrow, is an outdated notion. Since some histological findings indicate an active process, BMLs might not only characterize disease stage, but could also help to identify those patients at high risk of structural progression. A better understanding of pathological processes underlying BMLs could potentially lead to new targets in osteoarthritis treatment.

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Abstract Number: 2356

Comparison of Spa Therapy with or without Physical Rehabilitation for Knee Osteoarthritis: A Randomized Controlled Trial

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Background/Purpose: To demonstrate the non-inferiority of “Active” compared to “Standard” spa therapy at 6 months in symptomatic knee osteoarthritis (KOA) care.

Methods: Prospective, randomized, monocenter, non-inferiority trial with community-based recruitment of KOA patients. Inclusion criteria were: KOA according to the ACR criteria, pain VAS> 3 on a 0-10 scale, and Kellgren and Lawrence (KL) grade ≥2. "Standard" spa" comprised 18 days of standardized spa treatment, 6 days a week for 3 weeks. "Active spa" included iterative spa sessions, 3 days a week for 3 weeks, followed by a dedicated rehabilitation program, 3 days a week for 3 weeks. The primary endpoint was achievement of a minimal clinically important improvement (MCII) for pain VAS, and/or a MCII for function on WOMAC function subscale and no knee surgery, at 6 months (composite MCII). The secondary endpoints were composite MCII at 3 months and achievement of Patient Acceptable Symptoms States (PASS) for pain and function.

Results: Of 283 participants (mean age 64.3 (9.0) years, 181 (66.8%) women, 181(79.7%) bilateral OA, 151 (58.5%) KL grade III or IV), 145 were allocated to Standard spa and 138 to Active spa. Non inferiority could not be demonstrated for the primary endpoint at 6 months: difference of responders -0.01 90%CI [-0.18 to 0.02], p=0.14; number of patients achieving composite MCII: 86 (66.2%) and 66 (57.9%) in the Standard and Active spa group respectively. However, difference between the 2 groups was neither significant for the same criteria (p=0.18). At 3 months, active spa group was not inferior to standard spa group with composite MCII outcome criteria. The number of patients achieving PASS increased from baseline to 3 months and then decreased at 6 month (table). All the analyses using PASS criteria showed non-inferiority of the active spa group at six months.

		Standard spa		Active spa		Difference of responders		P
		N=145		N=138				(non -
Definition of responder		N	(%)	N	(%)		[IC 90%]	inferiority)
3 months	Composite MCII	76	(56.3)	75	(70.1)	0.14	(0.04 to 0.24)	<.0001
6 months	Composite MCII	86	(66.2)	66	(57.9)	-0.08	(-0.18 to 0.02)	0.14
Before Spa	PASS for pain	13	(9.8)	18	(15.1)	0.05	(-0.02 to 0.12)	<.0001
3 months	PASS for pain	54	(44.6)	66	(66.0)	0.21	(0.11 to 0.32)	<.0001
6 months	PASS for pain	51	(44.0)	47	(45.6)	0.02	(-0.09 to 0.13)	<.0001

Conclusion: Active spa can reasonably be proposed to patients with KOA. Such protocol could be more cost-effective while allowing benefiting spa therapy without absenteeism from work or avoiding accommodation costs for patients living close to the centre.

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Abstract Number: 2357

Topical Application of Aceclofenac Might NOT Produce a Significant Increase of Blood Pressure in Osteoarthritic Patients – a Continuous Automated Blood Pressure Monitor Study

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Background/Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used in Osteoarthritic patients for their anti-inflammatory and pain-killer proprieties. Various reports suggest an increase in blood pressure of about 3-5 mmHg in relation with systemic use of NSAIDs. This effect is observed from the beginning of the treatment; however, due to his "modest" amplitude, it was largely ignored both by patients and physicians. New epidemiological data suggest that such a small increase in BP could produces in USA about 21.000 deaths per year (higher than in case of gastrointestinal deaths produced by the unprotected usage of nonselective NSAID). For the time being much less is known about the blood pressure effect of topical NSAIDs. The interest for this subject is higher as long as both systemic and topical NSAID seem to have similar therapeutic effect on superficial exposed joints (e.g. knee, wrists, elbows etc.) but different safety profile. The aim of the study was to evaluate whether or not the use of a topical NSAID (acecelofenac) in osteoarthritis affects blood pressure or pulse rate values.

Methods: 52 patients with a clear diagnostic of osteoarthritis have been evaluated, by using a continuous Automated BP Monitoring system (ABPM), before and after the utilization of topical aceclofenac. Blood pressure and pulse rate have been continuously recorded for 48 hours at baseline (24 hours without topical NSAID use) and day1 (24 hours with topical NSAID use). Same NSAID (namely aceclofenac) in same dose have been used in all cases. Subjects that received antihypertensive therapy, those receiving therapeutic regimes with potential impact on blood pressure and those that changed their concomitant medication during the study have been excluded from the analyses. Daytime (0700-2200), nighttime (2201-0659) and all-day (24h) systolic and diastolic BP along with pulse rate values have been analyzed. Difference between Baseline and Day1 have been tested by using ANOVA and Fisher exact test; a $p<0.05$ was considered significant.

Results: : No difference has been observed between baseline (no drug) and Day 1 (topical aceclofenac day) regarding diastolic BP or Heart rate (see the table). For systolic BP a statistical significant reduction between Day1 and baseline (-1.88 mmHg , sd: 5.8 mmHg) has been found. Similar results have been obtained for all-day, nighttime and daytime sub analysis.

	N	Minimum	Maximum	Mean	Std. Deviation
Sys BP Baseline	52	101.75	147.90	122.8904	10.16477
Sys BP Day 1	52	103.9	140.3	121.007	7.6768
Dia. BP Baseline	52	55.05	88.10	75.4462	6.41531
Dia. BP Day 1	52	56.4	87.1	75.390	5.9851
HR Baseline	52	60.2	95.9	78.127	6.7779
HR Day 1	52	59.3	90.3	77.313	6.2257

Conclusion: Although this study has certain limitations our data suggest that no significant increase of BP or HR are associated with topic use of NSAID (in our case Aceclofenac). Larger studies should be made to confirm the conclusion of this study. **References:** 1.Snowden S, Nelson R- The effects of nonsteroidal anti-inflammatory drugs on blood pressure in hypertensive patients. Cardio Rev2011 Jul-Aug;19(4):184-91. 2.Howard Lee,MD; KeeSikKim,MD,- Ambulatory Blood Pressure Response to Once-Daily Fimasartan: An 8-Week, Multicenter, Randomized, Double- Blind, Active-Comparator, Parallel-Group Study in Korean Patients With Mild To Moderate Essential Hypertension Clinical Therapeutics/Volume 35, Number 9, 2013.

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Abstract Number: 2358

High-Fat Diet Is Associated with a Higher Incidence of Radiographic Knee OA and Progression of Knee Joint Space Narrowing: Data from the Osteoarthritis Initiative

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Background/Purpose: Animal studies have shown that high-fat diet may increase the risk of osteoarthritis (OA), while other evidence suggests that dietary polyunsaturated fatty acids may be protective.

Methods: We investigated the associations between high-fat diet and radiographic OA in a well-established knee OA incidence and progression cohort (Osteoarthritis Initiative) N = 4796. Fixed flexion radiographs of bilateral knees were evaluated for Kellgren and Lawrence score (KL) and joint space narrowing (JSN) at baseline, 12, 24, 36, 48, 72, and 96 months of follow up (mean follow-up 8 years); incident radiographic OA was defined as a new KL score ≥2 in either knee, and JNS progression was defined as progression from a previous radiograph by a partial grade or more. Diet was assessed at baseline by food frequency questionnaire. Dietary fat consumption was expressed as per cent of total calorie intake and categorized in quartiles (Q1:<29.05% (referent group), Q2: 29.06-34.29%, Q3: 34.30-39.42%, Q4: >39.43%). Logistic regression was used for analyses.

Results: After adjustment for age, race, and gender, higher dietary fat consumption was associated with increased odds of incident radiographic knee OA (aOR Q2 1.14 (0.89-1.45), Q3 1.37 (1.07-1.75), and Q4 1.52 (1.20-1.94), p = 0.003) and progression of knee JSN (aOR Q2 1.15 (0.96-1.38), Q3 1.40 (1.17-1.67), and Q4 1.28 (1.07-1.54), p = 0.002). Similarly, higher consumption of poly- and monounsaturated fats as well as saturated fats was associated with incident radiographic knee OA and JSN progression. Further adjustment for BMI attenuated the associations of higher dietary fat consumption with these outcomes; for example, the aORs for incident radiographic knee OA were Q2 1.05 (0.81-1.35), Q3 1.25 (0.97-1.61), and Q4 1.28 (0.99-1.65), p = 0.15).

Conclusion: In a cohort of high risk adults, high-fat diet was associated with an increased incidence of radiographic knee OA and progression of knee JSN due in large part to greater body weight among those with higher fat consumption. Biological mechanisms underlying the relationship between high dietary fat consumption, obesity and OA should be explored in further studies.

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Abstract Number: 2359

Dose-Related Risks of Cardiovascular, Gastrointestinal, and Renal Adverse Events Associated with Meloxicam Among Patients with Osteoarthritis: An Observational Study Using US Claims Data

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Background/Purpose: Safety studies have shown that risks associated with non-steroidal anti-inflammatory drugs (NSAIDs) are related to dose; however, there is little evidence regarding this dose-toxicity relationship for meloxicam, including in the United States (US). Prior studies assessing the meloxicam dose-toxicity relationship have been limited in sample size, the ability to control adequately for potential confounders and changes in dose over time, and the inclusion of a comprehensive set of adverse event outcomes. This study assessed the relationships between meloxicam dose and risks of gastrointestinal (GI), cardiovascular (CV), and renal events in a commercially insured US population.

Methods: MarketScan©claims databases (2010-14) were used to analyze the risks of GI (upper GI bleed/perforation [UGIB], uncomplicated ulcer [UU], lower GI bleed [LGIB]), CV (myocardial infarction [MI], stroke, congestive heart failure [CHF], hypertension), and renal events by meloxicam daily dose (DD) category (>7.5mg to ≤15mg [higher dose]; ≤7.5mg [lower dose]) in a cohort of adult new users of meloxicam with osteoarthritis (OA). A separate cohort was created to assess each event. Patients with prior history of GI, CV or renal disease were excluded from the cohort constructed for that event. Hazard ratios (HRs) were estimated using multivariable Cox analyses with DD as a time-dependent covariate. The models controlled for baseline patient demographics and clinical characteristics, selected a priori based on published NSAID analyses and clinical guidance.

Results: In total, 337,260 meloxicam new users (62.5% female; median age at index 59 years) met the initial study inclusion criteria. HRs and 95% confidence intervals are presented in Table 1. Increased risks of GI and CV events were associated with higher versus lower doses of meloxicam. HRs for higher dose (> 7.5 mg to ≤15mg) versus lower dose (≤ 7.5 mg) for MI (1.05), stroke (1.03), hypertension (1.07), UGIB (1.50), UU (1.18), and LGIB (1.10) were above 1.0.

Table 1. Cox Hazard Ratios for Gastrointestinal, Cardiovascular, and Renal Events Associated with Higher Versus Lower Doses of Meloxicam among Adult New Meloxicam Users with Osteoarthritis with No Observed History of the Event

Endpoint	Hazard Ratio (>7.5mg to <15mg vs ≤7.5mg)	95% Confidence Interval
MI	1.05	0.93, 1.18
Stroke	1.03	0.96, 1.11
First of MI or Stroke	1.03	0.97, 1.10
CHF	0.95	0.82, 1.10
First of MI, Stroke, or CHF	1.06	0.99, 1.13
Hypertension	1.07	1.03, 1.11
UGIB	1.50	1.20, 1.88
UU	1.18	1.02, 1.37
First of UGIB or UU	1.23	1.07, 1.40
LGIB	1.10	0.98, 1.23
First of UGIB, UU, or LGIB	1.14	1.04, 1.24
Renal Failure	0.99	0.89, 1.10

Conclusion: In this cohort study, numerically increased risks of CV and GI events were observed with higher doses versus lower doses of meloxicam among adult new users of meloxicam with OA and no prior history of the

event. Of note are increased risks of hypertension, an event of substantial clinical importance previously inadequately studied, and upper GI events. These findings support the US Food and Drug Administration (FDA) recommendation to use the lowest effective dose of NSAIDs. This study suggests the importance of studying the effect of meloxicam dose on risks of serious adverse events in a large sample, adequately adjusting for potential confounders, and treating dose as a time-dependent covariate.

Disclosure: **E. Hoffman**, RTI Health Solutions, 3; **D. M. Mladsi**, RTI Health Solutions, 3; **B. Cryer**, RTI Health Solutions, 5; **W. Hopkins**, Iroko Pharmaceuticals, LLC, 5; **D. C. Brater**, RTI Health Solutions, 5; **R. Parikh**, RTI Health Solutions, 3; **R. Goyal**, RTI Health Solutions, 3; **J. Castellsague**, RTI Health Solutions, 3; **D. Stafkey-Mailey**, RTI Health Solutions, 3; **C. Young**, Iroko Pharmaceuticals, LLC, 3.

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Abstract Number: 2360

The Association of Superolateral Hoffa's Fat Pad Edema and Synovitis with Structural Changes in the Patellofemoral and Tibiofemoral Joints: The Multicenter Osteoarthritis Study

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Background/Purpose: To determine the relation of superolateral HoffaÕs fat pad (SHFP) edema and Hoffa-synovitis to cartilage damage and bone marrow lesions (BMLs) in the patellofemoral (PF) and tibiofemoral (TF) joints.

Methods: The Multicenter Osteoarthritis (MOST) study is a NIH-funded longitudinal cohort study of older individuals with or at risk for knee OA. We used data from the 60-month study visit where all eligible subjects had knee MRI assessed for other structural features of knee OA. SHFP edema and Hoffa-synovitis (infrapatellar and/or intercondylar) were assessed on sagittal proton density-weighted fat-suppressed MRI images by two musculoskeletal radiologists and dichotomized into presence (>1) and absence (=0). Cartilage damage and BMLs were scored in the PF and TF joints. We used three definitions of structural damage: 1) any cartilage damage (WORMS score of ³2), 2) full-thickness cartilage damage (WORMS score 2.5, 5-6) and 3) any BML (WORMS

score of ³1). We further defined the location of PF and TF joint damage in the lateral and medial compartments. Separate logistic regression models were used to determine the relation of SHFP edema to our three definitions of structural damage in the medial and lateral PF and TF joints, adjusting for age, sex and BMI. The same models were used with HoffaÕs synovitis as the exposure instead of SHFP edema.

Results: 1041 knees were included; Mean (sd) age and BMI were 66.8 (7.5) and 29.6 (4.8), respectively; 65% were female. SHFP edema and Hoffa-synovitis was present in 12.7% and 59.3% of knees, respectively. Compared with knees without SHFP edema, knees with SHFP edema showed statistically significant increase in odds of any and full-thickness cartilage damage, and any BML in the lateral PF joint only. Compared with knees without synovitis, knees with Hoffa-synovitis showed statistically significant odds of any and full thickness damage, and BMLs in all 4 compartments (table).

Conclusion: While synovitis is a marker of whole-joint disease, SHFP edema is a surrogate of local lateral PF joint disease only. SHFP edema is likely the result of mechanical impingement and maltracking leading to local structural abnormalities like cartilage and osseous changes.

		Any Cartilage Damage		Full Thickness Cartilage Damage		BMLs	
		Medial	Lateral	Medial	Lateral	Medial	Lateral
SHFP Edema	PF Joint	1.6 (0.97-2.6)	**1.8 (1.2-2.6)**	1.3 (0.84-1.9)	**2.0 (1.3-3.0)**	1.4 (0.93-2.0)	**1.9 (1.3-2.7)**
	TF Joint	0.99 (0.67-1.5)	1.0 (0.72-1.5)	0.99 (0.63-1.6)	0.71 (0.40-1.3)	0.90 (0.61-1.3)	1.3 (0.82-2.1)
Hoffa-Synovitis	PF Joint	**2.5 (1.9-3.4)**	**2.7 (2.1-3.5)**	**2.3 (1.7-3.2)**	**2.9 (2.0-4.1)**	**1.6 (1.3-2.1)**	**2.2 (1.7-2.9)**
	TF Joint	**2.2 (1.7-2.9)**	**2.0 (1.5-2.6)**	**3.6 (2.5-5.1)**	**1.7 (1.2-2.4)**	**2.2 (1.7-2.9)**	**2.5 (1.7-3.7)**

Table. Odd ratios of cartilage damage and bone marrow lesions (BMLs) in knees with superior Hoffa's fat pad (SHFP) edema compared with knees without SHFP edema, and in knees with Hoffa-synovitis compared with knees without synovitis.

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Abstract Number: 2361

Association Between Osteoarthritis and Dyslipidemia: A Systematic Literature Review and Meta-Analysis

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Background/Purpose: Beyond obesity-related osteoarthritis (OA), association between metabolic syndrome and OA delineates the metabolic OA phenotype. Along this line, we aimed to investigate the prevalence of dyslipidemia in OA patients and whether OA and dyslipidemia are associated.

Methods: We performed a systematic literature review from 3 electronic databases (PubMed, Embase and Cochrane) until January 2016, and abstracts of 2013-2015 meetings (ACR, EULAR, OARSI). We included cross-sectional, cohort and case control studies to assess the number of patients with OA and/or dyslipidemia. We calculated the mean (±SD) prevalence of dyslipidemia in patients with and without OA and the odds ratio (OR) (95% confidence interval (95%CI)) of having dyslipidemia among patients with OA. We used Revman V.5.3 to perform a meta-analysis. A random-effects model was used in case of high heterogeneity. Quality of the studies was assessed with STROBE score (%) and sensitivity analyses were performed.

Results: From 605 published studies, 48 were included in the analysis (29 cross-sectional, 10 cohort and 9 case-control studies). The median of STROBE quality score was 69%. Twenty-one over 30 studies showed a positive association between OA and dyslipidemia. Twelve over 18 studies with a score STROBE > 60% found a positive association. Four over 7 studies that reported an OR adjusted on age and BMI were positive too. In 14,843 patients with OA, the mean prevalence of dyslipidemia was 30.2±0.6% (mean±SD), whereas in 196,168 patients without OA, the mean prevalence was 8%±0,1%. The risk of dyslipidemia was greater in OA than non-OA patients (OR=1.98 (1.43-2.75), p<0.0001*) (Figure 1)*, especially for knee (OR=2.27 (1.33-3.89), p=0.003) and hand OA localizations (OR=2.12 (1.46-3.07), p<0.0001). Results were unchanged in sensitivity analyses (exclusion of studies with STROBE score <60% or including OA diagnosis not based on ACR criteria or Kellgren-Lawrence grading).

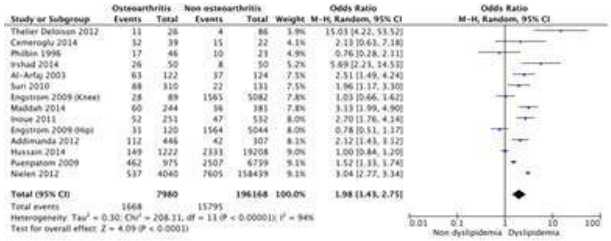

Figure 1: Forest Plot for dyslipidemia among patients with and without OA

Conclusion: OA Patients have a 2-fold increased risk for dyslipidemia, suggesting that this metabolic disturbance could be a risk factor of OA. Such a result supports the individualization of a metabolic OA phenotype.

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Abstract Number: 2362

Progression of Pain and Ultrasound Detected Synovitis in Patients with Erosive Hand Osteoarthritis over One Year

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Background/Purpose: Hand osteoarthritis (HOA) is a common and frequent cause of pain. HOA is a heterogeneous group of disorders with two main subsets including non-erosive disease and erosive, sometimes referred to as inflammatory, HOA. Few studies demonstrated inflammatory ultrasound changes and more severe clinical symptoms in patients with erosive compared with non-erosive disease, however the results are inconclusive. The aim was to evaluate progression of pain, stiffness, physical impairment and ultrasound features in patients with erosive and non-erosive HOA in a one-year longitudinal study.

Methods: Consecutive patients with symptomatic HOA fulfilling the American College of Rheumatology (ACR) criteria were included in this study. Joint pain and swelling were assessed. Patients reported joint pain on 100 mm visual analogue scale (VAS). Pain, joint stiffness and disability were assessed by the Australian/Canadian OA hand index (AUSCAN). Radiographs of both hands were examined and erosive disease was defined by at least one erosive interphalangeal joint. Synovial hypertrophy and power Doppler signal (PDS) were scored with ultrasound. Synovitis was graded on a scale of 0–3 and osteophytes were defined as cortical protrusions seen in two planes. Patients were examined at baseline and one-year follow-up.

Results: Altogether, 129 patients (12 male) with symptomatic nodal HOA were included in this study and followed between April 2012 and January 2015. Out of these patients, 72 had erosive disease. Patients took symptomatic slow-acting drugs (SYSADOA) twice a year, non-steroidal anti-inflammatory drugs (NSAIDs) and analgesics on demand. Duration of morning stiffness ($p<0.01$) and number of clinically swollen joints ($p<0.05$) were significantly higher in patients with erosive compared with non-erosive disease at study entry. Duration of morning stiffness ($p<0.05$) become shorter in patients with erosive, but not in those with non-erosive disease, however the number of clinically swollen joints were not significantly changed at one year follow-up in both groups. According to the AUSCAN, patients with erosive compared with non-erosive disease had more pain ($p<0.05$) and stiffness ($p<0.01$) at study entry. Pain, but not stiffness, got worse ($p<0.05$) in patients with erosive compared with non-erosive disease. US-detected pathologies such as gray-scale synovitis total score ($p<0.001$), intensity of PDS ($p<0.01$) and number of osteophytes ($p<0.01$) were significantly higher in patients with erosive compared with non-erosive disease at study entry and got worse in gray-scale synovitis total score ($p<0.01$), intensity of PDS ($p<0.01$) and numerically also in number of osteophytes ($p<0.1$) at one-year follow-up. There were no significant differences in consumption of NSAIDs for OA between both groups.

Conclusion: This study shows that pain associated with US-detected synovial hypertrophy, inflammatory signs and osteophyte formation is more severe in patients with erosive HOA than in patients with non-erosive disease and is more likely to progress over one year. Acknowledgement: This work was supported by the project (Ministry of Health, Czech Republic) for consensual development of research organization 023728.

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Abstract Number: 2363

Synovial Changes Detected By Ultrasound and Its Association with Knee Pain: A Population-Based Case Control Study

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Background/Purpose: To examine whether synovial changes on ultrasound (US) associate with knee pain (KP) and/or underlying structural radiographic changes of osteoarthritis (OA).

Methods: In this case-control study, participants with early KP and established KP (more than 3 years duration) were compared with participants without KP. Participants were selected from the Knee Pain and Related Health in the Community (KPIC, n=9514) survey in Nottingham, UK. Cases and controls were age and gender matched. KP was defined as pain in or around the knee on most days for at least a month. Synovial changes (effusion, hypertrophy and Power Doppler (PD) signal) were measured by the two observers (inter-observer concordance correlation was 0.8 (0.6 to 0.9) for effusion and 0.7 (0.5 to 0.9) for synovial hypertrophy). OA structural changes were measured by standardised radiographs (semi-flexed weight-bearing and flexed skyline views) using the Nottingham Line Drawing Atlas (NLDA). Odds ratio (OR) and 95% confidence interval (CI) were estimated with adjustment for age, gender, body mass index and the total NLDA scores. Multinomial logistic regression was used to handle the case control study with three groups and to estimate ORs between early KP, established KP and no KP groups. A subgroup analysis in participants with unilateral KP was performed using a multilevel generalized linear mixed regression to compare painful knees with pain-free knees within persons (a well matched case control analysis).

Results: A total of 420 participants were included of which 219 had early KP, 103 established KP and 98 no KP (mean age 60 years; 60% women). The prevalence of US effusion (≥4mm) were 24.5%, 39.8% and 62.1% in no KP, early KP and established KP. The prevalence of US hypertrophy (≥4mm) were 5.1%, 22.2% and 42.7% and the prevalence of PD signal were 0%, 3.2%, and 1.9% in these three groups. US effusion (≥4mm) increased the risk of early KP (OR 2.03, 95% CI 1.16 to 3.56) and established KP (4.75, 2.49 to 9.06). Similarly, hypertrophy (≥4mm) also increased the risk of early KP (5.63, 2.12 to 15.01) and established KP (14.24, 5.12 to 39.60). However, the association with effusion was diminished when adjusted for radiographic changes (Figure 1). In contrast, radiographic severity of OA on the NLDA was positively associated with KP, irrespective of the adjustment for the US features and other confounding factors.

Further analysis in people with unilateral KP (n=147) showed that the associations with both effusion and hypertrophy were diminished after adjusting for radiographic severity (1.02 (0.61 to 1.69) and 1.64 (0.85 to 3.17), respectively).

Conclusion: This study confirms that the association between US synovial changes and KP depends on the radiographic severity of OA, suggesting that US features reflect part of the overall structural changes occurring in OA joints and on their own are unlikely to be independent predictors of knee pain.

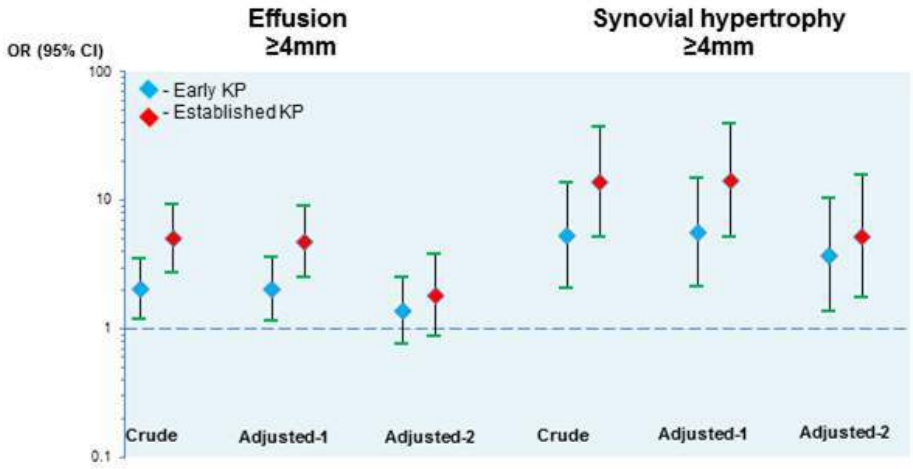

Figure 1. Association between US features and knee pain. Note that y axis is logarithmically scaled.

Abbreviations: OR – odds ratio; CI –confidence interval;

Adjusted-1 – adjusted for age, gender and BMI;

Adjusted-2 – adjusted for age, gender and BMI and global x-ray score.

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Abstract Number: 2364

Swimming May Associate with Less Osteoarthritis: Data from the Osteoarthritis Initiative

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Background/Purpose: Swimming is a non-weight-bearing exercise often recommended to people with knee OA because it is viewed as being less harmful to the knee despite that no epidemiologic studies have evaluated the effect of swimming on knee pain or OA. Therefore, we aimed to evaluate the relationship of a history of swimming with symptomatic knee OA in the Osteoarthritis Initiative (OAI), a community based cohort not recruited based on swimming status.

Methods: This is a cross-sectional study of OAI participants with knee x-ray readings, symptom assessments, and completed lifetime physical activity surveys where participants identified 3 most frequently performed physical activities (≥ 20 times in life) from a list of 37 for ages 12 – 18, 19 – 34, 35 – 49 and ≥50 years old. Those indicating swimming as an activity were defined as a swimmer in that time period. Any history of swimming included swimmers from all time periods. Data on number of swimming bouts performed were ascertained. Posterior-Anterior semi-flexed knee radiographs were obtained at 48-month visit and scored for Kellgren-Lawrence (KL) grade (0-4). Radiographic OA (ROA) was defined as KL ≥ 2. Frequent knee pain within a person required at least one knee with symptoms. Symptomatic radiographic OA (SOA) required that at least one knee had both ROA and frequent knee pain. Anyone with a total knee replacement was classified as having all outcomes. We performed logistic regression analyses where the predictor was any history of swimming and in the specific age ranges using dichotomous groups and groups based on tertiles of swimming bouts. The outcomes were ROA, frequent knee pain, and SOA; adjusted analyses included covariates age, sex, BMI, prior history of injury, and all other activities correlated with swimming, including walking, in the respective age ranges. Trends were tested using the Cochrane-Armitage test.

Results: The activities positively correlated with swimming were walking and other water-based activities, such as sailing.

Table 1. Characteristics of those with no history of swimming, any history of swimming, all participants, and those excluded from these analyses.					
Participant Characteristics	Non-Swimmers (n = 1575)	Swimmers (n =1062)	All Participants (n = 2637)	OAI Participants seen at 96-month visit before 9/12/12 who did not complete the historic physical activity survey (n = 699)	OAI Participants eligible for historic physical activity survey, but did not complete questionnaire (n = 618)
Age (years)	64.1 (9.0)	64.7 (8.9)	64.3 (8.9)	65.4 (8.5)	67.0 (9.4)
Sex (% Male)	48.5%	37.9%	44.2%	32.5%	38.8%
BMI (kg/m^2)	28.7 (4.8)	28.1 (4.9)	28.4 (4.9)	28.7 (5.1)	29.1 (5.2)
Frequent knee symptoms (%)*	40.1%	36.9%	39.3%	50.4%	48.5%
ROA (%)*	59.5%	53.9%	57.3%	65.7%	62.9%
SOA (%)*	29.4%	24.4%	27.4%	37.0%	38.7%
TKR (%)*	4.6%	3.2%	4.0%	7.0%	6.2%
Prior Injury (%)*	48.0%	47.0%	47.6%	55.5%	47.6%

Table 2. Odds Ratios of Prevalent Symptomatic Knee OA Compared to Non-Swimmers (referent) for Swimmers (dichotomous) and then Swimmers Divided into 3 levels of Activity: low, middle, and high.				
Swimming Time Period	Prev. of SOA	Unadjusted Odds Ratios	Adjusted Odds Ratios*	
Any History of Swimming				
Non-Swimmers (n = 1575)	29.5%	Referent	Referent	
Swimmers (n = 1062)	24.4%	0.78(0.65-0.92)	0.84(0.69-1.01)	
Low (n =402)	25.4%	0.82(0.64-1.05)	0.89(0.68-1.16)	
Middle (n = 306)	23.9%	0.75(0.57-1.00)	0.84(0.62-1.14)	
High (n = 354)	23.7%	0.74(0.57-0.97)	0.77(0.57-1.03)	
		p for trend=0.006	p for trend=0.05	
Ages 12 – 18 years old				
Non-Swimmers (n = 1899)	28.7%	Referent	Referent	
Swimmers (n = 738)	24.3%	0.80(0.66-0.97)	0.93(0.76-1.16)	
Low (n = 298)	22.6%	0.73(0.55-0.98)	0.90(0.66-1.22)	
Middle (n = 224)	24.8%	0.82(0.60-1.13)	0.88(0.63-1.24)	
High(n = 216)	26.1%	0.88(0.64-1.21)	1.05(0.75-1.47)	
		p for trend=0.10	p for trend=0.8	
Ages 19 – 34 years old				
Non-Swimmers (n = 2118)	28.6%	Referent	Referent	
Swimmers (n = 519)	22.8%	0.74(0.59-0.93)	0.77(0.60-0.98)	
Low (n = 181)	24.6%	0.82(0.57-1.16)	0.81(0.56-1.17)	
Middle (n = 145)	22.9%	0.74(0.50-1.10)	0.85(0.56-1.29)	
High(n = 193)	21.1%	0.67(0.47-0.96)	0.67(0.46-0.99)	
		p for trend=0.007	p for trend=0.03	
Ages 35 – 49 years old				
Non-Swimmers (n = 2228)	27.7%	Referent	Referent	
Swimmers (n = 409)	26.2%	0.93(0.73-1.18)	0.96(0.74-1.24)	
Low (n = 144)	26.6%	0.95(0.65-1.39)	0.98(0.66-1.47)	
Middle (n = 142)	28.6%	1.05(0.72-1.53)	1.13(0.76-1.68)	
High(n = 123)	23.0%	0.78(0.51-1.2)	0.76(0.48-1.20)	
		p for trend=0.4	p for trend=0.5	
Ages ≥ 50 years old				
Non-Swimmers (n = 2274)	27.7%	Referent	Referent	
Swimmers (n = 363)	26.0%	0.92(0.71-1.19)	0.87(0.66-1.14)	
Low (n = 132)	27.9%	1.01(0.68-1.50)	0.96(0.63-1.46)	
Middle (n = 115)	24.6%	0.85(0.55-1.32)	0.87(0.55-1.37)	
High(n = 116)	25.2%	0.88(0.57-1.36)	0.77(0.49-1.23)	
		p for trend=0.4	p for trend=0.2	

***Adjusted for age, sex, BMI, all leisure physical activities that significantly correlate with swimming during the relevant time frame, and prior knee injury.**
****Results were similar with frequent knee pain and ROA as the outcomes.**

Conclusion: We did not find an increased prevalence of symptoms or ROA in people with a history of swimming compared to those without. There may be a benefit to swimming for all these outcomes which could be tempered due to confounding by indication, particularly in older age groups. In the 19-34 year old group, a younger age group, where the result is strongest, there is less likely to be reverse causation. People who swim tend to also walk and participate in other water-based leisure activities. This is the first epidemiologic study to support that swimming does not appear detrimental and may be beneficial towards knee health.

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Abstract Number: 2365

The Cross-Sectional and Longitudinal Associations Between Metabolic Syndrome and Hand Osteoarthritis – Data from the Framingham Study

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Background/Purpose: The association between osteoarthritis (OA) and metabolic syndrome (MetS) is controversial. Hand OA, and especially erosive hand OA (1), may be more strongly related to systemic risk factors, such as MetS, than OA in lower limbs. Hence, our aim was to explore the associations between hand OA and MetS in the Framingham Offspring cohort.

Methods: Hand x-rays and clinical data on MetS were available in 1090 persons between 50-75 years, of whom 785 had follow-up hand x-rays after 7 years. Baseline hand radiographs were read according to Kellgren-Lawrence (KL) scale. The longitudinal x-rays were similarly read in pairs according to KL scale and were also read for central erosions. We examined whether MetS and its components were associated with presence of radiographic hand OA (≥1 finger joint with KL grade ≥2) and erosive hand OA (≥1 finger joint with erosions) at baseline using logistic regression. Linear regression was performed with KL sum score as outcome. In longitudinal logistic regression analyses, we examined the associations between MetS and its components at baseline and

incident radiographic hand OA in persons with no hand OA at baseline. Analyses were repeated using incident erosive hand OA in persons with no erosions at baseline. Age and sex were included in all models with/without additional adjustment for body mass index (BMI).

Results: Mean (SD) age was 59.2 (6.3) years and 52% were women. At baseline, radiographic hand OA was present in n=492/1090 (45%), whereas erosive hand OA was found in n=52/785 (7%). N=492/1090 persons (45%) had MetS. In cross sectional analyses, MetS, central obesity and hypertension were associated with hand OA presence after adjusting for age and sex, but only the latter reached statistical significance (Table). No associations were found for KL sum score (data not shown) or erosive hand OA (Table). Incident hand OA and incident erosive hand OA occurred in 166/375 (44%) and 55/733 (8%), respectively. Whereas no associations were found for incident hand OA, there was a trend that MetS was associated with development of erosive OA, and a significant association was found for central obesity (Table). All associations remained similar after additional adjustment for BMI. **Table:** Associations between MetS and hand OA.

	Cross-sectional analyses OR (95% CI)*		**Longitudinal analyses OR (95% CI)***	
	Hand OA presence	**Erosive hand OA presence**	**Incident hand OA**	**Incident erosive OA**
MetS	1.23 (0.95,1.61)	0.71 (0.39,1.30)	0.78 (0.51,1.19)	1.66 (0.95,2.92)
Central obesity	1.23 (0.94,1.61)	0.69 (0.37,1.27)	1.40 (0.92,2.15)	*1.78 (1.02,3.10)*
High BP or anti-hypertensive rx	*1.41 (1.08,1.84)*	1.01 (0.56,1.83)	1.10 (0.72,1.67)	1.19 (0.67,2.11)
Diabetes or antidiabetic rx	1.14 (0.86,1.51)	0.74 (0.38,1.45)	0.89 (0.56,1.42)	1.32 (0.73,2.40)
Low HDL or lipid-lowering rx	1.09 (0.83,1.42)	0.77 (0.41,1.44)	1.23 (0.81,1.87)	1.23 (0.70,2.15)
High triglycerides	0.92 (0.69,1.23)	0.49 (0.25,0.96)	0.67 (0.43,1.05)	1.23 (0.65,2.31)
OR=odds ratio; CI=confidence interval; OA=osteoarthritis, MetS=metabolic syndrome; BP=blood pressure, HDL=high-density lipoprotein, rx=treatment. * Adjusted for age and sex.				

Conclusion: No consistent results were found between MetS and the presence and development of hand OA. A significant association was found between central obesity and incident erosions, but the lack of associations in baseline analyses suggests that this may be a chance finding. **References:** 1) Marshall M. et al. Ann Rheum Dis. 2015;74:136-41.

Disclosure: M. P. Strand, None; **T. Neogi**, None; **J. Niu**, None; **D. T. Felson**, None; **I. K. Haugen**, None.

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Abstract Number: 2366

The Clinical Utility of the Bulge Sign in Evaluating Knee Osteoarthritis

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Background/Purpose: Despite clinicians commonly using the bulge sign test to assess presence of knee effusion, prior studies have questioned the validity of the test to detect the prevalence of knee effusion based on ultrasound imaging. It remains unknown if the bulge sign test over time is a sensitive test to detect changes in knee effusion. Hence, we evaluated the association between the bulge sign test and magnetic resonance (MR) imaging-based knee effusion volume at a single visit and change over 2 years.

Methods: We selected individuals from the Osteoarthritis Initiative (OAI) who had no radiographic knee osteoarthritis at baseline and had MR images and a clinical exam at baseline and 24-month OAI visits. We enriched the sample to include 250 individuals who had an increase in radiographic severity (Kellgren-Lawrence grade). We selected the 1 knee per person. Two readers used a semi-automated software to quantify MR-based knee effusion volume (includes synovitis and effusion; intra-tester reliability: 0.73 to 0.97). Reader 1 reviewed all segmented images to ensure consistency between readers, knees, and time. The bulge sign was performed during a standardized clinical exam. We defined an incident bulge sign as a person with a positive bulge sign at the 24-month visit but not at baseline. We used an independent-sample t-test to compare baseline effusion volume between those with and without a positive bulge sign at baseline. A second independent-test was used to compare change in effusion volume between those with an incident bulge sign and those who never had a positive bulge sign. We also used logistic regression with ROC curves to explore the optimal cutpoint for baseline effusion volume and change in effusion volume for baseline positive bulge sign and incident bulge sign, respectively.

Results are reported as mean (standard deviation). Results: At baseline of OAI visit 352 participants were eligible participants with a mean age of 59.6 (8.6) years, mean BMI of 28.4 (4.5) kg/m2, and 62% female. The 47 participants with a positive bulge sign (15.38 [12.83] cm^3) had greater knee effusion (t=-3.45, p=0.001) than those without a positive bulge sign (8.81 [6.14] cm^3). Based on an ROC curve, knee effusion volume had an area under the curve of 0.67 with an optimal cutoff between those with and without a positive bulge sign of 8.39 cm^3. At the 24-month OAI visit, the 40 (14%) participants with an incident positive bulge sign (9.85 [11.90] cm^3) had greater increases in knee effusion volume(t = -4.21, p = 0.0001) than the 251 participants without an incident positive bulge sign (1.65 [7.69] cm^3). Based on an ROC curve, change in knee effusion volume had an area under the curve of 0.70 with an optimal cutoff between those with and without a positive bulge sign of 2.06 cm^3.

Conclusion: The bulge sign test is associated with effusion volume and changes in effusion volume but may misclassify individuals with and without larger volumes of effusion or those with larger increases in knee effusion volume. Clinicians and researchers need to be aware of these properties when relying on the bulge sign test.

Disclosure: F. Al Eid, None; **T. E. McAlindon**, None; **M. Zhang**, None; **J. Driban**, None.

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Association Between MRI-Detected Osteophytes and Changes in Knee Pain and Structures in Older Adults: A Population Based Cohort Study

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Background/Purpose: Osteophyte (OP) formation is one of the clinical features of osteoarthritis (OA), so early detection of OP formation can be of diagnostic value. OP can be visualised using magnetic resonance imaging (MRI) that are not easily visualised by conventional radiography, and at greater sensitivity than radiographs for detection of early and central OP. Although some studies have examined relationships between MRI-detected OP and clinical features of knee OA, longitudinal studies are rare. Furthermore, clinical significance of x-ray-undetectable OP is unknown. Therefore, our study aims to describe cross-sectional and longitudinal associations between MRI-detected OP and knee pain and structural changes in older adults; and to evaluate the longitudinal associations between x-ray- undetectable OP and knee pain and structural changes.

Methods: 837 participants (mean age 62 years, 50% female) were randomly selected from local community at baseline. T1- or T2-weighted fat suppressed magnetic resonance imaging (MRI) was used to assess knee OP, cartilage volume (CV), cartilage defects (CD) and bone marrow lesions (BMLs) at baseline and after 2.6 years. Knee pain was assessed by self-administered Western Ontario and McMaster Osteoarthritis (WOMAC) Index questionnaire at baseline and after 5 years. Radiographic osteoarthritis (ROA) was assessed at baseline with a standing anteroposterior semiflexed radiograph scored using the Osteoarthritis Research Society International atlas. OPs detected by MRI but not by X-ray at baseline were defined as x-ray- undetectable OP. Analyses were performed using linear regression models and log-binominal regression models.

Results: 86.6% of participants had MRI-detected OPs at baseline, while only 10% of participants had radiographic OPs. Cross-sectionally, MRI-detected OPs at medial tibiofemoral, lateral tibiofemoral and patellar compartments were significantly and site-specifically associated with a higher prevalence of CD and BMLs, and reduced CV after adjustment for common covariates (all $p<0.01$). MRI-detected OPs in whole compartment were significantly associated with higher prevalence of total knee pain ($p<0.01$). Longitudinally, baseline MRI-detected OP site-specifically predicted increases in CD and BMLs and loss of CV (all $p<0.01$) in multivariable analyses.

Compared to participants without any OP, participants with x-ray- undetectable OP and definite OP (both radiographic and MRI-detected OP) had greater CV loss and increased CD and BMLs longitudinally. Presence of x-ray- undetectable OP predicted decreases in total knee pain over 5 years, while participants with definite OP predicted increases in knee pain, after adjustment for BMLs, CD and NSAIDs usage.

Conclusion: MRI-detected OPs were associated with knee structural abnormalities and knee pain cross-sectionally and longitudinally. Although x-ray- undetectable OP is associated with knee abnormal structural changes, it predicts decreases in knee pain over time suggesting an adaptive response.

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Abstract Number: 2368

Analysis of Pain and Function Components in Omeract-Oarsi Strict Responders from a Randomized, Double-Blind, Placebo-Controlled, Phase 1 Study of a Novel, Intra-Articular, Injectable, Wnt Inhibitor (SM04690) in the Treatment of Osteoarthritis of the Knee

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Osteoarthritis – Clinical Aspects - Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Knee osteoarthritis (OA) is characterized by pain, functional impairment, disability, and joint space narrowing due to degradation of articular cartilage and bone remodeling. The Wnt signaling pathway is known to play a central role in the formation of joint tissues, and altered Wnt signaling has been associated with cartilage loss in preclinical and clinical studies.[1] SM04690 is a small molecule inhibitor of the Wnt pathway in development as a potential OA therapeutic to be administered as an intra-articular (IA) injection into the affected joint. A phase 1, first-in-human, multicenter, 24-week, single-dose-escalation, randomized controlled trial (RCT) of SM04690 was completed. It assessed safety and tolerability of SM04690 administered IA to subjects with moderate to severe OA. This report provides a breakdown of components driving the Outcome Measures in Rheumatology (OMERACT)-Osteoarthritis Research Society International (OARSI) strict responder data to further evaluate proof of concept of efficacy of SM04690.

Methods: In the completed phase 1 RCT, escalation cohorts were dosed at 0.03 mg, 0.07 mg, and 0.23 mg SM04690 per 2 mL injection, in cohorts of 20 subjects (randomized, 16 active: 4 placebo). Subjects were administered a single IA injection in the target knee on treatment day 1, and participated in a follow-up period of 24 weeks. Safety, pharmacokinetics (PK), biomarker, and preliminary efficacy data, including the Western Ontario and McMaster Universities Arthritis Index (WOMAC Likert v3.1), were collected. The percentage of OMERACT-

OARSI "strict" responders in the modified Intention-to-Treat (mITT) population were evaluated. "Strict" responders were defined as reporting either WOMAC Function subscore or WOMAC pain subscore improvement of ≥50% coupled with at least a 20-point reduction in the given subscore (scaled to [0-100]).

Results: Sixty-one subjects (average age 62.6 [±5.7] years, female n=41 [67%], average BMI 30.4 [±4.7] kg/m^2) were enrolled. Versus placebo, there were statistically more OMERACT-OARSI strict responders in the 0.07 mg cohort at week 12 (76% vs. 36%; *P*=0.04), and numerically more in the 0.03 mg cohort at week 24 (73% vs. 36%; *P*=0.07) (Figure). More subjects in the 0.07 mg cohort met both the pain and function criteria vs placebo at 12 weeks (53% vs. 36%), and 24 weeks (44% vs. 27%). Responses in the 0.23 mg cohort were 44% at week 12 and 25% at week 24.

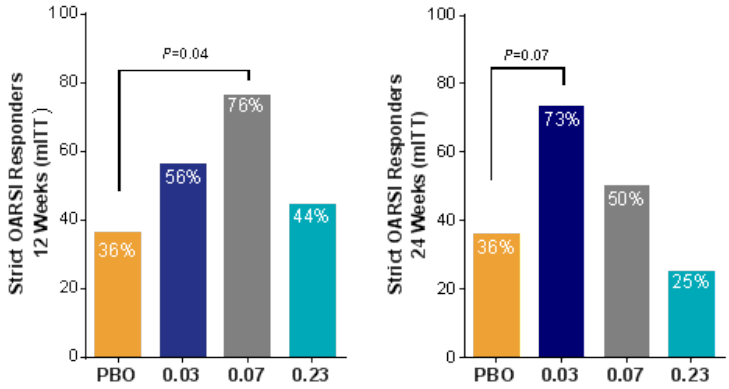
Conclusion:

Analysis of OMERACT-OARSI strict responders in this phase 1 study provides evidence of a potential treatment effect on both OA pain and function for the novel Wnt inhibitor SM04690 compared with placebo. These data support further development in an ongoing phase 2 RCT.

Reference:

1. Gelse K. Osteoarthr Cartil. 2012; 20(2):16271

Figure: Percent of OMERACT-OARSI "strict" responders at weeks 12 and 24



Disclosure: V. Strand, None; **C. J. Swearingen**, Samumed, LLC, 3; **I. Simsek**, Samumed, LLC, 3; **A. DiFrancesco**, Samumed, LLC, 3; **J. Tambiah**, Samumed, LLC, 3; **Y. Yazici**, Samumed, LLC, 3.

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Abstract Number: 2369

Obesity and Severity of Joint Space Narrowing Are Associated with Viscosupplementation Failure in Patients with Knee Osteoarthritis. Post-Hoc Analysis of a Double-Blind, Controlled, Multicentre, Randomized Trial

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Background/Purpose: Viscosupplementation (VS) is still controversial. One of the key points is the lack of well-identified factors of response. We aimed to identify clinical and radiologic factors associated with lack of a relevant response according to OMERACT-OARSI criteria after intra-articular (IA) hyaluronic acid (HA) injections in symptomatic knee OA patients.

Methods: We included the 166 patients with available data from the intent-to-treat population (n=205) of the HAV-2012 trial, a controlled, multicentre, double-blind, randomised, non-inferiority trial comparing 2 HA products for symptomatic tibiofemoral OA. At inclusion, demographic, anthropometric, clinical data (patient global assessment, WOMAC, knee effusion) and radiologic data (OARSI grade, patellofemoral OA) were recorded. Patients received 3 weekly IA injections of HA. At 6-month follow-up, VS response was defined according to OMERACT-OARSI criteria.

Results: Clinical characteristics at baseline and VS effectiveness were similar between the 2 HA groups, so their data were pooled**.** The mean age was 65.2 [63.7-66.8] years; 101 (60.8%) were women; 73 (44.0%) had severe tibiofemoral space narrowing. At baseline, mean WOMAC pain and function scores were 9.8 [9.3–10.3] and 27.5 [25.7–29.4], respectively. At 6 months, 113 patients (68.1%) were considered responders. Multivariate analysis showed that obesity and radiologic severity (OARSI grade 3 vs 1-2) were significantly associated with VS failure (p=0.0001 and p=0.011, respectively). Initial pain intensity and functional severity were not associated with VS response.

Conclusion: IA injection of HA for knee OA should mainly be considered in subjects with low BMI and mild tibiofemoral space narrowing.

Disclosure: F. Eymard, Labhra, 9; **X. Chevalier**, labhra, 5; **T. Conrozier**, Labhra, 5.

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Abstract Number: 2370

Factors Affecting Interval Changes in Perceived Fatigue over Five Years in Patients with Rheumatoid Arthritis Compared with Osteoarthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: In a previous cross-sectional study we noted higher fatigue levels in patients with advanced lower limb OA compared with RA, and identified differences in common outcome variables and their associations with fatigue between RA and OA groups. High levels of disability and depression correlated with fatigue in both conditions. In the current longitudinal study, we re-appraised patients in the initial cohort and assessed their fatigue levels and associated disease variables 5 years after their initial assessment in order to test the stability of these influences over time.

Methods: The original study recruited 103 patients each with RA or hip/knee OA (n=206). Of these 68 OA and 72 with RA were available for re-assessment after 5 years (n=140; 68% retention). Reasons for loss to follow-up were moving out of area, death and declining to take part. All participants were assessed for pain and fatigue using 100mm VAS scales; functional disability using the HAQ- disability index; and mood using the Hospital Anxiety and Depression Scale (HADS-Anxiety and HADS-Depression). CRP was measured in all participants and BMI calculated. In the RA group, the Disease Activity Score (DAS-28) was recorded. In the OA group, pain and disability were self-reported using the WOMAC score. Changes over time in the outcomes of interest were assessed separately for OA and RA using paired t-tests. Changes were compared between OA and RA using regression models of follow-up values adjusting for baseline values of the variable in question, along with baseline age, sex, and BMI. Similar models were used to examine the impact of joint replacement within the OA group. Correlations between change scores for all outcomes were investigated separately for OA and RA using Pearson's correlation coefficients.

Results: There was no evidence for interval changes over 5 years in RA for any of the outcomes including DAS-28 scores (change +0.00; 95% CI -0.33, 0.33; p=0.989) whereas in OA significant reductions in severity for a number of outcomes were recorded in the OA group: HAQ decreased by 0.38 (95% CI 0.20, 0.55; p<0.001), WOMAC-total by 21.6 points (95% CI 16.1, 27.1; p<0.001), pain (VAS) decreased by 27.1 (95% CI 19.4, 34.9; p<0.001), HADS-Depression decreased by 2.0 (95% CI 1.1, 2.9; p<0.001). In the OA group, changes between all 15 pairs of outcomes were positively correlated (p<0.045) aside from VAS fatigue and HAQ (p=0.087). However, there were fewer significant correlations in the RA group. Among the OA group, 57 (84%) had interval hip/knee joint replacement. There was no evidence that this was associated with better follow-up HAQ, pain, or fatigue (all unadjusted and adjusted p≥0.090), but was associated with improvement on WOMAC total (14.0 points unadjusted, 95% CI 1.0, 26.9; p=0.035; 13.8 adjusted, 0.9, 26.6; p=0.036).

Conclusion: After 5 years a range of common disease outcomes were surprisingly stable in RA, but significant reductions in pain, fatigue, disability and total WOMAC score were noted in OA, although only this last measure was associated with joint replacement. The strongest correlates with fatigue over 5 years were anxiety and depression in both groups.

Abstract Number: 2371

Effect of Etanercept on Several Soluble Biomarkers in a Randomized Controlled Trial of Patients with Erosive Hand Osteoarthritis

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Background/Purpose: Erosive hand osteoarthritis (OA) is a hand OA subset with high disease burden, although effective therapies are still lacking and clinical trials are scarce. Moreover, the low sensitivity-to-change of radiographs hampers outcome measurement of structural damage in short-term trials. Therefore, we explored the effect of etanercept on several biomarkers of bone, cartilage and inflammation.

Methods: Analyses were performed in a double blind trial comparing etanercept (50mg/week for 24 weeks, followed by 25mg/week up to 1 year) to placebo (NTR 1192). Ninety patients with symptomatic erosive OA with clinical and ultrasonographic signs of inflammation in ≥1 interphalangeal joint were included. The following biomarkers were measured with ELISA at baseline, 24 and 52 weeks: C-terminal collagen crosslinks I (CTX-I) in urine, and high sensitivity C-reactive protein (hsCRP), myeloperoxidase (MPO), matrix metalloproteinase 3 (MMP3) and hyaluronic acid (HA) in serum. In some patients additional measurements at 4, 12, and 36 weeks were available. The effect of treatment on each biomarker at 24 and 52 weeks was estimated with generalised estimating equations in the intention to treat (ITT) and per protocol (PP) population, adjusting for baseline and study center. Patients fulfilling all inclusion criteria who completed the trial were included in the PP population.

Results: Biomarkers were measured in 78 patients (n=39 per group, 80.8% women, mean age 58.6 (SD 6.8), mean BMI 25.9 (SD 3.8)). Biomarker levels were comparable between groups at baseline, with large interquartile ranges (IQRs; table). Levels of hsCRP decreased slightly in both groups, but there were no between-group differences (at 24 weeks median 1.1 (IQR 0.7 to 4.2) and 1.7 (IQR 0.9 to 4.1) mg/L in placebo and etanercept group respectively). However, MMP3 levels decreased more in the etanercept group compared to placebo after 24 weeks (mean difference -1.44 ng/mL, 95% CI -2.82 to -0.05 (n=63)), although this difference was not sustained after etanercept dose reduction. No differences in the other biomarker levels were noted. PP analyses showed similar results.

Conclusion: Anti-TNF therapy reduced serum MMP3 levels, but not CTX-I, hsCRP, MPO and HA, in patients with erosive OA. The secretion of MMP3 is known to be stimulated by TNFα, and viewed as a marker of cartilage destruction. It remains unclear whether the observed decrease is merely a marker for decreased TNFα biological activity after anti-TNF, or that it is a sign of reduced cartilage damage in the etanercept group.

Table. Baseline levels of each biomarker (median (interquartile range)) and between-group differences after 24 and 52 weeks (ITT population).

	Baseline		**24 weeks**	**52 weeks**
	Placebo	**Etanercept**	*mean difference (95% CI)*	*mean difference (95% CI)*
CTX-I	7.3 (3.4, 14.6)	10.2 (4.0, 16.5)	-5.90 (-12.67 to 0.88)	-3.88 (-12.85 to 5.09)
hsCRP	1.8 (0.8, 2.8)	2.3 (1.5, 4.3)	-0.29 (-1.91 to 1.34)	0.54 (-0.50 to 1.59)
MPO	420.6 (330.1, 618.8)	358.1 (235.7, 602.9)	-28.19 (-140.30 to 83.91)	55.72 (-99.26 to 210.70)
MMP3	4.5 (1.0, 6.6)	4.9 (0.8, 6.8)	-1.44 (-2.82 to -0.05)*	-0.21 (-1.83 to 1.41)
HA	51.6 (39.2, 65.9)	47.2 (34.4, 69.6)	12.56 (-14.17 to 39.30)	18.73 (-6.17 to 43.63)

*Significantly lower in the etanercept compared to placebo group (p=0.04).
CTX-I, C-terminal collagen crosslinks I (urine, ug/L); HA, hyaluronic acid (serum, ng/mL); hsCRP, high-sensitivity C-reactive protein (serum, mg/L); MMP3, matrix metallopeptidase 3 (serum, ng/mL); MPO, myeloperoxidase (serum, ug/L).

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Abstract Number: 2372

Effect of Oxytocin on Osteoarthritis

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Session Title: Osteoarthritis – Clinical Aspects - Poster II

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Background/Purpose: The relationship between oxytocine (OT) and osteoarthritis (OA) is poorly studied and remains unknown. However the subchondral bone is considered as a major player in osteoarthritis, and a protective effect of OT on bone mineralization is described in recent studies. The aim of our work was to investigate a possible link between OT and OA.

Methods: we used three different approaches: i) In vitro using MSC (adipose and bone marrow derived stem cells) that were maintained as mono-layer (2D) or as pellets in three dimension (3D) in the absence or the presence of OT. RT-PCR, histological and immunohistochemical analysis were performed. ii) in vivo using a rat animal model developing OA upon anterior cruciate ligament transection (ACLT) . Twenty female Wistar rats were divided in 2 groups: one group was sham operated whereas the second was ACL transected. Half of each group received either OT (1 mg/kg/day) injections or saline buffer. Histological analysis was performed on day 28. The severity of OA lesions was assessed on a scale adapted from Mankin's score at medial part of the femur. iii) Clinical analysis using a **human cohort**. Samples issued from a hand OA cohort (ADEM). 63 OA women have been included; men were excluded because of their low number. At baseline, all subjects benefited of OT and leptin circulating levels measurements and hand X rays (Scoring systems including Kelgren and Lawrence and Verbruggen scores). The control group consists in subjects of the same age range without osteoporosis, OA or inflammatory disease.

Results: OT treatment of differentiating MSCs for 21 days induced a significant increase of agrecan, Col X and COMP mRNA levels without variation of Col 1a. Immunostaining experiments showed an improvement of Sox9 and Col II expression in the presence of OT. The histological analysis of rat knee showed no differences in the severity of lesions between the different ACLT groups. The characteristics of the women cohorts is as follow: 63 OA women age=65 (+/-11), Body Mass Index (BMI) = 24(+/-4), OT=1.4 (+/-2) and 19 control women age=63(+/-10), BMI=26(+/-5), OT=6.5(+/-7).The multivariate analysis adjusted for age, BMI and leptin levels, showed a significant lower level of OT in hand OA women ($p=0.002$, $\beta=3.4$). In univariate analysis, there was no relationship between OT blood levels and the severity of OA (Verbruggen:$p=0.7$, KL:$p=0.2$), Joint Space Narrowing ($p=0.2$) and osteophytes ($p=0.1$).

Conclusion: Our study shows an anabolic effect of OT on chondrogenesis and that OT circulating levels was significantly lower in OA patients. OT might represents an interesting player in the pathophysiology of osteoarthritis and further studies will shed some light on its mechanism of action.

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Abstract Number: 2373

Patient Preference for Display of Electronic Patient-Reported Outcomes in Osteoarthritis Clinical Trials: Wording Emphasis, Question Format, and Navigation Button Placement

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SESSION INFORMATION
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Background/Purpose: Electronic patient-reported outcomes (ePROs) are a reliable method for collecting patient data in osteoarthritis clinical trials and offer many advantages over paper collection; however, it is essential to consider patient preference and ease of use when employing this technology. Improving the usability of ePRO in osteoarthritis clinical trials could ultimately reduce subject burden and improve subject engagement.

Methods: 104 subjects with osteoarthritis were surveyed regarding their preferences for ePRO display.

Results: When presented with options for showing emphasis in a sentence, subjects thought that underlining best drew attention to emphasized words (36%), followed by bold (35%) or capitalized (21%) lettering. Subjects were shown screens of a multi-select question formatted to read left to right (question to the left of the answers) or top to bottom (question above the answers). 39% could read and understand the screens equally. Of those with a preference, 75% preferred the top to bottom format. Subjects were shown screens of a tablet computer ePRO device with either one question per screen or several multi-select questions per screen in a matrix format. 68% preferred one question per screen; of these subjects, 58% thought it was easier to read and 45% thought it was easier to understand the question. 32% preferred multiple questions per screen; of these subjects, 50% thought it was faster to complete and 38% thought it was easier to read. Subjects were shown two screens with “back” and “next” navigation buttons at either the top or bottom of the screen. 28% thought it was equally easy to find the buttons; of those with a preference, 76% preferred them at the bottom of the screen.

Conclusion: When possible, questionnaire designers should consider these results to incorporate patient preference into the design of ePRO instruments; potentially reducing subject burden and increasing patient engagement in clinical trials.

Disclosure: L. Khurana, ERT, 3; **E. Durand**, ERT, 3; **S. Gary**, ERT, 3; **T. Otero**, ERT, 3; **C. Hall**, ERT, 3; **A. Ryan**, Endpoint Outcomes, 3; **C. J. Evans**, Endpoint Outcomes, 3; **S. Dallabrida**, ERT, 3.

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Abstract Number: 2374

Efficacy and Safety of Canakinumab in Patients with Systemic Juvenile Idiopathic Arthritis: Results from an Open-Label Long-Term Follow-up Study

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster III: Systemic JIA, Autoinflammatory Syndromes, Scleroderma, Vasculitis, Miscellaneous

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Canakinumab (CAN), a highly selective human anti-IL1 β monoclonal antibody, had demonstrated its efficacy and safety in patients (pts) with active systemic juvenile idiopathic arthritis (SJIA) in a comprehensive global clinical program consisting of one phase II and two phase III trials.[1,2]However, limited data was available on long-term efficacy and safety of CAN in SJIA. The study objective was to assess the long-term efficacy and safety of CAN treated SJIA pts over a 5-year (yr) follow-up observational period.

Methods: This was an open-label extension (OLE) study (NCT00891046) of SJIA pts participating in the global clinical trials of CAN.[3] Pts, 2 to <20 yrs of age at the time of enrollment in study, received subcutaneous CAN 4 mg/kg every 4 weeks. Baseline was defined as the starting point of the extension trial. Efficacy assessments were done every 3 months, including adapted pediatric response criteria (aACR), clinical inactive disease, and clinical remission on medication (continuous 12 months of clinical inactive disease). Safety assessments included adverse events (AEs) and serious AEs (SAEs).

Results: Overall, 147 pts to the OLE study had a median treatment duration of 3.2 yrs; total treatment exposure was approximately 365 pt-yrs. Of 147 pts, 100 (68%) completed 96 weeks of treatment, whereas 47 (32%) pts discontinued the study. Another 25 pts (17%) discontinued the study after Week 96. Of the 107 pts with an aACR 30 at entry to the OLE study, 61.7%, 79.4%, and 86.0% have had aACR 100, 90, and 70 responses, respectively at last assessment. At baseline, 32.7% of patients were with inactive disease which increased up to 60%-70% between Week 36 and Week 168. Clinical remission on medication was achieved in 43% pts. In total, 137 (93.2%) pts reported at least 1 AE during the 3.2 yrs median exposure in the study corresponding to 2.009 AEs/100 pt-days (733.6 AEs/100 pt-yrs) with infections (202.7 per 100 pt-yrs) being the most common AE. Overall, 47 (32.0%) pts had at least 1 SAE corresponding to 0.089 SAE/100 pt-days (32.6 SAE/100 pt-yrs) with the most common being JIA (14 pts) denoting disease flares or worsening of SJIA. Ten patients (6.8%) with a total of 12 macrophage activation syndrome (MAS) events were reported as SAE and 7 patients among them discontinued the study. No deaths were reported.

Conclusion: In patients previously treated with CAN in pivotal trials, response to treatment was sustained or improved during long-term treatment in the OLE study. Safety profile of CAN was consistent with safety findings from previous studies. References: 1. Ruperto N, et al. *N Engl J Med*. 2012;367(25):2396-406. 2. Ringold S, et al. *Arthritis & Rheum*. 2013;65(10):2499-512. 3. Ruperto N, et al. *Ann Rheum Dis*. 2015;74(2):608.

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Abstract Number: 2375

Biologic Therapy Modifies Clinical and Laboratory Features of Macrophage Activation Syndrome Associated with Systemic Juvenile Idiopathic Arthritis

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Session Type: ACR Poster Session C

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Background/Purpose: Macrophage activation syndrome (MAS) is a life-threatening episode of hyperinflammation and a substantial cause of morbidity and mortality in pediatric rheumatology. It occurs most often as a complication of systemic juvenile idiopathic arthritis (SJIA). Despite highly efficacious treatments for SJIA with biologic agents blocking IL-1 and IL-6, patients remain at risk for MAS. Additionally, it is unclear whether treatment with biologic agents alters the clinical presentation of MAS.

Methods: We performed a comprehensive literature review to identify published cases of MAS in SJIA patients which occurred while being treated with biologic agents. Where necessary, authors were contacted directly to obtain further demographic, clinical or laboratory information. These accumulated cases were then compared to the large database of MAS cases collected as part of the 2016 MAS classification criteria project, which we used as a historical cohort.

Results: Together, sixteen published manuscripts or abstracts were identified, describing 138 episodes of MAS occurring while patients were treated with biologic agents. Further data collection and removal of duplicates led to 85 cases of MAS where clinical and laboratory information was available for analysis. Of these, 34 cases occurred while on canakinumab and 46 while on tocilizumab. Patients who developed MAS while treated with canakinumab had no significant differences in their reported clinical features. These patients did have a lower median white blood cell count (3.4 $x10^9$/L vs 9.9 $x10^9$/L, $p<0.0001$) and serum ferritin level (2170 ng/ml vs 5353 ng/ml, $p<0.05$) at MAS onset than the historical cohort; all other laboratory features of MAS were not significantly different. In contrast, patients who developed MAS while treated with tocilizumab were less likely to present with fever or hepatomegaly than patients in the historical cohort. In addition, patients treated with tocilizumab had significantly lower white blood cell counts (3.6 vs 9.9, $p<0.0001$), serum ferritin levels (983 vs 5353, $p<0.0001$), and less severe anemia (12.0 g/dl vs 9.8 g/dl, $p=0.01$) than patients in the historical cohort. Additionally, other laboratory features of MAS were more pronounced in patients treated with tocilizumab, with lower platelet counts (96 $x10^9$/L vs 144 $x10^9$/L, $p<0.0001$) and fibrinogen levels (113 g/l vs 267 g/l, $p<0.0001$), and higher aspartate aminotransferase levels (244 U/l vs 134 U/L, $p<0.05$). Due to these differences, the 2016 MAS classification criteria only categorized 53-55%% of tocilizumab treated patients as having MAS, compared to 76-83% of patients treated with canakinumab and 78% of the historical cohort.

Conclusion: This represents the largest reported analysis of MAS cases occurring during treatment with biologic therapy, and reveals important differences in clinical and laboratory features when MAS occurs during treatment with canakinumab and tocilizumab. Taken together, these findings support the need for increased clinical vigilance for signs of developing MAS in these patients, as well as the use of supporting laboratory features such as platelet count, AST and fibrinogen in MAS surveillance.

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Abstract Number: 2376

The Disease Burden of Systemic Juvenile Idiopathic Arthritis for Patients and Caregivers: An International Health Related Quality of Life Survey and Retrospective Chart Review

Susan Shenoi[1], Gerd Horneff[2], Michal Cidon[3], Athimalaipet Ramanan[4], Yukiko Kimura[5], Pierre Quartier[6], Ivan Foeldvari[7], Andrew Zeft[8], Kathleen G Lomax[9], Jill Gregson[10], Sarah Campbell[11], Jeffrey Weiss[11], Nina Marinsek[11], Dony Patel[11] and Nico Wulffraat[12], [1]Seattle Children's Hospital, Seattle, WA, [2]Asklepios Kliniken GmbH, Hamburg, Germany, [3]Stanford University, Palo Alto, CA, [4]University Hospitals Bristol, Bristol, United Kingdom, [5]Hackensack University Medical Center, Hackensack, NJ, [6]Hôpital Necker, Paris, France, [7]Hamburger Zentrum für Kinder-und Jugend Rheumatologie, Hamburg, Germany, [8]Pediatrics Rheumatology, Cleveland Clinic, Cleveland, OH, [9]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [10]Novartis Pharma AG, Basel, Switzerland, [11]Navigant Consulting, Inc., London, United Kingdom, [12]Wilhelmina Kinderziekenhuis, Utrecht, Netherlands

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic juvenile idiopathic arthritis (SJIA) is a severe autoinflammatory disease characterized by systemic features including high fevers, rash, and arthritis. SJIA can impose a high physical, psychosocial, behavioral and financial burden on patients and their families. This international, real-world study conducts a detailed analysis of the impact of the burden of SJIA by evaluating caregiver perspectives of disease burden utilizing a SJIA-specific questionnaire combined with physician data about disease severity and treatment.

Methods: SJIA treatment centers in France, Germany, Netherlands, UK and the US participated. Patients were 4-18 years with confirmed SJIA and received one of the following biologic treatments for ≥2 months: anakinra (ANA), canakinumab (CAN), or tocilizumab (TOC). Caregivers had cared for the patients for the previous ≥6 months, were >18 years, spent ≥50% of their time with the patients, and completed a SJIA-specific survey. Physicians reported disease severity and treatment through retrospective chart review. Ethics committee approvals and written informed consent were obtained. The caregiver questionnaire assessed the impact of SJIA on the practical, social and emotional aspects of caregivers' lives. Validated and tailored patient-reported outcome (PRO) measures were used: the Child Health Questionnaire-Parent Form 50 (CHQ-PF50), 36-Item Short Form

Health Survey (SF-36), and Work Productivity and Activity Impairment Questionnaire: Specific Health Problem (WPAI:SHP). Tailored questions collected data on patient function, treatment satisfaction and direct/indirect resource utilization.

Results: Sixty patients enrolled from 6/15-5/16: 12 on ANA, 24 on CAN, 24 on TOC; 45% from the US; 47% female; mean age at survey was 11.3 years. Mean age at SJIA diagnosis was 6.7 years, mean age at start of ANA, CAN, and TOC Rx was 7.4, 8.9, and 6.7 years, respectively. Caregivers were 80% female, mean age 41.4 years, and 37% reduced or stopped working due to their child's SJIA. Of the patients enrolled on CAN and TOC, 71% and 46% respectively had previously been on ANA. Baseline CHAQ, CHQ-PF50, and WPAI scores were worse in CAN and TOC than ANA patients (Table). Highest caregiver stressors were worry over long-term SJIA impact on their child (44%) and uncertainty about the future (29%). Caregivers' treatment satisfaction and resource utilization varied (Table). **Conclusion:** Treatment sequencing and PRO measures indicate ANA is used as 1st line for mild SJIA while CAN and TOC are used as 2nd/3rd line for severe SJIA. Caregivers expressed stress over the long-term impact of SJIA and fear for the future and had variable treatment satisfaction and resource utilization levels.

Table. SJIA patient and caregiver reported outcomes

		Anakinra	Canakinumab	Tocilizumab	All
CHAQ global VAS score, mean ± SD [N]		0.0 ± 0.0 [9]	1.6 ± 2.7 [17]	1.9 ± 3.1 [12]	1.3 ± 2.6, [38]
CHQ-PF50	Physical (PhS) summary[1], mean ± SD [N]	44.5 ± 7.7[12]	38.1 ± 18.4 [23]	38.7 ± 18.6 [24]	39.7 ± 18.2 [59]
	Psychosocial (PsS) summary[2], mean ± SD [N]	48.9 ± 10.8 [12]	46.8 ± 12.8 [23]	45.2 ± 10.6 [24]*	46.6 ± 11.4 [59]
WPAI	Time missed due to child's SJIA over last 7 days (hours), mean ± SD [N]	0.0 ± 0.0 [11]	3.5 ± 6.9 [17]	3.8 ± 8.2 [16]	2.8 ± 6.6 [44]
	Overall work impairment due to child's SJIA (%), mean ± SD [N]	6 ± 15 [11]	21 ± 27 [15]	16 ± 33 [14]	15 ± 27 [40]
	Activity impairment (%), mean ± SD [N]	9 ± 16 [12]	19 ± 27 [24]	20 ± 30 [24]	17 ± 26 [60]
Caregivers treatment satisfaction	Children were not stressed/ anxious about receiving treatment, % [n/N] [3]	13 [5/40]	39 [11/28]	33 [10/30]	27 [26/98]
	Never missed a treatment, % [n/N] [3]	88 [35/40]	93 [25/27]	80 [24/30]	87 [84/97]
	Thought treatment was convenient, % [n/N] [3]	21 [8/39]	68 [19/28]	33 [10/30]	38 [37/97]
Resource utilization	Direct: Visited hospital/clinic for tests, % [n/N]	67 [8/12]	67 [16/24]	71 [17/24]	68 [41/60]
	Indirect: Receive help from informal caregivers at least once a month, % [n/N]	33 [4/12]	38 [9/24]	33 [8/24]	35 [21/60]

n represents respondents with a certain response; [N] represents total respondents for a datapoint
[1]CHQ PhS normative mean score 53.0 ± 8.8 SD (standard deviation)
[2]CHQ PsS normative mean score 51.2 ± 9.1 SD
[3]Caregivers were asked about experiences with any biologic the patient had ever been on, not just the biologic they were on during the study, so the total [N] can be >60
*Clinically moderate effect size only observed between normative and TOC based on mean difference >5

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Abstract Number: 2377

Innovative Use of PK and PD to Guide Dose Selection for a Monoclonal Antibody Aimed at Neutralizing the High IFNγ Activity Present in Patients with Macrophage Activation Syndrome (MAS)

Philippe Jacqmin[1], Kathy de Graaf[2], Maria Ballabio[2], Robert Nelson[2], Zoë Johnson[2], Walter Ferlin[2], Geneviève Lapeyre[2], Fabrizio De Benedetti[3] and **Cristina de Min**[2], [1]MnS, Dinant, Belgium, [2]NovImmune S.A., Geneva, Switzerland, [3]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù IRCCS, Roma, Italy, Rome, Italy

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Background/Purpose: Data from an animal model of MAS and the observed high IFNγ and IFNγ-related chemokines (CXCL9, CXCL10) levels in MAS/sJIA patients have prompted the design of a study to investigate the therapeutic role of IFNγ neutralization in patients with this disease. An ongoing study in primary HLH (pHLH) shows promising efficacy and favourable safety of NI-0501, an anti-IFNγ antibody, in the control of HLH, known to be driven by high production of IFNγ. PK and PD data of NI-0501 obtained from the ongoing clinical trial in pHLH have been used to define the NI-0501 dosing strategy to be used to investigate the role of IFNγ neutralization in MAS/sJIA patients.

Methods: In active HLH the measurable circulating IFNγ levels do not account for the total amount of the cytokine present in the body. Following the administration of NI-0501 in pHLH patients, the measurement of "total IFNγ", namely free and bound to NI-0501, is used as a surrogate for IFNγ production, revealing the high production of this cytokine, despite the relatively low "free IFNγ" levels at baseline in blood. Extrapolations from these data allowed the estimation of IFNγ production in MAS/sJIA patients, based on the levels of IFNγ-related chemokines present at baseline.

Results: The measurement of total IFNγ levels in pHLH revealed that the IFNγ concentration to be neutralized by NI-0501 was several hundreds fold higher compared to what indicated by the baseline free IFNγ level (median IFNγ at baseline <50 pg/ml; at peak 17'858 pg/ml). Total IFNγ at 48 hours post NI-0501 administration tightly correlates with IFNγ-related chemokine levels (CXCL9: r=0.6264, p=0.0008; CXCL10: r=0.6931, p=0.0001), suggesting that CXCL9 and CXCL10 concentrations are excellent markers of the presence of biologically active IFNγ. The amount of IFNγ produced in MAS/sJIA patients was then indirectly estimated on the basis of the total IFNγ concentration in pHLH patients with comparable levels of CXCL9 and CXCL10 following the administration of NI-0501. This information, coupled with modelling and simulation techniques, has allowed to i) determine the NI-0501 dose expected to neutralize rapidly the total amount of IFNγ in the majority of MAS/sJIA patients, ii) identify an appropriate frequency of NI-0501 administration to avoid unnecessary drug accumulation.

Conclusion: The methodology applied allowed a precise determination of the dosing strategy to be tested in the future trial, significantly reducing the risk of exposing patients to non-therapeutic NI-0501 doses.

Disclosure: P. Jacqmin, NovImmune S.A., 5; **K. de Graaf**, NovImmune S.A., 3; **M. Ballabio**, NovImmune S.A., 3; **R. Nelson**, NovImmune S.A., 3; **Z. Johnson**, NovImmune S.A., 3; **W. Ferlin**, NovImmune S.A., 3; **G. Lapeyre**, NovImmune S.A., 3; **F. De Benedetti**, None; **C. de Min**, NovImmune S.A., 3.

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Abstract Number: 2378

Pharmacokinetic and Pharmacodynamic Characteristics of Canakinumab in Patients with Periodic Fever Syndromes: Results from a Phase III Pivotal Umbrella Trial

Joost Frenkel[1], Jordi Anton[2], Avi Livneh[3], Eldad Ben-Chetrit[4], Paul Brogan[5], Segundo Bujan-Rivas[6], Tamás Constantin[7], Fabrizio De Benedetti[8], Marco Gattorno[9], Ahmet Gül[10], Hal M. Hoffman[11], Isabelle Kone-Paut[12], Helen Lachmann[13], Seza Ozen[14], Anna Simon[15], Jeroen Van der Hilst[16], Andrew Zeft[17], Antonio Speziale[18], Guido Junge[18] and Lucy Xu[19], [1]University Medical Center,Utrecht, Utrecht, Netherlands, [2]Hospital Sant Joan de Déu, Barcelona, Barcelona, Spain, [3]Department of Medicine F, Sheba Medical Center, Tel Hashomer, Israel, [4]Medicine A Rheum Unit, Hadassah University Hosp, Jerusalem, Israel, [5]Department of Paediatric Rheumatology, UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [6]Vall d'Hebron Hospital, Barcelona, Barcelona, Spain, [7]Unit of Paediatric Rheumatology, 2nd Dpt of Pediatrics, Semmelweis University, Budapest, Hungary, [8]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù IRCCS, Roma, Italy, Rome, Italy, [9]UO Pediatria 2, Istituto Giannina Gaslini, Genova, Italy, [10]Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [11]Pediatric Allergy, Immunology and Rheumatology, University of California at San Diego/Rady Children Hospital, La Jolla, CA, [12]PRINTO, Genoa, Italy, [13]UK National Amyloidosis Centre, University College London Medical School, London, United Kingdom, [14]Department of Pediatrics, Division of Rheumatology, Hacettepe University Faculty of Medicine, Ankara, Turkey, [15]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [16]Department of infectious disease and immunity, Jessa Hospital, Hasselt, Hasselt, Belgium, [17]Pediatric Rheumatology, The Cleveland Clinic, Cleveland, OH, [18]Novartis Pharma AG, Basel, Switzerland, [19]Novartis Pharmaceuticals Corporation, East Hanover, NJ

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Session Time: 9:00AM-11:00AM

Background/Purpose: The pharmacokinetics (PK) of canakinumab (CAN) and total interleukin (IL)-1β kinetics

have been well investigated in CAPS patients (pts).[1] Here we present the PK and pharmacodynamics (PD) of CAN (solution for injection-liquid in vial [LIVI]) from the randomized treatment epoch (primary analysis up to Week 16) of a Phase III study (NCT02059291) in colchicine-resistant/intolerant familial Mediterranean fever (crFMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD), and TNF receptor associated periodic syndrome (TRAPS) pts.

Methods: The study comprised 3 disease cohorts (crFMF, HIDS/MKD, and TRAPS). Each cohort followed the same study design across 4 epochs (screening epoch [up to 12 weeks], randomized treatment epoch [16 weeks], randomized withdrawal epoch [24 weeks] and open-label treatment epoch [72 weeks]). Pts (age, ≥2 years) with crFMF, HIDS/MKD, or TRAPS who had a flare during Epoch 1 were randomized (1:1) in Epoch 2 to receive subcutaneous (sc) CAN 150 mg (or 2 mg/kg for pts weighing ≤40 kg) every 4 weeks (q4w) or placebo. Blinded uptitration (up to 300 mg) was allowed for pts not resolving the index flare by Day 15. Serum samples for CAN concentrations and total IL-1β were collected at baseline (Day 1), and trough samples, at weeks 2, 4, 8, 12, and 16.

Results: In crFMF, HIDS/MKD, and TRAPS pts, the serum clearance and steady-state volume of distribution of CAN varied according to body weight, and were estimated to be 0.14±0.04 L/day and 4.96±1.35 L, respectively. The estimated half-life of CAN was 25.6±6.4 days. CAN minimal concentration at Week 16 following 150 mg sc q4w dosing was estimated to be 15.3±6.6 µg/mL. The estimated steady-state area under the serum concentration-time curve from time zero to the end of the dosing interval tau (AUC_{tau}) was 648±202 µg.day/mL. Similar results were obtained in all 3 diseases. CAN binding to circulating IL-1β was demonstrated by increase in total IL-1β following CAN dosing in all 3 diseases. In pts requiring uptitration to 300 mg, levels of total IL-1β were higher, suggesting higher production of IL-1β, and therefore the need for a higher dose.

Conclusion: This was the first study to evaluate the PK of canakinumab given in the LIVI form. The results observed in crFMF, HIDS/MKD, and TRAPS pts were similar to those observed in other indications (CAPS and SJIA) using the lyophilisate form. These data suggested that the new formulation did not affect the PK/PD of canakinumab and similar to CAPS, patients with higher levels of IL-1β require canakinumab uptitration to achieve optimal disease control. Reference: 1.Chakraborty A, et al. Clin Pharmacokinet. 2012;51:e1–18.

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Abstract Number: 2379

Effect of Canakinumab Treatment on Health-Related Quality of Life in Patients with Periodic Fever Syndromes

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Open label studies have shown the efficacy of canakinumab (CAN), a fully human and highly specific anti-IL-1β monoclonal antibody, in patients (pts) with Periodic Fever Syndromes (PFS), which include colchicine-resistant Familial Mediterranean Fever (crFMF), Hyper-IgD Syndrome/Mevalonate Kinase Deficiency (HIDS/MKD) and TNF-Receptor Associated Periodic Syndrome (TRAPS). Currently, no data is available on the effect of CAN on Health-Related Quality of Life (HRQoL) in pts with PFS. The study objective was to assess the effect of CAN on HRQoL using Child Health Questionnaire-Parent Form 50 (CHQ-PF50) and Short Form-12 Health Survey (SF-12) in pts with PFS.

Methods: In this Phase 3, randomized, placebo-controlled study of CAN in pts with PFS (NCT02059291), SF-12 Physical Component Summary (PCS) and Mental Component Summary (MCS) scores were assessed in adults, whereas CHQ-PF50 Physical Summary (PhS) and Psychosocial Summary (PsS) scores were assessed in children (>5–<18 years).

Results: Of the 181 pts (63 crFMF, 72 MKD/HIDS, 46 TRAPS) randomized to CAN or placebo, 71 were adults (age ≥18 years) and 110 were children (age ≥2–<18 years). Pts who initially received placebo and did not respond were switched to CAN. Treatment with CAN was associated with an early clinically meaningful improvement in SF-12 PCS scores reported at Week (Wk) 5, which were sustained and increased to a large effect size by Wk 16 for all indications (Table). Similarly, clinically meaningful improvement in SF-12 MCS, CHQ-PF50 PhS, and CHQ-PF50 PsS scores was observed for all indications, except for PsS in HIDS/MKD and TRAPS pts.

Table: Patient reported outcomes						
Outcome measures	Mean change from baseline (n/N)#,**					
	crFMF		HIDS/MKD		TRAPS	
	Week 5	Week 16	Week 5	Week 16	Week 5	Week 16
SF-12 PCS	7.9 (29/30)	9.55 (30/31)	13.81 (15/15)	13.81 (14/14)	9.63 (16/17)	11.64 (13/14)
SF-12 MCS	4.83 (29/30)	4.27 (30/31)	6.41 (15/15)	8.14 (14/14)	5.65 (16/17)	5.51 (13/14)
CHQ-PF50 PhS	13.2 (21/24)	20.1 (18/21)	5.5 (32/34)	9.9 (27/29)	7.4 (16/18)	14.9 (13/14)
CHQ-PF50 PsS	4.1 (21/24)	7.2 (18/21)	1.8* (32/34)	5.2 (27/29)	0.9* (16/18)	1.2* (13/14)

N=total number of pts; n=pts who received at least one dose of CAN.
#An increase in mean score from baseline is an improvement.
*Minimal important difference[1,2] from baseline was not achieved.
**In the general U.S. population, mean summary scores are 50 for CHQ-PF50 and 50 for SF-12 (50.01 and 49.98, respectively for PCS and MCS).[3,4]

Conclusion: Canakinumab showed rapid improvement by Wk 5 in pt-reported outcomes in adults and children with PFS, which was sustained through Wk 16. **References**: 1. User's manual for the SF-12v2 Health Survey, 3rd ed.; 2012 2. Cohen J, et al. Statistical power analysis for the behavioural sciences, 2nd ed.; 1988 3. HealthActCHQ. The CHQ Scoring and Interpretation Manual (Boston, MA: HealthActCHQ, 2013) 4. Maruish, M.E. ed. User's manual for the SF-12v2 Health Survey, 3rd ed. (Lincoln, RI: QualityMetric Inc., 2012)

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Abstract Number: 2380

Efficacy and Safety of Canakinumab in Patients Aged One to Six Years with Cryopyrin-Associated Periodic Syndromes: Results of an Open-Label, Phase III Extension Study

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Cryopyrin-Associated Periodic Syndrome (CAPS), is a rare hereditary auto inflammatory disorder representing 3 phenotypes: familial cold auto-inflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and chronic infantile neurologic cutaneous and articular syndrome/neonatal onset multisystem inflammatory disease (CINCA/NOMID).[1] Canakinumab (CAN), a fully human anti–IL–1β monoclonal antibody, has been shown to be effective over 56 weeks in patients with CAPS aged <24 months (core study).[2] Here we report the long-term efficacy and safety of canakinumab in these patients through 152 weeks in an extension study to the core study (NCT01576367).

Methods: CAPS pts who completed the core study received 2 mg/kg subcutaneous CAN every 8 weeks, in continuation with the core study. Pts who received a dose adjustment in the core study were continued on the same dose in the extension phase. Efficacy was evaluated by investigator clinical assessment of autoinflammatory disease activity, C-reactive protein (CRP) and serum amyloid A (SAA) levels. Safety was assessed in terms of adverse events (AEs).

Results: Of 17 pts (aged ≤6 years), enrolled in the extension study, 12 (70.6%), 4 (23.5%) and 1 (5.9%) had MWS, NOMID and FCAS phenotypes, respectively. All 17 pts were complete responders; 16 (94.1%) had no flare, and 1 (5.9%) NOMID patient had a flare at the end of extension study. Physician global assessment improved over the extension study, with decline in severity from baseline of the core study to the end of extension study (EOS). The number of pts with absent autoinflammatory disease activity improved from 4 (23.5%) to 11 (64.7%); minimal activity increased from 5.9% (1 pt) to 29.4% (5 pts); mild or moderate activity decreased from 47.1% (8 pts) to 5.9% (1 pt); moderate activity decreased from 23.5% (4 pts) to 0 patients. This improvement was also observed in the assessment of skin rash; proportion of patients with no skin disease increased from 29.4% (5 pts) at baseline of core study to 94.1% (16 pts) at EOS. The mean decrease in CRP and SAA levels from core study baseline was −10.4 and −54.36 mg/L, respectively at EOS. Overall, 10 (58.8%) pts had AEs suspected to be related to CAN; the most common were diarrhea, pneumonia, rhinitis and cough (3 pts each). Eight (47.1%) pts experienced at least 1 serious AE (4 MWS and 4 NOMID pts), with pneumonia being the most common (2 [11.8%]). No deaths occurred during the study.

Conclusion: Canakinumab effectively maintained clinical and serological efficacy in CAPS pts in the extension study. No new safety findings were observed, and the safety profile of canakinumab was consistent with previous studies, which corroborates the long-term use of canakinumab in the treatment of CAPS patients. **References**: 1. Kuemmerle-Deschner JB, et al. *Arthritis Res Ther*. 2011;13(1):R34. 2. Brogan, P et al. *Arthritis Rheumatol.2015;67(suppl 10).*

Disclosure: P. Brogan, None; **M. Hofer**, Novartis, 5; **J. B. Kuemmerle-Deschner**, Novartis Pharmaceutical Corporation, 2,Novartis, SOBI and Baxalta, 5; **B. Lauwerys**, None; **A. Speziale**, Novartis Pharma AG, 3; **K. Leon**, Novartis Pharmaceuticals Corporation, 3; **X. Wei**, Novartis Pharmaceutical Corporation, 3; **R. Laxer**, Database funding from Novartis, 2.

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Abstract Number: 2381

Canakinumab Monotherapy for the Treatment of Majeed Syndrome. Five-Year Experience

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Majeed syndrome is a rare, autosomal recessive disorder that presents with early onset chronic recurrent multifocal osteomyelitis (CRMO) and microcytic congenital dyserythropoietic anaemia caused by a mutation in the *LPIN2* gene (OMIM reference #609628). Occasionally, Majeed syndrome is associated with neutrophilic dermatosis. The chronic inflammatory bone disease starting before the age of two has previously been described having a recalcitrant debilitating course resulting in permanent joint contractures and growth disturbances after years of chronic inflammation. Aim: To report the long-term effect of IL-1 inhibition in two patients with Majeed syndrome.

Methods: Whole-body MRIs were performed at presentation, after 3 months and at regular yearly intervals using T1 weighted images and short tau inversion recovery (STIR) images. Patiens: Two brothers with consanguinity of the parents were diagnosed with Majeed syndrome. *LPIN2* gene resequencing of both patients revealed a homozygous 2-bp deletion (c.1312_1313delCT) resulting in a premature stop codon (p.Leu438fs-16X). Both patients were refractory to the treatment with corticosteroids and etanercept. Demonstration of the clinical and biochemical efficacy of IL-1 inhibition by anakinra led to the treatment of both children with canakinumab.

Results: Canakinumab 4 mg/kg subcutaneously every 4-5 weeks has now been given for 5 years as monotherapy. During the past years no fever related to the CRMO has been observed. The children have been well without any clinical signs of osteomyelitis, no physical restraints, and no skin changes. The drug has been well tolerated and

without any side effects. At no time corticosteroids and NSAIDs have been given after canakinumab was initiated. Repeated whole-body MRIs showed disappearance of osteomyelytic lesions in both patients already after few months. Whole-body MRIs have been performed yearly during the past 5 years showing no signs of relapse in Sib A. Sib B had normal whole-body MRIs during the first 4 years but showed transient, subclinical osteomyelytic lesion at the ossis pubis after 4 years and a subclinical lesion at the right corpus tibiae after 5 years. Growth of height has been normal for both children growing along the 25th percentile. ESR was still moderately elevated during the first year of treatment but normalized thereafter in both children. However, within the past year the ESR has been variably elevated (from 12 to 29 mm/hr) in Sib B. During the years hemoglobin has been within normal range for both children. Erythroblasts have been slightly elevated in Sib A (0.05-0.12 x 10^9/L), but not in Sib B (<0.01 x 10^9/L).

Conclusion: Sustained effect of IL-1 inhibition by canakinumab for the treatment of Majeed syndrome is described. The drug is well tolerated and although costly, the prevention of a debilitating course of this rare, chronic disease seems to be achievable by canakinumab.

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Abstract Number: 2382

Evaluation of Intestinal Inflammation in Children with FMF

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Familial Mediterranean Fever (FMF) is the most common auto-inflammatory disease with recurrent fever and serositis episodes. Abnormal pyrin protein due to MEFV gene mutations leads to clinical symptoms in FMF. Abdominal attacks happen due to the serosal inflammation in FMF. The sterile exudate which includes fibrin and polimorphonuclear cells occurs in the peritoneal space. Other gastrointestinal symptoms such as irritable bowel disease, colchicine related diarrhea and amyloidosis related malabsorption can be also detected. The rate of inflammatory bowel disease (IBD) is also shown to be increased in FMF. In recent years, some cases with FMF were reported with gastrointestinal involvement without amyloidosis, vasculitis and IBH. It is not yet known, whether the gastrointestinal involvement is a part of the disease or not. The aim of this study is to investigate the frequency of intestinal inflammation by using a noninvasive method, fecal calprotectin measurement, in pediatric FMF patients.

Methods: Sixty-five FMF patients, 30 healthy controls and 11 control patients with ulcerative colitis were included in the study. A standard survey which including gastrointestinal and other clinical symptoms and medications was used. MEFV mutations, whole blood count and CRP levels were recorded. Fecal calprotectin

was studied with the ELISA method from the feces samples of the all patients. The upper cutoff value was determined as 200 ug/g.

Results: The patients were similar in terms of age and gender among groups. None of the FMF patients had clinical signs of the IBD. Fecal calprotectin levels of the FMF patients were found significantly higher than the healthy controls (174.8 ± 150.8 vs 52.9 ± 36.5, p< 0.001). In contrast, fecal calprotectin levels of the ulcerative colitis patients were significantly higher than the FMF patients (523.5 ± 183 vs 174.8 ± 150.8, p< 0.001). Even though, there are no IBD signs, the fecal calprotectin levels were higher than the cutoff point in 19 of the FMF patients. There was a correlation between fecal calprotectin levels and neutrophil/lymphocyte ratio (r=0.324, p=0.009).

Conclusion: Our results supported the subclinical intestinal inflammation in pediatric FMF patients. Underlying chronic auto-inflammatory process or continuous colchicine usage could result this observation. Further studies are needed to clarify the reason of the intestinal inflammation in FMF patients.

Disclosure: O. Altug-Gucenmez, None; **T. Kume**, None; **B. Makay**, None; **O. Babayigit**, None; **N. Arslan**, None; **E. Unsal**, None.

Abstract Number: 2383

Analysis of the Use of Anticoagulants and Antiplatelet Agents in Strokes Caused By the Deficiency of Adenosine Deaminase 2

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Background/Purpose: Deficiency of adenosine deaminase 2 (DADA2) is a recessive genetic condition in which children develop recurrent strokes, intermittent fevers, elevated acute-phase reactants, livedoid rash,

hepatosplenomegaly, and hypglobulinemia caused by mutations in the *CECR1* gene. Blood levels of ADA2 are very low or absent, compromising endothelial integrity while polarizing macrophage and monocyte subsets toward proinflammatory cells. In this abstract we aim to determine the safety of treating DADA2 patients with a history of stroke with anticoagulants and/or antiplatelet agents.

Methods: A single center study evaluated 22 patients who were positive for 2 mutations in *CECR1*. All patients underwent a clinical history and physical examination, neurologic evaluation, brain MRI/MRA, and testing for ESR/CRP, paying special attention to whether there was a history of stroke, the type of stroke (ischemic or hemorrhagic), and the history of the use of ASA either alone or in combination with anticoagulants and/or other antiplatelet agents. The primary outcome measure was to determine occurrence of hemorrhagic strokes while on anticoagulant and/or antiplatelet treatment.

Results: Out of 22 patients, 15 had strokes and 13 of those were subsequently started on anticoagulants and/or antiplatelet agents. Amongst the 13, 4 of the patients had a total of 6 hemorrhagic strokes. All 4 patients with hemorrhagic strokes were on ASA plus other anticoagulants and/or antiplatelet agents. Six of the patients with no hemorrhagic strokes were on ASA alone. Patients not on anticoagulants and/or antiplatelet agents did not have any hemorrhagic strokes. Nine out of the 13 patients who were put on anticoagulants and/or antiplatelet agents had an ischemic stroke only. Upon analyzing the statistical data, the probability of a hemorrhagic stroke following anticoagulants and/or antiplatelet agents was 4/13 while the probability of a hemorrhagic stroke following no anticoagulants and/or antiplatelet agents was 0/9. A Fisher's exact test was be used to examine whether these 2 probabilities truly differ and the p-value was 0.115 which is short of statistical significance. The proportions of patients with hemorrhagic strokes on no antiplatelet or anticoagulant treatment, ASA alone, and ASA plus other anticoagulants and/or antiplatelet agents were 0/9, 0/6 and 4/7, respectively (p = 0.007, Fischer's exact test).

Conclusion: In patients with DADA2, we oberseved an increased frequency of hemorrhagic strokes in those treated with ASA plus other anticoagulants and/or antiplatelet agents, although we observed no hemorrhagic strokes in patients treated with ASA alone. These observations suggest extreme caution in the use of ASA plus other anticoagulants and/or antiplatelet agents in DADA2.

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Abstract Number: 2384

Variable Clinical Phenotypes and Relation of Interferon Signature with Disease Activity in ADA 2 Deficiency

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Background/Purpose: The deficiency of adenosindeaminase 2 (DADA2) is a recently described autosomal recessive autoinflammatory disease, caused by mutations of CECR1 and characterized by early onset vasculopathy with livedoid skin associated to systemic inflammation. In some patients, the disease is mild and skin-limited, in others is severe, with multi-organ involvement including ischemic or hemorrhagic strokes. In some DADA2 patients a mild immunodeficiency was detected involving adaptive immunity. TNF inhibitors are very efficacious. Recently, an upregulation of type I interferon-stimulated gene transcripts, so called interferon signature, was described also in two DADA2 patients. We describe the clinical course of a 4 patients with CECR1 mutations and we assess the role of interferon type I signature as marker of disease's activity

Methods: Molecular analysis of CECR1 was performed using next generation sequencing and confirmed by sanger sequencing. Blood was collected into PAXgene tubes and expression levels of IFI-27 IFI-44L IFIT-1, ISG-15, RSAD-2 and SIGLEC- determined. The IFN score was derived as described (1). The mean interferon score of the controls plus two SD was calculated: 1.62 and scores higher than this value were considered positive

Results: Four Caucasian patients (2 brothers males and 2 unrelated females) were identified carrying CECR1 mutations (compound eterozygous Leu249Pro/Pro344Leu in the two brothers, compound heterozygosity T360A/R49Gfs*4 deletion in one and homozygous Y453C mutation in one). Mean age was 12.2 ± 2.0 years. Three of the described patients presented with clinical features consistent with the phenotype of DADA2 already reported including recurrent fever, livedo reticularis, persistent elevation of inflammatory markers, arthralgia/ arthritis. Unusual/undescribed manifestation included in 1 patient: early onset gastrointestinal involvement with a biopsy consistent with unspecific inflammation, posterior reversible encephalopathy with seizures, deafness and malignant hypertension. The latter is due to nephrogenic hypertension secondary to kidney infarction. His younger brother showed a very mild phenotype characterized by a single episode of prolonged fever with abdominal pain and arthralgia. He is the 1 patient showing hypogammaglobulinemia. All patients showed a complete normalization of clinical and laboratory findings with no recurrences after treatment with etanercept (follow-up ranging from 8 months to 20 months). The interferon score before treatment was elevated in 3 (ranging from 3.6 to 10.4) out of 4 patients (except for the younger brother), and rapidly normalized after treatment

Conclusion: Our data confirm the highly variability of DADA2 regarding age of onset, severity and organ involvement, even within families and, for unknown reasons, among patients with the same mutations. Furthermore, these data suggest that type I interferon score could be used in DADA2 patients as a useful biomarker of disease's activity. The relation between type I IFN hyperactivity, deficiency of ADA2 and response to TNF inhibition remain elusive References: (1) Rice GI et al. Lancet Neurol. 2013 Dec;12(12):1159-6

Disclosure: A. Insalaco, None; **G. Moneta**, None; **M. Pardeo**, None; **C. Passarelli**, None; **C. Celani**, None; **V. Messia**, None; **F. De Benedetti**, Novartis, Novimmune, Hoffmann- La Roche, SOBI, AbbVie, Pfizer, 2.

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Abstract Number: 2385

Validation of Diary Score for the Assessment of Disease Activity in

Candle (Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature) and SAVI (STING associated vasculopathy with onset in Infancy) Patients

Megha Sawhney[1], Gina A. Montealegre Sanchez[2], Robert Wesley[3], Kost Bahar[1] and Raphaela Goldbach-Mansky[4], [1]NIAMS, National Institutes of Health, Bethesda, MD, [2]National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD, [3]Clinical Center, National Institutes of Health, Bethesda, MD, [4]Translational Autoinflammatory Disease Studies, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: CANDLE and SAVI are two rare autoinflammatory interferonopathies without validated outcome measures to assess disease activity; however, daily diaries of prominent disease symptoms have become standard in assessing clinical disease load and reporting treatment related outcomes in patients with the autoinflammatory disease spectrum CAPS (Cryopyrin associated periodic syndrome) where diary scores were accepted by the FDA in the context of drug approval. For novel AIDs with distinct organ manifestations new disease specific diaries need to be generated and validated. In pediatrics inflammatory diseases the Childhood Health Assessment Questionnaire (CHAQ), which measures physical function and the patient and physician-derived outcome measures, patient global VAS (PATG) and physician global VAS (PHYG) respectively are used to assess disease severity and response to treatment and have been used to validate patient related outcomes in the past.

Methods: The daily diary developed for NOMID was modified to reflect disease symptoms of CANDLE and SAVI. For CANDLE these include: fever, rash, joint pain, headache and fatigue (possible range, 0 to 20) For SAVI these also include respiratory symptoms and ulcerative lesions. Each symptom is rated on a scale from 0 to 4 for increasing severity. We correlated the diary score in CANDLE and SAVI patients against 6 validated outcome measures: Childhood Health Assessment Questionnaire (CHAQ), which measures physical function; physical global VAS (PHYG); global pain assessment (PAINGL); parent global(PARG); the patent quality of life (PATQL) and parent QL (PARQL) by correlating each symptom and the summary score with PHYG, PAINGL, PARG, PATQL and PARQL respectively. We used Pearson correlation and 1-sample t- test to assess whether these values plausibly centered at 0. P – values were not corrected for multiple comparisons but p-values of <0.01 were considered significant.

Results: 11 CANDLE and 4 SAVI patients and 3 undifferentiated interfernopathy patients were included. Mean diary scores computed for all patients correlated well with CHAQ (r-0.36, $p<0.001$).Mean diary score computed during the evaluation for CANDLE patients correlated well with CHAQ(r-0.36, $p<0.001$), pain global (r- 0.48, $p<0.001$). Individual symptoms like fever, rash etc correlated well with these outcome measures in both CANDLE and SAVI. However, the SAVI specific parameters, respiratory symptoms and ulcerative lesions did not show any significant correlation.

Conclusion: Our study shows that diary scores exhibit validity across other outcome measures validated for unrelated pediatric inflammatory diseases, but outcome measures in SAVI need to be further refined.

Disclosure: M. Sawhney, None; **G. A. Montealegre Sanchez**, None; **R. Wesley**, None; **K. Bahar**, None; **R. Goldbach-Mansky**, Baricitinib, 9.

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Abstract Number: 2386

Role of Pentraxin 3 in Patients with Juvenile Scleroderma

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster III: Systemic JIA, Autoinflammatory Syndromes, Scleroderma, Vasculitis, Miscellaneous

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile scleroderma (JS) is a rarely seen chronic connective tissue disorder. According to organ involvement, the disease is divided into two main forms: systemic and localized scleroderma. Localized form is more frequent in childhood, characterized with benign clinical course and favorable prognosis. Although extremely rare, juvenile systemic scleroderma (JSS) has far worse prognosis with multi-organ involvement and possible life-threatening complications. Its main pathophysiological characteristics include microvascular abnormalities and excessive fibrosis of the skin, subcutaneous tissues and internal organs. Pentraxin 3 (PTX 3) is a multifunctional protein produced at the inflammation site by macrophages, dendritic cells, endothelial cells, smooth muscle cells and fibroblasts. Previously studies reported an increased level of PTX 3 among adult patients with scleroderma. Study among patients with JS has not been provided yet. We aimed to measure the level of PTX 3 in patients with juvenile scleroderma comparing to healthy children. Thereby, we have tried to give an answer on question whether the PTX 3 could be a marker of fibrosis in patients with juvenile scleroderma.

Methods: We assessed patients with JSS and those with juvenile localized scleroderma (JLS) and age- and sex-matched health controls. A complete medical history, physical examination, and laboratory evaluation were performed for each patient at the time of enrollment. The same physical examination and laboratory investigation was performed in healthy controls, in order to exclude the coincidental disease. Circulating PTX3 levels were measured by enzyme immunoassay. The lower limits of detection for PTX3 was 0.1 ng/ml.

Results: We assessed 24 patients with JSS, 20 patients with JLS and 41 health controls. The mean age of patients was 15.38 ±3.156, 12.44 ±3.63 and 14.33±3.48 for JSS, JLS and healthy controls, respectively. Mean disease duration was 2 years (range: 0.6 -15 years) for JSS and 1.5 years (range: 0.6 - 18 years) for JLS patients. Mean serum level of PTX 3 was 10.63 ± 8.61 ng/ml, 11.75 ± 9.11 ng/ml and 2.76 ± 1.338 ng/ml for JSS, JLS and healthy controls, respectively. In both of patients group PTX 3 level was significantly higher comparing to healthy children ($p<0.001$). We didn`t find statistically significant difference between JSS and JLS patients according to level of

PTX3. A mean modified Rodnan skin score of JSS patients was 19.95 ± 11.088. PTX3 level was found to be in positive correlation with modified Rodnan skin score, in patients with JSS (Rho=0.497, p=0.030).

Conclusion: The circulating PTX3 level is significantly higher in both JSS and JLS patients than in healthy control subjects. The possible explanation is that fibrosis and increased fibroblast activation represent main pathophysiological mechanism in both form of the disease. This result support relevance of PTX 3 measurement in order to determinate fibrosis activity. PTX 3 should be considered a relevant marker of fibrosis in patients with juvenile scleroderma.

Disclosure: A. Adrovic, None; **S. Sahin**, None; **K. Barut**, None; **S. Durmus**, None; **H. Uzun**, None; **O. Kasapcopur**, None.

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Abstract Number: 2387

Response to Pamidronate Treatment Assessed By Whole Body Magnetic Resonance Imaging in Pediatric Chronic Non-Bacterial Osteomyelitis

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Pamidronate (PAM) may be effective in diminishing pain and permanent bone deformities in chronic non-bacterial osteomyelitis (CNO). Whole body magnetic resonance imaging (WB MRI) can be used to assess anatomical site, extent and inflammatory activity of bone lesions. The aim of this study was to evaluate the clinical and radiological outcome of children with CNO after one year of PAM treatment.

Methods: A retrospective evaluation of children diagnosed with CNO according to the Bristol criteria ADDIN RW.CITE{{216 Roderick,M. 2014}}(1). Children were treated with i.v. PAM 1mg/kg (max 60 mg/day) for 3 consecutive days every 3 months. We included 17 children (8 girls and 9 boys) median age 11 years (range 5-13). Medical history, clinical assessments and inflammatory biochemistry were obtained. WB MRI (1,5 Tesla) short tau inversion recovery (STIR) and T1-weighted images were performed at baseline, median -1 month (range -6-0) and after one year PAM treatment, median 12 months (range 9-19). Number of bone lesions are listed per patient

(median, range).

Results: Comorbidities were JIA (n=3) and IBD (n=1); none of the children had psoriasis. All children had been treated with NSAID as first line treatment. Further medical history was antibiotics (n=1), methotrexate (n=7), steroids (n=7) and anti-TNFα treatment (n=3). Six children had elevated sedimentation rate at baseline, which normalized after one year. At baseline there were in total 52 clinical symptomatic lesions, median 3 (range 1-8) and 113 radiological active lesions, median 6 (range 2-14). The most common sites of bone lesions were femur (19%), tibia (19%) and spine (12%). Six children had spinal lesions, median 1 (range 1-4), and 5 children had non-erosive lesions in relation to the sacroiliac (SI)-joints. After one year 11 children were still radiological active based on MRI with total number of 68 lesions, median 4 (range 1-21) (Table 1). Only one active spinal and one SI-joint lesion persisted. Ten children had new or worsening of lesions, median 2 (range 1-15). Three children had deformation of 11 vertebral bones (10 thoracic, 1 cervical) without sign of active inflammation. After one year the clinical symptoms in the radiological active group were; five with total pain relief, 5 with partial pain relief and 2 without any pain relief. In 6 children lesions resolved completely as assessed by MRI, but pain was still reported in 4 of them.

Conclusion: PAM given for one year is a potent second-line treatment for CNO. Axial lesions and SI-joint lesions respond well to PAM. Persistent pain or pain progression may exist despite total resolution as assessed by WB MRI. ADDIN RW.BIB (1) Roderick M. Efficacy of pamidronate therapy in children with chronic non-bacterial osteitis: disease activity assessment by whole body magnetic resonance imaging. Rheumatology (Oxford) 2014; 53(11):1973-1976

Tab. 1. Distribution and number of active bone lesions before and after pamidronate treatment

	Baseline		**Year 1**	
	Number of bone lesions n (%)	Number of children affected	Number of bone lesions n (%)	Number of children affected
Clavicle	1 (1)	1	1 (2)	1
Scapula	3 (3)	2	2 (3)	1
Humerus	5 (4)	3	3 (4)	1
Radius	2 (2)	1	0 (0)	0
Femur	21 (19)	10	10 (15)	6
Tibia	22 (19)	10	13 (19)	7
Fibula	3 (3)	2	2 (3)	1
Talus	1 (1)	1	0 (0)	0
Calcaneus	5 (4)	4	0 (0)	0
Feets (other)	8 (7)	4	3 (4)	2
Metatars	7 (6)	5	19 (28)	4
Spine	14 (12)	6	1 (2)	1
SI-joint	6 (5)	5	2 (3)	2
Pelvis	13 (12)	5	8 (12)	4
Mandible	2 (2)	1	2 (3)	1
Patella	0 (0)	0	2 (3)	1
Total	113	17	68	11

Disclosure: C. M. Andreasen, None; **A. G. Jurik**, None; **M. Glerup**, None; **C. Høst**, None; **B. Thorsted Mahler**, None; **E. M. Hauge**, None; **T. Herlin**, None.

Abstract Number: 2388

Clinical Characterization and Outcomes of Pediatric Chronic Nonbacterial Osteomyelitis

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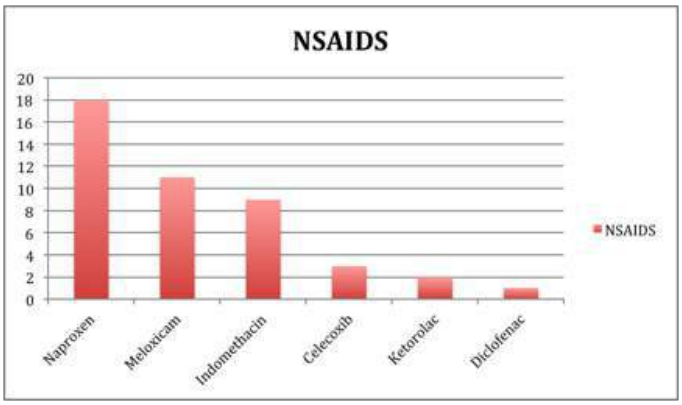
Background/Purpose: Chronic Nonbacterial Osteomyelitis (CNO) is a rare condition of largely unknown etiology with variable clinical and radiological features. It is an aseptic auto-inflammatory bone disease. The aim is to describe a cohort of patients with pediatric CNO and their outcomes.

Methods: This is a retrospective descriptive study of 26 cases seen from March 2009 to September 2015. We collected demographic and clinical data.

Results: Ages ranged from 2 to 19 years (mean 13.1) and F:M sex ratio was 16:10. Of 26 patients, 17 had a bone biopsy, 16 had a whole body MRI of whom 4 also had a bone scan, and 5 had only a bone scan. Of those with MRI, 15 children had multifocal lesions and in 13, asymptomatic lesions were detected. From those with labs, 18 of 23 had elevated ESR and 12 of 20 had elevated CRP. Other associated conditions included palmar plantar pustulosis (N=1), psoriasis (N= 1) and acne (N=2). Family history of psoriatic arthritis (N=1), psoriasis (N=1) and CrohnÕs disease (N=1) were present. Treatment consisted of NSAID (N=25), prednisone (N=7) and other immunosuppressive therapy (N=21). Almost all patients were treated with NSAID: naproxen (N=18), meloxicam (N=11), indomethacin (N=9), celecoxib (N=3), ketorolac (N=2) and diclofenac (N=1). However, in half (N=13) the therapy had to be escalated: oral prednisone (N=7), methotrexate (N=9), pamidronate (N=4), adalimumab (N=3), sulfasalazine (N=2), leflunomide (N=1), azathioprine (N=1), infliximab (N=1). The most common complication was vertebral body compression fracture (N=6). Four children needed bisphosphonate infusions due to vertebral involvement. Outcomes in regards to resolution of clinical symptoms and bone detected lesions were overall excellent since all but one patient responded to therapy.

Conclusion: Whole body MRI is the imaging modality of choice in CNO and has emerged as the most sensitive way to document the number and extent of lesions. In our cohort of children with a whole body MRI, the majority had asymptomatic multifocal lesions. Fifty percent of the cohort did not respond to NSAID monotherapy requiring second line immunosuppressive therapy. The most common complication was vertebral body compression fracture. We suggest the use of bisphosphonates for vertebral involvement.

CHARACTERISTICS	Mean age (years)	F:M (ratio)	Diagnostics (N=total)	Labs (%)	Complication (%)	Treatment (N=total)
	13.1					
		16:10				
Whole Body MRI			N=16			
Bone Scan			N=9			
Bone Biopsy			N=17			
ESR				78.2%		
CRP				60%		
NSAIDS						25
Prednisone						7
Methotrexate						9
Pamidronate						4
Adalimumab						3
Sulfasalazine						2
Leflunomide						1
Azathioprine						1
Infliximab						1
Vertebral fractures					23%	



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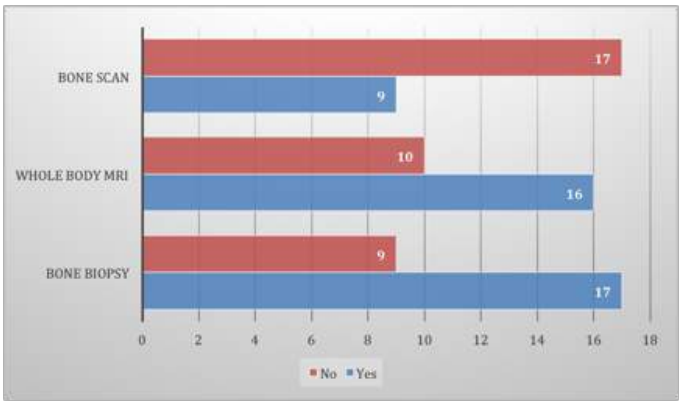

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Abstract Number: 2389

Is There a Difference in the Presentation of Diffuse and Limited Subtype in Childhood? Results from the Juvenile Scleroderma Inception Cohort

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. Several adult publications looked at the differences between limited (ljSSc) and diffuse subtype (djSSc). There is few data regarding this topic in pediatric jSSc. The juvenile scleroderma inception cohort is a prospective standardized register for patients with jSSc.

Methods: Patients with jSSc were included worldwide to the jSSc cohort. Patients fulfilled the ACR criteria for

jSSc. We compared the demographics and clinical features of the ljSSc and djSSc patients.

Results: Up till now 80 patients were enrolled, 58 (72.5%) with djSSc and 22 (27.5%) with ljSSc. 10% in djSSc and 23% in ljSSc showed overlap features. Disease duration at time of inclusion in the cohort was 3.7 years in the djSSc and 3.0 years in ljSSc. 83% in the djSSc and 81% in the ljSSc group were female. The mean age at onset of Raynaud symptoms was 9.0 years in the jdSSc and 10.4 years in ljSSc group and the mean age at onset of the non-Raynaud symptoms was 9.4 in djSSc and 10.9 ljSSc. At the time of inclusion the mean of modified Rodnan Skin Score was 18.2 in the djSSc and 9.1 in ljSSc. Anti-Scl 70 positivity was found in 30.4% of djSSc and 33.3% in ljSSc. Only 2 patients in the djSSc group and 2 in the ljSSc group presented anticentromere positive. Capillary changes occurred in 62.1% in the djSSc and 54.5% in ljSSc . History of active ulceration was present in 56% in the djSSc and in18% in ljSSc. Active ulcerations were present in 21.1% in the djSSc and 4.5% in the ljSSc. The mean of 6 Minute walk test was 392 m in the djSSc group and 504 m in the ljSSc group. 15.5% of djSSc and 41% of ljSSc had cardiac involvement. Pulmonary hypertension occurred in 8% in djSSc and 13% in ljSSc. 56% in djSSc and 31% in ljSSc group had signs of interstitial lung disease on imaging. Renal involvement occurred in 7% in djSSc and 4.5 % in ljSSc. None had systemic hypertension. 38% of djSSc and 18% of ljSSc had gastrointestinal involvement. 57% in djSSc and 73% in ljSSc had musculoskeletal involvement. Patient global disease activity measured by VAS was 44.2 in the djSSc and 46.3 in ljSSc. Patient global disease damage was 42.6 in the djSSc and 33.8 in ljSSc. Physician global disease activity measured by VAS was 40.3 in the djSSc and 25 in the ljSSc and physician global disease damage measured by VAS was 35.4 in the djSSc and 15.0 in the ljSSc.Mean CHAQ score was 0.4 in both groups.

Conclusion: Patients with djSSc were younger at onset; have more often capillary changes, active ulcerations and gastrointestinal involvement, and less pulmonary hypertension and musculoskeletal involvement. They also present moresevere disease and more disease damage. Features of the pediatric subtypes of jSSc differ from adults with SSc, especially the high proportion of patients with diffuse subtype.

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Abstract Number: 2390

Proposal of Assessment of the Activity of Juvenile Localised Scleroderma. Results of the Consensus Meeting in Hamburg, Germany December 2015

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile Localised Scleroderma (JLS) is an orphan disease which is complicated by difficulties in robust measurement of disease activity. Several outcome measures to assess disease activity have been described with some recent trials using the mLoSSI (modified localized scleroderma skin severity index which is a validated cutaneous assessment tool in JLS. Whilst such measures are a step forward in assessment of this disease, they do not capture all aspects of the disease that are taken into consideration by clinicians when judging the degree of disease activity and therefore making decisions regarding treatment. In particular extra-cutaneous manifestations are poorly captured. With potential innovative and more effective treatment options emerging, it has become extremely important to define a validated activity index that captures skin, extra-cutaneous disease activity and patient reported outcomes in order to monitor response to treatment.

Methods: Members of the PRES Scleroderma working group and other paediatric rheumatologists and dermatologists interested in JLS met to develop an activity index using the nominal group technique in a consensus meeting in Hamburg, Germany, in December 2015. Eithy percent agreement was chosen for the selected domains and items.

Results: Summarises the proposed domains and items to assess the activity of localised scleroderma. **Skin:** Change in skin thickening – *Modified Rodnan Skin Score (mRSS); Total Skin thickness score of mLoSSi; Research tool: A, durometer B, Ultrasound* Degree of change in white waxy appearence since last visit – *Marked worsening /some worsening and some improvemnet/no change/ significant improvement* Change in Erythema/violaceousness since last visit – *mLoSSI* Change in Subcutaneous induration since last visit – *Yes or no & elements of mLoSSi* Enlargement of the lesion since last visit – *Yes or no (captured within mLoSSi)* New lesion per anatomical region of mLoSSI – *mLoSSI* Worsening alopecia (eyelash, beard, body hair) – *marked worsening,/some worsening and some improvement/no change/ significant improvement/no hair in the lesion / decreased* Increase in face atrophy – only Parry Romberg patients – *3 D photography* **Optional item**: Change in blood flow in the lesion - *Ultrasound with doppler / laser doppler* **Extracutaneous involvement:** Change in Activity of anterior uveitis since last visit – *Yes or no* Change in active joint count – *Number of active joints* Worsening of lim discrepancy – *Yes or no* Active CNS involvement – *Yes or no* **Patient reported outcomes:** Change in subcutaneous induration since last visit – *marked worsening /some worsening and some improvemnet/ no change/ significant improvement* Uncomfortable feeling in the lesion (not including itch) – *VAS score 0-100* Itching in the lesion – *VAS score 0-100* Quality of life assessment – *PEDsQL, CHQ, CDLQII* Functional assessment of daily life – *CHAQ/HAQ*

Conclusion :

We propose extended domains to define an activity index for JLS which aim to capture the heterogeneity of disease activity. This may become an important instrument for evaluating treatment efficacy but requires prospective validation from the PRES and CARRA scleroderma working groups.

Disclosure: I. Foeldvari, None; **E. Baildam**, None; **M. Blakley**, None; **C. Boros**, None; **K. Fligelstone**, None; **A. Kienast**, None; **D. Nemkova**, None; **C. Pain**, None; **A. Saracino**, None; **G. Simonini**, None; **K. S. Torok**, None; **L. Weibel**, None; **N. Helmus**, None.

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Abstract Number: 2391

Update on the Juvenile Systemic Sclerosis Inception Cohort Project. Characteristics of the First 80 Patients at First Assessment

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Session Type: ACR Poster Session C
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Background/Purpose: Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. Currently just retrospective data exist regarding evolvement of organ involvement. In the retrospective studies assessment of the organ involvement is not standardized. Our project is the first project, where prospectively and with a standardized assessment data of jSSc patients are collected. We present the data of the patients at the entry into the cohort.

Methods: Patients with jSSc, according the ACR criteria, were recruited worldwide and were prospectively assessed, using the proposed standardized patient assessment protocol.

Results: 26 centers from 17 countries applied to participate on the project. The assent and consent forms were translated into the local native languages. Up till now 80 patients were enrolled. Sixty-six (82.5%) of the 80 patients were female. The mean age of the onset of Raynaud symptomatic was 9.4 years (0.2 – 15.9). The mean age at the onset of the non-Raynaud symptomatic were 9,9 years (0.3 -15.9). 58 (72.5%) had diffuse subtype and 22 had limited subtype (27.5%). 11 (14%) of them have an overlap symptomatic, in 6 (10%) in the diffuse and 5 (23%) in limited subtype. At the time of the inclusion the mean modified Rodnan Skin Score was 15.7 (0-51). ANA positive were 60/77 (78%), 24/77 (31%) of them were anti-Scl 70 positive and 4/46 (9%) were anticentromere positive. 48/80 (60%) had already capillary changes and 36/78 (46%) inactive ulcerations, 13/78 (17%) had active ulceration at the time of the inclusion. 39/80 (49%) had cardiopulmonary involvement, 22/45 (49%) of had signs of interstitial lung disease on imaging, 16/36 (44%) had FVC <80% and 10/19 (52%) had DLCO < 80%. 6/44 (14%) patients had pulmonary hypertension. The mean 6 Minute Walk Test was 419.3 m (60-615). 5/80 (6%) had renal involvement, none of them had hypertension. 26/80 (32.5%) had gastrointestinal involvement, and 18/26 (69%) of them esophageal involvement. 48/79 (62%) had musculoskeletal involvement, mostly limited range of joint movement in 21/49 (43%). Isolated muscle weakness occurred in 3/46 (6.5%). 2/80 (2.5%) showed neurologic involvement. The mean CHAQ score (n=51) was 0.4 (0-2.5). Patient global disease activity (n=40) on VAS (0-100) was 44.4 and disease damage 41.6. Physician global of disease activity (n=44) on VAS (0-100) was 37.5 and physician global of disease damage (n=43) was 32.1.

Conclusion: We present the data on the first 80 patients with jSSc at the time of inclusion in our cohort. The current recruitment data confirms that pediatric patients are different from the adult patients; there is a significantly higher proportion of diffuse subset patients with 72.5%. 14% of the patients had an overlap features. The patients had significant disease burden assessed by patients and physician at the entry of the cohort.

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Abstract Number: 2392

Establishing Quality of Life Content Domains in Pediatric Localized Scleroderma

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Background/Purpose: Localized scleroderma (LS) can affect patients' physical function and psychosocial well-being, but, published studies of the impact of pediatric LS on health-related quality of life (HRQoL) show mixed results (Table 1). Present studies are limited by small sample sizes and cross-sectional study designs. Furthermore, there is no current consensus on which HRQoL domains are most relevant in LS, resulting in use of generic HRQOL instruments which may not capture all HRQOL areas of interest. The goal of this study was to examine the domains captured by existing tools and to qualitatively identify new, potentially important domains of HRQoL impact through focus groups with pediatric LS patients and their parents.

Methods: Domains of LS HRQoL impact were identified in two ways: (1) review of extant literature using generic and dermatology-specific HRQoL instruments and 2) focus groups with LS patients and their parents. Three patient and 3 parent focus groups were conducted with 3-5 patients in each patient group and 4-7 parents per group. Groups were divided by patient age range (8 to 10 yo, 11 to 13 yo, 14 years and older).

Results: Table 1 summarizes generic HRQoL instruments available in the literature used with LS patients and the domains they measure. Skin symptoms and joint/muscle pain are the most well studied symptoms in pediatric LS, while effects on body image and peer relationships are less well-characterized. Seven domains were ultimately identified as potentially important contributors to HRQoL in LS (Table 2). Physical functioning is often studied but focus groups revealed effects on fine motor activity not readily captured by existing instruments (Table 2). Side effects from treatment with systemic medications are also not currently well studied in LS, although patients and parents indicate they are bothersome (Table 2).

Conclusion: LS patients experience adverse HRQoL impact across multiple physical and psychosocial domains, as corroborated by LS patients themselves. Existing generic HRQoL instruments do not assess all of these domains fully and underexplore domains such as treatment effects. The literature review and focus groups yielded candidate domain for LS HRQoL measurement, but future research is needed to assess how these domains can be quantified effectively. Development of an LS-specific HRQoL tool may be indicated. **Table 1: Current domains captured by existing quality of life instruments used with pediatric LS patients.**

Survey	No. items	Type of Instrument	Domains
DLQI/CDLQI[1,2,3,4,7,8]	10	Dermatology specific	Symptoms/ feelings, leisure, school/ holidays, personal relationships, sleep, treatment
Visual Analogue Scales[4,9,10,11]	1	Varied by study	Symptoms, severity, or quality of life.
ISDL[9,10]	22	Dermatology specific	Work, hobbies, sleep, sexuality, relationships, stigmatization, and illness cognitions.
CHQ[1,6]	87	Generic	Physical functioning, bodily pain, role/social-physical, general health perceptions, role/social-emotional behavior, mental health, general behavior, self-esteem, parental emotional impact, parental time impact, family impact.
Skindex[3,5]	29	Dermatology specific	Symptoms, emotions, and functioning
CHAQ[1]	30	Generic	Disability, discomfort, pain
CQOL[1]	15	Generic	Activities, appearance, communication, continence, depression, discomfort, eating, family, friends, mobility, school, sight, self-care, sleep, worry
KINDL[8]	24	Generic	Physical well-being, emotional well-being, self-esteem, family, friends school

DLQI = Dermatology Life Quality Index; CDLQI = Children's Dermatology Life Quality Index; CHAQ = Children's Health Assessment Questionnaire, CHQ = Childhood Health Questionnaire; CQOL = Child Quality of Life Questionnaire; KINDL = German generic quality of life tool for children, ISDL = The Impact of Chronic Skin Disease on Daily Life. [1]Baildam et al. (2011). Influence of childhood scleroderma on physical function and quality of life. *J Rheumatol, 38*(1), 167-73. [2]Klimas et al. (2014). Health-related quality of life in morphea. *Br J of Dermatol, 172,* 1329-37. **[3]**Condie et al. (2014). Comparison of outcomes in adults with pediatric-onset morphea and those with adult-onset morphea. *Arthritis Rheumatol, 66*(12), 3496-505. **[4]**Das et al. (2014). Correlates of self-reported quality of life in adults and children with morphea. *J Am Acad Dermatol, 70(*5), 904-10. **[5]**Szramka-Pawlek et al. (2013). Health-related quality of life, optimism, and coping strategies in persons suffering from localized scleroderma. *Psychol Health Med, 18*(6), 654-63. **[6]**Ennis et al. (2012). Children's and parents' beliefs about childhood onset scleroderma are influenced by child age and physical function impairment. *Rheumatol, 51*(7), 1331-3. [7]Saxton-Daniels & Jacobe. (2010). An evaluation of long-term outcomes in adults with pediatric-

onset morphea. *Arch Dermatol, 146*(9), 1044-5. [8]Orezechowski et al. (2009). Health-related quality of life in children and adolescents with juvenile localized scleroderma. *Rheumatol, 48*(6), 670-2. [9]Kroft et al. (2009). Psychological distress in patients with morphea and eosinophilic fasciitis. *Arch Dermatol, 145*(8), 1017-22. **[10]**Kroft et al. (2008). Physical burden of symptoms in patients with localized scleroderma and eosinophilic faciitis. *Arch Dermatol, 144*(10), 1394-1395. **[11]**Uziel et al. (2000). Children with morphea have normal self-perception. *J Pediatr, 137*(5), 727-30. **Table 2: Identified domains of health related quality of life that are impacted by pediatric localized scleroderma (LS) and corroborating quotations from LS patients and their parents.**

Domain	Examples from focus group transcripts
Uncomfortable skin sensations like itch, pain, and tightness.	"I keep [my skin] soft because if I don't I can feel it pull and it kind of hurts."
	"Mine doesn't usually hurt, but it sometimes itches."
	Parent: "[*Redacted*] doesn't have pain, but he does feel it."
Nuanced effects on fine motor functioning after prolonged repeated movements	"I've been taking standardized tests lately and my hand will cramp…I'm given 25 minutes to write an essay and…[I spend] 5 minutes just trying to wrestle my hand back to normal."
	Parent: "She had to wear braces on her fingers…she had to use putty. She had all these little mechanisms of things she had to squeeze."
Limitations or worry about elective activities	"They ask…'You've been dancing for so long why can't you do these basic things?' And [I] tell them that I'm physically unable to."
	"I love playing soccer…when I first noticed it, I would always be careful. I would always be watching everywhere just to make sure nothing would hit me."
	Parent: "She wanted to play volleyball, but I said, you'll hurt your fingers. You know, you hit with the palm of your hand [where your scleroderma is]"
Joint/muscle pain or cramping	"When I'm doing school work, [my hand] will just cramp up. Like what [*redacted*] said, you know, it's painful."
	"I play the viola in orchestra…and sometimes I have to position my hand a different way so my hand doesn't cramp up."
	Parent: "At one time her hand was hurting so bad they thought she was going to have to go to using a computer in school"
Body image/appearance	"You wake up and you just look in the mirror and you're just like what's wrong? Why is that here?"
	"The staring makes me feel different and I used to wear a bunch of long-sleeved shirts and never show my arms."
	Parent: "He wished his face would change and knowing he had to go to school that day and be seen by his friends and the girls in his classes."
Peer relationships	"The bad days are when people are commenting and… you just don't want to leave your room. You just want to stay inside because you are afraid of what people will say."
	Parent: "They laugh at her because [of] her skin condition and even her cousins are really mean. They laugh at her. They make fun of her and its terrible."
Systemic medication side effects	"In the middle of the week I'd get sick and start throwing up and… then I'd just throw up and then go to school and try to fight through it."
	"With the methotrexate it would just feel weird, it'd make me throw up, I'd feel dizzy."

	Parent: "She went from being a skinny little kid…to having big puffy cheeks and gaining weight from the steroids. She hated it…and I think that affected me horribly."

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Abstract Number: 2393

Medication Use in the Juvenile Systemic Sclerosis Inception Cohort. ARE There Differences in the Diffuse and Limited Subset Patients?

Ivan Foeldvari[1], Jens Klotsche[2], Ozgur Kasapcopur[3], Amra Adrovic[4], Valda Stanevicha[5], Maria Teresa Terreri[6], Ekaterina Alexeeva[7], Maria M. Katsicas[8], Rolando Cimaz[9], Mikhail Kostik[10], Thomas J. A. Lehman[11], Walter A. Sifuentes-Giraldo[12], Vanessa Smith[13], Flavio Sztajnbok[14], Tadey Avcin[15], Maria Jose Santos[16], Dana Nemkova[17], Cristina Battagliotti[18], Despina Eleftheriou[19], Liora Harel[20], Mahesh Janarthanan[21], Tilmann Kallinich[22], Jordi Anton[23], Kirsten Minden[2], Susan Mary Nielsen[24], Kathryn S. Torok[25], Yosef Uziel[26] and Nicola Helmus[1], [1]Hamburg Center for Pediatric and Adolescent Rheumatology, Hamburg, Germany, [2]Epidemiology unit, German Rheumatism Research Center, Berlin, Germany, [3]Department of Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical School, Department of Pediatric Rheumatology, Istanbul, Turkey, [4]Department of Pediatric Rheumatology, Istanbul University, Cerrahpasa Medical School, Istanbul, Turkey, [5]University Childrens Hospital, Riga, Latvia, [6]Pediatric Rheumatology Unit, Federal University of São Paulo, São Paulo, Brazil, [7]Rheumatology, Scientific Center of Children's Health, Moscow, Russia, [8]Service of Immunology & Rheumatology. Hospital de Pediatrìa Prof Dr.Juan.P. Garrahan, MD, Buenos Aires, Argentina, [9]Pediatrics, University of Firenze, Firenze, Italy, [10]Hospital Pediatrics, State Pediatric Medical University, Saint-Petersburg, Russia, [11]Chief Div Ped Rheum PTD, Hospital for Special Surgery, New York, NY, [12]Rheumatology, Hospital Universitario Ramón y Cajal, Madrid, Spain, [13]Department of Rheumatology, Ghent University Hospital, Ghent University, Ghent, Belgium, [14]Pediatric Rheumatology Division, Adolescent Health Care Unit, Universida de do Estado do Rio de Janeiro., Rio de Janeiro, Brazil, [15]University Children's Hospital, Ljubljana, Slovenia, [16]Rheumatology, Department of Rheumatology, Hospital Garcia de Orta, Almada, Portugal, Almada, Portugal, [17]Pediatric Rheumatology Unit, Department of Pediatrics and Adolescent Medicine, General University Hospital in Prague, Prague, Czech Republic, [18]Hospital de Niños Dr Orlando Alasia, Santa Fé, Argentina, [19]Paediatric Rheumatology Department, Great Ormond Street Hospital for Children NHS Trust, London, United Kingdom, [20]Pediatric Rheumatology Unit, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel, [21]Pediatric Rheumatology, Chennai, India, [22]Charite, University Medicine Berlin, Berlin, Germany, [23]Unitat de Reumatologia Pediàtrica, Hospital Sant Joan de Déu, Barcelona, Spain, [24]Rigshospitalet, Copenhagen, Denmark, [25]Pediatric Rheumatology, Univ of Pittsburgh Med Ctr, Pittsburgh, PA, [26]Meir Medical Center, Kfar Saba, Israel

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Juvenile systemic sclerosis (jSSc) is an orphan autoimmune disease. Currently there is no data regarding use of medication in jSSc patients. Our project is the first project, where prospectively and with a standardized assessment data of jSSc patients are collected and the applied medication assessed. We present the data of the medication us at the time point of entry into the cohort.

Methods: Patients with jSSc, according the ACR criteria, were recruited worldwide and were prospectively assessed, using the proposed standardized patient assessment protocol.

Results: Up till now 80 patients were enrolled. Sixty-six (82.5%) of the 80 patients were female. 58 (72.5%) had diffuse subtype (djSSc) and 22 had limited subtype (27.5% (ljSSc). 88% of the patients in the djSSc and 86% in the ljSSc patients received medication. Table 1.

	Whole group	**Diffuse subtype**	**Limited subtype**	
Number of patients	**80**	**57 (71%)**	**23 (29%)**	
Sex female /male	66/14 => 4.7:1	47/10 => 4.7:1	20/4 => 5:1	0.924
Medication	62/71 (87%)	44/50 (88%)	18/21 (86%)	0.945
Corticosteroids	36/62 (58%)	27/44 (61%)	9/18 (50%)	0.667
Cyclophosphamide	5/62 (8%)	5/44 (11%)	0/18 (0%)	0.159
Chloroquine/Hydroxy-chlorqquine	10/62 (16%)	6/44 (14%)	4/18 (22%)	0.485
Methotrexate	35/62 (56%)	24/44 (54%)	11/18 (61%)	0.804
Mycophenolate	11/62 (18%)	8/44 (18%)	3/18 (17%)	0.905
Azathioprin	1/62 (2%)	1/44 (2%)	0/18 (0%)	0.524
Tocolizumab	1/62 (2%)	0/44 (0%)	1/18 (6%)	0.125
Rituximab	2/62 (3%)	1/44 (2%)	1/18 (6%)	0.523
Bosentan	11/62 (18%)	10/44 (23%)	1/18 (6%)	0.165
PDE5 inhibitors	4/62 (6%)	3/44 (7%)	1/18 (6%)	0.863
Prostanoids	1/62 (2%)	0/44 (0%)	1/18 (6%)	0.125

Conclusion: Interestingly the most frequently used DMARD was Methotrexate, followed by Mycophenolate. Only small number of patients received biologics. Interestingly higher number of patients in the diffuse group received Bosentan. Interestingly 9 patients did not received any DMARDS /biologics or medication again pulmonary hypertension.

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Abstract Number: 2394

Patient and Parent Global Assessments of Disease Impact in Pediatric Localized Scleroderma: Correlates of Patient Reported Health-Related Quality of Life and Parent Reported Family Impact Domains

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Session Time: 9:00AM-11:00AM

Background/Purpose: Pediatric localized sclerodermaÕs (LS) effects on patient/family well-being are underexplored. Contributions of HRQoL domains and family dynamics to LSÕs impact on patients has not yet been examined. This study evaluates correlates of LS patient/parent global assessments of disease impact (Pt-GA; Par-GA).

Methods: Cross-sectional data from the National Registry for Childhood Onset Scleroderma (NRCOS) spanning 2015-2016 were used. Pt-GA/Par-GA were scored on a 100mm visual analogue scale. Clinical data (i.e. modified Localized Scleroderma Skin Index [mLoSSI], Localized Scleroderma Damage Index [LoSDI], physician global assessment of disease activity/damage [PGA-A; PGA-D]) were examined. Patients completed PedsQL-Generic Core Scales and Rheumatology Module (PedsQL-GC/-RM). Parents completed PedsQL-Family Impact Module (PedsQL-Fam). ChildrenÕs Dermatology Life Quality Index (CDLQI) assessed skin-specific HRQoL. Descriptive statistics, HRQoL score distributions, and SpearmanÕs correlations ($p<0.05$) were evaluated for Pt-GA, Par-GA, activity/damage, PedsQL-GC/-RM/-Fam (and individual domains), and CDLQI.

Results: Table 1 summarizes clinical/HRQoL data. Pt-GA/Par-GA were correlated (0.67, $p<0.001$), with Par-GA greater than Pt-GA by paired samples Wilcoxon ($p=0.007$). Pt-GA/Par-GA did not correlate with mLoSSI, LoSDI, PGA-A, or PGA-D. Pt-GA/Par-GA correlated comparably with CDLQI (0.44, $p=0.001$). Pt-GA correlated with PedsQL-GC/-Fam (-0.35, $p=0.012$; -0.45, $p=0.001$). Par-GA correlated with PedsQL-Fam (-0.49, $p<0.001$), not PedsQL-GC. Pt-GA correlated with PedsQL-GC psychosocial health summary score (-0.37, $p=0.008$), and social/school domains(-0.41, $p=0.003$; -0.37, $p=0.007$). Pt-GA correlated with PedsQL-RM worry (-0.35; $p=0.011$) and treatment domains (-0.28, $p=0.047$). Par-GA correlated with PedsQL-GC social domain (-0.32, $p=0.023$) and weakly with PedsQL-RM worry domain (-0.28, $p=0.047$). Par-GA correlated with all PedsQL-Fam domains (-0.36 to -0.51, $p\leq0.009$), as did Pt-GA for all but the cognitive domain (-0.32 to -0.52, $p\leq0.023$). CDLQI items most often scored > 0 were about teasing (25%), embarrassment (23%), treatment burden (21%), and itch/pain (17%). Table 2 lists PedsQL items showing most frequent HRQoL impact.

Table 1: Patient Characteristics (n = 52)		
Demographics		
Female, n (%)	35	67
Caucasian, n (%)	46	89
Age at study visit, median, IQR	12.8	10.4-15.4
Age at onset, median, IQR	7.2	3.8-9.6
Time from onset to diagnosis, median, IQR	1.1	0.5-2.4
LS Subtype, n (%)		
Linear Trunk/Limb	14	27
Linear Face/Scalp	17	33
Generalized Morphea	6	11
Circumscribed Morphea, Superficial	4	8
Circumscribed Morphea, Deep	2	4
Eosinophilic Fasciitis	1	2
Pansclerotic Morphea	1	2
Mixed Subtype	7	13
On Systemic Immunosuppressive Therapy, n (%)	37	88
Clinical measures (median, IQR)		
Cutaneous Activity/Damage		
mLoSSI	0	0-1
LoSDI	6	3.3-18.5
Physician Global Assessments		
PGA-A	0	0-0
PGA-D	32.5	22.3-39.8
Patient/Parent-Reported Measures (median, IQR)		
Patient/Parent Global Assessments		
Pt-GA	4	0-12
Par-GA	10	0-23
PedsQL-GC Total Score	93.3	83.5-97.9
PedsQL-RM - Pain	100	81.3-100
PedsQL-RM - Daily Activities	100	100-100
PedsQL-RM - Treatment	89.3	70.2-100
PedsQL-RM - Worry	91.7	83.3-100

PedsQL-RM - Communication	100	83.3-100
PedsQL-Fam Total Score	90	71.4-96.2
CDLQI	1	0-2

Table 2: PedsQL-GC/-RM/-Fam Items Most Frequently Scored < 75 (i.e. Sometimes/Often/Almost Always)

Scale/Item	Domain	n	%
PedsQL-GC			
I have low energy	Physical Functioning	13	25
I miss work or school to go to the doctor or hospital	School Functioning	24	46
PedsQL-RM			
I ache or hurt in my joints and/or muscles	Pain and Hurt	14	27
My medicines make me feel sick	Treatment	13	25
It is hard to be responsible for my medicines or physical therapy	Treatment	15	29
I get scared when I have to have blood tests	Treatment	12	23
I worry about my illness	Worry	12	23
It is hard for me to explain my illness to other people	Communication	14	27
PedsQL-Fam			
I feel tired during the day	Physical Functioning	14	27
I feel tired when I wake up in the morning	Physical Functioning	15	29
I get headaches	Physical Functioning	11	21
I feel anxious	Emotional Functioning	24	46
I feel sad	Emotional Functioning	19	37
I feel frustrated	Emotional Functioning	18	35
It is hard for me to keep my attention on things	Cognitive Functioning	12	23
I feel that others do not understand my family's situation	Communication	13	25
I worry about whether or not my child's medical treatments are working	Worry	32	62
I worry about the side effects of my child's medications/medical treatments	Worry	38	73
I worry about how others will react to my child's condition	Worry	21	27
I worry about how my child's illness is affecting other family members	Worry	13	25
I worry about my child's future	Worry	32	62
Stress or tension between family members	Family Relationships	11	21

Conclusion: Pt-/Par-GA correlate with measures of HRQoL and family impact, but not physician-scored disease activity/damage. Psychosocial function, child/parent worries, treatment burden, and family impact should be routinely measured as they may more fully explain LSÕs impact than cutaneous manifestations.

Disclosure: K. Ardalan, None; **K. Schollaert-Fitch**, None; **C. K. Zigler**, None; **M. A. Zidek**, None; **K. S. Torok**, None.

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Abstract Number: 2395

The Performance of the Kobayashi and Egami Scores in Detecting IVIG Resistance in Kawasaki Disease in a Single Centre Canadian Cohort Treated with IVIG and Low Dose Aspirin

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster III: Systemic JIA, Autoinflammatory Syndromes, Scleroderma, Vasculitis, Miscellaneous

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Kawasaki disease (KD) resistant to IVIG remain a challenge. IVIG resistance has been recognised as a risk factor for the development of coronary artery abnormalities (CAA). Prediction of IVIG resistance in Japanese patients has been successful with the Kobayashi and Egami scores. However, these scores lack sensitivity when applied to patients with KD outside of Japan. We aim to evaluate IVIG resistance, assess if it is a risk factor for CAA, and calculate the sensitivity and specificity of the Kobayashi and Egami scoring systems in predicting IVIG resistance in this single centre Canadian cohort treated with IVIG and low dose aspirin (ASA).

Methods: A retrospective chart review was performed for all patients diagnosed with KD and treated with at least one dose of IVIG (2 g/kg) and low dose ASA (< 10 mg/kg/day) between January 2004 and December 2014. Patients were excluded if they were transferred from another centre, if they had a significant structural cardiac defect not-related to KD, or if there was insufficient laboratory data to perform the Kobayashi and Egami scores. Demographic data, clinical criteria, coronary involvement, laboratory results, and doses of ASA and IVIG were recorded. IVIG resistance was defined as the requirement of a second dose of IVIG. Coronary arteries were considered abnormal if the dimension adjusted for body surface area and expressed in SD units had a z score > or equal to 2.5 at the 6 to 8 week echocardiogram. Sensitivity and specificity calculations were performed. P-values for categorical variables were calculated with the Chi-square test; Wilcoxon rank sum test for continuous variables.

Results: Of the 313 patients identified, 304 charts were reviewed and 262 patients met the inclusion criteria. There were 149 (56.8%) males; 113 (43.2%) females. The mean age was 3.3 years. Criteria for complete KD

were met by 198 (75.6%) patients and 64 (24.4%) had incomplete KD. IVIG resistance was seen in 29.8% (78/262) of the study cohort. In patients with complete KD, the sensitivity of the Kobayashi and Egami scores was low at 33.3% and 31.7% respectively but the specificity was high at 79.3% and 83%. In incomplete KD, the sensitivity of the Kobayashi and Egami scores was also low at 26.7% and 40% respectively but again the specificity was high at 87.8% and 79.6%. From the study cohort, 21 out of 262 patients (8%) had CAA. There was a statistically significant increase in CAA in those who were IVIG resistant with 15 patients (19.2%) developing CAA in the IVIG resistant group compared to 6 patients (3.3%) in those who responded to one dose of IVIG (p<0.0001). IVIG resistant patients did not differ statistically from IVIG responders in regards to age, gender or duration of fever at diagnosis.

Conclusion: To our knowledge, this is the largest non-Japanese cohort that assesses the performance of both the Kobayashi and Egami scores. In this Canadian cohort, both failed to predict IVIG resistance. Patients with IVIG resistance had a significantly higher incidence of CAA. These results further highlight the need for the development of a new risk assessment tool for the prediction of IVIG resistance in North American children with KD so that risk stratification could be considered in future treatment strategies.

Disclosure: D. Basodan, None; **R. Scuccimarri**, None.

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Abstract Number: 2396

Initiation of Dialysis in Pediatric ANCA-Associated Vasculitis

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Background/Purpose: ANCA-associated vasculitis (AAV) is a group of rare systemic vasculitidies with significant morbidity and mortality. There have been no comparative effectiveness studies of AAV in children. We aimed to determine if use of plasma exchange (PLEX), in addition to standard immunosuppression, was associated with a decreased need for dialysis among children hospitalized with AAV.

Methods: We used the Pediatric Health Information System (PHIS) database to conduct a retrospective cohort study of children hospitalized with AAV from 2004-2014. PHIS contains inpatient administrative and billing data from 47 hospitals in the United States. Patients with the ICD-9-CM code 446.4 as one of the discharge diagnoses

and ≥1 charge for glucocorticoids were included. Patients who underwent a renal transplant during their first hospitalization were excluded. We used multivariate mixed effects logistic regression models accounting for clustering by hospitalization to determine if initiation of dialysis within 6 months of the first admission was associated with use of PLEX within the first 7 days (primary exposure) or use of cyclophosphamide (CYC) or rituximab during the first admission. For regression modeling, patients initiating dialysis within the first 3 days of hospitalization were excluded (N= 36). We adjusted for intensive care unit (ICU) stay in the first 24 hours as a proxy for disease severity.

Results: During the study period there were 1284 admissions for 389 children with AAV, 78 (20%) of whom required dialysis at some point during the study period. Median age at first admission was 14.7 years (interquartile range (IQR) 12.2, 16.1) and 61% were female. Median time to initiation of dialysis was 3 days (IQR 1, 21); 68 (87%) patients started dialysis within 6 months of initial hospitalization. Twenty-five (6%) patients received a renal transplant at a median of 20.6 months (IQR 11.5, 26.4) after first admission. No patients received a renal transplant before initiation of dialysis. Of the 32 patients receiving dialysis included in the regression model, 60 % were female, with a median age of 13.7 years (IQR 10.8, 15.4), 14 (44%) had ICU admissions in the first 24 hours, and 25%, 65%, and 9% received PLEX, CYC , or rituximab, respectively, prior to dialysis. PLEX and ICU stay in the first 24 hours were significantly associated with increased odds of needing dialysis within 6 months in univariate, but not multivariate analysis (Table). CYC use was not associated with an increased or decreased likelihood of dialysis in univariate or multivariate analysis. Associations with rituximab could not be determined due the rarity of its use before dialysis.

Conclusion: Twenty percent of children hospitalized with AAV require dialysis with the vast majority initiating dialysis within 6 months of their first admission for AAV. Neither use of PLEX, nor use of CYC is associated with initiation of dialysis within 6 months in children with AAV.

Table: Treatments associated with initiation of dialysis within 6 months

Variable	Odds ratio	95% Confidence Interval	P-value
Univariate analysis			
Plasma exchange within 7 days*	2.58	1.10, 6.04	0.03
ICU stay within 1st 24 hours^	2.67	1.20, 5.94	0.02
Cyclophosphamide#	1.70	0.85, 3.40	0.14
Multivariate analysis			
Plasma exchange within 7 days*	1.55	0.58, 4.12	0.38
ICU stay within 1st 24 hours^	2.15	0.89, 5.20	0.09
Cyclophosphamide#	1.38	0.64, 2.96	0.41

*Plasma exchange receipt within the first 7 days of admission, ^Intensive care unit stay in the first 24 hours of hospitalization, #Cyclophosphamide receipt before dialysis and during first hospitalization

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Abstract Number: 2397

Developing a Role for 18f-Flurodeoxyglucose PET/MRI in Pediatric Takayasu Arteritis

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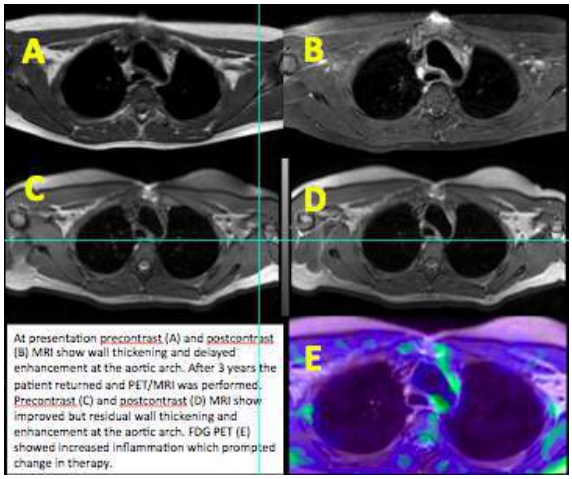
Background/Purpose: Assessing disease activity is often challenging in pediatric Takayasu Arteritis (TA). TA inflammation may be clinically silent and not always reflected on laboratory or clinical evaluation. The gold standard for vascular assessment, conventional angiography, cannot always be safely performed. Reliance on other modalities such as contrast-enhanced CT and MRI evaluate anatomy, but may not show the full extent of inflammation. PET/CT offers improved assessment of inflammation but at the expense of radiation exposure and poor anatomic resolution. Our facility is the first stand-alone pediatric hospital in North America with PET/MRI, which offers potential for superior functional and anatomic information with lower radiation exposure relative to stand-alone PET/CT with documentation of a 40% lower dose of radiation of whole body PET/MR relative to PET/CT. We describe cases where PET/MRI influenced pediatric TA patient care.

Methods: With IRB approval we reviewed ^{18}F-flurodeoxyglucose (FDG) PET/MRI on two pediatric patients with TA obtained as part of their clinical care. Anatomic whole body MRI sequences as well as FDG PET were acquired as part of the PET/MRI protocol.

Results: Two adolescents obtained PET/MRI during 2015. A 17-year old female had been in clinical remission (off medications) for two years had newly elevated inflammatory markers. Her contrast MRI was interpreted as showing improved disease activity as compared to prior scans. Corresponding FDG-PET indicated ongoing disease activity in the walls of the aortic arch, right innominate artery, and left common carotid artery. Analysis of lab and PET/MRI data led to re-initiation of infliximab, methotrexate, and corticosteroids. A 12-year old female diagnosed at an outside hospital 3 months earlier and on infliximab, methotrexate, and corticosteroids was transferred in acute heart failure. Her inflammatory markers were normal and clinical exam was unchanged from recent rheumatology evaluation. PET/MRI showed involvement of the right common and internal carotid arteries, the aortic root to the suprarenal abdominal aorta, the right pulmonary artery, as well as hypermetabolism within the pericardial fluid. The disease was more extensive than had recently been shown on conventional imaging and led to initiation of tocilizumab.

Conclusion: PET/MRI may delineate the extent of large vessel inflammation and persistence of disease activity in all stages of pediatric TA evaluation. PET vascular metabolic data may be obtained longitudinally with a reduced radiation burden and may allow for timely targeting of ongoing inflammation.



Disclosure: **M. Gillispie**, None; **P. Rosillo**, None; **M. De Guzman**, None; **V. Seghers**, None; **P. Masand**, None; **E. Muscal**, None.

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Abstract Number: 2398

Reaching the Masses: A Novel Approach to Pediatric Rheumatology Education Via Tele-Learning

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Background/Purpose: There is a dire need for pediatric rheumatologists in the US, as 11 states and several large cities are without these specialists. Likewise**,** 40% of pediatric residency programs lack pediatric rheumatology (PR). Thus pediatric residents insufficiently trained in PR may care for children with rheumatic disease. Telecommunication technology has helped close the geographic gap in delivery of health care, along with dissemination of distance learning. To address workforce shortage and bridge the knowledge gap in PR, we created a pilot PR tele-learning program sponsored by Baylor PR fellowship program for the pediatric residency at Texas Tech Univ. Health Sciences Center (TTUHSC) in El Paso, TX.

Methods: TTUHSC has 44 pediatric residents and the freestanding children’s hospital serves a catchment area of

2.5 mil. inhabitants (El Paso–Juárez–Las Cruces). We conducted a needs assessment by completing structured interviews with a focus group of residents and pediatric faculty. Using the needs assessment results, and the American Board of Pediatrics content outline, we designed a six lecture curriculum consisting of high priority PR conditions, presented by a senior PR fellow (B.S.). The first two lectures, including interactive musculoskeletal assessment training were conducted in person. Subsequent lectures were given live via TeamViewer®, a computer-based application that is free to use with with a personal license. TeamViewer® transmits live video and PowerPoint using widely available computer infrastructure. Residents interacted with the presenter by answering case questions and open responses via text messaging with Poll Everywhere®. Residents completed lecture evaluations after each didactic session. Members from the initial focus group provided midway feedback on program success.

Results: TeamViewer® was adequate in transmitting our tele-learning program and it was easy to use. Access to the lecture stream only required recipients to click an e-mail web link which connected the live feed automatically. Its limitation is primarily audio feed which was overcome by use of telephone connection. Mean response rate for evaluations was 74%. There was significant improvement in knowledge of all learning objectives compared to before the curriculum (Table 1). Residents indicated overall satisfaction with the PR tele-learning program (mean likert 4.8). Unintended outcomes included increase frequency of real patient consultations and greater resident interest in PR fellowship.

TABLE 1: Perceived level of knowledge based on lecture objectives (Likert scale 1-5)

Learning Objectives	Before (Mean)	After (Mean)	*p*	*n*
Diagnosis of jSLE	2.7	4	0.002	7
Laboratory testing for jSLE	2.7	4.1	0.002	7
General management of jSLE	2.6	4	0.004	7
When to use pGALS*	1.7	4.7	<0.001	26
How to perform pGALS*	1.6	4.7	<0.001	26
How to document pGALS*	1.6	4.5	<0.001	26
Clinical features of vasculitis	2.9	4.3	<0.001	23
Recognition and treatment of KD	3.1	4.6	<0.001	23
Disease course and refractory KD	2.8	4.4	<0.001	23
Different types of JIA*	2.1	4.3	<0.001	24
Limited role of labs to diagnose JIA*	2.1	4.2	<0.001	24
Complications of JIA*	2.4	4.3	<0.001	24
Primary care role for patients with JIA*	2.1	4.3	<0.001	24
Diagnosis of JDM	2.1	4.4	<0.001	28
Clinical features and complications of JDM	2.3	4.5	<0.001	28
Disease course and prognosis of JDM	2.2	4.4	<0.001	28

*Lecture given in person

Conclusion: The small PR workforce is inadequate to educate future pediatricians in many parts of the country. To help overcome this problem, we created a tele-learning program that is cost effective, satisfying to learners, generalizable to many locations and is scalable. Our tele-learning program is a novel educational intervention that enables PR divisions to reach beyond their locale and to stimualte resident interest in PR.

Disclosure: J. B. Shirley, None; **F. Gutierrez**, None; **E. Muscal**, None; **A. A. Ramirez**, None; **J. A. Rama**, None.

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Abstract Number: 2399

Waning Hepatitis B Immunity Status in a Significant Proportion of Immunocompromised Pediatric Rheumatology and Gastroenterology Patients

Emily A. Smitherman[1], Leslie A. Favier[1], M. Raphaelle Jean[2], Adam Furnier[3], Sandra Kramer[2], Allen Watts[1], Pamela Morgan[4], Dana MH Dykes[2] and Jennifer L. Huggins[5], [1]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [2]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [3]James M. Anderson Center for Health Systems Excellence, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Division of gastroenterology, hepatology and nutrition, Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [5]Division of Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Session Time: 9:00AM-11:00AM

Background/Purpose: Despite a historically robust vaccination program, hepatitis B infection remains a significant public health challenge, and particularly for patients on chronic immunosuppressive therapy. There is a considerable risk of hepatitis B reactivation while on these medications with reports of up to 25% mortality. A complete serologic screen should include hepatitis B surface antibodies (anti-HBsAb) to assess for immunity, in addition to hepatitis B core antibodies (anti-HBcAb) and hepatitis B surface antigen (HBsAg) to evaluate for acute or chronic infection. Our aim was to collect and examine hepatitis B serology screenings on patients receiving intravenous biologic medications within rheumatology and gastroenterology (GI) at Cincinnati Children's Hospital Medical Center (CCHMC).

Methods: We identified all rheumatology and GI patients receiving intravenous biologic medications between October 2015 and June 2016 and determined if a complete hepatitis B serology screening had previously been obtained. For patients without previous serology or with results older than 1 year, we ordered a complete panel at the time of a scheduled infusion.

Results: During the study period, we screened a total of 307 patients (109 rheumatology, 198 GI) with an age range from 2 to 27 years (mean 15.5, SD 4.3). A majority of patients (83%) were on infliximab, including all GI patients. In addition to infliximab, rheumatology patients were also on tocilizumab (12%), abatacept (3%), belimumab (1%), rituximab (1%), and golimumab (<1%). Of the total patients tested, 62% had either a negative or indeterminate result for anti-HBsAb, representing non-immune status. The most vulnerable age range for non-immune status (anti-HBsAb negative) was 11-20 years of age (see Figure 1). Interestingly, this trend was more pronounced in rheumatology patients on infliximab versus GI patients on infliximab. Surprisingly, there was 1 rheumatology patient on infliximab who had a positive anti-HBcAb, indicating chronic infection that presumably occurred via transplacental transmission. However, no patients had a positive HBsAg, or evidence of active infection.

Conclusion: Results from this study support the need for routine hepatitis B screening in immunocompromised patients. We determined that a majority of our patients on intravenous biologic medications were seronegative for hepatitis B and will require repeat vaccination. We also identified 1 patient with evidence of chronic infection who is now being closely monitored by hepatology. Our next steps include expanding hepatitis B screening to all patients identified as immunocompromised in rheumatology clinic; further investigating differences between

rheumatology and GI immunity; and collecting post-vaccination serology data on patients who require repeat vaccination.

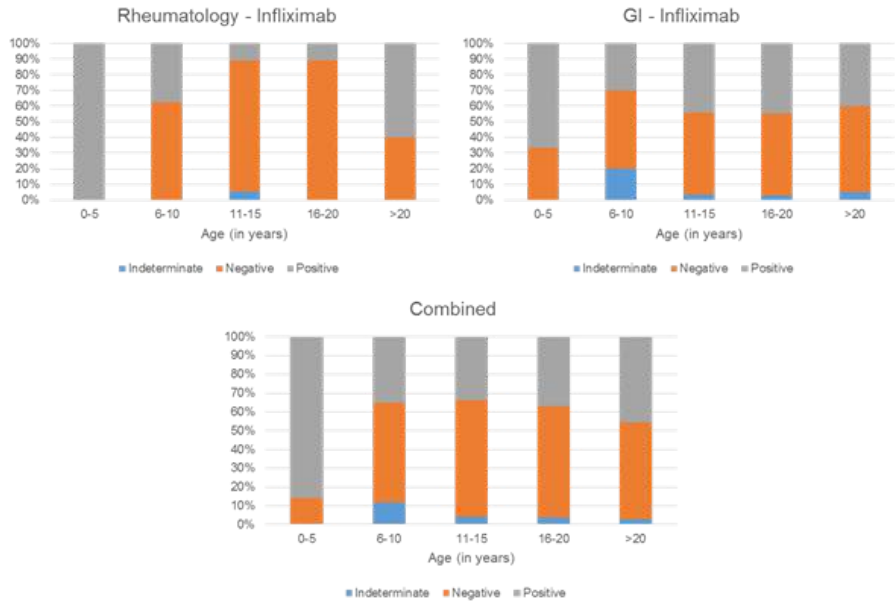

Figure 1. Hepatitis B surface antibody results by age.

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Abstract Number: 2400

Clinical and Treatment Factors Associated with Antibiotic-Refractory Lyme Arthritis in Children

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Background/Purpose: Few factors have been consistently linked to antibiotic-refractory Lyme arthritis (ARLA) other than premature intra-articular glucocorticoid injections. We sought to identify clinical and treatment factors associated with ARLA in children.

Methods: We identified children age 18 years and younger with a diagnosis of Lyme disease seen in pediatric rheumatology clinics across three hospital systems who met clinical and Western blot laboratory criteria for Lyme arthritis. ARLA was defined as having persistent, documented arthritis at least 2 months after adequate antibiotic treatment (≥56 days of oral or ≥14 days of parenteral antibiotics) per IDSA/Red Book guidelines. We compared prespecified demographic, disease, and early treatment characteristics of primary interest between children with ARLA and children whose arthritis resolved within 3 months using descriptive statistics and multivariable logistic regression.

Results: There were 46 children with ARLA and 119 children whose arthritis resolved within 3 months. Multiple clinical factors were independently associated with ARLA in univariable analysis (Table 1). These factors included older age; presentation with unilateral knee synovitis or continuous synovitis ≥6 weeks; and marked clinical worsening (e.g., joint capsule rupture, joint recruitment) after antibiotic initiation. Presentations with severe joint pain or with non-knee joints were associated with rapid resolution. There were few instances of premature glucocorticoid joint injections, limiting statistical power to detect a difference between groups. In multivariable analysis, ARLA was associated with age ≥10, clinical presentations with prolonged arthritis, knee-only synovitis, lack of severe features (fever, severe pain, high inflammatory markers), and worsening arthritis while on treatment (Table 2). Results were consistent after adjustment for clinical center and when using an alternate definition of persistent arthritis ≥6 months after antibiotic initiation. In exploratory analyses of variables that were not of primary interest, antibiotic regimens below the recommended dose were associated with ARLA ($P = 0.03$), but low-frequency regimens (e.g., twice daily amoxicillin) were not ($P = 0.48$).

Conclusion: Pediatric antibiotic-refractory Lyme arthritis is associated with multiple clinical factors, including older age, prolonged knee synovitis at diagnosis, and clinical worsening on antibiotics. In contrast, younger children presenting with non-knee synovitis, severe pain, and a robust inflammatory response often respond quickly to antibiotics.

Table 1. Clinical and treatment characteristics of primary interest			
Characteristic	**Arthritis resolved within 3 months of antibiotic initiation (N = 114)**	**Antibiotic-refractory Lyme arthritis (N = 46)**	**P-value**
Demographics			
Age in years, median (IQR)	9.6 (7.0, 11.9)	12.0 (9.1, 14.7)	<0.01
Male sex, N (%)	82 (69)	28 (61)	0.33
Clinical presentation			
Duration of current joint symptoms in days, median (IQR)	5 (2, 14)	22 (7, 60)	<0.01
Prior self-resolving episodes of joint pain/swelling, N (%)	41 (34)	11 (24)	0.19
Acute migratory arthritis, N (%)	4 (3)	0	0.21
≥6 weeks of continuous joint symptoms, N (%)	3 (3)	9 (20)	<0.01
Fever within 2 weeks of diagnosis not from another cause, N (%)	38 (30)	8 (22)	0.34
Severe pain preventing mobility or requiring hospitalization, N (%)	28 (24)	0	<0.01
More than 1 joint involved,[1] N (%)	29 (24)	2 (4)	<0.01
Non-knee joint involved, N (%)	23 (19)	1 (2)	<0.01
Laboratory values			
Number of Western blot IgG bands (N), median (IQR)	10 (8, 10)	9 (9, 10)	0.21
Maximum erythrocyte sedimentation rate (mm/hr), median (IQR)	35 (19, 49)	17 (8, 34)	<0.01
Treatment and clinical course			
Glucocorticoid joint injection before first antibiotic course, N (%)	2 (2)	2 (4)	0.32
Marked worsening within 6 weeks of antibiotic initiation,[2] N (%)	6 (5)	10 (22)	<0.01
Characteristics of			

spondyloarthritis within 6 weeks of antibiotic initiation,[3] N (%)	2 (2)	1 (2)	0.83
Exam or imaging with chronic changes within 6 weeks of antibiotic initiation,[4] N (%)	18 (15)	4 (9)	0.28

IQR, interquartile range. [1]Two knees would count as two joints [2]New massive effusion, joint capsule rupture, or joint recruitment [3]Personal history of psoriasis, inflammatory bowel disease, acute anterior uveitis, or inflammatory back pain; presence of enthesitis, tendonitis, or dactylitis on exam [4] Flexion contracture, muscle atrophy, condylar hypertrophy, erosions on imaging

Table 2. Multivariable model of clinical factors associated with antibiotic-refractory Lyme arthritis or prolonged arthritis

	Antibiotic-refractory Lyme arthritis		**Arthritis lasting at least 6 months**	
Characteristic	**Adjusted odds ratio (95% CI)**	**P-value**	**Adjusted odds ratio (95% CI)**	**P-value**
Age ≥10 years	2.7 (1.1, 6.5)	0.03	2.2 (1.01, 4.9)	0.05
Continuous joint symptoms for ≥6 weeks at presentation	19.0 (3.6, 99.4)	<0.01	10.2 (2.3, 45.1)	<0.01
Presenting in knee(s) only	10.1 (1.9, 54.0)	<0.01	4.3 (1.3, 14.9)	0.02
Severity features present[1]	0.3 (0.1, 0.8)	0.02	0.5 (0.2, 1.1)	0.07
Worsening within 6 weeks of antibiotic initiation[2]	5.3 (1.5, 19.2)	0.01	3.5 (1.03, 12.1)	0.04

CI, confidence interval. [1]Recent, otherwise unexplained fever, severe pain limiting mobility, hospitalization for pain, or erythrocyte sedimentation rate ≥40 mm/hour [2] New massive effusion, joint capsule rupture, or joint recruitment within 6 weeks of antibiotic initiation

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Abstract Number: 2401

Mucocutaneous Lesions and Recurrent Fevers in Patients with Trisomy 8 Mosaicism and Chromosome 8 Duplication

Kalpana Manthiram[1], Sandro Perazzio[2], Deborah Bruns[3], Ivona Aksentijevich[4], Troy R. Torgerson[5] and Daniel L. Kastner[4], [1]National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [2]Rheumatology, University of Washington School of Medicine and Seattle Children's Research Institute, Seattle, WA, [3]Southern Illinois University Carbondale, Carbondale, IL, [4]Inflammatory Disease Section, National Human Genome Research Institute, National Institutes of Health, Bethesda, MD, [5]Pediatric Immunology/Rheumatology, University of Washington School of Medicine & Seattle Children's Research Institute, Seattle, WA

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SESSION INFORMATION

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster III: Systemic JIA, Autoinflammatory Syndromes, Scleroderma, Vasculitis, Miscellaneous

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Many patients with myelodysplastic syndromes with somatic trisomy 8 in the bone marrow and Behcet's-like ulcerations have been described. A handful of patients with constitutional trisomy 8 mosaicism with Behcet's-like disease have been reported but the spectrum of phenotypes has not been characterized in detail.

Methods: Patients with trisomy 8 mosaicism and chromosome 8 duplications who contacted the NIH Autoinflammatory Clinic were interviewed by phone regarding symptoms of recurrent fever, mucosal lesions, and rashes.

Results: A total of 52 patients were interviewed of whom 19 (37%) had trisomy 8 mosaicism and 33 (63%) had chromosome 8 duplications. The average age of patients was 13 years (range 13 months to 40 years). Thirty-eight percent reported a history of 4 or more fever episodes in one year. The average age of episode onset was 23 months; episodes on average lasted 3.7 days with 6 week intervals. During episodes, 65% reported pharyngitis or sore throat, 45% oral ulcers, 45% rash, 35% cervical lymphadenopathy, 35% headache, and 35% abdominal pain. Twenty-five (48%) reported a history of mucosal ulcers of which 84% were oral, 20% were esophageal, 8% were gastric, 8% were colonic, and 20% were genital. Eleven patients (21%) reported having large (>1cm), painful, oral ulcers that took over a week to resolve. Eleven patients (21%) reported recurrent, painful papular or ulcerative rashes. Two patients reported rapid resolution of fever flares with 1 dose of corticosteroid, while two others required longer steroid courses. One patient had episode remission while on colchicine while another had transient improvement on colchicine. Two patients underwent tonsillectomy with no effect. One patient with severe ulcers underwent bone marrow transplant with significant improvement in ulcerative disease.

Conclusion: Patients with trisomy 8 mosaicism and chromosome 8 duplications have a propensity for systemic inflammatory disease that is similar to Behcet's disease in some patients and similar to periodic fever, aphthous stomatitis, pharyngitis, and cervical adenitis (PFAPA) syndrome in others. This could be due to duplication and subsequent overexpression of particular genes on chromosome 8 that regulate inflammatory responses. We are currently genotyping affected patients using high-density SNP arrays to identify a possible minimal duplicated region in common to these patients. We are collecting blood samples and biopsies from ulcers and rashes from these patients for future studies.

Disclosure: K. Manthiram, None; **S. Perazzio**, None; **D. Bruns**, None; **I. Aksentijevich**, None; **T. R. Torgerson**, None; **D. L. Kastner**, None.

Abstract Number: 2402

Predictive Value of the History and Labs in Distinguishing Inflammatory from Non-Inflammatory and Mechanical Joint Pain

Sonora Williams[1], Tracy R. Andrews[2], Yukiko Kimura[3], Jennifer E. Weiss[4], Suzanne C. Li[5], Kathleen Haines[6], Maddalena Allegretta[7], Alisha Valdez[7] and **Ginger Janow**[8], [1]University of Florida, Gainesville, FL, [2]Biostatistics, David & Alice Jurist Institute, Hackensack University Medical Center, hackensack, NJ, [3]Pediatric Rheumatology, Joseph M. Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [4]Hackensack Univ Med Ctr, Hackensack, NJ, [5]Pediatrics, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ, [6]Department of Pediatrics, Hackensack University Medical Center, Hackensack, NJ, [7]Rutgers New Jersey Medical School, Newark, NJ, [8]Pediatric Rheumatology, Joseph M Sanzari Children's Hospital, Hackensack University Medical Center, Hackensack, NJ

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Predictive Value of the History and Labs in Distinguishing Inflammatory from Non-Inflammatory and Mechanical Joint Pain

Background/Purpose: Joint pain is one of the most common reasons for referral to pediatric rheumatology clinics throughout the world. Typically, these patients ultimately fall into one of 3 categories of diagnosis: (1) inflammatory, (2) non-inflammatory, or (3) mechanical, each requiring different management. Our objective was to determine what factors on clinical history best predict the final etiology of the joint pain in the 3 categories.

Methods: New patients between the ages of 2 and 22 seen by the pediatric rheumatology clinic at Hackensack University Medical Center between 1/1/2013 and 12/31/2014 with joint pain were included in our retrospective chart review. Data were collected regarding demographics, symptom history, and physician assessment. Final diagnosis was categorized as one of the 3 stated categories. Univariate statistics were performed for all covariates in the sample. Significant differences were tested using a Fisher's Exact test. A multivariate multinomial regression model was estimated to assess whether the characteristics associated with Mechanical or Non-inflammatory joint pain were significantly different than Inflammatory joint pain. A multinomial logistic regression was performed

as there was not an inherent ordering of severity of the groups of joint pain.

Results: 288 charts were included in the analysis. 31.6% were inflammatory, 25.35% non-inflammatory, and 28.47% mechanical (table 1). 42 patients, or 14.58% of the patients did not have a clear final diagnosis, with either resolution of their symptoms or failure to follow up. These patients were not included in the multivariate multinomial regression analysis. An abnormal CRP, presence of swelling, a lower pain score and the absence of a history of anxiety or depression increased the odds of inflammatory joint pain as compared to non-inflammatory. Compared to patients who have symptoms present for <6 weeks, patients who have symptoms for 3-12 months are 6.89 times more likely to have mechanical pain (OR= 6.893, p=0.0370) and 8.85 times more likely to have non-inflammatory pain than to have inflammatory pain (OR=8.854, p=0.0772) (table 2).

Conclusion: Our results indicate that while patients with non-inflammatory pain have higher pain scores, a longer duration of pain and perhaps more subjective pain, the objective data (swelling and increased CRP) are more consistent with inflammatory joint pain. This information is especially useful for the general pediatrician when triaging patients with joint pain and deciding upon referrals. Educating pediatricians could result in better management and therefore improved outcomes.

Table 1. Breakdown of diagnosis by category

Inflammatory		Non-Inflammatory	Mechanical
Dactylitis JDM	Rheumatic	Fibromyalgia	Chondrolysis
HSP JIA/RA	fever Serum	RSD Growing	Costochondritis
Lyme arthritis	sickness SLE	pains	Hypermobility
Reactive	Systemic		Overuse syndrome
arthritis PSRA	sclerosis		Patellofemoral
	UCTD		Pain Tendonitis
	Vasculitis KD		TMJ syndrome
			Trauma

Table 2. Odds ratio of mechanical and non-inflammatory cause versus inflammatory

Diagnosis	Odds Ratio	95% Confidence Interval Low	High	P Value
Abnormal CRP				0.0294
Mechanical	0.176	0.046	0.673	0.024
Non-inflammatory	0.086	0.013	0.555	0.0066
History of Anxiety or Depression				0.0003
Mechanical	8.129	2.127	31.061	0.0022
Non-inflammatory	16.696	4.258	65.471	<.0001
30+ Minutes of Morning Stiffness				0.0752
Mechanical	0.152	0.027	0.845	0.0314
Non-inflammatory	0.306	0.058	1.6	0.1605
PAIN VAS				0.0037
Mechanical	0.969	0.822	1.142	0.0037
Non-inflammatory	1.254	1.048	1.499	0.0132
Presence of swelling				0.0252
Mechanical	0.748	0.328	1.707	0.4909
Non-inflammatory	0.262	0.096	0.712	0.0086
Symptom Duration				0.0056
6 wks-3 mo vs vs <6 wks: Mechanical	2.429	0.646	9.128	0.6362
6 wks-3 mo vs vs <6 wks: Non-inflammatory	4.559	0.912	22.778	0.8111
3-12 mo vs <6 wks: Mechanical	6.893	2.131	22.294	0.037
3-12 mo vs <6 wks: Non-inflammatory	8.854	2.178	36.001	0.0772
1+ yr vs <6 wks: Mechanical	4.995	1.86	13.412	0.1256
1+ yr vs <6 wks: Non-inflammatory	6.382	1.954	20.848	0.2133

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Abstract Number: 2403

Sleep Disruption in Children with Chronic Pain

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Session Time: 9:00AM-11:00AM

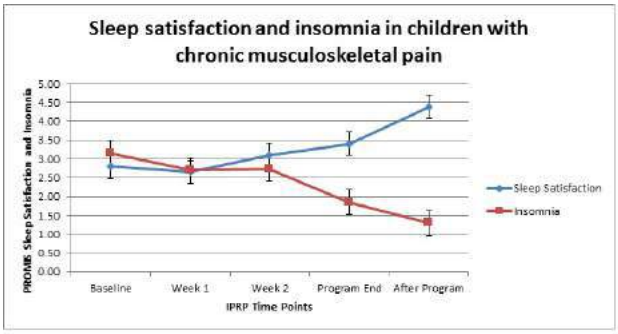
Background/Purpose: Sleep disorders and fatigue are common in children with chronic pain syndromes, and contributes to psychosocial dysfunction, healthcare utilization, and school absences. We hypothesize that pediatric patients with chronic pain who are treated in an interdisciplinary pain rehabilitation program (IPRP) will have significant self-report of fatigue and sleep disturbance at baseline that will be corroborated by physiological evidence using actigraphy. We postulate that self-report measures and sleep physiology will improve after program completion.

Methods: This is a prospective longitudinal study of adolescents with chronic pain who completed an IPRP. This outpatient program provides daily intensive physical and occupational therapy, sleep education, self-regulation training, and behavioral health intervention. All pain and sleep medications are discontinued prior to program entry. 20 patients (16 female) age 12-18 with chronic musculoskeletal pain were evaluated at baseline, weekly during treatment, and again at 1-month after program completion by self-report PROMIS measures of fatigue and sleep disturbance (including items assessing sleep satisfaction and insomnia), and by actigraphy using Motionlogger watches. Paired samples *t*-tests were conducted with SPSS (V.23) and supplemented with hierarchical linear modeling (HLM7) for time-series analyses.

Results: Participants report difficulty falling asleep at baseline with insomnia score of 3.15 on a scale of 1 to 5. They are unsatisfied with sleep, with a score of 2.80. Both insomnia and sleep satisfaction significantly improve by program end ($P<0.001$), with continued improvement to 1.29 and 4.39 ($P<0.001$), respectively at 1-month follow-up. At baseline, patients report high daytime fatigue 24.30 on a scale of 0 to 40 and sleep disturbance 31.65 on a scale of 8 to 40. Both of these measures improved significantly, with fatigue changing from significantly impaired to normal (8.43, $P<0.001$) at 1-month follow-up. Actigraphy showed improvement in total minutes asleep after the first week ($P=.02$) and this was maintained at program end ($P=.03$), but not in the weeks after the program ($P=.21$). Sleep efficiency, sleep latency, and duration of first sleep episode did not show significant change during the program.

Conclusion: Children with chronic musculoskeletal pain report severe sleep impairments prior to starting an intensive pain rehabilitation program. Following the program they report significant improvements with insomnia, sleep satisfaction, daytime fatigue, and sleep disturbance. Despite

statistically significant change in all patient-reported outcomes, these findings are not mirrored by objective data using actigraphy. Long-term follow-up and a larger sample size is needed to determine whether these outcomes will eventually more closely match patient report, or whether subjective issues are the most important improvement.



Disclosure: C. Hoffart, None; **S. Fortney**, None; **D. Wallace**, None.

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Abstract Number: 2404

Prevalence of Subclinical Entheseal Involvement in Children and Adolescents with Type 1 Diabetes: A Case Control Study

Alberto Batticciotto[1], Andrea Scaramuzza[2], Matteo Ferrari[3], Maria Chiara Ditto[4], Maria Chiara Gerardi[4], Fabiola Atzeni[1] and Piercarlo Sarzi-Puttini[4], [1]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milano, Italy, [2]Department of Pediatrics, University of Milan, Milano, Italy, [3]Department of Pediatrics, University of Milan, Milan, Italy, [4]Rheumatology Unit, ASST Fatebenefratelli - Sacco, L. Sacco University Hospital, Milan, Italy
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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The clinical course of type one diabetes (T1D) is frequently complicated by musculoskeletal manifestations such as Dupuytren's disease, trigger finger, shoulder adhesive capsulitis and in general tendinopathies (1). In a recent review Abate et Al. underline that an accepted hypothesis identified in the excess of advanced glycation end products (AGEs) the cause of tendon damages in T1D. There are several demonstrations that AGEs are able to form a covalent cross-link within collagen fibres causing a distortion of collagen layers that altered tendons structure and functionality (2). Previous ultrasonographic evaluations of diabetic patients tendons reported the presence of intratendinous areas with dishomogeneous ecostructure and an increase of normal tendon thickness. Up to now, at the best of our knowledge, no data about the ultrasonographic evaluation of T1DM patients enthesis has been published.

Methods: Twenty-three children and adolescents (12 M 11 F) affected by T1D, mean ages 13.9 years (range 9-18 yrs), mean disease duration 60 months (range 10-161 months), without any clinical sign or symptom of musculoskeletal involvement. A control group of 28 sex (12 M 16 F) and age-matched (14.2 years, range 8-18 yrs) was also evaluated. Both groups underwent an ultrasound examination with ESAOTE MyLAB 70 (Genova, Italy) equipped with 6-18 MHz linear array transducer. Brachial triceps, femoral quadriceps, Achilles, plantar fascia, and proximal and distal patellar entheses were all scored according with the 0-136 Madrid Sonographic Enthesis Index (MASEI).

Results: The percentage of enthesis with ultrasonographic revealed thickness (22.6% Vs 16.1% p= 0.04) and with dishomogeneous ecostructure (2.9% Vs 0% p=0.001) was statistically higher in T1D group. No difference has been observed in terms of percentage of bursitis presence (3.4% Vs 2.7% p= 0.76), percentage of enthesis with power Doppler score ≥2 (2.5% Vs 1.2% p= 0.21), erosions (0.4% Vs 0.3% p= 0.89) or calcification (4.7% Vs 3.3% p= 0.76). Hyperechoic spots can be observed at the level of the distal part of tendons in a percentage of T1D patients statistically higher than in controls (43.5% Vs 8.7%; p=0.0046).

Conclusion: In our study we observed that, even at the enthesis level, T1D patients present an higher percentage of thickness and dishomogeneity in echostructure when compared with an healthy control group. More investigations about the hyperechoic spots detected at the level of the distal parts of the tendons are needed. **References:** 1.Tom A Ranger et Al. "Is there an association between tendinopathy and diabetes mellitus? A systematic review with meta-analysis." Br J Sports Med 2015-094735 2.Michele Abate et Al. "Occurrence of tendon pathologies in metabolic disorders" Rheumatology 12, 2013

Disclosure: A. Batticciotto, None; **A. Scaramuzza**, None; **M. Ferrari**, None; **M. C. Ditto**, None; **M. C. Gerardi**, None; **F. Atzeni**, None; **P. Sarzi-Puttini**, None.

Abstract Number: 2405

Musculoskeletal Manifestations As Presenting Symptoms of Inflammatory Bowel Disease in Children and Adolescents

Rachel Levy[1], Gil Amarilyo[2,3], Jacob Amir[4], Rotem Tal[2,3], Amit Assa[3,5], Firas Rinawi[5] and **Liora Harel**[2,3], [1]The Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel, [2]Pediatric Rheumatology Unit, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel, [3]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel, Tel Aviv, Israel, [4]Mayanei Hayeshua Medical Center, Bnei Brak, Israel, [5]Institute of Gastroenterology Hepatology and Liver diseases, Schneider Children's Medical Center of Israel, Petach Tikvah, Israel

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Session Time: 9:00AM-11:00AM

Background/Purpose: Extra intestinal manifestations occur in 40-50% of patients with inflammatory bowel disease (IBD), with musculoskeletal involvement in 25%. Data regarding musculoskeletal manifestations in the pediatric population are scarce. The purpose of this study was to compare pediatric IBD patients initially presenting with arthritis, to patients presenting with arthritis of other etiologies, in order to identify clinical and laboratory red flags that may arouse suspicion of IBD.

Methods: This retrospective cohort study included patients followed up at "Schneider Children's Medical Center of Israel" between 1985-2016. We identified 23 children with IBD who presented with arthritis and matched them to a control group of 46 children. The latter included 21 patients with Juvenile Idiopathic Arthritis, 7 patients with Familial Mediterranean Fever and 18 patients with postinfectious arthritis. Clinical and laboratory data were collected and compared between the two groups. Fisher's exact test, χ^2 and analysis of variance were used for statistical processing.

Results: The most statistically significant clinical factor at presentation which predicted IBD was sacroiliitis (30.4% in IBD group vs. 2.2% in control group, P<0.001), and was more common in females (46.15% vs. 20% respectively). Additive arthritis was exclusive to the IBD group (21.7%). Twenty five percent of the IBD group reported a positive family history for IBD (mostly Crohn's Disease).The IBD group showed decreased hemoglobin and MCV levels as well as elevated RDW as compared to control (10.5, 69.1, 14.9 vs 12.0, 79.1, 13.2 respectively, P<0.001). Albumin mean

values were lower in the IBD group compared to control (3.5 vs. 4.3 respectively, P<0.001). Upon direct questioning of the IBD group at presentation, the following abdominal symptoms were reported: diarrhea (43.5%), abdominal pain (39.1%), weight loss (34.8%), fever (21.7%), aphthous ulcers (17.4%), bloody stools (13%) and vomiting (8.7%). Despite these signs and symptoms 8.7% of children were diagnosed with IBD at presentation, whilst 26% were diagnosed at a delay of >1 year. The overall mean time from arthritis presentation to IBD diagnosis was 1.17±1.89 years. Three patients (13.04%) from the IBD group developed residual joint damage.

Conclusion: Arthritis, specifically sacroiliitis, associated with microcytic anemia and/or hypoalbuminemia in children without specific signs of IBD should be considered red flags, and arouse suspicion for this disease, thus mandating thorough enquiry.

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Abstract Number: 2406

Mental Health Care for Adolescents with Rheumatologic Conditions: Perspectives from Pediatric Behavioral Health Providers in North America

Andrea Knight[1], Michelle Vickery[2], Eyal Muscal[3], Alaina Davis[4], Julia Harris[5], Aimee O. Hersh[6], Martha Rodriguez[7], Karen Onel[8], Laura Schanberg[9], Tamar Rubinstein[10], Beth S. Gottlieb[11], Nina Washington[12], Elissa Weitzman[13,14] and Emily Von Scheven[15], [1]Center for Pediatric Clinical Effectiveness, Children's Hospital of Philadelphia, Philadelphia, PA, [2]PolicyLab, Children's Hospital of Philadelphia, Philadelphia, PA, [3]Immunology, allergy and Rheumatology, Baylor College of Medicine, Texas Children's Hospital, Houston, TX, [4]Pediatric Rheumatology, Monroe Carell Junior Children's Hospital at Vanderbilt, Nashville, TN, [5]Children's Mercy Kansas City, Kansas City, MO, [6]Pediatrics/Rheumatology, University of Utah, Salt Lake City, UT, [7]Pediatrics, University of Chicago Medical Center, Chicago, IL, [8]Division of Pediatric Rheumatology, University of Chicago, Chicago, IL, [9]Pediatrics, Duke Medical Center, Durham, NC, [10]Division of Pediatric Rheumatology, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY, [11]Pediatric Rheumatology, The Steven and Alexandra Cohen Children's Medical Center of New York, The Hofstra North Shore-LIJ School of Medicine, New Hyde Park, NY, [12]Dept. of Pediatric Rheumatology, University of Mississippi Medical Center, Jackson, MS, [13]Boston Children's Hospital, Boston, MA, [14]Harvard Medical School, Boston, MA, [15]Dept of

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Session Time: 9:00AM-11:00AM

Mental Health Care for Adolescents with Rheumatologic Conditions: Perspectives from Pediatric Behavioral Health Providers in North America

Andrea Knight[1], Michelle Vickery[1], Natalie Stollon[1], Eyal Muscal[2], Alaina Davis[3], Julia Harris[4], Aimee Hersh[5], Martha Rodriguez[6], Karen Onel[6], Laura E. Schanberg[7], Tamar Rubinstein[8], Beth S. Gottlieb[9], Nina Washington[10], Elissa Weitzman[11], Emily von Scheven[12] and for the CARRA Investigators [1]Children's Hospital of Philadelphia, [2]Baylor College of Medicine, Texas Children's Hospital, [3]Vanderbilt University School of Medicine, Monroe Carell Junior Children's Hospital, [4]University of Missouri-Kansas City, ChildrenÕs Mercy Hospital, [5]University of Utah, [6]University of Chicago, [7]Duke University Medical Center, [8]Albert Einstein College of Medicine, Children's Hospital at Montefiore, [9]The Steven and Alexandra Cohen Children's Medical Center of New York, The Hofstra North Shore-LIJ School of Medicine, [10]University of Mississippi Medical Center, [11]Harvard University, Boston ChildrenÕs Hospital, [12]University of California San Francisco

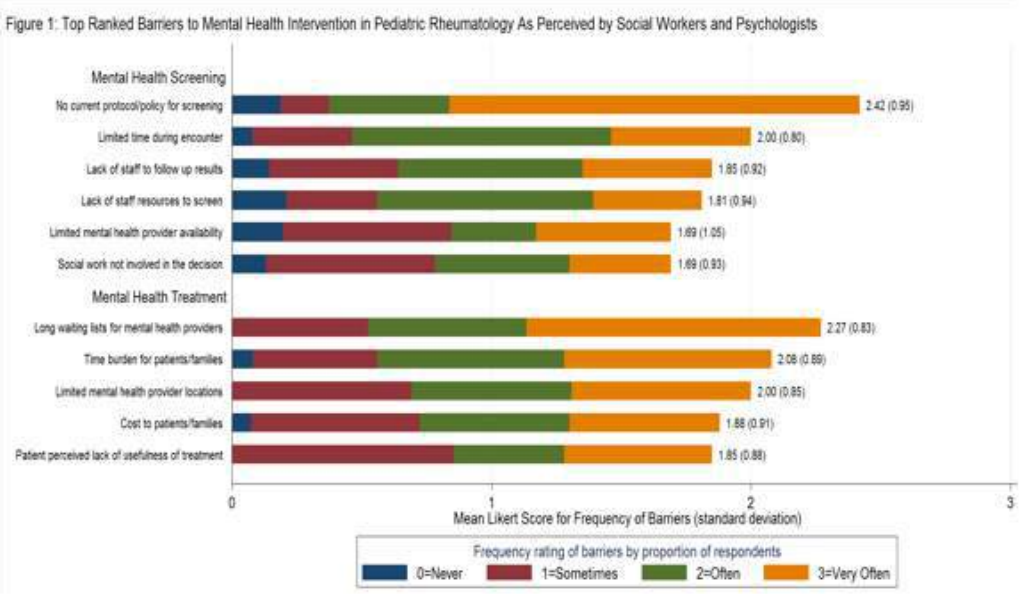
Background/Purpose: Mental health problems are common, but under-treated in adolescents with rheumatologic conditions. To identify gaps in mental health care, we examined perspectives from behavioral health providers working with adolescents in pediatric rheumatology clinics.

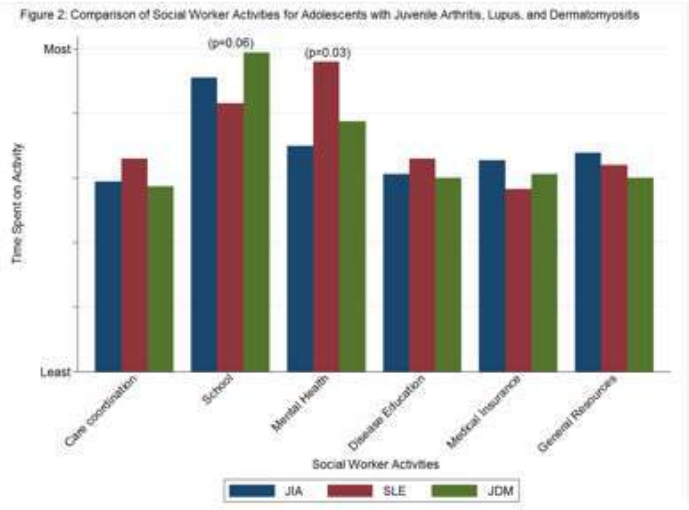
Methods: We surveyed social workers and psychologists at centers in the Childhood Arthritis and Rheumatology Research Alliance (CARRA) with recent clinical experience (past 5 years) in pediatric rheumatology. The online survey assessed participant demographics, practices and beliefs for mental health care of adolescents with lupus (SLE), juvenile idiopathic arthritis (JIA), or juvenile dermatomyositis (JDM). Participants rated the frequency of 15 barriers to mental health screening and 18 barriers to treatment on a 4-point Likert scale. Social workers ranked their activities by current and desired amount of time spent (most to least) on: care coordination, school, mental health, disease education, general resources, and medical insurance. Case examples elicited comparative rankings of these activities for 3 exemplary adolescents with SLE, JIA or JDM; 2-way ANOVA was used to test for differences.

Results: Only 45% of CARRA centers had an eligible social worker or psychologist. Of 60 providers contacted, 31 (52%) responded. After exclusions (3 incomplete and 2 non-clinical), 26 responses from 21 social workers and 5 psychologists at mostly US university-based (88%) and urban (77%) centers were analyzed. All reported that screening for depression and anxiety should be routine for adolescents with JIA/SLE/JDM, but none reported it as current practice. Of 11 (42%)

reporting screening of selected patients, only 3 used a validated screening tool. Eleven (42%) reported that their practice lacked a follow-up plan after mental health referral. Figure 1 shows the most frequent barriers to mental health care. Social workers spent most of their time addressing mental health for adolescents with SLE (p=0.03), in contrast to school issues for those with JIA and JDM (p=0.06) (Figure 2). Overall, 8 (38%) social workers desired more time for mental health, and 6 (23%) for disease education, and 20 (76%) had high interest in providing mental health interventions.

Conclusion: Many pediatric rheumatology centers lack behavioral health providers despite known mental health burden in their patients. Implementation of policies for routine screening and follow-up on referrals, as well as utilization of social workers to provide mental health intervention may improve mental health care for adolescents with rheumatologic conditions.





Shown are rankings of social worker time spent on six activities compared between disease groups (JIA=juvenile idiopathic arthritis; SLE=systemic lupus erythematosus; JDM=juvenile dermatomyositis. Rankings are based on mean score (0=least time to 5=most time) and 2-way ANOVA was used to test for differences among these disease groups.

Disclosure: **A. Knight**, None; **M. Vickery**, None; **E. Muscal**, None; **A. Davis**, None; **J. Harris**, None; **A. O. Hersh**, None; **M. Rodriguez**, None; **K. Onel**, None; **L. Schanberg**, None; **T.**

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Abstract Number: 2407

The Descriptive Epidemiology of Acute Rheumatic Fever and Post-Streptococcal Reactive Arthritis in Japan

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects - Poster III: Systemic JIA, Autoinflammatory Syndromes, Scleroderma, Vasculitis, Miscellaneous

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Acute Rheumatic Fever (ARF) and Post-streptococcal reactive arthritis (PSRA) are well known as post-streptococcal syndromes with arthritis in children. ARF have been declining in developed nations like Japan and it is generally thought to be a disease of the past. Despite decreasing incidence, focal outbreaks have been reported in developed nations. Despite its importance, ARF and PSRA epidemiology has not been reviewed recently. The aims of this study were to assess ARF and PSRA incidence between 2010 and 2015 in Japan.

Methods: This descriptive epidemiological study examined ARF and PSRA incidence in 2010-2015, using hospitalisation data included in a total of 528 hospitals.

Results: From a total of 323 hospitals (61% response rate), 44 cases of ARF and 21 cases of PSRA were reported. The mean age of ARF was 8.5 years (3-15 years), and female/male ratio was 16/28. Manifestations including; carditis, 27 (61.3%); arthritis, 36 (81.8%); Erythema marginatum in 7 (16%); Sydenham chorea, 3 (6.8%); Subcutaneous nodules, 1 (2.3%), respectively. And minor criteria were; fever, 39 (88.6%); first degree heart block, 9 (20.5%); elevated inflammatory markers (ESR, CRP), 43 (97.7%). ARF patients were treated with antimicrobial agent therapy.42 (95.5%); NSAIDs 29 (65.9%); and glucocorticoids therapy 24 (54.5%). During the follow up, four patients showed mild carditis and the other were improved. All ARF patients were prescribed with antimicrobial agent prophylaxis. On the other hand, the mean age of PSRA was 8.2 years (2-15 years), and female/male ratio was 12/9. Six (28.6%) patients had monoarthritis. And fever in 14

(66.7%) and Elevated inflammatory markers in 19 (90.5%). PSRA patients were treated with antimicrobial agent therapy.17 (81%); NSAIDs 16 (76.2%); and glucocorticoids therapy 1 (4.8%). During the follow up, there was no patient with carditis. Eleven (52.4%) patients with PSRA were prescribed with antimicrobial agent prophylaxis.

Conclusion: In this study, ARF is rare in the Japanese pediatric population, but ARF has not yet disappeared. We observed high incidence of arthritis, carditis and erythema marginatum. General pediatrician need to have updated information about ARF and PSRA even in industrialized countries.

Table

Acute Rheumatic Fever (ARF) and Post-streptococcal reactive arthritis (PSRA) cases

From January 1st, 2010 to December 31th, 2015

Year	2010	2011	2012	2013	2014	2015	Total
ARF	5	6	6	6	8	13	44
PSRA	1	4	2	3	6	5	21

Disclosure: S. Sato, None; **Y. Uejima**, None; **E. Suganuma**, None; **T. Takano**, None; **Y. Kawano**, None.

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Abstract Number: 2408

Severe Juvenile Arthritis Associated with a De Novo Gain-of-Function Germline Mutation in MYD88

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Background/Purpose: Myeloid differentiation primary response 88 (MyD88) is a critical adaptor protein that connects Toll-like and IL-1 receptor signaling to activation of NF-κB. Germline loss-of-function mutations in MyD88 cause immunodeficiency, while somatic gain-of-function mutations have been linked to lymphoma. We investigated a child with a progressively destructive small-to-medium joint polyarticular JIA since the age of 2 with persistent neutrophil predominant synovial infiltrates.

Methods: We evaluated the patient and family members by whole exome sequencing (WES), peripheral blood immunophenotyping, and phosphorylated-STAT3 (p-STAT3) quantitation. Functional studies in monocytes and dermal fibroblasts included gene/protein expression, quantitation of neutrophil chemotaxis, and siRNA-mediated knockdown of MyD88 and NF-κ□B subunit p65 (p65). Wild type or S222R MyD88-GFP fusion proteins were re-expressed in MyD88-deficient THP-1 cells. NF-κ□B activity in THP-1 cells was measured via secreted embryonic alkaline phosphatase reporter assay.

Results: WES revealed a *de novo* heterozygous missense mutation in *MYD88*(c.666T>G, p.Ser222Arg), which was confirmed by Sanger sequencing in both peripheral leukocytes and dermal fibroblasts. Immunophenotyping showed an absence of CD16+ monocytes, an expansion of CD4+ Th17 T cells, and the presence of a previously uncharacterized CD123+CD11c+ dendritic cell population, as well as markedly increased basal and stimulated p-STAT3 in monocytes and T and B lymphocytes in the patient. Peripheral monocytes exhibited a baseline interferon gene expression signature and increased expression of neutrophil and monocyte chemokines. Fibroblasts exhibited significantly greater baseline expression of CXCL chemokines compared to controls, which abated upon MyD88 or p65 knockdown. Re-expression of wild type or S222R MyD88-GFP fusion protein in MyD88-knockout THP-1 cells demonstrated increased NF-κB activation at baseline and with stimulation in S222R-MyD88-expressing cells.

Conclusion: This is the first description of a *de novo* germline MyD88 mutation associated with severe polyarticular JIA. The gain-of-function effects demonstrated in the patient's hematopoietic and non-hematopoietic cells offer a plausible mechanism for arthritis and support a role for single gene defects contributing to extreme JIA phenotypes.

Disclosure: K. A. Sikora, None; **J. R. Bennett**, None; **Z. Deng**, None; **W. L. Tsai**, None; **A. Brundidge**, None; **F. Navid**, None; **G. Layh-Schmitt**, None; **E. Hanson**, None; **M. G. Gadina**, None; **L. M. Staudt**, None; **T. A. Griffin**, None; **R. A. Colbert**, None.

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Abstract Number: 2409

Genetic Insights into Juvenile Idiopathic Arthritis Derived from Deep Whole Genome Sequencing

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Background/Purpose: Deep whole genome sequencing (WGS) provides an unprecedented opportunity to comprehensively study genetic landscapes at finer resolution than can be achieved with chip-based methods. We studied juvenile idiopathic arthritis (JIA), a complex trait that represents one of the most common chronic disease conditions in children. While previous candidate gene approaches and genome-wide association studies (Hersh et al J Autoimmunity 2015) and genetic fine-mapping studies (Hinks et al Nature Genet 2013) have revealed some useful information about genetic risk in JIA, a finer mapping is needed to decipher genetic landscapes of children with this disease to gain insights into pathogenesis and treatment responses.

Methods: We conducted deep WGS on 48 children with JIA over 2 independent cohorts, comparing results with publically available WGS data from healthy individuals. Each cohort contained a replicate to ascertain the fidelity of the sequencing reactions, the first cohort (n= 29) was homogeneous, consisting of non-Hispanic Caucasian children. The second cohort (n=19) was a more heterogeneous group including Hispanic and Caucasian-Native American ancestry children.

Results: We achieved an average of 38.7X sequencing depth per sample, and 41 Giga passed quality control measures. Paired-end reads gave an average per sample mapping rate of 97.9%. We found 1,205,197 novel SNPs and 283,554 novel indels in JIA patients that are not reported in dbSNP141 public repository. We also identified 1,902 novel structural variants (SV) not present in Database of Genomic Variants. By tabulating SNP density in 1Mb windows across the entire genome, we identified 24 SNP hotspots when compared with the 1000 Genome Projects (1KGP). It is of interest to note that some of the genes located within 5kb upstream or downstream 5kb to those SNP hotspots show statistically significant enrichment in immunological processes (including T cell receptor signaling pathways and innate immune responses). Further analyses indicated that JIA SNPs have significantly more regulatory potential (e.g. transcription factor binding motifs, DNase1 hypersensitivity sites, eQTL) compared to 1KGP SNPs. It is also important to note that the JIA specific genetic variation (indels and SNPs) showed ~72% concordance between the 2 cohorts despite the ethnic heterogeneity between the 2 cohorts.

Conclusion: These studies demonstrate the utility of WGS, even on relatively small sample numbers, for elucidating underlying genetics of JIA and its response to therapy. For example, segregation of variants from WGS of JIA individuals in array-based SNP LD blocks overcomes the limitations of depth and coverage of arrays in identifying JIA risk variants. Distribution of JIA novel variants in regulatory elements serves as valuable resource from which to develop insights into epigenetic alterations underlying the effects of genetic variants.

Disclosure: J. Jarvis, None; **L. P. Wong**, None; **K. Jiang**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/genetic-insights-into-juvenile-idiopathic-arthritis-derived-from-deep-whole-genome-sequencing

Abstract Number: 2410

Genetic Architecture of Systemic Juvenile Idiopathic Arthritis Distinguishes It from Oligoarticular and Polyarticular Forms of Juvenile Idiopathic Arthritis

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Background/Purpose: JIA is a heterogeneous group of conditions that are unified by the presence of chronic childhood arthritis without an identifiable cause. Systemic JIA (sJIA) is a rare form of JIA that is characterized by episodic systemic inflammation and chronic arthritis. Approximately half of children with sJIA go on to develop destructive, life-long arthritis that has phenotypic similarities with the oligoarticular / RF negative polyarticular (polygo) or RF positive polyarticular (RF+poly) forms of JIA. Therapies effective in treating other forms of JIA are much less effective in sJIA, particularly among patients with persistent arthritis. Investigating the genetic architecture of sJIA and comparing it with other forms of JIA may improve our understanding of these differences. However because of its rare nature, genomic studies of sJIA have been limited, providing few insights into its pathophysiology. Therefore we sought to identify genetic factors that influence sJIA pathogenesis and to compare the genetic architecture of sJIA with the other common forms of JIA.

Methods: We performed a genome-wide association study of 982 children with sJIA from 9 countries. Following stringent quality control procedures, over 6 million single nucleotide polymorphisms (SNPs) were tested for association with sJIA by logistic regression in 9 geographically-defined strata and association results were meta-analyzed. Weighted genetic risk scores (wGRS) based on established genetic risk factors for polygo or RF+poly JIA were calculated and wGRS were compared between sJIA cases and healthy controls using the Wilcoxon Rank Sum test. The correlation of wGRS with sJIA was tested by both logistic regression and by analysis of receiver operating characteristic (ROC) curves with calculation of the area under the curve. Quantile-quantile (QQ) plots were used to determine whether sJIA-associated SNPs were enriched within the set of polygo-associated SNPs from the Immunochip study by Hinks and colleagues.

Results: The HLA locus and a second locus on chromosome 1 both showed association with sJIA that exceeded the threshold for genome-wide significance ($p<5E-8$), and 23 additional loci had evidence suggestive of association with sJIA ($p<5E-6$). There was virtually no overlap between the sJIA susceptibility loci and the known risk loci for other forms of JIA. ROC curve analysis and

logistic regression of wGRS found no correlation between sJIA and either polygo or RF+poly JIA. QQ plots showed no evidence for enrichment of sJIA associations among polygo-associated SNPs. Collectively, we found no evidence of shared genetic architecture between sJIA and either polygo or RF+poly JIA.

Conclusion: sJIA has a distinct genetic architecture without evidence of shared genetic risk factors with other common JIA subtypes. This indicates that sJIA is unique in its pathophysiology, relative to the other JIA subtypes. As such, sJIA must be investigated separately from the other JIA subtypes to identify mechanisms and therapeutic targets specific to sJIA. Moreover, the management of children with sJIA should be directed by studies of sJIA, and not by trials or observations of other subtypes of JIA.

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Abstract Number: 2411

Multiple Genetic Susceptibility Loci in Juvenile Idiopathic Arthritis Are Bound By a Set of Transcription Factors

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Background/Purpose: Genome wide association studies (GWASs) and dense genotyping of immune-related disease regions have identified 17 loci associated with juvenile idiopathic arthritis (JIA) ($p<5\times10^{-8}$), 11 further loci with suggestive evidence for association ($p<1\times10^{-6}$), and 2 additional independent loci remaining after stepwise regression in the STAT1/STAT4 region. Given that the majority of these genome-wide associations are located in non-coding regions of the genome, we investigated if specific TFs might bind DNA at multiple JIA-associated genetic loci.

Methods: We defined a locus as those variants that had disequilibrium at $r^2>0.8$ with the most significant genotyped marker at the locus. We assembled a large collection of publically available datasets, including 1,613 chromatin immunoprecipitation with next generation sequencing (ChIP-Seq) datasets, and "Active Chromatin" maps generated from combinations of histone marks in 126 different cell and tissue types. We developed a simulation test to assess the statistical significance of the number of JIA loci that intersect with each ChIP-seq dataset. To generate a null distribution, 2,000 simulations were performed in which each JIA locus was randomly assigned to a genomic location, maintaining linkage disequilibrium and allele frequency structure, and the intersect with each dataset was calculated. Bonferroni corrected P-values (p_c) were estimated for each ChIP-seq dataset evaluated. We confined our attention to TF data sets that bound DNA in ≥3 JIA genetic loci and that had $p_c<0.01$. The Toppgene web portal was used to characterize functional annotations and protein interactions between TFs.

Results: Our procedure implicates several immune cell types in JIA pathogenesis, including multiple CD4+ cells (Th cells, Th17 cells, Tregs, and memory T cells), CD56+ NKT cells, and CD8+ T cells. 95 of the 1,613 ChIP-seq datasets had $p_c<0.01$. The top result involves STAT4 binding in IL-12 stimulated CD4+ Th1 cells ($p_c<10^{-12}$, 24-fold enrichment). Two Vitamin D receptor (VDR) ChIP-seq datasets are also highly significant (both $p_c<10^{-9}$), together comprising 7 of the 30 JIA loci. The 95 significant datasets collectively constitute 47 TFs (also including IRF3, STAT1, and RELA), which are significantly enriched for involvement in pathways that involve cytokine binding and activity ($p_c<10^{-4}$).

Conclusion: These data are consistent with common transcriptional control mechanisms operating across multiple JIA risk loci in a shared intracellular environment. Notably, most GWAS loci have small odds ratios (usually <1.2). If there are coordinated mechanisms across loci that alter disease risk with larger effect sizes, then shared gene regulatory mechanisms such as these are important in

generating disease risk.

Disclosure: L. C. Kottyan, None; **H. Moncrieffe**, None; **X. Chen**, None; **M. Pujato**, None; **J. B. Harley**, None; **M. Weirauch**, None; **S. D. Thompson**, None.

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Abstract Number: 2412

Human Gut Microbial Species Correlate with Arthritis in the K/BxN Mouse Model

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Title: Human gut microbial species correlate with arthritis in the K/BxN mouse model

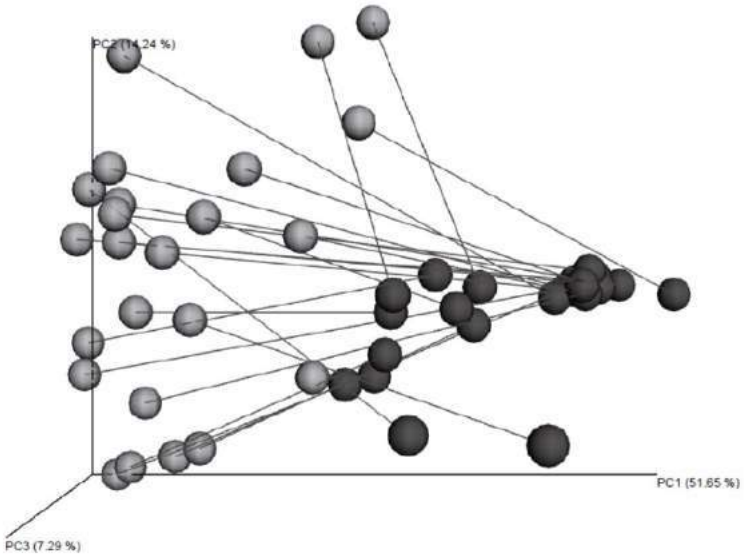
Background/Purpose: Studies have identified abnormalities in the microbiota of patients with arthritis. To evaluate the pathogenicity of human microbiota, we performed fecal microbial transplantation (FMT) from children with newly diagnosed enthesitis-related arthritis (ERA) and sex- and age-matched controls to germ-free KRN/B6xNOD (K/BxN) mice, a spontaneous arthritis model dependent upon an intact microbiota.

Methods: K/BxN mice were maintained under germ-free (GF) conditions and were gavaged with feces previously collected from children with ERA and healthy controls at 6 – 10 weeks of age, and maintained in isolators for 21 – 24 days following FMT. Additional controls included non-gavaged GF mice and mice transferred from the gnotobiotic to the conventional facility. Sequencing of the

fecal microbiota was performed on the Illumina MiSeq device, and analysis was performed with the Quantitative Insight into Microbial Ecology program.

Results: 24 mice were gavaged with human microbiota (12 each of ERA and controls). 23 non-gavaged mice were maintained in the gnotobiotic facility, and 11 additional non-gavaged mice were transferred into the conventional facility. Among transplanted mice, ankle swelling assessed 21 – 24 days post transfer was equivalent in those that received ERA (4.7 ± 0.5) vs control (4.4 ± 0.4) microbiota. Taken together, humanized mice had increased ankle swelling as compared to GF (3.5 ± 0.3, $p < 0.001$) and conventionally housed (4.0 ± 0.4, $p = 0.002$) mice. Principal coordinates analysis revealed incomplete uptake of the human microbiota, with clustering by species but not by donor-recipient dyad (Figure 1.) This was due to substantial over-representation of two genera (Bacteroides and Akkermansia) at the expense of the Firmicutes phylum among the transplanted mice. Taken together, the microbiota as a whole predicted the extent of ankle swelling ($R2 = 0.185$, $p = 0.018$, adonis test). At the level of the individual genera, the abundances of *Bacteroides* ($r = -0.510$, $p = 0.010$) inversely and *Akkermansia* ($r = 0.367$, $p = 0.078$) directly correlated with ankle swelling.

Conclusion: Perhaps due to incomplete humanization, there was no association between the diagnosis of the donor and extent of arthritis in the recipient mice. However, our study supports previous findings of a possible association between *Akkermansia muciniphila* and arthritis and opens up new avenues of research into the association between human microbiota and arthritis.



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Abstract Number: 2413

Inflammation Regulating microRNAs, Mir-146b, Mir-155 and Mir-192-5p Are Altered in Plasma and Synovial Fluid of Oligoarticular Juvenile Idiopathic Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: MicroRNAs (miRNAs) modulate gene expression by inhibiting the translation of targeted mRNAs and causing mRNA degradation in a transcript-specific manner. Several miRNAs have been reported to play an important role in inflammation and autoimmune diseases. Our aim was to identify miRNA biomarkers in oligoarticular juvenile idiopathic arthritis (JIA).

Methods: Total RNA was isolated and microarray profiling on 84 inflammatory miRNAs was performed to identify differentially expressed miRNAs on pooled (n=5) healthy plasma, JIA plasma and synovial fluid (SF) by digital droplet PCR (DDPCR) that enables absolute quantification of nucleic acids. Levels of four candidate miRNAs; miR-125b, miR-146b, miR-155 and miRNA-192-5p in plasma and SF were quantified by DDPCR individually in additional 10 healthy controls and 10 age and gender matched oligoarticular JIA patients. All patients satisfied the ILAR classification criteria, were all ANA positive and non- or only NSAID treated at the time of joint injection when also the blood was collected.

Results: We identified 11 and 13 miRNAs on the microarray analysis that were at least 2-fold increased or decreased in JIA plasma compared to normal plasma, and in JIA SF compared to JIA plasma, respectively. The differential expression of miR-146b, miR-155 and miR-192-5p were confirmed on individual samples. Levels of miR-146b and miR-155 was increased in plasma ($p=0.03$ and $p=0.01$ respectively) of JIA patients and miR-146b was enriched even more at the site of the inflamed joints ($p=0.02$). MiRNA-192-5p expression was reduced in arthritic joints ($p=0.003$). MiRNA-125b expression did not show any significant difference.

Conclusion: This is the first study to investigate miRNAs by DDPCR in JIA and especially in SF. Similar to what is known in rheumatoid arthritis, miRNA-146b and miRNA-155 may promote an inflammatory process in oligoarticular JIA. Our novel finding is that miRNA192-5p is down-regulated in JIA in the inflamed joint. This may be involved in suppressing proinflammatory signals.

Investigation of miRNAs and exploring their potential biological functions could help to understand the pathogenesis of JIA. The inflammation regulating miRNAs may have the potential to serve as biomarkers of disease or novel therapeutic targets.

Disclosure: B. Derfalvi, None; **S. Roberts**, None; **B. Hargreaves**, None; **S. McAlpine**, None.

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Abstract Number: 2414

Microrna Associated with Active Systemic Juvenile Idiopathic Arthritis Regulate CD163 Expression in Polarized Macrophages through Two Distinct Mechanisms

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: CD163 is a hemoglobin scavenger receptor and innate pattern recognition receptor, and a marker of activated monocytes and macrophages. It is also expressed on monocytes from children with active systemic juvenile idiopathic arthritis, and associated with emergence of macrophage activation syndrome. However, the regulation of CD163 expression during monocyte and macrophage polarization is poorly understood. MicroRNA post-transcriptionally regulate gene expression, often serving as feedback loops to “fine tune” gene expression programs. We hypothesize that **microRNA dysregulated in active SJIA modulate expression of CD163 in polarized macrophage populations**

Methods: Human THP-1 monocytic cells and primary monocytes and monocyte-derived macrophages from healthy donors were polarized in vitro. CD163 expression was determined by quantitative RT-PCR or on a single-cell level by RNA flow cytometry using the PrimeFlow kit.

Cells were also transfected with specific microRNA mimics or antagomirs to miR-125a-5p, miR-181a or miR-181c. Direct binding of miR-181 family members to the CD163 3' untranslated region (UTR) was determined using a luciferase reporter system and through RNA immunoprecipitation (RIP). RNA-sequencing was used to identify differentially regulated genes in macrophages overexpressing miR-125a-5p or control mimics.

Results: Significantly increased CD163 mRNA levels were detected only in monocytes and macrophages polarized towards M2c conditions by IL-10. Similarly, single-cell analysis showed markedly increased CD163 surface protein and mRNA levels only with IL-10 treatment. Several candidate microRNA which are overexpressed in monocytes from children with active systemic JIA may regulate CD163. Here, we find that overexpression of miR-125a-5p and miR-181c significantly reduced CD163 mRNA expression in IL-10 polarized macrophages. *In vitro*, both miR-125a and miR-181 family members were elevated in polarizing conditions that restrict CD163 expression, and inhibition of these with antagomirs increased CD163 mRNA levels. Interestingly, these microRNAs regulated CD163 expression through distinct mechanisms. Computationally, miR-181 is predicted to bind directly to the 3' UTR of CD163 mRNA. Using both a luciferase reporter system and RIP assay we found direct interaction between miR-181 family members and the CD163 mRNA. In contrast, CD163 does not have a predicted miR-125a binding site. RNA-seq based genome wide target analysis identified "Cytokine-cytokine receptor interactions" as the most significantly repressed gene pathway upon miR-125a overexpression, and specifically decreased levels of *IL10RA* and *TGFbR2*. This finding suggests that miR-125a exerts global effects on macrophages to modulate polarization.

Conclusion: Taken together, these data show that microRNAs regulate the IL-10-induced expression of CD163 in human macrophages through distinct mechanisms, directly targeting of CD163 mRNA and indirectly inhibiting cytokine receptor expression. These findings highlight the diverse ways microRNA regulatory networks affect macrophage polarization and phenotype in active SJIA.

Disclosure: T. Do, None; **R. Tan**, None; **M. Bennett**, None; **M. Medvedovic**, None; **N. Shen**, None; **S. Thornton**, None; **A. Grom**, Novartis Pharmaceutical Corporation, 5,novimmune, 5; **G. Schulert**, Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 2415

Next Generation Sequencing Analysis of Familial Haemophagocytic Lymphohistiocytosis (HLH) Related Genes in Macrophage Activation Syndrome (MAS) and Secondary HLH (secHLH)

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Background/Purpose: Macrophage activation syndrome (MAS) is a severe complication of rheumatic disease, particularly of systemic JIA (sJIA). It is currently classified among the secondary forms of HLH (secHLH). Primary HLH (pHLH) is caused by mutation of genes that code for proteins that are involved in cytotoxic functions. Mice carrying heterozygous mutations in more than one pHLH gene carry a higher risk to develop HLH following viral infection, suggesting that accumulation of partial genetic defects may be relevant in HLH (1).

Methods: Genes involved in pHLH were analysed with next generation sequencing (NGS) in patients with MAS in the context of different rheumatic diseases and in secHLH. We performed targeted resequencing on all patients using a panel including the 7 principal HLH-related genes (*PRF1, UNC13d, STX11, STXBP2, Rab27a, XIAP, SH2D1A*). Sequencing analysis were performed on the MiSeq® platform (Illumina, San Diego, CA); all variants identified were confirmed by Sanger. The possible functional impact of variants was studied by *in silico* analysis using SIFT and PolyPhen softwares. We took into account only variants with an allelic frequency in the global population <1%, in the dbSNP and Ensembl databases.

Results: We studied 25 patients, 20 MAS, 16 of whom developed this complication in the context of sJIA, and 4, in the context of other rheumatic diseases (vasculitis, Crohn's disease, systemic lupus erithematosus and Kawasaki disease, respectively) and 5 patients with secHLH. We identified at least 1 heterozygous variant in one of the pHLH associated genes in 14 (56%) patients: 10/20 MAS (50%), 4/5 secHLH (80%), with a detection rate of 56%. Nine patients showed variants in one gene, while variants in two or more genes were found in 5 patients. Five patients with MAS showed an heterozygous mutation in *PRF1* gene, the A91V variant was the most frequent (4), and 5 patients showed an heterozygous mutation in *UNC13d* gene. Three of the 20 MAS patients had mutations in two different genes, two of them had recurrent episodes of MAS with one presenting a severe disease with a prolonged ICU admission. Three (60%) patients with secHLH showed an heterozygous mutation of *Rab27a*, 2 of *UNC13d* gene and 1 of *PRF1*. Two of those patients had mutations in two different genes, one of them presented three episodes of HLH reactivation and the other one presented a severe disease and died. Overall patients carrying mutations in 2 genes showed higher frequency of recurrences (4/5, 80%) compared to patients carrying one mutations or no mutation (6/20, 30%) and higher frequency of severe disease (i.e. needed admission to intensive care unit or died) (4/5, 80% versus 7/20, 35%).

Conclusion: Mutations of *PRF1* and *UNC13d* genes are frequently observed in patients with MAS or secHLH; Rab27a variants may be more frequent in patients with secHLH. Re-occurrence and severe disease tend to be more frequent and more severe in patients who carry mutations in two genes. These data are consistent with a polygenic model of secHLH and MAS. **Reference.** 1. Sepulveda FE et al. *Polygenic mutations in the cytotoxicity pathway increase susceptibility to develop HLH immunopathology in mice.* Blood 2016.

Disclosure: C. Passarelli, None; **M. Pardeo**, None; **E. Pisaneschi**, None; **A. Novelli**, None; **F. De Benedetti**, Novartis, Novimmune, Hoffmann- La Roche, SOBI, AbbVie, Pfizer, 2; **C. Bracaglia**, None.

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Abstract Number: 2416

Antibodies to Citrullinated Peptides in Patients with Juvenile Idiopathic Arthritis and Rheumatoid Arthritis: Shared Expression of the Inherently Autoreactive 9G4 Idiotype

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Background/Purpose: Rheumatoid factor (RF) positive polyarticular JIA (RF+ve pJIA) frequently progresses into adulthood with a clinical phenotype that ressembles rheumatoid arthritis (RA). Antibodies to cyclic citrullinated peptides (anti-CCP) have also been detected in a high proportion of sera from patients with RF+ve pJIA. We have previously described the use of an inherently autoreactive VH (variable heavy immunoglobulin chain) by anti-CCP in patients with early and also established adult RA [1]. Immunoglobulins derived from this gene (VH4-34) can be tracked using the rat monoclonal antibody, 9G4. This study profiles RF, anti-CCP and 9G4-CCP serology of a large adolescent JIA cohort compared with that of adult patients with RA.

Methods: Serum from 88 poly-JIA, enthesitis-related arthritis (ERA;n=29), extended oligoarthritis (EOA;n= 38), 31 gender/age matched controls, 35 adult RA and 30 age-matched healthy controls (HC). IgG, IgA and IgM isotypes of anti-CCP was tested. Cut-offs for positivity were defined by manufacturer's instructions or determined with reference to known positive standards and expressed as arbitrary units (AU). RF status was determined by in-house ELISA. 9G4 expression on antibodies binding to CCP-coated ELISA plates was as previously described. A capture ELISA was used to measure serum total 9G4-IgM. Mann-Whitney U was used to compare groups and linear regression for relationships between variables.

Results: Of 88 patients with polyJIA, 65 were RF-ve with 4 (6%) positive for IgG-CCP. In RF+ve pJIA and RF+ve adult RA groups, 20/23 (87%) and 30/35 (86%) sera contained IgG-CCP respectively. 1 patient (with EOA) in adolescent patient group had IgG-CCP. Levels of IgG-CCP were similar between RF+ve pJIA and RF+ve RA but both IgA- and IgM-CCP levels were significantly lower in the adolescent group ($p<0.01$ for both). Binding of 9G4 to anti-CCP antibodies was significantly higher in the RF+ve pJIA vs RhF-ve pJIA (Median 9.8 vs 1.2; $p<0.0001$). Similar median levels of 9G4-CCP were present in RF+ve pJIA and adult RF+ve RA ($p=0.13$). 9G4 expression on serum total IgM was significantly higher in RF+ve pJIA patients compared with adult healthy control and JIA disease control groups (EOA, ERA and RF-ve pJIA all $p<0.01$), but similar to that of adult RF+ve RA.

Conclusion: This study is the first to describe the inherently autoreactive idiotope recognised by 9G4 being detected on anti-CCP antibodies in RF+ve pJIA. Restriction in VH gene usage in both JIA and RA patient immune systems may bias their immunoglobulin repertoire and be instrumental in the elicitation of anti-CCP antibodies. IgG-anti-CCP response of RF+ve pJIA and adult RA patients were similar. However, significantly higher levels of IgA- and IgM-anti-CCPs were present in adult RA patients. Interestingly, we previously showed that in adult RA with onset of <1 year, percentage of samples positive for IgM- and IgA-CCP followed, rather than preceded positivity for IgG-anti-CCP. This suggests that the emergence of IgG-antibodies to a citrullinated proteins may arise early in the underlying pathogenic process with a sequence of events not shared with conventional antibody responses to pathogens. 1.Cambridge G et al: *PloS one* 2014, 9(9):e107513.

Disclosure: H. Peckham, None; **L. Bourke**, None; **A. Radziszewska**, None; **M. J. Leandro**, None; **D. Sen**, None; **G. Cambridge**, None; **Y. Ioannou**, None.

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Abstract Number: 2417

High Dimensional Interrogation of the T Cell Immunome in Polyarticular Juvenile Idiopathic Arthritis Patients

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Background/Purpose: Clinical management of polyarticular JIA with anti-TNF-alpha has been met with moderate success, with up to 50% of patients demonstrating clinically meaningful efficacy. Concerns with medium/long term drug toxicities has driven the clinical need to find predictors for successful drug discontinuation. Based on a solid foundation of preliminary and published data, our hypothesis is that adaptive T cell immunity plays a pivotal role in the pathogenic mechanisms which determine clinical fate in JIA. To distill this pathogenic signal located within the T cell immunome, a high dimensional single cell resolution platform, CyToF, was deployed to phenotype activated antigen experienced T cells. Patients treated with anti-TNF-alpha were recruited in the Understanding TNF-alpha trial and segregated into flare, active and inactive arms after discontinuation of therapy. The central aim of the project is to identify pathogenic immune mechanisms of clinical relapse and signatures capable of distinguishing clinical fates.

Methods: Patients treated with anti-TNF-alpha biologics were recruited into the study (Improved Understanding of the Biology and Use of TNF inhibition in Children with JIA Trial) with clinically inactive disease on treatment (Wallace criteria) and initiated with therapy discontinuation. The patients are followed up and evaluated as flare, inactive and active based on 6 JIA core set parameters; number of joints with active arthritis and/or loss of motion, MD global assessment of current disease activity, patient/parent global assessment of overall disease severity in prior week, a validated measure of physical function and ESR.

Results: PBMCs from n=17 JIA patients (n= 6 flare, 5 active and 6 inactive) were stained with a 37 markers CyToF panel designed to interrogate the T cell compartment. Cluster analysis was achieved through dimensional reduction of 37 markers onto a bivariate X-Y plane via T-SNE algorithm (ACCENSE). Binary comparison of clinical fates with the clustered dimensions revealed that patients experiencing flare within 6 months of drug discontinuation, were enriched with these striking characteristics: pro-inflammatory, recently antigen stimulated, and, most importantly, pre-existing withdrawal of therapy. The phenotype comprised of $CD3^+$ $CD4^+$ memory ($CD45RA^-$) antigen experienced ($CD40L^+$, $CD69^+$) T cells, expressing co-stimulatory markers ($CD28^+$,

ICOS$^+$), immune checkpoints (CTLA4$^+$) capable of secreting high levels of TNF-alpha ($p < 0.0\ 5$). Intriguingly within the Treg compartment, CD3$^+$CD4$^+$CD25^{hi} Foxp3^{hi} CD45RA$^-$CTLA4^{hi}CD28$^+$ICOS$^+$were found to be significantly ($p < 0.05$) up-regulated in flare patients.

Conclusion: These results are striking, in our opinion, as they define some important concepts: i) Teff mechanisms which lead to clinical relapse are pre-existing withdrawal from therapy; ii) Tregs cells, are significantly elevated in patients who flare, representing probably a mechanism of overcompensation, probably ineffective due to resistance to suppression by Teff; iii) that the clinical fate is immunologically predetermined; iv) patients who achieve different clinical fates can be stratified immunologically.

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Abstract Number: 2418

Rnaseq Reveals Treatment-Associated Gene Expression Dynamics in Juvenile Idiopathic Arthritis CD4+ T Cells

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Background/Purpose: While the field of pediatric rheumatology has made enviable strides in improving the lives of children with juvenile idiopathic arthritis (JIA), there is still a great deal we do not understanding about the biology of treatment response and the achievement of remission. To gain a better understanding of how the adaptive immune system is altered during successful therapy for polyarticular JIA, we performed RNA sequencing (RNAseq) on purified CD4+ T cells during active disease and remission in a group of children with this disease.

Methods: We isolated RNA from CD4+ T cells of children with 3 distinct phenotypes: children with active, treated polyarticular JIA (ADt, n=12), children on medication who fit criteria for clinical remission by the Wallace criteria (CRM, n=10), and 10 healthy children, a control group. All JIA patients were on dual therapy with methotrexate and etanercept, and non were taking glucocorticoids. RNA sequencing was performed using the Illumina HiSeq 2500. Differentially expressed genes (DEGs) were considered with a cut-off of fold change >2.0 and false discovery rate <0.05.

Results: A comparison of ADt *vs* CRM transcripts revealed 143 differentially expressed genes, included 140 genes upregulated and 3 down regulated in the ADt group. The comparison of CRM vs. HC transcripts revealed 145 differentially expressed genes (3 up-regulated and 142 down regulated). The latter findings corroborate previous results from mixed populations of peripheral blood cells demonstrating that the CRM state is not associated with normalization of leukocyte transcriptomes. The top canonical pathways from IPA based on these DE genes (ADt vs CRM) include oxidative phosphorylation, mitochondrial dysfunction, EIF2 signaling and antigen presentation pathways. DE genes identified in the CRM vs HC comparison also included antigen presentation pathways, allograft rejection signaling, and NFAT regulation. Principle component analysis (PCA) of the expression genes in CD4+ T cells showed that ADt clearly separated with CRM. It was interesting to note, that CRM and HC subjects clustered closer together than ADt and CRM samples.

Conclusion: Our studies show that treatment response in JIA is associated with transcriptional alterations in peripheral blood CD4+ T cells. These responses involve gene regulatory networks associated with T cell activation (e.g., oxidative phosphorylation, antigen presentation). However, children who fit criteria for CRM, while phenotypically normal, have ongoing, underlying immune abnormalities.

Disclosure: K. Jiang, None; **L. P. Wong**, None; **Y. Chen**, None; **J. Jarvis**, None.

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Abstract Number: 2419

Single-Cell Analysis of CD163 mRNA and Protein Expression By Primeflow™ in Polarized Monocyte and Macrophage Populations

Rachel Tan[1], Sherry Thornton[2], Alyssa Sproles[2], Thuy Do[3], Jonathan Schick[4], Monica DeLay[4] and Grant Schulert[5], [1]University of Cincinnati, Cincinnati, OH, [2]Division of Rheumatology, Cincinnati Children's Hospital, Cincinnati, OH, [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH, [4]Cincinnati Children's Hospital, Cincinnati, OH, [5]Pediatric Rheumatology, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

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Background/Purpose: CD163 is involved in the regulation and resolution of innate inflammation and the removal of free hemoglobin from the blood via internalization of the hemoglobin-haptoglobin complex. It is also a cell surface marker of alternatively activated macrophages overexpressed in inflammatory disorders such as systemic juvenile idiopathic arthritis. To better understand the activation of myeloid cells in rheumatic disorders, a flow cytometry panel has been developed to define polarized monocyte and macrophage phenotypes. Along with detecting surface protein markers, the novel technique called PrimeFlow™ allows specific mRNA sequences to be detected at single cell resolution. This panel was utilized to define the expression of CD163 in polarized monocyte and macrophage populations.

Methods: A human monocytic cell line, THP-1, was cultured and stimulated in vitro with LPS and IFN-gamma, IL-4, LPS and IgG, TGFβ, or IL-10 toward M1, M2a, M2b, and M2c phenotypes, respectively. The cells were stained using the fluorochrome conjugated antibodies CD14-Pacific Blue, CD16-BV711, CD80-BV786, CD64-AF700, CD209-FITC and CD163-PE. Each condition also was stained for CD163 mRNA using the PrimeFlow™ kit's branching technology. Cells were acquired using an analytical cytometer, and data were analyzed by FACSDiva software.

Results: PrimeFlow™ staining of CD163 mRNA could reliably detect increased CD163 expression in THP-1 monocytic cells, primary CD14+ blood monocytes, and monocyte-derived macrophages. The PrimeFlow™ CD163 mRNA probe was also used simultaneously to detect protein surface markers, and this flow cytometry panel provided the same degree of positively stained cells as the results of staining for individual cell surface markers without mRNA labeling. This combined panel demonstrated that some alternatively activated populations, such as M2a (IL-4 conditions), show an increase in CD163 surface protein expression with no change in CD163 mRNA levels. In marked contrast and in agreement with qPCR data, increase in both CD163 mRNA and protein levels is limited to the IL-10 stimulated M2c conditions. The PrimeFlow™ technique was determined to be highly sensitive for increased mRNA expression, with a strong signal over a broad range of IL-10 concentrations in contrast to qPCR data and surface protein detection. The kinetics of CD163 induction with IL-10 stimulation were shown to be similar for both mRNA and protein. There is minimal increase in both mRNA and protein expression after 5 hours of stimulation, but significant increase after 24 hours.

Conclusion: PrimeFlow™ is a robust and sensitive system for RNA flow cytometry, and useful for studying CD163 expression in myeloid cells. CD163 shows distinct patterns of expression in different polarized populations. At single cell resolution, CD163 protein and mRNA levels increased in IL-10 stimulated M2c cells. This flow cytometry panel consisting of CD14, CD16, CD64, CD80, CD163, and CD209 cell surface markers can be used to identify different populations

of activated monocytes and macrophages in a broad range of inflammatory disorders.

Disclosure: R. Tan, None; **S. Thornton**, None; **A. Sproles**, None; **T. Do**, None; **J. Schick**, None; **M. DeLay**, None; **G. Schulert**, Novartis Pharmaceutical Corporation, 5.

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Abstract Number: 2420

Investigating Genome-Wide Inbreeding Coefficients and Age of Diagnosis in a Multi-Ethnic Population of Childhood-Onset Systemic Lupus Erythematosus (cSLE)

Chen Di Liao[1], Deanna Morra[1], Daniela Dominguez[1], Shazia Ali[1], Deborah M. Levy[2], Earl Silverman[3], Andrew Paterson[1] and **Linda T Hiraki**[1], [1]The Hospital for Sick Children, Toronto, ON, Canada, [2]Division of Rheumatology, The Hospital for Sick Children, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada

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Background/Purpose: Genetics plays an important role in the pathogenesis of systemic lupus erythematosus (SLE). Up to 20% of those affected with SLE are diagnosed in childhood or adolescence. There is evidence for a higher burden of SLE susceptibility loci in those diagnosed in childhood compared to adulthood. This higher genetic burden in children may in part be attributable to consanguinity in prior generations. We hypothesized that higher coefficients of inbreeding are associated with younger age of SLE diagnosis and family history of SLE.

Methods: We included children diagnosed and followed for cSLE at The Hospital for Sick Children Lupus Clinic, Toronto (≥ 4/11 ACR classification criteria and/or ≥ 4/17 SLICC classification criteria) between1982-2014. Participants were genotyped on the Illumina Immunochip. Standard quality control methods were performed including sex inconsistency and filtering low call rates (<95%). We completed principal components (PC) analyses seeding our population with the 1000 genomes project data, to generate PCs, remove outliers and to define ancestral groups (European, African, East Asian, South Asian). Inbreeding coefficients were

calculated for each child (FSuite), stratified by ancestral group. We tested the association between inbreeding coefficients and age of SLE diagnosis using linear regression models, and with family history of SLE using logistic models.

Results: Of the 389 subjects, 8 failed QC, and 23 outliers were removed from PC analyses. A total of 358 cSLE contributed to analyses. The median age of diagnosis was 13.4 (IQR10.9 – 15.1) years and the mean inbreeding coefficient was 0.05% (IQR 0.01% – 15.4%). One percent of cohort had an inbreeding coefficient comparable to the expected proportion for 1st cousins (12.5%). We did not observe a statistically significant association between the inbreeding coefficient and age of diagnosis, adjusting for ancestry (beta = 0.15, SE 0.1 years, p-value = 0.12) nor with family history of SLE (OR = 0.93, 95% CI 0.77, 1.12).

Conclusion: We did not observe a significant association between inbreeding coefficients and age of SLE diagnosis nor with family history of SLE. Our inbreeding coefficients were low in our cohort, limiting our power to detect an association with age or family history. Replication and meta-analyses in independent cohorts are planned next steps for validating our findings.

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Abstract Number: 2421

Cell-Bound Complement Activation Products Correlate with Disease Activity in Childhood-Onset Systemic Lupus Erythematosus

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Background/Purpose: Elevated levels of cell-bound complement activation products (C4d deposition on erythrocytes [EC4d] and B lymphocytes [BC4d], CB-CAPs) have been demonstrated to be sensitive and specific for the diagnosis of systemic lupus erythematosus (SLE) and C4d deposition on platelets (PC4d) to be specific for the diagnosis of SLE. We sought to evaluate the usefulness of CB-CAPs as a biomarker for disease activity in childhood-onset SLE (cSLE).

Methods: This is a longitudinal study of 28 patients with cSLE (diagnosed prior to their 19th birthdays) who fulfilled ACR-SLE classification criteria, with a mean follow-up of 6 months. Clinical and demographic data were recorded. Venous blood was collected every 3 months and shipped overnight to the reference clinical laboratory for the multi-analyte assay. The assay evaluates a full panel of autoantibodies, including anti-dsDNA, aPLs (beta-2 glycoprotein antibodies, aCL, and/or aPS-PT) and conventional serum complement levels (C3 and C4), as well as CB-CAPs; CB-CAPs results are reported as net mean fluorescence intensity (MFI). SpearmanÕs correlation was used to evaluate the correlation between CB-CAPs and disease activity scores; t-tests to evaluate the presence of CB-CAPs in APL patients.

Results: Clinical and demographic variables are presented in the Table. Mean SLEDAI was 4.3±3.8 (range 0-16). Elevated CB-CAPs correlated with SLEDAI scores in cSLE patients (r^2 range 0.23-0.38, $p<0.05$ for EC4d, BC4d, and PC4d, respectively) at baseline, 3 and 6 months. Higher levels of EC4d (>75 net MFI) were found to have better correlation with disease activity scores at all time-points ($p<0.05$). Additionally, in 11 cSLE patients with positive aPLs CB-CAPs were significantly elevated with $p<0.05$ for EC4d, but $p=0.06$ for BC4d and $p=0.15$ for PC4d; of note, C3 and C4 did not correlate with the presence of aPL in these patients (p=NS). Interestingly, several patients had normal levels of C3 and C4, but elevated CB-CAPs, possibly indicating fluctuating complement activation that was not captured by C3 and C4 measurements.

Conclusion: These pilot findings suggest that CB-CAPs could provide a useful biomarker for disease activity in cSLE, and may be particularly important in the monitoring of SLE patients with anti-phospholipid antibodies. Further longitudinal data is needed to establish CB-CAPs as a biomarker in cSLE and APS. Table: Patient demographics and results of CB-CAPs assays

	SLE (n=28)
Age (years)	18±2
Female %	75%
Duration of disease (years) Mean SLEDAI	4.7±3.2 4.3±3.8 (range 0-16)
Low Complement	50% (14/28)
ANA (IFA: ³1:80)	93% (26/28)
Anti-dsDNA (confirmed with Crithidia)	54% (15/28)
Anti-Smith	18% (5/28)
EC4d>14 net MFI	57% (16/28)
BC4d>60 net MFI PC4d>20 net MFI	63% (17/27) 29% (8/28)
Elevated CBCAPS (EC4d>14 net MFI, BC4d>60 net MFI, or PC4d >20 net MFI)	82% (23/28)

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Abstract Number: 2422

Cyclic Amp, Erk5, and Transdifferentiation of Cardiac Fibroblasts in the Pathogenesis of Autoimmune Congenital Heart Block

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Background/Purpose: Maternal autoantibodies (Ab) reactive with the Ro/La ribonucleoprotein complex are associated with the development of cardiac injury in a fetus passively exposed to these Ab. This study evaluated the irreversible scarring phenotype characteristic of heart block involving the mitogen activated protein kinase (MAPK) pathway and its regulation by cAMP.

Methods: The aorta from a healthy 2nd trimester fetal heart was cannulated using a Langendorff preparation with the addition of proteolytic enzymes to yield a single cell suspension of primary human fetal cardiac fibroblasts. Cultured cells were treated with secreted products generated from activated macrophages with or without BIX 02189 (10uM, a specific MEK5/ERK5 inhibitor) and forskolin (10uM to raise cAMP). After RNA isolation and cDNA library preparation, RNA-Seq, transcriptome analysis (Data as log2 transcripts per million) and qPCR were performed.

Results: Incubation of fibroblasts with supernatants from macrophages transfected with hY3 (ssRNA associated with Ro60), shown to induce a pro-fibrotic phenotype, resulted in the increased expression of 3836 genes. Based on DAVID functional annotation, the top clusters represented were Actin Binding, Cytoskeletal Protein Binding, Cell Adhesion, Signal Peptide, and Contractile Fiber, all processes considered typical of the myofibroblast phenotype. In addition, RAPGEF3, an endogenous ERK5 inhibitor, and Adrenomedullin, which increases cAMP, were downregulated while PDE4D, an inhibitor of cAMP generation, was upregulated (Table 1). These data are consistent with previous literature supporting the association of lowered intracellular cAMP and upregulation of pro-fibrotic genes. Given that cAMP attenuates the activity of ERK5, BIX 02189 was used to evaluate the transcriptome. Of the 3836 genes upregulated by hY3 macrophage supernatants, 617 were reversed by the subsequent addition of BIX. Among the upregulated genes were pro-fibrosing genes such as EDN1 and TGFβ2 and among those downregulated were genes that resist fibrosis including CLU, RAPGEF3, and ADM. The latter two are associated with a cAMP dependent inhibition of ERK5 and increased cAMP, respectively. The pro-fibrosing EDN1 result was confirmed by qPCR and as expected was attenuated by forskolin.

Conclusion: These data support that the link of anti-Ro immune complex activated macrophages and the pathogenic fibroblast phenotype may relate to a decrease in cAMP levels. These results highlight potential novel targets for therapy and solidify the role of ERK5 in the transdifferentiation of fetal fibroblasts in the context of congenital heart block.

Table 1

Gene Symbol	hY3 macrophage supernatants	Untreated
Genes that promote fibrosis		
EDN1*	11.1**	9.5
TGFB2*	13.7	12.7
PDE4D	8.4	6.9
Genes that resist fibrosis		
CLU*	10.8	12.4
TIMP1	12.9	14.3
MEST	12.5	13.2
RAPGEF3*	3.5	6.5
ADM*	6.0	6.9

*ERK5 dependent, ** Units,log2(average of transcripts)

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Abstract Number: 2423

Differential Interferon Score Expression in the Peripheral Blood in Mendelian Inflammatory Interferonopathies Versus Juvenile Dermatomyositis (JDM) Subtyped By Myositis Autoantibodies and Disease Activity

Hanna Kim[1], Terrance P. O'Hanlon[2], Adriana Almeida de Jesus[3], Yan Huang[3], Ira N. Targoff[4,5], Frederick W. Miller[2], Raphaela Goldbach-Mansky[6] and Lisa G. Rider[2], [1]NIAMS/NIH, Bethesda, MD, [2]Environmental Autoimmunity Group, NIEHS, NIH, Bethesda, MD, [3]National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD, [4]Oklahoma Medical Research Foundation, Oklahoma City, OK, [5]University of Oklahoma, Oklahoma City, OK, [6]Translational Autoinflammatory Disease Studies, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD

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Background/Purpose: JDM is a complex autoimmune disease with an interferon (IFN) signature, with a reported correlation with disease activity. Clinical features vary among myositis-specific autoantibody (MSA) groups, but partially overlap with 2 genetically defined autoinflammatory syndromes, Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE) caused by mutations in proteasome genes and Sting-Associated Vasculopathy with onset during Infancy (SAVI) caused by mutations in *TMEM173/* STING. The comparison of an IFN score in JDM versus CANDLE and SAVI may help elucidate the role of IFN in JDM. Evaluation of IFN scores by MSA group and disease activity in JDM may pilot their potential as biomarkers.

Methods: A standardized 25 gene IFN score (IFN_s) previously developed in CANDLE patients (H. Kim, A&R 2014) was assessed in JDM patient RNA extracted from whole blood using the Nanostring nCounter gene expression system (Seattle, WA). JDM sera were characterized for MSAs by validated immunoprecipitation and immunoblotting methods; physician global disease activity (PGA) was clinically assessed on a visual analog scale. CANDLE and SAVI samples were positive IFN-mediated disease controls. Non-IFN controls were NOMID (IL-1 mediated autoinflammatory monogenic disease) and healthy controls (HCs). Nonparametric tests were used for non-normally distributed data; MSA group analysis was done if n>5. IFN score comparisons among disease groups and MSAs were performed by Mann-Whitney test. Spearman correlation was performed between PGA versus IFN_s for JDM, and by MSA group.

Results:

IFN Score

A. Diagnosis	n	median	25th %ile	75th %ile
JDM	57	34.4	1.3	225.8
HC	18	-6.2	-11.0	0.7
NOMID	19	-12.2	-14.6	-1.7
CANDLE	11	476.7	311.1	812.2
SAVI	7	497.0	345.7	701.1
B. MSA group	**n**	**median**	**25th %ile**	**75th %ile**
TIF1	20	36.6	-4.6	158.8
MDA5	9	131.7	29.5	382.2
MJ	9	29.7	-0.2	368.4
MSA-neg	9	169.8	7.1	340.2

Table 1: 25 gene IFN Score by (A) diagnosis and (B) JDM mysotis-specific antibody (MSA) groups with n>5.

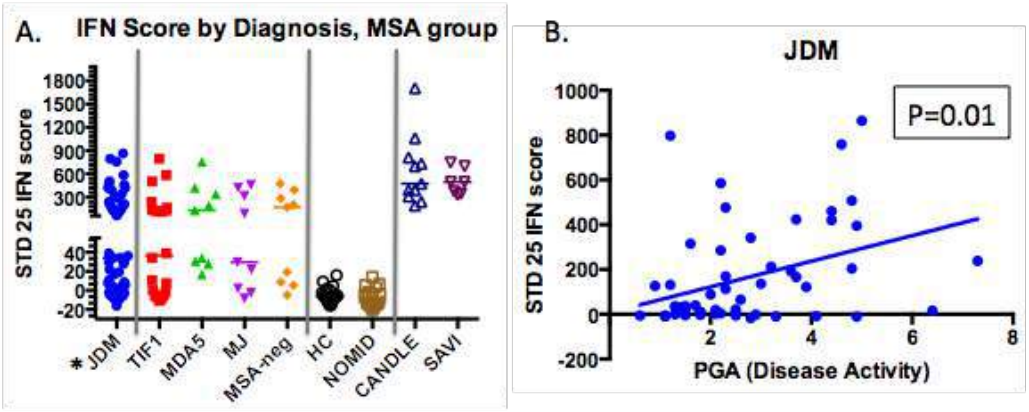

Figure 1. A. Standardized 25 gene IFN score (IFN_s) is plotted for JDM, then subtyped by 4 myositis-specific antibody (MSA) groups with n>5, non-IFN controls (Healthy controls and NOMID), and then Mendelian IFN positive controls (CANDLE and SAVI). Horizontal lines indicate medians. * P value is less than 0.001 for JDM versus each other diagnosis group (HC, NOMID, CANDLE, SAVI).
B. Interferon score is plotted versus physician global disease activity (PGA) on a visual analog scale of 0-10. Spearman r coefficient is 0.34 with a 95% confidence interval of 0.08-0.55.

JDM IFN_s was significantly lower than CANDLE and SAVI and significantly higher than HCs and NOMID (Table 1, Figure 1A). IFN_s was higher in MDA5 and MSA-neg groups (compared to anti-TIF1, MJ), but was not statistically significant. The 4 MSA groups remained significantly higher than HC and NOMID and significantly lower than CANDLE and SAVI. PGA (median 2.3, IQR 1.5-3.7) correlated significantly with IFN_s in JDM overall (Figure 1B), though correlation of IFN_s with PGA was not significant within the MSA groups analyzed.

Conclusion: Though JDM IFN_s is significantly higher than HCs and NOMID, it is significantly lower than CANDLE and SAVI, indicating IFN may not be the sole driver of pathogenesis in JDM. PGA does correlate with IFN score as a potential biomarker. No significant differences were found among MSA groups but further study is needed to identify what factors affect the IFN_s in JDM.
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Abstract Number: 2424

Novel Autoantigens for Anti- Endothelial Cell Antibodies in Pediatric Rheumatic Diseases Identified By Proteomics

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Background/Purpose: Juvenile dermatomyositis (JDM), a systemic autoimmune vasculopathy, and juvenile idiopathic arthritis (JIA) are representative rheumatic diseases in children. However the pathogenesis of these diseases are still poorly defined. More research in this area is required on identification of disease-specific biomarkers for clinical assessment. Anti-endothelial cell antibodies (AECA) have been detected in rheumatic diseases such as vasculitis. We aimed to detect target antigens for AECA in patients with pediatric rheumatic diseases comprehensively by proteomics and to investigate their clinical significance.

Methods: To comprehensively detect target antigens for AECA, we separated proteins extracted from human aortic endothelial cells by two-dimensional electrophoresis and then transferred them onto membranes. Autoantigens that were positive only in pediatric rheumatic disease sera from three patients with JDM and two patients with JIA but not in healthy children sera were detected by western blotting. The detected proteins were identified by peptide mass finger-printing. Bound IgG antibodies to antigens were detected using standard methods.

Results: We successfully identified 738 proteins out of eighteen protein spots that were candidate targets of AECA in pediatric rheumatic diseases. Antibodies appeared to target proteins with specific functions, e.g., ATP-related proteins (37%), muscle-related proteins (19%), calcium regulated protein and/or calcium binding proteins (13%) and redox related proteins (10%). Among the 140 muscle-related proteins were myosin light polypeptide 6 (MYL6) and myosin-9 (MYH9). IgG autoantibodies to MYL6 were detected in 20% of the patients with JDM (n=61) using ELISA assays. However, 50% of the untreated JDM patients with active disease (n=10) had anti-MYL6 antibodies, in contrast to 12% ($p<0.05$) of the patients with JIA (n=17) and in 16% ($p=0.05$) of control children (n=25). IgG autoantibodies to MYH9 were detected in 31% of the active patients with JDM (n=35), (50% of the untreated JDM patients with active disease), in comparison to 27% of the patients with JIA (n=15) and 12% ($p<0.05$) of control children. Among the 74 redox related proteins were peroxiredoxins (Prxs). IgG autoantibodies to Prx2 were detected in 24% of the active patients with JDM (n=25), (30% of the untreated JDM patients with active disease) and in 20% of the active patients with JIA (n=10), (40% of the untreated JIA patients with active disease) in contrast to 0% ($p<0.05$) of control children (n=20). Furthermore one of the identified 738 proteins was Von Willebrand Factor (vWF). IgG autoantibodies to vWF were detected in 20% of the active patients with JIA (40% of the untreated JIA patients with active disease), in comparison to 4% of the active patients with JDM and 0% of control children.

Conclusion: IgG antibodies to MYL6, MYH9, Prx2 and vWF were detected in the sera from

patients with pediatric rheumatic diseases, respectively. These antibodies were directed against autoantigens correlated with skeletal muscle function, redox functions and the coagulation/fibrinolytic systems and may be useful markers for pediatric rheumatic diseases.

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The Vasculopathy of Juvenile Dermatomyositis (JDM); Evidence of Persistent Endothelial Injury, Hypercoagulability, Subclinical Inflammation and Increased Arterial Stiffness

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Background/Purpose: Vasculopathy is considered central to the pathogenesis of Juvenile Dermatomyositis (JDM). The interplay between persistent JDM-vasculopathy, traditional cardiovascular risk factors, exposure to corticosteroids, and chronic inflammation could create a perfect storm for early atherogenesis. A major hurdle to the study of vasculopathy of JDM, monitoring of its trajectory over time and contribution to cardiovascular disease has been a lack of non-invasive biomarkers. Recently, we described 2 methods for detecting endothelial cell components in blood: circulating endothelial cells (CEC), and endothelial microparticles (EMP). We aim therefore to explore the vasculopathy of JDM by assessing: (i) biomarkers of endothelial injury (CEC and EMP), subclinical inflammation (cytokines) and hypercoagulability (MP-mediated thrombin generation); and (ii) structural arterial changes (indicative of premature atherosclerosis), and their relation to disease activity and treatment in children with JDM.

Methods: 64 patients recruited to the UK JDM Cohort & Biomarker Study were included; median age 10.5 (range 6.9 – 13.7) years with median disease duration of 1.5 (0.3-4.7) years. 40 (62.5%) were females. Inactive disease was defined as per modified PRINTO criteria: no skin rashes, CK≤150, CMAS≥ 48, MMT8≥78, Physician ‘s global assessment ≤0.2 on a visual analogue scale. CECs and MPs were identified with immunomagnetic bead extraction and flow cytometry, respectively. MP-mediated thrombin generation was determined using a fluorogenic assay. Cytokines and chemokines were measured by electrochemiluminiscence. Arterial stiffness was assessed using pulse wave velocity (PWV).

Results are expressed as median and range. Results:CECs were higher in JDM patients at 68 (32-128) cell/ml compared to 12 (8-21) cells/ml in 66 age-sex matched healthy controls, $p<0.0001$. Patients with active JDM had higher CEC than those with inactive JDM, $p=0.02$. CEC counts significantly correlated with levels of inflammatory cytokines/chemokines implicated previously in JDM disease pathogenesis: interferon regulated Monocyte Chemoattractant Protein-1 (MCP-1; $r=0.63$, $p=0.02$) and interleukin-8 (IL-8; $r=0.65$ and $p=0.01$). Total circulating MP counts were also significantly higher in active JDM, 1781 (981-2616) $x10^3$/ml compared to inactive JDM, 1116 (263-1393) $x10^3$/ml, $p=0.02$; and healthy controls 89 (25-236) $x10^3$/ml, $p=0.0001$. These circulating MPs were predominantly of platelet and endothelial origin. Enhanced MP mediated thrombin generation was demonstrated in active compared to inactive JDM ($p=0.03$) and controls ($p=0.001$). Lastly, children with JDM had increased carotid-radial PWV adjusted for age compared to healthy controls ($p=0.005$).

Conclusion: Our data demonstrate: 1. Increased endothelial damage in children with active JDM, possibly driven by pro-inflammatory cytokines; 2. High levels of circulating MP with propensity to drive thrombin generation and hence occlusive vasculopathy; and 3. Increased arterial stiffness, suggestive of accelerated atherosclerosis in patients with JDM. Validation of these biomarkers in multicentre prospective studies will provide data regarding their prognostic relevance.

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Abstract Number: 2426

Transcriptomic Analysis of Immune Subsets in Juvenile Dermatomyositis before and after Treatment Identifies Novel Pathways Involved in Pathogenesis

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Background/Purpose: Although proximal muscle weakness and skin rash are the typical features of juvenile dermatomyositis (JDM), little is known about disease pathogenesis, why other features develop, or why patients have differential responses to therapy. In complex diseases like JDM, large scale genomics and systems biology approaches may enable insight into dysregulated pathways involved in pathogenesis, and could lead to a more rational therapeutic approach.

Methods: Peripheral blood samples were obtained from patients enrolled in the Juvenile Dermatomyositis Cohort and Biomarker Study (JDCBS) at pre-treatment (n=13) and 11.8 [11.3-13.2] months post-treatment (n=13), including n=10 matched samples. CD4, CD8, CD14 and CD19 cells were sorted from PBMC by flow cytometry and RNA prepared for RNA-seq. Samples were

sequenced with 17.0 [14.5-18.5] million reads. Raw sequence reads were aligned to hg38 with TopHat and aligned reads processed using Picard tools and summarized by featureCounts. Differential expression analysis was performed using the edgeR package in R. Gene set enrichment analysis was performed using GSEA and the hallmark collection of gene sets. Over-represented gene sets are reported with the absolute value of the normalized enrichment score and Benjamini-Hochberg-adjusted q-value.

Results: Across all subsets, when pre-treatment samples were compared to post-treatment samples, GSEA uncovered over-representation of gene sets involved in "INTERFERON_ALPHA_RESPONSE" (2.8, $p<0.001$ for CD4; 2.8, $p<0.001$ for CD8; 3.2, $p<0.001$ for CD19; 3.3, $p<0.001$ for CD14) and "INTERFERON_GAMMA_RESPONSE" (2.6, $p<0.001$ for CD4; 2.7, $p<0.001$ for CD8; 2.6, $p<0.001$ for CD19; 3.1, $p<0.001$ for CD14). When post-treatment samples were compared to pre-treatment samples, gene sets over-represented across all subsets included "TNFA_SIGNALING_VIA_NFKB" (2.4, $p<0.001$ for CD4; 2.2, $p<0.001$ for CD8; 3.0, $p<0.001$ for CD19; 2.3, $p<0.001$ for CD14), and "HYPOXIA" (2.0, $p=0.004$ for CD4; 1.95, $p=0.002$ for CD8; 2.3, $p<0.001$ for CD19; 1.7, $p=0.016$ for CD14). Additionally, some pathways differed between cell types in over-representation either pre- or post-treatment. "IL6_JAK_STAT3_SIGNALING" was over-represented at pre-treatment in CD4 (2.1, $p<0.001$) and CD8 cells (2.1, $p<0.001$), but over-represented at post-treatment in CD19 cells. Similarly, the "COMPLEMENT" and "INFLAMMATORY RESPONSE" gene sets were over-represented pre-treatment in CD4 (1.7, $p=0.005$; and 2.0, $p=0.005$, respectively), CD8 (1.8, $p=0.005$; and 1.8, $p=0.005$, respectively) and CD14 cells (1.3, $p=0.03$; and 1.4, $p=0.02$, respectively), but over-represented at post-treatment in CD19 cells (1.4, $p=0.03$; and 1.9, $p<0.001$, respectively).

Conclusion: This study has identified several pathways that are altered during the first year of treatment of JDM. In addition to confirming involvement of the type 1 interferon pathway in active JDM disease, the purified subset approach enables identification of pathways that differ between immune subsets. Ongoing analyses are comparing pre- and post-treatment samples to age- and sex-matched healthy controls and investigating pathways associated with different clinical courses.

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Abstract Number: 2427

Identification of Biomarkers Using Tear Proteomics in Children with Chronic Anterior Uveitis

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Background/Purpose: Children with juvenile idiopathic arthritis (JIA) are at risk for anterior uveitis which can lead to ocular complications and vision loss. The ANA is the only biomarker that guides the schedule of uveitis screening, but it is not definitive. Potential biomarkers have been identified in the serum and aqueous humor of children with JIA-associated uveitis (JIAU) and idiopathic uveitis. However, few studies have examined protein levels in the tears of children with chronic anterior idiopathic uveitis (CAU) and JIA-associated uveitis (JIAU). Tear collection is non-invasive, easily accessible and better tolerated by children. Our aim is determine if we can identify biomarkers using tear proteomics in children with anterior uveitis.

Methods: We collected tear samples from 2 pediatric female controls, 2 JIAU (oligoarticular) and 2 CAU. Children with uveitis were ≥10 years old, non-Hispanic, female, and had anterior involvement. We placed a Schirmer strip 6mm from the lateral canthus of the anesthetized eye for 2-5 minutes. Then, 50 ug of proteins were extracted for TMT labeling. The TMT pool was loaded onto an offline electrostatic repulsion interaction chromatography (ERLIC) fractionation HPLC system and 20 fractions were collected. LC-MS/MS analysis was then performed on all 20 fractions. Proteome Discoverer 2.1 (ThermoFisher Scientific, San Jose, CA) was used to search all the MS/MS spectra against a Uniprot human reference protein database (retrieved April 20, 2015; 90,411 target sequences) and TMT reporter quantitation was performed. We compared JIAU and IU to controls, and JIAU to IU using ANOVA statistics.

Results: In all, we were able to quantify 1224 unique protein groups and found 120 proteins that showed significant statistical changes. Of those differentially expressed proteins, 19 were significant across JIAU versus control and IU versus control, but not between JIAU and IU. The most significant included RAB7A ($p = 1.23E-03$), NPC2 ($p = 1.23E-02$), VPS4B ($p = 3.05E-03$), CTSS ($p = 2.02E-02$), and ASAH1 ($p = 1.19E-02$). The gene ontology showed cellular component enrichment for lytic vacuole and biological pathway enrichment for sterol transport and transmembrane receptor signaling.

Conclusion: In our pilot study, we identified proteins that may be specific to pediatric chronic anterior uveitis. Our next step is to validate in larger cohorts of children with anterior uveitis, and to compare the tear proteomic profile of children with JIA alone. Tear proteomic analysis is a promising area since tear collection is non-invasive and can be used to examine children with JIA who do not have uveitis. Discovery of biomarkers for screening and early detection of uveitis in

children with JIA will help us identify those at highest risk for ocular disease.

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Autoantibody Diversity in Pediatric Patients Undergoing Evaluation for Autoimmune Encephalitis: A Retrospective Investigation

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Background/Purpose: Antibodies directed against N-methyl-D-aspartate type glutamate receptor (NMDAR), voltage-gated potassium channel (VGKC) or glutamic acid decarboxylase (GAD65) are frequently associated with autoimmune encephalitis (AE) in pediatric patients. Yet, the full repertoire of the autoantibody diversity in children remains poorly defined.

Methods: Eighty-eight consecutive patient samples (59 sera and 29 CSF) received at ARUP Laboratories from Intermountain Healthcare's Primary Children's Medical Center, Salt Lake City, Utah and Texas Children's Hospital, Houston, Texas for evaluation for NMDAR (cell based assays, CBA), VGKC (radioimmunoprecipitation), or GAD65 (enzyme immunoassay) antibodies were identified over a period of 12 months. Residual volume of patient samples were evaluated on a research basis by indirect immunofluorescence technique (IIFT) using cerebellum (monkey and rat), intestine (monkey), peripheral nerve and pancreas tissue sections for neuronal nuclear, Purkinje cell cytoplasmic, myelin, non-medullated and astrocyte autoantibodies (PNS Mosaic IFFT), and an CBA for Delta notch-like epidermal growth factor-related receptor (DNER). In addition, the AE mosaic

IIFT with hippocampus (rat) tissue and CBA to detect antibodies to NMDAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), gamma amino butyric acid type B receptor ($GABA_bR$), leucine-rich glioma inactivated 1 (LGI1), contactin associated protein-2 (CASPR-2), dipeptidyl-peptidase-like protein-6 (DPPX-6), and glycine receptor (GlyR) was utilized. This study was conducted in accordance with a University of Utah Institutional Review Board approved protocol and in compliance with ARUP policies.

Results: Samples were received from 60 unique patients including 32 females (median age 11.8; range 0-19 years) and 28 males (median age 9.0; range 0-18 years). Antibodies were detected in 30/60 patients (50%); 23 with single antibodies and 7 subjects with 2 or more antibodies. NMDAR antibody was the most prevalent (n=15) followed by GAD65 (n=7), VGKC (n=6), non-medullated (n=4), Purkinje cell (n=3), myelin (n=3), and astrocyte (n=1) antibodies. Of the 28 patients with paired serum and CSF, 16 possessed autoantibodies; 8 NMDAR-positive (7 seropositive, 8 CSF positive), and 5 GAD65- and 4 VGKC-seropositive only. Eighty percent (24/30) of the antibody-positive patients in our cohort had NMDAR, GAD65 and/or VGKC antibodies; however, a sizable number of patients possessed autoantibodies not typically associated with pediatric AE.

Conclusion: Overall, NMDAR, GAD and VGKC autoantibodies were the most prevalent antibodies detected in this two center pediatric cohort of samples analyzed at a large referral lab. Prevalence of these antibodies approximates previous reports in the pediatric literature. Additional autoantibodies targeting diverse proteins and associated neurologic functions were also detected demonstrating a need for the validation of additional markers for pediatric AE such as the Purkinje cell and nerve (i.e. non-medullated nerve and myelin) autoantibodies detected in this cohort of patients.

Disclosure: A. E. Tebo, None; **T. Haven**, None; **A. O. Hersh**, None; **E. Muscal**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/autoantibody-diversity-in-pediatric-patients-undergoing-evaluation-for-autoimmune-encephalitis-a-retrospective-investigation

Abstract Number: 2429

Mechanisms for the Development of Lung Fibrosis in Sting-Associated Vasculopathy with Onset in Infancy (SAVI)

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Background/Purpose: STING-Associated Vasculopathy with Onset in Infancy (SAVI) is a monogenic autoinflammatory interferonopathy caused by gain-of-function mutations in *TMEM173/STING*, a nucleic acid sensor adaptor linked to IFNβ transcription. Patients (Pts.) develop acral vasculitis and variable severity of interstitial lung disease (ILD)(Liu Y, NEJM, 2014). We hypothesized that a common STING variant modulates lung disease severity, and investigated a mechanistic role of STING in ILD.

Methods: We assessed chest computed tomography (CT) and pulmonary function tests (PFTs) in 12 SAVI pts. (*N154S, V155M, V147L, V147M*); lung biopsies were available for 7 pts. DNA samples were typed for the *STING* SNP R232H, rs1131769 (Yi G, PLoSOne 2013). Transfection studies in HEK293T cells with wildtype or "SAVI mutations" constructs on the R232 and H232 haplotypes, and stimulations of pt. fibroblast and endothelial cell lines (HUVECs) were performed. *IFNB1*luciferase reporter activity was assessed upon stimulation with the endogenous: 2'3'cGAMP, or the microbial: 3'3'cGAMP, c-di-AMP and c-di-GMP, STING activators. Gene expression (q-

RT-PCR, RNA-seq), cytokine production, and endothelial-mesenchymal transition (endo-MT, by cell morphology and gene expression studies), were assessed.

Results: The presence of R232 in *cis* with the disease-causing STING mutations is associated with severe lung disease. Of 9 pts. with severe ILD, 4 pts. succumbed to pulmonary complications; all but one were homozygous for R232/R232. The pt. with no ILD was homozygous for the H232 allele (H232/H232); 2 pts. with mild ILD were heterozygous (R232/H232) for the SNP. Transfection of HEK293T cells with mutant STING on the R232 and H232 haplotypes showed increased *IFNB1* expression upon stimulation with microbial stimulants but not endogenous cGAMP; which was only significant when the SAVI mutations were on the R232 but not on the H232 haplotype. Similarly, *IFNB1*transcription in response to exogenous stimuli in fibroblasts from 4 pts. were higher in cells with R232/R232 than in cells with H232/H232 haplotype. RNA-seq of stimulated pt. and control fibroblasts showed no expression of myofibroblast and extracellular matrix (ECM) markers ruling out that STING pathway activation would induce myofibroblast-differentiation as a mechanism for pulmonary fibrosis. Trichrome stains of SAVI lung tissues (n=2) revealed localized fibrosis around the pulmonary vessels, suggesting that STING pathway activation may induce endo-MT. Endogenous cGAMP stimulation on endothelial cells induced morphologic transition to fibroblasts with increased expression of the mesenchymal marker αSMA and the pro-fibrotic markers SLUG and TWIST. EndoMT was TGFβ independent and not induced by microbial STING stimuli. However, IFNβ significantly increased the endo-MT process over 2'3'cGAMP stimulation alone.

Conclusion: The minor allele H232 of a STING SNP confers a protective role by mitigating IFNβ responses in the context of STING activating infections while the R232 haplotype accelerates endo-MT amplified by IFNβ. Our findings suggest a novel mechanism for inducing endo-MT as a cause for the development of lung fibrosis in SAVI through endogenous STING activation.

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Abstract Number: 2430

Mutations in the Tyrosine-Protein Kinase Lyn Cause an Early-Onset Neutrophilic Vasculitis Syndrome

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Brundidge[7], David Kleiner[8], Stephen Hewitt[8], Dawn C. Chapelle[7], Yan Huang[1], Nirali Shah[8], Stephen Brooks[7], Eric Meffre[9], Paul Brogan[10], Hyesun Kuehn[11], Sergio Rosenzweig[12], Melinda Merchant[8], Zuoming Deng[7], Susan Moir[13] and Raphaela Goldbach-Mansky[14], [1]National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD, [2]Raigmore Hospital, Inverness, United Kingdom, [3]Royal Hospital for Children, Glasgow, United Kingdom, [4]University College London Institute of Child Health, London, United Kingdom, [5]Department of Laboratory Medicine, Hematology Section, National Institutes of Health Clinical Center, Bethesda, MD, [6]Dermatopathology Section, Laboratory of Pathology, National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD, [7]NIAMS/NIH, Bethesda, MD, [8]National Cancer Institute, NIH, Bethesda, MD, [9]Department of Immunobiology, Yale University School of Medicine, New Haven, CT, [10]UCL Institute of Child Health and Great Ormond Street Hospital NHS Foundation Trust, London, United Kingdom, [11]Department of Laboratory Medicine, Clinical Center, National Institutes of Health, Bethesda, MD, [12]Department of Laboratory Medicine/NIH, Bethesda, MD, [13]National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, [14]Translational Autoinflammatory Disease Studies, National Institute of Allergy and Infectious Diseases (NIAID), NIH, Bethesda, MD

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Background/Purpose: Tyrosine-protein kinase Lyn is a Src-family tyrosine kinase expressed by hematopoietic and non-hematopoietic cell types. Phosphorylation of a tyrosine residue at position 508 renders the molecule inactive. In a mouse model, amino acid modification Y508F causes severe anemia, autoimmune glomerulonephritis and positive ANA ($Lyn^{up/up}$ mice) but the human phenotype and its role in human disease remain unkonwn. We characterize the clinical phenotype and cellular function of mutant Lyn kinase in two patients with systemic inflammation and vasculitis both presenting with a *de novo* germline mutation at the regulatory tyrosine residue 508 in *LYN*.

Methods: Patients were clinically evaluated, records were reviewed, WES (Illumina HiSeq2000 platform) of the *de novo*mutations were confirmed by Sanger sequening. B and T lymphocyte and monocyte immunophenotyping were performed through flow cytometry.

Results: The *de novo* mutations in *LYN* leads to a premature stop-codon at p.Y508* which removes 5 terminal amino acid residues (pt.1) 1 and revealed the missense p.Y508F that was studied in the lyn up/up mice (pt.2). The clinical features of both patients included perinatal-onset of systemic inflammation. Patient 1 presented with hydrops fetalis, requiring an intra-utero blood transfusion and post partum, purpuric skin rash, hepatosplenomegaly, periorbital erythema and testicular pain and swelling with increased CRP. Cytopenias including anemia, and thrombocytopenia required a

splenectomy at the age of 9mo. Post-splenectomy development of chronic leukocytosis and thrombocytosis with persistent anemia and Increased liver enzymes led to a liver biopsy at age 23 mo showing a periportal lymphocytic infiltrate, vanishing bile duct disease and evidence of periportal bridging fibrosis. A skin biopsy confirmed neutrophilic small vessel vasculitis and low titer circulating autoantibodies (positive ANA, anti-Sm, anti-SSA, anti-phospholipids and anti-mitochondrial antibodies). Initiation of prednisone and IVIG infusions led to some improvement but prednisone could not be weaned. Pt. B lymphocytes showed constitutive phosphorylation of Lyn and a significantly diminished frequency of immature B cell populations in peripheral blood and in bone marrow. Reduced B cell activation in response to IgM stimulation compared to healthy controls was observed. The tyrosine kinase inhibitor dasatinib normalized lyn phosphorylation in pt B cells and was initiated with significant clinical and laboratory response. Patient 2 presented with a generalized purpuric skin rash and recurrent episodes of fevers since his first hours of life. Other symptoms included abdominal and testicular pain, headaches, conjunctival erythema, arthralgias, oral ulcers and fatigue. The recurrent symptoms have responded to short courses of oral steroids. He had a partial response to colchicine, no response to anakinra and tocilizumab and was recently started on etanercept.

Conclusion: We identified activating mutations in Lyn kinase gene (*LYN*) as cause for a novel immunedysregulatory syndrome presenting with neonatal-onset of fever, small vessel neutrophilic vasculitis and systemic inflammation.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mutations-in-the-tyrosine-protein-kinase-lyn-cause-an-early-onset-neutrophilic-vasculitis-syndrome

Abstract Number: 2431

Characterization of Innate Immune Cells in Patients with the Interferon-Mediated Autoinflammatory Diseases Sting Associated Vasculopathy with Onset in Infancy (SAVI) and Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE)

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Background/Purpose: We recently described two rare autoinflammatory interferonopathies, STING Associated Vasculopathy with Onset in Infancy (SAVI) and Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated temperature (CANDLE), caused by mutations in *TMEM173/STING* and in proteasome components, respectively which present with systemic inflammation and a strong IFN response gene signature. However the cellular source for Type I IFN remains unknown.

Methods: The cellular origin of Type I IFN was assessed in FACS sorted PBMCs (T, B, NK and monocytes) from SAVI (n=5) and CANDLE (n=6) patients compared to healthy controls (HC), and from lesional skin biopsies, n=3 for SAVI and for CANDLE. Type I IFN transcription and production and cell activation status were evaluated. Most CANDLE and SAVI pts were on JAK inhibitor treatment.

Results: Serum IFNa levels were increased in SAVI and CANDLE compared to HCs, IFNb is not reliably measured. SAVI pts' monocytes had 481-fold [IQR 56-38,242] increased *IFNB1* expression compared to HCs and CANDLE pts. However, during a CANDLE disease flare, monocyte *IFNB1* transcription increased 4 and 51 fold. *IFNA7/IFNA17* is constitutively 60 fold increased [IQR3-116] in SAVI but not in CANDLE. Monocyte depletion reduced the IFN message by 90% in the monocyte of PBMC/neutrophil fractions in SAVI pts., pointing to the presence of monocytes in the neutrophil fraction. Intracellular IFNa staining of monocytes confirmed that monocytes and not dendritic cells are the main source of IFNs for SAVI. The mean ratio of *IFNB1* to *IFNA7/17* was 1200:1 in SAVI and 1:1 in CANDLE monocytes. STING pathway activation with cGAMP in the presence of a blocker of translational elongation, cycloheximide (CHX), did not block *IFNB1* transcription but blocked *IFNA1,2,7,17,21* thus confirming constitutive *IFNB1* transcription. A left-shift with a 2.3 and 1.5-fold increase of immature CD13lo CD16+ neutrophils in CANDLE and SAVI compared to HC was seen. Activation markers CD36+, CD64, were 87%, 65% on monocytes, and 26.1%, 60.3% on granulocytes in SAVI and CANDLE respectively, (HC 0.22%-5.32%). Morphologically, CANDLE monocytes had the highest content of cytoplasmic vacuoles with 6.4+/-2.1SD vacuoles/cell (V/C) compared to SAVI 3.5+/-2.5SD V/C ($p>0.05$) and HC 2.2+/-1.2SD V/C ($p<0.004$). CXCL10/IP-10 serum levels are equally high in CANDLE and SAVI patients and nanostring IP-10 counts were similar in CANDLE and SAVI (314+/-63SEM and 357+/-66SEM p=0.0007), (HC 91+/-14SEM, $p<0.05$); in skin IP-10 levels were 30-400 fold

increased in CANDLE (81,803+/-28,605SEM) than SAVI (28,443+/-20,439SEM, compared to HC (28+/-20SEM, p>0.05).

Conclusion: In conclusion, the source for production of Type I IFNs varies in CANDLE and SAVI with constitutive transcription of *IFNB1* in predominantly monocytes in the blood in SAVI pts. In CANDLE and SAVI lesional skin showed similar elevated transcription in *IFNAs*, and higher levels for *IFNB1* in SAVI. IP-10 levels were highest in CANDLE skin samples. Understanding differences in intracellular signaling pathways activating IFN production and the IFN loop is needed to design targeted treatment approaches for the different interferonopathies.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/characterization-of-innate-immune-cells-in-patients-with-the-interferon-mediated-autoinflammatory-diseases-sting-associated-vasculopathy-with-onset-in-infancy-savi-and-chronic-atypical-neutrophilic

Abstract Number: 2432

Immune Abnormalities Leading to Exaggerated Production of IFN-Gamma (IFNγ) and the Therapeutic Response to an Anti-IFNγ Antibody in a Patient with NRLC4 Mediated Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: Animal and human data suggest that IFNγ plays a pathogenic role in HLH. A phase 2 trial with the anti-IFNγ monoclonal antibody NI-0501 in primary HLH provides encouraging preliminary data. Gain-of-function mutations in *NLRC4* are associated with a distinct autoinflammatory syndrome, with recurrent HLH, fever episodes and enterocolitis.

Methods: We reported a patient with severe early onset progressive HLH carrying a *de novo* missense mutation in *NLRC4*(T337N), the immune abnormalities leading to abnormal production of IFNγ and the response to treatment with NI-0501. We evaluated cytokine levels by multiplex assay and by specific ELISAs and expression of IFNγ in freshly isolated PBMCs by cytometry.

Results: LR, caucasian male, presented, at 20 days of age, fever and rash and progressively developed clinical and laboratory features of HLH leading rapidly to liver failure and subsequent multiorgan failure. Genes causing primary-HLH and functional tests were negative. High-dose glucocorticoids and cyclosporine-A led to partial improvement. Development of sepsis triggered HLH reactivation. Measurable IFNγ levels (6pg/ml) and high levels of the IFNγ inducible chemokines CXCL9 (5670pg/ml) and CXCL10 (4400pg/ml) were found, the latter demonstrating activation of the IFNγ pathway. NI-0501 was started (compassionate use) on background of dexamethasone (13.6mg/m2) and cyclosporine-A. After 3 months, the child was discharged in excellent conditions (prednisone 0.3 mg/kg). Markedly elevated production of IFNγ was revealed by the administration of NI-0501 through measurement of total IFNγ bound to circulating NI-0501. This IFNγ was fully neutralized, as shown by rapidly undetectable levels of CXCL9 and CXCL10. The percentage of CD4+, CD8+ and CD56+ cells expressing IFNγ was significantly increased in the NLRC4 patient without (0.95%, 0.88%, 0.80%, respectively) and with stimulation with PMA/ionomycin (6.44%, 10.20%, 25,00%). Serum levels of IL-18 were markedly higher (as expected in NLRC4-mediated disease) at >300 ng/ml before treatment and remained elevated throughout treatment (ranging between 25 and 35 ng/ml), with the patient showing no symptoms. Incubation of PBMCs from healthy controls with NLRC4 patient's sera in the presence of IL-12 (known costimulus for IFNγ synthesis) led to a marked hyperproduction of IFNγ (>20ng/ml), compared to sera from patients with other autoinflammatory diseases (0.59±0.47 ng/ml). This increase in IFNγ production was neutralized by incubation with an anti-IL18 receptor antibody. After 7 months of NI-0501 treatment, all therapies, including NI-0501, were discontinued, without any clinical or laboratory sign of HLH reactivation, even in the presence of occasional increases in IL-18 levels.

Conclusion: Our data suggest that in NLRC4-related disease overproduction of IL-18, induced by an hyperfunctional NLRC4 inflammasome, may be one of the contributors to the up-regulation of IFNγ production that appears to be driving HLH. In this patient, neutralization of IFNγ allowed control of all disease features, enabling withdrawal of all treatments, including glucocorticoid and cyclosporyn-A. No safety concern emerged. C.B. and G.P. contributed equally to this study

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immune-abnormalities-leading-to-exaggerated-production-of-ifn-gamma-ifn%ce%b3-and-the-therapeutic-response-to-an-anti-ifn%ce%b3-antibody-in-a-patient-with-nrlc4-mediated-disease

Abstract Number: 2433

Trends in Use of Hydroxychloroquine during Pregnancy in SLE Patients from 2001 to 2012

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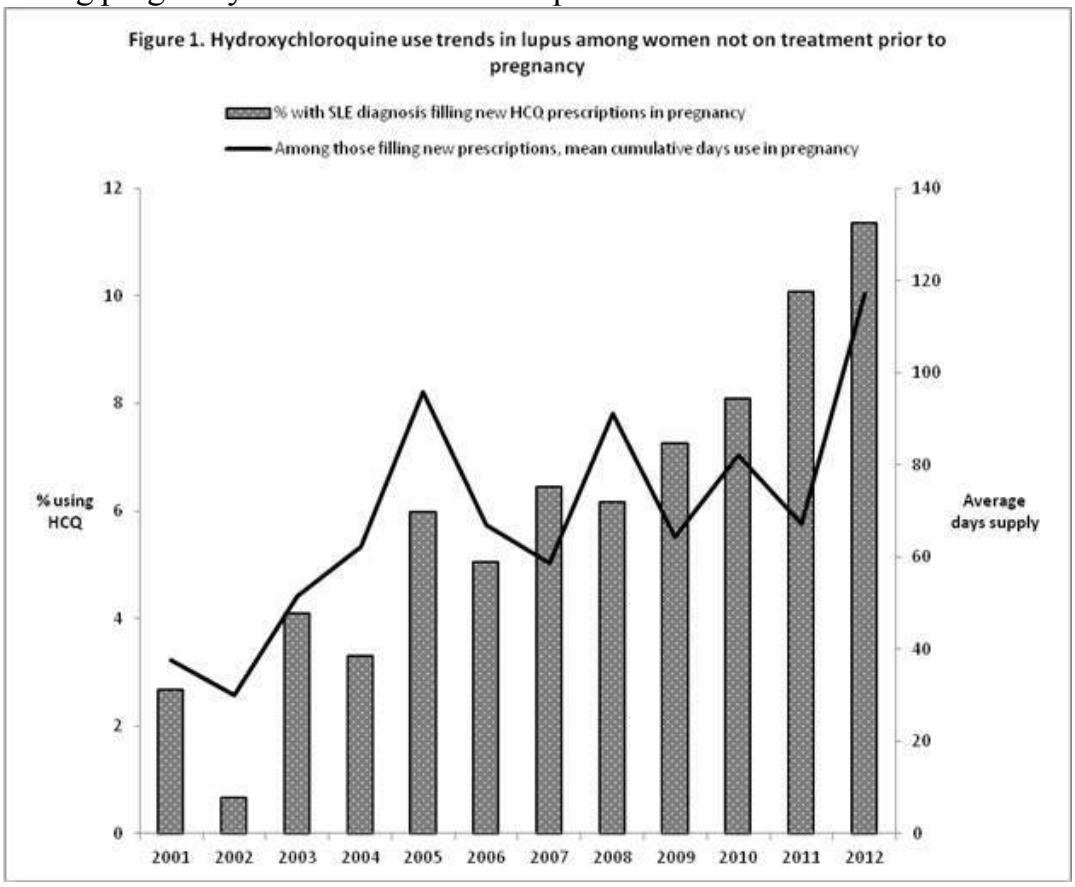
Background/Purpose : Data suggest that hydroxychloroquine (HCQ) use during systemic lupus erythematosus (SLE) pregnancies improves outcomes. In the past decade, single-center studies report that a high percentage of patients receive HCQ during pregnancy, yet HCQ use at a population level has not been studied. Therefore, we sought to describe time-trends in the use of HCQ in a large population-based cohort of pregnant women with SLE.

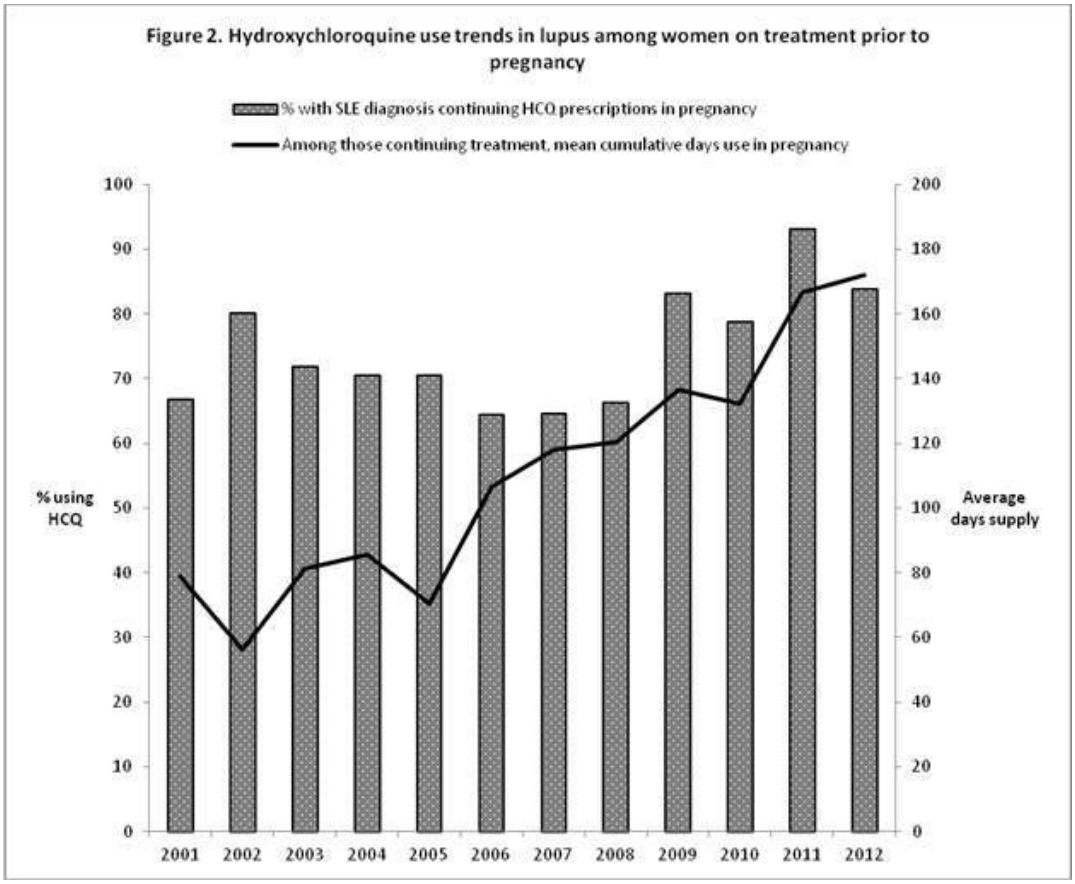
Methods : A cohort of pregnant women with SLE enrolled continuously in public (Medicaid, 2001-2010) or private (United Healthcare, 2004-2012) health insurance between three months prior to conception and one month after delivery was identified. Included patients were stratified based on their use of HCQ in the 3-month period immediately prior to pregnancy. Among women with SLE not using HCQ prior to pregnancy, we assessed the proportion initiating HCQ during pregnancy each calendar year. For women using HCQ prior to pregnancy, we calculated the proportion of women continuing HCQ during pregnancy each calendar year. Further, we described time-trends in the cumulative day-supply of HCQ prescriptions dispensed during pregnancy as a measure of the duration of HCQ use. Linear trend tests were conducted for proportions and total day-supply over the study years for both groups.

Results : A total of 4,904 women with diagnosis of SLE who became pregnant were included. Of those, 739 (15.1%) were on HCQ treatment in the 3-month period immediately prior to their pregnancy. The proportion of women initiating HCQ during pregnancy increased from 2.7% in 2001 to 11.3% in 2012 ($p<0.0001$, **Figure 1**) and the proportion of women continuing HCQ increased from 63.7% in 2001 to 83.8% in 2012 ($p=0.06$, **Figure 2**). Among women initiating HCQ, the

average cumulative day-supply of HCQ prescriptions during pregnancy increased from 37 days in 2001 to 117 days in 2012 ($p<0.01$). Similarly, among women continuing HCQ treatment, the average cumulative day-supply of HCQ prescriptions during pregnancy increased from 79 days in 2001 to 172 days in 2012 ($p<0.0001$).

Conclusion: The proportion of women with SLE initiating or continuing HCQ during pregnancy increased from 2001 to 2012. Similarly, average cumulative day-supply of HCQ prescription increased during the same time frame. While these findings are encouraging, overall HCQ use during pregnancy remains low and is a potential area for clinical intervention.





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Abstract Number: 2435

Counseling on Family Planning and Contraception, and Pregnancy Outcome in Women with Rheumatic Diseases: Analysis of 398 Patient-Reported Questionnaires from a Multicenter Italian Study

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COUNSELING ON FAMILY PLANNING AND CONTRACEPTION, AND PREGNANCY OUTCOME IN WOMEN WITH RHEUMATIC DISEASES: ANALYSIS OF 398 PATIENT-REPORTED QUESTIONNAIRES FROM A MULTICENTER ITALIAN STUDY

Background/Purpose: Rheumatic diseases (RD) predominantly affect young women during reproductive age. Pregnancy, contraception and family planning are crucial for the quality of life of these patients. We aimed at investigating 'women's health' issues through a self-reported questionnaire. Answers from patients with connective tissue diseases (CTD) vs. chronic arthritis (CA) were compared.

Methods: 24 Italian participating centers distributed a self-reported questionnaire (65 multiple-choice and 12 open-answer questions) to women with RD (> 18years).

Results: Answers were collected from 279 CTD and 163 CA; the mean age at diagnosis was 31.6 and 30.6 years respectively. Subsequent analysis was performed on 249 CTD vs. 149 CA. Patients who developed a RD after 45 years old were excluded from this analysis.

Nearly 40% of all patients declared that RD influenced their desire to have children: about 55% of them reduced the number of children they wanted (Table 1). In particular 39% CA vs.29%CTD declared to be afraid of being mother because of their disability.

24% CTD vs. 18% CA had at least one miscarriage; 21% CTD vs. 2% CA had more than one miscarriage.

31% CTD and 34% CA were never asked by their rheumatologist about the desire to have children. 61% CTD vs.70% CA received counseling about contraception, given by a gynecologist (58% vs. 64%), rheumatologist (22% vs. 14%), or both (7% vs. 9%).

About 60% in both groups received a counseling before pregnancy: 34% vs. 39% of them from both rheumatologist and gynecologists, 14% vs. 22% only by rheumatologist. The counseling positively changed the family planning in 64% and 59% respectively.

About 50% of all patients had no knowledge about the use of immunosuppressive drugs during pregnancy. About 40% of patients who were in menopause declared that it started before 45 years of age.

Conclusion: This survey suggested that CTD have a major impact on reproductive planning and restriction of family size, possibly mediated by the reported increased rate of miscarriages as compared to CA. The concerns about reproductive issues could be positively overcome by adequate counseling.

Rheumatologists should implement the discussion about family planning and the compatibility of drugs with pregnancy in the management of young women with RD. This is particulary relevant in CTD patients in whom contraception and pregnancy have particular implications.

Early menopause appears to be a relevant issue in women with RD.

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The disease has reduced your desire to have children?

	CTD	CA
NO	36/91 (40%)	22/54 (41%)
YES	**52/91 (57%)**	**28/54 (52%)**
No Answer	3/91 (3%)	4/54 (7%)

If yes, I reduced the number of children that I wanted, because I was afraid…	**CTD**	**CA**
…of not being able to take care of them because of the disease	**26/91 (29%)**	**21/54 (39%)**
…that the child could have the same disease	**15/91 (17%)**	**8/54 (15%)**

…that drugs or disease could harm the baby	**26/91 (29%)**	**20/54 (37%)**

Table 1. Reasons for reduced family size in patients who declared that their RD had influenced their desire of having children

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Birth Outcomes Significantly Worsen after the Development of Systemic Lupus Erythematosus in a Population-Based Registry

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Background/Purpose: SLE mothers are known to have higher rates of pre-term birth and low birth weight compared to women in the general population. We evaluated birth outcomes in women with systemic lupus erythematosus (SLE) before and after developing disease on a population level.

Methods: The Georgia Lupus Registry (GLR) is a population-based registry of SLE patients living in Atlanta, GA from 2002-04. Patients were validated by meeting ³4 ACR criteria or 3 ACR criteria with a final diagnosis of SLE by a board certified rheumatologist and were matched to the Georgia Birth Records database (1994-2013), which provided various information on the births. Births were dichotomized into 2 periods, one before lupus activity began (ÒPreLupusÓ) and the other after (ÒPostLupusÓ), and compared. In order to take into account subclinical and/or significant immunologic activity just prior to being diagnosed with SLE, the time point separating the periods was made to be 1 year prior to the physician diagnosis date.

Results: 345 total patients were incident in 2002-04. 87% were women and 73% were black. A total of 77 births in the PreLupus period and 247 in the PostLupus period were observed. Among incident SLE mothers, there were significant increases in pre-term births from 18.7% in the PreLupus period to 44.8% in the PostLupus period, number of low birth weight births from 20.8% to 55.2%, and number of births with low APGAR scores from 6.2% to 41.4%. There was a trend to increasing number of previous terminations from 25% to 33.3%. 1,446 patients were prevalent in 2002. 89.9% were women and 75.7% were black. Only low birth weight changed significantly from 14.7% in the PreLupus period to 30.1% in the PostLupus Period. There was generally good reported prenatal care and frequency of care and little, if any, reported alcohol or tobacco use during pregnancy on the birth certificates.

Conclusion: This is the first population-based description of birth outcomes in SLE in the US. The ratio of births to mothers in the PreLupus compared to the PostLupus periods predictably goes down but not dramatically, demonstrating reproductive capacity and resolve in these patients. Our study supports previous observations of more frequent rates of adverse birth outcomes in those with SLE. Pre-term birth, low birth weight, and low APGAR scores are significantly more frequent, particularly in incident SLE patients. More study is needed to better understand the impact of SLE on birth outcomes in order to guide patients interested in reproduction.

Birth Outcomes By Incident and Prevalent (prevalence in 2004, incidence in 2002-04)

		Incident			Prevalent		
		Pre Lupus	Post Lupus	P-value	Pre Lupus	Post Lupus	P-value
	# mothers	28	21		34	118	
	# births	48	29		61	186	
Previous Terminations, n (%)	Yes	7 (25)	7 (33.3)	0.52	13 (38.2)	59 (50)	0.23
	No	21 (75)	14 (66.7)		21 (61.8)	59 (50)	
Pre-term Birth	≥ 37 weeks	39 (81.3)	16 (55.2)	**0.01**	47 (77.1)	120 (64.5)	0.07
	<37 weeks	9 (18.7)	13 (44.8)		14 (22.9)	66 (35.5)	
Low Birth Weight	≥ 2500 g	38 (79.2)	13 (44.8)	**0.002**	52 (85.3)	130 (69.9)	**0.02**
	< 2500 g	10 (20.8)	16 (55.2)		9 (14.7)	56 (30.1)	
APGAR at 5 Minutes	≥ 9	45 (93.8)	17 (58.6)	**0.0002**	50 (82)	148 (79.6)	0.68
	< 9	3 (6.2)	12 (41.4)		11 (18)	38 (20.4)	
Mother: Prenatal Care	Yes	47 (97.9)	18/18 (100)	0.99	58/60 (96.7)	151/151 (100)	0.08
	No	1 (2.1)	-		2/60 (3.3)	-	
Mother: Late/No Prenatal Care	Yes	4 (8.3)	-	0.31	3/60 (5)	3/158 (1.9)	0.35
	No	44 (91.7)	20/20 (100)		57/60 (95)	155/158 (98.1)	
Prenatal Care Visits	< 5	2 (4.2)	1 (3.7)	0.99	5/60 (8.3)	10/174 (5.7)	0.54
	≥ 5	46 (95.8)	26 (96.3)		55/60 (91.7)	164/174 (94.3)	
Alcohol During Pregnancy	Yes	-	-	-	1/61 (1.6)	1/162 (0.6)	0.47
	No	48 (100)	20/20 (100)		60/61 (98.4)	161/162 (99.4)	
Tobacco During Pregnancy	Yes	3 (6.3)	-	0.29	4/61 (6.6)	15/185 (8.1)	0.69
	No				57/61 (93.4)	170/185 (91.9)	

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Causes of Cesarean Section and Labor Induction in Systemic Lupus Erythematosus and Rheumatoid Arthritis Pregnancies

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Background/Purpose: Women with SLE and RA have an increased risk of delivering a preterm infant. However, the causes of these preterm births remain unknown. Some theories suggest that maternal inflammation induces preterm labor and/or rupture of membranes. We sought to identify what prompted each preterm delivery, as well as the mode of delivery among a cohort of patients with SLE and RA.

Methods: SLE patients meeting ACR and/or SLICC criteria and RA patients meeting ACR criteria were prospectively followed in a pregnancy registry. Pregnancy outcomes were collected from the patient and medical records. Preterm birth was defined as a birth <37 weeks gestation. Only

singleton live births with a visit prior to 25 weeks gestation and data available on mode of delivery were included. At our institution, pregnancies in women with rheumatic diseases are routinely induced at 39 weeks for delivery, regardless of maternal complications. Differences between term and preterm births were determined by Fisher's exact test.

Results: Among 82 SLE live births, 46% of mothers were white and 46% were black, with a median maternal age of 30 years. Among 45 RA live births, 78% of mothers were white, with a median maternal age of 35 years. There were 20 preterm births (24%) among SLE pregnancies and 7 preterm births (16%) among RA pregnancies. While only 30% of preterm SLE births were spontaneous, 71% of preterm RA births were spontaneous. The frequency of C-section was greater in patients who had induced compared to spontaneous labor (65% vs. 24%, respectively, for SLE and 52% vs. 8%, respectively, for RA). Among SLE patients, preeclampsia and concern over the health of the mother were the primary drivers behind induced preterm labor and preterm C-sections (Table 1). Preeclampsia was diagnosed in 35% of preterm deliveries compared to 8% of term deliveries ($p=0.002$). Labor was induced in 70% of preterm births and 55% of term births. The reason for induction differed, however, with 64% of preterm births induced for maternal preeclampsia/hypertension compared to 15% of induced term births ($p=0.001$). In contrast, among women with RA, C-sections and preterm birth were both less frequent than in SLE, and labor was more often spontaneous. Half of term deliveries were induced, primarily for gestational age, although 21% of term births were induced due to maternal preeclampsia/hypertension and 16% were induced because the infant was not well.

Conclusion: Spontaneous preterm labor does not appear to be driving the high preterm birth rate among women with lupus. Instead, physician-directed labor induction to manage the risks of preeclampsia, placental insufficiency, and lupus activity prompts the majority of preterm births. These results suggest future research attention should focus on placental dysfunction and away from causes of spontaneous preterm labor.

Table 1. Live birth outcomes among SLE and RA pregnancies.

	SLE Births (n=82)		RA Births (n=45)	
	Preterm (n=20) n (%)	Term (n=62) n (%)	Preterm (n=7) n (%)	Term (n=38) n (%)
Pre-eclampsia	7 (35%)	5 (8%)*	1 (14%)	2 (5%)
Mode of delivery				
Vaginal	7 (35%)	36 (58%)	6 (86%)	26 (68%)
C-section	13 (65%)	26 (42%)	1 (14%)	12 (32%)
Reason for C-section[1]				
Prior C-section	3 (23%)	7 (27%)	0 (0%)	5 (42%)
Failure to progress	1 (8%)	8 (31%)	0 (0%)	5 (42%)
Baby not well	4 (31%)	4 (15%)	0 (0%)	1 (8%)
Mother not well	7 (54%)	5 (19%)	0 (0%)	1 (8%)
Breech/transverse	0 (0%)	3 (12%)	0 (0%)	2 (17%)
Poor fetal growth	0 (0%)	0 (0%)	0 (0%)	1 (8%)
Other	0 (0%)	0 (0%)	1 (100%)[5]	0 (0%)
Labor				
Spontaneous	6 (30%)	28 (45%)	5 (71%)	19 (50%)
Induced	14 (70%)	34 (55%)	2 (29%)	19 (50%)
Reason for induction[2]				
Gestational age	0 (0%)	18 (53%)*	0 (0%)	11 (58%)
Mother: preeclampsia or hypertension	9 (64%)	5 (15%)*	1 (50%)	4 (21%)
Mother: disease activity	2 (14%)	3 (9%)	0 (0%)	0 (0%)
Infant not well	3 (21%)	8 (24%)	0 (0%)	3 (16%)
Fetal growth restriction	0 (0%)	3 (9%)	0 (0%)	1 (5%)
Breech/transverse	0 (0%)	1 (3%)	0 (0%)	1 (5%)
Other	2 (14%)[3]	3 (9%)[4]	1 (50%)[6]	3 (16%)[7]

[1]patients may have multiple reasons for C-section; therefore, percentages do not total to 100%
[2]patients may have multiple reasons for induced labor; therefore, percentages do not total to 100%
[3]reasons for induction include cholestasis of pregnancy (n=1) and oligohydramnios + placental insufficiency (n=1)
[4]reasons for induction include baby with severe cardiac defect and prior pelvic organ prolapse surgery (n=1), obesity (n=1), oligohydramnios (n=1)
[5]reason for C-section include vasa previa (n=1)
[6]reason for induction include vasa previa (n=1)
[7]reasons for induction include cholestasis of pregnancy (n=1), oligohydramnios (n=2)

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Increased Risk of Postpartum Depression in SLE Pregnancies

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Background/Purpose: Chronic diseases have been shown to be a strong risk factor for postpartum depression. Although there is a 2-fold increased risk of major depression in SLE, the risk of postpartum depression in mothers with SLE is unknown. Within a large population-based cohort, we evaluated the risk of postpartum depression in women with SLE compared to unaffected women and explored potential mediators of postpartum depression in SLE pregnancies.

Methods: The "Offspring of SLE mothers Registry (OSLER)" includes all women who had ≥1 hospitalization for delivery after SLE diagnosis, identified through Quebec's universal healthcare databases (1989-2009). OSLER also includes a randomly selected control group of women, matched at least 4:1 for age and year of delivery, without an SLE diagnosis prior up to the time of delivery. We ascertained postpartum depression based on ≥1 hospitalization or physician visit with relevant diagnostic codes, within the first 12 months after delivery. We performed multivariate analyses to adjust for maternal education, race/ethnicity, and pre-existing mood disorders in the 2 years prior to delivery. In secondary analyses, we further adjusted for pregnancy complications, including preterm birth, gestational diabetes, and stillbirth, to explore potential mediators of postpartum depression in SLE pregnancies.

Results: 509 women with SLE had 729 births, while 5824 matched controls had 8541 births. We identified postpartum depression in 11.0% (95% CI 8.8, 13.5) of SLE pregnancies versus 8.3% (95% CI 7.7, 8.9) of unexposed pregnancies. More SLE pregnancies were preceded by a mood disorder in the 2 years prior to delivery as opposed to unexposed pregnancies [15.4% (95% CI 12.9, 18.2) vs 11.0% (95% CI 10.2, 11.5)]. In primary multivariate analysis, accounting notably for pre-existing mood disorders, SLE pregnancies were at increased risk of postpartum depression versus unexposed pregnancies [OR 1.32 (95% CI 1.01, 1.73)]. The effect estimate for SLE was attenuated when we further adjusted for pregnancy complications [OR 1.20 (95% CI 0.92, 1.58)]. Preterm birth [OR 1.55 (95% CI 1.20, 2.00)] and stillbirth [OR 6.49 (95% CI 3.32, 12.67)] were independent predictors of postpartum depression. Pre-existing mood disorders in the 2 years prior to delivery also was an independent predictor of postpartum depression in both primary and secondary multivariate analyses [OR for primary analysis 4.44 (95% CI 3.73, 5.29)].

Conclusion: Compared to women from the general population, women with SLE have an increased risk of postpartum depression. Mediators of postpartum depression in SLE potentially include pregnancy complications, such as preterm birth and stillbirth. Further research is needed to evaluate the role of disease activity and/or flare during pregnancy, as well as medication exposures on the risk of postpartum depression in SLE.

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Effect of Pregnancy Counseling on the Outcome of Pregnancies in Women with Systemic Lupus Erythematosus: A Prospective Observational Study

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Background/Purpose: Pregnancies in women with systemic lupus erythematosus (SLE) are associated with increased frequencies of adverse pregnancy outcomes (APOs). Preconception counseling including risk stratification and adjustment of medication is strongly recommended by EULAR[1]. However, a considerable number of women with SLE do not seek such advice before conception. Our aim was to assess the impact of pregnancy counseling prior to conception on the outcome of pregnancies in women with SLE referred to our lupus pregnancy clinic (2000-2015).

Methods: All pregnancies in women with SLE who received an individual pregnancy counseling prior to conception were prospectively followed during pregnancy and postpartum period according to a standard protocol (group A). Outcome of these pregnancies was compared to pregnancies in women with SLE who were already pregnant by the time of their first appointment in our clinic (group B). APOs were defined as fetal loss (spontaneous abortion or stillbirth), severe pregnancy disorders (preeclampsia, HELLP-syndrome), birth before 36 weeks (due to placental insufficiency, hypertension, or preeclampsia) and low birth weight (< 2500 g). Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI) was used to gauge disease activity during pregnancy.

Results: A total of 188 pregnancies in 151 women with SLE (median age 31 years) were included (group A = 137; group B = 51). 67 % of all women had been pregnant before, 33 % had experienced at least one fetal loss and 9 % severe pregnancy disorders. With respect to all pregnancies, a live birth was documented in 172 (91.5 %) [group A 94.2% vs group B 86.3 %)]. A fetal loss occurred in 16 (8.5 %) pregnancies [group A 5.8 % vs. group B 15.7 %). Twenty-three (12.2%) of all pregnancies were complicated by severe pregnancy disorders (group A 5.8 % vs group B 29.4 %)

and 28 (14.9 %) by preterm birth (group A 7.3 %; group B 35.3 %). One newborn (group B) died shortly after extreme preterm birth. After adjusting for maternal age and for higher disease activity in the first trimester (SLEPDAI ≥ 4) we observed significantly higher rates of fetal losses (RR = 3.4; 95%CI 1.4-8.6), severe pregnancy disorders (RR = 5.5; 95%CI 2.5 – 12.1), preterm birth (RR = 5.6; 95%CI 2.8 – 11.2) and low birth weight (RR = 3.2; 95%CI 1.9 – 5.4) in group B compared to group A.

Conclusion: The main prognostic risk factor for adverse outcomes in our observational cohort of 188 SLE-pregnancies was the lack of preconception counseling. These patients had significant higher risks of fetal loss, preterm birth, low birth weight and severe pregnancy disorders. Though our observed live birth rate was considerable high in both groups, probably due to an adapted multidisciplinary management during the course of pregnancy, consultation before conception was still associated with higher live birth rates (94,2 vs. 86,3%). Women with SLE and pregnancy wish should be informed about the obvious beneficial effect of preconception counseling. [1]Andreoli L. "EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy, and menopause in patients with Systemic Lupus Erythematosus and/or the Antiphospholipid Syndrome." (in press)

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Abstract Number: 2440

First Results from the Prospective German Pregnancy Register

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Background/Purpose: There is limited evidence on the safety of treatment during pregnancy and lactation. With the increasing number of new therapeutic options for inflammatory rheumatic diseases, there is a growing need for real-life data. Prospective randomized studies are not conducted in women who are pregnant or wish to conceive. The purpose of our register is to determine the safety of various drug treatments during pregnancy and the influence of the underlying rheumatic disease on pregnancy outcome and child development.

Methods: The Rhekiss register is designed as a web-based nationwide cohort study. Pregnant patients with confirmed diagnosis of inflammatory rheumatic disease are enrolled until the 20th week of pregnancy regardless of treatment. Rheumatologists and patients report each trimester during pregnancy and semi-annually after birth until the child's 2nd birthday. Information on all given drug treatments, the course of the maternal disease, maternal or fetal complications during pregnancy, pregnancy outcomes and child development are collected. At first visit sociodemographic parameters, prior pregnancies, and comorbidities are reported. Only pseudonymized data are used, data security issues conform with regulatory authorities have been implemented.

Results: The register started on 15th of September 2015. Until end of May 2016, 84 rheumatologists recruited 200 pregnant women. We report first data of 182 patients. Of these, 28% had rheumatoid arthritis (RA), 23% systemic lupus erythematosus, 19% other connective tissue diseases, 18% spondyloarthritis or psoriatic arthritis, 6% juvenile idiopathic arthritis (JIA), 4% autoinflammatory diseases and 2% systemic vasculitis. Mean age of all patients was 32.5 (± 4.6) years, mean disease duration 8.3 (± 7.5) years. Mean disease activity over all diagnoses assessed by the rheumatologist on a numeric rating scale from 0-10, was 2.3 (± 2.1). On a disease severity scale ranging from 1 to 5 (highest grade), two thirds of all patients were reported grade 2 or 3. With respect to the different underlying diseases up to 60 % received treatment with biological DMARDs within 12 months before first visit, mainly patients with RA or JIA. One quarter of these patients continued biological DMARDs at least until conception.

Conclusion: The German pregnancy register Rhekiss was initiated to fill the knowledge gap on the course and outcomes of pregnancies in patients with rheumatic diseases as well as on the current use and safety of treatments during pregnancy and lactation. The fast uptake of patients shows that there is a substantial need for and a high interest in real-life data to guide treatment decisions

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Abstract Number: 2441

Rheumatoid Arthritis Flares and Pregnancy Outcomes Among Women in a Longitudinal Registry

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Background/Purpose: Rheumatoid arthritis (RA) has been reported to improve during 50-60% of pregnancies. In this study, we evaluated RA disease activity during pregnancy and pregnancy outcomes in a longitudinal registry. <> <>

Methods: We identified women enrolled in a single-center, prospective RA registry at a large academic medical center, 2003-2015, who reported being pregnant on a semi-annual registry questionnaire. We performed a detailed electronic medical record review to identify occurrence of RA flares during each of three trimesters and up to three months post-partum, based on clinical documentation by the treating rheumatologist. Medication use was recorded during each trimester, and medication changes at the time of flare were recorded. The medical record was also reviewed for use of assistive reproductive technology (ART, including *in vitro* fertilization and ovulation stimulation), pregnancy outcomes, infant outcomes, and maternal complications. Pregnancy outcomes were categorized as live birth, elective termination, miscarriage (<12 weeks or 12-20 weeks gestation), or stillbirth (≥20 weeks gestation). <> <>

Results: 45 pregnancies occurred among 34 women with mean age 33.6 (SD 4.7) and mean RA disease duration 7.3 (SD 4.9) years at conception. 88.9% were White and 69.9% were seropositive (RF and/or anti-CCP). 39 (86.7%) pregnancies resulted in a live birth. Flares occurred in 26.7% of pregnancies; these were equally distributed among trimesters (Figure). Post-partum flare was documented after 56.4% of pregnancies that resulted in a live birth. Six (13.3%) pregnancies were the result of ART. There was one tubal pregnancy requiring elective termination. Five (11.1%) pregnancies resulted in miscarriage, all of which occurred at <12 weeks gestation; no stillbirths were documented. Among live births, one pair of twins required intensive care; no other adverse outcomes were documented. Maternal complications included gestational diabetes in two women, pre-eclampsia in one woman, and hemolysis with low platelets and elevated liver enzymes in one woman. <> <>

Conclusion: The majority of patients did not flare during pregnancy, but most flared within three

months post-partum. The majority of pregnancy outcomes were favorable in this prospective RA registry at an academic medical center.

Timing of RA Flares and Medication Changes during 12 Pregnancies

Record	Pre-conception (6 month period)	1st trimester	2nd trimester	3rd trimester	Post-partum (3 month period)	Seropositive (RF and/or CCP)
Gray shading indicates time period of flare(s)						
1	ETA Pred 1	ETA held, flared Pred 5, IA steroid			ETA resumed	No
2	ETA held Pred 5	Pred 5	Pred 2.5	Pred 2.5	ETA resumed	No
3	ETA	ETA held, flared Pred 5	Pred 2.5		No flare	No
4	ETA NSAID	ETA held	Pred 10	Pred 5	Pred 10	Yes
5	NSAID ADA Pred 10	ADA held		Declined meds	No flare	Yes
6	ETA	ETA held		Pred 10	ETA resumed	Yes
7	Pred 12.5 INF held 6 wks pre-conception	Pred 9	Pred 20		INF resumed	Yes
8	ETA held	CER started Pred 5	CER changed to ETA Pred 10	ETA held wk 28 Pred held wk 28	No flare	No
9	ETA changed to ADA Pred 10	ADA Pred 8	ADA Pred 8 (declined change)	ADA held wk 36	No flare	Yes
10	ETA	ETA held	Not seen by rheumatologist	Pred 10	ETA resumed Pred 10	Yes
11	HCQ NSAID Pred 10	Patient stopped HCQ Pred 7.5	Pred 10 IA steroid	Pred 12.5 Declined other meds	MTX started	Yes
12	MTX held Pred 5	Pred 14 Declined other meds	Pred 15	Pred 15	MTX resumed SSZ started Pred 15	Yes

Abbreviations ADA: adalimumab; CER: certolizumab; ETA: etanercept; HCQ: hydroxychloroquine; IA: intra-articular; INF: infliximab; Pred: prednisone, dose in milligrams; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; SSZ: sulfasalazine

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Abstract Number: 2442

Use of Nonsteroidal Anti-Inflammatory Drugs in Pregnant Women with Inflammatory Arthritis

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Use of Nonsteroidal Anti-inflammatory Drugs in Pregnant Women with Inflammatory Arthritis

Background/Purpose: Nonsteroidal anti-inflammatory drugs (NSAIDs) are generally contraindicated in the third trimester of pregnancy due to concerns for potential maternal or fetal complications. However, data are limited on NSAID use in pregnant women with inflammatory arthritis. The objective of our study was to describe the prevalence of NSAID use in pregnant women in this population and to explore associations between NSAIDs and selected adverse fetal or pregnancy outcomes

Methods: The sample was selected from the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy project, a North American prospective cohort study of pregnant women. Women with singleton, live births (enrolled 2005-2015) who had rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis were selected. NSAID exposure was captured through interviews; outcomes were obtained from interviews and medical records. ÒExposedÓ women were defined as those with any NSAID use in pregnancy. Women who reported no NSAID use were classified as ÒunexposedÓ. The primary outcome was prevalence of NSAID use in pregnancy. We also examined the incidence of premature closure of ductus arteriosus, patent ductus arteriosus, persistent pulmonary hypertension, intracranial hemorrhage, small for gestational age infants, preterm birth and postpartum hemorrhage in the exposed compared to the unexposed.

Results: A total of 855 pregnant women with inflammatory arthritis were included, of which 294 (34%) reported NSAID use at some time during pregnancy. The most commonly utilized NSAIDs were ibuprofen (39%), aspirin (30%), naproxen (17%), and celecoxib (14%). The prevalence of use was highest in the first trimester (88%), and decreased thereafter (46% second trimester, 31% third trimester). Among those who reported NSAID use in the third trimester (n=92), the mean cumulative days of use was 53.89±30.90 days, with average gestational age at cessation of use being 38.09±1.95 weeks. There was no evidence of an increased risk for any of the outcomes

studied except for maternal hypertension associated with 3rd trimester NSAID use (aRR 2.13, 95% CI 1.18,3.59) (Tables 1 and 2).

Conclusion: NSAID use in this cohort was common with almost one third of the women using this class of medication in the third trimester. Although the sample size was limited, we did not find evidence of increased risk for most of the evaluated outcomes. Additional studies are needed to determine whether NSAID use in the third trimester is associated with increased risk of gestational hypertension/pre-eclampsia.

Table 1. Fetal and Maternal Outcomes among NSAID Exposed and Unexposed

		Anytime during Pregnancy		**3rd Trimester Use**	
	NSAID Unexposed (n=561)	NSAID Exposed (n = 294)	RR	NSAID Exposed (n=94)	RR
Patent ductus arteriosus	5	3	1.14 (0.24,4.63)	2	2.44 (0.35,11.14)
Intracranial hemorrhage	1	3	5.72 (0.74,1.15)	1	6.10 (0.24,155.33)
Postpartum hemorrhage	31	14	0.85 (0.44,1.53)	6	1.15 (0.44,2.48)
Small for gestational age	48	33	1.31 (0.86,1.99)	7	0.88 (0.37,1.75)
Preterm Birth	71	43	1.16 (0.81,1.63)	16	1.37 (0.80,2.18)
Gestational hypertension / Preeclampsia	48	36	1.41 (0.93,2.12)	18	2.24 (1.32,3.59)

Table 2. Adjusted Models for Fetal and Maternal Outcomes among NSAID Exposed and Unexposed		
	Anytime during Pregnancy	3rd Trimester Use
	aRR	aRR
Small for gestational age	1.17 (0.72,1.86)	0.90 (0.35,1.89)[1]
Preterm Birth	1.02 (0.70,1.47)	1.32 (0.76,2.14)
Gestational hypertension / Preeclampsia	1.36 (0.86,2.12)[2]	2.13 (1.18,3.59)[2]
Models adjusted for disease activity, SES, and gestational age at enrollment unless otherwise specified. [1]Only adjusted for disease activity. [2]Adjusted for disease activity, SES, pre-pregnancy BMI, gestational age at enrollment		

Disclosure: **N. Amiri**, None; **G. Bandoli**, None; **D. L. Johnson**, None; **C. D. Chambers**, Contract Apotex, Inc., Barr Labs, Inc., 2,Contract Bristol Myers/Squibb, 2,University of British Columbia, 2,Contract Genzyme (Sanofi-Aventis), 2,Contract UCB Pharma, 2,Contract Janssen Biotech, Inc., 2,Contract Pfizer, 2,Contract AAAAI VAMPSS Post marketing Surveillance of Afluria, 2,Contract Celgene, 2,Contract Takeda, 2,Birth Defects Research Part A: Clinical and Molecular Teratology, 3.

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Pregnancy Comorbidities and Outcomes in Psoriasis and Psoriatic Arthritis: A Prospective Cohort Study

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Pregnancy Comorbidities and Outcomes in Psoriasis and Psoriatic Arthritis: A Prospective Cohort Study

Background/Purpose: While there is some evidence that women with psoriasis (Pso) and psoriatic arthritis (PsA) are at increased risk of various comorbidities, this has not been well described in pregnancy. In addition, there are limited data on the risks of adverse pregnancy outcomes in women with these conditions.

Methods: Individuals were selected (enrolled 2005-2015) from the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy project, a North American prospective cohort study of pregnancy outcome. The ÒexposedÓ were defined as women with singleton live births and PsA (with or without Pso) or psoriasis (Pso) alone. ÒUnexposedÓ were non-diseased pregnant women without exposure to known human teratogens or underlying chronic conditions. The outcomes of interest were baseline differences among the three groups (PsA, Pso, unexposed) and maternal comorbidities. As a secondary objective, we compared selected adverse birth outcomes in the exposed (PsA/Pso) and unexposed groups.

Results: A total of 180 exposed women were identified (91 with PsA and 89 with Pso alone). These were compared to 379 non-diseased unexposed women. Except for greater use of biologics in women with PsA, there were no baseline differences between women with PsA and Pso. However, compared to the unexposed group, the PsA/Pso women had a higher prevalence of unplanned pregnancies, pre-pregnancy overweight or obesity, smoking, and illicit drug use. Moreover, compared to the unexposed, Pso/PsA women had higher rates of pre-existing depression (19.4% vs. 9.4%) and hypertension (6.7% vs. 2.1%) (Table 1). In terms of pregnancy outcomes, there were no differences comparing women with PsA to those with Pso. However, pregnant women with either PsA or Pso were at increased risk for cesarean section (RR 1.42 (95% CI 1.10,1.83)) and preterm birth (RR 1.81 (95% CI 1.02,3.23)) compared to the unexposed (Table 2). There was no increased risk for preeclampsia/pregnancy-induced hypertension or small for gestational age infants in exposed.

Conclusion: In this prospective study, pregnant women with PsA (with or without Pso) and Pso alone were similar in their baseline demographics, comorbidities and frequency of adverse pregnancy outcomes. However, compared to healthy controls, PsA/Pso women had more risk factors for adverse pregnancy outcomes (tobacco use, increased pre-pregnancy BMI, and pre-existing depression and hypertension). After adjusting for covariates, PsA/Pso women had increased risks for cesarean section delivery and preterm birth compared to healthy controls.

Table 1. Baseline characteristics in PsA/Pso exposed compared to unexposed pregnant women			
Characteristic – mean (SD) or n (%)	Exposed (N=180)	Unexposed (N=379)	P value
Maternal Age, years	32.29 (4.52)	31.80 (4.86)	0.26
Race/Ethnicity			
- Non-Hispanic White	147 (81.67)	287 (75.73)	0.09
- Hispanic	13 (7.22)	49 (12.93)	
- African American	7 (3.89)	14 (3.69)	
- Asian/Pacific Islander	6 (3.33)	8 (2.11)	
- American Indian/Native American	3 (1.67)	2 (0.53)	
- Other/Missing	4 (2.22)	19 (5.01)	
Primi-Gravida	68 (37.78)	148 (39.05)	0.77
Prepregnancy BMI			
- <24.9	83 (46.11)	251 (66.23)	<0.05
- >=25	96 (53.33)	126 (33.25)	
Socioeconomic Status (SES)			
- Low	18 (10.00)	31 (8.18)	0.46
- High	155 (86.11)	325 (85.75)	
- Missing	7 (3.89)	23 (6.07)	
Household Income			
- <$10,000	10 (5.56)	11 (2.90)	0.19
- $10,000-$49,9999	43 (23.89)	80 (21.11)	
- >$50,000	119 (66.11)	273 (72.03)	
- Missing	8 (4.44)	15 (3.96)	
Planned pregnancy	105 (58.33)	282 (74.41)	<0.001
Tobacco use	36 (20.00)	8 (2.10)	<0.001
Alcohol use	89 (49.44)	171 (45.12)	0.39
Illicit drug use	7 (3.89)	2 (0.53)	<0.05
Folic acid supplementation	179 (99.44)	376 (99.21)	1
Disease modifying	18 (10.00)	2 (0.53)	

anti-rheumatic drug (DMARD) use*			<0.001
Biologic use$	121 (67.22)	0	-
Glucocorticoid use#	51 (28.33)	14 (3.69)	<0.001

*DMARD was defined as use of any of the following medications: apremilast , azathioprine, chloroquine, cyclosporine, cyclophosphamide, gold, hydroxychloroquine, leflunomide, mepacrine, methotrexate, mycophenolate mofetil, sulfasalazine, tacrolimus, tofacitinib $Biologics were defined as any of the following drugs: abatacept, adalimumab, anakinra, belimumab, certolizumab, etanercept, golimumab, infliximab, rituximab, tocilizumab, ustekinumab #Glucocorticoid use was defined as any orally administered glucocorticoids.

Table 2. Pregnancy outcomes in the PsA/Pso exposed compared unexposed pregnant women

	Exposed (N=180)	Unexposed (N=379)	RR (95% CI)	aRR* (95% CI)
Cesarean section - n (%)	77 (42.78)	98 (25.86)	1.65 (1.30,2.10)	1.42[1] (1.10,1.83)
Preterm birth – n (%)	25 (13.89)	23 (6.07)	2.29 (1.33,3.95)	1.81 (1.02,3.23)
Small for gestational age – n (%)	18 (10.00)	26 (3.86)	1.46 (0.81,2.58)	1.49[2] (0.78,2.77)
Pregnancy induced Hypertension/Pre-eclampsia – n(%)	20 (11.11)	25 (6.60)	1.69 (0.95,2.95)	1.40 (0.77,2.48)

*Adjusted for BMI, SES, tobacco use unless otherwise stated. [1]Adjusted for BMI, SES, race (Caucasian vs. other). [2]Adjusted for BMI, SES, tobacco use and race (Caucasian vs. other).

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Abstract Number: 2444

Effects of Disease Activity and Drug Exposure on Pregnancy Outcomes with Inflammatory Arthritis

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Background/Purpose: Pregnancy is often encountered in women who have inflammatory arthritis (IA), such as rheumatoid arthritis (RA), psoriatic arthritis (PsA), juvenile arthritis (JIA) or ankylosing spondylitis (AS). While patients often forego medications during pregnancy due to safety concerns, rheumatologists often are reluctant to start antirheumatic therapy or maintain tight control of disease activity during pregnancy. Uncertainty exists as to the best practice to achieve optimal pregnancy outcomes. Our goals were to evaluate the effects of disease activity and medication exposure on pregnant patients with IA.

Methods: A retrospective, observational cohort study was carried out at one center, enrolling females aged 18-45 years, diagnosed with RA, JIA, AS or PsA who had: 1) >12 months follow-up and a documented pregnancy in this period; and 2) clinic visits that qualified as being preconception (PRE), pregnancy (1^{st}, 2^{nd} or 3^{rd} trimester) and post-partum. Drug exposure was classified as occurring PRE (>1 month before conception), at risk (RISK- 1^{st} trimester plus 1 month preconception) or during 1^{st}, 2^{nd} and 3^{rd}trimesters of pregnancy (PREG). Data collected included therapies (DMARDS, biologics, steroids, NSAIDS), modified health assessment questionnaire (mHAQ), tender joint count (TJC), swollen joint count (SJC), pain score, and global arthritis score (GAS). GAS was the sum of TJC (0-28) + pt. pain (0-10) + mHAQ (0-24); and remission (REM) <3; low activity 3-7; moderate activity 8-19; high activity >20 Maternal disease activity was further classified as flared or improved (defined: 20% change in TJC+SJC or >3 increase in joint count if PRE count <2). Fetal outcomes were classified as live births or adverse fetal outcomes (AFO: defined as preterm labor, miscarriages, preeclampsia, fetal growth restrictions, or malformations). A $\chi 2$ test of homogeneity was calculated to determine if AFOs were more likely a result of drug exposure or maternal disease activity during pregnancy.

Results: 28 pregnancies (9 RA, 7 PsA, 4 AS, 8 JIA) were observed in 22 patients (8 RA, 6 PsA, 3 AS, 5 JIA). Mean age at delivery was 32 years and disease duration was 10.4 yrs. During PRE the most common drugs used were TNFi (61%), methotrexate (18%), other DMARDS (11%), other

Biologics (11%), Prednisone (21%), and NSAIDs (79%). Drug use during PREG: TNFi (57% same), DMARDS (14% same), Prednisone (21% same), NSAIDs (32% less) and no drugs (14% more). Of the 11 PRE patients in REM, 7/11 stayed in REM or LDAS during PREG; 4/11 were in MDAS or HDAS during PREG. Of the 17 PRE patients with GAS >4, only 4/17 improved to REM or stayed in LDAS during PREG; 13/17 were in MDAS or HDAS during PREG. There were 4 AFOs (2 preterm, 2 miscarriage), but no malformations. The 4 AFOs occurred in women with moderate/high disease activity during pregnancy, and none of the women in remission or low disease activity states had an AFO. There was no significant correlation between the different drug therapies and AFOs (p=0.95).

Conclusion: These observational data showed that adverse fetal outcomes were best avoided by being in REM or LDAS and that AFOs are more likely to be related to disease activity and not drug exposure.

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Abstract Number: 2445

Dermatomyositis and Pregnancy: Assessment of Disease Activity and Pregnancy Outcomes Complicated By Maternal Dermatomyositis

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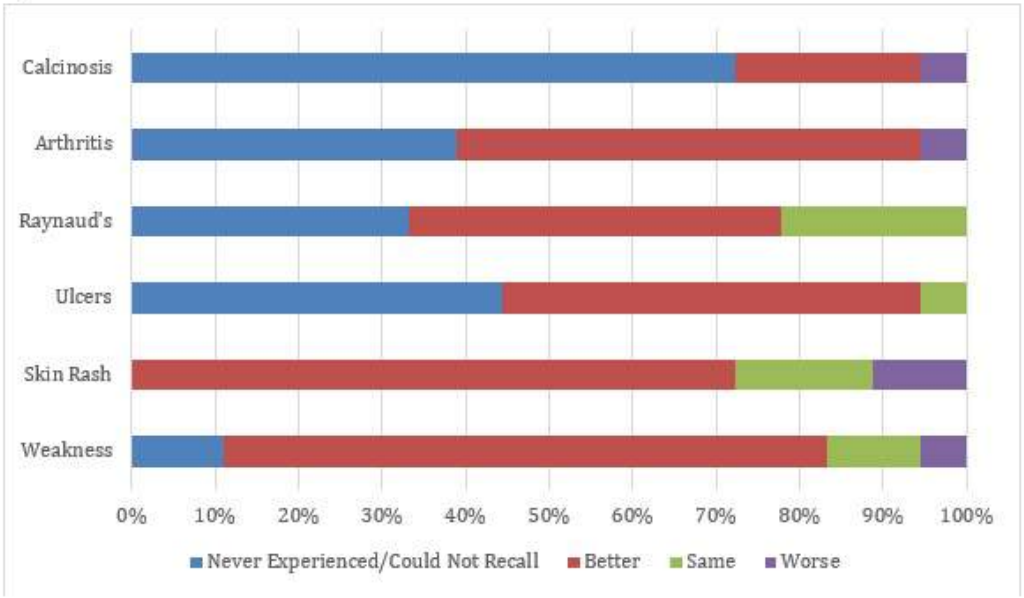
Background/Purpose: The effect of pregnancy on Dermatomyositis (DM) disease activity and on

maternal and fetal outcomes in patients with DM is unclear**.** Study objective is to evaluate disease activity and pregnancy outcomes complicated by maternal dermatomyositis.

Methods: A total of 10 patients with 21 pregnancies from a cohort of 438 DM patients of child-bearing potential, diagnosed between 2006 and 2015 from two centers, were eligible for interview with a specific questionnaire regarding pregnancy and fetal outcomes.

Results: Weakness, rash and arthritis were the most common clinical symptoms that improved during pregnancy in affected patients (Figure 1). In 16 out of 18 pregnancies, patients experienced weakness. Weakness improved during 13 pregnancies (81.3%), stayed the same during 2 pregnancies (12.5%), and worsened during one (6.3%). All 10 patients experienced cutaneous rash during all 18 pregnancies carried to live birth. Cutaneous rash improved during 13 pregnancies (72.2%), remain unchanged during 3 (16.7%), and worsened during 2 (11.1%). Five patients experienced arthralgias or arthritis in a total of 11 pregnancies. Symptoms improved during 10 of these pregnancies (91%) and worsened during one (9%).There were no cases of interstitial lung disease, cancer or antiphospholipid antibody syndrome among the 10 patients studied. One patient suffered from pre-eclampsia while diagnosed with DM. 3 total pregnancy losses: two early miscarriages (< 10 weeks gestation) one therapeutic abortion for an ectopic pregnancy. 3 neonates out of 18 live births went to the NICU after delivery – reasons for transfer: meconium aspiration; apnea and pre- term birth.

Figure 1.



Conclusion: Pregnancy does not appear to carry a worse prognosis for DM patients and all but one of our patients experienced improvement in clinical symptoms during pregnancy.

Disclosure: G. Miller, None; **E. Moore**, None; **A. Valenzuela**, None; **L. Chung**, None; **V. P. Werth**, None.

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pregnancy-outcomes-complicated-by-maternal-dermatomyositis

Abstract Number: 2446

Infantile Hemangiomas in Infants Born to Women with Autoimmune Diseases

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Background/Purpose: Infantile Hemangiomas (IH) are the most common benign vascular tumor in infants, estimated to occur in 4-5% of the general population. Many of the known risk factors for IH (low birth weight, female infant, white race, preterm birth, multiple gestations) are also seen with increased frequency in pregnancies with autoimmune disease. The purpose of this study was to compare the incidence of IH in infants born to women with autoimmune diseases to the incidence in infants born to healthy comparison women, to determine if specific diseases/treatments were associated with risk for IH, and to describe characteristics of infants with more severe IH.

Methods: Data were obtained from the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes among women in the U.S. and Canada. Pregnant women who were recruited into the study from 2004 to 2013, enrolled before 19 weeks gestation, and delivered at least one live born infant were eligible for analysis. To increase the reliability and validity of the diagnosis of IH, the sample was further restricted to infants that had received a blinded dysmorphological examination for major and minor defects.

Results: 1233 infants born to 1191 women met criteria for inclusion. The overall incidence of IH was 60/1233 or 4.9%. Of these, 52/993 (5.2%) infants with IH were born to mothers with an autoimmune disease, and 8/240 (3.3%) infants with IH were born to mothers without autoimmune disease ($p = 0.219$). There was a significant association between the presence of ulcerative colitis in the mother and IH in the child ($p = 0.014$) compared with other autoimmune diseases [See Table 1]. In multivariate analysis, this association remained. Of the 60 infants with IH, 5 were classified as at least 3x3cm; all 5 of these infants were born to mothers in the autoimmune disease group who were taking a biologic medication during pregnancy.

Table 1. Outcomes among women in OTIS cohort 2004-2013 with autoimmune disease (n = 993) categorized by presence of Infantile Hemangioma (IH)

Outcome	No IH (n = 941)	IH (n = 52)	p value
	n (%)	n (%)	
Presence of autoimmune disease (n = 993)	941 (80.2)	52 (86.7)	p = 0.219
Ankylosing spondylitis (n = 83)	79 (95.2)	4 (4.8)	p = 0.858
Crohn's Disease (n = 220)	208 (94.5)	12 (5.5)	p = 0.869
Lupus (n = 13)	13 (100)	0 (0)	p = 0.394
Psoriasis (n = 197)	190 (96.4)	7 (3.6)	p = 0.236
Psoriatic arthritis (n = 101)	96 (95)	5 (5.0)	p = 0.892
Raynauds Phenomenon (n = 20)	19 (95)	1 (5.0)	p = 0.962
Rheumatoid arthritis (n = 520)	492 (94.6)	28 (5.4)	p = 0.826
Sjogren's Syndrome (n = 14)	14 (100)	0 (0)	p = 0.376
Ulcerative Colitis (n = 35)	30 (85.7)	5 (14.3)	*p = 0.014*
Other autoimmune disease (n = 55)	52 (94.5)	3 (5.5)	p = 0.941
Medication Use			
NSAIDs (n = 300)	288 (96)	12 (4.0)	p = 0.250
Steroids (n = 409)	389 (95.1)	20 (4.9)	p = 0.682
Biologics (n = 773)	728 (94.2)	45 (5.8)	p = 0.121
DMARDs (n = 226)	220 (97.3)	6 (2.7)	*p = 0.047**

*negative association

Conclusion: The incidence of IH in this cohort was similar to the estimated incidence in the general population. While there was no significant difference between the overall incidence of IH in children born to women with autoimmune disease compared to healthy controls, the fact that all 5 of the largest and thus more clinically significant cases of IH occurred entirely within the autoimmune disease cohort may have important implications. These results add to the limited knowledge available regarding fetal outcomes and presence of malformations in this population.

Disclosure: C. Forbess Smith, None; **K. L. Jones**, None; **D. L. Johnson**, None; **C. D. Chambers**, None.

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Abstract Number: 2447

Does a History of Abnormal Pap Smear or Preceeding HPV Infection Affect Humoral Immune Response to Quadrivalent Human Papilloma Virus (qHPV) Vaccine in Women with Systemic Lupus Erythematosus (SLE)

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Background/Purpose: Cervical neoplasia is increased in women with SLE. HPV types 16 & 18 account for 70% of cervical cancer. Natural HPV cervical infection generates type specific anti HPV antibodies (HPV-Ab) which are usually cross protective and low titer. For this study, HPV-Ab to types 6, 11, 16 and 18 were obtained pre and post vaccine (Phase I trial for Gardasil® in SLE) and analyzed to determine if antibody (Ab) vaccine response (AVR) related to abnormal pap smear/cervical neoplasia (AP/CM) or history (h/o) of preceding HPV infection (HPV-I). AVR in SLE could be suppressed in those with AB/CN, due to inability to clear persistent infection; alternatively, previous exposure could lead to a more vigorous anamnestic response.

Methods: In this trial**,** approved by the Human Investigation Committee at Wayne State University & the U.S. Food and Drug Administration, 34 women ages 19-50 years (yrs.) with a h/o of mild to moderate SLE by ACR criteria & minimally active or inactive SLE received qHPV vaccine (Gardasil®) at the standard dosing schedule (0, 2 months, 6 months). Patients excluded if they had active disease (SELENA-SLEDAI >2), h/o of severe disease, deep venous thrombosis, on >400 mg/day of hydroxychloroquine, on >15 mg/day of prednisone, or had active infections. Ab titers to HPV 6, 11, 16 &18 and h/o of AB/CN were evaluated pre-vaccine. Ab titers were measured by HPV competitive Luminex Immunoassay. Pearson Chi Square & logistic regression controlling for patient demographics (PD) were used to evaluate pre-vaccine HPV-Ab titers in relation to h/o of AB/CN. Linear regression controlling for PD & t-test were used to evaluate the magnitude of rise of Geometric Mean Titers (GMTs) in relation to h/o of AB/CN or preceding HPV-I.

Results: Women in the study (n=34) were predominantly African-American (79%), mean age 38.1 yrs., mean age at diagnosis of SLE at 28.6 yrs., 32.4% had h/o of smoking, 91% had ≥4 sexual partners, 50% had a h/o of sexually transmitted diseases, & 27.3% used condoms on a regular basis. History of AB/CN occurred in 52.9% {ASCUS (atypical glandular cells of undetermined significance) to CIN 3 (cervical intraepithelial neoplasia grade 3)}. Seven women were negative at baseline for all 4 Ab types in the vaccine; positive HPV Ab titers at baseline were seen in 79 % (n=27) for ≥1 of the HPV types in the vaccine, indicating previous HPV-I in most patients (15=exposed to only one HPV type, 12=exposed to ≥1 of the 4 types). Statistical analysis showed: those with a h/o of AP/CN were likely to have a positive HPV Ab result pre-vaccine to ≥ 1 of the 4 types contained in the vaccine, p=0.035. However, there was no difference in the magnitude of rise of HPV-Ab GMTs between those with a history of AB/CN vs. those that had no h/o of AB/CN or between those with preceding HPV-I vs. those who were Ab negative at baseline.

Conclusion: Our study shows that in women with SLE, the presence of HPV-Ab for 6, 11, 16, and 18 prior to receiving q HPV vaccine clearly correlates with h/o of AB/CN. However, neither AB/CN nor preceding HPV-I had an impact on humoral response to vaccination, showing no anamnestic response to previous natural infection. This supports not checking HPV antibody status before vaccinating women with SLE.

Disclosure: J. P. Dhar, None; **L. Essenmacher**, None; **R. Dhar**, None; **A. Magee**, None; **J. Ager**, None; **R. Sokol**, None.

Abstract Number: 2448

Contraceptive Methods in Women with Rheumatoid Arthritis

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Background/Purpose: Women with rheumatoid arthritis (RA) often take medications to control disease activity that, should a woman become pregnant, may increase the risk of poor pregnancy outcomes, such as miscarriage and birth defects. The objective of this study was to determine if women with RA are using highly effective contraceptives, and if contraception differs by current medication use.

Methods: Women with RA (2010 ACR/EULAR criteria) aged 20-40 seen in a university clinic without a history of ovarian surgery or prior exposure to possible ovary-toxic medications were invited to participate in a cross-sectional survey. The survey included questions on current medications taken for RA and contraceptive methods used in the previous three months. Contraceptive methods were categorized as highly effective (tubal ligation or vasectomy, IUD, Implanon/Nexplanon), effective (progesterone-only pill, estrogen-containing pill, Depo-Provera injections), and ineffective (abstinence, patient didn't think she could get pregnant, withdrawal, condoms, diaphragm, and none). Additionally, patients were asked if they had discussed contraceptives with their rheumatologist. Contraceptive methods were reported as counts and frequencies overall and in each medication class, and Fisher's exact test analyzed differences across medication classes.

Results: There were 52 RA patients; 79% white with a mean age of 32 and mean RA duration of 9 years. Education beyond high school was completed by 98% of patients, 61% of patients were

married, and 56% of patients worked full time. Discussing contraception with their rheumatologist was recalled by 71% of patients. Current medications included TNF-inhibitor (50%), methotrexate (48%), hydroxychloroquine (38%), NSAIDs (31%), corticosteroids (29%), sulfasalazine (15%), other biologics (13%), and other DMARDs (8%). In the 47 patients of reproductive age who were not trying to conceive, 38% were using ineffective, 34% were using effective, and 28% were using highly effective contraceptive methods (Table 1). Among 25 methotrexate users, 44% were using highly effective contraceptives, compared to 9% of patients not taking methotrexate (p=0.02). However, 24% of methotrexate users were using ineffective contraceptives. Among patients taking other DMARDs or biologics, drugs with very limited pregnancy safety information, 18% were using highly effective, 45% were using effective, and 36% were using ineffective contraceptive methods.

Conclusion: In this highly educated group of RA patients, most women were using effective or highly effective methods of contraception. It appears that rheumatologists are targeting highly effective contraceptives to women who are taking methotrexate, a highly teratogenic drug. However, there is room for improvement for women taking newer DMARDs and biologics, for which we have inadequate safety data in pregnancy.

Table 1. Contraceptive methods in RA patients stratified by current medication use (n=47).

		Highly Effective	Effective	Ineffective
Overall (n=47)	n (%)	13 (27.7%)	16 (34.0%)	18 (38.3%)
Methotrexate (n=25)	n (%)	11 (44.0%)	8 (32.0%)	6 (24.0%)
TNF-inhibitor (n=22)	n (%)	4 (18.2%)	10 (45.5%)	8 (36.4%)
Hydroxychloroquine (n=18)	n (%)	4 (22.2%)	7 (38.9%)	7 (38.9%)
NSAIDs (n=14)	n (%)	4 (28.6%)	5 (35.7%)	5 (35.7%)
Steroids (n=13)	n (%)	6 (46.2%)	3 (23.1%)	4 (30.8%)
Other Biologics* (n=7)	n (%)	2 (28.6%)	2 (28.6%)	3 (42.9%)
Sulfasalazine (n=5)	n (%)	1 (20.0%)	0 (0.0%)	4 (80.0%)
Other DMARDs* (n=4)	n (%)	0 (0.0%)	3 (75.0%)	1 (25.0%)

*Other biologics included abatacept, rituximab, and tocilizumab. Other DMARDs included leflunomide and tofacitinib.

Disclosure: M. E. B. Clowse, Pfizer, Janssen, 2,UCB Pharma, 5; **G. McDaniel**, None; **A. M. Eudy**, GSK, 5.

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Abstract Number: 2449

Infertility in Women with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a rheumatic disease that can affect women of reproductive age, and data suggest infertility is increased in RA. The objective of this analysis was to determine the frequency of infertility among RA patients, as well as reasons for infertility.

Methods: Women with RA aged 20-40 seen in a university clinic without a history of ovarian surgery or prior exposure to possible ovary-toxic medications were invited to participate in a cross-sectional survey. The survey included questions on infertility, reasons for infertility, physician-assisted reproductive methods, and how RA affected the desired number of children. Infertility was defined as a patient reporting being unable to get pregnant after 12 months of trying or a patient reporting physician-diagnosed infertility. Ovarian reserve was assessed by measuring anti-Müllerian hormone (AMH). Decreased ovarian reserve was defined as AMH <1 ng/ml. Multivariate linear models estimated the effect of age, hormonal contraceptives, and cumulative methotrexate (MTX) dose on AMH levels.

Results: There were 52 RA patients; 79% white with a mean age of 31. Infertility was reported in 23% of 26 patients who had previously tried to conceive. Reasons for infertility included problems with ovulation (17%), unexplained infertility (50%), or unknown (17%). Physician-assisted reproductive methods had been used by 19% of patients who had previously tried to conceive, including taking oral medications (100%), injections (60%), insemination with partner's sperm (20%), and in vitro fertilization with patient's eggs (20%). Half of the 50 patients who had not completed childbearing prior to RA diagnosis responded that being diagnosed with RA led to wanting fewer children. The main reasons for wanting fewer children included concerns of being able to care for children, RA medications harming the baby, and a postpartum flare. Health was the most frequently reported factor patients took into consideration when making the decision to have children (73%), followed by financial concerns (56%), fatigue (50%), and pain (39%). Mean AMH was 3.2 ng/ml (SD: 2.6), with 21% of patients having decreased ovarian reserve. Decreased ovarian reserve was found in 23% of patients with prior MTX use and 11% of patients without prior MTX use (p=0.7). In a multivariate linear model, AMH decreased with age (-0.23 ng/ml per 1-year increase in age) and current hormonal contraceptive use (-1.43 ng/ml compared to patients not taking hormonal contraceptives), but cumulative MTX dose had no observed effect on AMH levels. There were no observed differences in AMH levels in women who reported infertility compared to fertile patients.

Conclusion: The prevalence of infertility among RA patients who had tried to conceive was greater than the prevalence in the general population (23% compared to ~10%). There was not obvious cause for infertility among these women with RA. Age and hormonal contraceptives appeared to be associated with decreased AMH levels. However, there was no evidence of decreased AMH levels with increasing cumulative MTX, and AMH levels did not differ in patients reporting infertility.

Disclosure: M. E. B. Clowse, Pfizer, Janssen, 2,UCB Pharma, 5; **G. McDaniel**, None; **A. M. Eudy**, GSK, 5.

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Abstract Number: 2450

Do Patients with Systemic Lupus Erythematosus and Rheumatoid Arthritis Have Reduced Fertility and Parity? a Systematic Review

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Background/Purpose: Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA) often affect women of reproductive age. It remains unclear as to whether these inflammatory rheumatic conditions have an impact on fertility and parity. The aim of our study was to perform a systematic review of the literature to determine if fertility and parity are affected in patients with SLE and RA.

Methods: MEDLINE and EMBASE databases were searched for relevant publications from their inception through to October 2015, using terms including SLE and RA combined with fertility and parity. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines were followed. MeSH terms such as fertility (fertil*) and pregnancy (pregn*) were included. Two authors screened abstracts to identify eligible articles.

Results: 2,444 articles were identified which consisted of 1,724 and 720 articles from EMBASE and MEDLINE databases respectively. 1,840 duplicated articles were excluded. After exclusion of non-rheumatological conditions, 334 articles remained. 38 papers related to SLE and RA were identified of which 4 papers had both SLE and RA data totalling RA=22 and SLE n=20. A total of 7293 patients, 4406 with RA and 2287 with SLE were included. Articles captured retrospective and prospective case control, cohort and cross-sectional studies ranging from years 1956 to 2015. There

was variation in SLE and RA diagnostic criteria used. Exclusion criteria such as other rheumatic diseases such as antiphospholipid syndrome, effects of fertility on disease, assisted reproduction, conference abstracts and non-English papers were applied. In the RA cohort, 5 studies reported no difference in fertility and/or parity. 8 RA studies reported reduced fertility/early menopause and 9 reduced parity/increased pregnancy loss. In the SLE cohort, 5 studies reported no difference in fertility and/or parity. 11 reported reduced fertility/ovarian reserve or menstrual dysfunction affecting fertility and 6 reported reduced parity/pregnancy loss.

Conclusion: This comprehensive review captured fertility and parity information on 7,293 patients. Limitations of our analysis included heterogeneity of outcome measures, which included ovarian reserve, anti-mullerian hormone (AMH) levels, TTP (time to pregnancy), nulliparity, premature menopause and pregnancy rates. Additionally, potential confounding factors included the effect of disease activity and differences between older and more recent studies. Despite the limitations, the majority of studies showed reduction in fertility and/or parity. Data from multicentre cohorts would be valuable.

Disclosure: C. L. Murphy, None; **H. Sharp**, None; **H. Nguyen**, None; **A. Rahman**, None; **I. Giles**, None.

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Abstract Number: 2451

Evaluation of Ovarian Reserve and Function in Adolescent Females with Systemic Lupus Erythematosus

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Background/Purpose: The onset of childhood systemic lupus erythematosus (cSLE) most frequently occurs after age 12. Studies in adolescents with cSLE suggest that ovarian dysfunction may be common, however little is known about mechanisms of ovarian dysfunction in these patients, the potential for permanent ovarian damage and the impact on future fertility. Anti-müllerian

hormone (AMH) has been found to be useful in assessing ovarian reserve. Human oocytes peak in number during fetal life and decrease with age. Accordingly,, AMH levels decrease very slowly from puberty until menopause. AMH is has been demonstrated as a highly sensitive marker of diminished ovarian reserve in patients with cancer after chemotherapy. Only one study of ovarian reserve in adult women with SLE suggests lower levels of AMH compared to healthy controls. To our knowledge, examination of ovarian reserve and its clinical implications has not been studied in adolescent females with SLE.

Methods: Data is being collected prospectively on an ongoing basis since October 2014. Female adolescents, 14 to 19 years old, with diagnosis of SLE by ACR criteria, oligoarticular and polyarticular JIA by ILAR criteria and healthy controls with gynecological age (chronological age minus age at menarche) ≥ 2 years, are eligible to participate. Pregnant patients, patients on any form of hormonal contraception and with a diagnosis of polycystic ovarian syndrome were excluded. The primary outcome is ovarian reserve, measured by AMH levels (AMH AssessR), for which normative data is available. Demographic and clinical data is collected, including: age, race, age of menarche, characteristics of menses, birth control behaviors, weight and BMI for all patients. Additionally,age of disease onset, disease activity measured by SLEDAI, disease damage measured by SLICC, current medications and prior exposure to cyclophosphamide is being collected for SLE patients.

Results: To date, 16 subjects with SLE, 26 healthy controls and 6 subjects with diagnosis of JIA have been enrolled. Median age at enrollment was 17.4 years (IQR: 16.5, 19.4). Race and ethnicity were similar in the two groups; 22.5% of subjects were black, 57,1% Hispanic, 18.4% other/ mixed race, 2% white. Median age at menarche was 12 years. AMH levels were obtained in all participants. Median AMH was significantly lower in SLE (2.87 ng/ml, IQR: 2.12-3.70) vs health controls (4.80 ng/ml, IQR: 3.26-5.78), (p value = 0.04). Three out of 16 (19%) SLE subjects had AMH levels below normative values for healthy adolescents. Out of these 3 patients one had previously received cyclophosphamide and one had been pregnant 3 years prior to enrollment with a normal pregnancy and delivery.

Conclusion: Ovarian reserve, measured by AMH levels, appears to be affected in a small proportion of pediatric SLE patient compared to healthy controls. This information is important to keep in mind when educating and counseling patients on expectations regarding fertility.

Disclosure: Y. Sterba, None; **T. Tanner**, None; **D. Wahezi**, None.

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Abstract Number: 2452

Reduced Ovarian Reserve in Young Juvenile Idiopathic Arthritis Patients

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Background/Purpose: Juvenile idiopathic arthritis (JIA) occurs during reproductive age and therefore ovarian reserve and future fertility are a relevant issue for this population. There is, however, no study performing a complete assessment of ovarian function in this chronic inflammatory disease.

Methods: One hundred and seven adolescent and young adult female patients with JIA (ILAR criteria) were selected for this study. Eight-four patients were excluded due to: hypothyroidism (n=6), current amenorrhea (n=4), current pregnancy/lactation (n=3), polycystic ovarian syndrome (n=2) and unwillingness to stop hormonal contraceptive or not agreeing to participate in this study (n=69). Therefore, 23 JIA patients and 23 healthy controls were studied. Complete ovarian function was assessed during the early follicular phase of the menstrual cycle (between the first and fifth day of menses) with estradiol, luteinizing hormone (LH), follicle stimulating hormone (FSH) - all three by radioimmunoassay, anti-Müllerian hormone (AMH) - by automated Access AMH immunoassay, Beckman Coulter, and antral follicle count (AFC) - by transvaginal or abdominal ultrasound. Demographic data, menstrual abnormalities, patient and physician visual analogue scales (VAS), number of active and limited joints, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and treatment were also evaluated.

Results: The median current age (22 vs. 23 years, p=0.834), menstrual flow duration (5 vs. 5 days, p=0.478) and cycle length (28 vs. 29 days, p=0.750) were similar in JIA patients and healthy controls. The median of AMH levels [2.66 (0.47-6.47) vs. 5.43 (0.98-17.24) ng/mL, p=0.010] were significantly reduced in JIA patients *versus*controls, whereas FSH [6.3 (4.7-12.2) vs. 5.7(2.6-9.8) IU/L, p=0.029], LH [7.7(2.4-13.2) vs. 4.9(1.1-14.4) IU/L, p=0.027] and estradiol levels [47.4 (25-8-160.2) vs. 35.1 (26.2-71.0) pg/mL, p=0.02] were significantly elevated in the latter group. AFC was comparable in JIA and controls (p>0.05). Further analysis of JIA patients revealed that current age, disease duration, number of active and limited joints, ESR, CRP, patient and physician VAS,

cumulative glucocorticoid and cumulative methotrexate dose were not correlated with AMH, FSH, estradiol levels or AFC ($p>0.05$).

Conclusion: The present study was the first to identify a subclinical ovarian dysfunction in JIA patients during reproductive age, not correlated with disease activity or treatment factors. Future studies are necessary to determine the possible role of ovarian autoantibodies for this condition.

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Abstract Number: 2453

The Prevention, Screening, and Treatment of Congenital Heart Block from Neonatal Lupus: A Survey of Provider Practices

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Background/Purpose: There are presently no official guidelines about the prevention, screening, and treatment of congenital heart block (CHB) due to maternal Ro antibodies. The objective of this study was to survey an international sample of providers to determine their current practices.

Methods: A survey was designed by the organizing committee of the 9thInternational Conference or Reproduction, Pregnancy and Rheumatic Diseases. The survey was sent to 330 people who had attended prior conferences or were registered for this conference, were authors of recent publications on rheumatic diseases and pregnancy, or were authors of abstracts on rheumatic

diseases and pregnancy from the ACR meetings in 2012, 2013, and 2014. Respondents who did not provide demographic information were excluded from the final analysis (n=11).

Results: There were 48 respondents. Most (55%) follow >15 pregnancies in rheumatic patients per year, and 33% were practicing rheumatologists for >15 years. Most were university-based physicians (88%) and from North America (42%) or Europe (42%). Screening: For anti-Ro/SSA positive women, 80% recommended serial fetal ECHOs, with most starting at gestational week 16 (59%) and stopping at week 28 (25%), although the time to stop varied widely between weeks 22 and 34. For women without a prior infant with neonatal lupus, respondents recommend every other week (44%) or weekly (28%) fetal ECHOs, and 5% of respondents preferred a plan of two fetal echoes. For women with a prior infant with neonatal lupus, 80% recommend weekly fetal ECHOs. Prevention: Hydroxychloroquine was recommended by 67% of respondents to prevent CHB and most would recommend starting the drug prior to pregnancy (62%). Treatment: Respondents were asked about medications for varying degrees of CHB in a 20-week pregnant, anti-Ro and La positive SLE patient.Respondents recommended dexamethasone (53%) or HCQ (43%) for 1st degree HB; dexamethasone (88%) for 2nd degree HB; and dexamethasone (55%), IVIg (33%), or no therapy (27%) for complete HB. When dexamethasone was started for 2nd degree CHB, 58% would stop dexamethasone if it progressed to complete heart block, 47% would stop if heart block disappeared, and 24% would stop if the 2nd degree CHB remained.

Conclusion: Despite the absence of official guidelines, many physicians with a focus on pregnancy and rheumatic disease have developed similar patterns in the screening, prevention, and treatment of CHB. These include serial fetal ECHOs, preventive HCQ, and treatment of early heart block with dexamethasone. These practices are not uniform, however, and have not been formally tested in prospective trials. The next step in this field must include testing of these approaches to identify the most cost effective and efficacious plan for these pregnancies.

Disclosure: M. E. B. Clowse, Pfizer, Janssen, 2,UCB Pharma, 5; **A. M. Eudy**, GSK, 5; **B. L. Bermas**, UptoDate, 7; **E. Chakravarty**, None; **L. R. Sammaritano**, None; **C. D. Chambers**, None.

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Abstract Number: 2454

Cohort of Pregnant Women with Ro/La Antibodies: Risk of Fetal Third Degree Atrioventricular Block and Use of Hydroxychloroquine

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Background/Purpose: Third degree atrioventricular block(AVB), a rare congenital complication, duplicate-triplicate frequency up to 2% when Ro/La maternal antibodies are present. Incidence rises to 17-20% in mothers with a previous child with AVB. Maternal consumption of hydroxychloroquine seems to reduce this risk. The purpose was to evaluate the incidence of fetal AVB and its relationship with the consumption of hydroxychloroquine in women with Ro/La antibodies whose pregnancies have been followed at our hospital.

Methods: We reviewed the electronic medical records from years 2000 to 2014 of a) all pregnant women with known Ro/La antibodies, b) all pregnant women with hydroxychloroquine consumption in the pharmacy registry and c) all mothers of children younger than 2 years old with AVB and/or pacemaker placement.

Results: 62 pregnancies in 47 mothers with Ro/La antibodies were identified. Pregnant women who had consumed hydroxychloroquine during all the pregnancy (n=14) were compared with those who had not(n=48). Demographic characteristics are shown in table 1. One newborn (7.1%) suffered a AVB in the hydroxychloroquine group versus 7 newborn in the group without hydroxychloroquine (14.6%)(p=0.5). None of the mothers had more than one pregnancy with AVB. AVB was detected at a median gestational age of 20 weeks and they were all intrauterine (table 2). Between 2000 and 2014, 23 AVB were diagnosed on children younger than 2 years old, 10 of them were associated with the presence of antibodies and/or a maternal rheumatologic disease. 3 of these children (30%) required the collocation of a pacemaker before 2 years of age and 2 children (20%) died before a pacemaker could be implanted. The other 13 (10 followed up for more than 2 years) congenital AVB were associated to congenital structural heart disease and 100% required a pacemaker implantation ($p<0.001$ versus AVB without structural heart disease)(table 2).

Conclusion: A high incidence of AVB in patients with Ro/La antibodies in our hospital was observed (12.9 %), perhaps due to derivation bias. Although AVB was more frequent in mothers without hydroxychloroquine (14.6% versus 7.1%), the difference was not statistically significant. All congenital AVB diagnosed at our hospital without structural heart disease were associated with a rheumatic disease or presence of maternal antibodies. Table 1: Pregnancy characteristics of women with Ro/La antibodies

	Women with Ro/La antibodies treated with Hydroxychloroquine during pregnancy(n=14)	Women with Ro/La antibodies without Hydroxychloroquine during pregnancy(n=48)	P value
Maternal age at the time of pregnancy, mean(SD)	34.1 (3.3)	34.6 (4.8)	0.7
Ro +, % (95% CI)	100	93.8 (86.6-100)	0.34
La +, % (95% CI)	42.9 (13.2-72.5)	50 (35.3-64.7)	0.64
Antiphospholipid syndrome % (95% CI)			
- Lupus anticoagulant	7.1 (8.2-22)	0	0.07
- Anticardiolipins	21.4 (3.1-46)	4.2 (1.7-100)	**0.04**
Maternal rheumatologic disease, n			
- Systemic lupus erithematosus	11	8	**<0.001**
- Sjogren	3	16	0.52
- Mixed connective tissue disease	0	5	0.58
- Rheumatoid arthritis	0	4	0.57
- Scleroderma	0	2	1
- Polychondritis	0	1	1
- Unknown maternal diagnosis	0	12	0.052
Pregnancy outcomes: % (95%CI)			
- Abortion	14.3 (-6.7-35.3)	4.2 (-1.7-100)	0.18
- Fetal death	0	2.1 (-2.1-6.3)	0.59
- Live newborn	85.7 (64.7-106)	93.8 (86.6-100)	0.33
Fetal complications: % (95%CI)			
- Intrauterine growth restriction	14.3 (6.7-35.3)	6.3 (-0.8-13.4)	0.31
- Preterm	0	0	
- AVB	7.1 (1.8-33.9)	14.6 (6.1-27.8)	0.5
- Neonatal complications	0	0	
- Neonatal cutaneous lupus	0	0	
Maternal complications: % (95%CI)			
- Pre-eclampsia	21.4 (-3.1-46)	8.3 (0.2-16.4)	0.17
- Eclampsia	0	0	
- Gestational diabetes	0	0	
- Gestational hypertension	7.1 (1.8-33.9)	4.2 (0.51-14.2)	0.54
Treatment during pregnancy: % (95% CI)			
- Aspirine	28.6 (1.5-55.6)	4.2 (-1.7-10)	**0.007**
- Glucocorticoids	28.6 (1.5-55.6)	10.4 (1.5-19.4)	0.09

- Azathioprine	14.3 (-6.7-35.3)	0	**0.008**
Pregnancy duration, weeks, median (IQR)	36.5 (35-38)	38 (35-39)	0.12
Hospital follow up, years, median (IQR)	9.1 (4.8-12.8)	9.1 (5-10.5)	0.47

Table 2: Newborn AVB before 2 years of age

	AVB with structural heart disease (n=13)	AVB without structural heart disease (n=10)	P value
Mother with Ro antibodies, n/tested (%)	0	8/8 (100)	0.0001
Mother with La antibodies, n/tested (%)	0	7/8 (87,5)	<0.0001
Neonatal death	0	1 (10)	0.2437
Pacemaker requirement before 2 years of age, n (%)	13 (100%)	3 (30%)	<0.001
Death before 2 years of age, n (%)	4/10 (40%)	2/10 (20%)	0.34
Gestational age at the time of AVB, median (IQR)	----	20 (20-25)	
PostnatalAVB, n (%)	13 (100%)	0	<0.0001
Pregnancy duration, median (IQR)	38 (37-38)	37 (35-37)	0.08

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Abstract Number: 2455

Transcriptome Profile of Cells Isolated from a CHB Heart

Support an Exuberant Inflammatory/Pro-Fibrotic Cascade

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Background/Purpose: Histologic correlates of anti-Ro associated congenital heart block (CHB) are apoptosis and calcification of cardiomyocytes with fibrosis of the AV node surrounded by infiltrating macrophages and giant cells. This study leveraged an unprecedented opportunity to interrogate the transcriptome of different cell types in a fetal heart dying with CHB.

Methods: Aortas from a 19 wk CHB fetal heart and a healthy 22 wk heart were cannulated using a Langendorff preparation with proteolytic enzymes to yield a single cell suspension. DAPI negative cells were isolated by flow using antibodies to CD14/CD45, CD31, and podoplanin, to yield leukocytes, endothelial cells, and fibroblasts, respectively. After RNA isolation and cDNA library preparation, RNA-Seq and transcriptome analysis were performed. Expression of lineage markers was consistent with the isolates based on flow markers. Data are expressed as log2 transcripts per million.

Results: Transcriptomes of the two hearts for each isolated fraction were compared. For leukocytes, in CHB vs healthy there were 5000 genes greater than a threshold ratio of 0.78 (expressed as log2 difference). Based on the DAVID annotation, data were organized into clusters of closely related genes. Within the term inflammatory response (p=1.66E-4) for the ratio of CHB/healthy, the genes were IL8 (4.13), IL6 (6.72), TNFa (0.78), and EDN1 (5.17). In addition, leukocyte gene expression of FCGR3A, TLR7 and IRF5 was higher in CHB vs control (2.6,1.37 and 0.91, respectively), a result supporting that the requisite machinery is upregulated to effect anti-Ro-hYRNA ligation and activate macrophages via TLR signaling. For endothelial cells, 7000 genes exceeded a ratio of 0.78 for CHB/healthy. Within the term inflammatory response (p=1E-5), FOS, FOSB, NFKB1A, and NFKBIZ were expressed with ratios of 1.47, 2.46, 1.03, and 2.75. Within the categories IMMUNE (p=4E-2) and cell adhesion (p=1.42E-06) higher expressed genes included CTGF (2.06), PTGS2 (2.53), SOCS3 (1.56), and OAS3 (2.52) along with ICAM1 (2.12), CCL2 (2.75), IL32 (2.81), VCAM1 (3.85), and SELE (2.4). Likewise within the death category (2.62E-08), PPP1R15A (1.39), XAF1 (3.77), GADD45B (1.94), and TNFAIP3 (3.06) were increased in CHB. These data support endothelial cells in leukocyte recruitment. For the fibroblasts, 4500 genes were above the CHB/healthy threshold (Table 1). CHB fibroblasts showed increased expression of

pro-fibrotic genes while attenuating anti-fibrotic genes. The cardiomyopathy marker, XIRP2 (3.15), as well as genes resisting and promoting vascular stiffness (ELN [-2.23] and TTN [2.12], respectively) were also identified.

Conclusion: These data support that autoimmune CHB is a complex disease with contributions from death pathways, inflammation and fibrosis. Scarring likely results from a multi pronged pro-fibrotic environment whereby fibrosis promoting genes undermine genes that forestall fibrosis.

Table 1 - Fibroblasts

Genes that promote fibrosis		
Candidate	CHB	Control
SCN5A	11.25*	9.96
CPEB4	11.23	9.76
EDN1	8.4	7.01
Genes that resist fibrosis		
CLU	11.77	13.52
DUSP1	12.37	13.54
TIMP3	12.88	15.05
TIMP1	9.94	12.65
CTHRC1	7.61	8.48
MEST	11.18	13.27

*Units, log2(average of transcripts)

Disclosure: R. M. Clancy, None; **A. Markham**, None; **T. A. Jackson**, None; **S. Rasmussen**, None; **M. Blumenberg**, None; **J. P. Buyon**, None.

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Abstract Number: 2456

Risk Factors for Adverse Pregnancy Outcome in Antiphospholipid Antibodies Carriers: Results from a Multicenter Italian Cohort over 20 Years of Experience

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Risk Factors for Adverse Pregnancy Outcome in Antiphospholipid Antibodies Carriers:

Results From a Multicenter Italian Cohort Over 20 Years Of Experience

Background/Purpose: Antiphospholipid antibodies (aPL) are risk factors for Adverse Pregnancy Outcome (APO). In particular, for aPL carriers (patients with aPL positivity with no thrombotic or obstetric history) pregnancy outcome and treatment are still not defined. Here we critically reviewed pregnancy outcome in a large multicenter cohort of aPL carriers patients, according to different serological profile and treatment protocols.

Methods: We reviewed 70 pregnancies in 62 patients, that were prospectively followed in 3 Italian centers over 20 years (1994-2015). Patients with previous clinical events (thrombosis, any APO in previous pregnancies and also preterm birth <37 w for any reasons) or concomitant autoimmune diseases were excluded. Patients with aPL positivity and non-criteria manifestations were included. aPL profile was defined as the combination of the 3 criteria tests for aPL (Lupus Anticoagulant, anti-cardiolipin, anti-Beta2 Glycoprotein I). APO was defined as at least one of the followings: miscarriage (<10^{th} week), fetal death (≥10^{th} week), severe preterm delivery (≤34^{th} week) with or without preeclampsia (PE), HELLP syndrome or perinatal death.

Results: Mean age at discovery of aPL was 31 years and mean age at pregnancy was 32 years. Regarding aPL profile: 44 (63%) were single positive, 17 (24%) were double and 9 (13%) were triple. aPL non criteria manifestations were present in 6 (8%) and lupus-like manifestations in 5 (7%). Nine pregnancies had a combination treatment with prophylactic low molecular weight heparin (LMWH) plus low dose aspirin (LDA), 37 had LDA alone and 24 had no treatment. We observed 2 thrombotic events (3%), 1 deep venous thrombosis (6th week, in a single positive low titer, before the start of treatment) and 1 ischemic stroke (37th week, in a triple positive, already in treatment with combination therapy). We recorded 6 APO, all in spontaneous pregnancies: 3 fetal deaths and 3 pre-term birth ≤34^{th} week with PE. We then performed a univariate analysis comparing

8 complicated pregnancies (6 APO plus 2 thrombosis) with 62 non-complicated pregnancies (Table 1). Acquired risk factors (p:0.007), non-criteria aPL (p:0.017) and lupus-like manifestation (p:0.009), triple positive aPL profile (p:0.0005) were associated with APO. The combination treatment was also more frequent in APO pregnancies (p:0.007).

Conclusion: Acquired risk factors, aPL profile (triple positivity), lupus-like and non-criteria aPL manifestations could represent risk factors for pregnancy complications and could determine failure even to conventional treatment with LDA plus prophylactic LMWH. These patients may deserve additional treatment, for example LMWH at higher/anti-coagulant dose or an immunomodulatory treatment to increase the probability of success during pregnancy, such as hydroxychloroquine, also considering its anti-platelet/anti-thrombotic effects.

LINK Excel.Sheet.8 "E:\\aPL carriers project\\database aPL carriers definitivo 270516.xls" "Foglio2!R1C1:R7C9" \a \f 5 \h * MERGEFORMAT

	Complicated pregnancies (n=8)	Non-complicated pregnancies (n=62)	P-value ^	OR (95% CI)
Mean age at pregnancy (mean (SD))	**28.3 (5.8)**	**32.7 (4.6)**	**0.016 §**	
Acquired risk factors #	**6 (75%)**	**15 (24%)**	**0.007**	**9.40 (1.46-76.4)**
Congenital thrombophilia	**2 (25%)**	**4 (6%)**	**0.136**	
Non criteria aPL manifestations °	**3 (38%)**	**3 (5%)**	**0.017**	**11.8 (1.39-109)**
Lupus-like manifestations	**3 (38%)**	**2 (3%)**	**0.009**	**18.0 (1.80-216)**
Single positive	**3 (38%)**	**41 (66%)**	**0.137**	
Double positive	**0 (0%)**	**17 (27%)**	**0.185**	
Triple positive	**5 (63%)**	**4 (6%)**	**0.0005**	**24.2 (3.28-215)**
No treatment	**1 (13%)**	**23 (37%)**	**0.249**	
LDA	**3 (38%)**	**34 (55%)**	**0.462**	
LDA+LMWH	**4 (50%)**	**5 (8%)**	**0.007**	**11.4 (1.69-84.2)**

Table 1. Complicated pregnancies (APO and thrombosis) compared with non-complicated pregnancies – univariate analysis ^ Fisher's exact test, except otherwise indicated; p significant <0.05 § Student's T- test # Acquired risk factors. Obesity (BMI>30w), hypertension (>140/90), hyper-cholesterolemia, hyper-triglyceridemia, hyper-homocysteinemia, diabetes mellitus ° Non-criteria aPL manifestations were defined as the presence of at least one of the followings: (livaedo reticularis, thrombocytopenia, headache, hemolytic anemia, cardiac valvulopathy, epilepsy)

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Abstract Number: 2457

Role of Hydroxychloroquine in Improving Pregnancy Outcomes in Women with Antiphospholipid Antibodies without Other Underlying Connective Tissue Disease

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Background/Purpose: Heparins and/or low-dose aspirin represent the treatment of choice for the management of pregnant women with antiphospholipid antibodies (aPL). However, despite these treatments, maternal, fetal, and neonatal adverse outcomes related to the presence of aPL may still occur. In this study we aimed to assess the pregnancy outcome in women with aPL without other underlying connective tissue disease (CTD) who were treated with hydroxychloroquine (HCQ) in addition to conventional treatment during pregnancy.

Methods: Eighty-nine pregnancies in 48 women with persistent aPL were included in this observational, retrospective, cohort study: -Group 1: 17 pregnancies that occurred in 13 women were treated with HCQ for at least 6 months before pregnancy, and the therapy continued throughout gestation; -Group 2: 72 pregnancies that occurred in 35 women with aPL that were not treated with HCQ were included as controls. All the patients were tested positive for aPL in the absence of conclusive clinical signs/symptoms of CTD.

Results: HCQ-treatment was associated with a higher rate of live births (82% group A vs 58% group B; p = .05). Placenta-mediated complications (pre-eclampsia and abruption placentae) were

not observed in group 1 but occurred in 5 cases of group 2. Pregnancy duration was longer in group 1 than group 2 (36.4 [6-40] vs 33.5 [6-40] weeks; p = .04).

Conclusion: Despite the limit of the small sample size, our observations support that HCQ may improve pregnancy outcome in women with aPL. A prospective randomised controlled trial of HYdroxychoroquine versus placebo during Pregnancy in women with AnTIphospholipid Antibodies (HYPATIA) also including women witn aPL without other underlying CTD is about to start recruiting.

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Abstract Number: 2458

Erectile Dysfunction in Men with Rheumatic Diseases: A Systematic Review

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Background/Purpose: Given the obvious female predominance of rheumatic diseases, significant attention has already been drawn to the impact of these conditions on female sexual function. Nevertheless, rheumatic diseases can also present with challenges that are unique to male sexual function and thus, we aimed to systematically review the prevalence of erectile dysfunction in rheumatic diseases.

Methods: Using Medline, EMBASE, and Web of Science electronic databases, we performed a systematic review to identify original articles evaluating the prevalence of erectile dysfunction, assessed using the validated international index of erectile function (IIEF-5) questionnaire, in men

with rheumatic diseases, including systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and ankylosing spondylitis (AS). The search was restricted to English articles and performed in May 2016. We hand-searched reference lists, review articles, and grey literature for relevant articles not captured by the electronic searches.

Results: Our literature search identified 54 studies of which 34 were selected for full-text review. Of the potentially relevant studies retrieved, 12 studies were included in the final analysis. Five studies (n=219) focused on patients with SSc and reported ED prevalence ranging from 81-88%. In these studies, ED was found to correlate with disease severity and was associated with ultrasonographic evidence of penile vascular impairment. Comparatively, in RA (3 studies, n=138) and AS subjects (4 studies, n=272), ED prevalence ranged respectively from 46-54% and 12-42%. In AS, increased Bath Ankylosing Spondylitis Disease Activity Index scores, duration of morning stiffness, and disease duration were associated with ED. In the aforementioned studies, the age-matched healthy control population had ED rates ranging from 11-27%. Of note, only 2 studies (n=35) examined SLE and/or antiphospholipid-antibodies-positive subjects but standardized questionnaires were not used to evaluate ED and thus, these studies were excluded.

Conclusion: Men with SSc, RA, and AS have a substantially higher prevalence of ED compared to age-matched healthy controls. Given the importance of normal erectile function in sexual health and quality of life, clinicians should be aware of the increased prevalence of ED in men with rheumatic diseases and offer preventative, as well as therapeutic strategies to minimize its impact.

Disclosure: O. Zahedi Niaki, None; **C. A. Pineau**, None; **S. Bernatsky**, None; **E. Vinet**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/erectile-dysfunction-in-men-with-rheumatic-diseases-a-systematic-review

Abstract Number: 2459

Epidemiologic Profile of Erectile Dysfunction in SLE: A Multi-Center Study in Latin American Patients

Javier Merayo-Chalico[1], Diana Gómez-Martín[2], Roberto Reyna[1], Sandra Morales[1], Ana Barrera-Vargas[2], Jorge Alcocer-Varela[2], Iris J. Colunga-Pedraza[3], Carlos Abud-Mendoza[4], Marco Ulises Martinez-Martinez[5], Roberto Ivan Acosta-Hernandez[6] and Christian Mauriel Uriarte-Hernández[7], [1]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [2]Department of Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico, [3]Rheumatology, Hospital Universitario UANL, Monterrey, Mexico, [4]Regional Unit of Rheumatology and Osteoporosis, Faculty of Medicine, Universidad Autónoma de San Luis Potosí and Hospital Central, San Luis Potosí, Mexico, [5]Unidad de Investigaciones Reumatológicas, Faculty of Medicine, Universidad Autónoma de San Luis Potosí and Hospital Central, San Luis Potosí, Mexico, [6]Reumatología,

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SESSION INFORMATION

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Session Title: Reproductive Issues in Rheumatic Disorders - Poster

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although systemic lupus erythematosus (SLE) has a higher prevalence in women, the disease usually has a more aggressive course in men. Information regarding erectile function in men with SLE is quite scant. Therefore, the aim of this study was to describe the prevalence of erectile dysfunction (ED) as well as associated demographic and clinical features in men with SLE, by means of a systematic, standardized evaluation.

Methods: We performed a transversal study in five tertiary care centers in Latin America (3 in Mexico, one in El Salvador and one in Nicaragua). We included male patients older than 16 years who fulfilled ≥4 ACR criteria for SLE, and who had reported regular sexual activity in the previous 6 months. Patients with other rheumatic diseases (except for APS), chronic viral infections, concomitant diagnosis of benign prostate hyperplasia, and late-onset SLE (≥50 years of age) were excluded. All patients answered the self-administered International Index of Erectile Function-5 Questionnaire (IIEF-5), which has been validated in Spanish. Other relevant demographic, clinical and serological characteristics were documented from the clinical records.

Results: We included 118 subjects. The prevalence of ED in our study population was 67.7% (80/118), the majority were classified as mild to moderate (17.5±3.8 points; normal score: 22-25 points). The mean age of patients with ED was 35.6±11, while in patients without ED it was 32.3±9 (p=0.11). There were no significant differences in most of the demographic and clinical variables between both groups, either (Table 1). There was a trend regarding current prednisone intake in patients with ED (67 vs 48%, p=0.066). Furthermore, patients with ED had a higher MMF dose (1461±989 vs 860±1011 mg p=0.036) and a lower lymphocyte count (1398±634 vs 1717±814 cells/µl, p=0.022) than controls. Complement levels, anti-dsDNA antibodies and serum creatinine did not differ between groups. Also, both SLEDAI (p=0.16) and SLICC (p=0.13) scores were similar between groups.

Conclusion: Regardless of acute disease activity, accrual damage, type of previous SLE activity and comorbidities, men with SLE have a high prevalence of ED, considering most are young patients. Interestingly, prednisone dose was not associated with this condition, and the only difference in immunosuppressive drugs between groups was a higher dose of MMF in the patients with ED. Besides, lymphopenia could play a physiopathogenic role, associated with microvascular damage. The high prevalence of ED could potentially be associated to diminished quality of life, which must be addressed by prospective studies. *Table 1. Demographic features and comorbidities of patient with and without ED and SLE*

Variable	SLE without Erectile Dysfunction (n=38)	SLE with Erectile Dysfunction (n=80)	p value
Age (years)	32.3±9.06	35.6±11.05	0.11
Weight (kg)	77.6±14.01	78.6±15.56	0.72
BMI (m^2/kg)	26.5±4.72	27.1±5.18	0.52
Time since SLE diagnosis (years)	7.9±6.63	8.2±7.14	0.84
SLEDAI score (points)	3.19±3.56	4.72±6.03	0.16
SLICC score (points)	0.67±1.26	1.1±1.48	0.13
Smoking (in the last 5 years) (%)	10/38 (26)	24/80 (30)	0.73
Diabetes mellitus (%)	0/38 (0)	6/80 (7)	0.17
Hypertension (%)	12/38 (31)	28/80 (35)	1
Dyslipidemia (%)	7/38 (18)	21/80 (26)	0.48
APS (%)	11/38 (29)	17/80 (21)	0.35
Lupus nephritis (biopsy) (%)	14/38 (36)	40/80 (50)	0.23
Use of cyclophosphamide ever (%)	11/38 (28)	38/80 (47)	0.10
SLEDAI (≤5 points) (%)	30/38 (78)	56/80 (70)	0.17
Immunosuppressive therapy (%)	33/38 (86)	71/80 (88)	1

Disclosure: J. Merayo-Chalico, None; **D. Gómez-Martín**, None; **R. Reyna**, None; **S. Morales**, None; **A. Barrera-Vargas**, None; **J. Alcocer-Varela**, None; **I. J. Colunga-Pedraza**, None; **C. Abud-Mendoza**, None; **M. U. Martinez-Martinez**, None; **R. I. Acosta-Hernandez**, None; **C. M. Uriarte-Hernández**, None.

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Abstract Number: 2460

Predictive Factors of Good Response to Conventional Dmards

in Patients with Early Seronegative Rheumatoid Arthritis: Data from the Espoir Cohort

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Clinical Aspects - Poster III: Treatment – Monitoring, Outcomes, Adverse Events

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Early seronegative rheumatoid arthritis (RA) is a separate entity. Less is known about its initial clinical presentation and outcome due to the difficulty in identification among patients with undifferentiated arthritis. The objective of this study was to determine predictors of good response to conventional DMARDs in seronegative RA patients in the ESPOIR cohort.

Methods: Patients from the ESPOIR cohort with an early seronegative RA fulfilling the ACR-EULAR 2010 criteria were included. Primary endpoint was a good or moderate EULAR response evaluated at one year, after at least three months of treatment with conventional synthetic DMARDs (csDMARDs). Secondary objectives were to compare the early therapeutic response to methotrexate (MTX) and leflunomide (LEF) versus other csDMARDs (hydroxychloroquine, sulfasalazine), and to identify factors associated with functional disability (HAQ-DI > 0.5 at one year) and structural progression (modified total Sharp score > 1 and >5 points at one year). A Fisher exact test was used to compare categorical variables, and the Student or Mann Whitney tests for quantitative variables. Logistic regression analysis was used to determine independent predictors of outcome in multivariate analysis.

Results: 172 patients were analyzed: 81% women, mean age of 49.5+12.8 years. Mean DAS28 was 5.5+1.1 at baseline. 57% of patients were then treated with MTX. csDMARDs instituted early, i.e. within three months following the first joint swelling was significantly associated with EULAR good or moderate response at one year (OR = 2.41 95% CI [1.07- 5.42] p = 0.03) on univariate and multivariate logistic regression. Observed response rates were neither influenced by the type of first line csDMARDs (MTX vs other DMARDs), nor by other classical prognostic factors. Presence of erosions at baseline was significantly associated with progression of the Sharp score > 1 point (p = 0.03) and > 5 points (p = 0.03) at one year. HAQ ≥1 at inclusion and active smoking were significantly associated with an HAQ > 0.5 at one year.

Conclusion: Our results suggest that more than baseline clinical, biological or imaging features, it is the delay in initiation of csDMARD that greatly affects the outcome in patients with early seronegative RA.

Disclosure: J. MARY, None; **B. Combe**, None; **C. Lukas**, None; **M. De Bandt**, None.

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Abstract Number: 2461

Identifying Flare in Rheumatoid Arthritis: What Is the Threshold?

Elena Myasoedova[1], Cynthia S. Crowson[2], John M. Davis III[3], Sherine E. Gabriel[4] and Eric L. Matteson[1], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Health Sciences Research, Mayo Clinic, Rochester, MN, [3]Division of Rheumatology, Mayo Clinic, Rochester, MN, [4]Dean's Office, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ

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Background/Purpose: The flare-assessment in RA (FLARE) questionnaire was developed for the detection of disease activity flares in patients with rheumatoid arthritis (RA) based on the joint symptoms and systemic impact of RA disease. As of now, there is no clear FLARE score cut-off for identifying a flare in RA. We aimed to establish a threshold for RA flare using the FLARE questionnaire in patients with RA.

Methods: Patients with RA (age≥18 yrs; 2010 ACR criteria) participating in an ongoing prospective study completed the FLARE questionnaire on a monthly basis. The Health Assessment Questionnaire-II (HAQ-II), visual analogue scales (0-100 mm) for pain (VAS pain) and patient and provider global assessments of RA disease activity; assessment of tender (TJC28) and swollen joint counts of 28 joints (SJC28), and C-reactive protein (CRP) measurement were completed during the baseline visit. Generalized estimating equations were used to model the relationship between the FLARE questionnaire and patient report of flare incorporating random patient and visit effects to account for within patient variability.

Results: The study included 66 patients with RA (mean age 59.7 years; 64% female). The mean (standard deviation, SD) for TJC28 joints was 2.3 (4.8), SJC28 was 1.1 (2.9), HAQ-II score 0.6 (0.5), VAS pain 33.3 (26.1), provider global assessment 17.2 (22.3), patient global assessment 33 (26.2) and CRP 7.7 (12) mg/L. A total of 307 monthly questionnaires were completed. As expected, the FLARE score overall, as well as systemic and joint subscale measures were significantly higher in months when patients reported flare vs no flare (Table). Several measures of RA activity including TJC28, HAQ-II, VAS pain, patient and provider global assessment were also significantly higher in patients reporting a RA flare vs those not reporting a flare (see the Table). Based on the ROC analysis, the optimal cutpoint (using the DeLong-Delong method) for the FLARE questionnaire was identified at 2.5. The sensitivity is 77.1% and the specificity is 78.9% using this cutpoint (Figure). The positive predictive value is 51.9% and the negative predictive value is 92.1%. The area under the curve was 89% for FLARE overall and 88% for both the joint and systemic subscales of the FLARE questionnaire.

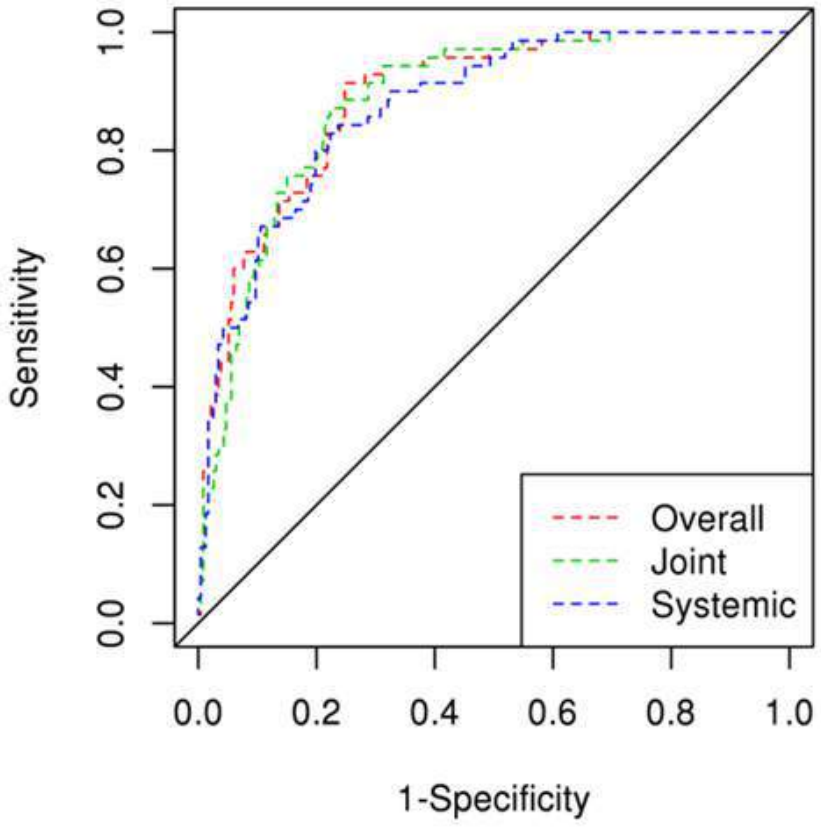
Conclusion: We suggest a threshold of 2.5 for the FLARE questionnaire score to aid in the accurate identification of flare status in patients with RA. This threshold may be particularly useful in helping to rule out flare in RA patients where the diagnosis of flare is questionable, if their FLARE score is <2.5. Further studies are needed to validate this threshold in other populations of patients with RA. Future identification of an individualized threshold for RA flare using the FLARE questionnaire may aid in disease management.

Table. FLARE scores and RA activity measures in patients reported to be in RA flare vs not in a flare

Variable	RA flare per patient report	Not in a flare per patient report	p-value
Overall FLARE score	5.0 (2.4)	1.5 (1.9)	<0.001
FLARE systemic subscale	4.6 (2.8)	1.3 (1.9)	<0.001
FLARE joint subscale	5.6 (2.3)	1.9 (2.2)	<0.001
TJC28	5.9 (6.5)	1.7 (3.6)	0.019
SJC28	2.8 (3.2)	1.2 (3.6)	0.20
HAQ-II	0.9 (0.5)	0.5 (0.6)	0.040
VAS pain	55.3 (21.5)	28.4 (26.4)	0.005
Patient global assessment	54.9 (21.6)	27.9 (24.7)	0.004
Provider global assessment	35.7 (19.6)	16.5 (25.2)	0.049
CRP, mg/L	6.4 (5.5)	7.7 (12.2)	0.73

*All measures are shown as mean (standard deviation)

Figure 1. Receiver operating characteristic (ROC) curve



Disclosure: E. Myasoedova, Pfizer Inc, 2; **C. S. Crowson**, Pfizer Inc, 2; **J. M. Davis III**, Pfizer Inc, 2; **S. E. Gabriel**, Pfizer Inc, 2; **E. L. Matteson**, Pfizer Inc, 2.

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in-rheumatoid-arthritis-what-is-the-threshold

Abstract Number: 2462

Higher Number of Tender Than Swollen Joint Count Is Associated to Higher Patient Reported Outcomes and Composite Scores As Well As Reduced Probability of Obtaining Remission: Results from a One-Year Follow-up Study of Established RA Patients Starting Bdmards

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Rheumatoid Arthritis – Clinical Aspects - Poster III: Treatment – Monitoring, Outcomes, Adverse Events

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The swollen and tender joint count is included in composite scores (DAS28, CDAI, SDAI, ACR/EULAR Boolean remission). Low swollen/tender joint ratio (STR) has been found to be associated with reduced clinical response[1]. Ultrasound (US), including grey scale (GS) synovitis and power Doppler (PD) assessment of vascularity is sensitive for detecting inflammatory activity. Presently we explored associations between STR and pain catastrophizing, PROs, composite scores, clinical evaluation and US assessments, and more importantly, with composite score remission, in a follow-up study of established RA patients initiating bDMARDs.

Methods: 209 patients with RA (mean (SD) age 53 (13) years, disease duration 10 (9) years, 81% women, 79% anti-CCP positive) were included when initiating bDMARDs and assessed at baseline and after 1, 2, 3, 6 and 12 months with PROs (joint pain VAS, patient's global VAS, RAID score and MHAQ), clinical examinations (assessor's disease activity VAS, tender and swollen joint counts (of 28)) and laboratory variables (ESR and CRP). STRs were calculated with insertion of 1 if 0 in the denominator. Pain catastrophizing was assessed by two questions from the Coping Strategies Questionnaire. All US examinations (semi-quantitative scoring (0-3)) of GS and PD (PIP 2-3, MCP 1-5, wrist (RC, IC, RU), elbow, knee, tibiotalar, MTP 1-5 and ext.carpi ulnaris/tib.post.tendons bilaterally) were performed by one rheumatologist (HBH) (Siemens Acuson

Antares, excellence version, 5-13 MHz probe). Statistical calculations included Pearson's correlations, independent samples T-test and cross-tabs for assessing risk levels.

Results: There was a wide distribution of STR levels (median 1.0 (IQR 0.6-2.5), mean (SD) 2.4 (3.8)). During follow-up there were no/low cross-sectional correlations between STR and all the PROs and laboratory markers (r= -0.03-0.24), but moderate to high correlations with assessor's global (r= 0.27-0.42, p<0.001) and the US examinations (GS; r=0.48-0.63/PD; r=0.38-0.67, p<0.001). Patients were divided into groups with STR ≥ 1.0 or <1.0. The table (including mean values) shows that patients with STR<1.0 during follow-up had significantly higher levels of PROs and composite scores but lower US scores. Patients with STR < 1.0 achieved less often remission according to the composite scores (STR<1.0/STR≥1; DAS28 4.3%/36.4% and 3.3%/35.5%, CDAI 2.7%/17.9% and 1.3%/23.7%, SDAI 3.3%/20.1% and 3.3%/24.3%/, Boolean 2.7%/18.5% and 1.3%/21.7% at 6 and 12 months, respectively).

Conclusion: Established RA patients with higher number of tender than swollen joint count had higher levels of PROs and composite scores, but lower US pathology, and more importantly, lower achievement of clinical remission. Thus, these patients may have a trait including higher subjective scores, which is relevant within the treat-to-target strategy. Reference: Kristensen LE et al, Arthritis Care Res 2014 Feb;66(2):173-9

	Baseline STR ≥ 1.0/<1.0	1 month STR ≥ 1.0/<1.0	2 months STR ≥ 1.0/<1.0	3 months STR ≥ 1.0/<1.0	6 months STR ≥ 1.0/<1.0	12 months STR ≥ 1.0/<1.0
Number of patients	125 /84	130 / 79	136 / 69	138 / 60	127 / 57	105 / 47
Pain catastrophizing	2.0 / 2.6 (p=0.002)	1.5 /2.6 (p<0.001)	1.4 /2.4 (p<0.001)	1.3 /2.3 (p<0.001)	1.3 / 2.0 (p=0.016)	1.2 / 1.7 (p=0.015)
Joint pain VAS	39.3 /53.6 (p<0.001)	22.5 / 45.3 (p<0.001)	19.3 / 41.4 (p<0.001)	17.7 /37.1 (p<0.001)	17.0 /33.7 (p<0.001)	17.3 / 32.9 (p<0.001)
Patient's global VAS	42.5/58.7 (p<0.001)	25.5 / 48.6 (p<0.001)	21.4 /44.2 (p<0.001)	19.0 /42.9 (p<0.001)	18.3 /37.4 (p<0.001)	19.6 / 35.8 (p<0.001)
RAID score	3.9/5.3 (p<0.001)	2.6 / 4.8 (p<0.001)	2.4 /4.3 (p<0.001)	2.1 /4.1 (p<0.001)	2.0 / 3.7 (p<0.001)	2.2 / 3.6 (p<0.001)
MHAQ	0.55 / 0.83 (p=0.001)	0.33 / 0.71 (p<0.001)	0.30 70.81 (p=0.011)	0.27 / 0.65 (p<0.001)	0.30 / 0.56 (p=0.004)	0.32 / 0.50 (p=0.026)
DAS28	4.1 / 5.2 (p<0.001)	3.4 / 4.7 (p<0.001)	3.1 /4.6 (p<0.001)	3.0 /4.5 (p<0.001)	2.8 /4.0 (p<0.001)	2.7 / 3.8 (p<0.001)
CDAI	17.4 / 23.8 (p<0.001)	13.0 / 20.0 (p<0.001)	11.0 /19.0 (p<0.001)	9.6 /18.7 (p<0.001)	8.7 / 14.2 (p=0.001)	8.2 / 12.8 (p=0.005)
SDAI	18.6 / 25.1 (p<0.001)	13.9 / 20.9 (p<0.001)	11.7 /19.7 (p<0.001)	10.1 /19.3 (p<0.001)	9.1 /14.7 (p=0.002)	8.8 / 13.1 (p=0.011)
CRP	12.5 / 13.5 (NS)	8.1 / 9.2 (NS)	7.1 / 6.4 (NS)	5.34 / 6.0 (NS)	4.6 / 5.0 (NS)	5.5 / 2.6 (p=0.38)
ESR	26.9 / 29.8 (NS)	21.4 / 24.3 (NS)	19.8 / 21.5 (NS)	17.9 / 22.9 (NS)	16.9 / 18.6 (NS)	17.1 /17.0 (NS)
Assessor's global	30.7 / 28.9 (NS)	23.0 / 23.2 (NS)	19.8 /20.4 (NS)	17.4 /18.5 (NS)	16.2 / 15.9 (NS)	15.8 / 14.8 (NS)
Sum score GS	33.8 / 24.3(p<0.001)	29.2 / 21.5 (p=0.001)	27.4 /20.3 (p=0.002)	23.9 /18.3 (p=0.01)	23.3 / 16.1 (p<0.001)	21.8 / 14.8 (p=0.001)
Sum score PD	17.0 / 10.0 (p<0.001)	12.8 / 8.2 (p=0.003)	11.3 / 7.6 (p=0.017)	9.7 /6.6 (p=0.03)	8.7 / 5.2 (p=0.007)	7.3 / 3.5 (p<0.001)

Disclosure: H. B. Hammer, None; **T. Uhlig**, None; **T. K. Kvien**, None; **J. Lampa**, None.

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Abstract Number: 2463

Association Between High Sodium Intake and Subclinical Atherosclerosis in Patients with Rheumatoid Arthritis

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: High sodium intake has been reported to be associated with increased ACPA positivity in smoker RA patients. However, apart from this, the associations with high sodium intake in the general population, elevation in blood pressure, endothelial dysfunction, albuminuria and cardiovascular (CV) morbidity and mortality, have not been examined in RA patients before. In this study, we assessed the association between sodium intake and subclinical atherosclerosis identified by the carotid ultrasound (US), in RA patients.

Methods: RA patients without any CV disease, diabetes, chronic kidney disease, or who were not on diuretic treatment were included. To estimate dietary sodium intake, sodium excretion in 24h urine samples were determined. High sodium intake was defined as >200mmol/day (>12g/day) sodium in 24h urine. Carotid US findings of carotid intima-media thickness (cIMT) > 0.90 mm and/or carotid plaques were regarded as subclinical atherosclerosis. Along with disease characteristics, traditional CV risk factors, DAS28 scores, ESR and CRP values of each visit during the entire followup were recorded. Average DAS28, ESR, and CRP were calculated. Multivariable logistic regression was used to adjust for RA severity measures and other CV risk factors influencing atherosclerosis.

Results: Of the 110 RA patients (F/M=89/21, age 54±11 years, disease duration 14±7 years, hypertension 27.3%) 24 (21.8%) had subclinical atherosclerosis (cIMT>0.90 mm: 14 patients, plaques: 20 patients). The mean daily sodium excretion was 189.2±72.9 mmol/day, equal to a sodium intake of 11.1±4.3g/day. Overall, 48 (44%) patients had high sodium intake (mean 15.1±2.8g/day). Sodium intake 14.8±4.5g/day *vs* 10.1±3.7g/day (P<0.001), and % of high sodium consumers 66.7% *vs* 37.2 % (P=0.010) were significantly higher in patients with subclinical atherosclerosis. Daily sodium intake was positively correlated with cIMT (r=0.32, P=0.001), average ESR (r=0.22, P=0.024) and CRP (r=0.29, P=0.003), and serum uric acid levels (r=0.27, P=0.005). There was a nonsignificant positive correlation between systolic and diastolic blood pressures and sodium intake. Sodium intake in NSAID or glucocorticoid using RA patients was similar to non-users. Similarly, hypertensive, obese, smoker or seropositive patients' sodium intake was not higher. When disease characteristics, cumulative disease activity, and traditional CV risk

factors were adjusted by using multivariable logistic regression analysis, sodium intake was found to be associated with subclinical atherosclerosis in RA patients (OR=1.46, 95% CI, 1.11-1.90, *P*=0.006).

Conclusion: Higher sodium intake is associated with subclinical atherosclerosis in RA patients. These preliminary results should be confirmed in a larger sample. Considering the high CVD risk in RA patients, further investigation is needed to determine whether high sodium intake is associated with inflammation, CV morbidity and mortality, and other comorbid conditions such as hypertension in RA. As recommended for the hypertensive adult population, sodium intake reduction may be considered in RA patients, particularly in hypertensive and high CV risk patients.

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Abstract Number: 2464

Comparison of Disease Activity Score (DAS) 28-CRP to DAS28-ESR in Patients with Active Rheumatoid Arthritis

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Background/Purpose: Assessment of disease activity is a key part of clinical decision in rheumatology care. High disease activity presented by disease activity score 28 ((DAS28) > 5.1 is used as a cutoff for biologic use in many countries include Korea. This study is to find confounding factors affecting erythrocyte sedimentation ratio (ESR) and C-reactive protein (CRP) to patients with rheumatoid arthritis to find the best tool to access rheumatoid arthritis (RA) disease activity, and to compare DAS28-ESR and DAS28-CRP to see whether we can use these indices interchangeably.

Methods: A cross-sectional study was conducted in 1117 patients with RA, using initial

registration data from Korean Biologics Registry (KOBIO).

Results: ESR levels were increased with age ($r = 0.120$, $p < 0.001$) and serum rheumatoid factor ($r = 0.111$, $p = 0.001$) but did not correlate with BMI, disease duration, and anti-CCP antibody titer. There were no differences in ESR levels according to the gender, smoking status, presence of diabetes mellitus, obesity (BMI ≥ 30) or low body weight (BMI < 20). CRP levels did not correlate with age, BMI, disease duration, RF and anti-CCP antibody. They were higher in female compared to male ($p < 0.001$) and higher in never-smoker compared to ever-smoker ($p = 0.003$). However, those differences of CRP levels were not significant when stratified by smoking status and gender, respectively. There were no differences in CRP levels according to the presence of diabetes mellitus, obesity (BMI ≥ 30) or low body weight (BMI < 18.5). In comparison of composite indices, DAS28CRP showed excellent correlation with DAS28ESR ($r = 0.943$, $p < 0.001$). However, in defining high disease activity, DAS28CRP showed only a fair agreement with DAS28ESR (kappa 0.381). To make best agreement with DAS28ESR in defining high disease activity, DAS28CRP need to be lowered to 4.5 (kappa 0.679, sensitivity 85.8%, specificity 88.0%, AUC 0.936).

Conclusion: DAS28CRP is a useful marker for inter-patient-comparison of RA disease activity when comparing patients with different age or rheumatoid factor status. DAS28CRP correlates well with DAS28ESR but the cutoff for high disease activity needs to be lowered to 4.5 to be used interchangeably with DAS28ESR in defining high disease activity.

Disclosure: I. A. Choi, None;

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Abstract Number: 2465

Discordance Between Tender and Swollen Joint Count and Patient's and Evaluator's Global Assessment May Reduce Likelihood of Remission in Rheumatoid Arthritis

Brigitte Michelsen[1,2], Karen M Fagerli[1], Elisabeth Lie[1], Hilde B Hammer[3], Eirik K Kristianslund[1], Glenn Haugeberg[4,5] and Tore K Kvien[1], [1]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [2]Dept. of Rheumatology, Hospital of Southern Norway Trust, Kristiansand, Norway, [3]Dept of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [4]Dept. of Rheumatology, Martina Hansens Hospital, Bærum, Norway, [5]Dept. of Rheumatology, The Norwegian University of Science and Technology, Trondheim, Norway

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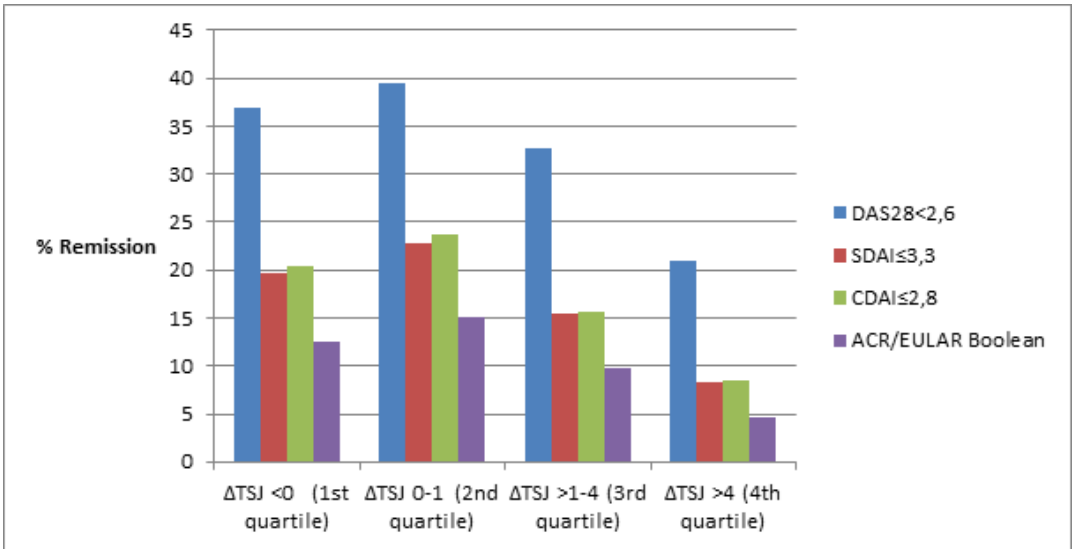
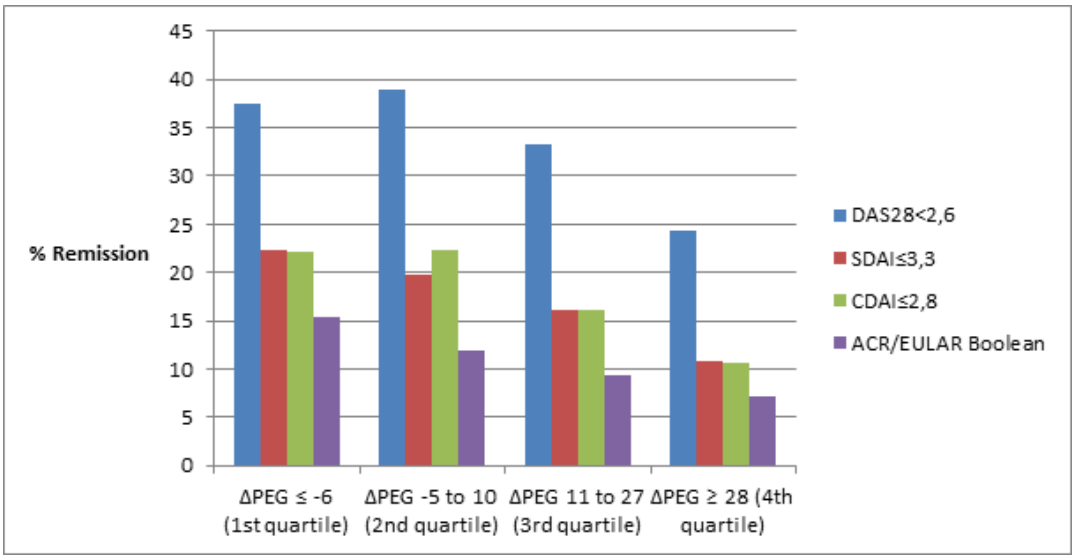
Background/Purpose: Chronification of pain and development of central sensitization and conditioned pain modulation can lead to disconnection between tender and swollen joint count, which may be challenging for disease evaluation and treatment. Studies exploring the relationship between tender and swollen joints discordance as predictor of remission in inflammatory arthritides are lacking in the current literature. In this study we aimed to investigate the predictive value of numeric differences between 28 tender and swollen joint count (deltaTSJ) and patient's and evaluator's global assessment (deltaPEG) on remission in rheumatoid arthritis (RA).

Methods: From the prospective, multicenter NOR-DMARD study we included RA patients starting first-time tumor necrosis factor inhibitors (TNFi) and DMARD naïve patients starting methotrexate between 2000 and 2012. The predictive value of deltaTSJ and deltaPEG on remission was explored in prespecified logistic regression models adjusted for age, sex, disease duration and smoking.

Results: A total of 2735 RA patients were included (mean (SD) age 55.0 (13.5) years, disease duration 4.5 (8.2) years, 69.7% females, 31.7% current smokers, baseline median (IQR) 28 tender joints 6 (9), 28 swollen joints 6 (7), deltaTSJ 1 (5), baseline mean (SD) evaluator's global assessment 40.3 (19.4), patient's global assessment 49.7 (24.8), deltaPEG 9.4 (25.0), DAS28ESR 5.0 (1.4), baseline median (IQR) SDAI 24.5 (19.6), CDAI 10.4 (13.3). Bar charts of percentages of patients in remission at 6 months according to categorization of deltaPEG and deltaTSJ into quartiles showed reduced probability of remission with increasing deltaPEG and deltaTSJ (unadjusted values; figures).





Baseline deltaTSJ and deltaPEG were negative predictors of achieving DAS28<2.6, SDAI≤3.3, CDAI≤2.8 and ACR/EULAR Boolean remission after 3 and 6 months (table).

	Months	DAS28ESR < 2.6	SDAI ≤ 3.3	CDA I ≤ 2.8	ACR/EULAR Boolean
deltaTSJ	3	0.97 [0.95, 0.99] p<0.001	0.96 [0.94, 0.98] p<0.001	0.95 [0.93, 0.98] p<0.001	0.96 [0.94, 0.99] p=0.003
	6	0.96 [0.95, 0.98] p<0.001	0.96 [0.94, 0.98] p<0.001	0.96 [0.94, 0.98] p<0.001	0.96 [0.94, 0.98] p=0.001
deltaPEG	3	0.96 [0.94, 0.99] p=0.009	0.99 [0.99, 0.998] p=0.01	0.99 [0.99, 0.997] p=0.004	0.99 [0.98, 0.996] p=0.001
	6	0.99 [0.99, 0.997] p=0.002	0.99 [0.98, 0.99] p<0.001	0.99 [0.98, 0.99] p<0.001	0.99 [0.98, 0.995] p=0.001

Data are presented as OR [95% CI]

Conclusion: Discordance between patient's and physician's evaluation of disease activity reflected through deltaTSJ and deltaPEG may reduce likelihood of remission in RA. The findings are relevant for use of the treat-to-target strategy.

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Abstract Number: 2466

Remission According to RAPID3 (routine assessment of

patient index data 3) in Patients with Rheumatoid Arthritis: A Cross-Sectional 3 Center Study from Routine Care

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Background/Purpose: Remission rates in patients with rheumatoid arthritis (RA) according to RAPID3 (routine assessment of patient index data) are reported at 25% in France[1] and 21% in Norway[2]. Remission according to RAPID3 or DAS28 (disease activity score) criteria are similar and less stringent compared to the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria. Addition of whether only one or no joint is swollen renders RAPID 3-based remission criteria similar to ACR/EULAR Criteria[1]. However, RAPID3 is more feasible for routine care. We examined the prevalence of remission according to RAPID3 in RA patients at three USA sites.

Methods: All patients with all diagnoses seen at 3 academic rheumatology centers complete a multidimensional health assessment questionnaire (MDHAQ), which includes RAPID3, at all visits in the waiting area, before seeing the rheumatologist in routine care. The MDHAQ includes 0-10 scores for physical function (FN), a pain (PN) visual analog scale (VAS), patient global estimate (PATGL) VAS, compiled into a 0-30 RAPID3, as well as a 0-10 fatigue VAS, RADAI self-report of painful joints of 16 joint groups bilaterally scored 0-3, and demographic data. RAPID3 categories for severity are high =≥12, moderate=6.1-12, low=3.1-6, and near-remission=≤3. Physicians complete a Rheumetric checklist, which includes 4 physician 0-10 VAS estimates for overall global status and 3 subscales for inflammation, damage and distress. A random visit for each RA patient from each site with complete data to calculate RAPID3 was analyzed for the percentage of patients in each category, compared using a chi-square test.

Results: 420 patients with RA from three different sites were analyzed. Demographic characteristics were similar at the 3 sites. RAPID3 remission rates ranged from 23% to 26%, comparable to reported rates from France[1] and Norway[2]. Other categories were virtually identical

at sites 1 and 2, but patients at site 3, a private practice, appeared to have better status; low severity ranged from 7-24%, moderate from 23-29% and high disease severity from 21-46%. Patients in remission had lower scores for fatigue and RADAI self-report painful joint than patients in other categories at all 3 sites, as well as lower physician global estimates for overall status, inflammation, damage and distress (data not shown).

Conclusion: RAPID3 remission rates at 3 US sites were 23%-26%, similar to 25% in France and 21% in Norway. RAPID3 provides a feasible approach to identify remission in busy clinical settings, as the patients do almost all the work, although addition of whether only one or no joint is swollen adds to stringency so that RAPID 3-based criteria are comparable to ACR/EULAR remission criteria. **References: 1)** Castrejon I, Dougados M, et al. *J Rheumatol* 2013, 40(4):386 - 393. 2) Uhlig T, Lie E, et al. *J Rheumatol* 2016, **43**(4):716-723.

	Site 1 **N=137**	**Site 2** **N=139**	**Site 3** **N=144**
Remission (≤3)	32 (23%)	32 (23%)	37 (26%)
Low (3.1-6)	11 (8%)	10 (7%)	35 (24%)
Moderate (6.1-12)	31 (23%)	33 (24%)	42 (29%)
High (>12)	63 (46%)	64 (46%)	30 (21%)

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Abstract Number: 2467

Validation of the FLARE Questionnaire for the Detection of a Disease Flare in Rheumatoid Arthritis

Ana Lizarraga[1], Margarita Landi[2], Emilce Schneeberger[2], Josefina Gallino Yanzi[3], Graciela Betancur[1], Cecilia Zaffarana[2], Maria Celeste Orozco[4], Osvaldo Luis Cerda[5], Fernando Dal Pra[3] and Gustavo Citera[2], [1]Reumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Rheumatology Section, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [5]IREP, CABA, Argentina

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Background/Purpose: Patients with Rheumatoid Arthritis (RA) commonly suffer disease flares. The FLARE questionnaire was developed in order to detect the presence of a flare within the 3 months previous to the medical visit. The objective of our study was to validate the FLARE questionnaire into the Spanish language and to estimate the cut-off value for defining a disease flare.

Methods: Patients with RA according to ACR/EULAR 2010 criteria, ≥ 18 years of age were included. Sociodemographic and disease characteristics were recorded. Patients attended a baseline visit and thereafter every 3 months. Disease activity (28 joints count, ESR, CRP, DAS28) and functional status (HAQ) were assessed at each visit. Baseline treatment was recorded and at each follow-up visit a treatment change was analysed. FLARE was translated into Spanish and cultural adapted. Patients completed the FLARE questionnaire, consisting of 13 statements that are answered on a 6/Likert scale. The final scores results of the addition of the 13 questions, with a final results range between 13 and 78; 13 representing the highest probability of having suffered a disease flare. Both patients and physicians had to answer if they considered having suffered a disease flare. Between each visit, patients completed a RAPID-3 questionnaire weekly. A disease flare was defined as an increase in DAS28 ≥ 1.2 or ≥ 0.6 if the previous DA28 was ≥3.2, a difference in RAPID-3 > 3.6 between each visit or a significant treatment change.

Results: 105 patients were included, 84.8% were women, with a median age of 44 years (IQR 34 to 54.7), median disease duration of 20.5 months (IQR 6 to 45.7 months). Patients were evaluated over 6 consecutive visits, however due to a lost to follow-up of more than 50%, only the first 3 visits were analyzed. The treatment change frequency at each visit was: N°1= 54/101 (53.5%), N °2= 31/57 (54.4%) and N°3= 16/33 (48.5%). And the types of treatment change frequency were: Steroid increase (43.8%), DMARDs increase (26.6%), DMARDs combination (8.3%), biologic therapy addition (16.3%), intraarticular steroid injection 41%. Association between mean FLARE values and changes in disease activity is shown in Table 1. In the ROC curve analysis a FLARE cut-off value of 50.5 showed a sensitivity and specificity greater than 60.

Conclusion: The FLARE questionnaire is a valid and simple to use instrument for detecting a disease flare in RA patients. A cut-off value ≤ a 50.5 determines the presence of a disease flare within the 3 months previous to the medical visit. **Table 1. Comparison between the FLARE questionnaire and other definitions of disease flare**

Flare according to RAPID (increase > 3.6 between 2 visits)			
	YES	NO	p
FLARE X (SD)	44 (±27.5)	51.3 (±22.1)	0.61
Flare according to DAS28 increase between visit 1 and 2			
	YES	NO	p
FLARE X (SD)	43.7 (±23.1)	54.7 (±18.7)	0.17
Flare according to physician´s opinion			
	YES	NO	p
FLARE X (SD)	43.6 (±15.9)	51.1 (±18.1)	0.24
Flare according to patient´s opinion			
	YES	NO	p
FLARE X (SD)	34.1 (±10.4)	57.2 (±15.4)	0.0001
Flare according to treatment change between visits			
	YES	NO	p
FLARE 1 X (SD)	46.1 (±16.4)	54.8 (±17.9)	0.012
FLARE 2 X (SD)	44.1 (±20.2)	61.1 (±14.9)	0.002
FLARE 3 X (SD)	36 (±16.4)	59.1 (±18.8)	0.003

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Abstract Number: 2468

Assessment of the American-English Version of the French FLARE in Rheumatoid Arthritis

Nashla Barroso[1], Thasia G Woodworth[2], Francis Guillemin[3], Daniel E. Furst[4], Jenny Brook[5], Suzanne Kafaja[6], David Elashoff[5], Bruno Fautrel[7] and Veena Ranganath[8], [1]Rheumatology, UCLA David Geffen School of Medicine, Los Angeles, CA, [2]Leading Edge Clinical Research, Stuart, FL, [3]CHRU Nancy, Clinical Epidemiology and Evaluation, Université de Lorraine, Paris Descartes University, APEMAC, EA 4360, Nancy, France, [4]David Geffen School of Medicine at UCLA, Los Angeles, CA, [5]Medicine, David Geffen School of Medicine, Los Angeles, CA, [6]Medicine/Rheumatology, University of California Los Angeles, David Geffen School of Medicine, Los Angeles, CA, [7]Rheumatology, Pitié Salpêtrière Hospital, Paris, France, [8]Cumberland Valley Rheumatology, P.C., Chambersburg, PA

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Background/Purpose: Due to the lack of consensus of the definition of a rheumatoid arthritis (RA) flare, the French "FLARE" (**FL**are **A**ssessment in **RA**) instrument was developed and validated to assess worsening of disease activity between visits for the purposes of clinical trials. Prior work by our group ensured a robust validation process of translation and back-translation from French to American English (1). The objective of this study was to assess the performance of the American-English version of the FLARE questionnaire and to assure its validity in an American Native English-speaking RA cohort.

Methods: Fifty consecutive RA patients were recruited from the UCLA multi-physician rheumatology clinics who met the 1987 American College of Rheumatology (ACR) RA criteria. Patients completed a questionnaire with the following information: demographics, Routine Assessment of Patient Index Data 3 (RAPID3), patient global visual analogue scale (VAS), self-reported flare (Y/N), and American-English FLARE. The FLARE questionnaire was subcategorized into: physical component and emotional component. Other items obtained included: MD global VAS, MD reported flare, seropositivity, disease duration, swollen joint count (SJC), and tender joint count (TJC). The clinical disease activity index was calculated (CDAI). Analyses included Wilcoxon rank sum test and Spearman correlations.

Results: Subjects were separated in to two groups based on their report of RA flare (Y/N). RAPID3, CDAI, and FLARE totals were all significantly different between the groups (Table, $p<0.05$). In addition, there was a strong correlation between FLARE total and RAPID3 (corr=0.66, $p<0.05$) and a correlation between FLARE total and CDAI (corr=0.52, $p<0.05$). In addition, the correlation between CDAI and RAPID3 was 0.76 ($p<0.5$).

Conclusion: The French/Danish and the American-English translation of the FLARE questionnaire correlate similarly with CDAI and RAPID3 (2, 3), and validates the suitable translation of the FLARE to American-English. There may be merit in using this instrument to assess flare in RA patients. However, further validation of the American-English FLARE questionnaire will be required to evaluate it prospectively in a randomized controlled trial. References:1) Woodworth et al EULAR14-4820; 2) Berthelot et al ACR2013-2871 3) Maribo et al. Patient-self assessment of flare in rheumatoid arthritis: translation and reliability of the Flare instrument. Clin Rheumatol.2016 Apr;35(4):1053-8.

Patient Assessment of Flare

	No Flare	Flare	*p-value
	Mean (SD)/ N (%)	Mean (SD)/ N (%)	
	n=30	n=20	
Age	53.57 (16.35)	48.55 (15.92)	0.34
Female	27(90%)	18(90%)	
Race	8(27)	2(10)	0.06
Asian	2(7)	2(10)	
Black	1(3)	1(5)	
Pac Island	18(60%)	15(75%)	
White	1(3%)	0(0)	
Other			
Seropositivity	22(73%)	13(65%)	0.53
Disease duration	11.60(10.77)	13.45(10.78)	0.54
RAPID3	8.64 (6.37)	15.33 (5.66)	0.001
CDAI	13.10 (9.28)	26.75 (13.60)	0.001
TJC	4.23 (4.97)	11.05 (7.76)	0.001
SJC	2.87 (2.71)	5.60 (4.27)	0.02
Patient Global	3.23 (2.27)	5.75 (2.29)	0.001
Physician Global	2.77 (1.70)	4.35 (2.46)	0.02
FLARE Total	4.64 (2.68)	6.73 (2.13)	0.03
FLARE Physical	5.08 (3.07)	7.31 (2.04)	0.02
FLARE Emotional	4.19 (2.77)	6.14 (2.78)	0.04

CDAI = Clinical Disease Activity Index; RAPID3 = Routine Assessment of Patient Index Data; TJC = Tender Joint Count; SJC = Swollen Joint Count; Seropositivity = either CCP+ or RF+; *Wilcoxon rank sum test

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Abstract Number: 2469

How Rheumatoid Arthritis Patients and Rheumatologists Communicate during Clinic Visits When a New DMARD Is Prescribed

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Background/Purpose: Over the last two decades, survey and observational studies of drug-related consultations have consistently shown a lack of adequate medication related discussions between patients and providers. The purpose of this study is to describe medication-related discussions between patients and rheumatologists concerning prescription of a new DMARD. We specifically address whether patient-provider discussions cover clinical guideline recommendations for DMARD communication, including discussion of medication side effects, treatment options, etc.

Methods: This observational study includes data from clinic visits of 38 RA patients (3 rheumatologists) that occurred in a southeastern state from May 2014 to December 2015. Patients were eligible if they were prescribed a new or different DMARD (never prescribed before) at their rheumatology appointment. Clinic visits were audio recorded and medication-related segments transcribed verbatim. Transcripts were coded to measure aspects of the following 15 DMARD topics concerning the DMARD prescribed during the clinic visit: dosage, how to take (e.g., with food), frequency, timing, duration, types of negative side effects, side effect severity, contraindications, long-term effectiveness, drug interactions, mechanism of action, cost, length of time until medication works, medication benefits, and strategies to reduce or monitor risk. Descriptive statistics were calculated using SPSS.

Results: Approximately one third of patients (32%; n=12) had never taken a DMARD. The number of DMARDs rheumatologists discussed with patients ranged from one to seven (M=1.82, SD=1.40). The number of prescribed DMARD-related topics ranged from 7 to 14 (M=11.03, SD=1.73). No

clinic visit addressed all 15 topics and rheumatologists initiated 88% of the topics. Patients initiated the most discussions related to the following topics: drug interactions (62%), long-term effectiveness (43%), and length of time until medication works (19%). Topics that were covered most often included types of negative side effects (100%) and strategies to reduce or monitor risk (97%). Cost was not covered in about one third (34%) of clinic visits – yet, cost was one of the top three topics for which patients (40%) asked the most question, the other two being drug interactions (67%) and types of negative side effects (42%). Rheumatologists discussed an average of 4.6 negative side effects (SD = 2.7, range 1-16). The majority of patients 84% (n=32) did not express concern about any side-effects.

Conclusion: Our findings counter other studies showing patient-provider medication-related discussions lack breadth and results show that DMARD topics covered during RA patient-rheumatologist encounters address many guideline recommended topics. Findings highlight areas of strength as well as areas for improvement regarding patient-provider medication-related discussion.

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Abstract Number: 2470

Treat to Target: Theoretical Agreement Vs Daily Applicability

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Clinical Aspects - Poster III: Treatment – Monitoring, Outcomes, Adverse Events

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Treat to target (T2T) strategy has been widely recognized as effective and leading to better outcomes. There have been no questions regarding its theoretical bases however its applicability in clinical practice is challenged, particularly when audit researches on patient files are reported. Composite indices of disease activity, cornerstones of T2T strategy, should be regularly applied in therapeutic decision making and readily available. Therefore were included as desirable but not as a mandatory item in association with a questionnaire dealing with patients perspectives and barriers to T2T implementation while information about social-economical and educational patient´s backgrounds were totally compulsory. The aim of this study was to analyze the availability of composite indices of disease activity and its optional inclusion in a data base with a different focus.

Methods: the data collected by 11 investigators committed to T2T strategy in different areas of the country, in rural and urban settings, in public academic centers and in private practice were reviewed regarding the noncompulsory inclusion of the composite measures of disease activity: DAS28, CDAI e SDAI.

Results: 485 RA patients were included in the database, 86% had DAS28 (mean=3.6±2,33) ; 53.4% SDAI(19.3±22.5) and 59% had CDAI(14.913.5). The percentages of patients with composite indices collected in each center are depicted below as well the percentage of patients in private practice(last column):

Investigator	DAS28 %	DAS28 mean(SD)	SDAI %	CDAI%	missing public	missing private	Private practice
1 -south/urban	98	3.5(1.6)	80	0.8	0	4	66
2 -south/urban	100	3.8(1.5)	100	100	0	0	68
3 -south/urban	90	3.4(1.3)	0	10	10	0	0
4 -west/urban	96	3.2(1.0)	26	13	4	0	30
5 - southeast/urban	92	3.7(1.4)	86	100	8	0	10
6 - southeast/urban	0	---------- -	0	0	90	10	10
7 -southeast/rural	85	3.5(1.7)	48	50	6	2	4
8 - southeast/urban	98	3.5(1.3)	66	68	2	4	10
9 - southeast/urban	100	3.8(1.7)	100	100	0	0	36
10- north/urban	100	3.8(1.3)	0	0	0	0	38
11- north/urban	100	3.6(0,9)	0	0	0	0	100

Conclusion: DAS28 was easily obtained in the vast majorities of cases; PCR dosage was the great

obstacle to SDAI application. In the absence of laboratory tests CDAI was applied by some investigators. Academic or private settings were not a factor.

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Abstract Number: 2471

What Are the Reasons of Discrepancies Between Patients and Physicians in Their Perceptions of Rheumatoid Arthritis Disease Activity and What Is the Impact of This Discordance on Remission, Function and Structure at 1 Year?

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Background/Purpose: Patients and physicians often differ in their perceptions of rheumatoid arthritis (RA) disease activity, as quantified by the patient's global assessment (PGA) and by the evaluator's global assessment (EGA). The quest for understanding the reasons for discrepancies in evaluations of disease activity becomes particularly important in the context of recent recommendations that define Boolean-based ACR EULAR remission as the treatment target. The objectives of this study were 1) to explore the extent and reasons for this discordance 2) to determine if this discordance at baseline is associated with RA outcomes at 1 year (remission, function and structure) in early arthritis (EA) in daily clinical practice.

Methods: -Patients: from the French cohort of EA ESPOIR (at least 2 swollen joints for less than 6 months, DMARD naïve), fulfilling the ACR-EULAR criteria for RA at baseline -Analyses: At baseline, agreement between PGA and EGA (Bland-Altman plot) was assessed. Multivariate linear regression was used to determine the patient and EA features independently associated with discordance (calculated as PGA - EGA). Logistic regression was used to analyze discordance as $|PGA - EGA| \geq 20$. Multivariate logistic models were used to determine if discordance at baseline is associated with remissions (Boolean, SDAI and DAS28), functional stability (HAQ≤0.5 and deltaHAQ≤0.25) and absence of radiographic progression (delta Sharp score<1) after 1 year of follow-up.

Results: In 645 patients with ERA (mean age=48.8±12.2 years, 77% female, 48.7% ACPA +) agreement was better at both ends of the spectrum, especially for patients with high disease activity. The direction of the discrepancy usually points toward a higher rating by the patients than by physicians themselves. Evaluation of disease activity yielded discordant scores between the patients and their physicians in 30% of our cohort: 153 patients (24%) had higher PGA scores, 41 patients (6%) had higher EGA scores, and 451 patients (70%) had concordant PGA and EGA scores ($|PGA - EGA| < 20$). In multivariate linear regression center-adjusted, higher PGA has been found to be associated with absence of fulfilling ACR 1987 revised criteria for RA (p=0.0005), higher levels of fatigue (p<0.0001) and lower number of swollen joint counts (SJC) (p=0.0022). With logistic regression center-adjusted, low number of SJC (OR 95%CI=1.92 [1.26-2.91]), low mental component of the SF-36 (OR 95%CI=1.82 [1.23-2.69]) and living alone (OR95%CI=1.68 [1.09-2.58]) were associated with discordance between PGA and EGA. In multivariate analyses, discordance at baseline was not associated with remission, function and structural progression at 1 year.

Conclusion: In early RA, the discordance between PGA and EGA is multifactorial with objective measures like low SJC and absence of ACR 1987 revised criteria for RA, but also patient reported outcomes like high level of fatigue and low mental status, and environmental factor: living alone. Discordance between PGA and EGA at baseline was not associated with RA outcomes at 1 year. Understanding the reasons for a discordant view of disease activity will help to facilitate the sharing of decision-making in the management of RA.

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Abstract Number: 2472

Early DAS28 Drop Is a Predictor for Clinical Response to

Anti-TNF Agents in Patients with Rheumatoid Arthritis: An Observational Study of a Real Life Inception Cohort

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Background/Purpose: Predictors of rheumatoid arthritis (RA) response to anti-TNF agents have been described. Except for certolizumab, the value of interim analysis before 24 weeks of treatment is not clear to predict response. The purpose of this observational study was to evaluate predictors of response of anti-TNF agents in RA patients in a real-life situation tertiary center.

Methods: An inception cohort of all RA patients (ACR 1987) who received the first anti-TNF dose in the rheumatology outpatient infusion center between July, 2007 and July, 2012 was analyzed. Demographic, clinical and laboratorial data, including disease activity score (DAS28) were recorded at baseline and each 6-8 weeks and at each therapeutic change or interruption. Drug response at 24 weeks was evaluated. Remission was defined as DAS28 was ≤ 2.6 at 24 weeks. Drug survival was also analyzed. Baseline data, early (6-8 weeks) and late (14-16 weeks) significant (≥ 0.6) and very significant (≥ 1.2) changes in DAS28 were evaluated in order to predict remission at 24 weeks. Any cycle of anti-TNF was included.

Results: One hundred sixty-six RA patients were included, corresponding to 215 cycles of anti-TNF treatments. Patients were predominantly female (n= 91%;n=151); and had a positive rheumatoid factor (RF) (80%; n=133). Mean age and mean disease duration: 49.2 ± 12.2 and 12.5 ± 8.8 years, respectively. The cycles analyzed corresponded to the first one in 54% (n=116), the second in 40% (n=85) and the third in 6% (n=14). Infliximab corresponded to the main used drug (41%; n=89 cycles), followed by adalimumab (32%; n=69) and etanercept (27%; n=57). The analysis per cycle showed that, after 24 weeks, only 35 (16%) patients achieved remission. Patients who achieved remission and those who did not were similar according to age, gender, RF positivity, disease duration, number of cycles of anti-TNF, drug used, or association with methotrexate,

leflumomide or any traditional disease-modifying antirheumatic drug (p>0.05). Patients who achieved response had lower disease severity at baseline according to DAS28 (4.7 ± 1.1 *vs*. 5.7 ± 1.2; p<0.001)**,** number of painful joints (10 ± 9 *vs*. 19 ± 14; p<0.001), pain visual analogue scale (VAS) (5 ± 2.6 *vs*. 6.4 ± 2.2; p=0.01), patient global VAS (4.9 ± 2.4 *vs*. 6.5 ± 3; p<0.001), physician VAS (4.9 ± 2.1 *vs*. 6.4 ± 2.7; p<0.001), ESR (20 ± 14 *vs*. 32 ± 24; p=0.006), and HAQ (1.2 ± 0.7 vs. 1.5 ± 0.7; p=0.012). Patients who achieved remission at 24 weeks also had deeper falls in DAS28 at 6-8 weeks (1.77 ± 1.27 *vs*. 1.06 ± 1.38; p=0.009). Moreover, significant (≥ 0.6) early (weeks 6-8) falls in DAS28 [26 (84%) *vs*. 102 (64%); p=0.032) and very significant (≥1.2) late falls (weeks 14-16) were also related to remission [22 (71%) *vs*. 76 (48%); p=0.018). Significant rises (≥0.6) in DAS28 in any interim analysis were less frequent among patients who achieved remission than in patients who did not [5 (17%) vs. 47(36%), p=0.047]. Mean drug survival was 57.1 ± 50.1 weeks, without differences among the anti-TNF drugs (p>0.05). At 52 weeks, remission rate was stable (14%), but has fallen continuously every 6 months: 7% to 5% (18 to 24 months), 3% to 1% (30 to 48 months), up to 0 in 54 months.

Conclusion: The low and not sustained remission rate, regardless of the anti-TNF treatment, with short drug survival, shows the actual difficulties in treating RA in a real-life setting. Interim positive and negative significant variations in disease activity before 24 weeks of treatment can help to avoid prolonged and unnecessary exposition to such drugs.

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Abstract Number: 2473

Concordance Between the Patient, Nurse and Physician Assessment of Clinical Outcomes in a Cohort of Rheumatoid Arthritis Patients Treated with Certolizumab Pegol

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Background/Purpose: The use of swollen (SJC) and tender joint counts (TJC) for rheumatoid arthritis (RA) disease activity and treatment effectiveness is well established. Patient reported outcomes (PRO) are important. However, it is unknown if patient scoring is as reliable as trained professionals.

Methods: PRO including SJC and TJC were assessed at baseline, 6 and 12 weeks by patients and clinicians. Data was collected using ePRO (electronic) and pPRO (paper) The Least Squares Method (LSM), Pearson correlation (Rs.) and weighted Kappa scores were used to assess inter-rater reliability and agreement of responses between the patient, nurse and physician for changes in TJC and SJC from 0 to 12 weeks treatment.

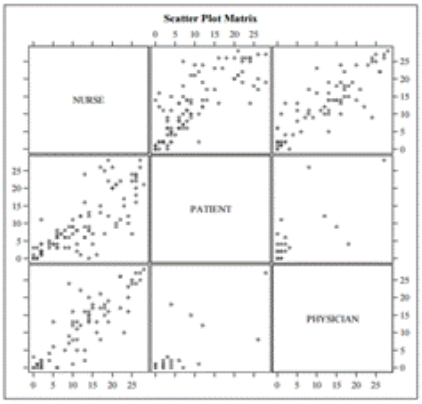
Results: Total 341 evaluable individual assessment episodes comprising 157 Nurse, 106 Patient and 78 Physician joint count episodes in 52 patients with RA of mean duration 11.7 (SD 10.97) years and mean age 55 (SD 14.3, 77% female) enrolled in the study. At baseline, matched joint count episodes were available for 104 Patient - Nurse, 72 Physician - Nurse and 21 Patient - Physician pairs. Correlation of TJC scores per assessor pairs were Rs. 0.83; $p<0.001$(Patient-Nurse), Rs 0.85; $p<0.001$(Physician-Nurse) & Rs. 0.59; $p=0.005$(Physician-Patient) (Table 1). The inter-rater reliability (agreement) of the Patient-Nurse pairs had a weighted Kappa of 0.59 (0.53, 0.68) (Figure 1). Correlation of SJC scores per assessor pairs were Rs. 0.69; $p<0.001$(Patient-Nurse), Rs 0.66; $p<0.001$(Physician-Nurse) & Rs. 0.42; $p=0.058$(Physician-Patient) (Table 1). The inter-rater reliability (agreement) of the Patient-Nurse pairs had a weighted Kappa of 0.48 (0.41, 0.55). The comparison suggests that the biggest discrepancy is from Physician assessments of improvement (interaction between assessor and time).

Conclusion: There is a moderate to high level of agreement between clinicians and patient TJC and SJC assessments that suggest it may be a useful option in assessing joints and response in RA. Further evaluation of activity tools ie DAS28, CDAI or SDAI utilising patient assessments may be worth exploring. Acknowledgements 1. UCB Australia for access to database, assistance with analysis and financial support. 2. Australian Rheumatologists contributing patients to the study.

Table 1: PRO Spearman Correlation coefficients scores (p values) for Swollen Joint Count(SJC) and Tender Joint Count(TJC) between Nurse, Physician and Patient

Joint Assess	Assessor	Nurse	Patient	Physician
PRO- TJC	Nurse	1.00	0.83(<.0001)	0.85(<.0001)
	Patient	0.83(<.0001)	1.00	0.59(0.005)
	Physician	0.85(<.0001)	0.59(0.005)	1.00
PRO- SJC	Nurse	1.00	0.69(<.0001)	0.66(<.0001)
	Patient	0.69(<.0001)	1.00	0.42(0.058)
	Physician	0.66(<.0001)	0.42(0.058)	1.00

Figure 1: Correlation coefficient scores for Tender Joint Count (Overall) between all Assessors



Disclosure: C. Inderjeeth, None; **A. Inderjeeth**, None; **W. Raymond**, None.

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Abstract Number: 2474

Patients' Experiences of Using a Smartphone App for Remote Monitoring of Rheumatoid Arthritis, Integrated into the

Electronic Medical Record, and Its Impact on Consultations

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Background/Purpose: Treatment of patients with rheumatoid arthritis (RA) is guided by monitoring changes in disease severity. At present, patients do not routinely record disease severity between clinic visits, despite the availability of a range of validated patient reported outcome measures (PROMs). In response this, the REMORA study (**RE**mote **MO**nitoring of **R**heumatoid **A**rthritis) is developing and evaluating a Smarthphone app which patients can use to record key ePROS (electronic patient reported outcomes) between clinic visits, and link these to the electronic patient record (EPR). The aim of this analysis is to examine patients' views of using the beta version of the app and explore its impact on their post-app clinical consultation. In particular we were interested in seeing if the app could overcome some of the limitations of the current consultation process, i.e. reliance on patient recall, eloquence and stoicism regarding their symptoms between clinic visits.

Methods: The 'beta app' was tested by eight patients for one month during which they completed routine question sets at home, with the data integrated into the hospital EPR. Question sets included seven visual analogue scales for daily symptoms including pain and fatigue; weekly self-reported count of tender and swollen joints, flares, and impact on work; and monthly completion of the health assessment questionnaire (HAQ). A free text diary function was provided for ad hoc recording of information, although this wasn't exported into the record. Patients were invited to a clinical consultation 'pre' and 'post' app use. These were used to determine the value of having access to routinely recorded ePROS at the consultation. Individual interviews were held with participants to discuss their experience of using the app and the use of the data as part of the clinical consultation. Feedback was also obtained from the consulting clinician.

Results: Patients' felt that the app was "a great idea" and made care "more personal to you". Data recording improved the consultation as it aided recall and made it easier for patients to have a "shared conversation" with the clinician at the consultation as "with a graph…you can see what's going on." "I found it made a difference, because it wasn't all me telling him and trying to remember. The information was there so you've got solid proof straightaway" These views were echoed by the consulting clinician as the ePROS made it possible to quantify responses to treatment across physical and mental health. The graphs highlighted flares that patients hadn't mentioned, and

demonstrated gradual improvements in symptoms in response to treatment that may otherwise have been missed, therefore supporting decision making regarding the continuation of treatment. Routine completion of data was relatively straightforward - "it's a doddle" - and not too onerous. A number of minor refinements to the app design and question sets were suggested by patients and will be incorporated into the app.

Conclusion: The app was well received by patients and feedback suggests that the data recorded will have a number of benefits for both patients and clinicians.

Disclosure: L. Austin, None; **C. Sanders**, None; **W. G. Dixon**, None.

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Abstract Number: 2475

Identifying Key Variables for Inclusion in a Smartphone App to Support Clinical Care and Research in Patients with Rheumatoid Arthritis

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Background/Purpose: Treatment for patients with rheumatoid arthritis (RA) is shaped by monitoring changes in disease severity over time. At present, clinicians managing RA have few (or no) objective measurements of disease activity between clinic visits, even though a number of patient related outcomes measures (PROMs) exist. Smartphones provide a possible solution to allow regular monitoring of disease severity between clinic visits with integration into electronic medical records. Benefits could include better information for consultations, triaging of outpatient appointments and aiding patient self-management. Such data can also support novel research by

providing temporally-rich data. REMORA (**RE**mote **MO**nitoring of **R**heumatoid **A**rthritis) is a study which is designing, implementing and evaluating a system of remote data collection for people with RA for health and research purposes. The project asks whether electronic collection of patient reported outcomes (ePROS) directly from patients between clinic visits can enhance clinical care and provide a sustainable source of data for research. The aim of this paper is to describe the process of determining the ePROS for inclusion in the app, in preparation for piloting the app in clinical practice, and to present the final dataset.

Methods: This study obtained stakeholders' views on the potential value of recording a range of ePROS. Interviews were conducted with 10 RA practitioners (clinicians, nurses and physiotherapists), 12 RA researchers and 21 patients. Interviews determined provisional ePROSs for inclusion, recording frequency, and value of a free text diary. Table 1 summarises the approach to gaining consensus on app components.

Results: All stakeholder groups wanted to capture information on changes in disease activity and the impact of the disease (physically and emotionally). Practitioners and researchers wanted routine data that had been recorded consistently using existing validated tools (such as the DAS 28 and the HAQ), but saw the value of a diary for recording triggers and alleviators of disease activity. Patients favoured recording notable events (such as flares) as they occurred, however, they could see the benefits of recording data routinely to see patterns in disease activity. The final data set therefore comprised a combination of routine data and a diary (table 2).

Conclusion: Consensus on the key components of the Smartphone app was achieved using the process outlined in table 1. The components shown in table 2 have now been incorporated into the 'beta app' in readiness for piloting within clinical practice.

Table 1: Consensus process

- Qualitative interviews were conducted with researchers and practitioners to determine their preferences regarding the components of the app and the rationale for their choices

- A table summarising the key components suggested by practitioners and researchers was generated in preparation for discussion and feedback from the PPI (patient and public involvement) group working alongside the research team

- The content and wording of the tabulated information was refined in response to suggestions made by the patient group in preparation for patient interviews

- Qualitative interviews were conducted with patients with RA to determine their preferences regarding the components of the app. Following this open discussion, patients were shown the tabulated information, derived from practitioner and researcher interviews, and patient feedback sought on the suitability of components suggested

- The components which had widespread consensus across the stakeholder groups were incorporated into the app

- Suggested components that did not have consensus across all groups, or were beyond the scope of the study, were documented with a view to being incorporated into future developments. Components suggested included the facility for taking photographs, and linking the app to a device, such as a pedometer, for measuring exercise

- PPI group members reviewed and commented on the final components prior to their incorporation into the beta app

Table 2: Final data set – frequency, components and mode of data capture		
Daily question set	Pain Difficulty with physical activities Fatigue Sleep difficulties Physical wellbeing Emotional wellbeing Coping	10 point visual analogue scale
	Morning stiffness	Fixed 7 point scale (radio button)
Weekly question set	Number of tender joints Number of swollen joints	Numeric value
	Global assessment of wellbeing	10 point visual analogue scale
	Employment status	Yes/No response (radio button)
	Impact on hours worked	Numeric value
	Experienced a flare	Yes/No response (radio button)
	Description of flare	Free text box
Monthly question set	Health Assessment Questionnaire (HAQ) impact of disease on daily activities including function, mobility and grooming	Fixed point scales (radio button) plus free text entry box

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Disclosure: W. G. Dixon, None; **C. Sanders**, None; **L. Austin**, None.

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Abstract Number: 2476

Performance of Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) Appears to be Better Than Gold Standard Disease Assessment Score (DAS-28 CRP)

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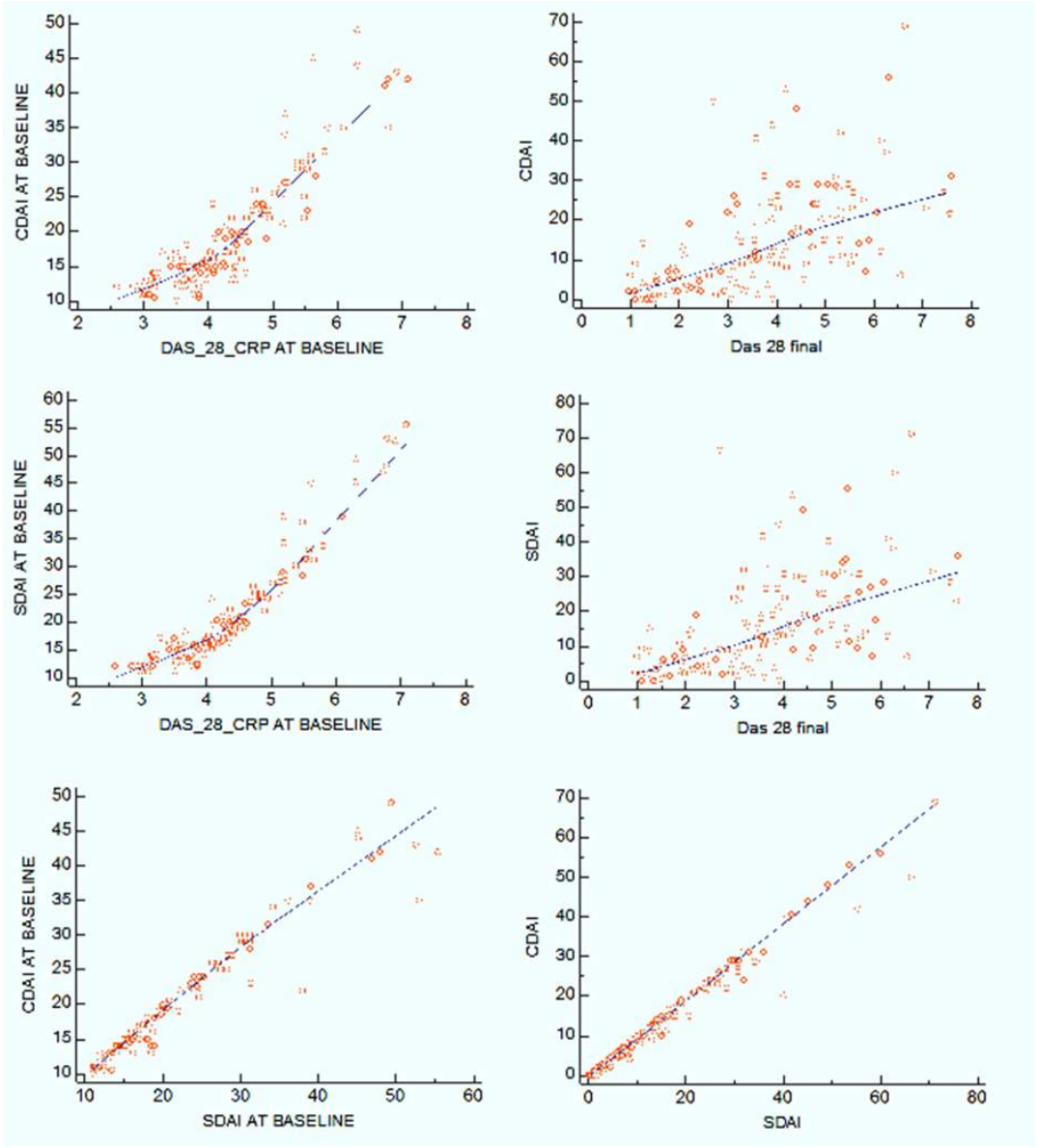
Background/Purpose : To compare the performance of DAS-28 CRP, CDAI and SDAI composite measures to assess status of patients with Rheumatoid Arthritis on Methotrexate, versus DAS-28 CRP as the gold standard.

Methods : 135 patients with RA as per the 2010 ACR/EULAR criteria were included in the prospective study. The disease activity was assessed at baseline and at every 6 weeks for 24 weeks, by DAS-28 CRP, CDAI and SDAI. Patients were divided into groups of remission, low, moderate and high activity on the basis of predefined cut-offs for DAS-28 CRP, CDAI, and SDAI. A Spearman correlation between composite measures and inter-group comparison of the measures were performed.

Results : There was an excellent positive correlation between DAS-28 CRP and CDAI (linear weighted k baseline – 0.545), DAS-28 CRP and SDAI (linear weighted k – 0.689) at baseline. There was moderate agreement between DAS-28 CRP and CDAI (linear weighted k final visit – 0.458) at final visit. There was moderate correlation between SDAI and DAS 28 CRP at final visit (linear weighted k– 0.470). (Fig shows excellent correlation between CDAI vs DAS 28 CRP and SDAI vs DAS28 CRP at base line but not at final visit. However, correlation between CDAI vs SDAI remained excellent). Patients in remission as per DAS-28 CRP had significantly more residual disease activity compared to SDAI and CDAI remission criteria.

Conclusion: The study shows an excellent strong positive correlation between DAS-28 CRP, CDAI and SDAI at initial evaluation but not at final visit. SDAI and CDAI based remission criteria seems to be better than DAS28-CRP based remission criteria.



Disclosure: P. Dhaon, None; **S. K. Das**, None; **R. Srivastava**, None; **U. Dhakad**, None.

Abstract Number: 2477

Short Term Clinical Response to Initial Treatment with High Versus Low Dose Methotrexate in Mono- and Combination Therapy in Early Rheumatoid Arthritis Patients

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Background/Purpose: Aiming at rapid decrease of disease activity, there has been a trend to start with higher doses of methotrexate (MTX) for newly diagnosed rheumatoid arthritis (RA) patients, not only for MTX monotherapy, but also in combination with other antirheumatic drugs (DMARDs). We hypothesized that in combination with other very effective medication, there might be no additional benefit of high over low doses of MTX. We studied the relationship with early clinical response of high versus low doses of MTX in mono- and combination therapy in DMARD naive early RA patients.

Methods: RA patients included in the observational international METEOR cohort with symptom duration ≤5 years, time between diagnosis and first visit ≤2 months, MTX prescribed at first visit, no medication change within 3 to 6 months and available disease activity information were selected. Patients were divided into 4 medication groups: MTX monotherapy, MTX + synthetic (cs)DMARDs, MTX + oral glucocorticoid (+ possibly csDMARDs) or MTX + biologic (b)DMARDs (+ possibly csDMARDs). Missing data were imputed using multivariate normal imputation. MTX dose was dichotomized: low dose ≤10 mg/week & high dose ≥15 mg/week. A propensity score (PS) was calculated to adjust the relationship between MTX doses and outcome for potential confounding by indication. Linear mixed model analyses for DAS, DAS28, and HAQ were performed for each medication group, with 'MTX-dose' & 'days between visit and baseline assessment (time)' as co-variates. Associations were adjusted for the PS. Random intercept and slope were used to account for irregular time intervals between visits. Each model was tested for the presence of an interaction between 'MTX dose' and 'time'.

Results: Patients on MTX monotherapy had lower baseline disease activity and fewer were erosive and autoantibody positive; other baseline characteristics were comparable between medication groups. The number of patients on combination therapy with bDMARDs was too small to perform analyses (n visits=26, n patients=11). For patients on MTX monotherapy, no differences in efficacy

between high and low MTX dose were seen for DAS28 and HAQ. Only DAS decreased slightly *less* in the high dose initial MTX compared to the low dose group (β=0.0021, 95% CI=0.00012; 0.0041) for interaction between MTX dose and time). No differences in clinical response between high or low dose MTX were seen in patients on combination therapy with csDMARDs or glucocorticoids (table 1).

Conclusion: In DMARD naive early RA patients, there seems to be no early clinical benefit of high over low initial MTX doses, neither for MTX monotherapy nor for combination therapy with MTX/csDMARDs or glucocorticoids. Contrary to expectations, DAS (but not DAS28 or HAQ) even appeared to decrease slightly less after higher doses of MTX monotherapy. However, this effect was very small and may be explained by unmeasured baseline differences between high and low MTX dose groups not captured by the PS.

Table 1. Results of the linear mixed model analyses to investigate the effectiveness of high versus low methotrexate doses on disease activity and physical functioning, stratified per medication group.

Methotrexate monotherapy (n patients = 450, n visits = 976)				
DAS	**β**	**SE**	**p**	**95% CI**
MTX dose group	-0.087	0.12	0.480	-0.33; 0.15
Time between visit and baseline (days)	-0.0094	0.00058	<0.001	-0.011; -0.0083
MTX dose group*Time	0.0021	0.0010	0.037	0.00012; 0.0041
Propensity score	-1.23	0.15	<0.001	-1.52; -0.94
constant	3.90	0.059	<0.001	3.79; 4.02
DAS28	**β**	**SE**	**p**	**95% CI**
MTX dose group	0.10	0.15	0.489	-0.18; 0.39
Time between visit and baseline (days)	-0.012	0.0070	<0.001	-0.013; -0.010
Propensity score	-1.87	0.21	<0.001	-2.29; -1.45
constant	6.09	0.078	<0.001	5.94; 6.24
HAQ	**β**	**SE**	**p**	**95% CI**
MTX dose group	0.049	0.068	0.469	-0.084; 0.18
Time between visit and baseline (days)	-0.0029	0.00031	<0.001	-0.0035; -0.0023
Propensity score	0.23	0.10	0.023	0.033; 0.43
constant	0.88	0.034	<0.001	0.82; 0.95
Methotrexate + csDMARDs (n patients = 259, n visits = 561)				
DAS	**β**	**SE**	**p**	**95% CI**
MTX dose group	0.055	0.13	0.671	-0.20; 0.31
Time between visit and baseline (days)	-0.011	0.00060	<0.001	-0.012; -0.0095
Propensity score	-0.82	0.24	0.001	-1.29; -0.34
constant	4.08	0.064	<0.001	3.95; 4.20
DAS28	**β**	**SE**	**p**	**95% CI**
MTX dose group	0.033	0.18	0.855	-0.33; 0.39
Time between visit and baseline (days)	-0.014	0.00088	<0.001	-0.016; -0.013
Propensity score	-1.09	0.33	0.001	-1.74; -0.43
constant	6.33	0.089	<0.001	6.15; 6.50
HAQ	**β**	**SE**	**p**	**95% CI**
MTX dose group	0.016	0.081	0.842	-0.14; 0.18
Time between visit and baseline (days)	-0.0037	0.00038	<0.001	-0.0045; -0.0030
Propensity score	0.31	0.16	0.047	0.0037; 0.62
constant	0.99	0.041	<0.001	0.91; 1.07
Methotrexate + oral glucocorticoid (+csDMARDs) (n patients = 686, n visits = 1543)				
DAS	**β**	**SE**	**p**	**95% CI**
MTX dose group	-0.012	0.10	0.906	-0.22; 0.19
Time between visit and baseline (days)	-0.010	0.00053	<0.001	-0.011; -0.0092
Propensity score	-0.65	0.15	<0.001	-0.94; -0.36
constant	4.07	0.077	<0.001	3.92; 4.22
DAS28	**β**	**SE**	**p**	**95% CI**
MTX dose group	-0.14	0.14	0.326	-0.41; 0.13
Time between visit and baseline (days)	-0.014	0.00071	<0.001	-0.015; -0.012
Propensity score	-1.04	0.20	<0.001	-1.42; -0.65
constant	6.37	0.10	<0.001	6.18; 6.57
HAQ	**β**	**SE**	**p**	**95% CI**
MTX dose group	-0.023	0.075	0.754	-0.17; 0.12
Time between visit and baseline (days)	-0.0042	0.00029	<0.001	-0.0047; -0.0036
Propensity score	0.34	0.11	0.002	0.13; 0.55
constant	1.10	0.051	<0.001	1.00; 1.20

DAS = disease activity score, HAQ = Health Assessment Questionnaire, ESR = erythrocyte sedimentation rate, SE = standard errror, 95% CI = 95% confidence interval. MTX dose group is a binary variable with low dose ≤10 mg/week and high dose ≥15 mg/week. Low dose is the reference category.

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Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Rhoche, Schering-Plough, TiGenix, UCB, Wyeth., 5,Abbott/AbbVie, Amgen, Bristol Myers Squibb, Janssen (formerly Centocor), Merck, Pfizer, Rhoche, Schering-Plough, UCB, Wyeth., 9.

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Abstract Number: 2478

Impact of Poor Prognostic Factors on Treatment Decisions in Clinical Practice in Patients with Rheumatoid Arthritis: Findings from a US Observational Cohort

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Background/Purpose: Poor prognostic factors can determine the extent of disease progression, disability and treatment outcomes in patients (pts) with RA. It is currently unknown whether the presence of poor prognostic factors influences treatment decisions in pts with RA. The purpose of this study was to report patterns of medication use and the change in CDAI score between baseline and 12 months by prognostic factors.

Methods: Using the Corrona RA registry, we identified pts with RA who were biologic naïve at enrollment and had a follow-up visit at 12 months (± 3 months). Pts were characterized at enrollment in terms of RA prognosis based on the 2008 ACR treatment recommendations,[1] including functional limitation (based on modified Health Assessment Questionnaire), extra-articular disease (Sjögren's syndrome, RA lung disease and/or nodules), seropositivity (RF and/or anti-cyclic citrullinated peptide antibodies) and erosions. Pts were categorized as having 0–1, 2 or 3+ poor prognostic factors. Outcomes investigated included the use of a biologic/targeted synthetic DMARD

(b/tsDMARD) over the 12-month follow-up period and examination of initiation of any DMARD (e.g. conventional or b/tsDMARD). Logistic regression models (unadjusted and adjusted for sex, age and baseline CDAI) examined the relationship between prognosis and outcomes. In the subset of pts with CDAI score at baseline and 12 months (n=3510), the reduction of disease activity was examined in adjusted models in the three poor prognosis groupings.

Results: There were 3621 pts enrolled on/after January 2005 who met the selection criteria: 1554 (42.9%), 1263 (34.9%) and 804 (22.2%) pts with 0–1, 2 or 3+ poor prognostic factors, respectively. An increased number of poor prognostic factors was associated with older age (median age: 58, 60 and 62 years, $p<0.001$), greater disease duration (median: 1, 2 and 4 years, $p<0.001$) and increasing disease activity (median CDAI score: 7, 9.6 and 14, $p<0.001$, for the 0–1, 2 or 3+ prognosis groupings, respectively). The proportion of pts initiating a b/tsDMARD was greatest in those with 3+ vs 0–1 poor prognostic factors ($p=0.024$). However, when adjusting for differences in baseline characteristics (including CDAI score), there was no significant relationship between poor prognosis and b/tsDMARD use (Table). There was no significant relationship between poor prognosis category and any DMARD initiation in the unadjusted and adjusted analyses (Table). After adjusting for CDAI score at enrollment, mean reduction in CDAI score over 12 months was significantly less for those with 3+ vs 0–1 poor prognostic factors (Table; $p<0.001$).

Conclusion: These findings suggest that the presence of poor prognostic factors does not influence treatment decisions. This may warrant reconsideration as there was a diminished reduction in disease activity in those with a greater number of poor prognosis factors. 1. Saag K, et al. *Arthritis Rheum* 2008;**59**:762–84.

Table. Logistic regression analysis to predict biologic use by the 12-month visit, change in overall treatment approach and change in CDAI from enrollment to 12 months according to poor prognosis category				
	Poor prognosis indicators			
	0–1	2	3+	p value**
Biologic use by the 12-month visit				
Unadjusted OR (95% CI)	Reference	1.16 (0.97, 1.39)	1.39 (1.14, 1.70)	0.005
Adjusted OR* (95% CI)	Reference	1.00 (0.82, 1.23)	1.10 (0.87, 1.40)	0.49
Change in overall b/tsDMARD treatment from enrollment to 12 months†				
Unadjusted OR (95% CI)		1.11 (0.95, 1.29)	1.19 (1.00, 1.41)	0.13
Adjusted OR* (95% CI)		1.00 (0.84, 1.18)	1.00 (0.81, 1.23)	>0.99
Change in CDAI from enrollment to 12 month				
Unadjusted, mean (SE)	–3.05 (0.32)	–4.96 (0.36)	–5.44 (0.45)	<0.001
Adjusted,‡ mean (SE)	–4.92 (0.24)	–4.50 (0.26)	–2.50 (0.34)	<0.001
*Adjusting for sex, age, duration of RA and baseline CDAI **p value is calculated based on an overall likelihood ratio test of the impact of poor prognosis †Change in overall treatment from enrollment to the 12-month visit reports the treatments a patient initiated over the 12-month period (e.g. conventional or b/tsDMARD) ‡Adjusted by CDAI at enrollment OR=odds ratio				

Disclosure: L. Harrold, Corrona, LLC, 1,Pfizer Inc, 2; **E. Alemao**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **H. Litman**, Corrona, LLC, 3; **S. Connolly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Kelly**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **W. Hua**, Corrona, LLC, 3; **L. Rosenblatt**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **S. Rebello**, Corrona, LLC, 3; **J. Kremer**, Corrona, LLC, 1,AbbVie, Bristol-Myers Squibb, Genentech, Lilly, Novartis, Pfizer, 2,Corrona, LLC, 3,Genentech, 8.

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Abstract Number: 2479

Work Productivity in Early Rheumatoid Arthritis Patients Treated before and after Implementation of a Treat-to-Target Strategy

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Background/Purpose: Rheumatoid arthritis (RA) is a known cause of work productivity loss. Participation in work-related activities is defined as part of the primary goal of RA treatment in the 2015 Treat-to-Target recommendations (1). The objective of the current study was to compare sick leave rates in early RA patients in a tight control Treat-to-Target study to early RA patients followed in an observation study without treatment algorithms.

Methods: We used data from two studies, ARCTIC (inclusion Oct 2010 – April 2013, fulfillment of 2010 classification criteria, symptom duration<2 years, DMARD-naive with indication for DMARD) and the NOR-VEAC study (inclusion Oct 2004 – Aug 2010, patients included in the analyses fulfilled 2010 criteria for RA, symptom duration <16 weeks, DMARD-naive). Patients in ARCTIC were treated according to a predefined algorithm with treatment target of DAS<1.6 and SJC44=0. In half the patients, an additional target was no ultrasound power Doppler signal. NOR-VEAC patients were treated according to the physicianÕs preference. Data collection included identical questions on work participation, and in the ARCTIC study additionally the Work Productivity and Activity Impairment Questionnaire. We compared the proportion of patients reporting sick leave among patients not reporting retirement or disability pension across studies at baseline, 8 and 16 months, the time points with most data available in both cohorts, by chi-square test.

Results: The mean (SD) age for the 229 patients in ARCTIC was 51.4 (13.7) years, disease duration 7.1 (5.4) months, DAS28 4.4 (1.2), 61% were female and 86% seropositive. The 259 NOR-VEAC patients had shorter mean (SD) disease duration (2.0 (1.0) months, p-value <0.001), higher DAS28 (5.3 (1.3), p-value<0.001) and lower seropositivity rate (74%, p-value <0.001). NOR-VEAC patients had comparable age (52.7 (14.1) years) and gender distribution (64% females) to ARCTIC. In ARCTIC, levels of presenteeism and absenteeism at two years were overall very

low, with substantial improvement from baseline (figure 1). While 30.9% of employed ARCTIC patients reported 100% absenteeism at baseline, the corresponding number at 24 months was 3.7%. When comparing the cohorts after 16 months 14.5% of patients in ARCTIC and 26.1% of patients in NOR-VEAC reported any sick leave (p-value 0.01). No difference in sick leave was found between ARCTIC and NOR-VEAC at baseline but a trend was observed at 8 months (figure 2).

Figure 1: Follow-up data from patients treated according to a tight control treat-to-target regimen (ARCTIC) **A)** Absenteeism (in employed patients) **B)** Presenteeism (patients with work attendance)

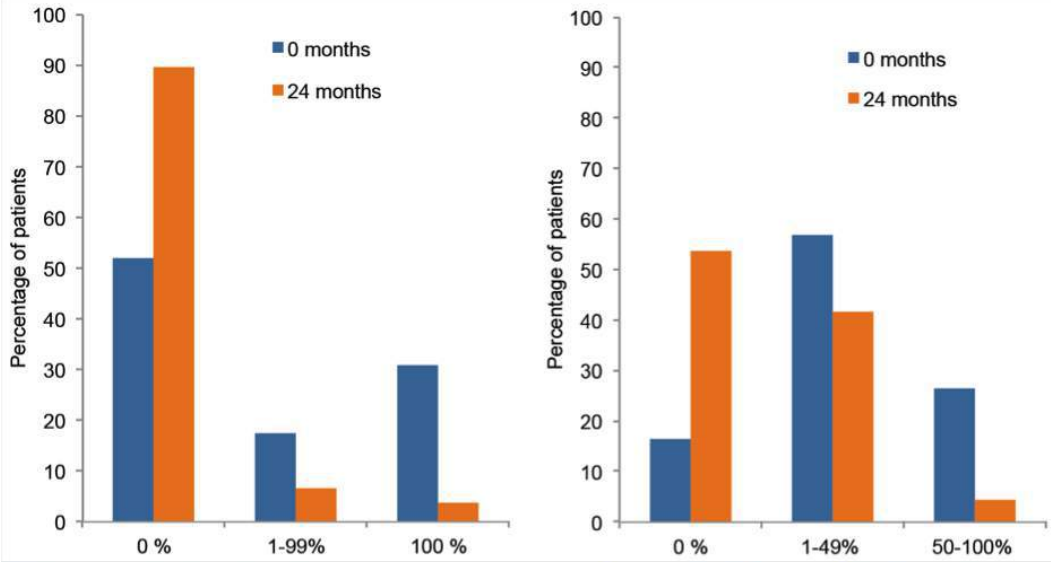
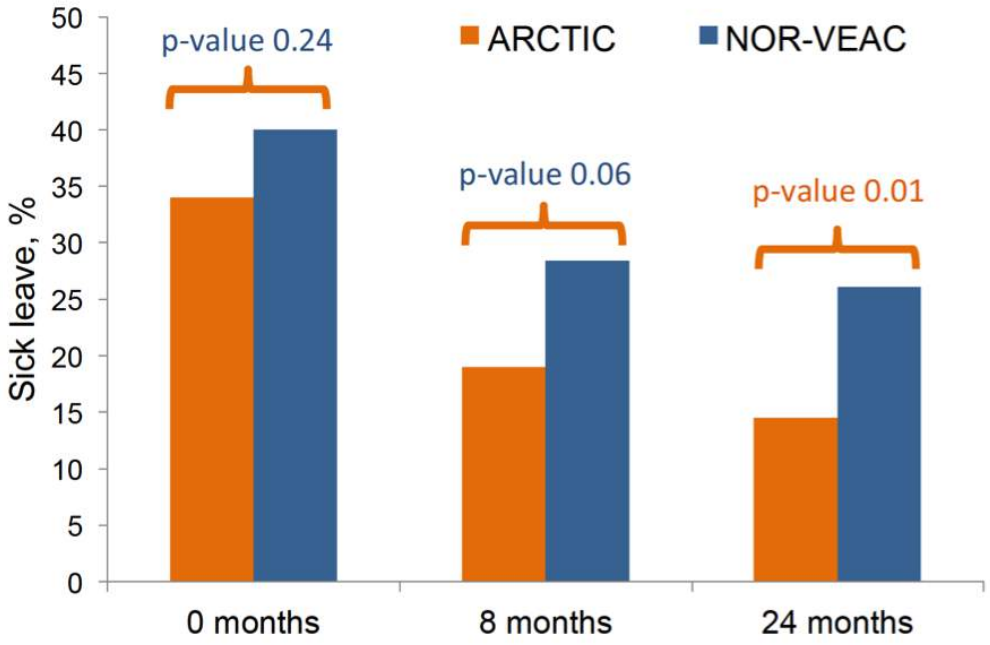


Figure 2: Sick-leave rates in patients followed with treat-to-target tight control (ARCTIC) and without (NOR-VEAC)



Conclusion: Patients with early RA in a tight control treat-to-target study reported very little work productivity loss after two years. Sick-leave rates were significantly lower than in a previous cohort of early RA patients followed without implementation of such principles. The results support that patient care based on modern treatment strategies improves participation in work-related activities, a defined goal for RA treatment. **References:** (1) Smolen et al. ARD 2015

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Abstract Number: 2480

Dose-Related Short Term Clinical Response to Initial Treatment with Methotrexate in Mono- and Combination Therapy in Early Rheumatoid Arthritis Patients – a Meta-Regression Analysis

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Background/Purpose: Recently, there has been a trend to start methotrexate (MTX) in higher doses, either as monotherapy or in combination with other drugs in rheumatoid arthritis (RA) trials –and likely also in daily practice. It is unclear whether higher initial doses are associated with better short term clinical responses, especially in combination therapy with other effective disease modifying anti-rheumatic drugs (DMARDs). We investigated the short term relationship with early clinical response of various doses of MTX in monotherapy and combination therapy in DMARD naive early RA patients.

Methods: A systematic literature search was performed, including early, DMARD naive RA patients, treated with MTX, showing disease activity results within 3 to 6 months follow-up.

Cohen's effect sizes (ratio of mean change in score and baseline SD, with negative scores indicating improvement) were calculated for the health assessment questionnaire (HAQ), erythrocyte sedimentation rate/c-reactive protein (ESR/CRP) and/or DAS/DAS28 in 4 treatment groups: MTX monotherapy, and MTX in combination with synthetic (cs)DMARDs, or with biologic (b)DMARDs or with oral glucocorticoids. Multivariate random-effects meta-regression analyses were performed for each outcome, with treatment group as predictor corrected for standardized baseline disease activity and month of assessment.

Results: Out of 2567 articles and 417 meeting abstracts, 31 studies including 5589 patients were extracted. The meta-regression (table 1) did not show any indication for higher effectiveness of increasing MTX doses in monotherapy. In combination with glucorticoids a higher MTX dose was statistically significantly associated with higher HAQ (β=0.012, 95% CI 0.00070;0.023), but not with DAS/DAS28 or ESR/CRP. In combination with bDMARDs a higher MTX dose was statistically significantly associated with higher HAQ (β=0.042, 95% CI 0.012;0.073) and DAS/DAS28 (β=0.033, 95% CI 0.0070;0.059). These effect sizes were too small to indicate clinical relevant effects on disease activity/functional ability. There were too few treatment groups using MTX in combination with csDMARDs to evaluate in the meta-regression.

Conclusion: In DMARD naive early RA patients, a higher initial dose of MTX either as monotherapy or in combination with a bDMARD or glucocorticoid was not associated with better clinical responses within 3 to 6 months of treatment start. Initial combination therapies with a bDMARD or glucocorticoid show higher effect sizes than initial monotherapy. The results suggest that such initial combination therapies give better short term clinical outcomes, but that the benefits to be expected from higher in stead of lower doses of MTX is negligible.

Table 1: Meta-regression on the effect of methotrexate-dose on HAQ (n=23), DAS/DAS28 (n=25) and ESR/CRP (n=21).

HAQ		**β**	**SE**	**P**	**95% CI**
MTX monotherapy	**MTX dose (mg)**	-0.008	0.014	0.584	-0.035; 0.020
	Month of assessment[a]	-0.0021	0.084	0.980	-0.17; 0.16
	Baseline HAQ	-0.11	0.19	0.570	-0.49; 0.27
	constant	-0.29	0.49	0.556	-1.26; 0.68
Combination therapy with glucocorticoids	**MTX dose (mg)**	0.012	0.0058	0.037	0.00070; 0.023
	Month of assessment[a]	-0.033	0.038	0.380	-0.11; 0.041
	Baseline HAQ	-0.42	0.11	<0.001	-0.63; -0.21
	constant	-0.33	0.23	0.151	-0.79; 0.12
Combination therapy with bDMARDs	**MTX dose (mg)**	0.042	0.016	0.007	0.012; 0.073
	Month of assessment[a]	0.094	0.12	0.430	-0.14; 0.33
	Baseline HAQ	-0.71	0.60	0.240	-1.88; 0.47
	constant	-0.97	0.73	0.186	-2.41; 0.47
DAS/DAS28		**β**	**SE**	**P**	**95% CI**
MTX monotherapy	**MTX dose (mg)**	-0.042	0.031	0.170	-0.10; 0.018
	Month of assessment[a]	-0.064	0.21	0.766	-0.48; 0.35
	Baseline DAS/DAS28	-0.62	0.077	<0.001	-0.78; -0.47
	constant	0.82	1.04	0.426	-1.21; 2.86
Combination therapy with glucocorticoids	**MTX dose (mg)**	-0.0010	0.018	0.954	-0.035; 0.033
	Month of assessment[a]	-0.046	0.11	0.672	-0.26; 0.17
	Baseline DAS/DAS28	-0.91	0.16	<0.001	-1.23; -0.60
	constant	0.10	0.73	0.885	-1.32; 1.53
Combination therapy with bDMARDs	**MTX dose (mg)**	0.033	0.013	0.013	0.0070; 0.059
	Month of assessment[a]	0.10	0.15	0.503	-0.19; 0.39
	Baseline DAS/DAS28	-1.03	0.18	<0.001	-1.38; -0.69
	constant	-0.14	0.64	0.827	-1.39; 1.11
ESR/CRP		**β**	**SE**	**P**	**95% CI**
MTX monotherapy	**MTX dose (mg)**	-0.043	0.048	0.372	-0.14; 0.052
	Month of assessment[a]	-0.20	0.37	0.593	-0.92; 0.53

	Baseline ESR/CRP	-0.81	0.75	0.281	-2.29; 0.66
	constant	1.47	1.29	0.252	-1.04; 4.01
Combination therapy with glucocorticoids	**MTX dose (mg)**	0.00074	0.092	0.994	-0.18; 0.18
	Month of assessment[a]	-0.061	0.65	0.926	-1.34; 1.22
	Baseline ESR/CRP	-0.83	4.33	0.848	-9.32; 7.66
	constant	-0.32	3.92	0.934	-8.01; 7.37
Combination therapy with bDMARDs	**MTX dose (mg)**	0.037	0.24	0.880	-0.44; 0.52
	Month of assessment[a]	-0.25	1.23	0.841	-2.66; 2.17
	Baseline ESR/CRP	0.21	9.37	0.982	-18.15; 18.57
	constant	-0.93	6.37	0.884	-14.18; 12.41
[a]Number of months after treatment start					

Disclosure: S. Bergstra, None; **C. Allaart**, None; **T. Stijnen**, None; **R. Landewé**, Abbott, Amgen, Centocor, Novartis, Pfizer, Rhoche, Schering-Plough, UCB, Wyeth., 2,Robert Landewé is director of Rheumatology Consultancy BV, which is a registered company under Dutch law., 4,Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Celgene, Janssen (formerly Centocor), Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Rhoche, Schering-Plough, TiGenix, UCB, Wyeth., 5,Abbott/AbbVie, Amgen, Bristol Myers Squibb, Janssen (formerly Centocor), Merck, Pfizer, Rhoche, Schering-Plough, UCB, Wyeth., 9.

Abstract Number: 2481

Infliximab Low Levels at Early Stages Predict the Loss of Drug Levels and the Clinical Response at One Year of Treatment in Patients with Rheumatoid Arthritis

Teresa Jurado[1], **Chamaida Plasencia-Rodriguez**[2], Ana Martínez[3], Victoria Navarro-Compán[4], Eva Olariaga-Merida[5], Diana Peiteado[6], Alejandro Villalba[6], Gema Bonilla[6], Cristina Diego[7], Alejandro Balsa[2] and Dora Pascual-Salcedo[8], [1]Immunology, University Hospital La Paz, Madrid, Spain, [2]Instituto de Investigación Hospital Universitario La Paz (IDIPAZ), Madrid, Spain, [3]Immunology Unit, La Paz University Hospital-IdiPaz, MADRID, Spain, [4]Rheumatology, University Hospital La Paz, Madrid, Spain, [5]Immunlogy, University Hospital La Paz, Madrid, Spain, [6]Rheumatology, Hospital La Paz - IdiPaz, Madrid, Spain, [7]Immunology, Hospital La Paz. IdiPaz,

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Background/Purpose: The anti-TNF monoclonal antibody Infliximab (Ifx), has proven effective in treating rheumatoid arthritis (RA), although in 40% of cases may fail, mainly due to immunogenicity. A good clinical response is usually associated with high serum drug levels; however, it is not clear why some patients have a faster drug clearance since the beginning of the therapy. Formation of immunocomplexes between antibodies to Ifx (ATI) and Ifx can increase drug clearance, leading to treatment failure.The aim was to analyze whether serum Infliximab trough levels (ITL) at the induction phase were related to Ifx disappearance and clinical outcomes at week (w) 54. The early development of immunogenicity as a related factor with low ITL was also investigated.

Methods: In this observational retrospective study ITL were measured from 66 RA patients from the prospective biological cohort of La Paz Hospital. Serum samples were taken at w2, w6, w14 and w22. Serum-dependent receiver operating characteristics (ROC) curves were used to establish the ITL value that better predicts the absence of Ifx atw54. ATI were measured by bridging ELISA and by an acid-dissociation method without drug interference IDK (Immundiagnostik®, Germany). Patients were grouped as ITLpos if they had detectable Ifx at w54 and ITLneg otherwise.

Results: ITLneg patients (n=25) had significantly lower levels at all time points than ITLpos (n=41). Based on ROC values ITL at w6 (4.44 μg/ml) had the best predictive value for disappearence of Ifx at w54 with a 70% sensitivity (95%CI 45.7-88.1), 95% specificity (95%CI 83.1-99.4) and positive likehood ratio of 14. Most patients in low disease activity or remission at w54 had at w6 ITL upper the predictive cut-off [20/44(45%) upper cut-off vs 3/20(15%) under cut-off p=0.02] and most EULAR responder at w54 had ITL upper the predictive cut-off at w6 [33/43(77%) vs 10/21(48%);p=0.08]. Treatment survival of patients with ITL upper 6w cut-off was longer: 5 years (1.6-5.0) vs 1.7 years (0.2-0.6); p=0.012.In the multiple logistic regression analysis, after adjusting for confounders (age, sex, body mass index, baseline DAS28, PCR, TNF and IL6) with ITL at w2 and at w6, the absence of Ifx levels at w54 was significantly associated with ITL under the cut-off at w2 (OR: 15.85; 95%IC 2.95-85.03; p=0.01), at w6 (OR: 86.64; 95%IC 6.58-1139.99; p=0.001) and no MTX use (OR: 12.26; 95%IC 1.83-82.22; p=0.001 for w2; OR: 6.9; 95%IC 1.04-45.84; p=0.04 for w6). Most patients with ITL under the cut-off at w6 were positive for ATI along the first year [15/20(75%) under cut-off vs 5/44(11%) upper cut-off, p<0.0001]. Most ATI were detected earlier by the IDK than with bridging.

Conclusion: Low ITL at early stages (w2 and w6) are associated with the Ifx absence, the early drop-out of the treatment and the clinical outcome at w54, being the presence of ATI the main reason for the low early circulating drug levels. We also conclude that the cut-off value at w6 (4.44 μg/ml)

provides the clinicians with a useful prognostic tool of treatment efficacy.

Disclosure: T. Jurado, None; **C. Plasencia-Rodriguez**, None; **A. Martínez**, None; **V. Navarro-Compán**, None; **E. Olariaga-Merida**, None; **D. Peiteado**, None; **A. Villalba**, None; **G. Bonilla**, None; **C. Diego**, None; **A. Balsa**, None; **D. Pascual-Salcedo**, None.

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Abstract Number: 2482

Long Term Drug Survival of Adalimumab and Etanercept Treatment for Rheumatoid Arthritis with and without Methotrexate

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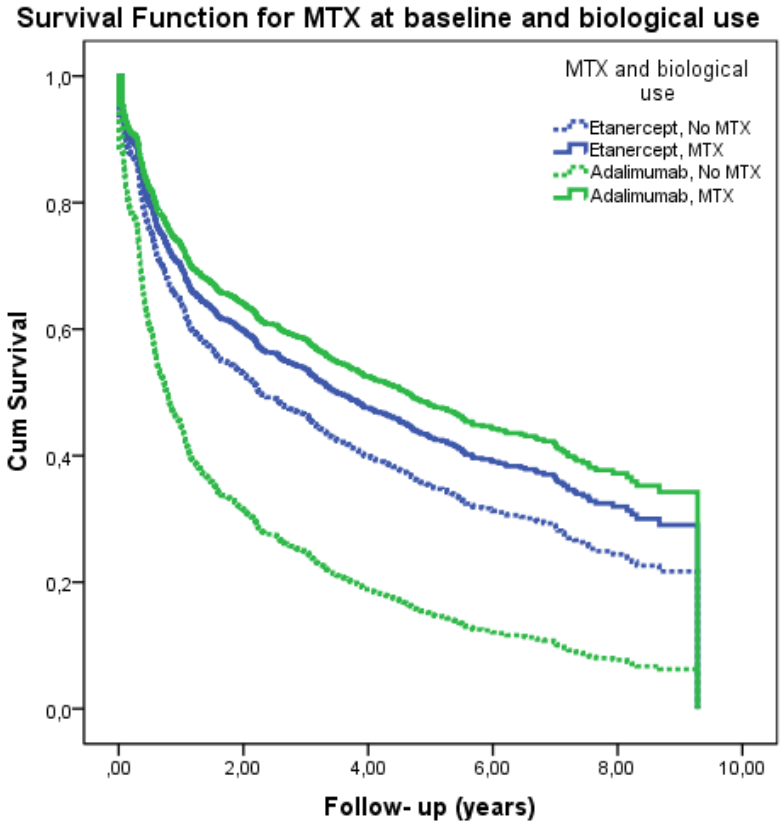
Background/Purpose: Tumor necrosis factor alpha (TNF-α) inhibitors are effective, safe and widely used treatment for rheumatoid arthritis (RA). The therapy is often started in combination with methotrexate (MTX). However, less is known about the effectiveness of the combination with (or without) MTX on long term TNF-α inhibitor use. The aim of this study was to assess the nine year drug survival of patients started on etanercept or adalimumab treatment with or without concomitant MTX.

Methods: A total of 1230 consecutive patients were included in the etanercept (EtRA, n=643, 52%) and adalimumab (AdRA, n=587, 48%) cohort at the Jan van Breemen research centre in Amsterdam,

The Netherlands, from Feb 6th 2004 to March 12th 2014. The choice of biological was determined by the treating rheumatologist. If patients switched between both biologicals, only the first biological was used in this study. All patients fulfilled the American College of Rheumatology classification criteria for RA. Drug survival was assessed with Cox Regression.

Results: For etanercept, 186 (28%) used MTX at baseline and 371 (58%) dropped out. Median survival was 1.6 (0.4-4.0) and maximum survival was 9.2 years. In the adalimumab treated group, 373 (64%) used MTX at baseline and 350 (60%) dropped out. Median survival was 1.3 (0.4-4.4)and maximum survival was 9.3 years. Adalimumab patients without MTX were 2.61 (2.11-3.24) times more likely to drop-out than adalimumab patients with concomitant MTX (Figure 1). For etanercept treated patients this was 1.23 (0.98-1.54) for those with versus without MTX.

Conclusion: Although the drug survival of etanercept patients with and without MTX differed slightly, there was a much greater difference in the drug survival of adalimumab patients with MTX versus without MTX. This is probably due to the inhibition of anti-adalimumab antibody formation by MTX, whereas no clinically relevant antibodies for etanercept have been found. Whether or not the choice for adalimumab or etanercept should be guided by tolerance for MTX remains to be established.



Disclosure: I. M. Visman, None; **M. l'Ami**, None; **G. Wolbink**, None; **M. T. Nurmohamed**, None.

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Abstract Number: 2483

Results of a Pilot Study of a Tailored Symptom Assessment Tool to Enhance Patient-Centered Care in Rheumatoid Arthritis: Choice RA

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Background/Purpose: Discordance in the assessment of rheumatoid arthritis (RA) disease activity has been reported in 30% of patient-clinician dyads, with discordance higher for those with depressed mood. Our objective was to pilot-test a tablet-based, patient-reported symptom tool to improve communication around preference-sensitive symptoms among diverse RA patients.

Methods: We conducted a pilot study to test the acceptability, feasibility and efficacy of CHOICE RA, a tablet-based, preference-sensitive symptom reporting tool. 58 symptoms derived from the literature and patient and rheumatologist focus groups populate the tool across 4 categories: 1) Physical symptoms, 2) Function; 3) Feelings and relationships, 4) Joint pain and swelling. Patients select and prioritize symptoms based on their perceived need for care. Eligibility was: age ≥18, Spanish or English speaking, and diagnosis of RA. Participants from two university-affiliated rheumatology clinics were enrolled into one of two study arms. All patients completed CHOICE RA before their appointment, and later a post-visit survey. In Arm 2, clinicians received a summary of patients' choices but not in Arm 1. The primary outcome was congruence between mean total patient-reported symptoms and those discussed in the visit. Congruence for high priority symptoms stratified by language was investigated. Acceptability and satisfaction were measured in clinicians and patients. We compared means using t-tests and proportion of high priority symptoms discussed using Fischer's exact tests.

Results: 45 patients enrolled (Arm 1: 24, Arm 2: 21), 91% were female; mean age 53±13, 56% Spanish-speaking, 42% had limited health literacy. There were no statistically significant differences in congruence scores by study arm. However, in subgroup analyses, a significantly

greater number of high-priority mood symptoms were discussed in arm 2 (55%) compared to Arm 1 (0%) among Spanish-speakers (p=0.04). Majority (≥ 90%) found the tool acceptable based on ease of use and usefulness. 98% reported the tool facilitated communication with their doctor.

Conclusion: CHOICE RA was highly acceptable to Spanish and English-speaking RA patients and clinicians, and helped patients communicate high priority symptoms to their clinician. While it did not increase congruity in total symptoms listed vs. discussed overall, it increased discussion of mood symptoms highly prevalent in this vulnerable group with communication barriers. Results from this promising pilot study should lead to a larger, multi-site trial to evaluate its impact on a broader population.

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Abstract Number: 2484

Real World Treat to Target Strategy in Rheumatoid Arthritis: Radiograph and MRI Outcomes in Three Cohorts with 18 Month Follow up

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Background/Purpose: The Treat to Target (TTT) model is well established in the treatment of rheumatic disease. Achieving DAS remission is one of the primary goals of clinicians managing RA.

It has become increasingly apparent that the Treat to Target approach is not feasible in all patient subgroups. Rather, patients often enter a low disease activity state but even with modern therapy, cannot achieve TTT remission. The important question is whether low disease activity state is sufficient to prevent joint damage progression. To assess the impact of TTT DAS low disease activity and remission states on MRI and x-ray progression in Rheumatoid Arthritis (RA) in patients treated with Adalimumab and synthetic DMARD's.

Methods: Single blind, observational radiological outcome study; four sites. Inclusion criteria: RF/CCP positive RA with stable therapy over 6 months. Cohort A: Disease Activity Score (DAS) of < 2.6 on conventional DMARD therapy; Cohort B: DAS score of > 3.2 on Adalimumab therapy; Cohort C: DAS score of < 2.6 on Adalimumab therapy. Participants reviewed every 3-months for 18 months. MRI (T1 GRE and T2 STIR) of the dominant MCP 2-5 / wrist and plain radiographs hands/feet undertaken at baseline and at 18 months. MRI and radiographs were be assessed by one blinded central reader using the RAMRIS score and van der Heijde modification of the Sharp score. Statistical analysis: Differences between Cohorts at baseline were assessed using the Wilcoxon Rank Sum Test. Logistic regression was used to examine associations between radiological progression and cohort, baseline MRI features of synovial thickening, erosion and osteitis.

Results: 110 patients completed the study: 54 in cohort A, 33 in cohort B and 23 in Cohort C. Baseline demographics were similar across all three groups. Cohort A mean age 61, B 58, C 59 years. Disease duration A mean 10 years, B 11 years, C 14 years. The cohorts demonstrated statistically significant differences at baseline for measures of pain, global status, RAPID 3 scores, and Patient Global Assessment (PGA) with no statistically significant differences between XRay and MRI scores at baseline. DAS28 CRP changed in all cohorts, increasing in Cohort A but decreasing in Cohorts B and C. There was no statistically significant difference in Xray progression or MRI measures of progression between the cohorts.

Conclusion: Despite differences in remission status at baseline and taking into account changes in DAS CRP over time, there were no statistically significant differences in radiograph or MRI progression between the three cohorts. This study underscores the need to continue to re-evaluate the Treat to Target approach. Smolen JS,Breedveld FC, Burmester GR,et al. Ann Rheum Dis 2015 annrheumdis-2015-207524

Disclosure: P. Bird, None; **M. Rischmueller**, None; **M. Feletar**, None; **G. Grant**, None; **M. P. Staples**, None; **S. Hall**, None.

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Abstract Number: 2485

Correlates of Successful Flare Management: The Role of Clinician-Driven Treatment, Home-Based Strategies, and

Medication Change

Taysir G. Mahmoud[1], M Frits[2], Christine Iannaccone[3], Vivian P. Bykerk[4], Clifton Bingham III[5], Michael Weinblatt[3] and N A Shadick[2], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [4]Divison of Rheumatology, Hospital for Special Surgery, New York, NY, [5]Division of Rheumatology, Johns Hopkins University School of Medicine, Baltimore, MD

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Background/Purpose: Flares are a common experience in RA, often associated with worse clinical outcomes such as cardiovascular disease, lower functional status, and radiographic progression. Many flares develop between rheumatology visits, thus little is known about management strategies. This study aims to examine which strategies contribute to a successful post flare outcome.

Methods: Data from 317 patients enrolled in a prospective RA registry were collected, including clinical and patient reported outcomes. Patients completed a flare survey asking about frequency, outcomes, and management; including a Likert scale assessing if post flare symptoms were better, unchanged, or worse (Figure 1). Ordinal logistic regression analysis adjusting for age, sex, number of flares in past 6 months, severity of most recent flare (0-10), home management, clinical treatment, and medication change was performed with symptoms post flare as the outcome.

Results: 114 patients had a flare that had ended (87.7% female, mean age 59 (±14.2) years, median disease duration 14 (IQR 9, 24) years). Median flare severity was 7 (5, 8). Compared with RA symptoms before the flare, 16 (14%) patients reported worsened RA symptoms post flare, 71(63%) were unchanged, and 26 (23%) were improved. To manage flares, 90 (79%) patients used home management (e.g. ice/heat (53%) and rest (61%)), and 58 (51%) reported making a medication change (50% NSAIDs, 32% corticosteroids, 26% DMARDs). Only 30 (26%) patients sought clinical advice (e.g. rheumatologist (87%) and PCP (7%)). Of note, 59% of patients who made a medication change did so without seeking clinical advice. The logistic model (Figure 2) revealed that patients who made a medication change, of any kind, to treat their flare were more likely to have improved RA symptoms post flare than patients who made no medication change (OR=3.715, p=0.004). No other covariates were significant, including flare frequency and severity. In a sub analysis, individual medication category did not influence post flare outcome.

Conclusion: Independent of home based or clinically guided care, making a medication change is strongly associated with improved post flare outcomes. This improvement was not attributable to any one category of medication and the decision to make a medication change was frequently made without seeking clinical advice. This has implications for understanding how best to intervene when patients flare. Future directions could examine if specific medication changes in combination with home or clinical management strategies facilitate better post flare outcomes. **Figure 1: RA Symptoms Post Flare**

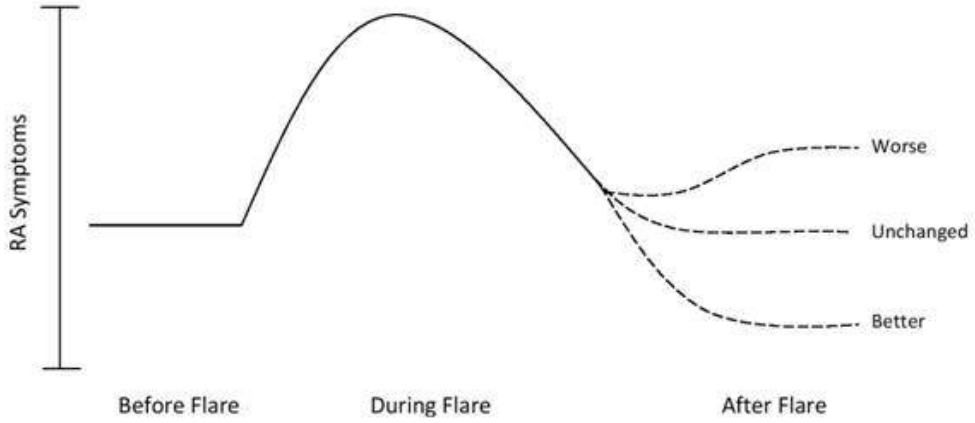
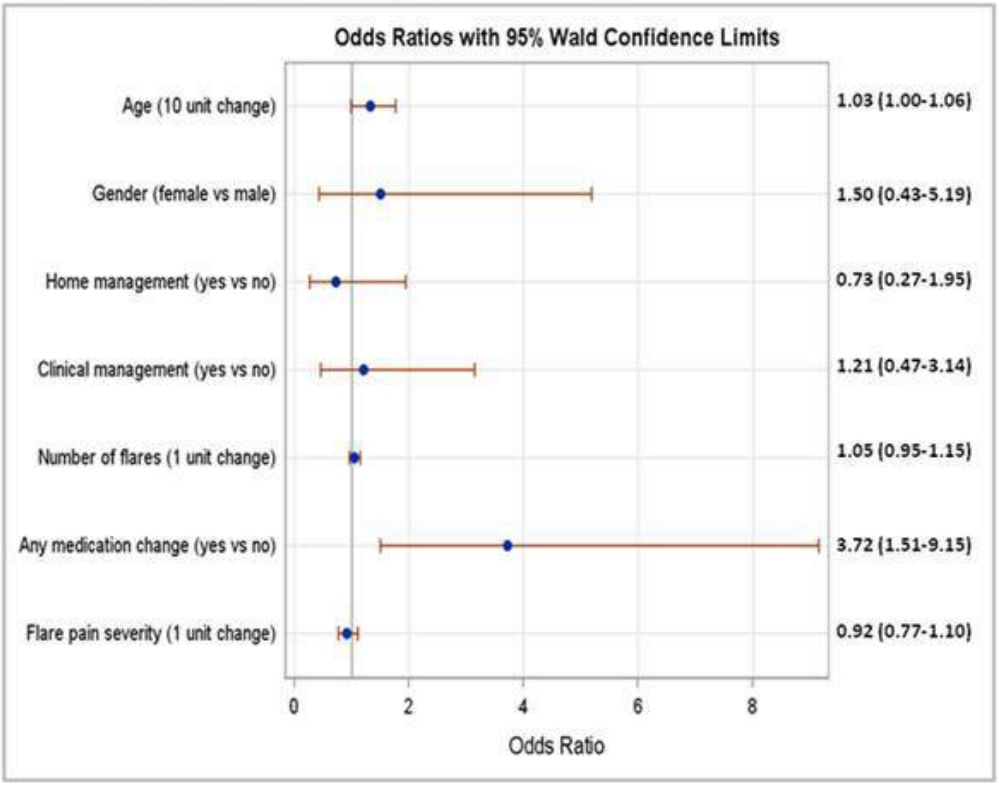


Figure 2: Odds Ratio Estimating Better Post Flare Outcomes



Disclosure: T. G. Mahmoud, None; **M. Frits**, None; **C. Iannaccone**, None; **V. P. Bykerk**, None; **C.**

Bingham III, None; **M. Weinblatt**, Amgen, 2,Bristol-Myers Squibb, 2,Crescendo Bioscience, 2,UCB, 2,Amgen, 5,Bristol-Myers Squibb, 5,Cresendo Bioscience, 5,UCB, 5; **N. A. Shadick**, UCB, Amgen, Crescendo Biosciences, BMS, Mallinckrodt, 2,Bristol-Myers Squibb, 5.

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Abstract Number: 2486

Effect of a Dynamic Exercise Program in Combination with a Mediterranean Diet in Strength, Joint Mobility and Disease Activity in Women with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by inflammation, joint pain, destruction of the synovial membranes and metabolic alterations due mainly by the liberation of tumor necrosis factor alpha and interleukin-1 beta, leading to rheumatoid cachexia. Dynamic exercise has demonstrated to improve muscular function and strength, as well as joint mobility without negative effects on RA. Also, a diet focused on the consumption of certain

fatty acids like the Mediterranean is recommended to reduce inflammation. Thus, the aim of this study was to assess the effect of a dynamic exercise program in combination with a Mediterranean diet (MD) in strength, joint mobility and disease activity in women with RA.

Methods: We undertook a randomized controlled trial including 95 women with diagnosis of RA (2010 ACR/EULAR classification criteria). Handgrip strength, goniometry and DAS28 score were evaluated at baseline and 6 months follow-up. Patients were classified into four groups: G1 (n=28) with dynamic exercise and MD; G2 (n=21) with dynamic exercise only; G3 (n=26) with MD only, and G4 (n=20) controls. G2 and G4 were given general dietary recommendations as well as G3 and G4 were given general physical recommendations. All patients received standard medical treatment for RA prescribed by a rheumatologist. Percentage change was calculated to assess the magnitude of effect and ANOVA test was used for comparison between groups. The results were adjusted according to functional class following the ACR guidelines.

Results: Ninety-five women were included, with a median age of 49.5 (40-60) years, median disease duration of 14 (6-20) years, and a median DAS28 score of 2.5 (1.6-3.2). Significant differences between groups were found in DAS28 score (G1= -13.1, G2= 6.1, G3= 6.4, G4= 20.8 % of change, p=0.02); handgrip strength (G1= 4.1, G2= 18.5, G3= -7.1, G4= 7.1% of change, p=0.005); joint mobility in ankle plantar flexion in the right side (RS) (G1= 17.6, G2= 10.7, G3= 10.7, G4= -30.4 % of change, p<0.001) and left side (LS) (G1= 30.5, G2= 23, G3= 5, G4= -11, p=0.002); in knee flexion in the RS (G1= 14.3, G2= 12, G3= 16.6, G4= 5.1, p=0.01) and LS (G1= 6.9, G2= 8.6, G3= 18.6, G4= 4.6, p=0.05) and hip internal rotation in the RS (G1= 3.3, G2= -16.4, G3= -15.5, G4= -3.4, p=0.09) and LS (G1= 16.6, G2= 7.5, G3= -0.3, G4= -10.4, p=0.05).

Conclusion: Dynamic exercise in combination with MD improves physical capacity, muscular strength and joint mobility as well as disease activity when compared with either therapy individually or controls.

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Abstract Number: 2487

In Patients with Rheumatoid Arthritis in Clinical Remission Undergoing Treatment Tapering Tenosynovitis and Synovitis Detected By Ultrasonography Predict Disease Flare

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Background/Purpose:

Ultrasound (US) detected synovitis predicts flare in patients with rheumatoid arthritis (RA), while the role of tenosynovitis has yet to be established. The aim of this study was to investigate the predictive role of US tenosynovitis and synovitis over disease flare in patients with RA in clinical remission in which treatment is tapered.

Methods:

STARTER is a multicentre cohort study of the US Study Group of the Italian Society for Rheumatology, involving rheumatologists selected by a reliability exercise and the availability of high-end equipment and high frequencies probes. At the beginning of the study, patients with RA in clinical remission were clinically evaluated. US synovitis (S) and tenosynovitis (T) were assessed categorically for Grey Scale (GS) and power Doppler (PD) at 11 joints, extensor and flexor tendons in both hands. Patients were seen at 6 and 12 months. Treatment tapering was defined as dose reduction or discontinuation of any DMARD or corticosteroids. Flare within 12 months was defined as increase in DAS28 $\geq$1.2 or $\geq$0.6 if final DAS28>3.2. The relationship between the presence of GS-T/-S, PD-T/-S and flare was tested by logistic regression models, presented as odds ratios (OR) and 95% confidence interval (CI), adjusted for pre-specified confounders (age, sex, disease duration, comorbidities, rheumatoid factor, synthetic or biologic DMARDs, corticosteroids or NSAIDs). The models were applied to the whole population and separately in subgroups of patients in which treatment was or was not reduced.

Results:

361 patients were included, in 161 treatment was tapered [72. % F, mean age (sd) 56.1 (13.3) years, mean disease duration (sd) 9.75 (8.07) years]. 98/361 patients had a flare within 12 months, 48/154

among those tapering treatment. Considering US variables separately, only PD-S significantly predicted flare both in the whole population and in patients tapering treatment, but not in patients on stable treatment. When the model included both T and S, only the concurrent presence of T and S predicted flare [PD-T+-S: OR 2.06(1.04, 4.07)] in the overall population, while isolated S and T did not. The predictive value of PD-T+-S was not confirmed in patients in stable treatment, while it was enhanced in patients tapering treatment [OR 3.16(1.18,8.45)]. In the whole population GS-T+GS-S led to an increased risk of flare [OR 2.27, (1.01,5.10)], but this was not confirmed in the subgroups (Table 1).

Conclusion:

In patients with RA in clinical remission PD-T and PD-S predict subsequent disease flare, especially if treatment is tapered down. In addition to clinical evaluation, US could provide helpful information to drive treatment strategies in patients in clinical remission.

US abnormality	Overall population		Stable treatment		Tapering treatment	
	Crude OR (95% CI)	Adj OR (95%CI)	Crude OR (95% CI)	Adj OR (95%CI)	Crude OR (95% CI)	Adj OR (95%CI)
GS-T	1.59 (0.53,4.72)	1.53 (0.47,4.92)	1.87 (0.47,7.36)	1.73 (0.34,7.77)	1.22 (0.18,7.89)	1.40 (0.18,10.50)
GS-S	2.18 (0.97,4.92)	1.93 (0.81,4.57)	2.0 (0.65,6.10)	1.77 (0.50,6.19)	2.37 (0.70,8.02)	2.22 (0.61,8.02)
GS-T+-S	***2.88 (1.34,6.14)***	***2.27 (1.01,5.10)***	2.29 (0.84,6.22)	1.64 (0.53,5.01)	***3.76 (1.16,12.20)***	3.42 (0.98,11.92)
PD-T	0.59 (0.16,2.15)	0.47 (0.12,1.79)	0.34 (0.04,2.86)	0.34 (0.03,3.04)	1.31 (0.23,7.41)	0.82 (0.12,5.42)
PD-S	1.64 (0.93,2.90)	1.56 (0.85,2.85)	1.78 (0.80,3.95)	1.48 (0.61,3.58)	1.54 (0.68,3.50)	1.56 (0.64,3.76)
PD-T+-S	***2.75 (1.45,5.20)***	***2.06 (1.04,4.07)***	2.31 (0.95,5.64)	1.58 (0.58,4.32)	***3.54 (1.40,8.98)***	***3.16 (1.18,8.45)***

Table 1. Logistic regression models analyzing the predictive role of US findings over disease flare. OR: Odds Ratio, 95% CI: 95% confidence interval; GS: grey scale; PD: power Doppler; T: tenosynovitis; S: synovitis

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A Randomised Controlled Trial Evaluating the Effect of Adalimumab upon Biomarkers of Cardiovascular Risk in ACPA-Positive Rheumatoid Arthritis

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Background/Purpose: Rheumatoid Arthritis (RA) is associated with increased cardiovascular (CV) risk. The mechanisms of CV disease in RA remain poorly understood. Observational data suggest that earlier treatment of RA produces better responses. This RCT (ACTRN12611000972921) evaluated whether adalimumab (ADA) improves CV risk biomarkers in patients ACPA-positive RA and to explore the contribution of known risk factors.

Methods: 60 (30 early, 30 established) patients with moderate-highly active ACPA-positive RA were enrolled in a RCT of humira versus placebo (1:1). Patients underwent assessments of Reactive Hyperaemic Index (RHI), carotid-femoral pulse wave velocity (PWV) and disease activity twice before receiving treatment and then at weeks 1,4,12 and 24. Intention-to-treat analysis compared changes in each treatment arm by t test. Secondary analysis by random effects GLS regression modelling evaluated effects upon RHI and PWV adjusting for clustering within individuals.

Results: There were no significant differences between in treatment arms for RHI. While preliminary analysis suggested that positive shared epitope (SE) status was associated with poorer endothelial function (p 0.02) rather than for inflammation (CRP p0.379) or treatment (p 0.487) this was not significant after adjustment for clustering. A large 0.65m/sec reduction in PWV was seen prior to treatment in both groups. At weeks 4 and 12 PWV was significantly lower in the ADA arm.

This trend was seen more consistently in patients with recent onset (<12 months) disease. Secondary analysis found that the most significant effects upon PWV were age (p 0.000), mean arterial pressure (p0.000) and CRP (p0.004).

Conclusion: Treatment with ADA may improve aortic stiffness and treatment may be more effective in early disease. However the greater effects are from blood pressure and ageing. While PWV is clearly influenced by CRP RHI may be influenced more by SE status. Further work is needed evaluating ACPA-negative and SE-negative subjective and pre-clinical RA.

Table:
Pulse Wave Velocity and Changes in Pulse Wave Velocity (dPWV) overall and in the Early RA Subgroup in Placebo vs Adalimumab Treatment Arms

		N	B1	B2	W1	W4	W12	W24
PWV	PLAC	27	13.2	12.5	12.5	12.5	12.6	12.5
	ADA	26	12.5	11.9	11.8	11.5	11.7	12.2
	p		0.20	0.29	0.18	0.02	0.04	0.64
PWV	PLAC	15	13.1	12.7	12.7	12.7	12.7	12.1
Early	ADA	14	12.7	12.3	12.0	11.3	11.8	12.2
	p		0.64	0.59	0.34	0.02	0.13	NS
dPWV	PLAC	27	0.71	Ref	0.24	0.07	0.27	0.25
	ADA	26	0.53	Ref	0.01	-0.33	0.35	0.23
	p		0.56		0.49	0.23	0.51	0.98
dPWV	PLAC	15	0.36	Ref	0.45	0.03	-0.07	0.21
Early	ADA	14	0.48	Ref	-0.05	-0.77	-0.33	0.32
	p		0.78		0.30	0.07	0.68	0.89

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Joint Damage Appears As Severe As Inflammation According to Physician Visual Analog Scales in Patients with Rheumatoid Arthritis Regardless of Disease Severity at 2 Sites, Which May Limit Results of a Treat-to-Target Strategy

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Background/Purpose: A physician estimate of global status (DOCGL) on a 0-10 visual analog scale (VAS) was developed initially to assess inflammation in patients with rheumatoid arthritis (RA), particularly to assess change in clinical trials, in which DOCGL has greater relative efficiency than the other 6 RA Core Data set measures to distinguish active from control treatments. Some rheumatologists interpret DOCGL as based entirely on inflammation, while others also may consider joint damage and/or psychological distress as in fibromyalgia, in addition to inflammation, in formulating a 0-10 DOCGL VAS estimate. One approach to clarifying this matter is for physicians to estimate 3 additional 0-10 VAS for inflammation, damage, and distress. We analyzed scores at 2 academic rheumatology sites for 4 VAS estimated by rheumatologists, for overall DOCGL, inflammation, damage, and distress, compared to high, moderate, low, and near-remission according to RAPID3 on an MDHAQ in patients in RA seen in routine care.

Methods: All patients seen at 2 academic sites complete an MDHAQ/RAPID3 at each visit. Rheumatologists complete 4 0-10 VAS for DOCGL, inflammation or reversible disease, damage or irreversible disease, and distress explained by neither inflammation nor damage. Mean estimates for overall status, inflammation, damage, and distress or fibromyalgia, were analyzed in patients according to RAPID3 categories for high (=≥12), moderate (=6.1-12), low (=3.1-6), and near-remission (=≤3), with statistical significance computed by analysis of variance (ANOVA). Differences between damage and inflammation estimates also were calculated.

Results: Site A included 71 RA patients, mean age 59 years, formal education 11 years, and 76% female; site B included 137 RA patients, mean age 57 years, formal education 14 years, 88% female. The mean DOCGL at both sites A and B was 3.8. DOCGL was 1.5 and 1.6 for patients in remission, at Sites A and B respectively, 1.4 and 3.7 for those in low severity, 3.4 and 3.1 for patients in moderate severity, and 5.3 and 5.4 in patients with high severity (all $p \leq 0.01$) (Table). Scores for damage were higher than scores for inflammation at both sites, 3.5 versus 2.3 at site A, and 2.7 versus 2.2 at site B for all patients, as well as in all 4 RAPID3 severity groups at both sites (Table); damage scores were 0.2-1.2/10 units higher than inflammation scores (Table). Scores for distress were somewhat higher for all patients than for inflammation but lesser than for damage at site A and lower than both inflammation and damage at site B for all patients.

Conclusion: Joint damage appears to be a more significant clinical problem than inflammation in RA patients at 2 sites. These findings may explain in part why most RA patients are not in remission despite a “treat to target” of remission with powerful biologic agents. Joint damage may be a more severe problem than inflammation in the management of RA at this time.

MEASURE;	**TOTAL**	**REMISSION**	**LOW**	**MODERATE**	**HIGH**	**P**
SITE A (n=71)						
DOCGL	**3.8**	**1.5**	**1.4**	**3.4**	**5.3**	**<0.001**
Inflammation	**2.3**	**0.5**	**0.7**	**2.4**	**3.2**	**<0.001**
Damage	**3.5**	**1.6**	**1.6**	**3.5**	**4.4**	**0.003**
Distress	**2.6**	**1.2**	**1.0**	**2.2**	**3.6**	**0.006**
SITE B (n=137)						
DOCGL	**3.8**	**1.6**	**3.7**	**3.1**	**5.4**	**<0.001**
Inflammation	**2.2**	**0.9**	**2.5**	**1.3**	**3.2**	**<0.001**
Damage	**2.7**	**1.5**	**3.0**	**2.4**	**3.4**	**0.07**
Distress	**1.1**	**0.4**	**0.1**	**0.6**	**2.1**	**0.004**
Inflammation-Damage						
Site A	**1.2**	**1.1**	**0.9**	**1.1**	**1.2**	
Site B	**0.5**	**0.6**	**0.5**	**1.1**	**0.2**	

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Impact of Obesity Activity Indices and Therapeutic Dosage in Patients with Rheumatoid Arthritis in Dominican Republic

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Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic arthritis that mainly affects small and medium joints. It is the most common form of inflammatory arthritis, capable of producing significant joint damage, deformity and functional disability. An association between increased body mass index (BMI) and some inflammatory and autoimmune conditions have been suggested in observational studies. Adipose tissue is considered as an active participant in physiological and pathological processes associated with inflammation and immunity. Evidence suggests that the effect of obesity on joint structure goes beyond overload, which is based on multiple complex factors such as cytokines, hormones, growth factors and intracellular regulators that can modify the course of disease and clinical response; so we set as main objective to assess activity indices in patients with rheumatoid arthritis and its relationship with BMI.

Methods: Descriptive cross-sectional study, in which 3,858 patient records were analyzed in the period from January 2012 to January 2016; 1,235 met RA criteria by the American College of Rheumatology (ACR) 2010, 131 patients met criteria for inclusion, it was assessed patient's age, sex, BMI, index of disease activity in 28 joints (DAS28), erythrocyte sedimentation rate, disease-modifying drugs (DMARDs) and glucocorticoids, data was obtained in the second visit. SPSS V.22 was employed for Windows 8, developing a database with the aforementioned variables, descriptive statistical analysis was performed with frequencies and percentages, crossed tables were made to establish association between different variables and finally to analyze age, mean and standard deviation (SD) were used.

Results: Females accounted for 96.2%, the average age was 56.48 ± 12 years, 33.5% of patients were overweight, 11.5% obesity class I, class II obesity for a 5.3%, 0.8% class III obesity; 51.1% had a BMI above normal levels; 48.9% were in normal range, 6% achieved remission in normal weight and 1.5% in the scale of overweight; in terms of low activity in normal weight was 6.6% versus 6% with high BMI; 29% was found in moderate activity in normal weight and 22.9% in the high BMI, 10% in normal weight had high activity, compared with 18% of increased BMI patients, the DMARD most used was methotrexate, the most common glucocorticoid used was prednisone.

Conclusion: In our population, we found that higher BMI limits the possibility of achieving low activity or remission and increased BMI was associated with higher doses of DMARDs and glucocorticoids. Prospective studies with more patients, longer follow-up are necessary and remind patients the importance of maintaining an adequate body mass index for better control of their disease.

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Abstract Number: 2491

Is It Possible to Predict Which Patients Treated with Biologic Agents for Rheumatic Diseases Will Develop Anti-Drug Antibodies ?

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Background/Purpose: All biologic agents (bDMARDs) currently used in rheumatology can induce anti-drug antibodies (ADAB), which will influence the drug levels and the drug effectiveness. Why only certain patients develop these antibodies is not yet clear, although there is already some literature dealing with anti-drug antibodies and trough drug level in rheumatic diseases.The aim of this study was to look for predictive factors of occurrence of such antibodies.

Methods: Since March 2013, we measure ADABs and trough levels for all anti TNF agent and also for rituximab and tocilizumab. Half of all our patients under biologic treatments have been tested. The method used is a sandwich ELIS A. ADABs, trough and TNF levels can be measured simultaneously. The reproducibility and the cut-offs have been tested among patients exposed and non-exposed to the medication. Clinical predictors of ADABs development were analyzed using multi and monovaraite regression analysis :.They comprised : gender, age, duration of the disease type of disease, duration of treatment, type of treatment, co-medication, previous biologic agent. Biologic predictors were: though level, TNF level, CRP and ESR

Results: 297 patients had at least one measurement of ADAB and drug through level up to January 2016. 124 patients tested were treated with a biologic agent for rheumatoid arthritis, 116 for spondylarthritis, 30 for psoriatic arthritis, 27 for other diagnoses. In 63 out of 297 (21%) ADABs against at least one of the bDMARD agents were detected. All the patients with ADABs were exposed to the medication, except for 3 patients (specificity: 98%). In patients exposed to bDMARDs, ADABs were found respectively for infliximab in 46/106 (44%) pts, adalimumab:

10/60 (16%) pts, certolizumab: 2/4 (50%) pts, etanercept: 1/20 (5%) pts, golimumab: 4/34 (12%) pts, tocilizumab: 1/75(1%) pts, rituximab: 4/46 (8%) pts. When ADABS against several bDMARDs were tested the % of patients developing ADABs against the second bDMARD: 33% tended to be higher than against a for the previous one : 21%, but not significantly p= 0.08).

	Monovariate analysis		**p**	**multivariate**	**p**
	ADBA+	**ADAB-**		**ADBA+ OR (CI)***	
Clinical predictors					
Age: mean (SD): years	50(13)	53(014)	0.11		
Sex (F/M/ n (%)	35/30(54%)	157/74 (69%))	0.035		
Type of disease (AS/apso/RA/ others)"	26/9/18/3	87/21/105/27	0.09+		
Duration of disease : mean (SD):years	8.(6)	11(10)	0.018		
Duration of treatments: mean (SD)/months)	41(33)	28(37)	0.015		
Type of treatments (mab ;antiTNF/others) n (%)	60/5 (94/6%))	137/60 (69/31%)	<0-0001	26(2.6-264)	0.005
Co-medication(Y/N/ n (%)	22/40 (35%)	78/122(38%)	0.6		
Previous biologic agent(Y/N/ (%))	51/13 (79%)	149/81 (65%)	0.027	5.9(1.14-30)	0.03
Biological predictors					
CRP: >5, (Y/N/ n (%)	26/44(37%)	31/152(16%)	0.0005		
ESR : >20 (Y/N/ n (%),	33/54(37%)	25/162(13%)	0.0001		
Trough level undetectable(Y/N (%))	41/15 (81%)	36/162/ (18%)	<0.00001	34(7.21-160.8)	0.0001
TNF level elevated (Y/N/ (%)	30/28(52%)	51/149 (26%)	0.00006	4.2(1.1-15)	0.025

On univariate analysis, several clinical and biological factors were significantly predictive of ADABS. After multivariate analysis only two clinical factors and two laboratory parameters remained independently associated: MAB anti-TNF treatments (OR: 26), previous bDMARD (OR: 5.9), undetectable through level (OR: 34) and High TNF trough level (OR:4.2).

Conclusion: In this large real world cohort of patients with rheumatological conditions requiring bDMARD therapy, either by anti TNF or other biological agents and tested for ADAbs at different time point of their treatments, the best predictors of the presence of ABABs were:treatment by an MAB anti TNF agent, previous exposure to another biologic agent, undetectable through level of the medication and elevated TNF levels

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Abstract Number: 2492

Mode of Administration in Rheumatoid Arthritis Treatments: An Exploration of Patient Preference for an 'Ideal Treatment'

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Background/Purpose: The high prevalence and significant burden of RA has led to the development of a wide variety of treatments; specifically, conventional synthetic DMARDs, and biologic DMARDs (bDMARDs). Mode of administration and dosing frequency can impact on patient treatment satisfaction and adherence. This study qualitatively explored patients' and clinicians' views of the 'ideal' treatment, and the preferred mode of administration, in patients with moderate to severe disease activity and on active treatment.

Methods: Semi-structured interviews were conducted with 46 patients with RA from Germany (n=15), France (n=15), UK (n=10), and Spain (n=5). Eligible patients had been diagnosed for 2-5 years and had a current disease activity score in 28 joints (DAS28) >3.2. Initial questions were open-ended followed by more probing questions. Patients reflected on their treatment experiences, in relation to mode of administration (oral and subcutaneous injection), dosing frequency, and advantages/disadvantages of each mode of administration. Patients completed an 'ideal treatment task' and answered the following question: "*How would the treatment be administered?"* Qualitative interviews were conducted with 10 rheumatologists from Germany (n=2), France (n=2), UK (n=4), and Spain (n=2), to explore their perspectives on modes of treatment administration.

Results: Patients had a DAS28 mean score of 4.23 (SD=1.0) and either, were eligible for but had not yet received bDMARDs (23/46; 50.0%), were receiving bDMARDs (12/46; 26.1%), had received >1 anti-TNF treatment previously and were now receiving a treatment with a different mode of action (3/46; 6.5%), or were receiving another treatment regimen (8/46; 17.4%). Of the 41 patients who took part in the 'ideal treatment task', 22/41 (53.7%) would prefer an oral treatment, 14/41 (34.1%) an injectable treatment, and 5/41 (12.2%) had no preference. Patients reported an oral treatment to be: easy to manage (2/41), convenient (especially when travelling) (1/41), and preferable to an injection (9/41); however, patients acknowledged that an oral treatment can be difficult to remember to take (4/41), can be harsh on the stomach (1/41), and can have a strange taste (1/41). Patients reported the advantages of an injectable treatment to be: independence associated with self-injecting (3/41), and less harsh on the stomach than an oral treatment (1/41); however, their disadvantages included: a dislike of needles (5/41), problems at injection site (1/41), and difficulty in gripping an injection device (1/41). The majority of clinicians (6/10; 60.0%) perceived patients to prefer an oral treatment, compared with 2/10 (20%) who perceived patients to prefer an injectable treatment (2/10 [20%] did not report a perceived preference). Of the 10 patients who discussed frequency of oral treatment, 8/10 (80%) would find a daily tablet acceptable.

Conclusion: Patients and physicians in this survey identified a range of perceived advantages and disadvantages associated with different modes of drug administration. These findings help inform the dialogue between patient and physician when considering the most appropriate treatment choice for an individual.

Disclosure: P. C. Taylor, GSK, UCB, JANSSEN, 2,JANSSEN, UCB, PFIZER, ABBVIE, LILLY, BMS, ROCHE, GSK, NOVARTIS, SANDOZ, BIOGEN, BAXALTA, SANOFI., 5; **R. Alten**, None; **J. J. Gomez-Reino**, None; **R. Caporali**, Lilly, Abbvie, MSD, Pfizer, UCB, Celgene, Mundiharma, 5; **P. Bertin**, None; **L. Grant**, Adelphi Values, 3; **E. Brohan**, Adelphi Values, 3; **J. Wells**, Adelphi Values, 3; **R. Vasilescu**, Pfizer Inc, 1,Pfizer Inc, 3; **M. Tarallo**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2493

Patient Characteristics and Medication Utilization Patterns of Infliximab-Treated Rheumatoid Arthritis Patients Subsequently Transitioned to Intravenous Golimumab

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Session Time: 9:00AM-11:00AM

Background/Purpose: Infliximab (IFX) and golimumab (GLM-IV) for intravenous use are anti-TNF agents indicated for rheumatoid arthritis (RA) and differ in weight-based dose, induction schedule, and infusion time. Few real-world GLM-IV utilization studies exist, and none compare GLM-IV to IFX utilization in the same patient (pt) population. To describe pt characteristics and utilization patterns in IFX-treated RA pts later treated with GLM-IV.

Methods: A large US health claims database was used for a retrospective analysis. Pts had ≥ 1 RA diagnosis (ICD-9 CM;714.0), ≥ 6 months continuous enrollment before IFX initiation and ≥ 1 GLM-IV claim after IFX discontinuation. Pts < age 18 years or with pregnancy were excluded. The IFX index date was defined as the 1st IFX infusion of the most recent IFX episode before GLM-IV initiation. GLM index was the date of first GLM-IV claim between 1/1/2014 and 6/30/2015. Patient characteristics, Claims-based Index for Rheumatoid Arthritis Severity (CIRAS), average vials per infusion (VPI), infusion interval and billed infusion time were studied over a variable length follow up. IFX or GLM VPI were estimated by dividing paid cost by drug wholesale acquisition cost. Infusion time was estimated by the proportion of claims with 2nd hour infusion codes (CPT- 96415 or 96366). Where appropriate, claims associated with $0 cost were removed from the analysis.

Results: A total of 188 IFX patients who transitioned to GLM-IV were identified**.** At the IFX index date**,** the population was 78% female; mean age was 56 years; 79% were commercially insured. The average time between end of IFX and GLM-IV index was 419 days (d); 86% of pts received GLM-IV as their next anti-TNF after IFX. Mean CIRAS was 5.4 at IFX and GLM-IV index dates. Concomitant methotrexate was used in 30% of IFX and 25% of GLM-IV pts. The mean (SD) duration of IFX was 512 (554) d. During IFX treatment, 2,176 IFX infusions were administered. Mean (median) number of infusions per pt were 12 (8) and median VPI was 5. The majority of IFX infusions (97%) had at least one 2nd hour infusion code. The average time between maintenance infusions was 51 d; 40% were 7 to 9 weeks apart. The mean (SD) observation period for GLM-IV treatment was 151 (142) d; the majority (66%) appeared to remain on therapy (censored) at end of data availability. During the observation period, 734 GLM-IV infusions were administered. Pts received a mean of 4 GLM-IV infusions during observation; 36% of pts received 5 or more infusions. Few (2%) GLM-IV infusions had a 2nd hour infusion code. Median GLM-IV VPI was 4. The average time between GLM-IV maintenance infusions was 57 days; 82% were 7 to 9 weeks apart.

Conclusion: This retrospective analysis describes pt characteristics and medication utilization for

IFX-treated RA pts who later used GLM-IV. On average, GLM-IV was associated with lower VPI, greater consistency in dosing patterns (proportion of maintenance infusion intervals every 7 to 9 weeks) and better administration time efficiency as evidenced by a lower proportion of claims for a second hour infusion billing code. These findings may be relevant for healthcare decision-makers interested in understanding potential variation in healthcare delivery.

Disclosure: L. A. Ellis, Janssen Scientific Affairs, LLC, 3; **R. J. DeHoratius**, Janssen Scientific Affairs, LLC, 3; **S. Kafka**, Janssen Scientific Affairs, LLC, 3; **H. Varker**, Janssen Scientific Affairs, LLC, 5; **M. Brouillette**, Janssen Scientific Affairs, LLC, 5; **E. Malangone-Monaco**, Janssen Scientific Affairs, LLC, 5.

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Abstract Number: 2494

The Effect of Body Mass on DAS28 Response in Patients with Rheumatoid Arthritis Treated with Abatacept

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Background/Purpose: Abatacept is an effective biologic agent indicated for the treatment of RA.[1] Recent studies have indicated that obesity and being overweight could reduce the effect of conventional DMARDs and of anti-TNF treatment in patients with RA. However, there are limited data on the effect of weight on the treatment response for abatacept.[2,3] The aim of this study was to evaluate whether BMI is a modifier for the effect of abatacept measured by DAS28 (CRP) over the first 6 months of treatment in patients with RA.

Methods: Patients with RA from Radboud UMC and the Maartenskliniek were consecutively included if they were treated for ≥5 months with abatacept. Length and weight to calculate BMI had been assessed before treatment start. DAS28 (CRP) was prospectively assessed at baseline and 6 months. Concomitant treatment and treatment history were assessed at treatment start, and closest values for RF and anti-cyclic citrullinated peptide (anti-CCP) positivity obtained before baseline were used. BMI was classified as normal (BMI ≤25 kg/m^2) or overweight (BMI >25 kg/m^2). The relationship between BMI and response according to DAS28 (CRP) was analyzed using multivariate linear regression to control for confounding baseline covariates.

Results: A total of 113 patients were included in this analysis: 81% were female, mean (SD) age was 59 (13) years and median (P25–P75) disease duration was 13 (9–20) years. All patients had previously used other biologics, including anti-TNF. Conventional DMARDs were used as concomitant therapy in 58% of patients, most often MTX (32%); 69% of patients used IV abatacept. There were some baseline differences (p<0.10) between normal weight (39%) and overweight (61%) patients. Overweight patients were on average older (mean [SD] 60 [13] vs 56 [14] years), the proportion of males was higher (26 vs 7%), RF (75 vs 57%) and anti-CCP (77 vs 61%) positivity occurred more often, and SC abatacept was more frequently used (38 vs 21%), while they used more (median [P25–P75]) previous biologics (4 [3–4] vs 3 [2–4]). The mean (SD) baseline DAS28 (CRP) was 4.2 (1.0) in normal weight and 4.2 (1.2) in overweight patients (p=0.81). The mean (SD) change from baseline in DAS28 (CRP) over 6 months was –0.51 (1.4) in normal weight and –0.70 (1.8) in overweight patients (p=0.55). The difference of –0.19 in change of DAS28 (CRP) was reduced to –0.10 (p=0.71) after correcting for age, sex and baseline DAS28 (CRP), and further attenuated to –0.026 (p=0.92) if also corrected for anti-CCP positivity and number of previous biologic agents. Remission percentages (DAS28 <2.6) at 6 months were 23% in normal weight patients and 26% in overweight patients with an odds ratio (95% CI) of 1.2 (0.5, 2.9), which became 1.1 (0.4, 2.8) after correction for the same confounders.

Conclusion: In patients with RA, BMI was not a modifier of the effect of abatacept on DAS28 (CRP) at 6 months after treatment start. After controlling for confounders, the reduction in DAS28 (CRP) was the same for normal weight (BMI ≤25 kg/m^2) and overweight (BMI >25 kg/m^2) patients.

1. Maxwell L, et al. *Cochrane Database Syst Rev* 2009*;7:CD007277.*

2. Gremese E, et al. *Arthritis Care Res* 2013;**65**:94–100.

3. Sandberg M, et al. *Ann Rheum Dis* 2014;**73**:2029–33.

Disclosure: J. Fransen, Bristol-Myers Squibb, 2; **L. Tweehuysen**, None; **A. den Broeder**, None; **R. Postema**, Bristol-Myers Squibb, 3; **E. Alemao**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **F. van den Hoogen**, None.

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Abstract Number: 2495

The Prevalence of Loss of Response to Treatment with a Tumor Necrosis Factor Inhibitor and/or Methotrexate in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients (pts) with rheumatoid arthritis (RA) who achieve disease control in response to treatment with a tumor necrosis factor inhibitor (TNFi) may lose that response permanently under continuous treatment (1). We examined whether pts with early RA, in sustained clinical remission (REM) or low disease activity (LDA) lose their state of clinical response during continuous treatment with originator adalimumab (ADA) and/or methotrexate (MTX).

Methods: This post hoc analysis used data from PREMIER, a 2-year trial in early RA pts who were TNFi- and MTX-naïve. Pts received ADA, MTX, or ADA+MTX. Responders were defined as pts who sustained one of the following states at both Weeks (Wk) 20 and 24: 28-joint disease activity state based on C-reactive protein (DAS28-CRP) <2.6 or <3.2 (LDA); simplified disease activity index (SDAI) SDAI ≤3.3 (SDAI REM) or ≤11 (SDAI LDA), clinical disease activity index (CDAI) ≤ 2.8 (CDAI REM) or ≤10 (CDAI LDA) or ACR-EULAR Boolean REM. A loss of response was defined as loss of DAS28-CRP LDA for all remaining visits (up to Wk 104 or premature discontinuation) starting after Wk 24 (with ≥2 consecutive visits of LDA loss). The percentage of pts who lost DAS28-CRP LDA response in each treatment arm, and mean CDAI values, were calculated at each visit.

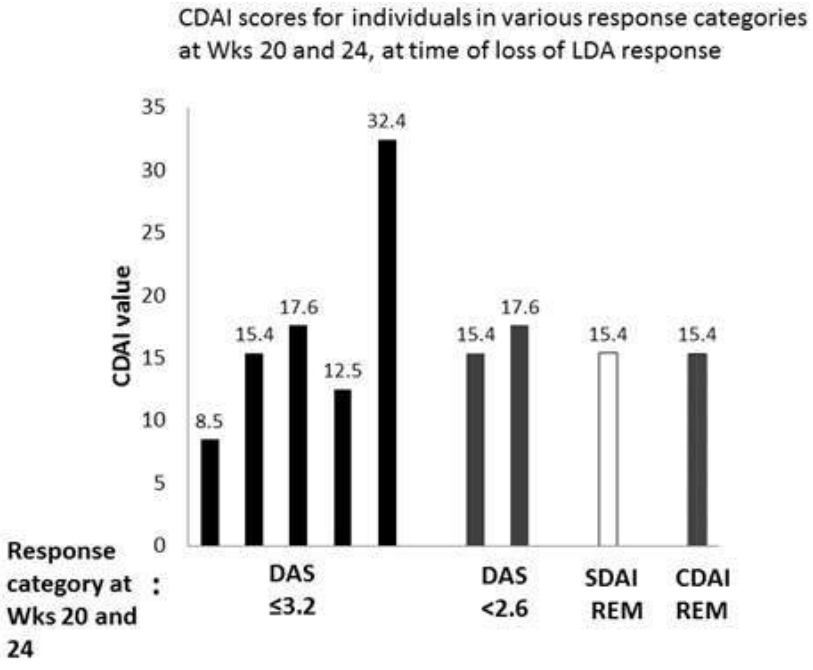
Results: Overall, for each response category, few pts permanently lost their DAS28-CRP LDA state after Wk 24 through Wk 104 (Table 1). Pts on ADA+MTX lost DAS28-CRP LDA less often, although the number of pts was small to begin with in some response categories in the monotherapy groups. For pts in DAS28-CRP LDA through Wk 104, the mean CDAI scores (shown at Wks 24, 26 and 104 in Table 1) ranged from 0.8-5, and these pts also remained in CDAI LDA at those time points. Pts in stringent REM (SDAI, CDAI or Boolean) at Wk 20 and 24 had lower mean CDAI scores than pts with DAS28-CRP <2.6 or LDA. Further, they maintained that response and a low CDAI value throughout the subsequent period, while pts with DAS28-CRP<2.6 experienced an increase of DAS28-CRP above that threshold on the group level. The CDAI score of pts who lost

their DAS28-CRP LDA state rose at the visit at which the first loss was recorded (Fig 1).

Conclusion: A majority of TNFi- and MTX-naïve pts with early RA in sustained REM or LDA after 20-24 wks of treatment maintained a low disease state through the period assessed. The loss of response was an infrequent phenomenon. **References:**

1. Finckh et al, Ann Rheum Dis, 2006;65:646-52

Table 1. Patients who permanently lost DAS28-CRP LDA starting from some visit post-Week 24, n/N (%)				
Response category at Wks 20 and 24 (N of pts with DAS28<3.2 at Wks 20 and 24)	ADA (45)	MTX+ADA (107)	MTX (50)	Overall (202)
DAS28(CRP)<3.2	2/45 (4.4)	2/107 (1.9)	1/50 (2.0)	5/202 (2.5)
DAS28(CRP)<2.6	2/21 (9.5)	0/56	0/24	2/101 (2.0)
SDAI ≤3.3	1/13 (7.7)	0/35	0/12	1/60 (1.7)
SDAI ≤11.0	3/46(6.5)	2/115 (1.7)	1/59 (1.7)	6/220 (2.7)
CDAI ≤2.8	1/12 (8.3)	0/35	0/14	1/61 (1.6)
CDAI ≤10.0	3/47 (6.4)	2/112 (1.8)	1/63 (1.6)	6/222 (2.7)
ACR-EULAR Boolean REMISSION	0/10	0/ 29	0/10	0/49
Mean CDAI values at each visit for patients who met a response definition at Weeks 20 and 24 and maintained DAS28-CRP LDA through Week 104				
Response category at Wks 20 and 24		Week 24	Week 26	Week 104
DAS28(CRP) <3.2		3.6	4.1	3.7
DAS28(CRP) <2.6		2.3	2.9	3.3
SDAI ≤3.3		0.8	1.3	2.5
CDAI ≤2.8		0.8	1.3	2.7



Disclosure: J. Smolen, AbbVie Inc., Amgen, AstraZeneca, BMS, Celgene, Centocor-Janssen, Glaxo, Lilly, Pfizer, MSD, Novo-Nordisk, Roche, Sandoz, and UCB, 2,AbbVie Inc., Amgen, AstraZeneca, BMS, Celgene, Centocor-Janssen, Glaxo, Lilly, Pfizer, MSD, Novo-Nordisk, Roche, Sandoz, and UCB, 5; **Y. Li**, AbbVie, 1,AbbVie, 3; **I. Sainsbury**, AbbVie, 1,AbbVie, 3; **S. Florentinus**, AbbVie, 1,AbbVie, 3; **K. Rambalee**, AbbVie, 1,AbbVie, 3; **G. Burmester**, UCB, 2,AbbVie, 5,BMS, 5,Hexal, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,MSD, 5,MedImmune, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,AbbVie, 8,BMS, 8,Hexal, 8,MSD, 8,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8.

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Abstract Number: 2496

DMARD, Biologic and Small Molecule Drug Use Among ACPA Positive and ACPA Negative RA Patients in a Tertiary Referral Center

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Background/Purpose: Rheumatoid arthritis (RA) can be divided into two major subsets based on the presence or absence of antibodies to citrullinated peptide antigens (ACPA). Some studies have indicated that RA patients who are positive for ACPA have a worse prognosis than ACPA negative patients and may require a more aggressive therapeutic approach to control disease. The purpose of this review was to determine if the presence or absence of ACPA antibodies is associated with a more active disease and if patients were more likely to be placed on biologics based on their ACPA

status.

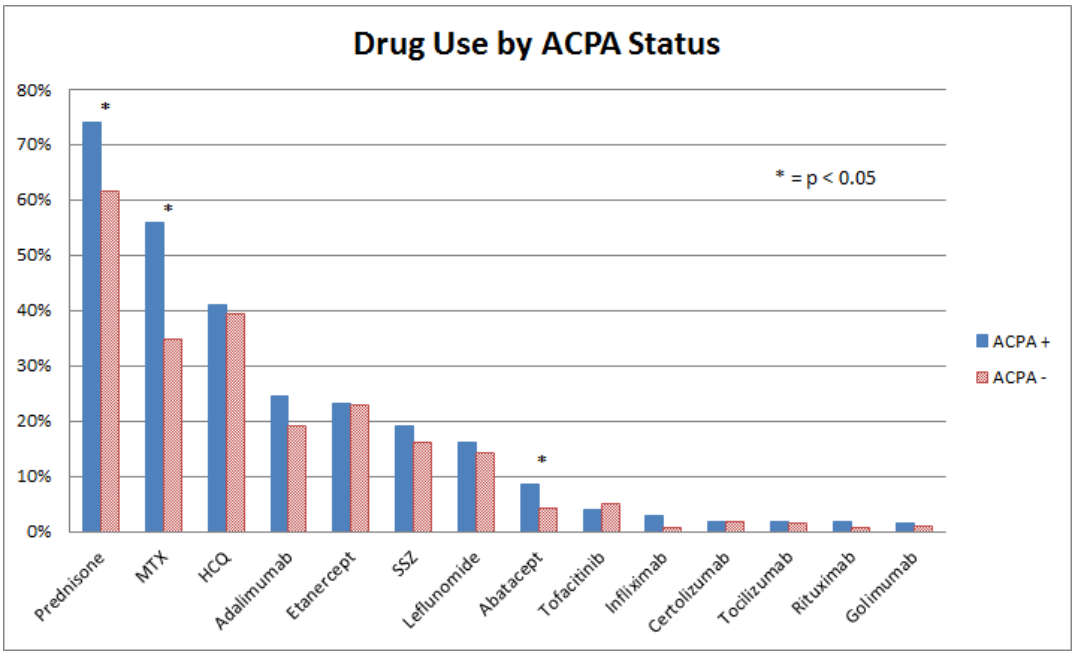
Methods: The de-identified data of RA patients were reviewed. Patients were seen in one academic center between 2008 and 2016. ACPA+ status was determined by at least one anti-CCP titer >20 units, using the QUANTA Lite CCP3.1 IgG/IgA ELISA testing. RF positive status was determined by a titer >14 units using turbidometry. RF data was available in 97% of ACPA positive patients and 96% of ACPA negative patients. RA patients with interstitial lung disease (N=130) were excluded. Self-reported disease activity was available for 43% ACPA+ and 35% of ACPA- patients using the Multidimensional Health Activity Questionnaire (MDHAQ) and RAPID 3 instruments on at least one visit. Fisher's Exact Test was used to determine differences in drug utilization between ACPA positive and negative RA patients. A Bonferroni-adjusted P <0.05 was considered statistically significant.

Results: The demographics of the study group (N=1070) are listed in Table 1. The characteristics of the patients in the two groups were quite similar. Disease severity was similar between the two groups as measured by RAPID 3 (11.2 and 11.9) or by MDHAQ (0.72 and 0.71). As expected, ACPA+ patients were also more likely to be RF+ (84%) than ACPA- patients (64%). The medications used to treat these patients are depicted in figure 1 showing that a higher percentage of ACPA+ patients used MTX and prednisone. Except for a slightly higher number of ACPA+ patients receiving abatacept, ACPA- and ACPA+ patients had similar use of biologics.

Conclusion: This retrospective study shows that ACPA+ and ACPA- RA patients had similar demographic characteristics and similar level of disease severity in our institution. The use of MTX and prednisone was higher among ACPA+ patients; however ACPA- patients had similar use of biologics, except for a slightly lower use of abatacept.

Table 1: Patient demographics and disease severity stratified by ACPA status

Results: Demographics		**CCP+**		**CCP-**	
Total		647	60%	438	40%
Gender	Female	479	74%	340	78%
	Male	168	26%	98	22%
Age	> 65	192	30%	131	31%
	40 - 65	347	55%	233	55%
	< 40	91	14%	56	13%
BMI	> 25	484	63%	317	62%
	<= 25	281	37%	191	38%
Smoking	Never	316	50%	234	55%
	Current	101	16%	41	10%
	Prior	217	34%	151	35%
Rheumatoid Factor	Positive (>=14)	530	84%	195	46%
Disease Activity	MDHAQ	0.72		0.71	
	RAPID3	11.2		11.9	



Disclosure: **R. Meehan**, Eli Lilly and Company, 2; **E. Hoffman**, Eli Lilly and Company, 2; **D. Muram**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **B. Goldstein**, None; **J. Crooks**, None; **P. Zelarney**, Eli Lilly and Company, 2.

Abstract Number: 2497

Associations Between Dietary Intake of Vitamin D, Omega-3 Fatty Acids, Folate and EULAR Response in Patients with Early Rheumatoid Arthritis

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Background/Purpose:

We hypothesized that increased dietary intake of vitamin D and omega-3 fatty acids (FA) prior to disease modifying anti-rheumatic drug (DMARD) initiation may associate with superior response to anti-rheumatic treatments. On the other hand, high dietary folate intake may be associated with worse response to methotrexate (MTX). The aim of this study was to investigate the association between dietary intakes of vitamin D, omega-3 FA, and folate and treatment results of DMARDs in patients with early RA.

Methods:

This study included 727 early RA patients from Epidemiological Investigation of Rheumatoid Arthritis (EIRA) study linked with the Swedish Rheumatology Quality register (SRQ). Data on dietary vitamin D, omega-3 FA and folate intake based on food frequency questionnaires were linked with data on response to DMARDs using European League Against Rheumatism (EULAR) response criteria at 3-month follow-up. Associations between dietary intakes of vitamin D, omega-3 FA, and folate and EULAR response, respectively, were analyzed with binary logistic regression adjusting for potential confounders.

Results:

The majority of the patients were initially treated with monotherapy of MTX (n=653 [89.9%]) and more than half of the patients had combined DMARD(s) with glucocorticoids (n=414 [56.9%]). Higher intakes of vitamin D and omega-3 FA were associated with good EULAR response. Folate intake around the recommended dose (300 µg/day), but not higher, was associated with EULAR response (Table). Similar associations were observed in the subgroup of patients who were initially treated with MTX monotherapy at baseline.

Nutrient intake	N	OR_{crude} (95 % CI)	$OR_{adjusted}$ (95 % CI)
Vitamin D	**727**		
1st quartile: ≤4.25 µg/day	182	1.00	1.00
2nd quartile: 4.26-5.42 µg/day	170	1.07 (0.70-1.64)	1.07 (0.69-1.65)
3rd quartile: 5.43-6.96 µg/day	184	1.15 (0.75-1.77)	1.25 (0.81-1.94)
4th quartile: >6.97 µg/day	191	1.75 (1.13-2.71)	1.71 (1.09-2.67)
p value		0.012	0.019
Omega-3 FA	**727**		
1st quartile: ≤0.45 g/day	180	1.00	1.00
2nd quartile: 0.46-0.62 g/day	192	1.25 (0.82-1.89)	1.27 (0.83-1.94)
3rd quartile: 0.63-0.83 g/day	183	1.35 (0.89-2.07)	1.37 (0.89-2.12)
4th quartile: >0.84 g/day	172	1.64 (1.07-2.53)	1.60 (1.03-2.48)
p value		0.024	0.038
Folate	**727**		
1st quartile: ≤244.88 µg/day	201	1.00	1.00
2nd quartile: 244.89-296.86 µg/day	182	1.32 (0.88-1.99)	1.36 (0.89-2.06)
3rd quartile: 296.87-365.70 µg/day	193	1.59 (1.07-2.38)	1.54 (1.02-2.33)
4th quartile: >365.71 µg/day	151	1.14 (0.74-1.75)	1.09 (0.70-1.70)
p value		0.557	0.712

OR_{crude}: Adjustment for age and sex.

$OR_{adjusted}$: Adjustment for age, sex, smoking, total energy intake and supplementation (vitamin D, omega-3 FA/fish oil, or folic acid).

p value: Comparison between 4th and 1st quartiles.

Conclusion:

Increased intake of dietary vitamin D and omega-3 FA during the year preceding DMARD initiation may associate to better treatment results in early RA patients. Moderate dietary folate intake, but not lower or higher, was associated with better response to treatment. Our results suggest that several specific nutrients may associate with enhanced treatment results in early RA.

Disclosure: C. Lourdudoss, None; **A. Wolk**, None; **L. Nise**, None; **L. Alfredsson**, None; **R. F. van Vollenhoven**, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma, 2,AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli-Lilly, Merck, Pfizer, Roche, UCB Pharma, Vertex, 5.

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Abstract Number: 2498

Tender Joints Is a Consistent Negative Predictor of Sustained Remission in Aggressively Treated Patients with Early Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) care has moved towards early diagnosis and treatment to improve long-term patient outcomes. Our objective was to assess prognostic factors for sustained remission and absence of clinical inflammation in an early RA population treated according to a strict tight-control algorithm with semi-personalized treatment adjustments.

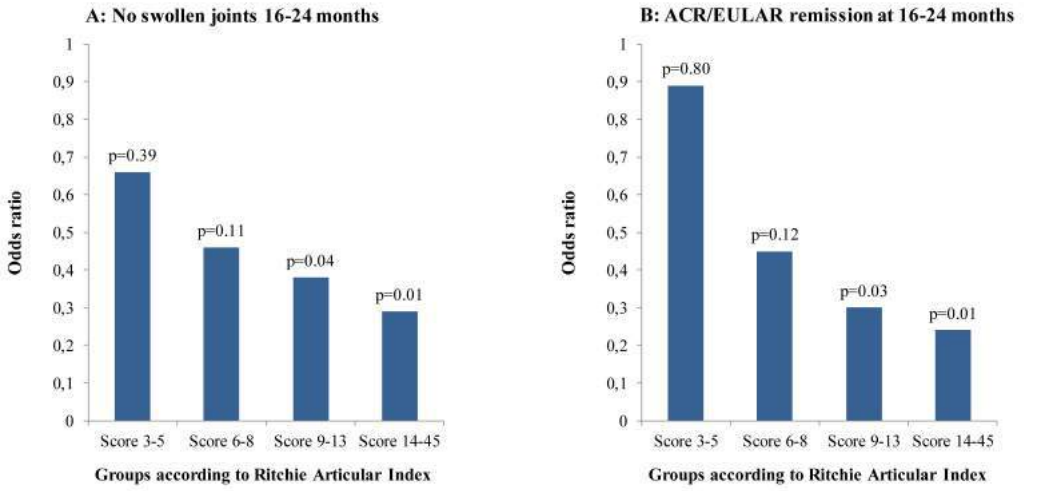
Methods: RA patients who fulfilled the ACR/EULAR 2010 classification criteria, with <2 years from first swollen joint and who were DMARD naive with indication for DMARD treatment were included in the ARCTIC trial. Patients were followed by a tight control regimen with defined treatment target (DAS <1.6, SJC44=0 + no power Doppler signal in half the patients) and response evaluation. Rapid escalation of medication was allowed if negative prognostic factors for joint destruction were present (seropositivity with baseline radiographic erosions or MRI bone marrow edema). Data collections included clinical examination, laboratory tests, patient reported outcomes, ultrasound examination and radiographs. Multivariate logistic regression was used to assess the associations between baseline variables and different definitions of sustained remission between 16 and 24 months.

Results: Mean [SD] disease duration of the 222 patients was 7.2 [5.4] months, mean original DAS 3.5 [1.2], 72% were RF and 82% ACPA positive, and 16% escalated treatment more rapidly to biologic therapy. Sustained (16 to 24 months) SDAI and ACR/EULAR remission were reached by 33% and 24% respectively. Tender joints assessed by Ritchie Articular Index was a consistent independent negative predictor of reaching sustained SDAI remission, ACR/EULAR remission, no swollen joints in any of the 44 joints evaluated, and a composite outcome of no swollen joints + radiographic progression≤0.5 per year + DAS remission between 16-24 months (table). Patients with high scores on the Ritchie Articular Index had low odds ratios for sustained remission and sustained absence of swollen joints when adjusting for baseline swollen joint count (figure).

Table: Baseline predictors for being in sustained remission between 16 and 24 months. The final multivariate models shown (corrected for age and gender).

Baseline variables	**Sustained SDAI remission** **N=73/222**	**Sustained ACR/EULAR remission** **N=53/222**	**Sustained no swollen joints** **N=121/222**	**Sustained no swollen joints, DAS remission, and radiographic progression ≤0.5** **N=71/222**
	OR **[25, 75 percentile]**	**OR** **[25, 75 percentile]**	**OR** **[25, 75 percentile]**	**OR** **[25, 75 percentile]**
Tender joints assessed by Ritchie Articular Index	0.94 [0.90, 1.00]	0.93 [0.88, 0.99]	0.94 [0.91, 0.98]	0.92 [0.87, 0.97]
Patient global (VAS 0-100)	0.98 [0.97, 1.00]	0.98 [0.97, 1.00]		
van der Heijde-modified Sharp erosion score	1.12 [1.01, 1.25]			
DMARD initation < 3 months	2.68 [1.35, 5.32]	2.15 [1.04, 4.45]		
Ultrasound power Doppler score (range 0-96)		1.04 [1.01, 1.08]		1.07 [1.01, 1.13]
Ultrasound grey scale score (range 0-96)				0.93 [0.89, 0.97]

Figure: Odds ratio for reaching sustained absence of swollen joints (**A**) and ACR/EULAR remission (**B**) according to quintiles of Ritchie Articular index at baseline, with the lowest quintile as reference category (score 0-2). Analyses adjusted for 44 swollen joint count.



Conclusion: In this early RA treat-to-target study, tender joints assessed by Ritchie Articular Index at baseline is a consistent negative predictor of reaching sustained remission. Our findings support that semi-personalized targeted treatment might modify the impact of known predictors.

Disclosure: N. P. Sundlisater, None; **S. Lillegraven**, None; **I. C. Olsen**, None; **A. B. Aga**, None; **H. B. Hammer**, None; **T. Uhlig**, None; **D. van der Heijde**, Imaging Rheumatology by Director, 9; **T. K. Kvien**, Biogen, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, Novartis, Orion Pharma, Prizer, Sandoz, UCB, 5; **E. A. Haavardsholm**, AbbVie, 2,Pfizer Inc, 2,MSD, 2,UCB, 2,Roche Pharmaceuticals, 2.

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Abstract Number: 2499

Tocilizumab Achieves Rapid Reduction of Disease Activity and Has Beneficial Effects on Bone Mineral Density in Patients with Rheumatoid Arthritis

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Tocilizumab achieves rapid reduction of disease activity and has beneficial effects on bone mineral density in patients with rheumatoid arthritis

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Background/Purpose: Tocilizumab (TCZ) leads to a rapid improvement of the clinical course in patients with highly active rheumatoid arthritis (RA). However, a residual rheumatic activity can still be detected.[1] RA is a known risk factor for osteoporosis related bone fractures.[2] It is well established that TCZ has beneficial effects on bone remodeling.[3]

The aim of this analysis was to investigate the effects of TCZ on bone mineral density in a real world patient population.

Methods: 50 rheumatoid factor positive patients with RA (17 male, age 20-72 years) who received TCZ as monotherapy since 2008 were prospectively investigated. At baseline and the following 4-6 clinical visits, DAS28 was determined and ultrasound performed. At baseline and every 6 months thereafter, biochemical parameters for bone metabolism and protein diagnostics were recorded. Once a year, the subjects underwent MRI, CT and DXA scan.

Results: In all 50 patients the DAS28 normalized at the latest by the 3rd infusion cycle of TCZ. The initial RAMRIS score of >5 was reduced to <2 after 6-18 months. Ultrasound revealed a decline of synovialitis and tenodynovialitis after 8 weeks and 12 months, respectively. At baseline in 22 women with early RA, axial QCT/DXA values and lateral DXA values were within reference. 3 patients with early RA had osteopenia, 2 had osteoporosis. Patients with manifest RA had a BMD in the reference range, 3 had osteopenia and 2 were diagnosed with osteoporosis. In 6 male patients, BMD values were within the reference range. 2 men with early RA had osteopenia and 2 had manifest osteoporosis. In 1 male patient with manifest RA, normal BMD values were documented. 2 men with manifest RA hat osteopenia and 4 had osteoporosis. 10 patients had vitamin D3 deficiency and were treated with vitamin D3. 2 patients with osteoporosis were treated with antiresorptive medication. In all patients, BMD values were within the reference range after 1 year of treatment with TCZ, despite 18% of patients presenting with a DAS score > 2.7. 2 patients presented with pustular dermatosis in the palms. No allergic reactions were observed.

Conclusion: Treatment with TCZ leads to a rapid decline of inflammatory activity of the affected

joints in patients with RA and minimizes cartilage destruction. TCZ showed a positive effect on bone remodeling and therefore BMD. Thus, the risk for the development of osteoporosis and its related fractures can be minimized by TCZ treatment. Furthermore, TCZ has a positive effect on BMD in manifest RA thus preventing sarcopenia. Temporary elevations of DAS28 during TCZ therapy do not negatively affect BMD.

Disclosure: M. Hoehle, None;

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Abstract Number: 2500

Prevalence of Sustained Remission in Patients with Rheumatoid Arthritis in Sweden. Impact of Criteria Sets and Early Treatment, a Nationwide Register Study in Sweden

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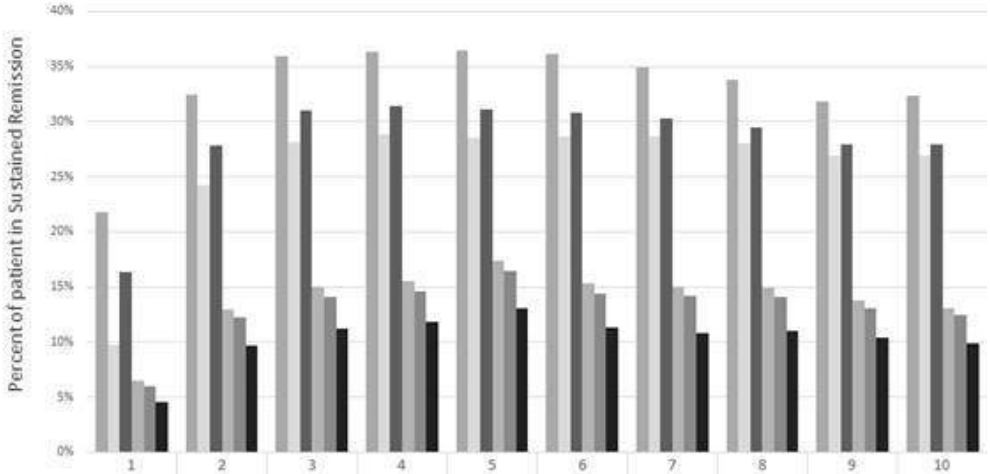
Background/Purpose: The Swedish Society for Rheumatology guidelines recommend remission as treatment goal for patients with rheumatoid arthritis (RA). The Swedish quality registry (SRQ) is a nationwide registry for rheumatic diseases in which all 64 rheumatology units in the country participate. The aim of this study was to examine how many patients reach sustained remission (SR) (DAS28<2.6 or SDAI<3.3 or CDAI 2.8 or ACR remission on at least 2 consecutive occasions and for at least 6 months) during follow up and to compare patients with early RA (first visit within 6 months symptom duration) with patients with established RA.

Methods: All adult patients with RA (n=29084) included in SRQ between 1992 and 2013, with at least 3 registered visits were eligible for the present study. 72% were female. Mean age was 58.8 years. 6691(20.5%) fulfilled the criteria for early RA described above. ACR 1987 criteria were satisfied by 95% of patients and 73.2% were ACPA positive. Duration of remission was defined as time between first visit fulfilling the remission criteria and subsequent first visit with higher disease activity.

Results: 12193 (41.9%) patients reached DAS28 SR, and 22.2%, 21.3% and 17.5% of patients reached sustained CDAI, SDAI and ACR remission, respectively, at some time point during follow up. The point prevalence of DAS28 SR 12 months after symptom onset was 16.4%, and 6.5%, 6.0% and 4.6% for CDAI, SDAI and ACR SR, respectively, and peaked after 5 years (figure1). The prevalence of DAS28 SR one year from symptom onset was 21.3% and 9.8% for early RA and established RA, respectively, and the difference remained for at least 10 years ($p<0.001$). Figure1 shows the percentage of patients being in SR in relation to symptom duration in years according to different remission criteria and stratified into early and established RA. The median time from symptom onset to DAS28 SR was 3.9 years, of those that reach SR, 75% have done so within 12 years (Range 0-74 years). Median time in DAS28 remission was 2.8 years (range 0.5-18.3), and 2.2 (0.5-17.1), 2.2 (0.5-17.1) and 2.1 (0.5-17.0) for CDAI, SDAI and ACR remission, respectively.

Conclusion: About 42% of patients with RA in Sweden reached DAS28 SR during the course of the disease, twice as many as those that reached SDAI, CDAI or ACR SR. The prevalence of SR is higher among early RA patients. Median time in DAS28 SR was just under three years and lower in SDAI, CDAI and ACR remission. The findings underline the need for early intervention but also shows that there is room for further improvement of the treatment strategy. Figure1. The percentage of patients being in SR in relation to symptom duration in years according to different remission criteria and stratified into early and established RA.



	1	2	3	4	5	6	7	8	9	10
DAS28 early RA	21,8%	32,5%	35,9%	36,4%	36,5%	36,2%	34,9%	33,8%	31,8%	32,3%
DAS28 established RA	9,8%	24,2%	28,2%	28,9%	28,6%	28,7%	28,6%	28,0%	26,9%	26,9%
DAS28	16,4%	27,8%	31,1%	31,4%	31,1%	30,8%	30,3%	29,4%	27,9%	27,9%
CDAI	6,5%	13,0%	15,0%	15,5%	17,4%	15,3%	15,1%	14,9%	13,8%	13,1%
SDAI	6,0%	12,2%	14,1%	14,6%	16,5%	14,4%	14,2%	14,1%	13,1%	12,5%
ACR	4,6%	9,7%	11,2%	11,8%	13,1%	11,3%	10,8%	11,0%	10,4%	9,9%

Disclosure: J. T. Einarsson, None; **M. Willim**, None; **S. Ernestam**, None; **T. Saxne**, None; **P.**

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Abstract Number: 2501

Radiographic Damage in Patients with RA Increases By 8.3% per Year Disease Duration, in the Era of Biologic Dmards. Results from the Scqm Cohort

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Background/Purpose: Rheumatoid arthritis (RA) is a chronic, inflammatory disease leading to joint destructions, if untreated. Treatment with biologic DMARDs has shown to favourably influence disease activity, joint destruction, and patient related outcomes (PROs). However, to our knowledge, no studies in larger patient cohorts have investigated the correlation between disease duration with radiographic outcome, disease activity, and disability in the new era of biologic treatment. To analyse cross-sectionally patients with RA for radiographic damage, PROs, and disease activity dependent on disease duration.

Methods: All RA patients from the Swiss national cohort (SCQM) with information on disease duration as documented in the database (time point of diagnosis) were included in the analysis. The primary endpoint was the association between disease duration and the status of radiographic joint destruction, assessed by Ratingen scores (range from 0 to 190, analysed by two independent and

blinded assessors) at the last clinical visit in the database. This endpoint was analysed by a multiple negative binomial regression model corrected for confounding factors (gender, age, rheumatoid factor (RF), antibodies to citrullinated protein antigens (ACPA), pre-exposition of anti-TNF drugs or methotrexate). Disease activity (DAS-28) and disability (HAQ DI) were analysed as secondary outcomes.

Results: The original 52'753 records on 8'678 patients resulted in 6'525 evaluable observations with documented Ratingen scores and disease durations. Disease duration ranged between less than 1 and more than 65 years (median 8.3). Anti-TNF drugs were used in 58.4% of patients. We found a significant association between disease duration and the status of radiographic joint destruction with an average increase of Ratingen scores by 8.3% per year of disease duration. RF was the highest predictor for radiographic destruction (estimate 1.41), whereas ACPA positivity was a negative predictor (estimate 0.812). In patients with a disease duration of less than 5 years, clinical disease activity and disability decreased depending on the time since diagnosis. While DAS-28-scores remained on a stable level thereafter (median DAS-28: 2.8, i.e. low disease activity), HAQ-DI scores increased continuously by 0.018 per year of disease duration. DAS-28 and HAQ-DI at the end of follow up correlated moderately (Kendall´s Rank-correlations 0.307) whereas no correlation was found between Ratingen scores and HAQ-DI (-0.009).

Conclusion: In this RA cohort, patients showed cross-sectionally a continuous increase of joint destruction and disability depending on disease duration, despite treatment with biologics and satisfactory control of disease activity, in the majority of patients. Even though, in the era of biologic treatment, a satisfactory control of disease activity can be achieved in most patients, RA remains a progressive disease leading to joint destruction.

Disclosure: R. Mueller, None; **K. Heinimann**, None; **R. Sauter**, None; **H. Schulze-Koops**, None; **T. Sokka-Isler**, None; **M. Schiff**, None; **J. von Kempis**, None.

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Abstract Number: 2502

Tocilizumab Therapy Reduces Corrected QT Interval in Patients with Rheumatoid Arthritis without Cardiac Symptoms

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Background/Purpose: Individuals with rheumatoid arthritis (RA) have a two-fold higher risk of sudden death than the healthy age- and sex-matched general population. Although the underlying mechanisms have not been clarified, evidence suggests the effects of systemic inflammation on ventricular repolarization. Consequently, prolongation of the corrected QT (QTc) interval in patients with RA is more frequent than in individuals without RA. We prospectively evaluated the impact of tocilizumab (TCZ) treatment on the QTc interval in patients with RA without cardiac symptoms and investigated the associations of QTc interval with RA disease activity and severity measures.

Methods: This was a prospective interventional study from March 2012 to December 2015 in Itabashi Chuo Medical Center. The RA study inclusion criteria were fulfillment of American College of Rheumatology (ACR) for the classification of RA or 2010 ACR/EULAR RA criteria. Exclusion criteria were diabetes, previous cardiovascular events, hypertension, dyslipidemia, cardiomyopathy, renal disease, and current atrial fibrillation. Healthy age- and sex-matched individuals without cardiac symptoms were selected as controls. TCZ (8 mg/kg IV every 4 weeks or 162 mg SC biweekly) was prescribed for patients with active RA with an inadequate clinical response to methotrexate. Electrocardiography and clinical and biological monitoring were performed at baseline and 24 weeks after TCZ treatment in patients with RA. A QTc interval of 440 ms was considered prolonged in this study.

Results: We enrolled 94 patients with RA (mean age, 56.4±10.4 years; 85% female) and 40 healthy age- and sex-matched controls (mean age, 55.6±9.4 years; 86% female). 20% and 14% of RA patients received anti-hypertensive and anti-hyperlipidemia therapy respectively. The 24-week disease activity scores (DAS28-ESR) were significantly lower than those at baseline. We identified 8 (8.5%) patients with a prolonged QTc interval. However, the QTc interval at baseline was higher in the control group (422.3±25.8 ms vs 402.3±31.2 ms; $p = 0.04$). The QTc interval decreased 20 ms from baseline to 24 weeks ($p = 0.001$) following TCZ treatment. The percentage change in the QTc interval significantly correlated with C-reactive protein (CRP), anti-cyclic citrullinated peptide antibody (ACPA), and DAS28 at baseline ($\rho = -0.43$, $p < 0.0001$; $\rho = -0.23$, $p = 0.024$; $\rho = -0.21$, $p = 0.04$, respectively). The percentage change in the QTc interval strongly correlated with that in matrix metalloproteinase-3 (MMP3) after TCZ therapy ($\rho = 0.38$, $p = 0.001$). After adjusting for confounding variables, such as age, RA duration, ACPA, and CRP, the association of percentage change in the QTc interval with ACPA remained significant ($p = 0.004$, $R^2 = 0.29$).

Conclusion: The data suggest that the anti-arrhythmic potential for TCZ therapy may have a beneficial impact on patients with RA. The data may provide further evidence of the degree of association between ACPA and QTc interval. Furthermore, MMP3, which may affect ventricular remodeling, might contribute to the QTc interval.

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Abstract Number: 2503

Making Room for RA Patient Symptoms into Treatment Decision: A Physician Perspective Study

Iris Navarro-Millán[1], Ronan O'Beirne[2], Melanie Morris[3], Bernadette Johnson[1], James Willig[4], Huifeng Yun[5], Andrea Cherrington[6], Liana Fraenkel[7], Monika M. Safford[8] and Jeffrey Curtis[9], [1]Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Continuing Medical Education, University of Alabama at Birmingham, Birmingham, AL, [4]Med - Infectious Diseases, University of Alabama at Birmingham, Birmingham, AL, [5]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, [6]Preventive Medicine, University of Alabama at Birmingham, Birmingham, AL, [7]Yale University School of Medicine, New Haven, CT, [8]Weill Cornell Medical College, New York, NY, [9]Division Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Birmingham, AL

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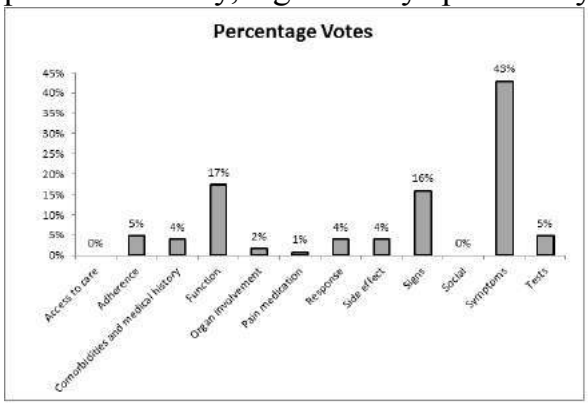
Background/Purpose: Little is known on what subjective or objective data that rheumatologists

consider most important for them to inform their treatment decisions for patients with rheumatoid arthritis (RA). **Objective:** To understand what data is most relevant for rheumatologists to inform treatment recommendations for their RA patients.

Methods: Participants were recruited nationally by email invitation to participate in one of 3 nominal groups held in March and April of 2016. Each of the 3 groups generated a list of elements from their patients' history, signs, and symptoms ('items'), that they deemed helpful in making treatment decisions. The results of each group were combined into a single data set, categorized by a sorting procedure, in which items were independently reviewed and then aggregated into common topic groups, redundant or duplicate items were removed, and the topic groups were then identified according to the major theme emerging from each group. These themes were then evaluated through calculation of a rank-order coefficients based number of items in each theme, number of items in each theme ranked in the top 3 in terms of importance, and the average score for each item within a theme.

Results: A total of 21 rheumatologists participated. Twelve themes emerged and 10 of these received ranking votes (Figure). Subjective information such as patient symptoms was the theme with the highest amount of votes (43%) while more objective data such as signs and tests captured only 21% of the ranking votes. These physicians did not rank assessment of medication adherence very highly. Among the unranked themes, "social relationships" had the fourth highest number of items (7 items emerged but no votes to any for any of these items), consistent with the concept that rheumatologists are aware of patients' social context for their health, but most do not yet recognize it as an important component in patients' care.

Conclusion: Most rheumatologists highly valued patients' symptoms to inform their treatment decisions. Collection of subjective data from patients between physician appointments (e.g. via Smartphone technology), even for domains not directly related to RA (e.g. sleep symptoms), appears valuable to rheumatologists to have a more complete representation of RA patient's health.
Figure: Themes that emerged during physician nominal groups regarding the elements of RA patient's history, signs and symptoms they value the most and their respective percentage of votes



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Willig, None; **H. Yun**, None; **A. Cherrington**, None; **L. Fraenkel**, None; **M. M. Safford**, None; **J. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 2504

Impaired Vasodilator Function in Rheumatoid Arthritis Patients Who Flared Due to Stopping Adalimumab or Etanercept

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Background/Purpose: Chronic inflammation in rheumatoid arthritis (RA) is associated with an increased cardiovascular risk, possibly due to disrupted vascular vasodilation. Within 12 weeks adalimumab and etanercept normalize vascular dysfunction. We here analyze whether stopping adalimumab or etanercept is associated with worsening of vasodilator function using the forearm vascular model using intraarterial AcetylCholine (ACh) and Sodium NitroPrusside (SNP) measuring forearm vasodilator function with plethysmography.

Methods: 35 patients participating in the nationwide tumor necrosis factor inhibitor stop study were assessed for eligibility and provided informed consent for this add-on study (exclusion criteria: uncontrolled hypertension); 8 were randomly allocated to the continuation arm of adalimumab/etanercept, 27 to the intervention arm of stopping the adalimumab or etanercept. Lost in follow up were 2 and 5 patients respectively. In the stopped group 8 flared and 14 did not flare. Forearm Vasodilation was assessed twice: before cessation of the intervention (visit 1) and 6 months afterwards (visit 2) or earlier when flaring occurred; flare defined as DAS28>3.2 plus increase exceeding 0.6 compared with baseline.

Results: In patients who stopped but did not flare (group B) vasodilator response to SNP and ACh did not differ between visit 1 and 2. In patients who flared after stopped adalimumab or etanercept (group C) vasodilator responses to ACh and SNP were significantly reduced during visit 2 when compared with visit 1, see table. In patients from group A who continued adalimumab/etancercept no flares were observed and vasodilator responses did not significantly differ between both visits. Table: percentage change in forearm blood flow (FBF) in infused versus non-infused arm in group C (n=8) vs group B (n=14); means (SE)

	ACh0.5	ACh2	ACh8	SNP0.06	SNP0.2	SNP0.6
A visit 1	124(34)	594(167)	1246(575)	52(21)	299(128)	651(223)
A visit 2	244(113)	477(228)	503(136)	222(45)	465(133)	821(256)
B visit 1	210(45)	582(156)	726(143)	93(16)	223(42)	358(54)
B visit 2	241(49)	418(74)	739(95)	99(14)	219(33)	486(94)
C visit 1	274(74)	608(185)*	1367(330)	121(30)	287(63)*	614(185)
C visit 2	142(33)	267(54)*	724(195)	105(24)	162(31)*	340(87)

* $P<0.05$ for comparison visit 1 to visit 2 (repeated measures ANOVA with vasodilator dose and visit as within subject factors)

Conclusion: Forearm vasodilator function is reduced after interruption of adalimumab or etanercept but only when rheumatoid arthritis reactivates. This indicates that without close rheumatological monitoring after interrupted biological treatment, ie stopped TNF inhibitor therapy, microvascular functional impairment will occur in those who flare, with potentially devastating implications for cardiovascular health. Funding for this study was gratefully acknowledged from Abbvie (unrestricted grant)

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Abstract Number: 2505

Thresholds of Benefit-Risk Trade-Offs from the Patient Perspective for Treatment Decisions in Moderate-to-Severe Rheumatoid Arthritis

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Background/Purpose: Given the increasing number of available treatments for RA with varying efficacy and safety profiles, it is critical to understand the level of trade-offs that patients are willing to make between benefits and risks. This study quantified the thresholds of benefit-risk trade-offs that patients are willing to accept in the treatment of RA.

Methods: Adult patients with moderate to severe RA were invited to participate in a discrete choice experiment that solicited their preferences for hypothetical RA treatments. These hypothetical RA treatments consisted of 9 attributes, including 3 efficacy measures (reduction in number of swollen joints, reduction of RA-related pain, and improvement of physical function), 3 adverse events (AEs; abnormal laboratory results [including abnormal liver function tests, blood count, and lipid profile], cancer, and serious infection), and 3 process-related features (route of administration, dose frequency, and out of pocket cost). Each participant completed 14 choice cards, and on each card was asked about their preference between two hypothetical RA treatments with varying levels of the 9 attributes. A multivariable logistic regression model was estimated to assess the association between the attributes and patient preference. Using the model, benefit-risk thresholds were calculated for the efficacy measures and AEs.

Results: 510 eligible patients with moderate to severe RA completed the experiment. The average age of the participants was 56.4 years, 64.7% were female, 38.4% were employed, 43.1% had RA for more than 10 years, and 45.1% received biologic agents. To achieve a 50% improvement in physical function, patients were willing to accept risk-increases of 91.1%, 4.7%, and 18.4% for abnormal laboratory results, cancer, and serious infection, respectively. Similarly, to achieve a 50% reduction in RA-related pain, patients were willing to accept risk increases of 70.6%, 3.7%, and 14.2% for each AE. Moreover, patients were willing to trade risk-increases of 42.0%, 2.2%, and 8.5% for each AE to obtain a 50% reduction in the number of swollen joints. Physical function affects patients' preference for the treatment the most (odds ratio [OR]=4.03 for a 50% improvement), followed by RA-related pain (OR=2.95 for a 50% reduction) and number of swollen joints (OR=1.90 for a 50% reduction). Increased risk of cancer affects patients' avoidance of the treatment the most (OR=0.74 for a 1% increase), followed by serious infections (OR=0.93 for a 1% increase) and abnormal laboratory results (OR=0.98 for a 1% increase). In addition, patients preferred oral and subcutaneous treatments (OR=2.30 for oral vs. intravenous and OR=1.69 for subcutaneous vs. intravenous), treatments with less frequent dosing (OR=1.69 for monthly vs. daily dosing), and lower out of pocket costs (OR=0.48 per $100 increase).

Conclusion: Patients with moderate-to-severe RA are willing to accept increased treatment risks to achieve improved physical function and disease control.

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Abstract Number: 2506

Seropositivity Predicts Bone Biomarker Change in an Inception Cohort of Rheumatoid Arthritis Patients Treated-to-Target with Combination Conventional DMARD Therapy

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Background/Purpose: There are limited data regarding the role of and response to treatment, of bone biomarkers in early rheumatoid arthritis (RA) treated with conventional DMARDs. We sought to determine whether levels of bone biomarkers associated with osteoclast activation [RANKL and Dickkopf-1 (Dkk-1)] or inhibition [osteoprotegerin (OPG)] correlated with response to treatment in an inception cohort of RA patients receiving treat-to-target combination DMARD therapy.

Methods: Patients with early RA (< 1 year; fulfilling 2010 classification criteria, n=112) received triple therapy (methotrexate, sulfasalazine and hydroxychloroquine) escalated to achieve DAS28 remission, without oral corticosteroids. RANKL, OPG and Dkk-1 were analysed by Luminex kits at 0, 6 and 12 month and in healthy controls (n=33). OPG levels were log-transformed prior to analysis; as a significant proportion of RANKL levels were below detection, results were dichotomised (positive/negative). Correlations between biomarkers and changes following treatment were analysed using Spearman's rank coefficient and mixed-model longitudinal regression respectively.

Results: At baseline, 69% were positive ('seropositive') for rheumatoid factor (RF) and/or anti-CCP (cyclic-citrullinated peptide), mean (±SD) age was 58(13) years, 72% were females, 60% current/past smokers, mean symptom duration prior to diagnosis of 18 (±11) weeks and mean DAS28 was 5.52 (1.30). Median (IQR) total SvH score was 3 (8); 20% had erosive disease. At baseline, compared to controls, OPG levels were elevated in both seronegative ($p < 0.001$) and seropositive ($p < 0.001$) patients. In seropositive patients, RANKL was more frequently detectable ($p < 0.001$) and negatively correlated with Dkk-1 ($p < 0.05$). In contrast, seronegative patients had higher Dkk-1 ($p < 0.001$) which strongly correlated with OPG ($p < 0.001$) and RANKL was not significantly different from controls ($p = 0.36$). Following treatment, mean DAS28 at 6 and 12 months was 3.55 (1.55) and 3.28 (1.60) respectively. In seropositive patients, there was a significant reduction in proportion of patients with detectable RANKL ($p = 0.002$) and an increase in OPG levels ($p < 0.01$) but no significant change in Dkk-1 levels. Seronegative patients, in contrast, had no change in proportion of patients with detectable RANKL ($p = 0.76$) or OPG levels ($p = 0.5$), but had a significant reduction in Dkk-1 ($p < 0.001$).

Conclusion: Individual bone biomarkers show significant differences at baseline and following conventional DMARD treatment, between seropositive and seronegative patients. Reduction in Dkk-1 and reduction in RANKL and increase in OPG may be useful biomarkers of treatment response in seronegative and seropositive patients respectively. The differential response of biomarkers, depending on seropositivity, may help direct therapeutic decisions in order to optimise prevention of joint damage. Further analysis of these biomarkers in relation to disease activity and erosive disease is warranted.

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Abstract Number: 2507

Assessment of Liver Fibrosis Using Transient Elastography in

Patients with Rheumatoid Arthritis Exposed to Long Term Methotrexate

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Background/Purpose: Methotrexate (MTX) has been recommended for the first line therapy of rheumatoid arthritis (RA), either alone or in combination with other DMARDs such as leflunomide. Although MTX is thought to have long term safety, there is still controversy whether long term use of MTX and its cumulative dose causes liver fibrosis in RA patients**.** This study was performed to assess the degree of liver fibrosis among the RA patients treated with MTX by transient elastography (TE), and to identify associated factors with liver fibrosis in those patients.

Methods: We restrospectively reviewed the medical records of 160 patients with RA taking MTX over 3 years, and who had liver fibrosis examination using TE. Liver fibrosis was defined as liver stiffness value over 5.3 kPa according to the reference of healthy Korean organ donor. The duration, cumulative doses of medications including MTX and leflunomide, and serologic markers related to liver fibrosis were analyzed by comparing 2 groups with and without liver fibrosis. E), and to identify associated factors with liver fibrosis in those patients.

Results: The mean disease duration of patients was 10.7 ± 5.1 years, and the median liver stiffness value was 4.5 ± 2.7 kPa. Twenty one (13.1%) patients showed liver fibrosis while only 1 (0.01%) patient progressed to liver cirrhosis. The cumulative dose of MTX and leflunomide showed no significant difference between 2 groups. A history of taking LFNM and concomitant medications did not affect to the development of liver fibrosis. Patients with liver fibrosis had higher glucose, aspirate aminotransferase (AST), and alkaline phosphate (ALP) level with a tendency of lower level of hemoglobin, platelet and longer treatment duration with MTX. The history of glucose

abnormality including pre-diabetes and diabetes mellitus (odds ratio [OR] 5.154, $P = 0.011$), serum hemoglobin (OR 0.608, $P = 0.023$), platelet (OR 0.989, $P = 0.025$), AST (OR 1.052, $P = 0.014$), and ALP level (OR 1.034, $P = 0.022$) were related with liver fibrosis in multivariate analysis.

Conclusion: Long term use of low dose MTX and combination of leflunomide in patients with RA were relatively safe in terms of severe liver fibrosis measured by TE. RA patients with risk factors such as impaired glucose tolerance should be more carefully monitored for development of liver fibrosis in long term use of MTX.

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Abstract Number: 2508

Significant Improvement of Rheumatoid Arthritis (RA) Outcome with Repeat Application of Disease Management (SSDM) Mobiles Tools: A Cohort Study of RA Patients in China

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Background/Purpose: There are more than 5 million rheumatoid arthritis (RA) patients in China, but only 5,000 rheumatologists. Treat-to-Target (T2T) strategy are critical for the treatment of RA, but the Chinese rheumatologists can hardly provide patients with a complete assessment in the clinic due to limited time. The purpose of this study is to explore the effectiveness of applying SSDM in improvement of disease activity after repeated self-assessment in Chinese RA patients.

Methods: The SSDM includes interfaces of both physicians' and patients' application. After entering the data of lab test records, treatment regiments, and executing DAS28 assessment by patients, all data can be synchronized automatically to the authorized physicians' mobile tool. The rheumatologist can adjust treatment regiments base on patients' profile. From August 2014 to June 2016, 126 rheumatologists from 83 hospitals in China participated in the study. Patients were educated to assess DAS28 with SSDM and asked to repeat the self-assessment once a month. Descriptive statistics were performed for patient and disease characteristics. According to DAS28 scores, disease activity was divided into four groups: remission (Rem), low disease activity (LDA), moderate disease activity (MDA) and high disease activity (HDA).

Results: 1,058 RA patients with repeated self-assessment of DAS 28 were recruited, 819 (77.4%) women and 239 (22.6%) men respectively. Mean age was 48.3 ± 13.1 (11 to 83) years. Mean interval of repeat self-assessment was 38.2±38.1 days. Mean self-assessment frequency were 3.39±2.84 (2 to 31) times. Mean DAS28 score was 3.78 ± 1.45 (0.56 to 8.66) at baseline and 3.31 ± 1.35 (0.08 to 9.07) at the last assessment. Proportion of patients in Rem, LDA, MDA and HDA was 22.12%, 16.26%, 43.29% and 18.34% respectively at baseline, and changed into 32.61%, 18.81%, 39.22% and 9.36% at the last assessment. The rate of T2T (DAS28≤3.2) at the last assessment was higher than that of baseline significantly ($P<0.01$). The rate of HDA patients for last assessment was significantly lower than baseline ($P<0.01$). To further explore weather tight control of disease activity with SSDM could influence RA patients' outcome, we stratified the patients who did not achieve clinical remission (DAS>2.6) at baseline into twice assessments group and multiple assessments group with 6 months follow-up. The result showed that 149 patients made only twice assessments of DAS28 within 160.8±94.9 (60-578) days. Their mean DAS28 score was 4.27±1.15 (2.61 to 7.86) at baseline and improvement of DAS28 score was 0.55±1.51 (-4.49 to 4.18) at their last assessment. While another 170 patients made 4 to 10 times of self-assessment during 178.9±139.3 (28 to 648) days follow-up. Their mean DAS28 score was 4.24±1.10 (2.61 to 7.77) at baseline and average improvement of DAS28 score was 1.09±1.37 (-1.86 to 5) at the last assessment, which was significantly better than patients who had only two self-assessments ($T=3.331$, $P=0.001$).

Conclusion: Under repeat self-assessment of DAS28 using SSDM, RA patients can achieve better T2T result. SSDM can assist rheumatologist to rationally adjust treatment for RA patients.

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Abstract Number: 2509

Implementation of the Treat to Target Concept in Evaluation of Rheumatoid Arthritis Patients

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Background/Purpose: To assess the implementation of the treat to target (T2T) concept in rheumatoid arthritis (RA) patients.

Methods: Academic rheumatology units were invited to participate in a retrospective study evaluating the implementation of the T2T concept in RA patients. The charts of consecutive RA patients attending the centers during June 2015, with 3 or more previous visits, were evaluated using a common questionnaire. Data collected included demographic parameters, alcohol consumption, smoking, concomitant diseases, age at RA onset, and the presence of rheumatoid factor (RF) and erosions. Validated disease activity scores [Disease Activity *Score* (DAS-28), Clinical Disease Activity Index (CDAI), Simple Disease Activity Index (SDAI), Routine Assessment of Patient Index

Data (RAPID3)], RA treatment including conventional or biological DMARDS, drug dosages, side effects, and patients' preferences were recorded. Two independent rheumatologists evaluated the data to assess the implementation of T2T concept. Statistical analysis: The associations between T2T concept implementation and categorical and continuous variables were assessed by Chi square test, t-test or Mann-Whitney test as appropriate. ANOVA or Kruskal-Wallis test was used to compare continuous variables between centers as appropriate.

Results: The seven participating centers reported 724 patients; age 62.6±13.97 years, 575 (80.4%) of them women. According to the reported data, 353 (65.4%) never smoked, 474 (73.3%) were married, 592 (86.8%) lived in cities, 191 (45.7%) had above high school education, 524 (72.4%) had comorbidities, 399 (66.4%) were RF positive and 125 (59.8%) had erosions. Four centers used more than one scoring method, DAS-28 and CDAI being the most popular. Only 276 (38.1%) of the patients had disease score results in ≥3 visits. The T2T approach was implemented in 245 (33.8%) of the 724 patients. The rate of implementation varied between centers (11.1%-87% $p<0.0001$), and was higher in younger patients ($p=0.028$), non-Jews ($p=0.048$), alcohol consuming ($p=0.009$) and RF positive patients ($p=0.011$). There was no correlation between the T2T implementation and gender, place of residence, education, smoking, treatment regimens, and the presence of erosions or comorbidities.

Conclusion: In our sample, the implementation of the T2T concept was limited. Further studies are needed to determine the reasons for this deviation from this desirable standard as well as its consequences.

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Abstract Number: 2510

Recommendations for the Use of Parenteral Methotrexate in Rheumatic Diseases

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Background/Purpose: To develop recommendations for the management of parenteral MTX in rheumatic diseases based on best evidence and experience.

Methods: A group of 21 experts on parenteral MTX use was selected. The coordinator formulated 13 questions about parenteral MTX (indications, efficacy, safety and cost-effectiveness). A systematic review were performed in order to answer the questions. Using this information, inclusion and exclusion criteria were stablishes as well as the search strategies (Medline, Embase and the Cochrane Library were searched). Three different reviewers selected the articles. Evidence tables were produced. At the same time, EULAR and ACR abstracts were evaluates. With this evidence the coordinator proposed preliminary recommendations that the experts discussed and voted in a nominal group meeting. The level of evidence and grade of recommendation was established using the Oxford Center for Evidence Based Medicine and the level of agreement with the *Delphi* technique (2 rounds). Agreement was established if at least 80% of the experts voted yes (yes/no).

Results: A total of 13 preliminary recommendations on the use of parenteral MTX were proposed of which 11 were accepted (see table). Two were not voted and were explained in the main text of the document.

Conclusion: This document pretends to help solve usual clinical questions and facilitate decision making when treating rheumatic patients with parenteral MTX. **Table**. Recommendations and their level of evidence (LE), grade of recommendation (GR) and grade of agreement (GA).

#	RECOMMENDATION	LE; GR; GA
1	Parenteral MTX biodisponibility compared with oral MTX is superior, mainly if the dose is ≥15 mg/w	NE 2b; GR B-C; GA 100%
2	In MTX-*naïve* patients, parenteral MTX efficacy compared with oral MTX is superior (doses of 15 mg/w)	NE 1b; GR A; GA 94%
3	In patients refractory to oral MTX (15 mg/w) the efficacy of dose escalation is higher with parenteral MTX	NE 2a; GR B; GA 94%
4	Safety profile and tolerability of parenteral MTX is similar to oral MTX	NE 1b; GR B; GA 100%
5	It is recommended to use parenteral MTX in patients with high disease activity, in those with low adherence to oral MTX, polypharmacy, obese patients, in order to avoid dosing errors, and always taking into account patients preferences	NE 4; GR D; GA 100%
6	It is recommended to initiate, increase and decrease parenteral MTX the same way as with oral MTX	NE 5; GR D; GA 81%
7	It is recommended to increase parenteral MTX dose up to 25-30 mg/w	NE 5; GR D; GA 88%
8	According to available pharmacokinetic data, the dose conversion between oral and parenteral dose would be: up to 15 mg/w the same dose, 20 mg of oral MTX would be 15 mg of parenteral MTX and for 25 mg of oral MTX, 20 mg of parenteral MTX	NE 2b; GR B; GA 100%
9	Subcutaneous MTX could be cost-effective in early RA naive to MTX	NE 2a; GR B; GA 94%
10	Parenteral MTX might increase patients adherence to MTX	NE 2b; GR B; GA 94%
11	Self-administration education provides a high adherence to treatment, satisfaction, patients autonomy and improves and adequate administration	NE 2b; GR B; GA 100%

Disclosure: J. Tornero Molina, None; **J. Calvo**, None; **F. J. Ballina-García**, None; **M. Á. Belmonte**, None; **F. J. Blanco**, None; **M. A. Caracuel-Ruiz**, None; **J. Carbonell**, None; **H. Corominas**, None; **E. Chamizo Carmona**, None; **C. Hidalgo-Calleja**, None; **J. A. Roman Ivorra**, None; **J. L. Marenco de la Fuente**, None; **J. V. Moreno**, None; **S. Muñoz Fernandez**, None; **J. M. Nolla**, None; **T. Perez Sandoval**, None; **R. Sanmarti**, None; **P. Trenor**, None; **C. Urrego**, None; **J. Vidal**, None; **J. Rosas**, None.

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Abstract Number: 2511

Longitudinal Observation of Disease Activity and Treatment of Rheumatoid Arthritis Who Developed Methotrexate-Associated Lymphoproliferative Disorders

Atsumu Osada[1], Koji Kobayashi[2], Yuji Yoshioka[3], Haruko Ideguchi[3] and Shohei Nagaoka[3], [1]Rheumatology, Yokohama Minami Kyosai Hospital, Yokohama, Japan, [2]Yokohama City University Medical Center, Yokohama, Japan, [3]Yokohama Minami Kyosai Hospital, Yokohama, Japan

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

Methotrexate-associated lymphoproliferative disorder(MTX-LPD) is rare but one of important complications in treatment of rheumatoid arthritis (RA). There are few reports about disease activity and optimal therapy of RA with MTX-LPD.

Methods:

We retrospectively analyzed background of patients, histology of LPD, treatment and disease activity of RA in 15 patients with MTX-LPD in our hospital between 2008 and 2014.

Results:

Our cases included 4 males and 11 females, and the median age of MTX-LPD onset was 70 years old (52-81). Average dose and period of MTX administration were 8.8 mg /week (4-16), 8.7 years (2.2-19.8), and 3681 mg in total (1372 -9485). Mean DAS28 (CRP) at MTX-LPD diagnosis was 2.00 (1.17-3.18). Extranodal lesions were observed in 8 cases. Three of 15 patients were diagnosed as Hodgikin lymphoma (HL), 2 as diffuse large B-cell lymphoma (DLBCL), 1 as Follicular lymphoma (FL), 1 as peripheral T-cell lymphoma (PTCL), 1 as Angioimmunoblastic T-cell lymphoma (AILT).

Lymphoproliferative lesions were improved spontaneously by discontinuation of MTX in 8 cases. Six of them showed relapse of RA in 3 to 65 months after MTX cessation, and Abatacept (ABT), administered in four cases, was effective without recurrence of LPD. Chemotherapy (CTx) was required in seven patients. Flare of arthritis, seen less common in CTx group, occurred in two cases in 18 and 36 months after CTx was finished. The propotion of patients associated with Sjögren's syndrome (SS) was significantly larger in CTx group (57 % v.s. 0 %, p=0.026).

Conclusion:

It is suggested that RA flare is common after MTX-LPD and ABT can be safe and effective treatment in RA relapse. Absense of SS was associated with spontaneous remission of MTX-LPD.

Patients With Spontaneous Remission

No	Age	Sex	SS	Extra-nodular lesion	Histology	RA Tx after MTXLPD	RA relapse after MTX cessation(month)	Current Tx (RA activity)
1	71	F	-	-	AITL	none	+(4M)	ABT(rem)
2	52	F	-	-	N/A	Tacrolimus (TAC)	+(3M)	ABT(rem)
3	71	F	-	Thyroid	hyperplasia	ABT	+(4M)	ABT(rem)
4	79	F	-	-	Hyperplasia	TAC	+(32M)	ABT +Iguratimod(rem)
5	75	F	-	Pleura	Malignant lymphoma	SSZ+TAC	+(65M)	Tocilizumab(rem)
6	72	M	-	pharynx	N/A	none	+(3M)	SSZ(rem)
7	70	M	-	-	N/A	TAC	-	TAC(rem)
8	76	F	-	Tongue	hyperplasia	TAC	-	none(rem)

Patients who required CTx

No	Age	Sex	SS	Extra-nodular lesion	Histology	CTx	RA Tx at CTx	RA relapse after CTx (month)	Current Tx And RA activity
9	81	F	-	Nasal cavity	PTCL	THP-COP	SSZ	+(36M)	N/A
10	60	M	-	testis	DLBCL	R-CHOP	ABT	+(18M)	none(rem)
11	72	F	-	skin	FL	RB	Bucillamine (BUC)	-	BUC(rem)
12	58	F	+	-	HL	ABVD	SSZ	-	none(rem)
13	69	F	+	-	HL	ABVD	none	-	none(rem)
14	79	F	+	-	DLBCL	R-THP-COP	Etanercept	N/A	N/A
15	59	M	+	-	HL	N/A	BUC	N/A	N/A

Disclosure: A. Osada, None; **K. Kobayashi**, None; **Y. Yoshioka**, None; **H. Ideguchi**, None; **S. Nagaoka**, None.

Abstract Number: 2512

Secular Trends of Sustained Remission in Rheumatoid Arthritis, a Nationwide Register Study in Sweden

Jon T. Einarsson[1], Minna Willim[1], Sofia Ernestam[2], Tore Saxne[1], Pierre Geborek[1] and Meliha C. Kapetanovic[1], [1]Lund University, Skane University Hospital, Department of Rheumatology, Lund, Sweden, Lund, Sweden, [2]Centre of Rheumatology, Stockholm County Council, Stockholm, Sweden, Stockholm, Sweden

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Background/Purpose: Remission has become a treatment goal in rheumatoid arthritis (RA) especially after the introduction of biologic treatment in 1999. The Swedish quality registry (SRQ) is a nationwide registry for rheumatic diseases in which all 64 rheumatology units in the country participate. The aim of the present study was to investigate the impact of changing treatment goals in the national guidelines on secular trends in achieving sustained remission (SR) i.e. DAS28<2.6 on at least 2 consecutive occasions lasting at least 6 months in a national Swedish RA cohort.

Methods: All adult patients with RA included in the registry 1992-2013, with follow up through 2014 with at least 3 registered visits were eligible, a total of 29084 patients. Their median age was 59.6 years and 72% were female. Symptom onset ranged from 1934 to December 2012, but for parts of the comparisons only patients with symptom onset between 1999 and 2009 were studied. The median time from symptom onset to inclusion was 2.6 years (range 0-78 years). Last follow up visit was median 10.5 years after symptom onset. In total, 95% of patients fulfilled the ACR 1987 classification criteria for RA and 73.2% were ACPA positive. Registrations were made with a median interval of 6 months (range 1 to 215). Duration of remission was defined as the time between first visit fulfilling the remission criteria and subsequent first visit with higher disease activity, after median 2.8 years. Estimated time to SR for each year was calculated with life table analysis and compared using log-rank test.

Results: 12193 (41.9%) patients reached DAS28 sustained remission at some time point during follow up. Figure 1 shows the fraction of patients with symptom onset in a certain calendar year reaching DAS28 remission occasionally or SR. Of patients with symptom onset between 1981-1990, 1991-2000 and 2001-2010, 35.0%, 43.0% and 45.6% reached SR respectively ($p<0.001$ for each increment). Figure 2 shows the estimated fraction of patients in SR during the first 5 years after symptom onset. The time period from symptom onset to SR decreased every other year with only

two exceptions ($p<0.001$; log-rank test). The estimated mean time to SR was 11.7 years in 1999 compared to 4.2 in 2009.

Conclusion: The prevalence of sustained remission was higher 2001-2010 compared to the previous two decades. Time from onset of RA symptoms to sustained remission decreased gradually between 1999 and 2009. The treatment strategy the last decade has improved outcome of RA but further improvement concerning time to diagnosis and early effective treatment is required to reach the treatment goal of sustained remission in the majority of patients.

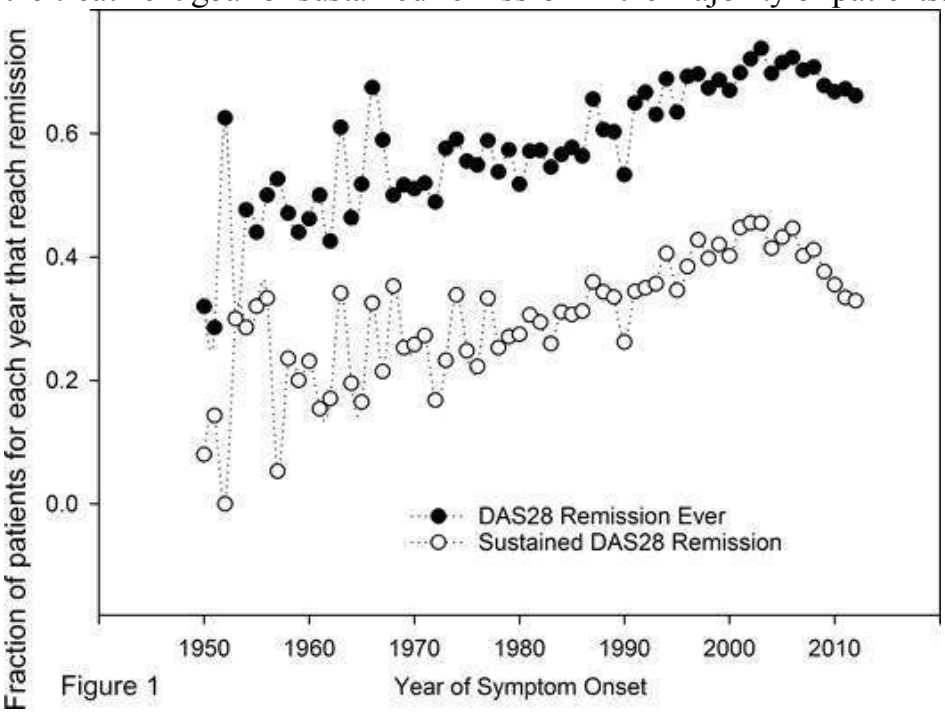

Figure 1

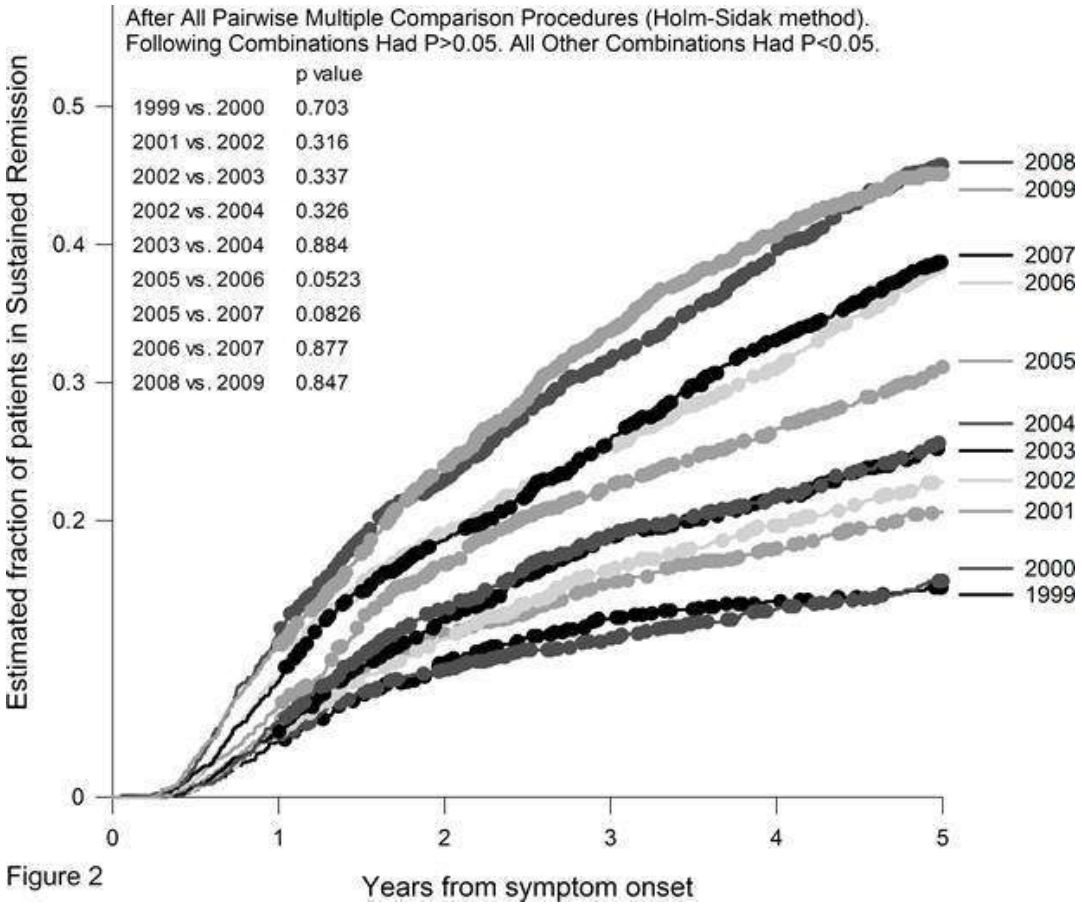

Figure 2

Disclosure: J. T. Einarsson, None; **M. Willim**, None; **S. Ernestam**, None; **T. Saxne**, None; **P. Geborek**, None; **M. C. Kapetanovic**, None.

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Abstract Number: 2513

Maintained Remission in Rheumatoid Arthritis over 7 Years in «Real Life Conditions» : A Monocentric Observational Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: Remission constitutes the best achievable state in patients with rheumatoid arthritis (RA). And if remission is a goal, it need to be maintained. The objective of this study was to evaluate stable remission in (RA) over 7 years follow-up in "real life" conditions and its predicitive factors.

Methods: The records (clinical, biological, immunogenetic, and radiographical data) of 364 patients with active RA, fulfilling the American College of Rheumatology (ACR) criteria, seen between January 2008 and December 2008 in a University Hospital Rheumatology were analyzed. Mean age was 62,9 years. 188 were treated with cDMARDs (monotherapy or association), 86 were treated with bioDMARDs (monotherapy or combined with methotrexate), 36 had only corticosteroids. The ACR-EULAR remission, defined as DAS28 <2.6 was achieved by 97 patients after 1 year (39 patients had only cDMARDs, 49 had bioDMARDs (43 anti-TNF and 6 others), 9 had no long-term treatment. Patients were seen at least once a year In out patient clinic. All data were collected until end of 2015.

Results: Data from 233 patients (75%) followed up to 7 years were avalaible. Remission was obtained for 133 patients (57%).102 were treated with cDMARDs (monotherapy with methotrexate, arava, plaquenil or tritherapy),130 were treated with bioDMARDs (30 had monotherapy and 100 had combined treatment with cDMARDs), 1 had only corticosteroids. Mean activity in DAS28 was 3,44 after 1 year and dicreases to 2,67 after 7 years follow up. Corticosteroids have been stopped for 38% of our patients. Among the 97 patients getting strict remission after 1 year, 82 patients (84%) kept long term remission and 51 others entered in remission during follow up. Remission rate was 31% after 1 year, remained stable for 84% of our patients and long term remission rates (DAS28<2.6) was obtain for 57% of our patients, and 38 patients (16%) kept a low disease activity (DAS28 <3,2). Long term remission was more frequent when cDMARDs was associated with bioDMARDs, especially anti-TNF.

Conclusion: In our study 84% of patients who had remission after 1 year of treatment kept long term remission. In RA patients, targeted treatment with a combination of conventional DMARDs and biologic induces a higher rate of long term remission.

Disclosure: J. Vix, None; **E. Loppin**, None; **E. Solau-Gervais**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/maintained-remission-in-rheumatoid-arthritis-over-7-years-in-real-life-conditions-a-monocentric-observational-study

Abstract Number: 2514

Does Combination of Conventional Synthetic Disease Modifying Antirheumatic Drug with Anti-TNF Influence the

Long Term Retention Compared to Anti-TNF Monotherapy in Psoriatic Arthritis? an Analysis from Rhumadata® over 12 Years

Isabelle Ferdinand[1], Louis Bessette[2], Josiane Bourré-Tessier[3], Boulos Haraoui[4], Jacques Brown[5], Frédéric Massicotte[3], Jean-Pierre Pelletier[3], Jean-Pierre Raynauld[4], Marie-Anaïs Rémillard[6], Diane Sauvageau[3], Angèle Turcotte[5], Édith Villeneuve[3] and Louis Coupal[3], [1]University of Montreal, Montreal, QC, Canada, [2]Rhumatology, Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [3]Rheumatology, Institut de Recherche en Rhumatologie de Montréal (IRRM), Montréal, QC, Canada, [4]1551, Ontario Street East, Institut de Recherche en Rhumatologie de Montréal (IRRM), Montreal, QC, Canada, [5]Rheumatology, Centre d'Ostéoporose et de Rhumatologie de Québec (CORQ), Québec, QC, Canada, [6]Rhumatology, Institut de Recherche en Rhumatologie de Montréal (IRRM), Montréal, QC, Canada

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Background/Purpose: In rheumatoid arthritis, it has been shown that anti-TNF therapy (TNFi) in combination with a conventional synthetic disease-modifying antirheumatic drug (csDMARD), often methotrexate (MTX), is more effective than anti-TNF monotherapy to improve clinical outcomes and TNFi retention. A recent article on psoriatic arthritis (PsA) has observed a trend towards better retention of TNFi in combination with MTX vs monotherapy. We assessed the long-term retention of TNFi with and without csDMARDs in the first-line treatment of PsA in the real world Rhumadata® clinical database.

Methods: The data of all PsA patients treated with a first biological agent was extracted from Rhumadata®. The data included age, gender, clinical variables, patient and physician specific assessments, and laboratory measures. Composite assessment of disease activity including the DAS28-CRP and the simplified and clinical disease activity indices (SDAI and CDAI) were calculated using readily available formulas. Concomitant use of csDMARDs (MTX, hydroxychloroquine, leflunomide, and sulfasalazine) was collected. Patients were classified into four groups: TNFi alone, TNFi+MTX alone, TNFi+non-MTX csDNMARDs and TNFi+MTX+other csDMARDs. Kaplan-Meier methods were used to compute the cumulative incidence of biologic agent discontinuation in those groups and differences in discontinuation rates were tested using the log-rank tests. Potential predictors of biologic retention were entered in univariate and multivariate proportional hazard regression models. Statistical analysis was performed using SAS version 9.4.

Results: Our cohort included 398 patients, 102 receiving anti-TNF monotherapy, 165 concomitant MTX only, 90 MTX + other csDMARDs and 41 concomitant non-MTX csDMARDs . Men represent 55% of our cohort with a mean disease duration of 6 years (SD=8). Mean baseline disease activity measured using DAS28-ESR or CRP are respectively, 4.1 and 4.0. Drugs survival analysis showed no significant difference between groups: Anti-TNF monotherapy versus combination with MTX only, or with MTX + other csDMARDs or with a non-MTX csDMARDs (p=0.09). Drugs survival analysis for each of the anti-TNF (adalimumab, etanercept or golimumab) did not demonstrate a significant difference when adding MTX +/- other csDMARDs. As for infliximab (IFX) used in combination with MTX +/- other csDMARDs showed a trend towards better retention (p=0.07). Multivariate analysis showed that anti-TNF in combination with MTX and at least one other csDMARDs was a predictor of improved retention (HR 0.49, 95% CI 0.31-0.78, p=0.003). Smoking, female gender and higher DAS28 (CRP) were associated with increased drug discontinuation. Main reason for treatment discontinuation in all groups was lack of efficacy.

Conclusion: In this real world analysis, anti-TNF therapy in combination with csDMARDs vs monotherapy, did not significantly influence the biologic long-term retention, except for IFX, where a tendency was observed. Combination therapy with MTX and at least another csDMARDs is a predictor of better retention whereas smokers, women and patients with higher DAS28 (CRP) were more likely to discontinue therapy.

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Abstract Number: 2515

Patient-Reported Outcomes in Two Randomized, Controlled Trials (RCTs) in Patients with Rheumatoid Arthritis (RA) Treated with Tocilizumab (TCZ) Monotherapy Compared with Methotrexate (MTX) or Adalimumab (ADA)

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Background/Purpose: Patient-reported outcomes (PROs) are important measures when determining response to therapy in patients with RA. Previous RCTs have shown that TCZ monotherapy is superior to both MTX alone and ADA monotherapy for improving RA disease activity.[1,2] These post hoc analyses compared the efficacy of TCZ monotherapy with MTX or ADA monotherapy for improvement of PROs in 2 RCT populations, providing change in Clinical Disease Activity Index (CDAI) as a reference.

Methods: AMBITION and ADACTA were independent RCTs evaluating the efficacy and safety of TCZ compared with MTX or ADA, respectively, in patients with active RA. In AMBITION, patients who were MTX-naive or had discontinued MTX ≥ 6 months prior to baseline without previous inadequate responses to MTX or tumor necrosis factor inhibitors received TCZ 8 mg/kg IV every 4 weeks or MTX. In ADACTA, biologic-naive patients intolerant to or inappropriate for MTX received TCZ 8 mg/kg IV every 4 weeks or ADA 40 mg SC every 2 weeks. PROs, assessed at 24 weeks, included patient global assessment (PtGA; visual analog score [VAS], 0-100 mm), pain (VAS), Health Assessment Questionnaire Disability Index (HAQ-DI, 0-3), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue (0-52) and Short Form (SF)-36 (0-100). The proportions of patients reporting PRO scores ≥ minimum clinically important differences (MCID) as well as ≥ age/sex-matched normative values were assessed for each treatment group.

Results: In both RCTs, patients receiving TCZ reported greater improvements across all PROs at week 24 compared with MTX or ADA. In AMBITION, 45.0-84.0% of patients who received TCZ reported scores ≥ MCID in PtGA, pain, HAQ, FACIT, SF-36 PCS/MCS and all domains at week 24 compared with 39.4-81.8% with MTX (**Table 1**); 24.3-52.1% who received TCZ reported scores ≥ normative values in HAQ (< 0.5), FACIT (≤ 40), SF-36 PCS/MCS (≥ 50) and all domains compared with 14.5-45.0% with MTX (**Table 2**). In ADACTA, 57.7-83.3% of patients who received TCZ reported scores ≥ MCID in PtGA, pain, HAQ, FACIT, SF-36 PCS/MCS and all domains at week 24 compared with 50.8-75.6% with ADA (**Table 1**); 22.1-49.3% who received TCZ reported scores ≥ normative values in HAQ, FACIT, SF-36 PCS/MCS and all domains compared with 13.6-37.8% with ADA (**Table 2**).

Conclusion: Consistent with the CDAI responses from these RCTs, TCZ monotherapy resulted in

more patients achieving MCID and normative values, indicative of clinically meaningful improvements, in PROs compared with either MTX or ADA monotherapy in AMBITION and ADACTA. **References:**

1. Jones G, et al. *Ann Rheum Dis*. 2010;69:88-96.

2. Gabay C, et al. *Lancet*. 2013;381:1541-1550.

Table 1. LSM changes from baseline in PROs at 24 weeks in the AMBITION and ADACTA trial populations.[1,2]

	AMBITION†					ADACTA†				
	LSM Change from Baseline‡		**Change ≥ MCID§, %**		**NNT//**	**LSM Change from Baseline‡**		**Change ≥ MCID§, %**		**NNT//**
	TCZ	**MTX**	**TCZ**	**MTX**		**TCZ**	**ADA**	**TCZ**	**ADA**	
Patient global	−33.5	−29.5	79.8	73.5	15.9	−42.3***	−31.8	82.6	75.6	14.3
Patient pain	−31.5	−29.5	78.9	74.0	20.4	−40.1***	−28.7	83.3**	70.1	7.5
HAQ-DI	−0.7*	−0.5	77.0*	67.8	11.0	−0.7	−0.5	71.3	64.8	15.4
FACIT-fatigue	8.7*	5.7	68.6*	55.7	7.8	11.4	8.9	71.5	61.9	10.4
SF-36 PCS	9.8*	7.8	77.4	77.6	−426.9	9.2	7.6	75.4	70.8	21.7
SF-36 MCS	6.8	4.8	64.3	56.6	12.9	7.9**	5.0	66.4***	50.8	6.4
Physical functioning	23.0*	16.5	76.3	71.7	21.7	20.0	16.0	74.3	70.4	25.7
Role - physical	37.3	29.8	58.3*	49.1	10.9	23.8**	16.4	71.5	63.0	11.7
Bodily pain	30.4*	24.8	84.0	81.8	46.9	29.3	23.8	79.6	74.3	18.9
General health	12.7	9.6	67.4	65.8	62.7	10.7	7.6	57.7	60.4	−35.9
Vitality	19.5*	12.9	78.9*	72.1	14.5	19.1**	14.0	78.8***	62.2	6.0
Social functioning	21.5*	16.4	68.3	61.0	13.7	23.4**	17.1	70.1	63.0	14.1
Role - emotional	28.5	22.2	45.0	39.4	17.8	15.4	9.7	58.1	53.3	21.0
Mental health	14.3*	10.2	62.0	52.2	10.2	13.5	9.3	70.6	60.7	10.2
CDAI	−25.6*	−19.8	–	–	–	−23.8***	−18.9	–	–	–

ADA, adalimumab; CDAI, Clinical Disease Activity Index; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; LSM, least squares mean; MCID, minimum clinically important difference; MCS, mental component summary score; MTX, methotrexate; NNT, number needed to treat; PCS, physical component summary score; PROs, patient-reported outcomes; SF-36, Short Form-36; TCZ, tocilizumab.

* Statistical significance is demonstrated by the lower limit of the 95% CI of TCZ – MTX > 0.

** $P < 0.05$; *** $P < 0.01$.

† Analyses were performed using the per-protocol population in AMBITION (TCZ, N = 265; MTX, N = 259) and the intention-to-treat population (TCZ, N = 163; ADA, N = 162) in ADACTA.

‡ Adjusted for site (AMBITION)/region (ADACTA), baseline score (ADACTA) and duration of RA.

§ MCIDs for PROs were defined as follows: HAQ-DI ≥ 0.22; patient global assessment, ≥ 10; patient pain, ≥ 10; FACIT-Fatigue, ≥ 4; SF-36 PCS/MCS ≥ 2.5; SF-36 domains ≥ 5.0.

// NNT is the number of patients who need to be treated with TCZ for one patient to benefit vs treatment with MTX or ADA. A negative number indicates benefit of MTX or ADA over TCZ.

[1] Webster K, et al. *Health Qual Life Outcomes*. 2003;1:79.

[2] Strand V, et al. *J Rheumatol*. 2011;1720-1727.

Table 2. Proportion of patients with ≥ age/gender-matched normative PRO scores at baseline and 24 weeks in the AMBITION and ADACTA trial populations.[1-3]

	Patients With Scores ≥ Normative Values†, %							
	AMBITION‡				ADACTA‡			
	Baseline		Week 24		Baseline		Week 24	
	TCZ	MTX	TCZ	MTX	TCZ	ADA	TCZ	ADA
HAQ-DI	9.1	8.1	38.3	31.6	5.0	3.7	37.4	26.6
FACIT-fatigue	14.5	15.4	47.1	34.7	9.3	9.3	42.4	37.8
SF-36 PCS	1.5	0.8	24.3	14.5	1.9	2.5	22.1	13.6
SF-36 MCS	23.6	24.2	44.3	42.1	21.1	20.8	49.3	36.4
Physical functioning	5.3	5.4	31.8	22.9	3.7	6.8	25.4	18.4
Role - physical	4.5	5.1	34.0	26.4	1.2	6.2	27.3	17.0
Bodily pain	3.4	1.2	38.3	25.5	3.7	2.5	35.3	27.9
General health	10.3	12.9	29.8	21.4	9.9	6.3	23.0	21.5
Vitality	15.8	15.1	52.1	36.5	6.8	9.9	38.8	32.6
Social functioning	10.9	11.6	36.2	26.4	12.4	12.3	39.6	31.9
Role - emotional	24.4	25.3	45.9	45.0	17.4	19.1	34.1	28.9
Mental health	21.1	24.8	43.8	40.7	13.0	17.9	40.6	31.1

ADA, adalimumab; FACIT, Functional Assessment of Chronic Illness Therapy; HAQ-DI, Health Assessment Questionnaire Disability Index; MCS, mental component summary score; MTX, methotrexate, PCS, physical component summary score; PROs, patient-reported outcomes; SF-36, Short Form-36; TCZ, tocilizumab.

† Normative values were defined as age/gender matched scores in a population of subjects without RA or comorbid conditions: HAQ-DI, ≤ 0.5; FACIT-Fatigue, ≥ 40; SF-36 PCS/ MCS, ≥ 50; SF-36 domains, AMBITION population: physical functioning, ≥ 78.8; role – physical, ≥ 79.1; bodily pain, ≥ 67.4; general health, ≥ 68.2; vitality, ≥ 56.6; social functioning, ≥ 81.7; role – emotional, ≥ 85.0; mental health, ≥ 72.9; SF-36 domains, ADACTA population: physical function, ≥ 78.3; role - physical, ≥ 79.0; bodily pain, ≥ 68.1; general health, ≥ 69.3; vitality, ≥ 58.3; social functioning, ≥ 83.4; role – emotional, ≥ 86.3; mental health, ≥ 75.1.

‡ Analyses were performed using the per-protocol population in AMBITION (TCZ, N = 265; MTX, N = 259) and the intention-to-treat population in ADACTA (TCZ, N = 163; ADA, N = 162).

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Abstract Number: 2516

Concomitant Use of Oral Vs. Subcutaneous Methotrexate at Biologic Initiation: A Comparison of Biologic Treatment Survival in a Rheumatoid Arthritis Cohort

Carter Thorne[1], Mohammad Movahedi[2], Angela Cesta[2], Xiuying Li[2], Emmanouil Rampakakis[3], John S. Sampalis[4] and Claire Bombardier[5], [1]University of Toronto and Southlake Regional Health Centre, Newmarket, ON, Canada, [2]Toronto General Hospital Research Institute, University Health Network, Toronto, ON, Canada, [3]JSS Medical Research, St-Laurent, QC, Canada, [4]McGill University, Montreal, QC, Canada, [5]University of Toronto, Toronto, ON, Canada
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SESSION INFORMATION

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Background/Purpose: Previous studies have shown differences in the effectiveness and survival of subcutaneous vs. oral methotrexate. Furthermore, concurrent methotrexate therapy has been shown to enhance the efficacy of anti-TNFs. The purpose of this study was to describe the pattern of methotrexate utilization in RA patients initiating biologic treatment in a large observational cohort and to compare the impact of methotrexate route of administration and dose on biologic durability in real-life.

Methods: Patients enrolled in the Ontario Best Practice Research Initiative (OBRI) initiating combination therapy with a biologic and methotrexate were included. Analysis was primarily descriptive. Cox regression was used to examine the impact of methotrexate route of administration and dose at baseline on biologic durability. Methotrexate dose was classified as low (≤15 mg/week), moderate (15-20 mg/week), and high (>20 mg/week).

Results: Among 2,585 RA patients enrolled in OBRI, 885 initiated biologic therapy. Of the latter, 517 (58.4%) were treated concomitantly with methotrexate and were included in the analysis. Mean (SD) age and disease duration were 55.8 (13.1) years and 9.2 (9.8) years, respectively, while the majority were females (78.9%) and treated with an anti-TNF agent (83.0%). Overall, 271 (52.4%) were treated with oral methotrexate and 236 (45.6%) with subcutaneous without any significant differences between biologic types. The predominant dose was 15-20 mg/week for oral methotrexate (43.2% of patients) and >20 mg/week for subcutaneous use (47.0%). Mean (SD) disease parameters at baseline were: DAS28 = 4.6 (1.4); swollen joint account = 6.3 (4.9); tender joint count = 6.9 (6.4); physician global = 5.1 (2.4); patient global = 5.3 (2.7). Over a mean (SD)

follow-up of 1.8 (1.5) years biologic discontinuation was reported for 39.5% of patients. Neither route of administration [$HR_{SC\text{-}Oral}$ (95%CI) = 1.2 (0.9-1.6)] nor dose [$HR_{Moderate\text{-}Low}$ (95%CI) = 1.05 (0.74-1.49); $HR_{High\ vs.\ Low}$ (95%CI) = 1.08 (0.76-1.53)] of methotrexate at baseline were significantly associated with biologic discontinuation. Similar results were observed upon adjusting for gender, baseline age, disease duration, and DAS28.

Conclusion: This analysis has shown that subcutaneous methotrexate is used in Canadian routine care in a significant proportion of patients which is higher than that in other international registries. Neither route of administration nor dose of methotrexate were significant predictors of biologic durability despite the fact that previous studies have shown differences in efficacy when methotrexate is used without a biologic. Additional analyses considering changes over time in the mode of methotrexate administration are required to further validate these findings.

Disclosure: C. Thorne, None; **M. Movahedi**, None; **A. Cesta**, None; **X. Li**, None; **E. Rampakakis**, employee of JSS Medical Research, 3; **J. S. Sampalis**, Employee of JSS Research, 3; **C. Bombardier**, None.

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Abstract Number: 2517

Long-Term Stability of the 5-Item Compliance Questionnaire Rheumatology As a Measure of Adherence in Patients with Rheumatoid Arthritis

Raquel Sweezie[1], **Mary Bell**[2], Charles H. Goldsmith[3], Imy Chiu[4], Anna Gutlin[4] and Sharron Sandhu[5], [1]Division of Rheumatology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Simon Fraser University, Vancouver, BC, Canada, [4]Rheumatology, Sunnybrook Health Sciences Centre, Toronto, ON, Canada, [5]Medicine, University of Toronto, Toronto, ON, Canada

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Background/Purpose: Adherence to disease modifying anti-rheumatic drug (DMARD) therapy is suboptimal in patients with rheumatoid arthritis (RA). Efficient, low-cost measures are required for optimal monitoring of medication adherence in the rheumatology clinic. Self-report tools are the most efficient and cost-effective measures available. Recently, a 5-item version of the Compliance Questionnaire Rheumatology (CQR5) was developed from the original 19-item version and was validated in a group of RA patients[1]. We also recently demonstrated that the CQR5 exhibits excellent test-retest reliability and significant correlation with medication beliefs in people with RA in the short-term[2], however long-term stability of the questionnaire remains unknown. Therefore, in the same group of patients, we investigated 1) test-retest reliability of the CQR5 and 2) correlation of the CQR5 with medication beliefs in the long term.

Methods: RA patients (disease duration ≥ 1 yr) taking at least one DMARD prescription were randomly selected from a rheumatology outpatient clinic database. Patients were assessed at baseline and three months. At each visit, medication adherence was assessed with the CQR5. Each item on the CQR5 was scored on a four point Likert scale (1 = strongly disagree, 4 = strongly agree). Scores for each item were then summed into a total score which varied between 0 and 20. Higher scores indicated greater adherence. Medication Beliefs were evaluated using the Beliefs about Medicines Questionnaire (BMQ)[3], which examines beliefs around concern, necessity, harm and overuse of taking medications (high scores reflect strong beliefs). Intraclass correlation coefficients (ICC) were used to evaluate test-retest reliability, and bivariate correlations (Pearson's r) were performed to determine relationships between medication adherence measured by CQR5 and medication beliefs measured with the BMQ.

Results: 100 RA patients, [age, mean (SD) = 60.75(12.67) yrs], were recruited and 10 dropped out of the study by three months. In this sample (n=90), the CQR5 demonstrated good test-retest reliability (ICC=0.73, 95% confidence interval = 0.61-0.81; Cronbach's $\alpha = 0.84$). At 3 months, adherence measured by CQR5 also had a significant positive correlation with BMQ necessity scores ($r = 0.67$, $p<0.01$) and significant negative correlations with BMQ concerns ($r = -0.24$, $p<0.05$), harm ($r = -0.39$, $p<0.01$), and overuse ($r = -0.44$, $p<0.01$) scores.

Conclusion: The CQR5 demonstrates long-term stability by maintaining its reliability and ability to predict medication beliefs over time. A more in-depth investigation of the predictive validity of the CQR5 using multiple chain imputation and multivariate analysis is currently underway.

References:

1) BMC Musculoskeletal Disorders. 2013; 14:286 2) Arthritis & Rheumatology. 2015; 67(suppl 10): Abstract # 2649 3) Psychology & Health. 1999; 14: 1

Disclosure: R. Sweezie, None; **M. Bell**, None; **C. H. Goldsmith**, None; **I. Chiu**, None; **A. Gutlin**, None; **S. Sandhu**, None.

Abstract Number: 2518

Intensive Treatment for Rheumatoid Arthritis Reduces Disease Activity over Time

Nicola J Gullick[1], Fowzia Ibrahim[2], Aneela Mian[1], Alexandra Vincent[3], Gabriel Panayi[1], Brian Tom[4], David L. Scott[1] and Bruce Kirkham[3], [1]Rheumatology, King's College London, London, United Kingdom, [2]Academic Rheumatology Dept, King's College London, London, United Kingdom, [3]Rheumatology, Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom, [4]Biostatistics Unit, Medical Research Council, Cambridge, United Kingdom

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Session Time: 9:00AM-11:00AM

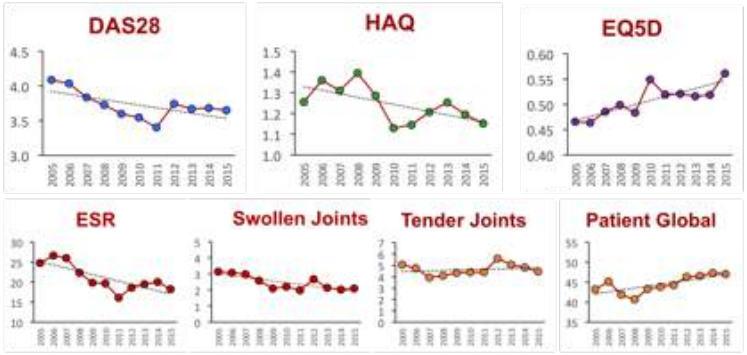
Background/Purpose: There has been increasing emphasis on intensive treatment of RA but little direct evidence of the impact of such strategies on long term outcome. We evaluated disease activity and outcomes in a prospective observational cohort study over 10 years at a single unit aiming to treat to a target DAS28<2.6.

Methods: We included 1,693 patients seen on 10,773 occasions between 2005 and 2015. At first visit, mean age was 55 years with mean disease duration 10 years. Treatments comprised DMARDs often in combination, and a range of biologics. DAS28, HAQ and quality of life (EQ5D) were recorded at each visit. Temporal changes were assessed by descriptive statistics and maximum likelihood regression models. To further understand outcome in different mean DAS28 categories, we also assessed a subgroup of 714 patients with ³5 follow-up visits between 2010 and 2015 (6728 visits). Mean HAQ, EQ5D and treatment were assessed for each group.

Results: 10 year follow up Mean DAS28 scores fell from 4.1 to 3.7 between 2005 and 2015. Mean HAQ fell from 1.26 to 1.15 and mean EQ5D scores improved from 0.47 to 0.56. Regression models showed annual changes for DAS28 scores were -0.03 (95% confidence intervals -0.04, -0.02), HAQ -0.019 (95% CI -0.025,-0.013) and EQ5D 0.006 (95% CI 0.003, 0.008). The number of patients with high disease activity (DAS28>5.1) decreased from 25% to 16% while DAS28 remission increased from 18% to 27%. The four components of DAS28 showed divergent patterns of change. Mean swollen joint count fell from 3.1 to 2.1 (33%), mean ESR fell from 25 to 18 (26%), and mean tender joint count fell from 5.0 to 4.5 (12%). Mean patient global responses increased by 9% (43.2 to 47.1). Impact of DAS28 category 154/714 (22%) had persistent high disease activity. Compared to patients in remission, HAQ was increased by 1.06, and EQ5D reduced by 0.27. All

groups had similar DMARD use, including combination DMARDs. Only 64 (9%) patients with persistent high disease activity were receiving biologics, compared to 18-20% of other groups (P=0.034). This variation results from failure to respond to biologics, an unwillingness to take them, or contraindications to their use.

Conclusion: Intensive management regimens are associated with progressive improvement in disease activity, function and quality of life. Improvements are seen across all strata of disease activity levels with less active disease and more remissions. However, patient global scores do not improve which requires further investigation. A minority of patients have continued high disease activity with substantial disability and reduced quality of life. This group of patients are less likely to receive biologics. Individualised strategies may be required for this group including novel therapies or psychological interventions.



Disclosure: **N. J. Gullick**, None; **F. Ibrahim**, None; **A. Mian**, None; **A. Vincent**, None; **G. Panayi**, None; **B. Tom**, None; **D. L. Scott**, None; **B. Kirkham**, Abbvie, Novartis and Roche, 2,Abbott, BMS, Chugai, MSD, Novartis, Pfizer, Roche and UCB, 5,Abbott, BMS, Chugai, MSD, Novartis, Pfizer, Roche and UCB, 8.

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Abstract Number: 2519

Predictors of Flare in Rheumatoid Arthritis Patients Treated Preventively with Rituximab: A Prospective Study Using Ultrasound and Patient Reported Outcomes

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Title: Predictors of flare in rheumatoid arthritis patients treated preventively with rituximab: a prospective study using ultrasound and patient reported outcomes

Background/Purpose: Rituximab (RTX) is an effective and relatively safe treatment for rheumatoid arthritis (RA). Following treatment, controversy remains on how best to optimise further retreatment while limiting risks of cumulative immunosuppression and cost. At UCLH/UCL RA patients are offered individualized preventive retreatment with RTX based on the duration of their response to initial treatment. This strategy, while allowing continued control of disease activity in many patients with flare prevention may lead to patient overtreatment. The aim of this study was to identify predictors of flare in patients with RA 1 month prior to RTX retreatment.

Methods: A prospective study of 18 RA patients retreated with RTX preventively, were assessed 4 weeks prior to scheduled RTX retreatment where clinical and laboratory assessment, US of wrists and small joints of the hands were performed. Patient reported outcomes (PROs) (HAQ (health assessment questionnaire), Facit-F (functional assessment of chronic illness therapy), SF-36 (short form health survey), EuroQol 5D 3L) were completed weekly until RTX retreatment 4 weeks later. At this time point clinical assessment and US scan were repeated. The study is ongoing.

Results: We have so far studied 11 females and 7 males, with a mean age of 64 years. The patients were assessed at mean 7.2 months after their previous RTX treatment. At initial assessment (week 0) 66.7% (12/18) of patients remained depleted (CD19 count <0.005) while 33.3% (6/18) had already started repopulating. ESR and CRP increased, decreased or remained stable as shown in Figure 1. The number of joints with synovial hypertrophy (SH) on US increased in 61.1%, and decreased in 27.8%. The number of joints showing power Doppler (PD) increased in 27.8%, and reduced in 33.3%. All patients with PD (9/18) on US, reported worsening of their joint pain and/or early morning stiffness. Surprisingly, the general VAS and DAS28 scores decreased by13.3% and 34.9% respectively in the majority of patients, (44.4% and 77.8% respectively) from week 0 to week 4. The weekly PROs were completed by 9/18 patients. HAQ, Facit-F and physical component summary (PCS) of SF-36 scores showed similar changes. The mental component summary (MCS) of SF-36 increased in 33.3% with no change in 44.4%. EuroQol 5D 3L scores increased in 22.2%.

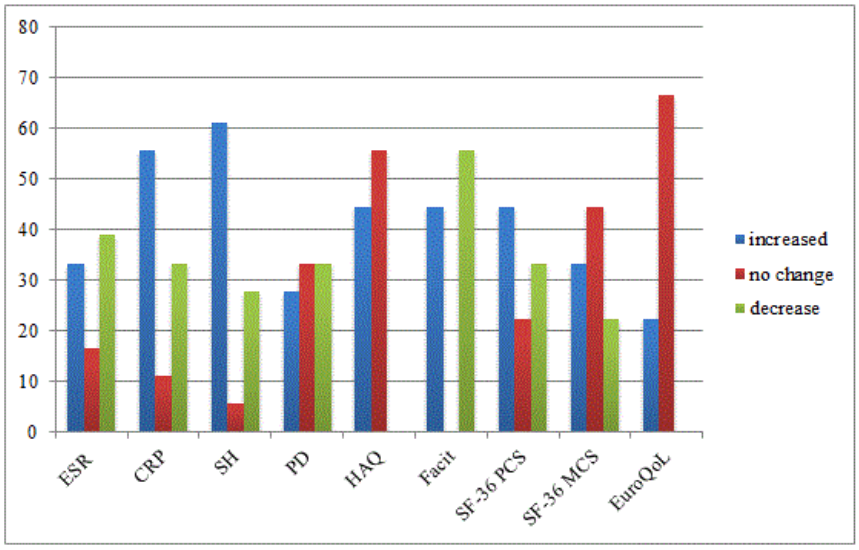

Figure 1. Percentages of all variables changing from week 0 to week 4.

Figure 1. Percentages of all variables changing from week 0 to week 4.

Conclusion: The data of this study which is ongoing, does not show any consistent pattern of variation within 4 weeks prior to RTX retreatment, and baseline assessments at week 0 did not seem to predict stability or worsening of symptoms in the following 4 weeks. The variables increased, decreased or remained the same in almost similar patient numbers. The ESR, CRP and SH on US showed an increase over the 4 week period. All patients with PD on US reported symptoms. Assessment of patients 1 month before preventive retreatment with RTX does not seem to be able to predict which patients are likely to be flaring shortly.

Disclosure: M. Ismajli, None; **M. J. Leandro**, None.

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Abstract Number: 2520

Multi-Biomarker Disease Activity (MBDA) Score and Prediction of Radiographic Progression in a Randomized Study of Patients with Early RA Treated with Methotrexate Alone or with Adalimumab

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Ching Chang Hwang[5], Xingbin Wang[4], Rebecca J. Bolce[4], Eric H. Sasso[4], Kim Hørslev-Petersen[6], Kristian Stengaard-Pedersen[7], Lykke Midtbøll Ørnbjerg[8], Peter Junker[9], Torkell Ellingsen[10], Palle Ahlquist[11], Hanne Lindegaard[12], Asta Linauskas[13], Annette Schlemmer[14], Mette Yde Dam[15], Ib Tønder Hansen[16], Tine Lottenburger[11], Christian G. Ammitzbøll[17], Anette Jørgensen[17], Sophine B. Krintel[8], Johnny Lillelund Raun[18] and Merete Lund Hetland[3,19], [1]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark, Glostrup, Denmark, [2]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark, Copenhagen, Denmark, [3]Danish Rheumatologic Biobank and DANBIO registry, Rigshospitalet, Glostrup, Gentofte and Herlev University Hospital, Copenhagen, Denmark, [4]Crescendo Bioscience Inc., South San Francisco, CA, [5]Biostatistics, Crescendo Bioscience Inc., South San Francisco, CA, [6]King Christian X Hospital for Rheumatic Diseases, Graasten, Denmark, [7]Rigshospitalet (Glostrup and Blegdamsvej), Århus University Hospital, Odense University Hospital, Herlev/Gentofte Hospital, Slagelse Sygehus, Chr X hospital (University of South Denmark) and Zitelab Aps, DANBIO Registry and Departments of Rheumatology, Copenhagen, Denmark, [8]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Copenhagen, Denmark, [9]Department of Rheumatology C, Odense University Hospital, Odense, Denmark, [10]Department of Rheumatology, Odense University Hospital, Odense, DK, Odense, Denmark, [11]Department of Medicine, Vejle Regional Hospital, Vejle, Denmark, [12]The DANBIO registry and the Danish Departments of Rheumatology, Odense, Denmark, [13]The DANBIO registry and the Danish Departments of Rheumatology, Copenhagen, Denmark, [14]9Department of Rheumatology, Aalborg University Hospital, Aalborg, Denmark, [15]Diagnostic Centre, Silkeborg Regional Hospital, Silkeborg, Denmark, [16]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [17]Department of Rheumatology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark, [18]King Christian X Hospital for Rheumatic Diseases, South Jutland Hospital, Graasten, Denmark, [19]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark,, Copenhagen, Denmark
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Background/Purpose: The multi-biomarker disease activity (MBDA) score, which combines 12 serum biomarkers to measure RA disease activity on a scale of 1−100, has been found to be predictive of risk for radiographic progression.[1] The objectives of this study were to evaluate early RA patients from the randomized double-blinded OPERA trial for: 1) associations between baseline (BL) MBDA score and 12-month radiographic outcomes; 2) the value of adding MBDA score to

anti-CCP for predicting radiographic progression.

Methods: In the OPERA trial, treatment-naive early RA patients (N=180) with moderate or high DAS28 were randomized to treatment with oral methotrexate and either adalimumab (ADA) (n=89) or placebo (n=91). Glucocorticoids were injected into up to 4 swollen joints per visit.[2] X-rays of hands and feet (n=164) from months 0 and 12 were assessed with the Sharp van der Heijde Total Sharp Score (TSS). The smallest detectable change (1.8 TSS units) defined radiographic progression (DTSS≥2). Anti-CCP status was dichotomized. MBDA score was determined at 0 and 3 months. Correlations between BL or change (D) MBDA score and radiographic progression were analyzed by Spearman´s rank correlation coefficient (r). Chi-Square test was used for comparisons. A logistic regression model, adjusted for BL demographics and disease activity measures, assessed association between MBDA score and radiographic progression.

Results: Patients had median (range) age 55 (19-86) years, disease duration 84 (42-214) days; 66% were female; 72% were positive for RF and 65% for anti-CCP. Median values at BL were DAS28-CRP 5.6 (3.3-8.6), MBDA score 59 (12-90) and TSS 2 (0-31). 42 patients had DTSS ≥ 2, median DTSS = 3 (2-22)/mean DTSS = 4.52 (3.84). BL MBDA score correlated with DTSS in the placebo (r=0.23, p=0.04) but not the ADA group (r=0.10, P=0.35). ΔMBDA score$_{0\text{-}3\text{months}}$ was not correlated with DTSS. Patients with high BL MBDA score (>44) were more likely to progress radiographically (31%), while only 1/31 (3%) patients with MBDA score ≤44 progressed (p<0.01), and this was significant also for each treatment group. Moderate/high BL DAS28-CRP was not associated with radiographic progression (Figure 1A, B). BL MBDA score (OR=1.03 per unit increase [1.01-1.06]), and anti-CCP (OR=4.45 if positive [1.66-11.95]) were significantly associated with RP in multivariate analyses. 34% of anti-CCP positive and 12% of anti-CCP negative patients had RP (p<0.002). No anti-CCP+ patients with MBDA score ≤44 progressed radiographically, whereas stratifying by DAS28-CRP had no added value to anti-CCP alone (Figure 1C, D)

Conclusion: High BL MBDA score (>44) was a strong, independent predictor of radiographic progression and added value to anti-CCP status. Only 3% of patients with low or moderate BL MBDA score (≤44) progressed radiographically. (1) Hirata et al. Current Biomarker Findings 2015, 5:69-78 (2) Hørslev-Petersen K, et al., Ann Rheum Dis 2014; 73:654-661

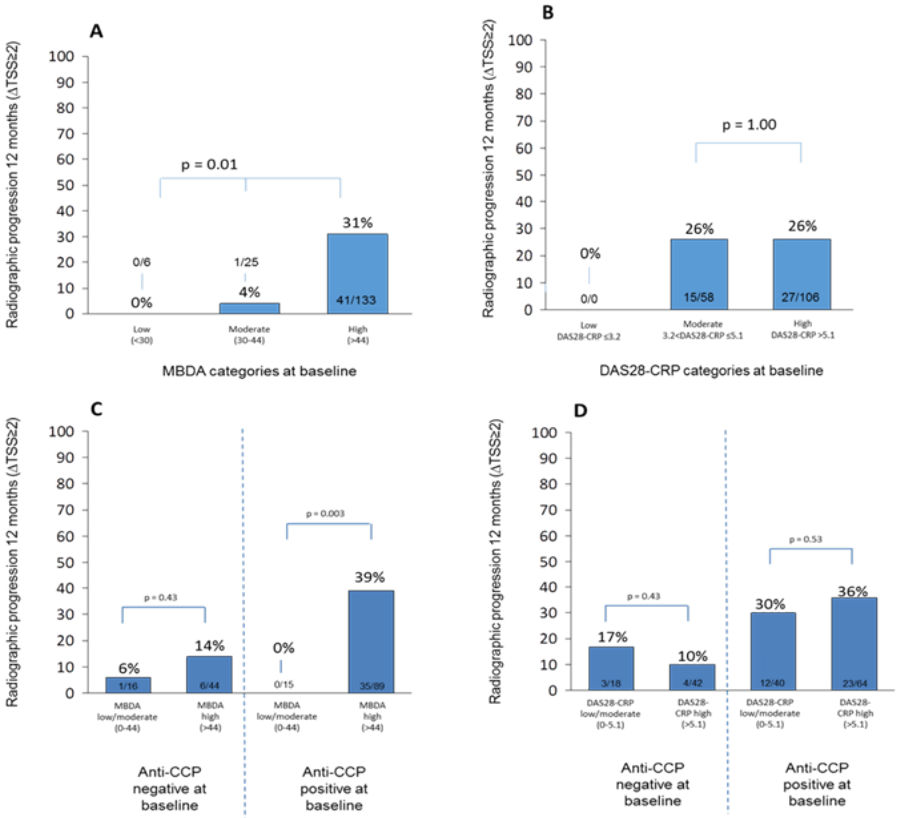

Figure 1: Risk of radiographic progression in 164 patients with early RA stratified by baseline MBDA score (A) and baseline DAS28-CRP (B). No patients with low DAS28-CRP had been included in the trial.
The value of adding baseline MBDA score (C) or DAS28-CRP (D) to anti-CCP status in calculating the risk of progression.
P-values calculated by Pearson Chi-square

Disclosure: **C. H. Brahe**, None; **M. Østergaard**, Abbott Immunology Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Boehringer Ingelheim, 2,Eli Lilly and Company, 2,Merck Pharmaceuticals, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,UCB, 2,Celgene, 2,Sanofi-Aventis Pharmaceutical, 2,Regeneron, 2,Novartis Pharmaceutical Corporation, 2; **J. S. Johansen**, None; **N. A. Defranoux**, Crescendo Bioscience Inc., 1,Crescendo Bioscience Inc., 3; **C. C. Hwang**, Crescendo Bioscience Inc., 1,Crescendo Bioscience Inc., 3; **X. Wang**, Crescendo Bioscience Inc., 3; **R. J. Bolce**, Crescendo Bioscience Inc., 3; **E. H. Sasso**, Crescendo Bioscience, 9; **K. Hørslev-Petersen**, None; **K. Stengaard-Pedersen**, None; **L. M. Ørnbjerg**, None; **P. Junker**, None; **T. Ellingsen**, None; **P. Ahlquist**, None; **H. Lindegaard**, Novartis, Eli Lilly DK, Boehringer Ingelheim Danmark, MSD Denmark, 5; **A. Linauskas**, None; **A. Schlemmer**, None; **M. Yde Dam**, None; **I. Tønder Hansen**, None; **T. Lottenburger**, None; **C. G. Ammitzbøll**, None; **A. Jørgensen**, None; **S. B. Krintel**, None; **J. L. Raun**, None; **M. Lund Hetland**, AbbVie, BMS, MSD, Roche, Pfizer, UCB, Crescendo, 2.

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Abstract Number: 2521

Lower Baseline 14-3-3η Levels Are Associated with Better Patient Reported Outcomes in Tocilizumab Treated Patients

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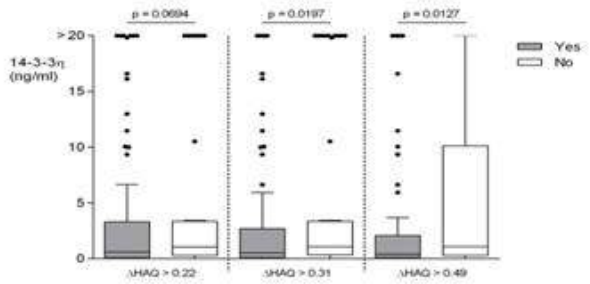
Background/Purpose: Serum 14-3-3η is a mechanistic marker that is involved in the pathogenesis of RA and is a potent up-regulator of IL-6. We previously reported that baseline 14-3-3η levels were significantly lower in a cohort of 49 established RA patients who achieved better clinical outcomes when treated with Tocilizumab. Recently there has been increased interest in assessing therapy response using alternative measures to DAS that are independent of CRP, including patient reported outcomes such as HAQ-DI. The aim of this study was to validate whether lower baseline levels of 14-3-3η is associated with and independently predicts clinical response in RA patients treated with tocilizumab.

Methods: Serum 14-3-3η levels were measured in a cohort of 106 Japanese patients prior to the initiation of tocilizumab therapy (BL). 14-3-3η positivity was defined by the diagnostic cut-off of ≥ 0.19 ng/ml, and 2 and 4 times that, at 0.40 and 0.80 ng/ml, respectively. Patients were sub-grouped according to changes in HAQ-DI based on the minimal clinically important difference (MCID) of ≥ 0.22, ≥ 0.31, and ≥ 0.49. Group differences were assessed by Mann-Whitney U-test. ROC curve analysis was performed to identify the optimal 14-3-3η cut-point for a ΔHAQ-DI ≥ 0.49. Uni- and multi-variable analysis controlling for baseline HAQ-DI was used to assess 14-3-3η's independence of other clinical/serological variables at informing patient reported outcomes.

Results: At baseline, 75 (71%) of the 106 patients were 14-3-3η positive. At year 1, 70 (66%), 58 (55%) and 52 (40%) of the 106 patients achieved changes in HAQ-DI of ≥ 0.22, ≥ 0.31, and ≥ 0.49, respectively. Baseline HAQ-DI values were significantly higher in those patients that achieved a Δ HAQ-DI ≥ 0.22 when compared with those that did not; $p = 0.009$. The HAQ-DI values were also significantly higher at the two other HAQ-DI cut-points (≥ 0.31, and ≥ 0.49), $p < 0.0001$. As shown in the Figure, serum 14-3-3η levels were significantly lower in patients that achieved HAQ-DI MCID of > 0.31 and >0 .49. In patients who achieved a ΔHAQ-DI ≥ 0.49, ROC analysis returned the best cut-off of ≤ 0.18 ng/ml yielding a specificity of 83.3% (95%CI: 70.7-92.1) and sensitivity of 42.3% (95%CI: 28.7-56.8), LR = 2.5. By univariate analysis, all three 14-3-3η cut-points were significantly associated with better clinical outcomes. Multi-variable modeling controlling for BL

HAQ-DI indicated that lower levels of 14-3-3η, age and disease duration, but not CRP, were independent predictors of achieving the HAQ-DI MCID outcomes.

	14-3-3η positivity cut-off					
	≤ 0.19 ng/ml		≤ 0.40 ng/ml		≤ 0.80 ng/ml	
	LR	p-value	LR	p-value	LR	p-value
ΔHAQ 0.22	>6.75	0.0098	2.36	0.0950	0.94	0.2222
ΔHAQ 0.31	>9.57	0.0021	6.18	0.0114	3.56	0.0456
ΔHAQ 0.49	>8.61	0.0034	6.61	0.0090	3.88	0.0382



Conclusion: Lower serum 14-3-3η levels prior to the initiation of therapy independently predicts better patient reported outcomes in patients treated with tocilizumab. The predictive capacity of 14-3-3η at informing therapy response to anti-IL-6 therapy should be investigated across all anti-IL-6 compounds.

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Abstract Number: 2522

Pharmacomicrobiomics of Methotrexate: Baseline Intestinal Microbiota Correlates with Therapeutic Response

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Background/Purpose: Despite significant advances in the therapeutics of inflammatory arthritides, methotrexate (MTX) remains the mainstay of treatment for rheumatoid arthritis (RA) and related conditions worldwide. However, it has a hihgly variable inter-individual bioavailabity (ranging from 20 to 80%) and there is currently no mechanism to predict efficacy. One of the fundamental roles of the intestinal microbiome is to metabolize xenobiotics and synthetic drugs. Here we characterize the effects of oral methotrexate on the gut community composition of patients with RA and the potential role of baseline human microbiota in predicting response to MTX therapy.

Methods: Demographic characteristics, drug use and disease activity scores-28 (DAS28) were recorded from new-onset rheumatoid arthritis (NORA) patients (n=33). For each participant, fecal samples were collected at baseline and at pre-established intervals for at least 3 months after initiation of oral methotrexate (range 3-48 months). 16S rDNA was extracted per protocol (MoBio, USA) and amplicons targeting the hypervariable V4 region were sequenced using 454 and MiSeq (Illumina) platforms to define the microbiota composition. The obtained 16S rRNA sequences were analyzed using the Quantitative Insights into Microbial Ecology (QIIME) pipeline. Taxonomic relative abundance at all hierarchical levels was determined to establish baseline microbiota composition prior to MTX initiation. Two-tailed Wilcoxon non-parametric test was applied to identify significant microbiota taxonomic changes that occur after MTX therapy. The False Discovery Rate (FDR) approach was applied to adjust for multiple hypothesis testing. Changes with a $P<0.05$ and $FDR<0.2$ were considered significant.Spearman correlations between baseline relative composition of intestinal microbiota and clinical response to MTX at each time point were also applied.

Results: To quantify microbiota similarities among fecal samples we used unweighted UniFrac and hierarchical clustering. Samples from MTX-treated patients clustered with their respective baseline samples, indicating that the gut microbiota is stable with inter-individual taxonomic differences maintained for at least 6 months. NORA patients receiving MTX developed minimal changes over time. Intriguingly, however, baseline microbiome signatures in these patients predicted clinical response to MTX at 3 and 6 months, including the overabundance of unclassified *Coriobacteriaceae* ($r=-0.756$; $P<0.01$) and a *Coprococcus*-related OTU ($r=-0.755$; $P=0.022$).

Conclusion: Although oral methotrexate does not induce significant changes in the over all structure of the human intestinal microbiota of NORA patients, the abundance of several taxa at baseline correlate with a significant improvement in clinical disease activity 3 and 6 months into therapy.

Whether specific intestinal commensals can modulate the pharmacokinetics and bioavailability of methotrexate (and other DMARDs), remains to be elucidated. Better understanding of MTX pharamcomicrobiomics will be necessary to achieve precision medicine strategies in RA and related conditions.

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Abstract Number: 2523

Reasons for Provider Non-Adherence to a Treat to Target Strategy in Rheumatoid Arthritis

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Background/Purpose: Provider adherence to a Treat to Target (TTT) strategy for management of rheumatoid arthritis (RA) requires setting a disease target, regular monitoring of disease activity, shared decision-making, and appropriate adjustment of therapy based on target and disease activity score. We conducted a quality improvement trial to test whether a Learning Collaborative would improve TTT implementation. This analysis examines documented reasons for non-adherence to TTT by providers in the intervention arm.

Methods: Medical record review conducted by trained study staff assessed TTT implementation

based on 4 components: designation of target (remission or low disease activity), disease activity measure (DAM), shared-decision making (when applicable to set target and/or change treatment), and change in treatment based on target and DAM. Within the Learning Collaborative, providers were encouraged to reports reasons for TTT non-adherence when treatment was not changed despite disease activity not achieving target. Provider non-adherence to TTT was defined as no treatment intensification when warranted by disease activity not at pre-determined target. Reasons for non-adherence were categorized as: patient-based preferences (i.e. financial barriers, fear of medication, and reluctance to change), drug side effects, elevated DAM unrelated to RA (i.e. pain from comorbid conditions or irreversible joint damage increases score), no active disease as deemed by provider examination, treatment contraindicated (i.e. pregnancy, renal disease, chemotherapy), medication time-lag (i.e. delayed treatment response), other, and no reason specified. Multiple reasons were possible for each visit. Patient DAM scores were classified based on CDAI or RAPID3.

Results: 81 visits with provider non-adherence to the TTT strategy were observed in 74 patients, distributed throughout the nine month study period. A total of 90 reasons for non-adherence were noted. Patient preference was the most frequently observed reason for provider non-adherence to TTT, cited in 30 (37.1%) visits (see Table 1). Of the 81 visits, 22 (27.2%) visits noted that the DAM was elevated but not due to RA, and 12 (14.8%) had an unspecified reason for non-adherence.

Conclusion: Patient preference was the leading documented reason for provider non-adherence to a TTT strategy in RA, highlighting the importance of patient involvement in the treatment decision-making process. Patients play a critical role within the TTT paradigm.

Table 1: Documented reasons for provider non-adherence to TTT among patients not at target*

Reason	Visits, n (%)†
Patient preference	30 (37.1)
Drug side effects	7 (8.6)
Elevated DAM unrelated to RA	22 (27.2)
No active disease on exam	10 (12.3)
Contraindicated	5 (6.2)
Medication time-lag	4 (4.9)
Unknown	12 (14.8)

*Based on patient disease activity measure (CDAI > 2.8 or weighted RAPID 3 > 1)
†Percent calculated out of total visits; does not equal 100 as multiple reasons possible per one visit

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Abstract Number: 2524

Achievement of Imaging Remission Among Patients with Rheumatoid Arthritis in Clinical Remission and Their Characteristics

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Background/Purpose: Therapeutic goal of rheumatoid arthritis (RA) is to achieve disease remission. However, several remission criteria have not always equated to the complete absence of true inflammation. Power Doppler Ultrasonography (PDUS) has been demonstrated to detect subclinical synovitis. The aim of this study was to elucidate the achievement rates of imaging remission and examine characteristics associated with achievement status among RA patients in clinical remission.

Methods: This study was conducted in 90 RA patients who attained clinical remission, defined by DAS28-ESR remission criteria. PDUS was performed in 16 joints and 2 tendons, including both first to third metacarpophalangeal, second and third proximal interphalangeal, radiocarpal (RC), second and third metatarsophalangeal joints and extensor carpi ulnaris tendons and graded on the basis of a dichotomous assessment (presence/absence). The clinical and laboratory data of patients with imaging remission were compared with only clinical remission.

Results: Rate of imaging remission was 51.1% in patients with clinical remission. Forty four patients (48.9%) were PDUS positive. PD was detected most frequently in right RC joint (n=38, 42.4%). In addition, eleven patients have arthralgia on not evaluation joint, PDUS positivity was 91%. PDUS positive patients had higher evaluator global assessment score (p<0.001), and all clinical disease activity score. Rheumatoid factor was correlated with imaging remission with positivity and level. Overall, Patients could not reach imaging remission tend to more tender and swollen joint count, higher patient global assessment score, higher health assessment questionnaire (HAQ) score. They use more nonsteroidal anti-inflammatory drug (NSAID).

Conclusion: Only 51.1% of the patients with RA in clinical remission had PDUS defined imaging remission. Patients who were in imaging remission have lower disease activity, lower pain score

and less frequent use of NSAIDs, compared to patients with only clinical remission.

Table1. Clinical and Demographic Characteristics of Enrolled patients

	DAS28-ESR remission (n=90)
Age, year, mean (SD)	59.25 (±11.64)
Gender	
Male, n (%)	15 (16.7%)
Female, n (%)	75 (83.3%)
Tender joint count, mean (SD)	0.22 (±0.54)
Swollen joint count, mean (SD)	0.04 (±0.21)
ESR (mm/hr), mean (SD)	13.19 (±7.22)
CRP (mg/dl), mean (SD)	0.33 (±0.17)
RF positive, n (%)	72 (80.0%)
RF (IU/mL), mean (SD)	239.93 (±541.66)
Anti-CCP positive, n (%)	79 (87.8%)
Anti-CCP (units/ml), mean (SD)	257.40 (±235.33)
Seronegative, n (%)	3 (3.3%)
Medication	
MTX user, n (%)	79 (87.8)
MTX dose (mg/week), mean (SD)	11.27 (±4.86)
Steroid dose (mg/day), mean (SD)	2.41 (±1.86)
NSAID use, n (%)	58 (64.4%)
Biologics user, n (%)	14 (15.6%)
Adalimumab, n (%)	4 (4.4%)
Etanercept, n (%)	2 (2.2%)
Abatacept, n (%)	2 (2.2%)
Tocilizumab, n (%)	6 (6.7%)
Patient Global Assessment (0-100), mean (SD)	8.78 (±9.49)
Evaluator Global Assessment (0-100), mean (SD)	4.83 (±4.53)
HAQ, mean (SD)	0.29 (±0.58)
SDAI remission	79 (87.8%)
CDAI remission	71 (78.9%)
ACR/EULAR remission criteria	69 (76.7%)

Table2. Comparison of demographic and clinical characteristics of RA patients with and without imaging remission patients with and without clinical remission

	Imaging remission (+) (n=46)	Imaging remission (-) (n=44)	*P* value
Age, year, mean (SD)	59.85 (±9.62)	58.62 (±13.52)	0.621
Gender			
Male, n (%)	7 (15.2%)	8 (18.2%)	
Female, n (%)	39 (84.8%)	36 (81.8%)	0.706
Tender joint count, mean (SD)	0.13 (±0.40)	0.32 (±0.64)	0.097
Swollen joint count, mean (SD)	0.02 (±0.15)	0.07 (±0.26)	0.290
ESR (mm/hr), mean (SD)	15.02 (±7.42)	11.27 (±6.54)	0.013
CRP (mg/dl), mean (SD)	0.32 (±0.13)	0.33 (±0.20)	0.730
RF (IU/mL), n (%)	42 (91.3%)	30 (68.2%)	0.006
RF (IU/mL), mean (SD)	362.87 (±725.28)	111.40 (±153.92)	0.027
Anti-CCP (units/ml), n (%)	43 (100%)	36 (92.3%)	0.064
Anti-CCP (units/ml), mean (SD)	270.60 (±198.03)	242.84 (±272.56)	0.603
Medication			
MTX dose (mg/week), mean (SD)	11.03 (±4.46)	11.52 (±5.30)	0.639
Steroid dose (mg/day), mean (SD)	2.61 (±1.86)	2.20 (±1.85)	0.306
NSAID use, n (%)	26 (57.8%)	29 (70.7%)	0.211
Biologics user, n (%)	4 (10.8%)	7 (19.4%)	0.303
Patient Global Assessment (0-100), mean (SD)	7.17 (±9.05)	10.45 (±9.75)	0.102
Evaluator Global Assessment (0-100), mean (SD)	2.72 (±3.45)	7.05 (±4.49)	<0.001
HAQ, mean (SD)	0.23 (±0.48)	0.36 (±0.67)	0.282
SDAI remission	44 (95.7%)	35 (79.5%)	0.025
CDAI remission	41 (89.1%)	30 (68.2%)	0.020
ACR/EULAR remission criteria	39 (84.8%)	30 (68.2%)	0.082

Disclosure: J. Y. Choi, None; **R. Song**, None; **S. J. Hong**, None; **H. I. Yang**, None; **S. H. Lee**, None; **Y. A. Lee**, None.

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Abstract Number: 2525

Patient Characteristics Predicting Remission Using Intensive Treatment Strategies in Early Rheumatoid Arthritis

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Background/Purpose: Guidelines recommend to treat newly diagnosed Early Rheumatoid Arthritis (ERA) with intensive treatment strategies using Methotrexate (MTX) or a combination of csDMARDs and a short course of glucocorticoids (GCs). However, patient characteristics predicting response to such treatments are unknown.

Methods: The Care in ERA (CareRA) trial compares remission induction regimens in a treat-to-target approach. DMARD naïve ERA patients were stratified into a high- or low-risk arm based on classical prognostic markers. High risk patients were randomized to COBRA Classic (MTX + Sulphasalazine + prednisone step-down from 60mg), COBRA Slim (MTX + prednisone step-down from 30mg) or COBRA Avant-Garde (MTX + Leflunomide + prednisone step-down from 30mg). Low risk patients were randomized to MTX tight step-up (MTX-TSU) without oral GCs, or COBRA Slim. Prednisone was tapered down over 6 weeks to 7.5mg in Classic and 5mg in the other COBRA arms. Oral GCs were stopped at week 34. Demographics were routinely registered. Treatment response was defined as achieving remission at Week52 (DAS28(CRP))<2.6). Firstly, differences in age, smoking status, alcohol status, BMI and gender between responders and non-responders were analyzed with χ^2 or Mann Whitney U tests where appropriate. Secondly, these patient characteristics were analyzed in a multivariate logistic regression model predicting response. Treatment strategy was put in the model to correct for any treatment differences. This analysis was intention-to-treat using all patients recruited at baseline and carrying last observation forward in case of missing data. A significance level of 0.05 was used.

Results: This analysis included 379 patients. Remission at Week52 was achieved in 62.3% of patients. The population reflected a typical Belgian ERA cohort aged 51.9 ±13.0 years with an average BMI of 26.4 ±4.2 kg/m², with 69.1% women, 25.6% current smokers and 56.2% drinking alcohol. No differences in gender, smoking status, alcohol status and age were found between responders and non-responders. BMI did however differ (p=0.036): individuals not responding to therapy had a higher BMI compared to responders (27.1 ±4.8 vs 26.0 ±3.8). Multivariate logistic regression confirmed these findings. Only BMI was statistically significantly related to treatment response (p=0.007, Odds Ratio (95%CI) = 0.934 (0.889-0.982)).

Conclusion: Intensive treatment strategies based on MTX or combinations of csDMARDs with short term glucocorticoids lead to high response rates. Chances of patients with a higher BMI to achieve remission after 1 year of treatment with these strategies are however lower. These results should be taken into account when choosing the initial treatment strategy in early RA.

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Abstract Number: 2526

TNF Blocker Concentrations or Detection of Antibodies Against Anti-TNF before a Tapering Process Are Not Predictive to Relapse

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Background/Purpose: The goal of rheumatoid arthritis (RA) strategy is to reach remission or at least a low disease activity. When this goal is reached, no clear guideline exists to manage therapy. Recently, STRASS (Spacing TNF-blocker injections in RA Study) provided evidence of step-down therapeutic strategy with adalimumab or etanercept (1). So, we investigated if drug dosages and their antidrug antibodies (ADAb) could predict relapse during the 18 months of STRASS study.

Methods: We assessed 131 serum among the 137 included in STRASS study (60 and 71 for adalimumab and etanercept, respectively). Sera were collected at the time of randomisation. Adalimumab and etanercept blood concentrations and theirs ADAb were assessed by ELISA (Theradiag, Marne-La-Vallee, France). For this study, relapse was defined as DAS28>2.6 with DAS28 increase >0.6 since the previous study visit. Non parametric analysis was performed.

Results: Characteristics of the 131 patients similar to 137 from the initial STRASS study (data not shown). These RA patient characteristics are summarised in the Table 1 according to TNF blocker used. The median age was 54.5 [48.3-61.8] years. One hundred and two (77%) were female. The median disease duration was 6.5 [4.5-12.4] years. The median DAS28, ESR, and CRP were 2.0 [1.5-2.3], 10 [6-17]mm/hr, and 3 [2-4]mg/mL, respectively. Methotrexate was the main DMARDs

used (n=91; 70%). No baseline characteristics were associated with relapse during tapering or not. Adalimumab or etanercept serum concentrations were not different in case of relapse or not (Table2). Some ADAb against etanercept or adalimumab were detected, but their concentrations were under the positivity threshold. **Table 1. RA patients characteristics**

	Adalimumab (n=60)	Etanercept (n=71)	P values
Age, years	54.1 [44.7-60.3]	58.3 [52.0-62.8]	0.062
Female sex, n (%)	44 (73)	58 (82)	0.294
Disease duration, years	7.9 [4.4-12.7]	5.8 [4.6-9.4]	0.937
IgM RF positivity, n (%)	32 (61.5)	46 (74.2)	0.349
ACPA positivity, n (%)	37 (75.5)	52 (81.2)	0.285
DAS28	2.0 [1.6-2.3]	1.9 [1.4-2.2]	0.275
ESR, mm/1st hour	12.5 [6.7-18]	8.0 [5.0-16.0]	0.470
CRP, mg/mL	3 [2-4]	3 [1-4]	0.728
Monotherapy (%)	18	31	0.110
Time to relapse, (months)	9 [3-12]	6 [3-12]	0.273

Table 2. Adalimumab or etanercept serum concentrations at the time of randomisation according to relapse or not

	Adalimumab			Etanercept		
	Relapse	No relapse		Relapse	No relapse	P value
Number	43	17		35	36	
TNF blockers concentration (µg/ml)	6.90±2.32	6.97±2.42	0.91	4.23±1.39	4.18±1.45	0.89

Conclusion: No difference was observed in adalimumab or etanercept serum concentrations at the time of randomization to predict relapse in RA patients with low disease activity. Further investigations at various time points during the tapering could be useful.

Disclosure: H. Marotte, None; **M. Rinaudo-Gaujous**, None; **S. Paul**, None; **B. Fautrel**, None.

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Abstract Number: 2527

Drug Retention of Biologics in Rheumatoid Arthritis Patients: The Role of Baseline Characteristics and Impact of Time-Varying Factors

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DRUG RETENTION OF BIOLOGICS IN RHEUMATOID ARTHRITIS PATIENTS: THE ROLE OF BASELINE CHARACTERISTICS AND IMPACT OF TIME-VARYING FACTORS

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Background/Purpose: While the associations of baseline characteristics with drug effectiveness have often been studied in rheumatoid arthritis (RA), little is known about how the evolution of disease characteristics influences drug retention, a measure integrating both drug's effectiveness and tolerance. Aim: To examine the association of time-varying disease characteristics with drug retention of abatacept (ABA).

Methods: This is a pooled analysis of nine RA registries (ARTIS, ATTRA, RHEUMA DATA, DANBIO, GISEA, NOR-DMARD, ORA, SCQM, Reuma.pt). Inclusion criteria were a diagnosis of RA, initiation of ABA treatment and information on date of visit. Each time-varying variable was divided into baseline assessments and changes from baseline at subsequent visits. The baseline

values capture the inter-individual differences at drug initiation, while the changes over time inform on the intra-individual differences. We used time-varying Cox regression models to examine the association of baseline and time-varying characteristics with drug discontinuation, adjusting for age, sex, seropositivity, disease duration, number of previous conventional synthetic disease modifying antirheumatic drugs (csDMARD), and biologics (bDMARDs), presence of a comorbidity, calendar year of drug initiation, and stratifying by registry.

Results: 5440 patients initiated ABA, contributing 9715.4 patient-years, and 2920 stopped ABA during follow-up. Patients had a mean age of 57.8 years (SD: 13.1), mean RA duration at ABA initiation of 12.5 years (SD: 10.0), and most patients had failed several previous DMARDs (median csDMARD: 2, median bDMARDs: 1).

Median time to ABA discontinuation was 1.40 years. Seropositivity was associated with a lower chance of discontinuing ABA (Table). Previous failure of bDMARDs was associated with ABA discontinuation, whereas there was no such association for previous csDMARDs failure.

For most time-varying characteristics, the change over time (intraindividual evolution) was a stronger predictor of discontinuation than the baseline values (interindividual differences). Overall, ABA discontinuation was most strongly associated with a poor evolution of physician global assessment (HR: 1.62, 95% CI: 1.52-1.72). It was further independently associated with an inadequate progression of DAS28 and patient global assessments. In contrast, only the changes in physician global and patient global assessments were associated with discontinuing ABA for AEs.

Conclusion: The decision to discontinue ABA appears to be mostly influenced by the physician judgment and in particular its evolution over time. The evolution of the patient's appraisal and disease activity over time also play a role above and beyond the impact of the physician's assessment. Table: Multivariable Cox models of discontinuing ABA treatment due to any reason, to ineffectiveness and to adverse event.

	Withdrawing ABA treatment due to								
	Any reason			Ineffectiveness			Adverse event		
	HR	*p*	95%CI	HR	*p*	95%CI	HR	*p*	95%CI
Age [years]	1.00	0.32	1.00-1.00	0.99	0.004	0.99-1.00	1.01	0.01	1.00-1.02
Gender (ref: male)	1.01	0.83	0.92-1.11	0.92	0.20	0.81-1.04	1.31	0.03	1.03-1.66
Seropositivity									
No	1		-	1	-		1		-
RF or ACPA +	0.87	0.01	0.78-0.97	0.85	0.03	0.74-0.98	1.02	0.86	0.79-1.33
RF and ACPA +	0.82	<0.001	0.75-0.90	0.75	<0.001	0.67-0.85	1.04	0.75	0.83-1.29
Dis duration (BL)	1.00	0.21	0.99-1.00	1.00	0.11	0.99-1.00	1.00	0.84	0.99-1.01
Past csDMARDs (ref: none)									
1	1.09	0.45	0.88-1.35	1.21	0.18	0.92-1.58	0.68	0.14	0.41-1.13
2	1.16	0.17	0.94-1.44	1.16	0.30	0.88-1.52	0.86	0.54	0.52-1.41
3	1.16	0.20	0.93-1.45	1.12	0.43	0.84-1.49	1.00	0.99	0.60-1.67
4+	1.18	0.15	0.94-1.47	1.19	0.22	0.90-1.58	0.81	0.41	0.48-1.35
Past bDMARDs (ref: none)									
1	1.78	<0.001	1-55-2.04	2.21	<0.001	1.84-2.66	2.35	<0.001	1.69-3.28
2	1.73	<0.001	1.49-2.00	2.27	<0.001	1.87-2.77	2.46	<0.001	1.73-3.51
3	1.86	<0.001	1.59-2.19	2.48	<0.001	2.00-3.08	2.47	<0.001	1.68-3.65
4+	1.80	<0.001	1.51-2.14	2.26	<0.001	1.79-2.87	2.55	<0.001	1.67-3.91
Comorbidity +	1.13	0.11	0.91-1.40	1.09	0.54	0.83-1.43	1.41	0.18	0.85-2.34
HAQ at baseline	0.93	0.01	0.88-0.98	0.91	0.01	0.85-0.98	1.00	0.97	0.89-1.13
HAQ change	0.96	0.12	0.91-1.01	0.96	0.23	0.90-1.03	0.97	0.58	0.86-1.09
DAS28 at baseline	1.10	0.01	1.02-1.18	1.26	<0.001	1.14-1.38	0.81	0.01	0.69-0.96
DAS28 change	1.26	<0.001	1.17-1.35	1.49	<0.001	1.36-1.64	0.88	0.15	0.73-1.05
PhGA at baseline	1.49	<0.001	1.40-1.59	1.62	<0.001	1.49-1.77	1.31	<0.001	1.13-1.52
PhGA change	1.62	<0.001	1.52-1.72	1.70	<0.001	1.57-1.85	1.50	<0.001	1.30-1.75
PGA at baseline	1.16	<0.001	1.10-1.23	1.18	<0.001	1.10-1.27	1.14	<0.001	1.01-1.30
PGA change	1.16	<0.001	1.10-1.23	1.15	<0.001	1.07-1.25	1.18	<0.001	1.02-1.35

HAQ: Health Assessment questionnaire; DAS28: disease activity score 28 joints; PhGA: physician global assessment; PGA: patient global assessment

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Predictors of Long Term Survival of Low-Dose Etanercept: An Observational Study

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Background/Purpose: The objective of the study was to investigate long-term survival of low-dose etanercept (ETN) (25 mg weekly) and possible predictors of survival.

Methods: We collected retrospectively data of RA patients starting full-dose ETN (25 mg twice a week) between April 2001 and September 2014 who tapered ETN and maintained low-dose ETN for at least 12 months. Patients were evaluated every 3 months with a treat-to-target approach. Patients who achieved and maintained remission (DAS28 <2.6) for at least 6 months with full-dose ETN, tapered ETN. If remission was lost in two consecutive visits the patient returned to full-dose. We recorded the time to achieve remission with full-dose ETN (TTR). We considered two different cut-offs of TTR: <=6 months and <=12 months. We then evaluated survival of low-dose ETN treatment and possible predictors. Variables collected are reported in Table I. Survival was analysed with Cox-regression. Covariates included were those achieving a $p<0.20$ in univariate analysis. A separate Cox regression analysis was run with TTR<=6 months and TTR<=12 months.

Results: Among 532 patients, 276 were excluded because of missing data or because they were lost to follow-up leaving 256 patients eligible. After 11.28±4.05 years, 50/256 (19.5%) returned to full dose because of disease relapse, 55/256 (21.5%) stopped the treatment with ETN, and 151/256 (59.0%) maintained low-dose. TTR<=6 months and TTR<=12 months resulted significant predictors of low-dose survival (OR 1.93, 95% C.I. 1.31-2.85, $p=0.001$ and OR 3.11, 95% C.I. 2.06-4.68; $p<0.001$, respectively) together with a lower mean prednisone daily dose (Table II, Figure 1).

Conclusion: A shorter TTR and a lower mean prednisone daily dose are predictors of long-term survival of low-dose ETN. TTR<=6 months and TTR<=12 months are associated with a 2-fold and 3-fold increased probability of low-dose ETN survival respectively.

Table I. Characteristics of the patents according to the maintenance of half-dose etanercept.

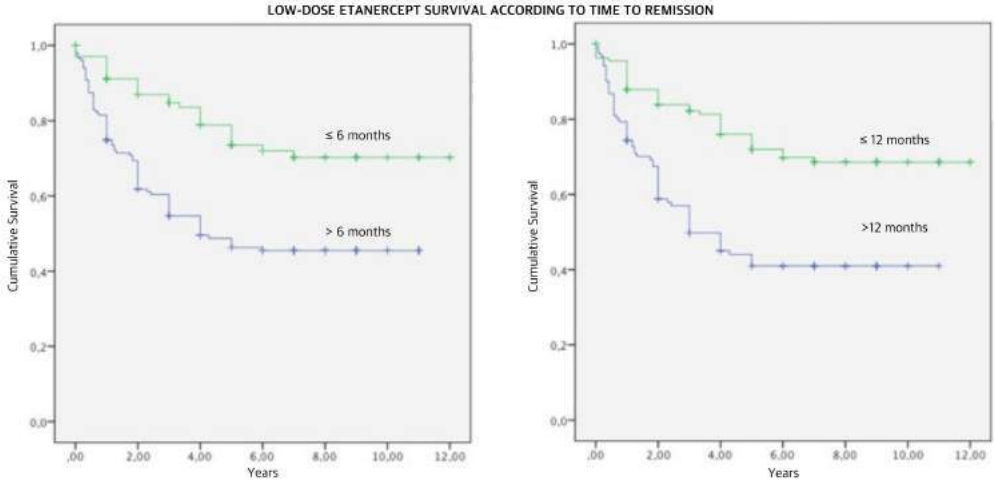
		Univariate Analysis		
	All patients	**Low-dose survival**	**Low-dose failure**	**p value**
Number	256	151	105	
Patients who stopped etanercept t, n (%)	55 (21.5)	-	55 (52.4)	-
Patients who returned to full-dose etanercept, n (%)	50 (19.5)	-	50 (47.6)	-
Age, median (IQR), years	59.00 (49.00;67.00)	60.00 (50.00;68.00)	58.00 (47.00;66.50)	0.266
Females, n (%)	217 (84.8)	126 (83.4)	91 (86.7)	0.301
Positive RF orACPA, n (%)	164 (64.6)	101 (67.3)	63 (60.6)	0.165
Disease duration, median (IQR), years	15.00 (9.25;21.00)	14.00 (9.00;21.00)	15.00 (10.00;22.00)	0.510
Etanercept treatment duration, median (IQR), years	8.00 (5.00;10.00)	8.00 (5.00;10.00)	7.00 (5.00;10.00)	0.177
Low-dose etanercept treatment duration, median (IQR), years	4.00 (1.27;8.00)	7.00 (4.00;9.00)	1.75 (0.58;3.00)	<0.001
Mean prednisone daily dose, median (IQR), mg	2.50 (0.00;5.00)	2.50 (0.00;5.00)	5.00 (2.50;5.00)	0.011
Combination with methotrexate	129 (50.4)	78 (51.7)	51 (48.6)	0.360

or leflunomide, n (%)	129 (50.4)	78 (51.7)	51 (48.6)	0.560
Baseline DAS28, median (IQR)	5.17 (4.50;5.53)	5.20 (4.48;5.47)	5.08 (4.68;5.65)	0.646
Baseline C-reactive protein, median (IQR), mg/L	12.00 (6.00;25.00)	12.00 (6.00;22.00)	12.65 (5.00;31.50)	0.491
Time to remission, median (IQR), years	0.50 (0.08;1.56)	0.25 (0.08;0.83)	1.17 (0.08;2.88)	<0.001
Time to remission <=6 months, n (%)	167 (65.2)	110 (72.8)	57 (52.3)	0.002
Time to remission <=12 months, n (%)	200 (78.1)	134 (88.7)	66 (62.9)	<0.001

Table II. Survival of low-dose etanercept according to time to remission: results of Cox regression analysis.

		Model I		**Model II**	
		Time to remission ² 6 months		**Time to remission ² 12 months**	
		OR (95% CI)	**p value**	**OR (95% CI)**	**p value**
Positive RF or ACPA		0.84 (0.56;1.25)	0.382	0.92 (0.62;1.37)	0.677
Mean prednisone daily dose	per milligram increase	1.13 (1.04;1.23)	0.004	1.12 (1.03;1.21)	0.010
Time to remission <=6 months		1.93 (1.31;2.85)	0.001	-	-
Time to remission <=12 months		-	-	3.11 (2.06;4.68)	<0.001

Figure 1. Low-dose etanercept survival according to time to remission.



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Comparative Effectiveness of Tofacitinib, Biologic Drugs and Traditional Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis

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Background/Purpose: Tofacitinib is an oral Janus kinase (JAK) inhibitor approved in the USA in November 2012 for the treatment of rheumatoid arthritis (RA). As the first oral JAK inhibitor for RA, little is known about the real-world effects of tofacitinib. Our aim was to compare the effectiveness of traditional disease-modifying antirheumatic drugs (DMARDs), biologic DMARDs and tofacitinib for RA patients with inadequate response to methotrexate.

Methods: We performed a retrospective cohort study using MarketScan Databases from 2011-2014. We studied RA individuals, 18 years or older, previously treated with methotrexate (oral or SQ, at any time) and newly prescribed one of the medications under study (DMARDs, biologics or tofacitinib), between January 2011 and December 2013. The date of first filled prescription or infusion drug was defined as the cohort entry and individuals must have had no prior use of biologics or tofacitinib at any point before cohort entry. We required subjects to be continuously enrolled in the medical and pharmacy plan for 12 months before and 12 months after the cohort entry. A patient's therapy was defined as effective if none of the following occurred during the first year of follow-up: 1) non-adherence, defined as medication possession ratio (MPR) lower than 80% or the number of infusions lower than the minimum expected for each biologic. 2) Switching or adding a new biologic agent or tofacitinib. 3) Switching or adding a new DMARD. 4) Having at least one glucocorticoid joint injection between the months 4 and 12 of follow-up. We presented descriptive analysis of baseline characteristics and the proportion of patients achieving therapy effectiveness and the individual criteria by exposure groups.

Results: 16,962 RA patients were included; 3,033 began therapy with DMARD, 13,843 with biologics and 86 with tofacitinib. Among all patients, 77.4% were female and the mean age was 56.1 years (standard deviation 12.6). Table 1 shows the proportion of patients that failed the effectiveness criteria. Table 1. Proportion and 95% confidence interval (CI) of patients who achieved therapy effectiveness and the individual criteria.

Effectiveness criteria	DMARD		Biologics		Tofacitinib	
	%	95% CI	%	95% CI	%	95% CI
Effective therapy (none of the criteria)	16.6	15.2;17.9	18.1	17.4; 18.7	19.8	11.3;28.2
Non-adherence	74.7	73.2; 76.3	54.4	53.5; 55.2	67.4	57.5; 77.3
Switch/add biologic agent or tofacitinib	15.7	14.4; 17.0	34.7	33.9; 35.4	18.6	10.4; 26.8
Switch/add DMARD	12.8	11.6; 14.0	16.5	15.8; 17.1	15.1	7.5; 22.7
Glucocorticoid joint injection	20.4	19.0; 21.9	27.5	26.7; 28.2	25.6	16.4; 34.8

Conclusion: Similar rates of therapy effectiveness were observed among groups, although the rates for the individual criteria differed. The number of RA patients starting therapy with tofacitinib was relatively low and most of them were non-adherent. Fewer patients using biologic agents were non-adherent compared to DMARD and tofacitinib therapy, while more patients using biologic agents switched to or added a new biologic agent or tofacitinib. The results suggest that tofacitinib are not usually prescribed as a therapy option after inadequate response to methotrexate. At least through the end of 2014, patients initiating tofacitinib before biologics appear quite dissimilar to initiators of first time biologics. Given this pattern of use, further analysis should focus on the comparative effectiveness and safety of tofacitinib and biologic drugs as second and third therapy options for RA

patients.

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Patient´s Motivations for Non-Persistence with Medication Impact How They Score Compliance

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Background/Purpose: In 2004 we initiated a cohort of rheumatoid arthritis (RA) patients with recent-onset disease. From 2008 onwards, both construct of compliance, persistence on therapy (P) and adherence with therapy (A) were prospectively assessed through a questionnaire (the CQ) that additionally investigated motivations for non-P, and a visual analogue scale for C (C-VAS). We hypothesized that how a patient subjectively attributed a motivation (patient-dependent vs. patient independent) impacted his/her evaluation of C. **Objectives** were to examine the correlation between compliance assessed as per the CQ and per the VAS, and to investigate if the selection of patient-independent motivation for non-P predicted better score of C.

Methods: Up to January 2016, the cohort comprised 180 patients with variable follow-up. Since 2008, CQ and C-VAS were concomitantly applied at regular six-months apart-intervals. The CQ is a 22-items questionnaire, where item 11 investigates 15 predefined patient´s motivations for non-P

and one open answer; a patient is considered CQ-compliant if A and P. The C-VAS is a 100 mm VAS, where 0 indicates “very good compliance”. Each motivation for non-P was classified as patient-dependent or patient-independent by 50 patients randomly selected and directly interviewed to such purpose (≥70% agreement among the patients interviewed). Multiple regression analysis was used to evaluate patient-independent motivation as a predictor of better compliance. The study was approved by the institution’s internal review board. Written informed consent was obtained.

Results: The final number of patients for which data were analyzed was 160. At inclusion in the cohort, patients were primarily middle-age female (90%), with 5.4±2.6 months of disease duration and high disease activity. The majority had RF (85.6%) and antibodies to cyclic citrullinated peptides (88.1%). To January 2016, the (mean±SD) length of follow-up was 6.7±3.4 years, during which patients completed 1516 pairs of CQ and C-VAS. The C-VAS significantly correlated with the CQ, r=0.468, p=0.001. Cut-off value of C-VAS to predict CQ-compliance was 7.5 mm. During follow-up, there 670 CQs scored as with non-P among whom, 654 had at least one motivation for non-P selected; of them, 549 CQs (70.2%) corresponded to non-P patients who selected only patient-independent motivations and 31 (4.7%) to those who selected only patient-dependent motivations. Patients from the former group had better C-VAS scores than their counterparts. The selection of exclusively independent motivations for non-P predicted C-VAS score and CQ score, ß: -0.15, 95%CI: -19.2 to -6.8, p≤0.001 and ß: 0.79, 95%CI: 0.01-0.819, p=0.045, respectively. Also, the selection of exclusively independent motivations for non-P predicted VAS-compliance (OR: 15.6, 95%CI: 5.4-45.3, p≤0.001) and CQ-compliance (OR: 2.25, 95%CI: 1.062-4.664, p=0.034).

Conclusion: Patient´s motivations for non-P impact how they perceived and scored their compliance; a potential consequence of such behavior is that non-compliant patients may be misidentified.

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Impact of Participation in the Adalimumab (Humira) Patient Support Program on Functional and Clinical Outcomes Among Patients with Rheumatoid Arthritis: Passion Study

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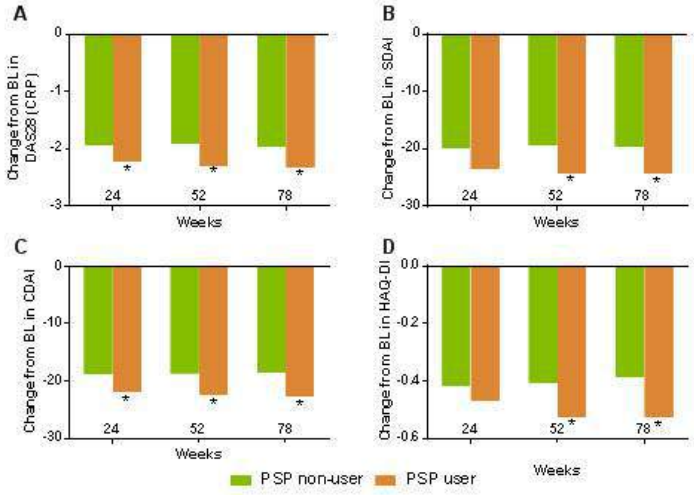
Background/Purpose: Patients (pt) with Rheumatoid arthritis (RA) who are treated with adalimumab (ADA) are offered a Patient Support Program (PSP) with variety of services. To date, no prospective study has been conducted to analyze the acceptance and the impact of these PSPs on treatment effectiveness and pt satisfaction. The purpose of this study was to examine the effectiveness of ADA on rheumatoid arthritis (RA) treatment course in the context of PSP participation.

Methods: PASSION (NCT01383421) was a 78-week (wk) post-marketing observational study of pts with RA receiving ADA in routine clinical care. Pts from the EU, Israel, Mexico, Puerto Rico, and Australia with an insufficient response to ≥1 disease-modifying antirheumatic drug (DMARD) newly initiating ADA (1 prior biologic DMARD was allowed) were enrolled. The primary endpoint was the % of pts achieving the minimal clinically important difference (MCID; improvement of ≥0.22) in the Health Assessment Questionnaire Disability Index (HAQ-DI) at wk 78 vs baseline (BL). Non-responder imputation (NRI) was used to account for the missing values. Secondary clinical parameters included % of pts achieving MCID in HAQ-DI at wks 24 and 52 vs BL and changes in the 28-joint DAS based on CRP (DAS28(CRP)), Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index (CDAI) at wks 24, 52, and 78 vs BL. Pts were categorized based on their participation in the PSP: ever (PSP users) vs never (PSP non-users) and outcomes were compared after adjusting for corresponding BL values.

Results: 1,025 pts were included in the Intent-to-treat population (BL: mean age, 54.3 years (y); % female, 77.1%; mean RA duration, 7.8 y; mean HAQ-DI, 1.5; mean DAS28(CRP), 5.3; mean SDAI, 35.6; mean CDAI, 33.3; 17.8% pts had received prior biologic DMARD. Overall, 48.7% pts were PSP users. Approximately 72.9 % (as observed) and 42.8% (NRI) of PSP-users surpassed the MCID in HAQ-DI at wk 78. The percentage of pts achieving MCID in the HAQ-DI was higher in PSP users vs PSP non-users (48.1% vs 37.8%, NRI) at wk 78 (P<0.001). Significant changes (P≤0.05) from BL to wk 78 were observed for pts using the PSP vs PSP non-users in HAQ-DI (0.53 vs 0.39), DAS28(CRP) (−2.33 vs −1.97), SDAI (−24.5 vs −19.8), and CDAI (−22.66 vs −18.55) scores **(Figure)**. Study discontinuation rates were significantly (P<0.001) lower among PSP-users vs PSP non- users (25.5% vs 41.6%). Reasons for discontinuations are listed in the **Table**.

Conclusion: The final study results showed that, in pts with moderate to severe RA who initiated ADA, significantly better improvement in functional and clinical outcomes was achieved in the PSP users vs the PSP non-users. Improvements were achieved at early timepoints and continued to increase throughout the study.

Figure: Changes from baseline in DAS28 (CRP) (A), SDAI (B), CDAI (C), and HAQ-DI (D) over time between PSP users and PSP non-users.



*significantly different between PSP users and PSP non-users ($P<0.05$). Data represented by LOCF imputation for intent-to-treat population. Results are adjusted for BL DAS28(CRP), SDAI, CDAI, and HAQ-DI. LOCF=Last Observation Carried Forward.

Table: All reasons for study discontinuation by PSP utilization category

Subject Disposition	All Patients N=1025	PSP user N=499	PSP non-user N=526
Discontinued (%)* **	**346 (33.8)**	**127 (25.5)**	**219 (41.9)**
Adverse event	52 (5.1)	22 (4.4)	30 (5.7)
Withdrew consent	37 (3.6)	13 (2.6)	24 (4.6)
Lost to follow-up	46 (4.5)	17 (3.4)	29 (5.5)
Serious adverse events	24 (2.3)	10 (2.0)	14 (2.7)
Lack of efficacy	168 (16.4)	66 (13.2)	102 (19.4)
Other	51 (5.0)	16 (3.2)	35 (6.7)

***Statistically significant at $P<0.001$

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Abstract Number: 2532

Methotrexate Adherence in an Online Network of Patients with Rheumatoid Arthritis

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Background/Purpose: Adherence to disease-modifying antirheumatic drugs (DMARDs) in patients with rheumatoid arthritis (RA) is varied; rates range from 30% to 80%.[1] Adherence to methotrexate (MTX), the most commonly prescribed DMARD in patients with RA, has been incompletely studied; available data come from third-party rather than patient-level sources. We aimed to describe self-reported MTX adherence among an online community of patients with RA and to explore the patient characteristics associated with MTX nonadherence.

Methods: US-based adult patients self-reporting RA were recruited from an online health-sharing network, PatientsLikeMe. Patients were invited to fill out a cross-sectional Web-based survey if they reported an RA diagnosis and current or past (within 6 months) treatment with MTX. Eligible patients were grouped by treatment regimen into 4 MTX groups (MTX alone, MTX with biologic DMARD[s] [bDMARD], MTX with nonbiologic DMARD[s] [nbDMARD], MTX with both bDMARD[s] and nbDMARD[s]), and they completed the 4-item Morisky Medication Adherence Scale (MMAS-4). MTX adherence was classified as high, moderate, or low based on MMAS-4 scoring criteria. Descriptive statistics were used to describe the sample, bivariable statistics were used to test for associations between MTX use and adherence, and multivariable logistic regression modeling with a backward selection procedure was used to identify factors predictive of moderate or low adherence.

Results: Of 745 patients who viewed the invitation, 232 eligible patients participated in the survey, for an online response rate of 31%. Participants were demographically similar to nonparticipants but were slightly older (54.7 vs. 50.5 years; $p<0.0001$). Most survey completers (n=210) were female (90%), white (93%), and, on average, 55 years of age. Thirty-four percent (n=60) took MTX with bDMARD, 28% (n=49) took MTX alone, 25% (n=44) took MTX with nbDMARD, and 13% (n=23) took MTX with both bDMARD and nbDMARD. There was a significant relationship between MTX medication group and nonadherence; of patients taking MTX with bDMARD, 58% were highly adherent compared with 92%, 75%, and 87% in the other MTX medication groups, respectively (overall χ^2 $p=0.0003$). In the final model adjusted for demographics, years since RA diagnosis, duration of MTX treatment, and mode of administration, MTX with bDMARD use was most strongly predictive of lower levels of MTX adherence; the MTX with bDMARD group had 4 times the odds of moderate/low adherence (OR, 4.1; 95% CI, 1.9-8.6; $p=0.0002$) compared to those taking MTX alone.

Conclusion: In this study, there was a strong relationship between MTX with bDMARD use and lower levels of self-reported adherence to MTX. Future research should explore how adherence is related to disease activity and should test whether these findings are replicated in other patient samples. Health care providers should be aware of this potential association and should appropriately counsel patients to optimize RA medication adherence. **Reference:** 1. van den Bemt BJ et al. *Expert Rev Clin Immunol*.2012;8:337-351.

Disclosure: B. Katic, PatientsLikeMe, 1,PatientsLikeMe, 3; **A. M. Rodriguez**, PatientsLikeMe, 5,PatientsLikeMe, 9; **C. Curran**, PatientsLikeMe, 1,PatientsLikeMe, 3; **M. Brethous**, F. Hoffman-La Roche, 5; **C. Bernasconi**, F. Hoffmann-La Roche, 5; **J. M. Nebesky**, F. Hoffmann-La Roche, 3,F. Hoffmann-La Roche, 1; **W. Reiss**, Genentech/Roche, 3,Genentech/Roche, 1.

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Abstract Number: 2533

Are There Differences in Baseline Comorbidities Between Rheumatoid Arthritis Patients Treated with Abatacept and Those Treated with Tumor Necrosis Factor Inhibitors?

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Background/Purpose: Rheumatoid arthritis (RA) patients frequently report concomitant

comorbidities that could worsen their prognosis. Tumor necrosis factor inhibitors (TNFi), the most common biological agents used, have shown efficacy in RA patients, although use in RA patients with certain comorbidities warrant caution (1). Abatacept, a biologic agent with a different mechanism of action, inhibiting the co-stimulation of the T-lymphocyte, has demonstrated differentiated safety profile (2), that could influence the biological agent prescribed in RA patients with some associated comorbidities. Our objective is to analyze differences in the frequency of baseline comorbidities in RA patients treated with abatacept compared with those treated with TNFi

Methods: Patients with RA recruited into the BIOBADASER 2.0 register from January 2008 to December 2014 and treated with abatacept or TNFi with comorbidities were selected. Comorbidity was defined as ≥ 1 of the following at initiation of biological therapy: Ischemic heart disease; lymphoma; malignancy (except lymphoma); diabetes; chronic pulmonary obstructive disease (CPOD); smoking; hypercholesterolemia; hypertension; heart failure; renal failure; osteoporosis; Epstein Barr, hepatitis B or C virus infection; and others. We analyzed the frequency of each comorbiditiy and the differences in the rate of baseline comorbidities between the two groups

Results: From January 2008 to December 2014, 640 and 252 RA patients treated respectively with TNFi or abatacept, were included in the BIOBADASER 2.0 register, of whom 51.6% had ≥ 1 comorbitity at baseline. Frequencies for every basal comorbidity described ere shown in Table 1. There was a significantly higher rate of heart failure in abatacept than in TNFi patients. Other comorbidities showed no significant differences **Table 1**

	Frequency (%)		
Comorbidities	Abatacept	TNFi	p-value
Ischemic heart disease	1(2.3)	14(2.1)	0.940
Malignancy (except lymphoma)	1(2.3)	13(1.9)	0.883
Diabetes	6(13.6)	46(6.9)	0.098
CPOD	2(4.6)	16(2.4)	0.382
Smoking	8(18.2)	109(16.4)	0.757
Hypercholesterolemia	9(20.4)	111(16.7)	0.519
Hypertension	10(22.7)	148(22.3)	0.942
Epstein Barr infection	0(0)	1(0.1)	0.797
Heart failure	**4(9.1)**	**6(0.9)**	**<0.001**
Renal failure	0(0)	8(1.2)	0.464
Lymphoma	0(0)	0(0)	
Osteoporosis	7(15.9)	89(13.4)	0.635
Hepatitis B virus infection	1(2.3)	13(1.9)	0.883
Hepatitis C virus infection	0(0)	1(0.1)	0.797
Others	22(50)	292(43.9)	0.431

Conclusion: RA patients treated with abatacept had a higher baseline frequency of concomitant heart failure compared with patients treated with TNFi, probably reflecting different recommendations on biological drug use. No differences in other baseline comorbidities were found

between groups References: (1) Singh et al. Arthritis Rheum 2016; 68: 1–26. (2) Singh et al. Cochrane Database Syst Rev. 2011; 16: CD008794

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Abstract Number: 2534

Radiographic Remission in Patients with Seropositive RA at Ten Years after Diagnosis, Treated in a Real Life Setting

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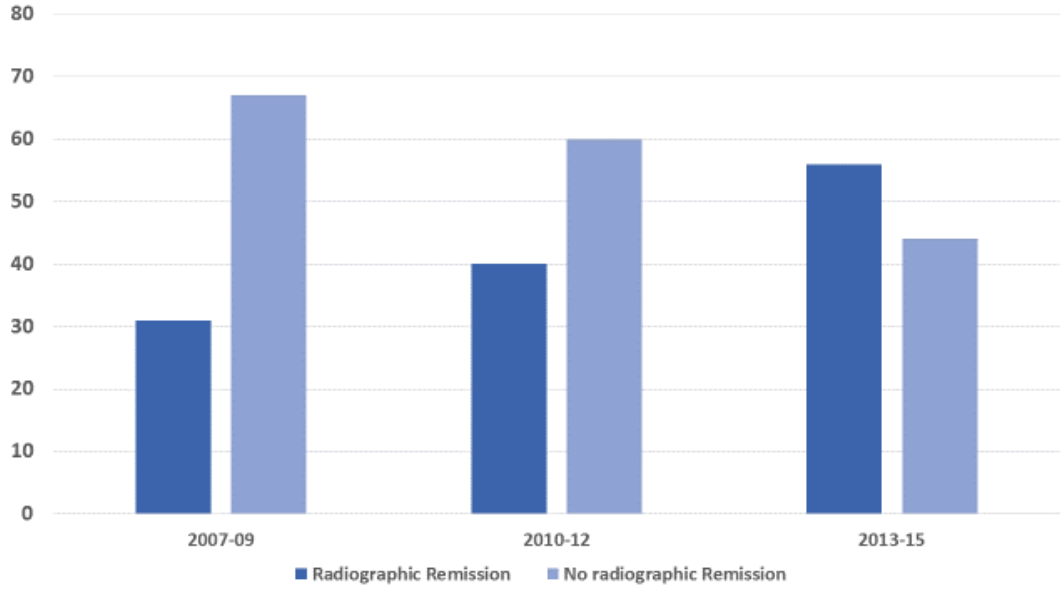
Background/Purpose: Radiographs of hands and feet represent an objective outcome measure of rheumatoid arthritis (RA). Joint damage is a result of cumulative disease activity over years. Unlike other clinical measures, radiographic damage is caused mainly by disease inflammatory activity. Therefore, radiographs provide a proper measure to analyze outcomes of RA over a long term. Our purpose was to analyze radiographic remission of patients with early RA at ten years after diagnosis in a real life setting.

Methods: All 1046 patients who were diagnosed with RA in 1997–2005 at a single rheumatology center were scheduled for a ten year follow-up with radiographs of hands and feet at years 0, 2, 5, and 10. Larsen score (0 -100) was employed including MCPs, wrists and 2-5 MTP joints. Radiographic remission was defined as no new erosions and no worsening of erosions between the baseline (at diagnosis), and ten years. Proportion of patients with radiographic remission/no remission ten years after diagnosis was compared in patients with a new diagnosis of RA in 1997-99, 2000-02, and 2003-05.

Results: Among 1046 patients (66% women, mean age 58, 60% seropositive, 13% with erosions at baseline), 743 patients (70% women, mean age 54, 65% seropositive, 12% with erosions at baseline) were seen at their 10-year follow-up visit. Among 480 seropositive patients, the median (IQR) progression of Larsen score was 3(0, 8) and in 263 seronegative patients 0(0, 2). Radiographic remission was met at the 10-year follow up visit by 31%, 40%, and 56% of seropositive patients who had the diagnosis in 1997-99, 2000-02, and 2003-05 (Figure 1); $p<0.001$. In seronegative patients, the figures were 75%, 79%, and 83%, respectively. Over ten years, anti-rheumatic medications included MTX in 79%, 84%, and 90% of the patients diagnosed in 1997-99, 2000-02, and 2003-05, subcutaneous MTX in 13%, 24%, and 25%, SSZ in 82%, 83%, and 72%, HCQ in 61%, 73%, and 76%, LEF in 13%, 16%, and 14%, im gold in 19%, 11% and 5%, Pred in 63%, 80%, and 82%, and biologic agents in 10%, 16%, and 19% of the patients, respectively. Mortality (a total of 15% of women and 30% of men died over 10 years) was the main reason for missing data.

Conclusion: Proportion of patients who meet radiographic remission at ten years after diagnosis of early RA is increasing over the recent years. A majority of patients with seropositive RA who were seen at the 10-year control in 2013-15 met radiographic remission (Figure 1). Over the observation period, the use of MTX, sc MTX, HCQ, Pred and biologics increased, and the use of SSZ and im gold declined. **Figure 1**. Proportion of patients with radiographic remission/no remission, ten years after diagnosis of early seropositive RA.



Disclosure: T. Sokka, None; **J. Asikainen**, None; **T. Rannio**, None; **P. Hannonen**, None.

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Abstract Number: 2535

Effect of Methotrexate in the Presence of Drug and the

Appearance of Antibodies Against Tumour Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis

Chamaida Plasencia-Rodriguez[1], Ana Martínez[2], Alejandro Villalba[3], Teresa Jurado[4], Eva Olariaga-Merida[5], Araceli Mezcua[6], Diana Peiteado[3], Gema Bonilla[3], Laura Nuño[3], Alejandro Balsa[1] and Dora Pascual-Salcedo[2], [1]Instituto de Investigación Hospital Universitario La Paz (IDIPAZ), Madrid, Spain, [2]Immunology Unit, La Paz University Hospital-Immunology, Madrid, Spain, [3]Rheumatology, Hospital La Paz - IdiPaz, Madrid, Spain, [4]Immunology Unit, La Paz University Hospital-IdiPaz, MADRID, Spain, [5]Immunology, University Hospital La Paz, Madrid, Spain, [6]Immunology Unit, La Paz University Hospital, Madrid, Spain

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Background/Purpose: Several factors influence pharmacokinetics of TNFinhibitors (TNFi). One relevant factor is the formation of anti drug- antibodies (ADA) associated with low drug levels and a worse clinical response. Recent publications in rheumatoid arthritis (RA) (1,2) have demonstrated a beneficial effect of concomitant use of anti-TNF drugs and methotrexate (MTX), with a dose-dependent effect[¥]. To analyze the MTX influence on the presence of drug and appearance of ADA in a cohort of RA patients treated with Infliximab (Ifx), Adalimumab (Ada) or Etanercept (Etn) with a long follow-up (3 years).

Methods: This is an observational study that analyzed patients with RA treated with Ifx (112 patients), Ada (71 patients) and Etn (110 patients), in a prospective observational biological cohort from the University Hospital La Paz, Madrid, Spain. Patients were grouped according to the use of MTX: no MTX, low dose (≤12.5 mg / week), intermediate dose (15-17.5 mg / week) and high dose (≥20 mg / week). Levels of drug and ADA were measured by capture and bridging. ELISA respectively at baseline, 0.5, 1, 2 and 3 years. All samples were obtained just before drug administration. Statistical analysis was performed using GraphPad Prism 5.0 software.

Results: Out of 293 RA patients with a TNFi treatment; 184 (71 with Ifx, 40 with Ada and 73 with Etn) were included. In this cohort, 111 (61%) were on MTX and 72 (39%) were on monotherapy. Most patients with high dose of MTX had levels of drug over 3 years of treatment (93% with MTX ≥20 mg/week vs 77% without MTX; p = 0.0003) being significant since 0.5years (60% with MTX ≥ 20 mg / week vs 39% without MTX; p = 0.003). To analyze the ADA development, patients treated with Ifx and Ada were grouped and we observed a low development of immunogenicity in the group which did not receive MTX (n = 37) compared to those who received high-dose MTX (n =27) close

to significance (32% vs 19%, p = 0.05). Analysing by separate drugs MTX significantly reduced the immunogenicity of Ada, (53% in patients with MTX vs 12% in monotherapy; p <0.0001).When we study the lack of circulating drug (Ifx, Ada and Etn) as an indicator of immunogenicity, patients who did not receive MTX (n = 56) had higher absence of drug than patients with high-dose MTX (n = 61) (34% vs 10%, respectively; p <0.0001) .This effect was significant since 0.5 years of treatment (16% MTX ≥ 20 mg / week vs 3% without MTX; p =0.001)

Conclusion: In our cohort of RA patients the concomitant use of MTX has a positive effect in the persistence of TNFi levels together with a decrease of immunogenicity. Furthermore, the MTX has a dose-dependent effect being greater at high dose of MTX.

Abstract Number: 2536

The Performance of a Single Centre Interventional Clinic in Early Rheumatoid Arthritis

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Background/Purpose: In early rheumatoid arthritis (RA), first assessment by a rheumatologist and/or initiation of disease-modifying anti-rheumatic drugs (DMARD) within 12 weeks of symptom

onset are associated with a significant benefit in long-term disease outcome. Our objective was to determine the proportion of patients with newly diagnosed RA in whom first rheumatology assessment and/or initiation of DMARD therapy was within the desired time frame.

Methods: A retrospective chart review of adult patients diagnosed with RA during years 2014 and 2015 was performed at the rheumatology department of an integrated secondary/tertiary teaching hospital that provides rheumatology services for a population of more than 500.000 residents. Potential cases were identified by searching the electronic medical records for ICD-10 codes M05.* and M06.* Electronic and paper records of patients were then thoroughly reviewed. In addition to demographic and clinical data, dates were recorded for onset of inflammatory joint symptoms, referral to rheumatologist, initial assessment by a rheumatologist and initiation of DMARD therapy. The percentage of patients assessed by a rheumatologist and/or treated with a DMARD within 12 weeks of symptom onset and the median times for delay were then calculated.

Results: Between January 1st 2014 and December 31st2015, 243 new cases of RA were identified at our Department of Rheumatology. Of those, 197 (81.1%) were referred to our early interventional clinic. Within 12 weeks of symptom onset, 111 (45.7%) new RA patients were examined by a rheumatologist and 87 (35.8%) were started on DMARD therapy; the median time from symptom onset to consultation was 13.0 (IQR 4.6–27.8) weeks, median time from referral to consultation was 1 (IQR 1–3) days and median DMARD treatment delay was 15.7 (IQR 8.7–31.9) weeks.

Conclusion: 46% of new RA patients were assessed by a rheumatologist and 36% were treated with a DMARD within the recommended time frame of 12 weeks. Most of the treatment delay was due to the time elapsed between symptom onset and referral to a rheumatologist. These results substantiate the efficacy of our early interventional clinic in diagnosing and treating patients with early RA: despite the heavily protracted nationwide waiting times for first rheumatologist assessment and significantly (40%) lower number of rheumatologists per capita compared to European Union average, the percentage of timely treated patients was comparable to recent reports.

Table: **Demographic data, clinical history, and delays**	
Gender (female/male) (%)	183/60 (75/25)
Age, years (median)	64.2 (IQR, 52.1–75.9)
Patients fulfilling 2010 ACR/EULAR classification criteria for RA, No. (%)	228 (93.8)
DAS28 3v (mean ± SD)	5.3 ± 1.3
Erosive disease (plain radiographs) at first rheumatologist assessment, No. (%)	67 (31.5)
Time from symptom onset to first rheumatologist assessment, weeks (median)	13.0 (IQR, 4.6–27.8)
Time from referral to first rheumatologist assessment, weeks (median)	0.14 (IQR, 0.14-0.43)
Time from symptom onset to glucocorticoid initiation, weeks (median)	13.1 (IQR, 5.6–26.9)
Time from symptom onset to DMARD initiation, weeks (median)	15.7 (IQR, 8.7–31.9)

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Abstract Number: 2537

High Retention Rates and Clinical Efficacy of Tocilizumab As First-Line Biologic Treatment in Patients with Rheumatoid Arthritis

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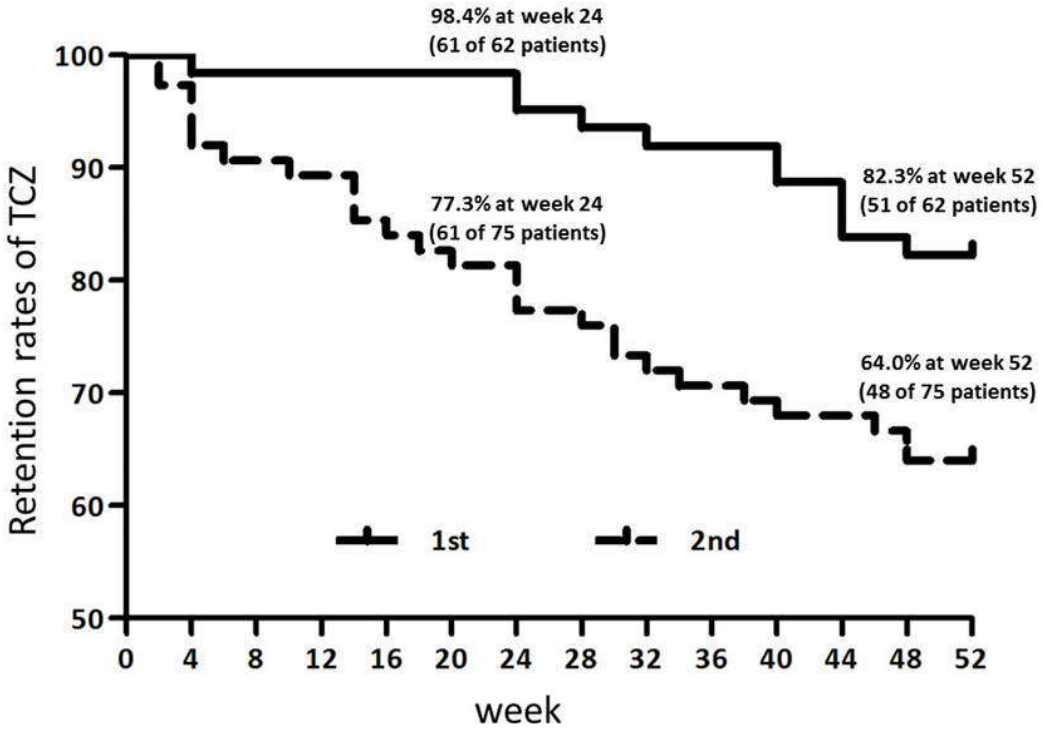
Background/Purpose: Biologic disease-modifying anti-rheumatic drugs (bDMARDs) that target cytokines and cytokine receptors such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-6 have been established as a standard therapy of rheumatoid arthritis (RA) for patients with conventional systemic DMARDs, such as methotrexate (MTX), resistant disease. Currently, TCZ is included as one of the first-line bDMARDs in the latest ACR guideline and European League against Rheumatism (EULAR) recommendations. However, it is unclear whether the effectiveness of TCZ is depended on previous administration of biologics. Therefore, we focused on the retention rate taking into account of both efficacy and safety under the daily setting care, and this study aimed to investigate optimal treatment strategy with TCZ as a first-line bDMARD treatment in comparison with second-line treatment for RA patients.

Methods: All RA patients who treated with TCZ in Osaka City Universityfs RA registry (including 1070 patients with RA and 353 patients using bDMARDs) were included in this analysis. These

patients were divided into two groups that TCZ was used as a first-line bDMARDs (1st group) and a second-line or more treatment (2nd group). Retention rates and clinical efficacy assessed by disease activity score in 28 joints (DAS28; on the basis of the erythrocyte sedimentation rate, ESR) and clinical disease activity index (CDAI) from week 0 to week 52 were assessed. Retention rates of TCZ were evaluated using Kaplan–Meier analysis. Furthermore, the discontinuation ratio of glucocorticoid was also evaluated.

Results: Sixty-two patients in 1st group and 75 patients in 2nd group were analyzed in this study. Retention ratio at week 52 was 82.3% in 1st group and 64.0% in 2nd group (p=0.01). Of 11 discontinued patients in 1st group, only 2 patients were withdrawal due to inadequate response. From the initiation of TCZ use, efficacy of 1st group patients were faster than that of 2nd group patients. DAS28 remission rates were 23.5, 47.0, 49.1, 41.2 and 35.3% in 1st group and 8.3, 22.9, 29.2, 33.3 and 37.5% in 2nd group at week 4, 12, 24, 36 and 52, respectively. Also, CDAI remission rates were 15.7, 13.7, 15.7, 25.5 and 13.7% in 1st group and 0, 6.3, 10.4, 14.6 and 10.4% in 2nd group at week 4, 12, 24, 36 and 52, respectively. During 52 weeks, the dose of glucocorticoid was reduced in 18 patients and withdrawal in 12 patients between 22 patients of 1st group using glucocorticoid at week 0. In 2nd group, the dose of glucocorticoid was reduced in 14 patients and withdrawal in 5 patients between 20 patients of using glucocorticoid at week 0.

Conclusion: High retention rates and clinical efficacy of TCZ as a first-line biologic treatment was found in this research. More than half of glucocorticoid user were able to withdraw glucocorticoid during 52 weeks. This result as 1st line use of TCZ supports for current treatment guidance of the latest ACR guideline and EULAR 2016 recommendations.



Disclosure: **T. Okano**, None; **K. Inui**, None; **M. Tada**, None; **Y. Sugioka**, None; **K. Mamoto**, None; **T. Koike**, None; **H. Nakamura**, None.

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Abstract Number: 2538

Comparison of Intravenous Versus Subcutaneous Abatacept for the Treatment of Rheumatoid Arthritis in a Routine Clinical Care Setting: A Preliminary, Time to Response Analysis

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SESSION INFORMATION

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Background/Purpose: With the availability of multiple biologic agents, each with different modes of action, use of real world registries provide the manner in which to examine comparative effectiveness in the absence of head-to-head clinical trials inform physicians how they might be used for the treatment of rheumatoid arthritis

Methods: Arthritis Registry Monitoring Database (ARMD) has been collecting prospective patient data since 2005 in all patients seen in routine care. Each patient in this setting (with any diagnosis) completes a 2-sided, 1-page MDHAQ (multidimensional health assessment questionnaire) at every visit while waiting to see the physician in the infrastructure of clinical care. The MDHAQ includes scales for physical function, pain, patient global estimate (PATGL), fatigue, and a self-report RADAI painful joint count. Usage of the biologic medication abatacept as well as its route of administration along with self-reported disease activity and clinic measures were abstracted. Time to first response defined as an improvement in RAPID3 of at least 3.6 was calculated; change from abatacept initiation to first response for self-reported disease activity and clinic measures was estimated by administration route. For those individuals with no response, time to last follow-up was calculated.

Results: 2168 encounters were reviewed for this analysis. 198 subjects were abstracted with an average of 10.9 followup encounters. The average age of the cohort was 53.0 years (±15.0), average duration 10.9 years (±9.0), 177 (89%) were female, and average baseline RAPID3 was 14.5 (±5.8). 154 subjects were given abatacept intravenously (IV), while 44 were administered abatacept subcutaneously (SC). PATGL was slightly higher in the SC group compared to IV, but the overall RAPID3 was not different; no other differences between demographics or baseline clinical features were observed (**Table**). However, the SC group had significantly less followup encounters compared to IV (SC 2.5±1.7 versus IV 13.3±13.8, poisson regression P<0.001). Despite the followup disparity, the average time for abatacept subjects to achieve clinical response was approximately six months regardless of administration route (SC 5.8±5.05 versus IV 6.0±7.0).

Conclusion: Our data suggest that there are no major differences in efficacy of the different administration routes of abatacept in time to response when treating RA patients. Further investigation into previous treatment history to determine refractory status and its impact on abatacept efficacy in warranted. **Table**. Demographic and Clinical Features at Abatacept Initiation as well as Followup Outcomes by Route of Administration

	Abatacept		
	Intravenous	Subcutaneous	P
N	154	44	
Age (years)	53.7 (14.9)	50.6 (15.4)	0.23
Duration (years)	11.4 (9.5)	8.9 (5.4)	0.36
Function [0-10]	3.1 (2.0)	3.5 (2.1)	0.42
Pain VAS [0-10]	5.6 (2.5)	6.4 (2.4)	0.11
Patient Global VAS [0-10]	5.2 (2.3)	6.2 (2.3)	**0.04**
RAPID3 [0-30]	14.2 (5.7)	16.0 (6.2)	0.14
ESR (mm/hr)	26.9 (18.2)	23.3 (28.1)	0.61
CRP (mg/dL)	9.1 (22.5)	11.0 (27.3)	0.78
Female [N(%)]*	140 (90.9%)	37 (84.1%)	0.20
Race [N(%)]			0.30
White	67 (43.5%)	21(47.7%)	
Black	25 (16.2%)	6 (13.6%)	
Hispanic	34 (22.1%)	5 (11.4%)	
Other	28 (18.2%)	12 (27.3%)	
Followup (N obs)†	13.3 (13.8)	2.5 (1.7)	**<0.001**
Clinical Response [N(%)]	42 (32.6%)	4 (5.9%)	**<0.001**
Time to Reponse (months)	6.0 (7.0)	5.8 (5.1)	0.96

*N (Column %) and Chi-square test reported.Otherwise, Mean (SD) and t-test reported.

†Poission regression on count of followup observations reported.

Disclosure: C. J. Swearingen, None; **J. Poon**, None; **H. Bernstein**, None; **Y. Yazici**, BMS, Celgene, Genentech, 2,BMS, Celgene, Genentech, 5.

Abstract Number: 2539

Analysis of Joints Susceptible to Rheumatoid Arthritis (RA) and Their Recovery Sequence Based on DAS28 and Physical Function Based on HAQ with Smart System of Disease Management (SSDM) in China： a Prospective Cohort Study

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Background/Purpose: The disease activity score in 28 joints (DAS28) and health assessment questionnaire (HAQ) serve as guides for the treatment of rheumatoid arthritis (RA). Smart System of Disease Management (SSDM) is a series of mobile phone applications for chronic diseases management, which includes interfaces of both physicians' and patients' applications. After entry the results of DAS28 and HAQ self-assessed by patients, all data can be synchronized automatically to the authorized rheumatologist' mobile terminals. We have confirmed in a validation study that Chinese RA patients can master the use of SSDM for accurate DAS28 self-assessments after training. The purpose of this study is to evaluate the susceptible joints and the recovery sequence of

swollen joint counts (SJCs) and tender joint counts (TJCs) based on DAS28 which self-assessed by Chinese RA patients with SSDM, and to describe the association between DAS28 and HAQ.

Methods: From August 2014 to May 2016, 5,756 RA patients did self-management and synchronized their data with the responsible physicians. The data were extracted online from the mobile terminals of 741 rheumatologists in 295 rheumatology centers across China. Patients were trained to self-assess DAS28 and HAQ with SSDM at baseline, and were asked to repeat the assessment once a month during the treatment. Descriptive statistics were performed for patient and disease characteristics. The mean of each variable was analyzed using t-test assuming.

Results: Among 5,756 RA patients, 4,299 (74.7%) women and 1,457 (25.3%) men. The mean age was 46.37 ±13.32 (18 to 99) years and the median disease duration was 2.58 (0 to 51.83) years. Total 8,533 times self-assessment of DAS28 and HAQ were performed. There were 37,501 joints tender and 22,029 joints swollen in the entire cohort. 807 RA patients did repeat self-assessment at least 28 days apart for 1,361 times. At baseline, 3,363 joints were swollen and 5,176 joints were tender. The top three swollen joints were right wrist (25.28%), right middle proximal interphalangeal (PIP) (25.15%) and left wrist (22.92%), and the top three tender joints were right wrist (43.25%), left wrist (42.63%) and right knee (40.40%). After treatment, the recovery rate of TJCs (25.54%) was significantly better than that of SJCs (21.80%), $p < 0.01$. Hand joints recovered more quickly than other joints. In the last assessment, the three worst recovery swollen joints were left shoulder (-15.50%), right shoulder (-1.79%) and right knee (0.00%). At baseline, HAQ score showed that the top two most difficult physical activities were “bending down to pick up clothing from the floor (reaching)” and “washing and dry entire body (hygiene)”. At the last assessment, the total HAQ score was significantly improved than the baseline in the entire group, $p < 0.01$. The top two difficult physical activities changed as “getting in and out of a car” and “reaching”, which match with joints swollen conditions.

Conclusion: In this study, most involved joints in tender and swelling are hand and wrist joints. After treatment, hand joints recovered quickly but shoulders and knees recovered slowlier, which matched with HAQ assessment results. The results will prompt future rehabilitation.

Disclosure: R. Mu, None; **J. Yang**, None; **H. Wang**, None; **X. Duan**, None; **J. Dong**, None; **F. Zhang**, None; **W. Fan**, None; **H. Guo**, None; **T. Xie**, None; **F. Xiao**, None; **H. Xiao**, None; **Y. Jia**, None; **M. Wang**, None; **Y. Liu**, None; **B. Wu**, None; **Z. Li**, None.

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Abstract Number: 2540

The Longitudinal Impact of Biologic Use on Disability within a RA Registry

N A Shadick[1], Nicole Gerlanc[2], M Frits[1], Bradley S. Stolshek[3], Brenna Brady[2], Christine Iannaccone[4], David Collier[5], Jing Cui[6], Alex Mutebi[7] and Michael Weinblatt[4], [1]Brigham and Women's Hospital, Boston, MA, [2]Health Analytics, LLC, Columbia, MD, [3]Amgen, Thousand Oaks, CA, [4]Rheumatology, Immunology and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [5]Amgen Inc., Thousand Oaks, CA, [6]Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [7]Global Health Economics, Amgen, Thousand Oaks, CA

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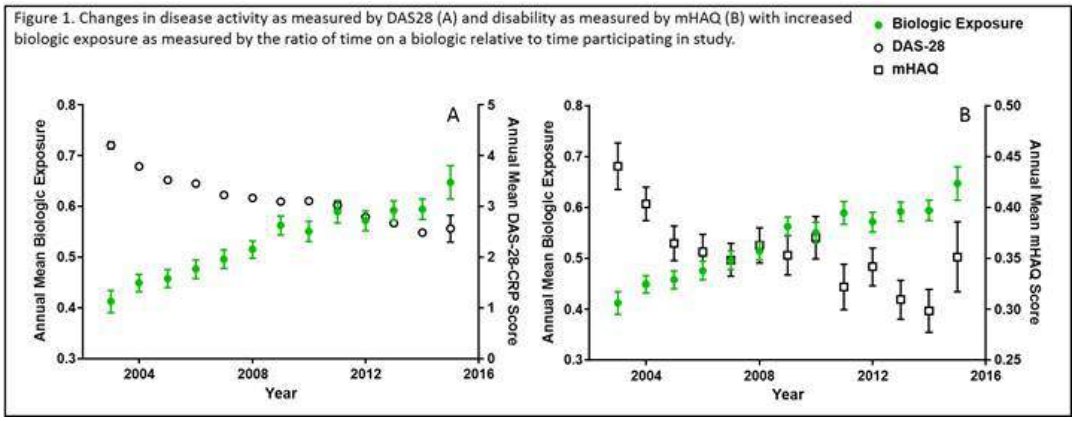
Background/Purpose: Biologics have become the standard of care for treating moderate to severe rheumatoid arthritis (RA) in patients with an inadequate response to small molecule disease modifying antirheumatic drugs. Although biologics have been proven effective in managing RA symptoms and disease activity, their long term impact on disability remains unclear. Longitudinal data from a cohort of RA patients enrolled from a single academic medical center were used to examine the link between RA patient disability and biologic exposure.

Methods: Linear mixed repeated measures regression was used to model the impact of biologic exposure on changes in disease activity (DAS-28 CRP) and disability (modified Health Assessment Questionnaire [mHAQ]). At each follow up, biologic exposure was quantified as the ratio of a patient's time on a biologic relative to their time participating in the cohort. Patients' yearly biologic exposure, outcome scores, and associated covariates were incorporated over a maximum of 13 years into the longitudinal regression models to identify predictors of disease activity and disability at the population level.

Results: The analysis included 1,395 RA patients, 82.2% female, with a total of 6,783 unique physician visits from 2003 to 2015. Average disease duration at enrollment was 12.7 years. Longer biologic exposure was associated with a significant reduction in annual population means for both disease activity and disability ($p < 0.0001$, *Figure 1*). Patients' DAS-28 or mHAQ score at enrollment was the strongest predictor of disease activity and disability in models, respectively ($p < 0.0001$). While, shorter disease duration ($p < 0.0001$), not using a biologic at enrollment ($p < 0.0001$), and use of methotrexate ($p < 0.0003$) were significant predictors of reduced disease activity and disability in the models.

Conclusion: Longer biologic exposure is associated with reduced disease activity and disability in this longitudinal population of RA patients. Although biologic use improves the functional status of the population, patient RA status at enrollment remains the most significant predictor of disability. The results of the longitudinal models developed here suggest that use of biologics may help to

reduce long term disease activity and disability in the RA population.



Disclosure: **N. A. Shadick**, UCB, Amgen, Crescendo Biosciences, BMS, Mallinckrodt, 2,Bristol-Myers Squibb, 5; **N. Gerlanc**, None; **M. Frits**, None; **B. S. Stolshek**, Amgen, 1,Amgen, 3; **B. Brady**, None; **C. Iannaccone**, None; **D. Collier**, Amgen, 1,Amgen, 3; **J. Cui**, None; **A. Mutebi**, Amgen, 1,Amgen, 3; **M. Weinblatt**, Amgen, 2,Bristol-Myers Squibb, 2,Crescendo Bioscience, 2,UCB, 2,Amgen, 5,Bristol-Myers Squibb, 5,Cresendo Bioscience, 5,UCB, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-longitudinal-impact-of-biologic-use-on-disability-within-a-ra-registry

Abstract Number: 2541

Glucocorticoid Use and Low Thoracic Bone Mineral Density Are Predictors for Clinical Fractures in Patients with Rheumatoid Arthritis: Five-Year Findings of the Tomorrow Study

Kenji Mamoto[1], Kentaro Inui[2], Tadashi Okano[1], Yuko Sugioka[3], Masahiro Tada[4], Tatsuya Koike[5] and Hiroaki Nakamura[6], [1]Orthopedic Surgery, Osaka City University Graduate School of Medicine, Osaka, Japan, [2]Rheumatology & Orthopaedics, Higashisumiyoshi Morimoto Hospital, Osaka, Japan, [3]o, Osaka, Japan, [4]Orthopedic Surgery, Osaka City General Hospital, Osaka, Japan, [5]Center for Senile Degenerative Disorders (CSDD), Osaka City University Graduate School of Medicine, Osaka, Japan, [6]Orthopaedic Surgery, Osaka City University Medical School, Osaka, Japan

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Background/Purpose: Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falls and fractures. The present study aimed to prospectively determine the incidence of clinical fractures and associated predictors in patients with RA who participated in the TOMORROW study (UMIN000003876) that started in 2010.

Methods: We evaluated anthropometric parameters, bone mineral density (BMD), disease activity, RA medication, and the incidence of clinical fractures over a five-year period in 202 patients with RA (mean age, 58.6 y; medication with biological agents, 54.9%) and 202 age- and sex-matched healthy volunteers (controls; mean age, 57.4 y). We compared the incidence of clinical fractures between patients and controls between 2010 and 2015 and analyzed associated predictors in the patients using cox proportional hazard regression analysis.

Results: The incidence of clinical fractures did not significantly differ between patients with RA (0.042/person-years; py) and controls (0.034/py) within the five-year period ($p = 0.35$). And also, there were no difference in fractures sites between the two groups. Multivariable cox proportional hazard regression analysis adjusted for confounding factors including age, sex, smoking, and body mass index revealed that low BMD of the thoracic vertebrae (< 0.7 g/cm^2) at entry was significantly associated with the incidence of clinical fractures (hazard ratio [HR], 2.63; 95% confidence interval [CI], 1.49 to 4.66; $p = 0.001$) in all participants group (Table 1). Although medication with glucocorticoid (GC) at entry was also a significant risk factor for fractures (HR, 2.14; 95% CI, 1.24 to 3.68; $p = 0.006$), RA morbidity was not (HR, 1.22; 95% CI, 0.74 to 2.01; $p = 0.437$). Among patients with RA, low BMD of the thoracic vertebrae (< 0.7 g/cm^2) at entry was the most prominent risk factor for fractures (HR, 3.53; 95% CI, 1.52 to 8.15; $p = 0.003$). Additionally, medication with GC at entry (HR, 2.46; 95% CI, 1.28 to 4.73; $p = 0.007$) was a significant risk factor for fractures in the patients. A mean GC dosage of ≥ 2 mg/day during the five-year period increased risk for fractures in the patients (HR, 2.67; 95% CI, 1.06 to 6.72; $p = 0.037$).

Conclusion: There were no difference in the incidence of clinical fractures between patients with RA and controls during a period of five years. Low BMD of the thoracic vertebrae and low GC doses (≥ 2 mg/day) are apparently significantly associated with the incidence of clinical fractures among patients with RA.

Disclosure: K. Mamoto, None; **K. Inui**, None; **T. Okano**, None; **Y. Sugioka**, None; **M. Tada**, None; **T. Koike**, None; **H. Nakamura**, None.

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Abstract Number: 2542

Reducing the Dosage of Glucocorticoid to Zero Might Decrease Risk of Clinical Fractures in Patients with Rheumatoid Arthritis: Five-Year Findings of the Tomorrow Study

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Background/Purpose: Patients with rheumatoid arthritis (RA) who have muscle weakness and stiff or painful joints might be at increased risk of falls and fractures. The present study prospectively investigates correlations between decreasing dosage of glucocorticoid (GC) and the incidence of clinical fractures in patients with RA based on the five-year findings of the TOMORROW study (UMIN000003876) that started in 2010.

Methods: We evaluated anthropometric parameters, bone mineral density, disease activity, RA medication, and the incidence of clinical fractures over a period of five years in 202 patients with RA (mean age, 58.6 years; mean disease duration, 14.0 years). We also assessed the effects of adjusting GC doses on the incidence of clinical fractures over the same period in patients with RA using cox proportional hazard regression analysis.

Results: The incidence of clinical fractures in patients with RA was 0.042/person-years (py). There were 84 RA patients (41.6%) treated with GC whose incidence rate and number of clinical fractures were significantly higher than those without GC treatment (27.4% vs. 11.9%; p = 0.008; 0.063 vs. 0.012 py; p = 0.012, respectively). After adjusting for confounding factors including age, sex, smoking, and body mass index, multivariable cox proportional hazard regression analysis revealed that GC administered within the five-year period was a significant risk factor for clinical fractures

(hazard ratio [HR], 2.35; 95% confidence interval [CI], 1.18 to 4.68; p = 0.015). An average of GC dose during the 5-year period of ≥ 2 mg/day increased risk for fractures in patients with RA (HR, 2.67; 95% CI, 1.06 to 6.72; p = 0.037). Although only reducing the GC dose did not decrease the risk of clinical fractures in patients with RA (HR, 0.75; 95% CI, 0.31 to 1.82; p = 0.521), risk was significantly decreased when the GC dose was reduced to zero within the five-year period (HR, 0.28; 95% CI, 0.11 to 0.72; p = 0.008).

Conclusion: Medication with GC was a significant risk factor for clinical fractures, and low GC doses (≥ 2 mg/day) are apparently significantly associated with an increased frequency of fractures among patients with RA. However, achieving freedom from GC among RA patients within five-years could decrease the risk for clinical fractures. We concluded that GC medication should be tapered to zero over a period of five years in patients after RA activity is controlled well.

Disclosure: K. Mamoto, None; **K. Inui**, None; **T. Okano**, None; **Y. Sugioka**, None; **M. Tada**, None; **T. Koike**, None; **H. Nakamura**, None.

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Abstract Number: 2543

Impact of Concomitant Methotrexate Administration on the Risk of Infections Among Rheumatoid Arthritis Patients Treated with Anti-TNF in Real-World

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Background/Purpose: Methotrexate (MTX) is routinely used among rheumatoid arthritis (RA) patients treated with anti-TNF agents to enhance treatment efficacy and minimize the dose of biologic therapy. The aim of this analysis was to evaluate the risk of infections among patients treated with infliximab (IFX) or golimumab (GLM) in combination with MTX in the first 12 months following the start of biologic therapy.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment with infliximab or GLM for RA, ankylosing spondylitis, or psoriatic arthritis (PsA), or with ustekinumab for PsA. Eligible participants for this analysis included RA patients treated with IFX or GLM enrolled since 2002 and 2010, respectively, in combination or in monotherapy with MTX. Patients were excluded from the analysis if concomitant corticosteroids were used during any time point from baseline to 12 months of treatment. Serious and non-serious infections were assessed with the incidence density rate (IDR) as events /100 patient-years (PY). Poisson regression was used to compare the IDRs of infections between treatments while controlling for baseline disease activity and length of exposure to biologic treatment.

Results: A total of 526 RA patients were included in the analysis. At baseline, 71 (13.5%) were on anti-TNF monotherapy, while 109 (20.7%) were on combination therapy with MTX ≤15mg (low-moderate dose), and 346 (65.8%) with MTX>15mg (high dose). The vast majority (93.3%) of patients were bio-naïve, 73.4% were female, mean (SD) age was 55.7 (13.4) years and disease duration since diagnosis was 7.5 (8.3) years. A total of 163 (37.4 events/100 PY) infections were reported by 104 (19.8%) patients and a total of 10 (2.8 events/100 PY) serious infections. Specifically, the mean (95% CI) adjusted IDR was 23.9 (14.4-39.8) events/100 PY for monotherapy, 30.2 (21.4-42.7) events/100 PY for MTX low-moderate dose, and 30.5 (24.9-37.4) events/100 PY for MTX high dose. Furthermore, among patients treated with MTX, no association between use of other concomitant DMARDs in the treatment regimen and risk of infection was observed while adjusting for MTX dose with mean (95% CI) IDR of 33.6 (25.6-44.1) events/100 PY for DMARDs vs. 33.8 (25.2-45.3) events/100 PY for no DMARDs.

Conclusion: The results of this real-world observational study have shown that, overall, a low incidence of serious infections is observed with anti-TNF treatment. Concomitant use of anti-TNFs and MTX, with or without other DMARDs, is not associated with a higher incidence of total infections.

Disclosure: J. Kelsall, Janssen Inc., 5; **A. Jaroszynska**, None; **L. Bessette**, Janssen Inc., 5; **R. Joshi**, Janssen Inc., 5; **I. Fortin**, None; **J. Stewart**, Janssen Inc., 5; **K. Anderson**, Janssen Pharmaceutica Product, L.P., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **F. Nantel**, Employee of Janssen Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3.

Abstract Number: 2544

Glucocorticoid Treatment for 12 Weeks in Early Rheumatoid Arthritis Is Related to an Increase in BMI

Samina A. Turk[1], Linda A. Rasch[2], Sylvia de Boer[1], Mike T. Nurmohamed[1,3], Willem F. Lems[2,4] and Dirkjan van Schaardenburg[1,5], [1]Rheumatology, Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [3]Rheumatology, Amsterdam Rheumatology and immunology Center, Location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [4]Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [5]Rheumatology, Amsterdam Rheumatology and immunology Center, location Academic Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands

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Background/Purpose: After the diagnosis of rheumatoid arthritis (RA), glucocorticoids (GCs) are a common initial treatment in addition to methotrexate (MTX)(1). However, many patients are afraid to gain weight as side effect of the GCs. Therefore, we studied the effect of GCs on body mass index (BMI) after 4 and 12 weeks of treatment.

Methods: Consecutive patients from our early arthritis cohort, with a disease duration of <2 years, at least 2 swollen joints and no prior DMARD treatment were investigated. Patients were divided in two groups: GC-users were treated with MTX and GC (week 1: 30 mg, week 2: 20 mg, week 3: 15 mg, week 4-8: 10 mg, week 9-12: 7,5 mg), and non GC-users were treated with monotherapy MTX. Patients were placed in the GC-users group when they had a high disease activity and/or unfavourable prognostic factors. For this study the 22 non GC-users were matched on age to 22 GC-users. At baseline, week 4 and week 12, weight, height, BMI and a DAS44 were assessed. For statistical analyses, patients with an increase in BMI were compared with patients with a stable or decreased BMI.

Results: Of the 44 early RA patients, 24 were male; mean age was 54 years. Patients with versus without GCs had a mean weight at baseline of 74.2 and 82.3 kg, respectively (table 1). Both groups had a similar, large mean improvement in DAS. After 4 weeks of treatment, BMI increased in 41% of the GC-users versus 32% in de non GC-users, (p= 0.532). After 12 weeks, 55% of the GC-users had an increase in BMI versus 23% in the non GC-users, (p= 0.025, table 2). There is no statistically significant difference in DAS44 between the high and low risk group at baseline or after 12 weeks of treatment.

Conclusion: Early RA patients treated with MTX and GCs more often have an increase in BMI compared to patients treated with MTX monotherapy after 12 weeks of treatment. This difference is not caused by a difference in disease activity. These substantial differences appear to be caused by GC-induced changes in body composition and need to be further investigated during a longer follow-up period. Literature: 1) Boers M et al. Lancet 1997 Aug 2;350(9074):309-18.

Table 1

	Baseline		Week 4		Week 12	
	MTX	MTX and GC	MTX week 4	MTX and GC	MTX	MTX and GC
Weight, kg	82.3 (18.1)	74.2 (16.1)	82.2 (18.1)	74.2 (15.8)	81.9 (18.1)	75.6 (15.7)
Height, m	1.74 (0.1)	1.74 (0.1)	1.74 (0.1)	1.74 (0.1)	1.74 (0.1)	1.74 (0.1)
BMI, kg/m²	27.0 (4.7)	24.5 (4.8)	26.9 (4.7)	24.5 (4.8)	26.8 (4.7)	25.0 (4.9)
DAS44	2.8 (1.9-3.0)	2.9 (2.6-4.0)	1.9 (1.3-3.1)	1.2 (0.8-1.6)	1.4 (1.2-2.5)	1.3 (0.7-1.8)
ESR, mm/hour	11.5 (6.5-26.3)	27.0 (8.8-58.0)	11.0 (5.0-23.5)	8.0 (5.0-12.0)	8.0 (5.0-20.0)	9.0 (2.0-16.5)

Values are reported as mean (SD) or median (IQR); GC: glucocorticoids, kg: kilogram, SD: standard deviation, m: meter, BMI: body mass index, kg/m²: kilogram per square meter, DAS: disease activity score of 44 joints, IQR: interquartile range, ESR: erythrocyte sedimentation rate, mm/hour: millimeter per hour

Table 2

		BMI increased	BMI constant or lost
After 4 weeks	Non GC-users	7 (31.8)	15 (68.2)
	GC-users	9 (40.9)	13 (59.1)
After 12 weeks	Non GC-users	5 (22.7)	17 (77.3)
	GC-users†	12 (54.5)	9 (40.9)

Values are reported as frequency (%); GC: glucocorticoids, BMI: body mass index; † 1 missing

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Disclosure: S. A. Turk, None; **L. A. Rasch**, None; **S. de Boer**, None; **M. T. Nurmohamed**, None; **W. F. Lems**, Pfizer Inc, 2,BMS, 8,Abbvie, 8,Lilly, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **D. van Schaardenburg**, None.

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Abstract Number: 2545

Physicians, but Not Patients, Agree That EULAR Good Response Indicates Remission after 12 Weeks Treatment of Early Rheumatoid Arthritis

Samina A. Turk[1], Dirkjan van Schaardenburg[1,2], Linda A. Rasch[3], Véronique Lugt[1], Willem F. Lems[1,3], Mike T. Nurmohamed[1,4] and Lilian van Tuyl[3], [1]Rheumatology, Amsterdam Rheumatology and immunology Center, location Reade, Amsterdam, Netherlands, Amsterdam, Netherlands, [2]Rheumatology, Amsterdam Rheumatology and immunology Center, location Academic Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [3]Rheumatology, Amsterdam Rheumatology and immunology Center, location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands, [4]Rheumatology, Amsterdam Rheumatology and immunology Center, Location VU University Medical Center, Amsterdam, Netherlands, Amsterdam, Netherlands
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SESSION INFORMATION

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Background/Purpose: The Disease Activity Score (DAS) and the European League Against Rheumatism (EULAR) response criteria are commonly used to describe disease activity in Rheumatoid Arthritis (RA) patients(1). This study investigates the relationship between remission perceived by physicians versus patients according to the EULAR response criteria.

Methods: Consecutive RA patients with high disease activity and/or unfavourable prognostic factors and no prior treatment were investigated. Patients were treated with methotrexate and prednisolone (week 1: 30 mg, week 2: 20 mg, week 3: 15 mg, week 4-8: 10 mg, week 9-12: 7,5 mg). After 12 weeks of treatment the EULAR response was determined, according to the DAS44. Physician perceived remission was defined as a physician global assessment ≤ 20 on a visual analogue scale (VAS), phrased: *"How active do you think the rheumatoid arthritis of your patient is today?"*. For patient perceived remission the following question was phrased: *"Would you say that, at this moment, your disease activity is as good as gone? (yes/no)*(2).

Results: In 75 early RA patients the mean (SD) DAS44 decreased from 3.4 (1.2) to 1.5 (1.0) after 12 weeks of therapy. The number of good, moderate and none EULAR responders were 54 (72%), 14 (19%) and 7 (9%) respectively. After 12 weeks 72% of the physicians perceived remission as well as 72% of the patients, see figure 1. The spearman's rho test showed significant correlations between the EULAR response versus perception of physicians, the EULAR response versus the perception of patients and the perception of patients versus physicians, respectively $r=0.645$ ($p<0.001$), $r=0.393$ ($p=0.001$) and $r=0.267$ ($p=0.036$). In 61% of the good EULAR responders the physician as well as the patient perceived remission, but in 33% only the physician perceived remission, see figure 2. Patients who did not perceive remission had a significantly different mean (SD) DAS44 of 1.4 (0.5) compared to 0.9 (0.5) in the patients who perceived remission ($p=0.001$). The difference in DAS44 is caused by tender joint count (TJC) and patient global (PG) but not by swollen joint count or erythrocyte sedimentation rate.

Conclusion: There is a significant correlation between EULAR response and both physicians and patients perceived remission in early RA patients. However, 33% of the patients with a good EULAR response and physician perceived remission, perceive no remission themselves. These patients had a significantly higher DAS44, caused by a higher TJC and PG. Literature:

1) Van Riel et al. Clin Exp Rheumatol 2005 Sep;23:S93-99

2) Van Tuyl LH et al., Ann Rheum Dis 2015 Jun;74(6):1004-10.

Figure 1.

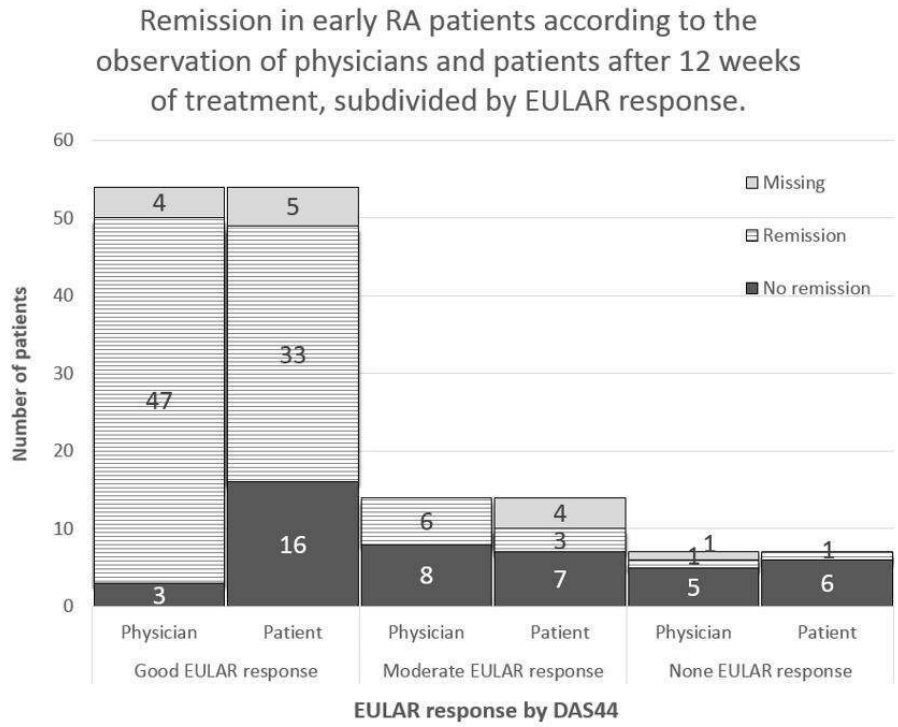

Figure 2.

		good EULAR response		moderate EULAR response		none EULAR response	
		Physician perceived remission		Physician perceived remission		Physician perceived remission	
		Yes	No	Yes	No	Yes	No
Patient perceived remission	Yes	28 (61%)	2 (4%)	1 (10%)	2 (20%)	0 (0%)	0 (0%)
	No	15 (33%)	1 (2%)	3 (30%)	4 (40%)	1 (17%)	5 (83%)

Values are reported as frequency (%)

Disclosure: S. A. Turk, None; **D. van Schaardenburg**, None; **L. A. Rasch**, None; **V. Lugt**, None; **W. F. Lems**, Pfizer Inc, 2,BMS, 8,Abbvie, 8,Lilly, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **M. T. Nurmohamed**, None; **L. van Tuyl**, None.

Abstract Number: 2546

Utilization of Biologic Therapy in Patients with Rheumatoid Arthritis and Cancer

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Background/Purpose: Biologic therapy for rheumatoid arthritis (RA) downregulates the immune response. Tumoral immunity is an important host mechanism against cancer progression, and for this reason, biologic therapy is often discontinued when a patient with RA develops cancer. Objectives: To determine the utilization of biologic therapy in patients with RA and cancer, after their cancer diagnosis.

Methods: We performed a retrospective cohort study of patients with RA and cancer seen at National Cancer Institute designated Comprehensive Cancer Center between 2002 and 2014. Patients were initially identified as having RA if they had a claim with a diagnostic code for RA (714) according to the International Classification of Diseases (ICD-9). Two independent reviewers examined all electronic medical records, and selected patients that fulfilled the following criteria in addition to a claim code: age ≥ 18 years, diagnosis of RA by a rheumatologist, and/or current or prior use of a DMARD or biologic agent. Patients with more than one primary or non-melanoma skin cancer were excluded. Descriptive statistics were generated to summarize patient characteristics, biologic use, and time to biologic therapy onset after cancer diagnosis. Kaplan-Meier methods were used to estimate time from biologic therapy onset to recurrence.

Results: 1719 patients met the inclusion criteria. Of these, 563 had received biologic therapy at any time, before and/or after cancer diagnosis. Most were female (72%), with a mean age at cancer

diagnosis of 59 years (±13 years). Eighty-one had a follow-up of less than 3 months after cancer diagnosis and were not included in the analysis; 43 had discontinued biologic therapy before the cancer diagnosis; 313 were receiving biologic therapy at the time of cancer diagnosis, and in this group 225 (72%) discontinued therapy within 3 months of diagnosis, and 88 (28%) continued treatment. In addition, 126 patients initiated biologic therapy after their cancer diagnosis with a median of 8 years (range 0.04-39). Overall, 214/1719 (12%) of the patients with RA received a biologic after their cancer diagnosis. The most common tumor site among the 214 patients was breast (28%) followed by lymphoma and prostate in 7% each, and melanoma in 6%. Biologic therapies included: tumor necrosis factor inhibitors (TNFi) (88%), rituximab (7%), abatacept (4%), and tocilizumab (1%). Almost 20% switched biologic therapy at a later stage. Fifty-seven (27%) patients who received biologic therapy had active cancer or developed a recurrence during follow-up, and 14 (7%) died. Recurrence/active cancer rate was 12% in first year after starting biologic therapy (or after diagnosis of cancer if biologic had been continued), 16% by 2 years, and 33% by 5 years.

Conclusion: Biologic therapy was used in 12% of patients with RA after their cancer diagnosis, most frequently TNFi. One third had active cancer or a recurrence during follow-up. Additional controlled studies are needed to determine if the risk of cancer recurrence is higher in patients with RA receiving biologic therapy after developing cancer.

Disclosure: N. V. Zamora, None; **H. Siddhanamatha**, None; **A. Barbo**, None; **J. Tayar**, None; **H. Lin**, None; **M. Suarez-Almazor**, National Institute for Musculoskeletal and Skin Disorders, 2.

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Abstract Number: 2547

Quantification of Adverse Glucocorticoid Effects on Skin in Rheumatoid Arthritis

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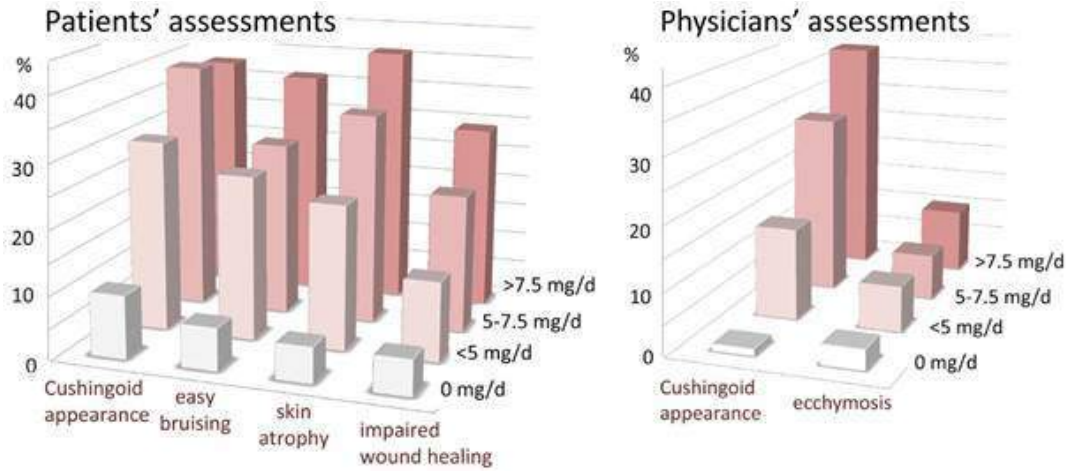
Background/Purpose: Glucocorticoids (GCs) are frequently and often chronically used for the treatment of rheumatoid arthritis (RA) and other immune diseases and vasculitis. An estimated 0.8–1.2% of the population in developed countries at any moment in time uses GCs. EULAR guidelines state that the adverse effects (AEs) of GC therapy should be considered and discussed with the patient before treatment is initiated.[1] However, reliable quantitative data on cutaneous AEs of low- to medium dose GC's are lacking.

Methods: We performed a study to assess the occurrence of cutaneous AEs of GCs and its association with current and cumulative GC-doses. This cross-sectional study was performed at the outpatient departments of the Charité University Medicine Berlin and the University Medical Center Utrecht; 381 RA-patients were included. Patients were classed into 4 groups, according their mean daily dose during the past 12 months: 0 mg (n=87), <5mg (n=108), 5–7.5 mg (n=130), and >7.5 mg (n=56) of prednisolone equivalent. Cushingoid appearance, ecchymosis, stretch marks, steroid acne, perioral dermatitis, hirsutism, and scalp hair loss were assessed by physical examination using a predefined scoring system, and by patients' self-assessments. Easy bruising, skin atrophy, and impaired wound healing were patients' self-assessed reports. Data were analyzed according GC dose categories and cumulative doses.

Results: Of the 381 patients, 76% was female; 67% was rheumatoid factor positive and 55% had erosive joint disease. The median (quartiles) disease duration was 9 (4-17) years. The mean number of lifetime conventional synthetic DMARDs used was 2.6 and for biological DMARDs it was 1.0. The median (quartiles) total duration of GC use was 4.0 (1.5-10) years, and the mean (sd) cumulative dose was 14 (17) g. Cushingoid habitus, easy bruising, skin atrophy, and impaired wound healing as reported by patients occurred significantly more frequent in those using GC the past 12 months, compared to those not using GC, see figure. At physicians' assessments, only Cushingoid habitus and ecchymosis were more prevalent in GC-users, see figure. The prevalence of these AEs was statistically significantly positively associated with current and cumulative GC dose. There was a low occurrence of abnormal stretch marks, acne, perioral dermatitis, alopecia, and hirsutism in our study, and there were no correlations between these AEs and GC therapy.

Conclusion: Cushingoid habitus, easy bruising, skin atrophy, impairment of wound healing, and ecchymosis are AEs of GC which can be observed relatively frequently in clinical daily practice. They are GC dose-dependent (current and cumulative dose). At the lower GC doses used in RA, abnormal stretch marks, acne, perioral dermatitis, alopecia, and hirsutism are rare AEs of GC.



Disclosure: F. Buttgereit, None; **J. Amann**, None; **F. Breitenfeldt**, None; **D. Huscher**, None; **J. W. Bijlsma**, None; **J. W. Jacobs**, None.

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Abstract Number: 2548

Single 1g Infusion Vs Double 1g Infusion of Rituximab in Rheumatoid Arthritis in a Large Teaching Hospital: Potential Clinical Benefits and Financial Savings

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Background/Purpose: Recent trial data from Mariette et al. investigating a single-dose 1g

rituximab regimen as opposed to a double-dose 1g rituximab regimen in patients with RA and a good or moderate EULAR response to an initial double-dose rituximab regimen, demonstrated non-inferiority in terms of a DAS-28 response [1]. There may be potential benefits of a lower dose rituximab regimen to patient safety and care, such as reducing the risk of hypogammaglobulinaemia and serious infection [2] and a reduced delay in repeat treatment time. There are also potential cost savings and health economic implications to a lower dose rituximab regimen. The aims of this audit were to assess whether our department was prescribing rituximab in accordance to National Institute of Clinical Excellence (NICE) guidance [3] and to evaluate the potential cost savings that could be made in a large cohort of patients receiving repeat rituximab treatment for RA.

Methods: Notes were reviewed from a random sample of 50 patients on our electronic biologic database receiving rituximab for RA at the Freeman Hospital, Newcastle-Upon-Tyne between 2013 and 2016. Data on prior biologic exposure, frequency of rituximab infusions and EULAR response to rituximab was recorded.

Results: The electronic database identified 210 patients who were receiving rituximab at least annually. Complete data was available from to audit from 44/50 of the random sample. 37/44 patients had received a prior anti-TNF therapy and 6 patients had documented reasons for not having received anti-TNF therapy (ie history of malignancy or interstitial lung disease). 1 patient had been started on rituximab pre-dating our electronic records. 36/40 (82%) patients had a good or moderate response to rituximab and in the other 8 patients, rituximab was either stopped or were under review pending a management decision. No-one had rituximab infusions more frequently than 6 monthly. This data was in keeping with NICE guidance [3]. In order to estimate the potential cost savings to our department by using a single-dose 1g rituximab regimen rather than a standard double-dose regimen, we calculated the mean number of treatments given to our cohort of patients with RA as 1.66 1g infusions per year. If this infusion number was halved to 0.83 1g infusions per year, the estimated annual saving to our department would be £435,000 (this is based on 210 patients receiving repeat rituximab infusions in 2015/2016 and the price per 1g rituximab infusion plus infusion costs of £2,495).

Conclusion: Current practice in the Freeman Hospital, Newcastle-Upon-Tyne is adherent to NICE guidance [3]. Using a single-dose repeat rituximab regimen rather than a double-dose repeat rituximab regimen has been demonstrated to have non-inferior clincial outcome data [1] and has potential long-term safety benefits to patients. In our trust, which prescribes a large amount of rituximab for RA, we could potentially save around £435,000 per annum by switching to a single-dose rituximab regimen. [1] Mariette X, Rouanet S et al. Evaluation of low-dose rituximab for the retreatment of patients with active rheumatoid arthritis: a non-inferiority randomised controlled. Ann Rheum Dis. 2014;73:1508–14. [2] Gottenberg JE, Ravaud P et al. Low serum IgG level after rituximab is associated with an increased risk of serious infections in rheumatoid arthritis: data of the AIR Registry. Arthritis Rheum 2011;63(Suppl):S641. [3] NICE TA195. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor. 2010. https://www.nice.org.uk/guidance/ta195

Disclosure: B. Roberts, None; **A. Langridge**, None; **J. Wilkinson**, None; **E. Jones**, None; **E. Lea**, None; **B. Hargreaves**, None; **D. Walker**, None; **M. Lee**, None.

infusion-vs-double-1g-infusion-of-rituximab-in-rheumatoid-arthritis-in-a-large-teaching-hospital-potential-clinical-benefits-and-financial-savings

Abstract Number: 2549

Effect of Interleukin-6 Receptor Blockade on Proprotein Convertase Subtilisin/Kexin Type 9 Serum Levels in Rheumatoid Arthritis Patients

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Background/Purpose: Rheumatoid arthritis (RA) has been acknowledged to increase cardiovascular mortality probably due, in part, to a lipid profile different from that observed in the general population. Tocilizumab (TCZ), is associated with increased lipid levels in the context of decreased levels of inflammatory markers. The mechanisms by which TCZ increases lipids are not yet fully understood. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that regulates cholesterol metabolism through low-density lipoprotein receptor degradation, linked to cardiovascular risk. The purpose of the present study was to examine whether PCSK9 serum levels are related to the abnormalities in the lipid profile that TCZ causes in RA patients.

Methods: The prospective TOCRIVAR study (Clin Trial.gov identifier: NTC01752335) analyzes the influence of TCZ on different cardiovascular risk factors in RA patients. Patients received TCZ

8 mg/kg IV q4w for 52 weeks. None of the patients was under statins treatment. Available serum samples were analyzed at baseline and at weeks 12, 24 and 52. PCSK9, lipoproteins serum concentrations and standard lipid profiles were assessed at every visit. Dual-x-ray-absorptiometry-derived body composition (DEXA) and abdominal adiposity by magnetic resonance imaging, were assessed at basal visits and at the end of the study. Cox-regression analysis was performed to study the influence of TCZ over PCSK9 serum levels and lipid profile, adjusting for body composition and PA.

Results: 26 RA patients, 2 males and 24 females, 52±2 years old, were included in the study. Median PCR (Δ-5.3[-0.2--14.8] mg/dl, p=0.00) and DAS28 (Δ-1.8[-1.5--2.2] p=0.00) were markedly reduced within the first 12 weeks and they remained significantly lower compared to basal visit levels throughout the one year of TCZ treatment. Average total cholesterol, HDL-C, and apolipoprotein A and B levels increased after 3 and 6 months of treatment; however, no statistical significant difference were observed, in these values, between the final visit at 12 months and the basal visit. In contrast, lipoprotein A serum concentration decreased after 6 months of TCZ treatment (Δ-3[-2--12] mg/dl, p=0.03). No changes were observed in triglycerides. PCSK9 basal serum concentration was not modified by TCZ treatment and did not differ respect to each visit (mean differences after 3, 6 and 12 months were, 72[-59-241], 67[-133-147] and 90[-252-137] CI95% ng/ml, respectively). Subcutaneous abdominal fat tissue was inferior after one year of treatment (Δ-1766[-6555--450] cm2, p=0.02); however, visceral abdominal fat tissue (p=0.99), VAAT/SAAT ratios (p=0.72) and the percentage of trunk fat (DEXA) (p =0.26) were not influenced by TCZ treatments.

Conclusion: TCZ-induced changes in the lipid profiles of RA patients are not related to degradation of the low-density lipoprotein receptor mediated by PCSK9. One year of treatment with TCZ does not seem to influence body composition adiposity of RA patients, two elements related with lipid profiles. Interestingly, TCZ treatment causes a marked reduction of lipoprotein a plasma concentration, an independent cardiovascular risk factor.

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Abstract Number: 2550

Long Persistence of Anti-Drug Antibodies in Adalimumab Treated RA Patients

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Background/Purpose: The application of biologic substances is subject to a risk to develop antibodies against these structures causing adverse events or loss of efficacy. For TNF blocking antibodies such as adalimumab a strong immunogenicity has been demonstrated which is associated with a formation of anti-drug antibodies. In numerous studies the frequency of anti-adalimumab (anti-ADL) antibodies has been described in detail. In our study we aimed to assess the persistence of anti-drug antibodies after termination of adalimumab (ADL) treatment.

Methods: Eighteen RA patients (16 female/ 2 male, mean age 53.1±8.2 years) treated with adalimumab for mean 23.4±17 months (range 4-74 months) were identified as anti-ADL antibody positive and were switched to another biological treatment, 5 patients were treated with another TNF inhibitor (4 with etanercept, 1 with golimumab), and 13 with a B-cell depleting therapy (rituximab). Patients were followed-up for at least two years to analyse the persistence of anti-ADL antibodies. For the determination of anti-ADL antibodies the Promonitor® -anti-ADL assay (Proteomika, Spain) was used according to the manufacturer's instructions. The assay is designed as a bridging assay with a cut-off value of 10 AU/ml. For calculation of results the data analysis software (http://www.myassays.com) was used.

Results: After termination of adalimumab therapy the mean±SD level of anti-ADL antibodies was 491±713 AU/ml (in a range between 13 and >2000 AU/ml). Within the following two years anti-ADL antibody levels decreased significantly ($p<0.05$ t-test for paired samples). In 5 patients anti-ADL antibodies disappeared completely. However, 13 patients remained anti-ADL positive with a mean±SD level of 237±463 AU/ml (range 10 – 1801 AU/ml) two years after termination of ADL therapy. In eight patients a serokonversion was observed within a further follow-up with the last positive result for anti-ADL antibodies after mean 47 months (range 24-72 months). We did not find an influence of the current treatment on the persistence of anti-ADL antibodies. Even in patients receiving a B-cell directed therapy anti-ADL antibodies persisted for ≥ 24 months in 12 out of 15 patients. However, patients with persisting anti-ADL antibodies had been treated longer with ADL and had higher antibody levels after termination of therapy, with mean treatment duration of 25±17.8 months and 15.4±11.3 months and antibody levels of 652±781 AU/ml and 74±50.0 AU/ml after termination of therapy, in patients with persisting antibody levels and patients without anti-ADL antibodies after 2 years, respectively.

Conclusion: Our results clearly show that anti-adalimumab antibodies are stable and persist for several months or even years after termination of therapy. High antibody levels are not completely resolved by several courses of a B-cell depletion therapy. Supported by Pfizer Pharma GmbH

Germany

Disclosure: J. Kekow, None; **S. Drynda**, None.

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Abstract Number: 2551

Impact of Multmorbidity on Disability and Disease Activity over Time in Patients with RA Taking Biologics: Results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis

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Background/Purpose: Multimorbidity is increasingly prevalent in western populations and has the potential to influence disease specific outcomes. Rheumatoid arthritis (RA) is a chronic inflammatory arthritis which has known associations with a number of specific other morbidities such as cardiovascular disease and cancer. However, the effect of the burden of multiple chronic diseases on RA specific disease outcomes is less well described, and may be of particular interest

in patients taking expensive biologic drugs. The aim of this study was to describe the relationship between multimorbidity and disability and disease activity over time in a large cohort of patients with RA taking biologic drugs.

Methods: The British Society for Rheumatology Biologics Register for RA (BSRBR-RA) recruited patients with a physician diagnosis of RA from across the UK starting biologic therapy. This study included only patients starting their first biologic, to exclude morbidity acquired as a consequence of previous biologic treatment. At baseline assessment, data were collected on demographics, multimorbidity, medication and disease specific variables, including disease activity (DAS28 score) and disability (HAQ). HAQ and DAS28 were collected 6 monthly for the first three years. The association at baseline between multimorbidity burden (assessed using the rheumatic diseases comorbidity index (RDCI) (ref)) and the outcomes HAQ and DAS28, adjusting for age, gender, smoking status, year of recruitment, disease duration and rheumatoid factor (RF) positivity was assessed using linear regression models; subsequently mixed effects models were used to investigate the same associations over time. Sensitivity analyses were performed to examine these associations in the subgroup of patients taking tumour necrosis factor inhibitors (TNFi).

Results: A total of 13957 patients were included, 10367 (76%) were female, median (IQR) age was 57 years (49-65) and 8655 (64%) were RF positive. Median (IQR) RDCI at baseline was 1 (0-2). Multimorbidity burden was significantly associated with disability but not disease activity at baseline(table 1); throughout follow up it was associated with both outcomes, adjusted beta (95% confidence interval (CI)) 0.17 (0.16,0.18) and 0.37 (0.35,0.40) for HAQ and DAS28 respectively. Similar results were seen when the analysis was confined to TNFi users alone.

Table 1

	All biologics n=13957		**TNFi users only** n=13094	
Linear regression	*Univariate* Beta (95% CI)	*Multivariate* Beta (95% CI)	*Univariate* Beta (95% CI)	*Multivariate* Beta (95% CI)
HAQ	0.08 (0.07, 0.08)	0.06 (0.05, 0.07)	0.08 (0.07, 0.09)	0.06 (0.05, 0.07)
DAS28	0.03 (0.02, 0.04)	-0.01 (-0.02, 0.01)	0.04 (0.02, 0.05)	-0.01 (-0.02, 0.01)
Mixed effects model				
HAQ	0.11 (0.10, 0.11)	0.17 (0.16, 0.18)	0.11 (0.10, 0.12)	0.17 (0.16, 0.18)
DAS28	0.24 (0.22, 0.26	0.37 (0.35, 0.40)	0.10 (0.08, 0.11)	0.37 (0.35, 0.41)

Conclusion: A higher burden of multimorbidity in patients with RA starting their first biologic drug is associated with more disability and higher disease activity over time. The presence of one or more comorbid conditions is an important factor to consider when assessing outcomes in these patients.

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Abstract Number: 2552

Predictive Value of Chest HRCT Patterns for Respiratory Adverse Event Among RA Patients Treated with Biological Therapy: Long-Term Results from an Observational Study

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Background/Purpose: Biological therapy brought an important advance in the treatment strategy for rheumatoid arthritis (RA). However, the safety of biological therapy on RA patients with respiratory involvement such as interstitial lung disease (ILD) and airway disease (AwD) is still controversial. The aim of this study was to assess the association between risk for respiratory adverse events (RAE) and chest High-resolution computed tomography (HRCT) patterns and to detect predictors for RAE among RA patients receiving biological therapy.

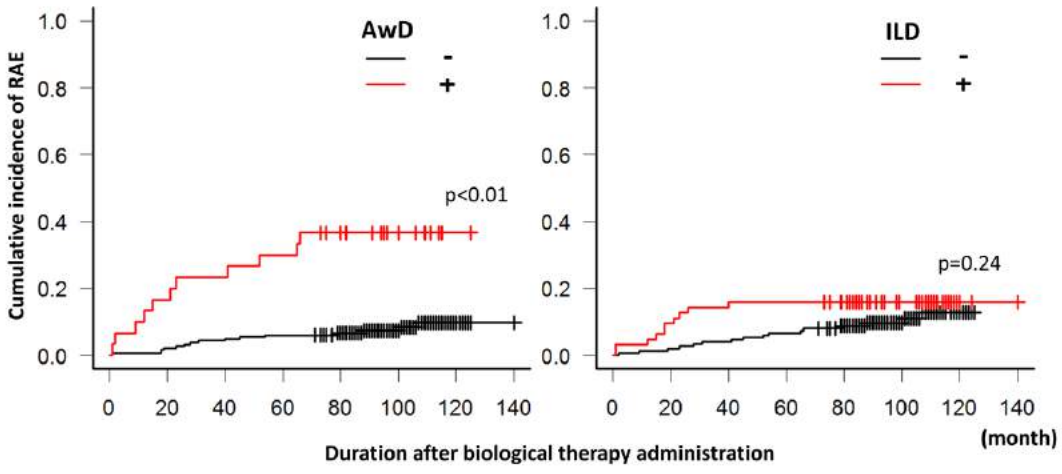
Methods: We conducted a retrospective observational study including 235 patients with RA who received biological therapy in the seven years period of 2004 to 2010. The patients were clinically followed up for at least 6 years. Chest HRCT was performed in 214 patients at the induction of biological therapy. The obtained images were reviewed by two experienced thoracic radiologist

independently. According to the detected ILD features (airspace-consolidation, ground-glass opacity (GGO), reticulation, honeycombing) and AwD features (bronchiectasis, bronchiolectasis, traction bronchiectasis, air trapping), we grouped the patients to ILD group (n=63), AwD group (n=30), and no abnormality group (n=121). We investigated the manifestations of respiratory infection, onset or worsening of ILD, and other respiratory events which required withdrawal of biological therapy as incidence of RAE. Cox regression models estimated the risk for incidence of RAE in each group and explored predictors for RAE incidence based on HRCT patterns and baseline characteristics.

Results: The mean age was 57.2 (range 20-84), 86.0% of patients were female, and mean (standard deviation) follow-up was 7.7 (1.3) years. Methotrexate was used in 77.1%, and oral corticosteroids in 37.9% at baseline. HRCT abnormalities were found in 35.8% of the all patients. ILD features were found in 27.8%, AwD in 9.7%. We identified 27 RAE episodes including bacterial pneumonia (10), acute onset or exacerbation of interstitial pneumonia (7), pneumocystis pneumonia: PCP (2), bronchitis (2), organized pneumonia (2), NTM (1), empyema (1), mycotic pneumonia (1), pleuritic (1). The incident rate of RAE was 15.7 cases per 1000 patient-years in all patients, 20.1 in IDL group, 49.5 in AwD group, and 8.75 in no abnormality group. Cumulative incident rate was higher in AwD group than ILD group (figure1). AwD (HR=6.27, 95%CI=2.83-13.9), old age (HR=4.23, 95%CI=2.07-9.41), level of anti-citrullinated peptide antibodies (ACPA) titer (HR=3.19, 95%CI=1.44-7.04) were associated with increased risk for RAE. However, ILD (HR=1.64, 95%CI=0.73-3.67) did not associated with the risk for RAE.

Conclusion: Pre-existence of AwD at induction of biological therapy was associated with higher risk for RAE than pre-existence of ILD. We identified Age, ACPA titer, and pre-existence of AwD as the predictors for RAE.

figure1



Disclosure: T. Matsumoto, None; **T. Kojima**, None; **N. Takahashi**, None; **S. Asai**, Takeda Pharma Co., 8,Janssen Pharmaceutica Product, L.P., 8,Astellas Pharma Co., 8,Tanabe Mitsubishi Pharma Co., 8,Eisai, 8,Bristol-Myers Squibb, 8,Chugai, 8,Pfizer Inc, 8,Abbvie Japan, 8,UCB Japan, 8; **N. Asai**, None; **T. Watanabe**, None; **T. Kobayakawa**, None; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8; **S. Iwano**, None; **S. Ito**, None.

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Pregnancy Outcomes in Patients with Rheumatoid Arthritis Treated with Abatacept – Review of a Safety Database

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Background/Purpose: Women are affected by RA 3–4 times more often than men. RA treatment choice during pregnancy can be a challenge for women to minimize fetal toxicity while maintaining disease control. The new FDA 'Pregnancy and Lactation Labeling Rule' removed pregnancy categories requiring product labels to be updated.[1] Given limited information, it is important to continually assess available data on RA therapy use during pregnancy.

Methods: All pregnancy cases reported to the manufacturer were re-coded based on ICH E2B (R2) Guideline[2] and MedDRA Points to Consider.[3] A comprehensive, post-coding change evaluation of pregnancy cases from available sources was performed cumulatively up to March 31, 2016.

Results: In total, 356 cases were reported: clinical trials (114), spontaneous/literature (133), patient support programs/Phase IV trials (89), and Organization of Teratology Information Specialists Pregnancy Register (20). Most abatacept exposure was limited to the first trimester (118). Outcomes were reported in 196 cases (Table 1): 48% normal newborn/live births (4 full-term abatacept exposure cases), 21% spontaneous abortions, 9% live births with complications including premature delivery and low birth weight. There were 10 congenital anomalies in patients with multiple risk factors[4] (2 full-term abatacept exposure cases, Table 2).

Conclusion: As shown, reports of spontaneous abortion, premature delivery, and low birth weight among patients treated with abatacept are low and consistent with the literature.[5–8] The available data do not suggest an increased risk of adverse pregnancy outcomes with abatacept in the indicated population. However, abatacept should be used during pregnancy only if the benefit to the mother

justifies potential risk to the fetus.[9] The outcomes of abatacept-exposed pregnancies will continue to be monitored via pharmacovigilance and the Pregnancy Registry. 1. FDA. Pregnancy and Lactation Labeling Final Rule. http://goo.gl/5CDV82. Accessed 6-2-2016. 2. ICH E2B (R2) Guideline. http://goo.gl/L5GQwK. Accessed 6-7-2016. 3. MedDRA. Points to Consider Release 4.11 Based on MedDRA Version 19.0. http://goo.gl/WJsF4x. Accessed 6-7-2016. 4. Krause ML, et al. *Ther Adv Musculoskelet Dis* 2014;**6**:169–84. 5. de Man YA, et al. *Arthritis Rheum* 2009;**60**:3196–206. 6. Bowden AP, et al. *J Rheumatol* 2001;**28**:355–9. 7. Rom AL, et al. *Arthritis Rheumatol* 2014;**66**:3265–73. 8. Wallenius M, et al. *J Rheumatol* 2015;**42**:1570–2. 9. Bristol-Myers Squibb. US Orencia Prescribing Information. http://packageinserts.bms.com/pi/pi_orencia.pdf. Accessed 6-2-2016.

Table 1. Summary of Pregnancy Cases With Reported Outcome (N=196)

		Report origin				Exposure, trimester (n)	Maternal age		Concomitant medication; pregnancy on contraceptive (oral or injectable) (n)
Pregnancy outcome (by preferred term)	n	Clinical trials (Phases I–III)	Phase IV trials/patient support programs	Pregnancy registry	Post-marketing/ literature	1st, 2nd, 3rd trimester; before conception [BC]; unknown	Age range, years (n)	Average age, years	
Live birth without anomaly (n=94)									
Normal newborn	77	38	11	8	20	1st, 2nd, 3rd (4); 2nd (1); 1st (46); BC (8); unknown (18)	17–40 (53)	29.8	Methotrexate (16); leflunomide (6); methotrexate + leflunomide (3)
Live birth	17	2	10	2	3	1st (7); BC (3); unknown (7)	22–39 (13)	26.4	Methotrexate (2); contraceptive (2)
Live birth with complications (n=18)									
Premature delivery	14	6		1	7	1st (6); unknown (8)	25–37 (7)	32.1	Methotrexate (2); leflunomide (2); methotrexate + leflunomide (1)
Low birth weight	4	2	2			1st (2); unknown (2)	Unknown	Unknown	Unknown
Abortion (n=67)									
Spontaneous abortion	41	18	12		11	1st (26); 1st, 2nd (2); BC (6); unknown (7)	18–41 (38)	32.4	Methotrexate (22); leflunomide (4); mycophenolate mofetil (2); pregnancy on contraceptive (13)
Elective abortion	24	14	1		9	1st (18); BC (2); unknown (4)	15–43 (21)	30.4	Methotrexate (5), methotrexate + leflunomide (1); pregnancy on contraceptive (7); methotrexate + contraceptive (3)
Abortion unspecified	2	1	1			1st (2)	Unknown	Unknown	Unknown
Congenital anomaly	10			6	4	1st, 2nd, 3rd (2); 1st, 2nd (1); 1st (6); BC (1)	25–39 (10)	32	Leflunomide (4); mycophenolic acid (1); steroids (6)
Fetal death (including still birth)	5	2		1	2	1st (4); unknown (1)	28–45 (4)	35.5	Methotrexate (1); suspected drugs for breast cancer treatment (1); pregnancy on contraceptive (1)
Ectopic pregnancy	2	1			1	BC (1); unknown (1)	32–33 (2)	32.5	Methotrexate (1)

Table 2. Summary of the Cases With Congenital Anomaly

Report type	Child age	Preferred term	Trimester of exposure (1st, 2nd, 3rd or before conception [BC])	Exposure to concomitant medication	Maternal age (years); medical history
OTIS		Pyloric stenosis; premature delivery (36.9 weeks gestation)	1st	Leflunomide, cholestyramine, prednisone	25; hypertension, depression, anxiety, fibromyalgia, hypothyroidism, smoker (20 cigarettes/day); passive smoker (2 h/day)
OTIS	1 day	Cleft palate; cleft lip; premature delivery (37.6 weeks gestation)	BC	Leflunomide, influenza virus vaccine, prednisone	36; diabetes, hypertension, anemia, influenza virus vaccine
Spontaneous		Meningocele; premature delivery (36 weeks)	1st	Mycophenolic acid, prednisone acetate, colchicine and valacyclovir from start of pregnancy to Week 36	33; hyper IgD syndrome (immunoglobulin D)
Spontaneous	17 weeks gestation age	Trisomy 21	1st, 2nd	No	28; the patient had premature breakage of membranes at 17 weeks of gestation, with cesarean section and fetal death
OTIS	1 day	Ventricular septal defect	1st	Leflunomide, prednisone, cholestyramine, influenza vaccine, pertussis vaccine, cortisone	37; hypothyroidism,
Spontaneous	2 months	Small for dates baby; skull malformation	1st	Leflunomide	31; not reported
Spontaneous	1 day	Congenital aortic anomaly	1st	No	27; diabetes
OTIS	1 day	Chordee	1st, 2nd, 3rd (Twin A)	Prednisone	39; Grave's disease; alcohol use, irritable bowel syndrome
OTIS	Neonate	Atrial septal defect; premature delivery (36.7 weeks)	1st , 2nd , 3rd	No	32; endometriosis; infertility
OTIS	33 months	Chromosomal deletion; premature delivery (36.9 weeks)	1st	Prednisone methylprednisolone, cortisone, influenza vaccine	31; treated with prednisone at doses of 2.5, 5 or 10 mg through delivery; influenza vaccine II during pregnancy

OTIS=Organization of Teratology Information Specialists

Disclosure: **H. Yu**, Bristol-Myers Squibb, 3; **K. Angelini**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **A. Dominique**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **T. Simon**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3.

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Abstract Number: 2554

Changes in Blood Pressure Following the Initiation of Disease Modifying Therapies in US Veterans with Rheumatoid Arthritis

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Background/Purpose: Chronic inflammation is associated with a greater risk of hypertension

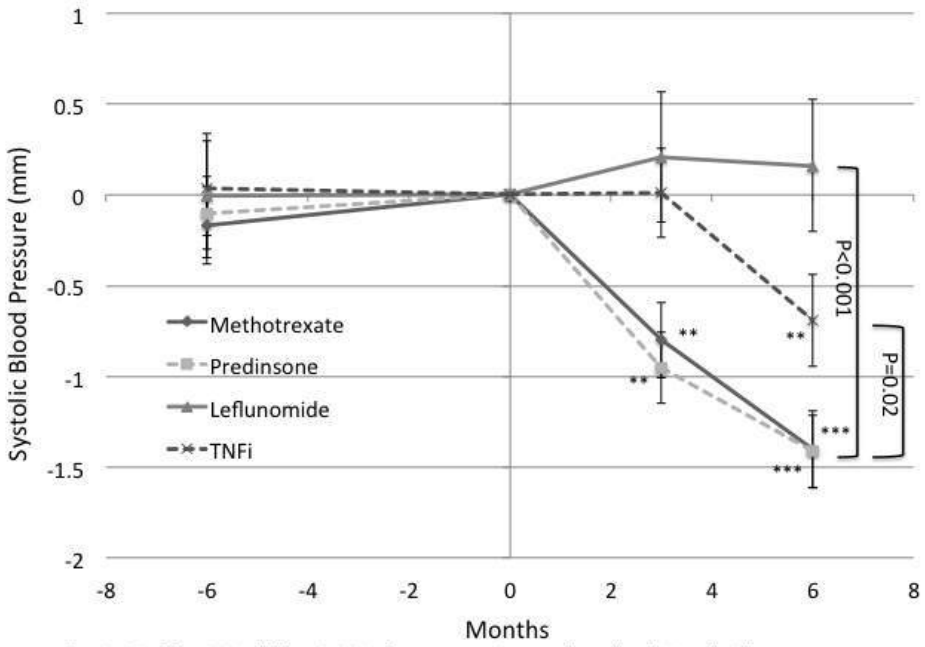
(HTN) while inflammatory cytokines such as TNF-α have been shown to have vasodilator effects. It thus remains unclear how treatment of rheumatoid arthritis (RA) might affect blood pressure (BP). Our goal was to quantify changes in systolic and diastolic blood pressure (SBP, DBP) in the 6 months after initiating new DMARDs in a large administrative database.

Methods: We used 3 VA database sources: the Corporate Data Warehouse (CDW), the Decision Support System (DSS) National Pharmacy Extract, and the Pharmacy Benefits Management (PBM) database. Among patients with at least one diagnosis code for RA, algorithms integrated sources to define unique dispensing episodes of methotrexate, prednisone, leflunomide, and TNF inhibitors (TNFi). The closest values for BP, CRP, CCP, and BMI within 30 days of the treatment start date were used as baseline values. Values -180, 90, and 180 days from the treatment start date (+/- 30 days) were also recorded. A significant increase in BP was defined as an increase in SBP >20 mm or DBP >10 mm. Incident HTN was defined as a new diagnosis code for HTN after the course start. Multiple imputation was utilized to account for missing laboratory values. Propensity analyses using matched-weighting techniques were used to address confounding by indication.

Results: There were 25,811 unique treatment courses in 18,119 patients identified. Overall, there were no changes in BP in the 6-months prior to drug initiation (all $p>0.62$). In contrast, there was a small but significant overall decline in SBP [β: -1.08 mmHg (-1.32, -0.85) $p<0.0001$] and DBP [β: -0.48 (-0.62, -0.33) $p<0.0001$] over the 6 months after initiating drug. The greatest decline was observed among those treated with methotrexate or prednisone (Figure). Patients treated with leflunomide had less decline in SBP and DBP and a greater odds of a significant increase in BP at 6-months compared to methotrexate (Figure, Table). Users of TNFi had less reduction in BP compared to methotrexate, however this difference was attenuated and not significant in sensitivity analyses (Table). The risk of an incident diagnosis of HTN over 3 years was greater for leflunomide [HR 1.42 (1.05, 1.93) $p=0.02$] and similar for prednisone and TNFi (all $p>0.14$) compared to methotrexate (not shown).

Conclusion: Patients initiating treatment for RA, particularly methotrexate, generally demonstrate reductions in BP over 6 months. Leflunomide use is associated with less improvement in BP and a modestly increased risk of incident HTN compared to the use of other DMARDS in a large

Figure: Actual change in systolic blood pressure over the 6-months prior to initiation of treatment and the 6 months after initiation of treatment.



population study.

Table: Associations between prednisone, leflunomide, and TNFi with 6-month change in systolic BP compared to methotrexate after applying matched-weighting techniques to consider propensity for receiving the drug.

		Excluding Concurrent MTX	
			Compared to MTX Alone
Change in SBP vs. Methotrexate (β-Coefficient)			
Prednisone	0.34 (-0.097, 0.78)	0.34 (-0.14, 0.81)	0.39 (-0.15, 0.93)
Leflunomide	1.79*** (1.07, 2.52)	1.71*** (0.87, 2.55)	1.70 *** (0.86, 2.54)
TNFi	0.91** (0.38, 1.44)	0.62 (-0.026, 1.26)	0.56 (-0.0.96, 1.21)

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None; **L. A. Davis**, None; **K. Michaud**, None; **J. R. O'Dell**, Lilly, 5,Bristol-Myers Squibb, 5,GlaxoSmithKline, 5,Coherus, 5,Medac, 5; **T. R. Mikuls**, None.

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Abstract Number: 2555

Efficacy and Safety of Conventional and Targeted Synthetic Disease-Modifying Antirheumatic Drugs As Well As Glucocorticoids: A Systematic Literature Review Informing the 2016 Update of the Eular Recommendations for the Management of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: To inform the task force for the 2016 update of the EULAR recommendations for the management of RA on the evidence regarding the efficacy and safety of

glucocorticoids (GCs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and targeted synthetic DMARDs (tsDMARDs) in RA by performing a systematic literature review (SLR). <>

Methods: A SLR update using PubMed, Embase and the Cochrane library was performed (2013 - 2016) to assess the efficacy and safety of GCs, csDMARDs (as monotherapy or combination therapy) and tsDMARDs (tofacitinib and baricitinib) in randomized clinical trials. Meta-analysis was performed when possible. Risk of bias (RoB) was assessed using the Cochrane Collaboration tool.

Results: With regard to GCs, among 348 hits 5 studies were included in the analysis (table 1). Even patients without poor prognostic factors benefit from the addition of GCs to methotrexate (MTX). Lower doses of GCs seem to be as effective as higher doses. Long-term results of the CAMERA II trial showed increased cardiovascular risk for the early RA patients treated for at least 2 years with 10mg/d prednisone (not included in the table). With regard to csDMARDs, among 518 hits 2 new studies comparing MTX monotherapy with MTX in combination with another csDMARD without differences in GCs usage were identified. The tREACH trial, which used tight-control principles, reported a statistically significant benefit of combination therapy over monotherapy at 3 months that had disappeared at 12 months (disease activity, functional ability and radiographic progression) (table 2). In addition, more medication adjustments were needed in the combination group. In the CareRA trial combination with other csDMARDs was not superior to methotrexate monotherapy in early RA and monotherapy was better tolerated. With regard to tofacitinib (n=7) and baricitinib (n=9) RCTs had been meta-analysed showing that both are more effective than placebo on background MTX or de novo MTX (MTX-naïve) in different patient populations (MTX-naïve, csDMARD and bDMARD inadequate responders) with a pooled OR (95% CI) for ACR20 response for tofa and bari vs placebo of 3.1 (2.0-4.7) and 3.6 (2.4-5.5), respectively.

Conclusion: New evidence on the efficacy and safety of DMARDs in RA confirmed the benefit of the addition of GCs to csDMARDs in early RA but pointed to long-term cardiovascular risk. MTX monotherapy is as effective as MTX in combination with csDMARDs but better tolerated. Tofacitinib and baricitinib are effective tsDMARDs in various RA populations.

Study	Study design	N patients	Glucocorticoid regimen	Trial duration	Primary Outcome	Result in glucocorticoid group	Result in control group	P value
Menon 2014	Superiority (open)	56	i.a. triamcinolone acetonide	12 weeks	DAS28, ACR 20/50/70 at 12 w	3.39 100/60/36	4.99 84/20/0	0.001 <0.05
CareRA, Verschueren 2015	Superiority (open)	90	p.o. Prednisolone (step down from 30mg)	2 years	DAS28(CRP) <2.6 week 16	65.1%	46.8%	0.08
CAPRA-2 Buttgereit 2013	Superiority (double blind)	350	Modified-release prednisone	12 weeks	ACR20 at w 12	48%	29%	<0.001
den Uyl 2013 ter Wee 2015	Non-inferiority (open)	164	COBRA light vs. COBRA	2 years	mean ΔDAS44 after 26 weeks	−2.50 (±1.21) in COBRA	−2.18 (±1.1) in COBRA light	0.08

Table 1. Efficacy of glucocorticoids (different type, doses and routes of administration) when added to csDMARDs (RCTs).

	Remission		SAEs		Medication adjustment due to AE	
Study	Mono	Combo	Mono	Combo	Mono	Combo
tREACH (1y)	51%	52.3%	10%	8.2%	45%	65%
CareRA	70%	73.5%	1%	2.7%	47%	~65%

Table 2. Efficacy and safety of MTX monotherapy (Mono) or in combination with other csDMARDs (Combo) in early RA.

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5,Director of Imaging Rheumatology bv, 3; **M. Dougados**, None; **J. W. Bijlsma**, None; **G. Burmester**, UCB, 2,AbbVie, BMS, Hexal, Janssen Pharmaceutica Product, L.P., Lilly, MSD, MedImmune, Novartis Pharmaceutical Corporation, Pfizer Inc, Roche Pharmaceuticals, 5,AbbVie, BMS, Hexal, MSD, Novartis Pharmaceutical Corporation, Pfizer Inc, Roche Pharmaceuticals, 8; **M. Scholte-Voshaar**, None; **R. van Vollenhoven**, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Pfizer, Roche, UCB Pharma, 2,AbbVie, Biotest, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Eli-Lilly, Merck, Pfizer, Roche, UCB Pharma, Vertex, 5; **R. Landewé**, None.

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Abstract Number: 2556

Deficient Expression of the Novel Rheumatoid Arthritis (RA) Risk Gene, LBH, Induces S Phase Arrest in RA Fibroblast-like Synoviocytes (FLS)

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Background/Purpose: *LBH* (Limb-bud and heart development) was recently identified as an RA risk gene that has abnormally methylated loci and a functional enhancer SNP in RA FLS. Low LBH expression has been observed in RA, which affects the cell cycle and contributes to aggressive behavior of RA FLS. We investigated the molecular mechanism of cell cycle regulation by LBH to understand why RA FLS exhibit this characteristic phenotype.

Methods: RA FLS were cultured from synovial tissues obtained at arthroplasty. LBH was knocked down using LBH siRNA, which decreased LBH expression by 88%. Gene expression was measured by qPCR and normalized to ß-actin. Cell cycle analysis was performed with propidium iodide staining and flow cytometry by synchronizing cells by serum starvation and then culturing FLS with

10% FBS. Western blot analysis was used to quantify protein expression and results were normalized to GAPDH.

Results: Cell cycle analysis of RA FLS showed that LBH siRNA silencing decreased S phase progression. The percentage of serum-starved cells in S phase was 2±1%, which increased to 18±4% in control FLS and from 2±1% to 15±4% in LBH-deficient FLS after adding complete medium for 24 hr. However, the percentage of control FLS in S phase decreased to 9±1% in control cells after 38 hr while LBH-silenced cells continued to increased to 25±4% ($p<0.05$ for control vs. LBH-deficient). These data suggest that LBH deficiency delays S phase progression. To understand the mechanism, we explored the influence of LBH on steps that activate the intra-S phase checkpoint. One key element is DNA replication stress, which can cause the DNA replication forks to stall. LBH-deficient FLS displayed 4±1-fold higher phospho-CHK1 at 24 hr compared to control FLS, which is induced by replication stress ($p<0.05$). DNA polymerase alpha catalytic subunit (POLA1) is required for initiation of DNA replication in S phase at the replication fork. LBH silencing reduced POLA1 mRNA by 38% ($p<0.01$) and POLA1 protein by 86% ($p<0.01$) compared with scrambled siRNA.

Conclusion: These data show that LBH deficiency reduces POLA1 expression and induces replication stress, which leads to S phase arrest. Lack of progression through S phase arrest in RA FLS could alter the growth patterns of FLS in RA and contribute to their aberrant behavior. Targeting the cell cycle in RA could potentially overcome these pathogenic steps, allow an appropriate response to replication stress, and allow normal progression through the cell cycle.

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Abstract Number: 2557

Tumor Necrosis Factor (TNF) Sensitizes Rheumatoid Synovial Fibroblasts to TRPA1-Mediated Calcium Flux, Anti-Proliferation and Cell Death

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Background/Purpose: In rheumatoid arthritis (RA), synovial fibroblasts (SF) are one main contributor of joint destruction since they resist apoptosis and secrete pro-inflammatory cytokines and matrix degrading enzymes. Previous studies already demonstrated the functional expression of several transient receptor potential channels (TRP) such as TRPV1, TRPV2, TRPV4, TRPA1 and TRPM8 in SF. Upon ligation, these receptors increase intracellular calcium but they have also been linked to modulation of inflammation in several cell types. TNF was shown to increase the expression of TRPA1, the receptor for mustard oil (allylisothiocyanate, AITC) and environmental poisons in synovial fibroblasts, but the functional consequences have not been investigated yet.

Methods: TRPA1 was detected by immunocytochemistry and western blot. Calcium signals were determined fluorometrically (Fura-AM red). Cell viability was assessed by quantification of lactate dehydrogenase (LDH) in culture supernatants. IL-6, IL-8 and MMP-3 were determined by ELISA. Proliferation was determined by cell titer blue incorporation.

Results: After 72h, TNF up-regulated TRPA1 protein levels in RASF which was accompanied by increased sensitivity to TRPA1 agonists AITC and polygodial. Under unstimulated conditions, polygodial but not AITC elicited modest calcium flux only in the highest concentrations used (50µM and 25µM). TNF pre-incubation substantially lowered the activation threshold for polygodial (from 25µM to1µM) and enabled AITC-mediated calcium flux, which was inhibited by TRPA1 antagonists A967079 (25µM) and HC030031 (50µM). In addition, TNF stimulation strongly enhanced TRPA1 mediated LDH release by AITC and polygodial, a marker for cell death. TNF not only reduced the threshold of AITC and polygodial but also led to a faster onset of LDH release. Furthermore, TRPA1 activation was associated with decreased proliferation of RASFs with TNF pre-incubation enhancing the anti-proliferative effect of AITC and polygodial. Secretion of IL-6, IL-8 and MMP-3 was attenuated by the TRPA1 antagonist A967079 but also polygodial, although the latter mediated this effect by reducing cell viability.

Conclusion: TNF up-regulates and sensitizes TRPA1 in RASF. Subsequent activation of TRPA1 increased calcium flux and reduced cell viability. Since TRPA1 agonists only showed effects in TNF stimulated RASF, this cation channel might an attractive therapeutic target in chronic inflammation to reduce the activity of pro-inflammatory SF in the joint.

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Abstract Number: 2558

Dissociation of the Inhibitory Apoptosis Stimulating Protein of p53 (iASPP) Binding with Transcription Factor p73 Induces Synovial Fibroblast Apoptosis in the Rheumatoid Joint

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Background/Purpose: Apoptosis-resistant synovial fibroblasts (SFs) constitute the major cell component of pannus tissues in rheumatoid arthritis (RA). In tumor cells, the binding of inhibitory apoptosis stimulating protein of p53 (iASPP) with transcription factor p53 family members can inhibit the downstream apoptosis signaling. We hypothesized that iASPP molecule is involved in the RA pathogenesis, and examined whether dissociation of such binding can induce SFs apoptosis in the rheumatoid joint.

Methods: Peripheral mononuclear cells (MNCs) from active RA before and after a TNF inhibitor therapy and osteoarthritis (OA) patients were examined for their iASPP expression by real-time RT-PCR. Synovial tissues and purified SFs from RA and OA patients as well as normal and collagen-induced arthritis (CIA) rats were subjected to immunohistochemical (IHC) and immunofluorescent staining for the expression of iASPP and p73, a member of p53 family. SFs transfected with adenoviral vectors encoding 37 amino acid (Ad37AA), a hybrid small peptide corresponding to p53 residues, were subjected to TUNEL assay and real-time RT-PCR for apoptotic status and the expression of p53 upregulated modulator of apoptosis (PUMA), respectively. The association of iASPP with p73 in Ad37AA-transfected SFs was identified by anti-iASPP immunoprecipitation, followed by anti-p73 immunoblotting assay. Therapeutic effects of intra-articular injection of Ad37AA on CIA joints were evaluated by articular index and histological score. Further synovial IHC staining was performed to analyze PUMA and IL-6 expression levels and SFs densities, and *in situ* apoptotic cells in synovial tissues were detected by the TUNEL assay.

Results: There were reduced iASPP levels by targeting TNF in MNCs from RA patients and increased iASPP levels with co-localized p73 expression in synovial tissues and purified SFs from RA patients and CIA rats. Enhanced cell apoptosis and increased PUMA expression were identified

in Ad37AA-transfected SFs with lower iASPP-associated p73 levels. Articular indexes and histologic scores were reduced in Ad37AA-injected CIA joints with decreased SF densities, increased apoptotic cells, higher PUMA and lower IL-6 expression levels.

Conclusion: Our results demonstrate a pathogenic role of TNF-mediated up-regulation of iASPP and induction of SFs apoptosis by dissociating the iASPP binding with transcription factor p73 in the rheumatoid joint, implicating iASPP as a potential therapeutic target molecule in RA patients.

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Abstract Number: 2559

Subgingival Microbiome Signatures in Patients with Established Rheumatoid Arthritis and Osteoarthritis

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Background/Purpose: Periodontitis (PD) is an inflammatory disease of tissues supporting the teeth, caused by microorganisms that adhere to and grow along the tooth's surface. Both PD and pathogens linked to PD have been proposed as risk factors in rheumatoid arthritis (RA). Previous studies have primarily targeted select organisms for investigation, failing to account for the complex nature of the local microbiome involved in PD. Thus, we characterized the subgingival microbiome in patients with established RA, comparing resident microbial communities with those of controls.

Methods: RA patients satisfying the 1987 ACR classification criteria and osteoarthritis (OA) controls underwent full-mouth examination and were classified as having PD based on Machtei criteria. Subgingival plaque was collected from up to 4 sites and pooled. Bacterial DNA was isolated and sequenced using 454 pyrosequencing; trimmed reads were searched against the Human Oral Microbiome Database. Hierarchical cluster analysis with averaging-linkage agglomeration on microbiome profiles were used to classify the samples into 3 clusters. Data were standardized by samples prior to the clustering. With only a 1 patient with membership, Cluster 3 was excluded from further analysis. Logistic regression was used to determine factors associated with membership in Cluster 1 vs. Cluster 2. Factors chosen a priori for analysis included: RA vs. OA case status, PD, smoking status, age, gender, marital status, education, race, body mass index (BMI), and diabetes.

Results: RA (n=260) and OA (n=296) patients were similar in terms of sociodemographic factors except marital status; OA patients were more likely to have diabetes (25% vs. 18%, p=0.04) and had a higher BMI (31.7 vs. 29.8 kg/m^2, p=0.0008); RA patients were more likely to have ever smoked (62% vs. 46%, p=0.0002), have PD (38% vs. 27%, p=0.007), and be married (69% vs. 61%, p=0.06). Patients segregated into 3 groups based on subgingival microbial composition with Clusters 1 and 2 accounting for all but one individual. Factors significantly associated with Cluster membership included PD, age, smoking, and race (Table). There was no association of RA-OA case status with Cluster membership, suggesting similar overall subgingival microbiome composition by arthritis diagnosis after accounting for other factors. Results were unchanged with RA cases limited to those with a positive anti-CCP antibody.

Conclusion: Patients with established RA demonstrated a subgingival microbial composition that was similar to patients with OA after accounting for the presence of PD and other PD risk factors. Further study will be needed to examine whether an abundance of individual bacterial species or microbial diversity is impacted in established RA or whether the overall microbial composition in RA evolves over time with the use of RA therapies and changes in underlying disease activity.

Association of patient factors with membership in Cluster 1 vs. Cluster 2 based on analysis of subgingival microbial composition

Effect	Odds Ratio	95% CI of Odds Ratio		p-value
RA vs OA	1.05	0.69	1.59	0.84
PD	0.23	0.15	0.35	<.0001
Ever Smoking	0.51	0.33	0.79	0.003
Age, years	1.03	1.01	1.05	0.001
White vs. Other	1.73	1.10	2.71	0.02

*Gender, BMI, education level, marital status and diabetes all non-significant and removed from final model

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Disclosure: T. R. Mikuls, None; **C. Walker**, None; **F. Qiu**, None; **F. Yu**, None; **G. M. Thiele**, None; **J. Payne**, None.

Abstract Number: 2560

Sputum Antibody to Malondialdehyde-Acetaldehyde Adduct in Subjects with Established Rheumatoid Arthritis

Bryant R. England[1,2], Peter Maloley[3], Eric Daubach[3], Michael J. Duryee[4], M. Kristen Demoruelle[5], Kevin D. Deane[5], Geoffrey M. Thiele[6] and Ted R Mikuls[6], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]VA Nebraska-Western Iowa, Omaha, NE, [3]University of Nebraska Medical Center, Omaha, NE, [4]Internal Medicine Division of Rheumatology, University of Nebraska Medical Center, Omaha, NE, [5]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [6]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE

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Background/Purpose: Anti-malondialdehyde-acetaldehyde adduct (MAA) antibodies target immunogenic products of oxidative stress, are detected in higher concentration in paired synovial fluid vs serum in RA, and are associated with higher RA disease activity. Moreover, MAA-modified proteins, citrullinated antigens, and immune cells colocalize in RA synovial tissues – suggesting a role in RA pathogenesis. Airway inflammation, a proposed mechanism of disease initiation and a common extra-articular manifestation in RA, is stimulated by MAA in mice. Whether MAA-modification and resulting anti-MAA immune responses occur within the lungs of individuals with RA is unknown.

Methods: Paired serum and sputum samples were collected from subjects with established anti-CCP positive RA (n = 27) and healthy controls (HC; n = 29). CCP2 (IgG), CCP3.1 (IgG/IgA), RF (IgA, IgM, IgG), and anti-MAA (IgA, IgM, IgG) antibodies were measured by ELISA and total Ig by nephelometry. We used Wilcoxon rank-sum tests to compare anti-MAA antibody concentrations between RA and controls and assessed associations with smoking, alcohol, chronic lung disease, and gender; Wilcoxon signed-rank tests to compare paired sputum and serum concentrations; and SpearmanÕs correlations to assess correlations between sputum anti-MAA and RA autoantibodies.

Results: Mean (SD) age was 50 (13) years with 75% female, 71% Caucasian, 11% current and 29% former smokers, and 18% with chronic lung disease. Sputum anti-MAA antibody concentrations in RA and HC are shown in Table 1. Sputum IgA and IgG anti-MAA were higher in RA than HC. After adjusting for total Ig, in both RA and HC, IgG anti-MAA antibody was higher in sputum than serum ($P < 0.001$), while IgM anti-MAA was higher in serum ($P<0.001$), and IgA anti-

MAA did not differ (P = 0.58). In RA subjects, sputum IgM anti-MAA antibody correlated with sputum CCP3.1 (r = 0.42, P = 0.03) and marginally correlated with sputum RF IgA (r = 0.38, P = 0.052). Sputum IgA anti-MAA antibody correlated with serum RF level (r = 0.46, P = 0.02) and sputum IgG anti-MAA antibody did not correlate with other autoantibodies. Sputum IgA anti-MAA antibody, but not IgM or IgG, was higher in current smokers vs non-smokers. There were no other associations between anti-MAA antibody and smoking status, alcohol use, chronic lung disease, or gender.

Conclusion: IgG and IgA anti-MAA antibody are enriched in the sputum of RA subjects, with relative concentrations of IgG higher in paired sputum than serum. These data suggest MAA modification and anti-MAA immune responses within the airways could contribute to disease pathogenesis. Additional studies will be needed to examine the relationship of anti-MAA antibody with measures of airway inflammation and lung function in RA and to determine mechanisms underpinning these associations.

Table 1. Sputum anti-MAA antibody concentrations for rheumatoid arthritis and healthy control subjects.

	Healthy Control	RA	P*
IgA	10.0 (4.0-32.9)	27.5 (5.6-57.3)	<0.05
IgM	4.0 (3.1-18.1)	4.0 (4.0-5.8)	0.91
IgG	4.0 (3.0-4.0)	5.0 (4.0-6.9)	<0.01

Values arbitrary units; median (interquartile range) *P value by Wilcoxon rank-sum test

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Abstract Number: 2561

A Novel Pharmacological Action of MTX on RA Fibroblast-like Synoviocytes Via Circadian Clock Genes

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Session Time: 9:00AM-11:00AM

Background/Purpose: The circadian rhythm is disrupted in patients with rheumatoid arthritis (RA), and we have shown that tumor necrosis factor(TNF)-*ƒ¿* inhibits the expression of circadian clock gene Period 2 (Per2) by interfering with D-box motifs to promote the proliferation of RA-fibroblast-like synoviocytes (FLS) (1). Recently, interactions between PER2 and Bcl2 family proteins were reported that forced expressions of Per2 on pancreatic cancer cells resulted in apoptosis-induction (2). In this study, we examined effects of Methotrexate (MTX) on the expression of circadian clock genes in RA-FLS.

Methods: Under treatments of MTX (10nM) on RA-FLS, cell viabilities were determined by WST-8 assay and expressions of PER2 were observed by fluorescent immunostaining. Total RNA was extracted from RA-FLS, treated with MTX(10nM) for 24 to 48hrs, to examine expressions of circadian clock genes, including circadian locomotor output cycles kaput (Clock), brain and muscle Arnt-like protein-1 (Bmal1) and Per 2 by real-time PCR. As transcriptional activators of Per2, the proline and acidic amino acidrich basic leucine zipper (PAR bZip) genes ;D site of albumin promoter binding protein(Dbp), hyrotroph embryonic factor(Tef) and hepatic leukaemia factor(Hlf) were also analyzed. In addition, pro-apoptotic Bcl-2- interacting killer (Bik) was examined as a marker of mitochondria-related apoptosis-induction.

Results: The cell viability of RA-FLS was inhibited by 10nM of MTX for 24h and 32h. MTX enhanced expressions of Per2, Dbp, Tef and Hlf after 24hrs' treatment, and Bik for 32hrs (Figure 1). PER2 protein was highly expressed in apoptotic RA-FLS in fluorescent observations (Figure 2).

Conclusion: Results clearly showed that MTX accelerated PAR bZip genes to bind D-box motif to transcribe Per2, resulted in apoptosis-induction of RA-FLS. This was also supported by the increased-expression of Bik, containing PAR bZip–binding site on its promoter region. We proposed a novel therapeutic efficacy of MTX on RA-FLS via circadian clock genes.

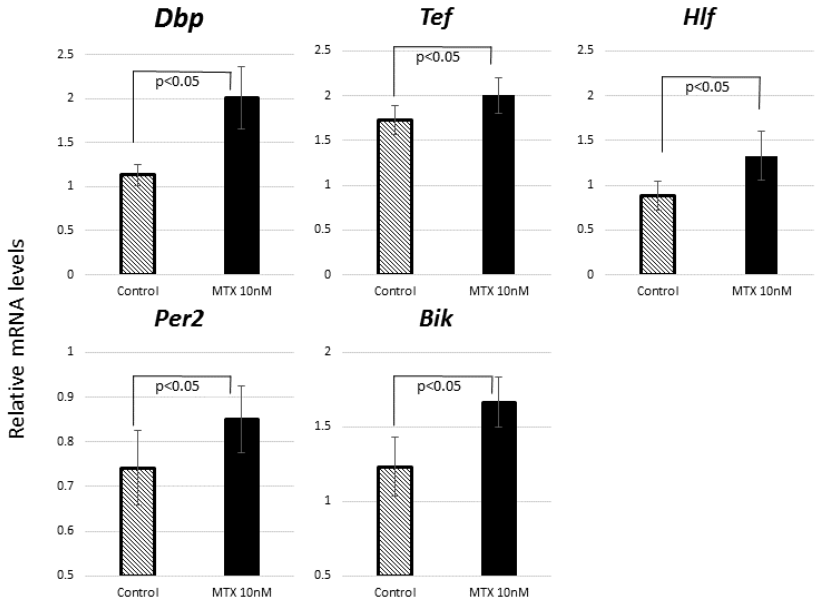

Figure 1. The mRNA expression of PAR bZip genes, *Per2*, and *Bik*. The mRNA expression of PAR bZip genes and *Per2* were increased with the 24hrs' treatment of MTX (10nM), and *Bik* with the 32hrs', compared to control.

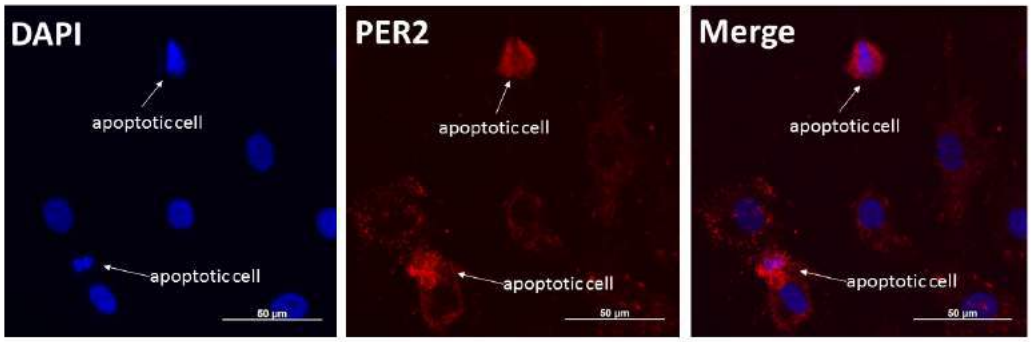

Figure 2. DAPI staining and fluorescent immunostaining of PER2 in 10nM MTX-stimulated RA-FLS. The overexpression of PER2 is observed in apoptotic cells. **Reference:** 1. Yoshida K, Hashiramoto A, et al. Scand J Rheumatol, Vol. 42, No. 4: 276-280, 2013 2. Oda A, et al. Anticancer Res. 2009;29:1201–1209.

Disclosure: K. Suzuki, None; **K. Yoshida**, None; **T. Hashimoto**, None; **K. Kaneshiro**, None; **A. Nakai**, None; **N. Hashimoto**, None; **Y. Kawasaki**, None; **N. Shibanuma**, None; **N. Nakagawa**, None; **Y. Sakai**, None; **A. Hashiramoto**, None.

pharmacological-action-of-mtx-on-ra-fibroblast-like-synoviocytes-via-circadian-clock-genes

Abstract Number: 2562

Human Seroreactivity to Gut Microbiota Antigens in Rheumatoid Arthritis and Controls-Lack of Association with Rheumatoid Arthritis Autoantibodies

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Background/Purpose: The human gut microbiome maintains normal immune homeostasis. Changes to the microbiota evolve with aging and have been implicated in the development of autoimmune disorders like rheumatoid arthritis (RA). Given the observed variability in microbiota composition among healthy individuals, immune responses to commensal microbiota may be more relevant to disease development. We compared adaptive immune responses to gut microbiota in RA patients and healthy controls and determined associations with RA autoantibodies.

Methods: IgG immune responses to intestinal microbiota were detected in sera of RA patients and controls using a protein microarray containing recombinant antigens cloned from murine microbiota that have been previously studied in humans (50 epitopes from >6 bacterial groups). Each antigen was present in quadruplicate per slide. Bound human sera IgG was detected and quantitated using an Axon GenePix 4000B dual laser and its software. Levels are reported as median net fluorescent values with lower detectable cut-off being assigned 0. Anti-citrullinated peptide antibodies (ACPA) were measured by ELISA and rheumatoid factor (RF) by nephelometry. Associations of IgG microbiota responses with subject group and RA antibodies were tested by nonparametric tests. Patterns of microbiota responses were assessed using non-hierarchical clustering. Given multiple comparisons, p values<0.001 were considered significant.

Results: RA patients (n=121; 78% female, mean (SD) age 58 (14) years; 43 with symptoms less than 12 months (ERA)) were compared to healthy controls (n=19, 63% female, mean(SD) age 39 (11)years). All anti-microbial IgG levels were detected in at least some subjects although there was individual variation in the expression patterns. No robust grouping of microbial responses was seen. Levels of 16 anti-microbial IgG titers were significantly elevated in RA compared to controls

whereas levels of 2 anti-microbial IgGs titers were decreased (all $p<0.001$). The epitopes with the highest IgG titers in RA compared to controls were rIB2 (firmicutes/bacteroides) and Pmel. The epitopes with the most reduced IgG titers in RA compared to control were Ftsz (proteobacteria) and rib16 (firmicute). Of four known universal gut microbiotia antigens (rIB1, rIB2, rIB10 and rIB20), only anti-rIB2 IgG levels were increased in RA ($p<0.001$). There were no robust associations of individual IgG titers with ACPA or RF positivity. The levels of five anti-microbial antigen IgG titers (3-2, bir1, cbir15, cbir63, m18-1) were higher in RA of recent onset than long standing RA (all $p<0.0001$).

Conclusion: Adaptive immune responses to selective gut microbiota differ between RA and controls but do not associate with other RA autoantibodies. Although environmental influences such as diet and medication were not addressed here, these results suggest a broader immune response alteration to microbial organisms exists in persons with disease.

Disclosure: C. Hitchon, None; **C. O. Elson**, None; **D. Robinson**, None; **I. Smolik**, None; **H. S. El-Gabalawy**, CIHR, 2.

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Abstract Number: 2563

Hypoxia Induce Slug Expression Via JAK/STAT3 Pathway in Rheumatoid Arthritis Fibroblast-like Synoviocytes

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Background/Purpose: Accumulating evidence implicates hypoxia in the pathogenesis of rheumatoid arthritis (RA). The effect of hypoxia on the expression of Slug, a transcriptional repressor that impairs apoptosis of RA fibroblast-like synoviocytes (FLS), remains unknown. The aim of this study is to investigate the role of hypoxia in the expression of Slug in RA FLS and to delineate the signaling pathway involved in the process.

Methods: After RA FLS were exposed to hypoxia, expression of HIF-1a and phosphorylation of ERK, JNK, and STAT3 were analyzed by Western blot. The experiment was repeated with RA FLS pretreated with WP1066, an inhibitor of the JAK/STAT pathway. RT-PCR was performed to measure HIF-1a mRNA and Slug mRNA expressions in RA FLS under hypoxia. RA FLS was transfected with HIF-1a cDNA to investigate the effect of overexpression of HIF-1a on Slug expression. Immunohistochemistry was used to assess the presence HIF-1a and Slug in RA synovial tissue. Microarray analysis was performed to investigate the change in Slug gene expression when FLS were exposed to hypoxia. Finally, the effect of TNF-α on Slug and HIF-1α expressions under normoxic conditions was assessed in RA FLS by Western blot.

Results: Hypoxia induced the expression of HIF-1a and phosphorylation of STAT3, but not JNK and ERK was increased in RA FLS. Pre-treatment of RA FLS with WP1066 before exposure to hypoxia inhibited the expression of p-STAT and HIF-1a. Hypoxic conditions induced Slug mRNA expression from RA FLS, and similarly, overexpression of HIF-1a in RA FLS reproduced enhanced Slug expression. Microarray analysis revealed a significantly up-regulated Slug expression. Immunohistochemical staining showed that HIF-1a and Slug were co-localized in the lining area of RA synovium. Stimulation of FLS with TNF-α alone without hypoxia resulted in increased expression of Slug HIF-1a and Slug.

Conclusion: Our study demonstrates that HIF-1a expression from RA FLS induced by hypoxia or TNF-a alone is mediated through JAK/STAT3 signaling pathway, which ultimately leads to the expression of Slug. Hypoxia-driven pathway of Slug expression may become a novel treatment target in RA.

Disclosure: H. Kim, None; **H. Jeong**, None; **J. Lee**, None; **H. S. Cha**, None; **E. M. Koh**, None; **E. J. Park**, None; **Y. H. Eun**, None.

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Abstract Number: 2564

Autophagy Alteration Affects Migration and Proliferation of Rheumatoid Arthritis Fibroblast-like Synoviocytes Stimulated By IL-17A

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School of Medicine, Daegu, Korea, The Republic of, [2]Keimyung University School of Medicine, Daegu, South Korea, [3]Division of Rheumatology, Department of Internal Medicine, Dongsan Medical Center, Keimyung University School of Medicine, Daegu, South Korea
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Background/Purpose: Autophagy is required to ensure cellular homeostasis. Perturbations in autophagy have been reported to be involved in the pathogenesis of several diseases such as cancer and infection. Rheumatoid arthritis (RA) is characterized by exaggerated synovial proliferation in which interleukin-17A (IL-17A) plays a key role. The aims of this study were (1) to evaluate whether IL-17A influences on autophagic flux in the synovium of the patients with RA and (2) to investigate whether the modulation of autophagy can regulate migration and proliferation of fibroblast-like synoviocytes (FLS) from the patients with RA (RA-FLS) under inflammatory milieu.

Methods: Synovial tissue was obtained from the patients with RA or osteoarthritis (OA). FLS was cultured with IL-17A and/or autophagy regulators. The expression of marker proteins for autophagic flux (LC3B, Beclin1, Atg5, p62) and the formation of autophagolysosome (LAMP1) were analyzed by western blot and immunofluorescence study. A migration scratch assay was used to assess FLS migration in response to stimulation with IL-17A. Proliferation of FLS was determined by the viable cell count using trypan blue.

Results: LC3 conversion from LC3-Ⅰ to LC3-Ⅱ was increased in RA-FLS than in OA-FLS. IL-17A upregulated the expression of LC3B, Atg5, Beclin1, LAMP1 in RA-FLS. The accumulation of p62 was also prominent in RA-FLS. Migration and proliferation of FLS stimulated by IL-17A was suppressed by Bafilomycin A1 which prevented the formation of autophagolysosomes. P62-silencing enhanced IL-17A-induced autophagy activation in RA-FLS.

Conclusion: This study reveals that IL-17A stimulates autophagy and that intervention of autophagy can control IL-17A-induced migration and proliferation of FLS. Our results also provide additional evidence for a significant role of autophagy in the pathogenesis of RA. Thus, we suggest that autophagy might be a potential therapeutic target for the management of RA.

Abstract Number: 2565

Common Biomarker Elevations in Idiopathic Pulmonary Fibrosis and Rheumatoid Arthritis-Associated Interstitial Lung Disease

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Background/Purpose: Interstitial lung disease (ILD) is an extra-articular manifestation of rheumatoid arthritis (RA) which contributes to increased morbidity and mortality. Clinico-epidemiological data indicate some overlap in disease course between RA-ILD and idiopathic pulmonary fibrosis (IPF), particularly in subsets of RA-ILD patients with UIP-like pathology. We therefore evaluated levels of specific peripheral blood protein markers in patients with RA-ILD and IPF to determine molecular profiles indicative of shared disease pathogenesis.

Methods: A cohort of patients that met ACR classification criteria for rheumatoid arthritis were enrolled and subclassified as having RA-no ILD versus RA-ILD (mild vs. advanced parenchymal lung abnormalities) based on high resolution computed tomography scans of the chest (HRCT). A cohort of patients with IPF was also enrolled through Brigham and Women's Hospital. Standard solid phase enzyme-linked immunosorbent assays (ELISAs) were used to assess serum levels of matrix metalloproteinase 7 (MMP-7) and interferon-ϒ-inducible protein 10 (IP-10), which had previously been found to be significantly elevated in RA-ILD. Levels of serum biomarkers were compared using Mann U Whitney testing.

Results: 71 patients with RA were enrolled and classified as RA-no ILD (n=22) versus RA-ILD (n=49). Serum specimens were obtained from these patients as well as a comparator cohort of IPF patients (n=44). 72.7% (n=16) of patients in the RA-no ILD group, 63.3% (n=31) of patients in the RA-ILD and 40.9% (n=18) of patients in the IPF group were women. The average age of the patients in the RA-ILD and IPF groups were 65 and 66 years, respectively, vs 50 years in the RA-no ILD group (p=<0.0001). 63.6% (n=28) of the IPF patients, 55% (n=27) of the RA-ILD patients and

36.4% (n=8) of the RA-no ILD patients were smokers. ELISA-based measurement of serum MMP-7 revealed significantly increased levels in patients with RA-ILD and IPF (8.19 ng/ml vs 6.16 ng/ml, p=0.02). IP-10 levels were also significantly elevated in both RA-ILD and IPF patients (209.71 pg/ml vs 187.61 pg/ml, p=0.71). In contrast, patients with RA-no ILD had significantly lower levels of MMP-7 (2.98 ng/ml) and IP-10 (82.32 pg/ml) compared to patients with RA-ILD (MMP-7: p=<0.0001, IP-10: p=0.001) and patients with IPF (MMP7: p=<0.0001, IP-10: p=0.003).

Conclusion: Serum levels of both MMP-7 and IP-10 were elevated in patients with IPF and RA-ILD relative to RA patients without evidence of ILD. This overlap in biomarker signatures encompassing both inflammatory (IP-10) and remodeling (MMP-7) pathways supports a possible link in pathogenesis that may suggest common therapeutic targets in RA-ILD and IPF.

Disclosure: K. Fernandez, None; **T. Doyle**, None; **L. Harlow**, None; **I. O. Rosas**, None; **D. P. Ascherman**, None.

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Abstract Number: 2566

Hexokinase 2 As a Novel Metabolic Target for Rheumatoid Arthritis

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Background/Purpose: Hexokinases (HKs) catalyze the first step in glucose metabolism. HK2 constitutes the principal inducible isoform with a restricted distribution in normal adult tissues. Up-regulated glycolysis and HK2 expression have a powerful growth advantage, which promotes cell proliferation and invasion. Fibroblast-like synoviocytes (FLS) are a key component of rheumatoid arthritis (RA) invasive synovium, and display unique aggressive features, including increased migration and invasion. We have recently showed that RA FLS present an altered glucose metabolism, which modulates FLS mediated functions. To determine whether HK2 is a key regulator

of FLS glycolytic and aggressive phenotype, we examined its role on FLS functions and in an arthritis animal model.

Methods: HK1 and HK2 expression were studied by immunohistochemistry (IHC) in RA and osteoarthritis (OA) synovial tissue. HK2 expression in FLS was studied by double IHC and qPCR in synovial tissue and FLS cell lines, respectively. RA FLS were transfected with HK2 siRNA, or infected with HK2 expressing adenovirus (ad) and the following FLS functions were conducted: migration (scratch assay) and matrigel invasion assay after PDGF stimulation, and metalloproteases (MMP) expression after LPS stimulation. We used $HK2^{F/F}$mice, harboring the ubiquitously expressed tamoxifen inducible Cre (UBCcreERT2) in order to systemically delete HK2. Passive KRN arthritis was induced injecting intraperitoneally 150µl of serum 3 weeks after tamoxifen treatment. Clinical scores were assessed daily and histopathological studies were carried on day 10.

Results: While HK1 is widely expressed in both RA and OA synovial tissue, HK2 is particular of RA histopathology (9/9 RA; 3/9 OA). HK2 is localized in the synovial lining and sublining and it co-localizes with vimentin as a marker for FLS. Basal HK2 expression was increased in RA compared to OA FLS, and its expression increased after LPS and PDGF stimulation. Silencing HK2 in RA FLS resulted in a less invasive phenotype (3.2 fold less invaded area in HK2-silenced FLS, $p<0.05$) and lower levels of MMP3 expression. Consistently, overexpression of HK2 resulted in an increased ability to migrate (scratch length: GFP-ad: 299.1±7.2; HK2-ad 90.7±2.5; $p<0.001$) and invade (3.1 fold invaded area in HK2-ad; $p<0.001$). The UBCcre-$HK2^{F/F}$ mice showed lower clinical and histological arthritis scores than wild type mice (WT) (clinical score at day 10: WT: 9±0.79; UBCCre-$HK2^{F/F}$: 3±0.49 ($p<0.001$)).

Conclusion: HK2 is more abundantly expressed in RA than OA synovial lining, and regulates FLS aggressive functions. HK2 also contributes to arthritis severity in the KRN animal model. Therefore, selective HK2 inhibition might be an attractive potential selective target safer than global glycolysis.

Disclosure: M. Fernandez Bustamante, None; **R. Garcia-Carbonell**, None; **J. Smith**, None; **G. Firestein**, None; **S. Miyamoto**, None; **M. Guma**, None.

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Abstract Number: 2567

The Effect of Fibroblast Growth Factor 4 on the Proliferation of Fibroblast-like Synoviocytes in Rheumatoid Arthritis

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Background/Purpose: Fibroblast-like synoviocytes (FLSs) contribute to synovial hyperplasia in rheumatoid arthritis (RA). Fibroblast growth factor 4 (FGF4) is a potent mitogen for tumor cells. The aim of our study was to investigate the expression of FGF4 in RA patients and its role in RA synoviocyte proliferation. Furthermore, the underlying pathways such as PI3K/Akt, p38-MAPK, and Erk-MAPK pathways were investigated to understand the potential mechanism of FGF4 in the pathogenesis of synovial hyperplasia.

Methods: The serum level of FGF4 were detected by protein arrays in 20 disease modifying antirheumatic drugs (DMARDs) naïve RA patients and in 20 age- and sex- matched healthy controls. The mRNA expression levels of FGF4 in PBMCs isolated from 50 patients with RA, and 50 healthy controls mathed with age and gender were analyzed by real-time PCR. FLSs were isolated from RA synovium, and were co-cultured with different concentrations of recombinant human FGF4 (rhFGF4) for 48 hours. Cell proliferation was quantified by Cell Counting Kit-8 assay and cell cycle distribution were evaluated by flow cytometry. Expression of cell cycle-related proteins were measured by western blot. Western blot analysis was also performed to determined the activation of PI3K/Akt, p38-MAPK, and Erk-MAPK pathways in RA-FLS after being treated with 50 ng/ml rhFGF4.

Results: The serum expression of FGF4 in RA group was higher than that in control group (P<0.05). The FGF4 mRNA was highly expressed in PBMCs of RA, compared with the control group (P<0.05). RA-FLS treated with different concentrations of rhFGF4 (12.5, 25, 50, 100 and 200 ng/ml) showed significantly increased proliferation，with cell proliferation rates of (1.21±0.08), (1.26±0.12), (1.29±0.12), (1.34±0.14), (1.39±0.13), compared with that of controls (1.00±0.00) (P<0.05). Incubation with various concentrations of rhFGF4 (25, 50, 100 ng/ml) resulted in a significant increase of G_2/M+S phase cells compared to controls (P<0.05). And the protein expression of cyclin D1 was also up-regulated after being treated with rhFGF4 (P<0.05). The protein expression of p-Akt, p-p38 and p-Erk was significantly increased in RA-FLS after a 5 min exposure to rhFGF4, compared with the control group.

Conclusion: Our results suggest that FGF4 is highly expressed in serum and in PBMCs of active RA patients. The proliferation of RA-FLS and the cell cycle G_1/S transition were promoted by rhFGF4. And cyclin D1 was up-regulated by treating with rhFGF4, indicating the aberrant activation

of FGF4 may play a role in RA-FLS proliferation, contributing to synovial hyperplasia. It is possible that rhFGF4 promotes the proliferation of RA-FLS via activation of PI3K/Akt, p38-MAPK and Erk-MAPK signaling pathways.

Disclosure: X. Feng, None; **S. Zhu**, None; **W. Peng**, None; **F. Liu**, None; **B. Zhang**, None; **J. Huang**, None.

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Abstract Number: 2568

ARL15 expressed By Rheumatoid Arthritis Synovial Fibroblasts Regulates IL6 and Plays a Role in Apoptosis and Hypoxia

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Background/Purpose: Rheumatoid Arthritis (RA) is a chronic, inflammatory condition that affects more than 1% population globally. Several studies suggest RA to be controlled by a combination of different genetic & environmental factors. While non-genetic factors remains elusive, a large number of genes/loci have been identified to confer susceptibility to RA. In the first ever GWAS on RA in north Indian populations, we had identified a novel gene *ARL15* (5p15.2) in addition to the already established HLA locus. ARL 15 is a small G Protein belonging to ADP ribosyl family (ARF). The inhibition of this protein family in the Collagen induced Arthritis model of RA has been shown to improve the arthritis score and inflammation. But importantly, expression of either *ARL15* or any other *ARF* genes in synovial fibroblast or in blood samples of RA patients has never been reported. Based on this background, the present study was aimed at functional characterization of *ARL15*, the novel GWAS hit to understand its implications, if any, for RA biology.

Methods: Synovial fluid and tissue samples were collected from each of the RA patients undergoing total knee replacements at AIIMS (As per American College of rheumatology criteria 2010), New Delhi with institutional ethical committee clearance and informed consent. Homogeneity of cells was checked by Fluorescence-Activated Cell Sorting. Presence of ARL15 gene and protein in RASF cells were tested by RT-PCR and western blots. TNF induction and siRNA knock down was carried out to find the expression of genes of interest by RT-PCR. Global expression profiling in knock down and control cells was captured by transcriptome sequencing. Apoptosis of *ARL15* knock down cells were detected by FACS using Annexin V staining. A549 cancer monolayer cells were used for checking the expression of *ARL15*under hypoxic condition.

Results: FACS experiment confirmed the cultures of synovial fibroblasts. RT-PCR showed the presence of *ARF2*, *ARF6* and *ARL15*. Western blot confirmed the presence of ARL15 protein in cell lysates. SiRNA mediated knock down experiments showed differential expression of *GAPDH*, *Adiponectin, Adiponectin receptorI and IL6* genes in RASF. RNAseq validated the above findings and also revealed differential expression of several additional genes involved in *IL6* signaling, RNAseq also indicated the possible role of *ARL15* in hypoxia which was then confirmed using A549 cancer cell line. Annexin V staining of *ARL15*knock down cells showed increase in apoptosis of RASF cells compared to control.

Conclusion: Our results confirm for the first time the expression of ARF genes including *ARL15* in the synovial fluid and tissue derived synovial fibroblast cultures of RA patients and its connection with IL6. Transcriptome sequencing data validated these findings in addition to identifying several other differentially expressed genes related to hypoxia and apoptosis. These preliminary findings taken together with previously available literature indicate the use of ARL15 as potential therapeutic target for RA.

Disclosure: S. KASHYAP, None; **P. Chattopadhyaay**, None; **A. K. Pandey**, None; **U. Kumar**, None; **C. S. Yadav**, None; **B. K. Thelma**, None.

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Abstract Number: 2569

Restoration of Decreased Lymphocyte Counts and the Shift to Th1 and Effector Memory CD8+T Cell Subsets Associate with Spontaneous Regression of Lympho-Proliferative Disorders Developed in RA Patients Treated with Methotrexate

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Background/Purpose: Lympho-proliferative disorder (LPD) developing under methotrexate (MTX) administration is a relatively rare but well known complication among rheumatoid arthritis (RA) patients. Spontaneous regression of LPD following MTX withdrawal is a singular aspect of LPD developing during MTX treatment with an incidence of 30-60%. The purpose of this study was to investigate the factors involved in spontaneous regression of LPD following MTX withdrawal.

Methods: This was a multi center retrospective observational study. Medical chart from January 1995 to October 2015 was reviewed. Age, sex, MTX dose, and RA duration matched control patients treated with MTX for more than 6 months were randomly selected. The time of MTX cessation (equally to LPD diagnosis) was defined as week 0, and blood sample was collected at week 0, 4 and 12 for flowcytometry when it was available (7 regressive, 3 persistent, 10 controls). LPD patients were divided into regressive group or persistent group depending on the status of LPD at week 12. Epstein Barr Virus (EBV) antigen specific CD8+ T cells was detected with MHC/EBV peptide tetramer.

Results: Forty-three RA patients complicated with LPD were identified and 76 control patients were selected. Among the 43 LPD patients, 28 were regressive and 15 were persistent. At week 0, the absolute number of peripheral lymphocytes was specifically and significantly decreased in LPD group, compared to control group. Flowcytometric analysis revealed significant decrease in absolute count of CD4+, CD8+ T cells, B cells and NK cells but not in proportion of these cell subsets. However, further subset analysis revealed that the proportion of effector memory CD8+ T cells (EM CD8+), EBV specific CD8+ and T helpler 1 (Th1) subset was specifically decreased in regressive group compared to control group. Following MTX withdrawal, a significant increase of these T cell subsets in addition to total lymphocytes was observed at week 4 and 12, only with the regressive group, but not with persistent group. Pathological category of LPD did not relate to change in lymphocytes.

Conclusion: Our study suggested that decreased lymphocytes at the time of LPD diagnosis and restoration following MTX withdrawal may associate with pathogenesis and clinical course of regressive LPD. Proportion of Th1 cells, EM CD8+, EBV specific CD8+ was restored following MTX cessation, indicating their involvement in regression of LPD.

Disclosure: **S. Saito**, none, 9; **K. Suzuki**, None; **K. Yamaoka**, None; **K. Amano**, Chugai, 2; **M. Tokuhira**, None; **T. Takeuchi**, None.

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Abstract Number: 2570

Pyruvate Regulates Reactive Oxygen Species (ROS) Production, Dysfunction and Aberrant Metabolism of Mitochondria in Fibroblast-like Synoviocytes of Rheumatoid Arthritis

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Rheumatoid Arthritis – Human Etiology and Pathogenesis - Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: In rheumatoid arthritis (RA), fibroblast-like synoviocyte (FLS) is a key component of invasive synovium and mediates inflammation and destruction of joint. Recently, change of metabolic pathways offers novel approach to understanding the inflammation in RA. However, it has remained unknown how mitochondrial metabolic profiles are associated with inflammation in RA. In addition, production of reactive oxygen species (ROS), formed as byproduct in metabolic pathway is reported to be attenuated by pyruvate supplement in *in vitro* study. This study aimed to evaluate mitochondrial ROS signaling, biosynthetic functions and cytokine production, and the effects of pyruvate supplement in RA-FLS.

Methods: We analyzed mitochondrial ROS signaling and mitochondrial functions by quantitative PCR and western blotting in RA-FLS lysates. Mitochondrial metabolism was evaluated by

mitochondrial respiration using a Seahorse Bioscience Extracellular Flux Analyzer (XF24). The oxidative damage and biogenesis in mitochondria was evaluated by transmission electron microscopy (TEM) and western blotting in RA-FLS. IL-6 was measured by ELISA.

Results: Generation of TNF-α-induced mitochondrial ROS was higher in the FLS from RA patients compared to patients with osteoarthritis (OA). Peroxiredoxin 3 (Prx3), mitochondrial specific H_2O_2-scavenging enzyme, was significantly decreased in the TNF-a stimulated RA-FLS at early time (p=0.019). In addition, we showed increased mitochondrial respiration (p<0.00001), dysfunction of mitochondria and mitophagy including up-regulation of p62 and LC3B in the RA-FLS compared with OA-FLS. These mitochondrial phenotypes of RA-FLS were attenuated by treatment of pyruvate in TEM and western blot analysis. In addition, pyruvate supplement decreased IL-6 release in the TNF-a stimulated RA-FLS.

Conclusion: Pyruvate may act as a new therapeutic metabolite for improvement of mitochondrial dysfunction and proinflammatory cytokine production in RA-FLS.

Disclosure: J. Y. Kim, None; **S. E. Kang**, None; **H. J. Yoo**, None; **J. S. Park**, None; **E. Y. Lee**, None; **E. B. Lee**, None; **Y. W. Song**, None.

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Abstract Number: 2571

Distinct Oral and Fecal Community Profiles Enriched in Opportunistic Pathogens in RA Patients and First Degree Relatives Are Influenced By Environmental Risk Factors, Including Smoking, Dental History and Lung Infection

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Background/Purpose: In the Rheumatoid Arthritis (RA) prodrome, genetic predisposition intersects with environmental risk factors, such as smoking, periodontal disease and respiratory infection, however no studies to date compare the microbiomes of at-risk first-degree relatives (FDR) with Healthy controls (HC) and RA probands. We hypothesized that specific microbial taxa (operational taxonomic units, OTUs) from the oral and fecal microbiota differentiate between RA and HC, and that FDR segregate based on similarity with RA patients or HC.

Methods: We chacterized a prospective cohort of RA probands, FDR and HC. Probands met ACR 2010 criteria and/or had a confirmed RA diagnosis. FDRs included parents, full siblings or offspring of an RA proband; HC were drawn from the community. From all individuals, we obtained demographics, medical history, epidemiological questionnaires and tissue collections. After DNA extraction from tongue and fecal swabs, we undertook targeted 16S rRNA gene sequencing using Illumina MiSeq then used standard QIIME workflows, visualizations with the Phyloseq R package and multivariate statistical analysis using the mixOmics R package.

Results: 116 RA patients, 63 FDR and 43 HC matched for age and gender were recruited. 56% and 57% of RA, 4% and 49% of FDR and 0% and 37% of HCs were ACPA+ and shared epitope positive respectively. 47% RA patients, 30% FDR and 37% HC had ever smoked. Based on multivariate analyses, oral and faecal microbiota were altered in RA relative to HC. The oral community profile in RA was enriched in opportunistic pathogens including *Streptococcus, Veillonella, Staphylococcus* and *Camplylobacter* spp., *Propionibacterium acnes* and *Prevotella melaninogenica.* The fecal community profile in RA patients was enriched in *Bacteroides*, *Enterococcus* and *Pseudomonas* spp., while in HC in *Clostridiales*, particularly members of the *Lachnospiraceae*. By univariate analysis, the abundance particular oral and fecal OTUs was strongly associated with environmental risk factors. For example, a fecal *Peptococcus* sp. was associated with smoking history, dental history and a history of respiratory infection. The oral and faecal OTU profile of some FDRs segregated with the RA patients and some segregated with HC.

Conclusion: We demonstrate distinct oral and fecal community profiles in RA patients relative to HC, which are influenced by environmental risk factors such as smoking, dental or respiratory infection. The oral and faecal associated microbiota of individual FDRs segregates either with RA or HC subjects. Thus, compound genetic and environmental risks may promote inhospitable mucosal environments for commensals abundant in HC, creating niches for opportunistic pathogens before and after the development of RA.

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Abstract Number: 2572

Study of Two Biomarkers of Biological Age in the Blood of Patients with Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Accelerated biological aging of blood cells could contribute to the pathogenesis of RA. However, biological age has multiple facets, some as epigenetic aging not yet addressed in RA, and the most studied, shortened telomere length, not replicated in all studies. Recently, DNA methylation age measures (DmAM) have been developed as biomarkers of epigenetic aging that correlate with survival, diseases of old age and fitness in the elderly. We aimed to address biological aging in RA with DmAM and telomere length.

Methods: DNA from blood of 365 patients meeting ACR classification criteria for RA and 375 healthy age-matched controls were analyzed. A DmAM based in 8 CpG sites was assayed by minisequencing after bisulfite modification (1). qPCR was used for evaluation of relative telomere length (2). A second set of 354 ACPA positive RA patients and 335 controls was used for replication of the DmAM results (3). Differences in DmAM and telomere length between patients and controls were evaluated with ANOVA. Cox proportional hazards regression models were used for survival analysis. All analyses were adjusted for age and sex.

Results: The 8 CpG DmAM showed a small premature aging in patients with RA in comparison with controls in the two sample collections analyzed (Table 1). However, premature aging did not persist after correction for changes in blood cell subpopulations (Table 1), and it was not consistently observed with other DmAM (Table 1). In addition, telomere length attrition was not observed in RA patients (Table 1). No association was observed between any of the two age biomarkers and time since disease onset, antibody status, and prevalence of erosions, shared epitope

or smoking (not shown). At the end of data collection, 246 of 734 subjects have died (33.51%). Hazard Ratio (HR) for all-cause mortality was higher for RA patients than for controls (HR = 1.89; 95% CI = 1.45 to 2.45; $P = 2.0 \times 10^{-6}$). However, mortality was not associated with age biomarkers, neither the DmAM, nor telomere length, after adjusting for chronological age.

Conclusion: We observed premature epigenetic aging of small magnitude in blood cells of patients with RA, but the difference is most likely irrelevant as it could be due to changes in blood cell subpopulations or to particularities of the specific DmAM. In addition, we did not observe the reported shortening of telomere length, further questioning the concept of premature biological aging in RA blood cells as a whole. Table 1. Differences in biological age

Sample set	ΔDmAM (years)	95 % CI	*P*	Telomere length (T/S)	95 % CI	*P*
1st	1.9	1.1 to 2.7	1.0 x 10-6	-0.05	-0.1 to -0.01	0.02
2nd	0.7	0.2 to 1.3	0.005	NA		
2nd adj*	-0.6	-1.2 to -0.1	0.03			
2nd alt**	-1.5	-2.2 to -0.7	7.0 x 10-5			

* Adjusted for blood cell composition according to Houseman *et al. BMC Bioinformatics* 13:86 (2012). ** Alternative DmAM from Horvath, S. *Genome Biology*14:R115 (2013) References: 1. Vidal-Bralo, L. *Submitted* 2. Cawthon, R. M. *Nucleic Acids Res.* **30,** e47 (2002) 3. Liu, Y. *et al. Nat Biotechnol* **31,**142–147 (2013) Funded by Instituto de Salud Carlos III (Spain) with participation of the European Regional Development Fund of the EU (grants PI14/01651 and RD12/009/008)

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/study-of-two-biomarkers-of-biological-age-in-the-blood-of-patients-with-rheumatoid-arthritis

Abstract Number: 2573

Galectin 1 As Potential Prognostic Biomarker in Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Galectin 1 (Gal1) is a type of lectin expressed in a wide variety of tissues and organs. In the immune context, is broadly described its function as a negative regulator in different animal models of autoimmune diseases. The treatment with recombinant Gal1 has a therapeutic effect in the murine model of collagen-induced arthritis. In this work we studied the effect of genetic variants on Gal1 gene (*LGALS1*) over the Gal1 expression and its relationship with clinical parameters of severity in patients with early arthritis (EA).

Methods: Princesa Early Arthritis Register Longitudinal (PEARL) study includes patients with early arthritis (EA). Demographic, clinical, laboratory, therapeutic and radiological data are collected along a 5 years follow-up (baseline, 6, 12, 24 and 60 months). Biological samples are obtained at each visit. We analyzed the genotype of 4 single nucleotide polymorphisms (SNPs) present in *LGALS1* by PCR with TaqMan probes (n=540). Next, we fit several multivariate models by generalized estimating equations for repeated measures to analyze the statistical correlation between these genotypes and clinical parameters [Disease Activity Score 28 (DAS28) and treatment intensity] as well as correlation between these genotypes and IL-6, a key inducer of systemic inflammation which is associated with activity and severity of RA. IL-6 serum levels were measured by Enzyme-Linked ImmunoSorbent Assay (ELISA) (n=190 patients with more than 2 visits). Gal1 serum levels were measured by ELISA and western blot (WB) was used to assess Gal1 expression in lymphocytes. Statistical analysis was performed using Stata 12 for Windows (StataCorp PL, College Station, USA). The effect of recombinant Gal1 over IL-6-secretion using anti-CD3/CD28-stimulated lymphocytes of healthy controls was also studied.

Results: We found that EA patients with at least one minor allele of the SNP rs9622682 had significantly lower levels of serum IL-6 (p=0.003 GA genotype and p=0.002 AA genotype). In addition, we observed that EA patients with AA genotype for rs9622682 showed higher levels of serum Gal1 and an increased expression of Gal1 on peripheral blood lymphocytes measured by WB compared to GG patients. That SNP showed partial linkage disequilibrium (LD) (R^2=0.6) with the rs929039 located in the *LGALS1* promoter. The presence of minor alleles of rs929039 displayed a similar effect over IL-6 and Gal1 levels than rs9622682. Different combinations of minor alleles of those SNPs could amplify the increased expression of Gal1 observed in EA patients. On the other

hand, treatment of anti-CD3/CD28-stimulated lymphocytes with recombinant Gal1 reduced IL-6 *in vitro* expression levels in healthy donors.

Conclusion: The presence of minor alleles of SNPs of *LGALS1* rs9622682 and rs929039 may affect the expression of Gal1 and this finding is associated with lower levels of IL-6 in serum of patients with EA, suggesting a potential prognostic value for these genetic variants.

Disclosure: **A. Lamana**, None; **A. Triguero-Martinez**, None; **I. V. Seoane**, None; **H. de la Fuente**, None; **C. Martinez-Mora**, None; **A. M. Ortiz Garcia**, None; **R. García-Vicuña**, None; **R. P. Gomariz**, None; **I. Gonzalez-Alvaro**, None.

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Abstract Number: 2574

IL-22 As a Biomarker for Erosive Disease in Rheumatoid Arthritis

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Background/Purpose: Consistent with models of experimental arthritis implicating IL-22 – as a cytokine produced by immune cells but acting on non-immune cells e.g. fibroblast and osteoclast – in the development of joint destruction could previously demonstrate that elevated IL-22 serum levels were associated with the development of erosive disease in patients with early rheumatoid arthritis (RA).

Methods: To study value of IL-22 as a marker for erosive disease in established RA, to assess whether IL-22 is increased in other joint destructive rheumatic diseases, and to evaluate the influence of comorbidities on IL-22 serum levels. We measured serum IL-22 levels by Enzyme-Linked Immunosorbant Assay (ELISA) and analyzed their correlation to erosive disease (assessed by radiographs of hand and feet) and clinical parameters in patients with established RA (n=142), psoriatic arthritis (n=15), gout (n=15), age-matched patients with hypertension (n=10), diabetes (n=10), coronary heart disease (n=10), and healthy individuals as controls.

Results: 81 of 142 patients with established RA demonstrated elevated IL-22 levels compared with the range of healthy controls. A significant greater percentage of these 'IL-22 high' patients (59%) demonstrated erosive disease compared the 'IL-22 normal' patients (37%, $p<0.05$). In the 'IL-22 high' compared to 'IL-22 normal' group the fractions of patients positive for RF (70% vs 83%) and ACPA (74% vs 64%) were slightly higher, however not statistical significant different. Similar, measures of disease activity including DAS28 (2.3 vs 2.8) and CRP (0.5 vs 0.3 mg/dl) only tended to be higher in the 'IL-22 high' than the 'IL-22 low' group. Irrespective of erosive joint disease, patients with psoriatic arthritis and gout demonstrated lower IL-22 levels compared to established RA and only slightly higher than healthy individuals. Of note, patients with hypertension, diabetes and coronary heart disease had IL-22 serum levels comparable to healthy controls.

Conclusion: High IL-22 levels are associated with erosive disease also in established RA, potentially in parts independent of serology and comorbidities, and might serve as a marker for joint destruction also in this cohort.

Disclosure: J. Leipe, None; **H. Schulze-Koops**, MSD, 5; **A. Skapenko**, None.

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Abstract Number: 2575

The Presence of Staphylococcal Toxins in the Urine of Patients with Rheumatoid Arthritis

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Background/Purpose: Rheumatoid arthritis (RA) is a disease of unknown etiology;with a pathogenesis that is due to a mixture of genetic, immunological and environmental factors. A T-cell immune response to the presence of pyrogenic toxin superantigens (PTSAgs) in the joints of RA

patients has previously been described.A link has been proposed between pathogenic micro-organisms and the development of chronic, autoimmune conditions. Potential pathogenic mechanisms include the hygiene hypothesis and molecular mimicry. Due to the widespread prevalence of RA, it has been hypothesised that the pathogenesis could involve a common bacterium.
Previously, *Porphyromonas gingivalis*, a periodontal pathogen, has been suggested due to its ability to citrullinate proteins. In RA one potential bacterial candidate that has been suggested is *Staphylococcus aureus*.

Current published data averages the presence of *S.aureus* at 30% in the general population from nasopharyngeal swabs[1]. Furthermore, our data has found immune complexes containing *S.aureus* antigens are detectable in urine(ref). **Objectives:** To investigate the presence of staphylococcal enterotoxins B and C (SEB/SEC), toxic shock syndrome toxin 1 (TSST-1) and alpha haemolysin (AH) in the urine of patients with RA to support the hypothesis that they may play a role in RA.

Methods: Following ethical approval, mid-stream urine samples were obtained from patients with RA and a control group (patients with closed fractures attending an orthopaedic clinic). Both populations had no active infection(s) and were recruited from British Rheumatology and Orthopaedic departments in the same hospital. Samples were collected and processed aseptically, then analysed by western blot using commercially available primary (sheep) antibodies to SEB, SEC, TSST-1 and AH; and a rabbit anti-sheep HRP conjugated secondary antibody.

Results: The RA population comprises 148 patients (74% females) The control population comprises 70 patients (52% female). Mean age was older in the RA group (63 vs 58 years $p<0.01$) results of the toxins and differences between cases and controls are shown in table 1 (below)

Table 1 Descriptive characteristics of the population(s).

All characteristics	**All (n=219)**	**RA (n=149)**	**Fracture (n=70)**	**Difference P value**
Female (%)	162 (74.0)	110 (73.8)	52 (74.3)	
Mean Age (SD)	62.1 (14.3)	63.9 (12.4)	58.1 (17.1)	<0.0045
Positive AH (%)	73(33.3%)	69(46.3%)	4 (5.7%)	P<0.001
Positive SEB (%)	54 (24.7%)	40 (26.9%)	14 (20%)	P=0.27
Positive SEC (%)	71 (32.4%)	57 (38.23	14(20%)	P=0.007
Positive TSST (%)	0 (0)	0 (0)	0 (0)	.
Any Toxin (%)	103 (47.0)	84 (56.4)	19 (27.1)	

The odds of being toxin positive for each was AH 13.7 (95%CI 4.7,39.6), SEB 1.34 (95%CI 0.66,2.71) and SEC 2.4 (95%CI 1.22,4.8). The odds of any toxin being positive was 3.5 (95%CI 1.9,6.4) and this remained significant after adjusting for age and gender

Conclusion: Our work demonstrates the presence of bacterial toxins in urine from RA patients, with 56% demonstrating the presence of at least one staphylococcal toxin. We also show that *S.aureus* toxins are differentially expressed in this population. The pathological basis of this finding is not clear.

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Abstract Number: 2576

uPAR Promotes Tumor-like Biologic Role of Fibroblast-like Synoviocytes through PI3K/Akt Signaling Pathway in Patients with Rheumatoid Arthritis

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Background/Purpose:

Urokinase-type plasminogen activator receptor (uPAR), is a multi-functional receptor on cell surface, widely present in endothelial cells, fibroblasts, and a variety of malignant cells. Current studies have suggested that uPAR overexpressed on synovial tissues or in synovial fluid or plasma in patients with rheumatoid arthritis (RA). However, there are limited researches regarding the role of uPAR on fibroblast-like synoviocytes of rheumatoid arthritis (RA-FLSs) and its underlying mechanisms.

Methods: All synovial specimens were taken from patients, in which 8 patients with RA (met the 2009 ACR/EULAR criteria) , 4 patients with OA (consistent with 1995 ACR classification criteria) , and 3 patients with severe trauma who had , no other joint abnormalities or systemic disease. To study effects of uPAR on RA-FLSs, chemically synthesized small interference RNA(siRNA) specifically targeting the uPAR gene was transfected into RA-FLS by cationic liposome. Western blot and ELISA were taken to test inhibition efficiency. The proliferative inhibition rate was examined by the CCK8 assay. Flow cytometry was used to determine the change of cell cycle distribution and apoptosis. The migration and invasion ability of RA-FLSs were examined by a

transwell assay. Western blot was performed to detect the influence of uPAR on the PI3K/Akt signaling pathway.Migration and tubule formation assays were used to explore the influence of RA-FLSs uPAR on angiogenesis.

Results: Our studies show that the expression of uPAR protein was significantly higher in FLSs from RA than those from OA or traumatic injury patients. uPAR-siRNA could effectively block the uPAR expression of mRNA, protein level in RA-FLSs and soluble uPAR secretion in cell supernatant. uPAR gene silencing inhibited RA-FLSs proliferation by (28.62 ± 4.82)% at 72h, restrained cell transformation from the G0/G1 phase to S phase obviously, reduced RA-FLSs cell migration by (74.82 ± 2.16)% and invasion by (74.51 ± 4.73)% , and interfered with activation of the PI3K/Akt signaling pathway significantly. Cell supernatants from uPAR gene-silenced RA-FLSs markedly inhibited the migration and tubule formation ability of HUVEC (human umbilical vein endothelial cell) (P <0.05).

Conclusion:

uPAR changes the biological characteristics of RA-FLSs and affects neoangiogenesis of synovial tissues in patients with RA, which may be associated with PI3K/Akt signaling pathway. These results imply that targeting of uPAR and its downstream signal pathway may provide beneficial therapeutic effects in RA.

Disclosure: Y. Liu, None; **Y. Pan**, None; **S. G. Zheng**, None.

Abstract Number: 2577

Elevated Matrix Metalloproteinases Levels in Oral Fluids of Most Rheumatoid Arthritis Patients, Even without Frank Periodontitis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Periodontitis shares pathogenic mechanisms with rheumatoid arthritis (RA) and may trigger its onset. However, little information is available about inflammatory responses in oral fluids of RA patients.

Methods: 33 RA patients (22 new-onset, 11 late RA), all meeting 2010 ACR/EULAR criteria, 20 age/gender-matched healthy subjects (HS) without periodontitis/RA, and 20 patients with chronic periodontitis (CP) without RA were enrolled. 20 analytes including matrix metalloproteinases (MMPs) and innate/adaptive immune mediators were measured by Luminex in serum, saliva, gingival crevicular fluid (GCF), and RA joint fluid (JF). Serum *P. gingivalis* (*Pg*) IgG was measured.

Results: The 33 patients were typical of RA cohorts (85% female, median age 51) and only one currently smoked. The majority (91%) received regular dental care with cleanings every 6 months. 58% had rheumatoid factor (RF) or anti-citrullinated protein antibody (ACPA). Of the RA patients, 10 (30%) had periodontal health, 13 (39%) had gingivitis, and 10 (30%) had periodontitis. Pocket depth (PD), clinical attachment loss (CAL), and bleeding on probing (BOP) were all increased compared with HS ($P<0.002$). Six of 33 patients had *Pg* IgG antibodies, and all 6 had periodontitis ($P=0.0002$). *Pg* antibodies strongly correlated with PD, BOP, and CAL ($P\leq0.0009$). ACPA and RF levels also correlated with CAL ($P=0.03$). Most mediators were significantly elevated in serum of RA patients versus HS; Th-1 mediators predominated in JF. However, RA patients had elevated salivary levels of IL-17, IL-10, IL-8, OPG, MMP-1, MMP-9, and MMP-13 versus HS ($P\leq0.03$). In GCF IL-8, MMP-8, and MMP-9 amounts were higher in RA versus HS ($P\leq0.02$). Notably in RA patients, MMP-8 or MMP-9 levels were even higher in the oral fluids than serum ($P<0.0001$) and JF. Salivary or GCF mediators were elevated in RA patients regardless of periodontitis. While 13 patients had elevation of MMP-8 or MMP-9 in saliva >3 SD above the mean of HC, only 30% had clinical periodontitis. In patients with non-RA CP, levels of MMPs were exceptionally elevated in serum and oral fluids compared to HS and RA, particularly MMP-8 and MMP-9 ($P<0.0001$). Highest levels were seen in GCF, which were 4X higher than serum. The subset of RA patients with CP had similar inflammatory profiles to CP without RA, with exception of a few inflammatory mediators enriched in RA, notably IL-12p70 in saliva ($P=0.001$), IFNα and CXCL10 in GCF ($P\leq0.003$). MMP levels were higher in all sites for non-RA CP ($P\leq0.01$). *Pg* antibodies did not directly correlate with any serum mediator, however in GCF, the most proximal site of periodontitis, they correlated with levels of IFNα, IL-10, IL-12p70, and IL-23 ($P\leq0.05$).

Conclusion: RA patients had oral inflammation despite lack of smoking and regular dental care. Highly elevated MMP levels and correlation between dental parameters and ACPA support pathogenic connections between the diseases. *Pg* antibodies may be a marker of periodontitis in RA patients. However, elevation of MMPs in oral sites, regardless of periodontitis status or *Pg* antibodies, suggests the oral muscosa may be a common, and often unrecognized, site of extra-articular inflammation in RA patients.

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Abstract Number: 2578

Plasma Levels of Bone Morphogenetic Protein (BMP) Subgroups and Their Inhibitors (noggin, sclerostin) in Rheumatoid Arthritis Patients and Correlation with Disease Activity, Clinical and Radiographic Progression

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Background/Purpose: Progressive bone destruction occurs in rheumatoid arthritis (RA) due to imbalance of osteoblast/osteoclast activity. Bone morphogenetic proteins (BMPs) regenerate bone damage by stimulating the differentiation of osteoblasts. Effects of BMPs and their inhibitors in the mechanism of bone destruction have not been identified yet. The aim of this 1 year follow-up prospective study which preliminary results were presented as poster in 2015 ACR Congress is to compare plasma levels of BMP 2, 3, 4, 5, 6, 7, 9, 14, noggin, sclerostin in RA patients and healthy volunteers and to assess correlations of these proteins with disease activity, clinical and radiographic progression in RA.

Methods: 138 RA patients (Group 1=85 using DMARDs, Group 2=53 using anti-TNFα) fulfilling the 1987 ACR criteria and 80 healthy volunteers aged 18-65 years were recruited. All groups were matched by age and sex. 125 RA patients (Group1=77, Group2=48) reached to the end of study.

Tender/swollen joint, ESR, CRP, DAS28-ESR, DAS28-CRP, pain and HAQ were evaluated. Structural damage was measured by modified total Sharp scoring method (mTSS). Plasma levels of BMPs, noggin and sclerostin were measured by ELISA method. Measurement of BMPs and their inhibitors, HAQ, mTSS and clinical assessment were repeated 1 year later in patient groups. Differences between group 1 and 2 were compared by Mann-Whitney U test. Baseline and 1-year datas were compared by Wilcoxon test. P value of 0.05 was considered statistically significant.

Results: Disease duration was statistically longer in anti-TNFα group (p=0.005). In our preliminary results plasma levels of BMP 2, 4, 5, 6, 7, 9, 14 were decreased; however, BMP subgroup inhibitors which are BMP 3, noggin and sclerostin were increased in RA patients. Also, the correlation between BMP 2,5, 14, sclerostin and disease activity scores were statistically significant in DMARD group. In 1 year follow-up datas BMP 2, 3, 4, 5, 7, 9, 14 were statistically significant in DMARD group and BMP2, 3, 7 and 9 were statistically significant also in anti-TNFα group when compared with the plasma levels of healthy volunteers. The comparison of basal and 1 year follow-up BMPs are shown in table 1. There was no correlation between BMP subgroups and HAQ, erosion scores, DAS28-ESR, DAS28-CRP in both of the patient groups in 1 year follow-up datas.

Conclusion: These results imply the relevance of BMPs and their inhibitors mainly with early diagnosis of RA rather than follow-up and prognosis.

Table 1. The comparison of basal and 1 year follow-up plasma levels of BMP subgroups and their inhibitors in patient groups (Test Statistics[a])

Group		Z	p value
DMARD	**BMP2 (1 year) – BMP2 (basal)**	-2.668[b]	**,008**
	BMP3 (1 year) – BMP3 (basal)	-2.615[c]	**,009**
	BMP4 (1 year) – BMP4 (basal)	-.140[b]	,889
	BMP5 (1 year) – BMP5 (basal)	-1.455[c]	,146
	BMP6 (1 year) – BMP6 (basal)	-.099[b]	,921
	BMP7 (1 year) – BMP7 (basal)	-4.396[c]	**,000**
	BMP9 (1 year) – BMP9 (basal)	-3.648[c]	**,000**
	BMP14 (1 year) – BMP14 (basal)	-2.856[c]	**,004**
	Noggin (1 year) – Noggin (basal)	-2.887[c]	**,004**
	Sclerostin (1 year) – Sclerostin (basal)	-5.740[c]	**,000**
TNF	**BMP2 (1 year) – BMP2 (basal)**	-3.005[b]	**,003**
	BMP3 (1 year) – BMP3 (basal)	-1.328[c]	,184
	BMP4 (1 year) – BMP4 (basal)	-3.836[b]	**,000**
	BMP5 (1 year) – BMP5 (basal)	-4.626[b]	**,000**
	BMP6 (1 year) – BMP6 (basal)	-2.380[b]	**,017**
	BMP7 (1 year) – BMP7 (basal)	-1.923[b]	,054
	BMP9 (1 year) – BMP9 (basal)	-3.939[b]	**,000**
	BMP14 (1 year) – BMP14 (basal)	-4.246[b]	**,000**
	Noggin (1 year) – Noggin (basal)	-1.621[c]	,105
	Sclerostin (1 year) – Sclerostin (basal)	-2.800[c]	**,005**

a. Wilcoxon Signed Ranks Test
b. Based on negative ranks.
c. Based on positive ranks.

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Etanercept Treatment Does Not Adversely Affect Traditional Cardiovascular Risk Factors in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at increased risk of cardiovascular (CV) disease. This analysis evaluated changes in metabolic and lipid CV risk factors in patients with RA treated with etanercept (ETN).

Methods: This was an exploratory analysis in a randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of ETN in patients with moderate RA despite disease-modifying antirheumatic drug therapy. Adults with active, moderate RA (3.2 <DAS28-CRP ≤5.1) for ≥6 months and receiving a stable dose of methotrexate for ≥8 weeks were randomized 1:1 to receive ETN 50 mg or placebo (PBO) weekly for 12 weeks; after week 12, all patients received ETN 50 mg weekly for 12 weeks. Laboratory tests evaluated baseline, week-12, and week-24 levels of metabolic and lipid analytes, and shifts in grade (low, normal, or high).

Results: In total, 210 patients enrolled: 104 PBO and 106 ETN; 77% female, 86% white, and mean (SD) age 56 (12) years. There were 14% with a medical history of type 2 diabetes and 30% a medical history of hyperlipidemia or hypercholesterolemia; 22% were receiving statins, 10% oral antidiabetic medications, 3% insulin, and 52% prednisone. Baseline, week-12, and week-24 values for each analyte are listed below. Over 24 weeks, there were no significant changes in metabolic or lipid analytes. Patients with diabetes and hyperlipidemia resembled the overall study population, except for decreases in fasting glucose and insulin through week 12 and slight decreases in hemoglobin A1C through week 24 in diabetics receiving ETN (n=17). For the majority of patients,

all analytes were in the normal range at baseline and remained normal at week 24.There were no gross abnormalities in liver function tests. Safety results are consistent with the current safety profile.

Conclusion: Treatment with ETN did not adversely affect the levels of traditional metabolic and lipid CV risk factors in patients with RA. Results in patients with diabetes are hypothesis generating and might be clinically relevant if demonstrated in a larger study.

	Baseline		Week 12		Week 24	
Analyte, mean (SD)	**PBO-ETN N=104**	**ETN-ETN N=106**	**PBO-ETN N=104**	**ETN-ETN N=106**	**PBO-ETN N=104**	**ETN-ETN N=106**
Fasting glucose, mg/dl	99.0 (30.7)	98.6 (30.3)	95.9 (22.3)	97.3 (26.6)	101.0 (22.8)	100.1 (24.0)
Fasting insulin, mIU/L	14.3 (17.6)	16.0 (34.9)	15.3 (22.4)	13.2 (13.5)	15.0 (18.4)	12.0 (12.1)
Hemoglobin A1C, %	5.7 (0.9)	5.7 (0.7)	5.7 (0.9)	5.6 (0.6)	5.6 (0.9)	5.6 (0.6)
Total cholesterol, mg/dl	195.2 (44.2)	186.6 (37.1)	190.9 (40.7)	184.8 (37.4)	197.0 (41.7)	191.1 (39.6)
HDL, mg/dl	62.0 (18.1)	62.1 (21.7)	60.5 (17.1)	61.6 (18.3)	62.1 (18.5)	62.2 (22.9)
LDL, mg/dl	105.6 (36.3)	97.8 (30.0)	103.2 (35.4)	96.9 (33.2)	105.5 (35.4)	101.7 (31.0)
Triglycerides, mg/dl	135.2 (91.6)	133.1 (80.1)	139.2 (85.5)	131.8 (69.4)	149.6 (104.0)	136.6 (76.2)
Apolipoprotein A1, mg/dL	159.6 (27.8)	160.5 (35.4)	159.2 (28.1)	162.0 (32.8)	163.7 (32.1)	161.6 (38.0)
Apolipoprotein B, mg/dL	91.6 (25.5)	86.2 (22.2)	89.5 (24.7)	84.9 (23.8)	91.8 (24.2)	88.7 (25.0)
Adiponectin, mg/L	11.6 (6.8)	11.5 (8.7)	11.7 (7.4)	11.6 (8.8)	12.3 (7.2)	11.6 (9.1)
Leptin, µg/L	29.3 (20.9)	33.5 (28.5)	30.1 (22.7)	35.6 (30.9)	30.8 (22.7)	34.5 (28.9)
Plasma NT-ProBNP, ng/L	242.0 (554.1)	170.1 (334.6)	232.2 (630.8)	168.2 (297.8)	244.2 (687.5)	164.2 (315.7)

Disclosure: **A. A. Deodhar**, AbbVie, 2,AbbVie, 9,Amgen, 2,Amgen, 9,Boehringer Ingelheim, 2,Boehringer Ingelheim, 9,Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 9,Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 9,Pfizer Inc, 2,Pfizer Inc, 9,UCB, 2,UCB, 9; **B. Bitman**, Amgen, 3,Amgen, 1; **Y. Yang**, Amgen, 5; **D. Collier**, Amgen, 3,Amgen, 1.

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Abstract Number: 2580

Tofacitinib Do Not Get Worse Subclinical Atherosclerosis Despite up-Regulating Serum Cholesterol in Methotrexate-Resistant Active Rheumatoid Arthritis Patients

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Background/Purpose: Patients with rheumatoid arthritis (RA) have an increased cardiovascular (CV) risk. We should have strategies for primary cardiovascular prevention in RA. Tofacitinib (Tofa) could possibly play a role in up-regulating levels of serum cholesterol[1].But there is no evidence of CV risk management about Tofa. To examine the effect of Tofa plus methotrexate (MTX) on subclinical atherosclerosis in MTX resistant RA patients in a cohort study design.

Methods: 45 RA patients with moderate to severe active disease despite MTX treatment (disease activity score: DAS28>3.2)were received Tofa plus MTX.Arterial structures, carotid intima media thickness(CIMT) and carotid artery plaque(CAP), were measured at baseline and 54 weeks follow-up.Arterial stiffness was assessed with cardio-ankle vascular index (CAVI) and augmentation index corrected for a heart rate of 75 beats per minute (AIx@75) at baseline and 54 weeks follow-up. Clinical data were collected at regular visits. CAVI is very similar to pulse wave velocity (PWV), and CAVI measures arterial wall stiffness independent of blood pressure and it is superior to brachial ankle PWV as an index of arterial stiffness[2].No new all treatments(statin, low lipids drug, and etc.) were allowed.

Results: Treatment with Tofa attenuated CIMT did not produce significant changes(0.92±0.09mm at baseline, 0.91±0.10 mm at 54 weeks: p=0.92), CAP did not produce significant changes(0.68±0.07 at baseline, 0.61±0.10 at 54 weeks: p=0.67)Treatment with Tofa attenuated the CAVI significantly from baseline to 54 weeks follow up(12.76 ± 1.68 and 10.22± 1.18%; p = 0.026). Treatment with Tofa attenuated the Aix@75 significantly from baseline to 54 weeks follow up(37.7

± 5.6, 32.9 ± 5.6 %; p = 0.028). DAS 28-ESR score improved significantly from baseline to 54 weeks(5.31±1.43, 2.23±1.63: p=0.01). On the other hand, fasting serum total cholesterol TC was significantly increased from baseline to follow-up at 54 weeks (185±21.7mg/dL, 201±18.2mg/dL, p = 0.03). No patients suffered from new CV disease.

Conclusion: These findings suggest that combination therapy, Tofa with MTX not only reduced RA disease activity but also limited vascular damage despite up-regulating cholesterol in patients MTX resistant active RA. References:

1) Kremer J. et al. Tofacitinib in combination with nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis: a randomized trial. Ann Intern Med. 2013 Aug 20;159(4):253-61.

2) Takaki A et al. Cardio-ankle vascular index is superior to brachial-ankle pulse wave velocity as an index of arterial stiffness. Hypertens Res.2008 Jul; 31(7):1347-55

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Abstract Number: 2581

Tripterygium Wilfordii Hook F Applied Topically in Patients with Active Rheumatoid Arthritis

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Background/Purpose: Tripterygium wilfordii Hook F (TwHF), a traditional Chinese herb, is widely used in China for treating Rheumatoid Arthritis (RA), but limited only for eldly RA patients because of its reproductive system toxicity. We were inspired by external therapy, an immemorial

therapy for thousands of years, and took its advantage to make TwHF topically in order to get an effective and safe treatment for active RA patients.

Methods: In this 4-week double-blinded, randomized, placebo controlled clinical trial, patients were 1:1 randomized to add-on topical TwHF twice a day or placebo for 4 weeks. The primary endpoint was the rate of achievement of 20% improvement in the American College of Rheumatology criteria (ACR20) at week 4. Secondary endpoints were 50% improvement in the ACR criteria (ACR50), 28-joint count Disease Activity Score (DAS28) improvement and safety profiles. Statistical analyses were performed using intention to treat analysis (ITT) set ·

Results: A total of 70 active RA patients were enrolled. At week 4, the ACR20 was 34.3% (12/35) in topical TwHF group and 11.4% (4/35) in placebo group (P=0.015). Similarly, a higher ACR50 responder proportion was seen in topical TwHF group with 17.1% (6/35) comparing to it in placebo group with 2.9% (1/35) (P=0.046). The topical TwHF group also had more improvement than the placebo group on DAS28-ESR (1.1 vs 0.5, P=0.001), DAS28-CRP (1.4 vs 0.7, P=0.001), tender joint count (5.5 vs 2.6, P=0.018), swollen joint count (3.5 vs 1.6, P=0.003) and Physician's global assessment (25.8 vs 13.0, P=0.002), as well as C-reactive protein (11.2 vs 2.7, P=0.048). Initial effect onset time of pain and swelling reductions were significantly shorter in topical TwHF group with Means of both 7 days (range: 2.5 hours to 11 days and 1 to 21 days, respectively) than those of 11 and 17 days (range: 4 to 24 days and 4 to 28 days, respectively) in placebo group (P=0.022, P<0.001), respectively. There were 2 adverse slight skin allergy events in topical TwHF group. No substantive differences in adverse events were observed.

Conclusion: Topical TwHF is an effective and safety complimentary treatment in patients with active RA.

Disclosure: J. Jiao, None; **H. B. Yin**, None; **X. P. Tang**, None; **X. Gong**, None; **Q. Jiang**, None.

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Abstract Number: 2582

N-Acetylcysteine Regulates Osteoclastogenesis and Th17 Cell Differentiation in Rheumatoid Arthritis

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Background/Purpose: This study aimed to determine the regulatory role of N-Acetyl-L-cysteine (NAC), an antioxidant, in T cell and osteoclast differentiation in rheumatoid arthritis (RA).

Methods: After RA synovial fibroblasts were stimulated by LPS, the expression and production of RANKL, IL-1beta, TNF-alpha was determined by real-time PCR and ELISA. After human peripheral CD4+ T cells were cultured under Th0 condition, IL-17, IFN-g, IL-4, Foxp3, RANKL and IL-2 expression was determined by flow cytometry and ELISA. Human peripheral blood monocytes were cultured with M-CSF, RANKL, and various concentrations of NAC, followed by staining of the cells for tartrate-resistant acid phosphatase activity to determine osteoclast formation. Osteoclastogenesis was also determined after cocultures of LPS-stimulated RA synovial fibroblasts or Th0-stimulated CD4+T cells and various concentrations of NAC with human PBMC.

Results: When RA synovial fibroblasts were stimulated by LPS, LPS stimulated their production of RANKL, IL-1beta, TNF-alpha and IL-6. NAC reduced the LPS-induced production of proinflammatory cytokines and RANKL in a dose-dependent manner. After human peripheral CD4+ T cells were cultured under Th0 polarizing condition, NAC decreased the proportion of IL-17^{+} and CD4^{+} T cells, and production of IL-17 and RANKL. When human peripheral blood CD14^{+} monocytes were cultured with M-CSF and RANKL, osteoclasts was differentiated, however, NAC significantly inhibited the osteoclastogenesis

Conclusion: NAC inhibits the production of proinflammatory cytokines and RANKL in RA synovial fibroblasts, differentiation of osteoclasts and Th17 cells. NAC could be a new therapeutic medication for regulation of autoimmune reaction and prevention of bone destruction in RA.

Disclosure: K. A. Lee, None; **H. R. Kim**, None; **S. H. Lee**, None; **B. Kim**, None; **K. W. Kim**, None.

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Abstract Number: 2583

Abatacept in Rheumatoid Arthritis with Interstitial Lung

Disease: A Multicenter Study of 55 Patients

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Background/Purpose: Interstitial Lung Disease (ILD) is a severe extra-articular manifestation of rheumatoid arthritis (RA). A potential association of anti-TNFα drugs and conventional disease-modifying anti-rheumatic drugs (cDMARDs), such as methotrexate (MTX) and leflunomide (LFN), with the development of ILD in patients with RA has been suggested. The aim of our study was to assess the efficacy and safety of abatacept (ABA) in RA patients with ILD.

Methods: Multicenter study of RA patients with ILD treated with ABA. ILD was diagnosed by high-resolution computed tomography (HRCT). ABA was used at standard dose (10 mg/Kg/4 weeks i.v. or 125 mg/week s.c.). To assess the efficacy of ABA, we have analyzed the following variables: **a)** 1-point change in the degree of dyspnea according to the Modified Medical Research Council (MMRC); **b)** FVC improvement > 10%; and improvement > 10% in DLCO; **c)** radiological improvement in HRCT scan, and **d)**changes in the joint assessment measured by DAS28 score. Values were compared with baseline. Continuous variables by means of Wilcoxon´s signed rank test, and percentages by using the Chi-squared test or Fisher´s exact test as appropriate.

Results: We studied 55 patients (30 women/25 men) with ILD associated to RA; mean age 62.7±9.05 years. The median [IQR, 25th-75th] duration of RA to ILD diagnosis was 7 [2.33-14.00] years. Patients had received a mean of 2.36±1.9 DMARDs. RA was seropositive in 46 cases (83.6%). Besides HRCT, the diagnosis of ILD was confirmed by biopsy in 10 patients. ILD was considered as drug-related in 14 patients: MTX (n=7), etanercept (n=3), adalimumab (n=3) and certolizumab (n=1). ABA was prescribed as monotherapy (n=28**)** or combined with cDMARDs (n=27); these were LFN (n=7), LFN and cyclosporine (n=1), sulfasalazine (n=2), MTX (n=3), MTX and LFN (n=1), hydroxychloroquine (n=6), hydroxychloroquine and LFN (n=4), and azathioprine (n=3). The results are summarized in **Table**. A significant improvement of the dyspnea was observed. The patients who did not have dyspnea at ABA onset remained asymptomatic during the follow-up. FVC and HRCT showed a significant improvement between 6 and 12 months after the onset of therapy. DLCO remained stable in the majority of the patients. DAS28 also improved. After a follow-up of 8.29±3.82 months, the most important adverse effects were: respiratory infection (n=2), urinary infection (n=1) and infusion reaction (n=1). ABA had to be withdrawn in 7 patients: due to severe infection (n=2); inefficacy in polyarthritis (n=2), lack of pulmonary improvement (n=2) and infusion reaction (n=1).

Conclusion: ABA appears to be an effective and relatively safe therapy in RA patients with ILD. These promising results require to be confirmed in a prospective and randomized study. **TABLE**

	Baseline	3 months	6 months	12 months
MMRC, - *No change* - *Improvement* - *Worsening*	- - -	81.8% 16.4%** 1.81%	72.2% 25%** 2.7%	62.9% 29.6%** 7.5%
FVC, - *No change* - *Improvement* - *Worsening*	- - -	84.6% 7.7% 7.7%	53.3% 26.7%** 2.0%	61.2% 27.7%* 11.1%
DLCO, - *No change* - *Improvement* - *Worsening*	- - -	58.4% 33.3%** 8.3%	58.3% 16.7% 25.0%	57.1% 28.6%** 14.3%
HRCT scan, - *No change* - *Improvement* - *Worsening*	- - -	66.7% 33.3%* 0.0%	38.4% 46.2%** 15.4%	35.7% 42.9%** 21.4%
DAS28, *median [IQR]*	5.25 [4.13-5.85]	2.61 [2.14-4.04]**	3.10 [2.20-4.18]**	3.55 [2.30-4.40]**
CRP (mg/dl), *median [IQR]*	2.28 [1.08-6.95]	1.70 [0.64-5.00]	0.87 [0.50-5.40]**	2.16 [1.43-7.69]
ESR (mm/1st h), *median [IQR]*	33.0 [16.8-51.8]	20.0 [10.0-44.0]**	22.0 [9.0-38.0]*	30.0 [12.5-53.0]**

Comparisons refer to baseline values. * $p< 0.05$; **$p< 0.01$. In the case of qualitative variables only "improvement" was considered in the calculations.

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Prevalence of Anemia Among Rheumatoid Arthritis Patients Treated with Conventional Disease-Modifying Antirheumatic Drugs

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Background/Purpose: Anemia in rheumatoid arthritis (RA) patients (pts) has a prevalence of 16%-64% depending on population and severity of disease[1,2,3] and is more common in women, pts with seropositive and erosive disease, and pts treated with systemic corticosteroids.[2] This *post hoc* analysis was performed to determine prevalence of anemia in a contemporary cohort of RA pts treated with conventional disease-modifying antirheumatic drugs (cDMARDs).

Methods: Data were pooled from screening for 2 phase 3 trials conducted from Oct 2012 to Sept 2015 in RA pts inadequately responsive to cDMARDs. Eligibility included ≥6/68 tender and ≥6/66 swollen joints. One study required erosions on radiographs and high-sensitivity C-reactive protein (hsCRP) ≥6 mg/L; the other required hsCRP ≥1.2x upper limit of normal (ULN), or 3.6mg/dL. Prior biologic disease-modifying antirheumatic drugs were prohibited. Analysis included data from pts who failed screening for any reason, such as hsCRP or number of tender or swollen joints below threshold for study entry. Anemia was defined as hemoglobin (Hgb) <8 g/dL, <10 g/dL, or below the age- and gender-adjusted lower limit of normal (gaLLN).

Results: Analysis included 3925 screened pts: 3159 women and 766 men, including 1591 women and 345 men who failed screening. Hgb <8 g/dL was observed in 8 women (0.3%). Hgb <10 g/dL was seen 10x more frequently in women, occurring in 128 women (4.1%) and 3 men (0.4%). When the less stringent definition of <gaLLN was used, anemia was identified in 718 women (22.7%) and 185 men (24.2%). Prevalence of Hgb <gaLLN was 24% among pts ≤65 years and 16% among pts

>65 years. Anemia (<gaLLN definition) was more prevalent among pts with more active disease. Using Simplified Disease Activity Index, prevalence of Hgb <gaLLN in pts who met screening criteria was 0% in pts in remission or with low disease activity, 3.37% in pts with moderate disease activity, and 21.8% in pts with high disease activity. Analysis by tertiles of acute phase reactant levels (hsCRP or erythrocyte sedimentation rate) yielded similar findings.

Conclusion: In a contemporary population of pts with active RA treated with cDMARDs, prevalence of Hgb <10 g/dL was low, but 10x more frequent in women. When anemia was defined as Hgb <gaLLN (rather than as Hgb <10), prevalence was higher in men and women, regardless of age. Hgb <gaLLN was observed more often in pts with more active RA. Inclusion of pts with RA who failed to meet entry criteria of these clinical trials allows assessment of the prevalence of anemia in an RA population treated with cDMARDs. **References**

1. Short CL, Bauer W, Reynolds WE. Red-cell, white-cell, and differential counts. In: *Rheumatoid Arthritis*. Cambridge, MA: Harvard University Press, 1957:349-356.
2. Peeters HR, Jongen-Lavrencic M, Raja AN, et al. Course and characteristics of anaemia in patients with rheumatoid arthritis of recent onset. *Ann Rheum Dis* 1996;55(3):162-8
3. Furst DE, Chang H, Greenberg JD, et al. Prevalence of low hemoglobin levels and associations with other disease parameters in rheumatoid arthritis patients: Evidence from the CORRONA registry. *Clin Exp Rheumatol* 2009;27(4):560-6.

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Abstract Number: 2585

Serum MMP-3 and OPG As Predictors of Response to Traditional Dmards in a Treatment NaïVe Early Rheumatoid Arthritis Cohort

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Background/Purpose: Bone and cartilaginous metabolites such as matrix metalloproteinase 3 (MMP-3), cartilage oligomeric matrix protein (COMP),receptor activator for nuclear factor κ B ligand (RANKL) and osteoprotegerin (OPG) have the potential to act as biomarkers in rheumatoid arthritis (RA) management. Objective To investigate the clinical utility of bone and cartilage biomarkers in a DMARD-naïve early RA cohort in predicting response to 6 months of therapy with synthetic DMARDs.

Methods: 140 patients with DMARD-naïve early RA (symptoms less than 2 years) were recruited as part of the GREAT study (previously reported[i]).Disease activity was measured at baseline and six months after therapy using the SDAI. Baseline serum MMP-3, COMP, RANKL and OPG were assayed (ELISA).

Results: The majority of patients were of black ethnicity (88.5%) and female (79.2%) with a median age of 47.8 (IQR 14.4). The median symptom duration was 9.7 months (11.4).Rheumatoid factor and ACPA were positive in 81.4% and 84.1% respectively.(Table 1) The median SDAI improved significantly from a median of 41.4 (n=140, IQR 24.1) to 16.4(n=104, IQR 14.8).Baseline MMP 3 and COMP levels were previously reported[i]. Baseline RANKL and OPG were elevated in 20.4 and 38.8 % of patients respectively. The sRANKL/OPG ratio was elevated in 56.3% of patients. Only elevated MMP 3 (p=0.048) and OPG (p=0.016) levels at baseline were statistically significantly associated with a moderate or higher disease activity (SDAI > 11) at 6 months .

Table 1: Baseline demographics of patients (n=140)

	n or Median	**% or IQR**
Black ethnicity (%)	124.0	88.5
Females (%)	110.0	79.2
Age in years, median (IQR)	47.8	14.4
Symptom duration in months, median (IQR)	9.7	11.4
Rheumatoid factor positive (%)	114.0	81.4
ACPA [n=126] (%)	106.0	84.1

Conclusion: Outcome measure of low disease activity (SDAI<11) within 3 to 6 months ofdisease onset is the therapeutic target in the management of patients with RA. The measurement of serum

MMP 3 has performed well as a biomarker in RA having been incorporated into a multi-biomarker assay. In this study, similar to findings elsewhere, low levels of OPG predicted better control of disease activity at 6 months.[ii]Thus, patients with elevated baseline MMP 3 and OPG may be a subgroup of poor responders requiring aggressive management. These biomarkers may be particularly useful in resource poor settings where regular monitoring aimed at tight control and biologic therapy is widely unavailable. References

[i]Mahmood M. T. M. Ally,et al. Serum Matrix Metalloproteinase-3 in Comparison with Acute Phase Proteins as a Marker of Disease Activity and Radiographic Damage in Early Rheumatoid Arthritis. Mediators of Inflammation,Volume 2013 (2013)

[ii]Van Steenbergen, et al. "Osteoprotegerin as biomarker for persistence of rheumatoid arthritis." Rheumatology (2015): kev415.

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Abstract Number: 2586

Comparison of Intra-Articular Methylprednisolone Acetate with Triamcinolone Acetonide in Acutely Swollen Knee Joint of Patients with Chronic Inflammatory Arthritis – a Randomized Controlled Trial

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Background/Purpose: Intra-articular steroids are in use since half-a-century, but choice of individual agents remains empirical in the absence of comparative trials. This study compared the efficacy of intra-articular injection of methylpredisolone acetate (MPA) with triamcinolone acetonide (TA) in treatment of acutely swollen knee joint in patients with chronic inflammatory arthritis.

Methods: This was a double-blind randomized controlled trial that included patients with rheumatoid arthritis (RA) or spondyloarthritis (SpA) having an acutely swollen knee (>1 week and <24 weeks). Patients were randomized (1:1) to receive intra-articular injection of either methylpredisolone acetate (MPA) or triamcinolone acetonide (TA) (80 mg, 2ml) and followed over 24 weeks. The primary outcome measure was time-to-relapse and secondary outcome measures were numerical rating scale (NRS) (0-10) of pain and swelling at 4, 12 and 24 weeks, range of motion and adverse effects. In addition assessed change in DAS28-3, Indian health assessment questionnaire and proportion with good improvement (>50% improvement). Primary analysis was intention-to-treat; in addition per-protocol (only completers) analysis also done. Trial # Clinical trials registry of India CTRI/2015/09/006187

Results: This study included 100 patients (RA:SpA=89:11, M:F=24:76). They were randomized (50 each) to MPA and TA, with no significant differences in baseline characteristics. At 24 weeks, 3 patients were lost and 9 relapsed in each group, with no significant difference in mean (+/-SEM) time-to-relapse (20.8±1.0, 20.9±1.0 weeks, p=0.96) (Figure 1). There was also no significant difference in change in NRS pain (-4.4±3.1, -3.9±2.8, p=0.46) and NRS swelling (-4.5±2.9, -3.9±2.8, p=0.36) in MPA and TA groups at 24 weeks from baseline. (Figure 2) At baseline, normal flexion of knee joint was present in 28 and 25 patients (p=0.17), and at 24 weeks, in 38 and 37 patients (p=0.7) respectively. There were no adverse effects in any patient. There was no significant difference in the change in DAS28-3 at 24 weeks from baseline (-1.4±1.1, -1.3±1.3) or in HAQ at 24 weeks from baseline (-0.7±0.5, -0.7±0.5, p=0.80).

Conclusion: There was no significant difference efficacy of intra-articular injection of MPA vs TA in knee arthritis over a period of 24 weeks. Figure 1:Kapan-Meier curve comparing time-to-relapse

in MPA and TA groups

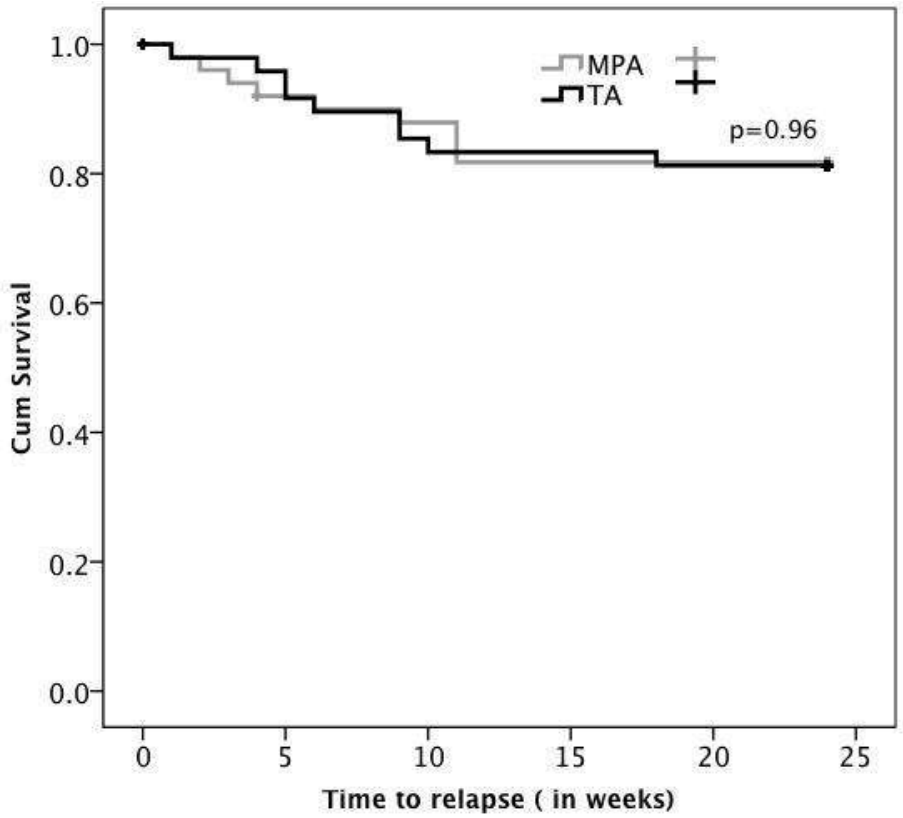
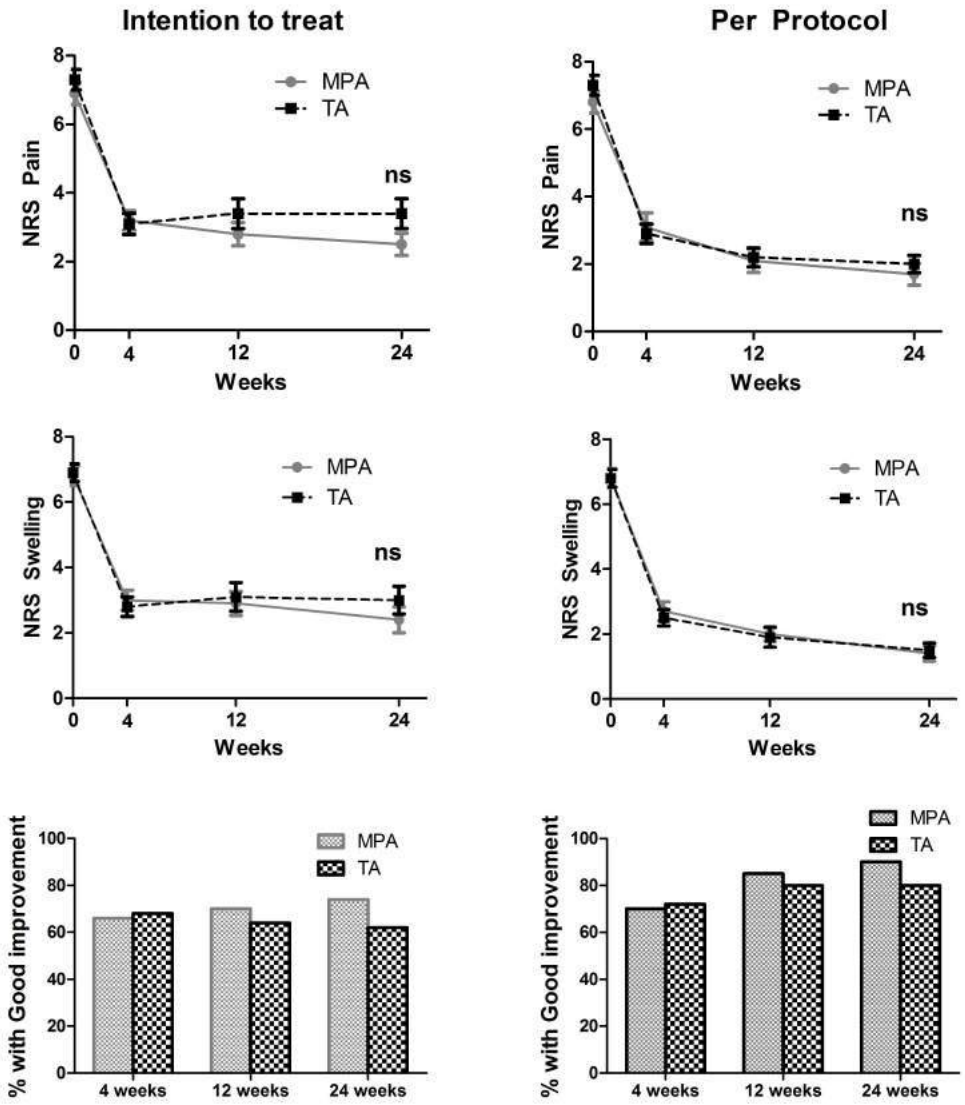


Figure 2: Composite outcomes over 24 weeks in the MPA and TA groups



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The Serum Level of Reactive Oxygen Metabolities (ROM) at 12 Weeks during Treatment with Biologic Agents for Rheumatoid Arthritis Is a Predictor for the 52-Week Remission

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Background/Purpose: Oxidative stress induced by reactive oxygen species is thought to be an important mechanism that underlies joint destruction and synovial proliferation. We have shown that serum levels of reactive oxygen metabolities (ROM) were associated with CRP and DAS28 in patients with rheumatoid arthritis (RA) and reduced temporally by the treatment with biologic agents (BAs). However, its clinical significance as a biomarker has not been elucidated.

Methods: Forty-eight BAs-naïve RA patients (mean age: 59.3}13.9 y, disease duration: 7.56}11.2 y) were included in this study. Association between serum levels of ROM, CRP, MMP-3, DAS28 (ESR) and HAQ at 12 weeks during the treatment and the remission in DAS28 (ESR) at 52 weeks was investigated. To measure ROM, the d-ROM test was performed using the FRAS4 analyzer (Wismarl, Italy). In order to identify predictor(s) for the 52-week remission, a multivariate logistic regression analysis was performed and an ROC analysis was also performed to determine their cut-off values.

Results: DAS28 (ESR) at baseline was 4.80}1.21 but decreased to 2.23}1.89 at 52 weeks and the remission rate was 70.8%. The serum level of ROM at baseline in the remission group (N=34) was 527.1}131.7 U.Carr (normal range <300 U.Carr), decreased to 334.9}79.1 at 4 weeks, and kept low levels after 12 weeks. On the other hand, in the non-remission group (N=14), the serum level of ROM at baseline was 592.2}112.9 U.Carr, decreased to 449.6}151.7 at 4 weeks, but gradually increased after 12 weeks (Figure 1). Significant factors at 12 weeks between the remission and non-remission group were ROM, CRP, MMP-3, DAS28 (ESR) and HAQ (P <0.05), which were then subject to a multivariate logistic regression analysis. As a result, ROM, other than DAS28 (ESR), was extracted as a predictor for the 52-week remission (odds ratio: 0.985, 95% CI: 0.97-1.000). An AUC of the ROC curve was 0.891, and the cut-off value of ROM that discriminated remission from non-remission was determined to be 381.5 U.Carr (sensitivity: 0.833, specificity: 0.871; Figure 2).

Conclusion: These results suggest that CRP, MMP-3 and HAQ cannot be a predictor for the remission during early stage of treatment with BAs. Instead, ROM at 12 weeks is able to predict the 52-week remission with high accuracy. The serum level of ROM could be a useful biomarker to achieve the remission in the current treat-to-target strategy for RA.

Figure 1. Changes in the serum level of ROM during the treatment in the 52-week remission and non-remission group. ROM, reactive oxygen metabolities.

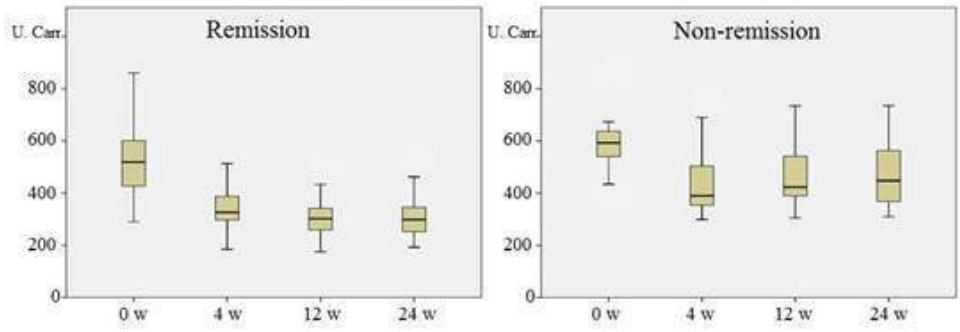
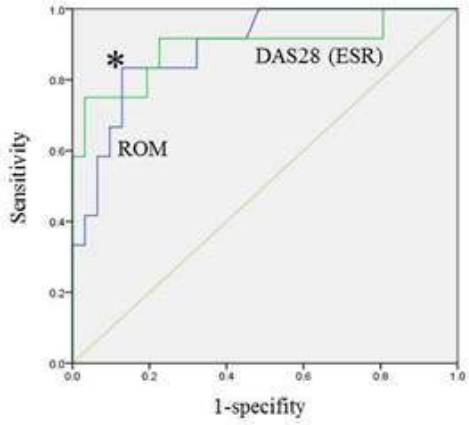


Figure 2. The ROC curves for ROM and DAS28 (ESR) at 12 weeks to predict the 52-week remission. The cut-off value for ROM corresponds to 381.5 U.Carr (indicated as an asterisk).



ROM, reactive oxygen metabolities

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Abstract Number: 2588

The Real World Comparative Safety of Certolizumab Pegol (CZP) As Compared to Other TNFi in a National US Cohort

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SESSION INFORMATION

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Background/Purpose: To examine the association of cardiovascular, malignant and serious infection events (SIEs) with certolizumab pegol (CZP) use as compared to other TNFi agents in patients (pts) with rheumatoid arthritis (RA).

Methods: RA pts enrolled in the Corrona national registry who were ≥18 years of age when initiating CZP or other TNFi agents (etanercept, adalimumab, golimumab or infliximab) on or after May 1st, 2009 with at least 1 follow-up visit post index drug initiation were identified. Physician-reported cardiovascular events, malignancies and SIEs were captured during the follow-up period, which were measured separately for each adverse event type in pt-years (PY), from drug initiation to either: occurrence of the first event, 90 days following pt/physician-reported discontinuation/switch of biologic (censored), or the 12 month Corrona visit (censored). The analysis before propensity score matching (PSM) included all initiators. After PSM, the analysis included CZP and other TNFi pts matched with a propensity score, to control for disease and pt characteristics that differed between the two groups (age, gender, disease duration, Clinical Disease Activity Index [CDAI] at initiation, and line of therapy).

Results: There were 975 RA pts initiating CZP and 5240 RA pts initiating other TNFi. CZP was initiated later in the treatment course in terms of 1st, 2nd or ≥3rd line of therapy (CZP: 26%, 29%, 45% respectively vs other TNFi: 50%, 30%, 20% respectively; $p<0.001$). Consequently, those initiating CZP were older (median age 58 vs 56 years; $p<0.001$), had longer median disease duration (9 vs 5 years; $p<0.001$), more active disease based on median CDAI (19 vs 17; $p=0.01$), and more functional impairment based on median modified health assessment questionnaire (0.5 vs 0.4; $p<0.001$). At initiation, history of cardiovascular events (5.8% vs 5.4%; $p=0.57$), malignancy (4.9% vs 4.3%; $p=0.38$), SIEs (6.6% in each group; $p=0.93$), and insurance status (yes/no) were balanced between groups. Before PSM, the incidence rates (IR) per 100 PY for cardiovascular events and malignancies were similar in the two groups, while the IR for SIEs was higher in the CZP group (Table). However, PSM resulted in the resolution of clinically significant baseline differences, and, in the 952 propensity score matched initiators, IRs of cardiovascular events, malignancies and SIEs were similar between the two groups (Table).

Conclusion: Accounting for baseline differences using PSM demonstrated that CZP is not associated with an increased risk of cardiovascular events, malignancies or SIEs compared to other TNFi agents utilized in earlier lines of RA therapy. Failure to account for baseline differences (disease duration, disease severity and functional impairment) may have contributed to the difference in SIE IRs between CZP and the other TNFi groups in the cohort before PSM.

	CZP		Other TNFi initiators	
	Number of events [a]	IR [b]/100 PY (95% CI) [c]	Number of events [a]	IR [b]/100 PY (95% CI) [c]
Before propensity score matching	N=975		N=5240	
Cardiovascular event [d]	17	2.02 (1.26, 3.26)	77	1.66 (1.33, 2.08)
Malignancies [e]	15	1.78 (1.08, 2.96)	96	2.08 (1.70, 2.54)
SIEs [f]	59	7.20 (5.58, 9.29)	215	4.71 (4.12, 5.38)
After propensity score matching [g]	n=952		n=952	
Cardiovascular event [d]	17	2.08 (1.29, 3.34)	17	2.05 (1.27, 3.30)
Malignancies [e]	14	1.71 (1.01, 2.88)	20	2.42 (1.56, 3.75)
SIEs [f]	57	7.13 (5.50, 9.25)	46	5.65 (4.23, 7.54)

[a] Events that occurred up to 90 days following discontinuation were considered; [b] Incidence rate is the ratio of events to PY at risk (per 100 PY); [c] 95% confidence interval (CI) for incidence rate based on Poisson distribution assumption; [d] Cardiovascular events include: myocardial infarction, stroke, congestive heart failure with hospitalization, cardiac revascularization procedure, ventricular arrhythmia, cardiac arrest, acute coronary syndrome, unstable angina, transient ischemic attack, hypertension with hospitalization, peripheral arterial thromboembolic event, urgent peripheral arterial revascularization, peripheral ischemia or gangrene (necrosis), or other cardiovascular event; [e] Malignancies include: non-melanoma of the skin, melanoma skin cancer, lymphoma, breast, lung, and other cancer; [f] Serious Infection events include infections for which the patient was hospitalized and/or received IV antibiotics. These events are categorized by type as follows: joint/bursa, cellulitis/ skin, sinusitis, diverticulitis, sepsis, pneumonia, bronchitis, gastroenteritis, meningitis/encephalitis, urinary tract infection, upper respiratory infection, tuberculosis, and other. Information is also provided about organism (opportunistic vs non-opportunistic) when data are available; [g] 23 patients in the CZP unmatched cohort could not be matched by propensity score, due to differences in baseline demographics and/or disease characteristics.

Disclosure: L. R. Harrold, Pfizer Inc, 2,Roche Pharmaceuticals, 5,Corrona, LLC, 3,Corrona, LLC, 1; **H. J. Litman**, Corrona, LLC., 3; **K. C. Saunders**, Corrona. LLC., 3; **K. J. Dandreo**, Corrona, LLC., 3; **B. Gershenson**, None; **J. D. Greenberg**, NYU School of Medicine, 3,Corrona, LLC., 3,Corrona, LLC., 1,AstraZeneca, 5,Celgene, 5,Genentech and Biogen IDEC Inc., 5,Janssen Pharmaceutical Products, L.P., 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5; **R. Low**, UCB Pharma, 3; **J. Stark**, UCB Pharma, 3; **R. Suruki**, UCB Pharma, 3; **S. Jaganathan**, UCB Pharma, 3; **M. Yassine**, UCB Pharma, 3.

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Abstract Number: 2589

Comparison of Two Enzyme-Linked Immunosorbent Assays Used for Drug Concentration Monitoring in Psoriatic Arthritis Patients Treated with Certolizumab Pegol

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Background/Purpose: Measurement of plasma anti-TNF concentration, in combination with the assessment of clinical outcomes, may be used to optimize dosing regimens for individual patients (pts). For successful implementation in clinical practice, an assessment of the different quantitative methods available is necessary. Here, we compare two enzyme-linked immunosorbent assays (ELISAs) for the quantitative measurement of plasma certolizumab pegol concentration ([CZP]), using data from the RAPID-PsA trial of CZP in pts with psoriatic arthritis (PsA).

Methods: Pts in RAPID-PsA (NCT01087788) were treated with a CZP loading dose (LD; 400 mg at Weeks [Wks] 0, 2, 4), followed by a maintenance dose (200 mg Q2W or 400 mg Q4W). Plasma samples were taken at baseline, Wks 2, 4, 12, 16, 24, 48, 72 and 96. A bespoke ELISA developed by UCB Pharma, validated in line with FDA/EMA regulatory requirements for bioanalytical methods (assay range: 0.4–33.3 μg/mL), was used to measure plasma [CZP] between 2010–2013. In 2016, a subset of frozen plasma samples was reanalyzed with the LISA-TRACKER® validated diagnostic kit (current range: 0.4–12.0 μg/mL). Paired CZP measurements were plotted and the degree of agreement between both assays was evaluated by the Bland-Altman method. Reproducibility of plasma [CZP] measurement with LISA-TRACKER® was evaluated by measuring in duplicate a set of 207 plasma samples from a different CZP study (NCT01500278).

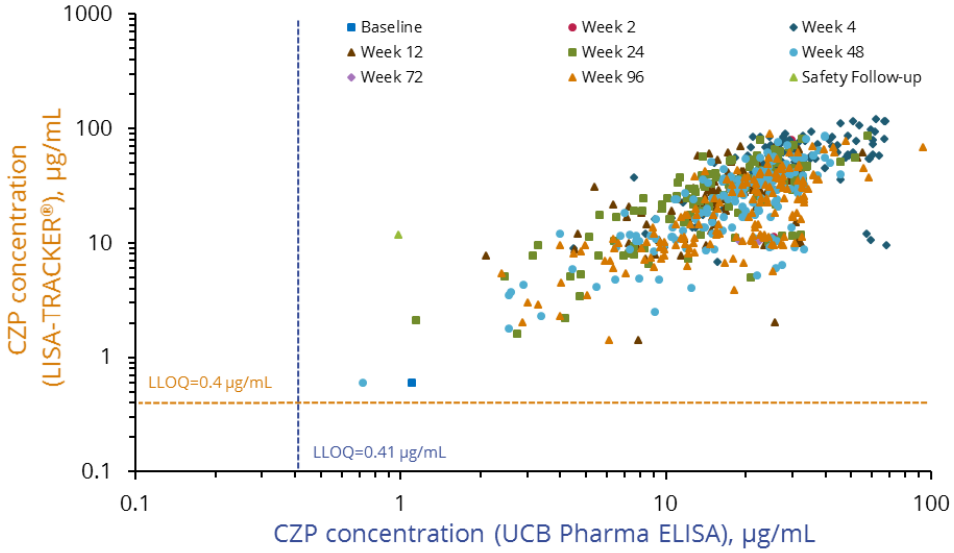
Results: 917 paired CZP measurements from RAPID-PsA pts were analyzed. Plasma [CZP] measured with LISA-TRACKER® showed good correlation with measurements obtained with the UCB Pharma ELISA, particularly for [CZP] between 10–100 μg/mL; [CZP] was highest at Wk 4, corresponding to the end of the LD period (Figure A). Bland-Altman analysis revealed a mean ratio LISA-TRACKER®/UCB Pharma ELISA of 1.19 (95% CI 1.13–1.25); the majority of paired measurements differed less than 3-fold from each other (Figure B). [CZP] <10 μg/mL were associated with greater variability. Reproducibility analysis showed a coefficient of variation of 13.5% for LISA-TRACKER® [CZP] measurements. Observed differences between assays should be interpreted with caution, as LISA-TRACKER® measurements were performed ≥3 years after the original analysis; over time, suboptimal sample storage conditions may have increased the difference in [CZP] detected by the two methods.

Conclusion: CZP concentrations measured with LISA-TRACKER®, a commercially available diagnostic kit, were 19% higher than those measured with the bespoke ELISA developed by UCB Pharma. The two assays showed good agreement, suggesting that data measured with both assays

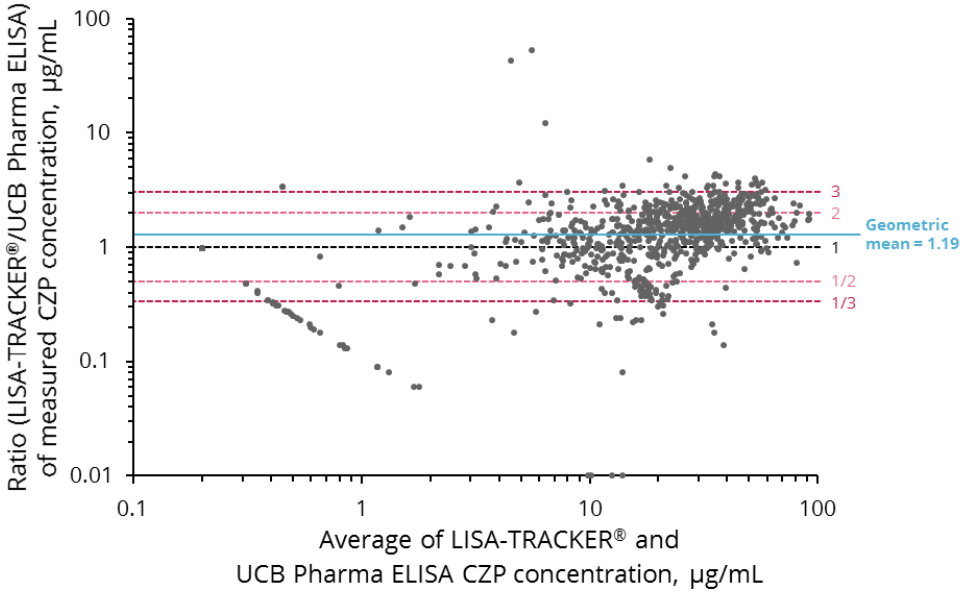
can be extrapolated to clinical practice.

Figure: Comparability of LISA-TRACKER® and UCB Pharma ELISA for the measurement of CZP concentration, tested on plasma samples from RAPID-PsA patients

A) Scatter plot of paired plasma CZP measurements obtained with LISA-TRACKER® and UCB Pharma ELISA (n=917 plasma samples) [a]



B) Bland-Altman plot of the ratio of CZP concentration measured with LISA-TRACKER® and UCB Pharma ELISA vs the mean of the two measurements [b]



[a] Dashed lines represent the lower limit of quantitation (LLOQ) of each assay (LISA-TRACKER® in yellow, UCB Pharma ELISA in blue); CZP measurements below assay LLOQs are not shown; [b] Horizontal lines represent: geometric mean of observed LISA-TRACKER®/UCB Pharma ELISA ratio (blue); no ratio difference (ratio=1; black); 2-fold difference limit (light red); 3-fold difference limit (dark red).

Disclosure: S. Paul, None; **J. Smeraglia**, UCB Pharma, 3; **M. de Longueville**, UCB Pharma, 3; **C. O'Brien**, UCB Pharma, 3; **E. Parussini**, Theradiag, 3.

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Abstract Number: 2590

The Efficacy of Additional Immunoadsorption on the Modulation of Disease Activity in Patients with Severe Rheumatoid Arthritis

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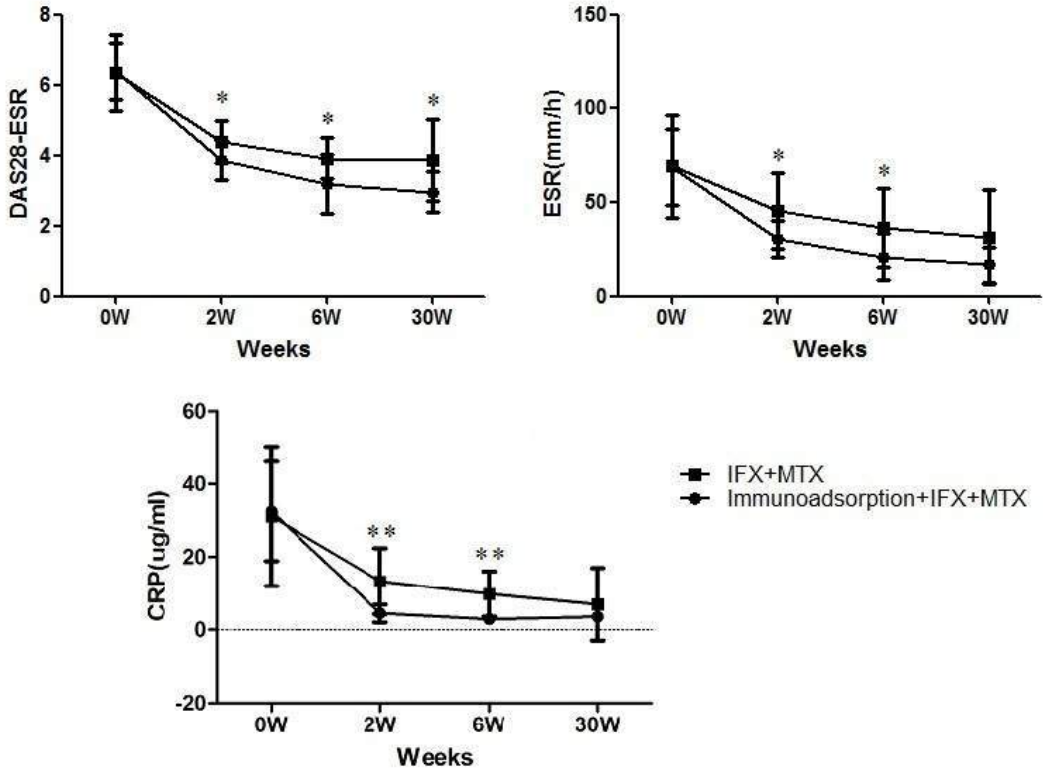
Background/Purpose: Immunoadsorption been used in patients with severe refractory rheumatoid arthritis (RA) was first reported in 1994, and the efficacy is promising. However, the subset of RA patients most likely to benefit from immunoadsorption treatment has not been defined. At present, immunoadsorption is presented as an alternative try for serve RA patients with chronic infection who cannot use anti- tumor necrosis factor (TNF) agents. Today, neutralize TNF, including infliximab (IFX), are widely used in the treatments for patients with serve RA (DAS28-ESR>5.1). However, even treated with IFX, there still approximate 40% of serve RA patients cannot reach low disease activity. Till now, there has no study report the additional immunoadsorption efficacy besides IFX therapy in serve RA patients. In this study, we evaluated the efficacy of additional immunoadsorption therapy besides IFX on disease remission in patients with severe RA.

Methods: 30 patients with serve RA were included in this study. 20 patients were treated with basic infliximab 3 mg/kg + methotrexate (MTX) therapy, and other 10 patients, besides of basic therapy, were previous gave 2 times additional immunoadsorption therapy (to removal of immunoglobulin and other pathogenic factor). IFX 3 mg/kg was infused at weeks 0, 2, 6, 14, 22 and 30. Age, sex ration, mean disease duration, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and Disease Activity Score including 28 joints using ESR (DAS28-ESR) from eligible patients in two treatment groups were collected at weeks 0, 2, 6, 14, 22 and 30 weeks and were compared between the two groups.

Results: The baseline age, sex ration, mean disease duration of RA, DAS28-ESR, ESR level and CRP level were comparable between the two treatment groups (P>0.05). At week 2 and week 6, decreases from baseline in DAS28-ESR, ESR and CRP were greater with additional

immunoadsorption treatment group versus only IFX treatment group (Figure 1, $P<0.05$), and with the exception of ESR and CRP (Figure 1, $P>0.05$), these difference was generally maintained to week 30 (Figure 1, $P<0.05$). At week 2, the percentage of patients receiving additional immunoadsorption therapy who achieved improvements of DAS28-ESR (improvements >1.8) was 80%, which was higher than 60% in only IFX treatment group. At week 30, the percentage of patients receiving additional immunoadsorption therapy who achieved low disease activity or remission was 70%, which was also higher than 50% in only IFX treatment group.

Conclusion: Additional immunoadsorption therapy can rapid relive the disease activity of serve RA patients, and the remission rate of 30W was significantly higher than only IFX treatment. However, due to the limited sample size of this study, the efficacy of additional immunoadsorption needs further observations. Figure 1 Disease activity in patients with severe RA



Disclosure: X. Kong, None; **C. Liu**, None; **D. Cui**, None; **Q. Zhang**, None.

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Abstract Number: 2591

Association Between Flare and Radiographic Progression in Patients with Rheumatoid Arthritis

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Background/Purpose: Biologic therapy has improved RA management and enabled some patients to achieve remission. Many clinicians decrease the biologic dose for patients in low disease activity (LDA) or remission. However, it is unclear which patients may flare and if flare contributes to radiographic progression. We assessed, post hoc, whether subjects who flared had a higher incidence of radiographic progression and compared subjects with and without flares.

Methods: PRESERVE (ClinicalTrials.gov: NCT00565409) was a 2-period trial in subjects with moderate RA despite MTX. Period 1 was open-label, single treatment induction; all subjects received etanercept (ETN) 50mg+MTX weekly (QW) for 36 wks. Subjects in LDA or remission (disease activity score for 28 joints [DAS28] ≤3.2) during wks 12 to 36 continued to Period 2, the randomized, double-blind phase to evaluate maintenance of LDA/remission. Subjects were randomized to receive ETN 50mg+MTX QW, ETN 25mg+MTX QW, or placebo+MTX QW to wk 88, when flare and radiographic progression were evaluated. Flare was defined 2 ways: 1) loss of LDA with/without DAS28 change of 0.6; and 2) relapse (DAS28>5.1 or DAS28>3.2 at ≥2 time points). Radiographic progression was evaluated according to 4 levels of stringency, based on modified total Sharp score (mTSS): 1) minimally clinically important difference (change of 5); 2) smallest detected difference (change of 2.3); 3) mTSS change >0.5; and 4) mTSS change >0.0. Demographics and baseline (BL) disease characteristics were compared for subjects with vs without flare, defined as loss of LDA and DAS28 change of 0.6. Analysis of covariance and chi-square test were used to compare continuous and categorical outcomes, respectively.

Results: Age, race, BMI, and disease duration did not differ significantly for flare vs non-flare subjects, total N=531. BL DAS28 was higher for flare than non-flare: mean (SD) 4.37 (0.45) vs 4.27 (0.45), respectively, p=0.046. Other BL disease characteristics were similar between the groups. When flare was defined as relapse, significantly more flare than non-flare subjects exhibited all 4 degrees of radiographic progression (table). When flare was defined as loss of LDA with/without DAS28 change of 0.6, there was no significant difference in radiographic progression for flare vs non-flare, but numerically more subjects with flare progressed. This was the trend for all treatments; the numbers were too small to analyze. Numerically more placebo subjects progressed, regardless of flare status or progression category (data not shown).

Conclusion: Using relapse as a rigorous definition of flare, radiographic progression occurs in significantly more flare vs non-flare subjects. This demonstrates that radiographic progression is a

consequence of flare, especially with biologic withdrawal. Patients should be closely monitored if biologic therapy is dosed down.

Table. Radiographic progression in flare and non-flare subjects at week 88

Outcome	Flare Subjects	Non-flare Subjects	P-value*
Flare defined as loss of LDA and DAS28 change of 0.6			
mTSS >0	43/271 (15.9)	31/260 (11.9)	0.2109
mTSS >=0.5	38/271 (14.0)	24/260 (9.2)	0.1045
mTSS >=2.3	20/271 (7.4)	10/260 (3.8)	0.0914
mTSS >=5.0	9/271 (3.3)	2/260 (0.8)	0.0633
Flare defined as loss of LDA			
mTSS >0	44/280 (15.7)	30/251 (12.0)	0.2586
mTSS >=0.5	39/280 (13.9)	23/251 (9.2)	0.1043
mTSS >=2.3	20/280 (7.1)	10/251 (4.0)	0.1338
mTSS >=5.0	9/280 (3.2)	2/251 (0.8)	0.0670
Flare defined as relapse†			
mTSS >0	35/181 (19.3)	39/350 (11.1)	0.0119
mTSS >=0.5	31/181 (17.1)	31/350 (8.9)	0.0065
mTSS >=2.3	19/181 (10.5)	11/350 (3.1)	0.0011
mTSS >=5.0	9/181 (5.0)	2/350 (0.6)	0.0015
*Fisher's exact test †DAS28 >5.1 at any visit, or 3.2<DAS28≤5.1 at 2 separate visits at least 2 weeks apart with an elevation of DAS28 ≥0.6 from baseline. Overall treatment group. Values are n/N (%) unless stated otherwise.			

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Abstract Number: 2592

The Impact of Biologic Therapy Introduction on Hip and Knee Replacement Among Rheumatoid Arthritis Patients: An Interrupted Time Series Analysis Using the Clinical Practice Research Datalink

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Background/Purpose: In several developed countries it has been observed that the incidence of orthopaedic surgery among rheumatoid arthritis (RA) patients has been in decline, despite a concurrent increase among non-RA patients. Whilst the introduction of biologic therapies may be an explanatory factor for the divergent trends, specific data testing this hypothesis is lacking. We set out to estimate the impact of approval and national guidance (National Institute for Health and Care Excellence (NICE) TA36) on anti-tumour necrosis factor alpha (TNF-α) therapy use for RA on rates of total hip (THR) and knee replacement (TKR) among incident RA patients.

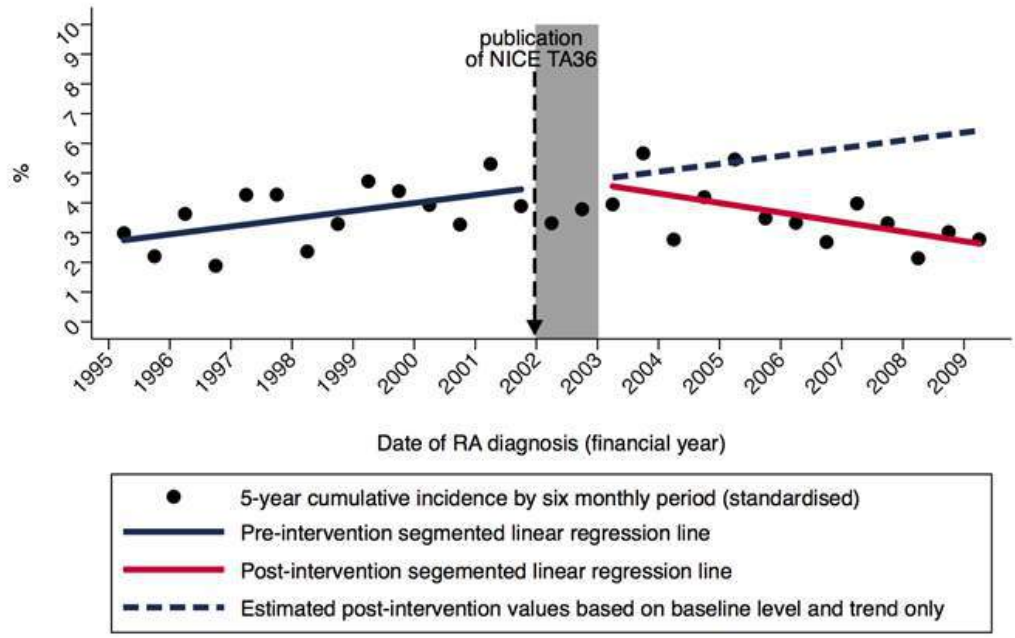
Methods: Primary care data (Clinical Practice Research Datalink (CPRD)) for the study period (1995-2014) were used to identify incident adult RA patients. The 5-year cumulative age and sex standardised incidence of THR and TKR was calculated for RA cohorts diagnosed in each six-months of the period 1st April 1995 to 30th September 2009. Interrupted time series analysis was used to estimate changes in level and trend following the publication of NICE TA36 in March 2002. In main analyses a 1-year time lag was used to allow for the delay associated with patients failing conventional DMARD therapy before initiating biologics. In sensitivity analyses a 2-year lag was used.

Results: We identified 17,505 incident RA patients. The number of THR and TKR events occurring within 5-years of diagnosis were 465 and 650, respectively. Throughout the pre-NICE TA36 period the cumulative incidence of THR remained stable at 2.48%. Following publication of guidance there was an immediate level increase (1.71%, P=0.001) but subsequent slope decrease (-0.21% per six months, P=0.001), equating to no significant difference in the mean absolute change in THR compared to that expected given prior level and trend only (using the mid-point of the post-NICE

TA36 period). Conversely, the cumulative incidence of TKR was 2.61% at the beginning of the study period and increased by 0.13% per six months (P=0.005) throughout the pre-NICE TA36 period (figure 1). Publication of guidance was associated with a significant downward slope change (-0.29% per six months, P=0.002), equating to a mean absolute change in TKR of -1.90% (95% C.I. -2.98 to -0.82) compared to values expected given prior level and trend only (figure 1). This represented a relative reduction of 34%. In sensitivity analyses using a 2-year lag, the cumulative incidence of THR was flat for the whole study period whilst results for TKR remained unchanged from the main analysis.

Conclusion: Among incident RA patients in England and Wales, approval of anti-TNF-α therapies and related NICE guidance was associated with reduced 5-year rates of TKR but not THR. Future work to further elucidate the impact of biologic therapies on the need for joint replacement surgery among RA patients is required.

Figure 1: percentage of incident RA patients undergoing Total Knee Replacement (TKR) within 5-years of diagnosis



Disclosure: S. Hawley, None; **R. Cordtz**, None; **L. Dreyer**, UCB, MSD, 8; **C. J. Edwards**, Abbvie, Celgene Corporation, Pfizer, MSD, Lilly, Roche, Samsung, Cellitrion, Napp, Mundipharma, GSK, UCB, BMS, 5,Abbvie and Pfizer, 2; **N. K. Arden**, Roche, Merck, Smith and Nephew, Q-Med, Nicox, Flexion, Bioiberica, Servier, 5,Roche Pharmaceuticals, 2; **A. Delmestri**, None; **C. Cooper**, Servier, Amgen, Eli Lilly, Merck, Medtronic and Novartis, 5; **A. Judge**, Servier, UK Renal Registry, Oxford Craniofacial Unit, IDIAP Jordi Gol, Freshfields, Anthera Pharmaceuticals INC. and Bruckhaus Deringer, 5,Roche Pharmaceuticals, 9; **D. Prieto-Alhambra**, Bioiberica S.A. and Amgen, 2.

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Abstract Number: 2593

The Effect of Tofacitinib on Bone Mineral Density in Patients with Methotrexate-Resistant Active Rheumatoid Arthritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: To analyze the effects of therapy with tofacitinib (Tofa), a Janus kinase inhibitor on the bone mineral density (BMD) of the lumbar spine and femoral neck in patients with rheumatoid arthritis (RA).

Methods: Thirty-seven patients with active RA (indicated by a 28-joint disease activity score ESR > 3.2) despite treatment with methotrexate(MTX) 10mg per week were included in this open label prospective study and started on Tofa (10 mg every day). All patients used a stable dosage of MTX, and were not allowed to use steroids or bisphosphonates during the study period. The BMD of the lumbar spine and femoral neck was measured by dual-energy X-ray absorptiometry at baseline and 52 weeks after initiating Tofa. The least significant detectable difference of lumbar spine and femur neck was +/-0.02.

Results: Thirty-one patients completed this study. The BMD of the lumbar spine and femoral neck remained stable after 1 year of Tofa treatment. In 11 patients who had osteopenia at baseline, there was a significant increase in the BMD of the lumbar spine (0.021 ± 0.034; $P < 0.05$) and femoral neck (0.005 ± 0.0125; $P < 0.05$; however it was not satisfied with detectable difference.).

Conclusion: Tofa affects the BMD in patients who had active RA despite treatment with MTX. The BMD of the lumbar spine in patients with normal BMD at baseline was stable. TCZ increased the lumbar spine BMD of patients who had osteopenia at baseline.

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tofacitinib-on-bone-mineral-density-in-patients-with-methotrexate-resistant-active-rheumatoid-arthritis

Abstract Number: 2594

Physician/Site Staff Assessments Contribute to High Placebo Response in Rheumatoid Arthritis Clinical Trials

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SESSION INFORMATION
Session Date: Tuesday, November 15, 2016
Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster III
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: High ACR responses in placebo group have been frequently observed in recent RA trials, most notably, in patients with inadequate response (IR) to methotrexate (MTX) or other disease modifying anti-rheumatic drugs (DMARDs). The factors that contribute to high placebo responses in RA trials were investigated.

Methods: Total 10 ph2 and 3 RA trials in a database were pooled for meta-analysis (981 placebo subjects). All were randomized, double-blind, placebo-controlled trials in active RA MTX/DMARD-IR (N=9) or TNF-IR (N=1) populations in combination with stable doses of MTX (N=8) and/or other DMARDs (N=2). Baseline demographic and disease characteristics of participants were similar across these trials. Placebo response in each ACR component was summarized. Univariate logistic regression was used to identify patient baseline risk factors for placebo response after adjusting for study and time point.

Results: In each of the 10 RA trials, at Week 12, median percent improvement from baseline in placebo group was consistently higher in physician/site staff assessments, ie swollen/tender joint counts, and physician's global assessment of disease activity, compared to patient's assessment of pain, global assessment of disease activity and function (HAQ-DI). Decrease in CRP in response to placebo was also observed (Table 1) however, often with more variability compared to other ACR components (data not shown). Patient baseline characteristics significantly predicting ACR20 placebo response are summarized in Table 2. A higher ACR Placebo response was observed in Latin America compared to Europe in 6 out of 7 RA trials that included Latin American sites (Figure 1).

Conclusion: The assessments performed by investigator or site staff are more sensitive to placebo response compared to the patient reported outcomes. Multiple patient baseline risk factors for ACR20 placebo response were identified and further investigation using multivariate model is warranted to delineate the independent predictors for high placebo response in RA trials. The Latin American region showed a consistently high placebo response across RA trials which often led to diminishing treatment effect detectable in this region.

Table 1: Placebo Response (Median Percent Change from Baseline) in ACR Components at Week 12

Median Percent Change from Baseline at Week 12	Swollen Joint Count	Tender Joint Count	Physician's Global Assessment of Disease Activity	Patient's Global Assessment of Disease Activity	Patient's Assessment of Pain	HAQ-DI	CRP
Study 1 Phase 2 Oral	-46.41	-46.42	-37	-11.48	-16.92	-15.38	-11.85
Study 2 Phase 2 Oral	-52.27	-36.69	-33.98	-26.38	-21.98	-14.84	-23.07
Study 3 Phase 2 mAb SC	-23.53	-18.52	-16.01	-13.79	-13.56	-10.53	-9.03
Study 4 Phase 2 mAb SC	-34.85	-20.36	-30.77	-14.38	-9.76	-9.81	-18.75
Study 5 Phase 2 mAb SC	-47.62	-55	-32.84	-23.53	-11.11	-12.89	-16.67
Study 6 Phase 3 mAb SC	-37.5	-29.86	-34	-13.31	-8.01	-14.84	0
Study 7 Phase 3 mAb SC	-8.71	0	0	2.08	4.2	0	14.96
Study 8 Phase 3 mAb SC	-18.18	-13.04	-18.06	-4.89	-7.32	0	0
Study 9 Phase 3 mAb IV	-25	-24.7	-28.57	-18.33	-16.55	-10.53	-14.29
Study 10 Phase 3 mAb IV	-20	-15.63	-20.51	-8.54	-11.39	-7.14	-13.4

Table 2: Odds Ratio of Patient Baseline Characteristics Significantly Predicting ACR20 Response While on Placebo	
Baseline Factors	**Odds Ratio (95% CI)**
Latin America Region vs Other Region	3.231 (2.793-3.738)
Race (Asian vs White)	1.325 (1.072-1.638)
Height (Cm)	0.974 (0.968-0.981)
Prior Use of DMARDs Other Than MTX (None vs Yes)	1.778 (1.541-2.052)
Function Class I vs II-IV	1.632 (1.374-1.940)
Anatomical Stage I vs II-IV	1.513 (1.207-1.895)
DAS28CRP	1.170 (1.101-1.242)
DAS28ESR	1.212 (1.130-1.299)
TJC (68)	1.011 (1.007-1.015)
SJC (66)	1.014 (1.007-1.020)
ESR	1.004 (1.001-1.006)
FACIT-Fatigue Score	1.032 (1.022-1.042)
SF-36 Physical Component Score	1.019 (1.011-1.028)
SF-36 General Health Score Norm-based	1.013 (1.006-1.021)
SF-36 Bodily Pain Score Norm-based	1.015 (1.006-1.023)
SF-36 Physical Function Score Norm-based	1.009 (1.003-1.016)
SF-36 Vitality Score Norm-based	1.024 (1.017-1.030)

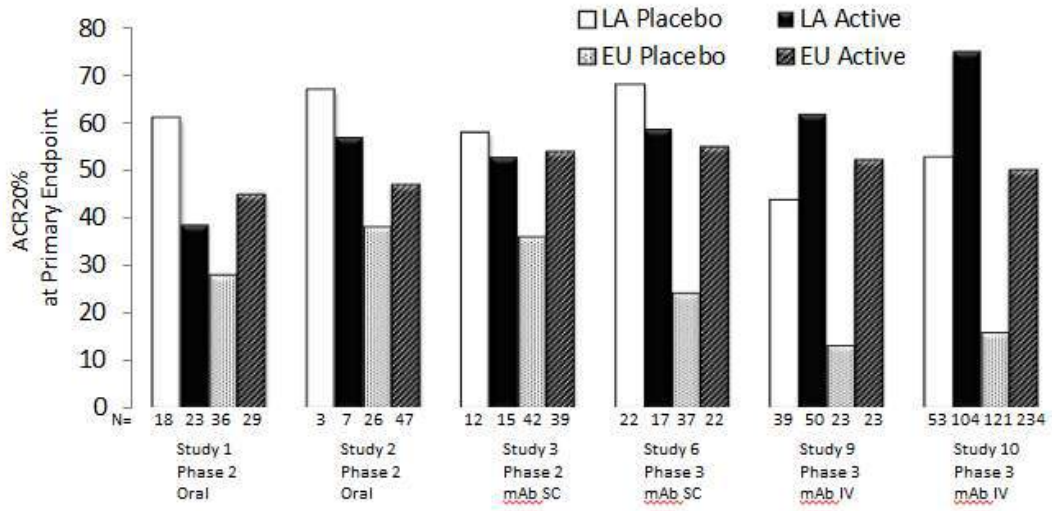

Figure 1: High ACR20 Placebo Response in the Latin American Region Observed in 6 RA Trials

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Disclosure: X. Xu, Janssen Research & Development, LLC, 3; **B. Dong**, Janssen Research & Development, LLC, 3; **C. H. Hsu**, Janssen Research & Development, LLC, 3; **C. Hu**, Janssen Research & Development, LLC, 3; **C. Lei**, Janssen Research & Development, LLC, 3; **J. Song**, Janssen Research & Development, LLC, 3; **J. Lu**, Janssen Research & Development, LLC, 3; **A. Beutler**, Janssen Research & Development, LLC, 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/physiciansite-staff-assessments-contribute-to-high-placebo-response-in-rheumatoid-arthritis-clinical-trials

Abstract Number: 2595

Real World Results from a Post-Approval Safety Surveillance of Tofacitinib (Xeljanz): Over 3 Year Results from an Ongoing US-Based Rheumatoid Arthritis Registry

Arthur F. Kavanaugh[1], Jamie Geier[2], Clifton Bingham III[3], Connie Chen[2], George W. Reed[4,5], Katherine C. Saunders[4], Yan Chen[6], Andrew Koenig[6], Laura Cappelli[7], Jeffrey D. Greenberg[4,8] and Joel M. Kremer[9], [1]University of California, San Diego School of Medicine, LaJolla, CA, [2]Pfizer, Inc., New York, NY, [3]Johns Hopkins University, Baltimore, MD, [4]Corrona, LLC, Southborough, MA, [5]University of Massachusetts Medical School, Worcester, MA, [6]Pfizer, Inc., Collegeville, PA, [7]Medicine/Rheumatology, Johns Hopkins University, Baltimore, MD, [8]NYU School of Medicine, New York, NY, [9]Albany Medical College and the Center for Rheumatology, Albany, NY

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: An interim analysis of a prospective observational 3+ year study, embedded within the US Corrona Rheumatoid Arthritis (RA) registry (14 years and ongoing), was initiated to evaluate the safety of tofacitinib (tofa) after US Food and Drug Administration (FDA) approval on 6 November 2012. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Rates of adverse events (AEs) are calculated and reported quarterly.

Methods: Interim results from a planned 5 year study (6 Nov 2012–29 Feb 2016, ~3 years and 3 months) are presented evaluating rates of targeted AEs in 3 populations 1) initiators of tofa 2) initiators of a biologic DMARD (bDMARD) and 3) initiators of a conventional synthetic DMARD (csDMARD). Patients who had at least one visit after initiation were included in this analysis. AE data are captured from prescribing physicians during follow-up. Standardized rates and 95% confidence intervals (CI) were estimated using the age and gender distribution of tofa initiators as the reference population.

Results: Standardized incident AE rates (i.e., new events per 100 patient-years) were calculated for 760 tofa, 4,628 bDMARD and 1,328 csDMARD initiators with 777.31 person-years (PY), 4395.55 PY, and 1059.19 PY respectively. Baseline characteristics were examined; number of years disease duration was longer for tofa patients (mean [SD] 13.4 [9.99] vs. bDMARD 10.1 [9.85] and nbDMARD 4.77 [7.49]) and number of prior bDMARDs as well as number prior anti-TNFs were higher in tofa patients (mean [SD] 2.79 [1.81] and 1.79 [1.19] respectively) as compared to the

bDMARD group (1.41 [1.34] and 1.09 [1.01]) and csDMARD group (0 by definition). Standardized incident rates for infections (figure 1) and cardiovascular disease (CVD), malignancies and gastrointestinal (GI) perforation (figure 2) are shown for the three groups.

Conclusion: In this interim analysis, despite some differences in baseline characteristics, patients initiating tofa, bDMARDs and csDMARDs for the treatment of RA experienced comparable age and gender adjusted rates of serious infections, cardiovascular events and malignancies overall.

References: Curtis JR et al. The validity of physician-reported hospitalized infections in an observational US arthritis registry. Rheumatology 2009:48(10); 1269-72. Fisher MC et al. Malignancy validation in a United States registry of rheumatoid arthritis patients. BMC Musculoskeletal Disorders; 2012 May 31; 13:85. Solomon DH et al. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. Ann Rheum Dis 2010; 69(11): 1920-5.

Figure 1

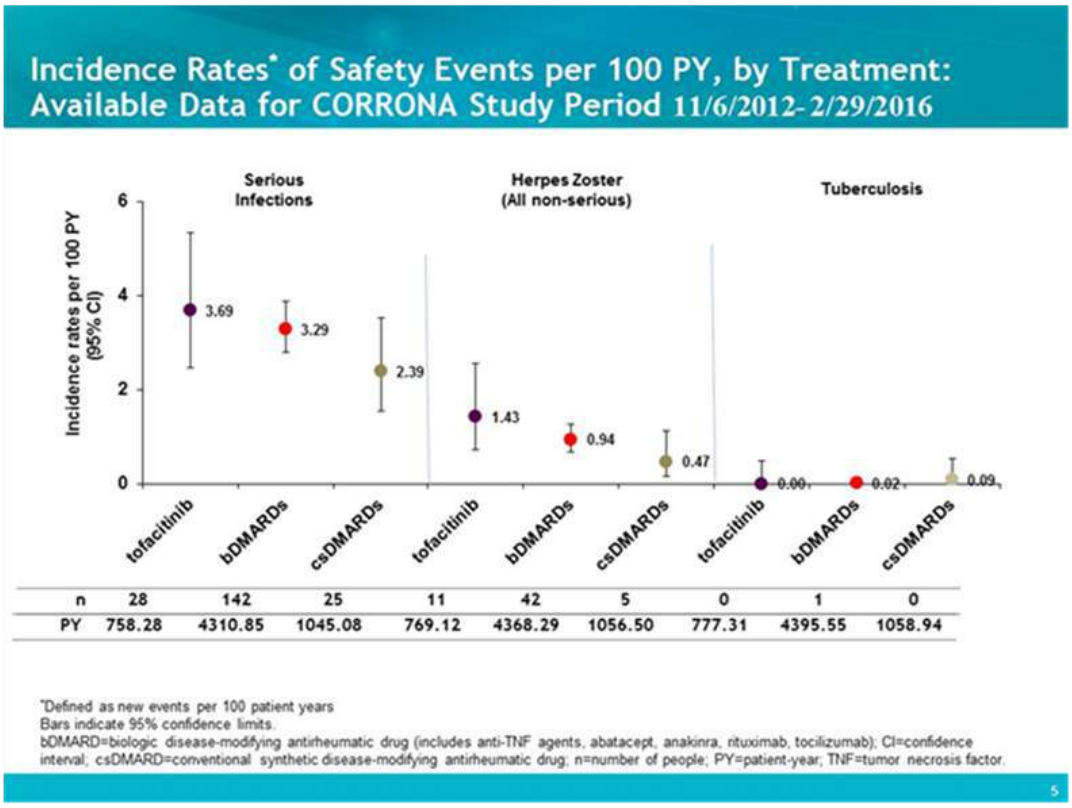
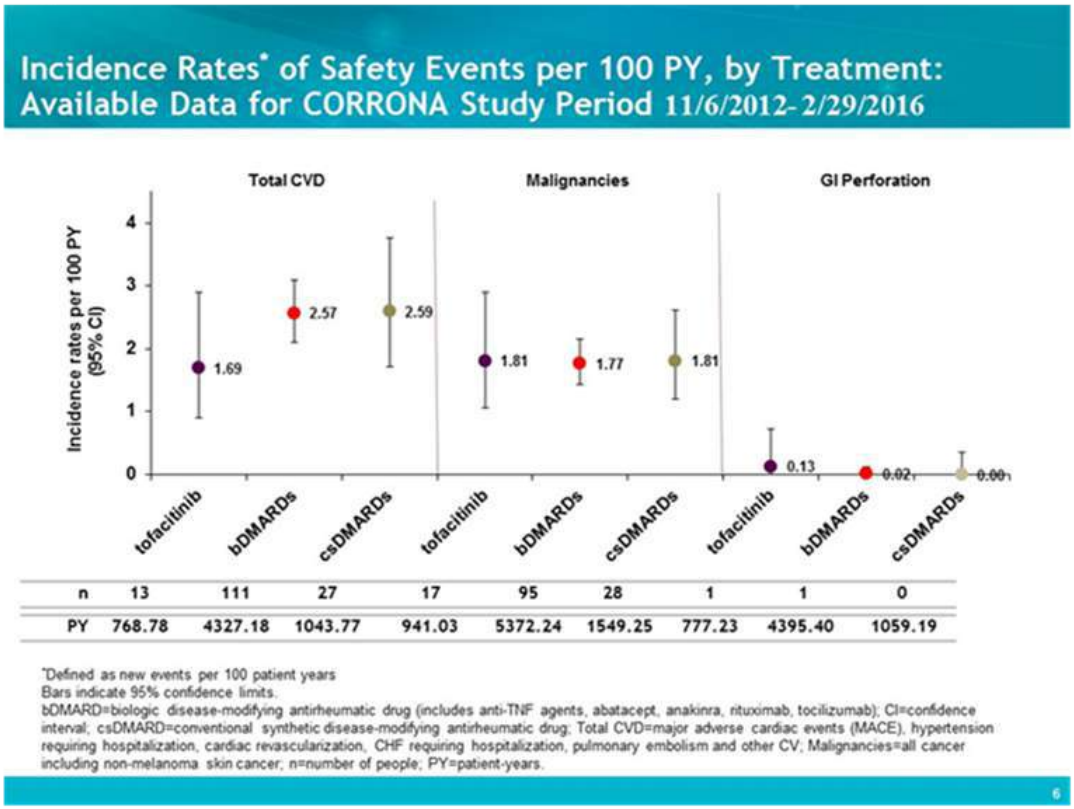


Figure 2



Disclosure: **A. F. Kavanaugh**, Amgen Abbvie Janssen Pfizer Novartis, 2; **J. Geier**, Pfizer Inc, 1,Pfizer Inc, 3; **C. Bingham III**, BMS, Janssen, Mesoblast, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene, EMD/Serrono, Genentech/Roche, Janssen, Lilly, Novartis, NovoNordisk, UCB, 5; **C. Chen**, Pfizer Inc, 3; **G. W. Reed**, Corrona, LLC, 3; **K. C. Saunders**, Corrona, LLC, 3; **Y. Chen**, Pfizer Inc, 1,Pfizer Inc, 3; **A. Koenig**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Cappelli**, None; **J. D. Greenberg**, Corrona, LLC, 1,Corrona, LLC, 3,Genentech, Janssen, Novartis and Pfizer, Eli Lilly, 5; **J. M. Kremer**, Corrona, LLC, 3,Corrona, LLC, 1,AbbVie, Amgen, BMS, Genentech, GSK, Lilly, Medimmune, Pfizer, Sanofi, 5,AbbVie, Genentech, Lilly, Novartis, Pfizer, 2.

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Abstract Number: 2596

Comparable Safety and Immunogenicity and Sustained Efficacy after Transition to SB2 (An Infliximab Biosimilar) Vs Ongoing Reference Infliximab (Remicade®) in Patients with Rheumatoid Arthritis: Results of Phase III Transition Study

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster III
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: SB2 is approved by the European Medicines Agency as a biosimilar of the reference infliximab (INF). The 30-week and 54-week results of Phase III study have been reported[1,2]. The objective of this transition period of Phase III study is to evaluate the safety, immunogenicity, and efficacy in patients with RA who transitioned from INF to SB2 vs maintained INF and who continued to receive SB2 after Week 54 up to Week 78.

Methods: This is a randomized, double-blind phase III transition study. Patients with moderate to severe RA were randomized in a 1:1 ratio to receive either SB2 or INF at Weeks 0, 2, 6, and then every 8 weeks thereafter until week 46. At Week 54, patients previously receiving INF were re-randomized in a 1:1 ratio to either receive SB2 (INF/SB2) or continue INF (INF/INF) up to week 70; patients receiving SB2 continued to receive SB2 (SB2/SB2) up to Week 70. Safety, immunogenicity and efficacy were assessed up to week 78.

Results: At Week 54, 94 patients from INF were transitioned to SB2 (INF/SB2), 101 patients from INF continued to receive INF (INF/INF), and 201 patients from SB2 continued to receive SB2 (SB2/SB2). The safety profile during the transition period was comparable between INF/SB2, INF/INF, and SB2/SB2. The incidence of adverse events during the transition period was 36.2% in INF/SB2, 35.6% in INF/INF, and 40.3% in SB2/SB2. The incidence of infusion related reaction during the transition period was 3.2%, 2.0%, and 3.5%, respectively. Among the patients with overall negative anti-drug antibodies (ADA) results up to Week 54, ADAs were newly developed in 14.6% (6/41) in INF/SB2, 14.9% (7/47) in INF/INF, and 14.1% (11/78) in SB2/SB2 among patients with negative ADA up to Week 54. The efficacy was sustained and comparable between the

treatment groups.

Conclusion: The safety, immunogenicity, and efficacy profiles remained comparable between the INF/SB2, INF/INF, and SB2/SB2 up to Week 78, revealing that there were no treatment emergent issues or clinically relevant immunogenicity after switching from INF to SB2.

Table. Safety Profile During the Transition Period (From Week 54 to Week 78)

Number of patients with	INF/SB2 (N=94)		INF/INF (N=101)		SB2/SB2 (N=201)	
	n	(%)	n	(%)	n	(%)
At least 1 treatment-emergent adverse event	34	(36.2)	36	(35.6)	81	(40.3)
At least 1 serious adverse event	6	(6.4)	3	(3.0)	7	(3.5)
Serious infections	2	(2.1)	1	(1.0)	1	(0.5)
Active tuberculosis	0	(0.0)	0	(0.0)	0	(0.0)
Infusion-related reaction	3	(3.2)	2	(2.0)	7	(3.5)
Malignancy[a]	2	(2.1)	1	(1.0)	0	(0.0)
Death	0	(0.0)	0	(0.0)	0	(0.0)
Overall ADA positive	43	(45.7)	51	(50.5)	104	(53.6)[b]
Newly ADA positive[c]	6		7		11	

[a] Lip and/or oral cavity cancer and basal cell carcinoma were reported in INF/SB2 and papillary thyroid cancer was reported in INF/INF
[b] Percentage is based on 194 patients with available ADA results
[c] Newly developed ADA in patients with negative overall ADA up to Week 54

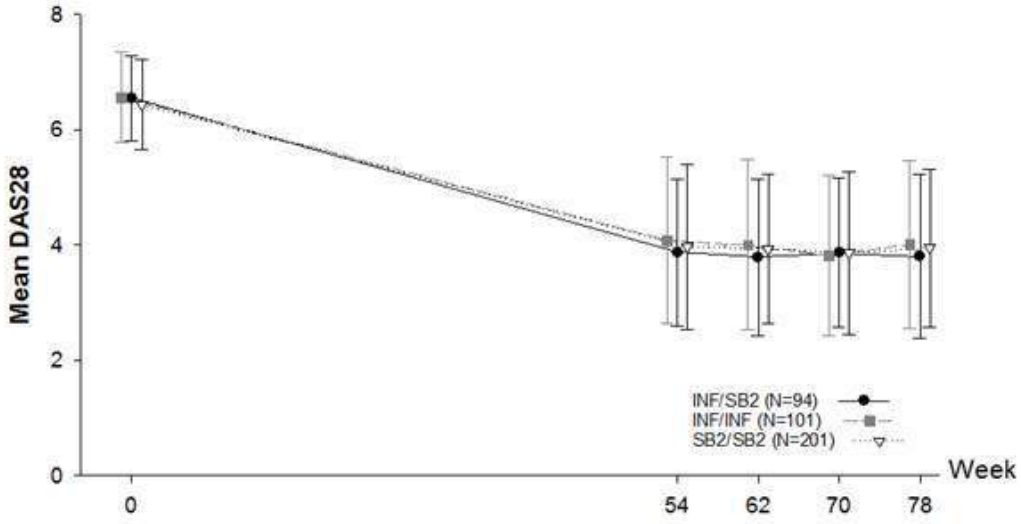

Figure. Mean and Standard Deviation of DAS28

Reference: 1. Choe JY et al. *Ann Rheum Dis*. 2015-207764 [Epub ahead of print] 2. Choe JY et al. *Arthritis Rheumatol*. 2015; 67 (suppl 10), 2056

Disclosure: J. S. Smolen, AbbVie, Jassen, MSD, Pfizer, Roche, UCB, 2,AbbVie, Amgen, AstraZeneca, Astro-Pharma, Celgene, GSK, Jassen, Lilly, Medimmune, MSD, Norvartis-Sandoz, Novo Nordisk, Pfizer, Roche, Samsung Bioepis, Sanofi, UCB, 5; **J. Y. Choe**, Samsung Bioepis, 2,Samsung Bioepis, 5; **N. Prodanovic**, Samsung Bioepis, 2; **J. Niebrzydowski**, Samsung Bioepis, 2; **I. Staykov**, Samsung Bioepis, 2; **E. Dokoupilova**, Samsung Bioepis, 2; **A. Baranauskaite**, AbbVie, Samsung Bioepis, 2; **R. Yatsyshyn**, Samsung Bioepis, 2; **M. Mekic**, Samsung Bioepis, 2; **W. Porawska**, Samsung Bioepis, 2; **H. Ciferska**, Samsung Bioepis, 2; **K. Jedrychowicz-Rosiak**, Samsung Bioepis, 2; **A. Zielinska**, Samsung Bioepis, 2; **J. Choi**, Samsung Bioepis, 3; **Y. H. Rho**, Samsung Bioepis, 3.

vs-ongoing-reference-infliximab-remicade-in-patients-with-rheumatoid-arthrit

Abstract Number: 2597

Time to Initiation of Biologic Agents Is Associated with Glucocorticoid Use: Results from the Corrona Registry

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Session Type: ACR Poster Session C

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Background/Purpose: Despite new effective therapies for Rheumatoid Arthritis (RA), glucocorticoids (GC) are widely prescribed. It is possible that dose and duration of GC therapy may have an impact on the timing of initiation of biologics. The objective of this study is to describe the GC patterns of therapy in patients with RA and its impact on time to biologic initiation in a real-world setting.

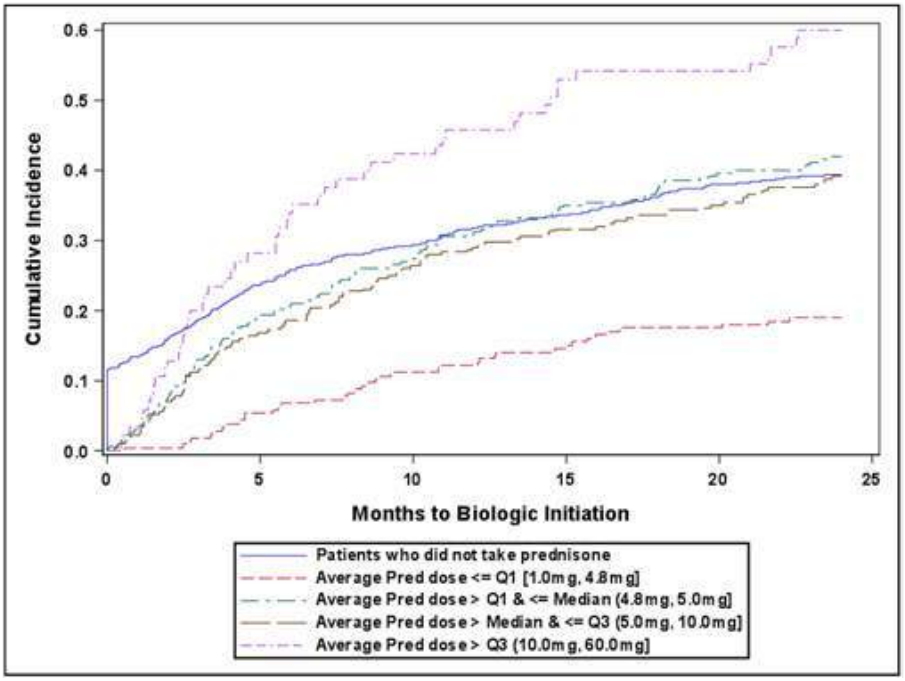
Methods: Biologic-naïve patients with early RA (≤1 year) treated with ≥1 csDMARD, who were enrolled in the Corrona registry after June 2008 and had 24 months (m) of follow-up were included in this study. Prospectively collected data on prednisone use reported by treating rheumatologists - was the primary measure to assess the GC use. GC use in milligrams (mg) was stratified into quartiles (Q): $1 \leq Q1 \leq 4.8$, $4.8 < Q2 \leq 5.0$, $5.0 < Q3 \leq 10.0$, $10.0 < Q4 \leq 60$, based on the average dose until the initiation of a biologic or until 24m after enrollment, which ever occurred first. Impact of average GC dose on time to biologic initiation was examined using cumulative incidence rates for each of the GC dose quartiles. Cox-proportional hazards models were used to evaluate the association between time to biologic initiation, GC use and disease activity as measured by clinical disease activity index (CDAI); mean prednisone dose and CDAI were time-varying covariates.

Results: A total of 1,998 patients were included in the study, there were n=1178 who did not take prednisone and of the remaining 820 who were on GC, n=360 initiated a biologic. Overall, 73% were female with an average age of 57 yrs, about 60% were in moderate/high disease activity (CDAI >10) with a mean disease duration of 0.5 yrs at enrollment. The average daily dose of GC was 7.0 mg from enrollment to 24m. Patients in the lower quartile (1-4.8 mg) compared to the highest quartile (>10 mg) of average GC use had significantly lower pain levels (27.4 vs 45.2),

patient global evaluation of disease activity (23.6 vs 42.5), better functional disability as measured by modified Health Assessment Questionnaire (0.2 vs 0.5) and spent lower number of days (198 vs 322 days) in moderate/high disease activity, defined as CDAI>10 (from enrollment to 24m) (all results with p<0.001). Patients on lower doses of GC (in the lowest quartile) had significantly longer time to initiation of a biologic compared to those who were in the highest quartile of average GC use (19.2m vs 9.2m respectively, p<0.001) (figure). A higher mean GC dose was significantly associated with a shorter time to biologic initiation after adjusting for time-varying CDAI (for every 5mg increase, HR: 1.13, p<0.0001).

Conclusion: In this large real world study of newly diagnosed RA patients, treatment with GCs was common and associated with time to biologic DMARD initiation. Patients treated with higher GC doses initiated biologics earlier and spent more time in moderate to severe disease activity prior to biologic initiation compared to those treated with lower GC doses.

Figure: Cumulative incidence curve for time to biologic initiation by mean GC dose category



Disclosure: D. A. Pappas, Corrona, LLC,, 3,Novartis Pharmaceutical Corporation, 9; **J. Griffith**, AbbVie, 1,AbbVie, 3; **H. J. Litman**, Corrona, LLC, 3; **C. A. Schlacher**, AbbVie, 3; **B. A. Salim**, Axio Research, 3; **C. Karki**, Corrona, LLC, 3; **J. M. Kremer**, Corrona, LLC, 3,Corrona, LLC, 1,AbbVie, Amgen, BMS, Genentech, GSK, Lilly, Medimmune, Pfizer, Sanofi, 5,AbbVie, Genentech, Lilly, Novartis, Pfizer, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/time-to-initiation-of-biologic-agents-is-associated-with-glucocorticoid-use-results-from-the-corrona-registry

Abstract Number: 2598

Conversion Rate of Tuberculosis Screening Tests in Patients with Rheumatic Diseases While Receiving Anti-Tumor Necrosis Factor Alpha (anti-TNFα) Agents

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First publication: September 28, 2016

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Session Time: 9:00AM-11:00AM

Background/Purpose: Risk of opportunistic infections, particularly mycobacterial infections, is increased among patients with rheumatic diseases treated with anti-TNF α agents. Therefore, screening of patients for latent tuberculosis infection (LTBI) is recommended prior to the initiation of anti-TNF α agents. However, there is a risk of seroconversion even among patients who tested negative for LTBI following treatment with anti -TNF α agents because of immunosuppression and exposure. There is paucity of data regarding the frequency of seroconversion and currently there is no clear recommendation on how often the patients should be screened for latent tuberculosis while receiving anti -TNF α agents.

Methods: We conducted a retrospective chart review of patients with various rheumatic diseases who received anti-TNF α agents from 2004 to 2014 in the VA Medical Center, Memphis TN. Patients with prior history of tuberculosis (TB) or prior treatment with TB medications were excluded. Any concomitant immunosuppressive medications including corticosteroids were also noted. We found a total of 133 patients on anti -TNF α agents, during this period, who had repeat testing for LTBI. All of these patients had tuberculosis screening test before starting anti TNF α agents either by Tuberculin Skin test (TST) or Quantiferon TB Gold Test. TB screening tests were variably repeated on these patients to evaluate for the possibility of seroconversion. Total number of TB screening tests and Chest radiographs each patient had, were also documented. We calculated incidence rate of TB screening test conversion per 100 patient year.

Results: Each of the 133 patients took anti -TNF α agents for a mean of 5.4 years (SD 3.25) and had mean of 3.6 (SD 1.57) TB screening tests. Only 1 out of 133 patients converted from negative TST to positive TST. This gentleman had seropositive Rheumatoid arthritis managed with Infliximab and Methotrexate for 6 years and 2 months before converting to positive TST. Risk of conversion of TB

screening test was calculated as 0.138 per 100 patient year.

Conclusion: Risk of conversion of TB screening tests while on anti -TNF α agents was found to be very low in our veteran population. This is much lower than what has been reported in the literature and worth reporting. We conclude that repeat testing on a scheduled basis is not necessary among low risk patients.

Disclosure: S. H. Raza, None; **S. Islam**, None; **A. Freire**, None; **D. Pattanaik**, None; **J. Stuart**, None.

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Abstract Number: 2599

TCZ Improves the Pro-Atherothrombotic Profile of Rheumatoid Arthritis Patients Modulating Endothelial Dysfunction, Netosis and Inflammation

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Background/Purpose: Inhibition of the interleukin IL-6 receptor pathway by tocilizumab (TCZ) is an effective treatment for rheumatoid arthritis (RA). TCZ reduces atherosclerosis markers and improves endothelial function. In peripheral blood, TCZ increases the percentage of natural killer and regulatory T cells and decreases the number of inflammatory Th1/Th17 lymphocytes. Monocytes activation and neutrophil extracellular traps (NETs) are key players in the development of cardiovascular disease; however, the specific effect of TCZ on these cells has not been described yet.**Objective:** To analyze the molecular changes (focused on monocyte and neutrophil

abnormalities) underlying the beneficial effect of TCZ on atherosclerosis and endothelial dysfunction in RA

Methods: Fifteen RA patients received 162 mg/week subcutaneous TCZ as combined therapy. Endothelial function was measured through post occlusive hyperemia using Laser-Doppler. To analyze the specificity of TCZ, blood samples from 5 RA patients at baseline was used to perform in vitro studies. Isolated monocytes and neutrophils were treated in vitro with IL6 and blocking FCRII plus TCZ for 18 and 6 hours, respectively. Oxidative stress markers in leukocytes were analyzed by flow cytometry. NETosis was measured through Sytox staining of DNA fibers. Myeloperoxidase (MPO) and neutrophil elastase (NE) were analyzed in neutrophils by flow cytometry. mRNA expression of peptidyl arginine deiminase (PAD4) was measured by RT-PCR. Percentage of low density granulocytes (LDGs) was analyzed through flow cytometry. mRNA expression of genes involved in monocyte activation, prothrombotic state, lipid uptake and insulin resistance was analyzed in monocytes through RT-PCR. Activation of intracellular pathways was analyzed in monocytes using pathscan intracellular signaling array.

Results: After 6 months of treatment TCZ reduced clinical parameters of inflammation, autoimmunity and joint damage. Endothelial function was significantly restored. TCZ decreased peroxide and peroxinitrite levels in RA leukocytes, most significantly in monocytes and neutrophils. Percentage of LDGs was also reduced after treatment. TCZ in vivo treatment reduced the expression of MPO, NE and PAD4 in RA neutrophils. The generation of in vitro induced NETs was also inhibited by TCZ. The expression of inflammatory and prothrombotic molecules, genes involved in cellular activation and insulin signaling and the activation of various intracellular pathways were modulated in monocytes after in vivo TCZ treatment. All these results were recapitulated after in vitro TCZ treatment of RA monocytes and neutrophils.

Conclusion:

TCZ improves endothelial dysfunction and atherothrombosis through the restoration of the oxidative status, inhibition of the monocyte prothrombotic and inflammatory profile and the generation of NETosis.

Funded by CTS7940, PI2013-0191, CP15/00158, PI15/01333

Disclosure: P. Ruiz-Limon, None; **R. Ortega-Castro**, None; **I. ARIAS DE LA ROSA**, None; **C. Perez-Sanchez**, None; **Y. Jiménez-Gómez**, None; **M. C. Abalos-Aguilera**, None; **P. Font-Ugalde**, None; **E. Collantes-Estévez**, None; **A. Escudero-Contreras**, None; **C. Lopez-Pedrera**, None; **N. Barbarroja**, None.

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Abstract Number: 2600

Tofacitinib Is Associated with an Impaired Function of NK Cells and a Defective Immunosurveillance Against B-Cell Lymphomas

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Background/Purpose:

Disease activity is the main risk factor for developing lymphoma in patients with rheumatoid arthritis (RA). However, the impact of immunosuppressive drugs remains an unsolved question. On one hand they might decrease the risk of lymphoma by controlling activity of the disease. On the other hand, they might alter anti-tumor immunosurveillance as observed in post-transplant lymphoproliferative disorders. Tofacitinib is an oral Janus Kinase (Jak) 3 and 1 inhibitor that has shown positive results in RA patients. Tofacitinib may impair NK-cell function due to its inhibitory action on IL2 and IL15 signaling. Given the fact that NK cells have been recently shown to participate to anti–lymphoma immunosurveillance, we aimed to assess if tofacitinib might impact NK cells function and anti-lymphoma activity.

Methods:

We have studied the consequences of in vitro exposure of NK to tofacitinib (10, 50 and 100 nM) or to DMSO (vehicle) during 6 days in presence of IL-2 (200 UI/ml): phenotype has been studied and then cytotoxicity against 2 non-Hodgkin B-cell lymphoma cell lines [Farage (EBV+) and SU-DHL4 (EBV-)] was assessed.

Results are shown as mean + standard of the mean (SEM). The Mann Whitney test was used to compare samples stimulated with tofactinib and DMSO (controls).

Results:

Firstly, we did not observe difference concerning the survival of NK cells in presence of tofacitinib or controls after 6 days culture. Secondly, we observed that culture in presence of tofacitinib was associated with a modification of NK phenotype with a decreased level of activation with a dose effect (Figure 1A). In addition we observed a decreased expression of activating receptors such as NKp30, NKp44 and NKG2D (Figure 1B-D). Last, we found that tofacitinib blocked NK cell maturation as observed with the significant decreased expression of CD57 on NK cells exposed to tofacitinib at 50 and 100 nM (Figure 1E). Conversely, CD16 expression was not modulated by tofacitinib. These phenotypic abnormalities were associated with an impaired function of NK as assessed by co-culture: degranulation was significantly decreased after exposure to tofacitinib 100nM in case of co-culture with Farage. A trend was observed with SU-DHL4. A trend for decreased NK cells cytotoxicity was observed with the 2 cell lines (Figure 2).

Conclusion:

This study demonstrates that tofacitinib treatment negatively impact the state of activation, maturation and functions of NK cells with impaired degranulation and less efficient lysis of B lymphoma cell lines . These results need to be confirmed in vivo. This negative impact of tofacitinib on NK cells activation and function might participate to the increased risk of herpes zoster infection in patients treated with tofacitinib and suggest to remains cautious about a possible increased risk of lymphoma.

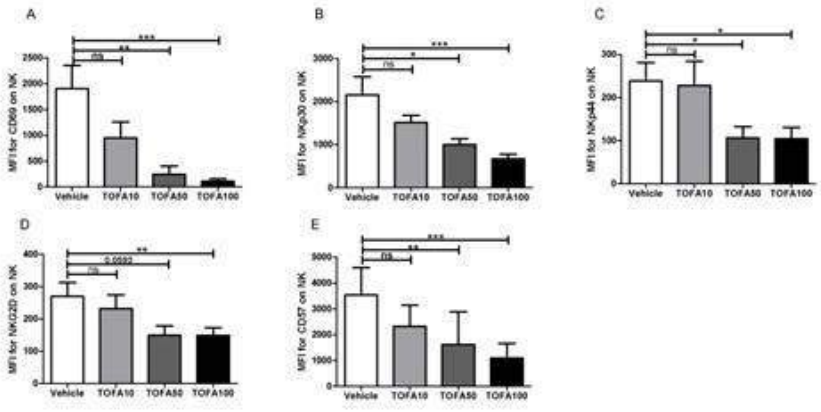

Figure 1: NK phenotype after 6 days culture to tofacitinib or control (*: $p<0.05$, **: $p<0.01$, ***: $p<0.001$, ns: non-significant).

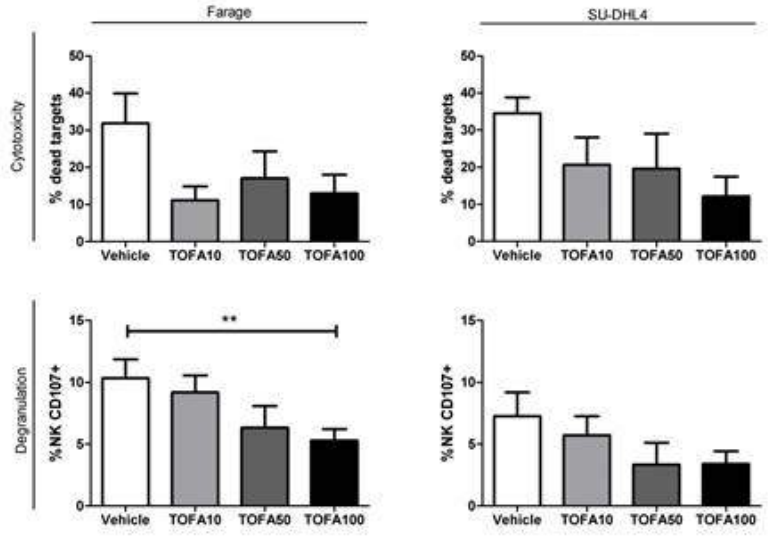

Figure 2: Anti lymphoma activity of tofacitinib exposed NK cells (**: p<0.01).

Disclosure: G. Nocturne, None; **F. Tahmasebi**, None; **S. Boudaoud**, None; **B. Ly**, None; **X. Mariette**, None.

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Abstract Number: 2601

A Cytometric Assay for Monitoring Adalimumab Immunogenicity and Drug Concentrations Can Distinguish Anti-Adalimumab Antibodies from Interference

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Background/Purpose: Tumor necrosis factor inhibitor (TNFi) biologics are a mainstay of therapy

for rheumatoid arthritis (RA) patients with disease-modifying antirheumatic drug failure. However, RA patients receiving TNFi biologics can develop anti-drug antibodies that neutralize drug action, decrease drug exposure, and lead to a loss of efficacy. Therefore, an assay that can monitor TNFi biologic immunogenicity and plasma concentrations can indicate when anti-drug antibodies diminish TNFi effectiveness and require drug substitutions. Our aim is to use a novel assay that simultaneously monitors anti-adalimumab (anti-ADA) IgG levels and plasma adalimumab (ADA) concentrations to determine the frequency of anti-ADA antibodies among patients enrolled on the Rheumatoid Arthritis Comparative and Effectiveness Research (RACER) study at University of Pittsburgh Medical Center.

Methods: Our cytometric assay uses streptavidin beads, biotinylated ADA F(ab')2 antibody fragment, biotinylated TNF-α, and anti-Fc antibody for measuring anti-ADA and ADA. A total of 168 normal human plasma samples (negative controls) and 207 RACER patient samples were evaluated using our cytometric assay and an anti-ADA bridging ELISA (116 from patients with no previous ADA exposure and 91 from patients receiving ADA for ≥ 6 months).

Results: Among patients receiving ADA, 49% tested positive for anti-ADA IgG. Surprisingly, 27% of ADA naïve patients were positive for anti-ADA, whereas all control human plasma samples were negative. Comparing our cytometric assay to the bridge ELISA: 78% and 66% of ADA treated and naïve patients were positive for anti-ADA antibodies, respectively. Of those samples positive by our cytometric assay, 94% were also positive by ELISA. Due to the unexpected high positive rate, we measured ADA concentrations before and after adding ADA to the following representative RACER samples: ADA naïve patient samples positive for anti-ADA, control patient samples negative for anti-ADA, and discrepant samples positive by flow cytometry but negative by ELISA. No ADA was detectable among naïve patients, whereas ADA was detectable among patients receiving ADA. Upon ADA addition, lower ADA levels were measured among discrepant samples compared to controls ($P < 0.05$). Furthermore, ADA decreased the anti-ADA levels of controls containing known amounts of anti-ADA IgG by 82%, whereas none of the naïve patient samples decreased anti-ADA levels, suggesting that the positive signals detected were not due to anti-ADA antibodies. Our results confirmed that samples collected from patients with no prior ADA exposure had no detectable ADA or anti-ADA IgG. In contrast, discrepant samples contained anti-ADA IgG antibodies that diminished detection of ADA.

Conclusion: Our cytometric assay can detect anti-ADA antibodies and distinguish anti-ADA immunogenicity from interference by measuring ADA drug concentrations and neutralization. The high positive rates estimated using our cytometric assay are likely due to anti-hinge antibodies and blocking strategies are currently being evaluated. Our method can be easily modified to measure the immunogenicity and drug levels of other TNFi biologics.

Disclosure: M. Casal, None; **M. Ramsey**, None; **L. W. Moreland**, None; **C. Fernandez**, None.

Abstract Number: 2602

Anti-TNF Therapy Is Associated with an Impaired Function of NK Cells and a Defective Immunosurveillance Against B-Cell Lymphomas

Gaetane Nocturne[1,2], Bineta Ly[3], Saida Boudaoud[4], raphaèle seror[5,6], Laurence Zitvogel[7] and Xavier Mariette[8,9], [1]Rheumatology Service, Bicêtre University Hospital, Le Kremlin Bicetre, France, [2]INSERM U1184, Université Paris Sud, Le Kremlin Bicêtre, France, [3]INSERM U1184, Paris Sud University, Kremlin Bicetre, France, [4]INSERM U1184, Paris Sud University, Le Kremlin Bicêtre, France, [5]Assistance Publique-Hôpitaux de Paris (APHP), Hôpitaux universitaires Paris Sud, Université Paris Sud, kremlin bicetre, France, [6]INSERM U1184, Paris Sud University, Le Kremlin Bicetre, France, [7]IGR - INSERM U1015, Villejuif, France, [8]Department of Rheumatology, APHP - Hopitaux universitaire Paris Sud, Le Kremlin Bicetre, France, [9]INSERM U1184, Université Paris-Sud, Paris, France, Le Kremlin Bicetre, France

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Background/Purpose:

Rheumatoid arthritis (RA) is associated with an increased risk of lymphoma linked to activity of the disease. Immunosuppressive drugs have been suspected to induce an additional risk. Since, NK cells have been recently shown to participate to anti–lymphoma immunosurveillance, we aimed to assess if anti-TNF might impact their anti-lymphoma activity.

Methods:

NK cells have been assessed ex vivo in patients with RA treated with methotrexate (MTX) with (n=19) or without (n=20) anti-TNF. Phenotype has been studied by flow cytometry and function (degranulation and IFNg production) has been assessed after NKp30-cross linking. Then, we have studied the consequences of in vitro exposure of NK to anti-TNF, to TNF-R inhibitors or to controls during 6 days: phenotype has been studied and then cytotoxicity against 2 B non-Hodgkin lymphoma cell lines [Farage (EBV+) and SU-DHL4 (EBV-)] was assessed.

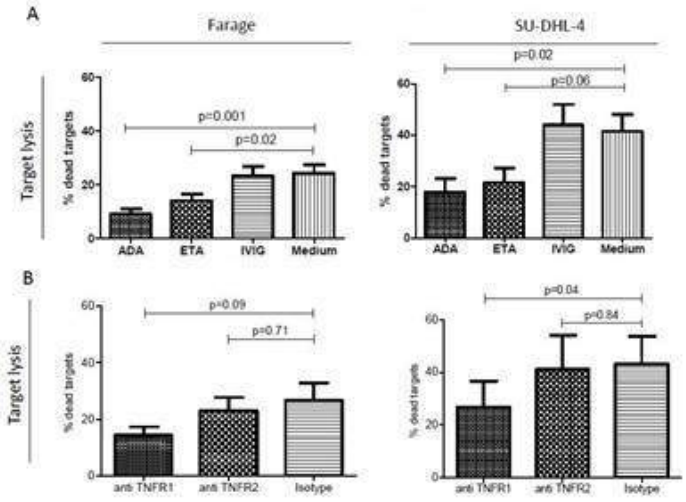
Results are shown as median [interquartile range (IGR)]. The Mann Whitney test was used to compare independent samples.

Results:

Firstly, in patients, we found that the proportion of activated NK cells, assessed by the expression of CD69, was significantly decreased in patients treated with anti-TNF + MTX compared to patients treated with MTX alone (8.9% [2.9 – 40.7] vs 48.4% [27.4 – 58.3], p=0.005). Moreover, we found that NK cells exhibited an impaired function in patients treated with anti-TNF compared to patients treated with MTX alone as assessed by the percentage of degranulation (20.9% [18.5 - 32.9] vs 31.3% [21.5 – 49.1], p=0.04) and the loss of capacity of IFN-γ secretion ((17.4% [8.9 – 25.9] vs to 29.7% [22.5 – 43.1], p=0.007). Secondly, we have confirmed that in vitro exposure to anti-TNF negatively impact NK cells activation and function leading to an impaired anti-lymphoma activity (figure 1A). In all these experiments, no difference was observed between etanercept and monoclonal anti-TNF. Last, we have demonstrated that negative impact of anti-TNF on NK cells may be the consequence of inhibition of TNF-R1 signaling (figure 1B).

Conclusion:

Even if meta-analysis of randomized controlled trials and of registries have not demonstrated to date an increased risk of lymphoma with anti-TNF, cautious must be pursued concerning this possible side effect in patients with long-term exposure. Moreover, negative impact of anti-TNF on NK cells may participate to infectious adverse events.



Disclosure: G. Nocturne, None; **B. Ly**, None; **S. Boudaoud**, None; **R. seror**, None; **L. Zitvogel**, None; **X. Mariette**, None.

Abstract Number: 2603

Real World Practice Based Clinical Study of Delayed-Release Prednisone Produces Comparable Results to a Controlled Clinical Trial: Morning Stiffness and Disease Measures in Moderate-Severe RA Patients Switched from Immediate-Release to Delayed Release-Prednisone

Ara H. Dikranian[1], Rubaiya Mallay[2], Mike Marshall[3], Megan Francis-Sedlak[3] and **Robert J. Holt**[4,5], [1]San Diego Arthritis Medical Clinic, San Diego, CA, [2]Suncoast Internal Medicine Consultants and Largo Med Center, Largo, FL, [3]Horizon Pharma USA, Inc, Lake Forest, IL, [4]Medical Affairs, Horizon Pharma, Inc, Lake Forest, IL, [5]College of Pharmacy, University of Illinois-Chicago, Vernon Hill, IL

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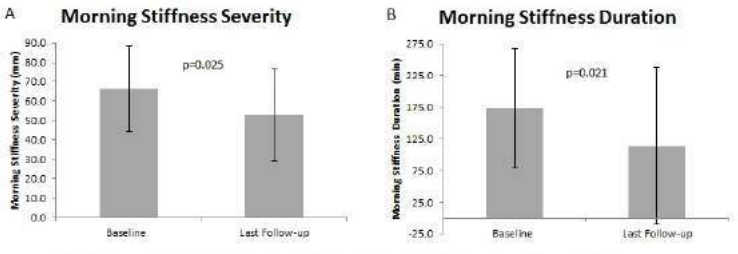
Background/Purpose: Patients with RA have previously demonstrated significant differences in morning stiffness (MS), a debilitating symptom of RA, and other disease measures with delayed release (DR)-prednisone versus immediate release (IR)-prednisone in a randomized trial and an open-label switch extension study (1,2). Previous randomized trials did not allow prednisone dose to be adjusted (1). We conducted a prospective open label switch study in the US to see if the results from controlled trials could be replicated in a real world clinical setting.

Methods: Twelve sites within the US enrolled 56 moderate-severe patients with RA into a 12 week study. At baseline patients were switched from IR- to DR-prednisone while maintaining other existing background therapies. MS severity (VAS1-100) the primary outcome, MS duration (minutes), swollen joint counts (SJC), DAS28, MDHAQ, RAPID3 and patient/physician global assessment (PGA/PhGA 10 cm VAS), among others, were measured (change from baseline). The overall group, those completing 10 wks, and those with >60 minutes of MS at baseline were analyzed, specifically. T-tests and Pearson's Correlations were used for significance and associations.

Results: 52 patients had at least one follow-up visit and were similar to patients in the previous controlled trial with regard to baseline mean age (63), DAS28CRP (5.2) but had lower baseline morning stiffness (114 minutes) and shorter duration of RA (5yrs). From a mean starting dose of 6 mg, the dose of prednisone decreased by 13% after switch to DR-prednisone in those treated ≥10 wks while demonstrating significant reductions in SJC, DAS28CRP, PhGA, RAPID3 and MDHAQ pain (all $p \leq 0.04$). Patients on treatment for ≥10 wks and who had baseline >60 min of MS produced similar results in SJC/PhGA as well as reductions in duration and severity of MS (both $p<0.03$, Figure 1). In the later analysis, MS severity (-20%) and duration (-34%) improvements were moderately correlated with each other ($R^2=0.43$) and no other correlations were demonstrated.

Conclusion: Patients switched to DR-prednisone from IR-prednisone in this practice based study maintained or improved their outcomes across a variety of domains and the results were comparable to previous controlled trials in which patients completed at least 10 wks of therapy. Further, there was a reduction in total prednisone dose over the treatment period comparable to the 18% found in a previous analysis (3). References: (1) Buttgereit, et al. Lancet 2008; 371: 205. (2) Buttgereit, et al. Ann Rheum Dis 2010;69:1275. (3) Cutolo, et al. Clin Exp Rheumatol 2013; 31:498.

Figure 1. Morning Stiffness in Patients Switched to DR-Prednisone from IR-Prednisone*



* Results from patients treated ≥10weeks with DR-Prednisone and baseline morning stiffness of >60 min;
DR = delayed-release; IR = immediate release

Disclosure: **A. H. Dikranian**, Horizon Pharma USA, Inc, 2,Horizon Pharma USA, Inc, 8; **R. Mallay**, Horizon Pharma USA, Inc, 2,Abbvie, 8; **M. Marshall**, Horizon Pharma, 1,Horizon Pharma USA, Inc, 3; **M. Francis-Sedlak**, Horizon Pharma, 1,Horizon Pharma USA, Inc, 3; **R. J. Holt**, Horizon Pharma, 1,Horizon Pharma USA, Inc, 3.

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Abstract Number: 2604

Ultrasound and Immunological Changes and Associations after One Year of IL-6/IL-6R Blockade with Tocilizumab in Rheumatoid Arthritis Patients

Cesar Diaz-Torne[1], Juan Jose De Agustin[2], Patricia Moya[1], Maria A. Ortiz[3], Delia Reina[4], Carme Moragues[5], Sergi Ros[6], Emili Gomez[7], Enrique Casado Burgos[8], Eli Garcia[9], Manel Pujol[10], Maria Pilar Lisbona Perez[11], Andrés Ponce[12], V Torrente[13], P. Estrada[14], Silvia Vidal[3] and ECOCAT group, [1]Rheumatology, Hospital Universitari de la Santa Creu i Sant Pau, Barcelona, Spain, [2]Rheumatology, Hospital Baix de Llobregat, Barcelona, Spain, [3]Institut de Recerca Sant Pau, Barcelona, Spain, [4]Rheumatology, Hospital de Sant Joan Despí Moisès Broggi, Barcelona, Spain, [5]Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [6]Rheumatology, Hospital de Viladecans, Viladecans, Spain, [7]Rheumatology, Hospital Clínic, Barcelona, Spain, [8]Hospital Universitari Parc Taulí, Sabadell, Spain, [9]Rheumatology, Hospital de Mollet, Mollet, Spain, [10]Hospital Mútua de Terrassa, Terrassa, Spain, [11]Rheumatology, Hospital de Sabadell, Sabadell, Spain, [12]Rheumatology. Internal Medicine, Hospital General de Granollers, Granollers, Spain, [13]Hospital de L'Hospitalet, L'Hospitalet de Llobregat, Spain, [14]Rheumatology, Hospital Moises Broggi, Barcelona, Spain

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Management of RA patients has improved in the last two decades in part with the use of ultrasound (US) in daily clinical practice. The use of US is helping to improve a tight control of RA patients and to predict clinical flares. Those inflammatory cytokines involved in RA pathology must be related with the US findings. We therefore evaluated the relationship between US patterns and cytokine levels in RA patients before and after IL-6 blockade.

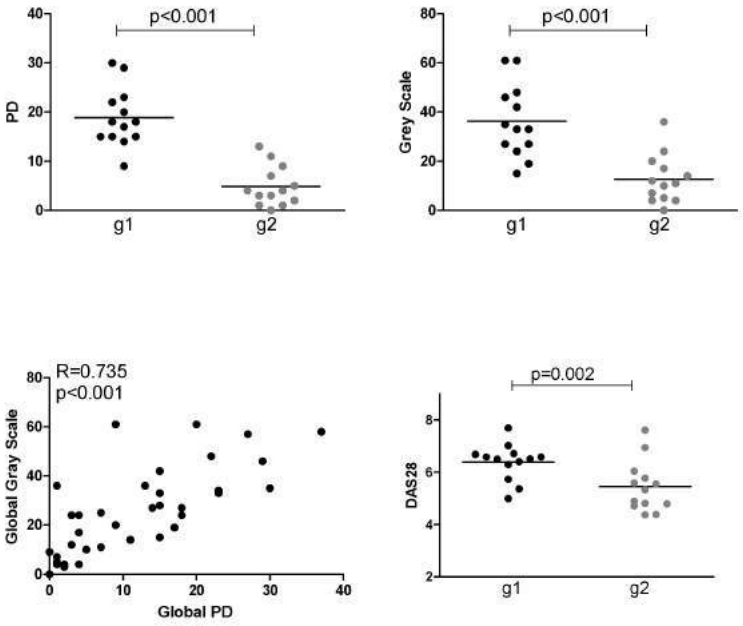
Methods: Peripheral blood was obtained from 30 RA patients, meeting the ACR criteria, that were treated with tocilizumab. In all patients, RA was refractory to treatment with DMARDs, including methotrexate. Tocilizumab treatment was begun following European and Spanish guidelines. Plasma was collected prior to first infusion and at 1, 3, 6 and 12 months after treatment. Laboratory analysis included haemogram, ESR, CRP, RF, ACPAs, IL-17, IL-22, VEGF, IL-6 and sIL-6R. US assessment was registered for each visit for 32 joints and 12 tendons of hands and feet in Gray Scales (GS) and Power Doppler (PD) using a semiquantitative scale (0-3 points). Clinical data collected was DAS28, SDAI and CDAI.

Results: Clinical and demographic baseline data of the patients is shown in table 1. We have found two groups of patients based on the baseline PD values (group 1: 18,9±5,9 vs group 2: 4,8±4,05) As expected, patients in group 1 also had higher GS (group 1: 36,2±14 vs group 2: 12,6±9,8) and DAS28 values (group 1: 6,38±0,69 vs group 2: 5,44±0,9) (Figure 1). Baseline PD correlated with plasmatic IL-17 (R=0,39; p=0,045) and IL-22 concentration (R=0,554; p=0,002), but not with other cytokines. IL-17 and IL-22 were correlated at baseline (R=0,913; p<0,001). IL-17 and IL-22 also correlated with RF titers (R=0,795; p<0,001 and R=0,67; p<0,0001) and VEGF (R=0,935; p<0,001 and R=0,784; p<0,001) values. After 12 months of treatment, we found significant changes in PD (11,81±9 vs 1,76±3,6), GS (25,36±17 vs 4,38±6,8), DAS28 (5,76±0,9 vs 2,8±1,4), IL-6R (447±368 vs 1892±960 ng/ml) and IL-22 (3107±5700 vs 5983±12022 pg/ml). There were no changes in IL-6 (819±896 vs 896±906 pg/ml), IL-17 (1677±3900 pg/ml) and VEGF (849±2115 vs 796±2016 pg/ml) plasmatic concentrations. After 12 months of tocilizumab PD values correlated with IL-17 (R=0,446; P=0,02) and VEGF (R=0,599; p<0,001) concentrations.

Conclusion: There is a correlation at baseline between PD and IL-17 and IL-22. After 12 months of IL-6 blockade there is a significant improvement in clinical and US values without changes in levels of IL-17, IL-6 and VEGF. IL-17 was the only cytokine that correlated with PD levels throughout the study.

Baseline clinic and demographic characteristics of the RA patients	
Age; years mean±SD	61,5±4,7
Gender; women %(n)	83,3 (25)
Years of evolution; mean±SD	10,3±9,2
Corticoids use; % (n)	66,7% (20)
Monotherapy (no DMARDs); %(n)	53,3 (16)
Methotrexate;%(n)	40% (12)
Others;%(n)	6,7% (2)
DAS28; mean±SD	5,76±0,9
HAQ; mean±SD	1,37±0,6
ESR mm/h; mean±SD	48±32
CRP mg/dl; mean±SD	4,6±9,8
CCP + %(n)	66,7%
CCP (UI/ml)	286±360
RF + %(n)	72,9%
RF (UI/ml)	350±426

Figure 1



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Abstract Number: 2605

Therapy with Biologic Agents after Diagnosis of Solid Malignancies; Results from the Corrona Registry

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SESSION INFORMATION

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Recently issued guidelines suggest that rheumatoid arthritis (RA) patients with previously treated solid malignancy may be treated as patients without such history (1). The recommendation is based on limited evidence and rheumatologists and patients are frequently hesitant to start biologic therapy after a cancer diagnosis. The objective of this study is to describe biologic utilization in real world RA patients following a malignancy diagnosis.

Methods: Patients (pts) with RA enrolled in the Corrona registry and diagnosed with a solid malignancy post enrollment were included in this analysis. Index date was defined as first visit after malignancy diagnosis. Proportion of pts initiating a biologic or targeted synthetic (ts) DMARD after diagnosis was estimated. Median time to the initiation of a biologic/tsDMARD after diagnosis was calculated using the Kaplan-Meier method and proportion initiating biologic treatment in 6-month time windows was estimated using the life-table method.

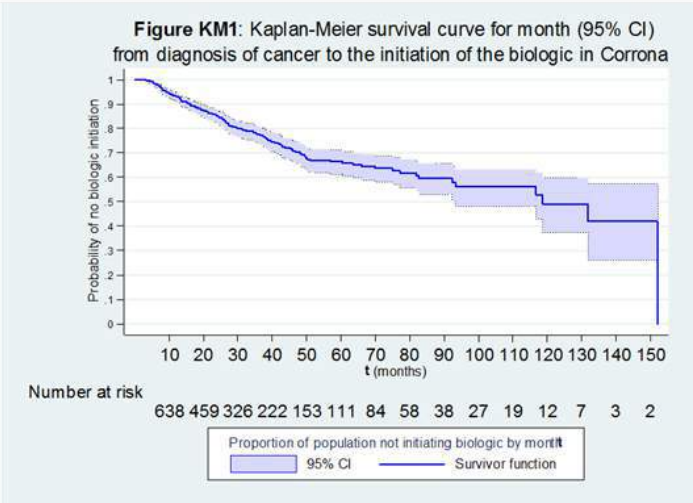
Results: Out of 42619 RA pts historically enrolled in Corrona, 934 pts had an incident solid malignancy after registry enrollment. 880 pts had at least 1 follow-up visit within 12 months after diagnosis and were included in the analysis. At index visit, mean disease duration was 14.1 years, mean age 66.6 years and 67% (n=592) were females. Mean CDAI for the population was 11.2 and 38.4% (n=329) of pts were in moderate or high disease activity. Total follow-up time after index date was 2585.6 person years. 41.7% (n=367) of the pts were treated with biologics/tsDMARDs within 12 months preceding malignancy and 30.7% (n=270) were on such agents at visit immediately following the diagnosis. Approximately 20% (n=170) initiated or switched a biologic/tsDMARD during the follow-up period, the majority of which started a TNF inhibitor (53.5%) The percentage of pts starting a biologic / tsDMARD and also a TNFi is shown in Table 1. The median time to initiation of the first biologic/tsDMARD was 118.7 months, approximately 10 years.

Conclusion: In real world practice, nearly one-third of RA patients continue therapy with biologic and ts agents after malignancy diagnosis and another one-third initiate biologic therapy within 5 years of solid malignancy diagnosis. The majority of biologic/tsDMARDs initiations was a TNFi. The proportion of biologic initiation is increasing in cancer survivors as time post diagnosis progresses. Reference:

1. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol. 2016 Jan;68(1):1-26. doi: 10.1002/art.39480. Epub 2015 Nov 6. Review. Table

Time period from index	Number of Patients Remaining	Number and Cumulative Probability [95% CI] initiating biologic/ts DMARD	Number and Percentage of those who initiate with TNFi
0-6 months	880	13 (1.6%), [0.9%,2.7%]	9 (69.2%)
6-12 months	761	36 (6.7%), [5.1%,8.8%]	20 (55.6%)
12-18 months	621	28 (11.4%), [9.2%,14.1%]	16 (57.1%)
18-24 months	524	18 (14.9%), [12.3%,18%]	10 (55.6%)
24-30 months	446	23 (20.1%), [17%,23.7%]	12 (52.2%)
30-36 months	373	9 (22.5%), [19.1%,26.3%]	4 (44.4%)
36-42 months	303	11 (26.1%), [22.3%,30.3%]	6 (54.5%)
42-48 months	239	9 (29.6%), [25.4%,34.3%]	4 (44.4%)
after 48 months (≥ 48 months)	208	23 (85.7%), [45.1%,99.8%]	10 (43.5%)

Figure



Disclosure: D. A. Pappas, Corrona, LLC,, 3,Novartis Pharmaceutical Corporation, 9; **S. Rebello**, Corrona, LLC, 3; **M. Liu**, Corrona, LLC, 3; **J. Schenfeld**, Amgen, 5,DOCS Global, Inc, 3; **Y. Li**, None; **D. H. Collier**, Amgen, 1,Amgen, 3; **N. Accortt**, Amgen, 1,Amgen, 3.

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Abstract Number: 2606

Effect of Glucocorticoids on Clinical and Radiographic Efficacy Outcomes in Methotrexate-Naive Patients with RA Receiving Tofacitinib or Methotrexate Monotherapy: Analysis of Data from a Phase 3 Trial

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Patients (pts) with RA often receive concomitant treatment with glucocorticoids (GCs) to control inflammatory symptoms. The purpose of this analysis was to investigate whether the presence or absence of GCs has an effect on the clinical and radiographic efficacy of tofacitinib or MTX administered as monotherapy in MTX-naïve pts with RA.

Methods: ORAL Start (NCT01039688) was a 2-year, randomized Phase 3 clinical trial in which 956 MTX-naïve pts with RA received either tofacitinib 5 mg twice daily (BID), tofacitinib 10 mg BID, or MTX titrated to 20 mg/week over 8 weeks. Pts receiving GCs (≤10 mg/day of prednisone or equivalent) prior to enrollment were required to remain on a stable dose throughout the study. All pts were required to meet the ACR classification criteria for the diagnosis of RA. Primary results have been reported previously. Endpoints

evaluated in this analysis at Months 6 and 24 included ACR20/50/70 response rates, the proportion of pts achieving low disease activity and remission as measured by Clinical Disease Activity Index (CDAI) ≤10 and ≤2.8, respectively, the proportion of pts with no radiographic progression as defined by a change from baseline of ≤0.5 in modified Total Sharp Score (mTSS), and least squares mean (LSM) change from baseline in CDAI, Health Assessment Questionnaire Disability Index (HAQ-DI), Disease Activity Score (DAS28-4[ESR]), and mTSS. This was an exploratory post-hoc analysis without multiplicity adjustment.

Results: Baseline demographics and disease characteristics were similar between treatment groups and among those receiving treatment with and without GCs. For assessments measured at Months 6 and 24, tofacitinib was more effective as monotherapy than MTX, regardless of GC status (Table). At Months 6 and 24, the proportions of pts achieving ACR20/50/70, CDAI ≤10, CDAI ≤2.8, and change in mTSS ≤0.5 were numerically similar between pts receiving tofacitinib with and without GCs, and between pts receiving MTX with and without GCs (Table). A similar trend was observed for LSM change from baseline in CDAI score, HAQ-DI, and DAS28-4(ESR) (Table). LSM change from baseline in mTSS was numerically similar in pts receiving tofacitinib with or without GCs, but showed a trend to be reduced (indicating less radiographic progression) in pts receiving MTX with GCs compared with those receiving MTX without GCs (Table).

Conclusion: GCs in low doses did not appear to impact clinical efficacy or inhibit radiographic progression when administered with tofacitinib monotherapy, and had a limited effect, if any, when given with MTX monotherapy. These findings might reflect the pt population, who had active disease at study entry despite receiving GCs and therefore may not be generalizable to pts starting GCs.

Table. Clinical and radiographic outcomes at Months 6 and 24 in patients receiving tofacitinib or MTX with or without GCs

			Tofacitinib 5 mg BID		Tofacitinib 10 mg BID		MTX	
			+GC (N=184[a])	-GC (N=189[a])	+GC (N=173[a])	-GC (N=224[a])	+GC (N=88[a])	-GC (N=98[a])
Month 6	Response, % (95% CI)	ACR20	67.4 (60.1, 74.2)	75.1* (68.3, 81.2)	77.1* (70.0, 83.2)	75.1* (68.9, 80.7)	55.3 (44.1, 66.1)	47.4 (37.2, 57.8)
		ACR50	42.5* (35.2, 50.1)	50.8* (43.4, 58.2)	56.5* (48.7, 64.1)	56.1* (49.3, 62.8)	28.2 (19.0, 39.0)	25.8 (17.4, 35.7)
		ACR70	23.8* (17.8, 30.6)	27.0* (20.8, 34.0)	36.5* (29.2, 44.2)	38.0* (31.6, 44.8)	9.4 (4.2, 17.7)	14.4 (8.1, 23.0)
		CDAI ≤10	40.9 (33.7, 48.4)	48.9* (41.4, 56.4)	58.6* (50.8, 66.1)	57.9* (51.1, 64.5)	31.8 (22.1, 42.8)	29.9 (21.0, 40.0)
		CDAI ≤2.8	9.4 (5.6, 14.6)	14.3 (9.6, 20.2)	21.9* (15.9, 28.9)	19.0* (14.1, 24.8)	7.1 (2.6, 14.7)	8.3 (3.6, 15.6)
		mTSS ≤0.5	87.6* (81.6, 92.1)	86.4* (80.5, 91.1)	91.4* (85.9, 95.2)	87.5* (82.2, 91.7)	76.6 (65.6, 85.5)	70.5 (59.8, 79.7)
	LS mean change from baseline (95% CI)	CDAI	-24.6 (-26.3, -23.0)	-25.1* (-26.6, -23.5)	-28.2* (-29.9, -26.5)	-27.9* (-29.3, -26.5)	-22.1 (-24.5, -19.6)	-19.6 (-21.8, -17.4)
		HAQ-DI	-0.84* (-0.92, -0.75)	-0.85* (-0.94, -0.77)	-0.96* (-1.05, -0.87)	-0.94* (-1.01, -0.87)	-0.63 (-0.76, -0.50)	-0.61 (-0.72, -0.49)
		DAS28-4(ESR)	-2.41 (-2.62, -2.20)	-2.62* (-2.81, -2.43)	-2.87* (-3.08, -2.65)	-2.97* (-3.14, -2.79)	-2.03 (-2.35, -1.72)	-1.89 (-2.17, -1.61)
		mTSS	0.28 (0.07, 0.50)	0.15* (-0.08, 0.38)	0.09* (-0.13, 0.31)	0.21* (0.00, 0.42)	0.51 (0.19, 0.83)	0.78 (0.46, 1.09)
Month 24	Response, % (95% CI)	ACR20	65.2* (57.8, 72.1)	62.7* (55.3, 69.7)	62.4* (54.6, 69.7)	66.1* (59.4, 72.3)	49.4 (38.4, 60.5)	37.1 (27.5, 47.5)
		ACR50	50.8* (43.3, 58.3)	47.0* (39.7, 54.5)	45.3* (37.7, 53.1)	52.5* (45.7, 59.2)	31.8 (22.1, 42.8)	25.8 (17.4, 35.7)
		ACR70	34.3* (27.4, 41.7)	34.1* (27.3, 41.4)	35.9* (28.7, 43.6)	38.9* (32.5, 45.7)	14.1 (7.5, 23.4)	16.5 (9.7, 25.4)
		CDAI ≤10	60.8* (53.3, 67.9)	58.2* (50.7, 65.5)	65.1* (57.4, 72.3)	62.9* (56.2, 69.3)	34.1 (24.2, 45.2)	38.1 (28.5, 48.6)
		CDAI ≤2.8	24.3* (18.3, 31.2)	22.5* (16.7, 29.3)	27.2* (20.7, 34.6)	28.5* (22.7, 35.0)	3.5 (0.7, 10.0)	9.3 (4.3, 16.9)
		mTSS ≤0.5	81.1* (74.3, 86.7)	78.5* (71.7, 84.3)	82.1* (75.3, 87.7)	84.7* (79.1, 89.3)	62.8 (51.1, 73.5)	65.9 (55.3, 75.6)
	LS mean change from baseline (95% CI)	CDAI	-30.5* (-32.0, -29.1)	-28.4* (-29.9, -26.9)	-30.8* (-32.3, -29.3)	-29.9* (-31.3, -28.6)	-26.1 (-28.3, -23.9)	-24.8 (-27.1, -22.4)
		HAQ-DI	-0.95* (-1.05, -0.85)	-0.86 (-0.95, -0.78)	-1.01* (-1.11, -0.91)	-1.02* (-1.10, -0.94)	-0.69 (-0.84, -0.54)	-0.72 (-0.85, -0.59)
		DAS28-4(ESR)	-3.08* (-3.31, -2.86)	-2.97* (-3.18, -2.76)	-3.12* (-3.35, -2.89)	-3.23* (-3.43, -3.04)	-2.39 (-2.72, -2.05)	-2.37 (-2.71, -2.02)
		mTSS	0.76 (0.23, 1.28)	0.55* (-0.19, 1.30)	0.45* (-0.08, 0.98)	0.25* (-0.43, 0.94)	1.64 (0.87, 2.41)	2.64 (1.60, 3.68)

*p<0.05 (without multiplicity adjustment for exploratory analysis) versus MTX within the respective subgroup.

[a]Please note that patient numbers given are from the full analysis set; however, patient numbers varied between outcome measures. Percentages are based on available data collected for each outcome measure.

ACR20/50/70 and CDAI ≤10/≤2.8 data were full analysis set, non-responder imputation; mTSS ≤0.5 data were full analysis set, linear extrapolation for missing data imputation; LS Mean change from baseline data were full analysis set, based on longitudinal model.

BID, twice daily; CDAI, Clinical Disease Activity Index; CFB, change from baseline; CI, confidence interval; GC, glucocorticoid; DAS28-4(ESR), Disease Activity Score-4(erythrocyte sedimentation rate); HAQ-DI, Health Assessment Questionnaire Disability Index; LS, least squares; mTSS, modified total Sharp score; MTX, methotrexate

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Abstract Number: 2607

Favorable Changes in Lipid Profile with Additive DMARD Therapy in Rheumatoid Arthritis Patients Failing Methotrexate Monotherapy

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Background/Purpose: Cardiovascular disease is a significant comorbidity among RA patients. As such, dyslipidemia and the effect of DMARD therapy on lipid profiles is an important consideration in RA management. Previous reports show that suppression of systemic inflammation, particularly in early RA, leads to increased cholesterol levels. While the magnitude of this effect appears to vary by treatment and populations studied, there has been limited study of this effect in the important subgroup of MTX suboptimal responders with subsequent escalation of DMARD therapy.

Methods: Statistical analyses were performed using data from the Rheumatoid Arthritis Comparison of Active Therapies (RACAT) trial. Patients with active RA despite treatment with MTX were randomized to receive triple therapy (MTX/HCQ/SSZ) or MTX/etanercept (ET). Those showing inadequate response were crossed over at 24 weeks. Using banked serum from baseline, 24, and 48 weeks (n=204), levels of total cholesterol (TC), LDL, VDL, HDL, and triglyceride (TG) were measured. Changes in lipids between each time point were examined using generalized estimating equations (GEE models), adjusting for baseline characteristics and DAS-28. To further examine the effect of treatment on lipid profiles, we compared changes in the first 24 weeks of exposure to each treatment (patients started on triple therapy plus those crossed over to triple therapy at 24 weeks versus patients started on MTX/ET plus those crossed over to MTX/ET at 24 weeks) using additional GEE models.

Results: There were significant decreases in VDL, TG, and TC:HDL ratio and a significant increase in HDL over observation after controlling for baseline characteristics (Table). With further adjustment for DAS-28, effect sizes were reduced and no longer significant. Comparing the effect of MTX/ET to triple therapy on lipids over the first 24 weeks of exposure, there was a larger decrease in VDL with triple therapy (β=3.32 mg/dL; p=0.037). In adjusted models, the effect size was largely unchanged with p-values of borderline significance (3.08, p=0.056 adjusting for baseline characteristics; 3.10, p=0.055 adjusting for baseline characteristics + DAS-28).

Conclusion: These data show favorable changes in VDL, HDL, TG, and the TC:HDL ratio in RA patients after escalating therapy following treatment failure with MTX. This is driven largely by improvement in DAS-28, differing from previous reports where suppression of disease activity is associated with elevation in cholesterol levels. In addition, data here show a trend toward more favorable levels of VDL with triple therapy relative to MTX/ET, supporting previous work showing more favorable lipid profiles with triple therapy in early RA. Additional research is needed to elucidate the clinical implications of these changes in lipids, as well as the effect of altered lipoprotein function in RA. **Table 1.**

	Model A*		Model B**		Model C***	
	Mean change/visit	p-value	Mean change/visit	p-value	Mean change/visit	p-value
TC (mg/dL)	-1.83	0.349	-1.84	0.349	-3.98	0.089
LDL (mg/dL)	-1.14	0.466	-1.18	0.451	-2.42	0.191
VDL (mg/dL)	-1.96	0.036	**-1.99**	**0.032**	**-1.09**	**0.251**
HDL (mg/dL)	1.21	0.040	**1.21**	**0.041**	**-0.38**	**0.563**
TG (mg/dL)	-9.17	0.041	**-9.34**	**0.037**	**-4.89**	**0.299**
TC:HDL	-0.10	0.005	**-0.10**	**0.005**	**-0.04**	**0.326**

*Model A = unadjusted
**Model B = adjustment for age, sex, race (non-hispanic white vs. other), smoking status (current, former, never), baseline body mass index category (underweight, normal, overweight), CCP positivity, and disease duration
***Model C = Model B plus adjustment for DAS-28

Disclosure: T. Johnson, None; **T. R. Mikuls**, None; **H. Sayles**, None; **M. J. Duryee**, None; **G. M. Thiele**, None; **M. Brophy**, None; **J. R. O'Dell**, Lilly, 5,Bristol-Myers Squibb, 5,GlaxoSmithKline, 5,Coherus, 5,Medac, 5.

Abstract Number: 2608

Anti-CCP Antibody Titers Decrease with Altered B-Cell Subpopulation in RA Patients Treated with Tocilizumab

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Background/Purpose: Tocilizumab (TCZ), an anti-IL-6 receptor monoclonal antibody, has been recognized as one of the highly effective therapeutic agents in RA, but its contribution to B-cell function remains to be elucidated. Our purpose was to analyze the effects of TCZ on B-cell subpopulation and its ability to produce anti-CCP antibody during the treatment for RA.

Methods: Consecutive RA patients who initiated treatment with TCZ between December 2013 and September 2015 were enrolled in our prospective study. All patients met 2010 ACR/EULAR classification criteria for RA and were treated with 162mg of TCZ subcutaneously every other week. Peripheral blood samples were collected and B-cell subsets were analyzed by flow cytometry at baseline, and during TCZ treatment at week 12 and 24. Clinical parameters, including disease activity and serum level of autoantibodies, were also evaluated in these periods. The protocol of this study was approved by the ethics committee of Hokkaido University Hospital.

Results: Fourteen patients were enrolled but one dropped out because of missing data. Remaining 13 patients were analyzed at the baseline and during the follow-up periods. DAS28-ESR significantly improved at week 12 (2.42 ± 1.14, $p < 0.001$) and week 24 (2.20 ± 1.00, $p < 0.001$) compared to baseline (5.00 ± 1.39). Anti-CCP antibody titers significantly decreased at week 24 compared to baseline

(p = 0.033, Fig. 1). In flow cytometry analysis, the percentages of post-switch memory B cells (CD19+CD27+CD38-IgD-) in the population of CD19 positive cells were significantly higher at week 12 than those at baseline (p = 0.011). The changes in naïve B cells (CD19+CD27-) and those in post-switch memory B cells from baseline to week 24 were inversely correlated (r = -0.703, p = 0.007). Furthermore, the ratios of naïve to post-switch memory B cells (naïve/post-switch) correlated positively with anti-CCP antibody titers regardless of the time-points (r = 0.621, p = 0.024 at baseline, r = 0.623, p = 0.023 at week 12, and r = 0.702, p = 0.007 at week 24, Fig. 2). The changes in naïve/post-switch and the changes in anti-CCP antibody titers also showed positive correlation from baseline to week 12 (r = 0.709, p = 0.007) and from baseline to week 24 (r = 0.588, p = 0.035).

Conclusion: Our study indicated that anti-CCP antibody titers reflect B-cell distribution and that TCZ has a potential to modulate the production of anti-CCP antibody by affecting naïve/post-switch ratio. The increment of post-switch memory B cells after TCZ treatment may reflect the re-distribution of this subset into circulation from arthritic joints, which results in suppressed production of anti-CCP antibody.

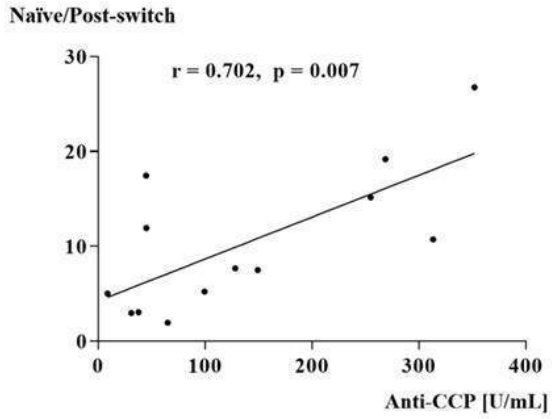

Fig. 2. Correlation between anti-CCP antibody titers and naïve/post-switch ratios at week 24. Correlation coefficient was assessed by Spearman rank method.

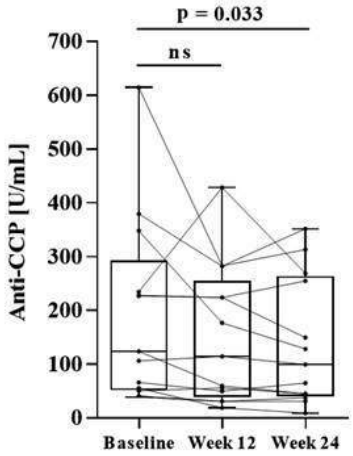

Fig. 1. Time course of the change in anti-CCP antibody titers during treatment with TCZ in RA patients (n = 13). Data are shown as symbols and lines in each patient and also as box plots, representing minimum, first quartile, median, third quartile and maximum. P-values were calculated for comparison between baseline and week 12, or between baseline and week 24, using Wilcoxon signed-rank test.

Disclosure: A. Noguchi, None; **S. Yasuda**, None; **R. Hisada**, None; **K. Ohmura**, None; **S. Shimamura**, None; **Y. Shimizu**, None; **M. Kato**, None; **K. Oku**, None; **T. Bohgaki**, None; **O. Amengual**, None; **T. Horita**, None; **M. Suzuki**, None; **Y. Matsumoto**, None; **T. Atsumi**, Chugai Pharmaceutical Co. Ltd, 8.

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Abstract Number: 2609

The Effectiveness of Zoster Vaccine in RA Patients Subsequently Treated up to 19 Months with Tofacitinib

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Hodge[2], Irina Lazariciu[6], Koshika Soma[2], Christopher F Mojcik[2] and William F.C Rigby[7], [1]Oregon Health and Sciences University, Portland, OR, [2]Pfizer Inc, New York, NY, [3]CREATE Center, Division of Infection and Immunity, Cardiff University School of Medicine, Cardiff, Great Britain, [4]CREATE Center, Division of Infection and Immunity,, Cardiff University, Cardiff, United Kingdom, [5]Pfizer Inc, Groton, CT, [6]Quintiles, Saint-Laurent, QC, Canada, [7]Geisel School of Medicine at Dartmouth, Lebanon, NH
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Background/Purpose: Rheumatoid arthritis (RA) patients are at increased risk for herpes zoster (HZ), and vaccination is recommended in patients over the age of 50 years, prior to starting biologics or tofacitinib, an oral Janus kinase inhibitor for the treatment of RA. In immunocompetent adults aged ≥50 years zoster vaccine has shown 70% efficacy (in 50–59 year-olds over 1.3 years) to 51% efficacy (in ≥60-year-olds over 4.9 years) for the prevention of HZ.[1] We previously reported the safety and immunogenicity of live zoster vaccine in RA patients on background methotrexate (MTX) before initiating tofacitinib or placebo.[2] Briefly, patients with RA who started 3 months of treatment with tofacitinib after zoster vaccination generated immunity to varicella zoster virus (VZV) similar to placebo-treated recipients. Furthermore their VZV immunity at Week 6 post-vaccination was comparable with immunity in healthy people aged 50 years and older.[2] However, the long-term effectiveness of the vaccine in this setting is unknown.

Methods: From a prior cohort of patients (n=100) given zoster vaccine and then randomized 2 to 3 weeks later to tofacitinib 5 mg BID, or placebo, for 12 weeks (A3921237 [NCT02147587]), we evaluated the incidence of HZ post-vaccination during long-term tofacitinib use. At 14 weeks post-vaccination, patients joining the long-term extension (LTE) study (ORAL Sequel; [NCT00413699]) initiated open-label treatment with tofacitinib 5 mg or 10 mg BID at the discretion of the investigator. HZ cases after tofacitinib exposure up to 19 months were evaluated. Among HZ cases, we described and compared measures of VZV-specific immunity with average immunity after live zoster vaccination.

Results: 112 pts were randomized to placebo (n=57) or tofacitinib 5 mg BID (n=55), and 100 of these patients continued to receive tofacitinib in the ORAL Sequel study. The overall exposure to tofacitinib ranged from 9 to 19 months. Two HZ cases occurred, one at 202 days (219 days from vaccination) and another at 267 days (281 days from vaccination) after tofacitinib start. Both were monodermatomal and resolved with antiviral therapy. Review of immunogenicity data at 6 weeks post-vaccination revealed that Case #1 had undetectable ELISPOT measures at baseline and at Week 6 post-vaccination. Case #2 responded adequately to vaccination by both IgG and ELISPOT measures, but had much lower than average post-vaccination IgG levels (Table 1).

Conclusion: The observed HZ incidence rate after vaccination was low among this cohort of tofacitinib-treated patients. Zoster vaccination prior to tofacitinib start is effective at boosting IgG levels and cell-mediated immunity towards VZV, although individuals with poor vaccine response may be more likely to develop HZ. **Reference:** 1. Hales CM et al. MMWR Morb Motal Wkly Rep 2014; 63:729-31. 2. Winthrop K et al. Arthritis Rheumatol 2015; 67 (suppl 10): Abstract 12L.

Table 1. Varicella zoster virus ELISPOT and IgG levels			
	Case #1 (HZ 219 days after zoster vaccine)	Case #2 (HZ 281 days after zoster vaccine)	Study A3921237 Tofacitinib 5 mg BID (N=54)
Mean VZV IFNγ ELISPOT at baseline (SFCs/10^6 PBMCs)	25 (LOD)	41	48
Mean VZV IFNγ ELISPOT at Week 6 (SFCs/10^6 PBMCs)	25 (LOD)	76	70
Change from baseline in VZV ELISPOT at Week 6 (SFC fold-rise; SFCs/10^6 PBMCs)	1.0	1.85	1.50
Mean VZV IgG titer at baseline (gpELISA units/mL)	224	37	201
Mean VZV IgG titer at Week 6 (gpELISA units/mL)	444	71	403
Change from baseline in VZV IgG titer at Week 6 (fold-rise; gpELISA units/mL)	1.98	1.92	2.11
One patient who lacked pre-existing varicella immunity developed disseminated primary varicella from the vaccine strain 16 days post-vaccination (reported previously[2]). This case was excluded from calculations for HZ. CMI, cell-mediated immunity; HZ, herpes zoster; IFNγ, interferon gamma; IgG, immunoglobulin G; LOD, limit of detection; PBMC, peripheral blood mononuclear cell; SFCs, spot-forming cells; VZV, varicella zoster virus			

Disclosure: **K. L. Winthrop**, Pfizer Inc, 2; **A. Wouters**, Pfizer Inc, 1,Pfizer Inc, 3; **E. H. Choy**, None; **C. Nduaka**, Pfizer Inc, 1,Pfizer Inc, 3; **S. Abramsky**, Pfizer Inc, 1,Pfizer Inc, 3; **P. Biswas**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Wang**, Pfizer Inc, 1,Pfizer Inc, 3; **J. Hodge**, Pfizer Inc, 1,Pfizer Inc, 3; **I. Lazariciu**, Pfizer Inc, 5,Quintiles, 3; **K. Soma**, Pfizer Inc, 3,Pfizer Inc, 1; **C. F. Mojcik**, Pfizer Inc, 1,Pfizer Inc, 3; **W. F. C. Rigby**, None.

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Abstract Number: 2610

Immunogenicity Assessment of Biologics in Clinical Studies in Chronic Inflammatory Disease: A Systematic Review

Boris Gorovits[1], Daniel Baltrukonis[2], Indranil Bhattacharya[3], Mary A Birchler[4], Deborah Finco[2], Daniel Sikema[4], Michael S Vincent[5], Sadiq Lula[6], Lisa Marshall[7] and **Timothy Hickling**[1], [1]Pfizer, Andover, MA, [2]Pfizer, Groton, CT, [3]Clinical Pharmacology, Pfizer, Cambridge, MA, [4]Clinical Immunology, Glaxo Smith Kline BioPharmaceuticals, Upper Merion, PA, [5]Inflammation and Immunology Research Unit, Pfizer, Cambridge, MA, [6]Envision Pharma Group, London, United Kingdom, [7]Inflammation Global Medical Affairs, Pfizer, Collegeville, PA

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Background/Purpose: A portion of patients without clinical response to anti-inflammatory biologics have been shown to develop anti-drug antibodies (ADA).[1] ADA prevalence varies widely among biologics, with variability attributed to several factors, particularly use of a broad range of assay formats. A systematic literature review was conducted to specifically assess immunogenicity of biologics,

differences in ADA assays, and associated clinical outcomes.

Methods: MEDLINE, EMBASE, and Cochrane databases, conference proceedings and review articles were searched for randomized controlled trials and observational studies of biologic therapies published before 4 September 2015 in which assay methods for ADA testing were reported. This analysis focuses on adalimumab and infliximab as they have been available for the longest period, with the greatest number of published studies and reports of immunogenicity.

Results: Of 21,889 publications screened and 358 publications (322 studies) included, 71 and 123 studies of adalimumab and infliximab, respectively, were retained. In >20% of studies in which adalimumab and infliximab ADA were assessed, the assay method was not reported. In most adalimumab and infliximab studies, an ELISA (48/71 and 92/123) or radioimmunoassay (RIA; 17/71 and 16/123) was used (table). ADA+ incidence varied widely in studies of adalimumab and infliximab across inflammatory diseases (table). Clinical and pharmacokinetic outcomes were only reported for ADA+ patients in 39% and 45% of adalimumab and infliximab studies, respectively. ADA formation was consistently associated with lower serum concentrations of both biologics and elevated rates of infusion-related reactions with infliximab.

Table. Incidence of ADA formation in patients treated with adalimumab and infliximab across chronic inflammatory diseases by immunogenicity assay method.

	Adalimumab studies		Infliximab studies	
Immunogenicity assay	ADA+ patients, % (No. of studies)	Assay cut points for ADA+	ADA+ patients, % (No. of studies)	Assay cut points for ADA+
ELISA	1.6–87.0 (26)	0.1–32 AU/mL, 10–20 ng/mL or optical densities of 0.02–1	4.8–79.0 (65)	2–50 AU/mL 5–10 ng/mL; 0.07–2.6 µg/mL; optical densities of 0.12–1.2, or 2x optical density in ADA– samples
Bridging ELISA	0–54.2 (18)		6.8–65.3 (26)	
Acid dissociation ELISA	10.4–35.0 (4)		25.6–35.0 (1)	
RIA	0–61.5 (18)	12 AU/mL; or 2x level in ADA– samples	0–71.4 (17)	10–12 AU/mL, >3% of BL value; or 2x level in ADA– samples
HMSA	4.3–27.0 (5)	1.7 µg/mL	12.7–59.0 (10)	3.1–8.0 AU/mL
ECL	–	–	22.5–49.5 (3)	NR
HPLC	–	–	13.6 (1)	NR
IMPACT	–	–	54.1 (1)	2x level in ADA– samples

AU, arbitrary units; BL, baseline; ECL, electrochemiluminescence; ELISA, enzyme-linked immunosorbent assay; HMSA, homogeneous mobility shift assay; HPLC, high performance liquid chromatography; NR, not reported; RIA, radioimmunoassay

Conclusion: To improve interpretation of immunogenicity data for biologics, greater consistency is needed in reporting of assay methods as well as clinical consequences of ADA formation. Standardization in immunogenicity testing and reporting as recently proposed by Shankar et al[2], application of modern assays with higher sensitivity and lower drug interference, and implementation of international standards for marketed products would allow greater insight into the impact of immunogenicity to biologics. **References: 1.** van Schouwenburg, PA et al. *Nature Revs Rheum*. 2013;9:164-72. **2.** Shankar, G et al. *AAPS J*. 2014;16(4):658-73.

Disclosure: B. Gorovits, Pfizer Inc, 1,Pfizer Inc, 3; **D. Baltrukonis**, Pfizer Inc, 1,Pfizer Inc, 3; **I. Bhattacharya**, Pfizer Inc, 1,Pfizer Inc, 3; **M. A. Birchler**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **D. Finco**, Pfizer Inc, 1,Pfizer Inc, 3; **D. Sikema**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **M. S. Vincent**, Pfizer Inc, 1,Pfizer Inc, 3; **S. Lula**, None; **L. Marshall**, Pfizer Inc, 1,Pfizer Inc, 3; **T. Hickling**, Pfizer Inc, 1,Pfizer Inc, 3.

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Abstract Number: 2611

Cardiovascular Safety of Tocilizumab Versus Tumor Necrosis Factor Inhibitors in Patients with Rheumatoid Arthritis

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Background/Purpose: Patients with rheumatoid arthritis (RA) are at elevated risk for cardiovascular (CV) disease. Patients using tocilizumab (TCZ) may experience increased serum lipid levels. It is not known whether TCZ affects the risk for CV events relative to tumor necrosis factor inhibitors (TNFi) in patients with RA.

Methods: To examine comparative CV safety, we conducted a cohort study of RA patients who newly started TCZ or a TNFi using claims data from Medicare (2010-2013) or commercial health insurance (IMS Health, 2011-2014; MarketScan, 2011-June 2015). All patients were required to have previously used a different TNFi, abatacept, or tofacitinib. The primary outcome was a composite CV end point of nonfatal myocardial infarction and stroke based on a validated claims-based algorithm of high specificity (positive predictive value >94%). For the primary as-treated analysis, follow-up time started the day after TCZ or TNFi initiation and ended on treatment discontinuation plus 30 days, outcome occurrence, disenrollment, death, or end of the study. To control for >90 potential confounders including demographics, previous DMARD use, CV comorbidities, medications, and health care use, TCZ starters were propensity score (PS) matched to TNFi starters, with a variable ratio of 1:3 within each database. We estimated the incidence rate (IR) of composite CV events in the TCZ group compared with the TNFi group separately in each database. Hazard ratios (HRs) from the three PS-matched cohorts were pooled by an inverse variance-weighted, fixed-effects model.

Results: We included 8790 TCZ starters PS matched to 17,821 TNFi starters in all three databases. Mean age of the patients was 72 years in Medicare, 51 in IMS, and 53 in MarketScan. More than 80% of patients were women. At baseline, 72% (Medicare), 73% (IMS), and 66% (MarketScan) of patients used methotrexate. In the as-treated analysis, the median follow-up time varied between 176 days (Medicare) to 205 days (MarketScan) in the TCZ group and 206 days (Medicare) to 231 days (MarketScan) in the TNFi group. Across the three databases, 35 CV events occurred in the TCZ group and 80 occurred in the TNFi group. The IR of composite CV events per 100 person-years ranged from 0.31 (MarketScan) to 0.87 (Medicare) in the TCZ group and from 0.31 (MarketScan) to 1.09 (Medicare) in the TNFi group. The risk for CV events was similar between TCZ and TNFi users across all three databases (Table), with a pooled HR of 0.90 (95% CI, 0.60-1.36) from the as-treated analysis. Adjustment for a potential overlap between the commercial cohorts (IMS and MarketScan) yielded consistent results.

Conclusion: This large multi-database cohort study found no increase in the rate of CV events in patients with RA who switched from a biologic agent to either TCZ or a different TNFi.

Table. HR (95% CI) for composite CV events in TCZ starters versus TNF inhibitors: a 1:3 variable ratio PS-matched analysis

Database	Medicare	IMS	MarketScan	Pooled[a]
As treated	0.76 (0.42, 1.37)	1.11 (0.49, 2.53)	1.01 (0.45, 2.29)	0.90 (0.60, 1.36)
ITT up to 180 days	0.49 (0.21, 1.14)	0.90 (0.32, 2.51)	0.76 (0.26, 2.23)	0.66 (0.38, 1.16)
ITT up to 365 days	0.80 (0.47, 1.38)	0.94 (0.45, 1.95)	0.85 (0.41, 1.76)	0.85 (0.58, 1.23)

CI, confidence interval; DMARD, disease-modifying antirheumatic drug; ITT, intention-to-treat (exposure status at cohort entry was carried forward until the end of follow-up).

The TNF inhibitor group was the reference group.

PS models included >90 covariates, among them demographics, previous DMARD use, CV comorbidities, medications, and health care use.

[a]HRs were pooled by an inverse variance-weighted, fixed-effects model.

Disclosure: S. C. Kim, Genentech, BMS, Pfizer, AstraZeneca, Eli Lilly, 2; **D. H. Solomon**, Genentech/Roche, AstraZeneca, BMS, Amgen, Pfizer, Eli Lilly, Corrona, 2,UpToDate, 7; **J. R. Rogers**, Genentech, Lilly, Novartis, 2; **S. Gale**, Genentech/Roche, 1,Genentech/Roche, 3; **M. Klearman**, Genentech/Roche, 1,Genentech/Roche, 3; **K. Sarsour**, Genentech/Roche, 1,Genentech/Roche, 3; **S. Schneeweiss**, Aetion, 1,Genentech, Boehringer Ingelheim, Bayer, 2.

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Abstract Number: 2612

Sero-Positivity for Rheumatoid Factor Is an Independent Predictor for Achievement of Good EULAR Response at 24 Weeks in ACPA Positive Rheumatoid Arthritis Patients Treated with Abatacept: Results from Japanese Multicenter Registry

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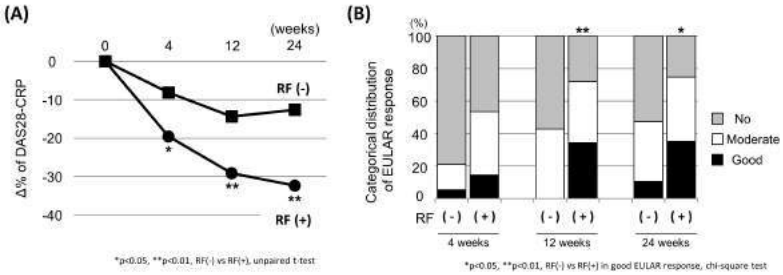
Background/Purpose: Abatacept is a new class of biologic agent for the treatment of rheumatoid arthritis (RA) that inhibits T cell activation by binding to CD80/86. Although some clinicians feel that the rapidity of treatment response of abatacept is slower than that of tumor necrosis factor (TNF)-inhibitors, some patients can respond to abatacept treatment quite rapidly. Recently, some reports have been published regarding the positive association between sero-positivity for anti-citrullinated protein antibody (ACPA) and clinical efficacy of abatacept in RA patients. The aim of this study was to demonstrate the effect of double-seropositivity for ACPA and rheumatoid factor (RF) on the rapidity of treatment response of abatacept using data from a Japanese multicenter registry system for RA patients treated with biologic agents.

Methods: Participants were selected from the consecutive 508 RA patients treated with abatacept who were registered in the Tsurumai Biologics Communication Registry (TBCR). We excluded the patients with previous biologic agent treatment history since it has been already reported as an independent factor affecting the clinical efficacy of abatacept. A total of 146 biologics-naïve and ACPA positive patients with baseline data of RF were included in this study. We compared the proportion of patients that achieved good EULAR response at 24 weeks between the RF negative and RF positive (>20 U/ml) group within the ACPA positive patients. We defined the ACPA positive as >13.5 U/ml of anti-CCP antibody (3 times cutoff value) to ensure that the positivity was reasonably sure.

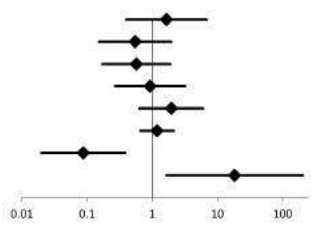
Results: In the ACPA positive patients, the percent decreasing of DAS28-CRP scores in the RF positive group were significantly greater than those in the RF negative group at all time points (Figure A, e.g. -32.3 vs -12.6% at 24 weeks, $p < 0.01$). The proportion of patients that achieved the good EULAR response was significantly higher in the RA positive group at 12 and 24 weeks (Figure B). Multivariate logistic regression analysis (adjusted with gender, age, Steinbrockerfs stage, concomitant MTX and oral steroid usage, and DAS28-CRP score at baseline) revealed that the RF positivity, along with the modified HAQ score at baseline, was the independent predictor for the achievement of good EULAR response at 24 weeks (Figure C).

Conclusion: We clearly demonstrated that the positive association of the double-seropositivity for ACPA and RF with the rapid and good clinical response for abatacept in the biologics-naïve RA patients. This new clinical evidence regarding the effect of double-seropositivity is the valuable real-world data for the prediction of clinical efficacy of abatacept in daily clinical practice.



(C)

Multivariate analysis	adjusted OR (95% CI)	p-value
Male	1.665 (0.405-6.842)	0.48
Age, < 65 years	0.552 (0.154-1.978)	0.361
Stage 1 or 2	0.573 (0.173-1.898)	0.362
concomitant MTX use	0.934 (0.272-3.201)	0.913
concomitant PSL use	1.959 (0.642-5.974)	0.237
DAS28 score @baseline	1.191 (0.660-2.149)	0.561
mHAQ score @baseline	**0.088 (0.020-0.387)**	***0.001***
RF positive	**18.379 (1.650-204.748)**	***0.018***



Disclosure: **N. Takahashi**, Takeda Pharma Co., 8,Janssen Pharmaceutica Product, L.P., 8,Astellas Pharma Co., 8,Tanabe Mitsubishi Pharma Co., 8,Eisai, 8,Bristol-Myers Squibb, 8,Pfizer Inc, 8,Abbvie Japan, 8,UCB Japan, 8,Chugai, 8; **T. Kojima**, Takeda Pharma Co., 8,Janssen Pharmaceutica Product, L.P., 8,Astellas Pharma Co., 8,Matsubishi Tanabe Pharma Co., 8,Pfizer Inc, 8,UCB Japan, 8,Bristol-Myers Squibb, 8,Eisai, 8,Abbvie Japan, 8,Chugai, 8; **S. Asai**, Takeda Pharma Co., 8,Janssen Pharmaceutica Product, L.P., 8,Astellas Pharma Co., 8,Tanabe Mitsubishi Pharma Co., 8,Eisai, 8,Bristol-Myers Squibb, 8,Chugai, 8,Pfizer Inc, 8,Abbvie Japan, 8,UCB Japan, 8; **N. Ishiguro**, Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, 2,Takeda, Mitsubishi-Tanabe, Astellas, Chugai, Abbott, Bristol-Myers Squibb, Eisai, Janssen, Kaken, Pfizer, Taisho-Toyama, Otsuka, 8.

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Abstract Number: 2613

Seropositivity for RF or ACPA Predicts Long Term Drug Retention with Rituximab, but Not with Abatacept and Tocilizumab : Long-Term Registry Data in 4498 Patients with Rheumatoid Arthritis

Jacques-Eric Gottenberg[1], Jacques Morel[2], Arnaud Constantin[3], Thomas Bardin[4], Alain G. Cantagrel[5], Bernard Combe[6], Maxime Dougados[7], Rene-Marc Flipo[8], Alain Saraux[9], Thierry Schaeverbeke[10], Jean Sibilia[11], Martin Soubrier[12], Olivier Vittecoq[13], Elodie Perrodeau[14], Philippe Ravaud[15], Xavier Mariette[16] and on behalf of the French Society of Rheumatology and of all the investigators participating to the AIR, ORA and REGATE registries, [1]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [2]Rheumatology, Department of Rheumatology, Montpellier University Hospital, Montpellier, France, [3]Rheumatology, CHU Purpan - Hopital Pierre-Paul Riquet, Toulouse, France, [4]Clinique de Rhumatologie, Hopital Lariboisiere, Paris Cedex 10, France, [5]Rheumatology, Centre Hospitalier Universitaire, Toulouse Purpan, Toulouse, France, [6]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [7]Rheumatology, Paris Descartes University, Paris, France, [8]Rheumatology, University Hospital, Lille, France, [9]Rheumatology, Brest University Hospital, Brest, France, [10]Rheumatology, CHU Bordeaux, Bordeaux, France, [11]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [12]Rheumatology, Department of Rheumatology, CHU Gabriel Montpied, Clermont-Ferrand, France, [13]Rheumatology, Rouen University Hospital &INSERM U905, Rouen, France, [14]Epidemiology, Hopital Hotel Dieu, Paris Descartes University, Paris, France, [15]Epidemiologist, PARIS, France, [16]Rheumatology, Rheumatology department, Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France
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Background/Purpose: Seropositivity for RF or ACPA is associated with a better short-term effectiveness and drug retention of abatacept (ABA) and rituximab (RTX). Data are very limited concerning the association with long term retention in real life and concerning the association between seropositivity and effectiveness of tocilizumab (TCZ).

Methods: This was a pre-specified sub-group analysis of a multicenter open-label observational study of patients with RA according to 1987 ACR criteria who were initiating RTX, ABA, or TCZ treatment and enrolled in three French Society of Rheumatology prospective registries (AIR for RTX, ORA for ABA, and REGATE for TCZ). Seropositivity was defined by positivity of either RF or anti-CCP. We used a propensity-score approach to adjust for differences in observed factors that might affect both treatment assignment and outcome.

Results: Data on seropositivity were available in 3540 patients out of 4498 patients(87.4%). 72, 76.7 and 80.9% of patients respectively treated with ABA, RTX and TCZ, had RF or ACPA. 3507 patients had a follow-up at 24 months for a total follow-up of 18898 patient-years (RTX, 10545; ABA, 4912; and TCZ, 3441). - Effect of seropositivity on the effectiveness of each drug Drug retention without failure of RTX at 2 years was 68.7[66.4; 71.0]% in seropositive patients and 51.9 [45.6;59.1]% in seronegative patients, HR of discontinuation of 0.56 [0.46;0.69], p< 0.001. Drug retention without failure of RTX at 5 years was 51.0[48.5; 53.5]% in seropositive patients and 30.9 [25.2;38.0]% in seronegative, HR of discontinuation of 0.57 [0.47;0.69], p< 0.001. Drug retention without failure of ABA at 2 years was 41.5[38.0; 45.2]% in seropositive patients and 40.0 [32.8;48.8]% in seronegative patients, HR of discontinuation of 0.92 [0.77;1.11], p=0.41. Drug retention without failure of ABA at 5 years was 22.4 [19.5; 25.7]% in seropositive

patients and 17.0 [11.7;24.7]% in seronegative, HR of discontinuation of 0.89 [0.75;1.04], p=0.17. Drug retention without failure of TCZ at 2 years was 63.4[60.4; 66.5]% in seropositive patients and 62.2 [54.5;71.1]% in seronegative patients, HR of discontinuation of 0.99 [0.73;1.33], p=0.93. No patient has reached the 5 year follow- up visit yet. - Impact of seropositivity on the comparative effectiveness between ABA, RTX and TCZ At 2 years, drug retention without failure among seropositive patients was significantly greater with RTX and TCZ than ABA (hazard ratio 1.99 [95% CI: 1.56;2.52], and 1.72 [95% CI: 1.22;2.42], respectively), with no difference between RTX and TCZ. At 2 years, drug retention without failure among seronegative patients was not significantly different between RTX and ABA (HR 1.39 [0.89; 2.17]). Drug retention without failure among seronegative patients was higher with TCZ than ABA (hazard ratio 1.93 [95% CI: 1.22;3.05], with no difference between RTX and TCZ. At 5 years, drug retention without failure among seropositive patients was significantly greater with RTX than ABA (HR 2.08 [95% CI: 1.75;2.48]. No significant difference was observed in seronegative patients.

Conclusion: Seropositivity for RF or ACPA has no impact on long-term retention for TCZ and ABA, and results in a marked improvement of long-term retention for RTX.

Disclosure: J. E. Gottenberg, Abbvie, BMS, Gsk, Janssen, Lilly, MSD, Pfizer, Roche, UCB, 5; **J. Morel**, None; **A. Constantin**, None; **T. Bardin**, None; **A. G. Cantagrel**, None; **B. Combe**, None; **M. Dougados**, Pfizer, AbbVie, Celgene, Eli Lilly, Novartis, Roche, and Sanofi-Aventis, 5,Pfizer, AbbVie, UCB, Merck, 8; **R. M. Flipo**, None; **A. Saraux**, None; **T. Schaeverbeke**, None; **J. Sibilia**, None; **M. Soubrier**, None; **O. Vittecoq**, None; **E. Perrodeau**, None; **P. Ravaud**, None; **X. Mariette**, None.

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Abstract Number: 2614

Similar Rates of Death, Serious Infections, Cancers, Major Cardiovascular Events in Patients Treated with Abatacept, Rituximab and Tocilizumab: Long-Term Registry Data in 4498 Patients with Rheumatoid Arthritis

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Background/Purpose: Assessment of safety in randomized controlled trials is limited by trial durations, and selection of patients with few or now comorbidities. Such limitations can be overcome by long term registry studies. We aimed to compare the safety of abatacept,

rituximab and tocilizumab in common practice.

Methods: This was a multicenter open-label observational study of patients with RA according to 1987 American College of Rheumatology criteria who were initiating rituximab, abatacept, or tocilizumab treatment and enrolled in three French Society of Rheumatology prospective registries (AIR for rituximab, ORA for abatacept, and REGATE for tocilizumab). Severe adverse events (death, serious infection, major adverse cardiovascular events [MACEs], and cancer) were validated by chart review by three experts. A serious infection was defined as an infection occurring during treatment with abatacept or tocilizumab, during the three months after withdrawal, or during the 12 months after a rituximab infusion and requiring hospitalization and/or intravenous antibiotics and/or resulting in death. MACEs were defined as death of cardiovascular origin, stroke, or myocardial infarction. MACEs and cancers were considered in the analysis regardless of their time of occurrence, even after registry drug discontinuation. A propensity-score approach was used to adjust the comparison between drugs.

Results: Among the 4498 enrolled patients (median disease duration: 11 [5-18] years; history of cancer: 8.9% of patients; previous serious or recurrent infection: 27.3%), 3507 had a follow-up at 24 months for a total follow-up of 18898 patient-years (rituximab, 10545; abatacept, 4912; and tocilizumab, 3441). At month 24, serious infections occurred in 5.2, 4.6, and 4.9/100 patient/years in patients treated with rituximab, abatacept, and tocilizumab, respectively (abatacept versus rituximab: IRR of 0.79 [0.49; 1.27], p= 0.33; tocilizumab versus rituximab: IRR of 0.93 [0.55; 1.57], p= 0.79; abatacept versus tocilizumab: IRR of 0.85 [0.47; 1.54], p= 0.59). At month 24, MACEs occurred in 0.56, 0.58 and 0.44/100 patient-years in patients treated with rituximab, abatacept, and tocilizumab, respectively (abatacept versus rituximab: IRR of 1.07 [0.54; 2.13], p= 0.84; tocilizumab versus rituximab: IRR of 0.81 [0.30; 2.17], p= 0.67; abatacept versus tocilizumab: IRR of 1.33 [0.47; 3.75], p= 0.59). At month 24, cancers occurred in 1.2, 1.4 and 1.1/100 patient-years in patients treated with rituximab, abatacept, and tocilizumab, respectively (abatacept versus rituximab: IRR of 0.80 [0.41; 1.56], p= 0.51; tocilizumab versus rituximab: IRR of 0.94 [0.43; 2.04], p= 0.87; abatacept versus tocilizumab: IRR of 0.85 [0.39; 1.88], p= 0.69). At month 24, deaths occurred in 1.3, 1.6 and 0.3/100 patient-years in patients treated with rituximab, abatacept, and tocilizumab, respectively (abatacept versus rituximab: IRR of 1.83 [0.87; 3.84], p= 0.11; tocilizumab versus rituximab: IRR of 0.59 [0.18; 2.01], p= 0.40; abatacept versus tocilizumab: IRR of 3.08 [0.78; 12.23], p= 0.11).

Conclusion: In patients with longstanding RA and comorbidities treated in common practice, long term safety seems similar in patients treated with abatacept, rituximab or tocilizumab.

Disclosure: J. E. Gottenberg, Abbvie, BMS, Gsk, Janssen, Lilly, MSD, Pfizer, Roche, UCB, 5; **J. Morel**, None; **A. Constantin**, None; **T. Bardin**, None; **A. Cantagrel**, None; **B. Combe**, None; **M. Dougados**, Pfizer, AbbVie, Celgene, Eli Lilly, Novartis, Roche, and Sanofi-Aventis, 5,Pfizer, AbbVie, UCB, Merck, 8; **R. M. Flipo**, None; **A. Saraux**, None; **T. Schaeverbeke**, None; **J. Sibilia**, None; **M. Soubrier**, None; **O. Vittecoq**, None; **E. Perrodeau**, None; **P. Ravaud**, None; **X. Mariette**, None.

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Abstract Number: 2615

Effect of Sarilumab on Circulating Biomarkers of Bone and Joint Destruction in Patients with Rheumatoid Arthritis with Previous Inadequate Response to Tumor Necrosis Factor Inhibitors

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Background/Purpose: Patients with RA develop bone and joint damage due to chronic synovial inflammation that is mediated by specific cytokines.[1] Cytokines (eg, IL-6) recruit activated inflammatory cells and fibroblast-like synoviocytes to generate a pannus that

results in bone resorption and cartilage destruction. Here we describe that blockade of IL-6 signaling by sarilumab, a human mAb blocking the IL-6Rα, decreased circulating markers associated with the pannus in adults with active, moderate-to-severe RA and inadequate response to TNF inhibitors (TNFi) from the phase 3 TARGET study (NCT01709578).

Methods: Sera were analyzed using ELISAs at baseline and posttreatment (through week 24) from a subset of patients who received placebo or sarilumab subcutaneously (150 or 200 mg every 2 weeks [q2w]) plus conventional synthetic DMARDs (csDMARDs; n=97/group). Percent change from baseline in biomarkers was analyzed using nonparametric methods (ANOVA-type or rank-based analysis of covariance) to evaluate differences between treatment groups at each time point. For exploratory purposes, percent changes from baseline in biomarkers were also compared, separately by treatment group, between ACR50 responders and nonresponders at week 24 using similar methods. *P* values <0.05 were considered significant.

Results: Both doses of sarilumab significantly decreased markers of tissue destruction, synovial inflammation, and bone resorption relative to placebo as early as week 2 for several biomarkers assessed, with greater reductions observed at week 24 (Table). For several biomarkers, numerically greater changes from baseline were observed following treatment with sarilumab 200 mg q2w vs sarilumab 150 mg q2w. Numerical increases observed in osteocalcin (OC) after treatment with sarilumab were not statistically significant compared with placebo. When changes from baseline in biomarkers were examined according to ACR50 response at week 24, larger decreases in MMP-3 and increases in OC were observed in patients achieving ACR50 compared with those who did not achieve ACR50; these changes were significant for the sarilumab 150 mg q2w group (Table). Other biomarkers suppressed by sarilumab treatment (eg, chemokine [C-X-C motif] ligand 13 and RANK ligand) did not significantly differ by ACR50 response (not shown).

Conclusion: Sarilumab significantly reduced biomarkers of bone resorption and joint damage in patients with RA and inadequate response to TNFi. Differences in some biomarker levels observed between ACR50 responders and nonresponders suggest that modulation of these biomarkers may contribute to a decrease in disease activity. **Reference: 1.** Srirangan et al. *Ther Adv Musculoskelet Dis*. 2010;2:247-256.

Table. Posttreatment Changes in Serum Concentrations of Circulating Biomarkers in Patients With RA From TARGET

	Week 2[a]			Week 24[a]		
	Placebo + csDMARDs (n=97)	Sarilumab 150 mg q2w + csDMARDs (n=97)	Sarilumab 200 mg q2w + csDMARDs (n=97)	Placebo + csDMARDs (n=97)	Sarilumab 150 mg q2w + csDMARDs (n=97)	Sarilumab 200 mg q2w + csDMARDs (n=97)
Median percent change from baseline in biomarker concentration[b]						
Acute-phase reactant						
CRP[c]	9.2	-10.2[§]	-67.5[§]	13.6	-48.6[§]	-85.0[§]
Marker of tissue destruction						
C1M[c]	-6.6	-16.5*	-45.8**	-7.6	-46.1**	-59.5**
Markers of synovial inflammation						
C3M[c]	-1.4	-9.7**	-21.9**	-7.7	-20.8**	-35.1**
MMP-3[c]	-8.0	-5.8	-1.7	-8.5	-34.6**	-48.5**
Markers of bone resorption						
Total RANKL[c]	---	---	---	-0.4	-20.0**	-20.2**
OPG[c]	---	---	---	-2.4	0.1	-5.2
Marker of bone formation						
Osteocalcin[d]	---	---	---	0.8	5.1	8.0
Marker of lymphoid RA synovial phenotype						
CXCL13[c]	2.3	-13.2**	-16.0**	-7.1	-28.5**	-38.1**
Marker of myeloid RA synovial phenotype						
sICAM-1[d]	-0.8	-1.8	-2.4	---	---	---

Median percent change from baseline in biomarker concentration at week 24 in ACR50 responder/nonresponder patients[e]				
	Sarilumab 150 mg q2w + csDMARDs (n=97)		Sarilumab 200 mg q2w + csDMARDs (n=97)	
	ACR50 responder	ACR50 nonresponder	ACR50 responder	AC50 nonresponder
CRP	-88.4	-77.5	-97.1[†]	-94.6
MMP-3	-49.3[‡]	-28.6	-49.4	-43.5
Osteocalcin	8.3[†]	3.1	11.7	2.7

ANCOVA, analysis of covariance; ANOVA, analysis of variance; C1M, collagen type I MMP-cleaved fragment; C3M, collagen type III MMP-cleaved fragment; csDMARD, conventional synthetic DMARD; CXCL13, chemokine (C-X-C motif) ligand 13; OPG,

osteoprotegerin; q2w, every 2 weeks; RANKL, RANK ligand; sICAM-1, soluble intercellular adhesion molecule 1. *Adjusted $P<0.05$ and ≥ 0.01 vs placebo. **Adjusted $P<0.01$ vs placebo. †Unadjusted $P<0.05$ and ≥ 0.01 vs nonresponders. ‡Unadjusted $P<0.01$ vs nonresponders. §Unadjusted $P<0.01$ vs placebo. [a]Patient numbers reflect maximum number of patients included in each group. Fewer samples may have been analyzed at a given time point because of missing or non-evaluable samples. [b]The Benjamini-Hochberg procedure was used to correct for multiplicity and control false discovery rate using all comparisons for most biomarkers tested; unadjusted *P* values are presented for CRP. Note that only selected comparisons are shown here. [c]Percent change from baseline was analyzed using ANOVA-type method, and adjusted *P* values of the comparisons vs placebo are reported. [d]Percent change from baseline was analyzed using rank-based ANCOVA. [e]Change in biomarker concentrations in ACR50 responders vs nonresponders was compared in active treatment groups at week 24 using ANOVA-type method, separately by group. Unadjusted *P* values are reported.

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Abstract Number: 2616

The JAK1-Selective Inhibitor Filgotinib Displays an Anti-Inflammatory Biomarker Signature in Rheumatoid Arthritis Patients

Peter C. Taylor[1], R Westhovens[2], Luc Meuleners[3], Birgen Meuleman[4], Yang Pan[5], Veerle Vyncke[3], Annegret Van der Aa[3], Pille Harrison[3], Chantal Tasset[3] and René Galien[6], [1]Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom, [2]Rheumatology, University Hospitals Leuven, Leuven, Belgium, [3]Galapagos NV, Mechelen, Belgium, [4]2Bridge, Turnhout, Belgium, [5]Gilead Sciences, Foster City, CA, [6]102 Avenue Gaston Roussel, Galapagos SASU, Romainville, France

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Background/Purpose : The potent and selective JAK1 inhibitor filgotinib (GLPG0634, GS-6034) has been evaluated in a 24-week phase 2B study in combination with methotrexate (MTX) in active rheumatoid arthritis (RA) patients with inadequate response to MTX (DARWIN 1 study). Significant improvement in signs and symptoms was observed after 12 weeks and efficacy was sustained or improved up to Week 24 with a safety profile overall acceptable. In order to gain insight in filgotinib mode of action in RA patients, we analysed the impact of this treatment on serum cytokines.

Methods : Patients with active RA on stable dose of MTX were randomized 1:1:1:1:1:1:1 in a double blind manner to receive either placebo (PBO) or one of three doses of filgotinib (50mg, 100mg or 200mg) as once (qd) or twice daily (bid) regimen for 24 weeks (DARWIN 1 study). At baseline, Week 4 and Week 12, sera were collected from all patients and analysed using the 18-plex panel kit from Merck-Millipore (HSTCMAG-28SK) on BioPLEX-200 apparatus to measure concentration of GM-CSF, IFNγ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17A, IL-21, IL-23, MIP-1α, MIP-1β and TNF-α. Data are presented as means of changes from the baseline.

Results : Following treatment with filgotinib, IL-6 was the cytokine showing greatest decreases in concentration at all time points and doses analysed. The pro-inflammatory cytokine IL-1β was also decreased at Week 12 at higher doses confirming the potent anti-inflammatory activity of filgotinib. Of interest, serum concentrations of IL-2 and IFN-γ, two T_H1 cell markers, reduced significantly at Week 12 at the higher doses used, suggesting that filgotinib may impact the promotion of this cell subset. Notably, this is consistent with the Week 4 decrease in IL-12 concentration, a cytokine that, together with IFN-γ, promotes T_H1 cell expansion. The T_H2-related cytokine IL-13 was decreased at Week 12 at all doses analysed, in contrast to IL-4 and IL-5 that were not impacted by filgotinib treatment. Of interest, concentration of IL-21 (a cytokine produced by T_H17 cells) was decreased after 12 weeks of treatment with the higher dose of filgotinib. Higher doses of filgotinib also reduced levels of the B and T cell development cytokine, IL-7. Finally, MIP-1β concentration was decreased by high doses of filgotinib after 4 weeks of treatment, in line with the effect observed on GM-CSF at all

time points.

Conclusion: Treatment of RA patients with filgotinib led to the decrease of multiple cytokines involved in various aspects of the inflammatory process. Reductions in IL-6 and IL-1β establish the anti-inflammatory activity of filgotinib. Treatment effects on IL-2, IL-6, IL-7, IL-12 and IFN-γ that play a key role in $CD4^+$ T-cell differentiation and expansion further highlight the anti-inflammatory effects of filgotinib, likely by limiting the promotion of T_H1, T_H2 and T_H17 cells. Finally, effects on innate immunity, through MIP-1β and GM-CSF decrease, were also mediated by filgotinib. Taken together, these data further demonstrate the anti-inflammatory activity of filgotinib in line with its efficacy observed in RA patients.

Disclosure: P. C. Taylor, Galapagos, Pfizer, Eli Lilly, UCB, GSK, 5; **R. Westhovens**, Galapagos NV, Roche, BMS, 5; **L. Meuleners**, Galapagos NV, 3; **B. Meuleman**, 2Bridge, 3; **Y. Pan**, Gilead Sciences, 3; **V. Vyncke**, Galapagos NV, 3; **A. Van der Aa**, Galapagos NV, 3; **P. Harrison**, Galapagos NV, 3; **C. Tasset**, Galapagos NV, 3; **R. Galien**, Galapagos SASU, 3.

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Abstract Number: 2617

Economic Burden of Non-Responders to Biologic DMARD Treatments in Rheumatoid Arthritis

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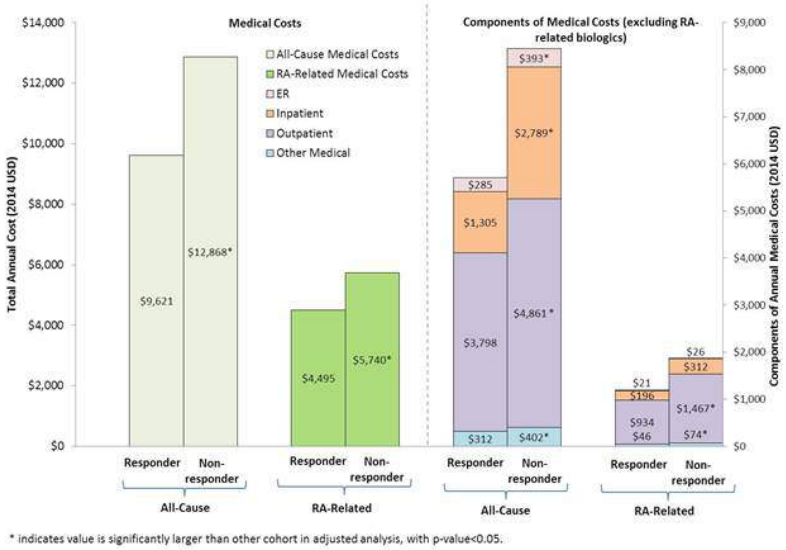
Background/Purpose: Biologic agents are effective in treating patients with rheumatoid arthritis (RA); however, some patients either fail to respond or lose response over time. This study assessed the direct and indirect economic burden among RA patients who had inadequate responses to initial biologic therapy compared with treatment responders.

Methods: Data from 1/1/1998-3/31/2014 were used from a large de-identified, privately insured claims database, which included work loss from a subset of reporting companies. Study sample consisted of patients with ≥1 claim for a biologic DMARD (bDMARD) approved for treatment of RA and ≥2 RA diagnoses in the claim history, with continuous eligibility for 6 months before (baseline) and 12 months after (study period) the date of the first bDMARD claim (index date). Patients were classified as responders and non-responders based on a validated, claim-based algorithm. All-cause and RA-related healthcare resource use and costs, work loss, and indirect costs during the study period were compared for bDMARD responders vs. non-responders. Multivariable regressions were used to adjust for baseline characteristics. As different treatments were approved over time and the pattern of costs and resources use may have changed, subgroup analyses of resource use and direct costs were conducted for patients with index dates in 1998-2007 and in 2008-2013.

Results: This study included 7,540 eligible RA patients, with 2,527 bDMARD responders and 5,013 non-responders; 407 responders and 723 non-responders had work loss data. Compared with responders, non-responders had significantly higher adjusted rates of resource use, including inpatient admissions (incidence rate ratio [IRR]=1.94), outpatient visits (IRR=1.19), emergency department visits (IRR=1.53), and number of prescription fills (IRR=1.09) (all p-values < 0.001). Non-responders had significantly higher adjusted all-cause and RA-related medical costs compared with responders (all-cause: $12,868 vs. $9,621, RA-related: $5,740 vs. $4,495, adjusted p-values<0.001) (Figure 1). Results for subgroup analyses of resource use and direct costs by index date were consistent with the full sample. Non-responders also had significantly more days of work loss compared with responders (22.1 vs. 16.7 days, IRR=1.21, adjusted p-value=0.007) and higher indirect costs ($3,548 vs. $2,890, adjusted p-value = 0.002).

Conclusion: Two-thirds of RA patients had inadequate responses to their initial bDMARD. These non-responders faced a significantly higher burden, including increased healthcare resource use, direct medical costs, and work loss compared to responders. **Figure 1.**



Medical costs of biologic non-responders vs. responders

Disclosure: V. Strand, AbbVie, 5; **N. Tundia**, AbbVie, 1,AbbVie, 3; **Y. Song**, Analysis Group, Inc, 3; **D. Macaulay**, Analysis Group, Inc, 3; **M. Fuldeore**, AbbVie, 1,AbbVie, 3.

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Abstract Number: 2618

Risk Factors of Severe Infections in Patients with Rheumatoid Arthritis Treated with Tocilizumab in the French Registry Regate (REGISTRY –ROACTEMRA)

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Background/Purpose: Observational studies have already reported the risk of serious infections in rheumatoid arthritis (RA) treated with tocilizumab but in limited samples. The aim of this study was to investigate the predictive risk factors of serious infections in the largest European registry of patients treated with tocilizumab for RA.

Methods: 1491 RA patients included in the French REGistry –RoAcTEmra (REGATE) were analysed to calculate incidence rate of severe infections and to identify independent factors associated with severe infections. Kaplan -Meier method was used to assess probability of remaining severe infection-free. Cox models were performed to identify independent factors associated with severe infections. Variables showing bivariate association with the dependent variable with a P value less than 0.15 were entered into the multivariate model. Multiple imputation was used to compensate missing data in some variables. A P value <0.05 was considered statistically significant.

Results: Exposure was 2,606 person-years (mean age±SD, 56.6±13.6). 125 serious infections occurred in 122 patients (4.7/100 patient-years). Most frequent infections were lung and respiratory tract and skin/soft tissue in 35 (28%) and 32(26%) cases respectively. Three deaths were related to one septic chock secondary to pyelonephritis, one pneumocystosis, and one Haemophilus influenzae infection. Favourable outcome was observed in most cases. Fouropportunistic infections were reported: 1 Pneumocystosis, 1 tuberculosis, 1 Haemophilus influenzae infection and 1infection related to Klebsiella pneumoniae. A pathogen was identified in 41 cases. TCZ was definitively stopped for 35patients. The incidence of serious infection was stable over the first 3 years of follow-up in the registry. Bivariate analysisidentified initial ACPA positivity as the only factor associated with a lower risk of severe infection (HR 0.55 CI95% 0.35-0.86). Factors significantly associated with a risk of severe infections were DAS28-CRP, DAS28-ESR, and number ofpolymorphonuclear neutrophils (PMN) at baseline. Initial PMN above 4.5 G/L (HR 1.62 CI95% 1.06-2.5, p=0.02) and negative ACPA (HR 0.63 CI95% 0.41-0.95, p=0.03) remains significantly associated with severe infections in multivariate analysis after imputation for missing data.

Conclusion: The rate of severe infections in current practice is similar to that reported in clinical trials. High PMN above 4.5 G/L at baseline and negative ACPA are predictive factors of serious infection requiring in this case a tighter surveillance.

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Abstract Number: 2619

Sustained Suppression of Peripheral Biomarkers By Mavrilimumab but Not Golimumab in Anti-Tumor Necrosis Factor-Inadequate Responders: An Exploratory Analysis in the Phase IIb Earth Explorer 2 Clinical Trial

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Background/Purpose: Treatment of rheumatoid arthritis (RA) patients by anti-tumour necrosis factors (anti-TNFs), such as golimumab, has improved patient outcomes. However, unmet therapeutic needs exist for a substantial proportion of patients. Mavrilimumab is a fully human monoclonal antibody which inhibits the granulocyte-macrophage colony-stimulating factor receptor α (GM–CSFR-α). Recently, a Phase IIb clinical trial has been completed to evaluate the efficacy and safety of mavrilimumab and golimumab in both disease-modifying antirheumatic drug (DMARD)-inadequate responder (IR) and anti-tumor necrosis factor-inadequate responders (anti-TNF-IR) patients (EARTH EXPLORER 2, NCT01715896). Our current study aims to assess peripheral biomarkers and pathophysiological pathways modulated by mavrilimumab and golimumab in RA patients.

Methods: The Phase IIb trial enrolled patients with active RA (28-joint Disease Activity Score [DAS28]-C-reactive protein/erythrocyte sedimentation rate ≥3.2), ≥4 swollen joints, and inadequate response to ≥1 DMARDs and/or 1-2 anti-TNFs. Patients were randomized (1:1) to receive subcutaneous mavrilimumab 100 mg (n=70) every other week (Q2W) or golimumab 50 mg (n=68) Q2W alternating with

placebo, in combination with methotrexate (7.5-25.0 mg/week) for 24 weeks. Serum levels of 18 RA-associated proteins and 3 protease-derived protein fragments were measured in 71 DMARD-IR and 61 anti-TNF-IR patients at baseline and 4 time points post-administration. Transcriptome sequencing was used to measure gene expression changes in whole blood of RA patients at baseline and day 169 post-administration.

Results: Serum levels of CCL22 (MDC) and CCL17 (TARC) were suppressed by mavrilimumab but not golimumab, while CXCL13 and ICAM1 were suppressed by golimumab but not mavrilimumab. Those four proteins may be specific pharmacodynamic markers for the two biologics respectively. Both mavrilimumab and golimumab induced early and sustained suppression of multiple protein markers in DMARD-IR patients, including CRP, SAA, MMP1, MMP3, IL6, VEGF, IL2R, and CD163. However, golimumab-induced early changes rapidly returned towards baseline levels in anti-TNF-IR patients, while mavrilimumab-induced changes were maintained through day 169. Similarly, mavrilimumab administration was associated with durable suppression of extracellular matrix markers, C1M, C3M, and P4NP7S whilst golimumab only induced a transient change of the three markers in anti-TNF-IR patients. Furthermore, RNA sequencing results demonstrated significant regulation of 1547 transcripts at day 169 after mavrilimumab administration while golimumab had no impact on gene expression in anti-TNF-IR patients. In contrast, significant changes of 1042 and 2058 transcripts were observed in DMARD-IR patients at day 169 post-treatment of mavrilimumab and golimumab respectively.

Conclusion: Our study demonstrated a sustained differential suppression of peripheral disease markers by mavrilimumab but not golimumab in anti-TNF-IR patients, suggesting the potential of greater long-term disease control by mavrilimumab than golimumab in this population of RA patients.

Disclosure: X. Guo, AstraZeneca, 1,AstraZeneca, 3; **S. Wang**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **A. C. Bay-Jensen**, Nordic Bioscience Diagnostic, 3; **M. A. Karsdal**, Nordic Bioscience Diagnostic, 3; **A. Godwood**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **M. Albulescu**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **D. Close**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **P. C. Ryan**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **L. Roskos**, AstraZeneca, 1,AstraZeneca/MedImmune, 3; **W. White**, AstraZeneca, 1,AstraZeneca/MedImmune, 3.

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Abstract Number: 2620

Retrospective Analysis for Determining the Signs and Symptoms of Infections before They Become Serious in Tocilizumab-Treated RA Patients Using a Postmarketing Adverse Events Reporting Database

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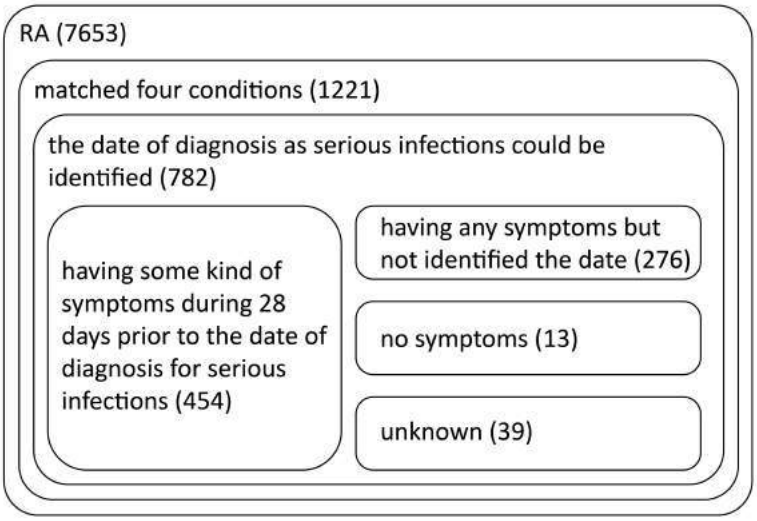
Background/Purpose: Given that tocilizumab (TCZ) directly inhibits IL-6 signaling and strongly suppresses the inflammatory reaction, there is concern that the signs and symptoms associated with infection are not easily detected in the early phase of infection during TCZ treatment. The aim of this study was to identify initial symptoms before serious infection (SI) developed in TCZ-treated patients using clinical narratives from a postmarketing adverse events (AE) reporting database.

Methods: A postmarketing AE reporting database maintained by Chugai Pharmaceutical Co. Ltd. was used to obtain individual case safety reports including structured (age, sex, drugs, AE term, laboratory test values) and unstructured (clinical narratives) data. Reports had to meet 4 criteria: (1) obtained between April 16, 2008, and April 10, 2015; (2) originated from Japanese patients with RA who received TCZ; (3) included SIs; (4) causality between TCZ and SIs reported by medical professionals. Patient characteristics were summarized by descriptive statistics, and clinical narratives were analyzed by automated text mining to explore symptoms. AEs and symptoms were coded using MedDRA/Japanese version 17.1.

Results: The database included 7653 RA patients with a mean ± SD age of 60.0 ± 12.7 years (<65, 45.8%; ≥65-<75, 22.1%; ≥75, 8.3%; missing, 23.8%). Of these, 1221 patients had reports meeting the 4 criteria (mean ± SD age, 63.4 ± 11.7 years) (<65, 35.5%; ≥65-<75, 25.9%; ≥75, 11.8%; missing, 26.8%) encompassing 1591 reported SIs. The most frequently reported SIs were pneumonia (n = 253, 15.9%), cellulitis (n = 158, 9.9%), and sepsis (n = 80, 5.0%). The date of diagnosis of SI was available for 782 patients: 454 (58.1%) had symptoms during the 28 days before diagnosis of SI, 13 (1.7%) had no symptoms, 276 (35.3%) had symptoms but the date of prodromal symptoms was not identified, and 39 (5.0%) were unknown (Figure). The most common prodromal symptoms among patients who had symptoms during the 28 days before diagnosis of SI were cough (n = 104, 22.9%), pain (n = 103, 22.7%), pyrexia (n = 100, 22.0%), swelling (n = 80, 17.6%), productive cough (n = 49, 10.8%), abdominal pain (n = 49, 10.8%), erythema (n = 47, 10.4%), dyspnea (n = 38, 8.4%), rash (n = 37, 8.1%), and malaise (n = 31, 6.8%).

Conclusion: The presence of prodromal symptoms in patients who developed SIs after TCZ administration was described in most cases. Therefore, data mining of clinical narratives may have additional value in characterizing SIs.



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Abstract Number: 2621

Incremental Benefit of Radiographic Inhibition on Long-Term Outcomes in Patients with Rheumatoid Arthritis

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Background/Purpose: For the treatment of rheumatoid arthritis (RA) a therapeutic window of opportunity exists– patients treated early have favorable outcomes compared with patients treated after they have progressed radiographically. This study investigated the impact of time of radiographic inhibition on the long-term outcomes of patients who achieved early disease control.

Methods: This analysis studied ten-year data from PREMIER (a phase 3, randomized clinical trial of adalimumab in patients with recent onset RA), and DE-019 (a phase 3, randomized clinical trial of adalimumab in patients with long-standing RA). Radiographic progression was defined as an increase of modified total Sharp score (mTSS) of at least 0.5 units relative to baseline. Patients who achieved remission at year 1 (defined as disease activity score 28-joint count [DAS28] < 2.6) were categorized into four groups according to the time of first recorded radiographic progression: (1) progressed within year 1, (2) progressed between year 2 and 3, (3) progressed between year 5 and 10, and (4) never progressed before the end of 10-year follow-up. Outcomes at year 10 were summarized for each of the groups, including health assessment questionnaire disability index (HAQ-DI), DAS28, simple disease activity index (SDAI), and proportion of patients in remission at the end of follow-up. Tests for trend were conducted for each outcome. A sensitivity analysis imputing year 10 outcomes was conducted using last observation carried forward for patients who did not complete all 10 years of follow-up.

Results: A total of 314 RA patients included in the two trials achieved remission at year 1, among whom 149 completed 10 years of follow-up. Delaying radiographic progression was associated with lower levels of physical dysfunction, as measured using HAQ-DI. The average HAQ-DI at year 10 was 0.53 for progressions within the first year, 0.39 for progressions between year 2 and 3, 0.31 for progressions between year 5 and 10, and 0.14 for patients did not progress before the end of follow-up. The incremental HAQ-DI score between the first year progressions and the no progression groups is approximately 1.8 times the minimal clinically important difference of 0.22. In addition, a linear trend of HAQ-DI was observed across different times to radiographic progression (p-for-trend = 0.01). Disease activity, measured using DAS28, SDAI, and remission at the end of follow-up, was not statistically different across the four groups. Results were consistent in the sensitivity analysis where year 10 outcomes were imputed for patients who did not complete the follow-up.

Conclusion: RA patients achieving early remission experienced normalized physical function. Patients who additionally delayed radiographic progression had an incremental benefit in terms of long-term physical function.

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Abstract Number: 2622

Safety, Pharmacokinetics, and Biomarker Profile from Phase 1 Clinical Trials of Healthy Volunteers Treated with GDC-0853, a Highly Selective Reversible Oral Bruton's Tyrosine Kinase (BTK) Inhibitor

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Background/Purpose: B cell depletion therapy has provided evidence of the importance of B cells in the pathogenesis of rheumatoid arthritis and other inflammatory diseases. Consequently, targeted B-cell treatments are being investigated in autoimmune disorders. BTK is a crucial kinase in signaling cascades following B cell antigen receptor (BCR) activation in B cells, in Fc receptor binding of immune complexes in myeloid cells, and some toll-like receptor (TLR) signaling events in B cells, myeloid cells, and dendritic cells. GDC-0853 is a small molecule inhibitor of BTK that is highly selective, orally administered, non-covalent, and reversible. GDC-0853 has demonstrated efficacy in pre-clinical autoimmune disease models and is being developed for the treatment of rheumatoid arthritis and

lupus, with future development for other autoimmune indications. This study evaluated the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of GDC-0853 in single ascending dose (SAD) and multiple ascending dose (MAD) studies in healthy adult volunteers.

Methods: GDC-0853 was evaluated in two randomized, double-blind, placebo- controlled phase 1 trials with 53 active and 18 placebo subjects dosed in the SAD study, and 30 active and 10 placebo subjects dosed in the MAD study. The SAD study evaluated 9 cohorts at doses ranging from 0.5 mg to 600 mg; the MAD study evaluated 5 cohorts at doses of 20, 60, 150, and 250 mg BID, and 500 mg QD for 14 days. Safety and tolerability were assessed by clinical, laboratory, and ECG assessments. PK was characterized using a validated LC-MS/MS assay. PD was assessed using phospho-BTK (p-BTK), and cellular activation assays.

Results: GDC-0853 was well-tolerated in both the SAD and MAD studies and there were no dose-limiting adverse events (AEs) and no serious AEs. No subjects withdrew due to an AE, and a maximum tolerated dose was not reached. AEs were all mild and transient. In the SAD study, the most common event reported was headache in 4 subjects (7.5%). In the MAD study, AEs included skin reactions in 3 subjects (rash, contact dermatitis, and ECG site rash in 1 subject each), nausea in 2 subjects (6.7%), and fatigue, contusion, and asymptomatic bacteriuria in 1 subject each. Following oral administration to fasted subjects, rapid absorption was observed (median t_{max} of 1-3 hours). The steady-state $t_{1/2}$ ranged from 8.3-11 hours, and exposures increased approximately dose-proportionally. Three target engagement assays were used to demonstrate dose-dependent inhibition of p-BTK and BTK-dependent cellular activation. Basophil activation via FcεR, B cell activation via the B cell receptor, and constitutive p-BTK activity in whole blood lysates were inhibited in a dose-dependent manner by GDC-0853, with IC50's ranging from 2-9 nM. Basophil and p-BTK activity in the MAD study were used to develop a PK/PD model to support dose selection for the phase II studies.

Conclusion: GDC-0853 was well-tolerated in healthy subjects at doses that inhibit BTK activity. The safety, PK, and PD profiles support further investigation in phase II studies in rheumatoid arthritis, lupus, and other autoimmune indications.

Disclosure: T. Katsumoto, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **H. Winter**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **S. Kotwal**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **E. Murray**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **R. Zhao**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **M. Florero**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **A. Lin**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **A. Moein**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **R. Wang**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **M. Bremer**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **S. Kokubu**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **A. Serone**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **A. Morimoto**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **L. Chinn**, Roche Pharmaceuticals, 1,Genentech, Inc., 3; **A. Herman**, Roche Pharmaceuticals, 1,Genentech, Inc., 3.

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Abstract Number: 2623

Intravenous Infusion of Umbilical Cord Blood-Derived Mesenchymal Stem Cells in Rheumatoid Arthritis: A Phase 1, Proof-of-Concept Clinical Trial

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Background/Purpose: The immunomodulatory actions of human umbilical cord blood (hUCB)-derived mesenchymal stem cells (MSCs) in rheumatoid arthritis (RA) have been studied extensively via *in vitro* or pre-clinical studies, yet few human trials have been conducted

investigating the outcome of hUCB-derived MSC infusion.

Methods: The CURE-iv (**C**linical and safety assessment of human **U**mbilical cord blood-derived mesenchymal stem cell therapy for **RhE**umatoid arthritis patients administered **i**ntra**v**enously) trial was a phase 1, proof-of-concept clinical trial for RA patient with moderate disease activity despite treatment with methotrexate. Patients meeting the 2010 ACR/EULAR classification criteria and with a DAS28-ESR >3.2 were eligible for the trial. Subjects were each given a single intravenous infusion of 2.5×10^7, or 5×10^7, or 1×10^8 cells of hUCB-derived MSCs for 30 minutes; 3 patients in each cluster, with increment of cell numbers when there was no dose-limited adverse events. Clinical and safety parameters were monitored and followed after the infusion period (first 24 hours, 72 hours, 1 week, and 4 weeks). Serum cytokines at baseline and 24 hours after the infusion were analyzed.

Results: Eleven RA patients were screened, 9 of which were enrolled from a single center. The mean age was 57.4 years, 78 % being female, with a disease duration of 9.5 ± 8.7 years, and DAS28-ESR 4.53 ± 1.35. There was no ominous safety signal in all clusters up to 4 weeks after the infusion. One patient stated joint pain 60 min after the infusion (5×10^7 group), but it was thought to be unrelated to the investigational product. ESR and CRP changes at 4 weeks (n=9) were -7.89 ± 10.36 (p= 0.0517), and -0.37 ± 1.09 (p=0.3362). DAS28 and HAQ changes at 4 weeks were -1.60 ± 1.57 (p= 0.0159), and -0.15 ± 0.48 (p= 0.3706), respectively. One patient in the 1×10^8 group showed substantial decrease in all serum levels of IL-1b, IL-6, IL-8, and TNF-a.

Conclusion: This phase 1 clinical trial - a single dose intravenous infusion of hUCB-derived MSCs - for established RA patients was completed without any short-term safety concerns (NCT02221258).

Disclosure: D. J. Go, None; **H. S. Lim**, None; **A. Cho**, Kangstem Biotech, 3; **K. Roh**, Kangstem Biotech, 3; **K. W. Seo**, Kangstem Biotech, 3; **K. S. Kang**, Kangstem Biotech, 4; **K. Shin**, None.

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Abstract Number: 2624

Anti-Citrullinated Protein Antibodies Titers Are Independently Modulated By Disease Activity and Synthetic or Biologic Dmards in a Seropositive Early Arthritis Population

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Background/Purpose: Early introduction of some biologic (b) DMARDs has been proposed to reduce anti-citrullinated protein antibodies (ACPA) titers in clinical trials settings. However, less information is available about which factors modulate ACPA titers in early arthritis patients under routine clinical practice, including the impact of synthetic (s) DMARDs. **Aim:** To analyze the factors that are related with the variation of ACPA titers in a seropositive early arthritis population under non-protocolized treatment with s and b DMARDs

Methods: We studied 124 patients enrolled in our prospective PEARL (Princesa early arthritis longitudinal) study. Appropriate ethical approval of the registry protocol and informed consent form from patients were obtained. Sociodemographic, clinical, laboratory, therapeutic variables and biological samples were collected by protocol at baseline, 6, 12, 24 and 60 months. Only baseline ACPA positive patients were include in the study (ELISA antiCCP2 IgG Euro Diagnostica Immunoscan CCPlus®, Arnhem, Holanda; positive >50U/ml). ACPA titers were assessed in 471 visits (3.8 visits/patient). The population was stratified into equal quartiles according to baseline CCP2 titers (median, range): Q1 (87, 50 – 160 U/ml), Q2 (308, 161 – 460 U/ml), Q3 (643, 461 – 1280 U/ml) and Q4 (2000, 1281– 5263) U/ml). Disease activity was assessed with DAS 28 and HUPI indexes. To estimate the effect of different variables (including DMARDs) on the variation of ACPA titers, multivariate linear regression models nested by visit and patients were fitted

using the xtgee command of STATA 12.1.

Results: 86 % patients were female, with age at disease onset (median [p25-p75]) 52 [41-73] years, median disease duration at entry 6 [3,6-9] months; 83% of patients met 2010 ACR/EULAR classification criteria for RA at baseline and 93% after two years of follow up. Median DAS28 at baseline was 4,5 [3,5-5,6] and HAQ 1 [0,5-1,6]. No differences in demographic variables, disease duration, activity or functional status were detected between patients clustered in the baseline ACPA quartiles. A significant decrease in baseline ACPA titers can be detected at 6 months (median reduction 48% [15-70]) that was maintained at 1 (44% [12-68]), 2 (49% [15-71] and 5 years (62% [38-72]), (p=0,0002; 0,0049; 0,0001 and 0,0137, respectively). This reduction was also significant in all visits when population were analyzed by quartiles (p=0,0001), with increasing magnitude of change and number of patients with titers reduction in the Q4. In the multivariate analysis, active smoking was associated with higher ACPA titers along the follow-up (p<0,001) while reduction in disease activity was associated with decreasing ACPA titers (p = 0.005). After adjusting for these variables, both synthetic [methotrexate (p = 0.001), leflunomide (p = 0.002), sulfasalazine (p = 0.014)] and biological DMARDs [anti-TNF (P = 0.002), rituximab (p = 0.049)], also account for decrease in ACPA titers as independent factors.

Conclusion: In real clinical practice, an early and sustained reduction in antiCCP2 titers can be detected in seropositive early arthritis patients associated to the decline in disease activity. Both synthetic and biologic DMARDs can also independently explain the decline in ACPA titers.

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Abstract Number: 2625

Safety of Multiple Retreatments with Rituximab in Real Life: Long Term Registry Data from 1984 Patients with Rheumatoid Arthritis

Jacques-Eric Gottenberg[1], Philippe Ravaud[2], Thomas Bardin[3], Alain Cantagrel[4], Bernard Combe[5], Maxime Dougados[6], RENE MARC FLIPO[7], Olivier Vittecoq[8], Thierry Schaeverbeke[9], Isabelle Pane[10], Jean Sibilia[11], Xavier Mariette[12] and on behaf of all of the investigators of the AIR registry and of the French Society of Rheumatology , [1]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [2]Epidemiology, Hotel Dieu, PARIS, France, [3]Clinique de Rhumatologie, Hopital Lariboisiere, Paris Cedex 10, France, [4]Rheumatology, INSERM CNRS UMR 1043, Paul Sabatier University Toulouse, Purpan Teaching Hospital, Toulouse, France, [5]Département Rhumatologie, Hôpital Lapeyronie, Montpellier, France, [6]Rheumatology, Paris Descartes University, Paris, France, [7]Rheumatology, Department of Rheumatology, CHU Teaching Hospital Lille, France., Lille, France, [8]INSERM U905 & Normandy University, Institute for Research and Innovation in Biomedicine, Rouen, France, [9]Rheumatology, CHU Bordeaux, Bordeaux, France, [10]Epidemiology, Hotel Dieu, Paris, France, [11]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [12]Institut National de la Santé et de la Recherche Médicale, Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France

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SESSION INFORMATION

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Background/Purpose: Data are very limited concerning the safety of multiple retreatments with rituximab (RTX) in rheumatoid arthritis in common practice.

Methods: This is a multicenter open-label observational study of patients with RA according to 1987 ACR criteria who were initiating RTX and enrolled in the French Society of Rheumatology prospective registry AIR (AutoImmunity and Rituximab) Severe adverse events (death, serious infection, and cancer) were validated by chart review by three experts. A serious infection was defined as an infection occurring during the 12 months after a rituximab infusion and requiring hospitalization and/or intravenous antibiotics and/or resulting in death. Cancers were considered in the analysis regardless of their time of occurrence, even after registry drug discontinuation. For serious infections, exposure time was defined as the time between inclusion and the first occurrence of serious

infection, end of follow-up, or last infusion of rituximab plus 12 months for rituximab. For cancers and deaths, exposure time was defined as the time between inclusion and first occurrence of an event or end of follow-up.

Results: Median age and disease duration before RTX in the 1986 enrolled patients were 58 [50-67] and 11 [6-18] years, respectively. 14% of patients had a history of cancer, 34.6% had a history of serious or recurrent infections. Median number of previous conventional DMARDs and of biologics were 3 [2 ;4] and 2 [1 ;2], respectively. Median DAS28-ESR at RTX initiation was 5.53 [4.72; 6.38]. 65.7% of patients initiated RTX in combination with a synthetic DMARD (methotrexate :75.6%). 78.7% of patients received concomitant oral corticosteroids (median dose 10 [7; 15] mg/day. Current total follow-up of the 1984 patients was 10 545 patient-years (mean follow-up : 5.3 years). 1280 patients have received less than 5 cycles of RTX, 551 patients between 5 and 9 cycles and 153 patients 10 cycles or more. Overall, 369 serious infections occurred (5.2 /100 patient-years) : 195 in patients treated with less than 5 cycles of RTX (6.1/100 patient-years), 134 patients treated with 5 to 9 cycles (4.0/100 patient-years) and 40 in patients treated with more than 10 cycles (4.0/100 patient-years). 134 cancers occurred (1.3/100 patient-years) including 85 in patients treated with less than 5 cycles of RTX 1.4/100 patient-years), 42 in patients treated with 5 to 9 cycles (1.2/100 patient-years) and 7 in patients treated with more than 10 cycles (0.7/100 patient-years). 196 deaths occurred (1.9/100 patient-years) including 177 in patients treated with less than 5 cycles of RTX (3.0 /100 patient-years), 17 in patients treated with 5 to 9 cycles (0.5/100 patient-years) and 2 in patients treated with more than 10 cycles (0.2/100 patient-years). RTX was discontinued in 820 patients treated with less 5 cycles, 155 treated with 5 to 9 cycles and 19 in patients treated with 10 cycles or more. Discontinuation was related to serious adverse events in 105 (2.8%) patients treated with less 5 cycles, 29 (18.7%) patients treated with 5 to 9 cycles and 4 (21.0%) patients treated with 10 cycles or more.

Conclusion: The rate of serious adverse events seems similar in patients with multiple retreatments with RTX as in patients less frequently retreated. However, these results must be interpreted with caution taking into account the depletion of susceptible effect (patients who remain on a drug are those who can tolerate it).

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Abstract Number: 2626

Soluble CD206 Plasma Levels Decreases with Treatment and Reflects Anti-Tnfa Discontinuation in Rheumatoid Arthritis

Line Dam Heftdal[1,2], Kristian Stengaard-Pedersen[2], Merete Lund Hetland[3,4], Kim Hørslev-Petersen[5], Peter Junker[6], Mikkel Østergaard[4,7], Malene Hvid[8,9], Bent Deleuran[2,8,9], Holger Jon Møller[8,10] and Stinne Greisen[2,9], [1]Department of Biomedicine, Department of Biomedicine, Aarhus University, Aarhus, Denmark, [2]Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark, [3]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Denmark, Copenhagen, Denmark, [4]Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark, Copenhagen, Denmark, [5]King Christian X's Hospital for Rheumatic Diseases,, University of Southern Denmark, Graasten, Denmark, [6]Department of Rheumatology, Odense University Hospital, Odense, Denmark, [7]Copenhagen Center for Arthritis Research, Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Denmark, [8]Department of Clinical Medicine, Aarhus University, Aarhus, Denmark, [9]Department of Biomedicine, Aarhus University, Aarhus, Denmark, [10]Department of Clinical Biochemistry, Aarhus University Hospital, Aarhus, Denmark

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Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy - Poster III

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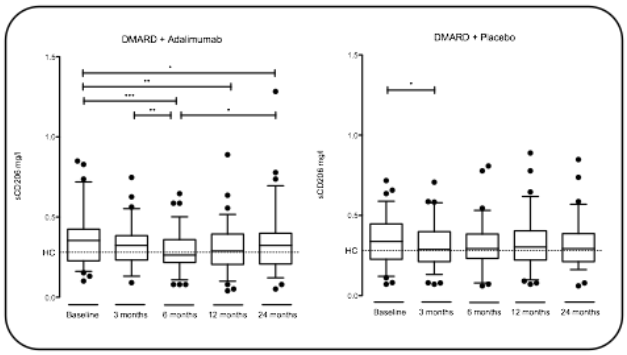
Background/Purpose: Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic inflammation of the synovial joints and infiltration by activated macrophages. TNFa is a central mediator in the process, leading to joint swelling and subsequent articular destruction. CD163 is a scavenger receptor expressed by M2C macrophages. We previously reported the soluble (s) form to be

associated with disease activity and reflect discontinuation of anti-TNFa treatment in RA[2]. The mannose receptor, CD206, is also a scavenger receptor, but expressed by M2A-macrophages and dendritic cells. It is involved in collagen internalization and degradation. The soluble form is suggested as biomarker of M2A-macrophage activation. In this study, we investigate sCD206 plasma levels in early RA patients, before, during and after anti-TNF_ treatment.

Methods: Plasma levels of sCD206 was measured by ELISA in samples from 155 early RA patients belonging to the OPERA cohort[1]. Age 53.5 years 70% females, average disease duration: 3 months. Patients were randomized to 12 months conventional methotrexate and placebo (PLA) or methotrexate and adalimumab (ADA) treatment, followed by open-label treatment with DMARD and if needed adalimumab. The disease was assessed at baseline and after 3, 6, 12 and 24 months by: Disease Activity Score (DAS28), Health Assessment Questionnaire (HAQ), C-Reactive Protein (CRP), Swollen Joint Counts (SJC40), Tender Joint Counts (TJC40), Clinical Disease Activity Index (CDAI), Visual Analogue Scale (VAS) for pain, IgM-RF and anti-CCP. Statistical analysis was performed by studentÕs t-test, SpearmanÕs Rank correlation and linear regression.

Results: Baseline plasma level of sCD206 in treatment na•ve RA patients was 0.33 mg/l (CI: 0.33 mg/l Ð 0.38 mg/l) corresponding to the upper part of the reference interval for healthy controls (0.10 mg/l Ð 0.43 mg/l). Anti-TNFa treatment significantly decreased plasma sCD206, whereas discontinuation of anti-TNFa resulted in increasing sCD206 plasma levels. In the PLA group, sCD206 levels was decreased after 3 months, and did not differ from those at baseline after 6 months. In the ADA group, however, levels remained lower than baseline throughout the treatment period (Figure 1). Soluble CD206 correlated with previously measured sCD163[2] at all 5 time points (r^2: 0.24-0.38, $p<0.001$). Soluble CD206 did not correlate with clinical nor biochemical disease markers, however sCD206 increased when adalimumab was discontinued.

Conclusion: Plasma sCD206 decreased with treatment in early RA patients. Treatment with anti-TNFa preserved this decrease in the entire follow-up period; however, discontinuation of anti-TNFa was reflected by increasing sCD206 plasma levels. Soluble CD206 did not reflect disease activity in early RA, but like sCD163, reflected anti-TNFa treatment. Figure 1



[1] Horslev-Petersen, K. *et al. Ann Rheum Dis* (2013)

[2] Greisen, S. R. *et al. Clin Exp Rheumatol* (2011)

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Abstract Number: 2627

The Effect of Fostamatinib with Methotrexate on Circulating Biomarkers of Synovium, Cartilage and Bone Metabolism: Potential Utility for Clinical Development Decision Making in Rheumatoid Arthriti

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Background/Purpose: Fostamatinib was developed for the treatment of RA and improved signs and symptoms of RA [1], but did not improve modified Total Sharp Score (mTSS) in the phase III OSKIRA-1 study. Previous publications have shown that interventions with tocilizumab (anti-IL6 receptor antibody) can modulate bone balance, and both cartilage and synovial turnover in a dose-dependent manner [2,3,4,5]. To better understand the underlying mechanism of fostamatinib changes in biomarkers of joint tissue turnover were prospectively evaluated in response to fostamatinib treatment in patients with rheumatoid arthritis (RA) from the Phase III OSKIRA-1 study.

Methods: The biomarker evaluable population included 450 patients from the OSKIRA-1 trial. All patients received methotrexate and were randomly assigned to Group A (fostamatinib 100 mg bid), Group B (fostamatinib 100 mg bid for 4 weeks followed by fostamatinib 150 mg once daily) or placebo. Serum biomarkers of bone resorption (CTX I), bone formation (osteocalcin and type I pro-collagen N-terminal pro-peptide [PINP]), joint tissue degradation (C1M, C2M, C3M and matrix metalloproteinase [MMP]-3) and inflammation (MMP-mediated C-reactive protein [CRPM] and interleukin-6 [IL-6]) were assessed at baseline and Week 24. CTX-I/osteocalcin ratio was evaluated as a measure of bone balance [2].

Results: Fostamatinib significantly reduced a bone resorption biomarker at Week 24, with reductions of 23–28% in CTX-I levels versus placebo (P<0.001), and statistically significantly improved biomarker bone balance versus placebo (P<0.05) (figure). However, no statistical significant changes for fostamatinib versus placebo were observed for C1M, a soft tissue marker shown to be predictive for structural efficacy [5], or for C2M, C3M and CRPM. Fostamatinib showed a significant decrease in MMP-3 levels (P=0.004) and IL-6 levels (P=0.004), although only in the high-dose group for IL-6.

Conclusion: Fostamatinib demonstrated a significant effect on the overall bone balance, but not on other biomarkers of joint tissue turnover, consistent with the structural data. Early and comprehensive analysis of biomarkers that encompass synovium, cartilage and bone metabolism may facilitate early clinical decision-making in RA drug development. *[1]Taylor PC et al. Ann Rheum Dis 2015. [2]Karsdal MA et al. Semin Rheum 2012. References:[3]Bay-Jensen AC et al. Arthritis Res Ther 2016. [4]Bay-Jensen AC et al Semin Arthritis Rheum 2014. [5]Siebuhr A et al. Arthritis Res Ther 2013.*

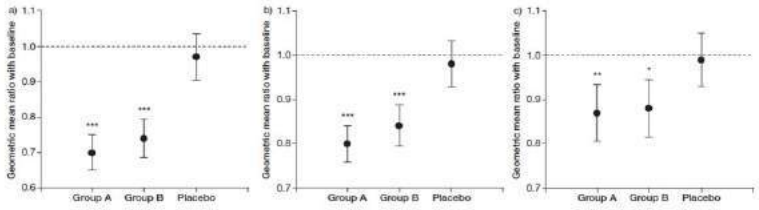

Figure. Change (mean ratio to baseline) in the bone biomarkers of a) CTX-I, b) osteocalcin and c) bone balance for Group A, Group B and placebo. *P<0.05; **P<0.01; ***P<0.001. Group A, 100 mg fostamatinib twice daily in combination with MTX; Group B, induction with 100 mg fostamatinib twice daily in combination with MTX for the first 4 weeks, followed by 150 mg fostamatinib once daily maintenance in combination with MTX; placebo, MTX only.

Disclosure: A. Platt, AstraZeneca, 3; **A. C. Bay-Jensen**, Nordic Bioscience A/, 1,Nordic Bioscience A/S, 3,D-BOARD, 2; **M. Braddock**, AstraZeneca, 3; **M. Jenkins**, AstraZeneca, 3; **K. Musa**, Nordic Bioscience A/S, 3; **C. S. Thudium**, Nordic Bioscience A/S, 3; **C. F. Kjelgaard-Petersen**, None; **E. Graham**, AstraZeneca, 3; **S. Keeler**, AstraZeneca, 3; **G. Slynn**, AstraZeneca, 3; **M. Weinblatt**, Amgen, BMS, Crescendo Bioscience, UCB, 2,mgen, AbbVie, BMS, Eli-Lilly, Gilead, Merck, Pfizer Inc, Novartis, Roche, Samsung Bioepis, UCB, 5; **M. A. Karsdal**, Nordic Bioscience A/S, 1,Nordic Bioscience A/S, 3.

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Abstract Number: 2628

Retention of Use and Safety of Subcutaneous Abatacept in Rheumatoid Arthritis: A Patient Record Assessment in a Compassionate Use Programme in South Africa, a Tuberculosis Endemic Country

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Background/Purpose: South Africa is a tuberculosis (TB) endemic country having one of the highest TB infection rates in the world with close to 1000 cases per 100 000 population per year[1]. Screening for latent TB infection (LTBI) and treatment of any positive patient has reduced reactivation however the chance of TB infection remains high. Use of a biologic therapy with a lower risk of TB infection is a high priority. Bristol- Myers Squibb introduced a compassionate use programme (CUP) for RA patients who had completed long-term extension phases of clinical trials using subcutaneous (SC) abatacept 125 mg per week. **Objective**: The primary objective was to gather information on the retention and safety of SC abatacept use over 30 months on the CUP in a TB endemic environment.

Methods: Demographic, safety and clinical data were retrospectively collected from patient records of 50 patients receiving regular follow up during the CUP (June 2013 to December 2015)

Results: Data were received for 50 patients who completed the CUP. Eighty-six percent of patients (n=43) were still on SC abatacept at the end of 30 months. Discontinuation was due to adverse events 4% (n=2), lost to follow up 4% (n=2) and joint replacement 2% (n=1). Only 4% (n=2) discontinued due to lack of efficacy. Ten percent of all patients (n=5) experienced an adverse event after commencement of the CUP. In total, 7 adverse events were reported; 5 were classified as moderate and 2 as severe. The adverse events were as follows: bunionectomy (n=1; moderate); elbow replacement (n=1; moderate); pneumonia (n=1; moderate); right shoulder acromioplasty (n=1; moderate); right wrist replacement (n=1; severe); spastic colon (n=1; severe) and upper respiratory tract infection (n=1; moderate). No TB cases were recorded and general infections were recorded in 4% (n=2) which is similar to data published from other countries (3.1%) [2, 3]. Seventy percent (n=35) of patients had one or more co-morbidity; of these 43% (n=15/35) were reported to have a co-morbidity that is cardiovascular in nature.

Conclusion: The evidence from the CUP programme provides insight into the retention of SC abatacept treatment as well as the safety of SC abatacept use in a TB endemic country. The results demonstrate that SC abatacept is a well-tolerated and safe treatment option with a good retention rate in South Africa.

1. WHO Global tuberculosis report 2014
2. Ruppert-Roth A. Rheumatology 2012; **51** (Suppl 5): v38-v47
3. Alten R et al. Arthritis and Rheumatology 2014; **66** (8): 1987-1997

Table 1. Demographic and Disease Characteristics of Patients on the CUP

Demographics	n/N (%)
Gender	
Male	8/50 (16%)
Female	42/50 (84%)
Age (in years)	
Mean	60
Population group	
Black African	5/50 (10%)
Caucasian	39/50 (78%)
Coloured	5/50 (10%)
Indian	1/50 (2%)
Disease duration (years from date of diagnosis)	
Mean	15
Minimum	7
Maximum	47
Sero-positivity	
Positive	27/42 (64%)
Negative	15/42 (36%)

Disclosure: I. Louw, None; **M. Ally**, None; **D. Janse van Rensburg**, None; **E. Van Duuren**, None; **D. Nel**, None; **H. Miller-Janson**, HEXOR PTY Ltd, 5; **M. de Necker**, HEXOR PTY Ltd, 5; **J. de Beer**, HEXOR PTY Ltd, 5; **H. Duvenhage**, Bristol-Myers Squibb, 3.

Abstract Number: 2629

Serious Adverse Events in Patients with RA Taking Abatacept Compared with Other Dmards. Results from a US-Wide Safety Registry

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Background/Purpose: Observational studies are critical in assessing medication safety and effectiveness in the real world. Nonrandom assignment can provide insight to how and when medications are prescribed. Since the US introduction of TNF inhibitors (TNFi) in 1998, several newer biologics with varying mechanisms of action are available to patients and physicians. Our objective was to compare characteristics and serious adverse events (serious infections, malignancies and autoimmune diseases) of patients who received abatacept (ABA) compared to those who received other biologic DMARDs (BDC).

Methods: Participating patients with RA in the National Data Bank for Rheumatic Diseases (NDB) provided treatment and other characteristics (sociodemographics and comorbidities) through self-reported biannual questionnaires. Only responses from 2005-2015 were used for greater comparability. Initiators of ABA were matched to patients initiating other DMARDs in a 1:3 ratio. All patient-reported outcomes were verified by medical record review except non-melanoma skin cancer. For cancer and autoimmune outcomes, ITT analyses were performed, holding the exposure constant from the start of treatment until the end of follow-up, and for infections, through its duration plus 90 days. Marginal structural models were used to estimate the effect of treatment on the outcome by an appropriate control for the effects of time-dependent confounders using stabilized weights. Variables included sex, employment, smoking, education, income, BMI, insurance, comorbidity index, RA severity, and co-medications. These results are reported as hazard ratios (HR), estimated through a pooled logistic regression. The analysis was also stratified by prior number of exposed biologics. The primary comparison group were RA patients starting biologic DMARD (BDC), and we also compared with non-biologic DMARD

(DC).

Results: A total of 1456 RA patients initiated ABA and 3222 a BDC during the study, representing total patient years of drug exposure (total follow-up time) of 2396.6 (4613.9) and 8576.5 (10462) respectively. The ABA patients were older, had longer RA duration, worse disease severity, more comorbidities and more exposure to prior DMARD use (Table 1). HRs are presented in Table 2. The results were similar when comparing with those initiating DC (1663 patients with 4340.0 patient years of drug exposure, 5215.7 follow-up time). **Table 1. Baseline mean (SD) characteristics of ABA and biologic comparison cohorts.**

	ABA (N=1456)	**BDC (N=3222)**
Age, yrs	61.57 (12.70)	60.77 (12.89)
Male sex %	14.49	15.70
Education, yrs	13.79 (2.33)	13.79 (2.34)
RA duration, yrs	16.66 (12.24)	16.28 (12.03)
HAQ (0-3)	1.33 (0.66)	1.22 (0.69)
Pain VAS (0-10)	5.61 (2.70)	5.03 (2.81)
Global VAS (0-10)	4.92 (2.41)	4.50 (2.47)
Body mass index (kg/m^2)	29.11 (7.24)	28.87 (7.12)
Cancer ever -%	26.51	26.08
Current smoker- %	4.95	5.52
Past smoker - %	42.86	45.13
IV antibiotics -%	0.41	0.28
Lifetime DMARD use	2.88 (1.86)	2.68 (1.73)
Lifetime biologic use	1.93 (1.14)	1.54 (1.05)
Methotrexate (MTX) -%	51.99	53.79
DMARDs not MTX - %	23.76	26.51
Hydroxychloroquine - %	15.11	17.23
Prednisone - %	42.65	35.63
Comorbidity index (0-9)	2.13 (1.67)	2.01 (1.65)
Hypertension - %	38.55	37.51
Diabetic - %	12.09	12.26

Table 2. Hazard ratios (95% CI) of incident events comparing ABA with other biologics.

	ABA vs BDC	
	Crude	**Adjusted**
All malignancies except skin cancer	1.46 (0.80 – 2.63)	1.18 (0.59 – 2.36)
Skin cancer	1.42 (0.76 – 2.64)	1.08 (0.52 – 2.22)
All hospitalized infections	0.83 (0.43 – 1.58)	0.52 (0.33 – 0.79)
Lupus	1.76 (0.50 – 6.10)	2.89 (0.74 - 11.36)

Conclusion: We found a trend of channeling with ABA, where patients starting ABA had worse disease outcomes and higher prior use of DMARDs. After adjustment there appeared to be less difference in the adverse events studied for both comparisons cohorts with exception of increased lupus co-diagnosis and statistically significant decreased hospitalized infections for ABA.

Disclosure: K. Michaud, Rheumatology Research Foundation, Pfizer, 2; **S. Pedro**, None; **T. Simon**, Bristol-Myers Squibb, 1,Bristol-

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Abstract Number: 2630

EBV Load Quantification in Peripheral Blood Mononuclear Cells of Patients with Rheumatoid Arthritis Treated By Abatacept and Tocilizumab

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Background/Purpose: For twenty years, the Epstein-Barr Virus (EBV) has been suspected to contribute to Rheumatoid Arthritis (RA). Immunity against EBV is impaired in RA. RA patients have high titer anti-EBV antibodies [1]. They also have defective EBV specific suppression by T cells. This contributes to a higher risk of developing lymphoma [2]. We hypothesized that, in RA patients, immunosuppressive drugs may enhance the risk to develop LPD (lymphoproliferative disorders), as it is seen in post transplant patients [3]. We have previously shown that Methotrexate and TNF alpha antagonists do not increase EBV load in RA [4,5]. Our purpose is to monitor EBV load in peripheral blood mononuclear cells (PBMC) of RA patients treated with 2 recent bDMARDs: Abatacept (CTLA4 Ig) a T cell activation inhibitor, and Tocilizumab, an anti IL6 receptor antibody to test whether they may enhance EBV load and lymphoma risk.

Methods: Patients :We included 90 patients with RA, 55 treated by abatacept (+/- methotrexate) and 35 treated with tocilizumab (+/- methroexate) followed at the Sainte-Marguerite Hospital Rheumatologic Department Marseille. All patients fullfilled the 1987 American College of Rheumatology criteria. All patients gave informed consent. (Patients Characteristics, Table1) Quantification of viral load - PBMC were separated on Ficoll gradient

- DNA was extracted and quantified by real time PCR [5].
- Quantification of EBV copy number

The Raji EBV positive Burkitt lymphoma cell line, containing 50 copies of EBV per cell, was used as external standard. Real time quantitative PCR (LightCycler, Roche Diagnostics) was performed on 500 ng of DNA. A 214 bp sequence of the Internal Repeat was amplified. Two internal probes were used to improve specificity. Statistics : Generalized estimating equation were used to test whether EBV load is influenced by treatment

Results: Abatacept does not enhance EBV mean load after 3 years of treatment. No lymphoma occured. Tocilizumab was associated with a significant decreased EBV load during time ($p = 0.021$). None of the patients had a detectable load at 36 months. No lymphoma occured.

Conclusion: Reliable tool to monitor EBV load No obvious change of EBV mean load under treatment with tocilizumab and abatacept Referances 1] Alspaugh M, et al. Journal of Clinical Investigation. 1981 // [2] Tosato G, et al. New England Journal of Medicine 1981 // [3] Baldanti F et al. Journal of Clinical Microbiology, 2000 // [4] Balandraud N, et al. Arthritis and Rheumatism. 2003. [5] Balandraud N et al. Arthritis and Rheumatism. 2007

Disclosure: E. Massy, None; **G. Texier**, None; **O. Muis Pistor**, None; **M. Martin**, None; **I. Auger**, None; **J. P. Mattei**, None; **S. Guis**, None; **T. Pham**, None; **J. Roudier**, None; **N. Balandraud**, Roche Chugai, BMS, 2.

Abstract Number: 2631

Trends and Factors Associated with Use of Biologic Agents As Monotherapy Among US Patients with Rheumatoid Arthritis

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Background/Purpose: For patients with rheumatoid arthritis (RA) receiving a biologic disease-modifying antirheumatic drug (bDMARD), the current standard of care is to use the bDMARD concurrently with a conventional synthetic DMARD (csDMARD) such as methotrexate (MTX). However, in reality, many patients may not take MTX for various reasons. This analysis aims to evaluate the trend of using bDMARDs as monotherapy in US RA patients, and to identify patient factors associated with use of monotherapy bDMARD.

Methods: Data were drawn from the Adelphi RA-DSP, a cross-sectional survey of US rheumatologists and their RA patients, using samples from the 1st quarter (Q1) of 2011 and Q1 2014. Rheumatologists provided information on patient demographics, insurance status, drug treatment, and patient involvement in their treatment decisions (scale: 1–5, with 4 or 5 considered to be indicative of high involvement). Patients who were currently prescribed a bDMARD without a csDMARD (monotherapy) were compared to those receiving a bDMARD in combination with a csDMARD (combination therapy). Multivariate analysis was performed to identify independent patient characteristics associated with mono- or combination therapy.

Results: Included in the analysis were 843 RA patient records (2011: n = 453, 2014: n = 390) with mean age of 55.4 years, 72.9% female, 72.1% Caucasian, 67.7% commercially insured, 22.4% on Medicare, and 6.4% on Medicaid. Overall, 20.9% of patients currently received bDMARD monotherapy (n = 176) and 79.1% currently received combination therapy (n = 667). Overall, there was no statistically significant difference in the proportion of patients receiving monotherapy between 2011 and 2014 (20.1% vs. 21.8%, P = 0.553). However, in the subgroup of non-tumor-necrosis-factor-inhibitor (non-TNFi) users (n = 192), significant increase was seen over time in use of monotherapy bDMARD (18.2% in 2011 vs. 32.3% in 2014, P = 0.030). While among TNF users, there was no statistically significant change over time in patients receiving TNFi monotherapy (20.6% in 2011 vs. 18.5% in 2014, P = 0.553). Multivariate analysis showed that, among patients receiving TNFi, they were more likely to receive it as monotherapy if they were Caucasian (odds ratio (OR) [95% CI] = 1.772 [1.015–3.093], P = 0.044). TNFi receiving RA patients were less likely to receive monotherapy when they were insured via Medicare (OR = 0.473 [0.235–0.951], P = 0.036), or were prescribed adalimumab (OR = 0.468 [0.279–0.784], P = 0.004) or infliximab (OR = 0.379 [0.199–0.723], P = 0.003). Among patients receiving non-TNFi bDMARD, they were more likely to receive it as monotherapy when prescribed tocilizumab (OR = 2.233 [1.076–4.635], P = 0.031), but less likely if perceived by rheumatologists to be highly involved in their treatment decisions (OR = 0.289 [0.107–0.783], P = 0.015).

Conclusion: The current study found no significant change in overall monotherapy bDMARD use from 2011 to 2014 in the US. However, there was a significant increase in the use of non-TNFi bDMARD as monotherapy from 2011 to 2014, mostly driven by anti-IL6 therapy.

Disclosure: C. I. Chen, Regeneron Pharmaceuticals, Inc., 1,Regeneron Pharmaceuticals, Inc., 3; **W. Wei**, Sanofi US, Inc., 1,Sanofi US, Inc., 3; **S. Blackburn**, Adelphi Real World, 3,Sanofi US, Inc., 9; **E. Sullivan**, Adelphi Real World, 3,Sanofi US, Inc., 9; **J. Piercy**, Adelphi Real World, 3,Sanofi US, Inc., 9.

Abstract Number: 2632

Effects of Baseline Patient Characteristics on Baricitinib Efficacy in Patients with Rheumatoid Arthritis

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Background/Purpose : This analysis assessed the effects of baseline patient characteristics on the response to baricitinib treatment in patients with rheumatoid arthritis (RA) and incomplete responses to conventional disease-modifying antirheumatic drugs (cDMARDs).

Methods: This post hoc analysis used pooled data from two phase 3, double-blind, randomized, controlled trials of 6-12 months' duration in patients with RA and an incomplete response to cDMARDs. Pooled clinical outcome data (e.g., ACR20 response, change from baseline in DAS28-hsCRP score, percent of patients who achieved SDAI score ≤11) for patients who received baricitinib 4 mg or placebo were summarized based on categories of baseline characteristics: age, gender, ethnicity, baseline disease activity, RF/ACPA serology, and time from RA diagnosis.

Results: Patients who received baricitinib 4 mg (n=714) achieved improved clinical outcomes compared to those who received placebo (n=716) in these trials, regardless of baseline characteristic subgroup (Table). No clear pattern emerged suggesting that any baseline characteristic, including age, gender, ethnicity, RF/ACPA serology, or disease activity at baseline, had a consistent effect on baricitinib efficacy.

Conclusion: No baseline characteristics were found to abrogate baricitinib treatment efficacy. Post hoc analysis of these pooled RA trial data suggests that baricitinib therapy is associated with improved clinical outcomes compared to placebo, regardless of any baseline characteristic categories.

	Outcome after 12 Weeks					
	ACR20 Response, n (%)		DAS28-hsCRP, Change from Baseline LSM (SE)		Patients Achieving SDAI ≤11, n (%)	
	Placebo (N=716)	Baricitinib 4 mg (N=714)	Placebo (N=716)	Baricitinib 4 mg (N=714)	Placebo (N=716)	Baricitinib 4 mg (N=714)
Age group (years) <65 ≥65 ≥75	237/603 (39.3%) 49/113 (43.4%) 4/14 (28.6%)	387/578 (67.0%) 92/136 (67.6%) 16/22 (72.7%)	-1.0 (0.06) -1.2 (0.17) 0.2 (0.67)	-2.1 (0.06) -2.4 (0.17) -1.6 (0.59)	102/603 (16.9%) 20/113 (17.7%) 2/14 (14.3%)	221/578 (38.2%) 63/136 (46.3%) 10/22 (45.5%)
Gender Female Male	228/571 (39.9%) 58/145 (40.0%)	373/562 (66.4%) 106/152 (69.7%)	-1.0 (0.07) -1.1 (0.14)	-2.1 (0.07) -2.3 (0.14)	97/571 (17.0%) 25/145 (17.2%)	226/562 (40.2%) 58/152 (38.2%)
Ethnicity Asian White Other	70/208 (33.7%) 191/455 (42.0%) 25/52 (48.1%)	130/202 (64.4%) 320/460 (69.6%) 29/51 (56.9%)	-0.5 (0.28) -1.1 (0.07) -0.8 (0.29)	-1.9 (0.29) -2.2 (0.07) -1.5 (0.30)	29/208 (13.9%) 78/455 (17.1%) 15/52 (28.8%)	82/202 (40.6%) 186/460 (40.4%) 16/51 (31.4%)
Serology RF and ACPA (-) RF and/or ACPA (+)	29/70 (41.4%) 257/646 (39.8%)	38/71 (53.5%) 441/643 (68.6%)	-1.1 (0.17) -1.1 (0.07)	-1.8 (0.18) -2.3 (0.07)	13/70 (18.6%) 109/646 (16.9%)	17/71 (23.9%) 267/643 (41.5%)
Time from RA diagnosis <1 year 1-5 years 5-10 years >10 years	33/105 (31.4%) 108/234 (46.2%) 62/166 (37.3%) 83/210 (39.5%)	73/113 (64.6%) 161/233 (69.1%) 111/166 (66.9%) 133/201 (66.2%)	-0.8 (0.14) -1.2 (0.10) -0.9 (0.14) -1.0 (0.16)	-1.9 (0.13) -2.2 (0.10) -2.3 (0.14) -2.2 (0.16)	12/105 (11.4%) 46/234 (19.7%) 28/166 (16.9%) 36/210 (17.1%)	31/113 (27.4%) 97/233 (41.6%) 79/166 (47.6%) 77/201 (38.3%)
DAS28-hsCRP score ≤5.1 >5.1	75/210 (35.7%) 211/502 (42.0%)	120/182 (65.9%) 359/530 (67.7%)	-0.7 (0.09) -1.2 (0.07)	-1.8 (0.10) -2.3 (0.07)	58/210 (27.6%) 63/502 (12.5%)	105/182 (57.7%) 177/530 (33.4%)
SDAI Lowest tertile Middle tertile Highest tertile	91/242 (37.6%) 94/240 (39.2%) 99/225 (44.0%)	147/223 (65.9%) 167/246 (67.9%) 161/235 (68.5%)	-0.8 (0.08) -1.0 (0.11) -1.3 (0.12)	-1.9 (0.09) -2.2 (0.10) -2.5 (0.12)	68/242 (28.1%) 33/240 (13.8%) 20/225 (8.9%)	129/223 (57.8%) 92/246 (37.4%) 57/235 (24.3%)
HAQ-DI Lowest tertile Middle tertile Highest tertile	104/250 (41.6%) 99/262 (37.8%) 83/200 (41.5%)	173/256 (67.6%) 157/238 (66.0%) 149/218 (68.3%)	-1.1 (0.10) -0.9 (0.10) -1.2 (0.12)	-2.2 (0.10) -2.2 (0.10) -2.2 (0.12)	64/250 (25.6%) 32/262 (12.2%) 25/200 (12.5%)	130/256 (50.8%) 85/238 (35.7%) 67/218 (30.7%)

Disclosure: J. M. Kremer, Corrona, LLC, 3,Corrona, LLC, 1,AbbVie, Amgen, BMS, Genentech, GSK, Lilly, Medimmune, Pfizer, and Sanofi, 5; **M. C. Genovese**, AbbVie, Astellas, Eli Lilly and Company,, 2,AbbVie, Astellas, Crescendo Bioscience, Eli Lilly and Company, Galapagos, 5; **D. Muram**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **J. Zhong**, Quintiles, 3; **J. Alam**, Eli Lilly and Company, 1,Eli Lilly and Company, 3; **M. Schiff**, None.

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Abstract Number: 2633

Effect of Different Biologic Agents on Lipid Profile in Rheumatoid Arthritis

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Background/Purpose: Risk of cardiovascular (CV) disease is increased among rheumatoid arthritis (RA) patients, and high inflammatory burden associated to traditional CV risk factors appears to be the major drivers. Inflammation has a deep effect on metabolism so that lipids may have paradoxical implications in RA, being lower cholesterol levels associated to increased CV risk. Different biologic treatments are effective in controlling inflammation and decreasing the number of CV events, but their effects on lipid profile are conflicting or not well documented. Therefore, the aim of this study was to examine any change between different biologic agents on lipid profile of RA patients.

Methods: Patients affected by RA, according to the 2010 EULAR/ACR classification criteria, exposed at least for one year to RA approved dosage regimens of Abatacept (ABA), Infliximab (INF), or Tocilizumab (TCZ) as first line treatment, or Rituximab (RTX) as second line agent, were retrospectively enrolled in this study. Before and after 24 and 52 weeks from treatment start lipid profile (Total Cholesterol, HDL-C and LDL-C, Tryglicerides) and DAS28 were assessed. The odds ratio (OR) for which treatment approach had the best benefit on patients lipid profile was calculated.

Results: A total of 204 (F/M: 179/25; mean age 54±12 years; mean disease duration 7±3 years) patients were eligible for this study and among them 86 (42%) had received INF, 42 (20.5%) TCZ, 37 (18.1%) ABA, and 39 (19.1%) RTX. After 52 weeks of treatment 101 (49.7%) patients achieved the DAS28-remission: 36 INF, 24 TCZ, 21 RTX, 16 ABA. Moreover we observed a mean increasing of 13% in cholesterol fractions levels compared to baseline (+10% for INF and RTX, +15% for ABA, and +18% for TCZ), with no significant changes in Total Cholesterol/HDL ratio. Among those patients that achieved DAS28-remission, in 63% of TCZ, 50% of INF, 45% of RTX, and 38% of ABA treated patients, respectively, a condition of hyperlipidemia was detectable. Compared to ABA group considered as reference, patients that had received TCZ presented an OR of 2.66 (95%CI 1.07-6.64; P=0.03) to develop hyperlipidemia, while patients that had received INF or RTX presented and OR of 1.64 (95%CI 0.74-3.61) and 1.40 (95%CI 0.56-3.51), respectively. No CV events have been detected during the follow-up period.

Conclusion: We demonstrated that a good disease activity control, and consequently an inflammation decrease, affects lipid profile independently from CV risk. Different biologic agents may have unlike impact on lipid levels, probably by a cytokine modulation on cholesterol metabolism.

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Abstract Number: 2634

Lack of Autoantibodies to Peptidyl Arginine Deiminase 4 Predict Increased Efficacy of Mavrilimumab in Rheumatoid Arthritis

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Background/Purpose: Mavrilimumab is an anti-GM-CSF receptor Ab that has recently demonstrated clinical efficacy in Phase 2 studies in rheumatoid arthritis (RA) patients. Predictive biomarkers to identify patients most likely to benefit from new RA therapies such as mavrilimumab would be of great utility. Recent work has demonstrated that a subset of RA patients has autoantibodies to peptidyl arginine deiminase 4 (PAD4), a citrullinating enzyme involved in NETosis and the formation of autoantigens targeted by anti-citrullinated protein antibodies (ACPA). Since PAD4 is expressed by neutrophils and macrophages, key cell types targeted by mavrilimumab, we explored whether anti-PAD4 autoantibodies may be associated with clinical response to mavrilimumab.

Methods: Novel assays to detect autoantibodies reactive with PAD4, PAD3 or PAD2 were developed and used to measure anti-PAD4, PAD3 and PAD2 levels in 288 subjects enrolled in the phase 2a study CP219 and anti-PAD4 and PAD3 levels in 323 subjects enrolled in the phase 2b study 1071. All subjects in the study met the ACR criteria for a diagnosis of RA.

Results: Overall, 35% of the subjects tested positive for anti-PAD4 antibodies and 20% tested positive for anti-PAD3 antibodies. In the phase 2b study 1071 in DMARD-IR patients, the subjects who tested positive for anti-PAD4 were enriched for the presence of ACPA (OR = 54.7, 95% CI = 7.5, 400.0), had higher baseline joint erosion (mean difference = 9.9, 95% CI = 2.6, 17.2) and higher modified total Sharp scores (mean difference = 16.2, 95% C.I. = 3.9, 28.5) than subjects who tested negative. There was a significant treatment-biomarker effect across clinical endpoints ACR20, ACR50, ACR70 and change in DAS28-CRP. Subjects treated with the 150 mg dose of mavrilimumab, the highest dose evaluated, and who tested negative for anti-PAD4 (68% of subjects), had significantly greater benefit from mavrilimumab compared to active placebo (36.7% difference from placebo; odds ratio for ACR50 response = 17.61, 95% CI =3.86, 80.29) relative to subjects who tested positive for anti-PAD4 (8.7% difference from placebo; odds ratio for ACR50 response = 1.46, 95% CI = 0.47, 4.56; P = 0.01 for treatment-biomarker interaction). Similarly, the DAS28-CRP response was enhanced in autoantibody negative (mean difference = -1.44, 95% CI = -1.91, -0.98) compared to autoantibody positive subjects (mean difference = -0.79, 95% CI = -1.45, -0.13; P = 0.022 for treatment-biomarker interaction). Similar trends were observed for an association between greater clinical responses to mavrilimumab relative to placebo in anti-PAD4 negative subjects in the earlier phase 2a trial CP219. Finally, this effect is specific to anti-PAD4 antibodies as no association between response and presence of antibodies to PAD3 was observed, and we only detected very low levels of anti-PAD2 antibodies in the vast majority of RA patients at levels comparable to healthy controls.

Conclusion: Autoantibodies to PAD4 are a promising novel predictive biomarker for the targeted GM-CSF receptor inhibitor mavrilimumab, and further validation of this biomarker in future clinical studies is warranted.

Disclosure: E. Grant, MedImmune, 3,AstraZeneca, 1; **M. Schwickart**, AstraZeneca, 1,MedImmune, 3; **A. Godwood**, MedImmune, 3,AstraZeneca, 1; **R. Moate**, AstraZeneca, 1,MedImmune, 3; **E. Song**, AstraZeneca, 1,MedImmune, 3; **C. Chavez**, AstraZeneca, 1,MedImmune, 3; **M. Albulescu**, AstraZeneca, 1,MedImmune, 3; **D. Close**, AstraZeneca, 1,MedImmune, 3; **M. Liang**, AstraZeneca, 1,MedImmune, 3; **T. Mustelin**, AstraZeneca, 1,MedImmune, 3; **Z. Yao**, AstraZeneca, 1,MedImmune, 3; **K. Ranade**, AstraZeneca, 1,MedImmune, 3.

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Abstract Number: 2635

Using Patient Reported Outcomes to Inform a Treat to Target Treatment Approach in RA

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Background/Purpose: The Patient Reported Outcomes Measurement Information System (PROMIS) is an NIH initiative to develop patient-reported outcome measures (PROs) for use across chronic conditions. PROMIS instruments assess outcomes relevant in Rheumatoid Arthritis (RA) including pain interference, physical function social function, fatigue, and depression. We sought to learn whether use of PROMIS instruments could inform the treat-to-target (T2T) approach to RA management, and whether patient reports of disease impact correlate with objective clinical measures. For this study, patients are treated for 1 year using a T2T approach. Using PROMIS item banks, we developed patient-centered targets in five domains: pain, fatigue, depression, physical function, and social function. We report on the preliminary physician assessment of the impact of the PROMIS instruments on their treatment decisions during the year.

Methods: Patients with RA diagnosed by 2010 ACR/EULAR criteria were recruited from our academic clinical practice. At baseline data collection, standard RA assessments included joint counts, RAPID3, and CDAI scores. The research assessment battery included clinical questionnaires, PROMIS CAT's (computer adaptive tests), prioritization of PROMIS domains, and selection of five items that patients felt were most important within their most highly prioritized domain.

Results: The baseline sample consists of 119 RA patients; median age was 57 (range: 21-77) and 91% were female. Approximately 54% (n=57) exhibited moderate or high disease activity (CDAI m=13.4; SD=11.0). At the time of this analysis, 71 patients (60%) had completed 1 year of therapy. CDAI was recorded for 172 post-baseline visits, with 87 (51%) reporting CDAI >10 and 85 (49%) CDAI ≤10. At each visit, physicians were asked whether the PROs influenced their treatment decisions. For patients with CDAI >10 who had a treatment change (in accordance with T2T recommendations), PROs influenced this decision at 18/68 visits. When CDAI was >10 and treatment was not changed, PROMIS data influenced this decision at 15/40 visits. When CDAI ≤10, PROMIS data influenced decisions at 2/17 visits at which treatment was changed and 41/142 at which it was not. When asked whether the PRO data affected their disease management in some other way, physicians reported that it did for 20/262 post-baseline visits.

Conclusion: The PROMIS instrument collects information on patient impact of disease. In 20/85 (23.5%) visits to date, when treatment decisions were made contrary to T2T recommendations, rheumatologists reported that the PROMIS data influenced their care, suggesting that these data may provide relevant information that is not captured on standard, objective disease activity measures. Further analysis will explore other factors that may have affected care decisions, as well as any differential impact of the PRO data on treatment decisions in patients with either low or high disease activity.

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Abstract Number: 2636

No Strong Evidence Supporting Predictors for Successful Dose Reduction or Discontinuation of a Biologic in Rheumatoid Arthritis: A Systematic Review

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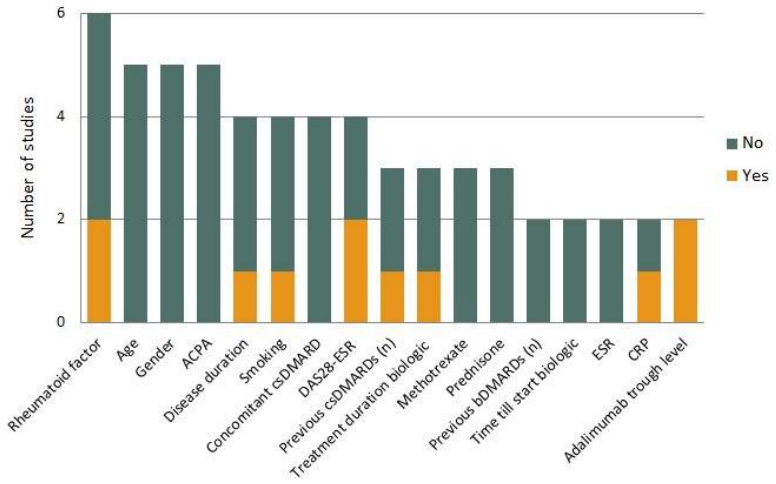
Background/Purpose: Tapering of biologics in rheumatoid arthritis (RA) is based on a trial-and-error disease activity guided strategy, because it is not known in advance which patient can successfully taper. Prediction of successful dose reduction or discontinuation of a

biologic could prevent flares and save drug exposition. In the last years, several cohort studies have investigated biomarkers for predicting successful tapering. However, these results have not yet been systematically summarized. The objective of our study was to systematically review studies that address prediction of successful dose reduction or discontinuation of a biologic in RA patients.

Methods: A broad literature search was performed in PubMed, EMBASE and Cochrane Library (November 2015). Studies that examined the predictive value of biomarkers for successful dose reduction or discontinuation of a biologic in RA patients were included. Two reviewers independently selected studies, extracted data and assessed risk of bias. A biomarker was classified as potential predictor if the univariate association was either strong (odds ratio or hazard ratio > 2.0 or < 0.5) or statistically significant. If these data were not provided, other association measures or textual conclusions were used. Qualitative best-evidence synthesis for biomarkers studied multiple times was performed separately for the prediction of successful dose reduction and discontinuation. Biomarkers that were defined in ≥ 75% of the studies as potential predictor were regarded as 'Predictor'.

Results: Out of 3029 non-duplicate articles, 16 articles on 15 cohorts were included. In total, 17/52 and 33/64 biomarkers were studied multiple times for the prediction of successful dose reduction and successful discontinuation of a biologic. Three predictors were identified: higher adalimumab trough level for successful dose reduction (Figure 1); and lower Sharp/van der Heijde erosion score and shorter symptom duration at the start of a biologic for successful discontinuation. Noteworthy, those three biomarkers were only studied twice, meaning that more frequently investigated biomarkers yielded no consistent predictors.

Conclusion: The predictive value of a wide variety of biomarkers for successful dose reduction or discontinuation of a biologic in rheumatoid arthritis has been investigated. We identified only three biomarkers as predictor in just two studies. The strength of the evidence is limited by the low quality of included studies and the likelihood of reporting bias and multiple testing. **Figure 1** Biomarkers for the prediction of successful dose reduction of a biologic



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Abstract Number: 2637

Clinical Trials Aiming to Prevent the Development of Rheumatoid Arthritis Cannot Detect Prevention without Adequate Risk Stratification; A Trial Performed in UA-Patients As Example

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Background/Purpose: Prevention of rheumatoid arthritis (RA) was the aim of several clinical trials performed in undifferentiated arthritis (UA). Overall these trials had negative results. As preparatory work revealed that only ~30%, of UA-patients develop RA, we hypothesized that inclusion of patients with a low-risk on this outcome, could dilute a possible positive effect and therefore result in false-negative results. This problem has been described in other fields of medicine and re-analysis of the data after post-randomization exclusion of non-informative patients can be a solution to this problem[1]. We therefore re-investigated the PROMPT-trial[2](1-year course of methotrexate (MTX) versus placebo in UA) after post-randomization exclusion of patients without a high risk on developing RA.

Methods: A validated prediction model[3]was used to determine the risk on RA in all patients included in the PROMPT-trial. Patients with a PPV≥84% (prediction score ≥8) were selected and the efficacy of methotrexate was re-evaluated; similar to previous analyses the primary outcome was progression to RA according to the 1987-criteria during 5 years of follow-up and the secondary outcome was drug-free remission.

Results: Of the 110 included patients, 22 had a high-risk on RA according to the prediction model. In the MTX-arm 6/11 (55%) developed RA after 5 years of follow-up, compared to 11/11 (100%) in the placebo-arm (p=0.011). The time to RA-development was longer in the MTX-arm (median of 22.5 months versus 3 months in the placebo-arm, p<0.001). Drug-free remission was achieved by 4/11 (36%) of patients in the MTX-arm and by 0/11 (0%) of the patients in the placebo-arm (p=0.031). These beneficial effects of MTX were seen in both ACPA-positive and ACPA-negative high-risk UA-patients, but not in ACPA-positive nor in ACPA-negative UA-patients without a high risk on RA-development.

Conclusion: Analysis on patients with a high risk on RA revealed that a 1-year course of MTX delayed and prevented RA-development. This emphasizes the importance of adequate risk prediction in trials that aim to prevent RA. 1. Fergusson D, Aaron SD, Guyatt G, Hébert P. Post-randomisation exclusions: the intention to treat principle and excluding patients from analysis. BMJ 2002;325(7365):652–4. 2. van Aken J, Heimans L, Gillet- van Dongen H, et al. Five-year outcomes of probable rheumatoid arthritis treated with methotrexate or placebo during the first year (the PROMPT study). Ann Rheum Dis 2014;73(2):396–400. 3. van der Helm-van Mil AHM, le Cessie S, van Dongen H, Breedveld FC, Toes REM, Huizinga TWJ. A prediction rule for disease outcome in patients with Recent-onset undifferentiated arthritis: How to guide individual treatment decisions. Arthritis Rheum 2007;56(2):433–40.

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Abstract Number: 2638

In Vitro Expansion of Treg By Adaimumab Predicts Clinical Response to Therapy in Patients with Rheumatoid Arthritis

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Background/Purpose: Regulatory T cells (Treg) are potent suppressors of immune responses and are considered a pivotal element in resolving inflammation and autoimmunity. We have previously shown that an increase in CD4 Treg numbers occurs in the peripheral blood of rheumatoid arthritis (RA) patients who have responded to adalimumab but not to the soluble TNF receptor etanercept. Most recently, we demonstrated that adalimumab expands Th17 suppressing Treg by paradoxically promoting membrane TNF–TNFRII binding in RA [1]. We hypothesized that an in vitro Treg expansion assay could predict RA patient's clinical response to anti-TNF antibody therapy.

Methods: RA patients (all fulfilled ACR criteria) who were to begin adalimumab (n=13) were recruited and blood samples taken before (baseline), 3 and 6 months after therapy. Disease activity was assessed using DAS28 and clinical response defined as a drop in DAS28 >1.2 compared to the pre-treatment value. PBMC isolated from RA patients before adalimumab treatment were cultured for 3

day with 10µg/ml adalimumab. On day 3, flow cytomety analysed CD4 and CD8 FoxP3 expression and membrane TNF staining on CD14+ monocytes. Treg expansion was defined as an increase of 45% compared to the unstimulated value.

Results: The addition of adalimumab to PBMC from patients with active RA before adalimumab therapy resulted in a significant increase in monocyte membrane TNF expression (p= 0.0078) and the percentage of CD4 Treg (p= 0.0039) only in patients (n= 9) who then responded to adalimumab therapy as assessed at 3 months post treatment. Moreover, the percentage of CD8+FoxP3+ Treg in PBMC from patients before therapy was elevated by addition of adalimumab in vitro (p=0.0078) and in the peripheral blood of patients analysed at 3 months who responded to therapy. The percentage of CD4 and CD8 Treg expanded by adalimumab in vitro at baseline correlated with the percentage of peripheral blood Treg in patients at 3 months post adalimumab therapy.

Conclusion: CD8 as well as CD4 Treg are expanded by adalimumab in patients with RA. Collectively our data suggest that an in vitro assay based on Treg expansion could predict clinical response to anti-TNF therapy in RA if confirmed in a larger cohort. This predictive test could be of benefit not only as a potential cost saving, prevent risks associated with exposure to numerous anti-TNF agents but represents a step forward to personalised medicine.

1. Nguyen DX and Ehrenstein MR. Anti-TNF drives regulatory T cell expansion by paradoxically promoting membrane TNF-TNF-RII binding in rheumatoid arthritis. *J Exp Med,* 2016 June 6.

Disclosure: D. X. Nguyen, None;

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Abstract Number: 2639

Predicting Flare and Sustained Clinical Remission after Adalimumab Withdrawal Using the Multi-Biomarker Disease Activity (MBDA) Score

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Background/Purpose: The multi-biomarker disease activity (MBDA) (Vectra® DA) score has been reported to predict disease relapses in patients with rheumatoid arthritis (RA) in sustained remission who tapered disease modifying anti-rheumatic drug in prospective randomized controlled trial.(1) The purpose of the present study was to evaluate MBDA score as predictor of flare or sustained clinical remission after discontinuation of adalimumab (ADA) in patients with established RA from the HONOR cohort.(2,3)It was previously shown that sustained biologic-free remission was possible and associated with deep clinical remission.

Methods: This retrospective sub-group analysis was conducted on 42/51 RA patients from the HONOR study with serum samples available at time of discontinuation. The study enrolled patients receiving ADA and methotrexate who maintained DAS28-ESR remission (<2.6) for ≥24 weeks and who subsequently agreed to discontinue ADA. Clinical disease activity, functional status, and joint damage were recorded at ADA discontinuation (baseline), and after 24 and 52 weeks. MBDA scores, a validated disease activity measure for patients with RA calculated based on serum concentration of 12 biomarkers (remission, ≤25; low, 26-29; moderate, 30-44; high, >44), were determined at baseline.(4) The ability of MBDA scores and patient characteristics to predict flare (DAS28-ESR ≥3.2) or sustained clinical remission (SC-REM) (absence of flare with DAS28-ESR <2.6 at all visits) at 6 months and 1 year were evaluated by the area under receiver operator curves as well as Kaplan-Meier estimates, Wilcoxon rank sum test and Cochran-Armitage trend test. Any p-value <0.05 was considered statistically significant and p-value <0.1 marginally significant.

Results: At ADA discontinuation, all patients had DAS28-ESR <2.6 with 81% female, 69% RF+, 81% ACPA+ and 30- month mean disease duration. The median MBDA score was 24.5 [interquartile range: 14.3, 30.8] with 22 (52.4%) patients in remission, and 6 (14.3%) low, 9 (21.4%) moderate and 5 (11.9%) high MBDA score. At 52 weeks, flare and SC-REM were observed in 12/42 (28.6%) and 19/42 (45.2%) patients, respectively. Rate of flare and percentage of SC-REM by MBDA category (remission/low/moderate/high) were 13.6%/50.0%/33.3% and 60.0% (p=0.033) and 63.6%/33.3%/33.3% and 0% (p=0.0066), respectively. Univariate regression analyses identified MBDA score, DAS28-ESR and disease duration as predictors of flare at 52 weeks ($p \leq 0.05$). In a multivariate linear logistic regression model, MBDA scores were marginally associated with flare and SC-REM after adjusting for disease duration.

Conclusion: These findings suggest that the MBDA score could predict flare and biologic-free SC-REM in RA patients in stable clinical remission, undergoing ADA withdrawal while maintaining MTX treatment in a clinical setting and point-out to the potential utility of the MBDA score for guiding treatment decisions in patients receiving biologics. **References:** 1. Rech J, et al, Ann Rheum Dis 2015;0:1–8. 2. Hirata S, et al, Arthritis Res Ther. 2013;15:R135 3. Tanaka Y, et al, Ann Rheum Dis. 2015;74:389–395 4. Hirata S, et al, Current Biomarker Findings 2015;5:69-78

Disclosure: S. Hirata, None; **X. Wang**, Crescendo Bioscience Inc., 3; **C. Hwang**, Crescendo Bioscience Inc., 3; **I. Miyagawa**, None; **S. Kubo**, None; **K. Nakano**, None; **S. Nakayamada**, None; **K. Saito**, None; **N. A. Defranoux**, Crescendo Bioscience Inc., 1,Crescendo Bioscience Inc., 3; **Y. Tanaka**, Bristol-Myers Squibb, MSD, Chugai, Mitsubishi-Tanabe, Astellas, AbbVie, Daiichi-Sankyo, 2,UCB Pharma, Mitsubishi-Tanabe, Abbott, AbbVie, Eisai, Chugai, Janssen, Pfizer, Takeda, Astellas, Daiichi-Sankyo, GlaxoSmithKline, AstraZeneca, Eli Lilly, Quintiles, MSD, Asahi Kasei, 5.

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Abstract Number: 2640

Can GP88 (Progranulin) be Used to Predict the Efficacy of Infliximab?

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Background/Purpose: GP88 (progranulin; PGRN) is a glycoprotein with a molecular weight of approximately 88,000 Da and is thought to play an important role in immune response and tumor proliferation, among other functions. An increasing number of studies have examined anti-inflammatory effect of GP88 in autoimmune diseases. We also reported that GP88 may become a new molecular biomarker for rheumatoid arthritis (RA) (Inflammation 37:1806-13, 2014). We examined the correlation between the efficacy of infliximab (IFX) and serum GP88 concentration in RA patients treated with IFX.

Methods: First, we measured the concentration of GP88 by using ELISA in the serum of 101 RA patients who met the 2010 ACR/EULAR classification criteria and 75 patients with undifferentiated arthritis (UA) prior to starting treatment, who were being treated at a specialist rheumatology outpatient clinic, and compared the results with those from the serum of 149 (men n = 78, women n = 71) healthy individuals undergoing medical check-ups as the control group. Next, we measured GP88 concentration during IFX treatment (start of administration was set as the baseline, and measurements were taken at 14 weeks and 52 weeks or at the time when IFX was discontinued or the dose was changed) by using the frozen stored serum of 50 RA patients who received IFX and were unresponsive to methotrexate.

Results: The GP88 concentration in healthy individuals was 40.5 ± 14.3 ng/mL in men (25–68 years: mean 54.2 years) and 41.0 ± 10.9 ng/mL in women (28–69 years: mean 51.0 years), and there were no gender or age differences. The GP88 concentration was 65.7 ± 2.72 ng/mL in RA patients and 57.4 ± 1.67 ng/mL in UA patients, indicating significantly higher levels in RA patients compared to those in UA patients ($p < 0.01$) and healthy individuals ($p < 0.001$). The background of RA patients treated with IFX was women, n = 40; men, n = 10; aged 26–81 years; mean 60.3 years. The oral methotrexate dose was 6–16 mg/week and IFX dose was 3 mg/kg. The GP88 concentration (mean value) for all 50 patients at each measurement point was baseline: 63.5 ng/mL; 14 weeks: 65.5 ng/mL; and 52 weeks: 69.7 ng/mL. These results indicate an increasing trend, but there were no significant fluctuations. Upon classification of the

groups based on IFX efficacy [effective n = 25 (patients continuing IFX treatment at 52 weeks), primary failure n = 4 (ineffective from the beginning), secondary failure n = 14 (effect weakened midway through treatment), adverse events n = 7 (patients who stopped treatment owing to development of malignant tumor, reaction at administration, among others)], the mean baseline GP88 concentrations (ng/mL) were 62.8, 48.4, 67.1, and 67.5 respectively. These results showed a low level of efficacy in patients with primary failure and higher levels in patients with secondary failure or adverse events. The mean GP88 concentration was 65.2 ng/mL at 52 weeks in responders, but increased to 82.5 ng/mL in patients with secondary failure when they switched from IFX to another drug.

Conclusion: Based on these results, measurement of the GP88 concentration may be useful for auxiliary RA diagnosis, predicting the efficacy of IFX in RA patients, and predicting weakening of the effect during treatment.

Disclosure: M. Sato, None; **M. Takemura**, None; **Y. Yamamoto**, None; **K. Saito**, None.

Abstract Number: 2641

Safety of Synthetic and Biological Dmards: Slr Informing the Update of the EULAR Recommendations for the Management of RA

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Background/Purpose: As part of the update of the EULAR recommendations for the management of RA, we performed a systematic literature review to assess the safety of synthetic (s) and biological (b) DMARDs for the management of RA.

Methods: Observational studies comparing any DMARD with another intervention for the management of patients with RA were identified by searches in Medline, Embase and Cochrane datasets (2013-2016). Interventions were any bDMARD, sDMARD or glucocorticoid and a comparator group was required for the study to be included. All safety outcomes were included. Observational studies, including registries, have been chosen, as they better reflect routine care and have a longer follow-up. Risk of bias (RoB) was assessed according to the Hayden's tool.

Results: Of 4,436 articles screened, a total of 25 papers met the inclusion criteria: 15 dealt with serious infections, 4 focused on cancer, 4 on cardiovascular events and 2 on interstitial lung disease. Studies were heterogeneous precluding meta-analysis. Five studies on serious infections were found and they showed no increased risk of serious infections in bDMARDs (both TNFi and non-TNFi) compared to conventional (c)sDMARDs (Table). The 2 low RoB studies showed no increased risk, while 2 of the 3 high RoB studies showed an increased risk of serious infections (Table). Eight studies, 1 at low RoB, 4 moderate RoB and 3 high RoB, showed no difference in the risk of serious infections between different bDMARDs (Table). One study at low RoB found no increased risk of herpes zoster in TNFi or non-TNFi. Based on 3 studies, all at low RoB, (overall) cancer does not occur more frequently in bDMARDs vs csDMARDs. The same holds true for solid cancers (2 low RoB studies). Based on one low RoB study, non-melanoma skin cancer does not occur more frequently in TNFi or rituximab vs csDMARDs; it may occur more frequently with abatacept (aHR 15.3 [95%CI 2.1; 114.0], but this is based on 2 cases only. One low RoB study addressing infections also analysed mortality, finding that mortality may be lower in bDMARDs, namely etanercept (aHR 0.7 [0.5; 0.9]), vs csDMARDs.

Conclusion: No increased risk of infections was found in patients under bDMARDs (TNFi or non-TNFi) vs csDMARDs, which contrasts to previous findings and possibly reflects an adaptation of clinical practice to avoid the risk of infections. No increased risk of malignancies was found, which is in line with previous findings. Table: Risk of serious infectious in patients on bDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (i vs c)	Risk of Bias
bDMARD vs csDMARD					
Aaltonen 2015	National Register for Biologic Treatment in Finland (ROB-FIN)	TNFi	csDMARDs	0.9 (0.6; 1.4)	Low
		ADA		1.0 (0.6; 1.6)	
		ETA		0.8 (0.5; 1.3)	
		IFX		1.2 (0.6; 2.3)	
		RTX		1.1 (0.6; 1.9)	
Chiu 2014	Taiwan's National Health Insurance Research Database	TNFi	csDMARDs	1.0 (0.9; 1.2)*	High
Lampropoulos 2015	Files Laiko University Hospital	bDMARDs	csDMARDs	***6.9 (3.1; 15.4)***	High
Miranda 2014	Files Colombian hospital	bDMARDs	csDMARDs	***2.7 (1.1; 6.3)***	High
Morgan 2014	BSRBR	ETA	csDMARDs	1.0 (0.8; 1.3)	Low
bDMARD vs bDMARD					
Aaltonen 2015	National Register for Biologic Treatment in Finland (ROB-FIN)	RTX	TNFi	1.4 (0.8; 2.6)	Low
Chiang 2014	Taiwan's National Health Insurance Research Database	ETA	ADA	2.0 (1.1; 3.6)*	High
Chiu 2014		ADA	ETA	1.8 (1.2; 2.8)	High
Curtis 2014	US Veterans (claims dataset)	ABA	ETA	1.1 (0.6; 2.1)	Moderate
		ADA		1.4 (0.9; 2.2)	
		IFX		2.3 (1.3; 4.0)	
		RTX		1.4 (0.8; 2.6)	
Johnston 2013	MarketScan (claims dataset)	ABA	RTX	1.2 (0.8; §)	Moderate
		ADA		1.1 (0.7; 1.7)	
		ETA		1.3 (0.8; 2.0)	
		IFX		1.6 (1.0; 2.6)	
Lampropoulos 2015	Files Laiko University Hospital	ADA	IFX	1.1 (p=0.819)	High
		ETA		0.7 (p=0.559)	
Sakai 2015	REAL	TCZ	TNFi	2.2 (0.9; 5.4)	Moderate
		ADA		1.1 (0.9; 1.3)	
		CZP		1.1 (0.9; 1.3)	
				1.2 (1.1;	

Yun 2016	Medicare claims dataset	ETA	ABA	1.2 (1.1; 1.5)	Moderate
		IFX		1.4 (1.2; 1.6)	
		GOL		1.1 (0.9; 1.4)	
		RTX		1.4 (1.2; 1.5)	
		TCZ		1.1 (0.9; 1.3)	

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Abstract Number: 2643

Risk Factors of Pneumocystis Jiroveci Pneumonia (PJP) in Patients with RA and Sulfasalazine As a Possible Protective Agent

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Background/Purpose: Pneumocystis jiroveci pneumonia (PJP) is a serious complication during the treatment in patients with variety of rheumatic disease. Postmarketing surveillance of infliximab and etnercept in Japan reported that the incidence of PJP was higher than those in Western countries. Harigai et al. reported that in patients under the treatment with infliximab, there are 3 risk factors, i.e., more than 65 years of age, more than 6 mg/day of prednisolone (PSL), and coexisting pulmonary diseases (Harigai M, N Engl J Med 2007). We again tried to find risk factors of PJP in this study and also possible protective factors.

Methods:

Subjects were 310 patients with RA. Out of 310 patients, PJP developed in 26 patients. Patients who took cotrimoxazole were excluded from the control group even duration of administration was short. Diagnosis of PJP was done according to the report of Harigai et al. Diagnosis of PJP was definitive if P. jiroveci was found on microscopical analysis of respiratory samples from patients with clinical manifestations, hypoxemia, and radiologic findings compatible with PJP. The diagnosis of PJP was presumptive if a patient met all three criteria and had either a positive PCR test for P. jiroveci DNA or an increased serum level of (1→3) β-d-glucan with an appropriate response to the treatments for PJP. We picked up items that may relate to the development of PJP, such as age, gender, stage, class, duration of illness, presence of interstitial lung disease (ILD), and drugs for the treatment of RA including the dose. Univariate and

multivariate analysis were done to find out risk and protective factors.

Results: Out of 26 cases of PJP, 4 cases were definitive and 22 cases were presumptive. By univariate analysis, advanced age, advanced stage and class, high daily dose of prednisolone (PSL), and high weekly dose of MTX were significantly related to the development of PJP. Moreover, patients with PJP had significantly higher % of ILD, and higher % use of bDMARDS. However, patients with PJP had significantly lower % use of sulfasalazine (SSZ) (7.7 % vs. 30.0 %). By multivariate analysis, 5 significant positive coefficients for the development of PJP were obtained, i.e. advanced age, advanced class, high daily dose of PSL, high weekly dose of MTX, and use of bDMARDS. Use of SSZ tended to be related to no development of PJP ($p < 0.1$). SSZ has been shown to be protective for P. jiroveci in vitro (Wang J, PRoS Pathogen 2010).

Conclusion: We obtained factors related to the development of PJP which suggest that RA is highly active and advanced. In contrast, SSZ may act as protective agents, but further study is needed to reach definitive conclusion.

Disclosure: S. Motojima, None; **T. Nakashita**, None; **A. Jibatake**, None; **A. Yoshida**, None; **Y. Yamamoto**, None.

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Abstract Number: 2644

Patient Survey Regarding Generic and Bio-Similar Drugs

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Background/Purpose:

In Japan the market share for generic drugs is 50%, lower than that in Western nations. This is partially due to Japan's insurance system, but the reasons why the patients themselves turn down the opportunity to switch to a generic drug when asked at the pharmacy are not clear. In addition, the use of bio-similar drugs became possible in Japan in September of 2015, but the degree of knowledge that patients have regarding them is unknown. Therefore we carried out a patient survey about generic and bio-similar drugs.

Methods:

The survey was carried out amongst patients being treated at research group member facilities. It was an anonymous written survey. After the section on patient background (age, gender, disease history) was completed, patients were asked their impressions of generic drugs, their attitudes towards changing to a generic, whether or not they had ever experienced an adverse effect with a generic drug, what knowledge they had regarding bio-similar drugs, and if they had any interest in or experience with using bio-similar drugs. This research and survey was conducted with the approval of the ethics committee.

Results:

Participants were from 20 facilities, 2384 patients, 83% female, with those in their 60s the majority. Many, 43%, had a disease history of over 10 years. Their impressions of generic drugs were equally good and bad, 45% each. However, those that had a bad experience with a generic (lessening of effect or an adverse event) only comprised 7%, leading to the conclusion that the bad impressions were not the result of experience. Regarding the choice of bio-similar drugs, 14% percent had heard of them, and about half stated no interest in bio-similar drugs, even after seeing explanatory materials. Regarding changing to a bio-similar drug, 70% said they would rely on the opinion of their physician. 11% of participants answered that they would switch for the cost benefits.In a recent online survey,

approximately 28% of physicians expressed a desire to use generic drugs, while 65% of patients expressed interest in using them, showing a gap between the two groups. In the current survey we found that there is anxiety regarding adverse events, and that resistance to a change in medication is more common in RA patients than with those of other illnesses. These factors may explain the tendency of RA patients to leave the decision of whether to use a bio-similar drug up to the physician instead of choosing one themselves.

Conclusion:

There is not enough education regarding switching to generic drugs and bio-similar drugs. The authors recommend that new avenues of patient education be explored, in order to help patients feel competent in making decisions about their medications.

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Abstract Number: 2645

Treatments for Early Rheumatoid Arthritis (RA): A Systematic Review of Randomized Controlled Trials

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Background/Purpose: The objective of this systematic review was to evaluate the clinical evidence on the efficacy of different drug regimens for the treatment of early rheumatoid arthritis (RA). Different cut-off points have been used to define early RA. For this review we used duration of symptoms of ≤2 years, since this limit has been used in several trials.

Methods: We conducted an overview of systematic reviews. We searched for reviews indexed in The Cochrane Library and PubMed through June 2016. Our search strategy was restricted to reviews published in English with efficacy data. Two reviewers screened the list of included references in each review independently. Specific criteria included: results clearly specified for all patients (or subgroup reported) in study having ≤2 years of duration of RA, and at least six months of therapy and follow-up. Data extraction and assessment of the methodological quality of the trials using the Cochrane risk of bias tool was performed by one reviewer and crosschecked by another. Our primary outcome was the proportion of patients achieving an American College of Rheumatology (ACR) 50% response. Secondary outcomes included ACR improvement criteria of 20 and 70%, and safety. We performed direct comparison meta-analyses when data was available for 2 or more studies with the same interventions and outcomes.

Results: Out of 684 reviews, over 764 relevant citations evaluating steroids, DMARDs or biologics were reviewed. There were 6 type of comparisons, including: i) conventional DMARDs vs placebo; ii) conventional DMARDs monotherapy vs another conventional DMARD monotherapy (e.g., methotrexate (MTX) vs sulfasalazine (SSZ); iii) combination therapy with conventional DMARD vs monotherapy (e.g., MTX+SSZ, MTX+Cyclosporine, MTX+ bucillamine, MTX+ doxycycline); iv) combination therapy with conventional DMARDs and added prednisone vs monotherapy (with or without prednisone); v) combination therapy with conventional DMARDs and added prednisone vs combination therapy with conventional DMARDs; and vi) combination therapy with biologic DMARDs vs conventional DMARD monotherapy. ACR 50 response criteria rates were statistically significantly improved with most combination therapies (except MTX + cyclosporine, MTX + Bucillamine) compared with MTX alone at 1 and 2 years (RRs ranged between 1.4 (95%CI 1.1 to 1.6) and 10.3 (95% CI 1.5 to 69.6)). Similar effects were observed with ACR 20 response criteria rates (RRs ranged between 1.2 (95%CI 1.0 to 1.4) and 3.0 (95%CI 1.3 to 7.1)). No differences were observed among the various conventional DMARD monotherapies examined in these trials.

Conclusion: In patients with early onset disease of less than 2 years and active disease, MTX in combination with other conventional or biologic DMARD results in greater ACR responses compared with MTX or DMARD monotherapy. These findings suggest that patient may benefit by early combination therapy, either at onset, or possibly by adding a second conventional or biological DMARD early on.

Disclosure: S. R. Garcia, None; **M. A. Lopez-Olivo**, Rheumatology Research Foundation, 2; **M. Suarez-Almazor**, National Institute for Musculoskeletal and Skin Disorders, 2.

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Risk of Hepatitis B Reactivation in Inflammatory Arthritis Patients Receiving Disease Modifying Anti-Rheumatic Drugs (DMARDs): A Systematic Review and Meta-Analysis

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Background/Purpose: There is limited information for the rate of hepatitis B reactivation in inflammatory arthritis patients. We conducted a systematic review and meta-analysis, assessing hepatitis B reactivation rates in patients who were with resolved or chronic hepatitis B, receiving non-biologic DMARDs, TNF-alpha inhibitors or other biologics and whether receiving antiviral prophylaxis.

Methods: We utilized the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement as the standard for protocol development. Electronic searches were conducted in Pubmed, Medline and EMBASE using OVID through 12/31/2015. A search strategy was developed for each database by combing the medical subject headings (MeSH) and/or text terms from following inclusion criteria: participants (rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, with resolved, or chronic hepatitis B infection), interventions (non-biologic DMARDs, TNF-alpha inhibitors and non-TNF biologics), and outcomes (hepatitis B reactivation). Four reviewers independently extracted study data and assessed quality of study with the Newcastle-Ottawa scales. To determine the pooled hepatitis B reactivation rate, the variances of the raw proportions were stabilized using a Freeman-Tukey-type arcsine square root transformation, using a random-effects model.

Results: 25 studies that met our inclusion criteria, including 2 case series, 10 prospective and 13 retrospective observational studies. The overall pooled rate of hepatitis B reactivation was 1.6% (**table1**, 95%CI, 0.8-2.6%, I^2: 51.0%) in patients with resolved hepatitis B and 14.6% (95%CI, 4.3-29.0%, I^2: 89.6%) in patients with chronic hepatitis B. Similar rates were observed in resolved patients on TNF-alpha inhibitors (Pooled rate: 1.4%, 95%CI, 0.5-2.6%) and non-biologic DMARDs (Pooled rate: 1.7%, 95%CI, 0.2-4.2%); whereas a higher rate was observed in other biologics users (Pooled rate: 6.1%, 95%CI, 0.0-16.6%). We also found the reactivation rate was lower in patients with chronic hepatitis B infection who received antiviral prophylaxis on TNF alpha treatments (**table 2**, Pooled rate: 4.4%, 95%CI, 0.4-11.7%), than those who did not (Pooled rate: 15.6%, 95%CI, 2.3-35.7%).

Conclusion: We found the hepatitis B reactivation rate in inflammatory arthritis patients was low in resolved patients and moderate in chronic hepatitis B patients. Further, higher rates were observed in chronic hepatitis B patients without antiviral prophylaxis. **Table 1. HBV reactivation rates in inflammatory arthritis patients with resolved hepatitis B , on various DMARDs exposures and without antiviral prophylaxis**

Resolved HBV*	Antiviral prophylaxis (-)			
	N	Event	Pooled Rate,% (95%CI)	P value**
Summary	1,032	16	1.6 (0.8-2.6)	0.27
TNF-alpha inhibitors	629	8	1.4 (0.5-2.6)	0.26
Non-TNF biologics	69	3	6.1 (0.0-16.6)	0.07
Non-biologic DMARDs	334	5	1.7 (0.2-4.2)	0.22

*Resolved HBV: HbsAg (-), HbcAb (+) **P value for study heterogeneity within drug classes. TNF: tumor necrosis factor; DMARD: Disease Modifying Anti-Rheumatic Drugs. **Table 2. HBV reactivation rates in inflammatory arthritis patients with chronic hepatitis B, without or with antiviral prophylaxis**

Chronic* HBV	Antiviral prophylaxis (-)				Antiviral prophylaxis (+)			
	N	Event	Pooled Rate,% (95%CI)	P value**	N	Event	Pooled Rate,% (95%CI)	P value**
Summary	160	24	14.6 (4.3-29.0)	<0.001	99	12	9.2 (1.4-21.6)	0.01
TNF-alpha inhibitors	64	11	15.6 (2.3-35.7)	0.05	57	2	4.4 (0.4-11.7)	0.73
Non-TNF biologic DMARDs	58	13	22.4 (8.1-40.8)	0.11	28	10	36.2 (19.4-54.8)	0.68

*Chronic HBV: HbsAg (+) **P value for study heterogeneity within drug classes. TNF: tumor necrosis factor; DMARD: Disease Modifying Anti-Rheumatic Drugs.

Disclosure: T. C. Lin, None; **M. M. D. Abreu**, None; **S. K. Tedeschi**, None; **K. Yoshida**, None; **D. H. Solomon**, None.

Abstract Number: 2647

Drug Trough Serum Levels Rather Than Antidrug Antibodies Explain Disease Flares in Patients with Rheumatoid Arthritis and Psoriatic Arthritis Treated with TNF Inhibitors in Clinical Remission/Low Disease Activity: A One Year Prospective, Multicenter Study (INMUNOREMAR)

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Background/Purpose: To determine predictive factors of disease flares, including drug trough serum levels and anti-drug antibodies (Ab) in patients with rheumatoid arthritis (RA) or polyarticular psoriatic arthritis (PsA) in clinical remission (CR) or low disease activity (LDA) receiving TNF inhibitors during a 1-year follow-up.

Methods: Prospective, multicentre study of RA and PsA patients attended in 3 hospital outpatient clinics (Catalonia, Spain) treated with ADA, ETN or IFX for ≥3 months in CR or LDA measured by DAS28-ESR at ≥2 consecutive visits. Ab and trough serum levels (ELISA

Kit Promonitor®, Progenika SA, Spain) were determined at 0, 4, 8 and 12 months. Disease flare was defined as DAS28>3.2 and a delta DAS28 > 0.6 during the 1 year follow-up compared with visit 0.Variables collected: demographic data; disease activity, diagnosis; disease duration; biologic drug; reduced dose, and concomitant csDMARD therapy. Differences between patients with and without disease flare were studied by univariate analysis. Associations between baseline variables and disease flares according to TNFi used were established using multivariate logistic regression analysis.

Results: 187 patients (RA 103 [57%], PsA 81 [43%]), 66% female, mean age 57±12 years, were included. 138 (74%) patients were in CR, 49 (26%) were on LDA, 69 ADA, 83 ETN and 35 IFX. Mean treatment duration was 60±41 months. Thirty-three out of 166 patients (19.9%) who completed follow-up had a disease flare (10 ADA, 13 ETN, 10 INF), 15 at month 4, 13 at month 8 and 5 at month 12. Six patients developed Ab (3 ADA, 3 INF): 3 at visit 0 and 3 during follow-up, of whom five had a disease flare. Patients with disease flares had lower mean baseline trough serum TNFi levels although the difference was significant only for ADA: 1.7 (1.1-2.7) µ/ml vs. 7.1 (3.5-11.4) $p<0.01$, higher baseline DAS28 (2.5±0.7 vs. 2.0±0.6 $p<0.01$), and a lower frequency of remission (54.5% vs. 78.9% $p<0.01$). In ADA-treated patients, but not in those treated with ETN and INF, drug serum levels at baseline were associated with disease flare in the logistic regression analysis (AUC 0.919). No other factors associated with disease flare were identified. During flares, trough serum levels of the three TNFi decreased in comparison with baseline values (median ADA 1.7 *vs*. 0.1, INF 1.3 *vs*. 0 and ETN 1.9 *vs*. 0.3. although the difference was significant only for ETN ($p<0.01$).

Conclusion: Over a one-year follow up, disease flares were observed in 20%of RA and PsA patients treated with TNFi for a prolonged period who achieved clinical remission/low disease activity. Ab explained only 15% of disease flares. A higher DAS28 and lower drug trough serum levels of ADA at baseline (but not ETN or INF) were associated with disease flare. During disease flares, there was a pronounced decrease in TNFi drug serum levels.

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Abstract Number: 2648

Predictive Role of Biomarkers for the Response to Biologic Therapy in Rheumatoid Arthritis. Old, New and How Future Looks like?

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Background/Purpose: discovery of biomarkers that can identify pretreatment patients who will respond to biologic DMARDs therapy is one of the major interests in RA. We proposed to test the possible predictive role of RF isotypes IgM and Ig A, anti-CCP, anti-mutated citrullinated vimentin (anti-MCV), 14-3-3 eta protein and COMP on a group of patients treated with anti-TNF α agents.We have also assessed the status of these biomarkers and response to biologic therapy.

Methods: prospective and observational study including 64 patients followed 12 months with active RA, uncontrolled by conventional synthetic DMARDs or declared nonresponders to one of the biologic DMARDs and required switch to another biologic DMARDs. Clinical assessment was performed at 0, 6 and 12 months according to ACR criteria approved by OMERACT and evaluation of treatment response according to EULAR criteria (good /moderate /nonresponder).

Results: mean age was 57.55 ± 9.427 years, of the 64 patients included in the study 59 (92.2%) were women and 5 (7.9%) men. At 6 months, 7 patients were declared nonresponders, 38 achieved a moderate response and 19 good response. Following baseline immunological parameters titres and the response at 6 months, general tests have identified significant differences between groups.Tests for identifying differences between the groups showed that lower titres of both RF isotypes , anti-CCP, 14-3-3 eta protein and COMP had predictive value on achieving a good EULAR response at 6 months. Grouping patients in 2 categories (responders/nonresponders), just 14-3-3 eta protein and anti-CCP maintained their predictive value for the response at 6 months.

	Nonresponder	**Moderate response**	**Good response**	**Comparison of responses (p value)**	**Nonresponder**	**Responder**	**Comparison of responses (p value)**
N	**7**	**38**	**19**		**7**	**57**	
RF type Ig M	132.35± 99.602	157.22±131.47	51.36±95.359	**0.01629**	132.35± 99.602	121.93±129.92	0.57168
RF type Ig A	122.81±99.876	102.08±128.33	22.45±61.256	**0.03336**	122.81±99.87	75.54±116.282	0.30787
Anti-MCV	74.04±47.951	80.06±149.543	33.77±113.069	0.45914	74.04±47.951	64.63±139.174	0.86037
14-3-3 eta protein	0.99±0.888	0.28±0.469	0.51±0.580	**0.04518**	0.99±0.888	0.36±0.515	**0.04042**
Anti-CCP	146.16±41.688	113.65±50.448	60.82±26.331	**0.00011**	146.16±41.68	96.04±50.355	**0.02834**
COMP	1042.2±181.71	1032.8±188.67	746.04±130.09	**0.00000**	1042.2± 181.717	937.27±218.10	0.22727

After 12 months, 1 patient was declared nonresponder, 11 achieved moderate response and 14 good response. For this visit, lower baseline titres for RF type Ig M (92.93±120.22U/ml, p=0.01032) and Ig A (49.96±98.08 U/ml,p=0.00247) had predictive value for achieving a good response at 12 months . We didn't obtain other informations grouping patients in 2 categories . Regarding the status of biomarkers and treatment response, the only differences were obtained for COMP (p = 0.0001) at 6 months for good response and RF type IgA (p=0.0041) for good response at 12 months. Using multivariate logistic regression methods we obtained a statistical model for predicting the response at 6 months including normal values for 14-3-3 eta protein, anti-CCP and COMP. The model is a good approximation for the situation analyzed (Hosmer and Lemeshow according test $\lambda^2 = 5.795$, $p = 0.670 \geq 0.05$) with a predictive response accuracy of 89.1%.

Conclusion: because until now has not been discovered a single biomarker capable of distinguishing pretreatment responders versus nonresponder, in the future a version using multiple biomarkers could increase accuracy for identifying pretreatment these patients.

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Abstract Number: 2649

Patient Preferences Regarding Rheumatoid Arthritis Therapies in Lebanon: Results from a National, Multicenter, Cross-Sectional Survey

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Background/Purpose: Treatment options in rheumatoid arthritis (RA) have expanded significantly over recent years, and several agents are now available for oral, subcutaneous (SC) or intravenous (IV) use. Route of administration may be an important differentiator between drugs that are used to treat RA, especially if patient preferences influence adherence and outcomes of therapy. The purpose of this study was to investigate patient preferences for attributes associated with RA treatments in Lebanon.

Methods: A national, multicenter, cross-sectional patient survey was designed to collect data across several private and university hospital clinics on the typical RA patient profile. Participants were asked about their use of RA therapies, preferences for oral, IV or SC therapy and their physician's role in their decision-making process. Data were analyzed using the Chi-square test and Mann-Whitney test.

Results: A total of 693 patients, consecutively recruited over a fixed period of 3 months, completed the survey. The median patient age range was 51–60 years (28.7%). The majority of respondents were female (83%). Over 81% of patients had health coverage. A large proportion (80%) of patients had established RA, with only 3% having early RA. One-third of patients (34.2%) were in DAS28 remission, while 32.9% had a DAS28 score of 3.3–5.1. Oral was the most common route of DMARD administration. Almost 60% of patients received medication by this route only, with a further 27% using the oral route in combination (with either IV or SC). Patient route preference mirrored this trend with almost two-thirds of patients (64%) preferring the oral route (**Table 1**). There was a significant association between route of administration and therapy preference. Patients with an IV route had a similar preference for IV therapy (43%) and oral therapy (40%). SC patients also had split preferences, with 41% preferring oral therapy and 38% SC therapy. Those with an oral route overwhelmingly preferred oral therapy (82%) (**Table 2**). The physician's advice was cited as the main influence when choosing a treatment, with over half (53%) of patients giving this as their top choice.

Conclusion: The majority (64%) of patients preferred the oral route of administration. There was a strong correlation between the route of administration in use and the preference. The patients' preferences of administration were influenced mainly by the physician, followed by experience with current or previous treatments. Understanding patient preferences may help to inform provider and payer decisions in treatment selection that may enhance patient adherence to therapy.

Table 1 Patient disease information			
Variable	**Category**	**Number**	**Percentage**
Disease stage	Very early (<3 months)	21	3.1%
	Early (3-24 months)	117	17.3%
	Established (>24 months)	538	79.6%
DAS28 score	Remission (≤2.6)	205	34.2%
	Low (2.7-3.2)	139	23.2%
	Moderate (3.3-5.1)	197	32.9%
	High (>5.1)	58	9.7%
Radiographic damage	Yes No	265 329	44.6% 55.4%
Length of	< 5 years	236	39.0%
symptoms	5 – 9 years	151	25.0%
(since onset)	10 – 19 years	157	26.0%
	20+ years	61	10.1%
	Median (IQR) (*) (years)	6 (3, 13)	
Time onset to	0 – 3 months	276	45.9%
diagnosis	3 – 6 months	81	13.5%
	6 – 12 months	84	14.0%
	1 – 2 years	66	11.0%
	2 – 5 years	52	8.7%
	5+ years	42	7.0%
	Median (IQR) (*) (months)	4 (0, 12)	
Current route of therapy	IV	30	4.6%
administration	Oral	388	59.2%
	SC	61	9.3%
	Oral + IV	88	13.4%
	Oral + SC	88	13.4%
Patient preference	IV	42	6.2%
	Oral	429	63.6%
	SC	56	8.3%
	Don't mind	148	21.9%

Table 2 Association between route of administration and therapy preference					
	Therapy preference				
Route of administration	**IV** **N (%)**	**Oral** **N (%)**	**SC** **N (%)**	**Don't mind** **N (%)**	**P-value**
IV	**13 (43.3%)**	12 (40.0%)	1 (3.3%)	4 (13.3%)	**<0.001**
Oral	5 (1.3%)	**315 (81.6%)**	16 (45.7%)	5 (13.0%)	
SC	2 (3.3%)	**25 (41.0%)**	23 (37.7%)	11 (18.0%)	
Oral + IV	18 (20.5%)	32 (36.4%)	1 (1.1%)	**37 (42.1%)**	
Oral + SC	4 (4.6%)	28 (31.8%)	15 (17.1%)	**41 (46.6%)**	

Disclosure: F. Fayad, NewBridge, 2,AbbVie, Pfizer, Roche, Novartis, Lilly, NewBridge, Bristol-Myers Squibb, and Sanofi-Aventis, 5,AbbVie, Pfizer, Roche, Novartis, Lilly, NewBridge, Bristol-Myers Squibb, and Sanofi-Aventis, 8,AbbVie, Pfizer, Roche, Novartis, Lilly, NewBridge, Bristol-Myers Squibb, and Sanofi-Aventis, 9; **N. Ziade**, AbbVie, 2,AbbVie, Pfizer, Janssen, Lilly, Roche, and Sanofi-

Aventis, 5,AbbVie, Pfizer, Janssen, Lilly, Roche, and Sanofi-Aventis, 8,AbbVie, Pfizer, Janssen, Lilly, Roche, and Sanofi-Aventis, 9; **G. Merheb**, Pfizer, AbbVie, Lilly, Roche, Sanofi-Aventis, NewBridge, and Janssen, 5,Pfizer, AbbVie, Lilly, Roche, Sanofi-Aventis, NewBridge, and Janssen, 8,Pfizer, AbbVie, Lilly, Roche, Sanofi-Aventis, NewBridge, and Janssen, 9; **S. Attoui**, Pfizer, AbbVie, Roche, Sanofi-Aventis, and Janssen, 5,Pfizer, AbbVie, Roche, Sanofi-Aventis, and Janssen, 8,Pfizer, AbbVie, Roche, Sanofi-Aventis, and Janssen, 9; **A. Aiko**, AbbVie, Roche, and Pfizer, 5,AbbVie, Roche, and Pfizer, 8,AbbVie, Roche, and Pfizer, 9; **K. Mroue**, AbbVie, Roche, and Pfizer, 5,AbbVie, Roche, and Pfizer, 8,AbbVie, Roche, and Pfizer, 9; **A. F. Masri**, Pfizer Inc, 5.

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Abstract Number: 2650

Prediction of Inhibition of Radiographic Progression By Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis Despite Disease-Modifying Anti-Rheumatic Drug Treatment: Results of a Global, Phase 3 Trial

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Background/Purpose: In the SIRROUND-D study, sirukumab, a human anti–IL-6 cytokine monoclonal antibody, significantly reduced radiographic progression after 52 wks of treatment vs placebo in patients (pts) with active rheumatoid arthritis (RA) despite DMARD treatment. This post-hoc analysis of data from that study was intended to identify potential predictors of radiographic non-progression after 52 wks of sirukumab treatment.

Methods: In this double-blind, Phase 3 study, 1,670 pts with active RA refractory to DMARDs were randomized (1:1:1) to SC sirukumab 50 mg q4w, sirukumab 100 mg q2w, or placebo q2w. In the placebo group, pts with <20% improvement in swollen/tender joints at Wks 18 or 40 or still taking placebo at Wk 52 were re-randomized to sirukumab . The change from baseline (BL) at Wk 52 in the modified Sharp/van der Heijde (SHS) radiographic damage score was evaluated as a co-primary endpoint. For this post-hoc analysis, radiographic non-progression was defined as a change from BL in the SHS score ≤0. Logistic regression analysis was used to select the list of factors associated with radiographic progression. Regression (with interaction term)/ANOVA was used to find factors that have interaction effects with treatment groups. Odds ratios and relative risk were used to compare radiographic progression between sirukumab and placebo under different levels of the factor. Observed SHS scores were used for all analyses.

Results: In this analysis, 1,374 pts with radiographs taken at BL and post-BL were included. The proportion of radiographic non-progressors (change in SHS ≤0) at Wk 52 was significantly greater with both sirukumab doses (50 mg q4w, 55%; 100 mg q2w, 61%) vs placebo (41%; both P <0.001). Based on logistic regression analyses, both clinical characteristics (RF+, anti- CCP+) and disease activity factors (SHS >median SHS at BL, BL SHS score, disease activity scores, swollen/tender joint counts, CRP, low hemoglobin, CDAI score, SDAI score, and SJC28) were confirmed to be associated with radiographic progression. Based on regression/ANOVA analysis, the following factors were found to have an interaction effect with treatment groups on radiographic progression: CCP+, BL SHS >cohort median SHS, and BL SHS >7.5. Odds ratios showed that pts were significantly more likely to be radiographic non-progressors with sirukumab if they were anti-CCP+, had a BL SHS > cohort median SHS, or had a BL SHS >7.5 (~25% quartile cutoff for SHS). For sirukumab 50 mg q4w and 100 mg q2w vs placebo, respectively, relative risk ratios [RR (95% CI)] confirmed anti-CCP+ (1.28 [0.93, 1.77]; 1.40 [1.01, 1.94]), SHS >median (1.40 [1.05, 1.87]; 1.48 [1.12, 1.94]), and SHS >7.5 (1.53 [1.17, 2.00]; 1.55 [1.20, 2.00]) as predictive factors for radiographic non-progression with sirukumab vs placebo.

Conclusion: In this Phase 3 study of sirukumab in pts with active RA despite DMARD treatment, pts with poor prognostic factors for RA, including those who were anti-CCP seropositive or had a BL SHS score >7.5 or > the cohort median, were more likely to have radiographic non-progression with sirukumab vs placebo.

Disclosure: G. Karpouzas, Bristol Myers Squibb, Genentech, GlaxoSmithKline, Janssen, Pfizer, Regeneron, Roche, Sanofi, 8,Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Novartis, Pfizer, Roche, Sandoz, 2; **T. Takeuchi**, Astellas Pharma Inc, Bristol–Myers K.K., Chugai Pharmaceutical Co, Ltd., Daiichi Sankyo Co., Ltd., Eisai Co., Ltd., AYUMI Pharmaceutical Corporation, Takeda Pharmaceutical Co., Ltd., Teijin Pharma Ltd., AbbVie GK, Asahikasei Pharma Corp., and Taisho Toyam, 2,Astra Zeneca K.K., Eli Lilly Japan K.K., Novartis Pharma K.K., Mitsubishi Tanabe Pharma Co., and Asahi Kasei Medical K.K.,abbivie GK, Daiichi Sankyo Co.,Ltd., Bristol–Myers K.K., Nipponkayaku Co.Ltd, Janssen Pharmaceutical K.K., Merck Serono Co.,Ltd., Tak, 5,AbbVie GK., Bristol–Myers K.K., Chugai Pharmaceutical Co,. Ltd., Eisai Co., Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Co., Pfizer Japan Inc., and Takeda Pharmaceutical Co., Ltd., Astellas Pharma Inc, and Diaichi Sankyo Co.,Ltd. ,Celtrion, 8; **C. Thorne**, Abbvie, Amgen, Celgene, Lilly, Novartis, Pfizer, Sanofi, and UCB, 2,Abbvie, Amgen, Celgene, Centocor, Genzyme, Hospira, Janssen, Lilly, Medexus/Medac, Merck, Novartis, Pfizer, Sanofi, and UCB, 5,Medexus/Medac, 8; **S. Sheng**, Janssen Research and Development, LLC, 1,Janssen Research and Development, LLC, 3; **X. Li**, Janssen Research & Development, LLC, 3,Janssen Research & Development, LLC, 1; **R. Rao**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **K. Fei**, Janssen Research and Development, LLC, 1,Janssen Research and Development, LLC, 3; **B. Hsu**, Janssen Research and Development, LLC, 1,Janssen Research and Development, LLC, 3.

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Abstract Number: 2651

Predictors of Inadequate Response and Rapid Radiographic Progression in Patients with Early Rheumatoid Arthritis Receiving Methotrexate: a Post Hoc Analysis of 2 Randomized, Controlled Trials of Adalimumab

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Background/Purpose: Methotrexate (MTX) is recommended as first-line therapy in patients (pts) with rheumatoid arthritis (RA).[1] However, information is limited regarding factors that may predict a poor response to MTX. The objective of this analysis was to identify predictors of MTX insufficient response (IR) and rapid radiographic progression (RRP) among pts with early RA receiving 6 months (mos) of MTX therapy.

Methods: In OPTIMA, pts with RA <1 year were randomized to receive either adalimumab (ADA) 40 mg every other wk (EOW) + MTX weekly (wkly) or placebo (PBO) EOW + MTX wkly for 26 wks. In PREMIER, pts with RA <3 years were randomized to receive ADA 40 mg EOW + MTX wkly, ADA 40 mg EOW + PBO wkly, or PBO EOW + MTX wkly for 2 years. This post hoc analysis compared MTX-IR pts, defined as not reaching stable low disease activity at wks 22 and 26 in OPTIMA and wks 20 and 24 in PREMIER, with pts who responded to initial MTX monotherapy. Comparisons were also made between pts who did and did not have RRP, assessed by an increase in modified Total Sharp Score (mTSS) of >1.5 from baseline (BL) to 6 mos. In pts with available data, backward logistic regression was used to identify potential predictors of MTX-IR and RRP. Candidate predictors included BL demographics, time-averaged disease parameters for 3 time intervals (through 4 wks, 8 wks, and 12 wks of MTX exposure), and BL disease characteristics for the 12-wk interval. Time-averaged variables were calculated as area under the curve standardized for length of time interval.

Results: This analysis included 525 MTX-IR and 162 MTX responders. Mean disease duration at BL was 6 mo for both groups. The mean Disease Activity Score 28 (C-reactive protein; DAS28[CRP]) was 6.2 vs 5.6, Health Assessment Questionnaire Disability Index (HAQ-DI) was 1.6 vs 1.3, and mTSS was 15.5 vs 12.2 for MTX-IR vs MTX responders, respectively. 171 pts experienced RRP, while 499 pts had no RRP; the mean disease duration at BL was 6 mo for both groups. The mean DAS28(CRP) was 6.4 vs 6.0 and HAQ-DI was 1.6 vs 1.5 for pts experiencing RRP vs pts who did not experience RRP, respectively. Mean mTSS at BL was higher for pts who

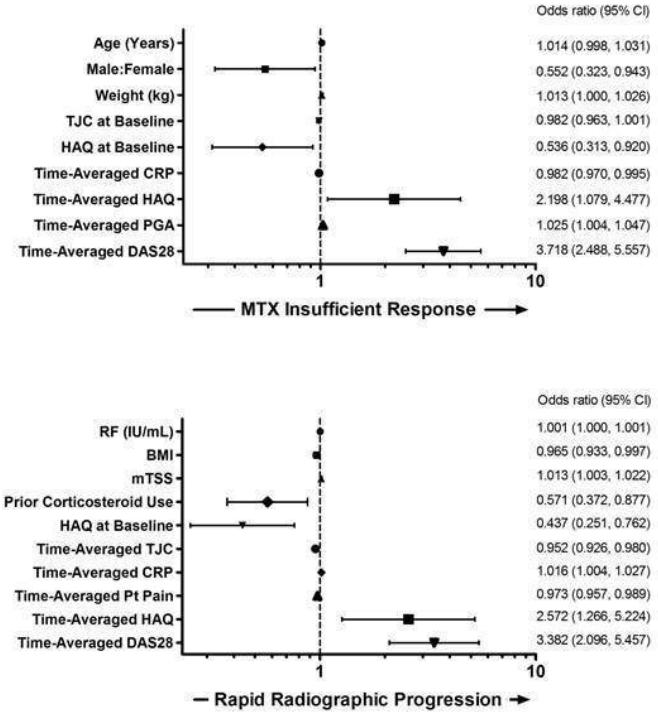
experienced RRP (20.7) vs those who did not (12.4). Predictors of MTX-IR and RRP at 6 mos are shown in the **Figure**. Time-averaged HAQ-DI and DAS28(CRP) through 12 wks were the strongest predictors of both MTX-IR and RRP. Additionally, early clinical response (time-averaged DAS28[CRP]) at both 4 and 8 wks was predictive of both MTX-IR and RRP; however, time-averaged HAQ-DI was not predictive until wk 12.

Conclusion: In the OPTIMA and PREMIER trials, post-BL measures of RA activity appeared to be the strongest predictors of subsequent MTX-IR and of RRP. Pts who are likely to progress on MTX or have RRP may be good candidates for switching to earlier step-up therapy to reduce the likelihood of permanent bone damage.

Reference:

1. Singh JA, et al. *Arthritis Care Res (Hoboken)*. 2016;68(1):1-25.

Figure. Predictors of Methotrexate Insufficient Response or Rapid Radiographic Progression in Patients With Early Rheumatoid Arthritis Receiving Methotrexate*



BMI, body mass index; CRP, C-reactive protein; DAS28, Disease Activity Score 28; HAQ, Health Assessment Questionnaire; mTSS, modified Total Sharp Score; MTX, methotrexate; PGA, Physician Global Assessment of disease activity; Pt pain, patient's assessment of pain; RF, rheumatoid factor; TJC, tender joint count.
*Time-averaged values through week 12 are shown.

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Abstract Number: 2652

Rheumatoid Arthritis and Excess Mortality Associated with Treatments: a Systematic Review and Meta-Analysis

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Background/Purpose: Patients with rheumatoid arthritis (RA) have a lower life expectancy than general population. The impact of RA treatments on global mortality is not known, and only long-term studies can approach it. Our objective was to assess currently available literature on all-cause mortality associated with treatments in patients with RA.

Methods: We systematically searched available literature (Pubmed, Embase and recent abstracts from ACR and EULAR congresses) for studies reporting observed mortality associated with the use of anti-tumor necrosis factor α (anti-TNFα), methotrexate (MTX) and glucocorticoids (GC) in RA, and having a comparison group. The relative risks of mortality associated with the use of respective treatments were collected and pooled in meta-analysis using Review Manager software (Cochrane collaboration). Random effects meta-analyses were conducted, and forest plots were constructed to summarise the risk ratio estimates and their 95% confidence intervals. Data were extracted by one investigator and confirmed by another.

Results: 13995 articles were of potential interest, and 20 finally met required criteria after screening and were included. Follow-up ranged from 2 to 13 years. 9 articles concerned mortality in RA patients treated with anti-TNFα (102621 patients). Observed mortality was reduced in these patients compared with non-users with pooled risk ratio (RR) at 0.73 [95% confidence interval 0.61-0.87], p=0.0004. Regarding MTX, 5 studies were included in the meta-analysis (25252 patients). Reported mortality was also decreased compared with non-users (RR 0.69 [0.49-0.97], p=0.03). Finally, 6 articles concerned mortality in RA patients treated by GC (45292 patients). In these patients, mortality was found to be increased (figure: RR 1.50 [1.17-1.93], p=0.002).

Conclusion: Despite methodological caveats, especially potential indication biases, currently available literature is in favor of a benefit of anti-TNF and MTX on observed mortality in RA, while the use of GC is associated with an increased risk of overall mortality. These data plead for a careful decision making in therapeutic decisions in patients having an apparently controlled disease at the cost of long-term use of GC.

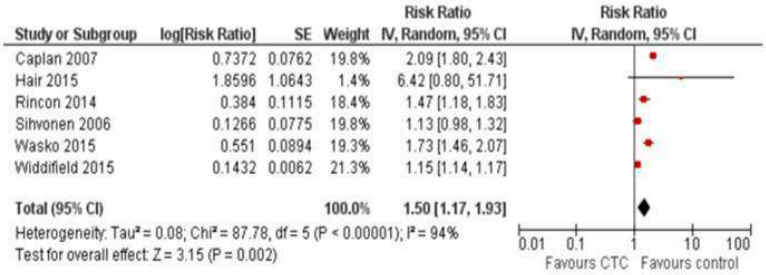

Figure: Pooled risk ratio of observed mortality in patients receiving corticosteroids

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Disclosure: M. Redondin, None; **B. Combe**, None; **C. Gaujoux-Viala**, None; **J. Morel**, None; **C. Lukas**, None.

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Abstract Number: 2653

Results of a Comprehensive Review of Pulmonary Function and Safety Data in a Phase IIb Clinical Program Testing Anti-GM-CSF Receptor Antagonist Mavrilimumab for Treatment of RA

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Background/Purpose: RA is associated with significant pulmonary comorbidity and declines in lung function over time; but longitudinal assessment of pulmonary abnormalities in the context of RA treatment needs further characterization. Mavrilimumab, an investigational human monoclonal antibody, inhibits GM-CSF by binding to the GM-CSF receptor α subunit. We investigated pulmonary safety of mavrilimumab because of its potential to inhibit alveolar macrophage function.

Methods: Pulmonary monitoring included standardized lung function testing (spirometry and diffusing capacity of lung carbon monoxide [DLCO]), chest X-rays, assessments of dyspnea and pulmonary adverse events (AEs) in two randomized, double-blind, multicenter studies (NCT01706926; NCT01715896) where pts with moderate to severe RA received mavrilimumab or placebo and mavrilimumab or golimumab, respectively, and the long-term open-label extension (NCT01712399) where all received mavrilimumab. All studies excluded pts with clinically significant uncontrolled pulmonary disease. Adjudication of lung function abnormalities and pulmonary AEs was by an Independent Pulmonary Expert Committee.

Results: The 442 pts receiving mavrilimumab had cumulative safety data exposure of approximately 900 pt-yrs and median (min–max) exposure of 2.5 (0.1–3.3) yrs. Baseline (BL) characteristics are shown in the Table. Mean forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), DLCO (Figure), and dyspnea (Table) were mostly maintained within 5% of BL values for pts treated during the randomized phases of NCT01706926 and NCT01715896. Few pts showed clinically significant (>20% from BL and <80% predicted) decreases in predicted FEV_1 and FVC (Table); these were mostly transient. Overall, 83 pts (9.24/100 pt-yrs) reported ≥1 pulmonary AE; bronchitis was reported most frequently (pts [per 100 pt-yrs]: 34 [3.78]), followed by respiratory tract infection and cough (14 [1.56] and 12 [1.34], respectively). The rate of pulmonary AEs reported was generally stable over time. No suspected/confirmed pulmonary alveolar proteinosis cases, no pulmonary-related deaths, and only one treatment-related pulmonary serious AE (acute bronchitis) were reported.

Conclusion: Many pts with BL pulmonary comorbidities were identified. Mavrilimumab was not associated with substantial effects on pulmonary function; the rate of pulmonary AEs was stable during the study. This may be the most comprehensive longitudinal study of pulmonary function in RA; further long-term studies should fully characterize these findings and any impact of therapies. ^Joint senior

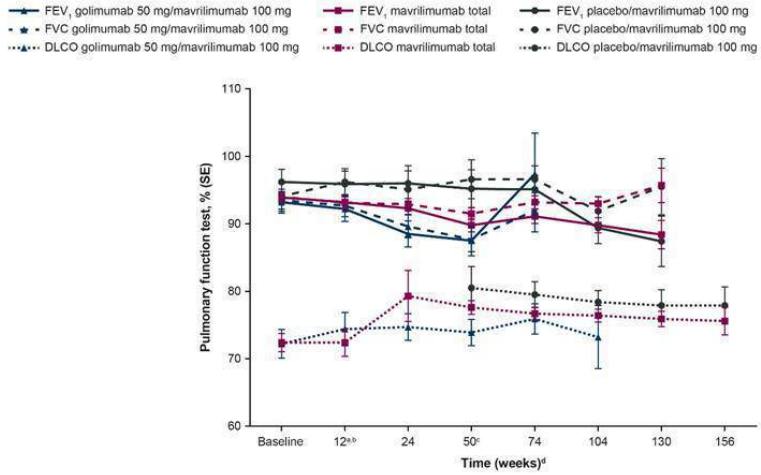
Table. Demographics, baseline disease characteristics, Borg dyspnea score and pulmonary function data in the as-treated population

	Mavrilimumab total[a] (n=442)	Golimumab 50 mg (24 weeks) then mavrilimumab 100 mg (n=68)	Placebo (up to 24 weeks) then mavrilimumab 100 mg (n=81)
Demographics			
Age, years, median (min–max)	52 (19–79)	50 (22–76)	54.0 (25–76)
Sex, % female	85.1	83.8	92.6
BL disease characteristics			
Years since RA diagnosis, mean (SD)	7.91 (6.85)	9.49 (7.41)	7.58 (7.23)
MTX dose, mg/week, mean (SD)	15.00 (6.84)	14.74 (3.81)	15.00 (3.69)
DAS28-CRP, mean (SE)	5.77 (0.04)	5.72 (0.10)	5.78 (0.09)
Concomitant pulmonary diseases, n (%)[b]			
Asthma	17 (3.8)	2 (2.9)	5 (6.2)
COPD	8 (1.8)	0 (0.0)	4 (4.9)
Other	21 (4.8)	5 (7.4)	1 (1.2)
Ever smoked, n (%)	134 (30.3)	17 (25.0)	23 (28.4)
Current smokers, n (%)	76 (17.2)	9 (13.2)	15 (18.5)
RF and ACPA positive, n (%)	359 (81.2)	57 (83.8)	65 (80.2)
% predicted FEV_1, mean (SD)	93.9 (14.7)	93.2 (13.2)	96.2 (16.8)
% predicted FVC, mean (SD)	94.0 (14.6)	93.5 (13.4)	94.1 (17.2)
% predicted DLCO, mean (SD) [n]	72.4 (9.3) [48]	72.2 (10.6) [25]	NA [0]
Borg dyspnea score, mean (SE)	0.4 (0.0)	0.5 (0.1)	0.3 (0.1)
Measure of breathlessness			
Borg dyspnea score, mean (SE) [N]			
Week 12[c,d]	NA	0.4 (0.1) [66]	0.2 (0.1) [76]
Week 74	0.3 (0.0) [279]	0.3 (0.1) [23]	0.3 (0.1) [63]
Week 134	0.3 (0.0) [58]	NA	0.3 (0.1) [24]
Pulmonary function tests			
>20% reduction from BL to 80% predicted FEV_1, n/N (%)			
Week 12[c,d]	2/298 (0.7)	1/64 (1.6)	0/80 (0.0)
Week 74	8/231 (3.5)	0/6 (0.0)	1/55 (1.8)
Week 104	11/178 (6.2)	0/1 (0.0)	1/45 (2.2)
Week 130	1/29 (3.4)	0/0 (0.0)	0/11 (0.0)
>20% reduction from BL to 80% predicted FVC, n/N (%)			
Week 12[c,d]	2/298 (0.7)	0/64 (0.0)	1/80 (1.3)
Week 74	7/239 (2.9)	0/11 (0.0)	2/55 (3.6)
Week 104	6/177 (3.4)	0/2 (0.0)	1/46 (2.2)
Week 130	0/32 (0.0)	0/0 (0.0)	0/13 (0.0)

[a]Mavrilimumab total = all patients who received mavrilimumab in either of the two randomized studies or in the OLE study
[b]Clinically significant uncontrolled pulmonary disease was an exclusion criterion for all three studies
[c]Between Weeks 12 and 24, 3 (3.8%), 8 (9.4%), 12 (14.8%), and 37 (45.7%) pts receiving mavrilimumab 150 mg, 100 mg, 30 mg eow, and placebo, respectively, transferred from NCT01706926 to the OLE study because of lack of efficacy
[d]Between Weeks 12 and 24, 2 (2.9%) and 0 (0.0%) pts receiving mavrilimumab 100 mg and golimumab 50 mg, respectively, transferred from NCT01715896 to the OLE study because of lack of efficacy
ACPA, anti-citrullinated protein antibody; BL, baseline; COPD, chronic obstructive pulmonary disease; DAS28-CRP, disease activity score 28 C-reactive protein; DLCO, diffusing capacity of the lung for carbon monoxide; eow, every other week; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; MTX, methotrexate; NA, not available; OLE, open-label extension; pts, patients; RA, rheumatoid arthritis; RF, rheumatoid factor; SD, standard deviation; SE, standard error

authors.

Figure. FEV_1, FVC and DLCO over time in the as-treated population



FEV_1 golimumab 50 mg/mavrilimumab 100 mg, n	68	64	67	40	6	NA	NA	NA
FEV_1 mavrilimumab total, n	442	298	282	236	231	178	29	NA
FEV_1 placebo/mavrilimumab 100 mg, n	81	80	42	34	55	45	11	NA
FVC golimumab 50 mg/mavrilimumab 100 mg, n	68	64	67	37	11	NA	NA	NA
FVC mavrilimumab total, n	442	298	282	233	239	177	32	NA
FVC placebo/mavrilimumab 100 mg, n	81	80	42	34	55	46	13	NA
DLCO golimumab 50 mg/mavrilimumab 100 mg, n	25	24	37	38	35	9	NA	NA
DLCO mavrilimumab total, n	48	25	33	165	203	165	144	52
DLCO placebo/mavrilimumab 100 mg, n	NA	NA	NA	17	33	43	37	19

[a]Between Weeks 12 and 24, 3 (3.8%), 8 (9.4%), 12 (14.8%), and 37 (45.7%) pts receiving mavrilimumab 150 mg, 100 mg, 30 mg eow, and placebo, respectively, transferred from NCT01706926 to the OLE study because of lack of efficacy
[b]Between Weeks 12 and 24, 2 (2.9%) and 0 (0.0%) pts receiving mavrilimumab 100 mg and golimumab 50 mg, respectively, transferred from NCT01715896 to the OLE study because of lack of efficacy
[c]Following the decision of the sponsor to discontinue NCT01712399, patients' exposure to a study drug/placebo ranged between 2 and 156 weeks, depending on their date of entry and reason for withdrawal from the studies
[d]For final time points where n≤5, results were not shown because the number of patients was too low to enable meaningful interpretation
eow, every other week; DLCO, diffusing capacity of the lung for carbon monoxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; OLE, open-label extension; pts, patients; SE, standard error

Disclosure: G. Burmester, UCB, 2,AbbVie, 5,BMS, 5,Hexal, 5,Janssen Pharmaceutica Product, L.P., 5,Lilly, 5,MSD, 5,MadImmune, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,AbbVie, 8,BMS, 8,Hexal, 8,MSD, 8,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 8,Roche Pharmaceuticals, 8; **M. Michaels**, AstraZeneca, 3,MedImmune, 3; **D. Close**, MedImmune Ltd, 1,MedImmune Ltd, 3; **A. Godwood**, AstraZeneca, 1,MedImmune, 3; **K. Middleton**, None; **P. Miranda**, MedImmune, 5; **J. Vencovský**, None; **J. Kremer**, MedImmune, 5; **I. McInnes**, MedImmune, 5; **M. Albulescu^**, MedImmune, 1,MedImmune, 3; **M. Weinblatt**, Amgen, 2,Crescendo bioscience, 2,Bristol myers squibb, 2,UCB, 2,Amgen, 5,AbbVie, 5,Roche Pharmaceuticals, 5,AstraZeneca, 5,MedImmune, 5,Paizer, 5,Lilly, 5,UCB, 5.

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Abstract Number: 2654

Association Between Rheumatoid Factor Positivity and Effects of Treatment with a First Biologic Agent in Rheumatoid Arthritis

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Background/Purpose: The presence of rheumatoid factor (RF) plays an important role in the diagnosis of rheumatoid arthritis (RA). However, whether RF positivity is related to the effects of treatment with biologic disease-modifying antirheumatic drugs (bDMARDS) remains unclear. This study aimed to determine whether RF positivity was associated with the effects of bDMARDS treatment in bio-naïve RA patients.

Methods: We used demographic and clinical data obtained from the Tsurumai Biologics Communication Registry, which comprises Nagoya University and 20 affiliated hospitals in Japan. Patients aged 20–80 years who fulfilled the ACR 1987 revised or the 2010 ACR/EULAR classification criteria for RA were included, whereas those with prior exposure to bDMARDS were excluded. The RF status was defined as negative (0–15 IU/ml) or positive (>15 IU/ml). Linear multiple regression analysis was used to assess the association between RF positivity and the effects of bDMARDS treatment, as defined by DAS28-ESR improvement at week 24. Unstandardized coefficients were calculated. Adjustment variables included sex, age, DAS28 at pre-treatment, tumor necrosis factor inhibitor (TNFi) or non-TNFi, baseline use of methotrexate and glucocorticoids, and baseline stage and class, as defined by the Steinbrocker classification.

Results: Table 1 summarizes the baseline demographic and disease characteristics of the patients. Some characteristics were different between RF-negative and RF-positive patients; however, they were adjusted using linear multiple regression analysis. Unstandardized coefficients are shown in Table 2. The value of interest was −0.38 ($P < 0.05$), suggesting that the DAS28 improvement in RF-positive patients is inferior to that in RF-negative patients to that extent. Other variables affecting the treatment effects were sex, age, TNFi or non-TNFi, which are well-known influential factors for biologic therapy.

Conclusion: This study demonstrated that RF positivity, in addition to some well-known variables, was independently associated with decreased effects of bDMARDS treatment in bio-naïve RA patients.

Table 1. Baseline characteristics of RF-negative and RF-positive patients

	RF negative (n = 110)	RF positive (n = 511)	P value
Age, Mean ± SD years	53.3 ± 14.4	57.7 ± 13.8	<0.05
DAS28ESR at pre-treatment	4.88 ± 1.25	5.27 ± 1.22	<0.05
Sex, % female	89.1	79.6	<0.05
Stage I, II/III, IV, %	50.9/49.1	38.9/61.1	<0.05
Class I, II/III, IV, %	81.8/18.2	73.6/26.4	0.09
Methotrexate use, %	89.1	77.1	<0.05
Oral steroid use, %	50.9	59.9	0.09
Tumor necrosis factor inhibitor, %	82.7	77.1	0.21

DAS28ESR: Disease Activity Score Calculator for RA with erythrocyte sedimentation rate

Table 2. Coefficients of variables in relation to the effects of bDMARDS treatment

	Estimate	Standard error	P value
(Intercept)	0.09	0.42	0.83
RF status (RF-negative patients as reference)	−0.38	0.13	<0.01
DAS28ESR at pre-treatment	0.74	0.043	<0.01
Sex (male as reference)	−0.31	0.13	<0.05
Age	−0.012	0.0039	<0.01
TNFi or non-TNFi (TNFi as reference)	0.35	0.13	<0.01
Methotrexate use	−0.013	0.13	0.92
Oral steroid use	−0.34	0.11	<0.01
Stage I, II/III, IV	−0.19	0.11	0.07
Class I, II/III, IV	−0.17	0.12	0.17

bDMARDS: biologic disease-modifying antirheumatic drugs, RF: rheumatoid factor, DAS28ESR: Disease Activity Score Calculator for RA with erythrocyte sedimentation rate, TNFi: tumor necrosis factor inhibitor

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Disclosure: Y. Ogawa, None; **N. Takahashi**, None; **T. Kojima**, None; **N. Ishiguro**, None.

Abstract Number: 2655

Prevalence and Risk Factors of Reactivation of Resolved Hepatitis B Virus in Rheumatoid Arthritis Patients Treated with Biological Disease-Modifying Anti-Rheumatic Drugs

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Background/Purpose: Reactivation of hepatitis B virus (HBV) is one of the most serious complications in rheumatoid arthritis (RA) patients treated with biological disease-modifying anti-rheumatic drugs (bDMARDs). De novo hepatitis induced by HBV reactivation in patients with resolved HBV can easily lead to fulminant hepatitis with poor prognosis. However, few studies have addressed the incidence and risk factors of HBV reactivation in RA patients with resolved HBV by treatment of bDMARDs. The purpose of this study was to identify the prevalence and risk factors for developing HBV reactivation in RA patients with resolved HBV who received bDMARDs therapy.

Methods: RA patients who were newly treated with bDMARDs at our department from April 2009 to March 2016 were reviewed for this study. Of these patients, registered were the patients who had been diagnosed as resolved HBV and whose HBV-DNA was repeatedly measured with the interval ranged from one to three months. The definition of resolved HBV was positive for antibody

against hepatitis B core antigen (anti-HBc) and negative for hepatitis B surface antigen (HBsAg). The study endpoint was reactivation of HBV determined as an HBV-DNA level higher than 2.0 log copies/ml. The association between HBV reactivation and clinical, laboratory and treatment data were retrospectively analyzed.

Results: A total of ninety-six RA patients with resolved HBV were included in this study. In these patients, etanercept was administered in 21 patients, abatacept (ABT) in 18, golimumab (GLM) in17, tocilizumab (TCZ) in 17, infliximab (IFX) in 11, adalimumab in 7 and certolizumab pegol in 5. The median follow-up period was 19 months (interquartile range 5-37 months). Six out of ninety-six patients (6.3%) developed HBV reactivation during the observation periods. ABT was used for 2 patients, IFX for 2, GLM for 1 and TCZ for 1. In five out of the six patients, HBV-DNA levels were below the quantitation limit (< 2.1 log copies/ml) without any antiviral therapy while they continued to receive bDMARDs. In contrast, HBV-DNA level over 2.1 log copies/ml was observed in one patient treated with ABT, however HBV-DNA became negative after the initiation of entecavil therapy. The prevalence of HBV reactivation was significantly higher in the patients negative for antibody against HBsAg (anti-HBs) ($p = 0.047$, Fisher's exact test).

Conclusion: HBV reactivation occurred in 6.3% of RA patients with resolved HBV during the bDMARDs treatment. Absence of anti-HBs can be risk for reactivation of resolved HBV in these patients.

Disclosure: T. Watanabe, None; **S. Fukaya**, None; **K. Akikawa**, None.

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Abstract Number: 2656

Resume of Biologic Therapy after Tuberculosis Infection in Patients with Inflammatory Arthropathies. Daily Clinical Practice Data from an Endemic Country

Liliana Uribe Botero[1], Margarita A Saldarriaga Alvarez[1], Natalia Duque Zapata[1], Johnny Urrego[1], Oscar Jair Felipe Diaz[1], Carmen Cerón[2], Alejandro Uribe[1], Luis Alonso Gonzalez[1,3] and **José A. Gómez-Puerta**[1], [1]Medicarte IPS, Medellín, Colombia, Medellín, Colombia, [2]Medicarte IPS, Medellín, Colombia, [3]Rheumatology Unit, Universidad de Antioquia, Medellin, Colombia

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Background/Purpose: Long-term extension studies and observational drug registers mainly from Western countries or non-endemic areas have reported an increased risk of tuberculosis (TB) infection in patients under biological DMARD (bDMARD) therapy. However, information about TB infection in patients with inflammatory arthropathies in daily clinical practice in endemic areas is limited. Our aim was to describe a series of TB infection in patients who received bDMARD treatment and to identify which patients were able to resume bDMARD therapy.

Methods: We included patients with inflammatory arthropathies treated at Medicarte IPS from March 2009 to March 2016. Medicarte is a referral center for the integral medical care and pharmaco-surveillance of patients under biologic therapies in 13 cities in Colombia for inflammatory arthropathies, mainly rheumatoid arthritis (RA), psoriatic arthritis (PsA) and spondyloartropathies (Spa), psoriasis and inflammatory bowel disease (IBD) among others. Clinical information was obtained from electronic clinical records and medical claims. In addition, clinical records from admissions were reviewed for relevant information related with TB. Only those cases with a confirmed diagnosis of TB, either by sputum, biopsies or tissues cultures were included.

Results: Among 6,508 patients under biological treatment followed in our centers, we identified 54 patients who develop a TB infection. Those patients with diagnosis of IBD (N=3) or psoriasis (N=8) were excluded. 13 cases who only received DMARD therapy [methotrexate (MTX) =2 and leflunomide (LEF)=11] were not included. Finally, our sample included 28 patients with inflammatory arthropathies. 68% of patients were female, with a mean age at the moment of TB infection of 50.5 ± 14.7 years. Diagnoses were: 20 RA; 6 Spa; 1 Psa and 1 Spa related with Crohn's disease. None of the patients had concomitant HIV infection. Pulmonary TB was diagnosed in 15 (53.6%) of patients, followed by disseminated TB in 5 (18%), pleural TB in 3 (11%) and laryngeal, miliary, bone, intestinal and lymph node TB in one case each. At the time of TB infection 64% were under steroids treatment (mean dose 7.9 ± 5.9 mg/d), 32% received MTX, 36% LEF and 21% chloroquine. bDMARD treatment before TB infections were as follows: Adalimumab in 13 (46%) patients, infliximab in 6 (21%), etanercept in 5 (18%), abatacept in 2 (7%) and rituximab and certolizumab in 1 case each.

Mean time of TB treatment was 8.2 ± 2.0 months. Two patients died as a direct consequence of TB infection. Thirteen (46%) out of 28 patients resume bDMARD after TB treatment. Five out of 13 patients reinitiated with the same biological agent. Mean follow-up of bDMARD therapy after TB infection was 15.7 ± 18.1 months. No new cases of TB infection have been reported during the follow-up.

Conclusion: In daily clinical practice in an endemic TB country, around half of patients with TB infection were able to resume bDMARD treatment. Extra-pulmonary TB represented more than 40% of cases of TB. In endemic TB countries, a TB infection does not preclude reinitiating of bDMARD therapy.

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Abstract Number: 2657

Withdrawal of Nonsteroidal Anti-Inflammatory Drugs in Rheumatoid Arthritis Patients with Low Disease Activity

Dong Jin Go[1,2], Kichul Shin[3], Han Joo Baek[4], Seong-Wook Kang[5], Young Mo Kang[6], Jae-Bum Jun[7], Yun Jong Lee[8], Sung-Hwan Park[9] and Yeong Wook Song[10,11], [1]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, Korea, The Republic of, [2]Department of Molecular Medicine and Biopharmaceutical Sciences, Graduate School of Convergence Science and Technology, Seoul National University, Seoul, Korea, The Republic of, [3]Division of Rheumatology, Department of Internal Medicine, SMG-SNU Boramae Medical Center, Seoul, South Korea, [4]Division of Rheumatology, Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, South Korea, [5]Department of Internal Medicine, Chungnam National University School of Medicine, Daejeon, South Korea, [6]Division of Rheumatology, Department of Internal Medicine, Kyungpook National University Hospital, Daegu, South Korea, [7]Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, The Republic of, [8]Division of Rheumatology, Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea, [9]Division of Rheumatology, Department of Internal Medicine, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea, [10]Division of Rheumatology, Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea, [11]Department of Molecular Medicine and Biopharmaceutical Sciences, BK21 plus Graduate School of Convergence Science and Technology, and College of Medicine or College of Pharmacy, Seoul National University, Seoul, South Korea

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Background/Purpose: Although nonsteroidal anti-inflammatory drugs (NSAIDs) are effective in relieving joint pain in rheumatoid arthritis (RA) patients, long-term use of NSAIDs can cause adverse effects. We aimed to examine the patient-reported outcome (PRO) and its associated clinical factors in RA patients with low disease activity (LDA) after discontinuing NSAIDs.

Methods: This study was a 16-week, multi-center prospective open-label trial. RA patients who achieved LDA (28-joint Disease Activity Score [DAS28] < 3.2) who were on NSAIDs for more than a month discontinued the NSAIDs. Acetaminphen (AAP) was used as the rescue medication. Changes of DAS28 and PRO including pain visual analogue scale (pain-VAS) and Routine Assessment of Patient Index Data 3 (RAPID-3) score were assessed. NSAID was restarted when patient's pain was intolerable with AAP. The endpoint was to analyze the group of patients who continued to withdraw NSAID. Patients were further classified to have "sustained effectiveness" who met the following: 1) pain-VAS ≤30 mm at week16 or increase less than 25% from baseline and 2) RAPID-3 score ≤6 at week16 or increase less than 25% from baseline.

Results: A total of 109 RA patients with LDA were enrolled in the study. At the end of the study, 89 (84.8%) patients had remained without restarting NSAID. In these patients, there was a difference in pain-VAS between baseline and week 16 (P= 0.010). However, changes in RAPID-3 and DAS28 were insignificant (P= 0.128 for RAPID-3 and P= 0.638 for DAS28) Moreover, 66 patients ended up to show sustained effectiveness without restarting NSAID. After adjustments of covariables, we found out joint swelling was the detrimental factor in NSAID withdrawal (odd ratio [OR] 0.150, 95% confidence interval [CI] 0.034-0.666, P= 0.013) and sustained

effectiveness (OR 0.312, 95% CI 0.101-0.964, P= 0.043).

Conclusion: NSAIDs can be attempted to discontinue in RA patients with LDA, especially in patients without joint swelling.

Disclosure: D. J. Go, None; **K. Shin**, None; **H. J. Baek**, None; **S. W. Kang**, None; **Y. M. Kang**, None; **J. B. Jun**, None; **Y. J. Lee**, None; **S. H. Park**, None; **Y. W. Song**, None.

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Abstract Number: 2658

Adverse Drug Reactions Due to Disease Modifying Drugs in Patients with Rheumatoid Arthritis

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Background/Purpose: There is a high risk of developing adverse drug reactions (ADR) in rheumatology due, mainly, to the Disease Modifying Drugs (DMARD) used. After more than twenty years using DMARD, is widely known their efficacy in rheumatoid arthritis (RA), but it is necessary to increase our knowledge of its ADR, especially those that lead to discontinuation in real life. The purpuse of our study was to describe the incidence rate and characteristics of moderate and severe ADR to DMARD in patients with RA.

Methods: Observational longitudinal study was conducted. Recent onset RA patients diagnosed between April 15th 2007 and 31st December 2010 followed in outpatient clinic at Hospital Clinico San Carlos until December 31st2015, which used any DMARD treatment were included. Primary outcome: development of an ADR that required discontinuation of the DMARD (moderate: discontinuation of the drug; severe: discontinuation and hospitalization or death as a result of the ADR). Incidence rates of discontinuation (IR) per 100 patient-years were estimated using survival techniques with their respective 95% confidence interval [CI].

Results: We included 293 courses of DMARD treatment in 97 patients (815 patient-years). Of these, 78% were women with a mean age at diagnosis of 55.6 ± 15 years. The median time to the start of the first DMARD was 0[0-41] days. 11.5% were taking biological DMARDs, 60.75% were using combined therapy and 86% were taking corticoids. Treatment was suspended due to ADRs in 110 cases (IR: 13.5 [11.2 -16.3]), being gastrointestinal the most frequent cause (21.4%), followed by infections (15.2%). The IR of moderate ADR was 11.2[9.2-13.8], being 11.1[8-15] for monotherapy regimen and 11.4 [8.8-14.9] for combined therapy. The IR of discontinuation related to synthetic and biological DMARDs was 13.2 [0.9-16.2] and 15.6 [8.6-28.2] respectively. The crude IR of discontinuation for moderate ADRs was higher for Gold (IR: 19.5[11.5-32.9]) and Leflunomide (IR: 20.5[10.7-39.5]) being 7.14 [4.8-10.4] for Methotrexate (MTX). 17.5% of the ADR were severe (n=20) with an IR of 2.5[1.6-3.8] being infections the most frequent cause (65%) followed by cancer (20%), gastrointestinal (10%) and exitus (n=1). The crude IR of discontinuation for severe ADRs was higher for biological DMARDs (IR: 4.2[1.3-13.2]) than for synthetic DMARDs (2.28 [1.4-3.6]). The crude IR of discontinuation for severe ADRs was the lowest for Antimalarials (IR: 1.5[0.5-4.8]) and MTX (IR: 1.3[0.5-3.1]. Regarding types of regimen, the IR of severe ADR on monotherapy was 1.5 [0.6-3.5], and with combined therapy was 3.1[1.8-5.1], being higher when we looked at triple therapy (IR: 4.5 [2.4-8.3]).

Conclusion: This study describes the incidence of ADRs occurred in RA patients taking DMARDs in real life conditions. The IR of ADR estimated was 13.5% patient-years, being 2.5% patient-years for severe ones. MTX was the drug with the lowest IR of ADRs. Regarding severe ADRs caution might be taken for those patients on triple therapy.

Disclosure: Z. Rosales Rosado, None; **J. Font Urgelles**, None; **D. Freites Núñez**, None; **C. M. León Cárdenas**, None; **C. Lajas Petisco**, None; **L. Leon**, None; **L. Rodriguez Rodriguez**, None; **J. A. Jover Jover**, None; **L. Abásolo Alcázar**, None.

Abstract Number: 2659

Respiratory Symptoms in Patients with Primary SjöGren's Syndrome – a Case-Control Study

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Background/Purpose: To evaluate the amount and impact of respiratory symptoms in patients with primary Sjögren's syndrome (pSS) and to assess if such symptoms are related to concomitant COPD or ILD.

Methods: Fifty-one consecutive outpatients diagnosed with pSS (median age 61, range 29-82 years, 49 females) and 80 population based controls (median age 61, range 31-80 years, 43 females), denying having been diagnosed with a rheumatological disease, asthma or COPD as well as using bronchodilators and/or inhalation steroids the last 6 months, were included in the study. The pSS patients were evaluated by pulmonary function test as well as CT scans of the lungs. 21 pSS patients fulfilled GOLD criteria for COPD and 9 patients showed radiologic signs of ILD. All subjects also completed a questionnaire on smoking habits from which tobacco consumption could be calculated as well as the St George's Respiratory Questionnaire (SGRQ) on respiratory symptoms. The controls were then stratified into females and males and a linear regression analysis was performed in which age, body-mass index (BMI) and pack-years were added as co-variates to calculate gender, age, BMI and pack-year standardised values for the SGRQ subscores and total score. From the equations of these analyses, expected values for the SGRQ subscores and total score in the pSS patients were calculated. The expected SGRQ-scores were then compared with the actual SGRQ-scores found in the pSS patients. To compare the SGRQ scores in pSS patients with vs. without COPD we calculated the deviation of SGRQ scores from expected values in each pSS patient and compared the groups. The same calculation was performed to compare pSS patients with and without radiologic signs of ILD.

Results: pSS patients had significantly increased SGRQ symptom (25.2 (6.6; 40.5) vs. 2.3 (1.4; 3.8); $p<0.001$), SGRQ activity (39.5 (12.2; 53.6) vs. 12.5 (8.2; 17.5); $p<0.001$), SGRQ impact (9.9 (0; 23.3) vs. 0.7 (0.5; 1.1); $p<0.001$) as well as SGRQ total scores (17.4 (7.4; 34.5) vs. 4.6 (3.3; 6.3); $p<0.001$) in comparison to expected scores based on the results of the population based controls. However, there was no significant difference in the deviation of SGRQ symptom, SGRQ activity, SGRQ impact or SGRQ total scores from expected values in pSS patients with and without COPD or ILD respectively.

Conclusion: In conclusion we showed that respiratory symptoms were more common amongst pSS patients than in the normal population. Concomitant COPD or ILD did not seem to significantly contribute to these, suggesting that other factors are more important in eliciting such symptoms in pSS patients, of which airway sicca is probably the most important. Since pulmonary involvement in pSS is associated with an increased mortality and respiratory symptoms is a poor marker for pulmonary involvement, we suggest that at least PFT should be performed liberally in all pSS patients regardless of symptoms to enable early detection of pulmonary involvement in these patients.

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Abstract Number: 2660

Do Ultrasonographic Lesions of Salivary Glands Evolve in SjöGren Patients during

Follow-up ?

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Background/Purpose: to evaluate if the salivary glands ultrasonographic score (SGUS) is modified during follow-up in primitive Sjögren patients (pSS) and to compare pSS with idiopathic sicca syndromes (non-pSS).

Methods: this study was performed in the Brittany cohort of patients with suspected pSS. All patients had standardized clinical, biological and imaging evaluation. pSS diagnosis was considered according to the AECG criteria. Patients with or without pSS had ultrasonography of both parotid glands and both submandibular glands; they were graded on a 5-point scale (0 to 4). During follow-up, a second ultrasonography was performed. Patients treated with Rituximab were excluded. Salivary-gland ultrasonography was performed by local expert who was unaware of the final diagnosis. We compared the ultrasonographic score between pSS and non-pSS at inclusion and at second evaluation for the sum of the score of the four glands and the maximum score among the four glands.

Results: of the 49 included patients, 29 received a diagnosis of pSS. At baseline, pSS and non-pSS were similar concerning demographics, Schirmer test and salivary flow. Biopsy positivity and SGUS were statistically different at inclusion between pSS and non-pSS ($p<0.001$). Sum of the scores of the four glands and maximum score among the four glands was respectively of 8.9 and 2.7 for pSS and 2.1 and 0.8 in non-pSS. Percentage of patients with at least one score > 2 was respectively of 75.8 % and 25.0 % in pSS and non-pSS. During follow-up, a second ultrasonography of salivary glands was performed with a mean delay of 1.9 (+/-1.6) years. There was no difference between sum of the score of the four glands and maximum score among the four glands at second ultrasonography examination between pSS and non-pSS. Significant difference between sum of the scores of the four salivary glands and maximum score among the four glands of pSS and non-pSS was still present at second salivary glands ultrasonography with ($p<0.001$). No difference was found when parotids and submandibular glands were analyzed apart.

Conclusion: with a mean delay of two years, SGUS is not modified, even in patients with pSS. This observation is also effective in parotid and submandibular glands when taken apart.

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Performance of the Proposed ACR-EULAR Criteria for Sjogren's Syndrome in a Prospective Multidisciplinary Diagnostic Cohort from Daily Clinical Practice

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Background/Purpose: Sjögren's syndrome (SS) is a systemic auto-immune disease with a heterogeneous clinical presentation. Recently, ACR-EULAR criteria were proposed for classification of SS, which combine features of the ACR and AECG criteria. The aim of this analysis was to assess the performance of the ACR-EULAR classification criteria for SS in a well-defined prospective diagnostic cohort from daily practice.

Methods: The study population consisted of consecutive patients who were referred to the University Medical Center Groningen Sjögren expertise center. Inclusion criteria were suspicion of SS, presence of sicca complaints and age of >18 years. Patients who did not complete the full diagnostic workup were excluded. The standardized diagnostic work-up included evaluation of focus score (FS) in minor salivary and/or parotid gland biopsy, anti-SSA antibodies, unstimulated whole salivary flow (UWS), Schirmer's test and ocular staining score (OSS). Patients had to score ≥4 points to fulfill the ACR-EULAR criteria for SS, receiving 3 points for FS≥1 and anti-SSA positivity, and 1 point for UWS ≤0.1 ml/min, Schirmer ≤5 mm/5min and OSS ≥5. Classification according to ACR-EULAR criteria was compared with clinical diagnosis according to the treating rheumatologist.

Results: Between December 2013 and March 2016, 119 patients were included at the start of their diagnostic work-up, of which 5 were excluded due to missing data. Of the 114 patients, 46 (40%) fulfilled the ACR-EULAR criteria for SS, of which 1 patient was classified as secondary SS. Comparing separate tests between SS (n=46) and non-SS patients (n=68), FS≥1 occurred in 85% vs. 4% of the patients, anti-SSA positivity in 78% vs. 6%, UWS ≤0.1 ml/min in 54% vs. 39%, Schirmer ≤5 mm/5min in 83% vs. 55% and OSS ≥5 in 53% vs. 14% (figure). Preliminary analysis showed that agreement between diagnosis according to the treating rheumatologist and classification according to ACR-EULAR criteria was excellent with Cohen's kappa of 0.87 and an absolute agreement of 94%. The ACR-EULAR criteria had a sensitivity of 95% and specificity of 93%.

Conclusion: In our prospective, multidisciplinary diagnostic cohort derived from daily clinical practice, 40% of the patients fulfilled the ACR-EULAR classification criteria for SS. FS≥1, anti-SSA positivity and OSS ≥5 occurred almost exclusively in SS patients, whereas UWS ≤0.1 ml/min and Schirmer ≤5 mm/5min were often found in non-SS patients too. Agreement between the ACR-EULAR criteria and clinical diagnosis was excellent. The present findings support use of the proposed ACR-EULAR criteria to classify SS patients for clinical diagnostic as well as research purposes. In future analysis, classification of SS according the ACR-EULAR criteria will be compared with classification according to an expert panel of rheumatologists.

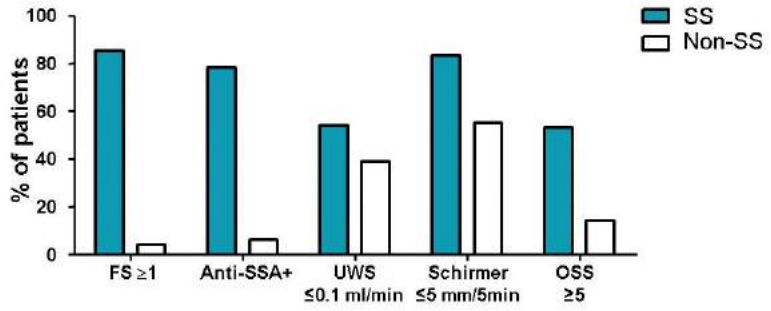

Figure: Proportion of SS and non-SS patients fulfilling the separate ACR-EULAR criteria.

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Abstract Number: 2662

Effect of Tobacco Smoking on the Clinical, Histopathological, and Serological Manifestations of SjöGren's Syndrome

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Background/Purpose: To assess the prevalence of smoking in patients with Sjögren's syndrome (SS) and non-Sjögren's sicca (non-SS sicca), and the association of smoking habits with the clinical, serological, and histopathological manifestations of SS.

Methods: Cross-sectional case-control study of 1288 patients with sicca symptoms (587 SS and 701 non-SS sicca) evaluated in a multi-disciplinary research clinic. Smoking patterns were obtained from questionnaire data and disease-related clinical and laboratory data were compared between current, past, ever, and never smokers.

Results: Current smoking rates were 4.6% for SS patients compared to 14.1% in non-SS sicca (p=5.17x10E-09), 18% in a local lupus cohort (p=1.13x10E-14) and 16.8% in the community (p=4.12x10E-15). Current smoking was protective against SS classification (OR 0.35, 95%CI 0.22-0.56, FDR q=1.35E10-05), focus score ≥1 (OR 0.22, 95%CI 0.13-0.39, FDR q= 6.78x10E-08), and anti-Ro/SSA(+) (OR 0.35, 95%CI 0.2-0.63, FDR q=0.0009); ever smoking was protective against the same features and against anti-La/SSB(+) (OR 0.52, 95%CI 0.39-0.70, FDR q=0.001). Duration of smoking was inversely correlated with SS even after controlling for socioeconomic status, BMI, alcohol and caffeine consumption.

Conclusion: Current tobacco smoking is negatively and independently associated with SS, protecting against disease-associated humoral and cellular autoimmunity. The overall smoking rate amongst SS patients is significantly lower than in matched populations and the effects of smoking are proportional to exposure duration.In spite of the protective effects of tobacco on SS manifestations, it is associated with other serious comorbidities such as lung disease, cardiovascular risk and malignancy, and should thus be strongly discouraged in patients with sicca.

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Abstract Number: 2663

Antimalarials Protect Against Damage Accrual in Primary SjöGren's Syndrome

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Background/Purpose: Antimalarials are frequently used in patients with primary Sjögren's syndrome (SS). The aim of this study was to assess their impact on damage accrual among this group of patients.

Methods: We included 377 consecutive patients with the diagnosis of primary SS according to the AECG criteria, attending tertiary referral centers from three countries: Argentina (n=110), Brazil (n= 49) and Mexico (n=218). We retrospectively registered demographics, age at disease onset, disease duration, use of prednisone (PDN), immunusupressors, comorbidities and use of antimalarials (cloroquine or hydroxychloroquine, time of use and indication). We also scored the cumulative ESSDAI at last follow-up as well as the SSDDI.

Results: The mean age at diagnosis was 48.9±12.7 years, 97.3% females, median disease duration 6 years, mean SSDDI score 2.7±1.8 and mean cumulative ESSDAI score 9.3±8.3. There were not differences regarding these variables among countries, with the exception of the SSDDI that was lower in Brazil (1.8±2.3, Mexico 2.8±2, Argentina 3±1.6, p≤0.001) and the median disease duration that was longer in Mexico (7 years, Argentina 4.5 years, Brazil 5 years). Thirty nine percent of patients used PDN, 37.4% immunosuppressors, 23.1% had hypertension, 16.5% dyslipidemia and 6.6% diabetes mellitus. A total of 190 patients (50.3%) had ever used antimalarials, mean use of 43.5±40 months, being the indications: arthritis (65.2%), parotid enlargement (6.3%), only sicca symptoms (19.4%) and other causes (8.9%). When we compared patients with and without antimalarials, the first ones were younger (46.6±11.7 vs. 51.3±13.1, p=0.0001), with a longer disease duration (median 7 vs. 4 years, p=0.0001), used more PDN (44.5% vs. 33.3%, p=0.002) and immunosuppressors (44% vs. 30.6%, p=0.007) and had a lower SSDDI score (2.4±1.7 vs 2.9±1.8, p=0.01). Regarding the domains of the SSDDI, the pulmonary domain was the only one with a significant difference among groups (6.7% with antimalarials vs. 14.9% without antimalarials, p=0.01). Then, we compared patients with a SSDDI ≥3 vs. SSDDI<3, the first ones had longer follow up (6 vs. 5 years, p=0.04), a higher cumulative ESSDAI score (12.4±9.3 vs. 6.7±6.2, p=0.0001) and less use of antimalarials (42.9% vs. 57%, p=0.007). At the logistic regression analysis adjusted by country and disease duration, the following variables were independent predictors of damage: use of antimalarial OR 0.58 (0.36-0.93 CI 95%, p=0.02) and cumulative ESSDAI OR 1.1 (1.07-1.15 CI 95%, p=<0.001).

Conclusion: During the course of disease, half of the SS patients received antimalarials. This drug was associated with a lower damage accrual independently of disease activity and duration.

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Abstract Number: 2664

Evaluation of Thyroid Autoimmune Disease in Primary SjöGren's Syndrome and Its Association with Disease Phenotype

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Background/Purpose: Notwithstanding the reported coexistence of autoimmune thyroid disease (ATD) and primary Sjögren's syndrome (pSS), it is unknown if this association is routinely searched and how it influences the SS phenotype. We aimed to describe the proportion of patients with pSS who has been screened for thyroid disease, the prevalence of ATD and its impact in pSS phenotype in a single tertiary center cohort.

Methods: We retrospectively reviewed the medical charts of 223 consecutive patients (1996-2016) with the diagnosis of pSS according to the AECG criteria. We registered demographics, glandular and extraglandular features, Schirmer-I test, non-stimulated whole salivary flow (NSWSF), ocular staining, serology (anti-Ro/SSA, anti-La/SSA, rheumatoid factor (RF), low C3 ever, low C4 ever, and hyperglobulinemia ever); as well as thyroid function tests (TFT), thyroid disease diagnosis, anti-thyroglobulin and anti-thyroid peroxidase antibodies and thyroid image studies. We scored the cumulative activity with the ESSDAI and damage accrual with the SSDDI at the end of follow-up.

Results: 149 patients (66.8%) had at least a set of TFT, these patients were older and had a longer disease duration than patients without a TFT assessment. Their mean age was 59.7±14.9 years, 95.2% female and median disease duration 10.4 years. Sixty-four of them (42.9%) had thyroid disease, being the main cause ATD in 24 patients (37.5%, CI 95% 27-50; 16 hypothyroidism and 8 hyperthyroidism). Other causes were non-autoimmune hypothyroidism (n=8, 12.5%), multinodular goiter (n=6, 9.3%), coloid goiter (n=4, 6%) and single thyroid nodule (one patient, 1%). We excluded for further analysis a group of 21 patients with hypothyroidism who lacked of anti-thyroid antibodies determination. When we compared patients with ATD (n=24) vs. without ATD (n=104) we did not find differences regarding the age, gender, disease duration, Schirmer-I test, impaired NSWSF, ocular staining, use of immunosuppressors, RF, low complement and hyperglobulinemia; as well as in the glandular and extraglandular features and cumulative ESSDAI (9.04±7.6 vs 11.4±8.9, p=0.19). However ATD patients had a lower prevalence of anti-Ro/SSA (58.3% vs. 88.3%, p=0.001) and anti-La/SSB antibodies (25% vs. 60.6%, p=0.002) than patients without ATD; as well as a lower SSDDI score (2.17±1.2 vs 2.77±2, p=0.05). At the logistic regression analysis, only anti-Ro/SSA and anti-La/SSB remained significant, conferring protection to ATD (OR 0.29, 95% CI 0.10-0.88, p=0.002 and OR 0.31, 95% CI 0.10-0.92, p=0.03, respectively).

Conclusion: Around one third of pSS patients were not evaluated for thyroid disease, and among those evaluated, 37.5% had ATD. These patients had a similar clinical prognosis than those without ATD, but were characterized by a lower prevalence of anti-Ro/SSA and anti-La/SSB antibodies.

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Abstract Number: 2665

Epratuzumab Treatment of Patients with Systemic Lupus Erythematosus and Secondary Sjogren's Syndrome: An Exploratory Analysis of Phase 3 Studies

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Background/Purpose: The EMBODY 1 (SL0009; NCT01262365) and EMBODY 2 (SL0010; NCT01261793) phase 3 studies investigated the efficacy and safety of epratuzumab (Emab; Immunomedics Inc), a CD22-targeted monoclonal IgG1 antibody, in patients (pts) with systemic lupus erythematosus (SLE).[1] The studies showed no significant difference from placebo (PBO) in any of the primary/secondary outcome measures, although B cell-specific immunological activity and a favourable safety profile were demonstrated. An analysis of the subset of pts with secondary Sjögren's syndrome (sSjS) is of special interest due to the pathogenic role of B cells in primary SjS.

Methods: In EMBODY 1 & 2, adult pts with moderately to severely active SLE were randomized to PBO or 1 of 2 dosing regimens of Emab (both received a cumulative dose of 2400 mg Emab delivered over the first 4 weeks [wks] of each of four 12-wk treatment cycles), with the primary endpoint measured at Wk 48.[1] This post-hoc analysis included pts with an additional diagnosis of sSjS who were SS-A positive at baseline. Biological markers (B cells, IgG/IgM, SS-A), primary/secondary outcome measures of SLE disease activity (BICLA, BILAG, PhGA) and overall safety were assessed.[1] For BICLA, missing data were imputed using modified non-responder imputation with p values calculated using logistic regression with factors for treatment, pooled region and baseline disease status. For BILAG and PhGA missing values were imputed using last observation carried forward and p values calculated using ANCOVA adjusted for baseline, region and baseline disease severity.

Results: Across both studies, 170 (11%) SLE pts had sSjS in their medical history; of these, 112 pts (40 PBO, 72 Emab) were SS-A positive at baseline and were included in this analysis. Demographics/disease characteristics did not differ between groups (Table A). A higher proportion of Emab pts achieved a BICLA response at Wks 24 and 48 compared with PBO (Table B). Similarly, reductions from baseline in BILAG total score were numerically greater for Emab than PBO pts at both time points. PhGA did not differ significantly between the two groups; both PBO and Emab pts showed improvements from baseline. During treatment, B cells, IgM, and SS-A decreased in Emab but not PBO pts (Figure, and data not shown); no substantial changes were observed in other parameters including IgG, rheumatoid factor, SS-B. Emab appeared safe and well-tolerated with no difference in the frequency of adverse events from PBO.

Conclusion: In this post-hoc analysis, pts with SLE and sSjS treated with Emab showed improvements in SLE disease activity compared to PBO, with decreases in B cells and B cell-related biomarkers (IgM and SS-A). Further evaluation in a larger SjS population, using SjS-specific outcome measures, is necessary to assess the clinical relevance of the data. **References:** 1. Clowse MEB, Arthritis

Table A: Baseline demographics and disease characteristics of patients with SLE and secondary Sjögren's syndrome

	Placebo (n=40)	All epratuzumab (n=72)
Age, mean years (SD)	44.3 (11.9)	46.8 (11.5)
Female, n (%)	40 (100)	71 (98.6)
White, n (%)	29 (72.5)	51 (70.8)
BILAG body system involvement, n (%)		
Mucocutaneous	40 (100)	72 (100)
Musculoskeletal	39 (97.5)	71 (98.6)
Hematology	29 (72.5)	51 (70.8)
Constitutional	25 (62.5)	49 (68.1)
BILAG total score, mean (SD)	20.6 (6.0)	21.3 (6.6)
PhGA, mean (SD)	52.7 (15.4)	56.8 (16.5)

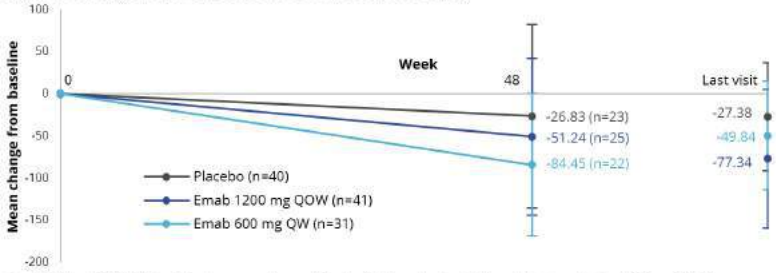
BILAG total score based on convention: A=12, B=8, C=1, D/E=0. BILAG: British Isles Lupus Assessment Group; PhGA: physician's global assessment of disease activity; SD: standard deviation.

Table B: Clinical outcomes at Weeks 24 and 48

	Placebo (n=40)		All epratuzumab (n=72)	
	Week 24	**Week 48**	**Week 24**	**Week 48**
BICLA [mNRI], n (%)	**4 (10.0)**	**11 (27.5)**	**25 (34.7)**	**27 (37.5)**
OR	–	–	5.627	1.703
[95% CI]	–	–	[1.648–19.212]	[0.700–4.144]
p-value vs placebo	–	–	p=0.006	p=0.241
Change from baseline BILAG total score [LOCF], LS mean (SD)	**-8.2 (6.9)**	**-10.9 (8.1)**	**-11.7 (8.0)**	**-13.3 (7.8)**
p-value vs placebo	–	–	p=0.019	p=0.112
Change from baseline PhGA [LOCF], LS mean (SD)	**-18. 6 (22.2)**	**-29.3 (22.3)**	**-25.4 (23.0)**	**-31.9 (22.8)**
p-value vs placebo	–	–	p=0.108	p=0.538

BILAG: British Isles Lupus Assessment Group; BICLA: BILAG-based combined lupus assessment; LOCF: last observation carried forward; LS: least squares; NRI: non-responder imputation; SD: standard deviation.

Figure: Change from baseline in SS-A (observed data)



Emab 1200 mg QOW: 1200 mg infusions every other week for the first 4 weeks of each 12-week dosing cycle; Emab 600 mg QW: 600 mg infusions every week for the first 4 weeks of each 12-week dosing cycle.

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Abstract Number: 2666

Therapeutic Efficacy of Iguratimod in Patients with Primary Sjogren's Syndrome

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Background/Purpose: Iguratimod (IGU), a methanesulfonanilide, has been used as a novel disease-modifying antirheumatic drug for

treatment of rheumatoid arthritis in Japan and China. IGU displayed significantly inhibition of immunoglobulin production and suppression of IL-1, IL-6 and TNF. Previous studies have indicated an overt activation of B cells leading to the abnormal secretory function and accompanied by autoantibody production and hypergammaglobulinemia in Primary Sjögren's Syndrome (pSS). The aim of this study was to investigate the efficacy of IGU in combination with conventional treatment in pSS and the effects of IGU on B cell activity.

Methods: A total of 50 female patients diagnosed with pSS meeting the international classification criteria (2002) were enrolled in this study, with a mean age of 29.3 ± 9.7 years. Active pSS patients were randomized (1:1) to conventional treatment (prednisone ≤ 10 mg daily, hydroxychloroquine 400mg daily and new hydrochloride bromide ethyl daily), or IGU treatment (conventional treatment plus IGU 50 mg daily). pSS disease activity was assessed using EULAR Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI). Expression of CD135, IgD, CD38, CD20 and B cell activating factor-receptor (BAFF-R) on peripheral blood B cells were analyzed by flow cytometry in 20 pSS patients before and after treatment at 12 weeks.

Results: As shown in Table 1, at week 12, ESSDAI and ESSPRI were significantly improved but with a much greater gratitude in IGU treated group as compared with those in conventional treatment group ($P<0.05$). There were no obvious adverse events reported in either group. At baseline, pSS patients showed a significant increased expression of BAFF-R, CD38, CD135 and IgD on B cells compared with that in healthy controls. After 12 weeks of treatment, expression of BAFF-R, CD38, and IgD in IGU treatment group decreased significantly than that in conventional treatment group (Table 2) ($P<0.05$).

Conclusion: In subjects with pSS, IGU treatment resulted in clinically meaningful improvements in disease activity compared with conventional therapy. IGU affected B cell frequency and functions in pSS via inhibition of BAFF-R expression on B cells and inhibition of B cell antibody production.

Table 1. Disease activity before and after treatment in pSS patients

	IGU (n=25)			Conventional (n=25)			P_{1*}
	Before	After	P	Before	After	P	
ESSPRI	6.3+1.5	2.9+ 1.4	<0.05	7.1 + 1.5	5.1+1.4	<0.05	<0.05
ESSDAI	13.7+ 2.4	6.4+1.8	<0.05	12.2+ 1.1	8.0+ 1.0	<0.05	<0.05

* P1 value represents comparison of changes after treatment between IGU and

Conventional groups.

Table 2. Expression of B cell markers before and after treatment in pSS patients

	IGU (n=10)			Conventional (n=10)			P_{1*}
	Before	After	P	Before	After	P	
BAFF-R (%)	92.5+ 3.4	69.4+ 5.4	<0.05	94.1+1.5	79.8+2.0	<0.05	<0.05
CD38,IgD (%)	74.9+ 10.4	43.4+8.8	<0.05	80.6+6.1	60.2+10	<0.05	<0.05

* P1 value represents comparison of changes after treatment between IGU and

Conventional groups.

Disclosure: L. Zhang, None; **W. Jiang**, None; **C. Q. Chu**, None; **Y. Liu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/therapeutic-efficacy-of-iguratimod-in-patients-with-primary-sjogrens-syndrome

Abstract Number: 2667

Whole Frequency Audiometrical Correlation with Disease Activity in Primary SjöGren's Syndrome in Hispanic Population

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Background/Purpose:

Sjögren's syndrome is an autoimmune disorder that can develop hearing loss, It can be diagnosed with high frequency audiometry. Our study aims to correlate the hearing according to the level of disease activity, using the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI) as an evaluation tool and performing high frequency audiometry and tympanogram in a population with primary Sjögren's syndrome.

Methods:

The audiological evaluation were performed by the same experienced audiologist in an Acoustic Systems soundproof chamber with calibration, model RE-142 manufactured in U.S.A, and Interacustic AC40 audiometer (125-16,000Hz frequencies with bone conduction thresholds at 500-4000Hz frequencies). Pure-tone speech audiometries were conducted measuring speech discrimination thresholds and word recognition. Tympanometry (Audiotest 425 h Interacustic) with acoustic reflex and static acoustic compliance for both ears were tested. Tympanometry was considered normal with middle ear pressures of ± 75 da Pa (deca Pascal: unit of pressure) with compliance of 0.28-1.5ml, and the presence of acoustic reflex when it occurred with stimulation at 70-95 dB in 500; 1000; 2000; and 4000Hz. The tympanograms were classified according to Jerger as types A, As, Ad, B, and C. Hearing loss was accepted if the hearing threshold was 20 dB or higher than 20dB.

Results: A total of 76 patients, 3(3.9%) male and 73(96.1%) women were recruited. The median age was 52.5 years. The disease activity was reported as mild in 23(30.3%) patients, moderate in 28(36.8%) and severe in 25(32.9%). The Pure Tone Average (PTA) in the right ear was 18.72dB (SD11.6) and left ear 20.72dB (SD12.19) in the frequency range 500 to 3000Hz. The comparison between the degree of illness and right and left PTA was P=0.399 and P=0.359 respectively. The PTA in the frequency range 4000 to 8000Hz in the right ear was 29.34dB (SD5.18) and the left ear was 31.40dB (SD17.68), P=0.198 and P=0.115 respectively. The PTA in the frequency range 10000-16000Hz was in the right ear 55.82dB (SD18.10) and the left ear was 55.17dB (SD19.58), P=0.134 and P=0.180, respectively. The prevalence of hearing loss in patients with primary Sjögren's syndrome in high frequencies (10,000-16,000) in the right ear was 62(94.7%) and the left ear 69(90.8%). No significant differences between the degree of disease activity and the level of hearing in patients with primary Sjögren's syndrome were found.

Conclusion:

Despite the high prevalence of hearing loss of high frequencies in this cohort of Sjögren's Syndrome Patients, we observed no correlation with disease activity

Table 1. Pure Tone Average and standard deviation

Test frequency (Hz)	Right ear	Left ear
500-3,000	18.72 ±11.6	20.72 ±12.19
4,000-8,000	29.34 ±5.18	31.40 ±17.68
10,000-16,000	55.82 ±18.10	55.17 ±19.58

Table 2. Mean PTA comparison with ESSPRI using Kruskal-Wallis test

Frequency range	Mean PTA (SD)	*P*
Right Ear		
500-3,000	21.19 (20.08)	0.399
Mild	16.98 (8.32)	
Moderate	18.90 (7.05)	
Severe		
4,000-8,000	29.83 (23.95)	0.198
Mild	26.01 (15.61)	
Moderate	33.07 (16.94)	
Severe		
10,000-16,000		0.134
Mild	56.37 (19.53)	
Moderate	51.57 (19.93)	
Severe	60.65 (13.30	
Left Ear		
500-3,000	19.88 (11.22)	0.359
Mild	21.05 (14.31)	
Moderate	21.00 (8.02)	
Severe		
4,000-8,000	27.92 (16.69)	0.115
Mild	30.11 (19.65)	
Moderate	35.80 (15.55)	
Severe		
10,000-16,000	52.87 (18.05)	0.180
Mild	51.69 (22.71)	
Moderate	61.32 (15.38)	
Severe		

Table 3. Prevalence of Hearing loss in primary Sjögren´s syndrome in Hispanic population

Test frequency (Hz)	Number of patients *N*=76 (%)
Right ear	8 (10.5)
500-3,000	
4,000-8,000	32 (42.1)
10,000-16,000	62 (94.7)
Left ear	18 (23.7)
500-3,000	
4,000-8,000	41 (53.9)
10,000-16,000	69 (90.8)

Disclosure: J. Riega-Torres, None; **Y. Hinojosa-Rios**, None; **J. L. Treviño-González**, None; **L. Pérez-Barbosa**, None; **M. A. Garza-Elizondo**, None; **D. Vega-Morales**, None; **A. Valdés-Mancha**, None; **J. Esquivel-Valerio**, None; **M. J. Villegas-Gonzalez**, None; **C. Skinner-Taylor**, None; **D. Flores-Alvarado**, None.

Abstract Number: 2668

Real Time Sonoelastography in Primary Sjögren's Syndrome Correlates with Morphological Ultrasonographic Features and Glandular Activity but Not with Glandular Fibrosis

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Background/Purpose: Salivary gland ultrasonography is a highly specific tool for the diagnosis of primary Sjögren´s syndrome (PSS). Real time sonoelastography (RTS) is a novel imaging option involving tissue stiffness assessment. Previous works have reported higher RTS values in PSS vs healthy and sicca controls. Herein we evaluated the stiffness of parotid and submandibular glands using RTS and correlated it with a multiparametric approach including morphologic ultrasonographic parameters, profibrotic chemokines and cytokines levels, serology and the presence of minor salivary gland fibrosis.

Methods: We included 26 patients with PSS according to the AECG criteria, who had a salivary gland biopsy with no more than 5 years previous the ultrasonographic evaluation. B-Mode ultrasonography and RTS (ARFI methodology) were performed by a trained radiologist. Parotid and submandibular glands were individually rated for parenchymal echogenicity, homogeneity, hypo-echogenic areas, hyper-echogenic reflections and clearness of borders using the Hocevar scale (global B-mode sum score 0-48 points). RTS was also conducted at both parotid and submandibular glands (8 areas of each gland to obtain a median value) and we registered the median value of shear wave velocity (SVV) expressed in m/s. We assessed the ESSDAI, ESSPRI, non-stimulated whole salivary flow rate (NSWSF), C3 and C4 levels, rheumatoid factor, anti-Ro/La antibodies and salivary levels of CXCL14, CCL28, TRAIL and TGb by ELISA. We also evaluated salivary gland fibrosis with the Masson's trichrome staining.

Results: The mean age was 51.1±11 years, median disease duration 6.1 years, 92.8% females, 92.8% had oral symptoms and 26.9% fibrosis at the minor salivary gland. The global B mode score was of 22.2 points (13-44) and the SVV 2.5 (1.64-3.28) m/seg. We found a correlation between SVV and the global B mode score (t=0.53, p=0.001), SVV between both parotids (t=0.58, p=0.0001) and both submandibulars (t=0.50, p=0.0001); but not between parotids and submandibular glands. The SVV correlated with the NSWSF (t=-0.53, p=0.001), ESSDAI (t=0.31, p=0.03), glandular ESDDAI domain (t=0.36, p=0.02), C4 levels (t=-0.32, p=0.04), but not with age or any other variable including fibrosis and salivary chemokines/cytokines. At the linear regression analysis, the glandular ESSDAI domain (B=0.49, p=0.04), the C4 level (B=-0.02, p=0.05) and the disease duration (B=0.04, p=0.04) correlated with the SVV.

Conclusion: SVV correlated with the ultrasonography morphologic score and glandular activity but not with fibrosis, suggesting that it rather represents glandular inflammation. Further prospective studies are needed to evaluate its sensitivity to change over time.

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Abstract Number: 2669

Biological Treatments in Primary SjöGren Syndrome

Monica Fernandez Castro[1], Jose Luis Andreu[2], Carlos Sánchez-Piedra[3], Víctor Martínez Taboada[4], Alejandro Olivé[5], José Rosas[6], Raúl Menor Almagro[7], Beatriz Rodriguez Lozano[8], Angel Garcia-Aparicio[9], Francisco Javier López Longo[10], Sara Manrique-Arija[11], Jesus Alberto Garcia Vadillo[12], Susana Gil Barato[13], Ruth Lopez Gonzalez[14], Javier Narváez[15], Carlos Galisteo[16] and on behalf of Sjogren-SER project (GEEAS-SER), [1]Rheumatology, Hospital Infanta Sofía, Madrid, Spain, [2]Rheumatology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, [3]Unidad de Investigación de la Sociedad Española de Reumatología, Madrid, Spain, [4]Rheumatology, Hospital Marqués de Valdecilla, Santander, Spain, [5]Rheumatology, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain, [6]Rheumatology, Hospital Marina Baixa, Villajoyosa (Alicante), Spain, [7]Rheumatology, Hospital General de Jerez de la Frontera, Jerez de la Frontera, Spain, [8]Rheumatology, Hospital de Canarias, S/C Tenerife, Spain, [9]Rheumatology, Hospital Virgen de la Salud, Toledo, Spain, [10]Rheumatology, Hospital Gregorio Marañón, Madrid, Spain, [11]Rheumatology, Hospital Carlos Haya, Malaga, Spain, [12]Rheumatology, Hospital La Princesa, Madrid, Spain, [13]Rheumatology, Hospital General de Alicante, Alicante, Spain, [14]Rheumatology, Hospital Virgen de la Concha, Salamanca, Spain, [15]Rheumatology Department, Hospital Universitari de Bellvitge, L'Hospitalet de Llobregat, Spain, [16]Rheumatology, Hospital Parc-Taulí, Sabadell, Spain

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Background/Purpose: Primary Sjögren syndrome (pSS) is a systemic autoimmune disease involving mainly the exocrine glandular system. Nevertheless, its clinical spectrum includes the development of multiple extra-glandular manifestations that will be determinant for the prognosis and the use of systemic therapy, including biological treatments. The aim of our study was to describe the biological treatments used in a pSS cohort of patients assisted in Spanish Rheumatology Departments.

Methods: This is a multicenter descriptive transversal study of pSS patients fulfilling European/American consensus criteria. Patients were included by randomization from thirty-three Rheumatology departments. Data were collected by reviewing clinical records and interviewing the patients. Signed informed consent was obtained and local ethics committees approved the study. Variables were analyzed by descriptive statistical methods, using means, medians, and rates. Chi-square was used to establish the statistical associations, being considered significant a $p<0.05$.

Results: Four hundred and thirty-seven patients were included. Ninety-five percent of them were women. The median age of the cohort was 58 years. Ten patients had been treated (currently or previously) with anti-TNF agents (2.29%); 31 patients had been treated with rituximab (7.1%); 3 patients had been treated with abatacept (0.69%) and 1 patient had been treated with tocilizumab (0.23%). Patients receiving anti-TNF agents had the following clinical manifestations: articular involvement (4 patients), pulmonar involvement (2 patients), central nervous system (CNS) involvement (4 patients) and cytopenia (2 patients). Patients receiving rituximab had: articular involvement (13 patients), pulmonar involvement (9 patients), renal involvement (6 patients), CNS involvement (5 patients), peripheral nervous system (PNS) involvement (8 patients) and cytopenia (16 patients). Patients receiving abatacept had: articular involvement (1 patient), pulmonar involvement (1 patient), CNS involvement (1 patient) and cytopenia (1 patient). The patient who received tocilizumab had: CNS involvement and cytopenia. All patients receiving biological therapy were ANA positive. Sixty percent of the patients receiving anti-TNF were anti-Ro+; 40% of the patients had anti-La; 10% of the patients had low C3 and C4, respectively; and 30% of the patients had hypergammaglobulinemia. Ninety-four percent of the patients receiving rituximab were anti-Ro+; 61% of the patients had anti-La; 29% had low C3 and C4, respectively; and 64% of the patients had hypergammaglobulinemia. Thirty-three percent of patients receiving abatacept were anti-Ro+; 33% of the patients had anti-La; 33% of the patients had low C3; and 66.7% of the patients had hypergammaglobulinemia. The patient who received tocilizumab was anti-Ro+, anti-La+ and had hypergammaglobulinemia. Hospitalization due to pSS activity was needed in 5 patients receiving anti-TNF agents; in 19 patients receiving rituximab; in 2 patients receiving abatacept and in the patient treated with tocilizumab. Biological treatments were significantly used more frequently in patients with a hospitalization for disease activity ($p<0.05$). The mean of EULAR Sjogren´s Syndrome Disease Activity Index (ESSDAI) was 8.78 in patients receiving anti-TNF agents; 10.39 in patients receiving rituximab; 11 in patients receiving abatacept and 14 in the patient treated with tocilizumab.

Conclusion: Despite the absence of clinical controlled studies demonstrating efficacy and safety, biological frequently used in patients with SSp. The most widely used biological agent is rituximab. Its use is associated with the presence of musculoskeletal, neurological, pulmonary and haematological manifestations, hospitalization for disease activity and a high ESSDAI.

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Abstract Number: 2670

Work Disability in Newly Diagnosed Patients with Primary SjöGren's Syndrome – a Population-Based Cohort Study

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Background/Purpose: To study long-term work disability (WD) and possible predictors in newly diagnosed patients with primary Sjögren's syndrome (pSS).

Methods: 51 pSS patients (mean age 46 years, range 18-61 years, 50 females) diagnosed with pSS between January 2001 and December 2012 were included in the study. For each patient we randomly selected four reference subjects from the general population matched for age, sex and area of residence as controls. We linked data to the Swedish Social Insurance Agency and calculated the proportion as well as net days of WD in 30-day intervals from 12 months before pSS diagnosis until 24 months after.

Results: WD, consisting of sick leave (SL) and disability pension (DP), was increased in pSS patients in comparison to general population controls (GPC) (Fig 1A and B). Two years after pSS diagnosis the relative risk for overall WD was 2.10 (95% CI 1.34 to 3.30) in comparison with the general population. At diagnosis, 26% of patients were work disabled increasing to 37% and 41%, 12 and 24 months after diagnosis, respectively ($p<0.05$ and $p<0.05$ vs. baseline). Prior work disability status at pSS diagnosis (OR=15.4, 95% CI 2.9 to 81.9; p=0.001), concomitant fibromyalgia (OR=10.5, 95% CI 2.0 to 56.0; p=0.006), and each additional year of age (OR=1.1, 95% CI 1.0 to 1.2; p=0.009) were found to be associated with WD 24 months after diagnosis.

Conclusion: pSS patients showed an increased WD in comparison with the general population. Furthermore, WD in pSS patients increased significantly during the first two years after diagnosis, initially due to an increase in SL and subsequently to an increase in patients receiving a DP. WD at diagnosis, concomitant fibromyalgia and increasing age were associated with long-term work disability.
Figure 1A. The prevalence of any degree of sick leave (SL) and disability pension (DP), for periods of 30 days for pSS patients and the general population controls (GPC) during the 12-month period before and 24-month period after pSS diagnosis.

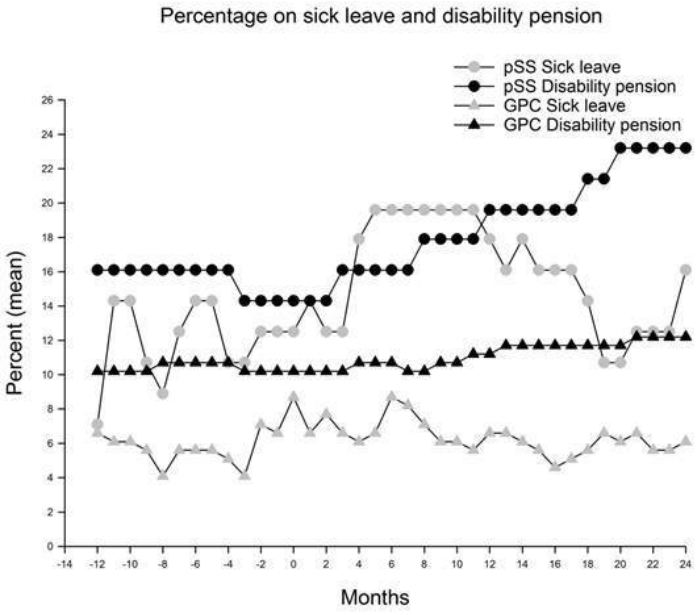
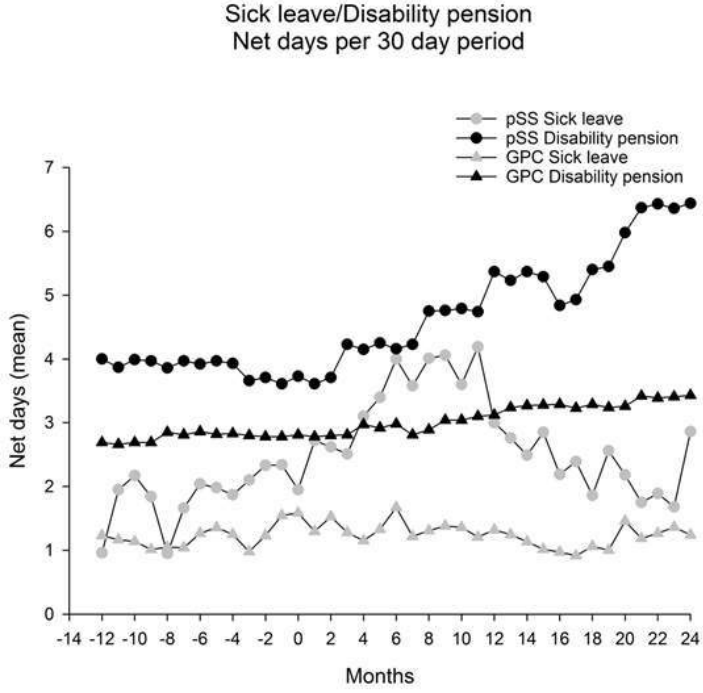


Figure 1B. The net amount of time (number of days out of 30-days periods) the pSS patients and the general population controls (GPC) were on sick leave (SL) and receiving disability pension (DP) during the 12-month period before and 24-month period after pSS diagnosis.



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Abstract Number: 2671

Impaired Bone Health in Patients with Primary Sjogren's Syndrome

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Background/Purpose: Primary Sjogren's syndrome (pSS) is a chronic rheumatic disease. The long-term use of drugs and its renal involvement may contribute to low bone mineral density (BMD). Our objective was to investigate the state of bone health in patients with pSS.

Methods: Patients were all Chinese from the outpatient and inpatient clinic of our hospital (Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China). Primary SS was defined according to the revised American-European classification criteria. Each patient had BMD measurement by dual energy x-ray absorptiometry. Diagnoses of osteopenia and osteoporosis were made using calculations based on the World Health Organization T-score (or Z-score in premenopausal women and men younger than 50) criteria (−1.0 to −2.5 SD was osteopenia and ≤−2.5 SD was osteoporosis). Their demographic and clinical features were recorded and analyzed whether they had impact on the results of BMD.

Results: Totally, 128 Chinese patients (male: female=19:109) were studied. 23 of them were premenopausal and the other 86 were postmenopausal. Their ages were 53.2±8.7 years old and their disease durations were 5.6±4.9 years. The serum levels of calcium and phosphorus of most of them were normal (except 3 had hypocalcemia). Their urinary pH were >5.5. Their mean T (or Z) scores of lumbar spine were -2.1±1.3, of femoral neck were -1.7±1.5, and of total hip were -1.1±1.8. 20 (15.6%) patients were with normal BMD results, 42 (32.8%) were osteopenia, and 66 (51.6%) were osteoporosis. 6 patients had history of pathological fracture. The prevalence of impaired bone health (both osteopenia osteoporosis) was significantly higher in postmenopausal than in premenopausal women (39.5% vs. 26.1%, $p<0.05$). BMD results were not correlated with disease duration, the serum levels of calcium and phosphorus, and the usage of glucocorticoids (all $p>0.05$), but significantly correlated with the age negatively ($p<0.01$).

Conclusion: The prevalence of osteopenia or osteoporosis was high in patients with primary Sjogren's syndrome and it was not due to the usage of glucocorticoids.

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Abstract Number: 2672

Elderly Patients Risk a False Positive Diagnosis of Primary Sjogren's Syndrome If a Positive Labial Gland Biopsy Is Solely Based on Focus Score

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic auto-immune disease affecting the exocrine glands leading to sicca complaints. For the diagnosis of pSS, a positive salivary gland biopsy is an important criterion. A salivary gland biopsy can either be obtained from the minor (labial) or major (parotid) salivary gland and is considered positive if focus score (FS) is ≥1. In this study, the parotid gland biopsy (PGB) and labial gland biopsy (LGB) were compared for their diagnostic value in a prospective diagnostic cohort.

Methods: The study population consisted of 94 consecutive patients referred to the Sjögren center of expertise at the University Medical Center Groningen. All patients presented with sicca complaints and had a complete diagnostic workup for suspicion of pSS according to the American European Consensus Group (AECG) criteria. As part of the routine diagnostic workup a PGB was taken. In addition, patients consented for a simultaneous LGB. Biopsies were assessed for FS and presence of lymphoepithelial lesions (LELs).

Results: Of the included 94 patients (mean age (yr) 49.9 SD 13.9), 39 patients were classified as pSS according to the AECG criteria. In the patients classified as pSS, 18 patients (46%) had both salivary gland biopsies positive. In 14 patients (36%) only the LGB was positive, while in 3 patients (8%) only the PGB was positive and 4 patients (10%) both biopsies were negative. Using the AECG criteria, including salivary gland histology, the PGB had a higher specificity (95% vs 88%), but lower sensitivity (54% vs 82%) than the LGB. Patients classified as pSS, according to the AECG criteria, with both salivary gland biopsies positive, were all anti-SSA positive. Of the 14 patients classified as pSS with solely a positive LGB, 9 patients (64%) would not have been classified as pSS according to the AECG criteria if the biopsy had been negative, since these patients all lacked SSA or SSB autoantibodies. In the small group of three patients classified as pSS with a positive PGB and negative LGB, two patients were anti-SSA positive and the remaining anti-SSA negative patient (33%) would not have been classified as pSS if the biopsy was negative. The 4 classified pSS patients with both salivary gland biopsies negative were all anti-SSA positive. Thus, a positive LGB positively influenced the classification as pSS stronger than a positive PGB. Strikingly, although all 14 patients with solely a positive LGB showed a FS≥1, none of these LGBs harbored LELs. In comparison, if both salivary gland biopsies were positive, LELs were found in 79% of the LGBs. Patients with a positive LGB, but negative PGB were significantly older than patients with a positive PGB (57.0yr versus 47.2yr, t-test p=0.021).

Conclusion: This study suggests that anti-SSA negative elderly patients, with a positive labial gland biopsy based upon FS≥1, are at risk of being falsely diagnosed as pSS, since these labial gland biopsies all lack LELs. We therefore propose that LELs are taken into account in elderly patients besides FS≥1. A parotid gland biopsy is more specific and might be recommended especially in elderly patients without SSA antibodies, suspected for pSS.

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Abstract Number: 2673

Glandular Ultrasonography in Primary SjöGren Syndrome: Clinical and Laboratory Correlation

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Background/Purpose: Primary SjogrenÕs syndrome (pSS) is a chronic autoimmune disorder that is characterized clinically by dryness of the eyes (xerophthalmia) and mouth (xerostomia). The assayÕs purpose was to observe which laboratory tests, clinical characteristics or activity index could have correlation with ultrasonography (US) glandular scores in a cohort of 66 patients with xerostomia in pSS, prospectively enrolled from September 2013 to May 2016 in two medical centers.

Methods: The glandular US score was correlated with clinical and laboratory data in 66 patients with pSS according to American-

European Consensus Group. criteria (AECG) (male/female ratio 2/64, mean age 55,55 (11.15) years) and median of disease duration 6.0(2.0-10.0). Imaging findings of US were graded using an ultrasonography score ranging from 0 to 4(1), which was obtained considering the worst score between each parotid and submandibular gland. All laboratory tests were done including Immunoglobulin G (IgG) level and salivary beta 2 microglobulin. Stimulated salivary flux was measured in the same conditions and hour for every patient, with <0,5 ml/min considered abnormal. The xerostomia inventory validated for portuguese language was applied for all patients by a blind investigator(2). One single rheumatologist was responsible for applying the European Sjšgren Syndrome Disease Activity Index (ESSDAI).

Results: Considering each score value in US, our cohort had almost the majority with 3 an 4 scores (83%). The correlation between higher US scores and clinical and laboratorial parameters was not found. However, higher US scores were correlated with high IgG levels (p=0,0134) and low salivary flux (p=0,0059).

Conclusion: Salivary gland US is a useful method in visualizing glandular structural changes in patients suspected of having pSS and it may represent a good option as a first-line imaging tool in the diagnostics of the disease. In our cohort it was important to show that more important changes matched with lower salivary flux and more inflammatory process. Maybe the ultrasonographic approach in earlier times of disease can change this scenario.

		N	Mean	PD	Median	M'n.	M‡x	*P*
Salivary Flux								
	Score 1	8	0.34	0.24	0.28	0.10	0.90	0.0059
	Score 2	9	0.19	0.17	0.20	0.01	0.46	
	Score 3	36	0.11	0.12	0.06**	0.00	0.50	
	Score 4	10	0.10	0.12	0.03**	0.00	0.32	
IGG								
	Score 1	7	959.57	174.59	951.00	701	1250	0.01034
	Score 2	9	1350.33	457.29	1220.00	920	2380	
	Score 3	32	1409.69	469.63	1286.00*	638	2293	
	Score 4	9	1959.33	845.20	2100.00**	946	3220	

References: 1. Cornec D et al. Contribution of Gland Salivary Ultrasonography to the Diagnosis of Sjšgren Syndrome. Arthritis Rheum 2013;65:216-225.

2. Mata ADSP et al. Translation, validation, and construct reliability of a Portuguese version of the Xerostomia Inventory. Oral Diseases 2012;18:293-298.

Disclosure: T. Fidelix, None; **V. Trevisani**, None; **A. Andriolo**, None; **A. Czapkowski**, None.

Abstract Number: 2674

Primary Sjögren's Syndrome: Extraglandular Manifestations and Hydroxychloroquine Therapy

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Background/Purpose: The use of Hydroxychloroquine (HCQ) in Primary Sjögren's Syndrome (PSS) has been assessed in different studies over the last years, with conflicting results regarding its efficacy in SICCA syndrome and extraglandular manifestations (EGM). The purpose of this study was to compare the incidence rate of EGM in PSS patients with and without HCQ therapy.

Methods: We performed a multicenter retrospective study, including patients with PSS (European Classification Criteria) with at least one year of follow-up. Subjects with concomitant fibromyalgia, autoimmune hepatitis, primary biliary cirrhosis and primary sclerosing cholangitis were excluded. Demographics and PSS characteristics were recorded. The EGM were defined by EULAR SS Disease Activity Index (ESSDAI). Patients were divided into 2 groups according to their use or not of HCQ therapy. We evaluated the use of HCQ and its relationship to EGM. HCQ therapy was defined as the continuous use of the drug for at least 3 months. Statistical analysis: a descriptive analysis of demographics and PSS characteristics was performed. We compared the incidence of EGM between groups defined by HCQ therapy using chi^2 test or Fisher’s exact test.

Results: A total of 221 patients were included (97.3% women), mean age: 55.7 years (SD, 14). Mean age at diagnosis: 48.8 years (SD, 15). Median disease duration: 60 months (IQR 35-84). One hundred and seventy patients (77%) received HCQ. About half of the patients had at least one EGM during the course of the disease, 20% of them developed an EGM before the onset of the SICCA syndrome and 26% simultaneously with dryness symptom. Overall, EGM were less frequent in those on HCQ therapy (36.5% vs 63.5%, p<0,001). Considering each EGM individually, the following manifestations were more frequent in the non-treated group: arthritis (p<0,001), fatigue (p< 0,001), purpure (p=0,01), Raynaud phenomenon (p= 0,003) and hypergammaglobulinemia (p=0,006). (Table I) Immunosuppressive treatment was indicated on 28 patients (12,7%), 13 of which were receiving also HCQ . The first reason for those treatments was the presence of arthritis in 12/28 patients (42.8 %), and the drug used in all the cases was methotrexate. Only three patients required immunosuppressive therapy with cyclophosphamide, due to the presence of glomerulonephritis, vasculitis and interstitial lung disease. None of the patients received biologic therapy.

Conclusion: The lower incidence of EGM observed in patients on HCQ therapy supports its efficacy in PSS. However, further large scale prospective studies are needed to confirm these findings.

Table I: Systemic involvement in PSS patients with or without HCQ therapy

Extraglandular Manifestations (EGM)	*HCQ therapy n (%)*	*No HCQ therapy n (%)*	*p- value*
One or more EGM (n=115)	42 (36,5)	73 (63,5)	**< 0,001**
Arthritis (n =49)	11 (22,4)	38 (77,5)	**< 0,001**
Fatige (n =30)	5 (16,7)	25 (83,3)	**< 0,001**
Purpura (n=11)	2 (18,2)	9 (81,8)	**0,01**
Cutaneos ulcers (n=4)	1 (25)	3 (75)	0,317*
Raynaud (n=20)	5 (25)	15 (75)	**0,003**
Intesticial Lung Disease (n=4)	1 (25)	3 (75)	0,314*
Pulmonary fibrosis (n=1)	0 (0)	1 (100)	0,425*
Pleural effusion (n=1)	0 (0)	1 (100)	0,425*
Glomerulonephritis (n = 2)	0 (0)	2 (100)	0,181*
Peripheral neuropathy (n = 10)	3 (30)	7 (70)	0,072
Lymphadenopathy (n = 14)	5 (35,7)	9 (64,3)	0,104
Lymphoma (n = 2)	2 (100)	0 (0)	0,508*
Hypocomplementemia (n = 18)	9 (50)	9 (50)	0,531
Hypergammaglobulinemia (n = 47)	18 (38,3)	29 (61,7)	**0,006**
Cryoglobulinemia (n = 8)	2 (25)	6 (75)	0,075
Chronic disease anemia (n = 17)	7 (41,2)	10 (58,8)	0,211

*Whenever chi^2 assumptions were not met, Fisher's exact test was applied

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Abstract Number: 2675

Essdai, Clinessdai and DAS Scoring at Diagnosis of Primary Sjogren Syndrome: Association with the Development of Hematologic and Solid Neoplasias in 1301 Patients

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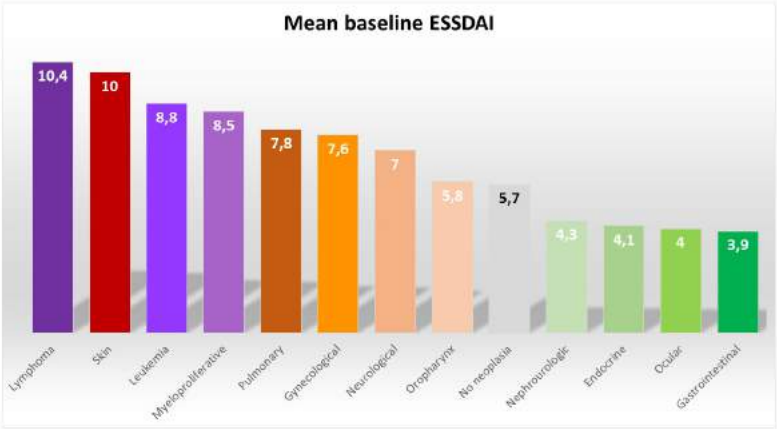
Background/Purpose: To score systemic activity at diagnosis of primary Sjogren syndrome (pSS) using the European systemic activity indexes ESSDAI, clinESSDAI and DAS in order to evaluate their influence in the development of cancer in a large cohort of patients.

Methods: The GEAS-SS multicenter registry was formed in 2005 with the aim of collecting a large series of Spanish patients with primary SS, and included 21 Spanish reference centers with substantial experience in the management of SS patients. By January 2016, the database included 1301 consecutive patients fulfilling the 2002 classification criteria for primary SS. ESSDAI, clinESSDAI and disease activity states (DAS) scores were retrospectively calculated at diagnosis. Neoplasias diagnosed before the pSS diagnosis were excluded.

Results: The cohort included 1202 (92%) women with a mean age at diagnosis of pSS of 52 years. According to the 2002 AE criteria, 1280 patients (98%) had dry mouth, 1235 (95%) dry eyes, 1013/1156 (88%) abnormal ocular tests, 498/630 (79%) positive minor salivary gland biopsy, 835/993 (86%) abnormal oral diagnostic tests, 982/1295 (76%) positive anti-Ro/SSA antibodies and 627/1295

(48%) positive anti-La/SSB antibodies. Other immunological markers included ANA in 1125/1296 (87%) patients, RF in 584/1246 (47%), low C3 levels in 144/1234 (12%), low C4 levels in 163/1219 (13%), cryoglobulins in 70/930 (7.5%) and monoclonal band in 115/1019 (11%). After a mean follow-up of 118 months, 70 (5.4%) patients developed solid cancer and 61 (4.7%) hematological neoplasia; according to the ICD codes, the most frequent neoplasia were lymphoma (n=50), gynecological (n=20), gastrointestinal (n=16) and endocrine (n=8) neoplasias. Systemic activity at diagnosis was significantly higher in patients who developed hematological neoplasia in comparison with those who developed solid neoplasia or those without neoplasia, both for the mean ESSDAI (10.4 vs 5.9 vs 5.7, p<0.001) and clinESSDAI (10.3 vs 5.8 vs 5.7, p<0.001) scores. In addition, high systemic activity (high-DAS) was found in a higher frequency in patients who developed hematological in comparison with those who developed solid neoplasia or those without neoplasia (40% vs 7.7% vs 10.8%, p<0.001). The highest baseline ESSDAI scores were found in patients who developed lymphoma (10.4), skin cancer (10), leukemia (8.8), myeloproliferative cancer (8.5), pulmonary (7.8) and gynecological (7.6) neoplasia (**Figure 1**).

Conclusion: Systemic activity at diagnosis measured using ESSDAI, clinESSDAI and DAS scores is closely related to the development of lymphoma, but not with solid cancer, in patients with pSS. Etiopathogenic factors such as B-cell hyperactivity and cryoglobulinemic-driven immunological responses may play a dual effect, enhancing the risk of development of both systemic involvement and hematological neoplasia.



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Abstract Number: 2676

Changes in Salivary Gland Echostructure in Patients with Primary SjöGren's Syndrome over the Time: A Four-Year Longitudinal Study

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Background/Purpose: Salivary gland ultrasonography (SGUS) has recently appeared as a promising tool for a non-invasive diagnosis

of primary Sjögren's syndrome (pSS). However, it is still debated whether it could be used to monitor clinical response during the follow-up. Objective of this study was to assess the usefulness of SGUS in monitoring salivary gland changes and response to treatment in patients with pSS.

Methods: In this longitudinal study, performed from January 2012 to February 2016, 111 patients with pSS (AECG 2002) were prospectively included and regularly followed over the time. The same operator performed SGUS by using a real-time US scanner (Esaote Technos MPX) with a 7.5-12.5 MHz transducer. The following US parameters were recorded: size, parenchymal echogenicity and inhomogeneity in the parotid and submandibular glands (SM) on both sides, number and location of hypoechoic areas, calcifications and lymph nodes. Changes in different SGUS items were analyzed by using MacNemar test for nominal variables and Wilcoxon test for continuous variables.

Results: We included 111 (109 F:2M) patients with pSS (AECG 2002). Out of them, 46/111 patients were enrolled at the diagnosis (i.e inception cohort). Patients were prospectively observed for a median (IQR) follow-up of 2 (1-3) yrs. At the inclusion, 75% of the entire cohort and 65% of the inception cohort presented already abnormalities in the echogenicity (i.e fibrosis) and homogeneity (i.e hyperechoic bands) in at least one of the four glands examined. Over the follow-up, a raise in echogenicity and homogeneity was observed only in less than 10% of the patients (p-value=n.s). Approximately 1/3 of the patients of the entire cohort and 15% of the inception cohort presented either reduced parotid glands or SM glands at the baseline. This percentage increased up to 45% and to 30% in the entire cohort and in the inception cohort respectively, at the end of the follow-up ($p<0.001$). A score ≥ 2 in the localization of the hypoechoic areas either in parotid or in submandibular glands was observed at the baseline in 42% of the patients (35% inception cohort) and was associated with anti-Ro/SSA, hypergammaglobulinemia, low C3, low C4 and leucopenia. Submandibular parenchyma echostructure (i.e number and location of hypoechoic areas) but not parotid echostructure tend to improve over the follow-up, although the difference was not significant.

Conclusion: SGUS represents an interesting tool to monitor the natural history of glandular involvement in pSS. The use of SGUS to monitor response to therapy in pSS warrants further investigation.

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Abstract Number: 2677

Clinical Features of Primary Sjogren's Syndrome Associated Lung Involvement with Extro-Glandular Manifestations at Onset

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Background/Purpose: To investigate the common initial clinical presentations of primary Sjogren's syndrome with pulmonary complications, and to explore the differences between patients with extro-glandular manifestations at onset (EGM) and those with glandular manifestations at onset (GM).

Methods: A total of 1341 hospitalized SS patients from 2003 to 2012 were retrospectively reviewed. Of them, 102 hospitalized patients with pSS-associated lung disease were analyzed and recruited.

Results: Fifty one percent were presented with EGM at onset, with significantly shorter disease duration [36.0 (12.0-156.0) vs. 102.0 (48.0-159.0) m，p=0.016]. Although mean diagnose time was equal, only 3.8% of EGM group can be confirmed the pSS diagnose at onset, which was significantly less frequently than that of GM group (34.0%, p=0.000).Case control study revealed that hyperglobulinemia, elevated RF titers and anti-SSA and/or anti-SSB positive were less predominant in EGM group [15.85 vs. 21.20g/L; 22.40 (20.00-171.00) vs. 104 (20.00-237.50)IU/ml; 32.7% vs. 72.0%；p<0.05]. TLC and FVC of predicted value were lower

(87.07±22.76% vs. 96.82±19.78%, p=0.050; 88.30±27.76% vs. 100.18±27.40%, p=0.089）and HRCT score was higher in EMG group [11.50 (7.75-15.25) vs. 8.00 (5.00-13.00), P=0.070].

Conclusion: EMG at onset is common initial manifestation of pSS-associated lung involvement patients. Pulmonary complication is more progressively and severe than those with MG at onset. Anti-SSA positive, elevated RF titer and hyperglobulinemia are not predominant for patients with EMG at onset.

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EULAR Primary SjöGren's Syndrome Disease Activity Index (ESSDAI), Results from the National Registry of the Spanish Society of Rheumatology (SJÖGRENSER)

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Background/Purpose: Primary Sjögren's syndrome (PSS) is a systemic disease primarily characterized by lymphocytic infiltration of exocrine glands, but lymphocytic infiltration, can also can affect extraglandular tissues. Recently, it has been validated the EULAR SS disease activity index (ESSDAI), that is a clinical index that measure disease activity in PSS. The ESSDAI, includes 12 domains (organ systems: cutaneous, respiratory, renal, articular, muscular, peripheral nervous system, central nervous system, haematological, glandular, constitutional, lymphadenopathic, biological). The ESSDAI is now in use as a gold standard to measure disease activity in clinical studies, and as an outcome measure. The purpose of this study is to evaluate the ESSDAI baseline characteristics in a large Spanish multicenter registry of PSS.

Methods: SJÖGRENSER, is a multicenter descriptive transversal study of a cohort of PSS patients fulfilling European/American consensus criteria 2012, collected from Rheumatology clinics all over Spain. Patients were included by randomisation from an anonymised list provided by every department. Two hundred and ninety eight variables were investigated: epidemiological, clinical, serological characteristics, treatments and complications. Specifically, ESSDAI domains were collected. The score may vary between 0-123. It is considered low activity an ESSDAI <5; moderate activity 5-13, and high activity if ESSDAI is ≥14. Variables were analysed by descriptive statistical methods, using means, medians, and rates, with their deviations and interquartile ranges (p25-p75).

Results: Of 437 patients included, 95% were women, with median age (p25-75): 58.63 years (50,02-67,98 years), and age at diagnosis of 50.24 years (42,99-58,29 years), with a disease evolution of disease of 10.4 years (6-16 years). The median of diagnosis criteria of SS was 5 (4-5). Minor salivary gland biopsy was positive in 69%. Rheumatoid factor, AAN, anti-Ro/SSA and anti-La/SSB and cryoglobulins, were positive in 64,76%, 62,23 %, 93,59%, 67,05%, 3% of patients respectively. Cytopenia was present in 27% of

patients and Beta-2 microglobulin serum levels was increased in 22% and C3/C4 reduced in 23% of patients. The median of ESSDAI of our population at enter to the study was 2 (0-4). In 31% of patients, ESSDAI, was 0, in 49% was concordant with low activity, moderate activity in 15% and 5% of patients show high activity. In table, the domains of ESSDAI, at enter to SJÖGREN-SER are shown. Table. ESSDAI results at enter at SJÖGRENSER cohort.

ESSDAI domains	**SJÖGRENSER** **N: 437** **%**
Constitutional	8
Lymphadenopathy	2
Glandular	4
Articular	35
Cutaneous	3
Pulmonary	6
Renal	5
Muscular	0,2
Peripheral nevous system	3
Central nervous system	2
Haematological	27
Biological	28

Conclusion: 1. In SJÖGRENSER, 20% of patients show moderate-high ESSDAI results and haematological, biological and articular domains are present in more than 10% of patients. 2. ESSDAI is a suitable tool to define and compare cohorts of patients with PSS.

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Abstract Number: 2679

Clinically Meaningful Improvement of Essdai and Esspri in Patients with Primary SjöGren's Syndrome in Real Life: A 12-Month Longitudinal Study

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Background/Purpose: The increasing use of ESSDAI and patient reported outcomes (PROs) in primary Sjögren's syndrome (pSS) clinical trials has pointed out that the performance of the single domains and scales of these indices may differ in the short term period. Objective of this study was to analyze the performance of single ESSDAI domains and ESSPRI scales in detecting changes of disease activity/PROs over a 12-month follow-up in real-life and to explore any eventual correlation between ESSDAI and ESSPRI.

Methods: This is a 12-month longitudinal single centre study including consecutive patients with pSS (AECG 2002). All the patients were evaluated at least twice during the study period. At each visit, patients completed the ESSPRI and the same researcher assessed the

ESSDAI domains. Minimal clinically important improvement (MCII), defined as an improvement of at least three points of the ESSDAI, and the patient acceptable symptom state (PASS), defined as an ESSPRI<5 points, were calculated at the end of the follow-up. A ≥30% reduction of the patient's dryness/fatigue/pain VAS was also evaluated as response outcome measure.

Results: We included 275 patients (267F: 8M) with pSS (mean age (DS): 57(13.6) yrs; mean follow-up (DS): 6(5) yrs. Out of them, at baseline: 14/275 (5.1%) presented a high disease activity (ESSDAI≥14), 69/275 (25.1%) a moderate disease activity (5≤ESSDAI≤13) and 192/275 (69.8%) a low disease activity (ESSDAI <5). Patients were treated according to the standard of care therapy for pSS. At the end of follow-up, MCII was reached by 17% of the patients. Levels of disease activity remained stable in the vast majority of the cases (79%) and worsened in 4% of the patients. Among the ESSDAI domains, those that showed the most significant tendency to improve were the "articular" and "cutaneous" domains (p<0.000), whereas "biological" domain tended to remain unchanged. The use of hydroxychloroquine and a high ESSDAI at baseline were associated to MCII (p=0.000 and p=0.002). An ESSPRI<5 was observed in 20.7% of the patients at the inclusion and in 22.2% at the end of the follow-up. ESSPRI remained unchanged in 80.8% of the patients, improved in 10.4% and worsened in 8.8%. A ≥30% reduction of the patient's oral and ocular dryness/fatigue/pain VAS was observed in 17%, 15.6%, 14.1% and 20% of the cases. No correlation was detected between ESSDAI and ESSPRI.

Conclusion: This study highlights the general concept that pSS is a slowly progressive disease and that disease activity and PROs are not correlated. Some domains of the ESSDAI seem to capture changes of disease activity better than others in the short term and this may have a value when using ESSDAI in clinical trials.

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Abstract Number: 2680

Determinants of Fatigue in Patients with Primary SjöGren's Syndrome and Impact of Fatigue on Patients' Treatments: A Cohort Study

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Background/Purpose: Fatigue is a common clinical feature in patients with primary Sjögren's syndrome (pSS). Objectives of this study were to assess major determinants contributing to fatigue development in a multicenter cohort of patients with pSS and to explore the impact of fatigue on pSS patients treatment in real-life.

Methods: This multicenter cross-sectional involved five Italian reference centers with substantial experience in the management of pSS. We included 360 pSS patients (AECG criteria) seen consecutively. A standardized data set including demographic, clinical and serological disease manifestations and patients' treatment was collected prospectively. The ESSDAI and the SSDDI were used to assess disease activity and organ damage, respectively. Fatigue was assessed according to the fatigue VAS scale of the ESSPRI. Multiple linear regression analysis was used to estimate the effect of each variable on fatigue severity.

Results: We enrolled 360 pSS patients (346 F:14 M); mean age(S.D.) at study inclusion was 58(15)yrs, mean disease duration (S.D.) was 6(7)yrs. Seventy-eight percent of patients (280/360) reported a fatigue score >5. Fatigue VAS scores correlated significantly with the other scales of the ESSPRI (i.e. Spearman r ranging from 0.49 to 0.62) and weakly with the ESSDAI (Spearman r= 0.12, p=0.03). No association was found between fatigue VAS scores and patients' demographics (i.e age at study inclusion, disease duration). In addition we did not find any association between fatigue and patients' serological/biological profile. Fatigue VAS scores were significantly higher in patients presenting inflammatory arthralgias (p=0.02) and fibromyalgia (p=0.000). At multivariate analysis fatigue severity was independently associated with fibromyalgia [OR (95%IC)=2.29 (1.24-4.22)] and arthralgias [OR (95%IC)=1.79 (1.01-3.17)] .

Regarding the impact of fatigue on patients' therapy we found that fatigue VAS scores were significantly higher in patients assuming corticosteroids (p=0.006) and hydroxychloroquine (p=0.001) and that in patients with a fatigue score >5 the prevalence of patients assuming only symptomatic drugs was significantly lower with respect to patients with a less severe fatigue (29.4% vs 45.3%, p=0.01).

Conclusion: In our study, arthralgias and fibromyalgia were the most significant determinants of fatigue in pSS. Fatigue may influence medical prescription of steroids and hydroxychlorochine in pSS in real life.

Disclosure: C. Baldini, None; **L. Quartuccio**, None; **E. Bartoloni-Bocci**, None; **R. Priori**, None; **A. Alunno**, None; **F. Carubbi**, None.

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Abstract Number: 2681

Clinical and Immunological Characteristics of Primary Sjogren´s Syndrome in Men

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Background/Purpose: Primary Sjögren syndrome (pSS) is a systemic autoimmune disease involving primarily the exocrine glandular system. pSS in men is uncommon. Data of pSS in male are controversial. Objectives: The aim of our study was to describe the epidemiological, clinical and serological features of male patients with pSS in a spanish pSS cohort (SJOGRENSER Registry)

Methods: This is a multicenter descriptive transversal study of pSS patients fulfilling European/American consensus criteria, from thirty-three Rheumatology departments. Patients were included by randomisation from an anonymized list provided by every department. Data were collected by reviewing clinical records and interviewing the patients. Informed consent was obtained and local ethics committees approved the study. Variables were analyzed by descriptive statistical methods, using means, medians, and rates, with their deviations and interquartile ranges (p25-p75).

Results: Four hundred and thirty-seven patients with pSS were included. Twenty-one men were identified. The ratio between women and men was 20:1. Median age at the time of the first symptoms was 53 years for men compared with 46 years for women (p=0.026). Median age at the time at pSS diagnosis was 56 years for men and 50 years for women (p=0.041). Twenty nine percent of men had a family history of autoimmune disease, most commonly pSS (40%). All male patients had ocular and oral dry symptoms.The most frecuent extraglandular manifestations in men were hematological involvement (48%) followed by upper airways involvement (38%), asthenia (38%), salivary gland enlargement (33%) and articular involvement (33%). A significant difference between men and women was found in the prevalence of asthenia, 38% for men and 64% for women (p=0.015), and genitourinary manifestations, 5% for men vs 51% for women (p=0.001). Systemic features, salivary gland enlargement, lymphadenopathy, vasculitis, peripheral neuropathy, pulmonary, cardiovascular, central nervous system and pancreatic manifestations tended to be more frequent in male patients, without statistical significance. The most frequent antibodies in male were ANA (95%), Anti-Ro/SS-A (95%), anti-La/SS-B (67%) and RF (76%). No significant differences in serological characteristics were found between men and women.Median score for the EULAR Sjogren´s

Syndrome Disease Activity Index (ESSDAI) was 6.5, for Sjogren´s Syndrome Disease Activity Index (SSDAI) was 1.76, for EULAR Sjogren´s Syndrome Patient Reported Index (ESSPRI) was 4.35, and for Sjogren´s Syndrome Disease Damage Index (SSDDI) was 2.67.ESSDAI and SSDDI tended to be more frequent in males patients compared with women. Morbidities such as hypertension (33%) and diabetes mellitus (10%) tended to be more frequent in male patients compared with women.

Conclusion: The median age at onset and diagnosis of pSS is higher in men. All pSS male patients showed ocular and oral dry symptoms. The most frecuent extraglandular manifestations in men were hematological involvement, upper airways involvement, asthenia, salivary gland enlargement and articular involvement. Most men had ANA and antiRo antibodies. The disease activity and damage indexes were higher in males.

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Abstract Number: 2682

How Does Primary Sjogren Syndrome Present in Biopsy-Proven Patients without Circulating Ro/La Autoantibodies? Characteristics at Diagnosis of 2073 Patients from the SjöGren Big Data Project

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
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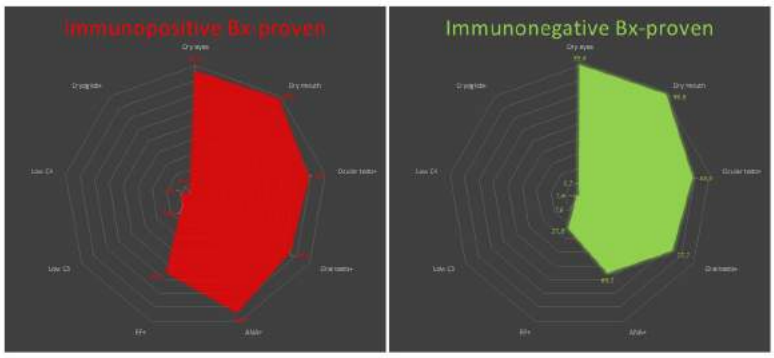
Background/Purpose: To analyse the main characteristics of patients with primary Sjögren syndrome (SjS) with focal lymphocytic sialadenitis (FLS) unrelated to the presence of circulating anti-Ro/La autoantibodies in a large international cohort of patients.

Methods: The Big Data Sjögren Project Consortium is an international, multicentre registry designed, in 2014, to take a “high-definition” picture of the main features of primary SjS at diagnosis by merging international databases including patients fulfilling the 2002 AE classification criteria. Patients came principally from Europe (n=6045), America (n=1134) and Asia (n=940).

Results: The cohort included 7748 (93%) women and 562 (7%) men, with a mean age at diagnosis of primary SS of 53 years. We selected 5245 patients who showed a Chisholm-Mason grade III or IV in minor salivary gland biopsy and that were also tested for Ro/La autoantibodies, and compared the main features at diagnosis between immunonegative patients (n=2073) and those carrying anti-Ro/La antibodies (n=3172). Immunonegative biopsy-proven patients were predominantly White ($p<0.001$), were 7 years older at diagnosis (57.44 vs 50.74 years, $p<0.0001$) and had a higher frequency of oral and ocular dryness ($p<0.001$), a lower frequency of abnormal salivary flows ($p=0.046$) and parotid scintigraphy ($p=0.012$), and a lower frequency of ANA ($p<0.001$), low C3 ($p<0.001$), low C4 ($p<0.001$), rheumatoid factor ($p<0.001$) and cryoglobulinemia ($p=0.001$) in comparison with Ro/La+ biopsy-proven patients (**Figure 1**). Abnormal salivary flows, parotid scintigraphy and ANA remained independent variables statistically associated with negative Ro/La autoantibodies after adjusting by age and gender.

Conclusion: Biopsy-proven patients with primary SS without circulating anti-Ro/SSA and anti-La/SSB antibodies have a specific phenotypic profile at diagnosis of the disease, characterized by an older age, a higher frequency of sicca symptoms, a lower frequency of abnormal diagnostic tests and a milder immunological profile. Patients carrying Ro/La autoantibodies are diagnosed earlier in spite of having sicca symptoms less frequently, probably due to the development of extraglandular features.



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Abstract Number: 2683

Isolated Anti-La/SS-B Positivity in Patients Diagnosed with Primary Sjogren Syndrome: Analysis of 222 Patients from the Sjogren Big Data Cohort

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
Session Title: Sjögren's Syndrome - Poster II: Clinical Science
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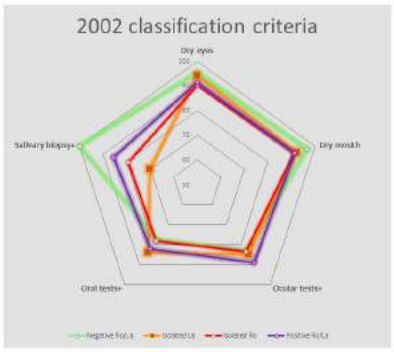
Background/Purpose: To describe the clinical, immunological and histopathological profile of patients with primary Sjögren syndrome (SjS) presenting with isolated circulating anti-La/SS-B antibodies in the absence of concomitant anti-Ro/SS-B antibodies in a large international cohort of patients.

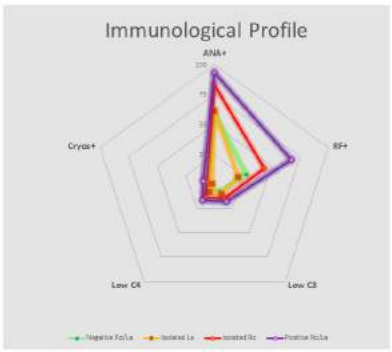
Methods: The Big Data Sjögren Project Consortium is an international, multicentre registry of primary SjS patients fulfilling the 2002 AE classification criteria. By January 2016, the participant centres had included 8310 patients. Determination of anti-Ro/SS-A and anti-SS-B antibodies were made using commercial tests used in daily practice. Patients were classified in 4 groups: A) Double positivity (Ro+La+); B) Isolated Ro positivity (Ro+La-); C) Isolated La positivity (Ro-La+); and D) Biopsy-proven immunonegative (Ro-La-).

Results: Anti-Ro/SS-A and anti-SS-B antibodies were tested in 8213 (99%) patients: 3372 (41%) were Ro+La+, 2546 (31%) Ro+La-, 222 (3%) Ro-La+ and 2073 (25%) were biopsy-proven Ro-La-. Epidemiologically, age at diagnosis of Ro-La+ patients was similar to the two Ro+ groups and was 5.5 years lower than that observed in Ro-La- patients ($p<0.001$). Clinically, Ro-La+ patients had a similar frequency of ocular dryness than Ro-La- patients (a figure significantly higher in comparison with the two Ro+ groups, $p<0.001$), while the frequency of oral dryness was similar to the Ro+ groups and significantly lower than that reported for the Ro-La- group ($p<0.001$) (**Figure 1**). With respect to diagnostic tests, Ro-La+ patients showed similar figures in comparison with the other groups but a significant higher frequency in abnormal diagnostic tests (salivary flows and parotid scintigraphy, $p<0.001$). Minor salivary gland biopsy was

carried out in 147 (66%) out of the 222 Ro-La+ patients, and showed Chisholm-Mason 3-4 grades in 103/147 (70%), a figure significantly lower than that reported for the 2 Ro+ groups (p<0.001). Immunologically, Ro-La+ patients showed a similar immunological profile than that reported for Ro-La- patients, with a significant lower frequency of ANA, RF, hypocomplementemia and cryoglobulinemia in comparison with the 2 Ro+ groups (p<0.001, **Figure 1**).

Conclusion: In the largest reported cohort of patients with primary SjS fulfilling the 2002 AE classification criteria, only 3% of patients had isolated anti-La/SS-B antibodies. This small subset of patients presents a specific clinical and immunological profile that mix some features characteristic of immunonegative patients and some of patients carrying anti-Ro/SS-A antibodies. Further studies are required to confirm this isolated anti-La positivity and should evaluate the differences in systemic activity and outcomes of this subset of patients with respect to the other immunological groups.





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Abstract Number: 2684

Diagnosis of Systemic Diseases in Patients Presenting with Sicca Syndrome Using a Minimally-Invasive Minor Salivary Gland Biopsy: Analysis of 901 Patients

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Background/Purpose: Sicca syndrome is a clinical presentation that is common for several systemic diseases that may infiltrate the exocrine glands. The most frequent disease is Sjögren's syndrome (SS), but other systemic diseases such as sarcoidosis, amyloidosis of IgG4-related disease may also infiltrate salivary glands. The objective was to analyze the safety and usefulness of the minimally-invasive biopsy of minor salivary glands in patients presenting with sicca syndrome suspecting a systemic disease.

Methods: We present a retrospective analysis of 901 patients presenting with sicca syndrome (xerostomia, xerophthalmia, positive ocular tests and/or parotid scintigraphy, overwhelmingly negative for anti-Ro/La antibodies) in whom a minimally-invasive biopsy of minor salivary glands was carried out between January 2005 and June 2016. All biopsy samples were obtained with the same technique and following the same study protocol, which included the evaluation of cumulative focus score of lymphoplasmacytic infiltration (Chisholm Mason score, CMs), together with investigation of granuloma, amyloid, IgG4-related disease or lipids.

Results: All biopsies but six disclosed salivary gland tissue. There are 793 (88%) women and 108 (12%) men, with a mean age of 54,46 years (range 14-86). The main histopathological diagnosis included non-specific chronic sialoadenitis (NSCS, CMs=1-2) in 429 (48%) patients, focal lymphocytic sialoadenitis diagnostic of Sjögren syndrome (FLS, CMs=3-4) in 255 (28%), normal glandular tissue (CMs=0) in 148 (16%) and chronic atrophic sialadenitis (CAS, CMs unclassifiable) in 34 (4%) patients. Other infiltrative diseases included lipoid infiltration (n=10), amyloidosis (n=4), IgG4-related disease (n=3) and sarcoidosis (n=1). The highest mean age was found in patients with CAS (66,35 years), followed by those with NSCS (54,66 years), FLS (54,04 years) and normal result (50,82 years) ($p<0.001$). Patients diagnosed with FLS were more frequently women (91% vs 87%, $p=0.05$), had a higher frequency of abnormal ocular tests (91% vs 66%, $p<0.001$), a higher frequency of ANA (59% vs 36%, $p<0.001$), RF (41% vs 18%, $p<0.001$), anti-Ro (28% vs 7%, $p<0.001$) and anti-La (11% vs 2%, $p<0.001$), and a higher frequency of associated autoimmune diseases (20% vs 10%, $p<0.001$). The percentage of patients diagnosed with SS varied according to the association or not with other autoimmune/viral diseases: 27% of patients with no associated diseases vs 34% of those with organ-specific autoimmune diseases, 42% of those with chronic viral diseases and 50% of those with other systemic autoimmune diseases ($p<0.05$). Abnormal ocular tests ($p<0.001$), ANA ($p<0.001$), RF ($p<0.001$) and anti-Ro ($p<0.001$) remained independent variables significantly associated with SS after adjustment by age and gender.

Conclusion: Minimally-invasive biopsy of minor salivary glands is a simple, safe, and reliable tool for the diagnosis of infiltrative systemic diseases of exocrine glands, overwhelmingly Sjögren syndrome but also amyloidosis IgG4-related disease and sarcoidosis. Lack of severe lymphocytic infiltration and atrophic histopathological data closely correlated with an older age.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/diagnosis-of-systemic-diseases-in-patients-presenting-with-sicca-syndrome-using-a-minimally-invasive-minor-salivary-gland-biopsy-analysis-of-901-patients

Abstract Number: 2685

Ultrasound of the Major Salivary Glands Is a Reliable Imaging Technique for Diagnosing Patients Clinically Suspected with SjöGren's Syndrome

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SESSION INFORMATION

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Background/Purpose: In the classification criteria of Sjögren's syndrome (SS), involvement of the salivary glands is currently assessed by sialography, scintigraphy, sialometry and histopathology. Recent discussions have focused on the diagnostic accuracy of ultrasound (US). The purpose of this study was to determine inter- and intra-observer reliability of US of major salivary glands in patients clinically suspected with SS.

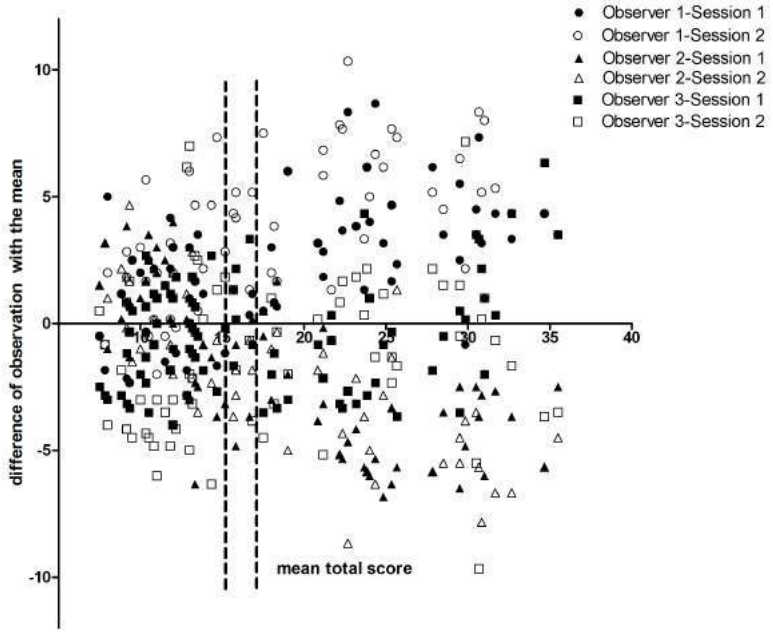
Methods: Eighty consecutive patients clinically suspected with SS were subjected to US as part of their diagnostic work-up. The following US variables of the parotid and submandibular salivary glands were assessed: echogenicity, parenchymal homogeneity, presence of hypoechogenic areas, hyperechogenic reflections and clearness of posterior glandular border (scoring range 0-48)[1]. The cut-off point to define positive or negative US for SS was set at 15 [2] and 17 [1]. Images were scored independently by three blinded observers in 2 sessions with a 2-week interval. Intra- and inter-observer reliability was calculated using Cohen's Kappa and Fleiss' Kappa, respectively, in combination with the percentage of absolute agreement for nominal variables and intraclass correlation coefficients (ICC) for continuous variables.

Results: Intra-observer reliability of the US total score was excellent, with ICCs ranging from 0.89 to 0.96 for the three observers. Inter-observer reliability was good to excellent, with ICCs of 0.84 and 0.76 for the US total score in sessions one and two, respectively. Kappa ranged from 0.60 to 0.83 and percentage of agreement from 80 to 92 depending on the cut-offs applied. Hypoechogenic areas and homogeneity of the parotid glands showed the highest inter-observer reliability with median ICCs of 0.74 and 0.71, respectively. Median kappa for echogenicity was low (0.22). The differences between the three observers were larger for higher US total scores (Figure). Our results suggest that observers may consistently identify in which patients US of the major salivary glands is positive or negative for SS, but scoring the severity of the US findings is more inconsistent.

Conclusion: US of the major salivary glands is reliable in diagnosing SS. There might be, however, some discrepancies between observers in assessing the severity of US findings making it more difficult to detect 'true' changes over time. Thus, when monitoring the progression of SS or treatment efficacy, it is advised that each particular patient is scored by the same ultrasonographer at every time point. **References**

1. Hocevar et al. Rheumatology (Oxford) 2005;**44** :768-772

2. Zhang et al. Rheumatology (Oxford). 2015;**54**:1680-7 **Figure:** Systematic differences in US total score. For each patient, the mean of the 6 observations (3 observers, 2 sessions) and the difference of these 6 observations with the mean were calculated and plotted against each other. The intermittent vertical lines indicate the cut-off points applied.



Disclosure: K. Delli, None; **S. Arends**, None; **P. U. Dijkstra**, None; **J. F. van Nimwegen**, None; **A. J. Stel**, None; **H. Bootsma**, None; **A. Vissink**, None; **F. K. L. Spijkervet**, None.

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Abstract Number: 2686

Objective Improvement in Fatigue Scores for Primary Sjögren's Patients Receiving a Tailored Multidisciplinary Fatigue Intervention in a Generic Fatigue Clinic

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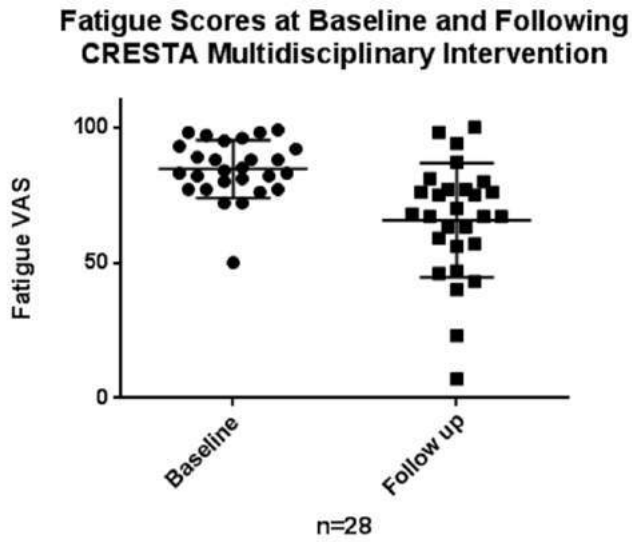
Background/Purpose: Primary Sjögren's syndrome (PSS) is an autoimmune disease which targets secretary glands resulting in dry eyes and mouth. Approximately 70% of PSS patients experience chronic fatigue. The Newcastle Fatigue CRESTA clinic was recently established in the north east of England to offer multidisciplinary care for people with the symptom of fatigue. A cohort of fatigued PSS patients (n=28) were referred from a rheumatology service to the Fatigue CRESTA clinic in order to support them in managing this troublesome symptom. All PSS patients were assessed by a physician and an occupational therapist at their first CRESTA appointment. They were subsequently offered a therapy intervention tailored to their individual requirements. This may include occupational therapy (activity management, goal setting and graded activity/exercise), physiotherapy (including Pilates based exercises to improve body posture and strength), cognitive behavioural therapy for insomnia, psychological therapy or a combination of several therapies. The aim of this study was to determine whether there was a difference in fatigue scores before and after a multidisciplinary intervention at the Fatigue CRESTA.

Methods: Patient reported outcomes were collected by the referring consultant at baseline and follow up at their routine rheumatology appointments. Fatigue (visual analogue scale 0-100) scores were compared for each consecutive patient pre and post a Fatigue CRESTA multidisciplinary intervention. Data were checked for normality and compared using a paired t-test.

Results: Participants attended a median of 8 appointments at the clinic. The mean fatigue scores improved from 84.52 (SD 10.66) at baseline to 69.61 (SD 15.30) at follow up. This finding was statistically significant ($p<0.001$) and represents a clinically important difference [1].



Conclusion: A tailored multidisciplinary fatigue intervention has objectively improved fatigue severity in this PSS patient group and warrants further investigation. These findings highlight the importance of an individualised, multidisciplinary approach for fatigue management in PSS. [1] George & Pope (2011) *Clinical and Experimental Rheumatology* 29(2)248-253.

Disclosure: K. Hackett, None; **R. Forder**, None; **D. W. Lendrem**, None; **B. Hargreaves**, None; **V. Strassheim**, None; **Z. Gotts**, None; **V. Deary**, None; **W. F. Ng**, None; **J. Newton**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/objective-improvement-in-fatigue-scores-for-primary-sjogrens-patients-receiving-a-tailored-multidisciplinary-fatigue-intervention-in-a-generic-fatigue-clinic

Abstract Number: 2687

Prevalence of Abortions and Fetal Atrioventricular Block in Patients with Positive ANTI-RO and ANTI-La Antibodies

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Background/Purpose: Anti-SSA/Ro and anti-SSB/La antibodies are present in inflammatory autoimmune disease patient sera, and there are related to different clinical manifestations. It is well known the association between the presence of these antibodies in maternal blood and fetal atrioventricular block. However, there are no much studies about infertility or repeated abortions and anti-SSA/Ro and anti-SSB/La antibodies in broad series. The aim of this study is to characterise a cohort of patients with positive anti-SSA/Ro and/or anti-SSB/La antibodies and to evaluate the prevalence of abortions and neonatal mortality.

Methods: Observational descriptive study with 162 patients older than 15 years old with pregnancies history and positive anti-SSA/Ro and/or anti-SSB/La antibodies from February 2011 to July 2015. We consider healthy women with pregnancies history and with comparable characteristics as negative control group.

Results: We included 162 patients with positive anti-SSA/Ro and/or anti-SSB/La antibodies with a mean age of 50.5±14.2 years old. Main diagnosis were systemic lupus erythematosus (n=85), Sjögren syndrome (n=40), rheumatoid arthritis (n=16), systemic sclerosis (n=6), mixed connective tissue disease (n=3) and other diagnosis (n=12). Lupus anticoagulant was positive in 8 cases and 57 patients showed low complement values. 37% of patients had at least one pregnancy, and the 36.7% aborted during pregnancy. There were no significant differences in the abortion incidence between our cohort of patients and the healthy control group considered. We observed 4 cases of fetal atrioventricular block, all of them with positive anti-SSA/Ro and/or anti-SSB/La antibodies and only in one case also with positive lupus anticoagulant.

Conclusion: In our series, pregnant women with positive anti-SSA/Ro and/or anti-SSB/La antibodies did not show high prevalence of abortion. However, the positivity of these antibodies was statistically correlated with the presence of fetal atrioventricular block.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/prevalence-of-abortions-and-fetal-atrioventricular-block-in-patients-with-positive-anti-ro-and-anti-la-antibodies

Abstract Number: 2688

Characteristics, Treatment and Outcome of Joint Involvement with Synovitis in Primary SjöGren's Syndrome: French Multicentric Retrospective Case-Control Study

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Session Type: ACR Poster Session C

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Background/Purpose: primary Sjogren's syndrome (pSS) articular manifestations include often tender joints and more rarely synovitis. The main objective of this study was to describe characteristics, treatment and outcome of patients presenting pSS-related joint involvement with synovitis.

Methods: we performed a French multicentric retrospective study including all cases of adult-onset pSS (AECG criteria) with at least one clinical and/or echographic synovitis from 1998 to 2015. Data concerning clinical, biological and radiological findings were collected, as well as treatments. Disease activity was assessed using ESSDAI scale. Complete treatment response for joint involvement was defined as disappearance of all signs and synovitis, partial response as more than 50% improvement. Controls with pSS without synovitis were used to determine the factors associated with joint involvement.

Results: we identified 57 patients (93% women) with median age at the diagnosis of joint involvement of 54 years-old (45-63). The number of tender joint was 8 (4-12) with 4 (2-6) swollen joints. Synovitis was clinical in 65.3% patients, and 26 (44.7%) patients had MRI or echographic confirmation of synovitis. No erosion was seen on X-ray in all cases. The more frequent articular finding was a symmetric polyarthritis (68.4%) and the predominant swollen joints were metacarpophalangeal joint (67.9%). C-reactive protein was 5 (3-9.3) mg/l at the time of synovitis diagnosis. Rheumatoid factor and CCP-antibodies were present in 44.9% and 13.7% patients,

respectively. Median ESSDAI scale was 7 (5-9). All patients received at least one therapeutic line. Steroids were used alone in 6 (10.5%) cases, in association with hydroxychloroquine (HCQ) in 19 (33.3%) cases, and in association with methotrexate (MTX) in 18 (31.6%) cases. A second line was initiated for 31 (54%) with HCQ in 13 (41.9%) cases, MTX for 14 (43.6%) patients, and rituximab (RTX) for 10 (34.5%) patients. Thirteen (23%) patients received a third line with MTX in 9 (69.2%) cases, and RTX in 6 (46.2%) cases. In this 101 therapeutic lines, steroids were used in 78 (77.2%) lines with a median amount of 10 (7-12.5) mg/day, HCQ in 57 (57%) lines with a daily dose of 400 mg, MTX in 44 (44%) lines with a weekly-dose of 15 (15-20) mg. RTX was used in 19 (18,8%) lines and TNFa antagonists in 4 (4%) cases. Number of swollen joints, ESSDAI score and steroids dose significantly decreased from the baseline considering HCQ alone (35 lines), MTX (17 lines), and significant ESSDAI score and steroids dose decrease was noted under RTX (19 lines). Number of swollen joints, ESSDAI score or steroids dose reduction decrease was similar considering patients treated by HCQ, MTX or RTX. Comparing 57 pSS with synovitis with 104 pSS controls without joint involvement, cases were younger (54 [23-81] vs. 55 [18-81] years, $p < 0.05$), with more frequent lymph nodes (12.3% vs 1.8%, $p = 0.007$). Patients with joint involvement and synovitis were treated more frequently with HCQ (67% vs. 15%, $p < 0.0001$), steroids (75% vs. 6%, $p < 0.0001$), and methotrexate (37% vs. 0.8%, $p < 0.0001$).

Conclusion: the pSS articular manifestations may include synovitis. Even the use of HCQ, MTH, and RTX seem to be effective for joint involvement, the best regimen remain to be determined.

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Abstract Number: 2689

Comparison of the 2016 ACR/EULAR and the 2002 AECG Classification Criteria in a Cohort of Patients with Suspected Primary SjöGren's Syndrome

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SESSION INFORMATION

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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: New consensual classification criteria for primary Sjögren's syndrome (pSS) have been recently developed, validated, and submitted to ACR and EULAR committees. They differ substantially from previously used AECG criteria in that they consider systemic involvement (defined as ESSDAI score ≥1) as well as sicca symptoms as entry criteria before applying a weighted score. Evaluation of the concordance and differences between the two sets of criteria in independent patient populations is mandatory to establish how future clinical studies using the new criteria will be comparable to previously published studies.

Methods: This cross-sectional study was conducted in the monocentric Brittany cohort (DIApSS cohort) of patients with suspected pSS (sicca symptoms, parotidomegaly or extraglandular manifestations suggestive of pSS). All patients had standardized clinical examination, basic biology, immunological tests and minor labial salivary gland biopsy. Major salivary gland ultrasonography (SGUS) in mode B was performed in all patients by the same experienced operator, who was blinded to the diagnosis. Agreement between the two sets of criteria was assessed using Cohen's κ coefficient and the characteristics of discordant patients were detailed.

Results: 163 patients were prospectively included between 2006 and 2016. Mean age was 56±14 years, female percentage 94%, and mean duration of the symptoms 6.8±7.9 years. More patients fulfilled ACR/EULAR criteria (n=93, 57%) than AECG criteria (n=83, 51%). 80 patients (49%) fulfilled both criteria, 13 (8%) fulfilled ACR/EULAR only, 3 (2%) AECG only and 67 (41%) none of the

criteria. Concordance between both criteria was good (kappa=0.8, agreement 90%). Compared to patients fulfilling both criteria, patients fulfilling ACR/EULAR but not AECG criteria (n = 13) had similar age (56 vs 57 years), shorter disease duration (mean 5.9±8.5 vs 8.2±8.9 years), less frequent sicca symptoms (eye dryness 50% vs 96%, mouth dryness 64% vs 96%) and salivary gland swelling (14% vs 28%). They had characteristic features of pSS, with frequent systemic involvement at diagnosis (88%), positive salivary gland biopsy (86%), abnormal SGUS (67%) and presence of anti-SSA/SSB autoantibodies (57%). Among patients negative for the two sets of criteria, 10% had an abnormal SGUS and received a clinical diagnosis of pSS based on physician opinion.

Conclusion: Agreement between AECG criteria and new ACR/EULAR criteria is good suggesting that they select quite similar patients. ACR/EULAR criteria display a slightly higher sensitivity and are able to detect more patients with early disease and systemic involvement. As previously demonstrated for AECG criteria, SGUS inclusion into ACR/EULAR criteria may further enhance their sensitivity.

Disclosure: D. Cornec, None; **M. Le Goff**, None; **S. Jousse-Joulin**, None; **D. Guellec**, None; **S. Costa**, None; **T. Marhadour**, None; **J. O. Pers**, None; **A. Saraux**, None; **V. Devauchelle-Pensec**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/comparison-of-the-2016-acreular-and-the-2002-aecg-classification-criteria-in-a-cohort-of-patients-with-suspected-primary-sjogrens-syndrome

Abstract Number: 2690

Detection of Dorsal Root Ganglionitis with Magnetic Resonance Neurography in Sensory Ataxic Neuropathy Associated with SjöGren's Syndrome

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Session Type: ACR Poster Session C

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Background/Purpose: Sensory ataxic neuropathy (SAN) is one of the neurologic complications in Sjögrenfs syndrome (SS). The underlying pathology was lymphocytic infiltration to the dorsal root ganglia (DRG), called dorsal root ganglionitis. 3-Tesla magnetic resonance neurography (3T MRN) clearly delineate DRGs and peripheral nerves, and has been used to evaluate various neurological disorders. However, there has been no reports correlating signal change in DRGs and subtypes of neuropathy. This study aimed to determine whether 3T MRN is useful for the diagnosis of SAN in SS.

Methods: On retrospective chart review from 2014 to 2016, we found that eight patients (including four patients with SS; three fulfilled American-European Consensus Group classification criteria) had been admitted for the evaluation of neuropathy and underwent 3T MRN of lumbosacral plexus. Data were collected on clinical examination including Romberg test and deep tendon reflex, electrophysiological tests, and spinal cord MRI/MRN with a 3T MRI scanner. In MRN, coronal and sagittal short-tau inversion recovery technique was used to detect abnormalities. In each patient with SAN, the signal intensity and size of DRGs were compared with those of non-SAN patients and age-matched control data (cases without systemic neuropathy)

Results: Among four patients with SS, three presented with SAN and one patient showed predominant motor neuropathy. Among four patients without SS, the diagnosis was Guillain-Barré syndrome (N = 3) or idiopathic chronic neuropathy (N = 1). All three patients with SAN showed sensory ataxia with positive Romberg sign, decreased or diminished sensory nerve action potential of sural nerve on nerve conduction study. Five patients without SAN presented with predominant motor symptoms and did not accompany sensory ataxia. On 3T MRN, DRGs in SAN patients were atrophic and their signal intensity were decreased compared to non-SAN patients and control data.

Conclusion: In this study, we described the clinical utility of signal abnormality of DRGs with 3T MRN for the diagnosis of SAN in SS. Larger prospective study would be warranted to establish efficacy of MRN and to elucidate the exact nature of this radiologic finding.

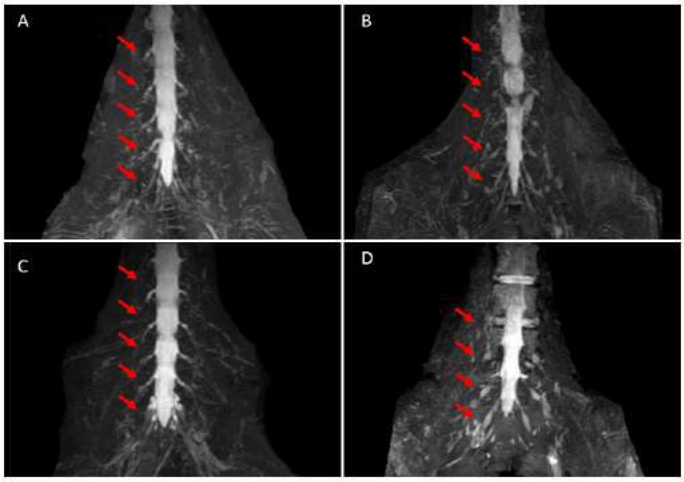

Figure 1. 3T-MRN findings in patients with SS (STIR sequence). Patient 1 (A), 2 (B), and 3 (C) showed atrophic DRGs, with low signal intensity. On the other hand, Patient 4 (D) showed normal-appearing DRGs.

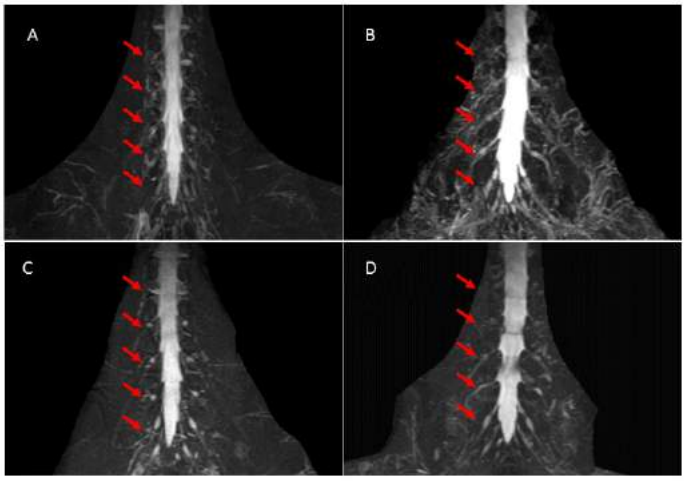

Figure 2. 3T-MRN findings in patients without SS (STIR sequence). Patient 5 (A), 6 (B), and two patients from control data (C, D) showed normal-appearing DRGs

Table. Correlation among clinical, electrophysiological, and radiological findings.

Case	Age/ Sex	Diagnosis	Clinical presentation	Romberg test	DTRs	Neurophysiological test	Posterior column on MRI	DRG on MRN
1	75 F	SS, seropositive SAN	Numbness, hands/feet Ataxia	Positive	PTR 1+ ATR -	Sural N SNAP ↓ Tibial SEP N20 ND	Normal	Atrophy
2	69 F	SS, seropositive SAN	Band-like sensation Ataxia	Positive	PTR 1+ ATR 1+	Sural N SNAP ↓ Tibial SEP N20 ND	Normal	Atrophy
3	49 F	SS, seronegative SAN B12 deficiency	Weakness, numbness Ataxia	Positive	PTR 2+ ATR -	Sural N SNAP ND Tibial SEP N20 ND	↑ T2 signal intensity	Atrophy
4	27 F	SS, seropositive Motor neuropathy	Numbness Severe weakness	Unable to stand	PTR 1+ ATR 1+	Sural N SNAP normal	Normal	Normal
5	33 M	Idiopathic chronic neuropathy	LE weakness	Negative	PTR 2+ ATR ±	Sural N SNAP ↓ Tibial SEP N20 ND	Normal	Normal
6	69 M	GBS	Numbness, hands/feet LE weakness	Negative	PTR - ATR -	Sural N SNAP normal	Normal	Normal
7	24 F	GBS	Numbness arms/legs Weakness	Negative	PTR 1+ ATR 1+	Sural N SNAP normal Tibial SEP N20 normal	Normal	Normal
8	68 M	GBS	Numbness of both feet Weakness	Negative	PTR - ATR -	Sural N SNAP ↓	Normal	Mixed normal/ atrophic

Abbreviations. ATR: Achilles tendon reflex, DTRs: deep tendon reflexes, F: female, GBS: Guillain-Barré syndrome, LE: lower extremity, M: male, N: nerve, ND: not detected, PTR: patellar tendon reflex, SAN: sensory ataxic neuropathy, SEP: somatosensory evoked potential, SNAP: sensory nerve action potential, SS: Sjögren's syndrome.

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Abstract Number: 2691

Clinical, Radiological and Functional Characteristics of Clinically Significant Pulmonary Involvement in Primary SjöGren's Syndrome

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Background/Purpose: Prevalence of symptomatic pulmonary disease in primary Sjögren's Syndrome (pSS) ranges between 9% and 27%. Xerotrachea, small airway disease and interstitial lung disease (ILD) are among the most common manifestations. However, the evidence is conflicting on which of the above mentioned respiratory disorders is the most prevalent in pSS patients. The purpose of the present study is to estimate the prevalence and type of chronic respiratory symptoms in a large cohort of pSS and associate them with disease-specific clinical and laboratory parameters.

Methods: Consecutive patients with pSS were questioned for chronic respiratory symptoms (cough, dyspnea or both). Patients with pre-existing respiratory symptoms before the onset of pSS were excluded from further investigation. The remaining symptomatic patients were assessed clinically, with PFTs (pre- and post-bronchodilator spirometry, static lung volumes and diffusion capacity) and high resolution CT (hrCT) on inspiratory and expiratory phase. Clinical and laboratory characteristics taken from the patient's records were compared between symptomatic and asymptomatic patients and between patients with ILD and other non ILD respiratory disorder related to pSS.

Results: Thus far, 348 patients have been screened from an initial cohort of 723 pSS patients. According to preliminary analysis, chronic respiratory symptoms were detected in 24% (*84/348*) of patients. Two thirds of the cases (*55/84*) were attributed to pSS. PFTs and chest hrCT were performed in 34 patients. Eighteen patients (*18/34 or 53%*) were diagnosed with small airway disease, while only 5 patients (*15%*) had ILD. Xerotrachea was considered responsible for chronic cough, in symptomatic patients with normal PFTs and normal or non-specific CT findings (*11/34 or 32%*). There were no statistically significant differences in clinical and laboratory parameters between symptomatic and asymptomatic patients, patients with ILD, patients with small airway disease or symptoms related to xerotrachea.

Conclusion: Small airway disease is the most common pulmonary manifestation in patients with chronic respiratory symptoms and pSS, while ILD is less frequent than previously thought.

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Abstract Number: 2692

Pulmonary Involvement, As Part of the Essdai, in Primary Sjogren's Syndrome

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Background/Purpose: In previous studies in primary Sjögren's syndrome (pSS), the prevalence of pulmonary involvement varied greatly depending on differences in inclusion criteria, imaging modalities and definitions of pulmonary involvement. The EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) has been developed for standardizing definitions of the main organ involvements. Our aim was to evaluate the prevalence and types of pulmonary involvement in pSS patients and to classify the manifestations using the respiratory domain of the ESSDAI.

Methods: This retrospective cohort study included all consecutive pSS patients, fulfilling the AECG and/or ACR classification criteria, who visited the department of Rheumatology and Clinical Immunology of the UMCG in 2015. Data were obtained from electronic patient records of the first visit in 2015. Pulmonary complaints were defined as persistent cough, dyspnoea during exercise, dyspnoea in rest and recurrent lower respiratory infections. Pulmonary additional tests included conventional chest radiography, (high-resolution; HR) CT and pulmonary function test (PFT). Pulmonary involvement was defined as the presence of conditions 1) for which therapy is needed and/or follow-up is recommended and 2) with (possible) relation with pSS instead of coincidental factors. The respiratory domain of the ESSDAI was determined for all these patients at time of visit. In some cases, the difference between pulmonary manifestations caused by pSS or coincidental factors remained unclear, resulting in a range of assumed to possible pulmonary involvement in pSS.

Results: Of the 262 included pSS patients, 93% were female and mean age was 56 ± 15 years. Pulmonary complaints were present in 88 (34%) patients; 70 (27%) patients with cough, 42 (16%) with dyspnoea during exercise, 17 (7%) with recurrent lower respiratory infections and no patients with dyspnoea in rest. Additional pulmonary diagnostics was performed in 225 (86%) patients; chest radiography in 203 (78%) patients, PFT in 147 (56%) patients and (HR)CT in 87 (33%) patients. Pulmonary involvement was present in 25-39 (10-15%) pSS patients. Overall, most common was interstitial lung disease (ILD), which was present in 15 patients; especially non-specific interstitial pneumonia (NSIP), followed by lymphocytic interstitial pneumonia (LIP) and organising pneumonia (OP). Isolated bronchiectasis and/or bronchopathy was present in 11 patients, pleuritis in 4 patients, pulmonary hypertension in 2 patients and 2 patients had a mucosa-associated lymphoid tissue (MALT) lymphoma in the lung. In total, 16 (6%) patients had a positive ESSDAI for the respiratory domain; 4 patients with low, 11 with moderate and one patient with high activity. Pulmonary involvement in pSS was not scored in the ESSDAI for patients with long lasting features (>1 year) which are assumed to be not active (n=14), MALT lymphoma which was rated in another domain (lymphadenopathy and lymphoma; n=2), or when (HR)CT and/or PFT was not recently performed (n=7).

Conclusion: In this cross-sectional study in daily clinical practice, pulmonary involvement was present in 10-15% of pSS patients. Of all pSS patients, 6% were scored as active on the respiratory domain of the ESSDAI.

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Abstract Number: 2693

Evolution of Disease Activity over a 5-Year Period in the 395 Patients with Primary SjöGren's Syndrome of the Assess Prospective Cohort

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Background/Purpose: Little is known about the natural history of primary Sjögren's syndrome due to the limited number of prospective cohorts followed up in a yearly manner. International validated disease activity scores were recently established and are now used as inclusion criteria and as primary outcome measures in many randomized controlled trials. This is therefore of critical importance to know the evolution of these scores and the proportion of patients experiencing a change in these scores.

Methods: The ASsessment of Systemic complications and Evolution in primary Sjögren's Syndrome (ASSESS) cohort is a prospective ongoing cohort of 395 patients. All patients have a medical examination every year by a trained physician, who collects the ESSDAI (Eular Sjögren's Syndrome Disease Activity Index), which scores systemic disease activity, clinical ESSDAI (clin ESSDAI, which scores systemic disease activity without the biological domain of the ESSDAI)and the ESSPRI (Eular Sjögren's Syndrome Patient Index), a patient-related outcome which scores dryness, pain and fatigue.

Results: Baseline data At enrollment in the 395 patients of the cohort, median ESSDAI, clin ESSDAI and ESSPRI were 3 [2-8], 3 [0-8] and 5.7 [4-7], respectively. 28.2% and 10.6% of patients had moderate systemic disease activity (5≤ ESSDAI < 13) or high systemic disease activity (ESSDAI ≥ 14), respectively. 62.2% of patients had an ESSPRI≥ 5. Follow-up data During the 5 years of annual follow up, 23.3 and 23.4% of patients with a baseline ESSDAI or a clinESSDAI < 5, respectively, had at least at one follow up visit, an ESSDAI or clinESSDAI ≥ 5. 10.5% and 12.9% of patients with a baseline ESSDAI<14 or clinESSDAI<14, respectively, had at least at one follow up visit an ESSDAI or clin ESSDAI≥14. Regarding changes in domains of the ESSDAI over the 5 years of follow up, the most frequent changes were observed in the biological (46.2% of patients), articular (34.9%), hematological (28.9%), pulmonary (25.1%), and glandular domain (20.5%). 25% of patients with a baseline ESSPRI<5 had at least at follow up one visit an ESSPRI ≥5. 39.8% of patients with baseline ESSDAI and ESSPRI<5 had at least at one follow up visit an ESSDAI or an ESSPRI ≥5.

Conclusion: Systemic manifestations and symptoms evolve over time during the 5-year follow-up in patients with primary Sjögren's Syndrome. Approximately one fourth of the patients with no systemic activity or an acceptable symptoms status at baseline evolved to a status of moderate disease activity or to disabling symptoms, respectively. 40% of patients without any active disease or disabling symptoms at baseline developed systemic complications or disabling symptoms within 5 years.

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Abstract Number: 2694

Treatment of ZAP-70 Mutant SKG Mice with Anti-IL-23 Antibody Alters Fecal Microbiota Composition and Prevents Outgrowth of Bacteria Associated with Susceptibility to Spondyloarthritis and Ileitis

Linda Rehaume[1], Nicholas Matigian[1], Alicia Kang[1], Olga Zbarskaya[1], Kristine Kikly[2], Nancy Lachner[3], Joshua Daly[3], Philip Hugenholtz[3], Mark Morrison[1], Kim-Anh Lê Cao[4] and Ranjeny Thomas[1], [1]Translational Research Institute, The University of Queensland Diamantina Institute, Brisbane, Australia, [2]Biotechnology Discovery Research, Eli Lilly and Co, Indianapolis, IN, [3]The University of Queensland, Australian Centre for Ecogenomics, Brisbane, Australia, [4]Translational Research Instiute, The University of Queensland Diamantina Institute, Brisbane, Australia

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Background/Purpose: Identification of disease-associated or protective bacteria may elucidate new biomarkers or probiotic supplements for people suffering from spondyloarthritis (SpA), or for people at-risk of disease development. The colitogenic *Prevotella copri* was associated with new-onset rheumatoid arthritis, and *Prevotella* spp. were increased in the cecum of HLA-B27 transgenic rats. Ankylosing spondylitis patients have increases in several bacterial families including *Porphyromonadaceae*. *Lactobacillus murinus* is protective in a murine model of colitis. Thus, microbes are associated with SpA disease progression but it is unclear how the microbial community structure differs as a result of genetic susceptibility to SpA, or the impact of additional pro-inflammatory triggers or drivers. Since IL-23 is a key driver of SpA, we hypothesized that IL-23 modifies the gut microbiota and the response to pro-inflammatory triggers of SpA.

Methods: BALB/c ZAP-70^{W163C}-mutant (SKG) mice housed under specific pathogen-free (SPF) conditions treated with microbial β-1,3-glucan (curdlan) develop IL-23- and microbiota-dependent SpA-like arthritis and ileitis. Altered Schaedler flora(ASF)-colonized SKG and BALB/c mice were treated one day prior to curdlan, and then weekly, with anti-IL-23 p19-specific mAb or isotype control mAb, or with curdlan or vehicle control. SPF-SKG mice were treated weekly with anti-IL-23 or isotype mAb for 3 weeks, then with curdlan or vehicle control. Fecal samples were collected longitudinally and the microbiota community profiles were analyzed by RT-PCR and next-generation sequencing. Arthritis, spondylitis and ileitis were assessed histologically.

Results: After colonization of germ-free mice with ASF, 4/8 bacterial strains were detected in ASF-SKG and ASF-BALB/c mice: *Clostridium* sp., *Lactobacillus murinus*, *Mucispirillum schaedleri* and *Parabacteroides* sp. Whilst the relative abundance of *Clostridium* sp. and *Parabacteroides* sp. was decreased in SKG, the most abundant bacterial species in both strains of mice was the *Parabacteroides* sp. After curdlan, the abundance of *L. murinus* and *M. schaedleri* but not *Parabacteroides* sp. declined in ASF-SKG mice over time, while the abundance of *L. murinus* and *M. schaedleri* did not decline in mice treated with curdlan and anti-IL-23 mAb. In SPF-SKG mice treated with anti-IL-23 mAb or anti-IL-23 mAb then curdlan, the abundance of multiple *Prevotellaceae* and *Porphyromonadaceae* spp. decreased relative to SPF-SKG mice treated with isotype then curdlan.

Conclusion: Interaction of the microbiota with the immune system of SKG mice alters the composition of both a simplified consortium and an unrestricted bacterial community. Curdlan triggers the decline of a gut-protective species within a simplified consortium. Treatment of SPF-SKG mice with anti-IL-23 mAb not only suppresses SpA development but shifts the fecal microbiota composition and prevents the usual outgrowth of bacteria associated with arthritis and inflammatory bowel disease in response to curdlan.

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Abstract Number: 2695

Genetic Association of Ankylosing Spondylitis with TBX21 Influences T-Bet and Pro-Inflammatory Cytokine Expression in Humans and SKG Mice As a Model of Spondyloarthritis and Alters Host Microbiome and Response to Microbial Stimuli

Max Lau[1], Patricia Keith[1], Madeline McCready[1], Mary-Ellen Costello[1], Linda Bradbury[1], Kelly Holiis[1], Ranjeny Thomas[2], Gethin P. Thomas[3], **Matthew A. Brown**[1] and Tony J. Kenna[1], [1]Translational Research Institute, Translational Genomics Group, Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Australia, [2]Translational Research Institute, The University of Queensland Diamantina Institute, Brisbane, Australia, [3]Translational Reserch Institute, The University of Queensland Diamantina Institute, Brisbane, Australia

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Background/Purpose: *TBX21* encodes the transcription factor T-bet and is genome-wide significant associated with ankylosing spondylitis (AS). T-bet is implicated in innate and adaptive immunity. However, the role of T-bet in AS pathogenesis is unclear. We recently demonstrated that T-bet expression is enhanced in AS patients and that T-bet controls IFN-gamma+IL-17+ NK cells and CD8 T cells. In the SKG model of spondyloarthropathy (SpA) mice lacking the *Tbx21* gene were protected from peripheral arthritis and gut inflammation. We hypothesized that enhanced T-bet expression in AS alters mucosal immunity in the gut and contributes to enhanced reactivity to microbial challenge. Furthermore we hypothesized that the enhanced T-bet expression seen in AS is antigen-driven and that T-bet+ cells express markers of prior antigen encounter.

Methods: We used 16S RNA sequencing to assess the impact of *Tbx21* on the gut microbiome in fecal samples from wildtype SKG mice or *Tbx21*-/- littermate controls. AS patient PBMC samples were used to investigate the response of T-bet+ cells to in vitro challenge with bacterial stimuli. Finally we looked for evidence of antigen-experience on T-bet+ NK cells and CD8 T cells from AS cases and healthy controls to determine whether these cells are being stimulated in vivo in AS patients.

Results: *Tbx21* influenced the intestinal microbial composition with decreased abundance of inflammatory species such as *Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae* observed in *Tbx21*-/- compared with *Tbx21*+/+ littermate control SKG mice. T-bet+ NK cells and CD8 T cells secreted IL-17 and IFN-gamma following in vitro challenge with a range of TLR agonists. In the periphery of AS cases T-bet+ NK cells and CD8 T cells displayed phenotypic markers of recent antigen exposure but the frequnecy of circulating memory T cells was profoundly reduced compared with healthy controls.

Conclusion: AS-associated variants in *TBX21* influence T-bet expression and numbers of IL-17 and IFN-gamma secreting NK and CD8+ T cells. T-bet is a major component of inflammatory pathways of spondyloarthropathy in humans and mice and may contribute to inflammation by influencing the gut microbiome and/or through influences on immune cell function in response to microbial challenge.

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Abstract Number: 2696

Identification of a Potential Commensal Immunologic Target in Enthesitis-Related Arthritis

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Identification of a Potential Commensal Immunologic Target in Enthesitis-related Arthritis

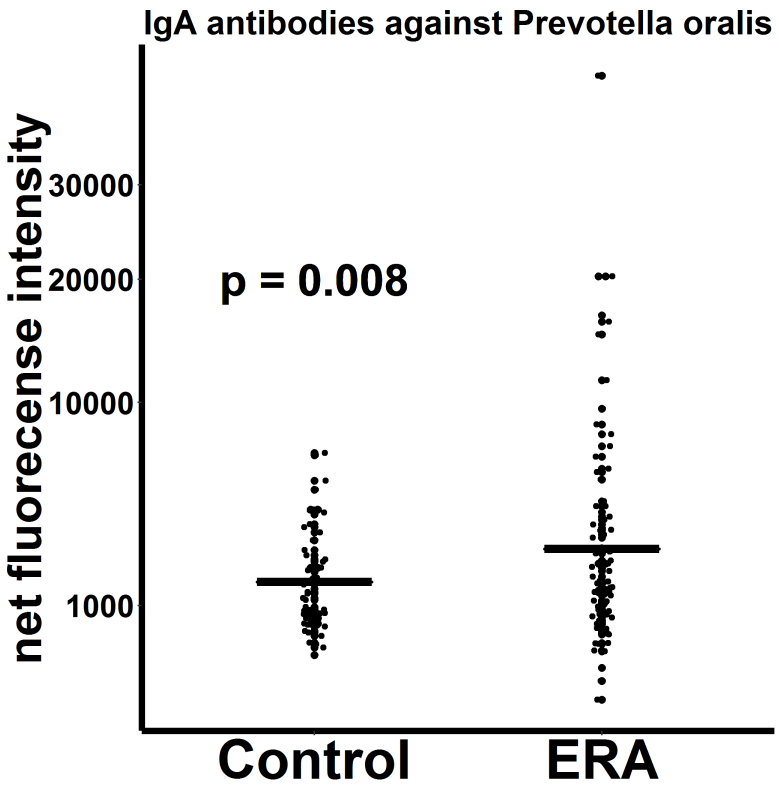
Background/Purpose: Research in inflammatory bowel disease (IBD) has identified commensal organisms that stimulate humoral and T cell immune responses. Although there is mixed data on whether similar antibodies are also present in spondyloarthritis (SpA), there has not been a comprehensive effort to identify commensal antigenic targets in SpA.

Methods: We used a novel antigen array developed by one of the co-authors (1) in which lysates of whole bacteria were plated, along with known flagellar and other commensal-derived antigens. Initial screening was performed with pooled serum samples from children

with enthesitis-related arthritis (ERA) and healthy control subjects, testing for IgG and IgA reactivity. Validation was performed with Western blots and with individual serum samples on the array.

Results: The initial screening studies were performed on pools of five ERA subjects and healthy controls. For most of the antigens tested on the array, there were no differences in binding between ERA patients and controls. However, IgG and IgA reactivity against *Prevotella oralis* was present only in the patients with ERA, not in controls or even in the pool of patients with ERA complicated by IBD. Western blots against *P. oralis* with ERA serum identified a high molecular weight glycoprotein that was not targeted by control serum. To confirm our findings, we repeated the array on individual serum samples from 83 patients with ERA (44 male; age 13; 6.0 – 19) and 59 healthy control subjects (33 male; age 13; 6.6 – 18). While there were no differences in IgG or IgA reactivity to most antigens, including the positive control Tetanus toxoid, ERA subjects had increased IgA reactivity against *P. oralis* (net signal intensity [NSI] 3761 versus 1835, p = 0.008; Figure) as well as to *P. buccalis* (NSI 962 versus 618, p = 0.008.) ERA patients also had increased IgG reactivity against *P. buccalis* (NSI 4936 versus 2718, p = 0.003) as well as a modest increase against the previously identified IBD-associated antigen Fla2 (NSI 1310 versus 1007, p = 0.026). Among the ERA patients, there was no association between HLA-B27 status and reactivity against these antigens.

Conclusion: Herein, we introduce members of the *Prevotella* genus, primarily *P. oralis* and *P. buccalis*, as potential antigenic targets in children with ERA. We also demonstrate increased Fla2 reactivity in children with ERA, consistent with data in adults with SpA. (1) Christmann B et al., JACI 2015;136:1378-86



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Abstract Number: 2697

Modulator Role of Inducible Costimulator (ICOS) in Spondyloarthritis Animal Model

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Session Time: 9:00AM-11:00AM

Background/Purpose: HLA-B27/hβ2m transgenic rats (B27 rats), a model of spondylarthritis (SpA) develop spontaneous colitis and arthritis. Recently, in vitro studies demonstrated that altered dendritic cells (DCs) function promoted a biased expansion of pro-inflammatory Th17 cells and alterations of regulatory CD4+ T cells (Treg) function, characterized by heightened IL-17 and decreased Il-10 production. Interestingly, *in vitro* blockade of ICOS-ICOSL interaction reversed IL-10/IL-17 imbalanced production by Treg. These data led us to investigate the *in vivo* consequences of ICOS/ICOSL interaction in experimental SpA using a genetic approach by producing B27 rats with *Icos* deletion (B27.ICOS$^{-/-}$ rats).

Methods: ICOS$^{-/-}$ rats were produced using TALEN technology, and backcrossed onto the B27 transgenic background (F344). B27.ICOS$^{+/+}$ and B27.ICOS$^{-/-}$ rats were weekly weighted, examined and scored for clinical symptoms (colitis, arthritis, alopecia and orchitis). Inflammatory pattern was determined by histological analysis and *ex-vivo* production of pro-inflammatory cytokines.

Results: As expected, chronic diarrhea was the most common manifestation, starting at 9 weeks of age in all B27.ICOS$^{+/+}$ rats. Arthritis and alopecia developed only in some B27.ICOS$^{+/+}$ rats. The clinical score progressively worsened in B27.ICOS$^{+/+}$ rats. In contrast, the B27-ICOS$^{-/-}$ rats did not develop any symptom of disease until age of 16 weeks and attenuated symptoms were observed until 24 weeks, a finding that was confirmed by histopathology analysis. Decreased *in vitro* production of pro-inflammatory cytokines and increased IL-10 production by CD4+ T cells were consistently observed in the B27-ICOS$^{-/-}$ rats.

Conclusion: Those results indicate a protective effect of *Icos* deletion on the onset and severity of SpA in the B27 rat. The protective effect was associated to a decrease of pro-inflammatory T cells and an increased proportion of IL-10-producing CD4+T cells. Those data corroborate previous observation suggesting a key role for ICOS signaling in the imbalanced production of IL-10 and IL-17 by Treg in the B27 rat and highlight ICOS as a putative therapeutic target in SpA.

Abstract Number: 2698

Regulation of Inflammation By Interleukin-27 in a Rat Model of Spondyloarthritis (SpA)

Quentin Jouhault[1], Maxime A. Breban[2], Luiza Krause[3] and Gilles Chiocchia[3], [1]Infection and inflammation, INSERM-U1173, University of Versailles Saint-Quentin-en-Yvelines, France, Montigny-le-Bretonneux, France, [2]Rheumatology Division, Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [3]Infection and Inflammation, INSERM-U1173, University of Versailles Saint-Quentin-en-Yvelines, France, Montigny-le-Bretonneux, France
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Background/Purpose: SpA is a chronic inflammatory rheumatic disorder with osteo-articular and extra-articular manifestations. HLA-B27/human β2-microglobulin transgenic rats (B27 rat) spontaneously develop a phenotype closely resembling human SpA and represent an adequate model to better understand the mechanisms involved in SpA development. Disease development in these rats is correlated with accumulation of pro-inflammatory interleukin-17 (IL-17)-producing helper T cells (Th17) and abnormal function of dendritic cells (DCs) which enhance the generation of Th17 cells. Moreover, dysregulated production of IL-17 and IL-10 in favor of IL-17 by regulatory T cells (Treg) was recently described, associated with inducible costimulator (ICOS) overexpression. Transcriptomic study of B27 DCs has revealed a decreased expression of IL-27, an anti-inflammatory cytokine able to decrease IL-17 and increase IL-10 production by T cells. Here, we investigated if addition of exogenous IL-27 would contribute to reverse the pro-inflammatory phenotype of T cells observed in the B27 rats.

Methods: Sorted T cell subsets and sorted CD103+ DCs from B27 rats were co-cultured in the presence or absence of recombinant IL-27. Effector T cells and Tregs were cultured 3 days with coated anti-CD3. Naive T cells were cultured 6 days with coated anti-CD3 in Treg- or Th17-polarizing conditions. Cytokine production was evaluated by intracellular staining after PMA/ionomycin stimulation and by ELISA in the supernatants.

Results: The addition of exogenous IL-27 inhibited IL-17 expression and increased IL-10 production on several CD4+ T cells subsets, such as effector T cells or Tregs. Moreover, IL-27 inhibited the development of Th17 and promoted IL-10 production from naïve T cells cultured in Treg- or Th17-polarizing conditions. We also observed a downregulation of ICOS expression on T cells cultured in the presence of IL-27. *In vitro*blockade of IL-10 with a specific antibody demonstrated that this cytokine was not implicated in the modulatory effect of IL-27 on IL-17 production. Moreover, IL-27 still significantly decreased IL-17 production by T cells from B27-ICOS-/- rats, indicating that this effect was also independent of ICOS.

Conclusion: Our results reveal that IL-27 is able to reverse the pro-inflammatory phenotype observed in T cells from B27 rats by reversing the IL-17/IL-10 imbalance in favor of IL-10. Moreover, the effect of IL-27 on IL-17 production was independent of IL-10 and ICOS modulation. Given that IL-17 is a confirmed therapeutic target in SpA, these results suggest that IL-27 may be a new promising therapeutic tool for SpA.

Disclosure: Q. Jouhault, None; **M. A. Breban**, None; **L. Krause**, None; **G. Chiocchia**, None.

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Abstract Number: 2699

Spa-Associated HLA-B*27 Subtypes Accumulate More in Endoplasmic Reticulum (ER) Compartment and in Association with β2-Microglobulin (β2m) Than Non-Associated HLA-B Alleles

Nadège Jah[1], Gilles Chiocchia[2], **Maxime A. Breban**[3] and Claudine Andre[1], [1]Infection and inflammation, INSERM UMR1173, Montigny-le-Bretonneux, France, [2]Infection and Inflammation, INSERM-U1173, University of Versailles Saint-Quentin-en-Yvelines, France, Montigny-le-Bretonneux, France, [3]Rheumatology, Ambroise Paré Hospital (AP-HP), Versailles Saint Quentin en Yvelines University, INSERM UMR1173, Boulogne-Billancourt, France

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Background/Purpose: Mechanisms underlying the striking association of SpA with the MHC class I molecule HLA-B27 remain poorly understood. SpA-like disease develops spontaneously in B*2705 transgenic rats in correlation with high HLA-B27 expression levels. This study was undertaken to examine the consequences of expressing HLA-B27 alleles which are differently associated with SpA on their intracellular distribution. It has previously been observed that high expression levels of HLA-B in HeLa cells induced cytoplasmic vesicles formation containing HLA-B molecules and that the density of vesicles was more important for HLA-B27 subtypes associated with SpA than for the non-associated HLA-B*2706 and HLA-B*0702 alleles. Here, we further examined the nature and composition of thoses vesicles and the putative differences between associated and non-associated HLA-B alleles.

Methods: HeLa cells were transfected with complementary DNA encoding for HLA–B proteins fused to yellow fluorescent protein. We studied the composition and nature of HLA-B-containing intra-cellular vesicles by antibodies staining and live-cell imaging.

Results: With increased expression, all HLA-B proteins accumulated in cytoplasmic vesicles. This phenomenon was more pronounced for the SpA-associated HLA-B*2702, -B*2704 and -B*2705 than for the non-associated -B*2706 and -B*0702. We observed comparable staining of those vesicles with HC10 antibody (anti-class I heavy chain) for all HLA-B alleles. In contrast, we observed differential staining with BBM1 antibody that binds to β2m: the SpA-associated HLA-B27 subtypes formed vesicles that were stained significantly more with BBM1 than the non-associated HLA-B*2706 and HLA-B*0702 alleles. On the other hand, we observed no staining of thoses vesicles for EEA1 (early endosome marker), Rab7 (late endosomes marker), LC3 (autophagosomes marker) and Rab6 (Golgi marker) antibodies. However, we found positive staining for ER chaperones (BiP, calreticulin and ERp57) indicating that the HLA-B-containing vesicles belong to the ER. Consistent with such interpretation, those vesicles were still observed using live-cell imaging of HeLa cells transfected with HLA-B after treatment with nocodazole or brefeldin-A that inhibit ER exit. Finally, a lack of staining for tapasin indicated that the peptide-loading complex (PLC) does not localize to those vesicles.

Conclusion: Under conditions of high expression, HLA-B molecules accumulate in vesicles that belong to the ER where they co-localize with chaperones but not with the PLC. Moreover, our data indicate differences between HLA-B-containing cytoplasmic vesicles, depending on the allele: vesicles formed with HLA-B27 subtypes associated with SpA were more abundant and contained significantly more β2m than those formed with non-associated alleles. This report establishes a correlation between the level of predisposition to SpA conferred by HLA-B alleles and their biochemical behaviors that may contribute to their pathogenicity.

Disclosure: N. Jah, None; **G. Chiocchia**, None; **M. A. Breban**, None; **C. Andre**, None.

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Abstract Number: 2700

The Lymphatic System: A Gatekeeper for Migration of Pathogenic T-Cells Towards Synovial Joints and Entheses in Psoriasis

Radjesh Bisoendial[1,2], Errol Prens[3], Annemarie Mus[2], Patrick Asmawidjaja[2], Nadine Davelaar[2], Arien Hofman[4], Jean-Bart Jaquet[4], Mieke Hazes[2], Marc Kok[1], Wolfgang Weninger[5] and Erik Lubberts[2], [1]Clinical Immunology and Rheumatology, Maasstad hospital, Rotterdam, Netherlands, [2]Rheumatology, Erasmus University Medical Center, Rotterdam, Netherlands, [3]Dermatology, Erasmus University medical Center, Rotterdam, Netherlands, [4]Plastic surgery, Maasstad hospital, Rotterdam, Netherlands, [5]Immune imaging, The Centenary Institute, Sydney, Australia

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Background/Purpose: Psoriasis (PsO) is a common inflammatory skin disease that is characterized by acanthosis, impaired immune cell migration, and remodeling of the vascular and lymphatic system. Up to ~30% of PsO patients develop psoriatic arthritis (PsA). The factors that determine the transition from PsO to PsA or vice versa are poorly understood. The lymphatic system may regulate the homing capabilities of disease-associated T-cells and control their migration to skin and extra-cutaneous sites like synovial joints and entheses.

Methods: Primary human dermal lymphatic endothelial cells (LECs) were preincubated for 3 days with TNF (10 ng/mL), IL-17A (100 ng/mL), rheumatoid arthritis synovial fluid (SF-RA; 20% v/v) or psoriatic arthritis synovial fluid (SF-PsA; 20% v/v). After removing the media, LECs were cocultured with allogeneic (CD3-enriched) skin-derived T-cells (SDTC) or peripheral blood mononuclear cells (PBMCs) for 48 hours (each from 3 separate donors) in the presence of 0.3 μg/ml αCD3 and 0.4 μg/ml αCD28. T-cells were then immunophenotyped by flow cytometry on a 4-laser LSRII analyzer using antibodies directed to CD45, CD3, CD4, CXCR3, CCR4, and CCR6. Based on the latter three, the most relevant T-helper (Th) subsets were characterized, including the CCR6+ subpopulations Th17.1 (CXCR3+/CCR4-), Th17/Th22 (CXCR3-/CCR4+), and double positives (DP; CXCR3+/CCR4+), and the CCR6- subsets, i.e. Th1 (CXCR3+/CCR4-), and Th2 (CXCR3-/CCR4+). In addition, we looked at cutaneous lymphocyte-associated antigen (CLA), a skin lymphocyte homing receptor. The percentage of these Th-subsets (normalized to untreated LECs), that were generated upon co-

incubation with LECs, were statistically tested using 2-way ANOVA.

Results: SDTCs upregulated CLA-expression upon incubation on LECs that underwent pretreatment with SF-RA and SF-PsA, as compared to LECs preincubated with TNF or IL-17A. In contrast, this effect was not observed in PBMCs. The increase of normalized mean fluorescence intensity (MFI) for CLA-expression in SDTCs was more pronounced in LECs preincubated with SF-PsA versus SF-RA, and increased 3.3-fold, 2.8-fold and 3.1-fold in the total CD4+ compartment, Th17.1 and DP subsets respectively ($P<0.01$ for all as compared to SF-RA). This finding was not explained by an increase in the proportion of the total CD4+ compartment or Th17.1 and DP subsets within the CLA+ SDTC population.

Conclusion: LECs are directly involved in T-cell homing capabilities, as shown by CLA regulation at the time of STDC activation. CLA regulation occurs in a highly tissue-selective manner. Thus, preincubation of dermal LECs with SF-PsA and to a lesser extent SF-RA reinforced CLA expression particularly in CCR6+ T-cell subsets that are abundant in psoriatic skin. This effect was not seen in CD3-enriched PBMCs, where the CLA+ T-cell proportion is far less. Further studies are underway to show that LECs derived from relevant biological tissues from PsA patients including skin, lymph nodes and synovium may be critical for inducing tissue-imprinting receptors at the time of T-cell activation, and for tissue-restricted migration to both skin and synovial joints and entheses in PsO and PsA.

Disclosure: R. Bisoendial, None; **E. Prens**, None; **A. Mus**, None; **P. Asmawidjaja**, None; **N. Davelaar**, None; **A. Hofman**, None; **J. B. Jaquet**, None; **M. Hazes**, None; **M. Kok**, None; **W. Weninger**, None; **E. Lubberts**, None.

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Abstract Number: 2701

Increased Frequency of Regulatory CD19+CD24high Cd38high B Cells in Patients with Ankylosing Spondylitis (AS)

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Background/Purpose: CD19+CD24highCD38high B cells have been described to have a regulatory capacity and their frequency is altered in the peripheral blood of patients with various autoimmune diseases. The pathogenesis of AS is not well understood, and evidence suggesting the implication of either autoinflammatory or autoimmune mechanisms has been reported. In addition, increased frequencies of circulating B cells bearing a regulatory phenotype has recently been described in spondyloartrhitis (1). Therfore our objective was to study the frequency of circulating CD19+CD24high CD38high B cells (Breg) in patients with Ankylosing Spondylitis (AS), and test the regulatory capacity of this B cell subset.

Methods: Peripheral blood was drawn from AS patients naïve for TNF blockers (AS/nb) (n=41) and healthy controls (HC) (n=41), that were matched with patients for age and gender. After isolation by Ficoll-Hypaque gradient, PBMCs were stained with antibodies to CD3, CD4, CD19, CD24, and CD38, and examined by flow cytometry. For functional studies, total CD19+ B cells were isolated from PBMCs of 3 HC by magnetical sorting. Breg-depleted CD19+ B cells were obtained after total CD19+ B cells were depleted of CD19+CD24highCD38high B cells by cytometry in a FacsVantage sorter (Beckton Dickinson). Total CD19+ B cells or Breg-depleted CD19+ B cells were established in culture and stimulated through their BCR. Secretion of IFNγ was determined by ELISA in culture supernatants.

Results: When compared with healthy controls, AS/nb patients demonstrated a significantly increased frequency of CD19+CD24highCD38high B cells (Breg). The frequency of circulating Breg was increased not only in AS/nb patients with high or very high disease activity (ASDAS-CRP) >2.1 but also in AS patients with low activity or no activity (ASDAS-CRP< 2.1). The frequency of circulating Breg cells did not correlate significantly with ASDAS-CRP, ASDAS-ESR, BASDAI, CRP or ESR values. Functional in vitro studies showed that the secretion of IFNγ was significantly higher in Breg-depleted CD19+ as compared with total CD19+ B cells,

indicating that Breg have the capacity to downmodulate B cell pro-inflammatory cytokine secretion.

Conclusion: An increased frequency of circulating CD19+CD24highCD38high B cells is observed in AS/nb patients, that is not related with disease activity. Functional in vitro studies confirmed that CD19+CD24highCD38high B cells are able to downmodulate B cell pro-inflammatory cytokine secretion. References: (1) Cantaert T, Doorenspleet ME, Francosalinas G, Paramarta JE, Klarenbeek PL, Tiersma Y, van der Loos CM, De Vries N, Tak PP, Baeten DL. Increased numbers of CD5+ B lymphocytes with a regulatory phenotype in spondylarthritis. Arthritis Rheum. 2012;64 :1859-68.

Disclosure: M. B. Bautista-Caro, Roche Pharmaceuticals, 2; **E. De Miguel**, None; **D. Peiteado**, None; **C. Plasencia-Rodriguez**, None; **A. Villalba**, None; **A. Puig-Kröger**, None; **P. Sanchez-Mateos**, None; **E. Martín-Mola**, Roche Pharmaceuticals, 2; **M. E. Miranda-Carus**, Roche Pharmaceuticals, 2.

Abstract Number: 2702

Taking Fly for Understanding the Molecular Role of HLA-B27/hB2m in Spondyloarthritis

Nadège Jah[1], Benjamin Grandon[2], Aurore Rincheval-Arnold[3], Isabelle Guénal[3], Sébastien Gaumer[3], Claudine André[4], Maxime A. Breban[5] and **Gilles Chiocchia**[6,7], [1]Infection and inflammation, INSERM UMR1173, Montigny-le-Bretonneux, France, [2]Inserm UMR 1173 and LGBC, 78180 Saint Quentin en Yvelines, France, [3]Laboratory of Genetic and Cellular Biology, Faculty of Health Sciences Simone Veil, Montigny-le-Bretonneux,, 78180 SAINT QUENTIN EN YVELINES, France, [4]UMR 1173, 78180 Saint-Quentin en Yvelines, France, [5]Rheumatology Division, Ambroise Paré Hospital (AP-HP), and Versailles Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [6]Infection and Inflammation, INSERM-U1173, University of Versailles Saint-Quentin-en-Yvelines, France, Montigny-le-Bretonneux, France, [7]Service d'Immunologie, Ambroise Paré Hospital, University of Versailles Saint-Quentin-en-Yvelines, Boulogne, France, Boulogne-Billancourt, France

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Background/Purpose: After more than 40 years of researches, the mechanisms underlying the association of HLA-B27 with spondyloarthritis (SpA) remain poorly understood. The *Drosophila* has been demonstrated to be an extremely useful genetic model in numerous systems. We hypothesized that *Drosophila* might be a relevant model to study HLA-B27 and particularly for deciphering the cellular cascade and the genetic pathways affected by HLA-B27 mutation. To do so we developed HLA-B2705, HLA-B0702 (control) and human Beta-2-microglobulin (hB2m) transgenic *Drosophila*.

Methods: Gateway Technology and UAS-Gal4 system was used for developing transgenic HLA-B/human hB2m *Drosophila*. *UAS-hB2m* transgene was inserted in long arm of chromosome 3 and *UAS-HLA-B2705* and *UAS-HLA-B0702* were alternatively inserted at another position in the short arm of the same chromosome. For each construct, various transgenic lines were obtained and crossed with several tissue specific driver strains, to induce the expression of the coding sequence for *HLA-B0702* and *hB2m* or *HLA-B2705* and *hB2m* placed under the control of UAS sequences.

Results: HLA-B2705/hB2m transgenes were first expressed in *Drosophila* by mean of vestigial Ga4 driver line allowing to produce targeted protein in *Vestigial* domain (dorso-ventral frontier of the wing epithelia). We observed positive staining with HC10 antibodies (class I heavy chain) and W6/32 antibody (HLA-A, HLA-B and HLA-C conformation) for both tested HLA-B/hB2m but only HLA-B27/hB2m was labelled with ME1 (anti-HLA B/C) antibodies, suggesting a different conformation of HLA-B27 and HLA-B7 with hB2m in the wing epithelia. Furthermore, by mean of the nubbin or engrailed drivers which drive the expression in a larger part of the wing, we observed specific loss of posterior cross-vein following HLA-B27/hB2m expression but not HLA-B7/hB2m.

Conclusion: We have established *Drosophila* lines allowing tissue specific expression of different HLA-B alleles. Our data suggest that the expression of HLA-B/hB2m transgenes in epithelial cells leads to a plasma membrane localization for HLA-B2705/hB2m but not for HLA-B0702/hB2m. Furthermore, we observed that tissue specific expression of HLA-B27/hB2m but not HLA-B7/hB2m induced

specific loss of cross-vein suggesting it interferes with developmental pathways involved in differentiation. This is the first time that difference in localization between HLA-B2705, subtype associated with SpA, and HLA-B0702, which is not associated with the disease are reported. These results show that transgenic *Drosophila* might be a pertinent model to decipher molecular mechanisms involved in HLA-B27 trafficking and to better understand potential different behavior of HLA-B subtypes.

Disclosure: N. Jah, None; **B. Grandon**, None; **A. Rincheval-Arnold**, None; **I. Guénal**, None; **S. Gaumer**, None; **C. André**, None; **M. A. Breban**, None; **G. Chiocchia**, None.

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Abstract Number: 2703

Apremilast May Improve Atherosclerosis By Promoting Cholesterol Efflux and Inhibiting Foam Cell Formation in Atherosclerotic Plaques

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Background/Purpose: Atherosclerosis is characterized by the accumulation of lipid-laden macrophages in the arterial walls. Patients with inflammatory arthritis and psoriasis are at greater risk of developing atherosclerotic plaques with their associated cardiovascular diseases. Recent studies indicate that effective therapy of inflammatory arthritis may reduce the risk of atherosclerotic cardiovascular disease although the basis for this risk reduction is not totally clear. Recently apremilast, an inhibitor of PDE4, has been introduced into the clinical armamentarium for the treatment of psoriasis and inflammatory arthritis. We and others have recently demonstrated that agents, such as adenosine A2A receptor stimuli, that stimulate cAMP accumulation in macrophages can reduce foam cell formation by a protein kinase A (PKA) – mediated mechanism involving enhanced efflux of cholesterol and lipids. We therefore asked whether apremilast might have a similar effect

Methods: RAW264.7 murine macrophage cell line was infected with lentiviruses expressing shRNA to silence PKA, EPAC1 and EPAC2, or scrambled shRNA. Knockdown was confirmed by Western Blot. The effect of apremilast on foam cell formation was tested by examination of 70% confluent cells in 48-well plates following treatment with Interferon-γ (IFNγ, 0.5u/ul) for 24 hours and then treatment with acetylated LDL (50ug/ml) with/without apremilast (10uM) for another 48 hours. Cells were stained with oil-O-red and then cells containing lipid droplets were counted. To determine whether apremilast affected cholesterol efflux cells (70% confluent in 48-well plates) were treated with IFNγ (0.5u/ul) for 24 hours and followed by treatment with acLDL (50ug/ml) for another 24 hours. After treatment with bodipy-cholesterol for 1 hour, cells were cultured in the equilibration buffer for 18 hours and treated with HDL (20ug/ml) and ApoA1(10ug/ml with/without apremilast (AP, 10uM) for 4 hours. 200ul of each supernant /cell lysate (lysed in 1% cholic acid) were analyzed by record fluorescence @482/515nm.

Results: Apremilast treatment reduced foam cell formation in RAW264.7 cells stably expressing scrambled, EPAC1 and EPAC2, but not PKA shRNA (45±2%, 43±5%, 42±1% and -14±6% reduction, respectively, $p<0.001$, ANOVA). Apremilast treatment enhanced HDL-induced and apoA1-induced cholesterol efflux from RAW264.7 cells (2.345 ± 0.03% vs. 1.733 ± 0.08%, $p<0.001$, n=4 and 9.74 ± 0.32% vs.3.96±0.77%, $p<0.05$, n=3). Furthermore, Apremilast treatment enhanced HDL-induced from Raw264.7 cells stably expressing scrambled, EPAC1, and PKA but not in EPAC2 shRNA (0.737±0.6% vs.1.19±0.04% of control, $p<0.05$, ANOVA); apremilast treatment enhanced ApoA1-induced cholesterol efflux from RAW264.7 cells stably expressing scrambled, but not EPAC1, EPAC2, and PKA shRNA (2.62±0.15%, 1.55±0.22%, 1.44±0.04% a vs. 0.95±0.15% of control, respectively, $p<0.01$, $p<0.05$ and $p<0.01$, ANOVA). Thus, these results suggested that 1)apremilast promotes HDL-induced cholesterol efflux through increasing intracellular cAMP with EPAC1dependent mechanism, and apoA1-induced cholesterol efflux through increasing intracellular cAMP with EPAC1, EPAC2, PKA dependent mechanisms, 2) apremilast inhibits foam cell formation through increasing intracellular cAMP by only PKA-dependent mechanism

Conclusion: These results suggest that apremilast may be useful for the treatment/prevention of atherosclerosis in patients with psoriasis

and inflammatory arthritis.

Disclosure: H. Liu, None; **T. Wilder**, None; **A. Mediero**, CP15/0053, 2, 9,Patent for the use of adenosine A2AR agonists to prevent prosthesis loosening. Patent on the use of Antibodies against Netrin-1 for the treatment of bone diseases., 9; **Z. Wei**, None; **C. Corciulo**, None; **B. Cronstein**, Canfite Pharma, 1,Celgene, AstraZeneca, Takeda, 2,Revive Therapeutics, 5,Always hopeful, 9.

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Abstract Number: 2704

Discovery of a Small Molecule Inhibitor of the Wnt Pathway (SM04755) As a Potential Topical Treatment for Psoriasis

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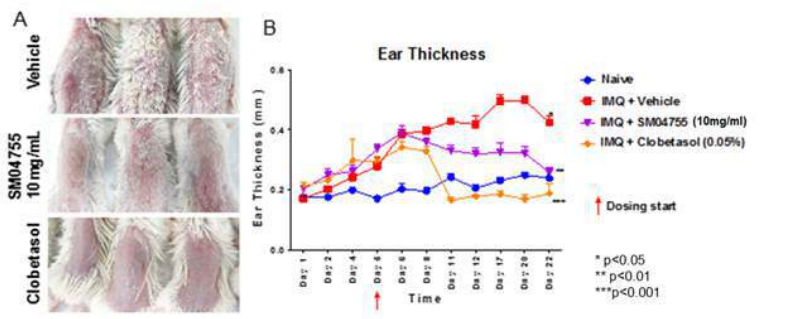
Background/Purpose: Psoriasis is an auto-immune disease of the skin, characterized by inflammation and fibrosis producing patches of red, itchy and scaly skin. Wnt signaling plays an important role in psoriasis by regulating inflammation, keratinocyte proliferation and dermal fibrosis. SM04755, a novel, topical small-molecule Wnt pathway inhibitor was evaluated in a series of preclinical studies to determine its potential to inhibit inflammation, keratinocyte proliferation and dermal fibrosis, thereby improving skin health in psoriasis.

Methods: Wnt pathway inhibition was measured using a cell-based reporter assay. Anti-inflammatory activity was evaluated by ELISA measuring TNF-α and IL-6 secretion in THP-1 monocytes stimulated with Lipopolysaccharides (LPS) and PBMCs stimulated with anti-CD3/anti-CD28. Cytokine induced keratinocyte proliferation was measured in HaCaT cells using an EdU incorporation assay. The effect on fibrosis was assessed in TGF-β stimulated human dermal fibroblasts by measuring smooth muscle actin (αSMA), plasminogen activator inhibitor (PAI-1), connective tissue growth factor (CTGF) and collagen expression by qPCR. Pharmacokinetics were evaluated by topical application in rats and mini-pigs, followed by analysis of compound concentrations in skin and plasma. *In vivo* efficacy was evaluated in an Imiquimod-induced mouse psoriasis model by measuring skin and ear thickness, spleen size and weight, *ex vivo* T cell activation and proliferation, and cytokine levels in plasma.

Results: SM04755 demonstrated potent (EC_{50} =152nM) and selective inhibition of Wnt signaling. SM04755 inhibited LPS- and anti-CD3/anti-CD28-induced TNF-α and IL-6 secretion (EC_{50} =500nM) in THP-1 cells and PBMCs. SM04755 inhibited cytokine induced keratinocyte proliferation (EC_{50} @900nM) and TGF-β stimulated dermal fibrosis as measured by a decrease ($p<0.05$) in gene expression of αSMA (EC_{50} =400nM), PAI-1, CTGF, and collagen in human dermal fibroblasts. Single topical application of SM04755 resulted in skin concentrations >EC50 for >24hrs, with minimal systemic exposure or toxicity. In the Imiquimod-induced mouse psoriasis model, topical SM04755 significantly ($p<0.01$) decreased skin and ear thickness, improved skin appearance, and significantly ($p<0.01$) reduced spleen size and weight as compared to vehicle. Clobetasol, a positive control, decreased skin thickness ($p<0.001$) below that of normal skin (a known adverse effect of steroid treatment). *Ex vivo* T cell activation, proliferation, and cytokine secretion were inhibited with SM04755 treatment compared to vehicle.

Conclusion: In a mouse model of Imiquimod-induced psoriasis, topically applied SM04755 inhibited inflammation, and decreased skin thickness compared to vehicle, with minimal plasma exposure or systemic toxicity. SM04755 has potential as a topical therapy for psoriasis.

Figure. SM04755 reduced the ear thickness and improved skin appearance relative to control in an Imiquimod-induced Psoriasis model in mice



Disclosure: V. Deshmukh, Samumed, LLC, 3; **M. Pedraza**, Samumed, LLC, 3; **M. Ibanez**, Samumed, LLC, 3; **L. Dellamary**, Samumed, LLC, 3; **J. Stewart**, Samumed, LLC, 3; **T. Seo**, Samumed, LLC, 3; **B. Melchior**, Samumed, LLC, 3; **J. Hood**, Samumed, LLC, 9; **Y. Yazici**, Samumed, LLC, 3.

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Abstract Number: 2705

Decreased Expression of Autophagy Genes and Their Association with Spinal Damage in Patients with Ankylosing Spondylitis

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Background/Purpose: Autophagy is a process of cellular self-digestion by enzymes originating within the lysosome of the cell. Autophagy primarily acts as a survival mechanism by removing damaged and dysfunctional proteins or organelles. It is well documented that autophagy has a potentially pivotal role in the induction and regulation of inflammatory responses by immune cells. However, a role of autophagy in ankylosing spondylitis has not been clearly elucidated and the association of autophagy-related gene expression levels with inflammatory or osteoproliferative processes observed in ankylosing spondylitis has not been reported. This study was performed to determine the expression levels of several key autophagy-related genes in patients with ankylosing spondylitis and investigate whether autophagy-related gene expression levels are associated with clinical parameters of ankylosing spondylitis and the production of inflammatory cytokines to elucidate the role of autophagy in pathogenesis of AS.

Methods: PBMCs from 43 AS patients and 40 healthy controls were obtained and mRNA expression levels of Atg genes (LC3, beclin1, and ATG5) were determined using quantitative real-time PCR. Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP and modified Stoke AS Spinal Score (mSASSS) were assessed at the time of blood sampling. Serum concentrations of TNF-alpha, IL-17, and IL-23 in AS patients were determined using enzyme-linked immunosorbent assays.

Results: LC3, beclin1, and ATG5 mRNAs were constitutively expressed in PBMCs of AS patients and healthy controls; however, expression of all three genes was significantly decreased in PBMCs of AS patients compared with those from controls. Expression levels of the autophagy-related genes were not significantly correlated with ASDAS-CRP or serum TNF-alpha, IL-17, and IL-23 concentrations. However, LC3 and beclin1 mRNA levels showed significant negative correlations with mSASSS of AS patients ($r = -0.805$, $p<0.01$ for LC3 and $r = -0.712$, $p<0.01$ for beclin1).

Conclusion: AS patients have decreased autophagy-related gene expressions and AS patients with more advanced spinal damage have further decreased LC3 and beclin1 expression levels. These results suggest that AS patients have defective autophagy activity and that compromised autophagy may contribute to the progression of spinal damage in AS.

Disclosure: M. C. Park, None; **H. W. Kim**, None; **J. J. Song**, None; **Y. B. Park**, None.

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Abstract Number: 2706

Elevated Levels of Serum Myeloid Related Protein 8/14 in Ankylosing Spondylitis: Associated with Peripheral Arthritis and Active Disease

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Background/Purpose: Monocytes of patients with Ankylosing Spondylitis (AS) show Toll-like receptor 4 (TLR4) over-expression. Myeloid-related proteins (MRP) 8/14 protein complexes are calcium-binding proteins, which act as endogenous ligands to TLR4. Thus we studied the levels of MRP8/14 in adult AS patients.

Methods: MRP8/14 levels were assessed in 99 adult AS patients satisfying ASAS 2010 criteria and 23 healthy controls by ELISA. Patient disease parameters like patient and physician global assessment, BASDAI, swollen and tender joint count, entheseal count by Maastricht Enthesitis index, Erythrocyte Sedimentation Rate (ESR) and C Reactive Protein (CRP) were also recorded. Levels were reassessed in 23 patients after 2-5 months of treatment with NSAIDs. All values are in median and IQR.

Results: The median serum MRP8/14 levels in patients [34.1 (17.94-264.58) mg/ml] were significantly higher than in healthy controls [5.97 (IQR 4.64-11.43) mg /ml ($p<0.0001$)]. Patients with peripheral arthritis (n=50) had higher levels than those with pure axial disease (n=49) [40.63 (IQR 28.41-73.15) mg /ml vs. 23.72 (11.04-61.55) mg /ml; p=0.012]. Levels of MRP8/14 correlated with ASDAS CRP (r=0.23, 95%CI=0.038-0.422, p=0.02) and CRP (r=0.28, 95%CI=0.081-0.45, p=0.01), and the correlation was better in early disease [≤5 years disease duration, (r=0.40, p=0.007) and (r=0.57, p=<0.0001) respectively]. MRP8/14 levels did not correlate with clinical disease activity measures such as BASDAI, Maastricht entheseal count, and patient and physician global assessment. Baseline levels were higher in treatment responders than in non-responders [51.17 vs. 32.22 mg /ml; p=0.02]. Change in MRP8/14 levels correlated with change in BASDAI and ASDAS CRP (r= 0.489, p=0.018 and r=0·498, p=0.016 respectively).

Conclusion: MRP8/14 levels may be used as a biomarker for activity, peripheral arthritis and response to therapy.

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Abstract Number: 2707

Autoantibodies Against CD74 – a New Diagnostic Marker for Spondyloarthritis (SpA)

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Background/Purpose: Spondyloarthritis (SpA) is a common debilitating inflammatory disorder. Pathogenesis of axial SpA (axSpA) including ankylosing spondylitis (AS) is still largely unclear. Diagnosis is difficult, since abnormalities in conventional X-rays develop with a latency of several years and only HLA-B27 is used as laboratory marker. The presence of radiographic sacroiliitis is essential for SpA diagnosis. To prevent destructive effects early diagnosis and intervention in SpA patients may be important. To evaluate antibodies to the human leukocyte antigen class II-associated invariant chain peptide (anti-CD74) as a diagnostic marker of SpA.

Methods: Sera of 117 patients with axial SpA and 38 non-SpA patients were analyzed for IgA and IgG antibodies against CD74 by ELISA. HLA-B27 status was available in 112 patients. All donors provided informed consent for the study approved by the local ethics committee (project number 4928).

Results: Anti-CD74 antibodies were detected in 85.1% of SpA patients but only in 5% of non-SpA patients ($p \leq 0.0001$). Detection of both IgG and IgA anti-CD74 antibodies for diagnosing SpA revealed a sensitivity of 77% and a specificity of 90%. Remarkably, IgA autoantibodies against CD74 alone had a sensitivity of 67% and a specificity of 95%. IgA anti-CD74 antibodies were even more frequent in SpA patients with short disease duration and significantly correlate with more advanced radiological sacroiliitis and reduced spinal mobility.

Conclusion: Anti-CD74 IgA antibodies were strongly associated with SpA. Antibodies against CD74 could provide an important additional tool for diagnosis of SpA.

Disclosure: T. Matthias, None; **E. Schweikhard**, None; **S. Reuter**, None; **M. Köhler**, None; **J. Georgi**, None; **N. T. Baerlecken**, None; **T. Witte**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/autoantibodies-against-cd74-a-new-diagnostic-marker-for-spondyloarthritis-spa-2

Abstract Number: 2708

Type 17 Immunity in Spondyloarthritis Is Expanded Across Multiple Lymphocyte Subsets

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Background/Purpose: The spondyloarthritides (SpA) are a group of chronic inflammatory disorders involving the axial spine and the peripheral joints. Genetic, functional and clinical trial evidences suggest an important role for IL17A within the context of *type 17* immunity. This study aims to understand the different components of the *type 17* immune axis in patients with SpA compared to healthy controls.

Methods: Peripheral blood was obtained (with ethical approval and informed consent) from 38 patients with SpA, 17 age and sex matched healthy donors, and 14 patients with Rheumatoid Arthritis (RA) matched for CRP. Mononuclear cells were analyzed by flow cytometry using a multicolor antibody panel staining surface phenotypic markers and intracellular cytokines.

Results: Patients with SpA had a higher percentage of CD4 Th17 cells than healthy controls (mean±SD) (1.27±0.69 *vs* 0.67±0.41%; p<0.001). The production of IL17A in the CD8 (1.30±1.01 *vs* 0.40±0.45%; p<0.001) and in the γδ T cell compartment (4.86±7.04 *vs* 1.01±0.85%; p<0.001) was also higher in SpA than controls. Within the *type 17* axis, polyfunctional cells coexpressing IL17A and GM-CSF were increased in the CD4, CD8, γδ and NK compartment in SpA, compared to healthy controls and Rheumatoid Arthritis patients (Figure 1). Analysis of the regulatory T cell pool showed a similar frequency of Tregs in the peripheral blood of SpA patients compared to healthy controls (SpA: 5.4±2.5% vs 4.7±1.9%; p=0.22), although in patients, Tregs appeared enriched in the synovial fluid compared to the peripheral blood (mean of difference±SEM: 8.8±1.3%, p<0.01).

Conclusion: Immunophenotypic analysis of the peripheral blood of SpA patients shows increased levels of *type 17* immunity across multiple lymphocyte compartments, with a specific increase of polyfunctional cells coexpressing IL17A and GM-CSF. This broad skewing towards *type 17* immune response in SpA supports an important role in disease.

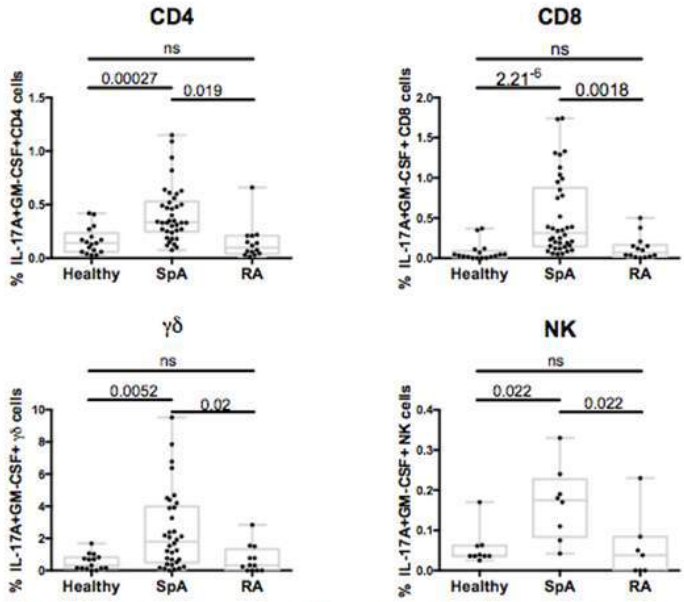

Figure 1. In SpA increased percentages of IL17A+ GMCSF+ cells are seen within the CD4, CD8, γδ and NK cell subsets. IL17A and GM-CSF producting cells were enumerated by FACS after 4 hours stimulation with PMA, ionomycin, brefeldin A and monensin.

Disclosure: D. Simone, Celgene, 2; **H. Al Mossawi**, None; **A. Ridley**, None; **J. De Wit**, None; **T. Sekine**, None; **N. Ansar**, None; **K. Doig**, None; **P. Bowness**, Celgene, 2.

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Abstract Number: 2709

Which Cells Correspond to the Typical Signals for Fatty and Inflammatory Lesions Seen in Magnetic Resonance Imaging in Ankylosing Spondylitis ? -a Prospective Study Using Biopsy Material Obtained during Spinal Surgery-

Xenofon Baraliakos[1], Heinrich Boehm[2], Ahmend Samir[2], Georg Schett[3] and Jürgen Braun[4], [1]Rheumatology, Rheumazentrum Ruhrgebiet, Herne, Germany, [2]Clinic for spinal surgery, Bad Berka, Germany, [3]Department of Internal Medicine 3 – Rheumatology and Immunology, Universitätsklinikum Erlangen, Friedrich-Alexander-University Erlangen-Nürnberg (FAU), Erlangen, Germany, [4]Rheumazentrum Ruhrgebiet, Herne, Germany

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Background/Purpose: The occurrence of bone marrow edema (BME) and fat metaplasia detected by magnetic resonance imaging (MRI) were shown to be significantly associated with syndesmophyte formation in patients with ankylosing spondylitis (AS). The cell type responsible for the fat signal seen in MRI has not been defined to date. Here we histologically analyze the cells seen in fatty lesions (FL) as detected by MRI in spinal biopsies of AS patients and compare them with controls.

Methods: The occurrence of bone marrow edema (BME) and fat metaplasia detected by magnetic resonance imaging (MRI) were shown to be significantly associated with syndesmophyte formation in patients with ankylosing spondylitis (AS). The cell type responsible for the fat signal seen in MRI has not been defined to date. Here we histologically analyze the cells seen in fatty lesions (FL) as detected by MRI in spinal biopsies of AS patients and compare them with controls.

Results: Biopsies mostly obtained from the lower thoracic and the lumbar spine of 13 AS patients (mean age 56.3 years, mean disease duration 26 years) and 6 controls (mean age 53.4 years) were available. Large proportions of AS patients, (12/13, 92%) and non-AS patients (4/6, 67%) had vital bone marrow. Fat cells were found in all 13 biopsies obtained from AS patients from the area of the fat signal vs. only 2 non-AS patients (33%), while inflammatory cells were found in 9 AS patients (69.2%), all of which also had BME on MRI, vs. 3 non-AS patients (50%). Fibroblasts were seen in 3 AS (23.1%) and 2 non-AS patients (33.3%).

Conclusion: The underlying cell types of FL and BME as detected by MRI in these long standing AS patients were fatty and inflammatory cells. The main difference between AS and non-AS patients was the proportion of biopsies containing fat cells. This suggests that fat cells are responsible for the MRI signal, at least in patients with longstanding ankylosing spondylitis.

Disclosure: X. Baraliakos, None; **H. Boehm**, None; **A. Samir**, None; **G. Schett**, None; **J. Braun**, None.

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Abstract Number: 2710

Bacterial Dysbiosis Associates with Functional Intraepithelial Lymphocyte Changes in Inflammatory Bowel Disease and Spondyloarthritis

Neha Ohri[1,2,3], Mark Gerich[3,4], Blair Fennimore[3,5], Diana Ir[6], Charles Robertson[6], Daniel Frank[6], Liron Caplan[7], Brandie Wagner[8] and Kristine Kuhn[9,10], [1]Division of Rheumatology, Mount Sinai West, New York City, NY, [2]Division of Rheumatology, University of Colorado, Aurora, CO, [3]Mucosal Inflammation Program, University of Colorado, Aurora, CO, [4]Division of Gastroenterology, University of Colorado, Aurora, CO, [5]Department of Gastroenterology, University of Colorado, Aurora, CO, [6]Division of Infectious Disease, University of Colorado, Aurora, CO, [7]Denver Veterans Affairs Medical Center and UC Denver SOM, Denver, CO, [8]Department of Biostatistics and Informatics, University of Colorado, Aurora, CO, [9]Division of Rheumatology, University of Colorado School of Medicine, Aurora, CO, [10]Mucosal Inflammation Program, University of Colorado School of Medicine, Aurora, CO
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Background/Purpose: The microbiome is hypothesized to influence human health and disease. Changes in resident bacteria, termed dysbiosis, occur in spondyloarthritis (SpA) and inflammatory bowel disease (IBD), which is subdivided into Crohn's Disease (CD) and Ulcerative Colitis (UC). However, the immunologic consequences of dysbiosis in SpA and IBD have not been established. Intraepithelial lymphocytes (IELs) are T cells within the intestinal epithelium that are in close contact with bacteria. As such, they are prime candidates to link the microbiome with downstream immune functions that result in SpA and IBD. We sought to correlate IELs with resident bacteria in individuals with SpA and IBD relative to controls.

Methods: Subjects with biopsy-proven IBD, axial SpA fulfilling ASAS criteria, and controls undergoing standard of care colonoscopies were recruited. Subjects with antibiotic use within two weeks, NSAID use, other rheumatic diseases, and enteropathic arthritis were excluded. A rectal swab was obtained for microbiome analysis by 16S sequencing and peripheral blood was analyzed for WBC, CRP, and HLAB27. Colonic pinch biopsies of grossly normal-appearing tissue from all participants were obtained during routine colonoscopy or research flexible sigmoidoscopy. IELs were harvested from the biopsies and characterized by flow cytometry for the surface markers CD3, CD4, CD8α, CD8β, CD45, TCRγδ, and TCRβ. Secreted cytokines, TNF-α, IFN-γ, IL-6, and IL-17A, were measured by ELISA in the supernatants of mitogen stimulated IELs. Cytokine secretion were then ranked and analyzed. Statistical analyses were performed with Kruskal-Wallis and Spearman's Rank.

Results: Thus far 13 controls, 10 cases of CD, 6 cases of UC, and 4 patients with SpA have been evaluated. Our preliminary data demonstrates IELs from subjects with CD had increased IL-17A, ($p=0.03$) TNF-α, ($p=0.04$) and IFN-γ ($p<0.01$) whereas UC had higher IL-1β compared to CD ($p=0.03$) or controls ($p=0.03$). Evaluating cytokines in relationship to the microbiome revealed a correlation between TNFα and the Simpson Index of Diversity in UC (Spearman's rank=0.943, $p<0.01$). In CD, *Fusobacterium* had negative correlation with TNFα+ IFNγ + IL-1β (Spearman's rank=-0.786, $p=0.02$). These relationships were not seen in other groups. The recruited SpA patients so far are all HLAB27 positive Caucasian males with a mean age of 35.8. They had been diagnosed an average of 8.5 years ago and had an average BASDAI of 5.2, and CRP of 10.8 mg/L. Preliminary data of the SpA patients suggests the presence of dysbiosis and a trend towards less IELs compared to controls ($p=0.08$).

Conclusion: Our data indicate differences in IEL populations between UC, CD, and controls. SpA patients are being actively recruited and their data will be analyzed. Reviewing the results from our IBD cohort, we hypothesize that patients with SpA will also have higher levels of inflammatory cytokine expression than controls which will have their own unique relationships with colonic microbiota. Our study is relevant to the pathogenesis of SpA and IBD as it shows that IEL cytokine secretion is associated with dysbiosis and this correlation varies by disease type.

Disclosure: N. Ohri, None; **M. Gerich**, None; **B. Fennimore**, None; **D. Ir**, None; **C. Robertson**, None; **D. Frank**, None; **L. Caplan**, None; **B. Wagner**, None; **K. Kuhn**, None.

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Abstract Number: 2711

Tissue-Resident IL-23 Responsive Innate T Cells in Mice Comprise Tcrαβ+ and TCRγδ+ Subsets with Overlapping Function

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Background/Purpose: Multiple lines of evidence suggest a critical role for the IL-23/IL-17A axis in spondyloarthritis. In susceptible inbred strains, hydrodynamic injection of IL-23 minicircles into adult mice induces an inflammatory disease with phenotypic features of human spondyloarthritis. IL-23 receptor expressing tissue-resident CD3+CD4-CD8- double negative (DN) innate T cells have been proposed to mediate disease pathogenesis in this model. The goal of this project was to investigate factors controlling the generation and function of these IL-23 responsive innate T cells.

Methods: C57BL/6 wildtype (WT), TCRγδ-/-, IL1R1-/-, IL23R-GFP, Tap1-/- and MHC II-/- mice were analyzed at 8 weeks of age. Single cell suspensions from blood, liver, spleen, skin and the Achilles tendon enthesis were analyzed by multicolor flow cytometry. IL-17A production was measured by intracellular staining after stimulation with cytokines (IL-1β, IL-23 or IL-1β + IL-23) or PMA/Ionomycin in the presence of Golgi-Stop for 4 hours.

Results: In WT mice, the CD3+ DN T cell compartment comprised both TCRαβ+ and TCRγδ+ cells with frequencies varying between tissues. Both subsets were present in MHC class I deficient Tap1-/- mice and in MHC II-/- mice. In TCRγδ-/- mice, an expanded population of DN TCRαβ+ cells compensated numerically for the absence of γδ T cells. Upon in vitro stimulation with IL-23, both

TCRαβ+ and TCRγδ+ subsets depended on an additional IL-1 receptor signal for IL-17A induction. While γδ T cells were the predominant IL-17A producing subset in WT splenocytes stimulated with IL-1β + IL-23, the frequency of total IL-17A positive cells in TCRγδ-/- mice was unchanged, attributable to a compensatory increase of IL-17A production by DN TCRαβ+ cells. PMA/Ionomycin stimulation resulted in the recruitment of additional cell types producing IL-17A including CD4+ TCRαβ+ cells. PMA/Ionomycin-induced IL-17A production did not require IL-1R or IL-23R signals.

Conclusion: Tissue resident CD3+ DN T cells in mice are either TCRαβ+ or TCRγδ+. IL-23 induced induction of IL-17A by either subset is strictly dependent on a second signal through the IL-1 receptor. DN TCRαβ+ T cells compensate for the absence of γδ T cells in TCRγδ-/- mice suggesting functional overlap in vivo.

Disclosure: K. Urso, None; **I. Hossain**, None; **J. Ermann**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tissue-resident-il-23-responsive-innate-t-cells-in-mice-comprise-tcr%ce%b1%ce%b2-and-tcr%ce%b3%ce%b4-subsets-with-overlapping-function

Abstract Number: 2712

Inverse Correlation Between IL-10-Producing Bregs and IFN-Gamma-Producing NK Cells in Psoriatic Arthritis and Psoriasis

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Background/Purpose: A recent study from our group has shown functional impairment and numerical decrease of transitional and memory IL-10-producing regulatory B cells (Bregs) in patients with psoriatic arthritis (PsA) and psoriasis (Ps) (*Ann Rheum Dis* 2015;74**:**423). Other cells such as natural killer (NK) have been involved in the development of PsA and Ps, but their relationship with Bregs has not been studied. The aim of the study was to investigate quantitative and qualitative variations of NK subsets expressing the pro-inflammatory IFN-γ and IL-17 cytokines and their relation with IL-10-producing Bregs.

Methods: Peripheral blood mononuclear cells from 100 subjects including 40 PsA, 40 Ps and 20 healthy controls (HC) were studied. Flow cytometric analysis was carried out with MoAbs against cell surface markers CD56, CD16, CD3, CD7, CD19, CD24, CD27 and CD38. Intracellular expression of cytoplasmic IFN-γ, IL-17 and IL-10 following bacterial CpG (ODN2006) and PMA/ionomycin stimulation was also examined by flow cytometry.

Results: There was a negative correlation between CD3negCD56pos (NK) and CD19posCD24hiCD38hi (transitional) Bregs and between CD3negCD56pos and CD19posCD24hiCD27pos (memory Bregs) ($p<0.05$, for both). IFN-γ-producing NK inversely correlated with IL-10-producing Bregs. IL-17-producing NK were also inversely correlated with IL-10-producing Bregs ($P<0.05$). A very small proportion of NK cell produced IFN-γ plus IL-17. NK from patients with PsA and Ps produced significantly higher IFN-γ compared to HCs, and this was also found for IL-17 ($p<0.05$, for both). Very few CD3posCD56pos (NKT) cells produced IFN-γ plus IL-17 but there was no correlation of these cells subsets with Bregs.

Conclusion: IL-10-producing Bregs is negatively correlated with IFN-γ- and IL-17-producing NK cells in PsA and Ps. This suggests a dominant role of the innate arm of immunity over suppressor adaptive responses, such as those exerted by regulatory B cells.

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Abstract Number: 2713

Differentially Expressed Microrna As Candidate Biomarker for Disease Activity in Ankylosing Spondylitis

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Differentially Expressed MicroRNA as candidate Biomarker for Disease Activity in Ankylosing Spondylitis

Background/Purpose: MicroRNAs (miRNAs) have evolved as a novel class of biomarkers We proposed to test the hypothesis that patients with ankylosing spondylitis (AS) have an altered miRNA expression profile compared to control subjects and selected miRNAs identified in the study correlate with disease activity as measured by BASDAI and ASDAS and markers of inflammation (ESR and CRP) .

Methods: 51 patients ≥18 years of age with AS based on modified New York classification criteria (grade 3 and 4 sacroiliitis) and 23 (age and sex matched) controls were prospectively recruited. Subjects with active malignancy in last 5 years, rheumatoid arthritis or systemic lupus erythematosus and evidence of HIV or chronic hepatitis B or C infection were excluded. Patients and controls were screened, consented and peripheral blood samples (5 ml) were obtained. The samples were centrifuged at 400 g for seven minutes; plasma transferred to nuclease free tubes and stored at -20°C until analyses. ESR and CRP were measured using routine laboratory methods. Various validated Questionnaires to assess disease, functional activity and patient reported outcomes in AS were administered to the patients. 62 circulating miRNAs in the plasma of all the study subjects were profiled by Firefly Multiplex Circulating miRNA Assay (Abcam) using the Immunology Panel. Forty microliters of plasma samples were first digested using the supplied enzyme mix and then the assay was performed following the instructions provided by the manufactures. The assay beads were scanned on BD Accuri C6 flow cytometer (BD Biosciences). Data were analyzed using Firefly Analyis Workbench (Abcam). Descriptive analyses included continuous variables (the mean ± SD) and the categorical variables (percentage). Linear regression analysis was performed to assess the association between BASDAI, BASMI, ASDAS, Rapid 3, ESR, CRP and differentially dysregulated candidate miRNAs in plasma of patients with AS.

Results: 34 males and 17 females with demographics and clinical characteristics in table 1. Mean (±SD) values of the disease parameters are shown in table 2. miR-181b-5p was differentially expressed in AS patients compared to healthy controls ($p < 0.05$). miR-181b-5p also showed a significant linear relationship with BASDAI score ($p=0.008$) and ASDAS($p=0.054$).

Conclusion: miR-181b-5p correlated with validated tools of disease activity in AS and may be proposed as a potential biomarker for disease activity in AS.

Table 1- Demographics and Clinical Characteristics of the Patients

Mean age in years ± SD	49.8 ± 12.2
% African-Americans	34.6
% Females	33.3
% HLA-B27 positivity	70.0
% Acute anterior uveitis	38.3
% TNF-i use	45.1

Table 2- Disease Activity Measures

Mean Variables ± SD	
BASDAI	5.2 ± 2.5
BASFI	4.7 ± 2.8
ASDAS-CRP	3.4 ± 1.4
RAPID 3	13.7 ± 7.2
ESR	22.4 ± 22
CRP mg/dl	1.3 ± 1.9

Disclosure: M. N. Magrey, None; **A. Haseeb**, None; **T. M. Haqqi**, None.

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Association of Polymorphisms of Activation-Induced Cytidine Deaminase with Ankylosing Spondylitis

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Background/Purpose: There was a biased repertoire of the immunoglobulin (Ig) heavy chain variable (VH) segment gene in B cells in patients with ankylosing spondylitis (AS). Activation-induced cytidine deaminase (AID) plays an important role in Ig class switch recombination (CSR) and somatic hypermutation (SHM) to generate Ab diversity and B cell tolerance. Peripheral blood mononuclear cells (PBMCs) express five different AID splicing variants [full-length (FL) and splicing variants (sv) 1–4]. In addition, translesion synthesis (TLS) DNA polymerases are involved in the repair of AID-mediated DNA lesions. We have previously reported that Ig SHM and CSR are upregulated in lupus autoimmune mice as a result of enhanced AID expression. In this study, we investigated the expression patterns of AID variants and TLS polymerase in PBMCs of AS patients so as to verify the relationship of the CSR and SHM bias with susceptibility to AS.

Methods: PBMCs were collected from 33 healthy controls (HC) and 62 patients with AS who fulfilled the modified New York classification criteria. We measured the mRNA expression of AID variants and TLS polymerases by quantitative RT-PCR.

Results: The number of subjects expressing sv2 was significantly greater in AS patients compared to HC ($p = 0.031$, odds ratio = 2.77) (Table 1). Next, we investigated whether the treatment with TNF inhibitors (TNFi) affected the gene expression of AID variants. A significantly higher proportion of TNFi-treated group expressed sv2 compared to TNF-naïve group ($p = 0.014$). And we compared the level of AID variants expression between TNFi-treated and TNF-naïve group. The expression levels of FL and sv1 were significantly lower in the TNFi-treated group than TNF-naïve group (FL: $p = 0.002$, sv1: $p = 0.045$) (Table 2). In addition, we investigated mRNA expression levels of TLS polymerases in PBMCs from patients with AS and HC. The expression level of TLS pol was significantly lower in AS patients than in HC ($p = 0.007$) (Table 3).

Conclusion: Our results showed that patients with AS expressed significantly higher levels of sv2 than HC. TNFi treatment restored the gene expression of the AID variants (FL, sv1 and sv2) in patients with AS. Therefore pre-existing TNFa-induced AID expression in B cells may play an important role in the pathogenesis of AS.

Table 1. Frequencies of sv1 and sv2 expressions

AID		No of negative expression (%)	No of positive expression (%)	p-value	OR (95% CI)
sv1	HC	4 (12.1)	29 (87.9)	0.232	
	AS	3 (4.8)	59 (95.2)		
sv2	HC	22 (66.7)	11 (33.3)	**0.031**	2.769 (1.146-6.691)
	AS	26 (41.9)	36 (58.1)		

AID: Activation-induced cytidine deaminase, sv: splicing variants, AS: ankylosing spondylitis
HC: healthy controls, OR: odd ratios

Table 2. Expression levels of AID FL, sv1, and sv2 before and after anti-TNFα drugs treatment in AS patients

AID	anti-TNFα drugs treatment		p-value
	before	after	
FL	n=10 1.230±1.157	n=45 0.427±0.544	**0.002**
sv1	n=10 1.051±0.787	n=44 0.623±0.543	**0.045**
sv2	n=4 0.827±0.637	n=27 0.444±0.484	0.165

AID: Activation-induced cytidine deaminase, FL: full-length, sv: splicing variants,
AS: ankylosing spondylitis, TNF: tumor necrosis factor

Table 3. Gene Expression of TLS polymerases

TLS polymerase	HC (n=53)	AS (n=59)	p-value
polθ	1.208±1.396	1.209±2.023	0.997
polζ	1.515±1.181	1.207±0.769	0.110
polι	1.563±1.346	0.992±0.670	**0.007**
polη	1.439±1.075	1.041±1.138	0.061

TLS: translesion synthesis, HC: healthy controls, AS: ankylosing spondylitis
pol: polymerase

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Genetic Variants in TNF, TNFRSF1A, and IL23R Are Associated with Risk of Ankylosing Spondylitis

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Background/Purpose: The objective of this study was to evaluate single nucleotide polymorphisms (SNPs) involved in TNFα signaling, NF-κB activation, interferon-γ signaling, or pattern recognition receptor signaling pathways (TLRs and inflammasome) and their association with ankylosing spondylitis (AS) and rheumatoid arthritis (RA) susceptibility. The genotyped SNPs have known functional effects or previously reported associations with chronic autoimmune disease.

Methods: In a cross-sectional study, we genotyped 53 SNPs in 709 AS patients and 58 SNPs in 538 RA patients from Denmark. Prospectively collected clinical data were obtained from the DANBIO registry. Genotype distributions among cases were compared with 796 population-based controls. Odds ratios for minor allele carriers among cases adjusted for gender and age were calculated assuming additive genetic effects. Correction for multiple testing was performed using false discovery rate (FDR), and associations with FDR q-values <0.1 were considered significant.

Results: We find a decreased risk of AS in minor allele carriers of two SNPs in *TNF* (rs1800629: odds ratio(OR)=0.59, 95% confidence interval(CI): 0.47-0.74, $p=3*10^{-6}$, $q=1*10^{-4}$; rs361525: OR=0.48, CI: 0.31-0.75, p=0.001, q=0.02), and of *IL23R* rs11209026 (OR= 0.60, CI: 0.43-0.85, p=0.004, q=0.05). Carriers of the minor allele of *TNFRSF1A* rs4149570 (OR=1.32, CI: 1.14-1.54, $p= 3*10^{-04}$, q=0.007) had increased risk of AS. Among RA patients, no statistically significant associations were observed. However, a previously reported RA risk allele in *PTPN22*(rs2476601) showed a similar trend in this cohort (OR=1.39, CI: 1.06-1.82, p=0.016, q=0.3).

Conclusion: In a Danish population, this study confirms a previously reported locus in the interleukin-23 receptor (rs11209026) as less common in AS patients, and identifies genetic variation in TNFα (rs1800629, rs361525) and TNF receptor-1 (rs4149570) as putative loci associated with AS. Among RA patients, no SNPs reached significant association but the previously reported risk allele *PTPN22* rs2476601 showed a borderline association with disease susceptibility.

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Abstract Number: 2716

Does Secretory Immunoglobulin a Influence Disease Activity in Patients with Reactive Arthritis and Undifferentiated Spondylarthritis?

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Background/Purpose: Spondylarthropathies (SpA) comprise a group of rheumatic diseases such as ankylosing spondylitis (AS), arthritis/spondylitis with inflammatory bowel disease, arthritis/spondylitis with psoriasis (PsA), reactive arthritis (ReA) and undifferentiated spondyloarthritis (uSpA). Their genetic background, familial aggregation, pathophysiology and overlapping clinical manifestations suggest a common origin between them. Previous trials have suggested the role of the intestinal mucosa in the etiopathogenesis of SpA. Increased serum levels of IgA and secretory IgA (SIgA) in AS patients have also been reported, but whether SIgA has a role in the pathogenesis of ReA and uSpA remains unknown.

Methods: Cross sectional study. Serum concentrations of SIgA and total IgA were measured using ELISA and nephelometry in patients and healthy subjects. Activity indices (BASDI, Ankylosing Spondylitis Disease Activity Score (ASDAS)) were applied in each patient. Statistical analysis was performed using Stata 11.2® software for Windows. t Student test was used to compare different groups or subgroups. Pearson correlation was used to measure the correlation degree between SIgA, IgA and disease activity. Multiple linear regression models were used to evaluate the strength of the association. The study was approved by the hospital's ethics committee.

Results: 46 patients (78,2% men, mean age 34,8±12,3y) and 53 controls (41% men, mean age 32y) were included. The mean serum levels of SIgA were higher in patients (19,85±9,97 µg/ml) than in healthy subjects (10,82 ±6,5 µg/ml p <0.000). Mean total IgA levels did not show statistical differences between patients and healthy subjects (275±123 mg/dl vs 284,33±107 p=0,72). SIgA levels correlated with disease activity in patients using the following activity index: BASDI (r= -0.42, p=0.0046), ASDAS-CRP (r= -0.37, p=0.014) and ASDAS-ESR (r= -0.45, p=0.0021). Negative correlation between SIgA and all activity index was higher in HLA-B27^{+} patients (BASDI r= -0.70, p=0.0009, ASDAS-CRP r= -0.58, p=0.0093 and ASDAS-ESR r= -0.57, p=0.0083) than in HLA-B27^{-} patients. Multivariate regression models showed linear association between SIgA and BASDI (-0,12 p=0,005), ASDAS-CRP (-0,04 p=0,014) and ASDAS-ESR (-0,048 p=0,002). **Table 1.**

Conclusion: High serum levels of SIgA were associated with decreased activity in patients with ReA and uSpA. SigA is a very important molecule participating in host defense of intestinal mucosa, playing an important role in homeostasis. These findings highlight the importance of the development of new studies to reach a better understanding of the role of the intestinal mucosa in the different SpA phenotypes.

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Abstract Number: 2717

Sclerostin and Dickkopf-1 but Not Periostin May Have a Role in Psoriatic Arthritis

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Background/Purpose:Psoriatic arthritis (PsA) is a chronic inflammatory disease. It is characteristically associated both peripheral

(arthritis, enthesitis and dactylitis) and axial skeletal involvement. A range of bone pathologies is common in PsA. Bone loss, either locally (erosions) or systemically, may present. Additionally new bone formation may also occur in both peripheral and axial skeleton. However, molecular mechanisms tunderlying these processes have not yet been fully understood. Secreted Wnt receptor antagonists, dickkopf-1(Dkk-1) and sclerostin, are negative regulators of bone formation. And it has been shown that periostin, as a matricellular protein, is involved in the early stages of osteoblast differentiation and bone formation. Therefore the aim of the present study was to evaluate bone formation markers in patients with with PsA.

Methods : In total 70 consecutive PsA patients [49 females (69%); with a median age (interquartile range, IQR) of 43 (17) years] according to the CASPAR criteria and 36 healthy control subjects [(23 females [63%]; with a median age (IQR) 38 (16) years] were included in the study. Serum periostin, Dkk-1 and sclerostin levels were measured by commercially available ELISA kits. We also assessed serum levels of high-sensitivity C-reactive protein (hs-CRP). Disease related characteristics of patients were evaluated by using BASDAI, BASFI, HAQ, DAS28. Because the data were not distributed homogenously the results are presented as median and interquartile range (IQR) and non-parametric tests were used for group comparisons.

Results : In our PsA group , median (IQR) duration of psoriasis and psoriatic arthritis were 13(20) and 6 (8) years, respectively. In total 27 patients were using corticosteroids, 41 metothrexate, 12 leflunomide and 23 tumor necrosis factor inhibitors. Some of the clinical and laboratory characteristics of patients and control subjects were shown in table. As expected serum CRP levels were significantly higher in PsA patients in comparison with control subjects. Serum periostin levels were not statistically different between study groups. However we found that circulating Dkk-1 and sclerostin levels were significantly lower in PsA patients. Serum Dkk-1 levels were associated with serum sclerostin levels (r=0.872 and $P<0.001$) and age (r=0.312 and $P=0.008$). Serum periostin, Dkk-1 and sclerostin levels were not different between PsA patients with and without axial incolvement.

Conclusion : Our results suggested that circulating Dkk-1 and sclerostin may have a role in disease susceptibility. Decreased Dkk-1 and sclerostin levels may contribute to the new bone formation, seen in the disease course, in patients with PsA. **Table1**. Some clinical and laboratory characteristics of study groups.

	PsA	**Control**	***P***
	(n=70)	**(n=36)**	
PsA symptom duration, years, median (IQR)	6 (8)	N/A	N/A
BASDAI, median (IQR)	2,9 (3,7)	N/A	N/A
BASFI, median (IQR)	1,9 (2,9)	N/A	N/A
PASI, median (IQR)	1,5 (4,6)	N/A	N/A
DAS28, median (IQR)	2,7 (1,7)	N/A	N/A
ASQOL, median (IQR)	6 (9)	N/A	
CRP (mg/dL) , median (IQR)	**0,5(1,4)**	**0,2(0,35)**	**0,003**
DKK-1, median (IQR)	**59,1 (33,3)**	**137,5 (101,2)**	**0,001**
Periostin, median (IQR)	92,9 (91,6)	98,5 (178,8)	0,492
Sclerostin, median (IQR)	**19,2 (11,8)**	**47,3 (30,7)**	**0,000**

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Abstract Number: 2718

Plasma Levels of the M2 Macrophage Markers, CD163 and CD206, Changes Reversely and Soluble CD163 Is Associated with Disease Activity in Spondyloarthritis

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Background/Purpose: Spondyloarthritis (SpA) covers a group of interrelated auto-inflammatory disorders where TNFa is a central mediator of disease. T cells and macrophages are abundant in the sacroiliac joint, and macrophage infiltration is associated with global disease activity. CD163 is a scavenger receptor primarily expressed by M2c macrophages. The soluble (s) form is cleaved from the cell surface by TACE/ADAM17, the metalloproteinase also responsible for the cleavage of TNFa. In RA, sCD163 is associated with disease activity and progression[i]. The mannose receptor, CD206, is a scavenger receptor responsible for collagen internalization and mainly expressed by M2a macrophages. The soluble forms of CD206 and CD163 are suggested as novel biomarkers of M2a and M2c macrophage activity. We investigated plasma levels of sCD163 and sCD206 and their association with disease activity markers in SpA patients.

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[i] Greisen, S. R. *et al. Clin. Exp. Rheumatol.* (2011)

Methods: Soluble CD163 and sCD206 were measured by ELISA, in plasma (PL) and synovial fluid (SF) from 23 SpA patients with peripheral joint activity, and plasma from 30 SpA patients at initiation of anti-TNFa treatment (baseline) and after 12, 20 and 52 weeks of treatment. Clinical disease was assessed by: BASFI, BASMI, BASDAI, ASDAS, CRP and MRI scoring of the whole spine. Statistical analyses were performed by student's t-test and Spearman's rank correlation.

Results: Synovial fluid levels (10.2 ±4.90 mg/l) of sCD163 were significantly increased compared with PL (2.37 ±1.05 mg/l) ($p<0.001$). Conversely, sCD206 levels in PL (0.25 ±0.08mg/l) were higher than in SF (0.12 ±0.07 mg/l) ($p<0.01$). In addition, PL levels of sCD206 correlated with sCD163 ($r=-0.48$, $p=0.02$), and CRP ($r=-0.50$, $p=0.02$). A strong correlation between PL and SF sCD206 was observed ($r=0.60$, $p=0.003$), which was not the case for sCD163. In the anti-TNFa treated cohort, PL sCD163 at baseline was not increased compared with healthy controls, and was not affected by the treatment regimen. In contrast, anti-TNFa treatment affected sCD206 PL levels, which increased significantly from baseline levels (baseline: 0.16 mg/l and at 3 months: 0.20 mg/l, $p<0.0001$). The high levels were sustained in the entire follow-up period. Soluble CD163 at baseline and at 12 weeks correlated weakly with the BASDAI score at 12 weeks ($r=-0.41$, $p=0.02$ and $r=-0.42$, $p=0.02$), whereas no associations were observed between sCD206 and disease activity- or MRI scores.

Conclusion: In SpA, sCD163 is not increased, but show association with disease activity measured as BASDAI. Conversely, sCD206 was decreased at baseline, but increased as a response to anti-TNFa treatment. This supports that M2 macrophages are involved in SpA, but points to differences between the two subtypes engagement.

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Abstract Number: 2719

Discriminating Value of Calprotectin in Disease Activity and Progression of Non-Radiographic Axial Spondyloarthritis and Ankylosing Spondylitis

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Session Title: Spondylarthropathies Psoriatic Arthritis – Pathogenesis, Etiology - Poster II

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Background/Purpose: Due to the limitation of early diagnosis of ankylosing spondylitis (AS), updated criteria in recent years introduced the concept of axial spondyloarthritis (axSpA) and non- radiographic axial spondyloarthritis (nr-axSpA) and facilitates classification management of disease. It has been controversial whether the two sub-phenotypes are separate or different phases of radiographic progression. Studies has revealed calprotectin as inflammation marker and the Wnt/β-catenin pathway contributed to the bone fusion in AS.

Methods: We enrolled 53 patients with AS, 59 patients with nr-axSpA and 47 healthy individuals. Patients were diagnosed with AS or nr-axSpA according to the modified New York criteria or ASAS classification criteria for axSpA. Laboratory tests including ESR, CRP and human leukocyte antigen (HLA)-B27 were conducted. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and Ankylosing Spondylitis Disease Activity Score (ASDAS) were evaluated. Imaging assessment was calculated using Spondyloarthritis Research Consortium Canada (SPARCC) scoring system for sacroiliac joints and modified Stoke's Ankylosing Spondylitis Spine Score. Serum levels of calprotectin, GSK-β,β-catenin, RUNX2 were determined by commercial ELISA kit. Data were described as mean and SD. Mann–Whitney U test or Kruskal–Wallis test was used to compare continuous variables. Correlations were assessed using the Spearman's rank correlation coefficient. Statistical analyses were performed with SPSS V.13.0 software. A p value <0.05 was considered statistically significant.

Results: Clinical characteristics and laboratory results were described in Table 1. Serum calprotectin level was higher in AS and nr-axSpA patients than that in healthy individuals. No difference was observed in calprotectin level between AS and nr-axSpA patients. Elevated calprotectin was positively correlated with ESR, CRP, BASDAI, ASDAS as well as SPARCC scoring and had no correlation with BASFI and mSASSS in these two sub-genotypes. No correlation was observed between calprotectin and Wnt/β-catenin pathway markers. Radiographic progression indicated by mSASSS was correlated merely with disease duration instead of other outcome measurements.

Conclusion: Calprotectin does not contribute to the discrimination of AS and nr-axSpA. Patients with nr-axSpA are not necessarily progress to AS. Calprotectin mediated inflammation was not correlated with principle effectors of Wnt/β-catenin pathway, indicating inflammation and bone fusion might be separate process of the disease . Long-term follow-up favors further investigation of value of inflammation subsequent bone information. Table 1 Clinical characteristics and laboratory results in AS and nr-axSpA patients

	AS group	nr-axSpA group
Age (mean±SD, years)	32.3±8.21	34.4±7.79
Disease duration (mean±SD, years)	5.17±3.55	4.98±4.14
ESR (mm/h)	32.21±16.97	34.58±18.54
CRP (mg/l)	13.75±8.61	13.11±10.16
BASDAI	3.44±1.11	4.20±1.44
BASFI	46.87±17.96	48.78±18.85
ASDAS	1.72±0.97	1.91±0.96
Calprotectin (ng/ml)	15.30±6.49	17.76±8.59
GSK-β(ng/ml)	0.32±0.02	0.53±0.21
β-catenin (ng/ml)	1.69±0.79	1.63±0.65
RUNX2 (ng/ml)	0.28±0.05	0.30±0.07
SPARCC	5.60±5.24	5.88±5.72
mSASSS	18.57±14.72	12.49±11.48

Disclosure: J. Huang, None; **Z. Yin**, None; **G. Song**, None; **S. Cui**, None; **J. Jiang**, None; **L. Zhang**, None.

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Abstract Number: 2720

Genome-Wide Association Study of Clinical Phenotypes in Psoriatic Arthritis

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Blanco[19], Alfredo Willisch[20], Jose Antonio Mosquera[21], Paloma Vela[22], Jesús Tornero[23], Simon Sanchez Fernandez[24], Hector Corominas[25], Julio Ramírez[26], Maria López-Lasanta[27], Mireia López[28], Raül Tortosa[29], Antonio Julià[29] and Sara Marsal[30], [1]Rheumatology Department, Hospital Clínic de Barcelona, Barcelona, Spain, [2]Rheumatology Division, INIBIC-Complejo Hospitalario Universitario A Coruña (CHUAC), A Coruna, Spain, [3]Rheumatology, Hospital de Sabadell, Sabadell, Spain, [4]H Central de Asturias, Oviedo, Spain, [5]Rheumatology, HOSPITAL CLÍNICO UNIVERSITARIO DE SALAMANCA, Salamanca, Spain, [6]H Monte Naranco, Oviedo, Spain, [7]Rheumatology, Hospital de Jerez de la Frontera, Jerez de la Frontera, Spain, [8]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain, [9]Rheumatology, Hospital Infanta Sofia, Madrid, Spain, [10]Servicio de Reumatología, Hospital Universitario Gregorio Marañón, MD, PhD, Madrid, Spain, [11]Rheumatology Service, Hospital Universitari de Bellvitge, Hospitalet de Llobregat- Barcelona, Spain, [12]H Fundación Alcorcón, Alcorcón, Spain, [13]CapiCAT group (Nailfold Capillaroscopy group from the Catalan Society for Rheumatology)., Catalonia, Spain, [14]Rheumatology, Hospital Universitari de Bellvitge, Barcelona, Spain, [15]Rheumatology, Hospital de la Princesa, IIS-IP, Madrid, Spain, [16]Rheumatology, Rheumatology, Seville, Spain, [17]Rheumatology Unit., Hospital Mutua de Terrassa. Barcelona, Barcelona, Spain, [18]Rheumatology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain, [19]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [20]Complexo Hospitalario de Ourense, Ourense, Spain, [21]Servicio de Reumatología, Complejo Hospitalario Hospital Provincial de Pontevedra, Pontevedra, Spain, [22]Dpt. Rheumatology, Hospital General Universitario Alicante, Alicante, Spain, [23]Rheumatology Department, Hospital Universitario Guadalajara, Guadalajara, Spain, [24]Rheumatology Department, Hospital General La Mancha Centro, Ciudad Real, Spain, [25]Rheumatology, Hospital Moises Broggi, Barcelona, Spain, [26]Rheumatology, Hospital Clínic, Barcelona, Spain, [27]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [28]Servicio de Reumatología, Hospital Universitario Vall d´Hebron, Barcelona, Spain, [29]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [30]Rheumatology Research Unit, Vall d'Hebron Hospital, Barcelona, Spain
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Background/Purpose: Genome-wide association studies (GWAS) in patients and healthy controls have allowed the identification of multiple variants associated with disease risk in Psoriatic Arthritis (PsA). To date, however, there has been no GWAS for PsA phenotypes. The main objective of this study was to identify new genetic variation associated with clinical phenotypes in PsA.

Methods: A total of n=835 patients diagnosed with PsA using CASPAR criteria were recruited for the discovery stage. In each patient >600,000 single nucleotide polymorphisms (SNPs) were genotyped. All patients were Caucasian and of Spanish origin. GWAS were performed for clinical and biological phenotypes associated with joint disease, as well as skin disease related phenotypes. After allelic association analysis, those SNPs with highest level of significance were analyzed in an independent cohort of n=414 PsA patients.

Results: In the GWAS stage, several genomic regions showing high evidence of association with different PsA phenotypes (P<5e-6) were identified. These included association with axial disease pattern, peripheral disease pattern, bone proliferation, degree of radiological sacroileitis and the presence of syndesmophytes. Also, GWAS on cutaneous variables identified two regions associated with nail disease and skin disease severity. Using the replication cohort, the association between one locus and peripheral pattern of disease, and two loci associated with axial pattern were nominally validated.

Conclusion: To our knowledge, this is the GWAS of clinical phenotypes in PsA. New candidate loci associated with axial and peripheral disease have been identified.

Abstract Number: 2721

Impact of Nail Psoriasis on Clinical Presentation of Psoriatic Arthritis—Descriptive Analysis from the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

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Background/Purpose: Studies have shown that psoriasis of the skin, scalp and/or nails precedes the appearance of psoriatic arthritis (PsA) by up to 12 years[1,2]; however, only a single European study from a German registry has examined PsA patients with nail psoriasis in clinical practice.[3] The objective of this descriptive analysis was to characterize the clinical and patient-reported outcomes of PsA patients with nail psoriasis in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) registry.

Methods: This cross-sectional descriptive study included all patients enrolled in the Corrona PsA/SpA registry between March 2013 and March 2016 with a diagnosis of PsA who had non-missing data on physician-reported nail psoriasis. Patients were stratified by presence vs absence of nail psoriasis, defined as having a non-zero response on the nail psoriasis visual analog scale of 0–100. Descriptive analyses of patient demographics, clinical measures, patient-reported outcomes and treatment characteristics were assessed at the time of enrollment and compared between subgroups using *P* values from Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables.

Results: As of March 2016, a total of 1661 patients with PsA in the registry met the inclusion criteria, including 739 patients (44.5%) with nail psoriasis and 922 patients (55.5%) without nail psoriasis. Both patient subgroups were similar in terms of age, race, body mass index, disease duration, prevalence of most comorbidities (e.g., cardiovascular disease, any cancer, diabetes and serious infection) and biologic use at the time of enrollment; however, patients with nail psoriasis were significantly more likely to be male (53.0% vs 43.8%) and have a higher history of depression (35.9% vs 27.4%), and were less likely to be underweight/normal (13.1% vs 19.0%) compared with patients without nail psoriasis. Patients with nail psoriasis had more moderate/severe psoriasis at enrollment (body surface area [BSA] > 3%) compared with patients without nail psoriasis, and had worse disease as assessed by percentage of affected BSA, achievement of minimal disease activity, Clinical Disease Activity Index scores, physical function, patient-reported pain and fatigue, quality of life and activity impairment (**Table**).

Conclusion: This analysis from the Corrona registry demonstrated that patients with PsA and nail psoriasis at the time of registry enrollment had significantly worse disease activity and had worse patient-reported outcomes compared with those patients without nail involvement. Nail psoriasis is common in patients with PsA; therefore, these findings emphasize the importance of early recognition and management of patients with nail psoriasis.

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2. Boehncke WH, et al. *Br J Dermatol.* 2014;170(4):772-86.

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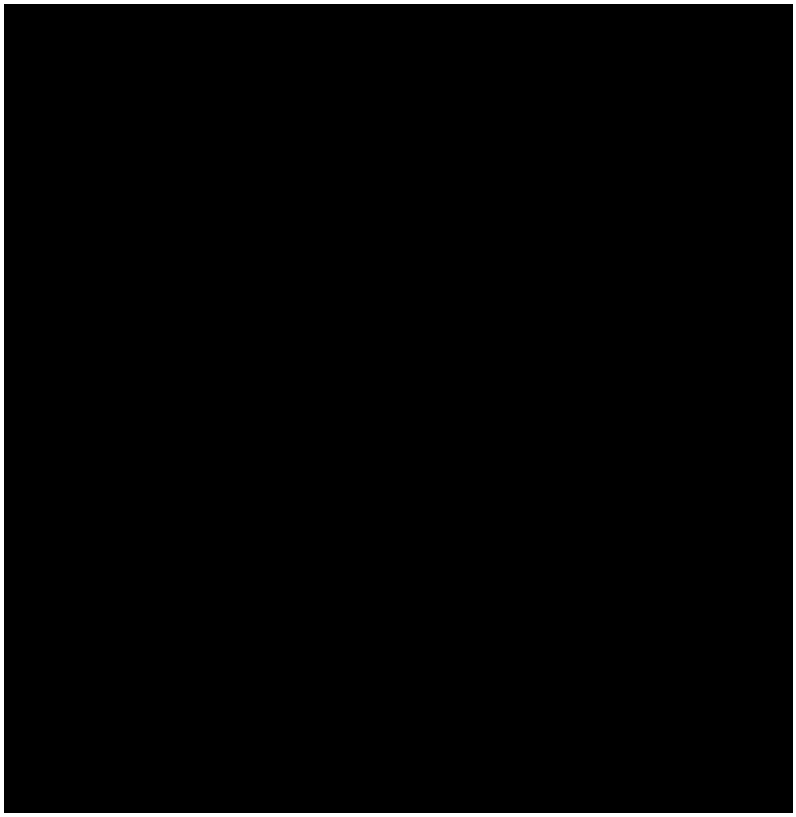

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Abstract Number: 2722

Evolution over Thirty Years of the Profile of Inpatients with Reactive Arthritis in a Tertiary Rheumatology Unit

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Session Time: 9:00AM-11:00AM

Background/Purpose: Reactive arthritis (ReA) are sterile arthritis occurring after extra articular bacterial infection, mainly located in gut or genito urethral mucosa. The aim of this study was to analyze, over 30 years, frequency as well as clinico-biological and therapeutic characteristics of inpatients with ReA, comparing two periods.

Methods: In this retrospective monocentric study, the charts of all the patients followed in our unit between January 1st 1984 and April 2014 with the diagnosis or ReA, according to International Classification Criteria (1), were recorded and clinic biological features,

management and outcome were analyzed, and compared between two periods : from January 1984 to December 1993, and from January 2004 to December 2013.

Results: 62 patients fulfilling international diagnosis criteria were analyzed. We found no significant differences (Table) between the two periods in frequency of new cases, clinical presentation (rheumatologic and extra articular features), biological and microbiological data or outcome.Change in therapeutic management was obvious with lower delay for DMARD initiation and occurrence of anti TNF use in the recent period.

	1984 - 1993	2004 - 2013	p
Number of ReA patients / hospitalizations	15 / 7438	31 / 11 823	NS
Median age at diagnosis	37	30	NS
HLA B27 + (%) / Evidence of infectious agent (%)	91 / 53	63 / 61	NS
Delay between infection/articular symptoms (days) median	5.5	9	NS
CRP (mean) (mg/l)	87	90	NS
TJC / SJC	2.8 / 1.8	3.2 / 2	NS
	1984 - 1993	2004 - 2013	p
Enthésitis (%) / Dactylitis (%)	40 / 13	26 / 29	NS
Extra articular features (%)	47	35	NS
Axial symptoms (%)	33	29	NS
DMARDs use (%)	36	62	NS
Median delay of DMARD introduction (days)	210	50.5	NS
Biologic agents use (%)	**0**	**45**	**0.005**
Remission at last follow-up (%)	57	47	NS

Conclusion: Reactive arthritis is still a current rheumatologic problem, with an apparently stable frequency in a developed country, with a need of early and tailored rheumatologic management.

Disclosure: D. Wendling, None; **A. Brinster**, None; **X. Guillot**, None; **C. Prati**, None.

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Abstract Number: 2723

The Co-Occurrence of Axial Spondyloarthritis and Fibromyalgia: A National Register-Based Study

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Session Time: 9:00AM-11:00AM

Background/Purpose: Some patients with axial spondyloarthritis (axSpA) are recognized clinically to have co-morbid fibromyalgia (FM). However, there are no trials to inform how these patients are best managed when axSpA and FM occur together. This study aims to provide data on their frequency of co-occurrence and, amongst persons with axSpA, features which characterize persons with co-morbid FM

Methods: The British Society for Rheumatology Biologics Register in Ankylosing Spondylitis (BSRBR-AS) recruits persons meeting any ASAS definition of axSpA. All patients recruited are naïve to biologic therapy and are either newly starting biologic therapy (biologic cohort) or not (non-biologic cohort). At recruitment, patients self-complete the ACR 2010 modified research criteria (2010m ACR) for FM, Bath measures of disease activity (BASDAI), function (BASFI) and global severity (BAS-G), Quality of Life (ASQoL and EQ-5D), sleep disturbance score (SDS), Chalder Fatigue Scale (CFS), and Hospital Anxiety and Depression Scale (HADS). Clinicians indicated whether they had made a clinical diagnosis of FM; Bath metrology index (BASMI) and Body Mass Index (BMI) were measured. The Index of Multiple Deprivation (IMD) is an area based measure of deprivation based on postcode.

Results: 430 patients provided clinical information and the recruting clinicians considered that 13 had a clinical diagnosis of FM (3.0%), while 274 provided self-report data, of whom 56 (20.4%) met the 2010m ACR FM criteria. Patients who met FM criteria were more likely to be female (difference in proportion 0.21; 95% CI (0.07, 0.36), reported worse BASDAI (mean difference (md) 2.7; 95% CI 2.0, 3.3), BASFI (md 2.7; 1.9, 3.4) and BAS-G (md 2.7; 2.0, 3.5). They reported worse Quality of Life (ASQoL md 6.3; 4.8, 7.8: EQ-5D md -0.23; -0.32,-0.14), higher levels of anxiety (md 3.9; 2.7, 5.1) and depression (md 4.0; 2.9, 5.2), more sleep problems (md 3.7; 2.0, 5.4) and higher levels of fatigue (md 4.0; 3.0, 5.0). There was no difference in age, IMD or whether they were commencing biologic therapy.

Conclusion: There is a large discrepancy between clinical diagnosis of FM and meeting FM research criteria in patients with axSpA. Patients who meet FM criteria show markedly worse markers of axSpA disease activity and generally poorer health. It is unknown whether such criteria are valid in the presence of axSpA, but there may be a large unmet and unrecognised need for treatment of FM symptoms amongst patients with axSpA.

Disclosure: G. J. Macfarlane, Pfizer Inc; AbbVie; UCB, 2; **M. S. Barnish**, None; **G. T. Jones**, Pfizer Inc, AbbVie, UCB, 2.

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Abstract Number: 2724

A Prospective Study of Ankylosing Spondylitis in China with Smart Management System for Spondyloarthritis: Study Design and Baseline Characteristics of the 449 Recruited Patients

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Session Time: 9:00AM-11:00AM

Background/Purpose: The aim of this study was to set up a large, longitudinal and prospective database to investigate the epidemiology, pathogenesis, diagnosis, and prognosis of ankylosing spondylitis (AS) through mobile health in the Chinese population.

Methods: 449 consecutive outpatients with confirmed AS or spondyloarthritis (SpA) were recruited and followed annually with Smart Management System for SpA (SMSP). Characteristics of registration and demography (age, gender, time of back pain onset, diagnosis, presence of AS-related clinical manifestations, family history) and the current condition (disease activity, severity, treatments, laboratory tests) were collected online with SMSP.

Results: 449 patients (mean age: 29.4±8.5 years, male 84.0 %, HLA-B27 positive rate 81.2%) were included in the analysis. In this cross-sectional analysis, only data at the first visit were used (from May 2014 to December 2014). A history or current symptoms suggestive of peripheral arthritis, enthesitis, acute anterior uveitis, psoriasis and inflammatory bowel disease were observed in 46.4%, 69.1%, 10.5%, 2.4% and 5.8% of the patients, respectively. Differences in symptom duration (≤ 5 years, 5 years to 10 years and > 10 years) were analyzed. The 3 groups did not differ in the frequency of gender, HLA-B27 positivity, family history, arthritis, enthesitis, inflammatory bowel disease, psoriasis, and abnormal CRP. Pain located in thoracic spine (34.1%), anterior chest wall pain (28.1%) and uveitis (18.5%) were detected significantly more frequently in patients with symptom duration of > 10 years.

The association of clinical variables and laboratory markers with patient's poor physical mobility (lumbar flexion Impairment, cervical

flexion Impairment and chest activity limitation) was evaluated with multivariate logistic regression model. The result revealed that 121 patients (26.9 %) had reduced lumbar mobility; 93 patients (20.7 %) had impaired cervical flexion and 104 patients (23.2 %) had reduced chest expansion. The analyses showed that symptom duration is independently associated with poor physical mobility of any of the body parts mentioned above (*OR* = 1.11, *OR* = 1.14, *OR* = 1.13, respectively). Age at onset is only significantly associated with chest expansion limitation (*OR* = 1.06). Cervical spine pain at onset is determined to be closely related to cervical flexion impairment (*OR* = 1.98). Also, smokers and ASDAS are determined to have an unfavorable effect upon outcomes of cervical flexion (*OR*=2.06, *OR* = 1.38, respectively). Smokers, abnormal CRP, and ASDAS correlate with a poor prognosis in lumbar flexion (*OR* = 2.44, *OR* = 2.05, *OR* =1.45, respectively).

Conclusion: This is the first prospective cohort study of ankylosing spondylitis and the first smart management system for SpA in China. With increasing global popularity of smart phone technology, there is a great opportunity for using mobile phone applications for disease management. This large cohort may improve our knowledge on the characteristics, pathogenesis and natural course in Chinese patients with AS.

Disclosure: X. Ji, None; **Q. Wen**, None; **J. Yang**, None; **J. Zhu**, None; **J. Zhang**, None; **F. Huang**, None.

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Abstract Number: 2725

Elevated Disease Activity in Disease-Related Spondyloarthritis Despite Use of Tumor Necrosis Factor Inhibitor Therapies

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Background/Purpose: Spondyloarthritis (SpA) includes a wide range of overlapping diseases for which there are a limited number of approved pharmacologic agents that have been shown to modify disease course. To date, tumor necrosis factor inhibitors (TNFi) are the most effective treatments available that improve function and alleviate symptoms. However, the extent to which TNFi ameliorates SpA disease activity in routine care remains unclear. We examined the frequencies of elevated Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores in SpA patients receiving TNFi.

Methods: Patients with SpA-related diseases who were receiving a TNFi and enrolled in the Veterans Affairs' Program to Understand the Long-term Outcomes in Spondyloarthritis (PULSAR) registry were eligible for study. Standardized electronic medical record templates obtained at routine clinic visits from Sept. 2007 – June 2016 provided the clinical study data. A modified, validated version of the BASDAI (replacing the term "Ankylosing Spondylitis" with "inflammatory arthritis"), was administered to subjects, and mean BASDAI scores were computed. We determined the prevalence of BASDAI≥4 among subjects with axial SpA, determined by SpA phenotype and use of TNFi.

Results: There were 596 PULSAR patients; 91% were male, 70% were Caucasian and 11% African American. The mean age at SpA diagnosis was 55 years. The majority either had ankylosing spondylitis or psoriatic arthritis. Forty-four percent were HLA-B27 positive, and the mean ESR and CRP value at enrollment was 18 mm/hr and 8.94 mg/L, respectively. Baseline BASDAI of SpA patients (regardless of phenotype) was 5.28. There were 385 on TNFi during the study period (Table). A BASDAI of ≥4 was recorded in approximately 60% of those treated with TNFi, including at their most recent encounter.

Conclusion: In a SpA cohort of US veterans, active disease persisted in a majority of TNFi- treated patients, potentially indicative of the need for more intensive or alternate therapies. **Table: Active BASDAI ≥4 scores in SpA patients receiving TNFi**

	AS	PsA	EAA	ReA
Total (n=596)	260	246	36	54
SpA on TNFi n =385, (% cohort)	172 (66.2%)	167 (67.9)	17 (47.2)	29 (53.7)
BASDAI≥4 ever	145 (84.3%)	136 (81.4%)	11 (64.7%)	22 (75.9%)
BASDAI≥4 (mean, all observations)	132 (76.7%)	118 (70.7%)	10 (58.8%)	22 (75.9%)
BASDAI≥4 (when receiving TNFi)	129 (75%)	115 (68.9%)	9 (52.9%)	21 (72.4%)
BASDAI≥4 (most recent visit)	104 (60.5%)	100 (59.9%)	8 (47.1%)	18 (62.1%)

AS = ankylosing spondylitis, PsA = psoriatic arthritis, EAA = enteric-associated arthritis, ReA = reactive arthritis, TNFi = Tumor necrosis factor inhibitor

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Abstract Number: 2726

Prevalence of HLA-B27 in the Normal Population and Patients with Axial Spondyloarthritis in Saudi Arabia

Fatima alduraibi[1], Mohammed Omair[2,3], Moheeb Al Awwami[4], Sultana Abdulaziz[5], Waleed Husain[6], Maha El Dessougi[7], Mahmoud Aljurf[8], Hind Alhumaidan[9], Hana Al Khabbaz[10], Ibrahim Alahmadi[11] and Salman Al Saleh[12], [1]Department of Internal Medicine, Section of Rheumatology ,Department of Internal Medicine,King Faisal Specialsed Hospital, Saudi Arabia, Riyadh, Saudi Arabia, [2]Rheumatology, King Khalid Hospital, Riyadh, ON, Saudi Arabia, [3]Division of Rheumatology, Department of Medicine, King Saud University, Riyadh, Saudi Arabia, [4]Histocompatibility and Immunogenetics Laboratory, Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [5]Dept of Medicine/Unit of Rheumatology, King Fahad Hospital, Jeddah, Saudi Arabia, [6]Hera Hospital , Division of Rheumatology, Department of Medicine, Makkah, Saudi Arabia, [7]Security Forces Hospital Division of Rheumatology, Department of Medicine, Riyadh, Saudi Arabia, [8]Department of Adult Hematology/Oncology and Stem Cell Transplantation, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [9]Blood Bank/Stem Cell/Cord Blood , Department of Pathology and Laboratory Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [10]Riyadh Colleges of Dentistry and Pharmacy, Riyadh, Saudi Arabia, [11]Organ Transplant Center, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, [12]King Faisal Specialsed Hospital, Riyadh, Saudi Arabia

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Background/Purpose: The prevalence of HLA-B27 varies between different ethnicities. Its presence is associated with susceptibility to axial spondyloarthritis (axSpA). The aim of this study is to evaluate the prevalence of HLA-B27 in the normal population and in patients with axSpA.

Methods: The prevalence of HLA-B27 in the normal population was evaluated in cord blood and healthy organ transplant donor databases. HLA typing was conducted with sequence-specific oligonucleotide probing and sequence-specific primer technologies. The data of patients with axSpA were collected retrospectively from five different hospitals. Patients with inflammatory bowel disease and psoriasis were excluded. Demographics, age at symptom onset/diagnosis, presence of extra-articular manifestations and use of biologics were obtained.

Results: A total of 136 axSpA patients were included, with a male predominance of 67.4%. The mean (±SD) ages at symptom onset and disease diagnosis were 29 (±10.9) and 33.4 (±10.7) years, respectively. The mean diagnosis delay was 51.7 (± 54.7) months. HLA-B27 was positive in 73 (53.7%) of patients. Male gender and HLA-B27 positive subtype were associated with a younger age at symptom onset/diagnosis (p<0.04), but no significant difference was observed in diagnosis delay, with a mean delay of 53.9±58.2 versus 49.1±50.6 months for HLA-B27-positive and negative patients, respectively (p=0.61). HLA-B27-positive patients were more likely to be on biologics (p=0.037), with no difference in the median number of biologics used. HLA-B27 was found in 82/3332 (2.5%) and 27/1164 (2.3%) in the cord blood and healthy organ transplant donor databases, respectively.

Conclusion: The prevalence of HLA-B27 is low in the Saudi population. A significant diagnosis delay has been observed in patients with axSpA regardless of HLA-B27 status and gender. HLA-B27 is positive in only half of axSpA patients limiting its usefulness.

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Abstract Number: 2727

Evaluating Psoriatic Arthritis and Psoriasis Skin Lesions: Ultrasound As a Complementary Measure

Yogan Kisten[1], Per T Larsson[2], Erik af Klint[2], Hamed Rezaei[2,3], Noémi Györi[1], Liv Eidsmo[4], Mona Ståhle[4] and Ronald F. van Vollenhoven[1,5], [1]Department of Medicine, Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [2]Medicine, Rheumatology Unit, Department of Medicine, Karolinska Institute, Karolinska University Hospital, Stockholm, Sweden, [3]Unit for Clinical Therapy Research, Inflammatory Diseases (ClinTRID), The Karolinska Institute, Stockholm, Sweden, [4]Dermatology and Venereology Unit, Department of Medicine, Karolinska Institute, Stockholm, Sweden, [5]Amsterdam Rheumatology and Immunology Center (ARC), Amsterdam, Netherlands

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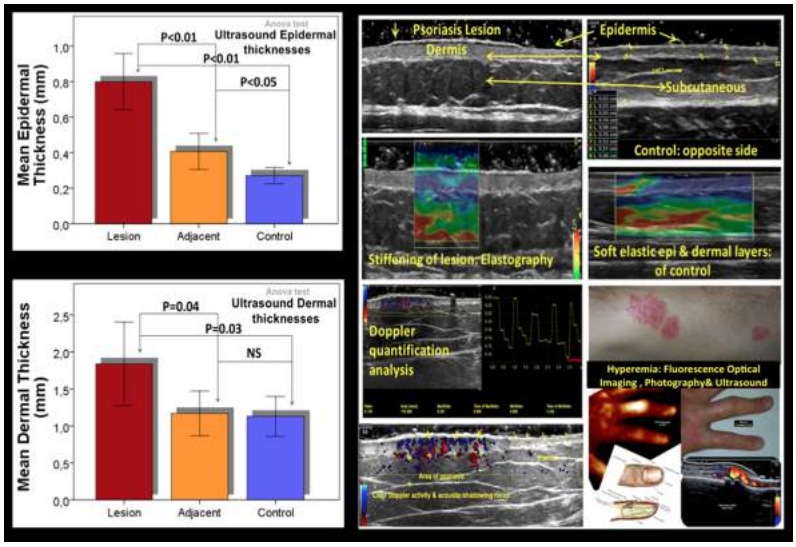
Background/Purpose: The diagnosis and assessment of psoriatic arthritis (PsA) and psoriasis (PsO) lesions are mostly done by visual inspection, and when in doubt, supplemented by a biopsy. Although PsA is primarily assessed by physical examination, the utility of ultrasound is beneficial. Here, we test the performance of advanced ultrasound skin imaging software applications in PsO & PsA assessment.

Methods: The rheumatologist and dermatologist performed standard clinical examinations on PsA and PsO patients respectively. Using ultrasound (US), we evaluated the hand, wrist, & symptomatic joints of PsA patients for synovitis & tenosynovitis (nail beds included). Blinded by the clinical results & treatment plans, the epidermal, dermal and subcutaneous tissue thickness of 2 of the most affected lesions were scanned by high frequency B-Mode, automated color Doppler quantification (CDQ) and elastography applications (measuring lesion size, depth, hyperemia and tissue elasticity). The skin tissues adjacent to the psoriatic lesion, and the unaffected skin

on the contralateral side (self-control) were measured for comparison.

Results: A total of 270 skin measurements in, around, & opposite to the 10 psoriatic lesions of 5 PsA/PsO patients were analyzed. Epidermal thickness differed significantly between adjacent and control tissue layers [F (2,27) = 30.95, MSE = 0.76, p<0.001]. Similar findings were evident for dermal thickness differences [F (2,27) = 5.05, MSE = 1.59, p=0.014]. Subcutaneous tissue depths were of no significance. Ultrasound CDQ & elastography revealed hyperemia in 80% of lesions (60% with plaque). Contrary, 20% of lesions showed no obvious Doppler activity, displaying reduced tissue stiffening on elastography (suggesting healed lesions). Two of 10 lesions were soft on elastography (no acoustic shadows) but had low-level CDQ activity (minimum 0.016:0.034 & maximum 0.103:0.135 ratios). In PsA patients, the presence of synovitis (intra &extra-articular Doppler) mostly in DIPs & PIPs, and tenosynovitis of flexor tendons were detected. Hyperemic nail beds (altered microcirculation) and hand psoriasis skin perfusion was evident on US, and confirmed by fluorescence optical imaging (FOI).

Conclusion: Several ultrasound parameters clearly distinguish between affected & normal skin and could be used as quantitative and objective measures in assessing psoriasis lesions. Some US parameters appear to distinguish between adjacent (non-involved) skin & self-control skin, while some show striking heterogeneity between different patients, suggesting that US may help subtype psoriasis lesions, but need to be investigated further. Ultrasound metrics of skin tissue (depth, plaque characteristics, elasticity and Doppler quantification) has potential to compliment the clinical assessment of PsO & PsA patients.



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Discontinuation of Biologic Therapy in Patients with Ankylosing Spondylitis—Data from the Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) Registry

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Background/Purpose: Clinical trials have demonstrated the efficacy of biologic therapy in improving the clinical and patient-reported outcomes in patients with ankylosing spondylitis (AS); however, there are limited data describing their use in real-world clinical practice. The objective of this analysis was to characterize and compare patients with AS who continued and discontinued their biologic therapy within 12 months of initiation in the US-based Corrona Psoriatic Arthritis/Spondyloarthritis (PsA/SpA) registry.

Methods: This descriptive analysis included all patients with AS aged ≥ 18 years enrolled in the Corrona PsA/SpA registry between March 2013 and March 2016 who received a biologic at the time of registry enrollment and had ≥ 1 follow-up visit. Patients were assigned to a cohort depending on their continued or discontinued use of their biologic agents at the first follow-up visit (mean [SD] follow-up, 8.8 [4.6] months). Patient demographics, clinical presentation, patient-reported outcomes and past/current treatments were assessed and compared between cohorts using *t*-tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Reasons for discontinuation of the index biologic (e.g., side effects, social reasons, lack of effect, doing well or other) were also described in this study.

Results: Of the total of 167 patients with AS who met the inclusion criteria, 32 patients (19.2%) discontinued the index biologic therapy by the first follow-up visit, including 12 patients who switched to another biologic therapy. Baseline characteristics of patients who continued vs discontinued a biologic by their first follow-up visit were similar with regards to sex, race, education, insurance type and past/current treatments. However, patients who discontinued their index biologic were significantly older (52.6 vs 46.8 years); were more likely to be obese (56.7% vs 33.3%) with greater body mass index (34.0 vs 28.2 kg/m^2); and had significantly worse Bath Ankylosing Spondylitis Disease Activity Index scores (4.8 vs 3.7) and Bath Ankylosing Spondylitis Functional Index scores (4.6 vs 2.8), but similar Ankylosing Spondylitis Disease Activity Scores (1.8 vs 1.9), at enrollment compared with patients who continued their biologic therapy (**Table**). Among the 9 patients (28.1%) who reported a reason for discontinuation, lack of effect (55.6%) was the most common reason, followed by other reasons (22.2%), side effects (11.1%) and social reasons (11.1%).

Conclusion: Results from the Corrona PsA/SpA registry demonstrated that patients with AS who discontinued their biologic therapy by the first follow-up visit were significantly older, more overweight and had worse patient-reported disease activity and function at enrollment compared to those who remained on the therapy. Lack of effect was the most common reason for biologic discontinuation.

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Abstract Number: 2729

Treatment Patterns, Unmet Need, and Impact of Psoriatic Arthritis on Patient-

Reported Outcomes in the United States

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Background/Purpose: This non-interventional, cross-sectional descriptive exploratory analysis aimed to characterize patients (pts) with PsA in the 2015 National Health and Wellness Survey (NHWS) and determine the impact of treatment, or no treatment, on pt-reported outcomes (PROs).

Methods: NHWS is a self-administered, web-based, voluntary, confidential questionnaire that used stratified randomized sampling to provide a representative sample of US adults. Respondents who reported PsA diagnosis were grouped by current treatment: advanced pharmacologic therapies (TNF inhibitors, IL-12/23 and IL-17 antagonists, PDE4 inhibitors) ± other drugs; other pharmacologic therapies (conventional synthetic DMARDs, COX2 inhibitors, NSAIDs, glucocorticoids, topical medications); or no current treatment. Short-Form 36 health survey (SF-36), Work Productivity and Activity Index (WPAI), and Patient Health Questionnaire (PHQ)-9) were investigated and summarized descriptively.

Results: Of 97,700 adults who completed the NHWS, 1059 pts reported PsA diagnosis. Of these, 216 reported treatment with advanced therapies, 206 with other therapies, and 637 reported no current treatment. Age and gender were generally balanced between treatment groups. Prior to treatment with advanced or other therapies, ~88–91% had self-reported moderate or severe PsA, and following treatment, ~54–57% reported moderate to severe PsA, which was similar to those reporting no current treatment (~58%; Table 1). SF-36 and PHQ-9 did not show wide variation in scores across treatment groups. WPAI showed that >40% of pts had work-related impairment due to PsA, despite being treated and having mild to moderate disease (Table 2).

Conclusion: We found that ~60% of pts who reported PsA diagnosis reported no current treatment. Regardless of treatment group, pts reported >20% work loss and >40% work impairment. Among pts treated with advanced and other therapies, >50% reported moderate to severe PsA, suggesting the need for additional therapies and overall better management of PsA to reduce disease activity and improve quality of life. A limitation of this analysis is that pts self-reported PsA diagnosis, and results may differ from pts having physician-reported PsA diagnosis. Further statistical analysis is needed to determine differences between groups and correlation to other health

Table 1. Demographics and characteristics

		Advanced therapies N=216	Other therapies N=206	Not treated N=637
Age in years, mean (SD)		46.0 (14.3)	52.5 (15.0)	44.9 (15.9)
Females, n (%)		98 (45.4)	118 (57.3)	268 (42.1)
White ethnicity, n (%)		141 (65.3)	150 (72.8)	416 (65.3)
PsA severity when treated, n (%)	Mild	93 (43.1)	94 (45.6)	NA
	Moderate	98 (45.4)	97 (47.1)	NA
	Severe	25 (11.6)	15 (7.3)	NA
PsA severity when untreated, n (%)	Mild	18 (8.8)	24 (12.4)	270 (42.4)
	Moderate	79 (38.7)	75 (38.9)	317 (49.8)
	Severe	107 (52.5)	94 (48.7)	50 (7.9)

PsA severity was self-assessed by patients

SD, standard deviation

indicators.

Table 2. Mean (SD) outcome scores by treatment type

	Advanced therapies N=216	Other therapies N=206	Not treated N=637
SF-36 MCS	40.3 (10.9)	42.1 (12.0)	39.7 (11.0)
SF-36 PCS	39.7 (9.2)	38.6 (10.7)	42.1 (9.6)
WPAI domain scores[a]			
% work missed	28.1 (28.4)	16.2 (25.8)	23.7 (26.4)
% impairment at work	57.8 (30.5)	43.3 (30.0)	49.8 (30.5)
% overall work impairment	63.5 (31.8)	46.7 (32.0)	56.5 (32.6)
% activity impairment	58.2 (29.3)	52.1 (29.8)	52.6 (29.3)
PHQ-9 total score[b]	10.6 (7.8)	8.1 (7.6)	9.9 (7.5)

[a]N for WPAI % work missed = 144, 82, 381, respectively for advanced therapies, other therapies, not treated; N for WPAI % Impairment at work = 145, 82, 380, respectively, for advanced therapies, other therapies, and not treated; N for % overall work impairment = 140, 80, 373, respectively, for advanced therapies, other therapies, not treated.

[b]N = 58, 42, 161 for advanced therapies, other therapies, not treated, respectively.

MCS, mental component summary; PCS, physical component summary; PHQ-9, patient health questionnaire 9; SD, standard deviation; SF-36, short form 36 health survey; WPAI, work productivity and activity impairment

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Disclosure: A. Gottlieb, Astellas, Akros, Centocor (Janssen), Celgene, BSM, Beiersdorf Inc, Abbott Labs (AbbVie), TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd, Pfizer Inc, Canfite, Eli Lilly, Coronado, Vertex, Karyopharm, CSL Behring Biotherapies for Life, Glaxo Smi, 5,Centocor (Janssen), Amgen, Abbott (AbbVie), Novartis, Celgene, Pfizer Inc, Eli Lilly, Coronado, LeviaMerck, Xenoport, Dermira, Baxalta, 2; **J. Gratacos-Masmitja**, None; **A. Armstrong**, Amgen, AbbVie, Janssen, Eli Lilly, 2,Janssen, Pfizer Inc, Celgene, Merck, Eli Lilly, 5,Janssen, Pfizer Inc, Celgene, Merck, Eli Lilly, 6,AbbVie, 8; **J. Lambert**, None; **A. van Tubergen**, None; **A. Dikranian**, Pfizer Inc, AbbVie, 5,Pfizer Inc, Abbvie, 8; **B. Emir**, Pfizer Inc, 1,Pfizer Inc, 3; **E. Bananis**, Pfizer Inc, 1,Pfizer Inc, 3; **T. Smith**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Aikman**, Pfizer Inc, 1,Pfizer Inc, 3; **L. Chen**, Pfizer Inc, 1,Paizer Inc, 3.

Abstract Number: 2730

Impact of Disease Flare Perception on Work Productivity and Treatment Satisfaction in Patients with Psoriatic Arthritis in Real World Setting

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Background/Purpose: Patients (pts) with psoriatic arthritis (PsA) may experience temporary worsening of symptoms or disease flare, which can be painful enough to interfere with day-to-day activities. The impact of pt perception of severity of disease flare on work productivity, treatment satisfaction, and other pt-reported outcomes (PROs) has not been quantified in detail. The purpose of this analysis is to evaluate the perception of disease flares in pts with PsA and its impact on work productivity and treatment satisfaction in real world setting.

Methods: Adelphi[1] 2014 Rheumatology Disease Specific Programme is a large multi-center, multi-country, cross-sectional survey of pts with a physician confirmed diagnosis of PsA. Pts filled out a self-completion survey providing an assessment of their symptoms (severity of disease and flaring), quality of life (QoL), and satisfaction with disease control. The self-assessment questionnaire also included pt-reported alternative Health Assessment Questionnaire-Disability Index (HAQ-DI, without aids and devices), Work Productivity and Activity Impairment–Specific Health Problem (WPAI-SHP), and treatment satisfaction. Statistical differences between the groups were evaluated using chi-square test (categorical variables) or analysis of variance (ANOVA, continuous variables).

Results: Of the 341 PsA pts analyzed from the Adelphi database, 236 (69.2%) pts experienced temporary worsening of symptoms or disease flare. Among pts who reported experiencing a flare, mean age was 51 years and 54% were female. At survey, 126 (55.3%) pts reported experiencing moderate flare, while 53 (23.2%) and 49 (21.5%) experienced mild and severe flare, respectively. Pt-reported severity of last flare increased significantly with increasing perception of PsA severity at survey (P<0.001), at its worst (P<0.001), or before current treatment (P=0.003, **Table**). The severity of disease flare, as reported by pts, was negatively associated with the ability of pts to go to work and perform well at work (P<0.001) and perform daily tasks (P<0.001). The mean HAQ-DI (P<0.001) and WPAI (P<0.001) scores significantly worsened with increasing severity of disease flare perception. Of the pts reporting mild, moderate, and severe flares, 32 (64.0%), 72 (60.0%), and 26 (53.1%), respectively, were receiving biologic medicine. Pts' satisfaction with the current treatment (P=0.002) was significantly lower with increasing severity of disease flare.

Conclusion: Pt perception of PsA severity increased with the severity of pt-reported disease flare. Increasing severity of disease flare perception was associated with decreased work productivity, reduced ability to perform day-to-day activities, and less treatment satisfaction. Pts reporting moderate to severe disease flare experience significantly higher disease burden. **References:**

1. Anderson et al., *Curr Med Res Opin*., 2008; 24 (11):3063-72.

Table. Summary of patient-reported outcomes stratified by severity of disease flare.

Characteristic	Severity of last flare			Total	P-value
	Mild	Moderate	Severe		
Severity of PsA at survey, *mean (SD)*[a]	1.4 (0.6)	1.6 (0.6)	2.2 (0.6)	1.7 (0.7)	<0.001
Severity of PsA at its worst, *mean (SD)*[a]	2.4 (0.5)	2.6 (0.5)	2.9 (0.3)	2.6 (0.5)	<0.001
PsA severity before current treatment, *mean (SD)*[a]	2.3 (0.5)	2.4 (0.6)	2.7 (0.5)	2.4 (0.6)	0.003
Impact of last flare on ability to go to work and perform at work, *n (%)*					
No Impact	27 (50.9)	32 (25.4)	3 (6.1)	62 (27.2)	
Some Impact	22 (41.5)	59 (46.8)	16 (32.7)	97 (42.5)	<0.001
Major Impact	2 (3.8)	25 (19.8)	23 (46.9)	50 (21.9)	
Impact of last flare on ability to perform usual daily tasks, *n (%)*					
No Impact	24 (45.3)	13 (10.3)	3 (6.1)	40 (17.5)	
Some Impact	27 (50.9)	92 (73.0)	15 (30.6)	134 (58.8)	<0.001
Major Impact	2 (3.8)	18 (14.3)	29 (59.2)	49 (21.5)	
Alternate HAQ-DI, *mean (SD)*	0.3 (0.5)	0.6 (0.6)	1.2 (0.6)	0.7 (0.7)	<0.001
WPAI–SHP (overall work productivity impairment due to PsA), *mean (SD)*	15.3 (17.9)	28.5 (26.6)	54.8 (31.8)	29.3 (28.4)	<0.001
Current biologic treatment status, *n (%)*					
Yes	32 (64.0)	72 (60.0)	26 (53.1)	130 (59.4)	
No	17 (34.0)	46 (38.3)	20 (40.8)	83 (37.9)	
Do not know	1 (2.0)	2 (1.7)	3 (6.1)	6 (2.7)	
Satisfaction with current treatment, *mean (SD)*[b]	5.3 (1.3)	5.0 (1.1)	4.4 (1.6)	5.0 (1.3)	0.002

P-value for significant difference between groups from chi-square test for categorical variables and ANOVA for continuous variables.
[a]PsA severity evaluated on a mild, moderate, and severe (1–3) rating scale.
[b]Treatment satisfaction evaluated on a 1–7 numeric rating scale with 1 and 7 indicating extremely dissatisfied or satisfied, respectively.
Abbreviations: PsA = psoriatic arthritis; HAQ-DI = health assessment questionnaire – disability index; WPAI-SHP = work productivity and activity impairment – specific heath problem.

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Abstract Number: 2731

Illness Perceptions and Health-Related Quality of Life in Patients with Axial Spondyloarthritis and Other Forms of Chronic Back Pain in the Spondyloarthritis Caught Early (SPACE)-Cohort

Miranda van Lunteren[1], Pauline Bakker[1], Margreet Scharloo[2], Ad Kaptein[3], Zineb Ez-Zaitouni[1], Camilla Fongen[4], Robert Landewé[5], Maikel van Oosterhout[6], Mariagrazia Lorenzin[7], Désirée van der Heijde[1] and Floris van Gaalen[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Leiden University Medical Center, Leiden, Netherlands, [3]Medical Psychology, Leiden University Medical Center, Leiden, Netherlands, [4]Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]Rheumatology, Academic Medical Center, Amsterdam, Netherlands, [6]Rheumatology, Groene Hart Ziekenhuis, Gouda, Netherlands, [7]Rheumatology Unit, Department of Medicine DIMED, Rheumatology Unit,University of Padova, Padova, Italy

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Background/Purpose: Knowledge about the impact of illness perceptions on health-related quality of life (HRQoL) in patients with axial Spondyloarthritis (axSpA) and other forms of chronic back pain (CBP) is lacking. The aim is to explore the association between illness perceptions and HRQoL in patients with short symptom duration of axSpA and other forms of CBP at baseline.

Methods: The SPACE study includes patients with CBP (≥3 months, ≤2 years, onset <45 years) from 5 European centers. Revised Illness Perception Questionnaire (IPQ-R) was completed at baseline. In illness identity dimension, patients reported if they have experienced and believed that a certain symptom is CBP related. Other IPQ-R dimensions used 5-point Likert scales (1 strongly disagree, 5 strongly agree). HRQoL was assessed by 36-item Short-Form (SF-36). Physical (PCS) and Mental Component Summary (MCS) scores were calculated ranging from 0 (worst) to 100 (best). Univariable regression models were built for each IPQ-R subscale as independent and PCS or MCS as dependent variable. The models were adjusted for age and gender and stratified in case of effect modification by gender ($p<0.20$).

Results: 450 patients were included; 176 fulfilled the axSpA ASAS criteria. Mean PCS was 28.3 (SD 16.1) for axSpA patients and 25.4 (SD 14.8) for CBP. As the MCS was only slightly decreased compared to the general population of 50 (SD 10) (48.8 (SD 13.7) axSpA and 48.3 (SD 12.1) CBP patients), analyses focused on PCS. Patients reported a mean of 4.3 (axSpA) and 4.5 (CBP) symptoms to be associated with back pain. Most reported symptoms were pain and joint stiffness. All other dimensions showed a mean of approximately 3, except psychological attributions, risk factors, immunity, and accident (mean approximately 2). All patients attributed their complaints mostly to genetic factors. In both patient groups attribution of multiple symptoms to CBP (Table 1; β=-1.9 axSpA, β=-2.0 CBP) was associated with lower PCS. Stronger belief in severe consequences in male axSpA patients (β=-11.3) and stronger belief in risk factors (β=-6.9) or immunity (β=-8.3) as a cause in male CBP patients were associated with lower PCS. Whereas, in male axSpA patients, being better in understanding their complaints (β=6.2) was associated with higher PCS. In female axSpA patients stronger belief in severe consequences (β=-7.3) and in female CBP patients more negative emotions towards their complaints (β=-3.8) and being better in understanding their complaints (β=3.3) were statistically significant. No gender differences were found for emotional representation (β=-5.0), psychological attributions (β=-3.4), immunity (β=-4.0), or accident (β=-3.0) in axSpA and consequences (β=-8.5) or chance (β=-2.0) in CBP patients.

Conclusion: Negative illness perceptions are associated with lower PCS of HRQoL in patients with axSpA and other forms of CBP.

Figure 1: Linear regression models of Physical Component Scale (PCS) of Health-Related Quality of Life (HRQoL) and subscales of the Revised Illness Perception Questionnaire (IPQ-R) at baseline adjusted for age and gender (n=450)

Scale	Range	axSpA (n=176)	Coefficient (SE)	p-value	CBP (n=274)	Coefficient (SE)	p-value
Illness identity		(n=166)			(n=247)		
Identity			*-1.9 (0.5)*	*<0.001*		*-2.0 (0.4)*	*<0.001*
Illness perceptions		(n=176)			(n=269)		
Consequences	1-5	Men	*-11.3 (2.4)*	*<0.001*		*-8.5 (0.9)*	*<0.001*
		Women	*-7.3 (1.5)*	*<0.001*			
Timeline (acute/chronic)	1-5		-2.0 (1.7)	0.241		-2.0 (1.2)	0.096
Personal control	1-5		2.1 (1.8)	0.239		2.4 (1.5)	0.106
Treatment control	1-5		3.3 (2.4)	0.178		1.2 (1.9)	0.548
Illness coherence	1-5	Men	*6.2 (2.6)*	*0.017*	Men	0.1 (2.2)	0.948
		Women	0.1 (1.4)	0.938	Women	*3.3 (1.1)*	*0.004*
Timeline (cyclical)	1-5		-0.2 (1.4)	0.882		1.0 (1.1)	0.389
Emotional representation	1-5		*-5.0 (1.2)*	*<0.001*	Men	-0.2 (2.0)	0.902
					Women	*-3.8 (1.1)*	*<0.001*
Causal attributions		(n=175)			(n=269)		
Psychological attributions	1-5		*-3.4 (1.4)*	*0.016*		-0.3 (1.2)	0.814
Risk factors	1-5		-3.1 (2.0)	0.132	Men	*-6.9 (2.9)*	*0.021*
					Women	2.4 (1.9)	0.208
Immunity	1-5		*-4.0 (1.5)*	*0.009*	Men	*-8.3 (2.1)*	*<0.001*
					Women	-1.4 (1.4)	0.298
Accident	1-5		*-3.0 (1.3)*	*0.018*		-0.9 (0.8)	0.309
Chance	1-5		-0.7 (1.1)	0.489		*-2.0 (0.8)*	*0.015*

Statistically significant results are printed in italics. Abbreviations: axial Spondyloarthritis, axSpA; chronic back pain, CBP; standard error, SE

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Abstract Number: 2732

Meaningful Involvement of Patients in the Development of a Core Outcome Set for Psoriatic Arthritis

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Background/Purpose: The Group for Research of Psoriasis and Psoriatic Arthritis (GRAPPA)-Outcome Measures in Rheumatology (OMERACT) Psoriatic Arthritis (PsA) working group recently obtained endorsement at the OMERACT 2016 conference for the updated PsA core domain set to be measured in PsA clinical trials. Our objective was to integrate patients in each research phase such that the updated PsA core domain set fully reflects a diverse patient perspective.

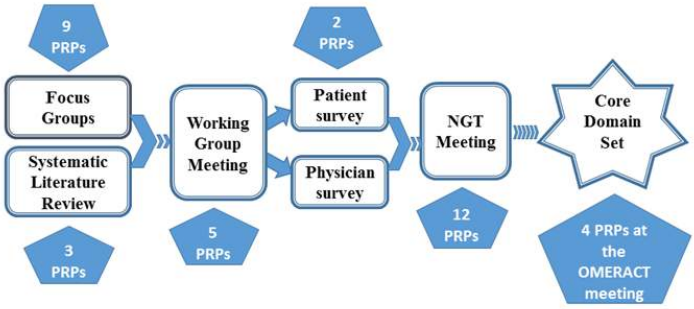
Methods: The patient voice was sought through an international focus group study covering five continents, two surveys of patients, a consensus meeting with patients and physicians, as well as active partnership of five patient research partners (PRPs) from GRAPPA in the working group. Patient involvement was regularly discussed during reflection meetings by the research team.

Results: Overall, almost 150 persons with PsA were involved in the study: 1) Systematic literature review. Three PRPs were involved in study protocol development, analysis of results and co-authorship; 2) International focus group study. Ninety patients with PsA participated in 16 focus groups. PRPs gave feedback on the focus group guide, co-moderated focus groups and analyzed and interpreted qualitative data; 3) Surveys. Fifty patients participated in two rounds. Five PRPs participated in the design and analysis of the patient surveys and assisted in writing the introduction text; 4) Consensus meeting. Twelve patients participated in a face-to-face meeting with 12 physicians to agree on a preliminary core domain set. Two PRPs helped in preparing the agenda and patient participant selection.

In total 14 PRPs contributed to one or more of the above research activities. Challenges were identified by physician-researchers (time-constraints and tight deadlines; use of jargon; motivation of PRPs) as well as PRPs (ensuring equal participation and acknowledgement; involvement of pharmaceutical industry).

Conclusion: Collaboration between physician-researchers and PRPs during all core-set development steps enhanced the integration of the patient perspective in a meaningful and representative manner and provided additional face validity. PRP involvement in qualitative data analysis and development of the domain list for the surveys ensured that domains important to patients were maintained throughout the research process and phrased in a manner understandable to patients.

Figure 1. Flow chart of research activities with active participation of patients and patient research partners (PRP) in the update of the OMERACT Psoriatic Arthritis core domain set.



Disclosure: M. de Wit, None; **A. Ogdie**, None; **W. Campbell**, None; **P. J. Mease**, None; **N. Goel**, Quintiles, Inc., 3; **L. Gossec**, None; **Y. Y. Leung**, None; **C. Lindsay**, Amgen, Inc., 3,Amgen, Inc., 1; **P. Palominos Jr.**, None; **I. Steinkoenig**, None; **S. Grieb**, None; **A. M. Orbai**, Celgene, 2,Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 5.

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Abstract Number: 2733

Fatigue, Pain and Patient Global Assessment Fluctuate Substantially in Spondyloarthropathy Patients with Stable Disease According to Basdai

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Background/Purpose: The use of patient-reported outcome measures has become routine in clinical practice and in clinical trials. In order to use any outcome measure in the daily clinic, the natural variation of the outcome measure must be known. Natural variation may also be characterized as measurement error and is assessed in individuals who are considered to be in "steady state". The objective of this study was to examine natural variation of fatigue, pain and patient global assessment (PaGl) in patients with stable spondyloarthropathy (SpA) defined on the basis of BASDAI (0-100).

Methods: 107 SpA patients treated in the daily clinic with a TNF-inhibitor and characterized by stable disease were identified in the Danish rheumatology registry (DANBIO). According to ASAS response criteria for biological treatment in SpA [1] and to previous reports on BASDAI measurement errors [2], stable disease was defined as a change in BASDAI ≤ 20 between two consecutive visits. Paired data from a single set of such two visits were extracted for each patient. Data comprised BASDAI, BASFI, PaGl, pain and fatigue scored on 0-100 visual analogue scales (VAS). Natural variation was examined using the Bland-Altman method with calculations of lower and upper 95% limits of agreement (LLoA;ULoA) between two consecutive assessments and the corresponding bias (mean of individual differences). Associations between intra-individual inter-visit differences (Δ) were described by linear correlation (r) and stepwise multiple regression analyses (partial regression coefficients (rp) and standard errors of estimation (SEE)).

Results: Mean age was 44±14 years, mean BASDAI 35.6±23.8, mean BASFI 33.0±24.8, mean fatigue 49.3±28.2, mean pain 35.6±26.9, mean PaGl 40.8±27.9, mean inter-visit time duration 16±13 weeks (range 3 – 91 weeks) and mean ΔBASDAI 0.0±10.5 (range -20 – 20, NS). Biases were close to 0 for all the variables indicating stable conditions on the group level between the two consecutive visits. On the individual level, however, differences were more pronounced: LoA;ULoA [bias] for fatigue was -37.4;36.2 [-0.6, NS], for pain -34.1;32.5 [-0.8, NS], for PaGl -35.7;32.9 [-1.4, NS] and for BASFI -23.2;22.6 [-0.3, NS]. No significant correlations were found between the absolute Δvalues of BASDAI, BASFI, fatigue, pain or PaGl and the inter-visit time duration (r range -0.1 – 0.2, ns). Δfatigue, Δpain, ΔPaGl and ΔBASFI were only weakly correlated with ΔBASDAI (r range 0.30 – 0.60, $p < 0.01$). In multiple regression analyses, Δfatigue, Δpain and ΔPaGl were best predicted by ΔBASDAI, and ΔBASFI by Δpain (rp range 0.40 – 0.49, $p < 0.0001$). Although these associations were highly statistically significant, SEEs were high (range 10.8 – 15.6) illustrating poor predictability in individuals.

Conclusion: Independently of time duration, fatigue, pain and PaGl fluctuated substantially and unpredictable in individual SpA patients who were considered to be in steady state. A change in these outcome measures of 35 or less (VAS 0-100) may be interpreted to reflect natural variation or measurement error which should be taken into account when managing individual patients in the daily clinic.
References: 1. Braun J et al. Ann Rheum Dis 2003; 62: 817-24. 2. Madsen OR et al. Clin Rheumatol 2010; 29: 849-54.

Disclosure: E. M. Egsmose, None; **O. Rintek Madsen**, None.

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Abstract Number: 2734

Is Disease Activity Associated with Negative Illness Perceptions in Early Axial Spondyloarthritis Patients in the Spondyloarthritis Caught Early (SPACE)-Cohort?

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Background/Purpose: Studies in patients with rheumatic diseases report that negative views of illness are associated with poorer disease outcomes, such as more disability and pain. Little is known about illness perceptions in patients with early axial Spondyloarthritis (axSpA). The aim is to describe illness perceptions and to explore the association with disease activity in patients with early axSpA at baseline.

Methods: The SPACE-cohort includes patients (chronic back pain ≥3 months, ≤2 years, onset <45 years) recruited from 5 participating centers in Europe. Patients completed the Revised Illness Perception Questionnaire (IPQ-R). The illness identity dimension asked patients if they have experienced a certain symptom (15 in total) and if they believed these symptoms are related to axSpA. The other illness perception dimensions (7 dimensions) and causal attributions (5 dimensions) used 5-point Likert scales to score all items ranging from 1 (strongly disagree) to 5 (strongly agree). For the IPQ-R dimensions, see Table 1. Disease activity was assessed by ASDAS (Ankylosing Spondylitis Disease Activity Score, CRP based). Univariable linear regression models were built for each IPQ-R dimension as dependent and ASDAS as independent variable adjusted for age and gender.

Results were stratified when gender was an effect modifier ($p<0.20$). P-values <0.05 were considered to be statistically significant.

Results: Only patients fulfilling the ASAS classification for axSpA (n=162/400) were included. Patients had a mean age of 30.0 (SD 8.0) years and 51.9% were male. The mean disease duration was 13.9 (SD 8.1) months and the mean ASDAS 2.5 (SD 0.9). Patients reported on average 4.3 (SD 2.3) symptoms to be associated with axSpA on average (Table 1). Pain, joint stiffness, fatigue, and sleeping problems were the most reported symptoms according to patients in the illness identity dimension. All other dimensions showed a mean of approximately 3, except psychological attributions, risk factors, immunity, and accident of the causal section, which had a mean of approximately 2. Patients with axSpA attributed their complaints mostly to heredity, chance and bad luck. Three dimensions of the IPQ-R were associated with ASDAS. A higher ASDAS was statistically significantly associated in all patients with stronger beliefs in severe consequences ($\beta=0.26$, $p<0.001$), more negative emotions towards their complaints ($\beta=0.18$, $p=0.027$), and in women with more symptoms attributed to axSpA ($\beta=1.53$, $p<0.001$). There was a trend between a higher ASDAS and less belief in personal control ($\beta=-0.10$, $p=0.082$) and less illness coherence ($\beta=-0.13$, $p=0.083$).

Conclusion: In patients with early axSpA, disease activity is associated with negative illness perceptions, such as attribution of multiple symptoms, believing in severe consequences, and experiencing negative emotions towards axSpA.

Table 1: Baseline characteristics of the Revised Illness Perception Questionnaire (IPQ-R) and linear regression models of ASDAS (CRP-based) and subscales of the IPQ-R at baseline adjusted for age and gender (n=162)

Baseline characteristics			Linear regression models with ASDAS (independent variable)			
Scale	Range	Mean (SD)		Coefficient (β)	Standard error	p-value
Illness identity (n=153)						
Identity	0-15	4.3 (2.3)	*Men*	0.17	0.25	0.511
			Women	1.53	0.24	<0.001*
Illness perceptions (n=161)						
Consequences	1-5	2.9 (0.8)		0.26	0.06	<0.001*
Timeline (acute/chronic)	1-5	3.7 (0.7)	*Men*	-0.09	0.08	0.282
			Women	0.11	0.07	0.204
Personal control	1-5	3.2 (0.6)		-0.10	0.05	0.082
Treatment control	1-5	3.4 (0.5)		-0.04	0.04	0.330
Illness coherence	1-5	3.3 (0.8)		-0.13	0.07	0.083
Timeline (cyclical)	1-5	3.6 (0.8)		-0.07	0.07	0.355
Emotional representation	1-5	2.7 (0.9)		0.18	0.08	0.027*
Causal attributions (n=161)						
Psychological attributions	1-5	2.0 (0.8)	*Men*	0.13	0.11	0.213
			Women	-0.08	0.10	0.426
Risk factors	1-5	2.2 (0.6)		0.001	0.05	0.976
Immunity	1-5	2.1 (0.8)		0.07	0.07	0.342
Accident	1-5	1.8 (0.9)		-0.05	0.08	0.585
Chance	1-5	3.3 (1.1)		0.07	0.10	0.503

** Statistically significant (p<0.05)*

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Abstract Number: 2735

Regional Variability of Minimal Disease Activity Among Psoriatic Arthritis Patients in Canada: An Analysis from a Prospective, Observational Registry

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Background/Purpose: Although remission remains the ultimate treatment goal in psoriatic arthritis (PsA) management, minimal disease activity (MDA), which encompasses remission and low disease activity, constitutes an attainable goal. Given that variability may exist across Canadian provinces both in regard to patient characteristics at anti-TNF initiation and in PsA management in routine clinical practice, the aim of the current analysis was to assess the regional variability in MDA achievement among Canadian patients initiating treatment with anti-TNF in real-world.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for PsA, ankylosing spondylitis, or rheumatoid arthritis with infliximab or golimumab. PsA patients who were enrolled during 2002-2015, had ≥1 follow-up assessment and MDA data available were included. MDA was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1 or BSA≤3, Pain (VAS) ≤15mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, tender entheseal points ≤1. Provinces were regrouped by region: Western (Alberta, British Columbia, and Saskatchewan), Ontario, Quebec and Maritimes. Continuous and categorical variables were assessed with the non-parametric Kruskal-Wallis test and the Chi-square test, respectively.

Results: 223 PsA patients (51.4% male) were included in the analysis. The mean (SD) age was 49.8 (11.1) years, and disease duration was 5.8 (6.6) years. The proportion of patients in BioTRAC by Canadian region was 6.4%, 50.5%, 29.7% and 13.4% for the Western region, Ontario, Quebec and the Maritime region, respectively. The mean (SD) disease duration was significantly different among regions with [Western: 5.00 (5.48), Ontario: 5.76 (6.51), Quebec: 7.47 (7.60), Maritimes: 1.8 (1.9) years; p=0.027]. Baseline disease parameters for TJC, SJC, pain, PtGA, and HAQ-DI were statistically comparable at baseline among Canadian regions. However, significant between-group differences were observed at baseline for mean (SD) enthesitis count [Western: 7.00 (4.21), Ontario: 1.14 (2.90), Quebec: 1.33 (2.14), Maritime: 3.16 (3.88); p<0.001], and PASI [Western: 4.76 (4.98), Ontario: 3.71 (5.51), Quebec: 1.45 (2.94), Maritime: 1.18 (1.32); p=0.001]. At baseline, 6 and 12 months of treatment, 11.7%, 43.5%, and 44.8% of patients achieved MDA, respectively. A statistical trend was observed between regions with respect to MDA achievement at 6 or 12 months of treatment (p=0.127). Ontario and Quebec patients had the highest MDA rates (55.9% and 52.1%), while 44.4% and 18.2% of patients in Maritime and Western provinces presented with MDA, respectively.

Conclusion: MDA achievement rates vary across Canada which could be attributed to differences in the patient profile and in disease duration at anti-TNF initiation.

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Inc., 3; **K. Maslova**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3.

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Abstract Number: 2736

Do Validated Tools of Disease Activity in Ankylosing Spondylitis Measure Fibromyalgia Pain?

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SESSION INFORMATION

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Session Title: Spondylarthropathies and Psoriatic Arthritis – Clinical Aspects and Treatment - Poster III

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Concomitant fibromyalgia syndrome (FMS) is a common problem in ankylosing spondylitis (AS) and its recognition is important for optimal management. BASDAI, a disease activity measures for AS has been shown to have poor specificity for AS and was reported to be high in patients with fibromyalgia. Hypothesis guiding our study was that the validated tools of disease activity in AS measure fibromyalgia pain. We studied the association of validated instruments of disease activity in AS with widespread pain index (WPI) and symptom severity score (SS) used in FMS.

Methods: Study was approved by our IRB. We prospectively recruited 62 AS patients ≥18 years of age and meeting the modified New York criteria with grade 3 or 4 sacroiliItis. Demographic and clinical data were collected and stored in Redcap data base. Various questionnaires to assess disease activity and patient reported outcomes in AS were administered to these patients. The frequency of FMS was determined using validated 2010 ACR diagnostic criteria for fibromyalgia. Patient met the fibromyalgia criteria if (i) WPI of ≥ 7 & SS ≥ 5 or WPI 3–6 & SS score ≥ 9,(ii) symptoms were present at a similar level for at least 3 months and (iii) the pain was not attributed to AS by the clinician. ESR and CRP was measured using routine laboratory methods. Descriptive analysis included continuous variables (mean ± SD) and the categorical variables (%). Data were compared by Student's t-test for continuous variables and chi-square for categorical variables. Linear regression analysis was performed to assess the association between BASDAI, BASMI, ASDAS, Rapid 3, ESR, CRP, WPI and SS scores.

Results: 27/62 (43.5%) patients with AS satisfied the ACR diagnostic criteria for fibromyalgia. Patient demographics and clinical characteristics Table 1.The patients with FMS had significantly higher disease activity as compared to patients without FMS (Table 2). There was no significant relationship of BASDAI, RAPID 3, ASDAS-CRP, physician's global and patient global scores, ESR, CRP when tested individually with the WPI and SS scores (Table 3).

Conclusion: Despite 43% prevalence of fibromyalgia in our patients with active AS and high disease activity, the validated tools of disease activity in AS did not measure fibromyalgia related pain and symptom severity.

Table 1- Demographics and Clinical Characteristics of Patients

	Patients who **fulfilled** the ACR Diagnostic Criteria for Fibromyalgia N= 27/62	Patients who **did not fulfill** the ACR Diagnostic Criteria for Fibromyalgia N=35/62	p- value
Mean age in years ± SD	48.9 ± 11.2	48.7 ± 13.2	0.94
% African-Americans	63.16	36.84	0.02
% Females	45	55	0.60
% HLA-B27 positivity	77.7	74.2	0.75
% Acute anterior uveitis	27.2	72.73	0.03
% TNF-i use	51.8	48.5	0.79

Table 2- Comparison of Disease Activity Scores between the two groups

Mean values ± SD	Patients **with** Fibromyalgia	Patients **without** Fibromyalgia	p-value
BASDAI	6.8 ± 1.9	3.8 ± 2.2	< 0.0001
RAPID 3	18.1 ± 6.2	10.3 ± 6.7	< 0.0001
ASDAS-crp	4.2 ± 0.9	2.8 ± 0.8	< 0.0001
Physician global	6.5 ± 2.3	4.1 ± 2.1	0.0002
Patient global	7.3 ± 2.2	4.4 ± 2.5	<0.0001
ESR mm/hr	29.5 ± 27.7	15.42 ± 16.3	0.01
CRP mg/dl	2.3 ± 3.5	0.8 ± 0.8	0.01

Table 3- Linear Regression modelling with SS scale and WPI as dependent variable

Variable	**BASDAI**	**RAPID 3**	**ASDAS-CRP**	**ESR**	**CRP**
Widespread Pain Index	P=0.30	P=0.77	P=0.59	P=0.18	P=0.83
Symptom Severity Scale	P=0.15	P=0.64	P=0.86	P=0.82	P=0.96

Disclosure: M. N. Magrey, None; **S. Diomampo**, None; **M. A. Khan**, None.

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Abstract Number: 2737

Posttraumatic Stress Disorder and Correlates of Disease Activity Among Veterans with Ankylosing Spondylitis

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Background/Purpose: Posttraumatic stress disorder (PTSD) has a prevalence of 11.5% in the outpatient setting and is associated with increased risk for multiple comorbid psychiatric and medical conditions. Studies have demonstrated an increased risk of incident RA in cohorts with PTSD, as well as increased pain scores in those with both RA and PTSD. We sought to examine variation in patient characteristics, medication use, pain level, and disease activity among Veterans with ankylosing spondylitis (AS) by PTSD status in a Veterans Affairs (VA) outpatient rheumatology clinic.

Methods: Veterans who had one or more visits at an outpatient rheumatology clinic at a single VA site between 1/1/14 and 12/31/15 were identified for inclusion by the presence of an ICD-9 or ICD-10 code for AS. Diagnosis of AS was confirmed by review of documentation by their primary rheumatologist. Chart review was conducted to collect information on PTSD by chart diagnosis, age, gender, race, pain score, medication use (including NSAIDs, synthetic DMARDs, biologics, and opiates), and disease activity measured using the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) when documented by the clinician. Characteristics were compared by PTSD status using t-tests for continuous variables and Fischer's exact test for categorical variables.

Results: Of 136 Veterans with ICD-9 or ICD-10 codes for AS, 113 had a rheumatologist diagnosis for AS and were included in the study. Of 113 Veterans, 20 (18%) had a diagnosis of PTSD. Those with PTSD were significantly younger, with a mean age of 52 ± 17 years as compared to those without PTSD, who had a mean age of 59 ± 14 years (p=0.04); both populations were mostly male and white. BASDAI was recorded for 30% with a mean score of 4.3 ± 2.0 indicating suboptimal control of disease. Those with PTSD had higher mean pain (see Table) and BASDAI scores as compared to those without PTSD, with a difference approaching statistical significance (p=0.06 for both comparisons). Prescribed medications were similar for both groups in regards to synthetic DMARDs, biologics, and opioids, although those with PTSD were significantly more likely to receive NSAIDs (p=0.03).

Conclusion: Veterans with AS and concomitant PTSD are younger and have higher reported pain and disease activity scores compared to those without PTSD in this single site study. The documentation of disease activity by validated instruments such as the BASDAI is recommended in the 2015 Treat to Target guidelines for AS, as higher disease activity is associated with increased mortality. This study underscores the importance of identifying PTSD in patients with AS who report higher pain and disease activity. Future research should include identifying and treating concomitant mental health disorders in Veterans with AS, as other studies have shown improvement in chronic pain with treatment of PTSD.

Table. Characteristics of 113 Veterans with Ankylosing Spondylitis by PTSD diagnosis

Characteristic	Total (n=113) Mean ± SD or (%)	PTSD (n=20) Mean ± SD or (%)	No PTSD (n=93) Mean ± SD or (%)	p-value*
Age, mean years	**58 ± 14**	**52 ± 17**	**59 ± 14**	**0.04**
Male gender	107 (95)	19 (95)	88 (95)	1.00
Race <span"> White	102 (90)	20 (100)	82 (88)	0.21
Pain, mean (0-10)	**3.8 ± 2.8**	**4.9 ± 2.4**	**3.6 ± 2.8**	**0.06**
NSAID, yes	**53 (47)**	**14 (70)**	**39 (42)**	**0.03**
Synthetic DMARD, yes	16 (14)	2 (10)	14 (15)	0.73
Biologic, yes	60 (53)	12 (60)	48 (52)	0.62
Opioid, yes	25 (22)	3 (15)	22 (24)	0.56
BASDAI recorded	35 (31)	6 (30)	29 (31)	1.00
Provider type Attending Fellow	96 (85) 17 (15)	18 (90) 2 (10)	78 (84) 15 (16)	0.73
BASDAI score, mean	**4.3 ± 2.0** **(n=35)**	**5.7 ± 2.7** **(n=6)**	**4.0 ± 1.8** **(n=29)**	**0.06**

*Students' t-test used for continuous variables, chi-2 or Fischer's exact used for categorical variables

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Disclosure: J. Liew, None; **J. L. Williams**, None; **S. Dobscha**, None; **J. Barton**, None.

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Abstract Number: 2738

The Effect of Pregnancy on Disease Activity Outcomes in Psoriatic Arthritis Patients

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Background/Purpose : Psoriatic arthritis(PsA) often affects patients at a childbearing age. The relationship between pregnancy and PsA, in terms of pregnancy outcomes and its effect on disease activity, has not been well studied. The aim of this study is to evaluate the effect of pregnancy on disease activity in PsA

Methods: A retrospective review of files of female patients followed at the Psoriatic arthritis clinic at the Tel Aviv Medical center was performed and patients with at least 1 pregnancy during follow up and one visit during or soon after pregnancy were included in this descriptive study. A thorough review of the files was performed which included the following data: age, disease duration, pattern of PsA, disease activity before during and after pregnancy, record of treatment, including IA injections before and during pregnancy. Postpartum period was defined as up to 1 year after pregnancy. PsA as well as psoriasis activity was defined by treating physician as follow: no disease activity (no active synovitis), mild disease (up to 1 joint involved), moderate to severe disease (more than 2 joints involved). Accordingly, the follow up during and after pregnancy was classified as: improvement, worsening or stable

Results: 13 PsA women and 20 pregnancies were identified. 19 resulted in live healthy babies. The mean age at pregnancy was 31.6 years. Table 1 summarizes the status of disease activity before, throughout pregnancy and during the postpartum period in the whole group. No significant change in disease activity was noticed throughout pregnancy while a significant proportion of patients flared at postpartum Before 12 pregnancies, the patients were treated with TNF α blockers. In 10, the biologic treatment was discontinued close to pregnancy or during the first trimester. In this group, 4 (40%) of patients were classified as mild to severe activity prior to pregnancy. This number increased up to 6 (60%), 7 (70%) and 10 (100%) during the 1st, 2nd trimester and postpartum period respectively. In the 2 patients in whom biologics were not stopped pregnancy, no change in the degree of disease activity was noticed. Interestingly, in the group of non-TNFα treated patients, an improvement in disease activity was observed – the proportion of patients with mild to severe disease activity decreased from 100% close to pregnancy to 71% in the 1st and 2nd trimester and 43% in the 2rd one while an increase to 86% was observed after pregnancy. During 5 pregnancies, corticosteroids were initiated or dosage increased - all in pregnancies where TNF α blockers were stopped before pregnancy. Table 1. Disease activity during pregnancy

No (%)	Before pregnancy	Trimester			Post partum
		1st	2nd	3rd	
No disease activity	7 (37%)	6 (32%)	6 (32%)	8 (42%)	2 (10%)
Mild dis. Activity	4 (21%)	5 (26%)	5 (26%)	5 (26%)	6 (32%)
Moderate to severe dis. Activity	8 (42%)	8 (42%)	8 (42%)	4 (21%)	11 (58%)

Conclusion: Patients with PsA definitively flare after pregnancy. Our results suggest that stopping treatment with TNF α blockers before pregnancy is associated with flare during pregnancy and the postpartum period. It seems that in terms of PsA disease activity, it is recommended to continue treatment with TNF α blockers throughout pregnancy

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Disclosure: M. Berman, None; **D. Paran**, None; **Y. Wolman**, None; **O. Elkayam**, None.

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Abstract Number: 2739

Subclinical Ungueal Distrophy in Patients with Psoriasis without Joint Involvement:

Is There Any Role for Nail Ultrasound?

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Background/Purpose: The joint involvement is observed in approximately 30% of patients with psoriasis (Ps). However, no clinical, lab or by imaging strategy is well established to identify them before progression to psoriatic arthritis (PsA). Purpose: To assess the association among the nail involvement and distal interphalangeal extensor enthesopathy (DIP-ExE), evaluated by ultrasound (US), with the subclinical joint involvement, including arthritis, enthesitis and dactylitis in patients with Ps.

Methods: A total of 89 patients with active Ps were included in this cross-sectional study and were compared with 21 healthy controls, paired for sex, age and ethnicity. After evaluation by a dermatologist, including the PASE and the PEST questionnaires, as well as PASI, BSA and NAPSI, the patients were classified in two groups, according to clinical nail involvement (CNI). Moreover, they were also evaluated by a rheumatologist, regarding enthesitis, dactylitis, axial complaints and peripheral arthritis, in order to apply the CASPAR criteria (2006). A third-blind physician performed a global and complete US evaluation, including 1246 enthesis, synovial thickness in 1958 joints, 1 active skin lesion and 2 bed-nails, according to OMERACT (2010), using the MyLab60® (Esaote, Italy). $P<0.05$ was set as statistically significant.

Results: There was no significant difference concerning time of disease, comorbidities, life habits and PASE in patients with CNI when compared to those no nail distrophy. However, patients with CNI (67.4%) had higher number of tender and swollen joints. The presence of nail power-Doppler (N-PwD) and the DIP-ExE was observed in 65-70% of patients with CNI ($p=0.035$). The nail US identified 58.6% of subclinical nail dystrophy and 70.6% had also positive N-PwD ($p<0.001$).

Conclusion: Our results showed that the nail US was able to identify subclinical nail dystrophy and DIP-ExE in almost 60% of patients with active Ps, but no nail or joint clinical involvement, suggesting that it could be used for early screening of patients with increased risk of developing PsA.

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Abstract Number: 2740

Cam Type Femoroacetabular Impingement Morphology Is More Frequent in Patients with Axial Spondyloarthritis

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Background/Purpose: Femoroacetabular impingement (FAI) is characterized by early pathologic contact of the proximal femur with the acetabulum. Pincer impingement is the acetabular cause of FAI.Whereas cam deformity seen as a flattening of the anterior contour of the head/neck junction or an osseous hump leading a decreased femoral head/neck offset. Patient with FAI presents with a hip or a trochanteric pain usually in the sitting position or during or after activity. It might also be an important cause of hip osteoarthritis (OA). Therefore in this study we evaluated the frequency of cam-type FAI in axial spondyloarthritis (axSpA) patients as a potential alternative cause of hip or trochanteric pain.

Methods: A total 180 patients (107 [59%] male, mean age 41.9 ± 12.8 years) with axSpA according to ASAS criteria and 198 patients (120 [61%] male, mean age 40.5 ± 14.8 years) admitted to the emergency department (mostly due to trauma) and who had pelvic X-ray were included in the study.Patients with hip OA, hip prosthesis, acetabular protrusion or who have radiographs taken improper technique were excluded. An experienced radiologist assessed all anteroposterior pelvic radiographs.

Results: The axSpA group consists 135 ankylosing spondylitis and 45 non-radiographic axSpA patients. The mean duration of symptoms was 13.8 ± 11.3 years in axSpA patients. Radiographic findings of cam abnormality (figure) were significantly more frequent in axSpA patients in comparison with control subjects (30/150 [20%] vs 17/193 [9%] and *P*=0.004). Cam-type radiographic abnormality was only present 2 female control subjects and none of female axSpA patients. FAI was significantly correlated with the presence of HLA-B27 (r=0.213 and *P*=0.048), smoking (r=0.194 and *P*=0.018), height (r=0.283 and *P*=0.001) and gender (r=0.443 and *P*<0.001).

Conclusion: This study for the first time showed that radiographic findings compatible with cam-type FAI were frequent in axSpA patients. In addition to repetitive injury to the proximal femoral physis, new bone formation may be responsible for increased FAI in axSpA. In axSpA patients with hip or trochanteric pain, FAI may be kept in mind as an alternative explanation of the symptoms.

Disclosure: S. Akar, None; **O. Tosun**, None; **D. Solmaz**, None; **G. Karaca**, None; **A. Tosun**, None; **M. Ozman**, None; **F. E. Topal**, None.

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Abstract Number: 2741

Reliability and Construct Validity of the Psoriatic Arthritis Impact of Disease (PsAID) Questionnaire – Independent Validation Study in a UK Cohort

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Background/Purpose: Patient reported outcomes (PROs) have been found to be reliable indicators of baseline status, change during treatment, and are predictive of long-term outcome. A EULAR taskforce developed the PsAID questionnaire as an impact measure of psoriatic arthritis (PsA) for use in clinical trials (PsAID9) and routine practice (PsAID12). We set out to validate the PsAID in an independent prospective cohort.

Methods: Data were collected prospectively for a single-centre cohort of PsA patients between July 2015 and January 2016. Clinical

measures and PROs including the PsAID were completed at baseline and the PsAID was repeated at 1 week. The primary objective was to assess the reliability of the PsAID in stable patients with PsA. Construct validity was assessed through correlation of the PsAID with other PROs including HAQ-DI, EuroQol (EQ-5D), Psoriatic Arthritis Quality of Life questionnaire (PsAQoL), Dermatology Life Quality Index (DLQI), visual analogue scale (VAS) scores for patient global assessment (PtGA), and joint global assessment (JtGA), as well as clinical measures. The influence of sex and disease activity as measured by the modified Composite Psoriatic Disease Activity Index (mCPDAI) was also assessed.

Results: Seventy-six patients (37 males) were recruited to the study. The median age was 56 years (IQR 14.25); 57 patients were treated with biologics, and 13 with conventional DMARDs. The median tender joint count was 2 (IQR 7), median swollen joint count was 0 (IQR 2) and median mCPDAI was 2 (IQR 2). Mean (SD) baseline PsAID12 score was 3.11 (2.29) and at 1 week was 3.06 (2.33). Intraclass correlation coefficient (ICC) was 0.93 (95% CI 0.88-0.96). Mean baseline PsAID9 score was 3.30 (2.38) and at 1 week was 3.22 (2.41) and ICC was 0.93 (95% CI 0.88-0.96). There was a weak floor effect with 37% of scores ≤2 and 8% of scores >7. The PsAID correlated strongly with most PROs (Table 1). There was a significant difference between sexes, with a mean PsAID12 in males of 1.97 (2.12) and in females 4.03 (2.01). When individual components of the PsAID12 were analysed females scored significantly higher in 9 of the 12 items. The correlation between the PsAID12, other PROs and clinical measures was stronger in males than females (Table 1). Out of the patients that fulfilled MDA criteria, only 1 patient had a PSAID12 score >4, the threshold for the patient acceptable symptom state (PASS).

Conclusion: In this cohort, the PsAID questionnaire had excellent test-retest reliability. There was a weak floor effect, likely related to the low disease activity of the cohort as measured by the mCPDAI. There was strong to moderate correlation with clinical and PRO measures providing evidence for the construct validity of the PsAID in this cohort, however females scored significantly higher than males with overall weaker correlation. Prospective data collection is underway to assess sensitivity to change.

TABLE 1: Comparison of the PsAID with PROs and clinical measures (Spearman correlation coefficient)

	PsAID12 (r)	**PsAID9 (r)**	**PsAID12 (r) Females**	**PsAID12 (r) Males**
PsAQoL	0.846	0.835	0.717	0.762
JtGA	0.737	0.762	0.645	0.672
EQ5D	-0.726	-0.731	-0.572	-0.711
PtGA	0.689	0.713	0.525	0.705
HAQ	0.638	0.640	0.478	0.637
mCPDAI	0.560	0.553	0.244	0.616
Tender Joint Count	0.557	0.551	0.268	0.615
Swollen Joint Count	0.476	0.486	0.212	0.466
DLQI	0.101	0.085	0.087	0.347

Disclosure: R. Holland, None; **W. Tillett**, None; **E. Korendowych**, UCB, 5,Abbvie, 5,Janssen Pharmaceutica Product, L.P., 5,Celgene, 5,Novartis Pharmaceutical Corporation, 5; **C. Cavill**, None; **M. Brooke**, None; **N. J. McHugh**, None.

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Abstract Number: 2742

How Are Enthesitis, Dactylitis and Nail Involvement Measured and Reported in Recent Clinical Trials of Psoriatic Arthritis (PsA)? a Systematic Literature Review

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Background/Purpose: Enthesitis, dactylitis and nail involvement are part of the core set of domains to be reported in trials of PsA. However, no specific instruments for these domains are recommended in the core set and cutoffs for reporting (ie how to report state or improvement) are also unclear. We aimed to obtain an overview of the instruments and the respective cutoffs used to report state or improvement, for enthesitis, dactylitis and nail involvement in recent randomised controlled trials (RCTs) in PsA.

Methods: A systematic literature review of RCTs on any pharmacological intervention in patients with PsA was conducted, by searching Medline, Embase and Cochrane datasets for the period 2010-2015 (1). Only published papers and only results of the placebo-controlled phases were analysed. The presence and type of all outcome measures reflecting enthesitis, dactylitis and nail involvement were collected. Cutoffs used for each measure (either as state or change, absolute or relative) were also collected. Analyses were descriptive.

Results: Of 2,278 articles screened, 14 trials met the inclusion criteria: 4 (29%) reported on non-biologic drugs (included targeted synthetic DMARDs, 1 trial), 5 (36%) on anti-TNF, 4 (29%) on other biologic modes of action and there was one strategy trial. The trials included a total of 4,744 patients. Five of the trials (36%) did not report any outcome on any of the 3 domains of interest (Table). Enthesitis and dactylitis outcomes were reported in the remaining 9 trials (64%), while nail involvement was only reported in 3 trials (21%). These three outcomes have been measured in several different ways, none of which having been used in more than 3 trials (21%), and the majority of them was actually employed in only 1 (7%) or 2 (14%) trials (table). Table - Outcome measures used in 14 recent trials in PsA

Extra-articular manifestation	Outcome measure	Level of measurement	N (%)
Any	No extra-articular manifestation reported		5 (36%)
Enthesitis	Absolute change in enthesitis score	Change (mean) in Leeds enthesitis index	2 (14%)
		Change (mean) in MASES	1 (7%)
		Change (median) in tenderness at entheses (comprising the MASES, LEI and tenderness at the plantar fascia)	1 (7%)
	Relative change (%) in enthesitis score	% change in MASES	2 (14%)
	Proportion of patients with enthesitis		2 (14%)
	Proportion of patients with change	% of patients with improvement in ≥1 tendon/ligament	1 (7%)
	Resolution of enthesitis	MASES=0	1 (7%)
		Enthesitis score=0 (range 0-4)	2 (14%)
Dactylitis	Absolute change in dactylitis score	Change (mean) in Dactylitis severity score (0-20)	2 (14%)
		Change (median) in Leeds dactylitis index	1 (7%)
		Change (mean) in Leeds dactylitis index	1 (7%)
	Relative change (%) in dactylitis score	% change in a 0-60 score	3 (21%)
	Proportion of patients with dactylitis		2 (14%)
	Resolution of dactylitis	Dactylitis score=0 (range 0-20)	3 (21%)
Nail involvement	Absolute change in score of nail involvement	Change (mean) in modified Nail Psoriasis Severity Index	2 (14%)
		Change (median) in modified Nail Psoriasis Severity Index	1 (7%)

Conclusion: There is substantial heterogeneity in the measurement of enthesitis, dactylitis and nail involvement in recent clinical trials of PsA. This heterogeneity relates to both the instruments used and the evaluation and interpretation of the results. Harmonization of measures to be used in trials and possibly also practive is desirable to allow for optimal assessment and better comparability of the efficacy of interventions. **References** (1) Ramiro et al, Ann Rheum Dis 2015

Disclosure: S. Ramiro, None; **J. Smolen**, Amgen, Abbvie, Astra-Zeneca, Astro, BMS, Celgene, Glaxo, ILTOO, Janssen, Merck-Serono, MSD, Novartis-Sandoz, Pfizer, Roche-Chugai, Samsung, UCB, 5; **R. Landewé**, Abbott, Amgen, Centocor, Novartis, Pfizer, Rhoche, Schering-Plough, UCB, Wyeth., 2,Robert Landewé is director of Rheumatology Consultancy BV, which is a registered company under Dutch law., 4,Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Celgene, Janssen (formerly Centocor), Galapagos, Glaxo-Smith-Kline, Novartis, Novo-Nordisk, Merck, Pfizer, Rhoche, Schering-Plough, TiGenix, UCB, Wyeth., 5,Abbott/AbbVie, Amgen, Bristol Myers Squibb, Janssen (formerly Centocor), Merck, Pfizer, Rhoche, Schering-Plough, UCB, Wyeth., 9; **D. van der Heijde**, AbbVie, Amgen, Astellas, AstraZeneca, Bristol- Myers Squibb, Boeringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Janssen, Merck, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, 5,Director: Imaging Rheumatology bv, 4; **L. Gossec**, Abbvie, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB, 5.

Abstract Number: 2743

Do Specific Entheseal Points in Spa Patients Impact Patient Reported Outcomes? Implications for Clinical Practice

John Kelsall[1], Pauline Boulos[2], Regan Arendse[3], Michelle Teo[4], Anna Jaroszynska[5], Michael Starr[6], Alexander Tsoukas[7], Emmanouil Rampakakis[8], Eliofotisti Psaradellis[9], Karina Maslova[10], Cathy Tkaczyk[11], Francois Nantel[12], Brendan Osborne[11] and Allen J Lehman[10], [1]Rheumatology, University of British Columbia, Vancouver, BC, Canada, [2]Rheumatology, McMaster University, Hamilton, ON, Canada, [3]University of Saskatchewan, Saskatoon, SK, Canada, [4]Rheumatology, Penticton Regional Hospital, Penticton, BC, Canada, [5]Private practice, Burlington, ON, Canada, [6]Rheumatology, Mcgill University, Pointe-Claire,, QC, Canada, [7]McGill University, Montreal, QC, Canada, [8]JSS Medical Research, St-Laurent, QC, Canada, [9]JSS Medical Research, Montreal, QC, Canada, [10]Janssen Inc., Toronto, ON, Canada, [11]Medical Affairs, Janssen Inc., Toronto, ON, Canada, [12]19 Green belt Dr, Janssen Inc., Toronto, ON, Canada

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Background/Purpose: Previous studies have shown associations between swelling or tenderness of specific joints in RA patients and patient pain. This analysis aimed to describe the impact of enthesitis count and enthesitis profile on functional status (HAQ) and patient global assessment of disease activity (PtGA) among SpA patients treated with anti-TNFs under Canadian routine clinical care.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment with infliximab (IFX) or golimumab (GLM) for RA, AS, or PsA, or with ustekinumab (UST) for PsA. In this analysis, AS and PsA patients treated with IFX between 2005-2016 or GLM between 2010-2016, and PsA patients treated with UST between 2014-2016, were included. Based on enthesitis location 8 groups were created: suprapsinatus, medial epicondyle humerus, lateral epinondyle humerus, greater trochanter, quadriceps patella, achilles, plantar fascia, and patellar-tibia. The impact of specific entheseal points on HAQ, PtGA, and pain (only for PsA) was assessed with the independent-samples t-test; general linear models were used to assess the relative impact of each location on these outcomes.

Results: A total of 503 AS patients and 330 PsA patients with 1669 and 1126 assessments, respectively, were included. At baseline, mean (SD) age was 45.4 (13.0) and 51.0 (12.3) years for AS and PsA patients, respectively, and disease duration was 6.6 (9.6) and 5.4 (7.1) years. In terms of disease activity, mean (SD) ASDAS and BASDAI were 3.5 (1.0) and 6.1 (2.2), respectively, whereas, among PsA patients, DAS28 was 4.3 (1.4). Overall, a weak correlation ($r<0.4$) was observed between enthesitis count and HAQ, PtGA and pain in both AS and PsA patients. Presence of enthesitis at all sites, however, was associated with significantly ($P<0.05$) higher HAQ and PtGA irrespective of SpA type. Upon adjusting for age and gender, among AS patients, enthesitis at supraspinatus, greater trochanter, and achilles were the main predictors of higher HAQ and PtGA whereas enthesitis at plantar fascia was associated with higher HAQ only. Among PsA patients, medial or lateral epicondyle humerus and greater trochanter were the main predictors of increased HAQ and PtGA, while patellar/tibia was associated with significantly HAQ only.

Conclusion: Although enthesitis at all sites was associated with significantly higher HAQ and PtGA, individual sites were differentially associated with these outcomes. In AS, supraspinatus, greater trochanter, and achilles were identified as the main predictors of poor patient outcomes, while, among PsA patients, medial/lateral epicondyle humerus and greater trochanter were the most important sites. These results suggest that, in addition to the presence of enthesitis, location of enthesitis may have an impact on patient reported outcomes.

Disclosure: J. Kelsall, Janssen Inc., 5; **P. Boulos**, Janssen Inc., 5; **R. Arendse**, Paid Consultant of Janssen Inc., Canada, 5; **M. Teo**, None; **A. Jaroszynska**, None; **M. Starr**, Janssen Inc., 5; **A. Tsoukas**, Janssen Inc., 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **K. Maslova**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3.

Abstract Number: 2744

Utilization of the Psoriasis Epidemiology Screening Tool (PEST) Questionnaire to Detect Psoriatic Arthritis in Clinical Practice: Data from the Validation of Psoriatic Arthritis Screening Tool for Korean Psoriasis Patients (VALOR) Study

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Background/Purpose: Several questionnaires have been developed to help identify psoriatic arthritis (PsA) among patients with psoriasis (PsO), but there is no screening tool yet tested through joint efforts by Dermatologists and Rheumatologists in Korea. The PsO Epidemiology Screening Test (PEST) is a simple self-administered questionnaire which has been validated in western countries. Our study aimed to investigate the utility and validation of PEST for screening PsA in Korean PsO patients.

Methods: The PEST, consisted of 5 questions, was translated into Korean and then back-translated to English for comparison. This form was tested on PsO patients visiting the Dermatology clinic at 5 hospitals in urban areas. Patients who checked ‘yes' to 2 or more questions were referred to Rheumatology for further evaluation. Patients meeting the classification criteria for psoriatic arthritis (CASPAR) criteria were confirmed to have PsA.

Results: A total of 191 PsO patients from 5 centers were enrolled. The mean age was 45.1 years, and male/female ratio was 1.27. Of these, 150 patients checked ‘yes’ to 0 or 1 question of PEST questionnaire. Among the 41 patients with PEST $\geq$ 2, 35 patients were eventually assessed by a Rheumatologist. Of these subjects, 17 (48.6%) patients were finally diagnosed as PsA. Compared with PsO only patients, PsA patients had higher rate of female and lower rate of phototherapy history, although statistically insignificant. When comparing the characteristics between PsA and non-PsA among the patients assessed by rheumatologist, patients with PsA showed higher patient’s global assessment, physician’s global assessment, and Routine Assessments of Patient Index Data 3 (RAPID3) score than those without PsA. Six patients of the 17 PsA patients (35.3%) had radiographic evidence of sacroilitis. Among PsA patients, the proportion of patients with PEST score of 2 was 47% (8/17). The overall specificity of PEST at a cut-point of 2 was 89.3%. Using the known PEST cut-off score of 3, its specificity increased to 94.0%, but sensitivity dropped to 52.9%.

Conclusion: This study supports that the Korean version of PEST is a convenient tool for screening PsA, and the PEST score of 2 points would be a favorable cut-off value for screening Korean PsO patients. However, its performance and utility in our region need to be further investigated.

- References

1. Ibrahim GH, Buch MH, Lawson C, Waxman R, Helliwell PS. Evaluation of an existing screening tool for psoriatic arthritis in people with psoriasis and the development of a new instrument: the Psoriasis Epidemiology Screening Tool (PEST) questionnaire. Clin Exp Rheumatol. 2009;27:469-74

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Abstract Number: 2745

Adult Axial Spondyloarthritis Screening and Referral Practices Amongst Primary Care Physicians, Physiotherapists, Chiropractors and Nurse Practitioners: Results from a Qualitative Study

Laura Passalent[1,2], Leslie Soever[2,3], Kathleen Bednis[1], Christopher Hawke[1,4], Andrew Bidos[5,6], Jeff Bloom[7,8], Y. Raja Rampersaud[6,8], Nigil Haroon[9,10] and Robert D Inman[8,9], [1]Allied Health, Toronto Western Hospital, Toronto, ON, Canada, [2]Physical Therapy, University of Toronto, Toronto, ON, Canada, [3]MSK, Geriatrics and Cardiac Rehab Programs, University Health Network, Toronto, ON, Canada, [4]Department of Physical Therapy, University of Toronto, Toronto, ON, Canada, [5]Health Quality Programs - ISAEC, University Health Network, Toronto, ON, Canada, [6]Orthopaedics, Toronto Western Hospital, Toronto, ON, Canada, [7]Family Medicine, Toronto Western Hospital, Toronto, ON, Canada, [8]University of Toronto, Toronto, ON, Canada, [9]Rheumatology, Toronto Western Hospital, University of Toronto, Spondylitis Clinic, Toronto, ON, Canada, [10]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada

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Background/Purpose: For the axial spondyloarthritis (SpA) population, early recognition is crucial in preventing major morbidity. Despite this, there exists an unacceptably long delay between the onset of symptoms and diagnosis, with an average wait time of 8 years between the commencement of back pain and time when patients are diagnosed by a rheumatologist. Compounding this issue is the uncertainty that exists with respect to initial screening and referral practices amongst primary care practitioners for adults with suspected axial SpA. The purpose of this study was to explore the screening and referral practices for suspected axial SpA in adults with chronic back pain amongst primary care physicians (PCPs), physiotherapists (PTs), chiropractors (DCs) and nurse practitioners (NPs) working in community practice in the province of Ontario, Canada.

Methods: Semi-structured key informant (KI) interviews were conducted with PCPs, PTs, DCs and NPs working in community practice. Interviews were conducted with KIs to address: 1) screening practices for axial SpA; and 2) referral practices for adults with suspected axial SpA. Interviews were conducted in-person or over the telephone. All interviews were recorded and transcribed verbatim. Interview transcripts were analyzed using a compare and contrast analysis by coding groups of words that addressed the research objectives. Two members of the research team undertook this exercise independent of each other and then met to reconcile an understanding of emergent themes. Groups of words with similar meaning were organized into themes. The themes were organized into two main categories: Screening Practices and Referral Practices. NVIVO V9 was used to assist with organization of codes.

Results: A total of 17 interviews were conducted: PCPs (5); PTs (3); DCs (6) and NPs (3). Practice locations for KIs were primarily urban (14 urban; 3 rural). Mean years of practice of key informants was 9.3 years (range, 1-22 years). Overall, 3 themes were identified related to Screening Practices for axial SpA: 1) knowledge of clinical manifestations of axial SpA; 2) role of investigations in early diagnosis, and 3) lack of awareness of assessment guidelines and screening tools. Themes related to Referral Practices included: 1) optimization of technology; 2) referral barriers, and 3) legislative hurdles.

Conclusion: Most primary care practitioners had a general understanding of the clinical manifestations of axial SpA; however, knowledge deficits existed related to rare clinical presentations and the role of investigations in early identification of the disease. With respect to referral practices, there are opportunities to address system-level barriers, including more extensive use of technology (e.g. use of online consultations and electronic referral templates). Our research has identified a number of opportunities for implementation of quality improvement initiatives and indication for collaboration with policy makers and other stakeholders, including patients. These results may be incorporated into a wider research initiative to gain better insight into primary care screening and referral practices for

adults with suspected axial SpA.

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Abstract Number: 2746

Comparing Prevalence of Comorbidities in Patients with Psoriatic Arthritis By Biologic Therapy

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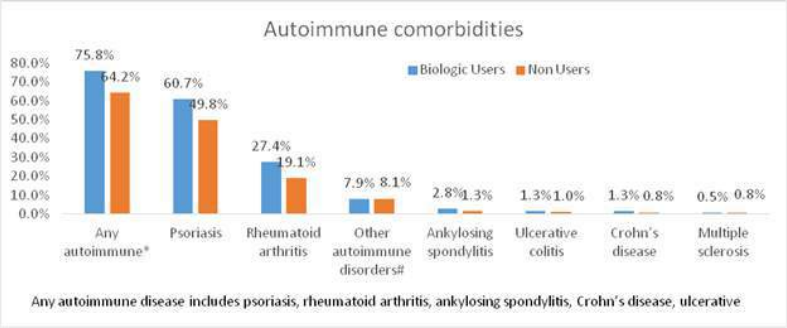
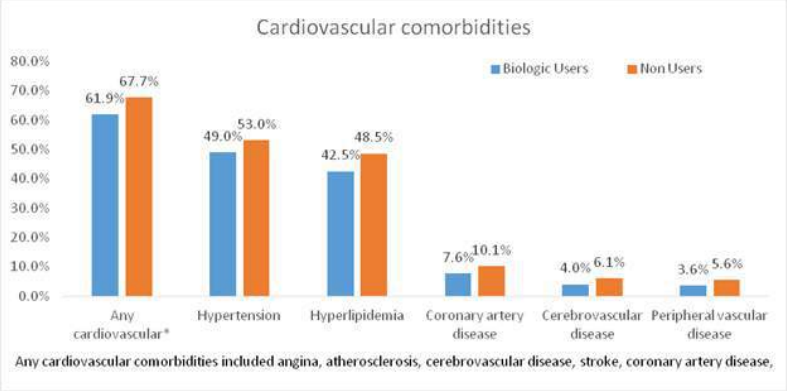
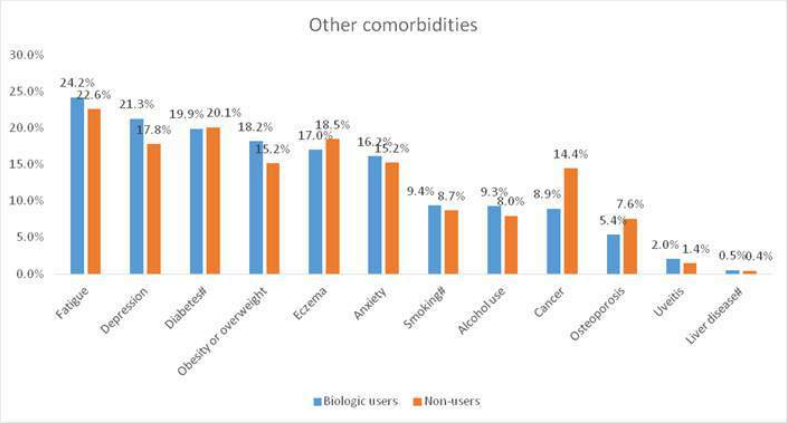
Background/Purpose: Psoriatic Arthritis (PsA) are known to be at higher risk for numerous comorbid conditions. This study looks at the impact of biologic therapy by comparing comorbidities between PsA patients who have biologic therapy versus those who do not, using a large national claims database in the US.

Methods: Adults with ≥1 inpatient or 2 outpatient diagnoses of PsA (ICD-9-CM 696.0) in 1/1/2008 - 9/30/2015 were extracted from the MarketScan Commercial and Medicare Databases. Biologic users had ≥1 biologic claim on or after the first observed PsA diagnosis, and the index date was the first biologic claim date. Non-biologic users had no biologic claim anytime during the study period. Their index date was randomly assigned based on the distribution of the index dates of biologic users. All patients were required to have ≥12 months continuous enrollment prior to index date and were followed for ≥12 months until the earliest of inpatient death, end of continuous enrollment, or end of the data. The prevalence of comorbidities during the follow-up period was examined.

Results: A total of 9,369 biologic users and 11,774 non-users met the study criteria (mean age: 49.8 years for users vs. 55.1 for non-users; male: 45.8% vs. 43.8%; mean length of follow up: 3.0 vs. 3.0 years; mean Charlson comorbidity index: 0.6 vs. 0.8). Compared with non-users, biologic users had significantly higher rates of autoimmune disease, fatigue, depression, obesity or overweight, anxiety, alcohol use, and uveitis, but significantly lower rates of cardiovascular disease, eczema, cancer, and osteoporosis (Figure 1, $p<0.05$ in all cases). Figure 1. Prevalence Rates of Comorbidities in PsA Patients, by Biologic Therapy







not significant (p>0.05).

Conclusion: PsA patients treated with biologics had higher rates of certain comorbidities, such as autoimmune diseases, fatigue, depression, obesity/overweight, and uveitis than those not on biologic therapy and lower rates of cardiovascular conditions, eczema, cancer, and osteoporosis. These results suggest use of biologics have an association with rates of certain comorbidities. Further studies looking at this topic could have an impact in treatment practice.

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Abstract Number: 2747

Dapsa-28 May be Used Instead of Dapsa-66/68 in Psoriatic Arthritis

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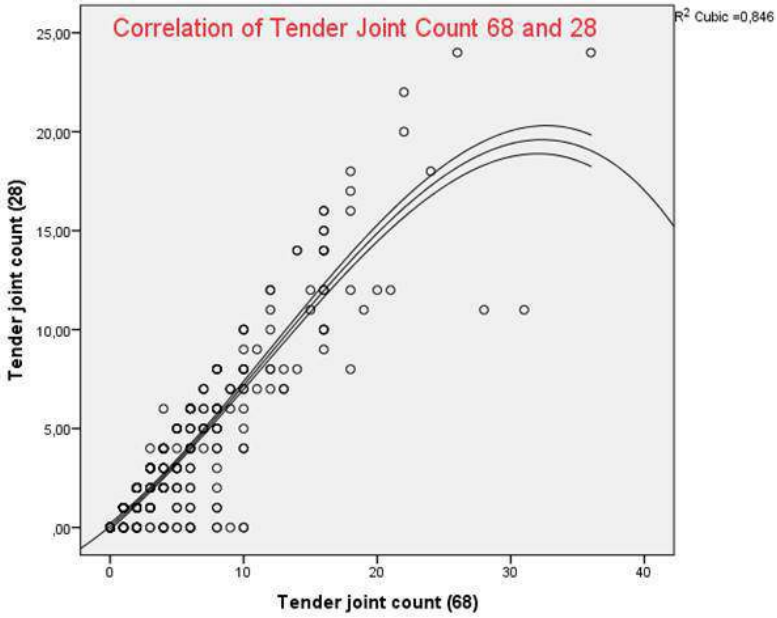
Background/Purpose: Disease Activity index for Psoriatic Arthritis (DAPSA) originally developed from patients with reactive arthritis and validated in psoriatic arthritis (PsA) patients. DAPSA includes swollen joint count (SJC) (66 joint), tender joint count (TJC) (68 joint), CRP (mg/dl), patient global assessment and pain. Although, assessment of 66/68 joints give more information, 28 joint assessment is more feasible, and frequently used in rheumatoid arthritis trials. Objective of this study was to assess correlation of DAPSA 28 joints with DAPSA 66/68 joints in a multicenter PsA registry.

Methods: PsART (Psoriatic Arthritis Registry of Turkey) is a national, web-based registry, including 1081 PsA patients. Overall, 601 patients had complete information about DAPSA score. All affected joints were recorded separately. Original DAPSA calculated to sum of CRP (mg/dl), pain VAS (cm), patient's global assessment of disease activity VAS (cm), SJC (66 joints), and TJC (68 joints). We calculated both 28 TJC/SJC (called DAPSA-28) and 66/68 joints for DAPSA. Spearman correlation was used for statistical analysis.

Results: 396 of 601 (65.9%) were female, mean age was 46.5 (12.6) years, mean PsA duration was 5.4 (6.6) years. Mean DAPSA 66/68 score was 14.5 (13.3) and DAPSA 28 score was 12.9 (9.7). Correlation of DAPSA 66/68 and DAPSA 28 was 0.97. Correlation of SJC 28 and SJC 66 was 0.83 and correlation of TJC 28 and TJC 68 was 0.88. Correlation of TJC 28 and 68 were shown in figure 1. 374 of 601 (62.2%) patients at least one active joint according to 66/68 joint assessment. When we consider those group, correlation coefficients were slightly unfavorable in TJC and SJC (SJC 28 vs 66 r=0.78, TJC 28 vs TJC 68 r=0.78), however almost identical in their DAPSA scores (DAPSA 28 vs DAPSA 66/68 r=0.94). Patients with swollen MTF, ankle and DIF joints were 41 (6.8%), 67 (11.1%), and 60 (10.0%), respectively. By doing a 28 joint count, 47 (7.8%) were missed compared to 66/68 joint count due to the DIP, MTF and ankles being the only site of arthritis.

Conclusion: DAPSA domains are almost universal for all kind of inflammatory arthritis. Simple sum of those domains seem valid and feasible in PsA patients. Although assessment of 66/68 joints is rationalized particularly for patients with distal interphalangeal and foot arthritis, our study showed that there was no added value of using 66/68 joints in the real life setting. On the other hand, almost 8% of patients did not capture when assess only 28 joints.



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Abstract Number: 2748

Prevalence of Comorbidities in Patients with Axial Spondyloarthritis and Its Association with Aspects of the Disease

Maria Celeste Orozco[1], Ana Lizarraga[2], Graciela Betancur[2], Natalia Zamora[1], Fernando Andres Sommerfleck[3], Emilce Schneeberger[4] and Gustavo Citera[4], [1]Rheumatology, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [2]Reumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [3]Rheumatologia, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina, [4]Rheumatology Section, Instituto de Rehabilitación Psicofísica, Buenos Aires, Argentina
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Background/Purpose: The presence of comorbidities in patients with rheumatic diseases affects functional capacity and quality of life, but also they can limit the therapeutic approach of the disease. Our purpose was to analyze the frequency of comorbidities in patients with Axial Spondyloarthritis (axSpA) and to assess their influence on different aspects of the disease.

Methods: Patients ≥18 years old diagnosed with axSpA (mNY 1987 and/or ASAS 2009 criteria) belonging to ESPAXIA (Estudio de Espondiloartritis Axial IREP Argentina) cohort were included. Demographic data, disease duration, and current treatment were collected. Pain, patient global assessment (VAS), disease activity (BASDAI), functional capacity (BASFI), enthesitis (MASES), axial mobility (BASMI), quality of life (ASQoL) and radiological damage (mSASSS) were assessed. The presence of comorbidities was evaluated and the Charlson comorbidity index was calculated.

Results: 204 patients were included, 74% were male, median age 46 years (IQR 35-57) and median disease duration 19 years (IQR 9-29). Seventy-three patients (35.8%) had at least one comorbidity, being the most common: cardiovascular (40.7%), gastrointestinal (38.7%), endocrine (16.2%), hepatobiliary (11.3%) and respiratory disease (9.3%). Patients with comorbidities were significantly older (56.9±13.6 yrs vs 41.4±12.1 yrs p= 0.0001) and had longer disease duration (26.9±14.4 yrs vs 16.8±11.2 yrs, p= 0.0001). After adjusting for these confounders, patients with comorbidities had worse functional capacity (mean BASFI 4.8± 2.9 vs 3.3± 2.8, p = 0.0001), lower quality of life (mean ASQoL 7.4±5.6 vs 5.8± 5.1, p= 0.02) and higher radiological damage (mean mSASSS 40.4±25.2 vs 20.4±21.7, p = 0.001). In multiple regression analysis, the presence of comorbidities remained significantly associated with worse functional capacity and quality of life. When we divide patients according to the number of comorbidities; 49 (24%) had one comorbidity, 18 (8.8%) two comorbidities and 6 (2.9%) three or more comorbidities, however, the number of comorbidities did not modify our findings.

Conclusion: 35.8% of patients with axSpA presented comorbidities and that was associated with worse functional capacity, poor quality of life and greater radiographic damage, regardless of the number of comorbidities present.

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Abstract Number: 2749

Characteristics of Ankylosing Spondylitis Patients with Primary and Secondary Lack of Efficacy to TNF-Inhibitor Treatments

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Background/Purpose: Anti-TNFi agents are effective in the treatment of active AS. Based on the available data, nearly 20% of the AS patients needed to switch their anti-TNF medications to another TNFi agent because of the lack of efficacy (LOE). The reasons underlying the LOE is still remain largely unexplained. Herein we have investigated the characteristics of AS patients who have primary and secondary LOE to TNFi.

Methods: Adult AS patients registered in the axial SpA database who received TNFi treatments were identified. Based on the response to TNFi treatments, these patients were then classified into three groups: primary LOE, secondary LOE and responders. Patients were defined as primary LOE if the first TNFi was stopped within 6 months after start and secondary LOE if the first TNFi was discontinued after a 6-month period. On the other hand, patients who responded to their first TNFi for > 12 mos and currently on same TNFi at the time of last visit were defined as responders. Clinical, demographic and laboratory data were collected and analyzed.

Results: There were a total of 221 patients stratified as follows: primary LOE=51, secondary LOE=83 and responders=87. The mean age and disease duration of the study group patients were 37.4±12.4 and 14.8±10.4 years respectively. 72.4% of the total group was male and B27 positivity was 77.8%. The mean follow-up duration of the responders was 53.4±35.4 months. Comparison of three groups showed that age and disease duration were significantly lower in the primary LOE group compared to secondary LOE ($p<0.05$; 41.9±12.1 vs. 34.7±12.1 and 17±12.3 vs. 12.8±8.9 respectively). Among the clinical variables, the arthritis frequency was significantly lower in the responders group compared to both primary and secondary LOE patients ($p<0.05$; 42.5% vs. 60.8 and 72.3 respectively). The other variables including sex, B27 status, baseline BASDAI, BASFI and CRP, frequency of hip involvement, iritis, enthesitis, dactylitis, psoriasis, IBD and family history of SpA did not differ between the groups. Table 1 represents the characteristics of the three groups. Regression analysis showed that the predictors for primary LOE were increased age and presence of arthritis ($p<0.05$; OR=1.1 and 2.3 respectively). On the other hand negative B27 and arthritis were the predictors for the secondary LOE ($p<0.05$; OR=2.4 and 4 respectively). When we considered TNFi failures collectively the predictors for the non-response found to be the negative B27 and presence of arthritis ($p<0.05$; OR=2.1 and 3.3 respectively).

Conclusion: The results of our study from a longitudinal observational cohort of axial SpA patients indicates that only 39.4% (87/221) of the AS patients were considered sustained responders to TNFi. Our analysis suggests that the most important predictors for lack of response in AS patients were a negative B27 and presence of arthritis. **Table 1:**Clinical and demographical characteristics of the study group

	Primary LOE (n=51)	Secondary LOE (n=83)	Responders (n=87)	p value
Age, yr	41.9±12.1	34.7±12.1	37.6±12.1	0.04
Males, %	74.5	69.9	73.6	0.8
Disease duration, yr	17±12.3	12.8±8.9	15.4±10.2	0.04
HLA-B27 positivity, %	72.5	74.7	83.9	0.21
Iritis, %	31.4	34.9	28.7	0.68
Arthritis, %	60.8	72.3	42.5	<0.0001
Psoriasis, %	23.5	9.6	13.8	0.08
IBD, %	13.7	21.7	9.2	0.07
Dactylitis, %	0	4.8	1.1	0.13
Enthesitis, %	52.9	49.4	42.5	0.45
Increased acute phase reactants, %	40	51.9	50.6	0.38
Family history for SpA, %	19.6	18.1	24.1	0.6
Hip involvement, %	15.7	13.3	5.7	0.13
Baseline BASDAI	6.3±1.4	6.4±2	5.9±2	0.36
Baseline BASFI	6.2±2.1	5.5±2.7	4.9±2.5	0.09
Smoking ever, %	7.8	16.9	18.4	0.53

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Concordance Between Patient and Physician Global Assessment of the Disease in Patients with Psoriatic Arthritis

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Background/Purpose: In Rheumatoid Arthritis it has been observed a significant discrepancy in the global assessment of the disease by the patient and physician and this was not extensively evaluated in patients with Psoriatic Arthritis (PsA). The purpose of our study was to evaluate the agreement and the variables that influence global disease assessment by the patient (PGA) and physician (PhGA) in patients with PsA

Methods: Patients with PsA according to CASPAR criteria ≥ 18 years, belonging to RAPSODIA (Registro de Artritis Psoriática IREP, Argentina) cohort were included. Demographic data, clinical features and treatment received were recorded. Peripheral joint assessment was performed by counting 66/68 swollen/tender joints and the following indexes were calculated DAS28, DAPSA, CPDAI and MDA. Cutaneous involvement was evaluated by PASI. Morning stiffness, pain and global assessment of disease activity by the patient and physician were assessed using visual analogue scale (VAS 0-10cm). Patients completed BASDAI, HAQ, BASFI, ASQoL and PsAQoL questionnaires.

Results: 110 patients were included, 56 males (50.9%), with a median age of 55 years (IQR 45-63) and median disease duration of 10 years (IQR 6-17). Pain *m* 5 cm (IQR 2.6-7), PGA *m* 4.25 cm (IQR 2.13-7) and PhGA *m* 3 cm (IQR 1.13-5). The PGA had very good correlation with pain (Rho= 0.76), BASFI (Rho= 0.7) and BASDAI (Rho= 0.7) and acceptable with PsAQoL (Rho= 0.56), and had no correlation with the number of swollen and tender joints (Rho: 0.04 and 0.05, respectively). By contrast, the PhGA had a good correlation with pain (Rho= 0.65), BASDAI (Rho= 0.62) and PGA (Rho= 0.64), acceptable with BASFI (Rho= 0.59), number of swollen joints (Rho= 0.52), number of tender joints (Rho: 0.41) and PsAQoL (Rho= 0.43) and low correlation with PASI (Rho= 0.21). In two multiple linear regression analysis, using PhGA and PGA as dependent variables, pain was the main variable that was significantly associated with both of them (βcoef: 0.529, $p<0.001$ and βcoef: 0.481, $p= 0.002$, respectively). Taking Minimal Disease Activity (MDA) as a measure of ideal state, we performed a logistic regression analysis, considering MDA as a dependent variable. PGA had a greater association as compared to the physician's global assessment [OR: 0.61 (95%CI: 0.42-0.89), $p= 0.01$ vs 0.49 (95%CI: 0.29-0.87), $p= 0.02$]

Conclusion: The evaluation of the global assessment of disease activity in PsA by the patient and physician showed good correlation. Pain was the variable most strongly influenced both assessments. The evaluation of the disease by the patient had more association with MDA.

Disclosure: J. Gallino Yanzi, None; **O. L. Cerda**, None; **M. Landi**, None; **C. Zaffarana**, None; **E. Schneeberger**, None; **G. Citera**, None.

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Abstract Number: 2751

Gender and Disease Duration Are Associated with Extra-Articular Manifestations in Axial Spondyloarthropathy

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Background/Purpose: The Ankylosing Spondylitis Registry of Ireland (ASRI) was established in 2013. The objectives of ASRI are to provide descriptive epidemiological data on the axial spondyloarthropathy (axSpA) population in Ireland and to establish a registry for potential future studies of genetics, aetiology and therapeutics. Extra-articular manifestations (EAM), comprising uveitis, psoriasis and inflammatory bowel disease (IBD), commonly occur in axSpA and contribute to the burden of disease. They may also impact choice of treatment. Knowledge regarding the characteristics associated with EAM is limited. The aim of this study is to evaluate the prevalence of EAM in a well characterised axSpA patient cohort, in particular identifying differences in early versus late disease and associated characteristics.

Methods: A standardised detailed clinical assessment is performed on each patient and entered in a database. Disease activity is assessed by Bath AS Disease Activity Index (BASDAI), spinal mobility by Bath AS Metrology Index (BASMI), function by the Bath AS Functional Index (BASFI) and Health Assessment Questionnaire (HAQ) and quality of life by AS Quality of Life (ASQoL). Structured interviews provide patient-reported data, which include the presence of EAM. Statistical analysis is performed using SPSS.

Results: As of June 2016, 564 patients have been entered into the database: 78.2% (n=441) males, mean age 47.1 (SD 12.4), mean disease duration 20.8 years (SD 12.2), mean delay to diagnosis of 8.6 years (SD 7.97), 78% fulfil modified New York criteria. Mean BASDAI is 3.9 (SD2.4), BASFI 3.7 (SD2.6), BASMI 3.2 (SD 2.5), HAQ 0.55 (SD 0.52) and ASQoL 6.4 (SD 5.5). When stratified by disease duration, 23.9% have early disease (less than 10 years). The prevalence of uveitis is 35.5%, psoriasis is 17.8% and IBD is 9.7%. Prevalence of uveitis is significantly higher in women (46.7% versus 32.3%, p=0.003), late disease (39.8% versus 21.7%, p<0.001) and presence of peripheral arthritis (42.4% versus 30.9%, p=0.007). There is a trend towards more prevalent uveitis in non-smokers (40.1%) compared to current (28.3%) or past (35.8%) smokers (p=0.06). The prevalence of IBD is significantly higher in women (16.5% versus 7.7%, p=0.004), patients with elevated CRP at baseline (11.9% versus 5.8%, p=0.045), peptic ulcer disease (21.7% versus 8.6%, p=0.004) and osteoporosis (23.5% versus 8.8%, p=0.005). The prevalence of IBD is not affected by disease duration or smoking status. The prevalence of psoriasis is not affected by early versus late disease, gender or smoking. HLA-B27 status and measures of disease severity have no impact on the presence of any EAM. In regression analysis, being female and disease duration > 10 years are predictive of uveitis. Female gender, elevated CRP at baseline and peptic ulcer disease are predictive of IBD.

Conclusion: EAM are common in this axSpA population. Thirty-six percent of the population have uveitis and 18% have psoriasis. Female gender and late disease predict uveitis. It is important to regularly screen for EAM. Predictive factors may guide screening.

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Abstract Number: 2752

Depression Is Associated with Worse Outcomes in Axial Spondyloarthropathy Population

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Background/Purpose: The association of depression with poor health outcomes in rheumatic diseases such as rheumatoid arthritis is well established. However, the impact of depression on disease outcomes in axial spondyloarthropathy (axSpA) is less well defined. The Ankylosing Spondylitis Registry of Ireland (ASRI) was established in 2013. The objectives of ASRI are to provide descriptive epidemiological data on the axSpA population in Ireland and to establish a registry for potential future studies of genetics, aetiology and therapeutics. The aim of this study is to determine the prevalence of depression in a well characterised axSpA cohort and explore relationships.

Methods: A standardised detailed clinical assessment is performed on each patient and entered in a database. Disease activity is assessed by Bath AS Disease Activity Index (BASDAI), spinal mobility by Bath AS Metrology Index (BASMI), function by the Bath AS Functional Index (BASFI) and Health Assessment Questionnaire (HAQ) and quality of life by AS Quality of Life (ASQoL). Structured interviews provide patient-reported data, including the presence of physician-diagnosed depression. Statistical analysis was performed using SPSS.

Results: As of June 2016, 564 patients have been entered into the database: 78.2% (n=441) males, mean age 47.1 (SD 12.4), mean disease duration 20.8 years (SD 12.2), mean delay to diagnosis of 8.6 years (SD 7.97), early disease (<10 years) 23.9%, 78% fulfil modified New York criteria. Mean BASDAI is 3.9 (SD2.4), BASFI 3.7 (SD2.6), BASMI 3.2 (SD 2.5), HAQ 0.55 (SD 0.52) and ASQoL 6.4 (SD 5.5). Prevalence of depression is 11.9%, with no significant difference between genders. The prevalence of depression is higher in patients with peptic ulcer disease (25.5% versus 10.6%, p=0.002), late disease (68% versus 13.5%, p=0.042) and current smokers (16.6% versus 10%, p=0.032). The mean delay to diagnosis was higher in patients with depression than without depression (10.9 ± 8.9 versus 8.3 ± 7.9 years, p=0.02). There is a trend towards a higher prevalence of depression in patients with diabetes (23.1% versus 11.3%, p=0.071). There is no association between depression and BASDAI, BASMI or BASFI. Patients with depression have higher mean ASQoL (9.7 ± 5.6 versus 5.9 ± 5.3, p<0.001) and HAQ scores (0.79 ± 0.57 versus 0.51 ± 0.51, p<0.001). In multiple regression analysis, peptic ulcer disease and ASQoL remained significantly associated with depression, with a trend towards association with current smoking.

Conclusion: Twelve percent of this axSpA population have depression. Presence of depression is associated with worse quality of life and function. However, there is no association between depression and advanced structural disease. AxSpA patients should be actively screened for depression.

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Abstract Number: 2753

Characteristic and Outcomes of Psoriatic Arthritis Patients with Hyperuricemia, Whether We Should Treat or Not?

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Background/Purpose: To determine the characteristics of psoriatic arthritis patients(PsA) with hyperuricemia(HUC)and their outcomes especially cardiovascular(CVS) and kidney diseases.

Methods: Patients have been followed prospectively at the PsA clinic according to a standard protocol at 6-12 month intervals. We identified PsA patients with at least one visit of HUC(cases) and matched to PsA patients with normal uric acid (NUC, control) based on gender and age +/-5yrs). We defined HUC in Male> 450 mumol/L or Female > 360 mumol/L. Information collected include: demographics, education, employment history, lifestyle habits, medical history including co morbidities, medication use (all collected prospectively and stored in the clinic database). Outcomes of HUC patients especially CVS and kidney diseases after follow-up were recorded. Conditional logistic regression was performed to determine factors independent associated with HUC in PsA patients.

Results: 325 (31.9%) out of 1019 PsA patients had HUC. 318 cases were matched to 318 controls.

Table1: characteristic of PsA patients at baseline

Covariate	NUC (n=318)	HUC (n=318)	p-value
Psoriasis duration n(%)	20 (14.5)	23.7 (14.1)	**0.0016**
PsA duration n(%)	8.4 (8.6)	13.9 (11.9)	**0.001**
Hypertension n(%)	77 (24)	141 (44)	**0.001**
Anginan(%)	2 (1)	10 (3)	**0.037**
Cardiomyopathy n(%)	1 (0)	1 (0)	1
Myocardial infarction n(%)	1 (0)	4 (1)	0.37
Congestive heart failure n(%)	0 (0)	4 (1)	0.12
High creatinine n(%)	6 (2)	26 (8)	**0.001**
Renal stones n(%)	9 (3)	28 (9)	**0.0019**
Diabetes n(%)	25 (8)	48 (15)	**0.0042**
Swollen joints count(SJC) mean (SD)	0.4 (1.4)	0.6 (1.9)	0.21
Tender joints count(SJC)mean (SD)	2.8 (6.8)	3 (6.3)	0.76
PASI n(%)	3.3 (5.4)	4.7 (7.3)	**0.0062**
Hypercholesterolemia n(%)	54 (20)	60 (20)	1
Hypertriglyceridemia n(%)	14 (5)	13 (4)	0.7
High Alanine transaminase (ALT) n(%)	23(9)	34(18)	0.01
High Aspartate transaminase (AST) n(%)	40(14)	70(22)	0.01
Body mass index mean (SD)	28.5 (6.5)	31.7 (5.7)	**0.001**

PASI: Psoriasis Area and Severity Index score

HUC patients had longer disease duration and higher PASI than NUC patients. They had more concurrent co-morbidities including CVS diseases (hypertension and angina) and metabolic co-morbidities such as diabetes and obesity, as well as higher prevalence of kidney stones and higher serum creatinine. Only one patient with HUC was treated with allopurinol at first elevation visit and seven patients during follow-up. Over the follow-up, HUC patients developed more CVS diseases and metabolic changes especially diabetes and hypercholesterolemia. No differences in kidney disease on follow- up were noted between HUC and NUC groups.98(30.8%) of HUC patients had persistent hyperuricemia for more than 2 visits. Multivariate analysis showed an association between hyperuricemia and PsA disease duration, BMI, and high liver function test.

Conclusion: Hyperuricemia is common in PsA patients especially in those with longer disease duration and obesity. Since CVS disease is increased among HUC PsA patients, proper control of serum uric acid and metabolic diseases may play a preventive role in improving PsA outcomes.

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Abstract Number: 2754

Self-Reported Physical Activity Questionnaire in Axial Spondyloarthritis: Modification of the Squash

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Background/Purpose: Improvement of physical function and physical activity are important goals in the management of axial spondyloarthritis (axSpA). Although physical function is included in the ASAS/OMERACT core domains for axSpA, a physical activity measurement tool specific for axSpA has not been developed. The Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) is a validated questionnaire that measures the duration, frequency, and intensity of physical activity in five domains (i.e. commute, work, household, recreation and sports). Our objective was to explore the opinion of axSpA patients and experts towards the content and adaptation requirements of the SQUASH in order to develop a disease-specific SQUASH.

Methods: A qualitative study design based on a stepwise approach was used. First, semi-structured, in-depth interviews were performed with 9 professional axSpA experts (e.g. rheumatologists, rehabilitations specialists, physiotherapists) concerning the SQUASH domains and items in relation to the axSpA. Second, a structured focus group concerning the SQUASH domains and items was performed with 8 axSpA patients (7 AS and 1 nr-axSpA) from the GLAS cohort and suggestions for possible adaptations were discussed. Data were recorded, transcribed, and analyzed using an objective thematic strategy. Finally, the SQUASH was adapted based on adaptations suggested by ≥5 experts and ≥5 patients.

Results: The SQUASH was found to be relevant and easy to complete. The experts and patients suggested 33 adaptations of which 16 were implemented. The most important adaptations were: explanation of intensity concepts (e.g. increased heart rate, sweating), changing intensity concepts, standardization of frequency across the entire questionnaire, and adding more specific options to the domains (e.g. exercise therapy, other transportation goals) (Table 1).

Conclusion: The original SQUASH was modified to a more standardized questionnaire in collaboration with both patients and experts to measure physical activity in axSpA. The next step will be to assess the construct validity and the test-retest reliability of this axSpA-specific SQUASH. **Table 1.**Domains, subdomains, activities, frequency, duration, and intensity concepts included in the modified SQUASH.

Domains	Subdomains	Activities	Frequency and duration	Intensity concepts*
Transport	Commuting activities	Walking, cycling	Days/wk, time/day (hrs, min)	Slow/light, moderate, fast/heavy
	Other returning transportation activities	Walking, cycling	Days/wk, time/day (hrs, min)	Slow/light, moderate, fast/heavy
Activities at work or school	Less heavy work	e.g. sitting/standing with some walking	Days/wk, time/day (hrs, min)	-
	Heavy work	e.g. regularly lifting heavy objects	Days/wk, time/day (hrs, min)	-
Household activities	Less heavy work	e.g. cooking, washing, ironing, childcare	Days/wk, time/day (hrs, min)	-
	Heavy work	e.g. scrubbing floors, walking with heavy shopping bags	Days/wk, time/day (hrs, min)	-
Leisure time activities		Walking (recreation), cycling (recreation), gardening, odd jobs	Days/wk, time/day (hrs, min)	Slow/light, moderate, fast/heavy
Sports		To fill in by yourself (e.g. tennis, fitness, skating, swimming, dancing, exercise therapy)	Days/wk, time/day (hrs, min)	Slow/light, moderate, fast/heavy
***Slow/light** refers to a physical activity in which the participant does not experience increased heart rate or increased respiratory rate. **Moderate** refers to a physical activity in which the participant experiences slightly increased heart rate and slightly increased respiratory rate. **Fast/heavy** refers to a physical activity in which the participant sweat, experiences accelerated heart rate, and accelerated respiratory rate.				

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Abstract Number: 2755

Comparison of Clinical Profile of Geriatric and Non-Geriatric Ankylosing Spondylitis (AS) Patients

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Background/Purpose: Data on disease characteristics of geriatric patients (>=65 years) with AS are lacking. The objective of this study is to compare: 1) the clinical profile of geriatric and non-geriatric patients with AS and 2) geriatric AS patients with aged-matched non-AS comparators.

Methods: Data were extracted from a Toronto based longitudinal SpA cohort. Patients with AS were divided by current age into geriatric (age >= 65 years) and non-geriatric (age < 65 years) groups. Clinical and laboratory data were then compared. Data for the non-AS geriatric age-matched control group was obtained from a Toronto tertiary care orthopedics clinic.

Results: There were 48 geriatric AS patients out of 890 AS patients in the clinic (table 1). 322 knee OA patients were included for the non-AS geriatric comparison (table 2). Initial comparison (young vs geriatric AS), showed no differences in sex distribution. Age at time of diagnosis was higher in the geriatric AS patients ($p<0.001$). In terms of clinical activity, there was no difference in mean inflammatory markers or BASDAI scores. Extra-articular manifestations were similar. There was no significant difference between the 2 groups regarding the usage of NSAIDs, DMARDS, corticosteroids and biologics, nor in their side-effects. Only 1% of the geriatric group started biologic therapy at age >=65 yr. Infection frequency was similar between the two groups. Mobility (BASMI) and function (BASFI) scores were higher in the geriatric group ($p<0.001$ and 0.04 respectively). The geriatric group were more likely to have a history of physical trauma/ injury ($p=0.03$). The SF-36 mental component was also higher in the geriatric group. Quality of life scores were similar. Comparison of geriatric AS and geriatric OA patients revealed more males in the AS group. Non-AS patients are more likely to be smokers and have a history of diabetes ($p=0.04$). Functional disability scores were also higher.

Conclusion: We show that geriatric AS patients have reassuringly similar treatment and disease activity parameters, but differed in a select few functional components and comorbidities when compared to the younger population. The younger population was diagnosed earlier than the elder group, which may reflect better disease awareness among physicians over the last few years. When compared to geriatric non-AS controls, there was a higher prevalence of females, diabetes and smokers in the non-AS geriatric patients. Further research into the geriatric AS population is needed to better define and manage their specific needs, especially as this patient population will be substantial in the coming years.

Table 1	Geriatric (age >= 65 years) N=48	Non geriatric AS (age < 65 years) N=842	p value
Male (%)	83.33	72.21	0.23
HLA-B27 positive (%)	64.58	70.78	0.35
Age at last visit (years)	70.6 ±5.25	41.2 ±12.06	<0.001
Age at time of diagnosis (years)	43.5 ±16.79	29.99 ±11.19	<0.001
Age at symptom onset (years)	35.21 ±16.46	23.39 ±9.28	<0.001
Disease duration at last clinic visit (years)	27.23 ±17.87	11.32 ±9.68	<0.001
Unemployed due to disability from AS (%)	8.33	12.95	0.35
Responsive to NSAIDs (ever)	75.0	68.63	0.16
NSAIDS ever	77.08	82.19	0.37
NSAID at last visit	56.10	53.12	0.70
NSAID related side effects (%)	25.00	25.18	0.97
DMARD use (%) ever	22.92	27.20	0.51
DMARD related side effects (%)	2.08	8.08	0.13
Current glucocorticoid use (%) (oral steroids)	25.86	16.58	0.06
Oral Steroid related side effects (%)	0	1.19	0.44
Biologic use (ever) (%)	39.58	51.19	0.11
Biologic at last visit	54.17	66.93	0.19
Biologic related side effects (%)	12.50	15.20	0.61
AS patients who started on Biologics after 65	5 (1%)		
CRP	9.84 ±10.56	10.39 ±12.36	0.73
ESR	14.68 ±12.05	13.16 ±13.19	0.40
BASDAI	4.26 ±1.98	4.29 ±2.25	0.92
BASMI	4.95 ±2.17	2.50 ±2.32	<0.001
BASFI	4.79 ±2.81	3.42 ±2.86	0.04
SF-36 mental component	55.39 ±10.19	46.51 ±11.99	0.01
SF-36 physical component	38.40 ±8.58	41.00 ±39.38	0.35
Fatigue severity scale	5.19 ±2.76	4.94 ±2.64	0.59
ASQoL	6.64 ±5.16	6.99 ±5.52	0.68
Peripheral arthritis - ever (%)	79.17	65.68	0.05
Dactylitis - ever (%)	2.08	1.54	0.77
Enthesitis - ever (%)	16.67	24.47	0.21

Uveitis - ever (%)	43.75	31.95	0.08
Psoriasis - ever (%)	8.33	11.05	0.55
IBD - ever (%)	8.33	11.52	0.49
Smoking (ever) (%)	33.33	30.40	0.66
Physical trauma or injury (ever)	29.17	16.98	0.03
Hypertension (ever)	70.83	13.42	<0.001
Diabetes (ever)	6.25	3.92	0.42
Angina (ever)	6.25	1.90	0.04
MI (ever)	0	1.43	0.40
Congestive heart failure (ever)	2.08	0.12	0.005
Infection (ever)	35.42	30.64	0.48
COPD (ever)	6.25	2.02	0.05
Asthma (ever)	4.17	7.48	0.39
CVA (ever)	4.17	0.36	0.006
Neuropathy (ever)	14.58	5.70	0.01
Stomach/Duodenal ulcer (ever)	6.25	7.84	0.68
Depression (ever)	18.75	10.57	0.07
Osteoporosis (ever)	12.50	4.39	0.01
HAQ (last visit)	0.99 ±0.73	0.80 ±0.63	0.08
Overall HAQ score	0.77 ±0.64	0.65 ±0.52	0.22
Dressing/shoe laces	0.89 ±0.79	0.75 ±0.72	0.24
Stand up from chair	0.79 ±0.81	0.75 ±0.68	0.75
Cane (ever)	22.92	10.69	0.009
Walker (ever)	12.50	2.26	<0.001
Crutches (ever)	6.25	0.95	0.001

Table 2:	Geriatric AS (age >= 65 years) N=48	Geriatric OA controls (age >= 65 years) N=322	p value
Gender male (%)	83.33	44.10	<0.001
Age	70.59 ±5.25	69.18 ±6.42	0.09
Unemployment due to disability	8.33	4.97	0.33
Smoking	33.33	50.31	0.02
Diabetes	6.25	17.78	0.04
MI	0	6.65	0.06
Heart Failure	2.08	0.32	0.12
Lung disease (Asthma, COPD)	10.42	7.05	0.40
History of Stomach/ Duodenal ulcer	6.25	5.10	0.73
Depression	18.75	15.11	0.51
Dress yourself/ socks on or off	0.89 ±0.79	1.76 ±1.03	<0.001
Stand up from chair	0.79 ±0.81	2.23 ±0.96	<0.001
Get in out bed	0.71 ±0.66	1.85 ±0.97	<0.001
Walk on flat ground	0.55 ±0.56	1.90 ±0.91	<0.001
Climb steps	0.66 ±0.81	2.50 ±0.91	<0.001
*Continuous variables were presented as mean ±SD for both tables			

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Abstract Number: 2756

Gender Differences in Body Composition with Dual-Energy X-Ray Absorptiometry in TNF-α Blocker Naive Ankylosing Spondylitis Patients

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Background/Purpose: Data on body composition (BC) in Ankylosing Spondylitis (AS) are sparse and controversial. Female AS patients have less response to TNF-α blockers and a shorter drug survival. This might be explained by differences in BC, as women have higher body fat (BF) levels and fat produces TNF-α. Our objective was to assess the BC in a cohort of AS patients naïve to TNF-α blockers, and to evaluate the differences between genders and with the reference population.

Methods: Patients included fulfilled the Modified New York criteria and were naïve to TNF-α blockers. Clinical assessments included age, disease duration, extra articular manifestations, therapies, hypertension, diabetes, dyslipidemia, lifestyle (tobacco, alcohol and marihuana use, physical activity), body mass index (BMI), ASDAS CRP and ESR, BASDAI, BASFI, BASMI. BC was assessed by whole body Dual-Energy X-ray Absorptiometry. BF%, Fat Mass Index (FMI), Fat Free Mass Index (FFMI), and android/gynoid (A/G) fat ratio were reported and compared with the reference population (percentiles, stratified by ethnicity, age and gender). Association between variables and differences between groups were assessed using t-test, Chi-Square, Mann-Whitney U test or linear regression depending on the variable.

Results: Seventy consecutive patients were included, 42 (62%) were men. The mean age was 43.9 (11.7 SD). By BMI 35.7% were overweight and 15.7% obese and there were no underweight patients. 62.9% had a BASDAI >4, and the median for ASDAS CRP was 3.4, for BASFI 4 and for BASMI 2. Disease duration, severity, extra articular manifestations, therapies, comorbidities and lifestyle were similar between men and women, except for dyslipidemia, present in 57.1% of men and in 14.3% of women ($p<0.001$). Women had a higher proportion of obese patients by BMI, higher BF % and FMI, and lower FFMI, but the percentile levels for BF% and FMI were similar to men, and better for FFMI. Men had a higher proportion of overweight patients and a higher A/G fat ratio (Table 1). After multivariate analysis, a higher A/G fat ratio was related to dyslipidemia in all patients. In men there was a significant association between BF% and categorical ASDAS CRP, and for FMI and FFMI with HTA. In women there was a significant association between FMI and categorical ASDAS ESR, and between FFMI and psoriasis. In the univariate analysis BASMI was significantly associated with BF% and FMI in men, and BASFI with BF % in women.

Conclusion: Women had higher BF% and FMI than men, but when BF%, FMI and FFMI were compared to the reference population they had a better than average BC. For men it was the opposite, with a trend for higher BF% and FMI percentile levels than women. There was a trend between higher fat percentages and increased disease activity measurements. The association of A/G fat ratio and dyslipidemia was significant independently of sex, which might contribute to the increased cardiovascular risk in AS.

Table 1. Body composition stratified by gender.

	MALE (n=42)	FEMALE (n=28)	P
Age, mean (SD)	44.5 (12.5)	42.8 (10.6)	NS
Years From Diagnosis to DEXA, median (IQR)	5 (1-10)	5 (1-15)	NS
Years From Symptoms to DEXA, median (IQR)	15 (7-20)	18.5 (11-26.5)	NS
BMI, median (IQR)	25.9 (22.6-27.4)	24.2 (22.9-31.9)	NS
BMI categories(kg/m2)			0.009
BMI underweight (<18.5), n (%)	0	0	
BMI normal (≥18.5 to 24.9), n (%)	19 (45.2)	15 (53.6)	
BMI overweight (≥25 to 29.9), n (%)	20 (47.6)	5 (17.9)	
BMI obese (≥30), n (%)	3 (7.1)	8 (28.6)	
Body Fat %, median (IQR)	30 (24.9-34.2)	40.8 (34.4-44.8)	<0.001
Percentile, median (IQR)[1]	53.6 (33.3-76.7)	41.2 (15.2-69.3)	NS
Fat Mass Index, median (IQR)	8 (5.4-9.4)	9.7 (7.8-13.7)	<0.001
Percentile, median (IQR)[1]	42.8 (22.5-66.1)	38.3 (20.6-68.7)	NS
Fat Free Mass Index, median (IQR)	17.7 (16.8-18.5)	15.1 (14.4-16.2)	<0.001
Percentile, median (IQR)[1]	31.7 (19.5-55.3)	56 (40.9-74.5)	<0.001
Android/Gynoid Fat, median (IQR)	1.2 (1-1.3)	0.9 (0.7-1)	<0.001
Dyslipidemia, n (%)	24 (57.1)	4 (14.3)	<0.001

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Abstract Number: 2757

Secukinumab Provides Sustained Improvements in the Signs and Symptoms of Active Psoriatic Arthritis: 104 Weeks Results from a Phase 3 Trial

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Background/Purpose: Secukinumab, a fully human anti–IL-17A monoclonal antibody, significantly improved signs and symptoms of psoriatic arthritis (PsA) over 52 weeks (wks) in FUTURE 2 study (NCT01752634).[1,2] Here we present longer-term (104 wks) efficacy and safety data from this study.

Methods: Overall, 397 patients (pts) with active PsA were randomized to receive s.c. secukinumab (300, 150, or 75 mg) or placebo (PBO) at baseline, Wks 1, 2, 3, and 4, and every 4 wks (q4w) thereafter. PBO pts were re-randomized to secukinumab 300 or 150 mg s.c. q4w depending upon ACR20 response at Wk 16; pts were classified as responders (≥20% improvement from baseline in tender and swollen joint counts) or non-responders, with non-responders switching at Wk 16 and responders at Wk 24. Exploratory endpoints assessed at Wk 104 are from pts originally randomized to secukinumab at the beginning of the trial and included ACR20/50/70, PASI 75/90, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Data were assessed by multiple imputation applied to missing

binary variables and mixed-model repeated measures for continuous variables. Analyses stratified by anti-TNFα status (anti–TNFα-naïve and anti–TNFα-inadequate response or intolerance to these agents [IR]) were pre-specified and are reported as observed. Safety analysis included all patients who received ≥1 dose of secukinumab and data presented as exposure adjusted incidence rates (EAIR) per 100 pt-years over entire treatment period.

Results: In total, 86/100 (86.0%), 76/100 (76.0%), and 65/99 (65.7%) pts in the secukinumab 300, 150, and 75 mg groups respectively completed 104 wks. At Wk 104, ACR20 response rates in the 300, 150, and 75 mg groups were 69.9%, 64.7%, and 50.1%, respectively. Sustained clinical improvements were observed through Wk 104 with secukinumab across other clinically important domains of PsA (Table). Responses were sustained through Wk 104 in anti–TNFα-naïve pts and anti–TNFα-IR. ACR20 response rates at Wk 104 in anti–TNFα-naïve pts were 80.4%, 86.8%, and 68.6% with 300, 150, and 75 mg, respectively; corresponding rates in anti–TNFα-IR pts were 60.7%, 41.7%, and 43.8%, respectively. Over the entire treatment period (mean [±SD] exposure to secukinumab of 709±210.99 days) the incidence, type and severity of adverse events were consistent with those reported previously. Specifically, EAIR for serious infections/infestations, candida infections, inflammatory bowel disease, malignant/unspecified tumors, and major adverse cardiac events with secukinumab were 1.6, 2.3, 0.5, 1.3, and 0.3, respectively.

Conclusion: Secukinumab 300 and 150 mg provided sustained improvements in signs and symptoms and multiple clinical domains of active PsA through 2 years of therapy. Secukinumab was well tolerated, with a safety profile consistent with that reported previously.
References: 1. McInnes IB, et al. *Lancet* 2015;386:1137–46. 2. McInnes IB, et al. *Ann Rheum Dis*. 2015;74:352–3.

Table: Summary of Efficacy Results at Wk 104

Variable	Secukinumab 300 mg s.c. (N = 100)	Secukinumab 150 mg s.c. (N = 100)	Secukinumab 75 mg s.c. (N = 99)
ACR20, % responders	69.4	64.4	50.3
ACR50, % responders	50.6	36.0	28.2
ACR70, % responders	33.1	23.1	14.9
[a]PASI 75, % responders	79.5	73.3	58.4
[a]PASI 90, % responders	69.6	52.5	33.7
SF-36 PCS, LS mean change from BL (SE)	6.8 (0.85)	5.0 (0.87)	4.1 (0.91)
DAS28-CRP, LS mean change from BL (SE)	–1.9 (0.12)	–1.7 (0.12)	–1.5 (0.13)
HAQ-DI, LS mean change from BL (SE)	–0.58 (0.05)	–0.48 (0.06)	–0.27 (0.06)
[b]Resolution of enthesitis, % responders	71.5	61.8	68.4
[c]Resolution of dactylitis, % responders	79.9	78.0	88.6

[a]PASI responses assessed in pts with psoriasis affecting ≥3% body surface area at BL (300 mg: n = 41; 150 mg: n = 58; 75 mg: n = 50); [b]Assessed in patients (n = 56 [300 mg s.c], 64 [150 mg s.c.], and 67 [75 mg s.c]) with this symptom at BL; [c]Assessed in patients (n = 46 [300 mg s.c], 32 [150 mg s.c.], and 33 [75 mg s.c]) with this symptom at BL. BL, baseline; DAS28-CRP, 28-joint disease activity score using C-reactive protein; HAQ-DI, health assessment questionnaire-disability index;LS, least squares; N, number of patients randomized; PASI, psoriasis area and severity index;SE, standard error; SF-36 PCS, short form-36 physical component summary

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Abstract Number: 2758

Minimal Disease Activity Among Psoriatic Arthritis Patients in Canada: Which Unmet Criteria Are More Prevalent Among Responders?

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Background/Purpose: Minimal disease activity (MDA) is now considered an objective target which is more attainable in psoriatic arthritis (PsA) compared to remission (DAS28 <2.6) which is more difficult to achieve and maintain. The criteria for MDA encompass different aspects of this distinct and heterogeneous disease. The aim of this analysis was to assess which unmet criteria were more common among patients who achieved MDA based on patient reported outcomes (PROs) in a real-world, routine clinical care setting in Canada.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab (GLM). Eligible patients for this analysis included PsA patients treated with IFX or GLM between 2005 and 2015. MDA was defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1, pain (VAS) ≤15 mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, tender entheseal points ≤1.

Results: A total of 223 PsA patients (51.4% male) were included with a mean (SD) age of 49.8 (11.1) years and disease duration since diagnosis of 5.4 (6.3) years. MDA was achieved by 11.7%, 43.5%, and 44.8% at baseline, 6 months and 12 months of treatment, respectively. The most commonly unmet MDA criteria in patients who achieved 5/7 criteria was patient-reported pain (69.2%), PtGA (48.7%), and HAQ (20.5%). The mean (SD) for these disease parameters were 31.8 (13.5) mm for pain, 39.3 (10.9) mm for PtGA and 0.95 (0.46) for HAQ. Furthermore, in these patients the most prevalent combination in unmet criteria was pain+PtGA with 38.5% followed by PASI+pain with 12.8%. In patients who achieved 6/7 MDA criteria, the most commonly unmet criteria included PASI with 21.9%, pain with 18.8% and HAQ with 18.8%. The mean (SD) for these disease parameters were 3.7 (2.1) for PASI, 22.8 (7.9) mm for pain and 0.75 (0.08) for HAQ.

Conclusion: The current analysis has shown that by 6 months of treatment almost 50% of patients achieved MDA. Among patients who achieved 5/7 criteria the most commonly unmet criteria in patients who achieved MDA are PROs including pain, PtGA and HAQ-DI. These results highlight the difference in the perception of disease activity by physicians and patients and in the relative importance placed on specific disease aspects.

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Abstract Number: 2759

Prevalence of Comorbidities and Risk Factors of Spondyloarthritis in Latin America: A Comparative Study with the General Population: Data from the Multinational

ASAS-Comospa Study

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Background/Purpose: Increased risk of several comorbidities has been reported in spondyloarthritis (SpA). Data and knowledge regarding the prevalence of these comorbidities and risk factors in Latin America are limited. The objective of this study is to determine the prevalence and risk of develop comorbidities as assessed in the ASAS-COMOSPA study in patients with SpA in three Latin American countries, and to compare this prevalence with the information in the general population to determine whether the prevalence and the risk of comorbidities is increased.

Methods:

Data from 390 consecutive patients with SpA enrolled in the international cross-sectional ASAS-COMOSPA study from Argentina, Colombia and Mexico were analyzed. The prevalence (95% CI) standardized by age and gender was estimated for arterial hypertension (AHT), tuberculosis (TB), and malignancies (colon, skin, lung, lymphoma, prostate, cervix and breast). Data from the general population (stratified by gender and age group) were obtained from the CARMELA study for AHT, the Global TB report and the GLOBOCAN project for malignancies. The prevalence in SpA patients was compared with the prevalence. in the general population by calculating the age- and gender-specific categories. A standardized risk ratio (SRR) was calculated for corrected age and gender groups between the SpA patients and the data from the general population. SPSS 22 was used to perform the statistical analyses.

Results:

In total, 64% were male, the mean age was 45 (14.7) years and the disease duration was 7.0 (8.1) years. The most common comorbidities were AHT (25.3%), hypercholesterolemia (21.8%), osteoporosis (9.4%) and gastrointestinal ulcer (7.8%). The prevalence of AHT was 25.3% (95% CI 21.2 to 29.4) and was higher compared with the general population (16.3%, 95% CI 15.4 to 17.2). The AHT risk of patients with SpA was increased 8.8 times compared with the general population The overall prevalence of TB was 3.33% (95% CI 1.8 to 5.7), and was higher compared with the general population (0.03%). The total risk of TB was found to increase 14.6 times than expected to general population. There was no a significantly increased prevalence of malignancies compared with the general population.

Conclusion:

In patients with SpA we observed a higher prevalence and risk for AHT and TB in three Latin American countries than expected from the age-and gender-adjusted general population. A systematic evaluation and screening of these comorbidities and risk factors may help to properly monitor and detect these conditions in SpA patients.

Disclosure: W. BAUTISTA-MOLANO, None; **R. Landewé**, None; **A. Molto**, None; **R. Burgos-Vargas**, Abbvie, Janssen, Pfizer, and UCB, 8; **J. A. Maldonado-Cocco**, None; **R. Valle-Oñate**, None; **D. van der Heijde**, None.

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Abstract Number: 2760

Assessment of Inflammatory Back Pain and Axial Spondyloarthritis in Brazil

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Background/Purpose: The concept of inflammatory back pain (IBP) was proposed in association with ankylosing spondylitis (AS), one prototype of Spondyloarthritis (SpA), more than 60 years ago. Spondyloarthritis (SpA) comprises several rheumatic diseases. Although several criteria sets have been developed, the diagnosis of SpA remains challenging. This study aims to evaluate the frequency of inflammatory back pain (IBP) among Brazilian subjects with chronic back pain (CBP), and to describe the results of rheumatologic evaluation based on the axial SpA classification criteria from the Assessment of Spondyloarthritis International Society (ASAS).

Methods: This was an observational study with retrospective (phase 1) and one-month prospective (phase 2) data collection. Medical records of subjects 18-60 years old, with onset of back pain at age <40 years, and with CBP (pain almost daily ≥3 months), were included in phase 1. Subjects with at least one ASAS screening parameter for IBP were contacted by phone, and confirmed IBP cases were invited to phase 2. At phase 2 visit 1, HLA-B27 and C-reactive protein (CRP) were requested. At phase 2 visit 2, the fulfilment of the ASAS classification criteria for axial SpA was verified. Frequency of IBP among subjects with CBP starting before the age of 40 years was estimated. For subjects included in phase 2, the proportions of positive HLA-B27, AS and non-radiographic axial SpA (nrAxSpA) were calculated.

Results: A total of 363 records of subjects with CBP were reviewed from five sites. Based on medical records and phone contact, 130 subjects had IBP confirmed (35.8%, 95%CI: 30.9-40.7%). From IBP population, only 52 subjects accepted to participate in phase 2. Mean age was 38.8±11.43 years, 64% were female, 85% professionally active, and 14% had family history of IBP related conditions. Time since CBP onset was 12.3±10.09 years and no subject had a prior diagnosis of SpA. Among the 50 patients that completed visit 2, 14% had positive HLA-B27, 82% had lesions of the sacroiliac joint assessed by MRI, 16% had abnormal clinically significant CRP results, and 10% had grade 3-4 lesions assessed by X-ray. The proportions of AS and nrAxSpA cases were 46% and 26%, respectively by ASAS classification criteria.

Conclusion: More than one third of the CBP subjects with onset <40 years had IBP by ASAS criteria. Of notice, subjects with a positive HLA-B27 test did not have prior diagnosis of axial SpA. The results in this Brazilian population suggest that patients with IBP may be under diagnosed, delaying their treatment, and that women may seek more for medical care than men. An eventual selection bias cannot be excluded.

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Abstract Number: 2761

Sleep Disturbance in Psoriatic Disease: Prevalence and Associated Factors

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Background/Purpose: Psoriasis is a chronic inflammatory skin disease characterized by scaling, erythematous plaques. Up to 30% of psoriasis patients develop an inflammatory arthritis termed psoriatic arthritis (PsA). Psoriatic disease (PsD) patients report impaired sleep quality, but the relationship between sleep quality and disease and demographic factors has not been examined. This study aimed to determine and compare the prevalence and quality of sleep disturbance in patients with PsA and patients with psoriasis without arthritis (PsC), and to identify associated disease-related and demographic factors.

Methods: The study included 113 PsA (CASPAR criteria) and 62 PsC (evaluated by a rheumatologist to exclude PsA) patients (mean age 57.4±11.6 and 56.9±14.2 years, men 55% and 40%, disease duration 17.1±11.6 and 25.9±17.0 years, respectively), and 52 healthy controls (mean age 42.2±13.6, men 29%). Clinical variables were collected using a standard protocol. The sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). Other patient reported outcomes collected included the Health Assessment Questionnaire (HAQ), Dermatology Quality Life Index (DLQI), EQ-5D, Medical Outcome Study Survey (SF-36), patient global assessment (PGA) and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT) Scale. Statistical analysis includes descriptive statistics, Wilcoxon rank-sum test and linear regression.

Results: The prevalence of poor sleep quality was 84% (95/113), 69% (43/62), 50% (26/52) in PsA, PsC and healthy controls, respectively. Total PSQI score was higher in both PsA and PsC patients compared to healthy controls (9.24 and 7.18 vs. 5.67, $p<0.01$) and higher in PsA patients compared to PsC patients (9.24 vs 7.18, $p<0.0001$). PSQI components of sleep disturbances, latency, daytime dysfunction, and subjective sleep quality contributed to worse sleep quality in PsA patients compared to PsC patients ($p<0.01$). Controlling for sex and group, anxiety, EQ-5D and FACIT were independently associated with worse PSQI in PsC and PsA patients ($p<0.05$). Controlling for age, sex, and BMI, actively inflamed (tender or swollen) joints were independently associated with worse PSQI in PsA patients ($p<0.01$).

Conclusion: Patients with PsD have poor sleep quality, especially in those with PsA. Poor sleep is associated with fatigue, anxiety, and lower EQ-5D in patients with PsD. In patients with PsA, poor sleep is associated with active joint inflammation. . However, given this was a cross-sectional study, whether anxiety and lower EQ-5D are the causes or the consequences of poor sleep remains to be determined.

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Smoking and Severity of Psoriatic Arthritis

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Background/Purpose: Smoking is a major modifiable risk factor for various inflammatory diseases including rheumatoid arthritis [1, 2] and psoriasis [3,4,5]. The presence of cyclic citrullinated peptide antibody (CCP) has been associated with smoking in rheumatoid arthritis [1]. Presence of CCP has also been shown to be associated with severe Psoriatic arthritis (PsA) in a few retrospective studies [6,7]. Our aim is to assess the association of smoking and CCP Ab positivity in PsA, with the hypothesis that smoking is associated with severe PsA, and CCP may also be associated with severe arthritis.

Methods: Medical records of patients with PsA followed in our clinic from 2010 to 2015, identified by ICD 9 code were analyzed for demographic characteristics, body mass index (BMI), smoking status, CCP positivity and clinical characteristics for severe PsA. Severe disease was defined as treatment with biologics and/or joint erosions identified on hand and foot radiographs. Chi square statistic was used to assess the relationship between smoking and disease severity. The association of CCP positivity with severe PsA was determined by Fisher's exact test.

Results: One hundred and twelve patients who were ever smokers and one hundred and thirteen never smokers were identified. 30.4% were found to have more severe disease in the ever smoker group and 36.3% were found to have more severe disease in the never smoker group with a relative risk of 0.84 (0.58-1.21, 95% CI)

Conclusion: A relationship between smoking status and disease severity was not identified. There were insufficient numbers of CCP positive patients to establish statistical significance for either positive association with smoking or disease severity. However, CCP positive patients were more likely to be on biologic medications, further studies are needed to establish relationship. References: 1. Klareskog et al. A new model for an etiology of rheumatoid arthritis: Smoking may trigger HLA–DR (shared epitope)–restricted immune reactions to auto antigens modified by citrullination. Arthritis and Rheumatism 2006;54:38–46 2. Stolt et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis:results from a population based case-control study, using incident cases. Ann Rheum Dis 2003;62:835-841 3. Mills et al. Smoking habits in Psoriasis: a case control study. British Journal of dermatology 1992;127:18-21 4. Setty et al. Smoking and risk of Psoriasis in Women: Nurses' Health Study II. Am J Med 2007;120:953-959 5. Armstrong et al. Smoking and pathogenesis of Psoriasis: a review of oxidative, inflammatory and genetic mechanisms. British Journal of dermatology 2011;165:1162-1168 6. Bogliolo et al. Antibodies to cyclic citrullinated peptides in psoriatic arthritis. Jrheum 2005; 32:511-515 7. Perez-Alamino et al. Are anti CCP antibodies in Psoriatic arthritis patients a biomarker of erosive disease. J Med Life 2013;6(4):376-82

Disclosure: S. Jarugula, None; **B. Libman**, Novartis Pharmaceutical Corporation, 2; **A. Kennedy**, None; **D. Howard**, None.

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Abstract Number: 2763

New Treatment Option for SAPHO?

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Background/Purpose: The SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis) is a rare autoimmune disease characterized by inflammatory osteoarticular and cutaneous manifestations. Despite improvements in diagnostic (e.g. MRI, scintigraphy) and therapeutic options (e.g. NSAR, bisphosphonates and TNF inhibitors) SAPHO syndrome is still diagnosed late and often treatment is challenging. Since data from larger studies are missing we assessed patient characteristics and treatment in our cohort.

Methods: 69 Patients with CRMO were analyzed in a cross-sectional study using medical records and questionnaires with regard to the patient characteristics (age, gender, disease duration, time to diagnosis), perception of satisfaction and disease burden (VAS), clinical manifestations (osteoarticular: osteitis, hyperostosis, spondylitis, and involvement of sternoclavicular and sacroiliac joints; dermatological: acne, palmoplantar pustulosis, psoriasis vulgaris), and treatment modalities (NSAIDs, opioids, steroids, bisphosphonates, antibiotics, biologicals currently or in the past).

Results: The time from onset to diagnosis was 4.0 ± 5.5 years and the age at diagnosis was 46.8 ± 12.8 years. Generally, the patients' overall satisfaction (on visual analogue scale from 0 to 100) with 22.5 ± 27.8 was rather low and overall disease burden with 43.7 ± 24.8 rather high indicating that treatment was suboptimal in a substantial portion of patients. Among other findings, we identified a subgroup of difficult-to-treat patients that were characterized by osteitis of the mandibles (n=9). They experienced stronger immunosuppressive therapies such as steroids ($p=0.03$) and TNFi ($p<0.005$) than patients without mandible involvement. Of note, in

three patients of our cohort who failed treatment including TNFi, we observed a significant improvement after treatment with secukinumab in patient pain, skin manifestation as well as in objective measures of osteoarticular inflammation as demonstrated by decrease of CRP and reduction of activity by MRI and bone scintigraphy.

Conclusion: Treatment of SAPHO is challenging particular in subgroups of patients. Therapies targeting IL-17 might constitute new efficacious treatment options.

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Abstract Number: 2764

Unhappiness Is Related to Worse Outcomes for Patients with Ankylosing Spondylitis and Increased Impairment in Daily Life Activities, Results from a Multinational Real-World Sample

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Unhappiness is Related to Worse Outcomes for Patients with Ankylosing Spondylitis and Increased Impairment in Daily Life Activities,

Results from a Multinational Real-World Sample

Background/Purpose: This study aimed to explore the relationship of self-reported happiness to disease activity and functional limitation in people with AS.

Methods: Data were from a cross-sectional sample of rheumatologists and their patients (pts) with AS in 15 countries. Physicians collected data on consecutively consulting AS pts including Physician Assessed Severity' (PA severity) (choice of mild, moderate, severe), perceived change in control (choice of improving, stable, unstable, deteriorating) and general health (0 – 100 VAS). Pts completed forms on ratings of current activity and pain, assessments of health related quality of life (SF-36, EQ-5D) and disease activity (BASDAI). SF-36 question 9h (Q9h; mental health domain) asks "How much of the time during the past week have you been happy?"; responses of "All" or "Most" formed *Happy* (Group 1); responses of "A little" or "None" formed *Not Happy* (Group 2); "some" were excluded from the analysis. Groups 1 and 2 were compared using bivariate analysis. SF-36 Question 3 (Q3; physical functioning domain) asks if the pts' health limits them performing 10 daily activities. **Results:** 1,392 pts answered Q9h: 45.7% were assigned to Group 1 (*Happy*), 20.3% to Group 2 (*Not Happy*). Significantly more pts in Group 2 had moderate or severe disease, unstable or deteriorating AS, poorer general health status, worse pain, and more active AS (higher BASDAI) than Group 1 (Figure 1). 1,405 patients answered Q3, of whom 60%, 34% and 6% were considered by their physician to have mild, moderate and severe AS, respectively. The proportion of pts who reported "a lot" of limitation in each of the 10 activities increased with perceived severity (Figure 1). Of pts with severe AS, 47–73% were limited in undertaking normal physical activities, such as climbing several flights of stairs (moderate AS, 23–43%), and 22–43% could not perform activities requiring limited physical effort, such as carrying groceries or dressing themselves (moderate AS, 7–23%). It also shows that among the pts who are impaired 'a lot' for each activity, unhappiness increases with perceived disease severity.

Conclusion: Unhappiness in AS pts is associated with more severe or active disease, and many AS pts are limited in their ability to

undertake everyday activities, with limitation and unhappiness more common with more severe disease. Thus evaluating patient unhappiness via enquiry in routine consultation may help in assessing clinical severity, disease impact, and help inform treatment decisions.

Figure 1. Association of happiness with clinical status

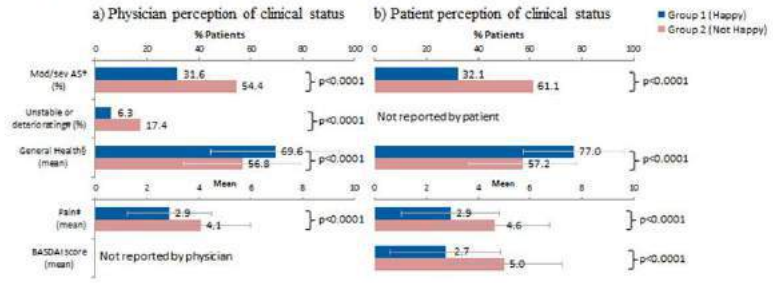

Figure 1) †Physician assessed severity or patient assessed severity (chosen from mild, moderate or severe); #Physician's description of patient's current condition; § Current health state (reported using VAS scale with 0=worst and 100=best health state); ‡Current level of pain reported as 1=none to 10=worst possible;.

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; Mod-sev, moderate or severe.

Figure 2. Limitation of daily activities by disease severity, and extent of unhappiness

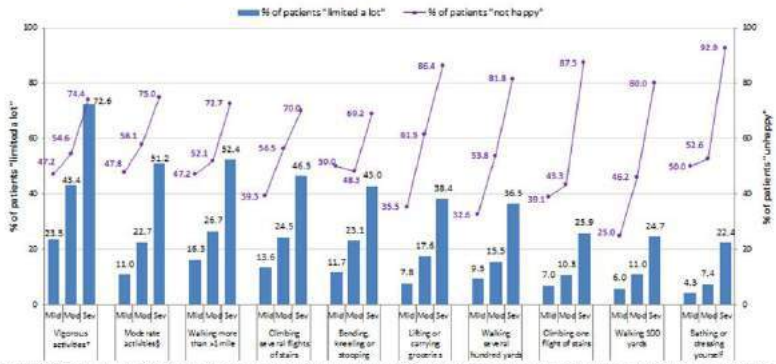

Figure 2) †Such as running, lifting heavy objects, participating in strenuous sports; ‡Such as moving a table, pushing a vacuum cleaner, bowling or playing golf
Mild/Mod/Sev: Physician assessed severity (chosen from mild, moderate or severe).
Mild n=848; Moderate n=471; Severe n=86.

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Abstract Number: 2765

Practicing What We Preach? Do Psoriatic Arthritis Patients Treated at an Academic Medical Center Meet Caspar Criteria?

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Background/Purpose: Psoriatic arthritis (PsA) is an autoimmune musculoskeletal disease with protean manifestations, and therefore can be difficult to diagnose. Although no diagnostic criteria are available, the CASPAR classification criteria (CC) have a sensitivity and specificity of 91.4% and 98.7%, respectively. The purpose of this study is to assess the validity of using ICD-9 codes to identify PsA patients for future clinical trials by applying the CC to patients with the ICD-9 code for PsA (696.0).

Methods:

This was a retrospective cohort study. All patients with a billing code of 696.0 seen at a single center from January 1, 2013 through December 31, 2014 were identified. Medical records were reviewed to identify all elements of CC including: Evidence of psoriasis - current psoriasis, personal history of psoriasis, family history of psoriasis; Psoriatic nail dystrophy - onycholysis, pitting, hyperkeratosis; Negative test for rheumatoid factor; Dactylitis - current dactylitis, history of dactylitis; Radiologic evidenceof juxta-articular new bone formation. The percentage of patients who met CC was calculated, and their clinical characteristics described.

Results:

1405 patients were coded as PsA. Of 1278 unique charts available for review, 629 met CC. 96 were excluded due to a concurrent clinical diagnosis of rheumatoid arthritis, inflammatory bowel disease, or gout, leaving 533 (41.7%) with PsA based on CC. Similar age and sex between ICD-9 vs. CC groups; 54.2 years vs 52.8 years; 55.2% vs 52.2% female, respectively. Compared to published data for the classification criteria,[1] in our cohort of 533 patients who met criteria, there was a similar prevalence of psoriasis (98.9% vs 98.3%), a lower prevalence of nail disease (27.0% vs 60.0%) and moderately similar prevalence of dactylitis (31.3% vs 57.5%). Other radiographic evidence of juxta-articular new bone formation was much less frequently reported. (1.7% vs 54.0%).

Conclusion:

In this study of patients with ICD-9 codes for PsA, only 41.7% met CASPAR classification criteria. This underscores differences between PsA patients meeting CC recruited for clinical trials, and those treated in an academic real world setting. These differences are important to understand when assessing generalizability of trial data, and for planning studies of clinical effectiveness in PsA.

Table 1. 1278 Charts Reviewed

CASPAR Criteria Present in Cohort	**Present**	**Absent/Not Available**
Any History of Psoriasis,* n (%)	957 (74.9)	321 (25.1)
Current, n (%)	800 (62.6)	478 (37.4)
History, n (%)	190 (14.9)	1088 (85.1)
Family History, n (%)	125 (9.8)	1153 (90.2)
***Patients can have more than one**		
Nail Disease, n (%)	185 (14.5)	1093 (85.5)
Dactylitis, n (%)	214 (16.7)	1064 (83.3)
Negative Rheumatoid Factor, n (%)	499 (39.0)	779 (61.0)
Radiographic Changes, n (%)	13 (1.0)	1265 (99.0)

Table 2. 533 patients who met CASPAR criteria (CASPAR score ≥3)

	Present	Absent/Not Available
History of Psoriasis n (%)	527 (98.9)	6 (1.1)
Current, n (%)	487 (91.4)	46 (8.6)
History, n (%)	107 (20.1)	426 (79.9)
Family History, n (%)	62 (11.6)	471 (88.4)
Nail Disease, n (%)	144 (27.0)	389 (73.0)
Dactylitis, n (%)	167 (31.3)	366 (68.7)
Negative Rheumatoid Factor, n (%)	310 (58.2)	223 (41.8)
Radiographic Changes, n (%)	9 (1.7)	524 (98.3)

1. Taylor et al. Arthritis & Rheumatism. Volume 54, Issue 8, pages 2665-2673, August 2006.

Disclosure: S. Schwartzman, Speaker for: Genentech, Janssen, AbbVie, Crescendo, Pfizer, Hospira, and Novartis, 8,National Psoriasis Foundation: Board Member, 6,Consultant for: Genentech, Janssen, AbbVie, Pfizer, Epirus, Hospira, Novartis, Regeneron, and Crescendo, 5,Scientific Advisory Board: Crescendo - Bioscience, 9,Speaker for: Novartis Pharmaceutical Corporation, 8,Speaker for: AbbVie, 8,Consultant for: UCB, 5,Speaker for: Janssen Pharmaceutica Product, L.P., 8; **R. Abhyankar**, None; **M. Bogardus**, None; **L. Mandl**, None.

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Abstract Number: 2766

The Predictive Value of Patient's and Evaluator's Global Assessment and Tender and Swollen Joint Count Differences on Treatment Efficacy in Psoriatic Arthritis: Data from a Longitudinal Multicenter Study

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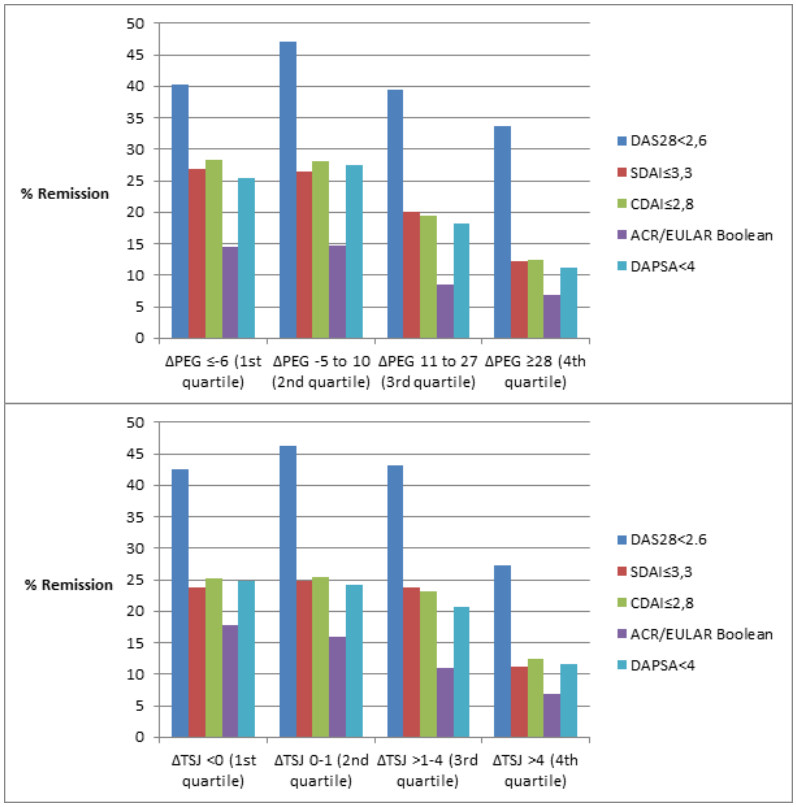
Background/Purpose: Discordance between patient's and physician's evaluation of disease activity may be challenging in psoriatic arthritis (PsA). The potential impact of such a difference on treatment outcome is to date unexplored. In this study we aimed to investigate the predictive value of baseline patient's and evaluator's global assessment difference (deltaPEG) as well as tender and swollen joint count difference (deltaTSJ) for achievement of remission in PsA.

Methods: From the prospective, multicenter NOR-DMARD study we included PsA patients starting first-time tumor necrosis factor inhibitors (TNFi) and DMARD naïve patients starting methotrexate between 2000 and 2012. The predictive value of deltaPEG and deltaTSJ on remission, defined by various criteria, was explored in prespecified logistic regression models adjusted for age, sex, disease duration and smoking.

Results: A total of 1236 PsA patients were included (mean (SD) age 48.3 (12.4) years, disease duration 4.8 (7.5) years, 48.4% females, 29.8% current smokers, baseline mean (SD) evaluator's global assessment 34.1 (16.6), patient's global assessment 51.1 (22.6), deltaPEG 17.0 (24.3), median (IQR) 32 tender joint count 5 (8), 32 swollen joint count 3 (5), deltaTSJ 1 (5), DAS28ESR 4.2 (1.3), baseline median (IQR) SDAI 16.9 (12.8), CDAI 8.6 (10.3), modified DAPSA 21.0 (14.1) (including 32 instead of the original 66/68 joint count). Bar charts of percentages of PsA patients in remission at 6 months according to categorization of deltaPEG and deltaTSJ into quartiles showed reduced probability of remission with increasing deltaPEG and deltaTSJ (unadjusted values; figures).



Baseline deltaPEG and deltaTSJ predicted DAS28<2.6, SDAI≤3.3, CDAI≤2.8, ACR/EULAR Boolean and DAPSA<4 remission after 3 and 6 months, except for deltaPEG and DAS28 remission at 6 months (adjusted analyses; table).

	Months	DAS28ESR < 2.6	SDAI ≤ 3.3	CDAI ≤ 2.8	ACR/EULAR Boolean	DAPSA < 4
deltaTSJ	3	0.92 [0.89, 0.96] p<0.001	0.91 [0.86, 0.95] p<0.001	0.93 [0.89, 0.97] p=0.001	0.93 [0.88, 0.98] p=0.004	0.91 [0.86, 0.95] p<0.001
	6	0.94 [0.90, 0.97] p=0.001	0.94 [0.90, 0.98] p=0.003	0.93 [0.89, 0.97] p=0.001	0.92 [0.88, 0.97] p=0.002	0.93 [0.89, 0.98] p=0.002
deltaPEG	3	0.89 [0.84, 0.94] p<0.001	0.98 [0.98, 0.99] p<0.001	0.99 [0.98, 0.995] p=0.001	0.99 [0.98, 0.99] p=0.001	0.99 [0.98, 0.995] p=0.002
	6	1.00 [0.99, 1.01] p=0.94	0.99 [0.98, 0.995] p=0.001	0.99 [0.98, 0.99] p<0.001	0.98 [0.97, 0.99] p<0.001	0.99 [0.98, 0.99] p=0.001

Data are presented as OR [95% CI]

Conclusion: DeltaPEG and deltaTSJ constitute new and important predictors of treatment efficacy in PsA and may be considered in the shared decision of a target in a treat-to-target strategy.

Disclosure: B. Michelsen, None; **E. K. Kristianslund**, None; **H. B. Hammer**, None; **K. M. Fagerli**, None; **E. Lie**, None; **G. Haugeberg**, None; **T. K. Kvien**, Biogen, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Epirus, Hospira, Merck-Serono, Novartis, Orion Pharma, Prizer, Sandoz, UCB, 5.

Abstract Number: 2767

Minimal Disease Activity Among Psoriatic Arthritis Patients in Canada: Evaluation of Modified Minimal Disease Activity upon Elimination of Each Component

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Background/Purpose: Minimal disease activity (MDA) is now considered an attainable target in psoriatic arthritis (PsA) reflecting a desired state of comprehensive disease control. MDA is defined as the fulfillment of ≥5 of the following criteria: TJC28≤1, SJC28≤1, PASI≤1, pain (VAS) ≤15 mm, PtGA (VAS) ≤20 mm, HAQ≤0.5, and tender entheseal points ≤1. It is made up of objective and subjective outcomes. The aim of this analysis is to assess the contribution of each criterion in preventing the achievement of MDA at 6 and 12 months.

Methods: BioTRAC is an ongoing, prospective registry of patients initiating treatment for rheumatoid arthritis (RA), ankylosing spondylitis (AS), or psoriatic arthritis (PsA) with infliximab (IFX) or golimumab (GLM). Eligible patients for this analysis included PsA patients treated with IFX or GLM between 2005 and 2010. Modified MDA (mMDA) was evaluated by removing patient-reported outcomes, one criterion at a time, and mMDA achievement was defined as patients who met 4/6 criteria.

Results: A total of 223 PsA patients (51.4% male) were included with a mean (SD) age of 49.8 (11.1) years and disease duration since diagnosis of 5.4 (6.3) years. MDA was achieved by 11.7%, 43.5%, and 44.8% at baseline, at 6 and 12 months of treatment, respectively. At 6 months of treatment the proportion of patients who achieved mMDA upon removing one criterion at a time increased to 54.3% for pain removal, 52.2% for PtGA removal, 50.7% for HAQ removal; while the removal of objective measures did not increase in substantial manner the percentage of patients achieving mMDA: 46.4% for TJC removal, 44.9% for PASI removal, 44.2% for SJC removal, and 44.2% for enthesitis removal. Similar findings were seen at 12 months: the proportion of patients achieving mMDA upon removing HAQ was 58.1%, pain was 57.1%, PtGA was 55.2%, TJC was 50.5%, SJC was 48.6%, PASI was 46.7%, and enthesitis was 45.7%. The highest proportion of mMDA achievement at 6 and 12 months of treatment was observed upon the removal of patient reported pain, PtGA and HAQ.

Conclusion: The results of the current analysis have shown that the most common limiting factors in achieving MDA in PsA are patient reported outcomes, including PtGA, pain, and HAQ. Elimination of each of these criteria from the MDA formula would result in as many as 13% additional cases of MDA.

Disclosure: B. Haraoui, Janssen Inc., 5; **P. Rahman**, Janssen Inc., 5; **L. Bessette**, Janssen Inc., 5; **P. Baer**, Janssen Inc., 5; **S. Kapur**, Janssen Pharmaceutica Product, L.P., 5; **J. A. Avina-Zubieta**, Janssen Inc., 5; **R. Arendse**, Paid Consultant of Janssen Inc., Canada, 5; **E. Rampakakis**, employee of JSS Medical Research, 3; **E. Psaradellis**, employee of JSS Medical Research, 3; **K. Maslova**, Employee of Janssen Inc., 3; **A. J. Lehman**, Employee of Janssen Inc., 3; **F. Nantel**, Employee of Janssen Inc., 3; **B. Osborne**, Employee of Janssen Inc., 3; **C. Tkaczyk**, Employee of Janssen Inc., 3.

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Abstract Number: 2768

Prevalence of Obesity in Patients with Psoriatic Arthritis and Its Impact on the Severity of the Disease

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Background/Purpose: Epidemiological studies have found a high prevalence of obesity in patients with Psoriatic Arthritis (PsA). It was described the association between obesity and severity of psoriasis, but the relationship to the severity of PsA has been less studied. Our purpose was to assess the prevalence of obesity in a cohort of patients with PsA and its association with clinical and sociodemographic characteristics

Methods: PsA patients ≥18 years old according to CASPAR criteria, belonging to RAPSODIA (Registro de Artritis Psoriásica, IREP Argentina) cohort were included. Socio-demographic data, disease duration, type of onset and evolution of PsA, comorbidities, acute phase reactants and lipid profile were collected. Treatment data were collected through direct interview with the patient, complementing with medical history. 66 tender and 68 swollen joints count, enthesitis (MASES), presence of dactilitis, cutaneous (PASI) and nail involvement (PNSS) were evaluated. Disease activity (BASDAI), functional capacity (HAQ, BASFI), quality of life (DLQI, PsAQoL) questionnaires were completed. DAS28, DAPSA and MDA (Minimal Disease Activity) composite indexes were calculated. Visual analog scale (VAS) was used to grade severity of skin psoriasis, pain and patient and physician global assessment of disease activity. Height (cm), weight (kg) and blood pressure (mm Hg) were measured. BMI was calculated. Patients were classified according to WHO in normal (BMI 18.5-24.9), overweight (BMI 25-30) and obesity (BMI ≥30). Obesity was classified as grade I or mild (BMI 30-34.9), grade II or moderate (BMI 35-39.9) and grade III or severe (BMI ≥40). Statistical analysis: Descriptive statistics. T test and ANOVA. Chi^2 and Fisher exact test. Multiple logistic regression (dependent variable: obesity). Univariate general linear model.

Results: 110 patients were included, 56 (50.9%) were men, median age 55 years (IQR 44.7-63.2) and median disease duration of PsA 10 years (IQR 6-17) and median duration of psoriasis was 24 years (IQR: 15.5-33.9). 19 patients (17.3%) met MDA. The median BMI was 28.4 (IQR 15.5-32.2). 23 patients (19.1%) had normal BMI, 48 (43.6%) overweight and 41 (37.3%) obesity. Of obese patients, 33 (80.5%) had mild obesity, 6 (14.6%) moderate and 2 (4.9%) severe. Obese patients had worse functional capacity that patients with normal weight (BASFI 4.4 ±2.8 vs 2.7± 2.5, p = 0.03) and higher pain (VAS 6.7 ±7.6 vs 4.6 ±2.4, p = 0.05). PASI score was higher in obese vs patients with normal BMI (2.8 ±2.9 vs 1.6± 1.7, p= 0.02). There were no differences according to sex, age, comorbidities, laboratory variables, disease duration, or extension of joint involvement. Obese patients had received steroid treatment more frequently in the past, but at the time of study evaluation no differences in treatment were observed. Type II diabetes was significantly more frequent in obese patients 16 vs 0 (p=0.03).

Conclusion: We observed that 81% of PsA patients are overweight or obese. The presence of obesity was associated with higher level of pain, greater skin involvement and worse functional capacity

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Disclosure: C. Zaffarana, None; **J. Gallino Yanzi**, None; **O. L. Cerda**, None; **M. Landi**, None; **E. Schneeberger**, None; **G. Citera**, None.

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Abstract Number: 2769

Does Gender Make a Difference in "Composite Psoriatic Disease Activity Index (CPDAI)" in Patients with Psoriatic Arthritis?

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Background/Purpose: "Composite psoriatic disease activity index (CPDAI)" includes 5 domains: peripheral joints, skin, enthesitis, dactylitis, and spinal manifestations in psoriatic arthritis (PsA) which is a heterogeneous disease known with widely variable clinical courses. Experiences in ankylosing spondylitis (AS) studies suggest that female patients report more symptoms and poorer scores on most of the self-reported questionnaires, including Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI) and AS Quality of Life [ASQoL]) despite fewer inflammatory spinal lesions or less radiographic damage as objective disease indicators with respect to male patients. The aims of this study are to investigate the relationship of CPDAI with other follow-up parameters and to evaluate gender differences in these measures in PsA patients.

Methods: This cross-sectional study included patients with PsA followed up at a Rheumatology outpatient clinic at a university hospital. Disease activity was assessed in the patients by using the CPDAI, BASDAI, Visual Analogue Scale Global (VAS global) and Disease Activity Score (DAS28). Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels were measured in all the patients. The Psoriasis Area and Severity Index (PASI) was used for the measurement of severity of psoriasis. The Patient Acceptable Symptom State (PASS), BASFI, Bath Ankylosing Spondylitis Metrology Index (BASMI), Health Assessment Questionnaire (HAQ), ASQoL and Dermatology Life Quality Index (DLQI) were also evaluated. The correlations were investigated by Spearman's correlation analysis (rho:<= 0.29 weak, 0.30-0.49 middle, >= 0.50 strong).

Results: There were 117 patients with PsA (78 female) who fulfilled the Classification *Criteria for Psoriatic Arthritis* (CASPAR) (3). Their mean CPDAI score was 3.67 (±2.46). The CPDAI was found to be correlated with tender and swollen joint counts, dactylitis and enthesitis. There was a strong correlation between CPDAI and BASDAI, $DAS28_{ESR}$, $DAS28_{CRP}$ and VAS global. Other follow-up parameters also correlated with CPDAI but no correlation was found between the CPDAI and ESR, CRP and BASMI. Mean CPDAI scores were similar in female and male patients. Female patients with PsA were found as having worse subjective scores including BASDAI, VAS global, BASFI, HAQ, ASQoL scores than males ($p<0.05$). Whereas objective disease parameters such as mean ESR and serum CRP levels, tender/swollen joint counts, DAS28 and BASMI scores were similar in both gender groups (Table 1).

Conclusion: This study confirmed that the CPDAI, a new scale to assess disease activity in PsA patients was well correlated with other disease activity measurements. Although subjective disease scores (BASDAI, VAS global, BASFI, HAQ and ASQoL) was higher in female patients, CPDAI was not affected from gender.

Table 1. Demographic and Clinical Data and Disease Activity Measures in Patients with Psoriatic Arthritis			
	Female patients (n=78)	**Male patients (n=39)**	**p value**
Mean age±SD (yrs)	48.1(±11.7)	45.5 (±12.6)	0.28
Mean education duration±SD (yrs)	8.8 (±4.2)	9.8 (±3.7)	0.26
Mean disease duration±SD (yrs)	7.9 (±8.7)	8.3 (±7.8)	0.80
Dactylitis (%)	6.4 (%)	10.2 (%)	0.48
Entesitis (%)	8.9 (%)	10.2(%)	0.82
CRP (mg/dL±SD)	8.8 (±11.1)	13.2 (±13.9)	0.09
ESR (mm/h±SD)	31.2 (±18.2)	29.3 (±23.2)	0.66
CPDAI (±SD)	3.63 (±2.4)	3.76 (±2.5)	0.79
Tender joint count (±SD)	2.5 (±3.0)	2.1 (±3.0)	0.55
Swollen joint count (±SD)	1.06 (±1.7)	1.1 (±2.1)	0.92
BASDAI (±SD)	4.61 (±2.6)	2.6 (±1.9)	0.00*
BASFI (±SD)	3.4 (±2.8)	1.6 (±1.6)	0.00*
BASMI (±SD)	28.7 (±11.2)	15.0 (±7.0)	0.13
DLQI (±SD)	5.75 (±6.6)	4.45 (±5.9)	0.32
PASI (±SD)	5.26 (±7.6)	8.83 (±11.6)	0.12
HAQ (±SD)	0.85 (±0.7)	0.60 (±0.5)	0.04*
ASQoL (±SD)	8.63 (±5.8)	5.70 (±5.4)	0.01*
VAS global (±SD)	46.12 (±30.5)	30.23 (±26.4)	0.00*
$DAS28_{CRP}$ (±SD)	2.67 (±1.08)	2.53 (±1.08)	0.53
$DAS28_{ESR}$ (±SD)	3.67 (±1.2)	3.25 (±1.4)	0.15
*p<0.05			

References: 1. Taylor W. et al. CASPAR Study Group. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum, 2006;54(8):2665-73.

Disclosure: G. Kenar, None; **H. Yarkan**, None; **B. Zengin**, None; **G. Can**, None; **M. Birlik**, None; **N. Akkoc**, None; **F. Onen**, None.

Abstract Number: 2770

Psoriatic Arthritis Limits Patients' Abilities to Undertake Activities Crucial for Normal Daily Life and Impacts Happiness, Results from a Multinational Real-World Sample

Rieke Alten[1], Vibeke Strand[2], Philip G. Conaghan[3], Louise Huneault[4], Emma Sullivan[5], Stuart Blackburn[5], Haijun Tian[6], Kunal Gandhi[6] and Steffen Jugl[7], [1]Schlosspark-Klinik, University Medicine, Berlin, Germany, [2]Division of Immunology/Rheumatology, Stanford University, California, CA, [3]NIHR-Leeds Musculoskeletal Biomedical Research Unit, Leeds, United Kingdom, [4]Novartis Pharma AG, Novartis Pharma AG, Basel, Switzerland, Basel, Switzerland, [5]Adelphi Real World, Manchester, United Kingdom, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Novartis Pharma AG, Basel, Switzerland

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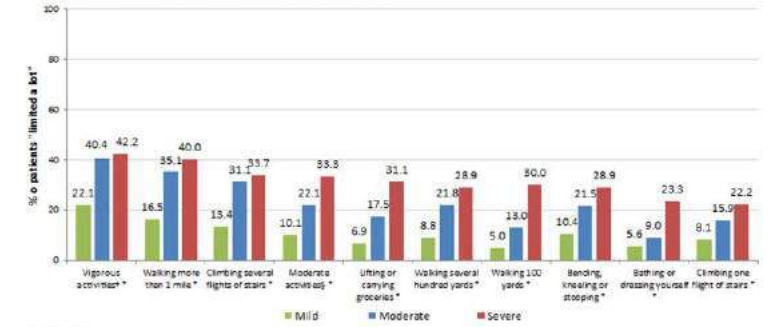
Background/Purpose: This study investigated the impact of psoriatic arthritis (PsA) disease severity on patients' (pts) ability to perform normal daily activities and their reported happiness.

Methods: Data from cross-sectional research with specialists treating pts with PsA in 16 countries were analyzed. Physicians completed a detailed form for consecutive consulting PsA pts recording Physician Assessed severity (PA severity) (choice of mild, moderate or severe), change in severity (choice of improving, stable, unstable, deteriorating), general health (1- 100 VAS), perceived pain (1 – 10 scale), swollen (/ 66) and tender (/ 68) joint counts and severity of skin symptoms (PASI). Pts completed a form rating severity of their PsA (mild, moderate, severe), current pain (1- 10 scale), and their health related quality of life (SF-36). Question 3 (Q3; physical function domain) of SF-36 asks if their health limits pts' performance of 10 daily activities. SF 36 question 9h (Q9h; mental health domain) asks "How much of the time during the past week have you been happy?"; pts answering "All" or "Most" were defined as *Happy* (Group 1), pts answering "A little" or "None" as *Not Happy* (Group 2); "Some" were excluded from the analysis. Bivariate analysis described differences between the Groups.

Results: 1,722 pts completed Q3; 61%, 34% and 5% with mild, moderate and severe PsA, respectively. 1,698 pts answered Q9h - 44.6% in Group 1 and 20% in Group 2. The proportion who reported "a lot" of limitation in the Q3 activities increased with disease severity (Figure 1). Of pts with severe PsA, 33–42% were limited in undertaking normal physical activities, such as climbing several flights of stairs (moderate PsA, 22–40%), and 22–31% could not perform limited physical activities, such as dressing themselves (moderate PsA, 9–30%). Unhappy pts were associated with worse health outcomes when physicians' and pts' perceptions of health status, as well as clinical characteristics, were compared between Group 1 and 2 (Figure 2). A lower level of satisfaction with the control their current treatment provided was also observed among Group 2 ("satisfied": Group 1, 83%; Group 2, 56.9%; *P<0.001*).

Conclusion: Many PsA pts cannot undertake everyday activities that would allow them to lead a normal life. Impairment increases with disease severity and unhappiness is also associated with more severe disease status. Thus strategies to proactively treat PsA to reduce severity should improve important components of health related quality of life.

Figure 1. Limitation of daily activities by PsA disease severity



* p<0.0001
†Such as running, lifting heavy objects, participating in strenuous sports; §Such as moving a table, pushing a vacuum cleaner, bowling or playing golf

Figure 2. Association of happiness with clinical status

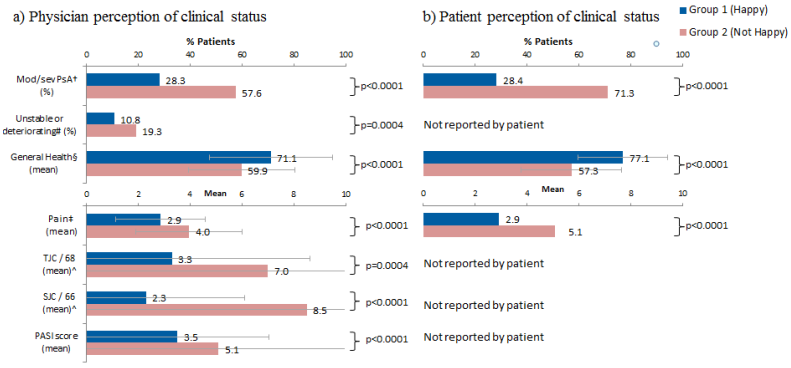


Figure 2) †Current PsA severity (chosen from mild, moderate or severe); ‡Physician's description of patient's current condition; § Current health state (reported using VAS scale with 0=worst and 100=best health state); ‡Current level of pain reported as 1=none to 10=worst possible.

^Based on pts where a joint count was available (TJC Group 1 n=118, Group 2 =89, SJC Group 1 n=121. Group 2 n =40).

Mod-sev, moderate or severe. PASI, Psoriasis Area Severity Index.

Disclosure: R. Alten, None; **V. Strand**, None; **P. G. Conaghan**, AbbVie, Flexion, Eli Lilly, Novartis, Pfizer Inc, Roche, 5,AbbVie, Novartis, Roche, 8; **L. Huneault**, None; **E. Sullivan**, Adelphi Real World, 3; **S. Blackburn**, Adelphi Real World, 3; **H. Tian**, Novartis Pharmaceuticals Corporation, 3,Novartis Pharmaceuticals Corporation, 1; **K. Gandhi**, Novartis Pharmaceuticals Corporation, 1,Novartis Pharmaceuticals Corporation, 3; **S. Jugl**, Shareholder of Novartis Pharma AG, 1,Full-time employee of Novartis Pharma GA, Basel, Switzerland, 3.

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Abstract Number: 2771

Higher Incident Rates of Comorbidities in Patients with Psoriatic Arthritis (PsA) Compared to Controls

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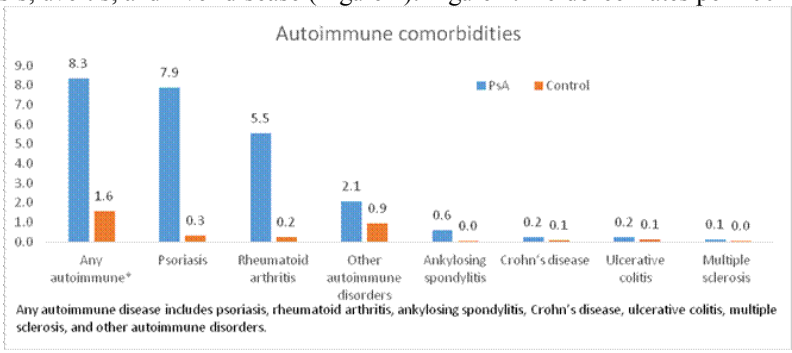
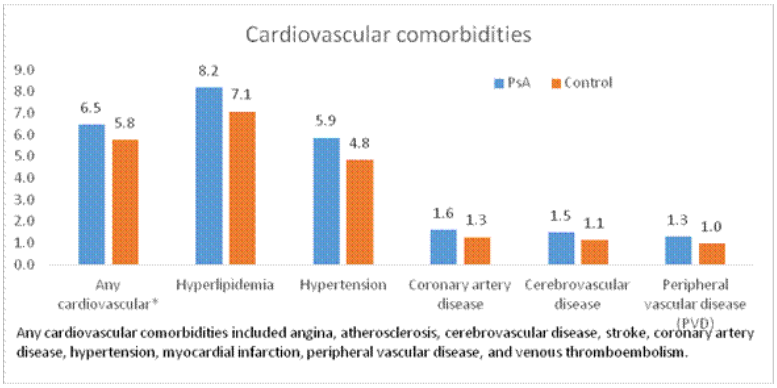
-

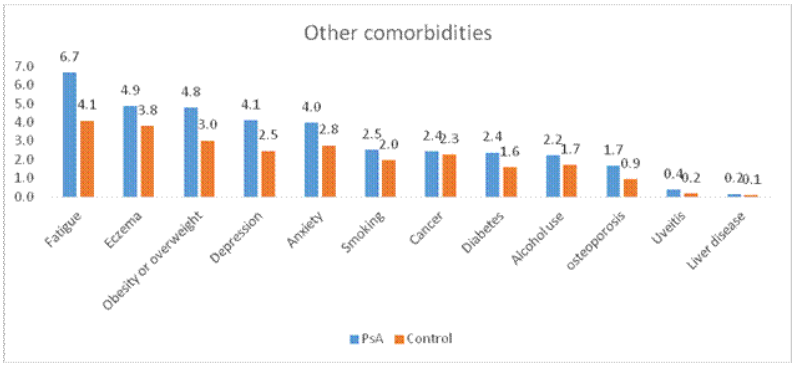
Background/Purpose: PsA is associated with higher rates of developing certain comorbidities, but little has been done to understand the incidence rates of comorbidities in American populations. This study compared incidence rates of comorbidities between patients with newly diagnosed PsA and a matched control cohort without PsA, using a large national US claims database.

Methods: Adults with ≥1 inpatient or 2 outpatient diagnoses of PsA (ICD-9-CM 696.0) in 1/1/2008 - 9/30/2015 were extracted from MarketScan Commercial and Medicare Databases, with the first PsA diagnosis as the index date. Patients had ≥24 months continuous enrollment prior to the index date (pre-period) and were followed for ≥12 months until the earliest of inpatient death, end of continuous enrollment, or end of the data. These PsA patients were matched on calendar year, age, gender, and geographic region to those with no PsA diagnosis anytime in 2007-2015 (controls). The incidence of new comorbidities (not present in the 24-month pre-period) per 100 person-years was estimated and compared between PsA patients and their controls.

Results: A total of 14,898 PsA patients were matched to 35,037 controls (mean age: 53.4 years for PsA vs. 54.8 for controls; male: 44.6% vs. 44.4%; mean length of follow up: 3.0 vs. 3.0 years). Compared with controls, PsA patients had higher incidence rate of autoimmune disease, cardiovascular disease, fatigue, eczema, obesity/overweight, depression, anxiety, smoking, cancer, diabetes, alcohol use, osteoporosis, uveitis, and liver disease (Figure 1). Figure 1. Incidence Rates per 100 Person-Years of New Comorbidities for PsA vs. Controls







Conclusion: PsA patients had high incidence rates of cardiovascular comorbidities, autoimmune conditions, fatigue, eczema, depression, and anxiety than controls. Understanding these comorbidity profiles will help evaluate the impact of comorbid conditions on disease management and costs associated with PsA.

Disclosure: J. Kaine, Novartis Pharmaceutical Corporation, 5,Bristol-Meyers Squibb, 5; **X. Song**, None; **G. Kim**, None; **J. Palmer**, Novartis Pharmaceutical Corporation, 3.

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Abstract Number: 2772

Back Pain in Psoriatic Arthritis: Defining Prevalence, Characteristics and Performance of the Different Inflammatory Back Pain Criteria in a Psoriatic Arthritis Cohort

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Background/Purpose: Estimates of axial involvement in PsA vary from 25% to 70% depending on the inclusion criteria. Three sets of criteria are available for defining inflammatory back pain (IBP) in Ankylosing Spondylitis (AS): Calin, Rudwaleit and ASAS criteria. We aimed to determine whether these criteria are useful screening tools for axial involvement in PsA and to describe the clinical features in PsA patients with IBP, mechanical back pain (MBP), no Back Pain (BP) and silent BP.

Methods: Patients with PsA have been followed prospectively at 6-12 month intervals according to a standard protocol since 1978. Radiographs of peripheral joints and spine are performed at 2 year intervals. All data are tracked in a computerized database. From the database we extracted data at the first visit since 2010 on the presence of back pain, as well as criteria for IBP (Calin, Rudwaleit and ASAS). At each visit a rheumatologist also recorded whether a patient had back pain, and whether it is inflammatory or mechanical based on independent clinical judgement. We tested the agreement between physician assessment (presence or absence of IBP) and IBP criteria. Patients whose radiographic changes met the New York (NY) Criteria for AS or had any radiographic changes consistent with sacroiliitis and/or syndesmophytes on x-ray and/or MRI were analyzed for the agreement with the presence of any BP, IBP by physician assessment, and fulfilling IBP criteria, using the Kappa coefficient. MRI was done only if there was a suspicion of axial involvement but the x-rays were negative. Descriptive statistics are provided.

Results: 171 patients were identified from the database. The patients were mostly male (52%), mean age of onset of PsA was 43.3±13.6, and mean age at first PsA clinic visit was 46.6±13.0 years. All patients had radiographic data available at clinic entry. The prevalence for BP was 56.2% (IBP 38.01%; MBP 18.12%). 27 out of 171 (15.79%) patients with baseline x-rays fulfilled the NY radiographic criteria for AS. 45 out of 171 (26.32%) patients had any radiological sacroiliitis and/or syndesmophytes. 9 out of 31

(29.03%) patients with no axial disease on x-ray had evidence of axial disease on MRI. 18 (24.0%) of the patients with no back pain had "silent" BP (evidence of axial disease on radiology (x-ray or MRI)). The agreement (kappa coefficient) between physician assessment and IBP criteria in all patients was highest for the Calin criteria (0.81, 95% CI (0.72, 0.91)), followed by the ASAS criteria (0.72, (0.61, 0.81)), and the Rudwaleit criteria (0.71, (0.59, 0.83)). There was no significant agreement between the presence of radiographic NY criteria and the presence of back pain, physician assessment of IBP, or the IBP criteria. There was also no agreement between physician assessment of IBP and any radiographic change (syndesmophytes or sacroiliitis of at least Grade 2). Mean BASMI, BASDAI, and BASFI were highest in PsA patients with IBP than those with MBP, no BP or "silent" BP.

Conclusion: Patients with PsA report less back pain than AS patients. The low level of agreement between physician assessment and radiological presence of axial PsA indicates that we should consider axial imaging in all patients with PsA regardless of the presence of the nature of BP.

Disclosure: K. Yap, None; **S. Li**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **V. Chandran**, None.

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Abstract Number: 2773

Assessment of the Static and Dynamic Balances in Psoriatic Arthritis (PsA) and Their Relations with Clinical, Radiological and Functional Parameters of Feet

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Background/Purpose: The feet are commonly affected in patients with psoriatic arthritis which cause impairment and disability. The purpose of the study is to assess the static and dynamic balances in PsA and to investigate their relation with clinical, functional and radiological parameters of feet.

Methods: Patients diagnosed with PsA according to CASPAR criteria and healthy controls were recruited consecutively into the study. The age, sex and body mass index (BMI) of the cases were recorded as demographic data. The disease activity was assessed by DAS-28 and PASI scores. Fear of falling and falling history in the recent year were recorded. Radiographic assessments of feet were done to consider the deformities (pes planus, hallux valgus, metatarsus primus valgus etc). 'Foot and Ankle Outcome Score' (FAOS) was applied for foot function assessment. The fatigue (Multidimentional Assessment of Fatigue: MAF), depression (Beck Depression Inventory: BDI) and sleep disorders (Pittsburgh Sleep Quality Index (PSQI) of all patients were evaluated. The state of balance of the patients was evaluated by means of 'Berg Balance Scale' (BBS) and also 'Modified Clinical Test of Sensory Interaction and Balance' and 'Unilateral Stance' tests were performed for static balance assessment, 'Step Up/Over' and Tandem Walk' tests were performed for dynamic balance assessment via the '*Neurocom Balance Master*' device available in our clinic.

Results: This study included 100 subjects that consist of 50 PsA patients (40 female) and 50 healthy controls (40 female) and their mean ages were 45.02 (SD:12.81) and 45.12 (SD:10.56) years, respectively. Age, sex and BMI data of both groups were similar. The mean score of DAS-28 and PASI of patients were 3.45 (SD: 0.87) and 7.80 (SD:1.05), respectively. Concerning the balance tests, there were significant differences ($p<0.05$) between patient and control groups about the all tests of sway velocity (except on firm and foam surface), eyes closed test, end sway of tandem walk test, movement time of bilateral step up over test and lift up index of left step up over test. There were not significant correlation of static and dynamic balance parameters with MAF, BDI, PSQI, falling history, fear of falling, DAS28 and PASI. The foot deformities according to X-ray assessment had not significant correlation with FAOS and balance parameters.

Conclusion: The static and dynamic balance disorders are increased in PsA. Because of the balance parameters had not significant

correlation with functional and clinical data they are acceptable as an independent parameters during the course of the disease.

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Abstract Number: 2774

Framingham Risk Score Discriminates Coronary Atherosclerosis in Psoriatic Arthritis Patient Better Than Other Cardiovascular Scores Do

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Background/Purpose: Patients with psoriatic arthritis (PsA) are associated with higher cardiovascular (CV) risks. The efficacy of established CV risk scores for predicting CV risks in PsA patients is unknown. The aim of this study is to evaluate the efficacy of different CV risk scores and their European League Against Rheumatism (EULAR) modified versions for discriminating the presence of coronary atherosclerosis evaluated by coronary Computed Tomography Angiography (CTA) in PsA patients.

Methods: Four different CV risk scores namely Framingham risk score (FRS), American College of Cardiology and American Heart Association (ACC/AHA) 10-year atherosclerotic cardiovascular disease (ASCVD), QRISK II and SCORE, together with their EULAR recommended modified versions (1.5 multiplication) were calculated. Presence of overall plaque (P+) and mixed plaque/non-calcified plaque (MP/NCP+), were identified by CTA.

Results: 88 PsA patients [50 ¡Ó 11, male: 54(61.4%)] underwent CTA were recruited. 84, 74, 88 and 88 patients were eligible to calculate FRS, ASCVD, QRISKII and SCORE respectively. All CV risk scores were significantly higher in both P+ and MP/NCP+ patients [FRS: P+ (13.5 ¡Ó 8.7 vs 6.5 ¡Ó 5.3; p<0.001), MP/NCP+ (13.7 ¡Ó 9.0 vs 7.4 ¡Ó 5.7; p<0.001); ASCVD: P+ (7.0 ¡Ó 5.3 vs 3.4 ¡Ó 3.4; p<0.001), MP/NCP+ (7.1 ¡Ó 5.5 vs 3.9 ¡Ó 3.6; p=0.005); QRISKII: P+ (9.6 ¡Ó 7.8 vs 6.4 ¡Ó 6.6; p=0.047), MP/NCP+ (9.9 ¡Ó 8.2 vs 6.5 ¡Ó 6.3; p=0.035); SCORE: P+ (1.4 ¡Ó 1.4 vs 0.5 ¡Ó 0.8; p=0.001), MP/NCP+ (1.4 ¡Ó 1.4 vs 0.6 ¡Ó 1.0; p=0.004)]. Areas under the receiver operating characteristic (ROC) curves, differentiating P+ and MP/NCP+, were 0.77 (0.67 ¡V 0.88 p<0.001) and 0.73 (0.62 ¡V 0.84 p<0.001) for FRS, 0.76 (0.636 ¡V 0.87 p<0.001) and 0.72 (0.60 ¡V 0.84 p=0.001) for ASCVD, 0.65 (0.53 ¡V 0.78, p=0.018) and 0.64 (0.52 ¡V 0.76 p=0.026) for QRISKII, 0.72 (0.614 ¡V 0.831 p<0.001) and 0.68 (0.56 ¡V 0.79 p=0.005) for SCORE, respectively. 38(45.2%), 23(31.1%), 6(6.8%) and 1(1.1%) patients were classified as having high CV risks according to FRS>10%, ASCVD>7.5%, QRISK II>20% and SCORE>5% respectively. By applying the EULAR multiplication factor, 51(60.7%), 32(43.2%), 22(25%) and 4(4.5%) patients were reclassified as having high CV risks. The sensitivity of FRS>10% increased from 56.9% to 76.5% for P+ (Figure 1), and from 53.3% to 75.6% for MP/NCP+ (Figure 2). Other risk scores generally underestimated coronary atherosclerosis (Figure 1&2).

Conclusion: FRS was better correlated with coronary atherosclerosis than other CV risk scores. EULAR modification further improved the sensitivity of FRS.

Figure 1. Left: Original risk scores, Right: EULAR modified risk scores (overall plaque)

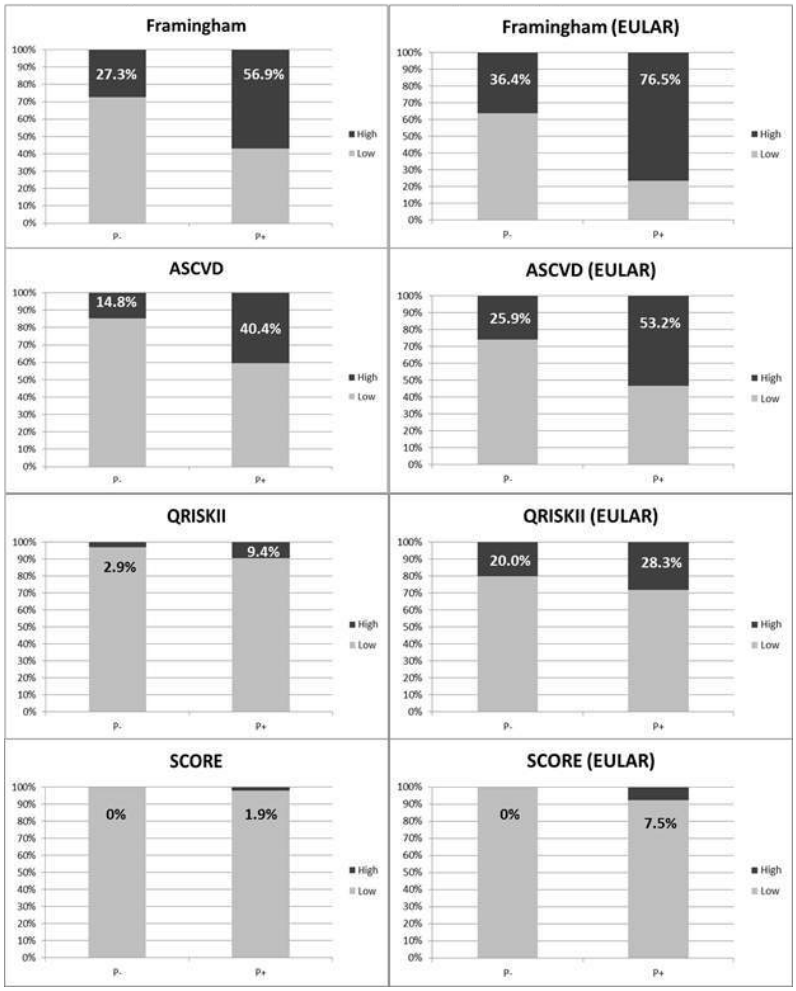
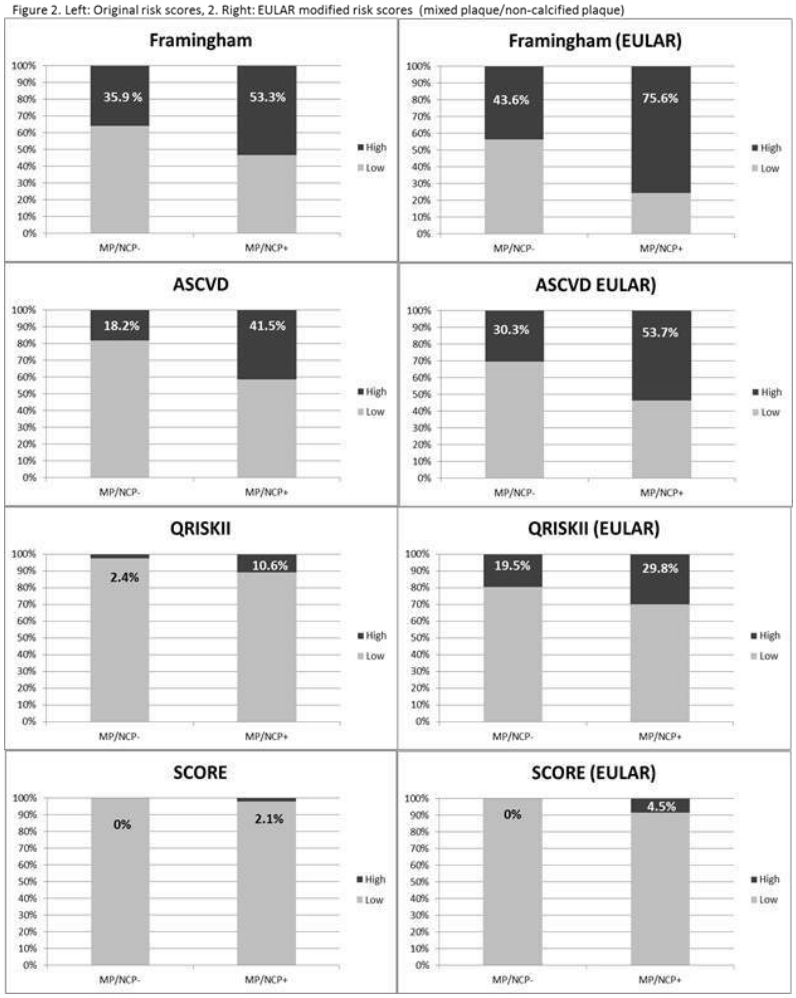


Figure 2. Left: Original risk scores, 2. Right: EULAR modified risk scores (mixed plaque/non-calcified plaque)



Disclosure: H. M. LAM, None; **J. Shen**, None; **Q. SHANG**, None; **T. H. CHENG**, None; **E. LI**, None; **K. T. WONG**, None; **L. S. TAM**, None.

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Abstract Number: 2775

Conductive Hearing Loss Is Common in Ankylosing Spondylitis

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Background/Purpose: Ankylosing spondylitis (AS) is a chronic inflammatory arthritis characterized by enthesitis, that primarily affects the spine and sacroiliac joints. While several studies had described sensorineural deafness in AS patients, conductive hearing loss has

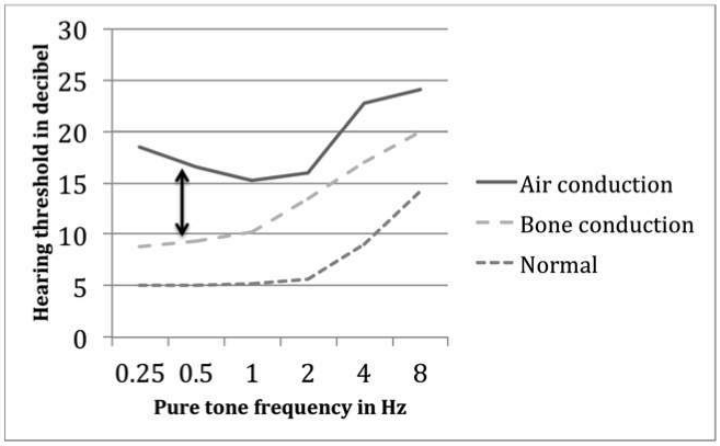
been reported as rare. We studied the prevalence hearing loss (HL) among patients with ankylosing spondylitis.

Methods: We studied 100 patients of ankylosing spondylitis fulfilling modified New York criteria after excluding patients with coexisting external and middle ear pathology. Pure tone audiometry was done in recruited patients. Hearing loss was considered to be present when the audiometric tests disclosed pure-tone thresholds greater than 20 dB (decibel) in at least 2 frequencies (0.25, 0.5, 1, 2, 4, 8 kilohertz (kHz)) of the audiogram. Mild, moderate, moderately-severe, severe and profound hearing loss were defined as hearing loss range 25-40, 40-55, 55-70, 70-90, >90 dB respectively. Clinical details such as age, disease duration, BASDI, BASFI, BASMI, cumulative NSAID dose etc. were noted of each patient. Cumulative NSAID dose was calculating using defined daily dose as given by WHO. All variables are expressed as median (25^{th} -75^{th} Interquartile range)

Results: Ninety-six of the 100 patients were male and the median age was 32 (23-42) years and median duration of illness was 6 (2-12) years. Median BASDAI, BASFI, BASMI and cumulative NSAID dose were 3(1.7-4.9), 2(1-4.15), 3.6(1.6-5.5) and 726 (210-1825) respectively. Of the 48 with hearing loss 28 patients had bilateral hearing loss. Twenty-nine patients had pure conductive hearing loss while 16 had mixed hearing loss (components of both sensory and conductive) and only 3 had pure sensory neural hearing loss. Hearing loss was mild in 38 patients while 10 had moderate to severe hearing loss. Presence of hearing loss was associated with higher age ($p=<0.05$). Conductive HL, when present, was at low frequency (0.25, 0.5, 1 kHz) in 70% cases. Sensorineural HL, when present, was at high frequency (4, 8 kHz) in 75% cases. Mean air and bone conduction of the patients in comparison to normal for age is depicted in Figure-1. There was no association of hearing loss with BASMI, BASDI, BASFI or cumulative NSAID dose.

Conclusion: Hearing loss is common among patients of ankylosing spondylitis (Table-1) and it is predominantly conductive type. HL is usually mild and occurs at low frequency.

Figure 1 Air and Bone conduction of AS patients



AS patients had a wide Air-Bone gap (arrow) suggestive of conductive hearing loss at low frequency

Table 1- Prevalence of hearing loss in Ankylosing Spondylitis

Study (n)	Prevalence
Current study (100)	48 (48%)
Amor et al (55)	29 (58%)
Adam et al (45)	32 (71.1%)
Erylimaz et al (59)	21 (35.5 %)
Dagli et al (56)	10 (35%)
Casellini et al (22)	13 (59%)

Disclosure: S. Ajmani, None; **A. Keshri**, None; **R. Srivastava**, None; **A. Lawrence**, None.

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Abstract Number: 2776

Comparability of Patients Classified As Non-Radiographic Axial Spondyloarthritis By the Imaging Vs Clinical Arms of the ASAS Criteria

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Background/Purpose: The ASAS classification criteria have provided new insights in the classification of axial SpA. Some studies suggested different characteristics between the imaging and clinical arms of axial SpA particularly in response to biologics. However, available data is still limited and additional information is required. We present our results in a large group of patients with non-radiographic axSpA (nr-axSpA).

Methods: Patients were recruited from two centers with dedicated programs in SpA. Among the registries of these institutes patients coded as nr-axSpA were identified. Two rheumatologist from each center re-scored the X-rays and excluded those with diagnostic changes of AS. SIJ MRI readings were done according to ASAS recommendations. Clinical and laboratory characteristics were then obtained for each group from the clinical database. Patients were stratified into imaging and clinical arms based on the clinical, imaging and laboratory findings. The imaging arm was further stratified into B27- and B27+ groups.

Results: There were a total of 200 nr-axSpA patients in the combined cohorts. The mean age and disease durations were 38±11.1 and 9.1±8.1 years respectively. 44.5% were male and 59% were HLA-B27-positive. There were 147 (73.5%) and 53 (26.5%) patients in the MRI-positive and clinical arms respectively. 28.6% of the patients have been treated with biologics. Comparison of imaging vs clinical arms of nr-axSpA demonstrated that age, sex, disease duration, BASDAI, BASFI and BASMI indices were similar between the groups. Uveitis and psoriasis were significantly increased in the clinical arm group. In contrast, increased acute phase reactants and

good response to NSAIDs were more prevalent in the imaging arm. Other variables such non-response to biologics were distributed evenly between the groups (Table-1). We compared B27+ vs B27- imaging patients and clinical arm patients (all B27+ by definition). Age, sex distribution and disease durations were similar between these three groups. Increased acute phase reactants and good response to NSAIDs were higher in the both imaging groups compared to clinical arm patients. Biological utilization rates, family history and presence of uveitis were higher in all B27+ patients regardless of whether they were in the clinical or imaging arm. The remainder of the extra-articular features, BASDAI, BASFI and BASMI levels and non-response to biologics were comparable between the three subsets (Table 1).

Conclusion: In this large cohort of nr-axSpA patients the clinical characteristics of nr-axSpA patients classified by the imaging vs clinical arms were comparable. It was of note that there was a comparable TNFi failure due to lack of response in both groups despite the higher CRP in the imaging arm. Our findings provide real world clinical support for the validity of the clinical arm for the classification of nr-axSpA.

	Clinical arm (n=53)	Imaging arm (n=147)	p
Age, yr	37.9±11.8	38±10.9	0.98
Sex, Male, %	47.2	43.5	0.74
Disease duration, years	10.7±9.4	8.6±7.6	0.18
Mean follow-up (months)	46.1±48.1	31.2±30.7	0.04
HLA-B27, %	100	44.2	<0.0001
Baseline BASDAI	3.8±2.6	4.5±2.5	0.11
Baseline BASFI	2.7±2.5	2.9±2.6	0.61
Baseline BASMI	1.3±1.3	1.4±1.2	0.53
Increased acute phase response, %	18.2	36.5	0.03
Good response to NSAIDs, %	50	70.2	0.03
Biologic ever, %	41.5	24	0.02
Switch ever, %	40.9	44.1	0.81
Switch due to LOE, %	80	83.3	0.9
BASDAI50 response, %	33.3	41.2	0.78
Arthritis, %	49.1	44.2	0.63
Uveitis, %	28.3	8.9	0.001
Psoriasis, %	13.2	4.8	0.04
IBD, %	1.9	2.1	0.9
Enthesitis, %	41.9	49.6	0.38
Dactylitis, %	1.9	4.8	0.68
Family history, %	30.8	26.9	0.59

	Clinical Arm (n=53)	Imaging Arm		P
		B27 pos (n=65)	B27 neg (n=82)	
Age, yr	37.9±11.8	37.4±11.2	38.5±10.7	0.83
Sex, Male, %	47.2	49.2	39	0.42
Disease duration, years	10.7±9.4	8.9±7.4	8.4±7.8	0.31
Mean follow-up (months)	46.1±48.1	35±31.2	28.3±30.2	0.02
HLA-B27, %	100	100	0	<0.0001
Baseline BASDAI	3.8±2.6	4.2±2.6	4.7±2.4	0.15
Baseline BASFI	2.7±2.5	2.8±2.6	3±2.5	0.74
Baseline BASMI	1.3±1.3	1.4±1.4	1.5±1	0.66
Increased acute phase response, %	18.2	40	33.8	0.05
Good response to NSAIDs, %	50	69.1	71	0.07
Biologic ever, %	41.5	33.8	16	0.003
Switch ever, %	40.9	57.1	23.1	0.14
Switch due to LOE, %	80	78.6	100	0.6
BASDAI50 response, %	33.3	38.1	46.2	0.77
Arthritis, %	49.1	50.8	39	0.3
Uveitis, %	28.3	15.4	3.7	<0.0001
Psoriasis, %	13.2	3.1	6.2	0.09
IBD, %	1.9	3.2	1.2	0.71
Enthesitis, %	41.9	46.7	52	0.56
Dactylitis, %	1.9	4.6	4.9	0.66
Family history, %	30.8	38.1	18.3	0.03

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Abstract Number: 2777

Is There a Difference in Clinical Features and Burden of Disease in Patients with Axial Spondyloarthritis with and without Extra-Articular Manifestations?

Kemal Erol[1], Gizem Cengiz[1], Kevser Gok[1], Gamze Kilic[2], Erkan Kilic[3] and **Salih Ozgocmen**[1], [1]Dept.PRM, Erciyes University, Faculty of Medicine, Division of Rheumatology, Kayseri, Turkey, [2]Afyon Kocatepe University, Faculty of Medicine, Dept.PRM, Afyon, Turkey, [3]Afyonkarahisar Kocatepe State Hospital, Division of Rheumatology, Afyon, Turkey

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Background/Purpose: Spondyloarthropathies include a group of disease which have similar clinical, radiographic and genetic features. Uveitis, psoriasis (PsO) and inflammatory bowel disease (IBD) are common extra-articular manifestations (EAMs) in spondyloarthritis and an important part of the ASAS classification criteria for axial and peripheral spondyloarthritis which has an influence on treatment choices. The aim of this study is to compare the burden of disease and clinical features in the patients with axial spondyloarthritis (axSpA) with and without EAMs.

Methods: Adult patients from Erciyes SpA cohort who met ASAS classification criteria for axSpA were included. Patients were assigned into two groups according to having EAMs (uveitis and/or IBD and/or PsO, all were proven by the related specialists). Radiographic axSpA was defined on the basis of presence of at least bilateral grade 2 sacroiliitis according to modified New York criteria, decided by the consensus of three rheumatologists. Patients' demographic and clinical data including symptom duration, VAS-pain, patient's and physician's global assessment, BASDAI were recorded. Short form-36 (physical and mental components, SF-36 PCS/MCS), health assessment questionnaire (HAQ) and ankylosing spondylitis quality of life questionnaire (ASQoL) were used to assess QoL and disability and hospital anxiety and depression scale (HADS) for psychological status. Anthropometric measurements included cervical rotation, tragus-to-wall distance (TWD), chest expansion, lumbar lateral flexion and Schober's test.

Results: A total of 591 patients with axSpA were included, 124 patients (%21) had EAMs (EAM +ve) and 467 patients (%79) did not have EAMs (EAM -ve). Demographic data and all anthropometric measurements were similar between EAM +ve and EAM -ve patients, except for TWD which was higher in EAM +ve patients (whole axSpA, p=0.034 and r-axSpA, p=0.002). EAM +ve patients had higher frequency of HLA B27 and peripheral arthritis than EAM –ve patients in the whole axSpA (p=0.031 and p=0.003, respectively) and r-axSpA (p=0.036 and p=0.001, respectively) groups.

Conclusion: EAMs positive and negative patients with r-axSpA differs in terms of HLA B27 and peripheral arthritis, however subgroups of patients with nr-axSpA and r-axSpA with or without EAMs have similar burden of disease.

Table. Demographic and clinical data in patients with axSpA, nr-axSpA and r-axSpA.

	axSpA (n= 591)			nr-axSpA (n= 237)			r-axSpA (n= 354)		
	EAM +ve (n=124) (21.0%)	**EAM –ve (n=467) (79%)**	**p**	**EAM +ve (n=49) (20.7%)**	**EAM –ve (n=188) (79.3%)**	**p**	**EAM +ve (n= 75) (21.2%)**	**EAM –ve (n=279) (78.8%)**	**p**
Age	36.75±9.81	36.57±9.86	0.849	33.51±9.07	34.32±9.56	0.584	38.96±9.75	38.13±9.84	0.514
Gender, F/M	50/76	208/267	0.408	104/84	26/23	0.777	23/52	99/180	0.436
BMI	25.91±4.67	26.19±4.85	0.571	25.12±5.35	25.76±4.85	0.473	26.52±4.09	26.49±4.85	0.954
Symp. duration	10.50±8.37	9.08±7.89	0.093	7.03±6.87	6.71±6.61	0.769	12.97±8.52	10.73±8.26	**0.041**
VAS-pain	4.67±3.00	4.65±3.68	0.948	4.76±3.00	4.70±2.69	0.900	4.52±3.00	4.57±4.23	0.919
PtGA	4.87±2.77	4.57±2.61	0.271	5.17±2.80	4.50±2.52	0.133	4.60±2.74	4.56±2.66	0.910
PGA	3.63±2.08	3.87±2.13	0.271	4.05±2.01	3.51±1.93	0.097	3.71±2.18	3.68±2.17	0.896
ESR (mm/h)	20.97±17.59	20.17±18.96	0.670	16.96±14.21	19.02±18.01	0.407	23.32±19.13	20.95±19.74	0.364
CRP (mg/l)	13.64±19.00	13.83±20.03	0.926	10.55±18.73	12.25±17.31	0.585	15.66±19.13	14.97±21.87	0.798
HLA B27+ve, n(%)	61 (69.3)	206 (56.7)	**0.031**	20 (57)	75 (48.7)	0.367	40 (78.4)	129 (62.9)	**0.036**
BASDAI	4.11±2.60	3.95±2.33	0.516	4.25±2.52	3.96±2.23	0.478	3.94±2.60	3.89±2.39	0.881
Perip. arthr., n(%)	38 (31.7)	89 (19.1)	**0.003**	14 (30.4)	47 (25.3)	0.476	23 (31.5)	39 (14.2)	**0.001**
HADS-a, n(%)	28 (23.3)	109 (25.2)	0.670	38 (29.2)	14 (23)	0.384	13 (18.6)	69 (26.6)	0.166
HADS-d, n(%)	57 (47.5)	211 (48.8)	0.795	23 (44.8)	74 (47.9)	0.707	33 (47.1)	134 (51.7)	0.495
SF-36/PCS	48.31±22.92	48.22±23.42	0.971	50.23±20.96	49.15±23.57	0.781	47.99±24.03	47.78±23.44	0.953
SF-36/MCS	53.21±23.79	52.58±22.27	0.812	54.85±23.09	53.84±22.00	0.806	53.15±24.05	51.97±22.29	0.729
HAQ	0.71±0.59	0.67±0.51	0.609	0.66±0.53	0.64±0.52	0.824	0.73±0.63	0.69±0.55	0.635
ASQoL	7.79±5.49	8.32±6.35	0.359	7.76±5.19	8.21±7.51	0.623	7.69±5.71	8.36±5.45	0.370

All values represent mean±standard deviations unless otherwise stated.

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Abstract Number: 2778

Is There Any Gender Specific Difference in Discriminative Value of Inflammatory Back Pain Criteria?

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Background/Purpose: Inflammatory low back pain (IBP) is the important presenting symptom in patients with axial spondyloarthritis (axSpA). Three criteria sets for IBP are frequently assessed in terms of discriminative ability from mechanical LBP, however the gender specific discriminative value of these criteria sets has not been investigated yet. Therefore the aim of this study was to evaluate gender differences in discriminative value of IBP criteria in a patient population of axial spondyloarthritis and non-spondyloarthritis chronic low back pain.

Methods: Adult patients with a history of chronic LBP (> 3 months) and age of onset less than 45 years were screened for ASAS criteria for axial spondyloarthritis (axSpA). Those who were between 18-50 years and met the axSpA criteria were assigned as axSpA group and those who did not met these criteria were assigned as non-SpA chronic LBP group. All of the patients were also screened for the items of IBP criteria according to the Calin, Berlin and ASAS criteria definitions. Receiver operating characteristic (ROC) curve analysis were performed for all the separate items and the criteria as a whole in both male and female patient groups. Area under the curve (AUC) were calculated for each item and criteria sets and statistically compared by using the De Long method.

Results: A total of 136 patients (59 women) with axSpA and 111 patients (48 women) with non-SpA LBP were included. In women, AUC was the highest for insidious onset 0.94 (95% CI 0.88-0.98), followed by alternating buttock pain 0.82, improvement with exercise 0.74, no improvement with rest 0.72, age at onset ≤ 40 years 0.68, morning stiffness > 30 min 0.67, improvement with exercise/not rest 0.66, morning stiffness 0.65, and awakening (second half of the night) because of pain 0.62 with the least value. In men, AUC was the highest for insidious onset 0.87 (95% CI 0.80-0.92), followed by morning stiffness 0.78, no improvement with rest 0.77, alternating buttock pain 0.75, improvement with exercise 0.698, improvement with exercise/not rest 0.696, morning stiffness > 30 min 0.668, awakening (second half of the night) because of pain 0.63, and age at onset ≤ 40 years 0.51 with the least value. AUC values for items in men were relatively lower than women. Similarly, the AUC values for IBP criteria sets were relatively lower in men compared to women. Also comparison of AUC values revealed that Calin criteria had significantly higher values compared to Berlin and ASAS criteria in both genders.

Conclusion: The AUC values revealed that discriminative ability of criteria sets were fair to excellent. All criteria items and sets perform similarly in both genders however criteria items perform relatively better in women than men. Also Calin criteria perfume significantly higher than Berlin and ASAS criteria in both genders.

Table Comparison of AUCs of different criteria sets in men and women

	axSpA vs non-SpA LBP n=136 vs n=111
Men	**AUC (95%CI)**
CALIN (1)	0.87(0.80-0.92)
BERLIN (2) n=76 vs n=59	0.77(0.70-0.84)
ASAS (3) n=76 vs n=60	0.71(0.62-0.79)
1 vs 2, p value	0.0021
1 vs 3, p value	0.0001
2 vs 3, p value	0.058
Women	
CALIN (1) n=57 vs n=47	0.93(0.87-0.97)
BERLIN (2) n=57 vs n=47	0.80(0.71-0.88)
ASAS (3) n=57 vs n=40	0.79(0.70-0.87)
1 vs 2, p value	0.003
1 vs 3, p value	0.0002
2 vs 3, p value	0.949

Disclosure: G. Cengiz, None; **K. Erol**, None; **K. Gok**, None; **G. Kilic**, None; **E. Kilic**, None; **S. Ozgocmen**, None.

Abstract Number: 2779

Better Health-Related Quality of Life and Work Capacity in Patients Achieving Inactive Disease and Clinical Response in Patients with Non-Radiographic Axial Spondyloarthritis

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Background/Purpose: Few studies have evaluated the relationship between disease activity/clinical response and patient-reported outcomes (PROs) of pain, fatigue, health-related quality of life (HRQoL), and work productivity in patients with non-radiographic axial spondyloarthritis. In post hoc analyses of findings of the EMBARK study, this association was assessed in patients with active, NSAID-resistant, nr-axSpA.[1-3] (ClinicalTrials.gov identifier: NCT01258738).

Methods: Patients who satisfied Assessment of SpondyloArthritis international Society (ASAS) classification criteria for axSpA (not modified NY radiographic criteria) were randomized to receive etanercept (ETN) 50 mg/wk or placebo (PBO) to wk 12, followed by ETN 50 mg/wk to wk 104. Patients were grouped based on Ankylosing Spondylitis Disease Activity Score (ASDAS) disease activity state (inactive disease [ID] vs active disease) and ASAS40 response (responders vs non-responders) at wk 12 and 104 regardless of treatment group assignment. Changes in least square (LS) means for PROs of pain, fatigue, HRQoL, and work productivity from baseline (BL) to wk 12 and 104 were compared between groups in the modified intent-to-treat (mITT) population with observed cases (ANCOVA; no imputation of missing data).

Results: At wk 12, 61/214 (29%) of patients receiving ETN or PBO achieved ASDAS-ID; 51/213 (24%) achieved ASAS40 response. At wk 104, 123/205 (60%) of patients overall achieved ASDAS-ID and 121/205 (59%) were ASAS40 responders. Patients with ASDAS-ID at wk 12 and 104 had significantly less BL pain and greater HRQoL (SF-36 PCS and AsQoL) than those with active disease; those achieving ASDAS-ID at wk 104 had better BL EQ-5D (P<0.05, all). ASAS40 responders at wk 12 had significantly less total back pain and better health utility (EQ-5D) at BL vs non-responders; ASAS40 responders at wk 104 had significantly less pain and greater

HR-QoL (SF-36 PCS) at BL ($P<0.05$, all). Significantly greater improvements were observed in pain/fatigue (nocturnal back pain, MFI general fatigue), utility (EQ-5D VAS), HR-QoL (SF-36 and ASQoL), and work productivity (WPAI-AS presenteeism) among patients with ASDAS-ID vs active disease (table). ASAS40 response was similarly associated with significantly greater improvements in these PROs.

Table. Changes in LS means from BL to wk 12 and wk 104 for PROs in nr-axSpA patients with ASDAS inactive vs active disease.

PRO	LS Mean Change (SE)			
	Wk 12		Wk 104	
	ASDAS Inactive Disease	ASDAS Active Disease	ASDAS Inactive Disease	ASDAS Active Disease
Nocturnal back pain (0–10 VAS)	-4.1† (0.3)	-1.0 (0.2)	-4.6† (0.2)	-2.1 (0.2)
MFI general fatigue (4-20)	-2.2* (0.4)	-0.5 (0.3)	-4.6† (0.4)	-0.5 (0.5)
EQ-5D (0–100 VAS)	20.6† (2.5)	1.9 (1.6)	26.9† (1.4)	12.0 (1.9)
SF-36 PCS (0–100)	9.3† (0.8)	3.0 (0.5)	13.1† (0.6)	4.7 (0.9)
SF-36 MCS (0–100)	4.7 (1.2)	2.1 (0.8)	6.3† (0.9)	0.5 (1.2)
ASQoL (0–18)	-3.7† (0.5)	-1.3 (0.3)	-5.6† (0.3)	-1.8 (0.5)
WPAI-AS absenteeism (0–100% work time missed)	-7.4 (3.4)	0.0 (2.5)	-8.8 (0.8)	-7.3 (1.4)
WPAI-AS presenteeism (0–100% impairment while working)	-27.1† (3.6)	-4.7 (2.6)	-28.8† (2.0)	-9.5 (3.7)

*$P\leq0.001$; †$P\leq0.0001$ ASQoL, ankylosing spondylitis quality of life; EQ-5D, EuroQol 5-Dimensions; MCS, mental component summary; MFI, Multidimensional Fatigue Inventory; PCS, physical component summary; VAS, visual analog scale; SF-36, 36-item Short Form Health survey; WPAI-AS: Work Productivity and Activity Index in ankylosing spondylitis

Conclusion: In patients with early, active nr-axSpA and an inadequate response to NSAIDs who participated in the EMBARK study, achievement of inactive disease and clinical response were associated with meaningful improvements in PROs of pain, fatigue, and HRQOL. Moreover, improvement in patients' symptoms resulted in improvement in their capacity to work. **References:** 1. Dougados M, et al. *Arthritis Rheum* 2014;66:2091-102. 2. Makysmowych WP, et al. *Ann Rheum Dis* 2015; Aug 12 [Epub ahead of print]. 3. Dougados M, et al. *J Rheumatol*. 2015;42:1835-41.

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Abstract Number: 2780

A Modification of the Psoriatic Arthritis Disease Activity Score (mPASDAS) Using SF-12 As a Measure of Quality of Life

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Background/Purpose: The Psoriatic Arthritis Disease Activity Score (PASDAS) is a newly developed composite disease activity measure that summarizes psoriatic arthritis (PsA) disease activity with a score ranging from 0-10. PASDAS captures articular and extra-articular manifestations of the disease and the impact of the disease on the patient via the following variables: swollen and tender joints, dactylitis, Leeds enthesitis index, C-reactive protein, physician and patient global disease activity, and the physical component summary score (PCS) of the medical outcomes survey Short Form 36 (SF-36). A limitation of PASDAS is that the score depends on the patient completing the SF-36, which requires significant time to complete. A shorter 12-question subset of SF-36, the SF-12, with the same range of values, agrees well with the SF-36 in many patient populations. The current objective was to measure the agreement between PASDAS calculated using the standard scoring formula and a modified PASDAS (mPASDAS) calculated by replacing the SF-36-PCS with SF-12-PCS in the scoring formula.

Methods: 100 patients meeting CASPAR criteria for PsA attending a PsA clinic for follow-up visits were consecutively recruited in June and July 2015. All variables required to calculate PASDAS were collected and PASDAS was calculated for each patient. The 12 item responses for SF-12 were extracted from the SF-36 questionnaires. The mPASDAS was subsequently calculated based on the PASDAS scoring formula where SF-36 –PCS was replaced by SF-12 - PCS. A Bland-Altman plot of the mean differences in scores calculated for PASDAS and mPASDAS measured agreement between the two sets of scores. The misclassification of patients based on disease activity as measured with mPASDAS compared to the classification based on the original PASDAS was also determined.

Results: An analysis of 100 patients [53% male, mean (SD) age 57.3 (11.9) years, mean (SD) disease duration 16.9 (11.7) years] revealed that the mean (SD) PASDAS was 3.29 (1.39) and the mean (SD) mPASDAS was 3.24 (1.27). The Bland-Altman plot produced a mean difference (95%CI) between mPASDAS and PASDAS of -0.05 (-0.07, -0.03). The lower limit of agreement was -0.24 (95%CI -0.21, -0.28) and the upper limit was 0.14 (95%CI 0.10, 0.17). The validity of the limits of agreement was supported by a number of normality tests indicating normally distributed differences. No relationship between the differences and the mean values of the scores exist indicating these limits of agreement are valid across the full range of the measures. Discrepancies were seen in 5 out of the 100 cases resulting in a misclassification rate of 5%. PASDAS classified 33 cases as low disease, 42 cases as moderate disease, and 25 cases as high disease. Using the same cutoff scores, mPASDAS classified 34 cases as low disease, 43 cases as moderate disease, and 23 cases a high disease.

Conclusion: The mPASDAS and PASDAS show strong agreement without clinically significant systematic bias in mPASDAS scores. In clinical settings, the mPASDAS may replace PASDAS in disease activity assessment given the strong agreement, low misclassification rate and significantly reduced patient questionnaire burden.

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Abstract Number: 2781

Immunization with ApoB100 Peptide Vaccine Reduces Atherosclerosis Development in a Mouse Model of Systemic Lupus Erythematosus

Ingrid Yao-Mattisson, Maria Wigren, Gunilla Nordin Fredrikson and Jan Nilsson, Lund University, Malmö, Sweden
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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by impaired self-tolerance causing damage to multiple organs including the cardiovascular system. Current therapies do not decrease the incidence of cardiovascular disease (CVD) in SLE. Previous studies have shown that immunizations with peptides derived from apolipoprotein B (ApoB) reduce atherosclerosis in hypercholesterolemic mice. In the present study we investigated if a vaccine based on the apo B peptide p210 (CVX-

14) can inhibit atherosclerosis in mice with an SLE-like phenotype.

Methods: *:* MRL/*lpr* ApoE$^{-/-}$ mice received subcutaneous injections with PBS, CVX-14 or adjuphos alone at week 6, 9, 11 and 21 of age. Atherosclerosis was assessed by Oil Red O staining of the aorta and plaque inflammation by CD68 immunostaining of aortic root sections and qPCR of carotid arteries. The response to immunization was also assessed by flow cytometry of spleen cells and measurement of antibodies

Results: : Immunization with CVX-14 reduced plaque development in the aorta by 55.5% (p=0.01) and plaque area with positive macrophage staining (CD68) by 66.2% (p=0.005) as compared with the PBS control. Arteries from CVX-14 treated mice were also found to have reduced expression of TNF-a and TGF-b mRNA. Plasma cholesterol was increased in CVX-14 treated mice, but there was no effect on plasma triglycerides, p210 IgG or cytokine levels. Both CVX-14 and adjuphos alone increased the fraction of regulatory T cells in the spleen

Conclusion: Apo B peptide based vaccines represents a possible novel approach for prevention of CVD in SLE that warrants further investigation

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Disclosure: I. Yao-Mattisson, None; **M. Wigren**, None; **G. Nordin Fredrikson**, None; **J. Nilsson**, None.

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Abstract Number: 2782

Bortezomib Treatment Prevents Glomerulosclerosis Associated with Lupus Nephritis in a Murine Model through Suppressive Effects on the Immune and Renin-Angiotensin Systems

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Session Title: Systemic Lupus Erythematosus – Animal Models - Poster II

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Background/Purpose:

Lupus nephritis (LN) is one of the main causes of morbidity and mortality in SLE. Although a combination therapy using steroids and immunosuppressant such as cyclophosphamide, azathioprine and mycophenolatemofetil has been well established in lupus nephritis, the therapy is often not effective. Establishment of new alternative therapy has been required. Proteasome inhibition by bortezomib has been recently expected to be a novel strategy for LN. However, the precise mechanisms of bortezomib for amelioration of LN have not fully been elucidated to date. Therefore, we conducted this study to clarify the mechanisms of the amelioration for the nephritis in the treatment with bortezomib.

Methods: Bortezomib (0.75 mg/kg) was administered subcutaneously every 3 days to NZB/W F1 mice, and the serum anti-double stranded (ds) deoxyribonucleic acid (DNA) antibody titers and proteinuria levels were monitored every 3 weeks. The kidneys samples were examined histologically or used for real-time quantitative reverse transcription-polymerase chain reaction (RT-PCR) analysis after 18 weeks of treatment. The peripheral blood mononuclear cells (PBMCs) were purified from spleen and used for real-time quantitative RT-PCR analysis. Serum cytokines levels were measured using flow cytometry. Anti-ds DNA antibody was measured by enzyme-linked immunoassays (ELISA). Immunohistochemical analysis was performed in the kidneys samples using antibodies to transforming growth factor (TGF)-β, angiotensin II (Ang II), angiotensin II type 1 receptor (AT1R), type I collagen, immunoglobulin G, CD138 and CXCL-13.

Results: Bortezomib reduced both the serum anti-dsDNA antibody titers and the proteinuria levels in the lupus prone mice. It prevented inflammatory cell infiltrations into and the deposition of immunoglobulin G within the glomeruli. Bortezomib reduced the interferon-g,

interleukin (IL)-4, and IL-10 levels in both the serum and the ribonucleic acid expression levels for these cytokines in the PBMCs. Bortezomib reduced the number of CD 138 positive plasma cells in the glomeruli by downregulating CXCL-13. It prevented type I collagen synthesis by downregulating the expression of TGF-b, Ang II and AT1R, which are involved in renin-angiotensin system (RAS) related molecules.

Conclusion: Bortezomib is an effective therapeutic reagent for LN through multiple mechanisms such as suppressive effects aginst cytokines production, chemokines production, antibodies production, and RAS. In particular, the suppressive effects on the formation of the fibrosis characterized by type I collagen synthesis by downregulating RAS related molecules may be beneficial in the treatment of refractory SLE patients who have refractory LN.

Disclosure: K. Nozawa, None; **Y. Matsuki**, None; **K. Yamaji**, None; **N. Tamura**, None; **Y. Takasaki**, None.

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Abstract Number: 2783

Human Mesenchymal Stem Cells from Different Tissues Exert Distinct Therapeutic Effect on Systemic Lupus Erythematosus

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Background/Purpose: Previous clinical data has shown that transplantation of umbilical cord mesenchymal stem cells (UC-MSCs) could effectively alleviate the disease symptoms in both patients with active and refractory systemic lupus erythematosus (SLE). Although MSCs isolated from different tissues were reported to possess immunomodulatory functions, it remains unknown whether they have comparable therapeutic effects in treating SLE patients. Here, employing the SLE mouse model, we assessed and compared the abilities of human UC-MSC, amniotic fluid MSC (AF-MSC), periodontal ligament stem cell (pDLSCs) and dental pulp stem cells (DPSCs) to treat SLE mouse model.

Methods: SLE-like B6.lpr mice were administered MSCs intravenously at age 25 weeks, while the control group received fibroblast-like synoviocytes (FLS). All mice were sacrificed at age 35 weeks. Anti-dsDNA antibody and ANA in the plasma were determined by ELISA. The frequencies of Th1, Th2, Treg, Th17, Tfh, Tfr and plasma cells were determined by flow cytometry. The pathology of kidney was analyzed by H&E and anti-IgG/IgM/C3 immunofluorescence.

Results: We found that all the four kinds of MSCs could significantly ameliorate the pathology of lupus nephritis and serological changes in B6.lpr mice. However, mice treated with UC-MSC and DPSCs prolonged the life span better than AF-MSC and pDLSCs. The concentration of anti-dsDNA antibody was reduced, especially in UC-MSC and DPSCs treated mice. The percentages of Th1 cells reduced after MSCs transplantation except AF-MSC treated group. The proportion of Treg only increased in UC-MSC treated group.

Conclusion: UC-MSC might be the optimum choice for SLE treatment.

Disclosure: X. Tang, None; **Z. Zhang**, None; **L. Sun**, None.

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Abstract Number: 2784

Mesenchymal Stem Cells Ameliorate Lupus By Promoting T Cell Apoptosis Via Bcl-2/Bim Independent Pathway in MRL/Lpr Mice

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Background/Purpose: Systemic lupus erythematosus (SLE) is an inflammatory autoimmune disease, involving in dysfunction of many organs. The abnormality of apoptosis plays an important role in the pathogenesis of SLE. Umbilical cord (UC)-derived mesenchymal stem cells (MSCs) have been confirmed to exert therapeutic effects on SLE. However, whether the benefit effects of UC-MSCs on SLE were mediated by regulating apoptosis remains to be elucidated. Mesenchymal stem cells (MSCs) have recently been used successfully in humans to control a lot of diseases. However, the mechanisms involved in their immunomodulatory effects remain a matter of debate. Here we explored whether lymphocytes apoptosis involved in the therapeutic effects of UC-MSCs in lupus mice.

Methods: One million human umbilical cord derived MSCs (UC-MSCs) were injected into B6.lpr mice via tail vein and 6 hours, 24 hours and four weeks later, all the mice were sacrificed, the apoptosis of lymphocyte in peripheral blood and spleen tissues as well as the expressions of Bim and Bcl-xl were detected by FACS, the immune cell subpopulations and cytokines in serum were also examined at 6 hours and 24 hours, respectively. The curative effects were assessed 4 weeks later.

Results: UC-MSCs ameliorated disease progression of lupus mice, by regulating the percentage of immune cells, decreasing spleen weight and repairing kidney lesion. UC-MSCs promoted the lymphocyte apoptosis in peripheral blood and spleen tissues at 6 hours and 24 hours, reduced serum TGF-β1 levels, but did not affect Bim and Bcl-xl expressions in CD4+ and CD8+ T cells. Meanwhile, the percentage of Treg was significantly increased in MSCs transplantation group at both 6 and 24 hours. Reductions in the proportions of plasma cells, Th1,Th2 cells were also evident at 24 hours after MSCs infusion, while the levels of Tfh and Th17 cells had no significant change among different groups neither at 6 hours nor 24 hours.

Conclusion: MSCs may promote the apoptosis of T cells in lupus mice through regulating the immune cell subpopulation, decreasing total TGF-β1 in serum. Bim and Bcl-xl are not involved in it.

Disclosure: S. Huang, None; **D. Wang**, None; **L. Sun**, None.

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Abstract Number: 2785

Translatable in Vitro Immunocyte Functional Measures of CC-292 and CC-90008 Inhibitors of the Bruton's Tyrosine Kinase (Btk)/Tec Family and the Pathology Observed in the MLR/Lpr Mouse Model of Systemic Lupus Erythematosus (SLE)

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Background/Purpose: CC-292 and CC-90008 are covalent Btk/Tec family kinase inhibitors that block Btk activity by binding with high affinity to the adenosine triphosphate (ATP) binding site of Btk and forming a covalent bond with cysteine 384 in the target Btk protein, providing rapid, complete, and prolonged inhibition of Btk activity. Despite similar inhibitory potencies towards Btk enzyme inhibition, CC-292 and CC-90008 differ significantly in their impact on B and T cell, basophil, monocyte, and mDC functions. The objective of this study was to compare the efficacy of two covalent modifiers of Btk/Tec family kinases with different, but overlapping in vitro functional immunoprofiles in the MRL/lpr model of SLE and determine which in vitro immunocyte functions best translate to pathological endpoints.

Methods: Immunoprofiling of B cell function was measured by proliferation, plasmablast differentiation, IgG and IL-6 production, and surface expression of activation markers (CD86, CD40, CD54, and CD69). T cell function was measured by proliferation, and cytokine production. CD8 T cell and NK function was measured by degranulation assays. Monocyte/macrophage and basophil activity was measured by Fcγ Receptor-mediated TNFα production and FcεR-mediated degranulation, respectively. Osteoclast and dendritic cell effects were each assessed by differentiation endpoints from precursor cells. Pathology in the MRL/lpr SLE model was assessed by body, spleen, and lymph node weight gain, dsDNA and ANA autoantibody titers, skin lesions, and kidney function (proteinurea) and lesions (histological assessment).

Results: In vitro, CC-292 and CC-90008 were most similar in their ability to inhibit plasmablast differentiation, antibody secretion, basophil IgE degranulation, T-cell cytokine inhibition, and osteoclastogenesis. Differences were observed in that CC-292 inhibited macrophage Fcγ-induced TNFα, mDC differentiation and weakly inhibited T-cell proliferation, while CC-90008 had no effect on these macrophage and mDC functions and strongly inhibited T cell proliferation. In the MRL/lpr SLE model, CC-292 and CC-90008 both reduced dsDNA and ANA autoantibody titers, proteinurea and kidney pathology. In contrast, CC-90008 inhibited increases in body weight, skin lesions, splenomegaly, and lymphadenopathy, while CC-292 had only partial effects.

Conclusion: The in vitro immunophenotyping of CC-292 and CC-90008 on immunocyte function had translatable correlates to SLE pathology in the MRL/lpr model. While plasmablast differentiation and antibody production correlated with in vitro B cell measures and in vivo autoantibody and kidney pathologies, the in vitro T-cell functions correlated with splenomegaly, lymphadenopathy, and skin pathology. These results indicate that while BTK and associated antibody and kidney function treat an important part of lupus pathology, activity associated with T-cell inhibition may be required for effects on skin and secondary lymphoid organ pathology.

Disclosure: G. Ringheim, Celgene, 3,Celgene, 1; **J. Kosek**, Celgene, 1,Celgene, 3; **L. Capone**, Celgene, 1,Celgene, 3; **M. Adams**, Celgene, 1,Celgene, 3; **E. M. Hur**, Celgene, 1,Celgene, 3; **P. H. Schafer**, Celgene, 1,Celgene, 3.

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Abstract Number: 2786

The Janus Kinase Inhibitor Tofacitinib Ameliorates Murine Lupus and Its Associated Vascular Dysfunction

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Background/Purpose: Dysregulation of innate and adaptive immune responses contributes to the pathogenesis of systemic lupus erythematosus (SLE) and its associated premature vascular damage. To date, no drug targets both systemic inflammatory disease and the cardiovascular complications of SLE. Tofacitinib is a Janus kinase (JAK) inhibitor that blocks signaling downstream of multiple cytokines implicated in lupus pathogenesis. While clinical trials have shown that tofacitinib exhibits significant clinical efficacy in various autoimmune diseases, its role in SLE and on its associated vascular pathology remains to be characterized.

Methods: MRL/*lpr*lupus-prone mice received tofacitinib or vehicle by gavage for 6 weeks (therapeutic arm) or 8 weeks (preventive arm). Nephritis, skin inflammation, serum autoantibody levels and cytokines, mononuclear cell phenotype and gene expression, neutrophil extracellular trap (NET) release, endothelium-dependent vasorelaxation and endothelial differentiation were compared in treated and untreated mice.

Results: Treatment with tofacitinib led to significant improvement in measures of disease activity including nephritis, skin inflammation, and autoantibody production. In addition, tofacitinib treatment reduced serum levels of pro-inflammatory cytokines and interferon responses in splenocytes and kidney tissue. Tofacitinib also modulated NET formation and significantly increased endothelium-dependent vasorelaxation and endothelial differentiation. The drug was effective as both preventive and therapeutic strategies

Conclusion: Tofacitinib modulates the innate and adaptive immune responses, ameliorates murine lupus and improves vascular function. These results indicate that JAK inhibitors have the potential to be beneficial in SLE and its associated vascular damage.

Disclosure: Y. Furumoto, None; **C. K. Smith**, None; **L. P. Blanco**, None; **W. L. Tsai**, None; **W. Zhao**, None; **V. Hoffmann**, None; **S. Thacker**, None; **G. Sciumè**, None; **L. Nuñez**, None; **A. Remaley**, None; **J. J. O'Shea**, None; **M. Kaplan**, None; **M. G. Gadina**, None.

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Abstract Number: 2787

Bortezomib Treatment Induces Higher Mortality Rate in Lupus Model Mice with High Disease Activity

Hiroshi Fujii[1], Tomoko Ikeda[1], Masato Nose[2], Tomoyuki Muto[3], Kanae Akita[1], Yukiko Kamogawa[1], Tsuyoshi Shirai[1], Yuko Shirota[1], Tomonori Ishii[4] and Hideo Harigae[1], [1]Department of Hematology and Rheumatology, Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Institute for Promotion of Advanced Science and Technology, Ehime University, Matsuyama, Japan, [3]Tohoku University Graduate School of Medicine, Sendai, Japan, [4]Tohoku University Hospital, Senndai, Japan
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Background/Purpose: SLE is a chronic inflammatory disease triggered by the deposition of autoantibodies. One of the goals for SLE therapy is to suppress the production of the pathogenic antibodies. Bortezomib (Bz) is a proteasome inhibitor and directly targeting antibody-producing plasma cells. Recently, we reported the first randomized control trial to evaluate the effect of Bz for SLE (Ishii et al.. ACR 2015). In that study, we showed that Bz treatment is associated with many adverse reactions for refractory lupus patients. Previously, several reports showed that Bz was effective on and improved survival rate of lupus model mice. However, since Bz treatments for lupus model mice were initiated around the onset of diseases in these reports, it is not clear whether Bz has therapeutic effect on mice with high disease activity as well as preventive effect on low disease activity. In this study, we examined therapeutic effect of Bz on 14 wks-old (high disease activity) MRL/lpr mice and compared the survival curves of 10 wks-(around disease onset) and 14wks-Bz initiated mice.

Methods:

(1) Female MRL/lpr mice at 10 wks- and 14 wks- (n=8, each) were analyzed for anti-dsDNA antibody, weight of lymph nodes and spleen, and cellular subsets of spleen and bone marrow. (2) MRL/lpr mice (14 wks) were treated with (i) PBS (n=13), (ii) Bz (750ug/kg, twice in a week) (n=12), (iii) cyclophosphamide (Cyc) (1mg/body, once in 2 weeks) (n=15) and analyzed for anti-dsDNA antibody, pathological index of glomerulonephritis and plasma cell number at 24 wks-old. (3) Survival curve of 10 wks- and 14 wks-Bz initiated groups were compared.

Results: MRL/lpr mice at 14 wks-old showed more weight of lymph nodes and spleen (p=0.0015, p=0.0013, respectively), and significantly higher anti-dsDNA antibody titer than those at 10 wks (p=0.033) (Fig-1), indicating higher disease activity at 14 wks old. Both treatments with Bz and Cyc significantly decreased the number of spleen cells (p<0.001, p=0.0136, respectively), glomerulonephritis index (p=0.0017, p=0.0034, respectively). Bz significantly decreased plasma cells (p<0.001) and anti-dsDNA antibody titer (p<0.001), while Cyc did not. In survival curve, 14 wks-Bz initiated group showed significantly higher mortality rate than control and 10 wks group (p=0.014) (Fig-2).

Conclusion: In spite of a therapeutic trial, Bz treatment had more toxic effect on mice with higher disease activity. Understanding the mechanism of the toxicity is important for clinical application of Bz to human SLE.

Figure-1 Titer of anti-dsDNA antibody of 10 wks and 14 wks MRL/lpr mice

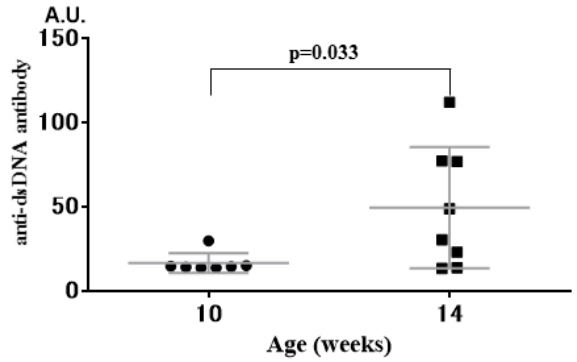
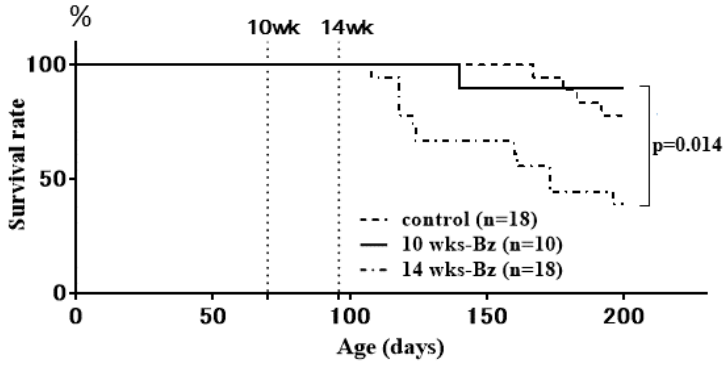


Figure-2 Survival curve of MRL/lpr mice with bortezomib treatment



Disclosure: H. Fujii, None; **T. Ikeda**, None; **M. Nose**, None; **T. Muto**, None; **K. Akita**, None; **Y. Kamogawa**, None; **T. Shirai**, None; **Y. Shirota**, None; **T. Ishii**, Chugai, Ono, Pfizer, Tanabe Mitsubishi, Astellas, 8; **H. Harigae**, None.

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Abstract Number: 2788

Suppression of IL-1 Signaling Ameliorates Dermatitis in a Murine Model of Systemic Lupus Erythematosus

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a prototypical autoimmune disease defined by autoantibody production, immune dysregulation, and end-organ damage. Our laboratory previously showed that MyD88, a signaling component of IL-1 and Toll-like receptors (TLR) 7 and 9, is a central mediator of SLE pathogenesis. Genetic studies have clearly implicated TLR7 and TLR9 in regulating disease. However, though evidence in humans and mouse models suggests a pathogenic role for IL-1, this has not been directly tested. Data from our laboratory suggest that dermatitis in murine SLE is MyD88 dependent but TLR7/9 independent, differing from systemic manifestations of the disease.

Methods: Tissue homogenates from diseased MRL.Fas^{lpr} (MRL/lpr) mice and non-diseased tissues were evaluated by qPCR. MRL/lpr mice were crossed with IL1R1$^{-/-}$ mice and evaluated initially as an F2 intercross cohort, a validated and rapid method for screening for genetic control of autoimmunity in the context of an autoimmune-predisposing genetic background. Subsequently, the *Il1r1* loss of function allele was backcrossed for 7 generations and then made homozygous; this cohort was analyzed for disease pathology at 16 weeks for females and 19 weeks for males. We evaluated proteinuria, renal histology, dermatitis, ANA, and immune cell activation via flow cytometry.

Results: IL-1β mRNA levels were increased in kidneys of MRL/lpr mice with proteinuria nearly 5-fold compared to non-diseased young MRL/lpr mice ($p=0.05$); and in inflamed skin, IL-1β mRNA levels were elevated nearly 50 fold compared to controls ($p<0.005$). There was no significant difference in proteinuria, glomerulonephritis, ANA production, or spleen size. However, dermatitis was significantly reduced in the IL-1R1 deficient F2 Fas^{lpr} mice ($p<0.008$) compared to littermate controls. This finding was recapitulated in the backcrossed cohort wherein we observed decreased rates of dermatitis in the IL1R1$^{-/-}$ mice compared with littermate MRL/lpr controls.

Conclusion: This study supports the theory that there are differential mechanisms for tissue specific manifestations of systemic autoimmune diseases, specifically, while TLR7/9 regulates systemic manifestations of SLE upstream of MyD88, IL-1 regulates dermatitis. Overall these findings provide evidence that IL-1 signaling is a significant contributor to autoimmune dermatitis in the MRL model and may be a potential target for treating cutaneous lupus manifestations.

Disclosure: J. Tilstra, None; **S. Bastacky**, None; **M. Shlomchik**, None.

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Abstract Number: 2789

Novel Glucocorticoid Prodrug Effectively Attenuates Late Stage Lupus Nephritis with Improved Safety Profile

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Background/Purpose: Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). Glucocorticoids (GCs) are recommended by ACR as one of the first line treatments for LN. Long-term clinical use of GCs, however, is associated with an array

of significant side effects. To address this challenge, we have developed a novel macromolecular prodrug (ZSJ-0228) of dexamethasone (Dex) that passively targeted to the kidney, thereby effectively attenuates lupus nephritis with improved safety profile.

Methods: Polyethylene glycol (PEG) was conjugated to Dex via hydrazone (an acid-cleavable linker) to create ZSJ-0228. NZB/W F1 female mice (28 weeks old) received monthly i.v. injection of the prodrug or daily i.v. injection of dose equivalent dexamethasone phosphate sodium for 2 months. The albuminuria level was monitored weekly. The end point serum cytokine panel was analyzed. The bone quality was evaluated using m-CT. The in vivo distribution of ZSJ-0228 was assessed using near infrared (NIR) imaging and the cell phenotypes that sequester the prodrug were investigated using flow cytometry.

Results: When compared to dose equivalent daily Dex treatment, ZSJ-0228 markedly improved the survival of NZB/W F1 mice and is significant more effective in normalizing albuminuria; no significant systemic toxicity of GCs (i.e. WBC reduction, adrenal gland atrophy and osteopenia) was observed in the prodrug treated group; and there was a significantly lower serum level of proinflammatory cytokines (MCP-1, IFN-beta, IL-17A and GM-CSF) after 2 months treatment with ZSJ-0228. NIR imaging showed that the prodrug primarily distributed in inflamed kidneys, and FACS results suggest that the Alexa 488-labeled prodrug was mainly sequestered by intraglomerular mesangial cells and proximal tubule epithelial cells.

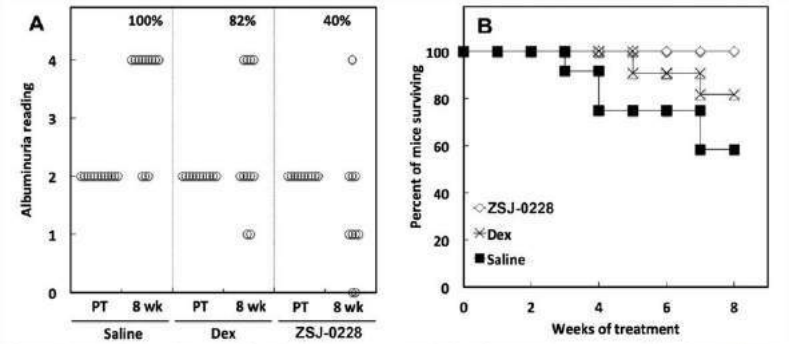

Figure 1. ZSJ-0228 ameliorates albuminuria, improves survival and attenuates severe nephritis in NZB/W F1 mice. (A) Albuminuria reading; (B) Kaplan-Meier survival curve.

Conclusion: Dex prodrug ZSJ-0228 significantly improves the therapeutic efficacy and safety of Dex. Further structural optimization of the prodrug may lead to a new drug candidate for better and safer treatment of lupus nephritis.

Disclosure: X. Wang, None; **Z. Jia**, None; **Y. Yu**, None; **K. Su**, None; **J. R. O'Dell**, Eli Lilly and Company, Medac, Coherus, BMS, GSK, 5; **D. Wang**, None.

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Abstract Number: 2790

Selective Disruption of Estrogen Receptor Alpha Expression in Dendritic Cells of Lupus-Prone Mice Results in Increased Female-Specific Death

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Session Time: 9:00AM-11:00AM

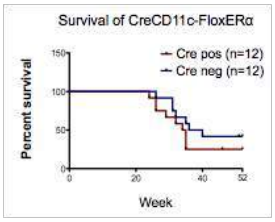
Background/Purpose: SLE is a disease that disproportionately affects females. The etiology of the sex bias in this disease is unclear. We previously showed that a functional knockout of estrogen receptor alpha (ERaKO) resulted in significantly reduced renal disease and increased survival in murine lupus. The mechanism of this effect, which requires estrogen, is not known. Interestingly, an ERa-/- (null mutant) mouse is not similarly protected. We and others have demonstrated a role for ERa in dendritic cell (DC) development. Here we

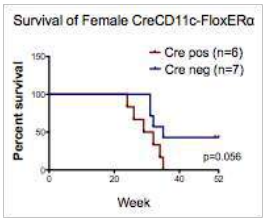
show that selective genetic disruption of ERa in DCs of lupus prone mice results in a survival difference, but only in females, who die prematurely compared with intact females.

Methods: Floxed-ERa and Cre-CD11c strains were backcrossed onto the NZM2410 lupus-prone background for 12 generations. Animals were validated by sorting CD11c+ DCs from Flt3L-cultured bone marrow; CrePos/Floxed-ERa mice had mRNA levels of ERa in DCs reduced by ~90%. Urine and blood were collected at select intervals and mice were sacrificed at 52 weeks, or earlier if they had high proteinuria or >10% weight loss. Spleen cells were isolated and flow cytometry was performed to determine number and subset of DC (cDCs: MHCII+/CD11c++/CD11b+; tolerogenic DCs: MHCII+/CD11c++/CD8a+; and pDCs: MHCII+/CD11c+/B220+/SiglecH+).

Results: n=12 CrePos/Floxed-ERa (DC-specific ERaKO) and n=12 CreNeg/Floxed-ERa animals were entered into the study. There was no significant difference in survival between the 2 groups (males and females). However, considered separately, survival of female lupus prone mice was significantly different. Median age at death was 30.0 weeks (± 1.807) n=6 for the CrePos and 40.4 weeks (± 3.891) n=7 for the CreNeg females ($p<0.042$). At 52 weeks: CrePos (DC-specific ERaKO) 0/6 were alive (0%) vs. CreNeg – 3/7 were alive (43%). Preliminary flow cytometry results revealed decreased percent of CD8a+ tolerogenic DCs in CrePos vs. CreNeg/FloxedERa, as well as increased percent of both CD11c++/CD11b+ cDCs and pDCs in CrePos vs. CreNeg/FloxedERa.

Conclusion: Selective deletion of ERa in DCs of lupus-prone mice results in reduced survival, but only in female animals. These mice had fewer tolerogenic DCs and increased numbers of both inflammatory cDCs and pDCs from spleen, which may partially explain the phenotype. This data joins a growing body of evidence that estrogen and ERa play critical roles in modulating immune cell development and function that impact autoimmune disease.





Disclosure: M. A. Cunningham, None; **J. R. Wirth**, None; **J. G. Eudaly**, None; **G. S. Gilkeson**, None.

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Abstract Number: 2791

Targeting Micro-RNAs Derived from Extracellular Vesicles to Inhibit of TLR7 and TLR8 Signaling Suppresses Inflammation in a Novel Human-Mouse Chimeric Model of Systemic Lupus Erythematosus

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Systemic Lupus Erythematosus – Animal Models - Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a prototypic autoimmune disease displaying a heavy female predominance during reproductive years. We have previously shown that toll-like receptor (TLR)7 and TLR8 are significantly up-regulated in peripheral blood mononuclear cells (PBMCs) of SLE patients and further induced with estrogen treatment. Conventionally, TLR7 and TLR8 binding to single-stranded RNA of viral origin to stimulate innate inflammatory responses, but recent studies have discovered that specific micro-RNA (miR) sequences can activate these receptors following packaging and secretion via extracellular

vesicles (EVs). Our objective in this study was to explore the therapeutic potential of using a cocktail of miR antagonists to block TLR7 and TLR8 inflammatory pathways induced by EV-derived miRs in SLE.

Methods: PBMCs were isolated from active SLE patients and adoptively transferred into immunodeficient NOD-scid IL-2rγ (null) mice to produce chimeras containing PBMCs from SLE patients using a similar protocol we have previously established for Sjöjren's syndrome. Prior to transfer, PBMCs were treated with a cocktail of several locked nucleic acid miR antagonists or nonsense, scrambled RNA controls prior to injection. Blood was collected for both flow cytometry and cytokine analysis and tissues were processed for histopathological examination by H&E and immunohistochemistry.

Results: Human T-cells (CD4+ and CD8+), B-cells, monocytes, and NK cells were all successfully recovered from whole blood of chimeric mice at similar levels in both treatment groups 21 days after adoptive transfer. However, inhibition with miR antagonists reduced levels of human IL-2, IL-6, IL-10, and TNF-α relative to scramble (control) treatment. While histopathological analysis revealed little to no inflammation in the skin and ear with either treatment, miR antogonists inhibited the robust responses detected with scramble RNA (control) treatment in the small intestine, liver, and kidney. Further characterization of infiltrates by immunohistochemistry confirmed the presence human CD3+ T-cells.

Conclusion: These data establish a novel human-mouse model to study SLE and provide an experimental platform to further explore the therapeutic potential of suppressing EV-encapsulated miRs that trigger TLR7 and TLR8 signaling.

Disclosure: N. A. Young, None; **G. R. Valiente**, None; **H. Steigelman**, None; **J. Hampton**, None; **W. N. Jarjour**, None.

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Abstract Number: 2792

Hyperhomocysteinemia in SLE

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First publication: September 28, 2016

SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster III: Biomarkers and Nephritis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Hyperhomocysteinemia has been correlated with the occurrence of blood clots, heart attacks and strokes. We investigated the association of the Hyperhomocysteinemia with other clinical and laboratory manifestations, in particular with urine protein/creatinine ratio.

Methods: 829 patients with at least one homocysteine measurement since 2014 were included in the analysis. Patients were followed quarterly after cohort entry.

Results: 762 (91.9%) were female. Majority (48.4%) were Caucasian, 42.1% African American. For the first homocysteine measurement, 79.4% were below 15 umol/L. The association of Hyperhomocysteinemia with other clinical and laboratory manifestations is shown in Table 1 and association with organ damage is shown in table 2. Table 1 the association between homocysteine and SLE manifestation, adjusting for ethnicity and sex **(Statistically Significant Result Highlighted)**

SLE manifestation		Homocysteine > = 15 umol/L (%)	Homocysteine < 15 umol/L (%)	Odd ratios (95% CI)	P value	Adj. Odd ratios (95% CI)	Adj. P value
Malar rash		44.14	44.35	0.99 (0.66,1.48)	0.9674	1.12 (0.74,1.7)	0.5812
Discoid rash		23.64	19.67	1.26 (0.78,2.04)	0.3349	1.08 (0.66,1.78)	0.7583
Photosensitivity		45.05	51.32	0.78 (0.52,1.16)	0.2190	0.91 (0.6,1.37)	0.6433
Oral/Nasal Ulcers		46.85	54.81	0.73 (0.49,1.08)	0.1183	0.84 (0.56,1.27)	0.4155
Arthritis		65.77	69.27	0.85 (0.56,1.3)	0.4583	0.79 (0.52,1.22)	0.2909
Serositis	**Pleurisy**	36.04	44.01	0.72 (0.47,1.08)	0.1153	0.69 (0.45,1.05)	0.0807
	Pericarditis	21.62	22.91	0.93 (0.57,1.51)	0.7641	0.82 (0.5,1.34)	0.4270
Renal disorder		11.11	2.93	**4.14 (1.97,8.68)**	**0.0002**	**4.48 (2.1,9.55)**	**0.0001**
Neurologic	**Seizures**	11.71	6.55	1.89 (0.99,3.63)	0.0541	1.81 (0.94,3.51)	0.0778
	Acute confusional state	5.41	2.23	2.51 (0.96,6.55)	0.0607	2.44 (0.91,6.51)	0.0760
Hematologic	**Hemolytic anemia**	11.82	7.41	1.67 (0.88,3.18)	0.1163	1.69 (0.88,3.25)	0.1150
	Leukopenia	53.15	51.39	1.07 (0.72,1.6)	0.7298	1.04 (0.69,1.57)	0.8431
	Lymphopenia	46.85	44.77	1.09 (0.73,1.62)	0.6824	1.06 (0.71,1.59)	0.7743
	Thrombocytopenia	17.12	18.99	0.88 (0.52,1.49)	0.6374	0.89 (0.52,1.52)	0.6727
Immunologic	**Anti-dsDNA**	55.86	63.74	0.72 (0.48,1.08)	0.1112	0.68 (0.45,1.03)	0.0678
	Anti Sm	29.09	22.63	1.4 (0.9,2.19)	0.1378	1.24 (0.78,1.97)	0.3720
Anti- phospholipid	**Anti-cardiolipin**	43.24	57.62	**0.56 (0.37,0.84)**	**0.0049**	**0.54 (0.36,0.81)**	**0.0033**
	Anti- B2 Gly	16.98	29.69	**0.48 (0.28,0.82)**	**0.0076**	**0.46 (0.27,0.8)**	**0.0054**
	False positive RPR	9.52	11.33	0.82 (0.41,1.65)	0.5826	0.85 (0.42,1.71)	0.6525
	LAC	19.82	29.29	**0.6 (0.36,0.98)**	**0.0404**	**0.54 (0.33,0.91)**	**0.0190**
ANA		95.5	97.21	0.61 (0.22,1.65)	0.3291	0.5 (0.18,1.39)	0.1856

Table 2 the association between homocysteine and organ damage, adjusting for ethnicity and sex (**Statistically Significant Result Highlighted**)

DAMAGE COMPONENT	Homocysteine >= 15 umol/L (%)	Homocysteine < 15 umol/L (%)	Odd ratios (95% CI)	P value	Adj. Odd ratios (95% CI)	Adj. P value
Cataract	28.18	19.61	**1.61 (1.02,2.53)**	**0.0404**	**1.67 (1.05,2.65)**	**0.0305**
Retinal changes	1.82	4.07	0.44 (0.1,1.86)	0.2619	0.46 (0.11,1.96)	0.2934
Cognitive impairment	8.18	6.56	1.27 (0.6,2.67)	0.5281	1.29 (0.61,2.74)	0.5046
Seizure	4.55	4.04	1.13 (0.43,2.98)	0.8055	1.15 (0.43,3.09)	0.7775
Cranial or Peripheral neuropathy	8.18	8.23	0.99 (0.48,2.07)	0.9867	0.94 (0.45,1.98)	0.8752
Transverse myelitis	0.92	0.14	6.63 (0.41,106.78)	0.1822	7.28 (0.44,120.39)	0.1656
GFR <50	14.55	2.51	**6.61 (3.26,13.4)**	**<.0001**	**6.54 (3.13,13.63)**	**<.0001**
Proteinuria	18.35	5.44	**3.91 (2.18,7)**	**<.0001**	**4.09 (2.23,7.52)**	**<.0001**
Pulmonary hypertension	7.34	4.75	1.59 (0.72,3.53)	0.2555	1.8 (0.8,4.04)	0.1549
Pulmonary fibrosis	12.84	9.34	1.43 (0.77,2.64)	0.2545	1.55 (0.83,2.9)	0.1685
Shrinking lung	0.92	0.7	1.31 (0.15,11.33)	0.8055	1.73 (0.2,15.25)	0.6206
Pleural fibrosis	2.73	4.34	0.62 (0.19,2.06)	0.4324	0.6 (0.18,2.01)	0.4050
Pulmonary infarction	2.75	3.49	0.78 (0.23,2.64)	0.6920	0.74 (0.21,2.55)	0.6287
Angina/ CABG	4.59	1.95	2.41 (0.85,6.84)	0.0973	2.04 (0.71,5.91)	0.1868
Cardiomyopathy	4.59	2.09	2.25 (0.8,6.31)	0.1245	2.34 (0.82,6.7)	0.1120
Valvular heart disease	2.75	2.09	1.32 (0.38,4.65)	0.6610	1.29 (0.36,4.61)	0.6997
Pericarditis/ pericardectomy	1.82	1.12	1.64 (0.34,7.83)	0.5343	1.53 (0.31,7.5)	0.5994
Claudication	5.45	3.07	1.82 (0.72,4.6)	0.2039	1.64 (0.63,4.24)	0.3087
DVT	2.73	0.98	2.84 (0.72,11.17)	0.1342	2.92 (0.73,11.63)	0.1285
Upper GI surgery	1.8	1.4	1.29 (0.28,5.98)	0.7418	1.29 (0.27,6.07)	0.7513
Muscular atrophy/ weakness	8.49	5.82	1.5 (0.71,3.18)	0.2905	1.52 (0.71,3.27)	0.2835
Osteoporosis	13.51	15.38	0.86 (0.48,1.54)	0.6091	0.94 (0.52,1.71)	0.8510
Alopecia	7.34	4.89	1.54 (0.7,3.42)	0.2869	1.33 (0.59,3.01)	0.4905
Scarring of panniculum	2.73	2.09	1.31 (0.37,4.6)	0.6733	1.11 (0.31,3.98)	0.8731
Skin ulceration	0.91	0.84	1.09 (0.13,9.1)	0.9396	1.21 (0.14,10.25)	0.8634
Premature gonadal failure	7.27	4.62	1.62 (0.73,3.6)	0.2381	2.06 (0.91,4.67)	0.0844
Diabetes	9.09	5.74	1.64 (0.8,3.38)	0.1788	1.64 (0.79,3.42)	0.1839
HTN	59.63	27.16	**3.96 (2.61,6.01)**	**<.0001**	**3.65 (2.37,5.6)**	**<.0001**

Among 829 patients, 604 have at least two homocysteine measurements, 272 have three or more. To account for correlations of measurement within patients, we used GEE model to estimate the association between homocysteine and urine protein creatinine ratio using serial tests of homocysteine. A 10 umol/L decrease in Homocysteine within a person corresponds to an average 0.011 (95% CI:

0.006 to 0.015) unit decrease in urine protein/creatinine ratio (P < 0.0001), after adjusting for sex and ethnicity. The association remains significant (0.004 (95% CI 0.002 to 0.007), P = 0.0005) when only including patients with first homocysteine greater or equal to 15 umol/L and corresponding urine protein creatinine ratio greater or equal to 0.2

Conclusion: homocysteine is showed to be strongly correlated with renal disorder, low GFR and proteinuria. Decreased homocysteine might also indicates improved renal functionality.

Disclosure: M. Petri, None; **W. Fu**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hyperhomocysteinemia-in-sle

Abstract Number: 2793

The Predictors of Sustained Complete Remission in Lupus Nephritis

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Sustained complete remission is an independent predictor of good long term prognosis in lupus nephritis (LN). We aimed to examine the predictors of sustained complete renal remission (CR) in patients with LN.

Methods: We reviewed patients with active LN at a single center Lupus Clinic where patients were followed prospectively according to a standardized protocol between 1970 and December 2015. We identified the patients who had a minimum of 5 years of follow-up after the diagnosis of LN. We compared demographic, disease activity, renal histology (according to the World Health Organization/ International Society of Nephrology classification), laboratory and treatment variables at the time of diagnosis of LN in patients who never achieved complete renal remission (group A), those who achieved sustained CR for less than 5 years (group B), and those who had at least 5 years of CR (group C). Proportional logistic regression models were constructed to identify the predictors of sustained CR among the 3 groups in multivariate models controlling for gender, age, disease duration, ethnicity, comorbidity and treatment. Subgroup analyses were also undertaken in patients with biopsy-proven LN.

Results: A total of 427 patients were identified, 82 (19%) in group A, 213 (50%) in group B and 132 (31%) in group C. At the diagnosis of LN, gender, age, SLE duration, ethnic origin, renal biopsy results and treatment were comparable in the three groups. The patients in group C had lower renal SLE disease activity index-2K (renal SLEDAI-2K) and lower frequency of hypocomplementemia (table 1). Multivariate analysis in the whole cohort revealed higher renal SLEDAI-2K had a lower probability of sustained CR (table 2). Subgroup analysis revealed older age had a higher probability of sustained CR (odd ratio (OR) = 1.03; 95% confident interval (CI), 1.00-1.05; P = 0.03) in addition to renal SLEDAI-2K. There was no association between renal histology class III or IV and the probability of sustained CR.

Conclusion: At the time of diagnosis of LN, higher renal SLEDAI-2K predicts less chance of sustained CR.

Table 1 Comparison of clinical variables at the time of LN diagnosis			
Variables	**Group A (N=82)**	**Group B (N=213)**	**Group C (N=132)**
Female, *n* (%)	68 (82.9)	182 (85.4)	113 (85.6)
Age (mean± SD, year)	26.71 ± 11.44	27.03 ± 11.61	29.09 ± 13.32
SLE duration (mean± SD, year)	5.90 ± 6.25	4.72 ± 5.69	4.85 ± 5.50
WHO/ISN Renal histology: class III, IV, or IV/V, n/N (%)	20/36(55.6)	79/146(54.1)	49/93(52.7)
Baseline serum creatinine (mean± SD, *umol/l*)	112.65 ± 133.70	92.55 ± 68.69	97.00 ± 97.56
Renal- SLEDAI-2K (mean± SD)	7.66 ± 4.23	5.35 ± 4.79	4.06 ± 4.50
Non renal- SLEDAI-2K (mean± SD)	6.13 ± 5.60	5.99 ± 5.92	5.92 ± 5.19
Low complement, *n* (%)	56 (68.3)	110 (52)	70 (53)
Abnormal double stranded DNA, *n* (%)	58 (70.7)	119 (55.9)	72 (54.5)
Treatment with steroids, *n* (%)	64 (78)	173 (81)	107 (81)
Treatment with anti-malarial agent, *n* (%)	38 (46.3)	86 (40.4)	53 (40.2)
Treatment with immunosuppressive agents, *n* (%)	41 (50)	77 (36.2)	48 (36.4)

SD = standard deviation

Table 2 Multivariate Proportional Logistic regression Analysis - cohort size = 427		
Predictors at the time of diagnosis of LN	**OR (95% CI)**	**P**
Age	1.01 (0.99-1.03)	0.19
Duration of LN	0.97 (0.97-1.01)	0.11
Caucasian	1.46 (0.99-2.14)	0.05
Renal SLEDAI-2K	0.89 (0.85-0.93)	<0.001
Cumulative steroid dose within 3 years prior LN (g)	1.02 (0.99-1.04)	0.10
Treatment with anti-malarial agent	0.78 (0.53-1.15)	0.22

Disclosure: R. Pakchotanon, None; **D. D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 2794

Sustained Complete Remission in Lupus Nephritis

Rattapol Pakchotanon[1], Dafna D. Gladman[2], Jiandong Su[2] and Murray Urowitz[3], [1]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [3]Medicine, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The durability of renal remission might be a predictor of good long-term renal outcome and survival in patients with lupus nephritis (LN). We aimed to examine the predictors of long-term outcomes in patients with LN who achieve sustained

complete remission.

Methods: We reviewed patients with active LN at a single center Lupus Clinic in which patients had been followed prospectively between 1970 and December 2015. We identified the patients who had a minimum of 5 years of follow-up after the complete renal remission (CR) (defined as proteinuria < 500 mg/24 hours or urine protein creatinine ratio < 0.5 and inactive urine sediment). We compared the outcomes of patients who achieved sustained CR, for a minimum of 5 years (group A) with those less than 5 years (group B). The outcomes were mortality, damage (measured by the SLICC/ACR damage index (SDI)), renal flare (any presence of cast, proteinuria, pyuria or hematuria after CR), end stage renal disease (dialysis or transplant) (ESRD) or estimated glomerular filtration rate (eGFR) < 50 mL/min, doubling of serum creatinine, and infection during 20 years after CR. Cox proportional regression models were constructed to identify the predictors of the outcomes in multivariate models controlling for gender, age, disease duration, ethnicity, hypertension and treatment for each outcomes.

Results: A total of 345 patients were identified, 132 patients in group A and 213 patients in group B. Most of patients were female (85%). Mean age at the diagnosis of LN was 33.94±12.85 years in group A and 31.75±11.41 years in group B. The duration between active LN and CR was 1.04±1.53 years in group A and 1.46±1.88 years in group B (P=0.03). The duration of CR in group A was 11.76 ± 7.34 years but only 1.24 ± 1.24 years in group B (P< 0.001). Death, increasing of renal SDI, renal flare, renal transplantation, ESRD or eGFR < 50 mL/min, and doubling of serum creatinine in group A were significantly lower than group B (Table 1). Multivariate analysis revealed that group A were at a lower risk of death (hazard ratio (HR)=0.20; 95% confidence interval (CI), 0.07-0.61; P=0.004), increasing of renal SDI (HR= 0.41; 95% CI, 0.21-0.76; P=0.01), developing ESRD or eGFR < 50 mL/min (HR= 0.27; 95% CI, 0.12-0.61; P=0.001), and doubling of serum creatinine (HR= 0.29; 95% CI, 0.14-0.61; P=0.001) compared with group B.

Conclusion: Sustained complete remission for at least 5 years is an independent predictor of better prognosis in lupus nephritis in terms of reduced mortality, chronic kidney disease and end stage renal disease. **Table 1** Outcomes over 20 years after complete renal remission in lupus nephritis

	Group A (N=132)	**Group B (N=213)**	**P**
Death, *n* (%)	5 (3.8)	26 (12.2)	0.01
Increasing of SDI, *n* (%)	73 (55.3)	134 (62.6)	0.16
Increasing of renal SDI, *n* (%)	13 (9.8)	53 (24.9)	<0.001
Renal flare, *n* (%)	61 (46.2)	213 (100)	<0.001
Renal transplantation, *n* (%)	2 (1.5)	15 (7)	0.02
ESRD or eGFR < 50 mL/min, *n* (%)	7 (5.3)	37 (17.4)	0.001
Doubling of serum creatinine, *n* (%)	19 (9.8)	45 (21.1)	0.005

Group A=patients who achieved sustained complete remission, a minimum of 5 years; Group B= patients who achieved sustained complete remission, less than 5 years; SDI= SLICC/ACR damage index; ESRD= end stage renal disease; eGFR=estimated glomerular filtration rate.

Disclosure: R. Pakchotanon, None; **D. D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

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Abstract Number: 2795

Effect of Complete or Partial Proteinuria Recovery Compared to No Recovery at 2 Years after the Diagnosis of Lupus Nephritis on Long Term Outcomes

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

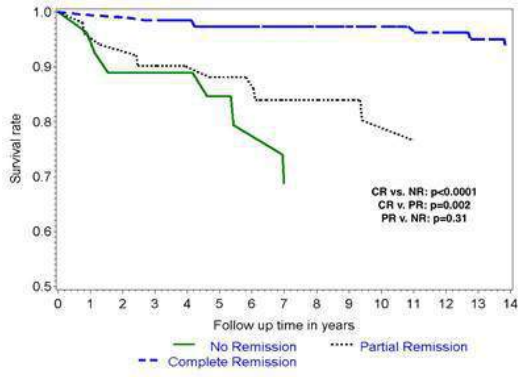
Background/Purpose: Proteinuria is the most common manifestation of lupus nephritis (LN) and it is an independent prognostic factor of long term outcomes. Recovery from proteinuria takes time with 52% of patients achieving complete proteinuria remission (CR) by 2 years from diagnosis of LN. We aimed to evaluate the effect of Complete Recovery (CR), Partial Recovery (PR), and No Recovery (NR) at 2 years from diagnosis of LN on long term outcomes.

Methods: Patients are followed at the Lupus Clinic at 2-6 month intervals according to a standard protocol which includes a complete history, physical examination and laboratory evaluation. Patients with LN (defined as proteinuria in a 24-hour urine sample [24H-P] > 0.5 g/day) attending the Lupus Center from 1970-2015 were included. At 2 years from diagnosis of LN, patients were divided in 3 groups (CR, PR, NR) based on 24H-P, and long-term outcomes were studied up to 15 years or last visit available. CR was defined as normal 24H-P (≤ 0.5 g/day), PR was defined as a reduction ≥ 50% in baseline 24H-P without achieving CR and NR was defined as a reduction < 50% 24H-P compared to baseline. Long term outcomes: 1-Renal outcomes (low [eGFR]: < 15 mL/min, end-stage renal disease requiring dialysis or transplantation [ESRD], and a Composite Renal Outcome [low eGFR or ESRD]); 2-Cardio-Vascular (CV) outcomes (angina or myocardial infarction); 3- Damage (SLICC/ACR Damage Index [SDI] ≥ 1); and 4- Death. Non-parametric tests (Log-rank tests) were applied to describe the effect of CR, PR or NR on long-term outcomes. Time-independent and time-dependent Cox proportional hazards models were applied to examine the CR, PR or NR effect by adjusting for demographics, disease, and treatment characteristics.

Results: Of 277 patients, 84.5% were female. Age at LN diagnosis and lupus duration at LN were 34.32 ± 11.66 and 5.40 ± 6.47 years, respectively. Of 277 patients, 63.9% patients achieved CR, 18.41% PR, and 9.75% NR at 2 years. -CR protected from all long-term outcomes compared to PR and NR on Kaplan-Meier analysis and Cox proportional hazards model (Figure 1). However, CR protected against CV outcomes only in the Cox proportional hazards model analysis. - Compared to NR, PR only protected against low eGFR. Neither CR nor PR protected from damage accrual. On time-dependent analysis, when comparing CR to NR and PR to NR, only NR was a risk factor for ESRD when compared to CR (HR=3.93, 95% CI: 1.31-11.73, p=0.01); all the other comparisons were not statistically significant.

Conclusion: CR at 2 years from diagnosis of LN protects against CV (angina or myocardial infarction), renal (low eGFR, ESRD and composite renal outcome) outcomes and mortality. PR protects against low eGFR. Clinicians should aim for CR to prevent long-term outcomes in LN.

Figure 1. Kaplan Meier analysis of long term outcome of low eGFR (<15 mL/min) among patients who achieved CR, PR or NR at 2 years of LN diagnosis



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Abstract Number: 2796

Low Versus High Dose Glucocorticosteroid Used in Lupus Nephritis: Is There a Difference

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster III: Biomarkers and Nephritis

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: The exact dose of glucocorticoids (GC) needed for the management of lupus nephritis in an individual patient is unknown. We aimed to compare the renal outcomes between patients with lupus nephritis (LN) treated early with high or low dose glucocorticoids (GC).

Methods: Inception patients (enrolled within one year of diagnosis) aged ≥ 18 years that were newly diagnosed with LN and followed for at least 3 years after LN formed our cohort. Patients are followed prospectively at 2-6 month intervals according to a standard protocol which includes complete history, physical examination and laboratory evaluation. Patients were divided into two groups based on the maximum dose of GC used at the time of LN diagnosis (including one visit before or one after LN). Group 1 patients were treated with a high-dose (>35 mg/d) and group 2 with a low-dose (<35 mg/d) GC. Disease activity was measured by the SLEDAI-2K and accumulated damage by the SLICC/ACR damage index (SDI). All information necessary to complete the SLEDAI-2K and the SDI is collected prospectively. Specific GC-related damage was documented by the presence of any of the following: cataracts, osteonecrosis or osteoporosis. Outcomes were: all cause mortality, SDI increase, and renal outcomes, including: complete renal remission, partial renal remission, renal flare, and end-stage renal disease.

Results: Of 786 inception patients in our cohort, 198 patients met LN definition and had 3 or more years of follow-up after LN. 99 (50.5%) patients received a high dose of GC (HD) with a mean dose of 55.6 ± 17.9 mg/d, and 97 (49.5%) patients received a low dose (LD) with a mean dose of 20.6 ± 8.8 mg/d. The majority of the patients (84%) were female. The mean disease duration from SLE to LN was longer in LD group (1.6 ± 2.4 years compared to 0.8 ± 2.2 years in the HD, p = 0.015). The HD group had higher disease activity than LD group as shown in table-1. The mean cumulative GC dose 6 months after LN was comparable between both groups 7.0 ± 8.3g in LD group and 8.2 ± 7.6g in the HD group (p= 0.31). Cumulative doses were similar five years after LN (22.3 ± 13.4g in LD group and 24.8 ± 14.2g HD group (p= 0.20). The mortality rate, renal outcomes, accumulated damage, and GC-related side effects were similar in both groups. Multivariable logistic regression analysis showed that age at LN and SDI were associated with increased mortality while the use of antimalarial agents had a protective effect. Moreover, age at LN and use of immunosuppressive medications were associated with an increase in damage, while the use of a low versus high doses of GC had no impact on any of the renal outcomes.

Conclusion: High dose GC was used in patients with more active disease but this was tapered more rapidly as the cumulative GC dose at 6 months and 5 years was similar in both groups, with comparable side effects and good renal outcomes and diseases control. GC dose sufficient to control active disease should be used early and tapered quickly for best results and least side effects.

Table 1: Disease characteristics at LN

Variable	Low Dose Group N=97	High Dose Group N=99	P-value
SLEDAI-2K	10.49 ± 6.96	15.55 ± 9.66	<0.001
Renal SLEDAI	5.03 ± 4.59	7.27 ± 5.09	0.001
Non-Renal SLEDAI	5.46 ± 4.43	8.27 ± 8.02	0.003
Low-complement	52 (53.6%)	62 (62.6%)	0.201
High ds-DNA	56 (60.9%)	57 (60.0%)	0.903
Serum creatinine (>140µmol/l)	7 (7.3%)	27 (27.3%)	<0.001
Antimalarial	56 (57.7%)	37 (37.4%)	0.004
Immunosuppression (IS)	54 (55.7%)	70 (70.7%)	0.029
Renal Biopsy			<0.001
II Mesangial	23 (41.1%)	14 (20.6%)	
III Focal proliferative	14 (25.0%)	15 (22.1%)	
IV Diffuse prolferative	8 (14.3%)	33 (48.5%)	
V Membranous	8 (14.3%)	6 (8.8%)	
VI Glomerosclerosis	3 (5.4%)	0 (0.0%)	

Disclosure: H. Al-Sheikh, None; **D. D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

Abstract Number: 2797

Prospective Validation of a Panel of Autoantibodies in Combination with C4d-Bound Complement Activation Products for the Differential Diagnosis of Systemic Lupus Erythematosus

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose:

A panel of autoantibodies in combination with C4d-bound complement activation products (CB-CAPs, EC4d and BC4d) has been established as a sensitive and specific testing method for systemic lupus erythematosus (SLE). The purpose of this study was to prospectively establish the performance characteristics of this testing method in an independent cohort of SLE subjects relative to subjects with diseases other than SLE.

Methods:

This cross-sectional prospective diagnostic validation study enrolled consented adult subjects at 12 sites across the USA. Venous blood was collected and transported overnight to a CAP-accredited reference clinical laboratory. The testing logic relied on two consecutive Tiers. In Tier 1, positivity for any of 4-lupus specific markers (inclusive of anti-dsDNA as confirmed by Crithidia, anti-Smith, and EC4d or BC4d levels above the 99th percentile of a control group) resulted a Tier-1 positive test assessment. All Tier-1 negative results were analyzed in a Tier 2, to yield a Tier-2 index score. This Tier-2 index score was inclusive of an ANA component, a CB-CAPs component (as component for complement activation), and a third component composite of autoantibodies for diseases other than SLE. Tier 2 positive test results (index score ≥0.1) were combined with Tier 1 positive test results to yield the overall two-tiered positive test results. Negative test results all presented with an index score lower than 0.1. All testing personnel were blinded to disease diagnosis throughout the study. Test performances in this independent validation cohort were assessed using sensitivity, specificity, positive (+) and negative (-) likelihood ratio (LR) the later reported with confidence intervals (CI).

Results:

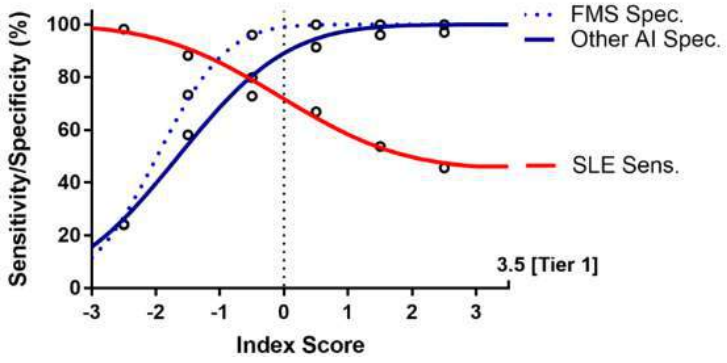
A total of 476 adult subjects inclusive of 184 subjects with SLE (all meeting the 1982 ACR criteria revised in 1997), 215 subjects with auto-immune rheumatic and non-rheumatic diseases (inclusive of 77 subjects with autoimmune thyroiditis or hepatitis, 107 subjects with rheumatoid arthritis and 31 subjects with other rheumatic diseases) and a group of 77 subjects with primary fibromyalgia syndrome

(FMS) were enrolled. Tier 1 yielded 45% sensitivity for SLE and 98% specificity in distinguishing SLE from other diseases (LR+: 24.6 [CI95%: 10.1-59.5]), LR-: 0.56 [CI95%: 0.49-0.64]). Tier 2 yielded 48% sensitivity and 91% specificity in distinguishing SLE from other diseases (LR+: 5.6 [CI95%: 3.6-8.8], LR-: 0.56 [CI95%: 0.46-0.69]). All together the performance characteristics of the two-tiered diagnostic method yielded 72% sensitivity for SLE and 90% specificity in distinguishing SLE from other diseases (LR+: 7.0 [CI95%: 4.9-10.0], LR-: 0.32 [CI95: 0.25-0.40]).

Conclusion:

These data indicate that a panel of autoantibodies in combination with C4d-bound complement activation products is sensitive and specific for SLE.

Figure 1: Sensitivity (Sens.) for SLE and specificity (Spec.) for fibromyalgia syndrome (FMS) and other autoimmune (AI) diseases at various tier-2 index scores (maximum theoretical value: 3.4). An index score of +3.5 was assigned to Tier 1 test results (sensitivity=45%). Open circles: observed sensitivities / specificities; solid lines: fitted normal models.



Disclosure: D. J. Wallace, Exagen, 2; **R. Ramsey-Goldman**, exagen, 2; **A. D. Askanase**, anca askanase, 2; **S. Manzi**, exagen, 2; **J. Ahearn**, exagen, 2; **R. Furie**, exagen, 2; **A. Weinstein**, exagen, 6; **C. Putterman**, exagen, 2; **E. Massarotti**, Exagen, 2; **C. Collins**, Exagen, 2; **K. Kalunian**, Exagen, 2; **C. Arriens**, Exagen, 2; **S. L. Silverman**, Exagen, 2; **S. Reddy**, Exagen, 2; **P. Chitkara**, exagen, 2; **C. Ibarra**, Exagen, 3; **D. Barken**, Exagen, 3; **R. Alexander**, exagen, 3; **J. Conklin**, Exagen, 3; **T. Dervieux**, Exagen, 3.

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Abstract Number: 2798

Multi-Center Validation of Platelet Bound C4d, a Biomarker for Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster III: Biomarkers and Nephritis
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose:

Previous studies have established the value of measuring complement activation products (C4d) bound to platelets (PC4d) for the diagnosis and monitoring of Systemic Lupus Erythematosus (SLE). Separately, Antiphospholipid (APL) antibodies have been associated with complement activation and PC4d expression. In this study, we sought to validate the performance characteristics of PC4d, stratified by the presence or absence of APL antibodies.

Methods:

This multi-centered validation cross sectional study (16 sites in the US) enrolled 402 SLE subjects fulfilling the 1982 American College of Rheumatology Criteria revised in 1997 (mean age 41 years; 91% female), 411 subjects with rheumatic and autoimmune diseases other than SLE (mean age 55, 86% female consisting of 181 rheumatoid arthritis, 90 primary fibromyalgia, 92 other rheumatic diseases, and 48 autoimmune thyroiditis or hepatitis) and 198 healthy volunteers (mean age 41 years; 66% female). PC4d densities were determined using flow cytometry (expressed as mean fluorescence intensity [MFI]). Positive PC4d consisted of PC4d levels greater than 20 net MFI. Anti-cardiolipin IgG, anti-Beta-2-glycoprotein 1 IgG, or anti-Phosphatidylserine/Prothrombin (PSPT) complex IgG antibodies were determined using ELISA (INOVA diagnostics, San Diego, CA). Presence of APL antibodies consisted of any of these antibodies above manufacturer cutoff. SLE Disease activity was assessed using the non-serological SLE Disease Activity Index SELENA modification (ns-SELENA-SLEDAI, without the complement and anti-dsDNA). Performance characteristics were established using sensitivity, specificity, and ROC Curve Area Under the Curve (AUC). Statistical evaluation was by t-test (for disease activity), by chi-squared test for equality of proportions (for sensitivities and specificities) and by the method of DeLong (for ROC Curve AUC).

Results:

PC4d was highly specific in distinguishing SLE from other rheumatic diseases (Table) and normals. Among SLE subjects, 47% (n=187) presented with at least one APL antibody as compared to 21% (n=86) of subjects with other diseases and 15% of normals. PC4d sensitivity for SLE was higher among APL positive subjects by comparison to APL negative subjects (p=0.003). Specificity was not significantly different between APL positive and negative subjects (p>0.372). ROC AUC was significantly higher among the APL positive compared to negative subjects (p=0.002). The incidence of APL antibodies among all PC4d positive subjects was 60% compared to 27% among PC4d negative subjects (p<0.001). SLE subjects presenting with positive PC4d had higher disease activity (4.1±0.5) than those presenting with negative PC4d (3.0±0.2) (p=0.03).

Conclusion:

We confirm that PC4d is highly specific for SLE, and is associated with disease activity.

Table: Performance characteristics of PC4d stratified by the presence of antiphospholipid antibodies (APL)

	All Subjects	APL Negative	APL Positive
Sensitivity	20.1%	14.4%	26.7%
Specificity: Other Diseases	98.1%	98.5%	96.5%
Specificity: Normal/Healthy	99.5%	100%	96.6%
ROC AUC (SLE vs other dis.) (95% C.I.)	0.698 (0.662-0.735)	0.640 (0.590-0.690)	0.761 (0.703-0.818)

Disclosure: R. Furie, exagen, 2; **A. D. Askanase**, anca askanase, 2; **K. Kalunian**, Exagen, 2; **E. Massarotti**, Exagen, 2; **R. Ramsey-Goldman**, exagen, 2; **D. J. Wallace**, Exagen, 2; **S. L. Silverman**, Exagen, 2; **S. Reddy**, Exagen, 2; **P. Chitkara**, exagen, 2; **C. Putterman**, exagen, 2; **C. Collins**, Exagen, 2; **J. P. Buyon**, exagen, 2; **C. Arriens**, Exagen, 2; **T. O'Malley**, exagen, 3; **R. Alexander**, exagen, 3; **D. Barken**, Exagen, 3; **J. Conklin**, Exagen, 3; **S. Manzi**, exagen, 2; **J. Ahearn**, exagen, 2; **A. Weinstein**, exagen, 6; **T. Dervieux**, Exagen, 3.

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Abstract Number: 2799

Outcomes in Patients with Early and Delayed Onset Lupus Nephritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: To compare disease characteristics in patients with early and delayed onset of lupus nephritis(LN) and their outcomes after 5 years of follow-up.

Methods: Patients with LN were identified from a prospective cohort of single lupus center. Only patients who entered the cohort within 2 years from SLE diagnosis were considered. Patients who developed LN within 3 years of diagnosis (Early LN group) were compared with patients in whom LN diagnosed after 3 years of SLE diagnosis (Delayed LN).Five outcomes were evaluated: complete renal remission (CR, normalization of all of RBCs, protein, casts, pyuria), partial renal remission (PR, 50% improvement),renal flares (Increase in any of renal SLEDAI-2K score after CR), renal failure, renal damage progression (SDI) and death. Outcomes were assessed by Cox proportional hazard regression analyses.

Results: A total of 277(85%)Early LN patients (83.3% female,61%caucasian) and 49(15%) Delayed LN patients(87.8% female, 65.3% Caucasian)were included.

Variables at LN	Early (N= 277)	Delayed (N=49)	P value
Age*	33.55 ± 13.03	41.97 ± 15.17	<0.001
Disease duration*	0.68 ± 0.69	7.78 ± 4.61	<0.001
SLEDAI-2k score*	12.71 ± 8.59	9.47 ± 6.93	0.013
SLEDAI-2k non renal score*	6.47 ± 6.32	4.57 ± 3.97	0.043
SDI Score*	0.15 ± 0.48	0.82 ± 1.07	<0.001
Low Complements †	155 (56.2%)	25 (51.0%)	0.505
Anti DNA †	152 (59.1%)	27 (55.1%)	0.599
High Serum creatinine†	55 (19.9%)	2 (4.1%)	0.007
GCS use	255 (92.1%)	39 (79.6%)	0.007
Antimalarial use	138 (49.8%)	33 (67.3%)	0.024
IS use	177 (63.9%)	27 (55.1%)	0.241
*Mean ± SD; †n(%); GCS: Glucocorticosteroid; IS: immunosuppressive			

At nephritis, Early LN patients had more active disease but less damage accrual. After 5 years of follow-up, CR was higher in Early LN group. SDI scores increased significantly in the early LN group. There were no differences in renal flares, renal failure or death. Multivariate regression analysis revealed that patients with higher SLEDAI-2K and SDI scores were less likely to achieve CR. Using GCS and IS increased SDI, whereas antimalarial use and high DNA levels were protective. Caucasian ethnicity, older age at diagnosis of LN, early onset of LN, high SDI scores, high SLEDAI-2K scores, low complement levels, and GCSuse, were associated with poorer survival, while the use of antimalarial and IS were protective. Older age at CR was the only factor predicting less renal flares.

Conclusion: Patients with delayed development of LN had a milder disease course and more favorable outcomes than those with early LN.

Disclosure: R. ALJohani, None; **D. D. Gladman**, None; **J. Su**, None; **M. Urowitz**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/outcomes-in-patients-with-early-and-delayed-onset-lupus-nephritis

Abstract Number: 2800

Cell-Bound Complement Activation Products in Multi-Analyte Assay with Algorithm Aid the Diagnosis of Systemic Lupus Erythematosus

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Session Time: 9:00AM-11:00AM

Background/Purpose:

Cell-bound complement activation products (CB-CAPs) are sensitive and specific biomarkers in the differential diagnosis of systemic lupus erythematosus (SLE) and other rheumatic diseases, as demonstrated in studies that enrolled patients from tertiary care centers. We sought to evaluate now the usefulness of CB-CAPs, as part of a multi-analyte assay, in the setting of community rheumatologists.

Methods:

We conducted a longitudinal, case-control, retrospective review of medical charts of patients for whom a multi-analyte assay with algorithm (MAAA) test was performed in 2014. The selected patients represented a difficult to diagnose population based on standard-of-care immunological tests, inasmuch all patients were ANA positive, anti-dsDNA and anti-Smith negative, and negative for five other autoantibodies (CENP, Jo-1, La, Scl-70, and MCV). The study population consisted of 23 pairs of matched cases (positive MAAA test results) and controls (negative MAAA test results); cases and controls were matched by gender, treating rheumatologist, date of testing (within 90 days), and ANA status (positive or strong positive). Features of SLE, physician diagnosis, and medications were recorded via medical chart review at two time points approximately a year apart, as all patients had remained in the care of the same rheumatologist for 9-12 months after the test was performed.

Results:

Overall, 20 of the 23 cases (87%) and 4 of the 23 controls (17%) were diagnosed with SLE by the treating rheumatologist (test sensitivity=83%; specificity=86%, Table). Anti-rheumatic medications were used in a higher percentage of cases than controls (83% vs. 35% at baseline, p=0.002), suggesting that MAAA positive patients were treated more aggressively, possibly leading to an improvement of the physician's global assessment (from 1.26 ± 0.87 at baseline to 0.70 ± 0.73 at the second time point (p=0.042), on a 0 to 3 scale, for the 11 cases for whom it was recorded). The ACR score at baseline was higher for cases than controls (average 2.9 vs. 2.3, p=0.044) and more cases than controls (43% vs. 17%) fulfilled 4 American College of Rheumatology (ACR) classification criteria of SLE, as expected. However, sensitivity of the of the MAAA test was higher than sensitivity of the ACR classification criteria (p=0.006) (Table). More patients who met the ACR classification criteria had elevated CB-CAPs, compared to patients who did not (43% vs. 22%), consistent with previous studies.

Conclusion:

In this study that included particularly difficult to diagnose patients drawn from a population treated by community rheumatologists, the MAAA test demonstrated sensitivity and specificity comparable to previously published results. CB-CAPs and the MAAA test may be helpful for the diagnosis of SLE especially when current standard-of-care immunological tests and clinical features are insufficient.

Table: Sensitivity and specificity of the ACR score and of the MAAA test.

	Physician DX Non-SLE (n=22)	Physician DX SLE (n=24)
MAAA Negative (controls)	19 (86% Spec)	4 (17% FNR)
MAAA Positive (cases)	3 (14% FPR)	20 (83% Sens)
ACR < 4	18 (82% Spec)	14 (58% FNR)
ACR ≥ 4	4 (18% FPR)	10 (42% Sens)

Disclosure: J. Mossell, Exagen, 2; **J. A. Goldman**, Exagen, 2; **D. Barken**, Exagen, 3; **R. Alexander**, exagen, 3.

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Abstract Number: 2801

Predictors of Incident Episodes of Proteinuria Among Patients with Systemic Lupus Erythematosus

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Background/Purpose: Lupus nephritis remains one of the most devastating SLE complications, occurring in over 50% of the patients. It is important to identify clinical conditions that precede nephritis for the purposes of patient care and to identify preventive strategies. Most previous studies of predictors of incident nephritis in SLE are cross-sectional or do not incorporate time-varying predictors. We leveraged a large clinical cohort which evaluated patients quarterly to identify fixed and time-varying predictors of lupus nephritis.

Methods: Since 2006, the urine protein/creatinine ratio was measured quarterly in patients in our SLE cohort. This analysis was based on cohort follow-up after 2006 in patients who did not have a history of diabetes and who did not have a prior episode of sustained elevated proteinuria, nor a history of nephritis, renal insufficiency, or failure. Among these patients, we defined an incident case of proteinuria as two or more measures of urine protein/creatinine (or 24-hour protein measure) greater than 0.5 in two visits separated by more than 30 days and less than 180 days, among patients with no prior episodes of proteinuria. We estimated rates of incident proteinuria in subgroups of patients defined by time-invariant and time-varying predictors.

Results: Among 895 patients included in the analysis, 840(94%) were female, and 518 (58%) were Caucasian, 304 (34%) African-American, with mean age of 42 at the start of follow-up. We observed 58 incident cases of proteinura over a span of 4669 person-years of cohort follow-up. The overall rate of incident proteinuria was 12.4 per 1000 person-years. The Table shows the association between select predictors and the rate incident proteinuria. The rate was significantly lower among those of older age, and significantly higher among those who were not Caucasian. Among those with a history of low C3, the rate was 8 times higher, and highest among those with a recent measure of low C3. The rate among those prescribed hydroxychloroquine was similar to those not prescribed hydroxychloroquine. Among those taking medicine for hypertension, the rate among those prescribed ACE inhibitor or ARB was similar to the rate among those prescribed other treatments. Table : Rates of incident proteinuria by patient characteristics.

Subgroup	Observed Number of new cases of proteinuria	Person-years of follow-up	Rate of events per 1000 py's	Rate Ratios	P-value
Everyone	58	4669	12.4		
Age 18-39 40-49 50-59 60+					
	39	1515	25.7	1.0 (Ref)	
	11	1171	9.4	0.4 (0.2, 0.7)	0.0031
	5	1183	4.2	0.2 (0.1, 0.4)	0.0001
	2	780	2.5	0.1 (0.0, 0.4)	0.0013
Sex Female Male					
	54	4376	12.3	1.0 (Ref)	
	4	293	13.7	1.1 (0.4, 3.1)	0.84
Ethnicity Caucasian American African American Other					
	20	2803	7.1	1.0 (Ref)	
	30	1548	19.4	2.7 (1.5, ,4.8)	0.0005
	8	319	25.1	3.5 (1.6, 8.0)	0.0026
Ever Low C3 No Yes					
	7	2463	2.8	1.0 (Ref)	
	51	2205	23.1	8.2 (3.7, 18.0)	<0.0001
Recent Low C3 No Yes					
	26	3893	6.7	1.0 (Ref)	
	32	559	57.2	8.6 (5.1, 14.4)	<0.0001
Ever anti-dsDNA No Yes					
	9	1928	4.7	1.0 (Ref)	
	49	2740	17.9	3.8 (1.9,7.8)	0.0002
Recent anti-dsDNA No Yes					
	17	3636	4.7	1.0 (Ref)	
	41	810	50.6	10.9 (6.2, 19.1)	<0.0001
Currently on Plaquenil? No Yes					
	11	699	15.7	1.0 (Ref)	
	46	3783	12.2	0.8(0.4, 1.5)	0.44
Currently on ACE/ARB[1] No Yes					
	10	628	15.9	1.0 (Ref)	
	24	1592	15.1	0.9 (0.5, 2.0)	0.89

Conclusion: Older SLE patients who have not previously had renal involvement are at low risk for developing proteinuria. There was not strong evidence that hydroxychloroquine or ACE inhibitor's reduced the risk of proteinuria. The highest rates of incident proteinuria

were among those with recent low complement. These results suggest that those with declines in complement should be monitored closely for renal disease.

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Abstract Number: 2802

Comparison of the Clinical, Serological, and Prognostic Differences Among Juvenile-, Adult-, and Late-Onset Lupus Nephritis in Korean Patients: A Case-Control Study

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Background/Purpose: SLE patients present with different clinical and serological manifestations according to the age at disease onset. However, it is not known whether there is an association between disease onset age and the clinical presentation of lupus nephritis (LN). Therefore, we investigated whether LN patients could be distinguished based on the time of disease onset and, if so, whether the groups differed in their clinical, laboratory features and long-term prognosis in ethnically homogeneous Korean patients.

Methods: We enrolled 117 SLE patients with available clinical data at the time of renal biopsy for LN from the lupus cohort at Chonnam National University Hospital. We divided the LN patients according to the age at LN diagnosis into three groups [juvenile-onset LN (JLN), diagnosed at ≤ 18 years; adult-onset LN (ALN), diagnosed at 18–50 years; and late-onset LN (LLN), diagnosed at >50 years] and compared the baseline demographic, clinical, histological, and relevant laboratory findings. We also compared the treatment and long-term prognosis of LN according to those three groups.

Results: Of the 114 LN patients, 20 (17.5%), 84 (71.8%), and 13 (11.1%) had JLN, ALN, and LLN, respectively. LLN patients were less educated than ALN and JLN patients ($p < 0.001$). Hypertension and diabetes mellitus at the onset of LN were more common in LLN patients than ALN or JLN patients ($p < 0.001$ and $p = 0.037$, respectively). Regarding the laboratory findings, LLN patients had a higher white blood cell count and lower eGFR than ALN or JLN patients ($p < 0.011$ and 0.002, respectively). Histologically, LLN patients had more chronicity indices and a higher chronic score ($p = 0.006$, $p = 0.019$, $p < 0.001$ and $p < 0.001$, respectively). Anti-Ro antibodies were found more frequently in ALN patients and less frequently in JLN patients ($p = 0.024$) and lower complement levels were more common in JLN patients and less common in LLN patients ($p < 0.011$ and 0.002, respectively). During a mean follow-up of 76.5 months, the development of chronic kidney disease and death from any cause were higher in LLN patients than in JLN and ALN patients ($p = 0.028$ and $p = 0.038$, respectively).

Conclusion: LN patients present with different clinical and serological manifestations according to age at disease onset. Interestingly, LLN patients had more chronicity at the time of renal biopsy, and more deterioration of kidney function and death on long-term follow-up, than JLN and ALN patients. Therefore, LLN patients should be monitored and managed carefully to avoid poor outcomes.

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Abstract Number: 2803

Comparison of Clinical and Serological Differences According to the Autoantibody Cluster in Women with Systemic Lupus Erythematosus: Results from the Korean Lupus Network (KORNET) Registry

Ji-Eun Kim[1], Dong-Jin Park[2], Ji-Hyoun Kang[2], Yi-Rang Yim[1], Jeong-Won Lee[1], Kyung-Eun Lee[2], Lihui Wen[1], Tae-Jong Kim[3], Yong-Wook Park[2] and Shin-Seok Lee[3], [1]Chonnam National University Medical School and Hospital, Gwangju, South Korea, [2]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, South Korea, [3]Rheumatology, Chonnam National University Medical School and Hospital, Gwangju, Korea, The Republic of

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Background/Purpose: Individual autoantibodies are associated with the clinical features in patients with systemic lupus erythematosus (SLE). However, few studies have investigated differences in disease presentation based on autoantibody profiles in Asian patients with SLE. This study evaluated autoantibody clusters and compared the clinical and serological presentation and clinical outcome in Korean SLE patients.

Methods: The Korean Lupus Network (KORNET) is a nationwide multicenter, hospital-based registry, set up to prospectively assess outcomes in Korean SLE patients. Of the 505 SLE patients enrolled in the KORNET registry from July 2014 to November 2015, the study group comprised 339 consecutive female SLE patients. Seven autoantibodies (anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, lupus anticoagulant (LAC), and anti-cardiolipin antibody [aCL]) were selected for cluster analysis using the K-means cluster analysis procedure.

Results: Three distinct autoantibody clusters were identified: cluster 1, anti-dsDNA and anti-Ro; cluster 2, anti-RNP; and cluster 3, anti-RNP, anti-Ro, and anti-La. Compared with patients in clusters 2 (n = 99) and 3 (n = 85), patients in cluster 1 (n = 155) had a shorter symptom duration before SLE diagnosis and higher incidence of biopsy-proven lupus nephritis. Patients in cluster 3 had a higher incidence of discoid rash, central nervous system involvement, lupus pancreatitis, pulmonary arterial hypertension, Raynaud's phenomenon, and premature gonadal failure. In addition, patients in cluster 3 had the lowest proportion of mean prednisolone > 7.5 mg/day in the medication history.

Conclusion: Autoantibody clusters were associated with the clinical features in women with SLE. Clustering autoantibodies could be a valuable approach for differentiating between various clinical subsets of SLE, and may help to guide prediction of the subsequent clinical course and organ damage in these patients.

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Abstract Number: 2804

Predictors of Survival in Renal Transplantation for Lupus Nephritis – 40 Patients in 40 Years

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Background/Purpose: Lupus nephritis (LN) is an important cause of morbidity and mortality in patients with systemic lupus erythematosus (SLE), leading to end stage renal failure (ESRF) in up to a quarter of the patients and often necessitating transplantation. Predicting adverse clinical outcomes in such patients remains challenging. We aimed to identify predictors of survival in our cohort of SLE patients undergoing renal transplantation (rTp).

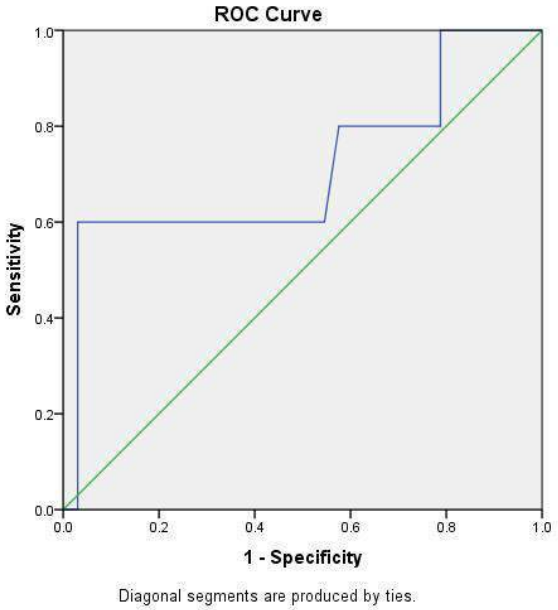
Methods: This was a retrospective analysis of all SLE patients under long term follow up who developed renal failure in the 40 year period (1975-2015) in two tertiary centres. Hospital notes, electronic records and correspondence from Family Physicians and colleagues in other hospitals were reviewed. Cox proportional hazard regression and receiver operator curves (ROC) were used to determine potential predictors. Amongst the factors considered were duration of SLE diagnosis, ethnicity, gender, age at onset of SLE and LN, serology (including dsDNA binding and antiphospholipid antibodies and complement levels), comorbidities (including diabetes, hypertension, dyslipidaemia and cardiovascular disease), class of LN on biopsy, decade of rTp, drugs and adherence to treatment.

Results: Over the last 40 years, from a total of 361 patients with LN, 40 patients (age 35±11 years, 34 female (85%), of which 15 Caucasian (38%), 15 Afro Caribbean (38%), and 10 Asian (25%)) underwent rTp. During a median follow up of 85 months (IQR 63,127) 6 patients died (15% mortality) and the five year survival was 95% (table 1). Univariate analysis only identified time on dialysis prior to rTp as a predictor of survival with a Hazard Ratio of 1.017 for each additional month spent on dialysis (95%CI= 1.000-1.034, p=0.044). ROC curves were used to calculate the optimal maximum time on dialysis prior to conferring an adverse outcome showing that ≥23 months on dialysis had an adverse effect with sensitivity of 0.800 and specificity 0.430 of death (figure1).

Conclusion: To predict adverse outcomes in rTp remains challenging. The only potential modifiable risk identified is time spent on dialysis prior to rTp with patients spending <23 months on dialysis having a beneficial outcome. **Table 1**: Cohort characteristics

	Dead (n=6)	**Alive (n=34)**
Gender	0/6 male	6/36 male
Age at lupus diagnosis (years)	22.8±10.1	20.7±9.5
Age at renal transplant (years)	34.5±12.9	35.2±10.9
Time (duration) on dialysis prior to transplant (months)	67±46	32±33
LN duration at transplant (months)	111±61	209±354
Ethnicity		
Caucasian	2 (33%)	13 (38%)
Black	0	15 (44%)
Asian	4 (67%)	6 (18%)
Class of LN Class IV	4 (67%)	12 (35%)
Analysis per decade	**Five year mortality**	**rTp's per decade**
1975-1985	0/2	2
1985-1995	1/3 (33%)	3
1995-2005	2/8 (40%)	8
2005-2015	0/19	27

Figure 1 Area under the curve showing fair accuracy (0.7) and indicating that patients on dialysis prior to rTp for more than 23 months



have an adverse outcome (sensitivity 0.8, specificity 0.43).

Disclosure: E. Ntatsaki, None; **A. Velo Garcia**, None; **B. D. C. Gracia Tello Sr.**, None; **A. D. Salama**, None; **D. A. Isenberg**, None.

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Abstract Number: 2805

Outcomes of Lupus Nephritis Patients Following Discontinuation of Treatment

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Background/Purpose: Lupus nephritis (LN) complicates 60% of systemic lupus erythematosus (SLE) patients within 5 years of diagnosis. Glucocorticoids and disease modifying immunosuppressive drugs (IS) are associated with adverse effects, treatment failure and relapses and treatment duration is uncertain. Our aims were to study long-term renal outcomes of LN patients who discontinued treatment after achieving disease remission and to identify predictors of renal relapse off IS therapy.

Methods: This was a retrospective cohort study of LN in our Lupus Clinic who discontinued IS treatment. Patient data was retrieved from October 1991 and through to 1stDecember 2015, or until their last follow-up date. Renal relapse was defined as raised urine protein-creatinine ratio (UPCR) of ≥ 50mg/mmol or ≥50mg/mmol from baseline (equivalent to proteinuria 0.5g/L), or with renal biopsy proven recurrence of nephritis. Predictive factors for renal relapse were identified using logistic regression model. Data analysis was performed using SPSS Version 23.0.

Results: 43 patients were identified, 25 (58%) had sufficient data for analysis. 60% were Caucasians, 28% of Afro-Caribbean origin and 12% were Asian. 23 patients (92%) were female. Mean age at LN diagnosis was 33.5 ± 11.4 years. 7 had class IV and 7 had class V LN (28% for each group). The remaining patients had class III LN (16%), class III/IV LN (12%), and class II LN (8%). An association with anti phospholipid syndrome (APS) was found in 28% and 7 with positive aPL antibodies that remained asymptomatic. Mean duration of LN treatment was 5.6±4.2years. 17 patients (68%) received IV cyclophosphamide (CYC) as induction therapy. Azathioprine was the commonest maintenance agent (76%). Most received hydroxychloroquine throughout maintenance phase (76%). At the time of

treatment discontinuation, mean eGFR was 87.7± 21.87 ml/1.73m^2/min. Mean serum albumin was 41.3± 3.88 mmol/L and mean UPCR was 59.0± 85.11 mg/mmol. Anti- dsDNA antibodies persisted in 24% of the cohort. Despite discontinuation, 80% remained under active surveillance. Only 4 patients lost to follow-up. There was 1 death with cause unknown. Renal relapses were recorded in 7 patients (28%) and 1 patient developed non-renal flare. Mean time to event estimated at 47.2months (95% CI: 36.7,57.7). None developed end-stage renal disease after treatment discontinuation. Young age at LN diagnosis, low C3/C4, high UPCR, low eGFR upon discontinuation of treatment and ethnicity were six predictors of possible renal relapse. Our fitted model was statistically significant, χ^2=18.22, p=0.011 and correctly classified 88% of cases.

Conclusion: Our long-term LN relapse rates after discontinuation of treatment are similar to previous studies. Nevertheless, reliable comparisons are limited by the retrospective nature of our study. It is possible to discontinue treatment for LN but the optimal duration of IS therapy remains uncertain and randomized clinical trials of treatment withdrawal are warranted.

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Abstract Number: 2806

A Type-I Interferon Signature Is Associated with Autoantibody Profiles in Connective Tissue Diseases: Results from the Lupus Extended Autoimmune Phenotype (LEAP) Study

John A. Reynolds[1,2], Mumtaz Khan[3], Tracy A. Briggs[4], Gillian Rice[5], Yanick Crow[5], Ben Parker[6] and Ian N. Bruce[1,7], [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [2]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [3]Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [4]Institute of Human Development, University of Manchester, Manchester, United Kingdom, [5]Manchester Academic Health Science Centre, Institute of Human Development, University of Manchester, Manchester, United Kingdom, [6]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [7]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

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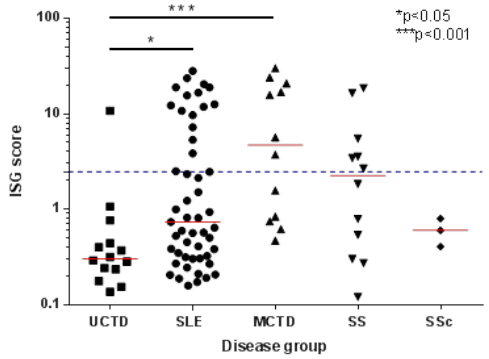
Background/Purpose: Type I interferon has been implicated in the pathogenesis of systemic lupus erythematosus (SLE), but much less is known about its role in other connective tissue diseases (CTDs). We aimed to determine the prevalence of a type I interferon signature across CTDs, and identify factors associated with elevated interferon activity.

Methods: Subjects were recruited from Central Manchester University Hospitals, UK between May 2014 and March 2016. Patients were categorised by their physician diagnosis into SLE, undifferentiated CTD (UCTD), mixed CTD (MCTD), Sjogren's syndrome (SS) and systemic sclerosis (SSc). RT-qPCR was performed on cDNA derived from whole blood and the median fold change of six interferon-simulated genes (*IFI27*, *IFI44L*, *IFIT1*, *ISG15*, *RSAD2*, *SIGLEC1*) was compared with the median of healthy controls, to create an interferon sensitive gene (ISG) score for each patient. Scores higher than the mean of the controls plus two sd (>2.466) were designated as positive.

Results: We recruited 92 subjects with a median (IQR) age of 48.3 (33.5, 57.4) years. 86 (93.5%) were female, 70/92 (76%) were Caucasian and the median disease duration was 7.21 (3.06, 13.78) years. The most commonly present autoantibodies were anti-U1RNP (25/92 [27.2%]), anti-Ro/SSA (24/92 [26.1%]) and anti-dsDNA (22/92 [23.9%]). In total, 58/92 (63%) subjects had at least 1 positive autoantibody (Ro, La, Smith, RNP, chromatin, Scl-70, dsDNA or anti-CCP). Across all subjects, 31/92 (33.7%) had a positive ISG score. ISG scores were significantly higher in patients with SLE or MCTD, compared to UCTD (p=0.003 across all groups) (figure).

All 3 SSc patients had a negative ISG score. In univariate logistic regression models, a positive ISG was significantly associated with the presence of anti-Smith, Ro, RNP and chromatin antibodies. Rheumatoid factor (but not anti-CCP) was also associated with a positive ISG score. These antibodies all remained significant after adjustment for age, gender, ethnicity (Caucasian or non-Caucasian) and clinical diagnosis (table). A significant association was observed between the number of autoantibodies (range 0-5) and a positive ISG score (OR 2.6 [1.73, 3.81], p<0.001). In a multivariable logistic regression model this observation remained significant after adjustment for age, gender, ethnicity and diagnosis (OR 2.2 [1.44, 3.50], p<0.001).

Conclusion: Expression of a type I interferon signature differs across CTD subtypes and is not observed in UCTD and SSc. The strongest factor associated with a positive ISG score was the type and number of autoantibodies, especially those binding to RNA antigens.



	Unadjusted model		Adjusted model* * for age, gender, ethnicity and diagnosis	
	OR	95% CI	OR	95% CI
Anti-dsDNA	2.50	(0.934, 6.684)	1.55	(0.521, 4.623)
Anti-Smith	**12.2**	**(3.111, 47.914)**	**14.5**	**(2.475, 85.491)**
Anti-RNP	**8.04**	**(2.883, 22.447)**	**5.19**	**(1.517, 17.749)**
Anti-Ro	**9.37**	**(3.250, 26.995)**	**13.0**	**(3.400, 49.542)**
Anti-La	2.30	(0.771, 6.890)	2.48	(0.589, 10.421)
Anti-chromatin	**7.55**	**(2.512, 22.683)**	**5.69**	**(1.512, 21.406)**
Rheumatoid factor	**5.33**	**(1.631, 17.442)**	**11.5**	**(2.100, 63.175)**
Anti-scl70	1.55	(0.320, 7.293)	2.32	(0.373, 14.512)
Anti-CCP	1.33	(0.211, 8.428)	1.27	(0.114, 14.091)

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Abstract Number: 2807

Skin and Muscle Sodium Concentrations in Patients with Systemic Lupus Erythematosus: A Proof of Concept Study

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Background/Purpose: Recent findings indicate that sodium is stored in the body and plays an important role in immune regulation. Studies in animals and humans show that sodium is stored in skin and muscle and can be measured with ^{23}Na magnetic resonance imaging (MRI). In animal models increased tissue sodium is associated with activation of the immune system and a high salt intake exacerbates autoimmune disease. However, there is no information about tissue sodium in human autoimmune disease. We hypothesize that skin and muscle sodium concentrations are higher in patients with systemic lupus erythematosus (SLE) than control subjects.

Methods: Skin and muscle Na^+ content in the lower leg was measured with a $^{23}Na^+$ knee-coil (Rapid Biomedical GmbH, Rimpar, Germany) at a Philips 3.0 Tesla Achieva scanner (Philips Healthcare, Best, the Netherlands) in 7 patients with SLE and 8 control subjects. Phantoms containing aqueous solutions with 10, 20, 30, and 40 mmol/L NaCl were included for calibration. Skin and muscle sodium concentrations between patients and control subjects were compared using Wilcoxon-rank sum tests.

Results: Demographic characteristics and systolic blood pressure (median and interquartile range) of patients with SLE and controls were similar (Table). The median SLEDAI score in patients with SLE was 2 (0-4). Patients with SLE had higher median skin and muscle ^{23}Na concentrations than control subjects. (Table) This association was unchanged after adjustment for age (p=0.06 and 0.05, respectively). Table: Comparison of clinical variables between patients with SLE and control subjects

	SLE (n=7)	Controls (n=8)	p-value
Age	41 (32-56)	34 (28-47)	0.42
Female n (%)	6 (86%)	7 (88%)	0.73
Systolic blood pressure (mm Hg)	129 (114-146)	125 (118-130)	0.39
Skin ^{23} Na+ (mmol/kg)	16.4 (15.0-19.6)	12.4 (10.9-15.9)	0.06
Muscle $^{23}Na+$ (mmol/kg)	17.4 (15.8-19.2)	15.0 (14.5-16.7)	0.049

Conclusion: This proof-of-concept study suggests that patients with SLE have higher skin and muscle sodium concentrations. Further studies are needed to examine the relationship between stored sodium with measures of disease activity, blood pressure, and cardiovascular disease in patients with SLE.

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Abstract Number: 2808

Role of Serum Autoantibodies in Blood Brain Barrier Damages in Neuropsychiatric Systemic Lupus Erythematosus

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Background/Purpose: Neuropsychiatric manifestation in systemic lupus erythematosus (NPSLE) is one of the most serious complications of the disease. We have recently demonstrated that the breakdown of blood brain barrier (BBB) plays a crucial role in the

development of diffuse psychiatric/neuropsychological manifestations (diffuse NPSLE), allowing influx of neuron-reactive autoantibodies from systemic circulation into the brain. However, the mechanism of BBB damages remains unclear. Of note, various autoantibodies have been implicated in the pathogenesis in NPSLE. The present study was designed in order to elucidate the roles of serum autoantibodies in the development of BBB damages In NPSLE.

Methods: Paired serum and cerebrospinal fluid (CSF) samples were obtained from 101 SLE patients when they presented active neuropsychiatric manifestations (69 patients with diffuse psychiatric/neuropsychological syndromes [diffuse NPSLE] and 32 patients with neurologic syndromes or peripheral nervous system involvement [focal NPSLE]). IgG anti-NR2 subunit of NMDA receptor (anti-NR2), anti-Sm, anti-RNP and anti-ribosomal P (anti-P) in sera and albumin in CSF and sera were measured by ELISA.

Results: Q albumin (CSF/serum albumin quotient) was significantly higher in acute confusional state (ACS) than in non-ACS diffuse NPSLE (anxiety disorder, cognitive dysfunction, mood disorder and psychosis) or in focal NPSLE. Serum anti-Sm, but not anti-RNP, anti-NR2 or anti-P, was significantly elevated in ACS compared with the other 2 groups of NPSLE. Accordingly, only serum anti-Sm ($r=0.2655$, $p=0.0073$), but not anti-RNP ($r=0.0551$), anti-NR2 ($r=0.0817$) or anti-P ($r=0.1280$), was significantly correlated with Q albumin.

Conclusion: These results confirm that the severity of BBB damages plays a crucial role in the development of ACS, the severest form of diffuse NPSLE. Moreover, the data indicate that serum anti-Sm might play a most important role in BBB breakdown in NPSLE.

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Abstract Number: 2809

Comparative Analysis of Anti-Nuclear Antibody Testing Using Blinded Replicate Samples Reveals Variability Between Commercial Testing Laboratories

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Background/Purpose: Serological positivity defined by presence of anti-nuclear antibodies (ANA) is frequently used in interventional lupus trials as an inclusion criterion and longitudinal biomarker. As such, consistent and sensitive quantification of ANA during conduct of clinical trials is important. In this study we compared ANA testing results between 3 different commercial laboratories vendors using shared samples to assess variability in analysis.

Methods: Serum samples obtained from commercial sources from 19 anonymous SLE donors meeting ACR criteria were banked and aliquotted. Triplicate samples from each donor were randomized and shipped to 3 different commercial labs for ANA testing with staining patterns (HEp-2.) Reports from each laboratory were unblinded to group each sample replicate for both ANA titer and staining pattern. Inter-sample and inter-laboratory variability were then analyzed descriptively.

Results: Identical SLE patient sera samples analyzed by three laboratories providing ANA testing revealed differences in detection, titer level and staining pattern identification. While high titer ANA were readily detected by all three laboratories, there was significant variability in the assessment of staining patterns by some labs, and patterns present at different titers were often missed. In general, titers within an individual vendor between samples were reported within one fold. Lower titer ANAs <1:160 were more consistently scored as equivocal or absent by some labs, indicating a difference in sensitivity limit utilizing the samples provided. **Table 1.** ANA identification by testing laboratories

Vendor 1	*Vendor 2*	*Vendor 3*
*19/19 (100%)**	*12/19 (63%)**	*13/19(68%)**

*Of note, staining patterns from Vendor 1 had 2/19 samples that missed patterns in one triplicate assessment, Vendor 2 had 6/19 missed patterns in one or more triplicate assessments, and Vendor 3 had 3/19 missed patterns in one or more triplicate assessments.

Conclusion: This study suggests that commercial laboratories exhibited variability in terms of ANA titers and staining patterns using identical samples, especially in those of low titer. This occurred in a format consistent with collection in a clinical study and provision to a central laboratory for analysis. Variability was present between sample replicates and also the level of detection between different commercial labs performing ANA testing. This variability may potentially impact patient enrollment in clinical studies, and also the ability to accurately assess the impact of therapeutic interventions using these serological readouts. A key limitation to this study is that samples were accrued and banked to be sent to the analytical laboratory, and some vendor laboratory methodology may be more prone to latency of assessment than others.

Disclosure: M. Chevrier, Janssen Research and Development, LLC., 1,Janssen Research and Development, LLC., 3; **J. Jordan**, Janssen Research and Development, LLC., 3; **J. Schreiter**, Janssen Research and Development, LLC., 3; **J. Benson**, Janssen Research and Development, LLC., 3.

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Abstract Number: 2810

Correlates of Spontaneous Cytokine Production in Individuals Undergoing Interferon-Gamma Release Assay Testing

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Background/Purpose: The interferon gamma (IFN-G) release assay (IGRA) estimates probability of latent TB infection (LTBI) based on IFN-G released by whole blood after 18h exposure to TB antigen, mitogen or no stimulation (negative control, NC). In a small percentage of individuals, the NC condition results in markedly elevated IFN-G levels, indicating spontaneous IFN-G production (SIP). Here we examine the clinical, laboratory and demographic features of SIP in a large, academic health care system. We hypothesized that SIP is associated with select immunologic and infectious diseases.

Methods: Analysis of the distribution of over 15,000 IGRA NC results obtained between 2010 and 2015 revealed an abnormally distributed population (n = 108) with values ≥ 5 SD above median (≥ 3 IU/mL). Using this discovery cohort, we catalogued all clinical diagnoses noted in the electronic medical record ± 6 wks of IGRA date. Next, we queried a de-identified clinical data repository (DCDR) for occurrences of related ICD9/10 codes and demographic data in all individuals undergoing IGRA testing (~11,820), comparing HIGH NC group (any NC result ≥ 3, n = 83) vs. LOW NC group (no NC ≥ 3, n = 11,740) with univariate (Chi square and Fisher tests) and multivariate (logistic regression) analyses.

Results: Several ICD9/10 codes were significantly ($p \leq 0.001$) enriched in the HIGH vs. LOW groups: HIV (27.7% vs. 16.0%), LTBI (22.9% vs. 7.6%), SLE (7.2% vs. 1.3%) and hemophagocytic lymphohistiocytosis (HLH) (3.6% vs. 0.1%). After controlling for race and other enriched ICD9/10 codes, these relationships remained significant: HIV (OR 2.16, 95%CI 1.31 – 3.58), latent TB (OR 3.9, 95%CI 2.2-6.7), SLE (OR 3.79, 95%CI 1.56-9.19) and HLH (OR 31.8, 95%CI 8.7-116.2). These relationships were also observed analyzing NC levels as a continuous variable. Univariate sub-analysis of subjects with ICD9/10 codes corresponding with SLE suggested a correlation between HIGH NC values and coincident low serum complement levels ($p = 0.0356$), but not cytopenias or specific autoantibodies.

Conclusion: In individuals undergoing IGRA testing in a large academic health care system, SIP was associated with a limited set of immunologic or infectious diseases. All of the identified diseases are known to involve IFN-G activation. For SLE, SIP may identify a subset of patients with high disease activity and have therapeutic implications. For a very rare disease like HLH, SIP may have diagnostic utility. The importance of SIP in HIV and LTBI remains to be determined.

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Abstract Number: 2811

Predictors of Persistent Disease Activity and Persistent Remission in Systemic Lupus Erythematosus – Results from the Hopkins Lupus Cohort

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Background/Purpose: Systemic lupus erythematosus (SLE) is characterized by a variability of disease expression, both between individuals and within individuals, over time. The aim of this study is to identify prognostic factors of persistent disease activity and remission.

Methods: Patients enrolled in the Hopkins Lupus Cohort from 1987 to 2014, who had at least 3 visits per year, at least 3 years follow-up and available information on disease activity were included. Three major patterns of SLE disease activity over time (1 year intervals) have been previously described1,2, as defined by the Modified SLE Disease Activity Index – modified to remove serology (M-SLEDAI): long quiescent (LQ), chronic active (CA) and relapsing-remitting (RR). Based on maintenance of the aforementioned patterns over 3 consecutive years, patterns are defined as: Persistent Long Quiescent (pLQ), LQ pattern in each of the 3 years; Persistent Relapsing-Remitting (pRR), RR pattern in each of the 3 years; Persistent Chronic Active (pCA), CA pattern in each of the 3 years; and Mixed, at least 2 different pattern types. Possible predictors of pCA (vs. pLQ, pRR and mixed) and pLQ (vs. pCA, pRR and mixed) were identified by univariate logistic regression analyses. Several baseline demographic and disease characteristics were used as independent variables. The results from theses analyses ($p<0.25$ as the criterion) and correlation analyses (Pearson and Spearman correlations) guided the selection of variables for the multivariate logistic regression analyses. The non-significant variables were removed by stepwise backward selection.

Results: 916 patients were identified. The results of the univariate regression analysis for pCA and pLQ are shown in table 1 and 2, respectively. In the multivariate model, African American race (OR: 2.43, 95% CI: 1.19-4.94) and high baseline SLEDAI (OR: 1.09, 95% CI: 1.03-1.16) remained significant predictors of pCA. Higher education (>12 years; OR: 2.16, 95% CI: 1.11-4.20) and low baseline SLEDAI (OR: 0.62, 95% CI: 0.52-0.75) were significant predictors of pLQ in the multivariate analysis while African American race (OR: 0.36, 95% CI: 0.16-0.78) and female patients (OR: 0.26, 95% CI: 0.12-0.56) were less likely to achieve stable remission.

Conclusion: African American race and high disease activity at the time of diagnosis predict chronic activity in SLE, even after adjustment for education years and income, while higher education, low disease activity at baseline and male sex predict long-term remission. References: [1] Györi N, et al. Disease Activity Patterns over Time in Patients with SLE – a Retrospective Descriptive Analysis of the Hopkins Lupus Cohort. ACR 2015. [2] Barr SG, et al. Patterns of disease activity in systemic lupus erythematosus. Arthritis Rheum. Dec 1999;42(12):2682-2688.

Table 1. Predictors of persistent activity (pCA) during the first three years after diagnosis; results of the univariate logistic regression analysis.

Univariate analysis pCA vs (pLQ, pRR and mixed)	p	OR	95%CI
Female sex (vs male)	0.54	1.57	0.37-6.69
Age > 40 yrs (vs ≤ 40 yrs)	0.32	1.42	0.71-2.81
Disease duration	0.17	1.03	0.99-1.08
African American (vs other)	0.007	2.64	1.30-5.34
Years of education >12 yrs (vs ≤ 12 yrs)	0.27	0.68	0.34-1.35
Income <30000$ 30000-65000$ ≥65000$	 0.06 0.12	 0.42 0.53	 0.17-1.03 0.24-1.18
Smoking at baseline (vs no)	0.06	2.10	0.96-4.60
SLEDAI baseline	0.002	1.10	1.04-1.17
PGA baseline	0.04	1.51	1.03-2.23

SLEDAI: SLE Disease Activity Index; PGA: Physician Global Assessment

Table 2. Predictors of remission (pLQ) during the first three years after diagnosis; results of the univariate logistic regression analysis.

Univariate analysis pLQ vs (pCA, pRR and mixed)	p	OR	95%CI
Female sex (vs male)	0.002	0.34	0.17-0.68
Age > 40 yrs (vs ≤ 40 yrs)	0.51	1.19	0.70-2.03
Disease duration	0.57	1.01	0.97-1.05
African American (vs other)	<0.001	0.23	0.11-0.49
Years of education >12 yrs (vs ≤ 12 yrs)	0.01	2.28	1.21-4.28
Income <30000$ 30000-65000$ ≥65000$	 0.47 0.007	 ref 1.34 2.56	 0.61-2.90 1.29-5.08
Smoking at baseline (vs no)	0.08	0.39	0.14-1.10
SLEDAI baseline	<0.001	0.62	0.52-0.73
PGA baseline	<0.001	0.26	0.16-0.44

SLEDAI: SLE Disease Activity Index; PGA: Physician Global Assessment

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Abstract Number: 2812

Clinical Trial Simulation Identifies Factors for Patient Engagement in Systemic Lupus Erythematosus and Lupus Nephritis Trials By African-Americans

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Background/Purpose: Clinical trials of patients with systemic lupus erythematosus (SLE) and lupus nephritis (LN) can be confounded by difficulties in engaging patients. Identifying factors of non-engagement informs strategies to increase involvement and compliance.

Methods: A unique approach was used simulating key study visits for an upcoming study involving patients with active SLE/LN and clinical staff from an indigent care hospital in Atlanta, GA. Patients underwent a consent procedure (30–45 minutes), simulated SLE/LN screening visit (2.5 hours), and simulated SLE/LN first dosing visit (4.5–5 hours). Patients and site staff were interviewed to obtain sentiments and perceptions relating to the simulated visits.

Results: Demographics**:** Six African-American patients (1 male, 5 female) aged 27–60 years with moderate to severe SLE/LN were recruited. Although the sample size was small, it provided value owing to its targeted clinical context. Patients differed in cognitive ability and health literacy. Communication: Patients expressed a preference for obtaining general disease and specific trial information from the Internet and stated that both strong online and community support were important. Patients valued help and support to discuss their conditions and options with family and friends. For support groups, the use of lupus community leaders was suggested for communicating the importance and relevance of clinical trial participation. Study sponsors were also advised to engage the lupus community through lupus community leaders. Despite completing full informed consent procedures, not all patients understood the degree of commitment at the time of study enrollment; in addition, a few patients thought the study might cure their disease. Patients suggested developing condensed and/or electronic versions of the informed consent form in text or audio format. Staff mentioned using electronic patient-reported outcome tools, which the patients found acceptable to complete. Patient needs: The extent of disruption to patients' lives due to study participation was cited as a major factor for potential study withdrawal. Limited flexibility in work schedules and inflexible commitments such as child care, leading to financial burden were raised as significant concerns. Although patients were generally happy with their current disease management, they were willing to consider changing their medications for a better outcome. Some patients were motivated by being part of developing a possible cure. The simulation also considered infusion visits, which required coordination between relevant parties, with post-infusion observation times potentially shortened. The duration of study visits (2+ hours) was a concern for patients and made them particularly sensitive to wait times between procedures.

Conclusion: Insights and techniques from this study at an urban indigent care lupus clinic with large numbers of African-Americans can be applied to the design of future clinical trials for patients with SLE/LN in high-risk populations to potentially improve recruitment, retention, compliance and advocacy.

Disclosure: S. S. Lim, AstraZeneca, 9; **D. McKinnell**, AstraZeneca, 5; **M. E. Pierson**, AstraZeneca, 3; **F. O'Brien**, AstraZeneca, 3.

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Abstract Number: 2813

Risk of Renal Failure within 10 or 20 Years of SLE Diagnosis, By Patient Characteristics

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) are at elevated risk for lupus nephritis and ultimately renal failure. While some risk factors for renal involvement among patients with SLE are well known, there has not been a recent systematic study of the relationship between SLE patient characteristics and renal failure. We leveraged a large American clinical cohort of patients with SLE to estimate the risk of renal failure within 10 and 20 years of diagnosis overall, and in subgroups defined by clinical and demographic patient characteristics.

Methods: This analysis is based on the time from SLE diagnosis until end of follow-up or renal failure for patients in our cohort. For patients diagnosed with SLE before entering our cohort, the data of diagnosis and clinical manifestations at the time of diagnosis were collected by a comprehensive history at cohort entry. Individuals with renal failure prior to SLE diagnosis were excluded. We estimated the risk of experiencing renal failure over time among all patients and within subgroups of patients using the Kaplan-Meier approach. Cox regression models were used to estimate the joint association between multiple patient characteristics and renal failure.

Results: Among the 2356 cohort patients included, 155 patients experienced renal failure after SLE diagnosis and before the end of their active participation in the cohort. Table 1 shows the relationship between selected patient characteristics and 10 and 20-year risk of renal failure. Table 2 shows association between patient characteristics and rates of renal failure based on a multivariate model.

Table 1: Relationship between demographic factors and risk of renal failure in the Hopkins Lupus Cohort

Subgroup	Estimated percent chance of developing renal failure within 10 years of SLE diagnosis (95% CI)	Estimated percent chance of developing renal failure within 20 years of SLE diagnosis (95% CI)	P-value (log-rank test)
Everyone (n=2356)	5.8 (4.8, 6.9)	9.6 (8.1, 11.5)	
Sex Female (n=2179) Male (n=177)	5.3 (4.3, 6.4) 12.2 (7.7, 19.1)	9.4 (7.8, 11.4) 12.2 (7.6, 19.1)	.021
Age of diagnosis <30 (n=1170) 30-39 (n=586) 40+ (n=600)	7.5 (6.0, 9.4) 5.2 (3.6, 7.7) 2.3 (1.3, 4.1)	12.0 (9.7, 14.9) 8.2 (5.7, 11.7) 5.0 (2.7, 9.0)	.0006
Ethnicity White (n=1260) Black (n=920) Other (n=176)	3.7 (2.7, 5.1) 8.5 (6.7, 10.8) 6.2 (3.2, 11.7)	7.0 (5.2, 9.5) 13.0 (10.3, 16.3) 11.4 (5.3, 23.9)	<.0001
Year of Diagnosis <1985 (n=296) 1985-1994 (n=634) 1995-2004 (n=947) 2004-2015 (n=479)	5.1 (3.1, 8.4) 6.5 (4.7, 8.9) 5.1 (3.8, 6.9) 4.8 (3.1, 8.4)	11.3 (8.0, 15.8) 9.7 (7.3, 12.9) 6.5 (4.8, 8.8) 4.8 (3.0, 7.6)	.40
Low C3 (ever) No (n=1063) Yes (n=1287)	2.4 (1.5, 3.8) 8.2 (6.7, 1.0)	5.9 (3.9, 9.0) 12.3 (10.1, 14.9)	<0.0001
Low C4 (ever) No (1228) Yes (1121)	3.7 (2.7, 5.1) 7.7 (6.2, 9.7)	7.5 (5.4, 10.3) 11.7 (9.4, 14.4)	0.0071
Anti-dsDNA (ever +) No (n=894) Yes (n=1455)	3.2 (2.1, 4.8) 7.1 (5.7, 8.7)	6.4 (4.2, 9.9) 11.2 (9.2, 13.6)	.0004
ACR Criteria satisfied at time of SLE Diagnosis			
Neurologic No (n=2218) Yes (n=138)	5.5 (4.5, 6.7) 9.8 (5.6, 16.7)	9.3 (7.7, 11.2) 15.6 (9.1, 25.8)	0.012
Photosensitivity No (n=1389) Yes (n=967)	7.1 (5.7, 8.8) 3.9 (2.7, 5.5)	11.9 (9.6, 14.6) 6.6 (4.8, 9.2)	.0068
Mucosal Ulcer No (n=1561) Yes (n=795)	6.4 (5.2, 7.9) 4.5 (3.1, 6.6)	10.5 (8.6, 12.9) 7.7 (5.2, 11.3)	.049
Arthritis No (n=1063) Yes (n=1296)	7.0 (5.4, 8.9) 4.8 (3.6, 6.3)	11.4 (8.9, 14.6) 8.2 (6.3, 10.6)	.045

Table 2: Joint association between multiple variables and rates of renal failure based on a Cox regression model

Variable	Rate Ratio (95% CI)	P-value
Male (vs. female)	2.0 (1.2, 3.3)	0.0069
Age of diagnosis 30-39 (vs. < 30) 40+ (vs. < 30)	0.8 (0.6, 1.2) 0.5 (0.3, 0.8)	0.30 0.0048
Race Black (vs. White) Other (vs. White)	2.1 (1.5, 3.0) 1.5 (0.8, 2.9)	<0.0001 0.18
History of anti-dsDNA (vs. no history)	1.4 (0.9, 2.1)	0.12
History of low C3	1.8 (1.2, 2.7)	0.0050
Neurologic involvement at diagnosis	1.7 (1.0, 2.9)	0.061
Musculoskeletal involvement at diagnosis	0.7 (0.5, 1.0)	0.045

Conclusion: Almost 10% of our patients develop renal failure within 20 years. Risk of renal failure is highest among males, African Americans, those diagnosed with SLE at a younger age, those with a history of low complement, anti-dsDNA and neurologic involvement. Those with musculoskeletal disease at SLE diagnosis appear to have lower risk.

Disclosure: L. S. Magder, None; **E. Barr**, None; **M. Petri**, None.

Abstract Number: 2814

Immunofluorescence Pattern and Titer of the Antinuclear Antibody Test Correlate with Disease Activity in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Antinuclear antibody (ANA) indirect immunofluorescence (IIF) assay on HEp-2 cells (HEp-2-ANA) is an important element for diagnosis and classification of Systemic Lupus Erythematosus (SLE), but is not considered as a parameter for monitoring disease activity. The objective was to determine whether HEp-2-ANA pattern and titer can be relevant for monitoring SLE disease activity.

Methods: 269 patients meeting the ACR criteria for SLE were consecutively retrieved during a one-year interval and classified into 3 groups according to SLEDAI2K: Remission Group (SLEDAI2K=0); Intermediate Group (SLEDAI2K=1-5); Active Group (SLEDAI2K≥6). In addition to HEp-2-ANA titer and pattern, the following putative parameters of disease activity were determined: 1) serum CH100, C3, C4 and C2; and 2) antibodies to native DNA, denatured DNA, C1q, and nucleosome. 101 of the 269 patients were prospectively reassessed after a six-month interval.

Results: there were 256 women and 13 men (37±11.4 years old) with disease duration of 9.3±7.5 years. Active (n=111), Intermediate (n=111) and Remission (n=47) groups did not differ in age, disease duration and gender. As expected, putative parameters of disease activity differed significantly among the 3 groups, indicating that they actually represent three different disease activity stages. Ten patients were ANA-negative (3.7%), equally distributed among the 3 groups (p=0.534). The nuclear homogeneous pattern (HO) occurred in 57 patients (51.4%) of the Active group and in 11 patients (23.4%) of the Remission group (p=0.003). The nuclear fine

speckled pattern (FSp) occurred in 19 patients (40.4%) of the Remission group and in 25 patients (22.5%) of the Active group (p=0.09). Patients with HO pattern had higher SLEDAI (9.2±7.9) than those with FSp pattern (4.8±5.2) (p=0.008). ANA titer was lower in the Remission group (median 1/640) in comparison with the Active (median 1/2560) and Intermediate (median1/1280) groups (p<0.001). In the follow-up analysis, 50 patients remained in the same group (SLEDAI2K change ≤3) and 51 changed disease activity status (SLEDAI2K change ≥4). ANA titer decreased significantly in the 33 patients with decreasing disease activity (p=0.002) but not in the 50 patients with irrelevant change in SLEDAI2K (p=0.677) and in the 18 patients with increasing SLEDAI2K (p=0.080). ROC curve analysis for determination of disease activity showed equivalent areas under the curve (AUC) for ANA titer and all putative disease activity parameters.

Conclusion: ANA pattern and titer are affected by SLE disease activity and can be considered in conjunction with other laboratory and clinical parameters in the assessment of SLE disease activity.

Disclosure: M. S. Prado, None; **A. Dellavance**, None; **S. H. Rodrigues**, None; **L. E. C. Andrade**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/immunofluorescence-pattern-and-titer-of-the-antinuclear-antibody-test-correlate-with-disease-activity-in-patients-with-systemic-lupus-erythematosus

Abstract Number: 2815

Comparison of Lupus Nephritis Induction Therapy with Cyclophosphamide High Dose Versus Low Dose

Juliana Valim[1], Verônica Lima[2], Fernanda Guimarães[3], Fernanda Chaer[4] and Branca Souza[5], [1]Rheumatology, Santa Casa de São Paulo, São Paulo, Brazil, [2]Rheumatology, Irmandade Santa Casa de São Paulo, São Paulo, Brazil, [3]Rheumatology, Irmandade Santa Casa de Misericordia de São Paulo, São Paulo, Brazil, [4]Rheumatology, Irmandade da Santa Casa de São Paulo, São Paulo, Brazil, [5]Reumatologia, Irmandade da Santa Casa de Misericordia de São Paulo, São Paulo, Brazil

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - Poster III: Biomarkers and Nephritis

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Session Time: 9:00AM-11:00AM

Background/Purpose: To Compare the induction therapy of lupus nephritis with cyclophosphamide (CYC) high dose or low dose and identify possible predictors of disease remission.

Methods: Retrospective study of patients with systemic lupus erythematosus (SLE), according to ACR criteria, diagnosed with lupus nephritis (LN), histological class III or IV, who underwent induction therapy with CYC high or low dose, respectively: CYC 0,5 to 1 g/m² body surface area monthly for six months or CYC 0,5 g every 15 days for three months. We compared the frequency of renal remission between these two groups, high dose CYC or low dose CYC, right after the induction period and after the 12 and 24 months following. Complete renal remission was defined as proteinuria less than 500 mg/24 hours. Partial remission was defined as a 50% reduction of the proteinuria starting with levels <3g. We collected clinical and laboratorial data before the induction therapy to identify possible predictors of remission.

Results: There were 55 patients, 35 underwent high dose therapy of CYC and 20 underwent low dose therapy of CYC. There were no significant statistical differences in baseline clinical and laboratory features between these two groups. The frequency of complete renal remission right after the induction therapy was 74 % in CYC high dose group compared to 45 % in the CYC low dose group (p = 0.03). 25% of patients in the low dose group, who did not achieved remission after the 3 months of therapy, started new treatment with CYC high dose. At the end of follow-up (24 months), the frequency of remission in CYC high dose group was 86% and did not differ from the CYC low dose group (80%, p=0,21). The initial proteinuria and the serum values of complement, creatinine and albumin before the start of induction therapy, as well as the use of anti-proteinuric and antimalarial drugs have not been predictors of renal remission (p> 0.05).

Table-Comparison of remission frequency between the CYC high dose group and low dose group at the end of induction therapy (after 6 and 3 months respectively)

	CYC HIGH DOSE GROUP	CYC LOW DOSE GROUP	
Achieved Remission n(%)	26 (74%)	9 (45%)	***p=0,03***
Did not achieved remission n(%)	9 (26%)	11 (55%)	

Conclusion: The group of patients undergoing CYC high dose induction therapy achieved higher frequency of remission than the group with low dose of CYC after the induction therapy period. We did not found any predictor of renal remission.

Disclosure: J. Valim, None; **V. Lima**, None; **F. Guimarães**, None; **F. Chaer**, None; **B. Souza**, None.

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Abstract Number: 2816

Broad Autoantibody Profiling in Ethnically Diverse SLE Cohorts Reveals a Set of Conserved Autoantibodies That Are Correlated to a Type I Interferon Signature

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease with a wide range of clinical manifestations. Production of autoantibodies is a hallmark of SLE and has been shown to contribute to disease pathogenesis as well as specific clinical manifestations such as nephritis. Despite the importance of autoantibodies in SLE, only a limited number of autoantibodies have been characterized and are utilized as lupus biomarkers, and many of these are not specific for lupus. We sought to address the question of whether broad autoantibody specificity profiling could identify novel and more specific autoantibodies to identify SLE patients, and if certain autoantibody specificities were enriched in patients exhibiting an interferon-I (IFN-I) signature.

Methods: To address this question, we carried out an unbiased analysis using the ProtoArray® platform (detection of >9400 autoantibodies), comparing five racially and ethnically diverse cohorts containing patients of African American, European, and Chinese descent (total of 131 healthy and 193 SLE patients).

Results: Each cohort had a group of SLE patients exhibiting very high autoantibody signals, a group that had moderate signal, and a group that had low signal against most of the 9400 autoantigens. The majority of healthy patients had very low autoantibody signals. Furthermore, we identified a core set of 17 autoantibodies that were significantly upregulated (FC>2, FDR<0.01) in SLE patients compared to healthy patients across all five cohorts. The levels of these core autoantibodies remained longitudinally stable over a 12-week period. We also demonstrated that the expression of these 17 autoantibodies correlated with levels of an interferon (IFN) signature present in whole blood from these patients.

Conclusion: Despite the diverse set of patients in our study, we were able to identify a small set of core autoantibodies that were commonly upregulated in SLE patients in all five cohorts. Importantly, we demonstrate that autoantibodies could be vital in patient stratification or as a biomarker of SLE, as our study reveals that levels of autoantibodies are potentially linked with IFN-I gene signatures.

Disclosure: T. Sato, Janssen Research and Development, LLC, 3; **M. Cesaroni**, Janssen Research and Development, LLC, 3; **J. Schreiter**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **J. Jordan**, Janssen Research and Development, LLC., 3; **M. Chevrier**, Janssen Research and Development, LLC., 1,Janssen Research and Development, LLC., 3; **J. Benson**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1.

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Abstract Number: 2817

Identification of Subsets of Systemic Lupus Erythematosus Patients By Principal

Component Analysis and Urine Biomarkers

José A. Gómez-Puerta[1], Blanca Ortiz[2], Tomás Urrego[1], Adriana L Vanegas[3], Carlos Horacio Muñoz[4], Mauricio Restrepo[3], Wilmer Rojas-Zuleta[3], Sofia Arteaga[3], Luis Alonso Gonzalez[5], Mauricio Rojas[2] and **Gloria Vásquez**[5,6], [1]Grupo de Inmunología Celular e Inmunogenética, Universidad de Antioquia, Medellín, Colombia, [2]Grupo de Inmunología Celular e Inmunogenética, Facultad de Medicina, Universidad de Antioquia, medellin, Colombia, [3]Rheumatology Unit, Universidad de Antioquia, Medellín, Colombia, [4]Hospital Universitario de San Vicente Fundación, Medellín, Colombia, [5]Rheumatology Unit, Universidad de Antioquia, Medellin, Colombia, [6]Grupo de Inmunología Celular e Inmunogenética (GICIG), Universidad de Antioquia, Medellín, Colombia
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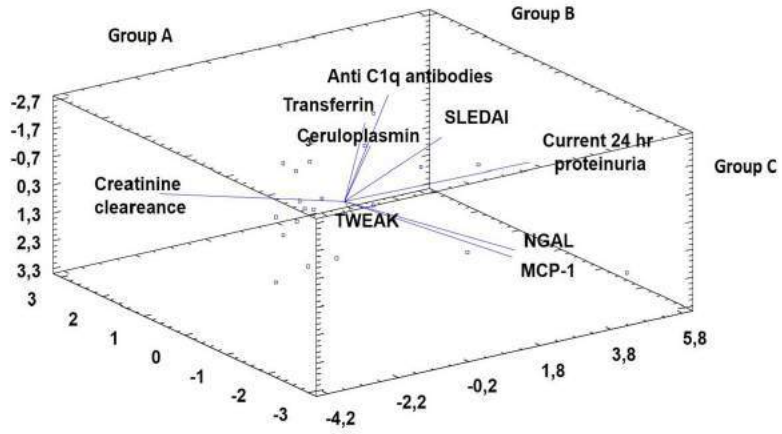
Background/Purpose: Systemic lupus erythematosus (SLE) is clinically heterogeneous disease, with a considerably variability of disease expression among patients. There have been several attempts to classify subsets or cluster of SLE patients according genes, clinical characteristics and autoantibodies. However, information about classification of SLE patients based on urinary biomarkers is scarce. We investigated whether subdivision of SLE is possible using a panel of urine biomarkers by principal component analysis (PCA).

Methods: We included in 100 consecutive SLE patients (ACR criteria 1997) from a tertiary University Hospital. We measured urinary levels of 5 different biomarkers: monocyte chemoattractant protein 1 (MCP-1), neutrophil gelatinase-associated lipocalin (NGAL), TWEAK, Ceruloplasmin (CP), and Transferrin (TF) using a commercial ELISA kits (R&D system and Assaypro, USA). In addition, serum anti C1q antibodies were measured by ELISA (Inova, USA). SLE activity was measured with SLEDAI. The PCA was performed by Statgraphics Centurion XVI.I for Windows (Statgraphics Corp., Rockville, USA). The PCA allowed simultaneous analysis of the relationship between 5 different urine biomarkers, as well as different clinical features and anti C1q antibodies. Creatinine clearance was considered as anchor factor of the PCA.

Results: 100 SLE patients were recruited (88% female) with median age of 33.6 ± 12.4 years and median disease duration of 11.5 ± 14.8 years. Hematologic disease (89%), arthritis (83%), cutaneous involvement (82%), and renal disease (66%) were among most common manifestations. Three components achieved an eigenvalue greater than 1.0. PCA revealed that the first 3 components accounted separately for a variability of 72%. According with those components we identified 3 subsets: Group A) patients with normal renal function and moderate disease activity, group B) patients with high disease activity and high levels of anti C1q, TF and CP and group C) patients with active lupus nephritis with high levels of 24 hours proteinuria, MCP-1, NGAL and TWEAK (Figure). Patients from Group B were older, had a shorter disease duration and higher SLEDAI scores than the other 2 groups.

Conclusion: We identified 3 different subgroups of SLE patients by PCA approach using urine biomarkers and serum Anti C1q antibodies. Whether these subgroups represent a different clinical outcome or a worst prognosis requires further analysis.

Biplot showing the first three loadings from a PCA



Clinical and biomarkers characteristics among different components

	Group A N=11	Group B N=8	Group C N=4	P value 1 vs 2	P value 2 vs 3	P value 1 vs 3
Current age (years ± SD)	29.5 ± 10.7	35.6 ± 10.0	28.5 ± 5.9	NS	NS	NS
Sex (Female), %	100	87	100	NS	NS	NS
Mean disease duration (years ± SD)	8.0 ± 4.35	2.33 ± 2.51	5.0 ± 1.0	0.038	NS	NS
Renal involvement	72	87	100	NS	NS	NS
Creatinine clearance	103.0 ± 35	100.7 ± 32.0	47.5 ± 12	NS	<0.001	<0.001
SLEDAI	6.45 ± 6.54	17.37 ± 6.11	16.0 ± 9.62	0.002	NS	NS
Proteinuria	716.0 ± 715.1	2592.8 ± 1802	6972 ± 2942	0.01	0.05	<0.001
MCP-1	666.6 ± 747	814.0 ± 328.8	2330.2 ± 2867.1	NS	NS	NS
NGAL	29.3 ± 34.3	49.5 ± 42.0	149.9 ± 72.1	NS	NS	0.039
CP	2571.1 ± 1299.3	4070.2 ± 274	3464. 4 ± 698.1	0.007	NS	NS
TF	1462.3 ± 532.9	1835.2 ± 40.8	1685.5 ± 131.4	0.043	NS	NS
TWEAK	1183.3 ± 841.6	2054.5 ± 1580.0	1598.0 ± 1081	NS	NS	NS
Anti C1q	50.9 ± 51.7	116.5 ± 78.3	103.2 ± 82.9	NS	NS	NS

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Abstract Number: 2818

High Sensitivity Multiplex ELISA Reveals Cytokine Expression Heterogeneity in Active SLE

John A. Reynolds[1], Sahena Haque[2], Eoghan M. McCarthy[3], Jamie C Sergeant[4], Elaine Lee[5], Eileen Holling Lee[5], Steven Kilfeather[5], Benjamin Parker[6] and Ian N. Bruce[7], [1]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [2]Rheumatology department, University Hospitals of South Manchester NHS Foundation Trust, Manchester, United Kingdom, [3]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospital NHS Foundation Trust, Manchester, United Kingdom, [4]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Manchester Academic Health Science Centre, University of Manchester, Manchester, UK, Manchester, United Kingdom, [5]Aeirtec Limited, UK, North Shields, United Kingdom, [6]Centre for Musculoskeletal Research, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [7]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

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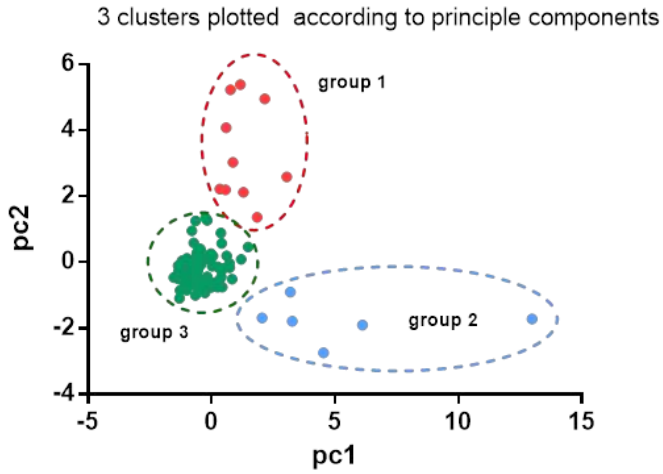
Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with SLE have a broad clinical and immunological phenotype in which multiple immune pathways may be sequentially or simultaneously activated. No reliable biomarkers exist to identify active disease across the spectrum of lupus patients. Cytokine expression in serum is often at low levels and therefore traditional ELISA methods have inadequate sensitivity. Custom high sensitivity Multiplex arrays offer the opportunity to measure multiple cytokines within a single serum sample. We aimed to investigate the association between cytokine expression and disease activity in patients with established SLE and determine whether clusters of patients could be identified.

Methods: Female healthy subjects and patients with SLE (≥4 ACR criteria) were recruited between 2007 and 2013 from Central Manchester NHS Foundation Trust. Disease activity was measured using the SLEDAI-2K and BILAG-2004 indices. Active disease was defined as presence of any of: SLEDAI score >4, 1 BILAG "A" score, or 2 BILAG "B" scores. The expression of 10 cytokines (covering B cell, T cell and innate immune pathways) was measured in serum by high sensitivity bead-based Multiplex ELISA (Aeirtec Ltd, UK). Principle component analysis (PCA) of the cytokines followed by unsupervised K-means clustering was used to identify patient groups according to cytokine expression.

Results: We recruited 13 healthy control (HC) subjects and 96 SLE patients with median (IQR) age of 40 (32, 49) and 51 (44, 59) years respectively. The SLE group was 77% (74/96) Caucasian with a median disease duration of 11.7 (6.8, 21.4) years. 22/96 (23%) patients had active disease. The median dose of steroids was significantly higher amongst patients with active disease (12.5 [7.5, 17.5] vs. 0 [0, 5]mg/day, $p<0.001$) but there were no differences in frequency of antimalarial or immunosuppressant use. Compared to HCs, SLE patients had significantly increased levels of CXCL10 and CXCL13. Patients with active SLE had significantly increased levels of BLys, IL-18, CXCL10, IL-17 and pentraxin-3 compared to inactive patients. Cluster analysis revealed 3 groups (high chemokines, including CXCL13 [n=10]; high inflammation initiators including Blys and IFNα [n=6]; all cytokines low [n=93]). All HCs were in group 3. SLE patients in group 1 and 2 had higher disease activity with 7/10 (70%) and 4/6 (67%) active patients compared to group 3 (11/80, 14%). Multinomial logistic regression models identified that group membership was associated with clinical subgroup (HC/inactive SLE/active SLE) and steroid use, but not age, ethnicity or disease duration.

Conclusion: Cytokine profiles are variable in active SLE but at least 2 distinct subgroups are apparent. Patients with inactive SLE have similar profiles to healthy controls. Our findings suggest that distinct immunophenotypes may exist amongst SLE patients and may be



detected using multiplex ELISA.

Disclosure: J. A. Reynolds, None; **S. Haque**, None; **E. M. McCarthy**, None; **J. C. Sergeant**, None; **E. Lee**, None; **E. Holling Lee**, None; **S. Kilfeather**, None; **B. Parker**, None; **I. N. Bruce**, None.

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Abstract Number: 2819

Clinical Utility of Anti-Aquaporin 4 Antibody Measurement in Patients with Neuropsychiatric Systemic Lupus Erythematosus with Neuromyelitis Optica Spectrum Disorder Manifestations

Simone Mader[1], **Yoshiyuki Arinuma**[1], Venkatesh Jeganathan[1], Yuichiro Fujieda[2], Irena Dujmovi[3], Jelen Drulovic[3], Yuko Sakuma[4], Shinsuke Yasuda[5], Joel Stern[6], Cynthia Aranow[6], Meggan Mackay[7], Tatsuya Atsumi[5], Shunsei Hirohata[8] and Betty Diamond[9], [1]Center of Autoimmune and Musculoskeletal Diseases, The Feinstein Institute for Medical Research, Manhasset, NY, [2]Medicine II, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [3]Clinical Centre of Serbia University School of Medicine, Belgrade, Serbia, [4]Department of Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan, [5]Division of Rheumatology, Endocrinology and Nephrology, Hokkaido University Graduate School of Medicine, Sapporo, Japan, [6]The Feinstein Institute for Medical Research, Manhasset, NY, [7]Autoimmune & Musculoskeletal Disorders, The Feinstein Institute for Medical Research, Manhasset, NY, [8]Rheumatology and Infectious Diseases, Kitasato University School of Medicine, Kanagawa, Japan,

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease characterized by the presence of autoantibodies. Among the complications of SLE, neuropsychiatric manifestations (NPSLE) can be very severe. They should be managed according to the disease pathogenesis. Previously we have shown that autoantibody against the amino acid sequence, DWEYS, a consensus sequence in the extracellular domain of the GluN2A/GluN2B subunits of the N-methyl-D-aspartate receptor (NMDAR) can induce apoptosis of hippocampal neurons through excitotoxicity and cause cognitive disorders in mice. DWEYS peptide reactive antibody displays reactivity to dsDNA with high affinity and is found in patients with NPSLE as well as SLE. Neuromyelitis optica spectrum disorders (NMOSD) are characterized by central nervous system damage, most commonly optic neuritis and acute myelitis, which can also be observed in NPSLE, and the presence of anti-aquaporin-4 immunoglobulin G antibodies (AQP4-IgG) in serum. However, association of NMOSD and AQP4-IgG in patients with NPSLE, especially complicated with manifestations of demyelination, has not been studied. The purpose of this study is to determine the utility of AQP4-IgG in NPSLE with NMOSD based on a large multicenter cohort study.

Methods: Sera of NPSLE patients (n=108), SLE (n=38) and healthy individuals (n=83) were collected from institutes in Europe, Japan and United States. As a disease control group, sera from 35 patients with NMOSD without any other autoimmune diseases were also used for this retrospective analysis. AQP4-IgG in serum were measured by a live cell-based assay using human embryonic kidney cells expressing AQP4. In addition, we measured serum anti-DWEYS antibodies as well as anti-dsDNA antibodies using an ELISA.

Results: Of 108 patients diagnosed as NPSLE, 9 patients had demyelination classified according to ACR nomenclature for NPSLE in 1999, which could be also diagnosed as manifestation of NMOSD. Of the 9 patients with demyelination syndromes, 4 patients exhibited positivity for AQP4-IgG (44%) and 2 were seropositive for both DWEYS peptide and for AQP4-IgG. In all NPSLE patients without demyelination syndromes as well as in all SLE patients without neuropsychiatric syndromes and healthy controls, AQP4-IgG serostatus was negative. In 25/35 (71%) of NMOSD patients without any other autoimmune disease, the AQP4 IgG serostatus was positive. Anti-DWEYS antibody was detected in 1 (2%) of the 35 patients with NMOSD alone. DWEYS peptide reactivity didn't differ between patients with NMOSD alone and healthy controls.

Conclusion: In NPSLE patients with demyelination such as myelitis which is commonly seen in NMOSD, measurement of AQP4-IgG with our live cell based assay has a great advantage for diagnosis. Our results suggest AQP4-IgG testing patients with NPSLE and demyelinating syndrome. It is also possible that there could be other autoantibody specificities causing manifestation of NMOSD in patients with NPSLE negative for AQP4-IgG.

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Abstract Number: 2820

Comprehensive Aptamer-Based Screening of 1129 Proteins Reveals Novel Urinary Biomarkers of Lupus Nephritis

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Session Time: 9:00AM-11:00AM

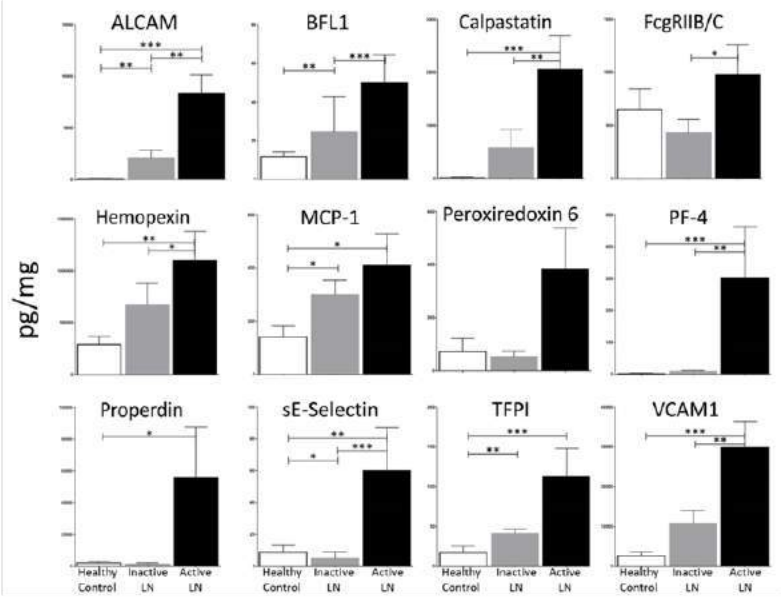
Background/Purpose: An aptamer-based screening assay was used to analyze the levels of 1129 different proteins in 24 human urine samples (8 active lupus nephritis (LN), 8 inactive LN, and 8 healthy controls).

Methods: The assay revealed 281 proteins to be significantly elevated in both SLE patients relative to healthy controls and in active LN relative to inactive LN. These proteins were then analyzed to determine their effectiveness as urinary biomarkers for lupus nephritis.

Results: Ingenuity Pathway Analysis revealed that the upregulated proteins belong to known inflammatory, fibrosis, and chemokine/cytokine networks. In an independent cohort of 93 subjects (16 active LN, 52 inactive LN, 25 healthy controls), urine ALCAM, BFL1, calpastatin, hemopexin, PRX6, PF4, properdin, sE-selectin, TFPI and VCAM1 were ELISA-validated and shown to be once again significantly elevated in active LN compared to disease/healthy controls (Fig 1); they also correlated strongly with various clinical or laboratory parameters, including renal-SLEDAI, PGA, eGFR, ESR and C3/C4. In ROC curve analysis, many proteins showed significant AUC in classifying active LN: ALCAM [0.89], calpastatin [0.82], FcgRIIBC [0.70], hemopexin [0.76], PRX6 [0.67], PF4 [0.77], properdin [0.71], TFPI [0.77] and VCAM1 [0.81]. Lasso logistic regression analysis identified a 4-marker-panel (PF4, TFPI, PRX6 and VCAM1) as the best discriminator of active LN, with an ROC AUC value of 0.93. A longitudinal cohort study of 18 LN patients with an average of 3 visits per patient revealed these urine markers to vary considerably in their ability to track with standard disease indices.

Conclusion: Urine ALCAM, BFL1, calpastatin, FcgRIIBC, hemopexin, MCP1, NAP2, PRX6, PF4, properdin, sE-selectin, TFPI and VCAM1 emerge as potential urinary biomarkers of lupus nephritis; further studies are warranted to establish their biomarker potential and pathogenic relevance.

Fig 1: Creatinine-normalized ELISA units of 12 urine proteins in 93 subjects (16 active LN, 52 inactive LN, 25 healthy controls)



Disclosure: S. Stanley, None; **H. Ding**, None; **C. Pedroza**, None; **R. Saxena**, None; **M. Petri**, None; **C. Mohan**, None.

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Abstract Number: 2821

Is Hyperuricemia an Independent Risk Factor for Arterial Thrombosis in Systemic Lupus Erythematosus?

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Background/Purpose: To evaluate whether hyperuricemia is independently associated with cardiovascular events in a cross-sectional study of Chinese patients with SLE.

Methods: Consecutive patients who fulfilled ≥4 ACR criteria for SLE were recruited from our rheumatology clinics. Fasting blood was taken for serum urate level, along with other atherosclerosis risk factors that included glucose and lipid profile (total, LDL, HDL cholesterol and triglyceride). Patients were assessed for body weight, body height, waist circumference and the presence of the metabolic syndrome (MetS) as defined by the updated joint consensus criteria, using the Asian criteria for central obesity. The 4-variable estimated glomerular filtration rate (eGFR) was also calculated. Patients were stratified according to different serum urate levels: <0.35mmol/L, 0.35-0.48mmol/L, 0.48-0.60mmol/L and >0.60mmol/L. Comparison of the prevalence of vascular risk factors, the MetS and arterial thrombotic events (acute coronary syndrome, stroke, peripheral vascular event) was made among patients with different levels of serum urate. Cox regression models were established to study whether hyperuricemia was independently associated with arterial events with adjustment of demographic variables, eGFR, vascular risk factors and the antiphospholipid (aPL) antibodies.

Results: 485 SLE patients were studied (93% women; mean age 46.2±14 years); 259 (53%) had renal involvement and 73 (15%) had chronic kidney disease stage 3 or more. Hyperuricemia (urate >0.35mmol/L) was present in 185 (38%) patients. The number of patients who had serum urate levels of 0.35-0.48, 0.48-0.60 and >0.60mmmol/L was 131 (27%), 40 (8.7%) and 14 (2.9%), respectively. Patients with hyperuricemia, compared with those without, were more likely to be men (14% vs 3%; p<0.001), have renal disease (72% vs 42%; p<0.001), hypertension (34% vs 15%; p<0.001), lower eGFR (73.4±34 vs 101±27; p<0.001) but longer SLE duration (14.3±8.7 vs 12.1±7.4 years; p=0.006). The LDL-cholesterol level (3.34±1.37 vs 2.89±1.51mmol/L; p=0.001), triglyceride level (1.62±0.77 vs 1.29±0.78mmol/L; p<0.001), body mass index (BMI) (23.2±4.5 vs 22.3±3.8kg/m^2; p=0.04) and occurrence of the MetS (22% vs 12%; p=0.007) were significantly higher in patients with hyperuricemia. On the contrary, patients with the MetS had significantly higher serum urate levels than those without (0.38±0.11 vs 0.34±0.13mmol/L; p=0.007). Over an observation of 12.9±8.0 years, 50 acute arterial events (17 acute coronary syndrome; 24 stroke, 7 peripheral vascular event and 2 retinal artery thrombosis) developed in 47 patients. The cumulative risk of arterial thrombosis was 5.2% and 6.4% in 10 and 15 years, respectively. Acute coronary events were significantly more common in patients with hyperuricemia than those without (7.6% vs 1.0%; p=0.001). Cox regression analysis revealed that HDL<1.0mmol/L (HR 3.44[1.62-7.27]; p=0.001], lupus anticoagulant (HR 3.84[1.92-7.65]; p<0.001) and age of SLE onset (1.03[1.004-1.05] per year; p=0.02) were independently associated with arterial thrombosis. In separate regression models, elevated urate levels (>0.35, >0.48 or >0.60mmol/L) were not significantly associated with arterial events after adjustment for age, sex, eGFR, smoking, LDL-cholesterol, HDL-cholesterol, triglyceride, BMI, diabetes mellitus, hypertension and the antiphospholipid antibodies.

Conclusion: Hyperuricemia was associated with renal dysfunction, obesity, hypertension and dyslipidemia in patients with SLE. Moreover, elevated serum urate level was also associated with the occurrence of the MetS and acute coronary events. However, in multivariate regression models, hyperuricemia was not an independent risk factor for acute coronary or any arterial events after adjustment for confounding factors.

Disclosure: C. C. Mok, None; **L. Y. Ho**, None; **C. H. To**, None; **K. L. Chan**, None.

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Serum 25-Hydroxyvitamin D3 Levels and Flares of Systemic Lupus Erythematosus: A Longitudinal Cohort Analysis

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Background/Purpose: To study the relationship between serum 25-hydroxyvitamin D3 levels and flares of systemic lupus erythematosus (SLE) in a longitudinal cohort of Chinese patients.

Methods: Patients who fulfilled ≥4 of the ACR criteria for SLE were recruited from our rheumatology out-patient clinics in November 2011. Blood was taken at 10 AM and was assayed for the serum levels of 25-hydroxyvitamin D3 by liquid chromatography tandem mass spectrometry (LC-MS/MS). Patients were stratified according to the 25-hydroxyvitamin D3 levels; group 1 (<15ng/ml, deficiency); group 2 (15-30ng/ml, insufficiency); and group 3 (>30ng/ml, adequate); and were followed longitudinally every 2-4 months for serial assessment of disease activity (by SELENA-SLEDAI) and the occurrence of mild/moderate or severe SLE flares (by SELENA flare instrument). Comparison was made among these groups in the baseline and mean summated SLEDAI over time (area under the curve), and the annual incidence of mild/moderate and severe flares by the one-way ANOVA test.

Results: 276 SLE patients were studied (94% women; age 41.0±13.8 years; SLE duration 8.7±6.6 years). 25(9.1%) patients had eGFR ≤60ml/min. The proportion of patients with 25-hydroxyvitamin D3 levels of <15, 15-30, >30ng/ml was 26%, 54% and 20%, respectively. Patients with vitamin D deficiency (group 1) were significantly younger, had lower body mass index (BMI) but higher baseline eGFR and SLEDAI scores when compared with the other groups. No significant differences in the clinical manifestations were observed among the three groups of patients except for lower prevalence of facial rash in group 3 (p=0.02). After a mean follow-up of 32.5±5.5 months, 153 mild flares and 91 severe flares developed in our patients. The mean summated SLEDAI score over time was: 3.2±2.0 (group 1); 2.4±1.9 (group 2); and 2.7±2.1 (group 3), respectively (p=0.02). The annual incidence of mild/moderate and severe flares was: 0.26±0.39 and 0.20±0.45 (group 1); 0.20±0.33 and 0.09±0.22 (group 2); and 0.20±0.32 and 0.14±0.46 (group 3), respectively (p=NS in all). In a subgroup of 73 patients who did not have clinical or serological SLE activity at baseline (SLEDAI=0), a similar but non-significant trend of higher annual rates of mild/moderate and severe flares over time was also observed in patients with vitamin D deficiency. At the last visit, 27 (10%) patients had new damage scores; 5 patients had new vascular events; and 4 patients had new onset diabetes mellitus. There were no significant differences among the three groups of patients with regard to the incidence of new damage or vascular events over time.

Conclusion: Vitamin D insufficiency and deficiency was frequent in our cohort of SLE patients. Patients with vitamin D deficiency were associated with higher baseline and mean disease activity scores, as well as a tendency of more severe lupus flares over time.

Disclosure: C. C. Mok, None; **E. Bro**, None; **L. Y. Ho**, None; **R. Singh**, None; **P. Jannetto**, None.

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Urinary Angiostatin, CXCL4 and VCAM-1 As Biomarkers for Lupus Nephritis

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Background/Purpose: Proteomic screening is an efficient approach for identifying protein biomarkers in various inflammatory diseases. Our preliminary proteomic analysis revealed elevated levels of urinary angiostatin, CXCL4 and VCAM-1 in patients with active lupus nephritis. This study aims to study the performance of urinary angiostatin, CXCL4 and VCAM-1 in differentiating between active renal and non-renal systemic lupus erythematosus (SLE).

Methods: Patients who fulfilled the ACR classification for SLE with active renal disease, active non-renal disease and inactive disease were randomly recruited from our out-patient clinics and hospital admission between 2010 and 2015. A group of healthy individuals were also recruited as controls. Stored urine samples of the participants were assayed for angiostatin (Raybiotech, Inc; Georgia, USA), CXCL4 and VCAM-1 (R&D Systems; Minneapolis, Minnesota, USA) and compared among the different groups. Elevated levels of these markers were defined as values ≥ mean+2SD of the controls. SLE disease activity was assessed by the SELENA-SLEDAI and physician's global assessment (PGA). Specificity and sensitivity of these markers in differentiating between active renal and non-renal SLE was determined by 2x2 contingency tables and compared with conventional markers such as anti-dsDNA and complement C3. In patients with active renal disease, correlation between these urinary biomarkers with clinical renal parameters was also performed.

Results: 227 SLE patients (80 inactive SLE; 67 active non-renal disease; 80 active renal disease; 94% women, age 39.2±13.8 years) and 54 healthy controls (96% women) were studied. All were ethnic Chinese. Urinary angiostatin, CXCL4 and VCAM-1 levels normalized for creatinine were significantly higher in patients with active renal than non-renal disease (angiostatin 1.8±2.7 vs 0.16±0.29 pg/ng; $p<0.001$; CXCL 4.9±1.6 vs 0.5±1.4 pg/ng; $p=0.002$; VCAM-1 41±1.31 $x10^2$ vs 0.72±1.10 $x10^2$ pg/ng; $p<0.001$). The levels of these urinary protein markers were also significantly higher in active non-renal SLE patients than inactive SLE patients or healthy controls. Urinary angiostatin, CXCL4 and VCAM-1 correlated significantly with the renal SLEDAI (Rho 0.66, 0.45 and 0.52, respectively; $p<0.001$ in all) and total SLEDAI score (Rho 0.60, 0.46 and 0.53, respectively; $p<0.001$ in all) in all the SLE patients studied. These urinary markers were also significantly associated with the serum anti-dsDNA and C3 levels. However, only urinary angiostatin correlated with the protein/creatinine ratio (Rho 0.34; $p=0.002$). 73/80 patients with active lupus nephritis had renal biopsy performed within 4 weeks of the urinary sample collection (34% RPS/ISN class III±V; 37% IV±V; 16% pure V; 12% I/II). The three urinary markers could not differentiate active proliferative (III/IV) from non-proliferative (I/II/V) lupus nephritis; and there was no significant correlation between these markers and histological activity indices in patients with class III/IV lupus nephritis. Urinary angiostatin and CXCL4 (specificity 0.75 and 0.78, respectively) were more specific than elevated serum anti-dsDNA and low C3 (specificity 0.28 and 0.21) in differentiating active renal from active non-renal SLE. Urinary angiostatin and CXCL4 were also highly specific (specificity 0.96 and 0.99, respectively) when compared to elevated anti-dsDNA and low C3 (specificity 0.54 and 0.59) in differentiating active SLE from inactive SLE.

Conclusion: Urinary angiostatin and CXCL4 are specific markers for lupus nephritis and may be useful in detecting subclinical / low grade renal disease in patients with active SLE. Further longitudinal studies are necessary to delineate the sensitivity and specificity of these two urinary protein markers in predicting renal flares in SLE patients.

Disclosure: C. C. Mok, None; **S. Soliman**, None; **L. Y. Ho**, None; **C. Mohan**, None.

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Abstract Number: 2824

Lack of Partial Renal Response By 12 Weeks after Induction Therapy Is an Indicator to Switch the Treatment in Lupus Nephritis Class III or IV for Reducing Future Damage Accrual

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Background/Purpose: Lupus nephritis (LN) class III or IV is associated with a poor prognosis for both patient and renal survival. The guideline or recommendation for LN has been recently established by both ACR and EULAR, and changing therapies is recommended for patients who do not respond adequately to the induction therapy for preventing damage accrual. However, it remains major challenge to determine when to switch the treatment. In this study, we determined appropriate period and targeted clinical status to switch the treatment in patients with an inadequate response in lupus nephritis class III or IV.

Methods: Eighty patients with biopsy-proven lupus nephritis class III or IV were retrospectively recruited and divided into 2 groups, with complete renal response (CR) or non-CR at 3 years after induction therapy. We investigated when clinical responses were obtained at each observational period from the baseline to year 3. Clinical responses were divided into 3 groups, CR, partial renal response (PR), and non-PR according to EULAR recommendation. Furthermore, patients were assessed by SDI, SLEDAI, and cumulative dose of corticosteroid for 3 years.

Results: Forty-four patients with CR and 36 with non-CR were enrolled. Cumulative CR rate was 85.0%. There is no significant difference in baseline clinical characteristics other than higher SLEDAI in patients with CR compared to those with non-CR ($p<0.01$). PR rates of patients with CR were significantly higher than those with non-CR from week 12 ($p<0.01$). We identified the achievement of PR at 12 weeks as an independent predictor (Odds ratio 3.57, $p=0.03$) by multivariate analysis. We next divided all patients into 2 groups according to PR achievement at week 12. The cumulative CR rate of the patients who achieved PR at week 12 was significantly higher than those who did not (96.5% vs 69.2%, $p<0.001$) (Figure1A). Moreover, a significantly higher SDI (Figure 1B) and cumulative dose of corticosteroid were seen in the patients who did not achieve PR at week 12 than those who did regardless of their CR status at year 3.

Conclusion: Lack of PR at week 12 predicts a lower likelihood of achieving CR at 3 years. Since achievement of PR at week 12 leads to less damage accrual without regard to CR status at year 3, switching treatment should be recommended for patients who failed to achieve PR at week 12 to reduce accrual of damage.

Figure 1A

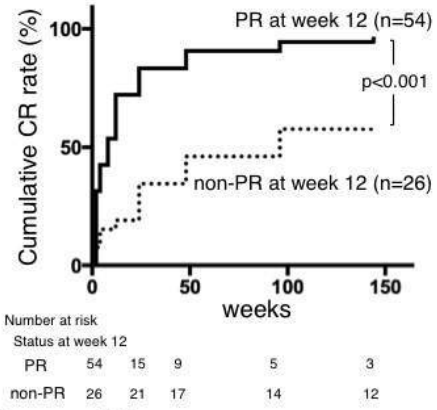
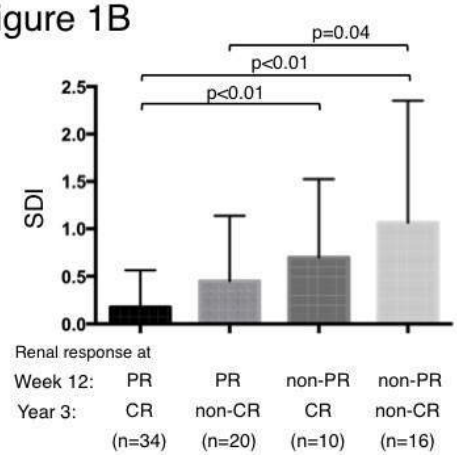


Figure 1B



Disclosure: H. Hanaoka, None; **H. Yamada**, None; **T. Kiyokawa**, None; **H. Iida**, None; **T. Suzuki**, None; **Y. Yamasaki**, None; **S. Ooka**, None; **H. Nagafuchi**, None; **T. Okazaki**, None; **D. Ichikawa**, None; **S. Shirai**, None; **Y. Shibagaki**, None; **J. Koike**, None; **S. Ozaki**, None.

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Abstract Number: 2825

Urinary BAFF and APRIL Levels: Potential Biomarkers of Active Lupus Nephritis

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Background/Purpose: B cell Activating Factor of the TNF Family (BAFF) and A Proliferation Inducing Ligand (APRIL) help B cell activation, maintenance and plasma cell survival. Consequently, these facilitate production of pathogenic autoantibodies in SLE and lupus nephritis. B cells infiltration has been demonstrated in kidneys of patients with Lupus Nephritis (LN). Serum levels of BAFF and APRIL have shown inconsistent relationships with lupus disease activity. We evaluated urinary levels of BAFF and APRIL as a biomarker for LN.

Methods: Thirty-six patients with proliferative lupus nephritis (AN), 10 with active lupus without nephritis (AL) and 15 healthy controls (HC) were studied. APRIL and BAFF levels were measured in both serum and urine using ELISA. Urine levels were normalized to urinary creatinine excretion. Urine levels were correlated with conventional disease activity markers like SLEDAI, renal SLEDAI, and proteinuria. Levels were reassessed in 20 AN patients at 6 months, after treatment with cyclophosphamide.

Results: At baseline, urinary APRIL (uAPRIL) and BAFF (uBAFF) were significantly raised in AN patients as compared to controls. [Table1] uAPRIL but not uBAFF had correlation with renal SLEDAI in patients with AN. ($r= 0.36$, $p<0.05$). On ROC analysis, uBAFF (AUC 0.825) and uAPRIL (AUC 0.781)performed better than low C3, C4 and raised anti-dsDNA antibodies in differentiating AN and AL patients. The uBAFF and uAPRIL levels did not correlate with their serum levels suggesting *in situ* generation in the kidneys. On follow up uAPRIL levels reduced (125 pg/mg to 36 pg/mg, $p<0.05$). However uBAFF levels reduced only in 16 responders (158 to 67 pg/mg, $p<0.05$). Two of the 4 non-responders had increase in uBAFF levels.

Conclusion: uBAFF and uAPRIL are potential biomarkers of proliferative lupus nephritis. Table 1: Disease activity and BAFF, APRIL levels at baseline.

Parameter	Lupus nephritis (n=36)	Active non-renal lupus (n=10)	Lupus, non nephritis
Age in years (median, range)	32 (19 - 59)	27 (23 – 36)	31 (19-50)
SLEDAI 2K (median, range)	18 (8-30)	9 (6-20)	NA
Renal SLEDAI (median, range)	8 (4-16)	0	NA
Urine 24 hour protein-g/24 hours	4.9 (3.6)	0.31 (0.13)*	NA
Normalized Urine BAFF (pg/mg)	240 (290)	60.9 (62)*	58 (101)*
Normalized Urine APRIL (pg/mg)	125 (116)	28.4 (20)*#	01 (05)*
Serum BAFF (ng/ml)	0.184 (0.26)	0.27 (0.20)	0.135(0.69)
Serum APRIL (ng/ml)	1.249 (0.72)	1.38 (0.53)	2.00 (1.74)
*p <0.05 compared to lupus nephritis, # p<0.05 compared to healthy control All values: mean with standard deviation NA: not applicable			

Disclosure: S. Phatak, None; **S. Chaurasia**, None; **S. Mishra**, None; **R. Gupta**, None; **A. Aggarwal**, None; **R. Misra**, None.

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Abstract Number: 2826

Clinical Utility of Circulating Anti-N-Methyl-D-Aspartate Receptor Subunits NR2A/B Antibody for the Diagnosis of Neuropsychiatric Syndromes in Systemic Lupus Erythematosus and Sjogren's Syndrome: An Updated Meta-Analysis

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Background/Purpose: Neuropsychiatric (NP) events are found in patients with rheumatic diseases, commonly in systemic lupus erythematosus (SLE) and Sjögren's syndrome (SS). The standard nomenclature and case definitions for 19 NPSLE syndromes by the American College of Rheumatology (ACR) Committee on Research cover a wide range of NP events seen in both SLE and SS. Despite advances in the understanding of SLE and SS, NP syndromes continue to pose diagnostic challenges. Correct attribution of NP events is critical in determining the correct treatment and prognosis. Anti-N-methyl-$_D$-aspartate receptor subunits NR2A/B (anti-NR2A/B) antibodies (Abs) have been demonstrated in the sera of SLE and SS patients and have been associated with collective or specific NP syndromes, though not consistently. Interpretation of anti-NR2A/B Abs data in the medical literature is rendered difficult by small sample size of patient groups. By combining different studies to generate a pooled effect size, a meta-analysis can increase the power to detect differences in the presence or absence of NP syndromes. Hence, we set out to perform a meta-analysis to assess the association between anti-NR2A/B Abs and NP syndromes in SLE and SS.

Methods: A literature search was conducted using PubMed and other databases from inception to June 2016. We abstracted data relating to anti-NR2A/B Abs from the identified studies. Random-effects model was used to calculate overall combined odds ratio (OD) with its corresponding 95% confidence interval (CI) to evaluate the relationship between anti-NR2A/B Ab and NP syndromes in SLE and SS patients with and without NP events. We also included our own series of 57 SLE patients fulfilling the ACR 1997 revised classification criteria and 58 healthy controls (HCs).

Results: In total, 17 studies with data on anti-NR2A/B Abs in 2,212 SLE patients, 66 SS patients, 99 disease controls (DCs) (e.g. antiphospholipid syndrome, myasthenia gravis and autoimmune polyendocrine syndrome I) and 538 HCs were used in this analysis. Overall pooled prevalence of serum/plasma anti-NR2A/B Abs was higher in SLE patients [24.6% (95% CI 18.5-32.0%)] and SS patients [19.7% (95% CI 11.8-31.0%)] compared to DCs [14.8% (95% CI 2.2-56.9)] and HCs [7.6% (95% CI 4.6-12.4%)] ($p = 0.001$). There was a significantly greater proportion of SLE and SS patients with NP syndromes who demonstrated positivity for serum/plasma anti-NR2A/B Abs [pooled OR = 1.607 (95% CI 1.041-2.479), $p = 0.032$] as compared to SLE and SS patients without NP syndromes in 13 studies. Usable data for cerebrospinal fluid anti-NR2A/B Abs was available in only 4 studies [pooled OR = 0.831 (95% CI 0.365-1.888), $p = 0.658$]. Among the 19 NP syndromes, serum/plasma anti-NR2A/B Abs were not specifically associated with any NP syndrome, including cognitive dysfunction ($p = 0.259$) and mood disorder ($p = 0.503$). Meta-regression identified proportion of anti-double-stranded deoxyribonucleic acid Ab positivity ($p = 0.009$) and SLE Disease Activity Index ($p = 0.028$) as moderators for the heterogeneity of serum/plasma anti-NR2A/B Abs.

Conclusion: Circulating anti-NR2A/B Abs testing has a diagnostic value for NP syndromes in SLE and SS collectively, but it is not helpful in differentiating specific NP syndromes.

Disclosure: S. H. Tay, None; **A. M. Fairhurst**, None; **A. Mak**, None.

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Abstract Number: 2827

Prognostic Significance of Repeat Biopsy in Lupus Nephritis: Histopathologic Worsening Is an Independent Risk Factor for End Stage Renal Disease and Death

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Background/Purpose: Approximately half of SLE patients develop lupus nephritis (LN), a major cause of morbidity and early mortality. It is known that prolonged renal inflammation is associated with irreversible kidney damage and leads to end stage renal disease (ESRD), making early aggressive treatment mandatory. Failure to achieve therapeutic response or recurrence of renal flare should prompt repeat biopsy, as changes in renal activity and chronicity are known to occur. However, the role of repeat biopsy in determining long-term renal prognosis remains controversial.

Methods: To test the hypothesis that histopathologic worsening between first and second biopsies might be predictive of ESRD and death, the medical records of 141 LN patients with >1 biopsy were obtained from a single large urban medical center. Cases were initially attained using procedure and diagnosis billing codes from 1/1999-1/2015, with subsequent retrospective chart review. Worsening of biopsies was defined as unfavorable histopathologic classification transitions or worsening of chronicity; if neither were present, the patient was defined as non-worsening. Covariates in the Cox proportional hazard models included age at first biopsy, gender, race, initial biopsy class, and initial induction therapy.

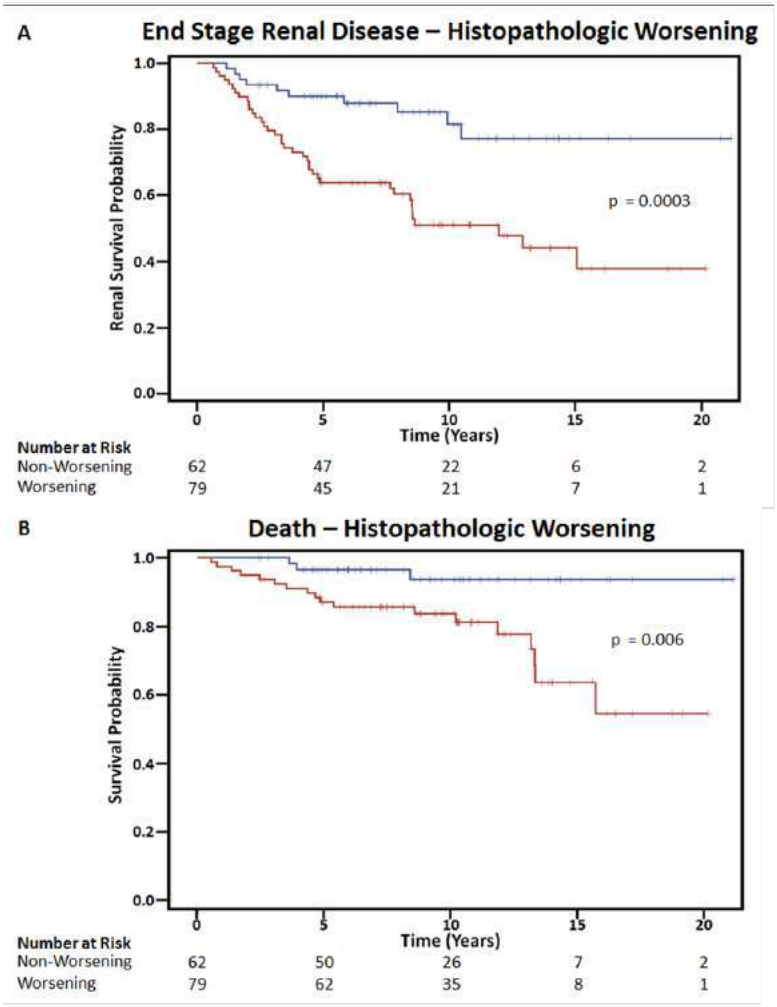
Results: Of 630 patients initially screened, 141 had >1 biopsy, with characteristics as noted in Table 1. Advancing chronicity was detected in 48(34.0%) and a renal class switch to higher grade of pathology was found in 54(38.3%). At least one of these biopsy progressions was reported in 79(56.0%) patients. Five years following initial biopsy, 28(35.4%) of those with worsening histopathology on second biopsy developed ESRD, compared to 6(9.7%) of non-worsening patients (Figure 1). After only five years, 10(12.7%) of the worsening histopathology patients had died compared to 2(3.2%) of non-worsening patients. Over a 20 year period, those with worsening of nephritis at second biopsy had a significantly greater risk of ESRD (Hazard Ratio 4.2, p=0.0001) and death (Hazard Ratio 4.3, p=0.022) after adjusting for age, gender, race, biopsy class, and treatment.

Conclusion: A repeat renal biopsy demonstrating worsening pathology is strongly prognostic for poor outcomes and could justify changes in treatment that might not have been assumed necessary on clinical grounds. The high frequency of worsening in nephritis class and chronicity supports the cost effectiveness of repeat biopsy.

Table 1. Patient Characteristics. 141 patients with >1 renal biopsy were included in the study. Demographics, initial biopsy International Society of Nephrology / Renal Pathology Society 2003 classification (ISN/RPS), initial induction immunosuppression therapy, and time between biopsies are displayed. Also included are the events of interest, death and end stage renal disease (ESRD), with median follow-up times for each group.

		Worsening		Non-Worsening	
Total (n,%)		79	56.0%	62	44.0%
Demographics					
Female (n, %)		65	82.3%	53	85.5%
Race/Ethnicity (n, %)					
	Black/African American	39	49.4%	22	35.5%
	Hispanic/Latino (Majority Mexican)	32	40.5%	32	51.6%
	White/Caucasian	8	10.1%	8	12.9%
Age in Years at First Biopsy (median, IQR)		25.8	[20.3-34.3]	26.9	[21.0-39.3]
Initial Biopsy ISN/RPS Class (n, %)					
	Proliferative (III, IV, III+V, IV+V)	55	69.6%	47	75.8%
	-Proliferative only (III, IV)	40	50.6%	27	43.5%
	-Proliferative and membranous (III+V, IV+V)	15	19.0%	20	32.3%
	Membranous only (V)	14	17.7%	10	16.1%
	Mesangial Proliferative (II)	10	12.7%	5	8.1%
Initial Induction Immunosuppression (n, %)					
	Mycophenolate Mofetile (MMF)	27	34.2%	30	48.4%
	Cyclophosphamide IV (CYC)	37	46.8%	26	41.9%
	Other (Azathioprine or Cyclosporine)	3	3.8%	2	3.2%
	None or Unknown	12	15.2%	4	6.5%
Time Between First & Second Biopsies (median, IQR)		2.1	[0.9-4.3]	2.2	[1.2-4.5]
Events and Follow-Up Time					
End Stage Renal Disease (n, %)		38	48.1%	10	16.1%
Follow-Up Time in Years (median, IQR)		7.3	[3.4-10.5]	8.0	[5.2-11.8]
Deaths (n, %)		18	22.8%	3	4.8%
Follow-Up Time in Years (median, IQR)		8.8	[6.0-12.1]	9.0	[5.8-11.9]

Figure 1. Kaplan-Meier Survival Analysis Curves. Time to ESRD (A.) or Death (B.) are compared for patients with histopathologic worsening from first to second biopsy (red, lower) and those with non-worsening (blue, upper).



Disclosure: **C. Arriens**, Mallinckrodt Pharmaceuticals, 2; **S. Chen**, None; **D. Karp**, None; **R. Saxena**, None; **K. Sambandam**, None; **E. Chakravarty**, None; **J. A. James**, None; **J. T. Merrill**, Lilly, Anthera, GSK, UCB, BMS, EMD Serono, Celgene, Biogen, Takeda, Seattle Genetics Abbvie, Questcor, 5,BMS, GSK, Pfizer, 2.

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Abstract Number: 2828

Difference of d-Dimer Between Two Time Points Predicts Prognosis of Admitted Patients with SLE Flare up

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Background/Purpose: Even though the survival rate among SLE patients has improved over the past few decades, the mortality rate caused by the acute flare of the SLE is still high. On the other hand, next to no information is available on the prognostic factors related to operations. D-dimer (DD) is especially known to rise in a thrombotic event; the purpose of this research was to learn more on the relationship between the prognosis of admitted patients treated with SLE d/t acute flare and the change in DD.

Methods: The subject of this research was 57 SLE patients whose DD was measured more than 2 times during one's admission. The division criteria of the groups was the amount of change in the of the first and last measured DD result. If the DD value decreased by more than 25% of the first value, the patient was designated as group A while if the value increased by more than 25%, the patient was put in group C. If the patient's change of DD value was within 25% of the first value, the patient was put in group B. Then, the difference in clinical features between each group as well as between group A+B and group C was investigated. The hospitalizations of SLE patients for reasons other than for SLE disease flare such as obvious infection, malignancy and thromboembolism were all excluded.

Results: There was a statistically significant difference between groups A, B, and C in relation to Lupus Nephritis (LN) and hospitalization mortality. In addition, there was a statistically significant difference in LN, C4, anti-dsDNA, anti-Ro, and hospitalization mortality between group A+B and C. *In other words, increased* pattern of DD significantly correlates with *poor prognosis* in hospitalized patients with SLE flares. On the other hand, unlike what we had expected, no meaningful difference was observed between each group and the SLEDAI-2K score, which measures disease activity.

Conclusion: The changing pattern of the DD value is related to the mortality rate as well as the presence of LN of a patient admitted due to SLE flare. This could be used as an adjuctive factor to predict the prognosis of the admission period.

Variables	Pattern A (n=23)	Pattern B (n=15)	Pattern C (n=19)	P value A vs B vs C	P value A+B (n=38) vs C (n=19)
Demographics					
Age, years (median, IQR)	41 (37-51)	41 (22-45)	50 (33-55)		
Female/male, Female (%)	19/4 (92.6)	13/2 (86.6)	17/2 (89.5)		
Clinical findings					
Arthritis	7 (30.4)	5 (33.3)	3 (15.8)		
New rash	2 (8.7)	2 (13.3)	3 (15.8)		
Lupus nephritis (urine protein > 0.5g/d)	12 (52.2)	7 (46.7)	16 (84.2)	< 0.05	< 0.001
Serositis	8 (34.8)	1 (6.7)	5 (26.3)		
Oral ulcer	1 (4.3)	3 (20.0)	1 (5.3)		
Abn.liver enz.	5 (21.7)	4 (26.7)	5 (26.3)		
SLEDAI-2K	6 (4-11)	8 (6-17)	9 (7-10)		
Laboratory results					
1st d-dimer	1239 (557-6318)	485 (375-845)	463 (316-739)		
WBC	6.80 (2.82-10.2)	6.29 (2.69-7.84)	5.73 (3.55-10.69)		
Hb	10.2 (9.35-12.75)	10.9 (9.6-11.9)	9.2 (8.6-11.6)		
PLT	110 (87-228)	125 (86-209)	162 (72-256)		
ESR	43 (18-64)	43 (31-78)	43 (12-81)		
CRP	43.0 (17.5-63.5)	15.2 (8.4-41.2)	10.4 (1.2-33.4)		
C3	53.3 (37.8-81.7)	60.8 (23.6-81.8)	60.0 (49.6-90.5)		
C4	11.2 (4.3-17.8)	8.1 (3.3-14.4)	13.8 (8.1-23.8)		< 0.05
Albumin	3.4 (2.9-3.7)	3.0 (2.3-3.4)	2.8 (2.4-3.4)		
Serum Cr	0.71 (0.58-1.05)	0.72 (0.59-1.24)	0.78 (0.56-1.78)		
LDH	438 (234-609)	278 (218-463)	505 (304-729)		
ANA	23 (100)	15 (100)	18 (94.7)		
Anti-dsDNA	17 (73.9)	13 (86.7)	10 (52.6)		< 0.05
Anti-Sm	3 (13.0)	5 (33.3)	8 (42.1)		
Anti-Ro	7 (30.4)	8 (53.3)	13 (68.4)		< 0.05
Anti-La	2 (8.6)	5 (33.3)	4 (21.1)		
Anti-RNP	7 (30.4)	7 (46.7)	8 (42.1)		
LA	7 (30.4)	8 (53.3)	8 (42.1		
aCL_IgM	6 (26.1)	5 (33.3)	6 (31.6)		
aCL_IgG	9 (39.1)	4 (26.7)	2 (10.5)		< 0.05
β2GP_IgG	4 (17.4)	2 (13.3)	1 (5.3)		
β2GP_IgM	3 (13.0)	1 (6.7)	0 (0)		
Clinical outcomes					
Hospitalization period	22 (11-49)	46 (17-73)	20 (12-31)		

Mortality	3 (13.0)	3 (20.0)	8 (42.1)	< 0.05	< 0.05

Disclosure: S. Byun, None; **S. M. Jung**, None; **S. W. Lee**, None; **Y. B. Park**, None; **J. J. Song**, None.

Abstract Number: 2829

Adherence to Treatment and Renal Transplantation Graft Failure in Lupus Nephritis

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Background/Purpose: Patient non-adherence has been reported as a potential adverse outcome predictor in renal transplantation (rTp) for patients with lupus nephritis (LN). We investigated potential factors leading to non-adherence and whether non-adherence is associated with increased rTp graft failure.

Methods: Patients with LN undergoing rTp in two major institutions were retrospectively included in this study, analysing prospectively captured data. The medical notes were reviewed for any documented concerns about non-adherence to prescribed treatment. Laboratory biochemical results (tacrolimus, mycophenalate mofetil (MMF) and ciclospirin levels) were also reviewed for evidence of non-adherence, defined as evidence of sub- therapeutic drug levels in routine measuring in >25% occurrences. Potential associations with poor adherence were examined including age, sex, race, age at SLE diagnosis, age at lupus nephritis diagnosis, age when dialysis was started, duration of SLE diagnosis, duration of lupus nephritis diagnosis, time on dialysis prior to rTp and medication use.

Results: All patients with rTp since 1975 were included. Forty patients had rTp from a total of 361 lupus patients in both centres. For 10 patients there were concerns documented in the medical records for non-adherence. For 9 patients (out of 16 biochemically tested) there was evidence of non-adherence, giving a total of 16 unique patients with concern about possible non-adherence to prescribed treatment for LN. There were no associations between patient demographics and non-adherence. In particular, in this cohort there was no association between age at SLE diagnosis or rTp, gender, race and diagnosis duration or medication prescribed and non-adherence (Table 1). However, having recorded a concern about possible non-adherence showed a trend in associating with increased graft rejection, hazard ratio of 3.40 when concerns existed compared to when no concerns were raised (95% CI=0.732-15.723, p=0.118).

Conclusion: There were no significant factors associating with non-adherence in this cohort. However, a concern about possible non-adherence (either recorded in the notes or as evidenced with biochemical assays) showed a trend towards a 3.4 higher risk of graft rejection. Further larger studies are warranted to investigate further the factors leading to non-adherence, and the true adverse effect of non-adherence on rTp in the context of LN.

	Non-adherent	**Adherent**
Gender (men/ women)	3/ 13	3/ 21
Ethnicity		
Caucasian	6	9
Afro-Caribbean	5	10
Asian	5	5
Age at SLE diagnosis (years)	20 ±11	22±9
Age at LN diagnosis (years)	26±6	27±8
Age at ESRF (years)	32±12	31±10
Age at rTp (years)	34±11	37±11
Graft failure	6	4

Table 1 Patient demographic and characteristics in patients with non-adherence concerns versus patients where no concerns about non-

adherence were raised.

Disclosure: E. Ntatsaki, None; **A. Velo Garcia**, None; **A. D. Salama**, None; **D. A. Isenberg**, None.

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Non-Calcified Coronary Artery Plaque Associates with Adverse Lipoprotein Profiles in Systemic Lupus Erythematosus

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Background/Purpose: Systemic lupus erythematosus (SLE) associates with atherosclerotic cardiovascular (CV) disease and related mortality. This is contributed to, but cannot be fully explained, by traditional CV risk factors, treatments and SLE-specific factors. Coronary artery calcium scores (CAC), by computed tomography (CT) measure atherosclerotic burden and can predict CV events. Non-calcified plaque (NCP), common in SLE, can also be quantified and may be more metabolically active and unstable. Routine lipids are unhelpful in distinguishing SLE patients with or without either CAC or NCP. Nuclear magnetic resonance (NMR) spectroscopy allows determination of the size and concentration of lipoprotein classes and subclasses, and has been used to evaluate CV risk in many populations. The aim of this work is to determine whether differences in NMR lipoprotein particle numbers or size can distinguish between SLE patients with and without CAC. An additional aim was to establish whether NMR parameters associate with quantified NCP or calcified plaque.

Methods: As part of a longitudinal lupus cohort, SLE patients, without known atherosclerotic disease, had coronary CT angiography performed. CAC scores were calculated according to the Agatston system. Lipoprotein particle numbers and size were evaluated by NMR. The initial statistical analysis compared those with and without calcified and NCP using t-tests. Further evaluation involved the calculation of correlation coefficients to evaluate the relationship between lipoprotein abnormalities and the burden of calcified and NCP.

Results: Sixty-nine SLE patients were evaluated, 64 (93%) female, 49 (71%) were African-American and 20 (29%) were Caucasian. Significant NCP was present in 41 (59%) and CAC was present in 14 (20%). Individuals with NCP had significantly larger very low-density lipoprotein (VLDL) particles (44.8 ±5.5 nm versus 47.7 ±6.1 nm, p= 0.042). None of the other lipoprotein parameters were significantly different between those who had calcified or NCP. Considering the volume and extent of CAC and NCP; (Table 1) higher triglycerides were observed with increasing levels of CAC. Increasing volumes of NCP were associated with higher LDL particle number and larger VLDL size. The lipoprotein insulin resistance scores were also positively associated with NCP.

Conclusion: The mechanisms underlying atherosclerosis in SLE are poorly understood. NCP is highly prevalent in SLE and may be contributed to by differences in LDL, VLDL and insulin resistance measures, not evaluated in routine lipid profiles. Further longitudinal analysis will determine whether these abnormalities associate with progression of disease and can be considered prognostic markers.

Biomarker		Calcified Plaque		Non-Calcified Plaque	
		Spearmen Correlation Coefficient	P-value	Spearmen Correlation Coefficient	P-value
VLDL & Chylomicron Particles (total) (nmol/L)		0.05	0.67	-0.06	0.62
Large VLDL & Chylomicrons Particles (nmol/L)		0.20	0.09	0.18	0.13
Medium VLDL Particles (nmol/L)		0.07	0.56	-0.00	0.97
Small VLDL Particles (nmol/L)		0.00	0.99	-0.05	0.68
LDL Particles (total) (nmol/L)		0.14	0.26	0.26	**0.034**
IDL Particles (nmol/L)		0.05	0.66	-0.02	0.89
Large LDL Particles (nmol/L)		0.09	0.44	0.15	0.22
Small LDL Particles (nmol/L)		0.02	0.89	0.14	0.22
HDL Particles (total) (µmol/L)		0.17	0.17	0.16	0.20
Large HDL Particles (µmol/L)		-0.04	0.75	-0.03	0.83
Large HDL Particles (µmol/L)		0.10	0.42	-0.07	0.57
Small HDL Particles (µmol/L)		0.11	0.36	0.21	0.086
VLDL Size (nm)		0.21	0.082	0.25	**0.038**
LDL Size (nm)		0.09	0.49	-0.05	0.70
HDL Size (nm)		-0.08	0.50	-0.13	0.30
Triglyceride (total) (mg/dL)		0.24	**0.043**	0.20	0.10
Lipoprotein Insulin Resistance Score		0.21	0.080	0.24	**0.044**

Disclosure: L. Durcan, None; **A. Zadeh**, None; **M. Connelly**, LabCorp, 3; **J. Otvos**, LabCorp, 3; **L. S. Magder**, None; **M. Petri**, None.

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Abstract Number: 2831

Associations of BAFF and Anti-BAFF Autoantibodies with Disease Activity in Oriental Systemic Lupus Erythematosus

Hwee-Siew Howe[1], Bernard Thong[2], Kok Ooi Kong[3], Hiok-Hee Chng[2], Tsui Yee Lian[2], Faith Chia[2], Karine Tay[2], Tang Ching Lau[4], Weng Giap Law[2], **Ee Tzun Koh**[5] and Bernard Pui Lam Leung[6,7], [1]Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, SINGAPORE, Singapore, [2]Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, ., Singapore, [3]Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, Singapore, Singapore, [4]Yong Loo Lin School of Medicine,, National University of Singapore, ., Singapore, [5]Department of Rheumatology, Allergy and Immunology, Tan Tock Seng Hospital, ., Singapore, [6]Physiology, National University of Singapore, ., Singapore, [7]Rheumatology, Allergy & Immunology, Tan Tock Seng Hospital, ., Singapore
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Background/Purpose: B cell activating factor (BAFF) is implicated in the pathogenesis of systemic lupus erythematosus (SLE). A

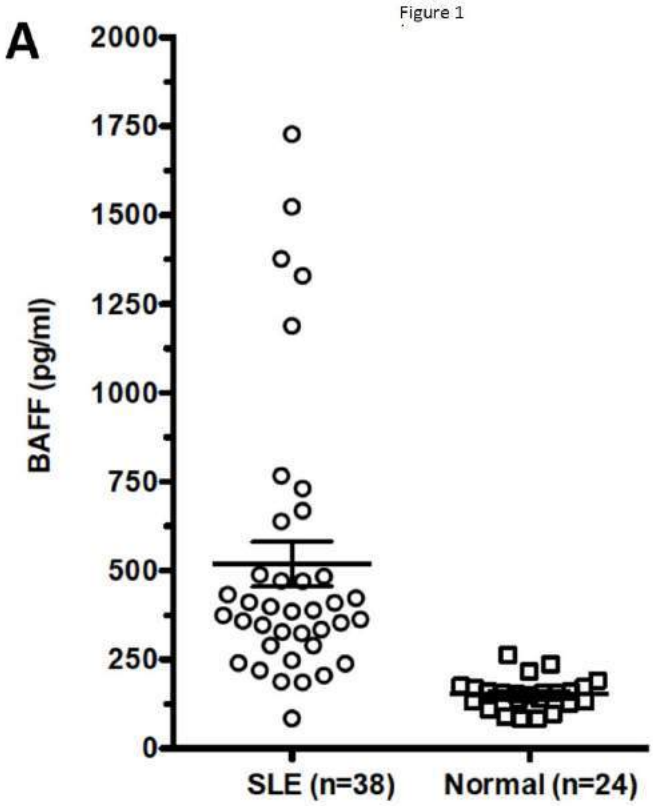
previous small scale study reported that endogenous neutralizing serum anti-BAFF autoantibodies were found in higher levels in SLE patients compared to healthy subjects, and were associated with increased SLE disease severity. We sought to evaluate levels of BAFF and endogenous autoantibodies to BAFF in our oriental SLE cohort, and to determine their correlation with disease activity.

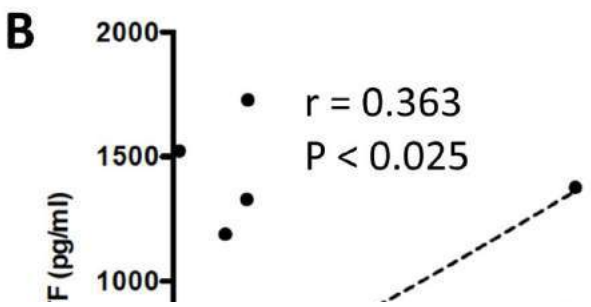
Methods: Serum BAFF and anti-BAFF IgG antibody levels were first assayed in 38 SLE patients and 24 healthy controls by ELISA. Correlation of serum BAFF and anti-BAFF IgG levels with disease activity scored by SLAM-R was determined in a larger cohort of 121 patients. The 121 SLE patients were predominantly female (85.9%), mean age 38.7±12.4 years, mean disease duration 102±89 months; and comprised 80.9 %(98) Chinese, 11.6 %(14) Malay, and 7.4% (9) Indian and other ethnicity; mean SLAM-R score and SDI of 2.8±2.2 and 0.6±0.97 respectively . SLE disease manifestations at the time of sample assay included mucocutaneous in 7(5.8%), fatigue in 4(3.3%), active urine sediment in 33(27.3%), hypocomplementemia in 88(72.7%), and raised anti-dsDNA antibody titres in 80(66.1%). The majority were on corticosteroids (72.7%) and hydroxychloroquine (67.8%). Immunosuppressive drugs included azathioprine in 35.5%, mycophenolate in 5.8%, and intravenous pulse cyclophosphamide in 3.3%.. SLE patients all fulfilled 1997 revised ACR classification criteria.

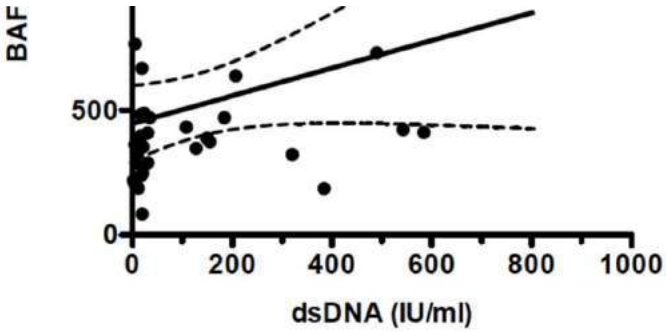
Results: Serum BAFF was elevated in SLE patients compared to controls; mean 1615pg/ml and 338pg/ml, respectively ($p<0.01$)(Fig 1A); and correlated with anti-dsDNA antibody levels ($r=0.363$, $p=0.025$)(Fig 1B), and SLAM-R scores($r=0.615$, $p<0.01$; $n=121$)(Fig 1C). Significantly higher levels of anti-BAFF IgG were found in over 80% of SLE patients (N/200-3200 serial dilution)(Fig 2A), which correlated negatively with SLAM-R ($r=-0.4161$, $p<0.01$; $n=121$)(Fig 2C), and levels of antidsDNA ($r=-0.335$, $p=0.039$)(Fig 2B) and BAFF($r=-0.459$, $p=<0.01$).

Conclusion: Elevated levels of anti-BAFF autoantibodies were found in over 80% of our oriental SLE patients in negative correlation with clinical disease activity, antidsDNA and BAFF levels. Our findings provide further information about the complexity of BAFF pathophysiology in different SLE disease populations and phenotypes, and may have implications in the selection of patients for the development and utilisation of anti-cytokine therapies.

Figure 1



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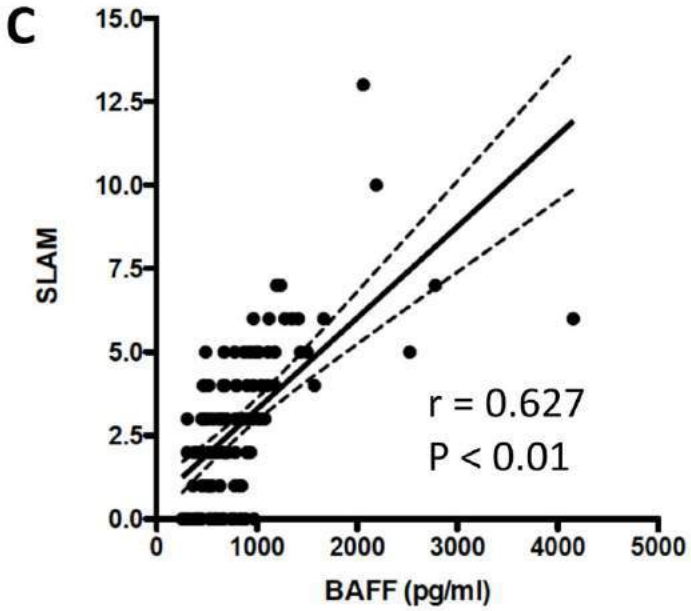
200
400
600
800
1000
dsDNA (IU/ml)


C
15.0
12.5
10.0
7.5
5.0
2.5
0.0
SLAM
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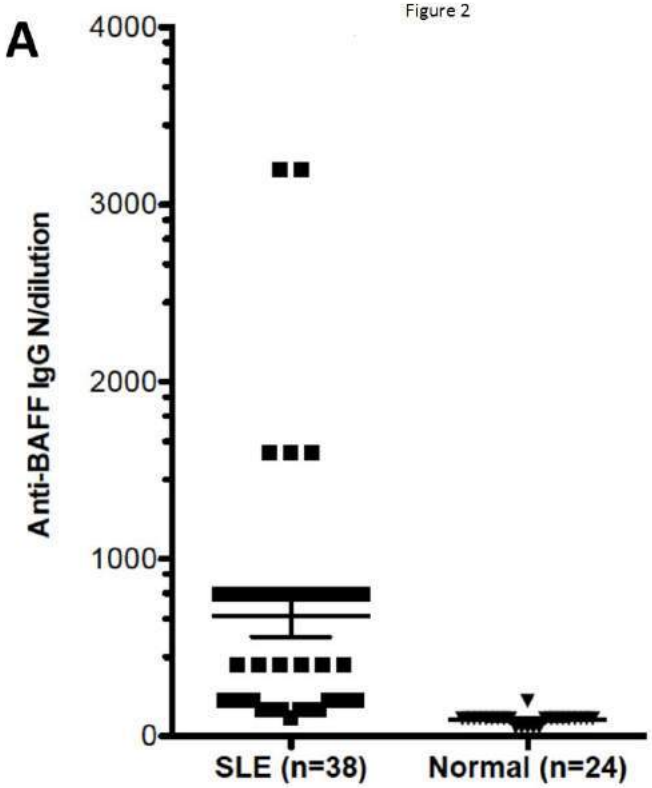
P < 0.01
0
1000
2000
3000
4000
5000
BAFF (pg/ml)

Figure 2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2000
1000
0
Anti-BAFF IgG N/dilution
SLE (n=38)
Normal (n=24)


B
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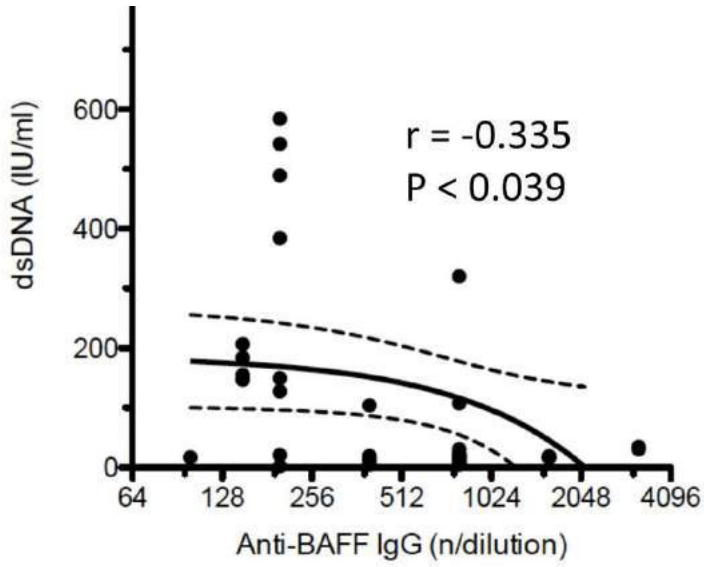

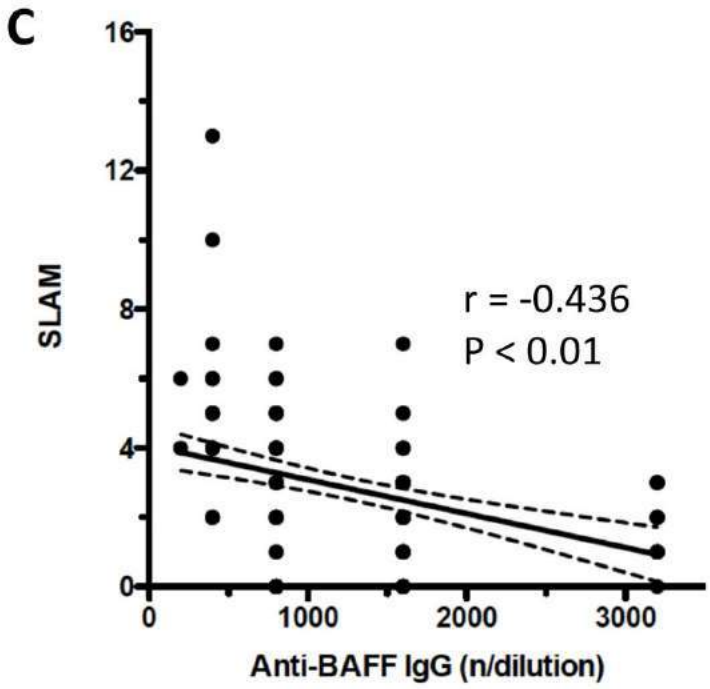

Disclosure: **H. S. Howe**, None; **B. Thong**, None; **K. O. Kong**, None; **H. H. Chng**, None; **T. Y. Lian**, None; **F. Chia**, None; **K. Tay**, None; **T. C. Lau**, None; **W. G. Law**, None; **E. T. Koh**, None; **B. P. L. Leung**, None.

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Abstract Number: 2832

Novel Gene Variants Associated with Cardiovascular Disease in Systemic Lupus Erythematosus

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SESSION INFORMATION

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Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: Patients with Systemic Lupus Erythematosus (SLE) have increased risk of cardiovascular disease (CVD). We asked if single nucleotide polymorphisms (SNPs) analyzed by the Immunochip were associated to CVD in SLE, and followed up with bioinformatics and functional analyses.

Methods: SLE patients (Sweden, n=1055) were genotyped using the 200K Immunochip SNP array (Illumina). The allele frequency was compared between patients with and without myocardial infarction (MI)/angina pectoris (AP), ischemic stroke (stroke)/transitory ischemic attack (TIA), pulmonary embolism/deep vein thrombosis and MI/stroke. Data was analyzed using a logistic regression model with sex and disease duration included as covariates. The SNPs showing the strongest association were re-analyzed in a second group of patients of European descent (United States, n=1043). Information regarding TIA and AP was not available for the US patients. Sex, disease duration and two principal components for population stratification were included as covariates. All patients fulfilled the 1982 ACR-criteria for SLE. Bioinformatic analysis was performed using several databases including RegulomeDB, GTEx and UCSC GB.

Results: An association between a locus located on chromosome 14 and stroke/TIA was shown in both the Swedish (OR 1.8, p=0.0002) and the US (OR 1.6, p=0.03) cohort. The SNP is located in an intron and is conserved in animals but not in humans. The gene variant is located in the middle of a Chip-seq peak for STAT1 and a few bases 3´of a USF2-peak. It is a predicted enhancer in B-cells and also an eQTL. By electrophoretic mobility shift assay (EMSA) we have demonstrated that STAT1 is one of the transcription factors binding at the risk loci. In both the Swedish (OR 2.6, p=0.0006) and US (OR 1.9, p=0.04) cohorts an association was demonstrated between a locus located on chromosome 1 and stroke/MI. The locus is a predicted enhancer in B-cells and is located in an intron 3´of a binding site for a cluster of transcription factors and at a Chip-Seq-peak for CTCF. By EMSA, differential protein binding between the alternative and reference allele was demonstrated using nuclear extract from T-cells activated by PMA/ionomycin. When comparing the level of IL10 in SLE patients with and without the risk gene variant the alternative allele was associated with higher serum levels of IL10 (n=255, p=0.001).

Conclusion: The results indicate that multiple genes in different pathways, including B cell function and cytokine signaling, are involved in the development of CVD in SLE. Thus, CVD in SLE is clearly dependent on the autoimmune and inflammatory disease process, which needs to be considered when therapeutic strategies are developed for the premature CVD observed in SLE patients.

Disclosure: D. Leonard, None; **A. Alexsson**, None; **J. Dahlqvist**, None; **K. Taylor**, None; **J. K. Sandling**, None; **C. Bengtsson**, None; **E. Svenungsson**, None; **C. Sjöwall**, None; **A. Jönsen**, None; **I. Gunnarsson**, None; **A. A. Bengtsson**, None; **S. Rantapaa-Dahlqvist**, None; **M. L. Eloranta**, None; **A. C. Syvänen**, None; **L. A. Criswell**, None; **L. Rönnblom**, None.

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Abstract Number: 2833

Low Plasma Concentrations of Apolipoprotein M Correlate to Disease Activity and Endothelial Dysfunction in SLE

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Background/Purpose: Human apoM is a 25kDa apolipoprotein present in 5% of HDL particles in plasma. In mouse models, apoM is antiatherogenic and vasculoprotective and seems to play a role in keeping endothelial barrier integrity. In SLE, decreased plasma levels of anti-oxidant and anti-inflammatory HDL may contribute to the development of atherosclerosis. The aims of the current study were to determine the impact of SLE disease activity and different organ manifestations on apoM levels and investigate if apoM levels reflect endothelial function in SLE.

Methods: Plasma concentrations of apoM were measured with ELISA in two SLE cohorts, all patients fulfilling ≥ 4 American College of Rheumatology (ACR) classification criteria for SLE, and 100 healthy controls (HC). In Cohort I (n= 85, 88% women, mean age 46 years), evaluation time points were selected to include a wide range of manifestations and SLEDAI scores, to assess if disease activity and certain organ involvement affect apoM levels. Cohort II was investigated cross-sectionally (n=148, 87% women, mean age 49 years) in order to measure endothelial function by EndoPAT 2000 (Itamar Medical, Israel), in relation to apoM levels. A low Reactive Hyperemia Index (RHI) value indicates endothelial dysfunction (ED). Serum-HDL and LDL were measured by routine laboratory test to analyse also these lipoproteins in relation to endothelial function. Subgroup analysis of the younger SLE patients (n=64, age 18-45 years) was performed, since the increased risk of cardiovascular disease seen in SLE is most pronounced in this patient group.

Results: In cohort I, the plasma levels of apoM were found to be significantly lower in patients with SLE (median 0.70 μM) as compared to controls (median 0.88 μM, $p<0.0001$). In SLE patients, the apoM concentrations correlated inversely to disease activity (SLEDAI, r= -0.29, p=0.0063) as well as to the acute phase markers CRP (r= -0.25, p=0.0192) and sedimentation rate (r= -0.27, p=0.021). ApoM was significantly lower in patients with active nephritis, leukopenia, anti-DNA antibodies or rash compared to patients without these manifestations: median concentration in μM: 0.54 vs 0.76 p=0.0053, 0.49 vs 0.75 p=0.0042, 0.54 vs 0.76 p=0.0147 and 0.55 vs 0.79 p=0.0077, respectively . In cohort II, using linear regression analysis, there was a positive correlation between apoM levels and the RHI value in the younger SLE patients: β=0.94 CI 95% 0.22,1.65 r=0.32 p=0.011. No correlation was seen between s-HDL levels and RHI: β= -0.075 CI 95% -0.57, 0.42 r= -0.042 p=0.76. Further, we found no significant correlation between s-LDL and RHI: β=0.18 CI 95% -0.013,0.38 r= 0.25 p=0.067.

Conclusion: SLE related inflammation has an impact by lowering plasma apoM, since high SLE disease activity was associated with low apoM levels. Hypothetically this may affect the endothelium. The lower apoM levels seen in the young SLE patients with impaired endothelial function, supports the hypothesis that apoM is important for maintaining endothelial health.

Disclosure: H. Tydén, None; **C. Lood**, None; **A. Jönsen**, None; **B. Gullstrand**, None; **B. Dahlback**, None; **A. A. Bengtsson**, None.

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Abstract Number: 2834

Utility of the Brain Perfusion Single Photon Emission Computed Tomography in Neuropsychiatric Manifestations of Systemic Lupus Erythematosus

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Background/Purpose: The diagnosis of Neuropsychiatric Events (NPE) in SLE is challenging and it is mainly based on the physician judgment. Structural brain imaging has limited utility in the assessment of NPE. We aimed to evaluate the utility of Brain perfusion Single Photon Emission Computed Tomography (SPECT), as a functional imaging, in the assessment of NPE.

Methods: This is a retrospective analysis on data from a single lupus centre. First, all SPECT done at the centre were identified. Second, we determined if the patients had an NPE (as determined by the physician) at the time corresponding to each SPECT. SPECT results were dichotomized as abnormal (hypoperfusion) or normal. Brain anatomical location (frontal, parietal, or others or multiple [4 or more locations]) and laterality (right, left or bilateral) of the SPECT findings were extracted. NPE were divided into focal (seizure, stroke, subarachnoid hemorrhage, aseptic meningitis [AM] or cranial neuropathy [CN]) and diffuse (organic brain syndrome [OBS], psychosis and headache). Patient weighted Sensitivity (Sn), specificity (Sp), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR) of the SPECT were determined. LR of 0.5-1 means minimal decrease, 1 no change, 1-2 minimal increase, 2-5 small increase, 5-10 moderate increase and >10 large increase in the likelihood of disease.

Results: 336 SPECT in 162 patients (46% patients had at least one NPE) were identified. 120 (35.7%) SPECT in 75 patients were abnormal (hypoperfusion). Of 75 patients, 93% were females, 68% Caucasian, 13% Black, 12% Asian, and 7% other ethnicities. Of the 88 NPE, 94.1% were diffuse and 26.7% were focal (Table 1). The prevalence of individual NPE on the basis of physician definitive diagnosis was 32.7% for headache 9.9% for OBS, 6.8% for psychosis, 5.6% for cranial neuropathy, 4.3% for seizures, 2.5% for stroke and 0.6% for aseptic meningitis. In diffuse NPE, the most commonly affected localizations of the SPECT hypoperfusion were the temporal lobe (18.8%) on the right side (31.5%). In focal NPE, the most commonly affected localizations of the SPECT hypoperfusion were the fronto-parietal (22.2%), temporal (22.2%) and bilateral (44.4%). Among the 3 most prevalent NPE (headache, OBS and psychosis), SPECT was useful only for headache (PLR 1.4, NLR 0.8). For headache, first, the decision to perform a SPECT should be driven by a high suspicion of lupus activity in a patient who met the definition of lupus headache (persistent nonresponsive to narcotic analgesia headache). Second, the definite diagnosis can be confirmed by an abnormal SPECT. Among diffuse and focal NPE, SPECT was useful for diffuse NPE (PLR 1.2, NLR 0.9) but not for focal NPE (PLR 1.0, NLR 1.0) (table 2).

Conclusion: The decision to perform a SPECT should be driven by a high suspicion of NPE. SPECT can be more helpful in the assessment of diffuse NPE in particular Lupus Headache and OBS/Psychosis.

Table 1. Characteristics of patients with NPE at diagnosis of NPE

	Total patients n=75	Seizure	Stroke	Headache	AM	CN	OBS	Psychosis	Diffuse events	Focal events
NPE	88	7	4	53	1	9	16	11	68	20
Female n (%)	70 (93.3)	5 (71.4)	4 (100)	50 (94.3)	1 (100)	8 (89)	15 (94)	10 (91)	64 (94.1)	17 (85)
Age	40.7 ± 13.0	41.4 ± 19.4	45.1 ± 14.8	40.1 ± 13.8	20.5 ± 0.0	49.7 ± 15.3	43.6 ± 12.1	37.8 ± 8.3	40.1 ± 12.9	44.9 ± 17.2
SLE duration	11.6 ± 8.9	15.4 ± 10.5	14.0 ± 7.4	11.2 ± 8.8	2.8 ± 0.0	18.6 ± 6.4	14.4 ± 8.3	8.1 ± 5.6	10.9 ± 8.4	16.1 ± 11.1
SLEDAI-2K	8.8 ± 6.4	14.9 ± 7.3	10.7 ± 3.9	12.8 ± 5.2	8.0 ± 0.0	7.7 ± 6.4	15.9 ± 4.9	16.1 ± 5.1	9.3 ± 6.1	6.7 ± 5.7
SDI	1.0 ± 1.6	2.3 ± 1.6	0.5 ± 0.6	1.3 ± 1.9	0.0 ± 0.0	2.0 ± 1.6	2.4 ± 1.8	1.0 ± 1.0	1.1 ± 1.7	1.3 ± 1.5
Patients on prednisone n (%)	75 (100)	7 (100)	4 (100)	53 (100)	1 (100)	9 (100)	16 (100)	11 (100)	68 (100)	20 (100)
Dosage of prednisone (mg/day)	20.2 ± 17.5	39.6 ± 24.0	16.9 ± 10.7	22.3 ± 17.8	40.0 ± 0.0	17.9 ± 19.3	21.0 ± 16.9	31.2 ± 30.1	19.4 ± 18.0	20.8 ± 17.9
Patients on antimalarials n (%)	75 (100)	7 (100)	4 (100)	53 (100)	1 (100)	9 (100)	16 (100)	11 (100)	68 (100)	20 (100)
Patients on immunosuppressants n (%)	75 (100)	7 (100)	4 (100)	53 (100)	1 (100)	9 (100)	16 (100)	11 (100)	68 (100)	20 (100)

Table 2. Prevalence of NPE and Sn, Sp, PLR and NLR of SPECT in 88 NPE

Type of NPE	Prevalence	Sn	Sp	PLR	NLR
Headache	32.7%	39%	73%	1.4	0.8
OBS	9.9%	30%	70%	0.9	1.0
Psychosis	6.8%	28%	70%	0.9	1.0
CN	5.6%	14%	69%	0.4	1.2
Seizures	4.3%	13%	70%	0.4	1.2
Stroke	2.5%	90%	77%	3.9	0.1
AM	0.61%	100%	71%	3.4	0.0
Diffuse NPE	77.3%	34%	72%	1.2	0.9
Focal NPE	22.7%	30%	70%	1.0	1.0

Disclosure: J. Medina-Rosas, None; **M. Urowitz**, None; **J. Su**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **Z. Touma**, None.

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Abstract Number: 2835

Longitudinal Analysis of Th1 and Th2 Cytokines in Systemic Lupus Erythematosus

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Session Time: 9:00AM-11:00AM

Background/Purpose: While autoantibodies production and immune complex deposition are cornered as hallmark features of systemic lupus erythematosus (SLE), there is growing evidence to propose the pathogenic role of cytokines in this disease. The aim of this follow-up study was to evaluate the sera levels of Th1 cytokines and Th2 in SLE patients, associating these cytokines with disease activity, clinical and laboratory manifestations and also, to assess Th1 and Th2 cytokines levels could be potential biomarkers.

Methods: Consecutive SLE patients followed at the Rheumatology unit of the State University of Campinas were enrolled in this follow-up study. Healthy volunteers, matched by age and sex, were included as control group. A complete clinical, laboratory and neurological evaluation was performed in all subjects. Neurological manifestations were analyzed according to the ACR classification criteria. SLE patients were further assessed for clinical and laboratory SLE manifestations, disease activity [SLE Disease Activity Index (SLEDAI)], damage [Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI)] and long-term therapy. Clinical, laboratory evaluation and blood withdrawal was performed every 4 months for 1 year. Sera for stored. Sera cytokines levels were performed by enzyme linked immunosorbent assay (ELISA) at the end of the study. Data were compared by non-parametric tests.

Results: Two hundred and eighteen (210 women) SLE patients, with a mean age of 42.62 ±11.98 years were included. The control group, matched by age and sex, consisted of 46 (40 women) healthy volunteers with a mean age of 40.04±13.54 years. Only IL-6 remained significantly increased in SLE patients [median sera levels (pg/mL): T_0 2.13; T_1 1.96; T_2 2.52; T_3 2.37] compared to healthy controls [T_0 0.91 ($p<0.001$); T_1 0.91 ($p<0.001$); T_2 0.93 ($p<0.001$); T_3 1.3 ($p=0.042$)] over time. Sera IL-10 levels correlated with disease activity in all evaluations (T_0 $r=0.28$ $p<0.001$; T_1 $r=0.23$ $p=0.001$; T_2 $r=0.19$ $p=0.007$ T_3 $r=0.14$ $p=0.049$). We also observed an association between sera IL-10 levels and nephritis in all evaluations (T_0 $p=0.008$; T_1 $p=0.036$; T_2 $p=0.024$ and T_3 $p=0.005$). In the paired analyses, significant variation in IFN-γ [median sera levels (pg/mL): T_0 25.7; T_1 31.22; T_2 35.98; T_3 26.3; $p=0.026$), IL-12 (T_0 1.86; T_1 0.94; T_2 1.09; T_3 1.34; $p<0.001$), IL-4 (T_0 0.41; T_1 0.34; T_2 0.34; T_3 0.5; $p=0.001$) and IL-10 (T_0 0.98; T_1 0.94; T_2 1.09; T_3 1.34; $p<0.001$) was observed. There was no significant variation in TNF-α (T_0 2.84; T_1 2.67; T_2 2.83; T_3 2.71; $p=0.304$) and IL-6 (T_0 2.13; T_1 1.96; T_2 2.52; T_3 2.37; $p=0.241$). In the paired analyses, we also observed an association between INF-γ ($p=0.039$) and IL-10 ($p<0.001$) and neuropsychiatric manifestations in SLE patients.

Conclusion: IL-10 may be considered a biomarker for disease activity and nephritis in SLE. IFN-γ and IL-10 may identify patients with CNS involvement. Identifying new SLE biomarkers might be a useful tool to sub-classify patients and predict which clinical manifestation these patients might develop.

Disclosure: M. Postal, None; **K. O. Peliçari**, None; **N. A. Sinicato**, None; **A. T. Lapa**, None; **F. A. Peres**, None; **A. M. Morcillo**, None; **L. T. Costallat**, None; **S. Appenzeller**, None.

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Abstract Number: 2836

Microparticles of Endothelial Origin in Women with Systemic LUPUS Erythematosus UNDER Treatment

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SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic Lupus Erythematosus (SLE) is an inflammatory and multisystem disease. Microparticles (MPs) are cell membrane-shedded fragments released during apoptosis and cell activation. Several diseases are associated with increased number of circulating MPs, and those from the endothelium (EMPs) can trigger neutrophil activation and stimulate coagulation. On the other hand, they act as potent proinflammatory inducers affecting the function of the endothelium. **Objective:** To determine the number of MPs of endothelial origin (EMPs) in women with SLE under treatment, compared to controls, as a tool to assess disease activity.

Methods: This study included 90 women with similar age distributed into 3 groups: Group 1: healthy women (control, n=30); Group 2: SLE patients under treatment with low disease activity (SLEDAI < 4, n=30); Group 3: SLE patients under treatment with /moderate high disease activity (SLEDAI ≥4, n=30). EMPs were purified by ultracentrifugation, labeled with antibody anti-CD51 / 61 and anti - annexin V and then analysed by flow cytometry

Results: The number of EMPs was significantly higher in patients with SLE compared to the control group (p = 0.0178). When SLE patients were stratified according to the activity disease, the number of EMPs was significantly higher in SLE women with moderate / high activity compared to the control group (p = 0.0074). However, no difference was observed between the control group and SLE women with low activity disease. Correlations between the number of EMPs and age (r = -0.3385, P = 0.0123) and between the number of EMPs and SLEDAI (r = 0.2785, p = 0.0377) were observed.

Conclusion: Data from this study suggest that EMPs measurement may be an useful tool in the evaluation of patients with SLE and monitoring of treatment.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/microparticles-of-endothelial-origin-in-women-with-systemic-lupus-erythematosus-under-treatment

Abstract Number: 2837

Importance of Mixed Speckled/ Homogeneous DFS70 ANA Patterns

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Background/Purpose: A Mixed Speckled/Homogeneous (MS/H) pattern is the single most common ANA pattern identified in our community hospital patient population, often in very high titers, and has been associated with a “Dense Fine Speckled” anti-DFS70 ENA specificity. The IFA pattern on a Hep-2 cell substrate is that of dense, finely speckled interphase nuclei with strongly fluorescent mitotic chromosomes—ICAP pattern #2. Patients with a DFS70 positive MS/H ANA are reported to rarely develop systemic autoimmune rheumatic disease (SARD), especially in the absence of significant clinical findings or other significant ENA specificities, prompting suggestion that an isolated DFS70-specific ANA may be an exclusionary finding for SARD.

Methods: All ordered ANAs are tested using Euroimmun Hep-2 substrate slides. All MS/H ANA pattern results are reported as

possibly DFS70-related, with ENA follow-up analysis recommended. ENA profiling uses the Euroimmun Immunoblot ANA Profile 3-plus DFS70 kit which includes a total of 15 separate ENA specificities. Chart reviews were done on these patients to determine if the isolated DFS70 pattern was useful as a rule-out for SARDS.

Results: 2,383 patient samples tested for ANA in a 4-month period showed 632 (27%) to have an MS/H ANA pattern. ENA profiling of these 632 MS/H ANA's showed: · 260 (41%) of MS/H ANA's positive for anti-DFS70, 73% of these an isolated anti-DFS70. · 71 (27%) of DFS70 ANA's showed an additional positive or borderline reaction to other ENA specificities. · 353 (59%) of MS/H ANA's were negative or showed only borderline (3%) reactivity for anti- DFS70; · 263 (75%) of DFS70-negative MS/H ANA's were also ENA profile negative; while the remainder showed varied presence of other ENA specificities. Ongoing chart reviews of patients positive for an isolated anti-DFS70 ANA affirms that evidence of SARD is rare in patients with isolated anti-DFS70 patients in the absence of clinical evidence or other ENA specificities. The presence other ENA specificities at a significant level has clinical relevance specific to those antibodies.

Conclusion: Recognition of an MS/H, Dense Fine-speckled, ICAP AC-2 ANA pattern should be a routine ANA testing service. A mitotic-rich Hep-2 cell substrate is essential for recognition of this and of varied cell-cycle ANA patterns. Recognition of an isolated DFS70 ANA specificity enables reassurance of ANA-positive patients who would otherwise be referred for more extensive testing and monitoring for the presence or development of SARD.

Disclosure: B. Goeckeritz, None; **J. Bruce**, None; **S. Carter**, None; **J. Carter**, None.

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Abstract Number: 2838

Histopatholgic Predictors of Poor Renal Outcomes in a Multi-Ethnic Cohort

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Background/Purpose: Lupus nephritis (LN) remains an important cause of morbidity and mortality in patients with SLE. Tubular atrophy and interstitial fibrosis on initial renal biopsies in Blacks with LN have been associated with poor renal outcomes. This study was initiated to evaluate the histopathologic predictors of poor renal outcomes on initial and subsequent renal biopsies in patients with lupus nephritis in a predominantly Hispanic and Black cohort.

Methods: All SLE patients with two or more renal biopsies performed at CUMC between 1996-2015 were identified from the pathology database; data on 63 patients with regular follow-up at the Columbia University Lupus Center were available for analysis. Demographics, clinical, laboratory and histopathologic characteristics were ascertained. Adverse renal outcomes were defined as a serum creatinine >1.4 mg/dL, ESRD, or renal transplant. Tubular atrophy and interstitial fibrosis was graded by the renal pathologist from mild (10-25% involvement) to severe (>60% involvement). The histopathologic predictors of adverse renal outcomes were evaluated using logistic regression, adjusting for pertinent confounders.

Results: Of the 63 patients, 87% were female, 46% Hispanic, 29% Black. The average age at SLE diagnosis was 27±12, the median time from the first renal biopsy to the occurrence of the first adverse renal outcome was 6 years (4-9) (Table 1). Fifty-three percent of patients with ≥ 2 biopsies had an adverse renal outcome: 31% developed ESRD (of which 58% received a renal transplant), and 22% had a serum creatinine >1.4 mg/dL. The degree of tubular atrophy and interstitial fibrosis (TAIF) in the second renal biopsy [OR 3.5 (CI 1.3-10.6) p=0.03] but not in the first [OR 2.5, (CI 0.7-8.2); p=0.15], was a strong predictor of adverse renal outcomes in a multivariate analysis, after adjusting for hypertension, smoking, race/ethnicity, LN class and activity index. Chronicity index was not a significant predictor of renal outcome in multivariable analysis. All subjects with severe TAIF on the second and third renal biopsies met the

primary outcome. Fibrinoid necrosis, number or type of crescent, number of sclerotic glomeruli and degree of foot process effacement were not significantly associated with a poor renal outcome.

Conclusion: Fifty-three percent of SLE patients that required a second renal biopsy for LN flare in this predominantly Hispanic and Black cohort had adverse renal outcomes within 6 years; 31% developed ESRD. Tubular atrophy and fibrosis were strong predictors of poor renal outcome. Their presence on a second biopsy should prompt intensification of therapy in patients with lupus nephritis to avoid ESRD and adverse renal outcomes.

	Biopsy #1 (n=63)	Biopsy #2 (n=63)	Biopsy#3 (n=18)
Age at Biopsy, years	30 ± 14	34 ± 14	31 ± 9
Year of Biopsy	2005 (1999-2010)	2008 (2005-2012)	2009(2007-2011)
No. Glomeruli in Sample	18 (14-28)	19 (13-23)	21 (14-25)
LN Class Biopsy			
II, n (%)	4 (1)	2 (3)	0
III, n (%)	7 (11)	5 (8)	1 (6)
IV, n (%)	16 (25)	18(29)	4 (22)
V, n (%)	2 (3)	3 (5)	0
III/V, n (%)	17 (27)	13 (21)	1 (5)
IV/V, n (%)	17 (27)	21 (34)	12 (67)
Activity Index	9 (4-14)	10 (4-13)	8 (5-12)
Chronicity Index	2 (0-4)	3 (2-6)	6 (4-8)
Proteinuria (gm)	2.2 (1.4-4.1)	2.4 (1.3-4)	4.9 (2-6)
Creatinine (mg/dL)	0.9 (0.7-1.4)	1.0 (0.8-2.0)	2.6 (1.4-5.2)
C3	56 (37-77)	67 (46-95)	54 (31-80)
C4	9 (6-12)	13 (7-19)	12 (7-20)
dsDNA	365 (100-2140)	433 (46-2050)	184 (98-754)
Degree Foot Process Effacement	70 (40-90)	80 (60-95)	90 (65-90)
Fibrinoid Necrosis, n (%)	16 (26)	11 (18)	4 (22)
Total # Crescents	5±10	4±6	8±6
-Fibrous	5±10	2±3	4±5
-Fibrocellular	1±1	1±2	1±2
-Cellular	4±7	2±5	4±6
Wire Loop	13 (21)	20 (32)	10 (56)
Tubulointerstitial Atrophy/Fibrosis			
-None, n (%)	24 (39)	6 (10)	0
-Mild, n (%)	29 (47)	36 (59)	11 (61)
-Mod, n (%)	9 (14)	11 (18)	5 (28)
-Severe, n (%)	0	8 (13)	2 (11)
Sclerotic Glomeruli	2±3	4±4	6±6

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Circulating CD4+CD28null T-Cells Predict the Occurrence of New Lung Damage in Systemic Lupus Erythematosus (SLE) Patients

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Velasquez[1], Jorge M. Cucho-Venegas[1], Jose Alfaro-Lozano[1], Zoila Rodriguez-Bellido[1,5], Cesar A. Pastor-Asurza[1,5], Graciela S. Alarcón[6] and Risto Perich-Campos[1,5], [1]Rheumatology, Hospital Guillermo Almenara Irigoyen. EsSalud, Lima, Peru, [2]Universidad Cientifica del Sur, Lima, Peru, [3]Diagnostic Support, Hospital Grau. EsSalud, Lima, Peru, [4]Molecular Biology, Hospital Guillermo Almenara Irigoyen. EsSalud, Lima, Peru, [5]Universidad Nacional Mayor de San Marcos, Lima, Peru, [6]Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL
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Background/Purpose: Peripheral CD4+CD28null T-cells constitute a subset of long-lived cytotoxic CD4+ T-cell with pro-inflammatory functions. This T-cell subpopulation has been reported to be associated with damage in SLE patients, but whether it may be predictive of such occurrence has not previously been reported. The aim of this study was to determine whether this T-cell subset predicts the occurrence of new damage in these patients.

Methods: This longitudinal study was conducted in consecutive SLE patients seen every six months in our Rheumatology Department since 2013. For the purpose of this study, patients in whom CD4+CD28null T-cells had been measured and who had at least one subsequent visit thereafter were included. Variables were evaluated during the same visit in which CD4+CD28null cells were measured (interview, medical records review, physical examination and laboratory tests) with the exception of damage which was evaluated in the subsequent visits. SLE was defined by the 1997 revised and updated ACR criteria. Disease activity was ascertained using the SLEDAI and disease damage with the SLICC/ACR damage index (SDI). Use of prednisone was recorded as current dose and total time of exposure. Use of antimalarials and immunosuppressives was recorded as current, past or never. CD4+CD28null T-cells frequencies were analyzed by flow-cytometry. Survival analyses using univariable and multivariable Cox-regression models were performed to determine the risk of overall damage and per each SDI domain individually as a function of the frequency of this T-cell subpopulation. The multivariable model was adjusted for age at diagnosis, disease duration, socioeconomic status, SLEDAI, SDI, use of prednisone, antimalarials and immunosuppressive drugs at the intake visit. All analyses were performed using SPSS 21.0.

Results: One hundred and nineteen patients were evaluated; their mean (SD) age was 43.5 (11.9) years, 113 (95.0%) were female; all patients were Mestizo (mixed Caucasian and Amerindian ancestry). Socioeconomic level was low in 50 (42.0%), medium in 48 (40.3%) and high in 21 (17.6%) patients. Disease duration was 7.8 (7.0) years. The SLEDAI was 5.3 (4.1) and the SDI 1.0 (1.4). At baseline, the dose of prednisone was 6.9 (5.1) mg/day and the total time of exposure to prednisone was 7.3 (6.8) years; 93 (78.2%) and 13 (10.9%) patients were current and former users of antimalarials. Fifty-six (47.1%) and 28 (23.5%) patients were current and former users of immunosuppressive drugs. The percentage of CD4+CD28null T-cells was 17.4 (14.0). Forty-six (38.7%) patients increase at least one point in the SDI. In the univariable and multivariable analyses, the percentage of CD4+CD28null predicted the occurrence of lung damage [HR: 1.042 (CI95%: 1.001-1.085); p=0.047 and HR: 1.099 (CI95%1.020-1.184); p=0.013, respectively] but neither the total SDI score nor all other SDI domain scores were predicted by the percentage of CD4+CD28null cells.

Conclusion: In SLE patients, CD4+CD28null T-cells predict the occurrence of new lung damage, independently of other risk factors.

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Abstract Number: 2840

Are There Genetic Predispositions to Diffuse Large B-Cell Lymphoma (DLBCL) in Systemic Lupus (SLE)?

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Are there genetic predispositions to diffuse large B-cell lymphoma (DLBCL) in systemic lupus (SLE)?

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Background/Purpose: The determinants of the increased risk of non-Hodgkin Lymphoma (NHL) in systemic lupus (SLE) are unclear. The most common type of NHL in SLE (as in the general population) is the Diffuse Large B-Cell lymphoma (DLBCL) subtype. Our purpose was to identify if known susceptibility loci for DLBCL occur more frequently in SLE.

Methods: We used data from a recent GWAS of SLE conducted in a North American case-control sample of European ancestry Our study comprised 7,219 SLE cases and 15,991 non-SLE controls, genotyped on Affymetrix Genome-Wide Human SNP Array 6.0. We studied 4 loci that have been associated with DLBCL in recent GWAS studies, to determine if these DLBCL-associated SNPs occur more frequently in SLE versus the general population.

Results: For the DLBCL SNP of interest rs2621416 on 6p21.32 (associated with HLA-DOB 1), while the G (versus A) risk allele is a risk factor for DLBCL, the same allele is protective for SLE (odds ratio, OR for the G allele in SLE versus the general population was 0.78, 95% confidence interval, CI 0.63, 0.97, p value 0.023). For the DLBCL SNP of interest rs4530903 on 6p21.32 (associated with HLA-DQA1), while the T (versus C) risk allele is a risk factor for DLBCL, the A allele was possibly protective for SLE (OR for the A allele in SLE versus the general population was 0.72, 95% CI 0.50, 1.02, p value 0.066). For the other two DLBCL SNPs of interest, the SLE OR was close to 1 with a wide confidence interval.

Conclusion: We did not identify an increased occurrence of known susceptibility loci for DLBCL in SLE in these analyses. **Odds Ratio Estimates for SLE risk, for Diffuse Large B Cell Lymphoma (DLBCL)-related SNPs**

DLBCL-related SNP	A1	SLE OR	95 % CI	P value	Chromosome	MAF_ALL	MAF_Case	MAF_Control	Nearest Gene
rs2621416	G	0.78	(0.63, 0.97)	0.023	p21.32	0.25	0.23	0.28	HLA-DOB
rs4530903	A	0.72	(0.50, 1.02)	0.066	p21.32	0.08	0.07	0.10	HLA-DQA1
rs948562	G	1.13	(0.87, 1.45)	0.367	q12.1	0.17	0.17	0.17	ZFP91-CNTF
rs4733601	A	1.04	(0.85, 1.27)	0.719	q24.21	0.50	0.51	0.48	MIR1208

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Abstract Number: 2841

Anti-Ro52/TRIM21 Antibodies Are Associated with QT Interval Prolongation in Patients with Systemic Lupus Erythematosus

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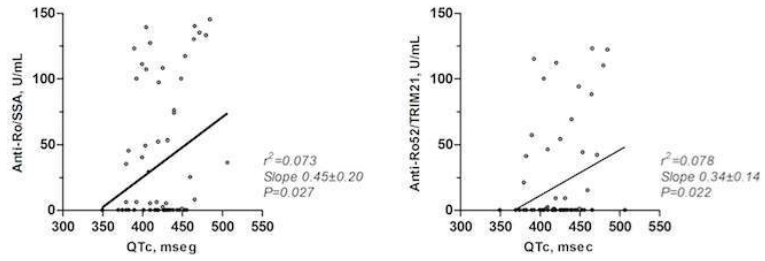
Background/Purpose: Long QT syndrome (LQTS) is characterized by an abnormal QT corrected (QTc) interval prolongation that is associated with increased risk of sudden death. Studies have associated LQTS with several rheumatic conditions, and evidence points towards a link between the degree of systemic inflammation and the duration of QTc interval. Moreover, recent evidence suggests that anti-Ro antibodies may play a role in the QTc prolongation by mechanisms not fully understood, thus constituting a novel autoimmune-mediated LQTS. This study was aimed to assess whether QTc interval prolongation is associated with the presence of anti-Ro antibodies in SLE, particularly with reactivities against Ro52/TRIM21 antigens.

Methods: Consecutive patients fulfilling the 1997 ACR criteria for SLE were included. Patients with history of ischemic heart disease, with implantable pacemakers, and those taking drugs that potentially could affect QT interval (except for antimalarials) were excluded. Patients underwent a resting 12-lead electrocardiogram recording to measure QT interval corrected by BazzetÕs formula. A QTc interval duration greater than 460 msec in women and 440 msec in men was set to be abnormal. Serum anti-Ro and anti-Ro52/TRIM21 antibody levels were measured by ELISA. Data were expressed as frequencies and means (± standard deviation), and differences were tested by YatesÕ continuity corrected chi square or Mann-Whitney tests, while linear regressions were performed to assess linearity between autoantibody levels and QTc duration. The GraphPad Prism 4.02 software was used for calculations.

Results: Sixty-six patients with mean age of 39±13 years (57 female gender) were included. A QTc prolongation was found in 10 patients (15%), with mean QTc interval of 470±18 msec as compared to 414±23 msec in those with no LQTS. Main clinical and demographic characteristics were similar for both groups, except for a lesser use of antimalarials and higher serum creatinine levels in patients with LQTS. Disease activity was similar between groups.Anti-Ro antibody levels were significantly higher in patients with prolonged QT interval (75±66 U/mL versus 29±44 U/mL; P=0.005); similarly, anti-Ro52/TRIM21 levels were higher in those with LQTS (50±55 U/mL versus 14±30 U/mL; P=0.01). Notably, a linear association (see the Figure) between the QTc intervals and levels of anti-Ro antibodies (r^2=0.073; P=0.02) and anti-Ro52/TRIM21antibodies (r^2=0.078; P=0.02) was observed.

Conclusion: Our results strengthen the hypothesis that a specific autoantibody-mediated LQTS occur in SLE patients positive to anti-Ro antibodies. This interference in the ventricular repolarization appears to be associated with increased levels of antibodies against Ro52/TRIM21 antigens, and supports the realization of an electrocardiogram as part of the routinely evaluation in SLE patient with circulating anti-Ro antibodies.



Disclosure: L. F. Perez-Garcia, None; **I. O. Estevez-Garcia**, None; **M. Moreno Ramirez**, None; **J. Loaiza Felix**, None; **R. Marquez-Velasco**, None; **P. Iturralde**, None; **L. H. Silveira**, None; **L. M. Amezcua-Guerra**, None.

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Abstract Number: 2842

Predictors of Good Long-Term Renal Outcomes in Lupus Nephritis

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Background/Purpose: Lupus nephritis (LN) manifests with proteinuria and/or active urine sediment. Renal composite indices include proteinuria, urinary active sediment (RBCs, casts) and serum creatinine. Complete proteinuria recovery (CR) is defined as <0.5 g/d but it is currently unclear which proteinuria cutoff best predicts good clinical outcomes.

We aimed to determine: a) the predictive ability of proteinuria, urinary sediment (uRBCs) and serum creatinine (Cr) at 1 year to predict good long-term outcomes, and b) the best proteinuria cut-off at 1 year to predict good long-term outcomes.

Methods: This retrospective analysis was performed on prospective data from a single lupus cohort of 1849 patients. Patients with LN (24-hr proteinuria [24H-P] >0.5 g/d) were identified and baseline was defined as the onset of LN. Patients on whom microscopic urine analysis with at least 7 years' follow-up were studied. Patients with end-stage renal disease (ESRD) or renal transplant/dialysis at baseline were excluded. Good renal outcome was defined as Cr <100 mmol/L and renal transplant/dialysis-free at 7 years.

Receiver operating characteristic (ROC) curves were generated to examine the predictive power of Cr, 24H-P, and uRBCs at 1 year post-LN diagnosis with respect to good renal outcome. Area under curves (AUC) were analyzed for: a) 24H-P at year 1, b) absolute change in 24H-P between year 1 and 7, and c) percent change in 24H-P between year 1 and 7. The proteinuria cutoff was identified by optimizing sensitivity and specificity. Additional sensitivity analyses were conducted for patients with baseline 24H-P of >2.5 g/d, >2.0 g/d, and >1.5 g/d. This analysis was repeated for uRBCs and Cr.

Results: 101 LN patients were analyzed, with baseline 24H-P of 2.36 ± 2.31 g/d. At 7 years Cr was 85.6 ± 40.0 mmol/L. 24H-P of 0.6 g/d at 1 year after LN diagnosis best predicted good long-term renal outcome, with sensitivity 62% and specificity 70% (Fig. 1). In the sensitivity analyses, proteinuria cut-off of 1.0 g/d was identified for groups with baseline 24H-P >2.5 g/d, >2.0 g/d, and >1.5 g/d.

The AUC analysis confirmed that 24H-P at 1 year, but not absolute/percent change, is a predictor of good long-term renal outcomes (Fig. 1, 2). uRBCs did not provide any predictive benefit while Cr at 1 year predicted long-term renal outcome with an AUC of 0.82 (Fig. 2).

Conclusion: Proteinuria of 0.6 g/d at 1 year post-LN diagnosis best predicted good long-term renal outcome. Serum creatinine at 1 year was also a strong predictor of long-term renal outcome, whereas urinary RBCs did not offer any prognostic benefit.

Figure 1. ROC curve for proteinuria at 1 year, absolute change and percentage of change between year 1 and 7

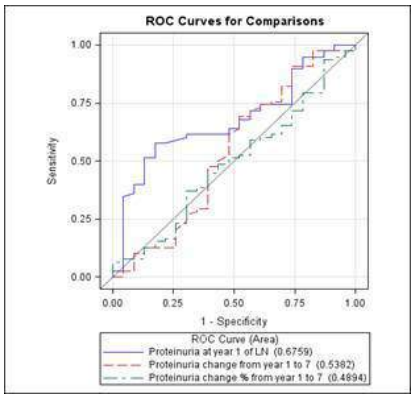
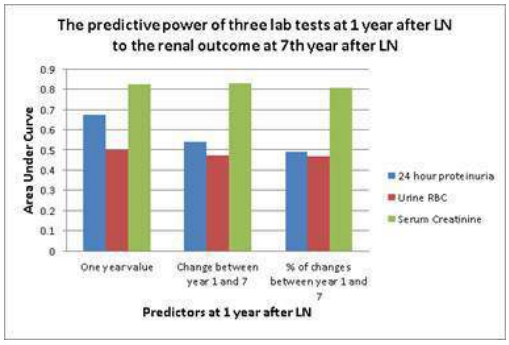


Figure 2. ROC analyses for proteinuria levels, Cr and uRBC at 1 year, absolute change and percentage of change between at year 1 and 7



Disclosure: W. Fung, None; **J. Su**, None; **Z. Touma**, None.

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Abstract Number: 2843

Prevalence of Anti-DFS70 Antibodies in Patients with and without Systemic Autoimmune Rheumatic Diseases

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Background/Purpose: Autoantibodies to the dense fine speckled 70 (DFS70) antigen are common among ANA (dense fine speckled pattern) positive healthy individuals and consequently reduce the specificity of the ANA test. This might lead to miss-diagnosis, unnecessary referral, increased healthcare expenditure and even miss-treatment. Therefore, the reliable identification of anti-DFS70 antibodies is of high importance. Recently, different methods were developed to identify samples containing anti-DFS70 antibodies including a chemiluminescence assay (CIA) for the detection of anti-DFS70 antibodies and an indirect immunofluorescence (IIF) immunoadsorption technology which blocks anti-DFS70 antibodies from binding to the native ligand on HEp-2 cells. Here, we assessed the prevelance of anti-DFS70 antibodies in patients with and without systemic autoimmune rheumatic diseases (SARDs) and compared two methods for the detection of these antibodies: IIF and CIA.

Methods: We evaluated 51 ANA-positive sera samples from patients with confirmed clinical diagnosis of SARD, 92 samples from healthy blood donors and 85 samples submitted to a reference laboratory for routine ANA testing. These samples were tested by QUANTA Flash DFS70 CIA on the BIO-FLASH instrument (Inova Diagnostics, San Diego, USA) to measure anti-DFS70 antibodies, and were evaluated by automated IIF (NOVA Lite HEp-2 Select, Inova Diagnostics, USA). Samples were tested with and without DFS70 inhibition. Mono-specificity of anti_DFS70 antibodies was define by successful and complete inhibition of ANA reactivity by the DFS70 antigen in the HEp-2 Select sample buffer.

Results: 24 samples (10.5%) tested by QUANTA Flash DFS70 CIA were positive for anti-DFS70 antibodies. The prevalence of monospecific anti-DSF70 antibodies was significantly higher in healthy subjects than in patients with SARDs (10.2% vs 1.9%, p=0.02). The frequency of anti-DFS70 antibodies in samples submitted to a reference laboratory for routine ANA testing was 27%. A very good agreement was found between QUANTA Flash DFS70 CIA and the DFS pattern identified by automated HEp-2 IIF (kappa=0.97). In 80% of the samples obtained from patients without SARDs, HEp-2 Select Kit effectively inhibited the anti-DFS70 antibodies, reducing false positive ANA results.

Conclusion: Our data confirm that mono-specific anti-DFS70 antibodies are a strong discriminator between ANA positive healthy individuals and SARD patients. In addition, anti-DFS70 antibodies are very common in ANA routine samples. Consequently, the detection of anti-DFS70 antibodies should be included in ANA testing algorithms to aid in the interpretation of ANA positivity without underlying SARD. In addition, anti-DFS70 antibodies should be considered for future revisions of disease classification criteria.

Disclosure: O. Shovman, None; **B. Gilburd**, None; **C. Chayat**, None; **H. Amital**, None; **A. Watad**, None; **A. Guy**, None; **C. Bentow**, Inova Diagnostics, Inc., 3, 9; **M. Mahler**, Inova Diagnostics, Inc., 3; **Y. Shoenfeld**, None.

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Abstract Number: 2844

Immunoglobulins Level and Risk of Infection in Systemic Lupus Erythematosus

Ibrahim Almaghlouth[1], Jiandong Su[2], Dafna D Gladman[3] and Murray Urowitz[4], [1]Division of Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada, [2]Rheumatology, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [3]University of Toronto, Toronto, ON, Canada, [4]Rheumatology, University of Toronto, Toronto Western Hospital, Toronto, ON, Canada

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SESSION INFORMATION
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Session Time: 9:00AM-11:00AM

Background/Purpose: Infection is a major cause of mortality in all stages of SLE. This is likely multifactorial in nature. We hypothesized that some patients with SLE have acquired immunoglobulin deficiency, which may put them at higher risk of infection. We aimed to examine the association and prediction of immunoglobulin levels and the risk for severe infections in lupus patients

Methods: Patients with SLE have been followed prospectively at 2-6 month intervals according to a standard protocol, which includes detailed clinical and laboratory assessments including immunoglobulin levels and recording of infections. All information is recorded in the Clinic database. Damage accrual was measured by the SLICC/ACR damage index (SDI). Included in this study were patients with severe infections, defined by either requiring parenteral antibiotics or 3 infections within 2 years. Controls were patients followed for the same period who did not have infections. Immunoglobulin levels were recorded as low, normal, or high according to the laboratory standard. Persistently low immunoglobulins were defined as two or more low consecutive measurements. Logistic regression analysis was performed to determine first the factors associated with infection and then factors predisposing to severe infection.

Results: We first identified from the database 250 patients with severe infections and 381 patients without infection. Patients with severe infections had lower IgG and IgA levels, and were treated with higher doses of glucocorticoids (GC). Logistic regression analysis revealed that age at SLE diagnosis (OR 1.019 95% CI 1.004,1035, P=0.014), low IgM levels (OR 2.175 95% CI 1.114, 4.245, p = 0.0228) and GCS dose (OR 1.079 95% CI 1.058, 1.101, p = <0.001) were associated with infection, adjusted for other demographic and clinical variables. We then examined 148 patients with persistently low immunoglobulins and no infection at first measurement and compared them to 430 controls for infection outcome. The low immunoglobulin group had more severe infections, higher SDI score, higher GC and immunosuppressive use. Logistic regression analysis revealed low IgG levels (OR 3.546 95% CI 1.852, 6.787, p = 0.0001), low IgM levels (OR 2.209 95% CI 1.274, 3.83, p = 0.0048), female gender (OR 2.285 95% CI 1.019, 5.125, p = 0.045), SDI (OR 1.188 95% CI 1.029, 1.373, p = 0.019) SLE duration (OR 1.056 95% CI 1.03, 1.084, p = <0.0001) to be predictors for severe infection and antimalarial treatment to be protective (OR 0.566 95% CI 0.355, 0.902, p = 0.0166) after adjustment for other demographic and clinical variables.

Conclusion: Our study shows consistent association between low immunoglobulin level and clinically significant infection in lupus patients. Furthermore, low IgG and IgM levels increase the risk of severe infection, while antimalarial treatment is protective. Thus immunoglobulin assessment should be performed routinely in patients with SLE.

Disclosure: I. Almaghlouth, None; **J. Su**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **M. Urowitz**, None.

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Abstract Number: 2845

Antineutrophil Cytoplasmic Antibodies in Systemic Lupus Erythematosus: Incidence, Outcome and Prognosis

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Background/Purpose: The presence of ANCA in SLE had been known for over 25 years with a reported prevalence as high as 31%. However, the relationship between the presence of ANCA and disease activity in SLE has yet to be understood. We aimed to evaluate the prevalence of ANCA in SLE patients and correlate it with lupus activity, organ involvement, association with vasculitis, and prognosis.

Methods: SLE patients have been followed prospectively in the lupus clinic at 2-6 month intervals according to a standard protocol, which includes a detailed clinical history, physical examination and laboratory evaluation. Only patients who were tested at least twice for c and p-ANCA were included. ANCA was considered positive if either c or p-ANCA was detected on at least two occasions. All information necessary to complete the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) and the SLICC/ ACR damage index (SDI) is collected prospectively. Vasculitis is defined by SLEDAI-2K vasculitis definition which includes ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, biopsy or angiogram proof of vasculitis, retinal hemorrhage or vasculitis found in renal biopsy. Damage increase was defined by the first increase of SDI score after baseline. Baseline was defined as first ANCA positive or second negative of ANCA tests. Univariate and multivariable Weibull regression was used to analyse the

effect of positive ANCA on the outcomes of vasculitis and organ damage.

Results: Features for 1212 SLE patients who were tested at least twice for ANCA are shown:

	Positive ANCA (127)	Negative ANCA (893)	P valve
Mean age (years)	38.64 ± 14.64	38.93 ± 13.83	0.823
Mean disease duration (years) at baseline	9.51 ± 9.25	8.46 ± 7.95	0.173
SLEDAI at baseline	5.80 ± 5.17	4.82 ± 5.00	0.04
Mean follow up from baseline to last date (years)	13.30 ± 7.08	7.36 ± 6.35	<0.001
Low complement at baseline	64 (50.4%)	338 (37.8%)	0.007
SLEDAI DNA positive at baseline	72 (56.7%)	405 (45.4%)	0.017
Vasculitis incidence	34 (26.8%)	97 (10.9%)	<0.001
SDI increase	81 (63.8%)	307 (34.4%)	<0.001

Regression analyses showed that patients with positive ANCA had more vasculitis (hazard ratio 1.67, CI 1.10-2.55). Furthermore, SDI increase after index was also more frequent in patients with positive ANCA (hazard ratio 1.39, CI 1.13-1.72) adjusted for patients' demographic/disease characteristics/treatment effects. Similar results were observed when analysing c-ANCA and p-ANCA separately.

Conclusion: Positive ANCA was detected on at least 2 occations in 10.5% of the lupus patients. Patients had two or more positive ANCA tests have higher risk of vasculitis and organ damage compared to ANCA negative patients.

Disclosure: A. Almutlaq, None; **M. Urowitz**, None; **J. Su**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5.

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Abstract Number: 2846

Application of a Novel Anti-Nuclear Antibody Multiplex Test Using Finger Stick and Venous Whole Blood in a Rheumatology Clinic – Demonstration of Feasibility

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Background/Purpose: Multiplex assays that measure anti-nuclear autoantibodies (ANA) in real time using whole blood were developed on the Maverick(TM) instrument (Genalyte, Inc., USA). Because the assay takes less than 10 minutes to complete, it would be possible to perform the test in a near patient setting in an outpatient clinic. The purpose of this study was to evaluate the feasibility of using this novel instrument to perform ANA 8 tests in the clinic and to compare those results to the same sample tested in Genalyte's CLIA registered laboratory.

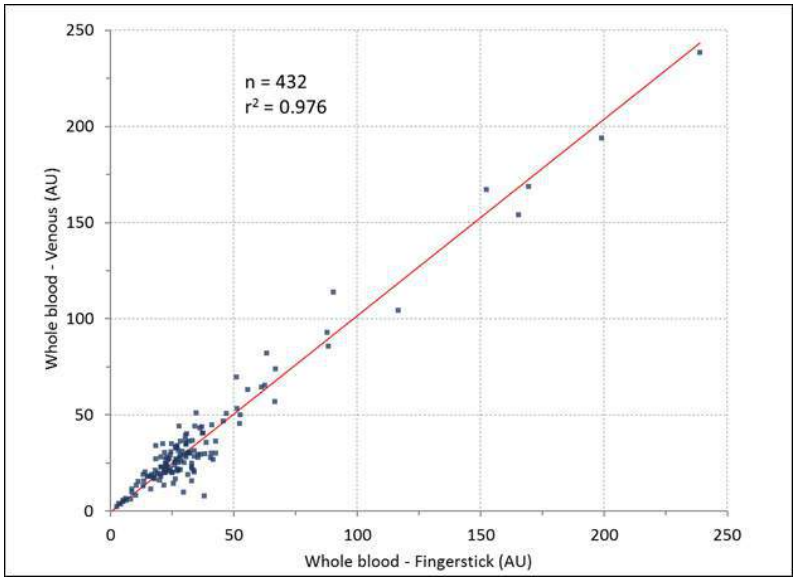
Methods: An Institutional Review Board (IRB) application was approved so that patients who were seeing a rheumatologist and were

going to be tested for ANA using the clinics' standard lab testing procedures could also volunteer to donate additional venous and/or finger-stick blood for further testing. Both the venous and finger-stick blood were immediately tested on the ANA 8 on the Maverick instrument in the clinic. This multiplex immunoassay measures autoantibodies to SS-A 60, SS-B, Sm, Sm/RNP, Scl-70, Jo-1, centromere B and dsDNA. The cutoff between negative and positive was standardized so that 40 AU and greater are positive. Even though results were available in real time, the protocol specified that the doctor would not be given results until the end of the study. 154 samples of venous blood were collected, tested on the Maverick and then returned to the Genalyte CLIA lab for processing into serum for comparison testing on the FIDIS Connective 10 (Theradiag, France). In addition, 54 samples of finger-stick blood were also collected for comparison testing.

Results: The results between whole blood finger stick (WBFS) and whole blood venous (WBVN) tested on the Maverick, and serum tested on the FIDIS for positive, negative and total agreement are shown in the table below.

	Positive Agreement Among 8 Markers	Negative Agreement Among 8 Markers	Total Agreement Among 8 Markers
WBFS vs WBVN	100%	98% to 100%	98% to 100%
WBFS vs FIDIS	100%	96% to 100%	96% to 100%
WBVN vs FIDIS	100%	97% to 100%	97% to 100%

The r^2 correlation between the values for all of the 8 ANA markers from finger stick (54 times 8 yields 432 results) versus venous whole blood is 0.98 as shown below.



Conclusion: This pilot study demonstrated the feasibility of performing multiplex ANA testing on whole blood in a near patient setting in an outpatient clinic. There is extremely high correlation for absolute value between venous blood and finger-stick blood, and between positive and negative results seen with whole blood on the Maverick and serum on the FIDIS. While further studies are required to quantify the impact such a diagnostic system might have on quality of care, there is potential for such a capability to improve timeliness of diagnosis, increase patient centricity and reduce overall healthcare resource utilization.

Disclosure: S. Reddy, None; **D. Copland Reddy**, Abbvie, 8; **R. Burlingame**, Genalyte, Inc., 3; **V. Nelson**, Genalyte, 3; **C. Buchner**, Genalyte, 3; **J. Stewart**, Genalyte, 3; **S. Mudumba**, Genalyte, 3; **J. Custodio**, Genalyte, 3; **J. Wang**, Genalyte, 3; **R. Romero**, Genalyte, 3; **A. Wu**, Genalyte, 3; **C. Cherwein**, Genalyte, 3; **S. Smith**, Genalyte, 3; **M. A. Gleeson**, Genalyte, 3.

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Abstract Number: 2847

Antibodies to Double Stranded DNA: Combined Standard ELISA and High-Salt ELISA Assays for the Detection of SLE Disease Activity

Laura Durcan, Jenna Thomason, Daniel Kuo and Mark H. Wener, University of Washington, Seattle, WA
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Background/Purpose: Serological markers in systemic lupus erythematosus (SLE) are crucial objective measures included in disease activity indices. Antibodies to double stranded DNA (anti-dsDNA) are included in composite outcomes, and changes in titers in response to therapy are frequently reported in clinical trials. Despite this, there are multiple disparate methods to evaluate anti-dsDNA. The classic Farr immunoassay for anti-dsDNA employs high concentrations of ammonium sulfate, and thus detects only high-avidity antibodies that bind in high ionic strength. The salt-resistant anti-dsDNA assay is considered highly specific for the diagnosis of SLE and reliable as a disease activity marker. In contrast, most ELISAs are performed with buffers of relatively low ionic strength, and thus detect both low-avidity and high-avidity antibodies. We screen for anti-dsDNA using the standard ELISA, and follow-up with a modified high salt ELISA which detects only higher avidity antibodies. Use of both forms of anti-dsDNA has not been evaluated as an additive tool for the assessment of disease activity. We aim to evaluate the sensitivity and specificity of anti-dsDNA measurement by standard and high-salt ELISA assays for the presence of SLE disease activity. We then wished to gauge the additive value of the high salt assay, performed as a reflex, in those with a positive ELISA evaluation, for the assessment of disease activity.

Methods: Patients fulfilling ACR classification criteria for SLE were identified in rheumatology clinic. Demographic data and disease activity (SLEDAI) were recorded. Anti-dsDNA titers were evaluated initially by standard ELISA. On identification of a positive ELISA, a high salt assay was performed reflexively. Active SLE was classified as SLEDAI ≥4. Those with disease activity were compared to those with quiescent disease. Statistical analysis involved the calculation of sensitivity, specificity, positive and negative predictive value of each assay.

Results: Seventy-seven patient encounters were evaluated (69 patients). The mean age was 41 (SD 14) years and 64 (92.8%) were female. The group was composed of mostly Caucasian patients, 39 (56.5%), 10 (14.5%) were African-American, 9 (13.0%) Asian and 8 (11.6%) were Hispanic. Forty-two (54.5%) assessments were of active disease by SLEDAI. Twenty-six (33.7%) had active renal disease. The sensitivity of antibodies to dsDNA for disease activity, by standard ELISA, was 90.5% with a specificity of 35.1%. The high salt avid assay resulted in a lower sensitivity (47.6%) and higher specificity, (78.4%). When considered in combination, given that both are performed, the sensitivity of our protocol was 90.5% with a specificity of 78.4% for disease activity. The correlation between the standard and high-salt anti-dsDNA assay, taking all cases where both was performed was moderate (r= 0.53), often with substantial discordance in results in individual patient specimens.

Conclusion: With an increasing focus on novel markers to evaluate SLE disease activity, there has been little priority placed on the optimal use of pre-existing laboratory tools. Here we demonstrate the clinical utility of a screening ELISA followed by a reflex high salt anti-dsDNA assay. We show high sensitivity and specificity for SLE disease activity through the use of a standard anti-dsDNA ELISA, and a high-salt modified assay that avoids the need for radioactivity and can be readily employed.

ASSAY		%	95% CI
Standard ELISA	Sensitivity	90.5	77.4-97.3
	Specificity	35.1	20.2-52.5
	Positive Predictive Value	61.3	48.1-73.6
	Negative Predictive Value	76.5	50.1-93.2
High Salt ELISA	Sensitivity	47.6	32.0-63.6
	Specificity	78. 4	61.8-90.2
	Positive Predictive Value	71.4	51.3-86.8
	Negative Predictive Value	56.9	42.3-70.7

Disclosure: L. Durcan, None; **J. Thomason**, None; **D. Kuo**, None; **M. H. Wener**, None.

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Abstract Number: 2848

Near Patient Anti-Nuclear Antibody Multiplex Testing Using Whole Blood for the Diagnosis of Connective Tissue Diseases in a Tertiary Care Center

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Background/Purpose: Detection of anti-nuclear antibodies for the diagnosis of connective tissue diseases (CTD) often requires complex algorithms to obtain conclusive results , including immunofluorescence on Hep2 cells, ELISA multiplex anlaysis and immunoblotting, which can delay the delivery of results to the physician and the patients. The Maverick™ Detection System (Genalyte, Inc. USA) performs multiplexed detection of autoantibody binding events by measuring the shift in wavelength of ring resonance as the antibodies bind to the antigens on the surface above the rings. The ANA 13 PRI Chips are functionalized with SSA/Ro-60, Ro-52, SS-B, Sm, RNP, PCNA, RiboP, dsDNA, nucleosome, Scl-70, Ku, Centromere B and Jo-1. Just 10 µL of whole blood is required and results are obtained in less than 15 minutes. The objectives of this study were to compare the results obtained in real time on the Maverick with those from the standard procedures in the lab, and to compare those results to the patient's diagnosis.

Methods: Whole blood from 205 consecutive patients followed-up between March and June 2016 at the Pitié-Salpétrière hospital (Paris, France) was analyzed on the ANA 13 PRI. 123 patients had systemic lupus erythematosus (SLE), 13 had Sjögren's syndrome, 10 had primary antiphospholid syndrome, 6 had ANCA associated vasculitis, 5 had Raynaud's phenomenon, 4 had rheumatoid arthritis, 2 had myositis and 1 systemic sclerosis. Other patients had symptoms that required the routine procedures for the diagnosis of CTD with final diagnosis different from CTD. Comparisons were made with results obtained on corresponding sera at the laboratory using IFA screening tests and confirmatory testing with FIDIS multiplex assays (THERADIAG) and when necessary Immunoblotting (D-TEK) or anti-DNA ELISA (DiaSorin), Farr assay and anti-nucleosome ELISA (Werfen).

Results: The Maverick Detection System showed excellent total, positive and negative percent agreement when compared to the final conclusion of the laboratory for Sm, Scl-70, Jo-1, SS-A/Ro 60, SS-B, Centromere, Ku antigens with total, positive and negative percent agreement above 95%, and for PCNA above 92 %. For RNP, total agreement was of 90%, positive was 100% and negative was 88.5%. Interestingly, 17 of 19 samples that were positive for RNP by Maverick but negative by the lab test, and all 8 that were positive for Sm by Maverick but negative by the lab test, were from patients diagnosed with SLE. For anti-nucleosome and anti-DNA the ANA 13 PRI displayed diagnostic performances close to commonly used ELISA systems. For Ro 52 and Ribosome P, the overall agreement and specificity were greater than 90%, but the sensitivity was lower. However, for all cases with false negative results for Ro52 and RiboP with the ANA13 PRI, other specific autoantibodies were present and detected with the ANA13 PRI. Therefore, no diagnosis of CTD would have been missed by using the ANA PRI 13.

Conclusion: The Maverick detection system, which uses whole blood as the matrix and gives results in under 15 minutes, offers a reliable rapid diagnosis solution for the search of autoantibodies in CTD.

Disclosure: M. Miyara, Genalyte inc, 5; **J. L. Charuel**, None; **S. Mudumba**, Genalyte Inc, 3; **A. Wu**, Genalyte, 3; **P. Ghillani-Dalbin**, None; **Z. Amoura**, None; **R. Burlingame**, Genalyte, Inc., 3; **L. Musset**, None.

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Abstract Number: 2849

Systemic Lupus Erythematosus Patients with Antibodies Against U1-

Ribonucleoprotein Exhibit a Specific Pattern of Disease Manifestations

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Background/Purpose: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the production of autoantibodies against nucleic acids and a variety of self-antigens. Recent work indicates that immune complexes containing anti-U1 Ribonucleoprotein (anti-RNP) can drive formation of neutrophil extracellular traps, which in turn can drive interferon-α production by plasmacytoid dendritic cells. (1) We hypothesized that patients with anti-RNP may be more likely to exhibit a specific pattern of SLE disease features, potentially implicating neutrophils in the pathogenesis of those features.

Methods: Clinical data from 160 patients enrolled in the FLARE cohort of SLE patients at Hospital for Special Surgery were reviewed in a retrospective fashion. All patients had been tested for anti-Ro, anti-La, anti-Sm, and anti-RNP at the time of enrollment, and patients were classified as being positive or negative for anti-RNP, whether alone or in combination with other autoantibodies. Each patient's record was reviewed and the presence or absence of a total of 90 disease manifestations and laboratory features at any point in their history were recorded. Differences in the incidence of various phenotypes in different groups were compared between groups using Chi square tests. P values were not adjusted for multiple comparisons in this exploratory analysis.

Results: We identified 83 patients who were positive for anti-RNP antibodies (anti-RNP+), and 77 patients who were anti-RNP negative (anti-RNP(-)). We identified several disease features that differed between anti-RNP+ and anti-RNP(-) patients (Table 1). Specifically, some features classically associated with mixed connective tissue disease were seen more commonly in the RNP+ patients, such as sclerodactyly and myositis. Additionally, a history of vasculitis or elevated serum globulin (>3.5g/dL) were observed more commonly in the anti-RNP+ group. In contrast, anti-RNP(-) patients were more likely to have had a history of immune thrombocytopenic purpura or thrombocytopenia. While there was no significant difference in the prevalence of nephritis overall between the groups, membranous (class V) nephritis was more common in the anti-RNP+ patients, while proliferative (class III/IV) nephritis was more common in the anti-RNP(-) patients.

Conclusion: We demonstrated several disease manifestations which were more likely to be occur in anti-RNP+ individuals, such as vasculitis and membranous nephritis, as well as some which were more likely in anti-RNP(-) patients, such as proliferative nephritis and thrombocytopenia. The role of neutrophil activation and anti-RNP antibodies in these specific disease manifestations merits further investigation. 1. Garcia-Romo, G.S. *et al*. Netting neutrophils are major inducers of type I IFN production in pediatric systemic lupus erythematosus. *Sci. Transl. Med.* **3**, 73ra20 (2011).

	RNP(-) n = 77	RNP(+) n = 83	Total n = 160	p value
Elevated total protein / IgG	15	45	60	0.00010751*
Myositis	1	9	10	0.01141204*
Sclerodactyly	0	6	6	0.01430588*
Vasculitis	8	22	30	0.01058714*
Avascular necrosis	10	13	23	0.67636863
Thrombocytosis	2	8	10	0.05777957
Thrombocytopenia / ITP	20	7	27	0.00701458*
Nephritis	36	53	89	0.08586625
Class III	7	4	11	0.06006046
Class IV	16	9	25	0.01430588*
No Class V (class III + class IV)	23	13	36	0.00684086*
Class III+V	5	11	16	0.60557662
Class IV+V	7	6	13	0.25421322
Isolated Class V	4	19	23	0.03266041*
Any Class V (Class V + (III+V) + (IV + V))	16	36	52	0.1576184

Disclosure: D. Fernandez, None; **M. Olferiev**, None; **L. Khalili**, None; **K. A. Kirou**, None; **M. K. Crow**, Medimmune, 5.

Abstract Number: 2850

Changes in Urinary Biomarker Levels Can Predict Treatment Responses in Lupus Nephritis

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Background/Purpose: The relapsing and remitting nature of lupus nephritis (LN) poses a challenge to clinicians who must balance the risk of long term kidney damage with the side effects of treatment. Management of this condition would be greatly aided by the identification of biomarkers that accurately reflect and predict treatment responses. We previously identified and validated a panel of urinary biomarkers that are specifically elevated in SLE patients with active LN as compared to active patients without LN or LN patients in remission. In this study we sought to determine whether changes in the levels of these urinary biomarkers predict treatment responses.

Methods: 21 SLE patients with biopsy-proven LN were followed longitudinally for a minimum of 2 years after treatment. Levels of 15 urinary biomarkers including Clusterin, Cystatin C, NGAL, PF4, vWF,sVCAM-1, GM-CSF, GRO, IL-15, IL-6, MCP-1, Adiponectin, PAI-1, MMP-7, and TIMP-1, were measured by Luminex. Patients were classified as having a complete response (n = 12), partial response (n=4), or treatment (Tx) failure (n=5) at 2 years following Tx, based upon previously established criteria. Urinary biomarker levels were considered abnormal if they were > 2 SD above the mean for 24 healthy controls. Data were analyzed using non-parametric statistics.

Results: At 3-6 months following treatment, the changes in biomarker levels from the first visit were not significantly different between complete responders and partial responders or Tx failures. However, at 1 year (11-17 months) following treatment, 5 urinary biomarkers, sVCAM-1, Adiponectin, IL-15, vWF, and MCP-1, demonstrated significantly different changes from baseline in complete responders as compared to Tx failures, with the majority of responders demonstrating improvement and the majority of Tx failures demonstrating worsening. Since urinary biomarker levels that were not corrected for urinary osmolality correlated best with clinical outcomes, subsequent analyses were done with the uncorrected values. The presence of a normal urinary Adiponectin by 11-17 months was the best predictor of a complete response, with 11 of 12 patients who normalized being complete responders and 1 a partial responder. Similar but slightly less discriminative results were obtained for the other 4 urinary biomarkers. Conversely, the presence of an abnormal urinary vWF at 11-17 months was the strongest predictor of an adverse outcome with 4 of 7 patients with abnormal levels being Tx failures. Notably, all patients that were Tx failures that had normal levels of urinary biomarkers at 11-17 months subsequently developed abnormal levels, whereas patients who were complete responders eventually normalized the majority of these five biomarkers. Partial responders demonstrated normalization with delayed kinetics. Comparison of changes in urinary biomarkers with changes in proteinuria in Tx Failures over time indicated that elevations in urinary biomarkers preceded elevations in proteinuria in some patients.

Conclusion: Measurement of urinary biomarkers can provide valuable insight into treatment responses in lupus nephritis.

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Abstract Number: 2851

An Antigen Microarray to Rule-out Systemic Lupus Erythematosus, the SLE-Key® Rule-out Test, Performs Well As an Aid in Clinical Practice

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Background/Purpose: The SLE-key® test to Rule Out lupus was developed by ImmunArray Ltd using serum samples of 246 SLE patients and 252 self-declared healthy controls. The test was validated to rule out SLE with 94% sensitivity and 75% specificity and a negative predictive value (NPV) of 93%[1]. Here we evaluate the performance of the SLE-key® test in aiding the management of suspected lupus patients in a large clinical practice.

Methods: We analyzed the SLE-Key® test results from 55 patients being evaluated and managed for SLE at the Rheumatology and Immunotherapy Center, in Franklin, WI. Serum samples were collected from individual subjects with informed consent and sent for testing at VERACIS (Richmond, VA), using the SLE-Key® iCHIP®[2] which contains ~200 antigens and detects profiles of IgG and IgM antibodies. We evaluated the 55 patients clinically using SLICC criteria, and we compared our clinical impression to the SLE-Key® test results. We also evaluated the impact of the test on our subsequent management decisions – terminating evaluation; further evaluation; or initiation of definitive SLE therapy.

Results:

Of the 55 patients tested, 24 were minimally symptomatic, 19 symptomatic patients fulfilled standard SLICC criteria and manifested scores of ≥4, and the remaining 12 patients were symptomatic but did not meet SLICC criteria and manifested a score <4 (Figure 1 shows a flowchart of the study).

The SLE-Key® test confirmed our clinical impression for 30 of the 55 patients (54.5%). SLE was definitively ruled out in 87.5% (21/24) of the minimally symptomatic patients who were assigned to "end of SLE evaluation" with no further follow up or laboratory testing. Of the 19 patients who fulfilled standard SLICC criteria and manifested ACR scores of ≥4, 17 were not ruled out by the SLE-Key® test. In 4 of these cases, clinical impression was revised to 'SLE' based on SLE-key® test results leading to accelerated initiation of therapy.

SLE-Key® test results contributed to a change in clinical diagnosis in 10 patients (18%); in 3 of the minimally symptomatic patients, we revised our diagnosis from "SLE" to "Not SLE" and no further evaluation was needed. In the remaining 7 symptomatic cases, (3 of whom manifested SLICC score of <4) we changed our diagnosis to SLE and accelerated time to therapy.

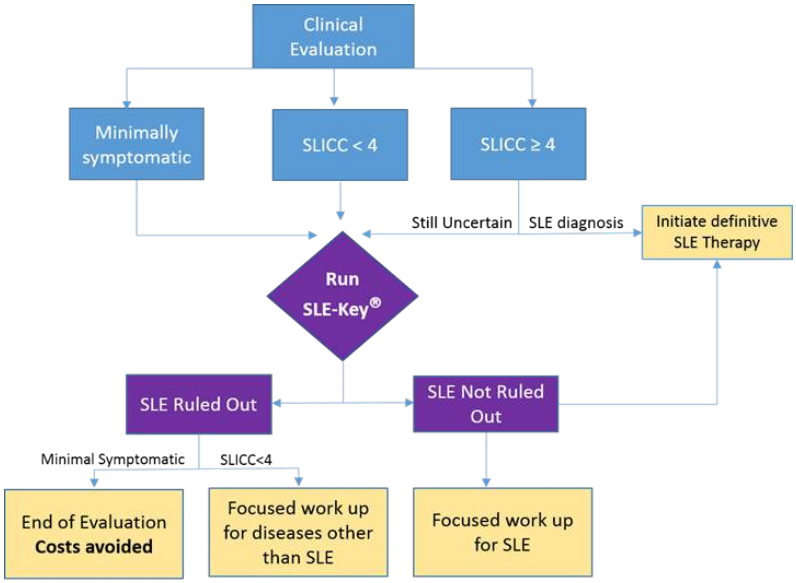
Conclusion: The SLE-key® rule out test provides a laboratory aid to improve the diagnostic and dispositive efficiency of a new clinical paradigm; thus saving undue concern, time and resources both to the patient and to the healthcare system. In 25/55 patients in this cohort, the SLE-key® test provided actionable clinical information, leading to termination of evaluation for SLE or initiation of therapy. Multi-center validation is warranted to further define the clinical advantages of this serologic test.

References:

[1]Putterman et al., Journal of Immunological Methods, 2016

[2]Fattal et al; Immunology, 2010

Figure 1:



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Abstract Number: 2852

Long Term Prognosis of Lupus Nephritis in the Afro-Caribbean Population of Martinique with Free Access to Healthcare

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Background/Purpose: In African-descent patients, lupus nephritis (LN) lead to a worse outcome than in Caucasians. Long term data are rare in countries where black populations have access to free healthcare. Here, we describe the long term prognosis of black Martinican patients with LN.

Methods: Population based, retrospective consultation of 1140 kidney biopsy provided by the pathology unit of the academic hospital of Martinique (French West Indies) from 2002 to 2015. 155 biopsies were related to SLE, concerning 126 patients. All patients diagnosed before 2013, followed a minimum of 24 month in Martinique (or death) after biopsy proven LN (ISN/RPS classification) were included. Complete remission (CR) was defined by no GFR decrease > 10%, no leucocyturia/hematuria and proteinuria ≤ 0.2 g/24h. Partial remission (PR) had the same definition except for proteinuria ≤ 0.5 g/24h. Renal flare flare was defined by an increase >1g/24h of proteinuria if CR, >2g/24h if PR, or a persistent increase >25% of creatinemia. Chronic renal failure (CRF) was defined by GFR<90ml/min/1.72m² (normal if above) and end stage renal disease (ESRD) by requiring chronic dialysis.

Results: 89 patients were included (women 93.3%), and 37 excluded. Mean (±SD) follow up times was 118.3 months (± 73.3). No patient was lost to follow-up. Median age at SLE diagnosis was 27 yo and 30 for LN. The initial mean proteinuria was 3.55g/d (range 0.6 to 27) and creatinemia 118.9 µmol/L (range 26 to 500). Eighteen percent (n=16) had antiphospholipid syndrome. LN was proliferative in 68/89 patients (76.4%): 17 were class III (19.1%), 22 class IV (24.7%), 18 class III+V (20.2%), 11 class IV+V (12.4%). 17 patients were Class V (19.1%), 3 class I (3.4%) and 1 class II (1.1%). Concerning proliferative LN, induction treatment was cyclophosphamide (CYC), mycophenolate mofetil (MMF) and azathioprine (AZA) in respectively 66.1%, 25%, 4.4%. MMF was used as maintenance treatment for 51 patients (75%), CYC and AZA for 5.9% each. All patients received steroids and 91% hydroxychloroquine. At one year, 65/89 had normal GFR (73%), 33 attain CR (37.1%), 9 PR (10.11%), 15 progress to CRF (16.8%), none to ESRD and 3 died (3.3%). During follow up, 23 patients experienced only one renal flare (26.1%), 8 two flares (9.1%) and 1 three flares (1.1%). 68 new biopsies were performed: in 13, class V (76.5%) turn into proliferative LN after a mean delay of 90.2 months. After a mean follow up of 118.4 months: 39/89 (43.8%) achieve CR, 7 (7.9%) PR, 20 (22.4%) progress to CRF, 14 (15.7%) to ESRD and 8 (9%) died. ESRD rates for all 89 patients were respectively at 5, 10 and 15 years : 4.29%, 19,57% and 46.8%**.** Mortality rates for all 89 patients were 5.7% at 5 years, 8.7% at 10, 12.5% at 15, and for proliferative LN patients respectively 7.5%, 12.9%, 17.4%.

Conclusion: Compared to other population based Afro-Caribbean study finding a 31 to 41% mortality rate at 5 years (Nossent et al., ARD 1993; Flower et al, Arthritis Care Res 2012), our data suggest a better prognosis mainly related in our opinion to free access to Healthcare.

Disclosure: A. Couturier, None; **V. Molinie**, None; **C. Cartou**, None; **S. ARFI**, None; **V. Emal-Aglae**, None; **K. Polomat**, None; **F. MOINET**, None; **G. JEAN BAPTISTE**, None; **C. Deligny**, None.

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Abstract Number: 2853

Neutrophilia in Systemic Lupus Erythematosus As a Potential Indicator of Disease Activity

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Session Time: 9:00AM-11:00AM

Background/Purpose: Neutrophilia and elevated neutrophil-to-lymphocyte ratio are being increasingly recognized as reliable markers of inflammation (and usually negative prognostic outcome) in scenarios as diverse as trauma, cancer, and autoimmune disease. While lymphopenia is well established as a marker of lupus activity, why and when lupus patients develop elevated neutrophil counts (neutrophilia) have not been comprehensively explored. Lupus neutrophils are known to produce interferons, release mitochondria, and expel neutrophil extracellular traps (NETs), all of which may be detrimental to the patient.

Methods: From a U.S. lupus cohort of more than 800 patients, we randomly selected 75 patients for a pilot study. Neutrophilia was defined as absolute neutrophil count higher than the upper limit of normal for the institution's laboratory, which was 7.2-7.5 K/µl, depending on the era. Charts were evaluated by two independent reviewers, and each episode was assigned to one of four categories: infection, corticosteroid burst, pregnancy, or unknown. All patients met American College of Rheumatology classification criteria for systemic lupus erythematosus.

Results: In characterizing 75 lupus patients, we identified 2,892 neutrophil measurements over a 20-year period (2001-2016). The median number of neutrophil measurements per patient was 22 (range 2 to 279). Of the 75 patients, 27 patients had no documented episodes of neutrophilia (median number of tests 8, range 2 to 89). We identified 227 unique episodes of neutrophilia (separated by at least 4 weeks, and not part of a continuous event such as an extended hospitalization). Of the 227 episodes of neutrophilia, 26 fell between 7 and 8 K/µl; 72 between 8 and 9; 36 between 9 and 10; 85 between 10 and 20; and 8 between 20 and 30. Of the 227 episodes, 41 were attributed to infection (median neutrophil count 11.2 K/µl), 79 to corticosteroid burst (median neutrophil count 10.8), and 11 to

pregnancy (median neutrophil count 9.5). The most common infections causing neutrophilia were pneumonia and urinary tract infections. 96 cases of neutrophilia (median neutrophil count 8.6) could not be attributed to any of the aforementioned explanations, and we considered that they might associate with heightened disease activity.

Conclusion: Neutrophilia in lupus patients is explained by infection, corticosteroid burst, or pregnancy 58% of the time. In the remaining cases, the explanation is not readily apparent, and analysis is underway to assess the possible contribution of disease activity (preliminary analysis is pointing away from a correlation). These unexplained neutrophilia cases did seem to cluster in a relatively small number of patients, suggesting that there may be particular lupus phenotypes that correlate with neutrophil elevations; analysis is underway in the larger cohort to define those phenotypes. The next phase of this work should also seek to correlate neutrophil counts with not just traditional markers of disease activity, but also novel readouts such as circulating NETs.

Disclosure: E. E. Lewis, None; **W. J. McCune**, None; **J. S. Knight**, None.

Abstract Number: 2854

Laboratory and Demographic Longitudinal Profile of a Large Cohort of Individuals Presenting with the ANA Nuclear Dense Fine Speckled Immunofluorescence Pattern

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Background/Purpose: The nuclear dense fine speckled (DFS) pattern observed in the ANA assay on HEp-2 cells is strongly associated with autoantibodies to the 70/75kD lens epithelium derived growth factor (LEDGF). Anti-DFS70/LEDGFp75 antibodies are rarely seen as the only autoantibody in individuals with systemic autoimmune rheumatic disease (SARD). Instead, they occur in high titer in a heterogeneous array of non-SARD inflammatory and non-inflammatory diseases, and in 1-9% of the general population. In contrast, the nuclear homogeneous (HO) and coarse speckled (CS) patterns are regularly caused by autoantibodies strongly associated SARD. It is intriguing to investigate the clinical and immunological significance of this peculiar autoimmune response. This study aimed to describe the temporal behavior of DFS reactivity and to compare the associated demographic and laboratory features with those observed in patients the HO or CS patterns and in individuals with non-reagent (NR) ANA.

Methods: We conducted a retrospective analysis of laboratory and demographic associations of the DFS pattern over an 8-year period (Jan/2006 to Dec/2013) using the databank of a large clinical laboratory (average 12,000 ANA/month). We considered only records containing at least one ANA test (NR, DFS, HO or CS patterns) and at least one of the following tests: hemoglobin, CRP, ESR, ferritin, albumin, liver enzymes, glucose, serum complement components, and white/red blood cell count.

Results: 254,840 records were eligible for analysis: DFS (7.1%), HO (0.8%), CS (0.7%), NR (91.4%) The DFS pattern was associated with younger age and male gender, comparing to HO and NR results. Individuals with the DFS pattern had lower frequency of abnormal results in most laboratory parameters in comparison to those with HO or CS patterns, and closely resembled individuals with no ANA reactivity (Table 1). Longitudinal analysis showed that DFS pattern is rather stable along the years, maintaining high titer and rarely changing to other patterns or to non-reagent ANA (Table 2). **Table 1 – Age, gender and frequency of abnormal and normal results for several laboratory parameters according to the ANA pattern**

Studied Variable		ANA PATTERN			
		DFS	HO	CS	NR
Number of cases (%)		17,994 (7.1)	2,115 (0.8)	1,798 (0.7)	232,933 (91.4)
Demographic Data	Male (%)	15.1	11.1*	7.7*	25.8*
	Age (years)	40.6±14.4	44.6±16.3*	40.9±14.3	44.7±16.4*
Hb, RBC & WBC	Hb (%↓)	9.7	27.9*	25.4*	10.1
	Total Leucocytes (%↓)	2.4	13.1*	17.6*	2.3
	Neutrophils (%↓)	3.5	10.4*	14.2*	3.9*
	Eosinophils (%↓)	8.1	20.8*	25.1*	7.3
	Monocytes (%↓)	7.2	20.1*	8.5	6.5*
	Lymphocytes (%↓)	1.1	12.8*	18.9*	1.2
Inflammatory Markers	CRP (%↑)	35.8	57.1*	45.6*	34.8
	ESR (%↑)	65.9	85.5*	90.0*	68.7*
	Ferritin (%↑)	18.3	36.3*	34.5*	27.7*
Thyroid Hormones	TSH (%↑)	8.0	14.1*	16.1	7.4
	Free T4 (%↑)	10.1	14.8	11.6	12.2*
Cholesterol	Total (%↑)	14.7	12.3	9.2	16.7*
	HDL (% normal)	89.4	80.6*	77.5*	86.4*
	VLDL (% normal)	82.7	76.5	83.1	78.7*
Liver Markers	AST (% normal)	93.4	86.7*	84.6*	91.6*
	ALT (% normal)	86.1	82.8	84.2	83.9*
Other Markers	Glycaemia (%↑)	13.1	15.2	10.2	18.6*
	Albumin (%↓)	2.3	15.9*	7.2*	3.8*
Complement System Proteins	CH50 (% normal)	86.7	60.6*	72.6*	86.7
	C2 (% normal)	94.8	77.0*	85.2	94.8
	C3 (%↓)	1.2	22.9*	11.4*	1.4
	C4 (%↓)	0.3	18.0*	7.8*	0.8
Globulins	Gamma globulins (%↑)	1.9	19.5*	33.9*	2.1
	IgG (%↑)	11.8	36.5*	84.6*	13.2

(%↓) and (%↑): relative frequency of individuals with abnormally low and abnormally high values, respectively; *groups differing from DFS at *p<0.001* **Table 2 - Frequency of temporal changes in ANA pattern and titer in patients presenting positive ANA with DFS, HO and CS patterns**

Studied Variable		ANA RESULT		
		DFS	Ho	CS
Positive/negative	**Change - n (%)**	285 (5.8)	12 (2.2)*	3 (0.8)*
stability	**No Change - n (%)**	4,602 (94.2)	545 (97.8)	375 (99.2)
Pattern stability	**Change - n (%)**	1,130 (23.1)	268 (48.1)*	87 (23.0)
	No Change - n (%)	3,757 (76.9)	289 (51.9)	291 (77.0)
Titer Stability**	**Change - n (%)**	269 (7.6)	10 (3.6)	5 (1.7)*
	No Change - n (%)	3,293 (92.4)	267 (96.4)	283 (98.3)

* significantly different from DFS at *p<0.001* ** *only for cases with no change in pattern and no change in the reagent status*

Conclusion: The ANA DFS pattern represents a temporally stable humoral response, with a laboratory profile closely resembling that of individuals with non-reagent ANA and definitely distinct from those with HO or CS ANA reactivity, especially regarding inflammatory markers, serum complement components, and red/white blood cell counts.

Disclosure: A. Mathias, None; **A. Dellavance**, None; **J. Sá**, None; **F. Muramoto**, None; **V. Marvulle**, None; **L. E. C. Andrade**, None.

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Abstract Number: 2855

The Long-Term Clinical Outcomes of Lupus Nephritis

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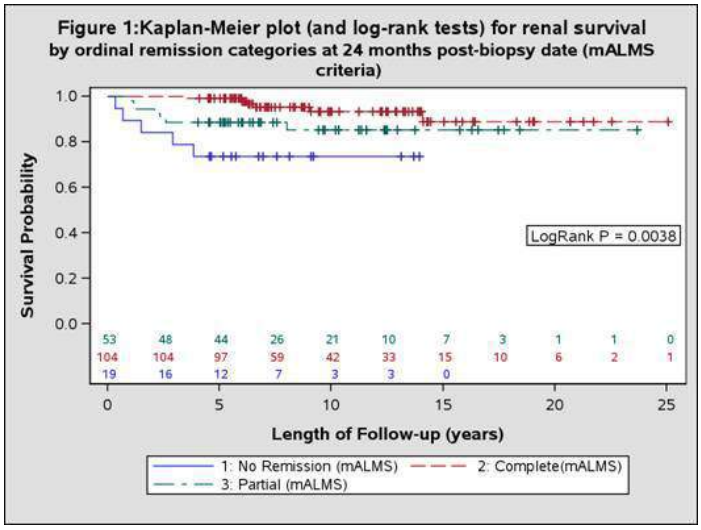
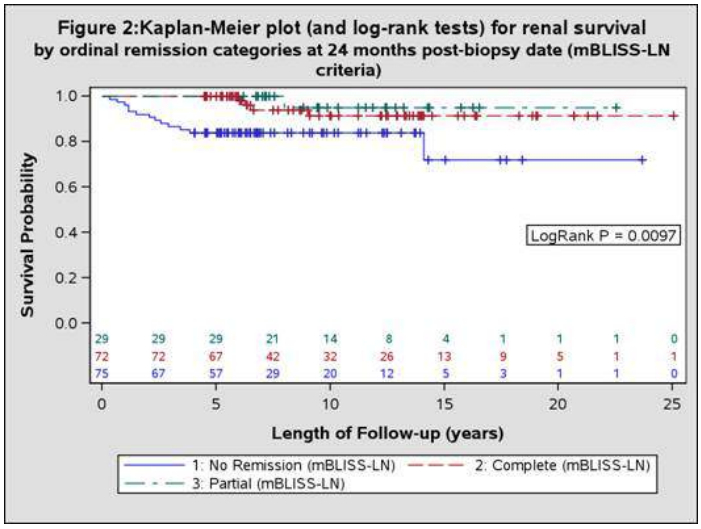
Background/Purpose: Clinical trials in lupus nephritis have often been designed to demonstrate renal response (or remission) following therapy based on categorical remission endpoints (often no remission, partial and complete) derived from laboratory measures of renal function and activity. The clinical relevance of these remission categories has been questioned. The primary objective of this study (WEUKBRE6068) was to compare long-term renal survival in patients with complete (CR), partial (PR) or no remission, as defined by criteria used in the Aspreva Lupus Management Study (ALMS) (NCT00377637) and Belimumab International Lupus Nephritis Study (BLISS-LN) (NCT01639339) with the modification of excluding urinary sediments (mBLISS-LN and mALMS), assessed at 24 months following positive lupus nephritis biopsy.

Methods: A retrospective analysis of the prospective Hopkins Lupus Cohort was conducted. Eligible patients had systemic lupus erythematosus (SLE) per revised American College of Rheumatology (ACR) or Systemic Lupus International Collaborating Clinics (SLICC) criteria plus biopsy record of ISN class III, IV, V or mixed lupus glomerulonephritis. The primary endpoint was renal survival (survival without end-stage renal disease (ESRD) or mortality). The primary exposure was remission status (CR, PR or no remission) by mBLISS-LN and mALMS criteria at 24 months post biopsy date. Survival analysis (Kaplan-Meier plots with log-rank test and Cox Proportional Hazards regression) was used to describe subsequent event rates and assess the association between renal survival and remission status at 24 months.

Results: We identified 176 SLE patients with lupus nephritis. At 24 months post biopsy date, more patients met mALMS remission criteria (CR = 59.1%, PR = 30.1%) than met mBLISS-LN criteria (CR = 40.9%, PR = 16.5%). During subsequent follow-up, 18 patients developed ESRD or died. The Kaplan-Meier plots suggested patients with no remission at 24 months post biopsy date were more likely than those with PR or CR to develop the outcome by both mALMS (p=0.0038) (Figure 1) and mBLISS-LN (p=0.0097) (Figure 2) criteria. Based on Cox regression models adjusted for key confounders, those in CR by both mBLISS-LN (HR 0.254, p=0.0176) and mALMS criteria (HR 0.228,p=0.0246) were significantly less likely to experience ESRD/mortality than those not in remission. Similarly, those in PR were less likely to experience ESRD/mortality (mBLISS-LN HR 0.141, p=0.0599; mALMS HR 0.575,p=0.3727)

Conclusion: Renal remission status at 24 months following lupus nephritis is associated with long-term renal survival.





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Serum C5a Is Elevated in Lupus Nephritis and in Neuropsychiatric Systemic Lupus Erythematosus through Different Mechanisms

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Session Time: 9:00AM-11:00AM

Background/Purpose: Neuropsychiatric manifestation in systemic lupus erythematosus (NPSLE) is one of the most serious complications of the disease. We have recently demonstrated that the breakdown of blood brain barrier (BBB) plays a crucial role in the development of diffuse psychiatric/neuropsychological manifestations (diffuse NPSLE), allowing influx of neuron-reactive autoantibodies from systemic circulation into the central nervous system. Notably, C5a, a split product of C5, has been recently shown to cause BBB damages, as evidenced by the decreased expression of barrier regulating proteins, such as claudin-5 and occludin. However, the relationship between serum C5a and BBB damages in NPSLE has not been explored. On the other hand, although association of C5a with some forms of lupus nephritis (LN) has been implicated, the involvement of C5a in LN has not been examined. The present study therefore explored the levels of C5a in sera from patients with NPSLE and LN.

Methods: Serum specimens were obtained from 29 patients with NPSLE including 18 patients with diffuse NPSLE and 9 patients with neurologic syndromes (focal NPSLE), 25 patients with LN, 26 patients without NPSLE or LN (SLE alone), and from 21 healthy individuals. Cerebrospinal fluid (CSF) specimens were obtained from 29 patients with NPSLE on the same day of the collection of serum specimens. The levels of C5a, C5, C3 and C4 were measured by ELISA. The BBB function was evaluated by CSF /serum albumin ratio (Q albumin).

Results: Serum C5a was significantly increased in 80 SLE patients compared with that in healthy individuals. Serum C5a was significantly elevated in NPSLE as well as in LN compared with that in SLE alone, whereas there were no significant differences in serum C5 among these 3 groups. Serum C4, but not serum C3, was significantly lower in LN than that in NPSLE, indicating the activation

of complement classical pathway in LN, but not in NPSLE. CH50 appeared to be also lower in LN compared with that in NPSLE. Q albumin was significantly elevated in diffuse NPSLE compared with that in focal NPSLE, whereas there were no significant differences in CSF C5a and in serum C5a between these 2 groups. Of note, both CSF C5 and CSF C5a were significantly correlated with Q albumin, whereas serum C5a, but not serum C5, was inversely correlated with Q albumin in NPSLE patients (Figure).

Conclusion: These results have disclosed that serum C5a was elevated in NPSLE as well as in LN through different mechanisms. Moreover, the data indicate that CSF C5a and C5 were elevated in NPSLE due to BBB damages. Finally, inverse correlation between serum C5a and Q albumin suggest that C5a might be consumed during the process of BBB damages.

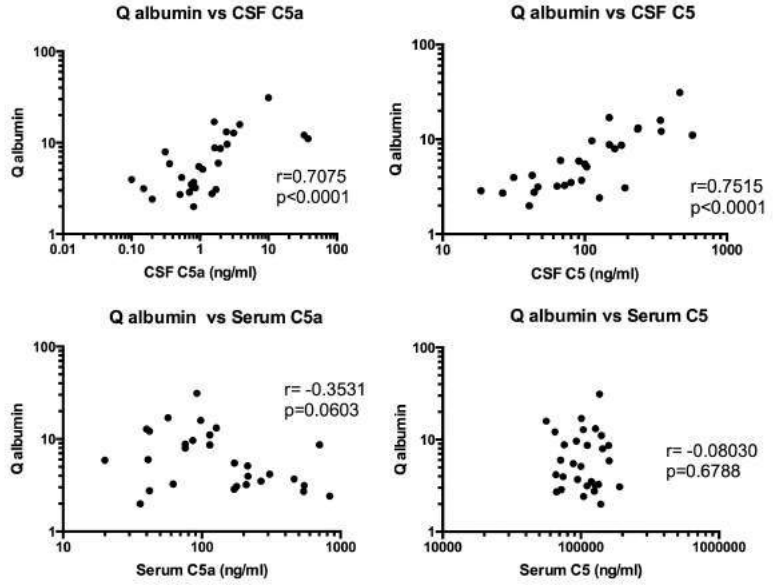

Figure Relationship of blood brain barrier integrity with C5a or C5 in cerebrospinal fluid (CSF) or in serum in NPSLE.

Disclosure: Y. Sakuma, None; **T. Nagai**, None; **T. Yoshio**, None; **S. Hirohata**, None.

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Abstract Number: 2857

Results from a Phase 0 Longitudinal Clinical Trial in Cutaneous Lupus Erythematosus: Analysis of the Type I IFN Signature in the Skin and Blood and Its Relationship with Disease Activity Scores and Autoantibody Profiles

Jessica Schreiter[1], Jarrat Jordan[1], Matteo Cesaroni[1], Marc Chevrier[2], Alexa Piantone[3], Ian Gourley[3], Jacqueline Benson[1] and Takahiro Sato[1], [1]Estrela Lupus Venture, Janssen Research and Development, LLC., Spring House, PA, [2]Janssen Research and Development, LLC, Collegeville, PA, [3]Immunology Translational Medicine, Janssen Pharmaceutical Research and Development, LLC, Spring House, PA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Type I IFN (IFN-I)-regulated gene expression is known to be elevated in blood and skin lesions of patients with two different forms of cutaneous lupus erythematosus (CLE): subacute cutaneous lupus erythematosus (SCLE) and discoid lupus erythematosus (DLE). A positive correlation between Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) scores of these patients and blood IFN-I signature has also been described. Using samples from a phase 0 longitudinal clinical study, we

examined the relationship between IFN-I signatures in skin and blood, total CLASI scores, and autoantibody (autoAb) profiles at weeks 1 and 12 of the study.

Methods: Under informed consent, 37 subjects with DLE and 16 subjects with SCLE were recruited for study participation. 18 of the DLE subjects and 12 of the SCLE subjects also had concomitant SLE. Total CLASI scores for each DLE and SCLE subject were collected at weeks 1 and 12 of the study. Lesional and non-lesional skin biopsies were collected at week 1 and an additional biopsy was collected at week 12 from the same region where the lesional biopsy had been collected. Blood RNA PAXgene tubes along with serum were also collected at each time point. In addition, serum, blood RNA PAXgene, and skin biopsies were collected from healthy volunteers at week 1 only. RNA was extracted from both blood and skin and an IFN-I gene expression score was computed using the following genes: IFI44, IFI44L, IFI27, and RSAD2. Serum was profiled for autoAb specificities at both time points using the ProtoArray® platform.

Results: Gene expression in the skin revealed that the IFN-I score was significantly elevated in both lesional and non-lesional skin biopsies from both the SCLE and DLE subgroups when compared to healthy control biopsies. There was no significant difference between skin IFN-I scores in SCLE versus DLE regardless of concomitant SLE and skin IFN-I scores were strongly correlated to blood IFN-I scores in all subsets with or without SLE. Additionally, a positive correlation between skin IFN-I scores and CLASI scores was noted. Many individuals exhibited a decrease in CLASI and skin IFN signature from week 1 to week 12, although a significant correlation was not found across the cohort. AutoAb signal was longitudinally stable in all subgroups; however, only subjects with concomitant SLE had significantly elevated autoAb signals when compared to healthy controls.

Conclusion: Our findings support previous reports of CLASI correlation with blood IFN-induced gene expression and elevation of autoAb signal in SLE subjects. To our knowledge, however, we are the first to show that skin and blood IFN signatures correlate in the same patient irrespective of their subclass of CLE or if they have concomitant SLE. We also show that IFN-I signature is not only elevated in lesional skin of CLE patients, but also in the apparently healthy, non-lesional skin. Additionally, we found that despite the presence of a systemic blood IFN-I signature in CLE subjects with or without SLE, there was no elevation of autoAbs in the non-SLE CLE subjects.

Disclosure: J. Schreiter, Janssen Research and Development, LLC, 3,Janssen Research and Development, LLC, 1; **J. Jordan**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **M. Cesaroni**, Janssen Research and Development, LLC, 3; **M. Chevrier**, Janssen Research and Development, LLC., 1,Janssen Research and Development, LLC., 3; **A. Piantone**, Janssen Research and Development, LLC, 3; **I. Gourley**, Janssen Research and Development, LLC, 3; **J. Benson**, Janssen Research and Development, LLC., 3,Janssen Research and Development, LLC., 1; **T. Sato**, Janssen Research and Development, LLC, 3.

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Abstract Number: 2858

Urinary PF4 and E-Selectin As Novel Biomarkers for Disease Activity and Renal Damage in Lupus Nephritis

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Background/Purpose: Lupus nephritis (LN) is the leading cause of morbidity and mortality in systemic lupus erythematosus (SLE). The objective of this study is to validate urine platelet factor 4 (PF4) and E-selectin as novel biomarkers for disease activity and renal damage in LN. Both markers were selected based on recently completed proteomic screens of urine from LN patients.

Methods: 113 biopsy-proven LN patients (89 active LN and 24 inactive LN), 45 chronic kidney disease (CKD) patients and 41 healthy controls were recruited for enzyme-linked immunosorbent assay (ELISA) testing of urine PF4 and E-selectin levels. Urine biomarker

levels were normalized by urine creatinine. Disease activity was assessed by the SELENA-SLEDAI. Renal disease activity was assessed by Systemic Lupus International Collaborating Clinics Renal Activity Score (SLICC-RAS) and R-SLEDAI (Total score of the four kidney-related parameters).

Results: Urinary PF4 and E-selectin levels were significantly increased in active LN patients (PF4 [median (Q1-Q3)]: 0.272 (0.0675-1.432) ng/mg; E-selectin: 30.84 (0-76.32) pg/mg) compared to inactive LN (PF4: 0.0225 (0-0.09325) ng/mg, P<0.001; E-selectin: 0 (0-0) pg/mg, P<0.001), CKD (PF4: 0.062 (0-0.18) ng/mg, P<0.001; E-selectin: 0 (0-36.16) pg/mg, P=0.046), and healthy controls (PF4: 0.005 (0-0.017) ng/mg, P<0.001; E-selectin: 0 (0-0) pg/mg, P<0.001), respectively. Urinary PF4 and E-selectin levels were able to discriminate LN patients from healthy controls (Area Under the Curve (AUC) for PF4: 0.84 (*P*<0.001); AUC for E-selectin: 0.77 (*P*<0.001)) as well as active LN from inactive LN (AUC for PF4: 0.79 (*P*<0.001); AUC for E-selectin: 0.80 (*P*<0.001)). The sensitivity and specificity of urinary PF4 (sensitivity: 0.75; specificity: 0.78) in detecting LN activity was higher than that of positive anti-dsDNA (sensitivity: 0.38; specificity: 0.67) or decreased C3/C4 (sensitivity: 0.56; specificity: 0.63). Urinary E-selectin (sensitivity: 0.92; specificity: 0.65) was more sensitive than anti-dsDNA or C3/C4, but less specific than anti-dsDNA in detecting LN activity. A significant positive correlation was noted between urine PF4 and E-selectin levels with SLEDAI (PF4: ρ=0.55, *P*<0.001; E-selectin: ρ=0.30, *P*=0.001), R-SLEDAI (PF4: ρ=0.55, *P*<0.001; E-selectin: ρ=0.41, *P*<0.001), SLICC (PF4: ρ=0.45, *P*<0.001; E-selectin: ρ=0.59, *P*<0.001), urine protein-creatinine ratio (PF4: ρ=0.39, *P*<0.001; E-selectin: ρ=0.58, *P*<0.001) respectively. PF4 also significantly correlated with serum creatinine levels (ρ=0.21, *P*=0.03). Importantly, in a urine/biopsy concurrent cohort, urine PF4 was good at discriminating type IV LN from type II/III LN with an AUC of 0.73 (*P*=0.02). Urinary E-selectin was able to discriminate type II LN from type III/IV LN (AUC: 0.84, *P*=0.03) and type II/III LN from type IV LN (AUC: 0.80, *P*=0.002).

Conclusion: Urinary PF4 and E-selectin are potential diagnostic biomarkers of disease activity in lupus nephritis and proliferative renal pathology. The performance of urinary PF4 and E-selectin in monitoring lupus nephritis should be further validated in larger longitudinal cohorts.

Disclosure: H. Ding, None; **L. Qin**, None; **S. Stanley**, None; **R. Saxena**, None; **C. Mohan**, None.

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Abstract Number: 2859

Health-Related Interference of Social Activities and Suicidal Ideation in Systemic Lupus Erythematosus: Georgians Organized Against Lupus Cohort

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SESSION INFORMATION

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Social integration has been found to be a protective factor from suicide-related ideation even after adjusting for mental health predictors. This is especially salient for people with systemic lupus erythematosus (SLE) who may have a wide-range of physical and emotional problems interfering with social activities. Previous cross-sectional data suggested an association between perceived inadequacy of social support and suicidal ideation (SI). To further delve into this concept, we aimed to examine whether 1-year change of health-related interference with social activities would be associated with 1-year increase in SI.

Methods: We examined longitudinal data from the GOAL Cohort, a large population-based cohort of patients with documented SLE from metropolitan Atlanta, Georgia. Since 2011, participants respond annually to a variety of validated self-administered health outcomes. We used the social activities interference question from the SF-12 Health Survey to assess 1-year change in the amount of time physical health or emotional problems hindered social activities. One question from the Patient Health Questionnaire-9 was used to assess 1-year change in the frequency of SI (4-point Likert scale ranging from “not at all” to “nearly every day”). A multivariable logistic regression was used to examine the effect of higher interference of social activities on increased SI, after controlling for demographics and disease-related factors.

Results: Among the 715 SLE participants studied (94% women, 79% Black, 38% uninsured or underinsured; mean age 48) 98

participants endorsed SI at either baseline, Year 1 or both time points. Multivariate analysis of those 98 participants showed that the odds ratio of increased SI at Year 1 was 6.8 for participants who endorsed higher interference with social activities, compared to those who had lower interference. No significant association with increased SI was found when we compared same with lower level of interference with social activities.

Table 1. Predictors of Increased Suicidal Ideation (SI) Over Time in SLE*

Characteristic	OR (95%CI)	P value
Social Activity Interference Change** (ref: Lower)		
Same	1.97 (0.57-6.79)	0.28
Higher	6.77 (1.62-28.24)	0.029
Gender (male)	0.66 (0.06-7.39)	0.74
Race (Black)	7.32 (1.17-45.69)	0.033
Age at survey, per 5 years ↑	0.99 (0.75-1.30)	0.94
Disease duration, per 5 years ↑	1.21 (0.88-1.67)	0.25
Disease activity score, per 1 unit ↑	1.10 (1.01-1.20)	0.026
MCS, per unit ↓	0.94 (0.88-1.01)	0.11
PCS, per unit ↓	0.96 (0.89-1.04)	0.32
Education (less than college)	0.90 (0.25-3.30)	0.87
Un-married	0.41 (0.13-1.30)	0.13
No medical insurance or under insured	0.95 (0.29-3.11)	0.93
Severe organ damage	1.03 (0.28-3.70)	0.97

*Defines as increased frequency of SI over 1 year of follow up, compared to those who remained the same or had lower SI frequency
**Change assessed over 1 year of follow-up

Conclusion: In a population-based SLE cohort with large numbers of African American subjects there is a consistent proportion contemplating suicide in each annual survey. Findings indicate that health-related interference in social activities is a significant contributing factor of SI. This association is particularly significant when there is increasing interference with social activities, which in turn increases the risk of more frequent SI. Social activities can be a resource to enhance social integration. Further development and recognition of social support resources to which SLE patients can be referred are warranted, especially in socioeconomically disadvantaged communities.

Disclosure: C. M. Dunlop-Thomas, None; **G. Bao**, None; **S. S. Lim**, None; **C. Drenkard**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/health-related-interference-of-social-activities-and-suicidal-ideation-in-systemic-lupus-erythematosus-georgians-organized-against-lupus-cohort

Abstract Number: 2860

Exercise Significantly Improves Cardiorespiratory Fitness and Reduces Disease-Related Fatigue without Adverse Effects on Disease Activity in Systemic Lupus Erythematosus: a Systematic Review with Meta-Analysis

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment - ARHP Poster

Session Type: ACR Poster Session C

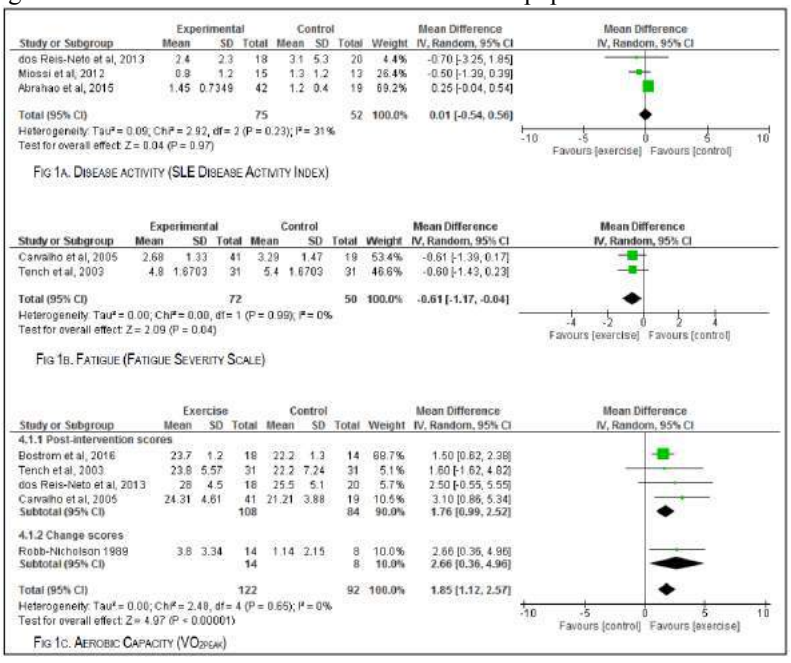
Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematous (SLE) associates with accelerated mortality, frequently attributable to cardiovascular (CV) causes, which is not fully explained by traditional CV risk factors. Individuals with SLE are commonly sedentary with many percieved barriers to exercise. Physical inactivity likely contributes to the burden of CV risk and may also be a significant factor in co-morbid chronic fatigue, poor sleep and fibromyalgia. This meta-analysis evaluates whether exercise has a deleterious effect on disease activity in SLE, and assesses the impact of exercise on cardiorespiratory fitness and fatigue.

Methods: A systematic review and meta-analysis was conducted, including quasi-randomised and randomised controlled trials in SLE comparing at least one exercise group to controls. Studies were retrieved by searching MEDLINE/PubMed, EMBASE, PEDro, AMED, CINAHL and The Cochrane Central Register of Controlled Trials for keywords and medical subject headings relating SLE and exercise. Relevant conference abstracts and reference lists of included studies were manually searched. Two reviewers independently determined study eligibility and assessed risk of bias (Cochrane Risk of Bias tool). Data were extracted using a standardised template. Random-effects meta-analyses were used to pool extracted data as mean differences (MD). Heterogeneity was evaluated with Chi^2 test and I^2, with p-values < .05 considered significant.

Results: The search strategy produced 2980 records. Titles and abstracts screening identified 30 full-texts for eligibility appraisal. Of these, seven were suitable for inclusion in the meta-analyses. Studies included 178 participants and 125 controls; mean age ranged from 31.2 to 52.9 years, and disease duration from 2.5 to 17.9 years. Median (IQR) duration of the interventions was 12 (0) weeks. All interventions included aerobic components, and three also included strength training. There was a high risk of bias relating to blinding of participants and personnel; remaining domains were largely under-reported, with the overall risk of bias unclear. Fig. 1 summarises meta-analyses results. Disease activity was not significantly changed following exercise interventions (MD 0.01; 95% CI, -0.54 to 0.56). Fatigue (MD 0.61; 95% CI, 0.04 to 1.17) and aerobic capacity (MD 1.85 ml/kg/min; 95% CI, 1.12 to 2.57) were significantly improved.

Conclusion: This meta-analysis demonstrates that exercise significantly improves cardiorespiratory fitness and disease-related fatigue in individuals with SLE, without adversely affecting disease activity. This review suggests that exercise may be safely prescribed in this population. Longitudinal studies examining the effects of exercise on CV risk factors in this population are recommended based on the promising findings of this meta-analysis.



Disclosure: T. O'Dwyer, None; **L. Durcan**, None; **F. Wilson**, None.

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Abstract Number: 2861

Proportions of Circulating Follicular Helper T Cells and Complement Levels, White Blood Cell Counts, and Skin Manifestations in Patients with Active Systemic Lupus Erythematosus

Jun Kikuchi[1], Masaru Takeshita[1], Katsuya Suzuki[2], Yoshiaki Kassai[3], Takahiro Miyazaki[3] and Tsutomu Takeuchi[2], [1]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan, [2]Keio University School of Medcine, Division of Rheumatology, Department of Internal Medicine, Tokyo, Japan, [3]Inflammation Drug Discovery Unit, Pharmaceutical Research Division, Takeda Pharmaceutical Company Ltd., Kanagawa, Japan

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis - Poster II

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: Although circulating B cells and T cells, including follicular helper T (Tfh) cells, are reported to be involved in systemic lupus erythematosus (SLE) [1,2)], relations between subpopulations and clinical manifestations have not been clearly determined. The aim of this study was to identify abnormalities of the subpopulations in correlation with clinical manifestations in active SLE patients.

Methods: Subsets of peripheral immune cells were quantified using a whole blood flow cytometry in total 51 subjects including 13 active SLE patients who all fulfilled ACR classification criteria and 38 normal healthy controls (NHCs). We compared the proportions of the subsets in SLE patients with those in NHCs and analyzed relations with the clinical parameters.

Results: Mean age of the SLE patients and NHCs was 44.1 and 39.8 years, respectively. All candidates were female. Mean SLE Disease Activity Index was 12. Blood samples of all SLE patients were collected before they received induction therapy. Eight patients were treatment-naïve, while the other patients had treatment with low-dose prednisolone and/or immunosuppressants. Among CD19+ B cells, the proportions of CD38-IgD+ B cells, Bm1 and CD38+IgD+ B cells (Bm2 cells), were lower in SLE patients than in NHCs ($p=0.003$ and $p=0.001$). The proportions of CD38++IgD- B cells (Bm3+Bm4 cells) and CD38+CD24- plasmablasts were higher in SLE patients (both $p<0.001$). Among CD4+ T cells, the proportions of effector memory T cells and HLA-DR+ cells were higher in SLE patients ($p<0.001$ and $p=0.010$). Among CXCR5+ Tfh cells, the proportion of CXCR3-CCR6+ Tfh17 cells was lower in SLE patients ($p=0.001$). In particular, the proportion of CXCR3-CCR6- Tfh2 negatively correlated with the titers of serum complement C3, C4 and white blood cell counts ($\rho=-0.66$, $p=0.021$, $\rho=-0.77$, $p=0.003$ and $\rho=-0.75$, $p=0.003$, respectively), and was higher in SLE patients with skin rash and leukopenia than in patients without them (both $p=0.022$). The correlations of Tfh2 to clinical parameters were similar to those of plasmablasts but opposite to those of Tfh17. (Fig.1) These results support a report in a lupus model mouse in which Tfh2 contributed to the hypocomplementemia-associated pathogenesis [3)].

Conclusion: Proportions of circulating differentiated B cells and T cells were higher in active SLE patients. Tfh2 and plasmablasts negatively correlated with titers of serum complements and were associated with skin rash and leukopenia. Reference 1) Choi J, et al. Curr Opin Immunol. 2012; 24: 651–7. 2) Le Coz C, et al. PLoS One. 2013. 8: e75319. 3) Futatsugi-Yukimura S, et al. Int Immunol. 2014. 26: 221–31.

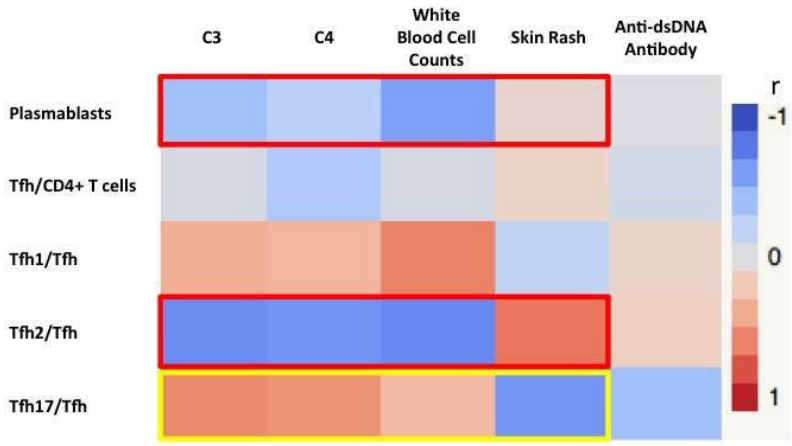

Fig. 1. Heat map representing correlations between peripheral cell subsets and clinical parameters and manifestations.

Disclosure: J. Kikuchi, None; **M. Takeshita**, None; **K. Suzuki**, None; **Y. Kassai**, Takeda Pharmaceutical Co, Ltd., 3; **T. Miyazaki**, Takeda Pharmaceutical Co, Ltd., 3; **T. Takeuchi**, None.

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Abstract Number: 2862

Whole Blood Phenotyping and Innate and Adaptive Stimulation Reveal Unique Differences in Granulocytes and Innate Pathways of African American SLE Patients with Variable Disease Activity

Samantha Slight-Webb[1], Krista M. Bean[1], Joseph Kheir[1], Bolanle Adebayo[1], Holden T. Maecker[2], Paul J. Utz[3], Judith A. James[4] and Joel M. Guthridge[5], [1]Arthritis and Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Division of Immunology and Rheumatology, Stanford University School of Medicine, Stanford, CA, [3]Medicine, Stanford University School of Medicine, Stanford, CA, [4]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [5]Arthritis & Clinical Immunology, Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disorder characterized by periods of heightened disease activity. Disease flares significantly affect quality of life and lead to organ damage that accrues over years of waxing and waning disease. African American SLE patients have more severe disease presentation, which is likely a result of differences in immune cell subsets and activation states.

Methods: Peripheral whole blood samples of 10 African American healthy controls and 12 SLE patients with either high (SLEDAI≥4) or low (SLEDAI<4) disease activity were stimulated with T-cell receptor (TCR), B-cell receptor (BCR), and Toll-like receptor (TLR) ligands for either 4 minutes (TLR and BCR) or 30 minutes (TCR) for phospho-protein analysis, and 24 hours for cytokine analysis of cell culture supernatants. Whole blood phenotyping and phospho-protein analysis were assessed by mass cytometry using 24 cell surface markers and 10 intracellular proteins and analyzed by hand gating and viSNE in Cytobank. Plasma cytokine and soluble mediator concentrations of stimulated cell culture supernatants were determined by 37-plex assay and by ELISA. Spotfire (version 6.0.1) and GraphPad Prism 5.04 for Windows (GraphPad Software, San Diego, CA) was used for analysis and Mann-Whitney test was used to compare non-normally distributed data. All SLE patients meet ACR classification criteria.

Results: African American lupus patients with high disease activity had significantly elevated CD24+ granulocytes (p=0.0173), which

negatively associated with IL-8 plasma levels ($p<0.05$) and positively associated with MCP-1 ($p<0.05$) compared to SLE-low disease activity patients. Granulocytes also exhibited a heightened response to TLR9 ($p=0.0062$), TLR4 ($p=0.0446$), and TLR3 ($p=0.0061$) stimulation with higher expression of pSTAT5 and pPLCγ2. Further, transitional B cell frequencies ($p=0.0317$) were also elevated in SLE-high patients versus SLE-low disease activity patients, which correlated with higher levels of Th2 plasma cytokines. Following stimulation with BCR and TLR3 stimulation, SLE-high patient B cells ($p<0.05$) and monocytes ($p<0.04$) had decreased pCREB levels, indicative of activation. Dendritic cells had decreased pSTAT1 ($p=0.0446$) and pSTAT5 ($p=0.0106$) signaling in response to BCR stimulation and decreased pSTAT3 ($p=0.0427$) signaling in response to TLR7/8 stimulation in SLE-high patients compared to SLE-low disease activity patients.

Conclusion: Our results suggest that SLE-high disease activity patients have a favorable environment for granulocyte apoptosis that may work in activating other innate and adaptive subsets to drive disease flare. Further, African American SLE-high disease activity patients are more susceptible to an exaggerated TLR response. Decreased pSTAT1 signaling in dendritic cells of SLE-high disease activity patients could indicate already activated IFN pathways during periods of elevated disease activity.

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Abstract Number: 2863

High Frequency of Terminally Differentiated CD8+ T Cells Characterize Systemic Lupus Erythematosus Patients with Renal Involvement

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Background/Purpose: SLE is a highly heterogeneous disease. The identification of disease subtypes with different pathological mechanisms is crucial to identify subjects with different disease progression who may have differential responses to treatment. Since CD8+ T cell exhaustion has been associated with better clinical outcomes, we decided to focus on the CD8+ T cell subpopulations in lupus patients.

Methods: We analyzed 50 SLE patients under standard of care from a single clinical center (Northwell Health Division of Rheumatology). For every patient, we obtained a heparinized blood sample and one PAXgene tube. At the time of phlebotomy, we collected SLEDAI, clinical manifestations and autoantibodies. We used an open population cohort as controls. All protocols were approved by the IRB at NorthWell Health. Whole blood was used for $CD8^+$ T cell phenotyping by flow cytometry, and PBMC were used for phospho-signaling and intracellular cytokine staining. The PAXgene tube was used for mRNA extraction and gene expression on an Affymetrix U-129 chip. The data from the gene expression study was used to evaluate gene modules (*1*). All statistical analysis were performed on JMP10 following published recommendations(*2*).

Results: Terminally differentiated $CD8^+$ T cells are significantly increased in a subset of lupus patients (and confirmed in a second, independent cohort). Importantly, this increase in terminally differentiated $CD8^+$ T cells is particularly noticeable in lupus patients with a history of lupus nephritis ($p<0.05$). SLE patients with higher proportions of terminally differentiated $CD8^+$ T cells have i) higher levels of basal pAKT, ii) a lower capacity to induce pAKT upon CD3/CD28 stimulation iii) a higher proportion of cells that produce

IFNg upon stimulation and iv) higher titers of ANA and anti-RNP70 autoantibodies. Importantly, the fraction of terminally differentiated $CD8^+$cells that is quantifiable by flow cytometry correlates with a genomic signature of cytotoxic activity.

Conclusion: A subset of SLE patients, with a history of lupus nephritis are characterized by a high fraction of terminally differentiated CD8+ T cells and associated secretion of INFg. These data suggest that terminally differentiated CD8+ T cells may drive disease in LN patients and may benefit from therapies that block $CD8^+$T cell activation.

1. L. Chiche *et al.*, Modular transcriptional repertoire analyses of adults with systemic lupus erythematosus reveal distinct type I and type II interferon signatures. *Arthritis & rheumatology (Hoboken, N.J.)* **66**, 1583-1595 (2014).

2. S. Lydersen, Statistical review: frequently given comments. *Annals of the rheumatic diseases* **74**, 323-325 (2015).

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Abstract Number: 2864

Identifying Dysregulated and Co-Dysregulated Markers in Systemic Lupus Erythematosus Using Multi-Modal Biomarker Data from a Large Pre-Clinical Study

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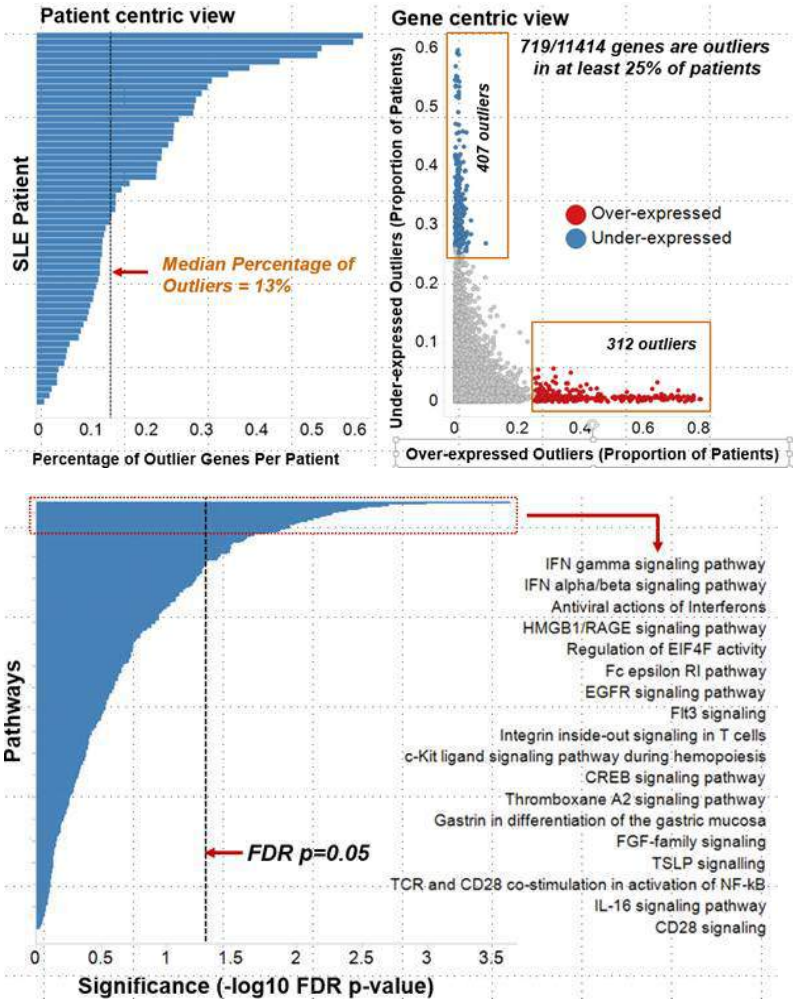
Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic, relapsing autoimmune disease affecting multiple organs and is a highly heterogeneous condition, with wide variations in the presentation and severity of disease and the biological markers identified [1]. We analyzed multi-modal biomarker (mRNA, miRNA, cytokines and autoantibodies) data from ~100 clinically annotated SLE patients under standard of care from a single clinical center (Northwell Rheumatology Clinic) along with ~100 NHVs to identify key dysregulated and co-dysregulated markers in SLE.

Methods: To address the issue of heterogeneity, we applied 2 approaches namely outlier analysis [2] followed by market basket analysis [3] to identify dysregulated and co-dysregulated markers in this multi-modal biomarker rich dataset. We also used pathway analysis and knowledge databases to assess the biological relevance of these markers.

Results: For the whole blood transcriptomic data, on an average, 13% genes were found to be dysregulated in an SLE patient and ~ 6% of genes were found to be dysregulated in at least 25% of SLE patients (Fig.1). Percentage of outlier genes showed weak correlation with SLEDAI scores . Pathway analysis of outlier genes showed an enrichment for IFN signaling pathways (Fig. 2). Market basket analysis identified several high-confidence (>0.8) co-dysregulated associations across a wide proportion of patients. The IFN genes formed the most promiscuous associations. The high-confidence associations were further prioritized based on multi-modality (e.g.

miRNA:mRNA) and opposing regulation.

Conclusion: Several key dysregulated markers were identified in SLE patients using outlier analysis, which might have been otherwise missed by traditional ANOVA-based approaches because of the heterogeneity in patients. Furthermore, the market basket analysis identified several co-dysregulated markers in patient sub-populations which might be missed by traditional co-expression analysis that requires co-dysregulation across all patients. These markers can be drivers and potential patient stratification biomarkers of SLE and might also help to understand the pathophysiology of this heterogeneous and complex disease.



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Abstract Number: 2865

Apoptotic Microparticles, but Not Exosomes, Induce an Inflammatory Response in Synoviocytes

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Background/Purpose: Circulating microparticles (MPs) and exosomes modulate immune responses and play a role in the pathogenesis of systemic lupus erythematosus (SLE). Exosomes are 50-250 nm in size, while MPs are between 500-1000 nm. These extracellular vesicles vary in their functions and mechanisms of formation. SLE patients have a unique population of inflammatory MPs which carry markers of apoptotic cells. We sought to determine if MPs and exosomes isolated from apoptotic cells in vitro induced an inflammatory response in fibroblast-like synoviocytes.

Methods: Human monocytes (THP-1) were treated with no additives or 100-1,000 U/mL of IFN γ for up to 72 hours to induce apoptosis. Apoptosis was assessed by measuring levels of caspase 3/7. Differential centrifugation was performed to obtain the MP and exosome fractions. A light scattering device (Nanosight) was used to determine the mean size and concentration of particles. Washed MPs and exosomes from apoptotic and normal THP-1 cells were added to human synoviocytes (Cell Applications) and incubated for 24 hours. The human cytokine antibody array (Abcam) was used to assess quantities of cytokines in conditioned media under various conditions.

Results: IFNγ at concentrations of 1000 U/ml successfully induced apoptosis in THP-1 cells as shown by a clear increase in caspase 3/7 levels ($p< 0.03$) (Figure 1). Both mean size ($p<0.05$) and concentration ($p<0.001$) of particles were increased over controls after 72 hours of IFNγ treatment. The addition of equal quantities of exosomes derived from apoptotic and normal cells produced similar synovial cell cytokine levels. In contrast, MPs from apoptotic cells produced a dramatic increase in an array of cytokines largely involving IL-1beta and interferon pathways compared to those from normal cells (Figure 2).

Conclusion: MPs from apoptotic cells induce an inflammatory response in synoviocytes, while this was not true of apoptotic exosomes. Our findings support major differences in the function of these two types of extracellular vesicles. They also lend additional support to a potential role for apoptotic MPs in the manifestations of clinical SLE.

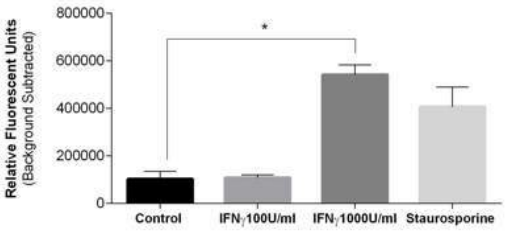
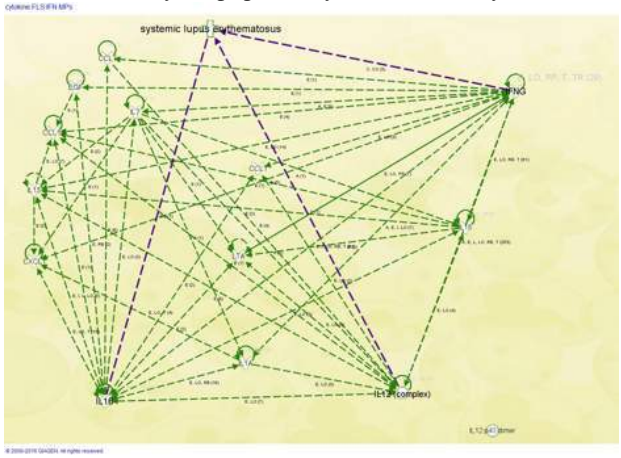


Figure 1. *Interferon γ induces apoptosis. Caspase 3/7 activity was measured as a marker for apoptosis after treatment of THP-1 cells with 1000 u/ml IFN γ. Staurosporine (1 μM) was used a positive control.*



Disclosure: B. Bettendorf, None; **E. Mitton-Fitzgerald**, None; **C. Gohr**, None; **A. K. Rosenthal**, None.

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Abstract Number: 2866

Lupus HDL Induces Pro-Inflammatory Responses in Macrophages By Binding LOX1Rand Failing to Promote ATF3 Activity

Carolyne K. Smith[1], **Nickie Seto**[1], Anuradha Vivekanandan-Giri[2], Wenmin Yuan[3], Martin Playford[4], Zerai G. Manna[5], Sarfaraz A. Hasni[6], Rui Kuai[3], Nehal N. Mehta[4], Anna Schwendeman[3], Subramaniam Pennathur[2] and Mariana Kaplan[7], [1]Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [2]Internal Medicine/Nephrology, University of Michigan Nephrology, Ann Arbor, MI, [3]Department of Medicinal Chemistry and the Biointerfaces Institute, University of Michigan, Ann Arbor, MI, [4]NHLBI, National Institutes of Health, Bethesda, MD, [5]National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD, [6]Lupus Clinical Research Program, Office of the Clinical Director, NIAMS/NIH, Bethesda, MD, [7]NIAMS/NIH, Bethesda, MD
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Background/Purpose: Recent evidence indicates that high-density lipoprotein (HDL) exerts vasculoprotective activities by promoting activating transcription factor 3 (ATF3), leading to down-regulation of TLR-induced inflammatory responses. Systemic lupus erythematosus (SLE) is associated with increased cardiovascular disease (CVD) risk not explained by the Framingham risk score. Recent studies have indicated oxidized HDL as a possible contributor. We investigated the potential mechanisms by which lupus HDL may lose its anti-inflammatory effects and promote immune dysregulation.

Methods: Control human macrophages were challenged with purified human control and SLE HDL *in vitro* in the presence or absence of TLR agonists and examined for induction of inflammatory markers by real time RT-PCR, confocal microscopy, ELISA and flow cytometry. The effect of an HDL mimetic (ETC-642) was examined *in vivo* in NZM2328 lupus-prone mice.

Results: Compared to control HDL, SLE HDL activates NFκB, promotes inflammatory cytokine production, and fails to block TLR-induced inflammation in control macrophages. This failure of lupus HDL to block inflammatory responses is due to an impaired ability to promote ATF3 synthesis and nuclear translocation. SLE HDL-induced pro-inflammatory responses in macrophages are dependent on its binding to lectin-like oxidized low-density lipoprotein receptor 1 (LOX1R), which promotes suppression of ATF3 activity in a ROCK1/2 kinase-dependent manner. This inflammation can be modulated *in vivo* as lupus-prone mice exposed to ETC-642 show improved ATF3 induction and significant abrogation of pro-inflammatory responses.

Conclusion: Lupus HDL promotes pro-inflammatory responses through activation of NFκB and decreased ATF3 synthesis and activity, in a LOX1R- and ROCK1/2 kinase-dependent manner. HDL mimetics should be further explored as potential therapies to hamper inflammation and reduce cardiovascular risk in SLE.

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Abstract Number: 2867

Aberrant Epigenetic Alterations at the Promoter up-Regulate cAMP Responsive

Element Modulator Alpha in CD4+ T Cells from Patients with Systemic Lupus Erythematosus

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Background/Purpose: Recently, accumulating studies have documented that up-regulated cAMP responsive element modulator α (CREMα) which can inhibit IL-2 and induce IL-17A in T cells plays a critical role in the pathogenesis of systemic lupus erythematosus (SLE). The aim of this research is to investigate the mechanisms that regulate CREMα expression in SLE.

Methods: Histone H3 lysine 4 trimethylation (H3K4me3, a hallmark correlated with transcription activation) amounts at various gene promoters in CD4+ T cells from SLE patients and healthy controls were assayed by chromatin immunoprecipitation (ChIP) microarray. Numbers of H3K4me3, H3K4 methyltransferases SET domain containing 1 (Set1) and mixed-lineage leukemia 1 (MLL1), H3ac and H4ac (both are marks of gene activation), and DNA methyltransferase (DNMT) 3a within the CREMα promoter were measured by ChIP and real-time PCR. DNA methylation (a hallmark of gene silencing) abundance at the CREMα promoter was tested by methylated CpG-DNA immunoprecipitation (MeDIP) and real-time PCR. Levels of CREMα and Set1 mRNA and protein were quantified by real-time RT-PCR and western blotting, respectively. IL-2 and IL-17A productions were detected by enzyme-linked immunosorbent assay (ELISA).

Results: From the ChIP microarray data, we found sharply increased H3K4me3 amount at the CREMα promoter in SLE CD4+ T cells compared to controls. Then by ChIP and real-time PCR, we confirmed this result. Moreover, H3K4me3 amount at the promoter was positively correlated with CREMα mRNA level in SLE CD4+ T cells. In addition, a striking increase was observed in Set1 enrichment, but no marked change in MLL1 enrichment at the CREMα promoter in SLE CD4+ T cells. We also proved Set1 enrichment was positively correlated with H3K4me3 amount at the CREMα promoter, and positively correlated with CREMα mRNA level in SLE CD4+ T cells. Knocking down Set1 with siRNA in SLE CD4+ T cells decreased Set1 and H3K4me3 enrichments, and elevated the levels of DNMT3a and DNA methylation, while the amounts of H3ac and H4ac didn't alter greatly at the CREMα promoter. All these inhibited the expression of CREMα, then augmented IL-2 and down-modulated IL-17A productions. Subsequently, we observed that DNMT3a enrichment at the CREMα promoter was down-regulated significantly in SLE CD4+ T cells, and H3K4me3 amount was negatively correlated with both DNA methylation level and DNMT3a enrichment at the CREMα promoter in SLE CD4+ T cells.

Conclusion: Our findings suggest for the first time that in SLE CD4+ T cells, increased Set1 enrichment up-regulates H3K4me3 amount at the CREMα promoter, which antagonizes DNMT3a and suppresses DNA methylation within this region. All these factors induce CREMα overexpression, consequently result in IL-2 under-expression and IL-17A overproduction, and contribute to the development of SLE at last.

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Abstract Number: 2868

NK Cell Characterization in Patients with Systemic Lupus Erythematosus: Increased Frequency of Ki67+ NK Cells Associated with Disease Activity and Type I Interferon Signature

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Background/Purpose: Systemic Lupus Erythematosus (SLE) is a complex autoimmune disorder whose pathology appears to involve many immune cell types. While it is clear that autoantibody producing B cells as well as $CD4^+$ T cell help are key contributors to disease, little is known regarding the role of innate lymphoid cells such as Natural Killer (NK) cells in the pathogenesis of SLE.

Methods: We have characterized the phenotype of NK cells by multicolor flow cytometry, proteomics and genomics arrays in a large cohort of patients with SLE.

Results: While the overall percentage of NK cells was similar or slightly decreased compared to healthy controls, a subset of patients displayed a high frequency of NK cells expressing the proliferation marker, Ki-67, which was not found in healthy donors. Only a moderate increase of Ki-67 was observed on other immune cell types such as total CD4+, CD8+ T cells or CD19+ B cells in the same donors. Increased NK cell expression of Ki-67 was found to correlate with clinical parameters. Interestingly, elevated frequencies of Ki67+ NK cells were highly associated with active nephritis. Proteomics analysis and auto-antibody arrays also revealed significant correlations between NK cell expression of Ki-67 and type I interferon (IFN) gene score as well as SLE associated auto-antibodies

Conclusion: These results will contribute to the understanding of the mechanistic role of NK cells in immune-mediated pathology of SLE.

Disclosure: K. Hudspeth, None; **S. Wang**, Medimmune, LLC, 1; **J. Wang**, MedImmune, LLC, 1; **S. Rahman**, MedImmune, LLC, 1; **M. Smith**, MedImmune, LLC, 1; **K. Casey**, MedImmune, LLC, 1; **G. Stephens**, AstraZeneca, 1; **M. Sanjuan**, MedImmune, LLC, 1; **A. M. Medicine group**, MedImmune, LLC, 1; **Z. G. Manna**, None; **S. Hasni**, None; **R. Ettinger**, MedImmune, LLC, 1; **R. Siegel**, None.

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Abstract Number: 2869

Critical Roles of IRAK4 Kinase Activity in Inflammation but Not B Cell Response in SLE

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Background/Purpose: Interleukin-1 receptor (IL-1R)-associated kinase 4 (IRAK4) is a key component of the Myddosome complex, which is essential for signalling downstream of IL-1R and most Toll-like receptors (TLRs) except TLR3. Aberrant TLR signalling has been implicated in the development of disease in both murine models of lupus and human systemic lupus erythematous (SLE). Herein we tested the hypothesis that inhibition of IRAK4 kinase activity can dampen the production of pro-inflammatory cytokines, type I interferon (IFN), and potentially autoantibodies.

Methods: An IRAK4 tool inhibitor (compound 1) was used to treat PBMCs from SLE or lupus nephritis (LN) patients followed by TLR7 or IL-1β stimulation overnight. Cytokine (IL-6) production in the culture supernatant was then measured by AlphaLISA. Either fresh SLE/LN whole blood or healthy control PBMCs stimulated with 5% SLE/LN plasma were treated with either 5 μM of compound 1, 20 μM of Hydroxychloroquine (HCQ) or DMSO control overnight, and gene expression was then measured by NanoString with a representative gene panel. The effect of the IRAK4 inhibitor on human plasmablast differentiation driven by TLR7 activation was also examined using freshly isolated B cells activated with a selective TLR7 ligand for 7 days, followed by flow cytometry analysis of the $CD38^{hi}$ $CD19^{low}$ plasmablast population. Lastly, the IRAK4 inhibitor was dosed by chow in a Pristane-induced lupus mouse model. Arthritis score, plasma levels of autoantibodies (anti-dsDNA, anti-Histone, anti-SmRNP, anti-RiboP, and anti-Ro/SSA), and gene expression were followed to evaluate disease development.

Results: Blockade of IRAK4 with a selective inhibitor (compound 1) led to concentration-dependent decrease of inflammatory cytokine (IL-6) production by TLR7 or IL-1β-stimulated SLE PBMCs. In addition, treatment with the IRAK4 inhibitor significantly reduced the expression of IRAK4-dependent genes, many of which were also observed to be elevated in whole blood from SLE and LN patients as well as in healthy control PBMCs stimulated with SLE plasma. Our data suggested that IRAK4 blockade produced unique but differential effects on type I IFN-inducible and other IRAK4-dependent genes compared to HCQ treatment. In contrast to its potent effects in suppressing inflammation/type I IFN-inducible genes, IRAK4 blockade with compound 1 only produced modest inhibition of plasmablast differentiation *in vitro* driven by TLR7, even at a saturating concentration. Lastly, we showed that dosing of the IRAK4-selective inhibitor in a Pristane-induced lupus model produced significant inhibition of joint inflammation measured by arthritis score, but no effect on autoantibody production.

Conclusion: IRAK4 kinase activity is essential for the induction of inflammatory cytokines and chemokines in myeloid cells, but less important for TLR-driven activation of B cells. Pharmacological inhibition of IRAK4 in SLE (and LN) could potentially relieve inflammation by dampening constitutively activated innate immunity and subsequently decrease end organ damage.

Disclosure: **C. C. Sun**, EMD Serono, 3; **G. Chen**, EMD Serono, 3; **N. Lewis**, EMD Serono, 3; **A. T. Bender**, EMD Serono, 3; **C. Sia**, EMD Serono, 3; **L. Zhang**, EMD Serono, 3; **C. Jorand Lebrun**, EMD Serono, 3; **H. Y. Lin**, Ferrumax Pharmaceuticals, 4,EMD Serono, 2,Protagonist Therapeutics, 5,Sentien Biotechnologies, 4; **R. I. Thadhani**, Fresenius Medical Care, 5,EMD Serono, 2; **H. Parmar**, EMD Serono, 3; **J. A. DeMartino**, Novartis Pharmaceutical Corporation, 1,Merck and Co, 1,EMD Serono, 3.

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Abstract Number: 2870

Overexpression of EZH2 at the microRNA-142 Regulatory Region Contributes to Down-Regulation of microRNA-142-3p/5p in Systemic Lupus Erythematosus

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Background/Purpose:

Recently, our group has demonstrated that decreased microRNA-142-3p/5p (miR-142-3p/5p) which contributes to T cell overactivation and B cell hyperstimulation plays an essential role in the pathogenesis of systemic lupus erythematosus (SLE). The aim of this study is to

investigate what regulate miR-142-3p/5p expression in SLE.

Methods:

CD4+ T cells were isolated from SLE patients and healthy controls. Amounts of H3K27me3, EZH2(H3K27 methyltransferases) within the microRNA-142 (miR-142) regulatory region were subsequently analyzed by chromatin immunoprecipitation (ChIP) and real-time PCR in CD4+ T cells from 20 SLE patients and 20 healthy controls. And miR-142-3p/5p expression levels were determined by real-time quantitative polymerase chain reaction.

Results:

By ChIP and real-time PCR experiments, we confirmed increased H3K27me3 enrichment at the miR-142 regulatory region of SLE CD4+ T cells relative to controls. Moreover, H3K27me3 enrichment at the miR-142 regulatory region was negatively correlated with miR-142-3p/5p expression levels in SLE CD4+ T cells. In addition, a striking increase was observed in EZH2 binding at the miR-142 regulatory region in SLE CD4+ T cells compared to healthy controls. We also proved the levels of EZH2 binding were positively correlated with H3K27me3 enrichment at the miR-142 regulatory region, and negatively correlated with miR-142-3p/5p expression levels. Knocking down EZH2 with siRNA in SLE CD4+ T cells led to decreased EZH2 binding and H3K27me3 enrichment at the miR-142 regulatory region, thus increasing the expression of miR-142-3p/5p.

Conclusion:

Our findings suggest for the first time that increased EZH2 binding up-regulates H3K27me3 enrichment at the miR-142 regulatory region, which inhibits miR-142-3p/5p expression in SLE CD4+ T cells, and contributes to the development of SLE at last. These results can help elucidate the molecular pathogenesis of SLE, and provide a novel way and target for effective SLE therapy.

Disclosure: S. Ding, None; **Q. Zhang**, None; **S. Luo**, None; **L. Tan**, None; **H. Long**, None; **M. Zhao**, None; **Y. Liang**, None; **Q. Lu**, None.

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Abstract Number: 2871

Unaffected Lupus Relatives Are Distinguished from SLE Patients and Unaffected Individuals Not Related to SLE Patients By Lupus-Specific Connective Tissue Disease Questionnaire Scores, Autoantibodies, and Distinct Soluble Mediators

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Background/Purpose: Identifying populations at risk of SLE is essential to curtail inflammatory damage and select individuals for

prevention trials. Blood relatives (Rel) of lupus patients have an increased risk of developing SLE, but no markers which identify individuals at highest risk are known. Using a large resource of SLE patients, lupus relatives, and unrelated controls, this study seeks to identify questionnaire responses and serologic factors that distinguish Rel from SLE patients and unrelated, unaffected individuals.

Methods: This study examined European-American (EA) (n=50) and African-American (AA) (n=50) individuals with medical record-confirmed, classified SLE matched 1:1 by race and gender to unaffected Rel (n=100) and unrelated, unaffected controls (Ctls, n=100). Study participants provided clinical and demographic information, and completed the SLE-specific portion of the CTD Screening Questionnaire (SLE-CSQ). Plasma samples were assessed for autoantibody production by bead-based assays and for 52 soluble mediators (BLyS, APRIL, cytokines, chemokines, and shed TNF receptors) by multiplexed bead-based assays or ELISA.

Results: EA SLE patients had more photosensitivity ($p=0.035$), with AA SLE patients having more discoid rash ($p=0.028$) and nephritis ($p=0.045$). Only 45% of Rel were positive for ANA (by IIF > 1:120) compared to 99% of SLE patients ($p<0.001$) and 21% of Ctls ($p=0.001$). Compared to Rel, Ctls had significantly lower SLE-CSQ scores ($p=0.001$), while SLE patients had significantly higher SLE-CSQ scores ($p<0.001$). Irrespective of race, a strong correlation exists between SLE-CSQ scores, number of ACR criteria, and number of autoantibody specificities ($p<0.001$) across Rel vs. SLE patients and Ctls. In addition, a number of soluble mediators strongly correlated with these 3 variables, including TNF superfamily members BLyS, TNFRI, and TNFRII, IFN-associated chemokines IP-10, MCP-1, and MIG, soluble receptor IL-2Rα, SCF, and IL-10 ($p\leq0.002$ for each mediator). In certain cases, levels of soluble mediators in Rel demonstrated up-regulation similar to SLE or intermediate between SLE and Ctls. Levels of MCP-1 and MIG were similar between Rel and SLE patients, and higher than Ctls ($p\leq0.004$), while levels of BLyS and IL-2Rα were similar between Rel and Ctls, and significantly lower than SLE patients ($p<0.001$). Rel had intermediate levels of TNFRI, TNFRII, IP-10, and SCF between SLE patients ($p\leq0.01$) and Ctls ($p\leq0.03$). In contrast, Rel had significantly higher levels of the regulatory mediator IL-10 than SLE patients ($p<0.001$). All soluble mediator findings were independent of race, except for TNFRI (EA>AA SLE patients, $p<0.001$) and TNFRII (AA>EA SLE patients, $p<0.001$).

Conclusion: Lupus Rel are distinguished from SLE patients and Ctls by inflammatory mediators that correlate with SLE-specific CSQ scores, with increased levels of the regulatory mediator, IL-10, compared to SLE patients. Identification of factors which discern unaffected lupus relatives from SLE patients may be beneficial to identify potential treatments to curtail inflammatory damage for prevention trials.

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Abstract Number: 2872

SLE Subjects Express High Levels of Intracellular Interferon-β That Acts in an Autocrine Fashion to Promote Survival of Transitional Stage B Cells

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Background/Purpose: Upregulation of interferon-β (IFNβ) is an important step in promoting maturation and survival of B cells. Secretion and autocrine action of IFNβ requires assembly of the IFNβ enhanceosome, including IRF3, IRF7 and NF-κB. Interestingly, TLR7 stimulation has been found to induce IRF7 in transitional B cells from SLE patients. The purpose of this study is to determine if IFNβ is upregulated in transitional B cells of SLE patients and if autocrine activity of IFNβ promotes B cell survival.

Methods: Peripheral blood samples were obtained from consented SLE patients with active disease (SLEDAI > 6) during visits to a Lupus Clinic. FACS analysis was carried out using surface staining antibodies IgD, CD24, CD38, CD27 and CD19. Intracellular IFNβ was detected using and antihuman IFNβ (PBL, clone MMHB3). Autoreactive B cells were detected using 9G4. Transitional and mature $9G4^+$and 9G4B cell subsets were FACS sorted. qRT-PCR was carried using validated primers. Purified B cells were stimulated with TLR7 (CL264, 5 μg/ml) and a goat polyclonal antihuman IgM+IgG (5 μg/ml). IFNβ and IFNα/βR blocking was carried out using a polyclonal anti-IFNβ (500 IU/ml, PBL) and an IFNα/βR blocking Ab (anifrolumab, 5 μg/ml, Creative BioLabs), respectively.

Results: There was a significant increase in intracellular IFNβ determined by both FACS analysis and by RT-PCR in $IgD^+CD24^+CD38^+CD27^-$ transitional B cells of SLE patients compared to control subjects ($p<0.01$). IFNβ was upregulated in both the $9G4^+$ and $9G4^-$ subpopulations of B cells. The expression of *Ifnb* in transitional cells further positively correlated with the expression of IFNα genes (*Ifna1*, *Ifna2*, and *Ifna4*) and IFN response genes (*Mx1* and *Ifit4*) ($p<0.05$). TLR7 plus BCR stimulation upregulated IFNβ and resulted in a significant upregulation of CD69 and CD86 at 4 hrs by both transitional and mature B cells, and increase in survival at 60 hrs in B cells from SLE patients. Importantly, IFNβ neutralization inhibited these responses. The inhibition was equivalent to the blockade of IFNα/βR, indicating that although both IFNα and IFNβ were expressed, these early responses required the release and autocrine activity of intracellular IFNβ.

Conclusion: The present results suggest that, in SLE, induction of type I IFN production by early transitional B cells is a 2-step process. IFNβ acts in an autocrine fashion to promote B cell survival and upregulation of IFNa. IFNa does not play an essential autocrine role but may act on other cells. B cell therapies directed at neutralizing IFNβ may be useful, especially in early-stage SLE prior to IFNβ enhanced development of IFNα producing B cells. Inhibition of IFNβ enhanceosome component(s) that are required for IFNβ production, may serve as a novel target for SLE. *(Supported by NIH R01-AI-071110, R01-AI-083705, P30-AR-048311, T32 AI007051, VA Merit Review grant 1I01BX000600, Lupus Research Institute, Lupus Foundation of America.)

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Abstract Number: 2873

B-Cell activating Factor Genetic Variants in Systemic Lupus Erythematosus and Lupus Related Atherosclerosis

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Session Time: 9:00AM-11:00AM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease with an increased atherosclerotic risk compared to healthy population, partially explained by traditional cardiovascular risk factors. Recent data suggest B-cell activating factor (BAFF) as an important contributor in the pathogenesis of both SLE and atherosclerosis. The aim of the current study is to explore whether genetic variants of the BAFF gene increase SLE susceptibility as well as lupus related atherosclerotic risk

Methods: Five single nucleotide polymorphisms (SNPs) of the BAFF gene (rs1224141, rs12583006, rs9514828, rs1041569 and the rs9514827) were evaluated in 234 SLE patients and 200 healthy controls (HC) of similar age and sex distribution by PCR-based assays. Allele, genotype and haplotype frequencies in SLE patients and HC were determined by SHEsis and SNPStats software. All patients underwent ultrasound determination of plaque formation in the carotid arteries. Clinical, laboratory and medication data as well as classical risk factors for cardiovascular disease were recorded in all patients. Patients were followed in the Department of Rheumatology, General Hospital of Athens and Rheumatology Unit First Department of Medicine, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece between 2013-2016 and fulfilled the American College of Rheumatology (ACR) criteria for the classification of SLE.

Results: The prevalence of the minor A allele and the AA genotype of the rs12583006 BAFF variant was significantly higher in SLE patients compared to HC (OR [95%CI]: 1.51 [1.12-2.04], p=0.007 and OR [95%CI]: 2.62 [1.04-6.61], p=0.03 in recessive model, respectively). Haplotypes TACAT and TTTAT also conferred a heightened risk for lupus susceptibility. Moreover, the AA genotype of the rs12583006 BAFF variant was significantly higher in SLE patients with evidence of atherosclerotic plaque formation compared to those without plaque after adjustment for age and sex (OR[95%CI]: 5.4 [1.5-19.7], p=0.007 in the recessive model). No other significant associations were detected

Conclusion: BAFF genetic variants increase susceptibility to lupus and lupus related atherosclerosis. These data imply B-cell related factors as potential contributors in the pronounced cardiovascular risk among lupus patients.

Disclosure: E. Theodorou, None; **A. Nezos**, None; **P. Kostantopoulou**, None; **M. Tektonidou**, None; **M. Koutsilieris**, None; **C. P. Mavragani**, GSK, 2.

Abstract Number: 2874

CD16+monocytes Are Enriched and Functionally Exacerbated in Driving B Cell Activation Under Systemic Lupus Erythematosus Condition

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- **Background/Purpose:** Systemic lupus erythematosus(SLE) was an autoimmune disease characterized by extensive B cell activation and autoantibody production. Human peripheral monocytes could be categorized into three subsets based on differential expression levels of CD14 and CD16: the classical monocytes (CM, CD14++CD16-), the intermediate monocytes (IM, CD14++CD16+) and the nonclassical monocytes (NCM, CD14+CD16++). NCM and IM were collectively addressed as CD16+monocytes. The three subsets had been described to demonstrate diffierent functions in inflammatory process. However, their effects on B cell response in SLE were not well studied.The aim of this study was to determine the frequencies of these subsets and investigate their possible roles in B cell activation and differentiation under SLE condition.

- **Methods:** The frequencies of monocyte subsets in the peripheral blood of healthy donors (HC) and patients with SLE were determined by flow cytometry (FACS). Monocyte subsets were sorted and co-cultured with CD19+ B cells. B cell were co-cultured for different subsets detection by FACS, while the supernatant were collected for IgG, IgA and IgM detection by enzyme-linked immunosorbent assay (ELISA). The function of monocyte subsets on B cell was defined as the ratio of the effects of monocyte subsets co-cultured with B cell versus the effects of B cell cultured alone.

- **Results:** CD16+monocytes were obviously expanded in SLE, while CM were significantly reduced. Compared to HCs, monocyte subsets in patients with SLE demonstrated different phenotypes about HLA-DR, CD163, CD80, CD86, CX3CR1 and CCR5 expression. CD16+monocytes induced CD19+B cells to differentiate into memory B (MB) and plasma B (PB) cells but inhibited the generation of regulatory B (Breg) cell in HC donors. However, both PB response and Breg differentiation induced by

CD16+monocytes were exacerbated in patients with SLE. IgG secretion from CD19 positive B cells was increased when cocultured with CD16+monocytes in HCs, which was significantly enhanced when co-cultured with CD16+monocytes in patients with SLE. IgA and IgM responses were differentially regulated by monocyte subsets from SLE and HC, respectively. Compared to CM, CD16+monocytes extensively promoted the expansion of IL-17A- and IL-10- producing B cells, suggesting the preferable role of CD16+monocytes in cytokines secretion from B cells in HCs,. In comparison to HCs, the generation of IL-17A-producing B cells in patients with SLE were significantly elevated in the presence of CD16+monocytes, in which the generation of IL-10 producing B cells were obviously attenuated .

- **Conclusion:** CD16+monocytes was enriched and shared different cell-surface marker profiles in SLE. These cells played a predominant role in orchestrating B cell activation and differentiation in SLE.

Disclosure: H. Zhu, None; **Y. Su**, None; **F. Hu**, None; **L. Xu**, None.

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Abstract Number: 2875

Depressed Serum IgM Levels in SLE Are Restricted to Defined Subgroups

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Background/Purpose: Natural IgM autoantibodies have been proposed to have protective properties, and decreased levels of IgM to phosphorylcholine (PC) in SLE are associated with higher risk of atherosclerotic plaques and cardiovascular events. In the current study we investigated levels of total IgM and IgM anti-PC levels in different SLE subgroups.

Methods: Serum IgM levels were compared in 322 population controls and 351 SLE patients meeting ACR criteria. SLE patients were subgrouped based on antibody profiles into antiphospholipid (APS)-like (n=54, with ≥2 positive tests among anti-CL/β_2GPI; LA), Sjögren's syndrome (SS)-like (n= 63, with ≥2 positive tests among anti-Ro52/Ro60/SSB), or SLE only with no "secondary syndrome" (n=234). A majority, but not all, of the APS-like and SS-like fulfilled clinical criteria for antiphospholipid syndrome or Sjögren's syndrome. Total IgM levels were determined in the clinical laboratory, and IgM anti-PC measured using PC-BSA by sandwich ELISA. Analyses used the 2-sided Mann-Whitney test or Spearman correlation.

Results: IgM anti-PC levels were moderately but significantly decreased in the SLE patients (41.3±45.3 RU/ml) compared to matched controls (48.9±43.15 RU/ml) (n=316, p=0.002). Similarly, the total IgM levels were only slightly lower in SLE than controls (n=310, 1.22±1.1; 1.26±0.68 mg/ml, p=0.0002). There was a weak inverse correlation with age and disease duration for IgM anti-PC (p=0.02, R=-0.13; p=0.0003, R=-0.19). Importantly, APS-like patients did not have significantly altered total IgM (1.51±1.1 mg/ml) or IgM anti-PC levels (58.7±58.7 RU/ml) compared to controls (IgM 1.26±0.7 mg/ml; IgM anti-PC 48.7±43.2 RU/ml), while the SLE only group had moderately decreased IgM levels (IgM 1.21±1.3 mg/ml, p<0.0001; IgM anti-PC 39.5±43.0 RU/ml; p=0.002), and the SS-like patients had considerably impaired IgM (IgM 0.96±0.6 mg/ml, p<0.0001; IgM anti-PC 23.4±24.2 RU/ml, p<0.0001). There were no statistically significant differences based on age, disease duration, female sex, or anti-dsDNA positivity. In all SLE patients, total IgG levels were significantly increased compared to controls, and were highest in the SS-like group.

Conclusion: Alterations in IgM levels between SLE subgroups further emphasize the immune heterogeneity of patients diagnosed with SLE. Patients have different clinical manifestations, risk of co-morbidities, and which also have distinct immunological features. Future studies are needed to investigate the clinical relevance of depressed IgM levels, and if the moderate IgM impairment in certain SLE patients reflects underlying immunological differences and/or is due to consumption of natural IgM or others causes resulting in skewing of the B-cell repertoire.

Disclosure: C. Grönwall, None; **U. Hardt**, None; **I. Gunnarsson**, None; **G. J. Silverman**, None; **E. Svenungsson**, None.

Abstract Number: 2876

SLE Serum Impairs NO Production in Huvecs through Induction of eNOS Uncoupling

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Background/Purpose: Systemic lupus erythematosus (SLE) induces endothelial cell dysfunction (ECD) that can manifest as glomerulonephritis or atherosclerosis. Lupus-prone mice lacking endothelial nitric oxide synthase (eNOS, a critical enzyme in endothelial cell (EC) function), have more severe proliferative nephritis. We hypothesized that SLE serum would induce ECD in vitro by reducing eNOS expression and increasing uncoupling of eNOS monomers, rendering the enzyme unable to produce protective nitric oxide (NO).

Methods: To address this hypothesis, we determined the extent to which serum from SLE patients induced ECD in vitro, whether serum-induced ECD was associated with reduced eNOS mRNA expression, and whether serum-induced ECD was reversed by addition of L-sepiapterin, a tetrahydrobiopterin donor that induces coupling of eNOS monomers to form functional, NO-producing homodimers. Human umbilical vein endothelial cells (HUVEC) were cultured with 20-50% serum from SLE patients (met ≥4 ACR criteria, mean SLE Disease Activity Index score = 4.6, n = 25) and connective tissue disease-free controls (n = 14) for 24 hours. Endpoints measured were: 1) EC NO production measured by staining with DAF-FM diacetate (an NO fluorescent probe) and performing flow cytometry; 2) EC eNOS mRNA measured via quantitative reverse transcription quantitative polymerase chain reaction (RTqPCR); and 3) Changes in HUVEC eNOS monomer and dimer formation in the presence of patient serum were determined by Western blot. The aforementioned endpoints were reassessed after co-culture of EC with serum and sepiapterin (5 μM). Data were reported as mean ± standard deviation and compared using a Student's t-test or Kruskal-Wallis test.

Results: HUVECs cultured in 50% SLE serum displayed significantly reduced median fluorescence intensity (MFI) indicative of diminished NO production compared to EBM-2 media cultured cells (0.28 ± 0.38 vs. 1.08 ± 0.92 fold change respectively, $p < 0.05$). This reduction was reversed when cells were co-cultured in L-sepiapterin (5μM) and healthy control (n=5) or SLE (n=12) serum (1.13 ± 0.60 and 1.28 ± 2.8, respectively). Conversely, 20% SLE serum increased relative ratios of NOS3 mRNA expression vs. control as measured by reverse transcriptase quantitative PCR (RTqPCR) (1.9 ± 1.0 vs. 1.0 ± 1.2, $p < 0.05$). Western blot analysis revealed increased monomerization in cell cultured using SLE serum. However, preliminary studies suggest that the addition of L-sepiapterin restores dimerization of eNOS homodimers.

Conclusion: These results suggest that SLE serum alone can induce ECD through reduction of functional NO production in EC. The reversal of this in vitro ECD with sepiapterin suggests that SLE serum induces uncoupling of eNOS homodimers, a process that increases eNOS superoxide and reduces eNOS NO production. Both of these changes induce ECD. The observation that SLE serum increased (rather than decreased) eNOS mRNA expression suggests a feedback loop in enzyme expression in response to reduced NO production; although, this hypothesis is not addressed here. Determining the mechanism and molecular pathway through which SLE serum induces ECD could lead to targets for pharmacologic intervention.

Disclosure: J. Oates, None; **D. L. Kamen**, None; **J. N. Jones Buie**, None.

Abstract Number: 2877

Notch Ligand Delta-like Ligand 4 (DLL4) Expression on Dendritic Cells Is Increased in Systemic Lupus Erythematosus

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Background/Purpose: Dendritic cells (DCs) activate the immune system with a variety of cytokines and co-stimulatory molecules. Our group recently described the Notch ligand Delta-like Ligand 4 (DLL4) on human DCs and discovered that DLL4+ DCs were critical in regulating Th1 and Th17 differentiation. Due to the association of DCs, Th17 and activity with SLE, the goal of this work was to evaluate DLL4 expression in human SLE DCs.

Methods: Peripheral blood from healthy controls and patients with SLE were collected after obtaining informed consent. A total of 11 SLE patients and 13 sex and aged matched control were investigated. A multicolor flow cytometric analysis using a BD LSRII flow cytometer was used to identify DCs. DLL4 expression was determined by surface staining of $CD1c^+$ DCs and pDCs. DCs were analyzed either in PBS or in the presence of the Toll-like Receptor (TLR) 7 agonist R848. Lupus activity was measured by SLE disease activity index (SLEDAI) and values were extracted from EPIC, the Temple University Hospital's Electronic Medical Record system. Statistical analysis was performed with JMP® Software. Student's t-test, ANOVA, MANOVA, and least squares regression were used with a $p < 0.05$ was considered to be significant.

Results: We found that $DLL4^+$ $CD1c^+$ DCs in lupus patients at rest were 5-fold higher than in controls (p=0.002). Moreover, $DLL4^-$ $CD1c^+$ DCs were 2.1-fold higher in controls at rest (p=0.002). Interestingly also $DLL4^+$ pDCs were 3.3-fold higher in lupus patients at rest (although not significant). After TLR7 stimulation, lupus patients had 3.3-fold more $DLL4^+$ pDCs and those were 3.3-fold more responsive (p<0.001). We next correlated DLL4 expression and disease activity measured by SLEDAI. Interestingly SLEDAI score correlated with DLL4+ CD1c+ DCs after TLR7 stimulation. In lupus patients with no disease activity, $DLL4^+$ pDCs were 3-fold more responsive to TLR7 triggering. Next we correlated DLL4+ DCs with SLE flares and found that $DLL4^+CD1c^+$ DCs were 2.3-fold more responsive to R848 (p=0.03) and 1.2-fold more responsive in a flare (not significant).

Conclusion: Our results suggest that DLL4+ DCs are a marker of chronic activation in SLE patients. Moreover, this particular group of DCs demonstrates propensity to activate upon TLR triggering, a major component of lupus pathogenesis. The SLEDAI scores and flares results findings are consistent. Finally $DLL4^+$ pDCs could be a marker for SLE disease.

Disclosure: J. Fragoso, None; **L. Meng**, None; **Y. Zhang**, None; **R. Caricchio**, None.

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Abstract Number: 2878

Major Lymphocyte Populations Share a Common Interferon Signature but Express Cell Type-Specific Interferon Pathway Genes in SLE

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Background/Purpose:

All lymphocyte populations contribute to SLE pathogenesis, but little is known of the specific gene transcripts particularly involved in each cell type. Activation of the type I interferon (IFN-I) pathway is observed in most lupus patients and is associated with more severe disease. To gain insight into the contribution of major lymphocyte subsets to autoimmune disease we studied gene expression and directed analysis to components of the IFN-I pathway.

Methods:

PBMC were isolated from 15 SLE patients and 10 matched healthy controls. Participating patients met ACR criteria for SLE and were adult females of different ages, racial backgrounds and disease manifestations. Patients had received stable doses of steroids and/or plaquenil but had not received biologics. $CD4^+$T, $CD8^+$T, $CD56^+$NK and $CD19^+$B cell fractions were isolated using magnetic beads, purity was assessed by flow cytometry, and RNA was extracted. Transcriptional profiles were obtained using Affymetrix U133Plus 2.0 microarray chips, and transcripts differentially expressed between SLE and control cell preparations were identified using the limma package. Weighted gene co-expression network analysis was performed using the WGCNA package. A difference in expression was considered statistically significant when $p<0.05$ and absolute fold change was more than two.

Results:

A linear blocking model identified differentially expressed genes in each of the studied fractions (PBMC 122; $CD4^+$T 107; $CD8^+$T 124; $CD56^+$NK 506; and $CD19^+$B 112 genes). A similar list was obtained using gene co-expression network analysis. All cell fractions and the unfractionated PBMC from SLE patients demonstrated the IFN-I signature, with 27 IFN-I-induced gene transcripts common to all fractions. The IFN-I signature correlated with a lower proportion of $CD3^+CD4^+$T (R=

-0.3, $p<0.01$) and $CD56^+$NK (R= -0.6, $p<0.01$) cells and an increase in monocytes (R = +0.6, $p<0.01$) in PBMC as measured by flow cytometry. Other SLE-associated transcripts were independent of the IFN-I signature but were cell-type specific and potentially affect immune functions. IRF7, IRF9, STAT1 and STAT2 were increased in all fractions, but IRF5 showed significant upregulation only in the CD56 cell fraction. Among Toll-like receptors, TLR5 was significantly higher in $CD4^+$T cells while TLR7 was significantly higher in B cells. Expression of IFN-I receptor genes was comparable in all fractions, and IFN-I transcripts were generally undetectable in lymphocytes.

Conclusion:

The IFN-I signature reflects an important pathophysiologic pathway in autoimmune conditions, particularly in SLE. Our data demonstrate that the IFN-I signature is ubiquitous among lymphocyte populations and includes common transcript components. Other pathway transcripts, including IRF5 and TLR7, point to distinct and significant roles of lymphocyte subsets in disease.

Disclosure: M. Olferiev, None; **K. A. Kirou**, None; **D. Fernandez**, None; **K. Leila**, None; **D. Greenman**, None; **M. K. Crow**, Medimmune, 5.

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Abstract Number: 2879

Genome-Wide Pathway Analysis Reveals That VEGF Genetic Pathway Is Associated with Oral Ulcers in Systemic Lupus Erythematosus

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Fuente[12], Antonio Zea[13], JM Pego-Reigosa[14], Mercedes Freire[15], Elvira Diez Alvarez[16], Adrià Aterido[1], Arnald Alonso[1], Maria López-Lasanta[17], Mireia López[18], Raül Tortosa[1], **Sara Marsal**[19] and Antonio Fernandez-Nebro[20], [1]Rheumatology Research Group, Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [2]Department of Rheumatology, Hospital Universitario 12 de Octubre, Madrid, Spain, [3]Rheumatology, Hospital Universitario Marqués de Valdecilla. IDIVAL, Santander, Spain, [4]Hospital Marqués de Valdecilla., Santander, Spain, [5]Rheumatology, HGU Gregorio Marañón, Madrid, Spain, [6]Rheumatology, Hospital de Jerez de la Frontera, Jerez de la Frontera, Spain, [7]Rheumatology, Hospital Universitario Germans Trias i Pujol, Barcelona, Spain, [8]Rheumatology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain, [9]Rheumatology service, IMIBIC/Reina Sofia Hospital/University of Cordoba, Cordoba, Spain, [10]Dpt. Rheumatology, Hospital General Universitario Alicante, Alicante, Spain, [11]Rheumatology, Bellvitge University Hospital, Barcelona, Spain, [12]Rheumatology, Hospital de Valme, Seville, Spain, [13]Hospital Ramón y Cajal. Madrid, Madrid, Spain, [14]Rheumatology Section, Hospital de Meixoeiro, Pontevedra, Spain, Vigo, Spain, [15]Servicio de Reumatología. Instituto de Investigación Biomédica de A Coruña (INIBIC). Complexo HospitalarioUniversitario de A Coruña (CHUAC), Sergas. Universidade da Coruña (UDC), A Coruña, Spain, [16]Rheumatology, Hospital de León, León, Spain, [17]Vall d'Hebron Hospital Research Institute, Barcelona, Spain, [18]Servicio de Reumatología, Hospital Universitario Vall d´Hebron, Barcelona, Spain, [19]Rheumatology Research Unit, Vall d'Hebron Hospital, Barcelona, Spain, [20]Rheumatology, Hospital Universitario Carlos Haya, Malaga, Spain
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Background/Purpose: Systemic lupus erythematosus (SLE) is a genetically complex rheumatic disease with heterogeneous clinical manifestations. Recent studies have suggested the existence of a genetic basis for the diverse SLE clinical phenotypes. Also, there is increasing evidence indicating that a substantial part of the genetic variation associated with complex diseases could be explained by small-effect genes from common genetic pathways. The objective of the present study was to identify new genetic variation associated with SLE phenotypes using a genome-wide association study at the pathway level.

Methods: A total of 598,258 SNPs were genotyped in a discovery cohort of n=482 SLE patients of southern European ancestry using the Illumina platform Quad610. After quality control analysis, including ancestry estimation using principal-component analysis, genome-wide pathway analysis was performed. A total of 14 clinically relevant SLE phenotypes were tested for association in n>700 reference genetic pathways. Significantly associated pathways (corrected P-value < 0.05) were subsequently tested for validation in an independent cohort of n=425 SLE patients from the same ancestry. Both discovery and validation cohort patients were Caucasian European and from Spanish origin, and were recruited by n=15 rheumatology departments from Spanish university hospitals. The validated genetic pathways were functionally characterized using *in silico* analysis on cell types of relevance in SLE pathogenesis.

Results: In the discovery stage, two genetic pathways were significantly associated with the presence of oral ulcers and antinuclear antibodies in SLE (P_{FDR}<0.05). In the replication stage, we validated the association between oral ulcers and the vascular endothelial growth factor (*VEGF*) genetic pathway (*P*=1.3e-2). Analyzing the transcriptional effect of the topical immunotherapies used for the treatment of oral ulcers in SLE, we found a significant differential expression of *VEGF* pathway genes (P<0.05).

Conclusion: In this work we have performed the first genome-wide association study for clinically relevant SLE phenotype using a pathway-based approach. With this new approach, we have identified and validated the association of VEGF genetic pathway with oral ulcers in SLE. These findings represent an important step towards the characterization of the genetic basis of phenotype heterogeneity in SLE.

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Abstract Number: 2880

Distinct Metabolic Pathways Regulate Lipid Antigen Presentation By Monocytes and

B Cells: Implications for SLE Patients with Pre-Clinical Atherosclerotic Plaque

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Background/Purpose: Systemic lupus erythematosus (SLE) patients have an increased risk of developing clinically apparent cardiovascular disease (CVD) and subclinical atherosclerotic plaque, detectable by vascular ultrasound (US). Although dyslipidaemia and immune dysfunction are widely described in SLE, their role in atherosclerosis is unclear. We propose that *invariant* Natural Killer T (*i*NKT) cells, which respond to lipid antigens presented by CD1d on antigen presenting cells, play a key role in linking the immune system, lipids and CVD in SLE patients. We observed differential defects in iNKT cell number and function in SLE patients with and without pre-clinical atherosclerosis (SLEP), a condition associated with altered lipid homeostasis. Here we investigate how cellular lipid metabolism influences CD1d-lipid antigen presentation in SLE and how this is altered in SLEP.

Methods: Vascular US on 100 patients with SLE but no history of CVD showed 36 had plaque (SLEP) and 64 had no plaque (SLENP). Blood from 40 SLENP, 34 SLEP and 28 female healthy controls (HCs) (mean age 39) was used to assess monocyte and B cell phenotype. Expression and colocalization of CD1d and lipid rafts (LR, plasma membrane signalling platforms), kinetics of immune synapse formation, and subsequent invariant T cell receptor (iTCR) signalling were assessed by flow cytometry and ImageStream. Expression of genes regulating cellular and membrane lipid content were analyzed using qPCR.

Results: LR expression was increased (p=0.01) and CD1d expression reduced (p=0.01) on B cells from SLE patients compared to HCs. This was associated with increased accumulation of CD1d within LRs in SLE compared to HC B cells (p=0.009). Conversely, no differences in LR and CD1d expression and location were detected in monocytes from HCs or SLE patients. The location of CD1d in relation to LRs can influence the potency of *i*NKT cell activation. We found that monocytes formed more stable interactions with *i*NKT cells compared to B cells (p=0.005); these interactions were more rapid between iNKT cells and monocytes from SLEP compared to SLENP patients and HCs and translated to significantly increased *i*TCR-z phosphorylation in SLEP-monocyte/*i*NKT cell conjugates (p=0.05). B cell-iNKT cell interactions were reduced in all SLE patients compared to HCs and resulted in altered down-stream iTCR signalling. Since LRs were unaltered in monocytes, we hypothesized that monocyte intracellular and/or CD1d lipid content may be different in SLE patients. mRNA expression of liver X receptor-α and its target genes (a transcriptional program which decreases cellular cholesterol) were decreased in monocytes from SLE patients (p=0.008) favouring accumulation of intracellular lipids. Furthermore monocyte phospholipid content was increased by culture with serum from SLEP compared to SLENP patients.

Conclusion: We propose that monocytes and B cells interact with iNKT cells differently. B cell-iNKT interactions are perturbed in all SLE patients and are associated with altered LR localization. In the setting of pre-clinical atherosclerosis changes in circulating lipids alter monocyte lipid metabolism and the nature of CD1d-lipid antigen they present.

Disclosure: K. Waddington, None; **E. Smith**, None; **S. Croca**, None; **D. A. Isenberg**, None; **A. Rahman**, None; **I. Pineda Torra**, None; **E. Jury**, None.

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Abstract Number: 2881

Reduced Hippocampal-Thalamic Fiber Tracts in Systemic Lupus Erythematosus

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Background/Purpose: SLE patients experience deterioration in cognitive function over time but attribution to disease-related mechanisms is confounded by medication effects, psychiatric disease, hormonal influences and infection. The hippocampus and thalamus are interconnected subcortical structures associated with memory, attention, and other higher cortical functions. Decreased hippocampal and thalamic volumes have been reported in SLE subjects with and without cognitive and behavioral impairment. By contrast, metabolic changes in these regions have been consistently associated with memory impairment. The purpose of this study is to use magnetic resonance diffusion tensor imaging (DTI) to evaluate changes in the integrity of pathways (i.e., anatomical connectivity) linking these two structures, as well as other pairs of regions exhibiting metabolic abnormalities in SLE subjects.

Methods: 17 SLE patients with inactive disease and no history of CNS involvement and 14 gender, age-matched healthy control (HC) subjects were imaged using DTI with a 3T MRI scanner (57 slices of 2.5 mm thickness, FOV 240 mm, data acquisition matrix 128 x128 zero filled to 256 x 256, TR 15s). Five b=0 images and 33 diffusion weighted images with b=800 s/mm2 were acquired. The DTI images were processed using FSL routines (FMRIB software library: www.fmrib.ox.ac.uk/fsl), and FA and MD maps were calculated. Group tractography was performed to evaluate the integrity (anatomical connectivity) of projection pathways linking areas with significant metabolic abnormalities in SLE subjects.[1] Tracts connecting the hippocampus, thalamus, putamen, and parietal cortex were reconstructed based on clusters identified by voxel-wise comparison of FDG PET scans from SLE and HC subjects using TrackVis software.

Results: Relative to HC, the SLE group displayed a 28% reduction in hippocampal-thalamic (HT) tract count. The basal ganglia-thalamic tract was preserved in the SLE group (% 8.5 difference), whereas hippocampal-parietal tract number was increased (+30%) relative to HC.

Conclusion: This is the first study to show abnormal HT tracts in SLE subjects. Although the SLE subjects had inactive disease and no history of CNS involvement, HT tract number was reduced in this group. Importantly, the hippocampus and thalamus are areas of the brain known to be integral to cognitive processes and metabolic increases in these areas have been found to correlate with memory impairment. In contrast, other tracts between the hippocampus and parietal lobe or basal ganglia and thalamus are preserved or increased. Abnormalities in the HT tract have been associated with impaired learning and memory as well as with increased symptoms in individuals at high risk for schizophrenia. Additional analyses of other imaging studies and neuropsychological testing are planned to evaluate the functional effects of this novel structural finding. 1. Mackay M. et al., Brain metabolism and autoantibody titers predict functional impairment in Systemic Lupus Erythematosus. Lupus SCi Med, 2015. 2(1): p. e000074.

Disclosure: M. Mackay, None; **P. Heshmati**, None; **A. Vo**, None; **C. Aranow**, GSK, UCB, Janssen, Rencor, 2,Celgene, GSK, Mallinckrodt, Takeda, 5; **B. Volpe**, None; **B. Diamond**, None; **D. Eidelberg**, None.

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Abstract Number: 2882

CD4+ T Helper Cells and Regulatory T Cells in Active Lupus Nephritis – an Imbalance Towards a Predominant Th1 Response?

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic inflammatory disease characterized by the involvement of multiple organs and systems with aberrations in T cell response, especially involving effector and regulatory lymphocytes subsets. Lupus nephritis (LN) has a significant impact on morbidity and mortality of SLE patients. Urinary markers are a potential tool for accurate assessment of LN, because they may reflect immediate local alterations in renal status. The objective of this study is to evaluate the frequency $CD4^+$ T cells in urine and in peripheral blood in LN and to analyze associations with clinical and immunological parameters.

Methods: Peripheral blood mononuclear cells (PBMC) and urinary cells from 17 patients with active LN, 20 disease controls with primary glomerulonephritis (GN) and 10 healthy controls (HC) were analyzed by flow cytometry for the frequency of Th1 ($CXCR3^+CCR5^+$), Th2 ($CCR4^+CD294^+$), Th17 ($CD161^+CCR6^+$) and regulatory T cells (T_{REG} cells) ($CD25^+CD127^{low}$). In LN, $CD4^+$ T-cell subtypes in PBMC were re-evaluated at six months of immunosuppressive therapy with cyclophosphamide or mycophenolate sodium. T-cell subsets were assessed in renal tissue of 12 LN patients who underwent biopsy by immunohistochemistry using the expression of transcription factors as markers: Tbet (Th1 cells), GATA3 (Th2 cells), ROR^{γ} (Th17 cells) and FOXP3 (T_{REG} cells).

Results: $CD4^+$ T cells were decreased in peripheral blood from LN patients compared with primary GN and HC [38.52% ± 10.39 vs. 56.63 ± 9.59 vs. 50.69% ± 8.10; $p = 0.0001$) as well as a lower frequency of peripheral Th2 cells was found in LN compared with HC [2.48% (0.04-16.40) vs. 4.21% (2.98-6.38); $p = 0.025$]. However, no differences were observed in the frequency of urinary $CD4^+$ T-cell subsets between LN and primary GN. When comparing T-cell subsets in peripheral blood from patients with and without proliferative forms of LN, no difference was found. However, a higher frequency of urinary Th17 cells was found in non-proliferative compared with proliferative LN [14.37% (4.42-57.80) vs. 3.85% (1.30-27.00); $p = 0.041$]. $CD3^+$ and $Tbet^+$ cells were found in glomeruli and interstice of LN patients, while FOXP3, RORγ and GATA-3 were present only in glomeruli. Expression of FOXP3 was significantly lower in glomeruli compared with other markers. Peripheral Th1 cells were negatively correlated with urinary Th1 cells (Rho=-0.531; p=0.028) and with Tbet in renal interstice (Rho=-0.782; p=0.004). At 6 months of treatment, LN patients showed a significant increase in peripheral Th17 cells regardless of response to immunosuppressive therapy [1.13% (0.02-8.70) vs. 5.15% (1.35-13.51); $p = 0.008$].

Conclusion: Associations between peripheral, urinary and renal Th1 cells indicate a potential role of Th1 response in LN. Urinary Th17 cells were associated with less severe LN, and peripheral Th17 increased at 6 months of therapy. Differences in $CD4^+$ T cells between LN and primary GN or HC were found only in peripheral blood, not in urine.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/cd4-t-helper-cells-and-regulatory-t-cells-in-active-lupus-nephritis-an-imbalance-towards-a-predominant-th1-response

Abstract Number: 2883

The CD4+CD52low T Cell Contributes to the Development of Systemic Lupus Erythematosus through the CCR8/TARC Pathway

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Background/Purpose: CD52 is a cell-surface glycoprotein that is widely expressed in lymphocytes, monocytes and eosinophils. $CD4^+CD52^{high}$ T cells inhibit the activation of $CD4^+CD52^{low}$ T cells through the release of cell-surface CD52. Soluble CD52, which is cleaved from $CD4^+CD52^{high}$ T cells, works as a ligand of siglec-10 on $CD4^+CD52^{low}$ T cells (1). $CD4^+CD52^{high}$ T cells were reported as distinct population from conventional regulatory T cells. The role of the immune regulation of these cells in systemic lupus erythematosus (SLE) is unknown. We evaluated the $CD4^+CD52^+$ T cells in the human peripheral blood mononuclear cells (PBMCs) of SLE patients and clarified their roles in the pathogenesis of SLE.

Methods: We isolated the PBMCs of 58 SLE patients, 22 non-SLE patients (19 with rheumatoid arthritis, 3 with mixed connective-tissue disease) and 33 healthy controls (HCs). The expressions of $CD4^+CD52^{high}$ T cells and $CD4^+CD52^{low}$ T cells were analyzed by flow cytometry. We also analyzed the correlations with clinical parameters including SLEDAI, anti-ds-DNA antibodies and complement. We then analyzed circulating follicular helper like T cells (Tfh like cells) identified as $CD4^+CXCR5^{high}ICOS^{high}PD\text{-}1^{high}$ and plasmablast identified as $CD3^-CD19^+CD38^+CD27^+$. To determine the genetic characteristics of $CD4^+CD52^{low}$@and $CD4^+CD52^{high}$ T cells from SLE, we performed cDNA microarrays (SurePrint G3 Human GE 8x60K) and examined the function of the genes in *in-vitro*.

Results: We found that the expression of $CD4^+CD52^{low}$ T cells in the SLE was significantly higher than HC and non-SLE. The expression of $CD4^+CD52^{low}$ T cells of the SLE were positively correlated with SLEDAI, anti-ds-DNA antibodies and IgG. The population of Tfh like cells were increased in SLE and its expression was positively correlated with $CD4^+CD52^{low}$ T cells. The microarray analysis revealed that the expression of chemokine receptor 8 (CCR8) is significantly increased in $CD4^+CD52^{low}$ T cells. In addition, in vitro experiments using CD4 T cells from patients with SLE showed that thymus and activation-regulated chemokine (TARC), known as a ligand of CCR8, induced the conversion of $CD4^+CD52^{high}$ T cells into $CD4^+CD52^{low}$ T cells.

Conclusion: Collectively, our data suggest that increased $CD4^+CD52^{low}$ T cells along with increased Tfh like cells are involved in the pathogenic autoantibodies production and that TRAC may contributes to the development of SLE via an aberrant induction of $CD4^+CD52^{low}$ cells. References@1DNat Immunol. 2013: 14:741-8.

Disclosure: T. Sato, None; **M. Umeda**, None; **T. Koga**, None; **T. Igawa**, None; **S. Kurushima**, None; **A. Takatani**, None; **T. Shimizu**, None; **S. Fukui**, None; **A. Nishino**, None; **Y. Horai**, None; **S. Kawashiri**, None; **N. Iwamoto**, None; **Y. Hirai**, None; **M. Tamai**, None; **H. Nakamura**, None; **T. Origuchi**, None; **A. Kawakami**, None.

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Abstract Number: 2884

Cell-Type Specific Epigenetic Features of Systemic Lupus Erythematosus

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SESSION INFORMATION
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Background/Purpose: Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that involves multiple organ systems and periods of variable disease activity. Although SLE, especially in patients with high disease activity, is often associated with increased circulating pro-inflammatory cytokines, a clear understanding of immune dysfunction preceding and during high disease activity is lacking. The identification of genes and gene pathways that are differentially regulated between SLE and healthy individuals, as well as between patients with varying disease activity, may allow better selection of directed therapeutics and development of new targets. To address this knowledge gap, we determined the chromatin accessibility landscape of three distinct compartments of the lupus immune system using the 'Assay for Transposase Accessible Chromatin Sequencing' (ATAC-seq) method.

Methods: Monocytes, B cells, and T cells were sorted by flow cytometry from frozen PBMCs of 9 SLE patients and 5 matched controls. Sorted cell fractions were processed for high-throughput open chromatin profiling by ATAC-seq. Reads were aligned to the hg19 genome and regions of enriched chromatin accessibility "peaks" were identified with MACS2. For each cell type, we identified the consensus set of epigenetically active peaks across all 14 subjects. We conducted enrichment tests of identified loci using the GREAT tool and performed differential accessibility analysis using the edgeR package in R. Transcription factor binding motif enrichment and overlaps with known SLE risk haplotypes were also determined.

Results: All cell types showed similar percentages (39~43%) of coding transcripts with open chromatin in promoters. The peaks unique to each profile were enriched in genomic loci specific to their cellular function: T cell development/activation for T cells, B cell development/activation for B cells, and phagocytosis, apoptotic cell clearance, and inflammatory cytokine regulation for monocytes. Analysis of transcription factor binding motifs in ATAC peaks identified cell type specific promoters including myeloid and lymphoid cell lineage commitment transcription factors. Quantitative analysis revealed chromatin accessibility loci that discriminate between SLE and controls, as well as between high and low disease activity. Of the total 53338 monocyte specific peaks observed in at least 7 samples, 308 peaks allowed us to differentiate between SLE and controls, whereas in T and B cells the numbers were 57 of 34818 and 553 of 39425, respectively. Motif analysis revealed that many consensus peaks occupy binding sites of cohesin complex subunits, suggesting that long-range chromatin interactions may mediate immune responses that drive SLE progression. In addition, of 2519 SLE genetic risk SNPs, 320 were located within an open chromatin peak suggesting functional relevance.

Conclusion: Our data suggest that SLE and controls show cell type specific differences in their chromatin accessibility, and these profiles differ across the spectrum of disease activity. Chromatin profiling, integrated with transcriptome data, may expand our knowledge of how specific cell states drive SLE pathogenesis.

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Abstract Number: 2885

Expression Levels and Function of the Inhibitory Molecule, Immunoglobulin like Transcript 7 (ILT7), Are Decreased on Circulating Plasmacytoid Dendritic Cells in SLE Patients with High ANA Titers

Mark A. Jensen[1], Jessica M. Dorschner[2], Danielle Vsetecka[2], Shreyasee Amin[3], Ashima Makol[3], Floranne C. Ernste[4], Thomas Osborn[3], Kevin Moder[3], Vaidehi Chowdhary[3] and Timothy B. Niewold[5], [1]Department of Immunology and Division of Rheumatology, Mayo Clinic, Rochester, MN, [2]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [3]Rheumatology, Mayo Clinic, Rochester, MN, [4]Division of Rheumatology, Mayo Clinic Rochester, Rochester, MN, [5]Rheumatology and Immunology, Mayo Clinic, Rochester, MN

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Background/Purpose: Systemic lupus erythematous (SLE) is a complex autoimmune disease often involving multiple organs. In SLE, immune complexes containing autoreactive antibody and nuclear material activate plasmacytoid dendritic cells (PDCs). Activated PDCs are thought to contribute to disease pathogenesis by secreting IFN-alpha and through presentation of autoantigen to T cells. PDC

activation is regulated by numerous inhibitory surface receptors including ILT7 which serves as a negative feedback pathway to limit PDC IFN production. We and others have linked numerous gene polymorphisms with blood IFN levels, disease severity, and clinical characteristics.

Methods: We studied expression of 12 inhibitory surface receptors on PDCs from a cohort of patients (n>60) and controls (n>20) by quantitative flow cytometry and correlated them with IFN levels, clinical characteristics, and disease severity. ILT7 function was studied by measuring the impact of ILT7 crosslinking on IFN and cytokine output using blood mononuclear cells and purified PDCs from patients and controls. A second inhibitory receptor, CD303, was studied as a comparator.

Results: We find selective downregulation of surface ILT7 expression and decreased ILT7 function by PDCs of patients with high ANA titers (p<.0001 for SLE with high vs low ANA titers).

Conclusion: These data suggest that decreased function of the ILT7 pathway leads to chronic PDC activation in SLE patients. The association with higher ANA titers suggests that dysfunction in this pathway may contribute to the formation of autoreactive antibodies and may contribute to disease pathogenesis in SLE via an impact on the IFN pathway as well as humoral autoimmunity.

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Abstract Number: 2886

Associations Between Type I Interferon and Antiphospholipid Antibody Status Differ Between Ancestral Backgrounds

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Background/Purpose: Autoantibodies in SLE that bind to double-stranded DNA or RNA-binding proteins are strongly associated with high levels of type I interferon (IFN), likely via their ability these antibodies to form nucleic-acid containing immune complexes that can stimulate Toll-like receptors. In this study, we examine whether anti-phospholipid antibodies, which should not have this capacity, are associated with greater type I interferon in SLE patients.

Methods: We studied 392 SLE patients (223 African-American, 101 European-American, and 68 Hispanic-American ancestry) and measured type I IFN in sera. Antiphospholipid (APL), anti-RBP, and anti-dsDNA antibodies were measured in the clinical laboratory, and standard clinical cut-offs were used to define a positive result. Non-parametric analyses were used to compare IFN data with the antibody data in each ancestral background.

Results: African-American subjects with a positive IgG APL antibody test had higher type I IFN levels than those without APL antibodies (p=0.02). This was not observed in the other ancestral backgrounds, and in fact the opposite trend was observed in Hispanic-Americans. African-Americans were less likely to have a positive IgG APL test than European-Americans (p=0.0067, OR=2.3), and those African-Americans with a positive IgG APL test were more likely to also have anti-dsDNA antibodies (p=0.04, OR=2.5).

Conclusion: These data suggest a distinct serological profile in African-American patients, in which a positive APL antibody test corresponds with a significantly greater type I IFN level and more frequent anti-dsDNA antibodies, and this is not shared with other ancestral backgrounds. These data support differences in the molecular pathogenesis of SLE by ancestral background that may impact treatment strategies.

Disclosure: T. Iwamoto, None; **M. Jolly**, Pfizer Inc, 9; **T. B. Niewold**, None.

Abstract Number: 2887

Clinical Predictors for Development of Interstitial Lung Disease in Mixed Connective Tissue Disease

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Session Time: 9:00AM-11:00AM

Background/Purpose: Mixed connective tissue disease (MCTD) is an immune-mediated systemic disorder characterized by serum autoantibodies against U1-ribonucleoprotein and diverse multisystemic clinical manifestations. Approximately 50% of patients with MCTD develop a radiological pattern of interstitial lung disease (ILD). In this study, we explore the phenotypic and clinical features in patients with MCTD that are associated with development of ILD.

Methods: We performed a retrospective case control study utilizing data from patients evaluated at a single tertiary care center from 2007-2014. Twenty-eight patients who met validated criteria for diagnosis of MCTD were included in the study. Fourteen patients had high-resolution computed tomography or biopsy-proven ILD, and 14 had MCTD without evidence of ILD . We performed a multivariate logistic regression with multiple demographic, clinical, and serologic predictor variables, and ILD as the outcome variable.

Results: Two clinical variables had an association with development of ILD in patients with MCTD:

1. Dysphagia with a R^2 value of 0.33 (p value < 0.001)
2. Raynaud's phenomenon with R^2 value of 0.28 (p value < 0.001)

We did not find a significant association between any other demographic, clinical, or serologic variables and development of ILD in patients with MCTD.

Conclusion: Dysphagia is one of the symptoms of esophageal involvement in patients with autoimmune connective tissue disorders. An association of dysphagia with the development of ILD in our study is in harmony with the existing literature, wherein esophageal dysmotility has been described in a cluster of patients with MCTD and ILD. Scant data, primarily case reports, suggest an association of Raynaud's phenomenon with development of ILD in patients with undifferentiated CTD. To our knowledge, this is the first study highlighting the association of Raynaud's phenomenon with development of ILD in patients with MCTD. This study is limited by its small size and retrospective nature. The mechanistic aspects of the association between Raynaud's phenomenon and ILD remain unexplored. The association of easily elicited historical and clinical features of MCTD with subtle, but worrisome, pulmonary pathology carries the promise of sensitizing the unsuspecting clinician about the entity of ILD in MCTD.

Disclosure: N. Narula, None; **T. Narula**, None; **B. Wang**, None; **A. Abril**, None.

Abstract Number: 2888

Usefulness of Bosentan in the Prevention of Pulmonary Hypertension in Patients with Systemic Sclerosis

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Background/Purpose: Systemic sclerosis (SSc) is a systemic autoimmune disease in which the damage of microcirculation is critical to develop the disease. In SSc, vascular complications have very similar pathogenic findings, which are relevant in the disease. For example, digital ulcers (DU) are a frequent complication in SSc patients and pulmonary arterial hypertension (PAH) is one of the leading causes of death. The use of endothelin receptor antagonists (ERAs) has been shown to be useful for the treatment of PAH related to SSc, and to prevent new episodes of DU in patients with the disease. However, it is not known if ERAs are useful for the prevention of PAH.The aim of our study is to determine if ERAs are useful to prevent PAH in SSc patients. Furthermore, we aim to determine if there are any differences in echocardiographic or pulmonary function tests for patients treated with or without ERAs.

Methods: This was a retrospective, multicentre case-control study with 237 SSc patients with DU. Data were analysed during follow-up for patients treated or not treated with Bosentan (BOS) to prevent DU. The occurrence of pulmonary hypertension (PH) was defined by an echocardiogram (ECO) exhibiting systolic pulmonary arterial pressure (sPAP) > 40 mmHg at any stage of the follow up. For all patients, demographic variables, gender, SSc subtype, clinical involvement, autoimmunity data, capillaroscopy findings and different echocardiographic and pulmonary function test data, performed from baseline to follow-up were collected. Statistical significance was denoted by p values less than 0.05

Results: Fifteen patients had ECO values of sPAP> 40mmHg and were excluded from the analyses. Of the remaining 222 patients the majority were women (91%) with a mean age (±SD) of 63.9 (±19.6) years. The first manifestation of the disease occurred at 40.7 (±17.9) years, while Raynaud's phenomenon was the most frequent initial finding (85.6%). Fifty-nine patients (26.6%) were treated with BOS. The most common dose was 250mg daily (60%) and BOS was taken for a median of 34 months. In 21% of patients, PH was suspected due to ECO findings. During the follow up 13.8% of patients treated with BOS presented with PH, in comparison to 23.7% of untreated patients (OR 0.52, 95% CI: 0.22-1.19; p = 0.13). Adjusted regression analyses showed patients not treated with BOS were 3.9 times more likely to develop PH during follow-up (OR 3.913, CI95%:1.32-11.58; p < 0.02). Analysis of the tools of patient evaluation showed that the percentage of diffusing capacity for carbon monoxide (DLCO) in BOS-treated patients did not significantly decrease from baseline to the end of follow-up (61.8±14% vs 57±20.1%, p=0.89). This was statistically significant (p < 0.04) when compared to BOS-untreated patients who showed a significant decrease in the percentage of DLCO at the end of follow-up (65.5±20.2% vs 60.5±19.9%; p < 0.01).

Conclusion: Our retrospective study shows that those patients treated with BOS to prevent UD have a lower risk to develop PH during the disease as well as stabilization of DLCO percentages. Our results support the need for a prospective, randomized, clinical trial to study the effect of ERA in prevention of PAH in SSc patients.

Disclosure: I. Castellví, None; **C. P. Simeón**, None; **M. P. Sarmiento**, None; **A. Guillen**, None; **C. Diaz-Torné**, None; **J. M. De Llobet Zubiaga**, None; **J. Casademont**, None; **V. Fonollosa**, None.

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Abstract Number: 2889

Therapeutic Plasma Exchange for the Treatment of Raynaud's and Digital Ulcers in Systemic Sclerosis: A Systematic Review

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Background/Purpose: Raynaud's phenomenon (RP) is an early marker of microvascular damage in systemic sclerosis (SSc) and digital ulcers (DU) are a serious complication of vascular dysfunction, occurring in about 50% of SSc patients. DU are painful, difficult to heal, and in some cases progress to gangrene and autoamputation. Current treatments for RP and DU focus on improving distal blood flow using vasodilators, vasoconstrictor antagonists, or drugs which reduce vasospasm. Nevertheless, many patients continue to develop DU over time, suggesting the need for alternative treatment options.

Methods: We reviewed all publications between 1978 and 2016 on the use of therapeutic plasma exchange (TPE) to treat patients with SSc. Out of the 40 papers reviewed, 13 reported effects on RP and DU. Four studies were confounded by simultaneous use of drug therapies and were excluded from the analysis shown in the table.

Results: A commonly reported finding was that a single course of a small number of weekly TPE treatments (typically four) had significant effects on both RP and DU as well as blood flow, microvessel patency, and blood rheology. In many patients, RP disappeared or was significantly improved, and even long-standing digital ulcers began to heal. Several studies documented abnormal blood rheology pre-treatment (elevated whole blood viscosity (WBV) and RBC aggregation) that was significantly reduced after four weekly TPE treatments. The improvements in symptoms and blood rheology were surprisingly long lasting: at least six months and in one study no reoccurrence of DU was observed at three-year follow-up.

Conclusion: In patients diagnosed with SSc, a limited course of TPE treatments appears to lead to significant improvements in RP and DU symptoms as well as objective improvements in blood flow, microvessel patency, and blood rheology that persist for several months. Since TPE treatments have no known direct effects on blood vessels, these results suggest that TPE may have an entirely different mechanism of action. Volkov (2006) noted that WBV is highest in patients with active DU, raising the possibility that the long-lasting normalization of whole blood viscosity and significant reduction of RBC aggregation may directly lead to enhanced microvascular blood flow and thus to improved microvessel patency and SSc symptoms. We recommend that a randomized, double blind, placebo-control study of TPE that includes measurements of blood rheology be conducted to better understand these effects.

Study	Type	N	TPE Protocol	Follow-Up	Summary / Notes
Cotton 1978	PS	12	Varied	Not reported	Letter. Improved microvessel patency in 10/12 Pts. Gangrene reversed in 1 Pt. after 6 TPE.
Talpos 1978	PS	5	1 TPE/week for 5 weeks	6 months post TPE	4/5 patients with DU before TPE. All DU but 1 healed after TPE. Significant improvement in RP and DU post TPE. Blood viscosity sig improved in 3/3 Pts.
Dodds 1979	PS	8	1 TPE/week for 4 weeks	6 weeks post TPE	DU healed in 3/3 Pts. Microvessel patency improved in 6/6 Pts.
O'Reilly 1979	RCT	27 (9 in TPE group)	1 TPE/week for 4 weeks	6 weeks, 6 months post TPE	Microvessel patency significantly improved in TPE group only at 6 week and 6 month follow-up. DU healed after TPE in 3/3 Pts and remained healed at 6 month F/U.
Zahavi 1980	CT	37 (9 Pts. with severe SSc in TPE group)	1 TPE/week for 4 weeks	3 months post TPE	At F/U, microvessel patency improved in 7/8 Pts. and DU healed in 3/3 Pts.
McCune 1983	PS	6	1 TPE or ÒshamÓ TPE/week for 4 weeks	3 months, 6 months post TPE	Complicated design with mixed TPE and autologous ÒshamÓ TPE. 5/6 maintained improvements in RP and DU at 3 month and

					6 month F/U. Some objective measures improved with sham TPE as well as standard TPE.
Von Rhede van der Kloot 1985	PS	14 (7 primary RP, 7 secondary RP)	1 TPE/week for 4 weeks	Post TPE only	RP disappeared or improved in 6/7 Pts. in secondary RP group and 2/7 in primary RP group, DU improved in 3/3 Pts. in secondary RP group.
Ferri 1987	PS	6 (severe SSc)	3 TPE/week for 6 to 8 weeks, then tapering down. Total duration 6 to 14 weeks.	Post TPE only	5 Pts. completed protocol. DU healed or significantly improved in 5/5 Pts. at end of TPE.
Jacobs 1991	PS	18	1 TPE/week for 4 weeks	Three, nine, 24, 36 months post TPE	Post TPE, all Pts. had either complete elimination of TP or significant reduction. Any DU healed. No reoccurrence of DU at 3-year F/U. In 14 Pts. RP returned after 6 to 9 months post-TPE. In 4 Pts, no RP at 3-year F/U. RBC aggregation was significantly less ($p<.001$) post TPE and gradually returned to pre-TPE levels after 9 months.
PS: Pilot Study RCT: Randomized Controlled Trial CT: Controlled Trial					

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Abstract Number: 2890

Feasibility of Same Day Adipose Tissue Harvest, Cell Processing and Subcutaneous Delivery of Adipose Derived Regenerative Cells into Fingers of Scleroderma Patients within a Randomized Double Blind Clinical Trial

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Background/Purpose: Current medical therapy to improve hand function has had very limited benefit in patients with systemic sclerosis (SSc). Cells present within a person's own adipose tissue (Adipose Derived Regenerative Cells [ADRCs]) have the potential to improve tissue injury in scleroderma by modulating inflammation, stimulating angiogenesis, improving vasomotor reactivity, and stimulating local repair cells.

Methods: The STAR Trial is a phase III, pivotal, prospective, randomized (1:1), placebo-controlled, multi-center trial to assess safety and efficacy of subcutaneous administration of ADRCs into fingers of patients with hand dysfunction due to scleroderma. Key inclusion criteria include a classification of SSc, based on 2013 ACR/ EULAR classification criteria and a baseline Cochin Hand Function Scale (CHFS) score ≥20 units (suggesting at least moderate hand impairment). All enrolled patients (ADRC and placebo) undergo fat harvest through small volume liposuction (~200 to 400 mL). Lipoaspirate is processed in the Celution® System (Cytori Therapeutics, San Diego) to isolate and concentrate ADRCs, which contain CD34+ multipotent cells, pericytes, endothelial cells, and other cellular constituents. Patients then receive subcutaneous administration of 1 mL test substance (ADRC [4 million cells per finger] or matching placebo [Lactated Ringers containing patient's own blood to visually match the placebo to ADRCs]) into all fingers. Placebo patients may cross-over to open label ADRCs at the end of the trial. Key endpoints include: CHFS, Raynaud's Condition Score (RCS), Scleroderma Health Assessment Questionnaire (SHAQ), global assessments, Hand Mobility in Scleroderma (HAMIS) test, digital ulcer counts/time to new ulcer, modified Rodnan Score (hands only), grip/pinch strength, and analgesic use. Follow up visits are scheduled for weeks 1, 4, 12, 24, 36, 48 weeks.

Results: Trial enrollment has been completed (n=88) with baseline blinded data available from up to 86 patients. Patient demographics from the cohort indicated a mean age 53.2±10.6 years, female 87%, 77% Caucasian, and %limited/diffuse 42/58. Baseline Cochin score

was 42.2±14.2 (0-60) and the baseline RCS was 3.9±2.1 (0-10); 73% of patients had a history of digital ulcers with 39% reported with digital ulcer(s) at baseline. Patients experienced expected adverse events such as liposuction related discomfort and ecchymosis; however, no peri-procedure complications or serious adverse events occurred. No cell related adverse events have been reported. All patients were discharged the same day following fat harvest, cell processing and cell injection. Mean adipose tissue harvest 293±50 mL, ADRC yield 120.6±66 x 10^6 cells, ADRC/gm adipose tissue 3.97±1.82 x 10^5, ADRC viability 89.1±2.7%. Data continues to be collected in the follow-up period.

Conclusion: The STAR trial demonstrates same day fat harvest, cell processing and subcutaneous injection of ADRCs to all fingers in patients with scleroderma is feasible and can be performed safely.

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Abstract Number: 2891

Prognostic Significance of Autoantibody Positivity in Interstitial Lung Disease: A Retrospective Case-Control Study

Christos F Kampolis[1], Aliki I Venetsanopoulou[1], Fotini Karakontaki[2], Vlassis Polychronopoulos[2], Panayiotis G Vlachoyiannopoulos[1] and Athanasios G. Tzioufas[3], [1]Pathophysiology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece, [2]Respiratory Medicine, "Hygeia" Hospital, Athens, Greece, [3]School of Medicine, Pathophysiology Department, National and Kapodistrian University of Athens, Athens, Greece

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Background/Purpose: Routine screening for circulating autoantibodies (AAbs) on the initial evaluation of interstitial lung disease (ILD) contributes to the diagnosis of underlying autoimmune disease. However, so far, few studies have focused on the role of AAbs as an independent prognostic factor in ILD, with conflicting results. In the present study, we investigated the possible association of AAbs with functional or radiological progression and survival in patients with ILD.

Methods: We retrospectively reviewed the medical records of patients with ILD followed up in a rheumatology and a respiratory outpatient clinic. Regular clinical, functional and computed tomography (CT) imaging follow-up for at least 2 consecutive years and complete testing for a panel of AAbs most commonly associated with ILD [such as antinuclear antibodies (ANAs) (positive titers ≥1:160), AAbs to extractable nuclear antigens, anti-neutrophil cytoplasmic antibodies, rheumatoid factor or anti-citrullinated protein antibodies] were our inclusion criteria. Eligible patients were subsequently classified into two groups: those without AAbs [ILD/AAb(-)] and those with positive ANAs and/or other specific AAbs, either with or without clinical manifestations compatible with connective tissue disease (CTD) [ILD/AAb(+)]. Serial pulmonary function tests (PFTs), including measurements of forced vital capacity [FVC (% pred.)] and single-breath diffusion capacity [$DLCO_{SB}$ (% pred.)], degree of dyspnea according to modified MRC scale (mMRC) (Grade 0 to 4), baseline and comparative follow-up high resolution CT (hrCT) findings and survival data were also collected. Progression of lung disease on PFTs was defined as a sustained decrease from baseline in absolute FVC of ≥10% and/or absolute $DLCO_{SB}$ of ≥15%. $DLCO_{SB}$<40% pred. on at least two consecutive measurements and disease progression on hrCT were defined as secondary endpoints.

Results: Among 185 patients with ILD initially screened, 78 met our inclusion criteria. Fifty three of them were ILD/AAb(+) and 45 had a definite diagnosis of CTD. Mean age at first outpatient visit was 57.8 years and mean duration of follow-up was 72.6 months.

ILD/AAb(+) patients were predominantly female (*77% vs 28%*), were significantly younger (*54.2 ± 15.1 vs 65.6 ± 13.0 years*), and had longer duration of follow-up (*84.5 ± 58.1 vs 47.5 ± 29.6*), compared with ILD/AAb(-) patients (*p<0.01 for each comparison*). Baseline FVC (% pred.) and $DLCO_{SB}$ (% pred.) did not differ significantly between the two groups. During follow-up, mortality rates and the percentage of patients with sustained FVC or $DLCO_{SB}$ decline, $DLCO_{SB}$ <40% pred., or severe dyspnea (Grade 3-4) were lower in the ILD/AAb(+) group (*p<0.05 for each*). In addition, rates of radiological deterioration were marginally significantly lower (*p=0.079*). In Cox regression for survival analysis, AAb positivity was also associated with a reduced adjusted hazard ratio for death, PFT decline (p<0.001 for each outcome), and radiological deterioration (*p=0.036*).

Conclusion: The presence of positive AAbs in patients with ILD is associated with better survival, less rapid decline of lung function and slower progression of CT findings.

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Abstract Number: 2892

Serum Level of KL-6, a Biomarker of Interstitial Lung Disease (ILD), Is Higher in Diffuse SSc Than in Limited SSc and RA Even When the Activity of ILD Is Low

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Background/Purpose: KL-6 is a glycoprotein expressed on and released from type 2 alveolar cells and the measurement of KL-6 in serum was developed by Kohno et al (Am J Respir Crit Care Med 1993). Serum levels of KL-6 have been reported to be higher in ILD (Ohnishi H, Am J Respir Crit Care Med 2002) and be a predictor of prognosis of ILD (Yokiyama A, Am J Respir Crit Care Med 1998). We also reported that serum levels of KL-6 increased when ILD exacerbated after administration of TNF-inhibitors in RA (Nakashita T, BMJ open 2014). Normal range of serum KL-6 is less than 500 U/ml and serum level of more than 1,000 U/ml is a predictor of poor prognosis. However, we have noticed that in some patients serum KL-6 levels are sustained in high levels even when the activity of ILD deceased. We tried to detect the factors that contribute in sustaining serum KL-6 levels high.

Methods: Subjects were 98 patients including 52 RA, 19 diffuse SSc, and 27 limited SSc. These patients fulfilled the following requirements; 1. presence of ILD proved by chest CT, 2. no changes in chest CT findings for more than 2 years, 3. less than 5 % changes in % VC for more than 2 years, suggesting that the ILD is stable during the period. Serum KL-6 levels were checked periodically, every 2 – 6 months, from the first visit to our department. Nine variables were checked including diagnosis (RA, d-SSc, l-SSC), age, gender, ILD pattern (UIP, NSIP, organizing pneumonia), ILD grade (1 – 3 according to Nakashita), % VC, peak serum KL-6 value, peripheral blood eosinophil count, ANA titer, and RF titer. These variables were statistically analyzed.

Results: Serum KL-6 value was highest in d-SSc followed by l-SSc and RA; the mean values were 776 U/ml, 439 U/ml, and 371 U/ml, respectively ($p < 0.0001$). % VC values were lowest in d-SSc followed by l-SSc and RA; the mean values were 90.1 %, 98.9 %, and 107.2 %, respectively ($p < 0.02$). Multivariate analysis was done using 10 variables to extract factors that contribute to discriminate 2 groups, i.e. a very high KL-6 group (KL-6 >= 900 U/ml) and another group (KL6 < 900 U/ml). In a very high KL-6 group included 10 patients. Factors that contribute to discriminate 2 groups ($p < 0.1$) were diagnosis (RA, d-SSc or l-SSc), % VC, and peak serum KL-6 values. Multiple regression analysis was also done. Multiple regression coefficient was moderately high (0.78), but significant regression factors were diagnosis and peak KL-6 value.

Conclusion: Patients with d-SSc, low % VC and high peak KL-6 value tend to show high serum KL-6 values even when ILD is not active. Our results can contribute to avoid aggressive treatment for patients with stable but very high serum KL-6 levels.

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Usefulness of the Eustar Preliminary Criteria for Vey Early Systemic Sclerosis and Le Roy Criteria for Early-Systemic Sclerosis in Identifying Patients at Risk of Development of Systemic Sclerosis

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Background/Purpose: Previously, Early Systemic Sclerosis (Early-SSc) patients were defined as patients with Raynaud phenomenon (RP) and either a scleroderma marker autoantibody or typical capillaroscopy abnormalities or both. Since 2013 the definition of Early-SSc has been updated: Patients should not meet the new 2013 ACR/EULAR criteria for the classification of Systemic Sclerosis (SSc). EUSTAR group also proposed preliminary criteria for the very early diagnosis of SSc which have not yet been validated. Our aim was to revise the usefulness of Le Roy criteria and Very Early EUSTAR criteria in identifying patients at risk of development of SSc.

Methods: Retrospective study of a wide and unselected series of patients with Early-SSc and SSc from a single university hospital from June 2012 to August 2015. We excluded patients who fulfilled 2013 ACR/EULAR criteria at first visit. Patients were classified as Early-SSc following Le Roy criteria and classified as SSc according to the 2013 ACR/EULAR criteria during follow-up. We reviewed EUSTAR criteria in both groups.

Results: We included a total of 56 patients with a mean age of 55±15 years (94.6% women; 5.4% men). At first visit, 15 (26.8%) of our patients fulfilled 2013 ACR/EULAR criteria and were excluded of the final analysis. 37 (66.1%) of our patients fulfilled Le Roy criteria at first visit. The remaining 4 patients (7.1%) did not meet any of these criteria in the first visit. During the follow-up of this group of 41 patients, 37 (90.2%) presented RP and 9 (22%) presented puffy fingers. Antinuclear antibodies (ANA) were present in 34 (82.9%) of the patients, Anti-centromere antibodies in 24 (58.5%) patients and 29 (70.7%) patients presented pathologic capillaroscopic exam. After a mean follow-up period of 26.1±16.6 months, 20 (48.8%) patients fulfilled 2013 ACR/EULAR criteria. The remaining 21 patients remaining classified as Early-SSc following Le Roy criteria. Of the following EUSTAR criteria, only significant positivity of ANA was observed more frequently in patients that fulfilled 2013 ACR/EULAR criteria: ANA (100%vs63.6%;p=0.005), anti-centromere antibodies (65%vs50%;p=0.41), raynaud phenomenon (95%vs85.7%;p=0.31), abnormal capillaroscopic exam (65%vs76.2%;p=0.8), presence of puffy fingers (25%vs19%;p=0.65).

Conclusion: In our study, over the half of the patients initially classified as Early-SSc progressed to SSc during follow-up. EUSTAR preliminary criteria were more frequent in patients who during follow-up fulfilled 2013 ACR/EULAR criteria for SSc, although only the positivity of ANA was statistically significant. Further studies are needed to better characterize the patients with Early-SSc and Very Early-SSc.

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Abstract Number: 2894

Efficacy of Rituximab in Systemic Sclerosis with Interstitial Lung Disease

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Background/Purpose: Systemic sclerosis (SSc) is a progressive fibrotic and autoimmune disease, which results to severe systemic complications. Rituximab (Rtx), an anti CD-20 antibody, has recently been started to use for complications of SSc especially interstitial lung disease (ILD). We aimed to asses the efficacy of Rtx therapy in SSc patients with ILD.

Methods: 39 SSc patients with progressive ILD disease included in to the study. 35 (89.7%) of these patients had experienced a worsening of ILD after the conventional cyclophosphamide therapy and 4 (10.2%) patients refused using cyclophosphamide because of potential infertility. All patients were treated with Rtx 1000 mg twice/six months. Functional vital capacity (FVC), diffusing capacity for carbon monoxide (DLCO), high resolution computed tomography (HRCT), modified Rodnan skin score (mRSS), Valentini activity index (VAI), Medsger disease severity index (MDSI) were recorded. Patients were eveluated with 6 months intervals for all these parameters. Initial and 12th month values were assessed and data was analysed by SPSS 18.0 (SPSS, Chicago, IL). Paired t and Wilcoxon Signed Ranks tests were used.

Results: Women (37; 94.9%) outnumbered men (2; 5.1%) significantly. Mean age was 58.1±11.8 years. Median disease duration was 30 (18-132) months. Median follow-up time was 25 (18-100) months. Demographic data were given in table 1. All of the patients had active ILD which demonstrated by ground-glass opacification on HRCT. From 35 patients resistant to cyclophosphamide; 26 (66.6%) switched to Rtx monotherapy, 7 (17.9%) continued with Rtx+cyclophosphamide combination therapy, 2 (5.1%) continued with Rtx+mycophenolate mofetil combination therapy. Additionally, 6 (15.4%) patients received IV iloprost and 3 (7.7%) received bosentan. mRSS was 9.1±5.9, VAI was 2.7±0.8, MDSI was 4.4±1.6 before Rtx. FVC (%), DLCO (%) were 86.4±21.0 and 64.2±17.9 respectively. The 12th month values were compared within initial ones and we demonstrated that mRSS (6.9±4.5, $p<0.001$), MDSI (4.0±1.2, $p=0.032$) scores had significant improvement. On the other hand VAI (2.4±0.5, $p=0.051$), FVC (92.1±17.0, $p=0.056$) and DLCO (68.1±16.1, $p=0.271$) values had no significant difference (table 2). Interestingly number of the patients with digital ulcers were decreased from 16 (41.0%) to 9 (23.0%).

Conclusion: In SSc, progression of ILD seems remained stable with Rtx therapy. This might be a good opportunity for the treatment. Skin score improvement in these patients might indicate the benefical effect of Rtx either.

Table 1. Demographic, Clinic and Immunological Features

	39 patients
Female/Male, n (%)	37 (94.9)/ 2 (5.1)
Age (m±SD)	58.1±11.8
Smokers n (%)	2 (5.1)
Disease Duration (month, median)	30 (18-132)
Follow-up Time (month, median)	25 (18-100)
Diffuse SSc, n (%)	21 (53.8)
Limited SSc, n (%)	18 (46.2)
Modified Rodnan Skin Score (m±SD)	9.1±5.9
Valentini Index (m±SD)	2.7±0.8
Medsger Index (m±SD)	4.4±1.6
Pulmonary Hypertension, n (%)	8 (20.0)
Patients with Digital Ulcers, n (%)	16 (41.0)
Anti-Sentromer, n (%)	8 (20.0)
Anti-Scl-70, n (%)	18 (46.2)
FVC, % (m±SD)	86.4±21.0
DLCO, % (m±SD)	64.2±17.9

Disclosure: **A. M. Onat**, None; **O. Zengin**, None; **S. Aksoy**, None; **M. E. Onder**, None; **K. G. Sacıntı**, None; **B. Kisacik**, None.

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Adaptation of UCLA Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0 Questionnaire into Turkish

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Background/Purpose: Nearly 90% of patients with scleroderma (SSc) have gastrointestinal tract(GIT) involvement in variable severities and is a challenging process for clinicians.The University of California Scleroderma Clinical Trial Consortium Gastrointestinal Tract 2.0(UCLA SCTC GIT 2.0) is a questionnaire including 34 items, 7 multi-item scales :reflux, distention/bloating, diarrhea, fecal soilage, constipation, emotional well-being and social functioning. By these parameters, a total GIT score is calculated (1). This scale translated in German, Italian, French, Polish, Spanish, Swedish, Dutch before, they are available in http://www.uclascleroderma.researchcore.org/ website (1,2,3). There is no Turkish version of this scale yet. Our aim is to make translation, cultural adaptation of UCLA SCTC GIT 2.0 into Turkish, and assess reliability of the scale in patients speaking Turkish.

Methods: UCLA SCTC GIT 2.0 scale was translated into Turkish according to international guidelines and applied to 97 SSc patients. The questionnaire repeated in 29 patients after an interval of 15 days for determining reliability. For internal consistency, Cronbach's alpha was calculated, reliability coefficient if item deleted and test-retest reliability also determined. External consistency was measured by comparing with the Short Form(SF)-36 by Spearman's correlation analysis (rho: ≤ 0.29 weak, 0.30-0.49 middle, ≥ 0.50 strong).

Results: 97 scleroderma patients were included in this study (female:87.6%, mean age:55.4±11.4). Internal consistency Cronbach's alpha was calculated as 0.89, reliability coefficient if item deleted was 0.89-0.90. External consistency of UCLA SCTC GIT 2.0 was measured by comparing with the SF-36, correlation was meaningful in medium level (Table 1,2).

Conclusion: UCLA SCTC GIT 2.0 scale had strong internal consistency, good reliability and acceptable validity when adapted into Turkish. Turkish-speaking patients with scleroderma, this scale will useful to assess GIT symptoms. The basic constraint of our study was, not using image procedures for objective GIT involvement evidences.

Table 1. Descriptive Statistics and Internal Consistency Statistics.

UCLA SCTC GIT 2.0 Scale	n	Mean score (SD)	Minimum score	Maximum score	Cronbach alpha	Floor Effect %	Ceiling Effect %
Reflux	97	0.64 (0.54)	0.0	2.6	0.83	17.5	0.0
Distension	97	1.02 (0.75)	0.0	3.0	0.58	7.2	1.0
Soilage	97	0.30 (0.72)	0.0	3.0	0.68	82.5	3.1
Diarrhea	97	0.28 (0.47)	0.0	1.5	0.36	69.1	0.0
Social Functioning	97	0.17 (0.32)	0.0	1.3	0.47	67.0	0.0
Emotional Wellbeing	97	0.30 (0.43)	0.0	2.2	0.73	41.2	0.0
Constipation	97	0.63 (0.69)	0.0	2.5	0.56	34.0	0.0
Total GIT score	97	0.45 (0.37)	0.0	1.6	0.82	3.1	0.0

All scales are scored from 0.00(better HRQOL) to 3.00(worse HRQOL) except the diarrhea and constipation (range from 0.00–2.00 and 0.00–2.50, respectively). The UCLA GIT 2.0 provides a total score of GIT severity and calculated by summation of all scales (except constipation) and ranges from 0.00–2.83(2).

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Table 2. External Consistency Statistics: Correlation Between SF-36 Items and Component Summaries and UCLA SCTC GIT 2.0 Items

UCLA SCTC GIT 2.0 / SF-36	RF	RP	RE	VT	MH	SF	BP	GH	PCS	MCS
Reflux	-,300 **	-,436 **	-,296**	-,421**	-,373**	-,235*	-,427**	-,312**	-,386**	-,313**
Distension	-,461 **	-,422 **	,258*	-,465**	-,474**	-,340**	-,427**	-,408**	-,437**	-,354**
Soilage	-,237 *	-,160	,001	-,170	-,165	-,131	-,328**	-,114	-,254*	-,027
Diarrhea	-,265 **	-,258 *	-,180	-,216*	-,215*	-,146	-,325**	-,083	-,296**	-,174
Social Functioning	-,208 *	-,203 *	-,242*	-,149	-,271**	-,210*	-,400**	-,242*	-,300**	-,243*
Emotional Wellbeing	-,397 **	-,379 **	-,433**	-,334**	-,372**	-,337**	-,445**	-,263**	-,304**	-,368**
Constipation	-,163	-,101	-,199	-,047	-,063	-,166	-,299**	-,065	-,167	-,132
Total GIT score	-,482 **	-,453 **	-,321**	-,492**	-,493**	-,369**	-,560**	-,395**	-,482**	-,343**

$p<0.05$ * and $p<0.01$ **. RF: physical functioning, RP: role limitations due to physical health, RE: role limitations due to emotional problems, VT: vitality, MH: mental health, SF: social functioning, BP: bodily pain, GH: general health, PCS: physical component summary, MCS: mental component summary.

References: 1)Khanna D, Reliability and validity of the UCLA SCTC GIT Instrument.Arthritis Rheum,2009. 2) Bae S, Development and validation of French version of the UCLA SCTC GIT Instrument.Clin Exp Rheumatol, 2011. 3) Meijs J, Translation,cross-cultural adaptation, and validation of the UCLA SCTC GIT 2.0 into Dutch. Clin Exp Rheumatol,2014.

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Abstract Number: 2896

Safety and Effectiveness of Hyperbaric Oxygen Therapy for Systemic Sclerosis Ulcers

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Background/Purpose: Vascular complications of systemic sclerosis (SSc, scleroderma) can result in ulcers in the distal extremities, which limit function and are often refractory to conventional treatments. Hyperbaric oxygen therapy (HBOT) has been used in the treatment of non-healing wounds, but its utility in patients with SSc is uncertain. The primary objective of this study was to evaluate the safety of HBOT for SSc ulcers. We secondarily evaluated the effectiveness of HBOT for SSc ulcers, and patient selection criteria for treatment of SSc ulcer patients with HBOT.

Methods: We conducted a cohort study of SSc patients who were evaluated for treatment with HBOT in the Toronto Scleroderma Program and the Toronto General Hospital Hyperbaric Unit between 2002 and 2015. HBOT treatments involved 30-50 sessions in a monoplace or multiplace chamber with compression to a maximum depth of 2.5 atm and breathing oxygen for a total of 90 minutes 5 days per week. Ulcers were defined as lesions with a visually discernable depth and loss of epithelial continuity. Reasons for declining access to HBOT, adverse events and effectiveness in ulcer healing were evaluated. An ulcer was categorized as healed if it achieved epithelial continuity or National Pressure Ulcer Advisory Panel (NPUAP) stage X (stable necrotic tissue core or eschar). Transcutaneous oxygen tension criteria for evaluating 'healability' in diabetic foot ulcers were applied as none have been validated for the SSc.

Results: 2261 subjects were reviewed to identify 36 HBOT treated ulcers in 10 SSc subjects. They had a mean ± SD age of 58.0 ± 13.9 years. Eighty-seven percent were female. Ulcer locations included fingertip (n=10 (28%)), hand-PIP/DIP (n=11 (31%)), hand-MCP (n=2 (6%)) and lower extremity (n=10 (28%)). Thirteen SSc subjects did not receive HBOT due to reasons that included lack of achieving "healable" response to oxygen on transcutaneous oximetry and technical limitations in sensor placement options (n=4), presence of moderate - severe pulmonary arterial hypertension (n=2) and confinement anxiety (n=1). Of the HBOT treated subjects, adverse events included brief episodes of otic barotrauma (n=2) and nausea (n=2). Twenty-three (64%) ulcers improved after HBOT.

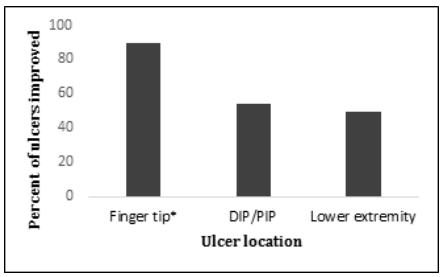

Figure 1. Ulcer improvement by location

Conclusion: HBOT may be an effective option for SSc patients with non-healing ulcers. Therapy was generally well-tolerated, with no significant adverse events although transient self-limiting otic barotrauma was reported. Patient selection criteria specific to the SSc population may need to be developed as the presence of pulmonary arterial hypertension is considered a contraindication to HBOT.

Disclosure: S. Armstrong, None; **A. W. Evans**, None; **Z. Ahmad**, None; **S. R. Johnson**, None.

Abstract Number: 2897

Microvascular Function in Systemic Sclerosis Patients with End-Stage Vascular Manifestations of the Disease

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Background/Purpose: Vasculopathy is a prominent feature of systemic sclerosis (SSc, scleroderma) and is involved in end-stage manifestations such as pulmonary arterial hypertension (PAH), digital ulcer (DU), and scleroderma renal crisis (SRC). However, the extent to which vascular function changes in patients diagnosed with SSc is uncertain. We hypothesized that microvascular function assessed by sublingual videomicroscopy would be worse in SSc patients with end-stage manifestations compared to those patients without.

Methods: SSc patients were recruited from the University of Utah SSc Clinic between October 2015 and April 2016 and data were obtained from 34 patients without (ES^-) and 19 patients with (ES^+) end-stage disease (one or more of DU, PAH, SRC). Microvascular function was assessed using sublingual videomicroscopy and automated capture and analysis of vessels between 5 and 25 µm in diameter (Glycocheck). Vessels were grouped into tertiles by diameter (5-9-, 10-19-, 20-25- µm) and analysed for the density of well perfused microvessels (density), red blood cell (RBC) filling percentage, and the depth of penetration of RBCs into the vessel wall (perfused boundary region, PBR; an estimate of glycocalyx integrity). Glycocheck data were analysed using one-tailed independent samples t-test and alpha set at 0.05 (SPSS, IBM).

Results: The mean (±SEM) age of ES^- was 55±2 (all female; 29 Caucasian, 4 Hispanic, 1 Native American) and ES^+ was 57±3 years (3 males; 15 Caucasian, 3 Hispanic, 1 Native American). Mean duration of SSc disease and duration of Raynaud's phenomenon was, respectively, 8±1 and 13±2 (ES^-) and 9±2 and 11±3 (ES^+) years. There were no differences in age, height, weight, BMI, systolic or diastolic blood pressure between groups. When microvessels of all sizes were analysed, there were no differences in microvessel density, RBC% or PBR. When analysed by tertile, there were significant differences in microvessel density (ES^- vs. ES^+: 171±17 vs. 122±15 µm/mm^2) and RBC filling (ES^- vs. ES^+: 72±1 vs. 68±3 %) in the microvessels with largest diameter (20-25- µm), but no differences in PBR. There were no differences in any microvascular measurements in the other (smaller diameter) tertiles.

Conclusion: From this small sample, we found that some, but not all, markers of sublingual microvascular function were worse in SSc patients with end-stage manifestations of the disease compared to those without. Follow-up is needed, but this initial finding suggests that deteriorating microvascular function may be part of the natural history of SSc. These specific aspects of vascular function may be useful targets in the treatment of SSc.

Disclosure: T. M. Frech, None; **P. E. Gates**, None; **D. Machin**, None; **A. Donato**, None.

Abstract Number: 2898

Anti-Reflux Medications in Diffuse Cutaneous Systemic Sclerosis: Is Empiric Use of Proton Pump Inhibitors Supported?

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Background/Purpose: Empiric long-term use of proton pump inhibitors (PPI) are implicated in concomitant renal dysfunction (1) and small intestinal bacterial overgrowth (SIBO)(2). Yet, experts recommend daily empiric PPI even in the absence of reflux symptomatology in SSc patients (3). The Prospective Registry of Early Systemic Sclerosis (PRESS) cohort of early diffuse cutaneous systemic sclerosis (dcSSc) permits determination of the utility of empiric PPI administration in this patient population.

Methods: The PRESS cohort includes dcSSc patients with < 2 years duration who are recruited at 11 United States Scleroderma Centers. Patients participate in detailed baseline and biannual clinical and laboratory assessments that permit examination of patient characteristics, PPI use, renal function and patient-reported clinical outcomes measures including the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract 2.0 (GIT 2.0)(4).

Results: As of May 2016, 166 PRESS patients were enrolled (Table 1). At baseline and 6 months, 132 and 67 patients had completed the GIT 2.0 respectively. Of the 88 patients taking a PPI at baseline, 6 had no reflux, 37 had mild reflux, 28 had moderate reflux and 15 had severe reflux. Five patients taking PPI had renal dysfunction at baseline (defined as reduced creatinine clearance). No patient taking a PPI developed renal dysfunction between baseline and 6 months. Only 11 of the 88 patients on PPI lacked bloating or distention at baseline. At 6 months, only 1 patient with a repeat GIT 2.0 was newly prescribed that PPI. This patient lacked renal insufficiency and bloating or distention.

Conclusion: Most dcSSc patients take PPI. PPI use was not associated with incident renal dysfunction over 6 months follow-up. Bloating and distension are common symptoms in dcSSc patients and may be associated with PPI use. Due to recent associations of PPI with SIBO and renal dysfunction experts may consider changes in practice patterns. Cohorts such as PRESS provide the opportunity to understand gastrointestinal disease and renal dysfunction in the dcSSc patient population as well as the opportunity to study potential adverse effects of medications. Table 1: PRESS Patient Characteristics

Characteristic (n=166)	Number or mean
Female	116
Age	48.7
BMI (kg/m^2)	25.7 ± 5.3
Ethnicity: • African American • Asian • White or Caucasian • Other • Hispanic	25 7 125 8 20
ANA positive • Negative Autoantibody in ANA positive patients: • RNA polymerase III • SCL70	128 6 60 38
SCTC completed: • Baseline • 6 month Follow-up visit	132 67
PPI use at baseline • No reflux SCTC GIT 2.0 • Mild reflux SCTC GIT 2.0 • Moderate reflux SCTC GIT 2.0 • Severe-very severe reflux	6 (23)* 37 (73) 28 (41) 15 (25)
PPI use at baseline: • No bloating/distention SCTC GIT 2.0 • Mild bloating/distention SCTC GIT 2.0 • Moderate distention/bloating SCTC GIT 2.0 • Severe-very severe bloating SCTC GIT 2.0	11(24) 36 (66) 8 (14) 12 (23)
PPI use and Renal function: • No hx SRC and serum creatinine < 1.3 mg/dL • Hx SRC and serum creatinine < 1.6 mg/dL • Hx SRC and serum creatinine between 1.7 and 2.9 mg/dL • Hx SRC and serum creatinine > 3.0 mg/dL • Hx SRC and dialysis required	69 (137) 3 (4) 1 (1) 1 (3) 2 (3)

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Abstract Number: 2899

Impact of the Clinical Characteristics of Systemic Sclerosis in Patients Quality of Life

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Background/Purpose: Systemic sclerosis (SSc) is a rare heterogenic disease, with visceral, skin and vascular damage associated with a reduced life expectancy, disability and worsening of quality of life. Evaluation of health related quality of life (HRQoL) is important for a more comprehensive approach to SSc patients. The purpose of our study was to assess the impact of SSc clinical manifestations in HRQoL from the patient and physician perspectives.

Methods: 44 consecutive SSc patients with limited (n=32) and diffuse (n=12) cutaneous subsets, from a single referral center and classified according to the 2013 ACR/EULAR criteria, were enrolled, together with a disease-control group of 28 consecutive patients with rheumatoid arthritis (RA). Health Assessment Questionnaire (HAQ-DI) and Short Form 36 (SF36), physical component summary (PCS) and mental component summary (MCS) scales were used to assess HRQoL, and the following ten clinical variables were considered for correlation: time since disease onset (first non-raynaud's phenomenon manifestation), modified Rodnan skin score, calcinosis, digital ulcers (DU), arthritis/myositis, clinically significant pulmonary hypertension (PH), interstitial lung disease (ILD), renal crisis, gastrointestinal (GI) and cardiac involvement. Physician's perception of the impact in HRQoL of each of the variables was assessed - scored from 1 (high impact) to 3 (mild impact). All physicians were SSc experts non-associated to this cohort. T-test and Fisher's exact test were used to compare binary variables. Pearson's correlation was used for continuous variables.

Results: in SSc patients the mean HAQ-DI score was 0.95±0.67 (0-best health), and the mean PCS and MCS scores were 44.3±44.1 and 39.1±13.1 (100-best health), respectively. None of the clinical variables correlated with HRQoL, except the GI involvement (HAQ-DI - p=0.01, PCS - p=0.04, MCS - p=0.005). From the physician's perspective, the 3 clinical variables considered as having a high impact on HRQoL were: 80% PH, 70% DU and 50% ILD. Only 40% of the physicians considered GI manifestations to have a high impact on HRQoL, whilst 20% rated it as having a mild impact. Comparing with RA patients, there was no statistically significant difference in HRQoL. RA patients had mean scores of: HAQ-DI 1.1±0.56 (p=0.41), PCS 35.0±10.0 (p=0.27) and MCS 43.7±12.2 (p=0.14).

Conclusion: SSc has a very significant impact in the quality of life as perceived by the patients. In this study, the GI involvement was the only independent clinical manifestation contributing to a poorer health status in SSc patients. Despite its proven significance, the physician's perspective of the GI involvement is significantly different from patients reinforcing the need for further studies on patient perpective and outcomes measures in SSc.

Disclosure: J. Caetano, None; **L. Melo**, None; **S. Oliveira**, None; **J. Delgado Alves**, None.

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Abstract Number: 2900

The Incidence and Prevalence of Systemic Sclerosis in Northwestern Part of Turkey

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Background/Purpose: Systemic sclerosis (SSc) is a multisystem, chronic, autoimmune disease. In this hospital based study, we aimed to evaluate the prevalence and incidence of SSc in our region.

Methods: During the 2003-2015, SSc patients diagnosed in our Department were included. Our Department is the only tertiary center of Rheumatology in this northwestern part of Turkey. The diagnosis of SSc was performed according to ACR 1980 criteria. Clinical and demographical data about SSc patients were obtained from medical charts.

Results: Of the 161 patients (146F, 15M) carrying the diagnosis the diagnosis of SSc, During the study period, the mean annual incidence rate was 2.16/100,000 for SSc. The annual incidence of SSc in women was 3.98/100,000, and in men was 0.4/100,000. In second period of study (2010-2015 vs. 2003-2009), general incidence rate increased especially in males (from 0.27 to 0.53/100,000). By December 2014, the overall point prevalence of SSc in our region was 23.2/100000 in population aged >16 years. The point prevalence in women (42.8/100000) was higher than the point prevalence in men (4.1/100000). Among women, SSc was more prevalent in the fourth and fifth decades of life. Among men, the peak orevalence was in the sixth decade of life. The period prevalence of SSc was 25.9/100000. The period prevalence in women was 47.7/100000 and in men it was 4.8/100000. The median age at diagnosis was 49 (21–84) years for SSc patients. 123 patients (76.4%) had limited cutaneous, 35 patients (22.4%) had diffuse SSc and 2 patients (1.2%) had sine scleroderma. Interstitial lung disease was detected in 55 patients (34.2%), pulmonary hypertension in 69 patients (42.9%), digital ulcers in 46 patients (28.6), arthritis in 47 patients (29.2%) and renal crisis in 2 patients.ANA positivity was detected in 90.1% of patients. Anti-centromer was positive in 26.7% of patients, anti-Scl-70 was positive in 28% of patients, anti-Ro in 15% of patients and anti-RNP in 11.9% of patients. The median follow-up time of all SSc patients was 48 months (3-160). 20 patients with SSc were died (16 females, 4 males). 5 and 10-years survivals of patients with SSc were 93.6% and 83.1% respectively. Univariate analysis revealed that, male sex (p=0.018), age older than >65 years at the time of diagnosis (p=0.016), pulmonary hypertension (p=0.005), digital ulcer (p=0.034), diffuse cutaneous disease (p=0.032), low level FVC (p=0.023) and anti-Scl-70 positivity (p=0.05) were poor prognostic factors. Multivariate Cox regression analysis showed that, male sex (p=0.05) and pulmonary hypertension (p=0.032) were independent poor prognostic factors in our SSc patients.

Conclusion: In conclusion, we found in our study from northwestern part of European Turkey that SSc prevalence (23.2/100,000) and incidence (2.1/100,000) is similar to data form European countries and US studies.

Disclosure: O. N. Pamuk, None; **M. A. Balci**, None; **S. Donmez**, None; **G. E. Pamuk**, None.

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Abstract Number: 2901

SSc and the Significance of Blood Group Antigens

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Background/Purpose : Systemic sclerosis (SSc) is a rare disease, with a mean incidence 3.8 cases, prevalence 99 per million in Sweden. The two most important blood group systems for hemagglutination are called AB0 and RhD. The AB0 system consists of two antigens, A and B which are oligosaccharide (Os). On the B antigen the terminal monosaccharide (Ms) always is a galactose (Gal), while on the A antigen, the terminal Ms is an acetylgalactosamine (GalNAc). This study examines the prevalence of different AB0 and RhD blood group antigens in SSc patients in comparison with the general Swedish population.

Methods : 150 patients, fulfilling the 2013 ACR/EULAR criteria for SSc, were included in the study. All patients were tested for the blood group antigens AB0 and Rhesus factor (Rh) and antinuclear SSc-associated antibodies (anticentromer; ACA, antitopoisomerase 1; ATA or anti RNA polymerase 3; ARA) were analysed.

According to our hypothesis, antigen present on the erythrocyte’s surface has a significant role in the formation of the SSc disease.

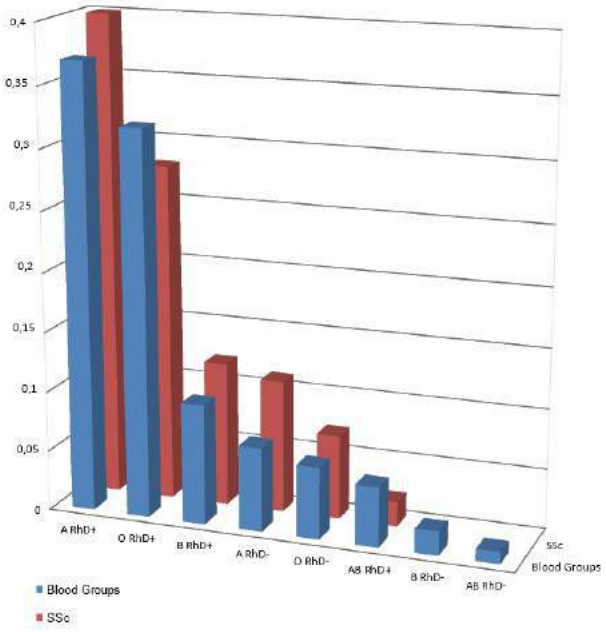
Results: In this studied group, the frequency of B antibodies was significantly lower (21%) compared to the average among the Swedish

population (36%).

Two blood groups, B RhD negativ and AB RhD negativ, were not found among the 150 patients in the study group; compared to the national expected average of 2% and 1% respectively.

The two main findings included 0 RhD positive cases with centromer antibodies (ACA) being 61% and A RhD positive with ACA being 57%.

Conclusion: In conclusion, the natural antibodies present on the surface of the erythrocytes are most likely to influence the emergence of SSc. Therefore, the presence of Gal most likely has a significant defensive roll against the development of the SSc disease.



	Blood group expected incidence % general population in Sweden	All SSc patient
A RhD+	37,00%	40,00%
O RhD+	32,00%	28,00%
B RhD+	10,00%	12,00%
A RhD-	7,00%	11,00%
O RhD-	6,00%	7,00%
AB RhD+	5,00%	2,00%
B RhD-	2,00%	0,00%
AB RhD-	1,00%	0,00%

Disclosure: Z. Fabianne, None; **A. Nordin**, None.

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Abstract Number: 2902

Preliminary Evaluation of Gastroesophageal Reflex Disease Outcome Measures in Scleroderma– Scleroderma Clinical Trials Consortium Gastrointestinal Working Group

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Background/Purpose: Gastrointestinal tract (GIT) involvement occurs in approximately 95% of patients with systemic sclerosis (SSc). There is consensus in the Scleroderma Clinical Trials Consortium (SCTC) Working Group on the importance of validating outcome measures in SSc. The goal of this project was to evaluate patient reported outcome measures in the SSc-associated domain of gastroesophageal reflux disease (GERD) through instrument assessment of responsiveness to change.

Methods: Patients who fulfill 2013 revised ACR/EULAR criteria for SSc and who had (1) GERD symptoms for at least 3 of the past 7 days; and (2) a plan to initiate a change in GERD management were eligible. At baseline, all patients completed GERD assessment questionnaires including: the UCLA GIT 2.0, Quality of Life in Reflux and Dyspepsia (QoLRAD), and in English-speaking countries, the NIH Patient Reported Outcome Measurement Information System (PROMIS®) GI Symptoms Scale. Cronbach's alpha was assessed for the GIT 2.0 and QoLRAD domains; an alpha >=0.70 is considered acceptable for group comparisons. Pearson correlation coefficients were interpreted as proposed by Cohen: 0.0- 0.10, no correlation; 0.10- 0.23, small correlation; 0.24- 0.36, medium correlation; >=0.37, large correlation.

Results: In this ongoing registry, 5 participating international sites have so far recruited 68 GERD patients who completed GIT 2.0 and QoLRAD, and 29 patients completed the NIH PROMIS GI Reflux scale. The diagnosis of GERD was made by clinical symptoms in 67 patients, 3 of whom had their diagnosis confirmed by barium swallow, and two of whom had an endoscopy with evidence of esophagitis. The patient sample has a mean age of 54.9 years, mean disease duration of 10.5 years, and is 83% female. Cronbach's alpha for GIT 2.0 was 0.83 and for QoLRAD domains ranged from 0.92-0.96. The mean scores for Reflux scales on GIT 2.0 (0.96) and NIH PROMIS (57.5) suggested moderate overall reflux symptoms. GIT 2.0 and PROMIS had large correlations with each other and QoLRAD domains (except PROMIS had medium correlation with emotional distress domain of QoLRAD).

Conclusion: This multi-center international prospective study of SSc-GERD suggests that current PROs (GIT 2.0, PROMIS, and QoLRAD) have acceptable reliability and have large correlations among each other (except for 1 domain for QoLRAD with PROMIS). This study highlights challenges for studying GERD in an international cohort, including the infrequent use of invasive studies for GERD diagnosis and the limitations in the availability of translated instruments. Nonetheless, this study underscores the value of international collaboration supported by the SCTC.

Mean score/ Correlations coefficients for the PROs

	GIT 2.0*	NIH PROMIS*	QoLRAD Emotional distress**	QoLRAD Sleep disturbance**	QoLRAD Food and drink problems**	QoLRAD Physical and social functioning**	QoLRAD Vitality**
UCLA GIT 2.0 (Reflux scale)	0.96/ 1.0	57.5/ 0.69	5.21/ -0.66	4.82/ -0.77	*4.70/* -0.75	5.64/ -0.72	*4.82/* -0.73
NIH PROMIS GI Reflux scale		1.0	-0.35	-0.52	-0.58	-0.47	-0.48

** Higher score denotes greater symptoms;** Lower score denotes greater symptoms (3.5-4.9 moderate; <3.5 severe)*

Disclosure: Z. McMahan, None; **T. M. Frech**, None; **G. Piemonte**, None; **M. Matucci-Cerinic**, None; **S. Proudman**, None; **V. J. Berrocal**, None; **R. Hays**, None; **D. Khanna**, NIH/NIAMS, NIH/ NIAID, Bayer, BMS, 2,Bayer, BMS, Genetech/Roche, GSK, Genkyotex, Sanofi-Aventis, Actelion, Gilead, 5.

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Abstract Number: 2903

Transition of Nailfold Microangiopathy throughout Different Patterns of Microvascular Damage and Correlations with Organ Involvement in Systemic Sclerosis: A Twelve Year Follow-up

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Background/Purpose: Nailfold capillaroscopy is the validated technique to assess scleroderma microangiopathy, an early and dynamic event that may progress through different patterns of microvascular damage ("early", "active" and "late") during follow-up (1,2). The time of transition is variable among patients, and it was little investigated (2). Several studies demonstrated correlations between microvascular damage extent and organ involvement degree (2-4). The aim of this longitudinal study was to investigate the time of transition of nailfold microangiopathy throughout different patterns of microvascular damage in SSc, assessing correlations with organ involvement.

Methods: Thirty-four SSc patients according to LeRoy criteria (mean age 57±11 years) with the "early" pattern of nailfold microangiopathy at first capillaroscopic visit were enrolled and followed for a mean time of 12±3 years. Only SSc patients with fully complete documentation were included into the study. The pattern of microangiopathy was recorded and the microangiopathy evolution score (MES) calculated by nailfold videocapillaroscopy (NVC) at each visit, as previously reported (1,2); organ involvement and antinuclear antibody (ANA) profile were also assessed.

Results: After a mean twelve years follow-up, 12 (35%) patients were still showing the "early" scleroderma-pattern, while the NVC pattern of microangiopathy was changed in 65% of the patients. The NVC pattern was found "active" in 10 patients (30%) and "late" in 12 patients (35%). The median time of progression from the "early" to the "active" pattern was 31 months, from "active" to "late" 38 months, and from "early" to "late" 66 months. In the subgroup of patients whose microangiopathy progressed from the "early" to the "late" NVC pattern through the "active" pattern, the median time of progression from the "early" to the "active" pattern was only 14 months, while in the subgroup of patients whose microangiopathy progressed only from the "early" to the "active" NVC pattern it was 42 months. A correlation was confirmed between microvascular damage extent and organ involvement degree, as MES progressively increased and organ involvement was progressively greater in SSc patients with "early", "active" and "late" NVC pattern of microangiopathy, respectively. The median time of progression from "early" to "late" pattern was shorter in SSc patients with either nucleolar IIF ANA pattern or Scl70 autoantibodies.

Conclusion: This study confirms the progression of nailfold microangiopathy through different patterns of microvascular damage in almost 65% of SSc patients. Patients showing a fast progression from the "early" to the "active" NVC pattern of microangiopathy (one year), as well as positive ANA with either a nucleolar IIF pattern or Scl70 positivity should be strictly monitored since at risk of rapid progression to the "late" NVC pattern of microangiopathy which is linked to a larger risk of organ involvement. **References**. 1. Cutolo M, et al. Rheumatology 2004;43:719-26. 2. Sulli A, et al. Arthritis Rheum. 2012;64:821-5. 3. Ingegnoli F, et al. Microvasc Res 2013;89:122-8. 4. Smith V, et al. J Rheumatol. 2013;40:2023-8.

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Rituximab in Systemic Sclerosis-Interstitial Lung Disease, a Case Series of 18 Patients

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Background/Purpose:

Interstitial lung disease (ILD) is a severe complication of systemic sclerosis (SSc). Immunosuppressives such as cyclophosphamide (CYC) and mycophenolate mophetil (MMF) are used in its treatment with no proven efficacy (1). Rituximab (RTX) appears to be an emerging agent according to case series.

This retrospective study aims to evaluate the efficacy of RTX on SSc-ILD in a group of patients followed in our center.

Methods: A chart review revealed 18 patients (16 women, 2 men; mean age 50.3±12.1 SD years (range 30-72 years), mean disease duration 8.3±9.3 SD years) with SSc who have been diagnosed as having ILD (confirmed by high-resolution thorax computed tomography and pulmonary function tests) and have been treated with one or more cycles of RTX. Efficacy was evaluated according to the criteria of the American Thoracic Society: improvement= an increase in FVC≥10% or DLCO≥15%; worsening= a decrease in FVC≥10% or DLCO≥15%; stabilization= changes in FVC less than 10% or DLCO less then 15% (2).

Results:

The mean follow-up of the patients after starting RTX was 19±11.8 SD months (Table 1). Four patients were treatment naive for ILD when they received RTX (Group 1). The mean duration between the diagnosis of ILD and RTX treatment in Group 1 was 3.5 months (range 0-14 months). The average RTX cycle in this group was 2 with 1 patient also receiving mycophenolate mophetil in combination with RTX. The mean follow-up time after the initiation of RTX in this group was 12.2±6.8 SD months (range 7-22 months). FVC/DLCO was stable or improved in 2/4 compared to baseline and worsened in 2/4 at the end of follow-up at group 1.

Fourteen patients had a 10.2 years-history of SSc and have been treated with immunosuppressives (cyclophosphamide, azathioprine, methotrexate, MMF) for ILD before RTX (Group 2). The mean duration between the diagnosis of ILD and RTX treatment in Group 2 was 71.2 months (range 5-246 months). These patients received a mean of 3 cycles of RTX with 5 receiving MMF (n=3) or AZA (n=2) in addition to RTX. One patient died after 3 months following the first RTX cycle (unknown reason) and 1 was unsuitable for spirometry because of microstomia. Of the remaining 12 patients in Group 2, improvement or stabilisation was seen in 7 and worsening was seen in the remaining 5 patients.

Conclusion:

RTX appears to be modestly effective for ILD of SSc. The duration of ILD as well as the presence or absence of previous immunosuppressive therapy do not appear as playing a role in response.

Table 1: Demographic findings of the patients and their response to RTX treatment

	Group 1 (ILD with short duration and naive to treatment)	Group 2 (ILD with long duration and previous IS therapy)	All patients
Number of patients	4 (22.2%)	14 (77.7%)	18
Sex (F/M)	3/1	13/1	16/2
Mean disease duration	2±0.8 SD years	10.2±9.8 SD years	8.3±9.3 SD years
Follow-up time after initiation of RTX	12.2±6.8 SD months	21±12.4 SD months	19±11.8 SD months
Baseline FVC%	69.2±20.9	65.1±14	
Last FVC%	66.7±13	61.6±19.6	
Baseline DLCO%	57.7±24.1	43.5±12.2	
Last DLCO%	52±18	41.2±21.8	
Outcome: Stable/Improvement (n)	2	7	9
Worsening (n)	2	5	7
Death	0	1	1
Unable to do PFT (n)	0	1	1

References:

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2. An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management.

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Abstract Number: 2905

Predictors of Poor Hand Function in Systemic Sclerosis

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Background/Purpose: Systemic Sclerosis (SSc) is a progressive systemic disease that can lead to variable degrees of morbidity and disability. Hand dysfunction in SSc patients [1] can result from pain, swelling and loss of mobility [1][2], affecting activities of daily living (ADLs) and work [3][4]. We aim to identify important clinical predictors of hand dysfunction in SSc.

Methods: We evaluated 192 outpatients who met criteria for SSc [5] and were seen between 2010 and 2015. We collected pertinent SSc clinical information, including laboratory and hand x-ray assessments obtained within 5 years of this analysis. Hand dysfunction was defined as the inability to make a fist due to inability to approximate the fingers onto the palm of the hand. This was corroborated by patientÕs history of difficulty with ADL tasks. We estimated unconditional logistic regression models adjusted for SSc type, current modified Rodnan skin score (mRSS), and overlap with rheumatoid arthritis (RA).

Results: Hand dysfunction occurred in 34% of patients (n=65). Patients with diffuse cutaneous SSc (dcSSc), high mRSS and overlap with RA had significantly more hand dysfunction. In multivariable models, after adjusting for these 3 variables, the following remained strongly associated with hand dysfunction: RNA polymerase III positivity (OR 3.3, CI 1.1-9.6), prior digital tip ulcers (DTUs)(OR 2.6, CI 1.3-5.4), current DTUs (OR 3.2, CI 1.4-7), prior tendon friction rubs (TFRs)(OR 5.0, CI 1.96-13), current TFRs (OR 3.5, CI 1.1-11), prior synovitis (OR 4.7, CI 1.9-26), osteoarthritis (OR 3.8, CI 1.6-8.9) and acro-osteolysis (OR 2.9, CI 1.3-6.6).

Conclusion: Hand dysfunction occurred in a third of our SSc population, and was more common in patients with dcSSc. Digital ischemia and inflammatory features (TFRs, synovitis) were strongly associated with hand dysfunction, which was independent of SSc type, degree of skin thickening, and overlap with RA. Prospective studies are needed to confirm if more aggressive treatment of digital ischemia and musculoskeletal inflammation in SSc patients would lead to less hand contractures and dysfunction.

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2. Fontaine et al. Chirurgie de la main 2014; 33:155
3. Sandqvist et al. Rheumatol. 2010; 49:1739
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Table-1: PatientsÕ demographics and Systemic Sclerosis clinical features in relation to fist formation					
		Hand Dysfunction n= 65 (34%)	**No Hand Dysfunction n= 127 (66%)**	**Univariable Analysis**	**Multivariable Analysis***
		Mean (SD) or Col%	**Mean (SD) or Col%**	**OR, (95%CI), p value**	**OR, (95%CI), p value**
Age (year)		56.7(14.2)	59.5 (12.1)	0.98, (0.96-1.01), p=0.2	1.00, (0.98-1.03), p=0.8
Sex	**Female**	53 (33%)	109 (67%)	0.73, (0.33-1.62), p=0.4	0.75, (0.3-1.83), p=0.5
	Male	12 (40%)	18 (60%)		
Race	**Caucasian**	46 (36%)	83 (64%)	0.96, (0.38-2.02), p=0.9	0.45, (0.15-1.34), p=0.2
	AA	8 (35%)	15 (65%)		
	Other	9 (36%)	16 (65%)		
Ethnicity	**Hispanic**	2 (17%)	10 (83%)	2.8, (0.58-13.0), p=0.2	2.29, (0.45-11.6), p=0.3
	Non-Hispanic	63 (36%)	114 (64%)		
SSc-type	**Limited**	12 (15%)	69 (85%)	0.18, (0.09-0.4), p<0.001	0.2, (0.09-0.46), p<0.001
	Diffuse	53 (49%)	56 (51%)		
Disease Duration (year)		13.9 (10.6)	15 (9.95)	P=0.14	/
RaynaudÕs Duration (year)		13.8 (11.1)	15.7 (10.9)	P=0.26	/
Overlap with RA	**Yes**	20 (50%)	20 (50%)	2.3, (1.17-4.84), p=0.02	4.4, (1.87-10.4), p=0.001
	No	45 (30%)	107 (70%)		
Overlap with myositis	**Yes**	16 (43%)	21 (57%)	1.6, (0.77-3.34), p=0.2	1.01, (0.42-2.4), p=0.98
	No	49 (32%)	103 (68%)		
Prior DTUs**	**Yes**	43 (44%)	55 (56%)	2.5, (1.31-4.58), p=0.005	2.6, (1.25-5.38), p=0.01
	No	22 (24%)	69 (76%)		
Current DTUs**	**Yes**	30 (58%)	22 (42%)	4.0, (2.02-7.85), p<0.001	3.17, (1.4-7.0), p=0.005
	No	35 (25%)	103 (75%)		
Prior TFRs**	**Yes**	31 (67%)	15 (33%)	10.4, (4.7-22.98), p<0.001	5.0, (1.96-13.0), p=0.001
	No	19 (17%)	96 (83%)		
Current TFRs**	**Yes**	18 (75%)	6 (25%)	7.9, (2.95-22.1), p<0.001	3.48, (1.08-11.2), p=0.04
	No	46 (28%)	121 (72%)		
Prior synovitis**	**Yes**	27 (56%)	21 (44%)	4.1, (2.03-8.35), p<0.001	4.7, (1.87-25.5), p=0.07
	No	29 (24%)	93 (76%)		
Current synovitis	**Yes**	13 (65%)	7 (35%)	4.3, (1.6-11.4), p=0.003	2.3, (0.6-8.77), p=0.2
	No	52 (30%)	120 (70%)		
Anti-topo I	**Positive**	25 (48%)	27 (52%)	2.2, (1.2-4.3), p=0.02	1.16, (0.53-2.6), p=0.7
	Negative	39 (32%)	94 (68%)		
RNA pol III	**Positive**	17 (71%)	7 (29%)	5.3, (2.05-13.8), p=0.001	3.3, (1.14-9.64), p=0.03
	Negative	42 (31%)	92 (69%)		
ACA	**Positive**	7 (18%)	31 (82%)	0.33, (0.13-0.8), p=0.01	1.5, (0.4-4.98), p=0.5
	Negative	58 (41%)	84 (59%)		
OA***	**Yes**	41 (47%)	46 (53%)	3.15, (1.55-6.4), p=0.002	3.75, (1.6-8.9), p=0.003
	No	15 (22%)	53 (78%)		
Acro-osteolysis***	**Yes**	24 (53%)	21 (47%)	3.2, (1.55-6.7), p=0.002	2.9, (1.25-6.6), p=0.01
	No	27 (26%)	76 (74%)		

Calcinosis* **	**Yes**	30 (39%)	46 (61%)	1.35, (0.7-2.6), p=0.4	1.67, (0.76-3.66), p=0.2
	No	26 (33%)	54 (67%)		
Erosions* **	**Yes**	14 (58%)	10 (42%)	2.98, (1.22-7.23), p=0.02	1.92, (0.67-5.47), p=0.2
	No	42 (32%)	89 (68%)		
ILD** **	**Yes**	41 (35%)	75 (65%)	0.9, (0.46-1.77), p=0.8	0.87, (0.38-1.97), p=0.7
	No	20 (38%)	33 (62%)		
%FVC		74.4(19.2)	82.8(20.7)	0.98, (0.96-0.99),p=0.009	0.99, (0.97-1.004), p=0.1
%DLCO		58.4(19.8)	63.7(24.5)	0.99, (0.98-1.003), p=0.1	0.99, (0.98-1.01), p=0.2
Current mRSS		7.1 (9.2)	2.3 (3.5)	1.17, (1.08-1.3), p<0.001	1.12, (1.04-1.2), p=0.002

*Adjusted for SSc type, overlap with RA, and mRSS **Documented on physical exam ***Documented by hand x-rays ****Documented by high resolution chest CT SSc: systemic sclerosis; DTU: digital tip ulcer; RA: rheumatoid arthritis; TFR: tendon friction rub; Anti-topo l: anti-topoisomerase I or Scl70; RNA pol III: anti-RNA polymerase III antibody; ACA: anti-centromere antibody; OA: osteoarthritis; ILD: interstitial lung disease; FVC: forced vital capacity; DLCO: diffuse capacity of the lung for carbon monoxide; mRSS: modified Rodnan skin score

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Disclosure: A. Raslan, None; **V. Hsu**, None.

Abstract Number: 2906

The Survival and Prognostic Factors of Patients with Systemic Sclerosis Turkish Experience

Orhan Zengin[1], Mehmet Ali Balci[2], Omer Nuri Pamuk[2], Bunyamin Kisacik[1], Salim Donmez[2], Mustafa Erkut Onder[1], Savas Aksoy[1] and **Ahmet Mesut Onat**[1], [1]Rheumatology, Gaziantep University School of Medicine, Gaziantep, Turkey, [2]Rheumatology, Trakya University Medical Faculty, Edirne, Turkey

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Background/Purpose: Systemic sclerosis (SSc) is a low-prevalence disease, characterized by fibrosis and vascular changes. It is the auto-immune rheumatic disease with the highest disease-related mortality and morbidity. Diagnosis of SSc is based on a set of clinical, immunological (specific antibodies) and capillaroscopic features. The progression in treatment modalities and supportive care methods yielded a better survival. However, major organ involvement such as pulmonary hypertension and diffuse interstitial lung disease still carries severe risk for mortality. The survival data and causes of death in patients with SSc is still not available in Turkey. The aim of the present study was to analyze the survival from disease onset and risk factors associated with mortality in 2 different rheumatology clinics of Turkish patients.

Methods: All patients who fulfilled the ACR 1980 criteria and classified with SSc since 2003 to 2016 were evaluated (totally 409 patients). The demographic features including autoantibodies of SSc patients and the mortality date were recorded from medical charts. Factors affecting the survival were calculated statistically by Kaplan-Meier test.

Results: Women (366; 89.5%) outnumbered men (43; 10.5%) significantly. The mean age at the time of diagnosis was 50.6+13.5 years. 241 (58.9%) patients were classified as diffuse SSc, 151 patients (36.9%) were limited SSc and 17 (4.1%) patients were diagnosed as sine scleroderma. 43 (10.5%) of the SSc patients were smoking. Prominent clinical manifestations were sclerodactily (95%), telangiectasis (42.8%), digital ulcers (38.5%), pulmonary fibrosis (40.5%), pulmonary hypertension (37.9%), dysphagia (19.7%), auto-amputation (7%), pleural effusion (5.1%), renal crisis (2.2%), inflammatory myositis (1.1%). At the time of

diagnosis 94.6% of SSc patients were ANA positive; 95 (23.2%) were anti-centromere positive, 126 (30,8%) were anti-Scl-70 positive and 21 (5.1%) were anti-RNP positive. Anti-Ro antibody was positive in 34 (8.3%) and anti-La antibody was positive in 7 (1.7%) patients. The mean follow-up from the time of diagnosis was 51.7+38.6 months and the median follow-up was 48 months (1-300 months). There were a total of 54 deaths in our cohort (13.2%). Overall, 5 years survival was 85.1% and 10 years survival was 75.5%. The probability of survival was reduced in men (5-year survival: 62.1% vs 72%, not-significant, p=0.09), in patients with pulmonary fibrosis (5-year survival: 67.8% vs 83.5%, not-significant p=0.81), renal crisis (40.6% vs 80.5%, p<0.001), pulmonary hypertension (5-year survival: 50% vs 70.7%, p<0.001), coronary arter disease (54.6% vs 83.5%, p<0.001) and in patients with essential hypertension (5-year survival: 44% vs 84.7%, p=0.003) (table 1). Cox regression analysis showed that pulmonary hypertension (OR: 0.39, 95%CI: 1.74-3.5, p=0.007) at the time of diagnosis was an independent factor effecting survival in patients with SSc.

Conclusion: In our SSc patients, we observed reduced survival in patients with pulmonary hypertension, coronary arter disease and essential hypertension. Any antibody including anti-centromer and Scl-70 were not meaningful. Table 1. Survival of Systemic Sclerosis Patients According to Clinical Features

Clinical Features	Survival 5-year %	p value
Pulmonary Fibrosis	67.8 vs 83.5	0.81
Renal Crisis	40.6 vs 80.5	**<0.001**
Pulmonary Hypertension	50 vs 70.7	**<0.001**
Coronary Arter Disease	54.6 vs 83.5	**<0.001**
Essential Hypertension	44 vs 84.7	**0.003**

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Abstract Number: 2907

Serum KL-6 Levels in Interstitial Lung Diseases (ILDs) Associated to Connective Tissue Diseases (CTDs)

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Background/Purpose: ILD is a frequent and potentially severe complication of CTDs. The course of ILD can be difficult to predict in this setting. The term IPAF (Interstitial Pneumonia with Auto-immune Features) has been recently created to design patients not fulfilling the diagnostic criteria for defined CTD. KL-6 (Krebs von den Lungen-6) biomarker, also known as Mucin1, is a glycoprotein produced by type II pneumocytes. Levels of serum KL-6 are well recognized to be correlated to the clinical outcome of idiopathic ILDs. However, its prognostic relevance in CTDs and IPAF-ILDs needs to be better determined.

Methods: The levels of KL-6 of the sera of 129 patients (66 males; age 61 ± 13 years; smokers or ex-smokers: n = 56(43%) have been retrospectively analyzed using the FUJIREBIO Lumipulse Chemiluminescent enzyme immunoassay at the time of ILD diagnosis. Cut-off for normal values has been set to 500 U/mL according to previous published studies. Among the 128 patients, 61 had CTDs-ILD, 21 had IPAF-ILD, 34 had idiopathic pulmonary fibrosis (IPF), and 13 had nonspecific interstitial pneumonia (NSIP). KL-6 levels were correlated with baseline forced vital capacity (FVC) and diffusion capacity for carbon monoxide (DLCO) using the Spearman non parametric correlation test. Correlation of KL-6 levels with the clinical outcome

(improvement/stabilization of ILD or worsening, as defined by a decrease of 10% in FVC or 15% in DLCO/death) at one year were studied using a U Mann-Whitney test.

Results: The mean levels of KL-6 for CTDs, IPAF, IPF, and NSIP were 2204 ± 2285, 2393 ± 2172, 1802 ± 1584, and 1839 ± 1328 U/mL, respectively. KL-6 levels were over the normal value in 87 % (53/61), 90 % (19/21), 91 % (31/34) and 100 % (13/13) in CTDs, IPAF, IPF, and NSIP, respectively. Overall, KL-6 levels were negatively correlated with FVC (r=-0.2, p=0.035) and DLCO (r=-0.28, p=0.004). As regards the clinical outcome of ILD, higher levels of KL-6 were observed in patients with poor outcome (progression/death) when compared to those with better outcome (stabilization or improvement) in CTDs (2855 ± 2490 vs 1932 ± 2166 U/mL, p=0.05). Similar trends were observed in IPF (2351 ± 1908 vs 1107 ± 561, p=0.04) and in NSIP (2628 ± 1667 vs 1360 ± 543.7, p=0.18), while no difference was observed in IPAF (2418 ± 1583 vs 2388 ± 2679, p=0.33).

Conclusion: High levels of KL-6 measured at early time points in the clinical history of CTDs-associated may be predictive of poorer outcomes. Similar trends were observed in IPF and NSIP. Further prospective studies are required to confirm these results.

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Anti-Vinculin Antibodies: A Novel Biomarker in Systemic Sclerosis, and Its Association with Vascular Involvement

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Session Time: 9:00AM-11:00AM

Background/Purpose: Vascular involvement has a major impact on the pathogenesis of Systemic sclerosis (SSc) and there is evidence that microvascular damage with endothelial cell activation may direct the phenotypic presentation of the disease. Endothelial Vinculin has a crucial regulatory role during angiogenesis(1). Villano et al., showed that expression of vinculin was significantly higher in endothelial cells challenged with the sera of SSc pts than endothelial cells treated with sera from healthy controls(2). Hence, the dysregulated vinculin expression may add to defective angiogenic processes already present in SSc. We hypothesize that over- expression of Vinculin in SSc may trigger anti-vinculin antibodies (abs) which may contribute to vasculopathic features in SSc. Objective: To measure the levels of anti-Vinculin antibodies in serum of scleroderma patients, in comparison to Healthy controls and to correlate their levels with SSc related outcome measures. M**ethods:** Serum samples from 72 SSc patients meeting the ACR/EULAR 2013 SSc criteria and 50 healthy controls were recruited. Serum levels of anti-vinculin antibodies were determined by ELISA. Clinical data were obtained from charts for statistical correlations.

Results: The 72 SSc pts' characteristics: 32(48.4%) diffuse SSc , mean age: 56.4(SD ± 18); active skin ulcers 17(25.7%), mean GIT 2.0 was 0.373; interstitial lung disease (ILD) 40 (55%)pts; Pulmonary artery hypertension (PAH) 23(31%)pts. Mean anti-Vinculin levels were significantly higher in SSc pts (1 ug/ml SD ±1) than in healthy controls (0.6 ug/ml SD ± 0.6) $p < 0.01$. Figure 1. In the linear regression models, BMI was a significant predictor of higher anti-vinculin (p<0.005). PAH trended to predict higher anti-vinculin (p=0.052). The lack of usual statistical significance may be due to low statistical power of (post-hoc power=0.44) and

might be detectable in a larger sample. Neither Skin ulcer (p=0.752) nor Raynaud's severity by visual analogue scale (p= 0.591) predicted higher anti-vinculin antibodies.

Conclusion: We report for the first time, higher levels of anti-vinculin antibodies(a potential marker of vascular involvement) in SSc patients than controls and a trend to correlation with PAH. Further research is warranted on more SSc patients to evaluate the role of anti-vinculin antibodies as markers of vascular involvement(i.e., PAH) and to identify their role in the pathogenesis of SSc /SSc-PAH.

References (1)Deroanne CF, Colige AC, Nusgens BV, Lapiere CM: Modulation of expression and assembly of vinculin during in vitro fibrillar collagen induced angiogenesis and its reversal. Exp Cell Res 1996, 224:215-223. (2)Villano et al. Systemic sclerosis sera affect fibrillin-1 deposition by dermal blood microvascular endothelial cells: therapeutic implications of cyclophosphamideArthritis Research & Therapy 2013, 15:R90

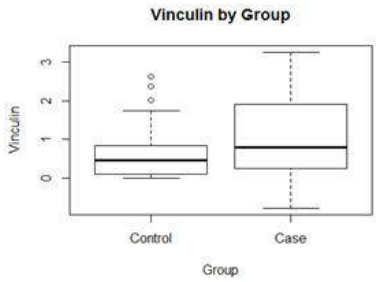

Figure 1: showing the Levels of antivinculin antibodies in SSc and healthy controls.

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Abstract Number: 2909

Attitudes Toward Patient-Reported Outcome Instruments for the Assessment of Raynaud's Phenomenon in Systemic Sclerosis

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Background/Purpose: The Raynaud's Condition Score (RCS) diary is a clinician-derived validated patient-reported outcome (PRO) instrument for assessing the frequency, duration and severity of Raynaud's phenomenon in systemic sclerosis (SSc-RP).

Methods: The Scleroderma Clinical Trials Consortium Vascular Working Group (SCTC-VWG) has been assembled to develop better methods for assessing and managing peripheral vascular manifestations of SSc. SCTC-VWG members (n=28) were invited to participate in a survey gauging attitudes towards the RCS diary and the perceived need for novel tools for assessing SSc-RP.

Results: Nineteen SCTC-VWG members (68% response rate) completed the survey. All were practicing rheumatologists with an interest in SSc (79% treating >15 SSc patients per month) affiliated with academic units based in North America (n=9), Europe (n=8), South America (n=1) and Australasia (n=1). The majority of respondents (95%) had participated in clinical trials of SSc and most (83%) had experience of SSc-RP endpoints. There were mixed views from respondents regarding the extent to which the RCS diary captures its intended conceptual framework (Table). There was broad consensus that RCS diary returns could be influenced by seasonal variation in weather, efforts made by patients to avoid or ameliorate attacks of RP, habituation to RP symptoms, the potential evolution of RP symptom characteristics with progressive obliterative microangiopathy, patient coping strategies, respondent burden and placebo effect (Table). There was consensus that the RCS diary might be a barrier to drug development (79% of respondents agree/strongly agree), that a novel PRO instrument for SSc-RP might aid drug development for SSc-RP (95% agree/strongly agree) and that a novel PRO instrument for SSc-RP should be developed with the combined input of clinicians and patients (84% agree/strongly agree).

Conclusion: The chief limitations of this pilot work are the relatively small survey size and selection bias derived from targeting SCTC-VWG members. Nevertheless, the SCTC-VWG benefits from its composition of highly experienced clinicians affiliated with specialized SSc centers across four continents. A number of perceived limitations of the RCS diary have been highlighted along with concerns that these factors might impede drug development programs for SSc-RP. There is support within the scleroderma community for the development of a novel PRO instrument for SSc-RP. **Table 1. Responses obtained from SCTC-VWG members in survey**

		Extent to which respondents agreed with each statement:					
		Unable to offer opinion	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly agree
The RCS diary accurately reflects:	Frequency of RP attacks	1 (5)	1 (5)	2 (11)	6 (32)	8 (42)	1 (5)
	Duration of RP attacks	1 (5)	1 (5)	3 (16)	8 (42)	5 (26)	1 (5)
	Overall severity and impact of RP	1 (5)	1 (5)	2 (11)	6 (32)	7 (37)	2 (11)
The RCS diary returns are influenced by:	Difficulty recognizing attacks of RP	0 (0)	0 (0)	7 (37)	2 (11)	7 (37)	3 (16)
	Seasonal variation in weather	1 (5)	0 (0)	0 (0)	0 (0)	9 (47)	9 (47)
	Efforts made to avoid attacks of RP	1 (5)	0 (0)	0 (0)	3 (16)	10 (53)	5 (26)
	Efforts made to ameliorate attacks of RP	1 (5)	0 (0)	1 (5)	3 (16)	11 (58)	3 (16)
	Habituation to RP symptoms over time	1 (5)	0 (0)	0 (0)	0 (0)	12 (63)	6 (32)
	Evolution of morphological digital microvascular disease	1 (5)	0 (0)	1 (5)	4 (21)	9 (47)	4 (21)
	Patient coping strategies	1 (5)	0 (0)	0 (0)	1 (5)	13 (69)	4 (21)
	Excessive respondent burden	1 (5)	0 (0)	1 (5)	2 (11)	9 (47)	6 (32)
	Placebo effect	2 (11)	0 (0)	1 (5)	2 (11)	8 (42)	6 (32)
The RCS diary:	Might impede drug development in SSc-RP	2 (11)	0 (0)	2 (11)	0 (0)	9 (47)	6 (32)
	Is satisfactory and no further research is required in this area	0 (0)	7 (37)	10 (53)	1 (5)	0 (0)	1 (5)
A novel PRO instrument for SSc-RP:	Might aid drug development in SSc-RP	0 (0)	0 (0)	0 (0)	1 (5)	11 (58)	7 (37)
	Should be primarily *PATIENT*-derived	0 (0)	0 (0)	1 (5)	3 (16)	9 (47)	6 (32)
	Should be primarily *CLINICIAN*-derived	0 (0)	0 (0)	9 (47)	8 (42)	2 (11)	0 (0)
	Should be	0 (0)	0 (0)	1 (5)	2 (11)	7 (37)	9 (47)

	CLINICIAN and *PATIENT*-derived						

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Abstract Number: 2910

Work Productivity in Systemic Sclerosis and Association with Health Related Quality of Life

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Background/Purpose: We sought to assess work productivity, factors associated with reduced productivity, and the relationship between work productivity and health-related quality of life (HRQoL) in systemic sclerosis (SSc).

Methods: This is a cross-sectional study of SSc patients identified through the Australian Scleroderma Cohort Study database. All patients were mailed 2 employment questionnaires (Workers Productivity and Activity Impairment Questionnaire (WPAI) and a self-made questionnaire) and 2 HRQoL questionnaires (SF-36 and PROMIS 29). Summary statistics, chi-square tests and linear regression were used to determine the associations of work productivity.

Results: Of 800 questionnaires, 476 were returned, equating to a response rate of 59.5%. Of those aged under 65 years (standard retirement age in Australia), 55.2% were employed. Unemployed patients were older at the time of survey completion (57.1 vs 53.7, $p<0.001$) and had longer disease duration from the first clinical manifestation of SSc (16.2 vs 14.9, $p=0.01$) than those who were employed. The mean age of unemployment was ten years less than the average Australian retirement age. Disease characteristics by employment status are outlined in Table 1. Of those in paid employment, 16.0% reported missing work (absenteeism) in the past week due to SSc, accounting for 32.9% of their working time. The mean number of missed work due to SSc was 11.4 (±10.9) hours. For all employed patients, the overall mean number of hours worked in the last week was 26.9 (±13.3), well below the average Australian full-time working week (38-hours). Only 27% of patients were working ≥38 hours a week. Of those working, 22% of their working time was impaired due to SSc ('presenteeism'). The mean overall work impairment accounted for 24.4% of working time. Additionally, 37.9% of the patients' daily activities had been prevented due to their SSc. Factors associated with overall work impairment (absenteeism and presenteeism) included a lack of tertiary education ($p=0.04$), synovitis ($p=0.05$) and sicca symptoms ($p=0.03$). Factors associated with impairments in daily activities included a lack of tertiary education ($p=0.04$), interstitial lung disease ($p=0.01$), digital amputation ($p=0.005$) and sicca symptoms ($p=0.001$). Unemployed patients had significantly lower HRQoL scores across a number of SF-36 domains compared with employed patients, which was mirrored in the PROMIS-29 (Table 2).

Conclusion: SSc is associated with substantial unemployment and reduced productivity, which is in turn associated with poor

HRQoL. Raising awareness and identifying modifiable risk factors are possible ways of reducing this burden.

Table 1 Patient characteristics according to employment status in those less than 65 years of age

Variables	Employed mean±SD or n(%)	Unemployed mean±SD or n(%)	p-value
Total number of patients	133 (55.2%)	108 (44.8%)	<0.001
Female	116 (87.2%)	98 (90.7%)	0.93
Age at completion of survey years	53.7±7.9	57.1±6.6	0.001
Disease duration at survey, years	14.9±8.3	16.2±9.7	0.31
Age at unemployment, years	n/a	48.3 (9.1)	
Race Caucasian Asian Aboriginal-Islander Hispanic Other	117 (90.7%) 5 (3.9%) 3 (2.3%) 1 (0.8%) 3 (2.3%)	93 (90.3%) 8 (7.8%) 2 (1.9%) 0 (0%) 0 (0%)	0.31
Tertiary education	82 (63%)	55 (52.9%)	0.12
Physical nature of job (current or past)	39 (32.5%)	44 (44.9%)	0.06
SSc subtype lcSSc dcSSc MCTD	98 (73.7%) 34 (25.6%) 0 (0%)	74 (68.5%) 32 (29.6%) 2 (1.9%)	0.01
Clinical manifestations[#] Gastrointestinal involvement Synovitis Small joint contractures in hands Digital ulcers Digital amputation Calcinosis Sicca symptoms PAH ILD Renal Crisis Myositis Tendon friction rubs Modified Rodnan Skin Score	75 (56.4%) 24 (18.9%) 58 (43.6%) 67 (50.4%) 7 (5.3%) 55 (41.4%) 71 (53.4%) 0 (0%) 32 (24.1%) 1 (0.8%) 1 (0.8%) 13 (9.8%) 10.9 ± 8.7	74 (68.5%) 33 (31.4%) 64 (59.2%) 53 (49.1%) 4 (3.7%) 48 (44.4%) 68 (62.9%) 10 (9.3%) 29 (26.9%) 8 (7.4%) 6 (5.6%) 15 (13.9%) 13.1 ± 11.3	0.05 0.02 0.04 0.33 0.08 0.63 0.06 <0.001 0.62 0.01 0.01 0.32 0.09

* age at unemployment according to self report in the questionnaire

Table 2. HRQoL according to employment status measured using SF- in those less than 65 years of age			
Patient reported outcomes	**Employed mean±SD**	**Unemployed mean±SD or n(%)**	**p-value**
Number of patients	133	108	
SF 36 Domains Physical functioning	67.6±24.4	50.6±25.3	<0.001
Role physical	57.9±42.8	29.0±40.4	<0.001
Role emotional	75.3±38.8	53.8±45.2	0.001
Vitality	49.2±21.6	38.3±23.4	0.001
Mental Health	71.1±17.5	66.6±19.8	0.06
Social functioning	75.5±23.1	61.2±24.4	<0.001
Bodily Pain	68.4±23.7	53.6±23.6	<0.001
General Health	48.2±22.9	36.2±22.2	0.001
Physical component score	41.9±10.3	33.9±10.3	<0.001
Mental component score	46.9±10.6	43.2±11.8	0.01
PROMIS 29 Domains Physical function	45.9 (±8.1)	40.8 (±7.5)	<0.001
Anxiety	52.2 (±9.8)	53.6 (±9.9)	0.27
Depression	50.3 (±9.5)	53.4 (±10.1)	0.01
Fatigue	54.4 (±10.4)	58.6 (±10.2)	0.002
Sleep disturbance	53.4 (±8.3)	55.0 (±8.6)	0.13
Satisfaction with participation in social roles	75.5 (±23.2)	61.2 (±24.4)	<0.001
Pain interference	68.4 (±23.7)	53.6 (±23.6)	<0.001
Pain intensity global (NRS 0-10)	2.8 ± 2.4	4.3 ± 2.6	<0.001

Disclosure: K. Morrisroe, None; **M. Huq**, None; **W. Stevens**, None; **J. Sahhar**, None; **S. Proudman**, None; **M. Nikpour**, None.

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A Comparison of Gastrointestinal Disease Severity in African American and Caucasian Scleroderma Patients

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A Comparison of Gastrointestinal Disease Severity in African American and Caucasian Scleroderma Patients

Background/Purpose: Systemic sclerosis (SSc) is a multisystem autoimmune disease. After skin involvement and RaynaudÕs, the gastrointestinal tract is the most commonly affected organ system with up to 90% of SSc patients affected. A limited number of studies suggest that African American (AA) SSc patients, particularly those with a nucleolar pattern anti-nuclear antibody, may be more likely to develop severe SSc-GI disease than Caucasian (C) SSc patients. The aims of this study are to determine if a patientÕs race or SSc-specific autoantibody profile is associated with the severity of SSc-GI disease.

Methods: A retrospective analysis of patient responses to the University of California Los Angeles Scleroderma Clinical Trials Consortium Gastrointestinal Tract questionnaire (GIT 2.0), demographic information (age, sex, disease duration, disease subtype), scleroderma-specific autoantibody profile (Nucleolar pattern ANA (NUC), anti-centromere (ACA), SCL-70, RNA Polymerase III (POL 3), and U1-RNP and Medsgar Gastrointestinal Disease Severity Score (Medsger GI Score) were extracted from the medical records of 70 AA SSc patients and 84 C SSc patients seen in the department between 2014 and 2016. SSc patients complete the GIT 2.0 at each clinic visit but only the first response was included for data analysis. Statistical analyses were carried out using Shapiro-Wilk, Kruskal-Wallis and Chi-Square tests.

Results: AA pts were younger, more likely to have diffuse cutaneous disease and had shorter disease duration (Table 1). More AA had NUC and U1 RNP antibodies whereas C were more likely to have ACA and Pol 3. The Medsger GI score was slightly higher in AA compared to C (1.29 vs 1.0, p=0.06). AA pts scored significantly higher on the GIT 2.0 in the reflux, diarrhea, and social function sections, as well as the total score (p=0.02). There were no significant associations of the GIT 2.0 with the NUC, although patients with U1-RNP had the highest GIT 2.0 total score and pts with POL 3 had the lowest total score. The GIT 2.0 correlated with the Medsger GI Score (r= 0.431 p<0.001) even though the Medsger GI Score does not include some of the features in the GIT 2.0.

Conclusion: This study suggests that AA may have more severe SSc GI disease as demonstrated by the Medsger GI severity score and the GIT 2.0. Using the GIT 2.0 in clinical practice can easily identify pts with significant GI symptoms, which should be treated. By identifying SSc patients at risk of developing significant GI system involvement, practitioners can perform targeted organ surveillance based on subset risk stratification levels and provide patients with earlier interventions when treatment is most effective. **Table 1**

	African American N=70	Caucasian N=84	P-value
Age	53.1	62.1	0.001
Female %	88.6	86.9	0.810
Disease duration (years)	9.1	12.5	0.026
Limited SSc %	41.4	61.9	0.026
NUC	21	13	0.034
ACA	3	23	0.001
SCL-70	14	15	0.837
POL 3	3	13	0.032
U1-RNP	9	3	0.038
Medsger GI Score	1.29	1	0.06
GIT-2.0 Reflux	0.686	0.440	0.002
Distention	1.043	0.851	0.160
Soilage	0.260	0.300	0.694
Diarrhea	0.500	0.244	0.004
Social Functioning	0.426	0.224	0.001
Emotional	0.326	0.251	0.957
Constipation	0.350	0.357	0.653
Total Score	0.598	0.444	0.020

Disclosure: C. Fridley, None; **V. D. Steen**, None.

Abstract Number: 2912

Performance of the Patient-Reported Outcomes Measurement Information System (PROMIS) 29 in Systemic Sclerosis -Associated Interstitial Lung Disease (SSc-ILD)

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Background/Purpose: PROMIS-29 is a generic health-related quality of life (HRQoL) instrument that was developed as part of the NIH Patient Reported Outcomes (PROs) Roadmap. Our objective was to assess the construct validity of PROMIS-29 in participants with SSc-ILD.

Methods: Ninety-four participants with SSc were recruited from a large Scleroderma Program. Participants included in the study satisfied 2013 ACR/EULAR criteria for SSc and had ILD on HRCT. Participants with FEV1/FVC less than 0.7 were excluded from study. At baseline, participants were administered PROs, consisting of PROMIS-29, Patient global assessment for disease severity on a visual scale (VAS), Dyspnea 12, Modified Medical Research Council Dyspnea Scale (MMRC; dyspnea measure), Leicester Cough Questionnaire (LCQ; cough measure), and the Saint George Respiratory Questionnaire (SGRQ; respiratory disease impact measure). Along with PROs, pulmonary function test (PFT), HRCT, medical history, physical exam, and medications data were obtained. PFT indices (forced vital capacity and DLCO) were compared across PROÕs. Pearson correlation coefficients were calculated and interpreted as proposed by Cohen: 0.0 – 0.10 indicates negligible correlation, 0.10 – 0.23 indicates a small correlation coefficient, 0.24 – 0.36 indicates a moderate correlation, 0.37 is indicative of a large correlation coefficient.

Results: The mean age of participants was 51.6 years, with a mean disease duration of 2.8 years after first non-ReynaudÕs symptom. Of the 94 participants, 60.6% were classified as diffuse SSc, 24.5% limited SSc, 13.8% sine, and 1.1% overlap. Mean FVC was 74.9%, DLCO was 53.5% and 88% had NSIP fibrotic pattern on HRCT. PROMIS-29 scores were 0.2 to 0.9 SD below the US population. Correlation coefficients were highest with PROMIS physical function scale (0.36 to -0.81 for all comparisons; $p< 0.05$). Correlations were higher for dyspnea scales compared to LCQ. The correlation coefficients with physiologic measures (FVC and DLCO) showed negligible-to-small coefficient vs. PROMIS measures.

Conclusion: PROMIS-29 has construct validity for assessment of HRQoL in SSc-ILD. It has moderate-to-large correlations with measures of dyspnea, dyspnea-specific QoL, and cough, and complements physiologic measures. We are currently assessing sensitivity to change in the longitudinal cohort.

PROMIS-29 & Other Scales Correlation Coefficients	Dyspnea PRO		Dyspnea-Specific QoL	Cough PRO	VAS†	Physiologic Measures	
	Dyspnea 12†	MMRCDS†	SGRQ Total†	LCQ Total§		FVC	DLCO
PROMIS-29 Physical Function§	-0.62*	-0.74*	-0.81*	0.36*	-0.55*	0.07	0.22
PROMIS-29 Social Role§	-0.57*	-0.57*	-0.69*	0.28*	-0.45*	0.1	0.13
PROMIS-29 Anxiety†	0.62*	0.49*	0.54*	-0.19	0.33*	-0.12	-0.1
PROMIS-29 Depression†	0.45*	0.35*	0.53*	-0.03	0.29*	-0.13	-0.12
PROMIS-29 Fatigue†	0.51*	0.50*	0.52*	-0.29*	0.43*	0.08	-0.04
PROMIS-29 Pain Interference†	0.49*	0.41*	0.61*	-0.15	0.53*	0.04	-0.03
PROMIS-29 Sleep Disturbance†	0.43*	0.24*	0.29	-0.24*	0.44*	-0.18	-0.15

§Higher score denotes better health
†Higher score denotes worse health
**p< 0.05*

Disclosure: C. Fisher, None; **R. Namas**, None; **A. Young**, None; **H. Wilhalme**, None; **D. Khanna**, BMS, 2,Pfizer Inc, 2,Bayer, 2,Actelion Pharmaceuticals US, 5,Genentech/ Roche, 5,Sanofi-Aventis Pharmaceutical, 5,Bayer, 5,Cytori, 5,EMD Serono, 5.

Abstract Number: 2913

Four Year Effects of Combined Bosentan and Iloprost Treatment on Nailfold Absolute Capillary Number, Fingertip Blood Perfusion and Clinical Status, in Systemic Sclerosis Patients

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SESSION INFORMATION
Session Date: Tuesday, November 15, 2016
Session Title: Systemic Sclerosis, Fibrosing Syndromes, and Raynaud's – Clinical Aspects and Therapeutics - Poster III
Session Type: ACR Poster Session C
Session Time: 9:00AM-11:00AM

Background/Purpose: In systemic sclerosis (SSc), microvascular damage progresses from capillary dilation to capillary loss and reactive angiogenesis, as detectable by nailfold videocapillaroscopy (NVC) [1]. The process is systemic and determines multiple clinical manifestations, from the early appearance of Raynaud's phenomenon, through formation of digital ulcers (DUs), until systemic organ involvement [2,3]. Objective of the study was to quantify, in SSc patients, absolute nailfold capillary number/mm and fingertip blood perfusion (FBP) during long-term treatment with the endothelin receptor antagonist (ERA) bosentan (BOSE) and the synthetic analogue of prostacyclin PGI2 iloprost (ILO) by multiple diagnostic tools. Observed values were correlated with clinical outcomes.

Methods: Thirty SSc patients, already receiving intravenous ILO (80 µg/day), for 5 continuous days (every 3 months) were recruited. Fifteen patients continued such treatment (ILO group), while in 15 patients BOSE (125 mg twice/day) was added (ILO+BOSE group), because of the onset of pulmonary arterial hypertension or digital ulcers (DUs). The follow-up was of 4 years (T0-T4). The following diagnostic tests were performed on a yearly basis: absolute nailfold capillary number/mm count by nailfold videocapillaroscopy (NVC), FBP by laser Doppler flowmetry (LDF) evaluation, DUs incidence, diffusing capacity of the lung for carbon monoxide (DLCO), systolic pulmonary arterial pressure (sPAP), renal arterial resistive index (RI) and other biomarkers analysis. From T2 to T4 laser speckled contrast analysis (LASCA) was added. Non-parametric tests were used for statistical analysis.

Results: Only in the ILO+BOSE group, multivariate analysis showed that absolute capillary number/mm and FBP had a progressive increase ($p= 0.01$ and $p<0.0001$, respectively), independently from other clinical variables. In the same group LASCA analysis of fingertips showed a significant improvement ($p= 0.045$). In addition, during follow up there was a significant reduction (80%) in the incidence of new DUs ($p= 0.002$), whereas DLCO and sPAP did not worse. No relevant side effects were observed.

Conclusion: The study shows in SSc patients up to four years of combined therapy, a progressive significant recovery in structure and function of microvasculature, together with improved clinical outcomes, independently from disease severity. 1] Cutolo M et al. Nat Rev Rheumatol 2010;6:578-87; [2] Berezne A et al. Arthritis Care Res 2011;63:277-85; [3] Wigley FM. Clin Rev Allergy Immunol 2009;36:150-75.

Disclosure: A. C. Trombetta, None; **C. Pizzorni**, None; **B. Ruaro**, None; **S. Paolino**, None; **A. Sulli**, None; **V. Smith**, None; **M. Cutolo**, Actelion, BMS, Sanofi-Aventis, 2,Actelion, BMS, Sanofi-Aventis, 5.

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Abstract Number: 2914

Association of Radiographic Findings in Hand X-Ray with Autoantibodies in Patients with Systemic Sclerosis

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Background/Purpose: Musculoskeletal involvement is a major complication for patients with systemic sclerosis (SSc). Various radiographic abnormalities are observed, especially in hands, however, the detailed prevalence and the association with autoantibodies are still unclear. Our objective was to clarify the characteristics of radiographic findings in hand X-ray and their association with autoantibodies in SSc.

Methods: One hundred Japanese patients with SSc without rheumatoid arthritis were included. Two directional hand X-ray was examined to evaluate joint and soft-tissue changes. Clinical and serological parameters were collected retrospectively from medical records. The prevalence of abnormal findings in X-ray and the associations with clinical features, SSc subtypes and autoantibodies were analyzed.

Results: The mean age was 65.7 years (range 25-88 years), 89% were female and the mean disease duration was 11 years (range 1-44 years). Twenty-six patients (26%) were positive for anti-Scl-70 antibody, 54% for anti-centromere antibody, 6% for anti-RNA polymerase III antibody, and 6% for anti-U1RNP antibody. Twenty-four percent was diffuse cutaneous SSc and 76% was limited cutaneous SSc. Sixty one patients (61%) showed abnormality in hand X-ray; acroosteolysis in 16%, erosive disease in 20%, calcinosis in 14%, and flexion contracture in 8%. Clustering analysis for clinical features demonstrated that acroosteolysis, calcinosis and flexion contracture were associated with digital tip ulcer, interstitial lung disease and gastrointestinal involvement, but erosive disease was only associated with older age. Anti-Scl-70 was significantly associated with acroosteolysis ($p<0.001$) and anti U1-RNP with acroosteolysis and flexion contracture ($p<0.05$ for both) while anti-centromere was inclined to associate with calcinosis ($p=0.08$).

Conclusion: Abnormal findings in hand X-ray were observed more frequently in SSc patients with longer disease duration, disturbed peripheral circulation, and internal organ involvement. The type of autoantibodies was also associated with the

radiographic findings. These results suggest that X-ray findings may reflect the underlying pathogenesis in SSc.

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Abstract Number: 2915

An Increased Circulating Level of Periostin in Patients with Systemic Sclerosis: Associations with Functional Impairment in Various Affected Organs

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Background/Purpose: Periostin is one of the matricellular proteins, a class of ECM-related molecules defined by their ability to modulate cell–matrix interactions. Several lines of evidences suggest that periostin serves as a regulator of wound healing, epithelial mesenchymal transition, and fibrosis. We have previously reported overexpressed periostin levels in patients with systemic sclerosis (SSc) and a correlation between its serum levels and skin thickness score in SSc patients. In this study, we further analyzed circulating periostin levels in associations with clinical phenotypes including organ involvements in larger SSc samples.

Methods: We enrolled 385 patients with SSc and 204 healthy controls, who were recruited form 3 medical centers in Japan. Circulating levels of periostin were determined by enzyme-linked immunosorbent assay, and univariate and multivariate analysis was conducted to investigate their correlations with disease duration, antibody profiles, the modified Rodnan total skin thickness score (mRSS), and SSc-related organ involvements. Furthermore, available serial samples were analyzed to evaluate if a consecutive variation of periostin level reflect a change of mRSS (n = 76).

Results: One hundred and forty-six patients (38%) were classified as having diffuse cutaneous SSc (dcSSc), and 78 (20%), 169 (44%), 29 (8%), 209 (54%), 21 (5%), and 6 (2%) of SSc patients had digital ulcers (DU), interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), gastrointestinal involvement (GI), heart and renal involvements, respectively at initial evaluation. Disease duration from first non-Raynaud symptoms at evaluation was 7.8 ± 7.4 years. Periostin level was significantly elevated in SSc patients than in healthy controls ($P < 0.0001$). Higher periostin levels were observed in patients with dcSSc, shorter disease duration, higher mRSS, and positive for autoantibodies against to topo-I and RNAPIII. Multivariate analysis revealed that elevated periostin was an independent parameter associated with the presence of DU ($P = 0.01$), ILD ($P = 0.0005$), PAH ($P = 0.003$), GI ($P = 0.017$), and heart involvement ($P = 0.024$). In addition, mRSS was strongly associated with periosin level, disease duration, anti-topo-I and anti-RNAPIII antibodies by the multiple regression analysis ($R2 = 0.35$, $P < 0.001$). Finally, serial variation of periostin level correlated with a change of mRSS ($R2 = 0.28$, $P < 0.001$).

Conclusion: Elevated circulating periostin in SSc patients was strongly associated with mRSS and the presence of SSc-related organ involvements. Periostin may be a potential biomarker reflecting for disease severity in patients with SSc.

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Abstract Number: 2916

The Number of Micro-Haemorrhages and Micro-Thrombosis Detected By Nailfold Videocapillaroscopy Is a Good Predictor of Disease Activity in Systemic Sclerosis: The Validation Study of NEMO Score

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Background/Purpose: In a previous study it was demonstrated that, in patients with systemic sclerosis (SSc) the cumulative number of micro-haemorrhages (MH) and micro-thrombosis (MT) (the so called NEMO score), observed in nailfold videocapillaroscopy (NVC), was strongly predictive of disease activity (DA). [1].The present study is aimed at validating NEMO score as predictor of DA in different cohorts of patients.

Methods: The NEMO score, total number of giant capillaries (GC) and mean number of capillaries (Cs) were computed by eight finger NVC in 122 patients with SSc referring to the Rheumatic Disease Unit of the 'Istituto G.Pini' of Milan, where the preliminary study had been carried out (internal validation). The same procedure was performed in 97 patients collected in a different centre, i.e., the Rheumatic Dept. of the II University of Naples (external validation). In all of the patients DA was assessed at the same time of NVC performance by means of the European Scleroderma Study Group (ESSG) scoring system.

Results: Demographic and clinical characteristics of the patients were summarised in Table 1.

	number of patients	male/ female	patients with lcSSc/dcSSc	age (years) median (range)	disease duration median (range)	patients with a ESSG score≥3
Milan Cohort	122	8/114	60/62	52 (17-82)	4 (0-28)	57
Naples Cohort	97	9/88	72/25	55 (19-79)	6 (0-36)	30
All patients	219	17/202	132/87	53 (17-82)	5 (0-36)	87

lcSSc= limited cutaneous SSc; dcSSc=diffuse cutaneous SSc. Table 2: Main statistical results obtained by the analysis of the two cohorts.

	correlation* between NEMO and ESSG score	correlation* between GC and ESSG score	NEMO ROC^ curve for ESSG score≥3	sens./spec. of NEMO>8 for ESSG score ≥3
Milan Cohort	R=0.69; p<0.0001	R=0.30; p<0.001	AUC°= 0.926	84.2/92.3
Naples Cohort	R=0.76; p<0.0001	R=0.39; p<0.0005	AUC°= 0.930	93.3/76.1

*by Spearman Rank correlation; ^ROC=receiver operating characteristic; °AUC=area under the curve; sens.=sensitivity; spec.= specificity. In a logistic regression model were NEMO, GC e Cs were considered the independent variables and a ESSG≥3 the dependent variable, only NEMO score showed to have a significant predictive value for DA.

Conclusion: This validation study confirms that the presence of a certain number of MH plus that of MT in eight finger NVC may represent a simple screening method to predict the presence of DA in patients with SSc. **References.** 1. Sambataro D, et al. Arthritis Res & Ther 2014;16:462.

Disclosure: N. Del Papa, None; **R. Andracco**, None; **R. Irace**, None; **S. Vettori**, None; **F. Pignataro**, None; **W. Maglione**, None; **E. Zaccara**, None; **D. Sambataro**, None; **G. Valentini**, None; **C. Vitali**, None.

Abstract Number: 2917

Nailfold Capillaroscopy and Mortality in Systemic Sclerosis

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Background/Purpose: To test the association of the severity of nailfold capillaroscopy (NFC) abnormalities with mortality in systemic sclerosis (SSc).

Methods: One hundred and seventy SSc patients underwent an extensive evaluation at baseline following a standard protocol. Capillary loss on NFC was evaluated using the avascular score (AS, ranging from 0 to 3), and the mean number of ectasias, megacapillaries, and hemorrhages per finger was also recorded. After a mean period of 9.3±4.0 years, the life status of the patients was ascertained. Univariate and multivariate Cox proportional hazards models were used for statistical analysis.

Results: Sixty-three patients died. By univariate Cox analysis, the AS was significantly associated with mortality (HR=1.54, 95%CI: 1.13 to 2.09, p=0.006), but the association weakened after controlling for skin score and a combination variables representing results of complementary exams. However, in bivariate analysis, the AS showed a stronger association with mortality than anticentromere and antitopoisomerase I antibodies, severity of interstitial lung disease, and similar to skin score. In secondary analysis, the association of the AS with mortality was particularly strong among patients in the lowest quartile of skin score (HR=2.35, 1.08 to 5.14, P=0.032, controlled for skin score) and limited disease. Other NFC variables were not related to mortality.

Conclusion: The AS is associated with higher mortality in SSc and, despite the weakening of the association after controlling for skin score, performed better in this context than some other variables reflecting disease severity. This association was particularly strong among patients with low skin scores or limited disease.

Disclosure: T. Rohde Pavan, None;

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Abstract Number: 2918

The Clinical Relevance of Common ANA Patterns in Systemic Sclerosis

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Background/Purpose: Antinuclear antibody (ANA) test is positive in nearly 95% of patients with systemic sclerosis (SSc) [1]. We aim to identify the clinical relevance of common ANA patterns in SSc, of which there are only few published studies [2][3].

Methods: We evaluated 186 outpatients who met criteria for SSc [4] and were seen between 2010 and 2015. We collected pertinent clinical information, including ANA patterns (Homogeneous (H-ANA), speckled (S-ANA), nucleolar (N-ANA), centromere (C-ANA), and mixed [3]) performed by Indirect Immunofluorescence (IIF) and SSc auto-antibodies: RNA Polymerase III (POL3), Anti-topoisomerase I (anti-topo I), U-1 RNP, and Anti-Centromere (ACA).

Results: ANA was positive in 92% of patients (n=171) with the following patterns: H-ANA 27%, S-ANA 26%, N-ANA 12%, C-ANA 20% and mixed 14% (homogeneous & speckled 3%, homogeneous & nucleolar 5%, speckled & nucleolar 4%, speckled & centromere 1% and nucleolar & centromere 1%). H-ANA was strongly associated with both anti-topo I (OR 24, CI 10.3-55.8) and diffuse cutaneous systemic sclerosis (dcSSc) (OR 5.5, CI 2.4-12.6). In addition, H-ANA was significantly associated with later age of disease onset, acro-osteolysis, hand contractures, interstitial lung disease (ILD), and lower forced vital capacity (FVC) and diffusion capacity of the lung for carbon monoxide (DLCO). S-ANA was strongly associated with POL 3 (OR 11.4, CI 4.4-29.9), U-1RNP (OR 7.3, CI 3-17.8), and tendon friction rubs (TFRs) (OR 2.8, CI1.3-5.9). C-ANA was strongly associated with limited cutaneous systemic sclerosis (lsSSc) (OR 71, CI 9.4-533), and strongly protective against myopathy (OR 0.1, CI 0.01-0.8), TFRs ($p=0.0002$), hand contractures (OR 0.2, CI 0.08-0.7), and ILD (OR 0.3, CI 0.1-0.7). These patients had higher %FVC ($p<0.0001$) and %DLCO ($p=0.006$). None of the SSc auto-antibodies were associated with the nucleolar pattern.

Conclusion: ANA patterns may be useful in predicting specific SSc auto-antibodies and clinical features. Larger studies could confirm our findings and help further understand the clinical significance of these ANA patterns in SSc. **References:**

1- Bernstein et al. Clin Exp Imm. 1982; 48:43

2- Hesselstrand et al. Rheumatology 2003; 42:534

3- Sulli et al. J.Rheum. 2013;40:5

4- Hoogen et al. Ann Rheum Dis. 2013; 72:1747 & Arthritis Rheum. 2013;65: 2737

		Table-1 Patient Demographics and Systemic Sclerosis subtypes in relation to ANA patterns						
		ANA Positive n=171 (92%)	**ANA pattern by Indirect Immunofluorescence**					**ANA Negative n=15(8%)**
			Homogenous n=47 (27%)	***Speckled n=45 (26%)***	***Centromere n=34(20%)***	***Nucleolar n=21(12%)***	***Mixed n=24(14%)***	
		Mean (SD) or Col%	Mean(SD) or Col%	Mean(SD) or Col%	Mean(SD) or Col%	Mean(SD) or Col%	Mean(SD) or Col%	Mean(SD) or Col%
Age (years)		58.4(13)	59.7(11)	56(13)	62.4 (14.2)	55(11.8)	57.4(14.8)	62.4(13)
Female **Male**		145(85%) 26(15%)	38(81%) 9(19%)	39(87%) 6(13%)	32(94%) 2(6%)	15(71%) 6(29%)	21(88%) 3(12%)	12(80%) 3(20%
Caucasian **AA** **Other**		114(67%) 20(12%) 36(21%)	31(66%) 7(15%) 9(19%)	31(69%) 7(16%) 7(16%)	25(76%) **0(0%)** 8(24%)	12(57%) 3(14%) 6(29%)	15(63%) 3(12%) 6(25%)	12(80%) 1(7%) 2(13%)
Hispanic **Non-Hispanic**		13(8%) 157(92%)	1(2%) 46(98%)	1(2%) 44(98%)	4(12%) 29(88%)	2(10%) 19(10%)	5(21%) 19(79%)	1(7%) 14(93%)
SSc type	**Diffuse** **Limited**	94(55%) 76(45%)	**39(83%)[a]** **8(17%)** **p<0.0001**	26(59%) 18(41%)	**1(3%)** **33(97%)[b]** **p<0.0001**	13(62%) 8(38%)	15(63%) 9(37%)	10(67%) 5(33%)
Age at SSc Onset (year)*		44.7(12.8)	**48.3(10.3)** **p=0.004**	44.4(12.4)	44(13.2)	42(12.9)	41.6(16.6)	48(11.7)
Overlap w/ RA	**Yes** **No**	38(22%) 131(78%)	12(26%) 34(74%)	14(31%) 31(69%)	5(15%) 29(85%)	4(19%) 17(81%)	3(12%) 21(88%)	3(20%) 12(80%)
Overlap w/Myositis	**Yes** **No**	31(19%) 136(81%)	9(20%) 37(80%)	13(29%) 32(71%)	**1(3%)[c]** **32(97%)** **p=0.008**	5(24%) 16(76%)	4(17%) 19(83%)	4(29%) 10(71%)

a-OR=5.5, CI(2.4-12.6) b-OR=71, CI(9.4-533) c-OR=0.1, CI(0.01-0.8) *From non-RaynaudÕs symptoms SSc: systemic sclerosis; dcSSc: diffuse cutaneous systemic sclerosis; lcSSc: limited cutaneous systemic sclerosis; RA: rheumatoid arthritis

		Table-2: Systemic Sclerosis-specific auto-antibodies in relation to ANA patterns						
		ANA Positive n=171 (92%)	**ANA pattern by Indirect Immunofluorescence**					**ANA Negative n=15 (8%)**
			Homogenous n=47 (27%)	***Speckled n=45 (26%)***	***Centromere n=34 (20%)***	***Nucleolar n=21(12%)***	***Mixed n=24 (14%)***	
		Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%
Anti-topo I	**Positive** **Negative**	50(29%) 120(71%)	**35(74%)** **12(26%)** **p<0.0001[a]**	4(9%) 41(91%)	0(0%) 33(100%)	**0(0%)** **21(100%)** **p=0.003**	11(46%) 13(54%)	**0(0%)** **15(100%)** **p=0.01**
RNA-polymerase III	**Positive** **Negative**	23(16%) 122(84%)	4(10%) 38(90%)	**17(45%)** **21(55%)** **p<0.0001[b]**	0(0%) 28(100%)	**0(0%)** **17(100%)** **p=0.05**	2(12%) 15(88%)	2(14%) 12(86%)
Anti-Centromere	**Positive** **Negative**	42(25%) 127(75%)	**0(0%)** **46(100%)** **p<0.0001**	**4(9%)** **40(91%)** **p=0.01**	**34(100%)** **0(0%)** **p<0.0001**	**0(0%)** **21(100%)** **p=0.003**	4(21%) 15(79%)	**0(0%)** **15(100%)** **p=0.02**
Anti-U-1 RNP	**Positive** **Negative**	26(16%) 141(84%)	3(7%) 42(93%)	**16(36%)** **28(64%)** **p<0.0001[c]**	2(6%) 31(94%)	1(5%) 20(95%)	4(17%) 20(83%)	0(0%) 15(100%)

a-OR=24, CI(10.3-55.8) b-OR=11.4, CI(4.4-29.9) c-OR=7.3, CI(3-17.8) Anti-topo I: anti-topoisomerase I or Scl70

Table-3 Systemic Sclerosis clinical features in relation to ANA patterns								
		ANA	**ANA pattern by Indirect Immunofluorescence**					**ANA**
		Positive n=171 (92%)	***Homogenous n=47 (27%)***	***Speckled n=45 (26%)***	***Centromere n=34 (20%)***	***Nucleolar n=21(12%)***	***Mixed n=24 (14%)***	**Negative n=15 (8%)**
		Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%	Mean (SD) or Col%
Digital ulcers*	**Yes** **No**	91(54%) 77(46%)	28(60%) 19(40%)	22(49%) 23(51%)	24(71%) 10(29%)	7(37%) 12(63%)	10(43%) 13(57%)	5(33%) 10(67%)
TFRs*	**Yes** **No**	42(29%) 103(71%)	14(34%) 27(66%)	**18(44%)** **23(56%)** **p=0.007**	**0(0%)** **30(100%)** **p=0.0002**	5(31%) 11(69%)	5(29%) 12(71%)	2(14%) 12(86%)
Synovitis*	**Yes** **No**	44(28%) 111(72%)	15(36%) 27(64%)	17(40%) 26(60%)	5(16%) 27(84%)	4(22%) 14(78%)	3(14%) 18(86%)	3(20%) 12(80%)
Acro-osteolysis**	**Yes** **No**	35(24%) 112(76%)	**15(38%)** **25(62%)** **p=0.04**	4(10%) 35(90%)	4(14%) 25(86%)	3(17%) 15(83%)	9(43%) 12(57%)	5(42%) 7(58%)
Calcinosis**	**Yes** **No**	69(48%) 76(52%)	18(45%) 22(55%)	15(38%) 24(62%)	16(55%) 13(45%)	8(47%) 9(53%)	12(60%) 8(40%)	6(50%) 6(50%)
Hand Contractures*	**Yes** **No**	54(34%) 104(66%)	**20(47%)** **23(53%)** **p=0.03**	15(36%) 27(64%)	**4(13%)** **27(87%)** **p=0.008**	5(25%) 15(75%)	10(45%) 12(55%)	3(23%) 10(77%)
ILD * **	**Yes** **No**	101(68%) 47(32%)	**39(83%)** **8(17%)** **p=0.01**	27(68%) 13(32%)	**10(43%)** **13(57%)** **p=0.005**	13(72%) 5(28%)	12(60%) 8(40%)	10(71%) 4(29%)
FVC (%)		81.6%(20)	**71.9%(17)** **p=0.02**	83.1%(16.8)	**97.2%(18.1)** **p<0.0001**	72.8%(19.4)	82.6%(21.8)	71.6%(26.3)
DLCO (%)		64.3%(23.2)	**55.2%(20.4)** **p=0.05**	65.5%(21.5)	**69.4%(20.8)** **p=0.006**	66.3%(29.9)	70.5%(24.2)	48.5%(24.6)
Current mRSS* (SD)		4(6.6)	5.2(7.4)	4.2 (6.3)	2.2(2.7)	3.3(8.0)	4.4(7.8)	2.1(4.4)

***Documented on physical exam **Documented by hand x-rays ***Document by high resolution CT chest TFRs: tendon friction rubs; ILD: interstitial lung disease; FVC: forced vital capacity; DLCO: diffusion capacity of the lung for carbon monoxide mRSS: modified Rodnan skin score**

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Abstract Number: 2919

Prevalence of Antiphospholipid Antibodies and Their Clinical Associations in Systemic Sclerosis: Data from a French Cohort

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Background/Purpose: Antiphospholipid antibodies (aPL) have been found in patients with various autoimmune and rheumatic diseases, including systemic sclerosis (SSc). However, in the absence of clinical events classically associated with the antiphospholipid syndrome, their significance remains unclear. This study aimed to determine the prevalence of aPL in a cohort of SSc patients, and to assess their clinical associations. AL and VS have contributed equally to this work.

Methods: A total of 249 adult patients who fulfilled 2013 ACR/EULAR criteria for SSc were consecutively included between October 2014 and January 2016. Patients were tested for lupus anticoagulant (LA), anticardiolipin (aCL) and anti-β2glycoproteine I (anti-β2GpI) antibodies. Positive titer was defined as ≥ 10 UGPL/mL (aCL) or ≥ 10 UA/mL (anti-β2GpI). aPL positivity was defined if at least one of the three antibodies was positive. Clinical associations between aPL positivity and thrombosis event, obstetrics event, pulmonary arterial hypertension (PAH) and digital ulcer were studied using binomial logistic regressions. Adjustments were done (i) *a priori* for gender, age, SSc subtype and tobacco history, and (ii) for the characteristics that differed significantly between aPL positive and negative patients. Similar analyzes were performed considering the titers of aCL and anti-β2GpI rather than the aPL status. Because these variables had a majority of zero values, they were categorized, as follows: (i) 0, ≥1 and <5, ≥5 and ≤20 UGPL/mL for aCL, and (ii) 0, ≥1 and <5, ≥5 and <10, ≥10 and ≤100 UA/mL for anti-β2GpI.

Results: The 249 patients were predominantly female (82.3%), with limited cutaneous SSc (81.5%). One or more type of aPL was present in 16 patients leading to a prevalence of 6.4% (95% confidence interval (CI) [3.4-9.5]). aPL positivity was associated with venous thrombosis in univariate analysis (OR=3.91; 95%CI [0.98-13.53]; p=0.027); there was a trend towards an association in multivariate analysis (OR=3.24; 95%CI [0.87-10.9]; p=0.064). aPL positivity was associated with miscarriage in multivariate analysis (OR=4.31; 95%CI [1.09-16.33]; p=0.031). We did not find any association between aPL positivity and PAH or digital ulcer. Titers of aCL ≥5 UGPL/mL were associated with PAH (OR=6.35; 95%CI [1-41.1]; p=0.043) and venous thrombosis (OR=3.69; 95%CI [0.98-12.9]; p=0.043) in multivariate analysis. Titers of anti-β2GpI ≥10 UA/mL and miscarriage were associated (OR=5.25; 95%CI [1.04-27.1]; p=0.041).

Conclusion: This study found a prevalence of aPL in SSc of 6.4% (95%CI [3.4-9.5]) in a French cohort. aPL positivity was associated with venous thrombosis and miscarriage. These data provide additional insights into the vascular involvement of SSc.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p	OR	95%CI	p
Arterial or venous thrombosis	2.92	0.82-9.50	0.085	2.59	0.77-8.12	0.108
Arterial thrombosis	2.56	0.43-10.54	0.160	2.14	0.87-10.9	0.307
Venous thrombosis	**3.91**	**0.98-13.53**	**0.027**	3.24	0.42-8.52	0.064
Miscarriage	2.84	0.67-11.11	0.136	**4.31**	**1.09-16.33**	**0.031**
Digital ulceration	0.31	0.03-1.47	0.150	0.45	0.07-1.86	0.327
PAH	0.97	0.02-7.26	1	0.73	0.04-4.43	0.776

Disclosure: A. Lemaire, None; **V. Sobanski**, None; **J. Giovannelli**, None; **E. Hachulla**, None; **S. Dubucquoi**, None; **M. Lambert**, None; **P. Y. Hatron**, None; **D. Launay**, None.

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Abstract Number: 2920

The Effect of Rituximab on B Cells in Skin and Peripheral Blood in Systemic Sclerosis

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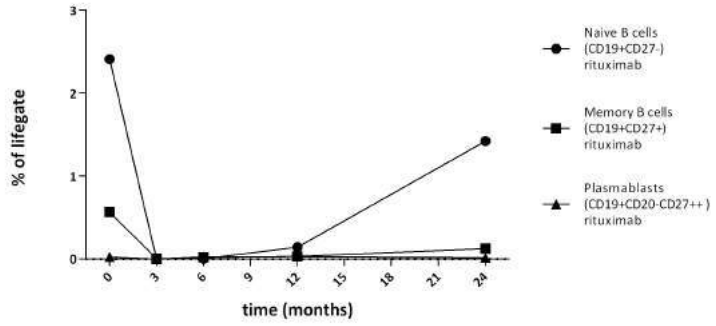
Background/Purpose: Open-label studies provided evidence for possible efficacy of rituximab (RTX) in systemic sclerosis (SSc). Previously, we reported on a randomized placebo-controlled clinical trial in early SSc showing no significant difference in clinical outcomes. In rheumatoid arthritis and systemic lupus erythematodus, clinical efficacy of RTX is associated with the extent of B cell depletion. Therefore, we aimed to investigate the effect of rituximab in SSc on B cells in peripheral blood and skin, as possible explanation for lack of clinical efficacy.

Methods: Sixteen patients fulfilling ARA criteria for SSc were randomized to either placebo or 1000 mg RTX IV on day 1, 15 and at 6 months and followed for 24 months. Immunophenotyping of peripheral blood mononuclear cells (PBMC) by flow cytometry for presence of CD19+CD27- naïve B cells, CD19+CD27+ memory B cells, CD19+CD20-CD27++ plasmablasts and detection of antibody secreting cells (ASC) by Enzyme-Linked ImmunoSpot assay (ELISPOT) was performed at baseline, months 3, 6, 12 and 24. 4 mm skin biopsies of the dorsal forearm were assessed for presence of B cells by immunohistochemistry with CD79a at baseline and 3 months.

Results: Mean age was 44.5 years (SE 5.6), 87.5 % of patients had diffuse cutaneous SSc, median disease duration since non-Raynaud was 1.2 years (interquartile range 0.8-2.8). At month 3, depletion of naïve and memory B cells to very low B cell counts was achieved with RTX. Naïve B cells repopulated first and were clearly detectable at month 12, while memory B cells reached pre-treatment levels only at month 24 (Figure 1). Some patients achieved undetectable counts of naïve B cells or plasmablasts, though no patient had undetectable B cells in all subsets (Figure 2). Persistence of ASC was confirmed by ELISPOT (Figure 3). Scattered B cells (range 2-7) were seen in skin biopsies at baseline (placebo 3 of 8; RTX 2 of 7 biopsies) and at 3 months (placebo 4 of 7; RTX 4 of 7 biopsies).

Conclusion: Treatment with RTX resulted in depletion of peripheral blood B cells to very low, though still detectable counts. Despite this depletion, no clinical effect was observed. Persistence of ASC and persistent detection of B cells in skin at 3 months provide evidence for treatment-resistant populations of B cells in SSc, which might influence treatment response.

Figure 1. Naïve B cell, memory B cell and plasmablast levels in SSc patients treated with RTX

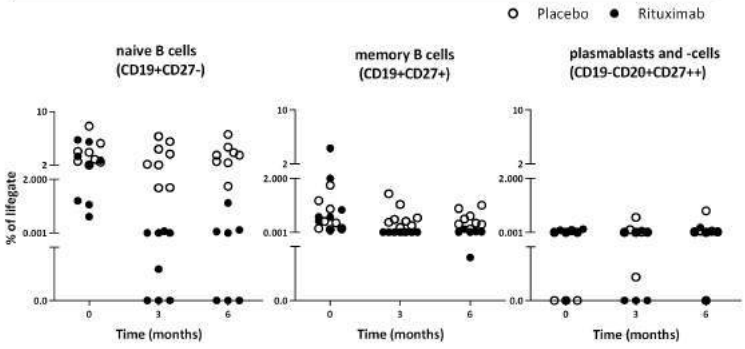


SSc - systemic sclerosis ; RTX – rituximab

Symbols indicate median values per group at given time. RTX: T0, n= 8; T3 n=8; T6 n=7; T12 n=6; T24 n=4; Placebo: T0, n=8; T3, n=8; T6 n=8; T12 n=7; T24 n=7

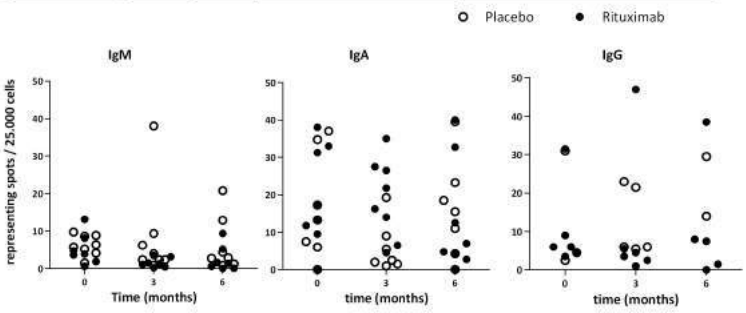
All patients receiving RTX had B cell depletion of naïve and memory cells, 3 months after rituximab treatment. Reduction of plasma blasts was non-significant compared to either baseline (p=0.10) or placebo (p=0.74).

Figure 2. Naïve B cell, memory B cell and plasmablast cell count for placebo and RTX treated SSc patients



SSc - systemic sclerosis; RTX – rituximab
RTX: T0, n= 8; T3 n=8; T6 n=7; Placebo: T0, n=8; T3, n=8; T6 n=8

Figure 3. Antibody secreting cells in placebo and RTX treated SSc patients



SSc - systemic sclerosis; RTX – rituximab
IgA - RTX: T0, n= 7; T3 n=7; T6 n=7; Placebo: T0, n=8; T3, n=8; T6 n=8;
IgM - RTX: T0, n= 7; T3 n=7; T6 n=7; Placebo: T0, n=8; T3, n=8; T6 n=7;
IgG* - RTX: T0, n= 7; T3 n=7; T6 n=7; Placebo: T0, n=8; T3, n=8; T6 n=7
Due to overexpression of IgG expressing cells, in some patients cell counts could not be determined

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Patient Participation in Patient Reported Outcome Instrument Development in Systemic Sclerosis

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Background/Purpose: The patient perspective captured using Patient-Reported Outcome (PRO) instruments provide valuable insight into the patient condition not always captured by physician-derived assessment tools. Target patient population involvement is considered an essential component of PRO instrument design and is assessed by regulatory bodies when considering labelling claims in medical product development. We have reviewed the level of patient involvement in the development of PRO instruments used in the assessment of systemic sclerosis (SSc).

Methods: A comprehensive literature review was undertaken to identify studies reporting PRO instruments in SSc. Studies were assessed to establish whether the PRO instruments had been developed specifically for SSc or adopted from other disease areas. Studies reporting PRO instruments specific for SSc were scrutinised for evidence of target patient population involvement in the development of the instrument.

Results: A total of 58 PRO instruments that have been used in SSc research were identified. Twelve (21%) of these were developed specifically for outcome assessment within SSc populations (Table). Of these, 5 (42%) had not reported any patient involvement in the development phase of the instrument. Five SSc PRO instruments (42%) involved target patient population in the domain/item generation stage. Four (33%) of SSc PRO instruments had undertaken cognitive interviewing/linguistic evaluation to ensure item wording adequately captured the intended conceptual framework. The SCTC GIT questionnaires and the Systemic Sclerosis Questionnaire had each involved SSc patients in both domain/item generation and cognitive interviewing/linguistic evaluation stages of instrument development.

Conclusion: PRO instruments are particularly valuable in SSc due to the multi-faceted nature of the disease and the paucity of effective objective methods for assessing disease status. The majority of existing PRO instruments used in SSc have not involved significant target patient involvement in their development. By involving patients in the development and design phase of novel PRO instruments in SSc, we can ensure that PRO instruments used in the clinical and research settings adequately capture experiences most relevant to our patients. **Table. Patient involvement in development of SSc-specifc PRO instruments** * Authors report patient involvement but no details supplied.

Organ system	Conceptual Framework	Author, Year	PRO	Patient involvement in:					
				Conceptual Framework	Domain generation	Item generation	Cognitive interviewing	Linguistic Evaluation	Respondent Burden
Disability & function	Disability & Function in SSc	Steen and Medsger, 1997	Scleroderma HAQ subscales	No	No	No	No	**Yes**	No
	Disability and Function in SSc	Silman et al., 1998	UK Scleroderma Functional Score	No	No *	No *	No	No	No
	Disability and Function in SSc	Guillevin and Ortonne, 1983	Scleroderma Functional Index	No	No	No	No	No	No
Global Assessment of Health Status	Global disease assessment	Suarez-Almazor, et al., 2007 & Kallen et al. 2010	Symptom Burden Index	No	**Yes**	**Yes**	No	No	No
	Global disease assessment in SSc	Ruof et al., 1999	Systemic Sclerosis Questionnaire	No	**Yes**	**Yes**	**Yes**	**Yes**	No
	Global disease assessment in SSc	Ostojic and Damjanov, 2006	Scleroderma Assessment Questionnaire	No	**Yes**	**Yes**	No	No	No
Skin	Skin thickening, tethering and thinness in SSc	Nagy et al. 2009	Patient Skin Self Assessment Questionnaire	No	No	No	No	**Yes**	No
Body Image	Body Image in SSc	Jewett, 2015	BCSS	No	No	No	No	No	No
	Body Image in SSc	Jewett, 2010	Brief-SWAP	No	No	No	No	No	No
Peripheral Vascular	Raynaud's phenomenon in SSc	Wigley et al., 1998 & Black et al. 1998	Raynaud's Condition Score Diary	No	No	No	No	No	No
Gastrointestinal	GI symptoms in SSc	Khanna et al. 2007 & Khanna et al. 2009	SCTC GIT 1.0 and 2.0	**No**	**Yes**	**Yes**	**Yes**	**Yes**	No
	Mouth Handicap in SSc	Mouthon et al., 2007	MHISS	**Yes** Postal survey	**Yes** Postal survey	**Yes** Postal survey	No	No	No

Disclosure: J. Pauling, None; **T. M. Frech**, None; **R. T. Domsic**, None; **M. Hudson**, None.

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Abstract Number: 2922

Disability, Fatigue, and Their Associates in Early Diffuse Cutaneous Systemic Sclerosis

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Background/Purpose: ESOS (European Scleroderma Observational Study) was a prospective observational study of 326 patients with early diffuse cutaneous systemic sclerosis (dcSSc) from 50 centres. Here we describe the burden of disease in terms of disability and fatigue in this very early disease cohort (median disease duration 11.9 months), and explore disease features that associate with this burden.

Methods: Patients completed questionnaires at study entry and at 12 months: the Scleroderma Specific Health Assessment Questionnaire (sHAQ, including HAQ-DI disability index), Functional Assessment of Chronic Illness Therapy [FACIT]-fatigue, the Short Form 36 [SF36] and the Cochin Hand Function Scale (CHFS). Covariates examined included the modified Rodnan skin score (mRSS) and other parameters listed in Table 1. The distribution of the HAQ-DI, fatigue and hand function scores was compared between levels of categorical variables using Kruskal-Wallis' test and correlations with other continuous variables were assessed using Spearman's coefficient (ρ). For continuous variables, correlations between 12-month changes were also computed.

Results: Baseline scores of HAQ-DI, FACIT and CHFS, and associates are shown in Table 1. High levels of skin fibrosis (mRSS) were associated with poor hand function (ρ=0.35) and high HAQ-DI scores (ρ=0.34). The median CHFS (0-90 scale) and HAQ-DI (0-3 scale) scores were higher by 8.5 and 0.6 units (indicating poorer hand function and increased disability) in patients with current digital ulcers. The median HAQ-DI score was higher by one unit in patients with muscle involvement, and was also higher in patients with lung fibrosis and heart involvement. Cardiac, pulmonary and renal involvement were each associated with higher levels of fatigue. Patients currently or previously on corticosteroids had more disability and fatigue than patients who had never been prescribed these. As anticipated, HAQ-DI, FACIT, CHFS and SF36 scores were all highly correlated. The 12-month change in HAQ-DI had a strong association with the change in hand function (ρ=0.56), and increasing levels of skin fibrosis were correlated with increasing HAQ-DI scores (ρ=0.40).

Conclusion:

1. ESOS benchmarks the burden of disability in early dcSSc, with high levels of disability and fatigue, and will provide comparative data for future clinical trials.

2. The degree of disability/fatigue is associated with severity of skin thickening (mRSS), with changes in HAQ-DI over 12 months correlating with changes in mRSS.

3. Impaired hand function is a major contributor to overall disability.

4. Disability and fatigue associate with internal organ involvement, and overall (HAQ-DI) and hand disability with digital ulcers.

Table 1. Baseline associates of disability, median and interquartile range (for levels within binary variables) and correlations

(for pairs of continuous variables).

	HAQ-DI (0-3) [3 most disabled]	FACIT fatigue (0-52) [0 most disabled]	Cochin hand function (0-90) [90 most disabled]
Overall indicator median (IQR)	1 (0.4 - 1.8)	31 (20 - 41)	11 (3 - 29)

Binary variables	Yes	No	p[a]	Yes	No	p[a]	Yes	No	p[a]
Female	1 (0.4 - 1.9)	0.8 (0.4 - 1.4)	0.134	30.7 (19 - 41)	32.5 (24.5 - 41.5)	0.317	12 (3 - 29)	9 (3 - 19)	0.542
Current or previous steroid use	1.3 (0.5 - 2)	0.9 (0.4 - 1.5)	0.002	27.5 (17.2 - 38.5)	34 (24 - 42)	0.004	16 (5 - 34)	8 (2 - 22)	0.009
Previous use of immunosuppressants	0.9 (0.5 - 2)	1 (0.4 - 1.6)	0.640	35 (24 - 38)	31 (20 - 41)	0.658	10 (3 - 22)	11 (3 - 29)	0.918
Digital ulcers	1.5 (0.6 - 2.3)	0.9 (0.4 - 1.6)	0.004	27 (20 - 37.5)	32.3 (20 - 42)	0.069	18.5 (3.5 - 43.5)	10 (3 - 26)	0.025
Pulmonary fibrosis	1.5 (0.8 - 2.1)	0.9 (0.4 - 1.6)	0.005	21.5 (14 - 30.5)	33 (22 - 42)	0.000	23.5 (11 - 40)	10 (3 - 26)	0.019
Pulmonary hypertension	1.4 (0.7 - 2.2)	0.9 (0.4 - 1.6)	0.082	22.5 (15.5 - 31)	32.5 (21 - 42)	0.006	13 (1 - 21)	11 (3 - 29)	0.664
Renal involvement	1.2 (0.6 - 2.1)	1 (0.4 - 1.6)	0.125	23.5 (17 - 34)	32 (21 - 42)	0.013	18 (4 - 33)	11 (3 - 26)	0.249
Cardiac involvement	1.3 (0.9 - 2.3)	0.9 (0.4 - 1.7)	0.005	23.5 (12 - 34)	32 (21 - 42)	0.001	11 (5 - 39)	11 (3 - 27)	0.357
Muscle involvement	1.9 (1 - 2.3)	0.9 (0.4 - 1.6)	0.002	25.5 (16 - 38)	32 (21 - 42)	0.071	16 (5 - 55)	10 (3 - 26)	0.104
Anti-topoisomerase (anti-ScL70)	0.9 (0.4 - 1.7)	1 (0.5 - 1.8)	0.374	30.3 (19 - 41)	32 (22 - 42)	0.475	11 (3 - 26)	10 (3 - 29)	0.631
Anti-RNA polymerase III	1 (0.6 - 1.6)	0.9 (0.4 - 1.7)	0.114	29.6 (18 - 41)	30.9 (20.5 - 41.5)	0.678	10.5 (6 - 29)	11 (2 - 26)	0.291
Anticentromere	0.6 (0 - 1.5)	1 (0.4 - 1.8)	0.089	34.5 (22 - 44)	31 (20 - 41)	0.263	8.5 (0 - 26)	11 (3 - 27)	0.312

	HAQ-DI (0-3)		FACIT fatigue (0-52)		Cochin hand function (0-90)	
Continuous variables	Spearman's ρ	p[b]	Spearman's ρ	p[b]	Spearman's ρ	p[b]
Age	-0.05	0.372	0.04	0.504	-0.04	0.587
Months since onset of skin thickening	0.01	0.930	-0.01	0.839	-0.01	0.901
mRSS (0-51)	0.34	0.000	-0.19	0.001	0.35	0.000
mRSS in fingers and hand dorsum (0-12)	0.23	0.000	-0.13	0.029	0.32	0.000
sPAP or RVSP mmHg	0.07	0.324	-0.04	0.575	0.01	0.894
FVC (% predicted)	-0.20	0.001	0.24	0.000	-0.16	0.016
DLCO (% predicted)	-0.21	0.001	0.22	0.000	-0.19	0.008
HAQ-DI Disability index (0-3)	1.00	0.000	-0.67	0.000	0.84	0.000
FACIT fatigue score (0-52)	-0.67	0.000	1.00	0.000	-0.63	0.000
Cochin hand function score (0-90)	0.84	0.000	-0.63	0.000	1.00	0.000
SF36 physical score (0-100) [0 most disabled]	-0.72	0.000	0.67	0.000	-0.61	0.000
SF36 mental score (0-100) [0 most disabled]	-0.18	0.001	0.29	0.000	-0.19	0.004

mRSS: modified Rodnan skin score (17 sites)
sPAP: Systolic pulmonary artery pressure
RVSP: Right ventricular systolic pressure
FVC: Forced vital capacity
DLCO: Carbon monoxide diffusing capacity
HAQ-DI: Health Assessment Questionnaire - Disability Index
sHAQ: Scleroderma Health Assessment Questionnaire

p[a]: p-value for Kruskal-Wallis' test, for differences in distribution between levels of categorical variables.
p[b]: p-value for Spearman correlation.

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Abstract Number: 2923

T-Cell Receptor Signaling Inhibition By CC-90005, a Selective Protein Kinase C Theta Antagonist, Reduces Antigen Mediated T-Cell Activation and Arthritis Pathology in the Mouse CIA Model

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Background/Purpose: PKC-θ is a member of the $Ca2^{+}$-independent novel PKC subfamily, most abundantly expressed in T-cells, and mediates early antigen recognition signal transduction and cell activation associated with T-cell receptor (TCR) stimulation. Inhibition of PKC-θ by CC-90005, a highly selective and orally active small molecule inhibitor of PKC-θ may provide new therapeutic treatment options for T-cell mediated rheumatic disease indications.

Methods: Human purified T cell cultures or whole blood samples were pre-treated with CC-90005 (0.1-10 μM) followed by anti-CD3 and anti-CD28 TCR stimulation to assess the impact of PKC-θ inhibition on TCR signal transduction, expression of cell surface activation markers, proliferation, and cytokine production. A collagen-induced arthritis (CIA) model in DBA mice was used to assess the therapeutic potential of CC-90005 in treating rheumatoid disease indications. Drug was given once or twice daily in a prophylactic dosing paradigm starting 1 day before collagen sensitization. Paw swelling was measured and scored throughout a 42 day treatment schedule. Cytokine gene expression, protein levels and circulating C-terminal telopeptide collagen breakdown products (CTX-I, CTX-II) were measured on day 42.

Results: TCR stimulation in the presence of CC-90005 resulted in the significant inhibition of T-cell activation in a concentration range of 0.3 to 10 μM in purified human T-cell and whole blood cultures. Consistent with PKC-θ being an early step in the activation of T-cells, inhibition by CC-90005 reduced TCR mediated T-cell activation at the level of target engagement (phosphorylated PKC-θ), signal transduction (phosphorylated ERK1/2 and NFkB; IkBα degradation), and cellular function (surface receptor activation marker expression, proliferation, and cytokine production). In the mouse CIA model of arthritis, reduction of clinical scores was observed at 30 and 100 mg/kg BID accompanied by reduced cytokine expression (IL-1β, IL-17 and IL-22) in the ankle joints and a dose related trend towards reduced serum levels of CTX-I and CTX-II.

Conclusion: CC-90005, a specific inhibitor of PKC-θ, significantly inhibits TCR signal transduction pathways resulting in the inhibition of functional T-cell responses including cell surface activation marker expression, proliferation, and cytokine production. Moreover, inhibition of these T-cell functions showed efficacy in a mouse CIA model of arthritis, suggesting that selective inhibition of PKC-θ is sufficient to provide therapeutic benefit in rheumatologic diseases.

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Abstract Number: 2924

Terminally Differentiated CD8 T Cell Subset Has Distinct Signiture in RA

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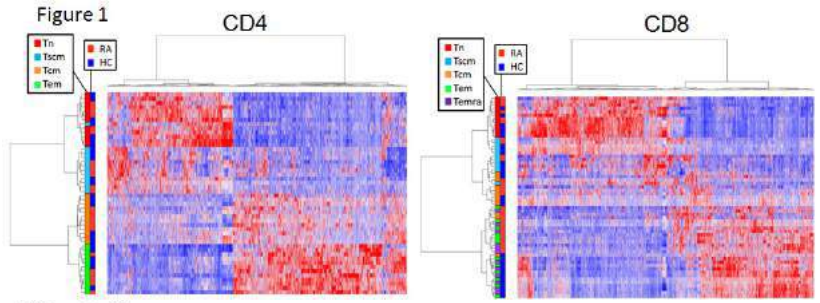
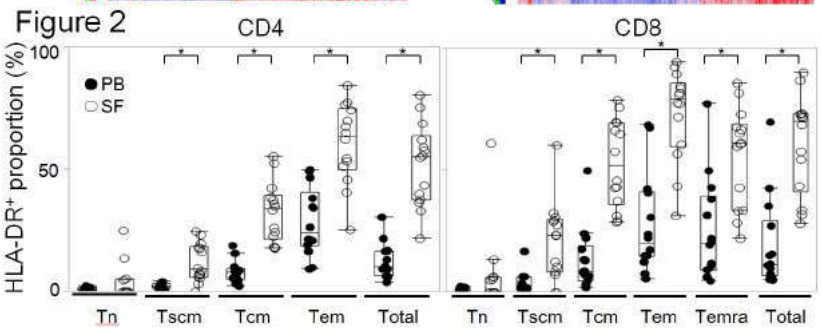
Background/Purpose: Previous reports showed that both CD4 and CD8 T cells were related to the RA disease activity, such as Th17, follicular helper 2, and activated CD8 T cells. On the other hand, T cells can be divided according to developmental stages, and it is controversial whether T cell proceeds development in RA, partly because aging greatly influences T cell development. Recently, the least developed memory T cell subset, stem cell memory T (Tscm), was found among cells with naive phenotype, therefore, peripheral blood (PB) T cells can be divided into naive (Tn), Tscm, central memory (Tcm), and effector memory (Tem) in CD4, and these plus CD45RA+ effector memory (Temra) in CD8. Although human Tscm were reported in patients with bone marrow transplantation, it has not been studied in autoimmune diseases. The purpose of this study was to elucidate the T cell abnormality among each developmental stages including newly identified Tscm in RA patients.

Methods: PB samples from 56 untreated RA patients and 38 healthy controls (HC), and 14 synovial fluid (SF) samples with paired PB from same RA patients were collected. The proportion of each developmental stage and activating status was determined by flow cytometry. Tn, Tscm, Tcm, Tem, and Temra subset from PB of 6 RA and HC were sorted, and analyzed gene expression by microarray.

Results: PB T cells were greatly influenced by age and individual differences, however, the proportion of developed cells tended to increases in RA. Especially, the proportion of CD4 Tscm was significantly high in RA (p=0.02), and CD8 Tscm also tended to be high. In transcriptome analysis, most of subsets were clustered by developmental stage rather than disease, suggesting that influence of disease was not so big among same developmental stages (Fig 1). Remarkably, CD8 Tem and Temra were apparently different between RA and HC. Pathway/upstream analysis showed that this difference may be derived from cytokines such as VEGF, PDGF, and IL-6. In comparison of T cells in PB and SF, the proportion of developed and activated cells was high in SF (Fig 2). Interestingly, most of CCR7+CD45RO-cells in SF, which had been classified as naive, were actually Tscm. In addition, the proportion of activated CD4 and CD8 Tscm in SF were correlated with RA disease activity.

Conclusion: Although the PB T cell in RA had smaller differences with that of HC than expected, several cytokine signatures were found in CD8 Tem and Temra of RA. In SF, almost all T cells, including cells which has been considered naive, were memory cells. Activating status of Tscm in both CD4 and CD8, correlated with RA disease activity, indicating that these subsets participated in RA pathophysiology.





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Abstract Number: 2925

Programmed Cell Death (PD)-1 May Play a Significant Role in the Pathogenesis of Rheumatoid Arthritis

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Background/Purpose: PD-1 is a co-inhibitory transmembrane protein with a significant effect on immune regulation. Several studies have shown elevated expression levels of PD-1 on T cells isolated from the blood and the synovial fluid of patients with rheumatoid arthritis (RA). Moreover, in some studies, PD-1 expression levels correlated with disease activity scores. The goal of our study was to uncover the signaling pathways downstream of PD-1 in RA T cells as well as its contribution to cellular function. Understanding the biology of PD-1 in RA T cells may lead to novel targets in the treatment of inflammatory arthritis.

Methods: Naïve primary T cells were isolated from RA patients and healthy controls. PD-1 expression was measured by flow cytometry. T cells were stimulated with beads coated with antibodies to T cell receptors as well as PD-L2, a ligand for PD-1. Western blot analysis was used to measure levels of key signaling proteins. Cytokine secretion, calcium influx, and adhesion to coated surfaces were concurrently recorded. Correlation analysis between these variables and clinical parameters were performed.

Results: Compared with healthy controls, T cells isolated from RA patients demonstrate higher plasma membrane PD-1 levels, which correlate with disease activity. When stimulated, these cells secrete more IL-2 in response to T cell receptor ligation, while concurrent PD-1 receptor activation led to an attenuated response. Higher levels of phosphorylated Erk were recorded in RA T cells compared to healthy control T cells. Moreover, stimulation of PD-1 led to Erk inhibition only in the RA T cells, but not in the cells isolated from healthy controls.

Conclusion: Given that PD-1 is a co-inhibitory receptor, one might expect that T cells from patients with autoimmune disease would express lower levels of PD-1 on their surface. In contrast, our data suggests that RA T cells express higher levels of PD-1 and that they are more activated when compared to healthy control T cells. It is not clear whether PD-1 is a cell surface marker of activation or if those T cells are “resistant” to signals downstream of PD-1. In conclusion, PD-1 may serve as a T cell regulator in RA with possible therapeutic potential.

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Abstract Number: 2926

Rorc Positive Th17, Th17/Th1, and Th17.1 Cells from the Blood of Treatment NaïVe RA Patients Differ in IL-17A but Are All Pathogenic When Co-Cultured with RA Synovial Fibroblasts

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Background/Purpose: T cells play a central role in the early stages of rheumatoid arthritis (RA). In this context, we have shown increased proportions of memory CCR6+ Th cells in the blood of treatment naïve patients with early RA compared to healthy individuals. These cells express high levels of IL-17A and are TNFalpha positive. In addition, these memory CCR6+ Th cells induced a proinflammatory loop when co-cultured with RA synovial fibroblasts. This interaction may underlie the development of chronic synovitis. Since the memory CCR6+ T cell populations is a heterogeneous population consisting of e.g. Th17, Th17/Th1, and Th17.1 subpopulations we examined the presence and pathogenic potential of these subpopulations from the blood of treatment naïve patients with early RA.

Methods: Memory CCR6+ Th cell subpopulations from the blood of treatment naive patients with early RA were distinguished based on chemokine receptor expression. Within these populations, cytokine and transcription factor expression were examined. In addition, CCR6+ subpopulations were sorted by FACS from peripheral blood of treatment naïve patients with early RA and analyzed for their pathologic potential in a co-culture system with RA derived synovial fibroblasts (RASF).

Results: Based on the expression of CXCR3 and CCR4 four memory CCR6+ Th cell subpopulations were distinguished: Th17, Th17/Th1, Th17.1, and double negative (DN) cells. All four CCR6+ subpopulations expressed RORC, but differ in IL-17A, IL-17F, IL-22, IFNgamma, and T-bet expression. Furthermore, all four subpopulations showed increased pathological potential in co-culture with RASF compared to naive and the classical Th1 cells. Interestingly, even Th17.1, the subpopulation with the lowest IL-17A expression, displayed high pathological potential as shown by stimulating IL-1β, IL-6, IL-8, COX-2 and MMP-3 expression upon co-culture with RASF.

Conclusion: The memory CCR6+ Th subpopulations differ in IL-17A, IFNgamma and T-bet expression However, all subpopulations express RORC. Interestingly, all subpopulations possess strong pathological potential in stimulating RASF to induce expression of proinflammatory cytokines and MMPs. These findings indicate that in addition to Th17 cells, also other CCR6+ Th subpopulations play a prominent role in the pathogenesis of synovial inflammation despite low IL-17A. Further insight in the molecular phenotype of these subpopulations is warranted to optimize targeted therapy in RA.

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Abstract Number: 2927

Mechanisms Regulating the Loss of Tregs in CD11c-Flip-KO Mice That Contribute to the Spontaneous Development of Inflammatory Arthritis

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Background/Purpose: CD11c-Flip-KO (**HUPO**) mice spontaneously develop inflammatory, erosive arthritis. We previously demonstrated that T regulatory cells (Tregs) were reduced in HUPO mice and that the adoptive transfer of Tregs isolated from

spleens of control mice suppressed not only the arthritis but also the expression of autoreactive T cells. The purpose of these studies was to identify the mechanism(s) responsible for the reduction of Tregs in HUPO mice.

Methods: Immune cell phenotype and apoptosis/necrosis were assessed by flow cytometry employing multicolor fluorochrome-antibodies. Conventional dendritic cells (cDCs), Tregs or $CD3^+$T cells are purified by positive or negative selection employing commercially available kits. In vitro cell culture or in vivo adoptive transfer were employed to examine T cell proliferation, Treg development and maintenance. Mice analyzed were HUPO vs. littermates, or *Rag*$^{-/-}$ vs. HUPO-*Rag*$^{-/-}$ as the lymphopenic recipients for in vivo homeostatic proliferation. Cytokines were determined by quantitative ELISA or rt-PCR.

Results: A marked reduction of IL-2 was identified in in vitro spleen culture supernatants of HUPO mice compared with littermate controls. Tregs were also reduced in the spleen cultures and the addition of IL-2 or cDCs increased Tregs but not other T cells. Further, cDCs from HUPO mice were deficient in TGFβ. In vivo, a significant increase of necrotic Tregs was identified in the spleens of young (4 weeks) and old (≥20 weeks) HUPO mice. Consistent with these observations central Tregs, which are highly IL-2 dependent, were greatly reduced in the spleens of young and old HUPO mice. Additional experiments were performed under lymphopenic conditions since the maintenance of Tregs is in part regulated by homeostatic proliferation. HUPO mice exhibit a reduction of cDCs, particularly the CD8a subset and of $CD11c^+$ macrophages. Crossing HUPO and Rag$^{-/-}$ resulted in HUPO-*Rag*$^{-/-}$ line with mild non-progressive arthritis. Following the adoptive transfer of control $CD3^+$ T cells no reduction of Treg homeostatic proliferation was observed in HUPO-*Rag*$^{-/-}$ mice. However at 6 and 20 days following adoptive transfer Tregs became significantly reduced, in the absence of increased cell death, suggesting a reduction of maintenance or increased dedifferentiation of Tregs. Supporting this mechanism the MFI of Foxp3 expression was significantly reduced in the Tregs of HUPO mice and the control donor T cells in the HUPO-*Rag*$^{-/-}$ recipients. Summary: Multiple mechanisms appear to contribute to the reduction of Tregs in HUPO mice. Increased Treg cell death and the reduction of central Tregs may be due to the reduction of IL-2. Increased dedifferentiation may also contribute to the reduction of Tregs in HUPO mice. Further studies with Foxp3-GFP Tregs will help determine the contributions of each mechanism.

Conclusion: IL-2 and TGFβ are the essential cytokines for Treg differentiation and stability. Our observations suggest that IL-2 may be the effective treatment strategies for HUPO arthritis. The documented reduction of IL-2 in patients with RA suggests similar approach might be effective in patients with RA.

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Abstract Number: 2928

Hypomethylation of an Intragenic Alternative Promoter Contributes to Impaired Treg Function in Rheumatoid Arthritis By Transcriptional Interference with Expression of the Treg-Specific Protein, Glycoprotein a Repetitions Predominant (GARP)

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Background/Purpose: The expression of Treg specific genes, such as the master transcription factor of Tregs, FoxP3 or the Treg specific surface molecule, glycoprotein A repetitions predominant (GARP) controls the function of regulatory T cells. As Tregs are functionally impaired in rheumatoid arthritis (RA), we have performed an in depth analysis of GARP promoter regulation in healthy controls and in patients with RA.

Methods: CD25+ CD127- CD4 Tregs and CD25- CD4 T cells were isolated from the peripheral blood of therapy-naive RA patients and of age- and sex-matched healthy volunteers by magnetic cell sorting. Genomic DNA was isolated and processed by bisulfite conversion. DNA regions of interest were amplified by PCR using primers specific for bisulfite converted DNA. The PCR products were cloned and subsequently sequenced to compare methylation between controls and RA patients.

Results: Two transcripts transcribed from two alternative promoters were identified for the human GARP gene. While neither transcript was expressed in conventional T cells, both transcripts were detected in Tregs. Luciferase reporter assays with the two isolated promoters in transfected primary CD4 Tregs indicated that both transcripts initiated gene transcription upon T cell specific activation (i.e. mAbs to CD3 and CD28). Treg-specific GARP transcription was initiated by synergistic interaction of Foxp3 with NFAT and was underpinned by permissive chromatin remodeling caused by release of the H3K4 demethylase, PLU-1. The transcript initiated from the up-stream P2 promoter was markedly more abundant, suggesting the P2 promoter to be the main promoter of GARP. Surprisingly, the promoter activity of the full length GARP promoter was markedly reduced when compared to the upstream P2 promoter alone. DNA methylation analysis revealed several CpG island in both promoter regions. While the CpG islands of the P2 promoter were fully demethylated in both, effector and regulatory T cells, they were hypomethylated in the downstream P1 promoter only in activated Tregs. Surprisingly, the transcriptional activity of the strong upstream P2 promoter was down-regulated upon demethylation of the weak downstream P1 promoter, suggesting an inhibitory interaction between both promoters within the full-length promoter sequence. Of great interest, demethylation-induced transcriptional attenuation regulated the magnitude of GARP expression in Tregs. As GARP expression is required for Treg function and Tregs are functionally altered in RA, we finally investigated GARP expression in RA Tregs and found significantly reduced expression in RA. This reduced expression strongly correlated with RA disease activity and was caused by hypomethylation of the downstream P1 promoter in RA Tregs, thereby facilitating increased hindrance of P2-induced GARP transcription.

Conclusion: Our findings describe a novel function of alternative promoters in regulating the extent of gene transcription in human T cells. They further show, that in RA, GARP promoter regions are altered with regard to DNA methylation, which affects GARP expression and, thus, Treg function. Altered promoter methylation of GARP might therefore contribute to RA pathogenesis.

Disclosure: A. Skapenko, None; **J. Leipe**, None; **H. Schulze-Koops**, None.

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Abstract Number: 2929

The Baseline Th17 Lymphocytes Level Is a Predictive Marker of Good Response to Biologics in Rheumatoid Arthritis

Sarah Salomon[1], Caroline Guignant[2], Pierre Morel[3], Brigitte Gubler[4], Patrice Fardellone[5], Jean-Pierre Marolleau[6] and **Vincent Goeb**[7], [1]Rheumatology, University Hospital of Amiens, Amiens, France, [2]Immunology Laboratory, University Hospital of Amiens, Amiens, France, [3]Hematology, University Hospital of Amiens, Amiens, France, [4]Immunology, University Hospital of Amiens, Amiens, France, [5]Department of Rheumatology, Amiens University hospital, Amiens, France, [6]hematology, University Hospital of Amiens, Amiens, France, [7]Rheumatology, Amiens University Hospital, Amiens, France

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Background/Purpose: In clinical daily practice, the response to biologic drugs is unpredictable in patients with rheumatoid arthritis (RA). Thus, there is a crucial need for predictive biomarkers of response. The main objective of our study is to describe the evolution of T and B cells in patients with RA treated with biologics and to investigate whether there is a correlation between the initial rate of blood cells and the clinical response under therapy.

Methods: This was a propective single-center pilot study, descriptive and not randomized. Patients were included with RA fulfilling the ACR/EULAR 2010 criteria, with an active disease according to the DAS28 score despite treatment, and in whom initiation or switch of a biologic (TNF-blockers, tocilizumab and abatacept) except rituximab was required. A control group of patients without any autoimmune disease or immune dysfunction was also assessed. B and T lymphocytes whole blood phenotyping, as well as an analysis of the production of IL-10 were performed by multicolor flow cytometry (FCM) in both patients and controls at baseline (M0) and in patients after 1 (M1), 3 (M3) and 6 (M6) months of treatment. The primary endpoint was the rate and absolute value of B and T cells as a percentage and absolute value measured at each time of the study and compared with disease activity.

Results: Thirty-one patients and 17 controls were included. There was a significant difference between responders and non-responders at M6 according to their initial level of Th17 cells (sifgnificantly decresased in good responders, p=0.005). No significant difference but a trend (p=0.06) was observed for circulating CD24hiCD27+Bregs (higher in good responders). There was no significant difference between responders and non-responders for Treg and CD24hiCD38hi Breg cells. The rate of CD19 + B producing IL-10 obtained by PBMC culturing seemed lower in controls as compared to the patients.

Conclusion: A low initial rate of Th17 circulating cells is associated with a good response to biologics during RA. Th 17 cells may represent a predictive biomarker of response to therapy for RA patients.

Disclosure: S. Salomon, None; **C. Guignant**, None; **P. Morel**, None; **B. Gubler**, None; **P. Fardellone**, None; **J. P. Marolleau**, None; **V. Goeb**, None.

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Abstract Number: 2930

Specific Metabolic and Functional Changes in Peripheral CD8+ T Cells Specifically Distinguish RA from PSA and SPA

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Session Time: 9:00AM-11:00AM

Background/Purpose: Studies by our team and others have shown that CD8 T cells (CD8s) in RA have a pro-inflammatory, cytotoxic effector phenotype and may, therefore, play a major role in RA. The presence of such effector CD8s in the blood and synovial fluid suggests that they have to adapt their metabolism to sustain their functional energetic demands in both oxygenated and in oxygen-deprived environments. Thus we focused on the characterization of the metabolic processes by ^{13}C NMR isotopomer analysis (to simultaneously monitor the glycolytic and citric acid cycle fluxes) in CD8s from RA, PsA and SpA patients comparing to healthy controls (HC). We also assessed whether metabolic changes accompanied alterations in the production of cytokines and cytotoxic molecules. The ultimate goal was to explore the potential of CD8s metabolic processes as new diagnostic tools to distinguish RA from PsA and SpA.

Methods: 50 RA, 17 PsA and 20 SpA patients (all fulfilling the ACR criteria), and 21 age and gender matched HC where recruited at the Heidelberg University Hospital. Blood CD8s were purified by negative selection magnetic separation. CSFE-labeled CD8s were cultured *in vitro* for 3 days in the presence of anti-human CD28/CD3, in medium containing [U-^{13}C]glucose. Proliferation, subset distribution and Caspase 3 and PD-1 expression were assessed by FACS. Cytokines and cytotoxic molecules were quantified by cytometric bead arrays. Changes in metabolic enzymes were quantified by western blot. Changes in lactate and acetate production were assessed by ^{1}H-NMR.

Results: At rest, in HC, SpA and PsA patients levels of [U-^{13}C]lactate, derived from the [U-^{13}C]glucose in the media, were quite low, denoting a basal metabolism not dominated by aerobic glycolysis and consistent with low biosynthetic activity. In contrast, in RA patient's unstimulated CD8s the [U-^{13}C]lactate levels were significantly higher, compatible with higher energetic and biosynthetic/proliferative demands even at rest. Upon *in vitro* activation levels of [U-^{13}C]lactate in the medium increased significantly, particularly in RA and PsA patients, and were consistent with an activation of aerobic glycolysis to cope with the greater biosynthetic demands for phenotypic changes, i.e. the transition from an naïve ($CD45RA^+CCR7^+$) to an effector phenotype ($CD45RA^+CCR7^-$), higher proliferation, and production of pro-inflammatory cytokines (TNF-α; IFN-γ IL-6) and cytotoxic molecules (Perforin; Granzyme B). This profile of arthritic CD8s was confirmed by a significantly higher expression of the enzymes pyruvate kinase M2, hexokinase 2 and lactate dehydrogenase, and reduced glutamate dehydrogenase expression. Receiver operating curves based on the levels of IL-6, TNF-α, Granzyme B, Perforin and [U-^{13}C]lactate could distinguish RA patients from PsA and SpA patients with high sensitivity and specificity (>70%).

Conclusion: CD8s from chronic arthritis patients present a Warburg-like metabolic profile, which may allow them to adapt to the environment of the inflamed synovium, and exert their pro-inflammatory and cytotoxic functions. More importantly, this altered CD8s metabolic profile provided a differential diagnosis for RA (including seronegative) from PsA and SpA.

Disclosure: R. Carvalho, None; **C. Tucher**, None; **L. Tykocinski**, None; **S. Neu**, None; **K. Klika**, None; **H. M. Lorenz**, None; **M. Souto-Carneiro**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/specific-metabolic-and-functional-changes-in-peripheral-cd8-t-cells-specifically-distinguish-ra-from-psa-and-spa

Abstract Number: 2931

Endogenous Nur77 Is a Specific Indicator of Antigen Receptor Signaling in Human T and B Cells

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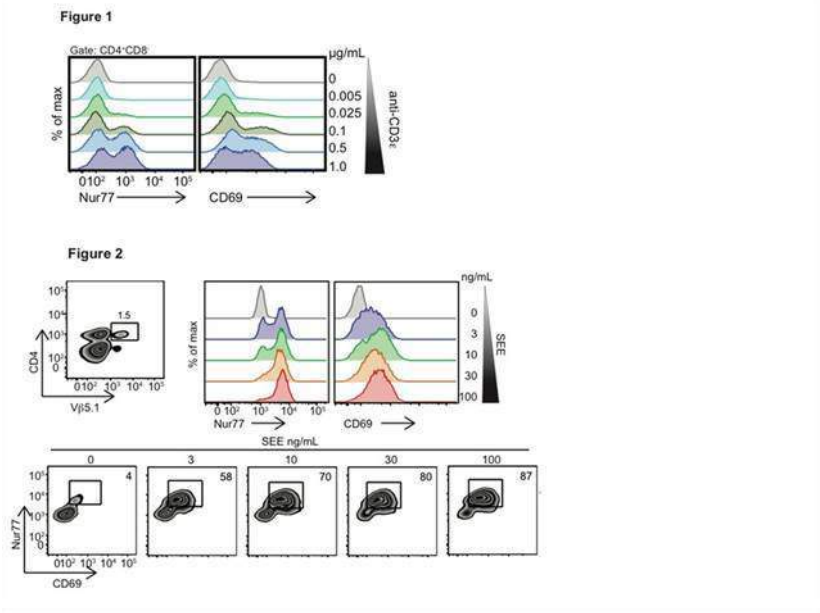
Background/Purpose: Distinguishing true antigen (Ag) stimulated lymphocytes from bystanders activated by the inflammatory milieu has been difficult. Infiltrating immune cells at sites of inflammation become activated not only through direct Ag stimulation, but also indirectly by other inflammatory mediators. Nur77 is an immediate early gene whose expression is rapidly up regulated by T cell receptor (TCR) signaling. Nur77-GFP transgenes serve as specific TCR signaling reporters in murine transgenic models. In this study, we demonstrate that Nur77 protein expression serves as a reporter of TCR and B cell receptor (BCR) specific signaling in human PBMCs. This can be used as a tool to identify Ag experienced lymphocytes in human disease.

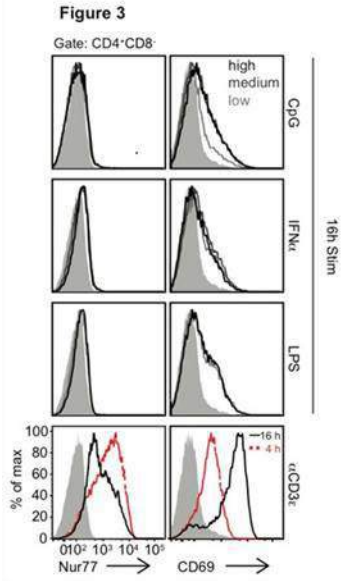
Methods: Intracellular Nur77 protein amounts were assessed by immunofluorescence and flow cytometry in T and B cells isolated from human PBMCs stimulated through their Ag receptors (anti-CD3 or anti-IgM Abs) or with immunostimulants: CpG oligodeoxynucleotides (CpG), IFN-α, or LPS.

Results: We demonstrate that *in vitro* TCR stimulation of human PBMCs from healthy donors rapidly induced Nur77 protein expression and reflected Ag receptor signaling strength, much like CD69, a commonly used marker of lymphocyte activation (**Figure 1**). In a more physiologic approach, PBMCs stimulated with Staphylococcus superantigen (SEE), which polyclonally activates Vβ5.1 expressing T cells through the TCR, resulted in enrichment of Nur77 positive cells in the population of responding cells with the appropriate Vβ (**Figure 2**). However, stimulation with various immunostimulants that do not signal via the TCR (i.e., IFN-α, CpG, LPS) did not induce Nur77 in human PBMCs, in contrast to CD69 (**Figure 3**), reflective of differences in their

upstream specific signaling events. Similarly, Nur77 induction in B cells reflected the strength of BCR signaling after crosslinking with anti-IgM. Likewise, non-BCR specific immunostimulants did not induce Nur77 in human peripheral B cells in contrast to CD69.

Conclusion: Nur77 is a reporter of Ag receptor signalling in peripheral human T and B cells. Furthermore, we demonstrate that Nur77 is a more specific reporter of Ag specific signaling than CD69 in both human T and B cells. This reporter strategy has great potential to identify Ag activated lymphocytes in human disease.





Disclosure: J. Ashouri, None; **A. Weiss**, None.

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Abstract Number: 2932

HLA-DR3 Restricted Response to Lupus-Related Auto-Antigen Smd: Autoreactive T Cells Are Inherent in Normal Immune Repertoires

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Background/Purpose: HLA class II is the major susceptibility region for systemic lupus erythematosus (SLE) and other autoimmune disorders such as rheumatoid arthritis, multiple sclerosis and type 1 diabetes. The current paradigm is that autoimmune response is the result of breaking tolerance. However, it's difficult to explain the presence of autoreactive Abs and T cells in normal people. Previously we showed HLA-DR3 (DR3) transgenic mice respond best to immunization with SmD and Ro60. To clarify the mechanisms for auto-Ab generation to SLE-related Ags, we undertook a detailed analysis of the anti-SmD T cell responses in $DR3^{+}AE^{0}$ mice.

Methods: T-T hybridomas were generated by fusing lymph node cells from $DR3^{+}AE^{0}$ mice immunized with SmD in IFA with $BW5147TCR^{-/-}$. IL-2 in the supernatants of T-T hybridomas stimulated by SmD with syngeneic splenic cells as APC was determined by ELISA. SmD T cell epitope regions were determined with 15mers overlapping by 3 amino acids covering the span of SmD with the established T-T hybridomas. The core epitopes were determined by alanine substitutions. TCR utilized by T-T hybridomas were sequenced. For response to SmD peptides and its mimics $DR3^{+}AE^{0}$ mice were immunized with 100μg peptide in CFA on day 1 and 50 μg of the immunogen in IFA on days 14 and 28. Sera were collected at 42, 56, 70, 90 and 120 days and assayed for Abs to SLE-related auto-Ags. Two hundred blood samples of healthy donors from Virginia Blood Services were analyzed for their HLA-DR types and auto-Abs titers.

Results: 47 stable T-T hybridomas reactive to SmD were generated by 7 fusions. They reacted with seven SmD antigenic regions. By alanine substitutions, they reacted with varied core epitopes. In some, the flanking sequences contributed to the core epitopes. The TCR of 17 hybridomas were sequenced. They used unique combinations of TCRα and TCRβ. By bioinformatics, we identified more than 10,000 potential bacterial peptide mimics of SmD T cell epitopes. Some of them are from commensal bacteria residing in the mucosal surfaces and skin. The ranking of affinities for SmD T epitopes to DR3 were in the mid-ranges among those of all potential bacterial mimics. 12 bacterial mimics from one of the SmD T epitopes with high, medium, and low affinities for DR3 were selected. Only those with modest binding affinities were able to stimulate relevant hybridomas and to induce auto-Ab in a similar fashion as the corresponding SmD peptide. The 200 blood donors were typed for HLA-DR2, DR3 and DR4. $DR3^{+}$ individuals had higher anti-SmD Abs than those who were negative for DR3 and DR2.

Conclusion: SmD has multiple T cell epitopes and the immune response to SmD is similar of those to conventional Ags with diverse TCRs. The T cells with cross-reactivity to auto-epitopes and to bacterial mimics are those with moderate binding affinities to the relevant DR molecules. They are likely to be positively selective for the purpose of host defense against pathogens. This thesis is supported by the finding of auto-Abs with high titers to SLE-related auto-Ags. These results provide us insight into the origin of SLE-related auto-Abs. On a basic level, they support the thesis that auto-reactive T cells are an inherent part of the normal immune repertoire.

Abstract Number: 2933

HLA-DR3 Restricted T Cell Response to Smd and Ro60 Reveals Multiple Cross-Reactive Intra- and Inter-Molecular T Cell Epitopes: Unique Antigenic Structures of Lupus-Related Auto-Antigens and the Basis for B Cell Epitope Spreading

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Background/Purpose: Complex auto-Abs targeting nuclear proteins is a hallmark of systemic lupus erythematosus (SLE). It is documented that this complexity is the result of "B cell epitope spreading" with unique patterns. The generation of SLE-related auto-Abs is T cell dependent and preferentially restricted to HLA-DR3 (DR3) and DR2. The current hypotheses for the generation of these auto-Abs such as the "B cell epitope mimicry hypothesis" and the "particle hypothesis" in that a limited auto-reactive T cell population is able to provide T cell help to B cells of multiple specificities, are inadequate to account for the above-stated observations. The results of our analysis of DR3 restricted T cell response to SmD and Ro60 provides an alternative to the current paradigms.

Methods: T-T hybridomas were generated by fusing lymph node cells from $DR3^{+}AE^{0}$ mice immunized with SmD in IFA with $BW5147TCR^{-/-}$. IL-2 in the supernatants of T-T hybridomas stimulated by SmD with syngeneic splenic cells as APC was determined by ELISA. SmD T cell epitope regions were determined with 15mers overlapping by 3 amino acids covering the span of SmD with the established T-T hybridomas. The core epitopes were determined by alanine substitutions. TCR utilized by T-T hybridomas were sequenced. For response to SmD peptides and its mimics $DR3^{+}AE^{0}$ mice were immunized with 100μg peptide in CFA on day 1 and 50 μg of the immunogen in IFA on days 14 and 28. Sera were collected at 42, 56, 70, 90 and 120 days and assayed for Abs to SLE-related auto-Ags.

Results: Multiple T-T hybridomas reactive to SmD were generated by 7 fusions. Many hybridomas were found to be reactive with more than one T cell epitope within SmD. Some of them reacted with SmB and the A protein (ARNP) of the snRNA particle. The core epitopes of 7 SmD peptides were ascertained by alanine substitution and they have no sequence homology. Several of 15mers of these core epitopes induced B cell epitope spreading to SmB, ARNP and certain proteins in the Ro60/La system. Some bacterial peptides induced B cell epitope spreading in a manner similar to that of the SmD peptide. Interestingly, cross reactive B cell epitopes were demonstrated among the SmD peptide and its bacterial mimics. Similar findings were obtained regarding the T cell responses to Ro60 and its 15mers.

Conclusion: The results showed that SLE-related auto-Ags have multiple cross-reactive intramolecular T cell epitopes. This is a feature shared by other auto-Ags such as GAD65 in type 1 DM and myelin basic protein in EAE, a model for multiple sclerosis. Although not the subject of this abstract, there are cross-reactive inter and intra molecular B cell epitopes among the SLE-related Ags. These structural features are likely the reasons why they are the targeted in autoimmunity. The presence of multiple cross reactive intermolecular T cell epitopes provides the basis for DR3 restricted B cell epitope spreading in SLE. The cross-reactivities at both T and B cell levels of the bacterial molecular mimics and their auto-epitopes provide a scenario for the presence of SLE-related auto-Abs in normal DR3 individuals.

Disclosure: Z. Zhao, None; **J. Ren**, None; **C. Dai**, None; **C. Kannapell**, None; **Q. Wang**, None; **F. Gaskin**, None; **S. M. Fu**, None.

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Abstract Number: 2934

Clinical Assessment of the Monoclonal Anitbody, PRX003, a Potential Novel Treatment for Th17-Mediated Inflammatory Disease

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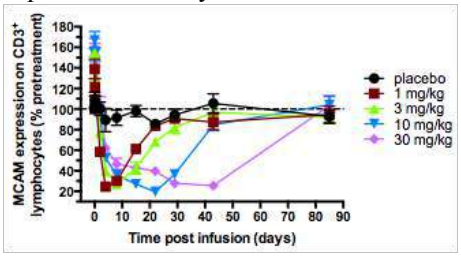
Background/Purpose: Melanoma cell adhesion molecule (MCAM; CD146) is expressed on the surface of Th17 cells, which have the capacity to produce IL-17 and a multitude of other cytokines. The expression of MCAM and production of IL-17 are defining characteristics of Th17 cells. MCAM is hypothesized to be central to the pathogenesis of numerous autoimmune disorders, including psoriasis and psoriatic arthritis by modulating the adhesion and transmigration of Th17 cells through its interaction with vascular Laminin a4 (LAMA4). Unlike targeting an individual cytokine, PRX003, a monoclonal antibody designed to bind MCAM and block its interaction with LAMA4, might prevent the release of IL17 and other cytokines by limiting Th17 cell infiltration and subsequent pathogenic inflammation. The study objective was to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity of PRX003 in healthy human subjects.

Methods: In a first-in-human, randomized, double-blind, placebo-controlled, Phase 1, single ascending dose-escalation study (NCT02458677) in healthy volunteers, PRX003 was administered by IV infusion over approximately 60 minutes. Five escalating dose cohorts received 0.3, 1.0, 3.0, 10, or 30 mg/kg of PRX003 or placebo (8 subjects/cohort in a 6:2 ratio) and were monitored for 24 hours and by periodic follow-up for 12 weeks. PD measurements included MCAM expression on circulating T-lymphocytes and serum soluble MCAM.

Results: After a single infusion, PRX003 was well tolerated at doses up to and including 30 mg/kg, the highest dose level tested. No PRX003-related serious or severe adverse events, no dose-limiting toxicities, no anti-drug antibodies or infusion-related reactions were reported. The most common treatment emergent adverse events (TEAEs), regardless of causality, were: headache (n=3, 10%), seasonal allergy (n=2, 6.7%), upper respiratory tract infection (n=2, 6.7%) and transient balance disorder (n=2, 6.7%). All TEAEs were mild to moderate. The PK of PRX003 were consistent with distribution to and saturation of MCAM with sustained exposures that fully saturated MCAM for >43 days at 30 mg/kg. Early and dose-proportional signs of demargination were observed.



This study supports the hypothesis that MCAM occupancy and down-regulation by PRX003 promotes demargination and sequestration of Th17 cells in the vascular space, limiting their extravasation.

Conclusion: These data collectively suggest that PRX003 may block MCAM-mediated extravasation of Th17 cells and support further examination of PRX003 in patients with inflammatory disease. A Phase 1b multiple ascending dose trial of PRX003 in patients with psoriasis (NCT02630901) is ongoing.

Disclosure: G. G. Kinney, Prothena Biosciences, Inc., 3; **K. Flanagan**, Prothena Biosciences, Inc., 3; **M. Skov**, Prothena Biosciences, Inc., 3; **R. Goldblum**, Prothena Biosciences, Inc., 5; **S. Griffith**, Prothena Biosciences, Inc., 5; **R. M. Barbour**, Prothena Biosciences, Inc., 3; **W. Zago**, Prothena Biosciences, Inc, 3; **T. Yednock**, Prothena Biosciences, Inc, 3; **M. Koller**, Prothena Biosciences, Inc, 3; **D. Ness**, Prothena Biosciences, Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/clinical-assessment-of-the-monoclonal-anitbody-prx003-a-potential-novel-treatment-for-th17-mediated-inflammatory-disease

Abstract Number: 2935

Activation Status of Mucosal-Associated Invariant T Cells Sensitively Reflects Disease Activity of Systemic Lupus Erythematosus

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Background/Purpose:

Mucosal-associated invariant T (MAIT) cells are innate-like lymphocytes that express a semi-invariant TCRα chain: Vα7.2-Jα33 in humans and Vα19-Jα33 in mice. MAIT cells are restricted by the MHC-related molecule-1 (MR1) and uniquely recognize microbial-derived vitamin B metabolites presented by MR1. Like other innate-like lymphocytes, MAIT cells are also activated by cytokines in the absence of exogenous antigens. Human MAIT cells are abundant and constitute approximately 5% of peripheral blood T cells, suggesting possible roles of MAIT cells in various types of immune responses. Previously we demonstrated that the frequency of MAIT cells was markedly reduced in patients with systemic lupus erythematous (SLE). In this study, we aimed to investigate whether MAIT cells are involved in the pathogenesis of SLE.

Methods:

Peripheral blood was collected from SLE patients and healthy volunteers. Informed consent was obtained from all individuals according to institutional ethical guidelines. Disease activity was measured based on the SLE disease activity index (SLEDAI) and a SLEDAI score ≥ 5 was defined as active disease. Peripheral blood mononuclear cells (PBMC) were stained with anti-human monoclonal antibodies against CD3, γδTCR, Vα7.2TCR, CD161, CD95(Fas) and CD69, and then analyzed by FACS. The activation status of MAIT cells was assessed by the expression of CD69. MAIT cells were sorted from PBMC of healthy individuals by using magnetic cell sorting (MACS) and FACS Aria. $CD19^+$B cells or $CD14^+$monocytes were isolated from PBMC of healthy controls (HC) or SLE patients by using MACS. MAIT cells were co-cultured with B cells or monocytes in the presence of MR1 ligand (MR1L), and the expression of CD69 on MAIT cells was evaluated by FACS. Cytokine levels in plasma samples and culture supernatants were measured by ELISA and Bioplex assay. PBMC were cultured in the presence of various cytokines, and CD69 expression on MAIT cells was analyzed by FACS.

Results:

MAIT cells from lupus patients with active disease expressed high levels of CD69, a lymphocyte activation marker, and the frequency of $CD69^+$MAIT cells positively correlated with SLEDAI. MAIT cells cultured with lupus monocytes displayed higher levels of CD69 compared with cells cultured with monocytes from healthy controls. The profound MAIT cell activating capacity of lupus monocytes was associated with enhanced IL-12 production in the culture supernatants.The plasma levels of cytokines including IL-6, IL-18 and IFNα positively correlated with the expression levels of CD69 on MAIT cells. MAIT cells were activated by cytokines including IFNα, IL-15, and IL-12 plus IL-18 in the absence of exogenous antigens.

Conclusion:

The activated state of MAIT cells sensitively reflected disease activity of SLE. We revealed two possible mechanisms of MAIT cell activation in SLE. First, we demonstrated that lupus monocytes displayed a profound MAIT cell activation capacity. Second, we found that the elevated levels of IL-18 and IFNα correlated with the activate state of MAIT cells in SLE, and this may elicit the cytokine-mediated activation of these cells. Because these cytokines have been suggested to be involved in the pathogenesis of SLE, activated MAIT cells may play an important in lupus pathology.

Disclosure: A. Chiba, None; **G. Murayama**, None; **M. Kitagaichi**, None; **N. Tamura**, None; **K. Yamaji**, None; **Y. Takasaki**, None; **S. Miyake**, ASUBIO PHARMA CO., LTD, 2,TAIHO PHARMACEUTICAL CO., LTD., 5.

Abstract Number: 2936

All-Trans Retinoic Acid Stabilizes Natural T Regulatory Cells Isolated from Patients with Systemic Lupus Erythematosus Under Inflammatory Conditions

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Background/Purpose: Recent studies have demonstrated that naturally occurring $CD4^+Foxp3^+$regulatory T cells (nTregs) are unstable and dysfunctional in the presence of pro-inflammatory cytokines. All-trans RA (atRA), the active derivative of vitamin A, has been demonstrated to regulate Treg differentiation and stabilize nTreg in the healthy subjects. We here plan to determine whether atRA can similarly stabilize nTreg cells isolated from patients with active systemic lupus erythematosus (SLE) under inflammatory conditions.

Methods: $CD4^+CD25^+CD127^{-/low}$ human nTregs were sorted from PBMCs in patients with SLE or healthy controls, and then expanded in the presence or absence of atRA for 7 days. These cells were extensively washed and restimulated with or without IL-1β/IL-6 for additional 3 days. Cell suspensions were harvested for cytokine assay with Elisa and cells were stained with flow cytometry analysis. In vitro, suppression assay was performed, $CD3^+CD25^-$T cells labeled with carboxyfluorescein succinimidyl ester (CFSE) were stimulated with anti-CD3 in the presence of APC with or without different populations of nTreg cells. The CFSE dilution was examined by flow cytometry, and the suppression ratio was then calculated. Xenograft-vs-host diseases (xGVHD) models were conducted for determining the suppressive activities of Treg cells in vivo. NSG mice after γ-irradiation irradiation were injected with human CD25-depleted PBMCs with or without expanded SLE nTregs pretreated with atRA, rapamycin, DMSO control, and nTreg that had been exposed to IL-1β/IL-6. Mouse survival was monitored twice per week, and survival curves were analyzed by the log-rank test. Pathology in organ organs, human CD3+ engraftment and IgG were analyzed accordingly. The statistical comparisons were performed by the Student t test by using Prism software (GraphPad).

Results: In the presence of IL-1β/IL-6, atRA also prevents nTregs isolated from active SLE patients from converting to Th1 and/or Th17 cells and sustains their Foxp3 expression and suppressive function in vitro. atRA also diminished IL-1β/IL-6 signaling events by reducing STAT1, STAT3 activation. Adoptive transfer of SLE nTregs pretreated with atRA enhanced their suppressive function on xGVHDs, and only atRA primed nTregs sustained the suppressive effect on xGVHD after stimulation with IL-1β/IL-6.

Conclusion: Our results have demonstrated that atRA also stabilizes the Foxp3 expression and Treg function of patients with SLE, particularly on the inflammatory condition. Thus, a new protocol has been developed that usage of autologous atRA-programed Treg cells likely treats patients with SLE and other autoimmune diseases.

Disclosure: J. Wang, None; **Z. Qiao**, None; **F. Huang**, None; **Y. Liu**, None; **N. J. Olsen**, Mallinckrodt Pharmaceuticals, 2; **S. G. Zheng**, None.

Abstract Number: 2937

Regulation of Follicular Helper T (TFH) Cells By ROCK2 (Rho-associated coiled-coil containing protein kinase 2)

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Background/Purpose: Follicular helper T (T_{FH}) cells promote humoral responses and serve as a limiting factor for the selection of high affinity germinal center B cells. T_{FH} cell numbers need to be tightly regulated, and T_{FH} cell expansion has been associated with autoimmune diseases including SLE. Rho-associated kinases (ROCKs), ROCK1 and ROCK2, are major downstream effectors of the small GTPase RhoA. The ROCKs regulate both gene expression and cytoskeletal reorganization. Increased ROCK activation has been observed in autoimmune disease both in mice and humans, and ROCK inhibition ameliorates autoimmunity in murine models. However, the underlying molecular and cellular mechanisms by which the ROCKs affect autoimmune disease are currently unknown. Here we investigated the role of ROCK2 in T_{FH} cell expansion under physiological conditions and in autoimmunity by employing mice lacking DEF6 and SWAP-70, which exhibit aberrant ROCK activation, accumulation of T_{FH} cells, and spontaneously develop a lupus-like disease.

Methods: Mice lacking ROCK2 in T cells were generated by crossing $CD4^{cre}$ mice with $ROCK2^{flox/flox}$ mice. The T_{FH} cell compartment was assessed in $CD4^{cre}ROCK2^{flox/flox}$ mice by immunizing with a T-dependent antigen. To evaluate the effect of T-cell ROCK2 on autoimmune disease $CD4^{cre}ROCK2^{flox/flox}$ mice were crossed with $Def6^{trap/trap}Swap\text{-}70^{-/-}$ mice (DKO mice), which develop a lupus-like disease primarily in females. Flow cytometry analysis and ELISAs were used to assess T_{FH} cell expansion and autoantibody production.

Results: The absence of ROCK2 in T cells did not lead to any abnormality in the frequencies or activation state of the T cell compartment at baseline. Lack of T cell ROCK2, however, resulted in a significant decrease in T_{FH} cell formation upon immunization with a T-dependent antigen. This was associated with a reduction in germinal center B cell and plasma cell formation suggesting that T-cell ROCK2 is essential for T-dependent immune responses. To evaluate the contribution of T-cell ROCK2 to T_{FH} cell formation in autoimmunity, we analyzed $CD4^{cre}ROCK2^{flox/flox}$ $Def6^{trap/trap}Swap\text{-}70^{-/-}$ mice (ROCK2ΔT DKO) mice. Upon deletion of T cell ROCK2, the spontaneous increase in T_{FH} cells observed in DKO mice was significantly reduced. This was associated with decreased GC B cells, plasma cell numbers, and diminished anti-dsDNA autoantibody levels.

Conclusion: Our current study indicates that ROCK2 regulates T_{FH} cells both during T-dependent immune responses as well as in autoimmune settings further supporting a role for ROCK inhibition as a potential treatment for SLE and other autoimmune diseases that exhibit dysregulation in T_{FH} cells.

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Abstract Number: 2938

U4ATAC Mutation Is Associated with an Immune Dysregulation Syndrome Characterized By Primary Immunodeficiency, Short Stature and Polyglandular Endocrinopathy

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: A host of primary immunodeficiencies, such as autoimmune polyendocrinopathy, candidiasis, ectodermal dysplasia (APECED), immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX), and STAT5b insufficiency can present as immune dysregulation syndromes. However, in many patients the molecular basis of these abnormalities remains uncharacterized. To investigate potential genetic and molecular links between PID, growth failure and systemic autoimmunity, we recruited a series of siblings with immunodeficiency, short stature, polyendocrinopathy and kidney disease. Since our patients feature growth hormone resistance, PID and systemic autoimmunity, we hypothesized that a functional defect in the signal transducer activator of transcription 5b (STAT5b) would underlie the phenotype.

Methods: Clinical data was extracted from the patients' medical record, patients were evaluated, and skin and blood samples were analyzed in the laboratory. PBMC and dermal fibroblast-derived gDNA was used for targeted gene analysis of known PID-causing genes. Additionally, whole genome sequencing (WGS) was performed on the parents, 3 affected sons, 3 unaffected sons and 2 unaffected sisters. Mutation search were performed with a combination of scripts developed in house and expert review. Cellular phenotyping by flow cytometry, STAT phosphorylation, T-cell proliferation in response to IL-2 and IL-7 stimulation were performed on affected individuals PBMC.

Results: The three affected individuals have a phenotype characterized by short stature with decreased IGF-1 and IGFBP-3 levels, PID with abnormal T-, B- and NK- cell subpopulations, polyglandular endocrinopathy and multisystem manifestations of immune dysregulation. Genetic analysis of candidate genes such as STAT5a/b and JAK-1 revealed no defect. Initial mutation searches were focused on rare protein coding changes that are consistent with X-linked, autosomal recessive or de novo inheritance models, however no probable candidate mutations were identified. Analysis of CNV data and haplotype analysis on X chromosome also came out negative. Linkage analysis identified 4 regions in the genome that have the maximum LOD score achievable for the given pedigree. One of the candidate regions on chr2 harbors a non-coding RNA gene (*RNU4ATAC*) that has been recently published to cause Roifman Syndrome. Our patients bear clinical and phenotypic similarities to those with Roifman Syndrome, suggesting *RNU4ATAC* as a likely candidate gene. We found two rare mutations in this gene that segregated with the disease: c.[13C>T] and c.[116A>C]. The first one has been reported as pathogenic in Roifman Syndrome. The second one is extremely rare (absent in public databases and more than 3700 internal WGS controls) residing in a gene region likely to be important for function. Sequential flow cytometry studies from three affected individuals in the same kindred revealed progressive B cell depletion and low numbers of T regulatory cells. We detected constitutive STAT5 phosphorylation in *ex vivo* CD4+ T cells, however, T cell blasts failed to proliferate in response to IL-2 following mitogen stimulation due to impaired upregulation of the high affinity IL-2 receptor. Therefore, *U4ATAC* may regulate immune cell functions such as T cell activation and the induction of T regulatory cells. Ongoing work in this area involves a combination of molecular and cellular approaches to determine whether *U4ATAC*controls minor splicing of genes important in activated T cells.

Conclusion: Using WGS and mutation analysis, we have found the likely disease-causing mutations in patients with clinical features consistent with Roifman syndrome. Furthermore, our work extends the spectrum of Roifman Syndrome to include immune dysregulation. *RNU4ATAC* plays an essential role in splicing minor introns found in about 800 human genes. Further work may provide novel insights into the molecular pathways that link the development and function of the musculoskeletal, endocrine and immune systems with RNA splicing

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Abstract Number: 2939

Risk of Venous Thromboembolism in Patients with Systemic Vasculitides: A Systematic Review and Meta-Analysis

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Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

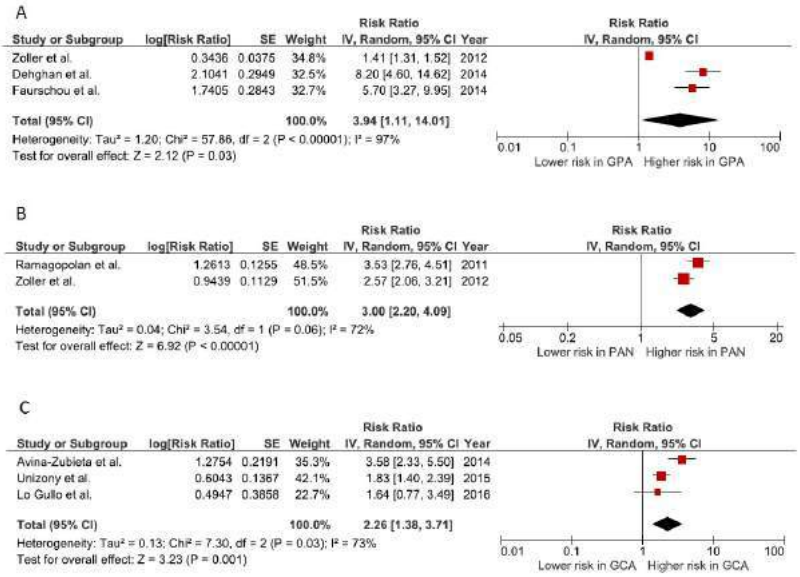
Risk of Venous Thromboembolism in Patients with Systemic Vasculitides: A Systematic Review and Meta-analysis

Background/Purpose: Venous thromboembolism (VTE) is a common medical problem with a significant morbidity and mortality. Chronic inflammatory state has been increasingly recognized as an important risk factor for VTE. Several immune-mediated inflammatory disorders, such as systemic lupus erythematosus and rheumatoid arthritis, are associated with increased incidence of VTE in epidemiologic studies. Systemic vasculitides are group of immune-mediated inflammatory disorders characterized by inflammation in blood vessels. Apart from Behcet's disease, it is unclear if these disorders are also associated with increased risk of VTE due to limited data. To further investigate this possible association, we conducted a systematic review and meta-analysis of observational studies that compared the risk of VTE in patients with systemic vasculitides versus participants without systemic vasculitides.

Methods: Two investigators independently searched published studies indexed in MEDLINE, EMBASE and the Cochrane database from inception to March 2015 using the terms for each type of vasculitis in conjunction with the terms for venous thromboembolism. A manual search of references of retrieved articles was also performed. The inclusion criteria were as follows: (1) observational studies evaluating the association between vasculitis and VTE and (2) odds ratios, relative risk (RR) or hazard ratio or standardized incidence ratio with 95% confidence intervals (CI) were provided. Study eligibility was independently determined by the two investigators noted above. Newcastle-Ottawa scale was used to assess the quality of included studies. RevMan 5.3 software was used for the data analysis. Point estimates and standard errors were extracted from individual studies and were combined by the generic inverse variance method of DerSimonian and Laird. Given the high likelihood of between study variance, we used a random-effect model rather than a fixed-effect model. Statistical heterogeneity was assessed using the Cochran's Q test.

Results: Seven studies investigating the risk of VTE among patients with granulomatosis with polyangiitis (GPA), polyarteritis nodosa (PAN) and giant cell arteritis (GCA) were identified. Elevated risk were seen in all three vasculitides (GPA, pooled RR 3.94, 95% CI 1.11 – 14.01; PAN, pooled RR 3.00, 95% CI 2.20 – 4.09; GCA, pooled RR 2.26, 95% CI 1.38 – 3.71). Forest plots are demonstrated in figure 1A-1C, respectively.

Conclusion: Our study demonstrated a statistically significant increased VTE risk among patients with GPA, PAN and GCA.



Disclosure: P. Ungprasert, None; **M. J. Koster**, None; **K. J. Warrington**, None.

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Abstract Number: 2940

Bechet's Disease and Sleep Quality in Korean Patients

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Background/Purpose: Behcet's disease is a chronic, systemic vasculitis that can involve all sizes of blood vessels. Sleep disturbance is one of the most particular concerns in patients with Behcet's disease. It has been known that the disease activity of rheumatoid arthritis and ankylosing spondylosis is associated with the sleep quality. However, studies about the sleep quality of patients with Behcet's disease in Korean population are limited. The purpose of this study was to find out the effects of sleep quality on Behcet's disease in Korean population. We also investigated the relationship between depression, quality of life, other clinical findings and Behcet's.

Methods: The study was performed by cross-sectional design in two tertiary hospitals. We surveyed one hundred patients with Behcet's disease. Sleep quality was assessed by the Korean version of Pittsburgh sleep quality index (PSQI). Disease activity of Behcet's disease was evaluated by Behcet's disease current activity form (BDCAF). Depression was assessed by the Korean version of Beck depression inventory second edition (BDI-2). Quality of life was assessed by the Korean version of the Leeds Behcet's Disease Quality of Life Measure (BDQoL).

Results: Among 100 patients, median age was 51 [44.5-56.0] years, median disease duration was 77.5 [24.0-136.0] months and 69% were female. Those who met the diagnostic critera of fibromyalgia were 28 patients. The frequency of poor sleep quality (PSQI ≥9) was 42%. Patients with poor sleep quality tend to have higher BDI2, BDCAF and pain VAS score ($P = 0.022$, $P = 0.005$ and $P < 0.001$). Female rate was significantly higher, and BDQoL was lower in poor sleeper group ($P = 0.004$ and $P < 0.001$). Among 7 PSQI components, daytime dysfunction was higher in patients with high disease activity ($P = 0.03$). Total PSQI score were strongly correlated with BDCAF score, BDI-2 score, BDQoL score, and pain VAS score ($P = 0.02$, $P < 0.001$, $P < 0.001$, and $P < 0.001$, respectively).

Conclusion: The low quality of sleep is associated with disease activity, depression and quality of life in Korean patients with Behcet's disease. Better disease control will improve the sleep quality.

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Abstract Number: 2941

Optimization of Adalimumab on Refractory Uveitis of Behcet's Syndrome. Multicenter Study of 23 Patients

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Background/Purpose: In non-infectious no anterior uveitis, adalimumab (ADA) is the only biologic drug that has shown efficacy in phase III randomized, double blind studies, such as VISUAL I and VISUAL II. After 80 mg loading dose, maintenance dose is the standard for other indications, 40 mg/sc/2 weeks. Our aim was to asses in patients with Behcet's syndrome with uveitis if once remission was obtained, it was possible to optimize the maintenance ADA dose.

Methods: Multicenter study of 71 uveitis related to Behcet's syndrome and refractory to at least one standard synthetic immunosuppressive drug in which ADA was started at standard dose. In 23 of 71 (32,39%) once remission was achieved, ADA dose was optimized. The degree of ocular inflammation was assessed by "the Standardization of Uveitis Nomenclature (SUN) Working Group" (Am J Ophthalmol 2005; 140: 509-516), and macular thickness by optical coherence tomography (OCT). A comparison was made between the first visit when ADA was started at standard dose, the onset of ADA optimization, and the final visit.

Results:

We studied 23 patients/42 affected eyes (15 men/ 8 women) that had an optimization in ADA dose, the median age was 37.2±13.4 years (range 10-62). Prior to ADA, and as systemic treatment besides oral steroids, they had received intravenous methylprednisolone boluses (n=7), cyclosporine A (CyA) (n=20), methotrexate (MTX) (n=11) and azathioprine (AZA) (n =11). ADA was used in monotherapy (n=5) and in combination with CyA (n=12), MTX (n=4) and AZA (n=2). The average interval from ADA onset to optimization was 15.3±9 months. Of the 23 patients the interval dose of ADA was progressively increased to 3 weeks (n =6), 4 weeks (n =13), 5 weeks (n =1), 6 weeks (n =1) and 8 weeks (n =2).

Only 2 patients had to return to the standard dose of ADA due to reactivation after optimizing, achieving again remission of uveitis. It was also possible to suspend ADA in 4 patients after 35.2±9.3 months in remission, not presenting a new reactivation after a mean of 20±6.9 months following the suspension.

Conclusion: Optimizing ADA therapy, once remission is achieved, seems feasible in Behcet's syndrome with uveitis. However, this data should be verified again in prospective and randomized studies. **TABLE**

	At onset of ADA	**At ADA Optimization**	**At Last Visit**
VA (median [IQR])	0,8 [0,3-1]	1 [0,8-1] *	1 [0,9-1] *
Anterior chamber cells (median [IQR])	0 [0-2]	0 [0-0] *	0 [0-0] *
Vitritis (median [IQR])	1 [0-2]	0 [0-0] *	0 [0-0] *
Retinal vasculitis (% affected eyes)	41.8%	10.8% *	0% *
OCT (µ) (mean ±SD)	306.7±122.9	253±20 *	250.5±17.9 *

* p< 0,05 Between at onset of ADA, At onset of ADA optimization and last visit (Wilcoxon test)

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Abstract Number: 2942

Sequencing of 16S rRNA Reveals a Distinct Salivary Microbiome Signature in Behcet's Disease

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Background/Purpose: Behçet's disease (BD) is a multisystem inflammatory disorder characterized by recurrent oro-genital ulcers, mucocutaneous lesions and serious organ involvement. The goal of this study was to investigate the structure of the salivary microbiome in patients with BD.

Methods: Stimulated saliva samples were collected from 31 BD patients and 15 healthy controls, and detailed oral health indices were recorded. In 9 BD patients a second oral health evaluation and saliva collection was performed following dental and periodontal treatment. High-throughput sequencing of the 16S rRNA V4 region in saliva samples was performed. Sequences were rigorously filtered and grouped into phylogenetically-related operational taxonomic units (OTUs), used to measure bacterial community diversity and richness. OTUs were classified using a 16S rRNA reference database at the species-level. AMOVA and LEfSe analyses were used to measure differences between patients and controls at the community- and species-level, respectively.

Results: Sequence analysis identified a total of 908 OTUs present across all samples. Patients had a microbial community structure that is significantly less diverse than healthy controls. The most overabundant species in BD patients compared to controls was *Haemophilus parainfluenzae*, while the most depleted included *Alloprevotella rava* and species in the genus *Leptotrichia*. Patients receiving periodontal treatment showed improvements in oral health indices, but no short-term differences in bacterial community structure. Neither the BD-associated genetic risk locus within the *HLA-B*/*MICA* region nor being on immunosuppressive medications explained the differences between patients and controls.

Conclusion: This is the first high-throughput sequencing-based evaluation of the salivary microbiome in BD. Salivary microbiome of BD patients has a specific signature characterized by changes at the community and species level.

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Abstract Number: 2943

Relationship Between Menstruation and Symptoms of Behcet's Syndrome

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Background/Purpose: It is well known that menstruation triggers several conditions such as migraine, recurrent aphtous stomatitis and acne vulgaris in otherwise healthy individuals (1). It may exacerbate chronic autoimmune diseases and familial Mediterranean fever (FMF) (2-4). There is also one study that briefly mentions menstruation causes activation in Behçet's syndrome (BS) (4). We investigated the relationship between menstruation and specifically the skin-mucosa lesions of BS. As controls, we studied FMF patients.

Methods: Premenopausal women with BS and FMF seen consecutively at the outpatient clinic of Cerrahpasa Medical Faculty at Istanbul, were interviewed. BS patients were asked whether they experienced increased skin-mucosa lesions during the menstrual

period. A similar questionnaire assessing this time the frequency of serositis and fever attacks was given to the patients with FMF. As a control the participants were also asked whether they experienced headaches during the same period as well.

Results: A total of 140 BS patients with a mean age of 36±8 and mean disease duration of 9±6 years were studied. While 21 (15 %) were off treatment, 103 (74 %) were using colchicine and the remaining were using other immunosuppressive agents. As shown in the Table, among BS patients, 78 (56 %) associated at least one symptom with menstruation. The most commonly reported symptom related with menstruation was the papulopustular involvement (50 %), followed by oral (30 %) and genital ulcers (21 %) and nodular lesions (21 %). We also studied 185 patients with FMF. Their mean age was 32±8 and mean disease duration was 12±8 years. All patients were using colchicine for a mean duration of 8±7 years. A total of 138 patients (75 %) reported that their attacks overlapped with menstruation. These attacks included mostly peritonitis in 126 patients (68 %), pleuritis in 102 (55 %), and fever in 73 (40 %). Among both BS and FMF patients, similar number of patients (41 % and 41 %, respectively) reported that menstruation triggered headaches.

	Yes	No	do not remember
Behçet syndrome (n=140)			
Oral ulcer, n (%)	42 (30)	45 (32)	53 (38)
Genital ulcer, n (%)	30 (21)	94 (67)	16 (11)
Papulopustular lesions, n (%)	70 (50)	56 (40)	14 (10)
Nodular lesions, n (%)	30 (21)	90 (64)	20 (14)
At least one BS symptom, n (%)	78 (56)	-	-
Headache, n (%)	58 (41)	45 (33)	37 (26)
Familial Mediterranean Fever (n=185)			
Peritonitis, n (%)	126 (68)	51 (28)	8 (4)
Pleuritis, n (%)	102 (55)	74 (40)	9 (5)
Fever, n (%)	73 (39)	100 (54)	12 (6)
At least one FMF symptom, n (%)	138 (75)	-	-
Headache, n (%)	76 (41)	77 (42)	32 (17)

Conclusion: This survey showed that, in about half of the patients with BS at least one skin mucosa lesion is exacerbated with menstruation. Most commonly reported were the papulopustular lesions. Menstruation had a stronger effect on FMF, triggering at least one symptom in about ¾ patients. The main limitation of the study was the self-reported assessment methodology, rather than a prospective diary assessment. Our findings provide further evidence that papulopustular lesions of BS and acne vulgaris are pathologically related (5).

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Abstract Number: 2944

Use of Muscle Biopsies for the Diagnosis of Systemic Vasculitis in a Rheumatology Service

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Background/Purpose: Systemic vasculitis comprises a group of diseases characterized by non-infectious inflammation of vessels in various organs. Histopathological confirmation of systemic vasculitis is required for the diagnosis; a biopsy is usually performed in clinically suspect organs, such as the skin, peripheral nerves and kidneys. The biopsy of an involved organ is invasive and carries the risk of complications. By contrast, gastrocnemius muscle biopsy is simple and minimally invasive technique that may be performed by a rheumatologist.

Methods: Retrospective study (1984-2015) Center: tertiary academic hospital, referral area 850.000 inhabitants. We analyzed the database of all muscular biopsies performed at our hospital. We selected all patients undergoing a gastrocnemius biopsy for possible diagnosis of systemic vasculitis, we analyzed the clinical, laboratory, neurophysiological and pathologic data. Biopsies were classified as positive or negative for vasculitis. A positive muscular biopsy was defined by the presence of necrotizing vasculitis or non necrotizing vasculitis seen by optical microscopy. Muscular biopsy was performed in all cases at the medial gastrocnemius muscle by a rheumatologist; all these biopsies were “open” and unilateral. The diagnosis of systemic vasculitis was based on clinical, serological and histological data.

Results: 619 muscular biopsies were performed, 55 were indicated with suspicion of systemic vasculitis, 29 (52.7%) female and 26 male (47.3%), median age 64.4 years (DS 15.22). Of the 55 muscular biopsies, 47 (85.4%) were positive (sensitivity of 85%) and 8 (14.6%) were negative. The final diagnosis was: 41 (74.5%) necrotizing vasculitis (microscopic polyangiitis and polyarteritis nodosa), 5 (9.1%) eosinophilic granulomatosis with polyangiitis, 4 (7.3%) granulomatosis with polyangiitis, 2 (3.6%) mixed cryoglobulinemia, 1 (1.8%) rheumatoid arthritis-associated vasculitis and 2 (3.6%) none diagnosed. Of 45 patients, 24 (53.3%) were ANCA-associated: 20 patients had positive biopsy and 4 negative biopsy. No significant differences were observed between the two groups in any of the assessment categories except in the electomiographic pattern. The positive biopsy group showed electromiographic alterations (p=0.01)Furthermore, the positive biopsy group showed more frequently systemic manifestations such as: weight loss, myalgia, paresthesias, purpura and testicular pain. These differences were not statistically significant. No complications were encountered in the procedure.

Conclusion: Muscle biopsy is a simple, clinically useful, safe and minimally invasive procedure for the diagnosis of vasculitis with high sensitivity. No significant differences were observed in clinical or analytical features between patients with positive or negative biopsy, except in electromyography patients with positive biopsy had more a frequent pathological pattern.

	Biopsy-positive (n = 47)	Biopsy-negative (n = 8)	p-value
male/female, n (%)	24/23 (51/49)	5/3 (62,5/37,5)	0.5
age at biopsy (years), mean (sd)	65,1 (14,34)	60 (20,2)	0.3
ANCA positive/ negative	20 (54,1)/17 (45,9)(n=37)	4(50)/4(50)	0.8
serum ESR (mm), mean (sd)	58,2 (35,6)	64,7 (36,3)	0.6
hemoglobine (g/dL), mean (sd)	11,24 (1,4)	10,25 (1,3)	0.8
weight loss (≥ 2 kg) n (%)	13 (27,7)	2 (25)	0.8
fever (≥ 38 °C) n (%)	20 (42,5)	5 (62,5)	0.3
myalgia n (%)	18 (38,3)	3 (37,5)	0.9
paresthesias n (%)	20 (42,6)	2 (25)	0.3
arthralgia n (%)	12 (25,5)	2 (25)	0.9
purpura n (%)	7 (14,9)	1 (12,5)	0.8
testicular pain n (%)	3 (6,4)	0	0.4
legs ulcers n (%)	5 (10,6)	2 (25)	0.3
abdominal pain n (%)	3 (6,4)	1 (12,5)	0.5
calf pain n (%)	12 (25,5)	3 (37,5)	0.5
patologic electromiography	36 (76,6)	2 (25)	0.01

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Abstract Number: 2945

Systematic Review: “Efficacy and Safety of Biological Versus Immunosuppressive Therapy Compared to Placebo in the Treatment of Uveitis Associated with BehçEt’s Disease.”

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Background/Purpose: Systemic treatments used in ocular involvement in Behçet's disease are corticosteroids, synthetic and biological immunosuppressants. Because of irreversible ophthalmic complications,it is a priority to know the efficacy of these drugs. Our purpose was to analyze the efficacy and safety of biological therapy vs. cyclosporine A(CyA),azathioprine(AZA)or placebo in reducing the rate of uveitis and improving the visual prognosis of Behçet's.

Methods: A systematic search of literature on MEDLINE,EMBASE,and Cochrane Central Register of Controlled Trials was conducted from inception to July 2015.A hand search was performed by reviewing the references of the included studies and the international congress.Criteria for study selection: 1)adults with Behçet's disease and uveitis, 2)Biological therapies, 3)placebo or

active comparator with CyA or AZA, 4)outcome measures to evaluate effectiveness as a number (no.)of recurrence of uveitis,visual prognosis,cystic macular edema, retinal vasculitis,vitritis,hypopyon,etc; and/or adverse events.Meta-analyses,systematic reviews,clinical trials and observational studies of >10 patients with comparator were included.The selection,review and evaluation of quality of the articles was independently conducted by two reviewers.The Oxford Level of Evidence scale was used to determine the quality of the studies.

Results: Of 195 articles,5 met the inclusion criteria:2 retrospective observational studies and 3 randomized clinical trials in 235 patients with Behçet and refractory uveitis.Age range was 12-69 years with male dominance,and follow up was 1-72 months.Evidence with infliximab(IFX) (2studies) is weak and suggests more effectivenes than CyA in reducing the rate of uveitis in short-term(6m) and more effective than CyA+AZA or methotrexate(MTX) to reduce the no. of retinal vasculitis relapse,and severe complications and to improve visual acuity in long term(LE 4).The weak and insufficient evidence of rituximab(RTX) associated with MTX (1study) suggested similar efficacy to cyclophosphamide(CYM)associated with AZA, improving the total adjusted rate of disease activity without improvement in short-term visual acuity (6m) (LE 3b).Regarding secukinumab and daclizumab vs placebo(1study respectively),the small but acceptable level of evidence suggests ineffectiveness in reducing relapses and in the improvement of visual acuity,with sparing effect on immunosuppressants in short-term for secukinumab (LE 2a-2b). Available evidence reveals few significant adverse events. All studies could be applicable in clinical practice.

Conclusion: With the limited evidence found, IFX appears to be safe and more effectiveness than CyA alone or in combination with other immunosuppressants in reducing short term uveitis relapse and the number of severe long-term complications.RTX is similar to CYM paired with AZA in improving rates of inflammatory activity in short term.Secukinumab as well as daclizumab is not effective in reducing relapses of uveitis but could spare immunosuppressants.The results of this review support the benefit of carrying out further well-designed comparative studies with IFX and RTX.

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Abstract Number: 2946

Large Scale Genetic Analysis in BehçEt Disease. Identification of Residues Associated in the HLA Class I Region and New Susceptibility Loci

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Background/Purpose: Behçet's disease (BD) is a complex immune-mediated vasculitis which aetiology remains unknown although some evidences suggest that certain infectious agents and environmental factors may trigger the disease in genetically predisposed individuals. The HLA class I genes are the most important genetic factors in BD although other genes are also involved in the susceptibility to this pathology. To improve the current knowledge of its genetic background, we conducted the first large-scale genetic analysis on Spanish population, with special focus in the HLA region.

Methods: A discovery cohort comprising 278 BD cases and 1,517 unaffected controls were genotyped using the Immunochip platform which is a custom high-density array that allows the analysis of 196,524 genetic variants across 186 known susceptibility *loci* for autoimmune and autoinflammatory disorders. We also imputed HLA data with a previously validated imputation method to perform a more comprehensive analysis of this genomic region. The validation step was performed on an independent replication cohort composed of 130 BD cases and 600 additional controls.

Results: The strongest association signals were observed in the HLA class I region, being HLA-B*51 the highest peak (overall P=6.82E-32, OR=3.82). A step-wise conditional logistic regression with classical alleles identified HLA-B*57 and HLA-A*03 as additional independent markers. The amino acid model that best explained the association, includes the position 97 of the HLA-B molecule and the position 66 of the HLA-A. Interestingly, these class I positions are located in the binding groove of their corresponding molecules. Among the non-HLA loci, the most significant in the discovery analysis were: IL23R (rs10889664: P=3.81E-12, OR=2.00), the JRKL/CNTN5 region (rs2848479: P=5.00E-08, OR=1.68) and IL12A (rs1874886: P=6.67E-08, OR=1.72), which were confirmed in the validation phase (JRKL/CNTN5 rs2848479: P=3.29E-10, OR=1.66; IL12A rs1874886: P=1.62E-08, OR=1.61).

Conclusion: Our results confirm HLA-B*51 as a primary-association marker in predisposition to BD and suggest additional independent signals within the class I region, specifically in the genes HLA-A and HLA-B. Regarding the non-HLA genes, in addition to IL-23R, previously reported in our population; IL12A, described in other populations, was found to be a BD susceptibility factor also in Spaniards; finally, a new associated locus was found in the JRKL/CNTN5 region.

Abstract Number: 2947

Adalimumab Versus Infliximab in Cystoid Macular Edema of Uveitis Associated to BehçEt Disease. Multicenter Study of 34 Patients

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Background/Purpose: Cystoid macular edema (CME) is the most serious complication of uveitis and the most common cause of blindness in uveitis. Our aim was to compare the efficacy and safety of adalimumab (ADA) vs infliximab (IFX) as the first biologic therapy in refractory CME of uveitis associated to Behçet Disease during one year period.

Methods: Multicenter study that included 175 patients with uveitis associated to Behçet Disease refractory to high dose of corticosteroids and at least one conventional systemic immunosuppressive drug. CME (OCT >300 μm) was present at baseline In 34 of these 175 patients, and it was the main reason for anti-TNFα therapy use. Infliximab (3-5 mg/kg/iv at 0, 2 and 6 weeks and after every 4-8 weeks) was used in 12 cases and ADA (40 mg/sc/2 weeks) in 22 cases. Our main objective was the complete resolution of CME. Secondary objectives were the improvement in visual acuity (VA) (VA improvement of at least 20% in one of the eyes), the complete absence of inflammation in the anterior chamber and resolution of vitritis, retinal vasculitis and retinitis. A bivariate analysis was performed to compare the response of the two types of biologic agents (ADA and IFX). A logistic regression model was performed to evaluate the effect of the biologic therapy on outcome. The analysis was performed using the SPSS version 20.0.

Results: We studied 34 patients (63 affected eyes). There were no significant differences between groups at baseline (IFX vs ADA) in sex (♂/♀; 4/6 vs 11/11; p =0.35), mean age (37.3±10.1 vs 41.5±8.3; p=0.2), positive HLA-B51 (70% vs 80.9%; p =0.5), uveitis duration before anti TNFα onset (median [IQR]; 36 [10-82] vs 33 months [15.5 to 83]; p =0.8), VA (0.4±0.33 vs 0.46±0.29; p =0.44), retinal vasculitis (75% vs 77%; p =0.87), retinitis (46% vs 30%; p =0.2), macular thickening (410.13±140.9 vs 409.46±138.55; p =0.98) and combined immunosuppressive therapy (58.33% vs 59.1 %; p =0.96). However, there were differences in the presence of cells in the anterior chamber (median [IQR] 1 [0-1.2] vs 1 [0-3]; p =0.02) and vitritis (median [IQR], 1 [0-2] vs 3 [0.5-3]; p =0.002). Although CME resolution (main objective) was more commonly found with ADA, no significant differences were found. No significant differences were found between ADA and IFX when the secondary objectives were assessed, even after the adjustment for duration of illness, age and sex **(TABLE)**

Conclusion: Both ADA and IFX are effective in CME associated to Behçet Disease refractory to conventional immunosuppressive therapy. These two anti-TNFα agents show equivalent efficacy. **TABLE**

	ADA/IFX (%)	crude OR	CI 95%	p	adjusted OR**	CI 95%	p
After one month							
- Absence of CME (OCT <300)	38.9%/18.2%	2.86	0.473-17.35	0.252	3.88	0.384-39.25	0.25
- VA improvement*	80.0%/72.7%	1.5	0.268-8.383	0.644	3.003	0.342-26.401	0.321
- Absence of cells in Anterior Chamber	56.2%/71.4%	0.514	0.076-3.488	0.496	0.174	0.00-1.98	0.199
- Inactive vitritis	23.5%/50.0%	0.308	0.052-1.829	0.151	0.385	0.053-2.807	0.346
- Inactive retinitis	57.1%/71.4%	0.533	0.058-4.912	0.579	-	-	-
- Inactive vasculitis	50.0%/63.6%	0.571	0.123-2.658	0.476	1.056	0.177-6.321	0.952
After one year							
- Absence of CME (OCT <300)	88.9%/66.7%	4	0.53-30.16	0.179	7.03	0.511-96.91	0.145
- VA improvement	68.2%/66.7%	1.071	0.239-4.794	0.928	1.1	0.171-7.086	0.92
- Absence of cells in Anterior Chamber	93.8%/100%	1.467	1.102-1.951	0.99	-	-	-
- Inactive vitritis	87.5%/100%	1.5	1.109-2.03	0.99			
- Inactive retinitis	-	-	-	-	-	-	-
- Inactive vasculitis	-	-	-	-	-	-	-

* improvement at least of 20% in VA **after adjusting for duration of illness, age and sex

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Abstract Number: 2948

Fecal Calprotectin Level Is Useful in Identifying Active Disease in Behçet's Syndrome Patients with Gastrointestinal Involvement: A Controlled Study

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Background/Purpose: The fecal calprotectin (FC) is widely used as a non-invasive method for identifying patients with active Crohn's disease (CD) and ulcerative colitis. Gastrointestinal involvement of Behçet's syndrome (GIBS) shows clinical and

endoscopic similarities to CD. A previous study in a small number of Behçet's syndrome (BS) patients with mainly mucocutaneous lesions showed serum calprotectin levels did not differ between active and inactive patients (1). Another study suggested FC may help to diagnose GIBS patients (2). We are not aware of studies addressing whether FC helps to distinguish active GIBS patients from those in remission. Therefore, we aimed to determine whether FC helped to predict active disease in GIBS patients.

Methods: We collected fecal specimens and serum from 23 GIBS (11 M, 12 F and mean age 44±9 yrs) patients before colonoscopy. The reasons for colonoscopy were assessing active disease in patients presenting with abdominal pain (with or without diarrhea) (n=9) or confirmation of a remission in asymptomatic patients (n=14). Seven of these patients had active GI involvement and the remaining 16 were inactive, based on colonoscopic findings. We also included 22 active and 25 inactive CD patients as controls. We used 150 µg/g as the cut-off for a positive FC level. We also looked at the correlations between FC and serum calprotectin and CRP levels, Crohn's disease activity index (CDAI) and disease activity index for intestinal Behçet's disease (DAIBD) scores.

Results: FC was >150 µg/g in all of the 7 GIBS patients with ulcers compared to 4/16 of GIBS patients without ulcers (OR: 42, 95%CI: 2 to 888). The median FC of active GIBS patients (n=7) was significantly higher than among inactive GIBS patients (n=16) (325 µg/g (IQR: 187-1800) vs 44 µg/g (IQR: 30-154); p=0.002). The mean serum calprotectin level was also higher among the active GIBS patients, however the difference was not significant (173.0 ± 273.7 µg/g vs 102.0 ± 135.4, p=0.13). There was a very low correlation between FC and serum calprotectin levels (r=0.08, p=0.72), a moderate correlation between FC and serum CRP levels (r=0.66, p=0.76), a moderate correlation between FC and CDAI scores (r=0.55, p=0.006) and very low correlation between FC and DAIBD scores (r=0.01, p=0.96). Among CD patients, 16/25 of the active patients and 3/22 of the patients in remission had FC level >150 µg/g (OR: 2.6, 95%CI: 3 to 49). Among the 4 GIBS patients who had high FC levels despite being in remission for gastrointestinal involvement, 1 had active mucocutaneous lesions, 1 had concomitant macrophage activation syndrome, and 1 had polycythemia vera with trisomy 8. None of the patients were receiving NSAIDs that could increase FC levels.

Conclusion: With further work FC may turn out to be a useful non-invasive tool for ruling out active GI lesions in asymptomatic GIBS patients. A high FC level demands caution for the presence of active ulcers especially in symptomatic patients while whether the presence of other BS manifestations can cause false positive results remains to be studied.

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Abstract Number: 2949

Surgical Method for Aortic Root Involvement of Behcet Disease

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Background/Purpose: Aortic regurgitation (AR) in Behcet disease is a rare but very fatal condition. Many patients require a second or third operation after simple aortic valve replacement (AVR) as a result of prosthetic valve dehiscence or destruction due

to flare. Recently, several case series have reported favorable outcomes after aortic root replacement (ARR). We evaluated if the surgical outcomes of AR in Behcet disease was dependent on surgical methods or materials. Here, we compared the long-term outcome of AR in Behcet disease who had undergone surgical treatment.

Methods: We have identified 33 patients who had been surgically treated for AR associated with Behcet disease from January 1996 through December 2013. A total of 23 patients fulfilled the international criteria for Behcet disease. AVR was performed in 9 patients and ARR in 14 patients. Bioprosthesis ARR was performed in 8 patients and composite graft ARR in 6 patients. The duration of follow-up was 10.7 years (median; IQR = 8.9-13.5) for the bioprosthesis ARR group and 6.4 years (median; IQR = 4.8-7.7) for the composite graft ARR group. The definition of the event was as follows; aortic valve/graft problem, infective endocarditis, cerebral infarction caused by thromboembolism or re-operation of aortic valve. We compared the events after first operation between the bioprosthesis ARR and composite graft ARR groups.

Results: In the 9 patients with AVR, events occurred in 6 patients (2.3 years after operation [median; IQR = 0.3-10.3]) and 11 cases required re-operation. In the 14 patients with ARR, events occurred in 7 patients (4.7 years after operation [median; IQR = 1.6-6.9] years after operation) and 6 cases required re-operation. However, steroid was prescribed for significantly more patients and with higher dosage in ARR group than those of AVR group.

In the 8 patients with bioprosthesis ARR, events occurred in 6 patients (3.0 years after operatin [median; IQR = 1.5-5.4)) and re-operation was performed in 6 cases. Interestingly, in the 6 patients with composite graft ARR, events occurred in 1 patient (6.2 years after operation [median; IQR = 4.8-7.5]), there was no case requiring re-operation. Kaplan-Meier curves displayed higher event free rate in composite graft ARR group compared to bioprosthesis ARR group (Figure 1). Overall mortality was 14.3% (2 of 8 patients in bioprosthesis ARR group, 0 of 6 patients in composite graft ARR group). The administration of steroid and immunosuppressants after operation were not significantly different between both groups.

Conclusion: In patients with AR related with Behcet disease, the rate of event was lower in patients with composite graft ARR compared to those with bioprosthesis ARR. Composite graft ARR was shown to be a feasible surgical option in patients requiring ARR for aortic root involvement of Behcet disease.

Disclosure: B. Ghang, None; **S. J. Choo**, None; **O. C. Kwon**, None; **S. Hong**, None; **Y. G. Kim**, None; **C. K. Lee**, None; **B. Yoo**, None.

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Abstract Number: 2950

Cogan Syndrome: Treatment and Outcome from French Nationwide Retrospective Study and Literature Review of 62 Patients

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Background/Purpose:

We aimed to describe the Cogan Syndrome, the efficacy of DMARDs and biological targeted agents.

Methods: A national multicenter retrospective study in France including patients from 2001 to 2015. Data were recorded at the time of each treatment initiation, at 6 months, and at the end of each treatment. Efficacy outcomes were the intention-to-treat rates of systemic, ocular and audiovestibular responses during the first 6 months of exposure, the evolution of the steroid doses and the number of relapses. Typical Cogan Syndrome was defined if ocular and audiovestibular involvements and the presence of interstitial keratitis were observed within less than 2 years. The efficacy of biologics was compared to DMARDs with Kaplan-Meier curves.

Results: Sixty two patients were included with median age 37 [2-76] and 31/62 (50%) women. At the diagnosis, 61 (98%) had audiovestibular involvement, with bilateral hypoacousia/deafness, 19 (31%), 38 (95%) 57 (92%) with ophtalmological symptoms (keratitis 54%, scleritis 35%), 42 (68%) systemic symptoms. The time between the appearance of audiovestibular and ophtalmological symptoms was 2 months [ranges; 0-180]. Median ESR and CRP levels were 26 [3-125] mm and 15 [1-355] mg/l. The median follow-up was 34 [0-228] months. Comparing typical Cogan Syndrome to atypical cases (n=31 each), women (68% versus 32%, $p<0.05$), the presence of scleritis/episcleritis (10% versus 55%, $p<0.05$), significantly differed between groups. The first-line treatment was used in 61 (98%) patients and consisted in steroids alone (n=42), with median dose 60 mg/day [20-120], combined with other immunosuppressive drugs in 19 patients (31%)(methotrexate=8; azathioprine= 3; cyclophosphamide=8). Although ocular, constitutional signs and acute phase reactants were improved in nearly 80% of patients, only 28% had complete audiovestibular response. A second-line treatment was used in 44 cases, for relapses (n=27), steroid dependence (n=5), adverse effects or non-response (n=12). Overall, 129 lines of treatment were used in 61 patients and consisted in steroids alone (n=50), with steroids associated with DMARDs (n=69) and biological-targeted drugs (n=10). No difference was noted between 3 treatment regimens for the number of audiovestibular, ocular, systemic involvements, neither for the median dose of steroids, although the number of previous lines of treatment was more important for patients using biologics (1 (1-3) for steroids, 2 (1-5) for DMARDs and 2.5 (2-6) for biologics, $p<0.05$). Although the response rates were similar for ocular and systemic signs, audiovestibular improvement was significantly more frequent under biologics in comparison to steroids alone and DMARDs (80% versus 39% and 35%, respectively, $p<0.05$).

Conclusion: Audiovestibular involvement has a poor prognosis, with less response to treatment than ophtalmological symptoms. Biological targeted drugs seem to improve the audiovestibular impairment, whereas the addition of DMARDs does not improve the audiovestibular outcome.

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Abstract Number: 2951

Patient Outcomes in Primary Angiitis of the Central Nervous System

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Background/Purpose: Primary angiitis of the CNS (PACNS) is a rare form of vasculitis confined to the brain and spinal cord, which often presents with severe cognitive and functional deficits. Although we have witnessed a tremendous progress in the recognition and diagnosis of this disease, there is still little known about the quality of life that these patients have following a diagnosis of PACNS. The aim of this study is 1) to evaluate patients' functional capabilities, quality of life, and frequency of depression after being diagnosed and treated for PACNS; and 2) to determine the effect of treatment duration on patient outcomes.

Methods: This is a cross-sectional study from a tertiary referral center. Eligible patient records were identified via retrospective chart review using the ICD-9 code for cerebral angiitis. Patients were included if they met 2 of the 3 following criteria: inflammatory CSF, angiogram typical of vasculitis, or vasculitis present on pathology of the brain. In addition, the diagnosis of PACNS was further agreed upon by 2 rheumatologists in the department who have particular expertise in this disease. Self-reported questionnaires were prospectively collected from eligible subjects. Measure of disability was assessed by the Barthel Index (BI), quality of life was assessed by EuroQOL (EQ-5D-5L), and depression was assessed with Patient Health Questionnaire (PHQ-9). Treatment history was collected from patient report and chart review.

Results: 1855 patient records were identified using the ICD-9 code for cerebral angiitis. 78 patients met inclusion criteria, of which 27 responded to the questionnaires (34.6%). Median follow-up of those who responded was 5.5 years (+/- 4.7 years) since diagnosis of PACNS. Using the Barthel Index scale, 19 of 27 patients (70.4%) scored 85 or more, indicating mild disability. Meanwhile, five (18.5%) patients scored 25 or less, indicating severe disability. Using the EQ-5D-5L questionnaire, 14 of 27 patients (51.9%) had no problems with mobility, 18 (66.7%) had no problems with self-care, 15 (55.6%) had no problems with usual activities, and 14 (51.9%) had no problems with pain, but only 8 (29.6%) had no problems with anxiety. Approximately 70% of patients had minimal or no depression using both the PHQ-9 scale and EuroQOL. There was a slight positive relationship between several of the outcome measures and duration of immunosuppressive therapy, although it is not statistically significant.

Conclusion: This is the longest reported follow-up of patients with PACNS described in the literature to-date. Most patients have mild long-term disability and minimal to no depression, which may be reflective of the advances of treatment. The data shows a slight tendency towards better scores being associated with longer treatments. However, larger studies are needed to verify the extent and strength of these relationships.

Disclosure: E. Ray, None; **D. Saygin**, None; **A. Morales-Mena**, None; **W. Messner**, None; **L. H. Calabrese**, None; **R. A. Hajj-Ali**, None.

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Abstract Number: 2952

Differentiation Between Neurosarcoidosis and Primary CNS Vasculitis Based on Clinical and Cerebrospinal Fluid Parameters

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Background/Purpose: Neurosarcoidosis is one of the great mimickers of primary angiitis of central nervous system (PACNS) in terms of disease presentation, imaging and pathologic findings. However treatment strategies are different specifically in term of biologics which is rarely used in PACNS. Therefore, distinguishing these diseases earlier would be important giving the distinct therapeutic implications. We aimed in this original study to distinguish demographic, cerebrospinal fluid (CSF) and laboratory characteristics of both diseases to enhance our diagnostic approach.

Methods: 79 patients with PACNS and 51 patients with neurosarcoidosis were included in the study. All the clinical, CSF and laboratory characteristics at the time of presentation were retrieved from electronic medical records. For comparisons on the basis of diagnosis, numerical variables were compared between groups using either ANOVA or the Kruskal-Wallis rank-sum test. Categorical variables were compared between groups using either Pearson's chi-squared test or Fisher's exact test. All analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC). All testing was two-sided, and considered significant at the 5% level.

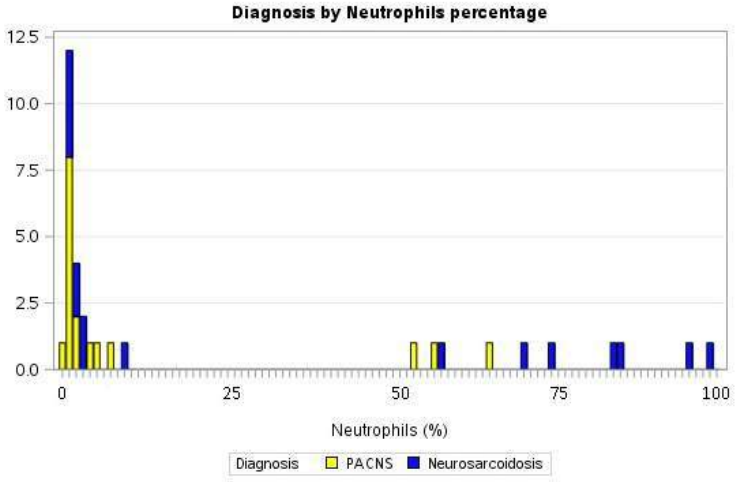
Results: Demographic and CSF characteristics, blood CRP, ESR, ANA, RF levels of the patients were shown in the Table. There was a statistically significant difference between diagnoses on two variables. The first was race, where African American patients tended to be diagnosed with neurosarcoidosis and Caucasian patients tended to be diagnosed with PACNS ($p < 0.001$). The second was ANA, where higher levels tended to be associated with neurosarcoidosis ($p = 0.047$), and lower levels tented to be associated with PACNS. Although not statistically significant, two other variables showed promise for distinguishing the two diagnoses: total nucleated cells ($p = 0.067$) and neutrophils ($p = 0.14$). Higher values of total nucleated cells showed some tendency toward neurosarcoidosis, whereas low values showed some tendency toward PACNS. Neutrophil counts in the high range tended to correspond to neurosarcoidosis, whereas neutrophil counts in the low range tended to correspond to PACNS (Figure).

Conclusion: African American race and positive ANA were found to be associated with the diagnosis of neurosarcoidosis rather than PACNS. Total nucleated cells and neutrophil counts in the CSF showed promise in differentiating the neurosarcoidosis and PACNS. A follow-up study with a larger sample size would be required to firmly establish such a relationship. Table. Demographic and CSF characteristics of patients with neurosarcoidosis and PACNS

	Total (N=130)	PACNS (N=79)	Neurosarcoidosis (N=51)	p-value
Age at presentation*	43.8±15.0	43.7±16.7	44.0±12.0	0.92
Gender*				0.40
. Male	70(54.3)	40(51.3)	30(58.8)	
. Female	59(45.7)	38(48.7)	21(41.2)	
Race*				***<0.001***
. Caucasian	110(88.0)	73(97.3)	37(74.0)	
. African American	15(12.0)	2(2.67)	13(26.0)	
CSF Glucose*	65.0±27.1	66.6±21.4	62.7±34.3	0.59
CSF Protein*	60.0[37.5,90.5]	59.0[37.0,73.0]	61.0[38.0,133.0]	0.25
CSF Reac Lymph%*	2.0±1.6	2.0±1.7	2.1±1.6	0.88
CSF RBC*	5.0[1.00,46.5]	6.5[0.00,32.0]	3.0[1.00,235.0]	0.47
CSF Neutrophils*				0.14
. Neutrophils < 40%	23(69.7)	14(82.4)	9(56.3)	
. Neutrophils ≥ 40%	10(30.3)	3(17.6)	7(43.8)	
CSF Lymph%*	86.5[57.0,92.5]	85.5[60.0,93.0]	87.0[41.0,91.0]	0.51
CSF Mono%*	7.0[4.0,16.0]	8.0[4.0,16.0]	7.0[4.0,11.0]	0.65
CSF Total nucleated cells*	12.0[2.0,36.0]	8.5[1.00,32.0]	17.0[6.0,50.0]	0.067
ACE/Angiotensin Blood*	28.6±20.2	25.1±19.7	29.9±20.5	0.44
Blood Soluble IL2-R levels*	641.0[425.0,1000.0]	600.5[397.0,722.0]	647.0[458.0,1000.0]	0.84
CRP*	0.60[0.20,3.7]	0.70[0.20,4.9]	0.55[0.15,1.00]	0.41
ESR*	12.5[5.0,28.0]	15.0[5.0,29.0]	8.0[7.0,24.0]	0.61
ANA*	0.30[0.20,0.70]	0.30[0.20,0.50]	0.50[0.30,0.80]	***0.047***
RF*	7.0[5.0,9.0]	7.0[2.5,9.0]	8.0[7.0,10.0]	0.31

*Data not available for all subjects. Missing values: ACE/Angiotensin Blood = 74, Age at presentation = 3, Glucose = 68, Reac Lymph% = 108, Blood Soluble IL2-R levels = 83, Lymph% = 66, Mono% = 67, Total nucleated cells = 66, Protein = 66, RBC = 66, Gender = 1, Neutrophils = 97. Additionally, 2 Asian, 1 Arabic, and 2 non-identifying patients are not included the analysis.
Values presented as Mean ± SD, Median [P25, P75], or N (column %).

Figure. Neutrophil Counts in Cerebrospinal fluid and its association with the type of diagnosis.



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Abbvie, Jannsen, 5; **E. Ray**, None; **W. Messner**, None; **J. Tavee**, None; **R. A. Hajj-Ali**, None.

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Abstract Number: 2953

Comparison of Patient Outcomes in Primary Angiitis of the Central Nervous System and Reversible Cerebral Vasoconstriction Syndrome

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Background/Purpose: Reversible Cerebral Vasoconstriction Syndrome (RCVS) is an important mimic of Primary Angiitis of the Central Nervous System (PACNS). Distinct clinical and diagnostic features differentiate both entities. However no available data exist in comparing the long term outcome of these two patient populations. The aim of this study is to compare the long term outcomes of PACNS and RCVS.

Methods: This is a cross-sectional study from a tertiary referral center. Eligible patient records were identified via retrospective chart review using the ICD-9 code for cerebral angiitis and reversible cerebral vasoconstriction syndrome, and the diagnoses were further agreed upon by 2 rheumatologists in the department who have particular expertise in these diseases. Self-reported questionnaires were prospectively collected from eligible subjects. Measure of disability was assessed by the Barthel Index (BI), quality of life was assessed by EuroQOL (EQ-5D-5L), and depression was assessed with Patient Health Questionnaire (PHQ-9).

Results: Of the 191 patients with RCVS, 45 responded to the questionnaires (23.5%). Of the 78 patients with PACNS, 27 responded to the questionnaires (34.6%). Median follow-up (from diagnosis to date of questionnaires) of those who responded with PACNS was 66 months (+/- 54 months) and with RCVS was 78 months (4-254 months). RCVS patients had significantly better functional capacity than PACNS as measured by Barthel Index (mean 95.9 in RCVS, 79.4 in PACNS, $p = 0.022$). RCVS patients scored significantly better in the self-care subscale of EuroQOL, although the remainder of the quality of life measures (mobility, usual activities, and anxiety/depression) were not statistically significant. Most patients with RCVS and PACNS scored low (minimal depression) on PHQ-9, and the mean PHQ-9 score between both groups was not statistically different ($p = 0.683$).

Conclusion: In a comparison of outcomes of patients with PACNS and RCVS, patients with RCVS were found to have better outcomes in terms of functional capabilities, and may have better quality of life. However, they appear to have a similar rate of depression.

Disclosure: E. Ray, None; **D. Saygin**, None; **S. John**, None; **W. Messner**, None; **K. Uchino**, None; **L. H. Calabrese**, None; **R. A. Hajj-Ali**, None.

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Abstract Number: 2954

Anti-IL6-R Tocilizumab in Refractory Uveitis Associated with BehçEt's Disease.

Multicenter Study of 11 Patients

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Background/Purpose: Treatment recommended in severe and/or refractory uveitis of Behçet disease is anti-TNFα therapy, usually infliximab (IFX) or adalimumab (ADA) (Levy-Clarke et al Ophthalmology 2014). However, in some cases these biologic agents are not effective, may be contraindicated or they are not well tolerated. IL-6 is a key cytokine in the pathogenesis of uveitis. Our aim was to evaluate the response to tocilizumab (TCZ) in uveitis associated with refractory Behçet disease.

Methods: Multicenter study of 11 patients with uveitis associated to Behçet disease. Patients had been treated with at least one conventional immunosuppressive drug and in most cases with anti-TNFα agents. The main parameters assessed were the visual acuity (VA) and the degree of intraocular inflammation. Cystoid Macular Edema (CME) was considered when OCT was greater than 300 μm.

Results: We studied 11 patients (7 men/4 women); mean age 38.45±20.42 years. Uveitis was bilateral (n=9) and unilateral (2) **(Table).** The pattern of ocular involvement was panuveitis (n=8; 7 of them with retinal vasculitis, 6 with CME and 1 with papillitis), anterior uveitis (n=2, also with severe arthritis) and posterior uveitis (1 case; also with retinal vasculitis and CME). The clinical course was chronic (n=4) or recurrent (7). Besides oral corticosteroids and before TCZ they had received: intraocular corticosteroids (n=10), i.v. methylprednisolone (10), methotrexate (MTX) (9), (cyclosporin A) CsA (8), azathioprine (AZA) (3), cyclophosphamide (2), mycophenolate (1) and colchicine (1). All of them had received other biologic drugs: Adalimumab (n=8), Infliximab (4), Golimumab (3), etanercept (1), canakimumab (1) and daclizumab (1)**.** In 10 patients TCZ was prescribed at 8 mg/kg/i.v. monthly and in 1 patient 162 mg/week/sc. TCZ was given in monotherapy (n=7) and combined in 4 cases (2 MTX, 1 CsA, 1 AZA). After a mean follow up of 9.5±8.05 months, improvement was observed in the following items: a) Mean VA (0.38±0.32 to 0.73±0.35; p=0.002); b) Median cells in the anterior chamber (1 [0-2.5] to 0 [0-0]; p=0.005; c) Median vitritis (1 [0-2] to 0 [0-0]; p=0.003); d) retinal vasculitis (n=10 eyes [45.45%] with resolution in all cases e) Mean OCT (μ) (from 359.46±115.96 to 257.66±71.7, p=0.0009; f) 8 patients achieved complete remission, g) reduction in median dose of prednisone (30 [20-30] to 0 [0-5]; p=0.1). TCZ was withdrawn in 2 cases, 1 due to an infusional reaction and 1 because of joint impairment.

Conclusion: Treatment with TCZ seems to be effective in patients with refractory uveitis due to Behçet's disease. **TABLE**

Case	Sex/age	*Conventional Immunosuppressive drugs* before TCZ	Biologic drugs before TCZ	*Immunosuppressive drugs* combined with TCZ	Anterior chamber cells (onset/last visit)	Retinal Vasculitis (onset/last visit)	OCT (onset/last visit)
1	M/27	MTX, CsA, CFM	-	MTX	0/0	Yes/No	296.5/243.5
2	F/42	MTX, CsA, AZA, CYM	ADA, GLM	-	1/0	Yes/No	314/249
3	M/50	MTX, CsA	ADA, GLM	-	1/0	Yes/No	314/240
4	M/35	MTX, CsA, AZA, daclizumab, MMF	IFX	-	3/0	Yes/No	257.5/233
5	F/67	MTX, CsA	ADA, IFX	-	2/1	Yes/No	377/235
6	M/31	MTX, CsA	ADA	-	1/0	Yes/No	460/239
7	F/22	MTX, CsA	ADA	CsA	2/0	No/No	433/221
8	M/75	MTX, CsA	ADA	-	0/0	Yes/No	474/391.5
9	M/10	Canakinumab	Canakinumab, ETN	-	4/1	No/No	-
10	F/48	MTX, colchicina	IFX, ADA, GLM	MTX	0/0	No/No	-
11	M/16	AZA	ADA, IFX	AZA	4/0	Yes/No	-

Abbreviations: M: Male; F: Female; MTX: Methotrexate; CsA: cyclosporin A; AZA: azathioprine; CYM: cyclophosphamide; MMF: mycophenolate; ADA: Adalimumab; IFX: Infliximab; GLM: Golimumab, ETN: Etanercept

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Abstract Number: 2955

Biologic Therapy in Severe Peripheral Ulcerative Keratitis (PUK). Multicenter Study of 27 Patients

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Background/Purpose: Peripheral Ulcerative Keratitis (PUK) is a severe inflammation of the outer portions of the cornea that may be associated with systemic conditions. The progression of marginal corneal thinning may lead to perforation of the cornea and to rapid and permanent vision loss in the involved eye. Treatment of PUK is based on corticosteroids and conventional systemic immunosuppressive drugs. Our aim was to evaluate the response to biologic therapy in cases with severe and refractory PUK.

Methods: Multicenter study of 27 (35 affected eyes) patients. All of them presented inadequate response to conventional therapy with corticosteroids and at least 1 systemic traditional immunosuppressive drug. The main outcome measures were visual acuity, signs of inflammation (scleritis and episcleritis), progression to corneal thinning, central keratolysis and ocular perforation.

Results: We studied 27 patients/35 affected eyes (7 men/20 women) with a mean age of 57.2±16.3 years. PUK was primary (n=1) and in the 26 remaining cases, the underlying diseases were Rheumatoid Arthritis (RA) (n=19), Psoriasic Arthritis (2), RA+Felty syndrome+common variable immunodeficiency (1), Behçet Disease (1), Type I diabetes mellitus (1), granulomatous polyangiitis (1) and microscopic polyangiitis (1). They received the following topical therapy: corticosteroids (n=18), antibiotics (17), lubricants (18), autologous serum (11), topical cyclosporin (11) and topical tacrolimus 0.03% (1). Besides oral corticosteroids and before the biologic therapy they had received iv methylprednisolone (n=8), methotrexate (16), oral doxycycline (9), azathioprine (3) and ascorbic acid (2). Moreover, 10 patients required surgery: amniotic membrane (n=7), penetrating keratoplasty (4), conjunctival resection (3), tissue adhesives (2), conjunctival flap (1) and lamellar keratoplasty (1). Anti-TNFα drugs were the most common biologic agents (n=19): Adalimumab (ADA) (10; 37%), Infliximab (IFX) (; 29.6%) and etanercept (n=1; 3.7%). In the remaining 8 cases the biologic agents were rituximab (n=7; 25.9%) and tocilizumab (n=1; 3.7%). The main outcome measures are summarized in the Table. After a mean follow-up of 23.7±20 months, all objective outcomes had improved with a reduction of the median prednisone dose from 33.7 [IQR 17.5-52.5] mg at baseline to 0 [0-2.5] mg (p=0.028). The main observed adverse effects were supraventricular tachycardia (n=1) and pulmonary Tuberculosis (n=1).

Conclusion: In our series, biological therapy, especially IFX and ADA, is effective and relatively safe in patients with PUK refractory to standard systemic treatment. **TABLE**

	Basal	1 week	1 month	6 months	1 year
Visual Acuity, mean ±SD	0.54±0.37	0.55±0.35	0.58±0.33	0.67±0.3*	0.69±0.27*
Peripheral thinning #	85.7	80*	57.1*	40*	34.3*
Central keratolysis #*	17.1	8.6*	0*	8.6*	5.7*
Ocular perforation #	11.4	14.3	0*	0*	2.8*
Scleritis #	34.3	22.8*	8.6*	0*	0*
Episcleritis #	22.8	11.4*	5.7*	2.8*	2.8*
Uveitis#	14.3	14.3	8.6*	2.8*	2.8*

* p <0.05 compared with basal data# Data are expressed as % of the active eyes

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Abstract Number: 2956

Optimization of Thiopurines with a Xanthine Oxidase Inhibitor in Patients with Autoimmune Systemic Diseases

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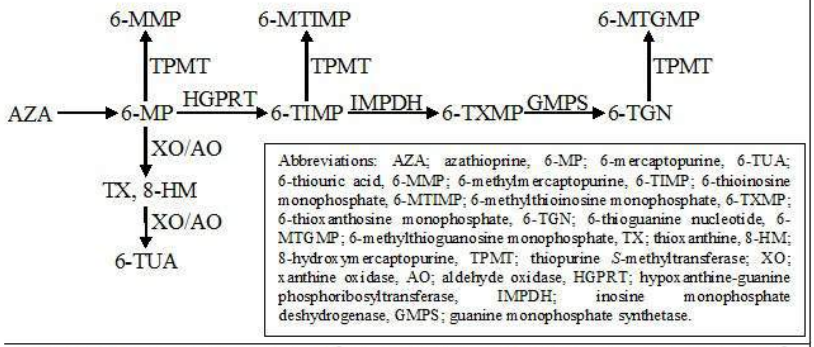
Background/Purpose: Thiopurines are a mainstay for the treatment of autoimmune diseases. However, in inflammatory bowel diseases (IBD), 14-18 % of patients manifest a skewed metabolism of these drugs leading to an overproduction of the 6-methylmercaptopurine (6-MMP) metabolite to the detriment of the active 6-thioguanine (6-TGN) metabolite (Figure 1). These patients are identified as shunters. In IBD, allopurinol is used to reverse this skewed metabolism, thus preventing thiopurines resistance or hepatotoxicity. However, this strategy has hardly been studied in a population with other autoimmune systemic diseases.

Methods: Patients were identified using the central laboratory database and data were retrospectively collected. Clinical and laboratory evolution of patients for whom azathioprine (AZA) was optimized with a xanthine oxidase inhibitor (XOI) was assessed on a 12-month period.

Results: Thirty-four shunters (33%) were identified over 103 patients treated with AZA for autoimmune conditions other than IBD. Twenty shunters were not optimized while 14 shunters were optimized with allopurinol (13) and febuxostat (1). Multiple reasons lead to optimization: 6 patients were depending on corticosteroids, 6 patients were non-responsive to therapy or had a relapse, 3 patients had hepatotoxicity and 3 patients were optimized solely based on their metabolites ratio. The maximal AZA dose decreased form 2.07 mg/kg (interquartile range (IQR): 1.77-2.45) on AZA alone to 0.86 mg/kg (IQR: 0.68-1.07) on AZA-XOI combination therapy. Despite this significant 58% (p=0.003) dose reduction, optimization with a XOI allowed to increase the 6-TGN blood level from 135 pmol/8×10^8 red blood cells (RBC) (IQR: 91-199) to 385 pmol/8×10^8 RBC (IQR: 237-449) (p=0.001) and to decrease the 6-MMP level from 6267 pmol/8×10^8 RBC (IQR: 3858-11306) to 271 pmol/8×10^8 RBC (IQR: 162-528) (p=0.001). All patients resumed a normal 6MMP/6TG ratio (<20) and 2 out of 3 hepatotoxicity resolved. Except for the mean corpuscular volume increase of 12% (p=0.001), the changes in the blood count were not considered clinically significant. Notable infections were reported in 3 patients. After 6 months of optimization, prednisone was reduced by 89% (p=0.005), 12 patients were in remission and 2 in partial remission.

Conclusion: In this retrospective study, the optimization of thiopurines with a XOI was safe and effective. This strategy represents a promising therapeutic option in patients with autoimmune systemic diseases.

Figure 1. Azathioprine and 6-mercaptopurine metabolism pathway



6-MMP target : <5700 pmol/8×10^8 erythrocytes, 6-TGN target : >235 pmol/8×10^8 erythrocytes, ratio target: <20

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Abstract Number: 2957

Primary Central Nervous System Vasculitis Associated with Lymphomas

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Background/Purpose: The occurrence of lymphoma, especially Hodgkin's lymphoma (HL), in patients with primary central nervous system vasculitis (PCNSV) has been reported but is considered uncommon. The aim of this study was to determine the frequency of lymphoma in a large cohort of patients with PCNSV and compare the presenting clinical, laboratory, and imaging features in those with both lymphoma and PCNSV to those without lymphoma.

Methods: We reviewed all patients seen at the Mayo Clinic, Rochester, MN over the 32- year period of 1982-2014, who were diagnosed with vasculitis and lymphoma. 10 patients associated PCNSV and lymphoma Cerebral biopsy specimens were reviewed by one pathologist (CG) without knowledge of clinical information. We also used as comparator our updated cohort of 158 consecutive patients with PCNSV without lymphoma who were examined at Mayo Clinic over a 29-year period from 1983 to 2011. The diagnosis of PCNSV was based on brain/spinal cord biopsy, or cerebral angiography, or both. Clinical data were collected.

Results: 10/168 (5.9%) patients were found to have both lymphoma and PCNSV: 6 of these 10 had HL and 4 non-HL. In 8 patients PCNSV diagnosis was established by cerebral biopsy and in 2 by cerebral angiography. Two of the 10 patients had brain and spinal cord vasculitis involvement. A granulomatous inflammatory histologic pattern was found in all 8 patients with cerebral biopsies, accompanied by vascular deposits of β-amyloid peptide in 2. In 7 patients (5 HL and 2 NHL) medical diagnostic workup for PCNSV revealed lymphoma. In one other patient PCNSV symptoms appeared during a recurrence of lymphoma, in another 6 months after an allogenic bone marrow transplant for a recurrence of lymphoma, and in one lymphoma occurred 26 years before PCNSV diagnosis. Cerebrospinal fluid (CSF) was negative for herpes virus when assayed by PCR. The 10 patients with lymphoma were compared with the 158 patients with PCNSV without lymphoma. The patients with lymphoma were more frequently males (80% vs 44%, $p = 0.04$). No other significant differences in the clinical manifestations at presentation and CSF findings were observed in the two groups, although cognitive dysfunction was more frequent in patients with lymphoma (80% vs 53%), while visual field defects and intracranial hemorrhage were less frequent (0% vs 19%, and 0% vs 10%, respectively). Systemic manifestations were infrequent in both groups (10% vs 9.5%). More patients with lymphoma showed meningeal gadolinium enhancing lesions on MRI (50% vs 19%, $p = 0.03$). The frequency of PCNSV relapse (20% vs 28.4%) and patients not requiring therapy at last follow-up (30% vs 25.5%) were similar in both groups. Patients with lymphoma had a higher frequency of poor outcomes (modified Rankin disability score > 4) at last followup (60% vs 21,5%, $p = 0.01$). Considering all 168 patients, univariate Cox proportional hazards modeling showed an increased mortality rate in those with increasing age (hazard ratio, HR, 1.3), lymphoma (HR 3.9), cerebral infarction on initial MRI (HR 3.4), and angiographic large vessel involvement (HR 3.9), while mortality rate was lower in those with gadolinium–enhancing lesions on MRI (HR 0.3).

Conclusion: Lymphoma was found in 5.9% of of 168 patients with PCNSV. Lymphoma may occur simultaneously with PCNSV, before or after the diagnosis of PCNSV. Most clinical characteristics of PCNSV were similar in those with or without lymphoma, however, patients with lymphoma had a more severe cerebral vasculitis with increased neurological disability and mortality.

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Abstract Number: 2958

Hypocomplementemic Urticarial Vasculitis (HUV) Syndrome in Two Geographically Defined Populations of Sweden

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Background/Purpose: Since first described by McDuffie *et al.* in 1973, hypocomplementemic urticarial vasculitis (HUV) syndrome has been recognized as a specific autoimmune disorder involving at least 6 months of urticaria with hypocomplementemia in the presence of systemic manifestations, such as arthritis/arthralgia, glomerulonephritis, uveitis and recurrent abdominal pain. Skin biopsy is essential in the diagnosis of HUV and the presence of antibodies against complement protein 1q (anti-C1q) has been judged 'a rule without exception'. The objective of this study was to describe the clinical characteristics and epidemiology of HUV in two geographically areas of Sweden during a 16-year period.

Methods: In the health care districts surrounding the Skåne University Hospital in Lund [mean population years (2000-2015), 950 560] and the Linköping University Hospital in Östergötland [mean population years (2000-2015), 428 503] all patients diagnosed with HUV during the period 2000-2015 were included in the study if they (i) were residing within the study areas at the time of onset of HUV-related symptoms, (ii) had received a diagnosis of HUV during the study period. The diagnosis of HUV was confirmed by medical records review. Only patients meeting the suggested diagnostic criteria for HUV [1] and/or the 2012 Chapel Hill consensus definitions [2] were included.

Results: Sixteen patients (Skåne 7 + Östergötland 9) with a clear female predominance were identified during the study period. Clinical characteristics of the patients are given in Table 1. The pooled annual incidence rate per million inhabitants was estimated to 0.7 (95% CI 0.4-1.1), with a significant higher incidence in Östergötland compared to Skåne [0.5 (95% CI 0.1-0.8) and 1.3 (0.5-2.2), P=0.02]. The prevalence did not differ significantly between the regions, Table 2). Two patients died during the follow-up period. One patient underwent lung transplantation and two patients proceeded to end-stage renal disease.

Table 1

Clinical and laboratory characteristics	
Number of patients	16 (9 Östergötland; 7 Skåne)
Female, n (%)	14 (87.5%)
Age at diagnosis	51 (IQR 40.7-56.7) years
Age at last follow-up	58 (IQR 47.0-67.2) years
Duration of follow-up	94 (IQR 46.5-136.2) months
Diagnosis delay	12 (IQR 5.0-19.7) months
Laboratory results at diagnosis, median (IQR)	
Hemoglobin	124.5 (116.5-131.5)
White blood cell count	7.2 (5.7-11.5)
Thrombocyte count	311 (250-451)
ESR (mm/h)	18.5 (8.5-30.2)
C-reactive protein (mg/L)	14 (10-29)
P-creatinine (µmol/L)	79.5 (57.5-85.0)
eGFR	75.5 (65.2-108.2)
Criteria at diagnosis	
Low complement	15 (94%)
Dermal venulitis	1 (6%)
Arthritis	14 (88%)
Glomerulonephritis (on biopsy)	3 (19%)
Episcleritis/scleritis	3 (19%)
Recurrent abdominal pain	2 (13%)
Anti-C1q antibody	16 (100%)
Histopathology diagnosis	13 (81%)
ESRD	2 (13%)
Death	2 (13%)
Serology data at diagnosis	
ANA positive	7 (44%)
ENA positive	5 (31%)*
Anti-dsDNA antibody	0
Anti-cardiolipin antibody	2 (13%)

* Ro/SSA 3; Ro/SSA+La/SSB 2

Table 2

Patients	N. of patients	Incidence (95% CI)	N. of patients	Point prevalence (95%)
All	16	0.7 (0.4-1.1)	14	9.5 (4.5-14.5)
Women	14	1.3 (0.6-1.9)	12	16.2 (7.0-25.4)
Men	2	0.2 (0-0.4)	2	2.7 (0-6.5)
Östergötland	9	1.3 (0.5-2.2)	7	15.7 (4.1-27.3)
Women	8	2.3 (0.7-4.0)	6	27.1 (5.4-48.8)
Men	1	0.3 (0-0.9)	1	4.5 (0-13.2)
Skåne	7	0.5 (0.1-0.8)	7	6.8 (1.8-11.8)
Women	6	0.8 (0.2-1.4)	6	11.6 (2.3-20.9)
Men	1	0.1 (0-0.4)	1	2.0 (0-5.8)

Conclusion: To our knowledge, this is the first epidemiological study of HUV. The high coverage of patients, which was enabled by the public and tax-funded Swedish healthcare system, constitutes a major strength of this study. The estimation of incidence and prevalence indicate that this condition is rare but not benign. Renal and lung manifestations were severe in some cases which highlights the need for careful screening and monitoring of this potentially serious condition. *References:* 1) Davis MD, Brewer JD. *Immunol Allergy Clin North Am* 2004;24:183-213 2) Jennette JC, et al. *Arthritis Rheum* 2013;65:1-11

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Abstract Number: 2959

Baseline Endothelial Dysfunction Might Predict Immunosuppressive Need in Young, Male Behcet's Patients with Early Disease: A Prospective Follow-up

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Background/Purpose: Major organ involvement, especially in young males, is one of the main causes of mortality and morbidity in Behcet's Disease (BD). However, the prognosis and predictors of major organ involvement is unsufficiently studied. We aimed to follow young, male BD patients which have the highest risk for major organ involvement prospectively.

Methods: Thirty-six male patients with BD consecutively consulted in the Outpatient Clinics of Marmara University, 35 males with ankylosing spondylitis(AS),36 healthy males were included in the study. Bilateral upper and lower extremity venous doppler ultrasonography(US) and brachial and carotid arterial US (for assessing endothelial dysfunction) were performed in baseline visit for all groups and in the first year follow-up visit for BD patients. Patients with BD were assessed prospectively with 3-6 months intervals and in any urgent visit.

Results: At baseline, the mean disease duration was 3.3 years in patients with BD. The rate of venous insufficiency was higher in male BD patients without vascular events, compared to healthy controls (BD vs HC: 30.5% vs 0%) and similar to patients with AS (BD vs AS. 30.5% vs 32%). Markers of endothelial dysfunction (FMD and NID) were similar between BD patients and healthy controls, however CIMT (Carotid intima media thickness) was significantly higher in BD (0.54 mm vs 0.47 mm, p=0.033). The mean follow-up duration was 44.6 months. Major organ involvement developed in 4 (11%, 3 vascular and 1 ocular involvement) patients during follow-up. All of them were in the first 2 years of follow-up. Immunsuppresive (IS) therapy was required in 22% (n=8) of patients, due to major organ involvement in 4 (11%) and refractory mucocutaneous symptoms in other four (11%) patients. In the first year follow-up visit, endothelial functions and CIMT were observed to be significantly improved compared to baseline (Baseline vs Follow-up: 6.8±4 vs 10.9±4.5, p=0.003 for FMD**,** 0.55±0.13 vs 0.47±0.1 for CIMT, p=0.004). The patients requiring IS treatment in the follow-up had significantly lower FMD at baseline compared to the rest of the group (4.4 vs 8.5, p=0.005).

Conclusion: Our study demonstrated a lower incidence of major vascular events in male BD patients during prospective follow-up compared to historic controls in the literature. However, our results confirmed an early onset of major organ involvement and IS use in the first year of disease follow-up. The decreased rate of baseline FMD in patients with later IS requirement suggest that FMD can be a predictor for major organ involvement in BD. **Table 1: Clinical charecteristic of patients developing immunosuppressive need during follow-up.**

	IS onset during follow-up.	Reason for IS use	Age	Disease duration when IS started	IS agent
Patient 1	1.month	Pulmonary aneurysm	35	1 year	Azatioprine
Patient 2	7.month	Refractory OU	25	5 years	Cyclosporine
Patient 3	6. month	Deep venous thrombosis	38	10 years	Azatioprine
Patient 4	10. month	Uveitis	20	5 years	Azatioprine
Patient 5	9. month	Refractory OU	28	7 years	Azatioprine
Patient 6	13. month	Refractory OU	23	6 years	Cyclosporine
Patient 7	9. month	Refractory EN	35	1 years	Azatioprine
Patient 8	8. month	Deep venous thrombosis	23	1 years	Azatioprine

IS: Immunosuppressive, OU: Oral ulcer, EN: ertyhema nodosum

Disclosure: F. Alibaz-Oner, None; **E. Karatay**, None; **B. Aldag**, None; **I. N. Akpınar**, None; **T. Ergun**, None; **H. Direskeneli**, None.

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Abstract Number: 2960

Increased Post-Thrombotic Syndrome Is Unassociated with Anticoagulant Use in Vascular Behcet's Disease

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Background/Purpose: Deep venous thrombosis (DVT) is the most common form of vascular involvement in Behcet's disease (BD). Chronic post-thrombotic syndrome (PTS) develops frequently in patients with DVT and is associated with impaired quality of life (QoL). However, factors associated with PTS and venous disease spesific QoL is unsufficiently explored in patients with VBD.

Methods: This study included 94 patients (Male/Female: 75/19) with VBD and 29 age and gender-matched individuals (Male/Female: 18/11) with DVT associated with non-BD causes. Villalta scale was used to assess PTS. Venous Disability Score (VDS) and Venous Clinical Severity Score (VCSS) were used for the assessment of venous disease. Venous disease-specific QoL was measured through Venous Insufficiency Epidemiological and Economic Study Quality of Life/Symptom questionnaire (VEINES-QoL/Sym). Behçet's Syndrome Activity Score (BSAS) questionnaire was used to assess disease activity.

Results: A high presence of PTS (61.7%) was observed in VBD. The rate of anticoagulant usage was significantly lower (63% vs 100%, p=0.001), and the number of DVT attacks were significantly higher in VBD (1.6 vs 1.3, p=0.001) compared to non-BD. VEINES-QoL and VEINES-Sym VCSS were significantly worse in VBD patients with PTS when compared to patients without PTS. BSAS was also significantly higher in patients with PTS. An inverse correlation was observed between VEINES-QoL and BSAS in multivariate analysis (p=-0.551, p< 0.001). There were no differences between anticoagulant users and non-users regarding the presence of PTS (60.8% vs 63.3%) and scores of all venous assessment tools in VBD (p>0.05).

Conclusion: A high presence of PTS and impaired venous disease spesific QoL, symptom severity and venous disability scores were observed in VBD. Venous disease spesific QoL negatively correlated with general disease activity. Better control of disease activity might decrease development of PTS and improve venouse disease spesific QoL, however, any additional benefit of anticoagulant treatment on the development of PTS and venous QoL was not observed.

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Abstract Number: 2961

Antiphospoholipid Antibodies in Adult IgA Vasculitis: Aps/PT Antibodies As a Potential Marker of Renal Involvement?

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Background/Purpose: Increased prevalence of IgA aCL and anti-PS/PT antibodies has been described in adult IgAV, making them potential markers of disease activity[1]. The aim of our prospective study was to evaluate the role of antiphospholipid antibodies (aPL-Abs) on the clinical presentation of adult IgA vasculitis (IgAV).

Methods: Adults with histologically proven IgAV, diagnosed for the first time between 1 January 2013 and 31 May 2016 at our at our secondary/tertiary rheumatology center were included. IgG, IgM and IgA isotypes of anticardiolipin antibodies (aCL), antibodies to β2-glycoprotein 1 (aβ2GP1) and antibodies to phosphatidylserine-prothrombin complex (aPS/PT) were determined at presentation. A cut-off level for positive result was set at 99th percentile for all aPL-Abs. Clinical characteristics of patients with and without aPL-Abs were compared. Additionally, characteristics of IgAV cases with positive IgA aPS/PT were analyzed as subgroup.

Results: During the 41-month observation period aPL-Abs were determined in 89 IgAV patients (53.9 % male; median (IQR) age 67.6 (50.3, 77.3) years). In total 32 patients (36.0%) had aPL-Abs. aCL, aβ2GP1 and aPS/PT were found in 9.0%, 13.5% and 23.6%, respectively. IgA aPS/PT subtype, found in 21.3% was the most common aPL-Ab present in our IgAV patients (Table 1). Characteristics of aPL-Abs negative vs. aPL-Abs positive patients vs. IgA PS/PT positive cases are presented in the Table 2. The presence of any aPL-Abs was associated neither with thrombotic events nor with distinct IgAV clinical manifestation. Yet, aPL-Abs positive IgAV patients had significantly higher erythrocyte sedimentation rate ($p<0.001$), C-reactive protein ($p=0.007$) and serum immunoglobulin A level ($p=0.023$) at presentation. However, IgA aPS/PT positive patients had more commonly had renal involvement than those without this antibody ($p=0.031$; RR 1.9 (95% CI 1.1–3.1)). This was unrelated to increased total serum IgA level. The latter was not a predictor of renal involvement in our cohort ($p=0.177$).

Table 1.	
aPL-Abs	*number of patients*
aCL	8 (9.0%)
IgG	7
IgM	1
IgA	1
aβ2GP1	12 (13.5%)
IgG	6
IgM	3
IgA	7
aPS/PT	21 (23.6%)
IgG	6
IgM	5
IgA	19

Legend: aPL-Abs antiphospholipid antibodies; aCL - anticardiolipin antibodies, aβ2GP1 - antibodies to β2 glycoprotein 1; aPS/PT antibodies to phosphatidylserine-prothrombin complex

Table 2.	*aPL-Abs (number of patients)*		*IgA aPS/PT (No of patients)*
Clinical characteristics	*Not present (57)*	*Present[#] (32)*	*Present (19)*
M : F ratio	1.0	1.2	1.1
Age (years)*	65.9 (43.6-77.3)	68.6 (55.0-78.2)	67.7 (54.6-79.9)
Disease duration (days)*	8 (5-21)	9 (5-14)	7 (5-14)
Prior infection (%)	40.4	28.1	26.3
General symptoms (%)	19.3	18.8	10.5
Generalized purpura	59.6	46.9	52.6
Skin necroses (%)	43.9	40.6	47.4
Isolated skin involvement (%)	29.8	18.8	21.1
Joint involvement (%)	36.8	40.6	26.3
Arthritis (%)	14.0	15.6	5.3
GI tract involvement (%)	38.6	21.9	26.3
Severe GI tract involvement (%)	8.8	9.4	10.5
Renal involvement (%)	**33.3**	**50.0**	**63.2**
Severe renal involvement (%)	12.3	18.8	21.1
Thrombosis (%)	1.8	3.1	0
IgA level (g/l)*	**3.68 (2.80-4.99)**	**4.56 (3.56-6.71)**	**5.49 (4.49-7.22)**
ESR (mm/h)*	**30 (14-46)**	**53 (34-63)**	**60 (44-70)**
CRP (mg/l)*	**25 (7-45)**	**48 (21-88)**	**43 (18-92)**
BVAS-3*	8 (3-13)	7 (3-13)	8 (3-15)
Legend: [#] at least one aPL antibody present (aCL, aβ2GP1 or aPS/PT), 24 cases were single positive, 8 double or triple positive); M - male; F - female; * median and IQR; severe GI tract involvement - bloody diarrhea or ileus or surgical intervention; severe renal involvement - acute kidney injury or nephrotic syndrome; BVAS-3 - Birmingham vasculitis activity score			

Conclusion: IgA aPS/PT antibodies emerged as a potential marker of renal involvement in adult IgAV.

Reference: 1 Kawakami T,et al. Arthritis Rheum 2008; 59(4):561-7.

Disclosure: A. Hocevar, None; **J. Ostrovrsnik**, None; **P. Žigon**, None; **S. Čučnik**, None; **Z. Rotar**, None; **M. Tomšič**, None.

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Expression Profile of Chemokines Is Skewed to Th17/Th22 Recruitment in Circulation of Patients with Behcet's Disease

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Background/Purpose: Behcet's disease (BD) is an inflammatory disease characterized by ocular, mucosal and skin lesions. However, the pathogenesis of BD is still unknown. Characteristics of histologic findings show granulocyte-dominant immune cell infiltration, suggesting dominancy of innate immune response or "inflammation-like immune response" rather than acquired immune response. Thus, BD is recently proposed to categorize as an autoinflammatory disease. To clarify the pathogenesis of BD and have an answer for activation status of immune system, levels of multiple chemokines in the circulating milieu were assessed as a reflection of the local production of chemokines for the recruitment of immune cells.

Methods: Twenty-seven patients with BD (12 active and 15 inactive patients) and 20 healthy controls were involved. Levels of chemokine in plasma were examined by enzyme-linked immunosorbent assay. Various chemokines were assessed, including RANTES (recruitment of general T cells), CX3CL1 (cytotoxic T cells, NK cells, gamma-delta T cells), MCP-1 (monocytes), CXCL9 (Th1 cells including Th1/Th17 cells, effector CD8+ cells), MIP3a (Th17) 、CCL27 (Th22) to cover recruitment of various lymphocytes. Comparison between 2 groups was assessed by non-parametric Mann-Whitney U-test.

Results: Levels of circulating RANTES, CX3CL1, MCP-1, and CXCL9 were comparable in both groups, suggesting that recruitment of general T cells, monocytes, cytotoxic lymphocytes were not expected based on profiles of these chemokines. On the other hand, plasma concentration of MIP3a and CCL27 were higher in BD compared to healthy controls (MIP3a: 39.6 ± 54.3 versus 14.5 ± 8.9, $P < 0.05$, CCL27: 354.2 ± 150.6 versus 238.3 ± 155.5, $P < 0.05$, respectively), suggesting the association with recruitment of Th17 and Th22. Interestingly, levels of CCL20 was comparable between patients with active disease and those without, whereas CCL27 was higher in patients with inactive disease compared to those with active disease.

Conclusion: In patients with BD, expression profile of the chemokine in circulation is skewed rather than global upregulation, suggesting that pathophysiological process in BD is not a non-specific inflammation from the point of view of chemokines. Upregulation of CCL20 in BD patients and downregulation of CCL27 in active patients might associate with regulation of infiltration of Th17 or Th22 to the lesions, and with pathogenesis of BD.

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Abstract Number: 2963

BehçEt's Disease in Children: Eastern Mediterranean Experience

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Background/Purpose: Behçet's disease (BD) is a variable vessel vasculitis which is more common in adults. The most widely used diagnostic criteria for adult onset disease is the International Behçet's Study Group (ISG) criteria. A new set of criteria for the classification of Behçet's disease (BD) in children (the pediatric BD [PEDBD] criteria) has been proposed recently. To evaluate

the disease activity; there are mainly two severity scores the BD dynamic activity measure (IBDDAM) and BD current activity form (BDCAF). We aimed to test the performance of the PEDBD criteria compared to the ISG criteria and to check the correlation between the severity score systems and physician global assessment (PGA) in pediatric BD patients.

Methods: Two centers from Turkey and one center from Israel participated in this study. The disease onset was ≤16 years of age. As controls, pediatric patients with rheumatologic other diseases.

Results: Sixty-eight BD (44.1% male) patients and 93 control patients were included. The sensitivity and specificity of the PEDBD and the ISG criteria were 73.5%/52.9% and 98.9%/100%, respectively. Thirty-two (47%) patients with BD failed to fulfill the ISG criteria. However, almost all of these patients met the PEDBD criteria. The median (min-max) IBDDAM and BDCAF scores at diagnosis were 6 (1-23) and 4 (1-7) and significantly decreased to 1 (0-8) and 1 (0-4) respectively at latest follow-up ($p<0.001$ for both). The median (min-max) PGA score at diagnosis was 5 (2-9) and significantly decreased to 1 (0-7) at latest follow-up ($p<0.001$). IBDDAM had a strong positive correlation with BDCAF ($r=0.637$; $p<0.001$). PGA positively correlated with BDCAF and IBDDAM ($r=0.502$; $p<0.001$ and $r=0.624$; $p<0.001$, respectively).

Conclusion: In our pediatric series, the PEDBD criteria showed better sensitivity than the ISG criteria and the specificities were close. The higher sensitivity is a big advantage for pediatric patients since early diagnosis is very important. Our study also demonstrated that the severity scores were positively correlated with each other and PGA and thus may be used in clinical practice to evaluate children with BD.

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Thromboangiitis Obliterans (Buerger's disease) : An Observational Study of 174 Patients

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Background/Purpose: Buerger's disease or thromboangiitis obliterans (TAO) is a nonatherosclerotic segmental inflammatory disease of small- and medium-sized arteries of the distal extremities. This disease mainly affect young male tobacco users but the pathophysiology remains unknown. Most series of TAO come from India and Japan. Herein, we aim report to describe clinical presentation, treatment and long-term outcome in a large cohort of TAO.

Methods: We reviewed the charts of 174 [136 (78,2%) male, sex ratio 3.7, mean age at diagnosis of 38,4 years] consecutive french patients with TAO criteria from two french university center of internal medicine diagnosed between 1967 to 2015.

Results: The mean time between onset of symptoms and diagnosis was of 2.5 ±0.7years. One hundred seventy one (98.3%) patients were tobacco users with a mean consumption of 23.4 pack-years and 34 (19.5%) were cannabis consumers. At diagnosis, 15

patients (8.7%) had deep vein thrombosis, 39 (22.5%) superficial vein thrombosis, 76 (43.9%) Raynaud's phenomenon and 14 (8%) arthralgia. Ischaemia of lower limbs, upper limbs and upper-lower limb were found in 98/173 (56.6%), 44/173 (25.4%) and in 18/173 (10.4%) patients, respectively. After a median follow-up of 3 (IQ25 :1 ; IQ 75 8,8) years, 89/171 (52%) had stopped their tobacco consumption and 26/34 (78.8%) their cannabis consumption. One hundred patients (57.4%) were treated by aspirin alone, 33(19%) by clopidogrel alone and 33 (19%) with both treatment. Ninety five (54.6%) had statins, 53 (30.5%) calcic inhibitors, 91 (52.3%) oral vasodilatators, 28 (16.1%) conversion enzyme inhibitors and 117 patients (67.2%) received at least one infusion of ilomedine. Forty five patients (25.9%) had at least one vascular intervention and 12/45 (26.7%) had an amputation. At the end of follow up, 104/169 patients (61.5%) were asymptomatic, 140/174 (80.5%) were amputation free. Among patient with amputation, 15/34 (44.1%) patients had more than one amputation. Mean time between diagnosis and first amputation was of 2.5 years. Two patients died at the end of folow-up.

Conclusion: TAO is a rare vasculitis, with few data coming from western countries. Functional prognosis is very poor with up to 20% of amputation at 3 years.

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Abstract Number: 2965

Late-Onset Relapse in Patients with Systemic Vasculitis

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Background/Purpose: Little is known about the incidence of late-onset relapse in systemic vasculitis. This study examined the incidence of relapse < 2 years and ≥ 2 years after diagnosis in 6 different types of systemic vasculitis.

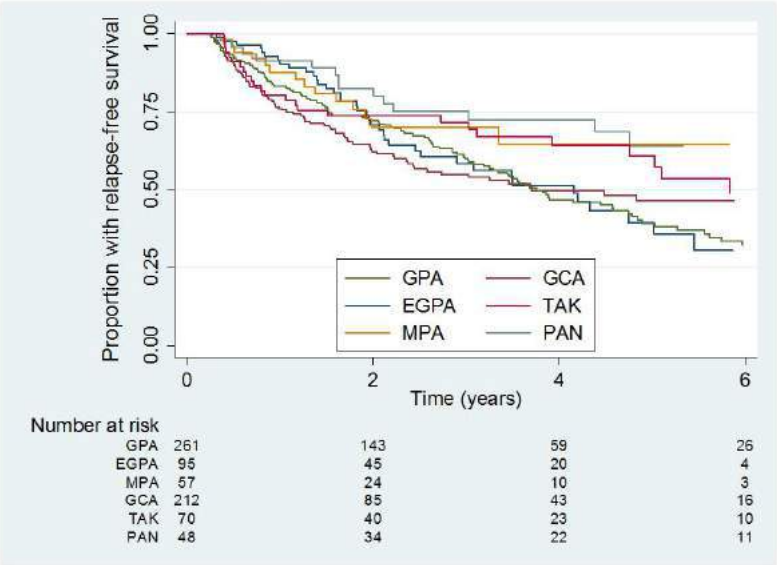
Methods: Data from patients in the Vasculitis Clinical Research Consortium Longitudinal Study, a prospective, multicenter North American cohort, were included if they had no relapse between the date of diagnosis and enrollment into the cohort. 6 vasculitides were studied: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), giant cell arteritis (GCA), Takayasu's arteritis (TAK), and polyarteritis nodosa (PAN). For GPA, EGPA, and MPA, the outcome of relapse was defined as new or worsening Birmingham Vasculitis Activity Score > 0; for GCA, TAK, and

PAN, relapse was defined by physician global assessment > 0. Kaplan-Meier curves of the incidence of relapse over time and incidence rates < 2 years and ≥ 2 years from diagnosis were compared within each type of vasculitis. Use of immunosuppressive medications at time of relapse was examined.

Results: There were 743 patients included in this study: 261 GPA, 95 EGPA, 57 MPA, 212 GCA, 70 TAK, and 48 PAN. The Kaplan-Meier curves for relapse-free survival are shown in **Figure 1**. A significant decrease in the incidence rate of relapse over time was seen in MPA and GCA but not in the other types of vasculitis (**Figure 2**). Among those who relapsed, the proportion on non-glucocorticoid immunosuppressive therapy at the time of relapse was not significantly different between the 2 time periods except for PAN. Compared to patients who relapsed within 2 years of their diagnosis, patients with GPA, GCA, and TAK who relapsed after 2 years were less likely to be on prednisone at the time of relapse.

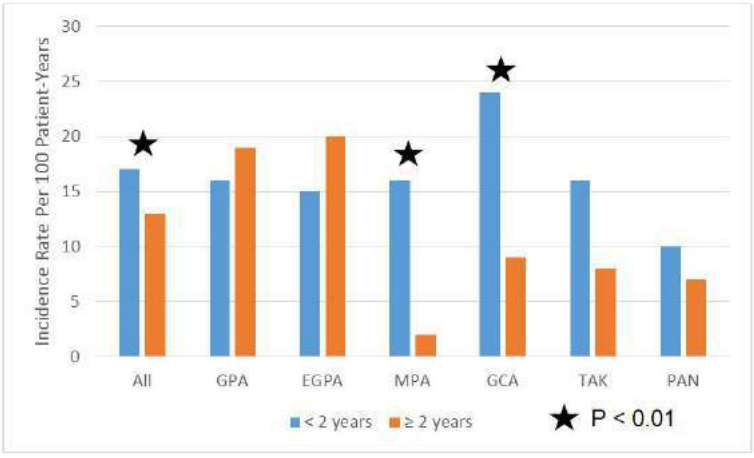
Conclusion: In MPA and GCA, the incidence of relapse significantly decreases after 2 years among those who maintain remission for at least 2 years after diagnosis. However, there are no significant differences in the incidence of relapse after 2 years in GPA, EGPA, TAK, and PAN. Use of maintenance immunosuppressive therapy at time of relapse is not significantly different between those who relapse within or after 2 years, suggesting medications alone cannot account for late-onset relapses. These data indicate that continued close monitoring years after diagnosis is required in patients with systemic vasculitis.

Figure 1. Kaplan-Meier curves for relapse-free survival stratified by vasculitis type.



GPA: granulomatosus with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic granulomatosus with polyangiitis
GCA: giant cell arteritis; TAK:Takayasu's arteritis; PAN: polyarteritis nodosa

Figure 2. Comparison of incidence rate of relapse between < 2 years and ≥ 2 years after diagnosis, stratified by type of vasculitis



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Carette, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2; **G. S. Hoffman**, None; **N. A. Khalidi**, Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2; **C. L. Koening**, None; **J. Krischer**, Bristol-Myers Squibb, 2; **C. A. Langford**, Genentech and Biogen IDEC Inc., 2,GlaxoSmithKline, 2,Bristol-Myers Squibb, 2; **C. A. McAlear**, None; **P. A. Monach**, Genentech and Biogen IDEC Inc., 2,Bristol-Myers Squibb, 2,MedScape, 5,GlaxoSmithKline, 2,Vasculitis Foundation Board of Directors, 6,Editorial Board of Arthritis and Rheumatology, 6; **L. W. Moreland**, Genentech and Biogen IDEC Inc., 2,Pfizer Inc, 2,questcor, 2,Roche Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 5,Boehringer Ingelheim, 5,Acerta, 5,CVS/Caremark, 5,Smith Kline Beecham, 5; **C. Pagnoux**, Chemocentryx, 5,Chemocentryx, 9,Roche Pharmaceuticals, 9,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,Hoffmann-La Roche, Inc., 8; **P. Seo**, None; **U. Specks**, Genentech, 5; **S. R. Ytterberg**, Sanofi-Aventis Pharmaceutical, 5; **P. A. Merkel**, Chemocentryx, 5,Chemocentryx, 9.

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Abstract Number: 2966

Assessment of Damage in Behcet's Disease: Do We Need a Specific Damage Index?

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Background/Purpose: Behcet's Disease (BD) is a systemic vasculitis characterized by involvement of vessels of any size and type. In the course systemic vasculitis, it is important to distinguish disease activity from damage to prevent unnecessary immunosuppression. Damage is also an important surrogate for long-term outcome in vasculitis. Although a well-established validated damage index, "vasculitis damage index" (VDI) is available for vasculitis, its performance in BD has never been assessed. In this study we assessed the damage in BD by using VDI, to determine whether VDI covers all BD-associated damage and lastly to develop a preliminary BD-specific damage index with the obtained data.

Methods: A total of 139 consecutive patients with BD (F/M: 58/81, mean age 38.9±10.9 yrs, disease duration 9.5±7.4 yrs) from a single center were evaluated for damage in a cross-sectional study using the VDI. Considering the patients data and items of VDI with further literature search for BD-specific damages, new items (detailed cardiovascular, ocular, and vascular involvement-, particularly venous disease-related damages) were added to VDI. This modified VDI (Behcet's Disease-VDI [B-VDI]) was also scored in allpatients.

Results: Seventy seven patients (55.4%) had major organ involvement and 105 (75.5%) patients were on immunosupressive (IS) treatment (Table 1). The mean VDI score was 0.3±0.7 and majority of the patients had score "0" ("0" in 107 [77%], "1" in 22 [15.8%], "2" in 7 [5%], "3" in 1 [0.7%], and "4" in 2 [1.4%] patients). The mean B-VDI score was 0.6±1.1 ("0" in 92 [66.2%], "1" in 25 [18%], "2" in 13 [9.4%], "3" in 4 [2.9%] and "4" in 3 [2.2%] patients, "5" in 1 [0.7%], and "6" in 1 [0.7%] patient) and was significantly higher than VDI ($p<0.001$). The main difference between VDI and B-VDI was in vascular (0.05±0.2 vs 0.3±0.6, $p<0.001$) damage items. Both VDI and B-VDI scores were significantly higher in patients with major organ involvement compared to mucocutaneous BD. Both scores were also positively correlated with the age, disease duration and total duration of IS treatment. When individual organ items evaluated, it was observed that damage in patients with major organ involvement was predominantly associated with ocular and vascular involvements. Although VDI-eye and B-VDI-eye scores were not significantly different (both 0.3±0.6, $p=0.32$), B-VDI-vascular scores were significantly higher than VDI-vascular scores both in the entire cohort and in patients with major organ involvement (0.6±0.8 vs 0.1±0.3, $p<0.001$).

Conclusion: Both VDI and B-VDI capture reliable data on damage among patients with BD. However, VDI does not cover all

vascular involvement-related damages of BD. Addition of new items, especially about vascular damage, to VDI will provide more comprehensive damage assessment in BD. Further prospective followup is required to determine the prognostic value of these damage indices in BD.

Table 1. Baseline demographic and clinical characteristics of patients with Behcet's Disease (n=139)*

Age, years	38.9±10.9
Male, n (%)	81 (58.3)
Disease duration, years	9.5±7.4
Oral ulcer, n (%)	139 (100)
Genital ulcer, n (%)	119 (85.6)
Erythema nodosum/folliculitis, n (%)	110 (79.1)
Arthritis, n (%)	84 (60.4)
Ocular involvement, n (%)	55 (39.6)
Vascular involvement, n (%)	41 (29.5)
Gastrointestinal involvement, n (%)	4 (2.9)
Neurologic involvement, n (%)	4 (2.9)
Glucocorticoid treatment, n (%)	86 (61.9)
Immunosuppressives, n (%)	105 (75.5)
Cyclophosphamide	7 (5)
Azathioprine	77 (55.4)
Others	21 (15.1)
Anticoagulant treatment, n (%)	27 (19.4)

*The values are presented as mean±SD, unless indicated otherwise.

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Abstract Number: 2967

Identifying Core Domains for BehçEt's Syndrome Trials: An International Physician and Patient Delphi Exercise

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Background/Purpose: An unmet need for reliable, validated, and widely accepted outcome measures for trials in BehetÕs syndrome (BS) was identified through: i) a systematic review; ii) a survey among BehetÕs experts; and iii) an outcome measures interest group meeting during the 16th International Conference on BehetÕs Disease (1,2). The OMERACT BehetÕs Syndrome Working Group has been working to advance outcome measures in BS with the goal of creating a core set of data-driven measures

for use in clinical trials. To identify domains, subdomains, and outcomes to be assessed in trials of BS, a Delphi exercise among BS experts and patients with BS has been initiated. This abstract describes the results for round 1 of the Delphi.

Methods: A list of possible domains, subdomains, and outcomes was prepared using the results of a systematic literature review on outcomes assessed in previous studies in BS, patient priorities identified through qualitative interviews, and expert opinion. A 3-round Delphi was begun among physicians from different specialties experienced in BS and among patients with BS. The patient survey was the same as the physician survey with medical terms explained. The web-based survey was formatted in both English and Turkish and emailed to 123 physicians and 130 patients. Agreement by ³70% of either physicians or patients resulted in an item being accepted.

Results: 74 physicians and 35 patients participated in Round 1. The physicians were experts in BS from 21 countries and from within a wide range of specialties, including Rheumatology (50%), Ophthalmology (12%), Internal Medicine (12%), Dermatology (16%), Gastroenterology (3%), and Neurology (1%). Among the participating patients there was good representation of each type of organ involvement. Table 1 shows the domains to be measured in all trials in BS that received ³70% endorsement by expert physicians and the additional subdomains endorsed for trials for each type of involvement. In addition to all of the domains identified by physicians, ³70% of patients endorsed the assessment of pain, fatigue, sleep, sexual functioning, psychological functioning, and acute phase reactants in all trials of BS.

Conclusion: Multiple disease-related domains in BS have been identified by physicians and patients as important to address in clinical trials, suggesting that a core set for all trials will be needed and subdomains for subsets of disease (specific manifestations) will also be useful. Rating and ranking of these domains and subdomains in the next 2 rounds will enable the development of a core set of domains to be assessed in clinical trials of BS. **Table 1. Domains and subdomains of BehetÕs syndrome endorsed by ³70% of physician-experts as necessary to measure in clinical trials**

Topic of the Clinical Trial in BehetÕs Syndrome						
All Trials	**Mucocutaneous**	**Eye**	**Vascular**	**Nervous System**	**Gastro-intestinal**	**Joint**
Activity	Number of oral ulcers	Visual Acuity	Disease related damage	Headache	Abdominal pain	Number of arthritis episodes
Function	Number of genital ulcers	Blurry vision	Post-thrombotic syndrome	Progression on MRI	Clinical remission	Duration of arthritis episodes
Damage	Pain of oral ulcers	Retinal vasculitis	New venous thrombus	Cognitive functioning	Endoscopic remission	Tender joint count
Remission	Pain of genital ulcers	Cystoid macula edema	Extended venous thrombus	Headache	Diarrhea	Swollen joint count
Patient global assessment	Duration of oral ulcers	Ocular attack	New aneurysm			Physical function
Physician global assessment	Duration of genital ulcers		New arterial thrombus			
Quality of life	Duration of nodular lesions		Hemoptysis			
Work productivity	New organ involvement					
Death						

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Efficacy of Anti-TNF Alpha in Severe and Refractory Cardiovascular Involvement of Behcet's Disease: A Multicenter Observational Study of 18 Patients

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Background/Purpose: In Behçet's disease (BD), vascular complications affect more than 30% patients. Cardiovascular involvement is the main cause of death, especially for pulmonary or aortic aneurysms and large vein thrombosis. Immunosuppressants (azathioprine, methotrexate, cyclophosphamide) are not always effective and are often associated with significant side effects. TNF antagonists have been shown to be very quickly effective in severe ocular manifestations of BD. Data on their efficacy in BD vascular complications are scarce. Objectives: To evaluate the efficacy and safety of anti-TNF alpha in severe and/or refractory vascular involvements in BD.

Methods: A multicenter and observational study evaluating 18 patients with severe BD associated- cardiac or vascular disease (defined by international standards) treated with anti-TNF [infliximab (n=15) and adalimumab (n=3)]. Anti-TNF alpha antibodies were initiated because of severe aneurysmal arterial disease [lung (n=4) or the aorta/one of its branches (n=4) or peripheral (n=1)] and/or large vein thrombosis [pulmonary artery (n=7), thrombosis of the inferior vena cava (n = 4) or Budd-Chiari syndrome (n=3)] and/or cardiac involvement [aortic valve disease (n=1), left ventricular aneurysm (n=1), myocardial ischemia (n=1) or intra-cardiac thrombosis (n=2)]. Clinical remission was defined by resolution of clinical and biological symptoms and the absence of occurrence of new vascular lesions or worsening of existing vascular lesions.

Results: Eighteen patients [(89% male) with mean age of 30 [10; 55] years] were included. Fourteen (78%) were refractory to immunosuppressants (n=12) and / or high doses of systemic corticosteroids (n=2). Fifteen patients received infliximab injections [5mg / kg (n=13) and 3mg / kg (n=2)] and 3 adalimumab [40mg / 15 days]. Fourteen patients also received immunosuppressants [azathioprine (n=7), methotrexate (n=5), mycophenolate mofetil (n=2)] and 17 corticosteroids associated with anti-TNF alpha. Vascular lesions observed (before or at the same time of anti-TNF initiation) included: arterial aneurysms (n=11), [pulmonary (n=7), aortic (n=3), spleen (n=1) or peripheral (n = 3)], arterial occlusions (n=3) and / or venous thrombosis [pulmonary embolism (n=9), lower vena cava thrombosis (n=7), deep venous thrombosis of lower limbs (n = 2) or Budd-Chiari syndrome (n=4)]. Eight patients also had cardiac involvement [intracardiac thrombosis (n=4), valvulopathy (n=2), myocardial ischemia (n=2) or pericardial effusion (n=1)]. Vascular remission was achieved in 16 patients (89%), partial (n=3) or complete (n=13). No patients died and 2 relapsed under TNF-antagonists. Two patients who stopped anti-TNFα antibodies [side effect (n=1) and poor compliance (n=1)] had neurological or vascular flare 3 and 5 months after treatment cessation, respectively. Side effects were observed in 4 patients [pulmonary edema (n=1) infection (n=3)], requiring discontinuation in 2 patients. After a median follow up of 15 [4, 164] months, 16/18 were still under anti-TNF [cessation for side effects (n=2)]. The median dose of corticosteroids was

significantly decreased in all patients at 12 months after treatment initiation [30 mg initially versus 6 mg, p=0.004]. At the end of follow-up, 94% achieved a dose of ≤10mg corticosteroids.

Conclusion: Anti TNFα antibodies represent an effective and safe treatment in 89% of BD patients with severe and refractory cardiovascular involvement. Results: Conclusion:

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10 Year Retrospective Analysis of 276 Cases of Histopathologically Confirmed Leukocytoclastic Vasculitis

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Background/Purpose: We identified leukocytoclastic vasculitis (LCV) patients seen over 10 years at our institution. Aims included 1) define cause; 2) record lab, imaging, and ancillary tests used in evaluation; 3) tabulate Medicare reimbursement costs.

Methods: All biopsy-confirmed LCV cases from 1/1/2004 to 12/31/2014 were identified by analysis of suspected cases in Dermatopathology registry. We analyzed pathology reports and only those cases with definite LCV on biopsy and available electronic health record (EHR) progress notes were included in this analysis. Clinical, epidemiologic, and other variables were then extracted from EHR and costs recorded. We calculated total lab and imaging costs, plus average costs/patient. Additionally, we determined if Rheumatology or other consultations were performed.

Results: Mean age of LCV cohort was 53.1 years, with 161 women, 115 men. Immunofluorescence was performed in 161/276 (58 %) biopsies. LCV etiology was divided into 6 major categories (Table 1), with Idiopathic in 41 %; Vasculitis in 32 %; Drug-induced 10 %; Infection-related 9 %; CTD 4 %; malignancy-related 3 %. Vasculitis or CTD accounted for 101/276 cases (Table 1). More than 50 % of Vasculitis cases were due to HSP. The HSP group mean age was 33 years, with 23/52 (44 %) being < 20 years old. Surprisingly, 56 % of our HSP patients were adults. Specific lab and imaging tests are shown in Tables 2 and 3. Total lab costs for all patients were $36,161 or $131/patient. Total imaging costs were $85,700 or $311/patient. Rheumatology accounted for 138/147 requested consultations (94%) at cost of $20,806. Nine renal biopsies were performed at $10,782 cost. Glucocorticoid therapy was used in 148/276 or 54 % cases.

Table 1: Causes of LCV (N= 276)			
1.	**Idiopathic**	**113**	**41%**
2.	**Vasculitis**	**89**	**32%**
	HSP	52	
	Cryoglobinemic	6	
	ANCA associated	10	
	PAN	6	
	Arteritis not otherwise specified	15	
3.	**Drugs**	**28**	**10%**
4.	**Infections**	**25**	**9%**
	Hepatitis C	4	
	Streptococcus	4	
	Staphylococcus	5	
	C-difficile	1	
	Viral	3	
	Other	8	
5.	**CTDs**	**12**	**4%**
	RA	5	
	SLE	4	
	Other	3	
6.	**Malignancy**	**9**	**3%**
	Solid Organ	5	
	Multiple Myeloma	2	
	MDS	2	

Table 2: Labs/Medicare Reimbursement (Costs)			
	Lab	N = 276	Percent Ordered
1	CBC	264	95.6%
2	BMP	263	95.2%
3	LFTs	245	88.7%
4	ESR/ CRP	210	76%
5	ANA	204	73.9%
6	Hepatitis Testing	148	53.6%
7	UA	234	84.7%
8	Streptococcal Testing	34	12.3%
Cost	***Total Imaging costs = $85,700**	**276**	**$311/patient**

Table 3: Imaging Tests/Medicare Reimbursement (Costs)			
	Test	N = 276	Percent Ordered
1	CXR	113	40.9%
2	Echocardiogram	56	20.3%
3	CT Abdomen/Pelvis	51	18.3%
4	CT Chest	48	17.4%
Cost	***Total Imaging costs = $85,700**	**276**	**$311/patient**

Conclusion: Our report of 276 biopsy-confirmed LCV patients seen over this 10 year period may be the largest analysis so performed. Idiopathic (41 %) and Vasculitis (32 %) were the most common causes. Definite Rheumatic disease (Vasculitis/CTD) was identified as cause of LCV in 36 % of patients. Within the Vasculitis group, HSP comprised more than 50 % of that subgroup, with a surprising 56 % adult-HSP. Importantly, our study includes a unique cost analysis for lab, diagnostic imaging, consultations, and renal biopsy. The evaluation of LCV remains clinically challenging and more costly than previously reported.

Disclosure: S. Butt, None; **T. Olenginski**, None.

histopathologically-confirmed-leukocytoclastic-vasculitis

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Incidence and Characteristics of Vasculitis Associated with Monoclonal Antibodies and Peptide Fusion Proteins: A Survey from the French National Pharmacovigilance Database

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Background/Purpose: Immunological classes of adverse events (AEs), including the immune related AEs and the paradoxical effects, have emerged with the used of biologics. Among them, vasculitis associated with TNF inhibitors has already been reported. As infections, cancers, and autoimmune diseases must be investigated in the vasculitis work-up, vasculitis secondary to biologics remain challenging for clinicians. Indeed, we investigate the incidence and the characteristics of vasculitis-associated with monoclonal antibodies (Mabs) and Fc-fusion proteins in real life.

Methods : A retrospective analysis of charts registered in the French National Pharmacovigilance Database (FNPVD) under the diagnosis of vasculitis in adults patients treated with approved Mabs or Fc-fusion proteins was performed between 1985 and 2015. After reviewing of the cases, the demographics and clinical data were recorded. Exposure to biologics proteins was searched to the observatory of drugs, medical devices and therapeutic innovation (OMEDIT) in order to estimate the incidence.

Results: During the study period, 434 423 AEs were registered in the BNPV leading to 143 clinical suspicions of vasculitis. Thus, the incidence of vasculitis is reported in table 1. Among the 143 vasculitis, 79 biopsy-proven vasculitis were analyzed showing a mean age at diagnosis of 51±17 years with a predominantly comprising women (65%). The therapeutic indications were autoimmune diseases in 69 patients, followed by solid cancers, with a significantly longer time to onset of vasculitis between patients with autoimmune diseases as compared with non-autoimmune diseases (244 vs 32 days, $P = .01$). TNF inhibitors were involved in 60 patients (76%). Rituximab, tocilizumab, cetuximab, trastuzumab, abatacept, and ranibizumab were less common. Indeed, patients undergoing anti-TNF biologics had a significantly later occurrence of the vasculitis as compared with the other drugs (318 vs 30 days, $P = .0002$). Cutaneous vasculitis (63%) was the most frequent as compared with systemic vasculitis. No difference was found between patients with cutaneous vasculitis and systemic vasculitis in terms of the age of onset (52 vs 48 years, $P = .2806$), the sex ratio ($P = .1159$), the median time to onset (196 vs 289 days; $P = .258$), and the therapeutic indications ($P = .2482$), except for higher extracutaneous manifestations in those with systemic vasculitis ($P = .0022$).

Biologics	Number of cases (2011-2014)	Number of courses (2011-2014)	Incidence/ 10^4 courses 95% CI
etanercept	7	5075	14 [5-28]
certolizumab	5	3487	14 [5-33]
adalimumab	17	35 020	5 [3-7]
tocilizumab	11	197 425	0,6 [0,3-0,9]
infliximab	15	628 395	0,3 [0,2-0,4]
rituximab	8	560 477	0,1 [0,05-0,2]

Table 1. Incidence of vasculitis under biologics treatment.

Conclusion: Vasculitis associated with Mabs and Fc-fusion proteins are rare and potentially challenging cases. TNF-inhibitors

remain usual suspects, mostly etanercept and certolizumab in our study. However, our data report other biologics that should be kept in mind. Moreover, systemic vasculitis, IgA vasculitis being the most frequent, need a more specific recognition for a specific management, including immunosuppressant.

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Characteristics and Management of IgA Vasculitis (Henoch-Schönlein purpura) in Adults: Data from the 260 Patients Included in the Igavas Survey

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Background/Purpose: Data on adults IgA vasculitis (IgAV) are lacking. This survey was designed to better define clinical spectrum and efficacy of treatments in this population.

Methods: We analyzed data from 260 patients with IgAV included in a French multicenter retrospective IGAVAS survey.

Results: Mean age at diagnosis was 50.1±18 years, and 63% of patients were male. At baseline, manifestations included purpura (100%), arthralgia or arthritis (62%), glomerulonephritis (70%) or gastro-intestinal involvement (53%). Thirty percent of the patients showed renal failure (eGFR <60ml/min/1.73m^2). Median eGFR in patients with renal involvement was 88 mL/min/1.73m^2 (Q1-Q3: 55; 103), median proteinuria level 1.5 g/day (Q1-Q3: 0.6; 3), and hematuria was noted in 88%. Median serum IgA level was 3.6 g/L (Q1-Q3: 2.7; 4.8) and 85/159 patients (53%) presented with elevated IgA levels. Skin biopsy demonstrated leukocytoclastic vasculitis in 205 patients (92%). Direct immunofluorescence revealed IgA and complement deposition in dermis blood vessels in 174/216 (81%) and 47/222 (21%) of patients, respectively. Renal biopsy demonstrated mesangial IgA deposits in 142/144 patients (99%) and extracapillary proliferation in 59/143 patients (41%). Data concerning therapeutic efficacy was available and analyzed in 127 patients. In univariate analysis, global response (complete or partial) was achieved in 80% (64/80) in patients treated with corticosteroids (CS) alone compared to 77% (23/30) in patients treated with CS and cyclophosphamide (CYC) (p=0.17). Multivariate analysis using inverse weighting on propensity score revealed that patients treated with CS plus CYC had higher response rate than patients treated with CS alone [OR (95% CI) 2.33 (1.29-4.18), p=0.005]. Sensivity analysis excluding outliers confirmed this result [OR 1.79 (1.00-3.20), p=0.049]. Conversely, full multivariate model without propensity score did not demonstrate a benefit of CS plus CYC compared to CS alone [OR 0.88 (0.29-2.67), p=0.82], or after adjustment on propensity score [OR 0.90 (0.29-2.78), p=0.86]. After median follow-up of 17.2 months (Q1-Q3: 9.1-38.3) corresponding to 593 patient-years, 8 patients died, including 3 deaths directly related to IgAV (2 mesenteric ischemia and 1 multivisceral failure). Eight patients experienced end-stage renal failure treated by renal transplantation (n=2) or dialysis (n=6). Among patients who received a treatment, 15 experienced minor relapse (14%) and 9 (8%) major relapse during the first 12 months after treatment.

Conclusion: In conclusion, this series provides interesting data on clinical and histological presentation and therapeutic efficacy, suggesting that CS alone appears to be a reasonable first-line therapy in patients with systemic IgAV, while the benefit of adding CYC to CS remains uncertain.

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Vaccination and Risk of Childhood IgA Vasculitis (Henoch–Schönlein): A Case-Crossover Analysis

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Background/Purpose: The etiology of IgA vasculitis (Henoch–Schönlein, IgAV), the most common systemic vasculitis in children, is unknown, although seasonality in disease onset and clinical observation strongly suggest an etiopathogenic link with preceding infectious episodes. There is also some concern that IgAV may occur after vaccination. Thus, the evidence for the relationship between vaccination and IgAV is essentially based on case reports, and robust pharmacoepidemiological data (e.g., from case–control studies) are lacking. We performed a case-crossover study, a variant of a traditional case–control study in which each case

serves as its own control, to investigate the effect of vaccination on short-term risk of IgAV.

Methods: The study enrolled children (≤17 years old) with newly or previously diagnosed IgAV fulfilling the EULAR/PReS classification criteria and who were seen in 4 pediatric hospitals from 2011 to 2016. Data on vaccinations administered during the 12 months before IgAV onset were retrieved from the children's immunization records. With a case-crossover analysis, we calculated odds ratios (OR) on conditional logistic regression by comparing exposure to vaccination in the 3-month "index period" immediately preceding disease onset with exposure in 3 consecutive 3-month "control" periods immediately before the "index period". A minimal sample size of 150 children was determined to detect a statistically significant OR ≥2.5 under the assumption of a baseline exposure to vaccines of 5% in each 3-month control period. On sensitivity analyses, we used 1 or 2-month windows for the index and control periods.

Results: We enrolled 167 children with IgAV (mean age 6.7 years, 52% boys) for whom complete information on vaccine exposure could be obtained; 42 (25%) received ≥1 vaccination during the 12 months before IgAV onset. The total recorded 54 vaccine doses mainly involved diphtheria-tetanus-pertussis-poliomyelitis (n=14), diphtheria-tetanus-poliomyelitis (n=12), hepatitis A (n=8), meningococcal (n=7), and measles-mumps-rubella vaccines (n=5). Fifteen children (9%) were vaccinated during the 3-month index period as compared to 4% to 7% in the 3 control periods. The OR for IgAV within 3 months of a vaccination was 1.6 (95%: CI 0.8–3.0). Analyses based on IgAV risk within 1 or 2 months of vaccination yielded ORs of 1.4 (95% CI: 0.5–3.5) and 1.3 (95% CI: 0.6–2.6), respectively. Seasonal distribution of IgAV onset was 25%, 35%, 26% and 13% for fall, winter, spring and summer, respectively; the corresponding proportions for seasonal distribution of vaccine administration were 28%, 28%, 13% and 32%.

Conclusion: This study does not support vaccination as a major etiological factor of childhood IgAV.

Disclosure: M. Piram, None; **F. Madhi**, None; **T. Ulinski**, None; **A. Mahr**, None.

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Abstract Number: 2973

A Comparison of Caregiving Burden and Impact in Systemic Vasculitis Versus Other Conditions

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Session Time: 9:00AM-11:00AM

Background/Purpose: Serving as an informal caregiver to a family member or friend with a chronic illness is associated with stress, reduced health status, and financial burden. However, effects of caregiving vary across conditions. We compared caregiving impact among caregivers of systemic vasculitis patients versus caregivers for other conditions.

Methods: Caregivers of systemic vasculitis patients (n=68) were recruited for an online survey via 1) direct mailings to patients in vasculitis registries at two large academic medical centers asking patients to share study information with their "primary vasculitis support person"; and 2) announcements via vasculitis support groups and social media. The survey included validated measures of caregiving activities, impact, and burden. Primary outcomes included number of days in the past 30 days of 1) poor mental health, 2) poor physical health, and 3) poor sleep; as well as 4) greatest caregiving difficulty (financial burden, not enough time for self, not enough time for family, interferes with work, creates stress, affects family relationships, other difficulty, or no difficulty). We constructed a comparison sample of non-vasculitis caregivers using publically available data from the Behavioral Risk Factor

Surveillance Survey (BRFSS), an annual telephone survey of a random sample of community-dwelling, U.S. adults. We used data from five states administering an optional caregiving module in 2009-10, in which those who report providing regular assistance to a friend/family member with a health problem were asked questions about caregiving, including the four caregiving impact and burden items asked of vasculitis caregivers described above. Because analyses revealed that all vasculitis caregivers in our sample were White, non-Hispanic and had health insurance, we limited the BRFSS sample to respondents with these characteristics (n=4,636). Chi-square tests and logistic regression were used to compare the caregiving impact variables for vasculitis vs. BRFSS caregivers before and after controlling for education, age, sex, and relationship to the patient (spouse vs. other).

Results: In unadjusted analyses, vasculitis vs. BRFSS caregivers were more likely to report ≥1 day of poor mental health (72.1% vs. 35.3%, p<.001), ≥1 day of poor sleep (82.4% vs 68.6 %, p<.05), and ≥1 day of poor physical health (51.5% vs. 37.8%, p = .059) in the past month. Vasculitis caregivers were also more likely to report caregiving difficulty (76.5% vs. 58.9%, p<.001), and that caregiving created financial burden (10.3% vs. 4.7%, p<.05) and stress (38.2% vs. 23.3%, p<.01). In multivariate logistic regression models, vasculitis caregivers had increased odds of poor physical health (OR = 1.81, CI 1.10-2.97), poor mental health (OR = 4.51, CI 2.59-7.86), and poor sleep (OR 2.35 CI 1.19-4.63), but no significant difference in caregiving difficulties.

Conclusion: Vasculitis caregivers may experience increased burden and negative impact from caregiving relative to caregivers for patients with other conditions. More efforts are needed to develop supportive interventions to understand and address the specific needs of caregivers of persons with vasculitis.

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Abstract Number: 2974

An Outcome Survey of 100 Patients with Cerebral Venous Sinus Thrombosis Due to Behcet's Syndrome Followed up at a Single, Dedicated Center

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Background/Purpose: Behçet's syndrome (BS) is a well-recognized cause of cerebral venous sinus thrombosis (CVST). We assessed the outcome of a large cohort of patients with CVST due to BS attending a single dedicated center.

Methods: We identified 100 (81 M/19 F) patients with BS who were diagnosed as having CVST. All contacted were called back to the outpatient clinic for a clinical, neurological and ophthalmological examination and cranial MRI /MR venography.

Results: Results: The mean age of the patients at the onset of the symptoms was 28 ± 10 years. A total of 48 patients developed CVST before or at the onset of ISG fulfillment, while 52 developed CVST after a median 3 [2-8] years of ISG fulfillment. Superior sagittal (n=47) and transverse sinuses (n=46) were most commonly involved followed by sigmoid sinus (n= 26) and jugular vein thrombosis (n= 15). A total of 59 (53 M/ 6 F) patients had vascular involvement in addition to CVST: these were deep vein thrombosis of the lower extremities (n= 47), pulmonary artery involvement (n = 17), Budd-Chiari syndrome (n= 9), vena cava

superior thrombosis (n= 6) and major arterial disease (n=3). In about half (32/59), CVST preceded any type of additional vascular involvement. Apart from vascular involvement, eye involvement was seen in 37 patients, parenchymal CNS involvement in 8 (all later than CVST) and gastrointestinal involvement in 5. Seven patients (all male) had died, due to causes unrelated with CVST. By the end of the study (December 2015), all remaining 87 patients were alive and contacted with a median follow-up time of 11 [6-15] years. Only 6 patients had a relapsing CVST course. Information about medical treatment was present in detail in 87 patients of whom 75 received short courses of glucocorticoids with (n=12) or without anti-coagulants. A total of 81 patients received immunosuppressive agents, most commonly azathioprine. Four patients underwent lumbo-peritoneal shunting surgery (1 was successful) and 1 with arterio-venous fistula underwent vascular embolization. By the end of December 2015, a total of 50 patients were re-evaluated at the clinic. None had of symptoms of intracranial hypertension. Ophthalmological examination showed that 17 patients had complications such as bilateral optic atrophy (n= 3), bilateral papilledema (n= 5), bilateral optic disc pallor (n=4) and fibrotic scars around optic disc (n= 5). Sensorineural type hearing loss was detected in 4 patients. Neurological examination was found to be normal among 43 patients with isolated CSVT, whereas abnormal in the remaining 7 patients with concomitant parenchymal CNS involvement. Cranial MR/MR venographies at the end of follow-up, were abnormal in 36 patients showing occlusion/ irregularity/ hypoplasia or collaterals in the sagittal (n=19) or transverse sinus (n=17). In the remaining 14, MR venographies were normal.

Conclusion: CVST due to BS is closely associated with vascular involvement in the body and may be considered as a risk factor for future vascular involvement. CVST relapses are rare; however, the course is not uneventful: visual acuity or field may be impaired totally or partially because of optic disc atrophy; in addition hearing deficits may occur.

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Abstract Number: 2975

Increase of Sacroiliitis By Follow-up and Routine CT in Patients with Behcet's Disease

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Background/Purpose: Widely various frequencies of sacroiliitis or spondylitis have been reported in different regions of patients with Behcet's Disease (BD). Although BD is also called Silk Road Disease, there are no reports about association of axial arthritis in patients with BD in China.

Methods: To determine the real frequency in our region, we followed up the disease history and routinely performed the axial joints CT scan in the 192 patients with BD who were treated in our hospital from January 2010 to June 2015.

Results: Among them, 28 cases showed sacroiliitis before follow-up (14.58%) and increased to 112 cases after (58.33%). Besides sacroiliitis, 192 cases had recurrent oral aphthous ulcers (100%), 111 cases skin lesions (57.8%), 117 cases genital ulcerations (60.9%), 70 cases ocular symptoms (36.5%), 78 cases peripheral arthritis (40.6%),76 cases axial skeleton involvement (39.6%), and 35 cases heel pain (18.2%). The 112 cases were found different degree of pathological changes of sacroiliac joint by CT scan. Consistently, the frequency of BD patients with SpA increased from 3.6% (ASAS) or 2.6% (Amor) before to 42.19% (ASAS) or

29.69 % (Amor) after follow-up.

Conclusion: The frequency of sacroiliitis and SpA in BD patients was increased by following up disease history and routinely examining sacroiliac joint by CT scan. Moreover, the frequency in our region was significantly higher than that in other regions reported before. All above suggest that missed diagnosis is also a possible reason for the lower frequency of axial arthritis and the BD patients in our region may have more severe manifestations.

Disclosure: Q. Chen, None; **J. Li**, None; **C. Gao**, None; **H. Wen**, None; **X. Li**, None.

Abstract Number: 2976

Disease Flares and Persistent Low-Level of Disease: Long-Term Outcome in a Cohort of Patients with BehçEt's Disease

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Background/Purpose: Behçet's disease (BD) is a multisystemic, chronic relapsing inflammatory disease classified among the vasculitis. Neurological and eye involvement are two of the most serious manifestation of BD and both still represent significant causes of morbidity. The primary aim of the study was to evaluate the long-term outcome in a cohort of patents with BD; the secondary aim was to explore any potential correlation between long-term outcome and demographic and clinical profile.

Methods: The study enrolled 122 patients, all fulfilling the International Study Group (ISG) criteria for BD. The male/female ratio was 1.6:1, with a mean disease duration of 11±4 years. Their mean age was 42±9 years (min:18, max:77), while the mean age at disease onset was 25±4 years. The mean ± SD duration of follow-up at our centre was 10±2 years. Long-term outcome was evaluated by means of disease flares according the BD Current Activity Form (BDCAF), persistent low-level of disease (defined as a level minimal activity of disease requiring only low-medium doses of corticosteroids), and disease damage according the Vasculitis Damage Index (VDI). The statistical analysis was performed using Student t-test, Mann-Whitney-U test, ANOVA and Pearson correlation

Results: The main clinical features presented during the follow-up by the cohort were: mucocutaneous involvement (100%), joint involvement (49%), ocular involvement (40%), neurological involvement (38%), vascular thrombotic events (22%), gastro-enteric involvement (16%). Globally, we observed 108 episodes of disease flare, of which: 25% of patients with neurological involvement, 60% of ocular involvement, 50% of muco-cutaneous involvement, 12% of joint involvement, 50% of vascular involvement and 28% of gastro-enteric involvement. Thirty-four patients presented a persistent low-level disease, that required a medium corticosteroids dose of 4 mg of 6-methylprednisolone. Moreover, 39 patients presented a VDI > 1. A significant correlation was found between disease flares and younger age and male sex; persistent low-level of disease and disease damage resulted significantly associated with early onset of disease and high number of disease flare in the first 2 years of disease. Notably, persistent low-level of disease and disease damage resulted inversely correlated with the use of anti TNF alpha agents, independently of the type of organ involvement.

Conclusion: As literature data suggest, a specific demographic profile exists of poor outcome in BD, represented by young males. The use of anti TNF alpha agents is associated with a positive effect on maintaining remission of disease, most likely due to their steroid sparing effect.

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Abstract Number: 2977

Treatment of Cryoglobulinemic Vasculitis with Sofosbuvir in Four Combination Protocols

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Background/Purpose: Cryoglobulinemic Vasculitis (CV) is a systemic vasculitis affecting small and medium-sized vessels. Following emergence of direct acting antiviral drugs, which paved the way to avoid both the side effects of immunosuppressive treatments; and also Interferon. The aim of our study was to assess the effect of Sofosbuvir in the treatment of HCV- CV manifestations

Methods: This is a multicenter interventional treatment trial, including 26 Egyptian patients and 9 Italian patients with CV, diagnosed according to the Classification criteria of Cryoglobulinemic Vasculitis, which were validated in 2014. Patients were treated with Sofosbuvir following four treatment protocols: 1- Sofosbuvir + Ribavirin for 6 months, 2- Sofosbuvir + Ribavirin + Interferon for 3 months, 3- Sofosbuvir + Daclatasvir for 3 months, and 4- Sofosbuvir + Simeprevir for 3 months. Clinical assessment (according to the Classification criteria of CV), cryocrit %, C4 serum level and serum level of rheumatoid factor (RF), were recorded soon before and at the end of the treatment. Response was assessed as complete, partial or absent (no response). Analytical procedures used were Pearson Chi-Square and Wilcoxon tests as indicated.

Results: 35 patients (24 females, mean age 56 ± 11 y) were enrolled in the study. Sixteen patients showed liver cirrhosis. All patients were Child- Pugh A stage. 13,8,5,9 patients were treated by first, second, third, fourth protocol, respectively. All patients showed a sustained viral response (SVR). All patients had purpura and all of them responded to treatment. 35 patients had Fatigue and 24 patients had fibromyalgia, 34, 22 patients responded respectively. 26 patients had arthralgia and 23 patients had non erosive arthritis, 22, 20 patients responded respectively. 13 patients had Raynaud's phenomenon and 2 patients had fibromyalgia, 12, 2 patients responded respectively after treatment. 25 patients had Peripheral poly neuropathy with total response after treatment in 21 patients. One of our patients had leg ulcer and mono- neuritis multiplex with complete response and completely healed ulcer after treatment. Nephritis was diagnosed in two patients, one of them had proteinuria and renal impairment and another one had proteinuria only, with total improvement of both by antiviral therapy alone. Serum level of Cryocrit (P value < 0.0001), RF (P value= 0.004), C4 (P value= 0.003), significantly decreased after treatment.

Conclusion: Antiviral combination therapy including Sofosbuvir appears very effective in the treatment of the most frequent CV manifestations. Since laboratory signs of CV improved but did not disappear, long-term clinical and biological effects of SVR by Sofosbuvir should be studied

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Abstract Number: 2978

Psychiatric Involvement and Behcet'S Syndrome: Does Bipolar Disorder Represent a Clinical Feature of the Disease?

Rosaria Talarico[1], Elena Elefante[2], Laura Palagini[3], Anna d'Ascanio[4], Chiara Stagnaro[4], Chiara Tani[4], Chiara Baldini[4], Rossella Neri[1] and Marta Mosca[4], [1]Rheumatology Unit, University of Pisa, PISA, Italy, [2]RHEUMATOLOGY UNIT, University of Pisa, Pisa, Italy, [3]Psychiatric Unit, University, PISA, Italy, [4]Rheumatology Unit, University of Pisa, Pisa, Italy

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Background/Purpose: Frequency of psychiatric disorders in Behçet's syndrome (BS) is a debated issue: while some experts attribute their presence to the chronicity of the illness, others think that they may be imputable to disease activity or to intrinsic features of the disease. The primary aims were to determine the frequency of psychiatric disorders in BS patients, both with neurological involvement or without; the secondary aims were: to investigate a possible association between disease activity/organ involvement and psychiatric profile of the BS patients and to compare the distribution of psychiatric disorders of patients with BS with those in patients with other chronic diseases.

Methods: One hundred and six-teen BS patients with a diagnosis of BS according the ISG criteria were studied. Demographic profile of the cohort studied are summarised in **Table 1**. Psychiatric disorders evaluated were: bipolar disorder, obsessive-compulsive disorder, depression and sleep disorders. Age and sex matched disease controls of systemic lupus erythematosus (SLE) and chronic arterial hypertension were included.

	Neuro- BS	**BS without neurological involvement**
Number of patients	46	70
M/F	36/10	44/26
Mean age ± SD (min-max) (years)	43±6 (15-68)	42±8 (18-71)
Mean disease duration ± SD (min-max) (years)	9±2 (2-28)	10±2 (3-28)

Table 1. Demographic profile.

Results: Prevalence of psychiatric disorders are shown in **Table 2**.

psychiatric disorders	**Neuro- BS %**	**BS without neurological involvement %**
bipolar disorder	67	64
obsessive-compulsive disorder	46	43
depression	32	36
sleep disorders	11	16

Table 2. Prevalence of psychiatric disorders.

The frequency of bipolar disorder resulted significantly higher than in disease controls ($p < 0.001$). Moreover, we found a

significant correlation between disease activity (evaluated by BDCAF) and the presence of bipolar disorder. No correlations were found between the presence of psychiatric disorders and organ involvement.

Conclusion: Our results show a high frequency of psychiatric disorders in BS patients. This elevated frequency, both in BS patient with or without neurological involvement, strongly suggest that BS patients may be characterised by a specific psychiatric profile. The correlation between disease activity and bipolar disorder could provide the basis for further analysis on lager cohorts, in order to better explore the mechanisms responsible for the occurrence of psychiatric disorders and BS .

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Abstract Number: 2979

a Systematic Literature Review on the Treatment of Skin, Mucosa and Joint Involvement of BehçEt's Syndrome Informing the Eular Recommendations for the Management of BehçEt's Syndrome

Pietro Leccese[1], Yesim Ozguler[2], Robin Christensen[3], Sinem Nihal Esatoglu[4], Dongsik Bang[5], Bahram Bodaghi[6], Aykut Ferhat Celik[7], Farida Fortune[8], Julien Gaudric[9], Ahmet Gul[10], Ina Kotter[11], Alfred Mahr[12], Robert J Moots[13], Ignazio Olivieri[14], Jutta Richter[15], David Saadoun[16], Carlo Salvarani[17], Frances Scuderi[18], PETROS P SFIKAKIS[19], Aksel Siva[20], Miles Stanford[21], Ilknur Tugal-tutkun[22], Richard West[23], Sebahattin Yurdakul[2], Hasan Yazici[2] and Gulen Hatemi[2], [1]Rheumatology, Rheumatology Department of Lucania, San Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera, Matera, Italy, Matera, Italy, [2]Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey, [3]The Parker instutute, RC, Copenhagen, Denmark, [4]Rheumatology, Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Rheumatology, Istanbul, Turkey, [5]Department of Dermatology, Severance Hospital, Cutaneous Biology Research Institute, Yonsei University College of Medicine, Seoul, Korea, Seoul, Korea, The Democratic People's Republic of, [6]Ophthalmology, Pierre and Marie Curie University - Paris 6 Paris, France, Paris, France, [7]Istanbul University, Cerrahpasa Medical Faculty, Department of Internal Medicine, Division of Gastroenterology, Istanbul, Turkey, [8]Dental Institute, Barts and The London NHS Trust, London, United Kingdom, [9]Department of Vascular surgery GHPS, Paris, France, [10]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [11]Internal Medicine, Robert-Bosch-Hospital, Stuttgart, Germany, [12]Hospital Saint-Louis, Paris, France, [13]Academic Rheumatology Unit, University of Liverpool, Liverpool, United Kingdom, [14]U.O. Reumatologia, A.O. Ospedale San Carlo, Potenza, Italy, [15]Tubingen University, Tubingen, Germany, [16]Department of Internal Medicine and Clinical Immunology, AP-HP Pitié-Salpêtrière Hospital, Paris, France, [17]Rheumatology Unit, Arcispedale S Maria Nuova, IRCCS, Reggio Emilia, Italy, [18]Patient partner, Catania, Italy, [19]First Department of Propedeutic Internal Medicine, Laikon Hospital, Athens University Medical School, Athens, Greece, [20]Department of Neurology, Istanbul University, Cerrahpasa Medical Faculty, Department of Neurology, Istanbul, Turkey, [21]Ophthalmology, Guy's and St. Thomas' Hospital, London, United Kingdom, [22]Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, [23]Patient partner, London, United Kingdom

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A Systematic Literature Review on the Treatment of Skin, Mucosa and Joint Involvement of Behçet's Syndrome Informing the Eular Recommendations for the Management of Behçet's Syndrome

Background/Purpose: The aim of this systematic literature review was to inform the task force for updating the European League Against Rheumatism recommendations for the management of Behçet's Syndrome (BS), about the evidence for treatment of skin, mucosa and joint involvement of BS.

Methods: A systematic literature search, data extraction and statistical analyses according to pre-specified eligibility criteria were performed using the GRADE approach. The protocol for the systematic literature review was registered at PROSPERO (CRD42015027033). The Cochrane Library, including the Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessments (HTA), MEDLINE (from 1950), EMBASE (from 1980) and International Pharmaceutical Abstracts Database (IPAD) were systematically searched. Randomised controlled trials (RCT), non-randomised controlled clinical trials and open label trials (OLT) on BS comparing an active intervention (alone or in combination) with any control or placebo were eligible. If controlled trials were not available for answering a specific research question, uncontrolled evidence from cohort studies or case series involving ≥ 5 patients were considered. The quality of evidence was assessed by using the GRADE approach. Risk ratios were calculated for the binary outcomes whereas for the continuous outcomes we calculated the standardized mean difference (SMD).

Results: Among the 3927 references that we have screened, 22 studies satisfied the inclusion criteria for mucocutaneous involvement and 15 studies for joint involvement. Seventeen of these studies were randomized controlled trials assessing mucocutaneous and/or joint involvement. RCTs with colchicine, azathioprine, interferon-alpha, thalidomide, etanercept and apremilast showed different levels of beneficial results on different types of skin and mucosa lesions and arthritis. Differences in the outcome measures that were used across the included studies made it difficult to compare the results. These agents were generally well tolerated with few adverse events causing withdrawal from the study in BS patients.

Conclusion: It was gratifying to see that randomized controlled trials formed the majority (17/22, 77%) of the sources forming the basis for the recommendations related to skin mucosa and joint involvement in the updated EULAR Recommendations for the management of BS.

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Abstract Number: 2980

Inflammation As an Under-Recognized Cause of Ascending Aortic Aneurysms: A Single-Center Clinical and Pathological Study of 53 Cases over 6 Years

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Vasculitis - Poster III: Rarer Vasculitides

Session Type: ACR Poster Session C

Session Time: 9:00AM-11:00AM

Background/Purpose: This study is aimed at estimating the prevalence of inflammatory ascending aneurysms, describing clinical and histopathological findings, and assessing whether appropriate follow-up was arranged post discharge

Methods: Data from Enterprise Data Warehouse was retrieved for all cases of ascending aortic aneurysms from Jan 2009-Dec 2015 requiring surgery at the University Health Network for the following diagnostic codes: thoracic aortic aneurysm, ruptured (I71.1) or without mention of rupture (I71.2); aortic aneurysm of unspecified site, ruptured (I71.8) or without mention of rupture

(I71.9). After eliminating duplicate retrievals, 743 had their ascending aorta resected. Of these, 730 had aneurysmal dilatation, defined as maximum diameter ≥40mm measured by pre-operative echo or cardiac CT/MRI. All cases with ascending non-infectious inflammatory aneurysms were identified and reviewed for clinical presentation, imaging, histopathological and management method.

Results: Among the 730 cases studied, 53 (7.3%) were of a non-atherosclerotic, non-infectious inflammatory pathogenesis. Mean age was 67 years (18-68), with 50.9% women. Asymptomatic presentation occurred in 52.9%, 7.8% had constitutional symptoms and 43.1% had symptoms that could be attributed to an aneurysm. Isolated aortitis with no other evidence of arterial involvement presented in 41 (77.3%), and 12 had underlying rheumatic disease: Rheumatoid Arthritis (4), Polymyalgia Rheumatica (3), Giant Cell Artertitis (3), Systemic Lupus Erythematosus (1) and Cogan's Syndrome (1). Echocardiographic findings demonstrated a maximum mean aneurysm diameter of 54.7± 6.8mm, aortic insufficiency (AI) in 73.5%, stenosis (AS) in 9.4% and mixed AS & AI in 3.8%. A bicuspid aortic valve was found in 15.1%. Twenty-five (47.1%) had the aortic aneurysm distal to the ascending aorta and changes of calcification or atherosclerosis seen on CT (10) or intraoperatively (12). Histopathology revealed Giant Cell Aortitis in 35.8% (19), Takayasu's Arteritis in 5.7% (3), Lymphoplasmacytic Aortitis in 22.6% (12), Mixed Lymphoplasmacytic with Giant Cells in 15.1% (8) and unclassified in 20.8% (11). No lymphoplasmacytic cases were stained for IgG4. Four patients received perioperative steroids. Only 1 had aortitis mentioned in the discharge summary. Of the 53, 24 had a follow-up visit, 8 of which had aortitis diagnosis in the follow-up notes. Two were referred to a rheumatologist, 4 had their family MD notified, and 2 already had a rheumatologist. Rheumatologist referrals status for the remaining 45 (84.9%) patients after discharge is unknown.

Conclusion: Ascending Aortitis is under-recognized as a cause of ascending aortic aneurysms. Diagnosis is often incidental as most patients are asymptomatic. The presence of an aortic bicuspid valve or aortic stenosis and changes of atherosclerosis on imaging or in the intraoperative period do not rule out an inflammatory aortic aneurysm. IgG4 staining should be routine practice for all patients with lymphoplasmacytic aortitis. Cardiovascular surgeons, Pathologists and rheumatologists need to develop protocols for appropriate care of this patient subset. Further multi-center studies are needed.

Disclosure: T. Al-Araimi, None; **A. Bookman**, None.

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Abstract Number: 2981

Prospective Cohort of Surgically-Diagnosed Aortitis at the Ottawa Hospital

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Background/Purpose: Idiopathic Aortitis (IA) is poorly defined, with no specific criteria for its classification or diagnosis, except for presence of aortic inflammation and the absence of clinical features of another systemic condition. We aim to establish a prospective cohort of patients with surgically diagnosed aortitis and compare disease features in patients with IA and aortitis secondary to a systemic inflammatory condition (SA).

Methods: This is a single-center, prospective cohort study. Patients are recruited following identification of aortitis on surgical specimen. Baseline assessment includes clinical assessment, inflammatory markers (ESR and CRP), serology to exclude a connective tissue disease and infectious causes, and full imaging of the aorta and its branches. Patients are classified as either IA or SA, and followed prospectively. Clinical assessments and measurements of ESR and CRP are done at least yearly, and full imaging of the aorta and branches at least every 2 years. Primary outcome of interest is radiographic progression of aortitis (new aortic or branch lesions or progression of existing lesions). Secondary outcomes include the need for delayed immunosuppressive therapy, need for aortitis-related surgeries, or a change in diagnosis (from IA to SA).

Results: Fourteen patients have been enrolled to date, 8 IA, 6 SA (5 giant cell arteritis (GCA), 1 rheumatoid arthritis (RA)). The majority of patients are female (7/8 IA, 6/6 SA); average age 74 and 75 years in IA and SA respectively. Four out of eight patients with IA and 2/6 with SA had aortic branch lesions at baseline. Mean follow-up is 2.3 and 1.8 years in IA and SA groups, respectively. One patient (with SA) was found to have worsening aortic dilatation 15.4 months post-biopsy (PB); new aortic branch involvement was observed in 3/8 patients with IA (identified at mean 9.3 months PB) and in 3/6 SA (identified at mean 13.3 months PB). Surgical re-intervention was required in 2 patients with IA (mean 6.5 months PB). Two patients with IA received a combination of prednisone (initiated at a mean dose of 45 milligrams (mg) daily) and methotrexate (20mg weekly) starting at 36.0 months 38.2 months PB respectively for worsening aortitis. Two patients with SA received prednisone for worsening of their underlying condition, not related to diagnosis of aortitis: one was finishing a course of prednisone initiated for flare of RA prior to diagnosis of aortitis and the other was treated for symptomatic GCA 3.2 months PB (starting dose of 40 mg daily). One patient with IA died due to a cause unrelated to aortitis 17.5 months PB.

Conclusion: Preliminary data suggest patients with IA and SA may experience a significant rate of radiographic vascular progression, particularly in terms of development of branch vessel abnormalities. The number of events was too low to detect significant differences between IA and SA with respect to any of the studied parameters. Further enrollment and a longer duration of follow-up are needed. Controlled studies would be required to assess whether treating IA with corticosteroids at the time of diagnosis would reduce radiographic progression or other complications.

Disclosure: K. Walker, None; **M. Boodhwani**, None; **N. Milman**, None.

Abstract Number: 2982

Tumor Necrosis Factor Inhibitors and the Risk of Malignancy in the Treatment of Juvenile Idiopathic Arthritis

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Background/Purpose: The possible association between tumor necrosis factor inhibitors (TNFi) in the treatment of juvenile idiopathic arthritis (JIA) and an increased risk of malignancy remains uncertain. We combined and analyzed data from two large administrative claims sources to further evaluate malignancy rates in JIA.

Methods: Using national U.S. Medicaid claims from 2000-2010 inclusive and U.S. MarketScan claims from 2010-2014 inclusive, we identified cohorts of children with JIA using physician diagnosis codes and medication prescriptions. We identified non-JIA comparator cohorts of children diagnosed with attention-deficit hyperactivity disorder (ADHD). Children with any physician diagnosis code for malignancy prior to the start of follow-up were excluded, and all children had a ≥ 6 month baseline assessment period. JIA medication exposures included MTX (methotrexate or leflunomide), TNFi, and other systemic immunosuppressant agents (non-TNFi biologics or other non-biologics (e.g., cyclosporine)). All follow-up time following any medication exposure was considered exposed. Incident cancers were identified using a combination of diagnoses and treatment codes (claims for chemotherapy, radiation, or surgery). SEER cancer surveillance data were used to calculate expected cancer rates according to the age, sex, and race distribution of each cohort. Standardized incidence ratios (SIR) were calculated for the observed cancer

outcomes compared to SEER estimates.

Results: We identified 2,657,899 children with ADHD and 27,621 children with JIA and observed 841 and 23 incident malignancies, respectively (Table). The outcome identification algorithm appeared specific and sensitive for incident cancer, since the large ADHD comparator had SIR of 1.18 [1.11-1.27]. SIRs were significantly increased among all JIA patients (2.7 [1.7-4.0]) and among those who did not receive any medications of interest (2.4 [1.1-4.5]). We observed 8 malignancies after 15,269 person-years of observation in children who received TNFi; the corresponding SIR (3.3 [1.4-6.6]) was similar to that for children who did not receive TNFi. Based on 7 cases, the SIR associated with any use of other systemic immunosuppression was markedly elevated (14.0 [5.6-28.9]), and included use of abatacept, cyclosporine, rituximab, tacrolimus, and tocilizumab each by 1 patient and anakinra by 2 patients.

Conclusion: We did not observe a marked incremental increase in incident malignancies following treatment with TNFi compared to malignancy rates associated with the diagnosis of JIA. Receipt of non-MTX, non-TNFi systemic immunosuppressive therapies, a likely indication of severe or uncontrolled JIA, was strongly associated with an increased rate of malignancy.

Patient Cohort	MTX use	TNFi use	Other systemic immunosuppression use	Cancer Events	Person-Years of Follow-Up	Cancer Rate per 100K	SEER Expected Events	SIR [95% CI]
ADHD	n/a	n/a	n/a	841	4,363,046	19.3	710.4	1.18 [1.11-1.27]
JIA	Yes or No	Yes or No	Yes or No	23	53,221	43.2	8.5	2.7 [1.7-4.0]
JIA	No	No	No	9	23,478	38.3	3.8	2.4 [1.1-4.5]
JIA	Yes	No	No	2	12,908	15.5	2.0	1.0 [0.1-3.6]
JIA	Yes	No	Yes or No	4	13,837	28.9	2.2	1.8 [0.5-4.7]
JIA	Yes or No	Yes	Yes or No	8	15,269	52.4	2.4	3.3 [1.4-6.6]
JIA	Yes or No	Yes	No	5	13,539	36.9	2.2	2.3 [0.7-5.3]
JIA	Yes or No	Yes or No	Yes	7	3,296	212.4	0.5	14.0 [5.6-28.9]

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Abstract Number: 2983

Efficacy and Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, or Adalimumab in Patients with Active Psoriatic Arthritis and an Inadequate Response to Conventional Synthetic Dmards: A Randomized, Placebo Controlled, Phase 3 Trial

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor under investigation for treatment of psoriatic arthritis (PsA). This study evaluated tofacitinib efficacy and safety vs placebo (PBO) in patients (pts) with active PsA.

Methods: This was a randomized, PBO- and active-controlled, double-blind, multicenter, Phase 3 study. Eligible pts had a diagnosis of PsA for ≥6 months, fulfilled ClASsification criteria for Psoriatic ARthritis (CASPAR), had active arthritis (≥3 tender/painful and ≥3 swollen joints) and active plaque psoriasis, inadequate response to ≥1 csDMARD, and were tumor necrosis factor-inhibitor-naïve. Pts were randomized 2:2:2:1:1 to tofacitinib 5 mg twice daily (BID; n=107), tofacitinib 10 mg BID (n=104), adalimumab 40 mg subcutaneous injection once every 2 weeks (n=106), PBO→tofacitinib 5 mg BID (n=52) or PBO→tofacitinib 10 mg BID (n=53). Pts who initially received PBO advanced to tofacitinib 5 or 10 mg BID in a blinded manner at Month (M) 3. Ongoing treatment with a stable dose of 1 csDMARD was mandatory. Pts were followed through M12. The primary endpoints were ACR20 response rate and change from baseline in Health Assessment Questionnaire Disability Index (ΔHAQ-DI) at M3.

Results: Pt demographics and baseline disease characteristics were similar across groups (Table 1). Of the 422 randomized pts, 405 (96.0%) completed M3 and 373 (88.4%) completed M12. Significantly greater improvements in ACR20 response rates and ΔHAQ-DI were observed for both tofacitinib doses vs PBO at M3 and were maintained to M12 (Table 2); greater improvements were also observed for adalimumab vs PBO. Tofacitinib 5 and 10 mg BID demonstrated superiority vs PBO for ACR20 response rate as early as Week 2 (22.4% and 31.7% vs 5.7%; $p<0.001$). Secondary efficacy endpoints supported the primary findings (Table 2). Safety findings through M12 were similar between groups (Table 3). The most common adverse events over 12 months were upper respiratory tract infection (7.5–10.6% of pts across groups), nasopharyngitis (7.5–11.5%), and headache (3.8–10.6%).

Conclusion: Tofacitinib was superior to PBO in ACR20 response rate and ΔHAQ-DI at M3, with superiority vs PBO as early as Week 2 (first assessment) for ACR20, which was maintained to M12. Secondary endpoints supported the primary analyses. No new safety risks were identified vs previous studies in RA or psoriasis pts.

Table 1. Patient demographics and baseline disease characteristics (safety analysis set[a])

	Placebo (N=105)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10 mg BID (N=104)	Adalimumab 40 mg SC Q2W (N=106)
Patient demographics				
Age, years, mean (SD)	47.7 (12.3)	49.4 (12.6)	46.9 (12.4)	47.4 (11.3)
Female, n (%)	56 (53.3)	57 (53.3)	62 (59.6)	50 (47.2)
White, n (%)	104 (99.0)	105 (98.1)	97 (93.3)	103 (97.2)
BMI, kg/m^2, mean (SD)	28.8 (5.8)	29.0 (5.2)	29.3 (5.5)	28.8 (5.3)
Baseline disease characteristics				
Duration of PsA, years, mean (SD)	6.4 (6.4)	7.3 (8.2)	5.4 (5.8)	5.3 (5.3)
HAQ-DI score, mean (SD)	1.1 (0.6)	1.2 (0.6)	1.1 (0.6)	1.1 (0.6)
Presence of enthesitis, LEI>0, n (%)	65 (61.9)	75 (70.1)	64 (61.5)	76 (71.7)
LEI score,[b] mean (SD)	2.8 (1.5)	2.5 (1.4)	3.0 (1.6)	2.3 (1.2)
Presence of dactylitis, DSS>0, n (%)	58 (55.2)	61 (57.0)	60 (57.7)	58 (54.7)
DSS,[b] mean (SD)	9.9 (8.4)	9.1 (8.0)	8.5 (8.2)	8.0 (7.4)
mTSS>0, n (%)	95 (90.5)	96 (89.7)	96 (92.3)	99 (93.4)
mTSS,[b] median (range)	5.0 (0.5–310.0)	6.0 (0.5–160.5)	3.3 (0.5–109.0)	4.0 (0.5–352.5)
PGA of arthritis, VAS (mm), mean (SD)	53.8 (19.0)	54.6 (19.3)	55.2 (16.3)	50.5 (16.5)
PtGA of arthritis, VAS (mm), mean (SD)	53.9 (22.7)	54.7 (22.1)	53.6 (22.9)	50.6 (23.0)
Patient assessment of arthritis pain, VAS (mm), mean (SD)	53.2 (23.4)	55.7 (22.8)	54.4 (21.6)	50.7 (21.7)
Swollen joint count (66), mean (SD)	11.5 (8.8)	12.9 (9.9)	11.7 (7.7)	9.8 (7.9)
Tender/painful joint count (68), mean (SD)	20.6 (14.4)	20.5 (12.6)	20.3 (12.9)	17.1 (11.2)
CRP, mg/L, median (range)	5.0 (0.2–113.0)	4.8 (0.2–115.0)	5.1 (0.2–92.9)	4.3 (0.2–131.0)
Affected BSA ≥3%, n (%)	82 (78.1)	82 (76.6)	70 (67.3)	78 (73.6)
PASI score,[c] mean (SD)	9.4 (8.8)	8.3 (8.3)	9.0 (6.4)	10.1 (8.7)
Oral corticosteroid use, n (%)	18 (17.1)	29 (27.1)	11 (10.6)	21 (19.8)
Concomitant csDMARD use up to Month 3, n (%) Methotrexate Other[d]	 92 (87.6) 13 (12.4)	 91 (85.0) 16 (15.0)	 92 (88.5) 12 (11.5)	 79 (74.5) 27 (25.5)

[a]All patients who received ≥1 dose of study medication; [b]Among patients with baseline score >0; [c]Among patients with baseline BSA≥3% and PASI>0; [d]Includes hydroxycholoquine, leflunomide and sulfasalazine

BID, twice daily; BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire – Disability Index; LEI, Leeds Enthesitis Index; mTSS, modified Total Sharp Score; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PsA, psoriatic arthritis; PtGA, Patient's Global Assessment; Q2W, once every 2 weeks; SC, subcutaneous; SD, standard deviation; VAS, visual analog scale

Table 2. Efficacy endpoints at Month 3 and Month 12 (full analysis set[a])

	Month 3 (Active treatment vs placebo)[f]				Month 12				
	Placebo (N=105)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10 mg BID (N=104)	Adalimumab 40 mg SC Q2W (N=106)	Placebo→ tofacitinib 5 mg BID (N=52)	Placebo→ tofacitinib 10 mg BID (N=53)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10 mg BID (N=104)	Adalimumab 40 mg SC Q2W (N=106)
ACR20,[b] n (%)	35 (33.3)	54 (50.5)*	63 (60.6)***	55 (51.9)**	35 (67.3)	31 (58.5)	73 (68.2)	73 (70.2)	64 (60.4)
ACR50, n (%)	10 (9.5)	30 (28.0)**	42 (40.4)***	35 (33.0)***	21 (40.4)	19 (35.9)	48 (44.9)	50 (48.1)	43 (40.6)
ACR70, n (%)	5 (4.8)	18 (16.8)*	15 (14.4)*	20 (18.9)*	12 (23.1)	12 (22.6)	25 (23.4)	32 (30.8)	31 (29.2)
ΔHAQ-DI,[λ] LS mean (SE) [N]	-0.18 (0.05) [102]	-0.35 (0.05)* [103]	-0.40 (0.05)** [103]	-0.38 (0.05)* [101]	-0.41 (0.08) [44]	-0.46 (0.08) [44]	-0.54 (0.05) [96]	-0.51 (0.05) [96]	-0.45 (0.05) [94]
PASI75,[c] n/N (%)	12/82 (14.6)	35/82 (42.7)***	31/70 (44.3)***	30/77 (39.0)**	15/42 (35.7)	21/40 (52.5)	46/82 (56.1)	47/70 (67.1)	43/77 (55.8)
ΔLEI,[λ] LS mean (SE) [N]	-0.43 (0.25) [63]	-0.82 (0.22) [70]	-1.46 (0.24)** [63]	-1.10 (0.23) [73]	-1.4 (0.30) [24]	-1.9 (0.28) [29]	-1.7 (0.19) [67]	-1.6 (0.21) [56]	-1.6 (0.20) [67]
ΔDSS,[λ] LS mean (SE) [N]	-2.0 (1.06) [55]	-3.5 (0.95) [58]	-5.5 (0.93)* [60]	-4.0 (0.97) [56]	-6.7 (0.93) [26]	-7.7 (0.96) [24]	-7.4 (0.65) [54]	-7.5 (0.62) [58]	-6.1 (0.67) [52]
ΔmTSS,[λ,e] LS mean (SE) [N]	-	-	-	-	0.00 (0.09) [48]	0.09 (0.10) [45]	0.01 (0.07) [98]	-0.01 (0.07) [99]	-0.07 (0.07) [95]
mTSS progression >0.5,[λ,e] n/N (%)	-	-	-	-	2/48 (4.2)	4/45 (8.9)	4/98 (4.1)	5/99 (5.1)	2/95 (2.1)

Nominal *p≤0.05; **p<0.001; ***p<0.0001 vs placebo at Month 3

[a]All randomized patients who received ≥1 dose of study medication; [b]Primary study endpoint at Month 3; [c]Among patients with baseline BSA ≥3% and baseline PASI>0; [d]Among patients with baseline score >0; [e]mTSS was assessed at Month 12 only; [f]The study was not designed as a superiority or a non-inferiority trial for comparison of tofacitinib with adalimumab

Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response. Missing values for mTSS and mTSS progression were imputed by linear extrapolation. Missing values for continuous endpoints except mTSS were not imputed

λ, change from baseline; BID twice daily; BSA, body surface area; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire – Disability Index; LEI, Leeds Enthesitis Index; LS, least squares; mTSS, modified Total Sharp Score; PASI, Psoriasis Area and Severity Index; PASI75, ≥75% improvement from baseline PASI; Q2W, once every 2 weeks; SC, subcutaneous; SE, standard error

Table 3. Safety summary to Month 12 (safety analysis set[a])					
	Placebo→ tofacitinib 5 mg BID (N=52)	Placebo→ tofacitinib 10 mg BID (N=53)	Tofacitinib 5 mg BID (N=107)	Tofacitinib 10 mg BID (N=104)	Adalimumab 40 mg SC Q2W (N=106)
AEs, n (%)	36 (69.2)	34 (64.2)	71 (66.4)	74 (71.2)	76 (71.7)
SAEs, n (%)	3 (5.8)	4 (7.5)	8 (7.5)	4 (3.8)	9 (8.5)
Discontinuation due to AEs, n (%)	2 (3.8)	2 (3.8)	6 (5.6)	3 (2.9)	4 (3.8)
Deaths, n (%)	1 (1.9)[b]	0	0	0	0
AEs of special interest, n (%) [day of onset]					
Serious infection	2 (3.8) [102, 331]	0	0	1 (1.0) [132]	1 (0.9) [170]
Herpes zoster (all non-serious)	0	0	2 (1.9) [61, 173]	2 (1.9) [221, 317]	0
Opportunistic infection	0	0	1 (0.9) [61]	0	0
Malignancy	0	0	3 (2.8) [1, 11, 232]	1 (1.0) [103]	0
MACE	1 (1.9) [139]	0	0	0	2 (1.9) [263, 345]
GI perforation	1 (1.9) [102]	0	0	0	0

[a]All patients who received ≥1 dose of study medication; [b]Cardiac arrest
AE, adverse event; BID, twice daily; GI, gastrointestinal; MACE, major adverse cardiovascular event; n, number of patients with event; SAE, serious adverse event; Q2W, once every 2 weeks; SC, subcutaneous

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Abstract Number: 2984

Novel Anti-Malarial Drug Derivative Inhibited Type I Interferon Production and Autoimmune Inflammation through Inhibition of CGAS-Sting Pathway in Trex1-/- Mouse

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Background/Purpose: Type I interferon, (IFN-I) is strongly implicated in the pathogenesis of SLE as well as rare monogenic 'interferonopathies' such as Aicardi-Goutieres Syndrome (AGS) caused by mutations in the DNA exonuclease, TREX1. A new DNA activated IFN-I pathway, cyclic GMP-AMP (cGAMP) synthase (cGAS), was recently discovered and linked to mouse models of AGS and Lupus. To identify potential inhibitors of the DNA-cGAS interaction, we performed *in silico* screening of chemical and drug libraries and tested the lead candidate, X6, in the mouse model of AGS.

Methods: *In silico* structure-based drug screening and ligand binding studies were performed by the CANDO platform followed by docking analysis via Autodock Vina and Chimera. In vitro cGAS activity/cGAMP production was analyzed by Thin Layer Chromatography (TLC). Following DNA cell transfections, cytokines were quantified by qPCR, ELISA or an ISRE-luciferase reporter assay. Trex1-/- mouse were treated orally with 25mg/kg/day drug X6 (n=8) for 8 weeks from birth. Multiple Reaction Monitoring by Ultra-Performance Liquid Chromatogram coupled with tandem Mass Spectrometer (UPLC-MS/MS) was used to quantify cGAMP. Heart pathology on Hematoxylin and Eosin stained slides was blindly scored by a pathologist.

Results: In silico analysis of drug libraries identified several antimalarial drugs (AMD) which could potentially inhibit cGAS activity by interacting with the cGAS/DNA dimer complex. TLC revealed that AMDs attenuated cGAS activity and inhibited cGAMP production in a dose dependent manner. These AMD also inhibited IFN-b expression in THP1 cells transfected with dsDNA and in 293T cells transfected with cGAS/STING plasmids validating that cGAS is a target of AMD. Based on the relative potencies of AMD and additional modeling, we synthesized several new AMD derivatives. One of these compounds, X6, had excellent water solubility and cell penetration. X6 localized to the cytosol and had a lower toxicity profile compared to quinacrine. Biochemical and cellular assays revealed that X6 was a potent inhibitor of IFN-I production. Since deficiency of the TREX1 in mice (TREX1-/-) leads to an autoimmune myocarditis and lupus-like systemic autoimmunity with increased Interferon Signature Genes (ISGs) expression and cGAMP production, we treated these mice with X6. When compared to vehicle control treated TREX1-/- mice, drug X6 reduced ISGs ISG15 ($p<0.01$) and ISG20 ($p<0.01$) expression in the spleen and CXCL10 ($p<0.01$) and ISG15 ($p<0.05$) expression in the heart. In addition, treatment with X6 resulted in a statistically significant reduction in cGAMP in the heart ($p<0.05$) as well as a reduction in endocardial fibrosis severity scores ($p<0.05$) compared to control.

Conclusion: Our studies indicate that, in addition to reducing activation of intracellular TLRs, AMD attenuate cGAS activity. Since disease in TREX1-/- mice is absolutely dependent on the cGAS pathway as indicated by rescue of disease in double knockouts, we show here that the novel AMD derivative, X6, attenuates disease by inhibiting cGAS activity and IFN-b expression in vivo. This class of drugs could be beneficial for the treatment of AGS and /or Lupus.

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Practice-Level Variation in Quality of Care in the Acr's Rheumatology Informatics System for Effectiveness (RISE) Registry

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Background/Purpose: The Medicare Access and CHIP Reauthorization Act (MACRA) of 2015 has put into place an aggressive timeline for a Merit-Based Incentive Payment System (MIPS) and for Alternative Payment Models (APMs). For rheumatologists to be successful under these payment reforms, it will be critical to understand and improve performance on quality measures. In this study, we used data from the ACR's Rheumatology Informatics System for Effectiveness (RISE), a national electronic health record (EHR)-enabled quality improvement registry, to examine variation in performance on quality measures across practices.

Methods: RISE's informatics platform continuously collects data from the EHRs of participating practices, allowing centralized aggregation and analysis of performance on quality measures. Rheumatologists can view their performance on measures using a web-based registry dashboard that is updated every 24 hours. We analyzed data collected between April 1, 2015 and March 31, 2016 on all patients seen by 223 clinicians across 49 practices in which EHR mapping is complete. Quality measures in the areas of rheumatoid arthritis, drug safety, osteoporosis, preventive care and gout were examined. Performance on quality measures, defined as the percentage of eligible patients receiving recommended care, was examined at the practice level.

Results: Data from 346,358 patients was examined. Mean (SD) age was 58 (16.6) years, 75.2% were female, 25.6% were racial/ethnic minorities, and 65.8% had commercial insurance. Most rheumatologists were in a group practice (90.0%); 8.8% were in solo practice and 1.2% part of a larger health system. Performance on quality measures varied significantly across practices (Table). Twelve of 17 measures had a maximum observed performance of >99% across practices. The largest gaps in quality of care at both the practice and clinician levels were observed for osteoporosis, gout and preventive care (e.g. body mass index screening and counseling), suggesting room for improvement in these areas. For 6 of 9 measures for which the Centers for Medicare and Medicaid Services has set national benchmarks, the average performance of RISE practices exceeded targets.

Conclusion: We found significant variation in performance on quality measures across RISE practices, with the largest gaps seen in osteoporosis, gout care and preventive care. We also found that some practices have achieved a very high level of performance. As rheumatologists aim to improve quality of care and prepare for upcoming MACRA payment reforms, RISE will, by design, allow participants to measure, benchmark, and continuously monitor performance improvement. **Table. Performance on selected quality measures in the RISE registry.**

Quality Measure			Performance across RISE practices	Performance across RISE practices	CMS Benchmark
	Measure Denominator (n)	Measure Numerator (n)	Average Performance (%)	25th, 50th, 75th, 100th percentile	
RA: Disease Activity Measurement	50,416	33,076	61.9	30.6, 70.9, 90.4, 100	
RA: Functional Status Measurement	50,416	29,546	56.4	23.6, 65.2, 87.5, 100	
RA: Disease Modifying Drug Use	50,236	45,804	90.3	87.5, 91.4, 94.8, 97.5	
Drug Safety: Tuberculosis Screening Prior to First Biologic Therapy	15,933	8,905	54.6	31.7, 52.4, 79.0, 99.2	
Drug Safety: Use of ≥ 1 High-Risk Medication in the Elderly	78,347	3,472	5.9*	6.1, 3.8, 2.4, 0*	9.0
Drug Safety: Use of ≥ 2 High-Risk Medications in the Elderly	78,347	110	0.17*	0.15, 0.05, 0, 0*	9.0
Osteoporosis: DXA measurement or treatment in women 65 years or older	62,924	39,790	64.7	48.9, 60.7, 81.5, 99.3	41.0
Osteoporosis: DXA measurement or treatment in high-risk patients	38,929	21,020	52.1	41.2, 54.9, 60.8, 85.2	
Osteoporosis: Post-fragility fracture DXA or treatment	6,269	3,657	67.3	50.0, 66.1, 83.8, 100	41.0
Low Back Pain: Lack of imaging within 28 days of primary low back pain diagnosis	7,843	4,853	64.4	35.1, 65.1, 95.0, 100	16.0
Preventive Care: Tobacco screening and	211,889	180,360	83.8	78.4, 88.8, 91.8, 99.1	90.0

counseling					
Preventive Care: BMI documentation and follow-up plan (per visit)	211,112	96,608	49.1	34.3, 44.0, 64.1, 94.0	58.0
Preventive Care: Blood pressure management	24,583	14,349	58.8	48.1, 61.2, 69.2, 90.6	69.0
Medication Documentation (per visit)	586,601	578,857	97.3	98.8, 99.5, 99.8, 100	88.0
Gout: Serum Urate Monitoring	5,208	1,832	35.4	16.7, 28.6, 60.2, 84.0	
Gout: Serum Urate Target less than 6.8 mg/dL achieved.	925	509	54.1	33.3, 53.9, 82.4, 100	
Gout: Urate Lowering Therapy	442	228	49.9	30.0, 50.0, 71.4, 100	

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Trends and Determinants of Osteoporosis Prevention and Management in Patients with Rheumatoid Arthritis Compared to Osteoarthritis

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Background/Purpose: Despite more aggressive treatment strategies and new biologic DMARDs, the prevalence of osteoporosis (OP) leading to fracture in RA remains high. It is unknown whether these treatment changes and release of the 2010 ACR glucocorticoid (GC) induced OP (GIOP) guideline changed physicians' OP management practices. To evaluate this, we assessed the frequency, trends, and predictors of OP management care in patients with RA compared with OA in the US.

Methods: Patients studied had RA or OA with ≥1 year participation from 2003 through 2014 in the National Data Bank for Rheumatic Diseases. OP management care was defined as either having a bone mineral density (BMD) test or treatment with any anti-OP medications (excluding calcium or vitamin D) in the prior 6 months. Calendar years were evaluated to detect trends for outcome, with 2003 as reference period. Andersen-Gill formulation of Cox proportional hazards models were used to determine adjusted trends of and factors associated with OP management care.

Results: During a median (IQR) followup of 5.5 (2.3-9.0) years in 11,669 RA and 2,829 OA patients, the frequencies of BMD testing were 57% *vs.* 54% and treatment with any anti-OP medication 44% *vs.* 42%. Only ~50% of RA and OA patients with prior fragility fractures or long-term GC exposure were on anti-OP treatment. In multivariable analysis, RA patients were 12% more likely to have OP management care compared to OA patients. Factors significantly associated with having OP management care in RA patients were older age, postmenopausal status, prior fragility fracture or diagnosis of OP, GC exposure ≥3 months, treatment with any biologic, and rheumatology care (*Table*). Cox models showed stable OP management trends between 2003 and 2009, with a significant downward trend after 2009 without any improvement in GC-exposed patients after the release of the 2010 ACR GIOP guideline (*Figure*). The same downward trend was also observed in long-term GC exposed by bisphosphonate-nonexposed RA patients.

Conclusion: The application of OP management care is slightly higher in RA patients compared to OA, but the frequency of such care in patients at high risk for fracture remains suboptimal. Despite the availability of advanced treatments, the care for OP has not been improving, which may be due to both patient (unwillingness to take more drugs, cost) and physician barriers (lack of time, and focusing more on disease activity and other comorbid conditions). To reduce the morbidity and mortality burden of OP fractures, clarification of the reasons for suboptimal management and effective interventions are needed.

Table. Potential predictors for both types of osteoporosis management care in patients with rheumatoid arthritis and osteoarthritis

Variables	OP management care, HR (95% CI)	
	RA patients, N=11,669	OA patients, N=2,829
Age groups		
<40 years (referent)	1.0	1.0
40-50 years	1.70 (1.38-2.09)	1.67 (0.57-4.87)
51-64 years	2.22 (1.78-2.78)	1.80 (0.61-5.36)
≥65 years	2.59 (2.07-3.28)	1.72 (0.57-5.12)
Gender		
Female		
Premenopausal (referent)	1.0	1.0
Postmenopausal	1.62 (1.37-1.92)	2.71 (1.49-4.91)
Male	0.59 (0.49-0.72)	0.65 (0.35-1.23)
Education level	1.03 (1.01-1.05)	1.05 (1.01-1.09)
No insurance	0.66 (0.50-0.86)	0.96 (0.53-1.73)
Residency in a rural area	0.88 (0.81-0.96)	0.92 (0.75-1.11)
Primary physician, rheumatologist	1.43 (1.26-1.63)	1.19 (1.00-1.41)
Vaccination for influenza	1.11 (1.03-1.20)	1.20 (1.01-1.43)
BMI in categories		
<18.5 kg/m2	1.14 (0.89-1.45)	0.83 (0.26-2.64)
18.5-24.9 kg/m2 (referent)	1.0	1.0
25.0-29.9 kg/m2	0.87 (0.79-0.96)	0. 79 (0.64-0.98)
30.0-39.9 kg/m2	0.80 (0.73-0.89)	0.68 (0.55-0.84)
≥40 kg/m2	0.56 (0.47-0.67)	0.55 (0.40-0.76)
HAQ	1.05 (0.99-1.11)	0.89 (0.78-1.01)
Glucocorticoid use		
Never-used (referent)	1.0	1.0
<3 months	1.12 (0.96-1.31)	0.90 (0.68-1.19)
3-12 months	1.24 (1.09-1.40)	1.24 (0.91-1.68)
>12 months	1.38 (1.26-1.51)	1.72 (1.32-2.22)
Use of DMARDs		
MTX monotherapy (referent)	1.0	-
Any TNFi	1.21 (1.08-1.36)	-
Non-TNFi biologics	1.34 (1.09-1.65)	-
Any others	1.15 (1.03-1.29)	-
Prior fragility fracture	1.10 (1.00-1.22)	1.22 (0.98-1.52)
Prior diagnosis of OP	1.52 (1.37-1.67)	1.35 (1.35-1.65)

**Other covariates included in the model, ethnicity, disease duration, Rheumatic Disease Comorbidity Index, smoking status, were not significantly associated with OP care. The model also included the each calendar from 2003 to 2014.*

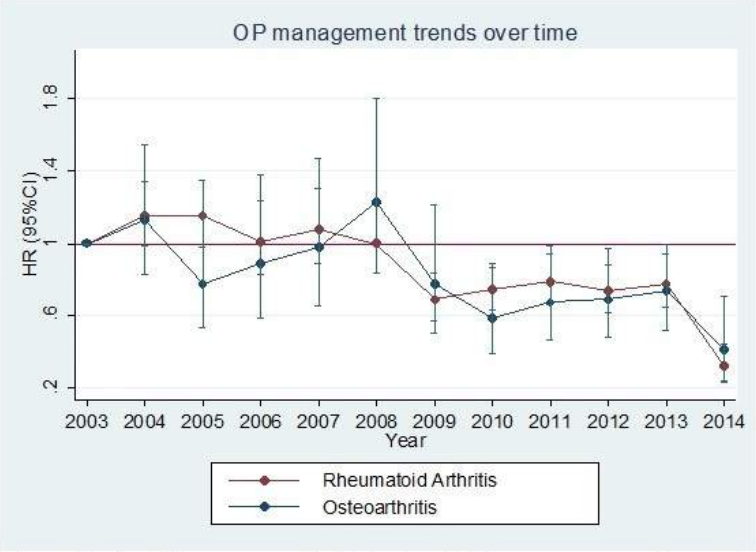

Figure. Trends of "OP management" (either having a BMD test or treatment with any anti-OP medications, excluding calcium or vitamin D) in patients with rheumatoid arthritis and osteoarthritis

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Disclosure: G. Ozen, None; **D. L. Kamen**, None; **T. R. Mikuls**, None; **F. Wolfe**, None; **K. Michaud**, None.

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Comparison of Certolizumab Pegol Versus Adalimumab: 2 Year Efficacy and Safety Results from a Superiority, Investigator-Blind, Head-to-Head Study

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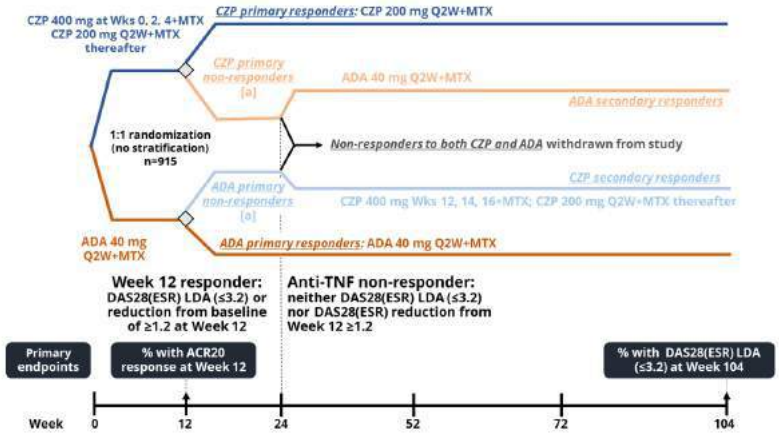
Background/Purpose: Head-to-head comparisons of biological (b)DMARDs in the treatment of RA should provide rigorous evidence on the comparative efficacy of different treatments. Although there are several head-to-head trials comparing TNF inhibitors (TNFi) with bDMARDs that have different mechanisms of action,[1-3] there have been no reports of prospective head-to-head trials comparing the efficacy and safety of bDMARDS within the same class, including TNFi.

Methods: EXXELERATE (NCT01500278) was a 104-wk randomized, investigator-blind, parallel-group, head-to-head superiority study comparing the early (Wk 12)- and later (Wk 104)-term efficacy and safety of certolizumab pegol (CZP)+MTX and adalimumab (ADA)+MTX (Figure). Patients (Pts) were randomized 1:1 to CZP+MTX or ADA+MTX. At Wk 12, pts were classified as responders (achieving either DAS28[ESR] ≤3.2 or DAS28[ESR] reduction from baseline [BL] of ≥1.2 at Wk 12) or non-responders (NR). NRs to one were switched to the respective other TNFi (Figure). Primary endpoints were the percentage of pts achieving ACR20 at Wk 12 and low disease activity (LDA; DAS28[ESR] ≤3.2) at Wk 104 (Wk 12 NRs were considered LDA NRs). Secondary endpoints included the proportion of pts achieving ACR20 at Wk 6, DAS28(ESR) LDA at Wks 6, 12, 52, and the proportion of Wk 12 responding pts achieving LDA at Wk 104. Exploratory endpoints included the proportion of Wk 12 responding pts achieving ACR20/50/70, and DAS28(ESR) and CDAI defined LDA and remission (REM), at each study visit.

Results: At BL, 915 pts were randomized to either CZP+MTX (n=457) or ADA+MTX (n=458). At Wk 12 there were 359 CZP+MTX (78.6%) and 369 ADA+MTX (80.6%) responder pts. No statistically significant difference was observed between ACR20 response at Wk 12 (69.2% and 71.4%; odds ratio (OR): 0.90 [95% CI: 0.67, 1.20]), and DAS28(ESR) LDA at Wk 104 (35.5% and 33.5%; OR: 1.09 [95% CI: 0.82, 1.45]) for CZP+MTX and ADA+MTX, respectively. No differences between treatment arms were evident in secondary and exploratory efficacy endpoints (Table). A similar proportion of CZP+MTX and ADA+MTX pts reported treatment emergent adverse events (TEAEs; 75.4% and 73.8%), serious TEAEs (13.0% and 11.1%), and serious infections and infestations (3.3% and 3.1%), by treatment at AE onset (event rate per 100 pt years 257.5 vs 260.0).

Conclusion: EXXELERATE, the first direct head-to-head comparison of two TNFis, reinforces the early and later term efficacy of both CZP and ADA in combination with MTX without demonstrating clinical evidence of differences between both agents. CZP+MTX and ADA+MTX demonstrated comparable safety over 2 years. **References:** 1. Porter D. Lancet 2016;S0140-6736(16)00380–9; 2. Gabay C. Lancet 2013;381(9877):1541–1550; 3. Weinblatt M. Arthritis Rheum 2013;65(1):28–38

Figure: EXXELERATE study design



[a] Week 12 non-responders did not have DAS28(ESR) LDA or reduction from baseline ≥1.2 at Week 12.

Table: The percentage of patients achieving different clinical responses

		CZP+MTX	ADA+MTX	Odds Ratio comparing CZP to ADA (referent) (95% CI)
Early-term efficacy variables (FAS)		**n=454**	**n=454**	–
ACR20	**Wk 6**	64.5	60.8	1.21 (0.92, 1.59)
ACR20	**Wk 12 [a]**	69.2	71.4	0.90 (0.67, 1.20)
DAS28(ESR) LDA	**Wk 6**	20.5	18.1	1.15 (0.81, 1.62)
	Wk 12	30.4	29.7	1.00 (0.75, 1.34)
Later-term efficacy variables (FAS) Patients withdrawing or switching recorded as not being in LDA		**n=454**	**n=454**	–
DAS28(ESR) LDA	**Wk 52**	41.6	38.3	1.15 (0.87, 1.51)
	Wk104 [a]	35.5	33.5	1.09 (0.82, 1.45)
Week 12 responders (Wk 12 FAS)		**n=353**	**n=361**	–
ACR20	Wk 12	86.1	85.9	–
	Wk 24	85.6	85.0	
	Wk 52	77.9	79.5	
	Wk104	64.9	66.8	
ACR50	Wk 12	51.3	53.2	–
	Wk 24	63.5	62.6	
	Wk 52	60.6	64.0	
	Wk104	53.3	56.8	
ACR70	Wk 12	28.0	26.9	–
	Wk 24	39.1	40.4	
	Wk 52	43.6	43.5	
	Wk104	39.7	41.3	
DAS28(ESR) LDA [b]	Wk 12	38.5	36.8	–
	Wk 24	51.8	46.0	
	Wk 52	53.5	48.5	
	Wk104	45.6	42.4	
DAS28(ESR) REM [c]	Wk 12	21.5	21.3	–
	Wk 24	32.9	29.4	
	Wk 52	31.4	32.1	
	Wk104	30.0	27.1	
CDAI LDA [d]	Wk 12	53.3	52.4	–
	Wk 24	68.9	66.3	
	Wk 52	65.7	65.7	
	Wk104	56.1	56.2	
CDAI REM [e]	Wk 12	13.6	13.9	–
	Wk 24	24.9	22.2	
	Wk 52	28.6	26.3	
	Wk104	29.2	26.3	

Primary and secondary analyses used a logistic regression model, including terms for gender, age, disease duration, and geographic region. For DAS28(ESR), BL value was included as a covariate. The study finished at Week 104. [a] Primary endpoint; [b] DAS28(ESR) ≤3.2; [c] DAS28(ESR) <2.6; [d] CDAI ≤10; [e] CDAI ≤2.8. Non-responder imputation was used to impute missing values; ADA, adalimumab; CZP, certolizumab pegol; LDA, low disease activity; REM, remission.

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Abstract Number: 2988

Cigarette Smoking Increases the Risk of Anti-Double-Stranded DNA Positive SLE Among Women in the Nurses' Health Studies

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Background/Purpose: SLE is heterogeneous with subtypes characterized by different systemic manifestations and autoantibodies. Past studies suggest that smoking may be a risk factor for SLE, although evidence is conflicting and prospective cohort studies have not demonstrated this association to date. Among SLE patients, current smokers have been found to be significantly more likely than never smokers to have anti-double stranded DNA (dsDNA) antibodies. We aimed to prospectively evaluate the association of smoking with risk of incident SLE in a large prospective cohort study, examining risk of the subtypes of dsDNA positive (+) versus negative (-) SLE.

Methods: NHS enrolled 121,701 U.S. female registered nurses in 1976. NHSII began in 1989, enrolling 116,430 female nurses. Lifestyle, environmental exposures and medical history are collected on biennial questionnaires. Incident SLE cases are identified using the connective tissue disease screening questionnaire, followed by medical record review for ACR criteria. Participants without smoking data at baseline were excluded. Time-varying smoking status was assessed categorically (never/past/current). Cumulative smoking in pack-years was also calculated biennially through the 2-year cycle prior to SLE diagnosis. Cox regression models assessed associations of smoking with SLE overall and stratified by dsDNA + or - at diagnosis, controlling for time-varying covariates. Hazard ratios (HR) from the two cohorts were meta-analyzed using DerSimonian and Laird random effects models. As alcohol and smoking behaviors are strongly correlated and alcohol intake is associated with reduced SLE risk, we analyzed age-adjusted, alcohol-adjusted, and multivariable-adjusted models.

Results: 160 incident SLE cases developed in NHS (1978-2012) and 123 in NHSII (1991-2013). Mean age at diagnosis was 53.8 (9.5) yrs in NHS and 43.4 (8.0) yrs in NHSII. In NHS, 33% were current smokers at baseline, and 13.4% were current smokers in NHSII. Among SLE, 46% of NHS and 58% of NHSII were anti-dsDNA+ at diagnosis; 20% in NHS and 11.8% in NHSII had renal involvement at diagnosis. Smoking status or pack-years was not associated with SLE risk overall **(Table)**. However, current (vs. never) smokers had greatly increased risk of dsDNA+ SLE (HR 1.89, 95% CI 1.20-2.98), but not of dsDNA- SLE, after adjustment for potential confounders including alcohol. Women who smoked >10 pack-years (vs. never) had a highly elevated risk of dsDNA+ SLE (HR 1.72, 95%CI 1.16-2.55).

Conclusion: We have uncovered a strong and specific association of smoking (both current smoking and increased pack-years) with risk of dsDNA+ SLE among women. This novel finding suggests a biologic mechanism in dsDNA+ SLE pathogenesis not involved

Table. Hazard Ratios for the Association of Cigarette Smoking and Incident SLE, Overall and by Anti-dsDNA subtype, among Women in the Nurses' Health Study (Meta-analyzed NHS and NHSII cohorts)

	Cigarette Smoking Status*		
	Never	Past	Current
Overall SLE			
Cases/Person-Years	148/3073175	90/1758722	49/808096
Age-adjusted HR (95%CI)[b]	1.00 (ref)	1.12 (0.86-1.46)	1.08 (0.78-1.51)
Alcohol-adjusted HR (95%CI)[c]	1.00 (ref)	1.22 (0.93-1.60)	1.18 (0.85-1.66)
Multivariable-adjusted HR (95%CI)[d]	1.00 (ref)	1.16 (0.88-1.52)	1.14 (0.81-1.60)
Anti-dsDNA Positive SLE			
Cases/Person-Years	68/3072373	48/1758287	32/807846
Age-adjusted HR (95%CI)[b]	1.00 (ref)	1.32 (0.91-1.93)	**1.77 (1.14-2.77)**
Alcohol-adjusted HR (95%CI)[c]	1.00 (ref)	1.43 (0.97-2.09)	**1.93 (1.23-3.03)**
Multivariable-adjusted HR (95%CI)[d]	1.00 (ref)	1.38 (0.94-2.03)	**1.89 (1.20-2.98)**
Anti-dsDNA Negative SLE			
Cases/Person-Years	80/3072352	42/1758029	17/807662
Age-adjusted HR (95%CI)[b]	1.00 (ref)	0.95 (0.65-1.39)	0.61 (0.36-1.05)
Alcohol-adjusted HR (95%CI)[c]	1.00 (ref)	1.04 (0.71-1.54)	0.68 (0.39-1.16)
Multivariable-adjusted HR (95%CI)[d]	1.00 (ref)	0.97 (0.66-1.44)	0.64 (0.37-1.09)

*Time-varying cigarette smoking status assessed through two years prior to outcome
[b]Adjusted for age and questionnaire period
[c]Adjusted for age, questionnaire period, and alcohol intake (none, >0 to <5g/day, ≥5g/day)
[d]Adjusted for age, questionnaire period, race/ethnicity (white, nonwhite), alcohol intake (none, >0 to <5g/day, ≥5g/day), menarche onset age (>10 versus ≤10 years), oral contraceptive use (ever, never), BMI in WHO categories (18.5 to <25, 25 to <30, ≥30), post-menopausal hormone use (premenopausal, postmenopausal-never postmenopausal hormone use, postmenopausal-ever postmenopausal hormone use)
CI, confidence interval; HR, hazard ratio

in dsDNA- SLE pathogenesis.

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Risk of Cardiovascular Disease Events Among Patients with Systemic Lupus Erythematosus Compared to Those with Diabetes Mellitus in a Nationwide Medicaid Cohort

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Background/Purpose: Cardiovascular disease (CVD) risk is elevated in SLE patients compared to non-SLE patients. However, how CVD rates differ in SLE patients compared with other chronic disease states, in particular diabetes mellitus (DM), has not been examined. To provide insights for clinicians seeking to understand the magnitude of CVD risk in SLE patients, we compared their risk to that of patients with DM, a known CVD risk factor. We examined annual rates and relative risks of CVD events (acute myocardial infarction [MI], stroke, and combined MI or stroke) in a nationwide cohort of US Medicaid recipients with either SLE or DM.

Methods : We utilized Medicaid Analytic eXtract (MAX) data, containing billing claims for Medicaid patients from the 29 most populated US states, 2007-10. We identified adults aged ≥18-65 with prevalent SLE or DM (≥3 ICD-9 codes for SLE or DM, each separated by ≥30 days) and >6 months of enrollment prior to 3rd code (index date). We performed 1: 2 matching (SLE: DM) based on age (month/year), sex, and index date. Sociodemographic data (including age, sex, race/ethnicity, calendar year, US region, zip code-level socioeconomic status) and medical/cardiac comorbidities were collected during the baseline period (6 months prior to and including index date). ICD-9, CPT, and DRG codes were used to identify outcomes. Outcomes were assessed from index date, including acute MI, stroke, and combined MI or stroke. Subjects were followed to first CVD event, death, Medicaid disenrollment,

or end of follow-up. We used Cox sub-distribution regression models to calculate hazard ratios (HR_{SD}) for CVD events, accounting for the competing risk of death and adjusting for sociodemographics and medical/cardiac comorbidities (**Table**).

Results : 32,089 prevalent SLE patients were matched to 64,178 prevalent DM patients. In both cohorts, 92.8% were female and mean age was 41.3 (±12.1) years. There were more Blacks (41.1 vs. 30.5%) and fewer Whites (36.3 vs 45.1%) in the SLE vs. DM cohort. Mean follow-up was 1.67 (±1.03) years for SLE patients and 1.79 (±1.07) years for DM patients. Baseline CVD risk factors were more prevalent among DM vs. SLE patients: hypertension (38.0 vs. 33.7%), hyperlipidemia (22.5 vs. 10.6%), and obesity (11 vs. 4.5%). In the SLE cohort in particular, the incidence of stroke was higher than that of MI (**Table**). Annual rates and adjusted risks of MI were similar in the two cohorts (multivariable-adjusted HR_{SD} 1.01 [95% CI 0.84-1.22] for SLE vs. DM). By contrast, stroke rates were higher among SLE vs. DM patients and the multivariable-adjusted HR_{SD} for stroke was 1.38 (95%CI 1.20-1.60).

Conclusion : Despite a lower prevalence of many traditional CVD risk factors compared to age- and sex-matched DM patients, SLE patients had similar adjusted risks of MI and 38% higher adjusted risks of stroke. These findings may signal potential additional SLE-specific and thrombotic risk factors associated with elevated risk of stroke among SLE patients.

Table. Rates and Multivariable Subdistribution Hazards Ratios (HR_{SD})* for Cardiovascular Disease Events among SLE compared to Diabetes Mellitus (DM) Patients in Medicaid, 2000-2010

	Events	Person-years	Rate** (95%CI)	HR_{SD} (95%CI)[A]	HR_{SD} (95%CI)[B]	HR_{SD} (95%CI)[C]
Myocardial Infarction						
DM	374	114,246	3.27 (2.95-3.62)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	180	53,097	3.39 (2.93-3.92)	1.05 (0.88-1.26)	1.06 (0.88-1.26)	1.01 (0.84-1.22)
Stroke						
DM	497	114,046	4.36 (3.99-4.76)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	338	52,917	6.39 (5.74-7.11)	**1.47 (1.28-1.69)**	**1.41 (1.23-1.62)**	**1.38 (1.20-1.60)**
Myocardial Infarction or Stroke						
DM	844	113,666	7.43 (6.95-7.95)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	504	52,731	9.56 (8.76-10.43)	**1.23 (1.16-1.45)**	**1.27 (1.13-1.42)**	**1.23 (1.10-1.38)**

*Subdistribution hazard ratios accounting for the competing risk of death
**Rate= Incidence Rate, events per 1,000 person-years
Model A: Age (continuous) and sex matched, additionally adjusted for age and sex
Model B: Model A, additionally adjusted for race and zip code-level socioeconomic status and U.S. residential region
Model C: Model B, additionally adjusted for baseline Charlson comorbidity score, number of drugs and cardiac risk factors (including hypertension, smoking, obesity, hyperlipidemia)
Bold= p<0.05

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Abstract Number: 2990

Cancer in Systemic Lupus Erythematosus: Results from the Systemic Lupus International Collaborating Clinics Inception Cohort

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Background/Purpose: Published studies of cancer risk in SLE to date have never focussed solely on clinically confirmed, incident patients. Prior studies thus may not reflect the cancer experience of all SLE patients. To fill this knowledge gap, our purpose was to describe cancer incidence in a large inception SLE cohort.

Methods: Patients meeting ACR criteria for new-onset SLE were enrolled across 32 centres. At enrolment and annual assessments, new cancer diagnoses were recorded by the examining physician. Cancers were confirmed by reviewing medical files including pathology reports. Of 1848 patients enrolled across 1999-2011, 1676 had at least one follow-up. Patients were followed until death, last visit, or end of study interval for this analysis(August 2015). Comparison general population cancer rates, weighted according to the age and sex structure of the SLE cohort, were obtained from participating countries.

Results: Mean age at SLE diagnosis was 34.6(standard deviation, SD 13.3). Mean follow-up was 6.85(SD 3.6), for a total of 11,481 patient-years. We observed 46 invasive cancers in 46 subjects. At cancer diagnosis, mean age was 51.6(SD 15.0) and average SLE duration was 4.8(SD 3.1) years. The most common cancer type was breast (n=10), followed by non-melanoma skin cancer (n=8), lung(n=6), prostate(n=5), 4 head and neck (tonsillar, tongue, and 2 oral), cervical(n=2), thyroid(n=2), melanoma(n=2) and one each of non-Hodgkin lymphoma, leukemia, multiple myeloma, , renal carcinoma, gastric carcinoid, thymoma, and dermatofibrosarcoma. Twenty of the 46 patients (43.5%) who developed cancers were current (n=4) or ex-smokers (n=16); five of the six lung cancers were current or ex-smokers. The over-all cancer rate in the SLE population was 4 events per 1000 patient-years(95% CI, 2.9 to 5.4) versus the general population rate of 2.7 events per 1,000 person-years. In young SLE patients(<40), the cancer rate was 2.2 events per 1,000 patient-years(95% CI 1.2, 3.7) which was more than twice that of the general population of this age (1 event per 1,000). The cancer rate in SLE after age 40 was 5 events per 1,000 patient-years, similar to the general population cancer rate for this age group. With very few hematological cancers observed in this inception cohort, the hematological cancer incidence in SLE was 2.6 cancers per 10,000 patient-years (95% CI 0.5, 7.6), which was a non-significant increase above the population rate of 2 per 1,000 person-years. Among other cancer types, only lung cancer was clearly increased versus the general population; the SLE incidence was 5.2 cases per 10,000 person years (95% CI 2-11), versus 1.7 cases per 10,000 person-years in the general population.

Conclusion: The cancer incidence rate in the cohort was 4 events per 1,000. Though higher than general population rates, it is still less than one-half percent per year. Comparisons of cancer in SLE versus the general population must be interpreted with caution, given differences in outcome ascertainment in the two populations. In our analyses, lung cancer was one of the most common cancers. The vast majority of these were smokers, supporting the belief that lung cancer risk in SLE (as in the general population) is largely driven by smoking.

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Abstract Number: 2991

A Molecular Signature Based on IFN Gene Signature and Serology Defines Two Populations of Patients with Different Baseline Disease Activity in a Large Multinational Phase 3 SLE Trial Population

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Background/Purpose: Registration trials for SLE therapeutics require large numbers of patients with active disease, which in turn necessitates the trials be multinational with many participating centers. While all patients meet ACR classification criteria for SLE, there is a range of disease activity at baseline that may influence response to treatment. To investigate this issue, we used objective molecular and biochemical parameters with high sensitivity (low false positive rate) to characterize patients as “SLE(+)” or “SLE(-)” and examined baseline demographics and disease characteristics to see if SLE(+) patients were distinct from SLE(-) patients.

Methods: Analyses are based on data from two phase 3 trials (n=2262) that evaluated the impact of an anti-BAFF antibody on SLE disease activity (1,2). ANA (≥ 1:80) and SLEDAI ≥ 6 was required at entry. Four dichotomous baseline parameters were used to categorize patients, IFN gene signature (high/normal), anti-dsDNA (+/-), C3 (low/normal) and C4 (low/normal). SLE(+) was defined by any of the following: IFN (high), anti-dsDNA (+), C3 (low) and/or C4 (low). SLE(-) required all of the following: IFN signature (normal), anti-dsDNA (-), C3 (normal) and C4 (normal). IFN gene signature was measured as previously described (3); anti-dsDNA, C3 and C4 were measured at a central lab.

Results: Baseline RNA transcript data were available for 1747 of 2262 patients, with 1318 (75%) of patients meeting the IFN (high) criteria. When IFN (high) was combined with the serology criterion, 1500 (86%) were classified as SLE(+) and 247 (14%) were classified as SLE(-). At baseline, SLE(-) patients had significantly lower mean SLEDAI scores (8.3) compared to SLE(+) (10.7 ; $p<0.001$). Baseline SLEDAI < 10 was observed in 72% of SLE(-) patients compared to 38% of SLE(+). SLE(-) patients had

83% less hematologic, 51% less renal and 70% less vascular organ system involvement at baseline compared to SLE(+) as measured by SLEDAI. Significantly fewer SLE (-) patients were on background medication at baseline. The proportion on corticosteroids at baseline was 49% in SLE(-) compared to 78% in SLE(+), and the proportion on immunosuppressants at baseline was 31% in SLE(-) compared to 44% in SLE(+). An evaluation of geographic distribution revealed that 22% of US patients were SLE(-) compared to 10% for Latin America, 7% for Europe, and 5% for ROW.

Conclusion: A subset of clinical trial patients was identified using biochemical and molecular markers with high sensitivity for SLE. Seronegative SLE patients with normal IFN gene signature represented 14% of the clinical trial population. These patients had lower disease activity and were taking less background medication at baseline, two factors which have been negatively associated with response to treatment in some previous trials. Further study is required to determine if seronegative/IFN normal patients in SLE trials represent a population of SLE patients that can confound the assessment of treatment benefit in SLE clinical trials.

1. Merrill et al., Ann Rheum Dis (2016) 75:332-40.
2. Isenberg et al., Ann Rheum Dis (2016) 75:323-31
3. Hoffman et al., 2015 ACR Mtg, Abstract 1072

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Abstract Number: 2992

In Systemic Lupus Erythematosus with Antiphospholipid Antibodies, Hypocomplementemia Associates with Thrombosis

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Background/Purpose: Hypocomplementemia is a common phenomenon in systemic lupus erythematosus (SLE) and antiphospholipid antibody syndrome (APS). Robust mechanistic data implicate complement activation in antiphospholipid antibody related thrombosis. However, many questions remain unanswered regarding the clinical implications of hypocomplementemia in SLE and APS. Whether low complement should be considered a risk factor for thrombosis in this population is unknown. This work was undertaken to evaluate the relationship between hypocomplementemia and thrombotic outcomes in SLE patients with antiphospholipid antibodies.

Methods: As part of a longitudinal lupus cohort, thrombotic events were noted at inception and updated at each quarterly visit. Anticardiolipin antibodies and the lupus anticoagulant were measured quarterly. The statistical analysis included patients who were found on longitudinal follow up to have antibodies to cardiolipin or the presence of the lupus anticoagulant. Patients were then categorized according to the type of thrombotic event, the presence of hypocomplementemia (low C3, low C4 and both low C3 and low C4) and type of antiphospholipid antibody encountered. Those with low complement were compared to those without and the odds ratio for each thrombotic outcome was calculated.

Results: 2399 SLE patients were included in this analysis, 1140 (47.5%) had antibodies to cardiolipin and 624 (26.0%) were found to have had a positive lupus anticoagulant. The relationship between the antiphospholipid antibodies, thrombotic outcomes

and low C3, low C4 or both is outlined in Table 1. Low C3 and low C4 in combination associated with deep venous thrombosis and stroke in those with anticardiolipin antibodies. This relationship remained significant on multivariate analysis, controlled for ethnicity and gender. The lupus anticoagulant and low C3 and C4 in combination was also associated with stroke. An association was also demonstrated with digital gangrene and low C4 in the presence of the lupus anticoagulant.

Conclusion: Hypocomplementemia (both low C3 and low C4), in the presence of either the lupus anticoagulant or anticardiolipin antibodies, associates with stroke. Low complement, with antibodies to cardiolipin, also associated with deep venous thrombosis. These finding support the mechanistic data implicating the complement system in APS related thrombus formation and indicate that hypocomplementemia, in association with antiphospholipid antibodies may represent an addition risk factor for thrombosis.

Type of APL	Thrombosis	Low C3 only	P value	Low C4 only	P value	Both Low C3 and Low C4	P value
Anti cardiolipin	**Superficial**	0.8 (0.25,2.51)	0.6981	1.23 (0.34,4.47)	0.7543	1.15 (0.56,2.37)	0.7041
	DVT	1.43 (0.85,2.42)	0.1798	0.83 (0.37,1.83)	0.641	1.64 (1.13,2.39)	**0.0095**
	Stroke	1.01 (0.51,1.98)	0.9838	0.29 (0.07,1.26)	0.0993	1.64 (1.06,2.56)	**0.0278**
	Myocardial Infarction	1.31 (0.51,3.34)	0.5768	0.37 (0.05,2.84)	0.3357	1.48 (0.76,2.89)	0.2501
	Digital Gangrene	2.03 (0.61,6.77)	0.247	2.49 (0.61,10.2)	0.2039	1.43 (0.54,3.79)	0.4766
Lupus Anticoagulant	**Superficial**	0.3 (0.07,1.36)	0.1199	0.67 (0.15,3.04)	0.6004	0.74 (0.36,1.51)	0.4024
	Deep venous thrombosis	1 (0.57,1.75)	0.9886	0.96 (0.45,2.06)	0.9202	0.88 (0.59,1.31)	0.5376
	Stroke	1 (0.46,2.21)	0.9909	0.4 (0.09,1.75)	0.2221	1.89 (1.14,3.15)	**0.014**
	Myocardial Infarction	0.79 (0.28,2.25)	0.6598	0.32 (0.04,2.53)	0.283	0.92 (0.46,1.83)	0.8164
	Digital Gangrene	4.21 (0.98,18.04)	0.0529	5.47 (1.06,28.19)	**0.0421**	2.25 (0.61,8.28)	0.2228

Disclosure: L. Durcan, None; **W. Fu**, None; **M. Petri**, None.

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Abstract Number: 2993

Membrane-Type 1 Matrix Metalloproteinase Controls Osteo- and Chondrogenesis By a Proteolysis-Independent Mechanism Mediated By Its Cytoplasmic Tail

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Background/Purpose: We aimed to understand the mechanism by which membrane-type 1 matrix metalloproteinase (MT1-MMP, MMP-14) controls bone and cartilage homeostasis. MT1-MMP, a cell-membrane-bound proteinase with an extracellular catalytic site and a 20-amino acid cytoplasmic tail, plays a key role in postnatal bone formation. The genetic deficiency of MT1-MMP in the mouse causes dwarfism, osteopenia and severe arthritis. Deletion of MT1-MMP in bone marrow-derived mesenchymal progenitor cells (BM-MSC) recapitulates this phenotype, showing that MT1-MMP controls osteogenic differentiation in MSC. The phenotype of MT1-MMP$^{-/-}$ mice has been proposed to result from lack of MT1-MMP proteolytic activity. However, mounting evidence shows a variety of proteolysis-independent signaling functions of MT1-MMP. The unique tyrosine (Y573) in the MT1-MMP cytoplasmic tail is fundamental for the control of intracellular signaling.

Methods: We generated a mouse with the Y573D mutation in MT1-MMP (MT1-MMP Y573D) and characterized its skeletal phenotype by histological and microCT analyses. Isolated BM-MSC were induced to differentiate into osteoblasts, chondrocytes and adipocytes, using qRT-PCR to analyze gene expression. Mouse C3H10T1/2 MSC were transfected with MT1-MMP cDNA and analyzed for Wnt signaling by luciferase reporter assays.

Results: MT1-MMP Y573D mice had increased trabecular bone relative to wt littermates, marked thinning of articular cartilage with disorganized tissue architecture, clustering and cloning of chondrocytes, and pronounced decrease in bone marrow-associated and total body fat. We induced BM-MSC from wt and MT1-MMP Y573D littermates to differentiate into osteoblast and chondrocytes, and myeloid precursors into osteoclasts. The Y573D mutation dramatically increased MSC expression of osteoblast markers and strongly downregulated chondrocyte and osteoclast markers. These findings indicated that Wnt signaling is upregulated in MT1-MMP Y573D-expressing MSC. Therefore, we analyzed Wnt signaling. We transiently transfected C3H10T1/2 MSC cells in osteoblast medium with the cDNAs for wt MT1-MMP and MT1-MMP Y573D. As controls the cells were transfected with the empty vector (pcDNA) or with MT1-MMP E240A, a mutant devoid of proteolytic activity. MT1-MMP Y573D dramatically upregulated Wnt signaling relative to wt MT1-MMP and MT1-MMP E240A.

Conclusion: MT1-MMP controls Wnt signaling by a mechanism independent of extracellular proteolysis and mediated by its cytoplasmic tail. MT1-MMP is a bifunctional protein, with an extracellular proteolytic activity that promotes bone formation through ECM remodeling and a cytoplasmic tail that controls osteogenesis by interacting with a key pro-osteogenic signaling pathway.

Disclosure: Y. Qing, None; **M. Attur**, None; **T. Kirsch**, None; **Y. J. Lee**, None; **S. Yakar**, None; **Z. Liu**, None; **S. B. Abramson**, None; **P. Mignatti**, None.

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Abstract Number: 2994

Binding of Periostin to Discoidin Domain Receptor-1 (DDR1) Promotes Cartilage Degeneration By Inducing MMP-13 Expression

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Background/Purpose: We and others have previously shown that periostin (Postn) expression is dramatically elevated in cartilage and sub-chondral bone in OA patients and surgical models of OA (medial meniscectomy and anterior crucial ligament resection or PMX, partial meniscectomy) in rodents. *In vitro* Postn promotes collagen and proteoglycan degradation in human chondrocytes by

upregulating MMP-13 and ADAMTS4 expression. Postn controls gene expression in bone cells by interacting with avb3 integrin. However, the nature of periostin receptor(s) in chondrocytes is unknown. DDR1, a collagen-binding receptor tyrosine kinase highly expressed in chondrocytes, controls MMP-13 expression during chondrogenesis. Therefore, we hypothesized that the effect of Postn on chondrocytes is mediated by DDR1 and Postn-deficient mice (*Postn*$^{-/-}$) are protected from surgically-induced post-traumatic OA.

Methods: (*Postn*$^{-/-}$) mice were purchased from Jackson Laboratory (B6;129-Posttntm1Jmol/J Stock No: 009067). We subjected 3-months old littermates (*Postn*$^{+/+}$, *Postn*$^{+/-}$ and *Postn*$^{-/-}$) to partial medial meniscectomy (PMX) or sham surgery, and harvested the knee joints 8 week post-surgery for histological assessment of OA progression. Human OA chondrocytes cultures were incubated in the presence or absence of the DDR1 inhibitor DDR1-IN-1 dihydrochloridein (100-500 nM) for 2 h before addition of Postn (1 µg/ml) or control vehicle to the culture medium. MMP-13 levels were determined by ELISA 24 h post stimulation.

Results: We observed abundant expression of DDR1 mRNA in human chondrocytes and we found comparable levels of DDR1 in OA and normal cartilage. However, Postn expression was 3-4 times as high in OA than in normal cartilage. Pre-incubation of human cartilage explants or cultured chondrocytes with DDR1-IN-1 dihydrochloridein inhibited both constitutive and Postn-induced MMP-13 expression in a dose-dependent manner. In contrast, neutralizing antibody to αvβ3 integrin had no effect on Postn induction of MMP-13 expression. Co-immunoprecipitation experiments showed that Postn physically interacts with DDR1 in human chondrocytes. Furthermore, *Postn*$^{-/-}$ mice showed reduced PMX-induced cartilage degeneration and osteophyte formation, and both *Postn*+/- and *Postn*-/- mice had reduced subchondral bone thickening, relative to *Postn*+/+ mice.

Conclusion: *Postn*$^{-/-}$ mice are protected from surgically-induced post-traumatic OA, showing that Postn promotes cartilage degeneration. DDR1 mediates the stimulatory effect of Postn on MMP-13 expression. Further studies are in progress to investigate the potential of periostin as a druggable target for the treatment of OA.

Disclosure: Y. Qing, None; **P. Mignatti**, None; **A. Ramme**, None; **T. Kirsch**, None; **J. Patel**, None; **M. Attur**, None.

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Abstract Number: 2995

WISP1/CCN4 Aggravates Experimental Osteoarthritis and Is Associated with Disease Progression in Early Osteoarthritis Patients

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Background/Purpose: Many osteoarthritis (OA) patients show synovial activation, which is thought to be involved in joint destruction. Previously, we described strongly increased expression of *Wnt2b* and *Wnt16* in the synovium of two experimental OA models. In addition, we found increased *Wisp1* expression, a protein induced by canonical Wnt signaling. Here, we determined whether there is a relation between synovial *WISP1* expression and OA progression in a cohort study of patients with early symptomatic OA. Furthermore, we elucidated whether WISP1 plays a role during experimental OA by inducing OA models in wild type (WT) and *Wisp1*$^{-/-}$mice.

Methods: Microarray analysis was performed on synovium from patients in the CHECK study, initiated to follow progression of early symptomatic OA patients. Expression data were correlated with progression of OA (defined as a decrease in joint space width of ≥1mm and progression of osteophyte formation of ≥4x in size) between baseline and the five-year follow-up measurement.

Human end-stage OA synovium was stimulated with WISP1. Joint pathology in WT or *Wisp1*$^{-/-}$mice was assessed by histology after induction of collagenase-induced OA (CIOA), destabilization of the medial meniscus (DMM) and anterior cruciate ligament transection (ACLT) experimental models of OA. The aggrecan neoepitope NITEGE was visualized using immunohistochemistry. Gene expression was evaluated using qRT-PCR.

Results: Microarray analysis of synovial tissue from patients in the CHECK cohort showed significantly increased WISP1 expression at baseline in OA progressors versus non-progressors. To determine the mechanism of how WISP1 might be involved in OA pathology, we stimulated human OA synovium with WISP1. This increased the expression of *MMP2/3/9/13* and *ADAMTS4/5*. Next, we determined the *in vivo* role of WISP1. First, we found that spontaneous cartilage damage was not different between WT and *Wisp1*$^{-/-}$ mice at 3, 6 and 12 months of age. Next, we assessed joint pathology 42 days after induction of CIOA. Cartilage damage was significantly decreased in the tibio-femoral joints of the *Wisp1*$^{-/-}$ mice as compared with the WT controls. In line, we found significantly decreased cartilage degeneration in the *Wisp1*$^{-/-}$ mice in the DMM and ACLT models, 56 days after induction. In addition we found decreased expression of *Mmp3/9* and the aggrecanases *Adamts4/5* in the synovium, 7 days after induction of CIOA in *Wisp1*$^{-/-}$ mice, in line with the increased expression of these factors after stimulation of human OA synovium with WISP1. Whereas *Wisp1*$^{-/-}$ mice showed decreased expression of the protease inhibitor *Timp1*, the expression of *Timp3*, an important inhibitor of ADAMTS4/5, was unaffected. Finally, the protease activity in the cartilage, as assessed by the staining of the neoepitope NITEGE, was decreased in the *Wisp1*$^{-/-}$mice.

Conclusion: Increased WISP1 expression may play an important role in OA pathology via increased synovial MMP/ADAMTS expression. Furthermore, because of the tight regulation and complexity of Wnt signaling and its role in many physiological processes, targeting WISP1 may more specifically target OA-related pathological events, while minimizing interference with physiological processes.

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Abstract Number: 2996

High Fat Diet-Induced Osteoarthritis Progression Is Dependent on Toll-like Receptor 4

Mary Beth Humphrey[1], Evangelia Kalaitzoglou[2], Camille Herron[2], Yanqing HU[2], Yao Fu[3], Erika Barboza Prado Lopes[3], Elise Donovan[3], Joanna Hudson[3] and Timothy Griffin[3], [1]Medicine/Rheumatology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [2]Medicine, University of Oklahoma Health Sciences Center, Oklahoma City, OK, [3]Aging and Metabolism, Oklahoma Medical Research Foundation, Oklahoma City, OK

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Background/Purpose: Obesity is considered the primary preventable risk factor for OA, increasing the risk of developing OA in weight-bearing joints, especially the knee, as well as in non-weight-bearing joints, such as the hand. Obesity is associated with alterations in systemic inflammation as well as locally within the knee joint compartment. Saturated free fatty acids (FFA) in high fat (HF) diets induce pro-inflammatory cytokine production in a Toll-like receptor 4 (TLR4)-dependent manner. Therefore, we hypothesized that HF diet-induced OA is dependent on TLR4. To test this hypothesis, mice replete or deficient in TLR4, as well as DAP12-deficient mice, that have exuberant TLR4 responses, were treated with control or HF diet to induce obesity and OA.

Methods: 12-14 month old female WT (n=12-22), DAP12 KO (n=15-18) and TLR4 KO (n=10) mice were equally randomized to control (CON) or HF diets (10% or 60% kcal from fat, Research Diets) for 12 weeks. Body composition by DXA (Lunar PIXImus),

micro-computed tomography (microCT) of knee joints, and serum cytokine analysis was performed at baseline and 12 weeks. Two blinded graders evaluated OA pathology in the medial and lateral femur and tibia using a Modified Mankin OA scoring system. Synovium- infrapatellar fat pad samples and gonadal fat were collected for inflammatory gene expression and histology.

Results: HF diet induced obesity with increased fat mass in all mice independent of genotype compared to CON diet. HF diet significantly increased maximum OA scores in WT and DAP12 KO, but not TLR4 KO mice. Cartilage damage scores and tidemark duplications were significantly increased in HF diet WT and DAP12 KO but not TLR4 KO mice. Interestingly, chondrocyte hypertrophy was significantly suppressed in DAP12 KO mice independent of diet. Glucose intolerance was induced in HF diet WT and TLR4 KO but not DAP12 KO mice. All HF fed mice had increased serum leptin levels compared to their CON groups. Gonadal fat depots increased, adipocytes were significantly hypertrophied, and crown-like structures increased in WT and DAP12 KO but not TLR4 KO mice. However, HF diet failed to increase serum proinflammatory cytokines in any group. Infrapatellar fat pads (IFP) from HF diet WT mice increased in size while IFP from DAP12 KO mice had increased adipocyte hypertrophy and crown-like structures. Synovial thickening or macrophage infiltration was similar between groups independent of diet. IFP gene expression revealed significant changes between DAP12 KO and WT and surprisingly few changes between WT and TLR4 KO.

Conclusion: This study is the first to use middle-aged mice for a short term feeding to induce HF diet-induced OA progression. DAP12 KO and WT mice developed similar OA while TLR4 mice were protected from HF diet-induced progression of OA. HF-diet DAP12 KO mice developed distinct differences in their OA including significantly reduced hypertrophic chondrocytes and significantly increased IFP adipocyte hypertrophy. Our findings show that TLR4 is required for HF-diet induced progression of OA in middle-aged female mice. TLR4-inhibitors may be attractive targets for disease modifying osteoarthritis drugs.

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Abstract Number: 2997

Microrna-29a Curtails Synovitis in the Development of Knee Osteoarthritis By Disrupting VEGF

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Background/Purpose: Intensive synovitis is a prominent feature that progressively aggravated excessive fibrosis reactions relative to joint stiffness in the pathogenesis of osteoarthritis (OA). MicroRNA-29a (miR-29a) is reported to modulate overabundant fibrotic matrix accumulation during tissue deterioration. This study is undertaken to verify whether miR-29a expression was linked to synovial fibrosis in end-stage knee OA and tested whether miR-29a signaling affected fibrogenic reactions in synovial fibroblasts and synovial remodeling and joint integrity during OA development.

Methods: Synovial tissues and fibroblasts were harvested from 20 patients with end-stage knee OA. For non-OA group, synovial specimens were biopsied from 10 patients with femoral neck fracture. Knee joints in mice that overexpressed miR-29a were subjected to superpatellar injection of collagenase to provoke OA. miR-29a and fibrogenic factor expression were quantified by RT-quantitative PCR and in situ hybridization. Synovial fibrosis and joint injury were analyzed by Masson's trichrome staining, immunohistochemistry and histomorphometry.

Results: Synovial tissues within end-stage knee OA exhibited 52% declines in miR-29a expression in conjunction with 2.1-3.3-

fold increases in fibrotic matrix deposition, capillary vessel formation, and membrane thickness compared to non-OA group. In vitro, miR-29a signaling interruption led to 1.8-2.6-fold increases in joint-deleterious factors collagen III, TGF-β1, MMP3, MMP9, ADAMTS5, and VEGF expression within synovial fibroblast cultures. Gain of miR-29a signaling enabled cell cultures to have 42-67% reductions in baseline expression of joint-deleterious factors. Of note, miR-29a transgenic mice exhibited moderate responses to the collagenase exacerbation of fibrosis, macrophage infiltration, and hypervascularization within synovial microenvironment. These synovium-protecting effects remarkably shielded knee joints from articular cartilage deterioration histopathology and gait irregularity. Likewise, exogenous miR-29a administration via intra-articular injection delayed the progression of excessive synovial angiogenesis, inflammation and fibrosis, a protective regime that improved joint damage and walking patterns of injured knees. Luciferase reporter analyses revealed that miR-29a directly targeted 3'-untranslated region (3'-UTR) of VEGF, which suppressed VEGF production and angiogenic activities in synovial fibroblasts cultures.

Conclusion: miR-29a deficiency is relevant to the occurrence of excessive synovial fibrosis within end-stage OA knees. miR-29a signaling is indispensable to fend off fibrogenic, angiogenic, and cartilage degradation factor expression in synovial fibroblast cultures. Gain of miR-29a function facilitates the maintenance of synovium homeostasis that alleviates OA knee pathogenesis. This study sheds a new light on the anabolic actions and therapeutic potential of miR-29a signaling to synovial integrity during OA progression.

Disclosure: F. S. Wang, None; **Y. C. Sun**, None; **Y. S. Chen**, None; **J. Y. Ko**, None.

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Abstract Number: 2998

Gut Microbiota Induce IGF-1 and Promote Bone Formation and Growth

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Background/Purpose: Appreciation of the role of the gut microbiome in regulating vertebrate metabolism has exploded recently. However, the effects of gut microbiota on skeletal growth and homeostasis have only recently been explored.

Methods: To understand the effects of short-term and long-term colonization of microbiota on bone, we colonized sexually mature germ-free (GF) mice with gut microbiota from SPF mice. In complementary experiments, SPF mice were treated with antibiotics to deplete microbiota. Bone parameters were examined by micro-computed tomography (micro-CT) and histomorphometry 1 month after colonization. Micro-CT analysis was also performed 8 months after colonization. Serum C-terminal telopeptide (CTX), amino-terminal propeptide (P1NP) and insulin like growth factor 1 (IGF-1) were measured by ELISA.

Results: Reduced bone mass was observed one month after colonization, reflecting increases in bone resorption as measured by CTX. However, bone formation was significantly increased. Increased bone formation was demonstrated by both elevated bone formation rate measured by dynamic histomorphometry and increases in serum P1NP, a marker of bone formation. In addition, short-term colonized mice displayed a widen growth plate, suggesting that microbiota promotes longitudinal bone growth. In mice colonized for 8 months, increased bone formation and growth plate activity predominate, resulting in equalization of bone mass and increased longitudinal and radial bone growth. Serum levels of IGF-1, a hormone with known actions on skeletal growth, were substantially increased in response to colonization, with significant increases in liver and adipose tissue IGF-1 production. Antibiotic treatment of conventional mice, in contrast, decreased serum IGF-1 and inhibited bone formation, suggesting that skeletal effects of microbiota are mediated by IGF-1. Treatment with vancomycin, a non-absorbable antibiotic that only targets gram positive bacteria, was sufficient to decrease serum IGF-1 and inhibit bone formation, indicating that gram positive commensals are

sufficient for the regulation of bone formation by microbiota.

Conclusion: Colonization increases both bone formation and resorption, with the net effect of colonization varying with the duration of colonization. Long-term colonization with microbiota provides a net anabolic stimulus to the skeleton, which is likely regulated by IGF-1. Manipulation of the microbiome may afford opportunities to optimize bone health and growth.

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Abstract Number: 2999

Autologous Osteoblastic Cells Versus Concentrated Bone Marrow Implantation in Osteonecrosis of the Femoral Head: A Randomized Controlled Single Blind Study

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Background/Purpose: Non traumatic osteonecrosis (ON) of the femoral head is characterized by epiphyseal necrosis leading to femoral head collapse and eventually hip replacement. The physiopathology of ON is multifactorial but it can be seen as a vascular, mesenchymal and bone cells disease. The treatment of early stages ON of the femoral head is still controversial. Core decompression using single or multiple drillings demonstrated contradictory results. Moreover core decompression associated with the implantation of bone marrow concentrate (BMC) containing mesenchymal stem cells (MSC) showed encouraging results in prospective and controlled trials. Indeed, it could delay ON of the femoral head progression to fractural stages and improve symptoms. Then, the possibility was raised that a cell-based medicinal product (PREOB®) consisting in a population of autologous osteoblastic cells (OB) could be more efficacious than BMC for the treatment of early stages ON of the femoral head. This study was undertaken to evaluate the efficacy of OB cells implantation in a randomized comparison with BMC implantation in early stages (prefractural ARCO stage 1 or 2) ON of the femoral head.

Methods: Patients with stage 1 or 2 ON were included in a randomized controlled single blind trial. Hips were randomized to receive a core decompression procedure followed by BMC or OB cells implantation. In the BMC group, 410.6 ± 84.9 ml of bone marrow (BM) was harvested from the iliac crest and concentrated to 41.8 ± 10.9 ml. In the OB group, MSC were isolated from BM aspirate (56.8 ± 36.3 ml), expanded and differentiated ex vivo under autologous conditions to obtain a population of OB cells with a target of 20 million of OB cells. Hip pain (as measured by visual analogue scale), WOMAC® score and ARCO stage (as assessed by X-Rays) were evaluated at 3, 6, 12, 24 and 36 months. For the final radiological evaluation, all radiographs were and given a random number. Four readers assessed all blinded radiographs for the progression of ON from non-fractural (stage 1 or stage 2) to fractural stage of ON (stage 3 or 4) by reference to ARCO-defined stages. The primary endpoint was the proportion of treatment responders at 24 months. A responder was defined as the absence of progression to fractural stage (stage 3 or 4) and a clinically significant pain improvement (i.e., at least the MCID, namely ≥10mm from baseline).

Results: From 72 hips randomized, 63 hips were treated, and 60 hips (30 hips per group) were assessable and analyzed as the efficacy cohort. Baseline demographic data such age (50.2 ± 13.1 years), gender, BMI, risk factors (corticosteroids, alcohol abuse and idiopathic ON), location and size of ON (more than 50% in each group were extensive C lesion; >30%) and symptoms (pain score and WOMAC® score subscales) were not statistically different between groups. At 24 months, 70.0% versus 36.7% of hips (p=0.011) and at 36 months, 60.0% versus 33.3% of hips in OB and BMC groups respectively were considered as treatment

responders. In post-hoc analysis, the rate of progression to stage 3 or 4 was in favor of the OB group: at 24 months, 20.0% versus 40.0% of hips and at 36 months, 20.0% versus 50.0% of hips in OB and BMC groups respectively progressed to stage 3 or 4 (corresponding to a 60% reduction in hip fracture; $p<0.05$). Over the 36-month period, the survival analysis showed a significant difference in the time to progression to stage 3-4 in favor of the OB group (Kaplan Meier; hazard ratio 0.37). In the OB group, the decrease in hip pain was clinically significant at all time points, and as early as 3 months, while no pain relief was observed in the BMC group. Finally, patients treated with OB cells demonstrated a decrease in joint symptoms at all time points according to the WOMAC® score. At 36 months, 3 hips in the OB group and 6 hips in the BMC group had undergone total hip replacement. Overall, 553 treatment emergent adverse events (TEAE) (226 in the BMC group and 327 in the OB group) were reported, of which 2.7% (15 TEAE) were possibly related to the procedure or the cell therapy products. 61.9% of subjects experienced at least one serious adverse event (SAE) during the study: 128 SAE (57 in the BMC group and 71 in the OB group) were reported in 39 hips (19 hips in the BMC group and 20 hips in the OB group).

Conclusion: This is the first trial studying the efficacy of a differentiated bone cell therapy product in ON of the femoral head. Compared to BMC, PREOB® is well characterized and its ability to form bone well defined which might explained its superiority to BMC. This study showed that OB cells implantation could be more efficacious than BMC treatment to delay the progression to subchondral fracture stage (ARCO stage 3) and to reduce pain in ON of the femoral head

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Disclosure: V. Gangji, Bone Therapeutics, 8; **M. Toungouz**, None; **C. Lechanteur**, None; **Y. Beguin**, None; **E. Baudoux**, None; **M. Malaise**, None; **V. De maertelaer**, None; **S. Pather**, None; **J. Ino**, Bone Therapeutics, 3; **J. P. Hauzeur**, Bone therapeutics, 5.

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Abstract Number: 3000

Safety of the Knee Needle Arthroscopy: A Review of 1136 Procedures in 919 Patients

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Background/Purpose: Knee needle arthroscopy (KNA) is a minimally invasive procedure consisting in insertion of a thin fiber-optic needle system in the joint cavity, followed by inspection, tissue sampling, therapeutic lavage, and if needed, steroids injection after the procedure. It is usually performed in an office-based setting, requiring only local anaesthesia, as an out-patient procedure. KNA is of particular interest as it can be used for diagnosis (in case of undifferenciated arthritis), scientific purposes (synovial biopsies serving for histology, proteomics, and genomics), and can serve as a therapeutic tool (mainly articular lavage). Few data have been published regarding safety of KNA, and available studies deal with a relatively small number of patients. Objective: To determine the incidence of overall and serious, notably septic, complications, and identify patients at higher risk.

Methods: We retrospectively reviewed the records of all arthroscopies performed in the rheumatology department of our teaching hospital between July 2002 and December 2015. Patients, suffering from a rheumatic disease, and knee complains underwent a KNA, either for the diagnosis, or for clinical research reason. The procedure was performed in a dedicated room under sterile conditions (extensive local disinfection and draping of the leg) and local anaesthesia, by a senior rheumatologist. Of note, joint needle aspiration was performed before the incision. The fluid (if obtained) was then sent for routine laboratory analysis: cellularity, crystal detection and culture. The patient was allowed to walk immediately after the procedure. All patients signed an informed consent before the procedure.

Results: A total of 919 patients were included in the study. Two-thirds (65.4%) were female and mean age was 52 years. A total of 1,136 KNA were performed. Almost half of the patients suffered from rheumatoid arthritis (47%), 20.2% from osteoarthritis, 10.7% from spondylarthritis, 10.7% from undifferentiated arthritis, 4.9% from microcrystalline arthritis, 3% from connective tissue diseases, and 1.8% from idiopathic juvenile arthritis A few patients suffered from sarcoidosis, hemochromatosis, villonodular synovitis and polymyalgia rheumatica. Of note, a diagnosis of septic arthritis was suspected in 7 patients by joint inspection and confirmed by positive cultures. The overall rate of complications was 1.5% and the rate of infection was 0.79%. Minor complications included 2 cases of subcutaneous hematoma, 4 cases of delayed healing with persistent superficial wound, 1 case of local skin atrophy after glucocorticoids (GC) injection and 1 case of pancreatitis, also attributed to the injection of GC in a HIV positive patient, treated with antiretrovirals. We observed no cases of post-intervention hemarthrosis, bleeding or thrombo-embolic complications. All serious complications were infectious. We identified 7 cases of confirmed septic arthritis, 1 case of septic bursitis and 1 case of possible septic arthritis (no bacteriological proof). Patients were predominantly male (6/9), most of them with ≥2 comorbidities. 4 out of 9 patients were treated by oral GC and all patients received intraarticular glucocorticoids during the procedure. As expected, *Staphylococcus aureus*was the most frequent pathogen identified. On the 9 infected patients, 7 were hospitalized, treated with IV antibiotics and underwent a surgical arthroscopic lavage 24-48 hours following the admission. Clinical evolution showed improvement in all cases with no long-term morbidity.

Conclusion:

KNA is a safe, and well-tolerated procedure, with less than 1% of septic complications. It's slightly lower than conventional arthroscopy, with the additional advantages of local anaesthesia, fast recovery and lower cost. Special caution should be applied to patients with comorbidities, previous infection, or treated with GC.

Disclosure: A. ISHCHENKO, None; **J. C. YOMBI**, None; **A. Nzeusseu Toukap**, None.

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Abstract Number: 3001

Lumbar CT-Guided Steroid Infiltration on the Refractory Low Back Pain. Study of 258 Procedures in the Same Center

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Background/Purpose: Low back pain of mechanical origin is a major cause of disability and surgical intervention. The lumbar computed tomography (CT)-guided steroid infiltration can accelerate the recovery process and sometimes avoid the surgery. Our aim was to review the indications, efficacy and complications of this technique in a wide series of unselected patients. In addition a comparative study of efficacy was performed according to the lumbar underlying pathology, type of steroid and approach of injection.

Methods: Study of lumbar CT-guided steroid injections performed in a University Hospital between January 2012 and June 2015. The minimum follow-up was 3 months. The procedure was performed in patients with low back pain refractory to standard medical therapy and Lumbar Spine Rehabilitation. Efficacy was assessed at 1 and 3 months according to a semiquantitative scale as the pain response as a) total response, b) partially c) no or d) worsening pain. A comparative study of the efficacy and safety was performed, regarding: a) underlying pathology, b) approach of injection and c) the different types of steroids used. Fisher's test and

Chi2 and the SAS System for Windows V program 9.2.were used for statistical analysis.

Results: During the study period 258 procedures were performed in 171 patients (132 men / 126 women) with a mean age ± SD of 58.24±13.45 years (range, 18-88). The indications for the injection were: a) disc herniation (44.57%), b) lumbar stenosis (34.11%), c) postoperative fibrosis and spondylolisthesis (20.15%) and d) facet joint synovial cysts syndrome (1.17%). Approaches used were: a) posterior epidural (24.42%), b) lateral recess (58.91%), and c) foraminal (16.67%). The chosen steroid was triamcinolone (74.81%), dexamethasone (23.64%) and methylprednisolone (1.55%). In a significant proportion of the procedures improvement in the patient´s sintomatology was reported at the first month, regardless of the indication, route of corticosteroid injection and steroid used (TABLE). Regarding the overall outcome, at 3 months 72.48% of the patients experienced clinical improvement. And only 21.71% of patients required a subsequent surgery. The clinical efficacy showed no statistically significant differences according to the indication of the procedure or the route used for the injection. However, the improvement of pain was significantly greater in patients treated with triamcinolone than those treated with dexamethasone (p = 0.01). Regarding safety there were 6 (2.3%) local complications (puncture of the thecal sac) and 3 (1.16%) systemic complications (allergic reaction). None of these complicationes were of clinical relevance and they were not associated with the corticosteroid used.

Conclusion: CT-guided corticosteroid injection is an effective and safe treatment in low back pain refractory to standard medical therapy in patients with spinal stenosis, disc herniation and postoperative fibrosis. Triamcinolone infiltration seems to be more effective than dexamethasone.

	Total response (%)	Parcial response n (%)	No response n (%)	Worsening n (%)	TOTAL n (%)
Indication					
- disc herniation	7 (6.9%)	83 (72.2%)	23 (20.0%)	2 (1.7%)	115 (44.6%)
- lumbar spinal stenosis	4 (4.6%)	60 (68.2%)	22 (25.0%)	2 (2.3%)	88 (34.1%)
- postsurgical pain syndrome	1 (2.1%)	36 (75.0%)	11 (28.6%)	0 (0.0%)	48 (18.6%)
- others	0 (0.0%)	5 (71.4%)	2 (28.6%)	0 (0.0%)	7 (2.7%)
Approach					
- posterior epidural	2 (3.2%)	43 (68.3%)	18 (28.6%)	0 (0.0%)	63 (24.4%)
- lateral recess	9 (5.9%)	107 (70.4%)	33 (21.7%)	3 (2.0%)	152 (58.9%)
- foraminal	1 (2.3%)	34 (79.07%)	7 (16.3%)	1 (2.3%)	43 (16.7%)
Steroid					
- Triamcinolone Acetonide	12 (6.2%)	142 (73.6%)	36 (18.7%)	3 (1.6%)	193(4.8%)
-Dexamethasone	0 (0.0%)	59 (63.93 %)	21 (34.4%)	1 (1.6%)	61 (23.6%)
- Methylprednisolone	0 (0.0%)	4 (100.0%)	0 (0.0%)	0 (0,0%)	4 (1.6%)
TOTAL, n= 258	12 (4.7%)	184 (71.3%)	57 (22.5%)	4 (1.6%)	258 (100%)

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Abstract Number: 3002

Does Morbid Obesity Negatively Affect Patient Reported Outcomes Following Total Knee Arthroplasty?

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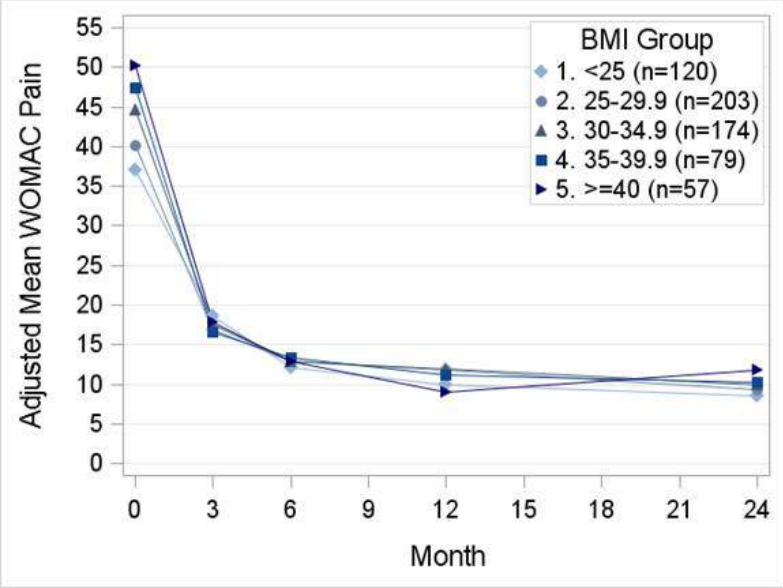
Background/Purpose: Utilization of total knee arthroplasty (TKA) continues to grow. Recent literature has questioned the appropriateness of TKA for patients that are morbidly obese, citing the high risk of complications. Data on the impact of obesity on patient-reported outcomes following TKA remain sparse. We assessed the extent to which obesity level affects patient-reported outcomes in pain, function, and satisfaction with surgery following TKA.

Methods: We followed a cohort of TKA recipients 40 years or older with a primary diagnosis of osteoarthritis scheduled for TKA at four tertiary medical centers. We stratified patients into 5 groups using the World Health Organization categories for obesity based on body mass index (BMI). We assessed whether obesity category is associated with post-operative pain and function evaluated at 24 months, as well as baseline to 24 month changes in pain and function. We used a piecewise linear model with a knot at 3 months to determine covariates associated with early and late TKA recovery. Multivariable models adjusted for age, sex, race, diabetes, musculoskeletal functional limitation index, medication use and study site.

Results: 691 patients were enrolled across 4 centers, with 633 providing baseline BMI information and outcomes at one or more follow-ups. At baseline 19% were normal weight (BMI < 25), 32% were overweight (25 ≤ BMI <30), 27% were obese (30 ≤ BMI <35), 12% were morbidly obese (35 ≤ BMI <40) and 9% were severely obese (BMI ≥40). There were differences in baseline characteristics between BMI groups. Heavier subjects tended to be younger, were more likely to be female, non-White, and have diabetes. Study participants with higher BMI had worse preoperative WOMAC Pain and Function, with mean pre-operative pain score ranging from 34 in normal weight participants to 50 in severely obese participants, and mean pre-operative function score ranging from 35 in normal weight participants to 51 in severely obese participants. Patients in all BMI groups showed substantial improvement in pain (Figure). At 24 month follow-up there was no significant difference in WOMAC Pain between the BMI Groups. The results suggested that more obese patients had a steeper recovery slope from baseline to 3 months, and no difference in slope by BMI group between 3 and 24 months. Results were similar for WOMAC Function. All groups reported high satisfaction with the results of surgery, with 75% very satisfied at month 6 and 80% very satisfied at month 24.

Conclusion: Despite worse pain and functional status preoperatively, subjects in all BMI groups achieved similar pain relief and functional improvements following TKA. From the standpoint of patient reported outcomes, TKA is highly effective in obese patients. **Figure**. Adjusted Mean WOMAC Pain by BMI Group and Timepoint



Disclosure: J. E. Collins, None; **H. Y. Yang**, None; **I. M. Usiskin**, None; **J. N. Katz**, None; **E. Losina**, None.

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Abstract Number: 3003

Impact of Preoperative Opioid Use on Total Knee Arthroplasty Outcomes

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Background/Purpose: Total knee arthroplasty (TKA) is an effective treatment for patients with end-stage knee osteoarthritis (OA); however, a growing body of evidence suggests that patients using opioids prior to TKA experience worse pain outcomes immediately following surgery. We evaluated the pain relief achieved from TKA in knee OA patients with and without opioid prescriptions pre-TKA.

Methods: We augmented patient-reported data from a longitudinal study of TKA outcomes with medical record-based information about opioid use. The study included patients >40 years old who underwent primary, unilateral TKA at a tertiary academic medical center. The Pain Catastrophizing Scale (PCS) and patient-reported outcomes, including the Western Ontario and McMaster Universities Arthritis Index (WOMAC), were assessed at baseline and 6 months post-TKA. Demographic and comorbidity information were collected at baseline via study questionnaire. We reviewed the electronic medical record of each subject to identify opioid use from two years pre- to one year post-TKA. We documented the dates of first and last opioid prescription and any additional surgeries done during the study period. We restricted our analyses to those who did not have additional surgery during the study period and who had no more than 2 comorbidities. To address confounding by indication we built a propensity score of opioid use based on age, PCS, comorbidities, and pain prior to TKA. The propensity score ranged from 10% to 75% likelihood of opioid use. The primary analysis included subjects with propensity scores from 20-75%. We compared WOMAC Pain scores (0-100, 100 worst) at 6 months after TKA in persons without opioid use to those with documented pre-TKA opioid use with a general linear model, adjusting for propensity score, PCS, and baseline pain.

Results: Our analytic cohort consisted of 134 patients with mean age 68 years (SD 8); 66% were female and mean pre-TKA WOMAC Pain was 43 (SD 16). Nineteen percent had at least one opioid prescription prior to TKA. Baseline WOMAC Pain scores were higher among those who used opioids pre-TKA (49 vs. 41, p=0.04). PCS was substantially greater among pre-TKA opioid users (18 vs. 12, p=0.004). Adjusted analyses showed that the opioid group had mean 6-month WOMAC pain of 18 points, while the non-opioid group had mean WOMAC Pain of 10 points (p = 0.0017). The adjusted difference in pain from pre-TKA to 6 month post-TKA was estimated at 25 WOMAC points among those who use opioids prior to TKR compared to 33 WOMAC points among those who did not use opioids (p=0.0017).

Conclusion: Patients with pre-TKA opioid use had higher levels of pain catastrophizing and WOMAC Pain at baseline, and, after adjusting for differences in baseline pain, pain catastrophizing, and likelihood of opioid use, had higher pain 6 months after TKA compared to patients without preoperative opioid use. With the substantial societal burden associated with opioid use, clinicians and policymakers may consider limiting the use of these analgesics prior to TKA to optimize the efficacy of the procedure.

Disclosure: S. R. Smith, None; **H. Y. Yang**, None; **J. E. Collins**, None; **J. N. Katz**, None; **E. Losina**, None.

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Abstract Number: 3004

The Choosing Wisely Initiative: Is It Complete?

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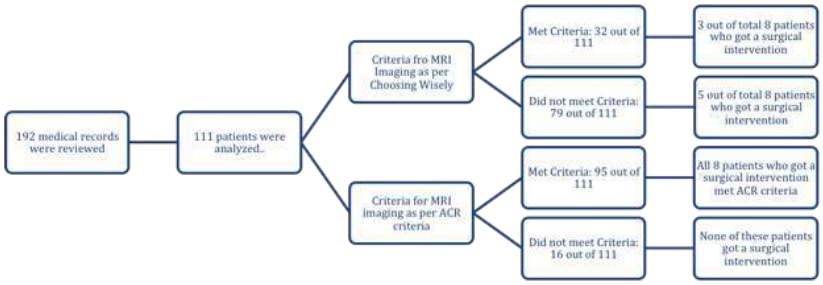
Background/Purpose: Low back pain is a highly prevalent problem affecting approximately 70-85% of Americans in their lifetime (1). American College of Physicians (ACP) has recommended in the Choosing Wisely Campaign by American Board of Internal Medicine (ABIM) in 2012, to avoid getting any radiological imaging in a patient complaining of non-specific lower back pain that cannot be attributed to a specific disease or spinal abnormality (2). The aim of this research is to compare the recommendations of the Choosing Wisely Campaign with American College of Radiology (ACR) in terms of evaluation of low back pain with MRI imaging.

Methods: This is a retrospective cross sectional study of all patients who had MRI of the lumbar spine from January 2013 to April 2015 for evaluation of low back pain. IRB approval was obtained. Indications as defined by the Choosing Wisely Initiative for MRI imaging in a patient with low back pain include history of fever, cancer, intravenous drug abuse, osteoporosis, focal neurological deficits or bowel/bladder incontinence, fever of 102 degrees and unexplained weight loss. In addition to above criteria, ACR also included age greater than 70 and pain persistent for more than 6 weeks after conservative measures as also indications for MRI imaging. We analyzed the data by calculating categorical subdivisions of different variables as percentages of the study group.



Results:

Mean age of the study group was calculated to be 59 with the majority being females (Females-59; Males-52).

Conclusion: Our study showed that 62.5% (5 out of 8 total patients with surgical intervention) of patients who were intervened surgically would not have received imaging in the initial evaluation, if choosing wisely recommendations were strictly followed. Although Choosing Wisely campaign was a great initiative to promote high value care in day to day practice, our study has showed that pain duration more than 6 weeks and age greater than 70, which were not clearly stated as indications for MRI imaging were risk factors by themselves necessitating MRI imaging and probable surgical intervention subsequently. This shows the requirement for clear-cut guidelines in the choosing wisely campaign as well as the need for larger studies comparing recommendations from various societies for MRI imaging in low back pain. **References:**

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Abstract Number: 3005

Development and Initial Validation of the “MH Score”, a New Diagnostic Tool That Differentiates Primary Hemophagocytic Lymphohistiocytosis from

Macrophage Activation Syndrome

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Background/Purpose: It is common view that macrophage activation syndrome (MAS) bears close similarities with primary hemophagocytic lymphohistiocytosis (pHLH). The resemblance of their clinical and laboratory manifestations may make it difficult to differentiate the two conditions, particularly when pHLH occurs at a later age or MAS develops at onset of systemic juvenile idiopathic arthritis (sJIA), when arthritis is not yet present. However, early recognition is important because pHLH is often more severe than MAS and the therapeutic approaches are different. The aim of our study is to develop and validate a diagnostic score that discriminates pHLH from sJIA-associated MAS

Methods: The clinical, laboratory and histopathologic features of 362 patients with sJIA-associated MAS and of 258 patients with pHLH were collected in a multinational collaborative project involving pediatric rheumatologists and pediatric hematologists. 80% of the study population was used to develop the score and the remaining 20% constituted the validation sample. The features with the strongest association with pHLH in univariate analyses (odds ratio > 5) were further scrutinized in multivariate logistic regression procedures. Each variable that entered the best fitting model was then assigned a score, based on its statistical weight. The MH score was made up with the individual scores of the selected variables. The cut-off in the MH score that discriminated best pHLH from MAS was calculated by means of ROC curve analysis. The sensitivity (SE), specificity (SP), area under the curve (AUC) and kappa value of the MH score were calculated for both the developmental and validation samples

Results: The following 6 variables entered the best fitted model of logistic regression analysis, that is, were most closely associated with a diagnosis of pHLH: age at disease onset ≤ 1.6 years, neutrophil count ≤ 1400/µl, fibrinogen ≤ 131 mg/dl, splenomegaly, platelet count ≤ 78000/µl, hemoglobin ≤ 8.3 g/dl. The MH score ranged from 0 to 123. Its median value was 97 (IQR 75-123) in pHLH patients and 12 (IQR 11-34) in MAS patients. The probability of a diagnosis of pHLH ranged from < 1% for a score < 11 to > 99% for a score ≥ 123. A cut-off value > 59 revealed the best performance in discriminating pHLH from MAS (SE=91%, SP=93%, AUC=0.92, kappa=0.85). The strong diagnostic power of the MH score was confirmed in the validation sample

Conclusion: The MH score is a powerful tool that facilitates timely discrimination of pHLH from MAS. Its application in routine clinical care may aid practitioners to identify those patients who are more likely to have pHLH and may, thus, deserve diagnostic confirmation with appropriate genetic and functional testing

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Abstract Number: 3006

IFN-Gamma (IFNγ), IFNγ-Induced Chemokines and Other Biomarkers in Macrophage Activation Syndrome (MAS)

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Background/Purpose: Evidence in animals and humans points to a pivotal role of IFNγ in primary HLH. We have recently generated data in an animal model supporting a role for IFNγ also in MAS and reported high levels of IFNγ and of the IFNγ-related chemokines, CXCL9, CXCL10 in patients with MAS, during systemic JIA (sJIA) (1).

Methods: Circulating levels of sCD25, IL-18 and neopterin, as well as levels of IFNγ, CXCL9 and CXCL10 were measured by Luminex assay in 57 samples obtained, from 24 patients with active sJIA and in 37 samples from 20 patients with MAS at sampling at variable severity and treatments. We evaluated the correlation between serum levels of sCD25, IL-18 and neopterin, as well as levels of IFNγ of CXCL9 and CXCL10 with laboratory parameters of MAS severity in patients with active sJIA with or without MAS at sampling.

Results: Levels of IFNγ, CXCL9, CXCL10, sCD25, IL-18 and neopterin were significantly elevated in MAS compared to active sJIA without MAS at sampling (p-values <0.0001, except for IL-18 p=0.012). In patients with MAS, but not in patients with active sJIA without MAS at sampling, laboratory parameters of disease severity were significantly correlated with IFNγ, CXCL9, CXCL10, sCD25 and neopterin (Table1). No correlation with IL-18 was found (IL-18 levels were available only for a portion of the samples). Interestingly, during active sJIA without MAS at sampling, levels of CXCL9 (median 3889,IQR 965-7142), CXCL10 (764,323-1259) and IL-18 (4405,582-7122) were significantly higher in patients with a history of MAS compared to those of patients without a history of MAS (519,IQR 385-1168; 215,IQR 152-470; 439,312-824, respectively). **Table 1.**Correlation between cytokines and laboratory parameters in active MAS (N=37).

	IFNγ	**CXCL9**	**CXCL10**	**sCD25**	**IL-18**	**Neopterin**
	***p* (r)**	***p* (r)**	***p* (r)**	***p* (r)**	***p* (r)**	***p* (r)**
Ferritin (ng/mL)	0.014(0.46)	0.034(0.43)	0.003(0.54)	0.002(0.63)	>0.1(0.35)	>0.1(0.39)
White blood cells (x10^9/L)	0.033(-0.47)	0.013(-0.56)	>0.1(-0.32)	>0.1(-0.42)	>0.1(-0.40)	>0.1(0.04)
Platelet (x10^9/L)	0.001(-0.55)	0.0001(-0.66)	<0.0001(-0.66)	0.003(-0.57)	>0.1(-0.14)	>0.1(-0.35)
Fibrinogen (mg/dL)	>0.1(-0.32)	0.0014(-0.73)	0.008(-0.60)	0.0005(-0.74)	>0.1(-0.38)	0.008(-0.61)
Triglycerids (mg/dL)	>0.1 (0.20)	>0.1 (0.23)	>0.1(0.13)	>0.1(0.29)	>0.1 (0.02)	>0.1 (0.17)
LDH (U/L)	0.005(0.64)	<0.0001(0.90)	<0.0001(0.94)	0.002(0.69)	>0.1 (-0.23)	0.0001 (0.85)
ALT (U/L)	0.012 (0.52)	0.0007 (0.68)	0.0005 (0.67)	0.008 (0.54)	>0.1 (0.38)	>0.1 (0.14)
Values are expressed as p value (r di Spearman).						

Conclusion: Levels of IFNγ, CXCL9, CXCL10, sCD25, and neopterin were higher during MAS and correlated with laboratory parameters of severity. IL-18 levels were not correlated with laboratory parameters of MAS severity and the observation that IL-18 levels are higher in patients with a history of MAS is consistent with the hypothesis that high levels of IL-18 may contribute to the

predisposition to MAS in sJIA as also suggested by Shimizu et al (2). Elevation of sCD25 is consistent with the presence of T cell activation in MAS. Elevation of neopterin and CXCL9, both of which reflects IFNγ production, and their correlation with laboratory parameters, supports the pathogenic role of IFNγ in MAS. Given the fact that circulating CXCL9 levels appear to reflect tissue IFNγ production, presence of high CXCL9 in patients with a history of MAS, but without MAS at sampling, suggests subclinical activation of the IFNγ pathway in these patients. **References.** 1. Bracaglia c. et al. Ann Rheum Dis 2016 2. Shimizu M. et al. Clin immunol 2015

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Long-Term Efficacy and Safety of Canakinumab in Patients with Active Systemic Juvenile Idiopathic Arthritis (SJIA): Results from a PHASE III Extension Study

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Background/Purpose: The management of SJIA with biological therapies is aimed to achieve and maintain clinical remission (CR), and accordingly taper corticosteroids (CS). Canakinumab (CAN) demonstrated high inactive disease (ID) rates in about 33% of patients (pts) in Day 15 and 30 respectively in previous studies[1]. However, little is known about high level response rates in SJIA pts using CAN long-term. The objective of this study was to evaluate the long-term treatment response in terms of safety and efficacy in CAN treated pts with active SJIA.

Methods: This was an open-label, non-comparative study of CAN-naïve SJIA pts (≥2 to <20 years) receiving subcutaneous CAN 4 mg/kg every 4 weeks. Efficacy was assessed every 3 months by the aACR (30/50/70/90/100) responses compared to baseline (BL), ID or CR (ID for >6 months) and changes in JADAS10-CRP scores over time. Safety was assessed by adverse events (AEs) and serious AEs (SAEs).The results are based on the observed data with imputations to carry the last observation forward.

Results: Of 123 pts with active SJIA, 70 (57%) had fever and 71 (57.7%) used corticosteroids at BL. Mean CRP was 117.8 mg/L (normal: 0-10 mg/L), and, on average, pts had 9.9 active joints and 8.9 joints with limited motion. A rapid response was observed at Day 15: 59 (51%) and 27 (26%) pts had aACR ≥70 and aACR 100 responses, respectively. These responses were maintained at subsequent time points (Table). At Month 6, CR was achieved in 52 (42.3%) pts. Overall, 33 (26.8%) pts had CR for at least 12

months. At BL, the median CRP score was 22.3, with median changes from BL of −12.0 at Day 15 and −16.8 at last assessment, respectively. At the last assessment, 59 (48.4%) pts had ID (JADAS10 ≤1); 14 (11.5%) had low disease activity (JADAS10 >1 and ≤3.8), while 14 (11.5%) had moderate and 35 (28.7%) had high disease activity. Overall, 24 (33.8%) pts were steroid-free at last assessment. In total, 108 (87.8%) pts had at least 1 AE. Overall, exposure adjusted AE and SAE rate was 8.22 and 54.8 events/pt-years (pyr) respectively, with 183.56 pyr exposure and 40 (32.5%) pts had SAEs; most commonly reported SAEs were disease flares or worsening of SJIA in 13 (10.6%) pts, macrophage activation syndrome in 6 (4.9%) pts, and fever in 4 (3.3%) pts. No deaths occurred in this study.

Conclusion: CAN treatment was associated with rapid response and sustained therapeutic effect over the long-term in the pts with active SJIA. The safety profile is consistent with other CAN studies. References: 1. Ruperto et al. *N Engl J Med*. 2012;367:2396-406.

Table: ACR responses achieved in the cohort by time point

Time point	CAN N=123		
	Minimum adapted ACR pediatric response	**n (n/m%)**	**Patients with inactive disease (n/m)%**
Month 12	m	85	(52/88) 59.1
	Non-Responders	4 (4.7)	
	aACR ≥30	81 (95.3)	
	aACR ≥50	77 (90.6)	
	aACR ≥70	73 (85.9)	
	aACR 100	49 (57.6)	
Month 21	m	65	(48/65) 73.8
	Non-Responders	3 (4.6)	
	aACR ≥30	62 (95.4)	
	aACR ≥50	58 (89.2)	
	aACR ≥70	54 (83.1)	
	aACR 100	39 (60.0)	
Last Assessment	m	121	(62/122) 50.8
	Non-Responders	28 (23.1)	
	aACR ≥30	93 (76.9)	
	aACR ≥50	89 (73.6)	
	aACR ≥70	81 (66.9)	
	aACR 100	62 (51.2)	

n= number of patients who satisfy the criteria, m = number of patients with an assessment in the time period.

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Clinical Factors Associated with Non-Response to Methotrexate in Children with Juvenile Idiopathic Arthritis: Results from the Childhood Arthritis Response to Treatment Consortium

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Background/Purpose: Although the recommended first line treatment for JIA, up to 50% of children will not respond to MTX. Currently, it is not possibly to identify at the start of therapy which children will not respond and thus initiation of effective therapies may be delayed. The aim of this analysis was to identify clinical factors measured at the outset of therapy associated with non-response to MTX with a view towards building an accurate multifactorial prediction model.

Methods: Children with JIA treated with MTX were identified from four large multi-centre UK observational studies participating in the Childhood Arthritis Response to Treatment (CHART) consortium: Childhood Arthritis Prospective Study, British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study, Biologics for Children with Rheumatic Diseases Study, and Childhood Arthritis Response to Medication Study. Demographic, clinical and laboratory variables at start of MTX and at 6 (4-12) months following treatment start were extracted and combined using a common data model. Non-response at 6-months was defined as lack of achievement of the ACR Pediatric (ACR Pedi) 30 criteria or initiation of biologics due to MTX inefficacy. Patients stopping MTX prematurely (< 4 months) due to intolerance were excluded. Each potential predictor of non-response was evaluated

using logistic regression. Significant factors were taken into a multivariate logistic regression model and estimated using stepwise backward elimination approach. Missing data including outcome data was addressed using multiple imputations.

Results: A total of 2211 patients were included in this analysis, mean age at MTX start 8.4years, 68% female, 41% polyarthritis, 34% oligoarthritis, 7% psoriatic, 8% systemic onset, 4% undifferentiated and 6% enthesitis related arthritis. The non-response rate (95%CI) was 32.7% (30.2 – 35.0). In the multivariate model, only lower ESR, Physician global assessment (PGA), Parent's general evaluation of well-being (PGE), ANA negativity and use of oral MTX versus subcutaneous route were significantly associated with non-response (Table 1), AUC 66.6%.There was no significant association between age, gender, disease duration, BMI, JIA subtype, joint counts and CHAQ score and non-response to MTX at 6 months.

Conclusion: Although some routinely collected clinical and laboratory factors were associated with non-response in this large JIA cohort, overall, clinical factors alone could not predict non-response to MTX. The addition of biological or genetic factors to clinical factors may be able to identify a more robust model to predict non-response and divert children onto more effective therapies earlier in their disease course.

Parameters at the start of MTX therapy that were significant in univariate analysis	**Non-responders 32.7% (30.2 – 35.0)**	**Responders 67.3% (64.9 – 69.7)**	**OR (95% CI)**	**P value**
Active joint count (median, IQR)	4(2,8)	6(3,10)	0.97(0.96-0.99)	0.004
Limited joint count(median, IQR)	3 (1,6)	4 (2,7)	0.96(0.95-0.98)	<0.0001
CHAQ score (median, IQR)	0.8(0.3,1.5)	1.1(0.5,1.7)	0.66(0.56-0.77)	<0.0001
ESR (median, IQR)	17 (7,40)	28 (10, 55)	0.99(0.98-0.99)	<0.0001
PGA (median, IQR)	3.1 (2.0,5.0)	4.0 (2.8, 7.5)	0.83(0.78-0.88)	<0.0001
PGE (median, IQR)	3.1 (1.0, 5.2)	4.8 (2.1, 6.8)	0.87(0.83-0.91)	<0.0001
Age at MTX start in years (median, IQR)	9.1 (4.3 , 12.8)	8.1 (3.8, 11.9)	1.03(1.01-1.06)	0.004
Disease duration in months (median, IQR)	12.6(5.9,32.1)	9.2(4.5,25.4)	1.00(1.00-1.01)	0.01
Route of MTX			1.57(1.20-2.07)	0.001
Subcutaneous(95%CI)	23.0%(18.1-27.9)	32.1%(28.3-35.7)		
Oral(95%CI)	76.9%(72.1-81.8)	67.9%(64.2-71.7)		
ANA status			0.74(0.57-0.96)	0.02
ANA positive(95% CI)	47.9%(42.9-52.8%)	55.2%(51.6-58.7)		
ANA negative(95%CI)	52.1%(47.1-57.1)	44.8(41.2-57.1)		
Final Multivariable Model				
Predictors of non-response	**OR (95% CI)**			
ESR	0.99(0.99-0.99)			
PGA	0.89(0.83-0.95)			
PGE	0.91(0.85-0.96)			
MTX by oral route	1.43(1.07-1.9)			
ANA positive	0.73(0.56-0.96)			
AUC = 66.6% Hosmer-Lemeshow goodness of fit statistic, p = 0.1				

Table 1: Factors Significantly Associated with Non-response to MTX and results of Final Multivariable Model

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Safety and Effectiveness of Adalimumab±Methotrexate for the Treatment of Polyarticular Juvenile Idiopathic Arthritis

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Background/Purpose: Juvenile Idiopathic Arthritis (JIA) is the most common chronic inflammatory rheumatic diseases of childhood. Due to their long-term safety and efficacy, biologic disease modifying antirheumatic drugs (DMARD) are commonly necessary for control of polyarticular JIA (pJIA) patients (pts). The objective of this study is to evaluate 6-year (y) safety and 2 y effectiveness profile of Adalimumab with or without methotrexate (ADA±MTX) when used in current clinical practice for the treatment of moderately to severely active pJIA.

Methods: This is a 6 y interim analysis of an ongoing, multicenter, non-interventional, observational registry of pts with moderately to severely active pJIA with up to10 y safety follow-up. Included pts are treated with either ADA±MTX or MTX alone as part of their routine clinical care enrolled in the US, EU, and Australia. MedDRA observational adverse events (AEs) were recorded from the first day in the registry through last contact, irrespective of the duration of registry treatment. Effectiveness was assessed by 27-joint juvenile arthritis disease activity score (JADAS27), based on CRP.

Results: As of January 2014, enrollment was complete. As of June 1, 2015 cut-off date, 846 pts (543 in ADA±MTX and 303 in MTX groups) were treated in the registry. There were 39 pts who rolled over from the MTX to the ADA±MTX arm. At registry entry mean pJIA disease duration was 1.4 y and 3.7 y for MTX and ADA±MTX arms, respectively. At baseline (BL), mean AJC71 was 5.8 and 5.3 for MTX and ADA±MTX arms, respectively, and Childhood Health Assessment Questionnaire Disability Index (CHAQ-DI) was 0.6 for both arms. At data cutoff, the mean duration of study exposure was 1.81 y and 2.15 y for MTX and ADA ±MTX arms, respectively. Overall, 206 pts (68%) in the MTX and 216 pts (39.8%) in the ADA±MTX arms discontinued registry drug through 6 y. The main reasons for registry drug discontinuation for the MTX arm: pts required additional therapy (32.3%), other (11.9%), lack of efficacy (10.9%), AEs (8.3%), or pts achieved JIA remission (7.6%), and for ADA±MTX arm: lack of efficacy (16%), lost to follow-up (7.2%), other (5.9%), and AEs (5.3%). Frequencies and rates of treatment-emergent AEs were similar to those reported for observational AEs **(Table)**. There were no reports of deaths, malignancies, opportunistic infections, active TB, oral candidiasis, or CHF. Mean JADAS27(CRP) improved from 12.2 at BL to 9.7, 5.2, 4.4, 3.5, 2.2 at months 1, 6, and 12, 18, 24 for pts in the MTX and from 11.8 at BL to 7.0, 4.-2, 4.2, 3.6, 3.9 in the ADA±MTX arms, respectively (observed data).

Conclusion: Overall, ADA±MTX was well-tolerated in these pts with pJIA with no new safety signals. Discontinuations from the registry drug were relatively high through 6 y, but greater in the MTX only arm.

Table: Overview of Observational Adverse Events (AEs)

	MTX		ADA±MTX	
	N=303 n (%)	PYs=1014.6 E (E/100 PYs)	N=543 n (%)	PYs=1562.7 E (E/100 PYs)
Any AE	156 (51.5)	470 (46.3)	229 (42.2)	683 (43.7)
At least "possibly drug related" per the investigator	83 (27.4)	171 (16.9)	110 (20.3)	222 (14.2)
Severe AE	14 (4.6)	18 (1.8)	34 (6.3)	55 (3.5)
Serious AE	29 (9.6)	45 (4.4)	66 (12.2)	117 (7.5)
AE leading to discontinuation of study drug or study	25 (8.3)	33 (3.3)	35 (6.4)	56 (3.6)
Infectious AE	85 (28.1)	164 (16.2)	134 (24.7)	226 (14.5)
Serious infectious AE	12 (4.0)	15 (1.5)	26 (4.8)	36 (2.3)
Injection site-related AE	6 (2.0)*	8 (0.8)	28 (5.2)	37 (2.4)

*3 pts experienced injection site-related AEs with etanercept injections. During the registry, 47 (15.5%) pts in MTX arm and 38 (7.0%) pts in ADA arm started with biologic DMARD other than ADA. All except one pt in MTX arm had been documented as permanently discontinued registry drug or registry, at time of cut-off date for this analysis.

Disclosure: D. J. Lovell, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Regeneron, Hoffman La-Roche, Novartis, UCB, and Genentech., 5,Genentech Pharmaceuticals., 8; **N. Ruperto**, AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., "Francesco Angelini", GlaxoSmithKline, Italfarmaco, Novartis, Pfizer, Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, and Wyeth Pharmaceuticals., 9,Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, Janssen Biologics B.V., MedImmune, Roche, and Wyeth/Pfizer., 8; **C. Wallace**, Pfizer and Amgen, 2,Amgen and Novartis., 5; **M. Toth**, None; **I. Foeldvari**, AbbVie and Novartis., 9; **J. Bohnsack**, Novartis., 5; **D. Milojevic**, Genentech and Novartis, 5; **C. E. Rabinovich**, UCB Pharma, Janssen Research & Development, LLC, Hoffmann-La Roche Inc., and AbbVie, 9; **D. Kingsbury**, AbbVie, 9; **K. Marzan**, AbbVie, 2; **P. Quartier**, AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum., 2,AbbVie, Novartis, Pfizer, BMS, Chugai-Roche, Medimmune, Servier, and Swedish Orphan Biovitrum., 5,Sanofi, 9; **K. Minden**, Pfizer, Abbvie, Roche/Chugai, Novartis, Medac and Pharma-Allergan., 5,Pfizer and Abbvie., 9; **E. Chalom**, AbbVie, 8; **G. Horneff**, AbbVie, Pfizer, and Roche, 2,AbbVie, Novartis, Pfizer, and Roche, 8; **R. M. Kuester**, AbbVie Inc. and Wyeth/Pfizer, 9; **J. Dare**, AbbVie, AstraZeneca, Bristol-Myers Squibb, Horizon Pharma, Medac, Pfizer, Roche and UCB, 9; **M. Heinrich**, AbbVie, 3; **H. Kupper**, AbbVie, 3; **J. Kalabic**, AbbVie, 3; **H. I. Brunner**, AbbVie Inc., AstraZeneca, Centocor, Bristol-Myers Squibb, Boehringer-Ingelheim, Pfizer, Regeneron, Hoffman La-Roche, Novartis, UCB, and Genentech, 5,Genentech Pharmaceuticals, 8; **A. Martini**, AbbVie Inc., AstraZeneca, Bristol-Myers Squibb, Janssen Biologics B.V., Eli Lilly and Co., "Francesco Angelini", GlaxoSmithKline, Italfarmaco, Novartis, Pfizer, Roche, Sanofi Aventis, Schwarz Biosciences GmbH, Xoma, and Wyeth Pharmaceuticals, 9,Astellas, AstraZeneca, Bristol-Myers Squibb, Italfarmaco, and MedImmune., 8.

Abstract Number: 3010

Improvement of Spinal Inflammation Induced By Etanercept in Enthesitis Related Arthritis JIA-Patients. Data of the Reminder-Study

Gerd Horneff[1], Ivan Foeldvari[2], Kirsten Minden[3,4], Hans-Iko Huppertz[5] and Ariane Klein[6], [1]Department of Pediatrics, Centre of Pediatric Rheumatology, Sankt Augustin, Germany, [2]Kinder- und Jugenrheumatologie, Hamburger Zentrum Kinder-und Jugendrheumatologie, Hamburg, Germany, [3]Epidemiology, Charite, DRFZ, Berlin, Germany, [4]Children's University Hospital

Charite/German Rheumatism Research Centre Berlin, Berlin, Germany, [5]Klinikum Bremen-Mitte, Prof.-Hess-Kinderklinik, Bremen, Germany, [6]Center of Pediatrics and Neonatology, Asklepios Clinic Sankt Augustin, Sankt Augustin, Germany
First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects II: Juvenile Arthritis
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: The data of the REMINDER study, a two-part, 48-week, randomized, placebo-controlled, double-blind withdrawal study on efficacy of etanercept (ETA) compared to placebo (PLC) in ERA patients is used to analyze the improvement of spinal symptoms (1).

Methods: Patients with active ERA received open-label ETA for 24 weeks. At week 24, patients with at least a JIA-ACR30 response entered a 24-week randomized (1:1 PLC or ETA), double-blind withdrawal period. Improvement was assessed by the number of active joints, the JIAACR30/50/70/90 and ACR remission criteria, the JADAS10, JADAS MDA and JADAS remission, the tender enthesitis points (TEP), and parameters of spinal involvement (BASDAI, BASFI and spinal pain (by VAS)).

Results: Forty-one patients (means for age: 13.4 years, baseline disease duration: 2.8 years, active joints count: 5.3, JADAS10: 15.8) were included and 39 received open-label ETA (0.8 mg/kg/week, max.50 mg/week) for 24 weeks. Two patients discontinued prematurely. Marked improvement was reached at week 24, the JIAACR30/50/70/90 response rates were 93%/93%/80%/56%. %. ACR remission was achieved by 23 patients (60.5%), respectively. JADAS MDA/remission was reached by 34 (87.1%)/23(60.5%) patients. The mean number of active joints decreased from 5.2+/-2.3 to 0.3+/-0.8. The mean BASDAI score decreased from 4.4+/-1.9 to 1.2+/-1.6 and the number of patients with a BASDAI of 0 increased from 0 to 26.3% (n=10). The mean BASFI improved from 2.7+/-2.4 to 0.36+/-0.68. 31(81.6%) of patients achieved an ASAS20 and 28 (73.7%) an ASAS40. Mean total spinal pain/spinal paint night also decreased from 5.2/2.9 to 1.5/0.5. The mean TEP count decreased from 1.8 [range 0-7] to 0.4 and the rate of patients with no tender enthesitis point more than doubled from 31.7% to 68.4%. Efficacy indicators were stable in patients receiving ETA in the double blind phase of the study, and worsened in part of the patients on PLC. Until week 48, 7/10 patients on ETA with BASDAI of 0 at week 24 remained with a BASDAI of 0. In all 3 cases with a JIA ACR30 flare, an increase of the BASDAI was noted (from 0 to 0.6, 1.1 and 7.6). All 7 patients randomized to placebo with a BASDAI of 0 at week 24 maintained a BASDAI of 0 until week 48 or until reset on ETA. Also 13/17 (76%) patients on ETA and 9 (69%) on PLC with no TEP at week 24 remained without TEP until week 48. A single uveitis event was reported in a patient randomized ETA at week 48.

Conclusion: In this placebo-controlled randomized study on ERA-JIA patients, ETA proved to be highly effective on peripheral disease as well as on spinal inflammation. A high rate of patients achieved JADAS remission, BASDAI 50, BASFI50, no spinal pain and no tender enthesitis points after 24 weeks of treatment. The study was underpowered to demonstrate differences between ETA and PLC cohort at week 48. (1) Horneff et al. Arthritis Rheumatol. 2015 Apr 17. doi: 10.1002/art.39145

	Baseline	ETAw24	P	OR[95%CI)	ETAw48	PLCw48
Active joints (0-71), mean	5.2+/-2.3	0.3+/-0.8	<0.001		0.8+/-1.2	1.2+/-1.5
No active joint, n(%)	0	31 (79.5%)	<0.0001	181[21-1553)	12 (60%)	9 (50%)
JADAS10 (0-40), mean	17.5+/-7.2	2.0+/-2.9	<0.001		3.3+/-4.3	4.4+/-5.3
JADAS MDA, n(%)	2(4.9%)	34 (87.1)	<0.0001	165[28-962]	12 (60%)	9(50%)
JASDAS Rem, n(%)	0	23 (59%)	<0.0001	62[8-507]	11 (55%)	9(50%)
ACR30,n(%)	na	38 (97.4%)			19 (95%)	16 (88.9%)
ACR50,n(%)	na	38 (97.4%)			18 (90%)	14 (77.8%)
ACR70,n(%)	na	33 (84.6%)			13 (65%)	9 (50%)
ACR90,n(%)	na	23 (59%)			11 (55%)	8 (44%)
ACRRem,n(%)	0	23 (59%)	<0.0001	62[8-507]	11 (55%)	6 (33%)
ASAS20,n(%)	na	31 (79.5%)			12(60%)	13(72%)
ASAS40,n(%)	na	28 (71.8%)			11(55%)	12(66%)
BASDAI(0-10), mean	4.4+/-1.9	1.2+/-1.6	<0.001		1.6+/-2.1	1.5+/-1.6
BASDAI50, mean	n.a.	28 (71.8%)			15 (75%)	13 (72.2%)
BASDAI=0,n(%)	0	10 (25.%)	0.002	14.6[1.8-120]	7 (35%)	6 (33%)
BASFI(0-10), mean	2.7+/-2.4	0,36+/-0,68	<0.1001		0.78+/-1.7	0.67+/-1.2
BASFI=0,n(%)	3 (7.3%)	19 (48.7%)	<0,0001	12.6[3.3-48]	11 (55%)	6 (33%)
BASFI 50,n(%)	n.a.	34 (87.2)			17 (85%)	12 (66.7%)
Spinal pain (VAS 0-10), mean	5.2+/-2.5	1.5+/-2.1	<0.001		2.3+/-3.1	1.7+/-1.2
No Spinal pain, n(%)	2 (4.9%)	21 (53.8%)	<0.0001	24.1[5.1-114]	8 (40%)	8 (44.4%)
Spinal pain night (0-10) , mean	2.9+/-2.8	0.5+/-1.2	<0.001		1+/-2	1+/-1.7
No Spinal pain, n(%)	12 (29%)	29 (74.4%)	<0.0001	7.8[2.8-21]	14 (70%)	11 (61.1%)
Enthesitis-Points, mean	1.8+/-1.9	0.4+/-1.3	<0.001		1.6+/-4.2	0,2+/-0.55
No Enthesitis points, n(%)	13 (31.7%)	26 (66.7%)	0.001	4.7[1.8-12.0]	16 (80%)	15 (83%)

Table1: Disease activity parameters

Disclosure: G. Horneff, AbbVie, Pfizer, Novartis and Roche, 2,AbbVie, Novartis, Pfizer, and Roche, 8; **I. Foeldvari**, None; **K. Minden**, Pfizer Inc, 2,Pfizer Inc, 9; **H. I. Huppertz**, None; **A. Klein**, None.

Abstract Number: 3011

Long-Term Outcomes after Disease Activity Guided Tapering of Tumor Necrosis Factor Inhibition in Rheumatoid Arthritis: 3 Year Data of a Randomised

Controlled Pragmatic Non Inferiority Strategy Study

Alfons A. den Broeder[1], Chantal A.M. Bouman[1], Frank H.J. van den Hoogen[1,2], Jaap Fransen[2], Ronald F. van Vollenhoven[3], Johannes W.J. Bijlsma[4], Aatke van der Maas[1] and Noortje van Herwaarden[1], [1]Rheumatology, Sint Maartenskliniek, Nijmegen, Netherlands, [2]Rheumatology, Radboud University Medical Center, Nijmegen, Netherlands, [3]Amsterdam Rheumatology and Immunology Center ARC, Amsterdam, Netherlands, [4]Department of Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
Session Title: Rheumatoid Arthritis – Clinical Aspects IV: Managing Patients in Remission
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Long-term Outcomes After Disease Activity Guided Tapering of TNF Inhibitors in Rheumatoid Arthritis: 3 Year Data of a Randomized Controlled Pragmatic Non Inferiority Strategy Study

Den Broeder AA[1], Bouman CAM[1], van den Hoogen FHJ[1,2], Fransen J[2], Van Vollenhoven RF[3], Bijlsma JWJ[4], van der Maas A[1], van Herwaarden N[1] [1]Department of Rheumatology, Sint Maartenskliniek, Nijmegen, the Netherlands [2]Department of Rheumatology, Radboud University Medical Centre, Nijmegen, the Netherlands [3]Amsterdam Rheumatology and Immunology Center ARC, Amsterdam, Netherlands. [4]Department of Rheumatology & Clinical Immunology, Utrecht University Medical Centre, Utrecht, the Netherlands

Background/Purpose: In a pragmatic, randomized, open label strategy study, non inferiority of a disease activity guided dose reduction (DR) strategy of adalimumab or etanercept compared to usual care (UC; non tapering tight control) was demonstrated after 18 months. Long term effects of this strategy are however unknown. We assessed whether the initial 18 months effects were sustained up to year 3 with regard to disease control, functioning, quality of life, radiographic outcome and cost (effectiveness).

Methods : In the intervention phase (months 0-18), patients were randomized to DR (stepwise TNFi interval increase until flare or discontinuation) or UC[1]. Consenting completers of this phase were included in the extension phase (months 18-36). Treatment in both groups converged to protocolized tight control and allowed dose optimization (Fig. 1). Intention-to-treat analyses were done on flare, medication use, disease activity (DAS28-CRP), functioning (HAQ-DI), quality of life (EQ5D-5L), adverse events (AE), radiographic progression (Sharp-Van der Heijde, SvdH), and costs.

Results : 172 (115 DR; 57 UC) were included in the extension phase (Fig. 2). Cumulative incidences of major flare were 10% and 12% (-2%, 95% CI -8 to 15) in the DR and UC group in the extension phase, and 17% and 14% (3%, 95% CI -9 to 13) from 0-36 month. In the DR group, 33/115 (29%, 95% CI 21 to 38%) still had successfully reduced their TNFi dose at 36 months, and 19/115 (17%, 95% CI 10 to 25%) discontinued TNFi at 36 months. In the UC group, 32/49 (65%, 95% CI 50 to 78%) attempted dose reduction in the extension phase of whom 19/49 (39%, 95%CI 25 to 54%) had successfully tapered and 7/49 (14%, 95% CI 1 to 27%) discontinued TNFi at 36 months. Mean DAS28-CRP, HAQ-DI, SvdH and EQ5D-5L remained stable over 36 months and did not differ significantly between groups (Fig. 3). Over 3 years, mean cost saving was −€13,451 (95% CI −€9,701 to−€17,198) per patient, which, with the small gain in QoL, resulted in a dominant cost-effectiveness ratio (€1.9 million savings per saved QALY).

Conclusion: Safety and efficacy of disease activity guided dose reduction of TNFi in RA patients are maintained up to three years. No difference in radiographic progression was found. Cost savings were considerable, no other benefits of tapering could be demonstrated. **Reference** Van Herwaarden N et al. BMJ 2015

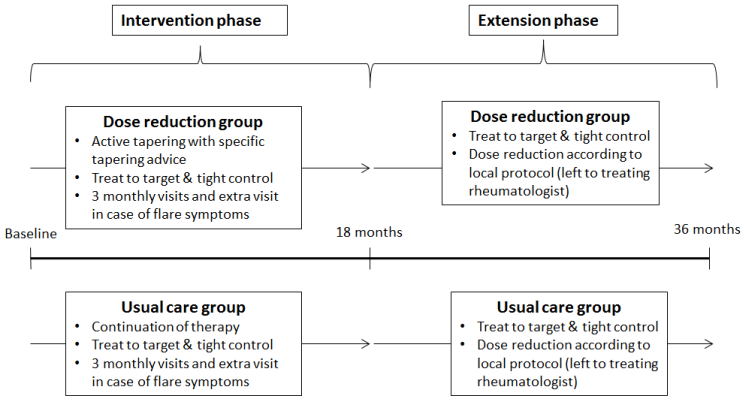


Figure 1. Study conduct

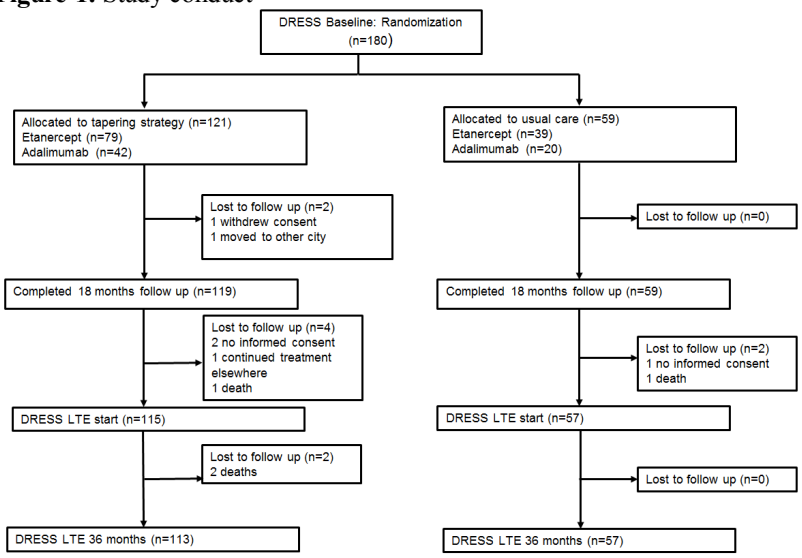
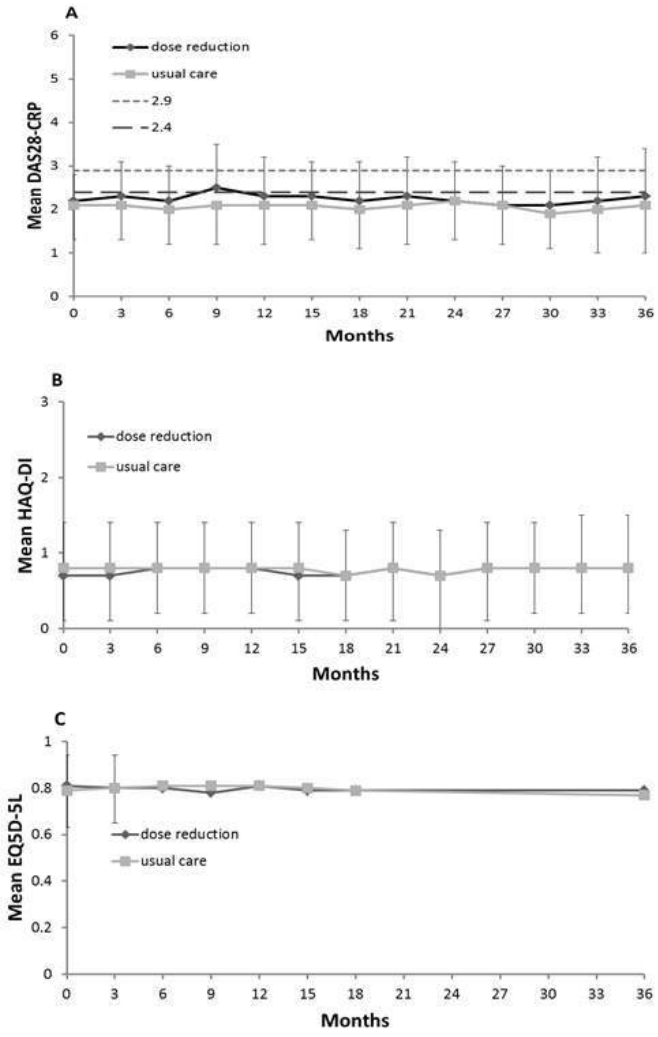


Figure 2. Flow chart

Figure 3. Mean **A:** Disease activity (measured with DAS28-CRP) **B:** Functioning (measured with HAQ-DI) **C:** Quality of life (measured with EQ5D-5L)



Disclosure: A. A. den Broeder, Amgen, Roche, Abvie, 5; **C. A. M. Bouman**, None; **F. H. J. van den Hoogen**, None; **J. Fransen**, BMS, 2; **R. F. van Vollenhoven**, AbbVie, Amgen, BMS, GSK, Pfizer, Roche, UCB, 2,AbbVie, Biotest, BMS, Celgene, Crescendo, GSK, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, UCB, Vertex, 5; **J. W. J. Bijlsma**, personal fees from AbbVie, BMS, MSD, Pfizer, Roche, UCB, 5; **A. van der Maas**, None; **N. van Herwaarden**, None.

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Abstract Number: 3012

Clinical Predictors of TNF-Inhibitor Free Disease Control in Patients with Rheumatoid Arthritis after Stopping TNFi Treatment: Results from a Dutch Multicentre Pragmatic Open-Label Randomized Controlled Trial.

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Background/Purpose: Tumor Necrosis Factor inhibitor (TNFi) free prolonged acceptable disease control in patients with rheumatoid arthritis (RA), in stable remission or low disease activity (LDA) during treatment with TNFi will benefit the balance between costs and effects. Therefore, using the data from the POET study, we evaluated the available potential clinical predictors of prolonged disease control after discontinuation of TNFi.

Methods: Data of 439 RA patients who were randomized to stop TNFi treatment in the POET study were analyzed post-hoc. The indicator of prolonged acceptable disease control over 12 months was: not restarting TNFi treatment. Available potential clinical predictors were: type of TNFi (antibody vs. receptor antagonist); concomitant conventional systemic DMARD; female sex; Younger age (<60 yrs.); short disease duration (<10 yrs.); RF positive; ACPA positive; erosive disease; normal weight (BMI 18.5 – 25); first TNFi; DAS28 deep remission (DAS28 ≤1.98) and MBDAscore ≤44, all at baseline. Associations between potential clinical predictors and disease relapse versus prolonged acceptable disease control were examined using univariate analysis and multivariate logistic regression.

Results: In the POET study 439 stable controlled RA-patients in remission or low-disease activity stopped their TNFi. During the following 12 months observation 50,1% of patients remained in low disease activity or remission. <span">Univariate analysis revealed an association of the following predictors: type of TNFi (antibody vs. receptor antagonist) OR: 2.26(1.53–3.34) p<0.0001; Short disease duration OR: 1.88(1.26–2.79) p=0.002; absences of erosions OR: 1.62(1.08–2.44) p=0.020 and MBDA score ≤44 OR: 2.32(1.32–4.05) p=0.003.Multivariate (backward deletion) of potential clinical predictors of prolonged acceptable disease control after TNFi discontinuation are: Type of TNFi (antibody vs. receptor antagonist) OR:2.39(1.57 – 3.65) p<0.0001; Short disease duration (<10 yrs.) OR 2.02 (1.34 – 3.05) p=0.001; and MBDA ≤44 OR: 2.01 (1.11 – 3.65) p= 0.022.

Conclusion: This post hoc analysis in well-controlled RA patients stopping their TNFi during participations in the POET study suggests that patients characterized by the use of an TNFi antibody (predominatly adalumimab but including infliximab, golumimab and certoluzimab) with a short disease duration and a low MBDA score are likely to remain well-controlled (remission or low disease activity) during the following 12 months. Their littermates using a receptor antagonist (etanercept) with a longstanding disease and a high MBDA are most likely to flare. These data allow the well-controlled RA-patient using a TNFi and their attending physician to make an educated shared decision on continuation or stopping this expensive treatment.

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Abstract Number: 3013

Dose Reduction or Discontinuation of Biological Therapy in Patients with Rheumatoid Arthritis in Remission – 1-Year Results of a Guideline-Directed Longitudinal Cohort Study

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Background/Purpose: Dose tapering in patients in remission has previously proven promising in randomized controlled trials. However, systematic implementation in clinical practice is lacking. A new guideline in the Capital Region of Denmark required that RA patients in sustained remission on biological therapy must attempt dose reduction according to a predefined algorithm. We aimed to 1) report the 1-year results of the implementation of the guideline and 2) investigate potential clinical baseline predictors of flare during the 1st year.

Methods: Patients with disease activity score (DAS28, 4 variables, CRP-based) ≤2.6 for ≥1 year and no radiographic progression the previous year were included. According to the algorithm, dosing of biological drug was to be reduced to 2/3 of standard dose at baseline, to ½ of standard dose after 4 months, and discontinued after 8 months. Patients who flared stopped tapering and were escalated to the previous dose to regain remission. Flare was defined as 1) DAS28≥2.6 AND DDAS28≥1.2 since baseline, or 2) erosive progression based on X-ray and/or magnetic resonance imaging (MRI). The relapse-free time since start of tapering stratified by gender and by median disease duration (11 years) was presented as Kaplan-Meier curves (time to flare). Breslow test was applied to test for significant difference between men and women and disease duration.

Results: A total of 143 patients from 5 departments of rheumatology were included as part of the implementation of the guideline. Baseline characteristics and medication are shown in table 1. During the 1st year, 101 (71%) patients flared and stopped tapering. All patients who flared were re-escalated and regained remission. At 1 year, 49 (34%) were on full dose, 28 (20%) patients were on 2/3 dose, 36 (25%) on half dose, and 30 (21%) had discontinued biological treatment. Median time to flare was 273 days (IQR:

247-299). According to figure 1 female sex and longer disease duration were associated with an increased risk of flare.

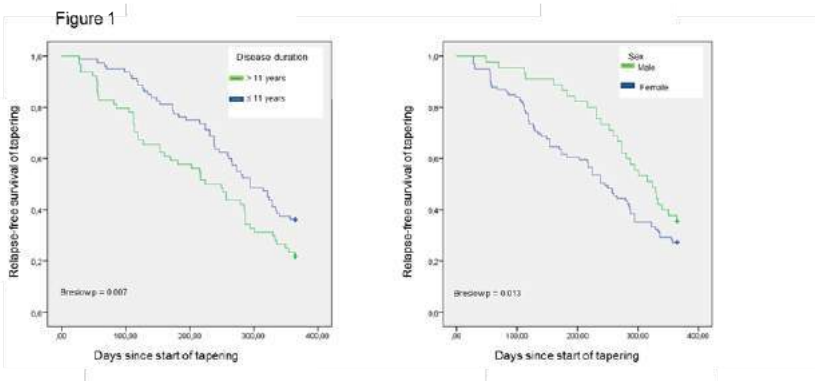
Conclusion: One year after initiating dose tapering in RA patients in remission in routine clinical practice, 66% of patients had been able to reduce the dose. Flares during tapering occurred in >70%, but were reversed by re-escalating patients to the previous dose. Female sex and longer disease duration were associated with increased risk of flare.

Tabel 1: Baseline demographics and treatment status at 1 year

Baseline	n= 143
Age (years)	59 (48-68)
Female gender %	69%
Disease duration (years)	11 (7-18)
RF %	66%
Anti-CCP %	80%
Number of tender joints (0-40)	0 (0-0)
Number of swollen joints (0-40)	0 (0-0)
Haq	0.25 (0-0.75)
Concomitant DMARD	80%
CRP	5 (2-6)
DAS28-CRP	1.8 (1.6-2.1)
VAS patient confidence to tapering	50 (47-80)
Days in remission before tapering	785 (490-1152)
Biologic drug (%)	
- Adalimumab	31%
- Etanercept	28%
- Infliximab	27%
- Tocilizumab	6%
- Certolizumab	3%
- Golimumab	2%
- Abatacept	1%
No. biologic drug before	
0	62%
1	26%
2	8%
≥3	4%
1-year status of biological treatment	n=143
Full dose (n, %)	49 (34%)
2/3 dose (n,%)	28 (20%)
½ dose (n,%)	36 (25%)
No biologics (n,%)	30 (21%)

Values are median (IQR)

Figure 1



Disclosure: C. H. Brahe, None; **S. Krabbe**, None; **M. Østergaard**, Abbott Immunology Pharmaceuticals, 2,Bristol-Myers Squibb, 2,Boehringer Ingelheim, 2,Eli Lilly and Company, 2,Merck Pharmaceuticals, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,UCB, 2,Celgene, 2,Sanofi-Aventis Pharmaceutical, 2,Regeneron, 2,Novartis Pharmaceutical Corporation, 2; **H. Rogind**, None; **H. S. Jensen**, None; **A. Hansen**, None; **J. Nørregaard**, None; **S. Jacobsen**, None; **L. Terslev**, None; **T. K. Huynh**, None; **D. V. Jensen**, None; **N. Manilo**, None; **K. H. Asmussen**, None; **P. Brown-Frandsen**, None; **M. Boesen**, None; **Z. Rastiemadabadi**, None; **D. Glinatsi**, None; **L. Morsel-Carlsen**, None; **J. M. Møller**, None; **N. S. Krogh**, None; **M. Lund Hetland**, AbbVie, BMS, MSD, Roche, Pfizer, UCB, Crescendo, 2.

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Abstract Number: 3014

Tapering of Adalimumab Based on Therapeutic Drug Monitoring in Rheumatoid Arthritis

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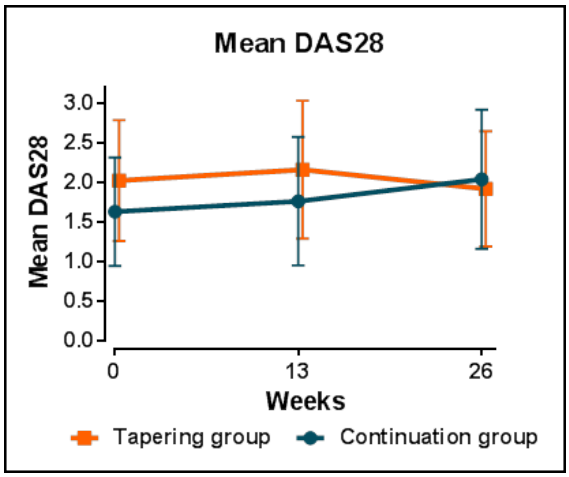
Background/Purpose: Treatment with biologicals is based on the principle of 'one size fits all' without taking differences into account for dosing schemes, patients' characteristics and pharmacokinetics. The aim of this study is to compare disease activity after 26 weeks between adalimumab dose interval prolongation and continuation of the regular dose in rheumatoid arthritis (RA) patients with high adalimumab serum concentration[1] .

Methods: In this open randomized controlled trial, patients with an adalimumab concentration >8 mL/L were randomly (1:1) assigned to continuation of 40 mg adalimumab every other week (continuation group) or prolongation of the dosage interval to once every 3 weeks (tapering group). This was independently of disease activity score in 28 joints (DAS28). Before the study, patients were treated with adalimumab 40 mg subcutaneous every other week for at least 28 weeks. Visits were scheduled at baseline, 13 and 26 weeks thereafter. The change in DAS28 (deltaDAS28) after 26 weeks compared to baseline was taken as outcome measurement. A clinical relevant difference was defined as a deltaDAS28 >0.6. Based on an intention to treat analysis, an independent t-test was used to compare mean deltaDAS28 between the two groups. A total of 102 patients was calculated as a priori sample size.

Results: Fifty-three patients out of 142 screened patients (37%) had adalimumab concentrations >8 mL/L and were included in the study. All patients completed follow up. Twenty-six patients were assigned to continuation group and 27 to tapering group. Baseline characteristics did not differ significantly between the two groups. After 26 weeks, mean deltaDAS28 did not meet the criteria for a clinically relevant difference in both continuation group (0.29 ± 0.58 standard deviation (SD)) and tapering group (-0.06 ± 0.58 SD) (see figure). The groups were not significant different (p=0.06). Six patients in the continuation group developed active inflammation (defined as an increase of ≥ 1 swollen joint compared to baseline) during follow-up. In the tapering group, two patients developed active inflammation of whom one returned to standard dose of adalimumab. Despite the absence of inflammatory signs, eight other patients in the tapering group returned to standard dose on request of patient or treating rheumatologist.

Conclusion: This study shows that disease activity remains stable in RA patients with adalimumab concentrations > 8 mL/L who prolonged their dose interval to once in the three weeks compared to patients who continued adalimumab every other week.

Reference: Pouw MF, Krieckaert CL, Nurmohamed, MT, van der Kleij D, Aarden L, Rispens T, Wolbink G. Key findings towards optimising adalimumab treatment: the concentration-effect curve. Ann Rheum Dis, 2015;74;513-8



Disclosure: M. J. l'Ami, None; **A. F. Marsman**, Pfizer Inc, 8; **C. L. Krieckaert**, Pfizer Inc, 8; **M. T. Nurmohamed**, None; **J. Ruwaard**, None; **I. M. Visman**, None; **E. L. Kneepkens**, Pfizer Inc, 8; **G. Wolbink**, Pfizer Inc, 5,AbbVie, 5,UCB, 5,Mundifarma, 5,BMS, 5,UCB, 8.

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Abstract Number: 3015

The Good, the Bad and the Ugly – Refractory Rheumatoid Arthritis in 2016

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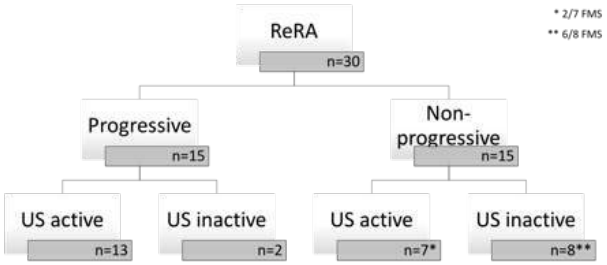
Background/Purpose: Rheumatoid arthritis (RA) is characterised by the presence of a progressively destructive joint inflammation. Even in times of modern therapeutics, a subgroup of patients continues to be refractory to numerous consecutive therapeutic interventions with regards to control of inflammation and joint damage. **Objective:** To explore the characteristics and causes of refractory RA in 2016.

Methods: We defined refractory RA as patients who had experienced ³3 treatment courses (with at least one biological) over a minimum of 18 months since diagnosis without reaching the treatment goal of low disease activity or remission (defined by a Simplified Disease Activity Index, SDAI, ³11). From our clinicÕs ongoing longitudinal data set we identified 64 refractory patients out of 737 RA outpatients. This is an interim report of the first 30 of these patients, who were prospectively included in our study (figure 1). Radiographic images were obtained prospectively, and were retrospectively scored by an experienced reader using the modified Sharp/van der Heijde (SvH) method. Average changes in SvH scores of ³3 per year were considered as progressive. After enrolment, we performed ultrasound examination of the hands among these refractory patients and semi-quantitatively scored them for signs of Greyscale and Power Doppler.

Results: 15 out of 30 (50.0%) patients showed radiographic progression (figure). In this group, almost every patient (86.7%) also showed signs of ultrasound activity (Power Doppler signs grade 2 or 3). Radiographic progressive patients showed significantly fewer tender joints than patients being non-progressive (p=0.032) (table). Of the 15 non-progressive refractory patients, 8 were diagnosed with fibromyalgia by the ACR 2010 fibromyalgia diagnostic criteria, and accordingly had failed their treatment target

due to high patient global scores and tender joint counts. The remaining seven had active synovitis, which was confirmed in five patients by ultrasound. Regardless of radiographic or sonographic state, patients evaluate their state of disease activity the same (Patient Global Assessment, PGA: 57.3 vs 62.2, p=0.502; or 59.9 vs 59.1, p=0.925; respectively).

Conclusion: There a several different types of patients being referred as ÒrefractoryÓ. Whereas almost all radiographic progressing patients also show signs of active synovitis by ultrasound, most non-progressing patients do not and are mainly classified as refractory due to pain components. Here, our clinical composite indices fail.



Descriptive	Progressive	Non-progressive	Sig.	Descriptive	US active	US inactive	Sig.
RF	89.5 (153.9)	73.6 (205.9)	0.809	**RF**	75.2 (136.0)	27.5 (35.7)	0.289
ACPA	98.9 (136.2)	96.7 (180.2)	0.970	**ACPA**	73.8 (127.4)	108.2 (135.3)	0.499
ESR	33.3 (24.1)	35.1 (20.3)	0.827	**ESR**	28.3 (21.6)	47.8 (18.0)	0.026
CRP	0.8 (1.1)	0.6 (0.6)	0.523	**CRP**	0.6 (0.7)	1.0 (1.0)	0.169
SJC 28	5.6 (5.1)	4.1 (4.4)	0.379	**SJC 28**	6.4 (5.3)	1.9 (1.7)	0.015
TJC 28	6.3 (6.7)	12.7 (8,9)	0.032	**TJC 28**	9.1 (8.5)	10.6 (9.3)	0.652
Pain	50.2 (15.0)	50.6 (21.0)	0.949	**Pain**	46.8 (18.3)	53.8 (17.4)	0.324
PGA	57.3 (18.1)	62.6 (24.1)	0.502	**PGA**	59.9 (20.0)	59.1 (21.4)	0.925
EGA	30.7 (14.7)	26.6 (16.9)	0.483	**EGA**	33.5 (15.5)	20.4 (13.5)	0.031
DAS28	4.8 (0.9)	5.6 (1.0)	0.031	**DAS28**	5.1 (1.1)	5.5 (1.0)	0.292
CDAI	20.7 (8.4)	25.8 (12.9)	0.202	**CDAI**	24.7 (11.5)	20.6 (10.7)	0.355
SDAI	21.5 (8.5)	26.4 (12.8)	0.219	**SDAI**	25.3 (11.5)	21.7 (10.7)	0.407
Ann. Prog. (SvH)	5.4 (1.7)	1.4 (0.9)	<0.001	**Ann. Prog. (SvH)**	4.1 (2.5)	2.0 (1.8)	0.021

Disclosure: M. Unger, None; **F. Alasti**, None; **G. Supp**, None; **J. S. Smolen**, None; **D. Aletaha**, None.

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Abstract Number: 3016

Validity of a 2-Component Disease Activity Score for Accurate Assessment of Synovitis in Rheumatoid Arthritis

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Background/Purpose: The original Disease Activity Score (DAS) was derived from clinicians' therapeutic decisions[1], which may have been influenced by patient-subjective factors such as general health status and joint tenderness. Modern imaging allows accurate measurement of synovitis and provides an objective standard against which to derive an updated DAS. We aimed to identify alternative forms of the DAS28 that are more strongly associated with ultrasound (US) measures of synovial inflammation than existing definitions.

Methods: Patients were included from 2 observational early RA cohorts [Inflammatory Arthritis CONtinuum (IACON n=433) and Pathobiology of Early Arthritis Cohort (PEAC n=117)], and a clinical trial (IDEA n=89); all satisfied ACR 1987 and/or ACR/EULAR 2010 criteria for RA. Data were available at repeated time-points [weeks 0, 26, 52, 78, 104 (IACON); 0, 26 (PEAC); 0, 50, 78 (IDEA)]; US scan was within 1 week of clinical exam. In IACON and IDEA US grey scale and power Doppler scores (0-3) for bilateral wrists, knees, MCPs 2&3, PIPs 2&3 and MTPs 1-5 were combined into a global GSPD score with Rasch analysis. In PEAC global GSPD was GS+PD in bilateral MCPs 1-5. Using linear mixed models with random intercepts for within-patient clustering we modelled the association in each cohort between GSPD and: original 4-component (4C) DAS28CRP score, a 2-component (2C) score with weights for SJC28 (0.15) and lnCRP+1 (0.49) from an existing MRI-based equation[2], and DAS28CRP components [SJC28, CRP or TJC28, SJC28, CRP, general health VAS (GH)]. We compared models using restricted maximum likelihood deviance. Multiple imputation addressed missing data. Analyses used R v3.2.5.

Results: Models included 843, 237 and 183 visits from IACON, IDEA and PEAC respectively. Using DAS28 scores, deviance differences favoured 2C-DAS28 for IACON (2C-4C: -31) and PEAC (-16) but original 4C-DAS28 in IDEA (8). Nevertheless, using individual components, in all 3 studies only SJC28 and CRP were associated with GSPD. Coefficients from models using individual components are presented in Table 1. Despite differences in joints measured and methods of creating GSPD, the ratio of coefficients in the 2C models (SJC:CRP) were consistent: IACON 2.2, IDEA 2.1, PEAC 2.5.

Conclusion: Using a more objective measure of synovial inflammation, US-derived GSPD, the subjective elements of the DAS28 equation (TJC28, GH) can potentially be removed without loss of association with underlying synovitis and their removal may even improve the association. A 2-component DAS28CRP would simplify clinical examination and reduce the likelihood of missing data in clinical studies. This has the potential to improve patient care by targeting escalation of therapy to those with synovitis. Additional modelling will determine optimal weights for a 2-component DAS28CRP.

1. van der Heijde DM et al. J Rheumatol. 1993;20:579-81.
2. Baker et al. Arthritis Rheum. 2014;66:794-802.

Covariate	Coefficient (SE) for association with GSPD	
IACON	**4-component**	**2-component**
sqrt(SJC28)	1.06 (0.13)	1.03 (0.10)
ln(CRP+1)	0.48 (0.13)	0.46 (0.12)
sqrt(TJC28)	-0.02 (0.11)	
GH VAS	0.00 (0.01)	
IDEA	**4-component**	**2-component**
sqrt(SJC28)	0.84 (0.27)	1.18 (0.18)
ln(CRP+1)	0.52 (0.24)	0.57 (0.22)
sqrt(TJC28)	0.39 (0.22)	
GH VAS	0.00 (0.01)	
PEAC	**4-component**	**2-component**
sqrt(SJC28)	5.48 (1.00)	5.32 (0.68)
ln(CRP+1)	2.17 (0.66)	2.09 (0.65)
sqrt(TJC28)	0.17 (0.88)	
GH VAS	-0.02 (0.03)	

Table 1: Associations between DAS28CRP components and GSPD in each cohort

Disclosure: E. M. A. Hensor, None; **P. McKeigue**, None; **P. G. Conaghan**, AbbVie, Flexion, Eli Lilly, Novartis, Pfizer Inc, Roche, 5,AbbVie, Novartis, Roche, 8; **M. H. Buch**, None; **J. H. Barrett**, None; **J. L. Nam**, None; **M. Colombo**, None; **A. Spiliopoulou**, None; **F. Agakov**, Pharmatics Limited, 4; **S. Kelly**, None; **M. J. Lewis**, None; **C. Pitzalis**, Abbot/Abbvie, Astellas, Astra-Zeneca/MedImmune, BMS, Celgene, Grunenthal, GSK, Janssen/JNJ, MSD, Pfizer, Sanofi, Roche/Genetech/Chugai, UCB, 2; **P. Emery**, None; **A. W. Morgan**, None.

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Abstract Number: 3017

Elevated Neutrophil Extracellular Trap Levels Correlate with Anti-CCP3-IgG and Anti-CCP3-IgA Levels in the Sputum of Individuals at-Risk for Future Rheumatoid Arthritis

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The initial site of anti-citrullinated protein antibody (ACPA) generation in RA has been proposed to be a mucosal site. We have previously demonstrated ACPA elevations (characterized by anti-CCP) in the lung of individuals at-risk of future RA and with established RA using induced sputum (*Willis 2013*). In recent pilot work, we found that anti-CCP-IgG and CCP-IgA are elevated in 25% of first-degree relatives (FDR) of RA patients who are at-risk of RA development based on familial risk. However, it is unknown what factors may trigger anti-CCP production in the lung. Neutrophil extracellular trap (NET) formation is

one mechanism that can externalize citrullinated proteins (e.g. cit-histones) and potentially trigger anti-CCP. Prior studies identified enhanced peripheral NETosis in patients with established RA; however the relationship between NETosis and mucosal anti-CCP production is unknown. To better understand anti-CCP development in the lung, we sought to evaluate NET levels in sputum associated with anti-CCP.

Methods: From the Studies of the Etiology of RA cohort, we evaluated 51 FDRs without inflammatory arthritis (IA). Induced sputum was tested by ELISA on a CCP3 substrate using isotype-specific IgA and IgG secondary reagents (Inova, for research only). In sputum, *in-vivo* NET levels were measured using a sandwiched ELISA for DNA-myeloperoxidase (MPO) complexes, and total citrulline level was quantified using colorimetric assays. A subset of 35 FDRs also had total neutrophils (per mL) quantified in sputum using cytocentrifugation. Analyses included SpearmanÕs correlation.

Results: FDRs had a mean age of 52 ± 13, and were 71% female and 33% ever-smokers. Sputum anti-CCP-IgG and CCP-IgA levels significantly correlated with sputum level of NETosis (Figure). Using linear regression, this correlation remained significant after adjusting for smoking. When considering only FDRs who were serum anti-CCP-IgG and IgA negative (n=40), these correlations also remained significant. In addition, sputum anti-CCP-IgG and IgA correlated with sputum total neutrophil cell count (Figure) and total citrulline level (for CCP-IgG, r=0.33, p=0.02; for CCP-IgA, r=0.52, p<0.01).

Conclusion: We identified a strong correlation between sputum anti-CCP-IgG and IgA levels and NET-associated biomarkers in RA-free FDRs that was independent of smoking and serum anti-CCP positivity. Sputum anti-CCP also correlated with neutrophil cell count and total citrulline levels. In aggregate, these data suggest that in the lung, in the setting of elevated neutrophils, NETosis may be a source of externalized citrullinated protein that can trigger sputum anti-CCP-IgA and anti-CCP-IgG production locally. Since these findings are in subjects without RA, longitudinal studies are needed to determine the relationships between these mucosal biomarkers, the development of systemic RA-related autoimmunity and progression to classifiable RA.

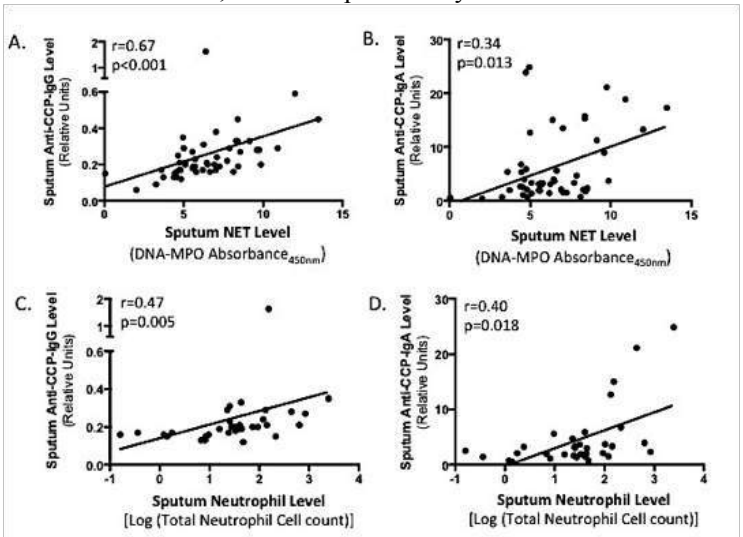

Figure. Correlations of Sputum Anti-CCP, Neutrophil Extracellular Trap (NET) and Neutrophil Levels in First Degree Relatives (FDRs). The correlation between sputum anti-CCP (Y axis) and NET levels (X axis) are depicted in Panels A (for anti-CCP-IgG) and B (for anti-CCP-IgA). The correlation between sputum anti-CCP (Y-axis) and neutrophil levels (log of total neutrophil count, X-axis) are depicted in Panels C (for anti-CCP-IgG) and D (for anti-CCP-IgA).

Disclosure: M. K. Demoruelle, Inova Diagnostics, Inc., 9; **M. Purmalek**, None; **H. Rothfuss**, None; **M. Weisman**, None; **L. Kelmenson**, None; **M. Mahler**, Inova Diagnostics, 3; **J. M. Norris**, None; **B. Cherrington**, None; **M. Kaplan**, None; **V. M. Holers**, Patents, 9; **K. D. Deane**, Inova Diagnostics, Inc., 9.

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Abstract Number: 3018

The Analysis of Severity of Arthritis in the Intestinal Microbiota-Humanized Mice

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Background/Purpose: Although various genetic factors have been implicated in susceptibility to rheumatoid arthritis (RA), environmental factors including smoking, periodontal disease and hormones are also necessary for the disease manifestations. We speculate that gut microbiota is one such environmental factor that may be correlated with the development of RA. Previous reports have demonstrated that RA patients have altered composition of gut microbiota. However, it remains unclear whether the altered composition of intestinal microbiota observed in RA patients causes the disease onset.

Methods: We first examined whether RA patients have particular patterns of microbiota. All the patients were diagnosed according to the American College of Rheumatology/European League Against Rheumatism 2010 classification criteria for RA. We collected human fecal samples from 17 untreated new-onset RA patients (disease duration 1.0±0.7 years, mean±SD) and 13 healthy volunteers to investigate the microbiota by 16S rRNA-based deep sequence technique. We further analyzed the correlation between bacterial counts of intestinal microbiota and disease activity in 50 treated RA patients (disease duration 9.6±9.0 years, mean±SD) by quantitative reverse transcription PCR (RT-qPCR) method. We also inoculated human fecal samples from new-onset RA patients or healthy controls into germ free SKG mice (intestinal microbiota-humanized mice) and analyzed for the severity of arthritis and immune responses. We next evaluated whether *Prevotella copri* (*P. copri*) has an ability to induce Th17-related cytokines *in vitro*. Bone marrow-derived DCs were stimulated with intestinal bacteria and analyzed for the production of Th17-related cytokines. Finally, we inoculated *P. copri* into germ free SKG mice and analyzed severity of arthritis.

Results: Six out of 17 new-onset RA patients showed high abundance of *Prevotella.* Especially, *P. copri* was dominant OTU in the RA patients. None of the healthy controls harbored increased abundance of *Prevotella.* The bacterial counts of *Prevotella* were positively correlated with the disease activity of treated 50 RA patients ($r = 0.36$, $P<0.01$). SKG mice harboring *Prevotella*-dominated microbiota from new-onset RA patients (RA-SKG mice) showed severe arthritis in the presence of zymosan injection. Increased number of Th17 cells in the regional lymph nodes and large intestine was observed in RA-SKG mice. *P. copri* induced high production of IL-6 and IL-23, indicating that *P.copri* has an ability to enhance Th17-biased immune responses. Mono-colonization of *P. copri* into germ free SKG mice also showed arthritis.

Conclusion: *Prevotella*–dominated gut microbiota may contribute to the development of arthritis both in human RA patients and SKG mice.

Abstract Number: 3019

Sputum Antibodies to Individual Citrullinated Protein/Peptide Antigens Are Elevated in Subjects at-Risk of Future RA and Subjects with Established Disease

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Background/Purpose: Multiple studies demonstrate that ACPAs are elevated in the serum years prior to the onset of seropositive RA during a preclinical period of autoimmunity. Importantly, the mechanisms and site of development ACPAs as well as their initial antigen targets in the preclinical period are unknown, although data suggest that initial production may occur at a mucosal site such as the lung. Therefore, we sought to explore ACPAs in the lung of subjects with RA and at-risk of future RA.

Methods: From the Studies of the Etiology of RA cohort, we included 17 established RA subjects, 45 subjects At-Risk of RA and 16 healthy Controls. RA subjects were all serum anti-CCP3.1 positive (IgG/IgA, Inova). At-Risk subjects were without RA, were at-risk of future RA based on familial (i.e. first-degree relative of RA patient) or serologic (i.e. serum anti-CCP3.1 positive identified in clinics or health fairs) risk, and included 19/45 (42%) who were serum anti-CCP3.1 positive. Paired serum and induced sputum were tested using a bead-based ACPA array for IgG reactivity to 29 individual citrullinated proteins/peptides and quantified by fluorescent intensity. A separate cohort of 22 healthy controls were used to set ACPA positive cut-off levels at a level that was positive in <5% of these controls. For analysis, At-Risk subjects were stratified as Serum ACPA(+) and Serum ACPA(-) based on our array results.

Results: Subject demographics are listed in the Table. Compared to Controls, positivity of ≥1 sputum ACPA was higher in RA (71%, $p<0.01$) and At-Risk subjects (40%, $p=0.01$). The median number of positive sputum ACPAs was higher in RA ($p<0.01$) and Serum ACPA(+) At-Risk subjects ($p<0.01$) compared to Controls. Several individual sputum ACPAs were more prevalent in RA and At-Risk subjects compared to Controls (Table footnotes 5-7). Of interest, antibodies to citrullinated fibrinogen, fibronectin and apolipoprotein E were more prevalent in Serum ACPA(-) and Serum ACPA(+) At-Risk subject compared to Controls. In RA, antibodies to citrullinated fibrinogen and fibronectin peptides were more prevalent than in Controls.

Conclusion: In this pilot study, we found ≥1 sputum ACPA in 71% of RA and 40% of At-Risk subjects. These data support our prior finding of elevated sputum anti-CCP-IgG in At-Risk and RA subjects by ELISA testing (*Willis 2013*). Furthermore, 25% of Serum ACPA(-) At-Risk subjects were sputum ACPA positive supporting these ACPAs may originate in the lung. In particular, citrullinated fibrinogen, fibronectin and apolipoprotein E may be early antigenic targets in the lung during preclinical phases of RA. Finally, the number of sputum ACPAs positive increased from Controls to Serum ACPA(+) At-Risk to RA subjects suggesting that epitope spreading likely occurs in the lung during phases of RA development. Additional longitudinal studies are needed to confirm and extend these findings as well as evaluate non-citrullinated protein reactivities in the lung.

Table. Subject Characteristics and Sputum ACPA Positivity in Controls, At-Risk and RA Subjects							
	Controls (N=16)	**At-Risk** (N=45)	**RA** (N=17)	**p-value[1]**	**Serum ACPA(-) At-Risk** (N=20)	**Serum ACPA(+) At-Risk** (N=25)	**p-value[2]**
Age, median (range)	30 (22-65)	57 (29-79)	52 (36-75)	<0.01	55 (29-75)	57 (32-79)	0.63
Female, %	81	71	65	0.62	70	72	0.88
Non-Hispanic white, %	81	76	56	0.23	65	84	0.18
Ever-smoker, %	25	36	53	0.26	35	36	0.94
Shared Epitope, %	39	51	44	0.72	55	48	0.64
≥1 Sputum ACPA (+), %	6	40	71[5]	**<0.01**	25[6]	52[7]	**<0.01**
Median (range) of positive sputum ACPAs (+)	0 (0-2)	0 (0-29)	1 (0-28)	**<0.01**	0 (0-10)	3 (0-29)	**0.04**
Median (range) of positive sputum ACPAs	0 (0-0)	1 (0-27)	23 (2-28)	**<0.01**	0 (0-0)	2 (1-27)	**<0.01**

1. P-value comparing Controls, At-Risk and RA subjects using Chi-square/Fischer's and non-parametric testing.
2. P-value comparing Serum ACPA(-) At-Risk and Serum ACPA(+) At-Risk subjects using Chi-square/Fischer's test and non-parametric testing.
3. The following sputum ACPAs were more prevalent in RA vs. Controls: **Cit-Histone 2B** (29 vs. 0%, p=0.04), **Cit-Fibrinogen (616-635) cyclic** (35 vs. 0%, p=0.02), **Cit-Filaggrin (48-65) cyclic** (47 vs. 0%, p<0.01), **Cit-Fibronectin (1029-1042)** (29 vs. 0%, p=0.04).
4. The following sputum ACPAs demonstrated a trend toward being more prevalent in Serum ACPA(-) At-Risk compared to Controls: **Cit-Fibrinogen** (20 vs. 0%, p=0.06), **Cit-Fibronectin** (15 vs. 0%, p=0.11), **Cit-Apolipoprotein E** (15 vs. 0%, p=0.11).
5. The following sputum ACPAs were more prevalent in Serum ACPA(+) At-Risk vs. Controls: **Cit-Fibrinogen** (36 vs. 0%, p<0.01), **Cit-Fibronectin** (36 vs. 0%, p<0.01), **Cit-Apolipoprotein E** (36 vs. 0%, p<0.01), **Cit-Histone 2B** (40 s.v 0%, p<0.01), **Cit-Vimentin** (28 vs. 0%, p=0.03**), Cit-Apolipoprotein E (277-296) cyclic** (28 vs. 0%, p=0.03).

Disclosure: E. Bowers, None; **M. K. Demoruelle**, Inova Diagnostics, Inc., 9; **M. Weisman**, None; **J. M. Norris**, None; **W. H. Robinson**, None; **V. M. Holers**, Patents, 9; **K. D. Deane**, Inova Diagnostics, Inc., 9.

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Abstract Number: 3020

Citrullination of Inhibitor of DNA Binding-1 at Specific Locations Leads to Autoantigenicity in Rheumatoid Arthritis

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Background/Purpose: Inhibitor of DNA binding-1 (Id1) is a nuclear transcription factor that regulates cell growth and differentiation via selective binding and sequestering of other transcription factors. We have shown Id1 is primarily fibroblast derived with elevated expression in rheumatoid arthritis (RA) synovial fluids (SFs) and functions as a potent angiogenic factor. We have found that in vitro citrullination of Id1 exhibits heterogeneity in the number of modified arginines observed, leading to remarkable differences in autoantigenicity and autoantibody formation in vivo. In this study, we investigated how targeted citrullination affects the potential autoantigenicity of citrullinated Id1 and autoantibody formation in RA.

Methods: RA SFs were immunodepleted of Id1 and measured by ELISA using anti-modified citrulline (AMC) antibody for total citrullinated antigens. RA synovial tissues (STs) were homogenized and immunoprecipitated of Id1 for Western blot analysis using anti-Id1 or AMC antibodies. In vitro citrullination was performed by incubating recombinant human (rh) PAD4 or rabbit PAD with the target protein. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was performed to localize the sites of citrullination. To test the presence of anti-citrullinated protein antibodies (ACPAs) to citrullinated Id1, normal (NL) and RA patient peripheral blood (PB) sera as well as SFs, immunodepleted of rheumatoid factor, were analyzed using immunodot blot (IDB).

Results: Immunodepletion of Id1 from RA SFs significantly reduced the levels of total citrullinated antigens in RA SFs by as much as 64%, with an average reduction of 31%, as measured by ELISA. Similarly, immunoprecipitated Id1 from homogenized RA STs was also significantly citrullinated as shown by Western blots. IDB analyses revealed antibodies to citrullinated Id1, but not native Id1, which were detected in RA sera and SFs, but not in NL sera. By a series of LC/MS-MS and immunoassays, we determined the citrullination sites of modified Id1. Of the 10 available arginines (R) in Id1, the critical arginines for autoantigenicity were located at positions R33, R52 and R121. Citrullinated Id1 protein lacking modified arginines at those residues did not bind to AMC antibody, did not migrate as citId1 on acrylamide gels due to charge differences, and were not recognized by ACPAs to citId1 in IDBs. In contrast, we observed a robust change in autoantigenicity of epithelial-derived neutrophil-activating peptide-78 (ENA-78)/CXCL5 modified with rabbit PAD, showing that a single modification at R48 converts it so that it is recognized by ACPAs in patient sera and SFs.

Conclusion: We identify key arginines in Id1 that may be an autoantigenic target for ACPA development in RA. Our findings also show that targeting select arginines for citrullination conversion can produce dramatic changes in autoantigenicity. The degree of citrullination of Id1 may alter the natural folding pattern and immune properties of Id1, leading not only to autoantigenicity, but potentially also to functional changes in this molecule. These findings could explain putative disease-associated properties of Id1: increased severity of certain cancers and perpetuation of inflammatory disease.

Disclosure: R. A. Ohara, None; **H. A. Remmer**, None; **P. L. Campbell**, None; **D. A. Fox**, None; **J. H. Ruth**, None.

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Abstract Number: 3021

Frequency of Arthralgia, Seropositivity, and Seropositive Arthralgia and Their Association with Development of Rheumatoid Arthritis in a Cohort of Indigenous North Americans with or without a First Degree Relative with Rheumatoid Arthritis

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Background/Purpose: Anti-citrullinated peptide antibodies and/or rheumatoid factor (RF) in the setting of arthralgia ("seropositive arthralgia") has been associated with a high risk of development of rheumatoid arthritis (RA). Models of the risk of imminent RA have used arthralgia as an inclusion criterion. The significance of arthralgia in an unselected population of first-degree relatives (FDR) and controls, with or without seropositivity, is not known. We recruited a high-risk group, FDR of indigenous North American (INA) people with RA, in addition to INA population controls, with or without arthralgia. The goal of this analysis is to describe the prevalence of arthralgia at baseline and the association of arthralgia, seropositivity, and other RA risk factors with development of RA.

Methods: INA FDR and healthy unrelated controls were recruited from two populations in Canada and the United States. Data collected at the baseline visit included demographic features, habits and environmental exposures, and self-reported joint symptoms. Sera were tested for the presence of anti-cyclic citrullinated peptide (CCP) antibodies and rheumatoid factor IgM by ELISA. Risk of future RA was estimated based on a previously reported risk model for imminent RA. Participants have been followed longitudinally for development of RA.

Results: 961 participants were included in the analysis (620 FDRs and 341 controls). The mean age at baseline was 36.0 years. The cohort was 62.2% female, with 74.4% residing in rural communities. Arthralgia of any joint was present in 51.3% of the cohort (58.4% of FDRs and 35.5% of controls, $p<0.0001$). Arthralgia of both the hands and other joints was present in 31.9% overall. Seropositive arthralgia was present in 128 participants (27.7% of those with arthralgia). Seropositivity for RF and/or CCP was associated with reduced odds of arthralgia at the baseline visit (OR 0.59 (95%CI 0.44-0.80)). The majority of those with arthralgia (91.2%) fell into the low-risk category for RA development based on the imminent RA prediction model. Participants who developed RA during the follow-up period (n=14) were no more likely to have arthralgia at baseline than those who did not develop RA ($p=0.9$). Those who developed RA were less likely to fall in the low risk group at baseline ($p<0.001$) and more likely to be seropositive for RF ($p=0.07$) and CCP ($p<0.001$) and to have seropositive arthralgia ($p=0.001$).

Conclusion: Although arthralgia is more common in FDRs than in controls, arthralgia is not associated with seropositivity or with development of RA in a healthy population. In contrast, both seropositivity and seropositive arthralgia are associated with RA development.

Disclosure: E. Ferucci, None; **C. Hitchon**, None; **I. Smolik**, None; **D. Robinson**, None; **H. El-Gabalawy**, None.

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Abstract Number: 3022

Autoantibodies to Peptidylarginine Deiminase 2 Protect Against Radiographic Progression in Patients with Rheumatoid Arthritis

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Background/Purpose: The mechanisms that drive clinical heterogeneity and outcomes in patients with rheumatoid arthritis (RA) are poorly understood, but precise biomarkers may identify clinically unique subgroups with distinct underlying disease

mechanisms. In a subset of patients with RA, autoantibodies that activate the peptidylarginine deiminase (PAD) 4 enzyme have been identified. These antibodies are associated with severe joint and lung disease, highlighting the potential importance of functional autoantibodies in disease pathogenesis. The PAD enzymes are central players in RA due to their ability to generate the citrullinated targets of anti-citrullinated protein antibodies (APCAs). Although PAD4 has garnered the most attention, PAD2 is also strongly implicated in RA pathogenesis, but antibodies to PAD2 have not been reported.

Methods: In this study, sera from 184 patients in the ESCAPE RA cohort and 37 healthy controls were screened for the presence of antibodies to human PAD2 by ELISA. The frequency of anti-PAD2 antibodies and associated clinical features were determined.

Results: The frequency of anti-PAD2 antibodies in patients with RA was 18.5%, compared with 5.4% of healthy controls ($p=0.001$). Interestingly, the clinical characteristics of anti-PAD2 positive patients were distinct from those previously observed for anti-PAD4 antibodies. While antibodies to PAD4 are associated with APCAs, the *HLA-DRβ1* shared epitope (SE), and severe joint and lung disease, anti-PAD2 antibodies were negatively associated with SE ($p=0.014$) and swollen joint count ($p<0.05$) and were not associated with APCAs ($p=0.94$). Significantly higher anti-PAD2 antibody titers were observed in RA patients who were female ($p=0.013$) or on biologic therapies ($p=0.036$), while significantly lower antibody titers were observed in patients with SE ($p=0.02$) or interstitial lung disease ($p=0.039$). In a multi-variable model adjusted for C-reactive protein, adiponectin, and baseline radiographic joint damage, anti-PAD2 antibodies were significantly protective against radiographic progression with a 9% lower odds of progression per log unit of anti-PAD2 antibody (OR=0.91; $p=0.021$) (Figure).

Conclusion: Anti-PAD2 antibodies represent a novel biomarker in RA that is not associated with the traditional risk factors linked to disease severity such as SE and ACPAs. Instead, patients with antibodies to PAD2 are protected against radiographic progression and have less interstitial lung disease. This novel biomarker has potential implications for disease monitoring and highlights an unappreciated role of PAD2 in RA pathogenesis. The less aggressive disease phenotype observed in patients with anti-PAD2 antibodies suggests that they may target a pathogenic function of PAD2 in patients with RA. The effect of anti-PAD2 antibodies on PAD2 enzyme activity is currently under investigation.

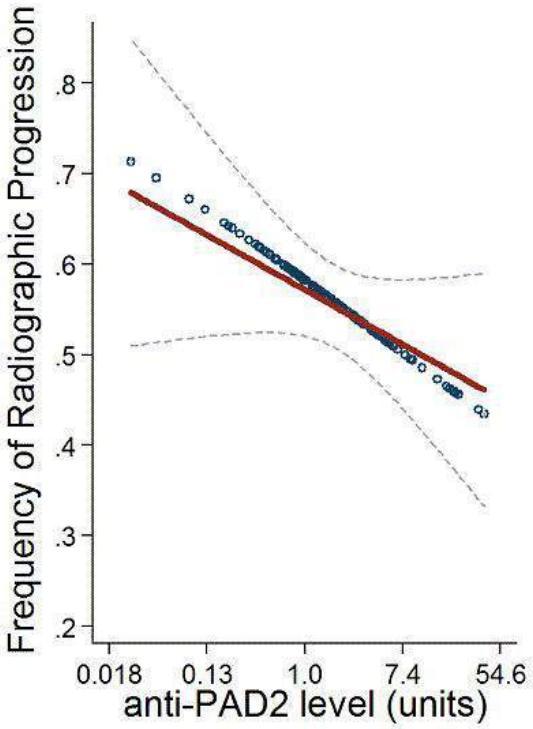

Figure. Crude and Adjusted Frequency of Radiographic Progression Over Three Years According to anti-PAD2 Level. The open circles represent the unadjusted average probability function derived from logistic regression. The solid line with its dashed 95% confidence interval represent the adjusted average probability function, adjusted for average CRP, baseline radiographic damage (i.e. Sharp van der Heidje Score), and average adiponectin level (OR=0.91; p=0.016)

Disclosure: E. Darrah, Medimmune, 2,Padlock Therapeutics, 5,Inova Diagnostics, Inc., 7; **J. T. Giles**, Inova Diagnostics, Inc., 7; **R. Davis**, None; **P. Naik**, None; **M. Konig**, None; **F. Andrade**, Medimmune, 2,Inova Diagnostics, Inc., 7.

Abstract Number: 3023

Lipid Profile and Effect of Statin Treatment in Pooled Phase 2 and Phase 3 Baricitinib Studies

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Background/Purpose: In patients with active RA an increase in lipid analytes has been observed after treatment with janus kinase inhibitors and other disease-modifying antirheumatic drugs.[1] The molecular mechanisms underlying these lipid changes are under active investigation.[2]

Methods: Data were analyzed from Phase 2 and Phase 3 studies of 4 mg oral baricitinib (bari) administered once daily in patients with moderately to severely active RA. The effect of statin therapy on lipid levels was evaluated in a subgroup of Phase 3 patients. In 1 Phase 3 study, the lipoprotein particle size and number were evaluated with nuclear magnetic resonance (NMR) at baseline and Week (Wk) 12.

Results: Treatment with bari was associated with increased levels of total cholesterol, triglycerides (TG), low density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL C) with a stable LDL C/HDL C ratio. The lipid elevation plateaued after Wk 12 (Table 1). By NMR, bari did not significantly affect total LDL particle number while the small, dense potentially more atherogenic LDL particle numbers decreased. Bari significantly increased HDL-C, the total number of HDL particles, all HDL subfractions, and TG-rich lipoproteins. The magnitude of lipid change from baseline was not significantly different between baseline statin users and nonusers (Table 2). In bari patients who initiated statin therapy before Wk 24 (N=18), the increased levels of total cholesterol and LDL-C decreased to baseline levels by Wk 24, while HDL-C levels remained elevated after statin therapy (Figure 1). Similar results in lipids changes and response to initiation of statin therapy were observed for apolipoprotein A1 and apolipoprotein B corresponding to HDL-C and LDL-C.

Conclusion: These analyses showed that bari was associated with increased LDL-C, HDL-C, and TG levels, with a stable LDL-C/HDL-C ratio. The magnitude of lipid change was not significantly different between baseline statin users and nonusers. In patients who initiated statin therapy during the study, the elevation in total cholesterol, LDL-C, and TG decreased to pretreatment levels in response to statin therapy, while HDL-C remained elevated with statin therapy. **References:**

1. McGrath et al. *Curr Rheumatol Rep.* 2015.
2. Robertson et al. *Nat Rev Rheumatol*. 2013.

Table 1. Change from Baseline in Lipids

	Placebo (N=1070)			BARI 4-mg (N=997)			BARI 4-mg vs. Placebo	
	Baseline	Mean percentage change from baseline (95% CI)		Baseline	Mean percentage change from baseline (95% CI)		p-value	
	Mean ±SD	Week 12	Week 24	Mean±SD	Week 12	Week 24	Week 12	Week 24
Total Cholesterol (mg/dL)	196±40	0 (-1, 1)	0 (-1, 1)	194±40	13 (12, 14)	13 (12, 15)	0.001	0.001
LDL-C (mg/dL)	118±35	-1 (-11, 10)	0 (-12, 11)	117±34	13 (2, 24)	14 (2, 25)	0.001	0.001
HDL-C (mg/dL)	60±16	1 (0, 2)	1 (0, 3)	61±16	16 (15, 17)	15 (14, 16)	0.001	0.001
Triglycerides (mg/dL)	127±79	5 (2, 8)	5 (1, 8)	125±69	17 (14, 20)	17 (14, 21)	0.001	0.001
LDL-C/HDL-C Ratio	2.1±0.9	1.4 (-0.3, 3.2)	1.6 (-0.2, 3.4)	2.1±0.8	1.0 (-0.8, 2.7)	2.8 (1.0, 4.6)	0.710	0.355

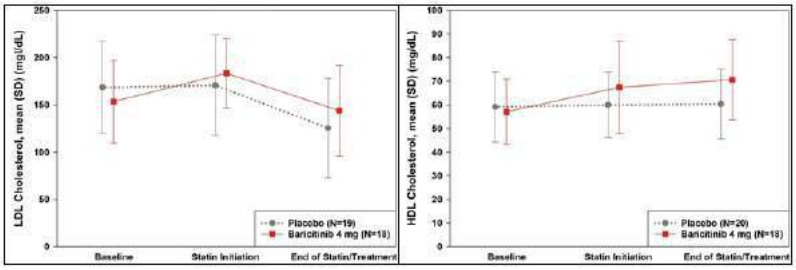
Abbreviations: ANOVA=analysis of variance; bari=baricitinib; CI=confidence interval; N=number of patients in the analysis set; HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; SD=standard deviation.
Note: Percentage change from baseline was based on the least squares mean calculated using the ANOVA model, including terms of baseline value, treatment, and study.

Table 2. Change in Lipids by Baseline Statin Use in Phase 3 Studies up to 24 Weeks

		LS Mean Change ±SE			
Statin Use Group	Treatment	Total Cholesterol (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	Triglycerides (mg/dL)
Baseline non-statin Users	Placebo (N=704)	-0.29 ±1.16	-1.16 ±0.90	-0.06 ±0.44	-1.03 ±2.36
	Bari 4-mg (n=735)	24.87 ±1.14**	15.31 ±0.88**	8.24 ±0.43**	15.63 ±2.31**
Baseline Statin Users	Placebo (n=84)	6.40 ±4.09	7.92 ±3.70	0.12 ±1.24	-0.57 ±10.26
	Bari 4-mg (n=92)	30.62 ±3.97**	20.70 ±3.59*	10.95 ±1.19**	15.02 ±9.87

Abbreviations: ANOVA= analysis of variance; bari= baricitinib HDL-C=high-density lipoprotein-cholesterol; LDL-C=low-density lipoprotein-cholesterol; LS=least squares; N=number of patients in the analysis set; SE=standard error.
Note: The LS mean change from baseline was calculated using the ANOVA model, including terms of baseline value, treatment, and study. Bari 4-mg vs. placebo: * p-value <0.05; **p-value ≤0.001.

Figure 1. Change in LDL and HDL from Baseline to Initiation of Statin Therapy and End of Statin Use up to Week 24



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Abstract Number: 3024

Major Adverse Cardiovascular Events: Risk Factors in Patients with RA Treated with Tofacitinib

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Background/Purpose: RA patients (pts) are at increased risk of myocardial infarction (MI) and stroke that cannot be completely explained by traditional cardiovascular (CV) risk factors. Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. Tofacitinib treatment may increase total cholesterol (TC), LDL-c and HDL-c in some pts. We evaluated major adverse CV event (MACE) risk factors in tofacitinib-treated RA pts in the clinical development program.

Methods: Data were pooled from pts with moderately to severely active RA receiving ≥1 tofacitinib dose in 6 Phase 3 and 2 long-term extension (LTE) studies (1 LTE study ongoing, data cut-off: March 2015). MACE was defined as any MI, stroke, or CV death (coronary, cerebrovascular, cardiac). Cox proportional hazard models evaluated associations between baseline (BL) values and time (BL to first tofacitinib dose) to first MACE. Changes (BL to Week [wk] 24) in MACE predictors and time to future MACE (first occurrence after 24 wks) were evaluated after adjusting for age, BL values and time-varying tofacitinib dose. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated.

Results: 52 MACE cases occurred over 12,873 pt-years (py) of exposure in 4076 pts (incidence rate: 0.4 pts with events/100 py). Table 1 shows BL characteristics for pts with/without MACE. In univariate analyses, traditional CV risk factors, corticosteroid and statin use were associated with BL MACE risk. BL disease activity and inflammation measures were not associated with MACE risk (Table 2). Increases in HDL-c ($p<0.001$) and decreases in TC/HDL-c ratio ($p<0.05$) after 24 wks of tofacitinib therapy were significantly associated with decreased risk of future MACE (Figure). In contrast, increases in ESR may be associated ($p=0.09$) with increased future MACE risk. Changes in TC or LDL-c or other disease activity measures were not associated with future MACE risk.

Conclusion: In pooled analyses of tofacitinib-treated pts (age and BL value adjusted), increases in HDL-c and decreases in the TC/HDL-c ratio after 24 wks of tofacitinib therapy were associated with reduced future MACE risk. Increases in ESR after 24 wks may be associated with increased future MACE risk. Increases in LDL-c and TC after 24 wks of tofacitinib therapy were not associated with future MACE risk. More data are needed to confirm these findings.

Table 1. Baseline demographics and disease characteristics

Parameter Mean ± SD	Adjudicated MACE (N=52)	No MACE (N=4024)
Age, years	60.2 ± 10.4	52.7 ± 11.9
Female gender, n (%)	43 (82.7)	3334 (82.9)
Geographic region, n (%)		
US/Canada	16 (30.8)	874 (21.7)
Europe	18 (34.6)	1440 (35.8)
Latin America	5 (9.6)	661 (16.4)
Rest of world	13 (25.0)	1049 (26.1)
BMI, kg/m^2	29.1 ± 8.2	27.0 ± 6.4
History of CHD, n (%)	0 (0.0)	21 (0.5)
History of cardiac disorders, n (%)	4 (7.7)	199 (4.9)
History of diabetes, n (%)	8 (15.4)	307 (7.6)
Abnormal BP, n (%)	4 (7.7)	334 (8.3)
Smoking status, n (%)		
Never	14 (26.9)	676 (16.8)
Current	11 (21.2)	678 (16.8)
Ex-smoker	27 (51.9)	2667 (66.3)
Corticosteroids use at baseline, n (%)	18 (34.6)	1909 (47.4)
Statin use at baseline, n (%)	12 (23.1)	420 (10.4)
NSAID use at baseline, n (%)	34 (65.4)	2817 (70.0)
Duration of RA, years	10.1 ± 8.8	7.7 ± 7.9
DAS28-4(ESR)	6.3 ± 1.3	6.3 ± 1.1
Tender joint count	14.3 ± 7.5	14.1 ±7.3
Swollen joint count	10.3 ± 5.9	10.4 ± 5.6
TC, mg/dL	208.2 ± 48.9	198.3 ± 42.1
HDL-c, mg/dL	55.3 ± 16.0	59.4 ± 16.9
LDL-c, mg/dL	123.3 ± 43.2	113.9 ± 34.2
TC/HDL-c ratio	4.0 ± 1.5	3.5 ± 1.1
Triglycerides, mg/dL	152.1 ± 86.9	125.3 ± 72.6
Apolipoprotein A-1, mg/dL	149.4 ± 27.8	153.6 ± 31.2
Apolipoprotein B, mg/dL	105.8 ±29.4	94.4 ± 24.7
CRP, mg/dL	15.7 ± 16.9	17.1 ± 22.7
ESR, mm/hr	47.9 ± 23.8	50.4 ± 26.9

BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CRP, C-reactive protein; DAS28-4(ESR); Disease Activity Score 28(ESR); ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; NSAID, non-steroidal anti-inflammatory drug; RA, rheumatoid arthritis; TC, total cholesterol.

This table shows a summary of descriptive data; between-group comparisons were not analyzed. CHD history and cardiovascular disease history were derived from medical history data.

Table 2. Association of baseline risk factors and development of MACE based on univariate Cox analysis

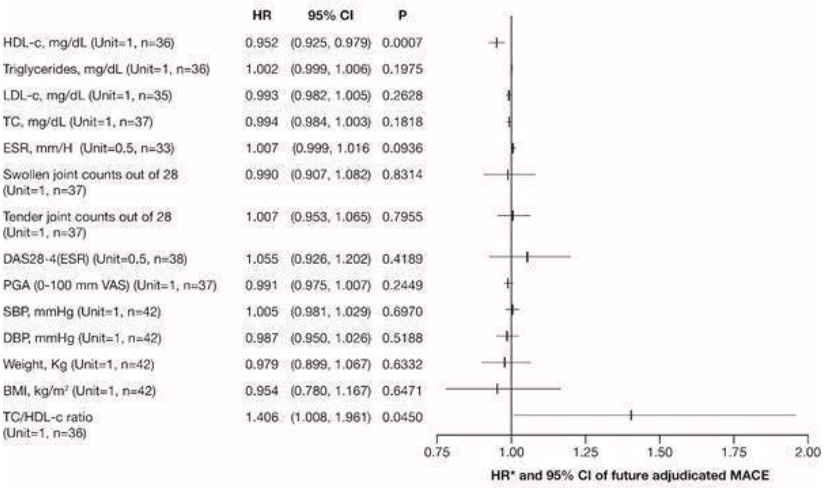
Baseline variable	HR	(95% CI)
Age (10 years, n=52)	2.02***	(1.53, 2.67)
Gender (male/female, n=52)	1.04	(0.51, 2.14)
Weight (kg, n=52)	1.01	(1.00,1.02)
BMI (kg/m^2, n=52)	1.05**	(1.01, 1.09)
Smoking status (Y/N, n=52)	1.38	(0.71, 2.69)
DAS28-4(ESR) (unit=0.5, n=50)	1.00	(0.89, 1.14)
ESR (mm/H, n=50)	1.00	(0.99, 1.00)
CRP (mg/dL, n=52)	1.00	(0.98, 1.01)
Swollen joint count out of 28 (n=52)	1.00	(0.95, 1.05)
Tender joint count out of 28 (n=52)	1.01	(0.97, 1.04)
Baseline MTX users (Y/N, n=52)	1.41	(0.78, 2.53)
Baseline MTX dose, (mg, n=36)	0.99	(0.93, 1.07)
Baseline statin users (Y/N, n=52)	2.77**	(1.45, 5.28)
Baseline corticosteroid users (Y/N, n=52)	0.55*	(0.31, 0.98)
TC (mg/dL, n=51)	1.01	(1.00, 1.01)
Triglycerides (mg/dL, n=51)	1.00**	(1.00, 1.01)
HDL-c (mg/dL, n=51)	0.98	(0.97, 1.00)
LDL-c (mg/dL, n=49)	1.01	(1.00, 1.02)
TC/HDL-c ratio (n=51)	1.42***	(1.16, 1.74)
Apolipoprotein B (mg/dL, n=48)	1.02**	(1.01, 1.03)
Apolipoprotein B/Apolipoprotein A-1 ratio (n=48)	2.76**	(1.50, 5.09)
Systolic blood pressure (mmHg, n=51)	1.02*	(1.01, 1.04)
Diastolic blood pressure (mmHg, n=51)	1.04*	(1.01, 1.07)
History of cardiac disorders (Y/N, n=52)	1.85	(0.67, 5.14)
History of diabetes (Y/N, n=52)	2.56*	(1.20, 5.43)
History of hypertension (Y/N, n=52)	2.86***	(1.65, 4.96)

*p<0.05; **p<0.01; ***p<0.001

BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; DAS28-4, disease activity score in 28 joints; ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein-cholesterol; HR, hazard ratio; LDL-c, low-density lipoprotein-cholesterol; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; TC, total cholesterol.

n represents number of patients with MACE (uncensored) analyzed for each variable.

Figure. Age-adjusted and baseline parameter-adjusted association of change from baseline to Week 24 in lipid levels, inflammation parameters, and RA disease activity measures with future MACE



BMI, body mass index; CI, confidence interval; DAS28-4(ESR); Disease Activity Score 28(ESR); DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; PGA, patients global assessment; RA, rheumatoid arthritis; SBP, systolic blood pressure; TC, total cholesterol
These data show results from a cox regression model: showing age-adjusted and baseline parameter-adjusted association of changes from baseline to Week 24, for future MACE risk.
*For each variable listed, a cox regression model was fit, with change in variable at Week 24, the variable at baseline and age at baseline and time varying dose as predictors. In this model, only patients with exposure after the tofacitinib-week 24 are considered (ie, patients who had MACE before tofacitinib-week 24 or who had withdrawn or completed the study by tofacitinib-week 24 are excluded.) Additionally, patients with missing data for a tofacitinib-week 24 variable are excluded from the analysis of that variable (no imputation method). The HR corresponds to increased risk MACE per 1-unit increase in the parameter. 'n' is the number of patients with future MACE for each predictor.

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Abstract Number: 3025

The Effect of Filgotinib (GLPG0634), an Oral JAK1 Selective Inhibitor on Patient-Reported Outcomes: Results from Two 24-Week Phase 2B Dose Ranging Studies

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Background/Purpose: Filgotinib (GLPG0634) is a novel oral, potent and selective JAK1 inhibitor that showed rapid and sustained improvements of signs and symptoms of active rheumatoid arthritis (RA) in patients with inadequate response to methotrexate (MTX) in two 24-week Phase 2B studies, with an acceptable safety profile. The effect of filgotinib add-on to MTX or monotherapy on patient-reported outcomes (PROs) is presented here.

Methods: In DARWIN 1 (add-on to MTX) and DARWIN 2 (monotherapy), patients with active RA were randomized in a double blinded manner to placebo (PBO) or one of the three daily doses of filgotinib (50mg, 100mg or 200mg) for 24 weeks. In DARWIN 1, once (qd) and twice daily (bid) regimens were assessed. At week 12, patients on PBO (in DARWIN 1) and 50mg daily dose (in DARWIN 1 and DARWIN 2) whose tender and swollen joint counts did not improve by at least 20% were reassigned to 100mg

daily dose. In DARWIN 2, all patients on PBO were reassigned to 100mg daily dose. Assessed PROs were patient evaluation of disease activity & pain, physical function, fatigue and HRQoL-SF36. This presentation reports results of the Phase 3 filgotinib doses, 100mg and 200mg qd.

Results: In total 594 and 283 patients were randomized and dosed in DARWIN 1 and DARWIN 2, respectively. Mean HAQ-DI baseline value was 1.74 and 1.81, respectively, indicating severe impairment. Filgotinib was associated with rapid and statistically significant improvement in PROs (patient assessment of disease activity and pain, physical function, fatigue and HRQoL-SF36) in both studies. The 200mg daily dose showed statistically significant effects as early as week 1-2 on HAQ-DI and patient VAS for global disease and pain, and from week 4 for FACIT and SF-36-PCS. With the 100mg qd dose, patient global assessment significantly improved from week 1-2 and FACIT from week 4 in both studies. SF-36 PCS improved from week 4 in DARWIN 2. After week 12, these responses were maintained or continued to improve through 24 weeks. At week 24, the clinical effect was comparable between filgotinib 100mg qd and 200mg qd and between add-on and monotherapy (between study comparison). Table 1. PRO responses for the 100mg and 200mg once daily doses

Mean change from baseline (LOCF)		Patient's VAS disease activity	Patient's VAS pain	HAQ-DI	FACIT	SF-36 PCS	SF-36 MCS
DARWIN 1							
PBO N=86	Wk12	-16.7	-16.9	-0.38	5.6	3.2	4.3
	Wk24	-17.9	-17	-0.37	6.0	2.8	4.7
100mg qd N=85	Wk12	-29.1*	-27.4*	-0.65*	9.5*	8.4***	5.1
	Wk24	-34.4**	-32.7***	-0.78***	11.1***	9.9***	6.7
200mg qd N=86	Wk12	-34.2***	-31.4**	-0.75***	11.4***	8.9***	8.1
	Wk24	-34.9**	-34.6***	-0.82***	11.6**	9.7***	7.2
DARWIN 2							
PBO N=72	Wk12	-11.5	-13.3	-0.23	3.9	3.0	2.7
	Wk24	-	-	-	-	-	-
100qd N=70	Wk12	-30.0***	-31.5***	-0.68***	10.2***	7.8***	6.9**
	Wk24	-32.2	-35.1	-0.79	11.3	10.0	7.7
200mg qd N=69	Wk12	-28.2***	-31.3***	-0.74***	11.2***	8.6***	6.8**
	Wk24	-35.1	-37.7	-0.85	13.7	9.7	8.5

* p< 0.05 ; ** p<0.01; *** p<0.001 vs. PBO Subjects who switched at wk 12 were handled as if they discontinued at wk 12 In DARWIN 2 statistical comparison vs. PBO is not possible after wk 12

Conclusion: In the DARWIN 1 and DARWIN 2 studies, filgotinib led to a rapid decrease in disease burden as demonstrated by the significant improvement in all assessed PROs. After 24 weeks of treatment, filgotinib 100mg qd or 200mg qd in combination with MTX or as monotherapy demonstrated comparable benefit in improving PROs in patients with active RA and the 200 mg qd dose was associated with a faster onset of action.

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Abstract Number: 3026

The Efficacy and Safety of Low Dose IL-2 Therapy in over-Treated Patients with Rheumatoid Arthritis: A Preliminary Study

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Background/Purpose: Current therapy for rheumatoid arthritis (RA) often leads to excessive immunosuppression induced by glucocorticoids and DMARDs. Low-dose Interleukin 2 (IL-2) has been showed to induce Treg cell expansion and activation, which is expected to control the development of RA. We studied the clinical efficacy and safety of IL-2 treatment in RA.

Methods: Total 41 RA patients with low Treg cells, who had been treated with glucocorticoids and DMARDs for over 6 months, were divided into two groups randomly. Patients in Non-IL-2 group (n=15) were still given traditional glucocorticoids and DMARDs treatment. Patients in IL-2 group (n=26) were not only given traditional treatment, but also injected subcutaneously IL-2 at 50 WIU per day for a 5 day course. The demographic features, clinical manifestations and laboratory indicators were compared before and after the treatment.

Results: There was no difference between Non-IL-2 group and IL-2 group in gender, age and course of the disease ($P>0.05$). The ratios of Th1/Th2 and Th17/Treg were significant correlated with ESR, the number of tender or swollen joints and DAS28-ESR ($P<0.05$) in all two groups of patients. After IL-2 treatment, the number of Th17 cells (16.51±19.06 vs 19.00±11.38, P=0.01) or Treg cells (18.67±14.08 vs 78.55±44.67, P=0.001) were significantly increased. Due to increased Treg cells were much more than the Th17, leading to a decrease in their ratio (1.36±1.49 vs 0.28±0.20, P=0.024). Before the IL-2 treatment, there was no difference in clinical manifestations between two groups ($P>0.05$), but in IL-2 group, there was a significantly decrease after the treatment in the number of tender joints (3.73±2.79 vs 0.94±1.00, P=0.001) or swollen joints (1.40±1.64 vs 0.42±0.70, P=0.011) and DAS28-ESR (3.60±0.96 vs 2.85±0.67, P=0.005). There was no difference in blood routine, liver and renal functions both before and after the treatment between two groups ($P>0.05$).

Conclusion: IL-2 can effectively up-regulate the level of Treg as well as that of Th17 to some degree and maintain the balance of Th17 and Treg cells. IL-2 subcutaneous injection combined with traditional antirheumatic drugs may help for RA patients' symptoms remission without over-treatment and evaluated side effect. IL-2 could be used as a novel therapeutic candidate for RA treatment but long term benefits of IL-2 therapy are required to further study.

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Abstract Number: 3027

Herpes Zoster in Patients with Moderate to Severe Rheumatoid Arthritis Treated with Baricitinib

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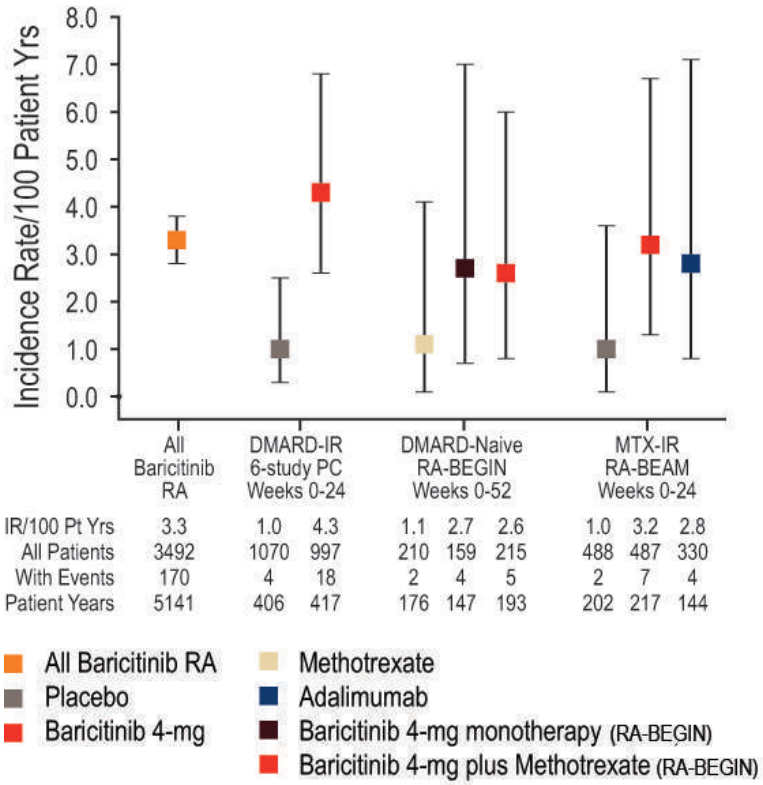
Background/Purpose: Compared to the general population, RA patients (pts) have an increased risk of herpes zoster (HZ) due to their disease and various DMARD therapies including JAK inhibitors.[1] The aim of this analysis was to evaluate HZ in RA pts treated with baricitinib (bari), an oral JAK1/JAK2 inhibitor in development for treatment of RA.[2,3]

Methods: Data were pooled from completed Phase (Ph) 1, 2, and 3 studies, and an ongoing long-term extension (LTE) study of bari in RA pts (data cutoff January 1, 2016). HZ events were identified using MedDRA preferred terms related to HZ. The incidence of HZ was evaluated for all RA pts who ever received bari (any dose, including LTE data), pts in the 6 randomized, placebo [PBO]-controlled studies (0-24 weeks, DMARD-inadequate responders), and pts in individual active-controlled studies with MTX (DMARD-naive: RA BEGIN) and adalimumab (ADA; MTX-inadequate responder: RA BEAM). Incidence rate (IR) was calculated as the number of pts with an HZ event per 100 patient-years of observation (PYO) with exposure censored at event date. The Mantel-Haenszel method was used for between treatment group comparisons, controlling for the study effect.

Results: In the All Bari group (1 Ph 1, 3 Ph 2, 4 Ph 3, and 1 ongoing LTE; 3492 pts, 5141 PYO), treatment-emergent HZ was reported in 170 pts (IR=3.3) (Figure 1). In the PBO-controlled studies HZ rates for bari 4 mg were significantly increased compared to PBO (IR difference [95%CI]: 3.2 [1.0, 5.4]) but were comparable to ADA in RA-BEAM. The majority of HZ events (95%) were reported as mild or moderate in severity; few were disseminated or complicated (7 distributed beyond primary or adjacent cutaneous dermatomes, 2 associated with facial nerve palsy, no visceral events). Rates appeared higher in Japan and in patients with advancing age, but not with longer RA duration, or corticosteroid use (Tables 1 and 2), and decreased with prolonged exposure.

Conclusion: In these integrated analyses, treatment with bari was associated with an increased risk of HZ compared to PBO, with an overall IR of 3.3/100 PYO in patients with RA. Rates appeared to diminish with prolonged exposure. **References:** [1]Smitten AL et al. *Arthritis Rheum* 2007;57:1431-1438. [2]Dougados M et al. *Ann Rheum Dis* 2015;74(S2):79. [3]Taylor PC et al. *Arthritis Rheumatol* 2015;67(S10):3927-3928.

Figure 1. Herpes Zoster Incidence Rates and 95% CI by Analysis Sets



Abbreviations: CI = confidence interval; DMARD = disease-modifying anti-rheumatic drug; IR = incidence rate; MTX = methotrexate; PC = placebo controlled; Pt = patient; RA = rheumatoid arthritis; Yrs = years.

Table 1. Herpes Zoster by Patient Characteristics in 6-Study Placebo-Controlled Set (DMARD-Inadequate Responders), 0-24 Weeks

	Placebo		Baricitinib		Odds Ratio Bari 4 mg vs. PBO [95% CI]*
	N	n {IR per 100 PY}	N	n {IR per 100 PY}	
Overall	1070	4 {1.0}	997	18 {4.3}	4.6 [1.5, 13.6]
Age, years					
<50	378	1 {0.7}	336	3 {2.1}	2.9
≥50 and <65	519	2 {1.0}	462	9 {4.7}	5.0 [1.1, 23.4]
≥65	173	1 {1.5}	199	6 {7.2}	5.9 [0.7, 52.4]
Gender					
Male	208	1 {1.3}	203	4 {4.7}	4.3 [0.5, 40.9]
Female	862	3 {0.9}	794	14 {4.2}	4.7 [1.3, 16.6]
Background MTX					
Yes	967	3 {0.8}	903	14 {3.7}	4.7 [1.3, 16.3]
No	103	1 {2.5}	94	4 {10.6}	5.1 [0.5, 48.2]
Corticosteroid use					
Yes	610	4 {1.7}	538	9 {4.0}	2.5 [0.8, 8.3]
No	460	0	459	9 {4.7}	--
Time from RA diagnosis					
<5 years	376	1 {0.6}	380	7 {4.2}	7.6 [0.9, 63.9]
≥5 years	515	3 {1.4}	510	10 {4.4}	3.5 [1.0, 12.8]
Diabetes					
Yes	118	2 {4.4}	92	1 {2.6}	0.4
No	952	2 {0.6}	905	17 {4.5}	8.7 [2.0, 37.9]

*CI calculated if ≥1 event in the PBO group and ≥4 events in treatment group.
Bari=baricitinib; CI=confidence interval; DMARD=disease-modifying antirheumatic drug; HZ=herpes zoster; IR=incidence rate; MTX=methotrexate; N=number of patients in the subgroup; n=number of patients with HZ; PBO=placebo; PY=patient years; RA=rheumatoid arthritis.

Table 2. Herpes Zoster by Region in the All Baricitinib Set Including LTE Data

	N	n	IR per 100 PY [95% CI]
Overall	3492	170	3.3 [2.83, 3.84]
Region			
USA/Canada	840	52	4.4 [3.3, 5.8]
Central and South America and Mexico	701	18	1.7 [1.0, 2.6]
Asia (excluding Japan)	226	18	5.6 [3.3, 8.9]
Japan	514	43	6.5 [4.7, 8.8]
European Union	783	27	2.1 [1.4, 3.1]
Rest of World	428	12	1.9 [1.0, 3.4]

Bari=baricitinib; CI=confidence interval; HZ=herpes zoster; IR=incidence rate; LTE=long-term extension; N=number of patients in subgroup; n=number of patients with HZ; PY=patient years; PYO=patient-years of observation.

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Abstract Number: 3028

A Single Infusion of Rituximab Delays the Onset of Arthritis in Subjects at

High Risk of Developing RA

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Rheumatoid Arthritis – Small Molecules, Biologics and Gene Therapy III: Small Molecules and Early Intervention

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: The development of clinical signs and symptoms of seropositive rheumatoid arthritis (RA) is often preceded by a phase of systemic autoimmunity. This offers a window of opportunity to delay or prevent the development of clinically manifest arthritis.This could represent a paradigm shift from treatment to prevention[1]. B cells could be a good target as they play a key role in the pathogenesis of the disease. The purpose of this study is to explore the effects of a single infusion of the anti-CD20 antibody rituximab on the onset of clinically manifest arthritis in individuals at risk of developing autoantibody positeve RA.

Methods: Eighty-two subjects with arthralgia and positive serology for both anti-citrullinated protein antibodies (ACPA) and rheumatoid factor, who never had clinically manifest arthritis and never used disease-modifying antirheumatic drugs were included in the PRAIRI study, a multicentre, randomised, double-blind, placebo-controlled clinical trial. Subjects were randomized to receive a single infusion of either 1000 mg rituximab or placebo after all receiving 100 mg methylprednisolone premedication. Subjects were prospectively followed to assess development of clinically manifest arthritis and change in biomarkers. Kaplan-Meier survival analysis, Cox regression analysis and Treatment*Time Cox proportional hazard ratios were used to determine the treatment effects.

Results: Eighty-one individuals (52 females; mean age 53 (IQR 13.5) years) received treatment, which was generally well tolerated. One patient withdrew before treatment. The median follow up was 29.0 months (0-54), during which 30 subjects developed arthritis: 16/40 (40%) in the placebo group and 14/41(34%) in the rituximab group, after a median period of 11.5 (interquartile range [IQR] 12.5) months in the placebo group versus 16.5 (IQR 19.0) months in the rituximab group. Rituximab decreased the risk with 55% (HR (95%CI) 0.45 (0.154-1.322) at 12 months follow up compared to the observed risk of developing arthritis in the placebo group of 40%. At the 25% quartile (75% free of arthritis) of the cumulative arthritis-free survival there was a delay in the development of arthritis of 12.0 months (12 months versus 24 months in the placebo vs rituximab group, respectively). As expected, this effect attenuated over time. Treatment*Time Cox proportional hazard analysis showed that the beneficial effect of rituximab was highly statistically significant (P<0.0001). Biomarkers were measured over time shedding light on the potential mechanism underlying the delay in arthritis development.

Conclusion: A single infusion of 1000 mg rituximab significantly delays the development of arthritis in subjects at risk of developing RA. This is the first study evaluating the effects of a biopharmaceutical in this population, and the results support the rationale for future clinical trials aimed at prevention of RA by a targeted intervention. **References**[1] *Gerlag DM, Norris JM, Tak PP. RA: from risk factors and pathogenesis to prevention: Towards prevention of autoantibody-positive rheumatoid arthritis: from lifestyle modification to preventive treatment. Rheumatology (Oxford). 2015 Sep 15. Review*

Disclosure: D. M. Gerlag, Filing for patent application has been done by the university. Author may - to a limited extent - become one of the beneficiaries. Author is currently employee of GSK, but was not involved in data analysis., 3; **M. Safy**, None; **K. I. Maijer**, None; **S. W. Tas**, None; **M. Starmans-kool**, None; **A. van Tubergen**, None; **M. Janssen**, None; **P. P. Tak**, Setpoint Medical Corporation, 2.

Abstract Number: 3029

Ultrasonography of Major Salivary Glands in Patients Suspected with Primary Sjögren's Syndrome: Comparison with Salivary Gland Biopsy and Classification Criteria

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SESSION INFORMATION

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Session Title: Sjögren's Syndrome I: Clinical Insights
Session Type: ACR Concurrent Abstract Session
Session Time: 2:30PM-4:00PM

Background/Purpose: Ultrasonography of major salivary glands (sUS) is applied in the diagnostic work-up of primary Sjögren's syndrome (pSS). This study aims to assess (i) the validity of sUS compared to salivary gland biopsy, sialometry and serology and (ii) the alignment of sUS with classification criteria in patients suspected for pSS.

Methods: 103 consecutive outpatients clinically suspected for pSS underwent sUS of both parotid and submandibular salivary glands between October 2014 and November 2015. Parenchymal echogenicity, homogeneity, hypoechogenic areas, hyperechogenic reflections and clearness of the salivary gland posterior border were scored. Ultrasound total score (UTS) was calculated as the sum of these domains (range 0-48), according to the Hocevar scoring system.(1) All patients underwent a complete diagnostic work-up. For the present analyses, UTS was compared to parotid (n=70) and labial (n=54) gland biopsy outcomes (focus score ≥1), sialometric data (unstimulated (UWS) and stimulated (SWS) whole saliva; n=99), presence of anti-SSA antibodies (n=103) and AECG, ACR and proposed ACR-EULAR classification criteria (n=98/99). ROC analysis with area under the curve (AUC) was performed to define the optimal cut-off point of UTS to predict positive salivary gland biopsy or fulfilling classification criteria.

Results: Of 103 included patients, median age was 51 years (range 18-82), 90% were female and median UTS was 12 (range 3-43). Accuracy of sUS outcomes to predict positive parotid gland biopsy (AUC 0.833) and labial gland biopsy (AUC 0.816) was good. The optimal cut-off point of UTS was 15 for parotid and 14 for labial gland biopsies. Agreement between positive UTS and positive parotid (κ=0.580, sensitivity 70%, specificity 88%) and labial (κ=0.556; sensitivity 70%, specificity 85%) gland biopsy was moderate. UTS showed high negative predictive value for parotid gland biopsy and high positive predictive value for labial gland biopsy. Accuracy of sUS outcomes to predict abnormal UWS (AUC 0.696) was poor and to predict abnormal SWS (AUC 0.731) was fair. There were fair reversed associations of UTS with UWS (ρ=-0.336) and SWS (ρ=-0.371). Accuracy of sUS outcomes to predict presence of anti-SSA antibodies (AUC 0.803) and agreement between positive UTS and anti-SSA antibodies (κ=0.633) were both good. Accuracy of sUS outcomes to predict AECG classification (AUC 0.804) and ACR classification (AUC 0.839) was good and to predict ACR-EULAR classification (AUC 0.782) was fair. The optimal cut-off point of UTS was 14 for AECG and 15 for both ACR and ACR-EULAR. Agreement between positive UTS and AECG (κ=0.573, sensitivity 73%, specificity 85%) and ACR-EULAR classification (κ=0.512, sensitivity 61%, specificity 93%) was moderate and agreement between positive UTS and ACR classification (κ=0.636, sensitivity 71%, specificity 92%) was good.

Conclusion: In our prospective inception cohort derived from daily clinical practice, sUS outcomes showed moderate agreement with salivary gland biopsies, poor to fair agreement with sialometry, good agreement with serology and moderate to good agreement with classification criteria in patients suspected for pSS. **References:** (1) Hocevar et al. Rheumatology 2005;44:768-72.

Disclosure: E. Mossel, None; **K. Delli**, None; **J. F. van Nimwegen**, None; **A. J. Stel**, None; **E. A. Haacke**, None; **F. K. L. Spijkervet**, None; **F. G. M. Kroese**, None; **A. Vissink**, None; **H. Bootsma**, None; **S. Arends**, None.

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Abstract Number: 3030

Evidence of Inflammasome Activation in the Peripheral Blood and Salivary Gland Tissues of Primary Sjögren's Syndrome Patients: Correlation with Clinical Indices of Severe Disease and Lymphoma Development

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Session Title: Sjögren's Syndrome I: Clinical Insights

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Inflammasomes are intracellular multiprotein complexes that sense pathogenic microorganisms, as well as danger signals released following tissue injury. Such activation of inflammasome leads to the upregulation of various inflammasome-related molecules and the release of pro-inflammatory cytokines, namely interleukin-1β (IL-1β) and interleukin-18 (IL-18). In this study, we sought to investigate the inflammasome activation status in the peripheral blood and the salivary gland (SG) tissues of SS patients and its relationship with indices of disease activity and severity.

Methods: PBMC mRNA expression of inflammasome-related molecules NLRP3, AIM2, ASC, pro-caspase-1, IL-1β, IL-18 as well as the interferon type I signature genes MX1 and IF44L was evaluated by RT-PCR. Serum expression of inflammasome proteins ASC, IL-1β and IL-18 was evaluated by ELISA. SG biopsies were examined for the presence of inflammasome-related proteins by confocal microscopy.

Results: Compared to healthy controls (n=20), SS patients exhibited significantly higher serum levels of ASC (n=56; p=0.002), IL-1β (n=37; p=0.003) and IL-18 (n=33; p<0.0001). The serum levels of ASC protein were significantly higher in SS patients at high risk for lymphoma development (SS-type I; n=17) and in SS patients with lymphoma (n=28), compared to SS patients with low risk for lymphoma development (SS-type II; n=11, for p=0.030 and p=0.004, respectively). In SS patients, the serum levels of ASC and IL-18 correlated positively with the total cumulative ESSDAI score values (p=0.005 and p=0.006, respectively), whereas ASC levels correlated with the presence of C4 hypocomplementemia (p=0.002), rheumatoid factor (p=0.02) and purpura (p=0.02). In addition, compared to healthy controls (n=16), the PBMC of SS patients expressed significantly higher levels of ASC, NLRP3, IL-1β, IL-18 and pro-caspase-1 transcripts (n=39, p<0.05). The calculation of the NLRP3-inflammasome score in PBMC indicated an optimal discrimination between SS clinical subgroups (AUC=0.915) and positively correlated with interferon type I expression (Spearman r=0.443, p= 0.0006, n=37). In the SG tissues of SS patients, CD68+ macrophages and epithelial cells manifested high expression of ASC protein that was localized in perinuclear aggregates (specks), suggesting inflammasome activation. Co-localization experiments showed significantly increased ASC expression in CD68+ macrophages in SS (p<0.0001), compared with non-SS control patients.

Conclusion: Our findings indicate that SS patients manifest evidence of inflammasome activation in both peripheral blood and the SG tissues. Several indices of inflammasome activation correlated with the presence of severe disease, as well as lymphoma development and may constitute valuable clinical biomarkers for these patients.

Disclosure: A. G. Vakrakou, None; **S. Boiu**, None; **M. N. Manoussakis**, None.

Abstract Number: 3031

Rethinking Primary Sjögren's Syndrome: Stratification By Clinical Phenotypes to Improve Understanding of Disease Pathogenesis, Trial Design, Clinical Management and Prospective Health Gains?

Dennis Lendrem[1], **Nadia Howard Tripp**[2,3], Xavier Mariette[4], Svein Joar A. Johnsen[5], Jessica Tarn[6], Katie Hackett[6], Bridget Griffiths[7], Sheryl Mitchell[8], Alain Saraux[9], Valerie Devauchelle[10], Katrine Norheim[11], John D. Isaacs[12], Peter McMeekin[13,14], Simon Bowman[15], Roald Omdal[16], Jacques-Eric Gottenberg[17] and Wan-Fai Ng[18], [1]Newcastle upon Tyne, Newcastle University, Newcastle upon Tyne, United Kingdom, [2]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, United Kingdom, [3]Newcastle-upon-Tyne Hospitals NHS Foundation Trust, Newcastle-upon-Tyne, United Kingdom, [4]Université Paris-Sud, AP-HP, Hôpitaux Universitaires Paris-Sud, Paris, France, [5]Clinical Immunology Unit, Department of Internal Medicine, Stavanger University Hospital, Stavanger, Norway, [6]Newcastle University, Newcastle-upon-Tyne, United Kingdom, [7]Rheumatology, Freeman Hospital, Newcastle Upon Tyne, United Kingdom, [8]Freeman Hospital, Newcastle upon Tyne, United Kingdom, [9]Rheumatology Department, CHU de la Cavale Blanche, Brest Cedex, France, [10]Service de Rhumatologie, Department of Rheumatology, Brest University Hospital, Brest, France, Brest, France, [11]Stavanger University Hospital, Stavanger, Norway, [12]Newcastle University and the Freeman Hospital, Newcastle-upon-Tyne, United Kingdom, [13]Institute of Health and Society, Newcastle University, Newcastle-upon-Tyne, United Kingdom, [14]Northumbria University, Newcastle-upon-Tyne, United Kingdom, [15]Department of Rheumatology, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [16]University of Bergen, Bergen, Norway, [17]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [18]Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom

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Background/Purpose: Primary SjšgrenÕs Syndrome (pSS) is a chronic autoimmune rheumatic disease causing a wide-range of symptoms including dryness, pain and fatigue. Individual patient experiences of pSS vary resulting in a heterogeneous patient population. We use patient reported symptoms to identify distinct clinical pSS phenotypes and use these to explore underlying biological differences.

Methods: We used Patient Reported Outcome Measures (PROMs) to clinically phenotype 594 patients on the United Kingdom Primary SjšgrenÕs Syndrome Registry. Phenotype patterns were identified using hierarchical cluster analysis of patient reported rating scales for pain, fatigue, dryness, anxiety and depression. Non-parametric analysis of variance was used to evaluate biological differences between these clusters. We then used the same PROMs to phenotype 463 pSS patients from Norwegian and French cohorts, in order to validate these four phenotypes independently.

Results: We identified four phenotypic clusters, which we refer to as Low Symptom Burden (LSB), High Symptom Burden (HSB), Dryness Dominant (DD) and Low Anxiety and Depression (LAD) – with marked differences in health status and quality of life (TTO p <0á0001, EQ-5D VAS p <0á0001). Furthermore, there were significant differences on clinical measures of disease activity (ESSDAI p=0á039), and objective dryness measures (salivary flow p=0á007, SchirmerÕs p=0á014). In addition, there were marked differences in biological parameters (IgG p<0á0001, lymphocytes p=0á0005, ESR p=0á003, IL-17 p=0á0174 and TNFα p=0á0133) between clusters, suggesting possible distinct underlying endotypes. Significant biological and clinical differences in IgG, Lymphocytes, ESR, ESSDAI, and Salivary Flow remained across the four phenotypes in our validation cohorts.

Conclusion: We have identified and independently validated four distinct pSS clinical phenotypes with associated biological

differences. There are marked differences in the potential health gains for these four clusters with important implications for clinical management, trial design and therapeutic development for pSS.

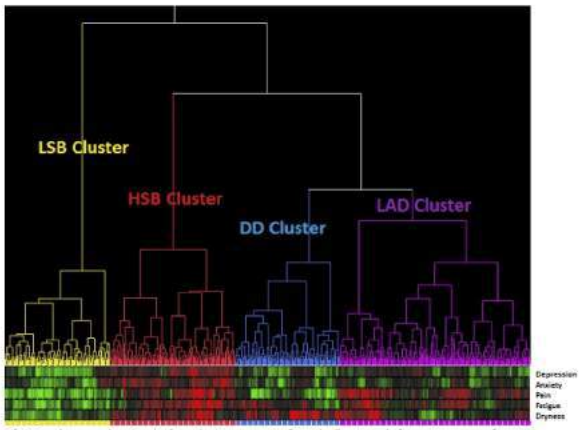

Fig1: Dendrogram showing the four clusters emerging from the 'heat map' of symptom scores for pain, fatigue, dryness, anxiety and depression below. Green is a low score, while black is middling and red is high.

Table 1: Clinical and biological differences across phenotypes. Median values in bold, 25th and 75th centile below, with UKPSSR cohort in white and the two validation cohorts shaded in grey.

Parameter	Cohort	LSB	HSB	DD	LAD	P-value
Lymphocytes (x 10^9 /L)	**UK**	**1.20** 1.00, 1.60	**1.50** 1.20, 1.80	**1.27** 0.95, 1.72	**1.32** 1.04, 1.70	**0.0005**
Lymphocytes (x 10^9 /L)	**Stavanger**	**1.35** 0.73, 1.73	**1.9** 1.6, 2.35	**1.2** 0.85, 1.4	**1.8** 1.3, 2	**0.0330**
Lymphocytes (x 10^9 /L)	**French**	**1.32** 1.0, 1.8	**1.48** 1.1, 1.7	**1.18** 1.0, 1.6	**1.5** 1.1, 1.8	**0.0251**
Lymphocytes (x 10^9 /L)	**Combined**	**1.25** 1, 1.62	**1.5** 1.2, 1.77	**1.2** 0.95, 1.67	**1.4** 1.08, 1.8	**<0.0001**
IgG (mg/dL)	**UK**	**17.97** 14.51, 22.94	**14.10** 11.05, 18.20	**16.63** 13.00, 20.85	**14.35** 11.03, 19.48	**<0.0001**
IgG (mg/dL)	**Stavanger**	**13.95** 10.7, 16	**11.1** 9.3, 11.9	**14.9** 12.4, 18	**11.7** 10, 13.1	**0.0054**
IgG (mg/dL)	**French**	**15** 12.3, 18.7	**12.8** 10.7, 16.7	**15.2** 11.1, 20.6	**12.45** 9.8, 16.1	**0.0028**
IgG (mg/dL)	**Combined**	**16.6** 13.2, 21.5	**13.4** 10.7, 17	**12.5** 16.0, 20.3	**13.2** 10.3, 17.9	**<0.0001**
Salivary Flow (ml/15 mins)	**UK**	**0.40** 0.00, 1.05	**0.20** 0.00, 1.00	**0.05** 0.00, 0.75	**0.30** 0.00, 1.20	**0.0097**
Salivary Flow (ml/15 mins)	**Stavanger**	**1.65** 0.4, 2.2	**0.8** 0.1, 2.5	**0.2** 0, 0.68	**0.9** 0, 1.7	0.1212
Salivary Flow (ml/15 mins)	**French**	**0.24** 0.1, 1.71	**0.4** 0.1, 2.23	**0.02** 0.00, 0.2	**0.22** 0.08, 1.5	**<0.0001**
Salivary Flow (ml/15 mins)	**Combined**	**0.3** 0.06, 1.45	**0.25** 0, 1.3	**0.05** 0, 0	**0.3** 0.04, 1.4	**<0.0001**
SchirmerÕs I test (mm/5 mins)	**UK**	**3.00** 0.00, 6.75	**3.00** 0.50, 10.50	**2.00** 0.00, 6.50	**4.00** 1.00, 10.50	**0.0136**
SchirmerÕs I test (mm/5 mins)	**Stavanger**	**7** 2.5, 13.6	**6.75** 2.8, 23.1	**1.5** 0, 4.5	**5.5** 2.5, 14.5	**0.0204**
SchirmerÕs I test (mm/5 mins)	**French**	**5** 2, 15	**5.75** 2.13, 14.38	**7** 0, 13	**7.5** 3.5, 15	0.2644
SchirmerÕs I test (mm/5 mins)	**Combined**	**3.9** 0.5, 9	**5** 1, 12.5	**2.3** 0, 7.1	**5** 2, 12.5	**<0.0001**
ESSDAI	**UK**	**2.00** 1.00, 6.00	**4.00** 1.00, 8.00	**4.00** 1.00, 7.00	**4.00** 2.00, 8.00	**0.0193**
ESSDAI	**Stavanger**	**2.5** 0.75, 5.75	**5** 0.5, 12.5	**5.5** 1.5, 8	**5** 0.75, 10.5	0.8333
CRP (mg/L)	**UK**	**4.00** 2.40, 5.00	**5.00** 3.00, 5.00	**5.00** 3.00, 5.00	**5.00** 2.00, 5.00	0.0327
CRP (mg/L)	**Stavanger**	**2.15**	**3** 1,	**1.4** 1,	**1.2** 1,	0.3522

		1.45, 4.6	3.05	2.6	2.3	
ESR (mm/hr)	**UK**	**24.00** 13.50, 42.50	**20.00** 10.00, 39.00	**23.50** 12.00, 43.00	**17.00** 8.00, 32.00	**0.0064**
ESR (mm/hr)	**Stavanger**	**10** 4.5	**3** 2.5, 9.5	**8.5** 5, 21.5	**7** 4, 16	**0.3286**
IL-17	**UK**	**42.2** 0, 203	**0** 0, 21	**2.8** 0, 68	**8.5** 0, 73	**0.0174**
TNF-α	**UK**	**29** 1, 88	**0** 0, 11	**3.4** 0, 26	**7** 0, 29	**0.0133**
EQ-5D (VAS)	**UK**	**80.00** 70.00, 89.50	**43.00** 30.00, 60.00	**67.00** 50.00, 79.00	**60.00** 50.00, 70.00	**[2]0.0001**
EQ-5D TTO	**UK**	**0.80** 0.76, 1.00	**0.52** - 0.02, 0.69	**0.80** 0.69, 0.85	**0.69** 0.59, 0.76	**[2]0.0001**

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Abstract Number: 3032

Abnormalities in the Biological or Haematological Domain of the Essdai Predict an Increase in Systemic Disease Activity the Year after: 5-Year Data from the Prospective Multicenter Assess Cohort

Jacques-Eric Gottenberg[1], Raphaele Seror[2], Alain Saraux[3], Valerie Devauchelle[4], Emmanuelle Dernis[5], Philippe Dieudé[6], Jean-Jacques Dubost[7], Anne Laure Fauchais[8], Vincent Goeb[9], Claire Larroche[10], Véronique Le-Guern[11], Eric Hachulla[12], Pierre Yves Hatron[13], Jacques Morel[14], Aleth Perdriger[15], Stephanie Rist Bouillon[16], Damien Sène[17], Olivier Vittecoq[18], Jean Sibilia[19], Philippe Ravaud[20] and Xavier Mariette[21], [1]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [2]Department of Rheumatology, Assistance Publique–Hopitaux de Paris, Hôpitaux Universitaires Paris-Sud, Le Kremlin Bicêtre, France, [3]Rheumatology, Brest University Hospital, Brest, France, [4]Service de Rhumatologie, Department of Rheumatology, Brest University Hospital, Brest, France, Brest, France, [5]Service de Rhumatologie, Centre Hospitalier, Le Mans, France, [6]Rheumatology, Hôpital Bichat, Paris, France, [7]Rheumatology department CHU Clermont-Ferrand, Clermont-Ferrand, France, [8]Rheumatology, Limoges, France, [9]Rhumatologie, CHU Amiens, Amiens, France, [10]Internal Medicine, Paris, France, [11]service de médecine interne, Department of Internal Medicine, Referral Center for Rare Autoimmune and Systemic Diseases, Hôpital Cochin, AP–HP, Université Paris Descartes, Paris, France, [12]Internal Medicine, Lille University Hospital, Lille, France, [13]Internal Medicine, Lille, France, [14]Rheumatology, Department of Rheumatology, Montpellier University Hospital, Montpellier, France, [15]C.H.R. Hôpital Sud, Rennes, France, [16]Rhumatologie, Hopital La Source, La Source, France, [17]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Paris, France, [18]Rheumatology, Rouen University Hospital &INSERM U905, Rouen, France, [19]Department of Rheumatology, Strasbourg University Hospital, Strasbourg, France, [20]Epidemiologist, PARIS, France, [21]Rheumatology, Rheumatology department, Bicetre Hospital, Paris-Sud University, Le Kremlin Bicetre, France

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SESSION INFORMATION

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Session Title: Sjögren's Syndrome I: Clinical Insights

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Background/Purpose: Very limited data is available regarding predictors of systemic disease activity in primary Sjögren's syndrome. The ESSDAI, the international systemic disease activity score of the disease, is mainly used in clinical trials, as an inclusion criteria and primary end point. The ESSDAI takes into account some routine laboratory parameters included in the haemotological (disease-related anemia, lymphopenia, neutropenia and thrombocytopenia) and biological domain (IgG levels, monoclonal component, cryoglobulinemia, complement levels). We therefore investigated whether abnormalities of either the haematological or the biological domain could predict the evolution of systemic disease activity.

Methods: The ASsessment of Systemic complications and Evolution in primary Sjögren's Syndrome (ASSESS) cohort is a prospective ongoing cohort of 395 patients. All patients have a medical examination every year by a trained physician, who notably collects the ESSDAI (Eular Sjögren's Syndrome Disease Activity Index), which scores systemic disease activity and clinical ESSDAI (clin ESSDAI), which scores systemic disease activity without the biological domain of the ESSDAI.

Results: At enrollment, 1, 2, 3 and 4 years of follow-up, 55%, 44.3%, 48.1%, 46.9%, and 46.5% had at least one biological abnormality (i.e. a positive biological domain of the ESSDAI), respectively. The mean (SEM) ESSDAI 1 year after: at 1, 2, 3, 4 and 5 years of follow-up were 5.0 (0.4), 5.3 (0.4), 6.2 (0.5), 5.6 (0.5), and 5.4 (0.5), respectively, compared to 3.9 (0.4), 3.7 (0.3), 3.7 (0.4), 3.5 (0.4), and 3.4 (0.3), in patients with no biological abnormality, respectively. Overall, mean (SEM) ESSDAI the year after, in patients with at one least biological abnormality the year before ESSDAI assessment, was 5.5 (0.2) compared to 3.6 (0.2) in patients with no biological abnormality ($p< 0.0001$). Significant associations were also observed between biological abnormalities and clinESSDAI the year after (clinESSDAI of 4.7 (0.2) with a positive biological domain the year before and 3.9 (0.2 without, $p= 0.007$) as well as between hypergammaglobulinemia, a frequent abnormal parameter in the biological domain, and ESSDAI and clinESSDAI the year after (5.8 (0.3) and 4.8 (0.3) versus 4.1(0.1) and 4.0 (0.1) in patients without hypergammaglobulinemia, $p<0.0001$ and $p= 0.002$, respectively). At enrollment, 1, 2, 3 and 4 years of follow-up, 26.7%, 25.3%, 24.2%, 25.7%, and 24.1% had at least haematological abnormality (i.e a positive haematological domain of the ESSDAI), respectively. The mean (SEM) ESSDAI 1 year after: at 1, 2, 3, 4 and 5 years of follow-up were 5.6 (0.6), 5.9 (0.6), 7.0 (0.7), 6.6 (0.9), and 6.5 (0.7), respectively, compared to 4.1 (0.3), 3.8 (0.3), 4.0 (0.3), 3.7 (0.4), and 3.6 (0.3), in patients with no haematological abnormality, respectively. Overall, mean (SEM) ESSDAI the year after in patients with at one least haematological abnormality the year before ESSDAI assessment, was 5.7 (0.3) compared to 3.7 (0.1) in patients with no haematological abnormality ($p< 0.0001$). Significant associations were also observed between haematological abnormalities and clinESSDAI the year after (5.7 (0.3) versus 3.7 (0.1) in patients with no haematological abnormality, $p< 0.0001$) and between lymphopenia, a frequent abnormal parameter in the haematological domain, and ESSDAI and clinESSDAI the year after (6.5 (0.3) and 5.9 (0.4) vs 3.9 (0.1) and 3.8 (0.1) in patients without lymphopenia, $p< 0.0001$ and $p< 0.0001$, respectively).

Conclusion: Abnormalities in the biological or haematological domain of the ESSDAI, prevalent in nearly one half or one fourth of patients, predict a significant increase in systemic disease score the year after. Therefore, in pSS, some routinely assessed parameters, such as serum IgG levels or lymphocyte blood count, can be considered, not only as part of this systemic disease activity score, but also as relevant biomarkers of future systemic disease activity in common practice.

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Abstract Number: 3033

Safety and Efficacy of Single Dose VAY736 (anti-BAFF-R mAb) in Patients with Primary Sjögren's Syndrome (pSS)

Thomas Doerner[1], Maximilian Posch[2], Frank Wagner[2], Andreas Hueser[2], Thomas Fischer[3], Louise Mooney[4], Olivier Petricoul[4], Paul Maguire[4], Parasar Pal[5], Julie Doucet[4], Maciej Cabanski[4], Esther Kamphausen[4], Remi Kazma[4] and Stephen Oliver[4], [1]Rheumatology and Clinical Immunology, Charité – Universitätsmedizin, Berlin, Germany, [2]Charité Research Organisation GmbH, Berlin, Germany, [3]Institut für Radiologie und Kinderradiologie, Charité - Universitätsmedizin, Berlin, Germany, [4]Novartis Pharma

AG, Basel, Switzerland, [5]Novartis Pharma AG, Hyderabad, India
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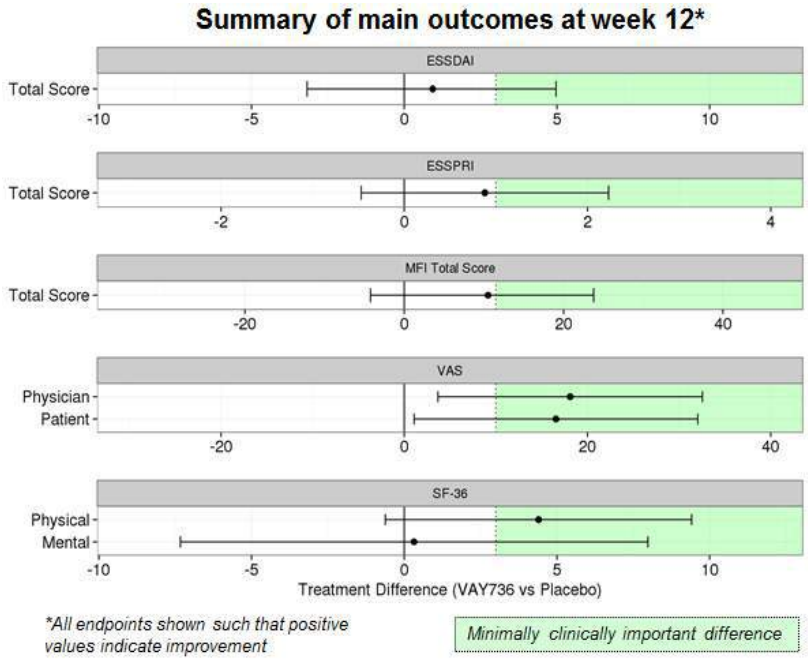
Session Time: 2:30PM-4:00PM

Safety and efficacy of single dose VAY736 (anti-BAFFR mAb) in patients with primary Sjögren's syndrome (pSS) T Dörner[1], M Posch[2], F. Wagner[2], A Hüser[2], T Fischer[1], L Mooney[3], O Petricoul[3], P Maguire[3], P Pal[3], J Doucet[3], M Cabanski[3], E Kamphausen[3], R Kazma[3], S Oliver[3] [1]Charité Hospital, Berlin; [2]Charité Research Organisation, Berlin; [3]Novartis Institutes for Biomedical Research, Basel

Background/Purpose: VAY736 is a novel, defucosylated, human IgG1 mAb targeting the receptor for B cell activating Factor of the TNF family (BAFF-R), providing both enhanced antibody-dependent cellular cytotoxicity-mediated depletion of B cells and blockade of BAFF:BAFF-R signaling that drives B cell differentiation, proliferation and survival. We evaluate here safety and efficacy of the dual mechanisms of action of VAY736 in patients with pSS, a highly BAFF-driven, systemic autoimmune disease involving lymphocytic infiltration and progressive dysfunction of exocrine glands along with various extra-glandular manifestations.

Methods: A single center, randomized, parallel group, double-blind, placebo-controlled trial recruited 27 seropositive pSS patients with EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI) ≥6 over a 10-month period for treatment with intravenous VAY736 at either a single high dose, (n=12), a single lower dose (n=6), or with placebo (n=9). Outcomes were measured at baseline and at weeks (w)6, 12 and 24. The primary outcome was change in ESSDAI at w12. Secondary outcomes included the EULAR Sjögren's Syndrome Patient Reported Index (ESSPRI), Short Form-36 (SF-36), Multidimensional Fatigue Inventory (MFI), physician/patient global VAS assessments, salivary flow rate, Ocular Staining Score (OSS), high resolution salivary gland ultrasound (US) de Vita scores/perfusion and elastography, serum markers of B cell hyperactivity and flow cytometry-determined lymphocyte subsets.

Results: Analyses to w24 included all 27 patients. VAY736 was safe and well-tolerated with no drug-related SAE, drop outs or discontinuations. Mean age was 50.5 years with 4 males, 2 in placebo and 1 in each treated arm. Baseline mean ESSDAI scores (range) were 11.5 (6-18), 14.5 (6-31) and 11.1 (6-19) in the high dose, lower dose and placebo arms, respectively. Target engagement was confirmed by serum BAFF levels and rapid, profound depletion of circulating B cells in all VAY736-treated patients; up to 99% by 24h and remaining so to 12-24w and beyond. The primary endpoint of ESSDAI was reduced within 12w but did not reach clinical or statistical significance versus placebo. However, improvements for VAY736-treated subjects were seen across clinical secondary outcomes, particularly for patient and physician global assessments and SF-36 physical. Reductions in parotid gland stiffness by US suggest early signs of salivary gland improvement. B cell hyperactivity markers were also reduced in treated patients. There were no consistent changes in salivary flow rate or OSS.



Conclusion: Despite a limited, single infusion, VAY736 achieved in this early phase trial trends for improvement in the primary outcome and across all secondary outcomes. Thus, this treatment was safe and suggests a positive therapeutic effect for this dual mechanisms of action in pSS that warrant further evaluation.

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Abstract Number: 3034

A Selective JAK1 Inhibitor, Filgotinib Suppresses Lymphocytic Infiltration in Salivary Gland of Non Obese Diabetic Mice Via Suppression of BAFF and Chemokine Production of Salivary Gland Epithelial Cells

Jennifer Lee[1], Seo Hwa Kim[2], Haneul Kim[3], Seung-Ki Kwok[4], Ji Hyeon Ju[5] and Sung-Hwan Park[5], [1]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, Republic of, [2]Division of Rheumatology,, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, The Republic of, [3]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, Korea, The Republic of, [4]seungki73@catholic.ac.kr, Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea, [5]Division of Rheumatology, Department of Internal Medicine, College of Medicine, The Catholic University of Korea, Seoul, South Korea

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Background/Purpose: Interferon(IFN) signatures are upregulated in patients with primary Sjogren's syndrome (pSS) and interferons are considered to play a pathogenic role in pSS. Therefore, Janus kinase (JAK) which mediates interferon signaling pathway may be a good therapeutic target. We set out to investigate whether a selective JAK1 inhibitor, filgotinib would ameliorate disease-related parameters in non-obese diabetic (NOD) mice, an animal model SS.

Methods: Filgotinib (1.5mg/kg) or vehicle (saline) was intraperitoneally injected three times per week from 8 weeks after birth. Salivary flow rate (SFR) was addressed on 8, 12, 16 and 20 weeks. Histologic analysis was performed on 20 weeks. The effect of filgotinib on the expressions of B cell activating factor (BAFF), IFN signature genes and chemokines (CXCL10 [IP-10], CXCL3 [fractalkine], CCL-2 [MCP-1]) in human salivary gland epithelial cell (SGEC) line or primary epithelial cells of patients with pSS was determined *in vitro*.

Results: The SFR of NOD mice in both groups decreased over time. Of note, SFRs of filgotinib-treated mice were greater than those of controls. Histologic evaluation of the salivary gland revealed that the lymphocytic infiltration of salivary gland was markedly reduced in the mice treated with filgotinib. Filgotinib suppressed STAT1 phosphorylation in IFN-treated SGECs. In addition, IFN-induced BAFF and chemokine production of SGECs or primary epithelial cells were abrogated by filgotinib treatment.

Conclusion: Filgotinib suppresses SFR decrease and lymphocytic infiltration of salivary glands of NOD mice by inhibiting inhibiting IFN signaling pathway, thus suppressing BAFF and chemokine production of salivary gland epithelial cells. JAK inhibition may be a novel therapeutic approach for SS.

Disclosure: J. Lee, None; **S. H. Kim**, None; **H. Kim**, None; **S. K. Kwok**, None; **J. H. Ju**, None; **S. H. Park**, None.

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Abstract Number: 3035

Characterization of DC-STAMP+ T Cells, a CD3+CD4+ T Cell Subset Uniquely Present in Patients with Psoriatic Disease

Yahui Grace Chiu[1], Edward Schwarz[2], Richard Bell[3], Dongge Li[4], Nelson Huertas[4], Cristy Bell[5], Sharon Moorehead[5], Debbie Campbell[5], Changyong Feng[6] and Christopher T. Ritchlin[7], [1]Allergy, Immunology, and Rheumatology, University of Rochester Medical Center, Rochester, NY, [2]Orthopedeatrics, University of Rochester, Rochester, NY, [3]Pathology, University of Rochester, Rochester, NY, [4]Allergy, Immunology and Rheumatology, University of Rochester, Rochester, NY, [5]Allergy, Immunology & Rheumatology, University of Rochester, Rochester, NY, [6]Statistics, University of Rochester, Rochester, NY, [7]Allergy Immunology & Rheumatology, University of Rochester Medical Center, Rochester, NY

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Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose:

Psoriatic arthritis (PsA) is an inflammatory joint disease that affects over 650,000 Americans. Bone damage occurs in half of these patients within the first 2 years of disease, which impacts the quality of life and function. Dysregulation of osteoclasts (OC), the only cells known to erode bone, is responsible for bone damage in PsA. Our study is centered on DC-STAMP, a transmembrane signaling protein essential for OC development. DC-STAMP-/- osteoclast precursors (OCP) fail to fuse and develop into mature OC with bone erosion activity. Although DC-STAMP is preferentially expressed by monocytes, intriguingly, we identified a unique DC-STAMP+ T cell subset in a small cohort of PsA patients but not in healthy controls. Given that Th17 and FoxP3(+) Treg T cell subsets are known to promote or suppress OC differentiation, respectively, we hypothesize that DC-STAMP+ T cells are a specialized T cell subset in PsA with Th17- or Treg-like properties.

Methods:

We analyzed the frequencies of DC-STAMP+ populations by 12-color cell lineage-specific flow cytometry, and determined OCP frequency by TRAP-based OC enumeration on 102 psoriasis (Ps), 41 PsA patients and 25 healthy controls (HC). The Spearman correlation analysis was performed to test the correlation between the frequencies of OCP and DC-STAMP+ T cells.

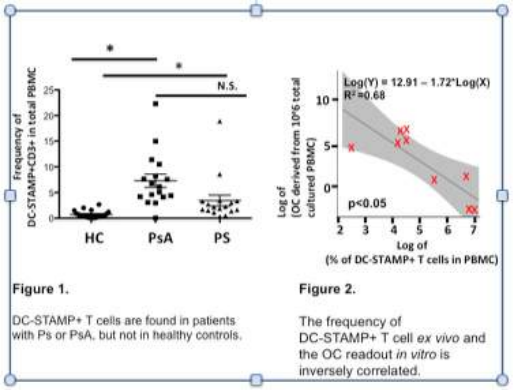

Figure 1.

DC-STAMP+ T cells are found in patients with Ps or PsA, but not in healthy controls.

Figure 2.

The frequency of DC-STAMP+ T cell *ex vivo* and the OC readout *in vitro* is inversely correlated.

Results:

Data from 143 patients (102 Ps & 41 PsA) and 25 HC demonstrated that DC-STAMP is primarily expressed by CD14+ monocytes in HC, whereas its expression on T cells was only observed in 22% of the Ps & PsA patient cohorts (21/67, 6/44 and 5/32 respectively in 3 separate clinical studies). DC-STAMP+ T cells were significantly elevated in Ps and PsA patients than HC (Figure 1). Flow cytometry analysis revealed that DC-STAMP+ T cells were CD3+CD4+CD8-CCR4-CCR6+ T cells, and 68% of circulating DC-STAMP+CD3+ T cells had detectable intracellular IL-4 expression *ex vivo*. An inverse correlation between the frequency of DC-STAMP+CD3+ T cells (*ex vivo*) and OC frequency (*in vitro*) (the correlation between OC and 1/ (T cell frequency) was 0.73, p=0.04) was confirmed by Spearman analysis (Figure 2).

Conclusion:

The presence of DC-STAMP+ T cells in Ps or PsA patients but not in HC suggests that this T cell subset is induced to proliferate in the inflammatory conditions of psoriatic disease. An inverse correlation between the *ex vivo* frequency of DC-STAMP+CD3+ T cells and *in vitro* OC generation together with detectable intracellular IL-4 expression *ex vivo* suggest that DC-STAMP+ T cells suppress OCP differentiation *in vitro* and *in vivo*. Modulating T cell activities toward OC-promoting Th17-like or OC-suppressive Treg-like properties remains an attractive option for the treatment of psoriatic disease.

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Abstract Number: 3036

IL-22 Is Dysregulated in Psoriatic Arthritis and Acts to Limit IFN-γ Driven Inflammatory Chemokine Production

Amara Ezeonyeji[1], Helen Baldwin[2], Milica Vukmanovic-Stejic[3] and Michael R. Ehrenstein[4], [1]Rheumatology, Medicine, University College London, London, United Kingdom, [2]Rheumatology, Centre for Rheumatology Research, University College London, london, United Kingdom, [3]Infection & Immunity, University College London, london, United Kingdom, [4]Medicine, University College London, London, United Kingdom

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Background/Purpose: IL-22 is an IL-10 family cytokine with both pro-inflammatory and anti-inflammatory effects and its dysregulation is associated with the development of autoimmune disease including psoriasis, rheumatoid arthritis and Crohn's disease. The purpose of this study was to characterize the role of IL-22 production from CD4 T cells in psoriatic arthritis (PsA).

Methods: Whole PBMCs from PsA patients and healthy controls (HCs) were stimulated with anti-CD3/CD28 (αCD3/28) and cultured for 3 or 5 days. CD4+ T cell populations were analysed for surface expression of CCR6, CXCR3, CCR4 and CCR10 and intracellular production of IL-22, IFN-γ and IL-17 measured by FACS. The percentage of IL-22+IL-17- cells within CD4+ T cells after 5 days culture were correlated with percentage naïve (CD27CD45RA+), central memory ($CD27^+$ $CD45RA^-$), and effector memory (CD27- CD45RA-). CD4 T cell subsets were isolated, and IL-22 and IFN-γ production from HCs and PsA patients measured by FACS and the concentration in the T cell supernatants quantified by ELISA. The effects of IL-22 and IFN-γ were investigated using the HaCaT keratinocyte cell line as a model of inflammation.

Results: In the peripheral blood of untreated PsA patients, there was an overall decrease in the percentage $IL\text{-}22^+CD4^+$ T-cells compared to HCs (p=0.0075). This was associated with a switch from an IL-22-producing central memory cells in HCs, towards effector memory cells capable of accumulating at sites of inflammation in PsA. Paradoxically, we found a significant increase in IL-22 (p=0.026) and IFN-γ (p=0.001) production by naïve T cells from patients with PsA upon stimulation associated with increased proliferation (p=0.01) compared to healthy controls. This aberrant control of IL-22 and IFN-γ in the naïve T cell subset was restored in adalimumab treated patients. $IL\text{-}22^+$CD4+ T-cells in HCs expressed CCR6 whereas there was a significant loss of CCR6 expression in CD4 T cells in untreated PsA patients (p=0.0027) but not adalimumab treated patients. Supernatants from anti-CD3/28+/-IL-21 stimulated naïve T cells from untreated PsA patients, but not patients treated with adalimumab, induced high levels of the T cell chemoattractant CXCL-9 in HaCaT cells compared to HCs (p=0.0079) in an IFN-γ dependent manner. Moreover, blockade of IL-22 in supernatants from anti-CD3/28 +IL-21 activated naïve T cells from untreated PsA patients enhanced the production of CXCL-9 from HaCaT cells (p=0.01), suggesting an ability of IL-22 to negatively regulate IFN-γ.

Conclusion: IL-22 and IFN-γ production is dysregulated in PsA. IL-22+ CD4+ T cells switch to an effector memory phenotype and show an altered migratory phenotype which may promote accumulation of these cells at sites of inflammation. Furthermore IL-22 can act to suppress pathogenic responses triggered by IFN-γ suggesting that IL-22 may play a protective role in PsA. Modulation of this axis may therefore be a potential target for therapy in in PsA.

Disclosure: A. Ezeonyeji, None; **H. Baldwin**, None; **M. Vukmanovic-Stejic**, None; **M. R. Ehrenstein**, None.

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Abstract Number: 3037

Calprotectin Is Highly Upregulated in Inflamed Axial Entheses in SKG Mice

Zheni Stavre[1], Yukiko Maeda[2] and Ellen M. Gravallese[3], [1]Internal Medicine-Rheumatology, University of Massachusetts Medical School, Worcester, MA, [2]Medicine, University of Massachusetts Medical School, Worcester, MA, [3]Lazare Research Bldg, University of Massachusetts Medical School, Worcester, MA
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Session Time: 2:30PM-4:00PM

Background/Purpose: SKG mice exhibit features of spondyloarthropathy (SpA) and inflammatory bowel disease (IBD). Their SpA-like phenotype is induced by a beta-glucan, curdlan, via the Dectin-1 pathway, residing upstream of TNFα, IL23 and IL17. In SpA, the mechanism for enthesial bone formation and ankylosis is not well understood. Currently, no treatment can reverse this

process, although recent evidence suggests that TNF inhibitors may prevent bone formation if initiated early. The goal of this study was to discover genes and pathways that lead to axial/enthesial inflammation and bone formation. SKG mice were chosen for this purpose as they were previously reported to develop axial bone formation within 12 weeks of curdlan injection.

Methods: Nine week old SKG or control BALB/c mice were injected intraperitoneally with curdlan. Histology and microCT were perfomed at various time points to evaluate axial bone formation. Laser capture microscopy was performed on formalin-fixed paraffin-embedded (FFPE) tissue sections. Samples were obtained from entheseal sites near tail vertebrae at early inflammation, 3 weeks after injection. These were compared with identical anatomical sites in non-arthritic BALB/c mice. RNA collected from these tissues was extracted using the Qiagen RNeasy FFPE kit. Gene expression was analyzed using Affymetrix mouse transcriptome assay 1.0 (MTA 1.0).

Results: SKG mice developed clinical inflammation scores similar to those reported in published studies, with findings of skin and eye inflammation, arthritis, enthesitis, colitis/ileitis and weight loss when compared to control mice. We found that inflammation at axial sites developed earliest at the base of the tail. Contrary to previous reports, we did not observe axial bone formation, but rather significant erosion of vertebral bodies, and laxity of tendons leading to tail base deformity, as late as 24 weeks post injection. Early axial inflammatory tissue captured via laser was found to express S100a8 and S100a9 at 23-fold and 35-fold higher, respectively, when compared to control. Upregulation of S100A8 protein was confirmed by immunohistochemistry. Pathway analysis demonstrated enrichment of bone related pathways including endochondral ossification, TGF-beta receptor signaling and the Wnt signaling pathway. S100A8/9 (or the heterodimer, calprotectin) are antimicrobial peptides (AMPs), secreted by activated phagocytes, that act as endogenous activators of TLR4, upstream of TNFα, to induce a proinflammatory response. Studies show that calprotectin serum levels are elevated in SpA, correlate with disease activity and decrease with TNF inhibition. Recently, it has been shown that Dectin-1 stimulation upregulates expression of S100A8. Our results suggest that S100a8/9 are highly upregulated, likely via Dectin-1 in axial sites, and may drive inflammation and axial erosion in SKG mice.

Conclusion: Our whole transcriptome analysis revealed that S100a8/9 are the most highly upregulated genes in inflamed axial sites in SKG mice. We hypothesize that these play a role in axial inflammation and bone erosion in SKG mice.

Disclosure: Z. Stavre, None; **Y. Maeda**, None; **E. M. Gravallese**, AbbVIe, 2.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/calprotectin-is-highly-upregulated-in-inflamed-axial-entheses-in-skg-mice

Abstract Number: 3038

Enumeration and Preliminary Characterisation of Peri-Entheseal Bone Type 3 Innate Lymphoid Cells

Richard Cuthbert[1], Yasser El-Sherbiny[1], Evangelos M. Fragkakis[1], Robert Dunsmuir[2], Helena Marzo-Ortega[3], Elena Jones[1] and Dennis McGonagle[1], [1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom, [2]Department of Spinal Surgery, National Health Service, Leeds, United Kingdom, [3]NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals and University of Leeds, Leeds, United Kingdom

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SESSION INFORMATION

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Session Time: 2:30PM-4:00PM

Background/Purpose: In an IL-23 overexpression animal model of spondyloarthropathy (SpA), primary entheseal disease is driven by innate like lymphocytes at peripheral and spinal enthesis with these cells being reported in the enthesis soft tissue-bone interface. We previously described that the normal human entheseal soft tissue (EST) also had a populations of innate lymphoid cells (ILCs) (Cuthbert *et al* ACR abstract 2015). However, in human SpA the earliest imaging changes may occur in peri-entheseal bone (PEB) with such bone changes, rather than soft tissue changes, being harbingers of eventual joint ankylosis. The purpose of this work was to define PEB ILCs, to examine ILC3 transcriptional profiles and test entheseal responsiveness to IL-23 stimulation in comparison to other ILC3 sources.

Methods: Human PEB and EST was harvested from normal spinous process in patients undergoing elective spinal orthopaedic procedures. Interspinous EST was dissected from PEB and enzymatically digested. Knee joint synovial fluid cells from active SpA were also collected as a comparator source of ILCs from an inflammatory environment. ILC3s were isolated for RNA analysis by FACS sorting using accepted phenotypic cell surface markers. For cytokine stimulation unsorted PEB digest was incubated for 48 hours in the presence of IL-1β and IL-23. In all cases TaqMan genes expression assays (Applied Biosystems) were used to measure transcripts of interest.

Results: Bone adjacent to interpinous process attachment sites contained ILCs including ILC3s ($6.1x10^{-3}$%). RORγt and IL-23R were significantly increased in PEB ILC3 isolates compared to unsorted mononuclear cells (p=0.032 and p=0.033 respectively). Expression of immunomodulatory transcripts IL-10 and TGFβ were comparable in ILC3s isolated from all tissues. STAT3 expression was elevated in ILC3s isolated from PEB (p=0.048) compared to both EST and synovial fluid ILC3s as was TNFα. IL-17A and IL-22 expression was not detected in EST but both were detected in PEB and synovial fluid ILC3s. IL-1β/IL-23 stimulation of PEB resulted in 47-fold induction of IL-17A, 43-fold induction of IL-17F and 51-fold induction of IL-22 transcript.

Conclusion: This is the first study to define the presence of type 3 ILCs in normal peri-entheseal bone. ILC3s from this location exhibit occasional IL17 gene transcripts which increased substantially following priming. This work adds to the emerging data on ILCs resident populations in the SpA associated target tissues.

Disclosure: R. Cuthbert, None; **Y. El-Sherbiny**, None; **E. M. Fragkakis**, None; **R. Dunsmuir**, None; **H. Marzo-Ortega**, None; **E. Jones**, None; **D. McGonagle**, None.

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Abstract Number: 3039

Anti-IL-17A, but Not Anti-TNF, Can Halt Pathological New Bone Formation in Experimental Spondyloarthritis

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Background/Purpose: Secukinumab, a monocloncal antibody to IL-17A, suppresses signs and symptoms as well as inflammation in ankylosing spondylitis and psoriatic arthritis, and inhibits bone and cartilage destruction in psoriatic arthritis. As to new bone formation, a distinct form of structural damage in spondyloarthritis (SpA), a 2-years Secukinumab study in AS showed that mean progression of new bone formation was low (0.3 mSASSS points) and that 80% of patients did not show any progression at all (Baraliakos X. et al [abstract] Arthritis Rheum 2015; 67 suppl 10). As formal demonstration of an effect of anti-IL17A on new bone formation in human SpA requires long term data and the inclusion of an appropriate control group, we aimed to assess the potential impact of anti-IL17A on new bone formation in a validated animal model of SpA.

Methods: SpA-like arthritis and spondylitis was induced in HLA-B27/huβ2m tg rats (23-1x283-2) by immunization with low dose heat-inactivated *M. tuberculosis*/IFA. The animals were treated with 15 mg/kg anti-mouse/rat IL-17A antibody versus IgG2a isotype control weekly or, alternatively, with 10 mg/kg anti-TNF (Etanercept) versus PBS twice weekly in both prophylactic and therapeutic experiments for a period of 5 weeks. Arthritis and spondylitis were scored clinically and hind paw swelling was measured by plethysmometry. At the end of the study rats were sacrificed for skeletal analysis by micro-CT (low density bone volume as a measure for new bone formation) and histology.

Results: Prophylactic treatment with anti-IL-17A or anti-TNF showed a significant delay in arthritis and spondylitis when compared to their control groups. In addition, arthritis was significantly less severe in the anti-IL-17A or anti-TNF treatment groups as assessed by clinical scoring as well as by hind paw swelling. Therapeutic treatment with anti-IL-17A showed a significant reduction in arthritis score and hind paw swelling compared to the control group, spondylitis incidence remained stable after treatment. In contrast, treatment with anti-TNF in a therapeutic setting did not affect arthritis severity and spondylitis incidence continued to increase over time. Micro-CT analysis after therapeutic treatment revealed low density/newly formed bone present in both control groups. Treatment with anti-IL-17A significantly reduced levels of low density bone in the ankle joints, when compared to the IgG2a treated controls, and were even comparable to healthy age matched HLA-B27/huβ2m tg rats. In the axial joints new bone formation was present in 11 vertebrae from 5/9 control rats and 9 vertebrae from 3/9 anti-IL-17A treated rats. Coloring by bone density suggests less new bone formation in the anti-IL-17A treated group. In contrast, therapeutic treatment with anti-TNF did not affect new bone formation in both peripheral and axial joints.

Conclusion: These data show that, although the model is dependent on both IL-17A and TNF, only blockade of IL-17A affects clinical symptoms in a therapeutic setting. Strikingly, micro-CT analysis indicates that anti-IL-17A but not anti-TNF can halt pathological new bone formation in a therapeutic treatment setting.

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Abstract Number: 3040

Th17 Migration into the Synovial Fluid of Patients with Active Psoriatic Arthritis Is Enhanced By Regulatory T Cells

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Background/Purpose: Uncontrolled migration of Th17 cells into the skin and joints is a major driver in the pathogenesis of psoriatic arthritis (PsA). Modulation of T cell migration is thus an attractive option in order to reduce inflammation and restore immune tolerance. Th17 cells and regulatory T cells (Treg) both express CCR6, and migrate into the site of inflammation in response to CCL20. Importantly, maintenance of the correct Treg: effector T cell (Teff) ratio via appropriate control of cell migration is critical in the establishment of immune homeostasis. Dysregulation of Teff migration leads to their accumulation within inflamed tissue, and a resultant imbalance in the Treg: Teff ratio at the inflammatory site, thereby perpetuating disease. Here, we investigated the ability of Treg to modulate Th17 migration, in order to understand whether Treg can control Th17 migration in healthy individuals, and whether this axis in perturbed in PsA patients.

Methods: IL-17 production and association with CCR6 within $FoxP3^+$ and $FoxP3^-$ cells was measured in healthy and PsA peripheral blood mononuclear cells (PBMC) and synovial fluid (SF). Modulation of Th17 cell migration by Treg was investigated using a transwell model of CCR6-mediated migration towards CCL20. Sorted $CD4^+$Treg ($CD25^{high}CD127^{low}$) were mixed with Cell Trace Violet (CTV)-labelled Teff ($CD25^{low}CD127^{high}$). The number of CTV^+Teff migrated towards CCL20 in the presence or absence of Treg was enumerated by FACS using counting beads.

Results: $CD4^+IL\text{-}17^+$ cells were significantly increased in the peripheral blood (PB) (p=0.03*) and synovial fluid (SF) (p<0.0001***) of PsA untreated/DMARD patients compared to healthy controls and Adalimumab (Ada) treated PsA patients. We also observed an increase in IL-17 within $CD4^+$ $FoxP3^+$ synovial fluid Treg compared to HC PBMC (p=0.05*). Overall, the percentage of $FoxP3^+$ Treg in PsA untreated/DMARD PBMC was significantly reduced compared to HC PBMC (p=0.007**) and Adalimumab treated PsA patients (p=0.02*). We found a 3-fold increase in the percentage of $CCR6^+$ Teff ($FoxP3^-$) cells within PsA SF compared to paired PsA PBMC (p=0.0026**). There was a small (1.5 fold), but significant (p=0.02*) increase in $CCR6^+$ Treg ($FoxP3^+$) in PsA SF compared to paired PsA PBMC. Co-culture of healthy Treg with healthy Teff down-regulated CCR6-mediated migration towards CCL20 (p=0.03*) but PsA untreated/DMARD Treg enhanced CCR6 mediated migration of PsA untreated/DMARD Teff (p=0.02*). PsA Treg could down-modulate healthy CCR6 mediated Teff migration, whereas healthy Treg were unable to decrease migration of PsA Teff towards CCL20

Conclusion: These data reveal an accumulation of $CCR6^+$Th17 cells within the synovial fluid of PsA patients, potentially due to an enhancement of Th17 migration by Treg. In contrast, healthy Treg suppress Th17 migration towards CCL20. We hypothesise that paradoxically, Treg may drive Th17 migration into the skin and joints in PsA, leading to accumulation of Th17 cells at the site of inflammation and propagation of disease. Modulation of this axis may provide an attractive future therapeutic target for patients with PsA.

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Abstract Number: 3041

Age-Related Defects in the Immune System of Patients with GCA

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Background/Purpose: Advancing age is the strongest risk factor for GCA, a disease that exclusively affects individuals >50 years of age. The immune system undergoes dramatic restructuring with aging, but aging-related cellular and molecule defects that predispose to GCA have remained undefined. In general, immune aging is associated with the declining ability to generate antigen-specific immune responses and the increasing propensity for inflammatory activity. Here, we have examined whether patients with GCA lack anti-inflammatory regulatory mechanisms in the adaptive immune system, rendering them susceptible to unopposed inflammation and tissue damage.

Methods: Patients with biopsy-positive GCA and age-matched healthy controls were enrolled into the study. Immunosuppressive T regulatory cells (Treg) in the CD4 and CD8 compartment were quantified by phenotypic and functional analysis. Expression of the lineage-determining transcription factor FoxP3 and the immunosuppressive NADPH oxidase 2 (NOX2) was determined by flow cytometry. Immunosuppression was measured by monitoring the pool of phosphorylated signaling molecules (pZAP70) in stimulated target cells.

Results: Frequency of $CD4^+FoxP3^+$ Tregs was maintained in GCA patients compared to controls (p=0.207). To assess the

population of $CD8^+FoxP3^+$ Tregs, we defined the phenotype of such cells as $CD39^+$, $CD26^-$ and $CCR7^+$ and identified the oxidase NOX2 as their functional element. $CD8^+CCR7^+NOX2^+$ Tregs were distinctly low in patients with GCA ($p<0.001$). By comparing untreated and treated patients, we found that anti-inflammatory therapy did not restore this functional T cell subset ($p=0.591$). Comparative studies in patients with other inflammatory conditions (e.g. small vessel vasculitis, psoriatic arthritis) indicated that the defect was selective for GCA. Understanding the functional implications of CD8 Treg deficiency required definition of the molecular mechanism underlying their suppressive activity and their distribution in the immune system. CD8 Tregs were positioned in the T-cell zones of secondary lymphoid tissues and suppressed the activation of CD4 T cells by the targeted release of NOX2-containing microvesicles ($p<0.001$). Exosomes generated from CD8 Tregs were able to mediate the suppressive function and limited the activation of CD4 T cells ($p<0.001$). In healthy individuals, CD8 Tregs lost NOX2 expression with progressive age ($p<0.001$). This age-related loss of Treg function was markedly accelerated in GCA patients ($p<0.001$).

Conclusion: In humans, CD8 Treg cells function by packaging the enzyme NOX2 into microvesicles and transferring them onto neighboring CD4 T cells, to effectively suppress their clonal expansion. In healthy aging, $CD8^+NOX2^+$ Tregs decline with age. In patients with GCA, such $CD8^+NOX2^+$ Tregs are reduced to minimal frequencies. With the loss of $CD8^+NOX2^+$ Tregs, GCA patients lack an immunoinhibitory principal, exposing them to uncontrolled expansion of proinflammatory CD4 T cells. Recovering the function of $CD8^+NOX2^+$ Tregs in GCA may allow for reparative instead of immunocompromising therapy.

Disclosure: Z. Wen, None; **Y. Shimojima**, None; **G. Berry**, None; **E. Hosgur**, None; **J. Liao**, None; **L. Forbess**, None; **M. Weisman**, None; **J. Goronzy**, None; **C. M. Weyand**, None.

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Abstract Number: 3042

PD-1–Expressing T Cells in GCA Fail to Promote Immune Tolerance Functions

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Background/Purpose: The vasculitic lesions in GCA are filled with differentiated effector T cells that sustain granuloma formation, vessel wall restructuring, neoangiogenesis and intimal hyperplasia. Persistent T cell effector functions are counterregulated by inhibitory immune receptors, such as programmed cell death-1 (PD-1), and $PD\text{-}1^+$ T cells have been identified as the mediators of immune exhaustion in chronic viral infection and anti-tumor immunity and are the target of novel immunotherapy to unleash tumor-destroying immune responses. Conversely, failure to upregulate PD-1 may perpetuate chronic immune reactivity and could contribute to the relentless inflammation in GCA

Methods: Patients with biopsy-positive GCA and age and sex-matched controls were enrolled. GCA-affected temporal artery tissues were examined for the expression of PD-1 on T cells. Dynamics of PD-1 expression following T cell activation were examined ex vivo in CD4 T cells from GCA patients and healthy controls. $PD\text{-}1^+$ and $PD\text{-}1^-$ CD4 T cells were sorted and examined for T cell effector functions (expression of the lineage-determining transcription factors RORγt, T-bet, GATA-3 and FoxP3, and intracellular cytokine stores).

Results: Frequencies of circulating $PD\text{-}1^+$ CD4 T cells were significantly reduced in GCA patients ($p<0.01$). No PD-1–expressing cells were identified in normal, noninflamed human arteries, but in GCA affected temporal arteries almost all tissue-infiltrating T cells were positive for PD-1. In inflamed arteries, PD-1 expression on tissue-residing T cells was predictive for the thickness of

the intimal layer ($p<0.05$) and correlated with the tissue expression of the proinflammatory cytokines IFN-γ ($p<0.05$) and IL-17 ($p<0.01$). Ex vivo, sustained PD-1 expression could be induced in CD4 T cells from GCA patients ($p<0.05$). PD-1^+ and PD-1^- CD4 T cells populations from healthy controls and GCA patients were sorted and compared for the expression of lineage-determining transcription factors, and the effector cytokines IFN-γ, IL-17 and IL-4. PD-1^+ $CD4^+$ T cells from GCA patients expressed higher levels of Th1 ($p<0.05$) and Th17 related genes ($p<0.01$).

Conclusion: In patients with GCA, T cells expressing the inhibitory immune receptor PD-1 are highly enriched in the vascular lesions. However, such PD-1^+ T cells are not exhausted and, to the opposite, display strong immune-stimulatory functions, including remodeling of the vascular wall. In GCA the immunoprotective effects from PD-1–mediated downregulation of chronic immunity are lost, depriving the patient of the beneficial effects of the PD-1–dependent immune checkpoint.

Disclosure: R. Watanabe, None; **H. Zhang**, None; **E. Hosgur**, None; **G. Berry**, None; **J. Goronzy**, None; **C. M. Weyand**, None.

Abstract Number: 3043

Dense Genotyping of Immune Related Loci in a Multi-Ethnic Behçet's Disease Cohort Identifies Genetic Associations in a Long Noncoding RNA Near QSOX2, RASIP1/FUT2, and IL12A-AS1

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Background/Purpose: Behçet's disease is a chronic relapsing inflammatory disease characterized by recurrent mucocutaneous involvement. We performed dense genotyping in immune related loci in a large multi-ethnic cohort of Behçet's disease patients and controls to further characterize the genetic basis of this disease.

Methods: We studied 5 independent cohorts of Behçet's disease patients and controls consisting of 1253 patients and 5799 controls from Turkey, Italy, Spain, Japan, and Korea. Genotyping was performed using the Immunochip platform (Illumina), which includes ~200,000 genetic variants in immune-related genetic loci. Genetic association analysis in each cohort and a meta-analysis were performed to identify genetic susceptibility loci for Behçet's disease. Additional genetic variants were imputed up to the 1000 Genomes Project density. Conditional genetic analysis and functional mapping using epigenetic marks of enhancer regions and expression quantitative trait loci (eQTL) analyses were performed to further characterize the genetic effects identified.

Results: We identified and fine-mapped genetic associations for Behçet's disease with a GWAS level of significance in a lncRNA near *QSOX2* (OR= 1.82, P= 1.08E-8), *RASIP1*/*FUT2* (OR= 1.41, P= 3.57E-09), and *IL12A-AS1* (OR= 1.71, P= 4.19E-08). The genetic association within the *RASIP1*/*FUT2* locus is located within an active enhancer region as indicated by H3K27 acetylation marks. The disease risk variant in this locus is associated with mRNA expression changes of multiple transcripts within this locus, including significantly increased expression of *RASIP1* and decreased expression of *FUT2* in mucocutaneous tissues, frequently a target in Behçet's disease. The association in the *QSOX2* genetic locus can be localized to genetic variants within WI2-1959D15.1, which is a 1235bp lncRNA, and is associated with increased expression of this transcript. Several previously identified susceptibility loci for Behçet's disease were also replicated.

Conclusion: We performed dense genotyping in immune-related genes in a multi-ethnic cohort of Behçet's disease patients and controls, and identified a novel genetic susceptibility locus in a lncRNA near *QSOX2*, a genetic association with a functional genetic variant within an enhancer region in *RASIP1*/*FUT2*, and replicated the recently reported association in *IL12A-AS1*.

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Abstract Number: 3044

Endothelin 1 Induces a Myofibroblastic Phenotype in Vascular Smooth Muscle Cells. A Mechanism Potentially Contributing to Vascular Remodeling and Intimal Hyperplasia in Giant Cell Arteritis

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Background/Purpose: Giant cell arteritis (GCA) is a vascular inflammatory disease involving large and medium sized arteries, particularly the cranial vessels. Inflammation-induced vascular remodeling leads to vascular occlusion and ischemic symptoms and complications including partial or complete visual loss and, in some cases, stroke or other symptoms of vascular insufficiency. Pathogenic mechanisms contributing to this process are incompletely understood although vascular smooth muscle cell (VSMC) acquisition of a myofibroblastic phenotype might be involved. Over-expression of endothelin-1 (ET-1) and its receptors ET_AR and ET_BR in GCA lesions as well as increased serum concentrations of ET-1 in patients with ischemic complications has been previously reported (Lozano E et al Ann Rheum Dis 2010). The most investigated function of ET-1 in VSMC is vascular tone regulation. In recent years, it has been shown that ET-1 may contribute to myofibroblast differentiation of fibroblasts, a crucial step in lung and skin fibrogenic diseases. Whether ET-1 has similar effects on VSMC contributing to vascular occlusion has not been investigated. The aim of this study is to investigate if ET-1 induces a migratory myofibroblastic phenotype in human temporal artery (TA) -derived VSMC which might contribute to vascular remodeling and ischemic complications.

Methods: *Ex vivo* culture of TAs into three-dimensional matrix, migration assays using primary cultures of TA-derived VSMC, co-culture of TA-derived VSMC with peripheral blood mononuclear cells. Immunofluorescence and confocal microscopy of TA, qRT-PCR, immunoassay and western-blot.

Results: In GCA lesions ET-1 was mainly produced by inflammatory cells whereas VSMC overexpressed ET-1 receptors which enhanced their ability to respond to ET-1. ET-1 promoted a spread morphology in cultured VSMC and stimulated their migration by inducing focal adhesion kinase (FAK) phosphorylation at Y397 permitting the association with p85 subunit of PI3Kinase which co-localized with FAK at the cell protrusions of migrating cells. Accordingly, inhibition of both FAK and PI3K abrogated ET-1 induced migration. Interestingly, ET-1 treatment of cultured non pathological TAs promoted the disorganization of the artery layers as a consequence of VSMC migration towards the intima layer. Consistently, blockade of ET_AR and ET_BR with BQ123 and BQ788 antagonists inhibited ET-1 induced VSMC migration and VSMC outgrowth from cultured GCA-arteries as well as reduced Y397FAK phosphorylation *in vitro* and *ex vivo*.

Conclusion: ET-1 may be involved in GCA vascular occlusion by promoting VSMC migration towards the intimal layer, a mechanism involving either ET_AR or ET_BR._Suported by SAF 2014/57708-R, PIE 13/00033 and FEDER.

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Abstract Number: 3045

Immunometabolism in ANCA-Associated Glomerulonephritis

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Background/Purpose: Mounting an inflammatory response requires immune cells to undergo major changes in metabolism. Mediators such as cytokines can specifically alter the metabolism of different immune cell populations, thereby influencing the inflammatory response. This study characterized global patterns of immunometabolic response in renal tissue from patients with ANCA-associated vasculitis (AAV).

Methods: The study population consisted of patients with AAV (granulomatosis with polyangiitis and microscopic polyangiitis) recruited from the European Renal cDNA Bank (ERCB) cohort (n=80), patients with nephrotic syndrome recruited from the ERCB (n=61), patients from a North American based cohort (n=126); and healthy living kidney donors (n=37). Kidney biopsies performed as routine clinical care were micro-dissected into glomerular and tubulointerstitial compartments. Whole genome gene-expression profiling across the two tissue compartments was conducted on Affymetrix microarray platforms. 104 genes representing the critical enzymes of glucose metabolism and 26 genes related to specific immune cell populations were selected for analysis. Differential gene expression was compared between patients with AAV and both living donors and patients with nephrotic syndrome. Correlation analyses were performed to study potential relationships between genes related to metabolic response and genes related to immune response. A false discovery rate (FDR) of <0.05 defined statistical significance.

Results: Every enzyme in the pentose phosphate pathway (e.g. G6PD) and key regulatory genes of glycolysis (e.g. enolases, hexokinases) were significantly upregulated in the glomerular and tubulointerstitial compartments from patients with AAV compared to controls and patients with nephrotic syndrome. Glucose transporter receptor expression significantly differed among patients with AAV and comparators. Genes related to the Krebs cycle, glutaminolysis, and fatty acid oxidation were significantly downregulated in kidney samples from patients with AAV. Several immune response genes were differentially upregulated in kidney biopsies from patients with AAV, most strikingly macrophage-related markers (e.g. CD14, CD68, CD163). Strong correlations ($r= 0.45\text{-}0.82$; $p<1.0E^{-07}$) were observed in the glomerular compartment between specific pentose phosphate pathway enzymes (G6PD, TKT), enzymes that regulate glycolysis (PKM, PFKFB3), and macrophage-related markers (CD14, CD68).

Conclusion: Distinct alterations in cellular metabolism are observed in the renal transcriptome from patients with ANCA-associated glomerulonephritis, reflective of metabolic reprogramming. Global patterns of gene expression suggest increased utilization of glucose and decreased oxidative phosphorylation in patients with AAV relative to comparators. The strong correlation between markers of glycolysis and macrophage-related markers suggest that altered immunometabolism may play a role in the pathophysiology of kidney disease in AAV. Modulation of glucose metabolism may offer a novel approach to treatment of AAV.

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Abstract Number: 3046

Inflammatory Pathways As Shared Molecular Targets Across ANCA-Associated Vasculitis and Nephrotic Syndrome

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Background/Purpose: Clinical trials in rare diseases typically test therapeutic efficacy in one disease defined by a particular clinical phenotype. Improved understanding of the molecular mechanisms of disease may identify shared pathways across different clinical diseases that could be leveraged to develop stratified approaches to treatment and enable novel disease classification strategies based upon molecular rather than clinical phenotyping. An unbiased analysis of kidney diseases suggests many rare kidney diseases share common molecular profiles (Martini et al., 2014). To expand on these findings, we explored shared transcriptional responses in patients with ANCA-associated vasculitis (AAV) and nephrotic syndrome (NS) to identify common targetable disease mechanisms.

Methods: Patients with various forms of NS (minimal change disease, focal segmental glomerulosclerosis and membranous nephropathy) were recruited from the NEPTUNE cohort (n=126) and the European Renal cDNA Bank (ERCB, n=61). Patients with AAV (granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA)) recruited from the ERCB cohort (n=80) and healthy living donors (n=37) were also studied. Patients with NS and AAV underwent standardized diagnostic kidney biopsies performed as routine clinical care. Biopsy material was micro-dissected into glomerular and tubulointerstitial compartments. Transcriptomic profiles across the two tissue compartments were generated on Affymetrix U133 and ST2.1 microarray platforms. Differential gene expression across the transcriptome was compared between patients with NS and AAV versus living donors, and shared transcriptional responses were assessed relative to living donors. Functional networks were interrogated for cross-cutting disease mechanisms, upstream regulators and potential therapeutic targets shared between both diseases.

Results: Overall, 5%-25% of expressed transcripts were differentially regulated compared to living donor in both NS and AAV in the glomerular and tubulointerstitial compartments (fold change ≥ 1.3, FDR<0.05). Findings were replicated and cross-validated across the different microarray platforms. There was significant overlap in shared directionality of change of differentially expressed genes between patients with AAV and NS in both tissue compartments (FDR<0.05). Functional analysis identified conserved, therapeutically targetable transcriptional networks in the glomeruli from patients with NS and AAV including activation of Tec kinase, IL-8 signaling, TNF, IFNG, TGFB1, and NFkappaB, while alpha catenin and retinoid-related signaling were suppressed. Transcripts causally downstream of TNF were used to develop a TNF pathway activity score across diseases, and increased TNF-related inflammatory signaling was observed in specific subsets of patients.

Conclusion: AAV and NS, two rare kidney diseases, share common intra-renal transcriptional profiles that can be readily mined to identify shared molecular targets. Shared molecular targets can be leveraged for drug development and repurposing efforts in these rare kidney diseases.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/inflammatory-pathways-as-shared-molecular-targets-across-anca-associated-vasculitis-and-nephrotic-syndrome

Abstract Number: 3047

Diabetes and BMI Modify the Association Between Painful Hip OA and All-Cause Mortality

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Background/Purpose: Individuals with specific comorbid conditions have increased risk of having hip osteoarthritis (OA). Some of these conditions are also associated with increased risk of premature death. In this study, we explored diabetes (DM) and body mass index (BMI) as modifiers of the association between hip OA measures and all-cause death.

Methods: We analyzed data from the Johnston County Osteoarthritis Project to investigate the association between baseline radiographic hip OA (rOA) and all-cause death, stratified by DM and BMI. Analyses were carried out using baseline data from 2,381 individuals with hip radiographs, including men aged 45 or older and women over 50 who entered the cohort during the original study enrollment (1990-1997; n=1,817) and those with their baseline assessment during the cohort enrichment (2003-2004; n=564). Vital status was assessed using National Death Index records to capture date of death. Person-years of follow-up were accrued from baseline assessment to the date of death, loss to follow-up or December 31, 2014, whichever came first. Hip rOA was defined as a Kellgren-Lawrence (KL) grade of ≥2 in either hip at baseline clinical assessment. Symptomatic rOA (sxOA) is a subset of those with rOA who also had symptoms of pain in the same joint. We used multivariable Cox proportional hazards regression models to estimate hazard ratios and 95% confidence intervals for the risk of all-cause mortality. Interactions by BMI group (<25, 25-<30, ≥30) and self-reported DM (yes/no) at baseline were assessed at the p=0.1 level.

Results: At baseline, the mean age was 61.1 years; 55.9% were women, 31.5% African American, 33.3% did not complete high school, 23.8% were smokers. There were 12.0% with DM and 33.4% had a BMI≥30. Mean follow-up time was 14.2 (SD=5.7) years. Adjusted HRs for the association of hip rOA and sxOA with death were higher among individuals with DM at baseline (Table). We observed interactions on the multiplicative scale for hip rOA with a KL grade ≥2 (interaction p=0.015) where those with DM and hip OA were 45% more likely to die than those without hip OA, whereas we observed no association between hip rOA and death among those without DM. A similar association was observed among those with hip sxOA (interaction p=0.018). Further, among those with a BMI≥30, we observed a 50% increase in hazards for the association of hip sxOA on mortality, no association with BMI 25-<30 and reduced hazards for BMI<25 (interaction p<0.001).

Conclusion: The associations between hip OA measures and mortality were increased among those with DM and higher BMI at baseline. These associations were particularly strong among those with symptomatic disease and were independent of other comorbidities and sociodemographic measures. Our results suggest roles for DM and BMI in the link between hip OA and mortality, findings that merit further investigation into potential mechanisms and clinical attention.

Table. Adjusted[1] hazard ratios (95% CI) for hip OA as a predictor of mortality, stratified by diabetes and BMI at baseline

	Diabetes at Baseline				BMI at Baseline					
	Deaths/ Cohort	No Diabetes	Deaths/ Cohort	Has Diabetes	Deaths/ Cohort	BMI <25	Deaths/ Cohort	BMI 25-<30	Deaths/ Cohort	BMI ≥30
KL grade ≥2										
No	553/1621	Ref.	126/214	Ref.	206/469	Ref.	265/746	Ref.	208/620	Ref.
Yes	208/473	0.95 (0.81-1.11)	52/73	**1.45 (1.04-2.03)**	91/168	0.84 (0.65-1.08)	98/204	1.24 (0.98-1.57)	71/174	1.07 (0.81-1.41)
KL grade ≥2 and symptoms										
No	685/1942	Ref.	76/152	Ref.	265/582	Ref.	330/888	Ref.	245/729	Ref.
Yes	265/746	0.93 (0.73-1.18)	23/30	**1.37 (1.00-2.44)**	32/55	**0.63 (0.48-0.92)**	33/62	1.33 (0.92-1.91)	34/65	**1.51 (1.05-2.18)**

[1]Adjusted for baseline measures of age, cohort, gender, race, education, smoking, BMI, CVD, diabetes, high blood pressure and NSAID use

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Disclosure: R. Cleveland, None; **T. A. Schwartz**, None; **J. B. Renner**, None; **L. F. Callahan**, None; **J. M. Jordan**, None.

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Abstract Number: 3048

Pain Severity As a Mediator of the Effect of Depressive Symptoms on Physical Performance in Knee Osteoarthritis

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Background/Purpose: Depression is a significant comorbidity of knee osteoarthritis (OA) that occurs in approximately 20% of OA patients. Depressive symptoms are associated with both subsequent increases in knee pain and decreases in physical performance. It is hypothesized that depression leads to exacerbations in pain severity which, in turn, results in a decreased ability to perform the activities of daily living. The study aim was to determine whether the effect of depressive symptoms on physical performance is mediated by pain severity in knee OA.

Methods: Eligible participants (N=1,487) were enrolled in the Osteoarthritis Initiative, a multi-center natural history study of persons with or at risk for knee OA, who had radiographic disease (Kellgren-Lawrence grade of 2 or 3) at study baseline (time *t*). Depressive symptoms were measured using the Center for Epidemiological Studies Depression (CES-D) scale at the first annual follow-up visit (time *t*+1). Knee pain severity was assessed using the Western Ontario and McMaster Universities Arthritis Index pain subscale at the second annual follow-up visit (time *t*+2). Physical performance was evaluated with timed 20-meter walking speed (meters per second (m/sec)) at the third annual follow-up visit (time *t*+3). Potential confounders of the exposure-outcome or mediator-outcome relationship were measured at time *t* or *t*+1 and included age, sex, race, marital status, health insurance, employment, smoking, alcohol consumption, history of knee injury, comorbidity, analgesic use, baseline knee pain, and baseline physical performance. Marginal structural models that use inverse probability weighting were used to estimate the total, indirect (mediated), and direct (unmediated) effect of depressive symptoms at time *t+1* mediated by knee pain severity at time *t*+2 on physical performance at time *t*+3 (**Figure 1**).

Results: Depressive symptoms were significantly associated with slower 20-meter gait speed. For each one-unit increase in CES-D score, a subjects' gait speed would be expected to decrease by -0.0039 m/sec (95% CI: -0.0065, -0.0013; P Value=0.004). Effect decomposition yielded statistically significant direct and indirect effects of -0.003 (95% CI: -0.0057, -0.0004; P Value=0.024) and -0.0009 (95% CI: -0.0013, -0.0004; P Value=<0.001), respectively, suggesting that approximately 25% (-0.009/-0.0039) of the effect of depressive symptoms on physical performance is mediated by knee pain.

Conclusion: Depressive symptoms in subjects with knee OA are associated with significantly worse physical function, and this adverse effect is mediated, in part, by knee pain. However, the larger direct effect of depressive symptoms on physical performance implies there are multiple mediators of this relationship. Given that depression negatively affects physical function, it may also result in greater structural disease progression in persons with knee OA.

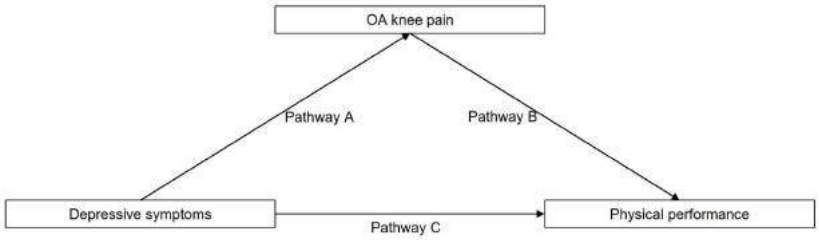

Figure 1. Model of mediation of the pathway between depressive symptoms and physical performance by OA knee pain. The C pathway shows the direct effect of depressive symptoms on physical performance. Pathways A and B show the indirect effects of depressive symptoms and OA knee pain on physical performance. The combined effects of pathways A, B, and C represent the total effect.

Disclosure: A. Rathbun, None; **M. Shardell**, None; **M. S. Yau**, None; **M. Baumgarten**, None; **E. Stuart**, None; **M. Hochberg**, None.

Abstract Number: 3049

Prevalence of Doctor-Diagnosed Arthritis Among Adults with Clinically Measured Pre-Diabetes— United States, 2009–2014

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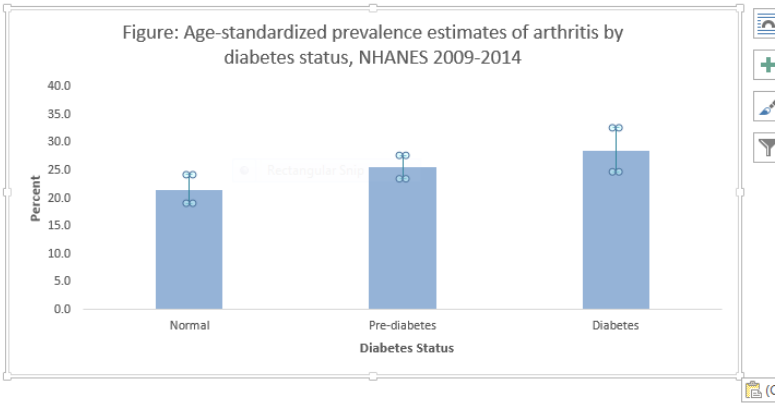
Background/Purpose: In the US, over 86 million adults have pre-diabetes; physical activity is recommended to reduce the high risk of developing diabetes. Arthritis is a common comorbid condition among persons with diabetes that is associated with reduced physical activity, presumably because of joint pain and swelling. Arthritis may have the same effect among adults with pre-diabetes, but population-based estimates of arthritis prevalence among adults with pre-diabetes are unknown.

Methods: We used the 2009-2014 National Health and Nutrition Examination Survey (NHANES) to estimate the prevalence of arthritis among adults with pre-diabetes, overall and by various sociodemographic characteristics, as well as those with diabetes or neither condition. NHANES is a nationally representative sample of the US non-institutionalized adult population with both interview and examination components. We limited our sample to adults aged ≥20 years with a fasting plasma glucose (fpg) measurement; unweighted sample sizes were 2,787 in 2009-2010; 2,471 in 2011-2012, and 2,574 in 2013-2014. Pre-diabetes was defined as glycated hemoglobin A1c (HbA1c) level of 5.7% to <6.5%, or a fasting plasma glucose (fpg) level of 100-125 mg/dL. Diabetes was defined as an HbA1c level of ≥ 6.5%, or fpg level of ≥ 126 mg/dL or a “yes” response to the questions “other than during pregnancy has a doctor or other health professional ever told you that have diabetes or sugar diabetes?” Arthritis was defined as a "yes" response to the questions "Has a doctor or other health professional ever told you that have arthritis?" For comparisons, estimates were age-standardized to the projected 2000 U.S. population; and pairwise comparisons were evaluated using a t-test with a Bonferroni-Holm correction for multiple comparisons.

Results: During 2009-2014, the prevalence (number) of adults with arthritis among those with pre-diabetes was 30% (27.9 million). The age-standardized prevalence of arthritis among adults with pre-diabetes (25.5%; 95% CI: 23.5-27.7%) was significantly (p-value=0.022) higher when compared with adults without diabetes (21.6%; 95% CI: 19.2-24.3%), but similar (p-value=0.182) to those with diabetes (28.6%; 95% CI: 24.8-32.7%) (Figure). Among adults with pre-diabetes, older adults (age ≥ 65 years), women, and those with <college degree had the highest age-standardized prevalence of arthritis.

Conclusion: Nearly 28 million adults in the US have pre-diabetes and arthritis, which may impact the physical activity recommended to prevent diabetes. Health care and public health professionals can address arthritis-specific barriers to physically activity among adults with pre-diabetes by promoting evidence-based physical activity, including programs such as EnhanceFitness and Walk with Ease, that reduce joint pain, which in turn may increase physical activity and reduce progression to diabetes.



Disclosure: K. E. Barbour, None; **M. Boring**, None; **C. Hemlick**, None; **J. M. Hootman**, None; **L. Murphy**, None; **G. Imperatore**, None.

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Abstract Number: 3050

Post-Partum Complications and Depression in New Mothers with Juvenile Arthritis

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Background/Purpose: There is little information regarding maternal post-partum complications in women with inflammatory arthritis conditions and none on persons with juvenile arthritis. Our objective was to evaluate the frequency of post-partum complications including depression in new mothers who had juvenile arthritis and to assess whether these differ from mothers who never had juvenile arthritis.

Methods: Our cohort study used data from physician billing and hospitalizations covering Québec, Canada. We identified all females with juvenile arthritis with a first-time birth between 01/01/1983 and 12/31/2010, and assembled a control cohort of first-time mothers without juvenile arthritis from the same administrative data source, matching 4:1 for date of first birth, maternal age and area of residence. Using a combination of physician billing codes and hospital codes and procedures, we compared the following post-partum complications: major puerperal infection, thromboembolic events, anaesthetic complications, post-partum haemorrhage, obstetrical trauma, complications of obstetrical surgical wounds, and depression in the first year following delivery, in the juvenile arthritis versus non-juvenile arthritis groups, using univariate and multivariate logistic regression analyses (adjusting for maternal age, education, caesarean delivery, hypertension, diabetes, birthweight, and adverse birth outcome).

Results: Mean age at delivery was 24.7 years in the juvenile arthritis group (n=1681) and 25.0 for the non-juvenile arthritis group

(n=6724). Mothers with juvenile arthritis were more likely to be diagnosed with depression in the first year post-partum (29.8% vs 6.7%, p<0.0001), and more had post-partum hemorrhage (10.0% vs 6.1%, p<0.0001) compared to the matched group of non-juvenile arthritis mothers. On the other hand those with juvenile arthritis had fewer major puerperal infections (1.6% vs. 2.5%, p=0.03) and less obstetrical trauma (4.3% vs. 7.2%, p<00001). In multivariate analyses, mothers with juvenile arthritis were more likely to experience depression in the first year post-partum (adjusted Risk Ratio (aRR): 4.25 95% Confidence Interval (CI) 3.78,4.77) and post-partum hemorrhage (aRR: 1.65, 95% CI 1.39,1.96). Mothers with juvenile arthritis were less likely to have a thromboembolic event (aRR 0.79, 95% CI 0.65,0.96) or obstetrical trauma (aRR 0.60, 95% CI 0.47,0.77) compared to mothers without juvenile arthritis.

Conclusion: Mothers with a history of juvenile arthritis were more likely to be diagnosed with depression in the first year post-partum and with post-partum hemorrhage. Possible explanations for the greater tendency towards depression might be higher pre-existing depression in juvenile arthritis or more frequent post-partum follow-up by physicians. Further research on these factors, and others (such as co-morbidity and medications) is warranted.

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Abstract Number: 3051

Is Frailty a Relevant Concept in Systemic Lupus Erythematosus (SLE)?

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Background/Purpose: Frailty, a syndrome of weight loss, weakness, slowness, exhaustion, and inactivity, has been examined primarily in geriatric cohorts and is associated with poor health outcomes, including mortality. Components of the frailty syndrome are relevant to SLE, but frailty has not been examined in SLE.

Methods: In an in-person research visit (2008-2009), frailty components defined by Fried[1] were assessed: unintentional weight loss, slow gait (based on 4-meter walk using sex and height criteria), weakness (grip strength, gender and BMI criteria), exhaustion (2 specific questions), and inactivity (physical activity questionnaire). Accumulation of 3+ deficits classifies an individual as "frail," one or two deficits as "pre-frail," and none as "robust." Outcomes examined were physical function, cognitive function, and mortality. Physical function was measured with the SF-36 Physical Functioning subscale (score range 0-100) and the Valued Life Activities (VLA) disability scale (range 0-3). Cognitive functioning was measured with a 12-test battery. Scores on each test below -1.0 SD of age-adjusted population norms were considered "impaired." Subjects were classified as cognitively impaired if they were impaired on ≥1/3 of indices completed. Mortality was determined as of December 2015. Differences in function and two-year changes in function were examined using multiple regression analyses controlling for age, SLE duration, race/ethnicity, glucocorticoid use, obesity, self-reported SLE activity and damage, and, for longitudinal analyses, baseline function. Analyses include women (n=138).

Results: Mean age was 48 (±12) years, mean SLE duration 16 (±9) years. 65% were white, non-Hispanic. 24% of the sample was classified as frail, and 48% as pre-frail (Table 1). Frail women had significantly worse physical function than robust and pre-frail women and were more likely to have cognitive impairment (Table 2). Frail women were also more likely to experience declines in function and onset of cognitive impairment. Mortality rates were significantly higher in the frail group (frail 16.7%; pre-frail 4.1%; robust 2.3%). Odds (95% CI) of death for frail women were elevated, even after adjusting for age, SLE duration, and baseline disease damage (5.1 [0.5, 51.3]).

Conclusion: Prevalence of frailty in this sample of women with lupus was more than double the prevalence in older adults. Frailty was associated with poor physical and cognitive function, functional declines, and mortality. [1] Fried J et al. *Gerontol A Med Sci* 2001; 56A:M146-M156

Table 1. Prevalence of frailty components and categorization, compared to other cohorts

		Older community-dwelling adults		
	Women with lupus	Fried, 2001[1]	Collard, 2012[2]	Shamliyan, 2013[3]
Age	48.5 ± 12.6	≥ 65	≥65	≥65
n	138	5317	56,183 (20 studies)	--- (24 studies)
Frailty components				
Weight loss	22%	6%	---	---
Exhaustion	45%	17%	---	---
Slow gait	9%	20%	---	---
Weakness	38%	20%	---	---
Inactive	29%	22%	---	---
Frailty classification*				
Robust (0)	28%	46%	46%	---
Pre-frail (1, 2)	48%	47%	44%	---
Frail (3+)	24%	7%	10%	14%

[1] Fried J et al. *Gerontol A Med Sci* 2001; 56A:M146-M156 [2] Collard R et al. *J Am Geriatrics Soc* 2012; 60:1487-1492 (systematic review) [3] Shamliyan T et al. *Ageing Res Rev* 2013; 12:719-736 (systematic review) *Frailty category: Presence of no deficits = Robust; 1 or 2 deficits = Pre-frail; ≥3 deficits = Frail

Table 2. Functioning by frailty classification: Cross-sectional and longitudinal analyses

	Cross-sectional, multivariate			Longitudinal, multivariate		
Frailty classification	VLA mean difficulty	SF-36 PF	Cognitive impairment	VLA mean difficulty	SF-36 PF	Cognitive impairment
Robust (n = 42, 28%)	--- (reference)	--- (reference)	--- (reference)	--- (reference)	--- (reference)	--- (reference)
Pre-frail (n = 66, 48%)	**0.32 (<.0001)**	**-5.3 (.0009)**	2.0 (0.6, 6.5)	**0.09 (.07)**	-2.1 (.24)	4.4 (0.4, 50.4)
Frail (n = 30,24%)	**0.65 (<.0001)**	**-11.7 (<.0001)†**	**4.4 (1.01, 19.6)**	**0.32 (.001)**	**-8.0 (.002)**	**26.2 (1.0, 716.4)**

• For VLA and SF-36PF, values are beta (p-value) from multiple linear regression • For cognitive impairment, values are odds ratio (95% confidence interval) from multiple logistic regression

• Cross-sectional multivariate analyses controlled for age, duration, low education, race, oral steroids, obesity, Systemic Lupus Activity Questionnaire (SLAQ), and Brief Index of Lupus Damage (BILD)

• Longitudinal analyses: Baseline frailty component/category predicting change in function 2 years later. Controlled for age, duration, low education, race, oral steroids, obesity, SLAQ, BILD, and baseline value of function

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Abstract Number: 3052

Causes of Death for Patients with Rheumatoid Arthritis

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Background/Purpose: Information on causes of death can assist in monitoring health trends and discovering health gaps. Our aim was to determine the primary causes of death among RA patients and to ascertain whether there are patterns in causes of death that differ from the general population.

Methods: We performed a population-based study using Ontario health administrative databases from 2000 to 2013. We identified an inception cohort of 28,322 RA patients (aged 66 years or older) using a validated algorithm (requiring 3 diagnostic codes over a 2 year period, with at least one provided by a specialist). To each RA patient we matched four non-RA general population comparators according to age, sex and region of residence. RA patients and comparators were followed for 142,534 and 502,823 person years, respectively. Vital statistics were used to identify the date and primary cause of death, which we tabulated according to International Classification of Disease Chapter. All-cause, cause-specific, and excess mortality rates were estimated.

Results: During a median follow-up of 4 years, 8,812 (31%) RA patients and 27,139 (24%) comparators died, with corresponding mortality rates of 61.8 (95%CI 60.6-63.1) and 54.0 (95%CI 53.3-54.6), per 1,000 person years, respectively (Table). Mortality rates were highest among males in both groups. The leading causes of death were similar in both groups, with circulatory system diseases, cancer, and respiratory diseases being the most frequent causes of death. Excess mortality rates in RA were observed for circulatory, respiratory, musculoskeletal, and digestive diseases, as well as infections.

Conclusion: Our findings corroborate previous studies illustrating that circulatory system diseases, cancer, and respiratory diseases (including pneumonia) remain the leading causes of mortality in RA. While we observed similar patterns of the leading primary causes of death in RA and comparators from the general population, the excess cause-specific mortality in RA warrants further investigation in order to identify modifiable factors in reducing inequalities in survival.

Death Characteristics	RA N=28,322		Matched Non-RA Comparators N=113,288		*Excess (Difference between RA and Comparators)*
	N (%)	*Rate per 1000 person yrs (95%CI)*	*N (%)*	*Rate per 1000 person yrs (95%CI)*	*Rate per 1000 person yrs*
Total (both sexes)	8,812 (31.1)	61.8 (60.6-63.1)	27,139 (24.0)	54.0 (53.3-54.6)	7.9
Females	5,713 (29.8)	57.9 (56.4-59.4)	17,343 (22.6)	49.9 (49.1-50.6)	8.0
Males	3,099 (33.8)	70.8 (68.3-73.3)	9,796 (26.7)	63.2 (61.9-64.4)	7.6
Causes of Death	*N=8,812 deaths*		*N=27,139 deaths*		
Disease of the circulatory system	2,846 (32.3)	20.0 (19.2-20.7)	8,793 (32.4)	17.5 (17.1-17.9)	2.5
Cancer	1965 (22.3)	13.8 (13.2-14.4)	7,320 (27.0)	14.6 (14.2-14.9)	-0.8
Diseases of the respiratory system	1,155 (13.1)	8.1 (7.6-8.6)	2,892 (10.7)	5.8 (5.5-6.0)	2.4
Diseases of the digestive system	433 (4.9)	3.0 (2.8-3.3)	995 (3.7)	2.0 (1.9-2.1)	1.5
Diseases of the musculoskeletal system & connective tissue	354 (4.0)	2.5 (2.2-2.8)	127 (0.5)	0.3 (0.2-0.3)	2.2
Infectious & parasitic disease (not classified by other categories)	331 (3.8)	2.3 (2.1-2.6)	621 (2.3)	1.2 (1.1-1.3)	1.1
Mental and behavioral disorders	321 (3.6)	2.3 (2.0-2.5)	1,527 (5.6)	3.0 (2.9-3.2)	-0.7
Diseases of the genitourinary system	306 (3.5)	2.1 (1.9-2.4)	727 (2.7)	1.4 (1.3-1.6)	0.7
Endocrine, nutritional and metabolic disease	299 (3.4)	2.1 (1.9-2.3)	1,073 (4.0)	2.1 (2.0-2.3)	0
External causes of morbidity	269 (3.0)	1.9 (1.7-2.1)	815 (3.0)	1.6 (1.5-1.7)	0.3
Diseases of nervous system	233 (2.6)	1.6 (1.4-1.9)	1,363 (5.0)	2.7 (2.6-2.9)	-1.1
Symptoms, signs and abnormal findings	108 (1.2)	0.8 (0.6-0.9)	397 (1.5)	0.8 (0.7-0.9)	-0.03
Diseases of the skin and subcutaneous tissue	43 (0.5)	0.3 (0.2-0.4)	52 (0.2)	0.1 (0.1-0.1)	0.2
Disease of Blood	43 (0.5)	0.3 (0.2-0.4)	109 (0.4)	0.2 (0.2-0.3)	0.1

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Abstract Number: 3053

Cartilage Loss Primarily Occurs in the Most Affected Tibiofemoral Compartment with No Evidence of a Ceiling Effect Among Advanced-Stage Disease: A Two-Year Longitudinal Study of Data from the Osteoarthritis

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Background/Purpose: Cartilage morphometry on magnetic resonance images (MRIs) is an important outcome measure for clinical trials among individuals with knee osteoarthritis (KOA). However, it remains unclear if investigators should measure both the affected (index) and less affected tibiofemoral compartments. If the less affected compartment shows little change over time then investigators may focus solely on the index compartment and reduce the burden involved with measuring both tibiofemoral compartments. Hence, we calculated the sensitivity to change of cartilage loss in the medial and lateral tibiofemoral compartments among knees selected to represent the full range of medial and lateral tibiofemoral KOA.

Methods: We selected 100 knees with baseline and 24-month MRIs stratified by medial joint space narrowing (mJSN, 25 knees in

each mJSN grade, 90 knees lateral JSN = 0) and 100 knees stratified by lateral joint space narrowing (lJSN, 25 knees in each lJSN grade, 94 knees medial JSN = 0) from the Osteoarthritis Initiative (OAI). One reader (MZ) used a customized software to measure the tibiofemoral cartilage damage index (CDI) on both the medial and lateral compartments of all 200 knees. The tibiofemoral CDI, which is a parsimonious articular cartilage assessment that focuses on areas where cartilage defects often develop, is based on 36 informative locations within medial and lateral tibiofemoral compartments (Figure 1, yellow stars) and adjusted by height. We calculated the mean percent of CDI change (MC %, the mean two-year change of CDI divided by the mean baseline CDI) for medial, lateral, and total (medial + lateral) tibiofemoral.

Results : Four knees (2 in mJSN and 2 in lJSN) were excluded because of image quality. The MC % value of medial CDI in the medial disease cohort are 5 to 17 times greater than MC % value of lateral CDI (table 1). The MC % value of lateral CDI in the lateral disease cohort are 4 to 15 times greater than MC % of medial CDI (Table 1). Even among knees with advance-stage disease (JSN=3) there was 29% and 19% cartilage loss in the index tibiofemoral compartment (medial and lateral, respectively), which was 5 and 15 times the change in cartilage within the other compartment.

Conclusion: The majority of the cartilage loss happens in the index compartment of the knee. We believe investigators could focus on cartilage loss in the index compartment, which would reduce the burden of measuring articular cartilage loss. Furthermore, adults with advance-stage disease should not be excluded from trials based on a fear that they will not progress during a 2-year period.

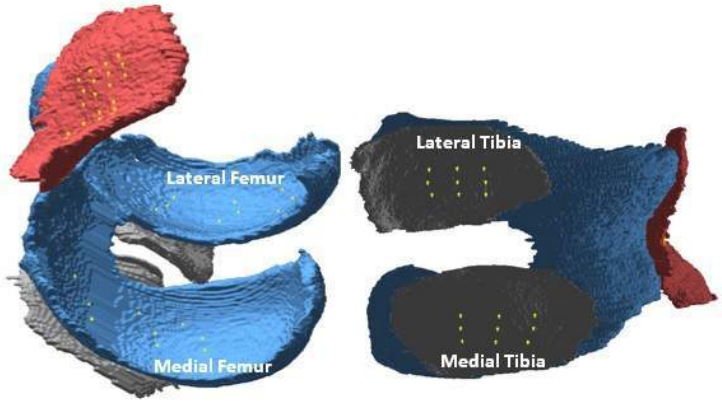

Figure 1. 3D femur and tibia cartilage images informative locations (yellow stars)
3D animation is available at http://canhelp2007.blogspot.com/

Table 1. The cartilage loss happens mostly at the index compartment

98 knees selected based on medial joint space narrowing (mJSN)			
mJSN grade	Medial CDI MC%	Lateral CDI MC%	Total CDI MC%
0 (n=25)	-9.60	-1.16	-4.96
1 (n=25)	-15.88	-0.92	-7.07
2 (n=24)	-22.42	-3.25	-8.62
3 (n=24)	-28.59	-5.72	-8.18
98 knees selected based on lateral joint space narrowing (lJSN)			
lJSN grade	Medial CDI MC%	Lateral CDI MC%	Total CDI MC%
0 (n=25)	-2.80	-11.28	-7.78
1 (n=24)	-2.56	-13.27	-8.16
2 (n=24)	-5.81	-22.40	-12.69
3 (n=25)	-1.29	-18.92	-5.69
MC% = mean percent CDI (two-year change of CDI value divided by the baseline CDI value).			

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Abstract Number: 3054

The Impact of Obesity on Knee Osteoarthritis Symptoms and Related Biomarker Profiles in a Bariatric Surgery Cohort

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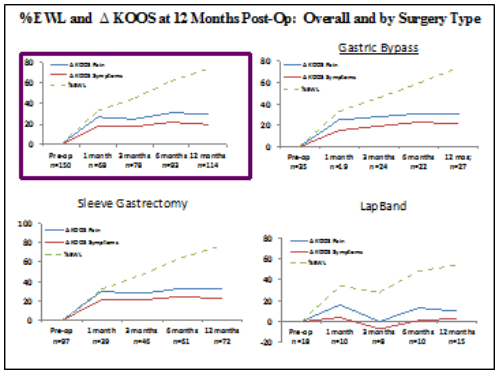
Background/Purpose: Obesity is a common risk factor for knee osteoarthritis (KOA). While it is intuitive that bariatric weight loss improves knee pain, it is not clear how much is due to decreased mechanical load vs metabolic changes.

Methods: Patients were screened for knee pain prior to sleeve gastrectomy, gastric bypass, or laparoscopic gastric banding. We required pain for ≥15 days/month and VAS pain ≥ 30, excluding lupus, inflammatory arthritis, crystal disease, psoriasis, and bilateral knee replacement. Enrolled patients took standing knee xrays for Kellgren-Lawrence (KL) grading. We measured BMI and used the Knee Injury and Osteoarthritis Outcome Score (KOOS) questionnaire at baseline and 1, 3, 6 and 12 months, calculating % excess weight loss (%EWL) and ΔKOOS. We collected blood at baseline and followup to study biomarkers for predicting KOOS scores.

Results: Of 536 patients considering bariatric surgery, we found 308 with knee pain and enrolled 176 (91.5% female; BMI 43.6 kg/m^2±7, 32-61; age 42 ±11, 18-73) well distributed in xray severity (KL0-4). For the 150 patients who had surgery, knee improvement paralleled weight loss at the followups. At 1 year, %EWL correlated well with ΔKOOS pain (R = .262, n = 114, p = 0.005), similar to other intervals and to other KOOS measures. The sleeve and bypass (n=72 and 27) vs banding (n=15) resulted in higher ΔKOOS pain at 1 year: 32.9 ±21.3 and 30.7 ±22.6 vs 10.2 ±21.4, p=0.001. Sleeve and bypass patients also achieved a higher % of their potential ΔKOOS pain improvement than did banding (65.2% and 60.1% vs 16.8% of remaining KOOS points to 100), and a higher % of patients improved to any degree (93.1% and 88.9% vs 66.7%). Radiographic severity did not predict ΔKOOS at 1 year, nor did the presence of key comorbidities. Patients lost weight in a near-linear fashion through 1 year (Fig. 1), but their KOOS improvements plateaued at 1 month. This held true in sleeve and bypass subgroups (with altered anatomy), while banding showed less consistent ΔKOOS despite a similar trend in %EWL. Baseline leptin levels in obese KOA were higher than non-obese KOA and non-obese/non-OA controls from other cohorts (100.2 ±61.9 vs 26.2 ±16.7 and 15.4±13.8, p<0.001). Similarly, IL-1Ra, a potential marker of OA progression, was much higher than non-obese KOA or controls (1123±940 vs 324.0±145.6 and 272±130.0, p<0.001). Within obese KOA, higher leptin levels predicted worse xrays (KL0/1 vs KL2/3/4, p = 0.037). After 1 year, mean leptin and IL1-Ra from obese KOA patients had decreased (p<0.001).

Conclusion: Bariatric surgery improves knee OA symptoms proportionally to %EWL. Most relief occurs during the 1st month before much weight loss, suggesting a metabolic impact beyond mechanical load reduction on joints – at least with the sleeve and bypass that alter digestive anatomy. Leptin and IL-1Ra serum levels are elevated in obese KOA vs non-obese KOA and controls - and fall after bariatric surgery which could contribute to knee pain relief.



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Abstract Number: 3055

Ultrasound Features of the First Metatarsophalangeal Joint in Gout and Asymptomatic Hyperuricaemia: Comparison with Normouricaemic Individuals

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Background/Purpose: The first metatarsophalangeal joint (1MTPJ) is frequently affected in gout. This study aimed to identity ultrasound features of the 1MTPJ in people with gout and people with asymptomatic hyperuricaemia compared with normouricaemic controls.

Methods: Participants with gout (n=23), asymptomatic hyperuricaemia (n=29) and age- and sex-matched normouricaemic control participants (n=34) underwent a grey-scale and power Doppler ultrasound assessment of both 1MTPJs using a Phillips iU22 ultrasound machine with a 10 MHz, 55mm linear array transducer. No participants had clinical evidence of gout flare at the time of scanning. The images were assessed by two blinded independent radiologists for the presence of the double contour sign, tophus, erosion, effusion, synovial hypertrophy, and synovitis. Cartilage thickness and tophus diameter were also measured. Inter-reader reliability was assessed using Cohen's kappa (k) and intra-class correlation coefficients (ICC). Binary logistic and linear regression models were used to determine between-group differences in the ultrasound features. A stepwise linear regression was used to determine which ultrasound features were independently associated with gout compared with asymptomatic hyperuricaemia.

Results: Inter-reader reliability was moderate for the presence of the double contour sign, tophus, erosion, synovial hypertrophy and effusion (k=0.42 to 0.59), good for synovitis (k=0.66) and excellent for cartilage thickness and tophus diameter (ICC=0.81 and 0.86 respectively). Compared to normouricaemic control participants, participants with gout and with asymptomatic hyperuricaemia had more frequent double contour sign (Table, odds ratio (OR) 3.91, *P*=0.011 and OR 3.81, *P*=0.009, respectively). Participants

with gout also had more erosion (OR 10.13, P=0.001) and synovitis (OR 9.00, P<0.001) and had greater tophus diameter (0.00mm vs. 1.68mm, P=0.035). There was no significant difference in cartilage thickness between groups. More severe erosion and synovitis grades and a less severe effusion grade were independently associated with a diagnosis of gout compared with asymptomatic hyperuricaemia (R^2 for model = 0.65, $p < 0.001$).

Conclusion: Urate deposition, synovitis and bone erosion are common at the 1MTPJ in people with gout, even in the absence of flare. Furthermore, although individuals with asymptomatic hyperuricemia lack ultrasound features of inflammation or structural joint changes, they demonstrate a similar frequency of urate deposition. These data support the concept that gout is a disease of chronic inflammation in response to intra-articular urate crystal deposition.

Table. Odds ratios for the presence of ultrasound features at the 1MTPJ

		Present, n (%)	Odds Ratio†	95% CI for OR		p
				Lower	Upper	
Double Contour Sign	Control	9 (13%)				
	Gout	17 (37%)	3.91	1.37	11.20	**0.011**
	AH	21 (36%)	3.81	1.41	10.36	**0.009**
Tophus	Control	0 (0%)				
	Gout	6 (13%)	5.08	0.96	27.08	0.057
	AH	0 (0%)	1.00	0.12	8.26	1.000
Erosion	Control	2 (3%)				
	Gout	15 (33%)	10.13	2.75	37.28	**0.001**
	AH	1 (2%)	0.83	0.14	4.88	0.83
Effusion	Control	12 (18%)				
	Gout	4 (9%)	0.45	0.13	1.61	0.22
	AH	13 (22%)	1.34	0.51	3.54	0.55
Synovial hypertrophy	Control	0 (0%)				
	Gout	1 (2%)	3.25	0.67	15.73	0.14
	AH	2 (3%)	1.72	0.32	9.13	0.52
Synovitis	Control	5 (7%)				
	Gout	20 (44%)	9.00	3.10	26.08	**<0.001**
	AH	2 (3%)	0.60	0.14	2.69	0.51

†Reference category: control group; AH = Asymptomatic hyperuricaemia

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Abstract Number: 3056

Efficacy of a Work Disability Prevention Program for People with Rheumatic and Musculoskeletal Conditions: A Randomized Controlled Trial

Julie J. Keysor[1,2], Michael P. LaValley[3], Carrie Brown[4], David T. Felson[5], Rawan AlHeresh[6], Molly Vaughan[7], Robert A. Yood[8], John Reed[9] and Saralynn Allaire[10], [1]Physical Therapy, Boston University, Boston, MA, [2]Clinical Epidemiology Research and Training, Boston University School of Medicine, Boston, MA, [3]Biostatistics, Boston University School of Public Health, Boston, MA, [4]Boston University School of Public Health, Boston, MA, [5]Clinical Epidemiology Unit, Boston University School of Medicine, Boston, MA, [6]Rheumatology, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia, [7]635 Commonwealth Avenue, Room 651, Boston University College of Health & Rehabilitation Sciences, Boston, MA, [8]Fallon Clinic, Worcester, MA, [9]Rheumatology, Reliant Medical Group, Worcester, MA, [10]Clinical Epidemiology Research and Training Unit, Clinical Epidemiology, BUSM, Boston, MA

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Background/Purpose: Rheumatic and musculoskeletal conditions are leading causes of work disability. A previous trial showed a preventive work disability intervention delivered by vocational rehabilitation counselors (VRCs) reduced job loss among people with arthritis; however, VRC services are not readily available to most people with arthritis. Occupational therapists (OTs) and physical therapists (PTs) could implement a similar intervention, yet this has not been evaluated. The aim of this study was to examine the efficacy of a structured work disability prevention program delivered by OTs and PTs on work limitations and unemployment over two years.

Methods: This single-blind, parallel-arm randomized trial enrolled participants age 21-65 who were employed 15 or more hours/week, and reported a doctor-diagnosed rheumatic or musculoskeletal condition and a concern about staying employed due to their health. The intervention consisted of a 1.5 hour meeting, a written action plan, written materials on disability-related employment issues and supports, and telephone calls at 3-weeks and 3-months by trained OTs or PTs. Control group participants received the written materials but had no contact with the interventionists. The primary outcome was work limitations, measured with the Output Job Demand subscale of the Work Limitations Questionnaire (WLQ). The secondary outcome was unemployment: i) permanent and ii) both temporary and permanent. Intent to treat analyses were performed. For the primary analysis, a two-sample t-test was used to assess the effect of the intervention on the 24-month change in the WLQ subscale. As the secondary analysis, we evaluated the intervention effect on time to permanent unemployment using the Kaplan-Meier procedure and the log-rank test. The same approach was also used to evaluate the time to the first job loss (temporary or permanent). ClinicalTrials.gov NCT01387100.

Results: Between October 2011 and January 2014, 652 individuals were assessed for eligibility and 287 participants were randomized: 143 intervention and 144 control participants. 264 participants (92%) completed two year data collection. There was no difference in the mean WLQ change scores from baseline to two year follow-up (-8.6 ± 1.92 intervention vs. -8.33 ± 2.22 control (p=.93)); however, there was an effect on unemployment: 11 (8%) participants experienced permanent job loss at 2-years in the intervention arm and 25 (18%) in the control arm (p=.03) (Figure 1a). 47 (35%) intervention participants and 65 (46%) control participants experienced any unemployment during the follow up period (HR: 0.70 (0.48, 1.01), p = 0.06) (Figure 1b).

Conclusion: The intervention did not have an effect on work limitations but did reduce work cessation.

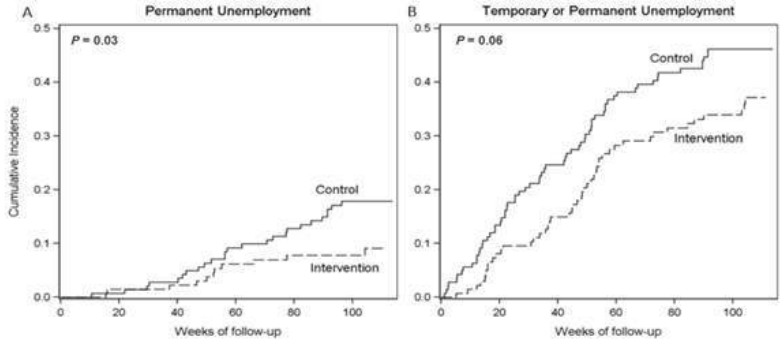

Figure 1: Cumulative Incidence of Time to Permanent (A) and Temporary or Permanent Unemployment (B)

Disclosure: J. J. Keysor, None; **M. P. LaValley**, None; **C. Brown**, None; **D. T. Felson**, None; **R. AlHeresh**, National Institute on Disability, Independent Living, and Rehabilitation Research, 2; **M. Vaughan**, None; **R. A. Yood**, None; **J. Reed**, None; **S. Allaire**, None.

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Abstract Number: 3057

Objectively Measured Physical Activity and Risk of Knee Osteoarthritis: The Osteoarthritis Initiative

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Background/Purpose: Regular physical activity (PA) reduces risk of cardiovascular disease, cancer, diabetes, and premature death. Moreover, PA can counteract the reduction in fitness, muscular strength, and endurance associated with aging, prevent or mitigate decline in physical function, and reduce risk and injury from falls. However, whether the increased joint loading associated with certain types or intensity of PA increases the risk of developing knee osteoarthritis (OA), or accelerate the progression of disease is uncertain. Prior studies about PA and knee OA risk used self-reported PA, which is subject to recall and social desirability bias, and activities captured may be limited. We analyzed the association between objectively measured physical activity and risk of developing knee OA in a community-based cohort of middle-aged and older adults.

Methods: We used data from the Osteoarthritis Initiative (OAI), an ongoing prospective cohort study of adults with elevated risk of symptomatic knee OA. Physical activity was measured by a uniaxial accelerometer worn on a waist belt for seven continuous days in two data collection cycles; minutes-per-week of moderate-equivalent intensity physical activity were calculated from these data. Incident knee radiographic OA (ROA), symptomatic OA (sROA), and joint space narrowing (JSN) were analyzed as outcomes. Incident ROA was assessed by Kellgren-Lawrence grade ≥2 in a knee that was KLG 0 or 1 at baseline, and sROA was defined as ROA plus pain, aching, or stiffness in the same knee. We defined knee JSN as ≥1 grade increase in either the medial or lateral tibiofemoral compartments from the previous clinical visit in a knee that did not have Kellgren-Lawrence grade ≥2 with JSN≥1 at baseline. The study population was free of the outcome at baseline (ROA n = 902, sROA n = 1,331, JSN n = 985), and were followed up to four years. Because outcomes were assessed every two years, we used discrete survival analysis and estimated hazard ratios (HR) and 95% confidence intervals (CI). Multivariable analyses adjusted for age, sex, race, body mass index, education, history of knee injury, and hip OA and symptoms.

Results: Participants who met the US Department of Health and Human Services (HHS) recommended physical activity level (≥150 min/week of moderate-intensity equivalent aerobic activity) had neither significantly increased nor decreased hazard of incident radiographic knee OA (HR: 1.57; 95% CI: 0.71–3.45), symptomatic knee OA (HR: 1.37; 95% CI: 0.58–3.21), or joint space narrowing (HR: 0.78; 95% CI: 0.35–1.72), compared with those who did not meet recommendations.

Conclusion: Meeting physical activity guidelines was not associated with the risk of developing knee OA or joint space narrowing over up to four years of follow up among OAI participants. Given the proven benefits of physical activity on joint health and general health, our results support the HHS physical activity recommendations to adults.

Disclosure: J. Qin, None; **K. E. Barbour**, None; **M. C. Nevitt**, None; **C. Hemlick**, None; **J. M. Hootman**, None; **L. Murphy**, None; **J. A. Cauley**, None; **D. D. Dunlop**, NIH, 2.

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Varus Thrust and Incident and Progressive Knee Osteoarthritis

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Background/Purpose: Varus thrust, bowing-out of the knee during gait, i.e., appearance (or worsening) of varus during stance improving in late stance or swing, was associated with medial tibiofemoral OA progression in a single-site study. To determine replicability in a multi-center study and if thrust is associated with incident OA, we undertook an OAI ancillary study. We hypothesized that: 1) in knees without OA [KL<2 at enrollment (0m) and 12m visits], thrust at 12m (our study *baseline*) is associated with subsequent a) incident OA (KL≥2) and b) medial joint space narrowing (JSN); and 2) in knees with OA (KL≥2 at 0m or 12m), thrust at 12m is associated with subsequent medial JSN. We further considered the hypothesized associations adjusted for *static* alignment, anticipating some but not complete attenuation.

Methods: Gait was observed for thrust at 4 sites by 2-3 trained examiners/site at 12m. In knees KL<2 at 0m and 12m, incident OA was analyzed as subsequent incident KL≥2, medial JSN by whole grade and by partial grade (all dichotomous), and annualized JSN in mm (continuous) after 12m. In knees KL≥2 at 0m or 12m, progression was analyzed as subsequent medial JSN by whole grade and by partial grade, and annualized JSN. Outcomes were assessed up to 96m. Alignment was measured in 3 other sub-studies: mechanical axis (hip-knee-ankle angle, HKA) using 2 full-limb x-ray measurement approaches (HKA-DC and HKA-JD), and anatomical axis (femorotibial angle) on knee x-ray (FTA). All analyses were knee-level; we used multivariable logistic and linear regression methods with GEE to account for between-limb correlation.

Results: The incident OA sample included 4187 knees from 2610 persons [age 60.5 (SD 9.2), BMI 27.8 (4.5), 1455 (56%) women]; the progression sample included 3421 knees/2284 persons [age 62.6 (9.0), BMI 29.6 (4.8), 1339 (59%) women]. Thrust was not associated with incident KL≥2 or medial JSN in knees without OA (Table 1, upper half), but was associated with all progression outcomes (Table 1, lower half). The thrust/progression association was attenuated (Table 2) but an independent association persisted in partial grade and annualized JSN models including HKA-JD and FTA. After adjusting for HKA-DC, thrust was no longer associated with progression.

Conclusion: Over up to 7 years of follow-up observation, varus thrust was associated with medial knee OA progression but not incident OA. Gait observation for thrust may offer a simpler (vs. radiographic methods for alignment) approach to predicting knee OA progression, which is translatable to larger scale studies with multiple examiners.

	Adjusted Odds Ratio (95% CI) **for Thrust for Each of 3 Dichotomous Outcomes** **n = 4187 knees** [987 (24%) with thrust] **KL<2 at enrollment and 12m visit**			**Adjusted Regression Coefficient (95% CI) for Thrust for Continuous Outcome** **n = 1736 knees** [425 (24%) with thrust] **KL<2 at enrollment and 12m visit**
Models and Covariates	**Incident KL≥2**	**Medial joint space narrowing, whole grade**	**Medial joint space narrowing, partial grade**	**Annualized loss of medial joint space width, measured at x = 0.250 location**
Varus thrust, *adj. for age, gender, BMI*	1.09 (0.86, 1.37)	0.98 (0.73, 1.32)	0.96 (0.71, 1.28)	0.011 (-0.006, 0.028)
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain*	1.09 (0.86, 1.37)	0.98 (0.73, 1.32)	0.96 (0.72, 1.28)	0.011 (-0.006, 0.028)
	n = 3421 knees [975 (29%) with thrust] **KL≥2 at enrollment or 12m visit**			**n = 3650 knees** [1085 (30%) with thrust] **KL≥2 at enrollment or 12m visit**
Varus thrust, *adj. for age, gender, BMI*	(not applicable)	***1.50 (1.22, 1.85)***	***1.81 (1.51, 2.17)***	***0.053 (0.032, 0.074)***
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain*	(not applicable)	***1.48 (1.20, 1.83)***	***1.80 (1.50, 2.16)***	***0.049 (0.028, 0.069)***
Table 1. Association of Varus Thrust with Incident Radiographic Knee OA and with Medial Joint Space Narrowing in Knees without OA (upper half) and with Medial Joint Space Narrowing in Knees with OA (lower half) over up to 7 years Subsequent Follow-up				

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	Adjusted Odds Ratio (95% CI) for Thrust for Each of 2 Dichotomous Outcomes		Adjusted Regression Coefficient (95% CI) for Thrust for Continuous Outcome
Models and Covariates	**Medial joint space narrowing, whole grade**	**Medial joint space narrowing, partial grade**	**Annualized loss of medial joint space width, measured at x = 0.250 location**
	n = 1511 knees	n = 1511 knees	n = 1581 knees
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain*	1.32 (0.96, 1.83)	***1.48 (1.12, 1.95)***	***0.029 (0.008, 0.050)***
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain + HKA-DC*	1.04 (0.74, 1.46)	1.16 (0.86, 1.56)	0.011 (-0.010, 0.031)
	n = 2875 knees	n = 2875 knees	n = 3078 knees
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain*	***1.37 (1.09, 1.74)***	***1.76 (1.45, 2.15)***	***0.053 (0.031, 0.074)***
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain + HKA-JD*	1.00 (0.78, 1.29)	***1.27 (1.03, 1.58)***	***0.027 (0.006, 0.047)***
	n = 3378 knees	n = 3378 knees	n = 3608 knees
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain*	***1.47 (1.19, 1.82)***	***1.80 (1.50, 2.16)***	***0.049 (0.029, 0.070)***
Varus thrust, *adj. for age, gender, BMI, WOMAC Pain + FTA*	1.09 (0.87, 1.37)	***1.28 (1.04, 1.56)***	***0.025 (0.005, 0.045)***

Table 2. Alignment Sub-study Data in Knees with OA (KL≥2 at enrollment or at 12m visit): Association of Varus Thrust with Medial Joint Space Narrowing, with and without Adjustment for Alignment, over up to 7 Years Subsequent Follow-up. *The 3 pairs of rows correspond to the 3 alignment sub-studies.*

Disclosure: L. Sharma, None; **A. H. Chang**, None; **C. Eaton**, None; **M. Hochberg**, None; **R. D. Jackson**, None; **C. K. Kwoh**, None; **M. C. Nevitt**, None; **O. Almagor**, None; **K. C. Moisio**, None; **J. S. Chmiel**, None.

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Abstract Number: 3059

Impact of a Musculoskeletal Training Program on Residents' Evaluation, Diagnosis, and Treatment of Osteoporosis

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Background/Purpose: The Center of Excellence (COE) in Musculoskeletal (MSK) Care and Education was established at the Salt Lake City Veterans Affairs Medical Center (SLCVAMC) in 2012. A major element of the COE is the MSK Week, an interprofessional, multidisciplinary, multilevel program for students and postgraduate trainees affiliated with the University of Utah. Objectives included increasing osteoporosis awareness among learners and improving access to appropriate screening and treatment for Veterans. We evaluated the impact of the MSK Week on internal medicine (IM) residents' recognition and treatment of osteoporosis during their VA-based continuity clinic experience before and after training.

Methods: We conducted a retrospective cohort study of patients ages 50+ enrolled at SLCVAMC from July 1, 2013 to May 31, 2014. We used time-dependent multivariable Cox proportional hazard models evaluating the impact of the MSK Week on 5 osteoporosis-related outcomes: (1) completion of 25-hydroxyvitamin D measurement, (2) completion of dual energy x-ray absorptiometry (DXA), (3) diagnosis of osteopenia, (4) diagnosis of osteoporosis, and (5) initiation of osteoporosis medications. Multivariable models adjusted for confounders including age, sex, alcohol and tobacco use, diabetes, fractures, hyperparathyroidism, vitamin D deficiency, renal disease, and medications

Results: We identified 26 IM trainees (PGY1) who completed the MSK Week in 7 groups. In our cohort of 43,678 veterans, 1,154 encountered a trainee who had completed the MSK Week (thus "exposed" to the training) and 42,524 patients who did not.

Table 1. Osteoporosis surrogate outcomes – crude rates

Outcome	MSK Education Week Patients					Non-MSK Education Week Patients					Rate Ratio		
	Number with event	Person-time (days)	Rate[a]	95% CI - LL	95% CI - UL	Number with event	Person-time (days)	Rate[a]	95% CI - LL	95% CI - UL	Rate Ratio	95% CI - LL	95% CI - UL
Vit D Lab	130	125,486	10.360	8.656	12.301	5479	13,117,423	4.177	4.067	4.289	2.48	1.91	2.68
DXA	28	155,527	1.800	1.196	2.602	576	13,956,364	0.413	0.380	0.448	4.36	3.02	6.06
Diagnosis of Osteopenia	7	159,872	0.438	0.176	0.902	266	14,005,290	0.190	0.168	0.214	2.31	1.11	4.77
Diagnosis of Osteoporosis	14	159,052	0.880	0.481	1.477	174	14,014,687	0.124	0.106	0.144	7.09	4.41	11.21
Bisphosphonate	5	160,027	0.312	0.101	0.729	107	14,026,193	0.076	0.063	0.092	4.10	1.79	9.36

[a]per 10,000 patient-days

Patients encountering a trained provider were more likely to have each outcome, with strongest effect in diagnosis of osteoporosis (RR = 7.1, 95% CI: 4.4, 11.2) and completion of DXA (RR = 4.4, 95% CI: 3.0, 6.1). In the univariate analyses, training was associated with increases in all outcomes, with HRs (95% CI) ranging from 7.0 (3.8-12.8) for osteoporosis diagnosis to 1.5 (1.3-1.8) for vitamin D measurement; $p < 0.0001$ for all. Adjusting for confounders, the effect of the MSK Education Week was significant for osteoporosis diagnosis (HR = 3.9, 95% CI: 2.1, 7.3), medication therapy (HR = 2.9, 95% CI: 2.0, 4.1), and evaluation with DXA (HR = 1.8, 95% CI: 1.1, 2.9).

Table 2 – Results from univariate and multivariate Cox proportional hazards regression

	Univariate Results				Multivariable Results			
		95% Confidence Interval				95% Confidence Interval		
Outcome	**HR**	**Lower**	**Upper**	**P-value**	**HR**	**Lower**	**Upper**	**P-value**
Vit D Lab	1.528	1.304	1.789	<.0001	1.017	0.867	1.192	0.839
DXA	3.300	2.063	5.279	<.0001	1.782	1.109	2.865	0.017
Osteopenia	2.414	1.515	3.846	<.0001	1.324	0.829	2.115	0.240
Osteoporosis	6.955	3.773	12.821	<.0001	3.904	2.090	7.293	<.0001
Bisphosphonate	3.403	2.400	4.825	<.0001	2.874	2.018	4.093	<.0001

Conclusion: Participation in the MSK Education Week was associated with improved access to appropriate care for Veterans, with increases in the rates of residents' use of screening DXA, diagnosis, and treatment of osteoporosis following training. Next steps will include evaluation of the impact of the MSK Education Week on long-term osteoporosis outcomes, including rates of fragility fracture.

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Abstract Number: 3060

Development and Implementation of a Question-Based Tool Promoting Learning of Relevant Epidemiology and Biostatistics in Rheumatology: The Critical Literature Assessment Skills Support – Rheumatology (CLASS-Rheum) Pilot

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Background/Purpose: Understanding epidemiology and biostatistics is crucial for rheumatologists to accurately interpret the rheumatic disease literature and make appropriate clinical decisions. In 2014 rheumatology program directors (PD) endorsed the need for materials to support teaching and learning in this area, with a preference for web-based interactive modules. Acknowledging this need, we developed Critical Literature Assessment Skills Support – Rheumatology (CLASS-Rheum). We report on the development, implementation, feasibility and results of our 6-month pilot.

Methods:

CLASS-Rheum was organized as 10 modules on topics encountered in relevant journals (data/distributions, case series, cohorts, case control studies, randomized controlled trials, crossover studies, survival analysis, non-inferiority trials, systematic review/meta-analysis, instrument performance). Based on the science of test-enhanced learning, we developed 3-9 questions/module in rheumatologic contexts. The Learning Catalytics® platform allowed participants to access CLASS-Rheum on any web-enabled device, in synchronous, asynchronous, individual and team formats, with immediate feedback, answer rationales and supporting references.

With IRB exemption, six rheumatology programs of varied size across the US participated from January-June 2016. Each program had autonomy over implementation format and timing. Demographics were collected anonymously via RedCap. Data on use and feasibility were collected in person, via conference calls, email and RedCap. Learning Catalytics® captured responses to CLASS-Rheum questions.

Results:

Thirty fellows participated; 12 first year of fellowship, 14 second year, three third year, and one fourth year. 80% were women, 17% had pediatrics or internal medicine/pediatrics training, 10% had degrees in epidemiology/biostatistics. 62% were very interested and 34% somewhat interested in improving their understanding of epidemiology/biostatistics.

Variability in responses to CLASS-Rheum questions suggested an appropriate range of item difficulty. When team format was used with fellows responding individually and again after small group discussion, correctness of trainees' responses increased.

Trainees reported CLASS-Rheum helped identify knowledge gaps, address learning needs and reinforce learning. Trainees' comments indicated it was "engaging" "fun" and "helpful in challenging me to assess/clarify my own knowledge in an applied manner." Trainees highlighted answer rationales as useful resources and described increased confidence and skill in assessing the quality of the literature after completing CLASS-Rheum.

Instructors/PD found CLASS-Rheum gave them insight into fellows' learning needs and a feasible program to address them. They expressed desire for additional modules to support longitudinal assessment.

Conclusion:

CLASS-Rheum can be successfully implemented to support teaching in a range of rheumatology training programs. It was well received, the content was perceived as relevant, and the formats feasible and useful. CLASS-Rheum should be evaluated in a larger number of programs, with subsequent isomorphic modules to provide longitudinal assessment.

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Abstract Number: 3061

Future Challenges in Pediatric Rheumatology: The Role of Graduate Medical Education (GME)

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Session Time: 4:30PM-6:00PM

Background/Purpose: The 2015 ACR/AHRP Workforce Study examined the adequacy of the future supply of and demand for rheumatology services in the U.S. Understanding the role that GME plays in training, recruitment, and bridging the gap in excess demand for pediatric rheumatology services was a critical component.

Methods: The 2015 ACR/ARHP Workforce Study was completed using several data sources including ACR member data, state licensure registries, ABP certificates, AAMC, ACGME, and National Matching Registry Program data and the ACR Workforce Survey. Significant factors affecting demand included healthcare utilization, practice trends, disease prevalence, population demographics, per capita income, and access to care trends. Clinical FTE was defined as 1.0 FTE for private practice and 0.5 FTE for academic practice. It was assumed 5% of the workforce was in private practice vs. 95% in academic practice. Regional practice patterns were also analyzed.

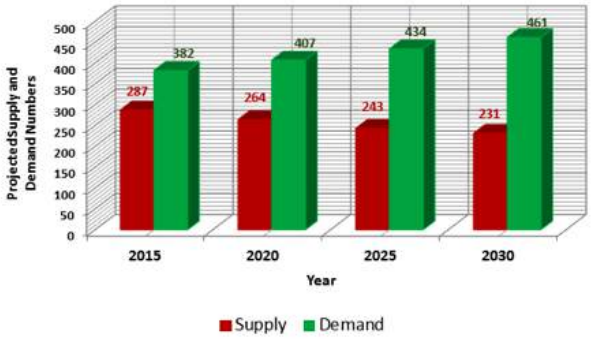
Results: According to ACGME, there are 34 pediatric rheumatology programs; currently up to 40 training slots are offered annually that are 3 years in length (Table 1). Of the 3,301 general pediatric residents graduating annually, 31% enter fellowships but only 0.7% choose rheumatology. More than half (68%) of all pediatric rheumatologists are female. Of the 30% international medical graduate (IMG) fellows, 76% plan to practice in the U.S. On average, approximately 30-45% of the first year fellowship positions

go unfilled with another 3.9% not graduating. By 2030, there is an anticipated 20% reduction in workforce (n=231) will result in an almost two-fold in excess demand (n=461).

Conclusion: The current U.S. pediatric rheumatology workforce is in jeopardy of accelerated decline due to inadequate productivity and increased attrition. GME future challenges include an increased unfilled positions rate, loss of 25% IMGs to practice outside the US, regional misdistribution, projected retirement rates, and increased percent women, many of whom indicate choosing part time work. Increasing training slots alone is unlikely to be effective. Innovation through GME efforts to bridge the excess demand gap is critical and may include loan repayment, recruitment incentives, further evaluation of GME requirements, IMG practice recruitment strategies, in addition to other mechanisms to improve access to care. Efforts targeting recruitment of pediatric trainees are essential to increase interest and commitment to GME in this underserved field. Table 1. Pediatric Rheumatology Fellows Trend Data

Pediatric	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**
Programs						
# Programs	20	23	21	30	29	30
Positions						
# Positions	24	27	27	36	38	40
# Filled	13	14	15	18	26	22
# Unfilled	11	13	12	18	12	18
Applicants						
# Applicants	18	18	19	21	30	27
# Matched	13	14	15	18	26	22
# Unmatched	5	4	4	3	4	5

Source: The MATCH: National Resident Matching Program. 2014 Appointment Year[19-20]



Disclosure: L. Imundo, None; **M. B. Bolster**, None; **S. Monrad**, None; **D. Battafarano**, None; **M. Klein-Gitelman**, None; **J. S. Hausmann**, None; **M. Ditmyer**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/future-challenges-in-pediatric-rheumatology-the-role-of-graduate-medical-education-gme

Abstract Number: 3062

Use of Script Concordance Testing to Evaluate the Efficacy of a Web-Based Module on Gout: Three Years of Experience

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SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Education
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Session Time: 4:30PM-6:00PM

Background/Purpose: Despite the prevalence of musculoskeletal conditions, the majority of internal medicine trainees at the University of Maryland complete residency with little exposure to rheumatology and score in 16th to 35th percentiles on the rheumatology portion of the annual in-training-exam. In order to improve trainee knowledge and clinical decision making in rheumatology, we created a web-based, self-directed core rheumatology curriculum; the first module addresses the topic of gout. Web-based learning is a standardized, convenient, and accessible method to deliver didactics. We assessed the efficacy of the gout module by using the script concordance testing (SCT) method.

Methods: This prospective observational study included internal medicine trainees at the University of Maryland Medical Center. Participants completed a baseline SCT and an electronic module on gout pathophysiology, clinical presentation, and therapeutic management. Immediate post-testing was performed with an identical SCT. A validated SCT was created for each module in the curriculum. Pre- and post-test scores were compared to the scores of the expert panel, which included 2 rheumatology fellows, 9 academic rheumatologists, and 1 community rheumatologist. A one-way ANOVA was used to compare trainee and expert groups as well as pre- and post-test scores. Cronbach's alpha was used to calculate test reliability. An effect size was calculated using Cohen's d. A one-way ANOVA was used to compare the effect of post-graduate year and academic year on SCT score.

Results: One hundred twelve trainees completed paired pre- and post-tests for analysis. The 20-case SCT achieved high reliability (Cronbach alpha > 0.75). At baseline, the trainees' average SCT score was 31 points (M=31.71, SD=3.15); whereas the experts' average SCT score was 40 points (M=40.65, SD=1.72). After the didactics, trainees' SCT scores increased on average 2.56 points $F(1, 232) = 43.12$; ($p<.0001$). Cohen's d showed a strong effect size (d=1.48). Expert SCT scores were on average 8.9 points higher than trainee pre-test scores; whereas at post-test experts' SCT scores were on average 6.3 points higher. Both of these differences were statistically significant ($p<.0001$). There were no significant score differences between second and third year residents on pre- or post-test ($p>.05$). In subgroup analysis by academic year, 2015 trainees scored on average 1.71 points lower on the pre-test compared to 2014 trainees ($p=.01$). There were no significant differences between 2014 and 2016 trainees on the pre-test ($p>.05$). There were no significant differences between academic years on the post-test SCT ($p>.05$).

Conclusion: Trainee test scores significantly increased after the educational intervention in this study. There were no significant differences in post-test SCT scores when analyzed by academic year or post-graduate year. Expert SCT scores were higher at baseline and remained higher after the didactics, which lends support to the construct validity of the tool as the experts had higher clinical competence. Re-testing after 12 months to evaluate durability of knowledge is currently ongoing.

Disclosure: B. C. Siaton, None; **E. Clayton**, None; **A. M. Kueider**, None; **M. Rietschel**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-script-concordance-testing-to-evaluate-the-efficacy-of-a-web-based-module-on-gout-three-years-of-experience

Abstract Number: 3063

Learning Rheumatology through Fellow-Generated Questions: The Rheumatology Image of the Week Project

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SESSION INFORMATION
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Session Title: Education
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Session Time: 4:30PM-6:00PM

Background/Purpose:

There has been increasing interest in using online tools to train physicians. However, most online content does not encourage active

learning, and as a result, does not translate into lasting knowledge. I sought to develop an active learning, learner-generated, question-based curriculum, and to disseminate this educational content through social media.

Methods:

Rheumatology Fellows-In-Training (FITs) were invited to participate in the Rheumatology Image of the Week project (#RheumIOW). Each fellow was asked to create questions from one topic of the ACR Image Bank. After participation, FITs were surveyed on their experience.

Questions were reviewed by the ACR Audiovisual Aids Subcommittee. Every Tuesday, starting on 8/4/15, one question was shared via ACR accounts on Twitter, Facebook, and LinkedIn. Online engagement was analyzed and number of Image Bank page views was recorded. For the first month, #RheumIOW tweets were compared with other tweets from the ACR, and Image Bank page views were compared for the month prior to and after starting #RheumIOW.

Results:

28 FITs from 23 different training programs participated. 50% of participants had Twitter accounts and most (78.5%) had "beginner" or "intermediate" experience with social media. The most common reasons to participate were "to learn" (50%) and "to teach" (28.6%).

116 questions were created; the first four are shown in Figure 1. Results from the FIT survey are shown in Figure 2.

Since August, #RheumIOW questions received 4003 Twitter clicks, 7790 Facebook clicks, and 645 LinkedIn clicks. For the first month, as compared to other ACR tweets, those relating to #RheumIOW had 32 times more clicks. Image Bank images relating to #RheumIOW increased in hits from 2- to 100-fold.

Conclusion:

In this project, rheumatology trainees generated educational micro-content, which they found to be a valuable educational experience and useful to learn rheumatology. Learner-generated questions have previously been shown to be highly effective for learning. At the same time, questions were popular with online users, who actively sought the answer from the ACR Image Bank. These users benefited from "practice testing," the finding that material is better learned and retained when it is tested, rather than when it is simply read.

#RheumIOW shows a novel, inexpensive, and effective way to engage learners through the creation of educational content, which can be shared with the public for their benefit. This method of active learning can be used in the future to address the educational needs of the rheumatology community.

Figure 1. #RheumIOW questions distributed in August 2015.

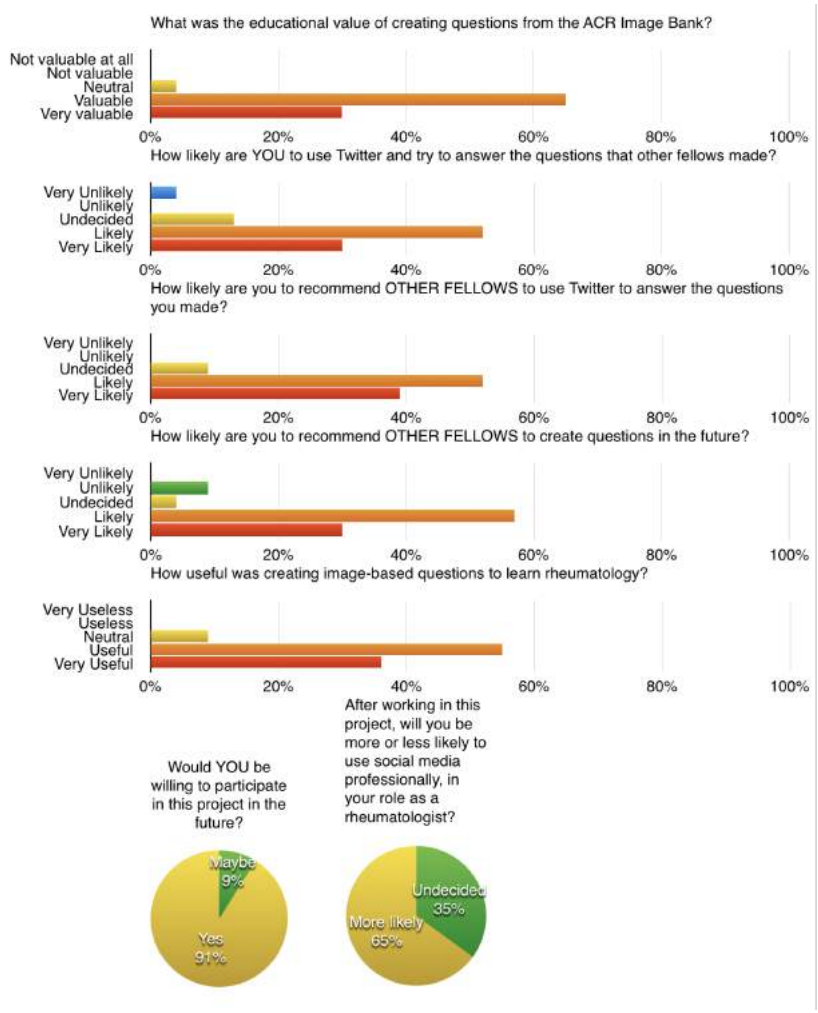

Figure 2. Results of FIT survey after participation in #RheumIOW.

Disclosure: J. S. Hausmann, None;

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/learning-rheumatology-through-fellow-generated-questions-the-rheumatology-image-of-the-week-project

Abstract Number: 3064

From Art to Science: A Mobile App for Point-of-Care Relevance Determination for the Musculoskeletal Exam

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First publication: September 28, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: Education

Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: The physical exam is an essential part of the assessment of patients with musculoskeletal (MSK) complaints. Few doctors are aware of the sensitivity and specificity of special tests in the MSK exam, which leads to

misconceptions regarding the relevance of a particular maneuver. Relevance can be further elucidated by determining the pre- and post-test probability of a particular diagnosis. However, it is impractical to perform these types of calculations at the bedside. To address this issue, we developed the MSK Application (app) based on a clinical decision-making support system with the major feature being called the '**Relevance Determination Engine**'.

Methods: A team of residents was created to generate ideas and outline an approach to the app's development. A literature search was performed to review the evidence behind various examination techniques in terms of sensitivity and specificity. We chose the Apple operating system (iOS) platform and used Xcode 8 as the software development tool. Information on each special test in the MSK exam was converted into JavaScript object notation language, which is simple and facilitates continuous maintenance by team members who are not technologically savvy. The app design is consistent with iOS Human Interface Guidelines. It will be published to the App Store in July, 2016.

Results: The MSK App allows users to search for a special test in the MSK exam according to anatomical region, patient's symptoms or differential diagnosis. A summary of how to perform the exam, as well as the sensitivity, specificity and likelihood ratios are given. Users are also provided with a link to a YouTube video demonstrating the exam. The app serves as a teaching tool in evidence-based medicine (EBM) by highlighting the relevance of each special test. This is achieved by utilizing a feature called the 'Relevance Determination Engine', which automatically calculates the post-test probability for a test. The default pre-test probability of 50% can be adjusted with simple manipulation of a slider bar (Figure 1).

Conclusion: The MSK App is an exciting and innovative approach to education at the bedside developed by residents for residents and medical students. It bridges the gap between physical diagnosis and EBM by calculating point-of-care post-test probability. Further developments will expand content by adding pictures and videos. Data from user surveys will also be analyzed.

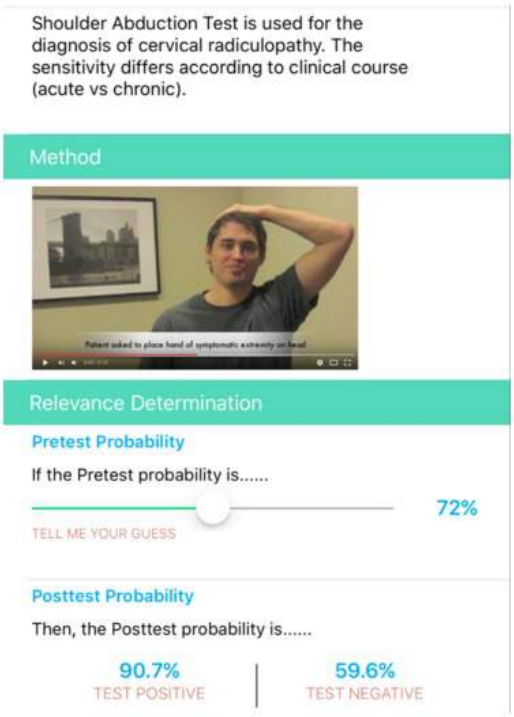

Figure 1. A screenshot from the MSK App prototype showing the Relevance Determination Engine.

Disclosure: J. A. Tabanor, None; **J. Park**, None; **H. A. Hanson**, None; **H. H. Oo**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/from-art-to-science-a-mobile-app-for-point-of-care-relevance-determination-for-the-musculoskeletal-exam

Abstract Number: 3065

Mortality in Patients with Rheumatoid Arthritis and Interstitial Lung Disease

Treated with First Line TNFi or Rituximab Therapies

Katie Druce[1], Kundan Iqbal[2], Kath Watson[1], Deborah P.M. Symmons[1], Kimme L. Hyrich[1] and Clive Kelly[3], [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]Newcastle University, Newcastle, United Kingdom, [3]Rheumatology, Queen Elizabeth Hospital, Gateshead, United Kingdom
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SESSION INFORMATION
Session Date: Tuesday, November 15, 2016
Session Title: Epidemiology and Public Health II: Obesity, Cancer and Mortality
Session Type: ACR Concurrent Abstract Session
Session Time: 4:30PM-6:00PM

Mortality in Patients With Rheumatoid Arthritis and Interstitial Lung Disease Treated With First Line TNFi or Rituximab Therapies Druce KL, Iqbal K, Watson K, Symmons DPM Hyrich KL, Kelly C on behalf of the BSRBR-RA

Background/Purpose: Pulmonary involvement, including interstitial lung disease (ILD), is common in patients with rheumatoid arthritis (RA) and is associated with increased mortality. Early reports suggested that TNFα inhibitors (TNFi) may be linked to the development, or exacerbation, of ILD, and in response, in 2005 the British Society for Rheumatology advised caution in their use for patients with RA-ILD. In contrast, no comparable recommendations have been provided for rituximab (RTX), which is often used where contra-indications for TNFi exist. This study aimed to examine 5-year mortality in patients with RA-ILD starting either RTX or TNFi as their first biologic therapy for RA.

Methods: Participants in the British Society for Rheumatology Biologics Register for RA with clinician reported RA-ILD at baseline starting either TNFi or RTX as their first biologic for RA were included in this analysis. Date and cause of death were captured on regular study follow-up forms and through linkage with the UK National Death Register. Death rates, per 1000 person years (pyrs) were calculated (95% CI); censoring occurred at death, 12/6/2015, or 5 years following first registration, whichever came first. The frequency with which ILD was mentioned on death certificates was examined. Kaplan-Meier survival curves were generated, with risk comparisons made between the RTX and TNFi cohorts using Cox regression using an ever exposed model, adjusted for potential confounders. Eligibility of confounders was determined by clinically relevant justification or statistical significance ($p<0.05$), after adjustment for treatment effects.

Results: Of 353 eligible RA participants with RA-ILD, 310 were treated with TNFi (all recruited before 2008) and 43 were treated with RTX patients (all recruited after 2008). During the first 5 years of follow-up, there were 76 deaths in 804.9 pyrs observed in the TNFi cohort and 8 deaths in 156.7 pyrs in the RTX cohort; death rates were 94.4 (74.4-118.1) and 51.0 (22.0-100.5) per 1000 pyrs, respectively. ILD was recorded on 36.5% of the 74 available death certificates from the TNFi cohort and all of the three certificates available in RTX cohort. The unadjusted mortality risk in the RTX treated patients was numerically half that in the TNFi treated patients, although this was not statistically significant (HR 0.51, 95%CI 0.25-1.06; Figure 1). Adjustment for baseline age, sex, disability, disease activity, and disease duration made little difference to the estimate (0.50, 0.23-1.08).

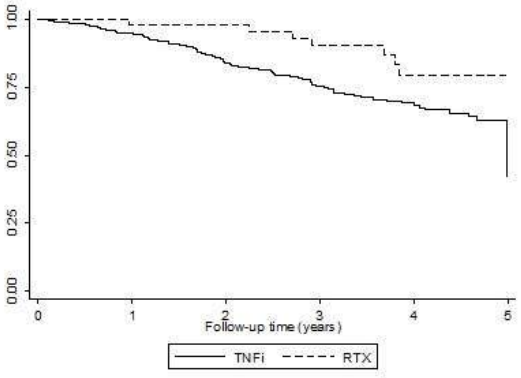

Figure 1 - Kaplan-Meier survival curves for death following exposure to TNFi or RTX over the first 5 years following therapy commencement, within an intention to treat analysis.

Conclusion: Patients who were selected to receive RTX as their first biologic for RA appeared to have better long-term survival compared to patients who had received TNFi, although this difference was not statistically significant. Absence of information on

severity or subtype of ILD prevents drawing conclusions regarding the relative safety of these 2 therapies for RA-ILD and more detailed analysis in a larger dataset should be undertaken.

Disclosure: K. Druce, None; **K. Iqbal**, None; **K. Watson**, None; **D. P. M. Symmons**, None; **K. L. Hyrich**, Abbvie, 9,Pfizer Inc, 9; **C. Kelly**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/mortality-in-patients-with-rheumatoid-arthritis-and-interstitial-lung-disease-treated-with-first-line-tnfi-or-rituximab-therapies

Abstract Number: 3066

Risk of Incident Cancer with Biologic and Tofacitinib Therapy in Rheumatoid Arthritis

Bryant R. England[1], Sofia Pedro[2], Ted R Mikuls[3] and Kaleb Michaud[2,4], [1]Division of Rheumatology, Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, [2]National Data Bank for Rheumatic Diseases, Wichita, KS, [3]Veteran Affairs Nebraska-Western Iowa Health Care System and University of Nebraska Medical Center, Omaha, NE, [4]Rheumatology, University of Nebraska Medical Center, Omaha, NE

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Session Time: 4:30PM-6:00PM

Background/Purpose: The immune system recognizes, controls, and eliminates tumors through a process of immunosurveillance. In RA, where there is an increased incidence of lymphoma and lung cancer, there has been much concern regarding the potential for biologic therapies to increase cancer incidence. While epidemiologic reports have been somewhat conflicting, several suggest an increased risk of skin cancer with anti-TNF therapy. Newer non-TNF biologic and small molecule therapies have been subject to limited investigation. We examined the associations of biologic and small-molecule therapies with incident cancer in RA.

Methods: We studied RA patients without prevalent cancer participating in the National Data Bank for Rheumatic Diseases (NDB), a longitudinal US-wide observational study that includes semiannual patient questionnaires from 1998 to 2015. Malignancy was determined per a standard protocol that included patient report, patient/family interview, review of medical records, and linkage with the National Death Index. We calculated cancer incidence rates using Poisson regression stratified by medications and the adjusted risk of incident cancer in multivariable Cox proportional hazards models. In Cox models, we analyzed medications individually (remains on drug indefinitely after initiation), grouped by mechanism of action (e.g. anti-TNF), and in a time-varying hierarchical model (MTX monotherapy, other DMARDs, anti-TNF, non-TNF biologics, and tofacitinib [TOF]).

Results: Among 11,582 patients, 6,262 biologic/TOF initiations (mean age 58 years, 80% female, and 48% current/former smoker; n=1,621 non-TNF and n=222 TOF) and 5,320 DMARD initiations (mean age 59 years, 79% female, and 49% current/former smoker) were identified with 1,456 incident cancers (812 excluding non-melanoma skin) occurring during 47,243 patient-years of follow-up. Cancer incidence rates/1,000 PY are shown in Table 1. Risk of incident cancer by medications in a hierarchical drug model and for individual therapies in separate models are shown in Table 2.

Table 1. Unadjusted cancer incidence rates (95% CIs) per 1,000/PY

	All Cancer	Solid Tumor	Lymphoproliferative
DMARD	18.68 (17.52-19.91)	7.50 (6.77-8.29)	11.78 (9.11-14.98)
Biologic/TOF	17.82 (16.29-18.44)	6.51 (5.60-7.52)	11.65 (7.97-16.44)
TNF	17.78 (16.24-19.42)	6.52 (5.60-7.55)	10.71 (7.17-15.38)
Non-TNF	14.91 (11.88-18.48)	3.40 (2.05-5.31)	22.73 (9.14-46.84)
Tofacitinib	22.76 (8.35-49.55)	11.38 (2.35-33.26)	0.0 (0-660.1)

Table 2. Associations of biologic and small molecule therapy with incident cancer (excluding non-melanoma skin cancer).

	HR	95% CI	P
*Hierarchical model**			
MTX monotherapy	*Referent*	-	-
DMARDs	0.67	0.50-0.90	0.01
TNF	1.18	0.86-1.63	0.31
Non-TNF	0.80	0.52-1.22	0.29
Tofacitinib	0.73	0.30-1.80	0.50
*Individual comparison vs mono MTX (separate models)**			
TNF	1.27	0.96-1.64	0.089
non-TNF	0.95	0.63-1.43	0.81
Etanercept	1.39	1.09-1.77	0.01
Adalimumab	0.99	0.73-1.36	0.97
Infliximab	1.60	1.25-2.04	<0.001
Golimumab	1.47	0.47-4.68	0.51
Certolizumab	1.09	0.48-2.48	0.85
Rituximab	1.87	1.07-3.27	0.03
Abatacept	0.80	0.44-1.46	0.47
Anakinra	0.28	0.09-0.88	0.03
Tocilizumab	1.90	0.77-4.73	0.16
Tofacitinib	4.36	1.36–13.96	0.01

*Covariates: age, sex, race, education, income, smoking history, comorbidity, HAQ, pain, global assessment, alcohol use, number prior DMARDs and biologics, RA duration

Conclusion: We observed increased rates of solid tumors with TOF and lymphoproliferative malignancies with non-TNF biologics, though both had imprecise estimates. After adjustment for several confounding variables, we did not find an increased risk of cancer with biologic or TOF relative to MTX monotherapy. Combination and non-MTX DMARD therapy had the lowest risk of incident cancer, and several therapies individually were associated with increased cancer risk modeled against MTX monotherapy. These findings highlight the complexity of determining cancer risk with therapies, and show how reasonable changes to methodological analysis can provide disparate results.

Disclosure: B. R. England, None; **S. Pedro**, None; **T. R. Mikuls**, None; **K. Michaud**, Pfizer Inc, 2.

Abstract Number: 3067

Treatment Decisions Following Diagnosis of Cancer during TNFi Inhibitor Treatment in Patients with Rheumatoid Arthritis: Results from the BSRBR-RA

Katie Druce[1], Diederik Decock[2], Kath Watson[1], Deborah P.M. Symmons[1] and Kimme L. Hyrich[1], [1]Arthritis Research UK Centre for Epidemiology, The University of Manchester, Manchester, United Kingdom, [2]KU Leuven Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium

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Treatment Decisions Following Diagnosis of Cancer During TNFi inhibitor Treatment in Patients with Rheumatoid Arthritis: results from the BSRBR-RA Druce KL, De Cock D, Watson K, Symmons D, Hyrich KL on behalf of the BSRBR-RA

Background/Purpose: Despite early concerns, evidence has suggested that use of TNFα inhibitors (TNFi) may not be associated with an increase in cancer risk in patients with rheumatoid arthritis (RA). Nevertheless, uncertainty remains about appropriate treatment decisions following a diagnosis of cancer in patients receiving TNFi. The aims of this analysis were to describe (i) treatment decisions and (ii) outcomes in the 5 years following a diagnosis of cancer in patients with RA receiving TNFi.

Methods: This descriptive analysis included participants from the British Society for Rheumatology Biologics Register for RA (BSRBR-RA) who develop a first cancer while receiving TNFi (+90 days) prior to 01/04/2011. Cancer and death data were captured through linkage with the UK National death and cancer registers held by the Health and Social Care Information Centre (HSCIC). Treatment data were captured via regular clinical follow-up forms. Initial treatment decisions in all patients following diagnosis and subsequent treatment decisions among patients who survived at least 6 months were examined. Decisions were examined in all cancers and separately for the five most common cancer sites. Overall and site-specific mortality are described using percent of deaths and Kaplan Meier survival function.

Results: During 118355 person years of follow-up in 12499 patients who had ever been exposed to TNFi, 404 first cancers occurred on TNFi (74 lung, 65 breast, 35 colorectal, 36 lymphoma, 18 prostate and 176 other). Within 6 months of diagnosis, 95 (24%) patients died (median time to death (TTD):52 days (IQR: 22-100)) with the highest death rate among patients with lung cancer. Of the 309 patients surviving the first 6 months, 67% stopped TNFi at cancer diagnosis. Over the subsequent 5 years, 47% remained off all biologics, 26% continued on TNFi and 25% started an alternative class of biologic after a median of 510 days. Only 2 patients restarted a TNFi therapy and 5 discontinued their TNFi after 6 months. Treatment decisions varied among the 5 most common cancer sites, with a majority of patients (64%) with prostate cancer continuing their initial TNFi treatment over 5 years. Of patients with breast cancer and lymphoma 32% and 40% of patients, respectively started an alternative treatment; the majority switched to rituximab.

Table. On TNFi (+90 days) cancer events, deaths and treatment decisions made by 6 months and 5 years						
	All cancers	Lung	Breast	Lymphoma	Colorectal	Prostate
N (all patients)	404	74	65	36	35	18
Died within first 6 months, n(%)	95 (23)	39 (53)	3 (5)	1 (3)	6 (17)	1 (6)
5 year survival, % (95% CI)	44 (39, 49)	5 (1, 13)	68 (55, 78)	69 (52, 82)	49 (31, 64)	72 (46, 87)
Initial treatment decision among patients surviving at least 6 months following cancer diagnosis (n=309)						
n	309	35	62	35	29	17
Stopped TNFi, n (%)	207 (67.0)	32 (91.4)	47 (75.8)	29 (82.8)	20 (69.0)	4 (23.5)
Remained on TNFi, n (%)	102 (33.0)	3 (8.6)	15 (24.2)	6 (17.2)	9 (31.0)	13 (76.5)
Subsequent biologic treatment decisions over 5 years among patients surviving at least 6 months following cancer diagnosis (n=309)						
Continued TNFi, n (%)	81 (26.2)	3 (8.6)	9 (14.5)	5 (14.3)	8 (27.6)	11 (64.7)
Initially continued but later stopped treatment, n (%)	5 (1.6)	0 (0)	2 (3.2)	0 (0)	1 (3.4)	1 (5.9)
Restarted TNFi, n (%)	2 (0.6)	2 (5.7)	0 (0)	0 (0)	0 (0)	0 (0)
Median days to treatment re-start (IQR)	171 (163-179)	171 (163-179)	-	-	-	-
Switched to analternative biologic, n (%)	76 (24.6)	3 (8.6)	20 (32.3)	14 (40.0)	5 (17.2)	2 (11.8)
Median days to treatment start (IQR)	503 (310.5-890)	499 (430-504)	696 (275-950)	547 (369-771)	661 (323-814)	410 (369-451)
Discontinued all biologics, n (%)	145 (46.9)	27 (77.1)	31 (50.0)	16 (45.7)	15 (51.7)	3 (17.6)
Still alive at 5 years, n (%)	174 (56%)	4 (11%)	44 (71%)	25 (71%)	17 (58%)	13 (76%)

Conclusion: Treatment decisions following cancer diagnosis in patients receiving TNFi were highly variable and differed by the site of cancer diagnosis. Although around two thirds of patients discontinued their TNFi, only one third of patients with prostate cancer discontinued. Patients with cancer at sites associated with longer survival were also more likely to continue or restart a biologic over the following five year period. If biologics were restarted, most patients started an alternative class of drug.

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Abstract Number: 3068

Smoking and Excess Weight Attenuate Rate of Improvement over First 3 Years in Early RA

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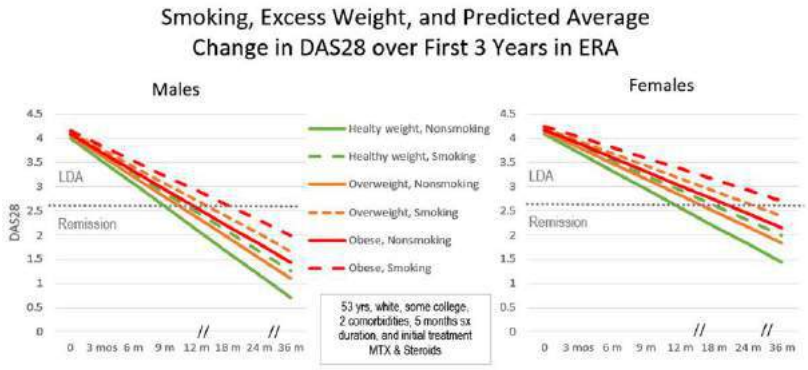
Background/Purpose: Early, aggressive treatment to achieve remission is the primary goal when treating early RA, and is associated with improved long-term outcomes. We have previously shown that individuals who smoke and have excess weight (potentially modifiable factors) are less likely to achieve sustained remission in the first 3 years. Here we explore how smoking, excess weight, and sex affect rate of DAS28 improvement in the first 3 years of early RA.

Methods: Data were drawn from a multicenter prospective cohort study of ERA patients seen in usual care settings. Inclusion criteria were: meeting 1987 or 2010 ACR criteria, <12 months symptom duration at entry, DAS28≥2.6 at entry, and information on BMI and DAS28 at baseline and at least 1 follow up visit. Patients were followed every 3 months in year 1, 6 months in year 2, and annually thereafter. We examined how sex, excess weight (overweight: BMI 25-29.9; obese: BMI 30+) and smoking (current/former/never) impacted DAS28 at baseline and over time using linear growth models. Covariates included baseline age, race, education, comorbidities, symptom duration, and treatment.

Results: The sample included 1109 patients with a mean [SD] age of 54 [15], symptom duration of 6 [3] months; most were female (n=795; 72%) and white (n=893; 81%). Among males 44% (n=138) were overweight, 35% (n=109) were obese and 22% (n=70) smoked; among females, 31% (n=248) were overweight, 32% (n=257) were obese, and 15% (n=121) smoked. At enrollment, most (n=810; 73%) were on MTX. Results of the growth curve model without covariates showed that average DAS28 at baseline was moderate to high (random average DAS28: 4.6, 95% CI: 2.7, 6.2), and DAS28 dropped significantly at each time point (random mean rate of change per visit: b -0.33 (95% CI: -0.60, -0.07). Sex, excess weight, and smoking were not significantly associated with baseline DAS28 (p>0.05). However, each attenuated the rate of DAS28 change over time. The average rate of improvement in DAS28 was lower in women vs men (b: 0.09; 95% CI: 0.05-0.12); those who were overweight (b: 0.05; 95% CI: 0.01-0.09) and obese (b:0.09; 95% CI: 0.05-0.13) vs. healthy weight, and current smokers vs. non-smokers (b:0.07; 95% CI: 0.03-0.12), at each time point. Former smoking did not significantly impact DAS28 trajectory (b:0.03; 95% CI: -0.01-0.06).

Conclusion : Results from a large multi-center ERA cohort study showed that sex, excess weight and smoking significantly attenuated the rates of improvement in RA disease activity over the first 3 years. Improvement among former smokers was similar to those who had never smoked. These results contribute to growing evidence of how lifestyle also may impact treatment outcomes and the potential value of referring patients to proven community-based smoking cessation and weight management programs.



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Aventis, UCB, 2,Abbott, AstraZeneca, Biotest, BMS, Crescendo, Hoffmann-LaRoche, Genentech, Janssen, Eli Lilly and Company, Merck, Pfizer, UCB, 5,Abbott, AstraZeneca, BMS Canada, Hoffmann-LaRoche, Janssen, Pfizer, UCB, Amgen, 9; **J. E. Pope**, AbbVie, Actelion, Amgen, BMS, Hospira, Janssen, Lilly, Merck, Novartis, Pfizer, Roche, Sanofi, UCB, 5; **J. C. Thorne**, Janssen Inc., 5; **D. Tin**, None; **V. P. Bykerk**, AbbVie, Bristol-Myers Squibb, Pfizer, Roche/Genentech, Regeneron, and UCB Pharma, 5.

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Abstract Number: 3069

Weight Loss in the Early Rheumatoid Arthritis Period Is Associated with Subsequent Increased Mortality in RA Patients and Matched Comparators: Evidence Against an RA-Specific Obesity Paradox

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Background/Purpose : Weight loss may explain the obesity paradox for mortality, since those who unintentionally lose weight to reach normal BMI may have higher mortality than those with obesity and stable weight. A prior study among RA patients found an association between weight loss and increased mortality. However, weight was examined close to time of death in established RA without a non-RA comparison so the findings may not be specific to RA. Therefore, we investigated the association of weight change in the early RA period with subsequent mortality, and included a matched non-RA group to evaluate the influence of RA.

Methods : We identified incident RA by 1987 ACR criteria during follow-up of the Nurses' Health Study (1976-2012) to form a cohort followed before and after RA onset. We created a comparison cohort by matching RA cases to non-RA comparators by age and year at the index date of RA diagnosis. Anthropometric, behavioral, and clinical data were collected through biennial questionnaires. To capture the entire early RA period, weight change was defined as the difference between weight at 4 years before and 4 years after RA diagnosis ("peri-RA") or index date ("peri-index"). We used Cox regression to estimate HRs for mortality by weight change categories separately in each cohort. We combined both cohorts to evaluate the RA-specific effect and weight change on mortality.

Results : Among 121,700 women, we identified 875 subjects with incident RA, matched to 7,459 non-RA comparators. In the RA cohort, 16.2% lost >10 lbs peri-RA; 12.1% of comparators had weight loss >10 lbs peri-index. There were 243 (27.8%) deaths in the RA cohort and 1,369 (18.4%) deaths among comparators. After adjustment for BMI, smoking, diet, physical activity, comorbidities (cancer, CVD, and diabetes), erosions, serostatus, and nodules, weight loss >10 lbs peri-RA had HR for mortality of 1.61 (95%CI 1.12-2.32, **Table**), identical to the comparison cohort (HR 1.61, 95%CI 1.38-1.89). Weight gain was not significantly associated with mortality in either cohort. When combining both cohorts, RA had higher absolute mortality risk, but there was no interaction between RA or comparators with weight change for mortality (p_{int}=0.86, **Figure**).

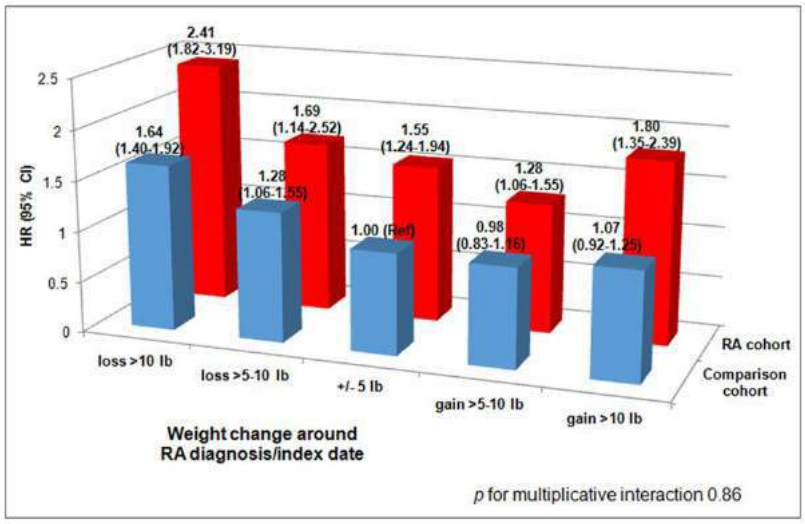
Conclusion : In this large prospective study with up to 36 years of follow-up, weight loss around RA diagnosis increased subsequent mortality risk among women. We found similar results in non-RA comparators and evaluated weight change in the early RA period when disease-specific processes are most likely to contribute to weight loss or gain. Therefore, an obesity paradox for mortality may occur in the general population but is not specifically related to RA.

Table. Hazard ratios for mortality according to peri-RA* or peri-index* weight change, analyzed separately in RA and comparison cohorts.

			Age-adjusted[1]		Age and pre-RA/index BMI adjusted[2]		Multivariable adjusted[3]	
	Deaths/ person-years	Mortality rate**	HR	(95%CI)	HR	(95%CI)	HR	(95%CI)
RA cohort (n=875)								
Loss >10 lb	56/1,882	2,973	**1.74**	**(1.24-2.45)**	**1.66**	**(1.16-2.37)**	**1.61**	**(1.12-2.32)**
Loss >5-10 lb	26/1,346	1,932	1.09	(0.70-1.71)	1.06	(0.67-1.65)	1.09	(0.69-1.74)
Stable (+/- 5 lb)	89/5,973	1,490	1.00	Reference	1.00	Reference	1.00	Reference
Gain >5-10 lb	19/1,927	986	0.80	(0.48-1.33)	0.79	(0.48-1.32)	0.79	(0.47-1.34)
Gain >10 lb	53/3,591	1,476	1.29	(0.91-1.84)	1.26	(0.88-1.80)	1.18	(0.82-1.71)
Comparison cohort (n=7,459)* **								
Loss >10 lb	244/11,995	2,034	**1.93**	**(1.66-2.24)**	**1.81**	**(1.54-2.11)**	**1.61**	**(1.38-1.89)**
Loss >5-10 lb	140/9,810	1,427	**1.40**	**(1.16-1.68)**	**1.39**	**(1.15-1.67)**	**1.28**	**(1.06-1.55)**
Stable (+/- 5 lb)	563/58,518	962	1.00	Reference	1.00	Reference	1.00	Reference
Gain >5-10 lb	183/23,066	793	0.99	(0.84-1.17)	1.00	(0.84-1.18)	0.98	(0.83-1.16)
Gain >10 lb	239/29,036	823	1.19	(1.02-1.38)	1.16	(0.99-1.35)	1.07	(0.92-1.25)

*Data on weight were obtained every two years in follow-up during the Nurses' Health Study. The "peri-RA" period was defined as up to four years before and four years after RA diagnosis in order to capture early symptoms and the entire early RA period after diagnosis. The "peri-index" period was similarly defined as up to four years before and four years after index date for matched non-RA comparators.
**Per 100,000 person-years
***Comparison cohort was formed by matching each RA case with up to 10 women without RA based on age and calendar year at the index date of RA diagnosis.
[1]Model adjusted for age (continuous, years) and calendar year.
[2]Model adjusted for age (continuous, years), calendar year, and pre-RA/index date BMI (<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35+ kg/m^2).
[3]Model adjusted for age (continuous, years), pre-RA/index date BMI (<18.5, 18.5-24.9, 25-29.9, 30-34.9, 35+ kg/m^2), smoking (never, >0-10, >10-20, >20 pack-years), physical activity (hours of moderate or vigorous exercise per week, continuous), census-tract household family income (<$40K, $40K+ per year), and Alternative Healthy Index dietary score (tertiles), diabetes, cardiovascular disease, and cancer. The RA cohort was additionally adjusted for RA serostatus (seropositive, seronegative), nodules, and erosions.

Figure. Multivariable hazard ratios for mortality according to peri-RA/index weight loss, combining the RA and comparison cohorts into a single analysis (n=8,334).



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Abstract Number: 3070

Effect of Sarcopenia, Subcutaneous Adipose Tissue and Abdominal Visceral Fat on Mortality Risk of Community-Dwelling Older Adults: A Population-Based Prospective Cohort Study

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Background/Purpose: Body composition changes resulting from ageing (decreased muscle mass and increased fat tissue) are frequently not accompanied by concomitant changes in body mass index (BMI). Thus, BMI has low accuracy for estimating death risk attributed to changes in body composition in the older adults. Currently, the best method for body composition analysis in routine clinical practice is dual energy X-ray absorptiometry (DXA). However, the few studies on body composition by DXA and mortality risk in elderly have some limitations, such as analysis not stratified by sex and not compartmentalized (subcutaneous and visceral tissues) assessment of body fat. Thus, we sought to investigate the association between body composition by DXA (including visceral fat measurement) and mortality in a longitudinal, prospective, population-based cohort of elderly subjects.

Methods: 839 community-dwelling subjects (516 women, 323 men), ≥65 years, were assessed by questionnaire on clinical data, laboratory exams and body composition by DXA using Hologic QDR 4500A equipment. DXA APEX software computes visceral adipose tissue (VAT) by subtracting the subcutaneous adipose tissue (SAT) from the total android fat, which was automatically set to 20% of the distance from the iliac crest to the base of the skull. All analyses were performed at baseline. Total body fat was expressed by fat mass index (FMI) [(total body fat (kg) / height^2 (m)]. Sarcopenia was defined as low appendicular muscle mass adjusted for fat. Mortality was recorded during 4 year-follow-up. Multivariate logistic regression was used to compute odds ratios for all-cause and cardiovascular mortality.

Results: Over a mean 4.06 ± 1.07 years of follow-up, there were 132(15.7%) deaths. In men, after adjustment for age, BMI, smoking, physical activity, alcohol, diabetes, dyslipidemia, cardiovascular event, recurrent falls, 25OHD and PTH, the presence of sarcopenia (OR 11.36, 95% CI: 2.21-58.37, p=0.004) and visceral fat mass(OR 1.99 95%CI: 1.38-2.87, p<0.001, for each 100g-increase) significantly increased all-cause mortality risk, while total body fat (FMI) was associated with decreased mortality risk (OR 0.48, 95% CI: 0.33-0.71, p<0.001). Similar results were observed for cardiovascular mortality in men: sarcopenia (OR 14.84, 95%CI: 5.15-47.72, p<0.001), visceral fat mass (OR 1.66, 95% CI: 1.31-2.10, p<0.001) and total body fat (OR 0.57,95% CI: 0.43-0.76, p <0.001). In women, only sarcopenia was predictor of all-cause (OR 62.88, 95% CI: 22.59-175.0, p<0.001) and cardiovascular death (OR 74.54, 95% CI: 9.72-571.46, p <0.001).

Conclusion: Sarcopenia and fat distribution are associated with all cause and cardiovascular mortality risk in elderly, and they are different according to sex. Visceral fat and subcutaneous fat have opposite roles on mortality risk in elderly men, and this is distinct from what is observed in young adults.These findings point to the risk of encouraging weight loss in the elderly aiming young adult goals. Furthermore, DXA seems to be a promising tool for evaluation risk of mortality in elderly, since it is easily applicable in clinical practice.

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Abstract Number: 3071

Recombinant Human Proteoglycan-4 (rhPRG4) Inhibits Monosodium Urate (MSU) Crystal Phagocytosis By Human Macrophages and Resultant Inflammatory Response

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Session Time: 4:30PM-6:00PM

Background/Purpose: Gout is an inflammatory arthritis caused by precipitation of monosodium urate (MSU) crystals in synovial joints. MSU crystals interact with resident macrophages that release pro-inflammatory cytokines, interleukin-1 beta (IL-1β) and chemokines, interleukin-8 (IL-8). MSU crystals are phagocytosed in a process mediated by toll-like receptor (TLR2). Proteoglycan-4 (PRG4) is a lubricating mucinous glycoprotein released by synovial fibroblasts and exhibits a multifaceted homeostatic role in the synovial joint. We have recently shown that recombinant human PRG4 (rhPRG4) can inhibit agonist-induced TLR2 activation. The objective is to evaluate the efficacy of rhPRG4 in modulating MSU activation of macrophages. We hypothesized that rhPRG4 inhibits MSU phagocytosis by human macrophages dose-dependently and inhibits MSU-induced IL-1β and IL-8 gene expression.

Methods: THP1 human monocytes were differentiated into macrophages using 5ng/ml phorbol 12-myristate13-acetate for 48 hours at 37^{o}C. A total of 500,000 macrophages were plated per well in sterile tissue culture plates and were treated with MSU crystals (100μg/mL) for 6 hours at 37^{o}C, and afterwards in the absence or presence of rhPRG4 (25, 50, 100, 200μg/mL) for 24 hours at 37^{o}C. Following incubation, the percent of macrophages that phagocytosed MSU was quantitatively determined using flow cytometry, based on an increase in cellular side-scatter. RNA was extracted and cDNA was synthesized followed by qRT-PCR using TaqMan Fast Advanced Master Mix and primers for human IL-1β and IL-8. IL-1β and IL-8 media supernatant concentrations were determined by commercially available ELISA.

Results: Flow cytometry scatter plots of MSU phagocytosis by macrophages in the absence or presence of rhPRG4 is shown in figure 1A. rhPRG4 treatment significantly inhibited MSU phagocytosis ($p<0.05$) (fig. 1B). MSU treatment resulted in a significant induction of IL-1β gene expression which was inhibited by rhPRG4 treatment (100 and 200μg/ml) ($p<0.05$; fig. 2A), and a significant reduction in IL-1β protein concentration at the 200μg/ml rhPRG4 concentration ($p<0.05$; fig. 2C). Likewise, MSU treatment resulted in a significant induction of IL-8 gene expression which was inhibited by rhPRG4 treatment (50, 100 and 200μg/ml) ($p<0.05$; fig. 2B), and a significant reduction in IL-1β protein concentration at the 100 and 200μg/ml rhPRG4 concentrations ($p<0.05$ and $p<0.001$; fig. 2D).

Conclusion: rhPRG4 inhibits MSU phagocytosis and the resultant inflammatory response by human macrophages and may be useful as a biological treatment for acute gout exacerbations.

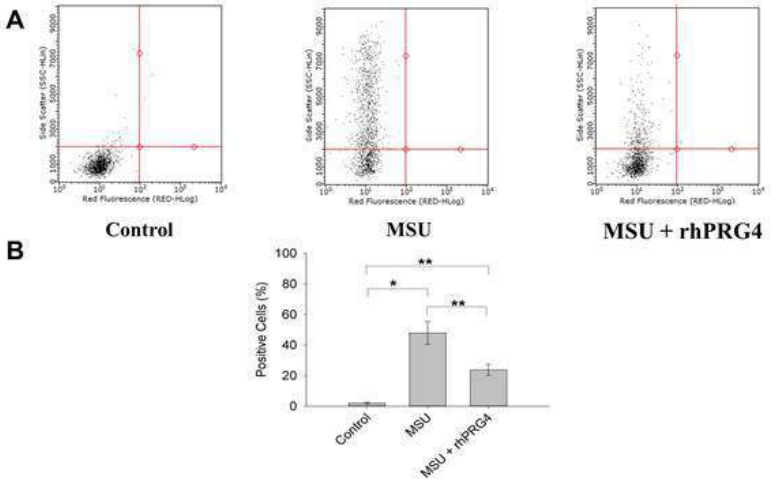

Fig. 1 Monosodium urate (MSU) phagocytosis by human macrophages in the absence or presence of recombinant human proteoglycan-4 (rhPRG4). **A** Representative scatter plots from untreated control, MSU-treated and MSU+rhPRG4 treated macrophages. Macrophages phagocytosed MSU crystals, as demonstrated by the increase in cell population in the top left quadrant. rhPRG4 treatment reduced MSU phagocytosis. **B** Quantitative estimation of MSU phagocytosis by macrophages using the percentage of cells in the top-left quadrant (positive cells). rhPRG4 inhibits MSU phagocytosis. *$p<0.001$; **$p<0.05$. Data is presented as mean ± S.D. of three independent experiments.

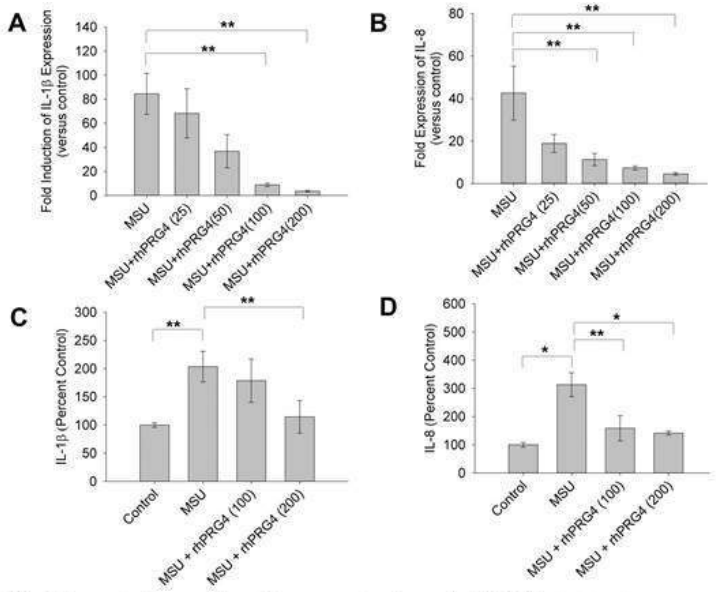

Fig. 2 Impact of recombinant human proteoglycan-4 (rhPRG4) treatment on monosodium urate (MSU) induced induction and secretion of IL-1β and IL-8 by human macrophages. *p<0.001; **p<0.05. Data is presented as mean ± S.D. of three independent experiments.

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Abstract Number: 3072

Increased Platelet Reactivity in Gout: Relationship to Tophus Burden and Colchicine Use

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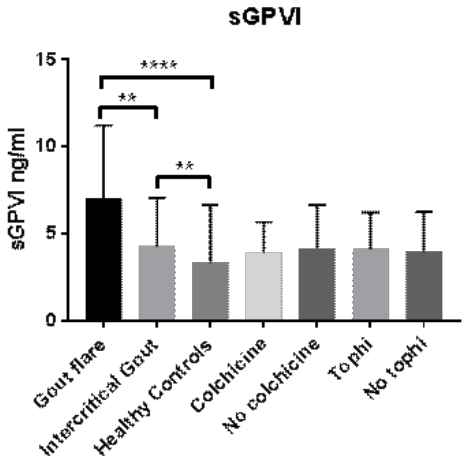
Background/Purpose: Patients with gout have an increased risk of cardiovascular events. The presence of tophi is associated with enhanced cardiovascular risk. Increased platelet reactivity is a risk marker for cardiovascular events. The glycoprotein VI (GPVI) receptor is found exclusively on platelets and megakaryocytes and is the predominant platelet receptor for collagen. It remains intact on platelets under resting conditions. The proteolytic cleavage of GPVI occurs upon specific activation of platelets and is detectable in plasma as soluble GPVI (sGPVI). Therefore elevated plasma sGPVI is a marker of platelet activation and a risk marker for adverse cardiovascular outcomes. The aim of this study was to assess platelet activation, as measured by plasma sGPVI

level in gout.

Methods: Following ethics approval and informed consent, blood samples were taken from patients with gout. Control samples were obtained from healthy volunteers. Demographic and clinical data were collected for all participants. Blood samples were processed as double spun platelet poor plasma. Plasma sGPVI levels were measured using ELISA. Mann-Whitney U test was used to compare groups. Spearmans Rank Correlation Coefficient was used to assess for associations between sGPVI and demographic and clinical markers. IBM SPSS Statistics Version 20 was used for data analysis.

Results: 121 patients were included, 27 during gout flare, 41 with intercritical gout, and 53 healthy controls. There were no significant differences in demographic details between the groups. Median (IQR) sGPVI levels were 6.51 ng/ml (4.52, 8.41) in gout flare, 3.58 ng/ml (2.11, 5.55) in intercritical gout, and 2.19 ng/ml (1.72, 3.31) in healthy controls.Plasma sGPVI levels in both gout groups were significantly increased compared to healthy controls ($p<0.005$ for each) (Figure 1). sGPVI levels were significantly increased in gout flare compared to intercritical gout ($p=0.001$). There was no significant difference in sGPVI levels in gout patients with and without tophi, median (IQR) 3.58 (2.26, 6.08) vs 2.94 (1.91, 6.01) ($p=0.441$), or in those prescribed colchicine, median (IQR) 3.60 (2.19, 6.06) vs 3.12 (2.12, 6.49) ($p=0.773$). There was moderate correlation between sGPVI levels and VASPain ($r=0.40$), and VASQOL ($r=0.33$). There was a weak correlation with CRP ($r=0.23$) and no correlation with ESR ($r=0.049$). sGPVI level did not correlate with presence of tophi ($r=0.115$) or colchicine use ($r=0.042$).

Conclusion: Patients with both tophaceous and non-tophaceous gout exhibit platelet hyperactivity as demonstrated by elevated plasma sGPVI levels. Platelet activation is exacerbated during acute gout flares. Colchicine therapy does not influence plasma sGPVI levels. Platelet activation probably contributes to the elevated cardiovascular risk in gout patients and antiplatelet therapy warrants consideration in this patient population. Figure 1



Disclosure: R. Conway, None; **C. L. Murphy**, None; **A. Madigan**, None; **P. Kavanagh**, None; **L. Geraghty**, None; **N. Redmond**, None; **L. Helbert**, None; **J. J. Carey**, None; **E. Dunne**, None; **D. Kenny**, None; **G. M. McCarthy**, None.

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Abstract Number: 3073

Non-Additive Interaction of the Glucokinase Regulatory Protein and APOBEC1 Complementation Factor Loci with Alcohol Consumption to Influence the Risk of Gout

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SESSION INFORMATION

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Session Time: 4:30PM-6:00PM

Background/Purpose: Genome-wide association studies (GWAS) have identified loci associated with serum urate levels and the risk of gout. Some of these loci interact in a non-additive fashion with dietary exposures to influence the risk of gout. This study aimed to systematically investigate non-additive interaction between alcohol exposure and urate-associated loci for the risk of gout.

Methods: A total of 3,312 New Zealand European and Polynesian (Maori/Pacific) people with and without gout were genotyped for 28 urate-associated genetic variants and tested for non-additive interaction with alcohol exposure (none versus any intake) influencing the risk of gout. Publicly-available genotype and serum urate data from the Atherosclerosis Risk in Communities (ARIC) study and the Framingham Heart Study (FHS) (n=7,110 European subjects) were used to test for non-additive interaction between specific genetic variants and alcohol exposure for the risk of hyperuricaemia (HU). Multivariate-adjusted logistic regression was done including an interaction term. $P<8.6x10^{-4}$ was the significance level after application of a correction factor of 58.

Results: Non-additive interaction of alcohol exposure with *GCKR* (*rs780094*) and *A1CF* (*rs10821905*) was observed in Europeans to influence the risk of gout ($OR_{Interaction}=0.28$, $P=1.5x10^{-4}$ and $OR_{Interaction}=0.29$, $P=1.4x10^{-4}$, respectively). There was evidence for interaction of *A1CF* with alcohol exposure in determining HU in the ARIC/FHS sample set ($OR_{Interaction}=0.60$, P=0.018), but not for *GCKR* ($OR_{Interaction}=0.82$, P=0.18). Analysis of genotype groups stratified by alcohol exposure revealed that at *A1CF* alcohol exposure suppressed the gout risk conferred by the A-positive genotype ($OR_{No\ Alcohol}=2.21$; $OR_{Alcohol}=0.93$) (Table). At *GCKR* alcohol exposure eliminated the genetic effect on gout - the ORs for each genotype group were equivalent ($OR_{T-}=2.07$; $OR_{T+}=2.39$) (Table). In Polynesians there was no experiment-wide evidence for non-additive interaction with alcohol in the risk of gout for any locus ($P>8.6x10^{-4}$). However at *GCKR* there was nominal evidence for interaction in a direction consistent with that observed in Europeans ($OR_{Interaction}=0.62$, P=0.05). At the five urate transporter loci (*SLC2A9, ABCG2, SLC17A1, SLC22A11, SLC22A12*) there was little or no evidence of interaction with alcohol in determining the risk of gout, with nominal evidence only in Europeans at *SLC17A1* ($OR_{Interaction}=0.46$, $P_{Uncorrected}=0.027$).

Conclusion: We describe a novel non-additive interaction of alcohol exposure with *GCKR* (glycolytic gene) and *A1CF* (apolipoprotein B mRNA editing gene) to influence the risk of gout in Europeans. These data support the hypothesis that alcohol influences the risk of gout via glucose and apolipoprotein metabolism. Table. Alcohol intake and gout association in genotype-stratified groups in Europeans for *A1CF* and *GCKR*.

		No Alcohol Intake		**Any Alcohol Intake**	
		Adj OR[95% CI]	**P**	**Adj OR[95% CI]**	**P**
A1CF	A-	1	1	1.47 [0.99-2.16]	0.054
	A+	2.21 [1.24-3.93]	0.007	0.93 [0.61-1.43]	0.76
GCKR	T-	1	1	2.07 [1.24-3.47]	0.0050
	T+	4.13 [2.35-7.26]	8.65E-07	2.39 [1.47-7.26]	0.00043

Adjusted for age, sex and BMI.

Disclosure: H. Rasheed, None; **L. K. Stamp**, None; **N. Dalbeth**, None; **T. R. Merriman**, None.

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Abstract Number: 3074

Population-Specific Association Between ABCG2 Variants and Tophaceous

Disease in People with Gout

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Background/Purpose: Tophi contribute to musculoskeletal disability, joint damage and poor health-related quality of life in people with gout. The aim of this study was to examine the clinical and genetic features of tophaceous gout.

Methods: Participants (n=1778) fulfilling the 1977 ARA gout classification criteria, recruited from primary and secondary care, attended a study visit which included a detailed clinical assessment. The presence of palpable tophi was recorded. *SLC2A9 rs11942223* and *ABCG2 rs2231142* (SNPs associated with gout) and *ABCG2 rs10011796* (SNP associated with allopurinol response in a US study population) were genotyped (linkage disequilibrium between the two *ABCG2* SNPs $r^2<0.11$ for all ancestral groups). Clinical and genetic features of tophaceous gout were analysed using a case-control study design (tophi vs. no tophi). Polynesian ancestry was separated into Western Polynesian (Tonga, Samoa, Niue, Tokelau) and Eastern Polynesian (Māori, Cook Island).

Results: Compared to participants without tophi, those with tophi were older, had an earlier age of gout onset, longer disease duration and higher serum creatinine, and were more likely to be of Māori or Pacific (Polynesian) ancestry. Participants with tophi also reported more frequent gout flares and higher use of colchicine, prednisone, non-steroidal anti-inflammatory drugs and urate lowering therapy. There was no difference in frequency of the minor (protective) allele for *SLC2A9 rs11942223* between the two groups (p=0.14, Table). In contrast, the risk alleles for both *ABCG2* SNPs were present more frequently in those with tophi (odds ratio (OR) 1.24 for *rs2231142* and 1.33 for *rs10011796,* p<0.05 for both). Analysis of *ABCG2* risk allele frequencies according to ancestry demonstrated that the effect of *rs2231142* was present only in participants of Māori or Pacific ancestry (OR 1.50, p=0.004), with the strongest effect in those of Western Polynesian ancestry (OR 1.71, p=0.017). The *rs10011796* risk allele was strongly associated with tophi in the Western Polynesian group (OR 3.76, p=0.002), but not in the Eastern Polynesian group (OR 0.87, p=0.60). The *ABCG2* associations persisted in the Western Polynesian group after adjusting for age, sex, highest recorded serum urate, serum creatinine, age of gout onset, disease duration, and when including both *ABCG2* variants in regression models.

Conclusion: Tophaceous gout is associated with prolonged disease duration and severe manifestations of disease. These data suggest that variation in ABCG2 function plays a role in development of tophaceous disease in some populations with high prevalence of severe gout.

Table. Allelic odds ratios [OR] for tophaceous disease according to ancestry

		All (n=1778)		Māori or Pacific ethnicity (n=851)		Non-Māori, Non-Pacific ethnicity (n=927)		Eastern Polynesian ancestry (n=464)		Western Polynesian ancestry (n=387)	
Genetic variant	Allele	Allelic OR [95% CI]	P	Allelic OR [95% CI]	P	Allelic OR [95% CI]	P	Allelic OR [95% CI]	P	Allelic OR [95% CI]	P
SLC2A9 rs11942223	Protective (C)	0.82 (0.63-1.07)	0.14	1.05 (0.82-1.35)	0.83	0.88 (0.64-1.22)	0.45	1.21 (0.85-2.13)	0.56	0.88 (0.35-2.21)	0.79
ABCG2 rs2231142	Risk (T)	1.24 (1.02-1.51)	0.033	1.50 (1.14-1.96)	0.004	0.97 (0.73-1.28)	0.80	1.28 (0.84-1.96)	0.25	1.71 (1.07-2.72)	0.017
ABCG2 rs10011796	Risk (T)	1.33 (1.01-1.74)	0.040	1.44 (0.94-2.20)	0.093	1.16 (0.81-1.66)	0.41	0.87 (0.52-1.46)	0.60	3.76 (1.63-8.77)	0.002

Disclosure: W. He, None; **A. Phipps-Green**, None; **L. K. Stamp**, None; **T. R. Merriman**, None; **N. Dalbeth**, None.

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Abstract Number: 3075

Mitochondrial Genetic Variation, Copy Number and Susceptibility to Gout in the New Zealand Polynesian Population

Tony R. Merriman[1], James Boocock[2], Nicola Dalbeth[3], Lisa K. Stamp[4], Eli A. Stahl[5], Hyon K. Choi[6], Elizabeth Matisoo-Smith[7] and Anna Gosling[8], [1]Biochemistry Dept, PO Box 56, University of Otago, Dunedin, New Zealand, [2]University of Otago, Dunedin, New Zealand, [3]University of Auckland, Auckland, New Zealand, [4]University of Otago, Christchurch, New Zealand, [5]Divisions of Rheumatology and Genetics, Brigham and Women's Hospital, Boston, MA, [6]Rheumatology, Allergy and Immunology, Massachusetts General Hospital and Harvard Medical School, Boston, MA, [7]Anatomy, University of Otago, Dunedin, New Zealand, [8]Biochemistry, University of Otago, Dunedin, New Zealand
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Background/Purpose: Mitochondria play a central role in induction of an NLRP3 inflammatory response essential for gouty pathology. Mitochondria are in part self-encoding, possessing a 16.5 kb genome which encodes 36 genes. The objective of this study was to test whether mitochondrial genetic variation and copy number could contribute to susceptibility to gout in New Zealand Polynesians. The Māori and Pacific (Polynesian) populations of New Zealand exhibit a high prevalence of gout (6 and 8%, respectively).

Methods: To test for association of mitochondrial genetic variation with gout 439 whole mitochondrial genomes from Māori and Pacific men with Polynesian maternal grandmothers (327 cases, 112 controls) were generated using Illumina MiSeq technology. Association of mtDNA copy number variation with gout was investigated by a relative read depth approach using high throughput sequence data from two independent data sets (whole genome sequencing (n=73) and resequencing of urate loci (n=385)). Quantitative PCR was undertaken for mtDNA copy number replication in an independent sample set of 632 Polynesian male and female cases and 579 controls. Association analyses were done using R v3.3.0 adjusting by age and proportion of Polynesian ancestry.

Results: Within Polynesia, there is relatively little mitochondrial genetic diversity, with around 96% of those sequenced belonging to the B4a1a and derived sub-lineages. A lineage-specific heteroplasmy in hypervariable region I was found to associate with a higher risk of gout (e.g. heteroplasmy at position 16179: OR 3.28, P = 0.009; heteroplasmy at position 16181: 3.86, $P = 9x10^{-5}$; heteroplasmy at position 16182: 3.43, P = 0.005). Relative to autosomal DNA an additional 10 mtDNA copies protected from gout in the whole genome sequence (OR=0.87, P=0.004) and resequence (OR=0.91, $P=3.3x10^{-4}$) sample sets, including when using asymptomatic hyperuricemic (urate > 0.40 mmol/L) control individuals (OR=0.81, P=0.004 and OR=0.90, P=0.002, respectively) (Table). To replicate, quantitative PCR of mtDNA from the 1211 gout cases and controls showed that with each unit decrease in ΔCt (which reflects an increase in mtDNA content), there was also a decrease in gout risk using asymptomatic hyperuricemic controls (OR=0.76, P = 0.03). However there was no significant association of increased mtDNA copy number with gout risk using all controls (OR=0.92, P=0.32).

Conclusion: It is unclear whether the reduced mtDNA copy number in gout is a consequence of the gouty pathology or whether the reduced mtDNA copy number causally contributes to the risk of gout. The latter possibility is supported by the consistent protection towards gout of increased mtDNA copy number using hyperuricemic controls, consistent with a role for mitochondria in monosodium urate crystal formation and/or the immune response. Alongside research showing that mitochondria play a central role in induction of the NLRP3 inflammasome, these genetic observations support a role for mitochondria in the etiology of gout.

	Cases/Controls	OR [95% CI]	P
Whole genome			
All controls	43/33	0.87 [0.79-0.95]	0.003
HU controls	43/18	0.81 [0.68-0.92]	0.004
Resequence			
All controls	162/249	0.91 [0.87-0.96]	0.00033
HU controls	162/53	0.90 [0.84-0.96]	0.002
Replication			
All controls	632/579	0.92 [0.76-1.09]	0.32
HU controls	632/168	0.76 [0.58-0.98]	0.03

Disclosure: T. R. Merriman, None; **J. Boocock**, None; **N. Dalbeth**, None; **L. K. Stamp**, None; **E. A. Stahl**, None; **H. K. Choi**, None; **E. Matisoo-Smith**, None; **A. Gosling**, None.

Abstract Number: 3076

Development of a Matrix-Binding Interlukin-1 Receptor Antagonist Fusion Protein for Extended Retention in the Joint Tissues

James Pancoast[1], Richard Lee[2,3] and **Parth Patwari**[1], [1]ProteoThera, Inc., Newton, MA, [2]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, [3]Department of Medicine, Division of Cardiovascular Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

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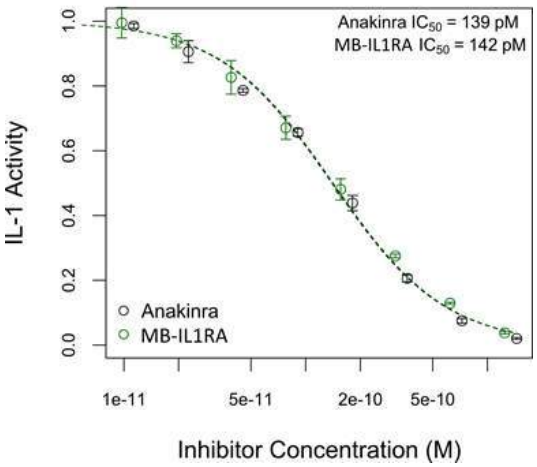
Background/Purpose: A primary challenge for intra-articular delivery of protein and peptide therapies has been their short residence time in the joint tissues. The IL-1 receptor antagonist (IL1RA) could be therapeutic for treating local joint inflammation in monoarticular gout flare, osteoarthritis flare, or post-ACL injury. However, it has been limited by its short half-life in the joint, and previous attempts to prolong its residence time have led to decreased potency. A novel strategy for tissue-targeted local delivery involves fusion of a matrix-binding domain that binds to charged proteoglycans within the extracellular matrix. We describe here the generation of a matrix-binding interleukin-1 receptor antagonist (MB-IL1RA) fusion without loss of activity.

Methods: The matrix binding peptide is 21 amino acid sequence derived from the heparin-binding domain of HB-EGF. The MB-IL1RA fusion protein was expressed in E. coli and purified to homogeneity. Activity was tested in a cell-based assay using IL-1 to stimulate an NF-kB-driven luciferase reporter. Retention in articular cartilage tissue was tested in newborn bovine cartilage tissue explants. After incubation of either anakinra or MB-IL1RA with the tissue, the cartilage was washed into medium with no drug and assayed via Western analysis for drug remaining in the tissue.

Results: The 50% inhibitory concentrations (IC50s) of MB-IL1RA and anakinra were determined in the NFkB reporter cells in the

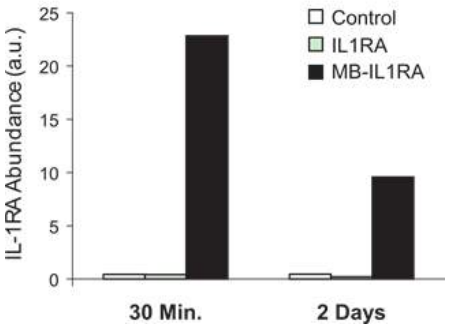
presence of 5 ng/ml interleukin-1β, yielding IC50s of 175 pM ± 23 pM for anakinra and 152 pM ± 26 pM for MB-IL1RA (mean of 9 experimental repeats; a representative run is shown in Figure 1).

FIGURE 1



After wash-out of bovine cartilage explant disks for 30 min., IL-1RA (anakinra) was undetectable in the tissue by Western analysis (densitometric analysis shown in Figure 2). In contrast, the MB-IL1RA fusion protein was robustly detectable within the tissue even after two days of wash-out in plain medium.

FIGURE 2



Conclusion: The novel therapeutic fusion protein MB-IL1RA allows delivery of an IL-1 inhibitor to the articular cartilage and extended residence time within the tissue, while retaining full potency of the inhibitor. MB-IL1RA is a candidate therapeutic for IA administration to treat local inflammation in the joint in acute flares of gout and OA.

Disclosure: J. Pancoast, ProteoThera, 3,ProteoThera, 1; **R. Lee**, ProteoThera, Inc., 1,ProteoThera, Inc., 5,ProteoThera, Inc., 6; **P. Patwari**, ProteoThera, Inc., 3,ProteoThera, Inc., 1.

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Abstract Number: 3077

Quiescence in Active and Inactive Non-Infectious, Intermediate, Posterior, or Panuveitis in Patients Treated with Adalimumab

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Background/Purpose: There is an unmet need for effective therapies for patients (pts) with non-infectious intermediate, posterior, or panuveitis who are at risk for long-term side effects from chronic corticosteroid use. The therapeutic goal in uveitis is to achieve quiescence and adalimumab (ADA) has been shown to lower uveitic flare or vision loss in pts with active (VISUAL I) and inactive (VISUAL II) uveitis[1,2]. As 40-50% of uveitis pts have accompanying extra-ocular rheumatic associations such as Behcet's disease, sarcoidosis, understanding ocular quiescence will not only aid ophthalmologists but also rheumatologists in the overall management of the pt[3]. The objective of this study is to assess the control of inflammation over time in pts treated with ADA in the VISUAL I and II trials.

Methods: Adults with non-infectious intermediate, posterior, or panuveitis were enrolled in 2 global phase 3, double-masked trials: VISUAL I (pts with active uveitis despite ≥2 weeks [wk] of prednisone [PS] 10–60 mg/d) and VISUAL II (pts with inactive disease dependent on 10–35 mg/d of PS to maintain inactivity). Pts were randomized 1:1 to receive placebo (PBO) or ADA (80 mg wk0, followed by 40mg every other wk from wk1 up to 80wks). In VISUAL I, all pts received a PS burst followed by taper to 0mg by wk15. In VISUAL II, PS taper to 0mg was mandatory by wk19. Quiescence as a pre-specified endpoint was defined as no new active inflammatory lesions and anterior chamber cell grade and vitreous haze grade ≤0.5+. Steroid free quiescence at each visit was additionally reported from wks16-52 for VISUAL I and from wk20- 52 for VISUAL II. Non-responder imputation was used for missing data. Statistical comparison between PBO and ADA was based on Chi-square test. Adverse events (AEs) were monitored.

Results: A greater proportion of pts in the ADA group than the PBO group achieved quiescence at each visit in both VISUAL I and VISUAL II. Statistical significance between ADA and PBO groups were observed at each visit from wks8-52 for VISUAL I, excluding wks 12 and from wks8-52, excluding wks12 and 32 for VISUAL II **(Fig. A,B)**.Similar results were observed for pts in steroid-free quiescence. Statistically significant differences between ADA and PBO groups occurred at each visit from wks20-52 for VISUAL I and from wks20-52, except wk32 for VISUAL II **(Fig. C,D)**.Safety data from the VISUAL I and II trials have previously been reported[1, 2]. Rates of AEs were similar between ADA and PBO groups.

Conclusion: Pts with non-infectious, intermediate, posterior, or panuveitis achieved significantly higher rates of quiescence and steroid-free quiescence with ADA treatment than PBO in the VISUAL I and II trials. The safety profile of ADA was consistent with the known safety profile across the approved ADA indications. **References:**

1) Nguyen et.al.Arthritis Rheumatol.2015; 67 (suppl10).

2) Jaffe et. al.Ann Rheum Dis.2015;74 (suppl 2): 849.

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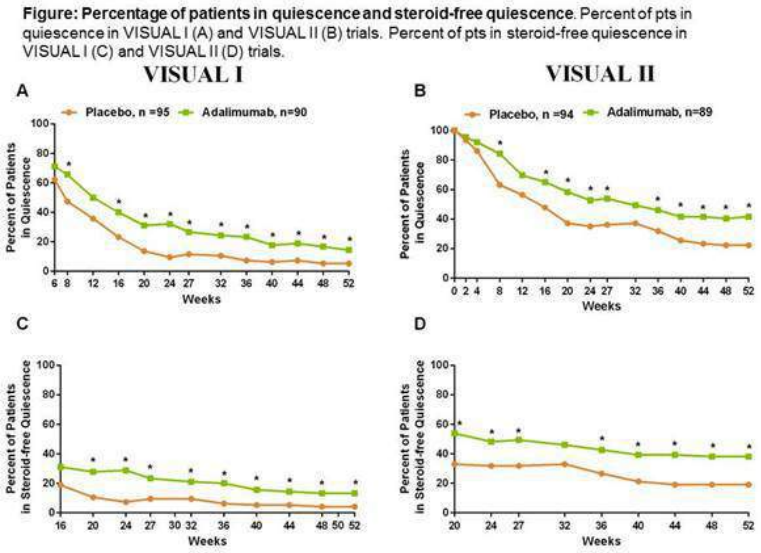

Figure: Percentage of patients in quiescence and steroid-free quiescence. Percent of pts in quiescence in VISUAL I (A) and VISUAL II (B) trials. Percent of pts in steroid-free quiescence in VISUAL I (C) and VISUAL II (D) trials.

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Abstract Number: 3078

Diffuse Idiopathic Skeletal Hyperostosis and Diabetes- Using Genetic Risk Scores to Explore the Association

Melissa Wang[1], Mariko Ishimori[2], Greg Kinney[3], Irina Ianculsecu[1], Elizabeth Regan[4], Michael Weisman[5] and Mark Goodarzi[6], [1]Cedars-Sinai Medical Center, Los Angeles, CA, [2]Rheumatology, Cedars-Sinai Medical Center, Los Angeles, CA, [3]Department of Epidemiology, Colorado School of Public Health, Aurora, CO, [4]Medicine, National Jewish Health, Denver, CO, [5]Rheumatology, Cedars-Sinai Medical Center, West Hollywood, CA, [6]Division of Endocrinology, Cedars-Sinai Medical Center, Los Angeles, CA
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Background/Purpose: Diffuse Idiopathic Skeletal Hyperostosis (DISH) is a poorly understood condition characterized by new bone formation mainly affecting the spine. An association of DISH with Type 2 DM (T2D) has been reported for years, but whether the relationship is genetic is unknown. To investigate whether genetic loci for T2D and related quantitative traits play a role in DISH pathogenesis, we constructed genetic risk scores (GRSs) for T2D, fasting insulin, and fasting glucose to assess the association of these GRSs with DISH.

Methods: A convenience sample of 3,117 patients from the COPDGene Study was used to investigate the association between T2D

and DISH. COPDGene is a multicenter study that enrolled 10,129 smokers between 2008-2011 to define subtypes of smoking related lung disease and their genetic associations. HRCT of the chest, DNA, medical history, and diabetes status (self-report or taking antidiabetic medications) were obtained. Two readers visually scored spine imaging on HRCT for DISH, based on Resnick criteria. Genotyping was performed using the Illumina Omni-Express Chip. An 83 SNP T2D GRS, a 43 SNP fasting glucose GRS, and a 22 SNP fasting insulin GRS based on validated GWAS loci, alone and in combination, were calculated. In the combined GRS, each SNP was used once. Univariate analyses between age, sex, race, BMI and DISH were performed. A logistic regression model adjusted for age, sex, race, and BMI was used to estimate the association of each GRS with DISH.

Results: We analyzed 437 DISH cases and 2,680 controls among men and women in the COPDGene study who had available HRCTs of the chest. See Table 1 for odds ratios (OR) for the univariate and multivariate models. In the univariate analysis, DISH was associated with male sex, increasing age, and the T2D phenotype (Table 1). The T2D GRS was associated with diabetes (OR 1.05, 95% CI 1.03-1.07, P<0.0001). None of the four GRSs tested (T2D, fasting insulin, fasting glucose, combination) were associated with DISH (Table 1).

Table 1. Association between DISH, clinical features and GRSs

Variable	Odds Ratio	Adjusted* Odds Ratio	Confidence* Interval	P-value for adjusted model*
Age (years)	1.06	1.07	1.06-1.08	<0.0001
Sex (male)	2.96	3.51	2.73-4.50	<0.0001
Race (non-Hispanic White)	1.52	.94	0.72-1.24	<0.0001
BMI (kg/m^2)	1.09	1.12	1.10-1.14	<0.0001
Diabetes status	2.64	1.49	1.13-2.0	0.005
T2D GRS	0.99	0.99	0.97-1.01	P=0.44
Fasting glucose GRS	0.98	1.01	0.98-1.04	P=0.51
Fasting insulin GRS	1.01	1.00	0.96-1.04	P=0.85
Combined GRS	0.99	1.00	0.98-1.02	P=0.96

***Adjusted for age, gender, race, BMI**

Conclusion: This is the first study to use GRS to examine the link between DISH and diabetes related traits. T2D genes are not associated with DISH despite a correlation to T2D, arguing against a genetic relationship. The previously reported associations of DISH with T2D may be due to the effects of increased levels of circulating proteins produced in diabetics, such as insulin and osteocalcin, on the bone formation pathway. The role of smoking remains to be explored. Further studies are warranted to better elucidate the mechanisms that associate diabetes with DISH.

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Abstract Number: 3079

The Characteristic Features of the Patients with Deficiency of Adenosine Deaminase 2 (DADA2)

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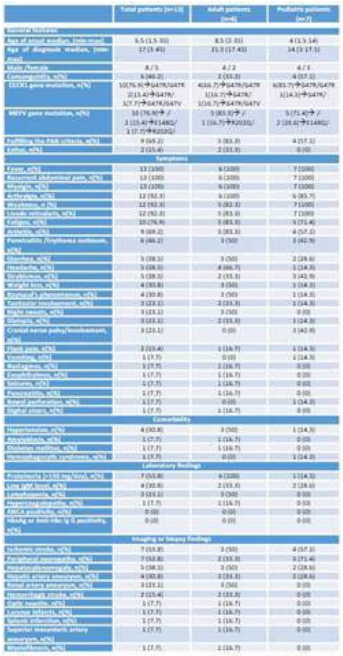
Background/Purpose: Deficiency of adenosine deaminase 2 (DADA2) is an autosomal recessive autoinflammatory disease resulting from a loss-of-function mutation in Cat Eye Syndrome Chromosome Region Candidate 1 (*CERC1)* gene encoding for ADA2 protein. Patients present with systemic inflammation and vasculopathy. In this study, we presented the characteristics of the pediatric and adult DADA2 cases.

Methods: Clinical and laboratory features of thirteen DADA2 patients (8 Male, 5 Female), diagnosed at Hacettepe University Pediatric and Adult Rheumatology Department between 2014-2016, have been summarized. Mutations in *CECR1* were detected by Sanger sequencing.

Results: Ten patients were homozygous for G47R; one was compound heterozygous for G47R and G47V while two patients were heterozygous for G47R mutation. Nine patients had been followed up with the diagnosis of polyarteritis nodosa (PAN). There was consanguinity in 6 cases, and 2 were siblings. The median (min-max) age at onset of the symptoms and diagnosis was 6.5 (1.5-35) and 17 (3-45) years, respectively. All patients suffered from recurrent episodes of fever and abdominal pain with elevated acute phase reactants. Livedo reticularis (n= 12, (92.3%)), erythema nodosum (n=6, (46.2%)), raynaud's phenomenon (n=4, (30.8%)) and digital ulcers (n=1, (7.7%)) were common skin manifestations. Neurological and musculoskeletal involvement was; in the form of myalgia (n = 13, (100%)), arthralgia (n= 12, (92.3%)), arthritis (n= 9, (69.2%)), peripheral neuropathy (n=7, (53.8%)), ischemic stroke (n=7, (53.8%)), strabismus (n=5, (38.5%)), hemorrhagic stroke (n=2, (15.4%)), spinal cord atrophy (n = 1, (7.7%)), and optic neuritis (n = 1, (7.7%)) . One patient had been diagnosed with core myopathy through co-incidental muscle biopsy finding. Eight patients had aneurysms in medium-sized abdominal visceral arteries (hepatic artery, renal artery, and superior mesenteric artery). As renal involvement, one patient had focal segmental glomerulosclerosis (collapsing variant), one mesangial proliferative glomerulonephritis, and one had renal amyloidosis. There was testicular involvement in 3 (23.1%) patients and one had testicular torsion. One patient had intestinal perforation. Two adult patients died soon after diagnosis of DADA2. One patient was asymptomatic on only colchicine for almost 10 years. Rest of the patients responded well to etanercept therapy.

Conclusion: ADA2 deficiency is a recently defined disease and the data about its phenotype increases with the introduction of new cases with different symptoms. Stroke, peripheral neuropathy, livedo reticularis, myalgia, recurrent episodes of fever and recurrent abdominal pain are important findings to suspect DADA2. In our series, we have described for the first time spinal cord atrophy, core myopathy, and mesangial proliferative glomerulonephritis in DADA2 patients.



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Rheumatologic Consequences of Immunotherapy to Treat Malignancies: The Tip of an Iceberg

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Rheumatologic Consequences of Immunotherapy to Treat Malignancies: The Tip of an Iceberg

Background/Purpose: Immune checkpoint inhibitors (ICIs) targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed cell death protein 1 (PD-1) pathways are increasingly used to treat multiple malignancies and prolong survival. By activating T-cells, ICIs also cause immune-related adverse events (IRAEs). Rheumatic IRAEs are not well described. We report our initial experiences with ICI-induced inflammatory arthritis, crystalline arthritis and sicca syndrome.

Methods: We report patients seen in Johns Hopkins Rheumatology clinics from 2012-2016 with new rheumatic symptoms during or following treatment with anti-CTLA-4 and/or anti-PD-1 therapy for solid tumors.

Results: We identified 17 patients receiving selected ICIs and developing rheumatic IRAEs (table 1). Mean age was 59.5 years. Cancer types included melanoma, non-small cell lung cancer, small cell lung cancer, colon cancer and renal cell carcinoma. ICI regimens included anti-PD-1 or anti-CTLA-4 monotherapy (n=8) or combination therapy (n=9). Eleven of 17 patients developed 3 subtypes of inflammatory arthritis (RA-like symmetrical polyarthritis, reactive arthritis, oligoarticular large joint arthritis); and 5/5 with arthrocentesis had inflammatory synovial fluid (WBC range 9854-28,400 cells/mm^3, >70% PMNs); 5 had confirmatory imaging (3 ultrasound, 1 MRI, 1 CT). RF and CCP were negative in these arthritis patients. Two patients developed new pseudogout or gout confirmed by joint aspiration or dual energy CT. Four patients developed severe sicca with marked salivary hypofunction. Non-rheumatic IRAEs experienced included: pneumonitis, colitis, interstitial nephritis, hypophysitis and thyroiditis. ANAs were positive in 6/17. Corticosteroids were given to 9/11 patients with inflammatory arthritis, several requiring prednisone >1 mg/kg. Three patients required methotrexate and anti-TNF therapy for inflammatory arthritis.

Conclusion: This is the largest series to our knowledge of inflammatory arthritis and the first report of sicca syndrome and crystalline arthritis due to ICIs. These rheumatic IRAEs cause severe symptoms, and arthritis may require significantly higher doses of steroids for management than for usual inflammatory arthritis. As ICIs are increasingly used for a range of malignancies, new cases of rheumatic IRAEs will likely emerge, and rheumatology referrals will increase. Further research is needed to understand mechanisms, determine risks, and develop management algorithms. Table 1: Demographic features, cancer types, and immunotherapy of included patients.

Patient	Age	Sex	Race	Type of malignancy	Cancer therapy	Rheumatic IRAE	Best overall response (RECIST 1.1)
1	58	Male	Caucasian	Renal cell carcinoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
2	46	Female	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
3	62	Male	African American	NSCLC	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
4	35	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Stable disease
5	56	Male	Caucasian	NSCLC	Anti-PD-1	Inflammatory arthritis	Stable disease
6	66	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
7	57	Male	Caucasian	Small cell lung cancer	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
8	42	Male	Caucasian	NSCLC	Anti-PD-1 Anti-CTLA-4	Inflammatory arthritis	Partial response
9	75	Female	Caucasian	NSCLC	Anti-PD-1	Inflammatory arthritis	Partial response
10	60	Female	Caucasian	NSCLC	Anti-PD-1	Inflammatory arthritis	Not measured*
11	55	Female	Caucasian	Colon cancer	Anti-PD-1	Inflammatory arthritis	Stable disease
12	61	Male	Caucasian	NSCLC	Anti-PD-1	Sicca syndrome	Stable disease
13	57	Male	Caucasian	Melanoma	Anti-PD-1 Anti-CTLA-4	Sicca syndrome	Progressive disease
14	74	Male	Caucasian	Melanoma	Anti-CTLA-4	Sicca syndrome	Partial response
15	74	Female	Caucasian	Melanoma	Anti-PD-1	Sicca syndrome	Tumor regression observed on clinical exam
16	71	Male	African American	NSCLC	Anti-PD-1	Crystalline arthritis	Complete response
17	62	Male	Caucasian	Melanoma	Anti-PD-1 CD137 agonist	Crystalline arthritis	Complete response
*: Not measured at time of submission due to limited amount of time on treatment.							

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Abstract Number: 3081

Prognostic Factors of Death in a Cohort of 116 Adults with Hemophagocytic

Syndrome: Impact of Underlying Disease and Laboratory Parameters

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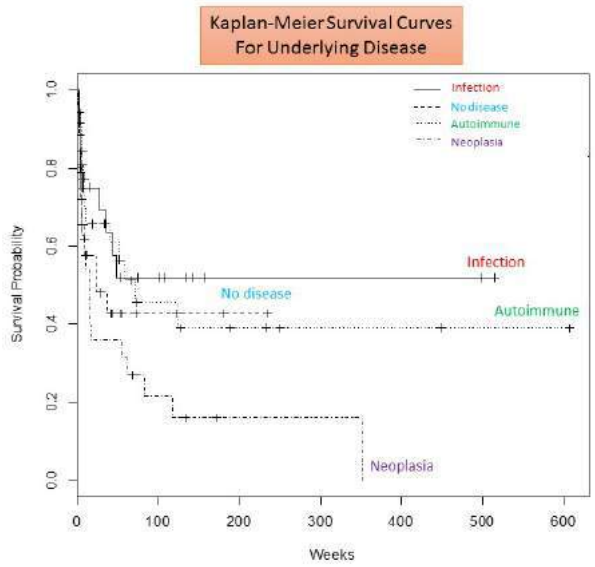
Background/Purpose: To analyze the potential use of the main features at diagnosis (epidemiological, clinical, laboratory) as prognostic factors and to estimate the risk of death in adult patients with hemophagocytic syndrome (HS).

Methods: In June 2013, the Spanish Autoimmune Diseases Study Group (GEAS-SEMI) created a national registry (REGHEM) of adult patients with HS. Patients were diagnosed according to fulfillment of the criteria of the Histiocytosis Society proposed in 1991 and updated in 2004. The HScore, a prognostic score, which includes 9 clinical, laboratory and histopathological features and ranges from 0 to a maximum of 337 points, was calculated at diagnosis. Time-to-event analyses for death are presented as Kaplan-Meier curves.

Results: By January 2016, the REGHEM registry included 116 adult patients with HS, 68 (59%) men and 48 (41%) women, with a mean age at diagnosis of 49 years (range 14-84 years); 19 (16%) were not born in Spain. The main underlying diseases were chronic infections in 20 (17%) cases, autoimmune/rheumatologic disease in 33 (28%), neoplasia in 23 (22%) and transplantation in 4 (3%); the remaining 36 (31%) patients had no identifiable underlying disease. Sixty-one (53%) patients died. Patients who died were more frequently male (69% vs. 47% in survivors, p=0.03), had a higher mean value of serum ferritin (6662 vs. 3570 ng/mL, p=0.028), a lower mean hemoglobin value (7.6 vs. 8.3 g/dL, p=0.021), a lower mean white blood cell count (1570 vs. 2450 $x10^6$/L, p=0.022), a lower mean platelet count (24000 vs. 66000 $x10^6$/L, p<0.001), and a higher mean HScore compared with survivors (230 vs. 205, p=0.05). Survival Kaplan-Meier curves (**Figure 1**) showed that the highest survival rate was in patients with underlying chronic infections while the poorest survival was found in patients with underlying neoplasia (HR 2.41, 95% CI 1.09-5.3).

Conclusion: Hemophagocytic syndrome is a multisystemic disease that remains fatal in > 50% of adults. Survival was significantly reduced in males, and in patients with underlying neoplasia, high ferritin values, severe cytopenias and high HScores. These prognostic factors could help identify patients at greater risk of death, who could benefit from more aggressive specific treatment of

potential triggers and intensive supportive care.



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Abstract Number: 3082

Macrophage Activation Syndrome Is Identified By Coagulopathy, Hyperferritinemia, Fever, and Cytopenia in Hospitalized Patients, Resulting in Poor Outcome

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Background/Purpose: Macrophage activation syndrome (MAS) constitutes over 5% of multi-organ dysfunction syndrome in adults, leading to 60-70% mortality without early treatment. H-Score, the only validated diagnostic tool in adults, is often too complex for bedside use. Our objective was to determine clinical predictors of MAS and build a simple yet accurate risk calculator for use by clinicians to facilitate early recognition.

Methods: Electronic Health Records were used to identify patients hospitalized at a single academic center between 2009-12 with

serum ferritin levels (SFL) of ≥ 2,000 ng/dL. Patients with chronic hemolytic disorders and those receiving chronic transfusions were excluded. Diagnosis of MAS was determined using a) ≥ 5/8 of HLH-2004 or ≥4/5 of adapted HLH-2004 criteria, or b) H score of ≥169, or c) treatment modified specifically for MAS. Control patients met none of these criteria. Organ Dysfunction and INfection (ODIN) definitions determined presence of organ dysfunction. Coagulopathy was determined based on score of ≥4 on "International Society of Thrombosis and Hemostasis Diagnostic Algorithm". Hepatobiliary dysfunction was defined as ≥2 of: ALP, ALT, AST elevation more than 3 times normal limits, or bilirubin ≥ 5.8 mg/dL (sepsis definitions). The optimum SFL cut point was identified based on prediction accuracy for MAS at various thresholds. Following standard univariate analysis, logistic regression determined independent predictors of MAS. Parameter estimates were used for a weighted risk score for MAS.

Results: Of the 527 hyperferritinemic patients identified, 67 MAS cases [70% women, 60% non-white, median age 41 (18-83)] were identified; 69 controls with similar demographics were selected from remaining patients [67% women, 60% non-white, median age 42 (19-84)]. Univariate analysis of clinical and outcome parameters associated with presence of MAS is presented in Table-1. A SFL cut-off of 5,000ng/dL had maximal accuracy predicting MAS. Independent predictors of MAS were coagulopathy, hematologic dysfunction, SFL≥ 5,000 ng/dL, and fever≥ 101.3° F. Using a simple count of signs positive, MAS incidence was 0% (0/19) in patients with 0 signs positive versus 93% (27/29) in patients with 4 signs positive ($p<.0001$).

Conclusion: MAS increases the need for critical care admission and intervention. Presence of 3 of: coagulopathy, SFL≥ 5,000, cytopenia, or fever≥ 101.3° F should alert the clinicians to the possibility of MAS in hospitalized patients.

Table 1. MAS is significantly associated with higher likelihood of fever, elevated ferritin level, organomegaly, and organ dysfunction, as well as higher probability of death, prolonged hospitalization, and higher need for critical interventions.

	MAS **N= 67**	**non-MAS** **N= 69**	***p* value***
Median Age (Range)	41 (18-83)	42 (19-84)	0.9999
Male Gender N (%)	20 (30)	23 (33)	0.7144
Non-White N (%)	27 (40)	28 (40)	1.000
Mean Ferritin (95% CI)	28,891 14,319-43,462	6,140 (3,973-8,307)	**0,0022**
Hematologic N (%)	55 (82)	39 (57)	**0.0015**
Hepatobiliary N (%)	48 (72)	32 (46)	**0.0032**
DIC N (%)	45 (67)	16 (23)	**<0.0001**
CNS N (%)	39 (58)	25 (36)	**0.0158**
Infection N (%)	48 (72)	32 (46)	**0.0032**
Renal N (%)	31 (46)	29 (42)	0.73
Respiratory N (%)	34 (51)	21 (30)	**0.0228**
CVS N (%)	41 (61)	29 (42)	**0.0274**
Fever ° (SD)	102.9 (1.9)	100.6 (1.8)	**0.0001**
Triglyceride: mg/dL (SD)	N= 59; 295(184)	N= 15; 166 (98)	**0.0108**
Hepatomegaly N (%)	35 (52)	20 (29)	**0.0085**
Splenomegaly N (%)	20 (30)	5 (7)	**0.0008**
CRP mg/dL (SD)	N=40; 159 (118)	N=11; 142 (114)	0.6719
ESR mmHg/Hr (SD)	N=44; 33 (49)	N=10; 37 (21)	0.8024
Immune-suppressed N (%)	37 (55)	20 (29)	**0.0030**
Dead	31 (46)	16 (23)	**0.0066**
Treated for MAS	36 (54)	0 (0)	na
Length of Hospital Stay Mean (SD) Median (Range)	34.8 (36); 25 (3-178)	12.3 (14.2); 9 (2-105)	**0.0001**
Critical Care Admission N (%)	48 (72)	29 (42)	**0.0006**
Mechanical Ventilation N (%)	40 (60)	19 (28)	**0.0002**
Vasopressor Use	36 (54)	22 (32)	**0.0149**
Renal Replacement Therapy (new)	29 (43)	10 (14)	**0.0003**

* *p*value is set at 0.05 MAS: macrophage activation syndrome; CI: confidence interval; SD: standard deviation; DIC: disseminated intravascular coagulation; CNS: central nervous system; CVS: cardiovascular system; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

Table 2: High ferritin, fever, coagulopathy, and cytopenia are independent predictors of MAS with equal weight.			
Predictor	**Parameter Estimate (SE)**	**Odds Ratio (95% CI)**	***p* value***
Ferritin > 5000	0.78 (.28)	4.75 (1.60-14.11)	**.0051**
Fever > 101.3	1.16 (.32)	10.26 (2.95-35.74)	**.0003**
Hematology	0.81 (.32)	5.05 (1.45-17.55)	**.011**
DIC	0.88 (.27)	5.77 (1.99-16.70)	**.0012**
Infection	0.48 (.29)	2.64 (0.85-8.19)	.09
Renal	0.50 (.30)	2.72 (0.83-8.89)	.098
* *p*value is set at 0.05 MAS: macrophage activation syndrome; CI: confidence interval; DIC: disseminated intravascular coagulation			

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Abstract Number: 3083

Utility of Patient-Reported Outcomes Measurement Information System (PROMIS) 29 Short Form for Understanding Interplay Between Patient-Reported Outcome Measures and Physician Driven Disease Activity Measures

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Discordance between patient and physician assessment of rheumatoid arthritis (RA) disease activity strongly associates with pain scores. Patient-reported outcomes measurement information system (PROMIS) 29 is recommended as the preferred battery of measures to collect in musculoskeletal pain studies. We evaluated the discordance between Routine Assessment of Patient Index 3 (RAPID3) and Clinical Disease Activity Index (CDAI) and investigated the associations between RA activity measures, discordance and patient-reported outcome measures using PROMIS29.

Methods: For RA subjects enrolled in the University of Pittsburgh Rheumatoid Arthritis Comparative Effectiveness Registry (RACER), a cross-sectional analysis was performed for all RACER patients who completed PROMIS29 short form and had RAPID3 and CDAI recorded. Association between CDAI and RAPID3 was evaluated by the percentage of agreement, Pearson¡¯s correlation coefficient, and kappa statistics. For subjects in remission/low disease activity by CDAI who had RAPID3 scores (0-10) consistent with near remission or low disease activity (¡Â 2) versus moderate or high disease activity (>2), predictors were

determined using logistic regression.

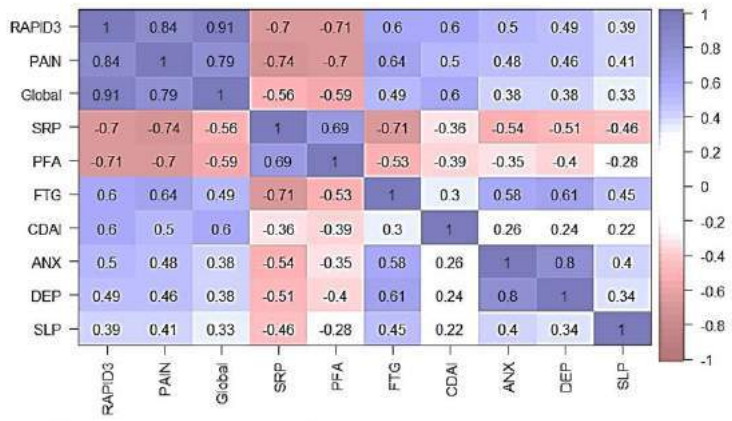
Results: For the 363 subjects analyzed, age was 64.2 +/- 13.8 (mean +/- SD) years with disease duration of 13.9 +/- 13.1 years. CDAI was moderately correlated with RAPID3 (r=0.60, p<0.0001). PROMIS domains were correlated with RAPID3 and CDAI with various degrees (Figure). RAPID3 had strongest correlation with pain intensity (r = 0.89, p<0.001) and pain interference (r=0.84, p<0.001). Overall agreement between disease severity categories of CDAI and RAPID3 were fair (percent agreement = 40.1, kappa=0.21) (Table). In subjects with remission to low disease activity by CDAI, pain intensity (standardized regression coefficient beta = 1.33, p<0.001) and physical function (beta = -0.21, p<0.001) among PROMIS29 domains predicted discrepancies between CDAI and RAPID (Akaike information criterion (AIC) =110.2). When pain intensity and physical function were removed from the model, pain interference (beta = 0.18, p<0.001 and impaired social roles (beta = -0.11, p=0.001) predicted discrepancies (AIC = 168.9).

Conclusion: Discordance between CDAI and RAPID3 was frequent, especially among subjects with remission/low disease activity by CDAI. These subjects were predicted by PROMIS29 measures associated with pain intensity. Our data suggest that PROMIS29 helps to understand the discordance between patient and physician assessment of disease activity.

Table. Disease activity categories by Routine Assessment of Patient Index 3 (RAPID3) and Clinical Disease Activity Index (CDAI)

	CDAI			
RAPID3	Remission	Low	Moderate	High
Near remission	**35**	16	3	0
Low	13	**27**	7	0
Moderate	12	59	**43**	4
High	0	43	63	**33**

Figure. Correlation among PROMIS29 domains, RAPID3, and CDAI



RAPID3: Routine Assessment of Patient Index, CDAI: Clinical Disease Activity Index, PAIN: pain interference, Global: pain intensity, SRP: abilities to participate in social roles and activities, PFA: physical function, FTG: fatigue, ANX: anxiety, DEP: depression, SLP: sleep disturbance

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Abstract Number: 3084

The Impact of Mental Health on Indicators of Disease Severity Among Patients with Inflammatory Arthritis: A Cross-Sectional and Longitudinal Investigation

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Background/Purpose: Rheumatoid arthritis, is the leading cause of disability and chronic pain. Psychiatric disorders such as depression and anxiety adversely impact reported pain and may also be influenced by systemic inflammation. We conducted a comprehensive, longitudinal investigation to assess the association of depressive and anxiety disorders, including severity of symptoms, with subjective and physician-assessed indicators of arthritis severity among outpatients with recent onset inflammatory arthritis.

Methods: Data included 148 subjects (mean age = 57.7, 72% female) from a prospective longitudinal Early Arthritis Cohort (<12 months symptoms at baseline) from 2012 to 2015. Presence of anxiety or depressive disorder was indicated via self-report annually, and severity of psychiatric symptoms was assessed using the Patient Reported Outcomes Measurement Information System (PROMIS) scales each visit. Arthritis activity indicators included patient reported visual analogue scales for pain fatigue, and functional status (modified health assessment questionnaire; mHAQ), physician global disease activity, swollen 28 joint count, tender 28 joint count, Lansbury weighted joint count, erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), and composite indices (DAS28ESR-3variable, Clinical Disease Activity Index (CDAI)). Patients were re-assessed at each visit (visit range = 1 thru 7 visits, median (IQR) months followed 18(11,22)). Linear regressions and bivariate and partial correlations (controlling for number of visits and presence of a current mood or anxiety disorder for symptom-based analyses) first examined the cross-sectional relationship between mental health variables and indicators of arthritis severity. Linear regressions controlling for number of visits examined the longitudinal relationship between change in mental health symptoms on indicators of arthritis severity. Only results significant at the 0.01 level are reported to adjust for multiple comparisons.

Results: The presence of a current mood or anxiety disorder was reported by 10.7% and 6.3%, respectively, of the cohort at any time. Fatigue was associated with both a mood disorder (*Beta* = 0.27, t (202) = 4.025, $p < 0.001$) and anxiety disorder (*Beta* = 0.197, t (197) = 2.814, $p < 0.01$). Increasing severity of anxiety and depressive symptoms were significantly associated with pain, fatigue, CDAI, tender joint count, mHAQ and the Lansbury index (r range = 0.156-0.514). Severity of depressive symptoms were associated with ESR, DAS28 and CRP. When controlling for the presence of a mood or anxiety disorder and number of visits, most associations remained statistically significant. Worsening of anxiety (*Beta* = 0.212, t (314) = 3.85, $p < 0.001$) and depressive symptoms (*Beta* = 0.207, t (314) = 3.75, $p< 0.001$) over time were significantly associated with CRP values.

Conclusion: Indicators of disease severity were impacted by mental health factors, particularly severity of chronic pain and fatigue. Severity of mental health symptoms were a better indicator of disease severity than the presence of a psychiatric disorder alone. These findings have important implications for screening, prevention, and treatment.

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Abstract Number: 3085

Do Depression and Anxiety Reduce the Chance of Remission in Rheumatoid Arthritis and Psoriatic Arthritis?

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Background/Purpose: Depression and anxiety are reported to predict poorer treatment outcomes in rheumatoid arthritis (RA).[1] Whether this can be confirmed in larger, prospective studies as well as in psoriatic arthritis (PsA) remains to be explored. In this study we aimed to assess if baseline depression/ anxiety is associated with remission rates in RA and PsA.

Methods: From the prospective, multicenter NOR-DMARD study we included RA and PsA patients starting first-time tumor necrosis factor inhibitors (TNFi) and DMARD naïve patients starting methotrexate between 2006 and 2012. Depression/anxiety was assessed using the EuroQoL (EQ5D) question 5. The predictive value of baseline moderate/extreme depression/anxiety (present/absent) on remission after 3 and 6 months treatment was explored in prespecified logistic regression models adjusted for age, sex, disease duration and smoking.

Results: A total of 1450 RA/ 805 PsA patients were included (mean (SD) age 54.4 (13.5)/ 48.0 (12.4) years, median (25^{th}-75^{th} percentile) disease duration 0.4 (0.0-5.0)/ 1.0 (0.1-6.8) years, 68.7/ 50.7% females and 28.6/ 28.6% current smokers). Similar percentages of RA and PsA patients reported to be moderately (40.7 vs. 40.7%)/ extremely (2.8 vs. 3.0%) depressed/ anxious at baseline (p=0.98). Baseline depression/ anxiety negatively predicted DAS28<2.6, SDAI≤3.3 and ACR/EULAR Boolean remission after 3 and 6 months treatment in RA (table 1). Corresponding findings in PsA were less consistent (table 2). In subgroup analyses of TNFi and methotrexate treated patients depression/ anxiety was found to be negatively predictive of remission at 6 months in RA, but not in PsA (table 1-2). **Table 1**

		Odds ratio (95%CI) for remission when depressed/ anxious at baseline (logistic regression analyses)		
		All RA patients	**RA patients treated with TNFi with or without methotrexate**	**DMARD naïve RA patients treated with methotrexate**
After 3 months	**DAS28ESR < 2.6**	0.65 (0.48-0.86) p=0.003	0.42 (0.26-0.67) p<0.001	0.84 (0.57-1.23) p=0.36
	SDAI ≤ 3.3	0.62 (0.43-0.88) p=0.008	0.75 (0.44-1.26) p=0.28	0.51 (0.31-0.83) p=0.007
	ACR/EULAR Boolean	0.53 (0.35-0.79) p=0.002	0.83 (0.46-1.49) p=0.53	0.33 (0.18-0.61) p<0.001
After 6 months	**DAS28ESR < 2.6**	0.50 (0.36-0.67) p<0.001	0.48 (0.30-0.78) p=0.003	0.50 (0.33-0.75) p=0.001
	SDAI ≤ 3.3	0.46 (0.32-0.65) p<0.001	0.48 (0.28-0.81) p=0.007	0.43 (0.27-0.68) p<0.001
	ACR/EULAR Boolean	0.43 (0.29-0.64) p<0.001	0.51 (0.29-0.92) p=0.03	0.36 (0.21-0.61) p<0.001

Table 2

		Odds ratio (95%CI) for remission when depressed/ anxious at baseline (logistic regression analyses)		
		All PsA patients	PsA patients treated with TNFi with or without methotrexate	DMARD naïve PsA patients treated with methotrexate
After 3 months	DAS28ESR < 2.6	0.73 (0.49-1.1) p=0.13	0.79 (0.42-1.48) p=0.46	0.67 (0.38-1.18) p=0.16
	SDAI ≤ 3.3	0.62 (0.39-0.97) p=0.04	0.61, (0.34-1.11) p=0.11	0.58 (0.27-1.22) p=0.15
	ACR/EULAR Boolean	0.52 (0.31-0.86) p=0.01	0.43 (0.22-0.85) p=0.02	0.64 (0.28-1.44) p=0.28
	DAPSA < 4	0.45 (0.28-0.72) p=0.001	0.44 (0.23-0.81) p=0.009	0.45 (0.21-0.95) p=0.04
After 6 months	DAS28ESR < 2.6	0.92 (0.60-1.41) p=0.69	0.93 (0.47-1.85) p=0.85	0.93 (0.52-1.65) p=0.80
	SDAI ≤ 3.3	0.69 (0.44-1.08) p=0.11	0.65 (0.33-1.27) p=0.21	0.81 (0.43-1.50) p=0.50
	ACR/EULAR Boolean	0.63 (0.39-1.03) p=0.07	0.81 (0.40-1.64) p=0.56	0.53 (0.26-1.05) p=0.07
	DAPSA < 4	0.66 (0.42-1.03) p=0.07	0.69 (0.36-1.34) p=0.28	0.67 (0.36-1.26) p=0.21

Conclusion: Baseline depression/ anxiety may reduce likelihood of remission in RA. Whether this also is the case in PsA needs to be explored in larger patient samples and using validated remission criteria. Depression and anxiety are factors with potential impact for disease outcome and should be considered in routine care and in treat-to-target strategies. 1 Matcham F, Norton S, Scott DL, et al. Symptoms of depression and anxiety predict treatment response and long-term physical health outcomes in rheumatoid arthritis: secondary analysis of a randomized controlled trial. *Rheumatology (Oxford)* 2016;55:268-78.

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Abstract Number: 3086

Changing Patterns over Time in Opiate Use in U.S. Rheumatoid Arthritis Patients

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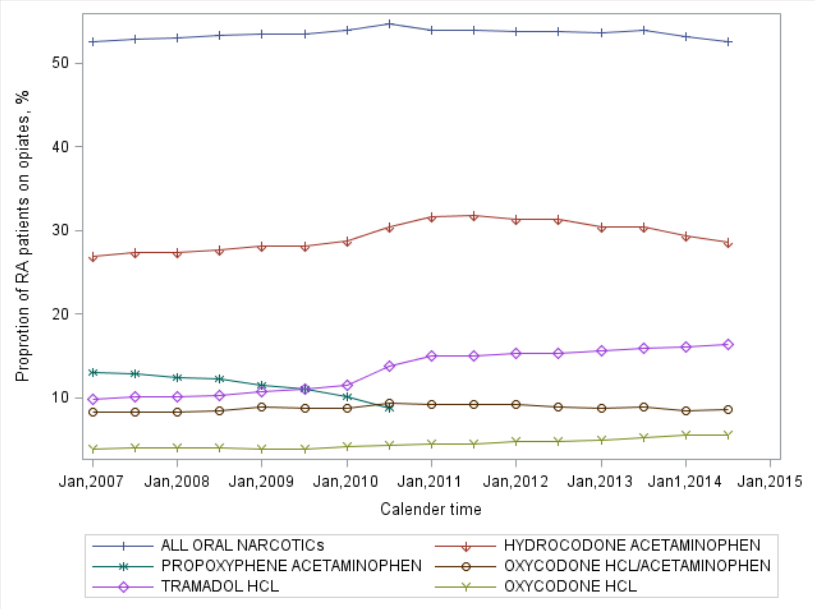
Background/Purpose: Opiate use has come under increasing scrutiny related both to over-use and under-use. The patterns of opiate use over time in a population-based cohort of patients with inflammatory diseases such as rheumatoid arthritis (RA) have not been well characterized. We used health plan data to characterize both trends over time as well as variability in individual physician prescribing of short and long term opiates.

Methods: We used national Medicare data from 2006-2014 and identified a closed cohort of RA patients by requiring two diagnosis codes (ICD9 714.0, 714.2, 714.81) from rheumatologists separated by 7 days. To be included in the analysis, patients must have at least 6 consecutive observable months (enrolled in Medicare Part A, Part B and Part D coverage, not enrolled in Part C) prior to 1/1/2007. Follow up started at 1/1/2007 and end at the earliest of: dis-enrollment, 90 days before death, or end of study (12/31/2014). Any oral opiates use (one or more filled prescriptions) was assessed every six months for patients who remained under follow-up over the entirety of each 6 month interval. Generalized estimating equations with repeated measure was used to calculate odds ratios for the receipt of opiates in each 6 month interval. A separate cohort was created using 2014 Medicare data to assess the variability in prescribing opiates among rheumatologists for their RA patients (assigned based on at least one physician encounter in 2014 with an RA diagnosis code). We restricted this analysis to rheumatologists with at least 10 RA patients enrolled in Medicare for the entire year. The proportion of RA patients using opiates was calculated by dividing RA patients with at least two opiate prescriptions in 2014 by the total number of RA patients treated by each U.S. rheumatologist.

Results: For the longitudinal analysis, we identified 73,834 RA patients meeting eligibility criteria. Patient characteristics were (mean age 67.6 (12.2), 80.0% Female, 80.1% White, 12.3% Black). In 2006, the most commonly used opiates were medications that combined acetaminophen with hydrocodone or with propoxyphene (withdrawn from U.S. in 2010). Over 2006-2014, trends (Figure) showed overall opiate use increased slowly but significantly and reach a peak in 2010, and decreased thereafter. Following the withdrawal of propoxyphene in 2010, use of hydrocodone and tramadol increased commensurately such that overall opiate use declined only slightly. Factors associated with opiate use included younger age, female, white race, disability, lower income and baseline NSAID use. In 2014, practice-level variability between U.S. rheumatologists (n=4,900) in the use of opiates for their RA patients was high. In rheumatology practices at the 50th percentile, 46% of RA patients used opiates. The proportion of patients using opiates at the 25th and 75th percentiles was 37% and 55%, respectively. At the extremes (1st and 99th percentile), 0-92% of RA patients within each rheumatologist's practice were treated with opiates. However, among all patients in the analysis, only 43% of RA patients had any of their opiate prescriptions written by a rheumatologist.

Conclusion: In the US, opiate use peaked in RA patients in 2010 and is now undergoing slight declines. There was substantial variability between rheumatologists in the proportion of their RA patients using opiates, although fewer than half of patients had their opiate prescriptions written by rheumatologists. Withdrawal of the 2nd most commonly used opiate (propoxyphene) from the U.S. market in 2010 had minimal effect on overall use, as it was replaced with greater use of other opiates.



Disclosure: J. Curtis, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5; **F. Xie**, None; **K. Saag**, None; **L. Chen**, None; **T. Beukelman**, Novartis Pharmaceutical Corporation, 5,UCB, 5; **M. Mannion**, None; **H. Yun**, Amgen, 2.

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Abstract Number: 3087

Association of Weight Loss with Improved Disease Activity in Patients with Rheumatoid Arthritis

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Background/Purpose : Obesity has been associated with worsened RA outcomes and increased disease activity. However, few longitudinal studies have investigated whether weight loss might improve RA disease activity. We hypothesized that weight loss improves RA disease activity in routine clinical care.

Methods : We conducted a retrospective cohort study among RA patients that met 1987/2010 ACR criteria at a single academic medical center from 2012 to 2015. We included patients with at least two Clinical Disease Activity Index (CDAI) measures and corresponding body mass index (BMI) measures at routine clinic visits. We collected data on sociodemographic, lifestyle, medications, laboratory values, and RA characteristics at each clinic visit. We identified the maximum and minimum weight for each individual to calculate Δweight, as well as corresponding CDAI measures at these visits to calculate ΔCDAI. We defined significant weight loss as losing ≥5 kg, and a significant improvement in disease activity as ≥5 point improvement in CDAI (validated as the minimally clinically important difference, MCID). We used logistic regression to estimate the odds ratio (OR) for improved disease activity according to significant weight loss and baseline BMI category. We used linear regression to evaluate the association between Δweight and ΔCDAI among those who were overweight/obese and lost at least 1 kg.

Results : We identified 178 RA patients to include in the study. There were a total of 854 clinic visits, with a median of 5 visits per patient (range 2-11) in 1.8 years (IQR 1.3-2.4) of follow-up. Mean age at baseline was 60.2 years (SD 13.5) and median time for Δweight was 1.1 years (IQR 0.6-1.5). At baseline, 66% were overweight/obese, mean RA duration was 11.9 years (SD 9.5), 78% were seropositive, and mean CDAI was 11.6 (SD 9.2) with 42% in high/moderate disease activity by CDAI. Patients who were overweight or obese and lost >5 kg had three-fold increased odds of disease activity improvement by MCID compared to those who did not lose 5 kg (OR 3.03, 95%CI 1.18-7.83, **Table**). Among those who were obese/overweight at baseline, for each kg of weight lost, CDAI decreased by 1.15 (95% CI -1.88, -0.42; p=0.0026, **Figure**), adjusted for age, sex, RA duration, smoking, steroid use, serostatus, and time for weight loss.

Conclusion : These results suggest that weight loss may be associated with improved disease activity in patients with RA in a routine clinical setting. Weight loss has the potential to be a non-pharmacologic intervention to improve RA disease activity. Further studies of weight loss interventions and RA disease activity are necessary to confirm these results in other populations.

Table. Odds ratio for significant RA disease activity improvement (≥5 point improvement in CDAI) according to significant weight loss (≥5 kg) and BMI category at baseline (n=178).

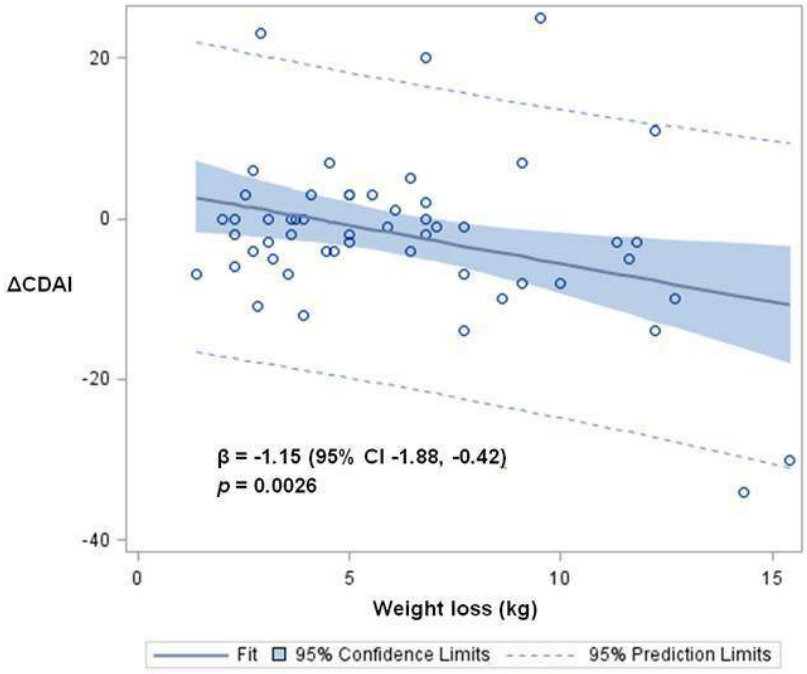
Weight loss and baseline BMI category	Outcomes / Total in category (n)	OR (95% CI)*
Did not lose 5 kg and overweight/obese at baseline	18 / 93	1.0 (Ref)
Lost 5 kg and overweight/obese at baseline	10 / 24	**3.03 (1.18-7.83)**
Did not lose 5 kg and normal BMI at baseline	19 / 57	1.90 (0.88-4.11)
Lost 5 kg and normal BMI at baseline	0 / 4	**

*Adjusted for sex

**No one in this category had disease activity improvement so we were unable to estimate the odds ratio. Weight loss was defined as the difference between the maximum and minimum weights (kg) at routine clinical visits. ΔCDAI was calculated using measures at these corresponding clinic visits.

BMI, body mass index; CDAI, Clinical Disease Activity Index; CI, confidence interval; OR, odds ratio; RA, rheumatoid arthritis

Figure. Scatterplot of weight loss vs. ΔCDAI among patients with rheumatoid arthritis who were overweight or obese at baseline and lost any weight* during follow-up (n=53).



*Weight loss was defined as the difference between the maximum and minimum weight (in kg) measures at routine clinic visits. ΔCDAI was calculated using measures at the corresponding clinic visits. The linear regression model was adjusted for age, sex, RA duration, smoking (ever/never at baseline), serostatus (seropositive/seronegative), steroid use (ever/never at baseline), and time for weight loss.

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Abstract Number: 3088

Predictors of Non-Adherence with Anti-Rheumatic Medication in Rheumatoid Arthritis Patients: Data from a Rheumatoid Arthritis Cohort

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Background/Purpose: Despite the availability of safe and effective treatments and the establishment of treatment guidelines, real-world effectiveness remains suboptimal largely due to low patient adherence with prescribed treatment. The purpose of this study was to systematically evaluate sociodemographic, health insurance, and disease-related factors associated with non-adherence with anti-rheumatic medications (ARM) in a large observational cohort of RA patients followed in Canadian routine clinical care.

Methods: RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) clinical registry and had at least two years of follow-up were included in the analysis. Non-adherence with treatment was defined as ARM discontinuation due to the patient non-adherence. Independent predictors of non-adherence with ARM were evaluated with multivariate cox-regression using both time-fixed and time-dependent variables. Factors considered included patient sociodemographics (age, gender, race, education status, annual income, smoking history), health insurance information (private vs. non-private, % coverage), disease parameters (RA duration, presence of erosion, RF positivity, DAS28, physician global, HAQ-DI, number of comorbidities), types of medications used, and physician characteristics (gender, academic position, urban vs. rural, distance from patient's residence).

Results: A total of 1,762 patients were included in the analysis with a mean (SD) age of 57.4 years and disease duration of 8.5 (9.3) at the time of enrolment to the registry (baseline). At baseline, the majority of patients were female (77.7%), Caucasian (85.1%), had post-secondary education (55.3%), and had private insurance (67.2%). In terms of disease severity, 54.5% had a prior erosion, 69.5% were RF positive, and mean (SD) DAS28 was 4.5 (1.5). Table 1 shows the association between all factors considered in the analysis and non-adherence with ARM. In multivariate analysis, married status, RF positivity and higher number of comorbidities were identified as significant predictors of increased adherence while higher physician global score, NSAID use, and polypharmacy were associated with non-adherence. **Table 1: Independent Predictors of Patient Non-Adherence with ARM**

	HR (95% CI), p-value		
	Univariate analysis	**Multivariate saturated analysis**	**Backward stepwise regression analysis**
Sociodemographics			
Age	**0.99 (0.98-0.99), 0.03**	**1.24 (1.02-1.51), 0.03**	-
Female gender	1.09 (0.85-1.38), 0.50	-	-
Marital status			
- Single/widowed/divorced - Married	Ref **0.82 (0.67-1.00), 0.05**	Ref **0.72 (0.55-0.95), 0.02**	Ref **0.73 (0.56-0.96), 0.02**
Race - Caucasian (white) - Non-Caucasian	Ref 1.04 (0.75-1.43), 0.83	-	-
Education status - High school or less - Post-secondary	Ref **1.20 (0.98-1.46), 0.07**	Ref 1.10 (0.85-1.43), 0.47	-
Annual Income class during follow-up - < $ 50,000 - ≥ $50,000	Ref 1.10 (0.87-1.38), 0.43	-	-
Smoking history during follow-up - Never smoked - Former smoker - Current smoker	Ref 0.99 (0.80-1.23), 0.95 0.96 (0.71-1.29), 0.80	-	-
Health insurance information Health insurance - No private - Private	Ref 1.08 (0.83-1.40), 0.58	-	-
% prescription covered by health insurance, during follow-up	1.01 (1.00-1.02), 0.25	-	-
Disease parameters			
Disease duration at baseline	0.99 (0.99-1.01), 0.70	-	-
Early RA - No - Yes	Ref 1.04 (0.84-1.29), 0.70	-	-
Ever presence of erosion - No - Yes	Ref 0.96 (0.82-1.12), 0.57	-	-
RF positive - No - Yes	Ref **0.79 (0.64-0.99), 0.04**	Ref **0.74 (0.56-0.97), 0.03**	Ref **0.73 (0.56-0.96), 0.02**
DAS28 during follow-up	**1.10 (1.02-1.18), 0.02**	0.98 (0.87-1.11), 0.74	-
Physician global score during follow-up	**1.10 (1.05-1.15), <0.0001**	**1.12 (1.04-1.20), 0.003**	**1.10 (1.04-1.15), 0.001**
HAQ disability index during follow-up	**1.09 (0.97-1.24), 0.15**	0.89 (0.74-1.08), 0.25	-
Comorbidity number during follow-up	**0.96 (0.90-1.01), 0.11**	**0.94 (0.87-1.01), 0.11**	**0.92 (0.85-0.99), 0.02**
Medication information			
Prior csDMARDs use at baseline - No - Yes	Ref 1.18 (0.89-1.57), 0.25	-	-
Prior bDMARDs use at baseline - No - Yes	Ref 1.04 (0.83-1.29), 0.76	-	-
Number of prior csDMARDs at baseline	**1.08 (1.01-1.15), 0.03**	1.03 (0.94-1.13), 0.57	-
Number of prior bDMARDs at baseline	1.04 (0.93-1.15), 0.50	1.04 (0.93-1.15), 0.50	-

csDMARDs use during follow-up - No - Yes	Ref 1.12 (0.90-1.29), 0.69	-	-
bDMARDs use during follow-up - No - Yes	Ref 1.04 (0.85-1.29), 0.69	-	-
Steroid use during follow-up - No - Yes	Ref **1.26 (1.00-1.60), 0.05**	Ref 1.04 (0.72-1.51), 0.83	-
NSAIDs use during follow-up - No - Yes	Ref **1.90 (1.54-2.34), <0.0001**	Ref **1.78 (1.28-2.48), 0.001**	Ref **1.75 (1.29-2.38), 0.003**
Number of ARM during follow-up	**1.30 (1.19-1.43), <0.0001**	**1.22 (1.03-1.44), 0.02**	**1.23 (1.07-1.40), 0.003**
Physician information			
Female gender	**1.21 (0.99-1.47), 0.06**	1.18 (0.90-1.53), 0.23	-
Academic position - Community-based - Academic or mixed based	Ref **1.24 (1.02-1.51), 0.03**	Ref 1.07 (0.82-1.39), 0.62	-
Location of clinical site - Urban - Rural	Ref 1.13 (0.88-1.45), 0.33	-	-
Distance from patient residence - ≤ 25 Km - > 25 km	Ref 1.13 (0.93-1.38), 0.22	-	-

Conclusion: In this systematic approach to identify factors associated with patient non-adherence with ARM, a variety of factors encompassing sociodemographic, disease, and medication characteristics, were identified as significant independent predictors of non-adherence. These results should be taken into consideration when developing patient adherence support programs and in the choice of treatment regimens.

Disclosure: V. Ahluwalia, None; **M. Movahedi**, None; **E. Rampakakis**, employee of JSS Medical Research, 3; **A. Cesta**, None; **X. Li**, None; **J. S. Sampalis**, Employee of JSS Research, 3; **C. Bombardier**, None.

Abstract Number: 3089

Predicting the Response to TNF Inhibition or B Cell Depletion Therapy from Peripheral Whole Blood Gene Expression Profiles in Patients with Rheumatoid Arthritis

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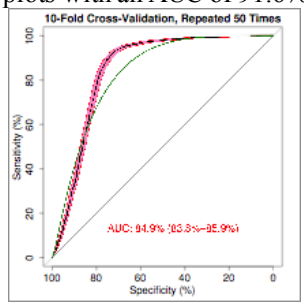
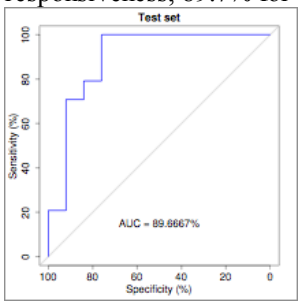
Background/Purpose: The ORBIT study demonstrated that rituximab is non-inferior to a TNFi-first strategy in biologic naive, sero-positive patients with active RA over 12 months (Lancet doi.org/10.1016/S0140-6736(16)00380-9). However, a significant

proportion of patients failed to respond to their first biologic drug and switched to an alternative. The ability to identify and stratify these patients prior to treatment would improve patient care and optimise the use of scarce financial resources. The aim of this study was to identify peripheral blood transcriptional biomarkers in the ORBIT cohort that can predict subsequent response/non-response to biologic therapy.

Methods: RNA was sequenced (Illumina NextSeq 500) from the peripheral blood of 241 patients recruited to the ORBIT study, after depletion of ribosomal and globin RNA. 70% (n=169) of samples were used to develop response prediction models, and 30% (n=72) were reserved for validation. Clinical response was defined as a fall in DAS28-ESR of >1.2 units between baseline and three months. Multiple machine learning techniques were used to train models that predicted 1) general responsiveness to both TNFi and rituximab therapy 2) differential response to TNFi or rituximab therapy. Tenfold cross validation was used to train the models, which were then tested on the validation set.

Results: Three gene sets were identified using support vector machine (SVM) recursive feature elimination. These predicted: general responsiveness to both TNFi and rituximab therapy (8 genes), response to TNFi therapy (23 genes) or rituximab (23 genes) respectively. When tested on the validation set, these models resulted in ROC plots with an AUC of 91.6% for general responsiveness, 89.7% for TNFi response, and 85.7% for rituximab response.





ROC plot showing the performance of the 25-feature SVM RBF classifier predicting specific response of TNFi therapy. When the drug specific models were combined, the sensitivity, specificity, PPV and NPV for response prediction at 3 months were 96%, 91%, 96% and 92%, respectively. Patients who were predicted to respond at three months were also more likely to have a DAS28 good response (43% v 23%) or DAS28 remission (23% v 10%) at 12 months.

Conclusion: At baseline, whole blood transcriptomic profiles of biologic naive patients with sero-positive RA predict future responsiveness to TNFi and rituximab therapy. These signatures needs to be validated but if they prove to be robust they will herald a new stratified approach to treatment selection resulting in improved patient outcomes.

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Abstract Number: 3090

Inflammation Detected with Modern Sensitive MRI Analysis Demonstrates That Therapeutic Response As Early As One Month Predicts 12-Month Radiographic Progression: Data from a Study Using Tofacitinib and Methotrexate in Early RA

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Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor for the treatment of RA. A novel automated quantification method for RA MRI-detected pathology using statistical shape modelling technology (RAMRIQ) provides a tool that may be even more responsive than the sensitive RAMRIS semi-quantitative standard.[1] We aimed to determine if early changes in RAMRIQ were predictive of subsequent MRI and radiographic damage progression in a study of tofacitinib for the treatment of early RA in methotrexate-naïve patients with minimal radiographic progression.

Methods: We used data from an exploratory, Phase 2 randomized controlled trial comparing tofacitinib, methotrexate, and the combination (n=109) in early active RA.[1] All patients met ACR classification criteria for active RA. MRI was performed at baseline, 1, 3, 6, and 12 months. A single centralized reader read all MRI data; data for each patient were randomized by time point, and read in the same sitting. We examined changes in synovitis, osteitis and erosions for RAMRIQ and RAMRIS at 1 and 3 months and performed univariate analyses on their relationship to RAMRIS, RAMRIQ, and radiographic progression (modified total Sharp score [mTSS]) at 12 months.

Results: Reduction in RAMRIQ synovitis and osteitis at 1 and 3 months were significantly associated with reduction in RAMRIS erosion progression at 12 months (Table). Improvement in RAMRIQ synovitis and osteitis at 1 and 3 months were also associated with reduction in radiographic progression at 12 months, while RAMRIQ erosions at 1 and 3 months were not significantly associated with radiographic progression (Table). Early changes in RAMRIS erosion at 1 and 3 months were associated with radiographic progression at 12 months (Table). Treatment with tofacitinib alone or in combination with methotrexate was also associated with reduced progression in RAMRIS erosions ($p=0.017$ and $p=0.007$, respectively).

Conclusion: In this study, sensitive automated detection demonstrated that change in synovitis and osteitis predict subsequent RAMRIS erosion and radiographic progression. Treatment with tofacitinib as monotherapy or in combination with methotrexate was also highly predictive of no progression of erosive damage. Because of its enhanced sensitivity, novel quantitative imaging analysis has the potential to change RA clinical trial design where assessing structural damage is an objective. **Reference: 1.** Conaghan et al. Ann Rheum Dis. 2016; 75:1024-33.

Table: Univariate analyses of the relationship between RAMRIQ and RAMRIS measurements at Month 1 and 3 and RAMRIS erosion and radiographic progression at Month 12.

p-value	RAMRIS erosion progression (Month 12)	Radiographic progression (mTSS; Month 12)
Change in RAMRIQ synovitis		
Month 1	0.004	<0.001
Month 3	0.008	0.008
Change in RAMRIQ osteitis		
Month 1	0.001	<0.001
Month 3	<0.001	<0.001
Change in RAMRIQ erosions		
Month 1	-	0.075
Month 3	-	0.530
Change in RAMRIS erosions		
Month 1	-	0.001
Month 3	-	0.005

mTSS, modified Total Sharp Score; RAMRIS, Rheumatoid Arthritis MRI Scoring System; RAMRIQ, quantitative RAMRIS

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Abstract Number: 3091

Effect of Sarilumab on Circulating Biomarkers of Bone and Joint Destruction in Patients with Rheumatoid Arthritis with Inadequate Response to Methotrexate

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Background/Purpose: Patients with RA develop bone and joint damage due to chronic inflammation that is mediated by a destructive synovial pannus.[1] The pannus is composed of inflammatory cell types that act in concert with resident activated

fibroblast-like synoviocytes to trigger bone and joint damage. Here we describe that blockade of IL-6 signaling by sarilumab, a human mAb blocking the IL-6Rα, decreased circulating markers associated with synovial inflammation and tissue damage in patients with active, moderate-to-severe RA with inadequate response to MTX from MOBILITY (NCT01061736).

Methods: Sera were analyzed using ELISAs at baseline and posttreatment through week 52 from a subset of patients (N=384) receiving placebo or subcutaneous sarilumab (150 or 200 mg every 2 weeks [q2w]) plus weekly MTX. Percent change from baseline in biomarkers was analyzed using nonparametric methods (ANOVA-type) to evaluate differences between treatment groups at each time point. For exploratory purposes, percent changes from baseline in biomarkers were also compared between ACR50 responders at week 24 using similar methods, separately by treatment group. *P* values <0.05 were considered significant.

Results: Both doses of sarilumab significantly decreased markers of tissue destruction and synovial inflammation relative to placebo as early as week 2, with greater reductions observed at week 24 (Table). For most biomarkers, numerically greater differences from baseline were observed in the sarilumab 200 mg q2w group vs the sarilumab 150 mg q2w group. When changes from baseline in biomarkers were examined according to ACR50 response at week 24, significantly greater reductions in chemokine (C-X-C motif) ligand 13, a marker of lymphoid RA synovial phenotype, and MMP-3, a marker of synovial inflammation, were observed in ACR50 responders relative to nonresponders in the sarilumab 150 mg q2w group. Additionally, ACR50 responders demonstrated greater posttreatment reductions in collagen type I MMP-cleaved fragment (sarilumab 200 mg q2w group) and CRP (sarilumab 150 mg q2w group) compared with ACR50 nonresponders. Other biomarkers suppressed by sarilumab treatment (eg, RANK ligand) did not significantly differ by ACR50 response (not shown).

Conclusion: Sarilumab significantly reduced biomarkers of bone resorption and joint damage in patients with RA and an inadequate response to MTX. Differences in some biomarker levels observed between ACR50 responders and nonresponders suggest that the suppression of these biomarkers may contribute to a decrease in disease activity. **Reference: 1.** Srirangan et al. *Ther Adv Musculoskelet Dis*. 2010;2:247-256.

Table. Posttreatment Changes in Serum Concentrations of Circulating Biomarkers in Patients With RA From MOBILITY						
	Week 2[a]			**Week 24[a]**		
	Placebo + MTX (n=126)	**Sarilumab 150 mg q2w + MTX (n=128)**	**Sarilumab 200 mg q2w + MTX (n=130)**	**Placebo + MTX (n=126)**	**Sarilumab 150 mg q2w + MTX (n=128)**	**Sarilumab 200 mg q2w + MTX (n=130)**
Median percent change from baseline in biomarker concentration[b,c]						
Acute-phase reactant						
CRP	-0.5	-69.9§	-91.8§	-12.2	-93.3§	-95.4§
Marker of tissue destruction						
C1M	0.5	-24.4**	-38.1**	-16.4	-39.3**	-50.1**
Markers of synovial inflammation						
C3M	-2.8	-15.9**	-20.0**	-4.2	-25.8**	-30.9**
MMP-3	-1.7	-15.0**	-5.5*	-6.7	-37.8**	-47.8**
Markers of bone resorption						
Total RANKL	---	---	---	-10.6	-20.4	-25.7*
OPG	---	---	---	2.2	1.2	-2.4
Marker of lymphoid RA synovial phenotype						
CXCL13	-1.3	-13.7**	-18.4**	-3.1	-16.8**	-32.1**
Marker of myeloid RA synovial phenotype						
sICAM-1	-0.7	-2.8	-3.5	0.1	-7.9**	-7.5**
Median percent change from baseline in biomarker concentration at week 24 in ACR50 responder/nonresponder patients[d]						
		Sarilumab 150 mg q2w + MTX (n=128)		**Sarilumab 200 mg q2w + MTX (n=130)**		
		ACR50 responder	**ACR50 nonresponder**	**ACR50 responder**	**AC50 nonresponder**	
CRP		-95.1†	-88.7	-96.3	-93.7	
C1M		-40.9	-38.0	-54.2†	-42.1	
MMP-3		-45.2†	-36.8	-48.8	-40.3	
CXCL13		-34.1‡	-13.4	-37.1	-26.1	

ANOVA, analysis of variance; C1M, collagen type I MMP-cleaved fragment; C3M, collagen type III MMP-cleaved fragment; CXCL13, chemokine (C-X-C motif) ligand 13; OPG, osteoprotegerin; q2w, every 2 weeks; RANKL, RANK ligand; sICAM-1, soluble intercellular adhesion molecule 1. *Adjusted $P<0.05$ and ≥ 0.01 vs placebo. **Adjusted $P<0.01$ vs placebo. †Unadjusted $P<0.05$ and ≥ 0.01 vs nonresponders. ‡Unadjusted $P<0.01$ vs nonresponders. §Unadjusted $P<0.01$ vs placebo. [a]Patient numbers reflect maximum number of patients included in each group. Fewer samples may have been analyzed at a given time point because of missing or non-evaluable samples. [b]The Benjamini-Hochberg procedure was used to correct for multiplicity and control false discovery rate using all comparisons for most biomarkers tested; unadjusted *P* values are presented for CRP. Note that only selected comparisons are shown here. [c]Percent change from baseline was analyzed using ANOVA-type method and adjusted *P* values of the comparisons vs placebo are reported. [d]Change in biomarker concentrations in ACR50 responders vs nonresponders was compared in active treatment groups at week 24 using ANOVA-type method, separately by group. Unadjusted *P* values are reported.

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Abstract Number: 3092

Predictive Factors for Better Outcome of Switching of Biologics for Patients with

Rheumatoid Arthritis in Daily Clinical Practice

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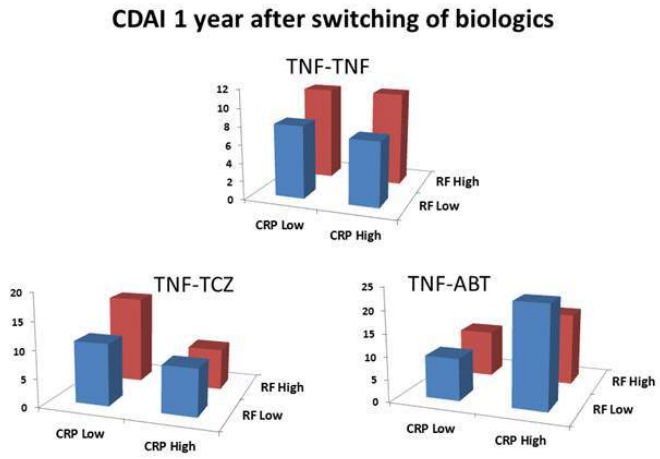
Background/Purpose: Eight biologics have been approved for rheumatoid arthritis (RA) in Japan. However, little is known regarding what to do when patients have an inadequate response to first biologics in daily clinical practice. This study aimed to evaluate the effectiveness of biologics as 2nd-line use in RA patients in daily clinical practice from our university cohort (FIRST registry).

Methods: We retrospectively examined more than 2500 patients who were treated with biologics in our institute between July 2003 and December 2015. We compared the effectiveness of TNF-inhibitors (TNFi), TCZ, ABA as 2nd-line use and efficacy of switching from 1st TNFi to 2nd TNFi, TCZ or ABA based on CDAI and biomarkers such as CRP, ESR and MMP3, IL-6 (LOCF). Propensity score (PS) were generated using multinomial logistic regression and the study groups were matched regarding baseline variables including age, disease duration, disease activity, concomitant use of MTX and PSL. In addition, in order to find out the characteristic of 2nd biologics, we conducted comparison between the upper (1yCDAI-H; low response) and lower (1yCDAI-L; good response) quartiles in CDAI at 1 y after switching.

Results: In terms of switching of biologics, CDAI at 1year was comparable among TCZ(n=141), 2ndTNFi（n=186）and ABT(n=91) after the adjustment by PS. Interestingly, comparison between the upper (1yCDAI-H) and lower (1yCDAI-L) quartiles in CDAI at 1 y after switching revealed that disease activity might improve despite of a high disease activity at switching in the case of TCZ. In addition, higher CRP, MMP-3 at switching were predictive factors for better outcome despite of higher RF factor in the case of switching to TCZ. Titer of Serum IL-6 but not TNF was markedly elevated in patients showed better outcome. In contrast, ABT showed a lower efficacy especially in the patients with RF low, CRP high. (Figure).

Conclusion: After adjustment using PS-score, RA patients with prior anti-TNF exposures had similar outcomes after switching. Our results imply us that CRP, MMP3 and RF titer at switching gives us important information for switching. Of note, higher CRP or MMP-3, suggesting inadequate suppression of IL-6 by first biologics, might predict better outcome of TCZ.

Figure: CDAI 1 year after switching biologics categorized by titer of CRP and RF at switching (cut off titer was defined using ROC



curve)

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Abstract Number: 3093

Comparison of Changes in Cardiovascular Risk-Associated Biomarkers in RA Patients Treated with Anti-TNF or Other Biological Agents: A Metabolic Study from a Randomized Trial

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Background/Purpose: Considering the increased cardiovascular risk in RA patients and the influence of biologics, especially tocilizumab (TCZ) on the lipid profile, we aimed to investigate the differential effect of biologics on cardiovascular risk-associated biomarkers.

Methods: This ancillary study used serum samples at inclusion (M0) and 6 months (M6) of active RA patients inadequate responders to a 1st iTNF participating to the randomized ROC (Rotation or Change of Biotherapy, NCT01000441) trial, which compared EULAR response at M6 between a 2nd iTNF and another biologic (IV TCZ, abatacept or rituximab). At baseline and M6,

we assessed lipoprotein-related apoproteins ($ApoA_1$ and $ApoB_{100}$ reflecting mainly high density lipoprotein (HDL) and low density lipoprotein (LDL), respectively) and cardio-metabolic markers: lipoprotein(a) (Lp(a)) and adipokines (leptin and adiponectin) for the calculation of leptin/adiponectin ratio (LAR), that estimates insulin resistance. We compared the M0-M6 change of each marker between the 2nd iTNF group and the other biologic group and between the 2nd iTNF group and TCZ. We also compared this M0-M6 change according to the EULAR response in each group of treatment.

Results: From the 300 patients included in the ROC trial, 203 were tested due to the availability of the serum samples: 96 in the 2nd iTNF group and 107 in the other biologic group (47 TCZ, 26 abatacept and 34 rituximab). None of the measured markers deteriorated between M0-M6 in the two groups. Conversely, $ApoA_1$ level significantly increased in the 2nd iTNF group (+0.008 ±0.22g/L mean ±standard deviation, p<0.001) as well as in the other biologic group (+0.06 ±0.29 g/L, p<0.001). Lp(a) level only decreased in the other biologic group (-0.02 ±0.09 g/L, p=0,02), mainly due to TCZ (-0,06 ±0.08 g/L, p<0,001). TCZ also improved ApoA1 (+0.11 ±0.32 g/L, p <0.001) and adiponectin (+ 0,48 ±1.38 mg/L, p=0.02) levels. Compared to the 2nd iTNF group, Lp(a) and LAR decreased more in the other biologic group and Lp(a) and ApoA1 levels were improved in the TCZ group (Table 1). The improvement in the biomarkers level was mainly due to the EULAR responders in each group of treatment. Thus, Apo1 level increased with 2nd iTNF (+ 0.14 g/L difference between responders and non-responders, p=0,001), with other biologic (difference +0.1 g/L, p = 0.04) and with TCZ (difference +0.3 g/L, p=0.03).

Conclusion: In active RA patients in inadequate response to a 1st iTNF, cardiovascular risk-associated biomarkers did not deteriorate whatever the 2nd line of treatment and even improved in responders. Lp(a) and ApoA1 levels, both involved in atherogenesis, improved with a 2nd iTNF as well as with other biologics, but more with TCZ. This improvement seems driven by EULAR responders arguing for the control of RA as a major factor for cardiovascular risk improvement.

	Second iTNF	Other biologic TCZ or abatacept or rituximab	Tocilizumab	Abatacept or rituximab
Lipoprotein(a) - g/L				
M0-M6 mean change (SD)	- 0.004 (0.106)	- 0.017 (0.09)	- 0.06 (0.08)	- 0.018 (0.086)
p-value versus 2nd iTNF		NS	< 0.001	0.03
ApoA1 - g/L				
M0-M6 mean change (SD)	+ 0.008 (0.23)	+ 0.056 (0.29)	+ 0.11 (0.32)	+ 0.013 (0.263)
p-value versus 2nd iTNF		NS	0.03	NS
Adiponectin - mg/L				
M0-M6 mean change (SD)	+ 0.017 (1.71)	+ 0.126 (1.49)	+ 0.48 (1.38)	- 0.153 (1.53)
p-value versus 2nd iTNF		NS	NS	NS
Leptin/Adiponectin ratio				
M0-M6 mean change (SD)	+ 0.1 (0.2)	- 0.5 (2.3)	- 0.5 (2.3)	- 0.4 (2.3)
p-value versus 2nd iTNF		0.03	NS	0.02

Table 1 - Mean change of cardiovascular biomarkers from baseline to M6 and comparison with 2nd iTNF group. iTNF = TNF inhibitory agent, SD = standard deviation, p value of comparison with 2nd iTNF group.

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Abstract Number: 3094

Factors Associated with Initial or Subsequent Choice of Biologic Disease Modifying Antirheumatic Drugs for the Treatment of Rheumatoid Arthritis

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Background/Purpose: Treatment with disease-modifying antirheumatic drugs (DMARDs) is considered the standard of care for rheumatoid arthritis (RA). Over the past two decades, major advances have occurred in the treatment of RA with development of biologic DMARDS including tumor necrosis factor (TNF) inhibitors. It is not well-studied in what sequence these biologic DMARDs are being offered in RA patients in recent years. We aimed to describe patterns of biologic DMARD treatment for RA and identify factors associated with initial and subsequent choice of biologic DMARDs.

Methods: We conducted a prospective cohort study using claims data from a US commercial health plan (2004-2013) and Medicaid (2000-2010). We identified patients who aged ≥18 years with two diagnoses of RA (ICD-9 diagnosis code 714.xx) that are 7-365 days apart, first of which was defined as the index diagnosis. We then identified three separate groups of patients based on their DMARD use in the 365 day period pre-index: 1) incident RA patients who were naïve to any DMARDs, 2) prevalent RA patients with or without non-biologic DMARDs but naïve to biologic DMARDs and 3) prevalent RA patients with prior use of a biologic DMARD. Multivariable logistic regression models examined the effect of patient demographics, clinical characteristics and health care utilization factors on the initial and subsequent choice of biologic DMARDs for RA.

Results: We identified a total of 195,433 RA patients including 78,667 DMARD-naïve incident RA patients and 93,534 biologic-naïve prevalent RA patients and 23,232 biologic-experienced patients (**Table 1**). Patients in the commercial health plan were 87% more likely to initiate a biologic DMARD than those in Medicaid. African Americans were 30-40% less likely to initiate or switch biologics in all three RA groups when compared to White, non-Hispanic population. Prior use of steroid and non-biologic DMARD had positive association with biologic initiation as well as subsequent switching to another biologic drug. Etanercept (51%), adalimumab (22%), and infliximab (22%) were most commonly used first- and second-line biologics; anakinra and golimumab were most likely to be switched by other biologics (**Table 2**).

Conclusion: Younger age, private insurance type, and White race were significantly associated with higher odds of getting initial and subsequent treatment with biologics. There may be a need for future research examining the impact of selective prescribing of biologics on RA-related clinical outcomes.

Table1. Factors associated with initiation or switching of biologics and corresponding adjusted* odds ratio (95% CI)			
	Incident RA patients	**Prevalent RA patients**	**Biologics users**
Total N	78,667	93,534	23,232
Biologic initiation/switch	3,873 (4.9%)	10,361 (11.1%)	2,761 (11.9%)
Data source Commercial vs. Medicaid	1.87 (1.70, 2.05)	1.13 (1.06, 1.2)	0.92 (0.81, 1.05)
Age (by 10 year increase)	0.87 (0.84, 0.89)	0.81 (0.79, 0.83)	0.87 (0.84, 0.91)
Gender			
Male vs. Female	0.90 (0.83, 0.98)	0.95 (0.89, 1.00)	0.87 (0.79, 0.97)
Race			
White, non-Hispanic	Reference	Reference	Reference
Black, non-Hispanic	0.59 (0.51, 0.68)	0.71 (0.61, 0.74)	0.71 (0.55 0.90)
Other non-Hispanic	0.88 (0.72, 1.06)	0.89 (0.81,0.99)	1.08 (0.85, 1.41)
Hispanic	1.24 (1.08, 1.42)	1.08 (0.99, 1.17)	0.92 (0.76, 1.12)
History of medication use in prior year			
Aspirin	0.99 (0.82, 1.19)	0.83 (0.73, 0.94)	0.75 (0.55, 1.01)
Cox-II inhibitors	1.46 (1.32, 1.61)	1.30 (1.23, 1.38)	1.11 (1.00, 1.23)
Non-selective NSAIDs	1.30 (1.20, 1.39)	1.07 (1.02, 1.12)	1.12 (1.03, 1.22)
Opioids	1.18 (1.09, 1.27)	1.19 (1.13, 1.25)	1.21 (1.10, 1.34)
Steroid dosage, prednisone equivalent mgs			
None	Reference	Reference	Reference
Low (< 5 mg/day)	2.42 (2.25, 2.60)	1.65 (1.57, 1.73)	1.52 (1.38, 1.68)
Medium (5-10mg/day)	3.12 (2.56, 3.80)	1.89 (1.76, 2.04)	1.53 (1.34, 1.75)
High (≥10mg/day)	2.61 (1.91, 3.57)	1.72 (1.55, 1.89)	1.81 (1.51, 2.15)
Number of non-biologics			
None	–	Reference	Reference
One	–	1.54 (1.42, 1.66)	1.44 (1.27, 1.64)
More than one	–	2.40 (2.17, 2.67)	1.98 (1.65, 2.36)
Prior methotrexate	–	1.79 (1.69, 1.90)	0.78 (0.70, 0.87)
Prior hydrochloroquine	–	0.57 (0.54, 0.61)	0.75 (0.65, 0.86)
c-statistic of logistic model	0.733	0.712	0.656
*Adjusted for demographics, data source, calendar year, comorbidities, history of medication use, and healthcare utilization in baseline period			

Table 2. Switching between TNF inhibitors and non-TNF biologic DMARDs in 23,232 biologic-experienced patients					
Prior biologic	N (% of all prior biologics)	N of switch (% of each prior biologic)	Adjusted* OR of any switch (95% CI)	Switch to TNF or to non-TNF inhibitors†	
				N of switch to TNF inhibitors (%)	**N switch to non-TNF inhibitors (%)**
TNF inhibitors					
Etanercept	11,753 (50.6)	1223 (10.4)	Reference	989 (80.9)	234 (19.1)
Adalimumab	5,119 (22.0)	732 (14.3)	1.22 (1.10, 1.35)	573 (78.3)	159 (21.7)
Certolizumab	104 (0.4)	20 (19.2)	1.44 (0.86, 2.39)	8 (40.0)	12 (60.0)
Golimumab	130 (0.6)	35 (26.9)	2.24 (1.48, 3.37)	22 (62.9)	13 (37.1)
Infliximab	5,102 (22.0)	567 (11.1)	1.06 (0.95, 1.19)	377 (66.5)	190 (33.5)
Non-TNF biologics					
Abatacept	407 (1.8)	70 (17.2)	1.31 (0.99, 1.72)	40 (57.1)	30 (42.9)
Anakinra	260 (1.1)	85 (32.7)	3.20 (2.41, 4.25)	79 (92.9)	6 (7.1)
Rituximab	334 (1.4)	27 (8.1)	0.57 (0.38, 0.85)	16 (59.3)	11 (40.7)
Tocilizumab	22 (0.1)	2 (9.1)	0.59 (0.14, 2.60)	0 (0.0)	2 (100.0)
Total	23231 (100)	2761 (11.9)	—	743 (76.2)	657 (23.8)
*Adjusted for demographics, data source, calendar year, comorbidities, history of medication use, and healthcare utilization in baseline period † TNF inhibitors include adalimumab, certolizumab, etanercept, golimumab, and infliximab; non-TNF inhibitors include abatacept, anakinra, rituximab, tocilizumab, and tofacitinib.					

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Abstract Number: 3095

What Should be the Primary Target of 'Treat to Target' in Psa?

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Background/Purpose: In 2013, Treat to Target (T2T) in SpA Recommendations by expert consensus stated that the target of treatment should be remission or inactive disease. The only data in PsA is the Tight Control of PsA (TICOPA) trial which confirmed that T2T using a target of minimal disease activity (MDA) was superior to standard care. However MDA is not remission. Potential definitions that would fit with the T2T Recommendations would be MDA meeting all 7 cut points, proposed as a definition of very low disease activity (VLDA), or the Disease Activity in PsA (DAPSA) remission cut point. Our aim was to investigate which patients achieve definitions of remission and VLDA and how much residual active disease is still present.

Methods: This analysis uses data from the TICOPA study where 206 patients with newly diagnosed PsA were randomised 1:1 to receive either tight control (4 weekly review and treatment escalated until in MDA) or standard care (12 weekly review, no protocol for treatment). Three potential definitions of remission/inactive disease were used

- VLDA where all 7 of the MDA cut points are met: tender joint count (TJC)≤1; swollen joint count (SJC)≤1; enthesitis count≤1;

PASI≤1; patient global visual analogue scale (VAS)≤20mm; patient pain VAS≤15; and health assessment questionnaire≤0.5.
- DAPSA remission where DAPSA≤4 (TJC + SJC + patient global VAS (cm) + physician global VAS (cm) + CRP (mg/l)
- Clinical DAPSA remission where DAPSA≤4 (TJC + SJC + patient global VAS (cm) + physician global VAS)

Results: At the end of the TICOPA study (48 weeks), 50 patients were in DAPSA remission, 58 in cDAPSA remission and 27 met VLDA. Unsurprisingly, the highest correlation in remission definitions was found between DAPSA and cDAPSA (Pearsons 0.927) with lower correlation between both DAPSA/cDAPSA and VLDA (0.609/0.593). The percentage exact agreement (PEA) for VLDA and the DAPSA/cDAPSA remission was 85.2/83.0% respectively. There were 25 people considered to be in DAPSA remission and 30 in cDAPSA remission who did not meet the VLDA cut off. In contrast only 2 people were not in DAPSA remission but did meet the VLDA cut off. Levels of residual active disease in patients meeting the remission/very low disease activity criteria are shown in the table. All definitions had similar proportions of people with residual disease but lower disease activity was seen in VLDA definition, particularly for swollen joint count and enthesitis as each domain had to score ≤1. All definitions had similar proportions of patients with raised CRP levels despite the CRP not being included in two of the definitions.

Conclusion: The VLDA criteria are more stringent than both DAPSA and cDAPSA remission, with a lower number of people meeting this definition and less residual disease activity. The inclusion of a laboratory marker seems unnecessary in the definition as high CRP levels are similar in all definitions, making target assessment easier in clinical practice.

		DAPSA remission n (%) (n=50)	cDAPSA remission n (%) (n=56)	VLDA n (%) (n=27)
PASDAS	Mean (SD)	1.63 (0.70)	1.71 (0.71)	1.47 (0.68)
Tender joint count	0	39 (78.0)	40 (71.4)	21 (77.8)
	1	8 (16.0)	11 (19.6)	6 (22.2)
	2	3 (6.0)	5 (8.9)	0 (0)
Swollen joint count	0	45 (90.0)	48 (85.7)	26 (96.3)
	1	2 (4.0)	4 (7.1)	1 (3.7)
	2	3 (6.0)	4 (7.1)	0 (0)
Enthesitis count	0	41 (82)	45 (80.4)	25 (92.6)
	1	5 (10)	5 (8.9)	2 (7.4)
	2	3 (6)	5 (8.9)	0 (0)
	3	1 (2)	1 (1.8)	0 (0)
Dactylitis count	0	46 (92)	52 (92.9)	25 (92.6)
	1	1 (2.0)	1 (1.8)	1 (3.7)
	2	2 (4.0)	2 (3.6)	1 (3.7)
	3	1 (2.0)	1 (1.8)	0 (0)
PASI	0	46 (92)	51 (91.1)	25 (92.6)
	0.3	1 (2.0)	1 (1.8)	1 (3.7)
	0.6	1 (2.0)	1 (1.8)	1 (3.7)
	0.8	0 (0.0)	1 (1.8)	0 (0)
	3	2 (4.0)	2 (3.6)	0 (0)
CRP	Normal (<5mg/dl)	37 (74)	40 (72.7)	19 (73.1)
	Raised	13 (26)	15 (27.3)	7 (26.9)

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Abstract Number: 3096

Association Between Smoking and Psoriatic Arthritis Among Psoriasis Patients and the General Population: Data from National Inpatient Sample

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Background/Purpose: Psoriatic arthritis (PsA) is an inflammatory arthritis affecting approximately 520,000 patients in the US and up to one third of patients with psoriasis. Studies in the past have found an increased risk of psoriasis and worsening disease with smoking. However, the association between smoking and psoriatic arthritis in psoriatic patients and the general population remains much debated with some studies showing an increased risk while other showing an inverse relationship. We aimed to study the risk of psoriatic arthritis with smoking among the general population and patients with psoriasis using a large inpatient US database.

Methods: Using the Nationwide Inpatient Sample (NIS) data from 2009-2011, we identified current smokers based on International Classification of Diseases, Ninth Revision (ICD-9) code 305.1 and identified previous smokers who had ICD-9 code V15.82 but without 305.1. NIS is the largest publicly available all-payer inpatient care database in the United States and is sponsored by the Agency for Healthcare Research and Quality as a part of Healthcare Cost and Utilization Project. Patients with Psoriasis were selected based on ICD-9 codes 696.1 and 696.8 while PsA were identified based on 696.0. Univariate and multivariate logistic regressions were used to derive odds ratio for measures of association. Statistical analysis was done using STATA version 13.0 (College Station, TX).

Results: NIS database from 2009-2011 contained 23,634,793 (weighted counts in the whole US population: N=117,033,987) records of discharges. Out of those, 13,850 (weighted N=68,392) had psoriatic arthropathy. Among the whole population, 81.66 % were non-smokers, 11.28 were active smokers while 7.06 % were previous smokers. Multivariate regression analysis after controlling for confounders (table 1) showed significantly higher incidence of PsA in active smokers as compared to non-smokers (OR 1.19, CI 01.12- 1.27, $p \leq 0.0001$) in the general population. The risk was further higher in active smokers with psoriasis (OR 3.02, CI 2.04- 4.47, $p \leq 0.0001$). Similarly, previous smokers were also at increased risk for PsA in the general population (OR 1.40, CI 1.31- 1.50, $p \leq 0.0001$) but the risk in patients with psoriasis was not statistically significant (OR 1.59, CI 0.93- 2.70, $p=0.091$). Hypertension, hyperlipidemia, obesity, diabetes mellitus and rheumatoid arthritis were all found to be independent risk factors in our multivariate regression model.

Conclusion: Active tobacco use was associated with a higher risk of PsA in the general population and a much higher risk was seen in patients with psoriasis. This is in sharp contrast to previous studies showing an inverse relationship. Moreover, the risk was significantly lower in previous smokers as compared to active smokers, suggesting that quitting smoking may lower the risk of PsA in patients with psoriasis. This lower risk was however not seen among the general population. As PsA usually develops 8-10 years later in patients with psoriasis, it may be considered a more severe phenotype that may develop in genetic susceptible patients (eg. HLA-C*06) with certain environmental exposures such as tobacco use. Hence, quitting smoking in psoriatic patients may prevent development of PsA. More studies are needed to get a better understanding of the mechanisms that explain this finding and identify gene-environment interactions.

Psoriatic Arthritis	Odds Ratio	Two tailed p-value	95% Confidence Interval	
No smoking Yes Psoriasis	2.87	<0.0001	2.26	3.66
Active smoking Yes Psoriasis	3.02	<0.0001	2.04	4.47
Active Smoking No Psoriasis	1.19	<0.0001	1.12	1.27
Previous smoking No Psoriasis	1.40	<0.0001	1.31	1.50
Previous smoking Yes Psoriasis	1.59	0.09	0.93	2.70
AGE	1.01	<0.0001	1.01	1.01
FEMALE	0.87	<0.0001	0.84	0.91
CKD	0.72	<0.0001	0.67	0.77
Major Transplant	0.95	0.73	0.72	1.26
Hypertension	1.32	<0.0001	1.26	1.39
Hyperlipidemia	1.18	<0.0001	1.12	1.23
Obesity	1.93	<0.0001	1.82	2.04
Diabetes Mellitus	1.17	<0.0001	1.11	1.23
Rheumatoid Arthritis	8.08	<0.0001	7.54	8.66

Table 1. Multivariate logistic regression showing risk of psoriatic arthritis with smoking (active and previous) in patients with psoriasis and general population.

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Abstract Number: 3097

Osteoclast Precursor Frequency and Imaging Findings Associated with Arthritis Onset in a Psoriasis Longitudinal Cohort

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Session Time: 4:30PM-6:00PM

Background/Purpose:

Psoriasis (Ps) precedes joint inflammation by an average of 10 years psoriatic arthritis (PsA) patients. Reports have demonstrated abnormal musculoskeletal imaging findings in psoriasis patients but arthritis biomarkers have not been identified. PsA patients demonstrate increased OCP frequency in the peripheral blood. We examined the association of imaging abnormalities and OCP frequency in a longitudinal psoriasis cohort without baseline musculoskeletal symptoms.

Methods:

Ps patients with > 5 years of psoriasis or >10% body surface area (any disease duration) were enrolled if they scored less than 36 on the PASE questionnaire and showed no active arthritis or enthesitis on rheumatologic exam. All patients were imaged with a 3-phase bone scan and Power Doppler Ultrasound (PDUS) of joints and entheses. If the bone scan revealed evidence of inflammation, a gadolinium enhanced 3T MRI was performed on the joint with the highest scintigraphy signal. Patients were contacted annually by phone or by a visit and those with new musculoskeletal symptoms were examined and PsA diagnosed by CASPAR criteria. Blood samples were drawn for OCP quantification from purified monocytes after 8-day cell culture.

Results:

42 Ps patients (50% female) were enrolled with a mean age 45±6 years, psoriasis duration 16±3 years, BMI 32±8 kg/m^2 and PASI score 8±5 and mean follow-up was 48.1±1 months. Eleven subjects had normal imaging studies (scintigraphy/MRI), 13 had active subclinical joint inflammation on imaging but 9 additional subjects, all with baseline imaging abnormalities, subsequently developed PsA. In the PsA group, 6/9 (66%) had synovitis/tenosynovitis (i.e. synovial thickening) and/or a knee effusion detected on ultrasound, compared to 5/33 (15%) in the patients without PsA. Characteristics of patients who developed PsA: 5 of 9 female, mean age 49, PASI 11.3, 5 of 9 with nail and 7 of 9 with scalp disease and mean psoriasis disease duration of 25.5 years. Active or prior enthesitis (calcification at insertions) by PDUS was noted in 9 patients without abnormal MRI or scintigraphy. Patients were categorized into 4 subsets based on the imaging analysis and/or clinical features: (1) no imaging abnormality, (Normal) n=11; (2) enthesitis or entheseal calcification, (Enthesitis), n=9; (3) sub-clinical joint inflammation, (Imaging); n=13; (4) development of PsA, (PsA) n=9. The OCP frequency was significantly different in the 4 patient subsets (P<.005) (Table 1). OCP frequency was similar in the patients who developed PsA and those with abnormal imaging findings and 3 to 4-fold higher than patients without imaging findings or enthesitis on US.

Conclusion:

Elevated OCP frequency was associated with abnormal imaging findings on scintigraphy and MRI. The combination of synovitis/tenosynovitis and/or a knee effusion on grey scale US and elevated OCP frequency identified psoriasis patients at risk for PsA.

Table 1. OCP frequency in 4 cohorts of Ps patients categorized by imaging results (mean+SEM).

	(1) Normal	(2) Enthesitis	(3) Imaging findings	(4) PsA
OC (per 10e6 cells)	266 ± 134	515± 863	1,271± 1103	1264± 1626

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Abstract Number: 3098

The Occurrence of Peripheral Arthritis Mutilans in Psoriatic Arthritis Is Associated with Certain Major Histocompatibility Class I Alleles

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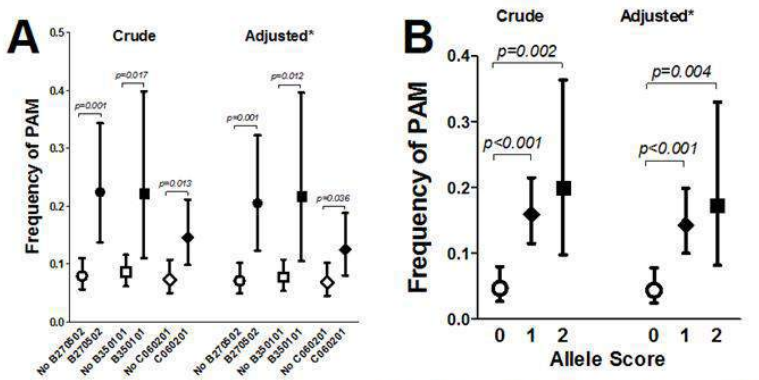
Background/Purpose: Several human leukocyte antigen (HLA) Class I loci encoding the major histocompatibility complex (MHC) have been implicated both in psoriatic arthritis (PsA) susceptibility and in overall severity of disease. However, associations of these HLA alleles with specific manifestations of PsA have received little study. In particular, the contribution of HLA Class I alleles to peripheral arthritis mutilans (PAM), a potentially devastating manifestation of PsA, is unclear.

Methods: Patients from two prospective PsA cohorts were genotyped for HLA-B and C alleles. PAM was defined radiographically as osteolysis affecting≥50% of the articular surface on both sides of a joint. Associations of alleles with PAM were explored in multivariable logistic regression models adjusting for potentially confounding characteristics. An allele scores was constructed as the sum of an individual's positively associated alleles minus the sum of their inversely associated alleles.

Results: A total of 501 PsA patients were studied [mean age=56 years, 53% female, median PsA duration=18 years]. PAM was observed in 52 (10%). B*27:05:02, B*35:01:01, and C*06:02:01 were significantly associated with PAM in multivariable analyses (Fig 1A). There were no significant inversely associated alleles. One PAM-associated allele was present in 208 (42%) and 35 (7%) had two alleles. Compared with those with no PAM-associated alleles, the odds of PAM was nearly 3.5-fold higher for those with one allele (OR=3.59; p<0.001), and more than 4.5-fold higher for those with two alleles (OR=4.51; p=0.004) after adjusting for PsA duration, which was the only meaningful confounder of the PAM/allele association detected (Fig 1B). The strongest associations were observed for B*27:05:02 in the context of its B*27:05:02-C*02:02:02 haplotype (OR=4.70 compared with those with no B*27:05:02; p=0.001), B*35:01:01 in the context of its B*35:01:01-C*04:01:01 haplotype (OR=3.46 compared with those with no B*35:01:01; p=0.014), and C*06:02:01 in the context of its two common haplotypes (B*13:02:01-C*06:02:01 and B*57:01:01-C*06:02:01: OR=1.93 compared with those with no C*06:02:01; p=0.041). The area under the receiver operator curve (AUC) for detecting PAM knowing only the PAM-associated HLA-B and C alleles in their haplotype contexts was 0.682 (95% CI 0.610, 0.766). Adding PsA duration to the model increased the AUC to 0.738 (95% CI 0.672, 0.805).



Panel A depicts the crude and adjusted associations of HLA B*27:05:02, B*35:02:01, and C*06:02:01 with the frequency of peripheral arthritis mutilans (PAM). Panel B depicts the association with the same outcome for an allele score based on the sum of the three PAM associated alleles. For both, Means and 95% confidence intervals are depicted. Crude analyses are adjusted only for the other PAM associated alleles. Adjusted analyses also include adjustment for psoriatic arthritis duration.

Conclusion: The associations of specific HLA-B and C alleles observed with PAM supports the concept that the particular PsA sub-phenotype observed in an individual is genetically determined. Additional study is warranted to define how penetrance is determined among those with susceptibility alleles

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Abstract Number: 3099

Higher Prevalence and Severity of Coronary Atherosclerosis in Psa Patients

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Background/Purpose: Patients with psoriatic arthritis (PsA) have increased risk in cardiovascular diseases (CVD) including subclinical atherosclerosis. However, previous knowledge was limited to carotid atherosclerosis. The aim of this study was to determine whether PsA patients had a higher prevalence and severity of coronary atherosclerosis compared to control subjects. We also aimed to test the association between the disease characteristics and coronary atherosclerosis in PsA patients.

Methods: 82 PsA patients [male: 51 (62%); 51±11 years] were recruited. Coronary atherosclerosis was evaluated by computed tomography angiography (CTA). 231 control subjects [male: 155 (67%); 49±10 years] without known CVD and rheumatic diseases, who were referred to receive CTA scan due to chest pain and/or multiple CVD risk factors, were also recruited.

Results: PsA patients and controls were well matched in age, gender, smoking status, history of hypertension and dyslipidemia, lipid profile and fasting glucose (p ranged from 0.158 to 0.978). PsA patients had a higher prevalence of diabetes mellitus than controls [13 (16%) vs 15 (7%), p=0.012]. The prevalence of overall coronary plaque [52 (63%) vs 74 (32%), p<0.001], calcified plaque (CP) [27 (33%) vs 30 (13%), p<0.001], mixed plaque (MP) [19 (23%) vs 13 (6%), p<0.001], non-calcified plaque (NCP) [38 (46%) vs. 51 (22%), p<0.001], and combined MP/NCP [45 (55%) vs. 57 (25%), p<0.001] were all significantly higher in PsA patients. PsA patients also had higher coronary calcium score (CAC) compared with control subjects (46±151 vs 5±19, p=0.018). In patients with coronary plaque, 3-vessle diseases were seen in 11 (21%) PsA patients and 4 (5%) controls (p=0.007); while severe stenosis was seen in 7 (13%) PsA patients and 1 (1%) controls (p=0.008). After adjusting for traditional CVD risk factors, PsA remained the strongest predictor for all types of coronary plaques (Table 1). In all subjects with plaque (52 PsA patients and 74 controls), PsA was the only independent predictor for 3-vessel disease after adjusting for CVD risk factors [odd ratio: 5.724 (1.506-21.759), p=0.010]. In PsA patients, the PsA disease duration was the only disease specific characteristic which was correlated with the more vulnerable plaque types (MP/NCP) in univariate [1.057 (1.003-1.113), p=0.037] and multivariate analysis [1.067 (1.010-1.127), p=0.020; adjusted for age, gender, hypertension, diabetes, hyperlipidemia, family history of CVD and smoking]. The other independent predictor was male gender [3.519 (1.306-9.480), p=0.013].

Conclusion: PsA patients had higher prevalence and severity of coronary atherosclerosis compared with control subjects. Longer disease duration, but not older age, was independently correlated with the more vulnerable MP/NCP in PsA patients. Table 1. Independent predictors in multivariate analysis for coronary plaque in PsA patients and control subjects.

		Odd ratio	95% CI	*p*
All plaque	PsA	4.552	2.517-8.232	<0.001
	Age	1.095	1.059-1.132	<0.001
	Male gender	2.538	1.350-4.769	0.004
CP	PsA	3.708	1.870-7.351	<0.001
	Age	1.107	1.057-1.159	<0.001
	Male gender	2.386	1.044-5.453	0.039
	Dyslipidemia	2.808	1.261-6.254	0.012
MP	PsA	4.523	2.048-9.991	<0.001
	Age	1.077	1.024-1.132	0.004
	Male gender	3.099	1.158-8.293	0.024
NCP	PsA	3.283	1.886-5.715	<0.001
	Age	1.039	1.008-1.070	0.012
MP or NCP	PsA	4.120	2.349-7.228	<0.001
	Age	1.061	1.029-1.094	<0.001
	Male gender	2.231	1.194-4.167	0.012

Adjusted for age, gender, hypertension, diabetes, hyperlipidemia, and smoking

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Abstract Number: 3100

Can Achieving Sustained Minimal Disease Activity (MDA) Prevent Progression of Subclinical Atherosclerosis? a Prospective Cohort Study in Psoriatic Arthritis

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Background/Purpose: Patients with PsA were reported to have a higher incidence of cardiovascular disease (CVD) and subclinical carotid atherosclerosis due to underlying inflammation. Minimal disease activity (MDA) is a validated treatment target for managing PsA. While achieving MDA was associated with benefits in articular disease, it's effect on co-morbidities including CVD risk remained uncertain. This study aimed to investigate the effect of achieving sustained MDA on subclinical atherosclerosis evaluated by carotid intima-media thickness (IMT).

Methods: 100 PsA patients without overt CVD were recruited. Patients were followed for 2 years with clinical assessment every 4 months. Treatment was guided by a standardized protocol aiming at MDA. Sustained MDA(sMDA) was defined as achieving MDA

at each visit from month 4 to 12. Carotid IMT were evaluated at baseline, month 12 and 24 using a high-resolution B-mode ultrasound machine. IMT was calculated based on the measurements at bilateral distal, bulb and proximal internal carotid artery.

Results: This is an interim analysis of the ongoing study. 51 PsA patients [male: 27 (52.9%); 50 ±12 years] who completed 12 months follow-up were analyzed. After 1 year of intensive treatment, significant improvement in disease activity [DAPSA: 15 (10,21) at baseline to 5 (2, 10) at 12 months (p<0.001)] was observed, and a significantly higher proportion of patient achieved MDA [8 (15.7%) at baseline vs 28 (54.9%) at 12 months p<0.001]. Mean carotid IMT increased significantly from 0.620 mm ±0.112 to 0.654 mm ±0.120 (p=0.04). 11/51 (21.6%) patients achieved sustained MDA. Baseline disease activity measures (PASI and DAPSA) and HAQ scores were lower in sMDA group. At 12 months, the mean carotid IMT were significantly lower in the sMDA group than the non-sMDA group [0.612±0.049mm vs 0.668±0.130mm (p=0.030)] while no significant changes were observed in the maximum IMT. Baseline mean carotid IMT was associated with month 12 mean carotid IMT (p<0.001). Using ANCOVA, the adjusted mean carotid IMT remained significantly lower in the sMDA group (0.612±0.023 mm vs 0.666±0.012 mm respectively, p=0.041) after adjusting for baseline mean carotid IMT (Table 1). There was also a significant difference in the change in mean IMT (-0.01± 0.08mm in sMDA group, vs 0.05± 0.08mm in non-sMDA group, p=0.046). The results remained significant when the changes were expressed as percentage changes of the baseline mean IMT (-0.1± 10.6% vs 7.9± 11.7%, p=0.046). The differences were statistically insignificant after adjusting for baseline differences probably due to small number. No significant changes were observed in the change in maximum IMT.

Conclusion: Effective suppression of inflammation by achieving sustained MDA may prevent progression of subclinical atherosclerosis in PsA patients Table 1 Changes in Carotid IMT over a 12 month period in patients who can or cannot achieve sustained MDA

	Non-sustained MDA group (n=40)	Sustained MDA group (n=11)	p	p*
Mean carotid IMT, mm				
Baseline	0.621 ± 0.117	0.620 ± 0.093	0.981	
Month 12	0.666 ± 0.012	0.612 ± 0.023	0.041	
Changes in mean carotid IMT, mm	0.05 ± 0.08	-0.01 ± 0.08	0.046	0.062
Percentage change in mean carotid IMT, %	7.9 ± 11.7	-0.1 ± 10.6	0.046	0.056
Maximum carotid IMT, mm				
Baseline	0.762±0.172	0.807±0.190	0.453	
Month 12	0.807±0.146	0.757±0.082	0.283	
Changes in maximum carotid IMT, mm	0.05±0.16	-0.05±0.17	0.094	0.094
Percentage change in maximum carotid IMT, %	8.6±19.6	-2.7±17.5	0.090	0.074

* Adjusted for baseline HAQ, PASI and DAPSA

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Abstract Number: 3101

Lipoprotein Profile and Serum Glycoprotein Acetylation As Markers of Cardiovascular Risk in Systemic Lupus Erythematosus

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Background/Purpose: The risk of atherosclerotic cardiovascular disease (CVD) is significantly increased in systemic SLE compared to age and gender matched controls. The implementation of nuclear magnetic resonance (NMR) analysis has allowed for the analysis of novel biomarkers of CVD, including assessment of lipoprotein particle counts/size as well as serum glycoprotein acetylation (GlycA) levels. GlycA is a proinflammatory biomarker that predicts 5 year all cause mortality and incident CVD in the general population. GlycA levels reflect the abundance of mobile N-acetyl sugar groups found in glycoproteins in circulating blood. We assessed the association of lipoprotein profiles and serum GlycA levels with vascular function, arterial inflammation, coronary plaque and lupus disease activity.

Methods: Clinical and demographic characteristics, SLE disease activity (by SLEDAI), damage accrual (by SLICC), Framingham risk score (FRS), and metabolic parameters were recorded at each visit. SLE (n=54) and matched healthy controls(n=32) underwent vascular function assessments by measuring peripheral arterial tonometry of the microvasculature (EndoPAT), arterial stiffness using a cardio-ankle vascular index (CAVI) and SphygmoCor, aortic inflammation by 18-fluorodeoxyglucose positron emission tomography/computerized tomography (FDG-PET/CT), and quantification of plaque by coronary CT angiogram (CTA). Lipoprotein profiles and GlycA levels were obtained by NMR analysis.

Results: Lupus and control individuals did not differ in gender, tobacco use, standard lipid profile or FRS but had higher prevalence of insulin resistance and BMI. Mean SLEDAI score was 3.5 ± 2.9. HDL, medium HDL and IDL particle counts were lower in SLE compared to controls ($p<0.001$), whereas medium VLDL particle counts and GlycA levels were significantly increased in SLE ($p =0.034$ and <0.001 respectively) when compared to controls. Among SLE patients, HDL particles negatively correlated with SLEDAI ($r= -0.33$, $p=0.015$) and non-calcified plaque by CTA ($r= -0.29$, $p=0.003$), VLDL particles positively correlated with non-calcified plaque ($r=0.24$, $p=0.015$) and arterial inflammation ($r=0.36$, $p=0.014$). Within SLE patients, GlycA levels significantly correlated with SLICC ($r=0.29$, $p=0.047$), insulin resistance ($r=0.36$, $p=0.007$), aortic inflammation, assessed by FDG-PET/CT ($r= 0.35$, $p=0.019$) and arterial stiffness using sphygmocor ($r=0.57$, $p<0.001$). In an unadjusted linear regression model, higher GlycA levels associated with increased arterial stiffness in SLE but not in controls ($r=0.62$, $p<0.001$) and this association remained significant after adjusting for FRS, BMI and insulin resistance. GlycA levels added incremental value in predicting non calcified plaque in lupus patients beyond FRS and Hs-CRP when added to nested models ($r=5.41$, $p=0.020$).

Conclusion: SLE individuals demonstrate significant increases in serum GlycA levels and a proatherogenic lipoprotein profile, even when lupus disease activity is low, in association with CVD risk markers. Future longitudinal analysis will assess the clinical implications of these findings and role of these tests as biomarkers of CVD in SLE.

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Abstract Number: 3102

Neutrophil Subsets, Arterial Inflammation, and Vascular Stiffness in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Patients with systemic lupus erythematosus (SLE) show a striking increase in risk of atherosclerotic cardiovascular disease (CVD) not explained by Framingham risk, when compared to age and gender matched controls. Immune dysregulation and innate immune responses associated to aberrant neutrophils (low density granulocytes, LDGs) may play a key role in conferring enhanced CV risk, driving vascular damage, oxidizing HDL and altering its function. Whether proinflammatory neutrophils are associated to and predict vascular inflammation, endothelial dysfunction, and eventually, clinical vascular events remains to be determined.

Methods: In this cross-sectional study, SLE patients fulfilling ACR classification criteria were compared to age and gender-matched controls. Clinical and demographic characteristics, Framingham Risk score, metabolic parameters, and lupus medications were recorded at each visit. Individuals underwent assessment of a) vascular function of various arterial territories: peripheral arterial tonometry of the microvasculature (Endopat), arterial stiffness by cardio-ankle vascular index (CAVI) and by Sphygmocor; b) aortic inflammation by FDG-PET/CT; and c) anatomical assessment of plaque by coronary CT angiogram. Circulating LDGs were quantified by flow cytometry. Cholesterol efflux capacity was quantified in radioactively-labeled cell lines upon exposure to control or lupus HDL.

Results: Lupus (n=54) and healthy controls (n=32) did not differ in gender, race, ethnicity or Framingham risk score. Mean disease duration was 16 ± 12 years and SLEDAI was 3.5 + 2.9. Arterial stiffness assessed by CAVI was increased in SLE (CAVI: 7.3[6.5-8.0]) vs. controls (6.3[5.9-7.4]; p = 0.004), and by Endopat augmentation index (AI75: 14.4 ± 18.7) vs. controls (5.5 ± 20.7, p = 0.022). Additionally, SLE patients displayed enhanced aortic inflammation by FDG-PET/CT (TBR: 1.63 [1.5-1.8]) vs. controls (1.56 [1.5-1.7], p=0.010). Differences between control and SLE persisted in multivariate regression analysis adjusting for Framingham Risk**.** HDL efflux was negatively associated with noncalcified plaque burden in SLE (b=-0.30, p=0.002), while LDGs were positively associated with noncalcified plaque burden (b=0.37, p<0.001), both persisting in multivariate regression analysis adjusting for Framingham Risk + body mass index or insulin resistance. In addition, number of lupus LDGs positively associated with damage (SLICC score (b=0.31, p=0.031)), CRP (b=0.46, p=0.001), and arterial stiffness (b=0.44, p=0.012).

Conclusion: Individuals with SLE demonstrate increased arterial stiffness and prominent arterial inflammation suggestive of widespread damage across both micro- and macro-vascular territories. These results support the hypothesis that aberrant neutrophil subsets significantly contribute to vascular damage and unstable plaque development in SLE. Results also support previous observations that neutrophils, through enhanced neutrophil extracellular trap formation, may disrupt HDL function and further promote atherogenesis.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/neutrophil-subsets-arterial-inflammation-and-vascular-stiffness-in-patients-with-systemic-lupus-erythematosus

Abstract Number: 3103

Apolipoprotein L1 Risk Variants Associate with Prevalent Cardiovascular Disease

in African American Systemic Lupus Erythematous Patients

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SESSION INFORMATION

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Background/Purpose: Two Apolipoprotein L1 (APOL1) risk variants (RV), G1 and G2, located on chromosome 22q12.3, have been associated with excess renal risk in African Americans (AA). The strongest correlations are in those with comorbid infectious or inflammatory diseases such as HIV or SLE collapsing glomerulonephropathy potentially owing to increased gene expression in the setting of chronic inflammation. APOL1 related cardiovascular disease (CVD) risk has been more controversial. Of four large, population-based studies, two reported 2-8 fold increased CVD in RV homozygotes while two others reported no increased risk. APOL1 associated CVD has never been assessed in a cohort with comorbid inflammatory disease. Accordingly, this retrospective cohort study evaluates prevalent CVD across APOL1 genotypes in SLE patients to test the hypothesis that the APOL1 cardiovascular phenotype is more penetrant in an SLE population.

Methods: PCR/sequencing was completed in 92 AA SLE patients. Subjects were stratified by genotype: ancestral (G0/G0), RV heterozygotes (RV/G0), and RV homozygotes (RV/RV). Clinical CVD endpoints including both *cardiac*: congestive heart failure, arrhythmia, and left ventricular hypertrophy; and *atherosclerotic*: coronary artery disease, myocardial infarction, peripheral vascular disease, vascular calcifications, and carotid artery disease were assessed by chart review. Logistic regression was used to test associations between the genotypes and a composite CVD end point defined by meeting one or more of the above parameters. Secondary analysis of atherosclerotic vs cardiac end points was also completed.

Results: The G0/G0, RV/G0, and RV/RV groups comprised 33%, 54%, and 13% of the cohort. Subjects were predominantly female (90%). There were no differences in history of SLE nephritis, diabetes, smoking, or age across the genotypes. Among patients with current or past nephritis, a larger percentage of the RV/RV group had progressed to ESRD at the time of study enrollment (G0/G0 or G0/RV: 8.3% vs RV/RV: 33%; OR: 3.8 p: 0.051). The RV associated with CVD; 21.2%, 41.7%, and 63.6% of the G0/G0, RV/G0, and RV/RV groups met the composite endpoint respectively (χ^2: 7.3; p: 0.026). When adjusting for CVD risk factors including smoking, ESRD, obesity, and hypertension, carrying one or more RV conferred a 3.1 fold increased risk of CVD (p: 0.03). The RV associated most strongly with atherosclerotic endpoints (OR: 7.5 p: 0.01) compared to cardiac disease end points (OR: 2.5, p: 0.22). These trends were present despite a shorter duration of SLE in the RV groups (groups (G0/G0: 15.1yrs ±8.6, G0/RV: 9.2±7.9, RV/RV: 12.9±10.5, p: 0.04).

Conclusion: The undulating inflammation of SLE plays an important role in each step of atherogeneisis from endothelial dysfunction to plaque rupture. In RV carriers, it may also increase the toxic protein burden leading to an amplified propensity towards CVD. Taken together, the RV is associated with prevalent CVD in this AA SLE cohort suggesting that SLE may be an important "second hit" in the relationship between APOL1 RV and CVD.

Disclosure: A. Blazer, None; **R. M. Clancy**, None; **H. M. Belmont**, None; **P. M. Izmirly**, None; **A. Markham**, None; **J. P. Buyon**, Exagen, 2,GSK, 5,UCB, 5,Abbvie, 5,Immunarray, 5.

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Abstract Number: 3104

Early Proteinuria Response in Real Life Situation Predicts Long-Term Lupus Renal Outcome in Ethnically Diverse Group with Biopsy-Proven Nephritis

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Background/Purpose: Treat to target strategies are becoming the best approach for several rheumatic disorders. Recently retrospective analyses of two important lupus trials have reported that proteinuria is the single best predictor of renal outcome in lupus patients. Samples from these trials were however mainly Caucasians and mostly from patients in the first nephritis episode with non-severe renal involvement at entry. In addition, on average, adherence to intervention protocols is higher in clinical trials than in non-research settings. The purpose of this study was therefore to determine in real-life situation if proteinuria was also a good predictor of renal outcome in a geographical region with more racial diversity.

Methods: 94 biopsy-proven lupus nephritis patients with at least 7 years longitudinal follow-up at the Rheumatology Division of a tertiary university hospital were consecutively selected. Data were obtained using a standardized electronic database protocol including demographic data, clinical and laboratorial findings and treatment. Proteinuria, serum creatinine (SCr), urine red blood casts (RBC) and anti-dsDNA antibody were evaluated at baseline and after 3, 6, 12 months and then 7 years of follow-up. We assessed the ability of these biomarkers at these different time points to predict good long term renal outcome (defined as SCr<1.5mg/dl) at 7 years. Receiver operating characteristic (ROC) curves were generated to assess parameter cutoff and performance at these time points and to select the best parameter considering sensitivity, specificity, positive and negative predictive values. Kaplan Meier curves were used to assess renal survival of each group.

Results: 80 (85.1%) were women, 38 (40.4%) were non-white patients and 38 (40%) were not in the first episode of nephritis. At baseline, patients had mean SCr of 1.73±1.34 mg/dl, proteinuria 5.46±4.51g/24h, albumin 2.45±0.78g/dl and SLEDAI 9.46±4.23. Proteinuria <0.83g/24h at 12 months of follow-up was the best single predictor of good long-term renal outcome (Sensitivity=90.3%, Specificity=78.3%, PPV=62.0% e NPV=90.3% AUC=0.86, p<0.001). The addition of other variables to proteinuria analysis such as SCr and RBC at month 12 did not improve the predictive performance of this parameter. Further evaluation of the proposed proteinuria cut-off (<0.83g/24h at 12 months) revealed that this parameter is a good predictor of 7 years renal survival (defined as years free of dialysis) for pure membranous (p=0.005), proliferative nephritis (p=0.043), blacks (p=0.002), whites (p=0.001), anti-dsDNA positive (p=0.001), males (p=0.028) and females (p=0.003) patients.

Conclusion: We demonstrated in a real-life situation that proteinuria at 12 months of follow-up was the single best predictor of good renal outcome at 7 years for an ethnically diverse group. We further validated this parameter as long-term predictor of renal outcome for distinct histological classes, races, gender and anti-dsDNA profile.

Disclosure: M. Lopes, None; **L. Seguro**, None; **M. Castro**, None; **D. Daffre**, None; **E. F. Borba**, None; **E. Bonfa**, None.

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Abstract Number: 3105

Relationships Between a Serum Biomarker of B Cell Differentiation and B Cell Activating Factor Suggest Possible Distinct Pathways of Response to Rituximab in Patients with Systemic Lupus Erythematosus

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Background/Purpose: Rituximab (RTX) has been used off-label in refractory SLE with variable clinical outcomes in different cohorts, with no predictive response markers available. However, the kinetics suggest that interruption of B cell maturation and differentiation, rather than removal of B cells per se, may underlie clinical success. The soluble form of CD23 (sCD23) is cleaved and released during B cell differentiation to memory phenotype (CD27+). Concerted binding of B cell activation factor (BAFF) to at least 3 receptors is a survival factor for naïve B cells, promotes class-switch and plasmablast differentiation. We aimed to investigate whether different sCD23 and BAFF profiles could be of value for predicting clinical response to RTX in patients with SLE.

Methods: We included 98 serum samples from 26 SLE patients (ACR 1982 revised criteria) taken 3 to 13 months prior to first RTX treatment. BAFF and sCD23 were determined using ELISA [upper limits of normal (ULN) given by manufacturers: sCD23 >5000pg/ml; BAFF >2ng/ml]. Data was analyzed in relation to B cell depletion (CD19+B cells<5/µl), clinical characteristics, anti-dsDNA and BILAG response at 6 months.

Results: Table 1 shows clinical data and results. Serum sCD23 and BAFF were weakly correlated in all samples (r^2=0.11; p=0.001). Levels of both analytes from individual patients were found to follow broadly consistent patterns. Patients could therefore be grouped according to levels greater or lower than ULN: Group I – High sCD23, Low BAFF; Group II – High sCD23, High BAFF; Group III – Low sCD23, Low BAFF; Group IV – Low sCD23, High BAFF. Patients in Groups I and IV had higher BILAG responses at 6 months. No patients in Group III had renal involvement.

Table 1.					
	Group I **High sCD23, Low BAFF** n=5	**Group II** **High sCD23, High BAFF** n=8	**Group III** **Low sCD23, Low BAFF** n=6	**Group IV** **Low sCD23, High BAFF** n=7	**Total** n=26
Ethnicity					
Caucasian	5 (100%)	3 (37.5%)	3 (50%)	3 (42.9%)	14 (53.8%)
Afro-Caribbean	0 (0%)	5 (62.5%)	2 (33.3%)	4 (57.1%)	11 (42.3%)
Asian	0 (0%)	0 (0%)	1 (16.7%)	0 (0%)	1 (3.8%)
Auto-antibodies					
dsDNA +	3 (60%)	7 (87.5%)	5 (83.3%)	5 (71.4%)	20 (76.9%)
Clinical Involvement					
Renal	2 (40%)	4 (50%)	0 (0%)	4 (57.1%)	10 (38.5%)
Neurological	0 (0%)	0 (0%)	1 (16.7%)	2 (28.6%)	3 (11.5%)
Fatigue	2 (40%)	6 (75%)	5 (83.3%)	2 (28.6%)	15 (57.7%)
Clinical Response					
3M Depletion	4 (80%)	3 (50%) *2 missing values*	4 (66.7%)	4 (57.1%)	15 (62.5%) *2 missing values*
6M BILAG Response					
Complete/Partial	4 (80%)	2 (25%)	2 (33.3%)	5 (71.4%)	11 (42.3%)
No	1 (20%)	6 (75%)	4 (66.7%)	2 (28.6%)	12 (46.2%)
M – Months; Depletion defined as less than 5 CD19+ B cells/µl					

Discussion: Group I: High sCD23: increased differentiation of naïve to memory B cells, together with a good response to RTX, suggest T cell stimulation is driving the process in a BAFF independent fashion. Group II: Poor depletion and high sCD23 suggests stimulation/maturation of post-germinal center B cells, with possible BAFF-driven differentiation to memory B cells and antibody producing B cells. B cell resistant to RTX-depletion in protected sites may explain poor clinical responses. Group III: Low sCD23 and BAFF suggests that B cells may not be central in the pathogenesis, with a more T cell dependent process. This could explain the poorer clinical response to RTX despite good depletion. Group IV: High BAFF stimulates autoreactive naïve B cell differentiation directly to plasmablasts and autoantibody production, bypassing memory B cells (Low sCD23). Resulting immune-complexes processed through antigen presenting cells (and IFN signature) continuously stimulate BAFF production.

Conclusion: Based on the patterns of sCD23 and BAFF and B cell biology observed in SLE we hypothesize that the combination of these biomarkers may identify distinct autoimmune pathways and likely predict clinical response.

Disclosure: R. Marques, None; **L. Heretiu**, None; **D. A. Isenberg**, None; **M. J. Leandro**, Roche Glycart, 2,Genentech and Biogen IDEC Inc., 9,Roche Pharmaceuticals, 9; **G. Cambridge**, None.

Abstract Number: 3106

A Simple Test for Assessing and Monitoring SLE Disease Activity Status

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Background/Purpose: SLE patients can experience chronically active disease, remissions and flares, or long periods of quiescence. Accurately assessing disease activity is crucial for prescribing appropriate drug regimens, evaluating treatment outcomes, and detecting early onset of flares; however, there is currently no "gold-standard" biomarker for this determination. Though not in routine clinical use, the SLEDAI scoring system is often applied in clinical trials to evaluate the efficacy of new drugs. Scores <3 are typically considered as inactive disease, 4-15 as mild to moderate, and >15 as severe. The Immuno*Signature* (IMS) Technology further described below was investigated as a potential single serological surrogate for lupus disease activity that is amenable to routine use.

Methods: Sera from 500 SLE patients meeting the ACR classification criteria at diagnosis were evaluated by IMS at different times post-diagnosis. SLEDAI scores ranged from 0 (n=150) to 27. Patients with scores 2-27 (n=350) were selected to sample the range as uniformly as possible (median = 8; IQR 4-10). IMS assays were used to measure serum antibodies bound to a microarray of ~126,000 unique peptides designed to broadly sample chemical space, thereby providing a library of diverse epitope mimetics for antibodies to selectively bind. Peptide features with binding intensities that were significantly different between active and inactive SLE were identified by t-test. Support vector machine classifiers and linear regression models were trained and tested by 100 iterations of 5-fold cross validation.

Results: A total of 34,147 peptides were identified that significantly ($p<0.05$ after Bonferroni correction) differentiated active from inactive SLE (Fig 1). Receiver-operator characteristic (ROC) curves demonstrated significantly superior classification of the samples as inactive or active by an IMS classifier model, compared to standard biomarkers of disease activity such as C4 (not shown), C3, anti-dsDNA, and proteinuria (Fig. 2). Good discrimination was achieved by training on SLEDAI >8 vs. 0, with performance further enhanced when applied to extreme contrasts. For example, a classifier of SLEDAI >15 vs. 0 had an AUC of 0.90 (95% CI 0.88 - 0.92). Correlations of a linear IMS (r=0.48), C3 (r= -0.41) and anti-dsDNA (r=0.36) to SLEDAI were also determined.

Conclusion: A single serologic test, using specific binding patterns of serum antibodies on a highly complex and diverse mimetic peptide array, can molecularly determine SLE disease activity and improve upon current methods of evaluating and monitoring patients.

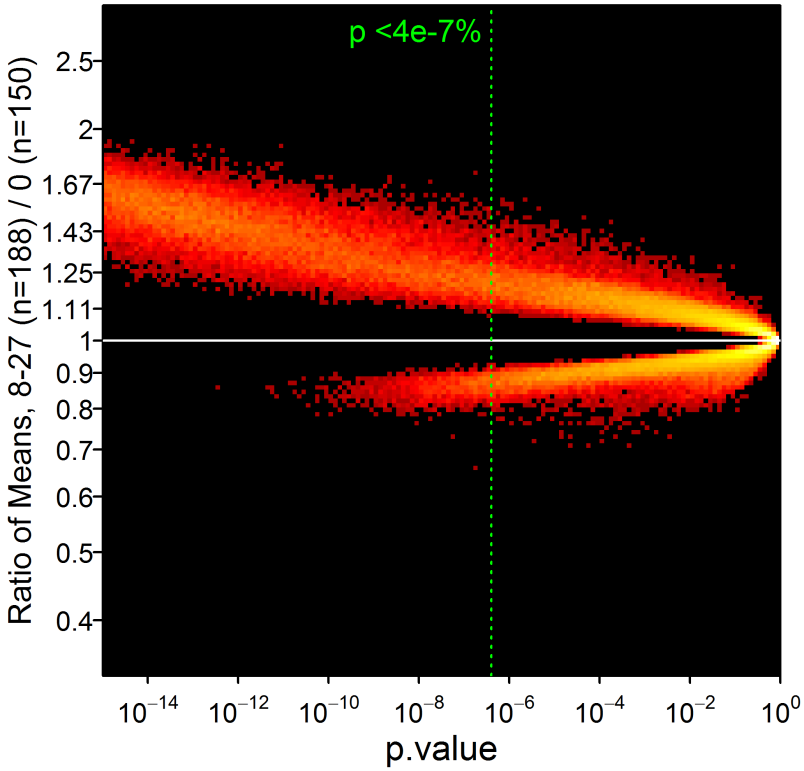

Figure 1. Differentiation of patients' lupus disease activity levels by peptide binding intensities. The ratio of mean intensity among samples from patients with SLEDAI >8 to mean intensity in patients with inactive disease (SLEDAI=0) is plotted vs. the p-value for the difference in means from a t-test.

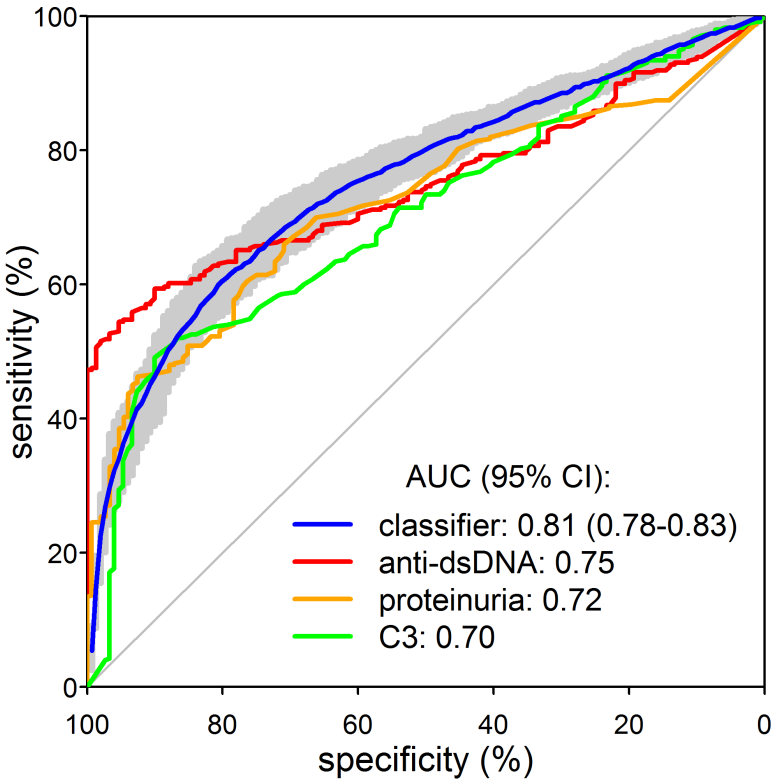

Figure 2. ROC curves for an ImmunoSignature classifier of disease activity compared to biomarkers, for identifying patients with active disease (SLEDAI >0). The gray region indicates the 95% confidence interval of the classifier.

Disclosure: C. Putterman, Healthtell, Inc., 9; **M. Rowe**, HealthTell, Inc., 1,HealthTell, Inc., 3; **J. B. Legutki**, HealthTell, Inc., 1,HealtjhTell,Inc., 3; **T. M. Tarasow**, Healthtell, Inc., 3,HealthTell, Inc., 1; **K. Sykes**, HealthTell, Inc., 1,HealthTell, Inc., 3.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-simple-test-for-assessing-and-monitoring-sle-disease-activity-status

Abstract Number: 3107

Switching from Anabolic to Catabolic Metabolism – a Novel Immunomodulatory Therapy in RA

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Background/Purpose: Inflammatory activity in RA relies on numerous anabolic processes; including cellular proliferation, cell trafficking, secretion of proinflammatory cytokines and release of antibodies. Lasting reversal of inflammation would require to correct such anabolic processes; ideally in the pinnacle pathogenic drivers of RA, HLA-class II-restricted CD4 T cells. CD4 T cells in RA patients are metabolically reprogrammed due to a lack of the catabolic enzyme phosphofructokinase 2 (PFK2) and an excess in the anabolic enzyme glucose-6-phosphate dehydrogenase (G6PD). It is insufficiently understood how metabolic reprogramming affects disease-relevant T cell effector functions and whether this metabolic defect is amendable to therapeutic intervention.

Methods: Patients with seropositive and clinically active RA as well as age-matched healthy controls were enrolled. For molecular and functional studies, the population of naïve $CD4^+CD45RA^+$ T cells was activated through TCR crosslinking. Metabolites and reactive oxygen species (ROS) were measured after 72 hr, cytokine production after 7 days. Arthritogenic activity was quantified by adoptive transfer into NSG mice carrying human synovium. To reset the cells' metabolic homeostasis, the following small molecule reagents were applied in vitro and/or in vivo: the G6PD inhibitor 6-amino-nicotinamide (6-AN), the gamma-glutamylcysteine synthetase (γ-GCS) inhibitor Buthionine-sulph-oximine (BSO), and the 1,4-naphthoquinone analog Menadione.

Results: Compared to healthy control T cells, RA T cells produced more NADPH ($p<0.05$), had lower ROS ($p<0.001$) and higher intracellular glutathione levels ($p<0.05$), indicative of excess glucose shunting into the pentose-phosphate pathway. Functional consequences included: higher cellular proliferation ($p<0.01$), faster cell-cycle passage ($p<0.001$), earlier naïve-to-memory conversion ($p<0.05$) and preferential Th1 and Th17 lineage commitment ($p<0.05$). G6PD inhibition restored intracellular ROS level, corrected the cell-cycle behavior and suppressed IFN-γ production. In human synovium-NSG chimeric mice, RA T cells promptly invaded into the synovial tissue ($p<0.001$), where they produced IFN-γ and IL-17 and stimulated production of TNF-α, IL-1β and IL-6. Treatment with BSO or Menadione corrected the metabolic abnormalities and suppressed inflammatory activity in the synovial tissue.

Conclusion: T cells in RA patients are biased towards anabolic metabolism, resulting in excessive biomass generation, hyperproliferation and secretion of proinflammatory effector molecules. The underlying molecular mechanisms involve the gain in NADPH and the shift of the redox balance towards reductive elements. Pharmacologic interventions that restore oxidant signaling are highly effective in normalizing the cell-cycle behavior of affected T cells and in suppressing synovial inflammation.

Disclosure: Z. Yang, None; **Y. Shen**, None; **E. L. Matteson**, None; **E. Hosgur**, None; **J. Hong**, None; **J. Goronzy**, None; **C. M. Weyand**, None.

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Abstract Number: 3108

Citrullinated Aggrecan Peptides Are Targets of Auto-Reactive CD4+ T-Cells in Rheumatoid Arthritis

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Background/Purpose: T-cell frequencies against citrullinated epitopes derived from major auto-antibody targets (vimentin, fibrinogen, α-enolase) are increased in rheumatoid arthritis (RA). Emerging serologic data suggests antibody reactivity against additional citrullinated proteins, including histones and aggrecan, in RA. Among these potential targets, previous studies found T-cell reactivity against aggrecan peptides in models of RA and to some extent in clinical samples (Boots AM *et al.,* 1997; Law SC *et*

al., 2012; Aggarwal A *et al.,* 2013). Here, we undertook a systematic approach to verify the relevance of aggrecan specific CD4+ T-cell responses in RA.

Methods: Citrullinated aggrecan epitopes were predicted for their binding to DRB1*04:01 and candidates confirmed using binding assays with recombinant protein. The immunogenicity of confirmed binders was then assessed using 14-day *in vitro* peptide stimulation cultures followed by tetramer staining and single-cell cloning from selected subjects. Epitopes eliciting a significant response were then used for *ex vivo* tetramer staining of PBMC from healthy controls and from CCP+ RA patients across a range of disease activities (based on RAPID3 scores).

Results: Starting with 28 cit-aggrecan peptides predicted to bind DR04:01, we identified 6 epitopes that activated and expanded CD4+ T cells with unusual strength for (modified) self-antigens. Using the corresponding tetramers we isolated cit-aggrecan specific T-cell clones specific for these peptides from RA patients. These clones selectively recognized citrullinated peptide and exhibited a Th1-like functional phenotype. *Ex vivo* tetramer analysis of PBMC revealed that a subset of RA patients had significantly increased frequencies of cit-aggrecan specific T-cells in comparison to healthy controls. Ongoing studies will determine whether cit-aggrecan specific T-cells arise early or late in disease, whether they have a distinct functional profile compared with healthy controls, and whether they exhibit expanded TCR clonotypes in established disease. Additionally, we are investigating the degree to which the serum from the blood or synovium contains antigens that specifically activate cit-aggrecan specific T-cell clones.

Conclusion: Citrullinated aggrecan, a protein associated with autoantibodies in a subset of RA patients, have the potential to elicit very strong CD4+ T cell responses. In a subset of patients these are apparent as strong *ex vivo* response and show a disease associated Th1-like phenotype and some signs of clonal expansion. So far the clinical correlations of these high frequencies remain unclear but are an intriguing target of our ongoing studies.

Disclosure: H. Uchtenhagen, None; **C. Rims**, None; **E. James**, None; **J. H. Buckner**, None.

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Abstract Number: 3109

Regulatory T Cells Deficient in Protein Phosphatase 2A Lose Suppressive Function and Convert to an Effector Phenotype

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Background/Purpose: Regulatory T cells (Tregs) represent the fundamental T-cell capable of promoting self-tolerance and balancing excessive inflammation. Quantitative and qualitative Treg deficiencies have been characterized in several systemic rheumatic diseases. Previously we found that the catalytic activity of protein phosphatase 2A (PP2A) in murine Tregs is increased at levels significantly higher than in conventional T cells. Furthermore, mice in which Tregs lack PP2A develop multi-organ inflammation and severe autoimmunity. PP2A-deficient Tregs displayed reduced suppressive function *in vitro*. This study investigates the underlying molecular mechanism whereby Tregs lose lineage stability, suppressive function and convert to an effector phenotype.

Methods: We constructed a *Foxp3*$^{YFP-cre}$*Ppp2r1a*$^{flox/flox}$ mouse that lacked PP2A only in Tregs and could be tracked by virtue of co-expressing yellow fluorescent protein (YFP). Age and sex-matched *Foxp3*$^{YFP-cre}$ were used as controls. Foxp3 expressing

Tregs were isolated from *Foxp3*$^{YFP-cre}$*Ppp2r1a*$^{flox/flox}$ mice by flow cytometry cell sorting ($CD4^+YFP^+$). The adoptive T-cell transfer colitis model was used to determine the suppressive function of Tregs with and without PP2A deficiency *in vivo*. One million Tregs were adoptively transferred into *Rag1* knockout recipients either alone or at a 1:1 ratio with conventional $CD4^+$ T-cells. Five weeks later colon, small bowel, spleen and lymph nodes were collected for both histologic and flow cytometry analysis. Standard ELISA was applied to detect cytokines.

Results: Tregs ($CD4^+YFP^+$) isolated from twenty week old *Foxp3*$^{YFP-cre}$*Ppp2r1a*$^{flox/flox}$ mice demonstrated decreased levels of intracellular Foxp3 and IL-10 by flow cytometry. Furthermore, PP2A-deficient Tregs acquired an inflammatory phenotype by producing IL-17. When PP2A-deficient Tregs were co-transferred with effector T cells into *Rag1*-deficient mice, they lost weight and developed inflammatory colitis. This demonstrated that the transferred Tregs lost their suppressive function *in vivo*. In fact, co-transfer of PP2A-deficient Tregs with effector T cells accelerated weight loss and worsened colitis compared to transfer of effector T cells alone. Elevated levels of IL-17 in the sera were detected by ELISA compared to sera obtained from the group of mice in which wild type Tregs and effector T cells had been co-transferred.

Conclusion: PP2A is essential for Treg function and maintenance of stable Foxp3 expression. Tregs deficient in PP2A produce less IL-10 and more IL-17. The dependence of Tregs on the presence of PP2A points to approaches to restore and empower Teg function in autoimmune disease.

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Abstract Number: 3110

Rab4A Is Required for Development of Tregs, Restricts Antiphospholipid Antibody Production and Pro-Inflammatory Expansion of Macrophages and Neutrophils, and Blocks Pristane-Induced Intra-Alveolar Hemorrhage in a Mouse Model of SLE

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SESSION INFORMATION

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Background/Purpose: Polymorphic haplotypes of the HRES-1 endogenous retrovirus at the 1q42 chromosomal locus have been associated with lupus susceptibility, in particular, with predisposition to antiphospholipid syndrome (APS) and protection from lung disease in patients with SLE (Arthritis Rheum. 58:532-540). Expression of the HRES-1/Rab4 protein of this genomic locus, which has been recently designated as Rab4A, is increased in T cells of SLE patients (J Immunol 182: 2063–2073) and lupus-prone mice (Ann Rheum Dis 73:1888–1897). Intra-alveolar hemorrhage is a rare but fatal complication of pulmonary involvement SLE. To determine the impact of this gene on disease development, mice with constitutively active Rab4A^{Q72L} alleles or lacking expression of Rab4A in T cells (*Rab4*A-KO^{CD4Cre}) have been generated in the C57Bl/6 strain.

Methods: Female mice were injected intraperitoneally with 0.5 ml of pristane and evaluated for pulmonary capillaritis (Rheumatology 46:1405-10). Mice were treated with 3 mg/kg rapamycin or solvent control for 7 days prior and 14 days post pristane injection. 14 days after pristane injection, spleen and lung tissues were examined for lineage specification within the adaptive and innate arms of the immune system by flow cytometry. Expression of Rab4A and activation of the mechanistic target of rapamycin complexes 1 (mTORC1) and 2 (mTORC2) were also examined by western blot. Production of antinuclear antibodies

(ANA) and antiphospholipid antibodies (aPL), such as anti-cardiolipin (ACLA) and anti-β_2 glycoprotein I autoantibodies (anti-β_2GPI) were measured by ELISA. Statistical analyses were performed using 2-tailed t-test and stated changes were significant at $p < 0.05$.

Results: Relative to wild-type (WT) mice (2.4±0.4), vasculitis scores were reduced in Rab4A^{Q72L} (1.1±0.1; p=0.021) and increased in Rab4A-KO^{CD4Cre} mice (3.6±0.2; p=0.042). ANA production was increased in Rab4A-KO^{CD4Cre} mice relative to age-matched WT (p=0.038) and Rab4A^{Q72L} controls (p=0.048). ACLA and anti-β_2GPI production was significantly reduced in Rab4A^{Q72L} mice relative to WT and Rab4A-KO^{CD4Cre} mice. mTORC1$^+$/mTORC2$^-$ IL-17-producing Th17 cells were increased 1.9-fold in the CD4$^+$ T cell compartment of Rab4A-KO^{CD4Cre} mice, and these cells were reduced by 48% in Rab4A^{Q72L} mice. In turn, mTORC1$^+$/mTORC2$^+$ CD4$^+$CD25$^+$ regulatory T cells (Tregs) were expanded 2.4-fold in Rab4A^{Q72L} mice, and these Tregs were reduced by 42% in Rab4A-KO^{CD4Cre} mice. Thymus-derived FoxP3$^+$Helios$^+$ Tregs were also expanded Rab4A^{Q72L} mice and depleted in Rab4A-KO^{CD4Cre} mice. IL-17-producing CD11b$^+$ pro-inflammatory macrophages were expanded 2.1-fold in the spleen and Gr1$^+$ neutrophils were expanded 8.4-fold in the lung of Rab4A-KO^{CD4Cre} mice. Rapamycin treatment did not block lung injury in pristane-treated WT or Rab4A-KO^{CD4Cre}mice.

Conclusion: Rab4A is required for mTORC1- and mTORC2-dependent development of Tregs, which restrict aPL production and pro-inflammatory expansion of macrophages and neutrophils and block pristane-induced intra-alveolar hemorrhage in a mouse model of SLE. Thus, constitutive activation of Rab4A blocks organ-specific disease development and offers a novel target for diagnosis and treatment of SLE.

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Abstract Number: 3111

Pathogenic T Cell Responses in Systemic Sclerosis Is Shaped By Novel Cytokine Axis in the Microenvironment: A Multidimensional, High Throughput Analysis

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Background/Purpose: Pathogenic immune responses can be profoundly shaped by the interplay between the periphery and the microenvironment. In this work we aimed at defining the immune mechanisms at the interface between the skin microenvironment and the periphery that are relevant for the disease pathogenesis in Systemic sclerosis (SSc), an autoimmune disorder of the connective tissue.

Methods:

Utilising an Immunomics platform that integrated in the same experimental flow: mass cytometry (CyTOF) for the identification of

disease-specific immune signatures (35 T cell specific markers), next generation RNAseq to characterize molecular patterns of antigen-specific T cells both in the periphery and in the skin microenvironment, NanoString platform to decipher the molecular characteristics of the skin microenvironment and various functional assays to validate the findings. Using this approach we interrogated peripheral blood (n=59) and compared them with healthy controls (n=33). We also compared paired lesional skin and peripheral blood derived T cells (n=7). Datasets were analysed by in-house developed computational tools.

Results:

Pathogenic Th17/Treg, Th17/Tfh cells and prototype Th17 cells were enriched in SSc subjects both in the periphery and in the skin microenvironment. Whole transcriptome analysis revealed skin derived T cells had elevated expression of IL-11 receptor (IL-11RA). Pathway analysis showed SSc skin derived T cells induced a distinct set of IL-17 regulated genes in dermal fibroblasts including IL-11. Skin derived IL-11 induced secretion of Th17 polarizing cytokines such as IL-1b and IL-6 from monocytes and polarized naive T cells to a Th17 phenotype. IL-11/IL-11RA signaling was regulated along a MAP3K8, STAT3 and PIM-1 signaling axis.

Conclusion:

By combining complementary *ex vivo* and *in vitro* approaches with non-biased data-driven analysis we could show that there exists a self reverberating pathogenic loop at the interface between the systemic and the skin microenvironment. This loop centred on the IL-17, IL-11 and IL11-RA triad expands and maintains disease-specific and pathogenic Th17 T cell subsets. Our findings have a dual translational valency both for targeted therapies and for understanding immune pathogenesis of SSc.

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Abstract Number: 3112

DOCK8 Associates with STAT5 and Promotes Regulatory T Cell Function

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Background/Purpose: DOCK8 deficiency leads to autosomal recessive Hyper-IgE syndrome (AR-HIES). DOCK8 deficient patients develop recurrent sinopulmonary infections, chronic mucocutaneous viral infections, hyper-IgE, eosinophilia, food allergies, and severe dermatitis [1, 2]. We previously reported that the number and *in vitro* suppressive function of circulating regulatory T (Treg) cells are significantly reduced in DOCK8 deficient patients [3]. Paradoxically, they seldom develop autoimmunity, we propose that this is due to their impaired T effector (Teff) cell function.

Methods: We generated and analyzed *Dock8*$^{-/-}$ mice and mice with a selective DOCK8 deficiency in their Treg cells. Treg cell markers and *in vitro* suppressive function were investigated using flow cytometry. STAT5 phosphorylation was measured by flow cytometry and confocal microscopy. Using co-immunoprecipitation experiments, we examined the association between DOCK8 and STAT5.

Results: We determined that *Dock8*$^{-/-}$ mice have decreased Treg numbers and impaired *in vitro* function of Treg cells, but do not develop autoimmunity. In contrast, mice with selective DOCK8 deficiency in their Treg cells spontaneously develop lymphoproliferation, autoantibodies, and severe gastrointestinal inflammation, despite normal percentages of Treg cells. We found that DOCK8 associates with STAT5 and plays crucial role in IL-2 driven STAT5 phosphorylation and nuclear translocation in Treg

cells. These findings indicate that DOCK8 expression in Treg cells plays a critical role in self-tolerance by enhancing IL-2 driven STAT5 signaling, which is essential for Treg cell function, and suggest that deficient Teff cell function might protect DOCK8 deficient patients from autoimmunity.

Conclusion: These findings suggest that DOCK8 expression in Treg cells plays a critical role in self-tolerance by enhancing IL-2 driven STAT5 signaling. Furthermore, our data support the hypothesis that deficient Teff cell function may protect DOCK8 deficient patients from autoimmunity. References:

1. Engelhardt, K.R., et al., *Large deletions and point mutations involving the dedicator of cytokinesis 8 (DOCK8) in the autosomal-recessive form of hyper-IgE syndrome.*J Allergy Clin Immunol, 2009. 124(6): p. 1289-302 e4.

2. Zhang, Q., et al., *Combined immunodeficiency associated with DOCK8 mutations.*The New England journal of medicine, 2009. 361(21): p. 2046-55.

3. Janssen, E., et al., *Dedicator of cytokinesis 8-deficient patients have a breakdown in peripheral B-cell tolerance and defective regulatory T cells.* The Journal of allergy and clinical immunology, 2014.

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Abstract Number: 3113

Evaluation of a Clinical Transition Pathway for Adolescents with Autoimmune Diseases

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Background/Purpose: It is clear that young people (YP) with an autoimmune disease need a transitional process before they are transferred to the adult clinic. Therefore, a clinical transition pathway was implemented in 2009. Purpose of this transition pathway was to improve transition with provision of care developmentally appropriate, focus on achievement of self-management skills and supporting parents. The aims of this study were I) to evaluate the effectiveness of this clinical transition pathway, II) to evaluate the experiences and satisfaction in YA with autoimmune diseases in the transitional process.

Methods: All YP with an autoimmune disease who have been transferred from the pediatric to the adult rheumatology between 2009-2015 via the clinical transition pathway, were enrolled in this study. Most important points are an early start (14 years) with focus on self-management skills and independency using an individual transition plan (ITP) for each patient, joint consultations with professionals from pediatric and adult rheumatology and supporting parents in letting go. The ITP, a tool for developing self-management skills is essential in this pathway. Outcome measures for effective transition were drop out of care and completed ITP. To evaluate effectiveness electronic patients records(EPR) (n=158) were reviewed on completed ITP's and drop out of care. Additionally YA were asked to complete questionnaires after transition for the experience and satisfaction. Satisfaction with transition was measured with a transfer experiences scale, the OYOF-TES[1] (range 18-90) and a VAS scale (range 0-10); higher scores indicating higher satisfaction. Self-efficacy as an important variable for measuring self-management behavior was evaluated with the OYOF-SES[2] (range17-68, higher score, more SE).

Results: 158 YP were asked to participate, 77 YP returned questionnaires, a response rate of 50%. No difference was found between responders and non-responders on demographics and disease activity. Of 158 YA who ran through the clinical pathway, the overall rate of drop out was only 3.2% after one year. Of all YA 75% were transferred with an ITP. Satisfaction with transition measured with the OYOF-TES was high, 73.45 (SD 13.07). The VAS satisfaction was high with a mean of 7.6 (SD 1.62). Topics important for adolescents were discussed in almost all YA (96%). The OYOF-SES 58.65 (SD4.52).

Conclusion: The implementation of a clinical transition pathway was successful, a low dropout rate was seen and YP were satisfied with the transition process. High levels on the self-efficacy scale were reported, suggesting confidence of YP to achieve enough self-management skills. [1] van Staa A, Sattoe JN Young adults' experiences and satisfaction with the transfer of care. J Adolesc Health. 2014 Dec;55(6):796-803. doi: 10.1016/j.jadohealth.2014.06.008. Epub 2014 Aug 19. [2]A.L. van Staa, H.A. van der Stege, S. Jedeloo, et al. Readiness to transfer to adult care of adolescents with chronic conditions: Exploration of associated factors. J Adolesc Health, 48 (2011), pp. 295–302

Disclosure: M. Walter, None; **S. S. M. Kamphuis**, None; **P. A. van Pelt**, None; **A. Vroed de**, None; **J. M. W. Hazes**, None.

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Abstract Number: 3114

Cardiorespiratory Fitness in Children with Juvenile Idiopathic Arthritis Treated in the Biological Era Is Comparable with Controls- a Cross-Sectional Study

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Cardiorespiratory Fitness in Children with Juvenile Idiopathic Arthritis Treated in the Biological Era is Comparable with Controls- a Cross-Sectional Study

Background/Purpose: Reduced cardiorespiratory fitness (CRF) has previously been found in children with juvenile idiopathic arthritis (JIA) compared to healthy children. However, little is known about CRF in JIA patients treated in the biologic era. The aims were to compare CRF in JIA patients who have had access to biological treatment from disease onset with controls, and to study associations between CRF and measures of disease activity in patients.

Methods: Patients with persistent oligoarthrtitis or polyarticular disease were recruited consecutively at Oslo University Hospital. Age- and sex-matched controls were selected randomly from the Norwegian Population Registry. In all participants, CRF was directly measured as peak oxygen uptake (VO_{2peak}) during a continuous graded exercise test on a treadmill until exhaustion. Present pain and pain and fatigue the last week were assessed by a Numeric Rating Scale (NRS). Puberty was self-rated using the Tanner

Scale. In patients, the Juvenile Arthritis Disease Activity Score 71 (JADAS 71) and the Childhood Health Assessment Questionnaire (CHAQ) were used to measure disease activity and functional disability, respectively. Differences between groups were tested with paired t-tests, or Wilcoxon rank test and correlations with Pearson or Spearman's rho correlation coefficients.

Results: Fifty-nine patients (50 girls, 9 boys) with JIA, 30 with persistent oligo arthritis and 29 with polyarticular disease (extended oligoarthitis and polyarticular RF +/-) aged 10-16 years and 59 controls were included. All patients had been encouraged to stay physically active with no general restrictions regarding physical activity. Twenty-five (42.4 %) patients used biological drugs. No differences were found in VO_{2peak} (mL/kg/min) in patients vs controls; 45.1 ± 8.5 vs 46.5 ± 8.5, (p=0.38). Furthermore, there were no differences in VO_{2peak} (mL/kg/min) in patients with persistent oligoarthritis vs polyarthritis; 45.0 ± 7.6 vs 45.3 ± 9.4, (p= 0.87) or in patients with active disease (n=39) vs patients in remission (n=20) (46.4 ± 9.7 vs 44.5 ± 7.9, p=0.43). In patients, there were no correlations between VO_{2peak} and JADAS 71, number of active joints in the lower extremities, use of medication, use of biological medication, disease duration, CHAQ, present pain and fatigue (all r<-0.3, p=NS). However, VO_{2peak} correlated weakly with pain last week (r= -0.28, p=0.03).

Conclusion: CRF in JIA patients treated in the biological era is comparable to controls, and also comparable between patients with persistent oligo arthritis and polyarticular disease. Even if less than half the patients used biological drugs, the positive results may be explained by advances in multidisciplinary treatment including less limitations regarding physical activity.

Table 1. Characteristics of patients and controls

	JIA (n=59)	Controls (n=59)	p-value
Age (yrs)	13.6 ± 2.2	13.5 ± 2.6	0.85
Height (cm)	157.6 ± 12.5	160.8 ± 12.3	0.17
Weight (kg)	48.3 ± 11.8	53.1 ± 15.2	0.06
BMI (kg/m^2)	19.2 ± 3.0	20.1 ± 3.5	0.12
NRS present pain (0-10)	0 (0-6)	0 (0-4)	0.04
NRS pain last week (0-10)	1 (0-7)	1 (0-6)	0.67
NRS fatigue last week (0-10)	3 (0-10)	3 (0-8)	0.90
Pubertal status (pre-, mid-, and postpubertal %)	23.7/61.0/15.3	16.9/67.7/15.3	0.65
Disease duration (yrs)	7.5 ± 3.8		
CHAQ score (0-3)	0.0 (0-1.4)		
JADAS (0-101)	3.2 (0-12.8)		
No medication	12 (20.3)		
NSAIDs	15 (25.4)		
DMARDs	39 (66.1)		
Biologics	25 (42.4)		
Numbers are mean ± SD, median (min-max) or N (%)			

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Abstract Number: 3115

Reconsidering the Juvenile Idiopathic Arthritis Core Set: How Patients and Caregivers Define Disease Activity

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Background/Purpose: The current JIA Core Set (ACR Pediatric 30) contains items that should be assessed in clinical trials for children with JIA. It was developed in 1997 without subsequent update. A shortcoming of the existing Core Set is the lack of patient/caregiver input in its development. The OMERACT JIA Core Set Group formed in 2015 as an international initiative to revise the existing Core Set with relevant patient/caregiver input. The aim of the current study, as part of the larger initiative, was to conduct focus groups to: 1) develop a comprehensive list of potential patient/caregiver outcome domains, 2) define the concept(s) represented by each domain, and 3) begin to prioritize these domains.

Methods: Patient and caregivers from North America participated in virtual focus groups (VFGs) about their experiences related to JIA. The VFGs utilized online discussion boards instead of in-person focus groups in order to accommodate more participants from diverse geographic regions, facilitate unrestricted sharing, and be efficient and cost-effective. Two sets of VFGs were performed: 1) caregivers and 2) adolescents and young adults with JIA. Eligibility was based on self-reported diagnosis of JIA and prior or current experience of JIA disease inactivity (>3 months). A qualitative researcher conducted the VFGs, which consisted of a 3-day online discussion board per group. Discussion guides sought to elucidate the impact of JIA on physical, mental and social health, and the perceived differences between active and inactive JIA. Participants answered questions individually and then could comment on others' responses. Transcripts were coded into domains with respect to OMERACT Core Areas and analyzed using NVivo 10.

Results: The caregiver VFG was split based on the age of their children: <15 years (n=10), and >15 years (n=10). The patient VFG was split into ages 15-17 (n=11), and 18-24 (n=13). Each group was diverse with respect to geography and categories of JIA, and included patients with active and inactive disease at the time of study. Participants discussed their experiences with JIA, life impact, resource use, pathophysiological manifestations, and adverse effects of JIA and its treatment. Data analysis revealed unique domains not represented in the current Core Set. Patients identified various psychosocial impacts of JIA and how it impacted participation in activities with their peers, school and/or job. Caregivers of younger children expressed fear for the future and unknown manifestations of JIA. Caregivers of older children identified the impact JIA had on the family and their child's participation in activities. Patients and caregivers characterized disease inactivity as the absence of pain, stiffness and swelling, increased activity participation, and improved mood and sleep quality.

Conclusion: The VFG format helped elicit concepts important to distinct and diverse groups of stakeholders affected by JIA. The current JIA Core Set lacks the patient/caregiver-centered domains identified in this study. Future efforts will perform VFGs in other geographic areas (Europe, Australia) and develop a model of the patient/caregiver experience of JIA that will inform the ongoing effort to expand the JIA Core Set.

Abstract Number: 3116

Risk of Infections in Juvenile Idiopathic Arthritis Patients Treated with Biologic Agentsand/or Methotrexate: Results from Pharmachild Registry

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Session Time: 9:00AM-10:30AM

Background/Purpose: Pharmachild is an international registry involving over 100 the Paediatric Rheumatology INternational Trials Organisation (PRINTO)/ the *Paediatric Rheumatology European Society (*PRES) centres in 38 countries. The registry was set up to evaluate long term safety and efficacy of treatments in children with JIA. The purpose of the study was to evaluate the occurrence of infections in JIA children and their relationship with biologics ± methotrexate (MTX) and other immunosuppressants.

Methods: Retrospective and prospective evaluation of moderate to very severe and serious infections. We investigated, by means of bivariate and multivariate modeling, the relationship between infections and the drugs used in the 6 month-history prior to the infection and, for patients without infections, in the 6 months prior to the last follow-up visit. The patients receiving only NSAIDs or intra-articular steroid injections were used as a reference.

Results: We analyzed 6969 patients, for a total of 689 (10%) patients with infections. Patients were systemic 639 (9%), polyarticular course 4587 (66%) and persistent oligoarthritis 1473 (25%). Patients with infections were treated in the previous 6 months primarily with MTX (82%), corticosteroids (32%), anti-TNF (52%), anti IL-1/IL-6 (8%), rituximab (2%) or other biologics (2%).Earlier age at diagnosis (≤7.7 years), ANA positivity, and systemic JIA category significantly increased the risk for infection (OR 2.3, 1.7 and 2.2, respectively). The analysis of the impact of the single immunosuppressive drugs showed that the risk for infection is increased by corticosteroids (OR 3.7), MTX (OR 2.8), cyclosporine (OR 5.3) and thalidomide (OR 13.7, 3/5 patients with infections). The same results were observed for biologics, in particular rituximab (OR 16.3, 14/22 patients with infections), IL-1 inhibitors as anakinra (OR 3.3) and, among TNF-α inhibitors, infliximab (OR 1.6). Conversely, abatacept resulted protective (OR 0.4). The multivariate analysis (table) revealed that the addition of steroids to both MTX and biologics (groups MTX + steroids and MTX + steroids + biologics) increased the risk of infections more significantly (OR 11.9 and 10.5, respectively) than only MTX (5.1) or MTX+Biologics (OR 3.7). A great increase in the risk for infection was associated with rituximab ± steroids ± DMARDs (OR 112, 95% CI 11-1000). The multivariate results were confirmed by removing rituximab patients from the model. **Table. Risk factors for infections in JIA patients by multivariate analysis. (REF: reference item)**

	Patients with infections N=689	Multivariate analysis OR (95%CI)
Drug Therapy		
Only NSAIDs and Intraarticular Steroids (REF)		
Rituximab ± Steroids ± DMARDS	12/16 (75%)	111.8 (10.7-999.9)
MTX+Biologics+Steroids	95/422 (23%)	10.5 (6.5-17.0)
MTX+Steroids	47/207 (23%)	11.9 (7.0-20.2)
Other combinations	102/689 (15%)	7.6 (4.8-12.0)
Only MTX	157/1418 (11%)	5.1 (3.3-7.9)
MTX+Biologics	181/2055 (9%)	3.7 (2.4-5.8)
Only Biologics	71/1077 (7%)	2.7 (1.7-4.3)
Diagnosis (Oligo Persistent arthritis as REF)		
Other JIA categories with polyarticular course	451/4587 (10%)	1.3 (1.1-1.6)
Systemic arthritis	100/639 (16%)	1.7 (1.3-2.3)
Age at JIA diagnosis (cut-off ≤7.7)	523/4136 (13%)	2.3 (1.9-2.7)
ANA (2 positive >1:160)	219/1595 (14%)	1.6 (1.3-1.9)

Conclusion: Pharmachild showed that MTX and biologics increase the risk of infection in JIA patients. This risk is significantly enhanced by the addition of steroids to immunosuppressive therapy. We recommend monitoring for infections in JIA patients on immunosuppressive therapy.

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Abstract Number: 3117

Development of Autoimmune Diseases and Genetic Predisposition in Children with Neonatal Lupus and Their Unaffected Siblings

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Background/Purpose: Neonatal Lupus (NL) is a model of passively acquired autoimmunity conferred by exposure to maternal anti-Ro antibodies. This study was initiated to address the development of de novo autoimmunity in these children and identify associated genetic risk factors. Of relevance, the initial NL congenital heart block (CHB) GWAS revealed associations with HLA class I genes of the PSORS1 region that are linked to psoriasis.

Methods: In a retrospective cohort study of enrollees in the Research Registry for Neonatal Lupus, 346 children exposed to anti-Ro in utero responded to a follow up questionnaire focused on symptoms of autoimmunity. Self-reported diseases were confirmed via medical record review. Bivariate analyses were performed with potential risk factors for autoimmune disease development including NL manifestation, a disease severity score based on mortality risk factors, and maternal diagnosis of systemic lupus erythematosus (SLE) or Sjogren's syndrome (SS). In a substudy of these children (188 with CHB and their parents), DNA was interrogated using the Immunochip, a 196,806 SNP array that maps 200 regions containing known autoimmune diseases. Findings were compared to published SNPs outside of the HLA region in cohorts of rheumatoid arthritis (RA), Type 1 Diabetes (T1D) and psoriasis.

Results: Of the respondents, 134 had CHB, 74 cutaneous NL and 138 were unaffected siblings. Females comprised 54% and 81% were Caucasian. The mean age was 11.3±8.3; 10% age 0-2 years, 49% 2-13, and 40% > 13. An autoimmune disease developed in 24; 17 had CHB, 2 cutaneous NL and 5 unaffected (Table 1). The most prevalent disease was psoriasis. The presence of CHB was significantly associated with autoimmunity vs the cutaneous or unaffected children (12% vs 3%, p=0.002). An association between higher NL severity score and autoimmune disease was also found (5.0±4.7 vs 2.5±4.2, p= 0.003). The development of autoimmunity was not significantly different in children whose mother had SLE or SS vs those with asymptomatic mothers (7% vs 7%, p=1.0). No mother had psoriasis. Genetic analysis revealed that for significant associations of CHB vs. controls ($p<0.01$), overlaps were observed with other autoimmune diseases: 2 SNPs associated with RA, 0 T1D, and 178 psoriasis. For the latter, gene regions at B3GNT2-TMEM17, TRAF31P2 and KEAP-SLC9A8-SPATA2-RNF114 were of particular interest as these were significant in CHB offspring but not mothers.

Conclusion: Genetic risks factors in NL may predispose affected offspring to autoimmune diseases later in life, including psoriasis. That the development of an autoimmune disease is most apparent in those with CHB and more severe disease may relate to an inherent susceptibility to inflammation, manifest both in utero and later in life. The absence of certain SNPs in the mothers and independence of maternal clinical disease suggests that NL offspring may occupy a unique place in the spectrum of autoimmunity.

Table 1:

Subject	Gender	Race	NL Manifestation	Autoimmune Diagnosis	Age of diagnosis	Maternal Rheumatic Disease	NL Severity Score
1	M	C	CHB	Hypothyroid	0	SLE	5
2	F	C	CHB	Hypothyroid/Celiac disease	0/6	SLE	5
3	F	C	CHB	Psoriasis/T1D	3/10	SS	14
4	M	C	CHB	ITP	3.5	SLE	8
5	F	C	CHB	JIA	7	SS	8
6	F	C	CHB	Psoriasis/Iritis	11/13	SS	5
7	M	C	CHB	IBD	16	SLE	NA
8	F	C	CHB	UAS (arthritis, ANA+, anti-Ro+)	16	Asymptomatic	5
9	F	C	CHB	Psoriasis	19	SLE/SS	NA
10	F	C	CHB	Hypothyroid	UNK	Asymptomatic	5
11	M	C	CHB	Psoriasis	UNK	SLE/SS	14
12	M	C	CHB	Psoriasis	UNK	Asymptomatic	5
13	M	C	CHB	JIA/UAS (arthritis, photosensitivity, oral ulcer, anti-Ro/La+)	UNK	SLE	5
14	F	C	CHB	UAS (oral ulcer, uveitis, sicca symptoms)	UNK	SLE/SS	NA
15	F	C	CHB	UAS (arthritis, proteinuria, pleuritis, Raynaud's)	UNK	SLE	14
16	M	C	CHB	Hypothyroid/T1DM	UNK	Asymptomatic	5
17	F	O	CHB	SLE	UNK	SS	8
18	M	C	Cutaneous	Psoriasis	14	SLE/SS	0
19	F	C	Cutaneous	SLE	17	SS	0
20	F	A	Asymptomatic	UAS (arthritis, oral ulcer, proteinuria)	11	SS	0
21	F	C	Asymptomatic	Hypothyroid	17	Asymptomatic	0
22	F	C	Asymptomatic	Myasthenia Gravis/Celiac Disease	18	SLE/SS	0
23	M	C	Asymptomatic	ITP/Sarcoidosis	22	SS	0
24	M	C	Asymptomatic	T1D	UNK	SLE/SS	0

M = Male; F = Female; C = Caucasian; O = Other Race; A = Asian; CHB = Congenital Heart Block; T1D = Type 1 Diabetes; ITP = Immune Thrombocytopenic Purpura; JIA = Juvenile Idiopathic Arthritis; IBD = Inflammatory Bowel Disease; UAS = Undifferentiated Autoimmune Syndrome; SLE = Systemic Lupus Erythematosus; SS = Sjogren's Syndrome; UNK = Unknown; NA = Not Available

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Abstract Number: 3118

Differences in Disease Phenotype, Management and Outcomes of Children with Juvenile Idiopathic Arthritis throughout the World – Analysis of 8,325 Patients Enrolled in the Epoca Study

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Background/Purpose: Several epidemiologic surveys have documented a remarkable, yet unexplained, disparity in the prevalence of juvenile idiopathic arthritis (JIA) subtypes among different geographic areas or ethnic groups. Moreover, the therapeutic approach to JIA is not standardized and the availability of the novel and costly biologic medications is not uniform throughout the world. This disparity may have significant impact on disease outcome. The multinational study of the EPidemiology, treatment and Outcome of Childhood Arthritis (EPOCA study) is aimed to obtain information on the variability of JIA phenotypes in different geographic areas, the therapeutic approaches of pediatric rheumatologists practicing in diverse countries, and the disease status and outcome of children with JIA currently followed worldwide.

Methods: Participation in the study was proposed to all pediatric rheumatology centers that are part of the Pediatric Rheumatology International Trials Organization (PRINTO), and to several centers in the US and Canada. Each center was asked to enroll 100 consecutive JIA patients or all consecutive patients seen within 6 months. Each patient received a retrospective and cross-sectional assessment. Parent- and child-reported outcomes were recorded through the administration of the Juvenile Arthritis Multidimensional Assessment Report (JAMAR). Participating countries were grouped into 6 geographic areas. Patients were then grouped according to their country's gross domestic product per capita (GDP) and the total expenditure on health per capita (HE) (source www.who.org).

Results: Currently, 8,325 patients from 44 countries have been entered in the web database. Comparison of main epidemiology, treatment, and outcome features across the different geographic areas is presented in the table. Patients living in countries with GDP or HE below the median had lower frequency of remission, higher median cJADAS, higher frequency of damage, and were less frequently prescribed biologic DMARDs. These results were confirmed when analyses were conducted by disease category.

	Africa N = 261	Asia N = 874	Eastern Europe N = 2587	Latin America N = 814	North America N = 422	Western Europe N = 3367
Median (IQR) age at onset, years	7 (3.6-10.5)	5.7 (2.9-9.2)	6.4 (2.9-10.5)	6.6 (3.6-10.3)	8.1 (3.7-11.1)	4.1 (2-8.7)
Systemic arthritis	17.2	26.5	8.1	17.7	4.7	6.9
Oligoarthritis	23	31.9	44.1	31.7	33.9	49.2
Uveitis	4.6	5.5	10	6.6	10.4	16.9
Use of biologics	22.6	23.6	28.9	34.2	47.6	39
Median (IQR) cJADAS10	7 (2-11)	2.5 (0-7.8)	4.5 (1-9.5)	2.5 (0-9.5)	2.3 (0-7)	2 (0-6)
Median (IQR) JAFS score	4 (0-8)	1 (0-5)	1 (0-4)	1 (0-5)	1 (0-4)	0 (0-3)
JADI-Articular > 0	27.6	19.2	23.7	31.9	15.2	12.2
JADI-Extraarticular > 0	24.5	16.8	14.8	14.5	5.9	9.1

Data are percentages unless otherwise indicated. cJADAS: clinical (3-item) JADAS; JAFS: Juvenile Arthritis Functionality Scale; JADI: Juvenile Arthritis Damage Index

Conclusion: These results provide further evidence of the wide difference of JIA characteristics across geographic areas in terms of age at disease onset, subtype prevalence, and frequency of anterior uveitis. Overall, patients living in countries with lower GDP or HE had higher levels of disease activity and cumulative damage than patients living in wealthier countries. This disparity may be partially related to differences in the availability or affordability of biologics.

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Abstract Number: 3119

Complete Whole Genome Transcriptome, DNA Methylation, and Histone Mark Analysis of Rheumatoid Arthritis (RA) Fibroblast-like Synoviocytes (FLS) Reveals a Distinctive Epigenetic Landscape and Critical Pathogenic Pathways

Rizi Ai[1], Deepa Hammaker[2], David L. Boyle[3], Andre Wildberg[4], Keisuke Maeshima[2], Emmanuele Palescandolo[5], Vinod Krishna[5], Bryan Linggi[6], Radu Dobrin[5], John W. Whitaker[7], Wei Wang[8] and Gary Firestein[9], [1]Chemistry and Biochemistry, UC San Diego, La Jolla, CA, [2]Division of Rheumatology, Allergy and Immunology, UCSD School of Medicine, La Jolla, CA, [3]Division of Rheumatology, Allergy and Immunology, University of California, San Diego, La Jolla, CA, [4]Chemistry and Biochemistry, UNIVERSITY OF CALIFORNIA SAN DIEGO, LA JOLLA, CA, [5]Janssen Pharmaceuticals, Spring House, PA, [6]janssen Pharmaceuticals, Spring House, PA, [7]Janssen Pharmaceuticals, La Jolla, CA, [8]Chemistry and Biochemistry, University of

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Background/Purpose: RA FLS display a unique aggressive phenotype with a distinctive DNA methylation profile that marks genes involved with cytokine signaling, cell recruitment, and matrix regulation. In this study, the epigenetic and transcriptomic signature was expanded by adding multiple omics technologies to the integrative analysis. Patterns that distinguish RA and osteoarthritis (OA) FLS lines were identified using RNA-seq, ChIP-seq and DNA methylation datasets from the same cell lines. This analysis allowed us to create the first high-resolution functional genomic map of aggressive RA FLS.

Methods: Genome-wide data were collected from 11 RA and 11 OA FLS lines: (i) gene expression using RNA-seq for differentially expressed genes (DEGs); (ii) epigenetic modifications of six histone marks by ChIP-seq for differentially modified histone regions (DMHR) (H3K4me1, H3K4me3, H3K27ac, H3K27me3, H3K36me3, H3K9me3); (iii) DNA methylation by Illumina chip for differentially methylated genes (DMGs) previously reported on the same FLS lines (Genome Medicine, 2013). One RA and one OA FLS were filtered because they overlapped in principle component analyses (PCAs). Unbiased hierarchical clustering and PCA assessed the relationships between RA and OA. Integrative analysis was performed with overlapping gene sets and identified multi-evidence genes (MEGs), i.e., found in more than one dataset. Enriched pathways were determined with Ingenuity Pathway Analysis.

Results: 997 DEGs for RA compared with OA were identified by RNA-seq, with 43 enriched pathways including RA-specific pathways “Osteoblasts, Osteoclasts and Chondrocytes in RA” and “Macrophages, Fibroblasts and Endothelial Cells in RA”. Hierarchical clustering and PCA showed that RA and OA FLS transcriptomes significantly separated. For histone marks, 18,642 DMHRs between RA and OA were identified for six histone marks; H3K27ac, H3K4me1 and H3K4me3 showed far more DMHRs than the other marks. Multiple histone mark-enriched pathways were identified in inflammation, immune response and cell migration processes. When combined with the previously identified 2375 DMGs, integrative analysis of the 3 datasets revealed MEGs with overlapping DEGs, DMGs with H3K27ac, H3K4me1 and H3K4me3 histone marks. 19 biological pathways among the MEGS were enriched including “Macrophages, Fibroblasts and Endothelial Cells in RA”, “JAK family kinases in IL-6-type Cytokine Signaling”, “Cytokine Regulation in Macrophages and Th Cells by IL-17A/F”.

Conclusion: This is the first genome-wide analysis of the RA FLS transcriptome, methylome and histone marks. Pathogenic gene expression and epigenetic marks identify a distinctive RA signature that sheds light on the pathogenesis RA. The MEGs participate in immune networks, which enables strategies to modulate the unique aggressive phenotype of RA FLS. The data also permit development of *in silico* models that prioritize non-obvious targets for drug discovery.

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Abstract Number: 3120

RA Net: A Systems Biology Approach to Identify Genes Regulating Pathogenic Pathways in Rheumatoid Arthritis (RA) Fibroblast-like Synoviocytes (FLS)

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Background/Purpose: Rheumatoid arthritis (RA) remains a significant unmet need despite improved therapy. Defining the interlaced nature of gene regulation and disease pathogenesis using integrative systems biology analysis is a powerful approach that can lead to experimentally verifiable predictions of novel therapeutic targets. We have developed a network that can potentially predict gene interactions that contribute to the pathogenic behavior of RA FLS and identify drug synergy to restore homeostasis.

Methods: Rheumatoid arthritis (RA) remains a significant unmet need despite improved therapy. Defining the interlaced nature of gene regulation and disease pathogenesis using integrative systems biology analysis is a powerful approach that can lead to experimentally verifiable predictions of novel therapeutic targets. We have developed a network that can potentially predict gene interactions that contribute to the pathogenic behavior of RA FLS and identify drug synergy to restore homeostasis. **Methods:** A novel computational systems biology method, known as RAnet, was designed and builds a probabilistic network model capturing the key regulations pertaining to the disease state of imprinted RA FLS. By comparing RA and osteoarthritis (OA) FLS, we curated genes that are critical in RA based on those that satisfied two of the three conditions: 1) differentially methylated genes (DMGs) in RA cells from 28 FLS lines, 2) differentially expressed genes (DEGs) in RA from 37 public microarray FLS lines, and 3) risk genes identified from GWAS studies. A set of 140 genes was selected to create a RA regulatory network. The network was determined by maximizing and adding or removing edges between randomly selected pairs of nodes. Using two and three gene combinations, predicted effects on gene expression were determined by calculating the Pearson and Spearman rank correlation coefficients.

Results: 403 gene-gene interactions were identified in RA Net. Because of the large number of potential combinations, we ranked and prioritized them in terms of the frequency in 1574 predicted models. The top gene/gene interactions included NFkB/GCLC, TP53/MDM2, CACL10/LINC0043, CYSLTR1/BHLHE22, and CARD16/C2orf88 because all were identified in at least 75% of the predicted models. We were also able to identify genes that regulate pathogenic pathways and cytokines in RA. For TNF regulation, top hits included TP53, PSMA4, IL1RN, CCR2, AIRE, JUN, and BMX. For IL-1 regulation, top hits included IL2RA, BMX, TNF, AIRE, and TP53. These core gene sets represent possible therapeutic targets that regulate these cytokines in RA. To determine combinations of genes that could be targeted to convert the RA FLS phenotype to a non-RA phenotype, we predicted the effect of knocking down combinations of genes. The maximum efficacy achievable with three-gene recipes ($r_{avg} = 0.576$) is significantly improved compared with two-gene recipes ($r_{avg} = 0.517$). The best three gene combination was the knockdown of genes the ring finger protein RNF144B (E3 ubiquitin-protein ligase), UGT2A3 and PLCH2. Interestingly, RNF144B expression is decreased by NSAIDs and RNF144B inhibitors are being developed as therapeutic agents.

Conclusion: This approach identifies synergistic therapeutic targets in RA using systems biology. The genes that regulate pathogenic pathways repeatedly appear in top gene “recipes” and could be promising candidates for combination therapy. This novel *in silico* method could offer a new way to determine disease mechanisms in RA.

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Abstract Number: 3121

Specific Antibody Subphenotypes in Rheumatoid Arthritis Are Associated with Unique HLA-DRB1 Residues at Position 11

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Background/Purpose: Antibody to citrullinated peptides/proteins (ACPA) is specific feature of rheumatoid arthritis (RA) and seen in 50 to 70% of RA patients. Amino acid (AA) position 11/13 in the HLA-DRβ1 is the strongest genetic risk factor in the HLA locus to ACPA(+) RA. We previously showed that HLA-DRB1 alleles interact to confer risk of ACPA(+) RA (Lenz et al Nat Gen 2015). However, genetic architectures underlying individual ACPA are still poorly understood. Here, we investigated the extent to which different individual ACPA are driven by distinct genetic factors within HLA locus.

Methods: We phenotyped RA cases with a multiplex peptide array to quantify 18 fine-specific ACPA as well as 2nd generation cyclic ctrullinated peptide antibody (CCP2), the representative method to quantify ACPA. We queried 6,267 patients and 12,054 controls across 3 independent cohorts. We performed clustering and principal component analysis to identify subgroups of ACPAs. We imputed HLA genotypes and tested for MHC associations with specific ACPA with logistic regression models correcting for 10 principal components and cohort effects. We also evaluate interactive effects of combinations of HLA-DRB1 alleles on fine-specific ACPA(+) RA susceptibility to assess whether allelic interactions influence expression of specific ACPAs.

Results: Clustering and principal component analysis of 18 fine ACPAs and CCP2 demonstrated that ACPAs could be classified into 2 distinct clusters, which we refer to as ACPA-A and ACPA-B. ACPA-A consisted of a total of 12 antibodies including CCP2 and an antibody recognizing a peptide derived from fibrinogen beta AA position 60 to 74 with positions 60, 72 and 74 citurillnated (Fibbeta60-74Ab) which was more strongly correlated with CCP2 than any other ACPA. ACPA-B contained a total of 7 antibodies including Fibbeta62-81cit72Ab, which reacts to a peptide sharing 12 AA sequences to the Fibbeta60-74Ab peptide but differs only in citrullination at one AA position. Position 11 of HLA-DRβ1 protein, which has six possible AA residues, showed the strongest associations in 14/18 ACPAs in intra-case analysis (omnibus $p \leq 1.1 \times 10^{-33}$). Intriguingly, Fibbeta62-81cit72Ab showed distinct association patterns of AA residues at the position 11 ($p=1.1 \times 10^{-50}$) from CCP2 associations. When we examined the subset of 175 case individuals that were positive for ACPA-B, but negative for all ACPA-A antibodies, we observed only weak evidence of association to position 11 ($p=0.066$), but did observe a significant association with HLA-B AA position 9 ($p=1.2 \times 10^{-7}$). We identified two novel allelic combinations specifically showing interactive effects on fine-specific ACPAs, for example DRB1*13:01 and 11:01 interact to influence expression of an antibody recognizing a peptide derived from heterogeneous ribonucleotide protein ($p=3.1 \times 10^{-4}$).

Conclusion: These findings suggest that specific HLA-DRB1 alleles, and their interacting combinations lead to a different repertoire of antibodies, with reactivities to different citrullinated peptide sequences. They suggest that reactivity to multiple antigen sets might independently lead to RA.

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Abstract Number: 3122

Genome-Wide DNA Methylation Association Study of Hand Osteoarthritis

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Background/Purpose: Heritability of hand osteoarthritis (OA) has been estimated to be as high as 65%. Despite having a strong genetic component, genome-wide linkage and association studies of hand OA have identified few replicated genetic loci. Other mechanisms such as DNA methylation, which affects gene expression without altering the DNA sequence, may be involved. We therefore aimed to identify differentially methylated loci across the genome that are associated with hand OA.

Methods: Analyses were based on the Framingham Study, a community-based study in the US in which subjects were studied irrespective of OA status. Peripheral blood samples were collected on 2,846 individuals from the second generation cohort. Genomic DNA was extracted from the buffy coat, bisulfite converted, and assayed with the Illumina Infinium Human Methylation450 Beadchip. Standard quality-control procedures were conducted, leaving 2,648 samples and 485,513 CpG probes for analysis. There were 1,261 individuals from this generation cohort without rheumatoid arthritis who obtained bilateral posteroanterior hand radiographs. We derived a summary index score for hand OA by summing semi-quantitative Kellgren-Lawrence (KL) scores at the 2^{nd}-5^{th} distal interphalangeal, 2^{nd}-5^{th} proximal interphalangeal, 1^{st}-5^{th} metacarpophalangeal, thumb interphalangeal, and 1st carpometacarpal joints (possible range=0 to 120). We implemented linear mixed effects regression models to test the effect of a hand OA summary index score on DNA methylation level at each CpG probe. All regression models were adjusted for age, sex, principal components, and estimated cell counts as fixed effects, and familial relationships and chip identifiers as random effects.

Results: A total of 1,073 individuals with hand OA assessments and DNA methylation data were included in the analysis. Mean age was 66±8 years and 57% were women. Mean summary index score for hand OA was 8±12. We applied a conservative Bonferroni correction for ~490,000 probes and identified 7 differentially methylated regions that met genome-wide significance ($p<1x10^{-7}$), including cg12762517, cg21838477, cg05400732, cg04299389, cg20277504, cg13225177, and cg20205818 (Table 1). Our top finding, cg12762517, is located in *PARP3*, which catalyzes poly-ADP-ribosylation of nuclear proteins needed for DNA repair and regulation of apoptosis. None of the other findings has been previously associated with hand OA; however, cg0500732 resides within *ARHGEF3*, a Rho gunanine nucleotide exchange factor that may play a role bone cell biology.

Conclusion: We identified 7 differentially methylated regions associated with hand OA at genome-wide significance. None of these regions has been previously associated with OA, though *ARHGEF3* has been implicated in osteoporosis, suggesting that regulation of bone mineral density may play an important role in hand OA pathogenesis.

Table 1. CpGs Significantly Associated with Hand OA

CpG	Chr	hg19 Position	Gene	Location	Beta	SE	P-value
cg12762517	3	51,975,968	*PARP3*	TSS	2.25E-04	3.48E-05	1.08E-10
cg21838477	12	6,657,972	*IFFO1*	Body	-4.58E-04	7.89E-05	6.75E-09
cg05400732	3	57,032,141	*ARHGEF3*	Body	-4.67E-04	8.40E-05	2.70E-08
cg04299389	20	25,129,296	*LOC284798*	Body	4.53E-04	8.16E-05	2.81E-08
cg20277504	10	29,821,389	*SVIL*	Body	-6.10E-04	1.10E-04	3.33E-08
cg13225177	X	136,509,076		Intergenic	7.94E-04	1.44E-04	3.59E-08
cg20205818	8	7,221,471	*ZNF705G*	TSS	-5.95E-04	1.09E-04	5.37E-08

study-of-hand-osteoarthritis

Abstract Number: 3123

Rare Mediterranean Fever (MEFV) Gene Polymorphisms Are Associated with Ankylosing Spondylitis in Turkish and Iranian Population

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Background/Purpose: Ankylosing spondylitis (AS) is a highly heritable inflammatory arthritis common in both Turkish and Iranian populations. Familial Mediterranean Fever (FMF) is an autosomal recessive autoinflammatory disease that usually occurs in people of Mediterranean origin. MEFV, a known FMF-associated gene, is a candidate gene for AS, because of increased co-familiality of AS and FMF, and suggestive association of MEFV with AS in candidate gene studies. Here we studied Turkish and Iranian case-control cohorts to identify AS susceptibility loci and also examine the association between MEFV and AS.

Methods: A genome wide association study was performed in 1001 Turkish AS patients and 1011 Turkish controls and also 479 Iranian AS patients and 830 Iranian controls, using Illumina Infinium CoreExome chips. Standard quality control and population stratification identification and control measures were applied (lambda1000 in Turkish, Iranian and combined datasets 1.039, 1.025 and 1.025 respectively).

Results: In this study we identified two non-MHC loci, MEFV and USP8 reaching genome-wide significance ($p < 5x10^{-8}$), and fourteen suggestive loci ($10^{-5} < p < 5x10^{-8}$), in the combined cohort. The lead MEFV SNP rs61752717 (M694V, $p = 7.6x10^{-12}$, OR = 5.3) is a rare coding variant (MAF=0.011 in Turkish controls) and also the most penetrant FMF-associated variant. This lead SNP also shows significant association with AS in Iranian cohort (p = 0.042, OR = 2.9), and in the combined dataset is very strongly AS-associated ($p = 1.5x10^{-13}$, OR = 4.9). Three coding variants in MEFV were significantly associated with AS (P369S, R408Q and M694V). AS cases with MEFV rs61752717 variants did not themselves have FMF, and had similar disease manifestations to non-carriers. This study confirms the previous identification of USP8 as an AS-associated locus (exm1161045, $p = 8.0x10^{-14}$, OR = 0.58 in combined dataset), and at previously reported AS-associated loci including HLA-B, ERAP1 and 2p15.

Conclusion: This study provides definitive evidence of the association of rare MEFV variants with AS, and confirms that FMF and AS have overlapping aetiopathogenic mechanisms. The association of MEFV in these populations has the highest odds ratio for AS of any non-MHC genetic variant confirmed at genome-wide significance to date. Functionally important MEFV mutations such as M694V have been demonstrated to lead to dysregulated inflammasome function and excessive IL-1b function. Given that IL-1 inhibition is effective in FMF, it will be interesting to study whether AS cases carrying FMF-associated MEFV variants also benefit from such therapy.

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Huntingtin Interacting Protein 1 (Hip1) Is a New Arthritis Severity Gene

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Background/Purpose: *Cia25/Pia42* is an arthritis severity and joint damage quantitative trait locus on rat chromosome 12 previously identified in an intercross between MHC identical but disease discordant DA (arthritis-susceptible) and ACI (resistant) rats. DA.ACI(Cia25/Pia42) congenic rats were significantly protected in both Pristane and Collagen-induced arthritis (PIA and CIA) compared with DA. This study aimed at positionally identifying the gene accounting for *Cia25/Pia42* gene.

Methods: Recombinant subcongenics covering the *Cia25/Pia42* interval were generated by backcrossing the original congenic strain with DA using a genotype-guided strategy. Recombinants sharing identical intervals were then intercrossed to homozygozity. PIA was induced in 8-12 week-old subcongenic rats and disease scored for 31 days using a system that correlates with histological damage. Fibroblast-like synoviocytes (FLS) from rats and patients with rheumatoid arthritis (RA) were studied in *in vitro* invasion assays previously shown to correlate with radiographic damage.

Results: Analyses of 12 different recombinant (R) subcongenic strains reduced the gene-containing interval from 33Mb to a 1.2MB region contained within subcongenic R6. R6 subcongenics had significantly 92% lower median arthritis severity score compared with DA ($P<0.001$) and were significantly protected from developing cartilage or bone damage ($P<0.002$). Sequencing of the 36 genes in the 1.2MB critical interval identified three genes with amino-acid changing SNPs with predicted protein functional consequences based on SIFT and PolyPhen2 analyses. These three genes were expressed in FLS from arthritic rats and patients with rheumatoid arthritis (RA). Huntingtin-interacting protein 1 (Hip1), a gene implicated in clathrin-mediated endocytosis, was one of these genes and was expressed in increased levels in DA FLS compared with R6. FLS from protected DA.ACI(Cia25/Pia42) subcongenic R6 were less invasive than those from DA rats, suggesting that the *Cia25/Pia42* gene operates via the regulation of FLS invasion. siRNA Hip1 significantly reduced the invasive properties of FLS obtained from DA rats and from patients with RA. Hip1 knock-out mice were obtained and were protected in KRN serum-induced arthritis, confirming the importance of this gene in arthritis.

Conclusion: Hip1 is a new arthritis severity and joint damage gene that mediates disease at least in part via the regulation of the invasive properties of FLS. The identification of this new gene is the first step towards developing new therapies and a new prognostic biomarker for RA.

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Secular Trend of Premature Mortality in Gout: A Contrast from Rheumatoid Arthritis

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Background/Purpose: Gout and rheumatoid arthritis (RA), the two most common inflammatory arthritides, are both associated with premature mortality. General population-based studies have found substantially reduced premature deaths in RA patients in recent years (likely due to improved RA care), including our own study spanning 1999-2014 (1). However, no equivalent secular trend data in gout are available. Given the well-documented suboptimal gout care, opposing mortality trends may exist between RA and gout, as was recently shown in their hospitalization rates (2). We evaluated this hypothesis by examining mortality trends of gout patients over the same period (i.e., 1999-2014) as in our recent study based on the same general population database (1).

Methods: Using an EMR database representative of the UK general population, we identified incident gout cases and up to 5 non-gout controls matched on sex, age, and entry time between Jan 1 1999 and Dec 31 2014. The gout cohort was divided into two sub-cohorts based on the year of diagnosis, forming the early (1999-2006) and late (2007-2014) cohorts. We calculated mortality rates and hazard ratios (HRs) using a Cox proportional hazard model to adjust for demographics, lifestyle factors, comorbidities, medications, and healthcare use. We then compared the HRs from the early vs. late cohorts using interaction analyses. We repeated these analyses limited to those who received at least one prescription for urate-lowering therapy or colchicine, which has been found to have a validity of 90%.

Results: Both the early and late cohorts (N = 44,783 and 58,478, respectively) had the same mean age (62 years) and sex proportion (~74% male) between the gout and comparison group. In both the early and late cohorts, gout patients showed similar levels of excess mortality compared to their corresponding comparison cohort (i.e., 29.1 vs. 23.5 deaths/1000 person-years (PY) in the early cohort and 23.0 vs. 18.8 deaths/1000 PY in the late cohort) **(Figure)**. The corresponding univariate mortality HRs (95% CI) were 1.25 (1.21-1.30) and 1.24 (1.20-1.29), and the multivariable mortality HRs were 1.10 (1.06-1.15) and 1.09 (1.05-1.13), respectively (both P for interaction >0.72). Our analysis limited to those who received a prescription for anti-gout medication showed similar findings (both P for interaction >0.88)

Conclusion: This population-based cohort study indicates that the level of excess mortality among gout patients remains unchanged over the past 16 years, contrasting the aforementioned substantial reduction in excess mortality observed among RA patients during the same period (1). This unclosing gap in premature mortality among gout patients calls for improved management of gout and its comorbidities. **References:**

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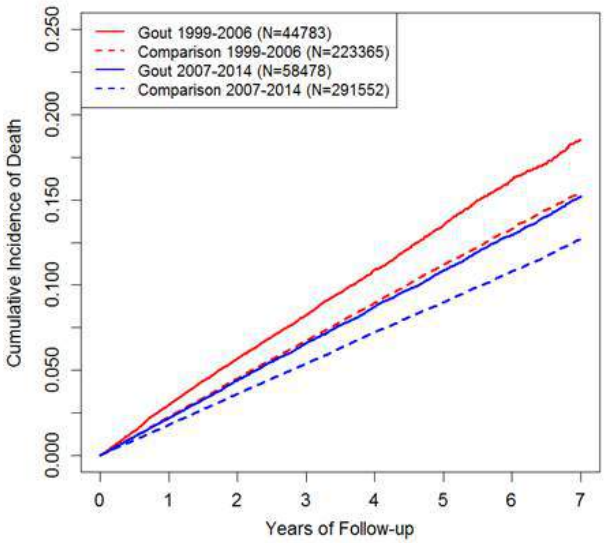

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Computational Polarizing Microscopy: A Novel Method to Detect Birefringent Crystals Using Lens-Free on-Chip Microscopy

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Background/Purpose: A compensated polarizing microscopy has been used for detecting monosodium urate (MSU) or calcium pyrophosphate dihydrate (CPPD) crystals to confirm the diagnosis of gout or pseudogout for more than 50 years. However, accuracy of the methodology is affected by crystal concentration, time invested reading the slide and operator skill. As the procedure is only billable through a Clinical Laboratory Improvement Amendments (CLIA)-certified lab, its bedside use has waned over the years. There is a need for a more efficient and accurate method. Herein, we present a novel method to detect birefringent crystals in synovial fluid by designing a lens-free on-chip polarizing microscope.

Methods: Lens-free on-chip microscopy based on digital in-line holography is a novel imaging technique that has achieved wide field of view (>20 mm^2) and high-resolution biomedical imaging in a simple, cost-effective and field-portable design. We modified this technology with a circular polarizer and an angle-mismatched analyzer so that the partially-coherent light that is passed through

the birefringent crystals can be enhanced and detected by a digital image sensor. Two images of every sample are taken with the sample rotated by 90 degrees to eliminate any non-birefringent objects. An image processing algorithm and post image color-coding was applied to enhance the quality and to reproduce the similar color images to those of a compensated polarizing microscope. Imaging of CPPD crystals are in progress at the time of this abstract submission.

Results: Figure 1 shows the comparison of MSU crystal images taken by a compensated polarizing microscope (A), a lens-free differential grayscale image (B) and a lens-free color-coded image (C). The images taken by the novel technique was able to accurately demonstrate the direction and the strength of birefringence and the shape of MSU crystals. Two independent experts reviewed multiple images and determined that they were comparable to those from a conventional polarizing microscope.

Conclusion: We developed a digital lens-free on-chip polarizing microscope that can detect birefringent crystals over a wide field of view. It uses a computerized image analysis algorithm and a digital image sensor, which overcomes the weakness of time-consuming, operator-dependent property of the conventional polarizing microscope. Its time-efficiency, small size and low cost could make it more easily used in a daily practice, to facilitate synovial fluid examination for the diagnosis of crystal arthropathy. The process is currently completed for MSU crystals. Validation of CPPD crystal images taken by this novel technology is currently in progress.

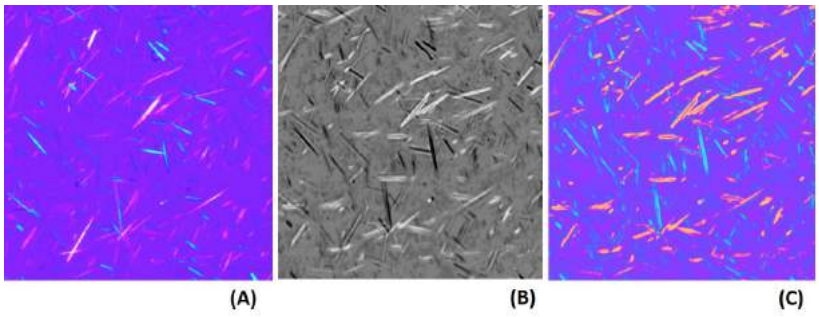

Fig. 1: Conventional and Lens-Free On-Chip Polarizing Microscopy images of MSU crystals.

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Abstract Number: 3127

Ultrasound Evaluation of the Achilles Tendon in Tophaceous Gout: A Case-Control Study

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Ultrasound Evaluation of the Achilles Tendon in Tophaceous Gout: A Case-Control Study

Background/Purpose: Tendon involvement in the lower limbs in gout is frequent. Tophus deposition to the Achilles tendon (AT) has been reported, however, data describing ultrasound (US) lesions to specific anatomical zones of the AT is limited. The aim of the study was to investigate frequency and distribution of US lesions of the AT in people with tophaceous gout compared to age and sex matched controls.

Methods: Twenty-four participants with tophaceous gout and 24 age- and sex-matched control participants without gout or other arthritis were recruited. All participants underwent US examination, using both greyscale and power Doppler (PD) technique by a musculoskeletal radiologist who was blinded to diagnosis. The AT was divided into three anatomical zones (zone 1: insertion, zone 2: pre-insertional and zone 3 proximal to the mid-section). US lesions were scored using a semi-qualitative scoring system assessing tophus, tendon echogenicity, tendon vascularity, tendon morphology, enthesis, bursal morphology and entheseal bone profile. All US scanning techniques and lesion definitions were used as proposed by the OMERACT ultrasound task force. Scans were scored independently by two musculoskeletal radiologists, blinded to diagnosis and each other's scores, with kappa levels of agreement ranging between 0.77 to 1.00. As lesions were nested within participants, a general estimating equation approach was used to data analysis. All tests were two-tailed, with $p < 0.05$ considered significant.

Results: The table shows the percentage of US lesions present in each group and defined by the zone of the AT. Tophus deposition was observed in the AT of 73% of participants with tophaceous gout and not observed in control participants ($p < 0.01$). Intratendinous hyperechoic spots and intratendinous PD signal were also more frequent in participants with tophaceous gout compared to control participants ($p < 0.01$ for both). Frequency of entheseal lesions, calcaneal lesions and AT thickness did not differ between groups. In participants with gout, there was no significant difference in distribution of tophi or intratendinous power Doppler signal at different zones. In contrast, intratendinous hyperechoic spots were most commonly observed in zone 1 and were least commonly observed in zone 3 of the AT.

Conclusion: The Achilles tendon is frequently involved in people with tophaceous gout. Ultrasound features of intratendinous urate deposition and inflammation are commonly observed. Table: Percentage of ultrasound lesions present between case and control participants

US lesion	Gout participants US lesions present %	Control participants US lesion present %	P	US lesions present in AT of gout participants %		P for between zones in gout participants
Tophus	73	0	<0.01	Zone 1	54	0.07
				Zone 2	52	
				Zone 3	29	
Intratendinous hyperechoic spots	98	19	<0.01	Zone 1	46	<0.01
				Zone 2	35	
				Zone 3	21	
Intratendinous power Doppler signal	81	19	<0.01	Zone 1	35	0.60
				Zone 2	31	
				Zone 3	35	
Entheseal echogenicity: calcifications	59	40	0.43			
Entheseal vascularity	21	15	0.65			
Calcaneal bone cortex irregularities	27	19	0.43			
Calcaneal enthesophytes	69	60	0.64			
Tendon thickness, mm, mean (SD)	4.65 (0.81)	4.32 (0.74)	0.85			

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Abstract Number: 3128

A Longitudinal Dual Energy Computed Tomography Study on the Effect of Urate Lowering Therapies on the Reduction of Tophus Burden in Patients with Chronic Gout

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SESSION INFORMATION

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Background/Purpose: Dual energy computed tomography (DECT) allows reliably detecting and quantifying tophus burden in patients with chronic gout. Longitudinal studies on the effect of uric acid lowering drug therapy on tophus burden assessed by DECT are currently lacking with the exception of a small study performed in patients treated with Pegloticase (1). Aim: To assess and compare the effects of uric acid lowering drugs on reducing tophus volume in patients with chronic gout by means of dual energy computed tomography scans

Methods: Follow-up DECT scans were performed in 94 patients with initially DECT positive chronic gout receiving stable treatment with either Allopurinol, Febuxostat, Benzbromaron or Pegloticase or had solely life-style intervention with no concomitant uric acid lowering drug therapy. Baseline and follow-up scans of both feet captured automatically the urate volume (Somatom Definition Flash/Force CT; Syngo DE Gout software; Siemens). Artefacts were manually excluded. Changes in tophus volume were calculated in a descriptive (tophus volume at baseline minus tophus volume at follow-up) and inferential way (Wilcoxon signed-rank test). Demographic data, medication and blood values (CRP, creatinine, serum urate) were recorded at the time of each DECT scan.

Results: 94 patients (75 men and 19 women) were analyzed. Mean disease duration until the first DECT examination was 3.3 years and mean interval between both DECT examinations was 17 months. The overall baseline serum uric acid level decreased from 7.3 ± 2.5 mg/dl to 5.9 ± 2.8 mg/dl at follow up (- 19%). Baseline tophus volume decreased by 77% with Allopurinol ($p < 0.001$, $r = -0.50$), 35% with Febuxostat ($p = 0.001$, $r = -0.51$) and 90% with Pegloticase ($p = 0.005$, $r = -0.58$). Only 2 patients were treated with Benzbromaron showing numerical decrease of tophus volume at a similar range as seen with Allopurinol (- 75%). Life-style intervention also led to a moderate (- 31%), though significant ($p = 0.007$, $r = -0.40$), decrease in tophus burden. Complete tophus resolution was found in 46,4% of the patients treated with Allopurinol, 34,8% treated with Febuxostat and 8,3% with Pegloticase.

Conclusion: Sustained uric acid lowering drug therapy leads to significant reduction of DECT tophus burden in patients with chronic gout. The effectiveness of urate lowering therapies on reducing serum urate concentration is not necessarily transferable on the resolution of monosodium urate crystal depositions (see in table 2). While Febuxostat led to the greatest change in serum uric acid levels with a reduction of 36%, its effect on reducing tophus burden was rather low (- 34 %). At present, it is common clinical practice to monitor gout treatment based on the uric acid level. However, in order to assess and monitor the real effect of urate lowering therapies on the resolution of monosodium urate depositions, dual energy CT is more accurate.

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Abstract Number: 3129

The Pharmacokinetics of Oxypurinol in Patients Treated with Hemodialysis and Allopurinol

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Background/Purpose: Allopurinol is recommended as a first-line pharmacologic urate-lowering therapy in gout. Oxypurinol, the active metabolite of allopurinol, is entirely cleared by the kidneys. Oxypurinol clearance decreases in proportion to glomerular filtration rate (GFR) in chronic kidney disease. However, the pharmacokinetics of oxypurinol in dialysis patients is not known. We hypothesised that oxypurinol clearance in patients receiving haemodialysis will be comparable to patients with a glomerular filtration rate (GFR) of 10-20 ml/min. The purpose of this study was to describe oxypurinol pharmacokinetics in people with gout treated with hemodialysis.

Methods: The pharmacokinetics of oxypurinol was assessed in a group of patients with gout receiving intermittent haemodialysis three times weekly for five hours per session (Hemoflow F8HPS Polysulfone dialyser). The blood flow for dialysis was 200mL/min and the dialysate flow was 500 mL/min. All subjects were taking long-term allopurinol 100 mg daily. During the study allopurinol was taken after dialysis on dialysis days. Six blood samples were collected from each subject at 0, 1, 2, 3, 4, and 5 hours after the start of dialysis for the measurement of oxypurinol plasma concentrations. Urine was collected from each subject over a 24 hour period. A further eight blood samples were collected from each subject across a non-dialysis dosing interval at 0, 0.5, 1, 1.5, 2, 4, 6 and 24 hours after the dose. Serum urate was measured at baseline, post-dialysis (6 hours), and at the end of the study (48 hours). Oxypurinol was measured by liquid chromatography–mass spectrometry and oxypurinol clearance was calculated from the area under the concentration time curve (AUC).

Results: Six patients were recruited; five male and one female. Their median age was 63 years (28-72 years). All had been taking allopurinol for > 1 year, were taking no other medicines for gout, and were not taking diuretics. Two patients were anuric and four had some residual renal function (urine output 0-260 ml/24 hrs). One patient was excluded after sample analysis as their results showed they were not adherent with treatment. At steady state, the oxypurinol median AUC was 30 umol/L*hr (range 23-50). The median oxypurinol clearance was 1.0 L/hr (0.60-1.3). This was higher than expected and comparable to the clearance in patients with normal kidney function. The median plasma urate concentration pre-dialysis was 5.9 mg/dL (4.7-8.9mg/dl). Serum urate dropped precipitously during dialysis and is either back to baseline (n=2) or within 80% of baseline (n=3) by 42 hours post-dialysis.

Conclusion: Allopurinol is likely to be more effective if administered after, rather than before, dialysis. Serum urate should be measured prior to dialysis to ensure target urate is maintained between dialysis. Hemodialysis was more effective at removing oxypurinol from the circulation than predicted. The dose of allopurinol in dialysis patients does not need to be restricted to 100mg daily. Further studies of allopurinol to treat gout in dialysis patients should examine conventional urate targeted dosing.

Disclosure: M. Doogue, None; **D. Wright**, None; **N. Cross**, None; **J. Irvine**, None; **P. T. Chapman**, None; **M. Barclay**, None; **L. K. Stamp**, None.

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Abstract Number: 3130

Development and Pilot Testing of an Online Educational Tool for Gout Patients — Mygoutcare®

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Background/Purpose: Recent management guidelines for gout have identified several unmet educational needs in gout patients. Qualitative studies have documented the paucity of patient-focused materials which facilitate ongoing patient-physician communication. Our objective was to develop and test a web-based interactive educational resource (electronic platform) for gout patients tailored to improve their knowledge and help facilitate communication with their physicians.

Methods: The website was developed in four phases: 1. Two advisory panels - 30 gout patients and 10 gout experts iteratively a) reviewed pre-identified content areas of modifiable gaps in pathogenesis, natural history and treatment goals from previously conducted focus groups[1] and b) evaluated the design (graphics and lay out) of the website. 2. Incorporation of a validated Gout Knowledge Questionnaire (GKQ)[2] on gout and a 5-minute post-survey to assess knowledge about critical take-home messages and satisfaction with their physician's care. 3. A team of web designers and health informatics experts tailored the content areas on the website to create a patient journey to learn various aspects of gout such as triggers of flares, comorbidities, pharmacologic and non-pharmacologic treatments, healthy gout diet, and lifestyle choices. 4. Beta testing was performed by 10 patients with gout in clinics for clarity and usability. The website is called MyGoutCare® and in the pilot study, the patient completes a baseline survey of demographics and gout knowledge, reviews the website and generates a list of customized questions (MyGoutReport®) to discuss at the upcoming visit with their physician. They next complete a post-survey within two weeks of the physician visit. Data was analyzed using a paired t-test and presented as mean change in scores between post and baseline surveys.

Results: The pilot study recruited 50 subjects with gout from general medicine, podiatry, and rheumatology clinics. The mean age was 54 years, 88% were males, 82% Caucasian, and 68% consumed 7.5 drinks per week. Disease duration was 9.5 years and they reported 3-5 flares per year. All subjects were extremely receptive of the e-learning tool that was accessible 24/7. Post-survey scores on GKQ (mean score= 9.06, 0-10) improved significantly (20%) when compared to pre-survey scores (mean score= 7.12) with mean (SD) at 1.95 (1.93), $p<0.0001$ and effect size of 0.95. All subjects reported satisfaction with discussion on the natural history of disease and treatment choices with their physicians. They reported significant actionable changes moving forward, such as changing urate-lowering therapy (72%) and dietary/alcohol changes (28%-38%) to achieve flare-free status.

Conclusion: Our pilot study suggests that web-based patient-focused materials can serve as a practical tool to positively impact the ongoing educational needs of patients in a busy clinical practice setting. Prospective adequately powered studies are needed to evaluate if this online tool will lead to better long term outcomes by improving patient-physician communication. References:
[1]Khanna P. Ann Rheum Dis. 2013;72(Suppl3):768. [2]Zhang LY. J Clin Rheumatol. 2011 Aug;17(5):242-8.

Disclosure: P. Khanna, AstraZeneca, 2; **A. Rankin**, None; **V. Berrocal**, None; **L. An**, None; **D. Khanna**, Bristol-Myers Squibb, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,BAYER, 5,CYTORI, 5,EMD Serono, 5,Roche Pharmaceuticals, 2,AstraZeneca, 5.

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Abstract Number: 3131

Pregabalin Is More Effective in Treating Hand Osteoarthritis Pain Than Duloxetine or Placebo: A Double-Blind Randomized Controlled Trial

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Background/Purpose: Pain is a major symptom in hand osteoarthritis (OA), with many patients taking analgesics including acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs) and even opioids. Patients with OA who do not respond to conventional analgesics may have 'sensitization', or heightened pain symptoms which are centrally mediated. We hypothesized that patients with hand OA who have features of sensitization may improve with centrally-acting analgesics including duloxetine or pregabalin.

Methods: A prospective, randomized, double-blind, placebo-controlled trial from 42 primary care and rheumatology clinics in the UK. We recruited 85 participants: 65 with hand OA confirmed by ACR criteria (mean age 62 years) and 20 age-matched non-OA controls. Patients were assigned 1:1:1 to treatment with duloxetine (up to 60 mg), pregabalin (up to 300 mg) or matched placebo. The primary endpoints were the Australian and Canadian Hand Osteoarthritis Index (AUSCAN) pain score change and the Visual Analogue Scale (VAS) pain rating 0-10 from baseline to 12 weeks treatment. Secondary endpoints were AUSCAN function, Hospital Anxiety and Depression Scale (HADS) and pain pressure thresholds (PPTs) for sensitization measured by algometry (Wagner).

Results: All participants were randomised and included in the intention-to-treat analysis. The highest mean reduction in AUSCAN pain scores was achieved for the pregabalin group (mean change -132.1, 95% confidence interval -181.1 to -82.9) followed by duloxetine (mean change -62.5, 95% confidence interval -141.6 to 16.6) and placebo (mean change -47.1, 95% confidence interval -93.9 to 11.7). The most significant improvement after treatment was in the pregabalin group compared with placebo (p=0.013), Figure 1. AUSCAN pain reduction for duloxetine was not significant (p=0.90). VAS pain outcome was significant for pregabalin (p<0.00001) and duloxetine (p=0.029) respectively with no change in depression or anxiety scores in any group. PPT were lower in hand OA than non-OA controls at baseline (p<0.05). Side effects were similar in pregabalin and duloxetine groups, although more neurological side effects occurred in the pregabalin group including dizziness, dry mouth, sleepiness and loss of balance. PPT were useful for screening for sensitization, but did not change significantly after treatment (p>0.05).

Conclusion: Pregabalin has significant efficacy at 300 mg in improving pain and function after 12 weeks compared with duloxetine or placebo in hand OA. VAS pain outcomes for pregabalin and duloxetine both showed significant efficacy over placebo. PPTs are useful for screening for sensitization and identifying participants who are likely to respond to centrally-acting analgesics. Our results demonstrate evidence for pregabalin as an alternative for OA pain in sensitized patients and clinical trials that examine the balance between efficacy and side effects should be encouraged.

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Protective Effects of Replacing Sedentary Time with Light and Moderate to Vigorous Physical Activity on Functional Limitation in Knee OA

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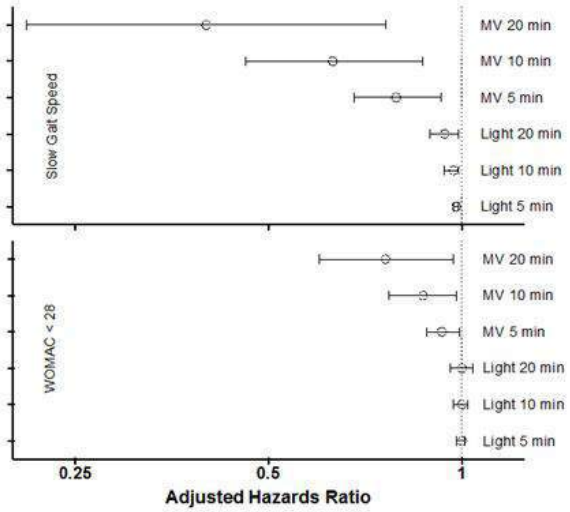
Background/Purpose: Physical activity protects the development of functional limitation in knee osteoarthritis (OA). But little is known about the protective effects of physical activity intensity, i.e., light and moderate to vigorous physical activity (MVPA). Knee OA-related pain may limit higher intensity activity, and the benefit of light intensity activity is not known. Moreover, it is unclear what amount of light intensity activity may be necessary to equal the health benefits attained from MVPA. The purpose of this study was to investigate the association of replacing sedentary time with light intensity and MVPA with the development of functional limitation two years later in people with or at high risk of knee OA.

Methods: Physical activity was objectively measured with an accelerometer in a subcohort of adults from the Osteoarthritis Initiative (OAI) at the 48- and 72-month visits (our study baselines). We included participants with at least four 10-hour days of valid monitoring and classified time in sedentary, light, and MVPA using established thresholds. Incident functional limitation over two years was assessed by: 1) Slow gait speed (< 1.0 meters/sec during a 20-meter walk), 2) Low WOMAC physical function (≥ 28; range 0-68) and 3) Low SF-12 (<40; range 0-100). We evaluated the association of replacing sedentary time with light or MVPA with incident functional limitation risk over two years using isotemporal substitution models. Hazard ratios were estimated from discrete survival models. All analyses were adjusted for potential confounders.

Results: We included 1873 study subjects (mean age (sd) = 65.0 years (9.0), 54.6% women, mean BMI (sd) = 28.4 kg/m^2 (4.7). Replacing 5 minutes of sedentary time with 5 min of light activity reduced the incident risk for slow gait function by 2%. Replacing with 5 min of MVPA reduced the risk by 21%. 78 min of light activity is necessary to achieve the same protective benefit of 5 min of MPVA. Replacing sedentary time with MVPA but not light activity significantly reduced the incident risk of low WOMAC. The protective effect of replacing sedentary time with light activity or MVPA was amplified with longer replacement periods. See Figure

Conclusion: Replacing sedentary time with light or MVPA reduced the risk of incident functional limitation. The protective effects of MVPA outweighed light activity.

Figure: Adjusted* hazard ratios of protective benefits of replacing sedentary time with an equal amount of light and moderate to vigorous (MV) physical activity.



* Adjusted for age, sex, race, education, BMI, radiographic knee OA, comorbidity, depressive symptoms, knee pain, and lower body pain

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Disclosure: D. White, None;

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Abstract Number: 3133

Association Between Quantitatively Measured Infrapatellar Fat Pad High Signal Intensity Alteration and Knee Structural and Symptomatic Abnormalities in Patients with Symptomatic Knee Osteoarthritis

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Background/Purpose: Infrapatellar fat pad (IPFP), a local adipose tissue, may have important contributions to knee osteoarthritis (OA). IPFP signal intensity alterations on MRI may represent pathological changes such as inflammation and oedema. This study aims to describe the associations between quantitative measures of infrapatellar fat pad (IPFP) signal intensity alterations and knee structural and symptomatic abnormalities in patients with symptomatic knee OA.

Methods: 261 participants (mean age 63.0 ± 7.2 years) with symptomatic knee OA (assessed according to American College of Rheumatology criteria) were selected from a randomized controlled trial. IPFP signal intensity alteration was quantitatively measured on T2-weighted fat-saturated MRI using MATLAB. These included the mean value [Mean (IPFP)] and standard deviation [sDev (IPFP)] of whole IPFP signal intensity, median value [Median (H)] and upper quartile value [UQ (H)] of high signal intensity, volume of high signal intensity regions [Volume (H)] and the ratio of Volume (H) to volume of whole IPFP [Percentage (H)] and Clustering factor (H) representing clustering effect of high signal intensity. Signal intensity alteration (SIA) was also measured semi-quantitatively (grade 0-3). Cartilage defects, bone marrow lesions (BMLs) and radiographic OA (ROA) were

measured. All measures except ROA were performed at both baseline and 24 months later. Linear regression analyses were performed after adjustment for age, sex, BMI, and/or intervention.

Results: Two hundred and sixty one participants (mean age 63.0 ± 7.2 years) participated in this study. There were no significant differences in demographic factors (age, sex, and BMI) between these participants and those unselected. sDve (IPFP), Median (H), UQ (H), Volume (H), Percentage (H) and Clustering factors (H) were associated with increased ROA at baseline in multivariable analyses. In the linear mixed-effects model, these measures were significantly and positively associated with cartilage defects and BMLs over 2 years in multivariable analyses. Mean (IPFP), sDev (IPFP), Median (H) and UQ (H) were also significantly associated with increased knee pain over 2 years (Table 1).

Conclusion: Quantitative measures of signal intensity alteration in IPFP were associated with knee structural and symptomatic abnormalities in patients with symptomatic knee OA, suggesting that IPFP signal intensity alterations may have a role to play in knee OA progression. Table 1. Associations of IPFP signal intensity alteration with cartilage defects and bone marrow lesions

	Cartilage defects*	Bone marrow lesions*
	β (95% CI)	β (95% CI)
Mean (IPFP)	3.18 (-4.74, 11.10)	**16.36 (6.27, 26.46)**
sDev (IPFP)	**31.39 (15.87, 46.90)**	**48.27 (31.19, 65.34)**
Median (H)	**6.46 (1.76, 11.16)**	**13.91 (8.49, 19.33)**
UQ (H)	**4.71 (1.17, 8.26)**	**10.06 (5.99, 14.14)**
Volume (H)	**1.33 (0.66, 1.99)**	**1.17 (0.46, 1.87)**
Percentage (H)	**37.91 921.64, 54.18)**	**46.36 (26.04, 66.69)**
Clustering factor (H)	**0.78 (0.44, 1.13)**	**1.16 (0.74, 1.58)**
SIA	**0.57 (0.30, 0.84)**	**0.83 (0.51, 1.15)**

*Adjusted for age, sex, BMI, treatment allocation and randomization.

Disclosure: W. HAN, None; **G. Jones**, None; **C. Ding**, None.

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Abstract Number: 3134

Hydroxychloroquine Is Not Effective in Reducing Symptoms of Hand Osteoarthritis: Results from a Placebo-Controlled Randomised Trial

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Background/Purpose: Synovitis is prevalent in OA and associated with pain. Hydroxychloroquine (HCQ) is used routinely for treating synovitis in inflammatory arthritis. The primary aim of the HERO RCT was to determine the effectiveness of HCQ as an analgesic treatment for hand OA, and secondarily to determine if synovitis was associated with treatment response, effects on structural progression and cost-effectiveness.

Methods: 248 participants with symptomatic (VAS pain ≥4/10) and radiographic hand OA recruited across UK primary and secondary care were randomized to HCQ or placebo for 12 months. Daily HCQ dose ranged from 200-400 mg according to ideal body weight. The primary endpoint was average hand pain during the previous 2 weeks (numerical rating scale, NRS) at six months. Secondary endpoints included other self-reported pain and function (NRS and VAS scales, AUSCAN), grip strength, quality-of-life measures (OAQol, SF-12) and radiographic structural change (on Kallman score) at 12 months. The effects of baseline radiographic severity were also assessed. In a sub-study, n=143 participants had ultrasound performed at baseline on small joints of a single hand. Longitudinal mixed models compared changes between groups. Analyses were conducted on intention-to-treat basis. A health economics analysis was also performed.

Results: Follow-up was 84.7% at 6 months and 76.6% at 12 months. The mean initial HCQ dose for the intervention arm (n= 114) was 320 mg. At the primary endpoint, the treatment difference estimate between HCQ and Placebo was -0.16 points on the NRS pain scale (95% CI: -0.72 to 0.41, p=0.584, Table 1). There were no significant treatment differences at 3, 6 or 12 months for any secondary outcomes including radiographic outcomes (Table 1). Baseline structural damage did not affect response to HCQ. On ultrasound, 94% had ≥1 joint positive for greyscale synovitis, 59% were Power Doppler positive; synovitis did not impact on treatment group differences. The economic analysis found that HCQ was less costly but produced a smaller quality-adjusted life year (QALY) gain than placebo, saving £6,545 per QALY lost, and was not considered to be cost-effective.

Conclusion: HCQ was not more effective than placebo in reducing symptoms or radiographic progression in people selected for moderate to severe hand pain and radiographic OA; HCQ is therefore not recommended for this patient group. Given the analgesic benefits of other anti-inflammatory therapies, these findings may reflect the mild anti-inflammatory action of HCQ, differing drug effects on certain OA pathologies, and also inclusion criteria in hand OA trials. Table 1: Adjusted group means and differences from longitudinal mixed models

	HCQ Mean (95% CI)	Placebo Mean (95% CI)	Between-group Difference (95% CI)
Hand Pain NRS (Primary endpoint at 6 months)			
3 months	5.52 (5.00, 6.04)	5.76 (5.25, 6.28)	0.24 (-0.30, 0.79)
6 months	5.64 (5.11, 6.16)	5.48 (4.95, 6.01)	-0.16 (-0.72, 0.41)
12 months	5.36 (4.81, 5.90)	5.50 (4.96, 6.03)	0.14 (-0.44, 0.72)
AUSCAN Pain			
3 months	11.29 (10.48, 12.09)	11.23 (10.43, 12.03)	-0.06 (-0.90, 0.78)
6 months	11.13 (10.32, 11.95)	11.00 (10.18, 11.82)	-0.14 (-1.00, 0.73)
12 months	10.92 (10.09, 11.76)	10.39 (9.56, 11.21)	-0.54 (1.43, 0.36)
AUSCAN Function			
3 months	19.76 (18.34, 21.18)	20.15 (18.75, 21.56)	0.40 (-1.08, 1.88)
6 months	19.72 (18.28, 21.15)	19.33 (17.89, 20.76)	-0.39 (-1.91, 1.14)
12 months	19.81 (18.33, 21.29)	19.02 (17.57, 20.47)	-0.79 (-2.37, 0.78)
Grip Strength (right hand, in lbs)			
6 months	37.34 (33.71, 40.97)	37.25 (33.63, 40.88)	-0.09 (-3.87, 3.69)
12 months	36.79 (33.08, 40.50)	38.89 (35.24, 42.54)	2.10 (-1.80, 5.99)
Osteoarthritis Quality of Life (OAQoL)			
6 months	8.56 (7.22, 9.90)	8.81 (7.48, 10.15)	0.25 (-1.11, 1.62)
12 months	8.92 (7.55, 10.30)	9.56 (8.21, 10.92)	0.64 (-0.79, 2.06)
SF-12 Physical Component Score			
6 months	39.61 (37.50, 41.73)	39.65 (37.54, 41.77)	0.04 (-2.16, 2.24)
12 months	38.30 (36.11, 40.49)	40.53 (38.40, 42.66)	2.23 (-0.06, 4.51)
SF-12 Mental Component Score			
6 months	51.54 (49.39, 53.70)	52.24 (50.10, 54.38)	0.70 (-1.59, 2.98)
12 months	53.17 (50.93, 55.41)	52.00 (49.83, 54.16)	-1.17 (-3.55, 1.21)
Total Kallman Score			
12 months	48.21 (47.39, 49.03)	48.33 (47.53, 49.13)	0.12 (-0.72, 0.97)

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Abstract Number: 3135

Influence of Baseline Magnetic Resonance Imaging Features on Outcomes of Operative and Non-Operative Treatment of Meniscal Tear in Patients ≥ 45

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Background/Purpose: In the treatment of meniscal damage in the setting of mild to moderate osteoarthritis (OA), several randomized trials found that both arthroscopic partial meniscectomy (APM) and physical therapy (PT) led to substantial pain relief. Whether certain subgroups of patients have worse outcomes with APM vs. PT is unknown. We hypothesize that increased baseline cartilage damage and presence of bone marrow lesions (BML) on magnetic resonance imaging (MRI) modifies the efficacy of APM compared to PT.

Methods: We used the data from the Meniscal Tear in Osteoarthritis Research (MeTeOR) Trial of APM vs. PT. Subjects were ≥45 years old and had meniscal damage on MRI, evidence of OA changes on imaging, and knee symptoms. Patients who were randomized to APM generally had surgery within three weeks after randomization. Patients who crossed-over between treatment groups were excluded from this analysis. MRIs were read using the MRI OA Knee Score (MOAKS). All 15 subregions were analyzed. Maximum, cartilage damage in any subregion (% of loss that is full thickness) was dichotomized at <10% vs. ≥10% and maximum BML in any subregion (% of subregion occupied) at none vs. any. The outcome was change from baseline to 6 months in the Knee Injury and Osteoarthritis Outcome Pain Score (KOOS, scored 0-100, 100 worst). We investigated the interaction between the imaging variables (cartilage damage, BML), treatment type (APM, PT) and change in KOOS Pain. We then calculated the difference in mean change between those receiving APM and PT for each imaging category.

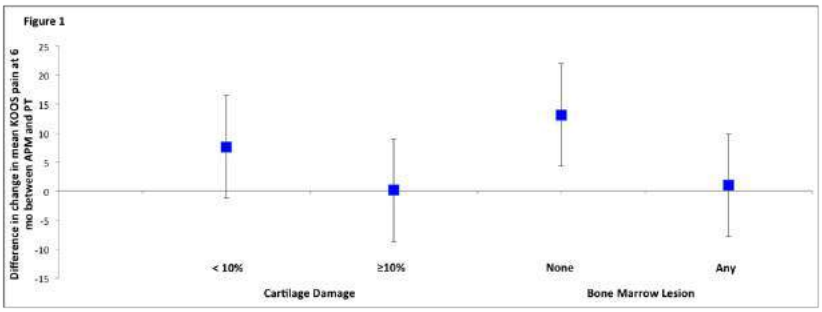
Results: The sample consisted of 223 knees (one per person); 129 (58%) had APM and 94 (42%) PT. The baseline KOOS Pain in all imaging categories ranged from 44-45 points. Patients with ≥10% cartilage damage had similar improvement in pain with PT and APM (23 points), while patients with <10% cartilage damage had greater improvement with APM than with PT (28 vs 20 points). Those with BML also had similar improvement with APM and PT (24 vs 23 points), while those with no BMLs had greater improvement with APM than with PT (29 vs 16 points). While these difference in efficacy of APM vs. PT were clinically relevant (MCID~8 points) they did not reach statistical significance. (p-value for interaction =0.17 for cartilage damage and 0.11 for BML).

Conclusion: These data suggest that for patients with more extensive baseline cartilage damage and BMLs there is no clinically meaningful difference in pain outcomes between management with APM vs. PT. However, though not statistically significant, our data suggest that patients with less cartilage damage and those with no BMLs at baseline may receive more symptomatic benefit from APM than from PT. These relationships should be pursued in larger cohorts to further assess the role of APM in management of meniscal tear in those with less cartilage damage or no BMLs.

Table 1

	N (%)	Baseline KOOS Pain, mean (SE)	ΔKOOS Pain (95% CI) at 6 months		
			APM	PT	P interaction
Cartilage Damage					
≥10%	151 (68)	45.8 (16.1)	-23.2 (-27.2,-19.4)	-23.1 (-27.5, -18.7)	0.17
<10%	69 (31)	44.4 (16.0)	-27.9 (-33.5,-22.4)	-20.3 (-27.2, -13.4)	
Bone Marrow lesion					
Any	185 (85)	45.3 (16.6)	-23.9 (-27.5,-20.4)	-22.9 (-26.9,-18.9)	0.11
None	33 (15)	45.9 (13.1)	-28.8 (-36.5,-21.2)	-15.7 (-27.4, -4.0)	

KOOS; Knee Injury and Osteoarthritis Outcome Score, SE; standard error, APM; arthroscopic partial meniscectomy, PT; physical therapy



Difference between APM and PT for change in KOOS Pain at 6 months for each imaging category with confidence intervals

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Impact of Novel Smartphone Application on Pain and Mobility in Osteoarthritis Patients Treated with Hylan G-F 20

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Background/Purpose: OA is a leading cause of disability in the US. Although no disease-modifying therapies exist, patients with knee OA who walk 6,000 steps/day or more reduce the risk of developing a functional limitation within the next 2 years by half.[1] The purpose of this study is to demonstrate the impact of a mobile application (OA GO) plus wearable activity monitor/pedometer in increasing the mobility of knee OA patients who were treated with hylan G-F 20.

Methods: This was a multicenter, open-label study in knee OA patients treated with a single 6-ml injection of hylan G-F 20 and randomized 1:1 to unblinded wearable activity monitor and OA GO (Group A; n=107) or blinded wearable activity monitor only (Group B; n=104). Participants were aged 30 to 80 years, were eligible to receive hylan G-F 20 per US labeling, and were familiar with smartphone technology. Outcome measures included mean number and percent change from baseline in steps/day, pain and distance of 6-minute walk test, patient/physician satisfaction surveys, Patient Activation Measure (PAM-13), and adverse events (AEs) at 90 days. Descriptive statistics were used to compare baseline characteristics and least square means were used to compare changes from baseline.

Results: Baseline characteristics were similar between groups. In both groups, significant increases in mean number and percent change of steps/day from baseline were observed; a significantly greater improvement in both outcomes was observed for Group A versus Group B (1199 vs 467, *P*=.0345 for number of steps/day; 35.81 vs 11.48, *P*=0.0189 for percent change of steps/day). In the 6-minute walk test, there was a greater improvement from baseline for Group A versus Group B in reducing pain (−55.3% vs −33.8%, *P*=0.0068) and increasing distance (18.2% vs 6.3%, *P*=0.9583). There was a greater number of patients (65.4%)/physicians (67.3%) who would be likely/very likely to use/recommend the devices than those who would be unlikely to do so. In both groups, PAM-13 scores improved from baseline however, no statistically significant differences were observed between

groups (5.0% vs 6.9%, *P*=0.9931). The AE profiles were similar for the two arms.

Conclusion: In this study, both groups were treated with hylan G-F 20 and showed significantly increased mobility and reduced pain, however, patients using the wearable activity monitor and OA GO mobile application had significantly improved mobility over controls without adding safety concerns. Overall, patient use of a novel smartphone application in conjunction with a wearable activity monitor enhanced the efficacy imparted by hylan G-F 20 treatment for knee OA in steps per day and pain with walking in the 6-minute walk test. Sanofi provided funding for the study. [1]White DK, Tudor-Locke C, Zhang Y, Fielding R, LaValley M, Felson DT, et al. Daily walking and the risk of incident functional limitation in knee OA: An observational study. *Arthritis Care Res (Hoboken)*. 2014;66:1328-36.

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Abstract Number: 3137

Assessing System-Level Performance Measures for Early Rheumatoid Arthritis in a Large Multicenter Cross-Country Prospective 8-Year Observational Cohort Study

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Background/Purpose: The Arthritis Alliance developed a set of 6 performance measures to evaluate timely access to care and treatment for inflammatory arthritis. A national study is currently underway to test these measures in different data sources. The objective of this study was to examine 3 of these measures in early rheumatoid arthritis (ERA) patients receiving usual care in rheumatology clinics participating in a national longitudinal early arthritis study.

Methods: This study included ERA patients enrolled between January 1st 2007-January 31st 2015 who met 1987 or 2010 ACR/EULAR RA criteria and had < 1 year of symptom duration at cohort entry. Patients who died or moved away within 1 year of the baseline visit or who had <1 year of follow-up were excluded. Each measure was computed annually. Measures included: i) percentage of patients with RA seen in yearly follow-up (operationalized at fixed 12 and 14 month windows from the patient's

baseline visit), ii) annual percentage of RA patients treated with a disease-modifying drug (DMARD, calculated as the proportion of patients with RA with at least one record of DMARD or biologic use) and, iii) time from new RA diagnosis to initiation of DMARD therapy (defined by the time between the date of diagnosis of RA to the date of first starting a DMARD and reported as 50th and 90th percentile times as well as the percentage prescribed DMARDs within 2 weeks of diagnosis).

Results: 1927 RA patients were included. The mean age of the cohort was 54, with 73% female and 82% Caucasian. The average disease duration was 5.8 months and the mean DAS28 was 5.1 at baseline. Over 8 years 72% of patients were seen in yearly follow-up; when using a 14-month window this increased to 76%. The yearly percentage of newly diagnosed RA patients on a DMARD ranged between 92-100%; however, considering the whole cohort overtime the total proportion on DMARDs declined from 94% in 2007 to 70% in 2015. Between 2007 and 2015 the percentage of RA patients who received DMARD treatment within 14 days of diagnosis increased from 74% to 90%. Median time to DMARD therapy was 0 days (50th percentile) during all years of measurement indicating treatment occurred at time of diagnosis; and the 90th percentile decreased from 89 to 6 days between 2007 and 2015.

Conclusion: Between 2007-2015 the percentage meeting benchmarks for time to DMARD therapy increased in CATCH from 74% to 90%. A drop-off in yearly follow-up is typical of many observational studies though less in this study, perhaps due to benefits of universal access to care. This may not necessarily reflect a gap in care as patients may have returned to usual follow-up with the rheumatologist. The decline in percentage on DMARD over time likely represents a number of factors including: DMARD-free remission associated with earlier diagnosis and treatment, patient engagement and non-adherence and a possible care gap. Analysis of medication use over time is an ongoing goal of this study. This study represents a best-case scenario for capturing performance measures from systematically collected data demonstrating the feasibility of rapid DMARD initiation. Our findings may be useful as a benchmark while testing the measures using other settings and data sources.

Disclosure: C. E. H. Barber, None; **C. Barnabe**, None; **G. Hazlewood**, None; **O. Schieir**, None; **L. Nadeau**, None; **J. C. Thorne**, abbvie, 5,Amgen, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Centocor, Inc., 5,Celgene, 5,Genzyme Corporation, 5,hospira, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genzyme Corporation, 8,Medac Pharma, 8,Antares, 8,Abbvie, 2,Amgen, 2,AstraZeneca, 2,Celgene, 2,Eli Lilly and Company, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2; **V. Ahluwalia**, None; **S. J. Bartlett**, None; **G. Boire**, None; **B. Haraoui**, Abbvie, 5,Amgen, 5,Bristol-Myers Squibb, 5,Celgene, 5,Eli Lilly and Company, 5,Janssen Pharmaceutica Product, L.P., 5,Merck Pharmaceuticals, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,UCB, 5; **C. Hitchon**, None; **E. Keystone**, Abbott, Amgen, AstraZeneca, BMS, Hoffman-LaRoche, Janssen, Eli Lilly and Company, Novartis, Pfizer, Sanofi-Aventis, UCB, 2,Abbott, AstraZeneca, Biotest, BMS, Crescendo, Hoffmann-LaRoche, Genentech, Janssen, Eli Lilly and Company, Merck, Pfizer, UCB, 5,Abbott, AstraZeneca, BMS Canada, Hoffmann-LaRoche, Janssen, Pfizer, UCB, Amgen, 9; **D. Tin**, None; **J. E. Pope**, Abbvie, 5,Actelion Pharmaceuticals US, 5,Amgen, 5,Bayer, 5,Bristol-Myers Squibb, 5,Genzyme Corporation, 5,Hospira, 5,Eli Lilly and Company, 5,Merck Pharmaceuticals, 5,Novartis Pharmaceutical Corporation, 5,Pfizer Inc, 5,Regeneron, 5,Roche Pharmaceuticals, 5,Sanofi-Aventis Pharmaceutical, 5,UCB, 5,Amgen, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,UCB, 2; **L. Denning**, None; **V. P. Bykerk**, AbbVie, Bristol-Myers Squibb, Pfizer, Roche/Genentech, Regeneron, and UCB Pharma, 5.

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Abstract Number: 3138

Sustained Improvement in Follow-up of Hypertension in Rheumatology Patients: Results of an Intervention Sustainability Assessment

Edmond Ramly[1,2], Daniel Panyard[3], Diane Lauver[4], Emmanuel Sampene[5], Zhanhai Li[5], Heather Johnson[6], Patrick McBride[6], Kristin Steffen Lewicki[7] and Christie M. Bartels[8], [1]Industrial and Systems Engineering, University of Wisconsin-Madison College of Engineering, Madison, WI, [2]Department of Medicine, University of Wisconsin-Madison, Madison, WI, [3]Population Health, University of Wisconsin School of Medicine and Public Health, Madison, WI, [4]University of Wisconsin-Madison School of Nursing, Madison, WI, [5]Biostatistics, University of Wisconsin School of Medicine and Public Health, Madison, WI, [6]Cardiology/Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, [7]Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, [8]Rheumatology/Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

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Background/Purpose: Hypertension (HTN) is the most prevalent comorbid cardiovascular disease (CVD) risk factor among adults with rheumatic conditions. However, we previously found that high blood pressures (BP) were addressed in <1/3 of rheumatology visits, even when severely elevated (≥160/100 mmHg). In this range, only 11 patients need to be treated for HTN to prevent one CVD event. In primary care, HTN protocols executed by nurses or medical assistants during vital sign assessment have improved control of high BP. In a prior six-month pilot study, we had tested a theory-based staff protocol intervention to facilitate timely (<4 weeks per a US quality measure) primary care follow-up for patients with high blood pressures at rheumatology visits, and had reported two-fold higher odds of timely follow-up. Here, our objective is to assess the 18-month sustainability of those improvements.

Methods: We conducted a pre-post study in three academic rheumatology clinics. All eligible adult (≥18 years-old) rheumatology visits with BP ≥140/90 mmHg (Dec. 2014-May 2016) were compared to pre-intervention visits (Jan. 2012-Sep. 2014). Our multi-dimensional intervention included (1) education of frontline staff on HTN and CVD risk in rheumatologic diseases, (2) electronic health record (EHR) alerts for staff to re-measure BPs if ≥140/90 and (3) cuing brief patient education and scheduling primary care follow-up if 2nd BP ≥140/90, and (4) monthly audit and feedback with staff about performance. We gave in-person feedback between months 1 and 6, then by email months 6-18. We assessed timely primary care follow-up for high BPs among patients who received primary care in our system using EHR data. We performed multivariable logistic regression and compared the odds (OR, 95%CI) of timely primary care follow-up before and during intervention, controlling for baseline socio-demographics, comorbidities, and utilization.

Results: We compared 1,737 intervention period visits to a comparable group of 4,683 pre-intervention visits with BPs ≥140/90. Staff initiated the protocol with BP re-measurement in 57%, 73%, and 69% of eligible visits during intervention months 0-6, 6-12, and 12-18 respectively, compared to <1% pre-intervention, with 66% overall improvement, p<0.0001. Months 4-6 showed peak improvement in BP re-measurement at 80% during monthly in-person audit-feedback. More patients received timely follow-up for HTN during the entire 18-month intervention period (46% vs 29% before, p<0.0001). Multivariable analysis showed that eligible visits during the intervention had two-fold higher odds of timely follow-up compared to pre-intervention (OR 2.1, 1.4-3.0 in months 0-6; OR 2.16,1.72-2.71 across entire intervention), indicating sustained improvement.

Conclusion: Our intervention with usual staff in rheumatology clinics doubled odds of timely BP follow-up, and these improvements were sustained over 18 months. Future studies should examine this intervention in other rheumatology clinics to evaluate its impact on HTN control and CVD event risk across rheumatology populations.

Disclosure: E. Ramly, None; **D. Panyard**, None; **D. Lauver**, None; **E. Sampene**, None; **Z. Li**, None; **H. Johnson**, None; **P. McBride**, None; **K. Steffen Lewicki**, None; **C. M. Bartels**, Pfizer, 2.

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Abstract Number: 3139

Breaking the Cycle: Analyzing Preventable Hospital Admissions Due to Gout

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Background/Purpose: Despite available effective treatment options and published guidelines for gout management, many patients suffer from recurrent gout attacks. Increases in gout prevalence and continued suboptimal gout care result in an increase in hospitalizations and health care utilization. We analyzed admissions due to gout in a community teaching hospital in order to ascertain whether these hospitalizations were preventable and to identify deficits in care prior to admission.

Methods:

We identified adult patients hospitalized at our institution from 01/01/2011 to 12/31/2014 with a primary discharge diagnosis of gout. A preventable admission was defined as a final diagnosis of gout without any coexisting conditions on presentation warranting admission, determined by chart review. We reviewed demographic characteristics, diagnosis on admission, prior history of gout, risk factors for gout, gout medication use prior to hospitalization, serum uric acid levels on admission, date and time of admission including overnight and weekend admissions, history of outpatient follow-up for treatment of gout, use of arthrocentesis, and duration of inpatient stay.

Results:

Ninety one patients were discharged with a primary diagnosis of gout, 71 (78%) of whom met criteria for preventable admission. Diagnosis on admission included pain 27 (38%), pain and joint swelling 4 (5%), joint effusion 4 (5%), acute gouty arthritis 26 (36%), cellulitis 10 (14%), osteomyelitis 2 (3%), and one patient was admitted to rule out deep vein thrombosis. Twenty four patients underwent arthrocentesis, but only 5 of these procedures were done in the Emergency Department (ED) prior to admission. Fifty patients (70%) had a prior history of gout, although 35 (70%) of them had no documentation of any outpatient provider managing their gout. 12 (23%) were managed by primary care providers, 3 (5%) by a rheumatologist. Risk factors for gout included hypertension 63 (88%), chronic kidney disease 27 (38%), aspirin therapy 34 (47%), and diuretic therapy 46 (64%). 20 (28%) were receiving urate lowering therapy (ULT), and 8 (11%) chronic colchicine. Seventeen (85%) of the patients treated with allopurinol received no prophylactic therapy. Only 10 (14%) had serum uric acid levels at target of <6 mg/dL, 27 (59%) had a uric acid level between 8-10 mg/dL, and 15 (21%) above 10 mg/dL. Ten (14%) had no documentation of their uric acid level. Twenty (28%) of the admissions were during the weekend, and 33 (46%) were admitted between the hours of 5pm and 7am. Overall aggregate length of stay for the preventable admissions was 179 days (mean 2.59 days).

Conclusion: Our findings demonstrate that 78% of the hospitalizations with a primary discharge diagnosis of gout were preventable. Lapses in the outpatient management of gout were apparent, as most of the patients did not have ongoing outpatient gout management, and few received concomitant prophylactic therapy when treated with ULT or had serum uric acid levels at target. A significant number of patients were admitted via the ED at night and on weekends. Arthrocentesis appeared to be underutilized in the ED. Interventions to address gaps in outpatient and ED care for gout are needed to prevent unnecessary admissions and decrease hospitalization-related costs.

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Assessment of American College of Rheumatology Gout Quality Measures at a University Practice Plan

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Background/Purpose: Gout is the most common chronic inflammatory arthritis. Gout prevalence has been rising over the past several decades, and gout is associated with significant health and financial burden. Numerous guidelines including 2012 American College of Rheumatology (ACR) guidelines have been published for management of gout. However, compliance with these practice guidelines remains poor. To promote adherence to management guidelines and improve quality of care for gout, ACR has developed a set of quality measures. We evaluated the performance of these quality measures at our university practice group.

Methods: We established a registry of patients receiving care for gout at our university practice group since 6/2013 using electronic medical record (EMR) and administrative database (ICD-9 codes 274.XX). Using a subset of this population being followed for gout over the past 12 months, we tested the three quality measures developed by ACR including: (1) Treat to Target: percentage of patients aged 18 and older with a diagnosis of gout treated with urate-lowering therapy (ULT) for at least 12 months whose most recent serum urate result is less than 6.8mg/dL; (2) ULT indications for therapy: percentage of patients aged 18 and older with a diagnosis of gout and either tophus/tophi or at least two gout flares (attacks) in the past year who have a serum urate level >6.0mg/dL, who are prescribed ULT; (3) serum urate monitoring: percentage of patients aged 18 and older with a diagnosis of gout who were either started on ULT or whose dose of ULT was changed in the year prior to the measurement period and who had their serum urate level measured within 6 months.

Results: From the university practice, 4988 patients were identified, 18 years of age or older with a diagnosis of gout. For the Treat to Target measure, 1183 (47.7%) of 2478 patients on ULT met the serum urate target of <6.8mg/dL. For the ULT indications measure, 329 (70.9%) of 464 patients with tophaceous gout or recurrent flares and serum urate level >6.0mg/dL were appropriately prescribed ULT. For the serum urate monitoring measure, 1259 (35.8%) of 3517 patients with new start or modification of ULT had serum urate level measured within 6 months. Several potential challenges in implementation were identified in our evaluation of the ACR quality measures. The Treat to Target measure appeared to be the most straightforward measure to implement, but outside labs not captured by the EMR posed a problem. For the ULT therapy measure, we encountered difficulties with establishing reliable criteria for capturing gout flares. Accurate recognition of modification of ULT dose was the primary challenge for the serum urate monitoring measure.

Conclusion: Analysis of gout patients at our university practice using the ACR quality measures confirms suboptimal adherence to available practice guidelines. Our analysis also identifies potential challenges in implementation of the ACR quality measures. Some of these challenges are practice specific (higher prevalence of outside labs at university referral practice), and others (identification of flares and medication changes) are amenable to modification of specifications to best match varying structures and available data from different EMR systems. Ability to accurately assess quality measures using EMR is an essential step in promoting adherence to practice guidelines. Continued efforts at optimizing quality measure assessments will help provide the foundation for design and implementation of future quality improvement projects.

Disclosure: S. Choi, None; **J. FitzGerald**, None; **R. Clarke**, Ursa Health, Inc, 4; **A. Hackbarth**, Ursa Health, Inc., 4.

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Abstract Number: 3141

Development of a Glucocorticoid Toxicity Index Using Multi-Criteria Decision Analysis

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SESSION INFORMATION

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Background/Purpose: Glucocorticoids (GC) are associated with substantial treatment morbidity. New immunomodulatory agents offer the possibility of limiting GC exposure. To assess the comparative benefits of such agents, investigators must accurately measure their ability to prevent or reverse GC-related toxicity. No comprehensive instrument for measuring GC toxicity has previously been developed. We aimed to develop a GC Toxicity Index (GTI) to assess GC-related morbidity and GC-sparing ability of new agents.

Methods: Nineteen experts from 11 subspecialties participated. Ten experts were from the United States; 9 from Canada, Europe, or Australia. Group consensus methods and multi-criteria decision analysis were utilized. The development process included ten 1-hour conference calls, group work between calls and a 12-hour face-to-face meeting. *GTI components* The GTI is composed of the Composite GTI (CGTI) and the Specific List. The CGTI reflects GC toxicity that is likely to change over the course of a clinical trial. The toxicities included in the CGTI occur commonly, vary with GC exposure, and are weighted and scored. The Specific List is designed to capture GC toxicity not included in the CGTI. The CGTI was evaluated by application to paper cases by the investigators and an external group of 17 subspecialists.

Results: *Item inclusion and definitions* Thirty-one toxicity items derived from the literature were included in the CGTI, and 23 were included in the Specific List (Table). Definitions were developed by experts using group consensus methods. The CGTI items reflect both improvement and worsening of GC toxicity and account for medication effects (e.g., anti-hypertensives) in scoring. The 31 mutually-exclusive CGTI items are organized in order of severity within nine domains. Only one item in each domain can be scored. *Weighting and evaluation of the CGTI* Relative weights for each item in the CGTI were derived at a face-to-face meeting utilizing multi-criteria decision analysis. CGTI evaluation showed high inter-rater agreement (investigators kappa 0.88, external raters kappa 0.90). To assess the degree to which the CGTI corresponds to expert clinical judgment, participants ranked 15 cases by clinical judgment in order of highest to lowest GC toxicity. Expert rankings were then compared to case ranking by the CGTI, yielding excellent agreement (investigators weighted kappa 0.87, external raters weighted kappa 0.77).

Conclusion: We describe the development and initial evaluation of the GTI - a comprehensive instrument intended primarily for use in prospective, randomized clinical trials for the assessment of GC toxicity. The GTI can be used across clinical disciplines in trials that employ GCs to assess the comparative value of GC-sparing therapies, and to measure the impact of GC toxicity. **Table – Composite GTI and Specific List**

Composite GTI	Item Weight	Specific List
Body mass index		
Improvement in BMI	-8	Major increase in BMI
No change in BMI	0	
Moderate increase in BMI	21	
Major increase in BMI	36	
Glucose tolerance		
Improvement in glucose tolerance	-8	Diabetic retinopathy
No change in glucose tolerance	0	Diabetic nephropathy
Worsening of glucose tolerance	32	Diabetic neuropathy
Worsening of glucose tolerance despite treatment	44	
Blood pressure		
Improvement in blood pressure	-10	Hypertensive emergency
No change in blood pressure	0	Posterior reversible encephalopathy syndrome
Worsening hypertension	19	
Worsening hypertension despite treatment	44	
Lipids		
Improvement in lipids	-9	
No change in lipids	0	
Worsening hyperlipidemia	10	
Worsening hyperlipidemia despite treatment	30	
Bone density		
Improvement in bone density	-1	Major decrease in bone density
No change in bone density	0	Insufficiency fracture
Decrease in bone density	29	
Steroid myopathy		
No steroid myopathy	0	Severe steroid myopathy
Mild steroid myopathy	9	
Moderate steroid myopathy or greater	63	
Skin toxicity		
No skin toxicity	0	Severe skin toxicity
Mild skin toxicity	8	
Moderate skin toxicity or greater	26	

Neuropsychiatric toxicity		
No neuropsychiatric symptoms	0	Psychosis
Mild neuropsychiatric symptoms	11	GG-induced violence
Moderate neuropsychiatric symptoms or greater	74	Other severe neuropsychiatric symptoms
Infection		
No significant infection	0	Grade 4 infection
Oral/vaginal candidiasis or uncomplicated zoster	19	Grade 5 infection
Grade 3 infection or greater	93	
Endocrine		Adrenal insufficiency
Gastrointestinal		Perforation
		Peptic ulcer disease
Musculoskeletal		Avascular necrosis
		Tendon rupture
Ocular		Central serous retinopathy
		Intraocular pressure elevation
		Posterior subcapsular cataract
Total	-36 to 439	

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Abstract Number: 3142

Improving Counseling, Documentation and Adherence to Highly Effective Birth Control in Women on Teratogenic Medications at a Rural Medical Center: A Quality Improvement Initiative

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Background/Purpose: Autoimmune and inflammatory diseases occur more often in women than in men, and often these women are of childbearing age. Many of the medications prescribed for such diseases are teratogenic. Discussions regarding contraception and pregnancy planning are crucial for patients on these medications. The use of effective contraception in these women is low. We aimed at understanding barriers to counseling, improving documentation, and increasing the use of effective contraception at our academic medical center outpatient Rheumatology clinic.

Methods: As part of the quality improvement initiative, we performed an IRB exempt chart review on women between 18-45 years on methotrexate, mycophenolate, leflunomide or cyclophosphamide seen at our outpatient Rheumatology clinic from January 2015 to January 2016. We surveyed providers to understand the barriers preventing consistent discussion and documentation of recommendations for contraception. We also surveyed patients to assess plans for pregnancy, choice of current contraception, and barriers to use of effective contraception. We used the Plan-Do-Study-Act (PDSA) methodology to implement cycles of change using input from stakeholders. These PDSA cycles include standardized documentation tools, templates, targeted alerts and nursing-led education.

Results: At baseline, 182 women took at least one teratogenic medication. Most women received methotrexate (76%), followed by leflunomide (13%), mycophenolate (9%) and cyclophosphamide (2%). We sampled 25% of the women on methotrexate (n=30) and found that only 33% used highly effective contraception (tubal ligation or intrauterine device), 24% used hormonal methods (contraceptive pills or implants) and 43% did not have a form of contraception documented. Of the 17 patients on mycophenolate, 29% used highly effective contraception (tubal ligation or intrauterine device), 24% used hormonal methods (contraceptive pills or implants) and 47% did not have a form of contraception documented. Surveying the providers (n=13) we found that 46% had a patient who got pregnant while on a teratogenic medication ,even though the majority felt that they were consistently counseling their patients (85%). Of all clinic providers, only 23% were registered on the mycophenolate risk evaluation mitigation strategy (REMS).

Conclusion: We have identified a cohort of patients on teratogenic medications who are either not using, or have no documentation of contraception type in the electronic medical record. There is room for improvement in documentation of contraception type, counseling about the use of contraception, and the rate of use of highly effective contraception. Effective intervention strategies to improve these parameters are discussed.

Disclosure: S. Bhalla, None; **J. Mecchella**, None; **A. Zbehlik**, None.

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Abstract Number: 3143

The Caspase 8/RIPK3 Signaling Axis in Dendritic Cells Controls Joint Homeostasis Under Steady-State and Arthritic Conditions

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SESSION INFORMATION
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Background/Purpose: Rheumatoid arthritis (RA) manifests in persistent synovial inflammation, cellular infiltration and pro-inflammatory cytokine production, and results in progressive joint destruction. Dendritic cells (DCs) have been implicated in RA progression and persistence through either antigen presentation to autoreactive T cells or differentiation into synoviocytes, yet the mechanisms underlying these activities are not fully elucidated. We identified that caspase 8, an enzyme that initiates apoptosis and suppresses necroptosis by inhibition of RIPK1/3 signaling in a multitude of cells, is a novel DC-specific inhibitor of inflammatory processes independent of its known role in cell survival. Further, a genome-wide association study identified an RA risk single nucleotide polymorphism within the locus that contains the gene encoding for caspase 8. However, the impact of DC-specific loss of caspase 8 on arthritis progression has yet to be examined.

Methods: Mice with caspase 8 flanked by *loxP* sites ($Casp8^{fl/fl}$, WT) were bred to mice expressing Cre under control of the CD11c gene promoter (Cre^{CD11c}) to generate $Cre^{CD11c}Casp8^{fl/fl}$ mice. $Cre^{CD11c}Casp8^{fl/fl}$ mice were crossed with $RIPK3^{-/-}$ mice to determine the involvement of this signaling partner. The K/BxN serum-transfer model of arthritis was utilized and clinical severity was assessed. Ankle sections were stained with H&E and scored by a pathologist blinded to the study to assess pathology. Flow cytometric analysis was used to characterize naïve and arthritic joints.

Results: $Cre^{CD11c}Casp8^{fl/fl}$ mice showed accelerated initiation of arthritis, as evidenced by increased changes in ankle width and clinical scores on day 2 and 4, as well as increased joint damage compared to WT. DC-specific deletion of caspase 8 affects not only synovial DCs but also synovial macrophage populations in both the naïve and arthritic joint. $Cre^{CD11c}Casp8^{fl/fl}$ synovial DCs show elevated expression of costimulatory molecule CD86 compared to WT. Further, we previously demonstrated that naïve mouse joints contain MHC II^{+} and MHC II^{-} macrophages, the majority being MHC II^{-} tissue-resident macrophages that can limit arthritis initiation, and $Cre^{CD11c}Casp8^{fl/fl}$ joints exhibit a reduced proportion of these disease limiting tissue-resident macrophages compared to WT. $Cre^{CD11c}Casp8^{fl/fl}$ MHC II^{+} and MHC II^{-} macrophage populations express reduced CD36, a scavenger receptor for oxidized low-density lipoprotein and apoptotic neutrophils, and CD206, a protein active in endocytosis/phagocytosis, compared to WT. Strikingly, these alterations are a function of overactive RIPK3 signaling, as knockout of RIPK3 in $Cre^{CD11c}Casp8^{fl/fl}$ mice is sufficient to reverse all effects of caspase 8 deletion on joint homeostasis under steady-state and arthritic conditions.

Conclusion: The caspase 8/RIPK3 signaling axis in the joint plays a vital role in controlling arthritis pathogenesis, as global knockout of RIPK3 prevents the pathogenic phenotypes within the joint initiated by DC-specific caspase 8-deletion. These data have implications for RA by elucidating previously unknown cell-specific functions of a potentially useful target for therapy.

Disclosure: S. Dominguez, None; **H. R. Perlman**, None; **C. Cuda**, None.

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Role of the Gut Microbiome in Modulating Arthritis Progression in Mice

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Abstract

Background/Purpose: Genetics alone cannot explain most cases of rheumatoid arthritis (RA). Thus, investigating environmental

factors such as the gut microbiota may provide new insights into the initiation and progression of RA.

Methods: In this study, we performed 16S rRNA sequencing to characterize the gut microbiota of DBA1 mice that did or did not develop arthritis after induction with collagen.

Results: We found that divergence in the distribution of microbiota after induction was pronounced and significant. Mice susceptible to collagen-induced arthritis (CIA) showed enriched operational taxonomic units (OTUs) affiliated with the genus *Lactobacillus* as the dominant genus prior to arthritis onset. With disease development, the abundance of OTUs affiliated with the families Bacteroidaceae,Lachnospiraceae,and S24-7 increased significantly in CIA-susceptible mice. Notably, germ-free mice conventionalized with the microbiota from CIA-susceptible mice showed a higher frequency of arthritis induction than did those conventionalized with the microbiota from CIA-resistant mice. Consistently, the concentration of the cytokine interleukin-17 in serum and the proportions of CD8+T cells and Th17 lymphocytes in the spleen were significantly higher in the former group, whereas the abundances of dendritic cells, B cells, and Treg cells in the spleen were significantly lower.

Conclusion: Our results suggest that the gut microbiome influences arthritis susceptibility. **Figure Legends Figure 1. Differences in microbiome composition between CIA-susceptible and -resistant mice.**

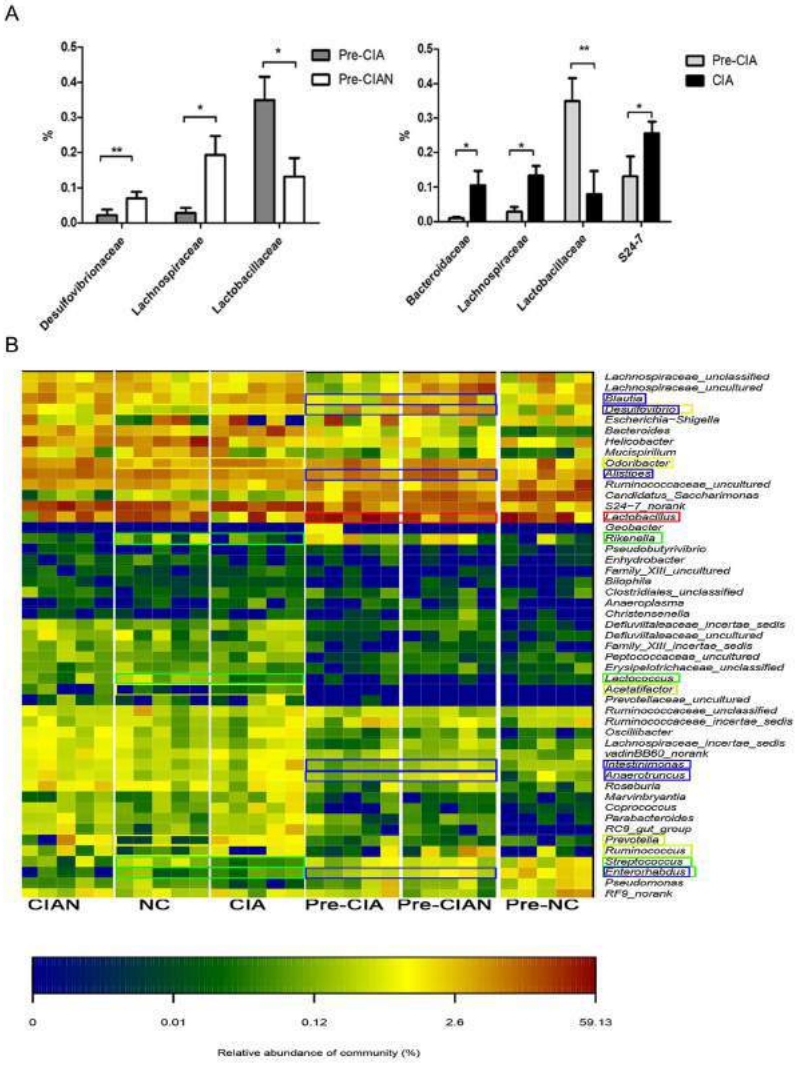


Figure 2. Analyses of faecal microbiomes of germ-free mice conventionalized with **CIA-susceptible or CIA-resistant mice.**

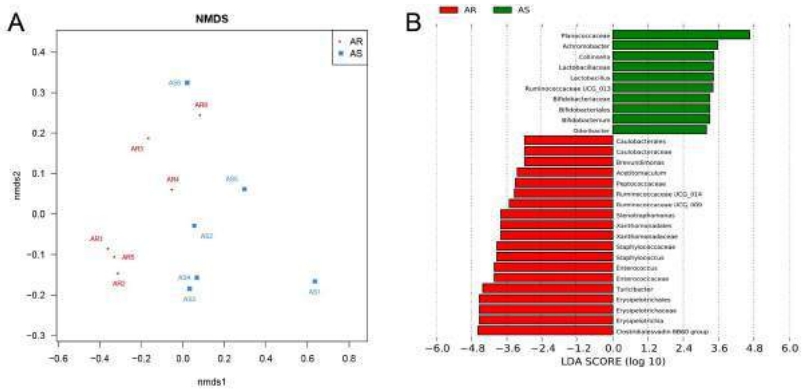
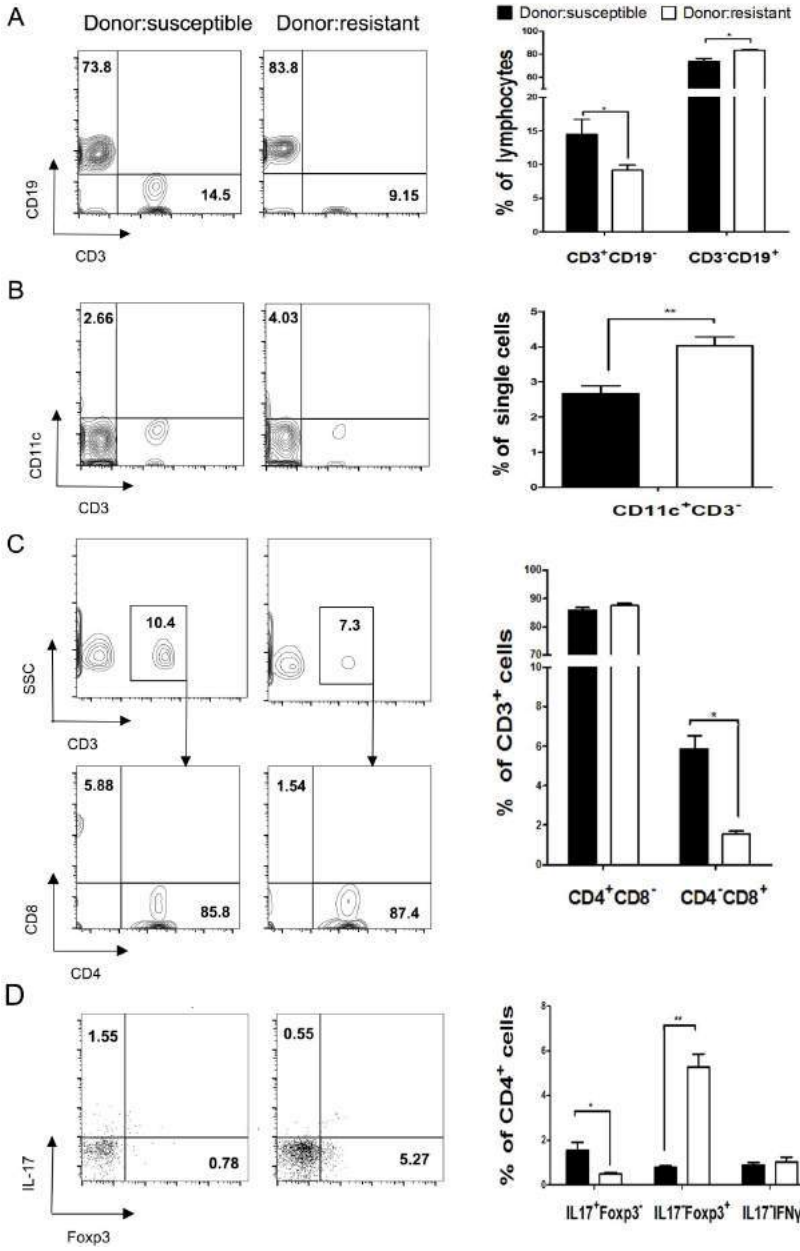


Figure 3. Phenotypic analysis of splenocytes from germ-free mice conventionalized with the microbiota from CIA-susceptible or -resistant mice.



Disclosure: X. F. Liu, None; **Q. H. Zou**, None; **B. Zhong**, None; **Y. F. Fang**, None.

Abstract Number: 3146

Selective Deletion of a Pathogenic Subset Synovial Fibroblasts Attenuates Synovial Inflammation

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Background/Purpose: Despite their role as key effector cells driving synovial inflammation and joint damage, fibroblast like synoviocytes (FLS) have yet to be targeted therapeutically. Fibroblast activation protein (FAP) is a cell surface serine protease, known to be expressed at a low level in resting FLS but up-regulated during inflammation (1). Genetic deletion of FAP has been shown to protect against cartilage damage despite no protective effect on inflammation or bone erosion (2). The pathogenic role of FLS expressing FAP is currently unknown. To determine the pathogenic role of FAP expressing FLS in inflammatory arthritis we selectively deleted these cells using a conditional cell deletion stratergy during the effector phase of inflammatory arthritis.

Methods: We utilized a transgenic mouse in which FAP expressing cells were conditionally ablated (FAP-DTR[3]) by administration of diphtheria toxin in either in a prophylactic or therapeutic regime. Inflammatory polyarthritis was induced by the passive transfer of K/BxN serum into naïve mice. Mice were scored for clinical signs of arthritis and flow cytometry of digested synovial tissue was performed to determine the expression of fibroblast subsets .

Results: We found that FAP expression in the human synovium predicts disease persistence in patients with early synovitis .FAP was dynamically expressed by FLS during inflammatory arthritis and defined a population of activated fibroblasts that co-express the lining layer marker Podoplanin (gp38). Therapeutic deletion of FAP+ cells during either the induction or peak phases of inflammatory arthritis significantly attenuated synovial inflammation leading to a reduction in the clinical severity of arthritis, reduced inflammatory cell infiltration and protection against inflammatory bone changes as measured by micro CT. In contrast, prophylactic deletion of FAP expressing cells led to a delayed onset of inflammatory arthritis, but did not impact on subsequent clinical severity.

Conclusion: These data support a pathogenic role for a subset of FAP expressing FLS in inflammatory arthritis and provide a rationale for the selective targeting of FAP+ fibroblasts as a novel therapeutic approach.

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Disclosure: A. P. Croft, None; **J. Campos**, None; **A. Filer**, None; **F. Barone**, None; **C. Buckley**, None.

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Abstract Number: 3147

Remote Inflammation Triggers Autoimmune Arthritis through Th17 Distribution

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Background/Purpose: Autoimmune diseases, such as autoimmune inflammatory arthritis, result through breakdown of immune tolerance and development of self-reactive T cells, or autoantibody-producing B cells. Tolerance breakdown and progression to autoimmune disease is multifactorial and usually involves a complex interplay between both genetic and external environmental factors. While past studies have extensively studied genetic associations, less attention has been paid to defining environmental factors that precipitate disease, or flares. For autoimmune inflammatory arthritis strong links have been reported for intestinal inflammation, bronchial stress and various infections. Nevertheless underlying molecular pathways whereby such remote challenges precipitate arthritis or flares remain unclear.

Methods: Here, we used a transfer model of self-reactive arthritis-inducing $CD4^+$ cells from KRNtg mice that, upon transfer, induce a very mild form of auto-inflammatory arthritis in recipient animals. Transfer of gene-deficient KRNtg $CD4^+$ cells and manipulation of the recipient animals allowed us to identify external factors that aggravated disease and to examine underlying mechanisms.

Results: We show that several distinct challenges precipitated full-blown arthritis, including intestinal inflammation through DSS-induced colitis, and bronchial stress through *Influenza* infection. Both challenges result in locally increased IL-1β levels what triggers strong IL-17 expression primarily in self-reactive $CD4^+$ cells in local lymph nodes draining the site of inflammation. Moreover, treatment of mice with IL-1β greatly exacerbated arthritis, while transfer of KRNtg $CD4^+$ cells lacking IL-1R significantly reduced disease and IL-17 expression. Thus, the results of this study suggest that IL-1β enhances the autoaggressive potential of self-reactive $CD4^+$ cells, through increased Th17 differentiation, and this influences inflammatory events in the joints. As $IL\text{-}17^+$ autoreactive CD4 T cells express high levels of CCR6 we speculate this may drive their migration to the joints, enriched in the chemokine ligand CCL20. In addition to that, our results suggest that IL-1β may exert direct inflammatory effects to the joints. In search of common downstream mechanisms for IL-1β production, we could demonstrate that Caspase-1/NLRP3 activation did not impact on inflammation-induced Th17 differentiation of autoreactive KRNtg $CD4^+$ cells, nor influence arthritis in our model. We therefore speculate that e.g. serine proteases secreted by locally infiltrating neutrophils, may be able to trigger Caspase-1-/NLRP3-independent IL-1β activation. Alternatively, Caspase-8 (possibly in concert with Caspase-1) may induce non-canonical IL-1β maturation.

Conclusion: We propose that diverse challenges including intestinal inflammation and bronchial stress/infection, result in IL-1β-driven Th17 differentiation, and this precipitates arthritis in genetically susceptible individuals. Thus the etiology of autoimmune inflammatory arthritis likely involves numerous challenges, that ultimately converge on a common pathway involving IL-1β/Th17. This may also explain why a single etiological factor for arthritis has been difficult to identify.

Disclosure: N. Chevalier, None; **J. Tan**, None; **L. Mason**, None; **R. Robert**, None; **C. McKenzie**, None; **S. Masters**, None; **C. Mackay**, None.

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Peptidylarginine Deiminase 2 Is Required for Tumor Necrosis Factor Alpha Induced Citrullination and Arthritis, but Not Neutrophil Extracellular Trap Formation

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Background/Purpose: The presence of anti-citrullinated protein antibodies in rheumatoid arthritis points to a potential role for citrullination in disease pathogenesis. Peptidylarginine deiminases (PADs) catalyze the conversion of peptidylarginine to peptidylcitrulline. PAD2 and PAD4 are expressed in immune cells, but it is not known if either of these PADs is required for the increased citrullination seen in inflammatory arthritis. Neutrophil extracellular traps (NETs) may be a source of citrullinated proteins in inflammation. PAD4 is critical for NETosis and inflammatory arthritis, but the role of PAD2 is unknown. Here we use mice with TNFα-induced arthritis, an inflammatory, destructive arthritis similar to rheumatoid arthritis, to determine if PAD2 and/or PAD4 are required for joint citrullination and if PAD2 is required for NETosis and inflammatory arthritis.

Methods: Joint lysates from wild type, TNFα overexpressing (TNF^+), $TNF^+PAD4^{+/+}$, $TNF^+PAD4^{-/-}$, $TNF^+PAD2^{+/+}$, and $TNF^+PAD2^{-/-}$ mice were assessed for citrullination by western blot using an anti-peptidylcitrulline antibody. PAD2 levels were determined by qPCR in $PAD4^{+/+}$ and $PAD4^{-/-}$ spleens and by western blot in $TNF^+PAD4^{+/+}$ and $TNF^+PAD4^{-/-}$ joints. NETs formed by LPS-stimulated $PAD2^{+/+}$ and $PAD2^{-/-}$ neutrophils were detected by immunofluorescent staining with DAPI and anti-citrullinated histone H4 and quantified. Killing of Candida by $PAD2^{+/+}$ and $PAD2^{-/-}$ neutrophils was determined by a modified XTT assay. In $TNF^+PAD2^{+/+}$ and $TNF^+PAD2^{-/-}$ mice, bone marrow plasma cells were identified by flow cytometry, serum IgG detected by ELISA, and arthritis assessed by blinded clinical and pathological scoring.

Results: TNF^+ ankles had increased citrullination compared to wild type. $TNF^+PAD2^{-/-}$ ankles had less citrullination than $TNF^+PAD2^{+/+}$ ankles, but citrullination was not reduced in $TNF^+PAD4^{-/-}$ compared to $TNF^+PAD4^{+/+}$ ankles. There was no compensatory increase in PAD2 in PAD4 deficient spleens or arthritic ankles. NETosis and killing of Candida were not reduced in $PAD2^{-/-}$ compared to $PAD2^{+/+}$ neutrophils. Plasma cells, IgG, and arthritis were reduced in $TNF^+PAD2^{-/-}$ compared to $TNF^+PAD2^{+/+}$ mice.

Conclusion: PAD2 contributes to TNFα-induced arthritis, plasma cell numbers, and IgG levels. Also, PAD2 is required for TNFα-induced joint citrullination, but not NETosis. In contrast, PAD4, which has been shown to be critical for NETosis, does not play a major role in TNFα-induced joint citrullination. Thus, NETs may not be the main source of citrullinated protein in arthritic mice.

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Abstract Number: 3149

"Early Use of Subcutaneous MTX Monotherapy Vs. MTX Oral or Combination Therapy Significantly Delays Time to Initiating Biologics in Early RA

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Canada, [3]McGill University, Montreal, ON, Canada, [4]Rheumatology Division, CHUS - Sherbrooke University, Sherbrooke, QC, Canada, [5]Institute de Rheumatologie, Montreal, QC, Canada, [6]University of Manitoba, Winnipeg, MB, Canada, [7]The Arthritis Program, Southlake Regional Health Centre, Newmarket, ON, Canada, [8]Division of Rheumatology, University of Calgary, Calgary, AB, Canada, [9]Mt. Sinai Hospital, University of Toronto, Toronto, ON, Canada, [10]Divison of Rheumatology, Hospital for Special Surgery, New York, NY, [11]University of Western Ontario, St Joseph's Health Care, London, ON, Canada, [12]Department of Medicine, Division of ClinEpi, Rheumatology, Respirology, McGill University, Montreal, QC, Canada
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Background/Purpose:

Optimal treatment for moderate-severe early rheumatoid arthritis involves using a methotrexate-based, treat-to-target strategy aiming for remission. Achieving remission without using biologics may be preferable due to their high cost and potential risk of infection. However, it is still unknown which initial treatment strategy is preferable. Our objective was to compare effects of initial treatment with MTX oral monotherapy, MTX subcutaneous (sc) monotherapy, and MTX combination therapy on time to first use of biologic DMARDs in a large national early RA cohort.

Methods:

Data were obtained from a multi-center prospective cohort study of patients with early RA. The present analysis included participants who met 1987 or 2010 ACR criteria for RA, with <12 months symptom duration, moderate or high disease activity based on the DAS28 at baseline and treated with MTX. Patients treated with a biologic at baseline were excluded. Patients were followed until they started a biologic or they were censored due to loss to follow up or the end of the 3-year study period. Cox proportional hazards survival analysis was used to estimate effects of oral MTX monotherapy, sc MTX monotherapy, and MTX combination therapy adjusting for age, gender, education level, symptom duration, comorbidities, baseline erosions, baseline DAS28, and corticosteroid use. Logistic regression analysis was used to determine predictors of ever vs. never biologic use.

Results: 1189 patients were included and 212 first events of biologic use. At baseline, 865 (71%) were female with mean (sd) age of 54 (15) years, symptom duration 6 (3) months, and DAS28 of 5.45 (1.2). Oral MTX monotherapy was used as initial treatment in 230 (20%), sc MTX monotherapy in 226 (20%), and MTX combination therapy in 664 (60%). In fully adjusted Cox regression models, patients treated with subcutaneous MTX monotherapy had a significantly delayed time to first biologic use (HR = 0.53, p = 0.02). There was no difference between MTX combination therapy and oral MTX monotherapy (HR = 0.95). In logistic regression models of ever vs. never biologic use, there were no significant differences between treatment strategies. Predictors of biologic use included younger age, use of corticosteroids, longer symptom duration, and higher baseline DAS28.

Conclusion:

Treatment with sc MTX monotherapy was associated with a delayed time to biologics. This may be due to increased treatment efficacy compared to oral MTX. Combination DMARD therapy was not associated with longer time to biologic initiation, potentially due to provincial regulations requiring a trial of combination DMARD therapy before initiating biologics. This study suggests that early use of sc MTX can potentially delay the need for more expensive biologic therapies.

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5,Amgen, 2,Bristol-Myers Squibb, 2,Pfizer Inc, 2,Roche Pharmaceuticals, 2,UCB, 2; **S. J. Bartlett**, None.

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Abstract Number: 3150

The Initial Dose of Methotrexate per Weight Is Determinant of Disease Activity and Early DAS28 Remission in DMARD-Naive Early Rheumatoid Arthritis Patients Receiving Usual Care

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Background/Purpose: Methotrexate (MTX) is considered as the anchor disease modifying antirheumatic drug (DMARD) in treatment of rheumatoid arthritis (RA). However, there is no advice concerning individualized dosing. We aimed to study whether the initial dose of MTX/weight is predictive for disease activity and remission over the first 6 months in early RA patients in usual care.

Methods: Patients with DMARD-naive newly diagnosed inflammatory arthritis were recruited in 5 Finnish sites for a longitudinal follow-up (FIN-ERA) study. Patients fulfilling ACR/EULAR classification criteria for RA and positive for rheumatoid factor (RF) were divided by tertiles of MTX dose/weight. The linearity for baseline characteristics was tested and a multivariate regression analysis was adjusted for age, sex and positivity for anti citrullinated antibodies (AntiCCP). Repeated measures were analyzed using mixed models approach with appropriate distribution and link function.

Results: Out of 611 recruited patients, 336 patients who started with MTX at baseline (65% F, mean age[SD] at diagnosis 57[15] yrs) were analyzed. The baseline characteristics are depicted in Table 1. Males had lower mean(SD) dose/kg of MTX than females (0.24[0.09] vs 0.22[0.07] mg/kg, P=0.007). Both heavier males and females received lower dose/weight of MTX. A concomitant therapy with hydroxychloroquine (HCQ), and combination with sulphasalazine and HCQ were more common in patients receiving higher dose of MTX/weight. Patients with higher dose/weight of MTX met lower disease activity early and higher DAS28-3 remission rates at 6 months than patients with lower dose after adjusting by confounding variables (Figure 1).

Conclusion: The initial dose of methotrexate per weight is determinant of disease activity and early remission of DMARD-naive early, RF positive RA patients in usual care.

Tertile of MTX dose/weight (mg/kg)	I <0.19 N=112	II 0.19-0.26 N=112	III >0.27 N=112	*p*-value
Number of female, n (%)	70 (63)	63 (56)	84 (75)	0.051
Age (yrs), mean (SD)	58 (15)	57 (14)	55 (17)	0.20
Weigth (kg), mean (SD)				
Females	82 (20)	78 (13)	63 (9)	<0.001
Males	88 (15)	82 (13)	73 (9)	<0.001
DAS28-3, mean (SD)	4.03 (1.26)	4.10 (1.28)	4.01 (1.37)	0.87
AntiCCP, n (%)	102 (92)	98 (89)	97 (87)	0.30
Duration of symptoms (mo), median (IQR)	5 (3, 12)	6 (3, 10)	6 (3, 12)	0.79
SJC, mean (SD)	6.2 (4.8)	6.4 (5.3)	7.4 (6.4)	0.13
TJC, mean (SD)	7.2 (5.8)	6.8 (6.1)	8.6 (7.0)	0.11
ESR (mm/h), mean (SD)	27 (22)	29 (24)	25 (22)	0.47
CRP (mg/l), mean (SD)	19 (30)	18 (26)	15 (20)	0.24
PatGlobal, mean (SD)	45 (30)	44 (30)	50 (27)	0.22
Pain, mean (SD)	49 (28)	47 (26)	49 (25)	0.97
MDGlobal, mean (SD)	38 (19)	39 (19)	38 (19)	0.96
HAQ, mean (SD)	1.05 (0.69)	0.91 (0.58)	1.00 (0.65)	0.58
Other medication, n (%)				
DMARD				
SSZ[a]	40 (36)	51 (46)	44 (39)	0.59
HCQ[b]	80 (71)	94 (84)	101 (90)	<0.001
Prednisolone	95 (85)	96 (86)	92 (82)	0.58
Triple Combination*	82 (73)	85 (85)	103 (92)	<0.001
Change of treatment strategy, n (%)	12 (11)	21 (19)	22 (20)	0.081

Table 1. Baseline characteristics of 336 DMARD-naive early RA patients divided by tertiles of weight-based dose (mg/kg) of methotrexate. The change of treatment strategy was defined as a change from DMARD monotherapy to a combination therapy or vice versa, start of a biologic DMARD, start/stop of prednisolone, or change of MTX to leflunomide (*P* for linearity).
[a]Sulphasalazine [b]Hydroxychloroquine *MTX+SSZ+HCQ

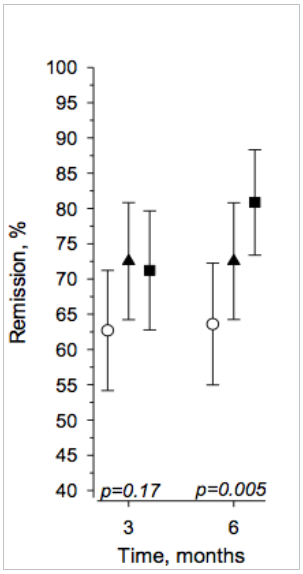

Figure 1. Proportions of DAS28-3 remissions during the first 6 months of DMARD therapy in DMARD-naive early RA patients divided by 3 tertiles of MTX dose/weight. White ball: MTX<0.19mg/kg, Black pyramid: MTX 0.19-0.26 mg/kg, Black square: MTX>0.27mg/kg (*P* for linearity).

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Abstract Number: 3151

The Diagnostic and Predictive Value of Anti-Acetylated Peptide Antibodies in RA Patients Starting Methotrexate Treatment

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Background/Purpose: Anti-acetylated-peptide antibodies (AAPA) have recently been described in rheumatoid arthritis (RA)

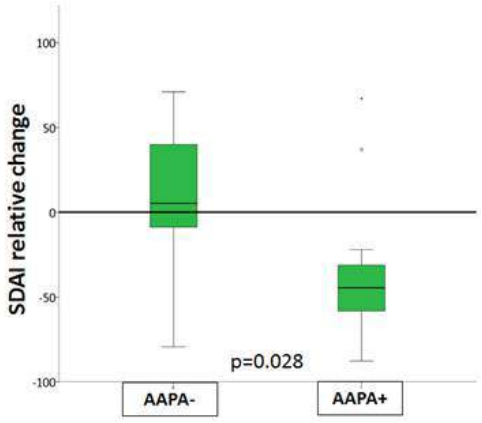
patients and may be used as a further diagnostic marker in patients with early arthritis. In this study we aimed to determine the prevalence of AAPA in a cohort of RA patients starting their first conventional synthetic DMARD treatment (csDMARD) and additionally evaluated the usefulness of AAPA as potential predictors of clinical response to methotrexate (MTX) therapy.

Methods: We measured IgG and IgA AAPA by ELISA using two acetylated peptides derived from vimentin. We tested by regression, parametric and non-parametric analyses of disease activity measures if AAPA show potency for predicting response to MTX.

Results: IgG and/or IgA AAPA were detected in 74.5% of the 110 RA patients who stated MTX treatment: 49% were positive for either IgA or IgG antibodies and 25.5% were IgA/IgG double positive. In the AAPA positive patients, 73.6% were positive for IgG AAPA while 26.4% showed IgA antibodies. Importantly, of the 36.4% of patients negative for both RF and ACPA (double negative), 55% were positive for IgG and/or IgA AAPA, and the remaining patients (i.e. 16% of the total cohort) were completely seronegative (triple-negative), see **Table**. When comparing triple negative patients with the AAPA positive double-negative ones, no significant difference in baseline characteristics was found but a trend that patients with more seroreactivities showed higher composite disease activity scores. Analyzing the clinical response to MTX, IgG-AAPA positive double-negative patients showed a significantly greater relative SDAI change after 6 months compared to triple-negative patients (p=0.028; median (IQR): -44.6% (-58.5 - -28.90) vs. 5.26% (-23.9 - 55.5%) (**Figure**). In addition, there was a significantly greater relative change in CRP (p=0.035) and erythrocyte sedimentation rate (p=0.003) in AAPA positive double-negative patients . **Table:** Crosstable of status of RF, ACPA and antiacetylated peptide antibodies

	Anti-acetylated peptide antibodies			
	Negative	**IgA or IgG positive**	**IgA and IgG positive**	Total
Negative	16.4%	16.4%	3.6%	36.4%
RF	3.6%	3.6%	2.7%	10%
ACPA	.9%	1.8%	0.9%	3.6%
RF+ACPA	4.5%	27.3%	18.2%	50%
Total	25.5	49.1	25.4	100%

Figure: Boxplots of relative changes of simplified disease activity score (SDAI) in RF and ACPA negative patients, shown for anti-acetylated (AAPA) positive and negative patients



Conclusion: AAPA commonly occur in RA patients . Measuring AAPA in addition to RF and ACPA reduced the prevalence of seronegative patients by more than 50 %. These AAPA positive but RF and ACPA negative patients responded significantly better to MTX. Therefore, AAPA positivity in RF and ACPA negative patients identifies a subgroup of patients with a more favorable response to MTX.

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Abstract Number: 3152

Rheumatoid Arthritis (RA): Premature Use of Biologics Accelerating in United

States (US)

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Background/Purpose: The treatment of RA has changed dramatically in the past several decades with the advent of a large number of new biologic agents as well as trials that have shown the benefits of optimizing the use of conventional disease modifying agents (DMARDs) alone or in combinations. It is not clear how the large number of clinical trials and treatment recommendations related to these issues have influenced RA management. This analysis considers two aspects of DMARD choice and delivery for RA: 1) use of biologic agents as initial DMARD treatment; and 2) use of subcutaneously (SC) administered methotrexate (MTX) in patients who cannot be managed with oral drug. To evaluate trends, these questions were addressed in two patient cohorts, one that started treatment in 2009 and a second that initiated therapy in 2012.

Methods: The analysis used Symphony Health Solutions' anonymized patient-level claims data which captures ~274 million US patients and 92% of all prescription drugs dispensed in the United States. The analysis included RA patients identified by ICD-9 codes 714.0 and 714.30 who initiated treatment with oral MTX or a biologic in 2009 or 2012 and were then followed through to 2014. Treatment in the year prior to these treatments was also evaluated. This analysis focused on patients who had a biologic agent as their initial DMARD in 2009 or 2012 and those in whom SC MTX was employed after initiation of therapy with oral drug.

Results: The study included 48,910 patients who started oral MTX or biologic treatment in 2009 and 107,536 who initiated such treatment in 2012. In the 2009 cohort, 13,270 patients (27.1%) initiated treatment with a biologic vs 38,209 (35.6%) in the 2012 cohort ($p<0.0001$). This difference did not appear to result from differences between groups in baseline demographic or clinical characteristics (Table). A higher percentage of patients in the 2012 cohort received a non-MTX DMARD in the year prior to biologic initiation vs the 2009 cohort (25.4% vs 15.3%, $p<0.0001$), but even when these patients are excluded from the analysis, the higher initial use of a biologic in the 2012 remained significant ($p<0.0001$). There was also significantly increased employment of SC MTX in the 2012 cohort. 35,640 patients in the 2009 cohort initiated oral MTX and 20,041 (56.2%) switched away from this treatment over 5 years. Of these, 2,513 (12.5%) were switched to SC MTX. 69,327 patients in the 2012 cohort started oral MTX and 18,989 (27.4%) switched away from this treatment over 2 years. Of these, 3,976 (20.9%) switched to SC MTX ($p<0.0001$ vs the 2009 cohort).

Conclusion: This analysis indicated three significant trends in the treatment of RA in the US: 1) increasing use of non-MTX DMARDs prior to the initiation of a biologic; 2) increasing use of a biologic without prior administration of any conventional DMARD; and 3) increasing, but not optimal, employment of SC MTX after use of oral MTX.

Characteristic	2009 Cohort		2012 Cohort	
	Initiated with Biologic (n=13,270)	Initiated with Oral MTX (n=35,640)	Initiated with Biologic (n=38,209)	Initiated with Oral MTX (n=69,327)
Age, years (mean [median])	59 (60)	62 (62)	57 (59)	57 (59)
Sex, %				
Female	82	78	85	83
Race/Ethnicity, %				
African American	8	10	8	8
Caucasian	63	58	62	58
Hispanic	7	7	7	7
Missing/Uncoded	22	24	23	21
Comorbidities, %				
Ischemic cardiovascular disease	18	16	12	12
Diabetes	29	26	25	24
Gastrointestinal disease	53	47	41	39
Received non-MTX DMARD (leflumomide, sulfasalazine, hydrochloroquine) prior to initiation of a biologic, %	15.3	-	25.4	-

Disclosure: **J. R. O'Dell**, Medac Pharma, 5,Antares, 5,Eli Lilly and Company, 5,Abbvie, 5,Bristol-Myers Squibb, 5; **S. B. Cohen**, Medac Pharma, 5; **J. C. Thorne**, Abbvie, 5,Amgen, 5,AstraZeneca, 5,Bristol-Myers Squibb, 5,Centocor, Inc., 5,Celgene, 5,Genzyme Corporation, 5,Hospira, 5,Pfizer Inc, 5,Roche Pharmaceuticals, 5,Genzyme Corporation, 8,Medac Pharma, 8,Antares, 8,Abbvie, 2,Amgen, 2,AstraZeneca, 2,Celgene, 2,Eli Lilly and Company, 2,Novartis Pharmaceutical Corporation, 2,Pfizer Inc, 2; **T. R. Mikuls**, Roche Pharmaceuticals, 2,Pfizer Inc, 5.

Abstract Number: 3153

Automated Cell Phone Monitoring of Disease Activity and Medication Adherence in Early Rheumatoid Arthritis

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Background/Purpose: Remission targeted treatment of early RA requires frequent monitoring. However, in clinical practice monitoring frequency is not always optimal due to factors like limited resources. Therefore, to ensure successful initiation of anti-rheumatic therapy and adherence to treatment during the crucial 6 months after the diagnosis, we have developed an automated text

message (SMS) based monitoring system for early RA called SandRA. Here we present the results of a randomized study comparing SMS-based follow-up to routine care.

Methods: We randomized 166 patients with early, untreated RA fulfilling the EULAR 2010 classification criteria to intensive SandRA-based follow-up (visits at 0, 3, and 6 months and 13 SMSs at 1–2 week intervals) and to routine follow-up (visits at 0, 3, and 6 months) in 2014–2015. The SandRA software sent questions about medication use, adverse effects, and disease activity (patient global assessment [scale 0–10]). Treatment was administered at the *physician's discretion.* The SandRA follow-up aimed to improve medication adherence and to identify early the patients responding poorly to treatment. If responses suggested medication problems or insufficient reduction in disease activity, the system alarmed and the patient was contacted. The primary outcome was a strict Boolean remission at 6 months, defined as no tender or swollen joints (46 joint count), and normal CRP.

Results: Follow-up data at 6 months were available for 162 patients. The randomization groups were nearly identical at baseline (Table 1). All patients started intensive therapy; 96% started MTX, and 89% started a combination of 2–3 conventional DMARDs. At 6 months, 62% of patients in the intervention, and 53% in the control group were in remission (p=0.34). DAS28 levels decreased similarly, 2.18 in the intervention group, and 2.21 in the control group (p=0.18). Alarms from SandRA increased the number of nurses telephone contacts in the intervention group (p=0.027 for scheduled calls; p<0.001 for non-scheduled calls). No differences were observed for other visit types. Of the patients in the intervention group, 94% found the monitoring messages easy to answer, >80% felt secure and were satisfied with their treatment, and 100% would recommend SandRA monitoring for other RA patients.

Conclusion: The vast majority of RA patients were satisfied with the SMS-based monitoring system. The remission rate was higher in the SandRA group than in the control group but the difference did not reach statistical significance. Overall, remission rates were remarkably high in both groups, possibly due to successful efforts to optimize the rheumatology service (1). Despite our study failing the primary outcome, SMS-based monitoring may be beneficial in less resourced settings, and may facilitate medication adherence. Reference: Vare P, et al. SAGE Open Medicine 2016; 6: 1–7.

Table 1. Baseline characteristics of the patients.

	Control N=80	Intervention N=82
Demographics		
Female/male, n	56/24	58/24
Age years, mean (SD)	59 (14)	54 (13) [1]
Positive serology (RF or ACPA), n (%)	69 (86)	70 (85)
EULAR score, median (range)	7 (6–10)	7 (6–10)
Education years, mean (SD)	11.3 (3.5)	12.6 (3.6) [2]
Body Mass Index, mean (SD)	27.5 (5.1)	26.7 (5.2)
Cohabiting, n (%)	56 (70)	66 (80)
Measures of disease activity, mean (SD)		
DAS28	4.4 (1.3)	4.1 (3.8)
Erythrocyte sedimentation rate (mm/h)	28 (18)	24 (22)
Serum C-reactive protein (mg/l)	20 (22)	16 (22)
Number of swollen joints	6.5 (5.4)	6.4 (5.1)
Number of tender joints	9.0 (7.4)	7.7 (7.0)
Patient global assessment (VAS)	46 (28)	45 (28)
Physician global assessment (VAS)	41 (19)	37 (20)
Physical function (HAQ)	1.00 (0.7)	0.91 (0.6)
Radiography		
Erosions in hand/foot radiographs, n (%)	14 (18)	17 (21)

[1]p=0.021 [2]p=0.026

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Abstract Number: 3154

Assessing Bone Erosions in the Metatarsophalangeal Joints of Patients with Early Rheumatoid Arthritis: a Comparison Between MRI and Ultrasound

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SESSION INFORMATION

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Background/Purpose: This cross-sectional study aimed to assess the agreement between Magnetic Resonance Imaging (MRI) and ultrasound (US) findings of bone erosions in the metatarsalphalangeal (MTP) joints of patients with early rheumatoid arthritis (RA).

Methods: Men and women with early RA (DMARD naïve) according to ACR criteria were recruited. Each patient underwent an MRI scan (1.0 Tesla peripheral MRI) and an US scan of MTPs 2-5 of the most symptomatic foot. MRI scans were scored by a musculoskeletal trained radiologist using OMERACT RAMRIS criteria for erosions (0-10). Using OMERACT criteria, US images were assessed for erosions (present/absent) on each joint by an experienced rheumatologist. To assess agreement using kappa statistics, MRI erosions which scored 0 were considered to have no erosions while those ≥1 were considered to have an erosion.

Results: The study included 39 patients (n=33 women), mean (standard deviation(sd)) age = 51.6 (10.3) yrs. MRI detected an erosion with a score ≥1 on 30 MTP2 joints, 28 MTP3 joints, 25 MTP4 joints and 15 MTP5 joints. US detected an erosion on 2 MTP2 joints, 1 MTP3 joints, 0 MTP4 joints and 6 MTP5 joints. The proportion of erosions detected by MRI that were also detected by US in MTPs 2, 3, 4, and 5 were 6.5%, 3.5%, 0% and 37.5%, respectively. In MTPs 2, 3 and 4, there were no erosions detected by US that were not also detected by MRI. However, in MTP5, there were 3 erosions detected by US that were not detected by MRI. Kappa statistics of agreement are presented in Table 1. Table 1: Agreement in Erosions detected by MRI and Ultrasound

Joint	kappa	95% CI	Prevalence Index	Bias Index
MTP2	0.0301	-0.0150, 0.0752	-0.1750	-0.7250
MTP3	0.0193	-0.0196, 0.0581	-0.2500	-0.7000
MTP4	0.0272	-0.0269, 0.0814	-0.3250	-0.6250
MTP5	**0.2620***	-0.0284, 0.5524	-0.3590	-0.1759

*denotes kappa is significant ($p<0.05$)

Conclusion: There was a high prevalence of bone erosions in MTPs 2-5 detected by MRI in this cohort of early RA patients. The proportion of erosions detected on MRI that were detected by US was generally very low. MRI appeared to show a greater sensitivity, detecting many more erosions than MRI which may help to explain the lack of agreement between modalities. Lack of agreement may also be explained by the physical size of the lesions that can be detected by MRI versus US due to resolution or because MRI shows more signal variation by tissue composition than US. The higher agreement for the 5th MTP may be because the US probe can almost encircle the bone allowing better visualization of the bone. In general, however, using MRI as the gold standard, the agreement between these two imaging modalities is poor, suggesting that US detected erosions likely underestimate the true prevalence of erosions in MTPs 2-5.

Disclosure: K. A. Beattie, None; **S. Scheffler**, None; **G. Ioannidis**, None; **E. Schreyer**, QMetrics Technologies, 4; **S. Totterman**, None; **M. Larche**, Abbvie, 2,Canadian Rheumatology Ultrasound Society, 6,Abbvie, 8.

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Abstract Number: 3155

Zygapophyseal Joint Fusion in Ankylosing Spondylitis Assessed Using Computed Tomography: Associations with Syndesmophytes and Spinal Motion

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Background/Purpose: Both zygapophyseal joint (ZJ) fusion and syndesmophytes contribute to structural spine damage in Ankylosing Spondylitis (AS). However, because ZJs are difficult to visualize on radiographs, little is known about the prevalence of ZJ fusion and its relationship to other features of spinal damage in AS. In particular it is not known if ZJ fusion occurs before syndesmophytes and which feature contributes most to spinal rigidity. We used computed tomography (CT) to visualize the ZJ and investigate those questions.

Methods: 50 patients (84% men) underwent thoracolumbar CT scans (Table 1). Six vertebral levels were examined (T10-T11 to L3-L4). Anonymized scans were read for the presence of ZJ fusion at each level after digitally masking the vertebral bodies to blind readers to the presence of syndesmophytes. Using a validated semi-automated computer algorithm, we quantitated syndesmophytes at the same vertebral levels. We measured syndesmophyte height in 72 angular sectors of 5 degrees around the vertebral rim. We then summed the results of the 72 angular sectors to yield the circumferential height. We used Pearson correlations to evaluate the association between ZJ fusion and the lumbar range of motion and multiple regression analysis to evaluate the relative contributions of ZJ fusion and syndesmophytes to spinal motion.

Results: Agreement on the presence of ZJ fusion between the two physicians' readings was good (kappa=0.84). 56% of patients had ZJ fusion at 1 or more vertebral levels. The median number of vertebral levels with ZJ fusion was 1 (range 0 -6). The 3 most superior vertebral levels were more often fused (39% of patients) than the lower 3 (15% of patients). Fusion was most often bilateral. Syndesmophytes were often present in vertebral levels without ZJ fusion. In all levels with syndesmophytes, only 35% had ZJ fusion. ZJ fusion was present in only 7% of vertebral levels without syndesmophytes. Bridging was also often present in levels without ZJ fusion. In levels with an extent of bridging < 50 degrees, only 35% had ZJ fusion. These results suggest that ZJ fusion most often follows the development of syndesmophytes. The number of levels with ZJ fusion correlated with the Schober test ($r=-0.58$, $p<0.0001$) and lateral thoracolumbar flexion ($r=-0.58$, $p<0.0001$). Syndesmophytes and ZJ fusion were equally associated with the Schober test (Table 2). Syndesmophytes were more strongly associated with lateral thoracolumbar movement.

Conclusion: ZJ fusion is common in AS, particularly in the T10-T11to T12-L1 levels. Although syndesmophytes seem to occur first, ZJ fusion is also important and contributes to spinal rigidity.

Table 1	Median	Min	Max
Age	48.0	22.0	69.0
Disease duration	17.1	1.29	53.1
BASFI	21.2	0	88.9
Schober (cm)	3.35	0.50	5.60
Lateral flexion (cm)	12.0	3.0	25.0

Table 2	Standardized beta (p value)			
	ZJ Fusion vs Circumferential height		ZJ Fusion vs Extent of bridging	
	ZJ Fusion	Circumferential height	ZJ Fusion	Extent of bridging
Schober	-0.29 (0.08)	-0.34 (0.04)	-0.30 (0.06)	-0.34 (0.04)
Lateral flexion	-0.28 (0.07)	-0.43 (0.006)	-0.32 (0.04)	-0.39 (0.01)

Disclosure: **S. Tan**, None; **J. Yao**, None; **L. Yao**, None; **J. Flynn**, None; **M. Ward**, None.

Abstract Number: 3156

Adding MRI of the Spine to the ASAS Classification Criteria for Axial Spondyloarthritis, Redundant or Beneficial? Results from the Spondyloarthritis Caught Early (SPACE)-Cohort

Zineb Ez-Zaitouni[1], Pauline Bakker[1], Miranda van Lunteren[1], Rosaline van den Berg[2], M. Reijnierse[3], Karen M Fagerli[4], Roberta Ramonda[5], Robert Landewé[6], Lennart T.H. Jacobsson[7], Floris van Gaalen[1] and Désirée van der Heijde[1], [1]Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Rheumatology, Leiden University Medical Center, Leiden, Netherlands, [3]Radiology, Leiden University Medical Center, Leiden, Netherlands, [4]Dept. of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway, [5]Rheumatology Unit, Department of Medicine DIMED, University of Padova, Padova, Italy, [6]Clinical Immunology and Rheumatology, Amsterdam Rheumatology Center, Amsterdam, Netherlands, [7]Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at Gothenburg University, Gothenburg, Sweden

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Background/Purpose: The ASAS definition of a positive MRI is solely based on inflammation in the sacroiliac joints (SI), although spinal inflammatory lesions on MRI suggestive of axial Spondyloarthritis (axSpA) may also occur. It is not well established yet how often inflammation in the spine is present in absence of inflammation in the SI and consequently if it is useful to change the definition of a positive MRI to include inflammation in the spine. The aim is to analyze the prevalence of spinal inflammation on MRI in patients with chronic back pain at baseline, and to evaluate the yield of adding MRI-spine as imaging criterion in the ASAS classification criteria for axSpA.

Methods: The SPACE-cohort includes patients with chronic back pain (≥3 months, ≤2 years, onset <45 years) in six participating Rheumatology centers. All available baseline radiographs (X-SI), MRI of SI (MRI-SI) and spine (MRI-spine) were independently scored by 3 well-calibrated readers for each method. MRI-SI was scored according to the ASAS definition. Bone marrow edema suggestive of axSpA was assessed in the entire spine and only counted if visible on ≥2 consecutive slices. For the definition of a positive MRI-spine two cut-off values for inflammatory lesions were used: **≥3 inflammatory lesions** (ASAS consensus definition) and **≥5 inflammatory lesions** (defined as the optimal cut-off value). All modalities were considered positive if 2/3 readers agreed.

Results: All patients with X-SI, MRI-spine, and MRI-SI available at baseline (n=487) were included in the analysis. Of the 487 patients, 73 (15.0%) patients had a positive MRI-SI, of which 23/73 (31.5%) patients had a positive MRI-spine (≥3 inflammatory lesions) and 17/73 (11.4%) patients had a positive MRI-spine defined by ≥5 inflammatory lesions. In total, 50/414 (12.1%) and 18/414 (4.3%) patients with negative MRI-SI had a positive MRI-spine according to ≥3 and ≥5 inflammatory lesions, respectively.

Addition of MRI-spine to the classification criteria by ≥5 inflammatory lesions would lead to classification of 16 additional patients via the imaging arm, with 8 patients already fulfilling the clinical arm. The newly classified patients (n=8) had a mean number (SD) of SpA-features of 1.5 (1.1) of whom 3/8 (37.5%) were HLA-B27 positive. Furthermore, one patient had inflammatory bowel disease and two patients were positive for peripheral arthritis. Most reported SpA-features were inflammatory back pain, good response to NSAIDs, and positive family history for SpA.

Conclusion: In this cohort, a positive MRI-spine in the absence of sacroiliitis on MRI was rarely seen. Addition of MRI-spine as an imaging criterion to the ASAS axSpA criteria had a low yield in number of classifications, and included mostly patients with a low probability of having axSpA. Therefore, performing MRI of the spine is of little value in the classification of patients with short duration CBP and suspicion of axSpA.

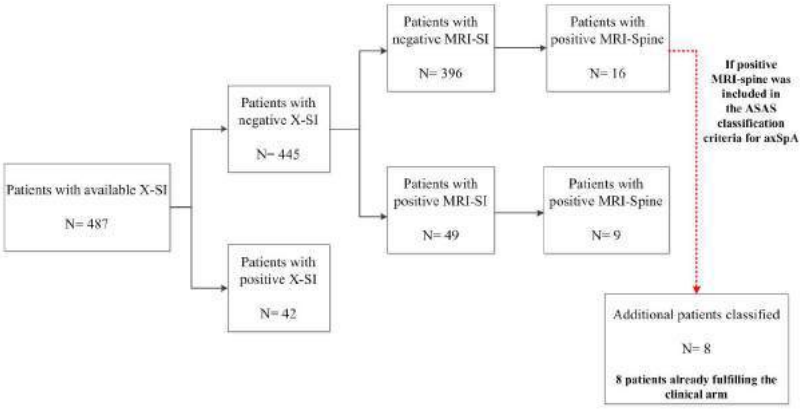

Figure 1 ASAS classification of chronic back pain patients with negative MRI-SI and positive MRI-spine defined by ≥5 inflammatory lesions, and the effect of adding positive MRI-spine as an imaging criterion to the ASAS axSpA criteria on classification of patients in the SPACE-cohort.

Disclosure: Z. Ez-Zaitouni, None; **P. Bakker**, None; **M. van Lunteren**, None; **R. van den Berg**, None; **M. Reijnierse**, None; **K. M. Fagerli**, None; **R. Ramonda**, None; **R. Landewé**, None; **L. T. H. Jacobsson**, None; **F. van Gaalen**, None; **D. van der Heijde**, None.

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Abstract Number: 3157

The Association Between Sonographic Enthesitis and Radiographic Damage in Psoriatic Arthritis

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Background/Purpose: Enthesitis is a common clinical finding and a key pathogenic feature in psoriatic arthritis (PsA). Ultrasound is emerging as a preferred method to assess enthesitis. Little is known about the relation between the presence of enthesitis and the severity of joint damage in patients with PsA. Our aim was to examine the association between sonographic enthesitis and the severity of radiographic features of damage in the peripheral and axial joints.

Methods: A cross-sectional analysis was conducted in patients from a large PsA cohort. The MAdrid Sonography Enthesitis Index (MASEI) scoring system was used to quantify the extent of sonographic entheseal abnormalities in 12 entheseal sites adjacent to large joints. Total MASEI was further categorized into: bone scores (enthesophytes, erosions) and soft tissue scores (structural entheseal changes, vascularization, bursitis). Radiographic joint damage in the peripheral joints and spine was assessed independently of the ultrasound results using the modified Steinbrocker score, Modified New York Criteria for sacroiliitis and the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS). Additionally, the presence of ankylosis, arthritis mutilans and periostitis in the hands or feet was determined. Linear and logistic regression models were used to assess the association between MASEI score and the radiographic features of joint damage after controlling for age, sex, body mass index, PsA duration and the use of DMARDs and biologic medications.

Results: Two hundred and twenty two patients were included. 58% were males, with mean (s.d.) age of 55.9 (12.9) years and PsA duration of 16.7 (12.4) years. The mean MASEI score was 15.6 (12.6). The mean modified Steinbrocker score was 18.1 (32.3), *mSASSS* was 1.7 (7.3) and 37% had sacroiliitis. Multivariate regression analyses found an association between higher scores of MASEI scores and peripheral joint damage: modified Steinbrocker score (β 9.26, p<0.0001), joint ankylosis (Odds Ratio (OR) 2.09, p=0.0001) and arthritis mutilans (OR 1.73, p=0.005). The association between MASEI scores and periostitis was of borderline statistical significance (OR 1.29, p=0.06). Similarly, an association was found in multivariate analyses between higher MASEI scores and axial damage as measured by mSASSS (β 1.55, p=<0.0001) and sacroiliitis (OR 1.36, p=0.02). Sub-analysis showed that the MASEI bone score were more strongly associated with radiographic damage outcomes than the MASEI soft tissue score.

Conclusion: The severity of sonographic enthesitis is a marker of radiographic peripheral and axial joint damage in PsA. The association was found with both destructive and bone formation lesions. These findings highlight the potential role of enthesitis in the pathogenesis of articular damage in PsA.

Disclosure: A. Polachek, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **R. J. Cook**, None; **V. Chandran**, None; **L. Eder**, None.

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Abstract Number: 3158

What Predicts Absence of Spinal Damage in Patients with Spondyloarthritis after Prolonged Follow up?

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Background/Purpose: After 20 years of follow up the majority of patients with aspondyloarthritis (SpA) have developed new bone in the spine although disease may remain isolated in the sacroiliac joints (SIJ) without any new bone in the spine. Assessment of these patients may provide new insights into the factors that influence disease progression. A new hypothesis has proposed that MRI can identify a “progressive phenotype” in early SpA characterized by the appearance of fat metaplasia in the SIJ. Fat metaplasia can occur both in subchondral bone and at the site of erosion after resolution of inflammation, this being termed backfill. We aimed to determine which clinical and MRI lesions in the SIJ are associated with absence of spinal damage after prolonged duration of symptoms.

Methods: In the FORCAST prospective cohort, AS patients (n=431) attending community and academic practices were assessed

for clinical and laboratory outcomes every 6 months, radiography every 2 years, and MRI annually. MR scans of the SIJ were assessed by Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ and Sacroiliac Structural Score (SSS) methods for inflammation and structural features, respectively, by 2 readers. Absence of spinal damage was pre-specified as no syndesmophytes or ankylosis on cervical and lumbar spine radiographs after ≥10 years from onset of symptoms and for the entire duration of prospective follow up. Patients with and without spinal damage were matched for age and symptom duration and compared by t-test, Mann-Whitney, and Fisher's exact tests. We used univariate and multivariate conditional logistic regression to determine which demographic, clinical, and imaging variables were associated with absence of spinal damage.

Results: Mean (SD) duration of symptoms and prospective follow up was 18.0(7.0) and 2.3 (0.49) years in cases with no damage (n=42) and 17.5(8.2) and 2.6 (1.4) years in those with damage (n=81). The group with no damage had fewer males (p=0.004), lower CRP (p=0.02), and lower MRI SIJ scores for fat (p=0.03) and ankylosis (p=0.003) while score for SIJ erosion was significantly higher (p=0.02). Definite SIJ ankylosis (SSS score ≥2 by both readers) was evident in 20.7% of cases in the no damage group versus 53.3% of those with damage (p=0.007). Univariate regression indicated that no damage was associated with female sex (p=0.002), lower ASDAS (p=0.048), and lower SSS values for fat (p=0.032), backfill (p=0.014), and ankylosis (p=0.001). Smoking and B27 were not significant. A multivariate logistic regression model that included gender, ASDAS, and MRI SIJ features indicated that lower values for SSS backfill and ankylosis were independently associated with no damage (OR [95%CI]= 0.83 [0.69-0.99] and 0.89 [0.82-0.96], respectively). When all definite MRI features (SSS score ≥2 by both readers) were included in the model, definite SIJ ankylosis was significantly less likely in those who did not develop spinal damage (OR [95%CI]= 0.24 [0.08-0.70].

Conclusion: The absence of radiographic damage in the spine after prolonged duration of symptoms is associated with the lack of fat metaplasia and ankylosis in the SIJ on MRI. This supports the hypothesis that fat metaplasia identifies a progressive phenotype.

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Abstract Number: 3159

Validation of MRI Structural Lesions Using Computed Tomography in Patients with Axial Spondyloarthritis

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Background/Purpose: MRI can detect both inflammatory and structural lesions in the sacroiliac joints (SIJ) of patients with axial SpA. However, standard MRI sequences do not directly depict bone and the appearance of erosion may vary according to the presence/absence of inflammation. Consequently, further validation using an accepted gold standard, namely, computed tomography (CT), is essential. We aimed to assess the detection of structural lesions of bone in the SIJ by MRI using CT as the gold standard.

Methods: CT scans from 44 patients (26 females, mean age 49.4 years, mean symptom duration 9.1 years) were reconstructed in the semicoronal plane parallel to the superior border of the sacrum, as for conventional MRI evaluation of the SIJ, and scoring of lesions by CT was confined to this plane. Structural lesions were scored in consecutive slices in SIJ quadrants (erosion, sclerosis)

or SIJ halves (ankylosis) on a dichotomous basis (present/absent) using the same anatomical principles for defining SIJ quadrants as developed for the SPARCC MRI SIJ inflammation and structural scores. Consecutive semicoronal slices from T1W MRI scans of the SIJ from the same cases conducted at the same time as CT were assessed independently for structural lesions (erosion, fat, backfill, ankylosis, sclerosis) blinded to CT assessments using the MORPHO modification of the SPARCC method. MRI lesions were defined according to the Canada-Denmark MRI group. An online scoring module recorded detailed scores for individual SIJ slices. Agreement between CT and MRI was assessed by kappa statistics. Sensitivity/specificity of MRI for CT lesions was calculated. The primary analysis was based on lesions detected concordantly by both readers at the level of the individual iliac/sacral joint surface (erosion, sclerosis) or the individual joint (ankylosis, backfill).

Results: With CT as gold standard and a lesion defined as being present when recorded in the same location on at least 1 coronal slice by both readers, MRI-defined ankylosis had 56.3% sensitivity and 100% specificity for CT ankylosis (Table). For erosion, sensitivity and specificity of MRI was 81.3% and 96.2%, and for sclerosis, sensitivity and specificity of MRI was 50% and 97%, respectively. Agreement between CT and MRI for erosion increased when the cut-off for presence of a lesion was set at 2 slices but only marginally for sclerosis, even when the cut-off for presence of a lesion was set at 3 slices. Lesions observed on CT corresponding to backfill on MRI were ankylosis, erosion, and sclerosis, in 66.7%, 66.7%, and 80% of backfill lesions, respectively.

Conclusion: Ankylosis and erosion on MRI correspond closely with the same type of lesion observed on CT. Both new bone formation and erosion are frequently evident on CT at locations where backfill is observed on MRI supporting the hypothesis that backfill is an intermediary tissue between erosion and ankylosis.

Concordance for 2 readers		Type of Lesion	K value	Sensitivity of MRI	Specificity of MRI
MRI lesion +	CT lesion +				
≥1 slice	≥1 slice	Ankylosis	0.67	56.3%	100%
		Erosion	0.76	81.3%	96.2%
		Sclerosis	0.47	50.0%	97%
≥2 slices	≥2 slices	Ankylosis	0.71	60.0%	100%
		Erosion	0.83	84.6%	98.1%
		Sclerosis	0.53	42.9%	99.2%
≥2 slices	≥3 slices	Ankylosis	0.83	75.0%	100%
		Erosion	0.84	90%	98.1%
		Sclerosis	0.53	42.9%	99.2%

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Abstract Number: 3160

Scoring Syndesmophytes on CT Spine Images of Patients with Radiographic Axial Spondyloarthritis from the Sensitive Imaging of Axial Spondyloarthritis (SIAS) Cohort

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SESSION INFORMATION

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Session Time: 9:00AM-10:30AM

Background/Purpose: Low dose Computed Tomography (CT) could potentially be more sensitive than radiographs in the follow

up of patients with axial spondyloarthritis (axSpA). First goal was to develop a scoring method for the spine and test its inter-reader variability.

Methods: Patients (pts) of the Sensitive Imaging of Axial Spondyloarthritis (SIAS) cohort fulfilled the modified New York (mNY) criteria and had at least 1 syndesmophyte in cervical or lumbar spine on radiographs. Baseline and 2 years follow up CT scans were performed. Syndesmophytes were scored in the coronal and sagittal planes for all ÔcornersÕ per view, thus scoring 8 ÒquadrantsÓ per vertebral unit (VU). Syndesmophytes were scored as absent (score 0), <50% of the intervertebral disc height (IVDH) (1), ³50% of the IVDH but no bridging (2) or as Òbridging the IDVHÓ (3). Score range 0-552. Two readers, blinded for clinical and laboratory information as well as time order, scored the 2 CT scans per patient. Scores of the 2 readers were compared using heatmaps. Inter-reader variability was assessed by (two-way average) intercorrelation coefficient (ICC) and smallest detectable change (SDC) analysis for the whole spine and per segment.

Results: In total, 58 pts (47 male, mean age 50.4) were included. The heatmap presents the similarity of baseline and change scores per reader per VU. Table 1 shows that both readers use almost the entire possible range, pick up a similar magnitude of change and have high ICCs. Most change is present in the thoracic spine. A change ³SDC is seen in 33.9% of the patients.

Conclusion: A fine-grained scoring system for CT spine was developed. Scoring syndesmophytes with good accuracy on CT images was feasible, picking up changes over a 2-year period in a high percentage of patients, especially in the thoracic spine, which is insufficiently visible on radiographs. Table 1 – Smallest detectable change (SDC) and inter-reader variability between readers on timepoint 1, timepoint 2 and for the difference between the timepoints (syndesmophyte growth).

Segment (max score)	Timepoint	Median and range reader 1	Median and range reader 2	SDC (inter-reader)	No. of patients with growth ³SDC (%) (n=58)	ICC
Whole spine (552)	Timepoint 1	144 (16 – 428)	135 (6 – 447)			0.99 (0.94 – 1.00)
	Timepoint 2	157 (18 – 428)	146 (8 – 461)			0.98 (0.92 – 0.99)
	Change score	9 (-11 – 96)	8 (-6 – 93)	12.4	19 (32.8)	0.75 (0.49 – 0.88)
Cervical (144)	Timepoint 1	8 (0 – 140)	8 (0 – 128)			0.96 (0.92 – 0.98)
	Timepoint 2	8 (0 – 140)	8 (0 – 128)			0.98 (0.95 – 0.99)
	Change score	0 (-12 – 38)	0 (-9 – 38)	5.41	9 (15.6)	0.85 (0.75 – 0.91)
Thoracic (264)	Timepoint 1	84 (2 – 250)	72 (0 – 264)			0.97 (0.92 – 0.99)
	Timepoint 2	93 (2 – 256)	81 (0 – 264)			0.97 (0.85 – 0.99)
	Change score	6 (-6 – 94)	6 (-12 – 93)	12.4	15 (25.9)	0.85 (0.75 – 0.92)
Lumbar (144)	Timepoint 1	32 (0 – 140)	36 (0 – 140)			0.91 (0.79 – 0.96)
	Timepoint 2	34 (0 – 144)	39 (0 – 144)			0.99 (0.98 – 1.00)
	Change score	2 (-10 – 14)	1 (-4 – 12)	4.51	14 (24.1)	0.56 (0.26 – 0.73)

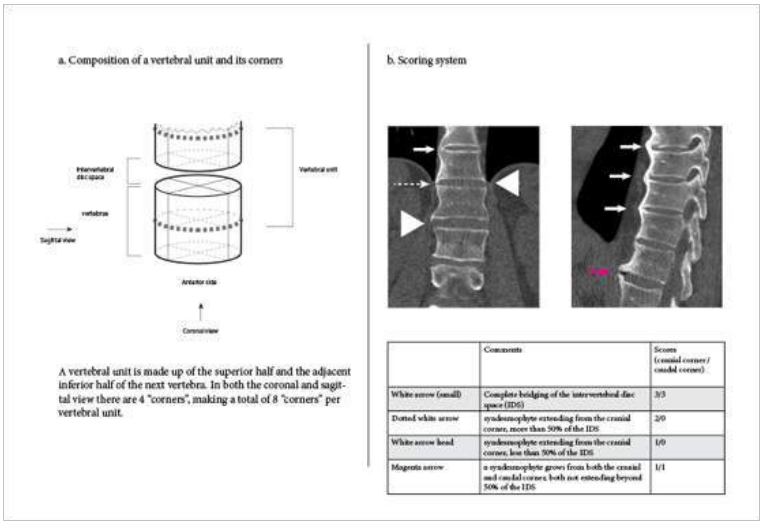
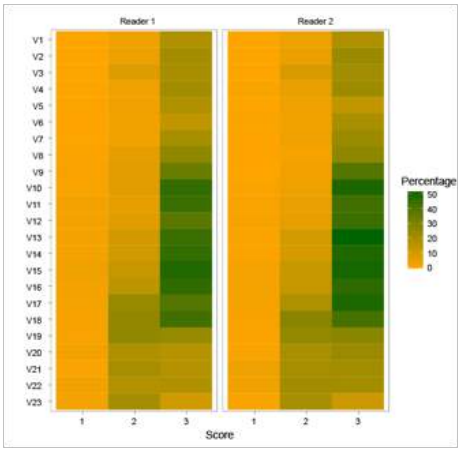
Fig 1 

Fig 2 – Heatmap presenting per reader the location of scores 

Distribution of syndesmophytes is similar between the two readers on both time points (vertebral unit level on the y-axis). Ankylosis (score 3) is most prevalent in the thoracic spine, and syndesmophytes in general are least prevalent in the cervical spine.

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Abstract Number: 3161

The Association Between HLA Genetic Susceptibility Markers and Sonographic Enthesitis in Psoriatic Arthritis

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Session Type: ACR Concurrent Abstract Session
Session Time: 9:00AM-10:30AM

Background/Purpose: Enthesitis is an important pathophysiologic component in psoriatic arthritis (PsA). Ultrasound is emerging as an optimal method to evaluate enthesitis. HLA genes are implicated in the pathogenesis of PsA. Little is known about the relation between HLA genetic susceptibility markers and enthesitis in PsA patients. Hence, our aim was to examine the association between HLA genetic susceptibility markers and sonographic enthesitis in patient with PsA.

Methods: A cross-sectional analysis was performed in patients followed at a large PsA cohort. Sonographic enthesitis was assessed according to the MAdrid Sonography Enthesitis Index (MASEI) scoring system which quantifies the extent of sonographic entheseal abnormalities in 12 entheseal sites adjacent to large joints. Total MASEI was further categorized into: bone scores (enthesophytes, erosions) and soft tissue scores (structural entheseal changes, vascularization, bursitis). HLA genotyping was performed using sequence-specific oligonucleotide probes. The association between 6 HLA susceptibility markers of PsA and the severity of sonographic enthesitis (by MASEI) was assessed using multivariate linear regression models adjusted for age, sex, BMI and disease duration.

Results: Two hundred and twenty five patients were included, 57% male with mean (s.d.) age of 55.8 (12.9) years and PsA duration of 16.4 (12.3) years. The majority of the patients were Caucasians (88%). The frequencies of the HLA alleles were: *HLA-B*27*: 15.1%; *HLA-B*38*: 18.2%; *HLA-B*39*: 4.9%; *HLA-B*44*: 21.8%; *HLA-B*08*: 17.3% and *HLA-C*06*: 27.5%. In the univariate analysis *HLA-B*27* (β 3.8, p=0.005) was associated with more severe enthesitis while *HLA-C*06* (β -2.4, p=0.03) was associated with less severe enthesitis. The results of the multivariate regression model are shown in Table 1. The interaction between HLA-B*27 and PsA duration was statistically significant, showing an increasing effect of *HLA-B*27* with longer PsA duration (p=0.004). The results remained essentially the same after restricting the analysis to Caucasians. Other predictors of enthesitis severity included male gender (p=0.02) and BMI (p<0.001). The interaction between *HLA-B*27* and PsA duration was also associated with higher MASEI-bone scores (p=0.002). *HLA-B*27* was also associated with higher MASEI-soft tissue scores (p=0.01).

Conclusion: *HLA-B*27* is associated with the severity of sonographic enthesitis in PsA, particularly in patients with longer disease duration. This finding highlights the potential role of genetic variants to predispose to severe enthesitis in patients with PsA.

Table 1: Multivariate Regression Model assessing the association between HLA alleles and MASEI score (Total MASEI include active GS and PD abnormalities)

Variable*	Multivariate Model (N=225)		Multivariate Model (Caucasians) (N=196)	
	Estimate (95% CI)	**P value**	**Estimate (95% CI)**	**P value**
HLA-B*27	4.64 (0.39, 8.89)	0.03	4.45 (0.12, 8.87)	0.04
HLA-B*27* PsA Duration	4.78 (1.54, 8.02)	0.004	4.62 (1.38, 7.87)	0.005
HLA-C*06	-2.27 (-5.62, 1.06)	0.18	-1.52 (5.08, 2.03)	0.40
Age (10 years)	1.02 (-0.26, 2.31)	0.12	1.37 (0.01, 0.27)	0.047
Sex	3.71 (0.67, 6.67)	0.02	4.32 (1.10, 7.54)	0.008
BMI	0.56 (0.31, 0.81)	<0.0001	0.56 (0.30, 0.82)	<0.0001
PsA Duration (10 years)	0.54 (-0.90, 2.00)	0.46	0.54 (-0.95, 2.04)	0.47
*This model included variables that were statitically significant in the univariate analysis GS – Gray scale, PD – Power Doppler				

Disclosure: A. Polachek, None; **R. J. Cook**, None; **V. Chandran**, None; **F. Abji**, None; **D. D. Gladman**, AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 2,AbbVie, Amgen, BMS, Celgene Corporation, Janssen, Novartis, Pfizer, UCB, 5; **L. Eder**, None.

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Abstract Number: 3162

Symmetric and Asymmetric Sacroiliitis Are Associated with Different Major Histocompatibility Class I Alleles in Psoriatic Arthritis

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Background/Purpose: HLA-B27 has been linked to sacroiliitis (SII) in psoriatic arthritis (PsA); however, the contribution to SII of other human leukocyte antigen (HLA) Class I loci encoding the major histocompatibility complex (MHC) has received little study. In particular, whether symmetric and asymmetric SII are differentially genetically determined.

Methods: Patients from two prospective PsA cohorts were genotyped for HLA-B and C alleles. Radiographs were evaluated for SII, which was defined as symmetric (symSII) or asymmetric (asymSII) without knowledge of HLA-B and C status. Associations of alleles with SII were explored in multivariable logistic regression models adjusting for potentially confounding characteristics. From these models, allele scores were constructed as the sum of an individual's positively associated alleles minus the sum of their inversely associated alleles

Results: A total of 490 PsA patients were studied [mean age=56 years, 54% female, median PsA duration=18 years]. SymSII and asymSII was observed in 44 (9%) and 75 (15%), respectively. In multivariable analysis, symSII was associated with 11 alleles (listed in Fig1). SymSII was observed in 3% of patients with a symSII allele score of -3 or -2 compared with 12% of those with a score of 0 (OR=4.05; p=0.009) and in 69% of those with a score of +2 (OR=68.4; p<0.001) (Fig1A). The area under the receiver operator curve (AUC) for detecting symSII with the allele score was 0.758 (95% CI 0.679, 0.836). Adjusting for body mass index and PsA duration did not substantially alter the associations. A different set of five alleles was associated with asymSII (listed in Fig 1). The prevalence of asymSII was 7% for those with an asymSII allele score of 0 compared with 18% for those with a score of +1 (OR=3.17; p<0.001) and 42% for those with a score of +2 or +3 (OR=10.18; p<0.001) (Fig1B). The area under the receiver operator curve (AUC) for detecting asymSII with the allele score was 0.684 (95% CI 0.624, 0.742). Adjusting for family history of psoriasis, current PASI score, and the presence of radiographic osteolysis did not substantially alter the associations.

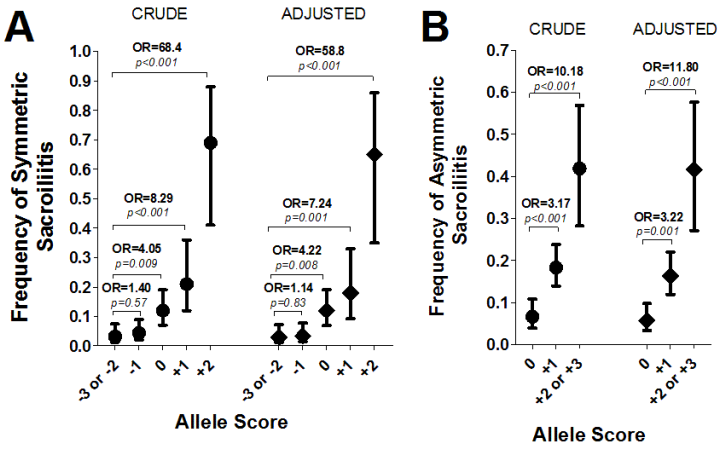

Figure. Associations of Allele Scores with Symmetric and Asymmetric Sacroiliitis in Psoriatic Arthritis. Mean and 95% confidence intervals are depicted. The symmetric sacroiliitis allele score was [B*27:05:02 + B*40:02:01 + B*44:02:01 + B*51:01:01] - [B*44:03:01 + C*06:02:01 + C*07:01:01 + C*07:02:01 + B*15:01:01 + B*37:01:01 + C*16:01:01]. The asymmetric sacroiliitis allele score was [B*08:01:01 + B*14:01:01 + B*15:01:01 + B*38:01:01 + C*05:01:01].

Conclusion: Symmetric and asymmetric SII are differentially genetically determined, such that the determination of HLA Class I alleles may be useful in predicting risk for SII within a given PsA patient.

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Abstract Number: 3163

SEC16A and Intracellular Trafficking Abnormalities in Axial Spondyloarthritis

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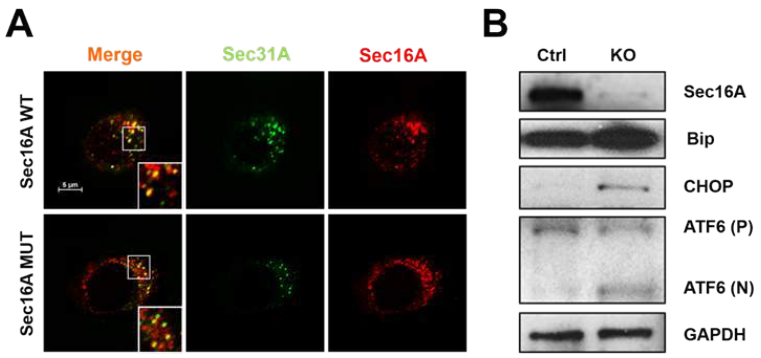
Background/Purpose: The pathogenesis of Axial Spondyloarthritis (AxSpA) is not well understood. A rare 9 base-pair deletion of SEC16A was recently identified to be strongly associated with AxSpA in a multiplex family. SEC16A plays an important role in endoplasmic reticulum (ER)-to-Golgi transport and the assembly of cargo carrier vesicles. We investigated if variations in SEC16A could affect the ER-Golgi transport of HLA-B27 and influence AxSpA pathogenesis.

Methods: EBV transformed B cells were isolated from 14 HLA-B27 positive members of the multiplex family. Out of 9 members with the SEC16A 9 bp deletion, 8 have been diagnosed with AxSpA and one 16-year-old was healthy. Five healthy family members had the wild-type (WT) SEC16A. C1R-B27 cells (B-lymphoblastoid cells with stable HLA-B27 expression) were used to replicate findings by knocking out (KO) SEC16A using CRISPR. Fluorescent tagged monoclonal antibodies against SEC16A and SEC31A (identifies ER-to-Golgi transport vesicle COPII) were used. The formation of ER-to-Golgi transport vesicles and the organization of ER exit sites (ERES) were studied using confocal microscopy. The vesicular stomatitis virus glycoprotein (VSVG-GFP) was

used to track ER-to-Golgi transport. In addition, Fluorescence Recovery After Photobleaching (FRAP) was performed to study the dynamics of ER-to-Golgi transport vesicles. Changes in surface and intracellular HLA-B27 and free heavy chain (FHC) expression were tested by flow cytometry. Activation of unfolded protein response (UPR) was measured using PCR and western blot for BiP, CHOP and ATF-6.

Results: EBV-B cells with the SEC16A mutation had a significantly ($P<0.001$) lower number of secretory vesicles at ERES (co-localization of SEC16A and SEC31A in Figure 1A) and impaired ER-to-Golgi transport (decreased VSVG-GFP trafficking). By FRAP, there was poor recruitment of SEC31A to ERES. There was significantly lower surface expression of intact HLA-B27 and FHC ($P<0.01$) and accumulation of both intracellularly ($P<0.01$). All findings were replicated in C1R-B27 cells after 90 % SEC16A suppression. UPR was significantly elevated due to the insufficient ER-Golgi transport in the SEC16A knock out C1R-B27 cells (Figure 1B).

Conclusion: Thus SEC16A is an important factor that can influence HLA-B27 trafficking, surface and intracellular expression and UPR. Abnormal SEC16A-HLA-B27 interaction may play an important role in the pathogenesis of AxSpA. **Figure 1. A 9-bp deletion of SEC16A (MUT) decreases COPII vesicle formation compared to wild Type SEC16A (WT) (A). SEC16A knockout (90%) leads to increased unfolded protein response (B).**



Disclosure: F. Zeng, None; **Z. Zhang**, None; **V. Ranganathan**, None; **D. Orielly**, None; **P. Rahman**, Janssen Inc., 5; **N. Haroon**, None.

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Abstract Number: 3164

Spondyloarthritis Pathogenesis Involves Interplay Between Gut Microbiota and Genetic Background

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Background/Purpose: HLA-B27 and human b_2m expression in rats induces a spontaneous inflammatory disease resembling human spondyloarthritis (SpA). While aspects of rat SpA have been studied in detail, understanding of gut inflammation remains limited. We recently showed that HLA-B27 affects the gut microbiota in rats. Here, we aimed to determine the relationship between intestinal microbiota and the gut immune response in B27 rats developing SpA-like disease.

Methods: HLA-B27/human b_2m transgenic (B27) rats (33-3 transgene locus) on 3 genetic backgrounds (Dark Agouti, DA; Lewis, LEW; and Fischer, F344), and HLA-B7/human b_2m transgenic (B7) rats on the LEW background, were examined at 2, 3, and 6 months of age. In a total of 194 rats, microbiota in the ileum, cecum and colon was determined by 16S rRNA gene sequencing. Cecum and colon histology was scored for inflammation, and RNA from whole tissue was analyzed by RNA-Seq to assess gene expression. Differences in microbiota and host immune response were identified as a function of genotype, genetic background, and disease severity.

Results: DA rats are resistant to B27-induced gut inflammation, while it progresses with age in LEW B27, and occurs early and is more severe in F344 rats. LEW B7 rats remain unaffected. Disease severity correlates with increased relative abundance of *Proteobacteria* and *Verrucomicrobia* at the expense of *Firmicutes*. While disease-associated microbes are similar in B27 LEW and F344, their relative frequencies are background specific. For example, *Clostridium* and *Akkermansia* are abundant in F344, while *Prevotella* and *Sutterella* exhibit greater increases in LEW. B27 DA and B7 LEW animals exhibit different microbial profiles compared to their WT controls, yet neither develops disease. Metagenome predictions revealed perturbed glutathione and steroid hormone biosynthesis B27 LEW and B27 F344. A striking finding was that LEW and F344 rats harbor segmented filamentous bacteria (SFB) in the ileum, whereas SFB are absent from the DA background and B7 LEW rats. Transcriptome analysis revealed robust activation of the IL-23/IL-17 axis, with IFN-g as well as TNF-a pathways upregulated with concomitant downregulation of metabolic pathways in B27 LEW and F344 rats. Interestingly, DA B27 showed a transient upregulation of these pathways including IL-17, IL-22, and TNF-a, but not IFN-g. LEW B7 rats had a remarkably similar transcriptome to LEW WT rats despite dramatic differences in microbial communities.

Conclusion: Integrated analysis of the gut microbiota and host transcriptome on different genetic backgrounds provides an unprecedented picture of the relationship between HLA-B27-induced gut inflammation and microbial communities. Microbial dysbiosis varies with genetic background, but contributes to a common disruption of gut metabolic pathways with activation of the IL-23/IL-17 axis, and IFN/TNF signaling leading to gut inflammation. The lack of SFB in DA rats may protect B27 animals given the well-known requirement for SFB for Th17 development in the lamina propria. Understanding SpA-associated microbial communities may lead to a better understanding of HLA-B27-associated disease pathogenesis.

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Abstract Number: 3165

HLA-B27 Expression Is Accompanied By a Profoundly Altered IgA Response to the Intestinal Microbiota and Microbial Translocation to the Joint

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SESSION INFORMATION

Session Date: Wednesday, November 16, 2016

Session Title: Spondylarthropathies Psoriatic Arthritis – Pathogenesis, Etiology II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: HLA-B27 is the strongest known genetic risk factor for ankylosing spondylitis and other spondyloarthropathies (SpAs). We have shown previously that Fisher 344 rats that express the human HLA-B27/β2m transgene (33-3 locus) develop a globally altered intestinal microbiome relative to wild type (WT) control animals. This mirrors the altered gut microbiota of SpA patient populations and indicates intestinal dysbiosis may be a functionally significant event in SpA pathogenesis. Intestinal IgA responses are known to shape the intestinal microbiota. We hypothesized that microbiota-specific IgA responses may be significantly impacted by HLA-B27 expression. Moreover, since IgA responses can regulate microbial translocation from the gut to the periphery, we examined B27-associated translocation of gut microbes to the joint – a site

predisposed to inflammation in the HLA-B27/β2m rat.

Methods: For IgA analysis, we used IgA-SEQ sequencing methodology, whereby fecal bacteria are flow-sorted based upon their coating with IgA and the IgA+ve and IgA-ve fractions subjected to 16s rRNA gene sequencing. The relative enrichment of each bacterial operational taxonomic unit (OTU) in the IgA+ve vs IgA-ve fraction was then calculated to profile the microbiota-specific IgA response in 16wk old HLA-B27/β2m or WT control rats. The frequency of IgA+ve B cells in intestinal lamina propria, mesenteric lymph node (MLN) and bone marrow (BM) was also enumerated by flow cytometry. We collected small and large intestinal contents (ileum, cecum and colon), MLN and ankle tissue from 16wk old HLA-B27/β2m rats and WT controls. DNA was extracted and subjected to 16s rRNA gene sequencing to profile microbial DNA at these intestinal and peripheral sites.

Results: HLA-B27 expression was associated with a markedly altered IgA response to the intestinal microbiota, with pronounced IgA-enrichment of many microbial OTUs vs WT animals. Amongst the most disproportionately IgA-coated fecal microbes in B27+ rats were *Prevotella, Blautia* and *Akkermansia spp.* and Segmented Filamentous Bacteria (SFB) – the latter of which is a known arthritogenic agent in rodents. These changes were accompanied by a B27-associated expansion of IgA+ve B cells specifically in the gut. Interestingly, we observed a highly polymicrobial DNA signature in joint tissue, including many microbes of putative intestinal origin. B27 expression was associated with a significant expansion of *Suturella, Roseburia, Akkermansia, Prevotella* and *Coprobacillus spp.*DNA at this tissue site.

Conclusion: The dysbiosis observed with HLA-B27 expression may be a result of highly perturbed mucosal IgA responses to the intestinal microbiota. The presence of microbial DNA in joint tissue implicates the translocation of gut microbes to joint may be a relevant mechanism in SpA pathogenesis. Further functional studies will provide valuable insight as to the relationship between these observations and their respective contribution to B27-associated spondyloarthropathy.

Disclosure: M. Asquith, None; **S. Davin**, None; **P. Stauffer**, None; **C. Mitchell**, None; **J. T. Rosenbaum**, Alcon Research Institute, 2,AbbVie, UCB, XOMA, Santen, Novartis, Medimmune, Cavtherx, Portage, Topivert, Regeneron, Allergan, Sanofi, Gilead and Mallinckrodt, 5.

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Abstract Number: 3166

HLA-B27 and Ankylosing Spondylitis Have Shared Effects on the Gut Microbiome

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Session Time: 9:00AM-10:30AM

Background/Purpose: Evidence for a discrete intestinal microbiome signature in the terminal ileum (TI) of ankylosing spondylitis (AS) patients, compared to healthy controls, has recently been described. It has been hypothesised that HLA-B27 induces AS by effects on the intestinal microbiome, in turn driving spondyloarthritis by inducing immunological processes, particularly IL-23 production. Here we examine the effect of HLA-B27 on the composition of the intestinal microbiome in healthy individuals and twins, using culture independent 16S rRNA amplicon sequencing.

Methods: 135 samples from 6 intestinal sites were collected from otherwise healthy persons undergoing routine colorectal

screening (age 40-75yrs). All patients were HLA-B typed and biopsies sequenced for the bacterial marker gene 16S rRNA and analysed. Further analysis was conducted using multivariate analysis package MixMC as implemented in R.The association between HLA-B27 status and intestinal microbiome was further examined in 1392 otherwise healthy twins with matched faecal 16S rRNA and genotype status from the TwinsUK registry. Linear mixed effects models were used to examine the association between the microbiome and genotype status. These models account for the correlation between twins within a family.

Results: Intestinal biopsy studies revealed that HLA-B27 genotype (n=10 B27+ and 85 B27- samples) influences overall microbial composition with increases in bacterial families *Ruminococcaceae* and *Lachnospiraceae* in the HLA-B27+ samples. Multivariate regression analysis of all samples demonstrated distinct clustering of HLA-B27+ from HLA-B27- samples (P=0.0063; PERMANOVA). The TI also showed clear and distinct clustering of HLA-B27+ from HLA-B27- samples driven by a decrease in *Veillonellaceae* (P<0.001) and the order Clostridiales *(*P<0.05), and increases in *Bacteroidaceae (*P<0.05) and *Ruminococcaceae (*P<0.05). The effect of genotype on the microbiome was further examined in the TwinsUK cohort (n=107 B27+ and 1285 B27- samples). HLA-B27 status was again associated with the bacterial families *Ruminococcaceae*, *Lachnospiraceae* and the order Clostridiales, in the same direction as seen in the intestinal biopsy data. This is consistent with the TI microbial signature previously described in AS cases and healthy HLA-B27+ patients.

Conclusion: This study shows that healthy HLA-B27+ individuals exhibit shared microbiota changes with AS, indicating an altered microbiota may be a primary event in AS pathogenesis rather than secondary to disease or its treatment. These findings support the hypothesis that HLA-B27 operates to cause AS through interaction with the intestinal microbiome, and suggests that therapies targeting the microbiome may be effective in AS prevention and/or treatment.

Disclosure: M. E. Costello, None; **M. Asquith**, None; **K. A. Lê Cao**, None; **T. Martin**, None; **S. Diamond**, None; **M. Beaumont**, None; **T. D. Spector**, None; **J. T. Rosenbaum**, Alcon Research Institute, 2,AbbVie, UCB, XOMA, Santen, Novartis, Medimmune, Cavtherx, Portage, Topivert, Regeneron, Allergan, Sanofi, Gilead and Mallinckrodt, 5; **M. A. Brown**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/hla-b27-and-ankylosing-spondylitis-have-shared-effects-on-the-gut-microbiome

Abstract Number: 3167

Total and Glucocorticoid-Related Damage Accrual in the Systemic Lupus International Collaborating Clinics Inception Cohort

Jayne Little[1,2], Mark Lunt[3], Benjamin Parker[1,2], Ian N. Bruce[2,4] and The Systemic Lupus International Collaborating Clinics (SLICC) Group, [1]Centre for Musculoskeletal Research, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [2]NIHR Manchester Musculoskeletal Biomedical Research Unit, Central Manchester University Hospitals NHS Foundation Trust, Manchester, United Kingdom, [3]Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [4]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom

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Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Total and Glucocorticoid-Related Damage Accrual in The Systemic Lupus International Collaborating Clinics Inception Cohort. **Jayne Little**[1], Mark Lunt[1], Ben Parker[1], Ian N. Bruce[1] and The Systemic Lupus International Collaborating Clinics (SLICC) Group, [1]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, MAHSC, The University of Manchester, Manchester, United Kingdom

Background/Purpose:

The Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) Damage Index (SDI) assesses irreversible damage in SLE and a higher SDI score predicts further damage and mortality. Glucocorticoid (GC) use, a modifiable risk factor, has been associated with increased total SDI score and specific individual damage items. In a previous consensus exercise we categorised SDI items according to their likely association with GCs. Our aim was to explore the accrual of total and GC-related damage in a large international inception cohort.

Methods:

From 2000-11, we recruited patients within 15 months of developing four or more 1997 American College of Rheumatology (ACR) criteria for SLE. The SDI was completed at enrolment (if >6 months from diagnosis) and at each annual assessment. Total SDI scores in the cohort over time were assessed using descriptive statistics (point estimates of the mean) and the cumulative incidence of SDI items (grouped according to systems or likely steroid association) was calculated using Cox proportional hazard regression.

Results: The mean (point estimate) SDI increased over time from 0.45 at assessments occurring between 1 and 2 years from diagnosis (n=1332) to 0.86 at 5 years (n=1067) and 1.38 (n = 429) at 10 years. For each of the 12 SDI organ-based systems there was a steady accumulation of damage over time (figure 1). By year 5 the highest incidence rates of damage were seen within the musculoskeletal group and the 'other' group. When items were grouped based on their likely association with GC use, the cumulative incidence of items thought to have definite, probable/possible and no association with GC were 0.097, 0.053 & 0.203 respectively by 5 years and 0.207, 0.092 and 0.411 respectively by 10 years (figure 2). By 10 years, 42.6% of all damage was potentially related to GC use.

Conclusion: In this inception cohort, the damage accumulated over time in a linear manner, whether damage items are grouped as a total SDI, according to organ-systems or when grouped according to their likely association with steroids. A significant proportion of all damage accrued (42.6%) is related to steroid use and better therapeutic strategies to reduce steroid exposure are needed to improve long-term outcomes in SLE.

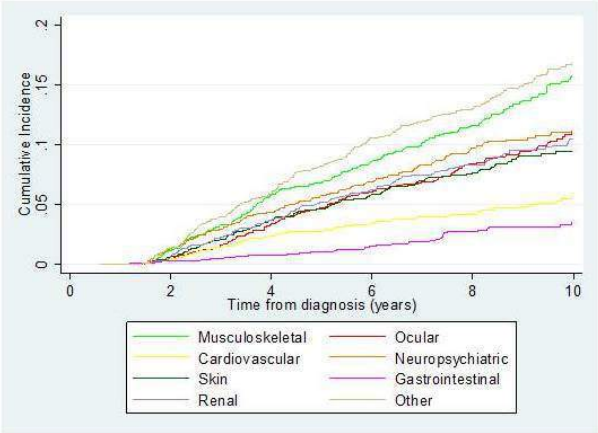

Figure 1 – Cumulative Incidence of items according to system groupings

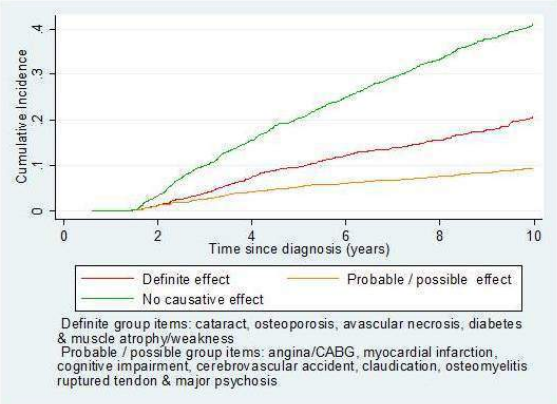

Figure 2 – Cumulative Incidence of items according to association with GC use

Disclosure: J. Little, UCB Pharma, 2; **M. Lunt**, None; **B. Parker**, None; **I. N. Bruce**, UCB Pharma, 2.

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Abstract Number: 3168

Economic Evaluation of Damage Accrual in an International SLE Inception Cohort

Megan Barber[1], Ian N. Bruce[2], Murray Urowitz[3], John G. Hanly[4], Li Su[5], Juanita Romero-Diaz[6], Caroline Gordon[7], Sang-Cheol Bae[8], Sasha Bernatsky[9], Daniel J Wallace[10], Joan T. Merrill[11], David A. Isenberg[12], Anisur Rahman[13], Ellen M. Ginzler[14], Michelle Petri[15], Mary Anne Dooley[16], Paul R. Fortin[17], Dafna D. Gladman[18], Jorge Sanchez-Guerrero[19], Kristján Steinsson[20], Rosalind Ramsey-Goldman[21], M Khamashta[22], Cynthia Aranow[23], Graciela S. Alarcon[24], Barri J. Fessler[25], Susan Manzi[26], Ola Nived[27], Andreas Jönsen[28], Asad Zoma[29], Ronald F. van Vollenhoven[30], Manuel Ramos-Casals[31], Guillermo Ruiz-Irastorza[32], S. Sam Lim[33], Kenneth C. Kalunian[34], Murat Inanc[35], Diane L. Kamen[36], Christine A. Peschken[37], Søren Jacobsen[38], Anca Askanase[39], Jill P. Buyon[40], Chris Theriault[41], Vernon Farewell[42] and **Ann E. Clarke**[43], [1]Division of Rheumatology, University of Calgary, Caglary, AB, Canada, [2]Central Manchester University Hospital NHS Foundation Trust and Manchester Academic Health Science Centre, Arthritis Research UK Epidemiology Unit, The University of Manchester, Manchester Academic Health Sciences Centre, Manchester, United Kingdom, [3]Medicine, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [4]Rheumatology, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [5]Nova Scotia Rehab Site, Division of Rheumatology, Capital Health and Dalhousie University, Halifax, NS, Canada, [6]Immunology and Rheumatology, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico city, Mexico, [7]NIHR/Wellcome Trust Clinical Research Facility, University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom, [8]Hanyang University Hospital for Rheumatic Diseases, Seoul, Korea, Republic of, [9]Divisions of Rheumatology and Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada, [10]Cedars-Sinai Medical Center, West Hollywood, CA, [11]Arthritis and Clinical Immunology Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [12]Centre for Rheumatology, Division of Medicine, University College London, London, United Kingdom, [13]Rayne Institute, Centre for Rheumatology Research, UCL Division of Medicine, London, United Kingdom, [14]Rheumatology, SUNY Downstate Medical Center, Brooklyn, NY, [15]Rheumatology Division, Johns Hopkins University School of Medicine, Baltimore, MD, [16]Dooley Rheumatology, Chapel Hill Doctors, Chapel Hill, NC, [17]Rheumatology, University of Laval, Quebec, QC, Canada, [18]Rheumatology, Centre for Prognosis Studies in the Rheumatic Diseases, Toronto Western Hospital and University of Toronto, Toronto, ON, Canada, [19]Rheumatology, Toronto Western Hospital, Toronto, ON, Canada, [20]Rheumatology, Univ. Hospital, Reykjavik, Iceland, [21]FSM, Northwestern University, Chicago, IL, [22]Lupus Research Unit, Lupus Research Unit, The Rayne Institute, King's College London School of Medicine, St Thomas' Hospital, London, United Kingdom, [23]Molecular Medicine and Medicine, Hofstra Northwell School of Medicine, Hempstead, NY, [24]Department of Medicine, Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, [25]Rheumatology, Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, [26]Lupus Center of Excellence, West Penn Allegheny Health System, Pittsburgh, PA, [27]Department of Rheumatology, University Hospital, Lund, Sweden, [28]Lund University, Department of Clinical Sciences, Rheumatology, Lund, Sweden, [29]Rheumatology, Hairmyres Hospital, East Kilbride, Great Britain, [30]Amsterdam Rheumatology and Immunology Center (ARC), Amsterdam, Netherlands, [31]Department of Autoimmune Diseases, ICMiD, Hospital Clínic, Sjögren Syndrome Research Group (AGAUR), Laboratory of Autoimmune Diseases Josep Font, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain, [32]Universidad del Pais Vasco, Servicio de Medicina Interna, Hospital de Cruces, Bizkaia, Spain, [33]Medicine, Emory University School of Medicine, Atlanta, GA, [34]Division of Rheumatology, Allergy & Immunology, UCSD School of Medicine Center for Innovative Therapy, La Jolla, CA, [35]Department of Internal Medicine, Division of Rheumatology, Istanbul University, Istanbul Faculty of Medicine, Istanbul, Turkey, [36]Medicine/Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC, [37]RR 149G, Univ of Manitoba, Winnipeg, MB, Canada, [38]Rheumatology, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark, [39]Rheumatology, Columbia University Medical Center, New York, NY, [40]Medicine, New York University School of Medicine, New York, NY, [41]Medicine, Queen Elizabeth II Health

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Background/Purpose: Little is known about the association of healthcare costs with damage accrual in SLE. We describe the costs associated with damage states across the disease course using multi-state modeling.

Methods: Patients fulfilling the revised ACR classification criteria for SLE from 32 centres in 11 countries were enrolled in the Systemic Lupus International Collaborating Clinics (SLICC) inception cohort within 15 months of diagnosis. Annual data on demographics, SLE disease activity (SLEDAI-2K), damage (SLICC/ACR Damage Index [SDI] if ≥ 6 months from diagnosis), hospitalizations, medications, dialysis, and utilization of selected medical/surgical procedures were collected. Annual health resource utilization was costed using 2015 Canadian prices. Annual costs associated with SDI states were obtained from multiple regressions adjusting for age, race/ethnicity, and disease duration. As there were relatively few transitions to SDI states 5 – 11, these were merged into a single SDI state. Five and 10-year cumulative costs were estimated by multiplying annual costs associated with each SDI state by the expected duration in each state, which was forecasted using a multi-state Markov model (*Bruce IN et al. Ann Rheum Dis 2015;74:1706-13*).

Results: 1641 patients participated, 89.2% female, 48.9% Caucasian, mean age at diagnosis 35.2 years (SD 13.4), mean disease duration at enrollment 0.5 years (SD 0.3), and mean follow up 6.1 years (range 0.1 – 13.7 years). Health resource utilization and annual costs (after adjustment using regression) were markedly higher in those with higher SDIs (Table 1).

Table 1. Predicted Annual Health Costs Stratified by SDI

SDI State	Health Care Costs, Mean, 95% CI 2015 Canadian $
0	1569 (691,2448)
1	3317 (2234, 4399)
2	4528 (2969, 6086)
3	7422 (5350, 9494)
4	14 631 (8450, 20 813)
≥5	31 692 (20 860, 42 524)

Five and 10-year cumulative costs stratified by baseline SDI were calculated by multiplying the annual costs associated with each SDI by the expected duration in that state (5-year example in Table 2).

Table 2. Expected Duration in each SDI state over 5 Years

Baseline SDI State	Expected Duration in each SDI State over 5 years					
	0	1	2	3	4	≥5
0	4.12 yrs	0.64 yrs	0.18 yrs	0.05 yrs	0.01 yrs	0.002 yrs
1		3.17 yrs	1.28 yrs	0.43 yrs	0.09 yrs	0.03 yrs
2			3.05 yrs	1.42 yrs	0.37 yrs	0.17 yrs
3				3.22 yrs	1.11 yrs	0.67 yrs
4					2.61 yrs	2.39 yrs
≥5						5 yrs

Five and 10-year costs were greater in those with the highest SDIs at baseline (Table 3).

Table 3. Predicted 5 and 10- Year Cumulative Costs Stratified by Baseline SDI		
Baseline SDI State	Health Care Costs, Mean, 95% CI 2015 Canadian $	
	5-Year Cumulative Costs	10-Year Cumulative Costs
0	7440 (2729, 12 151)	16 940 (4548, 29 333)
1	19 301 (11 991, 26 612)	54 122 (31 306, 76 937)
2	32 468 (20 557, 44 379)	92 155 (57 941, 132 368)
3	58 874 (38 022, 79 726)	157 626 (98 830, 216 422)
4	111 379 (68 987, 153 770)	250 293 (155 798, 344 789)
≥5	155 961 (101 449, 210 472)	306 919 (197 091, 416 747)

Conclusion: Patients with the highest baseline SDIs incur annual costs and 10-year cumulative costs that are approximately 20-fold higher than those with the lowest baseline SDI. By estimating the expected duration in each SDI state and incorporating annual costs, disease severity at presentation can be used to predict future healthcare costs, critical knowledge for cost-effectiveness evaluations of novel therapies.

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Abstract Number: 3169

Mortality Trends in Systemic Lupus Erythematosus: A General Population-Based Cohort Study

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Background/Purpose: Systemic lupus erythematosus (SLE) is associated with an increased risk of mortality. Despite improvements in the recognition and treatment of SLE, it remains a challenging illness to treat, and patients with SLE also frequently suffer from multiple comorbidities, including premature cardiovascular disease and infections. Rheumatoid arthritis (RA) has also been shown to be associated with increased mortality, but studies have found substantially reduced mortality rates in recent years, likely due to improved treatment for RA.[1] However, recent mortality trends in SLE are unknown. Our objective was to assess whether mortality rates in SLE patients have changed over time in a general population context.

Methods: We conducted a population-based cohort study using data from 1999-2014 in a medical record database representative of the UK general population. We identified incident cases of SLE and up to 10 controls matched on age, sex, and entry time. This cohort was divided into two subgroups based on year of SLE diagnosis, forming the early cohort (1999-2006) and late cohort (2007-2014). We compared mortality rates, hazard ratios (HRs) (using a Cox proportional hazard model), and rate differences (RDs) (using an additive hazard model) between SLE and non-SLE cohorts, adjusting for demographics, lifestyle factors, comorbidities, medications, and healthcare use.

Results: Both the early and late cohorts (N = 1,470 and 1,666) had a similar mean age (50 and 51 years, respectively) and sex proportion (18% and 17% male, respectively). In both cohorts, SLE patients had a higher risk of mortality compared to their corresponding comparison cohort (i.e., 15.9 vs. 7.9 deaths/1,000 person-years in the early cohort and 13.8 vs. 7.0 deaths/1000 person-years in the late cohort) (**Table 1**). The corresponding absolute mortality RDs were 8.1 (95% confidence interval (CI), 1.3-11.8) and 6.9 (95% CI, 3.5-10.0) deaths/1,000 person-years, and the mortality HRs were 2.51 (95% CI, 1.63-2.83) and 2.12 (95% CI, 1.61-2.80) in the early and late cohorts, respectively (both P values for interaction > 0.6). After adjusting for covariates, the HRs and RDs remained similar between the early and late cohorts (both P values for interaction >0.47), suggesting similar levels of excess mortality in SLE patients in the two cohorts.

Conclusion: This UK population-based cohort study suggests that the excess mortality among SLE patients has not improved over a recent 16-year period. This is in contrast to recent findings that RA patients have had substantially improved survival during the same study period.[1] This supports the need for improved treatment options and strategies for SLE as well as its associated comorbidities. **References:** 1. Zhang Y et al. Improved Survival in Rheumatoid Arthritis: A General Population Based Cohort Study. Ann Rheum Dis. doi: 10.1136/annrheumdis-2016-205269 (Epub ahead of print).

Table 1. Association between SLE and All-Cause Mortality According to Time Period

	1999 - 2006		2007 – 2014		
	SLE Cohort (n=1470)	Non-SLE Cohort (n=7348)	SLE Cohort (n=1666)	Non-SLE Cohort (n=8318)	P value
Mean follow-up (person-years)	3.24 ± 2.10	3.26 ± 2.13	3.31 ± 2.23	3.33 ± 2.25	
Number of Deaths	76	189	76	195	
Death rate/1000 person years (95% CI)	15.94 (12.56-19.96)	7.89 (6.81-9.10)	13.8 (10.87-17.27)	7.04 (6.08-8.10)	
Age-, sex-, and entry year-matched HR (95% CI)	2.15 (1.63-2.83)	1.00 (Ref)	2.12 (1.61-2.80)	1.00 (Ref)	0.95
Multivariable-adjusted HR (95% CI)	1.94 (1.44-2.61)	1.00 (Ref)	1.80 (1.32-2.44)	1.00 (Ref)	0.76
Age-, sex-, and entry year-matched RD/ 1000 PYs ((95% CI)	8.05 (4.30-11.81)	0.0 (Ref)	6.76 (3.51-10.02)	0.0 (Ref)	0.61
Multivariable-adjusted RD/1000 PYs (95% CI)	7.36 (3.73-10.99)	0.0 (Ref)	5.68 (2.50-8.86)	0.0 (Ref)	0.48

Disclosure: A. Jorge, None; **N. Lu**, None; **S. K. Rai**, None; **H. Choi**, None.

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Abstract Number: 3170

Association Between Insulin Resistance, Subclinical Artheriosclerosis and Activity/Damage Status in Systemic Lupus Erythematosus Patients

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Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment V: Damage and Morbidity

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: Insulin resistance (IR) may contribute to an increase in cardiovascular risk. The aim of this study was to examine the association between IR and disease activity, disease phenotypes, drug exposure and subclinical atherosclerosis in patients with SLE.

Methods: Cross-sectional study that encompassed 332 non-diabetes individuals; 102 SLE patients and 220 age/sex-matched controls. IR by homeostatic model assessment (HOMA2), insulin, C-peptide serum levels and lipid profile were assessed in both groups. Activity (SLEDAI), severity (Katz) and damage (SLICC) scores, carotid intima-media thickness (cIMT) and carotid plaques were assessed in SLE patients. A multivariable regression analysis, adjusted for IR related factors, was performed to evaluate the differences between groups in IR indexes and, in SLE patients, the interrelation between IR and disease activity/characteristics.

Results: Median disease duration was 16 (IQR 9-28) years. Body mass index and abdominal circumference did not differ between groups. HOMA-IR-C-peptide (mean difference [IQR], 1.26 [0.77-1.74], p=0.00) and HOMA-%B-C-peptide (56 [4-71], p=0.00) were increased in SLE patients compared to controls. Similarly, insulin sensitivity through HOMA-S% was inferior in SLE patients (-44 [-28-61], p=0.00). Forty percent of patients were in no activity SLEDAI score, while 32, 21 and 9% were in mild, moderate and high/very high activity respectively. Patients in the SLEDAI high or very high activity category disclosed a higher HOMA-IR level (4.8 ± 4.8 vs. 2.07 ± 1.40, p= 0.00) when compared to those in the no activity category. SLICC index was also clearly associated with IR indexes; higher index values were related with higher HOMA-IR (beta coef. 0.27 [0.08-0.46], p=0.01) and lower HOMA-S% (beta coef. -6 [-10--3], p=0.00) levels. These associations remained significant after adjustment for age, gender, smoking, hypertension, and dyslipidemia. Katz severity index did not revealed relation with IR indexes. Use of prednisone was positively associated with HOMA-IR both when it was considered binary (beta coef 1.75 [1.37-2.12], p=0.00) and continuous (beta coef 0.15 [0.07-0.23] per mg, p=0.00). Hydroxychloroquine/other DMARDs use was not related with IR indexes. Patients with higher anti-DNA titers and those with lower complement serum levels did not reach higher IR levels. 28% of the SLE patients had carotid plaques. The presence of carotid plaque was associated with higher HOMA-IR-C-peptide (3.75 ± 3.62 vs. 1.86-1.19, p=0.00). This difference remained significant after adjustment for demographics or cardiometabolic risk factors (1.50 [0.34-2.66], p=0.01).

Conclusion: IR is present in a significant proportion of SLE patients. Disease activity and damage are SLE-related factors that lead to IR development IR is independently associated with subclinical artheriosclerosis in SLE patients.

Disclosure: H. Sanchez-Perez, None; **B. Tejera**, None; **I. Ferraz-Amaro**, None.

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Abstract Number: 3171

The Impact of Statin Use on Mortality in Systemic Autoimmune Rheumatic Diseases

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SESSION INFORMATION

Session Date: Wednesday, November 16, 2016

Session Title: Systemic Lupus Erythematosus – Clinical Aspects and Treatment V: Damage and Morbidity

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: Individuals with systemic autoimmune rheumatic diseases (SARDs)—such as systemic lupus erythematosus (SLE) and systemic sclerosis (SSc)—have been found to have an increased risk of premature cardiovascular (CV) disease compared with healthy peers. Statins have been shown to reduce CV events and mortality in the general population as well as among those with rheumatoid arthritis (RA).[1] However, it is not known whether statins have a similar impact among those with SARDs. We examined the potential survival benefit of statin use on mortality among patients with SARDs in a general population setting.

Methods: We conducted an incident user cohort study with time-stratified propensity score matching using a United Kingdom general population database. Our population included patients with a SARD as determined by incident diagnoses of SLE, SSc, Sjogren's syndrome, dermatomyositis, polymyositis, mixed connective tissue disease, Behcet's syndrome, or ANCA-associated vasculitis between January 1, 2000 and December 31, 2014. To account for potential confounders, we compared propensity score-matched cohorts of statin initiators and comparators (non-initiators) within 1-year cohort accrual blocks. 50 variables were used to create the propensity scores, including but not limited to disease duration, socio-economic status, body mass index, lifestyle factors, and medication use.

Results: Of 2310 statin initiators, 303 died during the follow-up period (mean=5.09 years), whereas among 2310 propensity score-matched non-initiators, 335 died during the follow-up period (mean=4.89 years). This corresponds to a mortality rate of 25.77/1000 and 29.64/1000 person-years, respectively. The baseline characteristics were well-balanced between the two groups. Statin initiation was associated with a 17% reduction of all-cause mortality (HR=0.83, 95% CI 0.70-0.996). When we compared the unmatched cohorts to determine the effectiveness of our propensity score matching, the statin initiators (n=2863) actually showed an 85% higher risk of mortality (HR=1.85, 95% CI 1.58-2.16) compared to non-initiators (n=2863 randomly selected without propensity score matching) due to confounding by indication.

Conclusion: In this general population-based cohort study, statin initiation was shown to reduce overall mortality in patients with SARDs after adjusting for relevant determinates of CV risk. This is similar to what has been shown in the general population and in patients with RA.[1] These findings suggest that statins should be considered part of the optimal CV risk-reduction strategy for patients with SARDs. Rheumatologists can advocate for this beneficial treatment intervention among their patients. **References:** 1. Schoenfeld SR et al. Statin use and mortality in rheumatoid arthritis: a general population-based cohort study. Ann Rheum Dis. 2016 Jul;75(7):1315-20.

Disclosure: A. Jorge, None; **N. Lu**, None; **H. K. Choi**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/the-impact-of-statin-use-on-mortality-in-systemic-autoimmune-rheumatic-diseases

Abstract Number: 3172

Temporal Trends in SLE Mortality According to Sex, Race, Ethnicity, and Geographic Region in the United States over the Past Five Decades

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Background/Purpose: Over the past half-century, diagnostic and therapeutic developments for SLE have led to dramatic improvements in the 5- and 10-year survival. Whether these achievements have improved the long-term trends in mortality in SLE is unclear.

Methods: We measured temporal trends in age-standardized mortality rates (ASMR) for SLE and non-SLE causes by joinpoint

trend analysis using county-level data abstracted from the Centers for Disease Control and Prevention database. We calculated the annual % change in mortality over the past 46 years. Logistic regression was applied to model the association of sex, race and geographic region on SLE deaths. We calculated SLE case-fatality by dividing the SLE-mortality by the estimated SLE prevalence within each demographic variable. Since no national SLE prevalence is available, we estimated these values with weighted visit data from the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Medical Care Survey.

Results: SLE was listed as the primary cause of death in 50,249 individuals from 1968-2013 in the US. The crude mortality rate for SLE peaked during the 1970s-80s and declined during 2000s. Black race was associated with the highest SLE crude mortality rate in each period. While ASMR for non-SLE causes continuously declined throughout the 46 years, the SLE ASMR showed periods of sustained increase from mid-1970s-1990s followed by a decline in 2000s. The higher SLE mortality in the general population was associated with female sex, Black race, and residence in the West or South. The national estimates for SLE prevalence per 100,000 were 221.17 in females, 20.08 (males), 170.5 (Blacks), 107.44 (Whites) and 133.5 (Hispanics), and ranged from and 106.36 (Midwest) to 138.35 (Northeast). Using these national prevalence estimates, we calculated case-fatality. Analysis of the trend in SLE case-fatality showed an overall decline in rates from 1999-2013. The average annual % change in SLE case-fatality ranged from -2.5% per year to -3.1% per year in various subpopulations during 1999-2013. Analyses of case-fatality in different subpopulations revealed that in the SLE subpopulation, males had a higher mortality (odds ratio 1.94, $p<0.001$), and even after adjusting for the prevalence variability, the SLE mortality remained higher in Blacks (odds ratio 5.24, $p<0.001$), and in people living in the South (odds ratio 1.55, $p<0.001$) and the West (odds ratio 1.44, $p<0.001$) than in the Northeast. Age of death histograms showed that Blacks died from SLE at a younger age than Whites with 50% of total deaths occurring by age 45 years in Blacks versus age 59 years in Whites. Likewise, Hispanics died younger with half of the SLE deaths occurring by age 44 years versus non-Hispanics by age 54 years.

Conclusion: Mortality from non-SLE causes declined throughout the 46 years, however, SLE mortality rates had periods of increases and more recent declines. SLE deaths occur younger in Blacks and Hispanics, and SLE case-fatality is greater in males. Despite encouraging trends in overall SLE mortality, significant gender, racial, ethnic and regional disparities persist. The findings provide impetus to delineate the next steps to improve these disparities.

Disclosure: E. Yen, None; **M. Shaheen**, None; **J. M. Woo**, None; **N. Mercer**, None; **L. Duan**, None; **N. Li**, None; **A. Karlamangla**, None; **D. K. McCurdy**, None; **R. R. Singh**, None.

Abstract Number: 3173

Pan-PPAR Agonist IVA337 Is Effective in the Prevention of Experimental Lung Fibrosis and Related Pulmonary Hypertension

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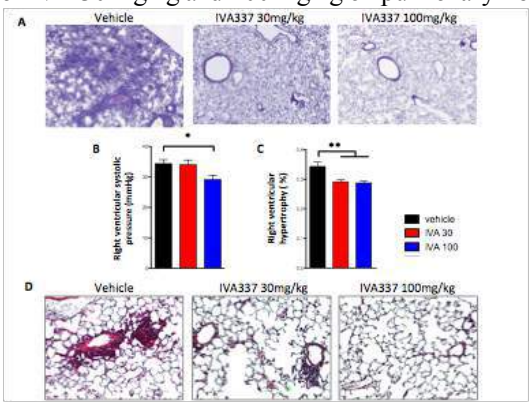
Background/Purpose: Peroxisome proliferator-activated receptors (PPARs) are nuclear receptors known to modulate fibrosis. The pan-PPAR agonist IVA337 recently demonstrated efficacy in prevention and treatment of experimental skin fibrosis (1). Our objective was to evaluate the antifibrotic effects of IVA337 in preclinical mouse models of pulmonary fibrosis and related

pulmonary hypertension (PH).

Methods: IVA337 has been evaluated in the mouse model of bleomycin-induced pulmonary fibrosis and in Fra-2 transgenic mice, this latter being characterized by non-specific interstitial pneumonia and severe vascular remodeling of pulmonary arteries leading to PH. Mice received 2 doses of IVA337 (30 mg/kg or 100 mg/kg) or vehicle administered by daily oral gavage up to 4 weeks.

Results: Both 30 mg/kg and 100 mg/kg doses of IVA337 were well tolerated in all mouse models. IVA337 demonstrated at a dose of 100 mg/kg a marked protection from the development of lung fibrosis induced by bleomycin compared to mice receiving 30 mg/kg of IVA337 or vehicle. Indeed, IVA337 (100 mg/kg) strongly reduced by 61% and 28% tissue density on histological measurements and total lung hydroxyproline concentrations, respectively, as compared to vehicle. IVA337 at 100 mg/kg also significantly decreased col1, col3, fibronectin and a-smooth muscle actin mRNA levels in lesional lungs. *In vitro* in primary human lung fibroblasts, IVA337 inhibited in a dose-dependent manner TGFβ-mediated fibroblasts to myofibroblasts transition and PDGF-mediated proliferation. Similarly, Fra-2 transgenic mice treated with 100 mg/kg of IVA337 displayed reduced lung density (20% *vs.* vehicle) and significant increase of functional residual capacity (30% *vs.* vehicle) when assessed by chest micro-CT imaging. These results were emphasized by a 50% reduction of the Ascroft fibrosis score (Figure 1A) and by a 48% reduction of hydroxyproline concentrations upon IVA337 (100 mg/kg) compared to vehicle treated mice. Regarding vessel remodeling and related pulmonary hypertension, treatment with 100 mg/kg of IVA337 led to a substantial attenuation of right ventricular systolic pressure and right ventricular hypertrophy compared to mice receiving the vehicle (Figure 1B and 1C). Furthermore, IVA337 given at 100 mg/kg markedly reduced medial wall thickness (Figure 1D) and the number of muscularized distal pulmonary arteries.

Conclusion: We demonstrate that treatment with 100 mg/kg IVA337 prevents lung fibrosis in two complementary animal models and substantially attenuates PH in the Fra-2 mouse model. These findings confirm that the pan-PPAR agonist IVA337 is an appealing therapeutic candidate for systemic sclerosis both, for skin and key cardiovascular complications. **Reference:** 1/ Ruzehaji et al, Ann Rheum Dis 2016, in press. **Figure 1:** Effects of IVA 30 mg/kg and 100 mg/kg on pulmonary fibrosis (A) and related pulmonary hypertension (B-D) in the Fra-2 mouse model



Disclosure: J. Avouac, INVENTIVA, 9; **I. Konstantinova**, INVENTIVA, 3; **C. Guignabert**, None; **S. Pezet**, None; **A. Cauvet**, None; **J. Sadoine**, None; **T. Guilbert**, None; **J. M. Luccarini**, INVENTIVA, 3; **J. L. Junien**, INVENTIVA, 3; **P. Broqua**, INVENTIVA, 3; **Y. Allanore**, INVENTIVA, 2,INVENTIVA, 6.

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Abstract Number: 3174

Apremilast Attenuates the Fibrogenic Phenotype of Dermal Fibroblasts from Patients with Systemic Sclerosis, Contributing to the Prevention of the Progression of Experimental Dermal Fibrosis

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose:

Systemic sclerosis (SSc) is a chronic fibrosing disorder that affects the skin and other internal organs. Inflammation, vasculopathy and fibrosis at the affected area are the major pathological aspects of SSc. Infiltration of inflammatory cells into the fibrotic lesions often occurs at an early phase of the disease; therefore, immunosuppressive therapy often prevents disease progression and accumulation of extracellular matrix (ECM) molecules. The PDE4 inhibitor, apremilast, acts on target cells as an anti-inflammatory agent by increasing intracellular cAMP levels and the subsequent activation of protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac). cAMP-elevating molecules have been extensively reported to ameliorate fibrosis in various fibrotic models. Based on these findings, we hypothesized that apremilast may prevent the progression of dermal fibrosis by inhibiting inflammation and fibrosis.

Methods: Dermal fibroblasts obtained from healthy individuals and patients with diffuse cutaneous SSc were incubated with apremilast at a concentration of 1-10 μM in the presence or absence of TGF-β1. Furthermore, to assess the anti-fibrotic effect of apremilast *in vivo*, we injected BALB/c mice with bleomycin together with intraperioneal administration of PBS or apremilast (1 mg/kg or 5 mg/kg daily) for 4 weeks, and dermal fibrosis was evaluated by the degree of skin thickness, αSMA-positive myofibroblast counts and collagen content. Intracellular cAMP levels were determined by an enzyme-linked immunosorbent assay (ELISA). mRNA levels of target molecules were determined by quantitative RT-PCR. Protein levels of target molecules were determined by immunoblotting and immunostaining.

Results: PDE4A, B and D were expressed in human dermal fibroblasts, and the mRNA levels of PDE4 subtypes did not differ between fibroblasts from healthy and SSc groups. Apremilast significantly suppressed the expression of *COL1A1*, *COL1A2* and *CTGF* mRNA in SSc dermal fibroblasts and healthy dermal fibroblasts treated with TGF-β1. Similarly, apremilast decreased the protein levels of type I collagen and CTGF in SSc dermal fibroblasts. With respect to the signal transduction of TGF-β1, phosphorylated Smad3, ERK1/2 and Akt were diminished in dermal fibroblasts treated with apremilast. These findings demonstrated that apremilast inhibited the production of ECM proteins by interfering with TGF-β signaling in both a Smad-dependent and a Smad-independent manner in dermal fibroblasts. Furthermore, in an *in vivo* analysis of a mouse model of bleomycin-induced dermal fibrosis, apremilast attenuated the development of dermal fibrosis compared with PBS.

Conclusion: Apremilast has anti-fibrotic effects on experimental dermal fibrosis, at least in part, by acting on activated dermal fibroblasts. Considering that apremilast is approved for psoriatic arthritis, apremilast may serve as a well-tolerated drug for the treatment of fibrotic lesions in patients with SSc.

Disclosure: T. Higuchi, None; **Y. Kawaguchi**, None; **K. Takagi**, None; **A. Tochimoto**, None; **Y. Ichimura**, None; **Y. Katsumata**, None; **H. Ichida**, None; **H. Kawasumi**, None; **H. Nishina**, None; **M. Tochihara**, None; **A. Nishino**, None; **S. Hirahara**, None; **R. Moriyama**, None; **H. Yamanaka**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/apremilast-attenuates-the-fibrogenic-phenotype-of-dermal-fibroblasts-from-patients-with-systemic-sclerosis-contributing-to-the-prevention-of-the-progression-of-experimental-dermal-fibrosis

Abstract Number: 3175

Longitudinal Analysis of MMF Clinical, Molecular, and Immunohistochemistry (IHC) Responses Shows SSc Patients Lose Their Inflammatory Signature and Rebound upon Treatment Cessation

Diana Toledo[1], Monique Hinchcliff[2], Jaclyn Taroni[1], Tammara A. Wood[3], Jennifer Franks[3], Sanjiv Shah[4], Rishi Agrawal[4], Lauren Beussink-Nelson[4], Mary A. Carns[5], Sofia Podlusky[6], Patricia Pioli[7] and Michael Whitfield[3], [1]Department of Molecular & Systems Biology, Geisel School of Medicine at Dartmouth, Hanover, NH, [2]Northwestern University, Feinberg School of Medicine

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Background/Purpose: We previously showed patients in the inflammatory subset were most likely to demonstrate improvement in modified Rodnan Skin Score (mRSS) during mycophenolate mofetil (MMF) treatment. Here, we show that MMF abrogates the molecular inflammatory signature and that the inflammatory signature and myeloid immune cell counts rebound after treatment cessation.

Methods: Sixty-eight SSc patients and 22 healthy controls were enrolled. Clinical data and 358 independent biopsies were obtained and analyzed at baseline, 6, 12, 24, and 36 months (mo). Immunohistochemistry (IHC) was performed on skin biopsy sections using a CD163 marker for macrophages and CD1c for myeloid dendritic cells (mDCs). Genome-scale gene expression was measured. Clinical improvement was defined as a decrease in mRSS $\geq$ 25%. Subjects with longitudinal skin biopsies and at least 24 mo of follow-up were termed completers. We calculated a normalized enrichment score (NES) for the inflammatory signature on a per-biopsy basis using ssGSEA.

Results: Six of the 11 completers showed 2 distinct response patterns between 24 and 36 mo determined by MMF therapy status. Three subjects showed a significant decrease in their inflammatory signature at 12 and 24 mo, paralleling decreases in T cell, macrophage and DC gene signatures, as well as mDC/macrophage IHC counts. MMF cessation at 24 mo resulted in a return of their inflammatory signatures and mDC/macrophage IHC counts, typically with an increase in mRSS. In contrast, 3 subjects that continued MMF therapy showed decreased inflammatory signatures through 36 mo with decreasing or stable mRSS. The remaining 5 completers largely showed an absence of the inflammatory signature at baseline and no improvement during MMF therapy.

Conclusion: A subset of patients receiving MMF lose their inflammatory signatures and show decreases in skin myeloid cells. After cessation of MMF, these patients show rebounding inflammation, worsening mRSS and increases in skin mDC/macrophages. Patients remaining on MMF show stable to decreasing inflammatory signatures that coincide with stable mRSS. These results show that significant mRSS improvement during MMF occurs slowly over a 12-24 mo period, and may involve T lymphocytes, macrophage and mDC molecular pathways. These data summarize the effects of MMF on gene expression pathways and myeloid cell localization in the skin and support MMF treatment beyond 24 mo in SSc patients that demonstrate mRSS improvement.

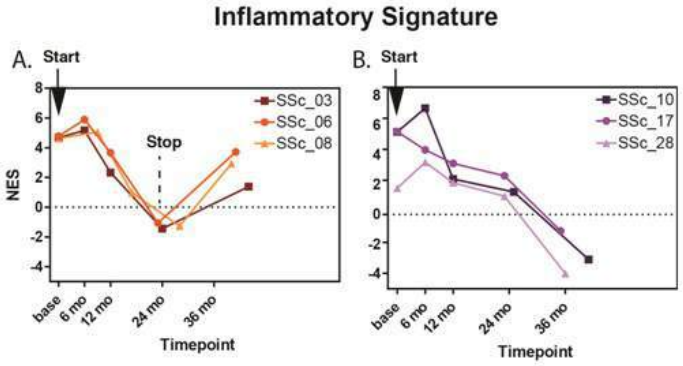

Figure 1. Kinetics of the MMF Response in SSc patients. A summary of inflammatory gene signature in six patients treated with MMF. Arrows indicate start of MMF treatment; dashed lines indicate MMF treatment cessation. **A**. Three patients that lose their inflammatory signature during (to 24 months) with improved mRSS and rebound at 36 months after MMF treatment is stopped, with a concomitant increase in MRSS. **B**. Three patients with sustained improvement in mRSS do not stop treatment and show a sustained loss of inflammatory signature.

Disclosure: D. Toledo, None; **M. Hinchcliff**, None; **J. Taroni**, None; **T. A. Wood**, None; **J. Franks**, None; **S. Shah**, None; **R.**

Agrawal, None; **L. Beussink-Nelson**, None; **M. A. Carns**, None; **S. Podlusky**, None; **P. Pioli**, None; **M. Whitfield**, None.

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Abstract Number: 3176

Meta-Analysis of SSc Clinical Trials with Molecular Gene Expression Data Suggests Potential Combination Therapies

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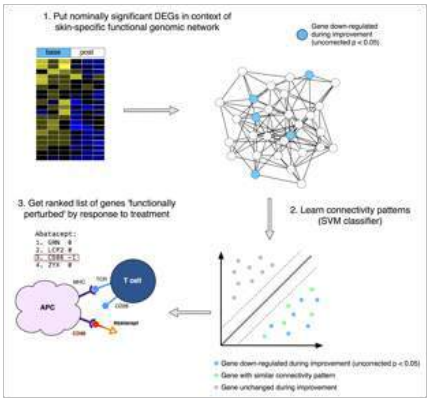
Background/Purpose: Clinical trials in SSc have tended to be underpowered and not meet clinical endpoints. Genome-wide gene expression measured in some studies can prove challenging to analyze and interpret due to the small sample sizes. Often, few differentially expressed genes can be detected pre- and post-treatment after multiple hypothesis testing correction. Here, we have leveraged data from thousands of experiments and utilized state-of-the-art machine learning to robustly identify genes and processes that are predicted to be modulated during clinically significant response to treatment and view the processes modulated in each through the lens of a functional genomic network.

Methods: We analyzed immunomodulatory therapeutics: **abatacept** (Chakravarty et al., 2015) (CTLA4-IgG), **MMF** (Hinchcliff et al., 2013; Mahoney et al., 2015), and **rituximab** (Lafyatis et al., 2009; Pendergrass et al., 2012) (anti-CD20), as well as a tyrosine kinase inhibitor (TKI): **nilotinib** (Gordon et al., 2015), and a monoclonal antibody to the pro-fibrotic cytokine TGF-β: **fresolimumab** (Rice et al., 2015). We applied a common improvement criterion to each study: -20% *OR* -5 modified Rodnan Skin Score (mRSS) (Khanna et al., 2006). Nominally significant genes that changed in each trial were placed in the context of a skin-specific functional genomic network and their connectivity patterns learned using a support vector machine (SVM) (Greene et al., 2015) (Figure 1).

Results: Our machine learning approach captures features beyond differential expression and is better at identifying predicted gene targets of each therapy than the t-statistic alone**.** As an example, *CD86* is captured when abatacept is analyzed due to its connectivity in the network, although the gene itself is not differentially expressed. We observe the abrogation of inflammatory pathways in improvers in multiple studies regardless of the mechanism of action of a drug, which suggests high expression of immune-related genes may represent an active disease state. The framework allows us to compare different trials and ask if the patients that failed one therapy could possibly improve on a different therapy. As an example, we find that genes with high expression at baseline in fresolimumab non-improvers were downregulated in MMF improvers, suggesting that these patients might have benefited from the combination therapy.

Conclusion: This work provides a systems biology framework for analysis of therapeutic trials in rare diseases and for prediction of potentially beneficial treatment combinations. Our results suggest that if a strong inflammatory signature is present in a patient it may need to be treated with an immunosuppressive treatment, but that this may show more efficacy if paired with an anti-fibrotic drug such as anti-TGF-β therapy, especially for patients with a weak baseline inflammatory signature.



Disclosure: J. N. Taroni, None; **V. Martyanov**, None; **M. L. Whitfield**, Gene expression biomarkers in SSc, 9,Celdara Medical LLC, 4.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/meta-analysis-of-ssc-clinical-trials-with-molecular-gene-expression-data-suggests-potential-combination-therapies

Abstract Number: 3177

Targeted Nuclear Imaging for the Early Detection of Lung Involvement in Systemic Sclerosis

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Session Time: 9:00AM-10:30AM

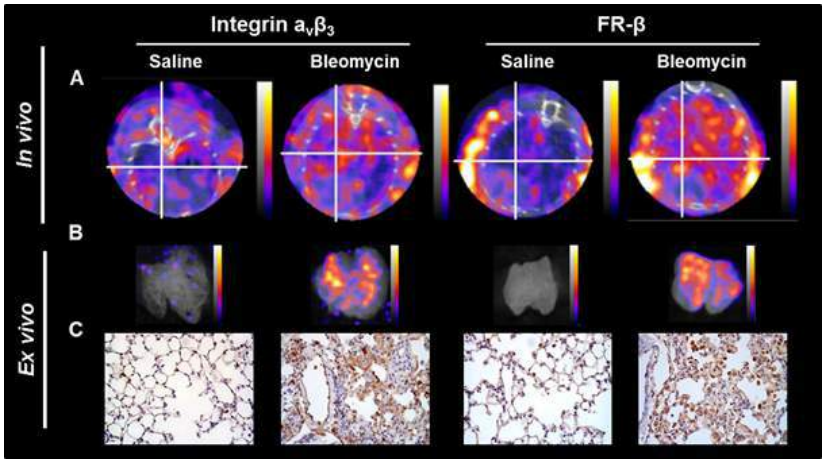
Background/Purpose: Interstitial lung disease (ILD) is one of the main causes of systemic sclerosis (SSc)-related deaths. Since routine diagnostics such as high resolution computed tomography and pulmonary function tests often only detect ILD at disease stages with already impaired organ function and/or damage, there is an unmet clinical need for the non-invasive diagnosis of ILD at earliest, still reversible stages. Here, we assessed new radiotracers for the detection of SSc-ILD specifically targeting integrin $\alpha_v\beta_3$ and folate receptor β (FR-β) as molecular players of inflammation and inflammation-dependent fibrosis in the murine model of bleomycin-induced lung fibrosis.

Methods: Expression of integrin $\alpha_v\beta_3$ and FR-β was analyzed in lung sections from patients with SSc-ILD, idiopathic pulmonary fibrosis (IPF) (n=5-6), healthy controls (n=4-5) as well as from bleomycin-treated mice and respective controls (n=6) using immunohistochemistry. *In vivo* imaging was performed using a RGD peptide derivative and a folate derivative radiolabeled with the gamma-radiation emitting radionuclide Lutetium-177 (^{177}Lu). SPECT (single photon emission computed tomography) was performed using a dedicated small-animal SPECT/CT scanner. Animals were scanned at day 7 after intratracheal installation of bleomycin to visualize pulmonary inflammation and incipient fibrosis. The specific pulmonary accumulation of the radiotracer was confirmed by *ex vivo* SPECT/CT, biodistribution, and autoradiography studies.

Results: In lung sections of patients with SSc-ILD and IPF, the expression of integrin $\alpha_v\beta_3$ was significantly increased compared to healthy controls ($p<0.009$, $p<0.02$). In contrast, FR-β expression was only significantly upregulated in lungs from SSc-ILD

($p<0.04$), but not in IPF patients. In line with the results obtained in SSc-ILD, lungs of bleomycin-treated mice, but not of controls showed a significant increase in integrin $\alpha_v\beta_3$ expression and FR-β expression ($p<0.03$. $p<0.05$, Fig. C). Notably, at day 7 after intratracheal installation of bleomycin, SPECT/CT with ^{177}Lu-RGD targeting integrin $\alpha_v\beta_3$, successfully visualized pulmonary inflammation and incipient fibrosis in the model of bleomycin-induced lung fibrosis. Similarly, SPECT/CT of FR-β showed a higher pulmonary uptake of the ^{177}Lu-folate radiotracer in bleomycin-treated mice than in controls (Fig. A). *Ex vivo* SPECT/CT, biodistribution and autoradiography studies confirmed the *in vivo* results and validated the specific uptake of both radiotracers in lungs from bleomycin-challenged mice as compared to controls (Fig. B).

Conclusion: The here presented data provide evidence that targeting molecular players of inflammation and inflammation-dependent fibrosis using nuclear imaging methods may lead to a novel promising non-invasive approach for the early detection of lung involvement in SSc.



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Abstract Number: 3178

Heart Dysfunction in Systemic Sclerosis: Involvement of a Novel Fibrogenic Stromal Cell Subset

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SESSION INFORMATION

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Session Title: Systemic Sclerosis, Fibrosing Syndromes and Raynaud's – Pathogenesis, Animal Models and Genetics II

Session Type: ACR Concurrent Abstract Session

Session Time: 9:00AM-10:30AM

Background/Purpose: Cardiac dysfunction is a significant cause of the high mortality in systemic sclerosis (SSc). Heart involvement in SSc patients resembles inflammatory dilated cardiomyopathy (iDCM) with inflammation and fibrosis. Myofibroblasts are the main players in cardiac fibrogenesis, but their origin remains unknown. Here, we aim to determine the role of specific myocardial stromal cell subsets in myocardial remodeling in SSc.

Methods: The Fos-related antigen 2 (Fra2) tg mouse model of SSc/iDCM was studied. Immunohistochemistry (IHC) and immunofluorescence (IF) were performed on endomyocardial biopsies (EMBs) from SSc/iDCM patients (n=10) and on hearts from Fra2 tg mice (n=5). Flow cytometry analysis was used to identify different subsets of myocardial stromal cells that were sorted, cultured and stimulated with TGFβ1. The differentiation potential was assessed by qPCR, IF, stress fiber staining, SIRCOL and contraction assay on sorted cells. Proliferation and apoptosis were assessed by BrdU incorporation and caspase 3/7 detection. The antisense oligonucleotide GapmeR was used to downregulate Fra2

Results: Fra2 tg mice showed increased $CD45^+$leukocyte infiltrates and massive collagen deposition in the heart tissue similarly to the myocardium of SSc/iDCM patients. Moreover, the myocardium of Fra2 tg mice revealed increased expression of pro-fibrotic markers such as αSMA, vimentin, collagen I and fibronectin compared to wild type mice. Among cardiac stromal cells ($Ter119^-CD45^-CD31^-Sca1^+CD29^+$) four specific stromal cell subsets were identified: $gp38^+CD90.2^-$, $gp38^+CD90.2^+$, $gp38^-CD90.2^+$ and $gp38^-CD90.2^-$. The frequency of $gp38^+CD90.2^-$ (single positive) cells and $gp38^+CD90.2^+$(double positive) cells was significantly higher in Fra2 myocardium compared to control mice (p= 0.009; n=11). Importantly, in the myocardium of Fra2 tg mice, the majority of $gp38^+$ cells co-expressed αSMA, vimentin, collagen and fibronectin, indicating that myocardial $gp38^+$stromal cells might proliferate and/or differentiate towards the myofibroblast phenotype. Myocardial single and double positive stromal cells were cultured *in vitro*. After TGFβ1 stimulation, both cell subsets up-regulated αSMA mRNA levels. Importantly, $gp38^+$stromal cells from Fra2 tg mice showed the presence of αSMA fibers and stress fibers, as well as a stronger contraction capability even without TGFβ1 stimulation. In addition, apoptosis and proliferation were increased in Fra2 cells compared to wild-type cells. These findings indicate that Fra2 overexpression might trigger the differentiation of these cells. Accordingly, Fra2 silencing resulted in a decreased differentiation capability of $gp38^+$stromal cells: mRNA levels of the pro-fibrotic genes αSMA and collagen I were significantly downregulated (p=0.0075 and p=0.0073; n=5). Moreover, Fra2 downregulation impaired the secretion of collagens and the formation of αSMA fibers

Conclusion: Cardiac $gp38^+$ stromal cells might serve as a cellular source of pathological myofibroblasts playing a pivotal role in TGFβ/Fra2-driven myocardial remodeling in SSc. A better understanding of the mechanisms triggering myocardial dysfunction in SSc might be helpful in developing effective therapies

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Abstract Number: 3179

Scale Structure and Measurement Properties of a Disease Specific Patient-Reported Outcome for Anti-Neutrophil Cytoplasmic Antibody-Associated Vasculitis

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SESSION INFORMATION

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Background/Purpose: ANCA-associated vasculitis (AAV) is an organ- and life-threatening disease. Patients present with active disease, followed by periods of remission and flare, and have impairments in mental and physical wellbeing due to disease and treatment. An international team has developed a disease- specific patient- reported outcome measure: the AAV-PRO, supported by a steering group, including four patient partners, in collaboration with the Outcome Measures in Rheumatology (OMERACT) Vasculitis Working group. Candidate questionnaire items were produced following in-depth qualitative research in the UK, US, and Canada plus cognitive interviews, extensive piloting and independent linguistic and translatability assessment.

Methods: Patients with AAV were recruited from Vasculitis UK, and the Vasculitis Patient-Powered Research Network, US. Patients completed the 35 candidate questionnaire items, plus information about their disease, at baseline and three months (included transition item charting change). Paper copies were used in the UK and an electronic online version in the US. UK patients also completed the Euro-Qol-5D (EQ-5D-5L). In the US, a test-retest exercise was completed 3-5 days following baseline. Exploratory factor analysis (EFA) and Rasch analysis defined the underlying scale (domain) structure. The following properties were determined for each domain: convergent validity, using Pearson correlations between domain scores and the EQ-5D-5L; known groups validity, using t-tests to compare mean scores for different disease states; test-retest reliability, analysing intraclass correlation coefficients (ICC), with respondents reporting “no change”; and longitudinal construct validity, analysing mean change scores and effect sizes in relation to transition item responses at three months.

Results: The survey included 626 patients with AAV**,** mean age 59.9 years (standard deviation (SD) 13.9), 29% reported current “active disease” and 43% a flare within the last 2 years. EFA and Rasch analysis supported a 29-item profile measure comprising 6 domains: “Organ-Specific Symptoms”, “Systemic Symptoms”, “Treatment Side Effects”, “Social and Emotional Impact”, “Concerns about the Future”, and “Physical Function”. Domains individually fitted the Rasch model (no significant item-trait interaction at the 1% level) and had good internal consistency (Cronbach’s alphas 0.73 to 0.93). Mean AAV-PRO domain scores were all higher for patients reporting “active disease” versus “remission” (all $p<0.001$). Correlations between domain scores and the EQ-5D-5L index ranged from r0.55 to r-0.78. In respondents reporting “no change” (n=97), ICC values were high (range 0.89 to 0.96) for comparisons of each domain’s 3-5 day test re-test scores. Comparison of mean score changes and effect sizes (ES) for each domain demonstrated stable scores in those reporting “no change” and appropriate positive and negative changes in “much better” or “much worse” disease.

Conclusion: The AAV-PRO, a new disease-specific PRO measure for use in ANCA-associated vasculitis, has good face, content, and construct validity, is reliable, feasible, and discriminates among disease states of importance.

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Abstract Number: 3180

Utility of Measurements of Urinary Soluble CD163 & MCP-1 in the Identification of Subtle Renal Flares in ANCA-Associated Vasculitis

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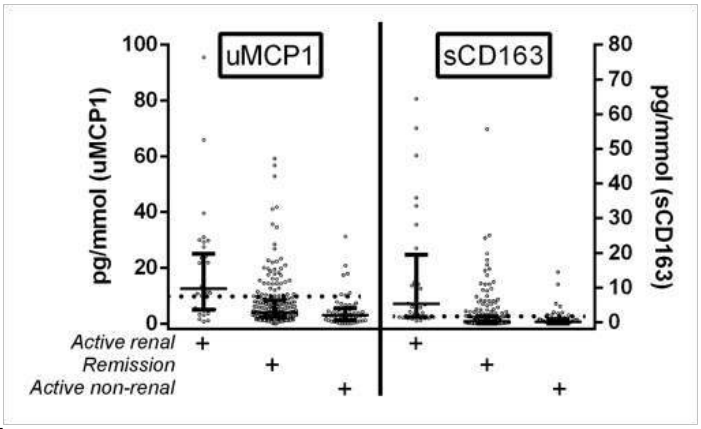
Background/Purpose: Prior work has shown that urinary soluble CD163 (usCD163) displays excellent biomarker characteristics for detection of active renal vasculitis using samples from patients with new diagnoses of ANCA-associated vasculitis (AAV) and highly active renal disease. This study focused on use of usCD163 in detection of the more clinically relevant state of mild renal flare, and to compare the performance of usCD163 directly to another proposed biomarker, urinary monocyte chemoattractant protein 1 (uMCP-1).

Methods: Patients with samples obtained during active AAV (n=88) with evidence of active renal involvement (n=34) or without current renal involvement (n=54) were identified within a serially-sampled longitudinal multi-center cohort. In addition, paired remission samples and samples from those with remission AAV were also identified. Creatinine-normalized usCD163 and uMCP-1 levels were measured simultaneously by ELISA. usCD163 and uMCP-1 levels during a flare of active renal vasculitis were compared to levels during remission or during active non-renal AAV.

Results: Samples were available from 320 study visits including times of active renal vasculitis (n=34), remission (n=278), and active extra-renal vasculitis (n=54). Mean creatinine levels in remission and during renal flare were 1.01 mg/dl (SD 0.47) and 1.43 mg/dl (SD 0.61), respectively. usCD163 levels were higher in patients with active renal vasculitis compared with patients in remission and those with active extra-renal vasculitis, with median values of 5.2 pg/mmol (interquartile range (IQR) 1.5-19.4pg/mmol), 0.8pg/mmol (0.1-2.5pg/mmol) and 0.6pg/mmol (0.1-1.6 pg/mmol), respectively ($p<0.001$). uMCP-1 levels were also higher in patients with active renal vasculitis compared with patients in remission and those with active extra-renal vasculitis, with median values of 12.6pg/mmol (IQR 5.1-25.1), 2.4pg/mmol (4.1-8.5) and 3.1pg/mmol (1.2-5.5), respectively ($p<0.001$, Figure 1). The optimal diagnostic cut-offs for usCD163 and uMCP-1 were 1.2pg/mmol and 10.0pg/mmol, respectively. Using these cut-offs, the specificities of usCD163 and uMCP-1 in identifying renal vasculitis flare were 91% and 80%, respectively. Specificities were the same whether comparison was made to remission or to active non-renal AAV. The corresponding sensitivities with these cut-offs were 68% and 64%. The addition of uMCP-1 to usCD163 did not further increase the specificity. usCD163 and uMCP-1 levels were moderately correlated ($r^2 = 0.36$, $p<0.001$), suggesting that additional information may be obtained from sequential modelling that incorporates traditional biomarkers.

Conclusion: In the context of subtle renal vasculitis flare, both usCD163 and uMCP1 levels are tightly associated with active renal disease in AAV. **Figure 1. Urinary sCD163 and MCP-1 levels in ANCA-associated vasculitis, stratified by disease activity**



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Abstract Number: 3181

The Utility of Urinalysis in Determining the Risk of Renal Relapse in ANCA-Associated Vasculitis

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Background/Purpose: The significance of persistent hematuria or proteinuria in patients with ANCA-associated vasculitis (AAV)

who are in clinical remission is still unclear. This study examined the utility of urinalysis in predicting renal relapse in AAV.

Methods: Participants enrolled in the Wegener's Granulomatosis Etanercept Trial (WGET) and the Rituximab in ANCA-Associated Vasculitis (RAVE) trial who had active glomerulonephritis due to AAV, positive ANCA, and achieved remission by month 6 were included. Exposures included persistent hematuria (or proteinuria) for the first 6 months from enrollment after onset of active renal disease and cumulative hematuria (or proteinuria) as a time-varying covariate. Renal relapse was defined as new or worsening RBC casts and/or rise in serum creatinine according to the Birmingham Vasculitis Activity Score for Wegener's Granulomatosis (BVAS/WG). In RAVE only, the relationship between worsening levels of hematuria and renal relapse was evaluated. Competing risk regression was used to examine renal relapse (with non-renal relapse and end-stage renal disease as competing events); results were expressed as subdistribution hazard ratios (sHR). All models adjusted for study, ANCA type, baseline serum creatinine, and pulmonary involvement.

Results: There were 149 patients included: 42% had persistent hematuria and 43% had persistent proteinuria beyond 6 months (**Table 1**). There was a significantly higher risk of relapse among patients with persistent hematuria beyond 6 months (sHR 3.99 [95% CI 1.20, 13.25], p = 0.02) (**Figure 1**) as well as with each additional month of cumulative hematuria (sHR per month 1.07 [95% CI 1.02, 1.13], p = 0.01) (**Table 2**). Persistent proteinuria was not associated with renal relapse (p = 0.53). Evaluation of changes in level of hematuria showed that an increase in hematuria level over the prior 6 months was associated with renal relapse (sHR 4.90 [95% CI 1.81, 13.27], p < 0.01) and larger changes in hematuria conferred greater risk.

Conclusion: Persistent hematuria and increasing hematuria, but not proteinuria, are associated with renal relapse among patients with AAV and recent renal disease. These findings suggest that the urinalysis may be a useful tool in predicting renal relapse in AAV.

Table 1. Characteristics of Study Population at Enrollment

	All (N = 149)	Persistent hematuria beyond 6 months		P-value
		Yes (N = 63)	No (N = 86)	
Age at baseline, years	55 (44, 66)	54 (43, 68)	55 (44, 63)	0.67
Female, %	41%	56%	30%	< 0.01
Achieved menopause (if female), %	62%	51%	77%	0.04
ANCA type by ELISA, %				0.45
Anti-PR3	68%	65%	71%	
Anti-MPO	32%	35%	29%	
Newly-diagnosed at enrollment, %	59%	57%	60%	0.68
Prior kidney involvement, %	98%	100%	94%	0.05
BVAS/WG at baseline	7 (5, 10)	8 (6, 10)	7 (4, 9)	< 0.01
VDI at baseline	0 (0, 1)	0 (0, 1)	0 (0, 1)	0.70
Serum creatinine at baseline, mg/dL	1.4 (1.1,2.3)	1.8 (1.1, 2.6)	1.3 (1, 2.2)	0.07
Renal disease at baseline, %				
Hematuria	100%	100%	100%	--
Proteinuria	74%	86%	66%	0.01
Red blood cell casts*	56%	62%	52%	0.24
Rise in serum creatinine*	50%	63%	41%	< 0.01
Duration of persistent hematuria, months	6 (3, 12)	17 (11, 26)	3 (2, 4)	< 0.01
Persistent proteinuria ≥ 6 months, %	43%	60%	31%	< 0.01
Pulmonary involvement at baseline, % Alveolar hemorrhage at baseline	60% 26%	54% 30%	65% 23%	0.17 0.44
Induction therapy, % Cyclophosphamide Rituximab	66% 34%	54% 46%	76% 24%	< 0.01

Values expressed as median (interquartile range) or percentage. *Based on BVAS/WG items.

AAV, ANCA-associated vasculitis. BVAS/WG, Birmingham Vasculitis Activity Score for Wegener's Granulomatosis. CI, confidence interval. ELISA, enzyme-linked immunosorbent assay. GPA, granulomatosis with polyangiitis. MPA, microscopic polyangiitis. PR3, proteinase-3. MPO, myeloperoxidase. VDI, Vasculitis Damage Index

Table 2. Risk of Renal Relapse in ANCA-Associated Vasculitis after Multivariate Adjustment for Duration of Hematuria and Proteinuria

Variable	sHR (95% CI)	P-value
Cumulative duration of hematuria (per month)	1.07 (1.02, 1.13)	0.01
Cumulative duration of proteinuria (per month)	1.04 (0.99, 1.08)	0.10
ANCA (PR3 vs MPO)	0.77 (0.30, 1.92)	0.57
Baseline pulmonary involvement	2.84 (0.34, 23.98)	0.34
Baseline Creatinine (per 1 mg/dL)	0.94 (0.48, 1.83)	0.85
Study (RAVE vs WGET)	0.30 (0.06, 1.64)	0.17

Cumulative duration of hematuria and proteinuria were analyzed as time-varying covariates. Hematuria-by-proteinuria interaction was not significant (p for interaction = 0.11).

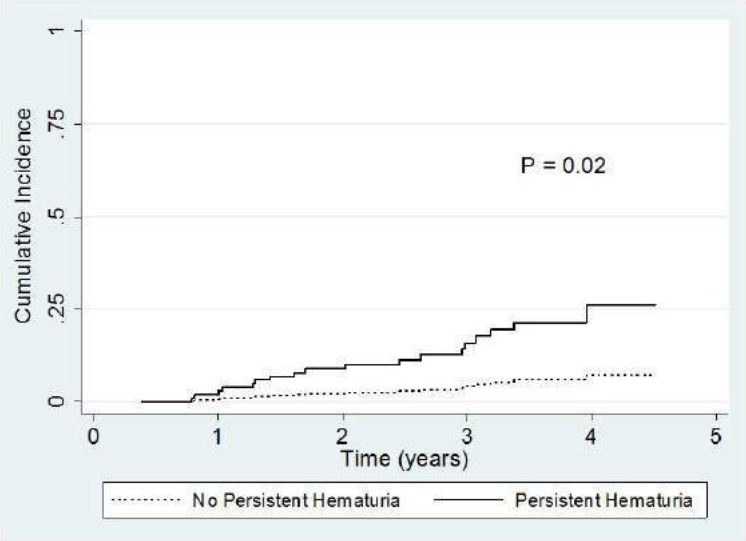
sHR, subdistribution hazard ratio. CI, confidence interval.

PR3, proteinase-3. MPO, myeloperoxidase.

WGET, Wegener's Granulomatosis Etanercept Trial.

RAVE, Rituximab in ANCA-associated Vasculitis trial.

Figure 1. Cumulative Incidence Curves for Renal Relapse in Patients With AAV With and Without Persistent Hematuria for 6 Months



Adjusted for study, ANCA type (anti-proteinase 3 vs anti-myeloperoxidase), pulmonary involvement, and baseline creatinine. Relapse without renal involvement and development of end-stage renal disease were competing events.

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Chemocentryx, 9; **E. W. St.Clair**, Eli Lilly and Company, 2,Bristol-Myers Squibb, 5,Biogen Idec, 2; **U. Specks**, Genentech, 5; **J. H. Stone**, Genentech/Roche, 2,Xencor, 2,Xencor, 5,Genentech/Roche, 5; **P. A. Merkel**, Chemocentryx, 5,Chemocentryx, 9.

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Abstract Number: 3182

Attenuation of Fluorine-18-Fluorodeoxyglucose Uptake in Large Vessel Giant Cell Arteritis after Short-Term High-Dose Steroid Treatment – a Diagnostic Window of Opportunity

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Background/Purpose: Fluorine-18-fluorodeoxyglucose (18F-FDG) PET/CT is, due to its excellent diagnostic accuracy[1], increasingly used to diagnose large vessel GCA (LV-GCA). However, PET/CT is not always readily available, which may compel the clinician to 1) either delay steroid treatment at the risk of GCA related complications, or 2) to initiate treatment at the expense of diagnostic sensitivity of the 18F-FDG PET/CT study. Therefore, evidence of a possible "18F-FDG PET/CT diagnostic window" after initiation of steroid treatment is needed.

Methods: Twenty treatment-naïve patients (14 women) with a mean age of 69 (range 56-83) years with 18F-FDG PET/CT (PET0) proven LV-GCA were randomized to repeat 18F-FDG PET/CT after either 3 (PET3, n=10) or 10 days (PET10, n=10) of treatment with oral prednisolone 60 mg daily. Prior to treatment, clinical examination and laboratory tests were performed to confirm GCA and exclude differential diagnoses. A temporal artery biopsy (TAB) was performed in all patients. An experienced nuclear medicine physician blinded to patients' clinical data reviewed the 18F-FDG PET/CT images. LV-GCA was suspected if increased 18F-FDG uptake in the wall of the aorta and/or supra-aortic branches was observed. A semiquantitative approach was applied (a.m. Meller) in which 18F-FDG uptake in 6 vascular regions (see table 1) was graded on a 5-point scale (0 = no uptake, 1 = uptake below or equal to blood pool, 2 = above blood pool but below liver, 3 = above liver, 4 = 2 times above liver). Any score ≥3 was considered consistent with vasculitis[2]. Data was either continuous or binomial. Normality was checked using QQ-plots. McNeemars and Wilcoxon signed-rank test was used to test statistical significance.

Results: Mean CRP and ESR were 77.2 (95% CI: 56.8; 97.7) mg/l and 77.3 (95% CI: 67.3; 87.3) mm/h, respectively. Fourteen of twenty patients fulfilled the ACR criteria for GCA and 13/20 had a positive TAB. Mean number of prednisolone doses before the post-therapeutic 18F-FDG PET/CT were 3.1 (95% CI: 2.9; 3.3) (PET3) and 10.2 (95% CI: 9.6; 10.8) (PET10). Vascular composite score in aorta did not decrease at PET3 whereas a significant decrease was observed in supraaortic branches at PET3 and all vascular domains at PET10 (table 1). Although, 18F-FDG uptake decreased in supra-aortic branches after 3 days, LV-GCA could still be accurately diagnosed in 10/10 patients. By contrast, LV-GCA could only be diagnosed in 5/10 patients after 10 days (PET0 vs. PET10, p=0.03).

Conclusion: In LV-GCA, high-dose steroid treatment for three or ten days differentially attenuates the regional uptake of 18F-FDG but diagnostic properties remains within the first three days. **Table 1**

Post-therapeutic LV-GCA diagnosis by 18F-FDG PET/CT

	PET3	PET10
PET positive	10/10	5/10

Median vascular composite score

	PET0	PET3	PET0	PET10
Aorta€	9 (9-9)	9 (6-9)	9 (9-9)	5 (3-6)*
Aortic branches#	6 (5-8)	4.5 (3-7)*	6.5 (6-8)	4 (3-5)*

PET positive was defined as vascular 18F-FDG uptake≥3. A vascular composite score in two different vascular domains was calculated by summarizing the grades for selected regions. Medians (interquartile range) in the two groups (PET3 or PET10, n=10 respectively) are presented. *Indicates that post-therapeutic vascular score was significantly different from pre-therapeutic score. €*Aortic: Aorta ascendens, aorta descendens and aortic arch.* #*Aortic branches: Vertebral, carotic and subclavian/axillary artery.*

References 1. Puppo et al. BioMed research international 2014;2014:574248. 2. Stellingwerff MD et al. Medicine 2015 Sep;94(37):e1542.

Disclosure: B. D. Nielsen, None; **I. Tønder Hansen**, None; **K. K. Keller**, None; **P. Therkildsen**, None; **E. M. Hauge**, None; **L. C. Gormsen**, None.

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Abstract Number: 3183

Tocilizumab for the Treatment of Giant Cell Arteritis – MR-Angiography Results from the First Randomized Placebo-Controlled Trial

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Background/Purpose: As published in The Lancet online, March 4, 2016, the first randomized, placebo-controlled trial (RCT) of tocilizumab (TCZ) in giant cell arteritis (GCA) showed clinical efficacy of the anti-IL-6 receptor biologic agent in the induction and maintenance of remission for up to 52 weeks. However, very little is known about inflammatory signals in the vessel walls of TCZ-treated patients. Therefore, the aim of this analysis was to evaluate the inflammation of the vessel wall as seen on magnetic resonance angiograms (MRAs) during the RCT and to compare the signals in the two treatment arms.

Methods: In this single-center RCT participants who satisfied the 1990 American College of Rheumatology criteria were randomly assigned in a 2:1 ratio to receive either TCZ (8 mg/kg of body weight) + glucocorticoids (GC) or placebo + GC. Participants

received infusions at 4-weekly intervals for 52 weeks, and GC were started at 1 mg/kg/d and then tapered down to zero. GCA was proven by positive temporal artery biopsy and/or assessed as large vessel vasculitis by MRA using a score 0 to 3; 0= no mural thickening (vessel wall diameter < 0.6 mm), no enhancement; 1= no thickening, slight mural enhancement; 2= mural thickening (> 0.6 mm), significant mural enhancement; 3= strong thickening (> 0.7 mm), strong mural and perivascular enhancement. Scores 2 and 3 were considered to represent active mural inflammation. The MRAs were analyzed by two experienced radiologists who were blinded to treatment allocation. If positive at inclusion, MRA was repeated after 3 month and at end of the study. The primary outcome for this analysis was the number of patients with complete remission on MRA based on the vasculitis score at week 12 (GC dose of 0.1 mg/kg/d). The secondary outcome was the number of patients with complete MRA remission at week 52 and the change in the vasculitis score.

Results: Twenty-eight of 30 randomized patients underwent baseline MRA, 20 in the TCZ + GC group and 8 in the placebo + GC group. 11 MRAs at baseline (9 in the TCZ + GC group and 2 in the placebo + GC group) had no signs of vasculitis. At week 12, MRAs were performed in 9 patients in the TCZ + GC group, all of whom were in clinical remission, and 4 patients in the placebo + GC group, 2 of whom were in remission. Three (33%) patients in the TCZ + GC group were in complete MRA remission, compared to 1 (25%) in the placebo + GC group. At week 52, there was additional improvement, but no complete remission, on MRA in 3 participants in the TCZ + GC group, resulting in a median change in the vasculitis score of -1.0, and no improvement in the remaining 2 participants in the placebo + GC group, resulting in a median change in the vasculitis score of -0.5.

Conclusion: TCZ induces and sustains clinical remission of GCA but does not completely suppress MR signals of vessel inflammation. Whether these signals are of prognostic importance remains to be determined and should be further evaluated in long-term studies.

Disclosure: S. Reichenbach, None; **S. Adler**, None; **J. Cullmann**, None; **H. Bonel**, None; **S. Kuchen**, None; **F. Wermelinger**, None; **D. Dan**, None; **M. Seitz**, None; **P. M. Villiger**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/tocilizumab-for-the-treatment-of-giant-cell-arteritis-mr-angiography-results-from-the-first-randomized-placebo-controlled-trial

Abstract Number: 3184

Antiphospoholipid Antibodies in Giant Cell Arteritis. What Can They Tell Us?

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Background/Purpose: The aim of our prospective study was to evaluate the potential impact of the antiphospholipid antibodies (aPL-Abs) on the clinical presentation of giant cell arteritis (GCA).

Methods: GCA patients diagnosed for the first time between 1 September 2011 and 30 April 2016 at our secondary/tertiary rheumatology center and in whom aPL-Abs were determined at presentation were included. Three types of aPL-Abs were studied in the patients' sera: anticardiolipin antibodies (aCL; IgG and IgM isotype), antibodies to β2-glycoprotein 1 (aβ2GP1; IgG, IgM and IgA isotypes) and lupus anticoagulants (LA). The patients were stratified according to the number of positive aPL-Abs tests into three groups: without aPL-Abs, those with a single aPL-Ab and those with two or more aPL-Abs. Medical records of GCA cases were analyzed and data compared between the three groups.

Results: During the 56-month observation period we performed aPL-Abs tests in 97/115 GCA patients (67 (69%) females, median (IQR) age 73.3 (67.2; 78.2) years). aCL, aβ2GP1 and LA were present in 47 (48%), 17 (18%) and 44 (45%) cases, respectively. 39 (40%) patients had single aPL-Ab, 28% had two and 5% had three aPL-Abs. aPL-Abs were not detected in 26 (27%) patients. Characteristics of aPL-Abs negative vs. positive (single and double or triple) groups are presented in Table 1. GCA patients with at least two aPL-Abs had more commonly had severe visual manifestations (transient and permanent visual loss) at presentation (100% vs. 22% of all visual disturbances; p=0.021), as well as symptoms (19% vs. 0%, p=0.029) and ultrasonographic signs of

large vessel vasculitis (62% vs. 33%, p=0.054) than those without aPL-Abs. At least 1 year follow-up data (median (IQR) 101 (50.4; 104.4) weeks) were available in 71 patients. 35 (49%) patients relapsed during follow-up and relapses were not associated with the aPL-Abs positivity at presentation in our group.

Table 1. GCA and aPL-Abs	*aPL-Abs* *(number of patients)*		
Clinical characteristics	*aPL negative*	*single positive*	*double or triple positive*
N	26	39	32
Gender (F) (%)	57.7	66.7	81.3
Age (years; median, IQR)	73.6 (68.7; 78.8)	75.1 (67.3; 78.5)	70.9 (66.4; 77.2)
Smoking (%)	38.5	38.5	43.8
General symptoms (%)	73.1	71.8	78.1
Fever (≥38◦C) (%)	23.1	23.1	28.1
Weight loss (%)	53.8	53.8	71.9
Rheumatic polymyalgia	23.1	15.4	12.5
Headache (%)	69.2	74.4	62.5
Jaw claudication (%)	38.5	46.2	37.5
Visual disturbances (%)	34.6	30.8	15.6
TVL or PVL (%)	**7.7 (22.2*)**	**10.3 (33.3*)**	**15.6 (100.0*)**
Stroke (%)	0	2.6	3.1
Dry cough (%)	**15.4**	**23.1**	**37.5**
Clin. changed TA (%)	53.8	74.4	53.1
TAB (%)	81.0	80.0	88.0
CDS TA (%)	84.6	79.5	68.8
LVV – clinically. (%)	**0**	**12.8**	**18.8**
LVV - CDS (%)	**33.3**	**56.8**	**62.1**
ESR (median, IQR)	88 (66; 95)	85 (64; 113)	95 (75; 109)
CRP (median, IQR)	66 (49; 116)	76 (48; 129)	75 (54; 127)
Patients with a relapse during follow up (%)	55.0	43.3	52.4
Legend: aPL-Ab antiphospholipid antibody; F female; TVL transient visual loss (amaurosis fugax); PVL permanent visual loss; * % of those with visual disturbances; TA temporal artery; TAB temporal artery biopsy; CDS color Doppler sonography; LVV large vessel vasculitis; ESR erythrocyte sedimentation rate; CRP C-reactive protein;			

Conclusion: Our results indicate that aPL-Abs could identify a subgroup of GCA patients with severe visual manifestations and extracranial large vessel disease.

Disclosure: A. Hocevar, None; **R. Jese**, None; **Z. Rotar**, None; **P. Žigon**, None; **S. Čučnik**, None; **M. Tomšič**, None.

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Abstract Number: 3185

Sensitivity Analysis for the Smoking Paradox in the Development of Psoriatic Arthritis Among Psoriasis Patients

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Background/Purpose: Smoking is a strong risk factor for psoriasis and psoriatic arthritis, but several studies have found that smoking is inversely associated with the risk of psoriatic arthritis (PsA) among psoriasis (PsO) patients. These paradoxical findings may occur due to index event bias (a selection bias also called collider bias) that arises from selecting a group of patients (e.g., PsO) on the causal pathway (e.g., between smoking and PsA), such that the total effect of smoking on risk of PsA among PsO patients cannot be appropriately assessed using conventional methods. Moreover, the obtained direct effect (i.e., effect of smoking on the risk of PsA not through PsO) may also be biased. We sought to confirm the paradox in a substantially larger sample and conduct sensitivity analyses to quantify the potential bias on the direct effect estimate.

Methods: We used 1995-2015 data from The Health Improvement Network (THIN), an electronic medical record database representative of the UK general population. We analyzed data from adults free of PsA after at least 1 year of enrollment into THIN, and with data on factors of interest. Follow-up began with the first record of smoking status (exposure) after the enrollment period and ended at the time of PsA diagnosis, death, loss to follow-up, or the end of the study, whichever came first. Using Cox regression, we assessed the effect of smoking on incident PsA in the general THIN population and then in patients with PsO. We conducted a "bias sensitivity analysis" for a range of possible relative risks for the association between smoking and potential unmeasured confounders "U" (e.g., genetic factors) and that between U and PsA. Analyses were adjusted for baseline confounders.

Results: There were over 6.6 million subjects without PsA at baseline (mean age 42 years; 53% female; 28% current smokers, and 16% ex-smokers). Of those, 88,469 developed incident PsO, among whom 1,708 developed incident PsA. The adjusted hazard ratio (HR) of smoking for the risk of PsA among PsO patients was 0.79 (95%CI: 0.69, 0.91), but the corresponding HR for PsA in the general THIN population was 1.27 (95%CI: 1.19, 1.36) (**Table**). Results from the bias sensitivity analysis indicated that if the association between U and smoking and that between U and PsA were as low as a relative risk (RR) of 1.8 and 1.9, respectively, then it could nullify a biased protective effect (RR=0.8) **(Figure)**.

Conclusion: This large cohort study confirms that conditioning on PsO can reverse the true association between smoking and PsA. Such index event bias can produce a misleading estimate of the impact of modifiable risk factors. We suggest that investigators perform sensitivity analyses to assess how sensitive the observed effect estimate is to unmeasured confounding and its associated index event bias.

Table. Association between Smoking and Psoriatic Arthritis in the General Population and among PsO Patients

	Non-Smokers	Ex-smokers	Current Smokers
General THIN Population	3,759,554	1,035,203	1,856,542
Number of PsA	3699	1178	2180
Total Follow-up Years	26,961,014	6,599,380	12,964,215
PsA Incidence Rate (1/1000 person-year)	0.14	0.18	0.17
Crude HR (95% CI)	1.0	1.32 (1.24, 1.41)	1.23 (1.17, 1.30)
Adjusted HR* (95% CI)	1.0	1.32 (1.22, 1.43)	1.27 (1.19, 1.36)
Among PsO Patients	37,101	24,646	26,722
Number of PsA	808	457	443
Total Follow-up Years	236,657	133,102	170,186
PsA Incidence Rate (1/1000 person-year)	3.41	3.43	2.6
Crude HR (95% CI)	1.0	0.97 (0.86, 1.09)	0.76 (0.68, 0.86)
Adjusted HR* (95% CI)	1.0	1.04 (0.91, 1.19)	0.79 (0.69, 0.91)

*Adjusted for age, alcohol, BMI, sex, and trauma.

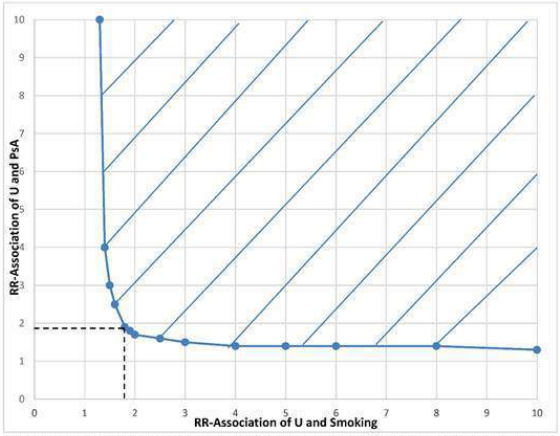

Figure. Sensitivity Analysis of Uncontrolled Confounders Contributing to the Index Event Bias behind the Association between Smoking and the Risk of PsA among PsO Patients. The areas above the curved line are the joint values of the RR of the U-smoking association and the RR of the U-PsA association for unbiased RR > 1.0 for the direct effect of smoking and PsA among PsO patients.

Disclosure: U. S. D. T. Nguyen, None; **Y. Zhang**, None; **D. T. Felson**, None; **M. P. Lavalley**, None; **H. K. Choi**, None.

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Abstract Number: 3186

Determinants of Patient-Physician Discordance in Global Assessment in Psoriatic Arthritis and Levels of Discordance According to Disease Activity: A Multicenter European Study

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Background/Purpose: In the management of chronic diseases, recommendations insist on the need to work in partnership with the patient. Patient-physician discordance in global assessment of disease activity is frequent but what does it reflect? The objectives of this study were to assess patient-physician discordance in global assessment in psoriatic arthritis (PsA), predictors of discordance (including patient reported domains of health) and the frequency of discordance according to disease activity levels.

Methods: The PsAID cross-sectional multicenter European study of patients with PsA according to expert opinion was analysed. Patient- and Physician-Global Assessment (PGA and PhGA) were rated with a 0-10 numeric rating scale. Discordance was defined as the difference (PGA–PhGA) and as the absolute difference |PGA-PhGA|≥3 points in the whole population and according to Disease Activity index for PSoriatic Arthritis (DAPSA) levels. Determinants of (PGA-PhGA) were assessed by a stepwise multivariate linear regression among 12 physical and psychological aspects of impact (pain, skin problems, fatigue, ability to work/leisure, functional incapacity, feeling of discomfort, sleep disturbance, anxiety/fear, coping, embarrassment/shame, social participation and depressive affects). A sensitivity analysis was also performed with a logistic regression model using the binary variable |PGA-PhGA|≥3 as outcome. There was no imputation of missing data.

Results: In 460 patients (mean age 50.6±12.9 years, 52.2% female, mean disease duration 9.5±9.5 years, mean DAPSA 30.8±32.4), mean PGA was higher than mean PhGA with a mean absolute difference of 1.9±1.8 points. Discordance defined by |PGA-PhGA|≥3 points concerned 134 (29.1%) patients and 115 (85.8% of patients with discordance) had PGA>PhGA. Higher fatigue (β=0.14), lower self-perceived coping (β=0.23) and impaired social participation (β=0.16) were independently associated with a higher difference (PGA-PhGA). The sensitivity analysis using |PGA-PhGA|≥3 as outcome shows that coping (OR=1.34, impaired social participation (OR=1.28) and depressive affects (OR=1.18) were related with discordance. According to DAPSA, more patients with discordance were in remission (30.8%) compared to high disease activity (26.1%).

Conclusion: Discordance concerned 29.1% of these PsA patients, which is less frequent than in rheumatoid arthritis (around 43%). Mean PGA was higher than mean PhGA. Factors associated with discordance were psychological rather than physical domains of health. Unlike most published articles on patient-physician discordance in RA, pain was not a predictive factor in this study, perhaps due to links with other outcomes. The patient's ability to self-manage seems to be important. Discordance was more frequent in patients in remission, indicating the meaning of remission should be further explored in PsA.

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Abstract Number: 3187

Societal Costs and Patients' Experience of Health Inequities from Psoriatic Arthritis: A Danish Cohort Study

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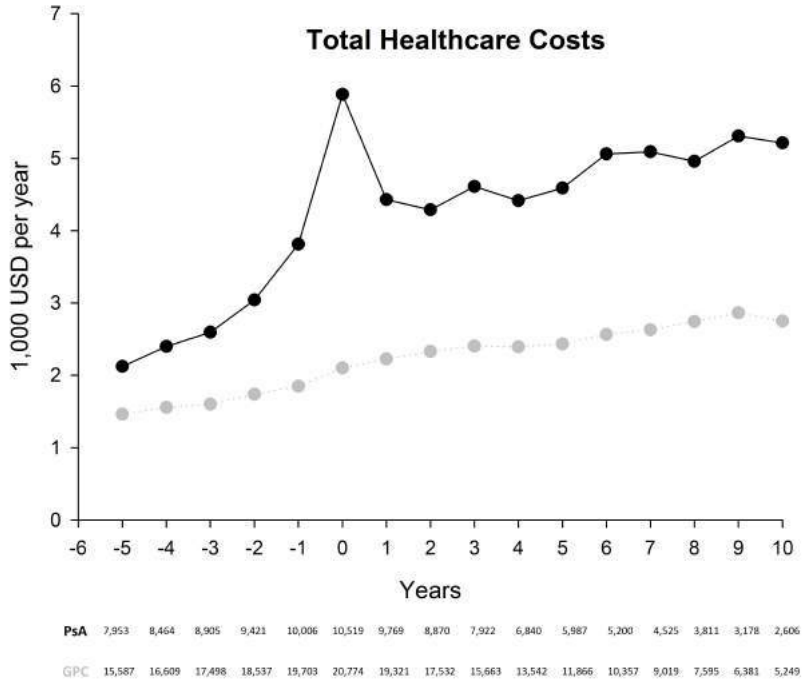
Background/Purpose: Psoriatic arthritis (PsA), a chronic inflammatory joint disorder typically affecting individuals with psoriasis of the skin, is associated with severe comorbidities, reduced quality of life, and increased work disability. Our study is the first to comprehensively examine PsA's comorbidties, healthcare and public transfer (allowance) costs.

Methods: A total of 10,525 PsA patients and 20,777 matched general population comparator (GPC) subjects were included in this nationwide cohort study, using data from Danish registries from January 1998 through December 2014. Societal costs, employment status, and occurrence of comorbidities in patients with PsA both before and after diagnosis were compared to GPC subjects matched on age, sex, time, and marital status.

Results: Median age of PsA patients and general population comparator subjects at study entry was 52 years (interquartile range 40 to 60 years), 41% were male. At baseline, PsA patients had significantly more comorbidities, including neoplasms (OR 1.25 95% CI 1.11 to 1.41), cardiovascular disease (OR 1.70 95% CI 1.55 to 1.86), respiratory diseases (OR 1.73 95% CI 1.54 to 1.96), infectious diseases (OR 2.03 95% CI 1.69 to 2.42), and haematological diseases (OR 1.94 95% CI 1.55 to 2.43) compared to GPC subjects. At all time-points, PsA patients had higher total healthcare costs (Figure) and public transfer costs; they also had lower income ($p<0.001$) and incurred a net average increased societal cost of 12,024 USD per patient year compared to GPC subjects following diagnosis. The relative risk (RR) for being on disability pension five years prior to PsA diagnosis was 1.36 (95% CI 1.24 to 1.49) compared to GPC subjects. The RR increased to 1.60 (95% CI 1.49 to 1.72) at the time of diagnosis and was 2.69 (95% CI 2.40 to 3.02) 10 years after diagnosis, where 21.8% of the PsA patients received disability pension.

Conclusion: The study not only demonstrates increased healthcare costs, lower income, higher unemployment rates, higher risk for disability pension, but also more comorbidities for PsA patients compared to the general population in the period prior to diagnosis. The study also clearly demonstrates attenuated socioeconomic burden as well as increased comorbidities in the years following a PsA diagnosis. **Figure**



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Abstract Number: 3188

Association of Gout with Risk of Advanced Chronic Kidney Disease

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Background/Purpose: It is speculated that gout is a risk factor for kidney disease progression. The aim of this study was to evaluate the association of gout with progression to advanced chronic kidney disease (CKD) in a national study.

Methods: This cohort study used primary care data from the UK Clinical Practice Research Datalink linked to national data on hospitalisation and mortality. From 1/01/2000 to 31/03/2013, each adult case of gout (≥18 years), based on clinical diagnosis or treatment with a urate lowering agent, was matched with up to 10 controls without gout on age, sex, and registered clinical practice. The median follow-up was 3.68 years (interquartile range 1.65-7.04 years). The incidence of advanced CKD (a composite outcome defined as progression to dialysis, kidney transplant, diagnosis of CKD stage 5 or eGFR < 10ml/min, death with CKD, or doubling of the serum creatinine) was estimated and relative risk of advanced CKD was compared in 68,897 gout patients and 554,964 matched controls. Multivariable Cox regression using marginal structural models and propensity-matching methods estimated hazard ratios (HRs) and 95% confidence intervals (CI) for the rate of advanced CKD. Analyses were adjusted for baseline demographic characteristics, 12 individual medical conditions including mild-moderate kidney disease, Charlston comorbidity index, lifestyle factors (drug use and alcohol use), socioeconomic status (Townsend score) and medication use (defined as treatment with NSAID, oral corticosteroid, angiotensin receptor blocker, angiotensin converting enzyme inhibitor, thiazide diuretic, other diuretic, statin, or aspirin).

Results: Accounting for baseline differences, patients with gout experienced significantly higher risk of advanced CKD (HR 1.29, 95 % CI (1.23-1.35) compared with those without gout (HR, 1.00 referent group). The findings were similar in the propensity-matched analysis (HR 1.23, 95% CI 1.17-1.29).

	Gout Cases (n=68,897)	95% CI	**Controls** (n=554,964)	95% CI
Incidence rate of advanced CKD per 1000 person-years	8.54	(8.26-8.83)	4.08	(4.00-4.16)
Incidence rate ratio	2.10	(2.07-2.12)	1.00 (reference)	
Adjusted hazard ratio (64,726 cases vs 489,842 controls)	1.29*	(1.23-1.35)	1.00 (reference)	
	Propensity-matched Gout Cases (n=64,420)		**Propensity-matched Controls** (n=286,110)	
Incidence rate of advanced CKD per 1000 person-years	7.58	(7.30-7.86)	4.43	(4.32-4.55)
Incidence rate ratio	1.71	(1.69-1.73)	1.00 (reference)	
Adjusted hazard ratio (60,339 cases vs 259,815 controls)	1.23*	(1.17-1.29)	1.00 (reference)	

*P < 0.001 for all

Conclusion: Gout is associated with an elevated risk of progression to advanced CKD. Future studies should investigate whether control of gout is protective and reduces future CKD risk.

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Patient Perceptions of Glucocorticoid Side Effects: A Survey of Users in an Online Health Community

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Background/Purpose: Glucocorticoids (GC) are widely used to treat inflammatory diseases, but are known to have many side effects. Patients' perspectives of side effects are known to influence treatment decisions and adherence, yet few studies have investigated which side effects are important to patients. The aim of this study was to identify the side effects most important to GC users through a survey of a UK online health community (healthunlocked.com).

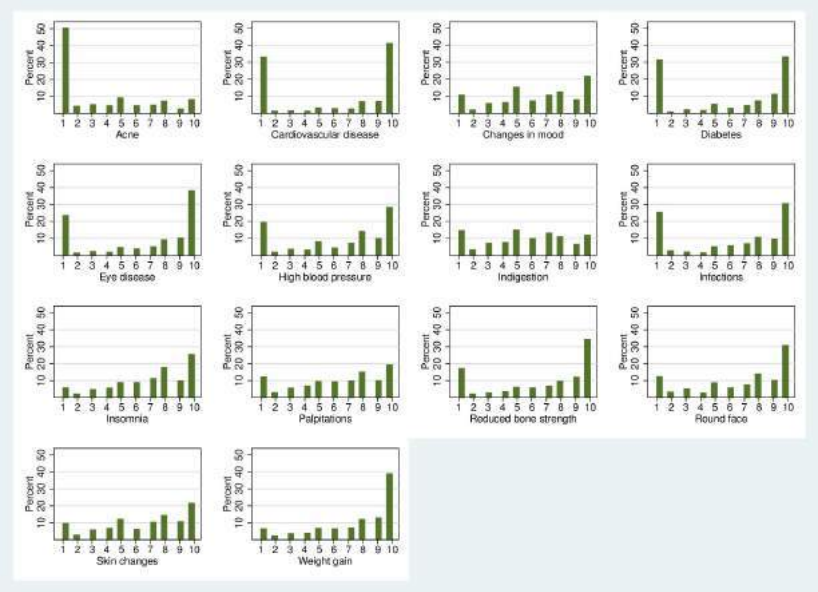
Methods: A short survey about GC use popped up when UK users viewed posts discussing steroids on healthunlocked.com. Responders were eligible if they were currently taking, or had taken GCs within the last month. Within the survey, responders had to score the importance of listed side effects from 1 to 10, with 10 being of high importance to them. The side effects shown in table 1 were listed alphabetically, with examples or descriptions as required. For each side effect, histograms were plotted, and the median rating and inter-quartile range (IQR) was determined. Side effects were ranked by median ranking (largest to smallest) and then IQR (smallest to largest) for those with the same median. The scores were categorised as low (scores 1-3), medium (scores 4-7) and high (scores 8-10) importance.

Results: There were 604 responders who completed the survey. The majority were over 50 years old (81%) and female (86%). Histograms of side effect scores showed a skew towards high importance for weight gain, a U-shaped distribution for CVD, diabetes, eye disease and infections, and a skew towards low importance for acne (Figure 1). When ranked the side effect of most importance to responders was weight gain (median score=9, IQR 6, 10) followed by insomnia and moon face with equal median score (8) and IQR (5, 10). Several side effects had the same median score of 8, but distribution across categories varied. Three clinically serious side effects: cardiovascular disease, diabetes and infection, were ranked of lower importance but had wide ranging scores (median score=8, IQR 1, 10). Acne was of least importance to responders (median score=1, IQR 1, 6) (Table 1).

Conclusion: The three most highly rated side effects were not clinically serious but remained important to patients, perhaps reflecting their impact on quality of life and their high prevalence. The importance of these less serious but potentially high impact side effects should be taken into consideration when discussing treatment options and planning future GC safety studies. Table 1: Median, inter-quartile range, rank and categories of side effect scores.

Side effect	Median(IQR)	Rank	Low (score 1-3) N (%)	Medium (score 4-7) N (%)	High (scores 8-10) N (%)
Weight gain	9 (6, 10)	1	74 (12.3)	145 (24)	385 (63.7)
Insomnia	8 (5, 10)	2	75 (12.4)	210 (34.8)	319 (52.8)
Moon face	8 (5, 10)	2	125 (20.7)	149 (24.7)	330 (54.6)
High blood pressure	8 (4, 10)	4	150 (24.8)	138 (22.8)	316 (52.3)
Reduced bone strength	8 (4, 10)	4	133 (22)	134 (22.2)	337 (55.8)
Eye disease	8 (3, 10)	6	164 (27.2)	93 (15.4)	347 (57.5)
Cardiovascular disease	8 (1, 10)	7	216 (35.8)	56 (9.3)	332 (55)
Diabetes	8 (1, 10)	7	206 (34.1)	86 (14.2)	312 (51.7)
Infections	8 (1, 10)	7	182 (30.1)	116 (19.2)	306 (50.7)
Changes in mood	7 (5, 9)	10	110 (18.2)	239 (39.6)	255 (42.2)
Skin changes	7 (5, 9)	10	109 (18)	214 (35.4)	281 (46.5)
Palpitations	7 (4, 9)	12	125 (20.7)	212 (35.1)	267 (44.2)
Indigestion	6 (3, 8)	13	152 (25.2)	276 (45.7)	176 (29.1)
Acne	1 (1, 6)	14	359 (59.4)	138 (22.8)	107 (17.7)

Figure 1: Histograms of side effect ratings. 1=rating of lowest importance, 10=rating of highest importance.



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Epidemiology of Polymyalgia Rheumatica 2000-2014: A Population Based Study

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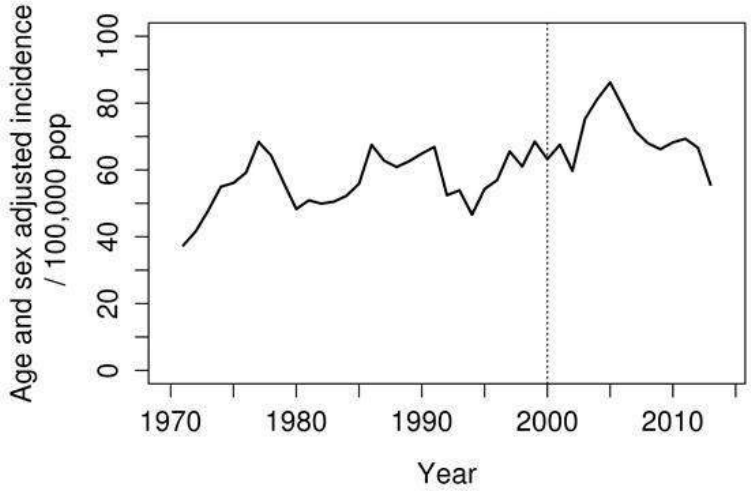
Background/Purpose: To determine time trends in the incidence and survival analysis of polymyalgia rheumatica (PMR) over a 15 year period in a geographically defined population and to descriptively compare the incidence of PMR in this time period to a previous incidence cohort from the same population base.

Methods: In a geographically defined population, we retrospectively identified all incident cases of PMR between January 1, 2000, and December 31, 2014. Detailed review of all individual medical records was performed. All but 4 of these cases (who were age<50 years) fulfilled EULAR/ACR classification criteria for PMR. Incidence rates were age and sex adjusted to the US white 2010 population and were graphically illustrated using 3 year centered moving averages. Survival rates were computed using Kaplan-Meier methods and were compared with the expected rates in the population of the US State.

Results: There were 407 incident cases of PMR during the 15 year study period. Of these 64% were female and the mean age at incidence was 73.9 years. The overall age and sex adjusted annual incidence of PMR was 68.3 (95% confidence interval [CI] 61.6, 75) per 100,000 population aged ≥50 years. Incidence rates increased with age in both sexes, but incidence fell after age 80 years among women. The incidence rates fluctuated over the period of observation (Figure) with evenly spaced peaks in 1970, 1990 and 2005. Comparing the two time periods, there was a significant increase in incidence of PMR in the recent time period compared to 1970-1999 (age and sex adjusted rate: 55.8 per 100,000; p=0.011). During median follow-up of 6.4 years, 120 patients died. Mortality among individuals with PMR was not significantly worse than that expected in the general population (standardized mortality ratio: 0.73; 95% CI: 0.60, 0.87).

Conclusion: The incidence of PMR has increased slightly in the past 15 years compared to previous decades. Survival among patients with PMR is not worse than the general population. Further research is needed to understand the determinants of the increase in incidence of PMR.



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Abstract Number: 3191

Coronary Revascularization Procedure Rates and Risks Among Patients with Systemic Lupus Erythematosus Compared to Those with Diabetes Mellitus in a Nationwide Medicaid Cohort

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Background/Purpose : We have recently found that myocardial infarction (MI) risk was similar among age- and sex-matched SLE patients compared to diabetes mellitus (DM) patients within a U.S. Medicaid cohort. However, little is known about rates and relative risks of coronary revascularization (CR) procedures, such as coronary artery bypass grafting (CABG) and percutaneous coronary interventions (PCI), among SLE compared to DM patients. We compared rates and relative risks of CR procedures among patients with SLE and DM enrolled in Medicaid.

Methods : We utilized Medicaid Analytic eXtract (MAX) data, containing billing claims for Medicaid patients from 29 most populated U.S. states from 2007-2010. We identified adults aged ≥18-65 years with prevalent SLE or DM (≥3 ICD-9 codes for SLE or DM, each separated by ≥30 days) and >6 months enrollment prior to 3rd code (=index date). We performed 1:2 matching (SLE:DM) by age (month/year), sex, and index date. Sociodemographic data and medical and cardiac comorbidities were collected during the baseline period (6 months prior to and including index date). Outcomes were assessed after index date, including CABG, PCI, and combined CABG or PCI. Subjects were followed to first procedure, death, Medicaid disenrollment, or end of follow-up. We used Cox sub-distribution regression models to calculate hazard ratios (HR_{SD}) of undergoing CR procedures, accounting for the competing risk of death and adjusting for sociodemographics and cardiac and medical comorbidities.

Results : 32,089 prevalent SLE patients were matched to 64,178 prevalent DM patients. In both cohorts, 92.8% were female and mean age was 41.3 (±12.1) years. There were more Blacks (41.1 vs. 30.5%) and fewer Whites (36.3 vs 45.1%) in the SLE vs. DM cohort. Mean follow-up was 1.67 (±1.03) years for SLE and 1.79 (±1.07) years for DM. Cardiac risk factors at baseline were more prevalent among DM vs. SLE patients: hypertension (38.0 vs. 33.7%), hyperlipidemia (22.5 vs. 10.6%), and obesity (11 vs. 4.5%). PCI rates were nearly 10-fold those of CABG rates in each cohort (**Table**). Annual rates of CABG and PCI were much higher among SLE than DM patients. Age- and sex-adjusted risks of CR procedures, particularly CABG, were higher among SLE than DM patients. Multivariable adjustment attenuated relative risks slightly. The multivariable-adjusted HR_{SD} for CABG was 1.83 (95%CI 1.48-2.25) and for PCI was 1.23 (95%CI 1.15-1.31) in SLE vs. matched DM patients.

Conclusion : Despite similar MI risks among SLE and DM patients, SLE patients had substantially higher rates of PCI and CABG compared to age- and sex-matched DM patients. SLE patients had > 80% increased risk of CABG compared to DM patients. While the etiology of these differences is not clear, they suggest that underlying cardiovascular disease may more severe or more likely to come to medical attention among SLE than similar age and sex DM patients.

Table. Annual Rates and Multivariable Subdistribution Hazards Ratios (HR_{SD})* for Coronary Revascularization Procedures among SLE compared to Diabetes Mellitus (DM) patients in Medicaid (2007-2010)

	Events	Person-years	Rates** (95%CI)	HR_{SD} (95%CI)[A]	HR_{SD} (95%CI)[B]	HR_{SD} (95%CI)[C]
Coronary Artery Bypass Graft (CABG)						
DM	200	114,400	1.75 (1.52-2.01)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	178	53,082	3.35 (2.89-3.88)	**1.90 (1.55-2.32)**	**1.84 (1.51-2.24)**	**1.83 (1.48-2.25)**
Percutaneous Coronary Intervention (PCI)						
DM	2,605	111,231	23.42 (22.54-24.34)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	1,611	51,296	31.4 (29.90-33.00)	**1.32 (1.24-1.40)**	**1.26 (1.19-1.34)**	**1.23 (1.15-1.31)**
Coronary Artery Bypass Graft or Percutaneous Coronary Intervention						
DM	2678	111,127	24.1 (23.20-25.00)	1.0 (ref)	1.0 (ref)	1.0 (ref)
SLE	1733	51,149	33.8 (32.32-35.51)	**1.38 (1.30-1.46)**	**1.29 (1.21-1.37)**	**1.29 (1.21-1.37)**

*HRsd= Subdistribution hazard ratios accounting for the competing risk of death
**Rate= Incidence rate, events per 1,000 person-years
Bold= p<0.05
Model A: Age (continuous) and sex matched, additionally adjusted for age and sex
Model B: Model A, additionally adjusted for race, zip code-level socioeconomic status and US residential region
Model C: Model B, additionally adjusted for baseline Charlson comorbidity score, number of drugs and cardiac risk factors (including hypertension, smoking, obesity, hyperlipidemia)

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Abstract Number: 3192

Influence of Temperature and Humidity on Disease Activity in Rheumatoid Arthritis

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Background/Purpose: To evaluate whether meteorological parameters influence pain and disease activity in patients with rheumatoid arthritis (RA).

Methods: We assessed correlations between individual meteorological variables and clinical measures of disease activity: clinical disease activity index (CDAI), self-reported pain (by visual analogue scale), tender- and swollen 28 joint counts (TJC and SJC) and patient global assessment (PGA). Assessments documented in our RA database as well as the average temperature and relative humidity, obtained from the Central Institute for Meteorology and Geodynamics, were matched on a daily basis for a period of 10 years between 2005 and 2015, and analyzed using generalized estimating equations (longitudinal data analysis). On average, an individual patient would have 3-monthly visits throughout this observation time.

Results: A total of 1437 patients with RA (average disease duration at first visit: 4.88±8.63 years; 77% female, mean CDAI 17.8±11.7,) were analyzed. Higher temperature and lower humidity were significantly associated with lower CDAI (p=0.0002, and p=0.0332, respectively). Both, temperature and humidity were significantly associated with pain (p=0.0076), PGA (p=0.0011), and SJC (p=0.0187). Temperature and humidity showed an interaction on pain: lower temperatures were associated with higher pain levels at the lower quartiles of humidity; in contrast, lower temperature corresponded to lower pain levels at the highest quartile of humidity (Figure 1).

Conclusion: In this largest association study of meteorological parameters with RA specific outcomes both temperature and relative humidity were shown to have significant effects on disease activity. Individual measures of disease activity and pain correlated either with temperature or humidity, while the composite CDAI measure correlated with both meteorological variables. These data are confirmatory of the influence of the climate environment on outcomes of an inflammatory disease.

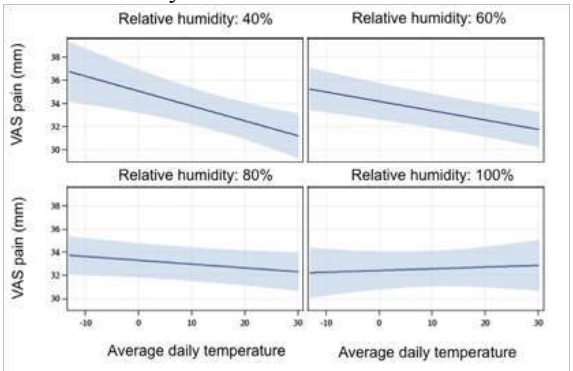

Figure 1. Effects of temperature on pain under different levels of humidity

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Abstract Number: 3193

Is an Intensive Diet and Exercise Regimen Cost-Effective for Obese and Overweight Patients with Symptomatic Knee OA?

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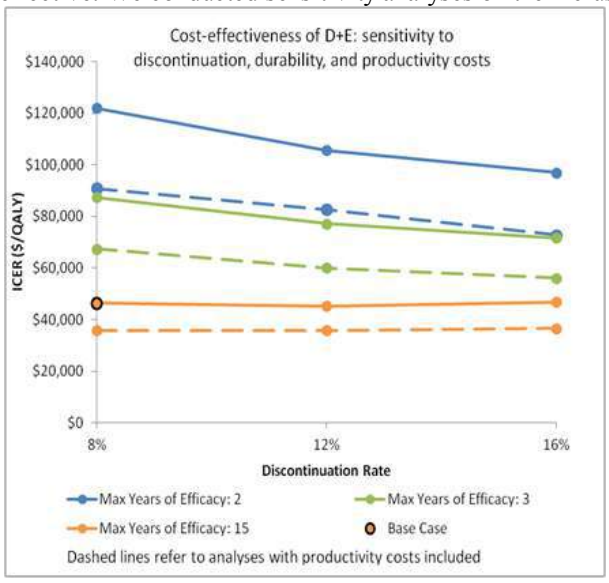
Background/Purpose: About 50% of persons with knee OA are obese. Quality-adjusted life-year losses due to knee OA and obesity exceed 3.5 per person. The results of the Intensive Diet and Exercise for Arthritis (IDEA) trial showed that an intensive diet and exercise (D+E) program, consisting of meal replacements and group exercise sessions led by a professional exercise interventionist, led to a mean 10.6 kg weight reduction and 50% reduction in pain over 18 months. We sought to determine the cost-effectiveness of the D+E program in overweight and obese (BMI>27 kg/m^2) OA patients.

Methods: We combined the data from the IDEA trial with the Osteoarthritis Policy (OAPol) Model, a validated computer simulation of knee OA, to evaluate long-term clinical and economic outcomes in knee OA patients similar to those enrolled in the IDEA trial. Mean age was 66, average WOMAC score 32 (0-100, 100 worst) and average BMI 33.6 kg/m^2. We evaluated the cost-effectiveness of adding a D+E regimen to clinical management consisting of intermittent analgesia until patients are eligible and willing to have TKR. D+E efficacy and sustainability over 18 months were derived from IDEA and assessed on two domains: BMI reduction and pain reduction. 29% of subjects in D+E arm of IDEA trial had a BMI reduction between 5-10% and 8% reached a reduction of 20-25%. The discontinuation rate was estimated at 8% per year. Annual costs for the D+E regimen included costs of program ($328 in year 1, $281 in subsequent years), meal replacements during the first six months ($790) and a hypothetical (the trial subjects did not have to pay for it) gym membership ($600/year). The base-case analysis assumed maximum duration of efficacy to be 15 years. We adopted a modified societal perspective (without productivity costs), discounted outcomes at 3%/year, and assumed a willingness to pay (WTP) threshold of $100,000 per quality adjusted life year (QALY). Strategies with incremental cost-effectiveness ratios (ICERs) below WTP were considered cost-effective. We conducted sensitivity analyses on the inclusion of productivity costs, duration of efficacy and discontinuation rates.



Results: In the base case, those who were offered the D+E regimen spent 7.4 years on the regimen, on average. They spent 2.9 years with at least 5% BMI reduction. The D+E regimen led to 12.4 quality-adjusted years of life gained per every 100 participants, resulting in an incremental cost-effectiveness ratio of $46,300/QALY. Inclusion of productivity costs decreased the ICER for the D+E regimen to $35,800. Reducing the duration of efficacy to 3 years increased the ICER for the D+E regimen to $87,400/QALY when productivity costs were not included ($67,500/QALY with productivity costs). (Figure)

Conclusion: Adding D+E to clinical management of overweight and obese patients with knee OA is cost-effective. Implementation of D+E into care of OA patients should be a public health priority.

Disclosure: E. Losina, None; **K. C. Smith**, None; **A. D. Paltiel**, None; **L. G. Suter**, None; **J. N. Katz**, None; **S. P. Messier**, None.

Abstract Number: 3194

Factors Related to Physicians' Prescriptions for Rheumatoid Arthritis Drugs Never Filled or Subsequently Discontinued By Patients

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SESSION INFORMATION

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Background/Purpose: Rheumatologists have many choices of medications to use for patients with rheumatoid arthritis (RA), but patients may not fill a prescription (primary non-adherence or PnA). Even for those who do initiate therapy, they may discontinue treatment shortly thereafter (secondary non-adherence or SnA). The factors that underlie never starting on therapy as distinct from early discontinuation are likely to be different but have not been well characterized. This study investigated predictors of PnA and SnA to to methotrexate (MTX), biologics/tofacitinib (B/T) in RA patients.

Methods: A retrospective cohort analysis was conducted using a U.S. integrated claims and electronic health records (EHR) database. Patients were required to have a new prescription or treatment of MTX or B/T (index event) (12+ month clean period) with >=2 RA physician diagnoses (714.0, 714.2, or 714.81), no other autoimmune diseases or cancer before index, and continuous pharmacy and medical insurance coverage and EHR data availability before and after index. PnA was defined as a new written prescription of MTX or B/T (EHR data) not initiated within 90 days (linked pharmacy claims data). SnA was defined using only pharmacy data as treatment discontinuation (a gap >=90 days) within 12 months of initiation. Potential predictors (n=414 from EHR and claims data) were selected based on clinical judgment and included in separate lasso-regularized logistic regression.

Results: Of 1,117 and 744 patients with a new written prescription, 24% (MTX) and 27% (B/T) failed to initiate them. For those who started on treatment 12-month discontinuation rate was 50% for MTX and 40% for B/T. For PnA, multiple baseline treatment-based comorbidity markers positively and diagnosis-based comorbidity markers negatively impacted MTX primary adherence, whereas for B/T almost no comorbidity markers were significant. Model discrimination was good (AUC=0.81 for MTX, 0.71 for B/T). For SnA, some psychosocial issues such as depression and anxiety were associated with MTX discontinuation. For B/T, infection-related conditions at baseline were associated with discontinuation (Tables 1 and 2).

Conclusion: Using novel linked EHR and pharmacy data, approximately 25% of new prescriptions for MTX, biologics or tofacitinib were not filled by patients within 90 days. Different factors were related to primary nonadherence (never filling first Rx) vs. secondary non-adherence (early discontinuation), implying the need for different interventions to improve adherence to MTX and B/T, both at the time of first fill and over time. Table 1: Logistic Regression Estimates of Primary Adherence: Odds ratio associated with filling first MTX and B/T prescription

		Primary adherence to MTX (n=1,117)	Primary adherence to B/T (n=744)
Age	2-51	-	-
	51-62	0.98	0.70
	62-73	0.81	0.44**
	73-86	0.64	0.36***
Male		0.97	1.00
Race	African American	-	-
	Asian	1.02	0.29
	Caucasian	1.11	0.73
	Other/Unknown	2.41	0.73
Product	Health Maintenance Organizatoin	0.71	-
	Preferred Provider Organization	2.94*	-
	Point of Service	-	1.52
Diagnosis-based disease groups (EDC)	ADM05: Administrative concerns and non-specific laboratory abnormalities	0.70	-
	CAR14: Hypertension, w/o major complications	0.62*	-
	END02: Osteoporosis	0.73	-
	EYE06: Cataract, aphakia	0.75	-
	GSI01: Nonspecific signs and symptoms	0.53**	-
	GUR08: Urinary tract infections	0.38***	-
	RES02: Acute lower respiratory tract infection	0.28***	-
	RES04: Emphysema, chronic bronchitis, COPD	0.47**	-
	RHU01: Autoimmune and connective tissue diseases	0.65	-
	SKN10: Skin keratoses	0.63	-
Treatment-based disease groups	ALLx030: Allergy / Immunology / Chronic Inflammatory	3.94***	-
	CARx030: Cardiovascular / High Blood Pressure	2.37***	-
	CARx040: Cardiovascular / Disorders of Lipid Metabolism	2.29***	-
	ENDx050: Endocrine / Thyroid Disorders	1.65	-
	GSIx020: General Signs and Symptoms / Pain	1.57*	-
	GSIx030: General Signs and Symptoms / Pain and Inflammation	1.29	-
	INFx020: Infections / Acute Minor	2.50***	
	MUSx020: Musculoskeletal / Inflammatory Conditions	-	3.97***
Signs, disease and symptoms	Stress	0.62*	-
	Arthritis	-	0.73

	Pain	-	0.87
	Synovitis	-	0.58
Prediction Accuracy	Mean AUC over 4 folds	0.81±0.05	0.71±0.05

P < 0.05; **P < 0.01; ***P < 0.001. Table 2: Logistic Regression Estimates of Secondary Adherence: Odds ratio associated with 12-continuation with MTX and B/T

		Secondary adherence to MTX (n=966)	Secondary adherence to B/T (n=788)
Age	2-51	-	-
	51-62	1.69*	0.86
	62-73	1.85**	0.96
	73-86	2.08***	0.9
Male		0.78	1.17
Race	African American	-	-
	Asian	1.59	3.06
	Caucasian	1.63*	1.09
	Other/Unknown	1.69	0.79
Product	Point of Service	-	1.41
Diagnosis-based disease groups (EDC)	GSI02: Chest pain	0.60**	-
	NUR03: Peripheral neuropathy, neuritis	0.75	-
	EAR11: Acute upper respiratory tract infection	-	0.55**
	GAS01: Gastrointestinal signs and symptoms	-	0.61*
	RES01: Respiratory signs and symptoms	-	0.49***
Treatment-based disease groups	INFx020: Infections / Acute Minor	0.67**	-
	NURx050: Neurologic / Seizure Disorder	0.71	-
	PSYx030: Psychosocial / Anxiety	0.69	-
	PSYx040: Psychosocial / Depression	0.66**	-
	GAS010: Treatment for acute minor gastrointestinal or hepatic condition	-	2.86***
	GSI030: Treatment for pain and inflammation	-	1.34
Signs, disease and symptoms	Stress	0.62*	-
Prediction Accuracy	Mean AUC over 4 folds	0.63±0.03	0.64±0.03

P < 0.05; **P < 0.01; ***P < 0.001.

Disclosure: H. J. Kan, None; **K. Dyagilev**, None; **P. Schulam**, None; **S. Saria**, None; **C. Molta**, None; **J. Curtis**, Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 2,Roche/Genentech, UCB, Janssen, Corrona, Amgen, Pfizer, BMS, Crescendo, AbbVie, 5.

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Abstract Number: 3195

Patterns and Predictors of Hydroxychloroquine Nonadherence in a Nationwide Cohort of Medicaid Beneficiaries with Systemic Lupus Erythematosus

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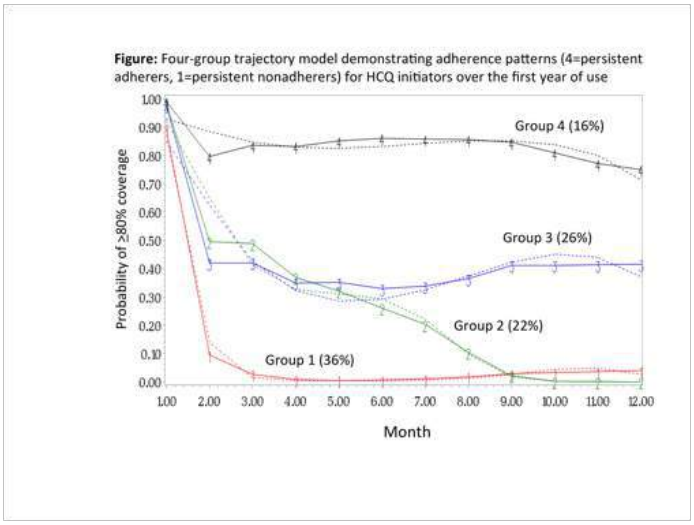
Background/Purpose: Hydroxychloroquine (HCQ) is the standard of care medication for most SLE patients, however cross-sectional studies suggest that nonadherence is common. Similar to the fluctuating nature of SLE, we hypothesized that adherence is dynamic and composite measures might not capture the nuances of medication use over time. We used a novel method, group-based trajectory modeling (GBTM), to investigate longitudinal patterns of nonadherence to newly prescribed HCQ, and demographic and disease-related predictors, in a U.S. nationwide SLE cohort.

Methods: We used Medicaid data with all claims and pharmacy data for beneficiaries in most states (2000-10), to identify adults 18-65 years with prevalent SLE. We restricted our cohort to new users of HCQ (≥6 months without HCQ use), and required ≥1 year of follow-up after first dispensing (index date). Predictors were collected in the 6 months pre-index date. The proportion of days covered (PDC) was used to describe overall 12-month adherence (<80%=nonadherent). We applied GBTM to examine patterns of monthly HCQ nonadherence (<80% of days/month covered), during the first 12 months post-index date. GBTM fit was assessed using Bayesian Information Criterion (BIC) and posterior probabilities. We used multivariable multinomial logistic regression models to examine predictors of nonadherence trajectories.

Results: We identified 10,900 HCQ new users with SLE. Mean age was 38 (±12) years, 94% were female, 43% black, 31% white, 19% Hispanic; 85% had a mean PDC <80%. The 4-trajectory group model had the lowest BIC and posterior probabilities >80%, suggesting the best fit (**Figure**); 36% were persistent nonadherers (group 1), 16% were persistent adherers (group 4). At 6 months, intermediate nonadherence trajectories diverged. Group 3 plateaued and group 2 declined; group 2 had fewer outpatient visits at 6 months vs. group 3 ($p<0.001$). Using multinomial regression, compared to adherers (group 4), the odds of nonadherence were increased for groups 1-3 for blacks and Hispanics vs. whites and for younger ages vs. older (**Table**). Increased SLE-related comorbidities (SLE risk adjustment index), was associated with reduced odds of nonadherence for groups 1 and 2, but not for 3.

Conclusion: Rates of HCQ nonadherence were extremely high and distinct patterns were uncovered. While younger age and black and Hispanic race/ethnicity increased odds of nonadherence overall, other predictors differed by nonadherence pattern. Six months was a critical juncture for intermediate nonadherers and utilization patterns suggest that improved access to outpatient care at this



point may improve long-term HCQ adherence.

Table: Multivariable multinomial logistic regression models comparing nonadherent trajectories (groups 1-3) to the persistently adherent trajectory (group 4)*

Baseline Characteristics**	Group 1: Persistent nonadherers OR (95% CI)	Group 2: Intermediate nonadherers OR (95% CI)	Group 3: Intermediate nonadherers OR (95% CI)	Group 4: Persistent adherers
Age group (50-65 years = ref)				
18-34 years	**1.64 (1.37-1.95)**	**1.64 (1.40-2.05)**	**1.41 (1.17-1.70)**	*ref.*
35-50 years	**1.31 (1.11-1.54)**	**1.40 (1.17-1.67)**	**1.32 (1.11-1.57)**	*ref.*
Race/Ethnicity (White = ref)				
Black	**1.73 (1.48-2.02)**	**1.95 (1.65-2.31)**	**1.80 (1.52-2.12)**	*ref.*
Hispanic	**1.43 (1.18-1.72)**	**1.70 (1.40-2.08)**	**1.54 (1.26-1.87)**	*ref.*
Asian	**0.66 (0.48-0.90)**	0.94 (0.68-1.30)	0.85 (0.62-1.16)	*ref.*
American Indian	1.10 0.62-1.95)	1.18 (0.63-2.20)	1.17 (0.64-2.16)	*ref.*
SLE risk adjustment[*] index	**0.95 (0.91-0.99)**	**0.96 (0.92-1.00)**	0.98 (0.94-1.02)	*ref.*
Lupus nephritis[#]	1.07 (0.80-1.43)	0.89 (0.65-1.20)	**0.77 (0.53-0.95)**	*ref.*
Diabetes mellitus	**1.28 (1.02-1.59)**	1.18 (0.94-1.49)	1.20 (0.96-1.51)	*ref.*
Number of medications[*]	**0.90 (0.88-0.92)**	**0.94 (0.92-0.96)**	**0.92 (0.90-0.94)**	*ref.*
Antidepressant medication use[#]	**1.19 (1.03-1.37)**	**1.28 (1.10-1.49)**	1.09 (0.94-1.27)	*ref.*
Corticosteroid use[#]	**0.86 (0.75-0.97)**	1.01 (0.88-1.16)	1.04 (0.91-1.19)	*ref.*

*Model additionally adjusted for sex, area-level socioeconomic status, comorbidities, preventive care, behaviors (smoking, alcohol use, illicit drug use), number of SLE-related laboratory tests, pain medications, immunosuppressive medications, state of residence, healthcare utilization, and calendar year
**Baseline characteristics from 6 months of continuous enrollment prior to and including the index date.
[*]SLE risk adjustment index and number of medications were included as continuous measures
[#]Lupus nephritis, diabetes mellitus, antidepressant and corticosteroid use were dichotomized as ever/never during the baseline period

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Disclosure: C. H. Feldman, None; **J. E. Collins**, None; **Z. Zhang**, None; **D. H. Solomon**, None; **K. H. Costenbader**, None; **I. Kawachi**, None.

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Abstract Number: 3196

A Natural Language Processing System Can Capture Rheumatoid Arthritis Disease Activity Measures in US Veterans Across Multiple Sites

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Background/Purpose: The retrieval of rheumatoid arthritis (RA) disease activity measures recorded in an electronic medical record through natural language processing (NLP) would significantly aid RA management and epidemiologic research. The Veterans Affairs Rheumatoid Arthritis (VARA) registry participants routinely collects disease activity measures including the 28 joint disease activity score (DAS28) at each site and enters these data into a VARA database. Each site uses independent methods for documenting clinical notes and placing these data into the VARA database using manual extraction (ManEx). The purpose of this work was to develop NLP code to automatically identify relevant notes and extract clinical measures of RA disease activity and determined the accuracy of the NLP in comparison to the ManEx system at three VARA sties.

Methods: All clinical notes for VARA enrollees at three VARA sites between January 1, 2015 and September 30, 2015 that contained one clinical component of the DAS 28 - tender joint count (TJC), swollen joint count (SJC), or patient global assessment (PtGA) identified by either ManEx in the VARA database or in an NLP note - were evaluated. Any ESR within two weeks before and after the clinic visit was identified and the value closest to the clinic visit combined with TJC, SJC, and PtGA to calculate DAS28. For each event/note the JTC, JSC, PtGA, and ESR was evaluated and classified as follows: correct by NLP and ManEx, correct by ManEx only, correct by NLP only, or missing data by both methods. During the same observation period, observations that allowed calculations of DAS28 (all four elements collected) were also identified. Any discrepancies between ManEx and NLP were resolved by investigator review of the clinic notes.

Results: There were 1273 notes identified on 474 patients at the three VARA sites with the percent of DAS28 elements identified by the two methods as noted in the table. Reasons for the ManEx and NLP not identifying clinical elements varied by the specific element detected but generally fell into the following categories. Reason for ManEx or NLP failure may have occurred more than once for each note. Errors for ManEx were note not identified for data extraction (basically missed by reviewer doing ManEx) (N=133, 10.4 %), and data entry errors by the ManEx reviewer (N=170, 13.6%). Reasons for NLP failure were: wrong template selected for rheumatology note (N=91, 7.1%), modified template during clinic visit(N=6, 0.4%), prose instead of numeric values entered into the template (N=5, 0.4%), and no note in the VA corporate data warehouse (electronic note source) (N=72, 5.7%) .

Conclusion: This NLP system can extract DAS28 from notes from three distinct VARA sites to aid in clinical care and research activities. Future efforts will emphasize the standardization of data collection to better support using NLP methods for more efficient and reliable collection of clinical outcomes in RA and the dissemination and evaluation of the methodology at other sites using similar electronic medical record systems.

Correct Detection of Components of Disease Activity by NLP & ManEx, ManEx only, NLP only, or neither NLP or ManEx

		Site #1 (n=439)	Site #2 (n=376)	Site #3 (n=458)	Total (n=1273)
Tender Joint Count (TJC)	NLP & ManEx	275 (62.7%)	283 (75.3%)	424(92.6%)	982 (77.2%)
	ManEx only	58 (13.2%)	44 (11.7%)	24(5.2%)	126 (9.9%)
	NLP only	105 (23.9%)	42 (11.1%)	10 (2.2%)	157 (12.3%)
	Neither NLP or ManEx	1 (0.2%)	7 (1.9%)	0 (0%)	8 (0.6%)
Swollen Joint Count (SJC)	NLP & ManEx	276 (62.9%)	278 (73.9%)	431 (94.1%)	985 (77.4%)
	ManEx only	58 (13.2%)	45 (12.0%)	20 (4.4%)	123 (9.7%)
	NLP only	104 (23.7%)	47 (12.5%)	7 (1.5%)	158 (12.4%)
	Neither NLP or ManEx	1 (0.2%)	6 (1.6%)	0 (0%)	7 (0.5%)
Patient Global Assessment (PtGA)	NLP & ManEx	309 (70.4%)	293 (77.9%)	404 (88.2%)	1006 (79.0%)
	ManEx only	41 (9.4%)	27 (7.2%)	37 (8%)	105 (8.2%)
	NLP only	86 (19.6%)	39 (10.4%)	17 (3.8%)	142 (11.2%)
	Neither NLP or ManEx	3 (0.6%)	17 (4.5%)	0 (0%)	20 (1.6%)
Erythrocyte Sedimentation Rate (ESR)	NLP & ManEx	336 (76.5%)	280 (74.5%)	416 (90.8%)	1032 (81.1%)
	ManEx only	34 (7.7%)	10 (2.6%)	20 (4.4%)	64 (5.0%)
	NLP only	67 (15.3%)	50 (13.3%)	22 (4.8%)	139 (10.9%)
	Neither NLP or ManEx	2 (0.5%)	36 (9.6%)	0 (0%)	38 (3.0%)
Disease Activity Score (DAS28)	NLP & ManEx	193 (44.0%)	251 (66.8%)	391 (85.4%)	835 (65.6%)
	ManEx only	121 (27.6%)	55 (14.6%)	36 (7.8%)	212 (16.7%)
	NLP only	56 (12.7%)	28 (7.4%)	19 (4.2%)	103 (8.1%)
	Neither NLP or ManEx	69 (15.7%)	42 (11.2%)	12 (2.6%)	123 (9.6%)

Disclosure: G. W. Cannon, Amgen, 2; **S. Mehortra**, Amgen, 2; **B. South**, None; **T. R. Mikuls**, Pfizer Inc, 5,Roche Pharmaceuticals, 2; **A. M. Reimold**, Abbvie, 2,Novartis Pharmaceutical Corporation, 2; **B. C. Sauer**, Amgen, 2.

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Abstract Number: 3197

Ultrasound Definitions for Cranial and Large Vessel Giant Cell Arteritis: Results of a Reliability Exercise on Images and Videos of the Omeract Ultrasound Large Vessel Vasculitis Task Force

Stavros Chrysidis[1], Christina Duftner[2], Christian Dejaco[3], Cristina Ponte[4], Annamaria Iagnocco[5], Bhaskar Dasgupta[6], Maria Antonietta D'Agostino[7], Eugenio De Miguel[8], Ulrich Fredberg[9], Wolfgang Hartung[10], Alojzija Hocevar[11], Tanaz A. Kermani[12], Matthew J. Koster[13], Tove Lorenzen[14], Pierluigi Macchioni[15], Marcin Milchert[16], Naina Rastalsky[17], Chetan Mukhtyar[18], Valentin S. Schaefer[19], Kenneth J. Warrington[20], Lene Terslev[21], George A. W. Bruyn[22], Petra Hanova[23], Uffe Møller Døhn[24], Esperanza Naredo[25], Carlo Alberto Scirè[26], Greta Carrara[27], Sofia Ramiro[28], Andreas P Diamantopoulos[29] and Wolfgang A. Schmidt[19], [1]Department of Rheumatology, Hospital of Southwest Denmark, Esbjerg, Denmark, [2]Medical University Innsbruck, Innsbruck, Austria, [3]Rheumatology and Immunology, Medical University Graz, Graz, Austria, [4]Rheumatology and Metabolic Bone Diseases Department, Rheumatology Research Unit - IMM, Lisbon Academic Medical Centre, Lisbon, Portugal, [5]Sapienza Università Di Roma,, Roma, Italy, [6]Rheumatology, Southend University Hospital NHS Foundation Trust, Westcliff-on-Sea, United Kingdom, [7]Rheumatology, Versailles-Saint Quentin en Yvelines University, Boulogne-Billancourt, France, [8]Hospital Universitario La Paz, Madrid, Spain, [9]Department of Internal Medicine, Diagnostic Centre Region Hospital Silkeborg Denmark, 8600 Silkeborg, Denmark, [10]Department of Rheumatology/Clinical Immunology, Asklepios Medical Center, 93077 Bad Abbach, Germany, [11]Department of Rheumatology, University Medical Centre Ljubljana, Ljubljana, Slovenia, [12]Rheumatology, University of California Los Angeles, Santa Monica, CA, [13]Rheumatology, University of California Los Angeles, CA, USA Mayo Clinic, Rochester, MN, [14]Diagnostic Centre, Region Hospital Silkeborg, Silkeborg, Denmark, [15]Arcispedale Santa Maria Nuova, Reggio Emilia,, Reggio Emilia, Italy, [16]Pomeranian Medical University, Szczecin,, Szczecin, Poland, [17]St. Elizabeth's Medical Center, Boston, MA, Boston, MA, [18]Norfolk and Norwich University Hospital, Norwich, United Kingdom, [19]Immanuel Krankenhaus Berlin, Med Ctr for Rheumatology Berlin-Buch, Berlin, Germany, [20]Rheumatology, University of California Los Angeles, CA, USA Mayo, Rochester, MN, [21]Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Copenhagen Center for Arthritis Research (COPECARE), Copenhagen, Denmark, [22]Rheumatology, MC Groep, Loenga, Netherlands, [23]Institute of Rheumatology and Department of Rheumatology, 1st Faculty of Medicine, Charles University in Prague, Prague, Czech Republic, [24]Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Copenhagen Center for Arthritis Research (COPECARE), Glostrup, Denmark, [25]Rheumatology, Hospital General Universitario Gregorio Marañón and Universidad Complutense, Madrid, Spain, [26]Epidemiology Unit – Italian Society for Rheumatology (SIR), Milano, Italy, [27]Epidemiology Unit, Italian Society for Rheumatology, Milano, Italy, [28]Leiden University Medical Center, Leiden, Netherlands, [29]Rheumatology, Haugesund Sanitetsforenings Revmatismesykehus, Haugesund, Norway

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Session Time: 11:00AM-12:30PM

Background/Purpose: By a Delphi process, the OMERACT Ultrasound (US) large vessel vasculitis task force has recently defined the US appearance of normal temporal arteries (TA) and normal extra-cranial large arteries (i.e. axillary arteries, AA), as well as the key elementary US-detected lesions in -giant cell arteritis (GCA) (i.e.:“halo sign” and “compression sign”; Table 1). The aim of the present study was to assess the reliability of those definitions on still images and videos in a web-based reliability exercise.

Methods: The reliability exercise was performed using a REDCap web application.One-hundred-fifty anonymized images/videos, provided by the members of the task force, were assessed: 20 videos and 20 still images of AA and 45 videos and 45 still images of TA with either no abnormality or the presence of a halo sign, and 20 videos of TA with either a positive or negative compression sign. The task force members (n26) were asked to rate all images and videos for normality/abnormality applying the definitions agreed upon in the previous Delphi exercise. In order to assess the intra-observer reliability the study was repeated two weeks later using the same images/videos presented in a different order. Cohen’s and Light’s κ were used for evaluating intra- and inter-reader reliability, respectively. K values 0–0.2 were considered slight, 0.2–0.4 fair, 0.4–0.6 moderate, 0.6–0.8 substantial and 0.8–1 excellent.

Results: The response rate was 25/26 (96%) in round 1 and 25/25 (100%) in round 2. The reliability of the 25 participants was excellent with mean inter-rater agreements over 90%, mean Lights's kappa values of >0.8 for inter-rater reliability (Table 2) and mean Cohen kappa values of 0.83-0.98 for intra-rater reliability.

Conclusion: Inter- and intra-observer agreement on the evaluation of US still images and videos from normal and vasculitis patients was excellent applying the new OMERACT definitions for key elementary US lesions for GCA. Further exercises are planned in order to test the reliability in patients with large vessel vasculitis. Table 1

Vessel	Definition of US appearance of normal arteries	Definition of US appearance of vasculitis – "halo sign"	Definition of US appearance of vasculitis - compression sign
Temporal Arteries	Pulsating, compressible artery with anechoic lumen surrounded by mid- to hyperechoic tissue. Using US equipment with high resolution, the intima-media complex presenting as a homogenous, hypo- or anechoic echostructure delineated by two parallel hyperechoic margins ("double line pattern") may be visible.	Homogenous, hypoechoic wall thickening, well delineated towards the luminal side, visible both, in longitudinal and transverse planes, most commonly concentric in transverse scans.	The thickened arterial wall remains visible upon compression, i.e. the echogenicity contrasts hypoechoic due to vasculitic vessel wall thickening in comparison to the mid- to hyperechoic surrounding tissue.
Axillary Arteries	Pulsating, hardly compressible artery with anechoic lumen; the intima-media complex presents as a homogenous, hypo- or anechoic echostructure delineated by two parallel hyperechoic margins ("double line pattern"), which is surrounded by mid- to hyperechoic tissue.	Same as for temporal arteries	The definition is not used for the axillary arteries

Table 2

Section	Mean agreement	mean Light's κ
Halo (all images & videos)	94%	0.89
Halo (images)	98%	0.95
Halo (videos)	92%	0.84
Halo temporal arteries (images & videos)	94%	0.87
Halo temporal arteries (images)	97%	0.94
Halo temporal arteries (videos)	91%	0.83
Halo axillary arteries (images & videos)	97%	0.93
Halo axillary arteries (images)	99%	0.98
Halo axillary arteries (videos)	94%	0.88
Compression sign (videos)	92%	0.83

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Abstract Number: 3198

Inter-Reader and Intra-Reader Reliability of the New Omeract Ultrasonographic Criteria for the Diagnosis of Calcium Pyrophosphate Deposition Disease

Georgios Filippou[1], Carlo Alberto Scirè[2], Nemanja Damjanov[3], Antonella Adinolfi[4], Greta Carrara[5], Valentina Picerno[1], Carmela Toscano[1], George A. W. Bruyn[6], Maria Antonietta D'Agostino[7], Andrea Delle Sedie[8], Emilio Filippucci[9], Marwin Gutierrez[10], Mihaela Cosmina Micu[11], Ingrid Moller[12], Esperanza Naredo[13], Pascal Zufferey[14], Carlos Pineda[15], francesco Porta[16], Wolfgang A. Schmidt[17], Lene Terslev[18], Violeta Vlad[19], Bruno Frediani[1], Annamaria Iagnocco[20] and OMERACT working group "US in CPPD", [1]University of Siena, Siena, Italy, [2]Epidemiology Unit – Italian Society for Rheumatology (SIR), Milano, Italy, [3]Institute of Rheumatology, University of Belgrade Medical School, Belgrade, Serbia, [4]Policlinico le Scotte, Siena, Italy, [5]Epidemiology Unit, Italian Society for Rheumatology, Milano, Italy, [6]Rheumatology, MC Groep, Loenga, Netherlands, [7]University of Paris, Paris, France, [8]Department Rheumatology, University of Pisa, Pisa, Italy, [9]Clinica Reumatologica, Università Politecnica delle Marche, Jesi, Italy, [10]Instituto Nacional de Rehabilitación, Mexico, Mexico, [11]Division of Rheumatology, Department of Rehabilitation II, Clinical Rehabilitation Hospital, Cluj Napoca, Romania, [12]Direction, Poal Institute of Rheumatology, Corbera de Llobregat, Spain, [13]Rheumatology, Hospital General Universitario Gregorio Marañón and Universidad Complutense, Madrid, Spain, [14]Department of Rheumatology, University Hospital Lausanne, Lausanne, Switzerland, [15]Instituto Nacional de Rehabilitation, Mexico, Mexico, [16]Hospital of Pistoia, Pistoia, Italy, [17]Immanuel Krankenhaus Berlin, Med Ctr for Rheumatology Berlin-Buch, Berlin, Germany, [18]Center for Rheumatology and Spine Diseases, Rigshospitalet, Glostrup, Copenhagen Center for Arthritis Research (COPECARE), Copenhagen, Denmark, [19]RCRD Research Center, Bucharest, Romania, [20]Sapienza Università di Roma, Roma, Italy

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Background/Purpose: ultrasonography (US) has been implemented recently as a possible diagnostic method for CPPD[1]. However, data on the reliability of US in CPPD diagnosis are lacking. Aim of the study was to assess the inter-reader and intra-reader reliability of US on detecting CPP deposition in fibrocartilage(FC), hyaline cartilage (HC), tendons (T) and synovial fluid (SF)

Methods: the OMERACT “US in CPPD” group defined firstly the US CPPD identification criteria following the methods adopted by OMERACT and described at the OMERACT handbook (http://www.omeract.org/omeract_publications.html). After a systematic literature review and a Delphi survey the set of US criteria for identification of CPPD by were defined (table 1).

Structure	Shape	Echogenicity	Localization	Behavior at Dynamic scanning
Fibrocartilage	deposits of variable shape	hyperechoic (similar to the bone cortex)	localized within the fibrocartilage structure	remain fixed and move together with the fibrocartilage during dynamic assessment (i.e. joint movement and probe compression).
Hyaline cartilage	deposits varying in size and shape	hyperechoic (similar to the bone cortex echogenicity) that do not create posterior shadowing	Localized within the hyaline cartilage	the deposits remain fixed and move together with the hyaline cartilage (i.e. joint movement and probe compression)
Tendon	multiple, linear (parallel to the tendon fibrillar structure and not in continuity with the bone profile) deposits	Hyperechoic (in relation to the tendon echogenicity), that generally not create posterior shadowing. The deposits maintain their high degree of echogenicity even at very low levels of gain and are not affected by anisotropy as the surrounding tendon.	Localized within the tendon	remain fixed and move together with the tendon during movement and probe compression.
Synovial fluid	deposits of variable size (from punctuate to large)	hyperechoic (similar to the bone cortex echogenicity), that generally not create posterior shadowing.	Localized within the synovial fluid	are mobile according to joint movement and probe pressure.

Subsequently, a two steps procedure for the assessment of the reliability has been followed. Firstly, the panel gave a dichotomous score on the presence absence of CPPD in 150 photos of FC, HC, T and SF equally distributed, on a web based platform. The assessment has been carried out twice in order to calculate both inter and intra-reader reliability. In the second step, the experts met for a real life-patient based assessment of CPPD in a workshop organised in Siena-Italy. In that occasion, FC/HC/T/SF of the right knee and FC and SF of the right wrist of 8 patients were assessed twice in a day by all experts giving again a dichotomous score for CPPD. 8 US scanners (ESAOTE mylab seven) equipped with the same probe and the same preset (made ad hoc before the meeting), have been used for the workshop.

Results: Reliability values of the web based exercise and of the workshop are presented in table 2. Tendons and synovial fluid analysis did not reach sufficient strength of agreement neither on the web based nor in the patient based exercise regarding the inter-reader kappa and independently of the site. However, in the static exercise, both tendons and SF reached a good intra-reader reliability meaning that scanning technique of these structures is very important for CPPD identification. On the other hand, menisci (but not triangular FC of the wrist) and HC reached good kappa values for inter-reader and intra-reader agreement both on static and web-based exercise.

Section	K inter-reader I round	K inter-reader II round	K intra-reader
	WEB based exercise		
Fibrocartilage	0.58	0.58	**0.80**
Hyaline Cartilage	**0.73**	**0.73**	**0.85**
Tendons	0.28	0.31	**0.64**
Synovial Fluid	0.50	0.47	**0.76**
	Patient based workshop		
ALL	0.44	0.45	**0.63**
- Knee	0.47	0.52	**0.65**
--- Menisci	**0.65**	**0.64**	**0.73**
----- Medial Meniscus	**0.72**	**0.74**	**0.78**
----- Lateral Meniscus	0.57	0.48	**0.70**
--- Synovial Fluid	0.09	0.12	0.41
--- Tendon	0.25	0.3	0.44
----- Quadriceps Tendon	0.13	0.19	0.28
----- Proximal Patellar Tendon	0.09	0.19	0.47
----- Distal Patellar Tendon	0.31	0.25	0.44
--- Hyaline Cartilage	0.58	0.55	**0.68**
- Wrist	0.31	0.2	0.50
--- Triangular fibrocartilage	0.27	0.15	0.47
--- Synovial Fluid	0.15	0.1	0.36

Strength of agreement: < 0.20 Poor, 0.21 - 0.40 Fair, 0.41 - 0.60 Moderate, 0.61 - 0.80 Good, 0.81 - 1.00 Very good

Conclusion: Knee cartilage and fibrocartilage structures resulted to be reliable enough for identification of CPPD. On the other hand, CPPD identification in tendons and synovial fluid is challenging and the actual OMERACT criteria for these sites do not ensure a safe classification of patients. OMERACT US criteria for CPPD identification in knee menisci and HC allow a reliable classification of patients and should be used when CPPD is suspected. References:

1 Zhang W, Doherty M, Bardin T, *et al*. European League Against Rheumatism recommendations for calcium pyrophosphate deposition. Part I: terminology and diagnosis. *Ann Rheum Dis* 2011;**70**:563–70. doi:10.1136/ard.2010.139105

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Abstract Number: 3199

Urate Crystal Deposition and Bone Erosion in Gout: Inside-out or Outside-in? a Dual Energy Computed Tomography Study

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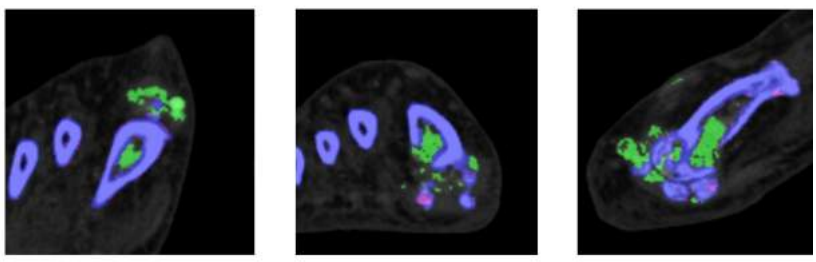
Background/Purpose: Imaging and pathology studies have shown that bone erosion is closely associated with monosodium urate (MSU) crystal deposition in tophaceous gout. It is currently unknown whether bone erosion in gout occurs through an inside-out mechanism with direct intra-osseous crystal deposition, or through an outside-in mechanism, whereby crystals deposit on the surface of articular cartilage surface or within synovium and then interact with bone to promote erosion. The aim of this study was to analyse the relationship between bone and MSU crystal deposition using dual energy computed tomography (DECT) in people with tophaceous gout.

Methods: One hundred and forty four participants were recruited from rheumatology clinics. All participants had gout according to the 1977 American Rheumatism Association classification criteria and at least one palpable tophus. DECT scans of both feet were performed on a dual X-ray tube 128 detector row scanner. Two readers independently scored all metatarsal heads (1433 bones available for scoring). Each site was initially scored for the presence or absence of urate deposition within the joint. If urate was present within the joint, the presence of urate in contact with bone was then scored. For bones in contact with urate, the site was then scored for whether urate was present within an erosion, on the surface of bone or within bone only (true intra-osseous deposit). In the case of reader disagreement, agreement was reached in a consensus re-scoring exercise. Pre-consensus inter-reader kappa for all scoring was >0.93. Differences between the location of urate deposits in each and all metatarsal heads were modelled taking into account clustering of results within individuals by general estimating equations using the GENMOD procedure of SAS v9.4.

Results: Urate deposition in the joint was present in 681/1433 (47.5%) sites. Urate in contact with bone was present in 370/681 (54.3%) joints with urate deposition. For those bones in contact with urate, deposition was present on the surface of bone in 143/370 (39%, 95% CI 34, 44%) and within erosion in 227/370 (61%, 95% CI 56, 66%). True intra-osseous urate deposition was not observed at any site (0%, 95% CI 0, 1%), GENMOD P<0.0001. For all bones with apparent intra-osseous deposition in one plane, examination in other planes demonstrated urate deposition within an *en face* erosion (Figure).

Conclusion: In tophaceous gout, MSU crystal deposition is present within the joint, on the bone surface and within bone erosion, but is not observed within bone in the absence of a cortical break. These data support the concept that MSU crystals deposit outside bone and contribute to bone erosion through an outside-in mechanism. **Figure.** Example of apparent metatarsal intra-osseous urate deposit in axial plane, with images in other planes showing urate within an erosion. Urate is colour coded as green and bone as purple.



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Abstract Number: 3200

Immunoscintigraphic Detection Of Tumor Necrosis Factor By Radiolabeled Certolizumab Pegol in Patients with Erosive Hand Osteoarthritis in Relation to Disease Activity: A Proof of Concept Study

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Background/Purpose: A recent randomized clinical trial in erosive osteoarthritis (OA) of finger joints with a TNF blocking agent, adalimumab, showed inhibition of radiographic progression in joints showing inflammatory signs (soft tissue swelling) at baseline (1). We anticipate the use of radio-labelled antibodies can help in identifying their *in vivo* abundance in joints (2) and might help to identify joints at particular risk for progression amenable for target therapies. The purpose of the current study is to investigate the uptake of radiolabeled Certolizumab pegol in patients with erosive OA and study associations with other markers of active disease.

Methods: Certolizumab Pegol was conjugated with S-HYNIC and radiolabeled with ^{99m}Tc. At baseline, static images of both hands of 5 patients with EOA (F/M: 4/1; median disease duration 8.4 years) were acquired at 2 time points (immediately following administration (early phase) and after 4-6 hours post injection (late phase)). All 18 IP finger joints were scored according to the anatomical phase scoring system (3) on hand radiographs. All patients underwent clinical examination (presence of tenderness and swelling) and Gray-scale and Power Doppler (PD) US one day prior to scintigraphy. Immunoscintigraphic findings were independently scored in a semi-quantitative way (uptake: 0 = absent, 1 = weak; 2 = strong). Descriptive statistics on joint level were calculated. Associations between uptake and other signs of disease activity, being presence of tenderness, soft tissue swelling and sonographic activity were calculated by Odds ratios (OR) (with 95% confidence intervals (95% CI)) with absence of tenderness/soft tissue swelling/sonographic activity as reference.

Results: In total, 90 IP joints were studied. Active tracer uptake was seen in 7 joints in early phase (7.8%) (all weak) and in at least 24 joints in late phase (26.7%) (19 weak, 5 strong). Considerably more uptake was present in joints with soft tissue swelling compared to non-swollen joints: in 14 (61.0%) of 23 swollen joints and in 10 (14.9%) of 67 non-swollen joints. Presence of soft tissue swelling is found to be significantly associated with uptake with OR = 8.9 (95% C.I. = 3.0 – 26.0). A trend towards more uptake in tender joints was seen compared to non-tender joints (OR = 2.1 (95% C.I = 0.8 -5.6). Similarly, a trend towards more uptake in sonographic active joints was seen (OR = 1.5 (95% C.I. = 0.5 -4.3)).

Conclusion: This is the first *in vivo* demonstration of TNF abundance in erosive OA. We found strong associations with presence of clinical swelling. The strongest association with TNF was found in the remodeling phases. These data further solidify the rationale for cytokine directed therapies in EOA. References: (1) Verbruggen G. et al. ARD 2012;71(6):891-8; (2) Barrera P. et al. ARD 2003;62:825-8; (3) Verbruggen G. and Veys E. A&R 1996;39(2):308-20

Disclosure: R. Wittoek, None; **P. Carron**, None; **B. Lambert**, None; **P. Meersseman**, None; **G. Verbruggen**, None; **F. van Den Bosch**, AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, UCB Pharma, 5,AbbVie, Bristol-Myers Squibb, Celgene, Janssen, Merck, Novartis, Pfizer, UCB Pharma, 8; **D. Elewaut**, None.

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Abstract Number: 3201

Diagnostic Value of Quantitative Sialoscintigraphy Compared to Labial Salivary Gland Biopsy in Patients with Suspected SjöGren' Syndrome

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Background/Purpose: Salivary gland dysfunction is one of the most common features of Sjögren' syndrome (SS). Sialoscintigraphy (sSC) is the only technique nowadays available to objectify salivary gland dysfunction that provides simultaneous information about type of functional defect, distribution and severity. In recent years its interpretation based mainly on qualitative indices and the appearance of the ACR criteria have shifted in favor of the biopsy (Bp). Some studies have analyzed the role of quantitative scintigraphic indices, mainly excretion fraction (EF%), in the diagnosis of SS, with mixed results. In our study we aimed to describe glandular involvement patterns and EF% values useful in SS diagnosis and to compare diagnostic accuracy of scintigraphic indices and Bp.

Methods: Patients with suspected SS and with sSC and Bp performed between 2006-2012 were included. sSC were performed in a 30 minutes protocol with 99mTc sodium pertechnetate and lemon juice stimulation. Patients already diagnosed of SS and/or with sSC or Bp requested by specialists other than rheumatologists were excluded. Correlations between glandular involvement patterns and EF% and diagnosis of SS were analyzed with Fisher exact test and Kruskal Wallis respectively. Sensitivity, specificity and receiver operating characteristic curve analysis of scintigraphic indices and Bp were performed.

Results: Among 272 patients with sSC performed in that period, 71 fulfilled inclusion criteria. Sixty-eight (96%) were women with a mean age of 52 ± 14 in the timing of sSC. Fifty-seven (80%) reported xerostomia, the majority (39%) with onset in recent months. Qualitative sSC were reported as abnormal in 51 cases (71%); data on age, xerostomia duration, xerostomia related drugs and presence of thyroid disease showed similar frequencies among normal and abnormal sSC groups. Sufficient data to apply American-European Consensus Group and ACR criteria were available in 69 and 48 patients respectively, with diagnosis of SS in 38 (54%). Uptake dysfunction (96 vs 77% p 0.134) and submandibular involvement (59 vs 30% p 0.236) were observed most frecuently in SS patients. All glands showed lower EF% medians in this group, with significant differences for submandibulary ones: right gland 29 (7-37) vs 49 (41-57) p 0.004; left gland 30 (10-45) vs 52 (29-64) p 0.007. Submandibular EF% (right gland AUC 0.793 ± 0.091 p 0.004 IC 95% [0.61-0.97]; left gland AUC 0.764 ± 0.083 p 0.007 IC 95% [0.60-0.93]) showed better diagnostic accuracy than qualitative sSC (AUC 0.601 ± 0.070 p 0.149 IC 95% [0.47-0.74]) and similar to Bp (AUC 0.789 ± 0.055 p 0.000 IC 95% [0.68-0.90]). Cutoff values of 39.5 (right gland) and 47.5 (left gland) of submandibular EF% showed a sensitivity of 95-82% and specificity of 71-67%, compared to 82% and 39% for qualitative sSC, and 58% and 100% for Bp.

Conclusion: 1) Patients fulfilling SS criteria show lower submandibular EF% compared to those who do not. 2) Diagnostic accuracy of submandibular EF% is better than qualitative sSC and similar to Bp. 3) Cutoff values of submandibular EF% of 39.5 (right gland) and 47.5 (left gland) show a sensitivity comparable to qualitative sSC but a significantly higher specificity.

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Abstract Number: 3202

Clinical and Ultrasonographic Evaluation of Joint Involvement in Patients with Systemic Sclerosis

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Background/Purpose: Systemic sclerosis is a multisystem disease characterized by the development of microangiopathy and subsequent fibrosis of skin and internal organs. The joint involvement is common, but its prevalence and characteristics differ in the literature. Traditionally, it has been assessed by clinical examination, which may underestimate the presence of synovitis and erosions. Objective: To evaluate the characteristics of joint involvement in a cohort of patients with systemic sclerosis assessed by clinimetric and ultrasonographic (US) measures.

Methods: Observational cross-sectional study. Consecutive patients with systemic sclerosis according to ACR-EULAR 2010 criteria were included. Acute phase reactants (erythrocyte sedimentation rate and C-reactive protein), immunology laboratory, rheumatoid factor and antiCCP were measured the day of clinical examination. Disease activity was measured by DAS28, hands' functionality was assessed by Duruöz Index and modified Kapandji Test, extension of cutaneous involvement by modified Rodnan Score and disability by HAQ-A. All US examinations were performed by an experienced rheumatologist, blinded to clinical and laboratory data. The US evaluation included examination in grayscale and power Doppler with a linear transducer (10-18MhZ) in the longitudinal and transverse sections of: radiocarpal and intracarpian joint, second to fifth metacarpophalangeal joint, tibiotalar joint, 1st to 6th wrist tendon extensor compartment, 1st to 5th digital flexor tendon, Achilles tendon, peroneal tendons, posterior tibialis tendon and tibialis anterior tendon, all bilaterally. For descriptive statistics, continuous variables were described as median (IQR) and categorical variables as percentages. To analyze the differences between the groups with and without ultrasound findings, Mann Whitney test was used for continuous variables, and Fisher exact test for categorical variables. It was considered as significant a p value < 0.05.

Results: 40 consecutive patients with systemic sclerosis were included. Median age was: 53 (IQR 45-59), 87.5% were women. The median time since the first not Raynaud manifestation was 4 years (IQR 2-6). The 72.5% of patients had limited scleroderma, Barnet subtype 1, 77.5% had Raynaud, 50% of patients reported suffering from arthralgia and only 4 patients arthritis, 35% (n = 14) had pitting and 17.5% (n = 7) active digital ulcers. Only 1 patient had a history of amputation and 2 had calcinosis. The median Duruöz index was 12.7 (SD 14.3), Kapandji Test 80 (SD 23), HAQ 0.79 (SD 0.83) and DAS28: 2.77 (IQR: 2.18- 3.34). The US findings were: 47.5% (n = 19) of patients presented at least one finding by ultrasound, 32.5% (n = 13) proliferative synovitis grade II in the radiocarpal joint and 2.5% (n = 1) Grade III. Only 2 patients had PD positive grade II. At the tibiotalar joint, only 2 patients had moderate synovitis. 15% (n = 6) had extensor compartment tenosynovitis and 30% (n = 12) digital flexor tenosynovitis. The 42, 5% of patients (n = 17) had tenosynovitis and/or tendinopathy in tibialis anterior tendon, posterior tibialis tendon, peroneal tendons and Achilles tendon. 12.5% (n = 5) had erosions in styloid process (n = 4) and 2nd metacarpophalangeal (n = 1). No statistically significant differences were found between the groups with and without ultrasound findings regarding the following variables: Median HAQ, DAS28, Score Rodnan, Duruöz Index and Kapandji Test, anti centromere and Scl-70 antibodies, RF, acute phase reactants, VAS, disease duration, age or treatments ($p > 0.05$).

Conclusion: The joint involvement in systemic sclerosis is frequent, evaluated both clinically and by ultrasound. This manifestation should be considered in daily care in patients with systemic sclerosis.

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Abstract Number: 3203

Analysis of Efficacy and Safety of Cyclophosphamide in Juvenile Dermatomyositis Using a Large National UK Cohort

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Background/Purpose: Cyclophosphamide (CYC) has been used as a second-line agent in the treatment of severe or refractory JDM. The published literature on the efficacy of CYC in JDM is limited to a small number of case series and case reports. The aim of this study was to describe the efficacy and safety of CYC in a large national UK patient cohort with severe or refractory JDM.

Methods: Patients treated with CYC met Bohan and Peter criteria and were recruited to the UK JDM Cohort and Biomarker Study (JDCBS). Patients received CYC at 500mg/m2 (max 500mg) every 2 weeks for first 3 doses and then 750mg/m2 (max 1.2g) every 3-4 weeks according to response for total 6-10 doses. Clinical data at baseline and 6, 12 and 24 months were recorded, including physician's global assessment (PGA) to assess overall disease activity, modified disease activity score (mDAS) to assess skin disease, and Childhood Myositis Assessment Scale (CMAS) and Manual Muscle Testing (MMT8) to assess muscle weakness. Data are presented as median [interquartile range] and were analyzed using Friedman's test for non-parametric repeated measures ANOVA, with post-hoc tests using the Wilcoxon signed rank test and Bonferroni adjustment.

Results: Of 525 patients in the JDCBS 83 patients were treated with CYC, of whom 62.7% were female. Age at diagnosis was 6.2 [4.0-10.0] years and disease duration at CYC start was 45 [26-320] days. Total duration of disease was 8.6 [5.0-12.8] years. Patients who received CYC had more severe disease compared to patients who did not receive CYC, as assessed by PGA (p=3.60e-12), mDAS (p=0.00056), CMAS (p=1.98e-9) and MMT8 (p=6.21e-5). Overall, disease activity improved over the time-points analyzed, with improvements in PGA (p=5.5e-13), mDAS (p=4.98e-10), CMAS (p=4.08e-13) and MMT8 (p=1.33e-5). For all outcome measures, the 6, 12 and 24 month time-points differed significantly from baseline. PGA reduced from 6.9 [4.1-8.0] at baseline to 2.0 [1.0-3.1] at 6 months (p=3.61e-9), 0.8 [0.3-2.3] at 12 months (p=3.89e-8) and 0.9 [0.0-1.8] at 24 months (p=4.13e-9). mDAS decreased from 4 [2.5-5] at baseline to 3 [0-4] at 6 months (p=0.00099), 2 [0-4] at 12 months (p=2.99e-5) and 0 [0-3] at 24 months (p=1.00e-7). CMAS increased from 22 [6.75-38] at baseline to 45 [38.75-49.25] at 6 months (p=9.32e-8), 47 [44-52] at 12 months (p=1.32e-7) and 49 [45-53] at 24 (p=1.77e-7) months. MMT8 increased from 52 [30.25-62.75] at baseline to 78 [67-80] at 6 months (p=9.82e-5), 76 [70-79] at 12 months (p=9.49e-5) and 80 [73-80] at 24 months (p=4.29e-5). Finally, CYC appeared to be well-tolerated with no serious adverse events including infections reported during the study period.

Conclusion: Significant improvement in both skin and muscle disease was observed in patients who received CYC at 6, 12 and 24 months after the onset of therapy. Ongoing analyses are exploring whether overall disease trajectories of patients treated with CYC differ from those of patients who were not treated with CYC.

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Abstract Number: 3204

Body Composition and Adipose Tissue Distribution in Juvenile Dermatomyositis and Associations with Cardiac Function

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Background/Purpose: Lipodystrophy and metabolic abnormalities occur frequently in juvenile dermatomyositis (JDM) and redistribution of adipose tissue has been reported in several rheumatic diseases. Visceral adipose tissue (VAT) is closely linked to cardiovascular disease. We aimed to assess body composition, with emphasis on VAT, in JDM patients and controls, and explore the associations with cardiac function.

Methods: Fifty-nine JDM patients and 59 age- and sex matched controls from the general population, were included in a cross sectional study median 16.8 years after disease onset. Body composition including fat mass (kg) and lean mass (kg) was analyzed by total body dual-energy X-ray absorptiometry (DXA). Total body fat percentage was defined as the ratio of total fat mass/(total lean mass + total fat mass). VAT (g) was quantified by DXA only in individuals above 18 years, including 38 JDM patient and 35 controls (missing data in 3 controls). Long axis strain (LAS) and early diastolic tissue velocity (E') assessed by echocardiography were used as markers for systolic and diastolic cardiac function, respectively. Inactive disease was measured by the PRINTO criteria.

Results: In JDM patients, median age was 21.5 (IQR 15.3-35.3) years and 36/59 (61%) were female; 29/59 (49.2%) had inactive disease. Cumulative prednisolone dose was median 7.9 g (IQR 3.5-12.8). 17/59 (28%) of the patients were on prednisolone and/or DMARD at follow-up. BMI was similar between JDM patients and controls (22.3kg/m^2 (4.8) vs 22.5kg/m (4.5), p=0.752). JDM patients had higher percentage total body fat (31.2% (7.9) vs 28.2% (7.5), p=0.017) and lower lean mass (41.4kg (12.9) vs 44.9kg (13.6), p=0.008) compared with controls. Fat mass was comparable in patients vs controls (data not shown). VAT was three times higher in patients compared with controls (726g (IQR 193-1183) vs 232g (IQR 72-751), p=0.022), no difference was seen between

patients with active and inactive disease. VAT correlated negatively with LAS in all patients, and even more in patients with active disease (rsp -0.397, p=0.018 and rsp -0.750, p=0.000 respectively). VAT correlated negatively with E' in all patients and in the subgroups with active and inactive disease (rsp -0.584, p= 0.000; rsp -0.567, p=0.014 and rsp -0.554, p=0.014 respectively). VAT correlated with systolic and diastolic blood pressure (BP) in all patients, and in patients with active and inactive disease. No correlation between VAT and LAS, E', Diastolic BP was observed in controls. No correlation was found between VAT and use of medication at follow-up or cumulative prednisolone dose.

Conclusion: Patients with JDM had a higher total body fat percentage and a lower lean mass compared with matched controls, despite similar BMI. A redistribution of adipose tissue in JDM patients was demonstrated, as VAT was three times higher in patients compared with controls. Both systolic and diastolic cardiac dysfunction were associated with higher VAT in patients, but not in controls. This suggests that the increased visceral adipose may contribute to subclinical heart disease in JDM.

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Abstract Number: 3205

Efficacy and Safety of Canakinumab in Patients with Periodic Fever Syndromes (Colchicine-Resistant FMF, HIDS/MKD AND TRAPS): Results from a Phase 3, Pivotal, Umbrella Trial

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Background/Purpose: Periodic fever syndromes (PFS) are rare auto-inflammatory conditions that include, among others, cryopyrin-associated periodic syndromes (CAPS), familial Mediterranean fever (FMF), hyper-IgD syndrome/mevalonate kinase deficiency (HIDS/MKD), and TNF receptor-associated periodic syndrome (TRAPS).[1] Canakinumab (CAN), a fully human, highly specific anti-IL-1β neutralizing monoclonal antibody, is effective in CAPS.[2] IL-1β has been shown to be involved in the pathogenesis of FMF, HIDS/MKD and TRAPS, for which no or limited treatment options exist.[1] Open-label studies have suggested the efficacy of CAN in colchicine-resistant/intolerant FMF (crFMF), HIDS/MKD, and TRAPS.[3-5] We report the efficacy and safety of CAN from the randomized treatment epoch of the Phase 3 pivotal study in patients (pts) with crFMF, HIDS/MKD or TRAPS.

Methods: The study (NCT02059291) consists of 3 disease cohorts (crFMF, HIDS/MKD and TRAPS) and 4 study epochs: a screening epoch (E1) of up to 12 wks, a randomized treatment epoch (E2) of 16 wks, a randomized withdrawal epoch (E3) of 24 wks and an open-label treatment epoch (E4) of 72 wks. Pts (aged ≥2 years) with a flare during E1 were randomized (1:1) in E2 to receive CAN or placebo (PBO). Primary objective was to demonstrate that CAN 150 mg (or 2 mg/kg for pts ≤40 kg) sc q4w is superior to PBO in achieving a clinically meaningful response, defined as resolution of the index flare at Day 15 and no new disease flares over 16 weeks (wks) of treatment. Safety assessments included adverse events (AEs) and serious AEs(SAEs).

Results: Of 181 pts (crFMF, n=63; HIDS/MKD, n=72; TRAPS, n=46) randomized in E2, 6 discontinued the study (5 PBO; 1 CAN). In all 3 disease cohorts, the proportion of responders for the primary outcome at Wk 16 was significantly higher with CAN vs PBO (Table). At Wk 16, a significantly higher proportion of pts achieved a PGA score <2, CRP ≤10 mg/L and SAA ≤10 mg/L in the CAN group vs PBO in all 3 cohorts. The most frequently affected system organ class across 3 cohorts was infections and infestations typically involving the upper respiratory tract. The incidence of SAEs was 8.6%, 4.7% and 11.8% in crFMF, TRAPS and HIDS/MKD cohorts,respectively.

Table. Proportion of responders at Week 16 by cohort

Cohort	CAN (150 mg q4w), n/m (%)	Placebo n/m (%)	p value
crFMF	19/31 (61.3)	2/32 (6.3)	<0.001*
HIDS/MKD	13/37 (35.1)	2/35 (5.7)	0.0020*
TRAPS	10/22 (45.5)	2/24 (8.3)	0.0050*

*Statistical significance (1-sided) at the 0.025 level based on Fisher exact test/logistic regression model. n=number of pts who responded; m=number of pts evaluated for response

Conclusion: These results demonstrated superior efficacy of canakinumab after a 16-week treatment period compared with placebo. The overall safety profile was not distinct from those reported in previous controlled studies. References: 1. Savic S and Wood P. *Clin Med.*2011;11(4):396–401. 2. Kuemmerle-Deschner JB, et al. *Ann Rheum Dis*. 2015;74:850. 3. Brik R, et al. *Ann Rheum Dis*. 2013;72:75. 4. Arostegui J, et al. *Ann Rheum Dis*. 2015;74:401. 5. Lachmann H, et al. *Ann Rheum Dis*. 2015;74:852.

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Abstract Number: 3206

Effectiveness of Childhood Vaccinations in CAPS Patients Treated with Canakinumab: Results from an Open-Label Phase III Extension Study

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Background/Purpose: Canakinumab (CAN) has been shown not to impair antibody production following vaccination in children in an open-label phase 3 study (NCT01302860).[1] Here we present the results from the extension of this study. The objective of this study was to evaluate the presence of protective antibody levels following immunization with inactivated vaccines in CAPS patients during extension study.

Methods: Patients who completed the core study were allowed to continue into the extension study on the standard dosing regimen of 2 mg/kg subcutaneous CAN every 8 weeks or on last dose/dosing regimen received in the core study. Vaccination response was evaluated using post-vaccination antibody titers at 4 and 8 weeks after immunization. Patients were considered assessable for an antibody response to a specific vaccination if they had a measurement of antibody titer 0-14 days post-vaccination (pre-vaccination assessment) and at least 1 subsequent measurement of antibody titer at 4 weeks and/or 8 weeks post-vaccination. However, for patients with adequate pre-dose antibody titers and maintained during the trial, the specific patient vaccination was deemed non-assessable.

Results: During the extension phase, of 17 patients (≤6 years), 4 received 8 types of vaccinations against *Corynebacterium diphtheria*, *Bordetella pertussis*, *Neisseria meningitidis*, *Clostridium tetani*, influenza type A and type B, *Haemophilus influenza* B, *Streptococcus pneumoniae*, or hepatitis B. Of 20 unique patient-vaccination cases, 17 were assessable for a vaccination response, whereas for the remaining 3, pre-dose antibody titer was not available. For 16 (94.1%) assessable cases, post-vaccination antibody titers increased above protective levels. For one patient who received Tetravec formulation (diphtheria, tetanus and acellular pertussis combination), the response observed for 1 (vaccination against *Clostridium tetani*) of the 3 vaccines included in Tetravac represented optical density rather than antibody concentrations and hence considered non-evaluable. For 19/20 patient-vaccinations, including those without pre-dose antibody titers, protective levels were observed during the study, which were maintained throughout the extension.

Conclusion: Canakinumab appeared to have no effect on post-vaccination antibody production following the administration of non-live vaccines in CAPS patients. **References**: 1.Brogan P, et al. *Arthritis Rheumatol*. 2015;67:(S10).

Disclosure: P. Brogan, None; **M. Hofer**, Novartis, 5; **J. B. Kuemmerle-Deschner**, Novartis, 2,Novartis, SOBI, Baxalta, 5; **B. Lauwerys**, None; **A. Speziale**, Novartis, 3; **X. Wei**, Novartis Pharmaceutical Corporation, 3; **R. Laxer**, Database funding from Novartis, 2.

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Abstract Number: 3207

The Deficiency of Adenosine Deaminase Type 2 (DADA2)—Results of Anti-TNF Treatment in a Cohort of Patients with a History of Stroke

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Background/Purpose: The deficiency of adenosine deaminase type 2 (DADA2) is an autosomal recessive disease resulting from biallelic mutations in *CECR1*. Patients commonly present with vascular and inflammatory manifestations including livedo racemosa, fevers, ischemic strokes, anemia and polyarteritis nodosa (PAN). Neurologic events can occur even when acute phase reactants are normal. Therapeutic options have included anti-thrombotic agents as well as anti-inflammatory agents without adequate disease suppression. Hematopoietic stem cell transplant has been reported to be a successful therapeutic option but has associated risks. Previous reports have demonstrated perivascular tumor necrosis factor (TNF) in DADA2, and suggest that TNF inhibitors ameliorate DADA2-associated PAN. We therefore aimed to assess whether anti-TNF agents would reduce the number of strokes in DADA2.

Methods: Patients with DADA2 and a history of ischemic stroke seen at the NIH between June 2013 and May 2016 were included in this cohort. Patients were initiated on anti-TNF therapy with etanercept, adalimumab or golimumab, and were monitored by follow-up visits to the NIH every six to twelve months. The primary outcome was the number of strokes after initiation of an anti-TNF agent compared to the number of strokes before anti-TNF treatment. Secondary outcomes included progression of other DADA2 related clinical manifestations, change in acute phase reactants, and hematologic markers.

Results: Out of 22 DADA2 patients followed at the NIH, 15 had a history of ischemic stroke. Before anti-TNF initiation, the 15 patients in the stroke cohort had 55 strokes over 1173 patient months (model based recurrence rate 0.043) compared to 0 strokes over 373 patient months occurring post-initiation of anti-TNF (recurrence rate 0). The P value for testing equal recurrence rate is 1.68×10^{-8}. A matched follow up time analysis using 328 patient months both prospectively and retrospectively has an estimated probability of 1 (15/15) for the strokes occurring before anti-TNF treatment as opposed to after, with a 95% Blyth-Still-Casella exact confidence interval of (0.7873, 1) ($P = 5.1 \times 10^{-5}$). This refutes the null hypothesis that anti-TNF therapy will not have an effect on stroke frequency and that the probability of stroke pre-anti-TNF initiation is 0.5. Laboratory studies showed statistically significant improvements in ESR, CRP, hematocrit, hemoglobin, platelets, leukocytes and serum iron.

Conclusion: These results show that anti-TNF treatment is highly effective in reducing the risk of stroke and improving laboratory parameters in DADA2. Although not directly addressed here, it may be advisable to initiate anti-TNF at the time of diagnosis of DADA2 even in the face of normal acute phase reactants.

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Abstract Number: 3208

Preliminary Response to JAK1/2 Inhibition with Baricitinib in “Candle”,“Savi” and “Candle-like” Diseases. a New Therapeutic Approach for Type I IFN Mediated Autoinflammatory Diseases

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Session Title: Pediatric Rheumatology – Clinical and Therapeutic Aspects III: Autoinflammatory Diseases and Juvenile Dermatomyositis

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Session Time: 11:00AM-12:30PM

Background/Purpose: Chronically elevated serum IP-10 (CXCL10) levels, and a prominent "interferon (IFN)-response gene signature" in patients with chronic neutrophilic dermatosis with lipodystrophy and elevated temperatures (CANDLE), CANDLE-like diseases or with gain-of-function mutations in *TMEM173/STING* with STING-associated vasculopathy with onset in infancy (SAVI), suggested modulation of IFN signaling might be a therapeutic option for patients with some autoinflammatory interferonopathies. The compassionate use program was developed to provide baricitinib (JAK1/JAK2 inhibitor) to CANDLE, CANDLE-like and SAVI patients who have no other comparable or satisfactory treatment options. Potential efficacy of treatment was assessed by a reduction in mean Autoinflammatory Diary Scores (ADS) to < 0.5 (CANDLE and CANDLE-like pt.) and to <1.0 (SAVI pt.) and reduction of steroid doses to <0.15mg/kg/day or by at least 50% reduction from baseline.

Methods: Paired t-tests were used to compare mean ADS and prednisone doses at the last clinic visit to baseline data

Results: Between October 2011 and March 4th, 2016, 18 patients (pt.) have been treated (mean duration 2.3 years, SD±1). 9 of 11 CANDLE pt. and 3 of 4 SAVI pt. achieved an ADS of < 0.5 and < 1.0 at the time of their last visit, respectively. None of 3 CANDLE-like pt. achieved an ADS of < 0.5 (mean ADS for all cohorts decreased from 1.5 ± 0.8 to 0.5 ± 0.5) ($p< 0.005$), 8 of 10 CANDLE pt. and 2 of 3 CANDLE-like pt. achieved a reduction in steroid doses > than 50% from baseline. 4 of 10 CANDLE pt. discontinued oral steroids completely and continued to have an ADS of <0.5. The only SAVI pt. on steroids at baseline continues at the same dose. Mean total prednisone dose decreased in patients receiving steroids at baseline from 0.7 mg/kg/day (0.2-1.8) to 0.2 mg/kg/day (0-0.8) ($p< 0.005$). The mean baricitinib dose at last patient visit was 6.9 ± 3.3 mg/day (0.2 mg/kg/day). 13 pt. reported at least 1 serious adverse event (SAE), infection being the most common. 2 CANDLE pt. have been discontinued due to SAEs (avascular necrosis; BK viremia and azotemia). Both pt. subsequently died: the first patient due to underlying liver and kidney disease 18 months after discontinuation of baricitinib, the second patient due to worsening interstitial lung disease with development of respiratory failure 4 months after discontinuation of baricitinib and initiation of another JAK inhibitor. 1 pt. required temporary interruption of baricitinib due to neutropenia, and 4 other pt. had their dose electively reduced after testing positive for BK viremia; patients were asymptomatic. The most common adverse events were upper respiratory infections, cough, and BK viruria (baseline BK virus screening was not performed).

Conclusion: Preliminary efficacy and safety data in 18 patients with autoinflammatory type I Interferonopathies treated with baricitinib are encouraging and suggest that targeting IFN signaling with a JAK1/JAK2 inhibitor may be a successful therapeutic strategy. Monitoring BK viral titers in blood and urine, in addition to other measures of safety and efficacy, may be important in dose selection and the benefit-risk assessment of baricitinib for these patients.

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Abstract Number: 3209

Clinical and Radiological Outcomes of 5 Years Remission Steered Treatment in Early Rheumatoid and Undifferentiated Arthritis Patients

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SESSION INFORMATION

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Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

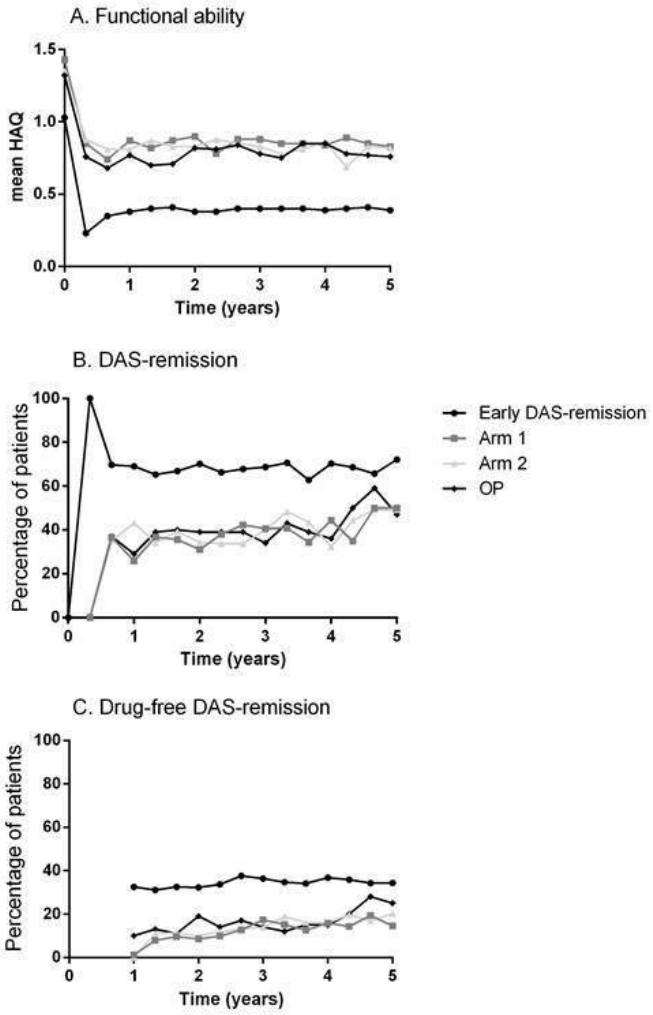
Background/Purpose: To assess clinical and radiological outcomes of induction therapy followed by 5 years disease activity score (DAS)-remission steered treatment in early arthritis patients.

Methods: The IMPROVED study enrolled 610 early rheumatoid arthritis (RA, 2010) or undifferentiated arthritis (UA) patients. All started induction therapy methotrexate (MTX) and tapered high dose of prednisone. If DAS-remission (<1.6) was achieved at 4 months prednisone was stopped (early DAS-remission (ER)) and if remission persisted at 8 months MTX was also stopped. Patients not in ER were randomized to MTX+sulfasalazine+hydroxychloroquine+low dose prednisone (arm 1) or MTX+adalimumab (arm 2), 50 patients were not randomized and were treated 'outside of protocol' (OP). Every 4 months treatment adjustments aimed at DAS<1.6: DAS<1.6 taper/stop medication and DAS≥1.6 restart/intensify. (Drug-free) DAS-remission percentages were compared between the different diagnosis and treatment strategies. Radiologic damage progression (Sharp-vanderHeijde Score, SHS) from baseline to 5 years was scored by 2 independent readers in chronologic order.

Results: Patients in the ER group had better functional ability over time, compared to arms 1 and 2 and the OP group, who between them had similar HAQ scores over time (figure). 295/610 (48%) patients achieved DAS-remission at 5 years: 220/387 (57%) in the ER group, 31/83 (37%) in arm 1, 29/78 (37%) in arm 2 (p=0.768 arm 1 vs arm 2) and 15/50 (30%) in OP (figure). 134/610 (22%) patients achieved DFR (drug-free DAS-remission): 105/387 (27%) in the ER group, 9/83 (11%) in arm 1, 12/78 (15%) in arm 2 (p=0.374 arm 1 vs arm 2) and 8/50 (16%) in OP (figure). DAS-remission percentages were similar in RA and UA patients and autoantibody positive (+) vs negative (–) patients. More UA patients achieved DFR (33% UA vs 19% RA, p<0.001), and more patients negative for anti-citrullinated protein antibodies (ACPA) (31% ACPAneg vs 15% ACPApos, p<0.001) or rheumatoid factor (RF) (28% RFneg vs 17% RFpos, p<0.001) achieved DFR. Median (IQR) SHS progression was 0.5 (0-3) in 306 completers in the ER group, 0 (0-1) in arm 1 (62 completers), 0 (0-1) in arm 2 (59 completers) (p=0.818 arm 1 vs arm 2) and 0 (0-3) in 31 OP completers. SHS progression ≥5 points had occurred in 40/306 (13%) in the ER group, 9/62 (15%) in arm 1, 7/59 (12%) in arm 2 (p=0.710 arm 1 vs arm 2) and 2/31 (6%).

Conclusion: Induction therapy followed by 5 years DAS-remission steered treatment resulted in 48% DAS-remission and 22% DFR in early RA and UA patients. More UA patients and more autoantibody negative patients achieved DFR. Radiologic damage progression was well suppressed in the majority of patients.

Figure: Outcomes over 5 years: A. functional ability, B. DAS-remission, C. Drug-free DAS-remission.



HAQ: health assessment questionnaire; DAS: disease activity score; OP: outside of protocol.

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Abstract Number: 3210

10+ Years' Follow-up of a Danish 2-Year Treat-to-Target RCT in Patients with Early Rheumatoid Arthritis: Baseline Predictors of Functional and Radiographic Outcomes

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Hørslev-Petersen[2], [1]Rigshospitalet (Glostrup and Blegdamsvej), Århus University Hospital, Odense University Hospital, Herlev/Gentofte Hospital, Slagelse Sygehus, Chr X hospital (University of South Denmark) and Zitelab Aps, DANBIO Registry and Departments of Rheumatology, Glostrup, Denmark, [2]Rigshospitalet (Glostrup and Blegdamsvej), Århus University Hospital, Odense University Hospital, Herlev/Gentofte Hospital, Slagelse Sygehus, Chr X hospital (University of South Denmark) and Zitelab Aps, DANBIO Registry and Departments of Rheumatology, Copenhagen, Denmark

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Background/Purpose: Few RCTs have investigated long-term (10+ years) outcomes of goal-directed synovitis suppression in early rheumatoid arthritis (RA). The CIMESTRA trial was a 2-year double-blinded Danish multicenter study on aggressive treatment with csDMARDS (methotrexate (MTX) versus MTX and cyclosporine) in combination with intra-articular glucocorticoids (1+2). Disease control after 2 years (yrs) was excellent with ≈50% in remission and halted radiographic progression in both groups. We here present 10+ year follow-up data. The aims were to 1) investigate the clinical and radiographic status and 2) identify baseline predictors of functional status and erosive progression.

Methods: Of 160 patients (pts) included, 93 pts also had MRI of the wrist performed at baseline. 13 pts had died since baseline. All living pts were contacted and 120 signed informed consent to participate in a 10+ yrs' follow-up visit assessing e.g. treatment, disease activity (DAS28, CRP, 4 variables), physical function (HAQ), X-ray of hands and feet. Baseline MRI was scored by OMERACT rheumatoid arthritis MRI scoring (RAMRIS) system, X-rays by Sharp-van der Heijde total Sharp Score (TSS). Descriptive statistics (medians (IQR) or percentages) were appliedMultivariable linear regression analyses of a panel of baseline variables (see foot note in table) with backward selection were performed with HAQ at 10+ yrs (HAQ_{10+}) and radiographic progression since baseline ($\Delta TSS_{0\text{-}10+}$) as dependent variables.

Results: 120 of 160 pts (75%) completed the 10+ yrs visit. 74 pts with available baseline MRI and X-rays of both time points were included in the prediction models. Withdrawal analysis comparing the 160 pts with the 120 and 74 pts showed similar baseline characteristics for all comparisons of demographic and disease-related variables,all $p > 0.20$. Follow-up was after 11.5 yrs (10.7-12.2). Pts were 63 yrs (55-72) and 70% females. 20% received biologics (+/- csDMARD), 53% csDMARD alone. 27% were in drug free remission. DAS28 was 2.0 (1.5-2.6); pain score: 1 cm (0.3-3); pt. global: 1.1 cm (0.2-2.9); swollen joint count (28SJC): 0 (0-0); tender joint count (28TJC): 0(0-1). 76% of pts were in DAS28 remission; HAQ-score was 0.25 (0-0.75); $\Delta TSS_{0\text{-}10+}$(median (IQR)):5(0-14); $\Delta TSS_{0\text{-}10+}$(mean±SD): 11.2±17.1). The annual progression rate since baseline was median (IQR):0.4 (0-1.2); mean±SD:0.99±1.53. Multivariable linear regression analyses are shown in Table.

Conclusion: 10+ years after diagnosis 75% were in DAS28 remission. HAQ-score was low, and mean radiographic progression was <1 TSS unit/year. High DAS28 and positive anti-CCP at baseline were independent predictors of poorer functional status. Baseline MRI bone marrow edema and anti-CCP positivity were independent predictors of radiographic progression . References: 1. Arthritis Rheum 2006; 54: 1401-9. 2. Ann Rheum Dis 2008; 67: 815-22. **Table.**Predictors of functional status and radiographic progression, final models.

Baseline predictors of:			
-Functional status (HAQ_{10+})*	**Coefficient**	**95% CI**	**p-value**
DAS28 (per unit increase)	0.10	0.02-0.18	0.02
Anti CCP (if positive)	0.24	0.02-0.46	0.03
-Radiographic progression (ΔTSS_{0-10+})*	**Coefficient**	**95% CI**	**p-value**
Anti CCP (if positive)	6.10	0.44; 14.33	0.03
MRI bone marrow edema (per unit increase)	0.87	0.18; 1.55	0.02

*:Initial baseline variables in the HAQ_{10+} (§) and ΔTSS_{0-10+}(#)multivariable linear models before backward selection were: Total Sharp-van der Heijde-Score (TSS)[§ #]; Health Assessment Questionnaire score[§]; Disease Activity Score (28-joint count, 4 variables)[§ #]; age[§ #]; anti CCP[§ #]; gender[§ #]; MRI erosion score[§ #]; MRI synovitis score[§ #]; MRI bone marrow edema[§ #]. CI, confidence interval; CCP, cyclic citrullinated peptide (dichotomized value); MRI, magnetic resonance imaging.

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Abstract Number: 3211

Early Radiological Progression in Rheumatoid Arthritis Leads to More Long-Term Joint Damage in Daily Clinical Practice; Six Year Radiological Outcomes of a Strict Treat-to-Target Cohort in the Netherlands

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Background/Purpose: Implementation of treat-to-target (T2T) in Rheumatoid Arthritis (RA) leads to limited radiological damage during follow-up of 3 years. Questions are whether these results are maintained over time and whether patients with progressive radiological damage can be recognized early. This study describes the 6 years radiological outcomes of patients with early RA following the implementation of T2T in daily clinical practice.

Methods: In the Dutch Rheumatoid Arthritis Monitoring tight control cohort I, patients with early RA were treated according to a

T2T step-up strategy starting with methotrexate monotherapy. Radiographs of hands and feet were obtained at baseline, after 6 and 12 months, and every 3 years thereafter. Primary outcome was the change in median Sharp/vanderHeijde score (SHS) of the total cohort using Friedman's repeated-measures analysis of variance on ranks with signed-rank post hoc Wilcoxon tests. Secondary outcomes were 1) median individual change in SHS scores at different time intervals, 2) percentages of patients with at least minimal clinical important difference in SHS (MCID; increase ≥ 5 SHS points) between consecutive time moments and baseline. Mann-Whitney U test was used to test the difference in radiological progression between patients with and without MCID between 6 months and baseline.

Results: Data of 221 patients were used (78% fulfilling the ACR 1987 criteria). Within the first year of treatment 77% reached remission or low-disease activity (Disease Activity Score in 28 joints ≤ 3.2) and this percentage remained stable during 6 years of follow-up. Median (IQR) total SHS score increased from 2.0 (0.0–7.0) at baseline to 12.0 (6.0–22.0) at 6 years of follow-up (P<0.001) (Figure 1). The median (IQR) of the individual SHS progression rates per time interval were as follows: 2.0 (1.0–4.0) between 1 year and baseline, 2.0 (0.0–4.0) between 3 years and 1 year, 3.0 (1.0–5.0) between 6 years and 3 years (P<0.001). Percentages of patients with at least MCID in SHS scores after 6 months, 1 year, 3 years and 6 years were 12.8%, 22.3%, 44.9% and 76.0% respectively. Patients with MCID between 6 months and baseline had significantly more radiological progression during further follow-up than patients without (Figure 2).

Conclusion: Maintaining strict treat-to-target in early RA in daily clinical practice results in only minor radiological progression in long-term follow-up. Most joint damage occurs in the first year of treatment. Patients with early important clinical radiological progression had significantly more joint damage during further follow-up.

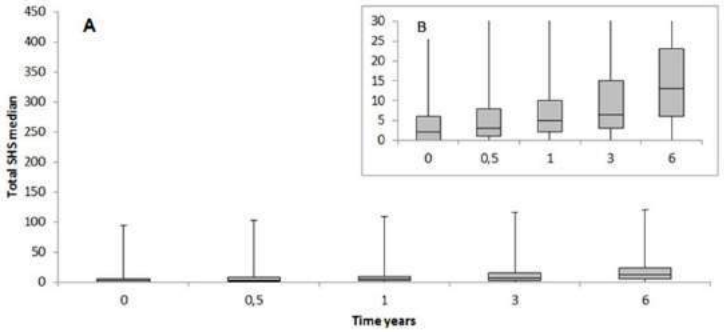

Figure 1. Box plots of the Sharp / van der Heijde score (SHS) over 6 years of follow-up. **A** shown on the full range of the score (0-448), and **B** zoomed into the range of the observed scores

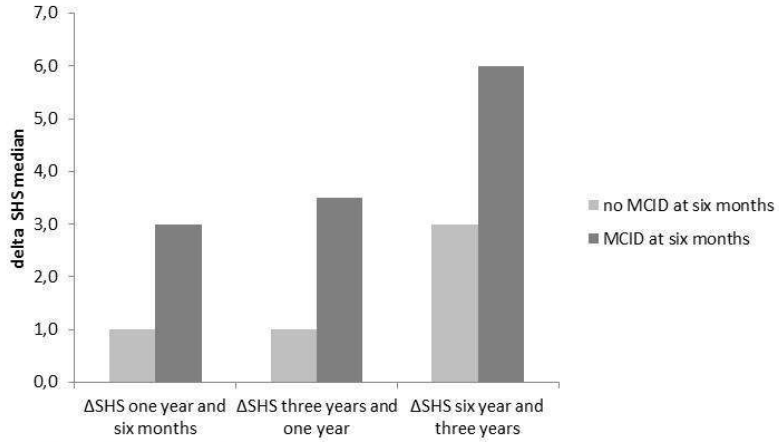

Figure 2. Median SHS progression at consecutive time intervals stratified between patients with and without MCID at six months. ΔSHS = difference in Sharp / van der Heijde score; MCID = minimal clinical important difference (increase in total SHS score ≥ 5).

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arthritis-leads-to-more-long-term-joint-damage-in-daily-clinical-practice-six-year-radiological-outcomes-of-a-strict-treat-to-target-cohort-in-the-netherl

Abstract Number: 3212

Treat-to-Target in RA: Does Early Simplified Disease Activity Index (SDAI) Remission Lead to Better 5-Year Functional Outcomes Than SDAI Low Disease Activity?

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Background/Purpose: The management of rheumatoid arthritis (RA) has evolved considerably during the last couple of decades, with current recommended practice being a treat-to-target approach, involving early intervention and tight monitoring of treatment effect. When starting a new therapy, the recommended target is remission (REM) or alternatively low disease activity (LDA). Limited data exist on the impacts of reaching REM rather than LDA on long-term outcomes. The objective of this study was to compare RA-patients who achieved Simplified Disease Activity Index (SDAI) REM versus LDA 6 months after initiating disease-modifying anti-rheumatic drug (DMARD) therapy, with regard to physical function, Health Related Quality of Life (HRQoL) and disease activity during 5-year follow-up in a real-life clinical setting.

Methods: Data were provided by the Norwegian DMARD study (NOR-DMARD), a multicentre longitudinal observational study. We selected DMARD-naive patients with RA who were consecutively enrolled from December 2000 to April 2009 (n=1617), starting treatment with methotrexate (n=1197), other conventional synthetic DMARDs (n=380) or a biological DMARD (n=33). Data on each patient were collected at baseline, after 3, 6 and 12 months, and yearly thereafter, including the modified Health Assessment Questionnaire (MHAQ), the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) with Physical and Mental Components Summary scores (PCS and MCS, respectively) and assessments that allowed the calculation of the composite disease activity scores SDAI, Clinical Disease Activity Index (CDAI) and the Disease Activity Score based on 28 joint counts with ESR (DAS28). Multivariate linear mixed models were used to explore the effect of SDAI status at 6 months on physical function (MHAQ), HRQoL (SF-36 PCS and MCS) and disease activity (SDAI, CDAI, DAS28) during 1-5 year follow-up. The statistical models were adjusted for potential baseline confounders such as age, sex, disease duration and disease activity.

Results: Of the 1617 eligible patients at baseline, 1301 (80.5%) had a registered visit at 6 months. 602 patients were in either SDAI REM (n=143, 11.0%) or LDA (n=459, 35.3%) at 6 months and were included in the main analyses. The achievement of SDAI REM rather than SDAI LDA at 6 months was associated with significantly better physical function (MHAQ) and HRQoL (SF-36 PCS) and with lower disease activity (SDAI, CDAI, DAS28) at all yearly follow-up visits between 1 and 5 years (table).

Conclusion: The achievement of SDAI REM rather than LDA 6 months after initiating DMARD-therapy, lead to better long term functional outcomes during 5-year follow-up in a real-life clinical setting. The results support the use of a stringent treatment target, such as SDAI REM, when initiating DMARD-therapy in RA-patients.

Impacts of achieving SDAI remission versus low disease activity at 6 months on long term physical function, HRQoL and disease activity

	Follow-up visits							
	12 months		24 months		36 months		60 months	
Achieved SDAI status at 6 months	**REM (n=124)**	**LDA (n=396)**	**REM (n=107)**	**LDA (n=350)**	**REM (n=82)**	**LDA (n=305)**	**REM (n=42)**	**LDA (n=180)**
MHAQ								
Mean value (SE)	0.10 (0.03)	0.29 (0.02)	0.16 (0.03)	0.28 (0.02)	0.15 (0.04)	0.30 (0.02)	0.16 (0.05)	0.32 (0.02)
Mean difference (SE)	0.19 (0.04)		0.12 (0.04)		0.15 (0.04)		0.16 (0.05)	
P value	**<0.0001**		**0.001**		**<0.0001**		**0.002**	
SF-36 PCS								
Mean value (SE)	46.9 (0.9)	40.3 (0.5)	45.3 (1.0)	40.3 (0.5)	46.3 (1.0)	40.6 (0.6)	44.7 (1.3)	39.3 (0.7)
Mean difference (SE)	6.6 (1.1)		5.0 (1.1)		5.7 (1.2)		5.4 (1.4)	
P value	**<0.0001**		**<0.0001**		**<0.0001**		**<0.0001**	
SF-36 MCS								
Mean value (SE)	51.3 (0.9)	50.1 (0.5)	51.2 (1.0)	49.7 (0.5)	52.8 (1.0)	50.6 (0.6)	54.1 (1.3)	51.3 (0.9)
Mean difference (SE)	1.2 (1.0)		1.5 (1.1)		2.2 (1.1)		5.4 (1.5)	
P value	**0.24**		**0.17**		**0.05**		**<0.0001**	
SDAI								
Mean value (SE)	4.42 (0.79)	9.04 (0.43)	5.73 (0.82)	8.75 (0.45)	4.48 (0.89)	8.81 (0.48)	5.91 (1.22)	8.87 (0.61)
Mean difference (SE)	4.62 (0.88)		3.02 (0.91)		4.33 (0.99)		2.96 (1.34)	
P value	**<0.0001**		**0.001**		**<0.0001**		**0.03**	
CDAI								
Mean value (SE)	4.09 (0.72)	8.42 (0.40)	5.27 (0.74)	8.04 (0.41)	3.91 (0.82)	7.94 (0.44)	5.04 (1.12)	8.01 (0.56)
Mean difference (SE)	4.33 (0.80)		2.77 (0.83)		4.03 (0.90)		2.97 (1.23)	
P value	**<0.0001**		**0.001**		**<0.0001**		**0.02**	
DAS28								
Mean value (SE)	2.02 (0.12)	2.75 (0.07)	2.33 (0.13)	2.79 (0.07)	2.28 (0.14)	2.74 (0.07)	2.30 (0.18)	2.72 (0.09)
Mean difference (SE)	0.73 (0.13)		0.46 (0.14)		0.46 (0.15)		0.42 (0.20)	
P value	**<0.0001**		**0.001**		**0.003**		**0.04**	

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Assessment of Two Different DAS Treatment Targets in Early Active Rheumatoid Arthritis Patients

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Background/Purpose: It remains to be determined if setting remission or low disease activity as treatment target affects significant outcomes in early active rheumatoid arthritis (RA) patients. We compared 2 patient groups who were treated for 5 years aiming at DAS<1.6 or DAS≤2.4.

Methods: Five years outcomes were compared in 133 patients from the BeSt study (inclusion criteria: early (≤2 years symptom duration) active (≥6 of 66 swollen joints, ≥6 of 68 tender joints, and either erythrocyte sedimentation rate ≥28 mm/hour or a visual analogue scale global health score ≥20mm) RA (1987)), randomized to initial therapy with methotrexate, sulfasalazine and tapered high dose of prednisone (arm 3), targeted at DAS≤2.4 ('LDA target group'), and 175 early RA patients from the IMPROVED-study who would have fulfilled the inclusion criteria of the BeSt-study, who started with methotrexate and tapered high dose of prednisone, targeted at DAS<1.6 ('remission target group'). To correct for baseline differences, the associations of treatment target with achieving DAS<1.6, Boolean remission at year 1 and drug-free DAS-remission (DFR) at year 5 were analysed by logistic regression analysis.

Results: At baseline, patients in the remission target group had earlier and less active disease than the LDA target group (mean DAS±SD 4.1±0.7 vs 4.4±0.9, p=0.012) (table), and they had better outcomes at the first evaluation point (after 4 months of treatment and 3 months in the LDA target group). The DAS target was achieved by 56% (LDA target group) and 53% (remission target group) (table). At year 1, the DAS target was achieved by 67% (DAS≤2.4) and 51% (DAS<1.6). Similar percentages in both groups had a DAS≤2.4 (67% (DAS≤2.4) and 73% (DAS<1.6), p=0.333), but DAS<1.6 was achieved more often in the remission targeted group (51% (DAS<1.6) vs 30% (DAS≤2.4), p<0.001). DFR was by protocol not possible at year 1 in the LDA targeted group. 15% of the remission target group were in DFR. There was less radiological damage progression in the remission target group (median (IQR)/mean±SD 0 (0-0)/0±0.2 (DAS<1.6) vs 0 (0-1)/0.9±2.3 (DAS≤2.4), p<0.001). At year 5, the target was achieved in 43% (remission target group) and 61% (LDA target group). DAS≤2.4 was achieved in similar percentages (61% vs 61%, p=0.092). More patients in the remission targeted group had DAS<1.6 and DFR (43% vs 32%, p=0.003, and 18% vs 8%, p=0.003, respectively).

DAS<1.6 as treatment target was associated with more DAS<1.6 (OR 3.04 (95% CI 1.64-5.62)) and Boolean remission (3.03 (1.45-6.33)) at year 1 and more DFR at year 5 (3.77 (1.51-9.43)) corrected for gender, symptom duration, baseline DAS, baseline SHS, and time on anti-TNF.

Conclusion: Early active RA patients had better outcomes after DAS<1.6 than DAS≤2.4 steered treatment. DAS-remission targeted treatment was an independent predictor for achieving DAS<1.6 and Boolean remission at year 1 and DFR at year 5.

Table: Clinical characteristics at baseline and follow up in BeSt and IMPROVED patients

Baseline	BeSt n=133	IMPROVED n=175	p-value
Age (years), mean ± SD	55 ± 14	53 ± 15	0.408
Female, n (%)	88 (66)	126 (72)	0.271
Symptom duration (weeks), median (IQR)	23 (15-53)	17 (8-28)	<0.001
DAS, mean ± SD	4.4 ± 0.9	4.1 ± 0.7	0.012
Tender joint count, median (IQR)	13 (9-19)	10 (8-14)	<0.001
Swollen joint count, median (IQR)	14 (10-18)	11 (8-17)	0.023
ESR mm/h, median (IQR)	35 (17-46)	32 (17-52)	0.761
VAS general health, mean ± SD	51 ± 22	57 ± 22	0.010
HAQ, mean ± SD	1.4 ± 0.7	1.5 ± 0.6	0.114
RF positive, n (%)	86 (65)	108 (62)	0.999
ACPA positive, n (%)	68 (51)	98 (56)	0.715
Total SHS, median (IQR)/mean ± SD	1.5 (0-3)/2.8 ± 3.8	0 (0-0)/0.8 ± 1.9	<0.001
3 month (BeSt) or 4 months (IMPROVED)			
DAS, mean ± SD	2.4 ± 1.0	1.8 ± 1.0	
Δ DAS, mean ± SD	2.0 ± 1.1	2.4 ± 1.1	
HAQ, mean ± SD	0.6 ± 0.6	0.5 ± 0.6	
DAS>2.4, n (%)	56 (42)	46 (26)	
DAS≥1.6 - ≤2.4, n (%)	48 (36)	34 (19)	
DAS-remission, n (%)	27 (20)	92 (53)	
1 year			
DAS, mean ± SD	2.0 ± 0.9	1.6 ± 1.0	0.004
Δ DAS, mean ± SD	2.4 ±1.1	2.5 ± 1.1	0.445
HAQ, mean ± SD	0.5 ± 0.5	0.6 ± 0.6	0.148
DAS>2.4, n (%)	33 (25)	36 (21)	0.333
DAS≥1.6 - ≤2.4, n (%)	49 (37)	38 (22)	0.002
DAS-remission, n (%)	40 (30)	89 (51)	<0.001
Drug-free remission, n (%)	-	27 (15)	
SHS progression, year 0-1, median (IQR)/mean ± SD	0 (0-1)/0.9 ±2.3	0 (0-0)/0 ± 0.2	<0.001
ACR/EULAR Boolean remission, n (%)	21 (16)	46 (26)	0.004
5 year			
DAS, mean ± SD	1.7 ± 0.8	1.5 ± 0.8	0.014
Δ DAS, mean ± SD	2.6 ± 1.1	2.7 ±1.0	0.849
HAQ, mean ± SD	0.6 ± 0.6	0.6 ± 0.6	0.738
DAS>2.4, n (%)	21 (16)	15 (9)	0.092
DAS≥1.6 - ≤2.4, n (%)	38 (29)	31 (18)	0.056
DAS-remission, n (%)	43 (32)	76 (43)	0.003
Drug-free remission, n (%)	10 (8)	31 (18)	0.003
ACR/EULAR Boolean remission, n (%)	15 (11)	33 (19)	0.069

DAS: disease activity score, ESR: erythrocyte sedimentation rate, VAS: visual analogue scale, HAQ: health assessment questionnaire, RF: rheumatoid factor, ACPA: anti-citrullinated protein antibodies, SHS: Sharp/van der Heijde Score; SHS progression: ≥0.5 point increase in SHS; ACR: American College of Rheumatology; EULAR: European League Against Rheumatism; SD: standard deviation, IQR: interquartile range. Δ DAS was calculated by extracting the baseline DAS.

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Implementation of Treat to Target in Rheumatoid Arthritis through a Learning Collaborative

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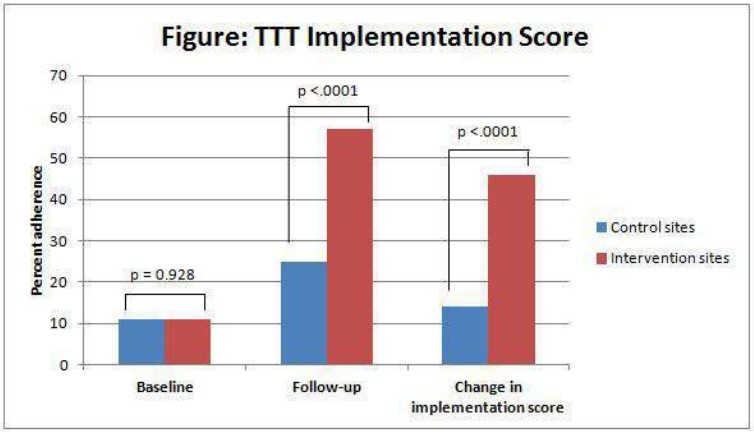
Background/Purpose: Treat to target (TTT) is a recommended strategy in the management of rheumatoid arthritis (RA), but various studies suggest that its uptake in routine US care is sub-optimal. We carried out a randomized controlled trial of a Learning Collaborative to facilitate implementation of TTT.

Methods: We recruited 11 rheumatology sites from the US and randomized them into 2 groups: 5 sites received the Learning Collaborative intervention over 9 months and the other 6 sites formed a wait-list control group. The Learning Collaborative used a description of the problem with strategies for improvement (Model for Improvement with Change Package) and action phases. The intervention included: 1 face to face meeting and 8 learning sessions via webinar; use of a web-based tool for sharing results of plan-do-study-act cycles; and collection by sites of their monthly improvement measures assessing progress. The primary outcome was the between group difference in the change in TTT implementation, as measured in medical records by study staff at baseline and follow-up. TTT implementation was scored using 4 items: shared-decision making, choice of a target, use of a disease activity measure (DAM), and changing treatments based on the target and DAM. The TTT implementation was scored on a 0-100% scale based on the presence/absence of the 4 items. The between group difference was measured at the patient-level, accounting for the clustering in a linear mixed model.

Results: 23 providers participated at the five intervention sites and 23 at the six control sites. The chart review included 320 RA patients from intervention and 321 from control. The patient groups were well matched, with a mean age of 60 years, 78% were female, 64% were seropositive, and treatments were similar at the start of follow-up. At baseline, mean TTT implementation score was 11% in both groups ($p = 0.93$) (see Figure). At follow-up, TTT implementation score in the intervention arm was 46% (SD 36%) compared with 14% (SD 28%) in the control arm ($p < 0.0001$) (see Figure). Improvements were observed for all four items in the implementation score (see Table). No negative consequences from the intervention were observed, with similar use of laboratory testing and x-rays, as well as similar rates of adverse events in the intervention and control arms.

Conclusion: A Learning Collaborative was an effective intervention to improve implementation of TTT for RA. Future steps will focus on analyzing the sustainability of change.



Note: Implementation score included 4 items in TTT, each scored as present or absent.

Table: Results for 4 Items Included in Implementation Score

	Wait List Control	Intervention	p-value
Visits, n	321	320	
Baseline visits with TTT items present			
Shared decision-making	24.5%	51.3%	<0.001
Treatment target	0%	0.6%	0.25
Disease activity measure (DAM)	30.2%	20.0%	0.003
Treatment decision based on target and DAM	0%	0.6%	0.25
Follow-up visits with TTT items present			
Shared decision-making	43.0%	85.9%	<0.001
Treatment target	12.5%	45.6%	<0.001
Disease activity measure (DAM)	52.3%	89.1%	<0.001
Treatment decision based on target and DAM	8.4%	27.8%	<0.001

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ASK1 Is Regulated By IL-1β and TNF and Modulates Key Rheumatoid Arthritis (RA) Fibroblast-like Synoviocyte Functions (FLS)

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Background/Purpose: RA fibroblast-like synoviocytes (FLS) possess a unique aggressive phenotype characterized by increased cell growth, cytokine production and invasion. Previous unsuccessful attempts to target the downstream kinases in the mitogen-activated protein kinase (MAPK) pathway in RA have led to increased interest in the MAPK upstream kinases. These interconnected signal transduction pathways can involve the highest level of the MAPKs, namely the MAP3Ks. One of these MAP3Ks, apoptosis signal regulating kinase-1 (ASK1), is upstream of p38 and JNK and could potentially overcome the pro-inflammatory effects of selective p38 inhibitors. To address this question, we examined the expression, regulation and function of ASK1 in RA FLS.

Methods: FLS were obtained from RA and osteoarthritis (OA) synovial tissues at arthroplasty. ASK1 expression was determined by immunohistochemistry (IHC), confocal microscopy and qPCR. ASK1 promoter activity was measured using a minimal promoter luciferase reporter construct (pGL4.23-luciferase) that included a 994 kb region subcloned from the ASK1 promoter. ASK1 was blocked with the selective inhibitor ASKI-1 (IC50=4.7 nM; used at 0.02-2 uM). Migration was assessed using a scratch-wound assay, cell growth using an MTT assay and invasion using a Martigel matrix invasion assay.

Results: IHC demonstrated ASK1 expression in RA synovium, particularly in the synovial intimal lining. Because FLS reside in this region, we then studied its expression in these cells. ASK1 is constitutively expressed in FLS with similar levels in RA and OA as determined by qPCR ($p>0.1$, $n= 6$ each). Unexpectedly, IL-1β (2 ng/ml) or TNF (5 ng/ml) for 1 – 48 hours increased ASK1 mRNA levels. Levels peaked at 6 hours, with 9±4-fold ($p<0.05$, $n=3$) and 9±2-fold ($p<0.05$, $n=3$) increases, respectively. Dose

responses for IL-1β and TNF showed a maximal effect with 0.02 ng/ml for IL-1β and 0.5 ng/ml for TNF. Confocal microscopy showed that ASK1 protein localizes to the nucleus and cytosol before and after treatment with IL-1β (2 ng/ml for 6 or 24 hr) with a 68±16% increase in protein levels compared to medium ($p<0.01$ at 24 hr, n=3). To explore the mechanism of increased gene expression, we used a luciferase reporter construct with the a portion of the ASK1 promoter. After 1 hr of IL-1β stimulation, luciferase expression increased 2±0.5-fold ($p<0.03$, n=3) confirming that ASK1 is induced at the transcriptional level. We then evaluated the effect of a selective inhibitor on FLS functions relevant to RA. ASK1 inhibition in RA FLS reduced invasion into Matrigel by 34±8% (24 hr, $p<0.05$, n=3), migration by 29±9% (24 hr, $p<0.04$, n =3) and cell growth by 29±8% (48 hr, $p<0.03$, n=3).

Conclusion: ASK1 gene transcription is induced by inflammatory cytokines implicated in RA FLS. Because it is perhaps the only inducible MAPK family member, inhibition could have a degree of site and event selectivity for inflamed tissues. ASK1 inhibition also significantly reduced FLS functions related to joint damage. Therefore, targeting ASK1 is a novel therapeutic strategy for FLS-mediated damage in RA.

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Abstract Number: 3216

Integrated High-Dimensional Analyses Reveal a Pathologically Expanded 'Peripheral' B Cell-Helper T Cell Population in Rheumatoid Arthritis

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Background/Purpose: Determining the pathologic functions of T cells that infiltrate target tissues remains a central challenge in autoimmune diseases. In rheumatoid arthritis (RA), the formation of T cell-B cell aggregates and differentiation of plasma cells within synovium suggest a pathologic role for synovial T cells with B cell-helper function. The prevailing view considers CD4+ T follicular helper (Tfh) cells, identified as PD-1^{+} CXCR5^{+}, as the principal T cell population capable of promoting B cell differentiation. However, Tfh cell migration is largely restricted to secondary lymphoid organs. It is thus difficult to reconcile the lymphoid-homing migratory patterns of Tfh cells with the development of T cell-B cell aggregates in inflamed synovium.

Methods: We used mass cytometry and multidimensional flow cytometry to interrogate T cells that express markers of activation, including PD-1, MHC II, CD69, CD25, and CD38, in synovial tissue, synovial fluid, and blood from patients with seropositive RA and other inflammatory arthritides. Sorted PD-1^{hi} T cells from blood and synovial samples were analyzed by RNAseq, RT-PCR, intracellular flow cytometry, and *in vitro* B cell helper assays. Synovial tissue was also evaluated by immunofluorescence microscopy.

Results: Mass cytometric analysis of seropositive RA synovial tissue cells revealed a strikingly expanded population of PD-1^{hi} CXCR5^{-} CD4^{+} T cells, which constituted ~25% of synovial CD4^{+} T cells and outnumbered Tfh cells by 8-fold. PD-1^{hi} CXCR5^{-} cells were similarly enriched in synovial fluid from patients with seropositive RA, but not seronegative inflammatory arthritides. PD-1^{hi} CXCR5^{-} cells, but not Tfh cells, were also expanded in the circulation of seropositive, but not seronegative, RA patients and decreased with DMARD therapy. Surprisingly, these cells were not exhausted, but instead highly expressed factors that enable B cell help, including IL-21, CXCL13, ICOS, SAP, and MAF. Like Tfh cells, PD-1^{hi} CXCR5^{-} cells from synovial tissue, synovial fluid, and blood induced plasma cell differentiation *in vitro*, which was blocked by neutralization of IL-21 or SLAMF5. However, RNAseq transcriptomics robustly separated circulating PD-1^{hi} CXCR5^{-} cells from Tfh cells. Compared to Tfh cells, PD-1^{hi} CXCR5^{-} cells expressed high levels of chemokine receptors that direct migration to inflamed sites, such as CCR2, CX3CR1, and CCR5, and a decreased Bcl6/Blimp1 ratio. Flow cytometry confirmed CCR2 expression on ~50% of synovial PD-1^{hi} CXCR5^{-} T cells. By microscopy, PD-1^{hi} CXCR5^{-} T cells were frequently found adjacent to B cells in RA synovium.

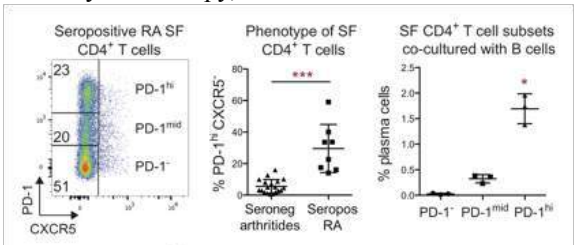

Figure 1. Frequency of PD-1^{hi} CXCR5^{-} CD4^{+} T cells in seropositive RA synovial fluid (left, middle), and ability of PD-1^{hi} CXCR5^{-} T cells to induce plasma cell differentiation *in vitro* (right).

Conclusion: We suggest that PD-1^{hi} CXCR5^{-} T cells represent a T peripheral helper (Tph) cell population, analogous to T follicular helper (Tfh) cells, that supports B cell responses in non-lymphoid tissues. Given their marked expansion in seropositive RA, these cells may be important in driving pathologic B cell responses and autoantibody production.

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Abstract Number: 3217

Broad-Based Interrogation of the Serum Proteome Suggests That RA Onset Is Associated with Activation of the Intrinsic Coagulation Cascade

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Background/Purpose: The establishment of longitudinal pre-clinical RA cohorts is beginning to provide important insights into the mechanisms that precede the onset of clinically detectable disease. In an attempt to identify candidate biomarkers that may suggest the activation of specific biological pathways associated with RA onset, we used aptamer based proteomic technologies to mine the serum proteome of a cohort of individuals who were followed longitudinally into disease onset.

Methods: We have prospectively followed a large cohort of first-degree relatives of North American Native RA patients, a subset of whom developed clinically detectable synovitis after an extended period of follow up. Representative serum samples were selected from 10 such individuals and analyzed using the SOMAmer (slow off-rate modified aptamer) platform (SOMAlogic Inc., Boulder, Co) to generate simultaneous quantitative levels on 1132 serum proteins. For each individual, a sample was obtained as close as possible to the RA onset date, while a matched sample had been obtained a minimum of 2 years prior to the onset. Fold changes for each individual protein at the two time points were derived from the data. The significance of the fold change was calculated by paired analysis using Stanford Analysis of Microarrays (SAM) software set at a false discovery rate <1%. For selected proteins, levels were confirmed using ELISA at multiple time points.

Results: Of the 10 patients who converted from pre-RA to clinical RA, 6 were female and all were active smokers. The average age at conversion was 34.8 (+/- 13.6) years, while the average number of months to conversion was 51.8 (+/- 30.6). Anti-CCP antibodies were detectable in the pre-RA sample in 4 patients. All 10 patients were anti-CCP positive at the time of clinical disease onset. Quantification using SOMAlogic platform indicated that 18 proteins had a mean fold increase of 3.2 (range=1.2-12.8), while 28 proteins had a mean fold decrease of 0.7 (range=0.3-0.8). Ingenuity pathway analysis revealed activation of angiogenesis, and both mucosal and cellular immunity. Of note, there was a consistent proteomic signature suggesting activation of the intrinsic coagulation cascade at the time of RA onset: Factor X increased by a mean fold increase=1.6, Factor IX increased by a mean fold increase=3.4, and Factor V increased by a mean fold increase=1.3, compared to the pre-RA sample. This pattern was detectable in 9 of 10 patients studied.

Conclusion: Based on broad-based quantitative analysis of more than 1000 serum proteins in longitudinally followed individuals who ultimately developed RA, we present evidence indicating activation of the intrinsic coagulation cascade at the time of clinical development of synovitis. Aligning with a growing body of evidence, we hypothesize that these hemostatic cofactors contribute to the pathophysiology of RA, possibly through cytokine signalling as well as synovial fibrin deposition. Our approach also demonstrates the utility of a novel assay for biomarker discovery, one that provided a rich dataset that will help shape the direction of future studies.

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Abstract Number: 3218

Synovial Mast Cells Associate with High Disease Activity and Predict Radiographic Progression at 12 Months in Patients with Early Rheumatoid Arthritis

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Background/Purpose: Mast cells (MCs) are immune cells present in the synovial membrane and implicated in the pathogenesis of Rheumatoid Arthritis, although their exact contribution to disease development and progression is still unclear. In particular, their presence in synovia has never been evaluated in correlation with longitudinal disease parameters. Aim of this study was to analyse mast cells in the synovia of early RA patients and their correlation with disease outcomes.

Methods: 99 DMARD-naive patients with early (<12 months) RA (n=99) fulfilling the 2010 ACR/EULAR classification criteria were recruited as part of the Pathobiology of Early Arthritis Cohort at Barts Health NHS Trust. Sections of paraffin embedded synovial tissue obtained by ultrasound-guided synovial biopsy were stained for CD117+ by immunohistochemistry to calculate the density of CD117+ MCs. Patients were stratified according to MC numbers and clinical parameters at baseline and 12 months follow-up were evaluated.

Results: At baseline, high synovial MC counts significantly associated with ACPA and RF positivity (p=0.029 and 0.013, respectively) and higher disease activity (DAS28 p=0.003). Accordingly, the density of synovial MCs at baseline correlated with DAS-28 (rS=0.308, p=0.002), ESR (rS=0.273, p=0.007), CRP (rS=0.217, p=0.033), and swollen joint count (rS=0.308, p=0.002). At 12 months follow-up, patients with high baseline MC counts showed a higher prevalence of radiographic progression (9/26 vs 3/26 vs 1/27 in high, medium and low MC counts, p=0.007, n=79), with no differences in terms of treatment and response to therapy. Among baseline characteristics, only age and MC counts showed a statistically significant difference in progressors Vs non-progressors (Table 1).

Conclusion: We show a significant association between synovial mast cells and a severe clinical phenotype and seropositivity for ACPA and RF in a DMARD-naive early RA cohort. Furthermore, patients with high mast cell counts were significantly more likely to develop radiographic damage at 12 months. Interestingly, several baseline parameters, potentially associated with a higher risk of radiographic progression (e.g. antibody positivity, disease activity), were not different in progressors Vs non-progressors, except for age, while mast cell numbers were significantly higher in progressors. Although additional studies are warranted to confirm the association and, possibly, the direct contribution of mast cells to radiographic progression, our work suggests that the analysis of synovial mast cell could be used as a prognostic biomarker for patient stratification in RA. **Table 1.** Baseline characteristics in radiographic progressors Vs non-progressors

		Radiographic progression		
	All (n=79)	**No (n=66)**	**Yes (n=13)**	**P value** (Anova or Chi sq as appropriate)
Female, %	70.7	69.7	69.2	0.973
Age, mean (SD)	52.7 (16.6)	50.16	62.15	0.010
ESR, mean (SD)	38 (30)	37 (31)	42 (25)	0.264
CRP, mean (SD)	17 (25)	14 (21)	17 (21)	0.650
RF+, %	73.7	71.2	76.9	0.675
ACPA+, %	75.8	74.2	76.9	0.839
DAS28, mean (SD)	5.65 (1.41)	5.55 (1.41)	5.95 (1.00)	0.405
Tender Joint Count	11.33 (7.14)	11.39 (7.33)	10.92 (6.33)	0.926
Swollen Joint Count	7.33 (5.88)	6.94 (5.53)	7.69 (6.16)	0.577
VAS	66.25 (24.5)	66.65 (25.80)	66.53 (19.35)	0.672
HAQ	1.51 (0.79)	1.46 (0.74)	1.56 (0.59)	0.624
Mast cell density (n/mm2)	24.7 (29.55)	19.26 (24.82)	49.73 (38.7)	0.001
Mast cell groups				0.007
Low MCs, %	34.2	39.4	7.7	
Medium MCs, %	32.9	34.8	23.1	
High MCs,%	32.9	25.8	69.2	

Disclosure: F. Rivellese, None; **F. Humby**, None; **S. Kelly**, None; **A. de Paulis**, None; **G. Marone**, None; **C. Pitzalis**, None.

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Altered microRNA Expression Pattern in Synovial and Blood Neutrophils in Rheumatoid Arthritis Reveals the Pathogenic Profile of These Cells. Effect of Biological Therapies

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Background/Purpose: MicroRNAs (miRNA) have recently emerged as a new class of modulators of gene expression, regulating inflammation, degradation of extracellular matrix and invasive behavior of the resident cells in rheumatoid arthritis (RA). **Objectives**: 1) To investigate the miRNA expression profile in synovial and blood neutrophils in RA and its role in the pathogenesis of this disorder. 2) To study the effects of biological therapies on the miRNA profile in neutrophils.

Methods: Neutrophils were isolated from peripheral blood of 20 healthy donors and 20 RA patients. Synovial neutrophils were isolated from paired synovial fluid of 10 RA patients. nCounter microRNA Assay was used to detect simultaneously 800 human microRNAs in each sample. Altered miRNAs were analyzed for potential mRNA targets using Ingenuity pathways analysis (IPA) software. Several mRNA targets of these miRNAs were analyzed by RT-PCR. Healthy neutrophils were treated in vitro with anti-CCPs isolated from RA patients. mRNA expression of DICER, Ago1, Ago2, exportin was evaluated through RT-PCR. DICER protein expression was analyzed by western blot. Synovial and peripheral blood RA neutrophils were treated in vitro with tocilizumab and infliximab.

Results: Among 800 miRNAs analyzed, 121 were detected in neutrophils from peripheral blood or synovial fluid. Using a 2 fold change cut off, 97 miRNAs were altered in peripheral blood neutrophils from RA patients compared to healthy donors. Most of them were downregulated (94 downregulated and 3 upregulated). Accordingly, RA neutrophils showed a downregulation of the proteins participating in miRNA biogenesis, including DICER, Ago1, Ago2, exportin 5. In addition, treatment of healthy neutrophils with IgGs anti-CCPs isolated from RA patients decreased the expression of these proteins, thus pointing at these autoantibodies as main modulators of microRNA neutrophil expression. Functional IPA analysis showed that altered miRNAs regulated cellular functions such as development, growth, proliferation and movement and were mainly involved in immunological disease. Among the miRNAs found deregulated blood, 34 miRNAs were found even more significantly reduced in synovial neutrophils compared to paired blood neutrophils from RA patients. These miRNAs were mainly involved in inflammatory response, suggesting the abnormal activation of this cell subtype in the joint. In vitro treatment of RA neutrophils with infliximab or tocilizumab reversed the expression of miRNAs and genes involved in their biogenesis.

Conclusion:

1) RA neutrophils exhibit a defect in the miRNAs processing, showed by a decrease in most of the detected miRNAs and the concomitant downregulation of proteins involved in their biogenesis. This defect seems to be modulated, at least partially, by anti-CCPs antibodies. 2) miRNA downregulation is even more pronounced in synovial resident neutrophils, which may contribute to the high inflammatory profile of these cells in the joint. 3) Tocilizumab and infliximab reverse the altered miRNA profile and the defect in the biogenesis machinery, reducing the proinflammatory pattern in these cells. Funded by CTS7940, PI2013-0191, CP15/00158, PI15/001333

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Abstract Number: 3220

Distinct Single Cell Gene Expression Signatures of Monocyte Subsets Differentiate Between TNF-Alpha Inhibitor Treatment Response Groups in Rheumatoid Arthritis

Theresa L. Wampler Muskardin[1], Wei Fan[2], Zhongbo Jin[3], Mark A. Jensen[4], Jessica M. Dorschner[3], Yogita Ghodke-Puranik[3], Kerry Wright[1], John M. Davis III[5], Eric L. Matteson[1], Clement Michet Jr.[1], Thomas G. Mason II[6], Scott T. Persellin[7], Daniel Schaffer[1], Betty Dicke[1], Danielle Vsetecka[3] and Timothy B. Niewold[8], [1]Rheumatology, Mayo Clinic, Rochester, MN, [2]Mayo Clinic, Rochester, MN, [3]Division of Rheumatology and Department of Immunology, Mayo Clinic, Rochester, MN, [4]Department of Immunology and Division of Rheumatology, Mayo Clinic, Rochester, MN, [5]Division of Rheumatology, Mayo Clinic, Rochester, MN, [6]Division of Rheumatology - Department of Medicine, Mayo Clinic Rochester, Rochester, MN, [7]Department of Rheumatology, Mayo Clinic Rochester, Rochester, MN, [8]Rheumatology and Immunology, Mayo Clinic, Rochester, MN

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Background/Purpose: In rheumatoid arthritis (RA), initiating effective treatment as soon as possible within the so-called therapeutic “window of opportunity” is the strategy, and remission is a primary goal. Recent work from our group demonstrated that pre-treatment serum type I IFN- β/α ratio >1.3 can predict non-response to anti-TNF-alpha therapy in RA patients. The cellular mechanisms that underlie the IFN-β/α ratio that predicts response are not known. Effects of IFN on single cells and immune cell subtypes may be masked in whole blood or mixed cell populations.

Methods: To better understand the underpinnings of the pre-treatment IFN-β/α ratio, we used single cell expression analysis to investigate whether monocyte gene expression differs significantly between RA patients according to their pre-TNF-α inhibitor serum IFN-β/α ratio. Single classical (CL) and single non-classical (NC) blood-derived monocytes were isolated from 15 seropositive RA subjects prior to biologic therapy. Subjects were grouped by pre-TNF-α inhibitor serum IFN-β/α ratio into two groups, IFN-β/α >1.3 (n=6) and IFN-β/α <1.3 (n=9). We performed unsupervised hierarchical clustering of 87 target genes, and compared groups by Mann-Whitney and Fisher's. Genes that differed in categorical analysis were tested in logistic regression models.

Results: *JAK1* and *IL1A* were strong differentiators between patients with IFN-β/α < 1.3 and IFN-β/α > 1.3, the groups which correspond to response/non-response to anti-TNF agents. In categorical analyses, in NC cells alone, expression (OR, p) of *STAT2* (19.2, <0.0001), *ILT7* (10.4, 0.02)), *PKR* (8.9, 0.03), *TLR7* (3.1, 0.03), and *IRAK1* (3.4, 0.04) was more likely in the non-response group. In CL monocytes alone, expression of *IFIT2* (8.9, 0.04) and *CD36* (9.7, 0.04) was more likely. In multivariate logistic regression, *IL1A*, *CD32a*, *IL-8*, *TYK2*, and *IRAK1* expression in monocytes (CL+NC) aligned with treatment response groups. Each was also strongly statistically significant in regression models of monocyte subsets. In comparison to the mixed monocyte model, *IL-8* and *IRAK1* in NC and *CXCR3* in CL cells demonstrated even stronger alignment with response groups. STAT2 was strongly predictive of response group in NC cells alone. CXCL9 was strongly predictive of response group in CL cells alone. Models from monocyte subsets provided higher area under the curve in ROC analysis in comparison to the mixed monocyte model.

Conclusion: Within-cell co-expression patterns demonstrate biological differences in monocyte subsets of RA patients with an IFN-β/α > 1.3, the ratio of type I IFNs which predicts non-response to anti-TNF therapy. Differentiation by gene expression was strongest among the response/non-response patient groups when monocyte subsets were analyzed separately, and distinct expression

signatures were identified, suggesting that further study of monocyte subsets will likely illuminate molecular differences that determine treatment response to TNF-α inhibition in RA. This work will help to develop a more individualized approach to therapy in RA based upon the underlying biology of disease in a given patient.

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Abstract Number: 3221

Efficacy and Safety of Sarilumab Versus Adalimumab in a Phase 3, Randomized, Double-Blind, Monotherapy Study in Patients with Active Rheumatoid Arthritis with Intolerance or Inadequate Response to Methotrexate

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Background/Purpose: Sarilumab is a human mAb that blocks IL-6 from binding to both membrane-bound and soluble IL-6Rα. Efficacy and safety of sarilumab + non-biologic DMARDs have been demonstrated.[1,2] However, 30% of patients with RA use biologics as monotherapy because of intolerance or contraindications to combination therapy.[3] In this phase 3 trial, safety and efficacy of sarilumab monotherapy were compared with adalimumab monotherapy in adult patients with active RA (NCT02332590).

Methods: Adults (N=369) intolerant of, inappropriate for, or inadequate responders to MTX received subcutaneous sarilumab (200 mg every 2 weeks [q2w]) or adalimumab (40 mg q2w) monotherapy for 24 weeks in this double-blind, double-dummy superiority study. Starting at week 16, patients with inadequate response could increase to weekly adalimumab (or matching placebo). The primary endpoint, change from baseline in DAS28-ESR at week 24, was assessed using a mixed model for repeated measures analysis. Secondary endpoints, including clinical disease activity index (CDAI), were also assessed (Table).

Results: Baseline demographics and disease characteristics were generally comparable between treatment groups. At week 24, significantly greater decrease in DAS28-ESR scores, greater incidence of DAS28-ESR remission and ACR20/50/70 responses, and improvement in HAQ–Disability Index were observed with sarilumab vs adalimumab (Table); results included patients switching to weekly adalimumab. Patients in the sarilumab group were twice as likely to achieve CDAI remission at week 24 vs adalimumab (nominal $P<0.05$). Incidences of adverse events (AEs) (64%) and serious AEs (sarilumab, 5%; adalimumab, 7%) were similar between groups. Neutropenia and injection site reactions were more common with sarilumab; headache and worsening of RA were more common with adalimumab. Incidences of infections (sarilumab, 29%; adalimumab, 28%) and serious infections (1%) were similar between groups. Neutropenia was not associated with an increased incidence of infections. Most injection site reactions were mild; only 2 cases led to treatment discontinuation in the sarilumab group. There was 1 death in the sarilumab group, 35 days after initiating treatment, due to acute cardiac failure.

Conclusion: Sarilumab monotherapy demonstrated superiority to adalimumab monotherapy in reduction of disease activity and improvement in signs and symptoms and physical function in patients with active RA who were inappropriate candidates for continued treatment with MTX due to intolerance or inadequate response. The overall incidences of AEs and serious AEs were

similar between groups, as was the rate of infections and serious infections. **References:** 1. Genovese et al. *Arthritis Rheumatol*. 2015;67:1424-1437. 2. Fleischmann et al. Presented at: ACR; November 7-11, 2015; San Francisco, CA. 3. Emery et al. *Ann Rheum Dis*. 2013;72:1897-1904.

Table. Efficacy Endpoints at Week 24

	Sarilumab 200 mg q2w (n=184)	**Adalimumab 40 mg q2w (n=185)**	***P* value**
DAS28-ESR Mean (SD) LS mean change from baseline (SE)	3.5 (1.4) -3.3 (0.1)	4.5 (1.4) -2.2 (0.1)	<0.0001 <0.0001
DAS28-ESR remission, n (%)	49 (26.6)	13 (7.0)	<0.0001
ACR20 response, n (%)	132 (71.7)	108 (58.4)	0.0074
ACR50 response, n (%)	84 (45.7)	55 (29.7)	0.0017
ACR70 response, n (%)	43 (23.4)	22 (11.9)	0.0036
HAQ-DI Mean (SD) LS mean change from baseline (SE)	1.0 (0.7) -0.6 (0.05)	1.2 (0.7) -0.4 (0.05)	0.0074 0.0037
CDAI Mean (SD) LS mean change from baseline (SE)	13.8 (11.4) -28.9 (0.8)	16.6 (10.4) -25.2 (0.8)	0.0244[a] 0.0013[a]
CDAI remission, n (%)	13 (7.1)	5 (2.7)	0.0468[a]

CDAI, clinical disease activity index; HAQ-DI, HAQ–Disability Index; LS, least squares; q2w, every 2 weeks; SD, standard deviation; SE, standard error. [a]Nominal *P* values.

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Abstract Number: 3222

Efficacy and Safety of Monotherapy with Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, Compared with Adalimumab Monotherapy in Biologic-Naive Patients with Active Rheumatoid Arthritis: Results of a Global, Randomized, Double-Blind, Parallel-Group, Phase 3 Study

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Session Time: 11:00AM-12:30PM

Background/Purpose: Sirukumab, a human monoclonal antibody that selectively binds to the cytokine IL-6 with high affinity, is under development for rheumatoid arthritis (RA) and other diseases. The objective of this study was to compare the efficacy and safety of sirukumab monotherapy and adalimumab monotherapy in biologic-naive patients (pts) with active RA.

Methods: In this Phase 3 global study (SIRROUND-H), 559 biologic-naive pts with active RA who were intolerant to methotrexate (MTX), considered inappropriate for MTX treatment for safety reasons, or were inadequate responders to MTX were randomized (1:1:1) to sirukumab SC 50mg q4w, sirukumab SC 100mg q2w, or adalimumab SC 40mg q2w, stratified by the reason for MTX failure. Pts with <20% improvement in swollen and tender joint counts at Wk 16 qualified for early escape (adalimumab to q1w dosing; sirukumab 50mg q4w to 100mg q2w). Co-primary endpoints were change from baseline in DAS28 (ESR) at Wk 24 and proportion of pts achieving ACR50 at Wk 24. The treatment comparison of interest for the primary hypotheses was sirukumab 100mg q2w vs adalimumab 40mg q2w. If the first or both of the primary hypotheses were met, the study would be considered positive.

Results: A significantly greater improvement in DAS28 (ESR) at Wk 24 was demonstrated with sirukumab 100mg q2w (P <0.001) and sirukumab 50mg q4w (P = 0.013) vs adalimumab 40mg q2w (**Table**). All 3 treatment groups showed clinically relevant improvements in ACR50 response at Wk 24, but differences between sirukumab and adalimumab were not statistically significant (ie, hypotheses for the second co-primary endpoint were not met). A clinically relevant proportion of pts attained the major secondary endpoints of DAS28 (ESR) remission and ACR20 response at Wk 24 in all 3 treatment groups. Numerical differences were observed in efficacy endpoints depending on the reason pts failed MTX (**Table**). Changes from baseline in CDAI, SDAI, HAQ-DI, SF-36 and FACIT-Fatigue were clinically important for all 3 treatment groups at Wk 24. Efficacy was observed with both sirukumab doses as monotherapy from as early as Wk 2 for most endpoints and sustained through Wk 24. A greater proportion of pts had ≥1 AE through Wk 24 with sirukumab 100mg q2w (63.6%) vs sirukumab 50mg q4w (57.0%) and adalimumab 40mg q2w (55.4%), and rates of serious AEs were 2.7%, 7.0%, and 4.3%, respectively; no deaths were reported through Wk 24.

Conclusion: In biologic-naive pts with active RA who were intolerant to, considered inappropriate for treatment with, or inadequate responders to MTX, sirukumab monotherapy SC 50mg q4w and 100mg q2w reduced signs/symptoms of RA. Significantly greater improvements in DAS28 (ESR) at Wk 24 were demonstrated with both doses of sirukumab monotherapy vs adalimumab monotherapy, while ACR responses were similar. The safety profile of sirukumab was similar to the known safety profile of anti-IL-6 receptor biologics.

Table 1. Key Endpoints for Full Analysis Set and by Reason for MTX Failure at Baseline

Endpoint	Adalimumab 40mg q2w (n = 186)	Sirukumab 50mg q4w (n = 186)	Sirukumab 100mg q2w (n = 187)
Primary endpoints			
Reason for MTX discontinuation at baseline			
DAS28 (ESR) mean (SD) change from baseline at Wk 24	−2.19 (1.44)	−2.58 (1.52)[a]	−2.96 (1.58)[b]
Efficacy reason[c,d]	−2.19 (1.34)	−2.39 (1.50)	−3.01 (1.60)
Safety reason[e,f]	−2.20 (1.56)	−2.84 (1.52)	−2.89 (1.56)
ACR50 at Wk 24, n (%)	59 (31.7)	50 (26.9)[g]	66 (35.3)[h]
Efficacy reason[c,i]	32 (30.2)	25 (23.6)	35 (32.7)
Safety reason[e,f]	27 (33.8)	25 (31.3)	31 (38.8)
Major secondary endpoints			
Reason for MTX discontinuation at baseline			
DAS28 (ESR) remission at Wk 24, n (%)	14 (7.5)	24 (12.9)[j]	38 (20.3)[k]
Efficacy reason[c,i]	8 (7.5)	8 (7.5)	19 (17.8)
Safety reason[e,f]	6 (7.5)	16 (20.0)	19 (23.8)
ACR20 at Wk 24, n (%)	105 (56.5)	100 (53.8)[j]	110 (58.8)[j]
Efficacy reason[c,i]	65 (61.3)	56 (52.8)	58 (54.2)
Safety reason[e,f]	40 (50.0)	44 (55.0)	52 (65.0)

[a] P = 0.013 vs adalimumab 40mg q2w.
[b] P <0.001 vs adalimumab 40mg q2w.
[c] Pts failed MTX purely for efficacy reason (inadequate response) with no tolerability or safety concern.
[d] Adalimumab 40 mg q2w, n = 106; sirukumab 50 mg q4w, n = 105; sirukumab 100 mg q2w, n = 105.
[e] Pts failed MTX due to tolerability issues or safety concerns, including pts who were inadequate responders in the presence of a tolerability or safety concern.
[f] Adalimumab 40 mg q2w, n = 80; sirukumab 50 mg q4w, n = 80; sirukumab 100 mg q2w, n = 80.
[g] P = 0.306 vs adalimumab 40mg q2w.
[h] P = 0.464 vs adalimumab 40mg q2w.
[i] Adalimumab 40 mg q2w, n = 106; sirukumab 50 mg q4w, n = 106; sirukumab 100 mg q2w, n = 107.
[j] Nominal P >0.05 vs adalimumab 40mg q2w.
[k] Nominal P <0.001 vs adalimumab 40mg q2w.

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Abstract Number: 3223

Efficacy and Safety of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, in Patients with Active Rheumatoid Arthritis Despite Anti-TNF Therapy: Results from a Randomized, Double-Blind, Placebo-Controlled, Global, Phase 3 Study

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Background/Purpose: Sirukumab is a human monoclonal antibody that selectively binds to the IL-6 cytokine with high affinity and is under development for rheumatoid arthritis (RA) and other diseases. This Phase 3 global study (SIRROUND-T) evaluated the efficacy and safety of sirukumab in patients (pts) with active RA who were refractory or intolerant to anti- TNF agents.

Methods: Eligible pts were ≥18 years, had moderate to severe active RA, and had documented lack of benefit to ≥1 anti-TNF agent or intolerance to ≥2 anti-TNF agents. Pts were randomized 1:1:1 to sirukumab SC 50mg q4w, sirukumab SC 100mg q2w, or placebo SC q2w. Pts randomized to placebo at Wk 0 who had <20% improvement in tender/swollen joints at Wk 18 and pts who remained on placebo at Wk 24 were re-randomized to sirukumab through Wk 52. The primary endpoint was the proportion of pts achieving ACR20 response at Wk 16; major secondary endpoints were change from baseline in HAQ-DI score, proportion of pts achieving ACR50 response, and proportion of pts achieving DAS28 (CRP) remission at Wk 24.

Results: 878 pts (placebo, n=294; sirukumab, n=292 per dose group) were randomized and evaluated for efficacy/safety. All pts had taken ≥1 prior anti-TNF, and 39.4% had taken ≥2 prior anti-TNFs. ~39% of pts had previously received biologics other than anti-TNFs. 74.6% of pts were currently taking methotrexate. A significantly higher proportion of pts achieved ACR20 at Wk 16 with sirukumab (50 mg q4w, 40.1%; 100 mg q2w, 45.2%) vs placebo (24.1%); all major secondary endpoints were met for both sirukumab doses (**Table**; all $P<0.001$). ACR responses, DAS28 (CRP) remission rates, and HAQ-DI score improvements on sirukumab were maintained through Wk 52. In pts with ≥2 prior biologics (including anti-TNFs; n = 523), both sirukumab 50 mg q4w (42.5%) and 100 mg q2w (42.4%) had greater proportions of ACR20 responders vs placebo (20.9%). Significantly greater improvements were also observed in the physical and mental component summary scores of the SF-36 Health Survey with both sirukumab doses vs placebo at Wk 24 (all $P<0.001$) and were maintained through Wk 52. For the placebo-controlled phase (up to Wk 24), the incidence of AEs was numerically higher in the sirukumab 100 mg group (68.2%) than in the placebo (61.9%) or sirukumab 50 mg (61.5%) groups. With placebo, sirukumab 50 mg, and sirukumab 100 mg, respectively, the incidence of SAEs was 5.1%, 8.3%, and 7.6%. Up to Wk 52 with sirukumab 50 mg q4w and 100 mgq2w, respectively, incidences of AEs were 79.6% and 81.3% and SAEs were 14.2% and 13.2%.

Conclusion: In this difficult to treat population that was intolerant/refractory to anti-TNFs and other biologics, sirukumab SC 50mg q4w and 100mg q2w reduced RA signs/symptoms, even in pts who had failed ≥2 prior biologics, and improved physical function and patient reported outcomes. The safety profile of sirukumab was similar to the known safety profile of anti–IL-6 receptor treatment.

Table. Key Endpoints

Endpoints	Placebo (n=294)	Sirukumab 50mg q4w (n=292)	Sirukumab 100mg q2w (n=292)
Primary endpoint			
ACR20 at Week 16, n (%)	71 (24.1)	117 (40.1)[a]	132 (45.2)[a]
Difference (95% CI), %		15.9 (8.5-23.2)	21.0 (13.6-28.5)
Major secondary endpoints			
HAQ-DI mean (SD) change from baseline at Week 24	−0.12 (0.49)	−0.31 (0.54)[a]	−0.33 (0.53)[a]
ACR50 at Week 24, n (%)	26 (8.8)	61 (20.9)[a]	63 (21.6)[a]
DAS28 (CRP) remission at Week 24, n (%)	24 (8.2)	56 (19.2)[a]	63 (21.6)[a]

[a]$P<0.001$ vs placebo (controlled for multiple testing).

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Abstract Number: 3224

Efficacy of Sirukumab, an Anti–IL-6 Cytokine Monoclonal Antibody, Based upon Prior Use of Non-Anti-TNF Biologics in Patients with Active Rheumatoid Arthritis Despite Anti-TNF Therapy: Results from a Global Phase 3 Study

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Session Time: 11:00AM-12:30PM

Background/Purpose: A global, phase 3 study (SIRROUND-T) evaluating the efficacy and safety of sirukumab, a selective, high-affinity human monoclonal antibody to IL-6, has recently been conducted in patients (pts) with active rheumatoid arthritis (RA) despite anti-TNF therapy. This post hoc analysis sought to compare the efficacy of sirukumab in subgroups of pts with active RA refractory to anti-TNF treatment who previously also received non-anti-TNF biologic therapy (TNFs + other biologics) and who did not previously receive other biologic therapy, other than anti-TNF biologic therapy (TNF only).

Methods: Pts were randomized in a 1:1:1 ratio to sirukumab subcutaneous (SC) 50 mg q4w, sirukumab SC 100 mg q2w, or placebo SC q2w. Pts on placebo with insufficient (<20%) improvement at Wk 18 or still on placebo at Wk 24 were re-randomized to 1 of the 2 sirukumab doses. The primary efficacy endpoint was ACR20 response at Wk 16, and major secondary endpoints included change from baseline (BL) in HAQ-DI score at Wk 24, ACR50 response at Wk 24, and DAS28 (CRP) remission at Wk

24. This post-hoc analysis compared efficacy for TNF only and TNF + biologics pts for sirukumab versus placebo, and across categories within sirukumab dose groups.

Results: In the placebo, sirukumab 50 mg q4w, and sirukumab 100 mg q2w groups, respectively, 104, 119, and 118 pts had previously received non-anti-TNF biologic therapy, in addition to prior TNF therapy. Improvements were observed in all outcomes for sirukumab versus placebo, regardless of prior biologic use (**Table 1**). Significantly more pts achieved ACR20 at Wk 16 with sirukumab 50 mg q4w and 100 mg q2w compared with placebo (all *P* £0.003). Both doses of sirukumab led to significantly greater improvements in HAQ-DI change from BL at Wk 24 than placebo (all *P* £0.012). Significantly more pts (TNF only at both sirukumab doses and TNF + biologics taking sirukumab 100 mg q2w) achieved ACR50 and DAS28 (CRP) remission at Wk 24 with sirukumab treatment compared with placebo; TNF + biologics pts on sirukumab 50 mg q4w had only numerically higher rates of ACR50 and DAS28 (CRP) remission at Wk 24 compared with placebo.

Conclusion: In general, comparable efficacy was observed with both sirukumab doses between pts with active RA despite anti-TNF therapy who had received TNFs only and TNFs + other biologics.

Table 1. Key Endpoints by Prior Biologic Use

	Placebo		Sirukumab 50 mg q4w		Sirukumab 100 mg q2w	
Prior Non–Anti-TNFα Biologic Use	**TNF only (n=189)**	**TNF + other biologics (n=104)**	**TNF only (n=173)**	**TNF + other biologics (n=119)**	**TNF only (n=173)**	**TNF + other biologics (n=118)**
Primary endpoint ACR20 at Wk 16, n (%)	46 (24.3)	25 (24.0)	68 (39.3)	49 (41.2)	78 (45.1)	54 (45.8)
P value[a]			0.003	0.003	<0.001	<0.001
Secondary endpoints HAQ-DI change from BL at Wk 24, mean (SD)	-0.132 (0.4847)	-0.109 (0.5056)	-0.358 (0.5752)	-0.250 (0.4885)	-0.322 (0.5685)	-0.344 (0.4567)
P value[a]			0.001	0.012	0.002	<0.001
ACR50 at Wk 24, n (%)	17 (9.0)	9 (8.7)	42 (24.3)	19 (16.0)	42 (24.3)	21 (17.8)
P value[a]			<0.001	NS	<0.001	0.030
DAS28 (CRP) remission at Wk 24, n (%)	16 (8.5)	8 (7.7)	41 (23.7)	15 (12.6)	41 (23.7)	22 (18.6)
P value[a]			<0.001	NS	<0.001	0.016

q4w, every 4 weeks; q2w, every 2 weeks; BL, baseline; NS, not significant.
[a]*P* value versus placebo.

Disclosure: Y. Tanaka, Abbvie, Chugai, Daiichi-Sankyo, Bristol-Myers, Mitsubishi-Tanabe, Astellas, Takeda, Pfizer, Teijin, Asahi-kasei, YL Biologics, Sanofi, Janssen, Eli Lilly, GlaxoSmithKline, 8,Mitsubishi-Tanabe, Takeda, Daiichi-Sankyo, Chugai, Bristol-Myers, MSD, Astellas, Abbvie, Eisai, 2; **D. Aletaha**, AbbVie, Pfizer, Grünenthal, Merck Medac, UCB, Mitsubishi/Tanabe, Janssen, and Roche, 2,AbbVie, Pfizer, Grünenthal, Merck Medac, UCB, Mitsubishi/Tanabe, Janssen, and Roche, 5; **C. Bingham III**, Janssen., 5,Janssen., 2; **P. Agarwal**, Janssen Research & Development, LLC, 1,Janssen Research & Development, LLC, 3; **R. Kurrasch**, GlaxoSmithKline, 1,GlaxoSmithKline, 3; **S. Popik**, Janssen Research & Development, LLC, 1,Janssen Research & Development, LLC, 3.

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Abstract Number: 3225

Dual Cytokine Inhibition with ABT-122, a Tnf– and IL-17–Targeted Dual Variable Domain Immunoglobulin (DVD-Ig™): Results from a 24-Week Open-Label Extension Study in Patients with Rheumatoid Arthritis

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Background/Purpose: ABT-122 is a dual variable domain immunoglobulin (DVD-Ig™) that targets human tumor necrosis factor-α (TNF-α) and interleukin-17A (IL-17A). The object was to investigate the long-term safety and maintenance of efficacy of dual cytokine inhibition with ABT-122 for 24 weeks following the completion of a 12-week double-blind study.

Methods: The 24-week open-label extension (OLE) enrolled 158 patients (pts) receiving background methotrexate (MTX). All received ABT-122 120 mg subcutaneously every other week (eow) with options for 1 extra 120-mg dose (for inadequate efficacy) or downtitration to 60 mg eow (for safety reasons). Safety assessments included adverse events (AEs) and laboratory parameters. Maintenance of efficacy at week 24 of the OLE was evaluated with ACR 20/50/70 responses and low disease activity and clinical remission defined by 28-joint Disease Activity Score using high-sensitivity C-reactive protein (DAS28[hsCRP]) or Clinical Disease Activity Index (CDAI). Analyses using nonresponder imputation (NRI) for missing data are presented.

Results: The AE frequency appeared to be unchanged from the double-blind study and in line with that seen with the adalimumab (ADA) control arm in the 12-week study. Most AEs were mild or moderate **(Table 1)**. Serious AEs were reported for 6 pts and included menorrhagia/anemia, myocardial ischemia, humerus fracture, joint dislocation, enterocolitis, and inflammation of the wound/skin ulcer; all events were unrelated to treatment as assessed by investigator and reported in a single term. Upper respiratory tract infection (n=14) and nasopharyngitis (n=4) were the most frequently reported infections. There were 1 nonserious report of basal cell carcinoma and 2 nonserious reports of liver events. There were no opportunistic infections, systemic hypersensitivity reactions, severe injection site reactions, cardiac failures, hematologic AEs, demyelinating disorders, or clinically concerning laboratory abnormalities. ABT-122 demonstrated consistent efficacy over 36 weeks across endpoints **(Table 2)**, including pts who switched from ADA to ABT-122. Two pts had a downtitration to ABT-122 60 mg eow starting at week 2 or 4. An extra 120-mg dose of ABT-122 was given in 5 pts. Overall ACR20/50/70 responses were 72.2%/48.7%/31.0% at week 24 of the OLE.

Conclusion: Dual cytokine inhibition of TNF-α and IL-17A with ABT-122 demonstrated good tolerability and maintenance of effect in the OLE when dosed up to 36 weeks in pts with rheumatoid arthritis receiving background MTX, including those switching from ADA to ABT-122.

Table 1. Safety in ABT-122 Phase 2 Study and following OLE

	Phase 2 Study (12 wk)				OLE (24 wk)
TEAE, n (%)*	ADA 40 mg eow (n=56)	ABT-122 60 mg eow (n=55)	ABT-122 120 mg eow (n=56)	ABT-122 120 mg ew (n=55)	ABT-122 120 mg eow (N=158)
Any TEAE	24 (42.9)	23 (41.8)	21 (37.5)	20 (36.4)	63 (39.9)
Severe TEAE	0	1 (1.8)	0	0	2 (1.3)
TEAE leading to discontinuation	0	2 (3.6)	0	1 (1.8)	2 (1.3)
Serious TEAE	0	2 (3.6)	0	2 (3.6)	6 (3.8)
TEAEs of special interest					
Infection	10 (17.9)	8 (14.5)	6 (10.7)	13 (23.6)	35 (22.2)
Malignancy	0	1 (1.8)	0	0	1 (0.6)
Ischemic TEAE	0	0	0	1 (1.8)	1 (0.6)
Hepatic TEAE†	0	0	0	0	2 (1.3)

ADA=adalimumab; eow=every other week; ew=every week; OLE=open-label extension; TEAE=treatment-emergent adverse event.
*Number and percentage of patients with TEAE; a patient may have ≥1 TEAE.
†Included 1 case of liver disorder (transient elevation of AST up to 2.5 x ULN resolved with continued study treatment) and 1 case of hepatic steatosis/hepatobiliary disease.

Table 2. Efficacy at the End of ABT-122 Phase 2 Study and following OLE

	Phase 2 Study (12 wk)				OLE (24 wk)
Efficacy endpoint, n (%)	ADA 40 mg eow (n=56)	ABT-122 60 mg eow (n=55)	ABT-122 120 mg eow (n=56)	ABT-122 120 mg ew (n=55)	ABT-122 120 mg eow (N=158)
ACR20	38 (67.9)	34 (61.8)	42 (75.0)	44 (80.0)	114 (72.2)
ACR50	27 (48.2)	19 (34.5)	26 (46.4)	26 (47.3)	77 (48.7)
ACR70	12 (21.4)	12 (21.8)	10 (17.9)	20 (36.4)	49 (31.0)
DAS28(hsCRP) <3.2 (LDA or CR)	25 (44.6)	18 (32.7)	29 (51.8)	30 (54.5)	72 (45.6)
DAS28(hsCRP) <2.6 (CR)	17 (30.4)	12 (21.8)	21 (37.5)	23 (41.8)	52 (32.9)
CDAI ≤10 (LDA or CR)	22 (39.3)	18 (32.7)	24 (42.9)	30 (54.5)	78 (49.4)

ACR=American College of Rheumatology; ADA=adalimumab; CDAI=Clinical Disease Activity Index; CR=clinical remission; DAS28(hsCRP)=28-joint Disease Activity Score using high-sensitivity C-reactive protein; eow=every other week; ew=every week; LDA=low disease activity; OLE=open-label extension.

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Crescendo Bioscience, and UCB Pharma, 2,AbbVie, Amgen, Bristol-Myers Squibb, Janssen, Pfizer, Roche, and UCB Pharma, 5; **H. T. Mansikka**, AbbVie, 3,AbbVie, 1; **P. M. Peloso**, AbbVie, 3,AbbVie, 1; **K. Chen**, AbbVie, 3,AbbVie, 1; **Y. Li**, AbbVie, 3,AbbVie, 1; **J. Liu**, AbbVie, 3,AbbVie, 1; **R. J. Padley**, AbbVie, 3,AbbVie, 1.

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Abstract Number: 3226

Maintenance of Clinical Remission and Radiographic Non-Progression with MTX after Completion of 1 Year Initial Treatment with Certolizumab Pegol in Japanese Patients with Early Rheumatoid Arthritis

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Background/Purpose: The efficacy and safety of certolizumab pegol (CZP) treatment in combination with dose-optimized MTX in Japanese MTX-naïve early RA patients (pts) with poor prognostic factors have previously been reported.[1] Here, we report the factors at Week (Wk) 52 associated with the maintenance of clinical remission and radiographic non-progression after discontinuation of CZP treatment to Wk 104.

Methods: MTX-naïve early RA pts entered C-OPERA (NCT01451203)[1] and were randomized to CZP+MTX (n=159) or placebo (PBO)+MTX (n=157); oral MTX was escalated to 16 mg/wk by Wk 8, if tolerated (optimized MTX). After completing the 52-wk double-blind period, CZP or PBO was discontinued and MTX therapy continued up to Wk 104 (post-treatment [PT] period; CZP+MTX→MTX). All pts (n=108) who were initially randomized to CZP+MTX and entered the PT period were included in these analyses. Clinical disease activity, remission (SDAI, DAS28[ESR], Boolean, at Wks 52 and 104), and radiographic non-progression rates (change from baseline [BL] or Wk 52 ≤0.5 in van der Heijde modified Total Sharp Score [mTSS], joint erosion score, and joint space narrowing score) were calculated. Missing values used last observation carried forward (LOCF) for remission and linear extrapolation for radiographic outcomes. Post-hoc logistic regression analyses were used to investigate the Wk 52 factors (DAS28[ESR], HAQ-DI, mTSS, rheumatoid factor [RF], anti-CCP antibody, and MMP-3) associated with remission and radiographic non-progression. Factors with $p<0.1$ in univariate analyses were included in multivariate analyses.

Results: At Wk 52, 77.8%, 79.6%, and 61.1% pts were in DAS28(ESR), SDAI, and Boolean remission, respectively. Remission rates decreased from Wk 52 to Wk 104 after stopping CZP, although most pts maintained remission (Figure A). Over 90% pts who entered the PT period achieved radiographic non-progression during CZP+MTX treatment; the non-progression rate was maintained after stopping CZP from Wks 52–104 (Figure B). In sensitivity analyses, DAS28(ESR) at Wk 52 was associated with DAS28(ESR), SDAI, and Boolean remission at Wk 104 (odds ratio: 0.23, 0.29, 0.36); Wk 52 RF was associated with SDAI and

Boolean remission at Wk 104 (odds ratio: 0.67 and 0.69) (Table).

Conclusion: Clinical remission can be maintained up to an additional 52 wks after CZP discontinuation in early RA pts with poor prognostic factors. Both low disease activity and low RF at CZP discontinuation (Wk 52) were associated with the maintenance of clinical remission. Radiographic non-progression was observed even after CZP discontinuation at Wk 52. **References:** 1. Atsumi T. Ann Rheum Dis 2016;75(1):75–83

Figure A: Clinical remission rates by criteria in the post-treatment population from the CZP+MTX→MTX group (n=108) (LOCF)

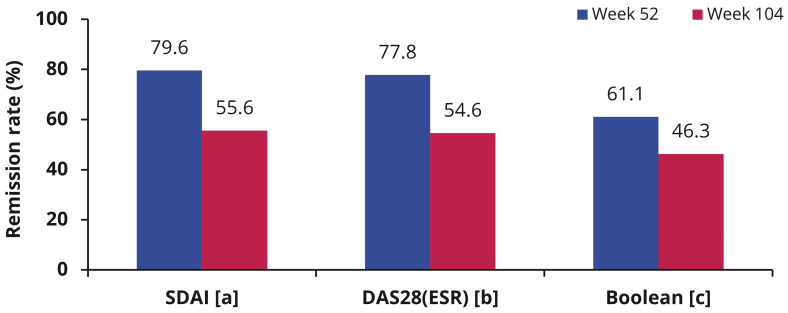
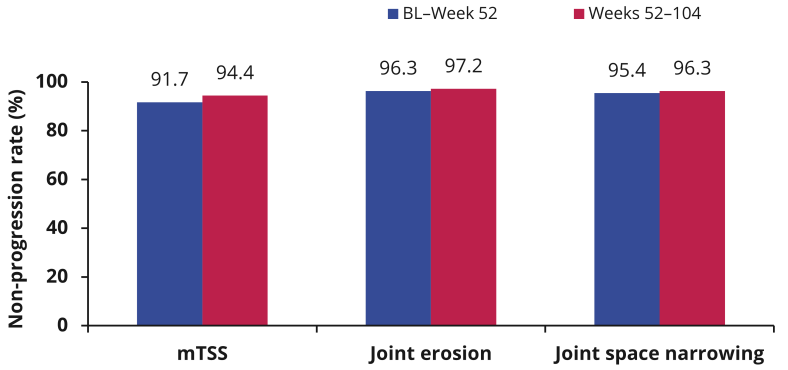


Figure B: Radiographic non-progression [d] rates in the post-treatment population from the CZP+MTX→MTX group (n=108) (linear extrapolation)



[a] SDAI ≤3.3; [b] DAS28(ESR) <2.6; [c] ≤1 on all of the following criteria: number of tender and swollen joint count (in 28 joints), CRP (mg/dL), and patient's global assessments of disease activity (0–100 mm visual analog scale converted to cm); [d] radiographic non-progression was defined as change from BL or Week 52 ≤0.5 in mTSS, joint erosion, or joint space narrowing score.

Table: Week 52 factors associated with disease activity and remission at Week 104 in the C-OPERA study

Odds ratio [a] (95% CI) p value	DAS28(ESR) LDA [b]		DAS28(ESR) remission		SDAI remission		Boolean remission	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
DAS28(ESR)	**0.41 (0.23, 0.73) p=0.003**	**0.40 (0.22, 0.73) p=0.003**	**0.23 (0.12, 0.45) p<0.001**	**0.23 (0.12, 0.45) p<0.001**	**0.29 (0.16, 0.54) p<0.001**	**0.29 (0.16, 0.54) p<0.001**	**0.34 (0.19, 0.61) p<0.001**	**0.36 (0.20, 0.64) p<0.001**
HAQ-DI	1.57 (0.30, 8.33) p=0.594	–	0.81 (0.19, 3.46) p=0.781	–	0.47 (0.11, 2.03) p=0.309	–	0.31 (0.06, 1.52) p=0.148	–
mTSS [c]	0.87 (0.57, 1.32) p=0.509	–	0.77 (0.51, 1.15) p=0.198	–	0.85 (0.57, 1.26) p=0.408	–	**0.66 (0.43, 1.02) p=0.060**	0.69 (0.42, 1.12) p=0.129
RF [d]	**0.67 (0.47, 0.94) p=0.021**	**0.66 (0.46, 0.95) p=0.025**	**0.77 (0.57, 1.05) p=0.097**	0.76 (0.54, 1.09) p=0.139	**0.69 (0.50, 0.95) p=0.022**	**0.67 (0.47, 0.96) p=0.028**	**0.70 (0.51, 0.96) p=0.026**	**0.69 (0.48, 0.98) p=0.037**
Anti-CCP antibody [d]	1.11 (0.79, 1.55) p=0.554	–	0.95 (0.69, 1.30) p=0.731	–	0.86 (0.63, 1.19) p=0.370	–	0.79 (0.57, 1.09) p=0.149	–
MMP-3 [d]	0.87 (0.37, 2.02) p=0.744	–	0.95 (0.43, 2.08) p=0.897	–	0.77 (0.35, 1.70) p=0.516	–	0.79 (0.36, 1.73) p=0.552	–

HAQ-DI: health assessment questionnaire–disability index; mTSS: van der Heijde modified Total Sharp Score; RF: rheumatoid factor. [a] Odds ratio based on 1 unit increase in Week 52 factor; [b] DAS28(ESR) ≤3.2; [c] Log+1 (mTSS) and [d] log (RF, anti-CCP antibody, MMP-3) were used for logistic regression analyses.

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Abstract Number: 3227

Modelling Primary Sjögren's Syndrome Using Salivary Gland Stem Cells

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Background/Purpose: Primary Sjögren's Syndrome (pSS) is characterized by lymphocytic infiltration of salivary glands. Unclear interactions between infiltrating cells and salivary gland ductal cells cause reduced gland function (hyposalivation), and significant decrease in patient quality of life. We recently isolated salivary gland stem cells from healthy human salivary gland biopsies, and characterized their self-renewal and differentiation capabilities. These stem cells are ductal cells and are therefore likely to be complicit in pSS manifestation. We sought to elucidate differences in salivary gland stem cells from pSS patients, compared to healthy controls.

Methods: Salivary gland stem cells were isolated as published from parotid gland biopsies of healthy control and pSS patients [1]. After 4 days, stem cells, grown as balls of cells termed 'salispheres', were dispersed into single cells and new salispheres generated. This passaging was repeated to ascertain the proliferative potential. Every week, culture medium samples were taken for mass spectrometry analysis. Immunohistochemistry stainings and electron microscopy were performed as standard.

Results: Yield of salivary gland stem cells from pSS biopsies was significantly lower than from healthy control tissues. The self-renewal capability of stem cells from pSS biopsies was markedly reduced compared to healthy control samples (Fig. 1). Secretome analysis via mass spectrometry revealed an abundance of keratins in culture medium, suggesting expulsion/secretion/mislocalization of keratins by ductal cells in pSS (Fig. 2). In preliminary data, ductal cells cytoplasm from pSS biopsies contained less keratins. Keratin fibers were observed extracellularly basally to pSS ductal cells by electron microscopy.

Conclusion: Our data demonstrates that there is an innate difference in regenerative potential and secretome of salivary gland stem cells from pSS biopsies compared to healthy controls. This deficit suggests an innate defect in stem cell ability to regenerate damaged glandular tissue in pSS, and may hereby contribute to the hyposalivation. We suggest for the first time that expulsion, secretion or mislocalization of keratins may underpin salivary gland stem cell defects in pSS and provide a novel insight into how salivary gland malfunction is manifested in pSS. Further characterization of stem cells from pSS biopsies, including organoid generation (mini salivary glands-in-a-dish), will further reveal mechanisms underpinning ductal cell involvement in pSS, and generate new therapeutic options.

Figure 1

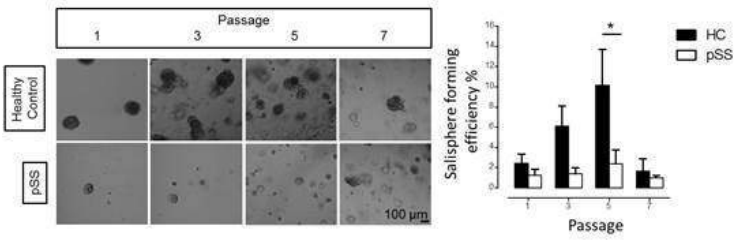

Figure 1. pSS-SGSCs display reduced regenerative potential.
A) Representative phase contrast microscopy of self-renewal cultures of SGSCs from healthy control (top row) and pSS biopsies (bottom row) with increasing passage number (week number). B) Quantification of salisphere formation efficiency in self-renewal cultures from healthy control and pSS biopsies. Error bars = S.E.M. $n = 9$ separate patient biopsies for healthy control, 8 for pSS cultures. [1] Pringle et al, 2016. Human salivary gland stem cells functionally restore radiation damaged salivary glands. Stem Cells34(4): 640-652.

Figure 2

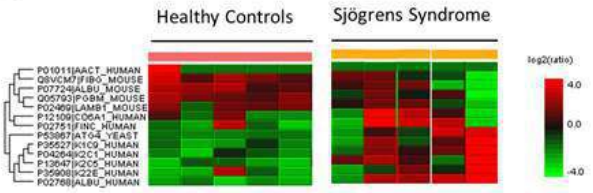

Figure 2. pSS-SGSCs secrete more keratins than HC-SGSCs.
Mass spectrometry was performed on conditioned medium collected from early passage SGSCs from healthy control (HC) and pSS cultures. Heatmap shows Log2 ratio of proteins detected, at a statistically different intensity (≥ 2.0 fold difference) and normalized for protein content. Blue box denotes human keratin proteins detected.

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Abstract Number: 3228

Specific T Cell and B Cell Distributions Characterize Subgroups of Patients with Primary Sjögren's Syndrome and Are Associated with Disease Activity and Pro-Inflammatory Cytokine Expression

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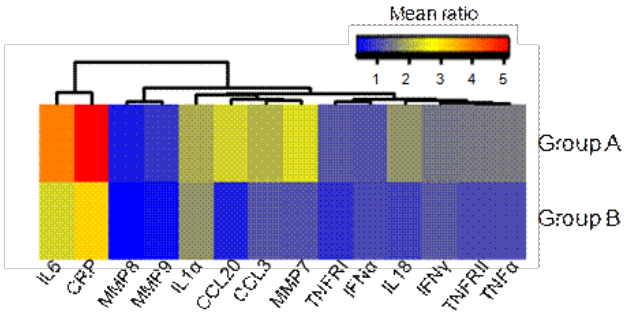
Background/Purpose : The goal of the IMI PRECISESADS project is to reclassify individuals affected by systemic autoimmune diseases (SADs) into clusters of molecular, instead of clinical entities. In this project, we investigated 40 individuals with primary Sjögren's syndrome (pSS), as diagnosed by the revised American-European classification criteria (3 men and 37 women, mean age: 56.3±12.3 years). and 53 healthy controls (HCs) (11 men and 42 women, mean age: 44.1±12.1 years) to determine whether a fine flow cytometry analysis of T and B cell distribution in whole blood could cluster individuals according to disease activity.

Methods: Two flow cytometry panels were designed. The first panel was dedicated to T cells and combined FITC-CD57, PE-CD45RA, PC7-CD62L, PC5.5-CD27, APC-CD38, AAF750-CD3, PB-CD4,KO-CD8 mAbs. The second panel was dedicated to B cells and combined FITC-IgD, PE-TACI, KO-CD5, PC7-CD24, PC5.5-CD27, PB-CD38, APC-CD19, AAF750-CD11b mAbs. Disease activity was determined according to ESSDAI. A Luminex-based system was used to analyze up to 88 cytokines, chemokines and soluble factors in serum of pSS patients and HCs.

Results: A combined analysis of T and B cell distribution highlighted two groups of individuals with a strong cluster of pSS patients in one of them. Indeed, the first cluster (group A) gathers together 24 pSS patients and 5 HCs while group B consists in 16 pSS patients and 49 HCs. Group A was characterized by the association of an increase of activated naïve B cells (IgD^+ $CD24^+$ $CD38^+$ $CD27^-$), a decrease of memory B cells (IgD^- $CD38^-$ $CD27^+$), an increase of central memory $CD4^+$ T cells ($CD45RA^-$ $CD62L^+$ $CD27^+$), an increase of effector memory $CD8^+$ T cells ($CD45RA^-$ $CD62L^-$ $CD27^-$) and a decrease of central memory $CD8^+$ T cells ($CD45RA^-$ $CD62L^+$ $CD27^+$) compared to group B and 91% of HCs. Interestingly, group A patients have a higher disease activity score when compared to group B (Mean ESSDAI score 5.0±1.9 versus 3.2±0.9 respectively). Finally, serum pro-inflammatory molecules (interleukin (IL)-6, C-reactive protein (CRP), Chemokine (C-C motif) ligand 20 (CCL20), CCL3, matrix metalloproteinase-7 (MMP-7), IL-18) were markedly up-regulated in group A patients compared to HCs and group B patients (See heat-map below).



Heat-map shows mean-ratio of pro-inflammatory molecule concentrations relative to HCs in each group of pSS patients.

Conclusion: A fine flow cytometry analysis of T and B cell subsets characterizes pSS patients with a higher disease activity score and a pro-inflammatory signature. Similar approaches are ongoing in the context of the PRECISESADS project for other SADs.

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Abstract Number: 3229

Bone Morphogenetic Protein 6 Receptor Inhibition Restores Salivary Gland Function in a Mouse Model of Primary Sjögren's Syndrome

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Background/Purpose: Bone morphogenetic protein 6 (BMP6) plays a critical mechanistic role in decreasing salivary gland dysfunction in primary Sjögren's syndrome (pSS) patients. Elevated BMP6 expression is associated with a loss of membrane water permeability and loss of gland function that is independent of inflammatory cell infiltration within the gland. The downstream signals activated by BMP6, which ultimately result in decreased salivary flow, are still unknown. BMP6 signals through type 1 receptors, which results in phosphorylation of SMAD1/5/8 transcription factors that ultimately alter gene expression within the nucleus. Two inhibitors,LDN-212854 and LDN-193189, have been developed to selectively target the ALK2 and ALK3 BMP type 1 receptors. This study examined the ability of these inhibitors to block BMP6 signaling, and their effect on expression of key proteins involved in salivary gland function and inflammation. We also investigated the ability of these inhibitors to restore salivary gland function in vivo.

Methods: BMP6 expression was detected in minor salivary glands (MSG) from N=80 pSS female patients (49.6 years old, range (21-74)) by immunofluorescent staining and quantified using Velocity software. Immunofluorescent staining was also used to confirm the presence of type I BMP6 receptors in human salivary glands. Water permeability was tested by regulated volume decrease (RVD) assay in BMP6 treated HSG cells with or without LDNs treatment, followed by observation of change of phospho-SMAD (pSMAD) expression as detected by Western blotting and immunofluorescent staining. In vivo activity of the ALK inhibitors was tested in C57BL/6.NOD-Aec1Aec2 mice, which have been shown to have decreased salivary gland function, by daily IP injection for 24 days and subsequent assessment of salivary gland flow rates. At the end of the study, local and systemic immune response was investigated by flow cytometric assay. In addition, the levels of pSMAD and aquaporin-5 (AQP-5) expression in submandibular glands from LDN treated mice were measured.

Results: Elevated BMP6 was found in 63/80 (78.8%) of pSS patients examined in this study. In humans, ALK2 and ALK3 receptors were found on both ductal and acinar cells. In vitro treatment of HSG cells with ALK2/3 inhibitors resulted in decreased BMP6 signaling and SMAD 1/5/8 phosphorylation and led to a recovery of fluid movement. Furthermore, daily treatment, with either inhibitor, of C57BL/6.NOD-Aec1Aec2 mice with established decreased salivary gland function, restored salivary flow rate. Associated with this increase in salivary flow was an increased expression of AQP5, a protein critical for membrane water permeability in salivary glands. LDN treatment also decreased infiltrating IFN-gamma producing CD4+ T cells in submandibular glands from C57BL/6.NOD-Aec1Aec2 mice.

Conclusion: BMP6 expression is increased in a majority of pSS patients. Treatment with BMP6 inhibitors can reverse the loss of function within the salivary gland as well as decrease inflammation. These findings suggest that inhibition of BMP6 is a promising approach to the treatment of primary Sjögren's syndrome.

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Abstract Number: 3230

Genome-Wide Association Study Identifies Novel Sjögren's Syndrome Risk Loci in the Regions of NAB1, TYK2, and PTTG1-mir146a

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Background/Purpose: Sjögren's syndrome (SS) is a complex autoimmune disease with both environmental and genetic factors contributing to pathophysiology. The goal of this genome-wide association study (GWAS) was to identify SS risk loci that exceed the genome-wide significance (GWS) threshold of 5x10E-8 in European-derived cohort.

Methods: We studied >20,000 subjects that were genotyped on OMNIexpress, OMNI1-Quad, or OMNI2.5 Illumina arrays. Following application of strict standard quality control measures, a total of 2,809 independent SS cases and 17,102 population controls remained. Analysis was performed using logistic regression and accounted for ancestry (first 4 principal components) and gender.

Results were combined using a weighted Z-score method to determine meta P-values. Results: In total, 3101 variants exceeded the GWS threshold and were supported by more than one dataset. The majority of these variants were located within previously established SS risk loci such as *HLA, IRF5, STAT4*, and *TNIP1*. In addition, 3 novel loci were identified that exceeded GWS. The first effect was located within the 5' untranslated region of the gene *NAB1* (NGFI-A binding protein 1) peaking at rs2293765 (P_{meta}=3x10E-11; odds ratio (OR)=1.23). Bioinformatics data in this region denote epigenetic marks that are indicative of enhancer activity in T cells, B cells, monocytes, and neutrophils. Moreover, variation at rs2293765 has also been shown to alter expression in monocytes of neighboring genes including *GLS* (interferon (IFN) stimulation), *TMEM194B* (LPS stimulation), and MFSD6 (naïve). NAB1 has been shown by others to form a complex with EGR3 leading to transcriptional downregulation of the IFNGR1 locus upon IFN stimulation. The second novel effect is a missense allele, rs2304256 (V>F; P_{meta}=1.22x10E-9; OR=0.81), located within *TYK2* (tyrosine kinase 2) and predicted to be damaging in 5 transcripts resulting from this locus by SIFT. Additionally, this variant is predicted to influence the expression in monocytes of multiple genes in the region under various conditions: IFN stimulation (*ICAM1, TMED1*), LPS stimulation (DNMT1), and naïve (*ICAM3, TYK2*). TYK2 is a Janus kinase family member that is responsive to both type I and III IFN signaling. The third novel effect maps to the intergenic space between PTTG1 (pituitary tumor-transforming 1) and mir-146a, peaking at rs2431697 (P_{meta}=3.38x10E-9; OR=0.82). Epigenetic marks in this region indicate enhancer element function in T cells, neutrophils, and monocytes as well as expression changes of *PTTG1* in whole blood. To date, the role of PTTG1 in the immune system remains elusive, but this locus is a risk factor for various forms of cancer. In addition, several loci showed suggestive association with SS (P_{meta}<1x10E-5) including *XKR6*, *PDHX-CD44*, and *ELMO1*.

Conclusion: We have established three novel genetic associations with SS involved in pathways important in the disease pathology. Further replication, imputation, fine mapping, and functional studies are needed to elicit the precise causal variants and the impact on SS etiology.

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Abstract Number: 3231

miR200b-5p Expression in Minor Salivary Glands (MSG): A Possible Predictor of Lymphoma Development in Sjögren's Syndrome (SS)?

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Background/Purpose: The miRNAs of the miR-200 family are critical regulators of oncogene and tumor suppressor genes. A preliminary study of several miRNAs in the MSGs of SS patients, including 4 patients with MALT lymphoma, suggested that the expression of miR200b-5p may be down-regulated in lymphoma (*Gourzi et al., Clin Exp Immunol. 2015*). The aim of our study is to validate the down-regulation of miR200b-5p in MSGs of patients with SS-related lymphoma and to investigate whether its expression is deregulated before lymphoma development.

Methods: miR200b-5p expression was analyzed by quantitative real-time PCR in total RNA from MSG tissues obtained from 74 SS patients and 9 patients with non-SS sialadenitis associated with sarcoidosis, HCV infection (4 each) or HBV (1 that was also diagnosed with MALT lymphoma). The SS patients group included 28 patients that did not develop lymphoma during follow up (without lymphoma; median follow up time since biopsy performance, range: 6yrs, 1-12.75yrs), 17 patients that developed lymphoma in the future (prelymphoma; median follow up time till lymphoma diagnosis, range: 3.67yrs, 0.42-8.5yrs, 13 MALT, 2 NMZL, 1 DLCBL and 1 SLL) and 30 patients with SS-associated lymphoma at the time of biopsy (lymphoma; 23 MALT, 2 NMZL, 2 DLCBL,1 BALT, 1 LP and 1 SLL). Prelymphoma and lymphoma MSG samples were obtained from the same SS patients in 13 cases (10 MALT, 2 NMZL and 1 DLCBL). Differences in miR200b-5p expression levels among the studied groups was analyzed by Tukey's multiple comparison test, whereas repeated measures analysis was employed to evaluate whether miR200b-5p expression changes over lymphoma development (in the prelymphoma and lymphoma MSGs from the 13 patients).

Results: miR200b-5p was significantly down-regulated in MSG tissues of prelymphoma and lymphoma SS patients (mean relative expression±SE: 0.38±0.10 and 0.27±0.06, respectively) compared to SS patients without lymphoma (0.77±0.12; $p \leq 0.05$ and $p \leq 0.001$ for pre- and lymphoma, respectively) or non-SS sialadenitis (0.82±0.25, $p \leq 0.05$ and $p \leq 0.01$, respectively). The expression of miR200b-5p was not found to differ between patients with SS without lymphoma and non-SS sialadenitis, or pre-lymphoma and lymphoma SS patients. Interestingly, low expression of miR200b-5p (0.17) was detected in the MSG tissue obtained from the HBV-infected patient that had MALT lymphoma. Finally, the expression levels of miR200b-5p were not found to differ in prelymphoma and lymphoma tissues of the 13 patients that had both samples.

Conclusion: The significantly lower expression of miR200b-5p in SS associated MALT lymphoma implicates it in lymphomagenesis, whereas its significant down-regulation in prelymphoma MSGs suggests that miR200b-5p can serve as a prognostic marker for future lymphoma development. The cell types that express miR200b-5p and the molecular pathways that regulates are under investigation.

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Abstract Number: 3232

Decreased Expression of Micro-RNA 130a and Micro-RNA 708 in Type-1 Classical Dendritic Cells of Patients with Primary SS Indicates Their Dysregulation

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Background/Purpose: Primary Sjögren's syndrome (pSS) is a systemic autoimmune disease characterized by lymphocytic infiltration of the exocrine glands and dryness of mouth and eyes. Type-1 classical dendritic cells (cDCs) are very potent antigen presenting cells known to induce strong T-cell proliferation and cytokine production. Despite the fact that especially cDC1s are candidate key players in the activation of local T and B-cells in pSS, they have rarely been studied in pSS. Considering the critical role of micro-RNAs (miRNAs) in regulation of gene expression, we investigated miRNA expression in isolated cDC1s of patients with pSS.

Methods: Two independent cohorts (discovery and validation) were established, consisting of 29 pSS patients who were classified according to the 2002 criteria. 17 healthy controls (HC) were included as control group. cD1c+ CD19- cells were isolated from peripheral blood using MACS and we performed miRNA profiling of 758 miRNA targets using the OpenArray platform in the donors included in the discovery cohort. A selection of 15 miRNAs found to be differentially expressed in the pSS group versus the control group (at $p<0.05$, with at least a difference between the groups of log2) was measured in the independent validation cohort using a custom made array. We performed pathway enrichment with the experimentally supported targets of the validated miRNAs to assess their function in these cells.

Results: A total of 24 miRNAs were downregulated in pSS patients versus HC in the discovery cohort. Of these, 16 targets were selected for validation. Pathway enrichment showed that the experimentally supported targets of these miRNAs are mainly involved in growth-factor signalling and vesicle trafficking ($p<0.05$, FDR corrected). We are currently performing functional experiments in primary cells to dissect the effects of the dysregulated miRNA expression in these cells.

Conclusion: miR-130a and miR708 are significantly downregulated in cDC1s of patients with pSS, which indicates dysregulation in a range of pathways that are involved in DC function. These are the first data from primary cells to indicate dysregulation of type-1 cDCs in this group of patients, urging for further assessment of these cells in future studies.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/decreased-expression-of-micro-rna-130a-and-micro-rna-708-in-type-1-classical-dendritic-cells-of-patients-with-primary-ss-indicates-their-dysregulation

Abstract Number: 3233

Determinants of Pain, Fatigue, Physical Function and Social Participation in SLE Patients, Measured with Patient Reported Outcomes Measurement Information System (PROMIS®) Computerized Adaptive Tests

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Background/Purpose: Poor SLE outcomes have been associated with certain clinical and socio-demographic characteristics, but the determinants of patient reported outcomes (PROs) in SLE are unknown. PROMIS, recently validated in SLE, offers dynamic computer adaptive tests (CATs) that precisely and efficiently measure PROs in physical, mental, and social health domains. The

aims of this study were to identify clinical and demographic characteristics independently associated with worse health status in SLE patients as measured by PROMIS CATs.

Methods: Adults meeting ACR SLE classification criteria were recruited from an SLE Center of Excellence. Subjects completed 4 PROMIS CATs: physical function, fatigue, pain interference, ability to participate in social roles. SLE disease activity, flare, and damage were evaluated with the SELENA-SLEDAI and SLICC-ACR damage index. Multivariable generalized linear models were used to assess the cross-sectional association between PROMIS CAT scores and clinical and demographic traits. All variables with $p < 0.2$ in univariate analyses were included in the multivariable analyses. 2-Way interaction terms were considered and significant interaction terms ($p < 0.05$) were included in the final models if doing so provided models of better quality (indicated by lower Akaike and Bayesian Information Criterion values).

Results: A diverse group of 204 SLE patients completed PROMIS CATs (table 1). Black race, Hispanic ethnicity, disability, Medicaid, active arthritis, SELENA-SLEDAI flare, history of cognitive impairment/psychosis, deforming/erosive arthritis, and avascular necrosis were associated with statistically and clinically significantly worse PROMIS scores in univariate analyses. In the final multivariable model only disability and active arthritis were independently associated with worse physical function, fatigue, and social participation, while arthritis and cognitive impairment/psychosis were independently associated with worse pain interference.

Conclusion: Surprisingly, neither flare status nor socio-demographic characteristics were independently associated with these four important PROs, whereas active arthritis, disability, and a history of cognitive impairment/psychosis were. These data suggest that: 1) pain and physical and mental dysfunction drive patient well-being regardless of race, ethnicity, and insurance type; and 2) the physician-derived SELENA-SLEDAI flare measure poorly captures the impact of disease activity on SLE patients.

Table 1. Clinical and Demographic Characteristics of Participants (n = 204)

Characteristic	**Value**
Age: mean ± SD years, (range)	40.0 ± 13.2, (19 -73)
Female: n (%)	189 (92.6)
Race: n (%)	
White	77 (37.7)
Black	61 (29.9)
Asian	26 (12.8)
Other	40 (19.6)
Ethnicity: Hispanic/Latino: n (%)	58 (28.4)
Insurance: n (%)	
Medicaid	73 (35.8)
Medicare	21 (10.3)
Private	110 (53.9)
Employment: Full or Part-Time: n (%)	96 (47.1)
Disability: n (%)	67 (33.0)
College Graduate: n (%)	120 (59.1)
Body Mass Index: mean ± SD kg/m^2, (range)	26.1 ± 5.6, (15.9 – 50.2)
Medications: n (%)	
Current Steroid Use	118 (58.1)
Current Hydroxychloroquine Use	170 (85.9)
Current Immunosuppressive Use	138 (69.7)
Disease Duration: mean ± SD years, (range)	12.2 ± 8.8, (0 - 48)
Physician Global Assessment: mean ± SD, (range) [Range 0 to 3, higher is worse]	0.8 ± 0.6, (0 – 2.8)
SELENA-SLEDAI: mean ± SD, (range) [Range 0 to 105, higher is worse]	4.2 ± 3.5, (0 – 20)
SELENA-SLEDAI Flare: n (%)	40 (19.6)
SLICC: mean ± SD, (range) [Range 0 to 46, higher is worse]	1.2 ± 1.7 (0 – 8)

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Abstract Number: 3234

Prevalence and Metric of Depression and Anxiety in Lupus: A Systematic Review and Meta-Analys

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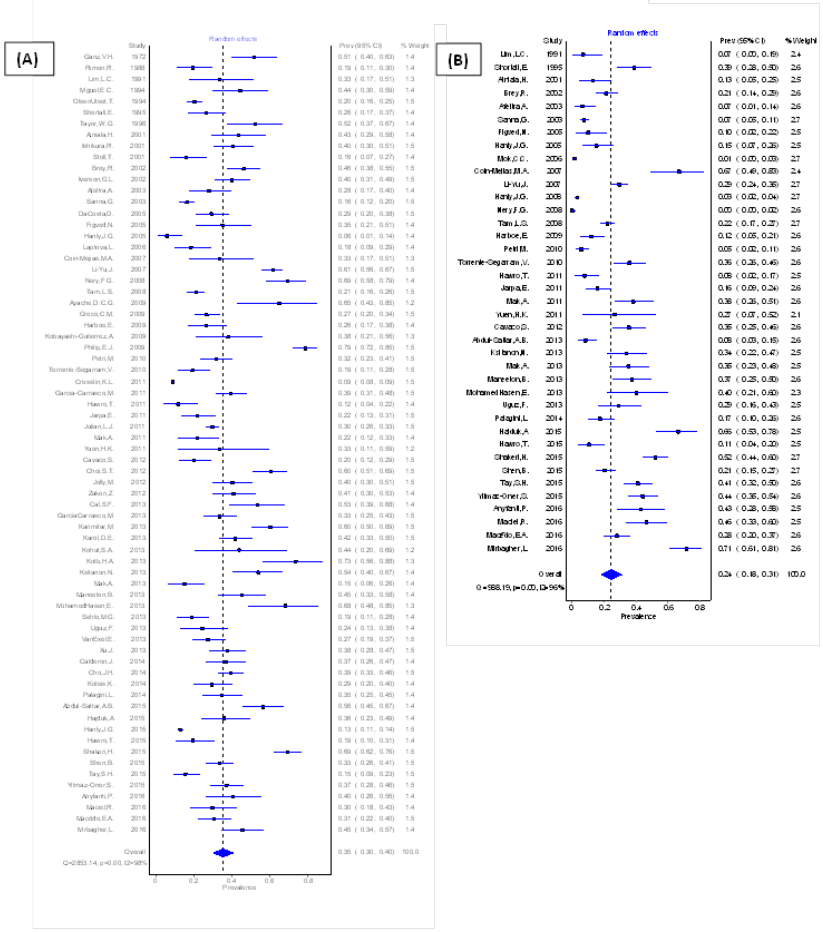
Background/Purpose: To systematically review the literature on the: 1) prevalence of depression and anxiety in SLE patients and 2) metrics of depression and anxiety.

Methods : This review was conducted based on the recommendation of Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols statement. A literature search (1954-2016) was performed in Ovid Medline, Embase, Psyc INFO and CINAHL for articles on the prevalence of depression and/or anxiety in adult SLE patients or on the metrics of depression/anxiety. Included studies were critically appraised and analyzed. The prevalence of depression and anxiety was studied for all instruments and whenever possible Pooled Prevalence (PP) was determined in the commonly used instruments [Centre for Epidemiological Studies - Depression (CES-D), Beck Depression/Anxiety Inventory (BDI/BAI), Hospital Anxiety/Depression Scales (HADS-D/A), Hamilton Rating Scales for Depression/Anxiety (HAM-D/A)].

Results: A total of 4394 references were identified, 278 were selected for detailed review and 121 were included in the final analysis**.** *Depression:* PP of Depression was 35.2% (95% CI: 30.1, 40.5%) (Figure 1A) based on data from 70 studies in 23399 patients. *Anxiety:* PP of Anxiety was 24.2% (95% CI: 17.9, 31.2%) (Figure 1B) based on data from 39 studies in 4495 patients. *CES-D:* was utilized in 13 studies in 1856 patients. Depression PP was 41.5% (95% CI: 35.1, 48.1%). *BDI/BAI:* was utilized in 14 studies in 1355 patients and 3 studies in 489 patients respectively. Depression PP was 39.9% (95% CI: 31.1, 49.1%) and Anxiety PP was 38.4% (95% CI: 34.2, 42.8%). *HADS-D/A:* was utilized in 14 studies in 1238 patients and 12 studies in 1099 patients respectively. Depression PP was 24.4% (95% CI: 19.1, 30.1%) and Anxiety PP was 38.3% (95% CI: 29.1, -47.9%). *HAM-D/A:* was utilized in 5 studies in 323 patients and 5 studies in 269 patients respectively. Depression PP was 43% (95% CI: 27.9, 58.7%) and Anxiety PP was 37.3% (95% CI: 31.7, 43.2%). We found high variability in the prevalence of depression and anxiety, and high statistical heterogeneity (I^2> 75%) which is attributed to the: 1) lack of standardization in the metrics and definitions of depression and anxiety in SLE, and 2) variability in other demographics such as patients age, education levels and other factors that associate/predict depression and/or anxiety.

Conclusion: The prevalence of depression/anxiety is high in patients with SLE, ranging from 5.7% to 78.6% and 1.1% to 71.4%, respectively. The CES-D, BDI, HAM-D yielded a similar prevalence of depression, ranging between 27.9% and 49.1%, whereas the prevalence of depression with the HADS-D was lower.(24.4%). All metrics (BAI, HADS-A, HAM-A) of anxiety yielded a similar prevalence of anxiety prevalence ranging between 29.1% and 47.9%.

Figure 1. Forest Plot of Depression (A) and Anxiety (B) in SLE patients



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Abstract Number: 3235

Long-Term Impact of Belimumab on Health-Related Quality of Life and Fatigue in Patients with Systemic Lupus Erythematosus: Up to 7 Years of Treatment Exposure

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Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that causes long-term organ damage over time and impairment in health-related quality of life (HRQoL). We examined the long-term administration of belimumab plus

standard of care (SoC) on HRQoL and fatigue in patients with autoantibody-positive SLE.

Methods: This multicenter continuation study (GSK study 112233, NCT00724867; Aug 2008–Mar 2015) enrolled patients who completed the BLISS-76 randomized controlled trial (RCT) in the US. Patients on belimumab in the RCT continued to receive the same dose (1 or 10 mg/kg IV, every 28 days; all 10 mg/kg post-Mar 2011) plus SoC (belimumab/belimumab group). Those who previously received SoC alone (the RCT placebo [PBO] group) received belimumab 10 mg/kg IV (PBO/belimumab group). Primary outcome measures included long-term safety and efficacy of belimumab, including HRQoL and fatigue, every 48 weeks including HRQoL and fatigue by Short Form-36 v2 (SF-36) Medical Outcomes Survey and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scale, respectively. As the primary endpoint was safety, the baseline (BL) for this analysis was at start of belimumab administration.

Results: The modified intent-to-treat population comprised 268 patients; 140 completed the continuation study, and 128 withdrew (patient request: n=31; adverse events: n=25). At BL, patients in the PBO/belimumab group reported higher SF-36 Physical (PCS) and Mental (MCS) Component, and FACIT scores than the belimumab/belimumab group (**Table**). Patients receiving long-term belimumab reported continued HRQoL and fatigue benefits, with improvements in SF-36 PCS, MCS and FACIT scores up to Year 6 Week 48 (**Table**). Mean changes from BL in the belimumab/belimumab group also exceeded minimum clinically important differences (MCID) at each yearly assessment to Year 6 (SF-36 PCS [range; 4.90–8.31], SF-36 MCS [range; 3.85–4.90], FACIT [range; 5.75–6.85]). At Year 6 Week 48, mean changes from BL in SF-36 domain scores exceeded MCID in 6 of 8 domains: bodily pain, general health, physical functioning, role physical, social functioning, and vitality.

Table: HRQoL scores from BL to Year 6 Week 48 (SF-36v2 health survey and FACIT-Fatigue)

	PBO/belimumab			Belimumab/belimumab			Total		
Mean (SD)	BL[1] (N=91)	Year 6 Week 48 (N=58)	Change from BL to Year 6 Week 48 (N=58)	BL (N=177)	Year 6 Week 48 (N=127)	Change from BL to Year 6 Week 48 (N=127)	BL (N=268)	Year 6 Week 48 (N=184)	Change from BL to Year 6 Week 48 (N=184)
SF-36v2 PCS	42.00 (9.839)	43.31 (10.225)	0.88 (7.790)	34.47 (8.975)	40.90 (9.837)	6.57 (9.566)	37.04 (9.927)	41.65 (9.995)	4.79 (9.406)
SF-36v2 MCS	47.90 (10.307)	48.76 (10.826)	-0.58 (9.287)	42.44 (11.425)	46.16 (11.812)	4.21 (11.805)	44.30 (11.338)	46.98 (11.546)	2.71 (11.274)
FACIT-Fatigue score	31.22 (13.284)	31.75 (13.995)	-0.37 (9.541)	24.06 (11.237)	29.54 (13.258)	5.58 (12.274)	26.50 (12.423)	30.24 (13.495)	3.70 (11.787)

[1]Baseline was set to the start of belimumab treatment. As such, the baseline values for the group assigned to PBO in the RCT study have higher HRQoL and fatigue scores (i.e. less disability and fatigue) and lower disease scores compared with the group commencing belimumab *de novo* in the RCT.

Conclusion: Largest improvements in HRQoL and fatigue were reported in Year 1 of treatment, and maintained during long-term exposure to belimumab. Although reported improvements in the belimumab/belimumab group were greater than those in the PBO/belimumab group, these changes may have been confounded by differences in BL SF-36 scores, as well as SoC treatment with optimized medical care during the RCT. These data suggest that long-term control of disease activity with belimumab plus SoC translates into meaningful benefits in patient fatigue and HRQoL. **Disclosure:** Study funded by GSK and Human Genome Sciences, Inc. Nicole Cash, MRes PhD, Fishawack Indicia Ltd, UK, provided editorial assistance, funded by GSK.

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Abstract Number: 3236

Socio-Demographic and Clinical Factors Influencing Generic and Disease-Specific Quality of Life in Patients with Systemic Lupus Erythematosus: Results of a Prospective Multicenter Study

Hervé Devilliers[1], Jean-François Besancenot[1], Sylvain Audia[2], Bernard Bonnotte[3], Francois Maurier[4], Christiane Broussolle[5], Nadine Magy-Bertrand[6], Denis Wahl[7], Jean-Loup Pennaforte[8], Thierry Martin[9], Olivier Aumaître[10], Gilles Blaison[11], Geraldine Muller[1], Alexis Mathian[12], Christine Binquet[13] and Zahir Amoura[14], [1]Department of Internal Medicine and Systemic Diseases,

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Background/Purpose:

To describe demographic, socio-economic and lupus-related factors associated with health-related quality of life (HRQOL) in systemic lupus erythematosus (SLE), as measured by 2 generic (Medical Outcome Study Short Form 36 [SF-36] and World Health Organisation Quality of life [WHOQOL] and 2 disease-specific (LupusQoL and SLEQOL) questionnaires recorded simultaneously.

Methods:

We conducted a prospective study involving SLE patients in 10 French tertiary hospitals. Disease activity was recorded by SELENA-SLEDAI (SS) and SS Flare Index Revised [SFI-R] alongside HRQoL and sociodemographic variables. Social precariousness was recorded using the validated "EPICES" questionnaire. Factors influencing HRQOL scores were studied using multivariate linear regression. All scores were transformed to a 0-100 scale (100 corresponding to the best QoL)

Results:

We included 336 patients, of whom 90% were women, mean age (SD) was 41(11.9), 51% were caucasian. Median (IQR) SLEDAI was 4 (0-8), and 39% of patients had at least a moderate flare. Social precariousness was recorded in 38% of patients, 62% had an education level greater than General Education Diploma and 31% were unemployed.

In multivariate analysis (figure 1), we found no effect of ethnicity on HRQOL. Social precariousness was strongly associated with the QoL score in all domains of generic and specific questionnaires, with mean estimated decreases ranging from -6.5 (SF-36 "Physical Functioning, p=0.02) to -17.84 (SLEQOL "Mood", p<0.0001). The occurrence of an articular flare was also associated with a decrease in HRQOL in all domains (e.g. -19.6 in SF-36 "Role Physical" [p<0.0001] and -10 in SLEQOL "mood", [p=0.01]), except for "psychological" and "environment" domains of the WHOQOL. Neuropsychiatric signs had a higher impact on specific questionnaires (figure 1). Obesity was associated with a significant decrease in HRQOL in SF-36 physical-related domains (-12.9, p=0.02 in "physical function" domain), but not in disease-specific questionnaires, except for the LupusQoL "Body Image" Domain (-8.57, p=0.02). Similarly, smoking was associated with a poorer HRQOL in some of the physical domains of generic questionnaires (-5.57 in WHOQOL "physical heath", p=0.03), but not with disease-specific ones.

Conclusion: The social environment is highly associated with HRQOL in SLE patients, regardless of the instrument or domain. Disease-specific questionnaires may be more strongly correlated with some aspects of the disease and may be useful to distinguish the SLE-specific burden from other conditions such as obesity or smoking-related disease.

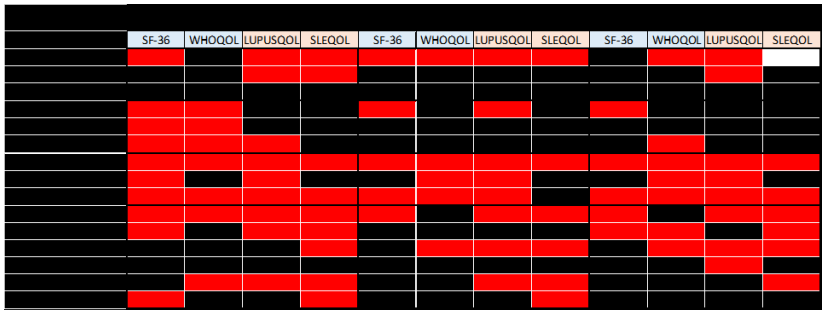

Figure 1: Summary of multivariate analysis. A red square indicates a significant independent association in multivariate linear regression ($p<0.05$) between a variable and at least one QoL domain score

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Abstract Number: 3237

Responsiveness and Its Magnitude in the 36-Item Short Form Health Survey and the Lupus Quality of Life Questionnaire in Patients with Active Disease

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Background/Purpose: SF-36 and LupusQoL are Health-Related Quality-of-Life (HRQoL) questionnaires used in SLE. We determined: (1) concurrent construct validity of SF-36 and LupusQoL against disease activity in patients with moderate-to-severely active lupus and (2) intra-individual responsiveness and its magnitude for both questionnaires' domains.

Methods: 99 active SLE patients [SLEDAI-2K ≥6] were recruited from a single centre. Patients completed both questionnaires at baseline and follow-up visits. Questionnaires' domains scores were correlated with SLEDAI-2K and evaluated for floor/ceiling effects. Anchors for responsiveness were defined by: 1-Minimal Clinically Important Difference (MCID) definitions of SF-36, 2-MCID of LupusQoL and 3- SLEDAI-2K. Each of these anchors grouped patients as improved, same, or worsened. The magnitude of change was measured with Standardized Response Means (SRMs).

Results: In the 99 patients, SLEDAI-2K was 7.7±5.2 at baseline and 6.5±4.8 on follow-up at 4.7±3.1 months. SLEDAI-2K did not correlate with questionnaires' domains confirming that HRQoL is an independent domain not associated with disease activity. Correlations among "comparable" domains of both questionnaires ranged from 0.70-0.79. Floor effect was present in 2 SF-36 domains (Role Emot, Role Phys). Ceiling effect was present in 4 SF-36 domains (Bod Pain, Role Emot, Role Phys, Social Funct) and 3 LupusQoL domains (Pain, Planning, Intimate Relat). The number of patients with worsening/improvement in the domains of SF-36 and LupusQoL is represented in table 1. The magnitude of change (SRM) for all domains were small when SLEDAI-2K was an anchor and large when MCID of SF-36 or LupusQoL were anchors (Figure 1 and 2). Responsiveness of SF-36 and LupusQoL using SLEDAI-2K as an anchor (47% patients improved and 16% worsened) was small (SRMs ranged -0.3–+0.3).

Conclusion: In active lupus patients, both SF-36 and LupusQoL are responsive to change with large SRMs in improving and worsening patients. Lupus-specific domains in LupusQoL (planning, burden to others, body image and intimate relationships) showed large SRMs. SF-36 and LupusQoL are acceptable questionnaires for monitoring HRQoL in patients with SLE.

Table 1. Number of patients with worsening, same and improvement in SF-36 and LupusQoL domains in 99 patients

	SF-36 N=99 patients									
	Comparable domains of SF-36 and Lupus QoL				Non-Comparable domains of SF-36 and Lupus QoL					
	Bodily Pain	Physical Fun.	Mental Health	Vitality	General Health	Role Emotional	Role physical	Social fun.	PCS	MCS
Worsening	30	32	30	37	34	21	22	34	30	30
Same	33	31	42	43	20	55	55	33	26	34
Improving	36	36	27	19	45	23	22	32	43	35

	LupusQoL N=99 patients							
	Pain	Physical Health	Emotional Health	Fatigue	Body image	Planning	Intimate	Burden
Worsening	29	31	41	36	34	26	55	39
Same	37	41	32	38	26	37	29	24
Improving	33	27	26	25	39	36	15	36

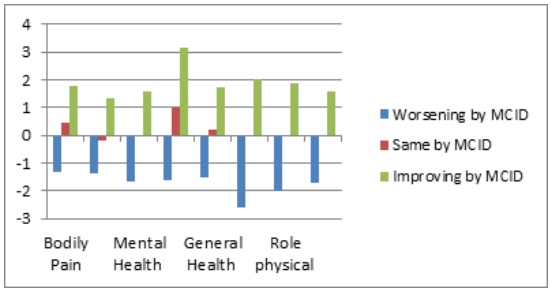

Figure 1. Magnitude of change (SRMs) of SF-36 domains

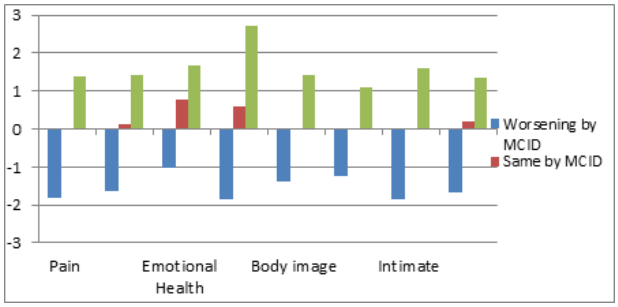

Figure 2. Magnitude of change (SRMs) of LupusQoL domains

Disclosure: S. Nantes, None; **J. Su**, None; **Z. Touma**, None.

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Abstract Number: 3238

Depression Symptoms throughout the Lifespan in a Low-Income, Minority Cohort of Lupus Patients: Who Is at Risk?

Tamar Rubinstein[1], Noa Schwartz[2], Nicole Jordan[3], Rebecca Lois[4], Dawn Wahezi[5,6], Ruth E K Stein[7,8] and Chaim Putterman[2], [1]Division of Pediatric Rheumatology, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY, [2]Division of Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [3]Montefiore Medical Center, New York, NY, [4]Psychiatry and Pediatrics, Albert Einstein College of Medicine, Children's Hospital at Montefiore, Bronx, NY, [5]Pediatric Rheumatology, Albert Einstein College of Medicine, Bronx, NY, [6]Pediatric Rheumatology, The Children's Hospital at Montefiore, Bronx, NY, [7]Pediatrics, Children's Hospital at Montefiore, Bronx, NY, [8]Pediatrics, Albert Einstein College of Medicine, Bronx, NY

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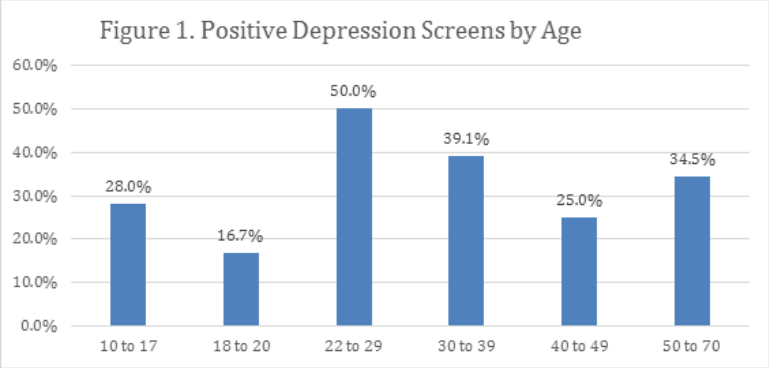
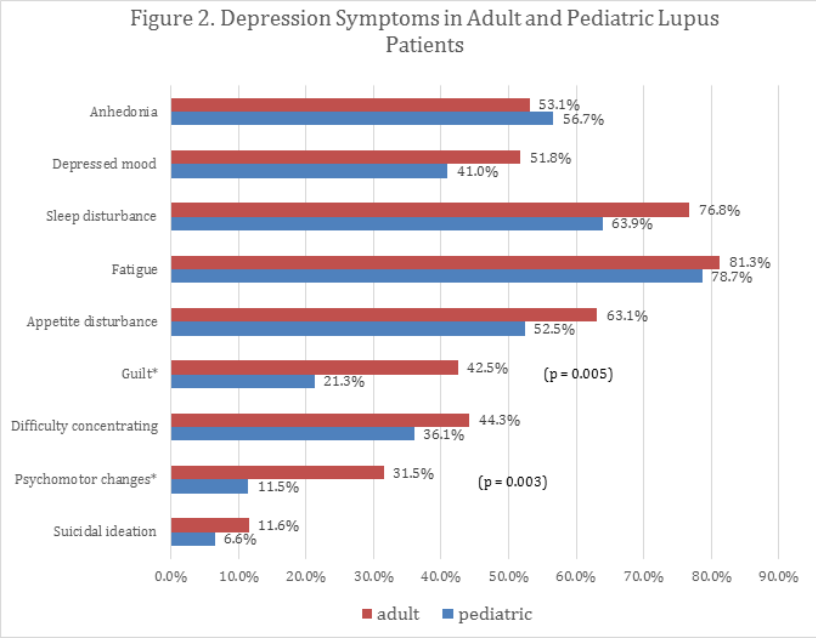
Background/Purpose: Depression is commonly seen in lupus, but widely varying prevalence rates have been reported. This may be due to different demographics and characteristics or varying detection methods across studies. Furthermore, few studies have looked at depression prevalence in lupus patient cohorts inclusive of both children and adults. Better describing the frequency of symptoms of depression in a lupus population at high risk for depression may help identify target populations for screening, treatment, and possible prevention.

Methods: Lupus patients at three affiliated hospitals, regardless of age, who met ACR criteria were enrolled in the Einstein Lupus Cohort. Patients enrolled in the cohort who agreed to depression screening, were given the Patient Health Questionnaire-9 (PHQ9), and extensive clinical and epidemiological data was recorded. Differences in prevalence rates were investigated across age groups using a chi-square analysis. Differences between pediatric and adult patients were examined in relation to depression symptoms and clinical and demographic characteristics by chi-square and Mann-Whitney U tests. Logistic regression was used to identify potential predictors for depression in the cohort.

Results: The median age was 28.4 (IQR 19.5, 45.3) for 175 screened patients; 47.7% were black, 45.5% Hispanic, and 6.9% other; 82% were Medicaid-enrolled; 31.4% had positive PHQ9 screens. Pediatric patients were similar to adult patients in most demographics and clinical characteristics, but had lower rate of comorbid chronic pain syndromes and previously diagnosed psychiatric disease. There was no linear correlation between age and depression, but a peak in prevalence of 50% was seen among patients 22-29 years old compared to a relatively low rate of 16.7% among 18-21 year olds (Fig. 1). Pediatric patients reported statistically significant lower rates of guilt and psychomotor changes, while rates of other endorsed depression symptoms were similar (Fig. 2). There were no significant predictors found for depression in the cohort, including steroid dose and disease activity measured by SLEDAI.

Conclusion: Younger patients with lupus have different depression symptoms than adults. A very high rate of depression was seen in young adult patients from our cohort, especially compared to patients immediately preceding them in age. Our observations have important implications for transitioning processes for teenage lupus patients, and may indicate the need to target adolescence for preventative measures to help minimize the substantial disease burden of depression that may occur in subsequent years.





Disclosure: T. Rubinstein, Lupus Foundation of America, 2; **N. Schwartz**, None; **N. Jordan**, None; **R. Lois**, None; **D. Wahezi**, None; **R. E. K. Stein**, None; **C. Putterman**, None.

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Abstract Number: 3239

Expression of IFN-Regulated Genes in Autoantibody Exposed Babies in Utero

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Background/Purpose: Ro/SSA autoantibodies and an IFN signature are commonly present in women with Sjögren's syndrome and SLE. During pregnancy, the autoantibodies are transported across the placenta and are associated with a risk of neonatal lupus erythematosus (NLE) including a congenital heart block (CHB) in the baby. Hydroxychloroquine, which inhibits toll like receptor signaling and decreases activity in the type 1 IFN system has been suggested to decrease the risk of NLE. Whether activation of the interferon system occurs in the baby is however not known. In the present study we therefore investigated whether the type 1 IFN system is activated in Ro/SSA autoantibody exposed newborns.

Methods: Seven Ro/SSA autoantibody positive mothers receiving no medication and 3 mothers treated with hydroxychloroquine and/or azathioprine and their newborn babies were included in the study together with 8 healthy mother-baby pairs. Blood was drawn from the mother and cord at birth, with immediate separation into plasma and peripheral blood mononuclear cells (PBMCs). Autoantibodies were analyzed by ELISA and IFN-α by DELFIA. Cell surface expression of molecules was investigated by flow

cytometry, and mRNA expression by microarrays. mRNA expression data was used for calculating an IFN score.

Results: Ro/SSA antibody positive women without treatment and their babies had higher levels of IFN-α than control mothers and control babies, respectively. Activation of the IFN system with increased expression of IFN-regulated genes was observed in both the Ro/SSA antibody positive women and their babies, with a significant correlation between maternal and fetal IFN-scores (R^2=0.53, p=0.005). Further, increased expression of MHC class II was observed on CD14+ monocytes in the Ro/SSA antibody exposed babies, suggesting higher activation of these cells. In babies of mothers receiving immunomodulatory treatment, the IFN score was similar to that of healthy control babies.

Conclusion: Babies exposed to Ro/SSA autoantibodies *in utero* have circulating IFN-α, an IFN-signature in their PBMCs and increased MHC class II expression on the cell surface of monocytes, which is partly reversed by treatment with hydroxychloroquine or other immunomodulatory drugs. This study proposes that fetal activation of the type I IFN system may contribute to the risk of NLE.

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Abstract Number: 3240

Interferon Kappa Is a Novel Type I IFN That Drives Cutaneous Inflammation in Systemic Lupus

Jasmine Stannard[1], Tamra J. Reed[2], Emily Myers[3], Lori Lowe[4], Mrinal Sarkar[4], Xianying Xing[5], Celine C. Berthier[6], Johann Gudjonsson[4] and **J. Michelle Kahlenberg**[7], [1]Int. Medicine/Rheumatology, University of Michigan, Ann Arbor, MI, [2]Internal Medicine, Rheumatology, University of Michigan, Ann Arbor, MI, [3]Internal Medicine, Rheumatology, Georgetown University, Washington, DC, [4]Dermatology, University of Michigan, Ann Arbor, MI, [5]Dermatology, University of Michigan, University of Michigan, Ann Arbor, MI, [6]Nephrology, Division of Nephrology, University of Michigan Medical Center, Ann Arbor, MI, [7]Internal Medicine, Division of Rheumatology, Division of Rheumatology, University of Michigan Medical Center, Ann Arbor, MI

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Background/Purpose: Cutaneous lupus erythematosus (CLE) lesions are disfiguring, scarring, difficult to treat, and affect up to 70% of patients with systemic lupus erythematosus (SLE). Type I interferons (IFN) are important in the pathogenesis of SLE and CLE, yet we have insufficient data on the source of type I IFNs in the skin and the effects of type I IFNs on cutaneous inflammatory predisposition. In this work, we investigate a novel keratinocyte-produced type I IFN, IFNκ, in promotion of epidermal inflammation and CLE.

Methods: SLE patients for study had biopsy-proven history of CLE and met 4/11 ACR criteria for SLE. Primary keratinocytes were isolated and cultured from the upper thigh of control or SLE patients. SLE keratinocytes were taken from unaffected skin. Keratinocytes from control and SLE patients were cultured and IL-6 production was measured after stimulation with toll-like receptor (TLR) ligands and ultraviolet light (UV). Neutralizing antibodies to the type I interferon (IFN) receptor and IFN kappa were used to define the role of type I IFNs on IL-6 production. IFN kappa production was measured via ELISA. Type I IFN expression in 80 CLE lesions was determined via microarray. IFNκ expression in CLE lesions was confirmed via immunohistochemistry.

Results: Keratinocytes from unaffected skin of lupus patients produced significantly more IL-6 compared with healthy controls following exposure to TLR2 agonist or UVB radiation. This increased IL-6 production was duplicated in control keratinocytes after

pretreatment with type I IFN. Importantly, secretion of keratinocyte-specific IFNκ was significantly increased after TLR2 and UVB treatment in lupus vs. control keratinocytes and neutralization of the type I IFN receptor or IFNκ was sufficient to abrogate the enhanced IL-6 production by lupus keratinocytes. *In vivo* relevance was documented as IFNκ was one of only two significantly increased type I IFNs in both discoid and subacute subtypes of CLE. Immunohistochemistry confirmed epidermal and dermal expression of IFNκ in CLE.

Conclusion: IFNκ is a novel type I IFN that is produced more abundantly by lupus vs. control keratinocytes. Importantly, it is a regulator of the hyperinflammatory response in lupus keratinocytes and is the most significantly regulated type I IFN in CLE lesions. Our data thus support a regulatory loop in which IFNκ is secreted by lupus keratinocytes and primes them for a robust interferon and inflammatory response following stimulation with microbial ligands or UV. IFNκ may thus serve as a novel and organ-specific target for treatment or prevention of CLE.

Disclosure: J. Stannard, None; **T. J. Reed**, None; **E. Myers**, None; **L. Lowe**, None; **M. Sarkar**, None; **X. Xing**, None; **C. C. Berthier**, None; **J. Gudjonsson**, None; **J. M. Kahlenberg**, None.

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Abstract Number: 3241

Genetic Variation and Tobacco Smoke Exposure in Systemic Lupus Erythematosus: A Case Control Study Among African Americans

Bethany Wolf[1], Paula S. Ramos[2], Paul Nietert[3], J. Madison Hyer[1], Viswanathan Ramakrishnan[1], Gary S. Gilkeson[4], Gerard Hardiman[2] and **Diane L. Kamen**[5], [1]Public Health Sciences, Medical University of South Carolina, Charleston, SC, [2]Medicine, Medical University of South Carolina, Charleston, SC, [3]Public Health Science, Medical University of South Carolina, Charleston, SC, [4]Department of Medicine, Division of Rheumatology, Medical University of South Carolina, Charleston, SC, [5]Medicine/Rheumatology & Immunology, Medical University of South Carolina, Charleston, SC

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Background/Purpose: Systemic lupus erythematosus (SLE) disproportionately affects African Americans, and the development of SLE is believed to be triggered by exposure to one or more specific environmental factors in genetically susceptible individuals. Tobacco smoke has been implicated as such a potential agent. In this study, we sought to discover whether smoking and/or secondhand smoke inhalation interacts with certain candidate genes, resulting in elevated risk of SLE in African Americans.

Methods: A case control design was used, and all subjects were African Americans of Gullah ancestry, from the Sea Islands of South Carolina or Georgia. All cases met ACR classification criteria for SLE, and all controls were evaluated by a rheumatologist and determined unaffected by autoimmune disease at the time of enrollment. All subjects completed questionnaires to assess smoking history and exposure to secondhand smoke. Candidate genes included ones previously identified in the literature as interacting with tobacco smoke in rheumatic diseases, and genes in the Comparative Toxicogenomics Database that were relevant to tobacco smoke or in an inference network between tobacco smoke and SLE. Genotypic data was available on subjects genotyped on the Illumina Immunochip genotyping array. After standard GWAS quality control, the following were available for analyses: *NAT2* (4 single nucleotide polymorphisms [SNPs]), *HLA-DRB1* (6 SNPs), *APOE* (2 SNPs), *IL6* (17 SNPs), *CXCL8* (1 SNP), *IRF5* (20 SNPs), *ITGAM* (67 SNPs), and *ITGAX* (31 SNPs). Logic forest, a relatively novel machine learning algorithm we developed, was used to highlight interactions between the environment (i.e. tobacco smoke) and the variants in the candidate genes.

Results: The study population included 204 participants (n=100 cases, n=104 controls), 86% of whom were female. The logic forest model identified secondhand smoke exposure during childhood as the most important predictor of SLE status. Consistent with the literature, the model identified several SNPs in the IRF5, ITGAM, and ITGAX genes as being risk factors for SLE. Although passive smoke exposure during childhood was of high importance and identified as a main effect, the logic forest detected weak to

moderate interactions (odds ratios ranging from 2.3 to 2.5) between it and SNPs in the *ITGAM* gene.

Conclusion: In this case-control study, both genetic and environmental risk factors for SLE were identified, with evidence suggesting potential interactions between exposure to secondhand smoke as a child and genetic variation in the *ITGAM* gene.

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Abstract Number: 3242

Identification and Functional Characterization of TNIP1 Causal Variants Associated with Systemic Lupus Erythematosus

Satish Pasula[1], Mandi Wiley[1], Ying-yu Wu[1], Ajay Nair[1], Jaanam Gopalakrishnan[2] and Patrick M. Gaffney[1], [1]Arthritis and Clinical Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, OK, [2]Department of Pathology, University of Oklahoma Health Sciences Center, Oklahoma City, OK

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SESSION INFORMATION

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Session Title: Systemic Lupus Erythematosus – Human Etiology and Pathogenesis II

Session Type: ACR Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

Background/Purpose: Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by autoantibody production and dysregulated interferon responses. Genome-wide association studies (GWAS) have identified more than 80 susceptibility or risk genes/loci associated with SLE and other autoimmune diseases, including TNFAIP3 interacting protein 1 (*TNIP1*). *TNIP1* encodes the adaptor protein ABIN1, which functions in the immune system by restricting NF-κB signaling. Previous fine mapping of the *TNIP1* locus demonstrated significant associations with SLE and single nucleotide polymorphisms (SNPs) that are carried on two independent risk haplotypes within *TNIP1*. Both risk haplotypes demonstrated reduced expression of *TNIP1* mRNA and ABIN1 protein. In this work we characterize associated SNPs in *TNIP1* and identify candidate causal SNPs that influence hypomorphic expression of *TNIP1*.

Methods: Eleven *TNIP1* SNPs from both SLE risk haplotypes which have lower binding scores (RegulomeDB) were selected for electrophoretic mobility shift assays (EMSA) to evaluate whether SLE risk alleles affect binding of nuclear protein complexes extracted from different immune cells that were treated with and without PMA/Ionomycin (P/I) in 3 independent EMSA tests. Affinity DNA pull-down assay and Western blotting (WB) was performed to identify proteins bound to rs10036748 probe.

Results: EMSAs using probes containing non-risk and risk alleles of 11 SLE associated SNPs in the *TNIP1* locus identified 3 variants with reduced binding of nuclear proteins to the SLE risk allele from the Jurkat T cell line, EBV transformed B cells and the monocytoid cell line, THP-1. Five of the 11 variants demonstrated P/I stimulation dependency of which 2 variants showed decreased binding to the risk allele and 3 variants showed increased binding to the risk allele. Interestingly, 3 *TNIP1* SNPs showed increased binding of nuclear proteins to the risk-allele under resting conditions; one of these was P/I stimulus dependent. Overall, the SNPs carried on both *TNIP1* SLE risk haplotypes demonstrated complex binding activity with the Jurkat T cell line having the most activity (8 of 11 SNPs showing differential binding). To begin verifying the identity of the nuclear proteins present in the EMSA, we used affinity pull-down followed by WB for the rs10036748 variant which had reduced binding of nuclear proteins to risk-allele in all 3 cell types. Based on ENCODE defined transcription factor binding, we confirm that early growth response 1 and NF-κB subunit, RelA are associated with this variant DNA and reduced with the risk allele of rs10036748.

Conclusion: Functional analyses of SNPs in *TNIP1* SLE risk haplotypes suggested a complex regulation at *TNIP1* locus. The association of transcriptional protein complexes at these SNPs is highly regulated showing cell type specificity, stimulation dependency and allele specific binding. The regulatory insights gained through *in-vitro* assays will better direct us to further separate and characterize individual SLE associated *TNIP1* variants *in-vivo* to decipher molecular mechanisms and cell states by which *TNIP1* risk haplotypes contribute to SLE pathogenesis.

Disclosure: S. Pasula, None; **M. Wiley**, None; **Y. Y. Wu**, None; **A. Nair**, None; **J. Gopalakrishnan**, None; **P. M. Gaffney**, None.

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Abstract Number: 3243

Intestinal Microbial Dysbiosis in SLE Is Linked to Elevated IgA and Induction of Autoimmunity

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Background/Purpose: SLE is a complex multifactorial systemic autoimmune disease, which has been attributed to poorly understood interactions between genetic and environmental factors. Recent reports have begun to elucidate how imbalances within intestinal communities of commensal bacteria may lead to triggering of inflammatory and autoimmune conditions. Our studies are designed to shed light on the interactions of the immune system and the gut microbiome that may contribute to lupus pathogenesis.

Methods: We have assembled a cohort of 60 female SLE patients and matched 20 healthy controls, and biobanked blood and stool samples. DNA was then extracted from fecal bacterial samples, and from sorted endogenous IgA-coated and non-coated bacterial fractions. 16S bacterial rRNA gene sequencing was then performed by illumina NGS technology. Fecal and serum total Igs and autoantibodies were measured by ELISA and by multiplex-bead autoantigen assays.

Results: Our analyses showed that SLE patients have significantly reduced diversity (i.e., number of different taxa) in their gut microbiomes compared to controls (p=0.038). This dysbiosis was treatment independent, with more marked contractions in patients with high disease activity, based on SLEDAI (p=0.002). The distribution of microbiome taxa was more heterogeneous among SLE patients than healthy individuals (p=0.002). Interestingly, patients with the most active disease commonly displayed expansions of genus and species with putative pathobiont properties, with reciprocal contractions of others associated with protective properties (e.g. *R. gnavus* (p= 0.001) vs. *F. prausnitzii* (p= 0.022) and *B. uniformis* (p=0.016). In immunologic surveys, we found that IgA (the most highly produced Ig isotype in the body), was significantly elevated in SLE patients compared to healthy subjects (p<0.002). Only a limited proportion of bacterial taxa are specifically coated by endogenous intestinal IgA. Yet, SLE patients with high disease activity displayed an increased abundance among IgA-coated taxa of *Prevotella copri (p= 0.018)*, a species which has recently been linked to new-onset RA. In addition, intestinal IgA in SLE patients included high levels of antibodies to lupus autoantigens, with the same IgA autoantibody profiles in the matched sera of individual patients.

Conclusion: Our studies document that SLE is associated with a dysbiosis in the gut microbiome with expansions of specific pathobiont bacteria and reciprocal contractions that may contribute to immune dysregulation. This imbalance was more significant in patients with high disease activity. Certain microbial taxa/species are preferentially recognized by the adaptive immune system of SLE patients and coated in vivo by intestinal IgA, and this correlated with elevated overall levels of fecal and serum IgA. Taken together, these data support the hypothesis that the pathogenesis of SLE may arise from imbalances in the gut microbiome and immune recognition of certain bacterial taxa.

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Abstract Number: 3244

Observations of Early and Late B Cell Alterations during Belimumab Treatment in Patients with Systemic Lupus Erythematosus Using Mass Cytometry (CyTOF)

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Background/Purpose: Belimumab is a recombinant monoclonal antibody that inhibits soluble B lymphocyte stimulator (BLyS), also known as BAFF or TNFSF13B, and is approved for treating patients with systemic lupus erythematosus (SLE). In this observational prospective cohort study, we sought to identify B cell and T cell alterations in SLE patients during treatment with belimumab.

Methods: Twenty-three SLE patients from the Karolinska University Hospital treated with belimumab were enrolled and followed longitudinally. Peripheral blood mononuclear cells were collected and cryopreserved at inclusion and at regular follow-up visits up to 3 years from treatment initiation. The sample series were assayed by mass cytometry (CyTOF) at the same time point, and analysed in the context of clinical parameters.

Results: Changes in B cell subsets were assessed by analysing the CyTOF data after adjustment for total lymphocyte counts from each visit. As expected, B cells decreased over time. More specifically, transitional and naïve B cells ($CD19^+CD20^+IgD^+IgM^+CD27^-$) showed a rapid reduction already at three months follow-up, and continued to decrease over time ($p<0.0001$). In contrast, the pre-switching ($CD19^+CD20^+IgD^+CD27^+$) and double negative memory B cells ($CD19^+CD20^+IgD^-CD27^-$) showed a more gradual decline ($p=0.01$ and $p=0.0001$, respectively). Moreover, we observed decreases ($p<0.0001$) in age-associated B cells ($CD11c^+CD21^-$), a recently described cell subset implicated in humoral autoimmune responses. However, plasma cells ($CD138^+CD38^+CD27^+CD19^+CD3e^-CD20^-$) and switched memory B cells ($CD19^+CD20^+CD27^+IgD^-$) remained stable ($p=0.7$ and $p=0.3$, respectively). In correlation analyses of individual markers with time from treatment initiation, average CD27 expression among B cells showed the greatest increase during the first 6 months of treatment ($r=0.70$) while expression of IgA ($r=0.46$), CD19 ($r=0.39$), and CD5 ($r=0.34$) also increased (<5% false discovery rate, FDR, for all). In contrast, IgD ($r=-0.75$), IgM ($r=-0.67$), CD22 ($r=-0.64$), Ki-67 ($r=-0.62$), CD20 ($r=-0.58$), CD38 ($r=-0.49$), and CD21 ($r=-0.51$) decreased (<5% FDR for all). During later follow-up times (from 6 months of treatment and during the remaining study period), CD5 ($r=0.53$) and CD38 ($r=0.51$) showed the greatest increases (<5% FDR for both), followed by CD20 ($r=0.36$) and Ki–67 ($r=0.34$) ($p<0.05$ for both), and CD22 continued to decrease ($r=-0.32$, $p<0.05$). In contrast to the clear B cell alterations following belimumab treatment, T cells and monocytes did not change significantly.

Conclusion: In this real-life clinical practice setting, belimumab resulted in an initial rapid reduction of naïve B cells and age-associated B cells, followed by a continuous gradual decrease, which also included pre-switching and double negative B cells. In contrast, memory B cells, plasma cells and T cells were preserved. Our observations of B cell alterations betiding in two distinct phases, a rapid early and a more gradual late phase, may have direct implications in the clinical use of belimumab, as early treatment evaluation and discontinuation might forfeit delayed clinical improvements reflecting the late B cell changes.

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Abstract Number: 3245

Surfactant Protein D and Krebs Von Den Lungen-6 Predict Severity of Systemic Sclerosis-Related Interstitial Lung Disease in Two Independent Cohorts

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Background/Purpose: A prior study of patients with systemic sclerosis-related interstitial lung disease (SSc-ILD) demonstrated that serum concentrations of surfactant protein D (SP-D) and Krebs von den Lungen-6 (KL-6), were higher in patients with active alveolitis compared with patients without alveolitis.[1] This present study aimed to further investigate the relationship between KL-6 and SP-D and extent and progression of SSc-ILD in two independent cohorts.

Methods: Patients enrolled in Scleroderma Lung Study (SLS) I and II were included. For SLS I, 158 patients were randomized to oral cyclophosphamide (CYC) versus placebo for 1 year. For SLS II, 142 patients were randomized to receive mycophenolate (MMF) for 2 years or oral CYC for 1 year followed by 1 year of placebo. ELISA kits determined the baseline levels of circulating SP-D and KL-6 in 66 and 136 SLS I and II participants, respectively. Extent of ILD was assessed using pulmonary function tests (FVC, DLCO) and quantitative image analysis (extent of fibrosis [QLF] and ILD [QILD] for the whole lung [WL] and zone of maximum involvement [ZM]). To investigate the relationship between baseline SP-D and KL-6 and progression of ILD, a mixed model was created with the outcome of the course of DLCO over 2 years, and a linear regression model was created with the outcome of QLF/QILD score at 2 years (SLS II cohort). Both models controlled for treatment assignment and baseline ILD severity.

Results: We observed significant correlations between KL-6 and SP-D and extent of ILD. In SLS II, KL-6 was correlated with (r; P-value): DLCO (-0.3; 0.0002), QLF-ZM (0.4; <0.0001), QLF-WL (0.5; <0.0001); QILD-ZM (0.5; <0.0001); QILD-WL (0.5; <0.0001); while SP-D was correlated with: DLCO (-0.3; 0.0005), QLF-WL (0.2; 0.03); QILD-ZM (0.3; 0.003); QILD-WL (0.3; 0.0007). In SLS I, KL-6 was correlated with (r; P-value): DLCO (-0.4; 0.003), QLF-ZM (0.3; 0.01); while SP-D was correlated with: DLCO (-0.3; 0.05), QLF-ZM (0.3; 0.02). However, neither KL-6, nor SP-D was significantly correlated with FVC in both cohorts (P>0.4). There were no significant differences in KL-6 or SP-D levels between patients with diffuse versus limited cutaneous disease or between treatment arms in SLS II. In the mixed model (SLS II data), patients with low KL-6 at baseline had a trend for an improvement in the DLCO over 24 months (P=0.06) (Table 1a). Low KL-6 at baseline was significantly associated with improvement in QILD-WL (P=0.03) (Table 1b).

Conclusion: KL-6 and SP-D each were associated with extent of ILD as measured by quantitative fibrosis and DLCO, but not by FVC, in SLS I and II participants. Patients with lower baseline KL-6 appeared to respond more favorably to immunosuppression with MMF/CYC, suggesting that levels of this glycoprotein may be used in conjunction with clinical factors to predict prognosis in SSc-ILD. **References**: 1. Hant FN, et al. *J Rheumatol* 2009;36:773-80.

Table 1a. Low baseline KL-6 is associated with improved course of DLCO over 24 months in SLS II participants in mixed model

Variable	Estimate	Standard Error	P-Value
Treatment arm*	-3.9	1.4	0.005
Baseline DLCO	0.8	0.06	<0.001
Low KL-6	2.7	1.5	0.06

Table 1b. Low baseline KL-6 is associated with improved QILD-WL at 24 months in SLS II participants in linear regression model

Variable	Estimate	Standard Error	P-Value
Treatment arm*	0.7	1.8	0.7
Baseline QILD-WL	-0.3	0.08	0.0003
Low KL-6	-4.3	2.0	0.03

*Reference group is CYC; MMF participants had improved course of DLCO.

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Abstract Number: 3246

Predictors of Long-Term Outcomes in Systemic Sclerosis Associated Pulmonary Arterial Hypertension from the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry

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Background/Purpose: Pulmonary arterial hypertension (PAH) is a leading cause of death in patients with systemic sclerosis (SSc). Predictors of short-term mortality include male sex, age>60 years, functional class IV, and lung diffusing capacity (DLCO) <39% (1). The purpose of this study was to identify independent predictors of long-term outcomes.

Methods: Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Registry is a prospective registry of SSc patients at high risk for PAH or with definite PH based on right heart catheterization within six months of enrollment. World

Health Organization Group I PAH patients were included (using the strict criteria of baseline pulmonary artery pressure (PAP) >= 25 mmHg, pulmonary capillary wedge pressure <=15 mmHg, and forced vital capacity >= 65%). Baseline characteristics, time to clinical worsening (TTCW), and cause of death in the short (<1 year), medium (1-4.9 years) and long (>=5 years) term were assessed. TTCW was defined as time to death, PAH-related hospitalization, lung transplantation, parenteral prostacyclin treatment, or worsening symptoms (decrease of >15% in the 6-minute walk distance (6MWD) *and* worsening of functional class *and*addition of PAH-specific medication). Cox proportional hazard models were used to identify the predictors of overall survival and TTCW.

Results: A total of 167 SSc-associated PAH patients were included. The patient population was predominantly Caucasian (80%), female (90%), and had limited cutaneous SSc (72%). The 1, 3, 5, and 8-year cumulative survival rates were 95%, 76%, 64%, and 50%, respectively. The majority of patient deaths in the short and medium term were due to PAH (62% and 60%, respectively), while in the long-term were due to causes unrelated to SSc (75%), including cancer (n=2), infection (n=1), cerebrovascular disease (n=1), sudden death (n=1), and unknown (n=1). Baseline 6MWD >165 m (HR 0.38 95% CI 0.16-0.88) and % predicted DLCO >40 (HR 0.45 95% CI 0.23-0.89) were predictors of long-term survival on multivariate analysis. The median TTCW was 4.15 years (95% CI 3.07-5.94). At 1, 3, 5, and 8 years the percentage of patients meeting criteria for clinical worsening was 23%, 40%, 57%, and 70%, respectively. Mean PAP (mPAP) >34 mmHg (HR 2.09 95% CI 1.16-3.79) and pulmonary vascular resistance (PVR) >4.76 WU (HR 2.04 95% CI 1.14-3.68) were predictive of progression to clinical worsening.

Conclusion: This is the longest-term prospective study to date evaluating outcomes in a US based multi-center cohort of patients with SSc-associated PAH. These data suggest that if PAH is well-controlled in the first several years after diagnosis, SSc patients have favorable outcomes, and typically die of causes unrelated to SSc. PVR and mPAP can predict progression to clinical worsening while 6MWD and % predicted DLCO values at the time of diagnosis predict long-term survival in this population.
Reference: Chung L et al. Survival and predictors of mortality in systemic sclerosis-associated pulmonary arterial hypertension: outcomes from the pulmonary hypertension assessment and recognition of outcomes in scleroderma registry. *Arthritis Care Res*. 2014 66(3): 489–95.

Disclosure: K. Kolstad, None; **S. Li**, None; **V. D. Steen**, None; **L. Chung**, Gilead, 5,Cytori, 5,Reata, 5,United Therapeutics, 2.

Abstract Number: 3247

Safety and Efficacy of Belimumab with Background Mycophenolate for Early Diffuse Cutaneous Systemic Sclerosis: A Randomized, Placebo Controlled, Pilot Trial

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Background/Purpose: Abnormalities of B cell function are part of the pathogenesis of systemic sclerosis (SSc), and B-lymphocyte stimulator (BLyS) is increased in the serum and skin of patients with SSc. Belimumab, a human monoclonal antibody, is a BLyS-specific inhibitor indicated for the treatment of some patients with systemic lupus erythematosus. It is not known whether there may be a role for the use of belimumab in the treatment of SSc.

Methods: This was an investigator-initiated, industry-sponsored, single-center, randomized, double-blind, placebo-controlled,

pilot study. Adults with diffuse cutaneous (dc)SSc of ≤3 years duration from first non-Raynaud's symptom were randomly assigned 1:1 to belimumab IV (10 mg/kg) or placebo after starting on background mycophenolate mofetil (MMF) 1000 mg po bid. The primary objectives were to assess the safety and tolerability of belimumab in patients with early dcSSc on background MMF as assessed by the number of adverse events (AE) and serious (S)AE and to assess efficacy as measured by change in Modified Rodnan Skin Score (MRSS) after 52 weeks.

Results: Baseline demographic information is shown below and was balanced between groups. After a MMF wash-in period, 20 patients were randomized: 10 to belimumab and 10 to placebo. One patient in each group was withdrawn by the investigators soon after randomization due to disease progression. A modified intent-to-treat analysis was performed including all patients who had at least one MRSS assessment after randomization. All randomized patients were included in the safety analysis. In the belimumab+MMF group, the MRSS decreased from a mean (SD) of 26.7 (5.4) to 19.1 (10.3), p = 0.039. In the placebo+MMF group, the mean MRSS decreased from 26.4 (5.4) to 19.9 (8.8), p= 0.023. The mean change in MRSS at 52 weeks was –8.6 (7.7) in the belimumab group and –6.6 (7.7) in the placebo group, p=0.40. In the belimumab group 7/9 patients achieved an MRSS improvement of ≥ 20% versus 3/9 patients in the placebo group, p=0.08. Patients in the belimumab group had a greater improvement in health assessment questionnaire - disability index (HAQ-DI). There were no significant differences in AE with 56 AE, 16 of which were infections, in the placebo group and 53 AE, 18 of which were infections, in the belimumab group. Three SAEs occurred after randomization, all in the placebo group and not deemed related to study medication.

Conclusion: Patients in both the belimumab+MMF and the placebo+MMF groups experienced clinically and statistically significant improvement in MRSS although the difference in the mean change in MRSS between the groups was not significant in this small pilot study. A higher proportion of patients in the belimumab group achieved an improvement in MRSS ≥ 20% although this missed statistical significance. Adverse events and rates of infection were similar in the groups. Additional study is needed to determine the role of belimumab in the treatment of dcSSc.

Table 1. Baseline Characteristics and Change in MRSS and HAQ-DI

	n	Belimumab + MMF	n	Placebo + MMF	P value
Age at baseline - (years, mean ± SD)	10	53 ± 12.1	10	56.7 ± 10.26	0.406
Disease duration - (months, mean ± SD)	10	9 ± 4.03	10	11.7 ± 7.82	0.567
Sex – n (% female)	10	7 (70)	10	8 (80)	0.999
Race – n (% Caucasian)	10	7 (70)	10	9 (90)	0.334
Ethnicity – n (% Hispanic)	10	1 (10)	10	3 (30)	0.569
ILD – n (%)	10	2 (20)	10	1 (10)	0.999
Anti-topoimerase – n(%)	10	3 (30)	10	2 (20)	0.999
Anti -RNA Pol III – n (%)	10	3 (30)	10	7 (70)	0.179
Change in MRSS after 52 weeks - mean ± SD	9	-8.56 ± 7.73	9	-6.56 ± 7.68	0.400
Change in HAQ-DI after 52 weeks - mean ± SD	9	-0.36 ± 0.39	9	0.06 ±0.36	**0.028**

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Abstract Number: 3248

Efficacy of Mycophenolate Mofetil and Oral Cyclophosphamide on Skin Thickness: Post-Hoc Analyses from the Scleroderma Lung Study I and II

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Efficacy of mycophenolate mofetil and oral cyclophosphamide on skin thickness: post-hoc analyses from the Scleroderma Lung Study I and II.

Background/Purpose: Assess the efficacy of mycophenolate mofetil (MMF) and cyclophosphamide (CYC) on the modified Rodnan skin score (mRSS) in patients enrolled in the Scleroderma Lung Study (SLS)-I and II.

Methods: SLS-I participants received daily oral CYC or matching placebo for one year followed for an additional year off therapy, whereas SLS-II participants received daily MMF for 2 years or daily oral CYC for 1 year followed by placebo for a second year. We assessed the within-treatment impact of MMF and CYC on mRSS in subjects with diffuse cutaneous systemic sclerosis (dcSSc) and limited cutaneous systemic sclerosis (lcSSc) participating in SLS-II over a 24-month period. We also compared the change in mRSS in the patients with dcSSc assigned to CYC and MMF in SLS-II and to the CYC group arm of SLS I with the change in the placebo arm of SLS I over a 24-month period.

Results: In SLS-II, the baseline (mean± SD) mRSS was 14.0±10.6 for CYC and 15.3±10.4 for MMF; 58.5% were classified as dcSSc. Each treatment was associated with a significant improvement in mRSS from baseline over 24 months ($P< 0.05$ at each time point, Figure 1. A and B) but there were no significant differences between the2 groups at any time point in either the dcSSc or lcSSc subset ($p> 0.05$ for all comparisons). In the dcSSc subgroup, the changes in mRSS from baseline to 6-, 12-, 18-, and 24-months were similar in the SLS-II pooled cohort (MMF+ CYC) and the SLS-I CYC cohort and showed statistically significant improvements compared to the SLS-I placebo group at 12, 18, and 24 months (Table 1).

Conclusion: In SLS-II, MMF and CYC each resulted in significant improvement from baseline in mRSS in the subset of patients with dcSSc over a 24-month period. In addition, MMF and CYC each resulted in statistically significant improvements in mRSS over the placebo group in the subjects with dcSSc at 12, 18, and 24 months.

Table 1.	N	SLS II Pooled data(CYC and MMF groups) (Mean±SD)	N	SLS I CYC group (Mean±SD)	N	SLSII and SLS I CYC (Mean±SD)	N	SLS I Placebo group (Mean±SD)
Baseline	83	20.8 (9.4)	49	21.6 (10.3)	132	21.1 (9.7)	46	20.4 (9.4)
6 month	69	-2.4 (6.4)†	45	-2.7 (6.4)†	114	-2.6 (6.4)†	43	-2.6 (5.7)†
12 month	66	-5.5 (5.9)*†	43	-5.3 (7.4)*†	109	-5.4 (6.5)*†	37	-1.7 (6.9)†
18 month	58	-6.4 (7.3)*†	36	-6.9 (7.4)*†	94	-6.6 (7.3)*†	33	-3.4 (6.2)*†
24 month	62	-7.0 (8.6)*†	32	-7.2 (7.3)*†	94	-7.1 (8.1)*†	34	-3.9 (5.9)*†

Table 1. Mean changes in modified Rodnan Skin Score from baseline at 6, 12, 18, and24 months in SLS-I and II in dcSSc. †P< 0.05 for mRSS at follow up vs. baseline within each group. *P< 0.05 for SLS-II pooled and SLS-I CYC groups compared to SLS-1 Placebo group. Negative score denotes improvement of skin score.

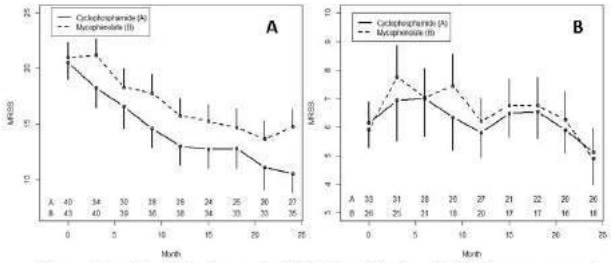

Figure 1 (Panel A and B). Course of modified Rodnan Skin Score (mRSS) in cutaneous systemic sclerosis over 24 month period in participants whom were either treated with cyclophosphamide vs. mycophenolate, **A.** diffuse (dcSSc): P ≤ 0.05 at each time point between CYC and MMF in dcSSc and **B.** limited (lcSSc) P ≥ 0.05 at each time point between CYC and MMF in lcSSC.

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Abstract Number: 3249

Improvement in Cough and Cough-Related Quality of Life in Participants Undergoing Treatment for Systemic Sclerosis-Related Interstitial Lung Disease

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Background/Purpose: While chronic cough occurs in the majority of patients with systemic sclerosis-related interstitial lung disease (SSc-ILD),[1] its impact on quality of life has not been adequately addressed. Furthermore, minimal literature exists on the relationship between cough and SSc-ILD treatment response. This study uses data from the Scleroderma Lung Study (SLS) II to evaluate the disease burden of cough in SSc-ILD and to determine whether cough changes in response to treatment for SSc-ILD.

Methods: SLS II randomized adult SSc-ILD participants to mycophenolate (MMF) for 2 years (N=69) versus oral cyclophosphamide (CYC) for 1 year followed by 1 year of placebo (N=73). The primary outcome was FVC%-predicted and key secondary outcomes included frequent cough, as assessed by the St. GeorgeÕs Respiratory Questionnaire (SGRQ), along with breathlessness, quantitative extent of ILD (QILD) and fibrosis (QLF) on HRCT imaging and cough-specific quality of life (QOL), as assessed by the Leicester Cough Questionnaire (LCQ).

Results: The majority of participants (61%) reported frequent cough at baseline, of whom 66% also had moderate-severe GERD. Compared with those without cough, participants with frequent cough more often had GERD (p=0.025) and had increased breathing difficulty, lower DLCO and greater QLF in the whole lung (WL) and greater QILD in the WL and the lobe of maximal involvement (LM). LCQ scores were significantly correlated with dyspnea, general QOL measures, severity of GERD and QILD/QLF (all P<0.05). A 42% reduction in the proportion of participants with frequent cough occurred over the 24-month trial with no difference noted between treatment arms or between those with/without GERD at baseline (See Figure 1). However, patients in whom frequent cough persisted at 2 years were more likely to have developed GERD compared with patients who had resolution of frequent cough at 2 years (P=0.03). Logistic regression demonstrated associations between a reduction in cough and improvements in FVC%-predicted (P=0.06), breathlessness (P=0.02), and QILD-WL (P=0.03) at 24 months.

Conclusion: The majority of SLS II participants experienced frequent cough that was significantly associated with the severity of GERD, physiologic and radiographic measures of extent of ILD and non-cough specific QOL. After SSc-ILD treatment, participants experienced a significant reduction in cough, which correlated with improvements in physiologic and radiologic outcomes. These findings suggest that changes in cough may serve as a surrogate measure of treatment response in SSc-ILD. However, the development of GERD may diminish improvement in cough with SSc-ILD therapy. **References**: 1. Theodore, et al. Chest 2012;142:614-21.

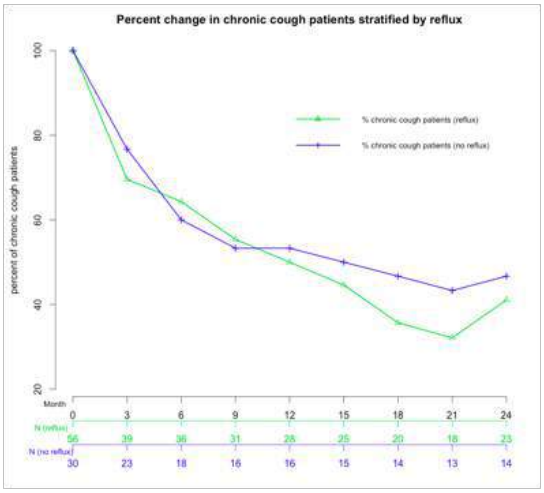

Figure 1. Changes in the proportion of patients with frequent cough for patients with and without reflux at baseline.

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Abstract Number: 3250

Serum MCP-1 Levels Predict Long-Term Progression of Interstitial Lung Disease in Systemic Sclerosis

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Background/Purpose: Currently available clinical biomarkers are not reliable predictors of long-term progression of interstitial lung disease (ILD) in the context of systemic sclerosis (SSc) A previous study of the GENISOS cohort demonstrated that higher plasma MCP-1 (CCL2) predicted a more rapid decline of forced vital capacity (FVC) while IL-10 levels were protective. IL-6 has also been proposed as a cytokine predictive for SSc-ILD progression (De Lauretis et al. J Rheumatol. 2013). Herein, we determined the predictive significance of baseline serum MCP-1, IL-10 and IL-6 levels for progression of ILD and survival in an independent cohort of patients with early SSc.

Methods: Baseline serum samples of SSc patients with disease duration < 5 years enrolled in the Canadian Scleroderma Research Group were investigated. Samples were collected according to a common standard operating procedure. The serum levels of 3 key cytokines MCP-1, IL-10 and IL-6 were determined by highly sensitive Mesoscale assays (Meso Scale Discovery, Rockville, MA). The primary outcome was decline in forced vital capacity (FVC% predicted) over time. The rate of change in a longitudinally obtained FVC % predicted value was investigated by a joint analysis of longitudinal measurements (sequentially obtained FVC% predicted) and Cox regression for survival. This approach allows inclusion of all FVC measurements and accounts for dependency on survival. Cytokines were analyzed as log-transformed continuous variable.

Results: A total of 190 patients with early SSc were investigated. The proportion of female patients was 82% (n=156) and diffuse skin involvement was present in 40% (n=76) patients. The mean disease duration at enrollment was 2.2 years and mean follow-up time was 5.72 years. 19 patients (10%) died during follow-up period. After adjustment for age, gender and ethnicity, there was a trend for an association between higher levels of MCP-1 and faster FVC decline (b=-0.50, 95% CI: -1.54; 0.04, p=0.072) while IL-6 and IL-10 levels were not predictive of differential rate of FVC decline (p=0.109 and p=0.679, respectively). When the model was additionally adjusted for treatment with immunosuppression and disease subtype, the relationship between baseline serum MCP-1 levels and long-term decline in FVC became significant (b=-0.54, 95% CI:-1.08; -0.00, p=0.048). IL-10 and IL-6 also did not show predictive significance in the expanded model (p=0.571 and p=0.116, respectively). Higher serum MCP-1 levels was also associated with poorer survival (HR: 5.31, 95% CI: 1.45; 19.43, p= 0.012).

Conclusion: We confirmed MCP-1 is an important biomarker predictive of ILD progression and poorer survival in SSc. MCP-1 might aid in informing clinical decisions and enrichment strategies for clinical trials. Furthermore, these data supports MCP-1, a

marker of pro-fibrotic macrophages as an important treatment target in SSc-ILD.

Disclosure: M. Wu, None; **M. Baron**, None; **M. Hudson**, None; **M. J. Fritzler**, None; **C. Pedroza**, None; **J. Ying**, None; **G. Salazar**, None; **J. Charles**, None; **M. D. Mayes**, None; **S. Assassi**, Boehringer Ingelheim, 5,Genentech and Biogen IDEC Inc., 2,Bayer HealthCare, 2.

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Abstract Number: 3251

Sleep and Physical Activity: A Nationwide Survey Among People with Rheumatic Disease in Ireland

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Background/Purpose: Sleep is an important aspect in maintaining the body's circadian rhythm and plays an important role in maintaining health. Disrupted or lower levels of sleep have been related to serious outcomes such as an increased risk of morbidities. Sleep disturbances and poor sleep quality are prevalent complaints in people with rheumatic disease and may exacerbate pain in this population, potentially leading to reduced levels of activity. The aim of this study was to investigate sleep quality, sleep disturbances and physical activity among Irish people who have Inflammatory Arthritis

Methods: Members from Arthritis Ireland, a national charitable organisation for patients with arthritis, were invited to participate in a cross-sectional survey hosted on SurveyMonkey$^{(R)TM}$. Ethical approval was received. Descriptive statistics, Chi-square tests/Fisher's exact tests were used to analyse the data using Statistical Package for the Social Sciences (SPSS) version 22

Results: Ninety (90) people with Inflammatory Arthritis responded and report an average of 5.7 (SD 1.46) hours sleep per night. Results found the mean number of years with inflammatory arthritis to be 10.09 (SD 9.92). A majority (61%) report their sleep quality as fairly bad/very bad, with 31% having taken medications at least once a week to help their sleep, over the previous month. Ninety three percent (93%) reported arthritis pain in the previous week, while 23% were limited a lot and 62% limited a little with moderate activities. A large majority report 'pain' (95%), 'waking up in the middle of the night or early morning' (97%) and 'cannot get to sleep within 30 minutes' (91%) as disturbances. There was a statistically significant association between longer years with symptoms (p=0.004), taking medication at least once a week (p=0.009) and limited in their activities (p=0.004), when rating their sleep quality as bad. When using the Short Questionnaire to Assess Health-enhancing physical activity (SQUASH), patients' physical activity levels were a low 1,210 minutes per week, compared to other physical activity surveys from their healthy counterparts, even-though 72% believe it is important to measure physical activity. Of those getting less than 1,210 minutes per week of physical activity, 73% report their sleep quality as fairly bad/very bad, while 65% received more than the reported average of 5.7 hours sleep per night

Conclusion: Irish people with Inflammatory Arthritis fall far below the 'sleep needs spectrum' with those having symptoms longer, taking medications regularly and having limitations with their activities, reporting poorer sleep quality. More research is needed with regards to investigating poor sleep quality and disturbances in order to promote health and well-being in people with Inflammatory Arthritis. In addition the effects of physical activity interventions on poor sleep needs to be examined to show if it is a positive non-pharmacological treatment approach for the management of poor sleep in patients with Inflammatory arthritis

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Disclosure: S. McKenna, None; **A. Donnelly**, None; **S. Fraser**, None; **N. Kennedy**, None.

Abstract Number: 3252

Content Analysis of Ergonomic Recommendations Using the Ergonomic Assessment Tool for Arthritis

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Background/Purpose: Work cessation and at-work productivity loss are common and early outcomes of inflammatory arthritis (IA). Ergonomic accommodations contribute to successful management of arthritis symptoms in the workplace. The self-assessment and interview format of the Ergonomic Assessment Tool for Arthritis (EATA) mitigates concerns about disclosing diagnoses to employers. However, evaluation of its utility is needed, including whether or not it adequately captures ergonomic issues and leads to appropriate recommendations. The purpose of the present study is to descriptively analyze the kinds of ergonomic issues experienced by working adults with IA and the potential solutions proposed by the occupational therapist (OT) as identified with the EATA.

Methods: This descriptive study is nested within a randomized controlled trial of the Making it Work program to prevent work loss secondary to IA. One element of the intervention is a 1:1 ergonomic consultation with an OT performed outside of the workplace. OTs were provided training in the EATA protocol. We extracted data from OT's written assessments and the solutions form of EATA for 67 consecutive participants at one provincial site of the trial. Content analysis of ergonomic issues and recommended solutions was conducted by two authors and verified by co-authors.

Results: Participants ranged from 23-60 years of age (mean=47); 81% were women; and all were currently employed 3-62 hours per week. The majority (62%) had rheumatoid arthritis. Issues identified during the consultation were predominantly related to work station design and symptom management in the workplace, especially fatigue. Recommended solutions to issues in the workplace, while predominantly ergonomic in nature, also included non-ergonomic suggestions to reinforce medical, therapeutic, and health lifestyle recommendations that participants identified as problematic. Ergonomic solutions tended to fit one of two primary categories: (1) strategies such as pacing (72%) or modifying work tasks (57%), and (2) equipment recommendations, such as adjusting current work stations (51%) to support improved work postures or recommending equipment like an adjustable chair or assistive device to improve biomechanics for task performance. A review of EATA data with the occupational therapists involved also showed that issues of greatest concern to participants were frequently outside the realm of this very specific work-based consultation, indicating the complexity of living with IA and need for ready access to a broad range of resources and/or interdisciplinary team.

Conclusion: A structured, interviewed-based assessment is feasible for identifying ergonomic issues faced by employed adults with IA, and proposing solutions to support work performance. Follow up research is recommended to assess the usefulness of the proposed solutions in achieving the goal of preventing work loss.

Disclosure: L. Allyn, None; **L. Zoller**, None; **C. L. Backman**, None; **D. Lacaille**, None.

Abstract Number: 3253

Minimum Physical Function Needed to Walk 6000 Steps/Day in People with Knee Osteoarthritis

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Title: Minimum Physical Function Needed To Walk 6000 steps/day In People With Knee Osteoarthritis.

Background/Purpose: Adopting a physically active lifestyle provides major health benefits to people with knee osteoarthritis (OA). Yet, most people with knee OA are sedentary. Difficulty with physical function, such as stair climbing and walking, may be one barrier to physical activity participation for people with knee OA. Little is known about what minimum level of physical function is necessary to engage in physical activity. Establishing minimum thresholds will help clinicians prioritize prescribing intervention for physical activity or physical function in knee OA. The purpose of the study was to identify minimum thresholds of performance on clinical tests of physical function required to target a goal of 6000 steps/day, an important benchmark of activity in knee OA.

Methods: We used publically available data from the Osteoarthritis Initiative (OAI). Physical activity was measured with an accelerometer (Actigraph GT1M) worn during waking hours during the 48-month follow-up visit, and quantified as steps/day. Physical function was quantified with three clinical tests: timed 5 repetition sit-to-stand test (STS), timed 400-meter walk, and walking speed (calculated from a 20-meter walk). We calculated Pearson correlation coefficients to examine the association between steps/day and physical function. To identify a minimum threshold for each, we calculated cut-points at 80% to 95% specificity for walking 6,000 steps/day, i.e., the proportion classified with good physical function and ≥ 6000 steps/day divided by all with ≥ 6000 steps/day.

Results: Participants who wore the monitor for ≥ 3 days (n=1790, age [mean (± sd)] 65.0 ± 8.8 years, BMI 28.4 ± 4.9 kg/m^2, 55% female), had 6319 ± 2920 steps/day with 47% walking ≥ 6000 steps/day. The mean STS was 10.2 ± 3.2 seconds, 400-meter walk was 305.3±51.4 seconds, and walking speed was 1.3 ± 0.2 meters/sec. Steps/day had a small negative correlation with STS (r=-0.2, p<0.001) and 400-meter walk (r=-0.4, p<0.001) and a small to moderate positive correlation with walking speed (r=0.4, p<0.001). Thresholds of high specificity (80-95%) of physical performance for walking ≥ 6000 steps/day ranged from 11 to 14 seconds for STS, 315 to 350 seconds for the 400-meter walk, and 1.10 to 1.25 meters/sec for walking speed (Table).

Conclusion: Physical function at or worse than stated thresholds may represent insufficient physical function for attaining an important benchmark of physical activity. Intervention targeting physical function may be more appropriate than directly targeting physical activity for those below these physical function thresholds with knee OA. **Table:** Physical function measures that reflect 80, 85, 90 and 95% specificity*.

	Specificity*			
Physical function measures	**80%**	**85%**	**90%**	**95%**
STS (seconds)	11.0	12.0	12.5	14.0
400-meter walk (seconds)	315	320	330	350
Walking speed (meters/sec)	1.25	1.22	1.18	1.10
*Specificity is defined as the proportion classified with good physical function and ≥ 6000 steps/day divided by all with ≥ 6000 steps/day.				

Disclosure: H. Master, None; **L. Thoma**, None; **M. Christiansen**, None; **E. Polakowski**, None; **L. Schmitt**, None; **D. White**, None.

Abstract Number: 3254

Use of the Short Valued Life Activities Scale in People with Systemic Sclerosis

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Background/Purpose: Systemic sclerosis is a chronic autoimmune connective tissue disorder that results in skin thickening, vascular insufficiency, and fibrosis of internal organs, such as the heart, lungs, kidneys, gastrointestinal tract, and joints and muscles. People have difficulty participating in daily tasks due to pain, finger ulcers, Raynaud's phenomenon, and internal organ involvement, particularly decreased pulmonary function. Most of the research on scleroderma has focused on performance of basic daily living and work tasks. Little is known about participation in household, leisure, and community activities. The Valued Life Activities Scale (VLA) measures difficulty in self-care, household, leisure and community activities (1). The VLA has been used to track changes over time in persons with different rheumatic diseases and thus, maybe useful for people with scleroderma. However, the 33 items may be too long for clinical use. Purpose: To examine the internal consistency and validity of the 14 item Short-VLA Scale in persons with systemic sclerosis.

Methods: The sample was a convenience sample of 83 people with systemic sclerosis recruited from the Scleroderma Foundation website and annual conference. Participants completed the VLA, a questionnaire with 33 items under three domains: obligatory, committed, and discretionary. Obligatory activities include self-care, committed activities include household tasks, and discretionary activities include leisure and community activities. For each item, participants rated difficulty with performance from 0 (no difficulty) to 3 (unable to do). A Short-VLA score is calculated as the mean from 14 of the items as described by Katz et al.(2). Participants also completed a demographics questionnaire, questions regarding the presence and severity of disease symptoms, the Health Assessment Questionnaire (HAQ), and Center for Epidemiologic Studies Depression Scale (CES-D) and the Adelaide Activities Profile (AAP), a measure of *frequency* of participation in household and community tasks.

Results: The majority of the participants were Caucasian (94%), female (90%), and married; 98% had Raynaud's phenomenon, 93% reported gastrointestinal problems and 50% reported lung involvement. Our participants had a mean age of 53 years and mean disease duration of 9 years. About half of the participants had limited SSc and half had diffuse SSc. The mean score on the S-VLA was 1.10 indicating mild difficulty. Internal consistency of the S-VLA was excellent (Cronbach's alpha=0.92). The correlation between the S-VLA and the original long form VLA was excellent (r=0.96). A moderate correlation was also found between the S-VLA and the HAQ (r=0.73) and AAP (r = 0.56), however the correlation with the CES-D was only fair (r=0.35).

Conclusion: The S-VLA was found to be a reliable and valid measure in persons with SSc. In addition, the S-VLA may be useful to monitor participation in household, leisure, and community activities as decreasing participation in these types of activities has been correlated with depression and decreased quality of life (1).

1. Katz PP et al. Ann Rheum Dis 2006; 65; 763-9.
2. Katz PP et al. Arthritis Care Res 2011; 63; 1664-71.

Disclosure: J. L. Poole, PCORI grant, 2; **B. Skipper**, None.

Abstract Number: 3255

A Randomized Trial of Automated Telephone-Linked Communication to Improve Exercise Adherence for a Progressive Resistance Training Program in People with Knee Osteoarthritis

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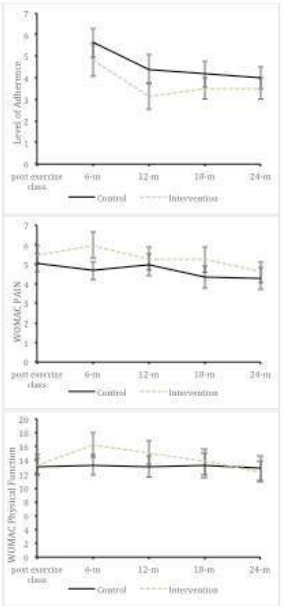
Background/Purpose: In knee osteoarthritis (OA) strengthening exercise improves pain and physical function, however a marked decline in exercise adherence has limited the long term efficacy of exercise. Adherence drops precipitously when trainer instruction and social support for exercise are withdrawn. We developed an interactive automated telephone calling system, Boston Osteoarthritis Strengthening telephone linked-communication (BOOST TLC), that provides low cost trainer instruction and behavioral counseling to motivate people with knee OA to continue strength exercises after participating in a group class. We tested the effect of BOOST TLC on exercise adherence over 24-m in a randomized trial.

Methods: Participants were recruited from the community and had painful, self-reported doctor-diagnosed knee OA. Participants initially completed a 6-week trainer led strength class using a protocol previously shown to improve pain and function in knee OA. The protocol included exercises for warm-up, posture, functional strength (squats and stair stepping), isolated knee strength with ankle weights (knee flexion and knee extension), hip abduction, core, and stretching. The instruction emphasized proper form and progressive resistance training. After completing the class, participants were randomized to BOOST TLC or control. BOOST TLC is an automated, interactive conversation system that asks questions, comments on responses, and educates and counsels users. TLC stores the question responses in a database to direct current and future TLC conversations and provides alerts and reports to staff. The BOOST TLC group received biweekly calls for 6-m and monthly calls for the subsequent 18-m. The control and BOOST TLC group received an automated monthly phone message encouraging continued strength training. The primary outcome was self-rated adherence to the strength exercises in the previous 3 months (from Ônot at allÕ to Ôcompletely as instructedÕ) on a 10-point scale. Evaluations occurred at 6-m, 12-m, 18-m and 24-m after the strength class. Secondary outcomes included WOMAC pain and physical function. 24-m adherence was analyzed using nonparametric Wilcoxon test and adjusted for baseline WOMAC pain using robust generalized estimating equations regression.

Results: There were 104 trial participants (82% female; 65 ± 8 years old; BMI 31 ± 7). The 24-m treatment difference in adherence was not statistically significant (Boost TLC 3.5 ± 3.3, control 4.0 ± 3.5, p= 0.53), and remained non-significant when adjusted for baseline pain (p=0.46). There was no 24-m treatment difference in WOMAC pain (Boost TLC 4.6 ± 3.7, control 4.3 ± 3.7, p= 0.68) or physical function (Boost TLC 12.3 ± 9.7, control 12.8 ± 11.7, p= 0. 0.82).

Conclusion: BOOST TLC provided no additional benefit for exercise adherence above that provided by an automated, non-



interactive message reminding participants to exercise.

Disclosure: K. Baker, None; **A. Ledingham**, None; **C. Brown**, None; **K. Pesanelli**, None; **F. Cochrane**, None; **R. Friedman**, None; **M. P. LaValley**, None; **D. T. Felson**, zimmer knee creations, 5; **J. J. Keysor**, None.

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Abstract Number: 3256

Functional Ability 'to Rise' and Autonomy Support for Physical Activity: Implications for Light Physical Activity Engagement and Psychological Wellbeing in People Living with Rheumatoid Arthritis

Sally Fenton[1,2], Jet Veldhuijzen van Zanten[2], George Metsios[2,3], Peter Rouse[4], Chen-an Yu[5], George D. Kitas[1,2] and Joan Duda[1], [1]School of Sport, Exercise and Rehabilitation, University of Birmingham, Birmingham, United Kingdom, [2]Department of Rheumatology, Russells Hall Hospital, Dudley Group of Hospitals NHS Foundation Trust, Dudley, United Kingdom, [3]Department of Physical Activity Exercise and Health, University of Wolverhampton, Walsall, United Kingdom, [4]Department for Health, University of Bath, Bath, United Kingdom, [5]School of Sport, Exercise and Rehabilitation Sciences, University of Birmingham, Birmingham, United Kingdom

First publication: September 28, 2016

SESSION INFORMATION

Session Date: Wednesday, November 16, 2016

Session Title: ARHP VI: Rehabilitation Sciences

Session Type: ARHP Concurrent Abstract Session

Session Time: 11:00AM-12:30PM

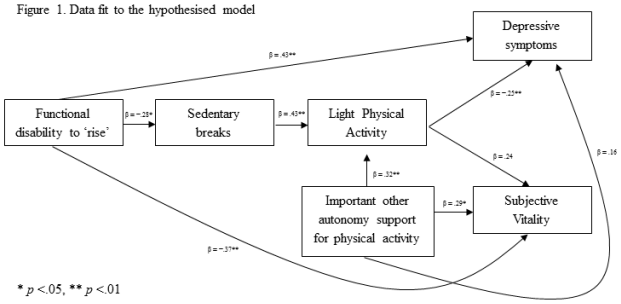
Background/Purpose: Epidemiological studies indicate participation in light physical activity (LPA) is positively associated with psychological wellbeing. For patients with Rheumatoid Arthritis (RA), reduced functional ability may result in lower LPA engagement and consequently, compromised mental health. In particular, lower-limb physical dysfunction in RA may result in a reduced ability to transition from a sitting (or sedentary) to a standing posture (i.e., 'sedentary breaks'), contributing towards lower LPA engagement. Since physical dysfunction is symptomatic of RA, it is also important to determine modifiable correlates of LPA. Studies framed by Self-determination Theory demonstrate autonomy supportive social environments to be relevant to levels of physical activity engagement in healthy and patient populations. Thus, the social environment may represent a malleable target for interventions that seek to promote LPA in RA. The primary aim of this study was therefore to test a model examining the

implications of 1) functional disability to 'rise', and 2) autonomy support for physical activity, for levels of objectively assessed LPA and associated psychological wellbeing.

Methods: RA patients (N = 50, Mage = 55.5 ± 12.5 yrs), completed questionnaires assessing; 1) functional disability to 'rise' [e.g., are you able to stand up from an armless straight chair, higher score = lower function], 2) autonomy support for PA [from a patient-specified important other], 3) depressive symptoms, and 4) subjective vitality. Sedentary breaks and LPA engagement were determined from 7-days of accelerometry (i.e., *sedentary breaks*, interruptions in sedentary time with ≥1 min activity ≥100 counts/min, *LPA,* activity 100 - 2019 counts/min).

Results: Path analyses supported a model (χ^2 (5) = 8.83, p =.12, CFI =.95, SRMR = .08, RMSEA =.13), in which functional disability to rise significantly negatively predicted the number of sedentary breaks (per/hour), which in turn, significantly positively predicted LPA engagement (min/hour). A significant positive association between important other autonomy support and LPA was observed, independent of functional disability 'to rise'. LPA then significantly and negatively predicted depressive symptoms. The association between LPA and subjective vitality was positive and approached significance (p =.06, Figure 1).

Conclusion: Functional disability to 'rise' may be adversely related to levels of LPA engagement in RA, via the patient's ability to transition from sitting to standing. However, autonomy support from an important other may represent a modifiable target for interventions seeking to promote LPA, independently of the negative consequence of lower limb functional disability. Subsequently, LPA engagement may hold positive implications for psychological health in RA. Figure 1: Data fit of the hypothesised model *Note:* * p < .05, ** p <.01



Disclosure: S. Fenton, None; **J. Veldhuijzen van Zanten**, None; **G. Metsios**, None; **P. Rouse**, None; **C. A. Yu**, None; **G. D. Kitas**, None; **J. Duda**, None.

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Abstract Number: 1L

The Cardiovascular Safety of Celecoxib Versus Ibuprofen or Naproxen in 24,081 Patients with Osteoarthritis or Rheumatoid Arthritis

M. Elaine Husni[1], Daniel H. Solomon[2], Katherine E Wolski[3], Lisa M Wisniewski[3], Steven E Nissen[4] and on behalf of the PRECISION Trial Investigators, [1]Rheumatology, Cleveland Clinic, Cleveland, OH, [2]Division of Rheumatology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [3]Cardiovascular Medicine, Cleveland Clinic, Cleveland, OH, [4]Cardiovascular Medicine, Chair, Cleveland Clinic, Cleveland, OH

First publication: October 19, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016
Session Title: ACR Late-breaking Abstract Session
Session Type: ACR Late-breaking Abstract Session
Session Time: 4:30PM-6:00PM

*Both authors (Husni, Solomon) contributed equally and will co present

Background/Purpose: The relative cardiovascular (CV) safety of non-selective NSAIDs and selective COX-2 NSAIDs remains unclear. Given the chronic use of NSAIDs in the osteoarthritis (OA) and rheumatoid arthritis (RA) population along with known concomitant risk for CV disease, the relative safety of these agents is of critical importance for rheumatologists and their patients. The best opportunity to answer this question is to conduct a very large randomized controlled trial (RCT) that directly and prospectively compares the CV safety of these agents, the PRECISION trial.

Methods: PRECISION was a double blind and triple dummy RCT conducted worldwide. Subjects enrolled in PRECISION had to have a known history of CV events (myocardial infarction, stroke, or coronary re-vascularization) or evidence of CV risk based on traditional CV risk factors. Additional criteria included a physician diagnosis of OA or RA, daily need for NSAID therapy, no CV events within the last 90 days and no contraindications to the use of these agents. Subjects were randomized to celecoxib 100-200mg bid, ibuprofen 600-800mg tid, or naproxen 375-500mg bid. All subjects were provided open-label esomeprazole at 20-40mg qd and aspirin was allowed as part of standard of care if applicable. The primary CV outcome was a composite of CV death (including hemorrhagic), non-fatal MI, and non-fatal stroke with at least 18 months of follow-up. The study was designed as a non-inferiority trial with the main hypothesis that CV risk among subjects randomized to celecoxib would have an upper confidence interval (CI) of ≤ 1.33 for the intention to treat (ITT) and a HR ≤ 1.12 with an upper CI of ≤ 1.40 for the on treatment population compared with naproxen or ibuprofen based on a one-sided confidence interval of 97.5%. The trial continued for 10 years until the required 580 CV events for 30 months ITT analysis and 420 events for 42 months on-treatment population analysis were observed. Additional measures of function, global arthritis activity, and VAS pain were recorded.

Results:

The trial enrolled patients from 13 countries, with 923 sites, and 80% of subjects came from the US. A total of 24,081 subjects were enrolled and included in the final analyses, with 90% having OA and 10% RA. The mean age of subjects with OA was 63.5 years and for RA 60.7 years; 63.1% of subjects with OA were female and 73.2% with RA were female. The age and gender distribution did not differ by NSAID treatment assignment. Adherence was 80% over at least 6-months of follow-up, with a median follow-up of 18 months. The comparative CV risk by NSAID treatment arm will be presented separately for subjects with OA and RA. Gastrointestinal (GI) and renal adverse events were also adjudicated and will be presented for subjects with OA and RA by treatment arm.

Conclusion: PRECISION represents the largest CV safety trial of commonly used NSAIDs among patients with OA or RA. The results to be presented will clarify whether these NSAIDs carry the same CV, GI and renal risk across OA and RA patients.

Disclosure: **M. E. Husni**, Lilly, Novartis, Abbvie, Celgene, Bristol Myers Squibb, Amgen, Janssen, & UCB pharma, 5,Pfizer Inc, 6; **D. H. Solomon**, Pfizer Inc, 2,Pfizer Inc, 6; **K. E. Wolski**, None; **L. M. Wisniewski**, Pfizer Inc, 2; **S. E. Nissen**, Pfizer Inc, 2.

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Abstract Number: 2L

Effect of Denosumab Compared with Risedronate in Glucocorticoid-Treated Individuals: Results from the 12-Month Primary Analysis of a Randomized, Double-Blind, Active-Controlled Study

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SESSION INFORMATION

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Session Title: ACR Late-breaking Abstract Session

Session Type: ACR Late-breaking Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Glucocorticoid (GC)-induced osteoporosis (GIOP) remains the most common

secondary cause of osteoporosis. Despite approved therapies, many subjects do not receive GIOP prevention or treatment. There is increased RANKL and decreased osteoprotegerin (OPG) expression in GIOP. Denosumab (DMAb) is a monoclonal antibody to RANKL. This study was designed to assess the safety and efficacy of DMAb compared with risedronate (RIS) in GC-treated individuals, in whom treatment guidelines advocate a GIOP intervention.

Methods: This was a phase 3, randomized, double-blind, active-controlled study to evaluate DMAb vs. RIS in GC-treated individuals for 24 mos. Eligible subjects were women and men ≥18 yrs receiving GC therapy at a dose ≥7.5 mg prednisone daily or its equivalent for ≥3 mos or <3 mos prior to screening (GC-continuing [GC-C] and GC-initiating [GC-I], respectively). All subjects <50 yrs were required to have a history of osteoporotic fracture. GC-C subjects ≥50 yrs were required to have a lumbar spine (LS), total hip (TH), or femoral neck bone mineral density (BMD) T score ≤–2.0; or a T-score ≤–1.0 with a history of fracture. Subjects were randomized 1:1 to SC DMAb 60 mg every 6 mos or oral RIS 5 mg daily for 24 mos. Subjects were to receive daily calcium (≥1000 mg) and vitamin D (≥800 IU) supplementation. The primary objective was to demonstrate in the GC-C and GC-I subpopulations separately that DMAb was not inferior to RIS with respect to percentage change from baseline in LS BMD at 12 mos. Secondary objectives were to assess superiority of DMAb over RIS with respect to percentage change from baseline in LS and TH BMD at 12 mos. The study remains blinded and is ongoing.

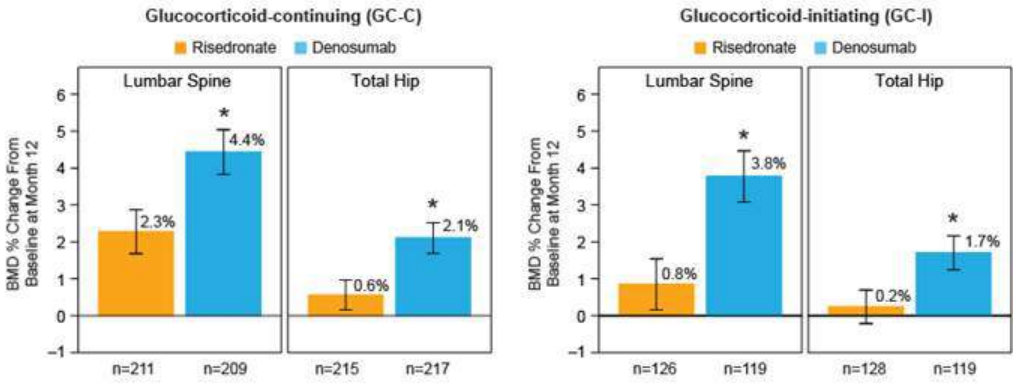
Results: A total of 795 subjects (505 GC-C and 290 GC-I) enrolled in the study. Baseline characteristics were balanced between treatment groups (Table). Non-inferiority and superiority with DMAb were demonstrated for both the GC-C and GC-I subpopulations, due to significantly greater gains in BMD compared with RIS at the LS and TH in both subpopulations (Figure). The incidences of adverse events (AEs) and serious AEs, including serious AEs of infection, as well as fracture, were similar between treatment groups and consistent with the known safety profile of DMAb.

Conclusion: DMAb significantly increased BMD more than RIS at the spine and hip at 12 months. The overall safety profile was similar between treatment groups. DMAb has the potential to become another treatment option for patients newly initiating or continuing GC who are at risk for fracture.

Table. Baseline Characteristics

	Glucocorticoid-continuing (GC-C)		Glucocorticoid-initiating (GC-I)	
	Risedronate N=252	Denosumab N=253	Risedronate N=145	Denosumab N=145
Sex – n (%)				
Male	67 (26.6)	68 (26.9)	52 (35.9)	52 (35.9)
Female	185 (73.4)	185 (73.1)	93 (64.1)	93 (64.1)
Age (years) – mean (SD)	61.3 (11.1)	61.5 (11.6)	64.4 (10.0)	67.5 (10.1)
Medical Conditions of Interest – n (%)				
Rheumatoid arthritis	118 (46.8)	96 (37.9)	43 (29.7)	48 (33.1)
Polymyalgia rheumatic	18 (7.1)	20 (7.9)	52 (35.9)	50 (34.5)
Systemic lupus erythematosus	16 (6.3)	15 (5.9)	4 (2.8)	2 (1.4)
Daily prednisone-equivalent dose (mg) – mean (SD)	11.13 (7.69)	12.29 (8.09)	15.61 (10.25)	16.57 (13.01)
25 (OH) vitamin D (ng/mL) – median (Q1, Q3)	28.0 (23.6, 36.3)	29.2 (24.2, 37.6)	28.6 (24.2, 36.4)	28.8 (23.6, 36.0)
BMD T-score – mean (SD)				
Lumbar spine	−1.96 (1.38)	−1.92 (1.39)	−1.06 (1.57)	−0.92 (1.86)
Total hip	−1.56 (0.96)	−1.66 (0.96)	−0.98 (1.07)	−1.14 (1.00)

Figure. BMD Percentage Change From Baseline at Month 12



n=Number of subjects with observed values at baseline and month 12. *p<0.001 compared with RIS.

Disclosure: K. Saag, Amgen, Merck, 5,Amgen, Merck, 2; **R. Wagman**, Amgen, 1,Amgen, 3; **P. Geusens**, Pfizer, Abbott, Lilly, Amgen, MSD, Will, Roche, UCB, BMS, Novartis, 9,Pfizer, Abbott, Lilly, Amgen, MSD, Will, Roche, UCB, BMS, Novartis, 9,Pfizer, Abbott, Lilly, Amgen, MSD, Will, Roche, UCB, BMS, Novartis, 9; **J. Adachi**, Amgen, Eli Lilly, Merck, Pfizer, 2,Amgen, Eli Lilly, Merck, 5,International Osteoporosis Foundation,, 6,Amgen, Eli Lilly, 8; **O. Messina**, GSK, Amgen, 2; **R. Emkey**, Amgen, 8; **R. Chapurlat**, Amgen, Merck, Chugai, 2,Amgen, Lilly, BMS, Abbvie, Pfizer, Chugai, UCB, 5; **N. Daizadeh**, Amgen Inc., 1,Amgen Inc., 3; **N. Pannacciulli**, Amgen Inc., 1,Amgen Inc., 3; **W. Lems**, Eli Lilly, Amgen, Novartis, MSD, 9,Eli Lilly, Amgen, Novartis, MSD, 9.

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Abstract Number: 3L

Comparative Cardiovascular Safety of Tocilizumab Vs Etanercept in Rheumatoid Arthritis: Results of a Randomized, Parallel-Group, Multicenter, Noninferiority, Phase 4 Clinical Trial

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First publication: October 19, 2016

SESSION INFORMATION

Session Date: Tuesday, November 15, 2016

Session Title: ACR Late-breaking Abstract Session

Session Type: ACR Late-breaking Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: Treatment of rheumatoid arthritis (RA) with tocilizumab (TCZ), a humanized monoclonal antibody directed against the IL-6 receptor, is associated with clinical efficacy and marked reduction in systemic inflammatory markers associated with atherogenesis and atherothrombosis, but treatment-associated increases in low-density lipoprotein (LDL-C) have called into question the net cardiovascular risk-benefit ratio of TCZ in RA.

Methods: Seropositive RA patients with active disease (≥8 swollen and ≥8 tender joints and CRP >3 mg/L) and inadequate response to ≥1 nonbiologic DMARD were randomized 1:1 to receive open-label TCZ 8 mg/kg infused monthly or etanercept (ETA) 50 mg injected weekly. Enrollment was restricted to patients ≥50 years of age with ≥1 cardiovascular disease (CVD) risk factor, extra-articular RA manifestations, or history of a CVD event. The primary outcome was the comparison of incident major adverse CVD event (MACE), defined as CVD death, nonfatal myocardial infarction or nonfatal stroke, for TCZ vs ETA. Rates of other CVD events and non-CVD safety outcomes were explored as secondary outcomes. Lipid levels were tracked throughout the trial. CVD events were adjudicated by an independent committee. The study was powered to rule out ≥80% relative hazard of MACE for TCZ vs ETA.

Results: A total of 3080 RA patients were enrolled (TCZ n=1538; ETA n=1542), and 2957 (96%) completed the study with a full assessment of CVD events. Average follow-up time was 3.2 years. Early discontinuation of randomized treatment occurred in 23% of ETA- vs 26% of TCZ-treated patients. Baseline characteristics (mean age 61 years, 22% male, 29% current smokers, 71% with hypertension, 18% with diabetes, mean CRP 19.3 mg/L) were balanced between treatment groups. A total of 161 MACE qualified for inclusion into the primary analysis. In the intention-to-treat analysis, 83 MACE occurred over 4900 PYs in the TCZ arm vs 78 over 4891 PYs in the ETA arm (HR 1.05; 95% CI 0.77, 1.43). HRs for TCZ vs ETA for other secondary CVD outcomes are summarized in the Table. By week 4, total cholesterol, LDL-C, HDL-C, and triglycerides increased significantly in the TCZ arm compared with the ETA arm, with median LDL-C increasing 12% for TCZ vs 1% for ETA. Thereafter, average levels remained consistent to trial conclusion. The overall rate of adverse events, serious infections, and medically confirmed gastrointestinal perforations was numerically higher for TCZ vs ETA.

Conclusion: This comparative study of TCZ with ETA excluded a >43% relative increase in the hazard of MACE (HR 1.05; 95% CI 0.77, 1.43), with an estimated 5% increase in TCZ compared with ETA among RA patients with severe active disease and elevated baseline CVD risk. Average treatment-associated increases in LDL-C were higher for TCZ vs ETA. The CVD safety of TCZ relative to ETA should be interpreted in the context of its non-CVD safety and clinical efficacy.

Table. Hazard Ratios of Major End Points for Tocilizumab vs Etanercept

	Etanercept N = 1542	**Tocilizumab N = 1538**	**Tocilizumab vs Etanercept**	
	First Events, n	**First Events, n**	**HR[a]**	**95% CI**
MACE-ITT population	**78**	**83**	**1.05**	**0.77, 1.43**
MACE-OT population	52	57	1.11	0.76, 1.62
CVD death	35	36	1.03	0.64, 1.63

Disclosure: J. T. Giles, Genentech and Biogen

CVD death	35	36	1.03	0.64, 1.65
Nonfatal MI	31	28	0.89	0.54, 1.49
Nonfatal stroke	15	24	1.53	0.80, 2.92
All-cause mortality	64	64	0.99	0.70, 1.41
Expanded composite end point[b]	84	84	0.99	0.73, 1.34
Hospitalized for HF	8	12	1.50	0.61, 3.67
MACE + hospitalized for HF	85	90	1.05	0.78, 1.41
Fatal + nonfatal MI	32	29	0.90	0.54, 1.48
Fatal + nonfatal stroke	16	26	1.55	0.83, 2.90

CI, confidence interval; CVD, cardiovascular disease; HF, heart failure; HR, hazard ratio; ITT, intention-to-treat; MACE, major adverse cardiovascular event (ie, any CVD death, nonfatal MI, and nonfatal stroke); MI, myocardial infarction; OT, on-treatment; PY, patient-years. [a]Based on time to first event; Cox regression model stratified by previous exposure to anti−TNF and CV history. [b]Expanded composite end point defined as MACE + nonelective coronary revascularization and hospitalization for unstable angina.

IDEC Inc., 5; **N. Sattar**, Roche, 9; **S. E. Gabriel**, Genentech, 5,Sanofi, 5,UCB, 5; **P. M. Ridker**, Genentech and Biogen IDEC Inc., 5; **S. Gay**, Roche/Genentech, 5,Pfizer, 2,Pfizer, 5,GlaxoSmithKline, 2,Novartis Pharmaceutical Corporation, 5,Tonix, 5,Lilly, 5; **C. Warne**, Roche Products Ltd., 3; **D. Musselman**, Roche/Genentech, 3; **L. Brockwell**, Roche/Genentech, 3; **E. Shittu**, Roche Products Ltd., 3; **M. Klearman**, Roche/Genentech, 1,Roche/Genentech, 3; **T. Fleming**, Roche/Genentech, 5.

Abstract Number: 4L

Efficacy and Safety Results of Guselkumab, an Anti-IL23 Monoclonal Antibody, in Patients with Active Psoriatic Arthritis over 24 Weeks: A Phase 2a, Randomized, Double-Blind, Placebo-Controlled Study

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First publication: October 19, 2016

SESSION INFORMATION

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Session Type: ACR Late-breaking Abstract Session

Session Time: 4:30PM-6:00PM

Background/Purpose: To evaluate the efficacy, safety, and tolerability of guselkumab (GUS), a fully human monoclonal antibody against the p19 subunit of IL-23, in patients (pts) with active psoriatic arthritis (PsA).

Methods: In this double-blind, placebo-controlled, multicenter study, pts with active PsA and ≥3% body surface area (BSA) of plaque psoriasis despite current or previous treatment with standard-of-care therapies, including those previously exposed to anti-TNFα agents, were randomized 2:1 to receive GUS 100 mg subcutaneously (SC) or placebo (PBO) at wks 0, 4, and every 8 wks (q8w) thereafter through wk44. At wk16, pts from either group with <5% improvement from baseline in both swollen and tender joint counts were eligible for early escape to open-label ustekinumab. At wk24, all remaining PBO pts crossed-over to receive GUS 100 mg, and then received GUS at wk28, and q8w thereafter through wk44. The primary endpoint was ACR 20 response at wk24. Major secondary endpoints were PASI 75 and ACR 50 responses, change from baseline in HAQ-DI, and improvement in enthesitis (Leeds enthesitis index) and dactylitis score (by a 0-3 scoring system) at wk24; and ACR 20 response at wk16. Other secondary endpoints included change from baseline in SF-36 and proportion of pts achieving Minimal Disease Activity (MDA). Through wk24, efficacy analyses were performed in a modified Intent-to-Treat (mITT) population. Pts who met treatment failure criteria, early escaped or had missing data at wk24, were considered non-responders for ACR and MDA endpoints at wk24.

Results: 149 pts were randomized to receive study agent (PBO: 49, GUS: 100). Baseline demographics and ACR component measures were generally similar between the two groups. Four [8.2%] pts in PBO and 9 [9.0%] pts in GUS were previously exposed to TNFα agents. The study met its primary and all secondary endpoints. Significantly more GUS pts achieved ACR 20/50/70 responses and PASI 75/90/100 responses at wk24 (Table 1). Significant treatment effect on ACR20 response was observed as early as wk4 (21% vs 0, $p<0.001$), and the effect increased over time reaching the maximum by wk16 (60.0% vs. 16.3%, $p<0.001$) vs. PBO. Results for other secondary efficacy endpoints are summarized in Table 1. Through wk24, proportions of pts with ≥1 AE were comparable between the two groups (PBO: 32.7%; GUS: 36.0%, respectively). Infections were the most common AEs (PBO: 20.4%; GUS: 17.0%, respectively). Two pts had SAEs (knee injury, n=1; myocardial infarction, n=1). There were no serious infections, malignancies, or deaths through wk24.

Conclusion: In pts with active PsA and ≥3% BSA of psoriasis, GUS demonstrated significant improvement on joint symptoms, physical function, psoriasis, enthesitis, dactylitis and quality of life. GUS was well tolerated with no unexpected safety findings in this population.

Table 1 Summary of Efficacy Results at Week 24 in mITT Population			
Efficacy Endpoints	PBO	GUS	p-value
ACR 20	18.4%	58.0%	p<0.001
ACR 50	10.2%	34.0%	P=0.002
ACR 70	2.0%	14.0%	P=0.023 (post hoc)
PASI 75	12.5%	78.6%	p<0.001
PASI 90	6.3%	66.3%	P<0.001
PASI 100	6.3%	39.8%	P<0.001
Mean (SD) change from baseline in HAQ-DI score	-0.06 (0.53)	-0.42 (0.51)	p<0.001
Median percent change from baseline in Leeds Enthesitits Index (LEI)[a]	-33.33%	-100.00%	p=0.009
% of patients with unresolved enthesitis[b]	71.0%	43.4%	P=0.012
Median percent change from baseline in dactylitis[c]	-33.33%	-100.00%	p<0.001
% of patients with unresolved dactylitis[b]	82.6%	44.8%	P=0.001
Mean (SD) change from baseline in SF-36 physical component summary (PCS) score	0.46 (6.51)	6.59 (7.47)	P<0.001
Mean (SD) change from baseline in SF-36 mental component summary (PCS) score	0.42 (6.74)	4.95 (9.06)	p=0.002
% of patients achieving Minimal Disease Activity (MDA)	2.0%	23.0%	p=0.001
Mean (SD) change from baseline in PASDAS	-0.49 (1.33)	-2.50 (1.59)	p<0.001
Mean (SD) change from baseline in GRACE Index	-0.35 (1.39)	-2.73 (1.76)	P<0.001
Mean (SD) change from baseline in mCPDAI	-0.5 (1.76)	-2.3 (1.96)	P<0.001
Mean (SD) change from baseline in DAPSA	-4.97 (20.11)	-23.08 (20.21)	P<0.001
[a]All subjects randomized into the study, received at least 1 administration of study treatment (guselkumab or placebo), and were analyzed according to their assigned treatment group regardless of their actual treatment received. [b]Among the patients with enthesitis at baseline (PBO: N=31; GUS: N=76) [c]Among the patients with dactylitis at baseline (PBO: N=23; GUS: N=58) PASDAS: Psoriatic ArthritiS Disease Activity Score GRACE: GRAppa Composite scorE mCPDAI: modified Composite Psoriatic Disease Activity Index DAPSA: Disease Activity Index for Psoriatic Arthritis			

Disclosure: **A. A. Deodhar**, AbbVie, 2,AbbVie, 9,Amgen, 2,Amgen, 9,Boehringer Ingelheim, 2,Boehringer Ingelheim, 9,Janssen Pharmaceutica Product, L.P., 2,Janssen Pharmaceutica Product, L.P., 9,Novartis Pharmaceutical Corporation, 2,Novartis Pharmaceutical Corporation, 9,Pfizer Inc, 2,Pfizer Inc, 9,UCB, 2,UCB, 9; **A. B. Gottlieb**, Amgen Inc., Astellas, Akros, Centocor (Janssen) Inc. , Celgene Corp., Bristol Myers Squibb Co., Beiersdorf Inc., Abbott Labs. (Abbvie), DUSA, TEVA, Actelion, UCB, Novo Nordisk, Novartis, Dermipsor Ltd., Incyte, Pfizer, Canfite, Lilly, Coronado, Vertex, Ka, 5,Centocor (Janssen) Inc., Amgen, Abbott (Abbvie), Novartis, Celgene, Pfizer, Lilly, Coronado, Levia, Merck, and Xenoport, 2; **W. H. Boehncke**, Janssen Research and Development, LLC, 9,Abbvie, 8,Biogen Idec, 9,Celgene, 9,Novartis Pharmaceutical Corporation, 8,Pfizer Inc, 9,Lilly, 9,Novartis Pharmaceutical Corporation, 9,Abbvie, 9; **B. Dong**, Janssen Research & Development, LLC, 3; **Y. Wang**, Janssen Research and Development, LLC, 3; **W. Barchuk**, Janssen Research and Development, LLC, 3; **X. Xu**, Janssen Research & Development, LLC, 3; **E. C. Hsia**, Janssen Research Development, LLC, 3.

Abstract Number: 5L

Speed of Remission with the Use of Voclosporin, MMF and Low Dose Steroids: Results of a Global Lupus Nephritis Study

Mary Anne Dooley[1], William Pendergraft III[2], Ellen M. Ginzler[3], Nancy J. Olsen[4], James Tumlin[5], Brad H. Rovin[6], Frédéric A. Houssiau[7], David Wofsy[8], David A. Isenberg[9], Neil Solomons[10], Robert Huizinga[11] and AURA Study Group, [1]Dooley Rheumatology, Chapel Hill Doctors, Chapel Hill, NC, [2]Kidney Center, University of North Carolina, Chapel Hill, NC, [3]Rheumatology, SUNY Downstate Medical Center, Brooklyn, NY, [4]Medicine/Rheumatology, Penn State Hershey Medical Center, Hershey, PA, [5]Nephrology, University of Tennessee College of Medicine, Chattanooga, TN, [6]Ohio State University Medical Center, Columbus, OH, [7]Rheumatology, Pôle de Maladies Rhumatismales, Université catholique de Louvain, Brussels, Belgium, [8]Rheumatology, University of California, San Francisco, San Francisco, CA, [9]Centre for Rheumatology Research, University College Hospital London, UK, London, United Kingdom, [10]Aurinia Pharmaceuticals Inc., Victoria, BC, Canada, [11]Clinical Affairs, Aurinia Pharmaceuticals Inc., Victoria, BC, Canada

First publication: October 19, 2016

SESSION INFORMATION

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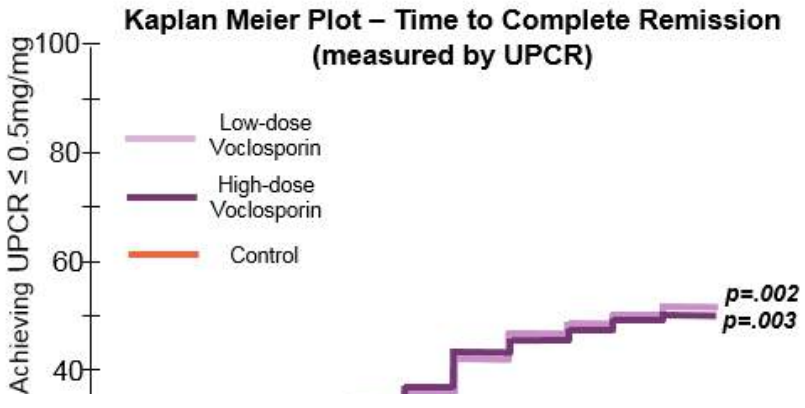
Session Type: ACR Late-breaking Abstract Session

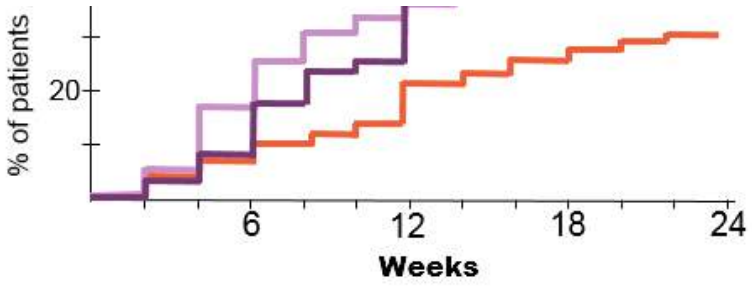
Session Time: 4:30PM-6:00PM

Background/Purpose: Voclosporin (VCS) is a novel CNI intended for use in the treatment of autoimmune diseases such as lupus nephritis. VCS's unique structure allows for less pharmacokinetic–pharmacodynamic variability and a potentially improved safety profile compared with other CNIs. The AURA study enrolled 265 subjects in over 20 countries using low (23.7 mg BID) or high dose VCS (39.5 mg BID) in addition to MMF 2g/day and steroids in active lupus nephritis (LN).

Methods: Entry criteria: renal biopsy within 6 months (Class III/V LN, ISN/RPS); UPCR≥1.5 (III/IV) or ≥2.0 mg/mg (V); serologic evidence of active LN; and eGFR >45ml/min. The steroid protocol was 20-25 mg (Day 1) with taper to 5 mg (Week 8), and 2.5 mg (Week 16-24). 24 week objectives included: Complete Remission (CR) defined as a urine protein/creatinine



ratio (UPCR) of ≤0.5 mg/mg using first morning void with an eGFR ≥ 60 mL/min without a decrease of ≥20%; time to CR, Partial Remission (PR: 50% reduction in proteinuria) and time to PR.



Results: The groups were generally well-balanced for age, gender and race, with a trend to higher proteinuria and lower eGFR data in the low dose VCS arm. The trial met its primary endpoint with superior CR rates in the low dose arm (OR: 2.03, p=0.045). There was a statistically significant improvement in time to CR and time to PR in both treatment arms (P<.01). A mean reduction in serum creatinine was seen in both arms (0.2 mg/dL low, 0.1 high; p<.001). BP did not vary by group. Over 90% of subjects experienced at least one adverse event; the most common being infectious (56.2% low, 63.6% high and 50.0% control), GI disorders (41.6% low, 52.3% high and 36.4% control). More serious adverse events occurred in the voclosporin groups (25.8% low, 25.0% high, 15.8% control), and were consistent with those observed in LN patients. Most deaths occurred in the first 2 months and were: low dose (infection-3, ARDS-2, thrombotic-3, cardiac tamponade, pulmonary hemorrhage), high dose (infection, PE) and control (CVA). All were considered unrelated to drug exposure by the investigators.

Study Demographics

		Control	Voclosporin 23.7 mg BID	Voclosporin 39.5 mg BID
n		88	89	88
Age (yrs)		33 ± 10	31 ± 12	31 ± 10
Race	White	42 (47.7)	30 (33.7)	36 (40.9)
	Black	5 (5.7)	3 (3.4)	6 (6.8)
	Asian	36 (40.9)	52 (58.4)	44 (50.0)
	Other	5 (5.7)	4 (4.5)	2 (2.3)
Biopsy Class (III/IV)		59 (67.0)	56 (62.9)	63 (71.6)
Baseline eGFR		100 ± 27	95 ± 28	105 ± 28)
Baseline UPCR		4.4 ± 3.6	5.2 ± 4.2	4.5 ± 3.0
Death:	Infection	0	3	1
	Thromboembolic	1	3	1
	Other	0	4	0

Conclusion: The AURA study is the first global LN study to meet its primary end point, Response rate was rapid; increasing CR in the VCS arms was seen by week 6. This study demonstrated the positive additive effects of VCS, despite the rigorous steroid taper (mean steroid dose 4 mg at Week 16). Adverse events were higher in the VCS treatment arms, consistent with increased immunosuppression. The overall mortality rate was similar to other recent LN trials (ALMS 3.8%, ALLURE 4.7%, BELONG 3.7%), with a higher mortality rate in the lowdose group. These promising data will be used to plan subsequent studies of voclosporin in LN.

Disclosure: **M. A. Dooley**, Aurinia Pharmaceuticals, 9; **W. Pendergraft III**, Aurinia Pharmaceuticals, 9; **E. M. Ginzler**, Aurinia Pharmaceuticals, 2; **N. J. Olsen**, Aurinia Pharmaceuticals, 9; **J. Tumlin**, Aurinia Pharmaceuticals, 9; **B. H. Rovin**, Chemocentryx, 9,Aurinia Pharmaceuticals, 9; **F. A. Houssiau**, None; **D. Wofsy**, None; **D. A. Isenberg**, None; **N. Solomons**, Aurinia Pharmaceuticals, 3; **R. Huizinga**, Aurinia Pharmaceuticals, 3.

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Abstract Number: 6L

Myeloablative Autologous Transplantation of CD34+ -Selected

Hematopoietic Stem Cells (HSCT) Vs Monthly Intravenous Cyclophosphamide (CYC) for Severe Scleroderma with Internal Organ Involvement: Outcomes of a Randomized North American Clinical Trial

Keith Sullivan[1], Lynette Keyes-Elstein[2], Peter McSweeney[3], Ashley Pinckney[2], Beverly Welch[4], Maureen D Mayes[5], Richard Nash[3], Leslie J. Crofford[6], Sharon Castina[2], Linda Griffith[7], Ellen Goldmuntz[8] and Daniel E. Furst[9], [1]Duke University, Durham, NC, [2]Rho, Inc, Chapel Hill, NC, [3]Colorado Blood Cancer Institute, Denver, CO, [4]6610 Rockledge Dr., NIAID/NIH, Bethesda, MD, [5]Department of Internal Medicine - Rheumatology, University of Texas-McGovern Medical School, Houston, TX, [6]Medicine, Vanderbilt University Medical Center, Nasville, TN, [7]NIAID, NIH, Bethesda, MD, [8]NIAID, National Institutes of Health, Bethesda, MD, [9]David Geffen School of Medicine at UCLA, Los Angeles, CA

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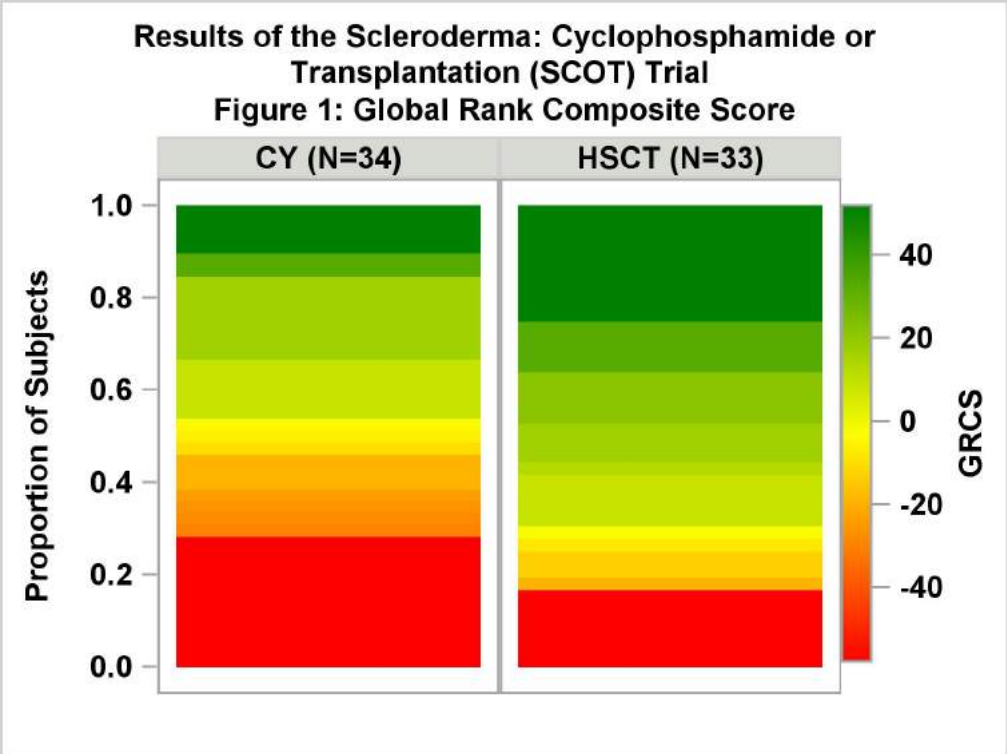
Background/Purpose: Therapeutic options for diffuse cutaneous systemic sclerosis (dcSSc) are limited. The Scleroderma: Cyclophosphamide or Transplantation (SCOT) trial was a multicenter study designed to evaluate the long-term benefit of myeloablative autologous HSCT compared to 12 monthly pulses of CYC.

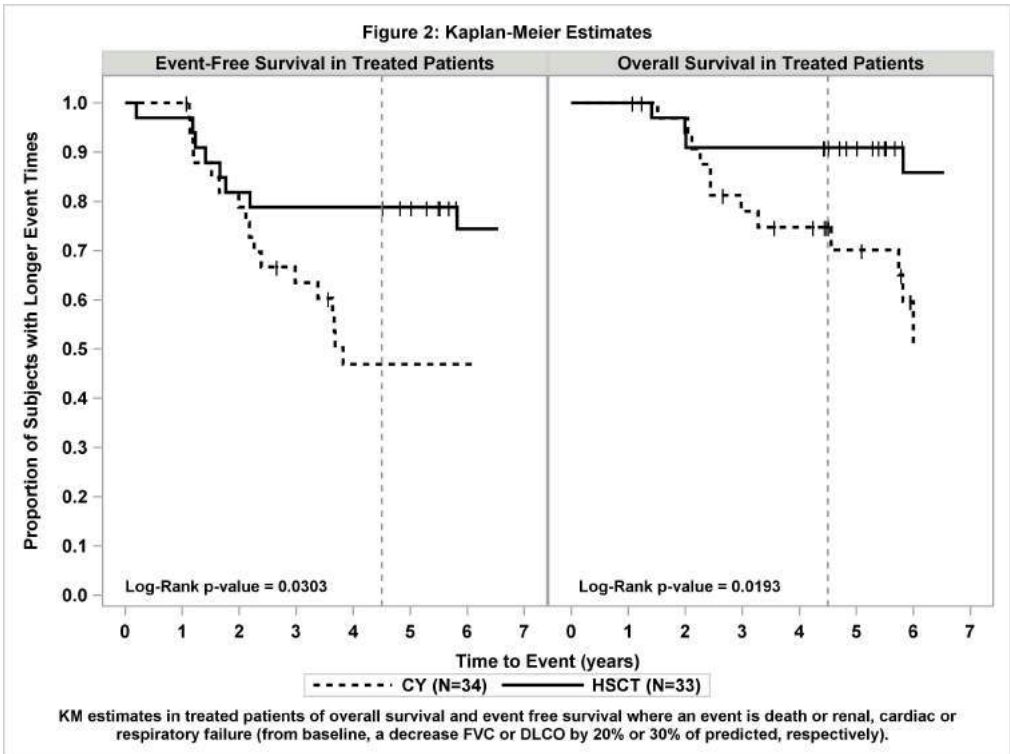
Methods: Adults (18-69 years) with dcSSc (ACR criteria) and high-risk lung and/or renal involvement were randomized to CYC (750 mg/m^2/mo.) or myeloablation (800 cGy total body irradiation with lung and kidney shielding, 120 mg/kg CYC and 90 mg/kg antithymocyte globulin) followed by CD34+selected autologous HSCT. The primary endpoint was a global rank composite score (GRCS) at 54 months that ordered subjects based on a hierarchy of outcomes: death, event-free survival (EFS), forced vital capacity (FVC), scleroderma health assessment questionnaire, and modified Rodnan skin score (mRSS).

Results: Seventy-five subjects were randomized (39 CYC, 36 HSCT) with mean baseline mRSS=30, mean FVC=74% and mean DLC0=53% of predicted. All but two had lung involvement. In the ITT (randomized) sample, GRCS comparisons favored HSCT and met the predefined primary endpoint at 54 months (p=0.013) and 48 months (p=0.008). In those who were transplanted or received ≥ 9 CYC doses (34 CYC, 33 HSCT), GRCS results (figure 1) were even stronger (p=0.004 and 0.003, respectively). Secondary analyses in treated subjects supported the primary results: at 54 months, EFS was 50% in CYC and 79% in HSCT (p=0.021) and overall survival (OS) was 77% and 91% (p=0.19), respectively. Treatment related mortality at 54 months was 0% CYC and 3% HSCT. Among HSCT recipients, 9% had initiated DMARDs by 54 months compared to 44% of CYC (p=0.001). As shown in figure 2, Kaplan-Meier estimates for EFS and OS differed significantly between groups (p=0.030, 0.019, respectively). The

rate of SAEs was similar in both arms. Grade 3 and above AEs including regimen-related cytopenias were more common in the HSCT arm. Herpes zoster was more frequent in the HSCT arm.

Conclusion: This study demonstrates long-term superiority of myeloablative autologous HSCT over CYC on efficacy endpoints, and shows a significant reduction in use of DMARDS among HSCT recipients. Transplant-related mortality was lower and overall survival was better than projected both during the peri-transplant period and long term. The SCOT trial supports myeloablative HSCT as a significant advance in the care of dcSSc. Funded by NIAID; ClinicalTrials.gov NCT00114530 _ _ _





Disclosure: K. Sullivan, None; **L. Keyes-Elstein**, None; **P. McSweeney**, None; **A. Pinckney**, None; **B. Welch**, None; **M. D. Mayes**, None; **R. Nash**, None; **L. J. Crofford**, None; **S. Castina**, None; **L. Griffith**, None; **E. Goldmuntz**, None; **D. E. Furst**, None.

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Abstract Number: 7L

Overall Reduction in Acute Flares during Treatment with Febuxostat Compared with Placebo over 2 Years in Patients with Early Gout

Nicola Dalbeth[1], Kenneth G. Saag[2], William Palmer[3], Hyon K. Choi[3], Barbara Hunt[4], Patricia MacDonald[4], Ulrich Thienel[5] and Lhanoo Gunawardhana[4], [1]University of Auckland, Auckland, New Zealand, [2]University of Alabama at Birmingham, Birmingham, AL, [3]Massachusetts General Hospital/Harvard Medical School, Boston, MA, [4]Takeda Pharmaceuticals International, Deerfield, IL, [5]RRD International, Rockville, MD

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SESSION INFORMATION

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Session Type: ACR Late-breaking Abstract Session

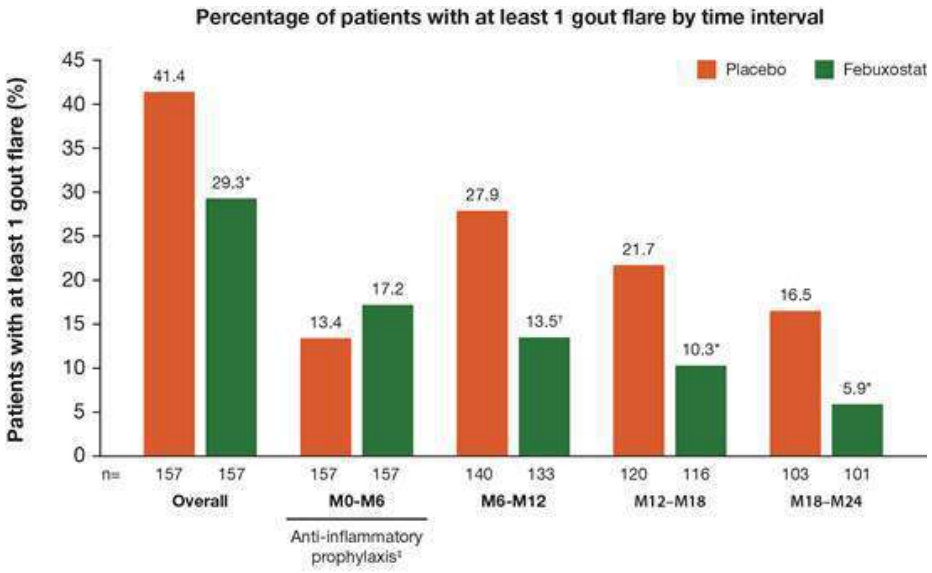
Session Time: 9:00AM-11:00AM

Background/Purpose: No clinical trials have previously investigated the frequency of acute flares in early gout or the benefit of instituting urate-lowering therapy (ULT) earlier in the course of the disease. Currently, the standard of care for a vast majority of patients with early gout who have experienced only a single gout attack is limited to acute flare treatment with no ULT. In this analysis of data from a Phase 2 study, we have evaluated the frequency of acute flares in patients with early gout treated with febuxostat versus placebo during a 2-year period.

Methods: In this randomized, double-blind, placebo-controlled trial, patients with serum urate (sUA) ≥7.0 mg/dL and estimated glomerular filtration rate ≥60 mL/min were randomized to either febuxostat 40/80 mg or placebo for up to 2 years. Febuxostat was titrated from 40 to 80 mg at the Month 1 visit if sUA was ≥6.0 mg/dL at the Day 14 visit. All patients had early gout, defined as having experienced 2 or fewer gout flares in total and only 1 flare during the previous 12 months. Patients in both treatment groups received standard of care for acute gout flares throughout the study at the discretion of the investigator. All patients also received gout flare prophylaxis for the first 6 months of the study; patients who were either nonresponsive or intolerant to prophylaxis could be managed at the discretion of the investigator. The percentage of patients with at least 1 gout flare was summarized by time interval (Months 0–6, 6–12, 12–18, and 18–24) as well as for the overall study. Each percentage was calculated based on the number of

patients who had at least 1 day of drug exposure in the corresponding time interval. Differences between treatment groups were assessed using Fisher's exact test.

Results: A total of 314 patients received treatment with placebo (n=157) or febuxostat (n=157). During the first 6 months, the febuxostat group showed a slightly higher percentage of patients with at least 1 flare, which was not statistically significant (Figure). During the subsequent time intervals (Months 6–12, 12–18, and 18–24), the percentage of patients with at least 1 flare was consistently and significantly lower in the febuxostat group than the placebo group (Figure). Over the entire study duration, the percentage of patients with at least 1 flare was significantly lower in the febuxostat group than the placebo group (29.3% vs 41.4%, p<0.05).



*p<0.05 and †p<0.01 for febuxostat 40/80 mg QD versus placebo;
‡Anti-inflammatory prophylaxis was given during the first 6 months of the study.
M=month; QD=once daily.

Conclusion: Recurrent flares commonly occur in early gout, affecting >40% of patients over a 2-year period. This first clinical trial in patients with early gout demonstrates that treatment with febuxostat, to a target sUA of <6.0 mg/dL, can achieve a significant reduction in gout flares compared with placebo over a 2-year period, with significantly fewer gout flares during Months 6–12, 12–18, and 18–24.

Disclosure: **N. Dalbeth**, Ardea/AstraZeneca, 2,Ardea/AstraZeneca, Crealta, Cymabay, Takeda, 5; **K. G. Saag**, Ardea/AstraZeneca, Horizon, Takeda, 5,Ardea/AstraZeneca, Horizon, Takeda, 2; **W. Palmer**, None; **H. K. Choi**, AstraZeneca, 2,Takeda, 5; **B. Hunt**, Takeda, 3; **P. MacDonald**, Takeda, 3; **U. Thienel**, Takeda, 3; **L. Gunawardhana**, Takeda Pharmaceuticals, 3,Takeda Pharmaceuticals, 1.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/overall-reduction-in-acute-flares-during-treatment-with-febuxostat-compared-with-placebo-over-2-years-in-patients-with-early-gout

Abstract Number: 8L

A Randomized, Double-Blind, Placebo-Controlled Study of Bimagrumab in Patients with Sporadic Inclusion Body Myositis

Anthony A. Amato[1], Umesh Badrising[2], Olivier Benveniste[3], Merrilee Needham[4], **Hector Chinoy**[5], Min Wu[6], Barbara Koumaras[6], Ana de Vera[7], Dimitris A. Papanicolaou[6] and Michael G. Hanna[8], [1]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, [2]Department of Neurology, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Internal Medicine, Pitié-Salpêtrière Hospital, Pierre et Marie-Curie University, Paris, France, [4]Fiona Stanley Hospital, IIID Murdoch University and Notre Dame University, Perth, Australia, [5]Centre for Musculoskeletal Research, NIHR Manchester Musculoskeletal Biomedical Research Unit, The University of Manchester, Manchester, United Kingdom, [6]Novartis Pharmaceuticals Corporation, East Hanover, NJ, [7]Novartis Pharma AG, Basel, Switzerland, [8]MRC Centre for Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom
First publication: October 19, 2016

SESSION INFORMATION

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Session Time: 9:00AM-11:00AM

Background/Purpose: Bimagrumab (BYM338) is a novel fully human monoclonal antibody that binds competitively to activin type II receptors with greater affinity than natural inhibitory ligands such as activin and myostatin, thereby inducing skeletal muscle hypertrophy. This study examined efficacy and safety of bimagrumab on physical function, muscle strength and muscle mass in patients with sporadic inclusion body myositis (sIBM).

Methods: RESILIENT was a multicenter, randomized, double-blind, placebo-controlled, dose-finding study (clinicaltrials.gov NCT01925209). Eligible participants were randomized (1:1:1:1) to receive i.v. infusions of bimagrumab 10, 3, 1 mg/kg or placebo every 4 weeks for at least 48 weeks. Change from baseline to Week 52 in 6-minute walk distance test (6MWD; primary outcome), quadriceps quantitative muscle testing (QMT), sIBM physical functioning assessment (sIFA) and lean body mass (LBM) were assessed. Safety assessments included recording of adverse events (AEs) and serious AEs.

Results: 251 patients (mean[SD] age: 68.1[8.2] years; 162[64.5%] men; mean time since sIBM diagnosis: 4.6[3.53] years) were randomized and treated. Participants on placebo and 1 mg/kg bimagrumab had a mean 6MWD decrease from baseline to Week 52 of 8.96 and 10.27 m, respectively, vs. an increase of 9.63 m for 3 mg/kg and 8.63 m for 10 mg/kg bimagrumab. Differences between treatment vs. placebo did not reach statistical significance ($p>0.1$). No consistent differences in quadriceps QMT were observed vs. placebo. However, at Week 52, there was less deterioration (mean treatment difference: 5.10; 0-100 scale) in the patient-reported outcome (PRO) instrument, sIFA, in 10 mg/kg bimagrumab vs. placebo ($p=0.03$), resulting in a clinically relevant and statistically significant increase in responders in this group (55% vs. 30%; $p=0.0115$). Bimagrumab showed a dose-dependent increase in LBM vs. placebo (mean treatment ratios: 3 and 10 mg/kg vs. placebo: 1.033 and 1.058, respectively). At Week 52, the difference was statistically significant for the 3 and 10 mg/kg doses ($p\leq0.0001$). The most frequently reported AEs in the bimagrumab groups were diarrhea and muscle spasm. About one-third patients in all groups reported serious AEs, except for bimagrumab 3 mg/kg (17.5%).

Conclusion: Bimagrumab was well-tolerated, increased LBM and showed a potential benefit in PRO, but did not reach the primary endpoint of improving 6MWD or showed an improvement in muscle strength.

Disclosure: **A. A. Amato**, Novartis, Acceleron, Biogen, Idera, Akashi, 5; **U. Badrising**, Novartis, 5; **O. Benveniste**, Shine, LFB, Novartis, CSL Behring, 2,Novartis, Neovacs, 5; **M. Needham**, Biogen, Bayer, Novartis, 5; **H. Chinoy**, MedImmune, Abbvie, Novartis, 2,Abbvie, Celgene, Johnson & Johnson, Pfizer, Roche, UCB, 5; **M. Wu**, Novartis Pharmaceuticals Corporation, 3; **B. Koumaras**, Novartis Pharmaceuticals Corporation, 3; **A. de Vera**, Novartis Pharma AG, 3; **D. A. Papanicolaou**, Novartis Pharmaceuticals Corporation, 3; **M. G. Hanna**, Novartis, 5.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/a-randomized-double-blind-placebo-controlled-study-of-bimagrumab-in-patients-with-sporadic-inclusion-body-myositis

Abstract Number: 9L

Efficacy and Safety of Canakinumab in Patients with Colchicine-Resistant Familial Mediterranean Fever, Hyper-Immunoglobulin D Syndrome/Mevalonate Kinase Deficiency and TNF Receptor-Associated Periodic Syndrome: 40 Week Results from the Pivotal Phase 3 Umbrella Cluster Trial

Fabrizio De Benedetti[1], Joost Frenkel[2], Inmaculada Calvo[3], Marco Gattorno[4], Michel Moutschen[5], Pierre Quartier[6], Ozgur Kasapcopur[7], Seza Ozen[8], Jordi Anton[9], Isabelle Koné-Paut[10], Helen Lachmann[11], Hal M. Hoffman[12], Eldad Ben-Chetrit[13], Anna Shcherbina[14], Michaël Hofer[15], Philip J Hashkes[16], Andrew Zeft[17], Karine Lheritier[18], Yankun Gong[19], Antonio Speziale[18] and Guido Junge[18], [1]Division of Rheumatology, Ospedale Pediatrico Bambino Gesù IRCCS, Rome, Italy, [2]University Medical Center Utrecht, Utrecht, Netherlands, [3]Pediatric Rheumatology, Hospital Universitario i Politecnic La Fe, Valencia, Spain, [4]Pediatric Rheumatology, G. Gaslini Institute, Genoa, Italy, [5]C.H.U. Sart-Tilman, Liege, Belgium, [6]Necker-Enfants Malades Hospital, Paris, France, [7]Department of Pediatric Rheumatology, Cerrahpasa Medical School, Istanbul University, Istanbul, Turkey, [8]Department of Pediatrics, Division of Rheumatology, Hacettepe University Children's Hospital, Ankara, Turkey, [9]Hospital Sant Joan de Déu, Barcelona, Spain, [10]Department of Paediatric Rheumatology, Hôpital Kremlin Bicetre, University of Paris SUD, Paris, France, [11]UK National Amyloidosis Centre, University College London Medical School, London, United Kingdom, [12]University of California, San Diego, La Jolla, CA, [13]Rheumatology Unit, Hadassah—Hebrew University Medical Center, Jerusalem, Israel, [14]Immunology, Federal Research and Clinical Center of Pediatric Hematology, Oncology and Immunology, Moscow, Russian Federation, [15]Unité romande d'immuno-rhumatologie pédiatrique, CHUV, University of Lausanne, Lausanne, Switzerland, [16]Pediatrics Rheumatology; Shaare-Zedek Medical Center, Jerusalem, Israel, [17]Pediatrics Rheumatology, Cleveland Clinic, Cleveland, OH, [18]Novartis Pharma AG, Basel, Switzerland, [19]Beijing Novartis Pharma Co. Ltd., Beijing, China

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Session Time: 9:00AM-11:00AM

Background/Purpose: Evidence points to the role of abnormal IL-1β production in familial Mediterranean fever (FMF), hyper-immunoglobulin D syndrome/mevalonate kinase deficiency (HIDS/MKD) and TNF receptor-associated periodic syndrome (TRAPS). Analysis of the efficacy of canakinumab (CAN), a fully human anti-IL-1β monoclonal antibody, in the double blind randomized epoch 2 of the phase 3 CLUSTER trial in patients (pts) with colchicine-resistant FMF (crFMF), HIDS/MKD or TRAPS has demonstrated highly significant differences vs placebo (PBO) in the primary outcome (resolution of the index flare by Day 15 and no subsequent flares up to week [wk] 16) in the 3 diseases[1]. Here we report the results from the subsequent epoch 3 (up to wk 40) that included a randomized withdrawal phase to evaluate CAN at a prolonged dosing interval (8 wks [q8w]) or complete discontinuation.

Methods: The study comprises 3 disease cohorts (crFMF, HIDS/MKD and TRAPS) and 4 epochs: a 12-wk screening epoch (E1), a 16-wk randomized treatment epoch (E2), a 24-wk randomized withdrawal epoch (E3) and a 72-wk open-label treatment epoch (E4). Pts who were initially randomized to CAN 150 mg every 4 wks (q4w) and did not flare in E2 were re-randomized 1:1 to CAN 150 mg q8w or PBO in E3. The endpoint of E3 was the proportion of pts who maintained control of disease (no flares: PGA ≤2 and CRP ≤30 mg/L) between Wk 16 and Wk 40 after re-randomization to CAN 150 mg q8w vs PBO. Moreover, in order to gain additional information on the maintenance dose in the long-term, pts who escaped to open-label CAN during E2, were dosed to open-label CAN 150mg q8w during E3. Pts with a flare could be escalated up to 300 mg q4w.

Results: 42 pts who were CAN (150 mg q4w) responders in E2 were re-randomized to CAN 150 mg q8w or PBO in E3. At Wk 40, the proportion of responders was numerically higher in the CAN vs PBO group in all 3 disease cohorts (Table). Overall in E3, including pts treated in open-label, 49% of the crFMF pts, 53% of the TRAPS pts and 23% of the HIDS/MKD pts maintained disease control with a prolonged dosing interval (150 mg q8w). Up-titration to 300 mg q4w was needed in few pts with crFMF (10%) or TRAPS (8%) and in 29% of those with HIDS/MKD. No new safety findings were reported in CAN-treated pts through E3, with no toxicity accumulation (Table). No deaths were reported in the 3 disease cohorts.

Conclusion: The results of E3 in this pivotal trial confirm long-term efficacy of CAN in crFMF, HIDS/MKD and TRAPS, and yield information on the long-term dose needed to control disease, with approximately half of the pts with crFMF or TRAPS and approximately 1/3 of the pts with HIDS/MKD showing no flare at a prolonged dose interval administration of 150 mg q8w. The higher dose of 300 mg q4w was needed in few pts with crFMF or TRAPS and in 1/3 of the pts with HIDS/MKD. No new safety issues were reported over 40 wks of CAN treatment; the safety profile was not distinct from previous controlled studies.

Table. Efficacy results up to 40 weeks and summary of safety							
Efficacy							
	Cohort	Re-randomized					
		CAN (150 mg q8w)		Placebo		p value (one-sided)	
Proportion of responders, n/M (%)	crFMF	7/9 (77.8)		3/10 (30.0)		0.0513	
	HIDS/MKD	3/6 (50.0)		1/7 (14.3)		0.2168	
	TRAPS	3/4 (75.0)		2/5 (40.0)		0.3571	
Safety							
	ALL	crFMF		HIDS/MKD		TRAPS	
	Placebo E2+E3	Any CAN# E2	Any CAN# E2+E3	Any CAN# E2	Any CAN# E2+E3	Any CAN# E2	Any CAN# E2+E3
Exposure to canakinumab (PY)	9.4	16.4	47.0	19.1	41.5	12.1	26.4
Number of AEs	139	134	300	251	465	112	197
Event rate/100 PY	1480	816.7	638.3	1313.6	1121	925.7	747.1
Number of SAEs	8	7	16	11	14	3	5
SAE rate/100 PY	85	42.7	34.0	57.6	34.0	24.8	19.0

#Any patient who received a dose of CAN during epoch 2 or 3.
M=number of evaluated for response in that cohort; n=number of patients who responded
AEs, adverse event; CAN, canakinumab; E, epoch; PY, patient-years; SAE, serious adverse event							

1. De Benedetti F, et al. *Ann Rheum Dis* 2016;75(Suppl2):615.

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Abstract Number: 10L

Efficacy and Safety of Tofacitinib, an Oral Janus Kinase Inhibitor, in Patients with Active Psoriatic Arthritis and an Inadequate Response to Tumor Necrosis Factor Inhibitors: OPAL Beyond, a

Randomized, Double Blind, Placebo-Controlled, Phase 3 Trial

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SESSION INFORMATION
Session Date: Sunday, November 13, 2016
Session Title: ACR Late-Breaking Poster Session
Session Type: ACR Late-breaking Abstract Session
Session Time: 9:00AM-11:00AM

Background/Purpose: Tofacitinib is an oral Janus kinase inhibitor under investigation for treatment of PsA. In this first study of tofacitinib in patients (pts) with active PsA and an inadequate response (IR) to TNF inhibitors (TNFi), efficacy and safety vs placebo (PBO) were evaluated.

Methods: Eligible pts in this 6-month, randomized, PBO-controlled, double-blind, multicenter, Phase 3 study had ≥6 months' PsA diagnosis, fulfilled ClASsification criteria for Psoriatic ARthritis, had active arthritis (≥3 tender/painful and ≥3 swollen joints) at screening and baseline, active plaque psoriasis at screening, and IR to ≥1 TNFi (discontinuation for inadequate efficacy or an adverse event [AE]). Pts were randomized 2:2:1:1 to tofacitinib 5 mg twice daily (BID; n=132), tofacitinib 10 mg BID (n=132), PBO→tofacitinib 5 mg BID (n=66), or PBO→tofacitinib 10 mg BID (n=65). Pts randomized to PBO advanced (blinded) to tofacitinib 5 or 10 mg BID at Month (M) 3. Ongoing treatment with 1 conventional synthetic DMARD was required. The primary endpoints were ACR20 response rate and change from baseline in Health Assessment Questionnaire Disability Index (ΔHAQ-DI) at M3.

Results: Pt demographics and baseline disease characteristics were broadly similar across groups (Table 1). Of the 395 randomized pts, 394 were treated, 361 (91.6%) completed M3, and 345 (87.6%) completed M6. There were significantly greater improvements in ACR20 response and HAQ-DI for both tofacitinib doses vs PBO at M3; improvements persisted to M6 (Table 2). Tofacitinib 5 and 10 mg BID demonstrated superior ACR20 response vs PBO as early as Week 2 (26.7% and 28.8% vs 13.0%; $p \leq 0.05$). Effects on secondary efficacy endpoints were generally consistent with the primary findings (Table 2). Serious AEs and discontinuations due to AEs were low in frequency (Table 3). The most common AEs were upper respiratory tract infection (5.3–10.8% of pts across groups), nasopharyngitis (1.5–10.7%), and headache (4.5–9.1%).

Conclusion: In this first study comprising only TNFi-IR pts with PsA, tofacitinib was superior to PBO in ACR20 response and ΔHAQ-DI at M3, with ACR20 superiority vs PBO as early as Week 2 (first assessment). Secondary endpoints were consistent with the primary analyses. No new safety risks were identified vs previous tofacitinib studies in RA and psoriasis.

Table 1. Patient demographics and baseline disease characteristics (safety analysis set[a])

	Placebo (N=131)	Tofacitinib 5 mg BID (N=131)	Tofacitinib 10 mg BID (N=132)
Patient demographics			
Age, years, mean (SD)	49.0 (12.6)	49.5 (12.3)	51.3 (10.9)
Female, n (%)	80 (61.1)	64 (48.9)	74 (56.1)
White, n (%)	118 (90.1)	121 (92.4)	124 (93.9)
BMI, kg/m^2, mean (SD)	29.5 (5.5)	30.5 (7.1)	31.0 (6.7)
Baseline disease characteristics			
Duration of PsA, years, mean (SD)	9.4 (8.1)	9.6 (7.6)	9.1 (6.8)
HAQ-DI score, mean (SD)	1.3 (0.8)	1.3 (0.7)	1.4 (0.6)
Presence of enthesitis, LEI >0, n (%)	93 (71.0)	83 (63.4)	99 (75.0)
LEI score,[b] mean (SD)	2.8 (1.6)	3.0 (1.6)	3.4 (1.8)
Presence of dactylitis, DSS >0, n (%)	63 (48.1)	66 (50.4)	65 (49.2)
DSS,[b] mean (SD)	6.8 (5.7)	7.8 (9.9)	9.5 (8.2)
PGA of arthritis, VAS (mm), mean (SD)	53.7 (21.2)	53.5 (20.9)	55.8 (20.8)
PtGA of arthritis, VAS (mm), mean (SD)	55.8 (23.7)	57.4 (22.9)	58.5 (22.3)
Patient assessment of arthritis pain, VAS (mm), mean (SD)	54.9 (25.3)	56.4 (24.1)	59.5 (22.3)
Swollen joint count (66), mean (SD)	10.5 (9.0)	12.1 (10.6)	12.8 (11.2)
Tender/painful joint count (68), mean (SD)	19.8 (14.9)	20.5 (13.0)	25.5 (17.5)
CRP, mg/L, median (range)	4.4 (0.2–164.0)	5.7 (0.2–126.0)	4.9 (0.2–163.0)
≥3% BSA affected by psoriasis, n (%)	86 (65.6)	80 (61.1)	81 (61.4)
PASI score,[c] median (range)	7.1 (1.6–66.0)	7.6 (0.6–32.2)	8.8 (0.8–41.6)
Day 1 oral corticosteroid use, n (%)	31 (23.7)	37 (28.2)	25 (18.9)
Concomitant csDMARD use up to Month 3, n (%) MTX	98 (74.8)	95 (72.5)	89 (67.4)
Other[d]	33 (25.2)	36 (27.5)	41 (31.1)

[a]All patients who received ≥1 dose of study medication; [b]Among patients with baseline score >0; [c]Among patients with baseline BSA ≥3% and PASI >0; [d]Includes hydroxychloroquine, chloroquine, leflunomide, and sulfasalazine BID, twice daily; BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment; PsA, psoriatic arthritis; PtGA, Patient's Global Assessment; SD, standard deviation; VAS, visual analog scale

Table 2. Efficacy endpoints at Month 3 and Month 6 (full analysis set[a])

	Month 3 (active treatment vs placebo)			Month 6			
	Placebo (N=131)	**Tofacitinib 5 mg BID (N=131)**	**Tofacitinib 10 mg BID (N=132)**	**Placebo→ tofacitinib 5 mg BID (N=66)**	**Placebo→ tofacitinib 10 mg BID (N=65)**	**Tofacitinib 5 mg BID (N=131)**	**Tofacitinib 10 mg BID (N=132)**
ACR20,[b] n (%)	31 (23.7)	65 (49.6)***	62 (47.0)***	33 (50.0)	35 (53.9)	78 (59.5)	65 (49.2)
ACR50, n (%)	19 (14.5)	39 (29.8)*	37 (28.0)*	21 (31.8)	23 (35.4)	50 (38.2)	39 (29.6)
ACR70, n (%)	13 (9.9)	22 (16.8)	19 (14.4)	10 (15.2)	12 (18.5)	28 (21.4)	19 (14.4)
DHAQ-DI,[b] LS mean (SE) [N1]	-0.14 (0.05) [117]	-0.39 (0.05)*** [124]	-0.35 (0.05)** [120]	-0.48 (0.07) [56]	-0.42 (0.07) [56]	-0.44 (0.05) [122]	-0.34 (0.05) [112]
PASI75,[c] n/N (%)	12/86 (14.0)	17/80 (21.3)	35/81 (43.2) ***	11/42 (26.2)	14/44 (31.8)	27/80 (33.8)	37/81 (45.7)
DLEI,[d] LS mean (SE) [N1]	-0.5 (0.2) [82]	-1.3 (0.2)* [79]	-1.3 (0.2)* [86]	-1.4 (0.3) [38]	-1.3 (0.3) [41]	-1.5 (0.2) [77]	-1.6 (0.2) [84]
DDSS,[d] LS mean (SE) [N1]	-1.9 (0.8) [55]	-5.2 (0.7)* [64]	-5.4 (0.8)* [58]	-5.4 (1.3) [25]	-5.2 (1.3) [26]	-6.0 (0.8) [61]	-6.0 (0.9) [55]

Nominal *p≤0.05; **p<0.001; ***p<0.0001 vs placebo at Month 3 [a]All randomized patients who received ≥1 dose of study medication (N=394); [b]Primary study endpoint at Month 3; [c]In patients with baseline BSA ≥3% and baseline PASI >0; [d]In patients with baseline score >0 Continuous endpoints were analyzed with a mixed model for repeated measures; P values for binary endpoints were based on the normal approximation for the difference in binomial proportions Missing values for ACR20, ACR50, ACR70, and PASI75 were considered as non-response. Missing values for continuous endpoints were not imputed D, change from baseline; ACR, American College of Rheumatology; ACR20/50/70, ACR20%/50%/70% response rate; BID twice daily; BSA, body surface area; DSS, Dactylitis Severity Score; HAQ-DI, Health Assessment Questionnaire Disability Index; LEI, Leeds Enthesitis Index; LS, least squares; N1, number of patients evaluable at a visit of interest; PASI, Psoriasis Area and Severity Index; PASI75, ≥75% improvement from baseline PASI; SE, standard error

Table 3. Safety summary to Month 6 (safety analysis set[a]; all causality)

	Placebo→ tofacitinib 5 mg BID (N=66)	Placebo→ tofacitinib 10 mg BID (N=65)	Tofacitinib 5 mg BID (N=131)	Tofacitinib 10 mg BID (N=132)
AEs, n (%)	40 (60.6)	38 (58.5)	93 (71.0)	96 (72.7)
SAEs, n (%)	2 (3.0)	1 (1.5)	5 (3.8)	8 (6.1)
Discontinuation due to AEs, n (%)	2 (3.0)	3 (4.6)	5 (3.8)	11 (8.3)
Deaths, n (%)	0	0	0	0
AEs of special interest, n (%)				
Serious infection	0	0	2 (1.5)	2 (1.5)
Herpes zoster (all non serious)	0	0	1 (0.8)	2 (1.5)
Opportunistic infection[b]	0	0	1 (0.8)	0
Malignancy[c]	0	0	0	0
MACE[d]	0	0	1 (0.8)	1 (0.8)
GI perforation	0	0	0	0

[a]All patients who received ≥1 dose of study medication; [b]herpes zoster; [c]including non-melanoma skin cancer; [d]for this trial, MACE includes any myocardial infarction, cerebrovascular event (stroke or transient ischemic attack), or cardiovascular death AE, adverse event; BID, twice daily; GI, gastrointestinal; MACE, major adverse cardiovascular event; n, number of patients with event; SAE, serious adverse event

---

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Abstract Number: 11L

BMS-986165 Is a Highly Potent and Selective Allosteric Inhibitor of Tyk2, Blocks IL-12, IL-23 and Type I Interferon Signaling and Provides for Robust Efficacy in Preclinical Models of Systemic Lupus Erythematosus and Inflammatory Bowel Disease

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SESSION INFORMATION

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Background/Purpose: Tyk2 mediates signaling downstream of the receptors for IL-12, IL-23 and Type I interferons, all key drivers of autoimmune disorders such as SLE. BMS-986165, an investigational agent entering Phase 2 studies for the treatment of multiple immune-mediated disorders, is a highly selective inhibitor of Tyk2-mediated signal transduction that acts by stabilizing the pseudokinase domain of the protein. The current report describes the preclinical pharmacology of BMS-986165, including mouse models of lupus and inflammatory bowel disease.

Methods: The affinity of BMS-986165 for the pseudokinase domain of Tyk2 was evaluated using recombinant protein, and functional assays used both cells isolated from peripheral human blood and whole blood from lupus patients. The efficacy in a mouse model of lupus nephritis employed NZB/W lupus-prone mice in which BMS-986165 was administered PO QD for 16 weeks. Body weight, proteinuria, anti-dsDNA titers, and gene expression (kidneys and blood) were measured, and kidneys were examined histologically for nephritis and immune complex deposition. In a model of inflammatory bowel disease, colitis was induced in SCID mice by an agonistic anti-CD40 Ab, and effect of BMS-986165 (administered PO QD) was evaluated against both the body weight loss and histologically evident colitis.

Results: BMS-986165 potently binds to the Tyk2 pseudokinase domain (Ki = 0.02 nM), and is highly selective against a panel of 265 kinases and pseudokinases. The compound potently inhibited IL-23-, IL-12-, and Type I interferon-driven cellular signaling and transcriptional responses (IC50 range 2-14 nM). BMS-986165 was approximately 200-fold selective against JAK1/3-dependent signaling in IL-2-stimulated T cells and >3,000-fold selective over JAK2-dependent EPO-induced signaling in TF-1 cells. In human whole blood, BMS-986165 inhibited Tyk2-dependent IFNa-induced signaling with an IC50 of 13 nM. Addition of BMS-986165 to whole blood from lupus patients led to reduced expression of Type I IFN response genes, a response identical to that achieved with an anti-IFNAR Ab and superior to an anti-IFNa Ab. BMS-986165 treatment in NZB/W lupus-prone mice rapidly (24 hours) reduced the elevated expression of Type I interferon-dependent genes and dose-dependently protected from nephritis and other disease endpoints with chronic dosing, with efficacy correlating with inhibition of Type I interferon-dependent gene expression. Protection from nephritis at 10 mpk trended to be superior to a blocking anti-Type I IFN receptor antibody (anti-IFNAR). BMS-986165 was also highly efficacious in the anti-CD40-induced colitis model in SCID mice, providing protection against both weight loss (wasting) and histologically evident colitis, and was as effective as an anti-p40 antibody.

Conclusion: In summary, the potent and highly selective suppression by BMS-986165 of the IL-23/TH17 axis, IL-12-mediated TH1 functions, and Type I interferon-driven modulation of immune pathways results in robust efficacy in preclinical models of SLE and IBD. These results provided the rationale for progression into human trials, and the compound is entering Phase 2 studies for the treatment of multiple immune-mediated disorders.

Disclosure: K. Gillooly, Bristol-Myers Squibb, 3; **Y. Zhang**, Bristol-Myers Squibb, 3; **X. Yang**, Bristol-Myers Squibb, 3; **A. Zupa-Fernandez**, Bristol-Myers Squibb, 3; **L. Cheng**, Bristol-Myers Squibb, 3; **J. Strnad**, Bristol-Myers Squibb, 3; **M. Cunningham**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **E. Heimrich**, Bristol-Myers Squibb, 3; **X. Zhou**, Bristol-Myers Squibb, 3; **J. Chen**, Bristol-Myers Squibb, 3; **C. Chaudhry**, Bristol-Myers Squibb, 3; **S. Li**, Bristol-Myers Squibb, 3; **K. McIntyre**, Bristol-Myers Squibb, 3; **J. Carman**, Bristol-Myers Squibb, 1,Bristol-Myers Squibb, 3; **R. Moslin**, Bristol-Myers Squibb, 3; **S. Wrobleski**, Bristol-Myers Squibb, 3; **D. Weinstein**, Bristol-Myers Squibb, 3; **J. Burke**, Bristol-Myers Squibb, 3.

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Abstract Number: 12L

Efficacy and Safety of Atacicept in Patients with Systemic Lupus Erythematosus: Results of a 24-Week Randomized, Placebo-Controlled, Phase IIb Study

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SESSION INFORMATION

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Session Type: ACR Late-breaking Abstract Session

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Background/Purpose: Atacicept targets B-cell stimulating factors BLyS and APRIL. In the APRIL-SLE trial, atacicept 150 mg was associated with reduced SLE flares in post-hoc analyses.[1]

Methods: ADDRESS II was a phase IIb, multicenter study (NCT01972568). Patients with active (SLEDAI-2K $\geq$ 6), autoantibody-positive SLE on standard-of-care therapy were randomized (1:1:1) to weekly SC injections of atacicept (75 or 150 mg) or placebo (PBO) for 24 weeks. The primary endpoint

was the % of patients achieving SRI-4 response at week 24.

Results: The ITT population included 306 patients (100 PBO; 102 atacicept 75 mg; 104 atacicept 150 mg). There was a trend towards improved SRI-4 response with atacicept vs PBO at week 24 (p=ns) (primary analysis; screening visit as baseline, BL) (**Table 1**). In a prespecified sensitivity analysis using study day 1 as BL, a significantly larger proportion of patients on atacicept achieved SRI-4 response at week 24: PBO, 41%; atacicept 75 mg, 55.9% (OR 1.88) p=0.029; atacicept 150 mg, 55.8% (OR 1.96) p=0.020. In predefined subpopulations with high disease activity (HDA; SLEDAI-2K ≥10, n=158), serologically active (SA) disease (dsDNA antibody-positive and low complement, n=84), or both (HDA SA, n=69), enhanced improvements in SRI-4 and SRI-6 response rates were seen with atacicept vs PBO (**Table 1**). SRI-6 response rates in HDA patients were significantly greater with atacicept 150 mg vs PBO at weeks 8, 16 and 24 (**Figure 1**). In HDA patients, severe flare was significantly reduced by atacicept 75 mg (BILAG A HR 0.1; p=0.002; SLEDAI flare index [SFI] HR 0.3; p=0.029) and 150 mg (BILAG A HR 0.3; p=0.038; SFI HR 0.2; p=0.004). In the ITT population, BILAG A flare was significantly reduced vs PBO with atacicept 75 mg (p=0.019), and severe SFI flare reduced with 150 mg (p=0.002). Atacicept was associated with increased serum complement C3/C4, and decreased IgG, IgM, IgA, and anti-dsDNA antibodies over time. Rates of AEs were similar between groups. Compared with placebo, the risks of SAEs and serious/severe infections were not increased with atacicept (**Table 2**).

Conclusion: Atacicept showed evidence of efficacy in SLE, particularly in HDA and SA patients; reduction in disease activity and severe flare was observed. Atacicept was associated with a favorable safety profile. 1. Isenberg D, et al. *Ann Rheum Dis*. 2015;74:2006-15.

Table 1: SRI response rates at week 24

	Responder rates (RR), n (%)			Atacicept 75 mg vs placebo			Atacicept 150 mg vs placebo		
	Placebo	Atacicept 75 mg	Atacicept 150 mg	Δ RR	Adjusted OR (95% CI)	p	Δ RR	Adjusted OR (95% CI)	p
ITT[*]	*n=100*	*n=102*	*n=104*						
SRI-4 (primary endpoint)[†]	44 (44.0)	58 (56.9)	56 (53.8)	12.9%	1.71 (0.97–2.99)	0.062	9.8%	1.55 (0.89–2.72)	0.121
SRI-4 (sensitivity analysis)[‡]	41 (41.0)	57 (55.9)	58 (55.8)	14.9%	1.88 (1.07–3.31)	0.029	14.8%	1.96 (1.11–3.46)	0.020
SRI-6	30 (30.0)	31 (30.4)	38 (36.5)	0.4%	1.03 (0.56–1.89)	0.932	6.5%	1.44 (0.79–2.62)	0.230
ITT SA[#]	*n=29*	*n=29*	*n=26*						
SRI-4	7 (24.1)	17 (58.6)	16 (61.5)	34.1%	5.10 (1.60–16.21)	0.006	37.4%	7.34 (2.09–25.77)	0.002
SRI-6	4 (13.8)	12 (41.4)	12 (46.2)	27.6%	4.80 (1.29–17.81)	0.019	32.4%	6.48 (1.66–25.35)	0.007
HDA[§]	*n=52*	*n=55*	*n=51*						
SRI-4	22 (42.3)	32 (58.2)	32 (62.7)	15.9%	1.95 (0.90–4.23)	0.090	20.4%	2.43 (1.09–5.42)	0.030
SRI-6	15 (28.8)	23 (41.8)	28 (54.9)	13.0%	1.83 (0.81–4.13)	0.143	26.1%	3.30 (1.44–7.59)	0.005
HDA SA[‖]	*n=24*	*n=25*	*n=20*						
SRI-4	6 (25.0)	15 (60.0)	13 (65.0)	35.0%	4.96 (1.43– 17.16)	0.012	40.0%	7.48 (1.84–30.43)	0.005
SRI-6	4 (16.7)	11 (44.0)	11 (55.0)	27.3%	4.12 (1.08– 15.75)	0.038	38.3%	7.13 (1.67– 30.45)	0.008

*All randomized patients; [†]screening visit as baseline; [‡]pre-specified analysis with study day 1 as baseline; [#]all patients with positive anti-dsDNA antibodies (≥15 IU/mL) and low complement (C3 <0.9 g/L and/or C4 <0.1 g/L) at baseline (screening visit); [§]all patients with SLEDAI-2K ≥10 at baseline; [‖]all patients with SLEDAI-2K ≥10 and with positive anti-dsDNA antibodies (≥15 IU/mL) and low complement (C3 <0.9 g/L and/or C4 <0.1 g/L) at baseline (screening visit)

Adjusted OR, 95% CI, and p-values were estimated from a logistic regression model, adjusted for pre-specified covariates

[a]Improvement in SLEDAI-2K of ≥4 points from baseline, no new BILAG 1A or 2B organ domain flares, no worsening in PGA (<10% increase), and no withdrawal from study or use of prohibited medications during the treatment period; [b]SRI response with improvements in SLEDAI-2K of ≥6 points from baseline (screening visit).

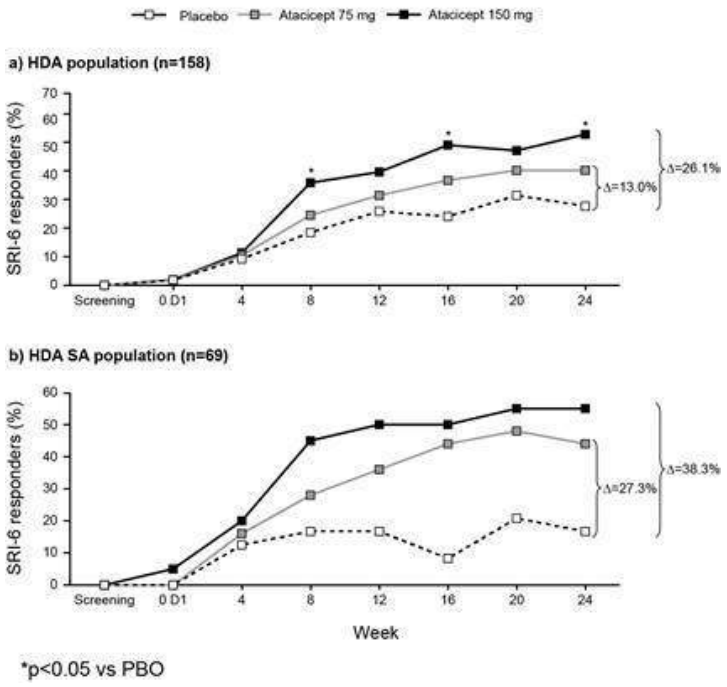
HDA, high disease activity; ITT, intention-to-treat; OR, odds ratio; RR, responder rate; SA, serologically active.

Table 2: Treatment-emergent adverse events (safety analysis set)

	Placebo n=100	Atacicept 75 mg n=102	Atacicept 150 mg n=104
Any TEAE, n (%)	71 (71.0)	83 (81.4)	84 (80.8)
Serious TEAEs, n (%)	11 (11.0)	9 (8.8)	6 (5.8)
TEAEs leading to treatment discontinuation, n (%)	6 (6.0)	5 (4.9)	6 (5.8)
Infections and infestations, n (%)	46 (46.0)	45 (44.1)	51 (49.0)
Serious/severe infections and infestations, n (%)	7 (7.0)	9 (8.8)	1 (1.0)
Deaths, n (%)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE, treatment-emergent adverse events

Figure 1. SRI-6 response in HDA and HDA SA subpopulations



*p<0.05 vs PBO

Disclosure: J. T. Merrill, Anthera Pharmaceuticals, Lilly, 5; **D. J. Wallace**, Merck Serono, 5; **S. Wax**, EMD Serono, 3; **A. Kao**, EMD Serono, 3; **P. Fraser**, EMD Serono, 1,EMD Serono, 3; **W. Chin**, EMD Serono, 3; **D. A. Isenberg**, Merck Serono, 5.

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Abstract Number: 13L

Low-Dose IL-2 Therapy in Refractory SLE: Results from Single Center Phase I/IIa Clinical Trial

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SESSION INFORMATION

Session Date: Sunday, November 13, 2016
Session Title: ACR Late-Breaking Poster Session
Session Type: ACR Late-breaking Abstract Session
Session Time: 9:00AM-11:00AM

Background/Purpose: Interleukin-2 (IL-2) is crucial for the growth and survival of regulatory T cells (Treg), and thus for the control of autoimmunity. In previous studies we have proven the significance of an acquired IL-2 deficiency and related Treg defects in the pathogenesis of systemic lupus erythematosus (SLE). Accordingly, we showed that compensation of IL-2 deficiency by low dose IL-2 therapy is capable to correct Treg defects in SLE patients.

Here, we conducted a combined phase I/IIa single center clinical trial (PRO-IMMUN; EudraCT-Number: 2013-001599-40; DRKS-ID: DRKS00004858) addressing the safety, tolerability, immunological responses and clinical efficacy of a subcutaneous low-dose IL-2 therapy in patients with refractory and active SLE.

Methods: 10 patients with active and refractory SLE (SLEDAI $\geq$ 6; at least two different immunosuppressive therapies) were enroled into the trial and 2 patients were treated „off-label“ with the same regimen. The therapeutic regimen consisted of four treatment cycles each with daily subcutaneous injections of recombinant human IL-2 (aldesleukin) at single doses of 0.75, 1.5 or 3.0 million IU on five consecutive days separated by washout-periods of 9-16 days and followed by a 9-week follow-up period. Cells from peripheral blood were analysed by flow cytometry at every study visit before the IL-2 injections and one day after the 5th IL-2 injection. The primary objective was to show an increase in the percentage of CD25hi cells among CD3+CD4+Foxp3+CD127lo Treg cells by at least 100% (2-fold) after the 4th treatment cycle compared to baseline. Safety and tolerability were evaluated descriptively. Secondary objectives included the clinical responses assessed by SLEDAI and changes in serological and other immunological parameters.

Results: All 12 patients showed an effective and cycle-dependent increase in the percentage of CD25hi cells among Treg ($p<0.001$). 10 patients showed a reduction in SLEDAI (83.3%, $p<0.05$) and 8 patients achieved a clinical response (66.7%) with a complete disappearance of clinical manifestations such as rash, arthritis, myositis and alopecia. Levels of complement were significantly increased after the treatment compared to baseline ($p<0.05$). However, we could not observe a reduction in levels of anti-dsDNA-Abs. Treatment-related adverse events were generally mild and transient.

Conclusion: Low-dose IL-2 therapy is capable to safely and selectively expand the Treg population and to decrease disease activity in patients with active and refractory SLE. This study provides the basis for

larger and placebo-controlled clincial studies aiming to prove the efficacy of this novel biologic treatment strategy.

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View Abstract and Citation Information Online - http://acrabstracts.org/abstract/low-dose-il-2-therapy-in-refractory-sle-results-from-single-center-phase-iiia-clinical-trial

Abstract Number: 14L

Use of Intravenous Epoprostenol As a Treatment for the Digital Vasculopathy Associated with the Scleroderma Spectrum of Diseases

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SESSION INFORMATION

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Session Type: ACR Late-breaking Abstract Session

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Background/Purpose:

Intravenous prostanoid therapy is recommended for severe systemic sclerosis related digital vasculopathy. Evidence to support this recommendation is limited. Our objective is to evaluate the safety and efficacy of treating scleroderma spectrum digital vasculopathy with intravenous epoprostenol.

Methods:

Patients with systemic sclerosis and received intravenous epoprostenol for scleroderma spectrum digital vasculopathy (defined as digital ischemic ulcers, digital ischemia with or without gangrene, but not uncomplicated Raynaud's) between 10/01/2003 – 09/01/2015 at Boston University Medical Center were identified using ICD-9 code search and their charts were reviewed in this retrospective case series. The epoprostenol infusion protocol used was as follows:

Continuous intravenous epoprostenol begun at 2ng/kg/min and increased every 15min to a maximum dose

of 8ng/kg/min. Epoprostenol was administered via central access (most frequently a PICC line); the final dose was dependent on tolerability, hemodynamic stability and oxygenation. This dose (most frequently 8ng/kg/min) was maintained for five days and then weaned by 2ng/kg/min every 12h unless there was recurrence of the digital ischemia. In that case, the dose was held or increased, depending on the severity of the ischemia, until the ischemic episode resolved. Prior to discontinuing the epoprostenol, another vasodilator (usually a PDE-5i) was added.

Results:

There were 46 epoprostenol infusions in 35 patients with scleroderma spectrum digital vasculopathy. 32 patients were female. Patients' ages ranged from 21 to 85 with a median age of 50. 19 patients had limited cutaneous systemic sclerosis, 5 had diffuse cutaneous systemic sclerosis, 3 had mixed connective tissue disease, 2 had systemic sclerosis sine scleroderma. Scleroderma spectrum subtype was not documented in 6 patients. Epoprostenol was usually titrated to 8ng/kg/min and held at that dose for 5 days.

Out of 46 epoprostenol infusions, 29 had documentation of improvement as indicated by pain relief, increased perfusion of digits as assessed by warmth or color, reduced number and size of digital ulcers. Two epoprostenol infusions resulted in no improvement. In 16 infusions, there was no documentation as to whether the digital vasculopathy improved or not. Although there was no documented clinical deterioration during an infusion, 5 patients ultimately required surgical intervention including amputation or debridement.

Out of 46 infusions, adverse effects occurred in 26. Adverse events were common and included nausea/vomiting, jaw pain, headaches and flushing, but were transient and typically occurred with dose escalation. Serious adverse events were uncommon and included hypotension (4), line infection (1) and line thrombosis (1).

Conclusion:

This is the largest study investigating the use of intravenous epoprostenol infusion in the treatment of scleroderma spectrum digital vasculopathy. We demonstrate that the use of our intravenous epoprostenol infusion protocol vasculopathy is generally safe and effective, and should be considered an important therapeutic option for scleroderma spectrum digital vasculopathy.

Disclosure: S. Law, None; **R. W. Simms**, None; **H. W. Farber**, None.

View Abstract and Citation Information Online - http://acrabstracts.org/abstract/use-of-intravenous-epoprostenol-as-a-treatment-for-the-digital-vasculopathy-associated-with-the-scleroderma-spectrum-of-diseases

Abstract Number: 15L

Selective Oral ROCK2 Inhibitor Reduces Clinical Scores in Patients with Psoriasis vulgaris and Normalizes Skin Pathology

Via Concurrent Regulation of IL-17 and IL-10 Levels

Alexandra Zanin-Zhorov[1], Jonathan Weiss[1], Alissa Trzeciak[1], Carmen Arencibia[1], Seetharam Polimera[1], Wei Chen[1], Jingya Zhang[1], Melanie Nyuydzefe[1], Judilyn Fuentes-Duculan[2], Kathleen Bonifacio[2], Norma Kunjravia[2], Inna Cueto[2], Mark Berger[1], James Krueger[2], Samuel Waksal[1] and John Ryan[1], [1]Kadmon, New York, NY, [2]Rockefeller University, New York, NY
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SESSION INFORMATION
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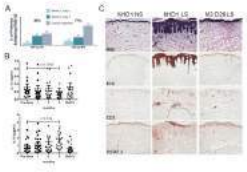
Background/Purpose: Rho-associated kinase 2 (ROCK2) was shown to be implicated in regulation of autoimmunity in mice and humans[1]. Previous findings demonstrated that oral administration of a selective ROCK2 inhibitor (KD025) in healthy subjects decreases IL-17 and IL-21 secretion induced by *ex vivo* stimulation[2]. Moreover, targeted ROCK2 inhibition shifted the balance between Th17/Tfh and Treg subsets via concurrent regulation of STAT3/STAT5 phosphorylation[2-4]. We have hypothesized that targeting of ROCK2 may therefore restore disrupted immune homeostasis and has a role in the treatment of Th17-driven inflammatory disorders.

Methods: We conducted a Phase 2, open-label, dose-finding study to evaluate the safety, tolerability, and activity of KD025 in subjects with psoriasis vulgaris who failed first-line therapy (NCT02317627 at ClinicalTrials.gov). KD025 was orally administrated at three daily dose regimens for 12 weeks. Decreases in Psoriasis Area and Severity Index (PASI) scores were measured and peripheral blood samples were collected on a monthly basis. The levels of cytokines in plasma samples were determined by using the Simoa® Immunoassay. Skin punch biopsies were obtained at baseline and at the end of treatment.

Results: KD025 treatment resulted in PASI score reductions in 85% of patients completing the study, with minimal side effects. In the 400 mg QD and 200 mg BID cohorts, 42% and 71% of patients respectively achieved at least a 50% decrease in PASI score (PASI 50) after 12 weeks of treatment. KD025 reduced levels of both IL-17 and IL-23, but not IL-6 and TNF-a in the peripheral blood of clinical responders, whereas IL-10 levels were increased at the end of the study. The clinical improvement and changes in cytokine levels were associated with decreased epidermal thickness and T-cell infiltration in the skin.

Conclusion: Collectively, our results demonstrate that selective ROCK2 inhibition with KD025 down-regulates Th17-driven autoimmune response and improved clinical symptoms in psoriatic patients via concurrent modulation of cytokines without deleterious impact on the rest of the immune system.
References: 1. Biswas, P.S. *et al.* Phosphorylation of IRF4 by ROCK2 regulates IL-17 and IL-21 production and the development of autoimmunity in mice. *J Clin Invest* **120**, 3280-3295 (2010). 2. Zanin-Zhorov, A. *et al.* Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. *Proc Natl Acad Sci U S A* **111**, 16814-16819 (2014). 3. Flynn, R. *et al.* Targeted Rho-associated kinase 2 (ROCK2) inhibition decreases clinical and immune pathology of murine and human chronic GVHD through Stat3-dependent mechanism. *Blood*

(2016). 4. Weiss, J.M. *et al.* ROCK2 signaling is required to induce a subset of T follicular helper cells through opposing effects on STATs in autoimmune settings. *Science signaling* **9**, ra73 (2016).



Disclosure: **A. Zanin-Zhorov**, Kadmon, 3; **J. Weiss**, Kadmon, 3; **A. Trzeciak**, Kadmon, 3; **C. Arencibia**, Kadmon, 3; **S. Polimera**, Kadmon, 3; **W. Chen**, Kadmon, 3; **J. Zhang**, Kadmon, 3; **M. Nyuydzefe**, Kadmon, 3; **J. Fuentes-Duculan**, None; **K. Bonifacio**, None; **N. Kunjravia**, None; **I. Cueto**, None; **M. Berger**, Kadmon, 3; **J. Krueger**, Kadmon, 5; **S. Waksal**, Kadmon, 3; **J. Ryan**, Kadmon, 3.

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Abstract Number: 16L

Comparison of Systematic Vs Individually Tailored Rituximab Regimen to Maintain ANCA-Associated–Vasculitis Remission: Results of a Prospective, Randomized–Controlled, Phase 3 Trial

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Background/Purpose: Remission of ANCA-associated vasculitides (AAVs) can be induced with combined glucocorticoids and cyclophosphamide or rituximab (RTX) with comparable efficacy.[1] RTX superiority to azathioprine was demonstrated for remission maintenance;[2] in that trial, at month 28, major relapses occurred in only 5% of the patients on RTX vs 29% taking azathioprine (AZA). Although, at present, neither ANCA-positivity and/or their titers nor peripheral blood CD19 B-cell detection are considered reliable predictors of AAV relapses, relapses are rare when they are negative.[3] This trial (MAINRITSAN2, registered with ClinicalTrials.gov, no. NCT01731561) was designed to evaluate RTX use, adapted to ANCA-positivity and/or titer and/or reappearance of circulating CD19 B cells, to maintain AAV remission.

Methods: Patients with granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) in complete remission after induction therapy with glucocorticoids and cyclophosphamide or rituximab or methotrexate were included in an open-label, multicenter, randomized–controlled trial to compare regimens with RTX given according to ANCA status/titer and/or circulating CD19 B-cell reappearance vs systematic RTX infusions (controls). The experimental arm received fixed, 500-mg RTX infusions on day-0 post-randomization, then every 3 months until month 18, when CD19 lymphocytes exceeded 0/mm^3 or ANCA status (reappearance)/titer (higher) differed from the previous determination. Controls received 500 mg of RTX on days 0 and 14 after randomization, and then 6, 12 and 18 months after the first infusion. The primary endpoint was the number of relapses (new or reappearing symptom or worsening disease with BVAS>0) at month 28; it was evaluated by an independent Adjudication Committee blinded to

treatment arms.

Results: The 162 patients included [117 (72.2%) GPA and 45 (27.8%) MPA] were equally allocated to the experimental arm (n=81; 50%) and control (n=81; 50%) groups. Pre-randomization induction therapy was cyclophosphamide for 100 (61.7%) patients, RTX for 61 (37.7%) or methotrexate for 1 (0.6%). Twenty-one (13%) patients suffered 22 relapses: 14 (17.3%) in 13 experimental arm patients and 8 (9.9%) in 8 controls (P=0.20). Median (interquartile range (IQR)) numbers of RTX infusions were 3 (2–4) for the experimental arm and 5 (IQR 5–5) for controls. Four patients died, 1 of an infectious complication.

Conclusion: AAV relapse rates for patients given individually tailored or systematic RTX-infusion schedules did not differ significantly. However, the experimental arm patients received fewer infusions and lower total RTX doses. [1]Stone JH *et al*. N Engl J Med 2010;363:221–32. [2]Guillevin L *et al*. N Engl J Med 2014;371:1771–80. [3]Specks U *et al*. N Engl J Med 2013;369:417–27.

Disclosure: P. Charles, Hoffmann-La Roche, Inc., 9; **B. Terrier**, Hoffmann-La Roche, Inc., 9; **P. Cohen**, Hoffmann-La Roche, Inc., 9; **S. Faguer**, Hoffmann-La Roche, Inc., 9; **A. Huart**, Hoffmann-La Roche, Inc., 9; **M. Hamidou**, Hoffmann-La Roche, Inc., 9; **C. Agard**, Hoffmann-La Roche, Inc., 9; **B. Bonnotte**, Hoffmann-La Roche, Inc., 9; **M. Samson**, Hoffmann-La Roche, Inc., 9; **A. Karras**, None; **N. Jourde-Chiche**, Hoffmann-La Roche, Inc., 9; **F. Lifermann**, Hoffmann-La Roche, Inc., 9; **P. Gobert**, Hoffmann-La Roche, Inc., 9; **C. Hanrotel-Saliou**, Hoffmann-La Roche, Inc., 9; **P. Godmer**, Hoffmann-La Roche, Inc., 9; **N. Martin Silva**, Hoffmann-La Roche, Inc., 9; **G. Pugnet**, Hoffmann-La Roche, Inc., 9; **M. Matignon**, Hoffmann-La Roche, Inc., 9; **O. Aumaître**, Hoffmann-La Roche, Inc., 9; **E. Lazaro**, Hoffmann-La Roche, Inc., 9; **L. Mouthon**, Hoffmann-La Roche, Inc., 9; **L. Guillevin**, Hoffmann-La Roche, Inc., 9.

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Abstract Number: 17L

Sofosbuvir Plus Daclatasvir for Hepatitis C Virus Associated Cryoglobulinemia Vasculitis

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Background/Purpose: Hepatitis C virus (HCV) is the aetiological agent for most cases of cryoglobulinemia vasculitis. Interferon containing regimens are associated with important side effects and may exacerbate the vasculitis. Objective: To evaluate safety and efficacy of an oral interferon free regimen, sofosbuvir plus daclatasvir in HCV cryoglobulinemia vasculitis.

Methods: We enrolled 35 patients (median age of 57 years and 45% of women) with HCV cryoglobulinemia vasculitis. Sofosbuvir (400mg/day) was associated with Daclatasvir (60mg/day) for 12 or 24 weeks. The primary efficacy end point was a complete response of the vasculitis at the end of treatment. Secondary endpoints included (i) immunological response (i.e. clearance of cryoglobulin), (ii) sustained virological response (viral eradication, i.e. prolonged negative viremia), and safety.

Results: HCV genotype was 1 (n=21), 2 (n=2), 3 (n=7), 4 (n=3) and 5 (n=2). Seventeen (48.6%) had cirrhosis. Main features of HCV cryoglobulinemia vasculitis included arthralgia (66%), purpura (54%) peripheral neuropathy (54%), skin ulcers (11%) and glomerulonephritis (11%).Thirty two (91%) were complete clinical response at end of treatment. The mean cryoglobulin and alanine aminotransferase levels decreased from [0.36 ± 0.12 to 0.10 ± 0.08 g/L, ($p=0.019$) and 57.6 ± 7.1 to 20.4 ± 2.0 IU/ml, ($p<0.0001$)], respectively at week 12 post treatment. Fifty percent of patients achieved complete immunological response (i.e. clearance of cryoglobulin). All patients had a sustained virological response at week 12 post treatment and the HCV viral load dropped from 5.6 to 1.18 IU/ml at week 4, ($p<0.0001$). The most common side effects were asthenia (14.3%), nausea (8.6%), and insomnia (3%). No serious adverse event was reported.

Conclusion: S Sofosbuvir plus daclatasvir antiviral combination is highly and quickly active in HCV-cryoglobulinemia vasculitis, with a good tolerance profile.

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Primary CNS Vaculitis Vs Neurosarcoidosis: Can We Predict the Diagnosis with MRI?

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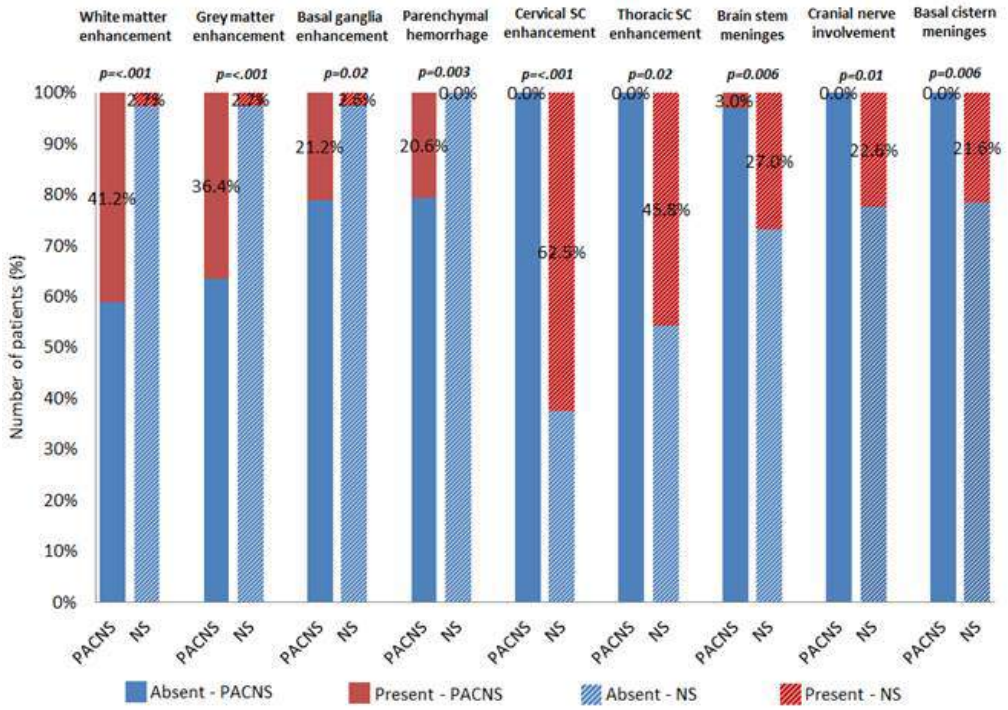
Background/Purpose: Neurosarcoidosis and primary angiitis of central nervous system (PACNS) are inflammatory diseases affecting central nervous system, with overlapping clinical and pathological characteristics. Differentiating between both conditions is crucial for differences in therapeutic options. In this study, we aimed to compare the MRI findings between these two conditions to enhance our diagnostic approach, which can lead to more accurate decisions about appropriate treatment strategy.

Methods: Thirty-four patients with PACNS and forty two patients with neurosarcoidosis were included in the study. Brain and/or spinal cord MRI performed near the time of presentation were blindly evaluated by two neuroradiologists. Data regarding involvement of pachy- and leptomeninges, basal meninges, cranial nerves, cerebral grey and white matter, and spinal cord were recorded for each patient. For each of these sites, presence, pattern (focal vs diffuse), localization (cerebral lobes, brain stem, cerebellum, tentorium, falx cerebri), and laterality of involvement (right, left, bilateral) were recorded. Additionally, ventriculomegaly, mass effect, and parenchymal hemorrhage were recorded. Chi square and Fisher's exact tests were used to compare the groups, as appropriate. All statistical analyses were performed using SAS 9.4 software.

Results: Mean age of patients was 45.6 (range, 5-80) and 44.1 (range, 25-66) in PACNS and neurosarcoidosis groups, respectively. MRI findings are summarized in the Table. Enhancement and abnormal signal in grey and/or white matter were significantly more common in patients with PACNS. However, localization and laterality of grey and/or white matter involvements did not show a difference between groups. In addition, basal ganglia enhancement and parenchymal hemorrhage were significantly associated with PACNS. On the other hand, patients with neurosarcoidosis had more common basal meningeal, spinal cord and cranial nerve involvements. Frequency, pattern, laterality and localization of pachy- and leptomeningeal, pituitary and hypothalamic involvements; frequency of brain mass effect and ventriculomegaly were similar between groups.

Conclusion: Patients with PACNS had higher frequency of cerebral and basal ganglia enhancement, and

parenchymal hemorrhage, while patients with neurosarcoidosis demonstrated more frequent spinal cord, basal meningeal and cranial nerve involvements. These findings suggest that MRI can be an efficient tool in distinguishing PACNS from neurosarcoidosis. **Table.** Frequencies and comparison of MRI findings in patients with PACNS and neurosarcoidosis (NS).



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Biosimilar Infliximab (CT-P13) Is Not Inferior to Originator Infliximab: Results from a 52-Week Randomized Switch Trial in Norway

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Background/Purpose: TNF-inhibitors (TNFi) have improved treatment of spondyloarthritis (SpA), rheumatoid arthritis (RA), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), and chronic plaque psoriasis (Ps). The NOR-SWITCH trial was funded by the Norwegian government. The aim of the NOR-SWITCH trial was to examine switching from originator to biosimilar infliximab regarding efficacy, safety and immunogenicity.

Methods: The study was designed as a 52-week randomized, double-blind, non-inferiority, phase IV trial. Adult patients with a diagnosis of SpA, RA, PsA, CD, UC or Ps on stable treatment with the originator infliximab (Remicade®, INX) for at least 6 months were eligible. Patients with informed consent were randomized 1:1 to either continued INX or switch to CT-P13 treatment (biosimilar infliximab, Remsima®), using unchanged dosing regimen. Data were collected at infusion visits. The primary endpoint was disease worsening during follow-up according to worsening in disease-specific composite measures and/or a consensus between investigator and patient leading to major change in treatment. Exploratory subgroup analyses were performed to examine disease worsening within each of the six diagnoses. The non-inferiority margin was set to 15% and power calculations indicated that 394 patients were required in the primary Per Protocol Set (PPS). The primary endpoint was analysed using logistic regression, adjusted for diagnosis and disease duration at baseline.

Results: Between October 6, 2014 and July 8, 2016, 481 patients (INX 241, CT-P13 240, Full Analysis Set, FAS) at 40 Norwegian study centres were randomized, received treatment and were followed for 52 weeks. The main demographic and baseline characteristics are shown in the table. Disease worsening occurred in 26.2% and 29.6% of patients in the INX and CT-P13 arms, respectively (PPS). The 95% confidence interval of the adjusted treatment difference (-4.4%) was -12.7 – 3.9 which was within the pre-specified non-inferiority margin. The frequency of disease worsening in each specific diagnosis is shown in the table (exploratory analyses). Changes in the generic disease variables and disease specific composite measures were similar in both arms (table). The incidence of anti-drug antibodies detected during the study was 17 (7.1%) and 19 (7.9%) in the INX and CT-P13 patients, respectively (FAS). The trough drug levels and the frequencies of reported adverse events including infusion reactions were also similar (data not shown).

Conclusion: The NOR-SWITCH trial demonstrated that switching from INX to CT-P13 was not inferior to continued treatment with INX.

Table. Demographic and baseline characteristics (FAS), percentage of patients with disease worsening and change in disease measures during 52 weeks follow-up (PPS)			
	INX	**CT-P13**	95% CI of group difference after 52 weeks
Number of patients (FAS)	**241**	**240**	
Demographics and baseline characteristics			
Age (years)	47.5 (14.8)	48.2 (14.9)	
Females	99 (41.1%)	87 (36.2%)	
Disease duration (years)	16.7 (10.9)	17.5 (10.5)	
Duration of ongoing infliximab treatment (years)	6.7 (3.6)	6.9 (3.8)	
Concomitant immunosuppressive medication	113 (46.9%)	129 (53.8%)	
Diagnoses			
Spondyloarthritis	45 (18.7%)	46 (19.2%)	
Rheumatoid arthritis	39 (16.2%)	38 (15.8%)	
Psoriatic arthritis	14 (5.8%)	16 (6.7%)	
Crohn's disease	78 (32.4%)	77 (32.1%)	
Ulcerative colitis	47 (19.5%)	46 (19.2%)	
Psoriasis	18 (7.5%)	17 (7.1%)	
Disease worsening			
All	53 (26.2%)	61 (29.6%)	-12.7 – 3.9%
Spondyloarthritis	17 (39.5%)	14 (33.3%)	-14.5 – 27.2%
Rheumatoid arthritis	11 (36.7%)	9 (30.0%)	-20.3 – 29.3%
Psoriatic arthritis	7 (53.8%)	8 (61.5%)	-45.4 – 28.1%
Crohn's disease	14 (21.2%)	23 (36.5%)	-29.3 – 0.7%
Ulcerative colitis	3 (9.1%)	5 (11.9%)	-15.2 – 10.0%
Psoriasis	1 (5.9%)	2 (12.5%)	-26.7 – 13.2%
Change in disease measures from baseline			
Physician Global Assessment of Disease Activity (0-10)	0.09 (1.62)	0.11 (1.56)	-0.39 – 0.09
Patient Global Assessment of Disease Activity (0-10)	0.43 (1.87)	0.30 (2.20)	-0.37 – 0.29
Log_{10} erythrocyte sedimentation rate (mm/h)	0.019 (0.254)	0.006 (0.308)	-0.065 – 0.028

Log_{10} C-reactive protein (mg/L)	0.020 (0.345)	0.023 (0.419)	-0.086 – 0.038
BASDAI (SpA)	0.25 (1.01)	-0.15 (1.38)	-0.50 – 0.47
ASDAS (SpA)	0.07 (0.59)	-0.19 (0.67)	-0.27 – 0.24
DAS28 (RA, PsA)	0.30 (0.98)	0.08 (0.93)	-0.08 – 0.61
CDAI (RA, PsA)	1.51 (5.54)	0.67 (3.94)	-0.35 – 2.94
SDAI (RA, PsA)	1.56 (5.67)	0.69 (4.41)	-0.68 – 2.86
Harvey-Bradshaw Index (CD)	0.26 (2.35)	0.49 (3.15)	-1.14 – 0.33
Partial Mayo Score (UC)	0.09 (1.28)	-0.17 (1.68)	-0.30 – 0.59
Log_{10} faecal calprotectin (mg/kg) (UC,CD)	0.035 (0.506)	0.096 (0.477)	-0.118 – 0.177
PASI (Ps)	-0.50 (1.88)	-0.44 (1.87)	-1.10 – 0.55

Data are n (%), mean (SD) or median (25 – 75 percentiles). 95% CI, 95% confidence interval of the adjusted treatment difference. BASDAI, Bath Ankylosing Spondylitis Disease Activity Index. ASDAS, Ankylosing Spondylitis Disease Activity Score. DAS28, Disease Activity Score in 28 joints. CDAI, Clinical Disease Activity Index. SDAI, Simplified Disease Activity Index. PASI, Psoriasis Area and Severity Index.

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